



Steroid-sensitive nephrotic syndrome in children: Korean Society of Pediatric Nephrology clinical practice recommendations

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Pediatric nephrotic syndrome is a clinical condition characterized by severe proteinuria, hypoalbuminemia, hyperlipidemia, and generalized edema, most commonly affecting children aged 2 and 6 years. Although standard oral steroid therapy is effective in managing most cases, relapses are common during childhood. Nephrotic syndrome presents significant challenges due to frequent relapses and the potential side effects of long-term drug therapy. In Korea, the absence of a unified national clinical guideline has led physicians to manage pediatric nephrotic syndrome based on diverse clinical guidelines and individual clinical judgment. To address this, the Korean Society of Pediatric Nephrology has developed an evidence-based guideline specifically tailored to the Korean healthcare system. This guideline provides recommendations for the diagnosis and management of steroid-sensitive nephrotic syndrome in children under the age of 18 years.

Keywords: Child; Evidence-based practice; GRADE approach; Nephrotic syndrome; Practice guideline

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Introduction

Pediatric nephrotic syndrome is a clinical condition characterized by severe proteinuria, hypoalbuminemia, hyperlipidemia, and generalized edema. It is diagnosed based on a urine protein-to-creatinine ratio of 2.0 mg/mg (200 mg/mmol) or higher, along with a serum albumin concentration of 3.0 g/dL or lower [1]. The condition primarily affects children between the ages of 2 and 6 years, with most cases showing a positive response to standard oral steroid therapy. Nevertheless, a substantial number of patients may experience disease relapse during childhood. Nephrotic syndrome is a prevalent glomerular disease in children, yet the most recent clinical guideline for its management in Korea was published in 2009 by the Korean Society of Pediatric Nephrology (KSPN). As a result, the diagnosis and treatment of nephrotic syndrome in Korea have largely followed international guidelines [1,2]. To improve management, the KSPN has developed an evidence-based guideline specifically tailored to the Korean healthcare system, providing recommendations for the diagnosis and treatment of steroid-sensitive nephrotic syndrome (SSNS) in children under 18 years of age.

Methods

The practice guideline was primarily developed by adapting existing national and international clinical practice guidelines. The main sources of evidence included prior recommendations and recent research findings, which were systematically reviewed and adapted to the Korean healthcare setting. The GRADE (Grading of Recommendations Assessment, Development, and Evaluation) methodology was used to assess the quality of evidence and formulate the recommendations. The KSPN Practice Recommendations Committee members, along with practice recommendations methodology experts (Supplementary Materials, available online), were actively involved in the development process. External nephrology experts and society members also contributed by identifying key clinical questions concerning the treatment of SSNS. The adaptation process focused on the practice guidelines published since 2015. Literature searches were conducted from 1 year before the publication of each selected guideline up to August 2023 to ensure the incorporation of the most current evidence.

Three practice recommendations, including the Kidney

Disease: Improving Global Outcomes (KDIGO), International Pediatric Nephrology Association (IPNA), and Japanese Society of Pediatric Nephrology, were utilized to formulate recommendations for five topics encompassing a total of six questions [1-3]. Detailed information on key processes related to the development of the recommendations, including the selection of clinical questions, literature review, evidence evaluation and synthesis, determination of the grade of recommendations and quality of evidence, recommendations drafting, and consensus formulation, can be found in the [Supplementary Materials](#) (available online). These recommendations consider the potential challenges of implementing them in real-world medical practice by considering patient values and preferences, as well as barriers and facilitators. They also suggest strategies to address these obstacles, ensuring a balanced approach that is tailored to the clinical setting and other resource availability in Korea. All members of the development committee submitted conflict of interest disclosure statements before participating in the practice recommendations development to identify and address any potential financial or nonfinancial conflicts of interest.

Key questions and recommendations

All key questions and recommendations for SSNS in children and adolescents are presented in [Table 1](#). Detailed explanations and supporting evidence for each recommendation are provided below.

Key Question 1: Is deflazacort more effective than prednisolone in terms of inducing remission and preventing relapse, with fewer side effects, in children diagnosed with primary nephrotic syndrome?

