



**KDIGO 2024 CLINICAL PRACTICE GUIDELINE FOR THE
MANAGEMENT OF NEPHROTIC SYNDROME IN CHILDREN**

**PUBLIC REVIEW DRAFT
APRIL 2024**

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REFERENCE KEYS
NOMENCLATURE AND DESCRIPTION FOR RATING GUIDELINE
RECOMMENDATIONS

Within each recommendation, the strength of recommendation is indicated as **Level 1** or **Level 2**, and the certainty of the supporting evidence is shown as **A, B, C, or D**.

Grade	Implications		
	Patients	Clinicians	Policy
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 a 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.

Grade	Certainty of evidence	Meaning
A	High	We are confident that the true effect is close to 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 it will be far from the true effect.

CURRENT CHRONIC KIDNEY DISEASE (CKD) NOMENCLATURE USED BY KDIGO

CKD is defined as abnormalities of kidney structure or function, present for > 3 months, with implications for health. CKD is classified based on Cause, GFR category (G1-G5), and Albuminuria category (A1-A3), abbreviated as CGA.

KDIGO: Prognosis of CKD by GFR and albuminuria categories				Persistent albuminuria categories		
				Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
GFR categories (ml/min/1.73 m ²) Description and range	G1	Normal or high	≥90			
	G2	Mildly decreased	60–89			
	G3a	Mildly to moderately decreased	45–59			
	G3b	Moderately to severely decreased	30–44			
	G4	Severely decreased	15–29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red: very high risk.

GFR, glomerular filtration rate

CONVERSION FACTORS OF CONVENTIONAL UNITS TO SI UNITS

	Conventional unit	Conversion factor	SI Unit
Albumin	g/dl	10	g/l
Creatinine	mg/dl	88.4	μ mol/l
Creatinine clearance	ml/min	0.01667	ml/s
Cyclosporine	ng/ml	0.832	nmol/l
Mycophenolic acid	μ g/ml	3.12	μ mol/l
PCR	mg/g	0.113	mg/mmol

PCR, protein-to-creatinine ratio; SI, International System of Units

Note: Conventional unit x conversion factor = SI unit

RELATIONSHIP AMONG CATEGORIES FOR ALBUMINURIA AND PROTEINURIA

	Categories		
	Normal to mildly increased (A1)	Moderately increased (A2)	Severely increased (A3)
AER (mg/d)	<30	30–300	>300
PER (mg/d)	<150	150–500	>500
ACR			
(mg/mmol)	<3	3–30	>30
(mg/g)	<30	30–300	>300
PCR			
(mg/mmol)	<15	15–50	>50
(mg/g)	<150	150–500	>500
Protein reagent strip	Negative to trace	Trace to +	+ or greater

Relationships among measurement methods within a category are not exact. For example, the relationships between AER and ACR and between PER and PCR are based on the assumption that average creatinine excretion rate is approximately 1.0 g/d or 10 mmol/d. The conversions are rounded for pragmatic reasons. (For an exact conversion from mg/g of creatinine to mg/mmol of creatinine, multiply by 0.113.) Creatinine excretion varies with age, sex, race and diet; therefore, the relationship among these categories is approximate only. The relationship between urine reagent strip results and other measures depends on urine concentration. ACR, albumin-to-creatinine ratio; AER, albumin excretion rate; PCR, protein-creatinine ratio; PER, protein excretion rate.

ABBREVIATIONS AND ACRONYMS

ARB	angiotensin II receptor blocker
CI	confidence interval
CNI	calcineurin inhibitors
eGFR	estimated glomerular filtration rate
ERT	Evidence Review Team
FRNS	frequently relapsing nephrotic syndrome
GFR	glomerular filtration rate
IPNA	International Pediatric Nephrology Association
i.v.	intravenous
KDIGO	Kidney Disease: Improving Global Outcomes
MMF	mycophenolate mofetil
MPA	mycophenolic acid
NS	nephrotic syndrome
PREDNOS	Prednisolone in Nephrotic Syndrome
RCT	randomized controlled trial
RASi	renin-angiotensin system inhibitor
SDNS	steroid-dependent nephrotic syndrome
SRNS	steroid-resistant nephrotic syndrome
SSNS	steroid-sensitive nephrotic syndrome

NOTICE

SECTION I: USE OF THE CLINICAL PRACTICE GUIDELINE

This Clinical Practice Guideline document is based upon literature searches last conducted in July 2022 and updated in April 2023. It is designed to assist decision-making. It is not intended to define a standard of care and should not be interpreted as prescribing an exclusive course of management. Variations in practice will inevitably and appropriately occur when clinicians consider the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Healthcare professionals using these recommendations should decide how to apply them to their own clinical practice.

SECTION II: DISCLOSURE

Kidney Disease: Improving Global Outcomes (KDIGO) makes every effort to avoid any actual or reasonably perceived conflicts of interest that may arise from an outside relationship or a personal, professional, or business interest of a member of the Work Group. All members of the Work Group are required to complete, sign, and submit a disclosure and attestation form showing all such relationships that might be perceived as or are actual conflicts of interest. This document is updated annually, and information is adjusted accordingly. All reported information is published in its entirety at the end of this document in the Work Group members' Disclosure section and is kept on file at KDIGO.

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ABSTRACT

The Kidney Disease: Improving Global Outcomes (KDIGO) 2024 Clinical Practice Guideline for the Management of Nephrotic Syndrome in Children represents a focused update of Chapter 4: Nephrotic syndrome in Children from the KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. The aim is to assist clinicians caring for individuals with nephrotic syndrome, both steroid-sensitive and steroid-resistant. The update takes into consideration evidence from randomized controlled trials published through April 2023. As in 2021, this guideline provides guidance related to diagnosis, prognosis, treatment, and special situations. Based on the new evidence, this update is mostly related to the guidance related to treatment of nephrotic syndrome. Development of this guideline followed an explicit process of evidence review and appraisal. Treatment approaches and guideline recommendations are based on systematic reviews of relevant studies, and appraisal of the certainty of the evidence and the strength of recommendations following the “Grading of Recommendations Assessment, Development and Evaluation” (GRADE) approach. Limitations of the evidence are discussed and areas of future research are also presented.

Keywords: evidence-based; glomerular diseases; guideline; KDIGO; nephrotic syndrome; systematic review

SUMMARY OF RECOMMENDATION STATEMENTS AND PRACTICE POINTS

NEPHROTIC SYNDROME IN CHILDREN

4.1 Diagnosis

Practice Point 4.1.1: The definitions relating to nephrotic syndrome in children are based on the clinical characteristics outlined in Figure 1.¹

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- **Nephrotic-range proteinuria:** First morning urine or *24-h uPCR ≥ 2 g/g (or 200 mg/mmol or $\geq 3+$ dipstick)
- **NS:** Nephrotic-range proteinuria and either hypoalbuminemia (serum albumin < 30 g/l (3 g/dl)) or edema when albumin level is not available
- **Complete remission:** First morning urine or *24-h uPCR ≤ 200 mg/g (0.2 g/g) (or 20 mg/mmol or negative or trace dipstick) on three or more consecutive occasions
- **Partial remission:** First morning urine or *24-h uPCR > 200 mg/g (0.2 g/g) but < 2 g/g (or > 20 and < 200 mg/mmol) and, if available, serum albumin ≥ 30 g/l (3 g/dl)
- **Relapse:** Recurrence of nephrotic-range proteinuria. In children, relapse is commonly assessed by urine dipstick and is thus defined as dipstick $\geq 3+$ for 3 consecutive days
- Typical dipstick results are expressed semiquantitatively as follows[†], or as stated by manufacturer:
Negative: 0 to < 15 mg/dl
Trace: 15 to < 30 mg/dl
1+: 30 to < 100 mg/dl
2+: 100 to < 300 mg/dl
3+: 300 to < 1000 mg/dl
4+: ≥ 1000 mg/dl
- **SSNS:** Complete remission with 4 weeks of prednisone or prednisolone at standard dose
- **Infrequent relapsing NS:** < 2 relapses per 6 months within 6 months of disease onset or < 4 relapses per 12 months in any subsequent 12-month period
- **Frequent relapsing NS:** ≥ 2 relapses per 6 months within 6 months of disease onset or ≥ 4 relapses per 12 months in any subsequent 12-month period
- **Steroid-dependent NS:** Two consecutive relapses during therapy with prednisone or prednisolone (either at full dose or during tapering) or within 15 days of prednisone or prednisolone discontinuation
- **SRNS:** Lack of complete remission with 4 weeks of therapy with daily prednisone or prednisolone at standard dose
- **Confirmation period:** Time period between 4 and 6 weeks from prednisone or prednisolone initiation during which response to further oral prednisone or prednisolone and/or pulses of i.v. methylprednisolone and RASi are ascertained in patients achieving only partial remission at 4 weeks. A patient achieving complete remission at 6 weeks is defined as a late responder. A patient not achieving complete remission at 6 weeks, although he had achieved partial remission at 4 weeks, is defined as SRNS.[‡]
- **Late responder:** Complete remission with 6 weeks of therapy.
- **Calcineurin inhibitor-responsive SRNS:** Partial remission with 6 months of treatment and/or complete remission with 12 months of treatment with a calcineurin inhibitor at adequate doses and/or levels
- **Calcineurin inhibitor-resistant SRNS:** Absence of partial remission with at least 6 months of treatment with a calcineurin inhibitor at adequate doses and/or levels
- **Multi-drug resistant SRNS:** Absence of complete remission with 12 months of treatment with 2 mechanistically distinct glucocorticoid-sparing agents at standard doses (see below)
- **Secondary SRNS:** A SSNS patient at disease onset who at a subsequent relapse fails to achieve remission with 4 weeks of therapy with daily prednisone or prednisolone at standard dose

Figure 1 | Definitions relating to nephrotic syndrome (NS) in children aged 1–18 years. *To rule out orthostatic proteinuria, the first morning urine should be collected separately for assessment. [†]van der Watt *et al.*¹ [‡]IPNA 2020.² PCR, protein-creatinine ratio; SRNS, steroid-resistant nephrotic syndrome; SSNS, steroid-sensitive nephrotic syndrome.

4.2 Prognosis

Practice Point 4.2.1: The prognosis for children with nephrotic syndrome is best predicted by the patient's response to initial treatment and frequency of relapse during the first year after treatment. Therefore, a kidney biopsy is not usually needed at initial

presentation, and instead is reserved for children with resistance to therapy or an atypical clinical course.

4.3 Treatment

A schematic approach to treatment is outlined in Figure 2.

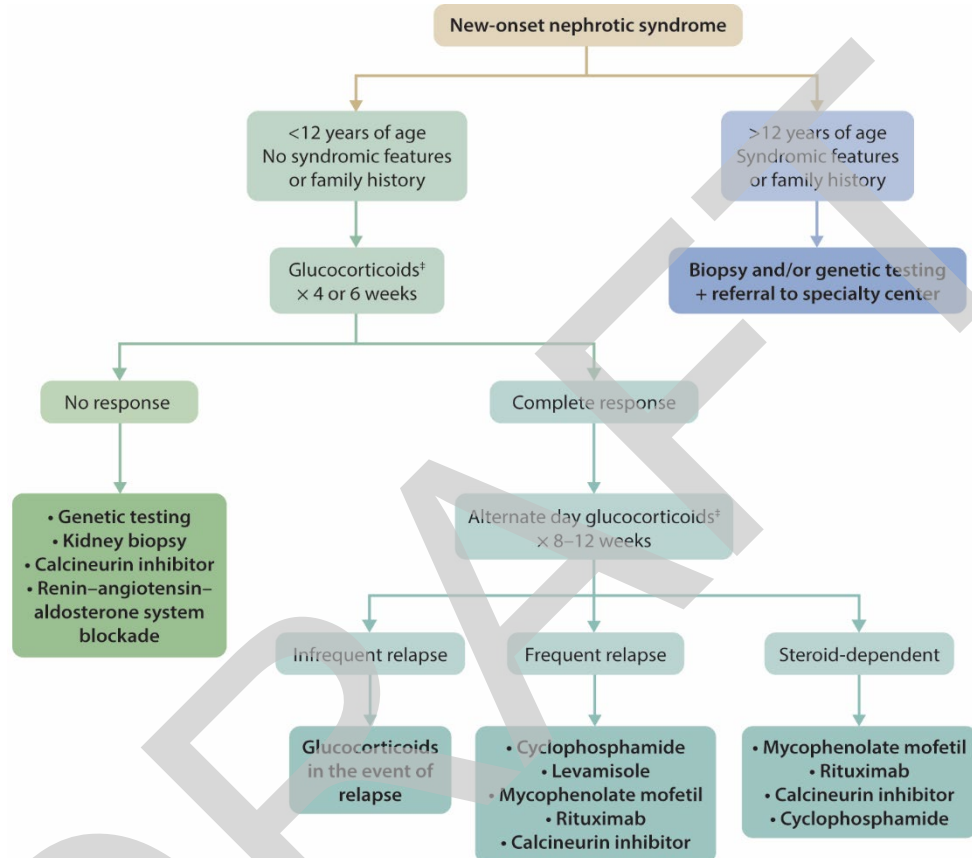


Figure 2 | Treatment algorithm for nephrotic syndrome (NS) from onset. Therapeutic approach to NS in children from onset. Refer to clinical trial where appropriate. Syndromic features defined as impaired statural growth, skeletal, neurodevelopmental and ocular abnormalities, deafness, genital ambiguity, facial dysmorphisms, etc. *Glucocorticoids: p.o. prednisone or prednisolone.

4.3.1 Initial treatment of NS in children

Recommendation 4.3.1.1: We recommend that oral glucocorticoids be given for 8 weeks (4 weeks of daily glucocorticoids followed by 4 weeks of alternate-day glucocorticoids) or 12 weeks (6 weeks of daily glucocorticoids followed by 6 weeks of alternate-day glucocorticoids) (1B).

