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CONSENSUS STATEMENT

Clinical Practice Guidelines for the Medical Management of Nonhospitalized Ulcerative Colitis: The Toronto Consensus

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See commentary on page 877.

BACKGROUND & AIMS: The medical management of ulcerative colitis (UC) has improved through the development of new therapies and novel approaches that optimize existing drugs. Previous Canadian consensus guidelines addressed the management of severe UC in the hospitalized patient. We now present consensus guidelines for the treatment of ambulatory patients with mild to severe active UC. **METHODS:** A systematic literature search identified studies on the management of UC. The quality of evidence and strength of recommendations were rated according to the Grading of Recommendation Assessment, Development and Evaluation (GRADE) approach. Statements were developed through an iterative online platform and then finalized and voted on by a working group of specialists. **RESULTS:** The participants concluded that the goal of therapy is complete remission, defined as both symptomatic and endoscopic remission without corticosteroid therapy. The consensus includes 34 statements focused on 5 main drug classes: 5-aminosalicylate (5-ASA), corticosteroids, immunosuppressants, anti–tumor necrosis factor (TNF) therapies, and other therapies. Oral and rectal 5-ASA are recommended first-line therapy for mild to moderate UC, with corticosteroid therapy for those who fail to achieve remission. Patients with moderate to severe UC should undergo a course of oral corticosteroid therapy, with transition to 5-ASA, thiopurine, anti-TNF (with or without thiopurine or methotrexate), or vedolizumab maintenance therapy in those who successfully achieve symptomatic remission. For patients with corticosteroid-resistant/dependent UC, anti-TNF or vedolizumab therapy is recommended. Timely assessments of response and remission are critical to ensuring optimal outcomes. **CONCLUSIONS:** Optimal management of UC requires careful patient assessment, evidence-based use of existing therapies, and thorough assessment to define treatment success.

Keywords: Ulcerative Colitis; 5-Aminosalicylate; Corticosteroid; Thiopurine; Anti–Tumor Necrosis Factor; Vedolizumab; Probiotics.

A substantial burden of illness is attributable to inflammatory bowel disease (IBD)—ulcerative colitis (UC) and Crohn's disease—due to the high prevalence and high per-patient costs of these chronic disorders.[1] The incidence and prevalence of IBD are highest in Western nations, including Canada, the United States, and Europe.[2] There are approximately 104,000 Canadians living with UC and ~10,200 incident cases each year (2012 estimates).[1] In the United States, the prevalence of UC in adults was estimated at 593,000 cases (2009 estimates).[3] In Canada, the total annual cost of IBD was C$2.8 billion (C$1.2 billion in direct costs and C$1.6 billion in indirect costs), corresponding to approximately C$12,000 per year for each patient with IBD (2008 estimates).[1] In the United States, direct medical costs alone are more than $4 billion annually (2004 estimates).[4,5] Furthermore, the personal impact of these disorders includes painful and bothersome symptoms, anxiety regarding the future, and functional impairment.[1] All of these factors are important determinants of health-related quality of life.

In a 2011 survey of Canadian gastroenterologists, topics relevant to IBD were among the most desired educational areas.[6] Four of the top 6 topics were linked to IBD, including difficult cases, therapeutics, pathogenesis and genetics, and nutrition. The management of IBD is complicated by an unpredictable and chronic course, inadequate or delayed access to drug therapies, and a lack of support for patients and caregivers.[1]

The most recent clinical practice guidelines for the medical treatment of ambulatory patients with UC are the second European evidence-based consensus, which incorporates data published until 2012.[7,8] Since that time, therapy has evolved with the approval of new agents (eg, budesonide multi-matrix [MMX], adalimumab, golimumab,

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Abbreviations used in this paper: ADA, antidrug antibodies; CAG, Canadian Association of Gastroenterology; CI, confidence interval; FMT, fecal microbial transplant; GRADE, Grading of Recommendation Assessment, Development and Evaluation; IBD, inflammatory bowel disease; MMX, multi-matrix; NS, not significant; OR, odds ratio; RCT, randomized controlled trial; RR, relative risk; TNF, tumor necrosis factor; TPMT, thiopurine methyltransferase; UC, ulcerative colitis.

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and vedolizumab) and a better understanding of strategies to optimize anti–tumor necrosis factor (TNF) therapy (eg, measuring anti-TNF trough levels and antibodies). Previous Canadian consensus guidelines addressed the management of severe UC in the hospitalized patient.[9] The purpose of these consensus statements is to review the literature relating to the medical management of UC and to develop specific recommendations for ambulatory patients with mild to severe active UC.

