

# Preoperative Optimization of Crohn's Patients before Abdominopelvic Surgery

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## Abstract

### Keywords

- ▶ Crohn's disease
- ▶ surgery
- ▶ nutrition
- ▶ venous thromboembolism
- ▶ perioperative optimization

In this article, we review and identify modifiable risk factors associated with postoperative complications of Crohn's disease. We highlight the importance of factors such as nutrition, corticosteroids, immunomodulators, abscesses, ideal timing of surgery, and biologic and small-molecule therapy on surgical outcomes. Herein, we discuss the strategies for attenuating these risk factors. Special consideration is given to venous thromboembolism prophylaxis in this patient population.

The incidence and prevalence of Crohn's disease (CD) have increased over the last two decades, and up to three-quarters of patients with CD require surgery during their lifetime.<sup>1–4</sup> It is thought that the cumulative surgery rate 30 years after symptom onset is as high as 94.5%.<sup>5</sup> As such, perioperative optimization of patients with CD is of utmost importance in mitigating the risk of perioperative complications. Multiple modifiable and nonmodifiable risk factors for complications have been identified.<sup>6,7</sup> The aim of this review was to identify modifiable risk factors and risk reduction strategies (▶ **Table 1**) to attenuate complication rates in CD patients undergoing abdominopelvic surgery. We discuss preoperative optimization (▶ **Tables 2–4**), timing of surgery, and venous thromboembolism prophylaxis in patients with CD.

## Materials and Methods

We performed a qualitative review of peer-reviewed articles published in PubMed. The following search terms were used: "Crohn's disease," "Crohn's," "inflammatory bowel disease," "IBD surgery," "surgery," "perioperative," "postoperative," "preoperative optimization," "venous thromboembolism," "prophylaxis," "VTE prophylaxis in Crohn's," "nutrition optimization," and "nutrition in Crohn's." Articles published in

languages other than English were also excluded. Additional references were obtained from these articles.

## Nutrition

Malnutrition is a major risk factor for postoperative complications among patients with CD. The etiology of malnutrition in CD is multifactorial due to reduced intake to avoid exacerbating GI symptoms, malabsorption due to active small bowel disease or foreshortened bowel, increased energy requirements due to GI losses or malabsorption, and increased metabolic demands due to chronic inflammation. The prevalence of malnutrition among patients with inflammatory bowel disease (IBD) has been reported to be 16%, but as high as 26.4%.<sup>8–10</sup> Given the widespread prevalence of malnutrition, the European Crohn's and Colitis Organization (ECCO) recommends nutritional optimization among patients with Crohn's disease undergoing surgery.<sup>10</sup> Nutritional assessment is commonly based on the body mass index (BMI in kg/m<sup>2</sup>) and weight loss, but these crude measures are relatively insensitive for the assessment of malnutrition. A study by Sandall et al advocated for nutritional assessment to incorporate factors such as fat mass, fat-free mass, muscle strength, micronutrient levels, and

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**Table 1** Summary of risk factors and strategies to attenuate their influence on postoperative complications after surgery for Crohn's disease

Variable	Risk factor?	Definition(s)	Treatment strategies
Malnutrition	Strong	Weight loss: >10% weight loss within 6 months Hypoalbuminemia: <30 g/L Sarcopenia: reduction of muscle mass Sarcopenic obesity: overweight patients with sarcopenia	Dietary optimization Oral nutritional supplements Enteral nutrition Parenteral nutrition
Frailty	Yes	Age-related loss of physiologic reserve in response to stress	Prehabilitation
Anemia	Moderate	Hgb <12 g/dL for women Hgb <13 g/dL for men Severe anemia: Hgb <10 g/dL	Parenteral iron supplementation Vitamin B12, folate, zinc, copper supplementation if deficient
Smoking, vaping, chewing tobacco	Moderate	Nicotine-containing products	Cognitive behavioral therapy, buspirone
Corticosteroids	Strong	High dose: >40 mg of prednisone eqv. Chronic: >3 wk	Tapering; EEN Vitamin A supplementation
Immunomodulators	No	Azathioprine, 6-MP, methotrexate	Discontinue at the time of surgery; resume according to gastroenterologist discretion
Biologics	No	Tumor necrosis factor (TNF) inhibitors, interleukin inhibitors, integrin inhibitors, others	Operate at nadir to avoid "wasting" the last dose; resume/initiate 2–4 wk post-operatively
Small molecules	Unknown	JAK inhibitors (recently FDA approved for CD)	Discontinue 3 d preoperatively
Intra-abdominal abscesses	Strong	–	Enteral or parenteral antibiotics; percutaneous drains if >3 cm
Ileostomy	Protective	–	Stoma site marking and education

Abbreviations: CD, Crohn's disease; EEN, exclusive enteral nutrition; FDA, U.S. Food and Drug Administration.

