

**STUDY OF INCIDENCE AND OUTCOME OF SEPSIS IN NEPHROTIC SYNDROME**Mangal Charan Murmu<sup>1</sup>, Arakhita Swain<sup>2</sup><sup>1</sup>Assistant Professor, Department of Paediatrics, SCB Medical College, Cuttack.<sup>2</sup>Associate Professor, Department of Paediatrics, SCB Medical College, Cuttack.**ABSTRACT****BACKGROUND**

Nephrotic syndrome is a syndrome comprising signs of nephrosis, chiefly proteinuria, hypoalbuminaemia and oedema. It is a component of glomerulonephrosis in which different degrees of proteinuria occur,<sup>[1]</sup> often associated with numerous episode of infection.

**MATERIALS AND METHODS**

This is a direct prospective study done in Department of Paediatrics, SCB Medical College, Cuttack from January 2015 to December 2016.

**RESULTS**

Minimal change nephrotic syndrome comprises of about 75% of cases of primary nephrotic syndrome and is the commonest type of nephrotic syndrome in childhood. The incidence of infectious complication is 90%. Higher incidence of infection in children with frequent relapse (100%) and steroid dependent (100%) nephrotic syndrome.

**CONCLUSION**

The prevalence rate of infection in nephrotic syndrome is high in paediatric age group. Upper respiratory tract infections and urinary tract infections are more commonly encountered. The incidence of peritonitis, cellulitis and pneumonia are seen as severe sepsis.

**KEYWORDS**

Infection, Nephrotic Syndrome, Glucocorticoids.

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**BACKGROUND**

Nephrotic syndrome is a common chronic disease worldwide.<sup>[1,2,3]</sup> It is characterised by alterations of permselectivity at the glomerular capillary wall, resulting in its inability to restrict the urinary loss of protein. Nephrotic range proteinuria is defined as proteinuria exceeding 1000 mg/m<sup>2</sup> per day or spot (random) urinary protein-to-creatinine ratio exceeding 2 mg/mg. The proteinuria in childhood nephrotic syndrome is relatively selective, constituted primarily by albumin.<sup>[2]</sup> Estimates on the annual incidence of nephrotic syndrome range from 2 - 7 per 100,000 children and prevalence from 12 - 16 per 100,000.<sup>[3]</sup>

**Aims and Objectives**

To study the incidence, cause, organ involved, predisposing factors, antibiotic sensitivity of different organism seen in cases with infection in nephrotic syndrome in Paediatric Department of 1 year to 14 years.

**Place of Study**

This study was done in the Department of Paediatrics, SCB Medical College, Cuttack.

**Period of Study**

April 2014 to March 2016.

**Sample Size**

A total 200 number of cases fulfilling the inclusion criteria were taken into study.

**Inclusion Criteria**

Children aged 1 year to 14 years fulfilling the guidelines laid by International Study of Kidney Disease in Children (ISKDC)<sup>[4,5]</sup> Society for Nephrotic Syndrome were included in the study.

**Exclusion Criteria**

Other condition present with oedema like cardiovascular disease, hepatic dysfunction, nutritional deficiency, Koch's abdomen, acute/chronic glomerulonephritis were excluded from the study with the help of allied investigations.

**MATERIALS AND METHODS**

This is an observational study. The children satisfying the ISKDC Society for Nephrotic Syndrome were included in the study. A detailed history was taken and clinical examination was conducted within the first day of admission and findings were noted in prescribed proforma. With the help of proper size cuff, the blood pressure was recorded in upper arm. Hypertension was defined as diastolic blood pressure more

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than 90 mmHg in children over 6 years and more than 80 mmHg below 6 years of age.<sup>[6]</sup>

Daily fluid intake and output chart was maintained. Daily weight was recorded and change was noted in the format prescribed. Oliguria is defined as a urine output that is less than 1 mL/kg/h in infants and less than 0.5 mL/kg/h in children.<sup>[7]</sup>

**Associated Infection in Nephrotic Syndrome**

Nephrotic syndrome is considered to be an immunosuppressive condition and hence is associated with increased prevalence of superimposed infections.<sup>[8]</sup> Infectious complications are common in Nephrotic Syndrome (NS), especially primary peritonitis which has been reported in 9% to 16% of patients.<sup>[9]</sup> Steroid use may aggravate infectious complications.<sup>[10]</sup> Sepsis is a life-threatening condition that arises when the body’s response to infection causes injury to its own tissues and organs.<sup>[11]</sup> The infectious conditions encountered in nephrotic syndrome in our study included are described below.

