Perioperative and Postoperative Management of Patients With Crohn's Disease and Ulcerative Colitis

Edward L. Barnes,[*,‡,§] Amy L. Lightner,[‖] and Miguel Regueiro[¶,#]

[*]Division of Gastroenterology and Hepatology, [‡]Multidisciplinary Center for Inflammatory Bowel Diseases, [§]Center for Gastrointestinal Biology and Disease, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; [‖]Department of Colorectal Surgery, [¶]Department of Gastroenterology, Hepatology, and Nutrition, The Pier C. and Renee A. Borra Family Endowed Chair in Gastroenterology and Hepatology, [#]Digestive Disease and Surgery Institute, Lerner College of Medicine, Cleveland Clinic, Cleveland, Ohio

Although the number of available therapies for the treatment of ulcerative colitis and Crohn's disease (CD) continues to expand, a significant portion of patients with inflammatory bowel disease will require surgical intervention. Surgery remains an integral part of the treatment algorithm for patients with ulcerative colitis and CD, and thus multidisciplinary approaches to the perioperative and postoperative management of patients with inflammatory bowel disease are critical to improving outcomes during these periods. New mechanisms of biologic therapies are emerging and new treatment strategies focused on earlier and potentially more aggressive use of immunosuppressive therapies are advocated in the current treatment era. In this review, we outline multidisciplinary strategies for the preoperative management of immunosuppressive therapies, including a discussion of the most recent evidence regarding the safety of biologic therapy in the preoperative period. We also discuss the postoperative medical management of patients undergoing intestinal resection for CD, with a particular focus on risk stratification and appropriate therapy selection in the immediate postoperative setting. Finally, we review potential postoperative complications after restorative proctocolectomy with ileal pouch–anal anastomosis and their management.

Keywords: Perioperative Therapy; Postoperative Crohn's Disease; Biologics; Pouchitis; Ileal Pouch–Anal Anastomosis.

Despite the emergence of novel strategies for the management of patients with inflammatory bowel disease (IBD), it is well recognized that a significant proportion of patients with Crohn's disease (CD) and ulcerative colitis (UC) ultimately will require surgical intervention. Surgery should not be viewed as a failure of medical therapy; rather surgery should be considered an integral part of the multidisciplinary treatment algorithm of IBD. As such, optimal care pathways bring gastroenterologists and surgeons together to provide best treatment practices in the perioperative phase, surgical phase, and postoperative phase.

The lifetime risk for intestinal resection among patients with CD is 50% to 80%.[1] Unlike the reported decrease in colectomy rates for UC since the advent of biologic therapy,[2] recent analyses have indicated that rates of intestinal resection in CD have not decreased significantly.[3] Therefore, whether biologics appreciably change the natural course of disease among patients with UC or CD remains controversial. Regardless, because biologics increasingly are being used, greater proportions of patients are exposed to immunosuppression at the time of surgery, mandating an improved understanding of the perioperative management of immunosuppressive therapies to maximize postoperative outcomes. We herein outline multidisciplinary strategies for the preoperative management of immunosuppressive therapies, postoperative medical management of patients undergoing intestinal resection for CD, and postoperative complications after restorative proctocolectomy with ileal pouch–anal anastomosis (IPAA).

Managing the Perioperative Patient

Perioperative Pharmacotherapy

Immunomodulators. Immunomodulators (mercaptopurine, methotrexate, azathioprine) are used as a glucocorticoid-sparing agent for the maintenance of remission or in conjunction with biologic therapy to decrease secondary loss of response resulting from antibody formation. Fortunately, evidence from both large retrospective reviews and systematic reviews has suggested that the perioperative use of immunomodulators does not increase adverse postoperative outcomes.[4,5] Given that the elimination half-life of mercaptopurine and azathioprine is approximately an hour, patients can be counseled to hold immunomodulators on the day of surgery and resume them on postoperative day 1.

Abbreviations used in this paper: **anti-TNF, anti-tumor necrosis factor α; CADP, chronic antibiotic-dependent pouchitis; CD, Crohn's disease; CLD, Crohn's-like disease; IBD, inflammatory bowel disease; IPAA, ileal pouch–anal anastomosis; N-RPFD, non–relaxing pelvic floor dysfunction; UC, ulcerative colitis.**

Most current article

1542-3565/$36.00
https://doi.org/10.1016/j.cgh.2019.09.040

Biologics. Early reports highlighted significant controversy regarding increased postoperative complications among patients exposed to anti–tumor necrosis factor α (anti-TNF) therapy[6–8] and vedolizumab in the preoperative period.[9–11] Among CD patients, higher detectable anti-TNF levels at the time of surgery have been associated with increased complications.[12] Among UC patients, the use of anti-TNF therapy within 90 days of IPAA was associated with a significant increase in pouch complications, although there was no increased risk among patients undergoing colectomy or total proctocolectomy with end ileostomy.[13] Despite early concerns regarding the perioperative use of vedolizumab,[9–11] recent literature has reported a more favorable safety profile.[14] Similarly, the use of ustekinumab was not associated with an increased risk of perioperative complications when compared with other biologic agents.[15,16] The relationship between preoperative biologics and perioperative complications of IBD remains uncertain. The studies that identified a relationship between biologics and postoperative complications may have inherent indication bias. Specifically, it is conceivable that the postoperative complications were related more to the severity of IBD that presented the indication for the biologic therapy rather than the biologic itself.

Perhaps the most informative study evaluating the risk of complications in the perioperative period owing to biologics is the Prospective Cohort of Ulcerative Colitis and Crohn's Disease Patients Undergoing Surgery to Identify Risk Factors for Post-operative Infection I (PUCCINI).[17] In this prospective cohort, 955 patients undergoing intra-abdominal surgery were evaluated for the development of any infection and surgical site infection. The rate of any infection was similar among those exposed to anti-TNF in the 12 weeks preceding surgery (19.4% vs 20.0%; $P = .80$), as was the rate of surgical site infection (12.4% vs 11.5%; $P = .70$). On multivariable analysis, current anti-TNF use and detectable anti-TNF levels at the time of surgery were not associated with an increased risk of any infection or surgical site infection, leading the authors of the PUCCINI study to conclude that the preoperative use of anti-TNF therapy was not an independent risk factor for postoperative infections. These findings suggest surgery should not be delayed and that a diverting ileostomy is not required for an intestinal CD resection in the setting of preoperative biologic exposure. Furthermore, delaying surgery in severe cases may increase the risk of complications, including mortality.[18]

Glucocorticoids. Before biologic therapy, corticosteroids were the cornerstone therapy for the treatment of IBD. Unfortunately, corticosteroid use has been associated with multiple postoperative complications including superficial surgical site infections, deep space infections, and anastomotic leakage.[19] Limiting corticosteroid exposure in the perioperative period by reducing the intraoperative stress dose[20] and rapidly tapering when possible (ideally to a prednisone dose of <20 mg/d at the time of surgery) may improve postoperative infectious complication rates.

