Gastroenterology 2016;■:1–19

American Gastroenterological Association Technical Review on the Management of Crohn's Disease After Surgical Resection

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Q3 Crohn's disease (CD) is a chronic, disabling gastrointestinal disease with a rising incidence and prevalence.[1] Affecting approximately 1 in 300 people in the Western world, CD typically evolves from an inflammatory process into penetrating and fibrostenotic disease. The end result is often surgical resection, either due to disease-related complications or progression to medically refractory disease. The cumulative risk of surgery in patients with CD at 1, 5, and 10 years is estimated to be 16.3%, 33.3%, and 46.6%, respectively.[2]

Surgery is not curative for ileal or ileocolonic CD, and most patients with primary ileocolonic anastomosis experience recurrence of CD after surgery, defined by a continuum of endoscopic, clinical, and surgical recurrence. Endoscopic recurrence, defined using the Rutgeerts' score, occurs in 30% to 90% of patients at the neoterminal ileum within 12 months of surgery and almost universally by 5 years.[3–9] Clinical recurrence, defined using the Crohn's Disease Activity Index (CDAI), occurs in 20% to 40% of patients within 12 months of surgery and 35% to 50% of patients by 5 years.[3–9] Surgical recurrence, defined as postoperative CD that requires another intestinal resection, occurs in approximately 25% of patients by 5 years and 35% of patients by 10 years after initial surgery.[10] Several major risk factors have been identified that modify the risk of postoperative recurrence, including penetrating disease phenotype, a history of $\geq$2 previous CD-related surgeries, and cigarette smoking.[11–18] Other potential risk factors include perianal disease, extensive small-bowel resection, a short interval between the time of diagnosis and surgery (<10 years), and young age at disease diagnosis (<30 years).[3,19]

Given the high rates of recurrence after surgical resection in patients with CD, several strategies have been studied to decrease the long-term risk of disease recurrence. These include routine early postoperative pharmacological prophylaxis within a few weeks of surgical resection using a variety of pharmacological agents, as well as routine endoscopic monitoring and treatment step-up within 6 to 12 months of surgery in case of asymptomatic endoscopic recurrence. Unfortunately, evidence on the comparative risks and benefits of different pharmacological therapies and management strategies is relatively limited, and current clinical guidelines do not adequately address the specific issues related to management of CD after surgical resection. Hence, the American Gastroenterological Association (AGA) prioritized this topic for generation of clinical guidelines.

Objectives of This Review

This technical review addresses focused clinical questions on strategies to reduce disease recurrence (at 18 months and beyond) in patients with CD who have undergone surgical resection. A key assumption is that patients have ileocolonic CD and surgery produces a surgically induced remission (ie, resection of all macroscopically visible disease and creation of an ileocolonic anastomosis). The focused clinical questions include the following:

- What are the risks and benefits of a strategy of routine early postoperative pharmacological prophylaxis (within 2–8 weeks of surgical resection) versus routine endoscopic assessment (within 6–12 months after surgery) and initiation of treatment only in the presence of endoscopic recurrence?
- What are the risks and benefits of putative pharmacological agents for prevention of recurrence of CD
  - when started within 4 to 8 weeks of surgical resection (early pharmacological prophylaxis)?
  - when started in patients with asymptomatic endoscopic recurrence?
- What are the risks and benefits of a strategy of routine endoscopic monitoring within 6 to 12 months of surgical resection (and treatment step-up if there was evidence of endoscopic recurrence) versus no endoscopic

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Abbreviations used in this paper: AGA, American Gastroenterological Association; 5-ASA, 5-aminosalicylate; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; NMA, network meta-analysis; OR, odds ratio; PICO, population, intervention, comparator, and outcome; RCT, randomized controlled trial; RR, relative risk; TNF, tumor necrosis factor.

0016-5085/$36.00
http://dx.doi.org/10.1053/j.gastro.2016.10.039

monitoring, regardless of early postoperative management?

The results of this technical review were used to inform the development of the accompanying clinical guideline on the management of patients with CD after surgical resection.

Methods

Overview

This technical review and the accompanying guideline were developed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework.[20] After focused questions formulated by the technical review team and the guideline panel were approved by the AGA Governing Board on June 12, 2015, the technical review team formulated the clinical questions, identified the relevant patient-important outcomes, systematically reviewed and summarized the evidence for each outcome across studies, and then rated the quality of the evidence across all outcomes for each clinical question.

