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KDIGO 2025 Clinical Practice Guideline for the Management of Nephrotic Syndrome in Children

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KDIGO 2025 CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF NEPHROTIC SYNDROME IN CHILDREN

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KDIGO 2025 Clinical Practice Guideline for the Management of Nephrotic Syndrome in Children

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Supplementary material is available online at www.kidney-international.org.

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NOMENCLATURE AND DESCRIPTION FOR RATING GUIDELINE RECOMMENDATIONS

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

	Implications		
Grade	**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.

Practice points are consensus-based statements representing the expert judgment of the Work Group and are not graded. They are issued when a clinical question did not have a systematic review performed, to help readers implement the guidance from graded recommendations (e.g., frequency of monitoring, provision of standard care [such as regular clinic visits], and referral to specialist care), or to issue "good practice statements" when the alternative is considered to be absurd. Users should consider the practice point as expert guidance and use it as they see fit to inform the care of patients. Although these statements are developed based on a different methodology, they should not be seen as less important or a downgrade from graded recommendations.

CURRENT CHRONIC KIDNEY DISEASE (CKD) NOMENCLATURE USED BY KDIGO

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

KDIGO: Prognosis of CKD by GFR and albuminuria categories

GFR categories (ml/min/1.73 m²) Description and range				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
	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	μmol/l
Creatinine clearance	ml/min	0.01667	ml/s
Cyclosporine	ng/ml	0.832	nmol/l
Mycophenolic acid	μg/ml	3.12	μmol/l
PCR	mg/g	0.113	mg/mmol

PCR, protein-to-creatinine ratio; SI, International System of Units.
Note: Conventional unit × conversion factor = SI unit.

RELATIONSHIP AMONG CATEGORIES FOR ALBUMINURIA AND PROTEINURIA

	Categories		
Measure	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 positive	Positive or greater

ACR, albumin-to-creatinine ratio; AER, albumin excretion rate; PCR, protein-to-creatinine ratio; PER, protein excretion rate.
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 ∼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 (*sex* refers to biological attributes; *gender* refers to sociocultural factors) at birth, race, and diet; therefore, the relationship among these categories is only approximate. The relationship between urine reagent strip results and other measures depends on the urine concentration.

Abbreviations and acronyms

ARB	angiotensin II receptor blocker
AUC	area under the curve
CI	confidence interval
CNI	calcineurin inhibitor
eGFR	estimated glomerular filtration rate
ERT	Evidence Review Team
FRNS	frequently relapsing nephrotic syndrome
GFR	glomerular filtration rate
GRADE	Grading of Recommendations Assessment, Development and Evaluation
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 conducted in April 2023 and updated in August 2024. 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.

Foreword

Kidney International (2025) **107** (Suppl 5S), S241–S289; https://doi.org/10.1016/j.kint.2024.11.007

The mission of Kidney Disease: Improving Global Outcomes (KDIGO) is to "improve the care and outcomes of people with kidney disease worldwide through promoting coordination, collaboration, and integration of initiatives to develop and implement clinical practice guidelines." Since the publication in 2008 of the very first KDIGO guideline, devoted to hepatitis C and chronic kidney disease, KDIGO has published guidelines on many distinct topics. The Clinical Practice Guideline for Glomerular Diseases was published in 2021. The guideline chapters covering lupus nephritis and anti-neutrophil cytoplasmic antibody–associated vasculitis were updated in 2024. The 2025 update of the Nephrotic Syndrome in Children and the forthcoming IgA Nephropathy (IgAN) and IgA-associated Vasculitis (IgAV) chapters reflects the rapid growth of evidence in glomerular diseases in general and in nephrotic syndrome and IgA nephropathy in particular. While an updated evidence review was conducted for the chapter dedicated to minimal change disease, no new evidence was identified; therefore, the 2021 chapter is still deemed current and valid.

Frequent updates to guidelines are important as new evidence is published. But frequent updates should not come at the expense of quality. KDIGO continuously strives to maintain the highest standards of excellence and to provide clinicians with the most relevant, evidence-based guidance, incorporating both recent advancements and widely accepted clinical standards through a systematic process. As such, the guideline updates provide guidance in the form of graded recommendations and practice points as put forth in the KDIGO Methods Manual. Graded recommendations are based on a systematic review of the evidence and are graded for the strength of the recommendation (Level 1 or Level 2) and certainty of the evidence (A, "high"; B, "moderate"; C, "low"; or D, "very low"). Practice points are ungraded, consensus-based statements representing the expert judgment of the Work Group. Although practice points are issued when there has not been a systematic review, most practice points aim to inform the implementation of graded recommendations; they are often provided in a graphical format. Readers should consider practice points to be expert guidance or "good practice statements" and use them as they see fit to inform the care of patients.

We are very grateful to Jürgen Floege, MD, and Brad H. Rovin, MD, FACP, FASN, for leading this important initiative, and we appreciate the continued dedication of the Work Group members, in particular the leads for this update to the Nephrotic Syndrome in Children guideline, Keisha L. Gibson, MD, MPH, and Marina Vivarelli, MD. Every Work Group member volunteered a considerable amount of time and expertise to the current guideline, with significant contributions from the independent Evidence Review Team from the Brown University School of Public Health led by Ethan M. Balk, MD, MPH, and Craig E. Gordon, MD, MS.

To ensure transparency and rigorous public review during guideline development, the draft of the 2025 update to the Nephrotic Syndrome in Children guideline was made publicly available for comment in April 2024, per KDIGO policy. We very much appreciate the feedback received from the scientific community, which further improved this update. All Work Group members have revised and approved the update for formal release.

In summary, we are pleased to present the KDIGO 2025 Clinical Practice Guideline for the Management of Nephrotic Syndrome in Children, reflecting the most recent and up-to-date global evidence for the care of children with steroid-sensitive and steroid-resistant nephrotic syndrome throughout the world. We are thrilled at the pace of scientific advancement and are exceptionally grateful to the Work Group Co-Chairs, Work Group members, the Methods Committee led by Reem A. Mustafa, MD, PhD, MPH, and other contributors to this very important KDIGO activity.

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Abstract

The Kidney Disease: Improving Global Outcomes (KDIGO) 2025 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 August 2024. As in 2021, this guideline provides guidance related to diagnosis, prognosis, treatment, and special situations. Based on the new evidence, the primary changes in this update are related to the 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; steroid-resistant; steroid-sensitive; systematic review

CITATION

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Summary of recommendation statements and practice points

1.1 Diagnosis

Practice Point 1.1.1: The clinical characteristics of and definitions for nephrotic syndrome in children are outlined in Figure 1.[1]

- **Nephrotic-range proteinuria:** Urinary protein-to-creatinine ratio (uPCR) ≥200 mg/mmol (2 g/g) in a spot urine, or proteinuria ≥1000 mg/m^2 per day in a 24-h urine sample corresponding to 3+ (300–1000 mg/dl) or 4+ (≥1000 mg/dl) by urine 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 or <100 mg/m^2 per day) on three or more consecutive days
- **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 a child who had previously achieved complete remission. In children, relapse is commonly assessed by urine dipstick and is thus defined as dipstick ≥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 within 4 weeks of prednisone or prednisolone at standard dose
- **Infrequently relapsing NS:** <2 relapses in the 6 months following remission of the initial episode or <3 relapses in any subsequent 12-month period
- **Frequently relapsing NS:** ≥2 relapses in the first 6 months following remission of the initial episode or ≥3 relapses per 12 months in any subsequent 12-month period
- **Steroid-dependent NS:** 2 consecutive relapses during recommended prednisone or prednisolone therapy for first presentation or relapse (either at full-dose or during tapering) or within 14 days of prednisone or prednisolone discontinuation
- **SRNS:** Lack of complete remission within 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‡
- **SSNS late responder:** A patient with new-onset NS achieving complete remission during the confirmation period (i.e., between 4 and 6 weeks of prednisone or prednisolone 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 within 4 weeks of therapy with daily prednisone or prednisolone at standard dose

Figure 1 | Clinical characteristics of and definitions for 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] ‡International Pediatric Nephrology Association 2020.[2,3] i.v., intravenous; RASi, renin-angiotensin system inhibitor; SRNS, steroid-resistant nephrotic syndrome; SSNS, steroid-sensitive nephrotic syndrome.

1.2 Prognosis

Practice Point 1.2.1: **The prognosis for children with nephrotic syndrome is best predicted by the patient's response to the initial treatment and frequency of relapse during the first year after treatment. Therefore, a kidney biopsy is not usually needed at initial presentation and is instead reserved for children with resistance to therapy or an atypical clinical course.**

1.3 Treatment

A schematic approach to treatment is outlined in Figure 2.