Perioperative Nutrition

Among CD patients, low albumin levels are a significant risk factor for intra-abdominal septic complications.[21] In addition, poor nutritional status has a well-documented impact on postoperative morbidity and mortality in multiple disease states.[22] In the preoperative period, enteral nutrition approaches are preferred if a patient is able to maintain their energy and protein requirements (Figure 1).[23] If malnutrition is diagnosed, then IBD-related surgery may need to be delayed until intensive artificial feeding can be initiated.[22] In the postoperative period, the introduction of early enteral nutrition within 24 hours of surgery may be associated with improved outcomes.[24]

Surgical Decision Making

Although an ileocolonic resection with ileocolonic anastomosis remains the most common surgical approach for patients with CD, a diverting ileostomy may represent a viable and necessary surgical approach in some patients. In a temporary ostomy, the fecal stream is diverted in an effort to promote distal healing, with an ultimate goal to restore intestinal continuity. This may occur in settings of frank perforation, long segments of distal disease, and as an alternative to colectomy as rescue therapy in severe refractory UC and CD-related colitis[25] and refractory perianal disease. Although fecal diversion can be effective in more than 60% of patients with perianal disease, a recent systematic review reported sustained perianal healing after restoration of intestinal continuity to be successful in only 17%.[26] Predictors of successful restoration of bowel continuity are limited, but include improvement in rectal inflammation.[27]

Other times, after an ileocecal resection, a diverting loop ileostomy and end ileostomy may be constructed to protect the anastomosis, and allow for restoration of intestinal continuity at a later date when both the bowel and overall health of the patient is improved. There are no specific guidelines as to when a patient may benefit most from diversion, and conflicting risk factors of intra-abdominal sepsis have been reported, thus surgeons often are left to their own subjective and anecdotal evidence as to who they consider high risk and warrant diversion. However, a few retrospective studies consistently have shown that in the setting of multiple risk factors (corticosteroids, biologic therapy, and multiple prior resections),[28,29] patients are at a significantly increased risk for developing intra-abdominal sepsis. In these scenarios a diverting ileostomy may be useful.[28,29] Until better scores predicting anastomotic leak are constructed, the decision will be left largely to the bias of the

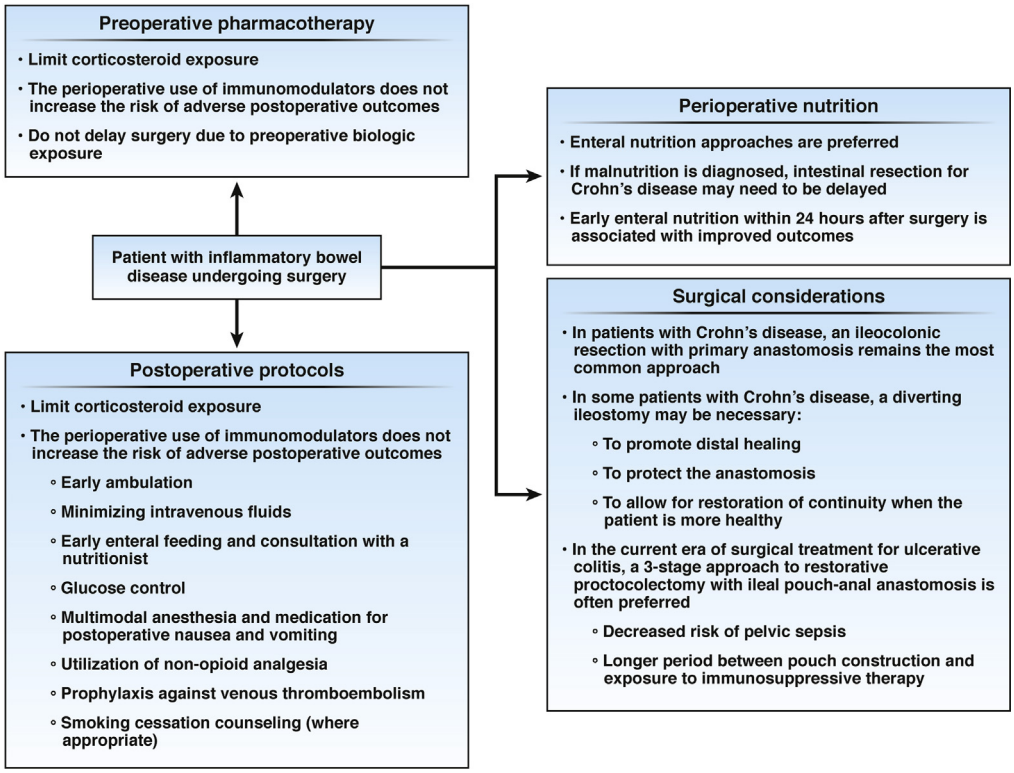

Figure 1. Multidisciplinary considerations for the perioperative management of patients with Crohn's disease or ulcerative colitis.

practicing surgeon and their personal experience related to bowel wall disease, patient disease severity, and an individual patient's ability to tolerate a leak based on their overall health state.

Immediate Postoperative Period

Enhanced recovery pathways, or enhanced recovery after surgery, are standardized protocols that increasingly are being used by colorectal surgeons owing to faster patient recovery, decreased overall morbidity, and decreased cost.[30–32] These pathways were studied more recently in IBD patients specifically, and have shown decreased postoperative superficial surgical site infection, anastomotic leaks, and ileus after implementation of hospital-wide surgical care bundles to prevent postoperative infections and enhanced recovery pathways.[33] Although each hospital system may have a slightly different protocol for enhanced recovery pathways or bundle to prevent surgical site infection,[34] in general, enhanced recovery after surgery protocols focuses on limiting fluids intraoperatively, limiting opioid pain medications by giving regional pain blocks and a cocktail of nonopioid pain medication, minimally invasive surgical approaches, early transition to a normal diet, fast removal of any catheters, and early ambulation. In addition, a focus on the prevention of venous thromboembolism is critical,[35] given the vulnerability of postoperative patients owing to decreased mobility and disease activity.

Table 1. Risk Factors Identified for Endoscopic and Clinical Recurrence of Crohn's Disease After Surgical Resection

High-risk factors	Current smoking
	History of perforating or penetrating phenotype
	History of perianal phenotype
	History of at least 2 prior surgeries
	Younger age (<30 y)
Moderate-risk factors	Longer segment of diseased bowel at the time of resection (>10 cm)
	Shorter time to initial surgery (<10 y)

The Postoperative Management of Crohn's Disease

Disease Recurrence

Although surgery effectively can address symptoms of complicated CD, it is not curative, with up to 90% of patients showing endoscopic recurrence in the neoterminal ileum by 12 months after surgery. Within 3 years, endoscopic recurrence is essentially ubiquitous,[36] and by 5 years clinical recurrence is present in up to 50% of patients.[37] Perhaps most concerning, a repeat intestinal resection is required in 25% of patients within 5 years and in 35% of patients within 10 years.[38]

Although no validated risk score has been identified for the prediction of postoperative recurrence of CD,[39] several risk factors have been identified. These include a history of penetrating disease phenotype, 2 or more prior CD-related surgeries, and current cigarette

smoking.[40–47] Other factors that may increase the risk of recurrent disease include an extensive small-bowel resection, age younger than 30 years at diagnosis, a short interval between diagnosis and surgery (<10 y), and the presence of perianal disease[36,48] (Table 1). Of these, cigarette smoking is the only modifiable risk factor and thus perioperative counseling regarding smoking cessation is paramount because even preoperative smoking cessation may offer benefits.[49]

Therapy Choices

The decision to initiate prophylactic therapy for the prevention of postoperative recurrence remains controversial, and thus risk stratification into low- and high-risk categories can be helpful in identifying which patients are most likely to benefit from immediate or early initiation of postoperative therapy. In the absence of identified risk factors, patients are believed to be at low risk for recurrence, and a reasonable postoperative strategy would be no therapy unless recurrent CD is present at the time of the 6-month ileocolonoscopy.