**Upper Respiratory Tract Infections (URI or URTI)**

All illnesses are caused by an acute infection which involves the upper respiratory tract including the nose, sinuses, pharynx or larynx. This commonly includes nasal obstruction, sore throat, tonsillitis, pharyngitis, laryngitis, sinusitis, otitis media and the common cold.<sup>[12]</sup> Most infections are viral in nature and in other instances the cause is bacterial.<sup>[13]</sup> Upper respiratory tract infections can also be fungal or helminth in origin, but these are far less common.<sup>[14]</sup>

Diagnosis of Pneumonia is being made by standard protocol of fast breathing and radiological evidence.<sup>[15]</sup>

A Urinary Tract Infection (UTI) is an infection that affects part of the urinary tract.<sup>[16]</sup> When it affects the lower urinary tract it is known as a bladder infection (cystitis) and when it affects the upper urinary tract it is known as kidney infection (pyelonephritis).<sup>[17]</sup> Symptoms from a lower urinary tract include pain with urination, frequent urination and feeling the need to urinate despite having an empty bladder.<sup>[16]</sup> Symptoms of a kidney infection include fever and flank pain, usually in addition to the symptoms of a lower UTI.<sup>[17]</sup> Rarely, the urine may appear bloody.<sup>[18]</sup> In the very old and the very young, symptoms may be vague or non-specific.<sup>[16,19]</sup>

Major infections were defined as those that are disseminated, affecting deep organs, requiring hospitalisation or potentially life-threatening, most common being peritonitis.<sup>[20-35]</sup>

Patient with nephrotic syndrome can have obvious symptoms, among which oedema is very common; and for patient with very severe condition they may even have pleural effusion, sometime empyema.

Bacterial infections are common in patients with nephrotic syndrome including peritonitis, sepsis, meningitis, urinary tract infection and cellulitis.<sup>[23]</sup>

Diarrhoea is not uncommon in Nephrotic Syndrome.<sup>[8,23]</sup>

Pyoderma and cellulitis were diagnosed clinically.

**Investigations**

Following investigations were done in Central Laboratory, Pathology Department, Biochemistry Department of SCB Medical College, Cuttack. I. Urine examination: Routine and Microscopic including Specific gravity, Turbidity, Reducing

sugar, Albumin, Culture and Sensitivity; II. Haematological tests like Haemoglobin, Total Leucocyte Count, Differential Count, Erythrocyte Sedimentation Rate, Blood Urea, Serum Creatinine, Serum Electrolyte, Serum Cholesterol, C-Reactive Protein and Serum Total Protein; III. Diagnostic paracentesis; IV. Stool examination; V. Pus examination; VI. Mantoux test; VII. Radiological examination; VIII. CSF examination; IX. Throat swab/skin swab was done.

Standard treatment protocol were being followed<sup>[24,25,26]</sup> and observations were obtained.

**RESULTS**

Year	Total Admission	No. of Case	Percentage
April 2014 - March 2015	10500	98	0.93
April 2015 - March 2016	11100	102	0.91
<b>Total</b>	<b>21610</b>	<b>200</b>	<b>0.92</b>

*Table 1. Incidence of Nephrotic Syndrome*

The average incidence of Nephrotic syndrome is 0.92%.

Age Group in Years	Total Number of Cases	Male		Female	
		No	%	No	%
0-1	-	-	-	-	-
1-3	72	51	70.83	21	29.17
4-6	68	42	61.76	26	38.24
7-9	32	23	71.87	9	28.13
10-12	16	10	62.5	6	37.5
13-14	12	9	75	3	25
<b>Total</b>	<b>200</b>	<b>135</b>	<b>67.5</b>	<b>65</b>	<b>32.5</b>

*Table 2. Age and Sex Distributions of Nephrotic syndrome*

This table shows male: female ratio of 2: 1.

Clinical Finding	No. of Cases	Percentage
Pallor	136	68
Oedema	200	100
1. Facial puffiness along with pedal oedema	174	87
2. Scrotal oedema	62	31
3. Scalp oedema	14	7
Fever	76	38
Oliguria	106	53
Ascites	96	48
Frank haematuria	22	11
Hypertension	20	10
Convulsion	6	3
Irritability	56	28
Pain abdomen	54	27
Diarrhoea	24	12
Anorexia	38	19
Respiratory symptoms/cough	54	27
Skin infection	8	4

*Table 3. Clinical Presentations of Nephrotic Syndrome*

Most common clinical presentation of nephrotic syndrome were presence of oedema (100%), pallor (68%), oliguria (53%) and ascites (48%).

