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Immunosuppressive burden and risk factors of infection in primary childhood nephrotic syndrome

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ABSTRACT

Introduction: Patients with primary childhood nephrotic syndrome (PCNS) develop alterations in their cellular and humoral immunity that predisposes them to the development of infection, and lead them to have frequent relapses. Also, infection could be significantly enhanced by immunosuppressive agents. This study aims to estimate the immunosuppressive burden, rate of infection and identify possible risk factors in PCNS requiring hospitalization.
Methodology: A cross-sectional study of hospitalized children ≤ 14 years of age diagnosed with PCNS in King Abdul-Aziz Medical City, Riyadh from January 2003 to December 2013.
Result: Out of 111 patients admitted with PCNS, 84 (76%) had both minor and major types of infection. Upper respiratory tract infection (URTI) was the most predominant type (n = 44, 52%). Among the major types of infection, urinary tract infection (UTI) was the most common infection (n = 21, 25%) followed by pneumonia (n = 17, 20%) then cellulitis (n = 6, 6%). Infection in children who received a higher annual cumulative dose of steroids (CDS) strikingly had a higher rate of infection in comparison to those who received lower CDS ($p < 0.01$). Moreover, those who received primary and secondary immunosuppressant's had 100% infection rate.
Conclusion: About half of infection encountered by PCNS patients were URTI followed by UTI and pneumonia. Higher annual CDS, combination of primary and secondary immunosuppressants were the highest independent risk factors for infection. Among the infection, URTI was considered as the predominant entity whereas among the major infection, UTI was predominant followed by pneumonia then cellulitis.

Background

Primary childhood nephrotic syndrome (PCNS) is a disease characterized by the presence of nephrotic range proteinuria, clinical edema, hypoalbuminemia, and hyperlipidemia [1] It is more common in children compared to adults, which accounts for 2–7 cases for every 100,000 children per year [1,2].

PCNS carries a risk of various complications including infection [3]. Pathogenesis and the related increase of infection frequency are mostly due to defect in cell mediated immunity, use of immunosuppressive therapy, malnutrition, and urinary loss of immunoglobulins, properdin factor B and complement factors [4,5]. The incidence of infection from different reported studies in PCNS vary from 8% to 84% [5–7].

Infection may result in frequent relapses and treatment failure in PCNS which may lead to significant morbidity [8]. Hence, it is important to know the clinical spectrum, risk factors, and prevalence of infection in PCNS. Moreover, detailed analysis of immunosuppressive burden in PCNS are rarely described in literatures. The main objective of the study was to estimate the immunosuppressive burden and to identify clinical risk factors in patients with PCNS.

Abbreviations: PCNS, primary childhood nephrotic syndrome; URTI, upper respiratory tract infection; UTI, urinary tract infection; CDS, cumulative dose of steroids; CDI, cumulative dose of immunosuppressant's; IMT, immunosuppressive therapy.

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Methodology

Study setting and participants

This is a cross-sectional study of hospitalized children diagnosed with PCNS from January 2003 to December 2013. The study was conducted in the Department of Paediatrics, Division of Nephrology, King Abdul-Aziz medical city, Riyadh, Saudi Arabia; a tertiary care center. The study included children ≤ 14 years of age with the diagnosis of PCNS. Children diagnosed with congenital nephrotic syndrome, secondary nephrotic syndrome (e.g. IgA nephropathy, lupus nephritis), primary immunodeficiency, malignancy, and patients on dialysis therapy were excluded.

Data collection

Cases of hospitalized children diagnosed from January 2003 to December 2013 with PCNS (diagnosis based on ISKDC criteria) were identified from hospital medical records, and they were reviewed. Both paper chart review (for patients' data) and electronic chart review (for lab results) were performed for all subjects.