Practice Point 4.3.1.1: The standard dosing regimen for the initial treatment of nephrotic syndrome is daily oral prednisone/prednisolone 60 mg/m² per day or 2 mg/kg per day (maximum 60 mg/d) for 4 weeks followed by alternate day prednisone/prednisolone, 40

mg/m² or 1.5 mg/kg (maximum of 50 mg) for other 4 weeks, or prednisone/prednisolone 60 mg/m² per day (maximum 60 mg/d) for 6 weeks followed by alternate day prednisone/prednisolone, 40 mg/m² or 1.5 mg/kg (maximum of 50 mg), for other 6 weeks.

4.3.2 Prevention of relapses of NS in children

Recommendation 4.3.2.1: For children with frequently relapsing and steroid-dependent nephrotic syndrome, we recommend that daily glucocorticoids not be given routinely during episodes of upper respiratory tract and other infections to reduce the risk of relapse (1C).

Practice Point 4.3.2.1: A short course of low dose (0.5 mg/kg per day) daily prednisone or prednisolone at the onset of an upper respiratory tract infection can be considered in children with frequently relapsing and steroid-dependent nephrotic syndrome who are already taking low-dose, alternate-day prednisolone and have a history of repeated infection-associated relapses or significant prednisone- or prednisolone-related morbidity.

4.3.3 Treatment of relapses of NS in children

Practice Point 4.3.3.1: The initial approach to relapse should include oral prednisone or prednisolone as a single daily dose of 60 mg/m² per day or 2 mg/kg per day (maximum 60 mg per day) until the child remits completely for ≥3 days.

Practice Point 4.3.3.2: After achieving complete remission in steroid-sensitive nephrotic syndrome patients treated for relapse, reduce oral prednisone/prednisolone to 40 mg/m² or 1.5 mg/kg (maximum 50 mg) on alternate days for ≥4 weeks.

Practice Point 4.3.3.3: For children with frequently relapsing nephrotic syndrome or steroid-dependent nephrotic syndrome without glucocorticoid toxicity, the same glucocorticoid regimen may be employed in subsequent relapses.

Practice Point 4.3.3.4: For children with frequently relapsing nephrotic syndrome without serious glucocorticoid-related adverse effects, low-dose alternate-day oral prednisone/prednisolone (optimally ≤0.5 mg/kg per day) can be prescribed to prevent relapse.

Recommendation 4.3.3.1: For children with frequently relapsing nephrotic syndrome who develop serious glucocorticoid-related adverse effects and for all children with steroid-dependent nephrotic syndrome, we recommend that glucocorticoid-sparing agents be prescribed, rather than no treatment or continuation with glucocorticoid treatment alone (1B).

Practice Point 4.3.3.5: Patients should ideally be in remission with glucocorticoids prior to the initiation of glucocorticoid-sparing agents such as oral cyclophosphamide, levamisole, mycophenolate mofetil (MMF), rituximab, or calcineurin inhibitors (CNIs). Coadministration of glucocorticoids is recommended for ≥2 weeks following initiation of glucocorticoid-sparing treatment.

Practice Point 4.3.3.6: Choosing the most appropriate glucocorticoid-sparing agent from among oral cyclophosphamide, levamisole, MMF, rituximab, and CNI is a decision that requires careful consideration of specific patient-related issues such as resources, adherence, adverse effects, and patient preferences. Oral cyclophosphamide and levamisole may be preferable glucocorticoid-sparing therapies in frequently relapsing nephrotic syndrome. MMF, rituximab, CNIs, and to a lesser extent, oral cyclophosphamide may be preferable to glucocorticoid-sparing therapies in children with steroid-dependent nephrotic syndrome (Figure 3⁷²).

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Treatment	Dose and duration	Clinical tips
First line:		
• Oral cyclophosphamide	2 mg/kg/d for 12 weeks (maximum cumulative dose 168 mg/kg)	Cyclophosphamide should not be started until the child has achieved remission with glucocorticoids. Moreover, second courses of alkylating agents should not be given. Weekly CBCs are recommended during the treatment course to assess for severe leukopenia or overall bone marrow suppression prompting dose reduction or treatment cessation
• Oral levamisole	2.5 mg/kg on alternate days, with a maximum dose of 150 mg	Monitor CBC every 2–3 months and alanine and aspartate aminotransferases every 3–6 months during therapy with levamisole. Check ANCA titers every 6 months, if possible, and interrupt treatment in case of ANCA positivity, skin rash or agranulocytosis. Maintaining low-dose alternate-day glucocorticoid dosing on the days not taking levamisole may be effective in some children. Levamisole should be continued for at least 12 months
Alternative agents:		
• Mycophenolate mofetil	Starting dose of 1200 mg/m ² /d (given in two divided doses)	Target area under the curve >50 µg·h/ml*. Mycophenolate mofetil should be continued for at least 12 months, as most children will relapse when it is stopped. In children experiencing significant abdominal pain on mycophenolate mofetil, other mycophenolic acid analogs (MPAAs), such as sodium mycophenolate, may be employed at equivalent doses (360 mg of sodium mycophenolate corresponds to 500 mg of mycophenolate mofetil)
• Rituximab	375 mg/m ² i.v. × 1–4 doses	Rituximab may be used as a treatment for steroid-sensitive nephrotic syndrome in children who have continuing frequent relapses despite optimal combinations of prednisone and glucocorticoid-sparing oral agents, and/or who have serious adverse effects of therapy. Current trials report 1 to 4 doses of rituximab. There are insufficient data to make a recommendation for specific number of needed doses. Where available, CD20 levels should be monitored. In children with complicated forms of FRNS or SDNS, the use of mycophenolate mofetil after rituximab can decrease the risk of treatment failure. Hepatitis B surface antigen, hepatitis B core antibody, and a quantiferon test for tuberculosis must be checked prior to rituximab administration. Monitoring IgG levels both before and after rituximab therapy may allow for earlier identification of risk for developing significant infection and identify patients who may benefit from immunoglobulin replacement
• Calcineurin inhibitors†		
– Cyclosporine	4 to 5 mg/kg/d (starting dose) in two divided doses	CNI should be continued for at least 12 months as most children will relapse upon discontinuation. Monitor CNI levels during therapy to limit toxicity
– Tacrolimus	0.1 mg/kg/d (starting dose) given in two divided doses	Cyclosporine may be preferable in patients at risk for diabetic complications. Target 12 hour trough level of 60–150 ng/ml [50–125 nmol/l] aiming for lowest levels to maintain remission and avoid toxicity
		Tacrolimus may be preferred over cyclosporine in patients for whom the cosmetic side-effects of cyclosporine are unacceptable. Target 12 hour trough level of 5–10 ng/ml [6–12 nmol/l] aiming for lowest levels to maintain remission and avoid toxicity

Figure 3 | Glucocorticoid-sparing therapies in children with steroid sensitive nephrotic syndrome (SSNS). *Gellermann *et al.*⁷² †The calcineurin inhibitor (CNI), while often used twice daily, may be dosed once a day, depending on individual formulations. In smaller children (<6 years of age), daily dose of cyclosporine can be divided into 3 doses (every 8 hour) to obtain steady hematic levels. Blood levels of CNI do not provide information on intracellular levels. The target ranges for CNIs have been based on the transplant literature. The Work Group

acknowledges that targets for glomerular diseases are not known. Most clinicians check these levels to verify adherence and avoid CNI toxicity. At present, the most reasonable dosing of a CNI may be to titrate in the individual patient to obtain the desired effect on proteinuria, balancing dose escalation against serum creatinine and reducing the dose if serum creatinine increases but does not plateau or increases over 30% of baseline. If the serum creatinine level does not fall after dose reduction, the CNI should be discontinued. ANCA, antineutrophil cytoplasmic antibody; CBC, complete blood count.

4.4 STEROID-RESISTANT NEPHROTIC SYNDROME IN CHILDREN

4.4.1 Treatment

Recommendation 4.4.1.1: We recommend using cyclosporine or tacrolimus as initial second-line therapy for children with steroid-resistant nephrotic syndrome (IC).

4.5 Special situations

Practice Point 4.5.1: Figure 5^{107, 108} outlines the general principles in children with nephrotic syndrome.

Indication for kidney biopsy	<ul style="list-style-type: none"> • Children presenting with nephrotic syndrome ≥ 12 years of age • Steroid-resistant nephrotic syndrome or subsequent failure to respond to glucocorticoids in steroid-sensitive nephrotic syndrome (secondary steroid-sensitive nephrotic syndrome) • A high index of suspicion for a different underlying pathology (macroscopic hematuria, systemic symptoms of vasculitis, hypocomplementemia, etc.) • At onset, kidney failure not related to hypovolemia. Subsequently, decreasing kidney function in children receiving calcineurin inhibitors or prolonged exposure to calcineurin inhibitors (2 to 3 years)
Genetic testing	<ul style="list-style-type: none"> • Steroid-resistant nephrotic syndrome • Congenital and infantile forms of nephrotic syndrome (<1 year of age) • Nephrotic syndrome associated with syndromic features • Family history of steroid-resistant nephrotic syndrome or focal segmental glomerulosclerosis
Vitamin D/calcium	In patients with steroid-sensitive nephrotic syndrome and normal vitamin D levels, supplementation is not required. However, in frequently relapsing nephrotic syndrome or steroid-dependent nephrotic syndrome in children or in the presence of a known vitamin D deficiency, a reduction in bone mineral content can be prevented by oral supplementation with oral calcium and vitamin D ^(1,2)
Gastroprotection	There is insufficient evidence of benefit to recommend prophylactic use of proton-pump inhibitors in children with nephrotic syndrome in the absence of risk factors for gastrototoxicity or of gastric symptoms

Figure 5 | General principles in children with NS. *If there is an evident extrarenal cause for proteinuria (i.e., lymphoma, monoclonal antibody treatment in ulcerative colitis, human immunodeficiency virus), a kidney biopsy may not be warranted. NS, nephrotic syndrome.

¹Gulati *et al.*¹⁰⁸, ²Gruppen *et al.*¹⁰⁷

NEPHROTIC SYNDROME IN CHILDREN

This guideline makes treatment recommendations for children with nephrotic syndrome (NS), aged 1–18 years. Below the age of 1 year, all children fulfilling the definition of NS should be referred to a specialist in pediatric nephrology as the therapeutic approach for such young children is beyond the scope of this work.

4.1 Diagnosis

Practice Point 4.1.1: The definitions relating to nephrotic syndrome in children are based on the clinical characteristics outlined in Figure 1.¹

DRAFT

- **Nephrotic-range proteinuria:** First morning urine or *24-h uPCR ≥ 2 g/g (or 200 mg/mmol or $\geq 3+$ dipstick)
- **NS:** Nephrotic-range proteinuria and either hypoalbuminemia (serum albumin < 30 g/l (3 g/dl)) or edema when albumin level is not available
- **Complete remission:** First morning urine or *24-h uPCR ≤ 200 mg/g (0.2 g/g) (or 20 mg/mmol or negative or trace dipstick) on three or more consecutive occasions
- **Partial remission:** First morning urine or *24-h uPCR > 200 mg/g (0.2 g/g) but < 2 g/g (or > 20 and < 200 mg/mmol) and, if available, serum albumin ≥ 30 g/l (3 g/dl)
- **Relapse:** Recurrence of nephrotic-range proteinuria. In children, relapse is commonly assessed by urine dipstick and is thus defined as dipstick $\geq 3+$ for 3 consecutive days
- Typical dipstick results are expressed semiquantitatively as follows[†], or as stated by manufacturer:
 - Negative:** 0 to < 15 mg/dl
 - Trace:** 15 to < 30 mg/dl
 - 1+:** 30 to < 100 mg/dl
 - 2+:** 100 to < 300 mg/dl
 - 3+:** 300 to < 1000 mg/dl
 - 4+:** ≥ 1000 mg/dl
- **SSNS:** Complete remission with 4 weeks of prednisone or prednisolone at standard dose
- **Infrequent relapsing NS:** < 2 relapses per 6 months within 6 months of disease onset or < 4 relapses per 12 months in any subsequent 12-month period
- **Frequent relapsing NS:** ≥ 2 relapses per 6 months within 6 months of disease onset or ≥ 4 relapses per 12 months in any subsequent 12-month period
- **Steroid-dependent NS:** Two consecutive relapses during therapy with prednisone or prednisolone (either at full dose or during tapering) or within 15 days of prednisone or prednisolone discontinuation
- **SRNS:** Lack of complete remission with 4 weeks of therapy with daily prednisone or prednisolone at standard dose
- **Confirmation period:** Time period between 4 and 6 weeks from prednisone or prednisolone initiation during which response to further oral prednisone or prednisolone and/or pulses of i.v. methylprednisolone and RASi are ascertained in patients achieving only partial remission at 4 weeks. A patient achieving complete remission at 6 weeks is defined as a late responder. A patient not achieving complete remission at 6 weeks, although he had achieved partial remission at 4 weeks, is defined as SRNS.[‡]
- **Late responder:** Complete remission with 6 weeks of therapy.
- **Calcineurin inhibitor-responsive SRNS:** Partial remission with 6 months of treatment and/or complete remission with 12 months of treatment with a calcineurin inhibitor at adequate doses and/or levels
- **Calcineurin inhibitor-resistant SRNS:** Absence of partial remission with at least 6 months of treatment with a calcineurin inhibitor at adequate doses and/or levels
- **Multi-drug resistant SRNS:** Absence of complete remission with 12 months of treatment with 2 mechanistically distinct glucocorticoid-sparing agents at standard doses (see below)
- **Secondary SRNS:** A SSNS patient at disease onset who at a subsequent relapse fails to achieve remission with 4 weeks of therapy with daily prednisone or prednisolone at standard dose

Figure 1 | Definitions relating to nephrotic syndrome (NS) in children aged 1–18 years. *To rule out orthostatic proteinuria, the first morning urine should be collected separately for assessment. [†]van der Watt *et al.*¹ [‡]IPNA 2020.² PCR, protein-creatinine ratio; SRNS, steroid-resistant nephrotic syndrome; SSNS, steroid-sensitive nephrotic syndrome.

