Canadian Association of Gastroenterology Clinical Practice Guideline for the Management of

Pediatric Luminal Crohn's Disease

David R. Mack, MD, FRCPC
University of Ottawa
Children's Hospital of Eastern Ontario

SCMD
Semaine canadienne des maladies digestives^MC

CDDW
Canadian Digestive Diseases Week™

Inflammatory Bowel Disease Centre
Centre des maladies inflammatoires de l'intestin
CHEO

CHEO RESEARCH INSTITUTE

uOttawa
Faculté de médecine
Faculty of Medicine

CanMEDS Roles Covered

X	**Medical Expert (as *Medical Experts*, physicians integrate all of the CanMEDS Roles, applying medical knowledge, clinical skills, and professional values in their provision of high-quality and safe patient-centered care. *Medical Expert* is the central physician Role in the CanMEDS Framework and defines the physician's clinical scope of practice.)**
X	**Communicator** (as *Communicators*, physicians form relationships with patients and their families that facilitate the gathering and sharing of essential information for effective health care.)
X	**Collaborator** (as *Collaborators*, physicians work effectively with other health care professionals to provide safe, high-quality, patient-centred care.)
X	**Leader** (as *Leaders*, physicians engage with others to contribute to a vision of a high-quality health care system and take responsibility for the delivery of excellent patient care through their activities as clinicians, administrators, scholars, or teachers.)
X	**Health Advocate** (as *Health Advocates*, physicians contribute their expertise and influence as they work with communities or patient populations to improve health. They work with those they serve to determine and understand needs, speak on behalf of others when required, and support the mobilization of resources to effect change.)
X	**Scholar (as *Scholars*, physicians demonstrate a lifelong commitment to excellence in practice through continuous learning and by teaching others, evaluating evidence, and contributing to scholarship.)**
X	**Professional** (as *Professionals,* physicians are committed to the health and well-being of individual patients and society through ethical practice, high personal standards of behaviour, accountability to the profession and society, physician-led regulation, and maintenance of personal health.)

CPG: Pediatric Crohn's disease

SCMD Semaine canadienne des maladies digestives^MC | CDDW Canadian Digestive Diseases Week™

- Presented on behalf of many others who contributed mightily to the success
  - Steering Committee members,
  - Pediatric Gastroenterology colleagues from across Canada; our USA colleague
  - GRADE Experts: Francis Tse, Paul Moayyedi
  - Representative from the Adult CD consensus group: John Marshall
  - Meeting moderator: Dan Sadowski
  - Canadian Association of Gastroenterology: Paul Sinclair
  - Co-Chair: Anne Griffiths

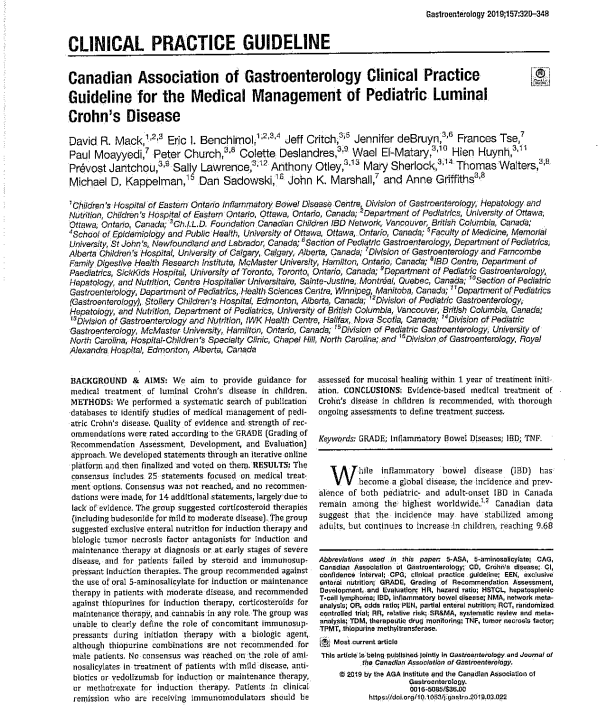
Conflict of Interest Disclosure

SCMD Semaine canadienne des maladies digestives | CDDW Canadian Digestive Diseases Week™

(Over the past 24 months)
Name: David Mack

Commercial or Non-Profit Interest	Relationship
MedBiome Inc.	Co-Founder, Board of Directors

CPG: Pediatric Crohn's disease



Gastroenterology 2019;157:320–348

CLINICAL PRACTICE GUIDELINE

Canadian Association of Gastroenterology Clinical Practice Guideline for the Medical Management of Pediatric Luminal Crohn's Disease

