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

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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.**

(95% confidence interval [CI], 9.11–10.25) per 100,000 children under age 16 years for the period 1999–2010.[2] Although the highest percentage increases in incidence were among children aged younger than 5 years at time of diagnosis, pediatric-onset IBD still develops most commonly in adolescence.[2] Crohn's disease (CD) predominates over ulcerative colitis, accounting for 65.6% of pediatric IBD based on national administrative data up until 2010,[2] and occurring in 62% of 1146 children in the Canadian Children IBD Network inception cohort study.[3]

Pediatric CD encompasses a heterogeneous spectrum of phenotypic features (as recognized by the Paris modification of the Montreal classification[4]), disease severity, and treatment responsiveness. Intestinal healing, rather than symptom control alone, has become an important therapeutic goal.[5] This may be especially important in young patients, given the potential for growth impairment as a direct effect of persistent chronic inflammation[6,7] and their long lives ahead, during which disease complications may occur. Mucosal healing became a realistic goal for patients with the advent of monoclonal antibodies directed against tumor necrosis factor (TNF)-α. As alternate pathway biologic agents and new small molecule therapies emerge, it behooves clinicians to recommend treatment of pediatric CD based on critical evaluation of efficacy and safety. Choice of treatment for active pediatric CD must always be made with a maintenance strategy in mind.

When the pediatric consensus group met in October 2017, the most recent consensus guidelines for the treatment of CD in pediatric patients were those from the European Society of Pediatric Gastroenterology, Hepatology and Nutrition and the European Crohn's and Colitis Organization published in April 2014, which incorporated data published until June 2013.[8] The Canadian Association of Gastroenterology (CAG) has established infrastructure for the development of consensus clinical practice guidelines,[9] but to date has focused on adult patients, including consensus guidelines for both luminal and fistulizing CD. Given the increasing prevalence of pediatric CD, the challenges specific to young patients, and the uncertainties around treatment choices, the Canadian Children IBD Network partnered with CAG to systematically review the literature relating to the medical management of luminal CD and to develop specific recommendations for pediatric patients.

Methods

Scope and Purpose

This guideline focuses on the medical management of luminal CD in pediatric patients, and does not specifically address the diagnostic evaluation of luminal CD, the role of surgical management, growth monitoring, social and psychological interventions, and preventative health measures, such as vaccinations. Specific questions pertaining to the medical management of luminal CD in pediatric patients were developed by the steering committee (DM, AG, EIB, JC, JD, and JM) and GRADE (Grading of Recommendation Assessment, Development, and Evaluation) experts (PM, FT). Recommendations were developed by all members of the group at a face-to-face meeting in October 2017.

Definitions Used in Framing Questions

Disease activity. The categories of disease activity discussed in this guideline (mild to moderate and moderate to severe active CD) were defined in many clinical trials according to the Crohn's Disease Activity Index in studies involving adult patients or the Pediatric Crohn's Disease Activity Index in studies involving children. Therefore, in general, descriptions of activity in this document reflect Crohn's Disease Activity Index or Pediatric Crohn's Disease Activity Index scores, as described in the evidence.

Outcomes. Clinical remission was consistently chosen as the primary outcome in the statements because of knowledge that until recently "clinical remission" (usually defined by a multi-item measure of disease activity) has been the primary end point in clinical trials assessing treatment efficacy.

Evidence of efficacy of specific treatments in achieving mucosal healing is limited, therefore, "complete" or "deep" remission (clinical remission plus mucosal healing) was not the chosen primary outcome in this guideline. Mucosal healing, however, is increasingly replacing "clinical remission" as a treatment target for adults and children with IBD.[5] Such healing has been associated with sustained clinical remission and a reduced need for hospitalization and surgery.[10–12] Statements regarding the importance of evaluating mucosal healing in pediatric patients achieving clinical remission were therefore discussed, despite the limitations of existing data precluding its choice as a primary outcome.

Clinical response was defined as reduction in symptoms determined by clinically meaningful changes in a multi-item measure of disease activity, in the absence of complete resolution of symptoms.

Sources and Searches

A systematic search of the literature relevant to the selected questions from January 2000 to June 2017 was conducted by the Editorial Office of the Cochrane Upper Gastrointestinal and Pancreatic Diseases Group at McMaster University using MEDLINE, EMBASE, Cochrane Central, and Cochrane database of systematic reviews. Key search terms included *pediatric*, *Crohn's*, *antibiotic*, *5-aminosalicylate*, *corticosteroid*, *anti-tumour necrosis factor*, *thiopurine*, *methotrexate*, *vedolizumab*, *ustekinumab*, and *enteral nutrition*. The search was limited to human studies and English publications; additional details of the search strategies utilized are provided in the Supplementary Material Appendix 1.

The consensus process was facilitated by the CAG via a web-based consensus platform (ECD Solutions, Atlanta, GA). Using this platform, the steering committee reviewed the results of initial literature searches and identified relevant references that were then "tagged" (selected and linked) to each statement. Copies of the tagged references were available to all members of the consensus group. The full consensus group voted anonymously on their level of agreement with the individual statements, using a modified Delphi process.[13,14] Participants suggested revisions and commented on the statements, after which, the specific statements were revised through 2 iterations.

Assessment of the Quality of Evidence

Two non-voting methodologists (PM, FT) used the GRADE approach[15] to assess the strength of the evidence for each statement. The quality of evidence for each consensus statement was classified as high, moderate, low, or very low, as described in GRADE[15,16] and used in previous CAG consensus guidelines.[17–21] Randomized controlled trials (RCTs) began as high-quality evidence but could be downgraded because of heterogeneity or inconsistency of results, imprecision, indirect study findings, reporting bias, or if it was determined that a high risk of bias existed across studies supporting the statement. Data from observational studies began as low-quality evidence, but could be lowered because of the same factors, or raised if a very large treatment effect or a dose–response relationship was identified, or if all plausible biases would change the magnitude of effect toward the opposite direction.[15,16]

Using the GRADE approach, it is rare to have high-quality evidence unless it fulfills all domains in terms of risk of bias, inconsistency, imprecision, indirectness, and no other bias (eg, publication bias). The evidence is always reviewed in relation to the PICO (patient population, intervention, comparator, and outcome) question. So, the trials may be high methodological quality, but if they do not address the PICO question directly in terms of populations, interventions, and outcomes, the evidence will be downgraded. In addition to an updated review of the literature, new meta-analyses were performed for this consensus.

Much of the evidence for the efficacy and safety of CD treatments was available from RCTs conducted in adult populations. In some cases, the quality of evidence was downgraded for indirectness with respect to the populations when no studies were found that evaluated the drug in children, and as such both safety and effectiveness data had to be extrapolated from adult studies. Considering the course of disease, responses to treatments and dose–response relationships may differ between pediatric and adult populations with CD and, as such, the evidence was less certain in children than in adults when only adult data were available. However, if there were studies done in children (even observational in nature) that supported the findings in adults, the evidence was not downgraded for indirectness. In some cases, when confronted by very-low-quality evidence in the absence of a compelling benefit to risk ratio, the consensus group agreed not to make a recommendation for or against a particular strategy.

Approved product labeling from government regulatory agencies varies from country to country, and although it was not ignored, recommendations were based on evidence from the literature and consensus discussion, and may not fully reflect the product labeling for a given country.

Consensus Process

The 2-day, face-to-face consensus meeting was held in Toronto, Ontario, Canada, in October 2017. The consensus group was composed of 15 voting pediatric gastroenterologists, from Canada and the United States with expertise in multiple areas, including nutrition (SL, WE, HH, AO), growth impairment in IBD (TW, AG), microbiome (DM), clinical epidemiology, health services research and quality improvement (EB, PJ, AO, MS, MDK, WE), and patient-reported measures or patient engagement (AO, MDK). Non-voting participants included the co-chairs (AG, DM), GRADE experts (PM, FT), a representative from the adult CD CAG consensus group (JM), non-voting observers, and the co-moderators (PM, DS). At the consensus conference, data and the GRADE evaluations of the evidence were presented, and each individual statement was discussed and the wording finalized. Participants voted on their level of agreement for each statement. If $\geq$75% of participants voted 4 (agree) or 5 (strongly agree) on a 1–5 scale (1, 2, and 3 being disagree strongly, disagree, and uncertain, respectively), then the statement was accepted. If a statement was accepted, a second vote on the strength of the recommendation was conducted. A level of agreement of $\geq$75% of participants was needed to classify a statement as "strong" (we recommend); if this threshold was not met, the statement defaulted to "conditional" (we suggest). The strength of a recommendation considers the benefit-to-risk balance, patients' values and preferences, cost and resource allocation, and the quality of the evidence. Consequently, a recommendation could be classified as strong despite low-quality evidence, or conditional despite high-quality evidence.[22] As per the GRADE method, a strong recommendation is indicative of a more broadly applicable statement ("most patients should receive the recommended course of action"), whereas a conditional recommendation suggests clinicians should ". . . recognize that different choices will be appropriate for different patients and that they must help each patient to arrive at a management decision consistent with her or his values and preferences."[22]

During the consensus meeting, voting members were unable to reach consensus on 14 statements (No recommendation A–N) and these statements were rejected. The evidence that was reviewed for these statements and the discussion has been summarized in the text, but the consensus group did not make a recommendation for or against these treatment strategies.

The manuscript was initially drafted by the co-chairs (DM, AG), and then reviewed and revised by the GRADE experts and members of the steering committee before being sent to the full consensus group for review. Upon approval from the group, the manuscript was made available to all CAG members for comment during a 2-week period before submission for publication.

In accordance with CAG policy, written disclosures of any potential conflicts of interest for the 24 months preceding the consensus meeting were provided by all participants, and made available to all group members, and CAG members reviewing the manuscript.

Role of the Funding Sources

Funding for the consensus meeting was provided by unrestricted, arms-length grants to the CAG by AbbVie and Takeda Canada, and a Planning and Dissemination Grant from the Canadian Institutes of Health Research. The CAG administered all aspects of the meeting, and the funding sources had no involvement in the process at any point, nor were they made aware of any part of the process from development of search strings and statements to drafting and approval of these guidelines.

Recommendation Statements

The individual recommendation statements are provided and include the strength of recommendation and

quality of supporting evidence (according to the GRADE approach), and the voting result. This is followed by a discussion of the evidence considered for the specific statement. A summary of the recommendation statements is provided in Table 1. See Supplementary Material Appendix 2 for more detailed quality of evidence summaries.

The majority of RCTs in patients with CD are conducted in adults, and therefore much of the evidence has been downgraded for indirectness and is of very low quality. As a result of the very low quality of evidence, there were insufficient data for the consensus group to make recommendations for or against many treatments (14 statements); however, the available evidence and ensuing discussion relevant to these treatments is presented.

Aminosalicylates

Statement 1: In patients with moderate Crohn's disease, we recommend against the use of 5-aminosalicylates to induce clinical remission.
GRADE: Strong recommendation, very-low-quality evidence.
Vote: strongly agree, 67%; agree, 33%.

No consensus A: *In patients with mild Crohn's disease, the consensus group does not make a recommendation (for or against) regarding the use of 5-aminosalicylates to induce clinical remission.*

Key evidence. Two systematic reviews and meta-analyses (SR&MAs),[23,24] and a network meta-analysis (NMA) of studies in adults provide data on the use of 5-aminosalicylate (5-ASA) in mild to moderate active CD.[25] These analyses included studies using various formulations and doses of non-sulfasalazine 5-ASAs (ie, mesalamine and olsalazine), and generally reported no benefit with these agents over placebo for induction of remission. In 1 analysis of 4 trials (n = 647), the relative risk (RR) of failure to induce remission with mesalamine compared with placebo was 0.91 (95% CI, 0.77–1.06).[23] One SR&MA reported no significant benefits with either low-dose or high-dose 5-ASA,[24] while the NMA showed that high-dose mesalamine was superior to placebo in inducing remission (odds ratio [OR], 1.87; 95% credible interval, 1.14–3.15), but low-dose was not.[25] In the induction studies, there was no significant difference noted in adverse events between mesalamine and placebo (RR, 0.99; 95% CI, 0.84–1.15).[23]

The data did not assess mild and moderate disease separately, and no RCTs in pediatric patients were found.

The quality of evidence was downgraded to very low due to serious risk of bias, serious indirectness with respect to populations (lack of pediatric data and inability to separate mild from moderate disease), and very serious imprecision.

Discussion. The SR&MAs generally do not report a statistically significant efficacy with 5-ASA for induction therapy in patients with mild to moderate disease activity, but also do not convincingly demonstrate that 5-ASAs are without benefits (eg, potential benefits with high-dose therapy[25]). The data cannot be separated into mild and moderate patients, however, the group strongly recommended against this option in patients with moderate (or greater) disease activity, because of the potential negative consequences of delaying the use of other therapies with more definitively demonstrated efficacy.

Data specifically in patients with mild disease were lacking, and the consensus group concluded that the evidence was not sufficiently convincing to recommend for or against 5-ASA for mild CD. The potential negative consequences of delaying use of more effective treatments would be of less concern than in the case of moderate CD. An additional concern was the rare cases of pancreatitis and interstitial nephritis that have been reported with mesalamine.[26]

In summary, because 5-ASAs have not demonstrated a consistent, significant benefit, the consensus group made a strong recommendation against their use in patients with moderate CD. However, because ineffectiveness in mild disease was not demonstrated in the literature, no recommendation was made for or against its use to induce clinical remission in patients with mild disease.

