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REVIEW ARTICLE

Surgical Considerations in the Treatment of Small Bowel Crohn's Disease

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Abstract Surgery remains a cornerstone of the management of Crohn's disease (CD). Despite the rise of biologic therapy, most CD patients require surgery for penetrating, obstructing, or malignant complications. Optimal surgical therapy requires sophisticated operative judgment and medical optimization. Intraoperatively, surgeons must balance treatment of CD complications against bowel preservation and functional outcome. This demands mastery of multiple techniques for anastomosis and strictureplasty, accurate assessment of bowel integrity for margin minimization, and a comprehensive skillset for navigating adhesions and altered anatomy, controlling thickened mesentery, and safely managing the hostile abdomen. Outside of the operating room, a multi-disciplinary team is critical for pre-operative optimization, patient support, and medical management. Postoperatively, prevention and surveillance of recurrence remain a matter of research and debate, and medical options include older drugs with limited efficacy and tolerability versus biologic agents with greater effect sizes and shorter track records. The evidence base for current management is limited by the inherent challenges of studying a chronic disease marked by heterogeneity and recurrence, but also by a lack of prospective trials incorporating both medical and surgical therapies.

Keywords Crohn's disease · Stricturoplasty · Small bowel

Introduction

Crohn's disease (CD) is a pan-intestinal disease with the majority of patients having some small bowel involvement, usually in the form of perforating, obstructing, or malignant disease. Terminal ileal disease is the most common site of small bowel manifestations. Unlike the colon and the upper gastrointestinal tract, the small bowel can be more challenging to assess and/or surveil radiologically or endoscopically. As the small bowel plays a critical absorptive role, patients requiring resection—particularly repeated resections—are at risk of losing their absorptive/digestive capacity and becoming dependent on parenteral nutrition. The goal of this manuscript is to analyze the impact of surgical management of small bowel CD on the long-term goal of intestinal preservation. This goal cannot be accomplished without an intelligent surgical and multidisciplinary approach tailored to the individual patient.

As frequently noted in the surgical and medical literature, surgery for CD is not curative, and the majority of patients with small bowel CD will require an operation with a 10-year cumulative probability of surgery as high as 83%.[1] Even in the modern era of biologic therapy, 12.5% of patients require an

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operation within the first year of diagnosis.[2] Surgery may resolve complications and produce lasting symptomatic relief in some patients, but iterative surgery is common. Within 5 years, 24% of patients will require a second operation.[3] An even greater percentage of patients will have recurrent, endoscopically visualized luminal disease of varying severity within the same time frame. Recurrent resections, postoperative complications, and ongoing mucosal damage can all contribute to the risk of intestinal failure. A retrospective analysis of postoperative CD patients found that 8.5% had suffered intestinal failure within 20 years after their initial operation, with additional superimposed risks of catheter-related sepsis, liver failure, and death.[4]

Selecting the right patient, right operation, and right timing for the treatment of CD remains a challenge for the surgeon; choosing effective, safe, and tolerable postoperative medical therapy is another dilemma. How can we improve outcomes in patients with small bowel CD? Strategies include clarifying and optimizing surgical indications, improving surgical technique, minimizing complications, and preventing postoperative recurrence.

Surgical Indications

In contrast to ulcerative colitis (UC), where a surgical resection is essentially able to eliminate the disease, all surgical interventions for CD are palliative. The decision to operate may be straightforward (e.g., in the case of massive hemorrhage or free perforation) but more often it is a difficult multidisciplinary decision (Table 1). In considering medical versus surgical therapy for the CD patient, inter-disciplinary management should define the goals of therapy in order of priority. Obviously, of highest concern are acute septic and hemorrhagic complications. In the elective or semi-elective setting, high priority should be given to keeping the patient functional in terms of work and quality of life, preserving bowel to maintain enteral nutrition, and avoiding secondary morbidity from both medical and surgical therapies. Of intermediate concern is avoiding ostomies and repeated resections. Finally, lower priority goals include preventing asymptomatic recurrence, avoiding surgery altogether, and employment of minimally invasive techniques.

Table 1 Surgical indications in Crohn's disease

Surgical indications in Crohn's disease
Free perforation
Hemorrhage
Bowel obstruction
Symptomatic fistula
Abscess[a]
Steroid dependence
Growth retardation
Refractory symptoms
Malignancy

[a] May be managed initially or definitively with percutaneous drainage, see text

Surgical Optimization

Prior to consideration of operative therapy, standard evaluation of the patient should include optimization of the patient's nutritional status and correction of hypovolemia, anemia, acid–base disturbances, and electrolyte abnormalities as necessary. Percutaneous abscess drainage and control of sepsis may forestall an urgent operation and allow for improvement of the patient's overall condition. Preoperative high quality computed tomography (CT) or magnetic resonance (MR) enterography imaging helps delineate the extent of stenosis, fistula, active inflammation, and/or abscess. These studies may allow the surgeon to prepare the patient for the magnitude of the operation. If an ostomy is a possibility, preoperative consultation with a stomal therapist allows for site marking and patient counseling. Key to the successful treatment of the CD patient is coordination of a multidisciplinary team including patient, family, surgeon, gastroenterologist, specialty nursing, nutritional support, psychosocial support, case management, and, in some cases, compassionate use programs from pharmaceutical companies.

