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KDIGO Commentary

Canadian Society of Nephrology Commentary on the 2012 KDIGO Clinical Practice Guideline for Glomerulonephritis: Management of Nephrotic Syndrome in Children

Susan Samuel, MD, MSc, FRCPC,[1] Martin Bitzan, MD, FRCPC,[2] Michael Zappitelli, MD, FRCPC,[2] Allison Dart, MD, FRCPC,[3] Cherry Mammen, MD, FRCPC,[4] Maury Pinsk, MSc, MD, FRCPC,[5] Andrey V. Cybulsky, MD, FRCPC,[6] Michael Walsh, MD, FRCPC,[7] Greg Knoll, MD, FRCPC,[8] Michelle Hladunewich, MSc, MD, FRCPC,[9] Joanne Bargman, MD, FRCPC,[9] Heather Reich, MD, FRCPC,[9] Atul Humar, MD, FRCP,[10] and Norman Muirhead, MD, FRCPC, FRCP, Ed[11]

The KDIGO (Kidney Disease: Improving Global Outcomes) clinical practice guideline for management of glomerulonephritis was recently released. The Canadian Society of Nephrology convened a working group to review the recommendations and comment on their relevancy and applicability to the Canadian context. A subgroup of pediatric nephrologists reviewed the guideline statements for management of childhood nephrotic syndrome and agreed with most of the guideline statements developed by KDIGO. This commentary highlights areas in which there is lack of evidence and areas in need of translation of evidence into clinical practice. Areas of controversy or uncertainty, including the length of corticosteroid therapy for the initial presentation and relapses, definitions of steroid resistance, and choice of second-line agents, are discussed in more detail. Existing practice variation is also addressed.

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Clinical practice guidelines provide a comprehensive assessment of the medical literature and the synthesis of that information into a practical and meaningful context for the practicing physician. In pediatric nephrology, clinical practice guidelines are few and existing guidelines are rarely adapted and contextualized for local use in many countries.

KDIGO (Kidney Disease: Improving Global Outcomes) was established in 2003 with the stated mission of "improving the care and outcomes of kidney disease patients worldwide through the development and implementation of clinical practice guidelines."[1] Since the launch of KDIGO, comprehensive clinical practice guidelines have been developed and published for chronic kidney disease (CKD)–mineral and bone disorder,[2] transplantation,[3] blood pressure in CKD,[4] acute kidney injury,[5] anemia in CKD,[6] and hepatitis C virus infection in CKD.[7] The KDIGO clinical practice guideline for glomerulonephritis[8] comprises a systematic review and synthesis of the relevant literature as of January 2011 with the addition of new data available as of November 2011. This guideline also devotes sections to glomerular diseases of childhood, such as childhood nephrotic syndrome, making the guideline relevant for a wide range of pediatric clinicians.

The Canadian Society of Nephrology (CSN) applauds KDIGO's efforts to prepare comprehensive and broadly applicable clinical practice guidelines for the international nephrology community. However,

From the [1]Division of Pediatric Nephrology, Department of Pediatrics, University of Calgary, Calgary, Alberta; [2]Division of Pediatric Nephrology, Department of Pediatrics, McGill University, Montreal, Quebec; [3]Department of Pediatrics and Child Health, Section of Pediatric Nephrology, University of Manitoba, Winnipeg, Manitoba; [4]Department of Pediatrics, Division of Pediatric Nephrology, University of British Columbia, Vancouver, British Columbia; [5]Department of Pediatrics, Division of Pediatric Nephrology, University of Alberta, Edmonton, Alberta; [6]Department of Medicine, McGill University, Montreal, Quebec; [7]Division of Nephrology, Department of Medicine, McMaster University, Hamilton; [8]Division of Nephrology, Department of Medicine, University of Ottawa, Ottawa; [9]Department of Medicine, University of Toronto, Toronto, Ontario; [10]Transplant Infectious Diseases, University of Alberta, Edmonton, Alberta; and [11]Division of Nephrology, Department of Medicine, Western University, London, Ontario, Canada.

Address correspondence to Susan Samuel, MD, MS, FRCPC, Division of Pediatric Nephrology, Department of Pediatrics, University of Calgary, 2888 Shaganappi Trail NW, Room C4-603, Calgary, Alberta T3B 6A8, Canada. E-mail: s.samuel@albertahealthservices.ca

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the CSN, the Canadian Association of Pediatric Nephrologists (CAPN), and other professional groups such as KDOQI (Kidney Disease Outcomes Quality Initiative) agree that local factors warrant consideration when using clinical practice guidelines to guide care. Therefore, the CSN has established working groups to review KDIGO clinical practice guidelines and to comment on their applicability to Canadian health care and, in this article, to child health care.