**Table 2** Preoperative history-based evaluation of Crohn's disease patients

History	<ul style="list-style-type: none"> <li>▪ Disease present for how long? Histologic diagnosis? Colorectal cancer screening current?</li> <li>▪ Validated questionnaires to evaluate disease activity.</li> <li>▪ Assess risk of morbidity and mortality, e.g., risk calculators.</li> <li>▪ Engage patient, track their symptoms: daily bowel movements caliber, bleeding; weight.</li> </ul>
Severity and extent	<ul style="list-style-type: none"> <li>▪ Disease location, severity, extent according to Vienna classification.</li> </ul>
Any recent flare?	<ul style="list-style-type: none"> <li>▪ How severe? Weight loss? Anemia? Steroids? Transfusions?</li> <li>▪ Is patient likely to need urgent/emergent surgery?</li> <li>▪ Does the patient need to be diverted?</li> <li>▪ Emergency surgery is an independent risk factor for morbidity and mortality.</li> </ul>
Previous procedures?	<ul style="list-style-type: none"> <li>▪ Presence of adhesions increasing operative time and risk of complications.</li> <li>▪ Open vs. minimally invasive? Minimally-invasive surgery associated with better outcomes.</li> </ul>
Comorbidities	<ul style="list-style-type: none"> <li>▪ Cardiopulmonary, renal status, and optimization of comorbidities.</li> </ul>
Smoking/nicotine products?	<ul style="list-style-type: none"> <li>▪ Independent risk factor for anastomotic leak (AL), poor wound healing.</li> <li>▪ Cotinine testing—assesses current exposure.</li> <li>▪ Advise cessation: reduces complications, decreases recurrence for Crohn's. Even a 50% reduction within 6–8 wk of surgery is associated with better outcomes.</li> <li>▪ Medication-assisted (buspirone), nicotine substitutes to wean off</li> <li>▪ Cognitive behavioral therapy.</li> </ul>
Medications: Current, past?	<ul style="list-style-type: none"> <li>▪ Steroids associated with increased risk of complications, especially at &gt;40 mg/d exposure. Wean as much as possible.</li> <li>▪ Immunomodulator: discontinue at time of surgery.</li> <li>▪ Biologics do not need to be held preoperative other than to save money.</li> <li>▪ Small molecules: discontinue 3 d preoperatively.</li> </ul>

**Table 2** (Continued)

VTE prophylaxis: already a high-risk population due to the presence of IBD.	<ul style="list-style-type: none"> <li>Factors further increasing risk: previous history of VTE is most important. Active inflammation, prolonged hospitalization, steroid exposure, hormone replacement medications increase the risk.</li> <li>Consider postoperative prophylaxis for at least 30 d postop, as VTE post-discharge is common.</li> </ul>
Fertility status	<ul style="list-style-type: none"> <li>Discuss family planning, fertility, pelvis nerve dysfunction, referral to high-risk OB/Gyn, assisted reproductive specialist.</li> </ul>
Social, mental health	<ul style="list-style-type: none"> <li>Patient education, setting up expectations, involvement with IBD groups help. Evaluation by and discussions with stoma nurses. Assess for depression, anxiety—more common in IBD patients. Involve professional help when necessary.</li> </ul>
Practice/volume related	<ul style="list-style-type: none"> <li>Know your practice, institution, resources and limitations.</li> <li>Working with a multidisciplinary, experienced team leads to better outcomes.</li> </ul>

Abbreviations: IBD, inflammatory bowel disease; OB/Gyn, Obstetrics and gynecology; VTE, venous thromboembolism.

