

**NEPHROTIC SYNDROME IN CHILDREN: CURRENT MANAGEMENT AND
FUTURE PERSPECTIVES**

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Abstract. Pediatric nephrotic syndrome (NS) is a significant glomerular disorder marked by heavy proteinuria, edema, hypoalbuminemia, and hyperlipidemia, predominantly affecting children aged 1-6 years. This paper reviews the current understanding of NS, emphasizing its pathophysiology, clinical presentation, diagnosis, and management strategies. Minimal Change Disease (MCD) is the leading cause, accounting for 70-90% of cases, with corticosteroids as the primary treatment, achieving remission in most cases. However, relapses and steroid resistance necessitate alternative therapies like calcineurin inhibitors and rituximab. Complications such as infections, thromboembolism, and growth retardation highlight the need for comprehensive care. Future perspectives include genetic testing, personalized medicine, and novel therapeutics to enhance outcomes and reduce steroid dependency. This review underscores the importance of ongoing research and global collaboration to refine treatment protocols and improve the quality of life for affected children.

Keywords: nephrotic syndrome, pediatric, minimal change disease, corticosteroids, personalized medicine

Introduction

Nephrotic Syndrome (NS) is a prevalent glomerular disease in children, characterized by heavy proteinuria, edema, hypoalbuminemia, and hyperlipidemia. It primarily affects children aged 1-6 years, with an annual incidence of 2-7 per 100,000 children, and is more common in males and certain ethnic groups, such as South Asians and Africans[1,2]. The syndrome is classified into primary, secondary, and congenital types. Primary NS, often idiopathic, is most commonly caused by Minimal Change Disease (MCD), which accounts for 70-90% of cases in children and is highly responsive to corticosteroids[3,4]. Secondary causes include systemic diseases like systemic lupus erythematosus, infections, and drug exposure[4,5]. The pathogenesis involves increased glomerular permeability due to various mechanisms, including immune factors and genetic mutations[6]. Management of NS primarily involves corticosteroids, with prednisone being the first-line treatment for MCD, leading to remission in up to 95% of cases[3]. However, relapses are common, and alternative therapies such as calcineurin inhibitors and rituximab are used for steroid-resistant cases[7,8]. Complications of NS include infections, thromboembolism, and acute kidney injury, necessitating careful monitoring and adjunctive therapies like albumin and diuretics for edema[4,8]. Future directions in NS management focus on reducing steroid-related side effects and exploring genetic and biomarker research to better understand and treat the disease[6,7]. Overall, while the prognosis for steroid-responsive NS is generally good, ongoing research and international collaboration are essential to improve outcomes and develop evidence-based recommendations[2,9].

Pathophysiology and classification

Pediatric nephrotic syndrome is primarily characterized by massive proteinuria, hypoalbuminemia, and edema, with its pathophysiology deeply rooted in podocyte injury and immune dysregulation. Podocytes, specialized cells in the kidney, play a crucial role in maintaining the glomerular filtration barrier, and their dysfunction is central to the development of nephrotic syndrome. In conditions like Minimal Change Disease (MCD) and Focal Segmental Glomerulosclerosis (FSGS), podocyte injury leads to the effacement of foot processes, disrupting the filtration barrier and resulting in proteinuria[10–12]. MCD, the most common form in children, is often associated with immune dysregulation, where T-cell mediated events and circulating factors like angiopoietin-like-4 (ANGPTL4) contribute to podocyte damage. This condition is typically steroid-responsive, although the exact mechanisms remain partially understood[13,14]. In contrast, FSGS is characterized by segmental scarring of the glomeruli and is often resistant to steroid treatment. It involves structural changes in podocytes and is associated with circulating factors such as soluble urokinase receptor (suPAR), which are not present in MCD[14,15]. Membranous Nephropathy, although rare in children, involves immune complex deposition on the glomerular basement membrane, leading to podocyte injury[13]. Genetic factors also play a significant role, with mutations in podocyte-specific genes like NPHS1 and NPHS2 contributing to disease susceptibility and variability in treatment response[10,16]. The classification of nephrotic syndrome into MCD, FSGS, and Membranous Nephropathy is based on histological findings, with MCD showing minimal changes under light microscopy, FSGS displaying segmental sclerosis, and Membranous Nephropathy characterized by thickened glomerular capillary walls[17]. Understanding these pathophysiological mechanisms is crucial for developing targeted therapies that address the underlying causes rather than just managing symptoms, potentially improving patient outcomes and reducing reliance on corticosteroids[10,11].