David R. Mack,[1,2,3] Eric I. Benchimol,[1,2,3,4] Jeff Critch,[5,6] Jennifer deBruyn,[3,6] Frances Tse,[7] Paul Moayyedi,[7] Peter Church,[3,8] Colette Deslandres,[3,9] Wael El-Matary,[3,10] Hien Huynh,[3,11] Prévost Jantchou,[3,8] Sally Lawrence,[3,12] Anthony Otley,[3,13] Mary Sherlock,[3,14] Thomas Walters,[3,8] Michael D. Kappelman,[15] Dan Sadowski,[16] John K. Marshall,[7] and Anne Griffiths[3,8]

[1]*Children's Hospital of Eastern Ontario Inflammatory Bowel Disease Centre, Division of Gastroenterology, Hepatology and Nutrition, Children's Hospital of Eastern Ontario, Ottawa, Ontario, Canada;* [2]*Department of Pediatrics, University of Ottawa, Ottawa, Ontario, Canada;* [3]*CIHR-IMD Foundation Canadian Children IBD Network, Vancouver, British Columbia, Canada;* [4]*School of Epidemiology and Public Health, University of Ottawa, Ottawa, Ontario, Canada;* [5]*Faculty of Medicine, Memorial University, St John's, Newfoundland and Labrador, Canada;* [6]*Section of Pediatric Gastroenterology, Department of Pediatrics, Alberta Children's Hospital, University of Calgary, Calgary, Alberta, Canada;* [7]*Division of Gastroenterology and Farncombe Family Digestive Health Research Institute, McMaster University, Hamilton, Ontario, Canada;* [8]*IBD Centre, Department of Paediatrics, SickKids Hospital, University of Toronto, Toronto, Ontario, Canada;* [9]*Department of Pediatric Gastroenterology, Hepatology, and Nutrition, Centre Hospitalier Universitaire, Sainte-Justine, Montréal, Québec, Canada;* [10]*Section of Pediatric Gastroenterology, Department of Pediatrics, Health Sciences Centre, Winnipeg, Manitoba, Canada;* [11]*Department of Pediatrics (Gastroenterology), Stollery Children's Hospital, Edmonton, Alberta, Canada;* [12]*Division of Pediatric Gastroenterology, Hepatology, and Nutrition, Department of Pediatrics, University of British Columbia, Vancouver, British Columbia, Canada;* [13]*Division of Gastroenterology and Nutrition, IWK Health Centre, Halifax, Nova Scotia, Canada;* [14]*Division of Pediatric Gastroenterology, McMaster University, Hamilton, Ontario, Canada;* [15]*Division of Pediatric Gastroenterology, University of North Carolina, Hospital-Children's Specialty Clinic, Chapel Hill, North Carolina; and* [16]*Division of Gastroenterology, Royal Alexandra Hospital, Edmonton, Alberta, Canada*

BACKGROUND & AIMS: We aim to provide guidance for medical treatment of luminal Crohn's disease in children. **METHODS:** We performed a systematic search of publication databases to identify studies of medical management of pediatric Crohn's disease. Quality of evidence and strength of recommendations were rated according to the GRADE (Grading of Recommendation Assessment, Development, and Evaluation) approach. We developed statements through an iterative online platform and then finalized and voted on them. **RESULTS:** The consensus includes 25 statements focused on medical treatment options. Consensus was not reached, and no recommendations were made, for 14 additional statements, largely due to lack of evidence. The group suggested corticosteroid therapies (including budesonide for mild to moderate disease). The group suggested exclusive enteral nutrition for induction therapy and biologic tumor necrosis factor antagonists for induction and maintenance therapy at diagnosis or at early stages of severe disease, and for patients failed by steroid and immunosuppressant induction therapies. The group recommended against the use of oral 5-aminosalicylate for induction or maintenance therapy in patients with moderate disease, and recommended against thiopurines for induction therapy, corticosteroids for maintenance therapy, and cannabis in any role. The group was unable to clearly define the role of concomitant immunosuppressants during initiation therapy with a biologic agent, although thiopurine combinations are not recommended for male patients. No consensus was reached on the role of aminosalicylates in treatment of patients with mild disease, antibiotics or vedolizumab for induction or maintenance therapy, or methotrexate for induction therapy. Patients in clinical remission who are receiving immunomodulators should be assessed for mucosal healing within 1 year of treatment initiation. **CONCLUSIONS:** Evidence-based medical treatment of Crohn's disease in children is recommended, with thorough ongoing assessments to define treatment success.

Keywords: GRADE; Inflammatory Bowel Diseases; IBD; TNF.

