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KDIGO Commentary

Canadian Society of Nephrology Commentary on the 2012 KDIGO Clinical Practice Guideline for Glomerulonephritis: Management of Nephrotic Syndrome in Children

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The KDIGO (Kidney Disease: Improving Global Outcomes) clinical practice guideline for management of glomerulonephritis was recently released. The Canadian Society of Nephrology convened a working group to review the recommendations and comment on their relevancy and applicability to the Canadian context. A subgroup of pediatric nephrologists reviewed the guideline statements for management of childhood nephrotic syndrome and agreed with most of the guideline statements developed by KDIGO. This commentary highlights areas in which there is lack of evidence and areas in need of translation of evidence into clinical practice. Areas of controversy or uncertainty, including the length of corticosteroid therapy for the initial presentation and relapses, definitions of steroid resistance, and choice of second-line agents, are discussed in more detail. Existing practice variation is also addressed.
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Clinical practice guidelines provide a comprehensive assessment of the medical literature and the synthesis of that information into a practical and meaningful context for the practicing physician. In pediatric nephrology, clinical practice guidelines are few and existing guidelines are rarely adapted and contextualized for local use in many countries.

KDIGO (Kidney Disease: Improving Global Outcomes) was established in 2003 with the stated mission of "improving the care and outcomes of kidney disease patients worldwide through the development and implementation of clinical practice guidelines."[1] Since the launch of KDIGO, comprehensive clinical practice guidelines have been developed and published for chronic kidney disease (CKD)–mineral and bone disorder,[2] transplantation,[3] blood pressure in CKD,[4] acute kidney injury,[5] anemia in CKD,[6] and hepatitis C virus infection in CKD.[7] The KDIGO clinical practice guideline for glomerulonephritis[8] comprises a systematic review and synthesis of the relevant literature as of January 2011 with the addition of new data available as of November 2011. This guideline also devotes sections to glomerular diseases of childhood, such as childhood nephrotic syndrome, making the guideline relevant for a wide range of pediatric clinicians.

The Canadian Society of Nephrology (CSN) applauds KDIGO's efforts to prepare comprehensive and broadly applicable clinical practice guidelines for the international nephrology community. However,

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the CSN, the Canadian Association of Pediatric Nephrologists (CAPN), and other professional groups such as KDOQI (Kidney Disease Outcomes Quality Initiative) agree that local factors warrant consideration when using clinical practice guidelines to guide care. Therefore, the CSN has established working groups to review KDIGO clinical practice guidelines and to comment on their applicability to Canadian health care and, in this article, to child health care.

REVIEW AND APPROVAL PROCESS FOR CSN COMMENTARIES

The CSN guidelines committee, having concluded that the KDIGO clinical practice guideline for glomerulonephritis was a priority for comment, set up working groups in summer 2012 to prepare 2 commentaries, one on the guideline statements relevant to children and another regarding guideline statements relevant to adults (see Cybulsky et al[9]). Individual members of CSN were invited and named to the working group by virtue of their interest and expertise, in a process that took careful note of potential conflicts of interest. This commentary, focused on the management of nephrotic syndrome in children, was under development through fall 2012, using the original KDIGO glomerulonephritis clinical practice guideline[8] and materials referenced in the report as information sources. The working group collaborated by regular teleconferences, and all authors approved the text of the final draft. Every effort was made to reach consensus, but when this was not possible, all viewpoints were discussed. CSN sent the final draft out to Canadian pediatric nephrologists for peer review, and the document was revised accordingly, prior to final ratification by the CSN guidelines committee and CSN executive.

STRUCTURE OF THIS COMMENTARY

This document does not comment on all the KDIGO recommendations for glomerulonephritis in children; rather, the focus is on areas for which there is more comprehensive evidence or an important clinical need. A list of the KDIGO recommendations for glomerulonephritis in children, specifying which were selected for further commentary, is provided in Table 1. When applicable, implications for Canadian health care are listed and important areas for future research are also discussed.

In this commentary, numbered text within horizontal rules is quoted directly from the KDIGO document, using the same numbering scheme as in the original. All material is reproduced with permission of KDIGO.

