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Nephrotic Syndrome: Updates and Approaches to Treatment

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Opinion statement

Nephrotic syndrome (NS) is among the most common pediatric kidney diseases with a high risk of morbidity and mortality due to infection and thrombosis. Goals of treatment are to reduce proteinuria to normal levels thereby reducing symptoms and risk of complications. Children with NS should initially be treated with prednisone or prednisolone at a dose of 60 mg/m^2/day daily for 6 weeks followed by 40 mg/m^2/day given every other day for an additional 6 weeks. While most children are steroid responsive, approximately 20 % of children with NS do not go into remission with steroids and should be treated with a calcineurin inhibitor such as cyclosporine or tacrolimus. Some children with NS who respond to steroids eventually have a frequently relapsing or steroid-dependent course and may have significant side effects from cumulative corticosteroid therapy. For these children, steroid-sparing medications are required. Treatment with mycophenolate mofetil is recommended as first-line therapy for treatment of frequently relapsing or steroid-dependent NS with steroid toxicity due to its favorable side effect profile compared to alternatives. If this is not effective, alternate agents such as cyclophosphamide, calcineurin inhibitors, or rituximab could be considered after careful review of the pros and cons of each medication with the child's family. Further randomized controlled trials are necessary to determine which agents are most effective and to determine methods to predict medication response in individual children.

Introduction

Nephrotic syndrome (NS) is among the most common pediatric kidney diseases and is defined as massive proteinuria (>40 mg/m^2/h or urine protein to creatinine ratio >2 g/g) leading to hypoalbuminemia (<2.5 g/dL), edema, and hyperlipidemia. The peak age at initial presentation of childhood NS is 2 years with 60–70 % presenting prior to age 6 years [1]. Most children with NS are treated initially with oral corticosteroids, and they can be clinically classified based on their ability to achieve remission (i.e., complete normalization of

proteinuria). Approximately 85 % of children under the age of 6 years are *steroid-sensitive*, whereas the remainder have *steroid-resistant* disease. Older children are more likely to have steroid-resistant NS. Children with steroid-resistant disease may have an underlying genetic cause for NS, and providers should consider genetic testing in this population, depending on the age of the child [2]. While inherited causes of NS are often resistant to all therapies, there are reports of complete or partial remission in some children [3]. Further studies are required to understand the response to therapy in children with inherited NS.

For those children who respond to steroids, the majority will have one or more relapses and half will have *frequently relapsing* (≥4 relapses/year) or *steroid-dependent* (two consecutive relapses during steroid therapy or within 14 days of stopping steroids) NS [4]. Children with frequently relapsing NS and steroid-dependent NS may have significant side effects from cumulative corticosteroid therapy so treatment with other agents is often required. Therapy for these children should be guided by a pediatric nephrologist.

Clinical NS can be the result of a number of different pathologies on kidney biopsy. *Minimal change disease* (MCD) is the most common histopathologic finding in children with NS [1]. Kidney biopsies from patients with MCD have a normal appearance by light microscopy with effacement of podocyte foot processes visible by electron microscopy (EM) [5]. In addition to podocyte effacement by EM, biopsy samples from children with *focal segmental glomerulosclerosis* (FSGS) demonstrate light microscopic findings of segmental sclerosis within some glomeruli [6]. Children with FSGS on renal biopsy are less likely to go into remission with steroids than children with MCD and are more likely to have progressive chronic kidney disease [1].

Prior to the 1950s, no treatments were available for children with nephrotic syndrome and outcomes were uniformly poor with mortality rates of up to 65 % primarily due to complications of infection and thrombosis [7]. Infection remains the most common complication of NS affecting approximately 20 % of hospitalized patients [8]. In addition to loss of albumin in the urine, nephrotic patients lose components of the alternative complement pathway, including factors B and D that increase their susceptibility to infection with encapsulated organisms such as *Streptococcus pneumoniae* [9–12]. Thromboembolism is less common, affecting ~3 % of children with nephrotic syndrome, but can be a catastrophic complication [13]. Children with active NS are at risk for thromboembolism for several reasons. First, there is urinary loss of factors that inhibit clot formation such as antithrombin III (ATIII). Second, there is increased production of pro-coagulant factors by the liver [14]. After successful treatment of nephrotic syndrome with corticosteroids in the 1950s and 1960s, mortality from infection and thrombosis dropped to 9 %, with further reductions to <1 % in the modern era with continued improvements in treatment and supportive care [7, 15]. Thus, successfully treating nephrotic syndrome to attain a remission is important in reducing the morbidity and mortality that go along with this disease. This review will discuss treatments for steroid-sensitive NS and steroid-resistant NS. Goals of treatment are to attain remission with minimal medication side effects.

