Review Article

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Strategies for Prevention of Infection in Nephrotic Children

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Abstract

Children with nephrotic syndrome (NS) develop complications due to either the disease state or its treatment. Infections, thromboembolism and acute kidney injury are the most common complications in children with NS. Several studies in children with NS have reported that urinary tract infections, upper respiratory tract infections, peritonitis and sepsis are the most commonly reported infections. Infection is one of the common triggering factors for relapse, and prophylaxis against infections is required in patients unresponsive to steroids or with frequently relapsing disease. In this review article, we summarize the strategies for prevention of infections in NS. The most commonly studied drug for the prevention of infection in NS is intravenous immunoglobulin G (IVIg), while other drugs include thymosin, oral transfer factor, Bacillus Calmette-Guérin (BCG) vaccine, mannan peptide tablet, polyvalent bacterial vaccine and Chinese herbal medications (Tiaojining and Huangqui granules). Several vaccination programs including pneumococcal, influenza A, varicella and measles have been effective in the prevention of infections in nephrotic children. However, established measures for preventing infections in nephrotic children are lacking, and to draw any conclusion, randomized controlled trials are required.

Keywords: Nephrotic Syndrome; Prevention; Infection; Children.

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Introduction

Idiopathic nephrotic syndrome (NS) is a clinical condition characterized by the presence of heavy proteinuria [≥50 mg/kg/day (or ≥40 mg/m^2/h), hypoalbuminemia (<25 g/L), edema and hypercholesterolemia. In childhood, the overall incidence of NS is ~2-7 cases/100,000 children/year, a prevalence of ~16 cases/100,000 children, and a boy to girl ratio of 2:1(1-3). In south Asia, the incidence is higher at 7.4-16.9/100,000 children. Minimal change disease (MCD) is the commonest type of NS in children constituting about 90% of the cases.

Focal segmental glomerulosclerosis (FSGS) and lupus membranous nephropathy (LN) are the other underlying pathologies in children aged between 3 months and 16 years (1,4-6)**.** Patients with NS are prone to complications either because of the disease itself or the treatment that they receive for the induction of remission. These complications can be categorized as acute complications which are associated with the nephrotic disease state, and long-term sequelae of NS and its treatment (7). Table 1 enlists the complications of NS in children (7,8).

Infections, thromboembolism and acute kidney injury are the major serious complications of NS (8,9). Of these, infections are the commonest complications, which can be life threatening. The objective of our review is to elaborate on infections and their prevention in children with NS.

Table 1. Complications of nephrotic syndrome in children

Kind of complications	Complications
Associated with disease state	Infections (Sepsis, Cellulitis, UTI Pneumonia, Peritonitis) Acute kidney failure Thromboembolism (DVT, PE, RVT) Endocrine abnormalities Hypertension Hypovolemia CV complications (Hyperlipidemia, Vasculitis) Anemia Malnutrition Hormonal and electrolyte imbalance Impaired growth
Treatment related complications	Hypertension Impaired growth Bone demineralization Hyperlipidemia Hemorrhagic cystitis Increased risk for infections Seizures Hematological disturbances

CV: Cardiovascular, DVT: Deep vein thrombosis, PE: Pulmonary embolism, RVT: Renal vein thrombosis, UTI: Urinary tract infection

Definitions

Infections in Nephrotic Syndrome

There is a high risk (~32-38%) of infections in patients with NS due to the disease state or the treatment with immunosuppressive agents (7). Kumar et al., reported the incidence of major infections to be 43.8% in hospitalized nephrotic children (10) The underlying pathophysiology of infections in NS include the abnormal functioning of suppressor T lymphocytes, low serum immunoglobulin G (IgG) concentrations, defective opsonization (reduced factor B and D concentrations), dilution of local humoral defenses by fluid collection due to edema, and low levels of complement C3 and C4 (characteristics of glomerulonephritis caused by deposition of circulating immune complexes) are the factors that may be associated with infections in patients with NS (Figure 1) (2,7,11). The complement deficiency (low C3 and C4 levels) leads to hypocomplementemia and place the patients at an increased risk of infections caused by encapsulated organisms (12).