GUIDELINE STATEMENTS AND COMMENTARY

Treatment of the Initial and Relapse Episodes of Steroid-Sensitive Nephrotic Syndrome

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^2 or 1.5 mg/kg (maximum 40 mg on alternate days) (*1D*) and continued for 2-5 months with tapering of the dose. (*1B*)

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*)

Commentary

Chapter 3 of the KDIGO guideline has 2 level 1 recommendations concerning the initial treatment of children older than 1 year presenting with (idiopathic) nephrotic syndrome. The CSN working group agrees that corticosteroids remain the first-line therapy for this group of patients. Children younger than 1 year are more likely to have a different (and genetically definable) cause for their nephrotic syndrome and should be managed differently.

In Canada, the majority of pediatric nephrologists treat children at their initial presentation of nephrotic syndrome with 6 weeks of daily prednisone (or prednisolone; the guideline notes that prednisone and prednisolone are equivalent), followed by alternate-day (48-hour) dosing for another 6 weeks.[10] Despite high early response rates, 80% of children experience at least one relapse of proteinuria and nephrotic syndrome and 50% experience relapse frequently or become corticosteroid (steroid) dependent (SD).[11,12]

In order to reduce these high relapse rates and the resulting adverse effects, modifications of prednisone dosing and therapy duration have been evaluated.[12-14] The KDIGO Work Group highlighted results from a meta-analysis of 422 children, which showed a reduced risk of relapse with 3 months of therapy compared with 2 months (relative risk [RR], 0.70; 95% confidence interval [CI], 0.58-0.84) and

Table 1. KDIGO Recommendation Statements on Management of Childhood Nephrotic Syndrome

No.	Recommendation Statement	Concur
3.1.1	We recommend that corticosteroid therapy (prednisone or prednisolone)* be given for at least 12 weeks. *(1B)*	Yes
3.1.1.1	We recommend that oral prednisone be administered as a single daily dose *(1B)* starting at 60 mg/m^2/d or 2 mg/kg/d to a maximum of 60 mg/d. *(1D)*	Yes
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^2 or 1.5 mg/kg (maximum 40 mg on alternate days) (*1D*) and continued for 2-5 months with tapering of the dose. (*1B*)	See comments
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^2 or 2 mg/kg (maximum of 60 mg/d) until the child has been in complete remission for at least 3 days. *(2D)*	Yes
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^2 per dose or 1.5 mg/kg per dose: maximum 40 mg on alternate days) for at least 4 weeks. *(2C)*	Yes
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*)	See comments
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*)	See comments
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*)	See comments
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*)	See comments
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*)	Yes
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*)	See comments
3.3.2.1	We suggest that cyclophosphamide (2 mg/kg/d) be given for 8-12 weeks (maximum cumulative dose 168 mg/kg). (*2C*)	See comments
3.3.2.2	We suggest that cyclophosphamide not be started until the child has achieved remission with corticosteroids. (*2D*)	Yes
3.3.2.3	We suggest that chlorambucil (0.1-0.2 mg/kg/d) may be given for 8 weeks (maximum cumulative dose 11.2 mg/kg) as an alternative to cyclophosphamide. (*2C*)	See comments
3.3.2.4	We suggest that second courses of alkylating agents not be given. (2D)	Yes
3.3.3	We recommend that levamisole be given as a corticosteroid-sparing agent. (*1B*)	See comments
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.	See comments
3.3.4	We recommend that the calcineurin inhibitors cyclosporine or tacrolimus be given as corticosteroid-sparing agents. (*1C*)	Yes
3.3.4.1	We suggest that cyclosporine be administered at a dose of 4-5 mg/kg/d (starting dose) in two divided doses. (2C)	Yes
3.3.4.2	We suggest that tacrolimus 0.1 mg/kg/d (starting dose) given in two divided doses be used instead of cyclosporine when the cosmetic side-effects of cyclosporine are unacceptable. (*2D*)	Yes
3.3.4.3	Monitor CNI levels during therapy to limit toxicity. (*Not Graded*)	Yes
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*)	Yes
3.3.5	We suggest that MMF be given as a corticosteroid-sparing agent. (*2C*)	See comments
3.3.5.1	We suggest that MMF (starting dose 1200 mg/m^2/d) be given in two divided doses for at least 12 months, as most children will relapse when MMF is stopped. (*2C*)	Yes
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*)	Yes