Methods

Scope and Purpose

Specific questions regarding therapy were identified and addressed by the participants, aided by evidence derived from review of the literature on UC. The process for guideline development is outlined in Figure 1. The process took approximately 1 year, with the first meeting of the steering committee in November 2013, the meeting of the full consensus group in June 2014, and submission of the manuscript for publication in November 2014.

Sources and Searches

The editorial office of the Cochrane Upper Gastrointestinal and Pancreatic Diseases Group at McMaster University conducted a systematic literature search of MEDLINE (1946 on), EMBASE (1980 on), and CENTRAL (Cochrane Central Register of Controlled Trials) up to February 2014. Key search terms were ulcerative colitis, 5-aminosalicylate, corticosteroid, anti–tumor necrosis factor, thiopurine, methotrexate, vedolizumab, and probiotics. The search was limited to human studies and the English language. The MEDLINE, EMBASE, and CENTRAL search strategies used are detailed further in Supplementary Appendix 1. Supplemental manual searches of these databases were performed up to June 2014.

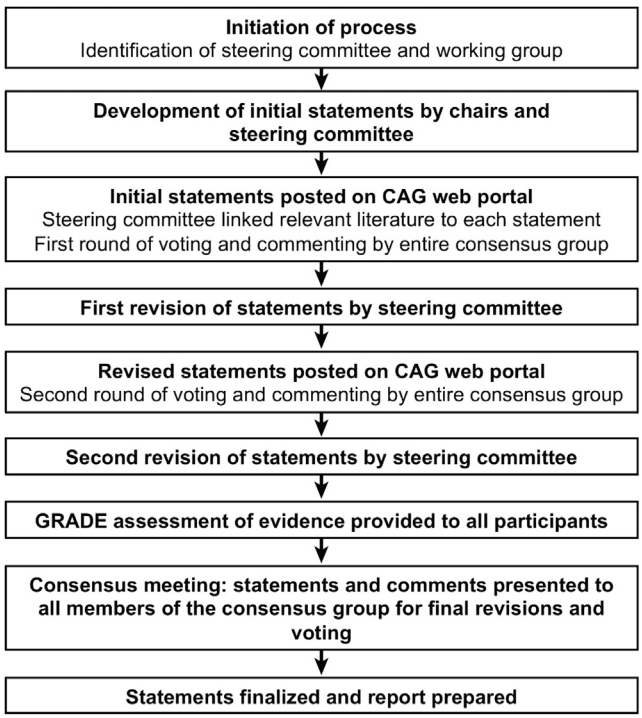

Figure 1. Guideline development process.

Review and Grading of Evidence

The quality of evidence was assessed according to the GRADE (Grading of Recommendation Assessment, Development and Evaluation) approach[10] and determined by 2 methodologists (Dr Grigorios Leontiadis and Dr Francis Tse) who did not vote on the statements. The methodologists determined the risk of bias within individual studies, the risk of bias across studies, and the overall quality of evidence across the identified studies for each statement. The voting members of the consensus group then reviewed and agreed on the GRADE assessments at the meeting.

The quality of evidence for each consensus statement was classified as high, moderate, low, or very low. Evidence from randomized controlled trials (RCTs) was initially classified as high quality but could be downgraded for the following reasons: heterogeneity among outcomes of individual studies, ambiguity in results, indirect study findings, reporting bias, or if it was determined a high risk of bias existed across studies supporting the statement. Data from cohort studies or case-control findings were initially categorized as low-quality evidence; however, the rating could be lowered as a result of the same criteria applied to RCTs, or raised if a very large treatment effect or a dose-response relationship was identified or if all plausible biases would tend to change the magnitude of effect toward the opposite direction.[10]

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

Consensus Process

The consensus group included 23 voting participants, including academic and community gastroenterologists with expertise in various aspects of UC management, a pharmacist, and a nonvoting facilitator (Dr Paul Moayyedi).

Working subgroups and the meeting cochairs (Dr Brian Bressler and Dr John K. Marshall) developed initial statements. A web-based consensus platform (ECD Marketing Solutions, Atlanta, GA) supported by the Canadian Association of Gastroenterology (CAG) was used to facilitate most aspects of the consensus process before the final face-to-face meeting. Via the consensus platform, the working groups (1) reviewed the results of initial literature searches and identified relevant references that were then "tagged" (selected and linked) to each statement, (2) used a modified Delphi process[11,12] to vote anonymously on their level of agreement with the statements, (3) suggested revisions to statements, and (4) provided comments on specific references and background data. Statements were revised through 2 separate iterations and finalized at the consensus meeting. All participants had access to all abstracts and electronic copies of the individual "tagged" references. The GRADE evaluations of the evidence for each statement were provided at the meeting.

The group held a 2-day consensus conference in Toronto, Ontario, Canada, in June 2014, at which data were presented, the wording of the statements was discussed and finalized, and