

Original research article

## Clinical Spectrum of Infections in Children with Nephrotic Syndrome

Pankaj Bhansali<sup>1</sup>, Anjali Kale<sup>2</sup>, Ajay Kale<sup>3</sup>, Nitin Adhane<sup>4</sup>

<sup>1</sup>Assistant Professor, Department of Pediatric IIMSR, Jalna

<sup>2</sup>Professor, Department of Pediatrics, MGM MCH, Aurangabad

<sup>3</sup>Assistant professor, Department of Pediatric, MGM MCH, Aurangabad

<sup>4</sup>Consultant Pediatrician, Aurangabad

Corresponding Author: Nitin Jagannath Adhane

E-mail: [adhanenitin@gmail.com](mailto:adhanenitin@gmail.com)

### ABSTRACT

The incidence of Nephrotic Syndrome is 2-7 cases per 1, 00,000 children per year and prevalence is nearly 16 cases per 1,00,000. Various infections are considered as most important complications of Nephrotic Syndrome associated with high mortality. Loss of complement factors in urine is one of the major factors in etiopathogenesis of infections. Acute Renal Failure was also described as one of the complications of Nephrotic Syndrome. The present study was carried out to study the incidence and severity of infections in Nephrotic Syndrome with respect to various parameters like the age of patients, number of relapses, duration of disease and mortality. **Methods:** The present descriptive observational study was conducted in indoor (IPD) and outdoor (OPD) patients in the pediatric department of tertiary care center amongst 82 Nephrotic syndrome patients visiting for various infectious complications from August 2013 to August 2015. **Results:** Maximum incidence was found in the age of 1-3 years (37%) and male predominance (61%) was seen. Commonest symptom was generalised swelling/ facial puffiness (92%), followed by fever (58%), cough (48%). Anasarca was commonest sign (92%), followed by pallor (39%), Scrotal/Vulval edema (22%). 31% were infrequent relapsers and 22% were frequent relapsers. On Ultrasonography, ascites was the commonest finding in 42% of patients and on Chest radiographs, perihilar opacities were seen in 40% of patients. 49% of patients had respiratory tract infections and 34% of patients had Urinary Tract Infections. **Conclusions:** From our study we concluded that infections are found to be common complication of Nephrotic Syndrome amongst of which respiratory tract infection appears to be the commonest infection. While Serum Albumin and Serum Immunoglobulin levels are considerably low while serum cholesterol level is considerably high in severe infections requiring hospitalization.

**Key Words:** Nephrotic Syndrome, Anasarca, ascites, Serum Albumin, respiratory tract infections

### Introduction

Nephrotic Syndrome is characterised by nephrotic range proteinuria and the triad of clinical findings i.e. hypoalbuminemia, edema and hyperlipidemia associated with large urinary losses of protein.[1] The incidence is 2-7 cases per 1, 00,000 children per year and prevalence is

nearly 16 cases per 1,00,000[2] and most of the affected children will have steroid sensitive minimal change disease. [1]

Most children with Nephrotic Syndrome have a form of primary or idiopathic nephrotic syndrome. Glomerular lesions associated with idiopathic nephrotic syndrome include minimal change disease which is the most common type, focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis, membranous nephropathy and diffuse mesangial proliferation. [1]

Patients of Nephrotic Syndrome of minimal change disease usually present with symptoms at the age of 2 to 6 years.[3] The presenting complaints are edema initially periorbital which spreads to involve the extremities and abdomen and if untreated may lead to generalised anasarca. Mild diarrhoea is also seen probably due to intestinal edema. Sometimes haematuria and oliguria may be seen. Such cases present mixed picture of nephrotic syndrome and acute nephritis and will require detailed evaluation including renal biopsy.[4]

The symptoms and signs of nephrotic syndrome have been described in Ayurvedas as “Vrikka Shotha”. Though the literal meaning of the term is nephritis, its description closely resembles that of Nephrotic Syndrome. [5]

Since the early times, infections were very rightly considered as most important complication of Nephrotic Syndrome. It was found to be associated with high mortality in patients of Nephrotic syndrome in pre antibiotic era. And in today’s era as well where we have got plenty of antibiotics, infections are a major concern. Peritonitis, particularly pneumococcal peritonitis was found to be the major cause of death in children. But it was rare in adults. Loss of complement factors in urine is one of the major factors in etiopathogenesis of infections. Cellulitis was also an important infection in past, mainly in pre antibiotic era. Acute Renal Failure was also described as one of the complications of Nephrotic Syndrome.[6]

The present study was carried out to study the incidence and severity of infections in Nephrotic Syndrome with respect to various parameters like the age of patients, number of relapses, duration of disease and mortality.