4.2 Prognosis

Practice Point 4.2.1: The prognosis for children with nephrotic syndrome is best predicted by the patient's response to initial treatment and frequency of relapse during the first year after treatment. Therefore, a kidney biopsy is not usually needed at initial presentation, and instead is reserved for children with resistance to therapy or an atypical clinical course.

Nephrotic syndrome is the most frequent glomerular disease in children, with an incidence of 1.15–16.9 per 100,000 children.³ Before the availability of antibiotics and glucocorticoids, about 40% of children with NS died of infection, kidney failure, and occasionally thromboembolism.⁴ Among children who survived, sustained spontaneous remission was observed only after years of disease activity. While antibiotics reduced mortality, it was the introduction of glucocorticoid use in the 1950s that changed the natural history of the condition.⁴ Since the 1970s, following onset of disease, children have been treated with a standard dose of glucocorticoids. Response to this standard dosing regimen and the number of relapses in the subsequent year allows classification of the child's NS, and this classification holds more prognostic value than a kidney biopsy, which is therefore not routinely performed at disease onset. In general, it is assumed that children with steroid-sensitive forms of NS (SSNS), if biopsied, would most frequently be found to have minimal change disease (MCD), although mesangial proliferation with immunoglobulin M (IgM) and focal segmental glomerulosclerosis (FSGS) (the lesion most frequently associated with steroid-resistant forms of NS) have also been described.

In children with SSNS who are receiving timely and appropriate treatment, kidney function is always maintained, and prognosis is correlated with the morbidity of prolonged exposure to glucocorticoids and to second-line glucocorticoid-sparing agents that are prescribed in frequently relapsing and especially in steroid-dependent forms of disease. SSNS has a chronic, relapsing–remitting course, which tends to resolve spontaneously following puberty. However, in 15%–25% of cases, it may progress to adulthood, maintaining the particular features of the childhood-onset NS with rapid response to glucocorticoids in case of relapse. Moreover, a small percentage (<5% of SSNS patients) of children may, in subsequent relapses, become secondarily steroid-resistant. These children have a high probability of both progressing to kidney failure and relapsing post-transplantation.

A kidney biopsy is therefore performed at onset only in children with atypical features, such as macroscopic hematuria, low C3 levels, acute kidney injury not related to hypovolemia, sustained hypertension, arthritis, and/or rash. Biopsy is subsequently indicated for all children with steroid-resistance at 4–6 weeks from onset (Section 4.5; Figure 5). During the disease course, it may be advisable to perform or repeat a kidney biopsy in children who have had a prolonged (>2–3 years) exposure to calcineurin inhibitors (CNIs) to monitor for signs of nephrotoxicity or in children who develop secondary steroid-resistance.

In children with steroid-sensitive and steroid-resistant but calcineurin-responsive forms of NS, the optimal treatment strategy is therefore aimed at employing the lowest cumulative doses of glucocorticoids and the safest and most effective glucocorticoid-sparing agents to maintain remission. The use of vitamin D/calcium, gastroprotection, and an appropriate vaccination strategy are also important to minimize morbidity.

In children with steroid-resistant nephrotic syndrome (SRNS), genetic testing to allow appropriate management of the kidney disease and, when present, extrarenal features, is highly encouraged. Optimal conservative therapy to minimize progression of kidney disease in children with prolonged proteinuria should be employed. Treatment with dialysis and transplantation must be performed in centers that have specific expertise in pediatric nephrology.

4.3 Treatment

A schematic approach to treatment is outlined in Figure 2.

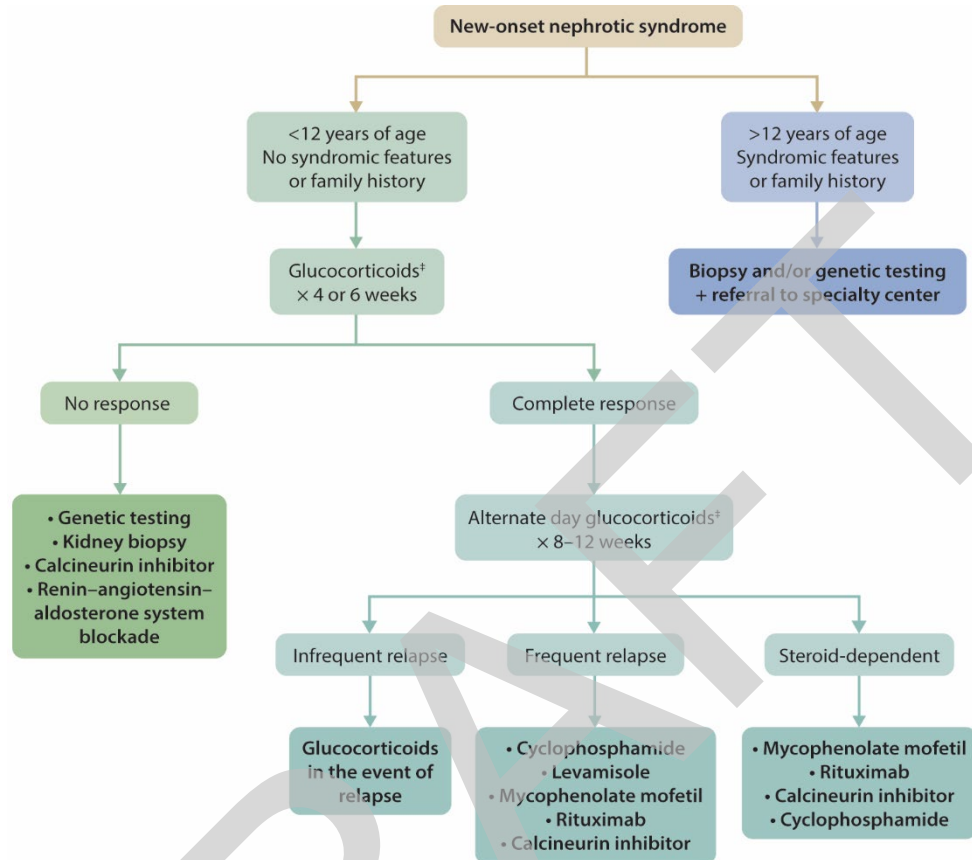


Figure 2 | Treatment algorithm for nephrotic syndrome (NS) from onset. Therapeutic approach to NS in children from onset. Refer to clinical trial where appropriate. Syndromic features defined as impaired statural growth, skeletal, neurodevelopmental and ocular abnormalities, deafness, genital ambiguity, facial dysmorphism, etc. *Glucocorticoids: p.o. prednisone or prednisolone.

4.3.1 Initial treatment of NS in children

Recommendation 4.3.1.1: We recommend that oral glucocorticoids be given for 8 weeks (4 weeks of daily glucocorticoids followed by 4 weeks of alternate-day glucocorticoids) or 12 weeks (6 weeks of daily glucocorticoids followed by 6 weeks of alternate-day glucocorticoids) (1B).

This recommendation places a relatively higher value on the moderate-certainty evidence of equivalent clinical outcome (frequent relapse) and favorable safety profile associated with

shorter-term (8–12 weeks) glucocorticoid treatment, and a relatively higher value on high-certainty evidence suggesting prolonged (>12 weeks) glucocorticoid treatment increases the risk of adverse effects without further improving clinical outcomes in terms of relapse rate. The recommendation places a relatively lower value on low-certainty evidence suggesting that prolonged glucocorticoid therapy may delay the time to first relapse as compared to 8–12 weeks of treatment.

In terms of oral glucocorticoids, prednisone and prednisolone are equivalent, used in the same dosage, and are both supported by high-certainty evidence. All later usages of “oral glucocorticoids” refer to prednisone or prednisolone.

Recent reports suggest that it may be prudent to dose by body surface area to avoid underdosing, particularly in younger children.⁵⁻⁸ A randomized controlled trial (RCT) comparing single versus divided dose showed that the 2 are equivalent in terms of time to remission and number of subsequent relapses.⁹ Therefore, a single daily dose may be preferable to optimize adherence.

Key information

Balance of benefits and harms

Without appropriate treatment, spontaneous remission is very rare for initial episodes of NS, whose morbidity and mortality, if untreated, are considerable.⁴ With the introduction of glucocorticoid treatment, prognosis had improved dramatically, and from the 1970s, standard protocols were implemented for children at disease onset. The prognosis of children with NS directly correlates with response to this treatment and subsequently with the number of relapses they experience. The majority of patients who are initially steroid-sensitive remain steroid-sensitive and never progress to kidney failure. Therefore, optimal management is based on minimizing toxicity of treatment, which initially and primarily consists of oral glucocorticoids,^{3, 10} preserving steroid sensitivity, and prolonging remission.

Since publication of the original Kidney Disease: Improving Global Outcomes (KDIGO) 2012 guideline, 4 RCTs have evaluated the optimal glucocorticoid dosage for treatment of the initial episode of SSNS in children: 2 studies comparing 12 weeks to 6 months, 1 study comparing 8 weeks to 6 months, and 1 study comparing 8 weeks to 4 months.¹¹⁻¹³ These studies show that extending initial glucocorticoid treatment from 8–12 weeks to 6 months may delay the first relapse but does not have an impact on the occurrence of frequent relapses, nor on the subsequent disease course. Since publication of the previous KDIGO 2021 guideline, a systematic review of all available studies has recently been published, summarized in supplementary Table S4.¹⁴

In an attempt to explain the difference between these more recent findings and earlier evidence, the 2015 Cochrane systematic review examined whether there were systematic differences in the findings of studies at lower versus higher risk of bias.¹⁵ When restricted to studies at lower risk of bias, the pooled findings suggested that prolonged treatment makes little or no difference in the number of children developing frequently relapsing disease. This was true for both studies comparing 12 weeks to 8 weeks of therapy and studies comparing 5–6 months to 8 or 12 weeks of therapy for the initial episode of SSNS. This finding was further confirmed by analysis of the more recently published Prednisolone in Nephrotic Syndrome (PREDNOS) trial, comparing 8 weeks to 4 months.¹⁶

In terms of harms, Sinha *et al.* showed that adverse effects related to glucocorticoids (hypertension, Cushingoid appearance, hirsutism, obesity, short stature, and aggressive behavior) and infectious episodes were comparable at randomization, end of intervention, and at 12 months of follow-up in the 2 treatment groups (12 weeks vs. 6 months).¹¹ Similar findings are reported by

Yoshikawa *et al.* (median follow-up 36-38 months),¹³ Teeninga *et al.* (median follow-up 47 months),¹² and Webb *et al.* (follow-up 24 months).¹⁶ Although these studies do not demonstrate that the shorter course of treatment has a better safety profile, the totality of evidence from other conditions strongly suggests that the risk of adverse events with glucocorticoid treatment is directly proportional to its duration and cumulative dose. Therefore, as the shorter course does not appear to result in more frequent relapses, its impact in terms of safety appears advantageous, as it entails giving less glucocorticoid at onset.

Certainty of evidence

There was moderate-certainty evidence from RCTs that compared glucocorticoid therapy for ≥ 12 weeks duration with glucocorticoid therapy of 8 weeks duration (Supplementary Table S4^{13, 15-25}). For the important outcome of frequent relapses, the certainty of the evidence was low (very serious study limitations). The certainty of the evidence was rated as high in a subgroup analysis after removal of studies with a high or unclear risk of bias for allocation concealment. For adverse events (Cushing's syndrome), the evidence was downgraded to moderate because of serious study limitations. However, other adverse events (infection and other glucocorticoid-related adverse events) were downgraded to low- or very low-certainty evidence because of study limitations and serious imprecision (wide confidence intervals [CIs]—indicating less certainty in effect), or serious inconsistency (substantial heterogeneity). However, these adverse events occurred relatively infrequently, so their low certainty was not considered critical to the overall certainty of the evidence rating.

Values and preferences

The potential benefits of glucocorticoid treatment, including reduction of morbidity from NS and a lower risk of progressive kidney function loss, were judged as critically important to patients and parents. The Work Group also judged that the relatively low risk of clinically important harms, including side effects of glucocorticoids, would be important to many patients. Since preserving steroid sensitivity and maintaining remission is associated with good clinical outcomes, healthcare providers and patients must weigh the side effects of glucocorticoids against the risk of undertreating the first episode, which may lead to relapse and a higher cumulative dose of glucocorticoids, along with a higher risk of progressive kidney function loss. Historically, it was thought that intense treatment of the first episode led to fewer relapses and, therefore, to a lower cumulative glucocorticoid dose over >12 months. This attitude, however, may have led to overtreating the first episode. Recent evidence indicates that prolonging glucocorticoid treatment for >12 weeks increases the risk of harm without the benefit of reducing the risk of relapse in the subsequent years. The Work Group judged that all or nearly all well-informed patients and parents would choose to receive 8–12 weeks of glucocorticoids as initial treatment of NS, compared to a longer course of glucocorticoids, another treatment, or no treatment.

There is insufficient evidence to choose between 8 and 12 weeks of glucocorticoid treatment, so usual local practice, available resources, and patient preferences may be used to choose between 8 weeks of treatment as opposed to 12 weeks. Consideration of patient characteristics may also be helpful. For example, 8 weeks, rather than 12 weeks, of treatment may be preferable in children achieving rapid remission (within 7 days from prednisolone initiation) or with comorbidities (obesity, hypertension, type 1 diabetes, etc.).

