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Infections in Indian Children with Nephrotic Syndrome

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Abstract

***Back ground:** Children with nephrotic syndrome are susceptible to different types of infections. However, the only causes for the infection reported to date are bacteria and prior reported series did not identify fungi as causative organism.*

***Methods:** A retrospective study of 2912 children with nephrotic syndrome was made to determine the demography, incidence of infections and bacterial and fungal etiologies.*

***Results:** Between January 2000 and August 2017, we identified that 29.60% of the children developed infections. The prevalence of bacterial and fungal infections in urinary tract is 42.11% and 8.01%, in lower respiratory tract 22.15% and 6.14%, in upper respiratory tract 12.65% and 1.62%, in diarrhoea 1.62% and 0.35%, in septicaemia 0.93% and 0.24% and in peritonitis 1.62% and 0.24% respectively. In skin lesions, 0.81% fungal presence was detected while in meningitis, tuberculosis and enteric fever 0.23%, 0.58% and 0.70% respectively with no traces of fungi. Statistical analysis was performed for biochemical indices and infections and was found significant for low serum albumin and high serum cholesterol ($p<0.05$).*

***Conclusions:** Thus, the present study clearly states that infections are important but are often under diagnosed in children with Nephrotic syndrome because steroid is anti inflammatory so classical symptoms of infections may not be noticed. Therefore, children suffering with nephrotic syndrome in relapse or those exhibiting steroid resistant should be screened for the presence of various infections. During screening, apart from the bacterial etiology, it is important to consider fungal etiology as well.*

Keywords: *Nephrotic syndrome, Children, Infection, Bacteria, Fungus.*

Introduction

Infections are an important cause of morbidity and mortality in children with nephrotic syndrome (NS) especially in developing countries such as India. Occult infections may manifest as a steroid non-response or relapse in a child who has already attained remission [1]. Common infections associated with either onset of disease or during the course of disease are acute upper and lower respiratory infections (ARI) including pneumonia with or without empyema, skin infections including impetigo and cellulitis, acute gastroenteritis (watery diarrhoea) or dysentery, urinary tract infections (UTI) and primary peritonitis [2-4].

Although there have been several studies published in the past pertaining to infections in nephrotic syndrome, most were from the developed countries and in hospitalized patients, but very few detailed series have been published from developing countries [1]. Determining the type of infection is important, not only from the therapeutic point of view, but also to establish preventive measures [2]. Here it is important to note that till this date only bacterial pathogen was

reported but fungal pathogen was never in children with nephrotic syndrome. Therefore, the aim of this retrospective study is to analyze the demography and incidence of infections in children with nephrotic syndrome along with their bacterial and fungal etiology.

Materials and Methods

Between January 2000 and August 2017, we retrospectively analyzed the data of 2912 children. These children were under 16 years of age and they fulfilled all the necessary criteria required for the International Study of Kidney Disease in Children suffering from Nephrotic Syndrome [5].

These 2912 children were treated using standard Arbeitsgemeinschaft für Pädiatrische Nephrologie (APN) protocol [6]. The initial episode was treated with prednisolone in doses of 60 mg/m^2 on daily for 6 weeks followed by 40 mg/m^2 on alternate days for 6 weeks. Any forms of relapse were treated with prednisolone in doses of 60 mg/m^2/day until remission for 3 days followed by 40 mg/m^2 on alternate days for 4 weeks. Adjunctive therapy (cyclophosphamide, tacrolimus, moefityl, and rituximab) was administered in standard regimens to children according to guidelines whenever indicated, who were frequent relapsers, steroid dependent and steroid resistant.

These children, along with routine and radiological examination, were also examined for microscopy and cultures of sputum, throat swab, blood, body fluids, skin scrapings, stool and urine as and when necessary. Two successive cultures were performed to establish the colonization of the pathogen because successive sampling rarely demonstrates the same contaminant [7]. Specimens were collected by the expert technical staff under the supervision of microbiologist and were processed immediately after receiving the samples which minimized the chances of contamination.