Associated Infections	No. of Cases	Percentage
Skin infection	8	4
Upper respiratory tract infection	54	27
Urinary tract infection	56	28
Peritonitis	20	10
Pneumonia	26	13
Pyogenic meningitis	2	1
Pulmonary tuberculosis	3	1.5
Cellulitis	3	1.5
Gastroenteritis	8	4
Without any infections	20	10

**Table 4. Distribution of Associated Infections in Nephrotic Syndrome**

The incidence of commonest associated infection encountered are Urinary Tract Infection, Upper Respiratory Tract Infection, Pneumonia and Peritonitis are 28%, 27%, 13%, 10% respectively.

Nephrotic Syndrome	No. of Cases n = 200	%	Associated Infections	%
First attack	64	32	52	80
Relapse and no steroid	87	43.5	63	72.4
Relapse with steroid	19	9.5	17	89.4
Frequent Relapse and no steroid	7	3.5	7	100
Frequent Relapse with steroid	15	7.5	15	100
Steroid dependent	13	6.5	13	100

**Table 5. Course of Nephrotic Syndrome on Admissions**

The table shows 32% patients were having first episode of nephrotic syndrome, of which 80% presented with infection. The episode of relapse was always associated with infections. The patient with frequent relapse and steroid dependent showed higher incidence of infections, almost 100%.

Age in Years	UTI		URTI		LRTI		EMPY		PERIT		GE		MEN		TB		CELLU	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
1-4	11	7	9	8	5	2	-	-	2	1	-	2	-	-	-	-	-	-
5-9	13	8	12	8	6	3	1	1	4	3	1	2	1	-	1	1	2	-
10-14	9	8	10	7	4	1	1	-	6	4	2	1	-	1	1	-	-	1
%	31.11		30		11.6		1.66		11.11		4.44		1.11		1.66		1.66	

**Table 6. Distributions of Infections Associated with Nephrotic Syndrome in Different Age and Sex**

Out of 180 cases presented with different infections males were 104 (57.77%) and females were 76 (42.23%). Most common were UTI (31.11%), URTI (30%), Pneumonia (11.66%) and Peritonitis (11.11%).

Organism n=63	UTI n = 56	Peritonitis n = 20	Pneumonia n = 21	Empyema n = 3	URTI n = 54	Meningitis n = 2	GE n = 8
E. coli (45)	39	3	-	-	-	-	3
Kleb (4)	2	1	1	-	-	-	-
Pseudomo (1)	1	-	-	-	-	-	-
Proteus (1)	1	-	-	-	-	-	-
GABHS (8)	-	-	-	1	7	-	-
Staph (2)	-	-	2	-	-	-	-
Pneumo (2)	-	2	-	-	-	-	-
Mixed (1)	1	-	-	-	-	-	-
No organism	12	14	18	2	47	2	5
Percentage	78.5	30	14.28	33.33	12.96	0	37.5

**Table 7. Organism in Different Infections in Nephrotic Syndrome**

Significant number of culture positive were found in patients with UTI (69.84%). The culture were negative in meningitis, low in URTI (12.96%), Pneumonia (14.28%) and peritonitis (30%).

Organism Isolated	No. of Cases	Ampi/%		Amika/%		Netro/%		Nitro/%		Cefo/%		Norf/%		Vanco/%		Chlora/%	
		9	20	34	75	7	15	9	45	32	50	6	13	4	8	2	4
E. coli	45	4	4	2	2	2	2	4	4	1	100	-	-	4	4	-	-
Proteus	1	-	-	2	50	1	25	-	-	3	75	-	-	2	50	-	-
Klebsiella	4	-	-	1	100	-	-	-	-	1	100	1	100	-	-	-	-
Pseudo	1	-	-	-	-	-	-	-	-	6	75	-	-	-	-	-	-
GABHS	8	5	62	6	75	-	-	-	-	2	100	-	-	-	-	2	100
Pneum.	2	-	-	-	-	-	-	-	-	2	100	-	-	-	-	2	100
Staph.	2	2	100	2	100	-	-	-	-	2	100	-	-	2	100	-	-
Mixed	1	1	100	1	100	1	100	-	-	-	-	-	-	1	100	-	-
<b>Total</b>	<b>64</b>	<b>21</b>	<b>32</b>	<b>48</b>	<b>75</b>	<b>11</b>	<b>17</b>	<b>13</b>	<b>20</b>	<b>47</b>	<b>73</b>	<b>7</b>	<b>10</b>	<b>13</b>	<b>20</b>	<b>4</b>	<b>6</b>

**Table 8. Sensitivity of Different Organism Isolated to Different Drugs**

The most sensitive drugs against all the infection was amikacin followed by cefotaxime. The organism isolated E. coli was sensitive to amikacin, cefotaxime, ampicillin, nitrofurantoin and netromycin in order. Pneumococcus isolated from peritoneal fluid culture is sensitive to Vancomycin.

