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GUIDELINE

Clinical practice guideline for pediatric idiopathic nephrotic syndrome 2013: medical therapy

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Introduction

Nephrotic syndrome is a disorder characterized by severe proteinuria, hypoproteinemia, and generalized edema resulting from damage to the glomerular basement membrane. In Western countries, nephrotic syndrome affects 2 of 100,000 children per year [1]. In Japan, approximately 1,300 new cases per year of pediatric nephrotic syndrome are reported to the Medical Aid for Specific Chronic Disease of Children and the disease develops in 5 of 100,000 children per year. Approximately 90 % of the cases of pediatric nephrotic syndrome are idiopathic, or of unknown cause. The first-line treatment for an initial episode of pediatric idiopathic nephrotic syndrome is oral steroid therapy, which leads to remission in approximately 80 % of cases (steroid-sensitive nephrotic syndrome) [2]. However, 80 % of children with steroid-sensitive nephrotic syndrome experience one or more relapses, [3] and 50 % of these children have frequent relapses [4]. Those with frequently relapsing nephrotic syndrome are prone to suffer steroid-induced side effects such as obesity, growth impairment, hypertension, diabetes mellitus, osteoporosis, and adrenal insufficiency. Many cases of steroid-resistant nephrotic syndrome, where steroids are ineffective, progress to renal failure.

Pediatric idiopathic nephrotic syndrome is a very important disease in the field of pediatric nephrology.

The Scientific Committee in the Japanese Society for Pediatric Nephrology previously published the "Clinical Practice Guideline for Pediatric Idiopathic Nephrotic Syndrome" (2013). This is the English translation from the "Medical Therapy" portion of the guideline.

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The Japanese Society for Pediatric Nephrology published the "Clinical Practice Guideline for Medical Treatment of Pediatric Idiopathic Nephrotic Syndrome (version 1.0) (in Japanese)" in 2005. The guideline, aiming to support appropriate decisions and treatment for pediatric idiopathic nephrotic syndrome, illustrated standard regimens of medical treatment of pediatric idiopathic nephrotic syndrome at that time and has been credited with standardization and optimization of the treatment. In 2011, 6 years after the publication, the need to revise the guideline became recognized against the background of changes in care settings, including the introduction of rituximab. Additionally, the development of guidelines covering general therapies such as management of edema, diet therapy, exercise limitations, side-effect management of steroids, and vaccination was required.

The Scientific Committee of the Japanese Society for Pediatric Nephrology established a new operation to revise the guideline and published the "Clinical Practice Guideline for Pediatric Idiopathic Nephrotic Syndrome 2013 (in Japanese)" (Shindan To Chiryo Sha, Inc., Tokyo, Japan) on September 25, 2013. The committee herein published the guideline in English, with an aim to introduce it to pediatricians around the world.

This clinical practice guideline was developed in accordance with the "Minds Handbook for Guideline Development 2007" published by the Medical Information Network Distribution Service (Minds) [5]. The guideline development committee members were pediatric nephrologists and nephrology internists with abundant experience in treating idiopathic pediatric nephrotic syndrome. Committee members were appointed from all over Japan, and included JMLA Health Sciences information professionals, distinguished with expertise on the development of clinical practice guidelines. Also on the committee were a patient and his guardian. The patient and guardian participated in the committee meetings to provide opinions, and this guideline was developed with efforts to eliminate their concerns and reflect their needs. A draft guideline was reviewed by outside pediatric nephrologists who were not members of the guideline development committee, and also by an epidemiologist as an outside reviewer. The draft guideline after the review was then published on the website of the Japanese Society for Pediatric Nephrology to obtain public comments. Guideline authors, who were appointed for individual chapters, prepared clinical questions (CQs) relevant to the themes, and then collected and appraised evidence. Evidence was collected via comprehensive and systematic literature searches conducted with the cooperation of the Japan Medical Library Association. Sources of evidence were, in principle, original articles on pediatric patients; case reports and non-English/non-Japanese language articles were excluded. Retrieved literature articles were thoroughly reviewed, and only those finally regarded as important articles were used as references, which are listed under "References" at the end of each chapter. Individual CQs used in the process of the guideline development are not presented in this guideline because some recommendation statements were based on multiple CQs; some CQs were used only for literature searches.

The main databases used were PubMed and the Ichushi Web (Japan Medical Abstracts Society). The searches retrieved articles up to June 30, 2012, but later articles were also included as necessary and whenever possible. For each chapter, a list of particularly important literature articles was prepared with their structured abstracts consisting of evidence level and quality level, and their contents were examined.

In addition to the literature articles retrieved in the above-mentioned manner, other articles were also used as bibliographies, which are also listed in each chapter. Bibliographies without any reference number in the body text were used to obtain the overall background information pertaining to the chapter. This guideline applies to

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idiopathic nephrotic syndrome. Conditions such as membranous nephropathy and nephrotic syndrome secondary to nephritis are out of the scope of this guideline. The intended users of this guideline are not only pediatric nephrologists but also all pediatricians in Japan.

Levels of evidence are presented in a ranking system to describe the strength of the results obtained from studies depending on the study design. Study designs with higher evidence levels are less likely to involve coincidences or biases and therefore should produce more reliable results. On the other hand, study designs with lower evidence levels are more likely to involve coincidences and biases and therefore should produce less reliable results.

Levels of evidence used in this guideline were ranked from Levels 1–6, in descending order of strength (Table 1).

Recommendation statements are provided at the beginning of each chapter. In light of busy schedules of clinical practitioners, brief evidence-based clinical guides based on published evidence are provided. The strength of each recommendation was ranked from Grades A–D (Table 2).

As stated above, the present guideline update employed an evidence-based medicine (EBM) approach to present recommendations, as this is currently the global standard method. Generally, however, diagnostic procedures and treatment methods with established evidence are limited and account for approximately 20 %. Also in the field of pediatric idiopathic nephrotic syndrome, high-level evidence is limited. For this reason, the contents of recommendations and the recommendation grades were determined after thorough discussions, including direct discussions during guideline development committee meetings and based on data intensively collected by the authors and their explanations of the collected data to the committee members. In particular for Grades C1 and C2, i.e., interventions that are generally accepted but with no well-established evidence, discussions were continued until a consensus among all committee members was achieved. To avoid any preferential influence by the members making comments, though the Delphi technique was not used.

Table 1 Levels of evidence

Level 1	Evidence from review articles or meta-analysis articles
Level 2	Evidence from randomized controlled trials
Level 3	Evidence from non-randomized controlled trials, non-controlled trials (i.e., single-arm prospective interventional trials)
Level 4	Evidence from cohort studies, case–control studies, cross-sectional studies, comparative observational studies, non-comparative observational studies
Level 5	Evidence from accumulated cases, case reports, or others (e.g., descriptive studies)
Level 6	Evidence from expert committee reports or personal opinions of experts that are not based on patient data

Table 2 Grades of recommendations

Grade A	There is strong scientific evidence that intervention is beneficial, and intervention is strongly recommended
Grade B	There is scientific evidence that intervention is beneficial, and intervention is recommended
Grade C1	There is no scientific evidence that intervention is beneficial, but intervention is suggested
Grade C2	There is no scientific evidence that intervention is beneficial, and it is recommended not to conduct any intervention
Grade D	There is scientific evidence that intervention is ineffectiveness or harmful, and it is recommended not to conduct any intervention

The concept of evidence-based clinical practice guidelines developed in the Western countries. Clinical practice guidelines are defined as "systematically development statements to assist practitioners and patient decisions about appropriate health care for specific circumstances." [6] A major characteristic of the development of clinical practice guidelines is the use of an EBM approach. However, when using guidelines, it is important to note that "guidelines" are not necessarily equal to "evidence-based medicine". As described earlier, many diagnostic procedures and treatment methods currently used in medical practice are still empirical without sufficient evidence. Guidelines do not preclude the use of practitioners' experience. Guidelines provide just one of the bases for the decision-making by healthcare professionals and patients and should be critically assessed by the users before the decision is made whether or not to apply the recommendation to the patient. In other words, in clinical practice, decisions should be made not only based on evidence but also in accordance with the condition of the patient's disease, medical environment, and the patient's request, and in light of the experience as a clinician and the feasibility of treatment.

The recommendation grades of the statements in this guideline were determined in light of the clinical situation in Japan, in addition to level of evidence. Thus, for the use of this guideline, the recommendation grade of the statement is of more significance than the evidence level.

This guideline is not intended for permanent use. After 1 year of the issuance, questionnaires will be sent to the councilor board members of the Japanese Society for Pediatric Nephrology to investigate the usage of this guideline. The academic committee members of the society will have periodic discussions, and the guideline will be updated roughly every 3–5 years.

This guideline is not intended to serve as a standard for the judgment in medical disputes or medical lawsuits.

Off-label drug use requires adequate understanding of the drug's characteristics and side effects. Inconsiderate off-label use should be avoided. It should be noted that the Adverse Drug Reaction Relief Service does not cover side effects or other problems resulting from off-label use of drugs and this

should be informed to the patients and their guardians. Adverse reactions to immunosuppressive agents are not covered by the Adverse Drug Reaction Relief Service.

This guideline uses the "standard body weight for the height of the patient" and not a measured body weight or a standard body weight for age. More specifically, the child growth curve prepared is based on the "2000 Report on Infants and Young Children Physical Development Research Report", issued by the Ministry of Health, Labour and Welfare and the "Annual Report of School Health Statistics Research 2000", issued by the Ministry of Education, Culture, Sports, Science and Technology. These reports were used to determine a calendar age where the standard height is equal to the patient's actual height, and the standard body weight for that age is used as the patient's standard body weight.

Definitions of terms

Term	Definition
Nephrotic syndrome	Severe proteinuria (≥40 mg/h/m^2 in pooled night urine) or early morning urine protein creatinine ratio ≥2.0 g/gCr, and hypoalbuminemia (serum albumin ≤2.5 g/dL)
Complete remission	Negative protein on dipstick testing of early morning urine for 3 consecutive days, or early morning urine protein creatinine ratio <0.2 g/gCr for 3 consecutive days
Incomplete remission	≥1+ protein on dipstick testing of early morning urine or early morning urine protein creatinine ratio ≥0.2 g/gCr, and serum albumin >2.5 g/dL
Relapse*[1,2]	≥3+ protein on dipstick testing of early morning urine for 3 consecutive days
Steroid-sensitive	Disease with complete remission within 4 weeks following the start of daily prednisolone therapy
Frequent relapses	Two or more relapses within 6 months after initial remission, or 4 or more relapses within any 12 consecutive months
Steroid-dependence	Two consecutive relapses during prednisolone tapering or within 14 days after discontinuation of prednisolone
Steroid resistance	Absence of complete remission after at least 4 weeks of daily prednisolone therapy
Initial nonresponder	Steroid resistance at initial episode of nephrotic syndrome
Late nonresponder	Steroid resistance after one or more remissions in response to steroid therapy
Refractory nephrotic syndrome	Steroid sensitive nephrotic syndrome with continuing frequent relapses or steroid-dependent despite of standard immunosuppressant therapy, and, thus requiring continuation of steroid therapy; or steroid resistant nephrotic syndrome without complete remission despite of standard immunosuppressant therapy

*1: In this guideline, in accordance with the KDIGO guideline and the Pediatric Nephrology Sixth Edition, a relapse is defined as ≥3+ protein on dipstick testing of early morning urine for 3 consecutive days. Note that this is different from the Guideline for Pharmacotherapy of Pediatric Idiopathic Nephrotic Syndrome, Version 1.0, in which a relapse was defined as "urinary protein ≥40 mg/h/m^2 or urinary protein ≥100 mg/dL (≥2+) on dipstick testing of early morning urine for 3 consecutive days after a relapse"

*2: If a patient has ≥2+ protein on dipstick testing of early morning urine for at least 3 consecutive days, a relapse should be considered in the treatment. An abrupt increase in proteinuria requires particular caution