Indications for Surgery: Penetrating Disease

Patients with a penetrating phenotype of CD present with abscess, fistula, or, rarely, free perforation. The traditional approach to intra-abdominal pyogenic complications is open surgical drainage and resection of involved bowel with or without stoma creation. The modern strategy attempts to convert urgent surgery into an optimized elective procedure. Sepsis is controlled by percutaneous drainage (PD) and antibiotic therapy while the patient's clinical condition, nutrition, and medical therapy are improved. Elective bowel resection after PD and resolution of sepsis is advocated by most authors, arguing that diseased bowel results in persistent fistulous connection and recurrent abscess. However, some have proposed PD as definitive treatment. Crucial to this argument is the fact that while some operations for CD can be accomplished with straightforward resection (Fig. 1a), other perforations alter and obscure anatomy and result in large resections (Fig. 1b). Multiple small, retrospective analyses have compared up-front surgery, preoperative PD, and PD alone. A meta-analysis of five studies including 108 patients undergoing attempted definitive PD found that 43 patients eventually came to operation.[5] Abscess recurrence was significantly increased in the PD-alone group compared to up-front surgery. While PD alone has a high failure rate, the same meta-analysis

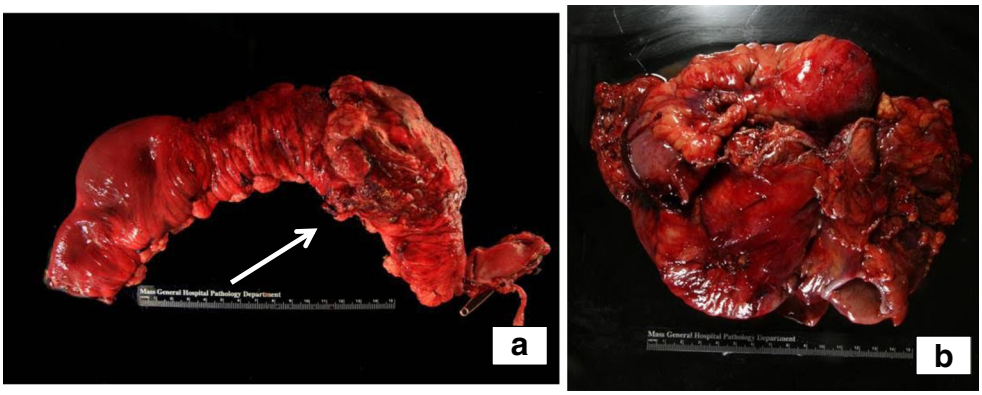

Fig. 1 Small bowel resections for penetrating phenotype of CD. **a** Limited resection for penetrating disease. **b** Complex extensive resection for penetrating CD. *White arrow* indicates area of focal perforation

found that preoperative PD, followed by elective resection, was associated with decreased complications and minimized the risk of stoma compared to up-front surgery. Not surprisingly, there is a strong national trend in increasing PD usage in CD.[6] Despite improvements in imaging, drainage, and supportive care, treating patients with perforating disease remains a challenge. Compared to other Crohn's patients, they are more likely to suffer postoperative anastomotic leaks (5 versus <1%, $p = 0.007$), have a diverting stoma (12 versus 3%, $p = 0.002$), and less likely to undergo laparoscopic surgery (54 versus 68%, $p = 0.004$, conversion rate 33%), even in high volume referral centers.[7]

Indications for Surgery: Bowel Obstruction

Bowel obstruction is the most common indication for surgery in patients with small bowel CD. Active luminal disease, fibrotic stricture, extramural compression by inflammatory phlegmon, postoperative adhesions, and/or malignancy can produce obstruction. Determining the etiology can be challenging, but ultimately determines the appropriate therapeutic approach. Active luminal disease is treated with medical therapy; fibrostenotic disease reflects a chronic process that typically is not amenable to medical therapy and requires surgery (Fig. 2); and other pathologies such as tumors and adhesions require a case-by-case approach.

