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Review

REVIEW

Perioperative use of immunosuppressive medications in patients with Crohn's disease in the new "biological era"

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Abstract

Crohn's disease (CD) is characterized by transmural inflammation of the gastrointestinal tract leading to inflammatory, stricturing and/or and fistulizing disease. Once a patient develops medically refractory disease, mechanical obstruction, fistulizing disease or perforation, surgery is indicated. Unfortunately, surgery is not curative in most cases, underscoring the importance of bowel preservation and adequate perioperative medical management. As many of the medications used to treat CD are immunosuppressive, the concern for postoperative infectious complications and anastomotic healing are particularly concerning; these concerns have to be balanced with preventing and treating residual or recurrent disease. We herein review the available literature and make recommendations regarding the preoperative, perioperative and postoperative administration of immunosuppressive medications in the current era of biological therapy for CD. Standardized algorithms for perioperative medical management would greatly assist future research for optimizing surgical outcomes and preventing disease recurrence in the future.

Key words: Crohn's disease, biological therapy, perioperative period, medical management

Introduction

One-third of patients with Crohn's disease (CD) will require a major abdominal resection within 5 years of their diagnosis, and two-thirds will ultimately require operative management at least once during the course of their disease [1–8]. Unfortunately, surgery for CD is not curative, and disease recurrence is common. Within the first year of surgery, 70 to 90% of patients will develop endoscopic recurrence, and this incidence increases to 80 to 100% within 3 years [2,9,10]. Thus, the decision of when to operate *vs* escalating medical therapy is highly individualized and requires a multidisciplinary, coordinated approach between the gastroenterologist, surgeon and patient. The decision of when to discontinue immunosuppressive medications preoperatively is left to the largely subjective discretion of the gastroenterologist as there are no formulated guidelines.

There is no question that the continuation and discontinuation of immunosuppressive medications in the preoperative, perioperative and postoperative periods has great impact on the medical and surgical outcomes for patients with CD. Whereas corticosteroids were historically the cornerstone of medical

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management, the introduction of biological therapy with and without concomitant use of immunomodulators (IMMs) has changed the timing of operative intervention and the patient population arriving in the operating room. The severity of disease is now greater, with patients having tried—and potentially failed—a variety of immunosuppressive medications, which results in patients who are increasingly malnourished, anemic and debilitated due to chronic disease.

At the time of surgery, bowel preservation is an important guiding principle. Strictureplasty, rather than segmental resection, or bypass, rather than removal of a long segment of disease, may be utilized to preserve bowel and prevent the dreaded complication of short gut. Similarly, once the diseased bowel is resected, preventing disease recurrence in the remaining bowel is imperative; however, the strategies by which we accomplish this task remain to be optimized. Several studies have investigated the incidence of disease recurrence with the type of anastomosis constructed, and results have not shown a definitive conclusion that 1 type is better than another. Other studies have investigated prophylactic resumption of medication, but again a lack of consistent protocols has left treatment practices to the subjective discretion of the gastroenterologist.

As we enter an era of expanding repertoire of Food and Drug Administration (FDA)- approved biological therapies and escalating disease severity at the time of operation, closer attention needs to be paid to consistent guiding principles for the preoperative, perioperative and postoperative medical management for CD. Ultimately, research will lead to standardized guidelines for the administration and optimization of medical management in the perioperative period to improve postoperative surgical outcomes and prevent disease recurrence.

Preoperative use of CD-Related Drugs

Until the introduction of biological therapy, corticosteroids remained the cornerstone of medical management for patients with CD. Once patients failed to improve on steroid and/or IMM therapy, surgery was the clearly next step. This was a markedly simplified algorithm as compared with the current era in which multiple biological therapies are available for treating CD.

The availability of biologics has resulted in a major paradigm shift in the management of moderate to severe CD. The previous algorithm of increasing the level of immunosuppression in parallel with disease progression is being supplanted by more aggressive early therapy with a combination of both a biological agent and an IMM in an effort to alter the trajectory of the disease—otherwise known as the "top down approach." This is especially true in patients with severe disease risk of developing CD-associated complications. Several studies have recently demonstrated that patients have higher rates of remission and response when using biological agents rather than IMMs and that the combination of these agents provides even greater benefit [11–13] while preventing the development of antidrug antibodies to biological therapy [14].

The loss of response to antitumor necrosis factor α (TNFα) agents is common in inflammatory bowel disease (IBD), resulting in the secondary failure of therapy. Up to 40% of patients will develop a loss of response to anti-TNFα agents [15]. This has been demonstrated in clinical trials of maintenance therapy for infliximab, adalimumab, certolizumab and combination therapy [16–19]. Currently, if a patient loses response to anti-TNFα therapy, antibody levels and drug levels can be tested to see if dose escalation may induce responsiveness. Otherwise, an alternative anti-TNFα agent can be initiated or even a biologic with an entirely different mechanism such as vedolizumab (anti-$\alpha 4\beta 7$ integrin) or ustekinumab (anti IL-12 and IL-23). Unfortunately, vedolizumab may take up to 28 weeks to demonstrate clinical improvement in the maintenance phase [20]; during that time, patients are encouraged to remain on the drug, even if symptomatic, to determine its effectiveness. During that interval, patients may either improve or become increasingly deconditioned, malnourished, develop disease-specific complications or, more rarely, develop complications requiring emergent surgery.

Aside from the clinically obstructed or perforated patient, it is ongoing discussion as to when to discontinue medical management or pursue more definitive management with surgery. Once the decision has been made to halt escalation of medical therapy and pursue an operative approach, the patient should be optimized; and timing when to discontinue immunosuppressive medication is up to the discretion of the treating gastroenterologist and surgeon.

Aminosalicylates

5-aminosalicylic acid (5-ASA) agents can be used to maintain remission in CD [21]. These compounds have a short half-life of 6–10 hours, and are excreted by the kidneys. Overall, aminosalicylates can be continued up to the day before surgery and then resumed on discharge after surgery [22] unless there is a concern for renal insufficiency.

