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EDUCATIONAL REVIEW

Treatment of steroid-resistant nephrotic syndrome in children: new guidelines from KDIGO

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Abstract Kidney Disease: Improving Global Outcomes (KDIGO) recently published the clinical practice guideline on glomerulonephritis (GN) to assist the practitioner caring for patients with GN. Chapter 4 of the guideline focuses on managing children aged 1–18 years with steroid-resistant nephrotic syndrome (SRNS), defined by an inability to achieve complete remission with corticosteroid therapy. Guideline development followed a thorough evidence review, and management recommendations and suggestions were based on the best available evidence. Limitations of the evidence, including the paucity of large-scale randomized controlled trials, are discussed. This article provides both the guideline recommendations and a brief review of relevant treatment trials related to each recommendation. This précis serves as a summary of the complete guidelines recently published.

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Introduction

Idiopathic nephrotic syndrome affects 1–3 per 100,000 children <16 years of age [1]. Whereas most children will be responsive to corticosteroid therapy, approximately 20 % will be classified as steroid resistant [1], i.e., failure to achieve complete remission after initial therapy with corticosteroids. Children with steroid-resistant nephrotic syndrome (SRNS) may have minimal-change disease (MCD), mesangial proliferative glomerulonephritis (MesPGN), or focal segmental glomerulosclerosis (FSGS), although other histopathologic diagnoses also occur. Treating these patients can be challenging and requires care by pediatric nephrologists. The lack of large-scale randomized controlled trials leads to a paucity of strong evidence to inform treatment decisions.

Kidney Disease: Improving Global Outcomes (KDIGO) recently published clinical practice guidelines on glomerulonephritis (GN) and addresses different forms including SRNS [2]. Recommendations are based upon a systemic review of the available literature using evidence-based principles [3]. The Kidney Disease: Improving Global Outcomes (KDIGO) guideline process and the method by which the work group assigns grades for evidence quality is discussed in this article's companion paper [4]. There, guidelines for treating steroid-sensitive nephrotic syndrome (SSNS) are discussed separately. Kidney Disease: Improving Global Outcomes (KDIGO) guidelines are aimed at providing guidance to assist physicians in treatment 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.

Evaluation of children with steroid-resistant nephrotic syndrome

KDIGO Glomerulonephritis Workgroup, 2012:

> "4.1.1: We suggest a minimum of 8 weeks treatment with corticosteroids to define steroid resistance. (2D)
> 4.1.2: The following are required to evaluate the child with SRNS (Not Graded):
>
> - a diagnostic kidney biopsy
> - evaluation of kidney function by glomerular filtration rate (GFR) or estimated GFR (eGFR)
> - quantitation of urine protein excretion" (172).

If partial or complete remission is not achieved, there is a 50 % risk of progression to end-stage kidney disease within 5 years of diagnosis [5–7]. Observational studies of patients with FSGS demonstrate a 5-year kidney survival rate of 90 % in patients with a complete remission following any single or combination of tested therapies [6, 7]. Partial remission is associated with an intermediate 5-year kidney survival rate of 80 % in adults, although these data are not available for children [7].

In the guideline, the International Study of Kidney Disease in Children (ISKDC) definition of steroid resistance was used, i.e., a minimum exposure of 8 weeks of prednisone with 60 mg/m^2/day; or 2 mg/kg/day for 4 weeks followed by 40 mg/m^2 or 1.5 mg/kg on alternate days for 4 weeks. The minimum duration of prednisone required to define resistance is unresolved. Data from the ISKDC have shown that 95 % of children with SSNS achieved remission with 4 weeks of daily prednisone; all patients were in remission with an additional 3 weeks of alternate-day therapy [8]. For patients who do not achieve remission with 8 weeks of therapy, remission is still possible with corticosteroid therapy. Remissions have been demonstrated following prolonged exposure in low dose steroid control arms of randomized controls trials (RCTs) and following high-pulse doses in observational studies [9, 10]. Why late remission is achieved following such regimens is not well understood.

A kidney biopsy is recommended to evaluate SRNS to determine the underlying pathology, which may dictate therapy. However, FSGS lesions may be missed if the biopsy specimen has <20 glomeruli. The biopsy will also provide information on the degree of interstitial and glomerular fibrosis, which helps to assess prognosis. Kidney function measured at the time of diagnosis is a predictor of the long-term risk for kidney failure. Proteinuria should be quantified at diagnosis and during treatment to allow treatment response to be defined as partial, complete, or no remission [5–7, 11, 12]. Urinary protein/creatinine ratio (uPCR) on the first morning specimen or measurements of 24-h urine protein may be used.