Occasionally, a chronic stricture is aggravated by acute inflammation that may or may not be evident through elevated inflammatory markers or radiologic findings. Stepping up the medical management, including steroid administration, for a short period of time may therefore be indicated to reduce inflammation leading to adequate symptomatic control. However, some cases will be recurrent or steroid-refractory. The physician is then faced with the choice to proceed directly to surgery or attempt a trial of biologic therapy first, typically in the form of a tumor necrosis factor alpha (TNF) inhibitor. Whether this therapy can prevent future surgery or minimize the extent of an inevitable surgical resection is unknown and the subject of a randomized controlled trial (RCT[http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=1150]).[8]

While RCT data are pending, concern for increased postoperative complications following biologic therapy has led to an understandable reluctance to administer these agents to potential surgical patients. TNF is critical to the granulomatous response to pathogens including mycobacteria and fungi. Whether this translates into impaired healing and an increased

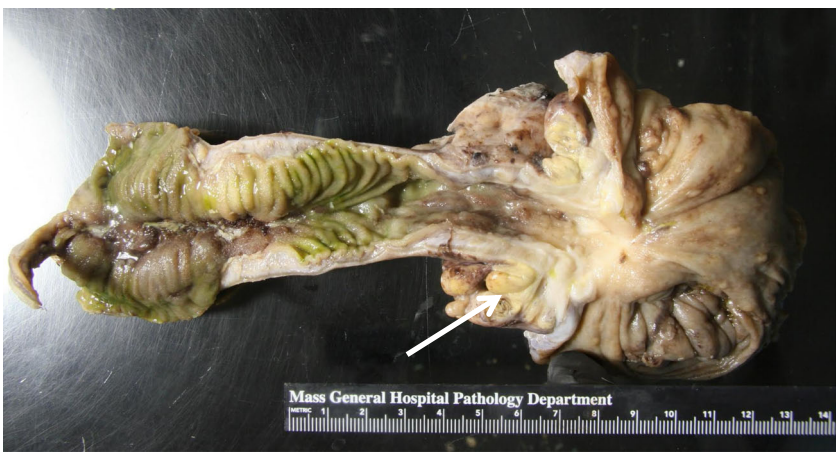

Fig. 2 Fibrotic stricture of terminal ileum in a patient with CD causing bowel obstruction. *White arrow* indicates area of stricture

risk of postoperative complications is a matter of debate. Multiple, retrospective cohort and case control studies have demonstrated conflicting data. The patients included in these studies have varied in terms of the TNF-inhibitor regimen, their disease severity, segregation of CD patients, and concomitant use of other immunosuppressive medications. A 2016 systematic review of these studies included 1024 patients receiving TNF-inhibitors compared to 4401 unexposed patients.[9] Similar to previous pooled analyses, the authors found an increase in "infectious complications," without an increase in overall complications, anastomotic leak, or re-operation. The data from the nine trials including CD patients only, reporting intra-abdominal and anastomotic outcomes, and limiting analysis to TNF-inhibitors (as opposed to combining the TNF-inhibitor arm with other immune-modulating drugs) are presented in Table 2.[9–18] Eight of nine trials found no significant difference in terms of anastomotic leak, intra-abdominal abscess, and infectious complications combined. While timing of the administration of the TNF-inhibitor regimen is heterogeneous in the above trials, there are some limited data to suggest that the interval between TNF-inhibitor administration and surgery does not influence complication rate.[17] Therefore, given the lack of literature consensus as to whether TNF-inhibitors increase anastomotic complications, a trial of biologics is reasonable in the well-selected patient who, failing response, will require an operation. Obviously, multidisciplinary collaboration and continued research is critical in this area.

Similarly, while exposure to anti-TNFs alone does not mandate diversion in these patients, additional risk factors such as intra-abdominal abscess, poor nutritional status, recurrent disease, and prolonged steroid therapy influence the decision to create a temporary stoma, as supported by the literature and the most recent guidelines from the American Society of Colon and Rectal Surgery Society.[19]

Indications for Surgery: Adenocarcinoma

A fixed obstruction in a patient with long-standing CD should prompt the clinician to consider malignancy on their differential. A high degree of suspicion is required to preoperatively identify these patients and perform an operation that is cancer specific. One tip off may be the sudden exacerbation of symptoms in a patient with quiescent disease. Recognition of cancer in a Crohn's patient is a challenge as small bowel adenocarcinoma is rare (1.6% of patients with Crohn's), but significantly more common than in the general population (OR = 12.07; 95% CI 6.07–20.80; $p < 0.001$).[20] Frustratingly, clinical and intra-operative features of adenocarcinoma are similar to benign CD, and for this reason, <5% of tumors are suspected preoperatively and many are diagnosed incidentally on pathology.[21] Because of this, the cancers are often at a more advanced stage at the time of diagnosis.[22]

Indications for Surgery: Failure of Medical Management

Patients failing medical therapy often require surgical intervention. Failure of medical therapy may be defined as insufficient symptomatic response to supportive measures and immunosuppression, inability to tolerate the necessary medications and their side effects, intractable fistula and/or abscess, steroid dependence, and/or growth retardation in children and adolescents.