Glucocorticosteroids

Many patients with IBD will require corticosteroids during the course of their disease, and approximately 30–40 percent of patients with moderate-to-severe disease will become steroid dependent [23–25]. Despite corticosteroids being commonplace, corticosteroid use in the perioperative period is highly variable, even within individual IBD referral institutions [26]. Because there is extensive literature documenting that steroids may have a negative impact on wound healing, postoperative surgical complications and glycemic control [27–30], a clear understanding of the indications, dosing and duration for perioperative corticosteroid use is essential for reducing the administration of unnecessary corticosteroids.

The administration of "stress-dose" corticosteroids to IBD patients in the perioperative period, even with limited prior corticosteroid exposure, has become a common practice. The historical context for this widespread practice dates back to the 1950s with the publication of two case reports of fatalities presumably related to adrenal crises among corticosteroid-dependent patients who did not receive corticosteroid supplementation postoperatively [31,32]. These case reports were not questioned, and stress dose corticosteroids have been commonly administered. However, recent retrospective studies have shown no advantage to stress dose corticosteroids [33], and prospective studies have demonstrated minimal differences in outcomes for IBD patients receiving high-dose, low-dose, or no perioperative corticosteroids [34,35]. Thus, IBD surgeons are starting to move away from stress dose corticosteroids in all patients exposed to corticosteroids and instead are using modified, lower-dose regimens. With this new emerging evidence in the setting of highly variable practice patterns, standardized regimens for corticosteroid use in the perioperative period are long overdue.

Hypothalamic pituitary adrenal axis and adrenal insufficiency

The hypothalamic pituitary adrenal (HPA) axis is a hormonal system that responds to systemic stressors by stimulating the production and release of cortisol from the adrenal glands. When the body encounters a stressor (e.g. surgery), the hypothalamus is activated to release corticotropin-releasing hormone. Corticotropin-releasing hormone acts on the anterior pituitary to stimulate the release of adrenocorticotropin hormone (ACTH), which in turn activates the adrenal glands to release cortisol into the blood stream [36].

In unstressed individuals with normal adrenal function, the basal secretion of cortisol is approximately 5–7 mg/m^2 per day (8.5–12 mg/m^2/day in a patient with average body surface area) [37]. During a minor surgery or illness (e.g. an examination under anesthesia or ileostomy reversal), cortisol secretion increases up to 5-folds to approximately 50 mg/day. In patients undergoing a major surgical stress (e.g. a subtotal colectomy), the secretion of cortisol is even greater, increasing up to 75–100 mg/day. In rare instances, the cortisol secretion rate can reach between 200 and 500 mg/day, usually in the face of emergent surgery or severe trauma. In most instances, basal cortisol levels normalize by postoperative day 5 [38].

Administration of corticosteroids is performed largely to prevent the consequences of adrenal insufficiency (AI) and an adrenal crisis. Patients with acute AI may present with significant cardiovascular impairment that mimics septic shock, including elevated cardiac output and low systemic vascular resistance. Acute AI can lead to serious consequences, including myocardial infarction and death. Chronic AI, which is more insidious, may cause fatigue, anorexia, nausea, weight loss, diarrhea and/or abdominal pain in patients. The basis behind perioperative corticosteroid dosing for patients with AI is to increase the corticosteroid supply preemptively to help overcome the potential stress-related insults of surgery.

Fortunately, adrenal crisis is a rare event. If suspected, a one-time dose of 4 mg of intravenous dexamethasone should be given. Steps that can be taken to prevent an adrenal crisis include: (i) taking a detailed medication history to determine if stress dosing in perioperative period is required, and keeping in mind that inhaled corticosteroids or intra-articular injection of corticosteroids can also cause suppression of the HPA axis and should be specifically asked about in the history-taking; (ii) continuing corticosteroids for those currently taking these medications; and (iii) switching steroid from oral formulation to intravenous or intramuscular if a patient is NPO status, has an ileus or is vomiting.

Steroid taper

There are no standardized published guidelines for corticosteroid tapers in the IBD patient population following surgery. However, based on the aforementioned evidence, we suggest varying regimens depending on the preoperative use of corticosteroids (**Table 1**).

i. Prednisone 20 mg daily. Rapid taper (less than 3 weeks of treatment)
   Preoperatively the patient was treated with prednisone 20 mg daily for CD or was in the hospital and got an IV equivalent for a week: Prednisone 20 mg PO daily X 3 days → Prednisone 15 mg PO daily X 3 days →Prednisone 10 mg PO daily X 3 days → Prednisone 5 mg PO daily X 3 days → Off.
ii. Prednisone 20 mg daily. Slow taper (> 3 weeks of treatment)
   Preoperatively the patient was treated with prednisone 20 mg daily for CD and now CD has been removed. Start with patient's baseline dose; if > 20 mg, start at that point and decrease by 10 mg each week until reaching 20 mg, then follow the taper as below: →Prednisone 20 mg PO daily X 1 week → Prednisone 15 mg PO daily X 1 week → Prednisone 10 mg PO daily X 1 week → Prednisone 5 mg PO daily X 2 week → Prednisone 2.5 mg PO daily X 2 week → Off.
iii. Prednisone 60 mg daily. Slow taper (more than weeks of steroid use, chronic)
   Preoperatively the patient was treated with prednisone 60 mg daily for CD, and now CD has been removed. Start with patient's baseline dose (if less than prednisone 60 mg, start at that point) and taper as follows: Prednisone 40 mg PO daily X 1 week →Prednisone 30 mg PO daily X 1 week → Prednisone 20 mg PO daily X 1 week →Prednisone 15 mg PO daily X 1 week →Prednisone 10 mg PO daily X 1 week

Table 1. Recommendations for perioperative corticosteroid usage—Case-based examples