**Table 3** Laboratory-directed perioperative optimization for Crohn's disease

CBC, type and screen	Preoperative correction of anemia is associated with improved outcomes. Conversely, postoperative red blood cell transfusion leads to increased morbidity and mortality.
Ferritin, iron + TIBC	Treat with IV iron (avoid oral supplements which causes GI distress).
Vitamin B12	5,000 micrograms intramuscularly or sublingual every month.
Folate	1 mg PO daily for 1 month.
Vitamin D	50,000 IU PO weekly x 12, then recheck.
Lipid panel	For patients taking cyclosporine.
C-reactive protein (CRP)	Indicator of inflammation. Trend might be more telling the value. Studies show the trend might predict complications such as AL.
Fecal calprotectin	Inflammation? for monitoring disease activity.
Stool sample	Clostridium difficile ± other enteric pathogens.
TB screening	QuantiFERON gold standard.
Hepatitis screens	HBsAg, anti-HBs, Hep C.
CMP with albumin, prealbumin	Hypoalbuminemia is associated with ongoing inflammation, sepsis, and malnutrition. Albumin level is the best predictor of 30-day morbidity and mortality. Evidence on IV albumin administration is weak, it is best to use as an indicator of patient's status and to treat any underlying sepsis, correct nutritional status, inflammation.
Adrenal testing for steroid-dependent patients	<ul style="list-style-type: none"> <li>Random cortisol level</li> <li>DXM suppression testing               <ul style="list-style-type: none"> <li>Low dose</li> <li>High dose</li> </ul> </li> </ul>

Abbreviations: AL, anastomotic leak; CBC, complete blood count; CMB, comprehensive metabolic panel; DXM, dexamethasone; GI, gastrointestinal; HBsAg, hepatitis B surface antigen; Hep C, hepatitis C; IV, intravenous.

**Table 4** Imaging- and endoscopy-directed perioperative optimization for Crohn's disease

Imaging	<ul style="list-style-type: none"> <li>US, CTE, MRI, manometry as indicated</li> <li>Consider using MRI in an elective setting to avoid unnecessary ionizing radiation.</li> <li>Abscesses, phlegmons?—Untreated abscesses are associated with increased postoperative complications.</li> <li>I&amp;D, and appropriate antibiotics based on cultures—usually at least 7–14-d treatment is needed.</li> <li>Fistulae, localized perforation? Ongoing inflammation? Hydronephrosis?</li> <li>Severe ongoing inflammation may lead to obstruction of the ureter, involve urology, and consider stenting.</li> </ul>
Colonoscopy, in-office flexible sigmoidoscopy	<ul style="list-style-type: none"> <li>Evaluate the severity and extent of ileocolonic disease</li> <li>Flex sig/colonoscopy</li> <li>Severity and location of disease</li> <li>CRC screening</li> </ul>

Abbreviations: CRC, colorectal cancer screening; CTE, chronic traumatic encephalopathy; MRI, magnetic resonance imaging; US, ultrasound.

micronutrient intake.<sup>11</sup> Severe nutritional deficiency is defined as BMI <18.5 kg/m<sup>2</sup>, albumin <3.0 g/dL, or >10% weight loss within 6 months.<sup>12</sup> Hypoalbuminemia, and not biologic, were found to be associated with postoperative complications among CD ileocolic resections (ICRs).<sup>13</sup>

Prior to elective surgery, all patients with CD should be screened for malnutrition. Patients with or at risk of malnutrition should undergo detailed nutritional assessment and dietary counseling with a registered dietitian. Preoperative dietary optimization with or without additional oral nutritional supplements is sufficient for most patients. Patients who are unable to meet their own nutritional requirements should receive preoperative nutritional support with enteral or parenteral nutrition. In malnourished patients with CD, preoperative nutritional optimization via enteral nutrition (EN) or parenteral nutrition (PN) has been shown to decrease the likelihood of postoperative complications by 74%.<sup>14</sup> Moreover, receiving early postoperative nutrition via any route was associated with decreased postoperative complications among patients with CD. However, ESPEN recommends the use of EN over PN when possible.<sup>15</sup> Among patients with CD, early nutritional supplementation with EN reduces the risk of postoperative complications.<sup>14</sup> Moreover, in a study from Sweden of patients with severe malnutrition, the rate of postoperative complications was lower in the PN group than in the non-PN group when given for at least 18 days preoperatively.<sup>16</sup>

One form of EN is exclusive enteral nutrition (EEN), in which the patient is limited to a liquid diet with four to six cans of commercially available protein supplements; we specifically recommend products with 20–30 grams of protein, and 450–500 kcal per can. Pragmatically, CD patients with fibrostenotic strictures often cannot tolerate solids, which increases their symptoms, but often tolerate a liquid diet. Preoperative initiation of EEN has been shown to result in a decrease in the rate of infectious complications.<sup>17</sup> This was confirmed in a study reported by Yamamoto et al, who showed that preoperative EEN decreased the risk of septic complications.<sup>18</sup> However, others noted the presence of penetrating CD limited the beneficial effect of preoperative EEN.<sup>19</sup> In lieu of this, ESPEN recommends that if possible, surgery should be postponed for 7 to 14 days after the initiation of EEN in order to convert the patient from a catabolic to anabolic state and thus optimize nutritional status.<sup>15</sup> For patients undergoing emergency surgery with severe protein-calorie malnutrition, many surgeons may choose to either divert the anastomosis or avoid an anastomosis altogether and bring out an end ileostomy with subcutaneous implantation of the colonic stump.<sup>20</sup>