Corticosteroids

Although used universally, the mechanism of action of corticosteroids in the treatment of NS is unknown. It has been hypothesized that NS is a disorder of the immune system, with T-cell dysfunction resulting in the release of a circulating factor that causes podocyte foot process effacement and proteinuria [16]. Corticosteroids are presumed to act by suppression of a T-cell-mediated factor; however, the definitive identification of this circulating factor has remained elusive [17]. Alternately, corticosteroids may also have an effect on the podocyte directly through stabilization of the actin cytoskeleton and alteration of gene expression [18, 19].

The 2012 Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines recommend initial treatment of childhood NS with either prednisone or prednisolone at a dose of 60 mg/m^2/day (or 2 mg/kg/day) as a single daily dose for 4–6 weeks, followed by 40 mg/m^2 (or 1.5 mg/kg/day) every other day for 2–5 months with tapering (Table 1) [20••]. The recommended daily starting dose of 60 mg/m^2/day was used empirically in the International Study of Kidney Disease in Children (ISKDC) in the 1960s and 1970s and adopted by the Arbeitsgemeinschaft Für Pädiatrische Nephrologie (APN) studies in the 1970s and 1980s. No randomized controlled trials have been performed to examine different initial doses of prednisone. The ISKDC treatment regimen went on to treat with daily steroids for 4 weeks followed by 40 mg/m^2/day for 3 consecutive days out of 7 for the following 4 weeks and found that 85 % of children <6 years of age and 60 % of children between 6–16 years responded to this regimen [1]. Unfortunately, a high percentage of children treated

Table 1. Recommended corticosteroid dose for children with nephrotic syndrome

	KDIGO recommendation
Initial episode of NS	Single daily dose of 60 mg/m^2/day or 2 mg/kg/day (max. 60 mg) for 4–6 weeks Then, 40 mg/m^2/day or 1.5 mg/kg/day (max. 40 mg) given every other day for 2–5 months with tapering Minimum 12-week duration
Relapse of NS	Single daily dose of 60 mg/m^2/day or 2 mg/kg/day (max. 60 mg) until complete remission for 3 days Then, 40 mg/m^2/day or 1.5 mg/kg/day (max. 40 mg) given every other day for 4 weeks

with this regimen have relapses of the disease, so a number of subsequent studies have been performed in an attempt to optimize the initial steroid course to minimize risk of relapse. A meta-analysis of randomized controlled trials showed that treatment with steroids for 3 months or more can decrease the risk of relapse at 1–2 years by 30 % compared to the shorter ISKDC regimen [21]. More recent randomized placebo-controlled trials have evaluated children with NS treated with 3 vs. 6 months of steroids for their initial course and did not demonstrate differences in rates of sustained remission or frequently relapsing disease between these groups [22•, 23]. Finally, studies have compared the 3 consecutive days per week steroid dosing to alternate day steroid dosing and found lower 1-year relapse rates for children treated with alternate-day steroids, leading to the widespread adoption of alternate-day dosing during the steroid taper [24].

There are no randomized controlled trials examining the optimal dose or steroid treatment period for children who experience relapse. KDIGO guidelines recommend treatment with 60 mg/m^2/day (or 2 mg/kg/day) as a single daily dose until the urine is negative for protein for 3 days, then 40 mg/m^2 (alternately 1.5 mg/kg/day) every other day for 4 weeks [20••]. While some clinicians may be tempted to use this "shorter" regimen for the initial episode of nephrotic syndrome in patients, it is not recommended, as this approach leads to a significant increased risk of relapse at 2 years and therefore more cumulative steroid exposure [25]. There is wide variability among pediatricians and pediatric nephrologists in their initial approach to treatment of NS, despite various national and international consensus guidelines published over the past decade [20••, 26–30].

Children with frequently relapsing or steroid-dependent NS should be treated with alternate-day steroids for at least 3 months after entering remission at the lowest dose possible to maintain remission [20••]. Some children will require prolonged, alternate-day steroids in order to maintain remission [31].