Surgical Techniques

The surgeon operating on a patient with CD should prepare to evaluate the entire small bowel for disease and stricture with mastery of the various techniques for strictureplasty and bowel preservation as described below. The surgeon should also

Table 2 Trials of TNF-inhibitors and postoperative complications. Restricted to trials only including Crohn's disease patients and not including non-biologic immunomodulators in biologic arm. Outcomes reported as exposed/unexposed. Significant difference ($p < 0.05$) in italics

Study	N exposed	N unexposed	Drug	Surgery	All infectious	Anastomotic leak	Intra-abdominal abscess
Appau 2008[10]	60	329	IFX	Ileocolectomy	NR	*10%/4%*	10%/4.3%
Canedo 2011[11]	65	160	IFX	Bowel resection	NR	6%/67%	3%/7%
Colombel 2004[12]	52	218	IFX	Abdominal surgery	17%/20%	NR	NR
El Hussuna 2012[13]	32	345	BIO	Resection or stricturoplasty	NR	9%/13%	NR
Kasparek 2012[14]	48	48	IFX	Abdominal surgery	NR	4%/13%	6%/10%
Myrelid 2014[15]	111	189	BIO	Resection or stricturoplasty	18%/26%	7%/8%	NR
Nasir 2010[16]	119	251	BIO	Resection or stricturoplasty	NR	NR	5.0/7.2%
Norgard 2013[17]	214	2079	BIO	Bowel operation	NR	4%/3%	NR
Syed 2013[18]	150	175	BIO	Abdominal surgery	36%/25%	6%/5%	14%/10%

BIO includes multiple biologics, *IFX* infliximab only

be versed in handling many of the complexities of CD that can make these procedures much more challenging. One such pitfall often encountered during operations for CD includes a thickened mesentery, which can prevent vessel-sealing devices from achieving adequate hemostasis. Careful attention should be paid to the avoidance of hematomas and hemorrhage when dividing this mesentery. Common techniques include placement of "toe and heel" suture ligatures, staggering of mesenteric clamps, and/or careful unfurling to avoid ligation of double mesenteries. Inflammation, adhesions, abscess(es), and local sepsis can lead to an extremely hostile intra-abdominal operating environment. Under these circumstances, the surgeon must recognize the dangers of proceeding further, consider bringing up whatever proximal stoma is possible, and allow a period of "cooling off" before attempting definitive operation.

Of note, at the time of abdominal exploration and resection for CD, it is advisable to measure the intestinal length before and after resection. This should be done assuming that the bowel is able to be visualized effectively without undo risk of bowel injury simply as a result of adhesiolysis or mobilization for the purpose of measurement. Note of the presence of an ileocecal valve in someone who has had a prior resection as well as the amount of residual colon can be meaningful. Attention to documentation in the operative report of this information related to areas of bowel remaining and the residual bowel length is helpful to clinicians and surgeons related to the future care of the patient as well as anticipating the potential for "short gut" syndrome and the need for longer-term parenteral nutrition.

Small Bowel Resection

The principle of small bowel resection in CD is removal of the symptomatic segment, not the entire disease-affected bowel. Resection margins need to be minimized, as wider resections will not improve long-term recurrence. Fazio and colleagues randomized 152 patients to 2 or 12 cm margins at the time of intestinal resection.[23] At an average of 6.7 years of follow-up, there was no difference in surgical recurrence between groups or between patients with and without microscopic disease at the resection margin.

Significant debate remains about the appropriate small bowel configuration and surgical technique to reconnect the two ends. Either stapled or hand-sewn anastomoses can be performed, and the decision as to which to perform should be based on the clinical situation as well as surgical judgment and expertise. When either technique is possible, retrospective data support stapling as the method of choice. Neither type of anastomosis appears to provide a long-term advantage from the standpoint of eventual disease recurrence. A recent meta-analysis of eight trials including 821 patients and three RCTs of stapled versus sutured ileocolonic anastomosis for CD led the authors to conclude that, as compared to sutures, a stapled anastomosis was superior in terms of anastomotic leak (OR 0.45; 95% CI 0.20–1.00), recurrence (OR 0.20; 95% CI 0.07–0.55), and re-operation (OR 0.18; 95% CI 0.07–0.45).[24] However, retrospective observational studies often suffer time bias with longer periods of follow-up for sutured as compared to stapled anastomoses. Pooled analysis limited to patients in RCTs ($n = 300$) failed to find any significant difference in leak, recurrence, or re-operation between the two approaches.[24] In the largest RCT, McLeod et al. included 179 patients randomized to sutures versus staples.[25] Follow-up at 1 year found no difference between configurations in terms of leak nor clinical or endoscopic recurrence. A smaller RCT including 67 patients with mean follow-up of 87 months (range 36–140) found a significantly lower rate of re-operation in the stapled group (18 versus 49%, $p = 0.022$).[26] The third RCT was unable to accrue enough patients to evaluate recurrence and re-operation rates, but found no difference in immediate postoperative outcomes.[27]