Statement 2: In patients with moderate Crohn's disease limited to the colon, we suggest against the use of sulfasalazine to induce clinical remission.
GRADE: Conditional recommendation, very-low-quality evidence.
Vote: strongly agree, 67%; agree, 20%; neutral, 7%; disagree, 0%; strongly disagree, 7%.

No consensus B: In patients with mild Crohn's disease limited to the colon, the consensus group does not make a recommendation (for or against) regarding the use sulfasalazine to induce clinical remission.

Key evidence. There was very limited evidence on the efficacy of sulfasalazine in CD. The 2 SR&MAs,[23,24] and the NMA,[25] all included the same 2 small, older RCTs in adults with active CD.[27,28] Meta-analyses of these 2 trials (n = 263), yielded a marginal benefit over placebo: RR for failure to achieve remission, 0.83 (95% CI, 0.69–1.00),[23] and RR for induction of remission, 1.38 (95% CI, 1.00–1.89).[24]

The NMA, also reported that sulfasalazine was not superior to placebo (OR, 1.50; 95% credible interval, 0.71–3.12).[25] Both of the original RCTs reported significant benefits with sulfasalazine only in the subgroup of patients with disease confined to the colon, however, the sample sizes were very small.[27,28]

No RCTs were found in pediatric patients, and while mild disease was analyzed separately, the subgroup of patients was very small.

The quality of evidence was downgraded to very low due to serious risk of bias, serious indirectness with respect to populations (lack of pediatric data and inability to separate mild from moderate disease), and very serious imprecision.

Discussion. As was the case in Statement 1, the consensus group concluded that there was insufficient evidence to warrant routine use of sulfasalazine in pediatric patients with moderate disease. Although the statement suggested against sulfasalazine, it was conditional because

of the trend toward efficacy in colonic disease, which is the location targeted by sulfasalazine. Similar to 5-ASA, given the potential efficacy of sulfasalazine in mild disease and the fact that treatment delays may be of less concern in such patients, the consensus group did not make a recommendation for or against its use in patients with mild colonic disease. Some participants argued that it is one of the few products that are available in a suspension, and recommending against a potentially effective treatment would limit the options available for some children who are unable to swallow capsules or tablets. However, others argued that the adverse events, albeit rare, may not be benign, and can include allergic reactions, agranulocytosis, and hepatitis.[29]

Statement 3: In patients with Crohn's disease in clinical remission, we recommend against sulfasalazine or 5-aminosalicylic acid to maintain clinical remission.
GRADE: Strong recommendation, very-low-quality evidence.
Vote: strongly agree, 33%; agree, 47%; neutral, 20%.

No consensus C: *In patients with mild Crohn's disease who have achieved clinical remission with sulfasalazine or 5-aminosalicylic acid, the consensus group does not make a recommendation (for or against) regarding continuing sulfasalazine or 5-aminosalicylic acid to maintain clinical remission.*

Key evidence. The data for sulfasalazine and mesalamine for maintenance of remission included 2 SR&MAs,[23,30] one of which[30] included 1 RCT in pediatric patients.[31] Using different eligibility criteria, 1 meta-analysis included 16 RCTs (n = 2496)[23] and the other 12 RCTs (n = 2146).[30] Sulfasalazine was not effective in preventing relapse of CD (n = 4 studies; RR, 0.98; 95% CI, 0.82–1.17), but there was a non-significant trend toward improvement over placebo with mesalamine (n = 11 studies; RR, 0.94; 95% CI, 0.87–1.01).[23] A meta-analysis of data from 12 maintenance trials showed no significant difference in the RR of adverse events between mesalamine and placebo (RR, 1.08; 95% CI, 0.87–1.34).[23]

A pediatric RCT in 132 patients reported no statistically significant difference in relapse rates at 12 months[31] with mesalamine compared to placebo (74% vs 69%; RR, 1.07; 95% CI, 0.86–1.33[30]).

The reviewed studies did not include analyses assessing efficacy according to baseline disease severity or treatment used for induction.

The quality of evidence was downgraded to very low due to serious risk of bias and very serious imprecision.

Discussion. Evidence suggests that 5-ASA and sulfasalazine are generally not effective for maintenance therapy, therefore, the consensus group made a strong recommendation against their use for most patients who have achieved remission.

However, a per-protocol analysis found a significant benefit of mesalamine for the reduction of risk of relapse (RR, 0.79; 95% CI, 0.66–0.95).[23] Therefore, the consensus group questioned whether these agents would be useful as maintenance therapy in patients whose remission had been induced with 5-ASA or sulfasalazine. There are few data to inform a maintenance strategy in such patients; it is unknown whether the best strategy would be to continue these agents, provide no maintenance therapy, or switch to a more effective medication. In most of the trials, the agents used to achieve remission were not specified, but in 1 RCT that used 5-ASA for induction, there was no significant benefit with continued 5-ASA maintenance therapy.[32] The consensus group did not make a recommendation for or against this strategy.

Antibiotics

No consensus D: *In patients with mild to moderate Crohn's disease, the consensus group does not make a recommendation (for or against) regarding the use of antibiotics to induce clinical remission.*

No consensus E: *In patients with mild to moderate Crohn's disease, the consensus group does not make a recommendation (for or against) regarding the use of antibiotics to maintain clinical remission.*

Key evidence. Two SR&MAs of RCTs have evaluated the efficacy of antibiotics for induction of remission in patients with CD.[33,34] While there was a significant benefit of antibiotics overall in inducing remission (n = 10 studies; RR for failure to achieve remission, 0.85; 95% CI, 0.73–0.99), the benefit was largely due to positive studies with rifaximin (n = 2 studies; RR for failure to achieve remission, 0.81; 95% CI, 0.68–0.97).[33] The RCTs in these meta-analyses used a variety of antibiotics and doses, therefore no conclusions could be drawn for specific antibiotic regimens, with the exception of rifaximin. There were no serious adverse events, and no significant differences in adverse events between rifaximin and placebo.[35,36]

The quality of evidence was downgraded to very low due to serious risk of bias, serious indirectness with respect to populations (lack of pediatric data) and interventions (diverse regimens), and serious imprecision.

Two SR&MAs assessed the efficacy of antibiotics for the maintenance of remission in patients with quiescent CD.[33,37] All of the RCTs included in these analyses assessed the efficacy of anti-mycobacterial therapies either alone or in combination. The most recent SR&MA including 4 RCTs (n = 206) found that antibiotics significantly reduced the risk of relapse compared to placebo in patients with quiescent CD (RR, 0.58; 95% CI, 0.45–0.75).[37] The anti-mycobacterial therapies were associated with a greater risk of adverse events compared to placebo (RR, 2.57; 95% CI, 1.45–4.55).[37] The most common adverse events included increased skin pigmentation and rashes. One additional RCT, which did not include an anti-mycobacterial agent, reported a statistically greater rate of maintenance of clinical remission at 48 weeks with rifaximin compared to placebo (71% vs 53%; $P < .05$).[38]

The majority of both induction and maintenance RCTs had small sample sizes, and no RCTs were found that included pediatric patients.

Table 1. Summary of Consensus Recommendations for the Management of Pediatric Crohn's Disease[a]

Aminosalicylates

Recommendation 1: In patients with moderate CD, we recommend against the use of 5-ASAs to induce clinical remission.
GRADE: Strong recommendation, very-low-quality evidence.
Vote: strongly agree, 67%; agree, 33%.

Recommendation 2: In patients with moderate CD limited to the colon, we suggest against the use of sulfasalazine to induce clinical remission.
GRADE: Conditional recommendation, very-low-quality evidence.
Vote: strongly agree, 67%; agree, 20%; neutral, 7%; disagree, 0%; strongly disagree, 7%.

Recommendation 3: In patients with CD in clinical remission, we recommend against sulfasalazine or 5-aminosalicylic acid to maintain clinical remission.
GRADE: Strong recommendation, very-low-quality evidence.
Vote: strongly agree, 33%; agree, 47%; neutral, 20%.

Budesonide

Recommendation 4: In patients with mild to moderate ileal and/or right colonic CD, we suggest oral controlled ileal release budesonide to induce clinical remission.
GRADE: Conditional recommendation, very-low-quality evidence.
Vote: strongly agree, 33%; agree, 67%.

Recommendation 5: In patients with CD, we recommend against oral controlled ileal release budesonide to maintain clinical remission.
GRADE: Strong recommendation, very-low-quality evidence.
Vote: strongly agree, 87%; agree, 13%.

Corticosteroids

Recommendation 6: In patients with moderate to severe CD, we suggest conventional corticosteroids (eg, prednisone) to induce clinical remission.
GRADE: Conditional recommendation, very-low-quality evidence.
Vote: strongly agree, 47%; agree, 53%.

Recommendation 7: In patients with mild to moderate active CD despite use of sulfasalazine, 5-ASA, oral budesonide, or exclusive enteral nutrition, we suggest oral prednisone to induce clinical remission.
GRADE: Conditional recommendation, moderate-quality evidence.
Vote: strongly agree, 33%; agree, 67%.

Recommendation 8: In patients with CD of any severity, we recommend against oral corticosteroids to maintain clinical remission.
GRADE: Strong recommendation, low-quality evidence.
Vote: strongly agree, 100%.

Exclusive enteral nutrition

Recommendation 9: In patients with CD, we suggest exclusive enteral nutrition to induce clinical remission.
GRADE: Conditional recommendation, very-low-quality evidence (for pediatrics).
Vote: strongly agree, 33%; agree, 67%.

Recommendation 10: In patients with CD, we recommend against partial enteral nutrition to induce clinical remission.
GRADE: Strong recommendation, very-low-quality evidence.
Vote: strongly agree, 80%; agree, 20%.

Recommendation 11: In patients with CD in remission, we suggest that if partial enteral nutrition is used it should be combined with other medications to maintain clinical remission.
GRADE: Conditional recommendation, very-low-quality evidence.
Vote: strongly agree, 13%; agree, 87%.

Immunosuppressants

Recommendation 12: In patients with CD of any severity, we recommend against thiopurine monotherapy to induce clinical remission.
GRADE: Strong recommendation, very-low-quality evidence.
Vote: strongly agree, 87%; agree, 13%.

Recommendation 13: In female patients with CD we suggest a thiopurine to maintain remission.
GRADE: Conditional recommendation, low-quality evidence.
Vote: strongly agree, 20%; agree, 73%; neutral, 7%.

Recommendation 14: In patients with CD, we suggest that testing for TPMT by genotype or enzymatic activity be done prior to initiating thiopurine therapy to guide dosing.
GRADE: Conditional recommendation, very-low-quality evidence.
Vote: strongly agree, 27%; agree, 67%; neutral, 7%.

Recommendation 15: In patients with CD we suggest parenteral methotrexate to maintain clinical remission.
GRADE: Conditional recommendation, low-quality evidence.
Vote: strongly agree, 40%; agree, 60%.

Recommendation 16: In patients with CD who are in clinical remission with a thiopurine or methotrexate as maintenance therapy, we suggest assessment for mucosal healing within the first year to determine the need to modify therapy if significant ulcerations persist.
GRADE: Conditional recommendation, very-low-quality evidence.
Vote: strongly agree, 13%; agree, 80%; neutral, 7%.

Anti-TNF biologic therapies

Recommendation 17: In patients with moderate to severe inflammatory CD who have failed to achieve clinical remission with corticosteroids, we recommend anti-TNF therapy (adalimumab, infliximab) to induce and maintain clinical remission.
GRADE: Strong recommendation, high-quality evidence.
Vote: strongly agree, 100%.

Table 1. Continued

Recommendation 18: In patients with moderate to severe inflammatory CD who fail to achieve or maintain clinical remission with a thiopurine or methotrexate, we recommend anti-TNF therapy to induce and maintain clinical remission.
GRADE: Strong recommendation, high-quality evidence.
Vote: strongly agree, 93%; agree, 7%.

Recommendation 19: In patients with severe inflammatory CD judged at risk for progressive, disabling disease, we suggest anti-TNF therapy as first-line therapy to induce and maintain clinical remission.
GRADE: Conditional recommendation, very-low-quality evidence.
Vote: strongly agree, 47%; agree, 53%.

Recommendation 20: When starting infliximab in males, we suggest against using it in combination with a thiopurine.
GRADE: Conditional recommendation, low-quality evidence.
Vote: strongly agree, 40%; agree, 47%; neutral, 13%.

Recommendation 21: When starting adalimumab in males, we suggest against using it in combination with a thiopurine.
GRADE: Conditional recommendation, very-low-quality evidence.
Vote: strongly agree, 40%; agree, 53%; neutral, 7%.

Recommendation 22: In male patients with CD receiving immunomodulator therapy in combination with an anti-TNF therapy, we suggest methotrexate in preference to thiopurines.
GRADE: Conditional recommendation, very-low-quality evidence.
Vote: strongly agree, 27%; agree, 53%; neutral, 20%.

Recommendation 23: In patients with CD who have a suboptimal clinical response to anti-TNF induction therapy or loss of response to maintenance therapy, we suggest regimen intensification informed by therapeutic drug monitoring.
GRADE: Conditional recommendation, very-low-quality evidence.
Vote: strongly agree, 53%; agree, 47%.