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Chapter 1. Kidney biopsy

Recommendation statements:

1. We recommend kidney biopsy at the onset of nephrotic syndrome to obtain a histological diagnosis to determine the treatment plan in patients (1) whose age is younger than 1 year, (2) with persistent hematuria and frank hematuria, (3) hypertension and renal dysfunction, (4) hypocomplementemia, and (5) extrarenal symptoms (e.g., rash, purpura), since these patients are likely to have other histological types than minimal-change disease. [Recommendation grade B]
2. In patients showing steroid resistance, we recommend kidney biopsy to obtain a histological diagnosis to determine the treatment plan. [Recommendation grade B]
3. In patients given long-term calcineurin inhibitor therapy, even without renal dysfunction, we suggest that kidney biopsy be considered at 2–3 years into the therapy to assess for any nephrotoxicity. [Recommendation grade C1]

Explanation

1. Indications for kidney biopsy at the onset of nephrotic syndrome

In a study conducted (from 1967 to 1974) by the International Study of Kidney Disease in Children (ISKDC) that enrolled 521 pediatric patients with nephrotic syndrome, the histological type of pediatric nephrotic syndrome was reported as minimal-change disease in 77.1 %, focal segmental glomerulosclerosis (FSGS) in 7.9 %, membranoproliferative glomerulonephritis in 6.2 %, and others in 8.8 % [7]. Given that ≥90 % of children with minimal-change disease, which is the most common type of pediatric nephrotic syndrome, respond to oral steroids, i.e., steroid-responsive [7], we recommend kidney biopsy to obtain a histological diagnosis to determine the treatment plan in patients suspected to have

histological types other than minimal-change disease. Clinical findings characteristic of patients with minimal-change disease or membranoproliferative glomerulonephritis were reported in one study conducted by ISKDC in pediatric patients with idiopathic nephrotic syndrome [8], and in another study, involving 222 pediatric patients (age 1–16 years) with idiopathic nephrotic syndrome in whom kidney biopsy was performed as indicated [9]. On the basis of these reports, indications for kidney biopsy have been set as (1) age younger than 1 year, (2) persistent hematuria and frank hematuria, (3) hypertension and renal dysfunction, (4) hypocomplementemia, and (5) extrarenal symptoms (e.g., rash, purpura) at the onset of nephrotic syndrome. Persistent hematuria in this guideline is defined as the repeated observation of 20 red blood cells per microscopic field.

2. Patients showing steroid resistance

In patients showing steroid resistance, we recommend kidney biopsy to obtain a histological diagnosis and rule out nephritis such as membranous nephropathy, and in order to determine the treatment plan (Fig. 1). The histological types are broadly classified as minimal-change disease, FSGS, and diffuse mesangial proliferative disease. FSGS failing to achieve complete remission progresses to end-stage renal failure over a period of 10 years in approximately 40 % of patients [10].

3. Patients given long-term calcineurin inhibitor therapy

Calcineurin inhibitor-induced nephrotoxicity cannot be diagnosed based only on urinalysis or blood tests, and requires kidney biopsy for the diagnosis. Before the use of calcineurin inhibitors, it is advisable to consult with a pediatric nephrologist and have a kidney biopsy performed. If persistent renal dysfunction occurs during calcineurin inhibitor therapy, a kidney biopsy should be performed to assess for any nephrotoxicity. Histopathological findings of nephrotoxicity consist of arteriolar lesions, and renal tubular and interstitial lesions (renal tubular atrophy and streaky fibrosis).

In patients given long-term calcineurin inhibitor therapy, even without renal dysfunction, this guideline suggests that kidney biopsy be considered at 2–3 years into the therapy to assess for any nephrotoxicity. The recommendation grade has been classified as C1 because no randomized controlled trials were retrieved that compared the efficacy and safety of long-term calcineurin inhibitor therapy with and without protocol-specified kidney biopsy. According to the studies in pediatric patients with nephrotic syndrome that investigated risk factors for nephrotoxicity induced by calcineurin inhibitors [11–14], the risk factors were reported as high-dose use of calcineurin inhibitors [11, 12], concomitant use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers [12], long-term use of calcineurin inhibitors over 2–3 years [13, 14], persistent severe proteinuria during calcineurin inhibitor therapy [14], and a younger age (5 years and below) [14]. These studies were conducted in patients with steroid-dependent, frequently-relapsing, or steroid-resistant disease, and many of the patients received Sandimmun® at moderate or higher doses. The mean duration of cyclosporine therapy was 2 years or longer in all mentioned studies.

In Japan, two clinical studies [15, 16] have investigated the dosage regimen of cyclosporine in Japanese children with frequently-relapsing nephrotic syndrome, of which the cyclosporine preparation was Sandimmun® in one study and Neoral® (cyclosporine) in the other study. One of these studies

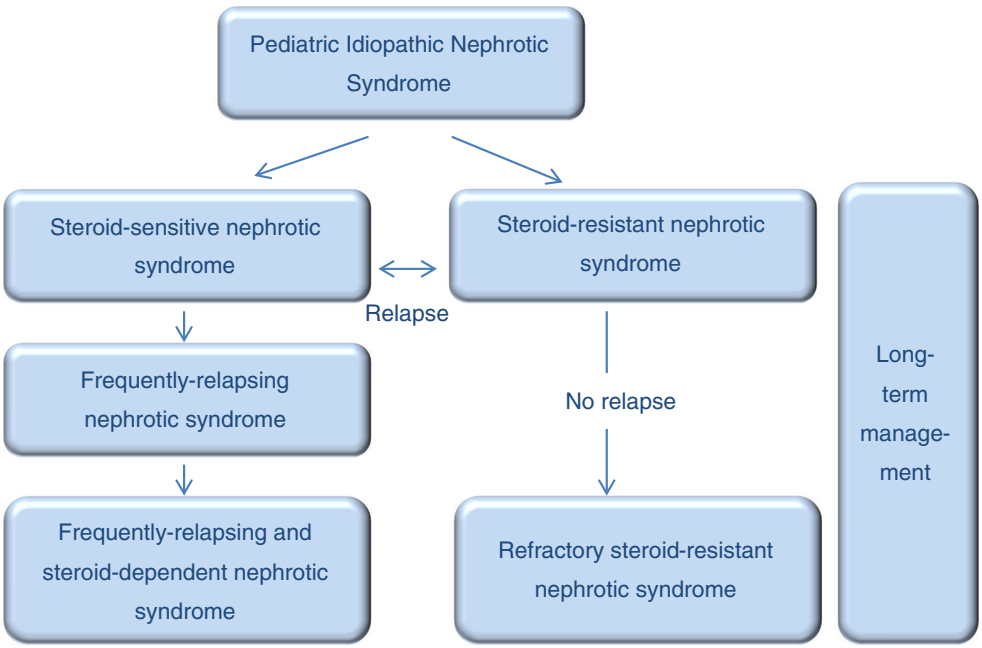

Fig. 1 Flow chart for the determination of treatment plan

was a multicenter, randomized, controlled trial investigating two different dosage regimens of Sandimmun®. Patients in the study were randomly divided into two groups, and in both groups the dose was adjusted to a target blood trough range of 80–100 ng/mL for the first 6 months. For the next 18 months, the dose was adjusted to a target blood trough range of 60–80 ng/mL in one group (i.e., dose-adjustment group), but was fixed at 2.5 mg/kg/day in the other group (i.e., fixed-dose group). In the dose-adjustment group, compared with the fixed-dose group, the relapse-free rate was significantly higher (50 vs. 15 %; $p = 0.006$), and the incidence of nephrotoxicity was higher (20 vs. 6.7 %), but all findings of nephrotoxicity were arteriolar lesions without any interstitial lesions [15]. In a single-arm study that investigated the efficacy and safety of Neoral®, a microemulsified preparation of cyclosporine (administered for 2 years), with the dose adjusted according to blood trough levels, the efficacy of Neoral® was comparable to Sandimmun® [relapse-free survival rate at month 24, 58.1 % (95 % CI, 45.8–70.3 %)], the incidence of nephrotoxicity was low at 8.6 % (5/58 patients), and the severity of nephrotoxicity was mild [16]. This incidence of renal toxicity was considerably lower than that in earlier research studies, with Sandimmun® [13] at 35.3 % and cyclosporine [15] at 20 %. Given that the incidence of cyclosporine-induced nephrotoxicity may be reduced in patients given Neoral® for 2 years, with dose adjustment according to blood trough levels or C2 (blood concentration at 2 h post-dose), for patients without risk factors for nephrotoxicity, one option would be that the attending physician decides when to perform kidney biopsy after discussion with a pediatric nephrologist and depending on the pathological condition of nephrotic syndrome and the patient's social life.

Tacrolimus is also known to induce nephrotoxicity as with cyclosporine. In one study conducted on 11 children with frequently-relapsing and steroid-dependent nephrotic syndrome and previously treated with cyclosporine, tacrolimus was administered (mean tacrolimus dose, 0.17 mg/kg/day; mean tacrolimus trough level, 7.9 μg/1L; median duration of tacrolimus therapy, 19 months). A kidney biopsy after the use of tacrolimus showed that the percent volume density of interstitial fibrosis increased by +1.8 % (median), and the higher dose (higher trough level) significantly correlated with an increase of interstitial fibrosis ($p = 0.005$) [17].

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Chapter 2. Steroid therapy for steroid-sensitive nephrotic syndrome

Recommendation statements:

1. For both the initial episode and relapse of pediatric idiopathic nephrotic syndrome, we recommend that steroids (prednisolone) be used as the first-line treatment because the condition is mostly minimal-change disease. [Recommendation grade A]

2. For treatment of the initial episode, we recommend the ISKDC regimen or the long-term, tapering regimen. [Recommendation grade B]

ISKDC regimen: Prednisolone for 8 weeks

(1) 60 mg/m^2/day or 2.0 mg/kg/day in three divided doses daily for 4 weeks (maximum 60 mg/day), followed by (2) 40 mg/m^2 or 1.3 mg/kg once in the morning on alternate days for 4 weeks (maximum 40 mg on alternate days).

Long-term, tapering regimen: Prednisolone for 3–7 months

(1) 60 mg/m^2/day or 2.0 mg/kg/day in three divided doses daily for 4 weeks (maximum 60 mg/day), followed by (2) 40 mg/m^2 or 1.3 mg/kg once in the morning on alternate days (maximum 40 mg on alternate days), continued for 2–6 months with tapering of the dose. The dose tapering method in (2) is largely left to the discretion of the attending physician.

3. For treatment of relapse, we suggest the modified ISKDC regimen or the long-term, tapering regimen. [Recommendation grade C1]

Modified ISKDC regimen: Prednisolone

(1) 60 mg/m^2/day or 2.0 mg/kg/day in three divided doses daily until confirmation of the resolution of proteinuria for at least 3 days but not exceeding 4 weeks (maximum 60 mg/day), followed by (2) 60 mg/m^2 or 2.0 mg/kg once in the morning on alternate days for 2 weeks (maximum 60 mg on alternate days), followed by (3) 30 mg/m^2 or 1.0 mg/kg once in the morning on alternate days for 2 weeks (maximum 30 mg on alternate days), followed by (4) 15 mg/m^2 or 0.5 mg/kg once in the morning on alternate days for 2 weeks (maximum 15 mg on alternate days). The dose-tapering manner from (2) to (4) is largely left to the discretion of the attending physician. The long-term, tapering regimen should be selected when appropriate.

Note: To calculate the dose for body weight, the standard body weight for the height of the patient should be used (similarly for body surface area as well).

Explanation

1. Treatment of pediatric nephrotic syndrome

In general, steroids are widely used in the treatment of nephrotic syndrome, and their efficacy is undoubted despite the absence of randomized controlled trials. Thus, a classification A grade was given for the recommendation statement. Since ≥90 % of children with minimal-change disease, which is the most common type of pediatric nephrotic syndrome, respond to oral steroid therapy (prednisolone), i.e., steroid-responsive, treatment is typically started with prednisolone without any kidney biopsy unless other histological types are suspected (see Definitions of Terms and Chapter 1). If oral administration is difficult (e.g., vomiting due to intestinal edema, oral intake inability) then temporary use of intravenous prednisolone at the same dose should be considered.