Example	On-call to operating room	Postoperative
Chronic stable low-dose (e.g. 5 mg PO) corticosteroid that will be continued postoperatively for a condition unchanged by surgery (e.g. prednisone 5 mg daily for COPD)	Regular daily dose in morning prior to surgery (e.g. 5 mg PO)	Reinitiate preoperative oral corticosteroid (e.g. prednisone 5 mg PO daily or IV version if NPO)
Patient who has been on 5–20 mg prednisone daily for treatment of IBD	Low-dose corticosteroid (e.g. dexamethasone 4 mg IV or IM)*	The day after surgery restart preoperative oral prednisone dosage (e.g. 20 mg PO daily and start *rapid taper*—see below). Use IV version if NPO.
Patient on > 20 mg prednisone daily (or equivalent) for treatment of IBD for 3 weeks or less	Stress low-dose corticosteroid (e.g. dexamethasone 4 mg IV or IM)*	The day after surgery restart preoperative oral prednisone dosage (e.g. 20 mg PO daily and start *rapid taper*—see below). Use IV version if NPO.
Patient on > 20 mg PO prednisone for > 3 weeks#	Stress low-dose corticosteroid (e.g. dexamethasone 4 mg IV or IM)*	The day after surgery restart preop oral prednisone dosage and start *slow taper* (see below). Use IV version if NPO.

COPD: chronic obstructive pulmonary disease; IBD: inflammatory bowel disease; IV: intravenous injection; IM: intramuscular injection; PO: per os (Latin), oral (English); NPO: nihil per os (Latin), nothing by mouse (English).

*Or equivalent.

#Patients who received > 20 mg/day of prednisone or its physiologic equivalent via IM, IV, oral, per rectum or topical routes for more than 3 weeks within 6 months prior to surgery.

→Prednisone 5 mg PO daily X 2 week →Prednisone 2.5 mg PO daily X 2 week → Off.

Regardless of the taper used, there are some important points to keep in mind. (i) Steroid tapers can be done more rapidly or slowly depending on the dose, the chronicity of use and whether the disease mandating corticosteroid use was removed (e.g. segmental resection in CD); (ii) corticosteroid withdrawal symptoms (myalgia, nausea, and fatigue) are not the same as adrenal crisis or adrenal insufficiency (hypotension, tachycardia, hyponatremia and hyperkalemia); (iii) the withdrawal symptoms are experienced by all patients tapering off long-term corticosteroids. Patients should be informed of this challenge and expectation and should clearly understand that it is an experience they will have to get through in order to be free of exogenous corticosteroids; (iv) the goal of the taper is to reduce the dose as quickly as possible while maintaining the patient's ability to function (e.g. work and leisure activities); and (v) the rate of taper should be adjusted if patient is incapacitated with corticosteroid withdrawal symptoms (e.g. myalgia, nausea and fatigue). We have found that if the patient does develop intolerable myalgias, nausea and fatigue, he/she should increase the prednisone dose to the prior step in the corticosteroid protocol and contact the primary care provider, gastroenterologist or endocrinologist. The rate of taper is completely dependent on the patient's ability to tolerate the steroid-withdrawal symptoms. Patients who have been on steroids for an extended period of time (e.g. months) may not be able to tolerate a taper as well and may require even slower tapers than those listed above (decreasing by 1 mg or 0.5 mg each step). For these patients, follow-up with their primary care provider, gastroenterologist or an endocrinologist should be initiated once the patient has tapered down to 5–10 mg/day.

Purine analogues (6-mercaptopurine/azathioprine)

Purine analogues, or IMMs, have been widely used as glucocorticoid- sparing agents for the maintenance of remission or in conjunction with biologic therapy to reduce the need for surgery in patients with CD [39,40]. Fortunately, evidence suggests that the perioperative use of IMMs does not adversely affect postoperative outcomes. For example, a study of 159 patients with IBD by Aberra *et al* did not show an increased risk of postoperative infectious complications among patients receiving either azathioprine (AZA) or 6-mercaptopurine (6-MP) [29]. A separate study by Colombel *et al* of 207 patients with CD who received either AZA or 6-MP and underwent intra-abdominal surgery also did not show an increased risk of postoperative complications [41].

The elimination half-life of 6-MP is 1–2 hours, and the elimination half-life of AZA is approximately 1 hour. Both drugs have metabolites with a half-life being approximately 5 hours. Since there has not been strong evidence suggesting an increased risk of postoperative complications, our recommendation is to withhold thiopurines on the day of surgery; if renal function remains normal, these medications should be resumed when oral medications are resumed.

Cyclosporine

Cyclosporine as a potent immunosuppressive agent has been largely used in patients with steroid refractory ulcerative colitis (UC) as rescue therapy before colectomy. Its use in patients with CD is relatively uncommon. Major adverse effects with the use of cyclosporine include nephrotoxicity, seizures and opportunistic infections; the mortality rate with opportunistic infections can approach 3.5%. Thus, patients receiving cyclosporine and corticosteroid therapy should be carefully monitored for any signs of renal impairment or infection.

Three retrospective series investigating postoperative outcomes associated with cyclosporine have been small, with only 25, 14 and 19 patients included in each. Despite the small size, the series all found that preoperative cyclosporine administration was not associated with increased postoperative morbidity [42–44]. Unfortunately, there is no published literature or clinical data to support either the continuation or discontinuation of this drug in the perioperative period. Thus, our recommendation is that cyclosporine can be continued through the perioperative period with careful consideration of renal function, hypertension, lipid panel and opportunistic infection.

Methotrexate

Methotrexate (MTX) has been shown to be effective in reducing the use of steroids, and inducing and maintaining remission in patients with CD [45]. Methotrexate competitively inhibits the enzyme dehydrofolatereductase, which impairs DNA synthesis and cellular reproduction. Perioperative considerations to include are infectious complications, renal impairment and bone marrow suppression. The majority of the literature on postoperative infectious complications in the setting of MTX have investigated patients with rheumatoid arthritis undergoing orthopedic surgery. These studies did not find an increased risk of postoperative complications and concluded the drug was safe to continue through the perioperative period [46–49].