Background

Nephrotic syndrome has various etiologies, but in children, it is mostly of primary origin [4]. The first-line therapy for primary nephrotic syndrome is oral glucocorticoids [2]. Glucocorticoids are effective treatments, but they also cause numerous drug-related side effects. These side effects include elevated blood glucose levels, increased blood pressure, decreased bone mineral density, growth retardation in children, weight gain, and a Cushingoid appearance. Among the glucocorticoids used worldwide for the treatment of nephrotic syndrome, prednisolone is commonly prescribed. However,

Table 1. Summary of recommendations

Topic	Recommendations	Strength of recommendation	Quality of evidence
First-line drugs for the treatment of SSNS			
Choice of first-line drug	1. In pediatric patients with primary nephrotic syndrome, there is no significant difference in remission rates and drug-related side effects between deflazacort and prednisolone. Therefore, either drug may be selected based on clinical circumstances and medication costs. [Clinical considerations] While deflazacort and prednisolone have similar remission rates and side effect profiles in pediatric primary nephrotic syndrome, some studies suggest that deflazacort may be associated with a lower relapse rate. However, due to the higher cost of deflazacort, treatment decisions should consider the values and preferences of both patients and guardians.	Weak	Very low
First-line drug duration	2. The recommended initial treatment for pediatric nephrotic syndrome patients is to administer oral prednisolone for 8–12 weeks. Additional long-term use is not advised. [Clinical considerations] For the initial treatment of pediatric nephrotic syndrome, oral prednisolone should be given for 8–12 weeks. The recommended dosage is 60 mg/m ² or 2 mg/kg (maximum 60 mg/day) daily for 4–6 weeks, followed by 40 mg/m ² or 1.5 mg/kg (maximum 40 mg/day) every other day for an additional 4–6 weeks. Further tapering after alternate-day treatment with oral prednisolone is not recommended.	Strong	Low
First-line drug dosage	3-1. It is recommended to administer oral prednisolone at a daily dose of 60 mg/m ² /day or 2 mg/kg/day (maximum 60 mg/day) to pediatric patients with nephrotic syndrome at the onset of the condition.	Strong	Very low
	3-2. It is recommended to administer oral prednisolone at a daily dose of 60 mg/m ² /day or 2 mg/kg/day (maximum 60 mg/day) to pediatric patients with nephrotic syndrome during relapse.	Strong	Very low
Second-line drugs for the treatment of SSNS			
Choice of second-line drugs	4. Mycophenolate mofetil is a viable option for maintaining remission in pediatric patients with steroid-dependent or frequently relapsing nephrotic syndrome. [Clinical considerations] In patients at risk for leukopenia, infections, gastrointestinal disturbances, and other side effects, it is essential to carefully monitor for potential drug-related side effects when using mycophenolate mofetil.	Weak	Low
	5. Cyclophosphamide is often utilized to decrease relapses and sustain remission in children and adolescents suffering from frequently relapsing or steroid-dependent nephrotic syndrome. [Clinical considerations] It is advisable to inform patients and their guardians about the potential side effects of the medication, particularly the risk of gonadal toxicity in patients undergoing puberty. Close monitoring of side effects should be conducted within the therapeutic range to avoid exceeding the maximum drug concentration.	Weak	Low

SSNS, steroid-sensitive nephrotic syndrome.

studies have suggested that deflazacort, a synthetic oxazoline derivative of prednisolone, has fewer side effects compared to other corticosteroids [5]. As a result, deflazacort is commonly used in Korea. Despite this preference, the evidence supporting this claim is less than convincing [1]. This study aims to analyze whether deflazacort has fewer drug-related side

effects, lower relapse frequencies, and higher remission rates compared to prednisolone in children diagnosed with primary nephrotic syndrome. The goal is to recommend the most appropriate drug choice for this condition.

Recommendation

In pediatric patients with primary nephrotic syndrome, there is no significant difference in drug-related side effects and remission rates between deflazacort and prednisone. Therefore, either deflazacort or prednisone can be selected based on clinical situation and drug costs. (Grade of recommendation: Weak, Quality of evidence: Very low)

[Clinical considerations]

- While deflazacort and prednisolone have similar remission rates and side effect profiles in pediatric primary nephrotic syndrome, some studies suggest that deflazacort is associated with a lower relapse rate.
- However, due to the higher cost of deflazacort, treatment decisions should consider the values and preferences of both patients and guardians.

Summary of evidence

There are three randomized studies that compare the drug-related side effects and effectiveness of deflazacort and prednisone in pediatric patients with nephrotic syndrome. Broyer et al. [6] conducted a study involving 40 pediatric patients diagnosed with steroid-dependent nephrotic syndrome (SDNS). Prednisone was administered at a daily dose of 60 mg/m² until remission was achieved, after which it was given every other day for 6 weeks. The dosage was then gradually tapered to 15–20 mg/m² over a period of more than 1 year. Deflazacort was administered at a dosage 1.2 times higher than the standard schedule. Additionally, changes in height growth, body weight, bone mineral density, blood glucose levels, and the number of relapses were compared over a 1-year period. Agarwal et al. [7] conducted a study on 42 children who were newly diagnosed with nephrotic syndrome. The children were treated with deflazacort and prednisone, and the researchers compared the changes in bone mineral density and blood glucose levels after 3 and 6 months of treatment. They also assessed the remission rates at the 2nd and 6th weeks of treatment [7]. Singhal et al. [8] conducted a study on 25 pediatric patients who were newly diagnosed with nephrotic syndrome or had infrequent relapses. In cases of initial treatment with prednisone, a dosage of 2.0 mg/kg was administered daily for 6 weeks, followed by a tapering regimen to 1.5 mg/kg every other day for an additional 6 weeks. In cases of relapse, prednisone was administered daily at a dosage of 2.0 mg/kg for 3 consecutive days until the urine sediment showed trace amounts or lower. Subsequently, the dosage was tapered to 1.5 mg/kg every other day for a duration of 4 weeks. Deflazacort was administered at a dosage 1.2 times

higher than the standard schedule. Height growth, weight changes, blood glucose levels, remission rates, and relapse rates were compared between the two drug treatments after a 6-month treatment period.

