Canadian Society of Nephrology/ Société canadienne de néphrologie CSN/SCN

CANADIAN JOURNAL OF KIDNEY HEALTH AND DISEASE
Journal canadien de la santé et de la maladie rénale

Original Research Article

Setting New Directions for Research in Childhood Nephrotic Syndrome: Results From a National Workshop

Canadian Journal of Kidney Health and Disease
Volume 4 : 1–7

DOI: 10.1177/2054358117703386
journals.sagepub.com/home/cjk
SAGE

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Abstract

Background: We report on the proceedings of a national workshop held in Canada with the aims to identify priorities for research in childhood nephrotic syndrome and to develop a national strategy to address these priorities.

Methods: A diverse group of participants attended the meeting, including patients, family members, researchers, and health care providers. We used small group discussions to explore priorities as perceived by patients and families and by health care providers and researchers.

Results: Research evaluating glucocorticoid minimization or glucocorticoid-sparing regimens was a consistent theme in the patient and family discussion group. Families also indicated the need for precise prognostic information at diagnosis, more information to help them choose the best available therapy, and more resources for disease management. Health care providers emphasized the importance of better disease characterization including genotyping and phenotyping patients, better understanding the pathogenesis, and the need of providing targeted therapy and precise prognostic information.

Conclusions: These priorities will inform the development and future directions of the Canadian Childhood Nephrotic Syndrome (CHILDNEPH) project, a national research initiative to improve care and outcomes of patients with childhood onset nephrotic syndrome.

Abrégé

Contexte: Nous rapportons les travaux d'un atelier national qui s'est tenu au Canada et qui avait pour objectif de définir les priorités dans la recherche sur le syndrome néphrotique de l'enfant et d'élaborer une stratégie nationale pour répondre à celles-ci.

Méthodologie: Un groupe diversifié de participants a assisté à la réunion, notamment des patients, des membres de leurs familles, des chercheurs et des fournisseurs de soins de santé. Nous avons utilisé de petits groupes de discussion pour explorer les priorités telles que perçues par les patients et leurs familles, de même que par les fournisseurs de soins et les chercheurs.

Résultats: La recherche évaluant la minimisation des glucocorticoïdes ou les traitements substituant les glucocorticoïdes a été un thème récurrent dans le groupe de discussion constitué des patients et de leurs familles. De plus, les familles ont souligné le besoin d'obtenir des informations précises sur le pronostic au moment du diagnostic. Ils ont notamment parlé d'obtenir plus d'informations pour aider à choisir le meilleur traitement disponible et davantage de ressources pour la gestion de la maladie. Les fournisseurs de soins de santé ont quant à eux insisté sur l'importance d'une meilleure caractérisation de la maladie, incluant le génotypage et le phénotypage des patients, une meilleure compréhension de la pathogenèse de la maladie et la nécessité de fournir des thérapies ciblées et des renseignements précis sur le pronostic.

Conclusions: Ces priorités guideront le développement et les futures orientations du *Canadian Childhood Nephrotic Syndrome project* (CHILDNEPH), une initiative de recherche nationale visant à améliorer les soins et les résultats des patients atteints du syndrome néphrotique apparu durant l'enfance.

Keywords

childhood nephrotic syndrome, workshop, priority setting, patient engagement

Received October 24, 2016. Accepted for publication February 13, 2017.

What was known before

Idiopathic nephrotic syndrome is the most common kidney disease in children. It presents with proteinuria, with consequent hypoalbuminemia and generalized edema. Many patients respond to glucocorticoids (GC), which is the first-line therapy, achieving remission from proteinuria. However, many of these GC-sensitive patients will require repeated courses of treatment due to relapse. Chronic exposure to GC results in significant toxicity, including obesity, growth retardation, hypertension, poor bone health, and cosmetic effects.

What this adds

The proceedings of this multidisciplinary stakeholder workshop identify patient and health care provider priorities for nephrotic syndrome research. The development of GC-minimizing therapeutic strategies as well as the establishment of clinical registries and biorepositories to facilitate research into pathogenesis of disease emerged as top priorities.

Introduction

Idiopathic nephrotic syndrome is a common acquired kidney disease in children, affecting approximately 16 of 100,000 children worldwide.[1] It has considerable morbidity due to recurring episodes of proteinuria, but also from its treatment.[2] Lack of understanding of the pathogenesis of nephrotic syndrome, a histologically, genotypically, and phenotypically heterogeneous condition, and lack of curative drug therapy are major barriers to improving care for children with this condition.[3-6] Furthermore, substantial practice variation between physicians and centers can lead to variable adverse effect profiles in patients and patient/family dissatisfaction.