Resource use and costs

Prednisolone is inexpensive, widely available, and does not require special monitoring (e.g., of drug levels). No published studies have addressed the cost-effectiveness of glucocorticoid treatment among children who are steroid-sensitive, but given its low cost and clinical benefit, this treatment is likely to be cost-effective in most settings.

Considerations for implementation

There are no data evaluating whether the best treatment approach could vary by sex or ethnicity. In children of a particularly young age at disease onset (i.e., 1 to 4–6 years of age) who may be at higher risk of progressing to a frequently relapsing or steroid-dependent form of NS,¹⁹ prolonging treatment of the initial episode to 16–24 weeks may be beneficial in terms of preventing subsequent relapses with similar side effects.¹¹ This, however, is true only in children within this age group who experience a delayed response to prednisolone (i.e., remission in 10–15 days from treatment initiation), whereas even in younger patients (1 to 4–6 years old), a standard 8–12-week prednisolone course may be preferable if they respond rapidly to prednisolone (i.e., in <7 days).

Rationale

This recommendation places a relatively higher value on the better clinical outcomes and relatively favorable safety profile associated with shorter-term (8–12 weeks) glucocorticoid treatment compared with no treatment, as well as a relatively higher value on evidence suggesting that prolonged (>12 weeks) glucocorticoid treatment increases the risk of adverse effects without further improving clinical outcomes. The recommendation places a relatively lower value on weaker evidence suggesting that prolonged glucocorticoid therapy may delay the time to first relapse as compared to 8–12 weeks of treatment. Evidence is insufficient to choose between 8 and 12 weeks of treatment.

The recommendation is a Level 1 because the Work Group judged that all or nearly all well-informed parents and patients would choose to receive 8 or 12 weeks of glucocorticoids as initial treatment of SSNS, compared to a longer course of glucocorticoids, another treatment, or no treatment. The Work Group arrived at a Level 1 recommendation also because the alternative (no treatment) is not an acceptable approach.

Practice Point 4.3.1.1: The standard dosing regimen for the initial treatment of nephrotic syndrome is daily oral prednisone/prednisolone 60 mg/m² per day or 2 mg/kg per day (maximum 60 mg/d) for 4 weeks followed by alternate day prednisone/prednisolone, 40 mg/m² or 1.5 mg/kg (maximum of 50 mg) for other 4 weeks, or prednisone/prednisolone 60 mg/m² per day (maximum 60 mg/d) for 6 weeks followed by alternate day prednisone/prednisolone, 40 mg/m² or 1.5 mg/kg (maximum of 50 mg), for other 6 weeks.

4.3.2 Prevention of relapses of NS in children

Children with SSNS have a good long-term prognosis with expected preservation of glomerular filtration rate (GFR) into adulthood. Between 80% and 90% of children with SSNS will relapse following an initial response to glucocorticoids. Half of these children will have infrequent relapsing NS. The remaining half of these children will experience frequent relapses (FRNS) or become steroid-dependent (SDNS).^{26,27} Many children relapse in response to an infectious trigger, but many others will have no identifiable trigger.²⁸ Prevention of relapse with a

preemptive short course of daily low dose corticosteroids may reduce overall glucocorticoid exposure and decrease the adverse effects of long-term glucocorticoids, which include impaired linear growth, obesity, hypertension, ophthalmologic pathology, behavioral changes, altered bone metabolism, impaired glucose tolerance, acne, and other physical changes related to Cushing's syndrome.²⁹⁻³²

Recommendation 4.3.2.1: For children with frequently relapsing and steroid-dependent nephrotic syndrome, we recommend that daily glucocorticoids not be given routinely during episodes of upper respiratory tract and other infections to reduce the risk of relapse (1C).

Practice Point 4.3.2.1: A short course of low dose (0.5 mg/kg per day) daily prednisone or prednisolone at the onset of an upper respiratory tract infection can be considered in children with frequently relapsing and steroid-dependent nephrotic syndrome who are already taking low-dose, alternate-day prednisolone and have a history of repeated infection-associated relapses or significant prednisone- or prednisolone-related morbidity.

This recommendation places a relatively higher value on evidence that preemptive daily prednisolone may not reduce the risk of SSNS relapse during infection, and a lack of evidence of potential benefits of this approach. Given the lack of evidence of a benefit of preemptive glucocorticoid treatment, this recommendation places low value on evidence comparing alternate-day and daily prednisolone as preemptive treatment.

Key information

Balance of benefits and harms

Infections have long been identified as triggers for relapses in children with FRNS. Several trials suggest that relapses might be reduced if glucocorticoids are administered daily for 5–7 days at the onset of upper respiratory tract infection in children with FRNS or SDNS who are either not currently taking glucocorticoids or taking alternate-day glucocorticoids. In the 2017 study by Abeyagunawardena *et al.*, 48 patients with SDNS (but off prednisone for ≥ 3 months) were randomized to receive either 5 days of daily prednisolone at 0.5 mg/kg at the onset of an upper respiratory tract infection, or 5 days of placebo.³³ In the treatment group, 34.3% of patients relapsed, whereas in the control group 59.4% of patients relapsed. These short courses of preemptive glucocorticoid treatment may avert the need for longer courses of glucocorticoids, thereby reducing toxicity. However, since publication of the previous 2021 guideline, the PREDNOS2 study was published.³⁴ This study randomized 271 children with FRNS across 91 sites in the United Kingdom to receive either a fixed dose of prednisolone or placebo for 6 days at the onset of upper respiratory tract infection. No differences in the incidence of upper respiratory tract infection-associated NS relapse were found between the 2 groups (42.7% on prednisolone vs. 44.3% on placebo relapsed, yielding an adjusted risk difference of -0.02, 95% CI: -0.14–0.10, $P=0.7$).

Although higher doses of glucocorticoids during infection might theoretically cause harmful immunosuppression, available data do not report an increased length or severity of the infections in the children receiving daily versus alternate-day glucocorticoids. In a recent cost-effectiveness

analysis of the PREDNOS2 study, it was found that the number needed to treat to prevent 1 relapse with daily oral prednisolone was higher than expected from other studies considered previously.³⁵ Therefore, as concluded in the recently published International Pediatric Nephrology Association (IPNA) guideline, there is insufficient evidence to recommend the routine use of a short course of low-dose daily prednisolone at the onset of an upper respiratory tract infection for prevention of relapses.² However, such an approach may be considered in children already taking low-dose, alternate-day prednisone/prednisolone and with a history of upper respiratory tract infection triggering relapse.²

Certainty of evidence

There is low certainty in the evidence (study limitations, single study) regarding prednisolone versus placebo during viral infections (Supplementary Table S5^{15, 33, 34, 36-38}) for NS relapse with infection, but no evidence for other outcomes. There is also low certainty of evidence regarding infection-related relapse (study limitations, each specific outcome with a single study) in comparisons of daily versus alternate-day prednisolone (Supplementary Table S6^{33, 36-38}). Overall, the certainty of evidence is low.

Rate of infection-related relapse at 1 and 2 years were the only critical or important outcomes examined in these studies. The certainty of the evidence was downgraded because of study limitations and serious imprecision.

Values and preferences

The Work Group judged that the recent data from the PREDNOS2 trial cautions that in most patients the use of low-dose oral prednisolone at the onset of an upper respiratory tract infection will not be effective in preventing NS-triggered by upper respiratory tract infection-triggered relapses of nephrotic syndrome. However, no differences in side effects were detected between the 2 study arms. Therefore, since giving daily oral prednisolone at the time of an upper respiratory tract infection does not carry a significant risk, it may be a viable approach to avoid prolonged exposure to high-dose prednisolone due to relapse in some patients, particularly in those with a history of upper respiratory tract infection triggering relapse. This preemptive strategy may also be preferable in children with FRNS who are more prone to develop untoward side effects from high-dose glucocorticoids—such as severe behavioral changes, sleep disturbance, obesity—or have comorbid conditions such as diabetes.

Resource use and costs

In a cost-effectiveness analysis of the PREDNOS2 study using a decision-analytic model to estimate quality-adjusted life-years and costs, giving daily oral prednisolone at the time of an upper respiratory tract infection was associated with a modest increase in quality-adjusted life-years and a modest decrease in average costs, when compared with standard care. The cost-saving was driven by background therapy and hospitalizations after relapse. Therefore, given the low risk, especially in children already on alternate-day oral prednisolone who would receive only 3 additional doses, this approach may remain reasonable in selected children who relapse regularly following an upper respiratory tract infection. Glucocorticoids are among the most widely available therapies for NS, whereas many other immunosuppressive treatments are either cost-prohibitive or unavailable.

Considerations for implementation

There are no data to suggest that treatment approach should vary on the basis of sex or ethnicity.

Rationale

The KDIGO 2012 guideline suggested treating children with FRNS who were receiving glucocorticoids on alternate days (or not receiving glucocorticoids) with daily prednisone/prednisolone for 5–7 days at the start of an infection. Following that publication, several randomized, but small, clinical trials demonstrated up to a 30% reduction in relapses with this treatment approach. More recently, after the KDIGO 2021 guideline publication, the PREDNOS2 RCT, a large and rigorous study, did not confirm these findings, showing no clear clinical benefit of this approach. For this reason, we have modified our recommendation 4.3.2.1. However, given the minimal risk of this approach, in selected cases daily prednisone or prednisolone for 5–7 days at the start of an infection may still be reasonable (i.e., in children already on alternate-day prednisolone who regularly relapse in case of upper respiratory tract infection and/or in children with significant prednisolone-related morbidity).

4.3.3 Treatment of relapses of NS in children

Practice Point 4.3.3.1: The initial approach to relapse should include oral prednisone or prednisolone as a single daily dose of 60 mg/m² per day or 2 mg/kg per day (maximum 60 mg per day) until the child remits completely for ≥3 days.

Practice Point 4.3.3.2: After achieving complete remission in steroid-sensitive nephrotic syndrome patients treated for relapse, reduce oral prednisone/prednisolone to 40 mg/m² or 1.5 mg/kg (maximum 50 mg) on alternate days for ≥4 weeks.

Recently, 2 RCTs addressing the treatment of relapses, more specifically the dose and length of alternate day oral prednisone following induction of remission, have been published. One study, the PROPINE trial, compared using 40 mg/m² on alternate days for 5 weeks versus using the same cumulative prednisone dose spread out over 10 weeks with a tapering schedule (Supplementary Table S12).³⁹ No benefit in terms of subsequent relapses was found in using the longer treatment schedule. The second study instead attempted to establish the noninferiority of employing a lower oral prednisone dose by comparing 40 mg/m² on alternate days for 4 weeks versus 40 mg/m² on alternate days for 2 weeks in children with infrequently relapsing nephrotic syndrome (Supplementary Table S13).⁴⁰ The rate of relapse was similar in the 2 groups of children. However, the study failed to show the short regimen was noninferior. Taken altogether, these results support the use of oral prednisone/prednisolone at 40 mg/m² on alternate days for about 4 weeks following induction of remission for children with SSNS as stated above. Future larger studies may establish that lower doses of oral prednisone or prednisolone can be employed effectively in this setting.

Practice Point 4.3.3.3: For children with frequently relapsing nephrotic syndrome or steroid-dependent nephrotic syndrome without glucocorticoid toxicity, the same glucocorticoid regimen may be employed in subsequent relapses.

Practice Point 4.3.3.4: For children with frequently relapsing nephrotic syndrome without serious glucocorticoid-related adverse effects, low-dose, alternate-day oral prednisone/prednisolone (optimally ≤0.5 mg/kg per day) can be prescribed to prevent relapse.

Recommendation 4.3.3.1: For children with frequently relapsing nephrotic syndrome who develop serious glucocorticoid-related adverse effects and for all children with steroid-dependent nephrotic syndrome, we recommend that glucocorticoid-sparing agents be prescribed, rather than no treatment or continuation with glucocorticoid treatment alone (1B).

This recommendation places a relatively high value on observational data and extensive clinical experience that demonstrate substantial risk of side effects associated with long-term glucocorticoids and efficacy of glucocorticoid-sparing agents in preventing relapse, compared with no treatment.

Key information

Balance of benefits and harms

The complications of NS can be divided into those that are directly disease-associated and those that are treatment-related. There are few studies that have compared glucocorticoids and glucocorticoid-sparing therapies to placebo alone. Historical observational data, however, are clear that the risk of mortality from infections, acute kidney injury, and complications from edema and thromboembolism is high in children who are not treated or fail to respond to any treatments.⁴¹

In a 10-year follow-up study of children with SSNS enrolled in a clinical trial assessing the efficacy of cyclosporine for reducing relapse rate, at least half of the children evaluated experienced severe side effects of glucocorticoids including severe growth failure, obesity, and low-bone density. These findings were attributed to glucocorticoid exposure for frequent relapses following the discontinuation of cyclosporine at 2 years.³⁰ Additional long-term follow-up of patients into adulthood with childhood-onset NS have demonstrated high prevalence of hypertension, osteoporosis, and cataracts attributable to chronic glucocorticoid exposure.^{31, 42, 43}

To avoid or mitigate glucocorticoid-related adverse effects, children with FRNS or SDNS require other agents, including alkylating agents (cyclophosphamide), levamisole, rituximab, mycophenolate mofetil (MMF), and CNIs (cyclosporine, tacrolimus).