### **Material and Methods:**

The present descriptive observational study was conducted in indoor (IPD) and outdoor (OPD) patients in the pediatric department of tertiary care center amongst 82 Nephrotic syndrome patients visiting for various infectious complications from August 2013 to August 2015.

### **Inclusion Criteria:**

Patients of Nephrotic syndrome, upto 18 years and parents giving consent.

### **Exclusion Criteria: Patients**

whose parents did not give consent, Children of Nephrotic Syndrome with complications like thromboembolic episodes without infections, Children with Chronic Renal Failure, Urogenital anomalies, Children with Congenital Nephrotic Syndrome.

### **Study Methods:**

- All patients of Nephrotic Syndrome diagnosed according to International Study of Kidney Disease in children (ISKDC) criteria were examined in detail and their detailed clinical history was taken.

- Appropriate laboratory investigations were done like urine routine and microscopy, Renal function tests, Serum Protein, Albumin, Cholesterol, Urine protein Creatinine ratio, Hemogram And if required Blood and Urine Culture were also done.
- Ultrasonography abdomen and Chest X – ray was done in all patients.
- Children were monitored regularly for proteinuria and improvement of infections.

#### Clinical Evaluation:

Detailed records were maintained on proforma including symptoms, signs and various investigations, previous attacks, hospitalisation and relapses, details regarding steroid therapy, its dosage and compliance were noted. Patients were examined in detail with special attention to temperature, blood pressure, abdominal tenderness and rigidity. Examination was also focused on respiratory system with special reference to crepts or abnormal breath sounds.

#### Investigations were done as follows,

**Urine examination, Urine Culture-** The culture was done by the standard loop method on blood agar and Macconkey's medium and its sensitivity various antibiotics were tested. Serum IgG levels were done by Turbidimetry method.

Data was analysed in SPSS 16 software and categorical values were compared by Chi Square test with a p value of less than 0.05 considered to be significant.

#### Results:

In this study total 82 patients were studied. Age and sex wise distribution is as follows

**Table 1: Age wise distribution of patients**

Age (Years)	Number of patients	Percentage (%)
Neonates and infants (<1 year)	1	1%
Toddlers (1-3 years)	30	37%
Pre-school (3-5 years)	14	17%
School age (6-11 years)	28	34%
Adolescents (>11 years)	9	11%

**Table no.1 shows that** out of total 82 patients, average age of patients was 6.04 years, with 5 as the median age and 3 as the most frequently occurring (mode) age of the presentation.

**Table 2: Distribution of patients according to the presenting symptoms**

Symptoms	Number of patients	Percentage (%)
Generalised swelling/ Facial puffiness	75	92
Fever	48	58
Abdominal pain	9	11
Vomiting	15	18
Diarrhea	12	15
Cough	40	48
Burning micturition	7	8
Decreased urine output	19	23

**Table no.2 shows that** almost all of them had either facial puffiness or generalised swelling (Abdominal distension or swelling of legs) as the presenting features. Fever was seen predominantly.

**Table 3: Distribution of patients as per no. of Relapses**

	Number of patients	Percentage (%)
First Episode	39	47
Infrequent Relapsers	25	31
Frequent Relapsers	18	22

**Table no.3 shows that** out of 82 patients, 47% were having their first episode, 31% were infrequent relapsers and 22% were frequent relapsers.

**Table 4: Histopathological classification of patients**

	Number of patients	Percentage (%)
Minimal Change Disease (Histopathologically proven)	4	58
Focal Segmental Glomerulosclerosis	1	14
Membranous Nephropathy	2	28

**Table no.4 shows that** out of the 7 patients on whom renal biopsy was done, majority (4) were histopathologically proven Minimal Change Disease. Among the rest, 2 were of membranous nephropathy and the other one was Focal Segmental Glomerulosclerosis.

**Table 5: Frequency of various signs**

Signs	Number of patients	Percentage (%)
Anasarca	75	92
Pallor	32	39
Scrotal/Vulval Edema	18	22
Steroid Facies	12	14
Hypertension	9	11
Abdominal Tenderness	1	1

**Table no.5 shows that** on examination Anasarca/Facial puffiness 75(92%) was the predominant sign. Pallor was the next common sign found in 39% of patients while Scrotal/Vulval edema was present in 22% of patients.

