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AGA SECTION

American Gastroenterological Association Institute Guideline on the Management of Crohn's Disease After Surgical Resection

Geoffrey C. Nguyen,[1] Edward V. Loftus Jr,[2] Ikuo Hirano,[3] Yngve Falck–Ytter,[4] Siddharth Singh,[5] Shahnaz Sultan,[6] and the AGA Institute Clinical Guidelines Committee

[1]*Mount Sinai Hospital Centre for Inflammatory Bowel Disease, University of Toronto, Toronto, Ontario, Canada;* [2]*Division of Gastroenterology & Hepatology, Mayo Clinic, Rochester, Minnesota;* [3]*Northwestern University School of Medicine, Chicago, Illinois;* [4]*Division of Gastroenterology, Case and VA Medical Center, Cleveland, Ohio;* [5]*Division of Gastroenterology, University of California San Diego, La Jolla, California; and* [6]*Minneapolis VA Health Care System, University of Minnesota, Minneapolis, Minnesota*

This article has an accompanying continuing medical education activity, also eligible for MOC credit, on page e18. Learning Objective: Upon completion of this activity, learners will be able to develop an approach to risk stratifying, monitoring and treating Crohn's disease patients following surgery.

This document presents the official recommendations of the American Gastroenterological Association (AGA) on the management of Crohn's disease (CD) after surgical resection. The guideline was developed by the AGA's Clinical Guidelines Committee and approved by the AGA Governing Board. It is accompanied by a technical review that is a compilation of clinical evidence from which these recommendations were formulated.[1]

Nearly one-half of patients with CD will require bowel resection within the first 10 years of disease.[1] However, surgery is not curative, and one-fourth of these patients will require at least another bowel resection within 5 years of index surgery.[1] Surgical recurrence is usually preceded by clinical and endoscopic recurrence, which can occur in the neoterminal ileum in as many as 90% of patients within 12 months of surgical resection.[1] Certain clinical features, such as the presence of penetrating disease, cigarette smoking, and multiple prior resections, are risk factors for disease recurrence. The presence and severity of endoscopic recurrence, as measured by the Rutgeerts' score, is a strong predictor of clinical and surgical recurrence. The prevention of postoperative disease recurrence is a high priority given the morbidity associated with clinical and surgical recurrence and the long-term risk of short gut syndrome that may arise from multiple bowel resections.

These guidelines were developed to outline strategies to reduce disease recurrence in patients who have achieved remission following bowel resection. When considering the effectiveness of these strategies, endoscopic and clinical recurrence were deemed primary outcomes. In these guidelines, we define endoscopic recurrence as a Rutgeerts' score of $\geq$i2 on ileocolonoscopy. Although the guideline panel acknowledged the importance of surgical recurrence, there were an insufficient number of events in clinical trials to inform this outcome. Therefore, prevention of endoscopic recurrence, a strong surrogate measure of surgical recurrence, was evaluated. These recommendations address the role of postoperative pharmacological prophylaxis and endoscopic monitoring in patients with an ileocolonic anastomosis who are asymptomatic without macroscopic evidence of CD after surgical resection. They are not applicable to patients with small-bowel anastomoses that are not accessible by colonoscopy, those who have residual disease following surgical resection, or those who already have clinical symptoms related to active CD.

The AGA process for developing clinical practice guidelines follows the standards set by the Institute of Medicine.[2,3] This process, described in more detail elsewhere, was used in the writing of the technical review and guideline.[2] The Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework was used to evaluate the certainty of the evidence and grade the strength of recommendations.[4] Understanding of this guideline will be enhanced by reading relevant portions of the technical review. The guideline panel and the authors of the technical review met face to face on May 24, 2016, to discuss the findings from the technical review. The guideline authors subsequently formulated the recommendations. Although quality of evidence (Table 1) was a key factor in determining the strength of recommendation (Table 2), the panel also considered the balance between benefit and harm of interventions, patients' values and preferences, and resource utilization. The recommendations, quality of evidence and strength of recommendations are summarized in Table 3.