In addition, EEN has been highlighted as an effective treatment that aids in inducing remission among patients with CD, especially within the pediatric population.<sup>21</sup> EEN has been recommended by several guidelines as the first-line treatment for active luminal CD among patients under 17 years of age.<sup>22</sup> The data regarding the effectiveness of EEN among adult CD patients are sparse. A randomized multicenter trial of adult patients with CD demonstrated that EEN induced clinical remission in two-thirds of the study population. However, intolerance and adherence remain the biggest hurdle toward EEN among adult patients with CD.<sup>23</sup>

When patients cannot tolerate EN or EEN, PN may be recommended, typically for a minimum of 2 weeks preoperatively, and is initiated in the hospital and continued as home PN (HPN). Patients and providers need to be aware that PN is not without risks, including thromboembolism and line sepsis related to peripherally inserted central catheters (PICC) or central venous access lines, which rarely may result in infectious endocarditis, vegetations, and septic emboli.<sup>24</sup> In a cohort multicenter study, the rate of central line-associated bloodstream infections with PICC line use was 1.6%, while the rate of deep vein thrombosis (DVT) was 1.5%.<sup>25</sup> In a study including 854 HPN patients, patients with central venous access devices had a higher infection rate than those with PICC lines.<sup>26</sup>

## Sarcopenia and Frailty

Sarcopenia, defined as a reduction in muscle mass and function, was found to be common and present in 52% of patients with CD in a meta-analysis.<sup>27</sup> This leads to the development of a condition known as sarcopenic obesity, as CD patients with sarcopenia tend to be overweight.<sup>28</sup> The significance of sarcopenia lies in its association with an increased risk of suboptimal surgical outcomes.<sup>27</sup> Frailty, defined as age-related loss of physiologic reserve in response to stress and placing patients at increased risk of adverse postoperative outcomes, is coincident with the greying of America, also called the Silver Wave, as the baby boomer generation enters senescence.<sup>29</sup> The incidence of IBD among individuals with older age is progressively increasing.<sup>30</sup> A meta-analysis involving 1.4 million patients showed that frailty was an independent predictor of mortality among patients with IBD.<sup>31</sup> Moreover, frailty was associated with increased risk of all causes and IBD-related hospitalization.<sup>32</sup> As such, it is important to identify patients at risk of frailty preoperatively and implement interventions such as physical therapy, ideally in the setting of a prehabilitation program, in order to prevent the progression of frailty.<sup>33</sup>

Recently, the concept of formal prehabilitation programs to improve postoperative outcomes in frail patients has been highlighted, and the PREHAB randomized trial, and other studies, have shown promising results.<sup>6,7,34</sup>

## Anemia

Anemia is another relatively common modifiable risk factor in patients with CD and may be related to nutritional deficiencies and blood loss from CD-related bleeding from ulcerations. A systematic review by Wilson et al showed the prevalence of anemia among patients with CD ranged from 10.2 to 72.7%.<sup>35</sup> Age is thought to be associated with an increased risk of anemia in IBD.<sup>36</sup> According to ECCO Guidelines, anemia in IBD is classified into either iron deficiency anemia (IDA), anemia of chronic disease, or B12/folate deficiency-associated anemia all of which are typically microcytic anemias.<sup>37</sup> According to the World Health Organization (WHO), anemia is defined as hemoglobin <12 g/dL for women and <13 g/dL for men, with severe anemia being

defined as hemoglobin <10 g/dL.<sup>37</sup> IBD patients with anemia are at higher risk of emergency surgery and the development of preoperative sepsis.<sup>38</sup> Furthermore, among patients with CD who underwent ICR, anemia was associated with a higher risk of septic complications.<sup>4</sup>

Anemia work-up includes a complete blood count with reticulocyte count, and serum levels of folate, vitamin B12, ferritin, zinc, copper, total iron binding capacity, and C-reactive protein, and correction of deficiencies with preoperative oral supplements is recommended. For anemic patients with normal iron stores and vitamin levels, and macrocytic anemia despite repletion, a referral to Hematology is considered. In terms of medical treatment of anemia, ECCO recommends oral iron supplementation among patients with mild IDA and intravenous iron in severe IDA anemia or in cases of intolerance to oral supplements.<sup>37</sup> Moreover, IBD patients who are treated for IDA should be monitored every 3 months in the first year and then every 6 to 12 months afterward. Patients receiving oral iron are recommended to concomitantly take ascorbic acid to increase iron absorption by maintaining it in the ferrous, as opposed to ferric, cationic state.