This guideline does not include routine evaluation for genetic mutations due to the variability in availability, significant cost, low to absent prevalence observed in some populations, and our current uncertainty about the individual response to therapy and prognosis when a mutation is identified. In children with SRNS >1 year of age, podocin mutations have been reported in 0–30 %. The prevalence of SRNS-associated mutations varies among ethnic groups, with no podocin mutations identified in an African American cohort of 18 children [13] compared with a 28 % prevalence in a European cohort of 25 children [14].

Calcineurin inhibitors for steroid-resistant nephrotic syndrome

KDIGO Glomerulonephritis Workgroup, 2012:

> "4.2.1: We recommend using a calcineurin inhibitor (CNI) as initial therapy for children with SRNS. (1B)
> 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)
> 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)
> 4.2.1.3: We suggest that low-dose corticosteroid therapy be combined with CNI therapy. (*2D*)" (173).

In three RCTs (49 children) [15–18] (Table 1), cyclosporine resulted in complete remission in 31 % and partial remission in 38 % during 6 months of therapy. The 69 % cumulative complete and partial remission rate was significantly better than the 0–16 % rate in the control arms of these randomized studies. Based on case series, complete and partial remissions are less common in the presence of nephrotic syndrome associated with podocin mutations [19–21]. Though uncommon, remissions have been reported in children with nephrotic syndrome with podocin mutations, suggesting that a trial of CNI therapy may induce at least a partial remission in these patients [22]. Tacrolimus was compared with cyclosporine in one study [23] and showed no significant difference in proteinuria control. The frequency of nephrotoxicity, hypertension, and diabetes mellitus were not different between cyclosporine and tacrolimus in this trial. Hypertrichosis and gingival hyperplasia were significantly more common with cyclosporine than with tacrolimus.

The optimal duration of CNI therapy is unknown. CNI therapy has been used for 6 or 12 months in RCTs. Reduction in proteinuria was achieved in 4.4±1.8 weeks in one trial [17]. In a second trial, median times to complete and partial remission were 8 and 12 weeks [23]. Relapse occurred in up to 70 % of those responding to CNI therapy

Table 1 Randomized controlled trials in steroid-resistant nephrotic syndrome

Author	No.	Intervention	Control	Duration (months)	Remission complete or partial	RR for remission	Conclusion
Lieberman and Tejani 1996 [17]	24	Cyclosporine	Placebo	6	12 (100 %) vs. 2 (17 %)	5.00 (1.63–15.31)	Remission cyclosporine > placebo
Ponticelli et al. 1993 [18]	17[a]	Cyclosporine	Supportive therapy	12 [b]	6 (60 %) vs. 0 (0 %)	9.45 (0.62–144.74)	Remission cyclosporine > control
Garin et al. 1988 [15]	8	Cyclosporine	None	2	0 (0 %) vs. 0 (0 %)	0 (0.0–0.0)	No significant difference
Choudhry et al. 2009 [23]	41	Tacrolimus + prednisone[c]	Cyclosporine + prednisone[c]	12	18 (86 %) vs. 15 (75 %)	1.14 (0.84–1.55)	No significant difference
Gipson et al. 2011 [26]	138	Cyclosporine	MMF[d] + dexamethasone	12	33 (45.8 %) vs. 22 (33 %)	1.35 (0.90–2.10)	No significant difference
ISKDC 1974 [9]	31	CPA[e] + prednisone	Prednisone	3	10 (56 %) vs. 6 (46 %)	1.20 (0.59–2.47)	No significant difference
Tarshish et al. 1996 [10]	53	CPA + prednisone	Prednisone	CPA 3 Prednisone 12[c]	16 (50 %) vs. 12 (57 %)	0.88 (0.53–1.45)	No significant difference

RR risk ratio for remission; [a] Children; [b] 6 months full dose followed by taper 25 % every 2 months; [c] prednisone given on alternate days; [d] mycophenolate mofetil; [e] cyclophosphamide

Adapted with permission from Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group. *KDIGO Clinical Practice Guideline for Glomerulonephritis* [2]

after discontinuation at 6 or 12 months. Extension of therapy beyond 12 months to prevent relapse is common practice, though the long-term effect on the risk of relapse, renal function, and risk of nephrotoxicity remains unclear. Drug-level monitoring is used, although the optimal levels are unknown for SRNS.

Renin–angiotensin system (RAS) blockade for steroid-resistant nephrotic syndrome

KDIGO Glomerulonephritis Workgroup, 2012:

> "4.2.2: We recommend treatment with angiotensin-converting-enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARBs) for children with SRNS. (1B)" (173).

Two RCTs demonstrated a significant reduction in proteinuria with ACEi therapy using enalapril [24] and fosinopril [25]. A crossover study demonstrated a 33 % reduction in proteinuria using 0.2 mg/kg dose of enalapril and a 52 % reduction in albuminuria using 0.6 mg/kg dose [24]. Monitoring eGFR and serum potassium levels is recommended during RAS therapy.

