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IDIOPATHIC NEPHROTIC SYNDROME IN CHILDREN: DIAGNOSTIC STRATEGIES AND CURRENT CRITERIA

SÍNDROME NEFRÓTICA IDIOPÁTICA NA CRIANÇA: ESTRATÉGIAS DIAGNÓSTICAS E CRITÉRIOS ATUAIS

SÍNDROME NEFRÓTICO IDIOPÁTICO EN LA INFANCIA: ESTRATEGIAS DIAGNÓSTICAS Y CRITERIOS ACTUALES

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Ryan Rafael Barros de Macedo[1], Isabella de Oliveira Sanches Vinci[2], Fernando Poli Aran Jallas[3], Danilo Francisco Bezerra do Nascimento[4]

ABSTRACT

Idiopathic nephrotic syndrome (INS) in childhood is the most common glomerulopathy in pediatrics and is characterized by nephrotic-range proteinuria, hypoalbuminemia, and edema. Current diagnostic criteria include nephrotic proteinuria defined by a urinary protein-to-creatinine ratio ≥ 2.0 mg/mg (or ≥ 200 mg/mmol) associated with serum albumin < 30 g/L, with laboratory confirmation recommended before initiating treatment (Trautmann et al., 2023). Clinical classification guides management: steroid-sensitive nephrotic syndrome (SSNS) is characterized by complete remission within up to 4 weeks of prednisone, and the definition of frequently relapsing disease (≥ 2 relapses within 6 months or ≥ 3 within 12 months) supports early introduction of steroid-sparing strategies (Trautmann et al., 2023).Recent advances suggest that a subset of INS has a humoral autoimmune basis, with identification of anti-nephrin autoantibodies correlated with disease activity and response to B-cell–depleting therapies (Chan; Boyer, 2025), as well as models in which immune triggers induce anti-podocyte antibodies leading to podocyte injury (Al-Aubodah et al., 2025). In congenital forms (onset < 3 months), the etiology is predominantly genetic, and genetic testing is recommended as first-line evaluation (Boyer et al., 2021). Management includes corticosteroids and, in cases of frequent relapses or steroid dependence, steroid-sparing agents and rituximab in selected cases, with monitoring for hypogammaglobulinemia (Trautmann et al., 2023; Chan; Boyer, 2025). Additionally, evidence-based nutritional management is recommended, avoiding high-protein diets and adjusting sodium restriction according to the clinical phase (Lella et al., 2023; Trautmann et al., 2023). Biomarkers and genotyping support the transition toward precision medicine (Chan; Boyer, 2025; Vincenti; Angeletti; Ghiggeri, 2023).

Keywords: Idiopathic Nephrotic Syndrome. Pediatrics. Corticosteroids. Anti-Nephrin Autoantibodies. Rituximab. Glomerulopathies.

[1] Medical student. Centro Universitário do Planalto Central Apparecido dos Santos (UNICEPLAC).
[2] Medical student. Centro Universitário Lusíada (UNILUS).
[3] Medical student. Centro Universitário Lusíada (UNILUS).
[4] Nursing Resident. REMUSC ESP-PB.

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RESUMO

A síndrome nefrótica idiopática (SNI) na infância é a glomerulopatia mais frequente em pediatria e cursa com proteinúria em níveis nefróticos, hipoalbuminemia e edema. Os critérios diagnósticos atuais incluem proteinúria nefrótica definida por relação proteína/creatinina urinária ≥ 2,0 mg/mg (ou ≥ 200 mg/mmol) associada a albumina sérica < 30 g/L, com recomendação de confirmação laboratorial antes do início do tratamento (Trautmann et al., 2023). A classificação clínica direciona condutas: a síndrome nefrótica cortico-sensível (SNCS) é caracterizada por remissão completa em até 4 semanas de prednisona, e a definição de recidivante frequente (≥ 2 recaídas em 6 meses ou ≥ 3 em 12 meses) favorece a introdução precoce de estratégias poupadoras de esteroides (Trautmann et al., 2023). Avanços recentes sugerem que parte da SNI possui base autoimune humoral, com identificação de autoanticorpos anti-nephrin correlacionados à atividade da doença e à resposta a terapias depletoras de células B (Chan; Boyer, 2025), além de modelo em que gatilhos imunes induzem anticorpos anti-podócitos levando à lesão podocitária (Al-Aubodah et al., 2025). Nas formas congênitas (início < 3 meses), a etiologia é predominantemente genética, e o teste genético é recomendado como primeira linha (Boyer et al., 2021). O manejo inclui corticosteroides e, em recaídas frequentes/dependência, agentes poupadores e rituximabe em casos selecionados, com vigilância para hipogamaglobulinemia (Trautmann et al., 2023; Chan; Boyer, 2025). Adicionalmente, recomenda-se abordagem nutricional baseada em evidências, evitando dietas hiperproteicas e ajustando restrição de sódio conforme fase clínica (Lella et al., 2023; Trautmann et al., 2023). Biomarcadores e genotipagem sustentam a transição para medicina de precisão (Chan; Boyer, 2025; Vincenti; Angeletti; Ghiggeri, 2023).