There are limited data on postoperative complications with the use of MTX in patients with IBD. A recent study of 180 IBD patients was conducted for early postoperative complications. Fifteen patients received MTX preoperatively, and there was no association with postoperative complications. A meta-analysis on the use of preoperative MTX in patients with IBD or rheumatoid arthritis was performed, and the investigators found no increased risk of postoperative complication in IBD or rheumatoid arthritis patients on preoperative MTX (odds ratio [OR] = 0.62; 95% confidence interval [CI], 0.34–1.15) [50]. Thus, our recommendation is to continue MTX in the preoperative and immediate postoperative period in the absence of renal failure and opportunistic infection.

Biological therapy

The era of biologic therapy initiated by inhibitors TNFα including infliximab, adalimumab and certolizumab pegol and their biosimilars has revolutionized the management of IBD. They are indicated for induction and maintenance of remission of moderate to severe luminal IBD and fistulizing CD refractory to conventional therapy [10]. Despite this, many patients using these therapies still require surgery either to manage their IBD or for unrelated medical conditions. While the anti-TNFα agents have remained the dominant biologic class of therapeutics, vedolizumab (an anti-integrin agent) and ustekinumab (an anti-interleukin) have recently been approved by the FDA.

Anti-TNFα

The impact of anti-TNFα medications on surgical outcomes is controversial. Several single center studies have found an increased risk of infectious complications with the use of anti-TNFα preoperatively [51–59]. A recent meta-analyses of 18 studies with 4659 patients suggested that perioperative treatment

with anti-TNFα medications significantly increased infectious complications (OR = 1.93) as well as total complications (OR = 2.19) and a trend towards increased non-infectious complications (OR = 1.73). Unfortunately, there is significant heterogeneity among studies, especially in regard to the interval between the last does of anti-TNFα and surgery. Only 1 study reported similar outcomes whether the medication was given 14 days prior to surgery *vs* 15–30 days or 31–180 days before surgery [60]. In contrast to these findings, there are a number of other studies that did not identify an increased risk for infectious complications in the setting of anti-TNFα therapy [41,61–71]. Additionally, the biological effect of infliximab does not appear to be sustained beyond 12 weeks [72], and drug levels at the time of surgery may be more important than the time from the last dose [58].

To date, results from several published single center retrospective reviews, prospective studies, and meta-analyses remain conflicting, with most trending toward a lack of significantly increased risk in postoperative complications with the use of anti-TNFα therapy in the preoperative period. The controversial results may be a reflection that it's patient severity of disease and their requirement biologic therapy, more than the medication itself, which lends to postoperative complications. However, it is challenging to isolate a drug's effect on postoperative complications independent of a patient's increased severity of disease. Interestingly, a study from the Cleveland Clinic on patients undergoing an ileal pouch anal anastomosis (IPAA) for ulcerative colitis found that anti-TNFα therapy did not increase the risk of postcolectomy infectious complications in patients who had a three-stage IPAA. However, it was an independent risk factor for pelvic sepsis if IPAA was performed as a -stage operation. This suggests that anastomoses should be protected with diversion when a patient with refractory UC is on biologic therapy [73]. Thus our recommendation is that the surgeon should strongly consider protecting the anastomosis with diversion when patients with refractory IBD have received a dose of anti-TNFα therapy within 2–4 weeks of surgery and are on concurrent immunosuppression,. The surgeon may have to make this decision intraoperatively depending on the location of the anastomosis and the health of the tissue. If the patient underwent a subtotal colectomy or segmental colectomy with a distal anastomosis, a stronger consideration should be given to diversion as compared with a lower risk ileocectomy anastomosis.

Given the aforementioned results, our recommendations are as follows:

i. In a patient with inflammatory CD who has been on maintenance biological therapy with dosing every 8 weeks, we would recommend discontinuing the biological therapy up to 4 weeks prior to surgery and resume 4 weeks following surgery depending on the risk of recurrence (discussed in greater detail later) in order to not miss a dose of biological therapy.
ii. In a patient with stricturing CD who has been on biological therapy without improvement, discontinue the therapy as soon as a surgical approach has been decided. Ideally, we recommend waiting 4 weeks before proceeding with an operation. Endoscopic stricture therapy may be attempted before surgery.
iii. For urgent or emergent situations, we would not delay surgery due to biological therapy. The increased risk of infectious complications, if even present, does not outweigh the risks of delaying surgery.
iv. When trying to decide intraoperatively, the surgeon should take into account whether or not to divert an anastomosis based on the overall health and total immunosuppression of the patient rather than the isolated factor of whether or not the patient is on biologic therapy.
v. It is rare to perform an ileal pouch-anal anastomosis (IPAA) in CD patients. If performed, we would recommend that those patients on biological therapy undergo a three-stage IPAA rather than a one- or 2-stage given the potential increased risk of pelvic sepsis. There is literature to suggest that perhaps a three-stage IPAA is overused [74]. However, regardless the overuse of the three-stage surgery, patients who undergo the three-stage approach are healthier at the time of pouch surgery and have decreased use of corticosteroids, and improved hypoalbuminemia and weight loss of optimal pouch function [75].