2. Treatment of the initial episode

For treatment of the initial episode, either the ISKDC regimen (8-week administration) or the long-term, tapering regimen (3–7-month administration) is currently recommended. The ISKDC regimen (8-week prednisolone therapy), originally proposed in the 1960s, was subsequently modified by the Arbeitsgemeinschaft für Padiatrische Nephrologie (APN). The modified regime suggests that after dose reduction on 3 out of 7 days, dosing then be changed to alternate days; this is now the most widely accepted practice and is used as the standard prednisolone regimen [3, 7, 18]. The regimen, however, leads to frequent relapsing and steroid-dependent disease in approximately 40 % of all treated patients. Therefore, the long-term use of prednisolone has thus been extensively studied [19–23]. The KDIGO guideline recommends that the initial episode be treated with daily oral prednisone for 4–6 weeks, followed by alternate-day medication and continued for 2–5 months, with tapering of the dose. Some reports, however, reported no difference in the frequency of relapses between the ISKDC regimen and the long-term, tapering regimen [24–27]. A cochrane review concluded that treatment of the first episode with a steroid for 4 weeks followed by alternate-day therapy as the long-term, tapering regimen (3–7-month administration) reduced the risk of relapse at 12–24 months, compared with the ISKDC regimen [28]. It also states, however, that these analyzed clinical studies had the limitation of including only small-scale, insufficient assessments for steroid-induced side effects, and therefore the results of this meta-analysis require confirmation by "an appropriately designed, large-scale, randomized controlled trial" [28]. Currently, in Japan, the ISKDC regimen (8-week administration) and the long-term, tapering regimen (6-month administration) are being compared in a randomized controlled trial (prednisolone therapy for the first episode of idiopathic nephrotic syndrome in children; UMIN ID, UMIN000000747), and study outcomes are eagerly awaited.

3. Treatment of relapse

The ISKDC regimen, modified ISKDC regimen, or long-term, tapering regimen is recommended for the treatment of relapse. The recommendation grade has been classified as C1 as there has been little evidence about steroid therapy for relapse. The effectiveness of the use of prednisolone is undoubted, but how to taper prednisolone remains controversial, as there are presently no randomized controlled trials on the tapering method. The KDIGO guideline recommends that prednisone be administered at 60 mg/m^2/day or 2.0 mg/kg/day (maximum of 60 mg/day) until the third day of remission, followed by 40 mg/m^2 or 1.5 mg/kg (maximum 40 mg) on alternate days for at least 4 weeks. For steroid-dependent or frequently-relapsing nephrotic syndrome, the KDIGO guideline recommends that steroid therapy be continued for at least 3 months following remission. A Cochrane review reported that the long-term tapering regimen, involving prolonged alternate-day dosing, would be more effective than the ISKDC regimen (60 mg/m^2/day until protein-free for at least 3 days followed by 40 mg/m^2 on alternate days for 4 weeks) [28]. However, it remains unclear whether the long-term, tapering regimen is associated with an increased frequency or increased severity of side effects. In clinical practice, the modified ISKDC regimen and the long-term, tapering regimen involving prolonged alternate-day dosing are more commonly used than the ISKDC regimen.

4. Others

The maximum dose of prednisolone has been set to 60 mg/day in this updated guideline; this is in line with the KDIGO guideline that states 60 mg/day as a maximum starting dose followed by 40 mg as a maximum maintenance dose, as well as also following the "2013 Evidence-

based Clinical Practice Guideline for CKD". In terms of initial therapy, however, the required effective dose remains unclear, and thus at this point clinicians may choose a maximum starting dose of 80 mg/day followed by a reduced maximum dose of 60 mg on alternate days. The Cochrane review does not give a statement regarding a maximum dose. The maximum dose may be lower in patients with repeated relapse for whom the dose required to induce remission is already known, or when concerns are raised about side effects such as increased blood pressure, glaucoma, or withdrawal syndrome.

The dosing frequency is usually three divided doses for daily administration, but this can also be two divided doses in order to improve adherence (compliance) to the medication. This guideline does not recommend single daily dosing, although there has been a report describing no difference between single daily dosing and three-divided dosing [29]. However, during alternate-day oral dosing at a reduced dose, it is recommended to administer a single daily dose at intervals of 48 h to reduce steroid-induced side effects.

Prolonged steroid therapy requires the utmost caution and recognition of side effects such as obesity, growth impairment, hypertension, osteoporosis, cataracts, and glaucoma. For details of steroid-induced side effects, see Chapter 4, Chapter 5, and Chapter 6.

Concomitant use of cyclosporine with prednisolone for initial treatment of nephrotic syndrome reduces the frequency of relapse as well as prolonging relapse time [30, 31], but inconsiderate use of concomitant cyclosporine should be avoided due to problematic side effects.

We do not recommend the use of "Saireito" (Chinese traditional medicine). Saireito had been previously used for prevention of relapse and some published reports indicate its efficacy [25, 32], but in recent years, its use has become uncommon. Also, a literature search has revealed low-level evidence on the efficacy of Saireito in the treatment of pediatric nephrotic syndrome.

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Chapter 3. Treatment of frequently-relapsing and steroid-dependent nephrotic syndrome

Recommendation statements:

1. We recommend that immunosuppressive agents (e.g., cyclosporine, cyclophosphamide) be used for the treatment of frequently-relapsing and steroid-dependent nephrotic syndrome due to the occurrence of various steroid-induced side effects. [Recommendation grade B]
2. Cyclosporine
(1) We recommend that cyclosporine be given at an initial dose of 2.5–5 mg/kg/day in two divided doses, followed by dose adjustment according to monitoring of blood drug concentration [Recommendation grade A] and with reference to the following:
Blood trough levels[*1]: 80–100 ng/mL for the first 6 months, followed by 60–80 ng/mL
(2) We suggest that kidney biopsy be performed at 2–3 years into the therapy to assess for any nephrotoxicity in patients given long-term cyclosporine therapy, even without renal dysfunction. [Recommendation grade C1]
3. Cyclophosphamide
(1) We recommend that cyclophosphamide be given at an initial dose of 2–2.5 mg/kg/day (maximum 100 mg), and then once daily for 8–12 weeks. [Recommendation grade A]
(2) We recommend that a second course of cyclophosphamide should not be given and that cumulative doses do not exceed 300 mg/kg. [Recommendation grade A]
4. Mizoribine
(1) We suggest that mizoribine not be given at the standard dose (4 mg/kg/day, maximum 150 mg/day), as it would be inadequately effective. [Recommendation grade C2]
(2) We suggest that mizoribine be administered at higher doses of 7–10 mg/kg/day once daily, with a peak blood mizoribine concentration (C2[*2] or C3[*3]) of 3.0 μg/mL or higher, on the basis of reported efficacy in preventing relapses. [Recommendation grade C1]

Note 1: To calculate the dose for body weight, the standard body weight for the height of the patient should be used (similarly for body surface area as well).
Note 2: Preferably, these treatments should be done in cooperation with a pediatric nephrologist.

*1: Blood concentration immediately before a next dose

*2: Blood concentration at 2 h post-dose

*3: Blood concentration at 3 h post-dose

Explanation

1. Immunosuppressive therapy for frequently-relapsing and steroid-dependent nephrotic syndrome

In Japan, three immunosuppressive agents commonly used in the treatment of frequently-relapsing and steroid-dependent nephrotic syndrome are cyclosporine, cyclophosphamide and mizoribine. Of these three, high-level evidence exists for cyclosporine and cyclophosphamide.

We recommend that immunosuppressive agents be used for the treatment of frequently-relapsing and steroid-dependent nephrotic syndrome as various steroid-induced side effects can occur, including growth impairment, obesity, diabetes mellitus, cataracts, glaucoma, hypertension, osteoporosis, and avascular necrosis of the femoral head. A Cochrane review stated that cyclophosphamide, chlorambucil, cyclosporine, and levamisole are drugs that can be significantly effective [33]. The KDIGO guideline recommends the use of two additional drugs, tacrolimus and mycophenolate mofetil, as well. In Japan, however, the immunosuppressive agents commonly used in the treatment of idiopathic nephrotic syndrome are the following three drugs: cyclosporine, cyclophosphamide, and mizoribine. Mizoribine is not recommended in the Cochrane review as no significant difference was observed when the drug was compared against placebo in the only available randomized controlled trial [33]; multiple reports, however, document the efficacy of high-dose mizoribine therapy. The Cochrane review [33] stated that cyclosporine was as effective as cyclophosphamide. According to the only available randomized controlled trial [34] that compared cyclosporine and cyclophosphamide in patients with frequently-relapsing and steroid-dependent nephrotic syndrome, the percentage of patients who remained in remission at 2 years was significantly higher with cyclophosphamide; the discontinuation of cyclosporine therapy at 1 year in this study, however, appeared to have affected the results.

When deciding which drug to choose for treatment, the decision should be based on drug efficacy, side effects and the patient's condition. During a relapse, however, patients may suffer oliguria and can be at an increased risk for cyclosporine-induced acute nephrotoxicity or posterior reversible encephalopathy syndrome (PRES), cyclophosphamide-induced hemorrhagic cystitis, as well as other side effects. Thus, it is safe not to start a new immunosuppressive therapy until after remission is achieved with steroid therapy. Also, since the onset of an immunosuppressive effect requires some time from the initiation of therapy, concomitant steroid therapy for a certain time period or other strategies may be considered to prevent further relapse. There is no published evidence on the safety of combination therapy, using two different immunosuppressive agents in refractory patients, although such a use has been empirically employed in some cases.

2. Cyclosporine

Cyclosporine is very effective in the treatment of frequently-relapsing and steroid-dependent nephrotic syndrome, and allows steroid tapering and discontinuation in the majority of patients [15, 16, 35–39]. The problem of cyclosporine therapy is that many patients suffer relapse after termination of cyclosporine therapy (cyclosporine dependence) [35–38, 40]. Some reports also describe that patients who respond initially to cyclosporine may lose the therapeutic responsiveness during the course of treatment and experience repeated relapse [41] or may not respond to resumption of the therapy [35].

The dose of cyclosporine should be adjusted along with monitoring of blood concentrations. According to a multicenter, prospective, randomized, controlled trial of Sandimmun® conducted in Japan on 44 children with frequently-relapsing nephrotic syndrome, the rate of sustained remission was significantly higher in the dose-adjustment group (initially the dose was adjusted to maintain blood trough levels within 80–100 ng/mL for the first 6 months, and then within 60–80 ng/mL for the next 18 months) compared with the 2.5 mg/kg fixed-dose group (initially the dose was adjusted to maintain blood trough levels within 80–100 ng/mL for the first 6 months, but then fixed at 2.5 mg/kg for the next 18 months) (50 vs. 15 %; $p = 0.006$) [15]. A subsequent multicenter clinical study assessed Neoral® [42], a newly-developed microemulsified preparation of cyclosporine, in 62 children with frequently-relapsing nephrotic syndrome, with adjustment of the dose using the same target trough levels as stated above. This study reported that microemulsified cyclosporine was effective and safe (relapse-free survival rate at month 24, 58 %; incidence of nephrotoxicity, 8.6 %), similar to conventional cyclosporine [16]. A 2-year follow-up report for the above-mentioned study indicated that 84.7 % of patients had a relapse within 2 years after completion of the 2-year cyclosporine therapy and 59.2 % of patients had regression to frequently-relapsing nephrotic syndrome. The report also stated that children in particular who experience relapse during cyclosporine treatment are at high risk for relapse after discontinuation [40].

