

The Need for a Children's Oncology Group–Oriented Approach to Advance the Care of Children with Idiopathic Nephrotic Syndrome

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Idiopathic nephrotic syndrome (INS) affects 16 per 100,000 children, making this condition one of the most common childhood kidney diseases. Because of the significant complications associated with INS and its treatments in children, childhood INS remains a daunting challenge for children, families, and medical professionals. Amazingly, the approach to childhood INS today is still based on decades-old pivotal studies that were impressive in scope but have limited applicability to the clinical challenges faced by pediatric nephrologists today. These foundational studies began with an international collaborative effort sponsored by the International Study of Kidney Disease in Children (ISKDC) (1). From 1967 to 1974, 521 children with new-onset INS underwent renal biopsies and standard prednisone treatment to demonstrate that normalization of urine protein excretion with 8 wk of corticosteroid therapy is predictive of minimal-change nephrotic syndrome (2). As a result, pediatric nephrologists began using the initial therapeutic response to glucocorticoids to guide the subsequent evaluation and therapy for children who present with INS.

This sentinel work of the ISKDC was followed by a series of studies by the *Arbeitsgemeinschaft für Pädiatrische Nephrologie*, which together form the basis for modern practice treatment of children with INS (3–5). Of note, these landmark studies are also almost 20 yr old, but the clinical characteristics and challenges of children who present with INS have clearly changed in recent decades. For example, the incidence of FSGS in children with INS has increased dramatically (6); children in the United States have a rapidly increasing prevalence of obesity and type 2 diabetes, which may be exacerbated by our standard treatments with glucocorticoids (7); and the importance of demographic status and treatment compliance in patient outcomes is being increasingly recognized (8).

In 2008, a survey regarding treatment of childhood INS among North American pediatric nephrologists at 10 US centers was performed. That survey highlighted significant disparities among practitioners, including wide practice variations in

even the most fundamental aspects of care, such as the management of initial presentations, relapses, and steroid resistance in children with INS (9). In this context, the North American Children's Nephrotic Syndrome Consensus Conference was convened to develop updated evidence- and opinion-based recommendations for the evaluation and treatment of children with INS for North American pediatric nephrologists (10). In that consensus conference report, only a limited number of treatment recommendations could be based on class 1 evidence; recommendations related to extent of evaluation, monitoring for complications, and treatment for steroid-dependent and steroid-resistant NS almost all were based on small case series and expert opinion. Of note, despite the 344 published original investigations reviewed during this process, only three of the 86 articles cited in that consensus conference report involved >10 yr of outcome follow-up in children with INS. This sobering reality emphasizes the value of the study of Kyrieleis *et al.* (11) in this month's *CJASN*, which addresses the long-term outcome of frequently relapsing minimal-change nephrotic syndrome in children and focuses on the effectiveness of continued immunosuppression and the complications of these agents in this population. In this report, at least 10 yr of follow-up is provided for all 15 patients with steroid-responsive INS that presented in childhood. All had at least one relapse after 16 yr of age, and the long follow-up offers insights into the ongoing treatment responsiveness in these children. Although this article indicates that corticosteroid responsiveness may persist for many years in some children, particularly in combination with second-line agents such as calcineurin inhibitors, complications are common and the risk-benefit ratios of treatments are unexplored. Although this report is only observational, it does reinforce the value and usefulness of detailed long-term observational studies of these children. Because the vast majority of our patients will survive to adulthood, there is a distinct need for studies of the long-term outcomes (and complications) of our therapies to help define the lifelong consequences of INS and its treatment in children. For too long, studies of treatment of children with INS have been limited to single centers and short-term perspectives, which inherently preclude us from gaining insight about important long-term issues.

One important take-home message from this article is the need for continued efforts to design and execute long-term

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studies that define the best evaluation and treatment strategies for children with INS. In light of the recent publications noted, the lack of good evidence and the need for prospective studies to determine the best current and future treatments for INS in children needs to be reemphasized. We believe that the only method to develop convincing evidence to drive future improvements in clinical care for these patients will be through careful prospective, multicenter, observational and interventional studies that address alternative treatment strategies and include comprehensive follow-up of children with INS. This process has been exceptionally productive for the Children's Oncology Group (COG) (<http://www.curesearch.com>) in the United States. This is a clinical trial cooperative group that is composed of investigators from 238 institutions that are supported by the National Cancer Institute to study childhood cancers (12). COG was formed in 2000 from the merger of four independent cooperative study groups, and it and its original members have been conducting prospective, randomized clinical trials since 1956 to study best treatments, quality of life, and impact of cost on families of children with cancer. Lessons learned from COG include (1) the power of sequential comparisons of novel *versus* standard-of-care treatments in prospective clinical trials to drive improvements in patient outcomes, (2) the critical importance of an established clinical trial infrastructure to enable repeated clinical trials with consistent and reliable participation among member centers, and (3) the essential need to combine patient results from multiple institutions to overcome the innate challenges of low patients numbers in pediatric studies. Although such efforts are extensive and the rewards will take time and patience, we believe that it will be through these types of prospective, multicenter, collaborative studies that we will be best able to advance the care of childhood INS, as well as other pediatric kidney diseases.

Disclosures

None.

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See related article, "Long-Term Outcome of Biopsy-Proven, Frequently Relapsing Minimal-Change Nephrotic Syndrome in Children," on pages 1593–1600.