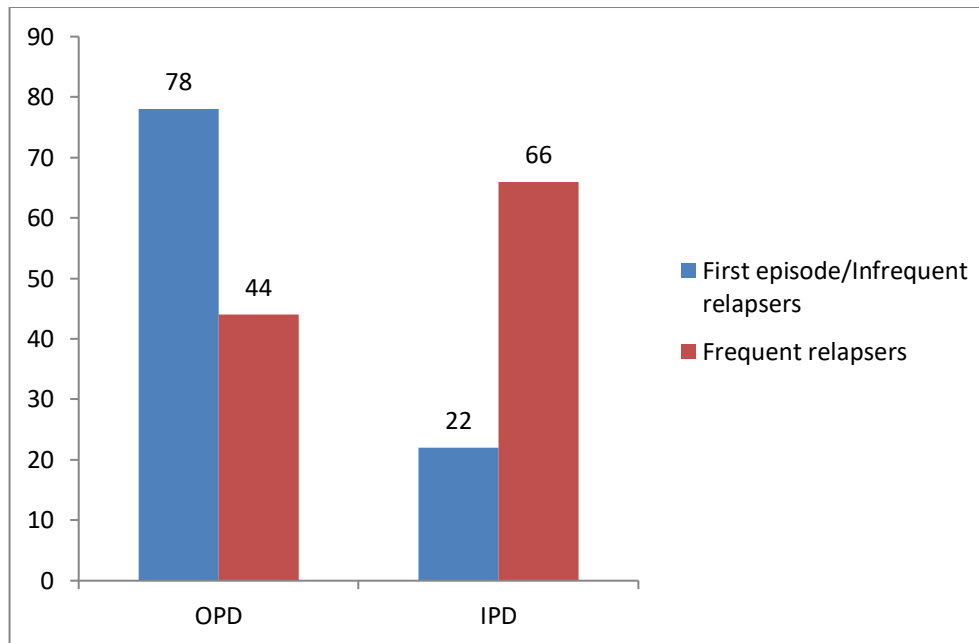
**Table 6: Summary of different infections in patients of Nephrotic syndrome in this study**

	Number of patients	Percentage (%)	
Respiratory Infections	40	49	Includes Bronchopneumonia, Upper Respiratory Tract infections, Tuberculosis.
Urinary Tract Infections	28	34	Includes Culture positive and clinically diagnosed UTI
Acute Gastroenteritis	13	16	
Spontaneous Bacterial Peritonitis	1	1	

**Table no.6 shows that respiratory infections** 40(49%) were seen in majority of patients, followed by Urinary Tract Infections 28(34%)

**Table 7: Relation between Serum Immunoglobulin G (IgG) levels, number of relapses and severity of infections.**

Parameter		OPD Patients	IPD Patients
IgG levels	less than or equal to 600mg/dl	21(36%)	14(58%)
	More than 600mg/dl	37(64%)	10(42%)
Relapses	First Episode / Infrequent relapsers	20(78%)	5(22%)
	Frequent relapsers	38(34%)	19(66%)
Total		58	24



**Fig 1: Comparison of number of relapses with severity of infections**

In Nephrotic syndrome, we all know there is decrease in serum IgG levels. We compared whether, decreased serum IgG levels of Nephrotic patients affects the severity of the disease and its infectious complications. We divided serum IgG levels in two groups less than or equal to 600mg/dl and more than 600 mg/dl. And we compared the number of OPD and IPD patients in these two groups. We found that 36% of OPD patients and 58% of IPD patients had their serum IgG levels less than 600mg/dl while 64% of OPD patients and 42% of IPD patients had their serum IgG levels more than 600mg/dl. Thus, it is seen that serum IgG levels were lower in patients who required hospitalisation due to severity of their disease and its infectious complications than patients who were treated on OPD basis. And the difference was statistically significant with a p value of 0.01.

Also, we divided patients in two groups first one with First Episode of Nephrotic Syndrome and Infrequent relapsers. We determined the severity of infections by looking whether they required hospitalisation for their infectious complications. And we found that 66% of frequent relapsers required hospitalisation while only 22% of First Episode and Infrequent relapsers required hospitalisation. The difference was significant with a p value of 0.01. Thus, it appears that severity of infections is more in frequent relapsers.

#### **Discussion:**

In our study average age was 6.04yrs with a standard deviation of 3.59 years. In a study by Gulati et al[7], average age of the patients with Nephrotic Syndrome was 7.11 years with a standard deviation of 4.57yrs.

Gender distribution of the patients showed a male preponderance with 61% of males and 39% of females. Study by Gulati et al[7] also showed similar picture, out of total 154 patients studied, 114 were males and 40 were females.

In the present study patients presented with generalized swelling (92%), fever (58%) and cough (48%), decreased urine output (23%), vomiting (18%), diarrhea (15%) were the most common symptoms. On detailed examination, 92% patients had anasarca, 39% had pallor and 22% had scrotal/ vulval edema. While few patients showed signs of steroid toxicity, 22% had steroid facies and 11% had hypertension and 11% of patients had crepts on auscultation.