In patients needing surgery, the clinical utility of oral iron supplementation for CD patients with IDA undergoing surgery is limited by GI-related side effects (constipation, GI upset, and black stools), poor absorption, slow speed of replacing iron stores, and the need to correct anemia in the often-short preoperative period; thus, we favor the liberal use of preoperative intravenous iron supplementation whenever possible, especially since multiple less costly forms are now widely available and its use is supported by level 1 data.<sup>39</sup> We also favor aggressive IV iron repletion postoperatively in all patients with CD with moderate-to-severe anemia.<sup>40</sup> Finally, patients with CD undergoing >30 cm resections of the terminal ileum are at risk of B12 malabsorption.<sup>41</sup>

## Smoking

Smoking is a known risk factor for postoperative complications and is associated with exacerbation of Crohn's disease activity. According to a recent meta-analysis by the U.S. Surgeon General, patients with CD were more likely to smoke than controls, while a study conducted in the United Kingdom showed that IBD patients portray smoking behavior similar to that of the general population.<sup>42,43</sup> Smoking is also associated with a more severe CD phenotype.<sup>44</sup> Moreover, smoking is known to increase the risk of postoperative complications among patients with CD.<sup>45</sup> A meta-analysis by To et al included 33 cohort studies and showed that smokers had up to an 85% increase in Crohn's severe phenotype of CD. Furthermore, smokers showed a twofold increase in clinical recurrence after surgery.<sup>46</sup>

Smoking and nicotine cessation for at least four weeks prior to surgery is recommended to decrease the postoperative risk of pulmonary and impaired wound healing-related complications. Individual cognitive behavioral therapy or pharmacological therapy (with bupropion, which decreases cravings) may aid smoking cessation and improve outcomes.

Delaying elective surgery for 4 to 6 weeks after smoking/nicotine cessation has been associated with improved outcomes but is often impractical in the CD population.<sup>45</sup>

## Stoma Site Marking

The importance of preoperative stoma site marking and education cannot be overemphasized in the preoperative optimization of patients with CD undergoing surgery and improves outcomes.<sup>47</sup> Engaging patients by having them meet with a stoma nurse and answering their questions is critical to demystifying the whole process of having a stoma and setting expectations, as patient fear of a stoma is often the fear of the unknown and knowledge is empowering. In the age of social media and other web-based support groups, patients are less likely to feel isolated during this often emotionally and physically difficult time of their disease course and lives.

Among patients with CD, the stoma rate can be as high as 35%.<sup>48</sup> A study conducted in Sweden, patients with CD showed that the 5-year cumulative incidence of stomas of 2.5%.<sup>49</sup> Temporary or permanent stomas are associated with complications such as parastomal hernias, dehydration and acute kidney injury secondary to high stoma output, and hospitalization due to bowel obstruction.<sup>50</sup> A systematic review by Malik et al showed that the incidence of stoma-related complications is as high as 81%.<sup>51</sup> Therefore, it is important to counsel patients with CD on the potential need for a stoma and its effect on their quality of life (QoL), as in many cases stomas in IBD may be restorative for QoL. A German study showed that individuals with stomas had lower QoL than healthy individuals; however, ostomates with CD had better QoL than ostomates with other diagnoses.<sup>52</sup> Preoperative stoma site marking, with good placement where the patient can see it, while avoiding creases and scars, is easier if the site is selected while the patient is awake and engaged. A meta-analysis performed showed that preoperative stoma marking can also decrease the risk of stoma-related complications.<sup>53</sup>

## Medication Management

By the time of surgery, the vast majority of CD patients will have received medical treatment with agents including immunomodulators, tumor necrosis factors inhibitors (TNFi), other biologics, small molecules, and corticosteroids.<sup>54</sup> As such, understanding the effect of such medications on surgical outcomes is of utmost importance.