The occurrence of infections in NS patients may alter the responsiveness of corticosteroid therapy, which may be fatal (11). Infections may cause disease relapses or trigger the onset of disease (13,14). Furthermore, a strong correlation of infections with morbidity and mortality is reported in nephrotic children. Studies have demonstrated the mortality rate due to infection to be 2.5% - 10% in nephrotic children (10,15). Hence, determining the types of infections in NS is important to establish preventive measures and accordingly plan the treatment strategies.

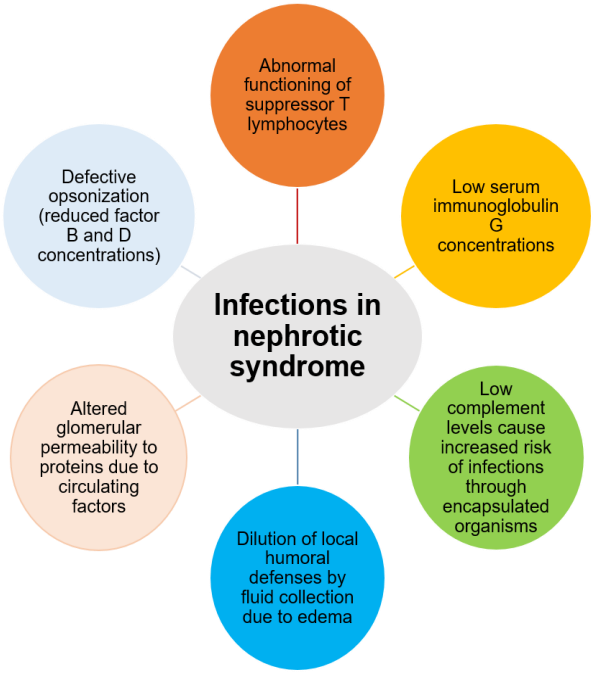

Figure1. Potential mechanisms of infections in patients with nephrotic syndrome (2,7,11)

Spectrum of Infections in Children with NS

Several researchers have studied the spectrum of infections in nephrotic children and their association with the disease severity (Table 2).

In hospitalized children with NS, infections are the most common acute complications. Gulati et al. evaluated the spectrum of infections in Indian children with NS and reported that UTI was the commonest followed by pulmonary tuberculosis, peritonitis, skin infections, upper respiratory tract infections (URTI), lower respiratory tract infections (LRTI) and pyomeningitis (13). In another study from India, pneumonia was found to be the most common infection followed by UTI, septicemia, SBP, cellulitis, perinephric abscess, and pulmonary tuberculosis. E. Coli, MRSA, Klebsiella, coagulase negative staphylococcus, proteus, and pneumococci were the most common pathogens causing these infections (16).

Table 2. Spectrum of infections in children with NS in different studies

Study	Spectrum of infections in children with NS
Rheault et al [5], US	Pneumonia, bacteremia/sepsis, peritonitis, UTI, and cellulitis
Gulati et al [9], India	UTI, PTB, peritonitis, skin infections, URTI, LRTI and pyomeningitis
Krishnan et al [12], India	Pneumonia, UTI, septicemia, SBP, cellulitis, perinephric abscess, PTB
Kumar et al [6], India	Peritonitis, pneumonia, UTI, cellulitis
Moorani et al [11], Pakistan	ARI, cellulitis, diarrhea, UTI, peritonitis
Wei et al [13], Taiwan	Pneumonia, UTI, sepsis, peritonitis, cellulitis
Alfakeekh et al [14], Saudi Arabia	URTI, UTI, pneumonia cellulitis

ARI: Acute respiratory infections, PTB: Pulmonary tuberculosis, LRTI: Lower respiratory tract infections, URTI: Upper respiratory tract infections, UTI: Urinary tract infections

A more recent study in India evaluated 148 children with NS with 162 admissions and reported that peritonitis was the commonest infection followed by pneumonia, UTI and cellulitis contributing about ~67% of major infections; Streptococcus pneumoniae was the predominant organism isolated in children with peritonitis and pneumonia (10).