In the study by Agarwal et al. [7], the remission rate at 2 weeks was 92.8% for the deflazacort group and 78.5% for the prednisolone group. By 6 weeks, both groups had the same remission rate of 92.8% [7]. In a study by Singhal et al. [8], there was no significant difference in the remission rate at 4 weeks between the group taking deflazacort and the group taking prednisolone (100% vs. 84.6%, $P=0.480$).

In the study by Broyer et al. [6], a lower proportion of patients with SDNS treated with deflazacort experienced a relapse during the 1-year treatment period, compared to those treated with prednisolone (40% vs. 90%, $P=0.002$). However, Singhal et al. [8] reported no significant difference in the relapse rate over a 6-month period between the groups treated with deflazacort and prednisolone (9.1% vs. 27.3%, $P=0.586$). In a study conducted by Broyer et al. [6], it was found that the group treated with deflazacort had a lower number of relapses during a 1-year period compared to the group treated with prednisolone (0.9 ± 1.4 vs. 2.8 ± 1.8 , $P<0.002$).

A study by Broyer et al. [6] compared the height growth between patient groups taking deflazacort and prednisolone over a 1-year period and found no significant difference (4.1 ± 1.2 cm vs. 4.4 ± 1.4 cm). In contrast, a study conducted by Singhal et al. [8] found that the group taking deflazacort experienced a significantly greater increase in height compared to the group taking prednisolone over a 6-month period (2.13 ± 0.50 cm vs. 1.44 ± 0.45 cm, $P=0.003$).

In terms of weight change, the study by Broyer et al. [6] demonstrated that patients administering deflazacort experienced a lesser increase in weight over a 1-year period compared to those taking prednisolone (1.7 ± 2.8 kg vs. 3.9 ± 4.1 kg, $P=0.06$). In contrast, Singhal et al. [8] found no significant difference in weight gain between patients treated with deflazacort and those treated with prednisolone over a 6-month period (1.36 ± 0.96 kg vs. 1.38 ± 0.56 kg, $P=0.958$).

In terms of bone mineral density, the study by Broyer et al. [6] revealed that patients treated with deflazacort experienced a 6% reduction in bone density from baseline, whereas those receiving prednisolone showed a 12% decrease. However, there was no statistically significant difference between the two groups [6]. In the study by Agarwal et al. [7], patients treated with deflazacort exhibited a 70.59% reduction in bone density

after 3 months compared to baseline, whereas those receiving prednisolone experienced a 73.3% decrease. Between 3 and 6 months, patients treated with deflazacort experienced an additional 11.6% decrease in bone density compared to those on prednisolone, who had a further 20% decrease. However, this difference was not statistically significant.

The study by Broyer et al. [6] did not find any significant differences in fasting blood glucose levels between the two drugs at 3, 6, 9, and 12 months. In the study by Agarwal et al. [7], there were no significant changes in fasting blood glucose levels observed before and after treatment with either drug. Similarly, in the study by Singhal et al. [8], all patients maintained normal blood glucose levels consistently throughout the study in all patients treated with the two drugs.

No randomized controlled trials (RCTs) comparing the incidence of toxic epidermal necrolysis or Stevens-Johnson syndrome between deflazacort and prednisolone could be found. However, a single-center retrospective study found that out of 54 pediatric nephrotic syndrome patients treated with deflazacort, three developed toxic epidermal necrolysis. In contrast, none of the 40 patients treated with prednisolone experienced this side effect [9].

There exists a cost disparity between deflazacort and prednisolone. Prednisolone 5 mg tablets are priced at approximately Korean won 16 per tablet under insurance coverage, whereas deflazacort 6 mg tablets, marketed under multiple brand names, are on average 10 to 15 times more expensive per tablet.

In conclusion, the literature review indicates that there is no significant difference between deflazacort and prednisolone in terms of side effects, including weight gain, blood glucose levels, and bone mineral density, as well as remission rates in pediatric nephrotic syndrome patients. While deflazacort seemed to be comparable to or slightly superior to prednisolone in terms of relapse rates and height growth, the evidence supporting this conclusion was derived from small-scale studies with variations in patient groups and dosing regimens. One study found that deflazacort resulted in fewer relapses compared to prednisolone [6]. Hence, it is challenging to establish a clear superiority between the two drugs in the treatment of pediatric nephrotic syndrome. However, due to the higher cost of deflazacort, treatment decisions should consider the values and preferences of patients and guardians.