Children with frequently relapsing NS and steroid-dependent NS can have high cumulative exposure to steroids and are at risk for developing steroid-associated side effects. These can include short stature, cataracts, hyperglycemia, cushingoid appearance, obesity, hypertension, mood and sleep disorders, avascular necrosis of the hip, decreased bone density, and stomach ulcers [32]. Children receiving long-term steroids should be monitored for complications of their use, including yearly eye exams to exclude the development of cataracts. Children with frequently relapsing NS and steroid-dependent NS who develop steroid-associated side effects should be offered steroid-sparing agents (Table 2).

Alkylating agents

Alkylating agents such as cyclophosphamide and chlorambucil are alternate agents for children with frequently relapsing NS and steroid-dependent NS and can induce a sustained remission in some children. Alkylating agents are not effective for children with steroid-resistant NS [33–35]. Cyclophosphamide directly prevents cell division by cross-linking DNA strands and decreasing DNA synthesis. Its mechanism of action in NS is unknown but is presumably due to immunosuppressive effects on T-cells. Concern about risks of severe side effects such as gonadal toxicity and increased incidence of malignancy limits the current use of chlorambucil despite its historic use in children with NS [36].

Cyclophosphamide is given orally for 8–12 weeks at a dose of 2 mg/kg/day. Children should be in remission with steroids before cyclophosphamide is started, and steroids should be continued at tapering doses during cyclophosphamide therapy [33, 37].

Table 2. Maintenance agents for frequently relapsing or steroid-dependent NS

Medication	Dose	Major side effects
Corticosteroids	Alternate day oral, lowest dose to maintain remission	Short stature Cataracts Hyperglycemia/diabetes Hypertension Cushingoid appearance Obesity Mood and sleep disorders Avascular necrosis of the hip Decreased bone density Gastritis/stomach ulcers
Cyclophosphamide	2 mg/kg/day orally for 8–12 weeks	Gonadal toxicity/sterility Leukopenia Infection Hair loss Hemorrhagic cystitis Malignancy Teratogenic
CNI: Cyclosporine Tacrolimus	4–5 mg/kg/day orally divided twice daily 0.1 mg/kg/day orally divided twice daily	Hypertension Renal toxicity Hypertrichosis Gingival hypertrophy Diabetes
Mycophenolate mofetil	600 mg/m^2/dose orally given twice daily	Stomach pain Diarrhea Leukopenia Infection Teratogenic
Rituximab	375 mg/m^2 intravenously weekly for 1–4 doses	Acute infusion reactions Pulmonary fibrosis Malignancy *Pneumocystis jiroveci* pneumonia Progressive multifocal leukoencephalopathy

Children with frequently relapsing NS have somewhat better outcomes (72 and 36 % sustained remission at 2 and 5 years, respectively) than children with steroid-dependent NS (40 and 24 % sustained remission at 2 and 5 years) [36]. Older children (>7.5 years) appear to be more likely to achieve long-term remission than younger children (<3.8 years) [38]. There is no difference in sustained remission rates between children treated with oral and intravenous (IV) cyclophosphamide at 12–24 months of follow-up, and IV cyclophosphamide is generally reserved for children with demonstrated poor adherence.

Cyclophosphamide treatment can be associated with significant side effects. Gonadal toxicity may be seen more commonly in males than in females, particularly in those treated with cumulative doses >200 mg/kg [36]. For this reason, a single course of therapy should be given with a maximum cumulative dose of 168 mg/kg (=2 mg/kg/day × 12 weeks). Fertility preservation strategies are

available for treated patients [39]. Leukopenia and infection are other potentially serious side effects of cyclophosphamide therapy and occur in up to 32 % of treated children [36]. White blood cell counts should be monitored along with dosing adjustments as necessary throughout treatment. Hair loss (~18 %), hemorrhagic cystitis (~2.2 %), and malignancy (~0.2 %) are also potential complications of cyclophosphamide treatment.

Calcineurin inhibitors

Cyclosporine and tacrolimus are calcineurin inhibitors that are commonly used as immunosuppressive agents in solid organ transplantation. Calcineurin inhibitors (CNIs) inhibit T-cell activation and may be exerting their effect in nephrotic syndrome through this mechanism. Alternately, cyclosporine has been shown to directly target the podocyte and stabilize the actin cytoskeleton responsible for maintaining cell shape [40]. CNIs are recommended as first-line therapy for children with steroid-resistant NS and as steroid-sparing agents for children with frequently relapsing or steroid-dependent NS [20••]. Although the majority of studies in nephrotic syndrome have been performed with cyclosporine, tacrolimus appears to be equally efficacious [41, 42].