## Systemic Corticosteroids

Preoperative use of systemic corticosteroids is widely known to be associated with an increased risk of postoperative complications.<sup>10</sup> Moreover, several studies have highlighted the increased risk of postoperative complications, especially infectious complications, among IBD patients on steroids.<sup>55</sup> Recommendations are therefore to use steroid therapy for the shortest period and the lowest dose possible.<sup>56</sup> Moreover,

**Table 5** Steroid-taper regimens

Rapid prednisone tapers for approximately 40 mg prednisone or IV equivalent for an approximately 1 wk			
<2 wk use: discontinue, no taper	2 to 4-wk use: faster q3 d taper		4 to 6-wk use: slower q3 d taper
Off	10 mg PO q24 × 3 d		15 mg PO q24 × 3 d
–	5 mg PO q24 × 3 d		10 mg PO q24 × 3 d
–	Off		5 mg PO q24 × 3 d
–	–		Off
Slower steroid tapers prednisone 20–40 mg, >4–6 wk			
Slow taper from 20 mg over 4 wk	Slow taper from 20 mg over 7 wk	Slow taper from 40 mg over 4 wk	Slow taper from 40 mg with over 7 wk
20 mg PO q24 × 7 d	20 mg PO q24 × 7 d	30 mg PO q24 × 7 d	30 mg PO q24 × 7 d
15 mg PO q24 × 7 d	15 mg PO q24 × 7 d	20 mg PO q24 × 7 d	20 mg PO q24 × 7 d
10 mg PO q24 × 7 d	10 mg PO q24 × 7 d	10 mg PO q24 × 7 d	10 mg PO q24 × 7 d
5 mg PO q24 × 7 d	5 mg PO q24 × 14 d	5 mg PO q24 × 7	5 mg PO q24 × 14 d
Off	2.5 mg PO q24 × 14 d	Off	2.5 mg PO q24 × 14 d
	Off		Off

Abbreviation: IV, intravenous; PO, per orum.

studies have shown a higher risk of complications with higher steroid doses (>40 mg).<sup>54</sup> According to the ECCO, an equivalent of 20 mg of prednisolone daily is considered a risk factor for surgical complications.<sup>10,17</sup> This is based on multiple meta-analyses.<sup>57,58</sup> Thus, steroids should be tapered (► **Table 5**) in the preoperative period to as low a dose as possible, and ideally discontinued altogether, at least one week prior to surgery.<sup>59,60</sup> If patients cannot be weaned off steroids, then higher doses of steroids should be avoided. Patients are counseled regarding fatigue and lethargy as steroids are withdrawn. If steroids cannot be weaned, many surgeons may choose to either divert the anastomosis or avoid anastomosis altogether and perform an end ileostomy. Data support the use of postoperative vitamin A (retinoic acid) supplementation (25,000 IU daily for 1 week only due to the risk of transaminitis and toxicity) in patients on or currently receiving corticosteroids.<sup>61,62</sup>

Patients who have recently been receiving systemic corticosteroids often receive stress-dose steroids at the time of anesthesia induction because of concerns about perioperative adrenal crisis. However, this traditional practice has been questioned recently. A randomized control trial performed by Zaghiyan et al showed that there was no difference in postural hypotension or adrenal insufficiency between low- and high-dose stress dose corticosteroids among IBD patients undergoing major colorectal surgery.<sup>63</sup> Moreover, a systematic review published by Khazen and El-Hussuna showed that there was no evidence to support preoperative stress dose steroids among patients who are on chronic steroids.<sup>64</sup> This is in concordance with another systematic review which concluded that preoperative stress dose steroids are not necessary for patients who are receiving their usual daily dose.<sup>65</sup>

For patients with CD who have recently been treated with steroids, surgeons should be vigilant for the possibility of acute adrenal insufficiency. Addisonian crisis typically man-

ifests with protean symptoms, including fever, abdominal and muscular pain, anorexia, nausea/vomiting, altered mentation, hypoglycemia, hyperkalemia, and hypotension refractory to intravenous fluid challenges. Treatment consists of prompt recognition, dexamethasone suppression, or cosyntropin testing if the clinical situation allowed, and administration of parenteral corticosteroids, such as 4 mg of dexamethasone or 100 mg of hydrocortisone, and consideration of endocrinology consultation and adrenocorticotropic hormone stimulation testing.