A study from Pakistan showed that acute respiratory infections (ARI), cellulitis and diarrhea were the most common infections followed by UTI and peritonitis (15). In a Taiwanese study, pneumonia followed by UTI, sepsis, peritonitis and cellulitis were the most common infections in children with NS (17). A cross-sectional study of hospitalized children ≤14 years of age diagnosed with NS from Saudi Arabia reported URTI as the most common infection followed by UTI, pneumonia and cellulitis (18). In the Western world, a study conducted in France reported bacterial infections with half of the infections involving peritonitis while 50% of the identified germs were S. pneumoniae (19). Rheault et al, reported that the most common infections in children with NS is pneumonia, followed by bacteremia/sepsis, peritonitis, urinary tract infections (UTI), and cellulitis (8). Viral infections can also result from immunosuppression due to corticosteroid use in nephrotic children, which are generally well tolerated, except chickenpox, which can be fatal (2,20). Lin and colleagues showed a significant association between enteroviral infection and NS from a National Health Insurance Research Database in Taiwan (21). Figure 2 details the causative organism for common infections in nephrotic children (22,23).

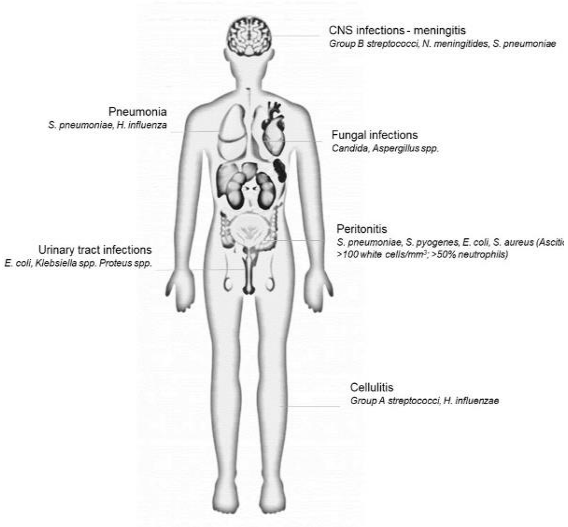

Figure 2. Causative organism for common infections in children with nephrotic syndrome (22,23)

Risk Factors for Infections and Monitoring

In a study by Gulati et al., the rate of infections was higher in frequent relapsers, steroid dependent and subsequent non-responders as compared with infrequent relapsers and initial responders; age of onset, gender, histological type of NS, duration of disease, serum creatinine, blood urea nitrogen, 24-h proteinuria and immunosuppressive therapy were not associated with increased risk of infections (13). Children with NS aged <10 years have pneumonia as the most common infection whereas it is UTI in children aged >10 years, suggesting a potential association between age and site of infection (17). Serum albumin <1.5 g/dL, IgG level <600 mg/dL, hypogammaglobulinemia and renal insufficiency are known risk factors for infections in NS (10,24). In a retrospective evaluation of 100 children with relapsed NS, Sarkar et al., reported that NS was more common among 2-6 years of age, with a male to female ratio of 2:1, and the patients had low serum albumin level, low serum total protein level and culture positive UTI at the initial attack (25). Hence, monitoring of the aforementioned laboratory parameters is recommended in nephrotic children.

Prevention of Infection in Nephrotic Syndrome

The immune status of children with NS should be evaluated by screening tests along with the history and physical examinations so that the appropriate immunization and other protective measures can be provided (26). Several studies have evaluated the etiological profile of infections in children with NS in order to establish prophylactic or therapeutic options. However, there are no specific guidelines available (27,28).