Clinical presentation

Pediatric nephrotic syndrome is classically characterized by a tetrad of clinical symptoms: edema, proteinuria, hypoalbuminemia, and hyperlipidemia. Edema is often the most noticeable symptom, presenting as swelling in areas such as the eyelids, abdomen, and extremities, and is due to fluid retention caused by low serum albumin levels[3,18]. Proteinuria, defined as a urine protein excretion rate greater than 40 mg/m² per hour, is a hallmark of the syndrome and can be measured using a 24-hour urine collection or estimated via a spot urine protein-to-creatinine ratio[3,19]. Hypoalbuminemia, with serum albumin levels typically below 2.5 g/dL, results from the loss of protein in the urine[20]. Hyperlipidemia, often manifesting as elevated cholesterol levels, is another common feature, although not indispensable for diagnosis[21]. Minimal change disease (MCD) is the most prevalent cause of nephrotic syndrome in children, accounting for 70% to 90% of cases, and is generally responsive to corticosteroid treatment[3,14]. However, clinicians should be vigilant for atypical presentations or red flags that may suggest alternative diagnoses or complications. These include the presence of hypertension, hematuria, or onset of symptoms in children younger than one year or older than puberty, which decrease the likelihood of MCD and may indicate other conditions such as focal segmental glomerulosclerosis or secondary causes like infections and systemic diseases[3,7]. Additionally, congenital nephrotic syndrome, presenting within the first three months of life, is rare but associated

with high morbidity and mortality, often requiring early intervention[22,23]. Clinicians should also be aware of potential complications such as infections, thromboembolism, and acute kidney injury, which necessitate careful monitoring and management[7,24]. Early and accurate diagnosis, along with appropriate treatment, is crucial to improving outcomes and preventing long-term sequelae in children with nephrotic syndrome[3,19].

Diagnosis

Pediatric nephrotic syndrome is diagnosed using a combination of clinical evaluation and laboratory tests, with urinalysis and blood tests being primary tools. Urinalysis with a spot protein/creatinine ratio is crucial, as a ratio greater than 2.5 is diagnostic of nephrotic syndrome, especially when intermittent proteinuria is excluded[3]. Blood tests measuring albumin, cholesterol, urea, and creatinine levels help assess the severity and impact of the syndrome, as hypoalbuminemia and hyperlipidemia are characteristic features[3,7]. Renal ultrasound is often employed to evaluate kidney size and structure, although it is not diagnostic for nephrotic syndrome itself[25]. Renal biopsy is a more invasive diagnostic tool and is typically reserved for specific circumstances. It is indicated in cases of steroid-resistant nephrotic syndrome, frequent relapses, or when a diagnosis other than minimal change disease (MCD) is suspected[6,26]. In children over the age of 10, a renal biopsy is often recommended at diagnosis due to a higher likelihood of non-MCD causes, although recent studies suggest it may be unnecessary in steroid-sensitive cases[27]. Biopsy is also considered when atypical symptoms such as hypertension, hematuria, or renal failure are present, as these may indicate more severe glomerular lesions[28]. The procedure is generally safe, with complications such as hematuria and hematoma being relatively rare[26]. Ultimately, the decision to perform a renal biopsy should weigh the potential diagnostic benefits against the risks, particularly in younger children who may require sedation or anesthesia[25].

Current management strategies

Pediatric nephrotic syndrome (NS) is a prevalent glomerular disease characterized by proteinuria and hypoalbuminemia, with corticosteroids being the cornerstone of initial treatment. The standard regimen involves prednisone or prednisolone at 60 mg/m²/day for six weeks, followed by 40 mg/m²/day on alternate days for another six weeks, which induces remission in most cases, classifying them as steroid-sensitive nephrotic syndrome (SSNS)[29,30]. However, 20% of children do not respond to steroids, leading to a classification of steroid-resistant nephrotic syndrome (SRNS), which often requires second-line therapies such as calcineurin inhibitors (cyclosporine or tacrolimus)[29,31]. For those who relapse frequently or become steroid-dependent, steroid-sparing agents like mycophenolate mofetil (MMF), cyclophosphamide, and rituximab are considered, with MMF being preferred due to its favorable side effect profile[29,32,33]. Supportive care is crucial and includes diuretics for edema, salt restriction, and the use of ACE inhibitors or ARBs to manage hypertension and reduce proteinuria[30]. Additionally, managing complications such as infections and thrombotic events is vital, with prophylactic antibiotics and anticoagulants being recommended in high-risk patients[8,30]. The choice of treatment is often individualized based on the severity of the disease, patient age, and drug tolerability, aiming to achieve remission while minimizing side effects[31,34]. Despite the effectiveness

of these strategies, the pathophysiology of NS remains elusive, and ongoing research is needed to optimize treatment protocols and improve patient outcomes[31,35].