Non–anti-TNF biologic therapies

Recommendation 24: In patients with moderate to severe CD who fail to achieve or maintain clinical remission with anti-TNF–based therapy, we suggest ustekinumab to induce and maintain clinical remission.
GRADE: Conditional recommendation, moderate-quality evidence for induction, low-quality evidence for maintenance.
Vote: strongly agree, 47%; agree, 53%

Alternative therapies

Recommendation 25: In patients with CD, we recommend against cannabis or derivatives to induce or maintain remission.
GRADE: Strong recommendation, very-low-quality evidence.
Vote: strongly agree, 87%; agree, 7%; neutral, 7%.

Statements with no recommendations

No consensus A: In patients with mild CD, the consensus group does not make a recommendation (for or against) regarding the use of 5-ASAs to induce clinical remission.

No consensus B: In patients with mild CD limited to the colon, the consensus group does not make a recommendation (for or against) regarding the use sulfasalazine to induce clinical remission.

No consensus C: In patients with mild CD who have achieved clinical remission with sulfasalazine or 5-ASA, the consensus group does not make a recommendation (for or against) regarding continuing sulfasalazine or 5-ASA to maintain clinical remission.

No consensus D: In patients with mild to moderate CD, the consensus group does not make a recommendation (for or against) regarding the use of antibiotics to induce clinical remission.

No consensus E: In patients with mild to moderate CD, the consensus group does not make a recommendation (for or against) regarding the use of antibiotics to maintain clinical remission.

No consensus F: In male patients with CD the consensus group does not make a recommendation (for or against) regarding a thiopurine to maintain remission.

No consensus G: In patients with mild to moderate CD, the consensus group does not make a recommendation (for or against) regarding methotrexate monotherapy to induce clinical remission.

No consensus H: In patients with CD, the consensus group does not make a recommendation (for or against) regarding oral methotrexate to maintain clinical remission.

No consensus I: In patients with moderate to severe inflammatory CD who have achieved clinical remission but not mucosal healing with a corticosteroid, thiopurine, or methotrexate, the consensus group does not make a recommendation (for or against) regarding anti-TNF therapy to induce and maintain mucosal healing.

No consensus J: When starting infliximab in females, the consensus group does not make a recommendation (for or against) regarding combining it with a thiopurine to maintain a durable clinical remission.

No consensus K: When starting adalimumab in females, the consensus group does not make a recommendation (for or against) regarding combining it with a thiopurine to maintain a durable clinical remission.

No consensus L: In patients with CD who have achieved a clinical remission with anti-TNF therapy, the consensus group does not make a recommendation (for or against) regarding assessment for mucosal healing within the first year to determine the need to modify therapy.

No consensus M: In patients with moderate to severe CD who fail to achieve or maintain clinical remission with an anti-TNF–based therapy, the consensus group does not make a recommendation (for or against) regarding the use vedolizumab to induce and maintain clinical remission.

[a]The strength of each recommendation was assigned by the consensus group, per the GRADE system, as strong ("we recommend...") or conditional ("we suggest..."). A recommendation could be classified as strong despite low-quality evidence to support it, or conditional despite the existence of high-quality evidence due to the 4 components considered in each recommendation (risk to benefit balance, patients' values and preferences, cost and resource allocation, and quality of evidence).

The quality of evidence was downgraded to very low due to serious risk of bias, serious indirectness with respect to populations (lack of pediatric data), interventions (variability in antibiotic regimens), and outcomes (definitions of relapse), and serious imprecision.

Discussion. A variety of antibiotic regimens were used in the trials, which makes interpretation difficult.[33,34] This is further complicated by the fact that, with the exception of rifaximin, the majority of patients were also receiving corticosteroids and other medications. While the data supported the efficacy of antibiotics overall for induction of remission in meta-analyses, this result was mainly driven by rifaximin.[33,34] In addition, anti-mycobacterial therapies have demonstrated efficacy as maintenance therapy.[33,37]

However, group members expressed substantial concern about the potential development of antibiotic resistance as well as cost, particularly when used for maintenance therapy. No serious adverse events were reported in the trials, but long-term complications were not reported.[37] In addition, there were no pediatric studies, and no safety data in children.

Although antibiotics play a role in the management of perianal and postoperative CD, their role in luminal disease remains poorly defined. The consensus group concluded that there are insufficient data to fully evaluate whether the potential benefit (very low quality of evidence suggesting efficacy) outweighs the potential risk (adverse effects and antimicrobial resistance) and therefore, did not make a recommendation for or against the use of antibiotics for induction or maintenance therapy.

Budesonide

Statement 4: In patients with mild to moderate ileal and/or right colonic Crohn's disease, we suggest oral controlled ileal release budesonide to induce clinical remission.
GRADE: Conditional recommendation, low-quality evidence.
Vote: strongly agree, 33%; agree, 67%.

Key evidence. Evidence for the efficacy of budesonide compared to placebo in inducing clinical remission in patients with mild to moderate ileal and/or right colonic CD was available from 3 SR&MAs.[39–41] and an NMA.[25] In a meta-analysis of 3 RCTs in adults, budesonide ≥9 mg/d was twice as likely to induce remission vs placebo (RR, 1.93; 95% CI, 1.37–2.73; 3 RCTs).[41] A lower dose of budesonide (3 mg/d) was not superior to placebo.[40,41] Budesonide was significantly less effective than conventional corticosteroids for induction of remission (RR, 0.85; 95% CI, 0.75–0.97; 8 RCTs), but was associated with fewer adverse events (RR, 0.64; 95% CI, 0.54–0.76).[41] There was no significant difference between budesonide and mesalamine (2 RCTs).[41] The NMA reported similar results.[25]

Three small RCTs were conducted in pediatric patients; 2 reported comparable clinical remission rates between budesonide and prednisone,[42,43] while the other found no significant difference in remission rates between high-dose and standard-dose budesonide.[44] Adverse events, such as Cushingoid facies, acne, and myopathy, were more common with conventional corticosteroids compared to budesonide.[42,43] Overall, the quality of evidence was downgraded to low due to serious risk of bias and serious imprecision.

These RCTs used the oral controlled ileal release preparation or the pH-dependent release formulation, and no studies that used budesonide MMX for the treatment of CD were found.

Discussion. A meta-analysis of RCT data in adult and pediatric patients has shown that budesonide is more effective than placebo, but less effective than conventional corticosteroids.[41] The more limited pediatric-specific data are underpowered to identify this treatment inferiority of budesonide compared with conventional corticosteroids.[42,43] In both adult and pediatric patients, budesonide was associated with fewer adverse events, and suppression of adrenal function was also less frequent, but was still reported with budesonide.[42,45] In an RCT in pediatric patients, mean morning plasma cortisol concentration was significantly higher with budesonide compared to prednisolone after 8 weeks.[42] However, in non-IBD studies of budesonide, morning cortisol concentration was demonstrated to be less sensitive in identifying adrenocortical suppression compared with ACTH-stimulation test.[46]

The consensus group suggested the use of budesonide based on clinical remission rates in comparative clinical trials of budesonide vs conventional oral corticosteroids in adults and children, and in trials of budesonide vs placebo in adults, as well as in light of the superior safety and tolerability profile of budesonide compared to conventional corticosteroids. However, this was a conditional suggestion because budesonide was less effective and more costly than conventional corticosteroids.

Statement 5: In patients with Crohn's disease, we recommend against oral controlled ileal release budesonide to maintain clinical remission.
GRADE: Strong recommendation, very low-quality evidence.
Vote: strongly agree, 87%; agree, 13%.

Key evidence. Two SR&MAs found no significant difference between budesonide and placebo for prevention of relapse or maintenance of remission in patients with quiescent CD.[39,47] In a meta-analysis of 5 RCTs, budesonide 6 mg/d was no more effective than placebo for maintenance of remission at 6 months (RR, 1.15; 95% CI, 0.95–1.39) or 12 months (RR, 1.13; 95% CI, 0.94–1.35).[47] However, an NMA showed that budesonide 6 mg/d was superior to placebo (OR, 1.69; 95% CI, 1.05–2.75).[40] For maintenance of remission there was no statistically significant difference between budesonide and azathioprine, but budesonide 6 mg was superior to mesalamine 3 g/d.[47]

The risk of corticosteroid-related adverse events was significantly higher with budesonide compared to placebo (RR, 2.19; 95% CI, 1.08–4.46).[39] A meta-analysis of maintenance RCTs found significantly higher rates of adrenal

suppression with budesonide compared to placebo.[47] In addition, a higher incidence of endocrine disorders, mainly due to a higher rate of Cushingoid symptoms, has been reported with budesonide.[48] A small, non-comparative, pediatric, cohort study also reported a high incidence of adverse events (74.0%) with budesonide.[45]

The RCTs included in these analyses pooled studies using oral controlled ileal release preparation and the pH-dependent release formulation. RCTs had small sample sizes, low event rates, and no maintenance RCTs in pediatric patients were found.

Discussion. The majority of the evidence from RCTs in adults fails to show benefit of budesonide over placebo for maintenance therapy. RCTs in pediatric patients were not found. In an observational pediatric study, maintenance therapy with budesonide was associated with a significant worsening of disease activity over 12 weeks of treatment.[45] As discussed in Statement 4, adrenal suppression in children is of concern.[42,45] In addition, in a cohort study, subnormal growth velocity was reported during up to 1 year of treatment.[49]

Based on the lack of demonstrated efficacy and the potential for negative long-term effects, including adrenal suppression and impaired linear growth, the consensus group strongly recommended against the use of budesonide for maintenance therapy in pediatric patients.

Corticosteroids

Statement 6: In patients with moderate to severe Crohn's disease, we suggest conventional corticosteroids (eg, prednisone) to induce clinical remission.
GRADE: Conditional recommendation, very-low-quality evidence.
Vote: strongly agree, 47%; agree, 53%.

Key evidence. Evidence for the efficacy of oral corticosteroids over placebo was derived from 2 positive RCTs in adults,[27,28] which have been included in 2 SR&MAs[39,50] and an NMA.[25] In the meta-analysis, which used failure to achieve remission as the primary outcome, there was no significant benefit of corticosteroids over placebo (RR, 0.46; 95 % CI, 0.17–1.28).[39] However, the SR&MA and the NMA both found that corticosteroids were significantly more effective than placebo for induction of symptomatic remission (SR&MA: RR, 1.99; 95% CI, 1.51–2.64;[50] NMA: OR, 3.64; 95% credible interval, 2.16–6.19,[25] respectively). Corticosteroids were associated with higher rates of adverse events than placebo (RR, 4.89; 95% CI, 1.98–12.07).[50]

One small RCT assessed corticosteroids vs exclusive enteral nutrition (EEN) therapy in pediatric patients and found no difference in clinical remission rates between the 2 active treatments.[51]

The quality of evidence was downgraded to very low due to serious risk of bias, serious indirectness with respect to comparisons (lack of placebo controlled pediatric data), and serious imprecision.

Discussion. Although the data are very low quality, corticosteroids appear to be more effective than placebo for induction of remission in adults with CD. In pediatric patients, there were no placebo-controlled RCTs, however, conventional corticosteroids appeared to be as effective as budesonide and EEN in several small RCTs.[42,43,51]

Based on evidence suggesting efficacy, and the fact that this is an inexpensive treatment option, the consensus group suggested conventional corticosteroids for short-term use for induction of remission. However, this statement was a conditional recommendation because of the potential negative consequences of delaying the use of other options with greater efficacy, as well as the adverse event profile of corticosteroids, which is of greater concern in children than in adults. Systemic corticosteroids (even short-term use) should be used with particular caution in patients with linear growth delay, osteoporosis, or mental health disorders.

Statement 7: In patients with mild to moderate active Crohn's disease despite use of sulfasalazine, 5-aminosalicylate, oral budesonide, or exclusive enteral nutrition, we suggest oral prednisone to induce clinical remission.
GRADE: Conditional recommendation, moderate-quality evidence.
Vote: strongly agree, 33%; agree, 67%.

Key evidence. The evidence for the efficacy of systemic corticosteroids compared to placebo was discussed in Statement 6. In addition, RCTs comparing conventional corticosteroids and budesonide were considered. As described in Statement 4, conventional corticosteroids were significantly more effective than budesonide for induction of remission in a meta-analysis of 8 trials.[41] The 2 small RCTs that compared prednisolone with budesonide in pediatric patients were inadequately powered to demonstrate a treatment benefit.[42,43] The quality of evidence was downgraded to moderate due to serious risk of bias. However, it was not downgraded for imprecision, inconsistency, or indirectness in relation to populations due to the availability of limited data from pediatric populations.

Discussion. Although less adequately examined in children, conventional corticosteroids have been shown to be more effective than budesonide and 5-ASA in adults.[25,41] In an SR&MA conducted for this consensus, conventional corticosteroids were more effective than EEN in adults, whereas both treatments were equally effective in pediatric patients with comparatively shorter duration of CD (frequently new onset) (see Statement 9). The data supporting superior efficacy of conventional corticosteroids in head-to-head trials suggest that patients have a greater likelihood of responding, and thus may benefit from these agents after failure of budesonide, 5-ASA, or EEN. Efficacy directly after other treatment failures, however, has not been assessed specifically. Therefore, the consensus group made a conditional suggestion in favor of the use of conventional corticosteroids as a second-line treatment option for induction of remission.

Statement 8: In patients with Crohn's disease of any severity, we recommend against oral corticosteroids to maintain clinical remission.
GRADE: Strong recommendation, low-quality evidence.
Vote: strongly agree, 100%.

Key evidence. A meta-analysis including 3 RCTs found no significant reduction in the odds of relapse with ongoing corticosteroid therapy compared to placebo (12-month OR, 0.82; 95% CI, 0.47–1.44).[52] In addition, attrition was high, with only about 36% of patients available for the 12-month analysis, primarily due to adverse events.