Two novel techniques to reduce anastomotic recurrence are the nipple valve anastomosis and the Kono-S anastomosis. Creation of a "nipple valve" anastomosis by telescoping the neo-terminal ileum for several centimeters into the colon has been proposed to reduce recurrence by reducing fecal reflux into the small intestine. A series of 59 patients undergoing this operation has been reported with 24% clinical and 16% surgical recurrence at 5 years, which compares favorably to published series for standard anastomosis.[28] The technique has not been studied in a randomized fashion, nor does it seem logical in the setting of data suggesting that ileal effluent can rapidly produce anastomotic inflammation.[29]

Within the context of how to reconnect the small bowel, there has been recent interest in changing the configuration of the newly created anastomosis to decrease its ability to bend when the bowel re-strictures. With this goal in mind, the Kono-S anastomosis uses the cut ends of the proximal and distal anastomotic limbs to form a supporting column, rather than form the anastomotic join per se. Anti-mesenteric enterotomies in the proximal and distal bowel are then created and anastomosed (Fig. 3a–d). To study this technique, the authors compared 69 patients undergoing the Kono-S to 73 historical controls undergoing standard resection and found significantly fewer cases of surgical recurrence and decreased endoscopic disease at 5 years follow-up in the Kono-S group (0 versus 15%, $p = 0.0013$).[30] Clinical recurrence was not reported, and endoscopic follow-up was not uniform. The theoretical basis of the technique is that the supporting column resists anastomotic distortion by recurrent disease. Additionally, the anti-mesenteric anastomotic technique excludes the mesenteric side of the lumen, which is the more typical side of recurrence. Whether the success of this technique can be repeated in other institutions and validated prospectively remains to be seen.

The surgeon's highest priority at the time of resection is avoiding anastomotic leak. With this goal in mind, patients with very small segments of residual small bowel and/or high risk

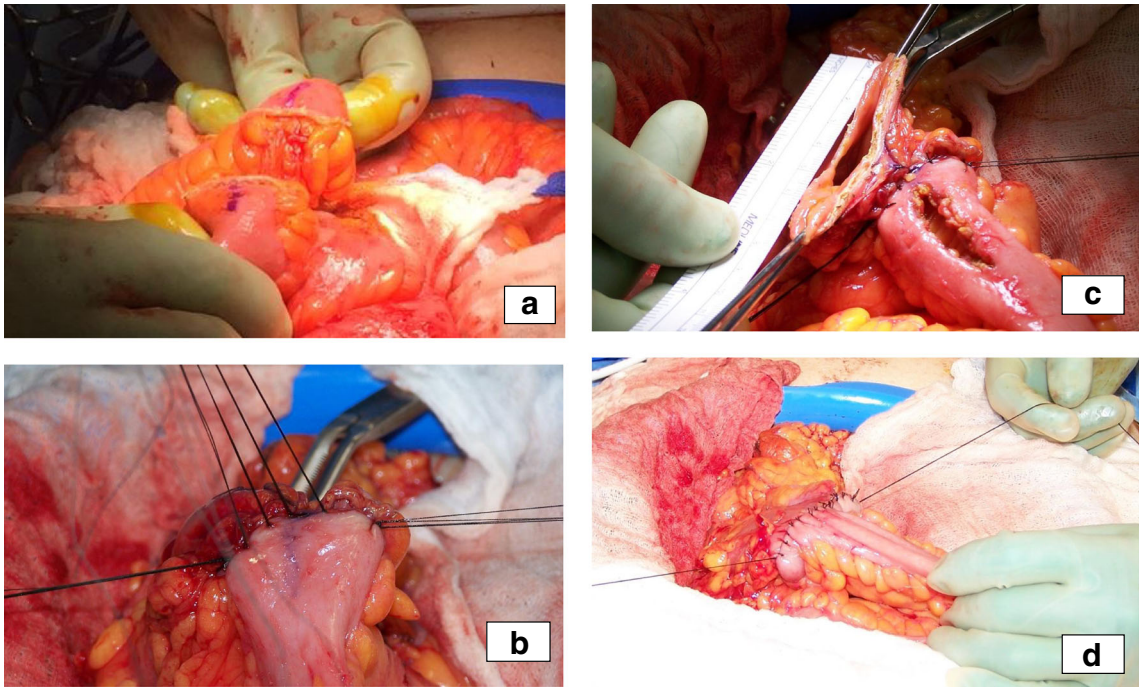

Fig. 3 Kono-S anastomosis. **a** Transected small bowel with planned anastomotic sites marked; **b** cut ends approximated to form central supporting column; **c** bowel opened along anti-mesenteric aspect for planned anastomosis; **d** Complete Kono-S anastomosis. *Photos courtesy of Dr. Alessandro Fichera*

anastomoses should be considered for anastomotic protection via proximal fecal diversion. Diversion will not help prevent risk of disease recurrences in the long term, however. Rutgeerts and colleagues performed proximal diverting ileostomies in patients undergoing ileocolectomy.[31] At 6 months, the neo-terminal ileum was free of macroscopic and microscopic disease in all patients, but 6 months after ileostomy reversal, all patients developed recurrent disease at the anastomosis. A complementary study found that infusion of ileostomy effluent into the excluded anastomosis in these diverted patients was associated with inflammatory changes within 1 week.[29] However, while diversion may not prevent recurrence, it may benefit long-term bowel preservation by decreasing the risk of bowel loss in a setting of a complication. The decision to divert should be individualized with careful consideration of the patient's condition (e.g., hemodynamic stability, nutritional status, medications, etc.).