In the present study patients 47% of patients presented with infections as their initial presentation. Among subsequent relapses, 31% were infrequent relapsers, whereas 22% of infections occurred in frequent relapsers. In a study by Gulati et al[8], it was found that daily corticosteroids prevent against infections in the Nephrotic syndrome. A study by Mattoo et al[9], also found that infections especially Upper respiratory tract infections (URTI's) are less frequent in patients on corticosteroids. Daily prednisolone therapy according to their findings was more effective than alternate day prednisolone therapy [9]. In a randomised control trial by Aveyagunawardena et al [10], found that prescribing prednisolone daily for 7 consecutive days at the same dose as taken by patients on an alternate day basis at the onset of a presumed viral URTI significantly reduces the risk of relapse in children with steroid dependent nephrotic syndrome. But in our study, it was found that relapsers on corticosteroids were having more infections. Studies indicate that infections are much more common in patients of relapses. [11] It is recommended that all patients of Steroid Resistant Nephrotic syndrome should undergo renal biopsy[12]. In our study, out of 82 patients, 7 underwent renal biopsy. Out of these 6 were steroid resistant. All of these patients had multiple relapses and hospitalisations. In a study by Gulati et al[13] complications like hypertension, hematuria and infections are more common in patients of steroid resistant nephrotic syndrome.[13] According to some studies, patients presenting with hypertension and hematuria have increased risk of infections because of their association with Focal Segmental Glomerulosclerosis, Membranoproliferative Glomerulonephritis and other aggressive forms of Nephrotic Syndrome.[14]

In the present study patients Majority of patients had ascites (42%), 24% had raised renal echogenicity, 19% had pleural effusion on Ultrasonography of abdomen. On Chest X-rays, 27% of X-rays were normal. 27% had pleural effusions. Lung opacities in the form of perihilar opacities were seen in 40% of patients.

In a study by Wiersma, Toorenvliet et al[15] it was found that renal cortex echogenicity was increased in patients with appendicitis, gastroenteritis, mesenteric lymphadenitis, ileocectitis, Crohn's disease and pneumonia. In a large study by Krensky et al, it was found to be associated with medical renal disease. [16] Krensky studied ultrasonographies of over 2500 patients and found this finding to be associated with medical renal disease in 94% of study population. Out of the cases he found 30% of the cases were glomerulopathies and 46% of the cases were tubulointerstitial diseases. [17]

In our study, ascites was present in 42% patients. While studying both adult and pediatric nephrotic syndrome patients, Ackerman et al found that 52% of pediatric patients had ascites whereas only 23% of adult had ascites with a p value of 0.024.[18] Temporary fluctuations in the liver enzyme levels, lower serum albumin levels were cited by them as the causes.

Cavina et al[19], found pleural effusion in 21% of patients of Nephrotic syndrome. In our study, it was found in 27% of patients which is consistent with their findings. All of the pleural effusions in our study were intrapulmonary and bilateral, which is consistent with the Kirkpatrick et al[20] description that, pleural effusions in nephrotic syndrome are frequently intrapulmonary and bilateral.

In the present study patients out of 82 cases 40 patients (49%) had respiratory tract infections, out of 40, 29 were of Upper respiratory tract infections while 11 were of Lower respiratory tract infections.

Out of 82 cases, 34% i.e. 28 cases were of urinary tract infections. In a study by Senguttuvan et al[21], patients showing signs and symptoms with presence of bacteriuria and/or more than 10 pus cells per high power field but negative cultures were considered as UTI. Senguttuvan et al[21] suggests that the causes of cases of UTI being culture negative is practice of prescribing antibiotics to the patients before being referred to a higher centre, potentially interfering with the culture results. Third most common infection was Acute Gastroenteritis, which was found in 16% of cases i.e. 13 cases.

In our study we also looked whether levels of serum albumin and cholesterol affected the severity of disease and its infectious complications. And found that lower serum albumin levels and higher cholesterol levels affects the severity of disease and its infectious complications. In a study by Gulati et al[7], they also found that children who had infectious complications had significantly lower serum albumin levels and higher serum cholesterol levels which is similar to our study.

In our study when we looked whether, levels of serum IgG level affects the severity of disease and its complications we found that, serum IgG level less than 600mg/dl does affects the severity of disease and its complications. Ogi et al[22] in their study found that in adult nephrotic patients, serum immunoglobulin G level less than 600mg/dl is an independent risk factor for infection. This is similar to our study.

### **Conclusions:**

From our study we concluded that infections are found to be common complication of Nephrotic Syndrome amongst of which respiratory tract infection appears to be the commonest infection, followed by urinary tract infection and Acute Gastroenteritis. While Serum Albumin and Serum Immunoglobulin levels are considerably low while serum cholesterol level is considerably high in severe infections requiring hospitalisation. Severe infections requiring hospitalisation and considerably Serum Immunoglobulin were more common in Frequent relapsers.

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