

# Treatment of steroid-sensitive nephrotic syndrome: new guidelines from KDIGO

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**Abstract** The 2012 Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline on glomerulonephritis (GN) is intended to assist the practitioner caring for patients with GN. Two chapters of this guideline focus specifically on nephrotic syndrome in children. Guideline development followed a thorough evidence review, and management recommendations and suggestions were based on the best available evidence. Critical appraisal of the quality of evidence and strength of recommendations followed the Grades of Recommendation Assessment, Development and Evaluation (GRADE) approach. Chapters 3 and 4 of the guideline focus on the management of nephrotic syndrome in children aged 1–18 years. Guideline recommendations for children who have steroid-sensitive

nephrotic syndrome (SNSS), defined by their response to corticosteroid therapy with complete remission, are addressed here. Recommendations for those with steroid-resistant nephrotic syndrome (SRNS) (i.e., do not achieve complete remission) are discussed in the companion article. Limitations of the evidence, including the paucity of large-scale randomized controlled trials, are discussed. This article provides a short description of the KDIGO process, the guideline recommendations for treatment of SSNS in children and a brief review of relevant treatment trials related to each recommendation.

**Keywords** Clinical practice guidelines · Steroid-responsive nephrotic syndrome · Management · Children

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## Introduction

Idiopathic nephrotic syndrome is a major contributor to the workload of pediatric nephrologists. Most children have steroid-sensitive nephrotic syndrome (SSNS), with about 20 % of children having steroid-resistant nephrotic syndrome (SRNS), depending on the geographic area [1]. Most children with SSNS have minimal change disease (MCD) [2], while children with SRNS have MCD, mesangial proliferative glomerulonephritis (MesPGN) or focal and segmental glomerulosclerosis (FSGS) [2]. Studies by the International Study of Kidney Disease in Children (ISKDC) and the Arbeitsgemeinschaft für Pädiatrische Nephrologie (APN) during the 1960s, 1970s, and 1980s, and subsequent studies by individual research teams form the basis of the clinical management of SSNS and SRNS in children. Transformation of local interpretation of the literature into a regional or national clinical practice guideline typically incorporates a systematic review and scoring of the literature. Published guidelines from France, North

America, and India have been generated using this approach [3–5]. While reflecting available evidence, these guidelines were largely based on consensus among experts in the field. Now KDIGO (Kidney Disease: Improving Global Outcomes) has published clinical practice guidelines on various glomerulonephritides including SSNS and SRNS in children using evidence-based principles [6]. In this article, we discuss the KDIGO process, present the guidelines for SSNS, and outline the evidence used to develop these guidelines. For reference, definitions typically used to discuss nephrotic syndrome are found in Table 1. The guideline for SRNS is presented in a separate article [7].

### What is KDIGO?

KDIGO ([www.kdigo.org](http://www.kdigo.org)), which was established in 2003, is an international non-profit organization aiming to improve the outcomes of kidney disease patients worldwide. It is governed by an international board and is managed by the National Kidney Foundation in the United States. The board comprises approximately 50 members of whom most are practicing nephrologists. The board elects an 11-person executive committee, which plans and oversees KDIGO activities and is chaired by two board members (currently Dr. Bertram Kasiske and Dr. Kai-Uwe Eckardt).

Topics for guidelines are chosen based on the worldwide burden of disease, the likelihood of the condition responding to prevention and/or treatment, the expected impact of management, the existence of sufficient evidence from

which to develop evidence-based guidelines, and the potential that such guidelines can improve outcomes.

### The KDIGO guideline process

Guidelines are developed by independent, international, multidisciplinary workgroups comprising 12–20 members. The two co-chairs choose the workgroup members. The Glomerulonephritis Workgroup was chaired by Drs. Daniel Cattiran (Canada) and John Feehally (the United Kingdom) and comprised 16 members from the United States of America, the United Kingdom, Australia, Canada, Chile, China, Germany, India, the Netherlands, and Spain. Each guideline workgroup is supported by an independent review team to provide methodological expertise using evidence-based principles to workgroup members. They perform literature searches for systematic reviews, randomized controlled trials (RCTs) and non-randomized comparator studies, undertake data extraction and data quality assessment, and ensure that the grading of guidelines is consistent with the available evidence. The Glomerulonephritis Workgroup was supported by a team led by Dr. Ethan Balk from the Tufts Center for Kidney Disease Guideline Development and Implementation. After completion, the guidelines were opened for public comment before further final revisions so that the published guideline [8] is based on the best available evidence to June 2011. KDIGO has an implementation team that works with national and regional societies to encourage dissemination. KDIGO has procedures in place to ensure that guidelines are updated every