Studies have consistently shown a benefit of second-line therapies in the reduction of relapses for children with FRNS or SDNS compared to either glucocorticoids alone or placebo. In a recent meta-analysis of 26 trials comparing the available immunosuppressive medications to placebo/no treatment, chlorambucil, cyclophosphamide, levamisole, and rituximab were associated with a significantly reduced relapse rate compared to placebo or no treatment at 6- and 12-months follow-up.⁴⁴

Adverse effects of these agents include reduced fertility (alkylating agents), kidney dysfunction, hypertension (CNIs), leukopenia, and an increased risk of serious infections (all second-line treatment options). Despite these challenges, it is the opinion of this Work Group that the overall benefit of these treatments outweighs the almost universal experience of toxicity related to chronic glucocorticoid exposure. Some of the adverse effects, such as leukopenia with

levamisole, are uncommon, mild, and reversible. Moreover, strategies to mitigate these potential side effects of some glucocorticoid-sparing agents exist, including limiting the cumulative exposure to cyclophosphamide to <168 mg/kg and monitoring CNI and MMF drug levels.

Certainty of evidence

The assessment of the certainty of evidence focused on glucocorticoid-sparing agents individually, but overall certainty was moderate (Supplementary Tables S7–S11). RCTs comparing alkylating agents, levamisole, or rituximab to placebo or glucocorticoids had moderate-certainty evidence for important outcomes. However, RCTs of CNIs and MMF compared with levamisole in patients with FRNS and SDNS was graded low because of the indirectness of the evidence, and study limitations. Despite the low certainty of the evidence for these therapies, the overall certainty of the evidence from RCTs was graded as moderate, as the majority of glucocorticoid-sparing agents that have been examined more extensively have a moderate certainty of evidence. Many of the RCTs do not report long-term clinical outcomes, such as all-cause mortality and kidney failure, given the rarity of these events in this population.

In patients with FRNS, the certainty of the evidence for the use of cyclophosphamide or chlorambucil compared to glucocorticoids or placebo was moderate for the outcome of relapse at 6–12 months (study limitations) and low at 12–24 months (study limitations, serious imprecision; Supplementary Table S7⁴⁵⁻⁵²). The evidence for the outcome of relapse at 6–12 months was weighted more heavily than at 12–24 months because there were few patients evaluated beyond 12 months resulting in imprecision. There was no evidence for other critical and important outcomes.

In children with FRNS or SDNS, the certainty of evidence for the use of levamisole compared to glucocorticoids or placebo was moderate for the outcome of relapse in either children with FRNS or children with SDNS (Supplementary Table S8^{9, 51-59}); although the RCTs were at low risk of bias, only a single study evaluated each outcome. Studies that reported relapse across the 2 populations (FRNS or SDNS) were heterogeneous and had methodological limitations. There was no evidence for other critical and important outcomes.

There was low certainty of evidence from 1 RCT that compared MMF with levamisole (Supplementary Table S9^{51, 60}). The single study had serious study limitations, providing low-certainty evidence for frequent relapse and infrequent relapse. Due to serious imprecision, there was very low certainty of evidence for adverse events and treatment failure.

There was low certainty of evidence from 1 RCT that compared cyclosporine combined with prednisone to prednisone alone in patients with their first episode of SSNS (Supplementary Table S10^{51, 61, 62}). There was low-certainty evidence for relapse due to being from a single study and because it was unclear how many patients had FRNS or SDNS. Other critical and important outcomes were not reported.

The certainty of the evidence for trials comparing rituximab with placebo or standard of care was moderate for the important outcome of relapse at 3 and 6 months because of serious risk of bias, but low-certainty evidence for relapse at 12 months due to additional imprecision (Supplementary Table S11^{5, 51, 63-69}). There was very low certainty of evidence for infections due to serious imprecision (due to relatively infrequent events).

There are no RCTs that have examined MMF alone compared with no treatment or glucocorticoids alone in patients with FRNS or SDNS.

Values and preferences

In the judgment of this Work Group, the adverse effects associated with prolonged glucocorticoid exposure would be critically important to patients and their parents. The high morbidity associated with uncontrolled nephrosis, and the high frequency of relapsing disease for many children with FRNS off glucocorticoids, makes the option of nontreatment unfeasible. The Work Group also judged that the potential adverse effects of glucocorticoid-sparing therapies (e.g., risk of infection, reduced fertility, kidney dysfunction, and hypertension) would be less detrimental to patients due to potential risk-mitigation strategies such as drug-level monitoring and dose limitations. Overall, the Work Group judged that avoiding the adverse effects associated with prolonged glucocorticoid exposure would be more important to patients and their parents than the potential adverse effects of glucocorticoid-sparing therapies.^{70, 71}

Resource use and costs

CNIs, alkylating agents, MMF, and rituximab are considerably more expensive than glucocorticoids and may require ongoing clinical and/or laboratory monitoring. Some glucocorticoid-sparing agents (or the monitoring that they require) are not available (e.g., levamisole) or affordable in all settings. However, the averted cost associated with preventing glucocorticoid-induced adverse events may offset the increased cost of glucocorticoid-sparing therapies.

Considerations for implementation

Relative efficacies of glucocorticoid-sparing therapies are described in practice points. In addition to expected efficacy, age, ability to tolerate frequent phlebotomy for safety labs, and patient preferences for daily oral therapy versus infrequent hospitalization for intravenous (i.v.) infusions are all factors that should be considered in treatment decision-making.

Rationale

The objective of limiting the long-term adverse effects of glucocorticoids in children with FRNS and SDNS has been consistent across guidelines from multiple bodies in every geographic region. The KDIGO 2012 and 2021 guidelines, the 2022 IPNA clinical practice recommendations, the British Association of Pediatric Guidelines, a 2015 Cochrane review for the treatment of SSNS in children, and Indian Pediatric Nephrology Group all recommend consideration of glucocorticoid-sparing therapies in children who are steroid-dependent, especially those who have exhibited glucocorticoid toxicity.

Practice Point 4.3.3.5: Patients should ideally be in remission with glucocorticoids prior to the initiation of glucocorticoid-sparing agents such as oral cyclophosphamide, levamisole, mycophenolate mofetil (MMF), rituximab, or calcineurin inhibitors (CNIs). Coadministration of glucocorticoids is recommended for ≥ 2 weeks following initiation of glucocorticoid-sparing treatment.

Although the goal of glucocorticoid-sparing agents is to let the patients be free of glucocorticoids, low-dose daily or alternate-day glucocorticoids may still be needed to maintain remission in SDNS despite administration of glucocorticoid-sparing agents. In children with SDNS, where alternate-day prednisone is not effective, daily prednisone can be given at the lowest dose to maintain remission without major adverse effects.

Practice Point 4.3.3.6: Choosing the most appropriate glucocorticoid-sparing agent from among oral cyclophosphamide, levamisole, MMF, rituximab, and CNI is a decision that requires careful consideration of specific patient-related issues such as resources, adherence, adverse effects, and patient preferences. Oral cyclophosphamide and levamisole may be preferable glucocorticoid-sparing therapies in frequently relapsing nephrotic syndrome. MMF, rituximab, CNIs, and to a lesser extent, oral cyclophosphamide may be preferable to glucocorticoid-sparing therapies in children with steroid-dependent nephrotic syndrome (Figure 3⁷²).

DRAFT

Treatment	Dose and duration	Clinical tips
First line:		
• Oral cyclophosphamide	2 mg/kg/d for 12 weeks (maximum cumulative dose 168 mg/kg)	Cyclophosphamide should not be started until the child has achieved remission with glucocorticoids. Moreover, second courses of alkylating agents should not be given. Weekly CBCs are recommended during the treatment course to assess for severe leukopenia or overall bone marrow suppression prompting dose reduction or treatment cessation
• Oral levamisole	2.5 mg/kg on alternate days, with a maximum dose of 150 mg	Monitor CBC every 2–3 months and alanine and aspartate aminotransferases every 3–6 months during therapy with levamisole. Check ANCA titers every 6 months, if possible, and interrupt treatment in case of ANCA positivity, skin rash or agranulocytosis. Maintaining low-dose alternate-day glucocorticoid dosing on the days not taking levamisole may be effective in some children. Levamisole should be continued for at least 12 months
Alternative agents:		
• Mycophenolate mofetil	Starting dose of 1200 mg/m ² /d (given in two divided doses)	Target area under the curve >50 µg·h/ml*. Mycophenolate mofetil should be continued for at least 12 months, as most children will relapse when it is stopped. In children experiencing significant abdominal pain on mycophenolate mofetil, other mycophenolic acid analogs (MPAAs), such as sodium mycophenolate, may be employed at equivalent doses (360 mg of sodium mycophenolate corresponds to 500 mg of mycophenolate mofetil)
• Rituximab	375 mg/m ² i.v. × 1–4 doses	Rituximab may be used as a treatment for steroid-sensitive nephrotic syndrome in children who have continuing frequent relapses despite optimal combinations of prednisone and glucocorticoid-sparing oral agents, and/or who have serious adverse effects of therapy. Current trials report 1 to 4 doses of rituximab. There are insufficient data to make a recommendation for specific number of needed doses. Where available, CD20 levels should be monitored. In children with complicated forms of FRNS or SDNS, the use of mycophenolate mofetil after rituximab can decrease the risk of treatment failure. Hepatitis B surface antigen, hepatitis B core antibody, and a quantiferon test for tuberculosis must be checked prior to rituximab administration. Monitoring IgG levels both before and after rituximab therapy may allow for earlier identification of risk for developing significant infection and identify patients who may benefit from immunoglobulin replacement
• Calcineurin inhibitors†		
– Cyclosporine	4 to 5 mg/kg/d (starting dose) in two divided doses	CNI should be continued for at least 12 months as most children will relapse upon discontinuation. Monitor CNI levels during therapy to limit toxicity
– Tacrolimus	0.1 mg/kg/d (starting dose) given in two divided doses	Cyclosporine may be preferable in patients at risk for diabetic complications. Target 12 hour trough level of 60–150 ng/ml [50–125 nmol/l] aiming for lowest levels to maintain remission and avoid toxicity
		Tacrolimus may be preferred over cyclosporine in patients for whom the cosmetic side-effects of cyclosporine are unacceptable. Target 12 hour trough level of 5–10 ng/ml [6–12 nmol/l] aiming for lowest levels to maintain remission and avoid toxicity

Figure 3 | Glucocorticoid-sparing therapies in children with steroid sensitive nephrotic syndrome (SSNS). *Gellermann *et al.*⁷² †The calcineurin inhibitor (CNI), while often used twice daily, may be dosed once a day, depending on individual formulations. In smaller children (<6 years of age), daily dose of cyclosporine can be divided into 3 doses (every 8 hour) to obtain steady hematic levels. Blood levels of CNI do not provide information on intracellular levels. The target ranges for CNIs have been based on the transplant literature. The Work Group

acknowledges that targets for glomerular diseases are not known. Most clinicians check these levels to verify adherence and avoid CNI toxicity. At present, the most reasonable dosing of a CNI may be to titrate in the individual patient to obtain the desired effect on proteinuria, balancing dose escalation against serum creatinine and reducing the dose if serum creatinine increases but does not plateau or increases over 30% of baseline. If the serum creatinine level does not fall after dose reduction, the CNI should be discontinued. ANCA, antineutrophil cytoplasmic antibody; CBC, complete blood count.

Cyclophosphamide

Patients with frequent relapses might have a superior response to cyclophosphamide and levamisole compared to patients with steroid dependency.⁷³ In 143 children treated with oral cyclophosphamide for FRNS, SDNS, or evidence of glucocorticoid toxicity, sustained remission was more frequent in children with FRNS versus SDNS (hazard ratio [HR]: 1.72; 95% CI: 0.99–2.98; $P = 0.05$).⁷⁴ Nonetheless, there may be a role for this treatment in some patients with SDNS, especially in areas of the world where other glucocorticoid-sparing agents are not accessible. In 90 children with SDNS who received a single course of oral cyclophosphamide (2 mg/kg per day for 10–12 weeks), a cumulative remission status of 57% at 1 year was achieved.⁷⁵ Children >7.5 years of age with FRNS are more likely to experience a long-term remission when treated with cyclophosphamide compared to children who are <4 years of age.⁷⁵ Younger age at presentation and having steroid dependence requiring higher doses (>1 mg/kg per day of glucocorticoids) to maintain remission appear to be associated with less-sustained remissions following treatment with oral cyclophosphamide.⁷⁶

Gonadal toxicity appears to affect males more than females, with data supporting a dose-dependent relationship. Azoospermia has been well-documented when cumulative cyclophosphamide exposure exceeds 168 mg/kg. For this reason, second courses of alkylating agents are not recommended.

Levamisole

Adverse effects of levamisole are uncommon and mild, including leukopenia and gastrointestinal disturbance. Data comparing cyclophosphamide and levamisole are quite limited and do not determine efficacy of one therapy over the other in regard to either relapse rates after treatment discontinuation or frequency of infection events.⁷⁷ Compared to placebo, levamisole has been shown to delay the time to relapse post-termination of glucocorticoids, and 26% of the patients treated with levamisole were relapse-free for at least 1 year, compared to only 6% of patients in the placebo group.⁵⁷ Adverse events in this trial were few and were mostly limited to neutropenia that was easily reversed with discontinuation of therapy. MMF was not superior to levamisole in a trial of 139 children with FRNS and SDNS in regard to sustained remission off glucocorticoids, although it showed a trend toward superiority in children with more severe forms (SDNS).⁶⁰

MMF

Variable outcomes for maintaining remission off glucocorticoids have been reported in children with FRNS or SDNS treated with MMF, and these are mostly limited to retrospective observational data. A recent crossover RCT of 60 children with FRNS compared the efficacy of MMF and cyclosporine directly. Relapses occurred in 36% of patients during MMF therapy versus only 15% during cyclosporine ($P = 0.06$). The time without relapse was significantly longer with cyclosporine than with MMF during the first year ($P < 0.05$), but not during the second year ($P = 0.36$). Notably, adverse events were similar between the treatment arms with the

exception of a lower estimated glomerular filtration rate (eGFR) and more anemia in the cyclosporine arm suggesting more nephrotoxicity.⁷²

Post hoc analysis of the Gellermann *et al.* study comparing MMF versus cyclosporine provided data that targeting higher area under the curve (AUC) levels may reduce relapses on therapy.⁷² Children with low mycophenolic acid (MPA) exposure (AUC <50 µg h/ml) experienced 1.4 relapses per year compared with only 0.27 relapses per year in those with high exposure (AUC >50 µg h/ml; $P < 0.05$). This study also suggested less nephrotoxicity compared to treatment with CNIs.