The identification of individual bacteria and yeast were done by Vitek-2 (Biomeurix, France) while identification of individual fungi was based on standard methods such as microscopy, morphology, colony characterization, pigment production and rate of growth [8].

Ultrasound of the abdomen was performed in all the cases with UTI. The presence of any three of the following criteria's were taken as evidence of tuberculosis (TB); (1) history of cough, fever or a family history of exposure to a case of TB, (2) clinical sign of non-resolving pneumonitis and/or matted lymphadenopathy, (3) a positive chest X-ray (mediastinal lymphadenopathy or non-resolving pneumonitis) or lymph node FNAB findings with AFB, (4) a positive ZN stain, (5) significant ADA levels, (6) Hains positivity for AFB, (7) positive mycobacterium culture by BactAlert [9].

Our data were obtained from positive fungal cultures, which is the gold standard [10] for the diagnosis of fungal infections. Galactomannan and (1-3)-β-D-Glucan tests are not appropriate for the isolation of yeast and yeast like fungi so these test were not used [11-12].

Various infections are defined as follows: UTI: Bacterial colony count of >10 5/mL in a clean-catch midstream sample with fever (≥ 38.5ºC), dysuria or increased frequency of urination. 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. Upper respiratory tract infection (URTI): The disease mainly involves the upper respiratory tract and is associated with fever, cough, sore throat, and rhinitis [13].

Data were expressed as mean ± standard deviation. Statistical significance was defined at a p value of 0.05 by using IBM SPSS 24 version.

Results

During the period January 2000 and August 2017, 2912 children with nephrotic syndrome were registered in the nephro OPD, Allahabad. Out of these 2912 children, 862 (29.60%) developed various infections and rest 2050 (70.40%) did not show any signs of infection. Out of the 862 children, 712 (24.45%) children developed bacterial infections while 150 (5.15%) developed fungal infections. Table 1 depicts the demographic and base line data of 862 children.

Table 1. *The demographic and base line data of 862 children.*

Demographic Features and Laboratory Test:	
Age	7.8 ± 2.1
Sex	76% (Male), 24% (Female)
Blood urea nitrogen	5.3 ± 0.81 (µmol/l)
Serum creatnine	82.2 ± 5.3 (µmol/l)
Serum protein	47.1 ± 1.8 (g/l)
Serum albumin	20.1 ± 8.4 (g/l)
Serum cholesterol	11.9 ± 2.7 (mmol/l)
24-h urine protein	64.0± 2.34 (mg/m^2/h)

Out of the 862 cases, the mean age of children with infections was 7.8 ± 2.1 years with males being about 76% and females about 24%. The mean duration of the follow up was 16.7 months. The age and sex distribution in children who developed infections were similar to the control group comprising of 2050 children with no infections while hypoproteinemia and hypercholesterolemia were significantly observed in children with infections. Figure 1 illustrates the frequency of infections in nephrotic children treated with prednisolone and different combinations. According to the response on steroids, incidence of infrequent relapsers, frequent relapsers, steroid dependent and non-responders were 310 (36%), 241 (28%), 181 (21%) and 130 (15%) respectively. Moreover, high frequency of infections was observed in relapsers, steroid dependent and non-responders. In our study 63.9% infections triggered relapses in which 67.9% UTI, 17.2% lower respiratory tract infection (LRTI), 14.2% URTI, 0.4% diarrhoea and 0.3% peritonitis are associated with relapse.