In a Canadian survey of pediatric nephrologists, we determined that the development of evidence-based consensus protocols for management of nephrotic syndrome was deemed a top priority.[7] With this mandate, we designed a national study (The Canadian Childhood Nephrotic Syndrome [CHILDNEPH] project) to develop a transformative model of care by building a national longitudinal observational cohort which allows us to study variation of care, while also incrementally building infrastructure needed to further our understanding of pathogenesis and patient-oriented outcomes.[8] The project's goal is to expand the research program into a clinical and translational research network that will address priority research questions using both observational cohort and interventional study designs, with strong engagement from patients, clinicians, and basic, clinical, and translational researchers. To achieve this goal, we convened a 1.5-day workshop in Canada, with national and international stakeholders including patients and families, to establish a Canadian strategy for research in childhood nephrotic syndrome.

Methods

Planning Workshop Summary

Context. Canada has a population of more than 35 million individuals, with tremendous geographic, ethnic, and socioeconomic diversity.[9] Canadians have the privilege of a single-payer universal access health system for all necessary medical care. Tertiary pediatric nephrology care is delivered in 13 major academic pediatric health centers within 7 Canadian provinces. Both urban and rural communities are serviced by community pediatricians, and some larger urban communities have pediatric nephrologists practicing outside academic health centers.

The CHILDNEPH project involves 12 of the 13 academic pediatric nephrology centers across Canada (see Figure 1). The longitudinal cohort study is designed with patients nested within their physicians, and physicians nested within their center, to understand factors influencing variability in care at center-, physician-, and patient-levels. To date, over 180 patients and 44 physicians have consented to participate in this study, which is funded by the Canadian Institutes for Health Research (grant MOP-142271), the Kidney Foundation of Canada (grant KFOC 140020), and the University of Calgary. Funding for the workshop was provided by planning grants from the Kidney Foundation of Canada/Canadian Knowledge Translation and Generation Network (KFOC 150001) and the Canadian Institutes for Health Research (grant PNI-134070).

Ethics approval. The workshop methods were approved by the University of Calgary Conjoint Health Research Ethics

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Figure 1. Canadian Childhood Nephrotic Syndrome project collaborating centers.
Note. Centers listed west to east: BC Children's Hospital, Vancouver, British Columbia; Alberta Children's Hospital, Calgary, Alberta; Stollery Children's Hospital, Edmonton, Alberta; Royal University Hospital, Saskatoon, Saskatchewan; Children's Hospital, Winnipeg, Manitoba; London Health Sciences Centre, London, Ontario; McMaster Children's Hospital, Hamilton, Ontario; SickKids Hospital, Toronto, Ontario; Children's Hospital of Eastern Ontario, Ottawa, Ontario; Montreal Children's Hospital, Montréal, Québec; Centre Hospitalier Universitaire Sainte-Justine, Montréal, Québec; IWK Health Centre, Halifax, Nova Scotia.

Board. All participants signed a consent form allowing the workshop organizers to record audio conversations in small groups and transcribe notes for publication in this report.

Participants. All CHILDNEPH investigators and study coordinators were invited to participate in the 1.5-day workshop in Calgary, Canada. They were joined by researchers with expertise in basic science, clinical epidemiology and clinical trials, translational research, and qualitative research methodology relevant to nephrotic syndrome. CHILDNEPH investigators were asked to identify and invite patients with nephrotic syndrome and parents interested in providing the patient/parent perspectives. All participants received reimbursement for their expenses to attend the meeting but were not remunerated for participation.

Agenda. The workshop began with patient and family testimonials to allow participants to develop an understanding of the patient/family perspective of the disease, its burden, and subjective outcomes. Participants were then divided into 2 groups: patients/families and care providers/researchers. A moderator with training in peer-to-peer patient engagement research (www.pacerinnovates.ca) engaged the patient and family group, with assistance from an experienced qualitative researcher (S.Sc.). The researcher and care provider group was moderated by 2 of the core investigators of the Project (S.Sa., C.Mo.). The question for the small group discussion was, "What are the most important issues that the research community should address in the area of childhood nephrotic syndrome?" All conversations of the free-flowing discussions were audiotaped and transcribed and also summarized verbally and in note form.