The quality of evidence was downgraded to low due to serious risk of bias and serious imprecision. However, it was not downgraded for indirectness with respect to populations due to the availability of limited data from pediatric populations.

Discussion. The consensus group made a strong recommendation against the use of corticosteroids for maintenance therapy because of the lack of demonstrated efficacy in preventing relapse and concerns around the adverse events associated with long-term use, particularly in children.

Exclusive enteral nutrition

Statement 9: In patients with Crohn's disease, we suggest exclusive enteral nutrition to induce clinical remission.
GRADE: Conditional recommendation, very low-quality evidence.
Vote: strongly agree, 33%; agree, 67%.

Key evidence. Seven SR&MAs have been published that evaluated studies comparing EEN to corticosteroids for induction of clinical remission in adult,[53–55] pediatric,[56–58] or a mixed population of patients with CD.[59] Due to limitations of these previous SR&MAs, an updated SR&MA was conducted to inform the development of this guideline.

The SR&MA conducted for this meeting included only RCTs published in full that compared EEN with placebo or other active treatments in patients with active CD. No placebo-controlled trials were identified. The MA included 9 RCTs (2 pediatric[51,60] and 7 adult trials[61–67]) comparing EEN with corticosteroids in 435 patients (57 pediatric and 378 adult patients). EEN was inferior to corticosteroids for induction of remission in the combined (OR, 0.43; 95% CI, 0.22–0.87) and adult patient populations (OR, 0.27; 95% CI, 0.17–0.43). In the 57 pediatric patients randomized, there was no significant difference in clinical remission rates between EEN and corticosteroids (83% vs 61%; OR, 3.04, 95% CI, 0.73–12.65). There was no significant difference in the incidence of adverse events between EEN and corticosteroids (21% vs 30%; OR, 0.41; 95% CI, 0.15–1.09). All adverse events were minor and included nausea, vomiting, abdominal pain, and diarrhea with EEN, and Cushingoid facies and acne with corticosteroids. However, the more serious adverse effects of steroids (eg, osteoporosis, growth failure, adrenal suppression) were not evaluated in these trials. EEN was associated with significantly higher withdrawal rates than corticosteroids in the adult RCTs (OR, 6.57; 95% CI, 2.24–19.24), but not in the pediatric RCTs (OR, 0.59; 95% CI, 0.09–4.01).

There was wide variation in disease activity, onset of disease, disease location, study designs, methods used to define disease activity and remission, duration of interventions, length of follow-up, and use of concomitant medication. In addition, due to the nature of the intervention, blinding was not possible.

In the combined population, the overall quality of evidence for the outcome of clinical remission was very low against the use of EEN, however, in the pediatric population, the evidence was very low in support of the use of EEN. The quality of evidence was downgraded to very low due to serious risk of bias, serious inconsistency, serious indirectness with respect to disease activity, onset of disease, and disease location, as well as variations in the types of enteral formula used and the use of concomitant medications, and serious imprecision.

Discussion. There were very-low-quality data showing that EEN was less effective than corticosteroids in a combined population of adults and pediatric patients. However, in 2 very small trials of pediatric patients alone, no difference in clinical remission rates with EEN vs corticosteroids was demonstrated. Most pediatric studies included newly diagnosed patients, whereas adult clinical trials have been conducted among patients with a much longer time since diagnosis. No placebo-controlled RCTs were found, and the available data suggested that at least in pediatric patients, EEN was as effective as an active therapy (corticosteroids) for the induction of remission (see Statement 6). In the pediatric trials, mucosal healing rates with EEN were significantly greater than those with corticosteroids, however, there were limitations, such as small numbers of participants and lack of blinding or allocation concealment.[51,60]

Withdrawal rates were high in the adult studies, but not in the pediatric trials. Adverse events with EEN were generally minor, and mainly gastrointestinal in nature.

Under-nutrition in children with CD, although less important than direct effects of pro-inflammatory cytokines released from inflamed intestine, can contribute to impairment of growth and pubertal development.[7,68] Use of EEN restores a normal nutritional status and avoids corticosteroid use, which may also impede linear growth.[69] Growth data reported in one of the pediatric EEN RCTs showed a significant improvement in weight gain with EEN compared to corticosteroids, but no difference in height gain.[51]

Protocols for EEN therapy varied with respect to specific formula used (although usually polymeric), mode of administration (nocturnally via nasogastric tube or via oral drinking), allowance of clear fluids other than water during treatment, and duration of therapy.[70] One RCT[71] and 1 prospective study[72] found EEN (defined as 100% EN) to be more effective than partial EN (PEN; defined as 50% of calories via EN while eating an unrestricted diet).

Shorter duration of CD among children vs adults included in clinical trials, as well as better adherence, may

explain the better results in the SR&MA of pediatric RCTs compared to RCTs in adults. In clinical practice, EEN is generally attempted early as first-line therapy in patients with new-onset CD.[8]

Nutrition is important in children with CD, and, based on similar efficacy and better safety compared to corticosteroids in the pediatric RCTs, the consensus group suggested a course of EEN for induction of remission was a reasonable first-line treatment strategy in pediatric patients, although the group concluded that there was not enough evidence to define the required duration of therapy. However, this statement was a conditional suggestion due to the conflicting evidence in adults, and the very small number of children included in individual pediatric RCTs, most of which had a high risk of bias. Moreover, reimbursement of formula in many Canadian jurisdictions has, until recently, required that the formula be administered via nasogastric tube. The inconvenience of such enteral feeding has been a major barrier to acceptance.

Statement 10: In patients with Crohn's disease, we recommend against partial enteral nutrition to induce clinical remission.
GRADE: Strong recommendation, very-low-quality evidence.
Vote: strongly agree, 80%; agree, 20%.

Key evidence. No RCTs comparing PEN to placebo or any active therapy (including steroids and immunosuppressants) were found. In 1 RCT in 50 children with active CD, PEN was less effective than total EN for the induction of clinical remission (15% vs 42%; $P = .035$).[71] This yielded an OR of 0.25 (95% CI, 0.07–0.97), but the CIs were very wide. Similarly, in a recent multicenter North American study, patients allowed 20% of total calories as regular food actually consumed 50% of calories as such, and were less likely to achieve either clinical remission or reduction in fecal calprotectin compared with those receiving EEN.[72] The quality of evidence was downgraded to very low due to serious risk of bias, serious inconsistency, very serious indirectness with respect to the interventions, and serious imprecision.

Discussion. PEN has been shown to be inferior to EEN. Similar to EEN, a protocol for PEN is poorly defined, and it is unknown what ratio of formula to oral food would be efficacious, if any.

The consensus group made a strong recommendation against the use of PEN for induction therapy based on the lack of efficacy, and concerns that using PEN will cause further delays in use of treatments with demonstrated efficacy.

Statement 11: In patients with Crohn's disease in remission, we suggest that if partial enteral nutrition is used it should be combined with other medications to maintain clinical remission.
GRADE: Conditional recommendation, very low-quality evidence.
Vote: strongly agree, 13%; agree, 87%.

Key evidence. An SR found 3 RCTs that assessed the efficacy of PEN to maintain remission in adults with quiescent CD.[73] Due to substantial differences in study designs, a meta-analysis was not performed. The trials compared PEN to regular diet alone in 1 study (with concomitant 5-ASA in both groups, and azathioprine permitted), to 6-mercaptopurine in 1 study (with concomitant 5-ASA in both treatment groups), and to 5-ASA plus regular diet in 1 study (with no concomitant therapy). There were substantial variations in the type and duration of EN and the duration of follow-up. All 3 RCTs concluded that PEN was similar to the comparator groups (regular diet with or without medication) for maintenance of clinical remission.

The majority of reported adverse events were mild and mainly gastrointestinal (ie, diarrhea, abdominal cramps, nausea, and vomiting). Intolerance and lack of compliance due to taste or smell of the formula were also reported.[73]

The RCTs included in this SR were very heterogeneous, had small sample sizes, low event rates, and none included pediatric patients.

The quality of evidence was downgraded to very low due to serious risk of bias, very serious indirectness with respect to the populations, interventions or comparators, and serious imprecision.

Discussion. The evidence for PEN maintenance therapy was very low quality, and in 2 of the 3 trials, PEN was used in combination with medications in Asian patients. Therefore, generalizability to other populations may be limited.

The SR[73] included 2 observational studies in pediatric patients.[74,75] In 1 retrospective study, maintenance PEN alone was more effective than no treatment, but less effective than the combination of azathioprine plus PEN. There were no differences in relapse rates between the combination of azathioprine plus EN and azathioprine alone.[74] In this study, only 31% of patients completed 8 weeks of EEN and were able to continue maintenance EN.

Older observational studies have reported improvements in growth with the use of supplementary PEN in patients also using conventional therapies.[73]

The consensus group suggested PEN for the maintenance of remission only when used as adjunctive therapy for patients receiving medications proven to be efficacious. Although a vote was conducted, both insufficient evidence and lack of consensus prevented the group from making any recommendation regarding the use of PEN as sole maintenance therapy.

Immunosuppressants

Statement 12: In patients with Crohn's disease of any severity, we recommend against thiopurine monotherapy to induce clinical remission.
GRADE: Strong recommendation, very-low-quality evidence.
Vote: strongly agree, 87%; agree, 13%.

Key evidence. Two SR&MAs,[76,77] which included the same 5 RCTs, reported no significant improvement in symptomatic remission rates with thiopurine therapy (azathioprine or 6-mercaptopurine) compared to placebo (RR for failure to achieve remission, 0.87; 95% CI, 0.71–1.06).[77] Four of the 5 studies combined thiopurines with a tapering course of steroid therapy during induction; therefore, the data demonstrated no additional benefit of adjunctive thiopurine therapy over steroids alone.

Data on serious adverse events were available from 2 trials; in the pooled analysis, the incidence was higher with thiopurines vs placebo (14% vs 4%), but this was not statistically significant (RR, 2.57; 95% CI, 0.92–7.13).[76]

The RCTs included in these SR&MAs had small sample sizes, low event rates, and no RCTs were found in pediatric patients.

The quality of evidence was downgraded to very low due to serious risk of bias, serious indirectness with respect to the populations, interventions, or comparators, and serious imprecision.

Discussion. RCTs in adults have not shown a significant benefit with thiopurines for induction therapy, and no pediatric RCTs were found. These agents are slow-acting and are associated with poor tolerability (eg, allergic reactions, leukopenia, pancreatitis, and nausea[76]) and safety issues (eg, lymphoma, including hepatosplenic T-cell lymphoma [HSTCL],[78,79] non-melanoma skin cancer,[80] and myelosuppression[81,82]). (See also Statements 13 and 14.)

Based on the lack of evidence of beneficial effects, and the safety concerns, the consensus strongly recommended against use of a thiopurine alone for induction therapy.

Statement 13: In female patients with Crohn's disease, we suggest a thiopurine to maintain remission.
GRADE: Conditional recommendation, low-quality evidence.
Vote: strongly agree, 20%; agree, 73%; neutral, 7%.

No consensus F: In male patients with Crohn's disease the consensus group does not make a recommendation (for or against) regarding use of a thiopurine to maintain remission.

Key evidence. Evidence for the efficacy of maintenance thiopurine therapy comes from 2 SR&MAs of RCTs in adults who had achieved remission, generally with a combination of corticosteroid and thiopurine therapy.[77,83] A meta-analysis of 6 studies found that azathioprine was significantly superior to placebo in maintaining remission over 6–18 months (RR, 1.19; 95% CI, 1.05–1.34).[83] One additional small RCT withdrawal trial, published after the meta-analyses, also reported a reduction in risk of relapse with ongoing thiopurine therapy, which was significant at 1 year, but not at 2 years.[84] Because most of the patients in these studies had achieved remission while on a thiopurine, they may have been more likely to show a positive effect with thiopurine maintenance therapy. Thiopurine use was associated with a 40% (hazard ratio [HR], 0.59; 95% CI, 0.48–0.73) reduction in the risk of first surgical resection in patients with CD in a meta-analysis of retrospective observational studies.[85]

One RCT[86] and 1 observational study[87] assessed thiopurine maintenance therapy in pediatric patients. The small RCT found that, in children receiving corticosteroid therapy, the addition of 6-mercaptopurine was associated with a lower rate of relapse compared to adjunctive placebo at 18 months (9% vs 47%; $P = .007$).[86] Thiopurine use was also associated with decreased use of corticosteroids. In the observational study, 47% and 23% of pediatric patients remained in remission with thiopurine therapy at 6 and 12 months, respectively.[87]

Compared to placebo, azathioprine demonstrated a significantly greater risk of adverse events (RR, 1.29; 95% CI, 1.02–1.64) and serious adverse events (RR, 2.45; 95% CI, 1.22–4.90). Common events included pancreatitis, leukopenia, nausea, allergic reaction, and infection.[83]

The quality of evidence was downgraded to very low due to serious risk of bias, serious indirectness with respect to the populations, and serious imprecision.

