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

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The Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for the Management of Glomerular Diseases was last updated and published in 2021. KDIGO continues to be committed to the nephrology community to provide periodic updates, based on new developments for each of the glomerular diseases. For children with nephrotic syndrome, the updated guideline now contains a treatment algorithm on when to perform a kidney biopsy and/or genetic testing and which immunosuppressive therapy to use in children with a complete response to glucocorticoids (steroid sensitive), who subsequently become infrequent or frequent relapsers or even steroid dependent. If a glucocorticoid-sparing agent must be considered after failure of an initial glucocorticoid therapy to induce remission, the choice among a calcineurin inhibitor, oral cyclophosphamide, levamisole, mycophenolate mofetil, and rituximab is a decision that requires consideration of patient-related issues such as resources, adherence, adverse effects, and patient preferences. Herein, an executive summary of the most important changes in the KDIGO 2025 Clinical Practice Guideline for the Management of Nephrotic Syndrome in Children is provided as a quick reference.

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In 2021, the Kidney Disease: Improving Global Outcomes (KDIGO) organization published a major revision of the Clinical Practice Guideline for the Management of Glomerular Diseases.[1] Since 2021, new data on the management of children with nephrotic syndrome have become available, prompting the present guideline update (Supplementary Table S1).

A crucial element in this particular guideline is the definition of various clinical scenarios such as type of remission (partial vs. complete), relapse, steroid-sensitive nephrotic syndrome (SSNS), steroid-resistant nephrotic syndrome (SRNS), and late responder. These definitions have been changed to align with those from the International Pediatric Nephrology Association (IPNA) guideline on the management of children with steroid-sensitive[2] and steroid-resistant nephrotic syndrome.[3] Further, a new addition is the definition of a "confirmation period," which is the time period between 4 and 6 weeks after glucocorticoid initiation during which responses to further glucocorticoid administration and renin-angiotensin system blockade are ascertained in patients achieving only partial remission at 4 weeks. A patient achieving complete remission during the confirmation period is defined as a "late responder." Not achieving complete remission at 4 weeks or achieving partial remission at 4 weeks but not complete remission during the confirmation period with daily prednisone or prednisolone is defined as SRNS.

Probably the most significant addition to the chapter is a treatment algorithm for nephrotic syndrome in children (Figure 1), which specifies in which cases a biopsy and/or genetic testing should be considered and which provides a detailed decision tree on immunosuppressive therapy in children with a complete response to glucocorticoids (steroid sensitive), who subsequently become infrequent or frequent relapsers or even steroid dependent.