After the meeting, the moderators (L.R., S.Sc., S.Sa., C.Mo.) reviewed the audio transcripts and written notes, and grouped the discussion and priorities into broad themes (eg, diagnostic concerns, treatments, cures, etc) using thematic analysis. Thematic analysis is a flexible approach that enables a detailed account of data.[10] It involves the identification of common threads across the data (ie, interview data, discussions, focus groups). Due to time constraints, the priorities were not rank ordered by the participants.

On the second day of the symposium, scientific presentations addressed the current understanding of the pathogenesis of nephrotic syndrome. Participants then split into 4 work groups according to self-declared interest and expertise. The aims were to start developing a comprehensive strategy that would strengthen the nascent Canadian research network for childhood nephrotic syndrome and to consider observational and interventional studies to generate new knowledge and knowledge translation strategies to optimize clinical care.

Work groups focused on establishing (1) a national registry, (2) a patient/parent engagement forum, (3) a basic and translational research program, and (4) clinical trial questions. Participants were specifically asked (1) what needs to be done and (2) who should lead the proposed initiatives. The discussion was not audio recorded, but detailed notes were kept in each work group for the workshop report.

Results

Fifteen clinicians/site investigators, 5 study coordinators, 10 parents of children with nephrotic syndrome, 2 patients, 8 project investigators/researchers, and 1 member of the media attended the workshop. Participants and their roles are listed in Table 1.

Patient and Health Care Provider Priorities

The moderated discussion from the first day of the symposium was summarized into key research priorities according to patients and care providers.

Participating parents and 1 adolescent patient unanimously expressed GC minimization or avoidance protocols as their top priority for the treatment of nephrotic syndrome. They discussed the need to develop drugs with lesser toxicity and questioned why physicians do not use GC-sparing drugs earlier in the treatment of nephrotic syndrome and avoid side

Table 1. Characteristics of Workshop Participants (N = 40).

Characteristics	n (%)
Role	
Patients	2 (5)
Families	10 (25)
Researchers	18 (45)
Clinicians	5 (12.5)
Coordinators	5 (12.5)
Geographical areas[a]	
West	19 (47.5)
Central	9 (22.5)
East	10 (25)
Other	2 (5)
Primary language	
English	30 (75)
French	8 (20)
Dutch	2 (5)

[a]West: Alberta, British Columbia; Central: Ontario, Manitoba; East: Quebec, Nova Scotia; Other: Netherlands.

effects by prednisone and other immune suppressants such as cyclophosphamide or cyclosporine.

Group members emphasized the need to generate information that will predict the course of the disease early on and allow the suppression of (frequent) relapses. Connection and community among patients and families were found to be lacking, and the group expressed a desire to create support groups. Self-management tools to assist parents caring for children with nephrotic syndrome, eg, to track medications and relapses, were also deemed important.

One parent of a young child with nephrotic syndrome made the following statement regarding her experience attending this workshop:

> It felt like a great opportunity to be invited by [Principal Investigator] to attend [this workshop] in Calgary, an opportunity to share my experiences and to support the valuable work being done by this consortium. For me the symposium created belief that this group of people, doctors and patients, were determined to take up the fight against nephrotic syndrome together. Patient stories set the stage for the rest of the program, which was positive, action oriented and felt like a genuine partnership between patients and doctors.

Another parent of an older child with nephrotic syndrome said that he "[looks] forward to further collaboration that hopefully leads to meaningful impact on the lives of children dealing with nephrotic syndrome."

The health care provider group indicated careful characterization of the clinical phenotype of the disease and investigations into the pathogenesis and optimization of its therapeutic management as top priorities (which drug at which time and what dose?). This group also prioritized outcome studies, in particular, outcomes after transfer to adult care. Other aspects were to reduce variation in patient management (treatment of edema including use of albumin infusions). Nurses in the group emphasized the importance of developing standardized procedures for nephrotic syndrome teaching and sought to understand whether teaching and provision of self-management materials influence patient outcome. Priorities grouped according to thematic areas are shown in Tables 2 and 3.

Table 2. Research Priorities in Nephrotic Syndrome According to Pediatric Patients and Family Perspective.