The diagnosis of PCNS was based on the International Study of Kidney Disease in Children (ISKDC) criteria, which defined PCNS as the presence of generalized edema, protein creatinine ratio >250 mg/mmol, (normal range <30 mg/mmol), hypoalbuminemia <25 g/L (normal range 38–54 g/L) and hypercholesterolemia >6.4 mmol/l (normal range <4.4 mmol/l). Infection was classified into major and minor types. The major types were UTI, pneumonia, and peritonitis. By definition, acute pyelonephritis or febrile UTI is an infection of the renal pelvis that usually results from ascent of a bacterial pathogen up the ureters from the bladder to the kidneys. A positive urine analysis or urine culture confirms the diagnosis in patients with a compatible history and physical examination involving high fever (>39 centigrade) and abdominal or flank pain. Peritonitis is defined as the inflammation of the peritoneum, the lining of the inner wall of the abdomen and cover of the abdominal organs. A diagnosis of peritonitis is based primarily on the clinical manifestations involving acute abdominal pain, with or without abdominal guarding, which are exacerbated by moving the peritoneum. In patients with significant ascites, a diagnosis of peritonitis is made via paracentesis (abdominal tap): More than 250 polymorphonucleate cells per μL is considered diagnostic. Pneumonia is an inflammatory condition of the lung affecting primarily the small air sacs known as alveoli. Physical signs and symptoms include some combination of productive or dry cough, fever, and difficulty in breathing. Pneumonia is typically diagnosed based on a combination of physical signs and a chest radiographs. Bacteremia is defined as the presence of bacteria in the blood. Cellulitis is defined as spreading bacterial infection underneath the skin surface characterized by redness, warmth, swelling, and pain. The minor types were URTI, otitis media, and gastroenteritis.

Collected data included age, gender, anthropometrics, infection rate, clinical presentation, treatment, duration, therapeutic status, annual cumulative dose of immunosuppressants mg/kg (CDI), and relevant laboratory investigations were obtained. The primary immunosuppressants is defined as patients treated with only steroids. On the other side, secondary immunosuppressants is defined as patients treated with either cyclosporine, tacrolimus, mycophenolate cyclophosphamide or rituximab. The annual individual CDI (mg/kg) is defined as total dose of mg/day multiplied by total duration and divided by weight of the patient. The investigations included complete blood count, renal function, serum electrolytes, spot urinary protein/creatinine ratio, urine analysis, urine culture, blood culture, chest radiographs, serum protein, serum albumin and serum cholesterol. Furthermore, the relationship between infections and annual CDI (mg/kg) were evaluated.

Table 1
Determinants related to infection in primary childhood nephrotic syndrome.

Variables (n = 84)	n	(%)
Age (n = 84)		
• Child (<10 years)	74	(76%)
• Adolescent (≥10 years)	10	(71%)
Gender (n = 84)		
• Male	59	(76%)
• Female	25	(76%)
[a]Received primary and secondary immunosuppressants		
• With Infection	65	(100%)
• No infection	0	

[a] Primary immunosuppressants include only ACDS — annual cumulative dose of steroids, Secondary immunosuppressants includes ACCSA — annual cumulative dose of cyclosporine, ACTAC — annual cumulative dose of tacrolimus, ACMYC — annual cumulative dose of mycophenolate, ACCYC — annual cumulative dose of cyclophosphamide, ACRTX — annual cumulative dose of rituximab.

Data analysis

Data entry was performed using Excel, and the statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS V.20). Descriptive statistics were presented as frequencies and percentages for the categorical variables (infection, and therapeutic status). The incidence, duration of infection, and annual CDI (mg/kg) was compared among different groups using Mann–Whitney test or Kruskal–Wallis test as appropriate. A p-value of <0.05 was considered statistically significant difference. Median, standard deviations, and interquartile range were calculated as appropriate.

Ethical considerations

This study was approved by the Institutional Review Board at King Abdullah International Medical Research Centre (KAIMRC).