**Table 1** Definitions of nephrotic syndrome in children

Classification	Definition
Nephrotic syndrome	Edema, uPCR $\geq 2,000$ mg/g ( $\geq 200$ mg/mmol), or $\geq 300$ mg/dl or 3+ protein on urine dipstick, hypoalbuminemia $\leq 2.5$ mg/l ( $\leq 25$ g/l)
Complete remission	uPCR $< 200$ mg/g ( $< 20$ mg/mmol) or $< 1+$ of protein on urine dipstick for 3 consecutive days
Partial remission	Proteinuria reduction of 50 % or greater from the presenting value and absolute uPCR between 200 and 2,000 mg/g (20–200 mg/mmol)
No remission	Failure to reduce urine protein excretion by 50 % from baseline or persistent excretion uPCR $> 2,000$ mg/g ( $> 200$ mg/mmol)
Initial responder	Attainment of complete remission within initial 4 weeks of corticosteroid therapy
Initial nonresponder/steroid resistance	Failure to achieve complete remission after 8 weeks of corticosteroid therapy
Relapse	uPCR $\geq 2,000$ mg/g ( $\geq 200$ mg/mmol), or $\geq 300$ mg/dl or 3+ protein on urine dipstick
Infrequent relapse	One relapse within 6 months of initial response, or one to three relapses in any 12-month period
Frequent relapse	Two or more relapses within 6 months of initial response, or four or more relapses in any 12-month period
Steroid dependence	Two consecutive relapses during corticosteroid therapy, or within 14 days of ceasing therapy
Late nonresponder	Persistent proteinuria during 4 or more weeks of corticosteroids following one or more remission

uPCR urine protein:creatinine ratio

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**Table 2** Grading of the quality of the evidence

	Grade	Quality of the evidence	Meaning
Reproduced with permission from Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group. KDIGO Clinical Practice Guideline for Glomerulonephritis [8]	A	High	We are confident that the true effect lies close to that of the estimate of the effect
	B	Moderate	The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
	C	Low	The true effect may be substantially different from the estimate of the effect
	D	Very low	The estimate of the effect is very uncertain, and often will be far from the truth

5 years and that earlier updates occur to one or more recommendations based on important new evidence.

KDIGO guidelines are intended to provide guidance rather than rules. Although the purpose of the recommendations is to assist in decision-making, a guideline recommendation does not take into account individual patient characteristics, provider variation, and system factors. Thus, each provider retains the privilege and responsibility to assess the appropriateness of a particular recommendation in a specific context.

### Strength of recommendations and quality of supporting evidence

KDIGO workgroups use the GRADE system [6, 9] to assign separate grades for the quality of the evidence (Table 2) and the strength of the recommendations (Table 3). As a starting point in the GRADE classification, systematic reviews of RCTs and individual RCTs are considered high-quality evidence (level A), observational studies are considered low-quality evidence (level C) and other studies including small case series are considered very low quality evidence (level D). However, the level in RCTs can be downgraded or the level in observational studies upgraded according to a number of criteria [6]. The strength of the recommendations is graded as level 1 (“we recommend”) if there is high-quality evidence that the intervention’s effects are clearly greater than its adverse effects (or the opposite), or as level 2 (“we suggest”) if the evidence is of lower quality and there remains some uncertainties about the trade-offs between benefits and harms (Table 3). Recommendations that provide general guidance about evaluation or general management are marked as “not graded”.

### The scope of the KDIGO Glomerulonephritis Clinical Practice Guidelines

The scope for each topic in the Glomerulonephritis Guideline was determined by the Glomerulonephritis Workgroup. The Glomerulonephritis Guideline aims to provide treatment guidelines for patients already diagnosed with a form

of glomerulonephritis [8]. The guideline covers SSNS in children, SRNS in children, minimal change disease (adults), focal and segmental glomerulosclerosis (adults), idiopathic membranous nephropathy, membranoproliferative glomerulonephritis, infection-related glomerulonephritis, IgA nephropathy, Henoch–Schönlein purpura nephritis, lupus nephritis, pauci-immune focal and necrotizing glomerulonephritis, and anti-glomerular basement membrane antibody glomerulonephritis.

### Corticosteroids for the initial episode of steroid-sensitive nephrotic syndrome

KDIGO Glomerulonephritis Workgroup, 2012:

#### “3.1: Treatment of the initial episode of SSNS

3.1.1: We recommend that corticosteroid therapy (prednisone or prednisolone)<sup>1</sup> be given for at least 12 weeks. (*1B*)

3.1.1.1: We recommend that oral prednisone be administered as a single daily dose (*1B*) starting at 60 mg/m<sup>2</sup>/day or 2 mg/kg/day to a maximum 60 mg/day. (*1D*)

3.1.1.2: We recommend that daily oral prednisone be given for 4–6 weeks (*1C*) followed by alternate-day medication as a single daily dose starting at 40 mg/m<sup>2</sup> or 1.5 mg/kg (maximum 40 mg on alternate days) (*1D*) and continued for 2–5 months with tapering of the dose. (*1B*)” (163).