Children with steroid-resistant NS should receive a 6-month trial of a CNI. Cyclosporine is administered at a starting dose of 4–5 mg/kg/day in two divided doses with monitoring of drug levels. Tacrolimus is administered at a starting dose of 0.1 mg/kg/day in two divided doses with monitoring of drug levels. Optimal initial and maintenance drug level targets are unknown, although trials have variably used troughs of 60–150 μg/L for cyclosporine and 5–10 μg/L for tacrolimus. Of steroid-resistant children, 60–80 % will achieve either a complete or partial remission (>50 % reduction in proteinuria) after treatment with CNIs [43–45]. The optimal duration of treatment for steroid-resistant children who attain a remission with CNIs is unknown, and relapse is common after discontinuing the medication, leading to prolonged therapy in many children. However, many children can successfully stop CNIs and maintain remission. A recent study of children with steroid-resistant NS treated successfully with cyclosporine for a median of 3 years found that 73 % of children who stopped CSA had no further relapses of NS over a median follow-up of 9.7 years [45].

Children with frequently relapsing or steroid-dependent NS can also be treated with CNIs at doses equivalent to those used for steroid-resistant NS. Of children with frequently relapsing or steroid dependent NS, 60–85 % will attain prolonged remission with this regimen [46••]. These children are also at high risk of relapse after discontinuing the CNI with up to 85–100 % of children experiencing a relapse after discontinuing CNI in some series [47, 48]. Two randomized controlled trials of cyclosporine vs. alkylating agents in children with frequently relapsing or steroid-dependent NS showed no difference in risk of relapse as long as the child was taking cyclosporine [49, 50].

Side effects of cyclosporine include hypertension (10 %), gingival hypertrophy (32 %), elevated creatinine (6 %), and hypertrichosis (70 %) [51]. Tacrolimus causes significantly less gingival hypertrophy and hypertrichosis and may be preferred for children for whom cosmetic side effects are a concern, particularly teenage girls. Tacrolimus has the additional potential side effect of diabetes mellitus [52]. Children treated with CNIs can develop permanent renal interstitial fibrosis, with 11 % of children treated for <2 years and 58 % of children treated for >2 years demonstrating this finding on kidney biopsy [53]. For this reason, minimizing the dose of CNI and duration of therapy to maintain remission is recommended.

Mycophenolate mofetil

Mycophenolate mofetil (MMF) is a medication that suppresses the immune system through inhibition of B- and T-lymphocyte proliferation. Its mechanism of action in NS is also unknown, but presumed to work through immune suppression. It is gaining popularity as a treatment for NS due to its favorable side effect profile compared to CNIs, specifically its lack of renal toxicity.

The majority of studies using MMF have been performed in the frequently relapsing or steroid-dependent NS population. Treatment is typically started at 600 mg/m^2/dose given twice daily and continued for at least 12 months [20••]. In studies of children with frequently relapsing NS, 64–80 % of children remained in remission after 6–12 months of MMF therapy [46••, 54–56]. Similar to treatment with CNIs, children with frequently relapsing or steroid-dependent NS frequently relapse after discontinuing MMF, and prolonged therapy may be necessary.

MMF has also been used to treat steroid-resistant NS, although with somewhat less efficacy [57, 58]. In a randomized multicenter trial, children and adults with steroid-resistant NS and FSGS on kidney biopsy were randomized to treatment with MMF + dexamethasone vs. cyclosporine. Partial or complete remission occurred

in 46 % of cyclosporine-treated patients and 33 % of MMF + dexamethasone-treated patients after 12 months; however, the difference was not significant between the two arms of the study [58].

Side effects of MMF include stomach pain, diarrhea, leucopenia, and infection, although it is generally well tolerated [59]. MMF is teratogenic, so caution must be used when recommending this agent to women and girls of childbearing age [60]. One study has suggested that fewer relapses occur in children with higher mycophenolic acid exposure, although optimal trough levels and area under the curve measurements are unknown [46••].

Rituximab

Rituximab is a chimeric monoclonal antibody against CD20 on B cells that leads to B cell depletion after treatment. Rituximab may act in NS via alterations in B-cell/T-cell interactions leading to changes in cytokine secretion or co-stimulation. Alternately, rituximab may have a direct effect on podocyte structure and function as it has been found to bind directly to the sphingomyelin phosphodiesterase acid-like 3b (SMPDL-3b) protein on the surface of podocytes [61].