Palavras-chave: Síndrome Nefrótica Idiopática. Pediatria. Corticosteroides. Autoanticorpos Anti-Nefrina. Rituximabe. Glomerulopatias.

RESUMEN

El síndrome nefrótico idiopático (SNI) en la infancia es la glomerulopatía más frecuente en pediatría y se caracteriza por proteinuria en rango nefrótico, hipoalbuminemia y edema. Los criterios diagnósticos actuales incluyen proteinuria nefrótica definida por una relación proteína/creatinina urinaria ≥ 2,0 mg/mg (o ≥ 200 mg/mmol) asociada a albúmina sérica < 30 g/L, recomendándose la confirmación de laboratorio antes de iniciar el tratamiento (Trautmann et al., 2023). La clasificación clínica orienta la conducta: el síndrome nefrótico sensible a corticoides (SNSC) se caracteriza por remisión completa en hasta 4 semanas con prednisona, y la definición de recaídas frecuentes (≥ 2 recaídas en 6 meses o ≥ 3 en 12 meses) favorece la introducción temprana de estrategias ahorradoras de esteroides (Trautmann et al., 2023). Avances recientes sugieren que una parte del SNI tiene una base autoinmune humoral, con la identificación de autoanticuerpos anti-nefrina correlacionados con la actividad de la enfermedad y la respuesta a terapias de depleción de células B (Chan; Boyer, 2025), además de modelos en los que desencadenantes inmunes inducen anticuerpos anti-podocitos que conducen a lesión podocitaria (Al-Aubodah et al., 2025). En las formas congénitas (inicio < 3 meses), la etiología es predominantemente genética y se recomienda la prueba genética como primera línea (Boyer et al., 2021). El manejo incluye corticosteroides y, en casos de recaídas frecuentes o dependencia de esteroides, agentes ahorradores y rituximab en casos seleccionados, con vigilancia de hipogammaglobulinemia (Trautmann et al., 2023; Chan; Boyer, 2025). Además, se recomienda un abordaje nutricional basado en la evidencia, evitando dietas hiperproteicas y ajustando la restricción de sodio según la fase

clínica (Lella et al., 2023; Trautmann et al., 2023). Los biomarcadores y la genotipificación respaldan la transición hacia la medicina de precisión (Chan; Boyer, 2025; Vincenti; Angeletti; Ghiggeri, 2023).

Palabras clave: Síndrome Nefrótico Idiopático. Pediatría. Corticosteroides. Autoanticuerpos Anti-Nefrina. Rituximab. Glomerulopatías.

1 INTRODUCTION

Idiopathic nephrotic syndrome (NIS) represents the most frequent glomerulopathy in the pediatric age group, with an overall incidence ranging from 1.15 to 16.9 per 100,000 children per year (Trautmann et al., 2023). The disease is clinically characterized by the classic triad of massive proteinuria, hypoalbuminemia, and edema, and may be associated with hyperlipidemia (Vincenti; Angeletti; Ghiggeri, 2023). Clinical classification is fundamentally based on the response to corticosteroid therapy, dividing patients into corticosteroid-sensitive (CNS) and corticosteroid-resistant (SNCR), which has prognostic and therapeutic implications Boyer, 2025).

Historically, the pathogenesis of NIS has been attributed to a dysfunction of the immune system, specifically of T lymphocytes, and the presence of an unidentified circulating permeability factor. However, recent advances point to a more complex autoimmune architecture, involving B-cell dysregulation and the discovery of autoantibodies against nephrin, a crucial component of the podocyte cleft diaphragm (Al-Aubodah et al., 2025). In addition, the understanding of the genetic basis, especially in congenital nephrotic syndrome (CNS) and steroid-resistant forms, has redefined diagnostic approaches, moving away from the need for routine kidney biopsies in favor of genetic panels in specific populations (Boyer et al., 2021).

The management of IBS is challenging, aiming to induce and maintain remission of proteinuria while minimizing toxicity related to long-term use of corticosteroids and other immunosuppressants. Diet also plays a relevant auxiliary role, not only in the acute phase, but in the prevention of long-term comorbidities such as obesity and cardiovascular disease (Lella et al., 2023).

The purpose of this study is to review current guidelines and emerging evidence on the diagnosis, pathophysiology, and therapeutic management of nephrotic syndrome in childhood, integrating the recommendations of the International Pediatric Nephrology Association (IPNA) with the most recent scientific findings.