## Immunomodulators

Immunomodulators (IMMs), including the 6-thioguanine drugs azathioprine and 6-MP and methotrexate, suppress inflammation via T cell-mediated pathways. It has been speculated that this may impair collagen synthesis and subsequently increase the risk of anastomotic dehiscence.<sup>14</sup> However, several meta-analyses have shown that immunomodulators do not increase the risk of perioperative complications and can be safely continued in the perioperative period.<sup>58–60</sup> A single-center study done showed that the perioperative use of methotrexate among patients with CD was not associated with an increased risk of postoperative complications.<sup>66</sup>

The role of IMMs is mainly adjunctive to decrease immunogenicity at the time of initiation of new biologic therapy. Thus, we recommend discontinuing them at the time of surgery and resuming them according to gastroenterologist discretion.

## Biologics

The perioperative safety of biologics in the perioperative period remains controversial. A study by Morar et al showed that biologic therapy was an independent risk factor for the

development of intraabdominal septic complications (IASC) among CD patients.<sup>67</sup> Another study showed that TNFi therapy was associated with unfavorable outcomes such as overall postoperative complications.<sup>55</sup> Appau et al highlighted the association between receiving TNFi within 3 months of ICR and increased septic postoperative complications.<sup>68,69</sup>

However, the recent "PUCCINI" study, which is the largest and most well-performed prospective study on the topic to date, demonstrated that the preoperative use of TNFi was not associated with an increased risk of postoperative infectious complications after surgery for IBD.<sup>70,71</sup> This is supported by several studies that have shown that the preoperative use of TNFi among CD patients did not lead to an increased risk of complications.<sup>71</sup>

Therefore, we do not recommend discontinuation of biologics preoperatively. Patients with CD may continue the biologic postoperatively, and holding doses for a prolonged period perioperatively places the patient at risk for the development of antidrug antibodies and loss of response to that medication. However, practically speaking, operating at nadir to avoid "wasting" the last dose and resuming or initiating therapy with new biologic 2 to 4 weeks postoperatively.

## Small Molecules

Recently, upadacitinib, a new selective JAK-Stat-1 inhibitor was approved for use in patients with CD. A recent randomized controlled trials highlighted the superiority of upadacitinib induction and maintenance over placebo in the management of moderate-to-severe CD.<sup>72</sup> A multicenter phase II trial showed the efficacy of filgotinib, also a JAK1 inhibitor, in inducing remission in patients with moderate-to-severe CD.<sup>73</sup> However, to date, no data exist regarding the effect of selective JAK inhibitors on surgical outcomes in CD patients. Given their short plasma half-life, and potential association with increased VTE risk, it is generally recommended that JAK1 inhibitors be discontinued 3 days preoperatively.

## Timing of Surgery

Postoperative complications after colorectal surgery are common and occur in up to 37% of patients with CD.<sup>69</sup> The rate of IASC after ICR was 9.7% in one study.<sup>67</sup> As such, choosing the ideal timing for surgery is an important factor in mitigating complications, and emerging data increasingly supports early surgery for terminal ileal CD. Early surgery before extensive bowel damage with fibrostenotic and penetrating complications is intuitive.

A study by An et al showed that ICR within 6 months of diagnosis correlated with better prognosis.<sup>74</sup> CD patients with stenotic or fibrotic disease may be offered surgery as the first-line treatment to avoid delays.<sup>75</sup> Surgery is also recommended among patients with ileocecal CD who have failed or relapsed after standard medical therapy.<sup>76</sup> In addition, the "LIR!C" trial highlighted laparoscopic ICR as a first-line treatment option for terminal ileitis among patients with CD.<sup>77,78</sup> Moreover, de Groof et al reported the cost-effectiveness of laparoscopic ICR compared to infliximab.<sup>79</sup>

## Proximal Diversion

In a large National Surgery Quality Improvement Program study, Neary et al developed a risk calculator for an anastomotic leak in patients with CD undergoing ICR. The study showed that diverting loop ileostomy decreased the rate of anastomotic leakage.<sup>80</sup> Furthermore, the presence of three or more risk factors was associated with an increased risk of anastomotic leakage. The authors recommend performing a diverting loop ileostomy in these patients. The study found that smoking, chronic steroid use, emergency surgery, prolonged operative time, wound class III and IV, weight loss, inpatient status, and lack of ileostomy were associated with an increased risk of anastomotic leak.