Discussion. Evidence from adult and pediatric RCTs supports the efficacy of thiopurines for maintenance therapy. However, thiopurines are associated with tolerability issues,[83] and a risk of rare, but serious adverse outcomes, including lymphoma (eg, HSTCL),[78,79] non-melanoma skin cancers,[80] and cervical cancer.[88] During longitudinal surveillance of more than 189,000 IBD patients for a median of almost 7 years, the risk of lymphoma among those exposed to thiopurine monotherapy was increased (adjusted HR, 2.60; 95% CI, 1.96–3.44; $P < .001$). However, the absolute incidence rate of 0.54 (95% CI, 0.41–0.67) per 1000 person-years was low among patients exposed to thiopurines. The risk with exposure to thiopurines and/or anti-TNFs was higher in males than females (adjusted HR, 1.56; 95% CI, 1.25–1.94), but was elevated in both groups compared to those without thiopurine exposure.[79] In 2014, Health Canada issued an alert warning of the risk of HSTCL with thiopurines.[89] This warning led to a position statement from the CAG recommending that continuation of thiopurine therapy consider the benefits and risks for an individual patient.[90]

In pediatric patients, the DEVELOP Registry (An Inflammatory Bowel Disease Multicenter, Prospective, Long-Term Registry of Pediatric Patients) has been established to provide post-marketing data on infliximab safety in pediatric patients with CD or ulcerative colitis.[91] The registry identified exposure to thiopurines as increasing the risks of malignancy compared to Surveillance, Epidemiology, and End Results Program database age- and sex-matched healthy peers, and of hemophagocytic lymphohistiocytosis occurrences in the setting of first exposure to Epstein-Barr virus.

The consensus group concluded that the evidence for efficacy suggested that thiopurines were a viable option for maintenance of remission, but there were safety concerns. In balancing the concern of teratogenicity with methotrexate, the consensus group made a suggestion in favor of their use in female patients, but this was conditional because although the risk of lymphoma is higher in males, it

remains elevated in both sexes. Although a vote was conducted, both safety concerns and lack of consensus prevented the group from making a recommendation regarding the use of thiopurine maintenance therapy in male patients. Some participants argued that the benefits outweighed the risks, while others argued that the potential for life-threatening adverse events was not acceptable given the availability of alternate therapies.

Statement 14: In patients with Crohn's disease, we suggest that testing for thiopurine methyltransferase by genotype or enzymatic activity be done prior to initiating thiopurine therapy to guide dosing.
GRADE: Conditional recommendation, very low-quality evidence.
Vote: strongly agree, 27%; agree, 67%; neutral, 7%.

Key evidence. Three RCTs assessed the benefits of thiopurine methyltransferase (TPMT) testing compared to no testing before initiating thiopurine therapy to individualize dosing and thereby minimize the risk of early profound neutropenia in those with low TPMT activity.[92–94] Genotyping was used in 2 studies[92,93] and enzymatic activity in 1 study.[94] Among the 1145 patients included, only 2 (0.17%) patients were homozygous, and 150 (13.1%) were heterozygous for variant alleles in the TPMT gene. A meta-analysis found no significant improvement with TPMT testing and dose adjustments compared to no testing in rates of hematologic events (RR, 0.94; 95% CI, 0.59–1.50) or treatment discontinuations (RR, 1.10; 95% CI, 0.94–1.27), and dose adjustments did not negatively impact clinical remission rates (RR, 1.03; 95% CI, 0.84–1.27).[95] While most patients with leukopenia in the largest study did not have reduced enzymatic activity, individuals with TPMT mutations and low or intermediate enzymatic activity had a significant reduction in the risk of hematologic adverse events with TPMT testing to guide dosing (RR, 0.11; 95% CI, 0.01–0.85).[92]

Although specific studies on the role of TPMT testing (genotype or enzymatic activity) in pediatric patients were not found, studies suggest that pediatric and adult patients have similar TPMT activity and similar adverse event frequencies.[96,97]

The quality of evidence was downgraded to very low due to serious risk of bias, serious indirectness (with respect to the populations), and serious imprecision.

Discussion. Although the incidence of patients with low or absent levels of TPMT (the enzyme needed to metabolize thiopurines) is low, these patients can be at risk of early severe myelosuppression if treated with standard thiopurine doses.[81,82] Of note, data suggest that thiopurines may be more likely to affect myelosuppression in East Asian populations than in Caucasian populations regardless of TPMT expression due to other genetic factors.[98] In a meta-analysis of 7 studies of patients with IBD treated with thiopurines, 3.2% developed leukopenia, and 0.09% of patients died.[81] Although rare, leukopenia can result in infectious or bleeding complications[99] and can be rapidly fatal.[81,100] Thus, there can be considerable harm associated with using thiopurines in patients with low or absent TPMT levels.

The risks of myelosuppression are reportedly highest in first 8 weeks of treatment,[99] but can occur at any time.[92–94] In patients with subnormal TMPT activity, clinical trials have suggested dose adjustments, such as a 50% dose in patients with intermediate enzymatic activity and even lower doses or not using thiopurines at all in patients with low/absent enzyme activity.[92–94] TMPT levels in pediatric patients appear to be similar to those in adults.

In light of the potential life-threatening consequences, the consensus group suggested TPMT testing (genotype or enzymatic activity) before initiating thiopurine therapy. This was a conditional suggestion because of concerns that TPMT testing may yield a false sense of security, as the majority of cases of leukopenia are unpredictable and independent of TPMT enzyme activity. TPMT testing results also do not correlate with the development of other adverse events, such as hepatotoxicity or pancreatitis.

Testing can be costly; however, 2 cost-effectiveness analyses in patients with IBD and rheumatoid arthritis,[81,101] and a prospective economic evaluation of the TARGET study,[93,102] suggested that TPMT testing (genotype) was a cost-effective strategy compared to no testing for patients initiating thiopurine therapy.

No consensus G: *In patients with mild to moderate Crohn's disease, the consensus group does not make a recommendation (for or against) regarding methotrexate monotherapy to induce clinical remission.*

Statement 15: In patients with Crohn's disease, we suggest parenteral methotrexate to maintain clinical remission.
GRADE: Conditional recommendation, low-quality evidence.
Vote: strongly agree, 40%; agree, 60%.

No consensus H: In patients with Crohn's disease, the consensus group does not make a recommendation (for or against) regarding oral methotrexate to maintain clinical remission.

Key evidence. *Methotrexate induction therapy.* Evidence for the efficacy of methotrexate for the induction of symptomatic remission comes from 1 SR&MA,[77] which included 2 RCTs conducted in adult patients with steroid-dependent CD. There was no statistically significant benefit on the outcome of failure to achieve remission (RR, 0.82; 95% CI, 0.65–1.03).[77] Although 1 of the RCTs found no benefit with oral methotrexate,[103] the other demonstrated a significant improvement in remission rates at 16 weeks, with an intramuscular methotrexate vs placebo (RR, 1.95; 95% CI, 1.09–3.48; $P = .025$).[104] Another SR without meta-analysis included 4 trials assessing methotrexate vs active comparators.[105] Methotrexate appeared to be as effective as thiopurines, and more effective than 5-ASA.

Very-low-quality pediatric data were available from an SR of 10, predominantly retrospective, case series. Short-term remission rates ($\leq$3 months) were only reported for parenteral methotrexate therapy. The remission rate in 1 study was 57% at 1 month and 29% to 70% at 3 months.[106]

The quality of evidence was downgraded to very low due to serious risk of bias, serious indirectness with respect to the populations and interventions, and serious imprecision.

Parenteral methotrexate maintenance therapy. Evidence for the efficacy of methotrexate for maintenance therapy in adults with CD in clinical remission was available from 2 SR&MAs.[77,107] Only 1 trial assessed intramuscular methotrexate as maintenance therapy.[108] In this trial, there was a significant reduction in the risk of relapse with methotrexate compared to placebo (RR, 0.57; 95% CI, 0.35–0.94) in adult patients who had achieved remission with a combination of steroid and methotrexate therapy. Two other small trials included in the SR&MAs showed no significant benefit of oral methotrexate on the risk of relapse.[103,109]

In the SR of pediatric observational studies, long-term remission rates were 37% to 62% at 6 months, and 25% to 53% at 12 months, primarily with parenteral methotrexate, although this was switched to oral in some case series.[106] The lack of a comparator group, varying patient populations, interventions, concomitant therapy, and definitions of remission, make these data difficult to interpret.

Oral methotrexate maintenance therapy. There were 2 RCTs using oral methotrexate for maintenance therapy, both of which demonstrated no significant benefit[103,109]; however, there was some question as to whether methotrexate was used to induce remission in these trials because patients had chronic steroid-dependent CD, and may not have been in remission.[77,107] The only positive maintenance RCT was the intramuscular trial.[108] If this is extrapolated to support the use of the oral form, the evidence would be further downgraded to very low quality. In the SR of pediatric data, some patients were switched to oral methotrexate, and the case series comparing oral and subcutaneous methotrexate reported similar remission rates.[106] However, these data are likely confounded by preferential use of oral therapy in patients with milder disease.

Safety. In the intramuscular study, withdrawals due to adverse events were significantly more common with methotrexate vs placebo (RR, 8.00; 95% CI, 1.09–59.51).[104] No serious adverse events were reported in the clinical trials.

In the SR of pediatric data, adverse events were similar to those seen in adults, with the most common adverse events being nausea and vomiting.[106] In a retrospective study, 31% of 102 pediatric patients with IBD experienced methotrexate intolerance (gastrointestinal or behavioral symptoms).[110] Strategies to reduce these effects in children have been reported.[111] Other adverse events included elevated liver function tests, headache, and hematologic toxicity.[106] Infectious adverse events were also reported (upper respiratory tract infection, varicella zoster reactivation).[106] An SR&MA of 12 cohort studies assessed the incidence of hepatotoxicity among children with IBD taking methotrexate. Overall, 10.2% (95% CI, 5.4%–18.5%) of patients had abnormal liver biochemistry and 4.5% (95%, CI, 2.8%–7.2%) of patients required discontinuation of the drug.[112] As the drug has the potential for teratogenic effects, embryotoxicity, abortion, and fetal defects in humans it cannot be used in pregnant females, raising significant concerns in those who provide care when pregnancy is possible.

The quality of evidence was downgraded to very low due to serious risk of bias, serious indirectness (with respect to the populations), and serious imprecision.

Discussion. Significant benefits with methotrexate for the management of CD are seen only in the 1 RCT, which used the intramuscular formulation for induction and maintenance therapy.[108] RCTs using oral methotrexate for induction or maintenance therapy have not shown significant benefit. There were no RCTs in pediatric patients, but the observational data suggested that about 25% to 50% of patients can achieve long-term remission with subcutaneous and/or oral methotrexate.[106]

Pharmacokinetic data show differences between oral and parenteral methotrexate,[113] and common practice in rheumatology has included switching from oral to parenteral in cases where oral methotrexate was not effective. In clinical practice, subcutaneous methotrexate is used more often than intramuscular delivery. The pharmacokinetics of the subcutaneously administered drug have been shown to be similar to intramuscular injection.[114,115] In addition, subcutaneous administration minimizes local reactions at the injection site, and may be more convenient and less painful.[113,114]

The RCTs using methotrexate as induction therapy provided conflicting results; the oral trials were negative, while the intramuscular trial was positive. Short-term results from the observational data in pediatric patients were only available for parenteral methotrexate. Based on these conflicting data, the consensus group did not make a recommendation for or against the use of methotrexate for induction therapy. Participants in support of this strategy cited the potential efficacy as demonstrated in the intramuscular trial, and the observational studies. Because there are very few treatments for CD, which is a lifelong disease, methotrexate is a potentially useful treatment that should not be discarded. Methotrexate has a slow onset of action, therefore, for patients who are not acutely symptomatic and in whom a delayed response would be acceptable, it may be an option to start it in the induction phase in order to use it as maintenance therapy. Participants who were against recommending methotrexate for induction therapy argued that the trials were not monotherapy trials; most patients were on other therapies (particularly corticosteroids), and the contribution of methotrexate is uncertain.

Based on evidence supporting beneficial effects of intramuscular methotrexate, the consensus group suggested parenteral methotrexate for use as maintenance therapy. However, there was insufficient evidence to make a recommendation regarding the use of oral methotrexate in this setting. While the RCTs using oral methotrexate were negative, these trials were very small, and the doses used may have been inadequate. The data from the intramuscular trial suggest the potential for efficacy with this medication. Some consensus participants argued that some patients in stable remission may continue to benefit when switched

from parenteral to lower cost, more convenient, oral methotrexate. This is supported by observational data reported in the SR of pediatric studies.[106]

Statement 16: In patients with Crohn's disease who are in clinical remission with a thiopurine or methotrexate as maintenance therapy, we suggest assessment for mucosal healing within the first year to determine the need to modify therapy if significant ulcerations persist.
GRADE: Conditional recommendation, very-low-quality evidence.
Vote: strongly agree, 13%; agree, 80%; neutral, 7%.

No consensus I: In patients with moderate to severe inflammatory Crohn's disease who have achieved clinical remission but not mucosal healing with a corticosteroid, thiopurine, or methotrexate, the consensus group does not make a recommendation (for or against) regarding anti-TNF therapy to induce and maintain mucosal healing. *(Note there was insufficient evidence at the time of the literature searches, but the consensus group recognized that this would need updating as new evidence becomes available).*

Key evidence. Observational data (1 SR of cohort studies, and post-hoc analyses of RCTs) have suggested that achieving deep remission is associated with improved clinical outcomes, including higher rates of clinical remission, improved quality of life, and reduced need for steroids, hospitalizations, and surgery.[10,11] The SR&MA of prospective cohort data, including 12 studies found that patients who had achieved mucosal healing had significantly increased rates of long-term clinical remission (OR, 2.80; 95% CI, 1.91–4.10) and mucosal healing (OR, 14.30; 95% CI, 5.57–36.74).[11] There was a trend to a greater CD-related surgery-free rate (OR, 2.22; 95% CI, 0.86–5.69), but this was not significant.