2 METHODOLOGY

This article was prepared in the form of a narrative literature review, with the aim of synthesizing and critically analyzing the most recent guidelines and scientific evidence on Idiopathic Nephrotic Syndrome in pediatrics. The selection of information sources was based on documents provided, using the descriptors "Nephrotic Syndrome", "Child" and

"Treatment", combined by the Boolean operators AND and OR, in alignment with the terminology of Medical Subject Headings (MeSH). Clinical guideline articles, systematic reviews, and recently published studies on pathogenesis, available in full in English, were included. Studies that did not directly address the clinical management or pathophysiology of the condition in question were excluded, as well as duplicate publications. The analysis of the texts occurred in two stages: initial relevance screening and in-depth reading for data extraction and categorization, which were organized in a descriptive manner to compose the results and discussion.

3 RESULTS

3.1 DIAGNOSIS AND CLINICAL DEFINITIONS

The definition of nephrotic syndrome requires the presence of nephrotic proteinuria (urinary protein/creatinine ratio $\ge$ 2.0 mg/mg or $\ge$ 200 mg/mmol) and hypoalbuminemia (serum albumin < 30 g/L), often accompanied by edema. The International Pediatric Nephrology Association (IPNA) recommends confirmation of nephrotic proteinuria before starting treatment (Trautmann et al., 2023).

Classification of the disease has evolved to better guide therapy. Corticosteroid-sensitive nephrotic syndrome (CNS) is defined by complete remission within 4 weeks of prednisone therapy. Patients who relapse frequently ($\ge$2 relapses within the first 6 months or $\ge$3 at 12 months) are classified as frequent relapsers (SNRF), an updated definition to promote steroid-sparing interventions earlier (Trautmann et al., 2023).

3.2 ADVANCES IN PATHOPHYSIOLOGY

The understanding of IBS is migrating from a purely idiopathic view to a humoral autoimmune etiology in many cases. Recent studies have identified anti-nephrin autoantibodies in a significant proportion of children with active disease, correlating with disease activity and response to B-cell depleting therapies (Chan; Boyer, 2025).

The proposed model suggests that in genetically predisposed individuals, immune triggers (such as viral infections) lead to the production of anti-podocyte antibodies (APAs) by short-lived plasmablasts or memory cells, causing podocyte injury (Al-Aubodah et al., 2025).

3.3 GENETICS AND CONGENITAL NEPHROTIC SYNDROME

In congenital nephrotic syndrome (onset within the first 3 months of life), the etiology is predominantly genetic. Pathogenic variants in the NPHS1, NPHS2, WT1, and PLCE1 genes are the most common. For these patients, genetic testing is recommended as a first-line diagnostic measure, replacing routine renal biopsy (Boyer et al., 2021).

4 DISCUSSION

4.1 THERAPEUTIC STRATEGIES IN THE CNS

The treatment of CNS aims to induce remission and prevent relapse. IPNA guidelines recommend the use of prednisone or prednisolone as a single daily dose during the initial episode and in relapses, avoiding weaning in the alternate-day phase to reduce total steroid exposure. In addition, the addition of another immunosuppressive/immunomodulatory drug to prednisolone is not recommended in the treatment of an early episode of nephrotic syndrome. (Trautmann et al., 2023)

After corticosteroid-induced remission, combination therapy with some drugs is being analyzed in clinical trials. Current responses suggest that with cyclosporine A, however, the benefit of this strategy was lost after stopping treatment. With Levamisole, it showed complete remission and improved survival (Chan; Boyer, 2025)

For patients with SNRF or steroid dependence, the use of corticosteroid-sparing agents is mandatory. First-line options include levamisole, mycophenolate mofetil (MMF), cyclophosphamide, and calcineurin inhibitors (cyclosporine or tacrolimus). The choice of agent should be individualized, considering the profile of side effects and family preference (Trautmann et al., 2023). Rituximab, an anti-CD20 monoclonal antibody, is recommended for cases not controlled with other therapies or when there is poor adherence, although the risk of hypogammaglobulinemia should be monitored (Trautmann et al., 2023; Chan; Boyer, 2025).

4.2 CRISIS PREVENTION STRATEGIES

The recurrences of this systemic inflammatory syndrome (SIS) often coincide with triggers such as allergic reactions, drugs, asthma, and especially viral infections. Although the factors that generate podocytopathic B-cell responses are unknown, they are likely to be precipitated by the immune responses associated with these events. Thus, children diagnosed with idiopathic nephrotic syndrome should adopt preventive measures

and in the face of these stimuli. (Al-Aubodah et al., 2025; Vincenti; Angeletti; Ghiggeri, 2023)

4.3 NUTRITIONAL MANAGEMENT

Nutrition therapy is an essential and often overlooked component. During the active phase and use of corticosteroids, a healthy diet is recommended, avoiding simple sugars and saturated fats to prevent obesity and dyslipidemia. Unlike old practices, high-protein diets are not recommended as they can increase proteinuria and accelerate the progression of kidney disease; protein intake should follow the recommendations for age (Lella et al., 2023). Sodium restriction is indicated during moderate to severe edema but may be relaxed during remission to prevent hyponatremia and improve palatability (Lella et al., 2023; Trautmann et al., 2023).