Results

In a period of 10 years, a total of 111 patients with PCNS were admitted to the Department of Paediatrics. Of these, 78 (70%) were boys and 33 (30%) were girls. The mean age of onset of nephrotic syndrome was 4.17 ± 2.1 years. The main clinical symptoms were edema (n = 101, 91%), followed by ascites (n = 29, 26%). Of the 31 nephrotic patients who underwent renal biopsy, minimal change disease was the predominant histopathological finding 16 (55%), followed by focal segmental glomerulosclerosis in 10 (35%) patients. All patients were treated with corticosteroids, in which 95 (86%) were steroid sensitive. Over 10 years, only two patients were admitted to paediatric Intensive Care Unit with complicated pneumonia. The patient who died with pneumonia was diagnosed with nephrotic syndrome since 2 years and was resistant to immunosuppressants including rituximab.

During that period, 84 (76.4%) had both minor and major types of infection. The overall incidence of infection among genders was equal, boys = 59 (76%) and girls = 25 (76%). Children < 10 years of age had a slightly higher rate of infection (76%) compared to those who are older (71%). Other major determinants of the infections is those who received primary and secondary immunosuppressants (100% — Table 1).

Among different types of infection, upper respiratory tract infection (URTI) was the predominant infection noted in our study (Table 2). Among the major infection, urinary tract infection (UTI) was the main type (n = 21, 25%) followed by pneumonia (n = 17, 20%) then cellulitis (n = 6, 6%). Nine out of 21 cases of UTI, had identified organisms; 5 of the positive cultures were *E. coli*, 2

Table 2
Types of infection and its association between immunosuppressants to infection in 84 patients with primary childhood nephrotic syndrome.

Type of infections	n = 84	CDS n = 19	CDS + CCSA n = 15	CDS + CTAC n = 9	CDS + CMYC n = 27	CDS + CCYC n = 7	CDS + CRTX n = 7
URTI	44 (52%)	8 (42%)	9 (60%)	1 (11%)	19 (70%)	4 (57%)	3 (43%)
UTI	[a]21 (25%)	2 (11%)	[a]6 (40%)	5 (56%)	[a]5 (19%)	2 (29%)	1 (14%)
Pneumonia	[a]17 (20%)	[a]4 (21%)	1(7%)	[a]3 (33%)	[a]5 (19%)	1 (14%)	3 (43%)
Cellulitis	[a]6 (7%)	[a]6(32%)	0	0	0	0	0
Bacteraemia	1 (1.2%)	1(5%)	0	0	0	0	0
Peritonitis	3 (3.6%)	0	1 (7%)	1 (11%)	0	0	1 (14%)

URTI: upper respiratory tract infection, UTI: urinary tract infection; CDS: cumulative dose of steroids, CCSA: cumulative dose of cyclosporine, CTAC: cumulative dose of tacrolimus, CMYC: cumulative dose of mycophenolate, CCYC: cumulative dose of cyclophosphamide, CRTX: cumulative dose of rituximab.
[a] Multiple episodes of infections.

Table 3
Comparison between infection and cumulative dose of immunosuppressant's (n = 111).

Groups	n	Duration (years) Median (Min–Maximum)	Annual cumulative doses Median (IQR) (mg/kg)	Annual cumulative doses (mg/kg) Range (Min–Maximum)	p Value
Received only CDS					
Infection not present	27	1.2 (0.3–3.5)	23.1 (20, 26.6)	(12.9–45.9)	<0.01*
Infection Present	19	2.4 (1.2–5.2)	45.8 (34.9, 60)	(16.6–135)	
Received-SI					
Infection absent	0				
Infection present (CCSA)	15	3.4 (1.2–4.6)	369.5 (320.5, 568.6)	(164–620)	<0.001*
(CTAC)	9	2.2 (0.8–3.8)	136.6 (110.950, 216.650)	(85.3–230)	
(CMYC)	27	2.7 (0.3–5.6)	1447.500 (1272.6, 1770)	(878–3480)	
(CCYC)	7	0.2 (0.2–0.2)	430 (365, 500)	(360–565)	
(CRTX)	7	0.4 (0.2–0.6)	605 (495–725)	(370, 795)	

Min — minimum, IQR — interquartile range, SI — secondary immunosuppressants, CDS — cumulative dose of steroids, CCSA — cumulative dose of cyclosporine, CTAC — cumulative dose of tacrolimus, CMYC — cumulative dose of mycophenolate, CCYC — cumulative dose of cyclophosphamide, CRTX — cumulative dose of rituximab.
* Means highly significant.

