

Original Research Article

To study the frequency, etiology and predisposing factors of urinary tract infection in children with nephrotic syndrome in Eastern Odisha Region: a hospital based study

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Received: 01 October 2016

Accepted: 24 October 2016

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ABSTRACT

Background: The increased prevalence of infection in nephrotic syndrome is due to immunoglobulin loss, defective T cell function, and presence of ascites, relative malnutrition, and immunosuppressive therapy and associated with other factors. The objective of this study was to study the incidence, aetiology and the antibiotic sensitivity pattern of urinary tract infections (UTI) in children at presentation of nephrotic syndrome (NS).

Methods: A retrospective hospital-based study carried out in IMS and SUM Hospital, Bhubaneswar, India. Seventy six children aged between two to twelve years with a diagnosis of NS at the time of were studied from April 2014 to March 2016.

Results: The mean age of males was 5.9 ± 0.5 years and females are 6.2 ± 0.8 years. Pyuria was noted in 44 (57.89%) of the patients. Boys were more commonly affected with urinary tract infection than girls with a ratio of 1.9:1. UTI is the most common encountered infection and was predominantly caused by *E. Coli* in 18 (39%), *Klebsiella* species 7 (15.21%) and culture negative in 8 (17.28%) cases. There was high in vitro resistance of these organisms to cefixime and ampicillin but sensitive to cefotaxime, amikacin, ceftriazone, piperacillin-tazobactam and vancomycin.

Conclusions: It is recommended that UTI should be sought for in patients with nephrotic syndrome and treatment should be prompt and appropriate taking into account of etiology and predisposing factors. UTI is one of the most common infections accompanying NS due to many factors. A high index of suspicion and early institution of appropriate antibiotics will help in reducing morbidity and mortality.

Keywords: Childhood, Nephrotic Syndrome, Prevalence, UTI

INTRODUCTION

Incidence of all forms of nephrotic syndrome in childhood is 2-4/100,000 population with a mortality rate of 1-2%.^{1,3} Apart from being a common cause of mortality it also associated with significant morbidity and also for a poor response to steroid therapy or induce relapse in a child with nephrotic syndrome. There have been numerous studies of infection in nephrotic syndrome but predominantly from developed countries.¹⁻³

Sepsis remains one of the main causes of death in children with nephrotic syndrome.⁴ Incidence is varied in different studies from India range from 19-36.6%.^{5,6} Therefore it is essential to know the current trend of prevalence of infection in children with nephrotic syndrome and the organisms prevalent in our set up to decide about appropriate antibiotics. Alterations in both cellular and humoral mechanism due to urinary loss of immunoglobulins, properdin factor B (opsonin), immunosuppressive therapy, malnutrition, edema and

ascites as a potential culture medium and defective cell mediated immunity is responsible for increased incidence of infections in nephrotic syndrome.^{7,8} Younger age, severe clinical types of nephrotic syndrome with severe ascites, use of cytotoxic drugs compared to prednisolone therapy alone and the presence of nephrotic range proteinuria itself have been identified as risk factors for the infections, whereas serum cholesterol more than 400 mg/dl and hypoalbuminemia less than 1.5 gm/dl is specifically identified for spontaneous bacterial peritonitis.^{4,6,7,9,10} In children with nephrotic syndrome organism frequently encountered in infection are *pneumococci*, *haemophilus influenzae*, *beta haemolytic streptococci* and gram negative bacteria.³ *Staphylococcus aureus* infections are seen less commonly though it can cause cellulitis, osteomyelitis in NS patients. In one case series of infants with congenital nephrotic syndrome of Finnish type upto 56% of infections was caused due to *Staphylococcus aureus* including coagulase negative and one infant died because of empyema.¹¹ Pneumonia is one of the common infection (up to 18%-30%) found in nephrotic syndrome but empyema thoracis particular rare and has been reported in only one study in which patients were not on glucocorticoid therapy.^{9,12}