Abbreviations used in this paper: **AGA, American Gastroenterological Association; 5-ASA, 5-aminosalicylate; CD, Crohn's disease; CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; POCER, Postoperative Crohn's Endoscopic Recurrence; RR, relative risk; TNF, tumor necrosis factor.**

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Table 1. GRADE Definitions of Quality/Certainty of the Evidence

High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very low	We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

Recommendations

1. In patients with surgically induced remission of CD, the AGA suggests early pharmacological prophylaxis over endoscopy-guided pharmacological treatment. *Conditional recommendation, very low quality of evidence.*
Comments: Patients, particularly those at lower risk of recurrence, who place a higher value on avoiding the small risks of adverse events from pharmacological prophylaxis and a lower value on the potential risk of early disease recurrence may reasonably select endoscopy-guided pharmacological treatment over prophylaxis.

It should be emphasized that there was significant uncertainty in estimating the relative effectiveness of early pharmacological prophylaxis (started within 8 weeks of surgery) over endoscopy-guided treatment, in which patients would be started on therapy only if there was evidence of endoscopic recurrence on colonoscopy performed 6 to 12 months after surgical resection. A single clinical trial of 63 postoperative patients with CD failed to show that early pharmacological prophylaxis with azathioprine compared with endoscopy-guided therapy resulted in nonsignificant reductions in clinical (relative risk [RR], 0.83; 95% confidence interval [CI], 0.46–1.50) or endoscopic recurrence (RR, 0.91; 95% CI, 0.59–1.42). Because there is clinical equipoise as to which strategy is superior, the decision of one approach over the other must be individualized and take into consideration the risk of postoperative recurrence and the patient's values and preferences. Although there is no validated clinical score that predicts recurrence, there are clinical features such as prior bowel resection, penetrating disease, and cigarette smoking that have been associated with higher risk of recurrence. Based on these clinical risk factors, the technical review panel synthesized 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 4). The panel favored early pharmacological prophylaxis over endoscopy-guided management because it is likely that the majority of patients who have undergone surgical resection in clinical practice may have one or more risk factors, conferring an increased risk of disease recurrence, as was observed in published clinical studies used to derive these estimates. In those with a lower risk of recurrence, the potential risk of adverse events from medical therapy may outweigh the potential benefits. Patients who share similar characteristics as those in the lower-risk illustrative group may reasonably choose endoscopy-guided pharmacological treatment.

2. In patients with surgically induced remission of CD, the AGA suggests using anti-TNF therapy and/or thiopurines over other agents. *Conditional recommendation, moderate quality of evidence.*
Comments: Patients at lower risk for disease recurrence or who place a higher value on avoiding the small risk of adverse events of thiopurines and/or anti-TNF treatment and a lower value on a modestly increased risk of disease recurrence may reasonably choose nitroimidazole antibiotics (for 3–12 months).

The selection of anti–tumor necrosis factor (TNF) therapy and/or thiopurines as first-line agents for early pharmacological prophylaxis is based on moderate quality of

Table 2. GRADE Definitions on Strength of Recommendation

	Wording in guideline	For the patient	For the clinician
Strong	"The AGA recommends…"	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	Most individuals should receive the recommended course of action. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.
Conditional	"The AGA suggests…"	The majority of individuals in this situation would want the suggested course of action, but many would not.	Different choices will be appropriate for different patients. Decision aids may well be useful helping individuals making decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working toward a decision.

Table 3. Summary of Recommendations of the AGA Clinical Guidelines for the Management of Crohn's Disease After Surgical Resection