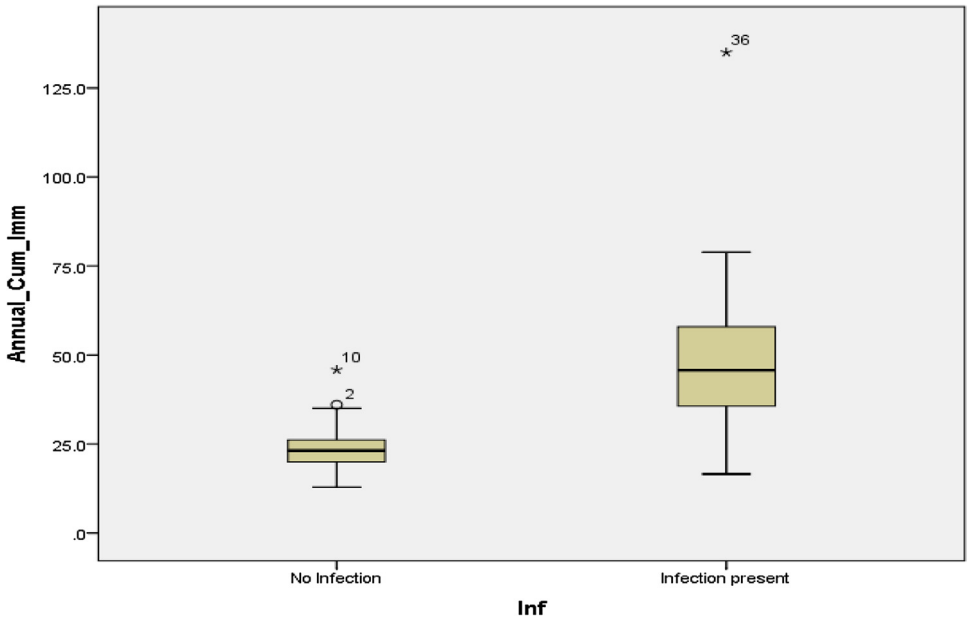

Fig. 1. Box plot analysis (X axis — annual cumulative dose primary immunosuppressants-steroids (mg/kg), Y axis — incidence of infections).

were *Pseudomonas*, and 2 were methicillin-resistant Staphylococcus aureus (MRSA).

Among those who received secondary immunosuppressive agents the most common type of infection was URTI (42%) except for those who received tacrolimus, who interestingly had UTI (56%) as the most common type of infection (Table 2).

The analysis of annual CDS (total mg/kg), duration of exposure and infection risks are depicted in Table 3. p Value for the groups who was on primary and secondary immunosuppressants were <0.01 and <0.001 respectively. This indicates that the higher annual CDS (mg/kg) increase the risk of infections significantly (Median (IQR) 45.8 (34.9,60)). Moreover, box plot analysis also describes the association between higher annual CDS and the incidence of infections (Fig. 1). Similarly, annual cumulative doses (mg/kg) of secondary immunosuppressants (cyclosporine, tacrolimus, mycophenolate, cyclophosphamide and rituximab) carries the highest risk of infections (100%) as illustrated in Table 3.

Discussion

Infection may potentially lead to a high rate of morbidity and mortality in children with nephrotic syndrome [8,9]. Although progress in antimicrobial therapy has resulted in better outcomes in the treatment of infection, the rise of antimicrobial resistance has posed new and complex challenges. [10] At the same time, the advancement and increase in the usage of potent immunosuppressive agents have increased the chances of serious infection, despite their benefits [11,12,13].

In the present study, 76% of children with PCNS had infection, and the most frequent type was URTI accounting for 52% of the cases. The geographic variation has a role in the pattern of infection. For example, in previously done studies, there were differences between the prevalence of infection in different countries like Taiwan, France and Nigeria. In a study done in Taiwan, 19% of childhood NS admissions were related to infection. Pneumonia was the most common type (49%), followed by UTI (30%), bacteraemia/sepsis (11%), peritonitis (11%) and cellulitis (5%) [5].