Therapies for children who fail to respond to CNIs

KDIGO Glomerulonephritis Workgroup, 2012:

> "4.2.3: In children who fail to achieve remission with CNI therapy.
>
> 4.2.3.1: We suggest that mycophenolate mofetil (MMF) (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.
>
> 4.2.3.2: We suggest that cyclophosphamide not be given to children with SRNS. (2B)" (173).

Mycophenolate mofetil

A single RCT [26] in 138 patients (93 children) with primary SRNS and FSGS compared mycophenolate mofetil (MMF) and high-dose dexamethasone with cyclosporine. Complete or partial remission occurred in 46 % in the cyclosporine arm and in 33 % in the MMF + dexamethasone arm (Table 1). This difference was not significant. However, as with all existing RCTs in childhood nephrotic syndrome, there is imprecision around the results associated with the sample size. Observational studies involving 42 children with SRNS who were treated for a minimum of 6 months with MMF demonstrated a complete remission rate of 23–62 %, a partial remission rate of 25–37 %, and no remission in 8–40 % [25, 27].

High-dose corticosteroids

In a comparator study, children with SRNS received either methylprednisolone or dexamethasone i.v. for six doses

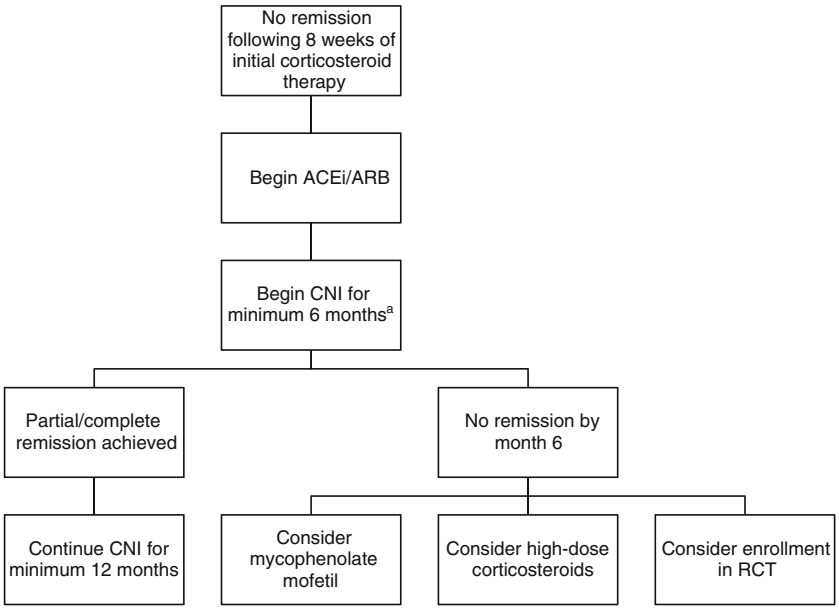

Fig. 1 Management strategy for children with steroid-resistant nephrotic syndrome. [a] ± low-dose corticosteroid therapy; *ACEI* antiotensive-converting enzyme inhibitor, *CNI* calcineurin inhibitor, *RCT* randomized controls trials, *ARB* angiotensin receptor blocker

combined with prednisone orally, and the short-term outcome was assessed at the end of a 2-week regimen. Because of cost, most children received dexamethasone. In 78 evaluable patients, corticosteroid pulse therapy induced a 34 % complete remission and 13 % partial remission [28]. On examining remission rates in the arms of RCTs, it appears that about 33–53 % achieved complete or partial remission with extended corticosteroid therapy [9, 10, 26]. In the 138-patient RCT [26], in the combination therapy MMF + dexamethasone, dexamethasone dose was high and had therapy duration of 6 months in a population that demonstrated SRNS FSGS with a minimum of 4 weeks of pretrial therapy. In the MMF + dexamethasone arm, complete and partial remission rates were not greater than expected for MMF alone. In contrast, RCTs in which the control arm received no corticosteroids, 0–17 % achieved remission [15, 17, 18]. In a retrospective study of 52 children with SRNS and FSGS, the cumulative proportion of sustained remission was significantly higher in children treated with cyclosporine and methylprednisolone i.v. compared with cyclosporine with prednisone orally [29].

Alkylating agents

Two RCTs [9, 10, 16] comprising 84 children with SRNS demonstrated no significant differences in the number achieving remission with cyclophosphamide and prednisone compared with prednisone alone (Table 1), with an increase in adverse effects in the cyclophosphamide groups providing moderate-quality evidence that cyclophosphamide should not be used in children with SRNS. Although imprecision may affect these risk estimates, risk ratios and confidence intervals were centered at around 1. At the present time, the potential harm from cytotoxic agents—including serious infections, increased risk for late-onset malignancy, reduced fertility, hemorrhagic cystitis, and alopecia—far exceeds any evidence of benefit [30].