Statement	Strength of recommendation	Quality of evidence
1. In patients with surgically induced remission of CD, the AGA suggests early pharmacological prophylaxis over endoscopy-guided pharmacological treatment.	Conditional	Very low quality
Comments: Patients, particularly those at lower risk of recurrence, who place a higher value on avoiding the small risks of adverse events from pharmacological prophylaxis and a lower value on the potential risk of early disease recurrence may reasonably select endoscopy-guided pharmacological treatment over prophylaxis.		
2. In patients with surgically induced remission of CD, the AGA suggests using anti-TNF therapy and/or thiopurines over other agents.	Conditional	Moderate
Comments: Patients at lower risk of disease recurrence or who place a higher value on avoiding the small risk of adverse events of thiopurines or anti-TNF treatment and a lower value on a modestly increased risk of disease recurrence may reasonably choose nitroimidazole antibiotics (for 3–12 months).		
3. In patients with surgically induced remission of CD, the AGA suggests against using mesalamine (or other 5-aminosalicylates), budesonide, or probiotics.	Conditional	Low; very low
4. In patients with surgically induced remission of CD receiving pharmacological prophylaxis, the AGA suggests postoperative endoscopic monitoring at 6 to 12 months after surgical resection over no monitoring.	Conditional	Moderate
5. In patients with surgically induced remission of CD not receiving pharmacological prophylaxis, the AGA recommends postoperative endoscopic monitoring at 6 to 12 months after surgical resection over no monitoring.	Strong	Moderate
6. In patients with surgically induced remission of CD with asymptomatic endoscopic recurrence, the AGA suggests initiating or optimizing anti-TNF and/or thiopurine therapy over continued monitoring alone.	Conditional	Moderate
Comments: Patients who place a higher value on avoiding the small risk of adverse events of thiopurines or anti-TNF treatment and a lower value on the increased risk of clinical recurrence following asymptomatic endoscopic recurrence may reasonably choose continued endoscopic monitoring.		

evidence. Based on clinical trials, anti-TNF therapy compared with placebo resulted in 49% and 76% relative reductions in clinical and endoscopic recurrence at 18 months, respectively. Similarly, postoperative prophylaxis with thiopurines resulted in 65% and 60% relative decreases in clinical and endoscopic recurrence, respectively. There was also moderate-quality evidence showing that antibiotics reduced the risk of endoscopic and clinical recurrence by approximately 50%.

Because the cumulative dosing of nitroimidazoles may lead to peripheral neuropathy, their use is usually limited to 3 to 12 months, and disease usually recurs within a couple of years after antibiotics are stopped. Moreover, antibiotics are probably inferior to anti-TNF agents by a large extent (moderate-quality evidence) and may be modestly inferior to thiopurines (low-quality evidence) in reducing disease recurrence. For these reasons, the panel designated antibiotics as second-line alternatives for patients who are concerned about the adverse effects of anti-TNF and thiopurine therapy and who have lower risk of recurrence. If the decision is to treat with antibiotics in the postoperative setting, nitroimidazole antibiotics (eg, metronidazole) should be used because they are the only class that has been adequately studied. There is low-quality evidence favoring

Table 4. Illustrative Risk Groups for Recurrence of CD After Surgical Resection in the Absence of Any Intervention

Illustrative risk groups	Typical patient characteristics corresponding to risk category	Illustrative risk of clinical recurrence (>18 mo after surgery)	Illustrative risk of endoscopic recurrence (>18 mo after surgery)
Lower risk	Older patient (older than 50 y) Nonsmoker First surgery for a short segment of fibrostenotic disease (<10 to 20 cm) Disease duration >10 y	20%	30%
Higher risk	Younger patient (younger than 30 y) Smoker, ≥2 prior surgeries for penetrating disease, with or without perianal disease	50%	80%

anti-TNF agents over thiopurines for reducing disease recurrence, with possibly a large effect size. The choice between anti-TNF and thiopurine monotherapy for preventing disease recurrence should include assessment of the patient's risk of disease recurrence and risk-benefit considerations in the context of patients' values and preferences. Although no direct evidence was available on the use of the combination of anti-TNF agents and thiopurines for reducing disease recurrence in the postoperative setting, indirect evidence from luminal CD supports its use as a potentially efficacious strategy in patients at highest risk.[5]

3. In patients with surgically induced remission of CD, the AGA suggests against using mesalamine (or other 5-aminosalicylates), budesonide, or probiotics. *Conditional recommendation, low quality of evidence and very low quality of evidence.*

The guideline panel conditionally recommended against the use of mesalamine (or other 5-aminosalicylates [5-ASAs]) because of the overall low quality of evidence to support its effectiveness in reducing postoperative recurrence. Although there was low-quality evidence to suggest that it reduced clinical recurrence compared with placebo (RR, 0.59; 95% CI: 0.43–0.82), the evidence favoring its use to prevent endoscopic recurrence was even less compelling due to imprecision, inconsistency, and strongly suspected publication bias. Additionally, indirect evidence from patients with inflammatory luminal CD also supports the lack of benefit of 5-ASAs for inducing or maintaining remission.[6,7] There was substantial uncertainty regarding the effectiveness of budesonide and probiotics in the postoperative setting due to very low quality of evidence. The main risk of using 5-ASA, budesonide, and probiotics is disease recurrence by foregoing more effective therapies.