(Continued)

Table 1 (Cont'd). KDIGO Recommendation Statements on Management of Childhood Nephrotic Syndrome

No.	Recommendation Statement	Concur
3.3.7	We suggest that mizoribine not be used as a corticosteroid-sparing agent in FR and SD SSNS. (*2C*)	Yes
3.3.8	We recommend that azathioprine not be used as a corticosteroid-sparing agent in FR and SD SSNS. (*1B*)	Yes
3.4.1	Indications for kidney biopsy in children with SSNS are (*Not Graded*): • late failure to respond following initial response to corticosteroids; • a high index of suspicion for a different underlying pathology; • decreasing kidney function in children receiving CNIs.	Yes [also see comments]
4.1.1	We suggest a minimum of 8 weeks treatment with corticosteroids to define steroid resistance. (*2D*)	See comments
4.1.2	The following are required to evaluate the child with SRNS (*Not Graded*): • a diagnostic kidney biopsy; • evaluation of kidney function by GFR or eGFR; • quantitation of urine protein excretion.	Yes
4.2.1	We recommend using a calcineurin inhibitor (CNI) as initial therapy for children with SRNS. (*1B*)	Yes [also see comments]
4.2.1.1	We suggest that CNI therapy be continued for a minimum of 6 months and then stopped if a partial or complete remission of proteinuria is not achieved. (*2C*)	Yes
4.2.1.2	We suggest CNIs be continued for a minimum of 12 months when at least a partial remission is achieved by 6 months. (*2C*)	Yes
4.2.1.3	We suggest that low-dose corticosteroid therapy be combined with CNI therapy. (*2D*)	Yes
4.2.2	We recommend treatment with ACE-I or ARBs for children with SRNS. (*1B*)	Yes
4.2.3	In children who fail to achieve remission with CNI therapy:	
4.2.3.1	We suggest that mycophenolate mofetil (*2D*), high-dose corticosteroids (*2D*), or a combination of these agents (*2D*) be considered in children who fail to achieve complete or partial remission with CNIs and corticosteroids.	Yes
4.2.3.2	We suggest that cyclophosphamide not be given to children with SRNS. (*2B*)	Yes
4.2.4	In patients with a relapse of nephrotic syndrome after complete remission, we suggest that therapy be restarted using any one of the following options: (*2C*) • oral corticosteroids (*2D*); • return to previous successful immunosuppressive agent (*2D*); • an alternative immunosuppressive agent to minimize potential cumulative toxicity (*2D*).	Yes

Note: This table omits recommendation statement 3.5.1 (immunizations in children with SSNS). Reproduced with permission of KDIGO from *KDIGO Clinical Practice Guideline for Glomerulonephritis*.[8]

*Prednisone and prednisolone are equivalent, used in the same dosage, and have both been used in randomized controlled trials depending on the country of origin. All later references to prednisone in this chapter refer to prednisone or prednisolone. All later references to oral corticosteroids refer to prednisone or prednisolone.

additional benefit when (alternate-day) prednisone was continued for 6 months (RR, 0.57; 95% CI, 0.45-0.71).[15,16] Despite this evidence, the guideline recommendation is for a broad range of 2-5 months of alternate-day steroids (guideline statement 3.1.1.2). The guideline authors comment on the lack of power of the available studies to assess harm from prolonged corticosteroid use, which may be the rationale for the wide range of the recommended treatment duration. However, due to higher relapse rates following shorter treatment courses, at least 2 studies found that the cumulative corticosteroid dose was less in the longer treatment arms, suggesting that prolonged corticosteroid therapy up to 6 months may be beneficial.[16]