For patients at moderate or high risk for early recurrence after surgical resection for CD, the use of anti-TNF monotherapy and thiopurine monotherapy have been associated with the greatest decrease in disease recurrence, particularly when compared with antibiotics, aminosalicylates, probiotics, or budesonide alone.[39] In a recent network meta-analysis, anti-TNF monotherapy showed the lowest rates of endoscopic recurrence when compared with placebo.[50] After earlier evaluations of the efficacy of anti-TNF therapy in this setting,[51–53] the Prospective, Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial Comparing REMICADE(R) (Infliximab) and Placebo in the Prevention of Recurrence in Crohn's Disease Patients Undergoing Surgical Resection Who Are at an Increased Risk of Recurrence (PREVENT) study showed significantly lower rates of endoscopic recurrence at week 76 among patients treated with infliximab as compared with placebo (22.4% vs 51.3%; $P < .001$), although there was no statistically significant difference in clinical recurrence (12.9% vs 20.0%; $P = .097$).[47] In a retrospective, multicenter, observational study from Spain, infliximab and adalimumab performed equally well in the prevention of postoperative recurrence.[54] Although the efficacy of anti-TNF therapy for the prevention of postoperative recurrence has been well established, the utility of newer biologic therapies such as ustekinumab and vedolizumab has not been determined. When initiating biologic therapy in moderate- or high-risk patients, our practice is to start therapy 2 to 4 weeks after surgery.

In addition to biologic therapy, thiopurines and nitroimidazoles are therapy options for the prevention of postoperative recurrence in select populations. The totality of postoperative prevention data with thiopurines are weak, with nominal benefit in preventing clinical, but not endoscopic, recurrence. The use of monotherapy thiopurines after surgery has waned and are used most commonly as combination agents with anti-TNFs.[55] Although most patients do not tolerate long-term metronidazole therapy because of adverse effects such as peripheral neuropathy, there are also data supporting the use of combination therapy with azathioprine and metronidazole,[56] or metronidazole monotherapy in the postoperative period.[57,58]

Postoperative Ileocolonoscopy

The risk of postoperative recurrence of CD can be modified significantly using standardized ileocolonoscopic assessment at 6 months postoperatively along with escalation or modification of treatment as necessary. In the randomized postoperative Crohn's endoscopic recurrence (POCER) trial, De Cruz et al[59] showed an 18% reduction in endoscopic recurrence at 18 months postoperatively among patients who underwent active evaluation with a colonoscopy and treatment escalation (as necessary) at 6 months postoperatively as compared with patients in a standard-care arm. Although clinical risk factors predicted recurrence, low-risk patients also showed the need for continued monitoring and early colonoscopy. In asymptomatic patients in whom endoscopic recurrence was noted, the initiation of therapy was recommended,[55] given the concern that patients with endoscopic recurrence are at high risk of progression to clinical recurrence and, ultimately, further surgery.

Choosing a Postoperative Strategy

When evaluating the postoperative patient with CD, the decision to initiate early pharmacologic prophylaxis as opposed to endoscopically guided therapy at 6 months should be an individual decision, based on risk stratification (Figure 2). Regardless of risk factors, all patients should undergo ileocolonoscopy with evaluation of the neoterminal ileum and Rutgeerts scoring at 6 to 12 months after surgery. If a patient shows endoscopic recurrence on the first ileocolonoscopy, even if asymptomatic, then an anti-TNF or thiopurine can be introduced.

Patients with risk factors for disease recurrence should be treated aggressively with the initiation of an anti-TNF therapy, likely in combination with an immunomodulator. If there is evidence of endoscopic recurrence on ileocolonoscopy, then the patient's therapy should be optimized or a new regimen should be initiated.

Further Considerations in Postoperative Assessment

Several studies have suggested that fecal calprotectin may serve as a predictor of postoperative recurrence in

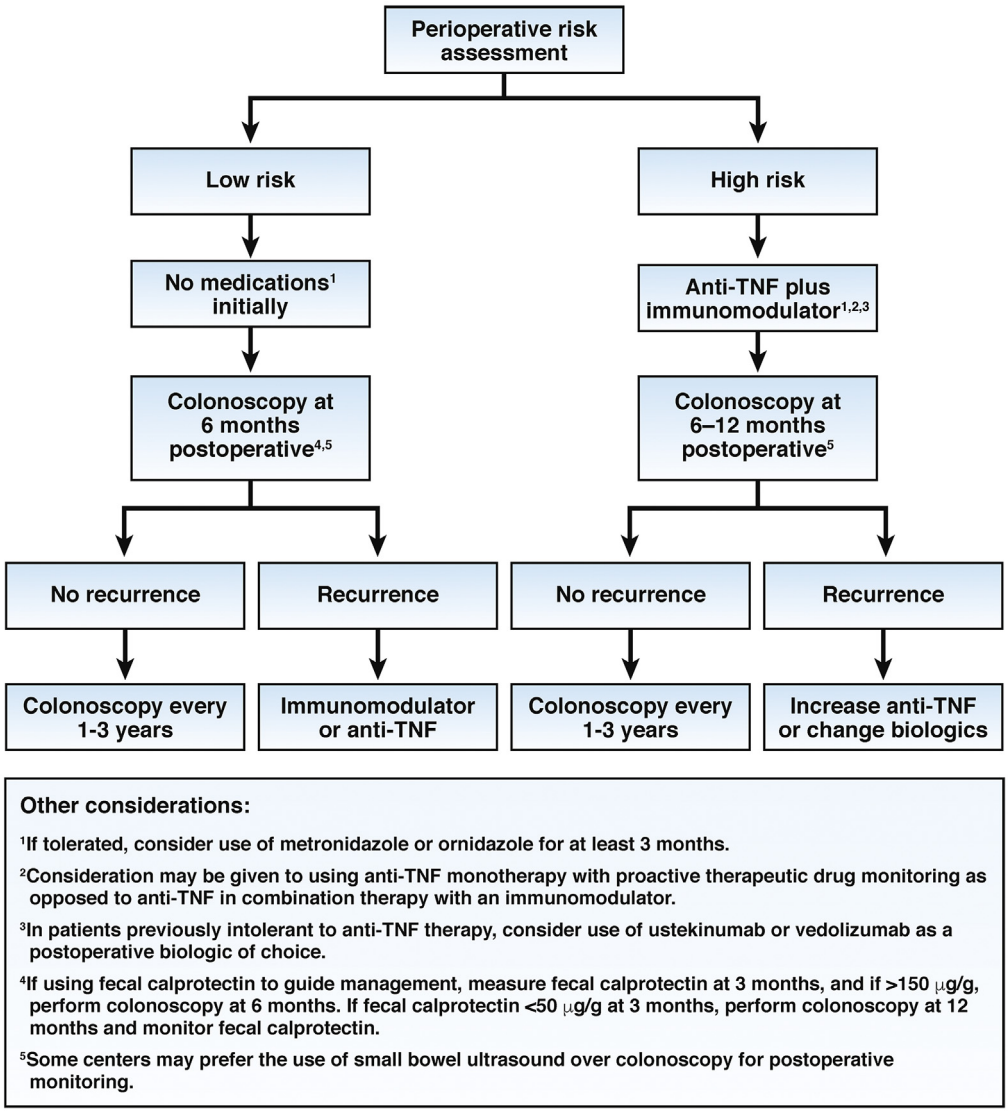

Figure 2. An algorithm for the postoperative management of Crohn's disease. anti-TNF, anti–tumor necrosis factor α.

place of ileocolonoscopy at 6 months.[60,61] In addition, more recent reports combining fecal calprotectin with serologic markers may offer a glimpse of predictive modeling approaches to improving risk stratification in individual patients.[62] Whether fecal calprotectin can serve as a reliable surrogate for endoscopic examination as a primary assessment of recurrence after intestinal resection for CD remains unknown.