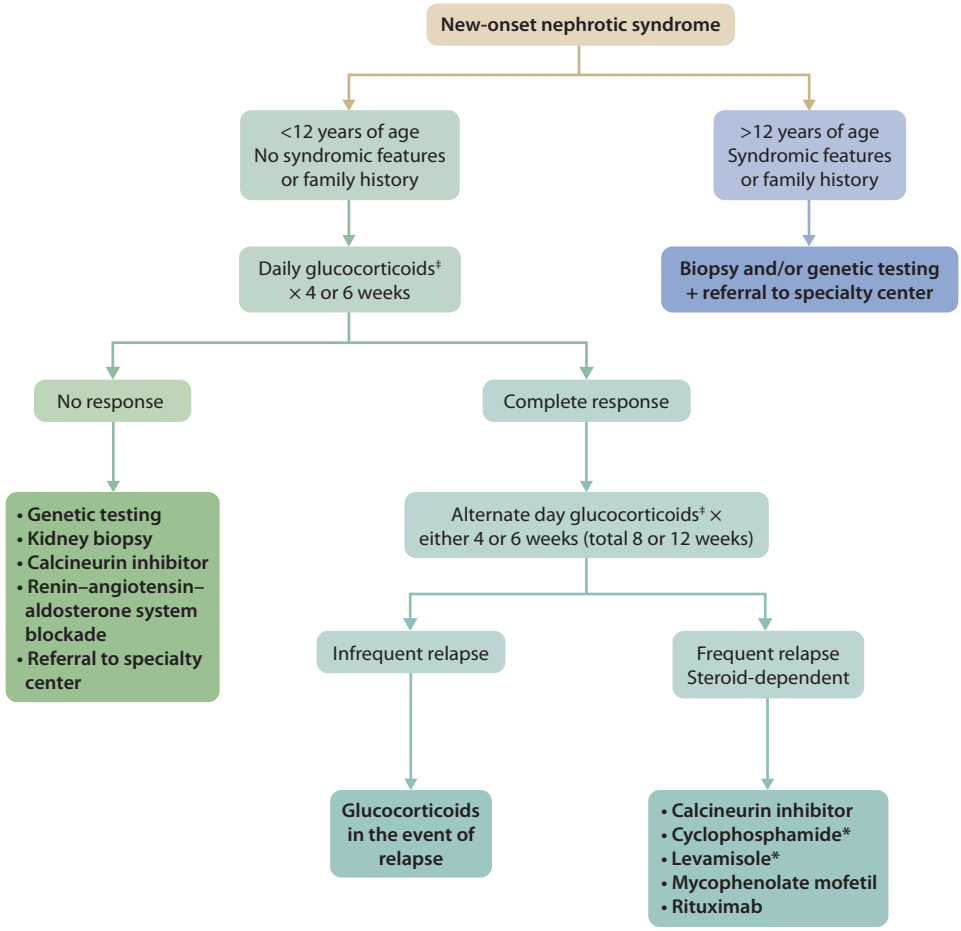

Figure 2 | Treatment algorithm for nephrotic syndrome (NS) from onset. Therapeutic approach to NS in children from onset. Refer to the clinical trial where appropriate. Syndromic features are defined as impaired statural growth; skeletal, neurodevelopmental, and ocular abnormalities; deafness; genital ambiguity; facial dysmorphisms; and so on. Glucocorticoid-sparing agents for children with frequent relapses or steroid-dependent nephrotic syndrome are listed here in an unbiased order. For the management of partial remission, please refer to the 2020 International Pediatric Nephrology Association guideline.[2,3] *May be more indicated for frequent relapses. In patients with frequent relapses without glucocorticoid complications, low-dose, alternate-day oral prednisone/prednisolone may also be considered before introducing a glucocorticoid-sparing agent (see Practice Point 1.3.3.4). ‡Glucocorticoids: oral prednisone/prednisolone.

1.3.1 Initial treatment of NS in children

Recommendation 1.3.1.1: 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 1.3.1.1: The standard dosing regimen for the initial treatment of nephrotic syndrome is daily oral prednisone/prednisolone 60 mg/m^2 per day or 2 mg/kg per day (maximum 60 mg/d) for 4 weeks followed by alternate-day prednisone/prednisolone 40 mg/m^2 or 1.5 mg/kg (maximum 40 mg) for another 4 weeks or prednisone/prednisolone 60 mg/m^2 per day or 2 mg/kg per day (maximum 60 mg/d) for 6 weeks followed by alternate-day prednisone/prednisolone 40 mg/m^2 or 1.5 mg/kg (maximum 40 mg) for another 6 weeks.

1.3.2 Prevention of relapses of NS in children

Recommendation 1.3.2.1: For children with frequently relapsing and steroid-dependent nephrotic syndrome, we recommend that daily glucocorticoids not be routinely given during episodes of upper respiratory tract and other infections to reduce the risk of relapse (*1C*).

Practice Point 1.3.2.1: A short course (i.e., 3 extra doses) 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.

1.3.3 Treatment and prevention of subsequent relapses of NS in children

Practice Point 1.3.3.1: The initial approach to relapse should include oral prednisone or prednisolone as a single daily dose of 60 mg/m^2 per day or 2 mg/kg per day (maximum 60 mg/d) until the child remits completely for ≥3 days.

Practice Point 1.3.3.2: After achieving complete remission in patients with steroid-sensitive nephrotic syndrome treated for relapse, reduce oral prednisone/prednisolone to 40 mg/m^2 or 1.5 mg/kg (maximum 40 mg) on alternate days for 4 weeks.

Practice Point 1.3.3.3: 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, while a shorter taper and/or more robust steroid-sparing approaches should be considered in children with signs of glucocorticoid toxicity.

Practice Point 1.3.3.4: 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 dose) can be prescribed to prevent relapse.

Recommendation 1.3.3.1: 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 to prevent relapses, rather than no treatment or continuation with glucocorticoid treatment alone (*1B*).

Practice Point 1.3.3.5: Patients should ideally be in remission with glucocorticoids prior to the initiation of glucocorticoid-sparing agents such as oral calcineurin inhibitors (CNIs), cyclophosphamide, levamisole, mycophenolate mofetil (MMF), and rituximab. Coadministration of glucocorticoids is recommended for ≥2 weeks following the initiation of glucocorticoid-sparing treatment.

Practice Point 1.3.3.6: Choosing the most appropriate glucocorticoid-sparing agent from among oral CNIs, cyclophosphamide, levamisole, MMF, and rituximab (listed here in an unbiased order) 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 glucocorticoid-sparing therapies in children with steroid-dependent nephrotic syndrome (Figure 3[75]).

Treatment	Dose and duration	Clinical tips
• **Calcineurin inhibitors**†		CNI should be continued for at least 12 months as most children will relapse upon discontinuation. Monitor CNI levels during therapy to limit toxicity
– **Cyclosporine**	4 to 5 mg/kg/d (starting dose) 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**	0.1 mg/kg/d (starting dose) given in two divided doses	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
• **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
• **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

Figure 3 | Glucocorticoid-sparing therapies in children with steroid-sensitive nephrotic syndrome, listed in an unbiased order. *Gellermann *et al.*[75] †The calcineurin inhibitor (CNI), while often used twice daily, may be dosed once a day, depending on individual formulations. In younger children (<6 years of age), the daily dose of cyclosporine can be divided into 3 doses (every 8 hours) to obtain steady hematic levels. Blood levels of CNIs do not provide information on intracellular levels. The target ranges for CNIs have been based on the transplant literature. The Work Group acknowledges that target ranges for nephrotic syndrome 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 achieve 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; FRNS, frequently relapsing nephrotic syndrome; i.v., intravenous; SDNS, steroid-dependent nephrotic syndrome.

1.4 Steroid-resistant nephrotic syndrome in children

1.4.1 Treatment

Recommendation 1.4.1.1: We recommend using cyclosporine or tacrolimus as initial second-line therapy for children with steroid-resistant nephrotic syndrome (*1C*).

1.5 Special situations

Practice Point 1.5.1: Figure 5[111,112] **outlines the general principles for children with nephrotic syndrome.**

Indication for kidney biopsy	• 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	• 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[(a,b)]
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 for children with nephrotic syndrome. [a]Gulati *et al.*[112] [b]Gruppen *et al.*[111]

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. Since the initial publication of this chapter, the International Pediatric Nephrology Association (IPNA) guideline on the management of children with steroid-sensitive nephrotic syndrome (SSNS) has been published.[2] The updated guideline has taken into account the results of this major international effort, which resulted from the research and debate of a large, qualified, and geographically diverse group of pediatric nephrology experts. Mainly, the definitions were revised and harmonized; the steroid-sparing agents were listed in an unbiased order; and recent high-quality studies that had not been finalized at the time of publication of the Kidney Disease: Improving Global Outcomes (KDIGO) 2021 guideline were taken into consideration.