The risk of relapse was reduced by 30 % at 12–24 months by 12 weeks or more of prednisone compared with 8 weeks (six RCTs; 422 children; risk ratio [RR] of relapse 0.70; 95 % confidence intervals [CI] 0.58–0.84) [10]. The quality of the evidence was downgraded from A (high) to B

<sup>1</sup> Prednisone and prednisolone are equivalent, used in the same dosage, and have both been used in RCTs. All later references to prednisone or oral corticosteroids refer to prednisone or prednisolone.

**Table 3** Description of criteria for strength of recommendations used by KDIGO

Grade	Implications		Clinicians	Policy
	Patients			
Level 1, “We recommend”	Most people in your situation would want the recommended course of action and only a small proportion would not		Most patients should receive the recommended course of action	The recommendation can be evaluated as a candidate for developing a policy or performance measure
Level 2, “We suggest”	The majority of people in your situation would want the recommended course of action but many would not		Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences	The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined

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(moderate) because of the poor methodological quality of some of the RCTs included in the systematic review. The daily dose of 60 mg/m<sup>2</sup>/day and the starting dose of 40 mg/m<sup>2</sup> for alternate day therapy were used empirically by the ISKDC [11] and the APN [12] and have not been examined in RCTs so while these doses are recommended, the quality of evidence supporting these data is very low. Theoretical studies [13] have suggested that underdosage with prednisone can occur if a per-kilogram dose is used particularly in children weighing below 30 kg. However, there are few data [14] to suggest that this is of clinical relevance, so the workgroup concluded that either method for calculating prednisone dose may be used.

The mean time to remission did not differ significantly when prednisone was given as a single daily dose compared to divided doses (two RCTs; 66 children; weighted mean difference 0.04 days; 95 % CI −0.98 to 1.06) [10]. The duration of daily and alternate day prednisone is harder to define. Daily prednisone should be given for at least 4 weeks based on one RCT [12], which showed that 8 weeks of prednisone (4 weeks of daily, 4 weeks of alternate day) was significantly more effective in maintaining remission at 6 and 12 months compared with prednisone given daily until remission and on alternate days until the albumin level exceeded 35 g/l (total duration about 4 weeks). An increase in benefit was seen when alternate-day prednisone was given for up to 6 months (risk ratio=1.26–0.112 duration;  $r^2=0.56$ ,  $p=0.03$ ) [10].

### Corticosteroids for relapsing steroid-sensitive nephrotic syndrome

KDIGO Glomerulonephritis Workgroup, 2012:

#### “3.2: Treatment of relapsing SSNS with corticosteroids

##### 3.2.1: Corticosteroid therapy for children with infrequent relapses of SSNS:

3.2.1.1: We suggest that infrequent relapses of SSNS in children be treated with a single daily dose of prednisone 60 mg/m<sup>2</sup> or 2 mg/kg (maximum of 60 mg/day) until the child has been in complete remission for at least 3 days. (2D)

3.2.1.2: We suggest that, after achieving complete remission, children be given prednisone as a single dose on alternate days (40 mg/m<sup>2</sup> per dose or 1.5 mg/kg per dose; maximum 40 mg on alternate days) for at least 4 weeks. (2C)

##### 3.2.2: Corticosteroid therapy for frequently relapsing (FR) and steroid-dependent (SD) SSNS:

3.2.2.1: We suggest that relapses in children with FR or SD SSNS be treated with daily prednisone

until the child has been in remission for at least 3 days, followed by alternate-day prednisone for at least 3 months. (2C)

3.2.2.2: We suggest that prednisone be given on alternate days in the lowest dose to maintain remission without major adverse effects in children with FR and SD SSNS. (2D)

3.2.2.3: We suggest that daily prednisone at the lowest dose be given to maintain remission without major adverse effects in children with SD SSNS where alternate-day prednisone therapy is not effective. (2D)

3.2.2.4: We suggest that daily prednisone be given during episodes of upper respiratory tract and other infections to reduce the risk for relapse in children with FR and SD SSNS already on alternate-day prednisone. (2C)” (164–165).