Rituximab

Several RCTs and non-RCTs have suggested a favorable response to rituximab in patients with SDNS and FRNS.^{64, 66, 68, 78} In an RCT by Iijima *et al.* of 48 children with FRNS or SDNS, a significant difference (267 vs. 101 relapse-free days [HR: 0.27; 95% CI: 0.14–0.53]; $P < 0.0001$) was noted for patients who received rituximab versus placebo.⁷⁹ In a randomized noninferiority trial of 30 children with SDNS, all but 1 child in the placebo arm relapsed within 6 months, compared to a median time to relapse of 18 months in the children treated with rituximab (95% CI: 9–32 months).⁶⁸ Rituximab was found to decrease the total number of relapses from 88 to 22 and the per-patient median number of relapses from 2.5 (interquartile range [IQR]: 2–4) to 0.5 (IQR: 0–1; $P < 0.001$) during 1 year of follow-up in 44 children and adults with either SDNS or FRNS in the Rituximab in Nephrotic Syndrome of Steroid-Dependent or Frequently Relapsing Minimal Change Disease Or Focal Segmental Glomerulosclerosis (NEMO) trial.⁷⁸

Reported rates of adverse events such as infection have been lower in children with FRNS treated with rituximab versus placebo. In the Ravani *et al.* trial, nausea and skin rash during infusion were common.⁶⁸ No such events occurred in the NEMO trial, and in fact, improvement in the growth velocity and reduction of BMI was noted in the participants after 1 year. There are no studies directly comparing adverse event rates in children treated with rituximab to cyclophosphamide. One retrospective study in 200 adult patients with MN reported that during a median follow-up of 40 months, patients who received rituximab had significantly fewer adverse events than those who received cyclophosphamide (63 vs. 173, $P < 0.001$), for both serious (11 vs. 46, $P < 0.001$) and nonserious (52 vs. 127, $P < 0.001$) adverse events.⁸⁰

Concerning other potential anti-CD20 monoclonal antibodies, a recent RCT showed that a single dose of ofatumumab was not superior to a single dose of rituximab in preventing relapse in children with SDNS and CNI-dependent NS (Supplementary Tables S141⁸¹).

Moreover, a recent RCT conducted in Japan showed that in children with complicated forms of FRNS or SDNS, the use of mycophenolate mofetil after rituximab can decrease the risk of treatment failure by 80% while on therapy (Supplementary Table S15⁸²).

CNIs (cyclosporine and tacrolimus)

Relapse following discontinuation of CNI treatment is frequent. Previous trials have reported relapse in up to 70% of children who discontinue their CNI, after 6 and 12 months of treatment. Tubulointerstitial lesions, however, have been reported in 30%–40% of children treated for more than 12 months with cyclosporine, and up to 80% of those treated for more than 4 years. The optimal duration of treatment based on these data for cyclosporine is not clear, and data for tacrolimus are even sparser. To reduce the cost of CNIs, coadministration of ketoconazole has been reported to reduce the dose needed to reach target trough levels by almost 50%, thereby yielding a cost savings of almost 38%, with no reduction in efficacy.

4.4 STEROID-RESISTANT NEPHROTIC SYNDROME IN CHILDREN

In a child who does not achieve complete response to glucocorticoids at 4 weeks, SRNS is diagnosed. Therapy with a renin-angiotensin system inhibitor (RASi) should be started and where available, genetic testing for known podocyte mutations and/or kidney biopsy pursued. If partial remission is achieved, SRNS can be strongly suspected, but a small percentage of children will achieve complete response at 6 weeks (defined as late responders). Between 4 and 6 weeks from the start of glucocorticoid therapy, a confirmation period which includes treatment with RASi along with continuation of glucocorticoid treatment either as daily or alternate day oral prednisolone in combination with three daily i.v. methylprednisolone pulses can be considered. Those who do not achieve a complete response will be defined as having SRNS at 6 weeks.

As soon as an established diagnosis of SRNS is made at 6 weeks, the first step is to consider the possibility of a genetic cause for which immunosuppression may not be useful. Therefore, if possible, genetic testing performed by experts should be rapidly implemented. Genetic forms of SRNS invariably progress over a variable time course to kidney failure and should be treated conservatively, although a few genetic mutations have been found to have some responsiveness to immunosuppressive therapies, primarily CNIs. Among those children without a genetic cause of SRNS, a substantial proportion will respond to a CNI in a variable amount of time (weeks to months). Children with initial SRNS who are subsequently CNI-responders either remain in stable remission with no or infrequent relapses or develop steroid-dependent forms of NS. For the latter patients, treat for SDNS as suggested previously and consider conversion to MMF to maintain steroid-free remission. MMF may also be considered in patients presenting with an eGFR <30 ml/min per 1.73 m² or used as an alternative to a CNI after remission status has been maintained for >1 year.⁸³ Rarely, children with an initial diagnosis of SSNS experience a subsequent relapse that does not respond to 4 weeks of glucocorticoid therapy (secondary SRNS). In these cases, multi-drug resistance often develops, leading to kidney failure and a high risk of post-transplant recurrence.

For children with CNI-resistant SRNS, consideration for entry into clinical trials evaluating novel therapies on the horizon should be strongly considered. Sparsentan, a dual endothelin and angiotensin II receptor blocker (ARB) was found to decrease proteinuria by 45% versus 19% in a phase 2 randomized double-blind trial of those treated only with irbesartan, with no differences in serious adverse events between the groups.⁸⁴ The phase 3 multicenter trial found a partial remission in 44.3% versus 23.2% in those treated with sparsentan versus placebo, respectively, but this finding did not translate into a statistically significant difference in the primary outcome of eGFR slope between study arms (total slope of 0.3 ml/min/1.73 m² per year and chronic slope of 0.9 ml/min/1.73 m² per year, $P > 0.05$).⁸⁵ Post-approval studies for low-density lipoprotein (LDL) apheresis are ongoing and provide additional clinical trial options for children with CNI-resistant SRNS. Where clinical trials are not available, there may be a limited role for treatment with rituximab.

For more detailed recommendations on these aspects of care and on management of complications of SRNS in children, refer to the recent IPNA guidelines.²

4.4.1 Treatment

Recommendation 4.4.1.1: We recommend using cyclosporine or tacrolimus as initial second-line therapy for children with steroid-resistant nephrotic syndrome (IC).

This recommendation places a relatively higher value on data suggesting that CNIs are more likely to induce remission than cyclophosphamide, MMF, or rituximab in treatment of children with SRNS. Conversely, it places a relatively lower value on evidence suggesting that prolonged exposure to CNIs may lead to significant nephrotoxicity.

Key information

Balance of benefits and harms

In patients with SRNS, the most commonly used second-line agents in children who have failed response to oral glucocorticoids include cyclosporine, tacrolimus, high-dose i.v. methylprednisolone, and MMF, although the efficacy of these agents is lower in SRNS compared to FRNS or SDNS. Several RCTs suggested that cyclosporine (with or without glucocorticoids) increases the likelihood of remission among patients as compared to no treatment.^{4, 86-89} Investigators with the Europe-based PodoNet Registry reported almost 62% of the 1174 children with SRNS followed in a 2015 study received cyclosporine.⁹⁰ Complete or partial remission was achieved in at least half of these children. An RCT of 138 children and young adults with steroid-resistant FSGS compared cyclosporine to the combination of MMF and pulse dexamethasone.⁹¹ In this study, no difference in remission rate between the 2 groups was found. This study was designed to randomize 500 patients; however, the low recruitment may have significantly underpowered the ability to measure a moderate effect. A more recent network meta-analysis of 18 clinical trials comprising 790 children diagnosed with SRNS found that tacrolimus and cyclosporine were more efficacious in achieving remission status and were associated with fewer adverse effects compared with i.v. or oral cyclophosphamide, MMF, leflunomide, chlorambucil, azathioprine, and placebo or nontreatment.⁹²

No role for cyclophosphamide has been identified for children with SRNS, and data for rituximab suggest that it has a limited role or no role in SRNS.^{45, 78, 93, 94} Partial and complete remission occurs significantly more frequently in children with SRNS who receive cyclosporine or tacrolimus compared to those receiving intravenous cyclophosphamide.^{95, 96} A recent RCT in 60 children who had achieved at least a partial remission with 6 months of tacrolimus treatment revealed that tacrolimus prevented relapses more effectively than MMF (24 relapses over 30.3 person-years in patients receiving tacrolimus compared with 39 relapses during 21.2 person-years in those treated with MMF).⁹⁷

Differences in efficacy between cyclosporine and tacrolimus have not been found, yet the body of literature for cyclosporine is more extensive.⁹⁸ The risk of nephrotoxicity is similar for cyclosporine and tacrolimus, but gingival hyperplasia and hypertrichosis are more prevalent with cyclosporine, and glucose intolerance occurs more frequently with tacrolimus. The differing side-effect profiles may guide the choice between cyclosporine and tacrolimus (see *Considerations for*

implementation). The large trial of cyclosporine versus MMF plus dexamethasone suggested similar rates of adverse events between the 2 treatment arms.

Certainty of evidence

The overall certainty of the evidence from RCTs was low (Supplementary Tables S12–S14). There were only a few small trials that examined the treatment of patients with SRNS. These trials were frequently not of sufficient size to determine differences between therapies; they had various study limitations such as high attrition bias. There was moderate certainty of evidence for cyclosporine (vs. placebo or no treatment) and CNIs versus i.v. cyclophosphamide, but low certainty of evidence for the comparison of cyclosporine with MMF versus dexamethasone and of tacrolimus versus MMF. Hence, the overall certainty of the evidence was rated as low.

For the comparison of cyclosporine with placebo or no treatment, the certainty of the evidence regarding relapse was moderate because of study limitations (Supplementary Table S12^{87-89, 99}). The effects on adverse events, such as infection, were unclear, because of very low certainty in the evidence due to serious imprecision. Compared with the large effect on reducing relapse, low weight was given to the uncertain evidence regarding infection.

For the comparison of CNIs with i.v. cyclophosphamide, the certainty of the evidence regarding complete remission was moderate because of study limitations (Supplementary Table S13^{95, 96, 99}). The evidence for infections was of low certainty due to serious imprecision.

There is low certainty of evidence for the comparison of cyclosporine versus MMF with dexamethasone (Supplementary Table S14^{91, 98-100}). There was low certainty of evidence for complete remission at 6 and 12 months and for infections, due to imprecise estimates from a single study. There is very low certainty of evidence for other outcomes due to relatively few events and very large imprecision.

There is low certainty of evidence for the comparison of tacrolimus versus MMF (Supplementary Table S15^{97, 99}). There was moderate certainty of evidence for frequent relapses; the single study was downgraded for study limitations and imprecision (related to being a single study), but upgraded given the large, statistically significant effect size. There was low certainty of evidence for complete remission, annual GFR loss (evaluated at 12 months), and infections, due to study limitations and imprecision.

Values and preferences

The Work Group placed a relatively high value on data suggesting that CNI treatment is superior to no additional treatment and comparators such as cyclophosphamide and MMF for inducing remission in children with SRNS. The Work Group also placed a relatively high value on the high risk of progressive kidney failure associated with untreated SRNS,⁹⁰ and the morbidity associated with untreated NS (e.g., edema, infections, thromboembolic complications). The Work Group placed a relatively lower value on the morbidity associated with side effects of CNI treatment, including nephrotoxicity. In the judgment of the Work Group, all or nearly all well-informed patients with SRNS would accept the risk of CNI-associated morbidity in exchange for a lower risk of kidney failure due to SRNS.

Resource use and costs

The financial burden imposed by both drug costs and need for therapeutic drug monitoring may limit the accessibility of cyclosporine or tacrolimus, especially in low-resource areas. In high-resource areas, payer variability may equally challenge widespread availability. Physicians

and patients will need to weigh the cost burden and potential long-term adverse effects of treatment against the high risk of kidney failure and other morbidities associated with nontreatment.

Considerations for implementation

Genetic testing is recommended for all SRNS patients. A comprehensive gene panel analysis including all currently known SRNS genes by next-generation sequencing is usually the most cost-effective. Identification of causative podocyte-specific mutations may avoid unnecessary cumulative exposure to immunosuppressive therapies in some cases and help predict possible treatment-responsiveness in others. In Trautmann *et al.*, 11% of the 74 children with an identifiable podocyte mutation achieved at least a partial remission with intensified immunosuppression protocols that included various combinations of glucocorticoids, tacrolimus or cyclosporine, and MMF.⁹⁰ Although treatment response rates among patients with podocyte-specific mutations are low, mitigating nephrotic complications in children with at least a partial response may be valuable. A few mutations have been associated with treatment-responsiveness. For example, patients with WT1 and PLCE1 mutations have been found to have variable steroid-responsiveness and responsiveness to low-dose CNIs.¹⁰¹⁻¹⁰³ Proteinuric disease has been mitigated in patients with identified COQ2, COQ6, and ADCK4 mutations with ubiquinone supplementation.¹⁰⁴⁻¹⁰⁶ The hypertrichosis and gingival hypertrophy associated with cyclosporine may impede treatment adherence, especially in adolescents. Tacrolimus may need to be avoided in patients with obesity or who may be at risk for diabetes or already have signs of glucose intolerance such as acanthosis. Therapy with CNIs should be discontinued in patients who fail to achieve at least a partial response within 6 months (Figure 4).