1.1 Diagnosis

Practice Point 1.1.1: The clinical characteristics of and definitions for nephrotic syndrome in children are outlined in Figure 1.[1]

- **Nephrotic-range proteinuria:** Urinary protein-to-creatinine ratio (uPCR) ≥200 mg/mmol (2 g/g) in a spot urine, or proteinuria ≥1000 mg/m² per day in a 24-h urine sample corresponding to 3+ (300–1000 mg/dl) or 4+ (≥1000 mg/dl) by urine 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 or <100 mg/m² per day) on three or more consecutive days
- **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 a child who had previously achieved complete remission. In children, relapse is commonly assessed by urine dipstick and is thus defined as dipstick ≥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 within 4 weeks of prednisone or prednisolone at standard dose
- **Infrequently relapsing NS:** <2 relapses in the 6 months following remission of the initial episode or <3 relapses in any subsequent 12-month period
- **Frequently relapsing NS:** ≥2 relapses in the first 6 months following remission of the initial episode or ≥3 relapses per 12 months in any subsequent 12-month period
- **Steroid-dependent NS:** 2 consecutive relapses during recommended prednisone or prednisolone therapy for first presentation or relapse (either at full-dose or during tapering) or within 14 days of prednisone or prednisolone discontinuation
- **SRNS:** Lack of complete remission within 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‡
- **SSNS late responder:** A patient with new-onset NS achieving complete remission during the confirmation period (i.e., between 4 and 6 weeks of prednisone or prednisolone 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 within 4 weeks of therapy with daily prednisone or prednisolone at standard dose

Figure 1 | Clinical characteristics of and definitions for 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] ‡International Pediatric Nephrology Association 2020.[2,3] i.v., intravenous; RASi, renin-angiotensin system inhibitor; SRNS, steroid-resistant nephrotic syndrome; SSNS, steroid-sensitive nephrotic syndrome.

1.2 Prognosis

Practice Point 1.2.1: The prognosis for children with nephrotic syndrome is best predicted by the patient's response to the initial treatment and frequency of relapse during the first year after treatment. Therefore, a kidney biopsy is not usually needed at the initial presentation and is instead 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.[4] Before the availability of antibiotics and glucocorticoids, ~40% of children with NS died of infection, kidney failure, or occasionally thromboembolism.[5] 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.[5] Since the 1970s, following the 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 allow 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 SSNS, if biopsied, would most frequently be found to have minimal change disease, although mesangial proliferation with IgM and focal segmental glomerulosclerosis (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 into adulthood, maintaining the particular features of childhood-onset NS with rapid response to glucocorticoids in cases of relapse. Moreover, a small percentage (<5%) of children with SSNS 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. In patients with a family history of NS or those with syndromic features, biopsy can be considered, especially when genetic testing may not be accessible. Biopsy is subsequently indicated for all children with steroid resistance at 4–6 weeks from onset (Section 1.5; 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 or 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. Also important to minimize morbidity is the use of vitamin D/calcium, gastroprotection, and an appropriate vaccination strategy.

In children with steroid-resistant nephrotic syndrome (SRNS), genetic testing is highly encouraged, as it can guide appropriate management of kidney disease and, when present, extrarenal features. 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.

1.3 Treatment

A schematic approach to treatment is outlined in Figure 2.

1.3.1 Initial treatment of NS in children

Recommendation 1.3.1.1: 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 that prolonged (>12 weeks) glucocorticoid treatment increases the risk of adverse effects without further improving clinical outcomes in terms of the 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.[6–9] A randomized controlled trial (RCT) comparing single versus divided dosing showed that the 2 are equivalent in terms of time to remission and number of subsequent relapses.[10] 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 the initial episodes of NS, and the morbidity and mortality associated with these episodes, if untreated, are considerable.[5] With the introduction of glucocorticoid treatment, prognosis improved dramatically, and since the 1970s, standard protocols have been 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

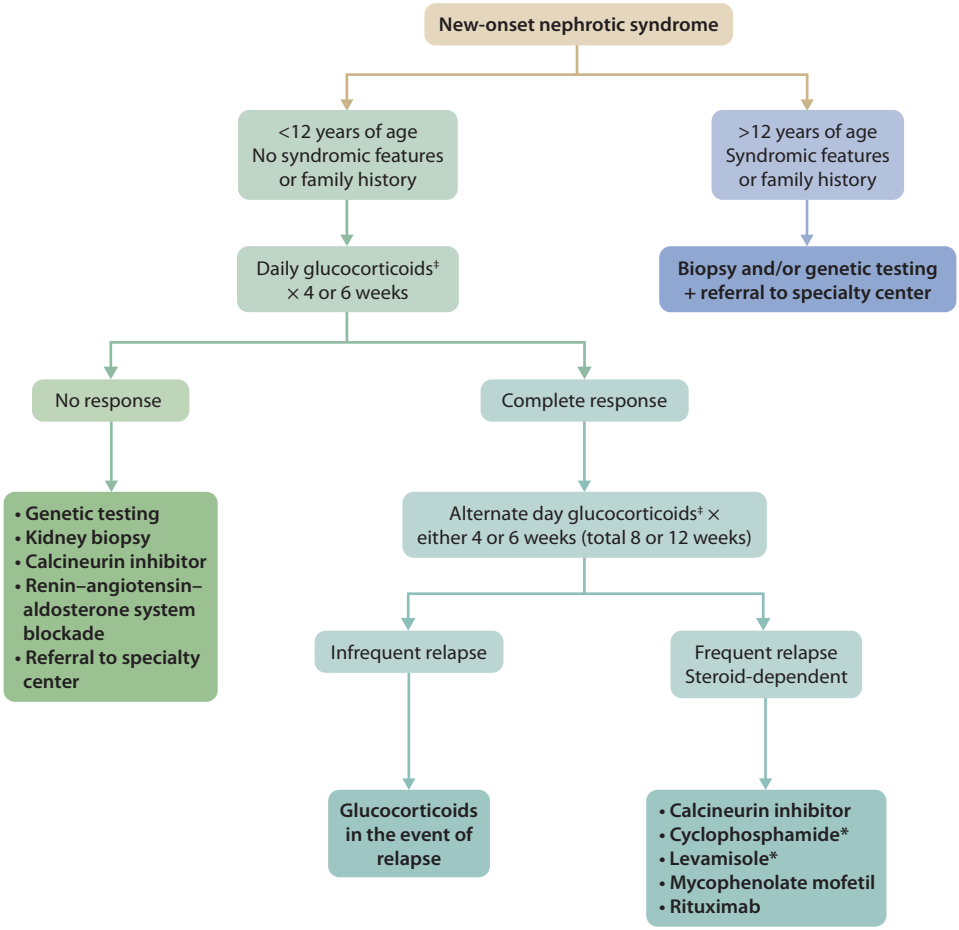

Figure 2 | Treatment algorithm for nephrotic syndrome (NS) from onset. Therapeutic approach to NS in children from onset. Refer to the clinical trial where appropriate. Syndromic features are defined as impaired statural growth; skeletal, neurodevelopmental, and ocular abnormalities; deafness; genital ambiguity; facial dysmorphisms; and so on. Glucocorticoid-sparing agents for children with frequent relapses or steroid-dependent nephrotic syndrome are listed here in an unbiased order. For the management of partial remission, please refer to the 2020 International Pediatric Nephrology Association guideline.[2,3] *May be more indicated for frequent relapses. In patients with frequent relapses without glucocorticoid complications, low-dose, alternate-day oral prednisone/prednisolone may also be considered before introducing a glucocorticoid-sparing agent (see Practice Point 1.3.3.4). ‡Glucocorticoids: oral prednisone/prednisolone.

minimizing the toxicity of treatment, which initially and primarily consists of oral glucocorticoids,[11,12] preserving steroid sensitivity, and prolonging remission.

Since the publication of the original KDIGO 2012 guideline, 4 RCTs have evaluated the optimal glucocorticoid dosing for treating the initial episode of SSNS in children: 2 studies comparing 12 weeks with 6 months, 1 study comparing 8 weeks with 6 months, and 1 study comparing 8 weeks with 4 months.[13–15,18] 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 the publication of the previous KDIGO 2021 guideline, a systematic review of all available studies has recently been published, summarized in Appendices C and D.[16]

In an attempt to explain the difference between these more recent findings and earlier evidence, a 2015 Cochrane systematic review examined whether there were systematic differences in the findings of studies at lower versus higher risk of bias.[17] 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 with 8 weeks of therapy and studies comparing 5–6 months with 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 with 4 months.[18]

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).[13] Similar findings are reported by Yoshikawa *et al.* (median follow-up 36–38 months),[15] Teeninga *et al.* (median follow-up 47 months),[14] and Webb *et al.* (follow-up 24 months).[18] 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 of ≥12-week duration with glucocorticoid therapy of 8-week duration (Supplementary Table S4[15,17–27]). For the important outcome of frequent relapses, the certainty of the evidence was low (very serious study limitations). The certainty of the evidence was graded 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 syndrome), the certainty of the evidence was downgraded to moderate because of serious study limitations. However, for other adverse events (infection and other glucocorticoid-related adverse events), the certainty of the evidence was downgraded to low or very low 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 grading.