Children with SSNS have an 80–90 % chance of having one or more relapses [15, 16]. Of those who relapse, about half will relapse infrequently while the remainder have frequently relapsing or steroid-dependent SSNS. There are few RCT data on prednisone treatment of relapsing SSNS. The Guideline for infrequently relapsing SSNS is based on data from an RCT, which found no significant difference in the number of children who relapsed between 8 weeks of daily prednisone compared with daily prednisone until remission followed by 4 weeks of intermittent prednisone (further relapse by 9 months RR 1.07; 95 % CI 0.77–1.50) [10]. The guideline for frequently relapsing and steroid-dependent SSNS is based on an RCT [10], which showed that the risk for relapse at 12 and 24 months was significantly reduced in children treated for 7 months of prednisone compared with 2 months. Data from three RCTs [17–19] (158 children) show that prednisone therapy for 5–7 days during an infection reduces the risk of relapse in children with steroid-dependent SSNS. There are no RCT data on the use of low-dose alternate-day or daily prednisone to maintain remission in frequently relapsing or steroid-dependent SSNS. Observational studies have shown that low-dose alternate-day prednisone (mean dose 0.48 mg/kg on alternate days) or daily prednisone (0.25 mg/kg/day) reduced the risk of relapse compared with historical controls [20, 21].

### Corticosteroid-sparing agents for frequently relapsing and steroid-dependent SSNS

KDIGO Glomerulonephritis Workgroup, 2012:

“3.3: Treatment of FR and SD SSNS with corticosteroid-sparing agents

3.3.1: We recommend that corticosteroid-sparing agents be prescribed for children with FR SSNS and SD SSNS, who develop steroid-related adverse effects. (1B)” (165).

The corticosteroid-sparing agents considered by the workgroup were alkylating agents (cyclophosphamide, chlorambucil), levamisole, calcineurin inhibitors (cyclosporine, tacrolimus), mycophenolate mofetil, rituximab, mizoribine, and azathioprine.

#### Alkylating agents

KDIGO Glomerulonephritis Workgroup, 2012:

“3.3.2: We recommend that alkylating agents, cyclophosphamide or chlorambucil, be given as corticosteroid-sparing agents for FR SSNS. (1B) We suggest that alkylating agents, cyclophosphamide or chlorambucil, be given as corticosteroid-sparing agents for SD SSNS. (2C)

3.3.2.1: We suggest that cyclophosphamide (2 mg/kg/day) be given for 8–12 weeks (maximum cumulative dose 168 mg/kg). (2C)

3.3.2.2: We suggest that cyclophosphamide not be started until the child has achieved remission with corticosteroids. (2D)

3.3.2.3: We suggest that chlorambucil (0.1–0.2 mg/kg/day) may be given for 8 weeks (maximum cumulative dose 11.2 mg/kg) as an alternative to cyclophosphamide. (2C)

3.3.2.4: We suggest that second courses of alkylating agents not be given. (2D)” (165–166).

Five RCTs (134 children) comparing alkylating agents and prednisone with prednisone alone have demonstrated that alkylating agents significantly reduce the risk of relapse (Table 4). These trials did not differentiate between frequently relapsing and steroid-dependent SSNS. There were no significant differences at 12 months in efficacy between cyclophosphamide and chlorambucil (RR 1.15, 95 % CI 0.69 to 1.94) [22, 23]. Since a post hoc analysis of this trial [22] and a review [24] of observational studies and RCTs showed that alkylating agents resulted in longer durations of remission in frequently relapsing compared with steroid-dependent SSNS (72 vs. 40 % after 2 years and 36 vs. 24 % after 5 years), the workgroup recommended alkylating agents for frequently relapsing SSNS (level 1B) but only suggested their use for steroid-dependent SSNS (level 2C).

Because of potential gonadal, hematological, and other toxicities of both agents [24–27] and some data suggesting that the margin between therapeutic effect and toxicity is



**Table 4** Meta-analyses of randomized controlled trials of corticosteroid-sparing agents compared with prednisone and/or placebo in children with frequently relapsing or steroid-dependent steroid-sensitive nephrotic syndrome

Agent	RCTs <sup>a</sup> N	Patients N	Risk ratio of relapse (95 % CI <sup>b</sup> )	Time of outcome (months)	Relative risk reduction
Cyclophosphamide	3	102	0.44 (0.26,0.73)	6–12	56 %
Chlorambucil	2	32	0.13 (0.03,0.57)	12	87 %
Levamisole	5	269	0.43 (0.27,0.68)	4–12	57 %
Mizoribine	1	197	Relapse rate ratio <sup>c</sup> 0.81 (0.61,1.05)	18	Not significant
Azathioprine	2	60	0.90 (0.59,1.38)	6	Not significant

<sup>a</sup> Randomized controlled trials<sup>b</sup> Confidence intervals<sup>c</sup> Relapse risk ratio = [total number of relapses ÷ observation period in treatment group] ÷ [total number of relapses ÷ observation period in control group]

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less for chlorambucil [25] than for cyclophosphamide, the guideline suggests maximum durations and cumulative doses for these agents and suggests that second courses of an alkylating agent not be given. Because cyclophosphamide is rarely associated with hemorrhagic cystitis, it is suggested that cyclophosphamide should be administered when the child is in remission and can receive a high fluid intake.