4. In patients with surgically induced remission of CD receiving pharmacological prophylaxis, the AGA suggests postoperative endoscopic monitoring at 6 to 12 months after surgical resection over no monitoring. *Conditional recommendation, moderate quality of evidence.*

Moderate-quality evidence from the Postoperative Crohn's Endoscopic Recurrence (POCER) randomized clinical trial suggested that endoscopic monitoring (with algorithmic treatment step-up in case of endoscopic recurrence) was superior to standard of care (continuing pharmacological strategy adopted in the early postoperative period) in reducing clinical (RR, 0.82; 95% CI, 0.56–1.18) and endoscopic recurrence (RR, 0.73; 95% CI, 0.56–0.95).[1,8] In this study, 83% of subjects were categorized as high risk for recurrence and received either azathioprine or adalimumab following surgery, and all subjects received metronidazole for 3 months postoperatively. Thus, even patients who were already on postoperative prophylaxis benefited from endoscopic monitoring with colonoscopy at 6 to 12 months. However, in making this recommendation conditional, the guideline panel acknowledged that patients who are already on long-term prophylactic therapy may reasonably choose to forego the inconvenience and small risks of colonoscopy. Moreover, if pharmacological therapy is unlikely to be escalated in the presence of asymptomatic endoscopic recurrence, because of either patient preference or clinician judgement, then the risks and costs of endoscopic monitoring likely outweigh the benefits. There is insufficient clinical evidence to inform how often endoscopic monitoring should be performed following the initial postoperative colonoscopy.

5. In patients with surgically induced remission of CD not receiving pharmacological prophylaxis, the AGA recommends postoperative endoscopic monitoring at 6 to 12 months after surgical resection over no monitoring. *Strong recommendation, moderate quality of evidence.*

There are no clinical trials comparing endoscopic monitoring with the standard of care in patients with surgically induced remission of CD who are not on any prophylactic therapy. As previously mentioned, patients enrolled in the POCER trial received some form of early pharmacological prophylaxis; all patients received metronidazole, and the vast majority also received a thiopurine or adalimumab.[8] However, this trial provides indirect evidence for the relative effectiveness of endoscopic monitoring (with algorithmic treatment step-up in case of endoscopic recurrence) in patients not receiving any early pharmacological prophylaxis. In fact, these data very likely underestimate the potential benefits of endoscopic monitoring in patients who are not on any pharmacological therapy. The AGA issued a strong recommendation because of the high likelihood of benefit from detection of endoscopic recurrence by colonoscopy, the risk of which is as high as 90% within 1 year of surgery in those not receiving any prophylaxis. This monitoring may prompt the initiation of medical therapy if endoscopic recurrence is detected. Although no studies on patients' values and preferences were available to inform this recommendation, the patient representative on the panel expressed that many patients who are not on any pharmacological prophylaxis may prefer to know if there is endoscopic recurrence, because it may prompt initiation of medical therapy.

6. In patients with surgically induced remission of CD with asymptomatic endoscopic recurrence, the AGA suggests initiating or optimizing anti-TNF and/or thiopurine therapy over continued monitoring alone. *Conditional recommendation, moderate quality of evidence.*
Comments: Patients who place a higher value on avoiding the small risk of adverse events of thiopurines or anti-TNF treatment and a lower value on the increased risk of clinical recurrence following asymptomatic endoscopic recurrence may reasonably choose continued endoscopic monitoring.