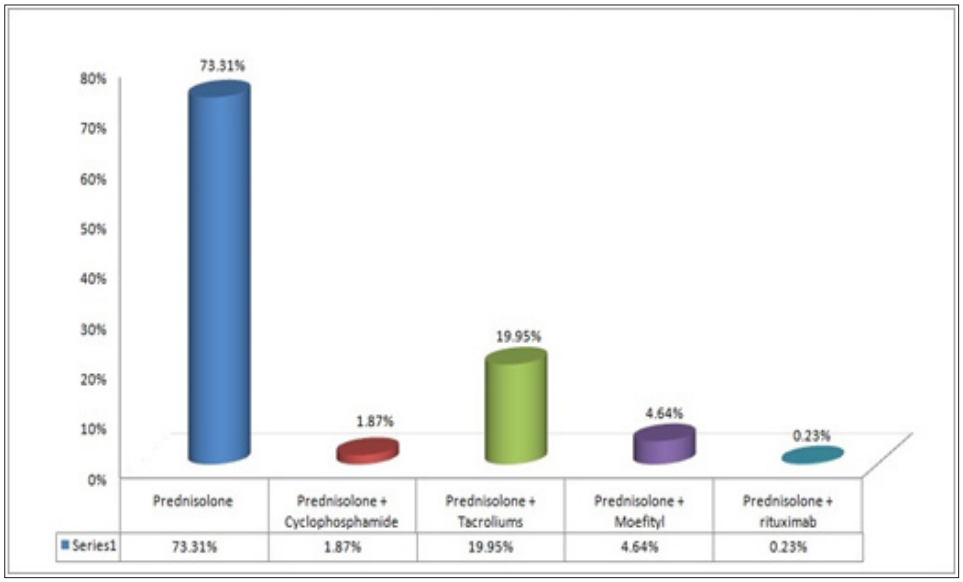

Fig 1: *Frequency of infections in children with nephrotic syndrome treated with different regimens.*

In our series we found the 16.82% *E.coli* is predominant in UTI, 28.80% *Klebsiella pneumoneae* in LRTI, 33.02% *Staphylococcus aureus* in URTI, 28.57% *E.coli* in diarrhoea, 37.50% *Klebsiella pneumoneae* in septicaemia, 100.0% *Mycobacterium tuberculosis* in TB, 35.71% *Staphylococcus aureus* in peritonitis, 83.33% *Salmonella typhi* in enteric fever, 50.00% *Klebsiella pneumoneae* and *Staphylococcus aureus* each in meningitis among bacterial etiology while 26.08% *Candida cruzi* in UTI, 35.85% *Candida tropicalis* in LRTI, 28.58% *Candida glabrata* in URTI, 66.67% *Candida tropicalis* in Diarrhoea, 71.43% *Tricophyton rubrum* in skin lesions, 50.00% *Candida tropicalis* and *Candida parapsilosis* each in septicaemia, 50.00% *Candida cruzi* and *Candida tropicalis* each in peritonitis among fungal etiology. Table 2 and 3 depicts the etiologic spectrum of infections and Figure 2 illustrates the incidence of bacterial and fungal infections.

Table 2. *Spectrum of bacteria isolated from the various specimens of children with NS.*

Bacteria	UTI	LRTI	URTI	Diarr-hoea	Septica-emia	TB	Perito-nitis	Meni-ngitis	Enteric Fever
Klebsiella aerogenes	11.01%	6.29%	6.42%	0.0%	0.0%	0.0%	7.15%	0.0%	0.0%
Klebsiella pneumoneae	14.32%	28.80%	22.01%	0.0%	37.50%	0.0%	14.28%	50.00%	0.0%
Citrobacter freundii	13.49%	3.14%	10.10%	0.0%	12.50%	0.0%	7.15%	0.0%	0.0%
Enterobacter aerogenes	7.43%	10.48%	16.51%	0.0%	12.50%	0.0%	14.28%	0.0%	0.0%
Enterobacter cloacae	0.0%	0.0%	0.0%	14.29%	0.0%	0.0%	0.0%	0.0%	0.0%
Pseudomonas aeruginosa	4.68%	1.04%	0.92%	14.29%	12.50%	0.0%	0.0%	0.0%	0.0%
Acinatobacter	5.24%	0.53%	0.92%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Morganella morgani	1.65%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Proteus rettgeri	1.37%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Proteus vulgaris	3.58%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Proteus mirabilis	7.43%	0.0%	0.0%	7.14%	0.0%	0.0%	0.0%	0.0%	0.0%
E.coli	16.82%	0.0%	0.0%	28.57%	0.0%	0.0%	21.43%	0.0%	0.0%
Moraxella	1.12%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Pseudomonas multisuda	0.83%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Salmonella typhi	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	83.33%
Salmonella paraB	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	16.67%
Staphylococcus aureus	4.41%	24.08%	33.02%	21.42%	25.00%	0.0%	35.71%	50.00%	0.0%
Staphylococcus saprophyticus	6.62%	6.28%	3.67%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Streptococcus pyogenes	0.0%	11.52%	4.59%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Micrococci	0.0%	6.80%	1.84%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Streptococcus viridans	0.0%	1.04%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Shigella boydii	0.0%	0.0%	0.0%	14.29%	0.0%	0.0%	0.0%	0.0%	0.0%
Mycobacterium tuberculosis	0.0%	0.0%	0.0%	0.0%	0.0%	100%	0.0%	0.0%	0.0%