## Intraabdominal Abscesses

Delayed resection is recommended for patients with penetrating CD and subsequent intra-abdominal abscesses because it enables patient optimization. This leads to a decrease in postoperative IASC rates and stoma rates.<sup>81</sup> Moreover, the presence of intra-abdominal abscesses is associated with an increased risk of anastomotic complications.<sup>5,82</sup> In addition, the presence of a phlegmon or an abscess reduces the likelihood of a minimally invasive approach to surgery.<sup>83</sup>

Therefore, it is imperative to control abscesses and phlegmons prior to any surgical intervention. This can be achieved via broad-spectrum antibiotics and percutaneous drainage (PD) catheter placement. It is recommended that abscesses >3 cm have PD. PD can serve as a cost-effective bridge to surgery and was shown to reduce complication rates and length of stay. However, there are no clear guidelines regarding the duration of antibiotic therapy or PDs prior to surgical intervention. One important point is not to discontinue PDs preoperatively, a practice which is associated with abscess recurrence and the increased use of diverting loop ileostomies.

## Venous Thromboembolism Prophylaxis

The risk of venous thromboembolism (VTE) is twofold higher among individuals with IBD. This is attributed to the systemic inflammatory state associated with IBD.<sup>84,85</sup> The risk of VTE was 74% greater among IBD patients compared to non-IBD patients.<sup>86</sup> The rate of VTE and pulmonary embolism (PE) at quaternary IBD referral centers was found to be 4.3 and 2.4%, respectively, with the majority of events occurring postdischarge.<sup>87</sup> This was confirmed by the study by Chu et al that highlighted the increased risk of VTE for IBD patients after leaving the hospital.<sup>86</sup>

A study involving 81,900 IBD patients showed that non-surgical IBD patients were more likely to develop VTE after discharge.<sup>87</sup> However, among surgical IBD patients, only ulcerative colitis (UC) patients had elevated risk, whereas CD patients did not.<sup>88</sup> This is speculated to be related to the increased inflammatory burden among UC patients compared to CD.<sup>89</sup> Furthermore, another study by McCurdy et al noted that surgery actually reduced the risk of VTE among

patients with CD.<sup>90</sup> Moreover, in the series by Lightner et al, surgical intervention alone was not a significant risk factor for the 90-day development of DVT or PE.<sup>87</sup> On the other hand, a study done in the United Kingdom showed that the rate of VTE was higher among surgical patients.<sup>88</sup>

Another risk factor that increase the risk of VTE among IBD patients was admission to medical service which was associated with higher rates of VTE.<sup>87</sup> Obesity and advanced age were also associated with a higher risk of DVT/PE. Another study found an association between increased risk of VTE and pancolitis.<sup>89</sup> Interestingly, PSC was found to be a risk factor for the development of DVT.<sup>85</sup> In addition, ESPEN recommends avoiding dehydration to minimize the risk of VTE.<sup>13</sup> The risk of VTE is further increased in individuals with active disease.<sup>89</sup> Steroids are thought to increase the risk of VTE.<sup>91</sup> It is suggested that glucocorticoid-induced alterations in fibrinolysis may lead to a hypercoagulable state. Steroids are also thought to increase the levels of plasminogen activator inhibitor 1 and clotting factors.<sup>92</sup>

Currently, thromboprophylaxis with low-molecular-weight heparin (LMWH), unfractionated heparin, or fondaparinux is recommended for all hospitalized IBD patients unless contraindicated.<sup>93</sup> However, in one study, inpatient prophylactic LMWH was not effective for the prevention of postoperative DVT among CD patients.<sup>94</sup> Postdischarge VTE prophylaxis in IBD patients has been suggested in several studies, however the evidence supporting that remains scant.<sup>60,87,95,96</sup> Although not found to be cost-effective, the study by Lee et al showed that 4 weeks of postdischarge VTE prophylaxis resulted in an improvement in quality-adjusted life years.<sup>97</sup> Presently, there are no standardized guidelines for extended or postdischarge VTE prophylaxis among IBD patients but the American Society of Colon and Rectal Surgeons made a conditional recommendation for the consideration of extended prophylaxis after surgery for IBD.<sup>98,99</sup> Schlick et al developed a postdischarge VTE risk calculator for IBD surgery patients to help tailor extended VTE prophylaxis in this patient population.<sup>100</sup> Finally, a new study examined the role of rivaroxaban for VTE prophylaxis and was able to reduce their VTE rate from over 4 to 0.5% without an apparent increase in major bleeding.<sup>101</sup>

## Conclusion

In conclusion, the increased incidence of CD has rendered surgery an important component of CD management. Therefore, preoperative optimization has become a cornerstone for the surgical management of patients with CD. There is an increased risk of complications associated with malnutrition, steroid use, and intraabdominal infection. Electing the ideal surgery time helps mitigate these risk factors. Understanding the elevated risk of venous thromboembolism among patients with CD and tailoring prophylaxis is essential.

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