In the POCER trial, initiation or escalation of therapy with thiopurines or azathioprine was part of the treatment strategy triggered by the detection of endoscopic recurrence at 6

months.[8] This therapeutic approach was associated with lower clinical and endoscopic recurrence. There was sparse direct evidence to inform the comparative effectiveness of various pharmacological agents for patients with asymptomatic endoscopic recurrence in the postoperative setting. The preference for an aggressive approach with anti-TNF agents and thiopurines either as monotherapy or combination therapy is based on indirect evidence from the AGA clinical guideline on the role of anti-TNF and immunomodulators in the maintenance of remission in patients with inflammatory luminal CD.[5] Thiopurine monotherapy, with its slower onset of action and potentially lower efficacy, may be more appropriate for those with less severe endoscopic recurrence (ie, Rutgeerts' score of i2). Patients who are apprehensive about the adverse effects of therapy and less concerned about the risk of clinical recurrence may choose to forego therapy and continue endoscopic monitoring. This approach may be reasonable, especially for patients with less severe endoscopic recurrence (ie, Rutgeerts' score of i2). Patients considering continued endoscopic monitoring should also take into account the inconvenience and small risks associated with serial colonoscopy while weighing the conceivable risk of ongoing mucosal injury. For those who choose continued endoscopic monitoring, it may be valuable to have a discussion about what end points may be used to help guide a decision to initiate pharmacological therapy. Patients who have endoscopic recurrence while already on a thiopurine should have step-up therapy with the addition of an anti-TNF agent either as monotherapy or combination therapy.

Summary

These actionable recommendations for the management of CD after surgical resection were developed using the GRADE framework and are consistent with the Institute of Medicine's Standards for Developing Trustworthy Clinical Practice Guidelines. These guidelines are intended to reduce practice variation and promote high-value care. The current evidence supports the early prophylactic use of thiopurines and/or anti-TNF therapy in patients who are at higher risk for clinical recurrence. However, some patients at lower risk may opt for close endoscopic monitoring instead. Although all patients should undergo ileocolonoscopy at 6 to 12 months after surgical resection, surveillance for endoscopic recurrence is most important for patients not on any pharmacological prophylaxis. In general, those with endoscopic recurrence should undergo treatment with anti-TNF and/or thiopurine therapy.

Although identifying patients who are at higher risk for endoscopic and clinical recurrence is paramount in managing postoperative CD, there is no validated score based on clinical features that predicts these outcomes. The development and validation of a postoperative recurrence scale would enable more effective implementation of these guidelines. Moreover, the Rutgeerts score, which correlates with natural history based on endoscopic recurrence at the neoterminal ileum, has not been validated for use in clinical trials of postoperative prophylaxis. The optimal frequency of endoscopic monitoring following the initial colonoscopy after surgical resection remains to be determined. Additionally, randomized clinical trials are needed to assess the comparative efficacy of medical therapies after the onset of asymptomatic endoscopic recurrence. Finally, there is a growing armamentarium of biologics for the treatment of CD, and the role of newer classes of biologics for the prevention of postoperative recurrence has yet to be determined.

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Reprint requests
Address requests for reprints to: Chair, Clinical Guidelines Committee, American Gastroenterological Association National Office, 4930 Del Ray Avenue, Bethesda, Maryland 20814. e-mail: msiedler@gastro.org.

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The AGA Institute Clinical Guidelines Committee included Steven L. Flamm (Northwestern Feinberg School of Medicine, Chicago, IL), Joseph K. Lim (Yale School of Medicine, New Haven, CT), Joel H. Rubenstein (Veterans Affairs Center for Clinical Management Research and University of Michigan Medical School, Ann Arbor, MI), Walter E. Smalley (Vanderbilt University School of Medicine, Nashville, TN), Neil Stollman (University of California San Francisco, Northern California Gastroenterology Consultants, San Francisco, CA), Santhi Swaroop Vege (Mayo Clinic, Rochester, MN), Sachin B. Wani (University of Colorado Anschutz Medical Campus, Aurora, CO), David S. Weinberg (Department of Medicine, Fox Chase Cancer Center, Philadelphia, PA), and Yu-Xiao Yang (University of Pennsylvania School of Medicine, Philadelphia, PA).

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Conflicts of interest
All members were required to complete a disclosure statement. These statements are maintained at the American Gastroenterological Association Institute (AGA) headquarters in Bethesda, Maryland and pertinent disclosures are published with the report.