Values and preferences. The potential benefits of glucocorticoid treatment, including reduction in morbidity due to 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 adverse events of glucocorticoids, would be important to many patients. Since preserving steroid sensitivity and maintaining remission are associated with good clinical outcomes, healthcare providers and patients must weigh the adverse events 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 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 of 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 in 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 (*sex* refers to biological attributes; *gender* refers to sociocultural factors) at birth or ethnicity. In children of a particularly young age at disease onset (i.e., 1–6 years of age) who may be at higher risk of progressing to a frequently relapsing or steroid-dependent form of NS,[21] prolonging treatment of the initial episode to 16–24 weeks may be beneficial in terms of preventing subsequent relapses with similar adverse events.[13] 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, a standard 8- to 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 the 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 with 8–12 weeks of treatment. Evidence is insufficient to choose between 8 and 12 weeks of treatment.

The recommendation is designated 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 with 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 1.3.1.1: The standard dosing regimen for the initial treatment of nephrotic syndrome is daily oral prednisone/prednisolone 60 mg/m^2 per day or 2 mg/kg per day (maximum 60 mg/d) for 4 weeks followed by alternate-day prednisone/prednisolone 40 mg/m^2 or 1.5 mg/kg (maximum 40 mg) for another 4 weeks or prednisone/prednisolone 60 mg/m^2 per day or 2 mg/kg per day (maximum 60 mg/d) for 6 weeks followed by alternate-day prednisone/prednisolone 40 mg/m^2 or 1.5 mg/kg (maximum 40 mg) for another 6 weeks.

1.3.2 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 (frequently relapsing nephrotic syndrome [FRNS]) or become steroid dependent (steroid-dependent relapsing nephrotic syndrome [SDNS]).[28,29] Many children relapse in response to an infectious trigger, but many others will have no identifiable trigger.[30] Prevention of relapse with a preemptive short course of low-dose, daily 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 syndrome.[31–34]

Recommendation 1.3.2.1: For children with frequently relapsing and steroid-dependent nephrotic syndrome, we recommend that daily glucocorticoids not be routinely given during episodes of upper respiratory tract and other infections to reduce the risk of relapse (*1C*).

Practice Point 1.3.2.1: A short course (i.e., 3 extra doses) 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 demonstrating that preemptive daily prednisolone may not reduce the risk of SSNS relapse during infection as well as on the lack of evidence of potential benefits of this approach. Given the lack of evidence of a benefit of preemptive glucocorticoid treatment, this recommendation places a 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 an 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.[35] 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 the publication of the previous 2021 guideline, the PREDNOS2 study was published.[36] 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 an upper respiratory tract infection. No appreciable difference in the incidence of upper respiratory tract infection–associated NS relapse was 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 to 0.10; $P = 0.7$).

Although higher doses of glucocorticoids during infection might theoretically cause harmful immunosuppression, available data do not report an increased duration or severity of infections in 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.[37] Therefore, as concluded in the recently published 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 preventing relapses.[2] However, such an approach may be considered in children already taking low-dose, alternate-day prednisone/prednisolone and having a history of upper respiratory tract infection–triggering relapse.[2]

Certainty of evidence. There is low certainty of evidence (single study with study limitations) regarding prednisolone versus placebo during viral infections (Supplementary Table S5[17,35,36,38–40]) for NS relapse with infection, but no evidence for other outcomes. There is also low certainty of evidence regarding infection-related relapse (each specific outcome with a single study with study limitations) in comparison of daily versus alternate-day prednisolone (Supplementary Table S6[35,38–40]). Overall, the certainty of the evidence is low.

The rates of infection-related relapses 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 caution 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 relapses of NS triggered by an upper respiratory tract infection. However, no differences in adverse events 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 relapse triggered by upper respiratory tract infection. This preemptive strategy may also be preferable in children with FRNS who are more prone to develop untoward adverse events from high-dose glucocorticoids—such as severe behavioral changes, sleep disturbance, or 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 as compared with standard care. 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 2021 guideline suggested treating children with FRNS who were receiving glucocorticoids on alternate days (or not receiving glucocorticoids) with daily oral prednisone/prednisolone for 5–7 days at the onset of an infection. Following that publication, several randomized, but small, clinical trials demonstrated up to a 30% reduction in relapses with this treatment approach. These findings were not confirmed in the PREDNOS2 RCT, a large and rigorous study that showed no clear clinical benefit of this approach. For this reason, we have modified our Recommendation 1.3.2.1. However, given the minimal risk with this approach, in select cases daily prednisone or prednisolone for 5–7 days at the onset of an infection may still be reasonable (i.e., in children already on alternate-day prednisone/prednisolone who regularly relapse in case of an upper respiratory tract infection and/or in children with significant prednisone-/prednisolone-related morbidity).

1.3.3 Treatment and prevention of subsequent relapses of NS in children

Practice Point 1.3.3.1: The initial approach to relapse should include oral prednisone or prednisolone as a single daily dose of 60 mg/m^2 per day or 2 mg/kg per day (maximum 60 mg/d) until the child remits completely for ≥3 days.

Practice Point 1.3.3.2: After achieving complete remission in patients with steroid-sensitive nephrotic syndrome treated for relapse, reduce oral prednisone/prednisolone to 40 mg/m^2 or 1.5 mg/kg (maximum 40 mg) on alternate days for 4 weeks.

Recently, 2 RCTs addressing the treatment of relapses, more specifically the dose and duration of alternate-day oral prednisone following the induction of remission, have been published. One study, the Prospective Randomized study to Optimize Prednisone therapy for relapses of Idiopathic NEphrotic syndrome in children (PROPINE) trial, compared using 40 mg/m^2 on alternate days for 5 weeks with using the same cumulative prednisone dose spread out over 10 weeks with a tapering schedule (Supplementary Table S12).[41] 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/m^2 on alternate days for 4 weeks with 40 mg/m^2 on alternate days for 2 weeks in children with infrequently relapsing NS (Supplementary Table S13).[42] The rate of relapse was similar in the 2 groups of children. However, the study failed to show that the short regimen was noninferior. Taken altogether, these results support the use of oral prednisone/prednisolone at 40 mg/m^2 on alternate days for ∼4 weeks following the 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 1.3.3.3: 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, while a shorter taper and/or more robust steroid-sparing approaches should be considered in children with signs of glucocorticoid toxicity.

Practice Point 1.3.3.4: 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 dose) can be prescribed to prevent relapse.

Recommendation 1.3.3.1: 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 to prevent relapses, 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 a substantial risk of adverse events associated with long-term glucocorticoids and efficacy of glucocorticoid-sparing agents in preventing relapse as 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 with 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 with NS who are not treated or fail to respond to any treatments.[43]

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 adverse events, including severe growth failure, obesity, and low bone density, which were attributed to glucocorticoid exposure for frequent relapses following discontinuation of cyclosporine at 2 years.[32] Additional long-term follow-up of patients into adulthood with childhood-onset NS have demonstrated a high prevalence of hypertension, osteoporosis, and cataracts attributable to chronic glucocorticoid exposure.[33,44,45]

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 and tacrolimus).

Studies have consistently shown a benefit of second-line therapies in reducing relapses for children with FRNS or SDNS as compared with either glucocorticoids alone or placebo. In a recent meta-analysis of 26 trials comparing the available immunosuppressive medications with placebo/no treatment, chlorambucil, cyclophosphamide, levamisole, and rituximab were associated with a significantly reduced relapse rate as compared with placebo or no treatment at 6- and 12-month follow-up.[46]

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). However, 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 adverse events 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 the evidence focused on glucocorticoid-sparing agents individually, but the overall certainty of the evidence was graded as moderate (Supplementary Tables S7–S11). RCTs comparing alkylating agents, levamisole, or rituximab with placebo or glucocorticoids had moderate-certainty evidence for important outcomes. However, the certainty of evidence from 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 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 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 and serious imprecision; Supplementary Table S7[47–54]). 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 the evidence for the use of levamisole compared to glucocorticoids or placebo was moderate for the outcome of relapse (Supplementary Table S8[10,53–61]); although 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[53,62]). 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 plus prednisone with prednisone alone in patients with their first episode of SSNS (Supplementary Table S10[53,63,64]). The certainty of evidence was low 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 a serious risk of bias, but the certainty of evidence was low for relapse at 12 months due to additional imprecision (Supplementary Table S11[6,53,65–71]). 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, make the option of no treatment 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.[72,73]

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, factors that should be considered in treatment decision-making are age, ability to tolerate frequent phlebotomy for safety labs, and patient preferences for daily oral therapy versus infrequent hospitalization for intravenous (i.v.) infusions.