While inflammatory bowel disease (IBD) has become a global disease, the incidence and prevalence of both pediatric- and adult-onset IBD in Canada remain among the highest worldwide.[1,2] Canadian data suggest that the incidence may have stabilized among adults, but continues to increase in children, reaching 9.68

Abbreviations used in this paper: 5-ASA, 5-aminosalicylate; CAG, Canadian Association of Gastroenterology; CD, Crohn's disease; CI, confidence interval; CPG, clinical practice guideline; EEN, exclusive enteral nutrition; GRADE, Grading of Recommendation Assessment, Development, and Evaluation; HR, hazard ratio; HSTCL, hepatosplenic T-cell lymphoma; IBD, inflammatory bowel disease; NMA, network meta-analysis; OR, odds ratio; PEN, partial enteral nutrition; RCT, randomized controlled trial; RR, relative risk; SR&MA, systematic review and meta-analysis; TDM, therapeutic drug monitoring; TNF, tumor necrosis factor; TPMT, thiopurine methyltransferase.

Most current article

This article is being published jointly in *Gastroenterology* and *Journal of the Canadian Association of Gastroenterology*.

0016-5085/$36.00
https://doi.org/10.1053/j.gastro.2019.03.022

- Gastroenterology 2019;157: 320-328
- J Can Assoc Gastroenterol 2019;2:e35-e63

- Funding grants
  - CIHR: Planning and Dissemination Grant
  - Unrestricted grants: Abbvie, Takeda Canada

- Scope of the Clinical Practice Guideline was limited to luminal disease
- Consensus group endorsed the importance of mucosal healing but deep remission (clinical remission + mucosal healing) could not be selected as primary outcome as majority of RCTs use clinical remission and response

CPG: Pediatric Crohn's disease

- 15 pediatric gastroenterologists (including 1 from USA)
- Literature search: January 2000 – June 2017
- Much of the evidence for efficacy and safety from RCTs was conducted in adult populations
- If pediatric studies (even observational) supporting the findings in adults, the evidence was not downgraded for indirectness
- When confronted with very-low-quality evidence in the absence of compelling benefit to risk ratio, the consensus group agreed not to make a recommendation for or against a particular strategy (N = 13 statements)

CPG: Pediatric Crohn's disease

SCMD Semaine canadienne des maladies digestives^MC | CDDW Canadian Digestive Diseases Week™

- Statements were accepted if ≥ 75% of participants voted for agree (4) or strongly agree (5) on a 1 – 5 scale

- For accepted statements, there was a second vote
  - A level of agreement ≥ 75% of participants was needed to classify a statement as "strong" (we recommend)
  - If < 75% agreement, the statement defaulted to "conditional" (we suggest)

- 25 statements in final document
  - 9 strong recommendations

Pediatric CD: 5-ASA/sulfasalazine

SCMD Semaine canadienne des maladies digestives | CDDW Canadian Digestive Diseases Week™

- Strong Recommendations: (i.e. For accepted statement; ≥ 75% agreement)
  - It is recommended against 5-ASA to induce clinical remission for moderate CD
  - It is recommended against 5-ASA/SAS to maintain clinical remission

- Conditional Recommendation (i.e. For accepted statements; < 75% agreement)
  - It is suggested against sulfasalazine to induce clinical remission for moderate colonic CD

Pediatric CD: 5-ASA/sulfasalazine

SCMD Semaine canadienne des maladies digestives | CDDW Canadian Digestive Diseases Week™

- No Consensus: (i.e. Very-low-quality evidence and lack of compelling benefit to risk)
  - No recommendation for/against 5-ASA to induce clinical remission for mild CD
  - No recommendation for/against sulfasalazine to induce clinical remission for mild colonic CD
  - No recommendation for/against 5-ASA/SAS to maintain clinical remission when these medications used to induce clinical remission

Pediatric CD: Antibiotics

SCMD Semaine canadienne des maladies digestives^MC | CDDW Canadian Digestive Diseases Week™

- No Consensus: (i.e. Very-low-quality evidence and lack of compelling benefit to risk)
  - No recommendation for/against antibiotics to induce clinical remission for mild/ moderate CD
  - No recommendation for/against antibiotics to maintain clinical remission for mild/ moderate CD

Pediatric CD: Budesonide

- Strong Recommendation: (i.e. For accepted statement; ≥ 75% agreement)
  - It is recommended against controlled ileal release budesonide to maintain clinical remission

- Conditional Recommendation (i.e. For accepted statements; < 75% agreement)
  - It is suggested to use controlled ileal release budesonide to induce clinical remission for mild/moderate ileal/right colon CD