Vedolizumab

Vedolizumab, a murine monoclonal antibody to α4β7 integrin with a half-life of 22 days, was recently approved by the FDA for the treatment of moderate to severe CD. The drug appears to be safe and effective for the medical management of CD and provides an alternative for those patients who are non-responders or who develop antibodies to anti-TNFα agents [76,77]. Since the drug was only recently approved by the FDA in 2014, there is only 1 study to date that has looked at postoperative infectious complications when receiving vedolizumab within 12 weeks of a major abdominal or pelvic operation. Lightner *et al* found that 30-day infectious complications and surgical site infections (SSIs) were seen in 53% and 37% of vedolizumab-treated patients, respectively; vedolizumab remained a significant predictor of postoperative SSI on multivariate analysis ($P < 0.001$) [78]. The results of this study suggest that when patients have received vedolizumab within 12 weeks of surgery, surgeons should consider diverting anastomoses and leaving high-risk wounds open to heal by secondary intention if surgery cannot be delayed. If surgery can reasonably be delayed, we would suggest waiting at least 1 half-life (15–22 days) before performing a major abdominal operation to minimize the risk of postoperative infectious complications.

Ustekinumab

Ustekinumab, a human monoclonal antibody to interleukin (IL)-12 and IL-23, has a biological half-life is 15 to 32 days. It was approved for treatment of psoriasis and arthritis, and was recently approved by the FDA for the treatment of moderate to severe CD. While no study to date has looked at postoperative adverse complications, a phase IIb randomized controlled trial assessing safety parameters did find equivalent numbers of overall infections in the treatment and control cohorts [79]. An ongoing study is currently being conducted to look at postoperative complications in the setting of the use of ustekinumab.

Perioperative blood transfusion

Anemia is the most common systemic complication of IBD [80–82] and is most commonly related to iron deficiency due to dietary restrictions, a degree of malabsorption and intestinal bleeding [83]. Because perioperative blood transfusion has been shown to be associated with immunosuppression, it was thought that blood transfusion in the preoperative or perioperative phase may have a protective effect on recurrence of CD. Some studies from the 1990s demonstrated a protective effect

of postoperative recurrence of CD with preoperative and perioperative blood transfusions [84–86], while others did not [87]. A pooled analysis of these studies, which included 622 patients, found that the 5-year recurrence rates were 26.9% for the transfused group and 25.2% for the nontransfused group ($P = 0.456$) g [88]. In the current era of biologic therapy, a recent study found that perioperative blood transfusion before an ileocolic resection for CD did not confer a protective effect on disease recurrence. Rather, blood transfusion was associated with both surgical and endoscopic recurrence of CD following the index operation ($P < 0.001$). Additionally, blood transfusion was associated with an increased risk of postoperative infectious and noninfectious complications ($P < 0.001$) [89]. Therefore, our recommendation is not to transfuse preoperatively unless the clinical context mandates transfusion (e.g. massive gastrointestinal hemorrhage) or when the hemoglobin is less than 6 g/dL as advised by the ASA guideline on blood transfusion [90].

In the setting of a non-urgent or emergent case, the administration of oral or IV iron supplements, with or without erythropoiesis-stimulating agents, should be considered standard therapy for anemia in a medical IBD patient. This recommendation is based on the Guidelines on the Diagnosis and Management of Iron Deficiency and Anemia in Inflammatory Bowel Diseases (Statement 3A), which states that the goals of anemia treatment are to increase hemoglobin and iron studies above the lower threshold of normal, to prevent a further fall in hemoglobin, to avoid the use of blood transfusion, to relieve symptoms related to anemia and to improve the quality of life (Grade D) [91]. Therefore, if the operative scenario allows for it, an intravenous iron transfusion could be beneficial in the preoperative period to increase the hemoglobin prior to undergoing an operation.

Perioperative medications and the risk of thromboembolic events

It is well established that patients with IBD are at increased risk of thromboembolic events in both the outpatient and inpatient setting [92–94]. In a case series of IBD-related venous thromboembolism (VTE) from the Mayo Clinic, the severity of disease and the extent of colonic involvement in patients with UC were found to be associated with increased risk of VTE. Interestingly, 87% of the patients in this study also had additional risk factors for VTE including hospitalization, immobilization, malignancy or recent surgery: all factors common in the perioperative IBD patient population [95]. Another study found that *C. difficile* increased the rate of VTE among IBD patients [96]. While there are no established guidelines for VTE prophylaxis in IBD patients undergoing surgery, the aforementioned risk factors are common among surgical patients, highlighting the need for aggressive prophylaxis in this patient population.

No studies to date have specifically investigated the potential benefit of VTE prophylaxis in the ambulatory, hospitalized, perioperative or postoperative setting. Given the increased risk of VTE in this patient population and the lack of evidence to suggest that a moderate dose of anticoagulant increases the bleeding risk in patients with IBD [97], it would seem that patients should receive prophylaxis during and after hospital stays.

During the perioperative period, we recommend that patients with IBD receive prophylaxis based on the American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition) [98]. These recommendations are for patients to receive 5000 units of subcutaneous heparin three times daily, 40 mg of subcutaneous enoxaparin once daily or 2.5–5.0 mg of subcutaneous fondaparinux daily while in the hospital. In addition, we recommend giving 5000 units of subcutaneous heparin prior to induction of anesthesia in the operating room. The question of whether to give 30 days of postoperative prophylaxis has recently been discussed, but guidelines have yet to be published. The national comprehensive cancer network (https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf) guidelines suggest that all colorectal cancer patients be discharged home on 30 days of postoperative enoxaparin for the prevention of DVT following surgery, and the recent literature has shown that VTE risk is higher in IBD patients than in colon and rectal cancer patients. Therefore, it would seem that all IBD patients should also receive 30 days of postoperative enoxaparin, as do colon and rectal cancer patients. This was recently investigated at the Mayo Clinic. The authors found that the risk of VTE was higher among patients undergoing a colectomy but was not increased in cases such as ileocolic resections or diverting loop ileostomy reversal. Therefore, the Mayo Clinic changed its practice to send all IBD patients home with 30 days of VTE prophylaxis following a colectomy or proctocolectomy but not following other surgical intervention (unpublished data).