The AUC_{0-4} (area under the time-concentration curve) of cyclosporine has been documented to be best predicted by C2 (cyclosporine blood concentration at 2 h post-dose) in kidney transplant patients [43]; similar findings were reported in children with nephrotic syndrome [44]. With this background, a multicenter, prospective, randomized, controlled trial in Japan on 93 children with frequently-relapsing nephrotic syndrome is being conducted to compare two different target C2 levels: a higher C2 group (target C2 600–700 ng/mL for the first 6 months, followed by 450–550 ng/mL for the next 18 months) and a lower C2

group (target C2 450–550 ng/mL for the first 6 months, followed by 300–400 ng/mL for the next 18 months); study results have not yet been released (A randomized controlled trial of cyclosporine C2 monitoring; UMIN ID: C000000008).

It has been indicated that absorption of oral cyclosporine after pre-meal administration (15–30 min prior to a meal) is greater than post-meal administration. Concomitant use with other drugs requires adequate attention since macrolide antimicrobials and many other drugs can affect metabolism. Grapefruit juice should be avoided as it inhibits metabolism of cyclosporine and causes increased blood concentrations of the drug.

Once-daily administration of cyclosporine has been reported to be similarly effective to twice-daily administration [45]. Once-daily dosing with lowered trough levels may be associated with reduced nephrotoxicity and increased drug adherence (compliance). However, a report described that the incidence of nephrotoxicity with once-daily dosing did not differ compared with twice-daily dosing [46], and further studies are required to clarify the efficacy and safety of once-daily administration of cyclosporine.

Chronic nephrotoxicity is the most problematic side effect of cyclosporine, and its risk is increased after prolonged cyclosporine use for 2 years or more [13, 14]. Cyclosporine-induced chronic nephrotoxicity cannot be diagnosed based only on urinalysis or blood tests. Thus, it is recommended to perform kidney biopsy to assess for nephrotoxicity after 2–3 years of cyclosporine therapy, and to avoid prolonged use of cyclosporine as far as possible (see Definitions of Terms, Chapter 1). However, the recommendation grade has been classified as C1 because there is no high-level evidence supporting the necessity of kidney biopsy and also in light that recent clinical studies of microemulsified cyclosporine [16, 45] have demonstrate a lower incidence of nephrotoxicity than earlier. It is recommended to perform kidney biopsy also before the start of cyclosporine therapy if possible.

Cosmetic side effects, such as hypertrichosis and gum hypertrophy, are characteristically common with cyclosporine [16, 35–39]. Infections, hypertension, and PRES are also known complications of cyclosporine therapy [15, 16, 35–39]. Before the use of cyclosporine as a treatment, sufficient information on its side effects should be given to patients.

3. Cyclophosphamide

Cyclophosphamide has long been documented by multiple randomized controlled trials to be effective in the treatment of frequently-relapsing nephrotic syndrome [47, 48]. A cochrane review also reported that cyclophosphamide significantly reduced the relapse risk at 6–12 months when compared against prednisolone alone (RR 0.44, 95 % CI 0.26–0.73) [33]. A randomized controlled trial, comparing 2 and 8 weeks of cyclophosphamide at 3 mg/kg/day in patients with frequently-relapsing nephrotic syndrome, reported significantly better efficacy from the 8-week therapy [49]. A non-randomized controlled trial in Germany reported that 12-week administration of cyclophosphamide at 2 mg/kg/day (cumulative dose, 168 mg/kg) was more effective than 8-week administration (cumulative dose, 112 mg/kg) in patients with steroid-dependent nephrotic syndrome [50]. A randomized controlled trial in Japan reported no difference between 8- and 12-week courses of cyclophosphamide 2 mg/kg/day, but the benefits of the treatment were limited with either method of administration [51].

Decreased efficacy of cyclophosphamide has been reported in patients with lower age, steroid dependence, and histological findings of FSGS. In terms of age, a decreased rate of sustained remission was reported in patients age younger than 3 years [52], 5 years [53], 5.5 years [54], 7.5 years [55], and 8 years [56]. The efficacy of cyclophosphamide has been shown to be better correlated with body surface area-based dosage than body weight-based dosage, and younger children have a larger body surface area relative to body weight. Thus, a body weight-based dosage may not provide adequate efficacy, as indicated by some reports [54, 55, 57]. Many reports also describe that steroid-dependent nephrotic syndrome does not adequately respond to cyclophosphamide [4, 51, 54, 57–59]. A meta-analysis reported that, on average, studies for non-steroid-dependent, frequently-relapsing nephrotic syndrome resulted in remission rates of 72 % after 2 years and 36 % after 5 years; the rates for steroid-dependent nephrotic syndrome were 40 and 24 %, respectively [60]. Other reports described that the rate of sustained remission was lower in patients with FSGS than in patients with minimal-change disease or diffuse mesangial proliferative disease [61, 62].

Intravenous cyclophosphamide therapy has been described to be efficacious in some reports [63–65]; in some studies, however, it is reported that intravenous cyclophosphamide has poorer efficacy than oral cyclophosphamide [66]. In the only available randomized controlled trial [65] published that compared oral ($n = 21$) and intravenous ($n = 26$) cyclophosphamide therapy, the relapse-free rate at 6 months was 23.8 % with oral therapy and 57.7 % with intravenous therapy ($p = 0.02$), and the median relapse-free time was 96 days with oral therapy and 360 days with intravenous therapy ($p = 0.05$). These results thereby show short-term outcomes being better with intravenous therapy. However, the relapse-free rate at 2 years was 19.0 % with oral therapy and 18.6 % with intravenous therapy, showing no significant difference in

rates. In this study, the total dose of cyclophosphamide was different between oral therapy (180 mg/kg) and intravenous therapy (132 mg/kg). Although intravenous cyclophosphamide may be more effective with fewer side effects compared with oral cyclophosphamide, the evidence is insufficient without high-quality clinical studies to date, and thus further studies are required.

Important side effects of cyclophosphamide include gonadal dysfunction, especially azoospermia in boys, of which the risk is particularly higher in those of pubertal age (Tanner stage 2 or greater, corresponding to a testicular weight of 3 mL or more in boys) or post-pubertal age [60]. A meta-analysis also reported that the risk of azoospermia is increased in boys when the cumulative dose of cyclophosphamide exceeds 300 mg/kg. Thus, cyclophosphamide should not be given more than one cycle, and cumulative doses should not exceed 300 mg/kg. This meta-analysis of studies including 119 patients stated that a cumulative dose up to 168 mg/kg is safe, while a cumulative dose of <300 mg/kg may cause oligo- and azoospermia. A cumulative dose up to 168 mg/kg is also recommended in a review report on adults with lupus nephritis [67], as reported in a recent educational review and a meta-analysis [68]. Another meta-analysis [69], however, described that gonadal dysfunction in boys occurred with the use of 100–200 mg/kg during puberty, or even 100 mg/kg or lower during post-puberty years, while a cumulative dose of up to 400 mg/kg during pre-puberty years was safe. Clinicians should note that the use of cyclophosphamide in boys of pubertal or post-pubertal age is associated with an increased risk of gonadal dysfunction. The risk of female infertility has been documented to be lower than the risk of male infertility, and meta-analyses reported that a cumulative dose up to 200 mg/kg was safe [60] and female infertility occurred at 300 mg/kg or higher [69].

Other common side effects include myelosuppression, particularly leukopenia with an incidence of 32 %, according to one meta-analysis report [60]. During cyclophosphamide therapy, blood tests should be performed periodically every 1–2 weeks to monitor white blood cell counts, and onset of leukopenia warrants cyclophosphamide dose reduction or suspension. Other important side effects to note include infection, alopecia, hemorrhagic cystitis, hepatic dysfunction, interstitial pneumonia, and inappropriate antidiuretic hormone secretion. Before use of cyclophosphamide, sufficient information on side effects should be given to patients.

4. Mizoribine

Mizoribine is a metabolic antagonist developed in Japan. A double-blind, placebo-controlled multicenter, randomized trial conducted by the Pediatric Mizoribine Study Group in Japan investigated the efficacy and safety of a 48-week treatment with mizoribine at 4 mg/kg/day compared with placebo in children with frequently-relapsing and steroid-dependent nephrotic syndrome [70]. The remission rate did not significantly differ between mizoribine and placebo in this study, and a Cochrane review does not recommend mizoribine for the treatment of frequently-relapsing nephrotic syndrome. Mizoribine at 4 mg/kg/day as the standard dose would be inadequately effective, and thus this treatment has been given a C2 classification recommendation grade. A subgroup analysis of children aged 10 years and younger in the above-mentioned study, however, demonstrated that the relapse rate was significantly lower in the mizoribine group than the placebo group.

Multiple studies of high-dose mizoribine therapy for frequently-relapsing and steroid-dependent nephrotic syndrome were then reported, including those investigating the efficacy and safety of mizoribine at 10 mg/kg/day (maximum 500 mg) twice a week [71], 6 mg/kg/day (maximum 300 mg) twice a week [72], a mean of 14.3 mg/kg/day twice a week [73], a mean of 10.1 mg/kg/day daily [74], and a mean of 8.4 mg/kg/day daily [75]. A cohort study comparing the standard dose (4–6 mg/kg/day) and high-dose (7–10 mg/kg/day) of mizoribine demonstrated superior efficacy of high-dose therapy, with a significant decrease in the number of relapses in patients with a peak blood mizoribine concentration of 3.0 μg/mL or higher [76]. The recommendation grade has been classified as C1 because, though high-dose mizoribine at 7–10 mg/kg/day may be efficacious, there is no high-level evidence report to support the efficacy.

Current difficulties for the use of mizoribine are that the drug is currently (at preparation of this guideline) indicated for nephrotic syndrome difficult to treat with steroids alone (excluding frequently-relapsing nephrotic syndrome) and that the approved daily adult dose stated in the package insert is 150 mg/day. To attain clinically adequate efficacy, 4 mg/kg/day is too low, and a high dose therapy at 7–10 mg/kg/day is required, but no valid evidence exists on its efficacy and safety and thus large-scale clinical trials should be performed. Since mizoribine is predominantly renally excreted, the dose of mizoribine should be reduced in patients with renal dysfunction. Hyperuricemia is a known side effect of mizoribine and requires caution, but otherwise mizoribine has relatively fewer side effects, which makes it an advantageous treatment.

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Chapter 4. Frequently-relapsing and steroid-dependent nephrotic syndrome—other treatments

Recommendation statements:
1. Rituximab
(1) Rituximab has been suggested to be effective for refractory frequently-relapsing and steroid-dependent nephrotic syndrome. We suggest that rituximab be considered only in refractory disease. [Recommendation grade C1]
(2) We suggest that rituximab be given at a starting dosage of 375 mg/m^2 per dose by intravenous drip infusion, administered one to four times (at 1-week intervals for multiple infusions). [Recommendation grade C1]
2. Mycophenolate mofetil
(1) We suggest that mycophenolate mofetil be considered as the treatment for frequently-relapsing and steroid-dependent nephrotic syndrome when standard immunosuppressive agents cannot be used because of their side effects. [Recommendation grade C1]
(2) We suggest that mycophenolate mofetil (1,000–1,200 mg/m^2/day or 24–36 mg/kg/day, maximum 2 g/day) be given in two divided doses. [Recommendation grade C1]
3. Tacrolimus
(1) We suggest that tacrolimus be considered as treatment for frequently-relapsing and steroid-dependent nephrotic syndrome when cyclosporine cannot be used because of its cosmetic side effects. [Recommendation grade C1]
(2) We suggest that tacrolimus (starting dose 0.1 mg/kg/day) be given in two divided doses, followed by dose adjustment according to monitoring of blood drug concentration. [Recommendation grade C1]

Note 1: To calculate the dose for body weight, the standard body weight for the height of the patient should be used (similarly for body surface area as well).
Note 2: It is preferable that a pediatric nephrologist performs these treatments.

Explanation

This chapter describes treatments for frequently-relapsing and steroid-dependent nephrotic syndrome that is refractory (see Definitions of Terms) or for which standard immunosuppressive agents (i.e., cyclosporine, cyclophosphamide, mizoribine) cannot be used because of their side effects.