Though not included as a guideline, cyclophosphamide may be given intravenously when non-adherence to therapy is a risk. Two RCTs [23, 28, 29] have demonstrated no significant difference (RR 0.99; 95 % CI 0.76 to 1.29) in the risk of relapse at 12–24 months follow-up between oral cyclophosphamide (8–12 weeks) and IV cyclophosphamide (monthly pulses for 6 months).

#### Levamisole

KDIGO Glomerulonephritis Workgroup, 2012:

“3.3.3: We recommend that levamisole be given as a corticosteroid-sparing agent. (1B)

3.3.3.1: We suggest that levamisole be given at a dose of 2.5 mg/kg on alternate days (2B) for at least 12 months (2C) as most children will relapse when levamisole is stopped” (166).

Five RCTs, comparing levamisole with/without prednisone with prednisone or no specific therapy, have shown that the risk for relapse was reduced by 57 % (Table 4). A sixth RCT [30] using a low dose (2.5 mg/kg given on two consecutive days each week) showed no significant benefit. Observational studies suggest that levamisole can be used for 12–24 months [31–33]. Levamisole is generally well tolerated, with minor leucopenia and/or gastrointestinal upsets described in some patients. Rarely, cutaneous

vasculitis has been reported [34]. Levamisole is not available in many countries and currently there is limited availability in other countries. The results of a large multicenter, double-blind, placebo-controlled RCT to assess the efficacy of levamisole (2.5 mg/kg on alternate days) in SSNS are expected in 2013 [35].

#### Calcineurin inhibitors

KDIGO Glomerulonephritis Workgroup, 2012:

“3.3.4: We recommend that the calcineurin inhibitors (CNI), cyclosporine or tacrolimus, be given as corticosteroid-sparing agents. (1C)

3.3.4.1: We suggest that cyclosporine be administered at a dose of 4–5 mg/kg/day (starting dose) in two divided doses. (2C)

3.3.4.2: We suggest that tacrolimus 0.1 mg/kg/day (starting dose) in two divided doses be used instead of cyclosporine when the cosmetic side-effects of cyclosporine are unacceptable. (2D)

3.3.4.3: Monitor CNI levels during therapy to limit toxicity. (Not Graded)

3.3.4.4: We suggest that CNIs be given for at least 12 months as most children will relapse when CNIs are stopped. (2C)” (166).

Two RCTs comparing cyclosporine with alkylating agents have demonstrated that there was no significant difference in the risk of relapse (95 children; RR 0.91; 95 % CI 0.55 to 1.48) during cyclosporine therapy [23, 36, 37]. However, since most children relapse when cyclosporine is ceased, the remission rate is lower after cyclosporine compared with alkylating agents when assessed at 12–24 months after

completing treatment. In observational studies, cyclosporine maintains remission in 60–90 % of children with SD SSNS, who had relapsed after alkylating-agent therapy [38–40].

Tacrolimus has not been studied in RCTs and there are limited observational data [41, 42] to support its use in SSNS. It is used increasingly because of the cosmetic side-effects of cyclosporine (hypertrichosis, gum hyperplasia). However, since there are no RCTs that compare the relative benefits and harms of tacrolimus and cyclosporine in SSNS, there are currently limited data to show that tacrolimus can replace cyclosporine in SSNS despite the grade 1C recommendation for its use by the KDIGO workgroup. This designation is tempered by the grade 2D recommendation to prescribe tacrolimus when cyclosporine's cosmetic side-effects limit its use.

Both medications may cause hypertension, kidney dysfunction [43], renal interstitial fibrosis [38, 44] and, in transplant recipients, diabetes mellitus [45]. Adding ketoconazole to cyclosporine resulted in no loss of efficacy but a 48 % reduction in the mean dose of cyclosporine with net cost savings of 38 % in a non-randomized comparator study [46].

The length of treatment with CNIs is controversial, with some authors suggesting that CNI therapy should be restricted to 2 years because of the adverse effects on kidney function and histology [47]. In children receiving cyclosporine for 12 months or more, tubulointerstitial lesions on kidney biopsy are reported in 30–40 % of cases. This increases to 80 % after 4 or more years of treatment [47]. However, cyclosporine-associated arteriopathy is uncommon. In an ungraded statement (not shown), the guideline suggests that kidney biopsy should be performed in children with decreasing glomerular filtration rates which persist after CNI doses are reduced. The guideline does not support the suggestion [47] that children should undergo annual biopsies if CNI therapy is continued beyond 2 years, because it is unclear whether the benefits of regular kidney biopsies exceed the harms.

