

Spectrum of Infections in Children with Primary Nephrotic Syndrome: Cross Sectional Study

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Received: October, 2020
Revised: November, 2020
Accepted: December, 2020

Abstract

Background and Aim: Nephrotic Syndrome (NS) is a common renal disorder in pediatric population. Children with primary nephrotic syndrome are more susceptible to bacterial infections. Spectrum of infections in NS is not much studied. To determine the spectrum of infections in children with primary nephrotic syndrome.

Methods: This study was a hospital based cross sectional study conducted in children with primary nephrotic syndrome (born to 18 years of age) admitted in a tertiary care hospital of Rajasthan, India. Seventy-six children with diagnosis of nephrotic syndrome were enrolled. Data for age, gender, type of infection and clinical manifestation were computed on SPSS -20 and analyzed using descriptive statistics.

Results: Boys were affected more than girls with a ratio of 3.47:1. The mean age was 6.4±3.74 years. Most common presentations in our study were fever (46.05%), cough (42.11%) and burning micturition (19.74%). Infection was associated in 71.05% cases of relapses of nephrotic syndrome. The most common infections were acute respiratory tract infection (34.21%) [-URI-22.37% and pneumonia-11.84%] followed by urinary tract infection (26.32%). In our study we found that infection rates in overall, newly diagnosed, infrequent relapsers, frequent relapsers steroid dependent and steroid resistant cases were 71%, 28%, 85%, 91% 40% and 50% respectively.

Conclusion: E coli, Klebsiella and Proteus were the most common bacteria in primary nephrotic syndrome. Respiratory and urinary tract infections were most common infections. Male are affected more commonly than females.

Keywords: Nephrotic syndrome; Infection; Children.

Conflict of interest: The authors declare no conflict of interest.

Please cite this article as: Lora SS, Choudhary R, Shekhawat YS, Gothwal S, Verma SK, Meena RK. Spectrum of Infections in Children with Primary Nephrotic Syndrome: Cross Sectional Study. J Ped Nephrol 2021;9(1):1-6. <https://doi.org/10.22037/jpn.v9i1.32665>

Introduction

Nephrotic Syndrome is a common renal disorder in pediatric population. Nephrotic syndrome is characterized by the presence of heavy proteinuria (more than 40 mg/m²/hr), hypo-albuminemia, edema and hyperlipidemia (1). Its incidence is 20-40 and 20-70 cases per million populations in UK and USA respectively, whereas in Asian countries it is 90-160 cases per million population (2). Infections are important cause of morbidity and mortality in nephrotic syndrome. These patients have an increased risk of developing bacterial infections due to defective cell mediated immunity, immunosuppressive therapy, malnutrition and urinary losses of immunoglobulins, properdin factor

B and complement factors (3). Edema and ascites also act as a potential culture medium for microorganism¹. Nephrotic syndrome often follows infections of upper and lower respiratory tract including pneumonia with or without empyema, skin infections including impetigo and cellulitis, acute gastroenteritis or dysentery, urinary tract infections and primary peritonitis (1). Among all infections, UTI may be asymptomatic and thus may be missed if active search is not made. Infections, if left untreated in a patient of nephrotic syndrome who has been started on steroid therapy will complicate the course nephrotic syndrome (4). Therefore, it is essential to know the current trend

of infections and prevalent organisms in Nephrotic Syndrome to decide about appropriate antibiotics. Hence, the present study was conducted.

Methods

Source of data: All children with nephrotic syndrome (newborn to 18 years of age) admitted in the Department of Pediatrics, Dr. S.N. Medical College, Jodhpur.

Type of study: This study was an observational study conducted over duration of 1 year.

Inclusion Criteria: All the hospitalized children with nephrotic syndrome from Newborn period to 18 years of the age were included in this study.

Exclusion Criteria: Children with refusal of consent for study participation.

Method of study: In this observational study, details of history, clinical examination, and laboratory reports were entered in a predesigned performa for all included subjects. Cases were enrolled continuously on first come first basis. No randomization and blinding were done. The eligibility criteria was applied by primary investigator and included in the study after receiving written informed consent.

Diagnosis of nephrotic syndrome (5): Nephrotic syndrome was diagnosed with ensuring heavy proteinuria, hypoalbuminemia (serum albumin <2.5 g/dl), hyperlipidemia (serum cholesterol >200 mg/dl) and edema. Nephrotic range proteinuria was present if early morning urine protein was 3+/4+ (on dipstick or boiling test), spot protein/creatinine ratio >2 mg/mg, or urine albumin excretion >40 mg/m² per hour (on a timed-sample).