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 on the treatment of SSNS in children, and the Indian Pediatric Nephrology Group all recommend consideration of glucocorticoid-sparing therapies in children who are steroid-dependent, especially those who have exhibited glucocorticoid toxicity. Choosing the most appropriate glucocorticoid-sparing agent, on the contrary, remains highly controversial. In the absence of high-quality RCTs comparing single agents, the choice depends on resources, patient preference, and the managing physician's habits. For this reason, as chosen in the 2022 IPNA guideline, we have listed the agents in an unbiased order. A recent multicenter study reported on the prevalence and clinical association with active disease of anti-nephrin autoantibodies in 357 adults and 182 children with primary NS, further supporting the rationale of immunosuppressive treatment in this patient population.[74]

Practice Point 1.3.3.5: Patients should ideally be in remission with glucocorticoids prior to the initiation of glucocorticoid-sparing agents such as oral calcineurin inhibitors (CNIs), cyclophosphamide, levamisole, mycophenolate mofetil (MMF), and rituximab. Coadministration of glucocorticoids is recommended for ≥2 weeks following the 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 1.3.3.6: Choosing the most appropriate glucocorticoid-sparing agent from among oral CNIs, cyclophosphamide, levamisole, MMF, and rituximab (listed here in an unbiased order) 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 glucocorticoid-sparing therapies in children with steroid-dependent nephrotic syndrome (Figure 3[75]).

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 a CNI after 6 or 12 months of treatment. However, tubulointerstitial lesions have been reported in 30%–40% of children treated with cyclosporine for >12 months and in up to 80% of those treated for >4 years. Based on these data, the optimal duration of cyclosporine treatment is not clear, and data are even sparser for tacrolimus.

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 cost savings of almost 38%, with no reduction in efficacy.

Cyclophosphamide. Patients with frequent relapses might have a superior response to cyclophosphamide and levamisole compared with patients with steroid dependency.[76] In 143 children treated with oral cyclophosphamide for FRNS, SDNS, or with a history of glucocorticoid toxicity, sustained remission was more frequent in children with FRNS than in those with SDNS (hazard ratio: 1.72; 95% CI: 0.99–2.98; $P = 0.05$).[77] Nonetheless, in some patients with SDNS, there may be a role for cyclophosphamide, 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 of 57% at 1 year was achieved.[78] Children with FRNS who are older than 7.5 years are more likely to

Treatment	Dose and duration	Clinical tips
• **Calcineurin inhibitors**†		CNI should be continued for at least 12 months as most children will relapse upon discontinuation. Monitor CNI levels during therapy to limit toxicity
– **Cyclosporine**	4 to 5 mg/kg/d (starting dose) 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**	0.1 mg/kg/d (starting dose) given in two divided doses	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
• **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
• **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

Figure 3 | Glucocorticoid-sparing therapies in children with steroid-sensitive nephrotic syndrome, listed in an unbiased order. *Gellermann *et al.*[75] †The calcineurin inhibitor (CNI), while often used twice daily, may be dosed once a day, depending on individual formulations. In younger children (<6 years of age), the daily dose of cyclosporine can be divided into 3 doses (every 8 hours) to obtain steady hematic levels. Blood levels of CNIs do not provide information on intracellular levels. The target ranges for CNIs have been based on the transplant literature. The Work Group acknowledges that target ranges for nephrotic syndrome 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 achieve 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; FRNS, frequently relapsing nephrotic syndrome; i.v., intravenous; SDNS, steroid-dependent nephrotic syndrome.

experience long-term remission when treated with cyclophosphamide than children younger than 4 years.[78] 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 shorter-duration remissions following treatment with oral cyclophosphamide.[79]

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, including leukopenia and gastrointestinal disturbance, are uncommon and mild. Data comparing cyclophosphamide and levamisole are quite limited and do not determine their relative relapse rates after treatment discontinuation or frequencies of infection events.[80] In one study, compared with placebo, levamisole delayed the time to relapse post termination of glucocorticoids; 26% of the patients treated with levamisole were relapse-free for at least 1 year compared with only 6% of patients who received placebo.[59] Adverse events in this trial were few and were mostly limited to neutropenia, which was easily reversed with discontinuation of therapy. MMF was not superior to levamisole in a trial of 139 children with FRNS and SDNS with regard to sustained remission off glucocorticoids, although MMF showed a trend toward superiority in children with more severe cases (SDNS).[62]

MMF. In children with FRNS or SDNS treated with MMF, variable outcomes for maintaining remission off glucocorticoids have been reported, and these are mostly limited to retrospective observational data. A recent crossover RCT of 60 children with FRNS directly compared the efficacy of MMF and cyclosporine. Relapses occurred in 36% of patients receiving MMF therapy versus in only 15% receiving cyclosporine therapy ($P = 0.06$). The time without relapse was significantly longer with cyclosporine than with MMF during the first year ($P < 0.05$) but not 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.[75]

A *post hoc* analysis of the study by Gellermann *et al.* comparing MMF with cyclosporine provided findings that targeting higher area under the curve (AUC) levels may reduce relapses on therapy.[75] Children with low mycophenolic acid 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 with MMF compared with treatment with CNIs.

Rituximab. Several studies, including RCTs, have suggested a favorable response to rituximab in patients with SDNS or FRNS.[66,68,70,81] In an RCT by Iijima *et al.* of 48 children with FRNS or SDNS, a significant difference (267 relapse-free days vs. 101 relapse-free days; hazard ratio: 0.27; 95% CI: 0.14–0.53; $P < 0.0001$) was noted for patients who received rituximab versus those who received placebo.[82] In a randomized noninferiority trial of 30 children with SDNS, all but 1 child in the placebo arm relapsed within 6 months as compared with a median time to relapse of 18 months in children treated with rituximab (95% CI: 9–32 months).[70] 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: 2–4) to 0.5 (interquartile range: 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.[81]

In children with FRNS, the reported rates of adverse events such as infection have been lower with rituximab than with placebo. In the trial by Ravani *et al.*, nausea and skin rash during infusion were common with rituximab.[70] No such events occurred in the NEMO trial, and in fact, improvement in growth velocity and reduction in body mass index were noted in participants after 1 year. There are no studies directly comparing adverse event rates in children treated with rituximab to those treated with cyclophosphamide. One retrospective study in 200 adult patients with membranous nephropathy reported that during a median follow-up of 40 months, patients who received rituximab had significantly fewer adverse events than did those who received cyclophosphamide (63 vs. 173; $P < 0.001$) including both serious (11 vs. 46; $P < 0.001$) and nonserious (52 vs. 127; $P < 0.001$) adverse events.[83] It is important to note that there is great uncertainty of the long-term safety profile of rituximab in children, in particular in children younger than 7 years and those receiving multiple courses.

Concerning other 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 or CNI-dependent NS (Supplementary Table S14[84]).

Moreover, a recent RCT conducted in Japan showed that in children with complicated forms of FRNS or SDNS, the use of MMF after rituximab can decrease the risk of treatment failure by 80% (Supplementary Table S15[85]).

1.4 Steroid-resistant nephrotic syndrome in children

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

combination with 3 daily i.v. methylprednisolone pulses can be considered. Those who do not achieve a complete response at 6 weeks will be defined as having SRNS.

After 6 weeks, as soon as a diagnosis of SRNS is established, 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 eGFR $<$ 30 ml/min per 1.73 m^2 or used as an alternative to a CNI after remission has been maintained for $>$1 year.[3] 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, multidrug 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. In a phase 2, randomized, double-blind trial comparing the dual endothelin and angiotensin II receptor blockers sparsentan and irbesartan, proteinuria was decreased by 45% with sparsentan compared with 19% with irbesartan, with no differences in serious adverse events between the groups.[86] The phase 3 multicenter trial found partial remission in 44.3% versus 23.2% in those treated with sparsentan versus irbesartan, respectively, but this finding did not translate into a statistically significant difference in the primary outcome of eGFR slope between the study arms (total slope 0.3 ml/min per 1.73 m^2 per year; chronic slope 0.9 ml/min per 1.73 m^2 per year; $P > 0.05$).[87] Postapproval studies for low-density lipoprotein apheresis are ongoing and may 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. In a retrospective study of 246 children with CNI-resistant SRNS across 19 countries, 36% of patients achieved at least a partial response after $>$6 months of treatment with a CNI followed by treatment with rituximab, and 52% achieved at least a partial response after $<$6 months of treatment with a CNI followed by rituximab.[88] Recent studies highlighting the presence of anti-slit diaphragm antibodies on biopsy and anti-nephrin autoantibodies in circulation may lead to the development of future biomarkers to identify patients who may be responsive to immunosuppressive therapies.[74,89]

For more detailed recommendations on these aspects of care and on the management of complications of SRNS in children, refer to the recent IPNA guideline.[3]

1.4.1 Treatment

Recommendation 1.4.1.1: We recommend using cyclosporine or tacrolimus as initial second-line therapy for children with steroid-resistant nephrotic syndrome (*1C*).

