



Special Section on Contemporary Practice in Colon and Rectal Surgery by Dr. Matthew Wilson

Modern surgery for Crohn's disease: When to divert, impact of biologics on infectious complications, and surgical techniques to decrease post-operative recurrence of Crohn's disease

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ABSTRACT

Crohn's disease is a complex condition that confers a significant risk of requiring multiple surgeries. Questions that surgeons must frequently answer include: which patients benefit from diversion? Does monoclonal antibody therapy increase post-operative complications? And, are there surgical techniques that can prevent the recurrence of Crohn's disease? This review examines current data to answer these questions.

Introduction

Crohn's disease (CD) is an idiopathic, inflammatory bowel disease in which the immune system attacks the gastrointestinal tract – anywhere from the mouth to the anus, with an especial penchant for the ileocolic junction. Its cause is a multifactorial, complex interplay of an individual's genetics and environmental exposures which haven't been completely and clearly elucidated. Inflammatory bowel disease (including ulcerative colitis), according to the best estimates affects 2.4–3.1 million (0.7–1.3 %) individuals in the United States [1,2]. CD is frequently subclassified by phenotype: inflammatory, fibrostenotic, or penetrating. Notably, these phenotypes are not mutually exclusive and patients may cross between phenotypes over time.

Despite best medical therapy, which is typically considered to be monoclonal antibodies (“biologics”), nearly 50 % of patients with CD will require surgery within 10 years of diagnosis [3,4]. Of patients who have undergone surgery, endoscopic recurrence occurs in 70–90 % at 1 year and 35 % will require an additional resection within 10 years [3,5]. The surgical burden is heavy and requires a thoughtful, comprehensive, multidisciplinary approach. Questions that surgeons must frequently consider in the perioperative period include: which patients benefit from diversion? What is the impact of monoclonal antibody therapy on postoperative complications? And, are there anastomotic techniques that decrease the incidence of recurrent CD? This review will attempt to answer these questions.

Which patients benefit from diversion?

The question posed – “Which patients benefit from diversion?” – is asked in the context of those patients undergoing elective or urgent intestinal resection. Diversion can be employed instead of, or antegrade to an anastomosis, to prevent “intra-abdominal septic complications” (IASC): abscesses, anastomotic leaks, and enterocutaneous fistulas. While diversion can understandably be distressing and demoralizing to patients facing this scenario, it can be lifesaving, especially considering the devastating effects of an anastomotic leak. Given the wide variability of patients and risk factors, the incidence of anastomotic leak is variable: 1–30 % [6]. Risk factors for IASC in patients with CD undergoing intestinal resection with an anastomosis were studied in a recent meta-analysis of 15 studies (813 screened) which included 3807 patients, 4189 operations, and IASC rate of 9.2 %. This study identified four risk factors: hypoalbuminemia (OR 1.93; 95 % CI 1.36–2.75), preoperative abscess (OR 1.94; 95 % CI 1.26–3.00), prior abdominal surgery (OR 1.50; 95 % CI 1.15–1.97), and steroid use (OR 1.99; 95 % CI 1.54–2.57) [7]. Surgeons, when time and circumstances permit, should attempt to modify these risk factors prior to operating.

Hypoalbuminemia

Hypoalbuminemia, in patients with CD, may be due to poor nutritional status, decreased nutritional reserve, inflammation, and/or sepsis

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[8,9]. It is frequently identified as a risk factor for post-operative complications [10]. An astounding number of patients with CD have been reported to be malnourished: 20–85 % [11]. Strategies to ameliorate hypoalbuminemia may include consultation with a nutritionist for consideration of oral, enteral or parenteral supplementation. Patients unable to tolerate oral or enteral nutrition should be started on parenteral nutrition given its salutary benefits [12,13].