Minimally invasive techniques can be employed in the treatment of small bowel and terminal ileal CD. These techniques do have short-term recovery benefits. Reassuringly, they are also found to be safe and without increased risk of anastomotic recurrence in the long term. However, even the expert minimally invasive surgeon should prepare the patient for the possibility of open operation if inflammation, adhesions, thickened mesentery, and altered anatomy preclude safe handling, complete inspection, and adequate manipulation of the bowel. Two randomized trials of laparoscopic ileocolectomy found laparoscopic procedures to have longer operative times but reduced morbidity and shorter hospital stays.[32,33] Long-term follow-up of patients enrolled in these trials revealed no difference in rates of intestinal recurrence.[34,35] At a median of 6.7 years after initial operation, analysis of 60 patients randomized to open or laparoscopic ileocolectomy found no difference in rates of surgical recurrence or re-operation for any indication in laparoscopic versus open groups. The laparoscopic group enjoyed better body image and cosmesis, which deserves appreciation in these often young and otherwise healthy patients.[34] A second RCT reported long-term outcomes at an average of 10.5 years following randomization to laparoscopic versus open ileocolectomy.[35] Rates of surgical, clinical, and endoscopic recurrence were similar between groups. Laparoscopic re-operative surgery is also possible in CD patients albeit with longer operative times and increased conversion rates. The available data suggest that laparoscopic surgery does not alter the natural history of CD, but does decrease short-term morbidity and hospitalization.

Alternatives to Resection

Given postoperative complications, frequency of recurrence, and long-term risk of intestinal failure, multiple alternatives to intestinal resection have been proposed. Modern alternatives for the patient with non-resolving small bowel obstruction include strictureplasty and endoscopic dilation.

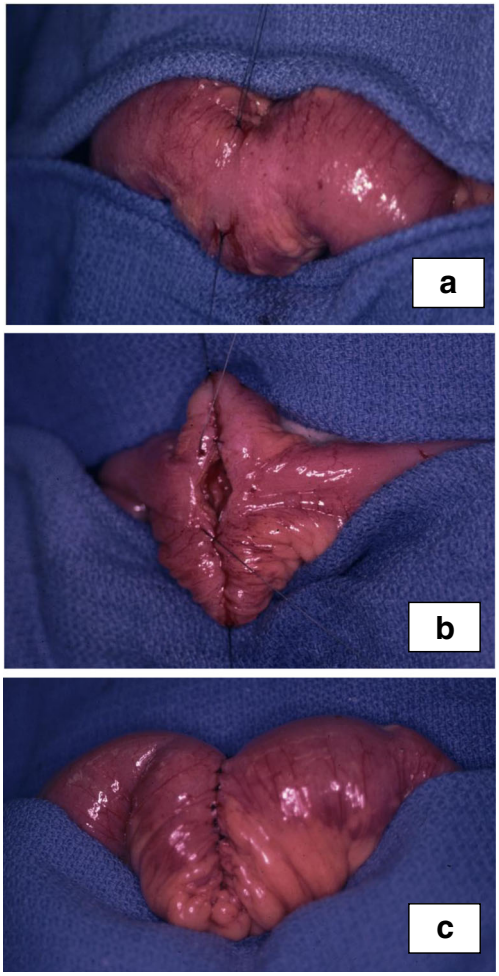

Fig. 4 **a**–**c** Heineke-Mikulicz stricturoplasty. **a** Short segment small bowel stricture delineated. Stay sutures in place. **b** Transected stricture closed transversely. **c** Completed stricuroplasty. *Photo courtesy of Dr. Fabrizio Michelassi*