Although much of the current literature examining the utility of small-bowel ultrasonography in the evaluation of postoperative CD has been limited by sample size, a recent systematic review and meta-analysis indicated that ultrasonography shows high sensitivity and specificity for the detection of postoperative recurrence.[63] European Crohn's and Colitis Organization guidelines also have defined ultrasonography as an emerging assessment tool for identifying postoperative recurrence.[64] Multiple findings on cross-sectional imaging have been identified as predictors of recurrent CD, including wall thickening greater than 3 mm at the anastomosis and anastomotic stenosis on computed tomography enterography.[65] In addition, magnetic resonance enterography has shown high agreement with the Rutgeerts score.[66] Video capsule endoscopy also has shown a high sensitivity and specificity for the detection of postoperative recurrence.[67]

With regard to more standard endoscopic assessment with ileocolonoscopy, the relative clinical significance of i2 disease remains controversial. After the initial publication of the Rutgeerts score, the i2 grade has been divided further into lesions confined to the ileocolonic anastomosis (i2a) and moderate lesions of the remainder of the neoterminal ileum (i2b).[68] This delineation between i2a and i2b disease initially was proposed because of the suspicion that ulcers contained to the anastomosis were more likely to be postsurgical or ischemic and not predictive of future CD-related complications. However, in recent evaluations, there has been no significant difference in the rate of postoperative recurrence[69] or the need for further endoscopic or surgical intervention[69] when comparing patients with i2a and i2b disease, suggesting that patients with i2a disease may require closer monitoring than initially suspected.

Management After Ileal Pouch–Anal Anastomosis

The Immediate Perioperative Period

Restorative proctocolectomy with IPAA is now the standard surgical approach for medically refractory UC or UC-related dysplasia. In patients with indeterminate colitis[70] and a minority of CD patients with disease limited to the colon, IPAA also may be used, depending on local practices.[71] Although IPAA offers significant improvements in quality of life,[71] postoperative morbidity can occur including short-term complications of pelvic sepsis from anastomotic leaks as well as long-term complications including new inflammatory pouch-related conditions.

In highly selected patients, the colectomy and the pouch creation can be performed in a single surgery without an ileostomy, or as a 2-stage IPAA in which the IPAA is created in the first surgery and the ileostomy is reversed in the second surgery. However, in the current era of combination immunosuppression and increased use of biologic therapy and small-molecule inhibitors, the more common approach to IPAA surgery is a 3-stage approach owing to improved outcomes, particularly in patients with medically refractory UC. For example, preoperative anti-TNF exposure and vedolizumab are associated with a significant increase in postoperative complications among patients who undergo IPAA within 12 weeks of biologic exposure. In contrast, if a colectomy was performed during the first surgery, biologic therapy did not increase the rate of complications in patients undergoing subtotal colectomy or total abdominal colectomy.[13]

In analyses using National Surgical Quality Improvement Program data, patients undergoing delayed pouch creation were at a decreased risk for unplanned reoperations as well as adverse events,[72] and 2-stage IPAA was associated with an increased risk for readmission for venous thromboembolism.[35] Most importantly, when a 3-stage approach is used, there is a decreased risk of pelvic sepsis because the IPAA is performed once the patient is off immunosuppression and their nutrition is improved. This is critical because pelvic sepsis is the leading cause of pouch failure and may result in poor pouch outcome. Therefore, a 3-stage approach should be used liberally in the setting of medically refractory disease, especially in the setting of recent exposure to corticosteroids and/or biologic therapy.

Long-Term Complications After Ileal Pouch–Anal Anastomosis

Acute pouchitis. When patients present with new symptoms after IPAA, a systematic approach to the initial evaluation is critical. There are multiple potential underlying diagnoses that may be present in patients with suspected inflammation of the pouch after IPAA (Figure 3). Approximately 40% of patients will develop an episode of acute pouchitis within the first year after IPAA,[73] and up to 80% of patients will develop acute pouchitis symptoms at 30 years after IPAA.[74,75] Classically, the symptoms of acute pouchitis have been characterized by increased frequency or urgency, potentially accompanied by abdominal cramping or incontinence.[76]

In the first presentation of suspected pouchitis, strong consideration should be given to performing a pouchoscopy because the severity of symptoms may not correlate with endoscopic or histologic activity in all patients.[77] In addition, pouchoscopy offers the ability to evaluate other potential etiologies of new-onset symptoms after IPAA, including cuffitis, ischemia, postsurgical phenomena such as strictures or sinus tracts, or nonsteroidal anti-inflammatory drug-induced inflammation. Consideration also should be given to other systemic disorders such as primary sclerosing cholangitis, which increase the risk for development of pouchitis and prepouch ileitis.[78]

Once a diagnosis of acute pouchitis has been made, prompt initiation of antibiotic therapy resolves symptoms in the majority of patients. Multiple antibiotic regimens have shown efficacy in treating acute pouchitis,[79] however, the optimal treatment regimen is unknown. In treating the first episode of pouchitis, we typically use a 14-day course of ciprofloxacin or metronidazole. In particular, ciprofloxacin may be associated with a greater response in acute pouchitis, with less associated adverse effects.[80]

Although primary prophylaxis to prevent pouchitis after IPAA also has been considered, the evidence to support the use of probiotics, antibiotics, and other agents such as sulfasalazine as a method of primary prophylaxis is limited.[73,79] A recent Cochrane review highlighted the need for well-designed studies to identify optimal treatment strategies for both the treatment of acute pouchitis as well as the prevention of pouchitis in this population.[79]

Chronic pouchitis. Although the majority of patients presenting with acute pouchitis will respond to a short course of antibiotics, up to 19% of patients will develop chronic antibiotic-dependent pouchitis (CADP),[76] which traditionally has been defined by at least 4 episodes of recurrent pouchitis per year that respond to antibiotic therapy. Initial randomized controlled trials of the efficacy of probiotic therapy as a secondary treatment for CADP showed that VSL#3 was effective for maintaining remission after an initial course of antibiotics.[81,82] In follow-up studies of real-world efficacy, however, the durability of VSL#3 seemed limited owing to recurrent symptoms or adverse effects.[83] Fecal microbiota transplant also has been attempted as a means of avoiding long-term antibiotic exposure, however this approach was not successful in an early study, perhaps owing to low levels of engraftment.[84] Given the lack of consistent data with regard to VSL#3 or other probiotics as a