Table 3. *Spectrum of fungus isolated from the various specimens of children with NS.*

Fungus	UTI	LRTI	URTI	Diarrhoea	Septicaemia	Skin Lesion	Peritonitis
Candida glabrata	8.69%	24.52%	28.58%	33.33%	0.0%	0.0%	0.0%
Candida guilliermondii	2.89%	1.89%	7.14%	0.0%	0.0%	0.0%	0.0%
Candida krusei	26.08%	3.78%	21.43%	0.0%	0.0%	0.0%	50.00%
Candida tropicalis	21.74%	35.85%	21.43%	66.67%	50.00%	0.0%	50.00%
Candida albicans	14.50%	11.32%	7.14%	0.0%	0.0%	0.0%	0.0%
Tricosporon	7.25%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Candida parapsilosis	18.85%	22.64%	14.28%	0.0%	50.00%	0.0%	0.0%
Tricophyton rubrum	0.0%	0.0%	0.0%	0.0%	0.0%	71.43%	0.0%
Tricophyton mentagrophyte	0.0%	0.0%	0.0%	0.0%	0.0%	28.57%	0.0%

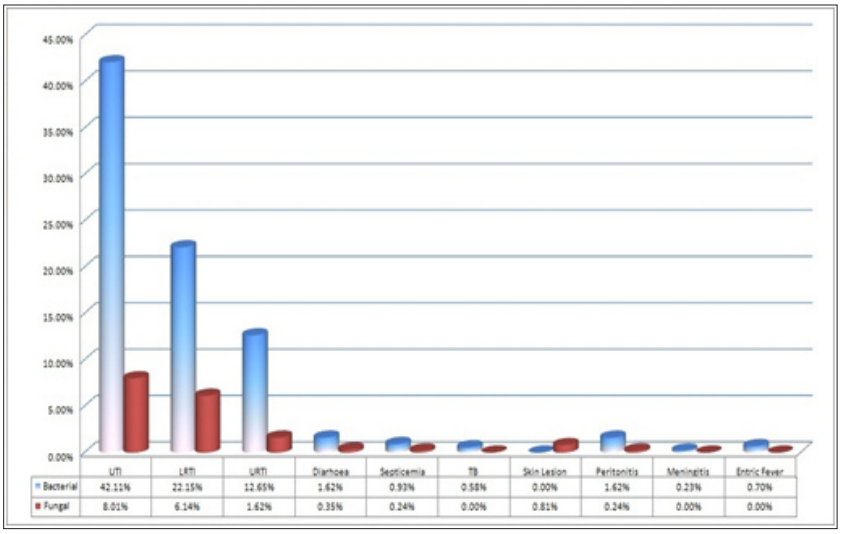

Fig 2. *Spectrum of infections in children with nephrotic syndrome.*

Children suffered from peritonitis (1.86%), septicaemia (1.17%) and LRTI (6.62%) required admission. Mortality was seen in 5 (0.58%) children in whom two were suffering with bacterial meningitis, two with fungal peritonitis and one child with septicaemia.