Rituximab has been found to be a useful drug to decrease relapse rates in children with frequently relapsing or steroid-dependent NS. Variable dosing regimens have been reported; however, 1–4-weekly doses of 375 mg/m^2 is most commonly utilized. A short-term (3 month) randomized study demonstrated lower relapse rates from 48 % in the standard of care arm to 18.5 % in the rituximab treatment arm [62]. Non-randomized trials have demonstrated 20–50 % 1-year remission rates in otherwise steroid- and CNI-dependent children, allowing for reduction in immunosuppressive therapy and improved linear growth [63, 64]. A randomized controlled trial comparing 4-weekly doses of rituximab vs. placebo showed a longer relapse free period of 267 days in the rituximab-treated children compared to 101 days in the placebo group [65••]. However, all rituximab-treated children relapsed by 19 months. Finally, a second randomized controlled trial showed that children treated with a single dose of rituximab had lower prednisone requirement at 3 months and longer relapse-free survival than children treated with steroid taper [66]. Evidence does not currently support the use of rituximab in children with steroid-resistant NS, although case reports and case series have suggested up to 20 % remission rates. In a single open-label randomized controlled trial, the addition of rituximab to baseline therapy of steroids and CNI did not reduce proteinuria at 3 months [67].

Use of rituximab in clinical practice is limited by concern for side effects. Approximately one third of treated children have acute infusion reactions consisting of fever, nausea/vomiting, diarrhea, rash, and bronchospasm [68]. Potentially serious and life-threatening side effects include pulmonary fibrosis, *Pneumocystis jiroveci* pneumonia, malignancy, and progressive multifocal leukoencephalopathy [69–71].

Emerging therapies

Adrenocorticotropic hormone (ACTH) was initially used in the 1950s to treat nephrotic syndrome and is the only US Food and Drug Administration-approved therapy for this indication [72]. ACTH fell out of favor for treatment of NS in the 1960s after the widespread availability of inexpensive oral steroids. Disadvantages of ACTH over oral steroids in children include the need to be injected and high cost. A current randomized trial of ACTH in children with frequently relapsing and steroid-dependent disease is ongoing and should shed light onto the efficacy and safety of ACTH in this population (NCT02132195).

Galactose is a monosaccharide sugar that binds to the focal sclerosis permeability factor in vivo and decreases its activity [73]. While some case reports have described remission after galactose treatment, a prospective study did not demonstrate any change in proteinuria after 16 weeks of therapy in seven children with steroid-resistant NS [74, 75]. A recently completed phase II study (Novel Therapies for Resistant FSGS-FONT II) randomized seven adult and pediatric patients to galactose and found that three achieved a reduction in proteinuria by 50 % at 26 weeks of therapy [76]. Further randomized controlled trials are necessary before galactose can be recommended for routine use. A second arm of the FONT II trial randomized seven pediatric and adult patients to treatment with adalimumab, an anti-TNF antibody, and found no patients with a favorable response to treatment [76].

Abatacept (cytotoxic T-lymphocyte-associated antigen 4 immunoglobulin fusion protein) is a costimulatory inhibitor that targets B7-1 (CD80). While normally present on antigen-presenting cells, B7-1 has also been shown to be upregulated in podocytes in experimental nephrotic syndrome and possibly in a subset of patients with FSGS [77, 78]. Abatacept is

hypothesized to act in NS via stabilization of podocyte β1-integrin activation and reduction of proteinuria. Abatacept treatment of four patients with recurrent nephrotic syndrome after transplant for FSGS and one patient with primary FSGS led to partial or complete remission in one case series; however, other reports have not demonstrated efficacy [78, 79]. Further clinical trials are required to determine which, if any, patients would benefit from treatment with abatacept.

Conclusions

In summary, a number of therapeutic options are available for treatment of children with NS. Careful consideration of potential complications should be discussed with families prior to prescribing treatments for NS. Further randomized controlled trials are necessary to determine which agents are most effective and to determine methods to predict medication response in individual children.

Compliance with Ethical Standards

Conflict of interest
Michelle Rheault has received researching funding from Amgen and Retrophin outside of the submitted work.

Human and animal rights and informed consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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