Key Question 2: Is an 8- to 12-week course of prednisolone in the initial treatment of pediatric nephrotic syndrome as clinically safe and effective as longer courses?

Background

Nephrotic syndrome is a prevalent glomerular disease in children. While its incidence is relatively low, ranging from 1 to 7 cases per 100,000 children annually, the condition is characterized by the significant challenges of frequent relapses and the adverse effects associated with long-term medication. Particularly in pediatric patients, remission is achieved in over 90% of cases with oral steroid treatment. However, 60% to 90% of these patients may experience at least one relapse. Given that recurrent nephrotic syndrome often requires prolonged steroid use, which can lead to side effects, optimizing treatment strategies to minimize relapses has been a key focus of clinical research. Current guidelines, including KDIGO (2021) and IPNA (2023), recommend an 8-week (4+4 weeks) or 12-week (6+6 weeks) course of oral prednisolone as the standard remission induction therapy for newly diagnosed pediatric nephrotic syndrome [1,2]. These clinical practice recommendations aim to reassess the medical evidence supporting current treatment strategies by reviewing key clinical studies that have influenced existing guidelines, as well as recently published research. Particularly, it seeks to determine the optimal duration of steroid therapy for the initial episode of pediatric nephrotic syndrome.

Recommendation

It is recommended to initiate treatment for pediatric nephrotic syndrome with oral prednisolone for 8 to 12 weeks. Prolonged treatment beyond this duration is not advised. (Grade of recommendation: Strong, Quality of evidence: Low)

[Clinical considerations]

- In the initial treatment of pediatric nephrotic syndrome, an 8-week (or 12-week) oral prednisolone regimen involves administering 60 mg/m² or 2 mg/kg (maximum 60 mg/day) daily for 4 weeks (or 6 weeks), followed by 40 mg/m² or 1.5 mg/kg (maximum 40 mg/day) on alternate days for 4 weeks (or 6 weeks).
- Additional tapering beyond the alternate-day oral prednisolone regimen is not recommended.

Summary of evidence

Bagga et al. [10] conducted a randomized study on 45 pediatric patients with nephrotic syndrome and found no significant differences in relapse frequency, incidence of frequent relapses, or steroid dependence between the 8-week standard

steroid treatment group and the 16-week extended steroid treatment group. Teeninga et al. [11] conducted a randomized, double-blind, placebo-controlled study involving 150 pediatric patients newly diagnosed with nephrotic syndrome. The study revealed no significant difference in relapse rates between the 12- and 24-week treatment groups (77% vs. 80%), and a comparable incidence of frequent relapses (45% vs. 50%) [11]. Similarly, Sinha et al. [12] conducted a 1:1 randomized, placebo-controlled trial with 181 children newly diagnosed with nephrotic syndrome, comparing 12- and 24-week treatment durations. The study found no significant difference in relapse frequency between the two groups. Yoshikawa et al. [13] conducted a multicenter randomized study and found no significant differences between the 8- and 24-week treatment groups in terms of time to first relapse or incidence of frequent relapses. Webb et al. [14] conducted a randomized, double-blind, placebo-controlled study with 237 pediatric nephrotic syndrome patients. The study revealed no significant differences in time to first relapse or incidence of frequent relapses during a minimum follow-up period of 24 months. In contrast, Jamshaid et al. [15] conducted a randomized study involving 150 patients and found that the group receiving 12 weeks of treatment had a significantly lower relapse frequency over 1-year posttreatment compared to the group receiving 16 to 24 weeks of treatment (62.7% vs 94.7%, $P < 0.001$).

Bagga et al. [10] conducted a randomized study involving 45 pediatric nephrotic syndrome patients. The study found that the long-term 16-week steroid treatment group had a significantly higher incidence of steroid toxicity, including obesity, hypertension, and Cushingoid appearance, compared to the 8-week standard steroid treatment group (0% vs. 41%, $P < 0.01$). However, four larger randomized studies [10–13] found no significant difference in the occurrence of steroid-related side effects between standard short-term and long-term treatment durations.