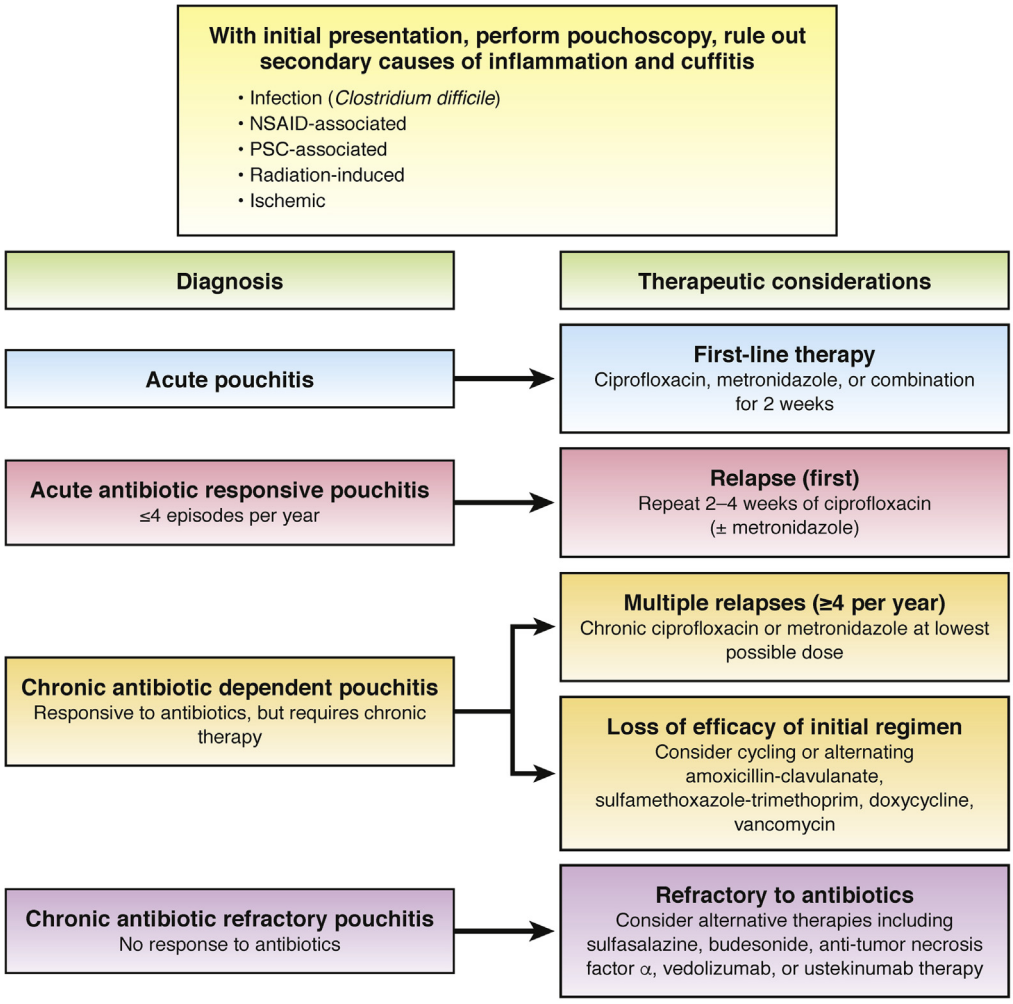

Figure 3. Diagnostic and therapeutic considerations in patients presenting with inflammation of the pouch after ileal pouch–anal anastomosis. NSAID, nonsteroidal anti-inflammatory drug; PSC, primary sclerosing cholangitis.

method of secondary prophylaxis in patients with CADP, we typically attempt to identify the minimal effective dose of antibiotic therapy. Identification of this dose can be accomplished using an individualized tapering schedule, in which patients record changes in symptoms including stool frequency, urgency, and nocturnal symptoms.

An even smaller group of patients will go on to develop chronic antibiotic-refractory pouchitis. This population is among the most difficult to treat, often requiring escalation to immunosuppressive therapies. In a systematic review and meta-analysis, the long-term rate of remission with anti-TNF therapy for chronic refractory pouchitis was 37%.[85] More recently, novel biologic therapies such as vedolizumab[86] and ustekinumab[87] have shown efficacy in this population. Although uncommon, approximately 10% of patients may develop *Clostridium difficile* infection after IPAA,[88] thus assessing for *C difficile* infection in patients with chronic refractory symptoms may be warranted.

Crohn's-like disease of the pouch. Despite a preoperative diagnosis of UC or indeterminate colitis, approximately 10% of patients will develop Crohn's-like disease (CLD) of the pouch after IPAA.[89] Unfortunately, several gaps in our understanding of this disease process exist, beginning with the terminology used to described these changes after IPAA. Multiple terms have been used to describe this condition,[90] including CD of the pouch, CD in IPAA, CD-like condition in ileal pouches, Crohn's pouchitis, and CLD of the pouch. Significant heterogeneity also exists in the diagnostic criteria used in identifying patients with CLD of the pouch. In a recent systematic review and meta-analysis, the 3 most common diagnostic criteria were the presence of a fistula/fistulae, a stricture involving the pouch or prepouch ileum, or the presence of prepouch ileitis.[89] Patients may present with these findings de novo, or after an initial period of treatment for suspected acute or chronic pouchitis.

Although complex, management decisions in this population are critically important given that CLD of the pouch represents one of the most common etiologies of pouch failure.[91] Similar to the reported evidence in patients with chronic antibiotic-refractory pouchitis, the experience with anti-TNF therapy for CLD of the pouch is heterogenous, with 12-month remission rates estimated at 57%.[85] Vedolizumab also has shown benefits in the treatment of CLD of the pouch,[86] with prior anti-TNF exposure being a risk factor for decreased response.[86] In an evaluation of patients with CLD of the pouch and

chronic pouchitis, 83% of patients showed clinical response to ustekinumab at 6 months.[87]

Few predictors of these inflammatory conditions of the pouch exist. In addition, the factors involved in the development of acute and chronic pouch inflammation may be differential.[92] Extensive colonic disease,[92] high levels of perinuclear antineutrophil cytoplasmic antibodies before colectomy,[93] and extraintestinal manifestations have been associated with an increased risk for chronic pouchitis.[92] Current decision making often rests in the treatment of symptoms after these conditions develop rather than in prediction and prevention or early intervention. Although preoperative counseling regarding the potential development of these conditions remains important, future research should be focused on standardizing our approach to patients with inflammatory conditions after IPAA, developing predictors, and evaluating comparative effectiveness of therapies in this population.

Functional and Defecatory Disorders of the Pouch

Patients also may present with functional and other defecatory disorders after IPAA. In a study of 111 patients with an IPAA, almost 75% of patients undergoing anorectal manometry met criteria for non–relaxing pelvic floor dysfunction (N-RPFD).[94] In addition, a significantly higher proportion of patients with chronic pouchitis were diagnosed with N-RPFD as compared with those patients without chronic pouchitis.[94] Although the exact etiology of this relationship is not clear, fecal stasis in the setting of abnormal defecation may play a significant role in bacterial changes and subsequent pouch inflammation. There are no standard criteria for the diagnosis of N-RPFD. However, if patients complain of abnormal defecation or other symptoms suggestive of a pouch evacuation disorder, prompt consideration of anorectal manometry and other evaluation for N-RPFD should be entertained because early results indicate that biofeedback therapy is effective in patients with an IPAA after a diagnosis of N-RPFD.[94]

Surveillance for Pouch Dysplasia and Neoplasia

Although proctocolectomy dramatically reduces the risk for a colorectal malignancy in UC patients, the risk for development of pouch neoplasia remains. Society guidelines on surveillance intervals are not uniform,[95] and significant heterogeneity in surveillance patterns exists in clinical practice.[96] This is likely because the overall incidence of pouch dysplasia (3.0%) and cancer (2.7%) are relatively low after 20 years,[97] with primary cancers of the pouch body (as compared with the rectal cuff) exceedingly rare.[98] In addition, rates are influenced by high-risk factors, including a preoperative diagnosis of dysplasia or cancer, a concomitant diagnosis of primary sclerosing cholangitis, or mucosal features such as type C pouch mucosa.[95] Because yearly surveillance for patients without high-risk factors for dysplasia does not seem efficient or guided by risk stratification, we would propose annual pouchoscopy only in patients with high-risk features and every 5 years in those without.