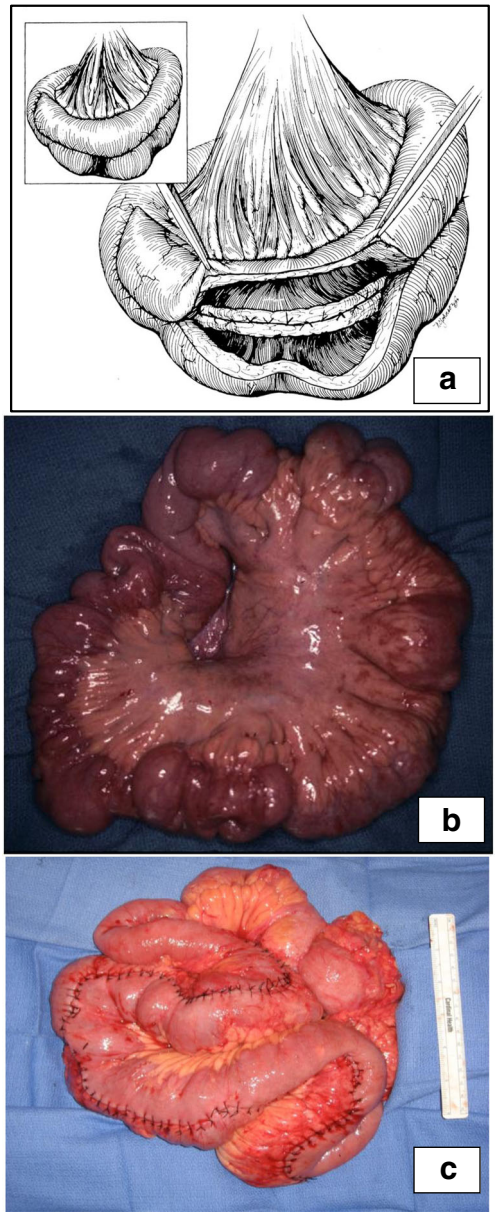

Fig. 5 Isoperistaltic side-to-side strictureplasty. **a** Illustration of strictured small bowel opened longitudinally and anastomosed via long side-to-side anastomosis. **b** Multiply strictured long segment of small bowel in patient with CD. **c** Completed long segment isoperistaltic side-to-side strictureplasty. *Photo courtesy of Dr. Fabrizio Michelassi*

Vigorous debate about the correct operation for CD is nothing new. In the 1930s–1950s, many surgeons elected to bypass or exclude ileocecal CD via the creation of an ileal-transverse colostomy. For the surgeons of this era, who were operating almost always in the emergency setting, resection was often prohibitively risky. Emergency ileo-transverse bypass was most famously performed on Dwight Eisenhower during his presidency, provoking a firestorm of controversy.[36] However, bypass and exclusion operations fell out of favor due to increased long-term rates of recurrence and concerns over development of malignancy in the excluded colon. Today it is of historical interest only, other than in the most unusual of circumstances.

Strictureplasty

Strictureplasty avoids resection and preserves intestinal absorptive capacity in obstructing CD. Traditional strictureplasty techniques including the Heineke-Mikulicz (Fig. 4a–c), Finney, and Jaboulay originated in the upper GI tract as alternatives to morbid resections for stricturing peptic ulcer disease and were first applied to the small bowel in the setting of tuberculosis. These traditional techniques remain the most commonly performed strictureplasties and can be applied to stenoses up to 20 cm in length. Longer strictures can be approached via an isoperistaltic, side-to-side strictureplasty (Fig. 5a–c).[37] In essence, all techniques involve incising the stricture and re-approximating surrounding bowel to preserve intestinal length while enlarging luminal diameter. Strictureplasty is ideally applied to chronically strictured small bowel which would otherwise require extensive resection. It is of particular use in patients already status post

extensive small bowel resection. Strictures are often easily seen, but others can be identified by threading a Foley catheter through the bowel and identifying points of resistance. It can also be applied to gastroduodenal disease, colonic strictures, and anastomotic stenoses, although these applications are uncommon and less well-studied.

Concern over the application of strictureplasty to CD includes safety due to creation of an anastomotic line through macroscopically diseased bowel, recurrence due to diseased bowel left in situ, and failure to identify and resect small bowel adenocarcinoma. Since the application of strictureplasty to CD in the 1970s, large series have found it to be as safe and effective as resection. Pooled analysis of 3529 strictureplasties in 1112 patients found an overall complication rate of 13% in jejunoileal strictureplasty.[38] Anastomotic leak, fistula, and abscess occurred in 4%, similar to reported rates for intestinal resection in CD. Non-traditional and traditional strictureplasties appear to be equivalent in terms of safety.[39] Recurrence after strictureplasty is common; meta-regression revealed a 28% recurrence rate at 5 years.[38] In the series with the longest mean follow-up of 107 months, 54% of patients had developed a symptomatic recurrence and 44% required surgery at 10 year,[40] similar to published rates of recurrence following intestinal resection. Case reports of small bowel adenocarcinoma in strictureplasty sites, including one fatal case, have been described,[40] leading some authors to recommend intra-operative mucosal biopsy. No prospective trials have compared strictureplasty to resection. These data are unlikely to be forthcoming, given the individualized nature of CD and the limited ability to generate a precise preoperative plan. Intra-operative disease patterns and surgeon preference govern the decision to resect or perform strictureplasty, and both techniques may be incorporated into the same operation. The surgeon operating for CD should be familiar with the various strictureplasty techniques in order to preserve bowel and tailor the operation to the patient's particular pathology.