In pediatric patients, complete mucosal healing was associated with significantly higher rates of long-term remission for up to 3 years compared to ongoing active endoscopic disease.[12]

Rates of mucosal healing with anti-TNF therapy (27%–31%) were higher than those seen with immunosuppressants (16.5%) or placebo (0–13%).[116–118] Combination anti-TNF and immunosuppressant therapy (43.9%) provided even higher rates compared to anti-TNF (30.1%; $P = .06$) or immunosuppressant therapy (16.5%; $P < .001$) alone.[118] In addition, a higher rate of mucosal healing with combination therapy compared to conventional therapy at 2 years (73% vs 30%; $P = .0028$)[119] was a significant predictor of remaining in remission at 3 and 4 years (OR, 4.35; 95% CI, 1.10–17.22).[120]

Several case series in pediatric patients have reported rates of mucosal healing associated with anti-TNF therapy. Complete mucosal healing was seen in 22%–25% of patients, and endoscopic improvement in 44%–67%.[121–123]

The evidence was downgraded to very low due to serious risk of bias, serious indirectness with respect to the use of surrogate outcomes (mucosal healing) and serious imprecision.

Discussion. There are long-term benefits associated with mucosal healing. Assessment for mucosal healing generally requires endoscopy, which is both costly and invasive. Imaging (eg, magnetic resonance enterography) and biomarker levels (eg, C-reactive protein and fecal calprotectin) have been shown to correlate with endoscopy,[124] and changes in these parameters were recently shown to correlate with mucosal healing. The open-label, RCT CALM (published outside the search window) compared treatment escalation with an anti-TNF therapy based on both clinical symptoms and biomarkers (tight control) to symptom-driven decisions alone (clinical management) in 244 adult patients. At week 48, significantly more patients in the tight control group achieved mucosal healing (46%) than in the clinical management group (30%, risk difference, 16.1%; 95% CI, 3.9–28.3; $P = .010$).[125]

Based on the potential benefits associated with mucosal healing, the consensus group suggested that assessing this outcome was a useful management strategy in patients receiving immunosuppressant therapy. Data suggest higher mucosal healing rates with anti-TNF therapies and better long-term outcomes when healing is achieved. The consensus group, nevertheless, did not make a universal recommendation regarding switching to or adding an anti-TNF to therapy in all patients who have achieved clinical remission but not mucosal healing with immunosuppressant therapy. This was largely related to the fact that the degree of mucosal healing required to achieve clinically relevant benefits needs to be more clearly defined. The REACT-2 trial is underway in adults to assess whether early treatment intensification based on mucosal healing will reduce the risk of hospitalization, surgery, and CD complications compared to conventional step-up therapy.

Anti–Tumor Necrosis Factor Biologic Therapy

Statement 17: In patients with moderate to severe inflammatory Crohn's disease who have failed to achieve clinical remission with corticosteroids, we recommend anti-TNF therapy (adalimumab, infliximab) to induce and maintain clinical remission.
GRADE: Strong recommendation, high-quality evidence.
Vote: strongly agree, 100%.

Statement 18: In patients with moderate to severe inflammatory Crohn's disease who fail to achieve or maintain clinical remission with a thiopurine or methotrexate, we recommend anti-TNF therapy to induce and maintain clinical remission.
GRADE: Strong recommendation, high-quality evidence.
Vote: strongly agree, 93%; agree, 7%.

Key evidence. Anti-TNF therapy has been extensively studied in double-blind RCTs in adults, which have been assessed in a number of SRs with or without meta-analyses.[126–128] In most of the studies assessing its use to induce remission, patients had previously received other treatments, including corticosteroids and immunosuppressants, and analyses according to type of prior treatment were not

performed. For induction therapy, a meta-analysis including 10 trials found that anti-TNF therapy alone or with concomitant therapies was significantly more effective than placebo for the outcome of failure to achieve symptomatic remission (RR, 0.87; 95 % CI, 0.80–0.94; $P = .0004$). Results were significant for infliximab and adalimumab, but not certolizumab pegol.[126] For maintenance therapy, meta-analysis of 5 RCTs showed that anti-TNF therapy significantly reduced the risk of relapse in patients with CD in clinical remission compared to placebo (RR, 0.71; 95% CI, 0.65–0.76; $P < .00001$).[126] Results were significant for infliximab and certolizumab pegol, but not adalimumab. In another meta-analysis, all 3 anti-TNFs were significantly more effective than placebo for both induction and maintenance of remission.[129]

In the SR&MA, there were no significant differences in the incidence of adverse events with anti-TNF used for induction (RR, 0.99; 95% CI, 0.90–1.08) or maintenance of remission (RR, 0.93; 95% CI, 0.84–1.03) compared with placebo.[126]

The quality of evidence was rated as high with no concerns for risk of bias, inconsistency, indirectness, or imprecision.

Discussion. There is high-quality evidence for the efficacy of anti-TNF therapy for patients who have failed corticosteroids, or immunosuppressant therapies. These subgroups are not clearly differentiated in most trials, and most of the RCTs included both populations. Adalimumab and infliximab have demonstrated efficacy in adults in RCTs and in children in trials with open-label induction and randomized dose-ranging maintenance therapy. Results from studies assessing certolizumab for induction of remission did not demonstrate significant benefit, but benefit was demonstrated for maintenance of remission.[126] However, there were no controlled trials in pediatric patients, and generally maintenance therapy is continued with the agent used for induction, making certolizumab less appropriate.

In pediatric patients, anti-TNF induction therapy has been reported only in open-label trials.[130–133] For maintenance, 1 double-blind RCT[132] and 2 open-label RCTs (REACH-1[131] and a French trial[133]) were found. None of these trials was placebo-controlled, but rather compared different doses, different dosing intervals, or scheduled vs on-demand therapy. The majority of patients were receiving concomitant immunosuppressant therapy. The 1 double-blind RCT (IMAgINE-1) assessed adalimumab dose-ranging maintenance therapy after open-label weight-adjusted induction therapy, and reported a remission rate of 33.5% at week 26, with no significant difference between high- and low-dose adalimumab.[132] In the open-label RCT (REACH) of infliximab every 8 weeks vs every 12 weeks after open-label induction, the clinical remission rate was 56% after 1 year.[131]

Impaired growth, particularly if defined by the most sensitive parameter of reduced height velocity, has historically been a frequent complication of pediatric CD developing before puberty. Risk factors include prolonged disease before diagnosis and the inter-related factors of chronically, uncontrolled, intestinal inflammation, undernutrition, and chronic corticosteroid use.[6,69] Anti-TNF therapies have been associated with improved growth in IMAgINE-2,[134,135] REACH-1,[131] the French trial,[133] the RISK study,[136] and a prospective cohort study.[137]

Anti-TNFs are generally well tolerated; however, increased risk of infections and reactivation of tuberculosis have been reported in adults.[79,138,139] In pediatric patients, upper respiratory tract infections and nasopharyngitis were frequent, being reported in about 37%–43% of children in open-label extension trials.[134,140] During almost 5 years of follow-up of 100 pediatric patients who entered the IMAgINE-2, open-label, extension study, the incidence of opportunistic infections was 5.7% (2.2/100 patient-years), with all but 1 being considered non-serious adverse events.[134] Only one opportunistic infection was reported in the open-label extension of the REACH trial (n = 60, up to 3-year follow-up), also considered non-serious.[140] In adults, the risks of lymphoma were highest in those exposed to combination therapy, but were also elevated in patients exposed to anti-TNF monotherapy compared to no exposure (adjusted HR, 2.41; 95% CI, 1.60–3.64; $P < .001$).[79]

Based on the efficacy demonstrated in RCTs in adults and children, the consensus group strongly recommended anti-TNF therapy for patients with moderate to severe CD who have failed corticosteroid or immunosuppressant therapy.

Only 2 members of the consensus group reported no conflict of interest regarding anti-TNF therapies. Two separate votes were conducted for statement 17, one for these 2 members, and another for the consensus group as a whole, in both cases the vote was unanimously "strongly agree."

Statement 19: In patients with severe inflammatory Crohn's disease judged at risk for progressive, disabling disease, we suggest anti-TNF therapy as first-line therapy to induce and maintain clinical remission.

GRADE: Conditional recommendation, very low-quality evidence.

Vote: strongly agree, 47%; agree, 53%.

Key evidence. The efficacy of anti-TNF therapy in adults with CD is described under Statements 17 and 18. The majority of RCTs were conducted in patients who had received previous non-biologic therapies. These data were extrapolated to the use of these agents as first-line treatments, and therefore downgraded in assessment of quality to very-low-quality evidence.

Additional support for the early use of anti-TNF therapy comes from open-label, prospective trials using combined anti-TNF and immunosuppressive therapy in newly diagnosed, treatment naïve patients.[119,141] In these studies, "top-down" treatment was associated with significantly higher rates of symptomatic remission at earlier time points compared to not using early anti-TNF therapy. Post-hoc analyses of several other adult RCTs have suggested that rates of deep remission (clinical remission plus mucosal

healing) may be highest in patients with early CD (<18–24 months duration) with anti–TNF-containing regimens.[142,143]

Discussion. Some evidence has demonstrated the benefits of using early anti-TNF therapy in adults who are treatment naïve[119,141] and those who are naïve to anti-TNF and immunosuppressant therapy.[119,142]

Secondary analysis of data from the RISK observational study using propensity scores compared the early introduction of anti-TNF therapy, immunosuppressant therapy, and no immunotherapy, within 3 months of diagnosis in pediatric patients in a real-world clinical setting.[136] Early anti-TNF therapy was superior to early treatment with an immunosuppressant (85.3% vs 60.3%; RR, 1.41; 95% CI, 1.14–1.75; $P = .0017$), or no early immunotherapy (54.4%; RR, 1.57; 95% CI, 1.23–1.99; $P = .0002$) in achieving corticosteroid-free remission at 1 year after diagnosis. In addition, the mean height *z*-scores increased compared with baseline only in the early anti-TNF group.

The consensus group suggested the use of anti-TNF agents as a first-line treatment based on the demonstrated efficacy as induction therapy, and supportive data suggesting benefits in newly diagnosed patients. This was a conditional suggestion because of the same concerns discussed under Statements 17 and 18.

The group discussed that early anti-TNF may be warranted in pediatric patients with extensive disease or deep colonic ulcerations, or in those in whom corticosteroids could be expected to provide no benefit or could have the potential to exacerbate underlying conditions, such as complex perianal disease, severe bone disease, mental health disorders, or linear growth delay. The group also emphasized that there is an urgent need for better predictors of chronically active, severe inflammatory disease, and disease that will result in progressive intestinal damage that would necessitate intestinal resection.

Statement 20: When starting infliximab in males, we suggest against using it in combination with a thiopurine.

GRADE: Conditional recommendation, low-quality evidence.

Vote: strongly agree, 40%; agree, 47%; neutral, 13%.

No consensus J: When starting infliximab in females, the consensus group does not make a recommendation (for or against) regarding combining it with a thiopurine to maintain a durable clinical remission.

Key evidence. Evidence of a treatment benefit for infliximab in combination with a thiopurine comes from the prospective randomized SONIC trial in adults, which demonstrated higher rates of clinical remission and endoscopic healing at week 26 with combination vs infliximab monotherapy (57% vs 44%; $P = .02$).[118] In an SR&MA, this yielded an RR of failure to achieve remission with combination vs infliximab monotherapy of 0.78 (95% CI, 0.62–0.97).[144]

An SR&MA of cohort data from RCTs of anti-TNF therapy (adalimumab, certolizumab, or infliximab), found no significant differences in the rates of clinical remission with the combination of an anti-TNF plus an immunosuppressant (thiopurine or methotrexate) compared to an anti-TNF alone for induction (OR, 1.28; 95% CI, 0.77–2.16) or maintenance therapy (OR, 1.02; 95% CI, 0.80–1.31).[145] There were no significant differences in rates of clinical remission between monotherapy and combination therapy for maintenance treatment when the 3 anti-TNF agents were pooled, or when they were analyzed separately.

In the SONIC trial, the incidence of adverse events was generally similar in the combination and monotherapy groups, and there were no significant differences in the RR of serious infection.[118,144] Evidence on rare, but important adverse events was very low quality. Observational data suggest a higher risk of lymphoma[79] and activation of tuberculosis[138] in patients exposed to combination vs anti-TNF monotherapy.

One open-label, pediatric RCT randomized patients after 10 weeks of combination induction therapy to maintenance with either 54 weeks of combination therapy or 26 weeks of combination therapy, followed by 26 weeks of anti-TNF monotherapy.[146] At the end of the 10-week open induction phase, 65.5% of patients were in clinical remission. At the end of the 54-week maintenance phase, there was no significant benefit of combination therapy with <5% of patients in either group experiencing a loss of response. The incidence of serious adverse events was 9%, of which the most common was primary Epstein-Barr virus infection.

The evidence was downgraded to low due to serious inconsistency and serious imprecision.