Complications

Pediatric nephrotic syndrome (NS) is associated with a range of complications, both disease-related and treatment-induced. Infections are a significant concern, with peritonitis and cellulitis being common due to the immunocompromised state induced by proteinuria and hypoalbuminemia. Cellulitis, often caused by bacteria such as Streptococcus and Staphylococcus, is marked by redness, swelling, and pain, and requires prompt antibiotic treatment[36]. Thromboembolic events, including venous thromboembolism and pulmonary embolism, are also prevalent due to hypercoagulability associated with NS[37]. Growth retardation is another complication, often exacerbated by long-term corticosteroid use, which can lead to short stature and other growth issues[38]. Corticosteroids, the mainstay of NS treatment, are linked to several adverse effects, including hypertension, obesity, osteoporosis, and behavioral disturbances[38,39]. These side effects necessitate the use of steroid-sparing agents to maintain remission and minimize long-term impacts[38]. Additionally, NS can lead to cardiovascular complications such as hyperlipidemia, which further complicates the disease management[40]. The risk of acute kidney injury and other renal complications is heightened during disease relapses, emphasizing the need for regular monitoring and early intervention[41]. Overall, the management of pediatric NS requires a comprehensive approach to address both the disease and its complications, with a focus on minimizing the side effects of long-term corticosteroid therapy to improve patient outcomes[8,37].

Future perspectives

The future management of pediatric nephrotic syndrome (NS) is poised for significant advancements through the integration of genetic testing, personalized medicine, artificial intelligence, novel therapeutics, and improved vaccination strategies. Genetic testing plays a crucial role, especially for congenital and steroid-resistant cases, as it helps identify monogenic causes in approximately 30% of childhood-onset steroid-resistant nephrotic syndrome (SRNS) cases, thereby guiding treatment decisions and avoiding unnecessary procedures like kidney biopsies[42,43]. The use of next-generation sequencing (NGS) and whole-exome sequencing (WES) has enhanced the diagnostic accuracy for these conditions, allowing for early and precise interventions[44,45]. Personalized medicine is further advanced by the identification of specific biomarkers and molecular diagnostics, which enable tailored therapeutic strategies based on individual genetic profiles. This approach is complemented by the development of patient-specific kidney organoid models and pharmacogenomics, which promise to refine treatment options and improve outcomes. Artificial intelligence (AI) is increasingly being integrated into prediction and treatment planning, offering potential improvements in the accuracy of prognosis and the customization of treatment regimens[46]. In terms of therapeutics, novel immunomodulators and biologics, such as monoclonal antibodies and stem cell therapies, are being explored to address the challenges of SRNS, which is often resistant to conventional treatments[47]. These advancements are crucial for reducing the progression to end-stage renal disease (ESRD) and improving the quality of life for affected children[43]. Additionally, improved vaccination strategies are essential for immunocompromised patients, ensuring they are

protected against infections without exacerbating their underlying condition[6]. Collectively, these innovations represent a comprehensive approach to managing pediatric nephrotic syndrome, emphasizing early diagnosis, personalized treatment, and preventive care to enhance patient outcomes[6,48,49].

Conclusion

Pediatric nephrotic syndrome remains a complex yet manageable condition, with significant strides made in its diagnosis and treatment. Advances in understanding podocyte injury and immune dysregulation have paved the way for targeted therapies, while genetic testing and personalized medicine offer hope for more precise interventions. Despite challenges such as relapses and treatment-related complications, the integration of novel therapeutics, artificial intelligence, and improved vaccination strategies promises a brighter future for affected children. By fostering international collaboration and prioritizing research into biomarkers and steroid-sparing agents, the medical community can transform the management of nephrotic syndrome, ensuring better outcomes and enhanced quality of life for young patients worldwide.

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