Among the six randomized studies, four were conducted in Asian countries (Pakistan, India, and Japan), and two in European countries (the United Kingdom and the Netherlands), which adequately accounted for potential variables related to ethnicity. A literature review confirmed that in pediatric patients with nephrotic syndrome, 8 to 12 weeks of steroid treatment at the onset of the condition, compared to additional long-term treatment, showed no significant difference in relapse frequency or the incidence of frequent relapses. Additionally, it reduced the cumulative steroid dose. In conclusion, current international

guidelines widely recommend 8 to 12 weeks of steroid therapy as the optimal initial treatment for pediatric patients with nephrotic syndrome, without the need for additional long-term therapy. This approach minimizes unnecessary drug burden, decreases the occurrence of drug-related side effects, improves the quality of life for patients and caregivers, and lowers healthcare costs. Moreover, studies have shown no significant differences in steroid side effects between daily administration of oral prednisolone and divided doses. However, a once-daily regimen may enhance medication adherence.

Key Question 3-1: Is the administration of an initial dose of prednisolone at 60 mg/m²/day or 2 mg/kg/day more effective and safer than lower doses in the initial management of pediatric nephrotic syndrome?

Background

For many years, an initial dose of 60 mg/m²/day or 2 mg/kg/day of prednisolone has been the standard treatment for pediatric nephrotic syndrome during initial diagnosis or relapse [15,16] and has become the standard treatment [1]. Prednisolone is an effective treatment for nephrotic syndrome, but it can lead to various complications [17]. Efforts to minimize these complications have resulted in the establishment of the current standard treatment. Despite these efforts, complications still occur, and there is a lack of comprehensive exploration into further dose-reduction strategies. Therefore, this review aims to investigate the feasibility of reducing steroid dosage in the initial treatment phase for pediatric nephrotic syndrome patients compared to the standard treatment dose.

Recommendation

It is recommended to administer oral prednisolone at a dose of 60 mg/m²/day or 2 mg/kg/day (maximum 60 mg/day) for pediatric patients with newly diagnosed nephrotic syndrome. (Grade of recommendation: Strong, Quality of evidence: Very low)

Summary of evidence

Through a literature search, the only RCT finally selected was the study conducted by Hiraoka et al. [18]. In this study, there was no significant difference in the remission rate between patients receiving prednisolone at a dose of 60 mg/m²/day compared to those receiving 40 mg/m²/day. However, the cumulative and sustained remission rates were higher in the 60 mg/m²/day group than in the 40 mg/m²/day group. Conversely,

the group treated with 60 mg/m²/day had a higher incidence of moon face, obesity, glaucoma, mental disorders, hirsutism, and acne compared to the group treated with 40 mg/m²/day.

In the literature reviewed, it was found that a dose of 60 mg/m²/day was clinically effective in maintaining remission in pediatric nephrotic syndrome. However, the frequency of steroid side effects was higher when compared to using a dose of 40 mg/m²/day. Due to a lack of sufficient evidence, there was not enough support to justify changing the current standard treatment. Thus, the recommendation was to maintain the existing treatment approach, and its grade was rated as strong due to its clinical significance.

Key Question 3-2: Is the use of 60 mg/m²/day or 2 mg/kg/day of prednisolone in the initial treatment of relapsed pediatric nephrotic syndrome safer and more effective than using a lower dose?

Background

This study aims to investigate the feasibility of reducing steroid dosage from the standard treatment dose in cases of relapses in pediatric nephrotic syndrome patients.

Recommendation

It is recommended to administer oral prednisolone at a dose of 60 mg/m²/day or 2 mg/kg/day (maximum 60 mg/day) for pediatric patients with relapsing nephrotic syndrome. (Grade of recommendation: Strong, Quality of evidence: Very low)

Summary of evidence

A literature search identified only two RCTs conducted by Sheikh et al. [19] and Borovitz et al. [20]. Sheikh et al. [19] conducted a randomized study involving 60 pediatric patients with SSNS, comparing low-dose (1 mg/kg/day) and standard-dose (2 mg/kg/day) prednisolone or prednisone. Borovitz et al. [20] conducted a study involving 30 pediatric patients with SSNS, comparing the administration of 2, 1.5, and 1 mg/kg/day of prednisolone or prednisone through randomization.

In the study by Sheikh et al. [19], there was no significant difference in the time to remission and the relapse rate between the 2 and 1 mg/kg/day treatment groups. In the study by Borovitz et al. [20], only the 2 and 1.5 mg/kg/day treatment groups showed a significant difference in the time to remission ($P=0.04$), while there was no significant difference between the 2 or 1 mg/kg/day and 1.5 or 1 mg/kg/day in terms of the time to

remission. In addition, one patient from each of the 1.5 and 1 mg/kg/day groups failed to achieve remission initially but responded after the dose was increased to 2 mg/kg/day [20]. The study by Borovitz et al. [20] evaluated the cumulative steroid dose. The groups treated with prednisolone or prednisone at 1 or 1.5 mg/kg/day had significantly lower cumulative steroid doses compared to those treated with 2 mg/kg/day.