This recommendation places a relatively higher value on data suggesting that CNIs are more likely to induce remission than cyclophosphamide, MMF, or rituximab in the 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 than in FRNS or SDNS. Several RCTs suggested that cyclosporine (with or without glucocorticoids) increases the likelihood of remission in patients as compared with no treatment.[5,90–93] Investigators of the Europe-based PodoNet Registry reported receipt of cyclosporine for almost 62% of 1174 children with SRNS followed in a 2015 study.[94] Complete or partial remission was achieved in at least half of these children. An RCT of 138 children and young adults with steroid-resistant focal segmental glomerulosclerosis compared cyclosporine with the combination of MMF and pulse dexamethasone.[95] In this study, there was no difference in remission rate between the 2 groups. This study was designed to randomize 500 patients; the subsequent 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 and were associated with fewer adverse effects compared with i.v. or oral cyclophosphamide, MMF, leflunomide, chlorambucil, azathioprine, and placebo or no treatment.[96]

No role for cyclophosphamide has been identified in children with SRNS, and data on rituximab suggest that it has a limited role or no role in SRNS.[47,81,97,98] Partial and complete remission occurs significantly more frequently in children with SRNS who receive cyclosporine or tacrolimus than in those receiving i.v. cyclophosphamide.[99,100] A recent RCT of 60 children who had achieved at least partial remission with 6 months of tacrolimus treatment revealed that tacrolimus prevented relapses more effectively than MMF (24 relapses during 30.3 person-years in patients receiving tacrolimus versus 39 relapses during 21.2 person-years in those treated with MMF).[101]

Differences in efficacy between cyclosporine and tacrolimus have not been found, yet the body of literature for cyclosporine is more extensive.[102] 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*). A 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 graded as low (Supplementary Tables S16–S19). 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 comparisons of cyclosporine with MMF plus dexamethasone and of tacrolimus with MMF. Hence, the overall certainty of the evidence was graded 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 S16[91–93,103]). The effects on adverse events, such as infection, were unclear, because of very low certainty of 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 S17[99,100,103]). The evidence for infections was of low certainty due to serious imprecision.

There is low certainty of evidence for the comparison of cyclosporine with MMF plus dexamethasone (Supplementary Table S18[95,102–104]). 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 with MMF (Supplementary Table S19[101,103]). There was moderate certainty of evidence for frequent relapses; the certainty of evidence for 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[94] and the morbidity associated with untreated NS (e.g., edema, infections, and thromboembolic complications). The Work Group placed a relatively lower value on the morbidity associated with adverse events 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 limit accessibility. 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 no treatment.

Considerations for implementation. Genetic testing is recommended for all patients with SRNS. A comprehensive gene panel analysis including all currently known SRNS genes by next-generation sequencing is usually the most cost-effective means. The 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 the study by Trautmann *et al.*, 11% of the 74 children with an identifiable podocyte mutation achieved at least partial remission with intensified immunosuppression protocols that included various combinations of glucocorticoids, tacrolimus or cyclosporine, and MMF.[94] 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.[105–107] Proteinuric disease has been mitigated in patients with identified *COQ2*, *COQ6*, and *ADCK4* mutations with ubiquinone supplementation.[108–110] 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 those who may be at risk of 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).

Rationale

CNIs appear to increase the likelihood of remission compared with no treatment in children with SRNS and have consistently shown greater efficacy than cyclophosphamide and MMF. The risk of kidney failure is significantly higher for patients who fail to achieve partial or complete remission with

Treatment	Dose and duration	Clinical tips
Calcineurin inhibitors	• 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	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. 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
Glucocorticoids	• i.v. Methylprednisolone bolus of 500 mg/m^2/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)	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
Cyclophosphamide	• Not recommended	Two randomized controlled 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
Mycophenolate mofetil	• Starting dose of 1200 mg/m^2/d (given in two divided doses) for 1 year	This approach may be employed in children who have achieved stable remission on a CNI, to maintain remission without accumulating nephrotoxicity
Rituximab	• 375 mg/m^2 i.v.	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

Figure 4 | Treatment of steroid-resistant nephrotic syndrome in children. CNI, calcineurin inhibitor.

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.

1.5 Special situations

Practice Point 1.5.1: Figure 5[111,112] outlines the general principles for children with nephrotic syndrome.

Indication for kidney biopsy	• 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	• 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[a,b]
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 for children with nephrotic syndrome. [a]Gulati *et al.*[112] [b]Gruppen *et al.*[111]

Research recommendations

RCTs are needed to:

- Compare 8 versus 12 weeks of oral prednisone/prednisolone for initial therapy and 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 onset 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 the identification of podocytopathy-related genetic mutations
- Determine the mode of action of glucocorticoids and other immunosuppressive medications in SSNS; determine the potential role of pharmacogenomics in treatment; and identify biomarkers or genetic risk haplotypes to stratify disease subgroups
- Determine the long-term safety of therapies that deplete B cells
- Include quality-of-life measures as endpoints in clinical trials assessing the treatment of children with both SSNS and SRNS
- Evaluate anti-nephrin and anti-slit diaphragm antibodies as biomarkers as well as predictors of response to treatment and outcome of NS in children

Methods for guideline development

Aim

This guideline represents an update of Chapter 4: Nephrotic Syndrome in Children of the KDIGO Clinical Practice Guideline for the Management of Glomerular Diseases published in 2021.[113] Based on the 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 NS 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).[114] This guideline has been developed and reported in accordance with the AGREE II reporting checklist.[115] The processes undertaken for the development of the KDIGO 2025 Clinical Practice Guideline for the Management of Nephrotic Syndrome in Children are described as follows:

- 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 the 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 supporting text, as well as grading the strength of each recommendation.

For the 2025 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 the scope and topics and formulating key clinical questions. Due to resourcing and the probability of practice-changing studies, clinical questions on the effectiveness and safety of interventions included in the guideline update were limited to RCTs. Guideline topics and clinical questions focusing on nonrandomized studies were not included in the guideline update. 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.[113] 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 that all identified studies were included in the evidence review.[113] Details of the PICOD questions and associated Cochrane Kidney and Transplant systematic reviews are provided in Table 2.[17,53,103] All evidence reviews were conducted in accordance with the *Cochrane Handbook*,[116] and guideline development adhered to the standards of GRADE (Grading of Recommendations Assessment, Development and Evaluation).[117]

Table 1 | Hierarchy of outcomes

Hierarchy	Outcomes
Critical outcomes	• All-cause mortality
	• Kidney failure
	• ≥50% loss of GFR
	• Infection
	• Glucocorticoid-related adverse events
	• Malignancy
Important outcomes	• Complete remission/relapse
	• Annual GFR loss (minimum 3-year 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

PICOD 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, including frequently relapsing NS and steroid-dependent NS
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, Samuel SM, Willis NS, et al. Corticosteroid therapy for nephrotic syndrome in children [review]. *Cochrane Database Syst Rev.* 2020;2020:CD001533.16
SoF tables	Supplementary Tables S4–S6, S12, S13, and S20–S38
Clinical question	**In children (3–18 years of age) with SSNS, what non–glucocorticoid immunosuppressive 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 including frequently relapsing NS and steroid-dependent NS
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, Liu ID, Willis NS, et al. Non-corticosteroid immunosuppressive medications for steroid-sensitive nephrotic syndrome in children [review]. *Cochrane Database Syst Rev.* 2020;4:CD002290.53
SoF tables	Supplementary Tables S7–S11, S14, S15, and S39–S61
Clinical question	**In children (3–18 years of age) with SRNS, what immunosuppressive therapy, compared with 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, Willis NS, Craig JC, et al. Interventions for idiopathic steroid-resistant nephrotic syndrome in children [review]. *Cochrane Database Syst Rev.* 2019;2019:CD003594.103
SoF tables	Supplementary Tables S16–S19 and S62–S73

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

Literature searches and article selection. For the KDIGO 2025 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 and updated on August 22, 2024. These search updates included terms for NS, minimal change disease, and 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 those, 479 RCTs and 102 observational studies were included in the evidence review for all diseases. For the current 2025 update, a total of 4548 citations were screened (for NS, minimal change disease, and IgA nephropathy) (Figure 6). From those, we found 23 new eligible articles on NS in children, representing 21 new RCTs.