Themes	Brief summary of comments
Medications	New nonsteroid therapies or steroid minimization in treatment protocols
	New medications with fewer side effects
	Need better information regarding efficacy of medications to assist in decision making
	Need better prognostic information regarding steroid response and relapse frequency at start of disease
	Understand long-term side effects of medications
	Investigate complementary and alternative therapies
Predicting relapses	Identify markers to predict relapse
	Prevent relapses if possible
Underlying pathogenesis	Understanding of immune processes, triggers of disease
	Develop more targeted therapy and possibly a "cure"
Connection and community	Resources for understanding disease in clear, plain language suitable for lay readers
	Need a Canadian patient/family community to allow families to connect with each other
	Putting experiences into perspective for patients/families
Self-management	App or tool to keep track of urine results, steroid dosing, anthropometric measurements
	Information (decision tool) to help make decisions regarding medications
	Transition from pediatric to adult care
	Road map or navigator tool to assist families through the "journey" of nephrotic syndrome

Crafting a National Research Strategy

On the second day of the symposium, the participants were divided into 4 work groups (based on interest and expertise) and developed work plans for a national research strategy for nephrotic syndrome. The work group discussions are summarized below.

Establishing a national nephrotic syndrome patient registry. Patient registries can facilitate research in rare diseases such as nephrotic syndrome, where individual centers have

Table 3. Research Priorities in Nephrotic Syndrome According to Health Care Providers and Researcher Perspective.

Theme	Comments
Characterization of disease	Precision diagnostics for prognosis (steroid response, frequency of relapses) Predictors of response to nonsteroidal drugs Role of puberty, hormones Differences in incidence of disease by gender
Triggers for relapses	Predictors of relapses (eg, food allergens, immunization, viral triggers)
Management of disease	Is steroid the best treatment for first presentation, and are there alternatives? Best treatment protocols for relapses What are the best steroid sparing drugs, and when to start and which drug? Are there novel drugs or old repurposed drugs that can be investigated for use?
Optimal symptomatic management	For edema, and when to use IV albumin and diuretics
Renal biopsy	What further prognostic information can a biopsy give us and when should it be done?
Educational approaches	How important is structured education regarding disease course, medications, and side effects in improving adherence?
Long-term outcomes	What are the long-term health outcomes, and how can we predict these outcomes?

few eligible patients. Leveraging the multicenter collaborative network and infrastructure developed for the national observational cohort (CHILDNEPH study), the work group set a goal to develop a comprehensive prospective patient data registry with linked clinical and biological data. The patient registry will be used to document both long- and short-term outcomes including relapse rates and other patient outcomes, including exposure to GC and GC-sparing treatments. The patient registry infrastructure will assist in identifying patients and provide recruitment and sample size estimates needed for future clinical trials. Such a registry will also be valuable to develop quality indicators (processes of care and outcome measures). Although registries are labor intensive and expensive to maintain, a registry with a large patient cohort is essential to generating transformative knowledge.

During the planning meeting, we developed a framework for the creation and maintenance of a Canadian registry for children with first presentation of childhood nephrotic syndrome. The plan includes the collection of pertinent demographic and clinical data using a population-based cohort. The work group called for common definitions for outcomes, common time points for assessment, and relevant disease phenotyping. Exploiting the universal health care system, the registry could be linked to provincial and national health administrative data sets, supplemented with clinical health service utilization data. Acknowledging the existence of several established registries, the group sought to harmonize our registry with others to compare data originating from other jurisdictions and countries.

The main challenges for this type of initiative are funding and comprehensive provincial and cross-national collaboration. For governance, the work group recommended setting up steering and scientific advisory committees with all relevant stakeholders, including representation from patients and parents.

Patient/parent group to inform the research program. Developing a patient-oriented research program with strong engagement from patients and parents was determined to be a high priority for this network. Attending patients/families planned to create an advocacy and support group that would further liaise with the research team to inform and guide research activities. Several patient-oriented projects were suggested including (1) development of tools (eg, smartphone applications) for relapse and day-to-day symptom tracking, (2) development of a patient support group and opportunities for families to connect online and in person, (3) better involvement of primary physicians in the care of patients with nephrotic syndrome, and (4) development of a road map and other tools for parents to project disease course and treatment. The parents expressed a desire to have all materials translated into French and other languages.