In an RCT, the sustained remission rate was significantly higher in children established on cyclosporine and maintaining a 12-h cyclosporine trough level of 60–80 ng/ml (mean dose 4.7 mg/kg/day) compared to children treated with a fixed dose of 2.5 mg/kg/day [48]. Limited data suggest peak (C2) levels rather than trough (C0) levels can be used for monitoring [49].

#### Mycophenolate mofetil (MMF)

KDIGO Glomerulonephritis Workgroup, 2012:

“3.3.5: We suggest that MMF be given as a corticosteroid-sparing agent. (2C)

3.3.5.1: We suggest that MMF (starting dose 1,200 mg/m<sup>2</sup>/day) be given in two divided doses for at least 12 months, as most children will relapse when MMF is stopped. (2C)” (p 166).

To date, most studies on mycophenolic acid prodrugs in SSNS have used MMF. Though a small RCT (24 children) found no significant difference in the risk of relapse between MMF and cyclosporine (RR 5; 95 % CI 0.68, 36.66), there was considerable imprecision in the results indicated by the very wide confidence interval [23, 50]. As it underpowered with small patient numbers, a difference in the efficacy between these medications has not been excluded by this study. Preliminary data from a crossover study [51] suggest that MMF is less effective than cyclosporine in maintaining remission, with one or more relapses occurring in 21 children when receiving MMF and in nine children during cyclosporine treatment among the 60 children included in the study. Also, this study suggested that relapses were related to lower mycophenolic acid levels. However, glomerular filtration rate is maintained with MMF while it falls during CNI therapy [50, 51]. In observational studies, MMF has been used for up to 45 months and has been well tolerated [52], with few children developing abdominal symptoms or leucopenia.

#### Rituximab

KDIGO Glomerulonephritis Workgroup, 2012:

“3.3.6: We suggest that rituximab be considered only in children with SD SSNS, who have continuing frequent relapses despite optimal combinations of prednisone and corticosteroid-sparing agents, and/or who have serious adverse effects of therapy. (2C)” (166).

The place of rituximab, an anti-CD20 monoclonal antibody, in the treatment of steroid and CNI-dependent SSNS remains to be established. A single open-labeled RCT enrolling 54 children with SD SSNS dependent on prednisone and CNIs found that rituximab significantly reduced the rate of relapse at 3 months (18.5 % and 48.1 % in experimental and control arms, respectively) and increased the probability of a child not requiring prednisone and CNI treatment [53]. Case series report prolonged remissions in 80 % of children following rituximab [54, 55]. Rituximab caused acute reactions (fever, vomiting, diarrhea, skin rash, bronchospasm) in about one-third of patients [55]. Other reported serious side-effects include *Pneumocystis jiroveci* pneumonia and pulmonary fibrosis [54, 56].

#### Other medications

KDIGO Glomerulonephritis Workgroup, 2012:

“3.3.7: We suggest that mizoribine not be used as a corticosteroid-sparing agent in FR and SD SSNS. (2C)

3.3.8: We recommend that azathioprine not be used as a corticosteroid-sparing agent in FR and SD SSNS. (1B)” (166).

A single RCT (197 patients) demonstrated that the relapse rate (measured as the ratio of the total number of relapses/duration of observation in the mizoribine-treated group and placebo group) did not differ significantly between treatment and placebo groups (relapse-rate ratio 0.81; 95 % CI 0.61–1.05) [57] (Table 4).

Two RCTs have demonstrated no significant difference in the risk of relapse between azathioprine and placebo (RR 0.90; 95 % CI 0.59–1.38) [23] (Table 4).

Choice of first corticosteroid-sparing agent for frequently relapsing or steroid-dependent SSNS

A few small RCTs [36, 37, 50, 51, 58] have compared different corticosteroid-sparing agents and have not demonstrated

significant differences in efficacy between medications. However, because of insufficient power, clinically important differences between medications cannot be excluded, so conclusions cannot be drawn about which corticosteroid-sparing agent should be used as the first agent in a child with frequently relapsing or steroid-dependent SSNS. In the guideline, the advantages and disadvantages of alkylating agents, levamisole, CNIs and MMF are presented to allow clinicians and families to determine which agent a child should receive as their first corticosteroid-sparing agent taking into account efficacy, adverse effects, local availability, and cost (Table 5).