Preoperative abscess

Patients with penetrating CD are prone to developing abscesses which typically occur in the setting of a concomitant stricture, inflammation, and fistula. The presence of an abscess has been noted in several reports to be a risk factor for anastomotic leak [7,8,14]. Abscesses occur in 7–28 % of patients with CD [15,16]. It has been demonstrated that abscesses <3 cm can be treated with antibiotics and may not need percutaneous drainage [3,17,18]. Simultaneous stricture and inflammation may impede success with an antibiotic-alone approach. When percutaneous drainage, without surgery, is employed, 23–78 % of patients may avoid surgery however the risk of recurrent abscess is significant (OR, 2.16; 95 % CI 1.03–4.54; $p = 0.04$) [3,19,20].

A strategy to successfully treat patients with CD presenting with abscess has been reported: percutaneous drainage with 5–7 days of parenteral nutrition, IV antibiotics, and short-term, high-dose IV steroids. Patients treated with this approach underwent same-hospitalization resection. In their report, Poritz and Koltun found that 18/19 patients underwent primary resection and anastomosis with only two patients requiring upstream diversion. With a mean follow-up of 32 months, only 1 patient developed a recurrent abscess which occurred 4 weeks after operation [15].

Prior abdominal surgery

Huang et al. reported in their meta-analysis of 9 studies ($n = 2737$), that the odds ratio of IASCs was 1.5 (95 % CI 1.15–1.97) in patients who had undergone prior intestinal resection [7]. Unfortunately, 35 % of patients who have undergone intestinal resection for CD will require a repeat resection within 10 years [35]. In these patients, this is a non-modifiable risk factor for which surgeons must account. Surgeons should appropriately counsel patients that an ostomy is more likely to be needed to prevent IASC.

Steroid use

Despite having many untoward side effects, steroids are a mainstay of treatment of acute inflammation in patients with CD. In many situations, patients have been on extended or multiple courses of steroids to stave off surgery or to control inflammation. In Huang et al.'s meta-analysis, 13 studies ($n = 3502$) were found to have examined steroid use. Steroid use was associated with IASC with an odds ratio of 1.99 (95 % CI 1.54–2.57) [7]. Additionally, a prospective study of 209 patients reported that steroid use in the four weeks before surgery was associated with postoperative complications (OR 2.69; 95 % CI 1.15–6.29) [21]. While any amount of steroid use has been associated with infectious complications there does appear to be a dose-response with patients receiving >40 mg of prednisone or its equivalent having the highest incidence of complications with a relative risk of 6.48 (2.47–16.97) [22]. Surgeons operating on patients with CD who have been administered steroids should take the duration and dose into account, along with the other risk factors previously enumerated when deciding on diversion of patients undergoing intestinal resection in CD. One of my mentors frequently says, "I'd rather temporarily deal with a high output, proximal ostomy than an anastomotic catastrophe."

What is the impact of monoclonal antibody therapy on postoperative complications?

There have been multiple conflicting reports on the influence of monoclonal antibody therapy on postoperative complications in patients with CD. Nearly all of this data has been clouded by being retrospective and heterogeneous. Current antibody therapies (biologics) are directed against three targets: tumor necrosis factor (TNF) (i.e. infliximab and adalimumab), interleukins (i.e. ustekinumab), and integrins (i.e. vedolizumab). Data for the anti-TNF agents is most robust and mature given that infliximab was approved for the treatment of CD in 1998. Recent, prospective data seems to indicate that biologics are not associated with postoperative complications. A meta-analysis of 6 studies ($n = 1833$) found that biologics were not associated with IASCs (OR 1.29; 0.79–2.11) [7].

Anti-TNF (infliximab and adalimumab)

A Cochrane review from 2020 found that preoperative anti-TNF therapy increased the incidence of postoperative infectious complications (OR 1.27; 1.07–1.47) but was based on "very low certainty evidence" [23]. Also, the GETAID Chirurgie cohort indicates an increased incidence of complications with the use of anti-TNF therapy within 3 months preceding surgery. This study did not measure serum anti-TNF levels [24].

However, prospective data with anti-TNF agents substantiates that anti-TNF agents are not associated with IASC. In 2017 Fumery et al. reported that exposure to anti-TNF agents within the 4 weeks before surgery was not associated with postoperative complications. The authors substantiated this finding with serum anti-TNF levels, finding that they also were not associated with postoperative complications [21].