Postoperative prophylaxis of recurrent CD

Disease recurrence is common following an operation for CD, with 80% of patients having endoscopic recurrence and 30% having clinical recurrence at 1 year [2,9,10]. A third of these patients will require a reoperation at 10 years, and up to 80% will require an additional operation by 15 years [99,100]. This undoubtedly leads to increased probability of malabsorption syndrome and decreased quality of life. Even though studies of recurrence have centered around ileocolonic resection (ICR) and ileocolonic anastomosis (ICA), the results implicate that in general there is a high recurrence of CD despite removal of grossly diseased bowel. Additionally, we have learned that endoscopic and histological lesions precede clinical symptoms and that the severity of lesions can predict the subsequent symptomatic course of the disease.

Ileocolonoscopy has been the gold standard for monitoring disease after ICR and ICA. An endoscopic instrument, the Rutgeerts Score (RS), was developed in the early 1990's for grading ulcers and inflammation of the neoterminal ileum in the setting of the first ICR and ICA [101,102]. The RS consists of 5 grades of severity (i0–i4)m, which has been shown to be a suitable endoscopic model for predicting clinical recurrence after ICR in CD. In fact, the RS has been incorporated into professional guidelines. We recommend that the first ileocolonoscopy be performed 6 months after ICR and ICA, then yearly afterwards for disease monitoring. We also recommend that ileocolonoscopy be performed as needed with or without concurrent measurement of laboratory markers, such as C reactive protein and fecal calprotectin, if a major adjustment of medication is made, to monitor the response to the therapy. Close monitoring is also recommended of the postoperative disease course in patients with ileocolonic disease undergoing ICR and ICA and concurrent perianal, distal bowel or proximal small bowel, or concurrent stricturoplasty. In addition, patients with permanent stoma following total proctocolectomy should also have close surveillance since CD can recur in the small bowel [103,104].

The prevention of postoperative recurrence of CD remains a challenge to patients and physicians. While we know that the vast majority of patients develop recurrence, the time frame

remains difficult to predict, with some patients experiencing immediate recurrence and others remaining free of symptoms for many years. Thus, there are many options for timing postoperative medical treatment. One option is to treat at the time a patient develops clinical symptoms. However, this is less than ideal given that the disease may be irreversible at this point and thus put the patient on a path of a subsequent operation. The second option is to tailor therapy to endoscopic recurrence. While only 20% of patients who develop endoscopic recurrence become symptomatic, the severity of endoscopic findings predicts clinical recurrence. Over a 4-year follow-up, 100% of patients with severe endoscopic recurrence (RS of i2–i4) developed symptomatic recurrence compared with only 9% of patients with a low score (i0–i1) [102]. Endoscopically tailored therapy was found to be an effective strategy in the Postoperative Crohn's Endoscopic Recurrence study (POCER) [105]. In this trial, 174 patients across 17 centers received 3 months of antibiotics, and high-risk patients (smoker, penetrating disease, $\geq$ second operation) received a thiopurine (or every-other-week adalimumab if thiopurine intolerant). Patients were then randomized to active care with a colonoscopy at 6 months and step-up of therapy if evidence of histologic recurrence or standard of care. At 18 months, significantly less endoscopic recurrence was seen in the active care group *vs* the standard of care group (49% *vs* 67%, $P = 0.028$). Of note, in this trial, high-risk patients were treated immediately after surgery. Thus, the third treatment option, which may be the best for high-risk patients, is medical treatment initiated within 1 month of surgery in order to maximally prevent disease recurrence.

Predictors of recurrence and operation performed

The risk for disease recurrence should ultimately drive the timing options for initiating medical treatment, as mentioned above. Published risk factors for disease recurrence include active smoking [106], penetrating disease phenotype [107], perianal location [1,108], prior intestinal resection [109], extensive small bowel resection (> 50 cm) [1] and presence of granulomas in mesenteric lymph node [110]. The most significant of these seems to be smoking status with an OR of 2.15 (95% CI: 1.42–3.27) found on a meta-analysis [111].

The likelihood of disease recurrence is also largely affected by the type of operation performed to treat the disease. For example, while nearly 100% of CD patients will have endoscopic recurrence of disease following an ileocolic resection, only 30% of CD patients will experience recurrence in the small bowel following total proctocolectomy with end ileostomy [112]. Thus, the management strategies of postoperative medical treatment differ based on the operation performed and the remaining intestine.

We need to define the postoperative recurrence here and describe the commonly used RS and its predictive value and pitfalls (**Figure 1–3**).

Current recommendations

There are currently no formal published guidelines for the medical prevention of postoperative recurrence of CD. We herein review the most recent literature investigating postoperative recurrence and finish with our own recommendations based on the available evidence.

Antibiotic therapy

Because antibacterial agents against anaerobic bacteria have been effective in reducing the severity of endoscopic recurrence [113,114], an early study by D'Haens *et al* investigated adding 3 months of metronidazole to AZA [115]. They found a decreased risk of 12 month endoscopic recurrence as compared with metronidazole alone and concluded this dual therapy was an optimal treatment approach. A subsequent randomized controlled trial did not find that adding metronidazole to AZA significantly reduced the rate of endoscopic recurrence beyond AZA alone [116]. Given that metronidazole may have an advantageous effect on the prevention of postoperative recurrence, its use is favored. However, this is generally for short periods of time (e.g. 2 weeks to 3 months) given its poor tolerance due to gastrointestinal upset and polyneuropathy with chronic use.

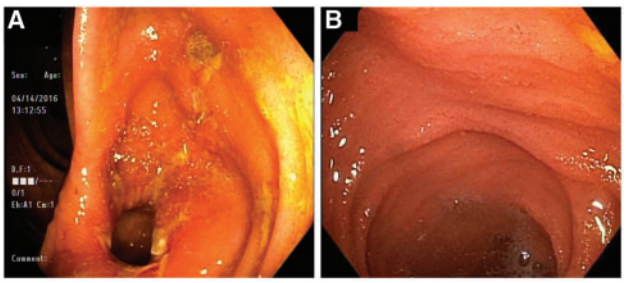

Figure 1. Colonoscopy of post-ileocolonic resection and anastomosis in Crohn's disease. **A)** Mild anastomotic stricture with suture line ulcers; **B)** Normal neoterminal ileum.