Regarding fluid balance, fluid restriction is not widely recommended, despite the retention and edema commonly present in the pathology addressed. It is limited to selected cases, such as significant hyponatremia, massive anasarca, or oliguric renal failure. (Lella et al., 2023)

4.4 FUTURE PERSPECTIVES AND PRECISION MEDICINE

The identification of biomarkers, such as anti-nephrin autoantibodies, and genotyping are paving the way for precision medicine. Reclassification of the disease based on underlying biological mechanisms, rather than steroid response alone, will allow for more targeted therapies such as the use of obinutuzumab in rituximab-resistant patients or coenzyme Q10 supplementation in specific genetic deficiencies (Chan; Boyer, 2025; Vincenti; Angeletti; Ghiggeri, 2023).

5 CONCLUSION

Idiopathic nephrotic syndrome in childhood remains the most frequent and clinically heterogeneous pediatric glomerulopathy. The current recommendations consolidate the diagnosis of nephrotic proteinuria with a urinary protein/creatinine ratio ≥ 2.0 mg/mg (≥ 200 mg/mmol) associated with serum albumin < 30 g/L, reinforcing the need for laboratory confirmation and objective monitoring of remission and relapse (Trautmann et al., 2023). The operational classification by response to corticosteroids remains central: the corticosteroid-sensitive form is defined as complete remission within 4 weeks of

treatment, whereas frequent relapses are characterized by ≥ 2 relapses at 6 months or 3 ≥ 12 months, a pattern that is associated with a higher burden of disease and greater cumulative exposure to steroids. (Trautmann et al., 2023)

From a therapeutic point of view, the studies converge on maintaining prednisone/prednisolone as the basis of initial treatment, but highlight that the high proportion of relapses and cumulative toxicity justify sparing strategies in frequent and/or dependent relapse (Trautmann et al., 2023; Chan; Boyer, 2025). Among the sparing alternatives discussed are levamisole, mycophenolate mofetil, cyclophosphamide, and the calcineurin inhibitors cyclosporine and tacrolimus, with a choice guided by clinical profile and risk of adverse effects (Trautmann et al., 2023). In selected cases (especially dependence/relapse), recent literature reinforces the role of B-cell-targeted therapies, especially rituximab, requiring vigilance for complications such as hypogammaglobulinemia and infectious risk (Chan; Boyer, 2025; Trautmann et al., 2023).

On the pathophysiological axis, contemporary reviews support the transition from a purely "T-cell" model to a broader spectrum, in which a relevant part of the cases present humoral autoimmune architecture, including the description of anti-podocyte autoantibodies (anti-nephrine) associated with disease activity and response to anti-B therapies (Al-Aubodah et al., 2025; Chan; Boyer, 2025). This reading explains the clinical heterogeneity and variability of therapeutic response among patients with similar phenotype, reinforcing that the classification based only on the response to the steroid, although useful, is biologically incomplete (Chan; Boyer, 2025; Vincenti; Angeletti; Ghiggeri, 2023).

In the genetic component, the consensuses and reviews highlight that the congenital forms (beginning < 3 months) are predominantly genetic and that a relevant portion of the steroid-resistant forms also have pathogenic variants in podocyte genes. In these scenarios, early genetic testing is recommended to avoid ineffective immunosuppression and guide family management and counseling (Boyer et al., 2021; Vincenti; Angeletti; Ghiggeri, 2023). Finally, the articles emphasize that non-pharmacological care also changes outcomes: nutritional management should avoid high-protein diets, and sodium restriction should be applied in a clinical-dependent manner, especially in phases with edema, composing an evidence-based multidisciplinary approach (Lella et al., 2023).

In summary, the conclusions of the analyzed studies indicate that the current best practice requires integrating: (1) objective diagnostic and activity criteria (including uPCR and albumin), (2) clinical stratification by relapse/dependence, (3) rational use of prednisone/prednisolone and sparing therapies (levamisole, mycophenolate, cyclophosphamide, cyclosporine, tacrolimus) and, when indicated, targeted therapies (rituximab), and (4) incorporation of immunological (anti-nephrine) and genetic evidence (especially in congenital and resistant diseases), in addition to nutritional support. (Trautmann et al., 2023; Chan; Boyer, 2025; Al-Aubodah et al., 2025; Boyer et al., 2021; Lella et al., 2023; Vincenti; Angeletti; Ghiggeri, 2023)

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