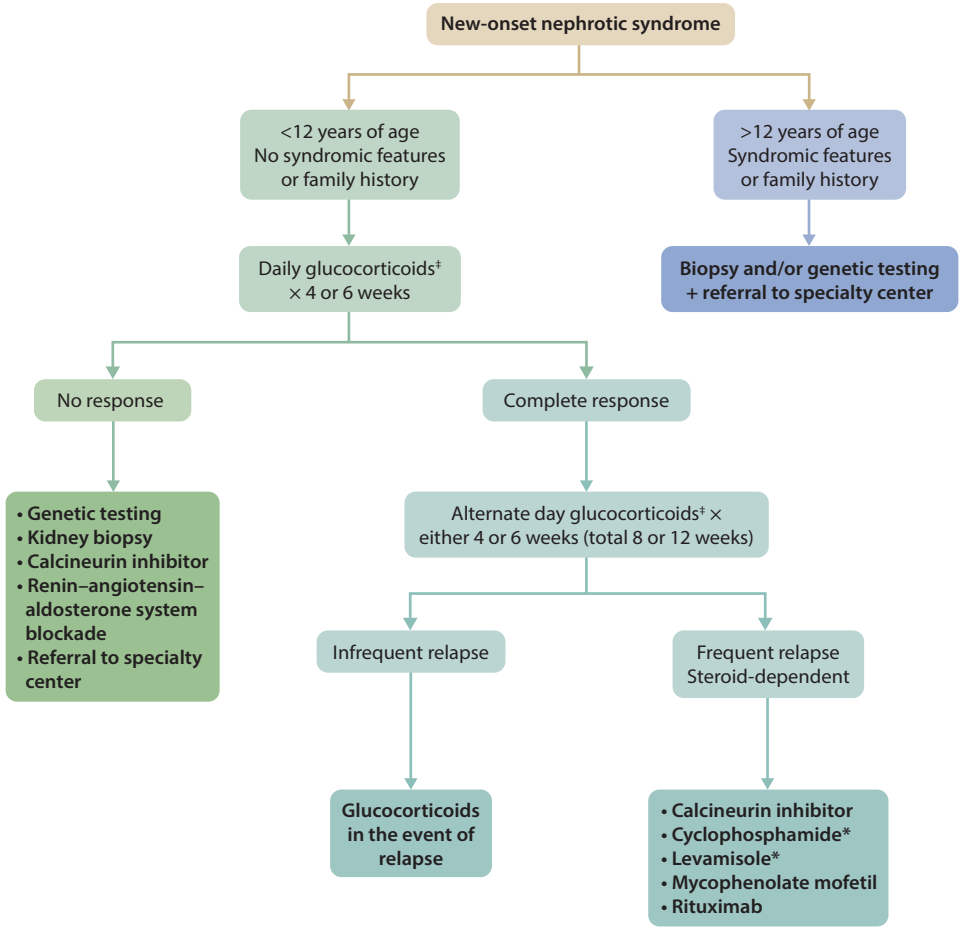

Figure 1 | Treatment algorithm for nephrotic syndrome (NS) from onset. Therapeutic approach to NS in children from onset. Refer to the clinical trial where appropriate. Syndromic features are defined as impaired statural growth; skeletal, neurodevelopmental, and ocular abnormalities; deafness; genital 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 in the full guideline). ‡Glucocorticoids: oral prednisone/prednisolone.

No change has been made to the central recommendation, *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)*. However, Section 1.3.2 has now been divided into 2 subsections: one on the prevention (1.3.2) and one on the treatment and prevention (1.3.3) of subsequent relapses of nephrotic syndrome in children. Based on the data from the Prednisolone in Nephrotic Syndrome 2 (PREDNOS2) study demonstrating no differences in the incidence of upper respiratory tract infection–associated relapses of nephrotic syndrome between a fixed dose of prednisolone and placebo for 6 days at the onset of an upper respiratory tract infection,[4,5] Recommendation 1.3.2.1 now states that 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*). Additionally, Practice Point 1.3.2.1 specifies that 3 extra doses of low-dose (0.5 mg/kg per day), daily prednisone or prednisolone can be considered at the onset of an upper respiratory tract infection in children with frequently relapsing or 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.

The statements related to the treatment of children with relapses also did not undergo major changes. As before, 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 1.3.3.1). After achieving complete remission, oral prednisone/prednisolone should then be reduced to 40 mg/m^2 or 1.5 mg/kg (maximum 40 mg) on alternate days for 4 weeks (Practice Point 1.3.3.2). 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 1.3.3.3). To prevent relapses, in children with frequently relapsing nephrotic syndrome without glucocorticoid toxicity, low-dose, alternate-day oral prednisone/prednisolone can be used (Practice Point 1.3.3.4). Similarly, no changes have been made to *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).*

The section on how to use glucocorticoid-sparing agents such as calcineurin inhibitors, cyclophosphamide, levamisole, mycophenolate mofetil, and rituximab again did not undergo major changes. As before, patients should ideally be in remission with glucocorticoids prior to initiating glucocorticoid-sparing agents, and continuation of glucocorticoids is advised for ≥2 weeks following the initiation of such glucocorticoid-sparing agents. The KDIGO Work Group felt, however, that there should no longer be a formal distinction of first-line and alternative agents. Rather, oral cyclophosphamide and levamisole may be preferable in frequently relapsing nephrotic syndrome, whereas mycophenolate mofetil, rituximab, calcineurin inhibitor, and, to a lesser extent, oral cyclophosphamide may be preferable in children with steroid-dependent nephrotic syndrome. With respect to rituximab, current trials report administration of 1–4 doses, but there are insufficient data to make a specific recommendation. In children with complicated forms of frequently relapsing or corticosteroid-dependent nephrotic syndrome, the use of mycophenolate mofetil after rituximab can decrease the risk of treatment failure.

Finally, in the section related to SRNS in children, Recommendation 1.4.1.1 remains unchanged. We still recommend using cyclosporine or tacrolimus as initial second-line therapy for children with SRNS *(1C)*. Evidence on the use of mycophenolate mofetil in these patients is very limited, while recent evidence suggests that rituximab may be helpful in attaining remission in ∼30% of children with calcineurin inhibitor–resistant SRNS.[6]

This executive summary can only give a brief snapshot of the 2025 update of the KDIGO Clinical Practice Guideline for the Management of Nephrotic Syndrome in Children. Readers are encouraged to read the full guideline for a more detailed discussion and useful practice points (https://kdigo.org/guidelines/gd/).

DISCLOSURE

The development and publication of this guideline were supported by Kidney Disease: Improving Global Outcomes (KDIGO). The opinions or views expressed in this summary are those of the authors and do not necessarily reflect the opinions or recommendations of the International Society of Nephrology or Elsevier. Dosages, indications, and methods of use for products that are referred to in the supplement by the authors may reflect their clinical experience or may be derived from the professional literature or other clinical sources. Because of the differences between *in vitro* and *in vivo* systems and between laboratory animal models and clinical data in humans, *in vitro* and animal data do not necessarily correlate with clinical results.

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

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