Discussion

Nephrotic syndrome is a common chronic disorder, characterized by alterations of permselectivity at the glomerular capillary wall, resulting in its inability to restrict the urinary loss of protein [14]. The chief complication of nephrotic syndrome is infection, followed by thromboembolic events. Hypertension, hyperlipidaemia, features of corticosteroid toxicity and behavioural disorders are less frequent [15]. Increased predisposition to infections occurs due to loss of immunoglobulins, complement and properdin, altered T cell functions, immunosuppressive therapy and presence of oedema [14]. Infections in the body increased protein catabolism and hence lowering of serum albumin. The serum albumin levels have been found to correlate well with serum properdin B levels [16].

In our present study the prevalence of bacterial and fungal pathogens in urinary tract is 42.11% and 8.01%, lower respiratory tract is 22.15% and 6.14%, upper respiratory tract is 12.65% and 1.62%, diarrhoea is 1.62% and 0.35%, septicaemia is 0.93% and 0.24% and peritonitis is 1.62% and 0.24% respectively. In skin lesions, 0.81% fungal presence was detected without any bacterial presence while in meningitis, TB and enteric fever 0.23%, 0.58% and 0.70% respectively with no traces of fungi. Gulati *et al* reported most common infection as UTI (13.63%) followed by TB, peritonitis, URTI, skin, LRTI and meningitis [2]. Pakistan and Taiwan found UTI as the second most common infection while Bangladesh, Iran, Taiwan and Brazil reported ARI is the commonest infection among nephrotic children [17-19]. As the above detail make it clear that all the researchers till this date reported only bacterial etiology of infections while none identified and reported any fungal etiology in such type of cases in children with nephrotic syndrome.

Yield of fungal isolates was 5.15% in our study. This may be due to the fact that most of the children with nephrotic syndrome under follow up, were reporting directly to our centre for major symptoms without receiving any prior treatment. Children in the fungal infection group exhibited the following - longer duration of NS; increased doses of prednisolone and greater use of immunosuppressor. Different studies have demonstrated that steroid therapy increases the susceptibility for infections because of impairment of cellular immunity [20].

Infections are responsible for high morbidity and mortality due to severe infections such as pneumonia, primary peritonitis and septicemia leading to multi organ failure [21-22]. These infections are also the main reasons for hospitalization along with delayed response to steroid or discontinuation of steroid therapy in some cases [23-24]. In the third world, sepsis is still a major problem in nephrotic children and the commonest cause for hospitalisation [25].

In our series children suffered from peritonitis (1.86%), septicaemia (1.17%) and LRTI (6.62%) required admission and mortality was seen in 5 (0.58%) children in whom two were suffering with bacterial meningitis, two with fungal peritonitis and one child with septicaemia. Gulati *et al* reported 3 deaths in children in which 2 were directly due to infectious complications (bronchopneumonia and pyomeningitis). Lawson *et al* reported that all the 5 deaths in their series were due to sepsis [26]. In the ISKDC series, there were 10 deaths of 389 children. Of these, infections accounted for 6, while 4 were due to other causes [27].

During follow up we could not observed any noticeable difference in the frequency and severity of infections among non-responders, frequent relapsers or steroid dependents. Statistical analysis was done between infections and biochemical parameters and it was found significant for serum albumin and serum cholesterol at 0.05 levels.

Registering a total of 2912 children, this study is the largest study till date. Also worth mentioning is the fact that never before has such a varied infections ever been reported in the cases of NS and fungal isolates have not been mentioned as of yet.

Conclusion

The present case series, illustrates the incidence of bacterial and fungal etiologies of various infections in children suffering from NS is 24.45% and 5.15% respectively, therefore, the detection of these pathogens should necessarily be carried out in children especially those not responding to steroid therapy of any kind and relapsers. Moreover clinician should also think about yeast or fungi as a causative agent while screening such cases.

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