Conclusions

The perioperative and postoperative management of patients with IBD continues to increase in complexity with the addition of novel therapies, more widespread utilization of biologic therapies, and the recognition that earlier assessment and proactive intervention improves outcomes in the postoperative period. Although careful consideration should be given to an individual's risk factors in the perioperative evaluation, the use of biologic therapies in the preoperative period appears to be safe and should not overly influence surgical decision making. Among patients with CD, a standardized approach to postoperative therapy, based on risk stratification and ileocolonoscopy at 6 to 12 months after surgery, significantly has improved outcomes. In patients with UC, a similar standardized approach to diagnosing and managing postoperative disorders would aid significantly in improving our understanding of the natural history of pouch-related disorders and outcomes.

References

1. Bernstein CN, Loftus EV Jr, Ng SC, et al. Hospitalisations and surgery in Crohn's disease. Gut 2012;61:622–629.
2. Kaplan GG, Seow CH, Ghosh S, et al. Decreasing colectomy rates for ulcerative colitis: a population-based time trend study. Am J Gastroenterol 2012;107:1879–1887.
3. Murthy SK, Begum J, Benchimol EI, et al. Introduction of anti-TNF therapy has not yielded expected declines in hospitalisation and intestinal resection rates in inflammatory bowel diseases: a population-based interrupted time series study. Gut 2020;69:274–282.
4. Colombel JF, Loftus EV Jr, Tremaine WJ, et al. Early postoperative complications are not increased in patients with Crohn's disease treated perioperatively with infliximab or immunosuppressive therapy. Am J Gastroenterol 2004; 99:878–883.
5. Aberra FN, Lewis JD, Hass D, et al. Corticosteroids and immunomodulators: postoperative infectious complication risk in inflammatory bowel disease patients. Gastroenterology 2003; 125:320–327.
6. Kopylov U, Ben-Horin S, Zmora O, et al. Anti-tumor necrosis factor and postoperative complications in Crohn's disease: systematic review and meta-analysis. Inflamm Bowel Dis 2012; 18:2404–2413.
7. Brouquet A, Maggiori L, Zerbib P, et al. Anti-TNF therapy is associated with an increased risk of postoperative morbidity after surgery for ileocolonic Crohn disease: results of a prospective nationwide cohort. Ann Surg 2018;267:221–228.
8. Kunitake H, Hodin R, Shellito PC, et al. Perioperative treatment with infliximab in patients with Crohn's disease and ulcerative colitis is not associated with an increased rate of postoperative

complications. J Gastrointest Surg 2008;12:1730–1736; discussion 1736–1737.
9. Lightner AL, McKenna NP, Tse CS, et al. Postoperative outcomes in vedolizumab-treated Crohn's disease patients undergoing major abdominal operations. Aliment Pharmacol Ther 2018;47:573–580.
10. Lightner AL, Raffals LE, Mathis KL, et al. Postoperative outcomes in vedolizumab-treated patients undergoing abdominal operations for inflammatory bowel disease. J Crohns Colitis 2017;11:185–190.
11. Yamada A, Komaki Y, Patel N, et al. Risk of postoperative complications among inflammatory bowel disease patients treated preoperatively with vedolizumab. Am J Gastroenterol 2017;112:1423–1429.
12. Lau C, Dubinsky M, Melmed G, et al. The impact of preoperative serum anti-TNFalpha therapy levels on early postoperative outcomes in inflammatory bowel disease surgery. Ann Surg 2015;261:487–496.
13. Kulaylat AS, Kulaylat AN, Schaefer EW, et al. Association of preoperative anti-tumor necrosis factor therapy with adverse postoperative outcomes in patients undergoing abdominal surgery for ulcerative colitis. JAMA Surg 2017;152:e171538.
14. Novello M, Stocchi L, Steele SR, et al. Case-matched comparison of postoperative outcomes following surgery for inflammatory bowel disease after exposure to vedolizumab vs. other biologics. J Crohns Colitis 2020;14:185–191.
15. Lightner AL, McKenna NP, Tse CS, et al. Postoperative outcomes in ustekinumab-treated patients undergoing abdominal operations for Crohn's disease. J Crohns Colitis 2018; 12:402–407.
16. Novello M, Stocchi L, Holubar S, et al. Surgical outcomes of patients treated with ustekinumab vs. vedolizumab in inflammatory bowel disease: a matched case analysis. Int J Colorectal Dis 2019;34:451–457.
17. Cohen BL, Fleshner P, Kane SV, et al. Anti-tumor necrosis factor therapy is not associated with post-operative infection: results from prospective cohort of ulcerative colitis and Crohn's disease patients undergoing surgery to identify risk factors for post-operative infection I (Puccini). Gastroenterology 2019;156:S-80.
18. Kaplan GG, McCarthy EP, Ayanian JZ, et al. Impact of hospital volume on postoperative morbidity and mortality following a colectomy for ulcerative colitis. Gastroenterology 2008; 134:680–687.
19. Lightner AL. Perioperative management of biologic and immunosuppressive medications in patients with Crohn's disease. Dis Colon Rectum 2018;61:428–431.
20. Zaghiyan K, Melmed GY, Berel D, et al. A prospective, randomized, noninferiority trial of steroid dosing after major colorectal surgery. Ann Surg 2014;259:32–37.
21. Huang W, Tang Y, Nong L, et al. Risk factors for postoperative intra-abdominal septic complications after surgery in Crohn's disease: a meta-analysis of observational studies. J Crohns Colitis 2015;9:293–301.
22. Forbes A, Escher J, Hebuterne X, et al. ESPEN guideline: clinical nutrition in inflammatory bowel disease. Clin Nutr 2017; 36:321–347.
23. Stoner PL, Kamel A, Ayoub F, et al. Perioperative care of patients with inflammatory bowel disease: focus on nutritional support. Gastroenterol Res Pract 2018;2018:7890161.
24. Herbert G, Perry R, Andersen HK, et al. Early enteral nutrition within 24 hours of lower gastrointestinal surgery versus later commencement for length of hospital stay and postoperative complications. Cochrane Database Syst Rev 2018;10: CD004080.
25. Russell TA, Dawes AJ, Graham DS, et al. Rescue diverting loop ileostomy: an alternative to emergent colectomy in the setting of severe acute refractory IBD-colitis. Dis Colon Rectum 2018; 61:214–220.
26. Singh S, Ding NS, Mathis KL, et al. Systematic review with meta-analysis: faecal diversion for management of perianal Crohn's disease. Aliment Pharmacol Ther 2015;42:783–792.
27. Regimbeau JM, Panis Y, Cazaban L, et al. Long-term results of faecal diversion for refractory perianal Crohn's disease. Colorectal Dis 2001;3:232–237.
28. McKenna NP, Habermann EB, Glasgow AE, et al. Intra-abdominal sepsis after ileocolic resection in Crohn's disease: the role of combination immunosuppression. Dis Colon Rectum 2018;61:1393–1402.
29. Johnston WF, Stafford C, Francone TD, et al. What is the risk of anastomotic leak after repeat intestinal resection in patients with Crohn's disease? Dis Colon Rectum 2017;60:1299–1306.
30. Aarts MA, Okrainec A, Glicksman A, et al. Adoption of enhanced recovery after surgery (ERAS) strategies for colorectal surgery at academic teaching hospitals and impact on total length of hospital stay. Surg Endosc 2012;26:442–450.
31. Zhuang CL, Ye XZ, Zhang XD, et al. Enhanced recovery after surgery programs versus traditional care for colorectal surgery: a meta-analysis of randomized controlled trials. Dis Colon Rectum 2013;56:667–678.
32. Liska D, Bora Cengiz T, Novello M, et al. Do patients with inflammatory bowel disease benefit from an enhanced recovery pathway? Inflamm Bowel Dis 2020;26:476–483.
33. D'Andrea AP, Khetan P, Miller R, et al. Outcomes after bowel resection for inflammatory bowel disease in the era of surgical care bundles and enhanced recovery. J Gastrointest Surg 2020; 24:123–131.
34. Keenan JE, Speicher PJ, Thacker JK, et al. The preventive surgical site infection bundle in colorectal surgery: an effective approach to surgical site infection reduction and health care cost savings. JAMA Surg 2014;149:1045–1052.
35. McKenna NP, Habermann EB, Glasgow AE, et al. Risk factors for readmission following ileal pouch-anal anastomosis: an American College of Surgeons National Surgical Quality Improvement Program analysis. J Surg Res 2018; 229:324–331.
36. Buisson A, Chevaux JB, Allen PB, et al. Review article: the natural history of postoperative Crohn's disease recurrence. Aliment Pharmacol Ther 2012;35:625–633.
37. Greenstein AJ, Sachar DB, Pasternack BS, et al. Reoperation and recurrence in Crohn's colitis and ileocolitis crude and cumulative rates. N Engl J Med 1975;293:685–690.
38. Frolkis AD, Lipton DS, Fiest KM, et al. Cumulative incidence of second intestinal resection in Crohn's disease: a systematic review and meta-analysis of population-based studies. Am J Gastroenterol 2014;109:1739–1748.
39. Regueiro M, Velayos F, Greer JB, et al. American Gastroenterological Association Institute Technical Review on the management of Crohn's disease after surgical resection. Gastroenterology 2017;152:277–295 e3.
40. Sorrentino D. State-of-the-art medical prevention of postoperative recurrence of Crohn's disease. Nat Rev Gastroenterol Hepatol 2013;10:413–422.