Rituximab

Rituximab has not been included in this guideline as a treatment option for SRNS due to the lack of RCTs and the risk for serious adverse events, which may persist long after treatment discontinuation [31]. Observational studies [32, 33] suggest

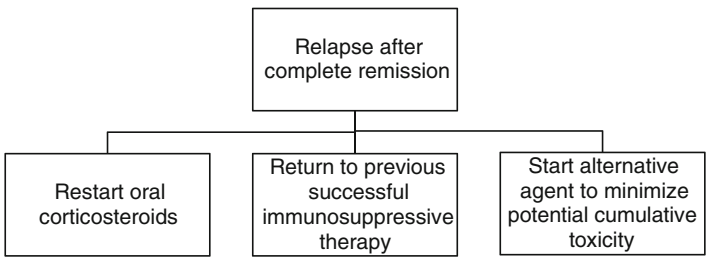

Fig. 2 Management strategy for children with steroid-resistant nephrotic syndrome and relapse

that it is not as effective in SRNS as in SSNS. This is an area that will benefit from future RCTs.

Relapsing disease after initial response in SRNS

KDIGO Glomerulonephritis Workgroup, 2012:

> "4.2.4: In patients with a relapse of nephrotic syndrome after complete remission, we suggest that therapy be restarted using one of the following options: (2C)
>
> - oral corticosteroids (2D);
> - return to previous successful immunosuppressive agent (2D);
> - an alternative immunosuppressive agent to avoid cumulative potential toxicity (2D)" (173).

In SRNS patients with relapse after complete remission, we suggest that immunosuppressant therapy be reinstated. This recommendation is based on the concern that uncontrolled SRNS is likely to lead both to complications from the persistent nephrotic state as well as a high risk for kidney failure. There are no RCTs to support a specific treatment choice, so possible options are provided without prioritization. The benefits of immunosuppressive therapy must be assessed against the potential adverse effects at each relapse and remaining kidney function to determine whether it is in the child's interest to continue active therapy.

Discussion

The purpose of the recently published KDIGO guidelines is to present treatment recommendations for SRNS in children based on the most current available evidence as of June 2011 (Figs. 1 and 2). Several treatment options are provided if first-line therapies (CNI and RAS blockade) fail. Recognizing that the expected response rate to any therapy is 20–50 %, we acknowledge that the process of finding the best therapy for an individual patient may be one of trial-and-monitoring until a satisfactory result is achieved.

The next step in the process of optimizing patient care is to implement and test the guidelines and to generate new evidence about existing and novel therapeutic approaches. Clearly, many opportunities exist for ongoing research. Specific questions that warrant investigation include: What is the expected CNI dose that will induce and maintain remission? How do we balance the potential nephrotoxicity of CNIs with their benefit? When is it appropriate to use MMF? What is the role of rituximab? In view of the continuing uncertainties in SRNS management, pediatric nephrologists are strongly encouraged to consider entering patients into RCTs so that we can determine the benefits and harms of new therapies and thus optimize therapy for SRNS.

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

1. For patients with steroid-resistant nephrotic syndrome, what agents may be considered for therapy?

   A. Cyclosporine
   B. Tacrolimus
   C. Mycophenolate mofetil
   D. High-dose corticosteroids
   E. All of the above

2. The risk of end-stage renal disease within 5 years of diagnosis for patients with steroid-resistant nephrotic syndrome who do not achieve a partial or complete remission is:

   A. <5%
   B. 10%
   C. 25%
   D. 50%
   E. 75%

3. Which steroid-sparing agent has been shown to induce at least partial remission in some patients with steroid-resistant nephrotic syndrome with podocin mutations?

   A. Cyclosporine
   B. Cyclophosphamide
   C. Mycophenolate mofetil
   D. Levamisole
   E. Rituximab

4. Cosmetic changes including gingival hyperplasia and hypertrichosis are side effects of which steroid-sparing agent?

   A. Cyclophosphamide
   B. Chlorambucil
   C. Cyclosporine
   D. Tacrolimus
   E. Mycophenolate mofetil

5. To be considered an adequate tissue sample, what is the minimum number of glomeruli a biopsy sample should have to detect or exclude glomerular lesions that may be focal or segmental?

   A. 5
   B. 10
   C. 20
   D. 30
   E. 50

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Answers:

1. E
2. D
3. A
4. C
5. C (KDIGO Guidelines, Chap. 2)