In the analysis of relevant evidence, no significant difference was observed in the remission rate or time to remission between standard and lower-dose treatment groups in relapsed pediatric nephrotic syndrome. Despite the higher cumulative dose in the standard treatment group, the study's small sample size and the limited number of related studies posed challenges in assessing the benefit-harm balance. Consequently, it was determined that the evidence was inadequate to warrant a modification of the current standard treatment, and it was advised to continue with the existing protocol. Due to its clinical significance, the recommendation was given a strong grade.

Key Question 4: Does mycophenolate mofetil reduce relapse rates and cause fewer side effects compared to calcineurin inhibitors in pediatric nephrotic syndrome patients with steroid dependency or frequent relapses?

Background

Mycophenolate mofetil (MMF) is a commonly used immunosuppressant in solid organ transplantation. It functions by inhibiting purine synthesis, leading to the suppression of T lymphocytes, B lymphocytes, and mesangial proliferation. Notably, MMF is considered to be free of nephrotoxicity, making it an appealing option for reducing steroid usage in primary glomerular diseases [21]. According to the KDIGO (2021) guidelines, oral cyclophosphamide (CPM) and levamisole are recommended as second-line immunosuppressants for patients with frequently relapsing nephrotic syndrome (FRNS). Calcineurin inhibitors (CNIs) such as cyclosporine (CsA) and tacrolimus (Tac), MMF, and rituximab (a monoclonal antibody targeting the CD20 antigen) are suggested as second-line options for SDNS. The IPNA (2023) recommendations also recommend CNIs, CPM, levamisole, MMF, and rituximab as second-line immunosuppressants. It is important to consider the preferences of the family and doctors, as well as the potential risks associated with drug-related complications when choosing the appropriate medication [1,2]. These clinical practice recommendations aim to compare the clinical efficacy and safety of MMF and CNIs,

which are currently used as second-line immunosuppressants. The comparison is based on clinical studies and recent trials that have informed the pediatric nephrotic syndrome treatment guidelines.

Recommendation

Mycophenolate mofetil is a viable option for maintaining remission in pediatric patients with steroid-dependent or frequently relapsing nephrotic syndrome. (Grade of recommendation: Weak, Quality of evidence: Low)

[Clinical considerations]

- In patients at risk for leukopenia, infections, gastrointestinal disturbances, and other side effects, it is essential to carefully monitor for potential drug-related side effects when using mycophenolate mofetil.

Summary of evidence

A total of six studies were identified through a literature search, comprising two RCTs [22,23] and four other studies [24-27]. Dorresteijn et al. [22] conducted a randomized study involving 24 pediatric patients with nephrotic syndrome under 18 years of age who experienced frequent relapses despite receiving CPM treatment at six hospitals in the Netherlands and Belgium. The study compared the efficacy of MMF treatment with the standard treatment of CsA over a 12-month period. The researchers analyzed the frequency of nephrotic syndrome relapses and drug-related side effects in both treatment groups [22]. Gellermann et al. [23] conducted an RCT at 15 pediatric nephrology centers in Germany. The study involved 120 patients with FRNS, divided into two groups: one group received MMF treatment for 1 year followed by CsA for another year, while the other group received the reverse sequence (CsA first followed by MMF). The study compared relapse rates and drug-related side effects between the two groups. Wang et al. [26] conducted a prospective study at a single institution in China involving 72 pediatric patients with nephrotic syndrome who were steroid-dependent or frequently relapsing. The study compared the relapse rates and drug-related side effects after 12 months of treatment with either MMF or Tac. Jin et al. [27] conducted a retrospective study at a single institution in China, examining the medical records of 56 patients with steroid-dependent or steroid-resistant nephrotic syndrome who were treated with second-line immunosuppressants. The study compared the treatment outcomes of MMF and Tac. Fujinaga et al. [24] conducted a prospective study at a single institution in Japan in-

volving 29 SDNS patients. These patients received either MMF or CsA as maintenance therapy following a single dose of rituximab. The study aimed to compare the treatment failure rate and remission maintenance rates between the MMF and CsA groups. Lim et al. [25] conducted a retrospective study at a single institution in Korea, comparing the relapse rates between 11 patients receiving MMF and 12 patients receiving CsA for SDNS.

Relapse rates have been reported in four studies. Dorresteijn et al. [22] reported a relapse rate of 0.83 relapses per year in the MMF treatment group and 0.08 relapses per year in the CsA treatment group. Gellermann et al. [23] observed that in the first year, the relapse rate was higher in the MMF treatment group compared to the CsA treatment group (1.10 vs. 0.24, $P=0.03$). However, in the subsequent year, there was no statistically significant difference between the two groups (0.40 vs. 0.20, $P=0.14$). They also noted that 64% of patients in the MMF group and 85% of patients in the CsA group experienced no relapses. Wang et al. [26] found no significant difference in relapse rates between the two groups during the first 6 months and the subsequent 6 months. However, both groups showed a decrease in relapse rates from 2.56 relapses/year in the MMF group and 2.39 relapses/year in the Tac group before treatment to 0.72 relapses/year in the MMF group and 0.41 relapses/year in the Tac group at 6 months. These rates further decreased to 0.67 relapses/year and 0.42 relapses/year in the following 6 months. Lim et al. [25] reported a reduction in the relapse rate from 3.4 relapses per year before treatment to 0.2 relapses per year after MMF treatment in a cohort of 10 patients with SDNS.