The KDIGO guideline contains only level 2 recommendations for the treatment of relapsing steroid-sensitive nephrotic syndrome (SSNS) with corticosteroids. It separates children with infrequent relapses from those with frequently relapsing (FR) and SD nephrotic syndrome. The CSN working group agrees that for both patient groups, treatment of relapses should consist of a daily prednis(ol)one dose of 60 mg/m^2 until remission over 3 consecutive days is achieved, followed by alternate-day corticosteroid treatment with a dose of 40 mg/m^2 (recommendations 3.2.1.1-3.2.2.1). The suggestion for the duration of alternate-day corticosteroid treatment once remission has occurred differs based on whether patients have infrequent relapses ("at least 4 weeks," 3.2.1.2) or whether they have FR or SD nephrotic syndrome ("at least 3 months," 3.2.2.1). The guideline highlights findings from a 2005 Cochrane review[17] that demonstrated no difference in number of relapses by 7 months whether patients with FR nephrotic syndrome were treated with 8 weeks of daily corticosteroids or with daily dosing until remission, followed by 4 weeks of corticosteroids for 3 days of the week.

The working group therefore agrees with suggestion 3.2.1.2, which stipulates a 4-week course of alternate-day prednisone for infrequent relapsers after remission induction. The evidence presented to justify 3 months of alternate-day corticosteroid treatment in patients with FR or SD SSNS (3.2.2.1) was based mostly on unpublished results of a randomized controlled trial (RCT) from Sri Lanka that favored a total of 7 over 2 months of corticosteroid therapy for preventing relapses over the following 3 years.[18] The recommendation to treat at least 3 months, rather than 7 months, may be an attempt to balance these latter findings with the risk of corticosteroid adverse effects and to allow for consideration of second-line agents. The working group thought that it therefore was reasonable to suggest a total course of 3 months of alternate-day prednisone in FR or SD SSNS patients. Unfortunately, the recommended corticosteroid tapering strategy for FR SSNS is not specified in the guideline, which may contribute to significant practice variation with respect to total steroid dosage. This omission is due to a lack of evidence favoring one regimen over another in the literature and thus is a target for future research.

Suggestions 3.2.2.2 and 3.2.2.3 refer to the use of low-dose daily or alternate-day maintenance prednisone during relapse-free periods in children with SD nephrotic syndrome. They lack sufficient evidence for both efficacy and harm and are driven by noncontemporaneous and possibly nongeneralizable cohorts. Alternative approaches exist with potentially similar or superior efficacy (see the discussion of second-line agents under 3.3). The decision to use low-dose prednisone or an alternative agent should be based on patient preference, drug availability, and potential harm. In conclusion, this area is a research priority in the treatment of nephrotic syndrome.

Suggestion 3.2.2.4 addresses the relapse risk due to upper respiratory tract infections of patients with SD nephrotic syndrome already treated with alternate-day low-dose maintenance therapy. While the cited studies[18,19] concluded that changing from alternate-day to daily prednisone prevented relapses during infection, a more relevant and practical question is whether children off immunosuppressant therapy benefit from a short prednisone "bridge" during trivial relapse-inducing infections. Such a strategy deserves consideration for a well-designed trial.

Implications Within Canadian Health Care

1. The first KDIGO recommendation (3.1.1.1) is in line with the standard practice of the majority of pediatric nephrologists for children with a first presentation of idiopathic nephrotic syndrome in Canada.[10] Once corticosteroid (steroid) sensitivity is established, most patients will be treated for the initial presentation of nephrotic syndrome for a total of 12 weeks. However, the CSN working group thought that the evidence presented in the KDIGO guideline supports a longer total initial treatment course, possibly up to 6 months. Prolonged initial corticosteroid therapy therefore could be a target for future knowledge translation strategies in Canada.

2. In the Canadian health care context, which includes availability of second-line agents, the CSN working group does not agree with the use of low-dose daily or alternate-daily maintenance corticosteroids for patients with SD nephrotic syndrome, since there is higher quality evidence for the use of second-line agents in these patients. Nevertheless, the working group agrees that the lowest dose of steroids should be used based on titration and patient response.