Few important case definitions

Remission: Urine albumin nil or trace (or proteinuria <4 mg/m²/hr) for 3 consecutive early morning specimens

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

Infrequent Relapse: Patients who have three or less relapses a year and respond promptly to prednisolone are managed using the aforementioned regimen for each relapse. Such children are at a low risk for developing steroid toxicity.

Frequent Relapse: Frequently relapsing nephrotic syndrome (FRNS) is defined as steroid-sensitive nephrotic syndrome (SSNS) with two or

more relapses within 6 months, or 4 or more relapses within a 12-month period.

Steroid Dependence: Children with frequently relapsing nephrotic syndrome (FRNS) in whom two consecutive relapses, or two of four relapses in any 6-month period, occurred while still on a dose of steroids or within 14 days of discontinuing steroid therapy.

Steroid Resistance: (SRNS) Absence of remission despite daily steroid therapy at a dose of 2 mg/kg/day for 4 weeks.

Initial evaluation: A detailed evaluation was done before starting treatment with corticosteroids. The height, weight, and blood pressure was recorded. Daily weight record was taken for monitoring the decrease or increase of edema. Physical examination is done to detect infections and underlying systemic disorders. Infections were treated before starting therapy with corticosteroids. **Investigations:** at the initial episode included urinalysis, complete blood count, SERUM albumin, cholesterol, urea and creatinine were done. Estimation of anti-streptolysin O titer and C3 was done in patients with gross or persistent microscopic hematuria. Appropriate tests were performed, if necessary, for associated conditions (e.g., chest X-ray and tuberculin test, hepatitis B surface antigen, and antinuclear antibodies). Urine culture was done when clinical features suggestive of a urinary tract infection. Besides routine investigations, specimen for gram stain and culture sensitivity were obtained from blood, urine in all the cases whereas ascetic fluid, pleural fluid, throat and dermal lesions were cultured as and when required. Mantoux test, X-ray chest and abdominal ultrasound were done in all the subjects.

Urine culture procedure - Urine collection was done after thorough washing the genitalia; a clean-catch midstream urine specimen was directly collected in a sterile container. The samples were plated on Mac-conkey agar, Nutrient agar and Chrome agar within one hour of collection. Urine routine microscopy was sent at the same time and if suggestive of UTI empirical antibiotics were started and later modified as per culture report.

Method used for bacterial culture: Around 3 ml blood was collected in all cases at admission and repeat sample prior to upgradation of antibiotics with all due aseptic precautions. BD BACTEC 9050 automated blood culture system designed for the rapid detection of both aerobic and anaerobic

bacteria and fungi in the clinical culture of blood was used. Blood culture bottles were incubated at 37C for 7 days. Routine blind subcultures were taken between 48-72hrs and again on 7th day on all apparently negative culture bottles. Subcultures were done on blood agar and Mac-Conkey agar at 37C for 24-48hrs. If any growth was found, then organisms were identified biochemically and antibiotic sensitivity test was done as per standard laboratory procedure. Blood investigations and x ray: Other blood investigation including routine investigation and chest x ray were sent to central lab attached to our hospital.

Specific major infections were defined as follows:

- (1) Peritonitis: Abdominal pain, fever, vomiting, with ascitic fluid showing >100 leukocytes/mm³.
- (2) Pneumonia: fast breathing and chest in drawing with chest X-ray confirmation.
- (3) Urinary tract infection (UTI): Bacterial colony count of >10⁵ organisms/ml in a clean-catch midstream urine sample¹.
- (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.

Statistical analysis: The entire data was collected and compiled into MS-Excel spread sheet. Continuous variables were presented as mean and standard deviation and categorical variables as number and proportion. Informed written consent was taken after admission of the eligible study subjects from parents and/or guardian

Results

In the present study, 76 children in the age group of birth to 18 years with nephrotic syndrome were included. Half of cases was found in age group of 2-6 years (50%), while 7.89% of the cases belonged to <2 years and 42.11% and to >6 years age group. The mean age was 6.4±3.74 years . Boys were affected more than girls with a ratio of 3.47:1. Among the 76 children newly diagnosed cases were 32.89% and relapses were 67.11% and among the 51 relapses patients infrequent relapsers were 78.43% and frequent relapsers were 21.57%. In the present study, all patients presented with puffiness of face. Other symptoms at presentation were decreased urine output (86.84%), fever (46.05%),

cough (42.11%), abdominal distension (22.37%), burning micturition (19.74%), abdominal pain (14.47%) and chest pain in 5.26% of cases. The least common presentation was red color urine which was seen only in 2.63% of cases. In the present study infection was associated in 71% cases of nephrotic syndrome. Newly diagnosed cases had 28% infections. Almost 91% of frequent relapsers and 85% infrequent relapsers had infection. 40% cases of steroid dependent and 50% cases of steroid resistant nephrotic syndrome had infections (table 1).