METHODS

A retrospective study of all the patients with a diagnosis of nephrotic syndrome (edema, hypercholesteremia, hypoalbuminemia and massive proteinuria) admitted to the Paediatric Ward of IMS and SUM Hospital Hospital, Bhubaneswar, from August 2014 to July 2016. Patient's demography, age, sex, results of urine culture, invitro antibiotic sensitivity pattern of isolated organisms was noted. Urine specimens from children with nephrotic syndrome were routinely obtained by clean catch method following careful preparation of the urethral orifices and were collected into sterile containers and promptly transported to the laboratory. The specimens were processed immediately. Five millimetres (5mml) loopful of the sample were inoculated on a blood agar and CLED agar plates. The blood agar plate was incubated aerobically for 18 - 24 hours at 37°C. Samples showing at least 105 bacterial colonies per millilitres of urine were considered to indicate significant bacteriuria (UTI). Cases with sign symptoms of UTI with pyuria also considered as UTI. Identification of the organisms to species level was by standard biochemical methods and antimicrobial sensitivity test were carried out using stokes disc diffusion technique.²⁸ The chi squared test and student's t-test were used for statistical analysis.

RESULTS

Out of the seventy six patients studied 50 (65.78%) were males and 26 (34.21%) females, (a male to female ratio of 1.92:1). The mean age of female was 6.2±0.8 years compared with 5.9±0.5years for males. The age range

was two to twelve years. The age and sex distribution of patients is as shown in Table 1.

Table 1: Age and sex distribution of 76 patients with nephrotic syndrome.

Age (years)	Sex		Total	%
	Males	Females		
1-3	10	04	14	18.42
4-6	30	18	48	63.15
7-10	09	04	13	17.1
>10	01	0	1	1.31

Most of the patients belong to four to six year of age. The spectrum of infections encountered are UTI 46 (60.52%), peritonitis 18 (23.68%), respiratory tract infections 16 (21.05%), tuberculosis 4 (9.21%) and other less frequent occurring are cellulitis, candidiasis as depicted in Table 2.

Table 2: Types of infections.

Infection	Male N (%)	Female N (%)	Total (%)
Urinary tract infection	32	14	60.52
Peritonitis	14	4	23.68
Acute respiratory infection	12	4	21.05
Cellulitis	3	0	03.94
Enteric fever	2	0	02.63
Hepatitis	2	1	03.94
Chickenpox, measles, impetigo, vulval candidiasis	1	1	02.63
Tuberculosis	3	1	09.21
Others	11	3	18.42

Table 3: Urinary findings of patients with nephrotic syndrome.

Urine	Number (%)
Appearance	
Normal and clear	46 (76)
Cloudy	22 (24)
Straw colored urine microscopy	08 (06)
WBC casts	18 (28)
Epithelial cells	32 (50)
Microscopic hematuria	14 (20)
Pyuria (cells/HPF)	
Less than 10 cells/HPF	32 (42.10)
More than or equal to 10 cells/HPF	44 (57.89)
WBC: White blood cell	

Urinary microscopic finding in all cases are presented in Table 3. Pyuria more than 10/hpf are seen in 44 (57.89%) cases. Characteristics of nephrotic syndrome in children with and without UTI are mentioned in Table 4. Forty six

patients (60.52%) had urinary tract infection. *E. Coli* was the most common offending organism and was isolated in 18 (39%) patients followed by *Klebsiella* species in 7 (15.21%), *Proteus* species in 5 (10.86%) and

Pseudomonas species in 1 (2.17%) patients. *Staphylococcus aureus* is found in 06 (13.04%) cases and culture negative reports in 8 (17.04) patient respectively (Table 5).

Table 4: Demographics variables and characteristics of nephrotic syndrome in children with and without UTI.