Response after 10 days of Treatment					
Drugs Used	No. of Patients	Improvement (Clinical and Laboratory)	%	Retreatment Required	%
Ampicillin	27	27	100	No	-
Amikacin	76	76	100	No	-
Netromycin	9	9	100	No	-
Nitrofurantoin	2	2	100	2	100
Cefotaxime	62	62	100	No	-
Chloramphenicol	1	1	100	No	-
Vancomycin	3	3	100	No	-
<b>Total</b>	<b>180</b>	<b>180</b>		<b>2</b>	

**Table 9. Therapeutic Response to Different Drugs**

There was significant improvement clinically and laboratory investigation wise except two cases of nitrofurantoin.

Infections	No. of Cases	Nephrotic State	No. of Cases	%
URTI	54	SD	6	11.11
		SR	7	12.96
UTI	56	SD	7	12.5
		SR	8	14.28
LRTI	26	-	-	-
Peritonitis	20	-	-	-
Cellulitis	3	-	-	-
Meningitis	2	-	-	-
PTB	3	-	-	-
GE	8	SR	1	12.5
Septicaemia	2	Death	2	-
Skin Infection	6	-	-	-
Without INF	20	-	-	-
<b>TOTAL</b>	<b>200</b>		<b>16</b>	<b>8</b>

**Table 10. Nephrotic State at the End of Treatment**

Spontaneous remission rate was 10%. Rest of the patients were treated with glucocorticoid. Two patients who died (1%) after admission and on treatment for frequent relapse case of Nephrotic Syndrome were found to have septicaemia.

## DISCUSSION

The primary or idiopathic nephrotic syndrome, majority of which are histopathologically classified as Minimal Change Nephrotic Syndrome (MCNS). MCNS comprises about 75% of cases of nephrotic syndrome and is the most common type of nephrotic syndrome.<sup>[27]</sup>

We encountered that 92% admissions of every year were Nephrotic Syndrome. Eddy AA et al estimates on the annual incidence of nephrotic syndrome range from 2 - 7 per 100,000 children and prevalence from 12 - 16 per

100,000.<sup>[2,3]</sup> The incidence of NS as reported by Schlesinger et al in 1968 is 1.3 to 2.8 per one lakh white children under 16 years.<sup>[28]</sup> Our study shows little higher rate of incidence.

70% of NS were encountered in the age group of 1 - 6 years with peak incidence of cases in 1 - 3 years' age period. Males are predominant over females in the present study. The present observation is in accordance with the study made by Heymann, Marker et al 1972,<sup>[27]</sup> Agarwal et al 1975<sup>[29]</sup> and Srivastava et al 1975.<sup>[30]</sup>

The most common clinical presentation of nephrotic syndrome were presence of oedema (100%), pallor (68%), oliguria (53%) and ascites (48%). Cases of anuria, frank haematuria, hypertension and convulsion were observed in 6 (3%) cases 5 (2.5%) cases and 1 (0.5%) case respectively. Similar type of finding has been documented by Agarwal et al 1975<sup>[29]</sup> and Srivastav et al 1975.<sup>[30]</sup>

The percentage of the commonest associated infections encountered are Urinary Tract Infection, Upper Respiratory Tract Infection, Pneumonia and Peritonitis are 28%, 27%, 13% and 10% respectively. The study was done by Brod et al 1973<sup>[31]</sup> and Rubin 1975. It also is in agreement with the report from Children's Hospital, Sao Paulo, Brazil and Noorani et al 2003 and Alwadhhi RK et al 2004.<sup>[32]</sup>

32% patients were having first episode of nephrotic syndrome, of which 80% presented with infection. The episode of relapse was always associated with infections. The patient with frequent relapse and steroid dependent showed higher incidence of infections, almost 100%.

Out of 180 cases presented with different infections males were 104 (57.77%) and females were 76 (42.23%). Most cases of culture were negative in URTI (87%), Pneumonia (85%) and peritonitis (87%). Significant number of culture positive were found in patients with UTI (78.5%). The most sensitive drugs against all the infections was amikacin followed by cefotaxime. The organism isolated E. coli was sensitive to amikacin, cefotaxime, ampicillin, nitrofurantoin and netromycin in order. Pneumococcus isolated from peritoneal fluid culture is sensitive to Vancomycin. The other organisms were Klebsiella (4%), GABHS (12%) and mixed growth. Gulati S and Kher V et al 1995<sup>[9]</sup> found 61% of culture isolates were E. coli and non-E. coli organism.