Table 1. Spectrum of infections in different types of cases

Cases	Infection	Percentage (%)
New Case (25)	07	28
Infrequent Relapsers (40)	34	85
Frequent Relapsers (11)	10	90.91
Steroid Dependent (05)	03	40
Steroid Resistant (02)	01	50

In the present study Infection was associated in 71.05% cases of nephrotic syndrome. Most common infections were acute respiratory tract infection (34.21%) -URI-22.37% and Pneumonia-11.84%. Urinary Tract Infection was detected in twenty children (26.32%), Tuberculosis was in 7.89% cases, Peritonitis in 1.32% and Cellulitis was detected in 1.32% patients (table 2).

Table 2. Types of infections in nephrotic syndrome

	No of cases	Percentage (%)
UTI*	20	26.32
URI*	17	22.37
Pneumonia*	09	11.84
Tuberculosis	06	7.89
Peritonitis	01	1.32
Cellulitis	01	1.32
Total	54	71.05

*Two patients of UTI also had Pneumonia and one patients of UTI also had URI.

In this study, urine culture and sensitivity was done in all patients and was positive in 20 cases. Among the twenty cases of urinary tract infection, the commonest micro-organism isolated from urine was *Escherichia coli* (45%), followed by *Klebsiella* (20%), *Proteus* (20%), *Staphylococcus aureus* (10%) and *Enterococcus* (05%) (table 3). Most of the micro-organisms isolated from urine were sensitive to Fluoroquinolone (ofloxacin and levofloxacin) and cephalosporins (cefepime). In this study, blood culture and sensitivity was done in all patients and was positive in eight cases. Among the eight cases, the commonest micro-organism isolated from blood was *Staphylococcus aureus* (03.94%) followed by *Escherichia coli* (02.63%), *Proteus* (01.32%), *Klebsiella* (01.32%) and *Streptococcus pneumoniae* (01.32%). Most of the Micro-organisms isolated from blood were sensitive to Fluoroquinolone and cephalosporins.

Table 3. Bacteriological Profile as per culture report

Positive Blood Culture (N=8)		
1	<i>Staphylococcus aureus</i> (N=3)	37.5%
2	<i>Escherichia coli</i> (N=2)	25%
3	<i>Proteus</i> (N=1)	12.5%
4	<i>Streptococcus pneumoniae</i> (N=1)	1.52%
5	<i>Klebsiella</i> (N=1)	12.5%
Positive Urine Culture (N=20)		
1	<i>E Coli</i> (N=9)	45%
2	<i>Klebsiella</i> (N=4)	20%
3	<i>Proteus</i> (N=4)	20%
4	<i>Staphylococcus aureus</i> (N=2)	10%
5	<i>Enterococcus</i> (N=1)	05%

Discussion

In the present study, half number of cases was found in the age group of 2-6years (50%) and 42.11% of cases belonging to >6 years age group. Similar observations were made by Shah et al and Balgopal et al (6,7). The mean age in the present study was 6.4 ± 3.74 years which is similar to previous study done by Payyadakkath Ajayan et al (6.8 ± 3.5 years) (8). Male: female ratio in the present study was noted to be 3.47:1. Among the 76 children, newly diagnosed cases were 32.89% and relapses were 67.11% (infrequent relapser-52.63% and frequent relapse-14.47%). Out of total cases 97.37% cases were steroid sensitive, 6.58% of patients were steroid dependent and 2.63% of patients were steroid resistant. Gulati S et al (9) was reported in