Use of Corticosteroid-Sparing Agents to Treat FR and SD SSNS

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/d) be given for 8-12 weeks (maximum cumulative dose 168 mg/kg). (*2C*)
3.3.2.3:	We suggest that chlorambucil (0.1-0.2 mg/kg/d) may be given for 8 weeks (maximum cumulative dose 11.2 mg/kg) as an alternative to cyclophosphamide. (*2C*)
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.
3.3.5:	We suggest that MMF be given as a corticosteroid-sparing agent. (*2C*)

Commentary

Section 3.3 relates to use of corticosteroid-sparing agents in FR and SD SSNS. There are 5 level 1 recommendations. The CSN working group thought that several issues deserve further comment. Statements 3.3.2 and 3.3.4 both recommend that either alkylating agents (3.3.2) or calcineurin inhibitors (CNIs) (3.3.4) can be given as steroid-sparing agents. The evidence level stated for alkylating agents in FR SSNS (level 1) is higher than that stated for SD SSNS (level 2) (3.3.2). There is no difference in evidence level for the use of CNIs for treatment of FR versus SD SSNS (3.3.4). We agree with these recommendations; however, the timing and use of cyclophosphamide relative to CNIs in FR SSNS and SD SSNS remain unresolved for the clinician (for example, which agent should be used first

and in which patients?). There are 2 RCTs directly comparing cyclosporine and alkylating agents. Both revealed similar relapse rates during treatment.[20,21] Cyclosporine is also found to maintain remission in patients who have relapsed after a course of alkylating agent therapy.[22] The guideline states that "cyclosporine has a higher relapse rate compared to alkylating agents when assessed 12-24 months after treatment."(p168) Of note, CNIs suppress the activation of immune-competent lymphocytes by interfering with essential signal transduction processes foremost, but not exclusively, in T cells and CNIs may exert direct effects on podocytes. As with other therapeutic indications, CNIs have to be administered long term to maintain the therapeutic effect. Alkylating agents lead to DNA cross-linking and death of target cell populations, with a long-lasting biological result. While disease mechanism and precise lymphocyte types involved in the causation of podocyte injury as the basis of nephrotic syndrome remain unclear, it is apparent that a direct or simple comparison (or comparative trial) between CNIs and alkylating agents are conceptually problematic.

In a recent meta-analysis, Hodson et al[23] concluded that cyclophosphamide and chlorambucil similarly and significantly reduced the relapse risk at 6 and 12 months compared with corticosteroids alone and that continued cyclosporine therapy was as effective as treatment with an alkylating agent to maintain remission. Indeed, the guideline authors acknowledge that "there are no data from RCTs to determine which corticosteroid sparing agent should be used as the first agent in children with FR or SD SSNS."(p169)

There is an increasing tendency among pediatric nephrologists in Canada to avoid the use of cyclophosphamide and to use CNIs, in particular tacrolimus, as the first second-line agent as parents (and physicians) consider the gonadotoxic effects of alkylating agents. While a cumulative cyclophosphamide dose of 168 mg/kg is generally regarded as safe, studies have demonstrated a continuum of reduced sperm counts and motility without a clear safety threshold.[24,25]

In North America, cyclosporine has been largely replaced by tacrolimus due to the comparatively lower cosmetic effects of the latter.[26,27] We agree with guideline statement 3.3.4.2 and suggest that tacrolimus be used if adverse effects of cyclosporine are unacceptable.

In the absence of independent dose-finding studies in children with nephrotic syndrome, drug dosing and target levels for tacrolimus have been largely adapted from the experience with kidney transplant recipients. The CNI dose is often reduced, if tolerated, to minimize the risk of nephrotoxicity.[26] The working group thought that further head-to-head comparisons are needed to help determine the best first agent for steroid-sparing therapy. In the meantime, considering advantages and disadvantages as per Table 4 in chapter 3 of the guideline appears to be a reasonable approach.

In guideline section 3.3.2, chlorambucil is recommended as an alternative alkylating agent to cyclophosphamide. Chlorambucil is rarely used in Canada for the treatment of nephrotic syndrome. The systematic review published by Hodson et al[23] showed that on direct comparison, there was no significant difference between chlorambucil and cyclophosphamide treatment in the risk of relapse at 12-24 months (12-month RR, 1.15; 95% CI, 0.69-1.94; 24-month RR, 1.31; 95% CI, 0.80-2.13). Both alkylating agents are associated with a substantial risk of leukopenia, thrombocytopenia, and infections, with some studies finding higher rates of malignancies for chlorambucil.[24] Currently, cyclophosphamide is the preferred alkylating agent for both FR SSNS and SD SSNS in Canada. The guideline (statement 3.3.2.1) suggests administering cyclophosphamide between 8 to 12 weeks at a dose of 2 mg/kg/d. Oral dosing of cyclophosphamide is more practical within Canadian context due to the need for repeated hospital admission and intravascular access for parenteral cyclophosphamide therapy.