In 2022 the PUCINI study, a prospective, multicenter, observational study, examined the incidence of postoperative infectious complications in patients undergoing intra-abdominal surgery who had been exposed (<12 weeks) to anti-TNF agents. Enrollment included 947 patients, 382 of whom received anti-TNF agents. Exposure to anti-TNF agents was not associated with any postoperative infection or surgical site infection. Notably, detectable serum anti-TNF agents were also not associated with infection [25].

Anti-interleukin (ustekinumab)

In a recent Cochrane review, only one study evaluating ustekinumab's association with postoperative infectious complications met inclusion criteria, subsequently a meta-analysis could not be done [23,26]. This study by Liang et al., an observational, cohort study of >3000 individuals, demonstrated no difference in infectious complications (OR 0.80; 95 % CI 0.10–6.51) when comparing postoperative outcomes of 8 patients who received ustekinumab and 3352 patients who did not. In a meta-analysis by Garg et al. that analyzed 5 studies, there was no difference in rates of intra-abdominal sepsis in patients undergoing abdominal operations in patients receiving ustekinumab versus an anti-TNF agent (7.2 % vs 11.9, $p = 0.4$) [27].

Anti-integrin (vedolizumab)

In patients with IBD, Law et al., in their Cochrane review, combined data from nine studies and found with "very low certainty" no difference in postoperative infectious complications (OR 1.1; 95 % CI 0.76–1.62). A sub-analysis of the four studies that examined only patients with CD also found no association with complications (OR 1.32; 0.51–4.42) [23]. Other meta-analyses have reported similar findings: no difference in infectious complications [28,29].

In summary, the recommendation found in the American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the Management of Crohn's Disease is apropos: "Whether or not preoperative

exposure to monoclonal antibody therapy influences outcomes remains controversial, but delaying surgical intervention based on monoclonal antibody therapy alone is not typically recommended.” [3] In most instances, the benefit of operation outweighs the risk of delay. The benefit of “washing out” the monoclonal antibody by waiting is likely minimal.

Are there anastomotic techniques that decrease the incidence of recurrent Crohn's disease?

The influence of the type of anastomosis on the recurrence of CD after resection has long been debated given the unfortunate need for repeat surgery in many patients with CD. In 2009 the results of an international, multi-center, randomized, controlled trial of 170 patients with CD undergoing ileocolic resection, comparing stapled, side-to-side versus hand-sewn, end-to-end anastomoses was published. Endoscopic and symptomatic recurrence were similar in both groups (37.9 % vs 42.5 %, $p = 0.55$ and 22.7 % vs 21.9 %, $p = 0.92$ respectively) [30]. Additionally, a Cochrane review did not identify a difference in outcomes between hand-sewn and stapled anastomoses in patients with CD [31]. However, in the past decade, two intriguing studies have been published that have drawn attention to the possibility that certain surgical techniques can prevent the recurrence of CD at the anastomosis [32,33].

Kono-S anastomosis

The first study of this technique reported the initial results of the Kono-S anastomosis (KSA). For a detailed description of the construction of this anastomosis, readers are directed to this manuscript. Briefly, the key concepts of the KSA, are sparing of the mesentery, construction of the supporting column, and a generous side-to-side, handsewn anastomosis. Kono et al. reported that with this technique, despite endoscopic recurrence being similar, the intensity, as measured by the Rutgeert score, was decreased. Most notable though was the finding that only 3 % (2/69) of patients with a KSA required repeat surgery versus 26 % (19/73) in the control group ($p = 0.0007$). Median follow-up was 42 months for the KSA group and 52 months for the control group ($p > 0.05$). Additionally, they noted no differences in complications between the two groups [33].