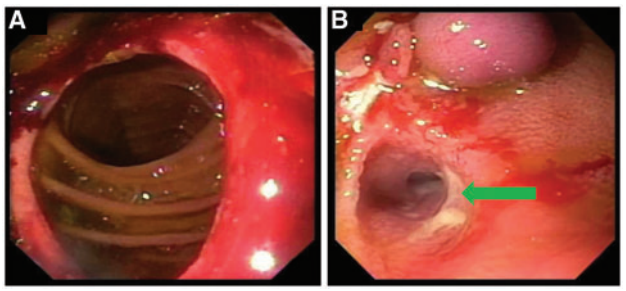

Figure 2. Colonoscopy of post-ileocolonic resection and anastomosis in Crohn's disease. **A)** Friable mucosa at the anastomosis. Normal neoterminal ileum in distal view; **B)** Suture line leak (green arrow) at the blind end of the ileum of the side-to-end anastomosis.

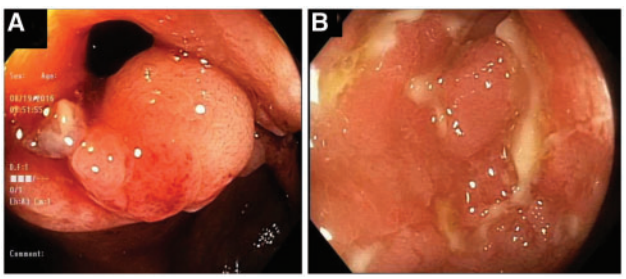

Figure 3. Colonoscopy of post-ileocolonic resection and anastomosis in Crohn's disease. **A)** Stricture at the anastomosis; **B)** Ulcers and inflammation in the neoterminal ileum, a classic example of recurrent Crohn's disease after the surgery.

Aminosalicylates

The use of 5-ASA agents in the postoperative setting is appealing given that they have a favorable safety profile, are easy to administer and are considerably cheaper than biologic therapy. However, controversy exists regarding the utility of 5-ASA with some studies demonstrating a decrease in symptomatic recurrence [117] and endoscopic recurrence [118,119], while others have failed to demonstrate an effect [120,121]. A recent meta-analysis of available prospective studies did demonstrate that mesalamine decreased clinical as well as severe endoscopic recurrence at 12 months (relative risk [RR] *vs* placebo: 0.76, 95%CI: 0.62–0.94) [114].

Immunomodulators

AZA and 6-MP have been extensively studied in the postoperative setting for CD. These agents are clearly effective as compared with placebo and are questionably superior to 5-ASA agents but limited by the lack of compliance due to side effects. Two studies that compared AZA/6-MP to placebo found a significant decrease in endoscopic recurrence at 12 months [115,122]. A later Cochrane Database Review of compiled data found a decrease in clinical (RR *vs* placebo: 0.59, 95%CI: 0.38–0.92) and severe endoscopic recurrence (RR *vs* placebo: 0.64, 95%CI: 0.44–0.92) with AZA/6-MP as compared with placebo [114]. In contrast to placebo, multiple trials have not found thiopurines are superior to mesalamine [122–126]. These may be true efficacy differences or may be a reflection of poor adherence to thiopurines as compared with mesalamine, most commonly reflected in leukopenia and thrombocytopenia [125,126]. However, in a meta-analysis, mesalamine was associated with a higher risk of endoscopic recurrence as compared with thiopurines, but again mesalamine had a lower risk of adverse events [114]. A long-term study found decreased surgical recurrence with thiopurines when treated for 36 months as compared with no treatment at all [40]. Thus, long-term treatment for prevention of recurrence with thiopurines may be beneficial. However, overall, the side effect profile may limit the utility of these agents in favor of mesalamine.

Anti TNFα therapy

Anti-TNFα has been studied in the postoperative prophylaxis of CD recurrence. The most well studied to date is infliximab, but an increasing body of evidence demonstrates favorable data for adalimumab (ADA) as well. Initial reports of randomized controlled trials comparing infliximab to placebo administered 4 weeks postoperatively showed significant decrease in histologic recurrence at 1 year (27.3% *vs* 84.6%; $P = 0.01$) [127]. In another 3-year prospective randomized clinical trial of early infliximab at 4 weeks postoperatively compared with placebo showed significant increase in clinical remission at 12 and 36 months (100% and 93.3% *vs* 68.8% and 56.3%; $P < 0.03$) [128]. Infliximab therapy also seems superior to thiopurines for the prevention of postoperative recurrence. A prospective trial compared the efficacy of infliximab to AZA and mesalamine by studying clinical remission and endoscopic recurrence at 6 months. Over a course of 6 months, 10 patients were treated with mesalamine, 8 with AZA and another 8 with infliximab. During the 6-month observation period, no patients in the infliximab group, 3 patients (38%) in the AZA group and 7 patients (70%) in the mesalamine group developed clinical recurrence (CDAI $\geq$150) ($P = 0.01$), and endoscopic inflammation was improved in 75% of patients in the infliximab group, 38% in the AZA group and 0% in the mesalamine group ($P = 0.006$) [129]. A later randomized controlled trial compared infliximab to AZA for the reduction of endoscopic, histologic and clinical recurrence of CD at 12 months postoperatively. Infliximab was found to have significantly reduced histologic recurrence (80% *vs* 18%; $P = 0.008$) but no significant difference in clinical recurrence [130].