For the prevention of infection in NS, the most commonly studied drugs are IVIg. Other drugs studies with few published evidences are thymosin, oral transfer factor, Bacillus Calmette-Guérin (BCG) vaccine injection, mannan peptide tablet, polyvalent bacterial vaccine and two Chinese herbal medications named Tiaojining and Huangqui granules. Wu et al., conducted a Cochrane review in 2012 from 12 studies in 762 children with NS to evaluate the effectiveness of prophylactic interventions for reducing the risk of infections (29). The authors reported that oral antibiotics, pneumococcal vaccination, some immunomodulators and Chinese medicinal herbs have been used/recommended for reducing the risk of infections in nephrotic children. There were no studies available on the prophylactic use of antibiotics, vaccination or other drugs. Overall, the authors reported that intravenous immunoglobulin (IVIg), thymosin, oral transfer factor, BCG vaccine injection and Chinese medicinal herbs (Huangqi granules and Tiaojining) may help prevent infections in nephrotic children. However, there was insufficient evidence on recommending any intervention that could be used for preventing infections in children with NS in view of the small number of randomized controlled trials and low methodological quality (29).

Immunoglobulin replacement therapy

Serum immunoglobulins are markedly diminished in NS due to increased urinary loss. A higher risk (6.74 times) for bacterial infection was reported among patients with serum immunoglobulin G (IgG) levels <600 mg/dL compared with >600 mg/dL (95% confidence interval, 1.22 to 36.32; P=0.029) by Ogi et al (24). In these patients, administration of immunoglobulin (10 to 15 g every 4 weeks) resulted in a decreased rate of bacterial infections to a level equal to that in patients with endogenous levels >600 mg/dL.

Overall, the authors concluded that maintaining the IgG levels >600 mg/dL may reduce the risk of infections (24). Hence, it seems rational to administer exogenous immunoglobulins for the prevention of infections in NS patients with persistent hypoglobulinemia. Clinical studies (n=4) have evaluated the efficacy of IVIg in the prevention of infection in NS.(30-33) The pooled results of 4 studies (n=248) reported a total 28 episodes of infections in 117 children in the IVIg group (IVIg plus standard steroid protocol) compared with 68 episodes in 131 children in the control group (standard steroid protocol) with a risk ratio of 0.47 (95% CI: 0.31-0.73; P=0.0006). E. Coli was the major pathogen isolated from abdominal, respiratory and urinary tract infections which were commonly diagnosed in both groups of children with documented infections (29-33).

Thymosin (Thymosin α1)

A naturally occurring peptide 'Thymosin α1' is known to enhance the immune functions, and has shown to improve patients' response in several infections (34,35) Zhang et al., demonstrated positive outcomes in terms of a smaller number of infections with thymosin plus standard steroid protocol (7/20 patients) when compared with standard steroid protocol alone (14/20 patients) with a RR of 0.5 (95% CI 0.26-0.97). The thymosin doses used were - 5 mg/d (2 to 4 years); 10 mg/d (4 to 7 years); 20 mg/d (7 to 10 years) added to 5% glucose 50 to 100 mL intravenously for 2 weeks, followed by every other day intramuscularly for 3 weeks, and then once a week intramuscularly. Respiratory and urinary tract infections were the most common in both groups (29,36).

Oral transfer factor

Transfer factor (TF) is a low molecular weight lymphocyte extract which can transfer antigen specific cell mediated immunity to T lymphocytes. Apart from its use in infections, specifically viral infections like herpes, it can be used in a wide array of conditions like malignancies, allergies, immunodeficiency and autoimmunity mediated conditions (37). TF increases the expression of interferon (IFN)-γ and RANTES (regulated on activation, normal T cell expressed and secreted, CCL5), while it decreases the expression of osteopontine (38). Because it affects cell mediated immunity, theoretically it might help in NS. In a study by Rao et al., 20 of 50 patients in the treatment group (polypeptide 10 mg + nuclear glucose 30 μg 10 mL daily) developed infections and in the control (standard steroid protocol) group, 38 episodes of infections were documented in 48 patients with a RR of 0.51 (95% CI 0.35-0.73) (39). Respiratory, intestinal and urinary tract infections were reported in both groups.