Levamisole is another recommended corticosteroid-sparing agent with grade 1B evidence (statement 3.3.3). However, it is rarely used and not readily available in Canada.

Although mycophenolate mofetil (MMF) has increasing popularity due to its favorable adverse-effect profile, particularly with regard to nephrotoxicity, we agree with the guideline statement 3.3.5 that the evidence for its use in childhood nephrotic syndrome is limited. There is one small RCT in which 12 children were treated with MMF and 12 were treated with cyclosporine for 1 year. The sample size was too small to determine relative efficacies of MMF and cyclosporine.[28] A small prospective open "Bayesian" trial from France in children with SD SSNS reported a probability of relapse during the first 6 months of MMF therapy of 17.6% (95% CI, 5.4-35.0) under concomitant reduction of alternate-day prednisone dosing by 75%.[29]

Of note, several Canadian provinces do not provide drug coverage for MMF and therefore it is not uniformly available for patients across the country. We conclude that MMF should be considered as an alternative agent in patients with adverse effects due to cyclosporine or tacrolimus. However, the working group cannot endorse its widespread use due to its cost and limited evidence for effectiveness.

The working group agrees with the guideline statement that the place of rituximab in treatment of SD SSNS remains to be established. Use of the

B-cell–depleting antibody for patients with nephrotic syndrome in Canada is still limited, but appears to be changing as physicians become more comfortable with its administration to patients with FR, SD SSNS, and corticosteroid-resistant nephrotic syndrome (SRNS). Recent publications suggest that rituximab may be more effective in maintaining remission of proteinuria in children with SSNS than in SRNS,[30] while others found no improvement of proteinuria in SRNS following rituximab therapy.[31] Patients with corticosteroid and CNI dependence may benefit from rituximab infusion(s) by reducing exposure to these drugs and associated toxicity.[32] Availability of public and private insurance coverage for the antibody varies among jurisdictions. We support statement 3.3.6 that rituximab be used only after a trial of alternative steroid-sparing agents and/or to mitigate serious adverse effects due to other treatments.

Implications Within Canadian Health Care

1. There is significant practice variability in the use of corticosteroid-sparing agents for FR and SD SSNS in Canada.[33] Many practitioners favor CNIs (particularly tacrolimus due to its favorable side effects) as corticosteroid-sparing agents over cyclophosphamide. The CSN working group thought that a single short (2-3 months) course of cyclophosphamide or cyclosporine for a minimum of 12 months is best justified in the literature. There is also variability in drug insurance coverage for tacrolimus across provincial jurisdictions, limiting its use in some provinces. The choice of first-line corticosteroid-sparing agents in SSNS will be the target for future exploratory studies and knowledge translation strategies in Canada.

2. In the Canadian context, several of the recommended corticosteroid-sparing agents are not (chlorambucil and levamisole) or not uniformly (MMF) accessible. Clinicians may choose drugs according to the resources available in their jurisdictions and patient preference.

Indications for Kidney Biopsy

3.4.1: Indications for kidney biopsy in children with SSNS are (*Not Graded*):
- late failure to respond following initial response to corticosteroids;
- a high index of suspicion for a different underlying pathology;
- decreasing kidney function in children receiving CNIs.

Commentary

The guideline recommends that biopsies in children with FR or SD SSNS are not required prior to initiating corticosteroid-sparing therapies because response to therapy is cited as the most important predictor of kidney survival. Interestingly, a significant proportion of nephrologists still perform biopsy on children with FR and SD SSNS before starting corticosteroid-sparing therapies. Possible reasons for biopsy include the desire to reassure parents if minimal change disease is identified or, alternatively, prepare parents for a complicated prolonged course if the tissue reveals focal segmental glomerulosclerosis. The indications cited by clinicians for biopsy in FR and SD SSNS need to be further explored. This information will be essential for developing a successful knowledge translation strategy to ensure best practice for kidney biopsy in SSNS patients.