A recent multicenter, prospective, observational study investigated the use of postoperative ADA given 2 weeks after ileocolic resection in 29 high-risk CD patients for the prevention of postoperative recurrence. Four of the 29 patients (13.7%) developed clinical recurrence, 6 of 29 (20.7%) endoscopic recurrence and 7 of 19 (36.8%) morphological recurrence after 1 year, and the authors concluded that ADA was safe and effective for preventing postoperative recurrence [131]. A later study randomized 51 patients to receive ADA, AZA or mesalamine 2 weeks after ileocolic resection to better understand the efficacy of ADA in preventing postoperative endoscopic and clinical recurrence. The rate of endoscopic recurrence was significantly lower in ADA (6.3%) compared with the AZA (64.7%; OR = 0.036, 95% CI: 0.004–0.347) and mesalamine groups (83.3%; OR = 0.013, 95% CI: 0.001–0.143). There was also a significantly lower proportion of patients in clinical recurrence in the ADA group (12.5%) compared with the AZA (64.7%; OR = 0.078, 95% CI: 0.013–0.464) and mesalamine groups (50%; OR = 0.143, 95% CI: 0.025–0.819). Thus, the authors concluded that the ADA was greatly effective in reducing postoperative recurrence following ileocolic resection for CD [132].

Later studies were conducted to compare infliximab and ADA. This started with a small open label prospective study of 20 patients performed to compare ADA to infliximab for the prevention of postoperative endoscopic, clinical and histologic recurrence. No differences were found between the 2 groups [133]. To capture a larger number of patients, an international multi-institution database was used to perform a retrospective direct comparison of ADA *vs* infliximab in the prevention of 1-year endoscopic postoperative recurrence of CD. Among 168 patients, the recurrence rates were 24.3% and 27.1% ($P = 0$ .815) in the 2 groups [134].

Summary recommendations for postoperative prophylaxis of recurrence

In summarizing the above information, we consider high-risk patients to be those with two or more of the following factors: young age at diagnosis (< 30 years), penetrating disease behavior, active smoking, perianal disease at diagnosis of CD, previous surgery and less than 3 years since the previous surgery. High-risk patients should be placed on metronidazole for 2 weeks postoperatively and then started on infliximab or ADA at 2–4 weeks postoperatively barring any complications. If a patient has a contraindication to biologic therapy or develops an infusion reaction, the patient should then be started on AZA (**Table 2**). Not all patients will develop clinical recurrence of their CD. Given the potential risk with medical therapy and the lack of cost effectiveness of postoperative prophylactic therapy with infliximab [135,136], patients at moderate to low risk of recurrence should perhaps best be treated with early endoscopic surveillance at 3–6 months. If there are findings of endoscopic recurrence, postoperative therapy can then be initiated at that time.

When to discontinue postoperative prophylaxis

A challenge remains on when to discontinue therapy as there are no established prognostic factors that predict relapse or

Table 2. Anti-TNFα biological therapy following segmental resection for Crohn's disease

Patient risk	Preoperatively	30 day postoperative	3–6 month postoperative
Low risk (none of the risk factors)*	Discontinue 4 weeks prior to operation	–	Endoscopy at 6 *months* to look for evidence of histologic recurrence and resume treatment based on these findings
Moderate risk (1 or 2 of the risk factors)*	Discontinue 4 weeks prior to surgery	–	Endoscopy at 3 *months* to look for evidence of histologic recurrence and resume treatment based on these findings
High risk (2 or more of the risk factors)*	Discontinue 4 weeks prior to surgery	Resume 4 weeks following surgery	Continue medical therapy

*The risk factors include young age at diagnosis (< 30 years), penetrating disease behavior, active smoking, perianal disease at diagnosis of Crohn's disease, previous surgery and less than 3 years from the previous surgery.

sustained remission after discontinuation of anti-TNFα therapy. Additionally, there is little information as to whether that drug can be safely restarted if needed, or whether the efficacy will remain similar once restarted. One retrospective study found that patients who achieved clinical remission on infliximab and remained on maintenance therapy for one year have a 69% change of remaining in remission in the year following infliximab discontinuation [137]. Another single center cohort study found that half relapsed within 1.5 years of infliximab discontinuation [138]. A longer term retrospective study found that half of the patients who discontinued infliximab upon clinical remission had sustained clinical remission after a median period of 10 years, although most of these patients remained on IMM therapy [139]. The STORI trial is a prospective cohort study following a group of patients who have received > 1 year of therapy with infliximab and an immunomodulator and then stopped infliximab. More than half of the patients did not relapse at 1 year [140]. Thus, it would be reasonable to discontinue biologic therapy in patients who remain in surgical remission 1 year following their operation with consideration of starting or continuing AZA. This strategy would also have decreased side effects and be more cost effective than indefinite treatment.

Summary and conclusions

Our current literature is limited by the heterogenicity of studies, retrospective design and small patient numbers from several individual tertiary care institutions. Our practice would greatly benefit from prospectively designed studies, uniformity across studies (e.g. the use of biological agents within 4 weeks *vs* 12 weeks *vs* 26 weeks after surgery), multicenter (including community hospitals) randomized control trials to capture larger numbers of patients and trials to investigate the impact of immediate postoperative resumption of medical therapy on disease recurrence. In the meantime, without published guidelines, we continue to make decisions on timing of medical therapy largely based on empiric practice. We herein have suggested a starting point for practice guidelines and have highlighted areas needing further research.

The large cost associated with the treatment of CD combined with a growing body of research-based evidence create an ideal environment for creating and utilizing a standardized pathway to delivering patient-centered care. A recent study by Hoverman *et al* showed that adherence to evidence-based colon cancer treatment pathways positively impacted clinical outcomes with a concurrent reduction in the cost of care [141]. Therefore, an increasing number of institutions are now moving toward standardized treatment pathways for colon cancer patients. Perhaps we should be doing the same for the management of IBD.

Regardless, it remains critical that gastroenterologists and surgeons join forces in the management of these patients. We rely on one another and our collaborative spirit to continue to improve the care of patients with CD.

Conflicts of interest statement: Bo Shen, MD, has served as a consultant to Johnson & Johnson and Abbvie and as a speaker for Abbvie.

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