Discussion. In the REACH pediatric study of infliximab, all patients were required to be administered immunosuppressants, and 10-week remission rates were 59%. However, there was no monotherapy comparison group.[131] One RCT in adults (downgraded to low-quality evidence for indirectness [extrapolated to pediatric] and imprecision [low number of events]) suggested a potential efficacy benefit with combination therapy over anti-TNF monotherapy. However, administration of infliximab monotherapy in the SONIC study was strictly according to standard protocol (precisely 5 mg/kg every 8 weeks) without any attention to optimizing drug exposure via therapeutic drug monitoring. There is also an important benefit of concomitant immunomodulators in prolonging clearance of infliximab and reducing rates of anti-infliximab antibody development, as demonstrated in SONIC and in pediatric cohort studies.[137,147] Avoiding secondary loss of response related to anti-drug antibody development is extremely important in young patients, given the long lives ahead, during which treatment will be needed. The modest increment in efficacy of combination therapy might be overcome via individualized dosing regimens of infliximab monotherapy to avoid low or absent trough titers to help avoid development of anti-drug antibodies.

The consensus group recognized the improved durability of infliximab response with combination therapy, but suggested against selection of thiopurines as the concomitant drug for males based on safety concerns, as described in Statements 12 and 13. Specifically, the risk of the extremely rare but almost uniformly fatal HSTCL, is attributable to

thiopurine use, both alone and in combination with anti-TNF. The highest risk has been reported among males aged <35 years receiving combination thiopurine and anti-TNF therapy.[148] Post-marketing surveillance of infliximab continues to identify at least 2 occurrences worldwide annually and always in patients receiving anti-TNF in combination with a thiopurine. Two such occurrences were reported in the DEVELOP pediatric IBD registry.[91]

In adults, the risk of other lymphomas (usually Epstein-Barr virus–driven), which is age-related and of lesser concern for pediatric patients, was increased in patients exposed to combination thiopurine plus anti-TNF therapy compared to no exposure, thiopurine monotherapy, or anti-TNF monotherapy.[79] In the open-label, RCT in 84 pediatric patients, there were 4 occurrences of primary EBV infection, 1 of herpes simplex virus, and 1 of chickenpox infection, throughout the study.[146]

The group concluded that the benefits of thiopurine in combination with infliximab did not outweigh the risk of HSTCL in males. However, the consensus group did not make a recommendation regarding the use of combination therapy for females. The risk of HSTCL, although lower in females, remains elevated compared to no exposure, therefore, some participants argued that the risks outweighed the benefits, while others disagreed and noted that combination therapy with thiopurines remains a potentially useful strategy for some patients.

Statement 21: When starting adalimumab in males, we suggest against using it in combination with a thiopurine.
GRADE: Conditional recommendation, very-low-quality evidence.
Vote: strongly agree, 40%; agree, 53%; neutral, 7%.

No consensus K: When starting adalimumab in females, the consensus group does not make a recommendation (for or against) regarding combining it with a thiopurine to maintain a durable clinical remission.

Key evidence. An open-label, RCT (DIAMOND), in adults who were immunosuppressant- and biologic-naïve found no difference in 26-week clinical remission rates between the combination of adalimumab plus azathioprine (68.1%) and adalimumab monotherapy (71.8%; $P = .63$). The rate of endoscopic improvement was significantly higher with combination therapy at 6 months but not 12 months.[149] Similarly, post-hoc analyses of cohort data from RCTs in adults did not show a significant benefit with combination adalimumab and immunosuppressant therapy (thiopurine or methotrexate) over adalimumab alone for induction (OR, 0.88; 95% CI, 0.60–1.27) or maintenance of remission (OR, 0.88; 95% CI, 0.58–1.35).[145]

Additional very low quality of evidence data in pediatric patients also reported no benefit with the combination of adalimumab plus an immunosuppressant. In a post-hoc analysis of the IMAgINE-1 RCT, there was no difference in remission rates between those who received concomitant immunosuppressants and those who did not (35.9% vs 29.6%).[132,150]

The evidence was downgraded to very low due to serious risk of bias and very serious imprecision.

Discussion. There were very few data to suggest a benefit of adding a thiopurine when starting adalimumab therapy. In the DIAMOND trial, the primary end point was negative, but there was evidence of more rapid mucosal healing in the combination group.[149]

Although not statistically significant, there were trends toward higher adalimumab trough levels and lower rates of anti-adalimumab antibodies in the combination group compared to the monotherapy group. Although overall there were not significant differences in the rates of adverse events or study discontinuations between the combination and monotherapy groups, withdrawals specifically for side effects were significantly more frequent in the combination group.

For the same reasons as described in Statement 20 for infliximab/thiopurine combination therapy regarding safety concerns and less evidence of benefit, the consensus group suggested against the combination in males and did not make a recommendation regarding the use of combination therapy in females.

Statement 22: In male patients with Crohn's disease receiving immunomodulator therapy in combination with an anti-TNF therapy, we suggest methotrexate in preference to thiopurines.
GRADE: Conditional recommendation, very-low-quality evidence.
Vote: strongly agree, 27%; agree, 53%; neutral, 20%.

Key evidence. SRs have found few studies assessing the efficacy of concomitant methotrexate.[129,145] One RCT, the COMMIT study, compared the efficacy of combination therapy with infliximab plus methotrexate to infliximab alone, and found no difference in rates of symptomatic remission between the 2 treatment groups (HR, 1.16; 95% CI, 0.62–2.17; $P = .63$).[151] A very, small, open, pilot study reported an early benefit of combination therapy that was not sustained.[152]

The open-label, RCT in pediatric patients, described under Statement 20, included patients on either azathioprine or methotrexate in the combination treatment group, but did not specify the proportion receiving each drug. Overall combination therapy with infliximab plus an immunosuppressant was not associated with a benefit over infliximab alone in preventing loss of response over the 1-year follow-up.[146] Similarly, in the RCT assessing adalimumab in pediatric patients (IMAgINE-1), >60% of patients received immunosuppressants; however, the proportion receiving methotrexate was not reported, and a post-hoc analysis did not demonstrate a difference in remission rates between those who received concomitant immunosuppressants and those who did not.[132,150] All pediatric patients in the REACH study received concomitant immunosuppressants, but only 10% specifically received methotrexate.[131]

The quality of evidence was downgraded to very low due to serious risk of bias and very serious imprecision.

Discussion. Although the double-blind, placebo-controlled RCT failed to show a benefit with combination anti-TNF and methotrexate therapy, the evidence was assessed as very low quality.[151] The trial demonstrated that combination infliximab plus methotrexate was associated with a lower likelihood of developing antibodies to infliximab (4% vs 20%; $P = .01$), and there was a trend to higher median serum trough infliximab concentrations (6.35 μg/mL vs 3.75 μg/mL; $P = .08$). However, there was no significant clinical benefit. Of note, there were very high success rates among the patients in this trial, potentially due to the use of systemic corticosteroids to induce remission in all patients. The high success rate in both arms of the trial may have resulted in a lack of power to demonstrate clinical benefit of concomitant methotrexate.[151]

The most frequent adverse event with methotrexate therapy is nausea (up to 25% of patients), however, there is a risk of rare, but serious adverse events, including hepatotoxicity, bone marrow suppression, hypersensitivity pneumonitis, gastrointestinal toxicity, teratogenicity, and infections.[153] In contrast to thiopurines (see Statement 20), methotrexate has not been associated with an increased incidence of lymphoma, however, historic rates of use in CD are low.[153]

Although a vote was conducted, both insufficient evidence and lack of consensus prevented the group from making a recommendation regarding combining infliximab or adalimumab with methotrexate to maintain a durable clinical remission in all patients or males alone. However, if a clinician judges a patient to require the combination of an anti-TNF and an immunosuppressant, the consensus group suggested that methotrexate should be used over thiopurines in males. This was a conditional suggestion, as, despite the lower risk of lymphoma, there are other safety concerns in addition to a lack of evidence demonstrating the efficacy of combination therapy with methotrexate in CD.

Statement 23: In patients with Crohn's disease who have a suboptimal clinical response to anti-TNF induction therapy or loss of response to maintenance therapy, we suggest regimen intensification informed by therapeutic drug monitoring.
GRADE: Conditional recommendation, very-low-quality evidence.
Vote: strongly agree, 53%; agree, 47%.

Key evidence. One RCT (TAXIT) evaluated the efficacy of regular therapeutic drug monitoring (TDM) in adults with IBD, who were stable on infliximab maintenance therapy, and had their dose proactively optimized before study entry to achieve an infliximab trough concentration between 3–7 μg/mL.[154] Among CD patients, there was no significant difference in clinical remission rates between those who were randomized to dosing guided by TDM and those randomized to standard clinically-based dosing (62.6% vs 54.9%; $P = .353$). Relapse rates were significantly lower in patients who received TDM-based dosing compared to those who received clinically based dosing (17% vs 7%; $P = .018$); however, this was in the combined IBD population.

The majority of data related to TDM come from observational studies, which have been assessed in SR&MAs of studies in adults using infliximab[155,156] or adalimumab.[157] These analyses showed that antibodies to anti-TNFs were associated with greater likelihood of loss of response,[156,157] and higher serum anti-TNF levels were associated with a greater probability of clinical remission and mucosal healing.[155,157] However, these studies do not assess whether using TDM proactively will have an impact on patient outcomes, as opposed to reactive TDM when patients are symptomatic.

In the IMAgINE-1 study in pediatric patients, higher trough levels were associated with greater rates of remission, but there was no correlation between antibodies to anti-TNF therapy and remission/response (n = 6 patients with antibodies).[158] In a retrospective case series of pediatric patients with IBD, those with very low infliximab drug levels had high rates of infliximab antibodies, non-response, or loss of response.[159]

The quality of evidence was downgraded to very low due to serious risk of bias and very serious imprecision.

Discussion. Evidence suggests that regimen intensification (increasing the dose or shortening the dosing interval) may help increase remission rates. In TAXIT, dose optimization before randomization resulted in significant improvements in remission rates (88% vs 65%; $P = .02$) and median C-reactive protein concentrations (3.2 mg/L vs 4.3 mg/L; $P < .001$) compared to before dose escalation.[154] Two SRs of case series have shown response rates of about 54%–90%, and remission rates of about 31%–40% among patients who underwent dose intensification.[160,161] In addition, among pediatric patients losing response in the REACH trial, planned dose intensification resulted in 75% of patients (n = 24/32) regaining response.[131]

Observational data suggest that antibodies to anti-TNFs are associated with greater likelihood of loss of response, and higher serum anti-TNF levels are associated with a greater likelihood of maintained remission. However, the only RCT that prospectively assessed the impact of proactive TDM to guide dosing during infliximab maintenance therapy demonstrated no significant benefit in its primary outcome of higher clinical remission rate at 1 year.[154] In a small, single-blind RCT, treatment of secondary anti-TNF failure using an algorithm based on combined drug serum levels and antibody measurements significantly reduced average treatment costs per patient compared with routine dose escalation.[162] The TDM-guided approach did not have a negative effect on clinical efficacy, and was cost-effective during longer-term follow-up.[163]

Based on the evidence that regimen intensification can improve outcomes, the consensus group suggested this strategy before considering a change in therapy. The statement was a conditional suggestion because of uncertainties of TDM, not uncertainty pertaining to the value of dose intensification.

No consensus L: In patients with Crohn's disease who have achieved a clinical remission with anti-TNF therapy, the consensus group does not make a recommendation (for or against) regarding assessment for mucosal healing within the first year to determine the need to modify therapy.

Key evidence. Evidence for the potential benefits of mucosal healing and the rates of mucosal healing with anti-TNF therapy were discussed under Statement 16.

Discussion. The discussion around the utility of assessing for mucosal healing was discussed under Statement 16.

In the context of anti-TNF therapy, the consensus group did not make a recommendation regarding endoscopic assessment of mucosal healing among patients in clinical remission. Data concerning endoscopic healing achieved with other agents, including alternate pathway biologic therapies, are very sparse. In addition, the degree of mucosal healing warranting a change in therapy has not been defined, nor has the ideal duration of therapy before assessing for endoscopic healing.

Non-Anti–Tumor Necrosis Factor Biologic Therapy

Statement 24: In patients with moderate to severe Crohn's disease who fail to achieve or maintain clinical remission with anti–TNF-based therapy, we suggest ustekinumab to induce and maintain clinical remission.

GRADE: Conditional recommendation, moderate-quality evidence for induction, moderate-quality evidence for maintenance.

Vote: strongly agree, 47%; agree, 53%

Key evidence. Evidence for the efficacy of ustekinumab for induction of remission was available from 4 RCTs in adult patients, including both patients who had and those who had not failed anti-TNF therapy.[164–166] In an SR&MA of these 4 trials (n = 1947), ustekinumab was significantly better than placebo for the outcome of failure to achieve remission (RR, 0.91; 95% CI, 0.86–0.95).[167]

Two RCTs were conducted in patients who had previously failed anti-TNF therapy.[164,165] In CERTIFI, there were no significant differences in remission rates at week 6, despite ustekinumab being associated with a higher response rate compared to placebo.[165] However, in the UNITI-1 trial, 1 intravenous infusion of ustekinumab at 6 mg/kg resulted in improved rates of both response (34%) and remission (21%) at week 8, compared to placebo (22% and 7%, respectively).[164]

Two RCTs assessed the use of ustekinumab as maintenance therapy in patients who previously failed anti-TNF therapy.[164,165] In the CERTIFI trial, ustekinumab resulted in significantly increased rates of clinical remission at 22 weeks compared with placebo (41.7% vs 27.4%; P = .03).[165] In the combined population in the UNITI-IM trial, which included responding patients who had previously failed either anti-TNF or were biologic-naïve but had failed conventional therapy, significantly more patients were in remission with maintenance ustekinumab after 1 year of treatment compared to placebo (49%–53% vs 36%). In the UNITI-1 subgroup of patients with prior anti-TNF failure, there were no significant differences in clinical remission rates between ustekinumab and placebo at 1 year.[164]

In the SR&MA, there were no significant differences in the rates of adverse events, serious adverse events, or withdrawals due to adverse events.[167]

No RCTs assessing ustekinumab in pediatric patients with CD were found.