Data extraction. For the KDIGO 2025 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 items[118]:

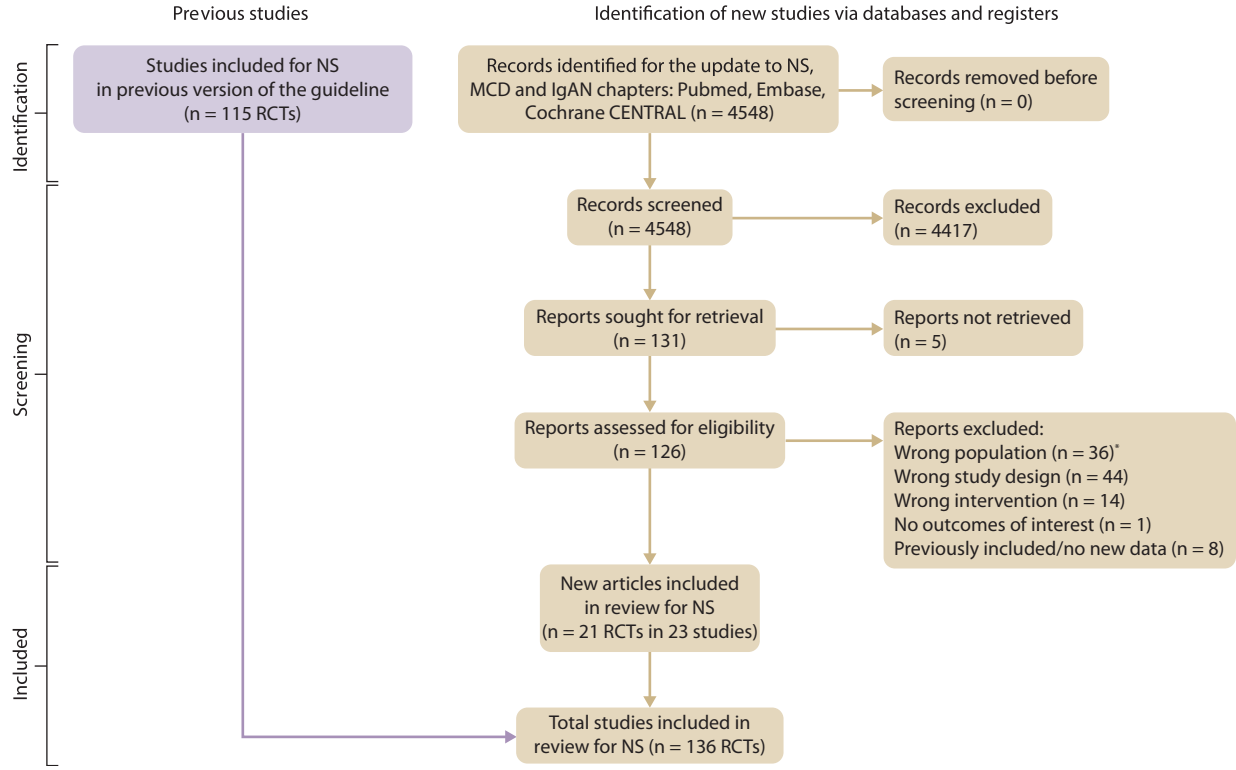

Figure 6| Search yield and study flow diagram. *Includes studies identified for concurrent guideline updates relevant to minimal change disease (MCD), IgA nephropathy (IgAN), and IgA vasculitis in children. NS, nephrotic syndrome; RCT, randomized controlled trial.

- 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, ≥50% loss of GFR, infection, malignancy, complete remission/relapse, and glucocorticoid-related adverse events) results were expressed as a risk ratio with a 95% CI. The continuous scale outcome, annual GFR loss, was evaluated as a mean difference 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.[116]

Assessment of heterogeneity. Heterogeneity was assessed by visual inspection of forest plots of standardized mean effect sizes, and of risk ratios, and by the I^2 statistic, which measures the proportion of the total variation in the estimates of treatment effect that was due to heterogeneity beyond chance. We used conventions of interpretation as defined by Higgins *et al.*[119]

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).[116] 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, and 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).[116]

Table 3 | Classification for the grade of the 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.

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,[117,120] 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 the risk ratio, 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.[120] 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 grading the certainty of the evidence, see Table 4.

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 the evidence for each critical and important outcome is also provided in the SoF tables. For the 2025 update, the SoF tables were updated or created manually. The SoF tables are available in Data Supplement: Appendices C and D.

Developing the recommendations. For the KDIGO 2025 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 the initial and final drafts of the guideline statements

Table 4 | GRADE system for grading the certainty of evidence

Study design	Step 1—starting grade for the certainty of evidence	Step 2—lower the grade	Step 3—raise the grade for observational studies
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	

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

Table 5 | KDIGO nomenclature and description for grading 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.

KDIGO, Kidney Disease: Improving Global Outcomes.

and text and approved the final version of the guideline. The ERT also provided a descriptive summary of the certainty of the 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).

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 the 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 as A, B, C, or D (Table 3).

Patient values and preferences. No patients or caregivers were involved 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.

Resource use and costs. Healthcare and non-healthcare resources, including all inputs in the treatment management pathway, 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 from the 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. Although systematic reviews are not performed for clinical questions underlying practice points, they are often crafted to help readers implement the guidance from graded recommendation. Practice points represent the expert judgment of the guideline Work Group, but they may also be based on limited evidence. For example, practice points were provided on monitoring, frequency of testing, dosing adjustments for the severity of chronic kidney disease, 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

Table 6 | Determinants of the strength of a recommendation

Factor	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.

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, and 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. Therefore, 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 this guideline, neither a scoping exercise with patients nor formal qualitative evidence synthesis examining patient experiences and priorities was undertaken; limited searches of the qualitative literature were conducted. As noted, although resource implications were considered in the formulation of recommendations, formal economic evaluations were not undertaken for all topics.

Biographic and disclosure information

Jürgen Floege, MD (Work Group Co-Chair), is a senior professor in the Division of Nephrology and Immunology at the University of Aachen, Aachen, Germany. Professor Floege is a former executive council member of the International Society of Nephrology (ISN), European Renal Association–European Dialysis and Transplant Association (ERA-EDTA), and Kidney Disease: Improving Global Outcomes (KDIGO). He is a distinguished fellow of the ERA-EDTA and recipient of the 2018 ERA-EDTA Award for Outstanding Clinical Contributions to Nephrology, a past president of the German Society of Nephrology, as well as an honorary member of the Japanese and Polish, Portuguese, Serbian, and Slovakian societies of nephrology. Together with Professors Richard Johnson and Marcello A. Tonelli, he edits the best-selling textbook *Comprehensive Clinical Nephrology*. He is an associate editor of *Kidney International*, editor-in-chief of *Clinical Kidney Journal*, and a member of the editorial board of *Journal of the American Society of Nephrology*, *Journal of Nephrology*, and other journals. Until 2017, he served as Associate Editor of *Nephrology Dialysis Transplantation*.

His research interests encompass progression of kidney disease, particularly kidney fibrosis, immune-mediated kidney disease, particularly IgA nephropathy, as well as chronic kidney disease-mineral and bone disorders and cardiovascular disease in patients with uremia. His scientific work encompasses ~750 original papers, reviews, and editorials and 40 book chapters.

JF reports receiving consultancy fees and/or speaker honoraria from AstraZeneca, Bayer, Boehringer Ingelheim, Calliditas, Chinook, GlaxoSmithKline, HiBio, Novartis, Omeros, Otsuka, Roche, STADApharm, Travere, and Vera Therapeutics and serving on data safety monitoring boards of Novo Nordisk and Visterra.

Brad H. Rovin, MD, FACP, FASN (Work Group Co-Chair), is the Lee A. Hebert Professor of Nephrology at the Ohio State University Wexner Medical Center, Columbus, Ohio, USA. He is the Director of the Division of Nephrology and Medical Director of the Ohio State University Center for Clinical Research Management. Dr. Rovin conducts translational research on autoimmune glomerular diseases and applies these studies to clinical trial development and design for investigator-initiated and industry-sponsored trials of novel therapeutics.

*BHR reports receiving consultancy fees from Alexion, Artiva, AstraZeneca, Aurinia, BioCryst, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Calliditas, Exagen, Genentech/Roche, Gilead, GlaxoSmithKline, Kezar Life Sciences, Kyverna, Lilly, Novartis, Otsuka, Travere, Vera Therapeutics, and Vertex and grant/research support from Biogen.**
**Monies paid to institution.*

Keisha L. Gibson, MD, MPH, received her medical degree and Master of Public Health degree in epidemiology from the University of North Carolina, Chapel Hill, North Carolina, USA. She completed a residency in general pediatrics at the Medical University of South Carolina, Charleston, South Carolina, USA, and a clinical fellowship in pediatric nephrology from UNC Chapel Hill. She is currently an associate professor of medicine and pediatrics, the Chief of Pediatric Nephrology in the Division of Nephrology and Hypertension, and the Vice-Chair of Health Equity and Community Engagement for the Department of Medicine at UNC Chapel Hill.