their study that infrequent relapsers were (37.9%), frequent relapsers were (21.6%), steroid-dependent were (18.1 %) and steroid resistant were (5.1%). Facial puffiness (100%) and decreased urine output (86.84%) were the commonest presenting complaints. The commonest clinical features of our study were well compared with other studies done by Rajendra K et al (10). Most common presentations related to infections in our study were fever (46.05%), cough (42.11%) and burning Micturition (19.74%) which is similar to another study from Pakistan done by Moorani et al (11). In our study abdominal distension was present in 22.37% cases, but a study done by Rajendra K et al (10) in which abdominal distension was in 78% of cases. In our study pain abdomen was present in 14.47% cases. Similar observations were made by Rajendra K et al (10). In the present study 5.26% patients presented with chest pain and 2.63% patients presented with red colour urine. In the present study according to USG Abdomen finding 40.79% patients had ascites at presentation. Similar observations were made by Shah et al (5). In our study, Periorbital edema was present in all cases (100%). Similar observations were made by Rajendra K et al (10) and Moorani et al (11) In the present study infection was associated in 71.05% cases of nephrotic syndrome. Similar observations were made by Moorani et al (11). In our study the most common infections were acute respiratory tract infection (34.21%) [-URI-22.37% and Pneumonia-11.84%] followed by urinary tract infection. UTI was found in 26.32% of cases, which is consistent with the findings of Moorani et al (11)(25% prevalence among nephrotic syndrome). In comparison to present study Akl et al and Paul et al noted lower (9.5% and 7.14% respectively) and Rajendra et al found higher (34%) prevalence of UTI (10,12,13) Paul et al included only fresh cases (first attack), which could be the reason of lower prevalence of UTI in their study (13). Senguttuvan et al demonstrated UTI to be the most common (46%) among all infections in these patients (14). Nephrotic syndrome predisposes to various systemic infections leading to overall higher prevalence of UTI in comparison to general population (1-3%). Moorani et al (11), Kamal F. Akl et al (12) and Shanjoy Kumar Paul et al (13) have also reported respiratory tract infection being the commonest infection. In contrast Gulati et al (9) and Senguttuvan P et al (14) have found the UTI to

be the commonest. Among the microorganisms isolated from urine culture ; E coli was the most common followed by Klebsiella and Proteus in the current study, which is similar to the observations of Moorani et al, Gulati et al, Senguttuvan et al and Paul et al.(9,11,13,14) In a striking contrast Adeleke and Odedoyin found staphylococcus aureus to be the commonest pathogen of UTI (15,16) In our study pulmonary tuberculosis was seen in 7.89% of cases, based on Mantoux test and chest X ray, with overall incidence of 2.5% in nephrotic syndrome children. This is 2.5 times the incidence of TB in general population (1%). This is more than that seen by Rajendra K et al (10) (6%) and Kala. U. et al (17) (6%) but is less than that seen by Gulati et al (9) (9.3%). Meningitis was not found in our study though it is a recognized complication of NS. In two studies abroad, it was 0.64% & 0.6% (9,11.) This might be due to small sample size in our study. Skin infection was found only in 1.32% patient in our study whereas in other studies, it was reported 5.2% and 4.5% respectively (9,14). In our study Peritonitis was associated in 1.32% cases of nephrotic syndrome; similar observations were made by Moorani et al (11). In our study Cellulitis was associated in 1.32% of the cases, which is similar to another study done by Senguttuvan P et al (14). Kumar M et al found that Streptococcus pneumoniae was the predominant organism isolated in children with peritonitis and pneumonia (18). In the present study, most of the micro-organisms isolated from urine were sensitive to Fluoroquinolone and cephalosporins. Similar observations were made by Rajendra K et al (10), in their study most of the micro-organisms isolated from urine were found to be sensitive to cephalosporins. Among major types of infection, UTI was found to be the most common, and the second most common among all types of infection accounting for 13% of the cases in our study. Alfakeekh K et al Among major types of infection, UTI was found to be the most common, and the second most common among all types of infection accounting for 13% of the study cases (19). Mandal S et al found that majority of UTI caused by E. coli 33.3% followed by Klebsiella 25%, Proteus 16.7%, Staphylococcus aureus 12.5%, Citrobacter, Acinetobacter and mixed growth were found in 4.2% each (20). The major strength of present study was adequate sample size and stringent criteria used

to define Infections. Lack of follow up and detailed evaluation of UTI were our weakness.

Conclusion

In our study we found that infection rates in overall, newly diagnosed, infrequent relapsers, frequent relapsers steroid dependent and steroid resistant cases were 71%, 28%, 85%, 91% 40% and 50% respectively. E coli, Klebsiella and Proteus were the most bacterial infection. Respiratory and urinary tract infections were most common infections. Male are affected more commonly than females.

Conflict of Interest

The author declares no conflicts of interest.

Financial Support

Not declared.

Ethics

Approved by the Institutional Ethics Committee
Sno: SNMC/EC: 101/18

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