Mannan peptide tablet

The cell wall glycoprotein of Candida albicans contains a glycoprotein named mannan. Mannan and oligosachharide fragments of mannan are potent inhibitors of cell-mediated immunity. They act upon monocytes, and suppressor T lymphocytes, interfere with cytokine activity, lymphocyte–monocyte interaction and lymphocyte homing (40). Hence, there is a possibility of its use in altered immunity conditions like NS. Guo et al., reported no significant difference in infection rates among treatment (oral mannan peptide 10 mg three times/day) group and the control (standard steroid protocol) group (number of patients developing infection: Mannan peptide 7/36 vs control group 13/31; RR 95% [CI]: 0.46 [0.21, 1.01]) (41).

BCG vaccine

Kang et al., studied the effect of BCG vaccine (1mL [0.5g] every other day) and reported that 14/22 patients developed infections compared to 15/16 in the control group (standard steroid protocol) with no statistically significant difference (RR [95% CI]: 0.68 [0.48, 0.95]) (42).

Polyvalent bacterial vaccine (Lantigen B)

Ye et al., evaluated the polyvalent bacterial vaccine (Lantigen B; six different inactivated strains of bacterial lysates - Streptococcus pneumoniae type 3, Streptococcus pyogenes, Branhamella Catarrhalis, Staphylococcus aureus, Haemophilus influenza and Klebsiella pneumoniae) and reported that 2/22 patients in the polyvalent bacterial vaccine arm developed infections as compared to 9/24 in the standard steroid protocol group; RR: 0.24 (95% CI: 0.06-1.00) (43).

Tiaojining

Tiaojining is a Chinese herbal medicine containing 6 principal herbs used in the Chinese alternative medicine system. The study done by Li et al., showed that Tiaojining (1.5 bag/time [< 5 years]; 2 bags/time [5 to 9 years]; 3 bags/time [> 9 years], 3 times/day [one bag = 15 g] prevented infections in children with NS when compared with the standard steroid protocol (17/30 patients vs. 29/30; RR: 0.59, 95% CI: 0.43, 0.81);(44) URI, acute enteritis, purulent tonsillitis, bronchitis and pneumonia were reported.

Huangqi (Astralagus) granules

Huangqi is an immunomodulating Chinese herb with a beneficial effect seen with improvements in the immune function and is used extensively in the Chinese alternative medicine therapy. Chen et al.,(45) and Kang et al.,(46) have studied the

effects of Huangqi in children with NS. On analyzing both studies, a total of 28 infectious episodes occurred in 67 patients in Huangqi in the treatment group compared with 43 episodes in 63 patients in the standard steroid protocol group with a RR of 0.62 (95% CI: 0.47-0.83).

Avoidance of nephrosis

A high incidence of infections has been observed during the period of relapse in nephrotic children (11). Corticosteroids along with other therapies (cyclophosphamide, levamisole, and cyclosporine) are used to minimize the nephrotic state. This is a widely advocated management protocol for the prevention of infections in children with NS (47).

Chemoprophylaxis against bacterial infection

There is no strong evidence supporting the efficacy of prophylactic antibiotics (penicillin) in preventing infections, especially peritonitis, in children with NS as per the American Academy of Pediatrics (AAP) as there are no randomized controlled trials available (48).

Several treatment guidelines including the French and UK guidelines have recommended the use of antibiotics only if infection is evident (49). According to the Royal Children's Hospital, a routine prophylaxis for infections in NS is not indicated unless there is a risk of pneumococcal infection (e.g. gross or symptomatic edema, unimmunized), and if indicated, it should be managed with oral penicillin V (phenoxymethylpenicillin) 125 mg/dose 12 hourly if under 5 years, or 250 mg/dose 12 hourly if over 5 years, and should be stopped after edema subsides (50). However, there have been reports of occurrences of serious infections in children with NS receiving penicillin V prophylaxis (51).

McIntyre and Craig estimated that ~110 children with NS would need to be treated for 1 year to prevent one episode of pneumococcal infection (28).