Treatments described in this chapter are currently off-label indications for nephrotic syndrome in Japan as well as in other countries. Thus, the patient's pathological condition and the risks and benefits of treatment should be carefully evaluated before the use of treatment is decided. Preferably, a pediatric nephrologist should perform these treatments.

1. Rituximab

Rituximab is a monoclonal antibody against the CD20 differentiation antigen expressed on the surface of B lymphocytes. Recent cohort [77–83] and randomized controlled studies [84] indicate the efficacy of rituximab for refractory frequently-relapsing and steroid-dependent nephrotic syndrome, and thus this guideline suggests that rituximab should be considered only in refractory disease. An open-label, randomized controlled trial [84] on 54 children with refractory (steroid- and calcineurin inhibitor-dependent) nephrotic syndrome evaluated add-on rituximab (375 mg/m^2, administered once or twice) compared with standard therapy alone (consisting of a steroid and a calcineurin inhibitor). At 3 months, the relapse rate was significantly lower in the intervention group (18.5 %) than in the standard group (48 %) ($p = 0.029$). The probability of being prednisolone- and calcineurin inhibitor-free at 3 months was significantly higher in the intervention group (62.95 %) than in the standard group (3.7 %) ($p < 0.001$).

While rituximab has not been approved for the indication of nephrotic syndrome within Japan or in other countries, it is often used in an off-label manner in clinical practice. The recommendation grade has been classified as C1, as randomized controlled trials are needed to determine the appropriate type of patient to be treated, the rituximab dosage and mode of administration, and long-term efficacy and safety. An overseas, placebo-controlled randomized trial is currently ongoing in cyclosporine-dependent refractory patients (ClinicalTrials.gov Identifier, NCT01268033). In Japan, a placebo-controlled, double-blind, randomized trial of rituximab is also actively ongoing to expand the indications (investigator-initiated study; UMIN Clinical Trial Registry ID, UMIN000001405); study results are not yet available.

We suggest that rituximab (375 mg/m^2 per dose by intravenous drip infusion) be administered one to four times (at 1-week intervals for multiple infusions). Published studies used 375 mg/m^2 per dose up to 4 intravenous infusions (at 1-week intervals) [77–85]. In a retrospective analysis of long-term outcomes in 37 patients given 1–4 infusions of rituximab [85], data at 12 months showed that the time to first relapse was significantly shorter in 16 patients who received one or two initial infusions compared to 11 patients who received three or four initial infusions ($p < 0.05$). This article reported that there was no association between long-term (at least 2 years) remission and the number of initial infusions of rituximab. In this study, 19 of 37 patients received repeated administration of rituximab; 20 patients (69 %) out of 29 patients that

were followed for >2 years remained in remission for at least 2 years; and 14 (48 %) of 29 patients remained off immunosuppression [85]. Without any reports of randomized controlled trials on 4 doses of rituximab, the recommendation grade has been classified as C1.

In an observational study in 30 patients with refractory steroid-dependent nephrotic syndrome who received 1–4 infusions of initial rituximab therapy, disease outcome was evaluated after a minimum CD19 depletion period of 15 months obtained by repeated rituximab infusion [86]. The study reported long-term remission after definitive CD19 recovery in almost two-thirds of the patients, without oral immunosuppressive drugs. There was no occurrence of any serious adverse events with the use of cotrimoxazole (20 mg/kg; three times a week; off-label) during B cell depletion for pneumocystosis prophylaxis. Further investigation, however, should be performed to determine the appropriateness of repeated rituximab infusion to cause CD19 depletion.

Side-effect characteristics of rituximab include infusion reactions typically occurring within 24 h after intravenous infusion (with manifestations including fever, vomiting, chills, nausea, headache, pain, itching, rash, bronchospasm, cough, weakness, angioedema). Infusion reactions have been reported also in patients with refractory nephrotic syndrome [81–86]. Premedication for prophylaxis of infusion reactions is commonly performed with drugs such as oral antipyretic analgesics, oral antihistamines, and intravenous methylprednisolone [81, 84, 86].

Neutropenia and agranulocytosis, among other side effects of rituximab, are known to occur not only with early onset but also with late onset (1–5 months after last dose). One Japanese report described serious agranulocytosis, with fever 3 months after 4 infusions of rituximab, in a child with refractory steroid-dependent nephrotic syndrome [87]. After administration of rituximab, blood tests, including CD19 measurement, should be performed periodically and the patient's condition should be closely monitored. Also, depletion, or a decrease, of peripheral B cells can lead to onset of bacterial or viral infections, for which caution is required, particularly in children. In Japan, onset of atypical *Pneumocystis jiroveci* pneumonia after rituximab therapy was reported in a patient with refractory steroid-resistant nephrotic syndrome [88]. Use of sulfamethoxazole/trimethoprim during the period of peripheral B-cell depletion for prophylaxis of pneumocystis infection has been investigated [81, 85, 86].

Known serious side effects (including death) that have been described with rituximab use include progressive multifocal leukoencephalopathy and fulminant hepatitis, with reactivation of hepatitis B virus in hepatitis B virus carriers [89]. Patients with systemic lupus erythematosus, who were treated with rituximab, experienced progressive multifocal leukoencephalopathy and marked impairment of immune function as a result of concomitant use of immunosuppressive therapy. The risk of long-term B-cell depletion was also indicated in these patients. Based on these cases, the FDA issued an alert warning about off-label use of rituximab. Fatal fulminant hepatitis, after hepatitis B virus reactivation in carriers with malignant lymphoma, has also been reported. Hepatitis B virus antibody and liver function should be assessed before initiation of rituximab therapy [89]. Serious adverse events, such as pulmonary fibrosis (fatal) [90] and immune ulcerative colitis [91], have been reported in patients with refractory nephrotic syndrome.

2. Mycophenolate mofetil

Mycophenolate mofetil is a purine synthesis inhibitor with a mechanism of action similar to that of mizoribine and is typically used for immunosuppression after organ transplant. Recent reports indicate the efficacy of mycophenolate mofetil in the treatment of frequently-relapsing and steroid-dependent nephrotic syndrome, including refractory disease. In Japan, this usage is off-label, but this guideline suggests mycophenolate mofetil may be considered for the treatment of frequently-relapsing and steroid-dependent nephrotic syndrome when standard immunosuppressive agents cannot be used due to their adverse side effects. The recommendation grade has been classified as C1 in this guideline, as the efficacy and safety of the treatment should first be evaluated by appropriate studies such as randomized controlled trials.

Mycophenolate mofetil has been suggested to reduce relapse by cohort studies conducted in patients without sustained remission on cyclophosphamide [92–94], cyclosporine-dependent patients [95–100], and patients with cyclosporine nephrotoxicity [101]. In a small-scale, randomized controlled trial of mycophenolate mofetil (compared with cyclosporine) conducted on 31 children with frequently- relapsing nephrotic syndrome and who had received cyclophosphamide, the change from baseline in GFR, which was the primary endpoint of the study, was significantly smaller over the treatment period in the mycophenolate mofetil group when compared to the cyclosporine group ($p = 0.03$). However, in part because of the small sample size, no significant difference was shown between the two groups in terms of relapse-free time ($p = 0.06$) or person-year relapse rate ($p = 0.08$) [102]. The efficacy and safety of this treatment should be further evaluated in studies such as appropriately-designed, randomized controlled trials. An overseas randomized, cyclophosphamide-controlled trial is currently ongoing, as of August 2013 (ClinicalTrials.gov Identifier, NCT01092962).

Mycophenolate mofetil is well tolerated compared with other immunosuppressive agents, and its efficacy as a first-line treatment for frequently-relapsing and steroid-dependent

nephrotic syndrome has been suggested [103–105]. The guideline by the Children's Nephrotic Syndrome Consensus Conference (CNSCC) (US) and the KDIGO guideline describe a 1-year administration of mycophenolate mofetil as an option for immunosuppressive therapy in patients with frequently-relapsing and steroid-dependent nephrotic syndrome.

Many published studies used a body surface area-based dosage (1,200 mg/m^2/day) of mycophenolate mofetil [93, 95–97, 102, 103]. This guideline has employed the dosage and mode of administration of mycophenolate mofetil in line with CNSCC and KDIGO guidelines. The recommendation grade has been classified as C1, since mycophenolate mofetil has not yet been approved for the indication of nephrotic syndrome in Japan or other countries, and a safe and effective dosage and mode of administration to treat frequently-relapsing and steroid-dependent nephrotic syndrome, including refractory disease, have not yet been established.

Since absorption of mycophenolate mofetil varies among individuals, it is advisable to perform monitoring of blood mycophenolic acid concentration. An increased likelihood of relapse has been reported with trough levels below 2.0 μg/mL [97, 99]. Reports of short-term mycophenolate mofetil therapy for 6 months described that treatment withdrawal resulted in an immediate relapse in approximately 50 % of patients [93, 97]. Guidelines by CNSCC and the KDIGO recommend a duration of 1-year or longer for the administration of mycophenolate mofetil, but the efficacy and safety of long-term therapy have not yet been clarified.

Reported side effects of mycophenolate mofetil include gastrointestinal symptoms (diarrhea, abdominal pain) [92–95, 97, 103, 105], myelosuppression (leukocytopenia, anemia, thrombocytopenia) [93, 100, 105], and infection (herpes, varicella) [93, 100, 104] but can generally be reversed with dose reduction.

3. Tacrolimus

Tacrolimus is a calcineurin inhibitor similar to cyclosporine. For post-kidney transplant immunosuppression, it is now the first-line drug, surpassing the use of cyclosporine. Cyclosporine is often associated with side effects, including hypertrichosis and gingival hypertrophy. In comparison, Tacrolimus, is known to have fewer cosmetic side effects, and in North America the use of tacrolimus is becoming a popular treatment for frequently-relapsing and steroid-dependent nephrotic syndrome. CNSCC and KDIGO guidelines designate tacrolimus as an immunosuppressive agent, along with cyclosporine and mycophenolate mofetil. Tacrolimus may be considered for the treatment of frequently-relapsing and steroid-dependent nephrotic syndrome when cyclosporine cannot be used because of its untoward cosmetic side effects.

There are no randomized controlled trials that compare tacrolimus to cyclosporine or other immunosuppressive agents, and reports that are available are only small-number case series [17, 83, 106–108]. Other reports describe that switching from cyclosporine to tacrolimus is only effectively reducing cosmetic side effects and such a switch merits caution for the potential onset of diabetes mellitus [105, 108]. The recommendation grade has been classified as C1 in this guideline due to the efficacy and safety of the treatment not having yet been evaluated by appropriate studies such as randomized controlled trials.

Tacrolimus requires adjustments of dosage by monitoring blood concentration. Tacrolimus has been an off-label indication of frequently-relapsing and steroid-dependent nephrotic syndrome in Japan and other countries, but safe and effective dosage and modes of administration have not yet been established. Although many published studies used an adjustment to target blood trough levels of 5–10 ng/mL, based on clinical studies done on kidney transplantation cases [17, 83, 106–108], the efficacy and safety of long-term therapy have not been clarified. Thus, in line with the KDIGO guideline, this guideline suggests that tacrolimus therapy be started at 0.1 mg/kg/day in two divided doses, with the dosage then adjusted based on the monitoring of blood trough levels. The recommendation grade has been classified as C1. In a currently ongoing, multicenter, open-label, randomized controlled trial of tacrolimus versus cyclosporine for frequently-relapsing nephrotic syndrome in children (JSKDC06; UMIN ID, UMIN000004204) conducted in Japan, tacrolimus is given for 2 years, with the starting dosage of tacrolimus set to 0.1 mg/kg/day in two divided doses. The dosage is adjusted to maintain blood trough level within 5–7 ng/mL for the first 6 months and then 3–5 ng/mL for the next 18 months. The study results have not yet been made available.