41. Binder V, Hendriksen C, Kreiner S. Prognosis in Crohn's disease–based on results from a regional patient group from the county of Copenhagen. Gut 1985;26:146–150.
42. Lautenbach E, Berlin JA, Lichtenstein GR. Risk factors for early postoperative recurrence of Crohn's disease. Gastroenterology 1998;115:259–267.
43. Reese GE, Nanidis T, Borysiewicz C, et al. The effect of smoking after surgery for Crohn's disease: a meta-analysis of observational studies. Int J Colorectal Dis 2008;23:1213–1221.
44. Pascua M, Su C, Lewis JD, et al. Meta-analysis: factors predicting post-operative recurrence with placebo therapy in patients with Crohn's disease. Aliment Pharmacol Ther 2008; 28:545–556.
45. Simillis C, Yamamoto T, Reese GE, et al. A meta-analysis comparing incidence of recurrence and indication for reoperation after surgery for perforating versus nonperforating Crohn's disease. Am J Gastroenterol 2008;103:196–205.
46. McLeod RS, Wolff BG, Ross S, et al. Recurrence of Crohn's disease after ileocolic resection is not affected by anastomotic type: results of a multicenter, randomized, controlled trial. Dis Colon Rectum 2009;52:919–927.
47. Regueiro M, Feagan BG, Zou B, et al. Infliximab reduces endoscopic, but not clinical, recurrence of Crohn's disease after ileocolonic resection. Gastroenterology 2016;150:1568–1578.
48. Bernell O, Lapidus A, Hellers G. Risk factors for surgery and postoperative recurrence in Crohn's disease. Ann Surg 2000; 231:38–45.
49. Nolan MB, Martin DP, Thompson R, et al. Association between smoking status, preoperative exhaled carbon monoxide levels, and postoperative surgical site infection in patients undergoing elective surgery. JAMA Surg 2017;152:476–483.
50. Burr NE, Hall B, Hamlin PJ, et al. Systematic review and network meta-analysis of medical therapies to prevent recurrence of post-operative Crohn's disease. J Crohns Colitis 2019; 13:693–701.
51. Regueiro M, Schraut W, Baidoo L, et al. Infliximab prevents Crohn's disease recurrence after ileal resection. Gastroenterology 2009;136:441–450 e1; quiz 716.
52. Papamichael K, Archavlis E, Lariou C, et al. Adalimumab for the prevention and/or treatment of post-operative recurrence of Crohn's disease: a prospective, two-year, single center, pilot study. J Crohns Colitis 2012;6:924–931.
53. Savarino E, Bodini G, Dulbecco P, et al. Adalimumab is more effective than azathioprine and mesalamine at preventing postoperative recurrence of Crohn's disease: a randomized controlled trial. Am J Gastroenterol 2013;108:1731–1742.
54. Canete F, Manosa M, Casanova MJ, et al. Adalimumab or infliximab for the prevention of early postoperative recurrence of Crohn disease: results from the ENEIDA registry. Inflamm Bowel Dis 2019;25:1862–1870.
55. Nguyen GC, Loftus EV Jr, Hirano I, et al. American Gastroenterological Association Institute guideline on the management of Crohn's Disease after surgical resection. Gastroenterology 2017;152:271–275.
56. D'Haens GR, Vermeire S, Van Assche G, et al. Therapy of metronidazole with azathioprine to prevent postoperative recurrence of Crohn's disease: a controlled randomized trial. Gastroenterology 2008;135:1123–1129.
57. Rutgeerts P, Hiele M, Geboes K, et al. Controlled trial of metronidazole treatment for prevention of Crohn's recurrence after ileal resection. Gastroenterology 1995;108:1617–1621.
58. Glick LR, Sossenheimer PH, Ollech JE, et al. Low-dose metronidazole is associated with a decreased rate of endoscopic recurrence of Crohn's disease after ileal resection: a retrospective cohort study. J Crohns Colitis 2019; 13:1158–1162.
59. De Cruz P, Kamm MA, Hamilton AL, et al. Crohn's disease management after intestinal resection: a randomised trial. Lancet 2015;385:1406–1417.
60. Wright EK, Kamm MA, De Cruz P, et al. Measurement of fecal calprotectin improves monitoring and detection of recurrence of Crohn's disease after surgery. Gastroenterology 2015; 148:938–947.e1.
61. Yamamoto T, Shimoyama T. Monitoring and detection of disease recurrence after resection for Crohn's disease: the role of non-invasive fecal biomarkers. Expert Rev Gastroenterol Hepatol 2017;11:899–909.
62. Cerrillo E, Moret I, Iborra M, et al. A nomogram combining fecal calprotectin levels and plasma cytokine profiles for individual prediction of postoperative Crohn's disease recurrence. Inflamm Bowel Dis 2019;25:1681–1691.
63. Rispo A, Imperatore N, Testa A, et al. Diagnostic accuracy of ultrasonography in the detection of postsurgical recurrence in Crohn's disease: a systematic review with meta-analysis. Inflamm Bowel Dis 2018;24:977–988.
64. Gionchetti P, Dignass A, Danese S, et al. European evidence-based consensus on the diagnosis and management of Crohn's disease 2016: part 2: surgical management and special situations. J Crohns Colitis 2017;11:135–149.
65. Soyer P, Boudiaf M, Sirol M, et al. Suspected anastomotic recurrence of Crohn disease after ileocolic resection: evaluation with CT enteroclysis. Radiology 2010;254:755–764.
66. Sailer J, Peloschek P, Reinisch W, et al. Anastomotic recurrence of Crohn's disease after ileocolic resection: comparison of MR enteroclysis with endoscopy. Eur Radiol 2008;18:2512–2521.
67. Yung DE, Har-Noy O, Tham YS, et al. Capsule endoscopy, magnetic resonance enterography, and small bowel ultrasound for evaluation of postoperative recurrence in Crohn's disease: systematic review and meta-analysis. Inflamm Bowel Dis 2017; 24:93–100.
68. Domènech E, Mañosa M, Bernal I, et al. Impact of azathioprine on the prevention of postoperative Crohn's disease recurrence: results of a prospective, observational, long-term follow-up study. Inflamm Bowel Dis 2008;14:508–513.
69. Riviere P, Vermeire S, Irles-Depe M, et al. No change in determining Crohn's disease recurrence or need for endoscopic or surgical intervention with modification of the Rutgeerts' scoring system. Clin Gastroenterol Hepatol 2019;17:1643–1645.
70. Netz U, Galbraith NJ, O'Brien S, et al. Long-term outcomes following ileal pouch-anal anastomosis in patients with indeterminate colitis. Surgery 2018;163:535–541.
71. Fazio VW, Kiran RP, Remzi FH, et al. Ileal pouch anal anastomosis: analysis of outcome and quality of life in 3707 patients. Ann Surg 2013;257:679–685.
72. Kochar B, Barnes EL, Peery AF, et al. Delayed ileal pouch anal anastomosis has a lower 30-day adverse event rate: analysis from the National Surgical Quality Improvement Program. Inflamm Bowel Dis 2018;24:1833–1839.
73. Gionchetti P, Rizzello F, Helwig U, et al. Prophylaxis of pouchitis onset with probiotic therapy: a double-blind, placebo-controlled trial. Gastroenterology 2003;124:1202–1209.