Treatment	Dose and duration	Clinical tips
Calcineurin inhibitors	<ul style="list-style-type: none"> • Oral cyclosporine 5 mg/kg/d (starting dose) in two divided doses. Target 12-h trough level of 60–150 ng/ml [50–125 nmol/l] aiming for lowest levels to maintain remission and avoid toxicity or • Oral tacrolimus 0.1 mg/kg/d (starting dose) given in two divided doses for a minimum of 6 months. Target 12-h trough level of 5–10 ng/ml [6–12 nmol/l] aiming for lowest levels to maintain remission and avoid toxicity 	<p>CNIs should be continued for at least 12 months as 70% of those who achieve a complete response or partial response will relapse upon discontinuation. They should be discontinued in those without at least a partial response by 6 months.</p> <p>Tacrolimus may be preferred over cyclosporine in patients for whom the cosmetic side-effects of cyclosporine are unacceptable. Cyclosporine may be preferable in patients at risk for diabetic complications. There are no studies that investigate differences in long-term outcomes in SRNS on the basis of treatment duration. Median time to complete response or partial response is variable. Response can be seen as long as 6 months following treatment initiation. Trough levels could be measured to minimize nephrotoxicity</p>
Glucocorticoids	<ul style="list-style-type: none"> • i.v. Methylprednisolone bolus of 500 mg/m²/d for 3 days prior to starting CNI. Followed by taper: alternate-day oral prednisolone to be tapered gradually over 6 months • Low-dose prednisone (<0.25 mg/kg/d alternate day dosing) 	<p>Most clinical trials and observational studies have included low-dose glucocorticoids in combination with CNIs to induce remission. No studies compare the outcomes between children treated with CNIs alone or in combination with low-dose glucocorticoids</p>
Cyclophosphamide	<ul style="list-style-type: none"> • Not recommended 	<p>Two randomized control trials provide moderate-level data demonstrating no benefit using cyclophosphamide to treat children with SRNS. However, in countries with limited resources where CNIs are not available, this approach may be considered</p>
Mycophenolate mofetil	<ul style="list-style-type: none"> • Starting dose of 1200 mg/m²/d (given in two divided doses) for 1 year 	<p>This approach may be employed in children who have achieved stable remission on a CNI, to maintain remission without accumulating nephrotoxicity</p>
Rituximab	<ul style="list-style-type: none"> • 375 mg/m² i.v. 	<p>Giving two infusions (day 1 and day 8) at this dose may be preferable in the presence of nephrotic-range proteinuria to achieve complete B cell depletion. Hepatitis B panel must be checked prior to rituximab administration. Monitoring IgG levels both before and after rituximab therapy may allow for earlier identification of risk for developing significant infection and identify patients who may benefit from immunoglobulin replacement</p>

Figure 4 | Treatment of steroid-resistant nephrotic syndrome (SRNS) in children. CNI, calcineurin inhibitor; i.v., intravenous.

Rationale

CNIs appear to increase the likelihood of remission compared to no treatment in children with SRNS and have consistently shown greater efficacy than cyclophosphamide and MMF. The risk for kidney failure is significantly greater for patients who fail to achieve a partial or complete remission with any single or combination therapy. The data comparing the efficacy of cyclosporine versus tacrolimus in children with SRNS are sparse and of low certainty, and therefore, a decision to use one versus the other should be based on preferences of the provider, patient, and family, after consideration of the different side effect profiles. Although CNI treatment is associated with adverse effects, the Work Group judged that all or nearly all well-informed patients with SRNS would choose to be treated with a CNI because of the high risk of kidney failure associated with untreated SRNS.

4.5 Special situations

Practice Point 4.5.1: Figure 5^{107, 108} outlines the general principles in children with nephrotic syndrome.

Indication for kidney biopsy	<ul style="list-style-type: none">• Children presenting with nephrotic syndrome \geq 12 years of age• Steroid-resistant nephrotic syndrome or subsequent failure to respond to glucocorticoids in steroid-sensitive nephrotic syndrome (secondary steroid-sensitive nephrotic syndrome)• A high index of suspicion for a different underlying pathology (macroscopic hematuria, systemic symptoms of vasculitis, hypocomplementemia, etc.)• At onset, kidney failure not related to hypovolemia. Subsequently, decreasing kidney function in children receiving calcineurin inhibitors or prolonged exposure to calcineurin inhibitors (2 to 3 years)
Genetic testing	<ul style="list-style-type: none">• Steroid-resistant nephrotic syndrome• Congenital and infantile forms of nephrotic syndrome (<1 year of age)• Nephrotic syndrome associated with syndromic features• Family history of steroid-resistant nephrotic syndrome or focal segmental glomerulosclerosis
Vitamin D/calcium	In patients with steroid-sensitive nephrotic syndrome and normal vitamin D levels, supplementation is not required. However, in frequently relapsing nephrotic syndrome or steroid-dependent nephrotic syndrome in children or in the presence of a known vitamin D deficiency, a reduction in bone mineral content can be prevented by oral supplementation with oral calcium and vitamin D ^(1,2)
Gastroprotection	There is insufficient evidence of benefit to recommend prophylactic use of proton-pump inhibitors in children with nephrotic syndrome in the absence of risk factors for gastrotoxicity or of gastric symptoms

Figure 5 | General principles in children with nephrotic syndrome (NS). *If there is an evident extrarenal cause for proteinuria (i.e., lymphoma, monoclonal antibody treatment in ulcerative colitis, human immunodeficiency virus), a kidney biopsy may not be warranted. NS, nephrotic syndrome. ¹Gulati *et al.*¹⁰⁸, ²Gruppen *et al.*¹⁰⁷

Research recommendations

RCTs are needed to:

- Compare 8 versus 12 weeks of oral prednisone/prednisolone for initial therapy: explore further shortening of the initial glucocorticoid regimen and assess combination therapy with a glucocorticoid-sparing agent at disease onset
- Optimize subsequent treatment of SSNS after relapse in different forms of disease
- Optimize dosing regimen for glucocorticoid treatment at the start of an infection
- Define the optimal dosing and choice of glucocorticoid-sparing agents in FRNS and SDNS
- Evaluate the optimal duration of glucocorticoid treatment in SRNS, in particular when CNIs are initiated, and stratify patients based on identification of podocytopathy-related genetic mutations
- Determine the mode of action of glucocorticoids and other immunosuppressives in SSNS; determine the potential role of pharmacogenomics in treatment; identify biomarkers or genetic risk haplotypes to stratify disease subgroups
- Include quality-of-life measures as endpoints in clinical trials assessing treatment of children with both SSNS and SRNS

METHODS FOR GUIDELINE DEVELOPMENT

Aim

This is an update of the Nephrotic syndrome in children chapter (Chapter 4) of the KDIGO Clinical Practice Guideline for Glomerulonephritis published in 2021.¹⁰⁹ Based on recently published evidence in the field, it was decided that a guideline update was required.

The objective of this project was to update the evidence-based clinical practice guideline for the management of nephrotic syndrome in children. The guideline development methods are described below.

Overview of the process

This guideline adhered to international best practices for guideline development (Appendix B: Supplementary Tables S2 and S3).¹¹⁰ This guideline has been developed and reported in accordance with the AGREE II reporting checklist.¹¹¹ The processes undertaken for the development of the KDIGO 2024 Clinical Practice Guideline for the Management of Nephrotic Syndrome in Children are described below.

- Appointing Work Group members and the Evidence Review Team (ERT)
- Finalizing guideline development methodology
- Defining scope of the guideline
- Implementing literature search strategies to update the evidence base for the guideline
- Selecting studies according to predefined inclusion criteria
- Conducting data extraction and critical appraisal of the literature
- Updating evidence synthesis and meta-analysis to include newly identified studies
- Updating the certainty of the evidence for each outcome across studies
- Grading the strength of the recommendation, based on the certainty of the evidence and other considerations
- Convening a public review in April 2024
- Amending the guideline based on the external review feedback and updating the literature search
- Finalizing and publishing the guideline

Commissioning of Work Group and ERT

The KDIGO Co-Chairs appointed the Work Group Co-Chairs, who then assembled the Work Group, to include content experts in adult and pediatric nephrology, epidemiology, and public health. The Work Group was responsible for writing the recommendations and practice points and underlying rationale, as well as grading the strength of each recommendation.

For the 2024 update, the Brown University School of Public Health Center for Evidence Synthesis in Health was contracted to update the systematic evidence review and provide

expertise in guideline development methodology. The Brown ERT consisted of a senior physician-methodologist who led the ERT for the 2012 KDIGO Clinical Practice Guideline for Glomerulonephritis, an adult nephrologist, and a librarian–methodologist, all with expertise in evidence synthesis and guideline development, including for KDIGO guidelines. Cochrane Kidney and Transplant was contracted to conduct systematic evidence review and provide expertise in guideline development methodology for the 2021 Guideline.

Defining scope and topics and formulating key clinical questions

Due to resourcing and the probability of practice-changing studies, clinical questions on effectiveness and safety of interventions included in the guideline update were limited to randomized controlled trials (RCTs). Guideline topics and clinical questions focusing on nonrandomized studies were not included in the guideline update (Supplementary Table S1). The guideline Work Group, with assistance from the ERT, determined the overall scope of the guideline. A preliminary list of topics and key clinical questions was informed by the previous KDIGO guideline.¹⁰⁹ The majority of clinical questions for this guideline were based on RCTs to avoid bias by design. Clinical questions adhered to the population, intervention, comparator, outcomes, and study design (PICOD) format (a list of critical and important outcomes was compiled after voting by the Work Group [Table 1]). Clinical questions were mapped to existing Cochrane Kidney and Transplant systematic reviews. These systematic reviews were updated accordingly. For clinical questions that did not map to any Cochrane Kidney and Transplant systematic reviews, *de novo* systematic reviews were undertaken. The previous guideline was reviewed to ensure all identified studies were included in the evidence review.¹⁰⁹ Details of the PICOD questions and associated Cochrane Kidney and Transplant systematic reviews are provided in Table 2.^{15, 51, 99} All evidence reviews were conducted in accordance with the Cochrane Handbook,¹¹² and guideline development adhered to the standards of GRADE (Grading of Recommendations, Assessment, Development, and Evaluation).¹¹³

Table 1 | Hierarchy of outcomes

Hierarchy	Outcomes
Critical outcomes	<ul style="list-style-type: none"> • All-cause mortality • Kidney failure • $\geq 50\%$ loss of GFR • Infection • Glucocorticoid-related adverse events • Malignancy
Important outcomes	<ul style="list-style-type: none"> • Complete remission/relapse • Annual GFR loss (minimum 3 years follow-up)

GFR, glomerular filtration rate.

The critical and important outcomes were voted on by the Work Group using an adapted Delphi process (1–9 Likert scale). Critical outcomes were rated 7–9, and important outcomes were rated 4–6 on the 9-point scale.

Table 2 | Clinical questions and systematic review topics in PICOD format

PICOSD criteria	NS in children
Clinical question	In children (3–18 years of age) with SSNS, what glucocorticoid therapy regimens, compared with no treatment, placebo, or standard of care, improve efficacy outcomes and reduce adverse effects?
Population	Children (3–18 years of age) with SSNS
Intervention	Glucocorticoid therapy
Comparator	No treatment, placebo, or standard of care
Outcomes	Outcomes listed in Table 1
Study design	RCTs
Cochrane systematic review	Hahn D, <i>et al.</i> Corticosteroid therapy for nephrotic syndrome in children (Review). <i>Cochrane Database of Systematic Reviews</i> . 2020;8;CD001533 ²¹⁸
SoF tables	Supplementary Tables S4–S6 and S16–S35
Clinical question	In children (3–18 years of age) with SSNS, what non-glucocorticoid immunosuppressive regimens, compared to no treatment, placebo, or standard of care, improve efficacy outcomes and reduce adverse effects?
Population	Children (3–18 years of age) with SSNS
Intervention	Non-glucocorticoid immunosuppressive therapy
Comparator	No treatment, placebo, or standard of care
Outcomes	Outcomes listed in Table 1
Study design	RCTs
Cochrane systematic review	Larkins NG, <i>et al.</i> Non-corticosteroid immunosuppressive medications for steroid-sensitive nephrotic syndrome in children (Review). <i>Cochrane Database of Systematic Reviews</i> . 2020;4;CD002290 ²⁵³
SoF tables	Supplementary Tables S7–S11 and S36–S57
Clinical question	In children (3–18 years of age) with SRNS, what immunosuppressive therapy, compared to no treatment, placebo, or other immunosuppressive medication, improves efficacy outcomes and reduces adverse effects?
Population	Children (3–18 years of age) with SRNS
Intervention	Immunosuppressive therapy

Comparator	No treatment, placebo, or other immunosuppressive therapies (including glucocorticoids)
Outcomes	Outcomes listed in Table 1
Study design	RCTs
Cochrane systematic review	Liu ID, <i>et al.</i> Interventions for idiopathic steroid-resistant nephrotic syndrome in children (Review). <i>Cochrane Database of Systematic Reviews</i> . 2019:11; CD003594 ²⁹⁴
SoF tables	Supplementary Tables S12–S15 and S58–S69

NS, nephrotic syndrome; PICOD, Population, Intervention, Comparator, Outcomes, Study design; RCT, randomized controlled trial; SoF, summary of findings; SRNS, steroid-resistant nephrotic syndrome; SSNS, steroid-sensitive nephrotic syndrome.