### Comparison with previous guidelines for SSNS

The KDIGO guideline for SSNS is compared with three recently published guidelines from the USA [4], India [3], and France [5] (Table 6). In the initial episode of SSNS, the US and Indian guidelines use a maximum of 12 weeks of prednisone, while the French and KDIGO guidelines

**Table 5** Advantages and disadvantages of corticosteroid-sparing agents as first agent for use in frequently relapsing and steroid-dependent steroid-sensitive nephrotic syndrome

Agent	Advantages	Disadvantages
Cyclophosphamide	Prolonged remission off therapy Inexpensive	Less effective in SD SSNS Monitoring of blood count during therapy Potential serious short- and long-term adverse effects Only one course should be given
Chlorambucil	Prolonged remission off therapy Inexpensive	Less effective in SD SSNS Monitoring of blood count during therapy Potential serious adverse effects Only one course should be given Not approved for SSNS in some countries
Levamisole	Few adverse effects Generally inexpensive	Continued treatment required to maintain remission Limited availability Not approved for SSNS in some countries
Cyclosporine	Prolonged remissions in some children with SD SSNS	Continued treatment often required to maintain remission Expensive Nephrotoxic Cosmetic side-effects
Tacrolimus	Prolonged remissions in some children with SD SSNS	Continued treatment often required to maintain remission Expensive Nephrotoxic Risk of diabetes mellitus Not approved for SSNS in some countries
Mycophenolate mofetil	Prolonged remissions in some children with FR and SD SSNS Few adverse effects	Continued treatment often required to maintain remission Probably less effective than CNIs Expensive Not approved for SSNS in some countries

FR frequently relapsing; SD steroid-dependent; SSNS steroid-sensitive nephrotic syndrome; CNI calcineurin inhibitors

Reproduced with permission from Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Workgroup. KDIGO Clinical Practice Guideline for Glomerulonephritis [8]



**Table 6** Comparison of KDIGO guidelines for steroid-sensitive nephrotic syndrome (SSNS) with some existing guidelines

	Children's Nephrotic Syndrome Consensus Conference USA, 2009 [4]	Haute Autorité de Santé France, 2008 [5]	Indian revised guidelines, India 2008 [3]	KDIGO Guidelines International, 2012 [8]
Prednisone in initial episode	2 mg/kg/day × 6 weeks 1.5 mg/kg alt day × 6 weeks No taper	60 mg/m <sup>2</sup> /day × 4 weeks 60 mg/m <sup>2</sup> alt day × 8 weeks Taper by 15 mg/m <sup>2</sup> every 2 weeks	2 mg/kg/day × 6 weeks 1.5 mg/kg alt day × 6 weeks No taper	60 mg/m <sup>2</sup> /day (2 mg/kg/day) × 4–6 weeks 40 mg/m <sup>2</sup> (1.5 mg/kg) alt day × 2–5 months with taper
Prednisone in IF <sup>a</sup> SSNS	Duration 12 weeks 2 mg/kg/day until urine protein –ve × 3 days 1.5 mg/kg alt day × 4 weeks	Duration 18 weeks 60 mg/m <sup>2</sup> /day until 6 days after remission 60 mg/m <sup>2</sup> alt day × 4 weeks Taper by 15 mg/m <sup>2</sup> alt day 4 wkly	Duration 12 weeks 2 mg/kg/day until urine protein –ve × 3 days 1.5 mg/kg alt day × 4 weeks	Minimum duration 12 weeks 60 mg/m <sup>2</sup> /day (2 mg/kg/day) until urine protein –ve × 3 days 40 mg/m <sup>2</sup> (1.5 mg/kg) alt day × 4 weeks
Prednisone in FR <sup>b</sup> and SD <sup>c</sup> SSNS	2 mg/kg/day until urine protein –ve for 3 days 1.5 mg/kg alt day × 4 weeks Taper by 0.5 mg/kg alt day over 2 months	60 mg/m <sup>2</sup> /day until 6 days after remission 60 mg/m <sup>2</sup> alt day × 4 weeks Taper by 15 mg/m <sup>2</sup> every 4 weeks to 15 mg/m <sup>2</sup> and continue 12–18 months	2 mg/kg/day until urine protein –ve for 3 days 1.5 mg/kg alt day × 4 weeks Taper to 0.5–0.7 mg/kg alt day and continue 9–18 months	60 mg/m <sup>2</sup> /day (2 mg/kg/day) until urine protein –ve for 3 days 40 mg/m <sup>2</sup> (1.5 mg/kg) alt day and taper for ≥ 3 months Lowest alt day or daily dose to maintain remission Daily during infection
Steroid-sparing agents	FR SSNS 1. CPA <sup>d</sup> 2 mg/kg/day × 12 weeks 2. MMF <sup>e</sup> 25–36 mg/kg/day × 1–2 years 3. CyA <sup>f</sup> 3–5 mg/kg/day or Tac 0.05–0.1 mg/kg/day × 2–5 years SD SSNS 1. CyA 3–5 mg/kg/day or Tac <sup>g</sup> 0.05–0.1 mg/kg/day 2. MMF 24–36 mg/kg/day 3. CPA 2 mg/kg/day × 12 weeks	FR & SD SSNS Lev <sup>h</sup> 2.5 mg/kg alt day CPA 2 mg/kg/day × 8–12 weeks CyA 150 mg/m <sup>2</sup> /day MMF 1,200 mg/m <sup>2</sup> /day	FR & SD SSNS Lev 2–2.5 mg/kg alt day × 1–2 years CPA 2–2.5 mg/kg/day × 12 weeks CyA 4–5 mg/kg/day or Tac 0.1–0.2 mg/kg/day × 1–2 years MMF 800–1,200 mg/m <sup>2</sup> /day × 1–2 years	FR & SD SSNS CPA 2 mg/kg/day × 8–12 weeks Chlorambucil 0.1–0.2 mg/kg/day × 8 weeks Lev 2.5 mg/kg alt day × ≥ 1 year CyA 4–5 mg/kg/day × ≥ 1 year Tac 0.1 mg/kg/day × ≥ 1 year if excess cosmetic effects with CyA MMF 1,200 mg/m <sup>2</sup> /day × ≥ 1 year