74. Lightner AL, Mathis KL, Dozois EJ, et al. Results at up to 30 years after ileal pouch-anal anastomosis for chronic ulcerative colitis. Inflamm Bowel Dis 2017;23:781–790.
75. Barnes EL, Herfarth HH, Sandler RS, et al. Pouch-related symptoms and quality of life in patients with ileal pouch-anal anastomosis. Inflamm Bowel Dis 2017;23:1218–1224.
76. Shen B. Pouchitis: what every gastroenterologist needs to know. Clin Gastroenterol Hepatol 2013;11:1538–1549.
77. Shen B, Achkar JP, Lashner BA, et al. Endoscopic and histologic evaluation together with symptom assessment are required to diagnose pouchitis. Gastroenterology 2001;121:261–267.
78. Quinn KP, Lightner AL, Faubion WA, et al. A comprehensive approach to pouch disorders. Inflamm Bowel Dis 2019; 25:460–471.
79. Nguyen N, Zhang B, Holubar SD, et al. Treatment and prevention of pouchitis after ileal pouch-anal anastomosis for chronic ulcerative colitis. Cochrane Database Syst Rev 2019;5: CD001176.
80. Shen B, Achkar JP, Lashner BA, et al. A randomized clinical trial of ciprofloxacin and metronidazole to treat acute pouchitis. Inflamm Bowel Dis 2001;7:301–305.
81. Gionchetti P, Rizzello F, Venturi A, et al. Oral bacteriotherapy as maintenance treatment in patients with chronic pouchitis: a double-blind, placebo-controlled trial. Gastroenterology 2000; 119:305–309.
82. Mimura T, Rizzello F, Helwig U, et al. Once daily high dose probiotic therapy (VSL#3) for maintaining remission in recurrent or refractory pouchitis. Gut 2004;53:108–114.
83. Shen B, Brzezinski A, Fazio VW, et al. Maintenance therapy with a probiotic in antibiotic-dependent pouchitis: experience in clinical practice. Aliment Pharmacol Ther 2005;22:721–728.
84. Herfarth H, Barnes EL, Long MD, et al. Combined endoscopic and oral fecal microbiota transplantation in patients with antibiotic-dependent pouchitis: low clinical efficacy due to low donor microbial engraftment. Inflamm Intest Dis 2019;4:1–6.
85. Huguet M, Pereira B, Goutte M, et al. Systematic review with meta-analysis: anti-TNF therapy in refractory pouchitis and Crohn's disease-like complications of the pouch after ileal pouch-anal anastomosis following colectomy for ulcerative colitis. Inflamm Bowel Dis 2018;24:261–268.
86. Gregory M, Weaver KN, Hoversten P, et al. Efficacy of vedolizumab for refractory pouchitis of the ileo-anal pouch: results from a multicenter US cohort. Inflamm Bowel Dis 2019; 25:1569–1576.
87. Weaver KN, Gregory M, Syal G, et al. Ustekinumab is effective for the treatment of Crohn's disease of the pouch in a multicenter cohort. Inflamm Bowel Dis 2019;25:767–774.
88. Seril DN, Shen B. Clostridium difficile infection in patients with ileal pouches. Am J Gastroenterol 2014;109:941–947.
89. Barnes EL, Kochar B, Jessup HR, et al. The incidence and definition of Crohn's disease of the pouch: a systematic review and meta-analysis. Inflamm Bowel Dis 2019; 25:1474–1480.
90. Li Y, Wu B, Shen B. Diagnosis and differential diagnosis of Crohn's disease of the ileal pouch. Curr Gastroenterol Rep 2012;14:406–413.
91. Tulchinsky H, Hawley PR, Nicholls J. Long-term failure after restorative proctocolectomy for ulcerative colitis. Ann Surg 2003;238:229–234.
92. Achkar JP, Al-Haddad M, Lashner B, et al. Differentiating risk factors for acute and chronic pouchitis. Clin Gastroenterol Hepatol 2005;3:60–66.
93. Fleshner PR, Vasiliauskas EA, Kam LY, et al. High level perinuclear antineutrophil cytoplasmic antibody (pANCA) in ulcerative colitis patients before colectomy predicts the development of chronic pouchitis after ileal pouch-anal anastomosis. Gut 2001;49:671–677.
94. Quinn KP, Tse CS, Lightner AL, et al. Nonrelaxing pelvic floor dysfunction is an underestimated complication of ileal pouch-anal anastomosis. Clin Gastroenterol Hepatol 2017; 15:1242–1247.
95. Samaan MA, Forsyth K, Segal JP, et al. Current practices in ileal pouch surveillance for patients with ulcerative colitis: a multinational, retrospective cohort study. J Crohns Colitis 2019; 13:735–743.
96. Derikx LA, Nissen LH, Oldenburg B, et al. Controversies in pouch surveillance for patients with inflammatory bowel disease. J Crohns Colitis 2016;10:747–751.
97. Derikx L, Nissen LHC, Smits LJT, et al. Risk of neoplasia after colectomy in patients with inflammatory bowel disease: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 2016;14:798–806 e20.
98. Selvaggi F, Pellino G, Canonico S, et al. Systematic review of cuff and pouch cancer in patients with ileal pelvic pouch for ulcerative colitis. Inflamm Bowel Dis 2014;20:1296–1308.

Reprint requests
Address requests for reprints to: Edward L. Barnes, MD, MPH, Division of Gastroenterology and Hepatology, University of North Carolina at Chapel Hill, 130 Mason Farm Road, Bioinformatics Building, CB #7080, Chapel Hill, North Carolina 27599-7080. e-mail: edward_barnes@med.unc.edu; fax: (919) 966-1036.

Conflicts of interest
The authors disclose the following: Edward L. Barnes has received fees for consulting for AbbVie, Inc; Amy L. Lightner has consulted for Takeda; and Miguel Regueiro received unrestricted educational grants from AbbVie, Janssen, UCB, Pfizer, Takeda, Salix, and Shire, and served on the advisory boards and consulted for AbbVie, Janssen, UCB, Takeda, Pfizer, Miraca Labs, Amgen, Celgene, Seres, Allergan, Genentech, Gilead, Salix, and Prometheus.