DRAFT

Literature searches and article selection

For the KDIGO 2024 Clinical Practice Guideline for the Management of Nephrotic Syndrome in Children, updated literature searches were conducted in MEDLINE (via PubMed), Embase, and the Cochrane Central Register of Controlled Trials (Appendix A: Supplementary Table S1). The searches were restricted to records entered into the databases since January 1, 2020. This was done to provide a 6-month overlap with the prior searches. The searches were conducted on April 19, 2023. These search updates included terms for NS, minimal change disease (MCD), and immunoglobulin A (IgA) nephropathy (which all underwent concurrent updates).

The titles and abstracts resulting from the searches were screened by the 3 members of the ERT who independently assessed retrieved abstracts, and for accepted abstracts, the full text, to determine which studies satisfied the inclusion criteria. Disagreement about inclusion was resolved by discussion among the 3 members of the ERT.

For the KDIGO 2021 guideline, a total of 25,925 citations were screened. Of these, 479 RCTs and 102 observational studies were included in the evidence review for all diseases. For the current 2024 update, a total of 4094 citations were screened (for NS, MCD, and IgA nephropathy) (Figure 15). From these, we found 18 new eligible articles on NS in children, representing 16 new RCTs.

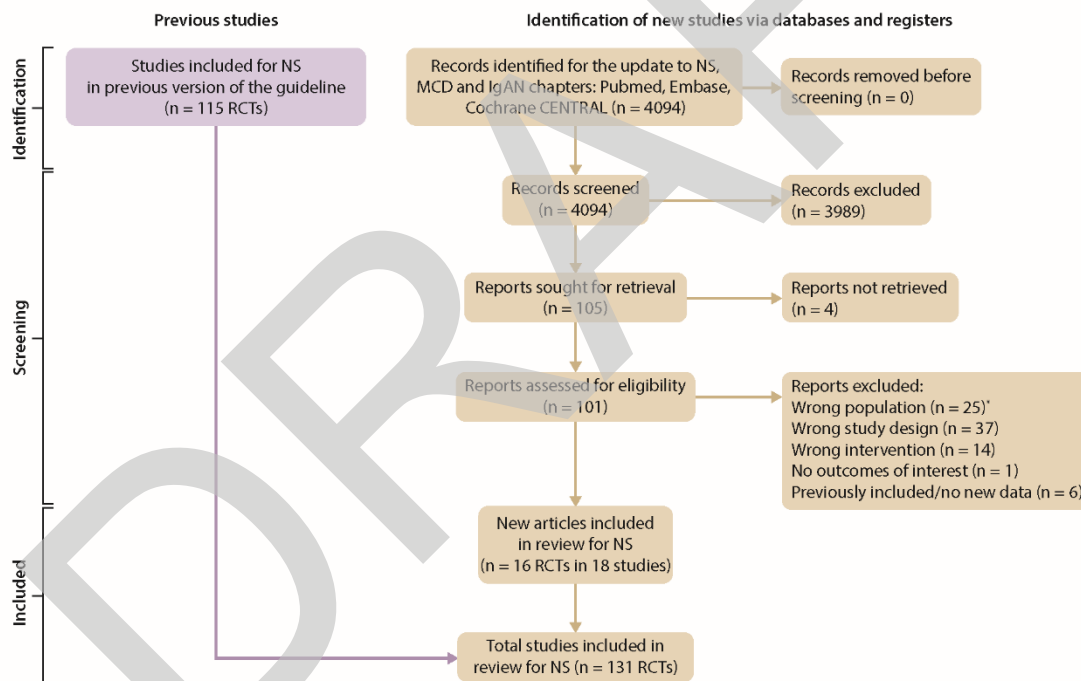


Figure 6 | Search yield and study flow diagram. IgAN, immunoglobulin A nephropathy; MCD, minimal change disease; NS, nephrotic syndrome; RCT, randomized controlled trial

Data extraction

For the KDIGO 2024 Clinical Practice Guideline for the Management of Nephrotic Syndrome in Children, data extraction was performed by 1 member of the Brown ERT and confirmed by the 2 other members of the ERT. The Brown ERT extracted data into the forms designed by the Cochrane ERT. The Cochrane ERT designed data extraction forms to capture data on study design, study participant characteristics, intervention and comparator characteristics, and critical

and important outcomes. Any differences in extraction between members of the ERT were resolved through discussion. A third reviewer was included if consensus could not be achieved.

Critical appraisal of studies

The update included only RCTs. For these studies, the Cochrane Risk of Bias tool was used to assess individual study limitations based on the following items¹¹⁴:

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study (detection bias)?
 - Participants and personnel (performance bias)
 - Outcome assessors (detection bias)
- Were incomplete outcome data adequately addressed (attrition bias)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at risk of bias?

All critical appraisal was conducted independently by 2 members of the ERT, with disagreements regarding the risk of bias adjudications resolved by consultation with a third review author.

Evidence synthesis and meta-analysis

Measures of treatment effect

Dichotomous outcome (all-cause mortality, kidney failure, $\geq 50\%$ loss of GFR, infection, malignancy, complete remission/relapse, and glucocorticoid-related adverse events) results were expressed as risk ratio (RR) with 95% confidence interval (CI). The continuous scale outcome annual GFR loss was evaluated as a mean difference (MD) with 95% CI.

Data synthesis

Data were pooled using the Mantel-Haenszel random-effects model for dichotomous outcomes and the inverse variance random-effects model for continuous outcomes. The random-effects model was chosen because it provides a conservative estimate of effect in the presence of known and unknown heterogeneity.¹¹²

Assessment of heterogeneity

Heterogeneity was assessed by visual inspection of forest plots of standardized mean effect sizes, and of RRs, and by the I² statistic, which measures the proportion of total variation in the estimates of treatment effect that was due to heterogeneity beyond chance.³⁶⁵ We used conventions of interpretation as defined by Higgins et al.¹¹⁵

Assessment of publication bias

To assess publication bias, we used funnel plots of the log odds ratio (effect vs. standard error of the effect size) when a sufficient number of studies were available (i.e., >10 studies).¹¹² Other reasons for the asymmetry of funnel plots were considered.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis was undertaken to explore whether there were clinical differences among the studies that may have systematically influenced the differences that were observed in the critical and important outcomes. However, subgroup analyses are hypothesis-forming rather than hypothesis-testing and should be interpreted with caution. The following subgroups were considered: baseline kidney function (GFR, proteinuria, presence of albuminuria, presence of macroscopic hematuria), histopathologic class of disease, primary versus secondary forms of disease, sex, and adult versus pediatric. The test of subgroup differences used the I^2 statistic and a P value of 0.10 (noting that this is a weak test).¹¹²

Sensitivity analysis

The following sensitivity analyses were considered:

- Repeating the analysis excluding unpublished studies
- Repeating the analysis, taking account of the risk of bias, as specified
- Repeating the analysis excluding any very long or large studies, to establish how much they dominate the results
- Repeating the analysis excluding studies using the following filters: language of publication, source of funding (industry vs. other), and country in which the study was conducted.

However, the available data were insufficient to determine the influence of these factors on the effect size of critical and important outcomes.

Grading the certainty of the evidence and the strength of a guideline recommendation

Grading the certainty of the evidence for each outcome across studies

The overall certainty of the evidence related to each critical and important outcome was assessed using the GRADE approach,^{113, 116} which assesses the certainty of the evidence for each outcome. For all outcomes, the data were from RCTs; thus, the initial grade for the certainty of the evidence is considered to be high. The certainty of the evidence is lowered in the event of study limitations; important inconsistencies in results across studies; indirectness of the results, including uncertainty about the population, intervention, and outcomes measured in trials and their applicability to the clinical question of interest; imprecision in the evidence review results; and concerns about publication bias. For imprecision, we considered the width of the 95% CI, such that for RR, if the 95% CI extended beyond both 0.5 and 2.0, the evidence was considered very imprecise. We also considered sparse data (only 1 study) to be imprecise.¹¹⁶ The final grade for the certainty of the evidence for an outcome could be high, moderate, low, or very low (Table 3). For further details on the GRADE approach for rating certainty of the evidence, see Table 4.

Table 3 | Classification for certainty of the evidence

Grade	Certainty of evidence	Meaning
A	High	We are confident that the true effect is close to 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 it will be far from the true effect.

Table 4 | GRADE system for grading certainty of evidence

Study design	Starting grade for the certainty of evidence	Step 2—Lower grade	Step 3—Raise grade for observational evidence
RCT	High	Study limitations: -1, serious -2, very serious	Strength of association +1, large effect size (e.g., <0.5 or >2) +2, very large effect size (e.g., <0.2 or >5)
	Moderate	Inconsistency: -1, serious -2, very serious	Evidence of a dose–response gradient
Observational	Low	Indirectness: -1, serious -2, very serious	All plausible confounding would reduce the demonstrated effect
	Very low	Imprecision: -1, serious -2, very serious -3, extremely serious Publication bias: -1, strongly suspected	

RCT, randomized controlled trial; GRADE, Grading of Recommendations Assessment, Development, and Evaluation.

Summary of findings (SoF) tables

The SoF tables were developed to include a description of the population, intervention, and comparator. In addition, the SoF tables included results from the data synthesis as relative and absolute effect estimates. The grading of the certainty of evidence for each critical and important

outcome is also provided in the SoF tables. For the 2024 update, the SoF tables were updated or created manually. The SoF tables are available in the Data Supplement: Appendix C and Appendix D.

Developing the recommendations

For the KDIGO 2024 Clinical Practice Guideline, the existing recommendations were reviewed and revised, as necessary, and new recommendations were drafted by the Work Group and Co-Chairs. Recommendations were revised in a multistep process by email and teleconferences. The Brown ERT participated in these discussions to ensure consistency with the evidence base and to provide additional feedback.

The final draft was sent for external public review, and reviewers provided open-ended responses. Based on the external stakeholder feedback, the draft was further revised by the Work Group. All Work Group members provided feedback on initial and final drafts of the guideline statements and text, and approved the final version of the guideline. The ERT also provided a descriptive summary of the certainty of evidence in support of the recommendations.

Grading the strength of the recommendations

The strength of a recommendation is graded as Level 1, “we recommend” or Level 2, “we suggest” (Table 5). The strength of a recommendation was determined by the balance of benefits and harms across all critical and important outcomes, the grading of the overall certainty of the evidence, patient values and preferences, resource use and costs, and considerations for implementation (Table 6).

Table 5 | KDIGO nomenclature and description for grading of recommendations

Grade	Implications		
	Patients	Clinicians	Policy
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 a 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.

Table 6 | Determinants of the strength of recommendation

Factors	Comment
Balance of benefits and harms	The larger the difference between the desirable and undesirable effects, the more likely a strong recommendation is provided. The narrower the gradient, the more likely a weak recommendation is warranted.
Certainty of evidence	The higher the certainty of evidence, the more likely a strong recommendation is warranted. However, there are exceptions for which low or very low certainty of the evidence will warrant a strong recommendation.
Values and preferences	The more variability in values and preferences, or the more uncertainty in values and preferences, the more likely a weak recommendation is warranted. Values and preferences were obtained from the literature, when possible, or were assessed by the judgment of the Work Group when robust evidence was not identified.
Resource use and costs	The higher the costs of an intervention—that is, the more resources consumed—the less likely a strong recommendation is warranted.

Balance of benefits and harms

The Work Group and ERT determined the anticipated net health benefit on the basis of expected benefits and harms across all critical and important outcomes from the underlying evidence review.

Overall certainty of evidence

The overall certainty of the evidence was based on the certainty of the evidence for all critical and important outcomes, taking into account the relative importance of each outcome to the population of interest. The overall certainty of the evidence was graded (A, B, C, or D—Table 3).

Patient values and preferences

No patients or caregivers participated in the Work Group. The Work Group, from their experience in managing patients with glomerular diseases and their understanding of the best available scientific literature, made judgments on the values and preferences of patients. Formal qualitative evidence synthesis on patient priorities and preferences was undertaken by the Cochrane ERT for the 2021 update, but there was limited evidence available to inform the formulation of guideline recommendations (Appendix D).

Resource use and costs

Healthcare and non-healthcare resources, including all inputs in the treatment management pathway,³⁷⁰ were considered in grading the strength of a recommendation. The following resources were considered: direct healthcare costs; non-healthcare resources, such as

transportation and social services; informal caregiver resources (e.g., time of family and caregivers); and changes in productivity. Economic evaluations, including cost-effectiveness analysis, were not conducted for any of the guideline topics.

Practice points

In addition to graded recommendations, KDIGO guidelines now include “practice points” to help clinicians better evaluate and implement the guidance from the expert Work Group. Practice points are consensus statements about a specific aspect of care, and they supplement recommendations for which a larger quantity of evidence was identified. They are issued when a clinical question was not supported by a systematic review, often to help readers implement the guidance from graded recommendation. Practice points represent the expert judgment of the guideline Work Group, but they also may be based on limited evidence. For example, practice points were provided on monitoring, frequency of testing, dosing adjustments for the severity of CKD, and use of therapies in specific subgroup populations. Practice points were sometimes formatted as a table, a figure, or an algorithm to make them easier to use in clinical practice.

Format for guideline recommendations

Each guideline recommendation provides an assessment of the strength of the recommendation (Level 1; or Level 2) and the certainty of the evidence (A, B, C, D). The recommendation statements are followed by Key information (Balance of benefits and harms, Certainty of the evidence, Values and preferences, Resource use and costs, Considerations for implementation), and Rationale. Each recommendation is linked to relevant SoF tables. An underlying rationale may support a practice point.

Limitations of the guideline development process

The evidence review prioritized RCTs as the primary source of evidence. The reviews were not exhaustive, as specialty or regional databases were not searched, and manual searching of journals was not performed for these reviews. In the development of these guidelines, no scoping exercise with patients, limited searches of the qualitative literature, nor formal qualitative evidence synthesis examining patient experiences and priorities were undertaken. As noted, although resource implications were considered in the formulation of recommendations, formal economic evaluations were not undertaken for all topics.

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