The quality of evidence was downgraded to moderate due to indirectness with respect to populations (lack of pediatric data).

Discussion. Ustekinumab has demonstrated efficacy for induction and maintenance of remission in the overall patient population, as well as patients who have previously failed or were unable to tolerate anti-TNF therapy.

No RCTs in pediatric patients with CD were found; specific, pediatric case-series and experience among participants are still limited.[168–170] Among the 6 cases reported, all had previous primary or secondary failure, or intolerance to, anti-TNF therapy, and 3 of the 6 successfully achieved clinical remission.

Ustekinumab has been studied in a RCT in adolescent patients from 12 to 17 years of age with plaque psoriasis.[171] There were no significant differences in the rates of adverse events between ustekinumab and placebo at 12 weeks.[171] Infections were the most common adverse events, primarily nasopharyngitis, upper respiratory tract infections, and pharyngitis. During the 60-week follow-up, there were no reported malignancies, tuberculosis, opportunistic infections, anaphylactic reactions, or serum sickness-like reactions.

Based on the evidence for efficacy in adults and the reported safety in pediatric patients with plaque psoriasis, the consensus group made a conditional suggestion in favor of ustekinumab therapy in patients who have failed anti-TNF therapy. This was a conditional suggestion because of the lack of RCTs in pediatric patients with CD and the modest effect sizes in the adult trials.

No consensus M: In patients with moderate to severe Crohn's disease who fail to achieve or maintain clinical remission with an anti-TNF–based therapy, the consensus group does not make a recommendation (for or against) regarding the use vedolizumab to induce and maintain clinical remission.

Key evidence. Evidence for the efficacy of vedolizumab for induction therapy was available from 3 RCTs in adults with CD who had previously failed anti-TNF therapy.[172,173] or had no prior anti-TNF exposure,[174] which have been analyzed in several SR&MAs.[129,175] For the outcome of failure to induce symptomatic remission, vedolizumab was superior to placebo in the combined patient group (RR, 0.87; 95% CI, 0.79–0.95), and trended to benefit in the subgroup of patients who had previously failed anti-TNF therapy (RR, 0.89; 95% CI, 0.78–1.01).[175]

In the RCT that assessed the efficacy of vedolizumab maintenance therapy among responders to induction therapy, vedolizumab resulted in significantly higher 1-year remission rates compared to placebo (36%–39% vs 22%; OR, 2.20; 95% CI, 1.40–3.44).[129,172] Among those who had previously failed anti-TNF therapy, but who achieved clinical "response" at week 6 and were then re-randomized to vedolizumab vs placebo maintenance therapy, continuation of vedolizumab was significantly more effective than placebo.[172] There were no significant differences in the rates of serious adverse events, infections, or malignant neoplasms between vedolizumab and placebo.[129]

The evidence was assessed as very low quality due to the significant heterogeneity among the induction studies, as well as imprecision and indirectness. No RCTs assessing vedolizumab in pediatric patients with CD were found.

The evidence was downgraded to very low due to serious inconsistency, indirectness with respect to populations (paucity of pediatric data), and serious imprecision.

Discussion. No RCTs in pediatric patients with CD were found, but a small, prospective observational study[176] and case reports[177,178] suggest it may be beneficial in some children who have previously failed anti-TNF therapy. In the prospective study, 25% of patients with CD achieved remission at week 14 and 31% at week 22.[176] The retrospective case reports of pediatric patients with IBD found that vedolizumab tended to be slower acting and have lower remission rates in patients with CD compared to those with ulcerative colitis.[177,178] Long-term, open-label follow-up data report low rates of infusion reactions, serious infections, and malignancy.[179,180]

The consensus group did not make a recommendation for or against the use of vedolizumab in patients who had failed prior anti-TNF therapy. Vedolizumab did not show a significant benefit over placebo for induction of remission in prior treatment failures in the SR&MA.[175] One RCT in the setting of maintenance of remission suggested benefit in patients who had responded to vedolizumab induction therapy compared to placebo, but anticipated efficacy is overall very low in this anti-TNF failure population.[172] Finally, there were no RCTs in pediatric patients in any disease state, and very limited safety data in the pediatric population. It is anticipated that experience will gradually accrue in pediatric patients with less treatment-refractory disease. In the current era of access only for patients having failed anti-TNF, the consensus group concluded that evidence of efficacy in CD was less convincing than that for ustekinumab, the other non-anti-TNF biologic.

Alternative Therapies

Statement 25: In patients with Crohn's disease, we recommend against cannabis or derivatives to induce or maintain remission.
GRADE: Strong recommendation, very-low-quality evidence.
Vote: strongly agree, 87%; agree, 7%; neutral, 7%.

Key evidence. Cannabis or derivatives has been assessed in 2 small RCTs in adults with CD inadequately controlled on steroids, immunomodulators, or anti-TNF therapy.[181,182] Both trials reported no significant differences in remission rates with either medical cannabis cigarettes or oral cannabidiol compared to placebo.[181,182] These studies included a total of 40 patients. No side effects and no withdrawal symptoms on discontinuation were reported. A patient survey reported higher rates of surgical intervention among patients with IBD who smoked cannabis to relieve their symptoms, compared to those who did not.[183] However, because of the cross-sectional design, this could represent reverse causation.

The quality of evidence was downgraded to very low due to serious risk of bias, serious indirectness with respect to populations (no pediatric data), and very serious imprecision.

Discussion. There is increasing interest in medical marijuana; however, there is currently no support for the use of cannabis for the treatment of CD. Although one RCT showed improvement in quality of life with cannabis cigarettes,[181] both RCTs demonstrated no significant benefit of cannabis for clinical remission, or an objective measure of disease activity (C-reactive protein).[181,182]

A review of the literature by the Canadian Paediatric Society concluded that cannabis use during adolescence can cause changes to the developing brain, and has been linked to substance use disorders, tobacco smoking, increased rates of psychiatric illnesses, cognitive decline, and diminished school performance and lifetime achievement.[184,185] They recommended that sales of all cannabis products to children and adolescents be prohibited in order to protect these individuals from the potential harms associated with cannabis use.[184,185]

Based on the lack of evidence for efficacy in the treatment of CD, and the potential harms associated with long-term use, the consensus group made a strong recommendation against the use of cannabis products in pediatric patients with CD.

Future Research Directions

The management of CD in pediatric patients has been inadequately studied, with most data being extrapolated from studies in adult patients. Overall, there is a need for more RCTs of CD management strategies in pediatric populations, including positioning of biologic therapies relative to immunomodulators. The identification of molecular markers predictive of disease course would constitute a significant advance, allowing early selection of the most appropriate treatment plan for individual patients. More data are needed to define the efficacy and optimal protocol for EEN in pediatric patients, especially as a first-line treatment.

There is an absence of RCT data on the use of non–anti-TNF biologic therapies in pediatric patients, for both induction and maintenance therapy. The role of switching out of class in pediatric patients who have achieved clinical

remission with anti-TNF therapy should be assessed. All trials in pediatric CD should include outcomes of mucosal healing and, importantly, should strive to determine the degree of healing required to meaningfully modify the long-term course of the disease beginning in childhood.

Summary

Previous guidelines on the medical management of pediatric Crohn's disease were developed through traditional expert consensus-based methodology without formal assessment of the quality of evidence.[8] The current guidelines present recommendations for pediatric patients with CD based on the GRADE framework with systematic review of the literature and rigorous assessment of the quality of evidence. Consensus was reached for or against 25 statements relating to main treatment options: aminosalicylates, budesonide, systemic corticosteroids, exclusive enteral nutrition, thiopurines, methotrexate, anti-TNF biologics, non–anti-TNF biologics, and cannabis (Table 1). When consensus was not reached for a particular statement even after a thorough systematic review of the quality of evidence, balance of harms and benefits, values and preferences, as well as resource use, no recommendation was made. Instead, we presented the evidence and discussed the reasons we were not able to make a judgment. It is hoped that the available information will enhance the discussion between the clinician and the patient and enable the patient to make an evidence-based informed decision that is consistent with his or her own values and preferences.

It is important to note that there is discordance in the strength of recommendation and quality of evidence in 7 statements where strong recommendations were made against certain treatments based on low- or very-low-quality evidence of no benefit, but of potential harms due to side effects of medications. A judgment was made by the consensus group that there was also harm in not providing more effective treatment options in children. The implications of inadequately treated CD are of particular importance in children because of the potentially serious and irreversible consequences of growth impairment, delayed sexual maturation, as well as psychosocial, mental, and emotional maldevelopment. These effects may be long-lasting, persisting even after recovery from the disease. Undoubtedly, there is subjectivity in making this judgment regarding the strong desirability of avoiding irreparable harms to a child. However, GRADE does not seek to eliminate subjective judgments (appropriate or inappropriate). Such judgments are an inevitable part of rating evidence and making recommendations, but one merit of the GRADE system is that judgments are made in a systematic, explicit, and transparent manner.

While the goal of therapy is typically deep remission (clinical remission and mucosal healing), this could not be selected as the primary outcome for this guideline because, until recently, only clinical remission and response (not mucosal healing) have been assessed in the majority of RCTs. However, the consensus group endorsed the importance of achieving endoscopic mucosal healing, while acknowledging that more research is required to fully understand other aspects of intestinal healing, including the transmural nature of the disease and submucosal inflammatory histology.

These guidelines should help to optimize the use and proper positioning of existing medical therapies and improve outcomes in pediatric patients with CD. However, substantial unanswered questions remain. Studies in pediatric patients are needed to define optimal use of exclusive EN, positioning of biologic therapies vs immunomodulators, and of established anti-TNF agents vs emerging alternate pathway biologic therapies. As well, with the rapid advent of new treatments and therapies for CD, the term *conventional therapy* may become obsolete, as many of today's novel therapies will become tomorrow's standard treatments. These guidelines will be reconsidered and updated as appropriate when important new evidence emerges.

Canadian Association of Gastroenterology Statement

This clinical practice guideline (CPG) on the management of pediatric CD was developed under the direction of Drs David Mack and Anne Griffiths, in accordance with the policies and procedures of the CAG and under the direction of CAG Clinical Affairs. It has been reviewed by the CAG Practice Affairs and Clinical Affairs Committees and the CAG Board of Directors. The CPG was developed following a thorough consideration of medical literature and the best available evidence and clinical experience. It represents the consensus of a Canadian and International panel composed of experts on this topic. The CPG aims to provide a reasonable and practical approach to care for specialists and allied health professionals are charged with the duty of providing optimal care to patients and families, and can be subject to change as scientific knowledge and technology advance and as practice patterns evolve. The CPG is not intended to be a substitute for physicians using their individual judgment in managing clinical care in consultation with the patient, with appropriate regard to all the individual circumstances of the patient, diagnostic and treatment options available, and available resources. Adherence to these recommendations will not necessarily produce successful outcomes in every case.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2019.03.022.

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Conflicts of interest
These authors disclose the following: EIB participated in an advisory board for AbbVie but did not receive compensation for participation, financial or otherwise. JC has served on advisory boards for Janssen, and consulted for Nestle Health Sciences. JD has served on advisory boards for AbbVie and Janssen, received research support from Janssen, and participated in speaker's bureaus for AbbVie and Janssen. PM has served on advisory boards for Allergan and Shire, received research support from Takeda, and participated in speaker's bureaus for AbbVie and Allergan. PC has served on advisory boards for Janssen, and participated in speaker's bureaus for AbbVie and Janssen. CD has served on advisory boards for AbbVie and Janssen and has participated as a speaker/moderator for both companies, though not part of a speaker's bureau. WE has served on advisory boards for AbbVie and Janssen, and received research support from Janssen. HH has served on advisory boards for AbbVie and Janssen, and received research support from AbbVie, Allergan, and Janssen. PJ has served on advisory boards for Ferring. AO has served on advisory boards for AbbVie and Janssen, and received research support from AbbVie, Astellas, Janssen, and Shire. MS has served on advisory boards for AbbVie and Janssen. TW has served on advisory boards for AbbVie and Janssen, received research support from AbbVie, and participated in speaker's bureaus for AbbVie, Janssen, and Nestle Health Sciences. MK has consulted for AbbVie, GlaxoSmithKline, and Janssen, received research support from AbbVie and Janssen, participated in speaker's bureaus for AbbVie, and has owned stock in GlaxoSmithKline and Janssen. JM has served on advisory boards for AbbVie, Allergan, AstraZeneca, Boehringer-Ingelheim, Celgene, Celltrion, Ferring, Hospira, Janssen, Merck, Proctor & Gamble, Pfizer, Pharmascience, Shire, and Takeda, and participated in speaker's bureaus for AbbVie, Allergan, Ferring, Janssen, Proctor & Gamble, Shire, and Takeda. AG has served on advisory boards for AbbVie, Janssen, Celgene, Ferring, Pfizer, Gilead, and Lilly, received research support from AbbVie, and participated in speaker's bureaus for AbbVie and Janssen. The remaining authors disclose no conflicts.

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