Spontaneous remission rate was 10%. Rest of the patients were treated with glucocorticoid. Two (1.11%) patients who died after admission were on treatment for frequent relapse case of Nephrotic Syndrome were found to have septicaemia. Lewis et al<sup>[33]</sup> studying the natural history of disease before the introduction of glucocorticoids found that in 25% cases with control of infection remission occurs within 15 days. Wingen et al<sup>[34]</sup> in their study concluded that delay up to 10 days in stating steroid therapy did not adversely influence the further course of this or subsequent relapse in the absence of progressive clinical signs.

## Summary

The overall incidence of hospital admission of nephrotic syndrome was 0.92%. The most vulnerable group was 1 - 6 years. Male overscore female. Oedema was the most prominent clinical features followed by Haematuria and Hypertension. Infections were found in 90% cases of nephrotic syndrome. The most common associated infections causing sepsis were URI, UTI, LRTI and Peritonitis respectively. Cellulitis, gastroenteritis, meningitis and

tuberculosis do occur, but less in number. 75% of the infections were present with 1<sup>st</sup>, 2<sup>nd</sup> or 3<sup>rd</sup> relapse and 25% cases occurred in 1<sup>st</sup> episode of NS. *E. coli* was the commonest organism isolated. Amikacin was effective in 63.6%, Norfloxacin in 45.4% and Cefotaxime in 45.5% of organism. *E. coli* was sensitive to following drugs in order of Cefotaxime, Amikacin, Norfloxacin, Ciprofloxacin, Ampicillin, Nitrofurantoin, Netromycin and Chloramphenicol. Overall, gram negative organisms were predominant cause of different infections. All the causes had effective therapeutic response to their sensitive drugs within 10 days of treatment except for one case who did not respond to Nitrofurantoin. 7% children had spontaneous remission when infection was treated without requiring glucocorticoids. Death due to sepsis in nephrotic syndrome in our study is 1.11%; 13.9% people per 100,000 population died from nephritis, nephrotic syndrome and nephrosis each year in the US 2001 (Deaths: Final Data for 2001, NCHS, CDC).

### CONCLUSION

Infection is more common in male baby as compared to girl baby in between 1 and 5 years' age group. Upper respiratory tract infection and urinary tract infections are more common and are usually associated with relapse. Infections are more common with frequent relapse, steroid dependent nephrotic syndrome. UTI is an important occult infection, which is often underdiagnosed. Peritonitis cellulitis and pneumonia are most serious infections. Infections with gram negative organism are emerging, a combination of antibiotics covering pneumococcus and gram-negative organisms should be started empirically according to the sensitivity pattern. In our study, we set up a combination of ampicillin and cefotaxime. Therapy should be tailored according to the culture and sensitivity report. In serious life-threatening case, vancomycin is lifesaving. Immunosuppression resulting from glucocorticoid therapy may make the child more susceptible to develop serious infection, but as per our study even children who are not on glucocorticoid therapy presenting with relapse often have concomitant infection. As a chronic disease with high morbidity, prevention of infection in nephrotic syndrome children need consideration. Relapse is more often due to infections. The best way to control the nephrotic state is to prevent infection.

### Abbreviations

A: G:	Albumin: Globulin.
AGN:	Acute Glomerulonephritis.
BP:	Blood Pressure.
CNS:	Central Nervous System.
DC:	Differential Count.
<i>E. coli</i> :	<i>Escherichia coli</i> .
ESR:	Erythrocyte Sedimentation Rate.
Exam:	Examination.
FR:	Frequent Relapse.
GI:	Gastrointestinal.
GE:	Gastroenteritis.
Gp:	Group.
Hb:	Haemoglobin.
Ig:	Immunoglobulin.
Inf:	Infection.
Kleb:	<i>Klebsiella</i> .
KUB:	Kidney Ureter Bladder.

LRTI:	Lower Respiratory Tract Infections.
No:	Number.
NS:	Nephrotic Syndrome.
Perito:	Peritonitis.
PTB:	Pulmonary Tuberculosis.
Prim:	Primary.
Syn:	Syndrome.
R:	Relapse.
RBC:	Red Blood Cell.
RR:	Respiration Rate.
SD:	Steroid Dependent.
SR:	Spontaneous Remission.
TLC:	Total Leucocyte Count.
URTI:	Upper Respiratory Tract Infections.
UTI:	Urinary Tract Infection.
USG:	Ultrasonography.
WBC:	White Blood Cell.

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