Among the side effects of tacrolimus, the potential onset of diabetes mellitus is important. Particular caution is required when tacrolimus is used in patients with a family history of diabetes mellitus or if risk factors for impaired glucose tolerance (e.g., obesity) are present [106]. Renal interstitial fibrosis has also been reported, as with cyclosporine; one report described a significant correlation between higher tacrolimus trough levels and renal interstitial fibrosis [17].

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Chapter 5. Treatment of steroid-resistant nephrotic syndrome

Recommendation statements:

1. We recommend kidney biopsy to obtain a histological diagnosis for the evaluation of steroid-resistant nephrotic syndrome. [Recommendation grade B]
2. We recommend cyclosporine as a first-line treatment* for steroid-resistant nephrotic syndrome. [Recommendation grade A]
   (1) We recommend cyclosporine at the starting dosage of 2.5–5 mg/kg/day in two divided doses, followed by dose adjustment, referencing the following blood trough levels [Recommendation grade B]:
   Trough level 100–150 ng/mL (3 months)
   Trough level 80–100 ng/mL (3 months –1 year)
   Trough level 60–80 ng/mL (after 1 year)
   (2) If the patient fails to achieve at least partial remission within 4–6 months of cyclosporine therapy, we suggest the treatment plan be reconsidered. [Recommendation grade C1]
   (3) If a partial or complete remission is achieved within 4–6 months of cyclosporine therapy, we suggest continuation with the treatment for 1–2 years. [Recommendation grade C1]
   (4) We suggest combination therapy with a low-dose steroid (prednisolone 0.5–1.0 mg/kg on alternate days) as it is associated with an increased remission rate. [Recommendation grade C1]
3. (1) We suggest that combination therapy of steroid pulse therapy and cyclosporine be considered, as it can be effective in inducing remission. [Recommendation grade C1]
   For steroid pulse therapy, one course consists of intravenous methylprednisolone 20–30 mg/kg per dose (maximum, 1 g) administered once daily for 3 consecutive days per week.
   (2) We suggest that steroid pulse therapy alone not be considered for the induction therapy. [Recommendation grade C2]
4. We suggest that cyclophosphamide not be considered for induction therapy in children with steroid-resistant nephrotic syndrome. [Recommendation grade C2]
5. We recommend combination therapy of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers with cyclosporine, as this combined therapy is effective in reducing proteinuria. [Recommendation grade B]
6. We suggest prednisolone therapy to treat nephrotic syndrome relapse following remission. [Recommendation grade C1]

Note: To calculate the dose for body weight, the standard body weight for the height of the patient should be used (similarly for body surface area as well).

*Immunosuppressive therapy in patients in a nephrotic state requires extreme caution for serious complications and side effects, including infection and hypertension, can occur. Thus, it is highly preferable that a pediatric nephrologist treats children with steroid-resistant nephrotic syndrome.

Explanation

In this guideline, steroid resistance is defined as the "absence of complete remission after at least 4 weeks of daily prednisolone therapy." This chapter describes treatment of serum albumin $\leq$2.5 g/dL for steroid-resistance patients.

A Cochrane review and the 2012 KDIGO guideline place cyclosporine as the first-line drug for induction therapy in patients with steroid-resistant nephrotic syndrome. Recommendations from the guidelines include: (1) calcineurin inhibitor therapy for a minimum of 6 months and then stopped if partial or complete remission is not achieved; (2) calcineurin inhibitor therapy for a minimum of 12 months when a partial or complete remission is achieved; and (3) low-dose steroid therapy combined with calcineurin inhibitor therapy. Cyclophosphamide, on the other hand, is not recommended for induction therapy in steroid-resistant nephrotic syndrome patients. According to the cochrane review, the remission rate does not significantly differ between oral cyclophosphamide and prednisolone, and cyclosporine is more efficacious than cyclophosphamide pulse therapy. Randomized controlled trials of steroid pulse therapy have not yet been reported, but multiple studies have suggested the efficacy of steroid pulse therapy [109–111]. While drugs that inhibit the renin-angiotensin system, such as angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers, have been reported to be efficacious in reducing proteinuria in steroid-resistant nephrotic syndrome [112], as detailed in "Renin-angiotensin system inhibitors" in this chapter, combination therapy with cyclosporine is recommended rather than single-drug therapy. Thus, at this point, cyclosporine has high-level evidence as a first-line therapy for steroid-resistant nephrotic syndrome. For use in combination with cyclosporine, low-dose steroids, renin-angiotensin system inhibitors, and steroid pulse therapy are recommended on the basis of increasing evidence, but the efficacy and safety of these combinations require further evaluation.

Various genetic mutations (e.g., *NPHS1*, *NPHS2*, *TRPC6*, *CD2AP*, *PLCE1*, *INF2*, *WT1*, *ACTN4*) have been reported in patients with familial or low-age onset, steroid-resistant nephrotic syndrome [113–115]. For childhood-onset FSGS,

published reports of genetic mutations involved small sample numbers of patients and thus no conclusive implications can be derived. However, a report from a Spanish observational study recommends to first screen for *NPHS1* in patients with congenital steroid-resistant nephrotic syndrome, *NPHS*2 in infantile- to childhood-onset cases, and for *p.R229Q* in the *NPHS2* gene in adolescent- and adult-onset cases [116]. Thus, genetic testing should be considered in patients with refractory, familial, or low-age onset disease.

1. Kidney biopsy

If steroid resistance is determined, then kidney biopsy is recommended to obtain a histological diagnosis and to rule out conditions such as membranous nephropathy, and to decide the most effective treatment plan. The histological types are broadly classified as minimal-change disease, FSGS, and diffuse mesangial proliferative disease. Steroid-resistant nephrotic syndrome failing to achieve complete remission progressed to end-stage renal failure over 10 years in approximately 40 % of patients [2]. In Japan, FSGS is the cause of pediatric end-stage renal failure in 20 % of observed cases.

2. Cyclosporine

Cyclosporine is recommended as the first-line treatment if steroid resistance is determined. Among randomized controlled trials on cyclosporine in children with steroid-resistant nephrotic syndrome, a report in 1993 described partial or complete remission rate at 12 months of 60 % [117];a report in 1996, at 6 months of 100 % [118]; and a report in 2009, at 6 months of 80 % [119]. All of these trials indicated high remission rates. In a Japanese non-randomized controlled trial in 35 children with steroid-resistant nephrotic syndrome, treatment was modified according to histopathological findings of the kidney, and 28 children with minimal-change disease or mesangial proliferation were treated with cyclosporine (with dose adjustment to maintain a trough level of 120–150 ng/mL for the first 3 months, followed by 80–100 ng/mL for the next 9 months; and thereafter, as an optional recommended treatment to maintain 60–80 ng/mL for 12 months) plus prednisolone (1 mg/kg/day in three divided doses daily for 4 weeks, followed by 1 mg/kg on alternate days for 12 months starting week 5). Seven children with FSGS were treated with cyclosporine and prednisolone as mentioned above, as well as 5 cycles of steroid pulse therapy (at weeks 1, 2, 5, 9, and 13). The study reported high remission rates of 82.1 and 85.7 %, respectively [111].

The time where assessment for the therapeutic response to cyclosporine should be conducted in patients with steroid-resistant nephrotic syndrome has not yet been established. However, 4.4 ± 1.8 weeks were required for observed decreases in proteinuria [118], and 8–12 weeks were required for a partial or complete remission in a randomized controlled trial published in 2009 [119]. The mean duration to a partial/complete remission was 9.9 ± 3.4 weeks (2–16 weeks) in another observational study [120]. Moreover, a prospective 5-year follow-up study in Japan on 35 children with steroid-resistant nephrotic syndrome reported that response to cyclosporine at 4 months predicted the 5-year outcome in the majority of patients [121]. Multiple randomized controlled trials have assessed the efficacy of cyclosporine at 6 months. Thus, in terms of the timing for assessment of the cyclosporine therapeutic response, this guideline recommends to reconsider the treatment plan if the patient fails to achieve at least partial remission within 4–6 months of cyclosporine therapy.

The dose of cyclosporine should be adjusted while monitoring blood concentrations. Although some reports use a trough level of 100–200 ng/mL [122–125], the incidence of nephrotoxicity is approximately 50 % in patients that are given 2-year cyclosporine therapy with a trough level of 100 ng/mL [13]. Similar to the starting dosage used in kidney transplant patients, this guideline also recommends to maintain a trough level of 100–150 ng/mL for the first 3 months before remission, and for patients treated with cyclosporine for more than 1 year, to maintain a trough level of 60–80 ng/mL from the second year of the treatment. For children with steroid-resistant nephrotic syndrome, although dose adjustment according to C2 (blood concentration at 2 h post-dose) has not been established, some reports described a correlation between the AUC_{0-4} (area under the concentration curve) of cyclosporine and C2 [43], or C2 control in children with frequently-relapsing nephrotic syndrome and in adults with steroid-resistant nephrotic syndrome (A randomized controlled trial of cyclosporine C2 monitoring; UMIN ID, C000000008) [126, 127]. Evidence is expected to accumulate regarding C2 control in children with steroid-resistant nephrotic syndrome.

Many side effects are known to be associated with cyclosporine, including nephrotoxicity, hypertension, susceptibility to infection, gingival hypertrophy, and hypertrichosis (See Definitions of Terms, Chapter 1 and Chapter 4). In the development of posterior reversible encephalopathy syndrome (PRES), in particular, edema (or nephrotic state) has been suggested as a risk factor, and steroid resistance was reported in 5 of 7 patients with nephrotic syndrome who suffered PRES [128], thereby warranting careful observation and actions.

Because of high relapse rates of 10–76 % after withdrawal of cyclosporine, and another calcineurin inhibitor, tacrolimus, in the treatment of steroid-resistant nephrotic syndrome [120, 121, 127, 129], prolonged cyclosporine therapy is often required. However, with concerns about cyclosporine nephrotoxicity, long-term remission rates and renal outcome require further evaluation.

3. Steroid pulse therapy

Combination therapy involving steroid pulse therapy and cyclosporine should be considered as it can be effective in inducing remission of steroid-resistant nephrotic syndrome. However, steroid pulse therapy alone is not recommended for induction therapy. During use of methylprednisolone, we suggest discontinuation of cyclosporine.

The combination of steroid pulse therapy plus cyclosporine, compared against cyclosporine alone, has long been an issue in the treatment of children with steroid-resistant nephrotic syndrome, but there have been no published randomized controlled trials investigating this comparison. In a non-randomized controlled trial in Japan, children with FSGS were treated with steroid pulse therapy + cyclosporine + prednisolone for 12 months, leading to a high remission rate of 85.7 % [111]. Another non-randomized controlled trial of steroid pulse therapy + cyclosporine + prednisolone for FSGS also reported remission in 8/10 patients within 8 weeks of beginning treatment [130]. Based on these data, addition of steroid pulse therapy to cyclosporine can lead to a higher remission rate. A questionnaire among the councilor board members of the Japanese Society for Pediatric Nephrology also showed that steroid pulse therapy and cyclosporine were used in combination at the majority of medical institutions. However, the current evidence level is not high for this combination therapy. A Japanese randomized controlled trial is currently ongoing to compare the combination of cyclosporine + prednisolone + steroid pulse vs. the combination of cyclosporine + prednisolone (UMIN ID, C000000007).