Integration of basic and translational research components. To facilitate the discovery of diagnostic tools and develop rational, individualized therapies, future clinical and basic research programs should address phenotype/genotype relationships. A national registry will be essential to establish and maintain a biorepository for serum, plasma, lymphocytes (peripheral blood mononuclear cells), DNA, and urine specimens. Basic science investigators with expertise in glomerular disease, podocyte biology, and nephrotic syndrome were key participants in this group. Work group members proposed not to replicate other initiatives but to focus efforts on specific, novel features of the biorepository: (1) collection of biological samples at first presentation of nephrotic syndrome (many repositories collect samples only at first biopsy); however, collection of the first blood/urine specimens in the proteinuric phase prior to the initiation of any immunosuppressive treatment, typically prednisone, is critical for the envisioned biological studies; (2) collection of paired blood/urine samples in relapse and remission, ideally free of medications.

Themes of investigation that could stem from this biorepository include precise diagnostics; prediction of treatment response, relapse, and chronic kidney disease progression; and understanding the mechanisms underlying the development of the disease. Specific examples are (1) targeted screening for known gene mutations; discovery of novel genes linked to nephrotic syndrome using whole exome

sequencing or whole genome sequencing, (2) pharmacogenomics studies exploring and applying responsiveness to GC and mycophenolate mofetil, (3) T-cell immunophenotyping using paired samples before and after proteinuria relapse or administration of therapeutics, viral infection, or spontaneous remission, (4) discovery proteomics of the elusive permeability factor using urine/blood samples. Experts in each area were identified. Some of the discoveries can be validated in animal or cell culture models within the Canadian nephrology research community. Finally, an established biorepository will enhance the quality of future clinical trials.

Clinical trial work group. The work group was composed of Canadian clinicians with interest and expertise in nephrotic syndrome and an invited researcher from the Netherlands (M.S.) with expertise conducting clinical trials in nephrotic syndrome. Members deliberated possible trial questions and examined their merits and feasibility. The existing longitudinal CHILDNEPH study has developed infrastructure and a network of collaborating centers to facilitate initiation of clinical trials with the ability to ask the right question at the right time. The work group took into consideration the first patient priority, GC minimization. They identified various barriers to trials including variation in practice and obtaining buy-in for clinical trial intervention arms from pediatric nephrologists across Canada. The group deliberated whether prednisone exposure can be reduced and how this may impact overall relapse rates in light of recent evidence that questions the widely held belief that prolonged prednisone treatment is beneficial.[9,11,12] The group listed obstacles (and facilitators) of clinical trials, such as patient/family and clinician buy-in and the need for multicenter (and possibly international) participation to power trials adequately.

Discussion

We summarize the proceedings of a first CHILDNEPH project symposium and planning meeting to develop and align patient and investigator goals and priorities. The most important and consistent message we heard from patients and families was the wish to minimize GC exposure in the treatment of nephrotic syndrome. Families also demanded precise prognostic information at the time of diagnosis and more information at decision points to help them choose best available therapies. Health care providers expressed the importance of better disease characterization including genotype and phenotype correlation, better understanding the pathogenesis of nephrotic syndrome, and the ability to provide targeted therapy and precise prognostic information.

An overarching goal of this planning meeting was to develop a comprehensive strategy to strengthen the novel, nascent Canadian research network for childhood nephrotic syndrome. Leading into this planning meeting, the network consisted primarily of clinical and health services researchers. Engaging basic and translational researchers during this workshop added expertise and depth to the network; 2 consequences are plans to develop a biorepository and to establish cross-disciplinary collaborations. Patient-oriented research is a high priority in the current Canadian research environment. The meeting offered many opportunities to listen and learn among patients, clinicians, and researchers; it set the tone for the CHILDNEPH project moving forward. Transforming the current observational study and network into a national registry of children with nephrotic syndrome has the potential to facilitate knowledge generation for this rare disease with respect to basic and translational research, improvement of clinical practice, and to build infrastructure for future clinical trials.

This is the first time a Canadian work group of interested individuals has convened to advance the care of childhood nephrotic syndrome in Canada. The project is the first of its kind bringing almost all Canadian centers together and obtaining national funding. The concept is comprehensive, enabling a productive dialogue between patients and families, clinical practitioners and researchers. It provided a unique perspective to guide patient- and outcome-oriented research in this relevant field. Importantly, participants represented a diverse spectrum of clinical experience and professional expertise, regional distribution, and language (English and French).