The risk of infection in children with NS corresponds to several pathogens, hence, penicillin monotherapy prophylaxis may not provide significant results. Furthermore, after the introduction of universal pneumococcal vaccination, the topic of antibiotic prophylaxis has become less relevant (22).

Pneumococcal vaccine

Pneumococcal vaccination has been used for the prevention of pneumococcal infections in children with NS (27). Other immunizations include hepatitis B, diphtheria pertussis tetanus (DPT), polio (Salk), H. influenzae type B, pneumococcal, meningococcal, flu, human papillomavirus (HPV), varicella, measles, mumps and rubella. The increasing pneumococcal resistance to penicillin and cephalosporins strengthens the aim to prevent pneumococcal infections. The Italian Society for Pediatric Nephrology (SINePe) consensus document on the management of NS in children has recommended that all unimmunized children with NS should receive pneumococcal vaccine (2). The American Academy of Pediatrics (AAP) recommends vaccination with pneumococcal conjugate vaccine (PCV) 7 in children aged <2 years and with pneumococcal polysaccharide vaccine (PPV) 23 after two years of age (48). A reduction in the incidence of pneumococcal infections is reported with the use of PCV7 and PCV13 (Prevnar) vaccines, particularly in the young children. The AAP further recommend a single dose of PCV13 in children aged 6-18 years in an ideal sequence of PCV13 first followed by PPV23 ≥8 weeks later (52). These guidelines recommend the use of live attenuated vaccines after 3 months of corticosteroid discontinuation.

Influenza vaccination

A yearly seasonal influenza vaccine administration in children with NS is recommended by the AAP (48). Also, the current UK guidance recommends a second dose 1 month after administration of the first dose (either inactivated intramuscular vaccine or live attenuated intranasal vaccine) (53).

Varicella zoster vaccination (VZV)

Alpay et al., reported that immunization with a single dose of VZV vaccine was safe and effective in children with steroid sensitive NS in remission (54). The UK guidelines recommend VZV vaccination ≥3 months after the discontinuation of high-dose prednisolone (2 mg/kg/day for ≥1 week, or 1 mg/kg/day for ≥1 month) (53).

In addition to the above vaccinations, measles immunization is a routine part of childhood

vaccination in the UK, Europe and USA, and a measles-specific immunoglobulin therapy should be considered for non-immune children with NS (22).

Role of probiotics

Probiotics are commonly used as the immune defense system due to increasing antibiotic resistance, which is termed as 'microbial interference therapy' (55). The mechanisms by which probiotics exert their effects are largely unknown, however, gut pH modification, production of antimicrobial compounds and antagonizing pathogens, immunomodulation, and lactase production are the potential ones (56). Lactobacillus salivarius can produce lactic acid, which inhibits the growth of H. pylori in vitro. Lactobacillus rhamnosus GR-1 and lactobacillus reuteri RC-14 are known to be effective in UTI (57). The prophylactic use of probiotics can help infection prevention in immunocompromised individuals such as nephrotic children.

Summary

Urinary tract infections, upper respiratory tract infections, peritonitis and sepsis are the most commonly reported infections in children with nephrotic syndrome and bacterial infections are generally caused by encapsulated organisms (streptococcus pneumoniae). Prophylaxis against infections is required in children with nephrotic syndrome who are unresponsive to steroid therapy or have frequently relapsing disease. Hypoalbuminemia, proteinemia, hypogammaglobulinemia, renal insufficiency are the major risk factors for infections in nephrotic children and warrants careful monitoring. The use of prophylactic antibiotics for prevention of infection syndrome is debatable and the benefit-risk evaluation is recommended for the risk of drug related side-effects and the development of penicillin-resistant organisms. Several vaccination programs including pneumococcal, influenza A, varicella and measles have been effective in the prevention of infections in children with nephrotic syndrome. However, there are no established measures for preventing infections in nephrotic children, and further randomized controlled trials are required to draw any conclusion.

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Conflict of Interest

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