There are also no randomized controlled trials yet published regarding steroid pulse therapy alone for patients with steroid-resistant nephrotic syndrome; only some observational studies were found during literature searches. Yorgin et al. reported that, of a total of 11 children with steroid-resistant nephrotic syndrome (mean age, 3.6 ± 1.5 years), complete remission was attained in 9 children after steroid pulse therapy (methylprednisolone 30 mg/kg/dose, maximum 1 g/dose) with an average of 24.8 ± 10.5 pulse methylprednisolone therapy doses. Side effects were mild and infrequent, and the authors concluded that pulse methylprednisolone therapy appears to safely and effectively induce remission in young children with steroid-resistant nephrotic syndrome [131]. Another study in 16 children with steroid-resistant nephrotic syndrome (median age, 3.8 years) reported remission in 10 children after methylprednisolone 15 mg/kg/day administered for 3 or 5 days. The remaining 6 children were given immunosuppressive therapy (cyclophosphamide in 3 children, cyclosporine in 2 children, and tacrolimus in 1 child), leading to clinical remission [132]. An additional study performed 14 courses of steroid pulse therapy (methylprednisolone 30 mg/kg/dose, maximum 1 g/dose, 3 days per course) with heparin in 10 children with steroid-resistant nephrotic syndrome, resistant to cyclophosphamide or cyclosporine. One of the 10 patients discontinued the pulse therapy because of peritonitis; of the remaining patients, complete remission was achieved in 4/9 patients, partial remission in 3/9 patients, and there was no response observed in 2/9 patients. The findings concluded that methylprednisolone pulse therapy with heparin can induce remission in children with steroid-resistant nephrotic syndrome, even when the patient is resistant to cyclophosphamide and cyclosporine [110]. Although these data indicate that steroid pulse therapy can be effective in inducing remission of steroid-resistant nephrotic syndrome in children, the evidence level is not high due to the limited number of patients studied and the absence of randomized controlled trials.

Adverse side effects of steroid pulse therapy include hypertension, hyperglycemia, bradycardia, thrombosis, and PRES, for which monitoring is required during therapy.

4. Cyclophosphamide

Cyclophosphamide is not recommended as a first-line induction therapy in children with steroid-resistant nephrotic syndrome. Two randomized controlled trials have been published on cyclophosphamide therapy in children with steroid-resistant nephrotic syndrome [48, 133]. In both of these studies, combination therapy of cyclophosphamide plus a steroid was compared with a steroid treatment alone, but no significant differences were shown in the remission rate or side effects.

A randomized controlled trial compared oral cyclosporine versus cyclophosphamide pulse therapy as the initial therapy in children newly diagnosed with steroid-resistant nephrotic syndrome (histologically-proven, minimal-change disease, FSGS, or mesangial hypercellularity). The investigation reported that at week 12 of therapy, at least partial remission was attained in 9/15 cyclosporine-treated patients (60 %; complete remission in 2 patients, partial remission in 7 patients) and 3/17 cyclophosphamide pulse-treated patients (17 %; complete remission in l patient, partial remission in 2 patients), with cyclosporine evidently superior ($p < 0.05$). Given these results, the study was therefore discontinued. After 24 weeks of therapy, complete remission was achieved by 2/15 cyclosporine-treated patients (13 %), and in 1/17 cyclophosphamide pulse-treated patients (5 %) (p = n.s.), while partial remission was achieved by 7/15 cyclosporine-treated patients (46 %) and 2/17 cyclophosphamide pulse-treated patients (11 %); these results show significantly higher rates with cyclosporine. The number of

adverse side events was comparable between the groups. The authors concluded that cyclosporine is more effective than cyclophosphamide in inducing at least partial remission in steroid-resistant nephrotic syndrome in children [134].

5. Renin-angiotensin system inhibitors

Renin-angiotensin system inhibitors are expected to be effective in reducing proteinuria in children with steroid-resistant nephrotic syndrome and are recommended for combination therapy with cyclosporine. Two randomized controlled trials have been published on the use of angiotensin-converting enzyme inhibitors [enalapril, fosinopril (unapproved in Japan)] in this setting. In one of these trials, patients were treated with enalapril at low (0.2 mg/kg) and high (0.6 mg/kg) dose levels in a crossover manner; the 0.2 mg/kg administration resulted in an insignificant reduction in urine albumin/creatinine ratio from 3.9 to 2.3, and the 0.6 mg/kg administration resulted in a significant reduction in urine albumin/creatinine ratio from 5.2 to 2.5, compared with the low-dose administration. Serum creatinine and potassium levels were unchanged during the study [112]. The other trial compared the combination therapy of fosinopril plus a steroid against a steroid alone in normotensive children with steroid-resistant nephrotic syndrome, and reported that the add-on fosinopril significantly reduced 24-h urinary protein excretion volume without any changes in blood pressure or components of the renin-angiotensin system [135]. Prolonged proteinuria has been described as a risk factor for renal failure, according to observational studies on long-term outcome of steroid-resistant FSGS [2, 136–139]. In adults with idiopathic FSGS, renin-angiotensin system inhibitor therapy reduced proteinuria but achievement of complete remission was difficult and the incidence of renal failure did not decrease [139–141].

To conclude, renin-angiotensin system inhibitor therapy is not indicated as the first-line induction therapy in children with steroid-resistant nephrotic syndrome, but is, rather, recommended for combination therapy with cyclosporine, in line with the KDIGO guideline. Administration of renin-angiotensin system inhibitors requires great caution as an abrupt decrease in intraglomerular pressure may occur by decreasing the glomerular filtration rate (GFR), resulting in increased serum creatinine and hyperkalemia. Thus, in patients with moderate or severe renal dysfunction (GFR <60 mL/min/1.73 m^2), renin-angiotensin system inhibitor therapy should only be given with caution and using a reduced starting dose, with careful monitoring of serum creatinine and potassium levels. In the presence of dehydration, patients should be advised to temporarily discontinue treatment since increased serum creatinine, hyperkalemia, and circulatory collapse is more likely to occur. Renin-angiotensin system inhibitors are contraindicated during pregnancy because of teratogenicity and require caution for use in females of childbearing age. Other reports described that patients treated with cyclosporine and renin-angiotensin system inhibitors in combination are at higher risk for cyclosporine nephrotoxicity [12] and renal dysfunction, thereby warranting careful observation.

6. Treatment of a relapse of nephrotic syndrome after remission

Children with steroid-resistant nephrotic syndrome often relapse after remission (complete or partial remission). After achieving remission, patients are likely to regain steroid sensitivity, and thus prednisolone therapy is recommended to treat relapse of nephrotic syndrome.

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Chapter 6. Steroid-resistant nephrotic syndrome—other treatments

Recommendation statements:

1. LDL apheresis and plasmapheresis

We suggest that LDL apheresis and plasmapheresis be considered for patients with refractory steroid-resistant nephrotic syndrome. [Recommendation grade C1]

2. Rituximab

We suggest that rituximab be considered for patients with refractory steroid-resistant nephrotic syndrome. [Recommendation grade C1]

3. Tacrolimus

(1) We suggest that tacrolimus be considered as a treatment option for patients with steroid-resistant nephrotic syndrome, where cyclosporine cannot be used because of its cosmetic side effects. [Recommendation grade C1]

(2) We suggest that tacrolimus (starting dosage 0.1 mg/kg/day) should be given in two divided doses, followed by dose adjustment according to monitoring of blood drug concentration. [Recommendation grade C1]

Note 1: To calculate the dose for body weight, the standard body weight for the height of the patient should be used as well as body surface area.

Note 2: LDL apheresis and plasmapheresis should be performed at an institution that has pediatric nephrologists with abundant experience in pediatric extracorporeal circulation due to the involved risks associated with extracorporeal circulations, vascular access procedures and management in small children.

Note 3: Rituximab and tacrolimus have not been approved for the indication of nephrotic syndrome at the time of the preparation of this guideline. Considering the off-label status, the risks and benefits of treatment and the patient's pathological conditions should be carefully evaluated before treatment initiation. Preferably, an experienced pediatric nephrologist should perform these treatments.

Explanation

This chapter describes treatment for steroid-resistant nephrotic syndrome that is refractory to steroids and conventional immunosuppressive agents, where complete remission is not obtained, or in cases where cyclosporine cannot be used due to the cosmetic side effects.

1. LDL apheresis and plasmapheresis

There is not a lot of evidence for LDL apheresis and plasmapheresis in the treatment of refractory steroid-resistant nephrotic syndrome. However, LDL apheresis and plasmapheresis may be considered when a poor prognosis is given to patient who have refractory steroid-resistant nephrotic syndrome and who are resistant to the various treatments and show persistent severe proteinuria. The recommendation grade has thus been classified as C1.

When choosing between LDL apheresis and plasmapheresis as a treatment, highly-selective proteinuria appears to be a good basis for selecting LDL apheresis, given that one clinical study has shown the efficacy of LDL apheresis in patients with highly-selective proteinuria. For physically small patients, however, plasmapheresis with a smaller blood circuit volume (priming volume) should be the treatment choice.

(1) LDL apheresis

Clinical studies have been limited on LDL apheresis for refractory steroid-resistant nephrotic syndrome, and currently, no established evidence from randomized controlled trials exists for LDL apheresis for the treatment of steroid-resistant nephrotic syndrome; this includes refractory steroid-resistant nephrotic syndrome. However, some clinical studies in adults show benefits of LDL apheresis in inducing remission of steroid-resistant nephrotic syndrome [142–145]. In children, a clinical study involving 11 patients with refractory steroid-resistant nephrotic syndrome reported a (complete or partial) remission rate of 63 %, suggesting that LDL apheresis can help induce remission of refractory steroid-resistant nephrotic syndrome in children [146]. Specific mechanism(s) behind the beneficial effects of LDL apheresis on this disease remain unclear, but it has been suggested to go beyond the improvement of dyslipidemia. Some reports indicate that LDL apheresis can improve the responsiveness to steroids [143, 144, 146, 147] and cyclosporine [148], and thus combination therapy of LDL apheresis with these drugs is recommended rather than LDL apheresis alone. Efficacy of LDL apheresis has been described to be associated with highly-selective proteinuria (one study showed that patients with complete remission after LDL apheresis had a lower selectivity index [SI], which is calculated as [urinary immunoglobulin G (IgG)/serum IgG] × [serum transferrin (Tf)/urinary Tf], of 0.05 ± 0.02, compared with 0.25 ± 0.04 in patients who did not respond to LDL apheresis [146]) or minor renal tubular interstitial damage [146], and thus early LDL apheresis after the onset of the disease is considered advisable [142, 146]. Currently, in Japan, "A Prospective Observational Survey on the Long-Term Effects of LDL-Apheresis on Steroid-Resistant Nephrotic Syndrome (POLARIS Survey; UMIN ID, UMIN000000871)" is ongoing. Data from this study should help establish higher-level evidence regarding LDL apheresis for refractory steroid-resistant nephrotic syndrome.

Side effects of LDL apheresis, particularly hypotension, require caution. These side effects include those generally associated with extracorporeal circulation i.e., (1) decrease in blood pressure, tachycardia, nausea and vomiting, shock, and other manifestations induced by extracorporeal blood circulation; (2) manifestations in an allergic reaction to drugs or artificial materials; and (3) complications associated with coagulations and anticoagulant therapy, intracircuit coagulation, bleeding from the vascular access site, and others. Vascular access infection has also been reported [146]. Angiotensin-converting enzyme inhibitor therapy should be discontinued before LDL apheresis because of the possible shock with LDL apheresis during angiotensin-converting enzyme inhibitor therapy, but there have been no reports of serious side effects of LDL apheresis in patients with refractory steroid-resistant nephrotic syndrome [142–147]. However, since LDL apheresis requires a large amount of blood to fill the circuit, it is safe to limit the use of LDL apheresis to children weighing more than 30 kg.

(2) Plasmapheresis

In patients with a post-kidney transplant relapse of FSGS, plasmapheresis has been performed to remove humoral factors likely associated with the disease and has been accepted to some extent though no randomized controlled trials have been performed. For refractory steroid-

resistant nephrotic syndrome, however, limited clinical studies on plasmapheresis have shown inconclusive results. Although plasmapheresis has been described as leading to decreased proteinuria and stabilized renal function in some patients, reports have varied in terms of the characteristics of patients studied, the presence or absence of concomitant use of immunosuppressive agents, and conditions of plasmapheresis; reported plasmapheresis efficacy rates have been 57, 25, and 72 %, respectively, with significant variation and without known long-term benefits [149–151]. One report has suggested that plasmapheresis would be more useful when applied early in the course of the disease and prior to any histopathological changes [149]. Combination therapy of plasmapheresis with immunosuppressive therapy is therefore recommended.