In contrast to the existing nephrotic syndrome networks and registries, the CHILDNEPH registry focuses on collecting clinical and biological data from the onset of nephrotic syndrome in mostly young children and on GC-sensitive nephrotic syndrome, before a kidney biopsy. Other registries collecting data on patients with childhood- and adult-onset nephrotic syndrome are (1) National Registry of Rare Kidney Diseases [Radar] in the United Kingdom; (2) Podonet, a European consortium to investigate diseases affecting the podocyte, collecting data from steroid resistant patients; (3) Nephrotic Syndrome Study Network (NEPTUNE), a multicenter study in United States and Canada, collecting data from patients with nephrotic syndrome at the time of kidney biopsy; and (4) CureGN, a multicenter observational study of adults and children with nephrotic syndrome who have had a kidney biopsy in the past 5 years. Therefore, the CHILDNEPH patient registry is uniquely positioned to make significant contributions to research and practice improvement in nephrotic syndrome.

Limitations

The participants were limited due to selection of patients and families who were able to travel to Calgary. We did not follow a set procedure to elicit priorities (eg, James Lind Alliance methods[13]) but permitted free-flowing discussion and review of themes generated by qualitative thematic analysis. The 1.5-day workshop did not allow sufficient time to rank order priorities.

The priorities or thematic areas as identified in this workshop will be considered in future endeavors to develop research questions in nephrotic syndrome. Synthesis of this

process into the present report will also help engage patients, researchers, and clinicians nationally and internationally in future research endeavors.

Conclusions

A multidisciplinary stakeholder workshop and planning meeting to determine future research priorities helped us set new directions for nephrotic syndrome research in Canada. Glucocorticoid-sparing and minimization and establishment of a clinical registry and biorepository for patients with GC-sensitive nephrotic syndrome emerged as top priorities. Establishing the outlined infrastructure will facilitate the research consortium to develop standardized data and biological sample collection procedures, and also help to address priority research questions in a timely fashion targeting pathogenesis, therapeutics, and improving overall clinical management in nephrotic syndrome.

Ethics Approval and Consent to Participate

The workshop methods were approved by the University of Calgary Conjoint Health Research Ethics Board.

Consent for Publication

All participants signed a consent form allowing the workshop organizers to record audio conversations in small groups and transcribe notes for publication in this report. The final version of the manuscript was reviewed and approved by all authors.

Availability of Data and Materials

The materials analyzed during the study (audio transcripts and written notes) are available from the corresponding author on reasonable request.

Acknowledgments

The Canadian Childhood Nephrotic Syndrome Team members and workshop attendees are as follows: Steven Arora, MD, McMaster Children's Hospital, Hamilton, Canada; Heather Beanlands, RN, PhD, Ryerson University, Toronto, Canada; Geneviève Benoit, Université de Montréal; Panojot Bifsha, PhD, Université de Montréal, Montréal, Canada; Martin Bitzan, McGill University, Montreal, Canada; Allison Dart, MD, University of Manitoba, Winnipeg, Canada; Allison Eddy, MD, University of British Columbia, Vancouver, Canada; Robin Erickson, MD, Royal University Hospital, Saskatoon, Canada; Janusz Feber, MD, Children's Hospital of Eastern Ontario, Ottawa, Canada; Guido Filler, MD, London Health Sciences Centre, London, Canada; Pavel Geier, MD, Children's Hospital of Eastern Ontario, Ottawa, Canada; Silviu Grisaru, MD, University of Calgary, Calgary, Canada; Elie Haddad, MD, PhD, Université de Montréal, Montréal, Canada; Cherry Mammen, MD, University of British Columbia; Julian Midgley, University of Calgary, Calgary, Canada; Catherine Morgan, University of Alberta, Edmonton, Canada; Daniel Muruve, MD, PhD, University of Calgary, Calgary, Canada; Alberto Nettel-Aguirre, PhD, PStat, University of Calgary, Calgary, Canada; Rulan Parekh, MD, MSc, SickKids Hospital, Toronto, Canada; Maury Pinsk, MD, University of Manitoba, Winnipeg, Canada; Laurel Ryan, University of Calgary, Canada; Susan M. Samuel, University of Calgary, Canada; Shannon Scott, University of Alberta, Canada; Tomoko Takano, McGill University, Canada; James Tee, MD, IWK Health Centre, Halifax, Canada; Andrew Wade, MD, PhD, University of Calgary, Calgary, Canada; Michael Zappitelli, MD, McGill University, Montreal, Canada; Michiel Schreuder, MD, PhD, Radboud University, Nijmegen, the Netherlands.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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