*KDIGO* kidney disease: improving global outcomes; *SSNS* steroid sensitive nephrotic syndrome; *FR* frequently relapsing; *SD* steroid dependent; *MMF* mycophenolate mofetil

<sup>a</sup> Infrequent relapse

<sup>b</sup> Frequent relapse

<sup>c</sup> Steroid-dependent

<sup>d</sup> Cyclophosphamide

<sup>e</sup> Mycophenolate mofetil

<sup>f</sup> Cyclosporine

<sup>g</sup> Tacrolimus

<sup>h</sup> Levamisole

suggest longer tapering doses. For infrequently relapsing children, the US, Indian, and KDIGO guidelines use the same regimen originally used by the ISKDC and adapted by APN, while the French guidelines use a longer course. For FR and SD SSNS, the US guidelines use a 3-month regimen of prednisone while the other guidelines suggest long courses of low-dose prednisone to maintain remission. The US guidelines specifically recommend the order of selection for corticosteroid-sparing agents, which differ for FR and SD SSNS. The remaining guidelines do not specify the order of usage of different agents. The Indian and KDIGO guidelines suggest that second courses of alkylating agents not be used and the Indian guidelines recommend that chlorambucil not be used because of toxicity. Mizoribine is not considered in any guideline except KDIGO, which suggests that it should not be used. Levamisole is not considered in the US guideline as this agent is not available in the US.

## Discussion

The KDIGO guidelines aim to provide recommendations and suggestions for the treatment of children with SSNS with immunomodulating agents in all parts of the world. The guidelines are evidence-based. However, there are many areas where RCT data do not exist to inform the guidelines so we have relied on lower levels of evidence and current practice to formulate the guidelines. To have more accurate information on how to treat children with these conditions, the world-wide pediatric nephrology community needs to design and participate in RCTs. In SSNS, more information is needed on the relative efficacies of different corticosteroid-sparing agents and the place of rituximab in management. Quality randomized controlled trials with adequate power, sufficient follow-up, and appropriate monitoring are imperative to further our understanding of nephrotic syndrome and implement evidence-based management strategies to best serve our patients.

## Educational review questions (answers are provided following the reference list)

1. Based on the GRADE system used by KDIGO workgroups, results from observational studies would usually be classified as having which level of evidence?
  - A. Level A
  - B. Level B
  - C. Level C
  - D. Level D
  - E. Level C or D

2. What is the minimum recommended duration of corticosteroid therapy for the initial episode of steroid-sensitive nephrotic syndrome?
  - A. 4 weeks
  - B. 8 weeks
  - C. 12 weeks
  - D. 18 weeks
  - E. 24 weeks
3. When counseling families on the expected course of steroid-sensitive nephrotic syndrome, what is the chance of a child having one or more relapses?
  - A. <5 %
  - B. 15–20 %
  - C. 30–40 %
  - D. 60–70 %
  - E. 80–90 %
4. A patient who had achieved remission following the initial corticosteroid therapy but had two relapses in a 12-month period would be classified as having:
  - A. Infrequent relapsing steroid-sensitive nephrotic syndrome
  - B. Frequently relapsing steroid-sensitive nephrotic syndrome
  - C. Steroid-dependent nephrotic syndrome
  - D. Steroid-resistant nephrotic syndrome
5. Based on available data from randomized controlled trials, which medication should be considered as the first steroid-sparing agent in frequently relapsing or steroid-dependent steroid-sensitive nephrotic syndrome?
  - A. Alkylating agents (cyclophosphamide, chlorambucil)
  - B. Levamisole
  - C. Calcineurin inhibitors (cyclosporine, tacrolimus)
  - D. Mycophenolate mofetil
  - E. Any of the above

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## Answers

- 1) Answer: E
- 2) Answer: C
- 3) Answer: E
- 4) Answer: A
- 5) Answer: E