Characteristics	Nephrotic syndrome cases without UTI (n = 30) (%)	NS with UTI (n = 46) (%)	Total number of cases (n = 76) (%)
Age			
1-3 years	06 (20)	08 (17.39)	14 (18.42)
4-6 years	19 (63.33)	29 (63.04)	48 (63.15)
7-10 years	5 (16.66)	8 (17.39)	13 (17.10)
>10 year		1 (02.17)	01 (01.31)
Sex			
Males	16 (53.33)	34 (73.91)	50 (65.78)
Females	14 (46.66)	12 (26.08)	26 (34.21)
First episode NS	21 (70)	30 (65.21)	51 (67.10)
Relapsed NS	9 (30)	16 (34.78)	25 (32.89)
Pyuria			
>10 pus cells/HPF	12 (40)	36 (78.26)	48 (63.15)
<10 pus cells/HPF	18 (60)	10 (21.73)	28 (36.84)
Raised RFT	2 (04.34)	01 (02.17)	03 (03.94)

UTI: Urinary tract infection, NS: Nephrotic syndrome; RFT: Renal function test (BUN).

These culture negative children when presented with dysuria, fever, loin pain, suprapubic tenderness with documented pyuria in urine, though had negative urine culture, had given full treatment depending upon sign, symptoms and urinary microscopic finding of pyuria. The negativity may be due to prior exposure to antibiotics before admission in the hospital as partial treatment by private practitioners. The in-vitro sensitivity pattern of isolated organisms to various antibiotics is as shown in Table 6. All *E.coli* species were 100 percent sensitive to amikacin and ceftriaxone.

Table 5: Organisms causing UTI.

Organism	UTI	%
<i>E. Coli</i>	18	39.12
<i>Klebsiella</i>	07	15.21
<i>Proteus</i>	05	10.86
<i>Staphylococcus aureus</i>	06	13.04
<i>Pseudomonas</i>	01	02.17
Culture Negative	08	17.39
Others	01	02.17

Table 6: Culture and Sensitivity pattern of organisms isolated from urinary tract of nephrotic cases (% sensitivity).

(Organism isolates)	Ampicillin	Gentamycin	Amikacin	Cotrimoxazole	Nitrofurantoin	Cefotaxim	Ceftriaxone	Cefixime	Ciprofloxacin	Piperacillin-Tazobactam	Vancomycin
<i>E. Coli</i>	48	54	100	46	88	22	100	46	98	98	68
<i>Klebsiella</i>	42	56	98	68	76	46	96	48	78	100	70
<i>Proteus</i>	46	74	96	52	92	78	96	68	98	98	88
<i>Pseudomonas</i>	52	86	94	76	84	89	96	60	96	100	98
Culture negative	98	96	90	86	100	94	99	70	100	100	92
<i>Staphylococcus aureus</i>	84	86	94	66	76	92	100	66	78	96	100

However, in-vitro sensitivity of the same organism to commonly used antibiotics including trimethoprim-sulphamethoxazole, ampicillin and nitrofurantoin was less as mentioned in Table 6. *Klebsiella* and proteus sepsis are shown good sensitivity towards amikacin, ceftriaxone and piperacilin -tazobactam.

DISCUSSION

Children with nephrotic syndrome are more susceptible to various forms of bacterial, viral and fungal infections than the general paediatric population. Lawson et al reported that all the five deaths in their series were due to sepsis.²⁹ In the ISKDC series too the most common cause of death was infections. Reasons for this increase in predisposition has been extensively evaluated.¹³⁻¹⁵ In our study, out of all cases studied about more than two third [58 (76.31%)] admission was due to an infection. Another Indian study had shown the rate of infection was 38.3%.¹⁶ The ratio of boys and girls in our study was 1.9:1. In our study UTI was the commonest infection followed by peritonitis, acute respiratory tract infection and tuberculosis. The incidence of UTI in general population is 1% in boys and 3% in girls.¹⁷

In this study incidence of UTI was very high at 60.52% out of which boys comprises of 69% and 30% in girls. Regarding organism of UTI 82.60% of urine cultures turned out to be positive for various organisms' while 17.39% cases had negative culture. These children when presented with dysuria, fever, loin pain, suprapubic tenderness with documented pyuria in urine, though had negative urine culture, had given full treatment. The negativity may be due to prior antibiotics treatment before admission in the hospital by private practitioners. In our study *E. coli* was the most common organism isolated from urine culture (39.12%) followed by *Klebsiella* (15.21%). This is less than a study revealed by Gulati et al where *E. coli* constituted 60% of urine cultures.