Panel Composition

Members of the technical review panel were selected by the AGA based on their clinical and methodological expertise after undergoing a vetting process for potential financial conflicts of interest.

Formulation of Clinical Questions

Using the PICO format, which frames a clinical question by defining a specific population (p), intervention (i), comparator (c), and outcomes (O), the team finalized four questions (Table 1). Potentially relevant patient-important outcomes were considered and rated in terms of importance. The following outcomes were considered critical for decision making: prevention of surgical recurrence, clinical recurrence, and endoscopic recurrence of CD. However, data on surgical recurrence were limited because the majority of studies were short term and not powered to show differences in rates of surgical recurrence. Hence, for this review, the technical review panel used the presence of endoscopic recurrence as a strong surrogate predictor of future surgical recurrence based on data from a pivotal prospective cohort study supporting this association.[21] Serious adverse events leading to treatment discontinuation were considered to be important for decision making. Given the paucity of data on serious adverse events, specifically in the postoperative setting, indirect evidence from luminal CD or other forms of inflammatory bowel disease was used to inform evidence for this outcome.

Outcome Measurement

Clinical recurrence. CDAI >150[22]; when not available, other CDAI cutoffs (CDAI >200) or clinical relapse as defined by the authors of individual studies were used (in that order).

Endoscopic recurrence. Rutgeerts' score of i2 to i4 (presence of more than 5 aphthous lesions with normal intervening mucosa [i2], diffuse aphthous ileitis [i3], or diffuse inflammation with ulcers/nodules/narrowing [i4]; Supplementary Figure 1)[21]; when not available, Rutgeerts' score of i1 to i4, author-defined measure of endoscopic relapse, or a combination of endoscopic and/or imaging relapse based on cross-sectional imaging or barium studies were used (in that order).

It is important to note that neither of these outcome measures (CDAI or Rutgeerts' score) has been validated in the postoperative setting. CDAI (score range, 0–600) has been extensively used as a research tool for assessing clinical activity in luminal CD, with a cutoff of <150 used to define clinical remission. However, the performance characteristics of this threshold in the postoperative setting have not been established, and several factors related to surgery but not to recurrence of CD may modify different components of this score. For example, diarrhea related to small intestinal bacterial overgrowth, bile salt malabsorption, irritable bowel syndrome, or nonspecific postoperative abdominal pain all could affect the CDAI. Likewise, although the Rutgeerts' score has been traditionally used to assess severity of endoscopic recurrence, this index has not been formally validated in treatment trials of postoperative CD. In a recent prospective study, the interobserver variability of the Rutgeerts' score was moderate, especially when differentiating <i2 and ≥i2 (cutoff for endoscopic remission and recurrence in this review), potentially resulting in inappropriate therapeutic decisions in approximately 13% of patients.[23]

Baseline Risk of Clinical and Endoscopic Recurrence of CD

To provide a synthesis of the risks and benefits of different management strategies, the technical review team tried to ascertain the baseline risk of recurrence of CD to calculate absolute effect estimates. In a meta-analysis of 16 randomized controlled trials (RCTs) of pharmacological prophylaxis after surgical resection of CD, Renna et al estimated that rates of clinical and endoscopic recurrence in the placebo arms were 24% (95% confidence interval [CI], 13–35) and 50% (95% CI, 28–73), respectively, with considerable unexplained heterogeneity; baseline risk factors that modify the risk of CD recurrence could not be adequately accounted for.[24] Given this heterogeneity, the members of the technical review panel developed 2 illustrative risk groups with corresponding rates of clinical and endoscopic recurrence at 18 months in the absence of any intervention in postsurgical patients with CD (Table 2). Although the presence of multiple risk factors is likely to result in a higher risk of recurrence compared with patients with no risk factors or only one risk factor,[25] the exact risk of disease recurrence corresponding to the presence or absence of a combination of risk factors is not known, and hypothetical values were assigned to enable estimation of absolute effects of various interventions.

Search Strategy and Study Selection Criteria

The systematic literature review, data abstraction, and initial quality assessment for this technical review were conducted by the Pacific Northwest Evidence-based Practice Center in conjunction with the technical review team. Details of the search strategy and study selection criteria are reported in the Supplementary Appendix and Supplementary Figure 2.

Data Extraction and Statistical Analysis

Data abstraction was independently conducted in duplicate by 2 investigators at the Pacific Northwest Evidence-based