Treatment response has been reported in two studies. In the study by Jin et al. [27], 17 patients with SDNS and three with steroid-resistant nephrotic syndrome achieved complete remission in 75% and partial remission in 25% with MMF treatment. In comparison, 10 patients with SDNS and two with steroid-resistant nephrotic syndrome reached complete remission in 58.3% and partial remission in 33.3% with Tac treatment. In the study by Fujinaga et al. [24], both the MMF and CsA groups demonstrated a reduced relapse rate following rituximab administration. However, treatment failure was observed in 43.8% of the MMF group and 15.4% of the CsA group. Additionally, the remission maintenance rate was significantly higher in the CsA group compared to the MMF group.

Three studies investigated the occurrence of drug-related side effects, namely hirsutism and gingival hyperplasia. Dorresteijn et al. [22] found that three out of eight patients in the CsA treatment group developed hirsutism, while six out

of 10 patients experienced gingival hyperplasia. In a study by Gellermann et al. [23], eight cases of hirsutism and four cases of gingival hyperplasia were reported in the CsA treatment group. Fujinaga et al. [24] observed hirsutism in the majority of patients in the CsA treatment group. Three studies also investigated the drug-related side effects of leukopenia. Dorresteijn et al. [22] found no cases of leukopenia in either the MMF or CsA treatment groups. Gellermann et al. [23] reported a single case of leukopenia in the group receiving CsA treatment. Wang et al. [26] reported one case of leukopenia in each of the MMF and CsA treatment groups.

In conclusion, the use of MMF for maintaining remission in pediatric nephrotic syndrome that is steroid-dependent or frequently relapsing has been shown to be clinically effective, as recommended by various international guidelines. MMF has been found to have fewer drug-related side effects when compared to CsA or Tac. However, the evaluation of the benefit-harm balance is limited by the absence of large-scale RCTs that directly compare the efficacy and safety of CNIs and MMF in pediatric patients with steroid-dependent or FRNS.

Key Question 5: Is cyclophosphamide more effective and safer than calcineurin inhibitors in reducing relapse in pediatric and adolescent patients with frequently relapsing or steroid-dependent nephrotic syndrome?

Background

CPM is a second-line drug, classified as a steroid-sparing agent, that is utilized to reduce the reliance on steroids in patients with FRNS or SDNS. Compared to other second-line drugs, this medication is relatively cost-effective and has a high likelihood of achieving remission with a short treatment duration of 8 to 12 weeks. Due to its efficacy and affordability, it has been a commonly used treatment for over 50 years and continues to be recommended in international guidelines for reducing frequent relapses or relapses in SDNS [1]. However, serious side effects such as leukopenia, gonadal toxicity, and hemorrhagic cystitis may occur with the use of this drug, so it is crucial to carefully weigh the benefits against the harms when making medication choices. It is imperative to engage in comprehensive discussions with both the patients and guardians regarding these potential adverse effects [28]. Furthermore, there is a paucity of data on RCTs that have directly compared the effectiveness and adverse effects of CPM with alternative second-line medications. The practice guideline aims to review the

randomized clinical trial literature comparing the effects and side effects of CNIs and CPM, two commonly used second-line agents in pediatric and adolescent patients with FRNS or SDNS. The goal is to provide evidence-based recommendations for using CPM in the treatment of this condition.

Recommendation

Cyclophosphamide is often utilized to decrease relapses and sustain remission in children and adolescents suffering from frequently relapsing or steroid-dependent nephrotic syndrome. (Grade of recommendation: Weak, Quality of evidence: Low)

[Clinical considerations]

- It is important to obtain informed consent from both the patients and guardians regarding potential drug-related side effects, particularly the risk of gonadal toxicity in adolescent patients, before administering the medication. Monitoring for side effects should be conducted while ensuring that the drug does not exceed the maximum concentration level.