Reports from clinical studies have been limited with regards to side effects of plasmapheresis for refractory steroid-resistant nephrotic syndrome [149]. Typical side effects of plasmapheresis that require caution include those associated with extracorporeal circulation, allergic reactions to the replacement fluid, and infection, including sepsis [149].

Plasmapheresis can be performed in physically smaller children because a smaller amount of blood is required compared with LDL apheresis. While the advantages of plasmapheresis include removal of pathological humoral factors and correction of dyslipidemia, its disadvantages include removal of beneficial substances from blood as well as the use of a blood product as the replacement fluid, which should be well understood before application.

LDL apheresis and plasmapheresis up to 12 sessions in 3 months are covered by health insurance, in dyslipidemic patients with refractory nephrotic syndrome with FSGS (diagnosis in the list of health insurance coverage, focal glomerulosclerosis).

2. Rituximab

Given that data is currently insufficient to clarify the efficacy and safety of rituximab in the treatment of refractory steroid-resistant nephrotic syndrome, it appears too early to recommend the use of this drug. However, rituximab therapy may be considered in the treatment of refractory steroid-resistant nephrotic syndrome because its use seems justified due to the poor prognosis of patients with refractory steroid-resistant nephrotic syndrome who are resistant to various treatments and continue to have severe proteinuria. The recommendation grade has thus been classified as C1. Considering the off-label status of its usage at this point (at preparation of this guideline), as well as the serious side effects reported with rituximab, risks and benefits should be carefully weighed before use and careful administration is advised.

Limited clinical studies for rituximab use in for refractory steroid-resistant nephrotic syndrome have been published. One study reported that 83 % of patients with steroid-dependent nephrotic syndrome sustained remission at 12 months and 48 % of patients with refractory steroid-resistant nephrotic syndrome showed remission (complete or partial) at 6 months [81]. Another study of rituximab reported a good initial response in 82 % of patients with steroid-dependent nephrotic syndrome and 44 % of patients with steroid-resistant nephrotic syndrome [79]. These data support an increasing view that rituximab is also efficacious for steroid-resistant nephrotic syndrome, though less so than it is for steroid-dependent nephrotic syndrome. The KDIGO guideline does not recommend rituximab for steroid-resistant nephrotic syndrome due to lack of randomized controlled trials and the risk of serious side effects. A recent report from an open-label, randomized, controlled trial states that rituximab was not efficacious for refractory steroid-resistant nephrotic syndrome [152]. However, this conclusion is doubtful given that the follow-up duration in the randomized controlled trial was as short as 3 months and treatment given concomitantly with rituximab could be insufficient.

For the use of rituximab in the treatment of refractory steroid-resistant nephrotic syndrome, the dosage, number of doses, dosing intervals, therapy duration, or effective concomitant treatments have not yet been fully established; many reports, however, have used 375 mg/m^2 once every week for a total of 4 doses [81].

Side effects of rituximab are mostly acute and insignificant, but rare cases of serious side effects have been reported. Late-onset side effects, occurring long after rituximab therapy, are unclear (for details on side effects of rituximab, see Chapter 4.

3. Tacrolimus

Tacrolimus has been documented to be efficacious in five observational studies and one randomized cyclosporine-controlled trial [119, 153–157], but no large-scale randomized controlled trials exist. Thus, the recommendation grade has been classified as C1. The only available randomized, controlled trial conducted in a small number of children at a single center in India reported no difference between tacrolimus and cyclosporine in the complete remission rates of 85.7 % (18/21) and 80.0 % (16/20), respectively, after 6 months of treatment. The proportion of patients who experienced relapse, however, was significantly smaller in those receiving tacrolimus compared with cyclosporine (11 vs. 50 %; $p = 0.01$) [119]. Patients in both groups experienced nephrotoxicity (38.0 vs. 60.0 %), hypertrichosis (0.0 vs. 95.0 %), gingival hypertrophy (4.7 vs. 60.0 %), and diarrhea (28.6 vs. 5 %). With

the exception of diarrhea, the frequency of side effects, especially cosmetic side effects, was lower in tacrolimus-treated patients compared with cyclosporine-treated patients.

The dosage of tacrolimus recommended in the guidelines by the KDIGO and the Children's Nephrotic Syndrome Consensus Conference (CNSCC) (US) is 0.05–0.1 mg/kg/day in two divided doses, with a target trough level of 5–10 ng/mL. This dosage is based on clinical studies in kidney transplant patients, and the efficacy and safety of its long-term use in the treatment of steroid-resistant nephrotic syndrome are unclear.

Side effects reported with tacrolimus include impaired glucose tolerance and hemolytic uremic syndrome requiring discontinuation of the treatment, as well as chronic nephrotoxicity at follow-up kidney biopsy similar to that associated with cyclosporine [155, 156, 158].

4. Other (mycophenolate mofetil)

Mycophenolate mofetil use in the treatment of steroid-resistant nephrotic syndrome has been described in very few reports [159–161] and the remission rates have been low. A high remission rate was shown only by one Chinese uncontrolled study, but this could be due to the small proportion of initial non-responders, who typically have poor responses to treatments, as well as patients with FSGS that were part of the study [160]. Although mycophenolate mofetil may be effective in the treatment of steroid-resistant nephrotic syndrome if combined with steroid pulse therapy or other treatments, current evidence is insufficient. The KDIGO guideline recommends mycophenolate mofetil in children who fail to achieve remission with calcineurin inhibitors and steroids. This recommendation is based on a National Institute of Health-funded randomized controlled trial that compared a combination of mycophenolate mofetil and dexamethasone to cyclosporine in patients with steroid-resistant FSGS. The report demonstrated no inter-group differences in the remission rate (46 % in the cyclosporine group vs. 33 % in the mycophenolate mofetil/dexamethasone group; $p = 0.11$) [162]. However, interpretation of the results requires caution; this randomized controlled trial enrolled patients aged 2–40 years who had early morning urine protein creatinine ratio of >1 g/gCr and the eligibility criteria did not include hypoproteinemia. Therefore, the study included many adult patients and non-nephrotic syndrome patients.

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Chapter 7. Long-term pharmacotherapy for pediatric idiopathic nephrotic syndrome

Recommendation statements:

1. In steroid therapy for the induction of remission in patients around transition age, we suggest that a switch from the ISKDC regimen to a regimen close to that used for adults be considered as necessary. [Recommendation grade C1]
2. Cyclosporine may be repeatedly used for 2 to 3 years when unavoidable, but attention should be given to the appropriateness of the therapy duration, blood drug concentration, and cumulative dose, and we suggest the consideration of kidney biopsy to monitor for nephrotoxicity, as necessary. [Recommendation grade C1]
3. We recommend cyclophosphamide therapy be limited to one course during a patient's lifetime, with cumulative doses taken into account. [Recommendation grade A]
4. When combination therapy of steroids and multiple immunosuppressive agents is required, we suggest that prior to use, a thorough understanding of all characteristics and side effects for each of the steroids and immunosuppressive agents be known. [Recommendation grade C1]

Explanation

A considerable population of patients, with frequently-relapsing idiopathic nephrotic syndrome that originates in childhood, can relapse in adulthood, and some patients require prolonged medicinal therapy [163]. In children with long-standing disease, it is important to minimize the physical, mental, and social disabilities from treatments as they grow into adults. Caution should be used to avoid life-long side effects that can occur with excessive treatments in exchange for a shortsighted, unnecessary fear of relapse. What matters most is not relapse but prolonged disabilities. For example, long-term steroid therapy can be beneficial to a patient if it is selected after anticipated relapse-preventing effect and foreseeable side effects are considered along with the patient's relapse history. Having a

sense of how safely the long-standing disease can be managed is a key strategy. The attending physician as well as the patient's family should all understand the impact of extended treatments. Literature articles that directly relate to the recommendation statements provided in this chapter are scarce, but search results are provided as references. Also, respective chapters should be looked at for the use of individual drugs in long-term management.

High-level evidence, such as randomized controlled trials, on long-term management of nephrotic syndrome has not yet been published. Reported clinical studies typically aim to evaluate the short-term effects of drugs. Some studies follow patients over a long period of time, but only obtained long-term outcomes under very limited conditions; this data often cannot be generalized to the real clinical setting. For this reason, the recommendation levels in this chapter of the guideline have been determined by committee consensus and using previous reports as references.

When providing long-term care, the attending physician should well understand the characteristics of the drugs, to use them as a single agent or in combination as appropriate at his/her discretion, and according to the clinical course and circumstances of individual patients [163].

Patients with steroid-resistant nephrotic syndrome and failing to achieve remission over an extended period of time are ultimately likely to suffer renal failure and require strong immunosuppressive therapy. However, the decision to decrease or discontinue immunosuppressive therapy will also be essential to avoid a fatal outcome as a result of jeopardizing the patient's life in an attempt to improve renal outcome.

Off-label drug use may be acceptable in patients when the use is desirable, based on available evidence accumulated from Japan and other countries [92, 100]; inconsiderate use, however, can lead to unforeseeable adverse events and other problems that may preclude clinical trials aiming to expand the indications. The use of unapproved drugs after adequate procedures can provide useful basic data for later clinical trials or expansion of indications, and therefore can be helpful.

1. Steroids

In steroid therapy for induction of remission in patients around the childhood-adult transition age, it may be considered necessary to switch from the ISKDC regimen to a regimen close to that used for adults [164]. This was a controversial issue in the questionnaire among the councilor board members of the Japanese Society for Pediatric Nephrology (conducted in May 2010): 15 members (29 %) indicated that "after puberty, the ISKDC regimen should be changed to a regimen close to that for adults"; 23 members (44 %) indicated that "after puberty, the dose for daily dosing should be 40 mg or lower, followed immediately by alternate-day dosing; and 14 members (27 %) indicated that "even after puberty, the regimen should remain in line with the ISKDC regimen." No evidence exists on any superiority or inferiority of these approaches. Taken together, it appears that, as long as steroid therapy induces remission and has no effects on subsequent relapse, the maximum steroid dose in the induction therapy may be changed as necessary. Often in the context of long-term care, treatment of a relapse can be difficult in certain patients, such as those who already have avascular necrosis of the femoral head, because steroid therapy is the only available option for induction of remission. In such patients, the steroid use for remission induction should be minimized in both dose and duration and strong immunosuppressive therapy should be given to prevent relapse, with the risks taken into account. In summary, steroid use during the long course of the disease often entails difficult decisions in individual cases, and decisions should be made after careful assessment concerning the incidence of side effects and other pertinent information. An association between steroid use and height has been described [165–168].

2. Cyclosporine

Although many reports describe that cyclosporine can be used over a long period, attention should be paid to the appropriateness of therapy duration, blood drug concentration, and cumulative doses, and a kidney biopsy should be considered as appropriate to monitor for nephrotoxicity [13, 14, 36, 41, 122, 169–177]. Some specialists point to the tendency of nephrotic syndrome to be protracted after use of cyclosporine therapy, but whether this is true or not should be fully examined in future studies. Whichever is the case, it is important that clinicians recognize cyclosporine as a drug better avoided. Inconsiderate long-term use of cyclosporine for prevention of relapse should be avoided. When long-term use is unavoidable, maintaining the blood drug concentration below the target concentration recommended for initial treatment, and within the range that is efficacious, should be considered.

3. Cyclophosphamide

Cyclophosphamide has been associated with gonadal dysfunction [178, 179], and may be given only one course during a lifetime, with cumulative doses taken into account (see Chapter 3 of Part 1, page 10).

For mizoribine, there has been little evidence provided for long-term use, and further investigation is warranted. Mycophenolate mofetil, tacrolimus, and rituximab are currently used off-label for nephrotic syndrome in Japan, and evidence for their long-term use has been scarce.

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