In France, 8% of childhood NS patients had infection, and most the cases were peritonitis [6]. In Nigeria, it was observed that UTI was the most common type of infection in childhood NS accounting for 44.8% of the cases, followed by skin sepsis, and peritonitis [14]. From these studies, the geographic variation in the rate of infection in PCNS patients can be noticed. This variation in the rate of infection might be possibly accentuated due to the reason that some studies, like the one done in Taiwan, have evaluated specific types of infection while others included all infection types encountered by PCNS patients.

Some of the possible risk factors for infection are age, gender and usage of multiple immunosuppressive agents. In our study, children < 10 years of age had a slightly higher rate of infection (76%) in contrast to those who are older (71%), and the most common infection was URTI for both age groups. Another study found that children ≤ 10 years old had pneumonia as the most frequent infection while UTI was the most common infection among children > 10 years old [5]. There was no significant difference of overall incidence of infection among genders in our study and other studies [5,8,14].

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. A study conducted in Kano, Nigeria concluded that 67.9% of UTI cases were caused by *Staphylococcus aureus*, followed by 17.9% in *Klebsiella species* and 14.2% by *Pseudomonas* [15]. *E. coli* is still considered as the most common pathogen causing UTI according to several studies as so with our study [7,8].

Patients on tacrolimus, in the present study, had UTI as the predominant infection, unlike other immunosuppressive agents where URTI was the most common type. However, we could not come to a definitive conclusion because of the limited number of patients. In addition, none of the studies showed a clear association between tacrolimus and UTI. Analysis by Abeyagunawardena et al. linked tacrolimus with increased risk of fungal and viral infections [16].

Immunosuppressive therapy (IMT) is one of the main modality of treatment in PCNS, especially steroid resistant and steroid dependent nephrotic syndrome. In this context, the most frequently used IMT are corticosteroids, mycophenolate, cyclosporine, tacrolimus, cyclophosphamide and rituximab [17,18,19]. These drugs can increase the risk of life threatening complications. A clear association between infections and IMT have been linked to their mechanism of action and the immune profile.

In the present study, there was a significant analysis in the incidence of infection between those who received a higher and lower CDS. In addition, our patients who received secondary immunosuppressants possessed highest risk of infection including mortality. Rituximab for example results in potent depletion of B cells resulting in poor antibody responses and patients may exhibit both opportunistic and non-opportunistic infection [18,19]. It also may explain the mortality of our patient due to severe chest infection.

Similarly, in one of the meta analysis of pooled data, overall rate of steroid associated infectious complications was 12.7% [20]. Cyclosporine was linked with Gram-negative sepsis and pneumonia in controlled clinical trials but not so in our analysis, where we had URTI and UTI as the predominant infection [20–22]. Moreover, a study done in India found no difference in the rate of infection between PCNS children who received an immunosuppressants (cyclophosphamide) combined with prednisolone, and children who received prednisolone only [8]. There are no universal consensus in the prevention of infectious complications in PCNS. Our analysis reflects an overview suggestion of high index of suspicion of infections, patient education, and appropriate vaccines.

Finally, controlling infection in PCNS continues to be control of the proteinuria and avoidance of multiple immunosuppressants when possible. It is also clear that high index of suspicion regarding infection should be consistently retained while evaluating children with PCNS. Hence, a long-term randomized multi-centered study on the span of infection in nephrotic children is highly suggested.

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Analysis and interpretation of data and in writing the manuscript are done by Department of Paediatrics.

Competing interest

None declared.

Data availability

The data that support the findings of this study are available from the corresponding author on request.

Authors' contributions

KA carried out review of the manuscript, MA carried out the data analysis and writing, review of the the manuscript. BA carried out the data collection and data analysis. SA carried out the data collection and data analysis SAM carried out the data collection and Data analysis. AM carried out the statistical Review. EA carried out the expert opinion on pneumococcal vaccination. MS carried out the data analysis.

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