Other studies have substantiated this finding. An uncontrolled, international study of 187 patients (Japan 144, USA 43), many of whom were patients in the original KSA report, with a median follow-up of 65 months, continued to report only two surgical recurrences [34]. In 2019 Shimada et al. compared 117 consecutive KSA to a historical control group of 98 handsewn end-to-end anastomoses. Median follow-up was 38 and 89 months respectively ($p < 0.001$). Endoscopic recurrence rates were not reported, but surgical recurrence was found to be significantly higher in the control group (3.4 % vs 24.5 %, $p < 0.001$). The anastomotic leak rates were also disparate: 5.1 vs 17.4, $p = 0.007$ [35].

In 2020 the results of the SuPREMe-CD study were reported. This was the first randomized, controlled trial to compare the KSA with a side-to-side stapled anastomosis. There were 79 patients randomized: 36 KSA and 43 stapled. At 18 months, endoscopic recurrence was noted in 25 % of patients with a KSA and 67.4 % with a stapled anastomosis ($p < 0.001$). Median Rutgeert scores were 1.05 and 2.3 respectively ($p < 0.001$). At 24 months, clinical recurrence occurred in 18 % and 30.2 % respectively ($p = 0.04$). Surgical recurrence between the two groups at 24 months was similar: none in the KSA group and 2 in the conventional group ($p = 0.3$) [36].

While not conclusive, these data are compelling and provocative. They seem to indicate that a KSA decreases the intensity of recurrence and can prevent or delay the need of future operations. Further studies are needed to bring additional context and to determine which patients benefit in the era of modern medical management of CD. Surgeons treating patients with CD should consider constructing a KSA when performing a resection for symptomatic CD.

Extended mesenteric excision

The second study reporting a possible influence of surgical techniques on CD recurrence theorized that the mesentery was the driver of inflammation in CD and performing an extended mesenteric excision (EME), similar to an oncologic resection, would lead to decreased surgical recurrence. Coffey et al. prospectively studied 34 patients with CD undergoing ileocolic resection, after 2010, utilizing an EME, and matched them with 30 historical, control patients with CD that underwent ileocolic resection before 2010. The mean duration of follow-up was 51.7 and 69.9 months, respectively. The cumulative reoperation rate was 2.9 % (1/34) in patients undergoing EME and 40 % (12/30) in the control group ($p = 0.003$) [32].

While this theory and these data are intriguing, they require more study and analysis to determine if this effect is sustained and attributable to the EME. Notably, the authors did not include in their manuscript, any description of the type of anastomosis in either cohort. Additionally, they did not report on endoscopic recurrence. Some have theorized that combining a KSA with EME could be beneficial. Holubar et al. published their preliminary report in 2022 of 22 patients in whom they performed an EME and KSA, finding that it was “highly feasible and safe.” [37] Data on recurrence are forthcoming. Additionally, the Mesenteric Excision and Kono-S Anastomosis Trial (MEERKAT), a UK trial, proposes to randomize patients into one of four groups: close mesenteric excision and KSA, EME and KSA, close mesenteric excision and “standard” anastomosis, or EME and “standard” anastomosis. The study opened in September 2021 and to date has enrolled 110 patients at 21 study sites. The target sample size is 308 patients with an anticipated end date of April 2026 [38,39].

Conclusion

CD is a complex condition that requires multidisciplinary care. Surgeons are core providers of this care as patients frequently require operations to relieve obstruction and treat abscesses and fistulas. Patients presenting with any of the following issues at the time of intestinal resection should be considered for diversion due to the risk of anastomotic leak and IASC: hypoalbuminemia, abscess, prior intestinal resection, and steroid use. Anti-TNF, anti-interleukin, and anti-integrin monoclonal antibody therapy do not appear to be associated with an increased risk of postoperative infectious complications.

In the future KSA, EME, or a combination of the two may become the standard for anastomotic construction but at this time the data is sparse and these techniques have not been incorporated into guidelines. Surgeons treating patients for CD eagerly await the results of upcoming trials which aim to elucidate the role of these techniques. If future data also show that the incidence of recurrent CD is reduced with these techniques, surgeons will no longer be on the sidelines, waiting to “fix problems.” Instead, they will begin to play a larger role in preventing future surgeries, reducing the surgical burden of CD.

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Declaration of competing interest

I have no declarations of interest.

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