The present study shows that 60.52% of 76 patients with nephrotic syndrome had urinary tract infection, this observation of high prevalence of UTI among nephrotic syndrome patients have been reported by other workers.^{16,18,19} Ibadin\ reported a prevalence of 44.8% and this is similar to the present study.¹⁹ However, Gulati et al reported 13.8% and McVicar reported a prevalence of 21%.^{16,18} The differences in the types of nephrotic syndrome seen in our region as compared to those seen in Caucasians may account for the varying prevalence rates of UTI in patients with nephrotic syndrome.²⁰ It is possible that impaired immunity associated with nephrotic syndrome is more marked in patients with secondary syndrome which is very common in the tropics.¹⁶ About 18% of our patients were aged six years and above which makes it unlikely to be primary nephrotic syndrome.²⁰

In general population, post-neonatal UTI is relatively rare in males, sex did not influence the development of UTI.²¹ The immune compromise associated with nephrotic syndrome is not sex discriminatory, this may be the reason to explain the high prevalence of UTI in males in our series this is also similar to the study by Ibadin in (Southern Nigeria).¹⁹ *Staphylococcus aureus* organism comprising 13.04% of isolates, followed by pseudomonas (02.17%) cases. This finding is not consistent with the study by Ibadin who reported 54.3% of isolates were that of *Staphylococcus aureus* and also with Tsai et al who reported gram-negative bacilli as the predominant cause of infections, including UTI, in patients with nephrotic syndrome.^{19,22} The sensitivities of *Staphylococcus aureus* organism to ceftriaxone, amikacin, piperacillin-tazobactam and vancomycin was very promising out of which vancomycin shows 100% coverages. Their sensitivities to commonly used antibiotics such as cefixime and ampicillin were low. There is an increasing trend of resistance by common bacteria to routine antibiotics, this had been noted in the region.^{23,24} In our study the documentation of TB was 09.21% in nephrotic syndrome children. This is more than the incidence of TB in general population (1%). This prevalence is more than that seen by Kala U et al (6%).²⁵ But is less than that seen by Gulati et al (10.4%).¹⁶

The high prevalence of UTI found in the study and its complications mandates its aggressive treatment.²⁶ It is therefore very important that routine urine cultures and sensitivity should be done on patients with nephrotic syndrome in both first attack and relapse cases. The irreverent practice of self-medication, use of substandard drugs, antibiotic misuse and drug abuse is also stand by for this unfortunate trend. Indian paediatric nephrology group recommends that all children with nephrotic syndrome who are in remission and not on immunosuppressive.

CONCLUSION

Infections continue to be a major problem of children with nephrotic syndrome due to many factors especially in the developing countries such as India. UTI was the most common encountered infection, followed by peritonitis and respiratory tract infection. *E. coli* was the leading infecting agents responding well to a combination of ceftriaxone and amikacin.

Other organism is present in more than half the cases. Urine cultures and sensitivity patterns with appropriate adjustment of antibiotic choices are necessary before starting empirical antibiotic therapy. With high index of suspicion, early institution of appropriate antibiotics and aggressive management of infections the complication i.e. Morbidity and mortality can be prevented. Infections (i.e. UTI) which most of the time triggers a relapse should be ruled out in all cases both in first attack and relapse cases before starting immunosuppressive therapy for a better outcome.

ACKNOWLEDGEMENTS

Authors would like thankful to Central Research Laboratory, IMS and SUM Hospital for the help for drafting of the manuscript.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Dash DK, Bisoi SK, Mohanty MD, Dash M, Acarya NC. To study the frequency, etiology and predisposing factors of urinary tract infection in children with nephrotic syndrome in Eastern Odisha Region: a hospital based study. *Int J Contemp Pediatr* 2017;4:140-4.