Pediatric CD: Corticosteroids

- Strong Recommendation: (i.e. For accepted statement; ≥ 75% agreement)
  - It is recommended against corticosteroids to maintain clinical remission

- Conditional Recommendations (i.e. For accepted statements; < 75% agreement)
  - It is suggested to use corticosteroids to induce clinical remission for moderate/ severe CD
  - It is suggested to use corticosteroids to induce clinical remission for mild/ moderate CD who failed other therapies (5-ASA/SAS/EEN/budesonide)

Pediatric CD: EEN

- Strong Recommendation: (i.e. For accepted statement; ≥ 75% agreement)
  - It is recommended against partial enteral nutrition to induce clinical remission

- Conditional Recommendations (i.e. For accepted statements; < 75% agreement)
  - It is suggested to use exclusive enteral nutrition to induce clinical remission
  - It is suggested to use partial enteral nutrition only in patients in remission with other medications to maintain their clinical remission

Pediatric CD: Immunosuppressants

SCMD Semaine canadienne des maladies digestives^MC | CDDW Canadian Digestive Diseases Week™

- Strong Recommendation: (i.e. For accepted statement; ≥ 75% agreement)
  - It is recommended against thiopurine monotherapy to induce clinical remission

- Conditional Recommendations (i.e. For accepted statements; < 75% agreement)
  - It is suggested to use a thiopurine to maintain clinical remission in females
  - It is suggested to test for TPMT prior to initiation of a thiopurine
  - It is suggested parenteral methotrexate to maintain clinical remission
  - It is suggested that mucosal healing be assessed within the first year for patients in clinical remission on a thiopurine or MTX

Pediatric CD: Immunosuppressants

SCMD Semaine canadienne des maladies digestives | CDDW Canadian Digestive Diseases Week™

- No Consensus: (i.e. Very-low-quality evidence and lack of compelling benefit to risk)
  - No recommendation for/against using thiopurines to maintain clinical remission for mild/moderate CD in males
  - No recommendation for/against methotrexate monotherapy to induce clinical remission for mild/moderate CD
  - No recommendation for/against oral methotrexate to maintain clinical remission

Pediatric CD: Anti-TNFα therapy

SCMD Semaine canadienne des maladies digestives^MC | CDDW Canadian Digestive Diseases Week™

- Strong Recommendations: (i.e. For accepted statement; ≥ 75% agreement)
  - It is recommended to use anti-TNFα therapy (IFX, ADA) to induce and maintain clinical remission for patients with moderate/severe CD who failed corticosteroids
  - It is recommended to use anti-TNFα therapy (IFX, ADA) to maintain clinical remission for patients with moderate/severe CD who failed thiopurine/MTX

Pediatric CD: Anti-TNFα therapy

SCMD Semaine canadienne des maladies digestives^MC | CDDW Canadian Digestive Diseases Week™

- Conditional Recommendations (i.e. For accepted statements; < 75% agreement)
  - It is suggested to use anti-TNFα therapy as first line therapy in selected cases to induce and maintain clinical remission
  - It is suggested not to use a thiopurine in males in combination with anti-TNFα therapy (IFX, ADA)
  - It is suggested MTX as immunomodulator for combination therapy with anti-TNFα agent in males
  - It is suggested when suboptimal clinical response to anti-TNFα agent, dose intensification strategy guided by therapeutic drug monitoring
  - It is suggested to try ustekinumab for moderate/severe CD who fail induction or maintenance of clinical remission using an anti-TNFα therapy

Pediatric CD: Anti-TNFα therapy

SCMD Semaine canadienne des maladies digestives | CDDW Canadian Digestive Diseases Week™

- No Consensus: (i.e. Very-low-quality evidence and lack of compelling benefit to risk)
  - No recommendation for/against initiating anti-TNFα therapy that started with moderate/severe CD in clinical remission but not having mucosal healing
  - No recommendation for/against assessment of mucosal healing in first year if in clinical remission on anti-TNFα therapy
  - No recommendation for/against thiopurine + anti-TNFα therapy (IFX, ADA) combination therapy in females
  - No recommendation for/against vedolizumab for moderate/severe CD who fail induction or maintenance of clinical remission using an anti-TNFα therapy

Pediatric CD: Cannabis

- Strong Recommendation: (i.e. For accepted statement; ≥ 75% agreement)
  - It is recommended against cannabis or derivatives to induce or maintain remission

Canadian Association of Gastroenterology Clinical Practice Guideline for the Management of

Pediatric Luminal Crohn's Disease

Thank-you

SCMD
Semaine canadienne des maladies digestives^MC

CDDW
Canadian Digestive Diseases Week™