Evaluation and Treatment of Children With SRNS

4.1.1: We suggest a minimum of 8 weeks treatment with corticosteroids to define steroid resistance. (*2D*)

4.2.1: We recommend using a calcineurin inhibitor (CNI) as initial therapy for children with SRNS. (*1B*)

Commentary

The CSN working group believes that statement 4.1.1 deserves further discussion. The International Study of Kidney Disease in Children (ISKDC) reported that almost 100% of children with nephrotic syndrome who responded to corticosteroids did so by 8 weeks of therapy.[34,35] This was the rationale for selecting 8 weeks as the threshold defining corticosteroid resistance for this guideline. However, several publications, including previous guidelines on management of childhood-onset nephrotic syndrome, have suggested a minimum of 4 weeks of treatment to define corticosteroid resistance and many clinicians use pulse steroids before confirming corticosteroid resistance even at 4 weeks.[36-41] Approximately 95% of patients who responded by 8 weeks had already entered remission by 4 weeks of therapy.[35] Others documented urinary remission of >80% of patients after 2 weeks of treatment.[12] Therefore, the CSN working group disagrees with "a minimum 8 weeks of prednisone" (treatment) and suggests a range of 4-8 weeks to define steroid resistance. Defining steroid resistance earlier than 8 weeks may lead to a shorter overall course of high-dose steroids in a patient who is clearly resistant to steroids at 4-6 weeks of therapy. This will potentially reduce steroid-related toxicity and lead to earlier initiation of second-line agents to induce a full or partial remission.

Section 4.2 contains 2 level 1 recommendations. With respect to recommendation 4.2.1, the CSN working group agrees that a CNI, either cyclosporine or tacrolimus, should be used "as initial therapy for SRNS" (following the standard course of prednisone in most cases). However, guideline chapter 4 does not offer specific calcineurin dosing strategies for patients with SRNS. All 5 published CNI SRNS clinical trials

have used cyclosporine at a dose of 5-6 mg/kg/d.[42-45] One trial showed that cyclosporine at this dose was similarly effective to tacrolimus (at a dose of 0.1-0.2 mg/kg/d).[46] The CSN working group suggests that it would be reasonable to use these dose ranges (cyclosporine, 5-6 mg/kg/d, and tacrolimus, 0.1-0.2 mg/kg/d) in steroid-resistant patients. Target trough levels are not given for cyclosporine or tacrolimus in the guideline statements for SRNS. Nevertheless, we suggest that tacrolimus levels should be 5-7 ng/mL in accordance with levels achieved in the recently published clinical trial by Gulati et al.[47] For cyclosporine, it is reasonable to adopt 12-hour trough levels of 80-150 ng/mL as suggested by studies in FR nephrotic syndrome, SD nephrotic syndrome, and SRNS. Again, it should be noted that drug insurance coverage for tacrolimus is not uniform across Canada.

The CSN working group agrees with the suggestion to stop CNI therapy of patients with SRNS if partial or complete remission cannot be achieved (4.2.1.1). While the guideline reserves the use of mycophenolate for "children who fail to achieve … remission with CNIs and corticosteroids" (4.2.3.1), we think, based on the North American Clinical Trial for Focal Segmental Glomerulosclerosis,[42] that it is reasonable to attempt treatment with MMF (with or without corticosteroids) if faced with CNI-related adverse effects.

We agree with the suggestion that children with SRNS should not be treated with cyclophosphamide (4.2.3.2). Interesting, since completion of the guideline a trial has been published demonstrating superiority of (continued) tacrolimus over 6 monthly intravenous infusions of cyclophosphamide in children with SRNS, both at the 6- and 12-month end points.[47]

Implications Within Canadian Health Care

1. Most Canadian pediatric nephrologists prefer using tacrolimus to cyclosporine in SRNS based on the more favorable adverse-effect profile of tacrolimus. Only one small trial has shown a nonsignificant difference between these medications in the control of proteinuria in patients with SRNS.[44] An adequately powered RCT comparing tacrolimus and cyclosporine in the treatment of SRNS is needed.

2. Although there is little evidence to support the use of alkylating agents as dominant therapy in SRNS, cyclophosphamide is occasionally prescribed for this indication in Canada. The reasons for its continued use should be explored in future knowledge translation activities.

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