Summary of evidence

A literature search identified two RCTs that examined the efficacy of CPM and CNIs in reducing relapse rates and managing side effects in patients with SSNS who experience frequent relapses or are dependent on steroids [29,30]. In a study conducted by Ponticelli et al. [29], 55 patients with SSNS were randomly assigned to two treatment groups following remission induction with steroids. One group (25 patients) received CPM at a dose of 2.5 mg/kg/day for 8 weeks, while the other group (30 patients) received CsA at a dose of 6 mg/kg/day for 9 months, with a tapering regimen over 3 months and discontinuation of treatment after 12 months. The study evaluated the efficacy of these treatments in reducing relapse rates at 9 months and 2 years of follow-up. At 9 months, 64% of patients in the CPM group achieved complete remission and 4% achieved partial remission. In the CsA group, 74% achieved complete remission, and 12% achieved partial remission. There was no statistically significant difference between the two groups in terms of remission rates. After 2 years, 68% of patients in the CPM group and 20% in the CsA group remained free from relapse, suggesting that the CPM group exhibited a more sustained remission. In a study conducted by Wang et al. [30], 51 patients diagnosed with FRNS or SDNS were randomly assigned to three treatment groups: rituximab, Tac, and CPM, with 17 patients in each group. Among the three groups, the relapse rates after 1 year between the Tac and CPM groups, the two groups of interest for this practice guideline, were compared. The median relapse

rate in the CPM group was 1.2, while in the Tac group, it was 1.1, showing no significant difference between the two groups. The 1-year relapse-free survival rates were 11.8% in the CPM group and 64.7% in the Tac group, indicating a trend toward higher relapse-free survival in the CNI treatment group. However, the exact p-value was not provided in the study. In summary, the findings from the two RCTs suggest that CPM is as effective as or even more effective than CNIs in reducing relapses.

In the study conducted by Ponticelli et al. [29], the researchers evaluated common side effects of both medications, focusing on kidney function and diastolic blood pressure. During the treatment period, there were no significant changes observed in serum creatinine levels or average diastolic blood pressure in either the CPM or CsA groups. In terms of specific side effects, 12 patients in the CPM group experienced leukopenia, leading to a reduction in drug dosage. However, they subsequently recovered from this adverse event. In the CsA group, four patients experienced a greater than 30% increase in serum creatinine levels, necessitating a reduction in dosage. However, their creatinine levels returned to baseline after the dosage adjustment. In summary, both groups did not report any significant adverse effects from the drug. In a study by Wang et al. [30], the incidence of infections was compared between the CPM group, which had an average of 2.6 infections per patient, and the Tac group, which had an average of 1.6 infections per patient. The results indicated a significantly higher rate of infections in the CPM group [30].

These two studies have confirmed that in patients with FRNS or SDNS, CPM offers comparable or even superior relapse reduction effects when compared to CNIs such as CsA or Tac. However, the number of comparative studies and the sample sizes in the existing literature are limited. Furthermore, observational studies examining the efficacy of CPM as a standalone treatment for reducing relapse in patients with nephrotic syndrome have yielded less favorable outcomes, thereby hindering the assessment of the medication's benefit-harm profile [31-34]. To assess potential harms, it is crucial to consider the latest recommendations outlined in the IPNA guidelines [1]. The most frequent side effect of CPM is leukopenia. It is advisable to monitor the complete blood count every 2 weeks, and if the white blood cell count drops below 4,000/ μ L, the absolute neutrophil count falls below 1,500/ μ L, or the platelet count falls below 50,000/ μ L, the medication should be stopped. Once the blood cell counts return to normal, the dosage should be reduced and reintroduced at a lower level.

Gonadal toxicity is influenced by factors such as the patient's sex, age, and cumulative drug dose, and the most fundamental principle is to not exceed the total cumulative dose of 168 mg/kg. It is advisable to refrain from treatment during puberty, and CPM should be avoided in the first 10 weeks of pregnancy due to its teratogenic potential.

Overall, considering the benefits and harms, CPM can be considered for use in patients with FRNS or SDNS to reduce relapses and maintain remission. However, current evidence is insufficient to conclude that it is more effective or safer than CNIs. It is advisable to administer CPM to prepubertal patients, with thorough education provided to both patients and guardians regarding the potential benefits and harms. Monitoring of drug concentration levels should be conducted within safe limits, and close observation of potential side effects is essential.

Conclusions

The practice guideline is designed to offer evidence-based recommendations for pediatricians managing nephrotic syndrome in children. The goal is to support clinical decision-making in order to enhance patient survival rates, preserve kidney function, and minimize the occurrence of drug-related side effects. The practice guideline provides five recommendations for managing SSNS in pediatric and adolescent patients. Not all recommendations are supported by high certainty of the evidence, underscoring the importance of conducting well-designed and rigorous RCTs. However, the development of this practice guideline is crucial as it provides a suitable clinical framework for the healthcare setting in Korea.

Conflicts of interest

HKL, MHC, JYK, JHL, HGK, EP, and JSS are editorial board members of the journal but were not involved in the peer reviewer selection, evaluation, or decision process of this article. No potential conflicts of interest relevant to this article were reported.

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Author contributions

Conceptualization: all authors

Data curation: all authors

Investigation: all authors

Methodology: DAP

Supervision: HC

Writing—original draft: all authors

Writing—review & editing: HKL

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Supplementary Material

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