Dr. Gibson's research and clinical interests focus on nephrotic syndrome and other glomerular diseases. In the area of epidemiology, she is interested in ethnic and socioeconomic disparities and their effect on patient outcomes. She has been involved as a coinvestigator in large consortium studies such as the Nephrotic Syndrome Network Study and the Cure Glomerulonephropathy Network Study.

KLG reports serving as an advisory board member of Travere (formerly Retrophin) and receiving research support from Aurinia, Roche, Travere, and Vertex.

Adrian Liew, MD, MBBS, MRCP, FAMS, FASN, FRCP, MClinEpid, FISN, is a senior consultant nephrologist and director of the Kidney & Transplant Practice at Mount Elizabeth Novena Hospital in Singapore. He received his medical degree from the National University of Singapore, Singapore. Dr. Liew is an elected executive and honorary secretary of the International Society for Peritoneal Dialysis (ISPD). He chairs the International Society of Nephrology (ISN) End-Stage Kidney Disease Strategy Dialysis Subgroup and is the current deputy chair of the ISN Continuing Medical Education (CME) Committee. He received the John Maher Award from the ISPD in 2020 for his contribution to peritoneal dialysis. Dr. Liew is also an associate editor of the journal *Nephrology* and

serves on the editorial boards of *Kidney International*, *Peritoneal Dialysis International*, *Kidney and Blood Pressure Research*, and *Kidney Research and Clinical Practice*.

His research interests include glomerular diseases, peritoneal dialysis, and diabetic kidney disease. He sits on the steering committees and is the national leader for several multicenter clinical trials.

AL reports receiving consultancy fees from Alexion, Alnylam, Alpine Immune Sciences, Arrowhead Pharmaceuticals, AstraZeneca, Baxter Healthcare, Bayer, BioCryst, Boehringer Ingelheim, Chinook, Dimerix, Eledon Pharmaceuticals, George Clinical, GlaxoSmithKline, Kira Pharmaceuticals, Otsuka, ProKidney, Vera Therapeutics, Vertex, Visterra, and Zai Lab.

Jai Radhakrishnan, MD, MS, MRCP, FACC, FASN, is a professor of medicine at Columbia University Medical Center, New York, New York, USA, and the clinical director of the nephrology division at New York-Presbyterian Hospital, New York, New York, USA. After completing his initial medical training in India and the United Kingdom, he completed his nephrology training at the Massachusetts General Hospital in Boston, Massachusetts, USA, and Columbia University Medical Center in New York, New York, USA. He completed his master's degree in biostatistics from the Mailman School of Public Health, Columbia University, New York, New York, USA.

His clinical and research interests are in glomerular diseases. He is an associate editor of *Kidney International* and a founding editor/editor-in-chief of *Kidney International Reports*. As a clinician-educator, Dr. Radhakrishnan has served on educational committees with the American Society of Nephrology and the ISN and is a global education ambassador for the ISN. He has lectured extensively both nationally and internationally.

JR reports serving as an advisory board member of Novartis and receiving consultancy fees from Apellis, BeiGene, Boehringer Ingelheim, Nkarta, Novartis, Otsuka, Sanofi Genzyme, Travere, and Vera Therapeutics; royalties from UpToDate and Wolters Kluwer; speaker honoraria from Amgen and GlaxoSmithKline; and grant/research support from Travere.

Marina Vivarelli, MD, trained in pediatrics at the University of Pavia, Pavia, Italy, and completed a 2-year pediatric immunology research fellowship at Children's Hospital, Boston, Massachusetts, USA, with Professor Raif Geha.

Since 2006, in the Division of Nephrology of the Bambino Gesù Children's Hospital in Rome, Italy, she has worked to establish a new front of translational research in pediatric immune-mediated kidney diseases. Her focus has been on nephrotic syndrome and on complement-mediated kidney disease. She has designed and conducted phase 1–3 trials for pediatric glomerular diseases. Since 2023, she is Chief of the Laboratory of Nephrology and Chief of the Clinical Trial Center of Bambino Gesù Children's Hospital. She has served on the European Society for Pediatric Nephrology (ESPN) council and is a Fellow of the ESPN, has chaired the European Rare Kidney disease Network (ERKNet) Working Group on Immune-Mediated Glomerulopathies, and now chairs the Working Group on Thrombotic Microangiopathies and is a steering committee member of the ERKNet Registry. She has participated in or coordinated the preparation of the International Pediatric Nephrology Association or ERKNet guidelines on steroid-resistant and steroid-sensitive nephrotic syndrome, congenital nephrotic syndrome, and IgA nephropathy and IgA vasculitis with nephritis. She serves on the editorial boards of *Pediatric Nephrology*, *Kidney International*, and *Journal of the American Society of Nephrology*.

MV reports receiving consultancy fees from Apellis, Bayer, BioCryst, Chinook, Novartis, Purespring, Roche, Santhera, and Travere and speaker honoraria from Alexion, GlaxoSmithKline, Novartis, Roche, and Vifor.

KDIGO Chairs

Michel Jadoul, MD, has been chairing the Division of Nephrology of the Cliniques universitaires Saint-Luc for 20 years (2003–2023) and is now a young emeritus full clinical professor at UCLouvain, both in Brussels, Belgium. His clinical activities still include follow-up of patients with chronic kidney disease (CKD) undergoing hemodialysis.

His research interests encompass various complications of hemodialysis, including hepatitis C, cardiovascular complications after kidney transplantation, various causes of drug nephrotoxicity, and the epidemiology of CKD in sub-Saharan Africa.

Professor Jadoul has (co-)authored over 360 scientific papers, most of them published in major nephrology journals. He is an associate editor of *Nephrology Dialysis Transplantation*. In 2008, he received the International Distinguished Medal of the National Kidney Foundation and he has been a member of the European Renal Association Council (2013–2016). Professor Jadoul has co-chaired the development of the 2008, 2018, and 2022 versions of the Kidney Disease: Improving Global Outcomes (KDIGO) Hepatitis C Virus in Chronic Kidney Disease Guideline and is a KDIGO Co-Chair since January 1, 2019.

MJ reports receiving consultancy fees from Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Cardiorenal, CSL Vifor, GlaxoSmithKline, Mundipharma, and Vertex; grants/research support from AstraZeneca; speaker honoraria from Astellas, AstraZeneca, Bayer, and Boehringer Ingelheim; funding for expert testimony from STADA-Eurogenerics*; and travel support from AstraZeneca and Boehringer Ingelheim.**

**Monies paid to institution.*

Morgan E. Grams, MD, PhD, MHS, is a nephrologist, PhD-trained epidemiologist, and the Susan and Morris Mark Professor of Medicine and Population Health at New York University, New York, USA, where she helps lead the Division of Precision Medicine, a multidisciplinary research unit. Dr. Grams is Co-Principal Investigator of the Chronic Kidney Disease Prognosis Consortium (CKD-PC), a consortium of over 30 million participants, 100 cohorts, and 250 investigators from around the globe. Her research encompasses epidemiology of chronic kidney disease, pharmacoepidemiology, and analysis of real-world evidence as well as the integration of multimodal omics, histology, and imaging data. She was the winner of the Young Investigator Award in 2018 given by the American Society of Nephrology/American Heart Association Kidney Council, the top award for investigators under 45 years of age, and she is a member of the American Society of Clinical Investigation. Her formal training was completed at Yale, Columbia, and Johns Hopkins universities. She is a Kidney Disease: Improving Global Outcomes (KDIGO) Co-Chair.

MEG declared no competing interests.

Methods Chair

Marcello A. Tonelli, MD, SM, MSc, FRCPC, is a nephrologist, professor, and clinician-scientist at the University of Calgary.

Dr. Tonelli's research focuses on improving the care of people with chronic kidney disease and other noncommunicable diseases. He is chair emeritus of the Canadian Task Force on Preventive Health Care, a past president of the Canadian Society of Nephrology, a Fellow of the Canadian Academy of Health Sciences and the Royal Society of Canada, and the President of the International Society of Nephrology. He is the Director of the World Health Organization's Collaborating Centre for the Prevention and Control of Chronic Kidney Disease.

MAT declared no competing interests.

Evidence Review Team

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Dr. Gordon provided methodological expertise to the Work Group during the guideline development process and assisted in the collection, evaluation, grading, and synthesis of evidence for the guideline as well as providing guidance to the Work Group members in the areas of topic refinement, key question formulation, data extraction, study assessment, evidence grading, and recommendation formulation. His primary research and clinical interests are in the management of HCV in patients with CKD, polycystic kidney disease, and thrombotic microangiopathies as well as evidence-based medicine and systematic review related to other areas of nephrology.

CEG reports receiving consultancy fees from Alexion and Calliditas and speaker honoraria from Alexion and Novartis.

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GPA declared no competing interests.

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