REVIEW AND APPROVAL PROCESS FOR CSN COMMENTARIES

The CSN guidelines committee, having concluded that the KDIGO clinical practice guideline for glomerulonephritis was a priority for comment, set up working groups in summer 2012 to prepare 2 commentaries, one on the guideline statements relevant to children and another regarding guideline statements relevant to adults (see Cybulsky et al[9]). Individual members of CSN were invited and named to the working group by virtue of their interest and expertise, in a process that took careful note of potential conflicts of interest. This commentary, focused on the management of nephrotic syndrome in children, was under development through fall 2012, using the original KDIGO glomerulonephritis clinical practice guideline[8] and materials referenced in the report as information sources. The working group collaborated by regular teleconferences, and all authors approved the text of the final draft. Every effort was made to reach consensus, but when this was not possible, all viewpoints were discussed. CSN sent the final draft out to Canadian pediatric nephrologists for peer review, and the document was revised accordingly, prior to final ratification by the CSN guidelines committee and CSN executive.

STRUCTURE OF THIS COMMENTARY

This document does not comment on all the KDIGO recommendations for glomerulonephritis in children; rather, the focus is on areas for which there is more comprehensive evidence or an important clinical need. A list of the KDIGO recommendations for glomerulonephritis in children, specifying which were selected for further commentary, is provided in Table 1. When applicable, implications for Canadian health care are listed and important areas for future research are also discussed.

In this commentary, numbered text within horizontal rules is quoted directly from the KDIGO document, using the same numbering scheme as in the original. All material is reproduced with permission of KDIGO.

GUIDELINE STATEMENTS AND COMMENTARY

Treatment of the Initial and Relapse Episodes of Steroid-Sensitive Nephrotic Syndrome

3.1.1.2: We recommend that daily oral prednisone be given for 4-6 weeks (*1C*) followed by alternate-day medication as a single daily dose starting at 40 mg/m^2 or 1.5 mg/kg (maximum 40 mg on alternate days) (*1D*) and continued for 2-5 months with tapering of the dose. (*1B*)

3.2.2: Corticosteroid therapy for frequently relapsing (FR) and steroid-dependent (SD) SSNS:

3.2.2.1: We suggest that relapses in children with FR or SD SSNS be treated with daily prednisone until the child has been in remission for at least 3 days, followed by alternate-day prednisone for at least 3 months. (*2C*)

3.2.2.2: We suggest that prednisone be given on alternate days in the lowest dose to maintain remission without major adverse effects in children with FR and SD SSNS. (*2D*)

3.2.2.3: We suggest that daily prednisone at the lowest dose be given to maintain remission without major adverse effects in children with SD SSNS where alternate-day prednisone therapy is not effective. (*2D*)

3.2.2.4: We suggest that daily prednisone be given during episodes of upper respiratory tract and other infections to reduce the risk for relapse in children with FR and SD SSNS already on alternate-day prednisone. (*2C*)

Commentary

Chapter 3 of the KDIGO guideline has 2 level 1 recommendations concerning the initial treatment of children older than 1 year presenting with (idiopathic) nephrotic syndrome. The CSN working group agrees that corticosteroids remain the first-line therapy for this group of patients. Children younger than 1 year are more likely to have a different (and genetically definable) cause for their nephrotic syndrome and should be managed differently.

In Canada, the majority of pediatric nephrologists treat children at their initial presentation of nephrotic syndrome with 6 weeks of daily prednisone (or prednisolone; the guideline notes that prednisone and prednisolone are equivalent), followed by alternate-day (48-hour) dosing for another 6 weeks.[10] Despite high early response rates, 80% of children experience at least one relapse of proteinuria and nephrotic syndrome and 50% experience relapse frequently or become corticosteroid (steroid) dependent (SD).[11,12]

In order to reduce these high relapse rates and the resulting adverse effects, modifications of prednisone dosing and therapy duration have been evaluated.[12-14] The KDIGO Work Group highlighted results from a meta-analysis of 422 children, which showed a reduced risk of relapse with 3 months of therapy compared with 2 months (relative risk [RR], 0.70; 95% confidence interval [CI], 0.58-0.84) and