Endoscopic Balloon Dilation

Endoscopic balloon dilation (EBD) is a relatively novel therapy for both disease-related and postoperative strictures. Balloon enteroscopy facilitates dilation anywhere in the GI tract, but to date, most procedures have been described in stenotic ileocolic anastomoses. Multiple small series have demonstrated the safety and short-term efficacy of endoscopic dilation to 15–25 mm. According to one systematic review of 347 patients with 353 symptomatic stenoses, technical success was possible in 86% of patients, mainly with short (<3 cm) stenoses.[41] Surgery was ultimately necessary in 42% of patients over 33 months of mean follow-up, at an average interval of 15 months. Examining small bowel strictures approached by double balloon technique, Hirai and colleagues were technically successful in 52/65 cases.[42] Long strictures (>3 cm) were associated with technical failure. Major complications, including hemorrhage, bowel perforation, and pancreatitis, occurred in 9.2%. At 3 years, 73% of patients were surgery-free, but 47% had undergone re-dilation. Given the high rates of recurrence and re-operation following more traditional interventions for CD, EBD presents an attractive, but early, approach to stenoses in the disease. No study directly compares EBD to strictureplasty, but literature review suggests similar recurrence.[43] Intralesional injection of steroids or infliximab appears safe and may prolong the interval between dilations or surgical intervention.[44,45] Endoluminal stenting with metal or biodegradable stents has been attempted by some authors but at this point has an unacceptable rate of migration and complications.[46]

Prevention of Postoperative Anastomotic Recurrence

Postoperative recurrence can be studied in terms of need for re-operation, clinical symptoms, radiologic features, laboratory biomarkers, and/or endoscopic disease. Re-operation is the most important outcome for patients and surgeons, but ideally, recurrent disease can be identified and treated well before this point. At present, endoscopy is the only reliable method for assessing sub-clinical recurrence, as clinical and radiologic methods lack specificity. Radiologic evaluation is challenging, and formal radiologic scoring systems for disease activity are yet to be routinely employed in research or clinical care. As such, small bowel fluoroscopy, ultrasonography, CT enterography, and magnetic resonance imaging techniques have each demonstrated promise but are yet to be widely adopted. Similarly, biomarkers such as fecal calprotectin are emerging, adjunctive indicators of disease recurrence.[47] Symptomatic, clinical recurrence is subjective, of course. In many studies, symptoms are measured via the Crohn's Disease Activity Index (CDAI),[48] which includes abdominal pain, stool frequency, subjective general well-being, weight, hematocrit, anti-diarrheal medication use, presence of an abdominal mass, and extra-intestinal manifestations into a numerical score. CDAI >200 is generally used as a cutoff for clinical recurrence, but in fact correlates poorly with objective measures of disease and is generally reserved for disease of the colon and terminal ileum.[49] Symptoms may manifest for other reasons (e.g., adhesive partial small bowel obstruction, medication effects, bacterial overgrowth, etc.) or not appear until complications develop. Endoscopy, therefore, has become the gold standard in the identification of postoperative recurrence. Given the endoscopic inaccessibility of much of the small bowel, the majority of studies on postoperative recurrence are drawn from ileocolectomy.

Endoscopic recurrence is common and clinically relevant. In their seminal paper, Rutgeerts and colleagues followed 122 patients after resection of the terminal or neo-terminal ileum and creation of an ileocolic anastomosis.[50] All macroscopic

disease was resected with 5–15 cm margins. The patients underwent ileocolonoscopy within 1 year with anastomotic disease activity scored via the Rutgeerts score (i0-i4 disease with i0 indicating no lesions and i4 indicating diffuse ulceration). The study found that 73% of patients had endoscopic disease at the anastomosis within 1 year. The severity of this inflammation predicted the subsequent disease course. Thirty-five (39%) patients had i0 or i1 disease at 1-year follow-up. These patients did well, with minimal clinical symptoms: 80% had i0 or i1 disease on endoscopy at 3 years and almost all were asymptomatic. In contrast, 39 (44%) had i3 or i4 disease at 1-year follow-up, and 92% of these patients experienced progressive or severe clinical evolution at 3 years. Over 6-year follow-up, 18 of those patients underwent re-resection, 11 for inflammatory complications, and 7 for late stricturing. All 11 patients re-resected for inflammatory disease had i3-i4 disease at first endoscopy and all developed i3-i4 disease at the new anastomosis following re-resection. Regardless of the degree of inflammation, no patient demonstrated healing or improvement of endoscopic disease. In the same study, 22 patients undergoing ileal resection for CD underwent intraoperative inversion of the proximal limb of the anastomosis with visual confirmation of the lack of macroscopic disease and performance of multiple mucosal biopsies prior to ileocolonic anastomosis. Clinical and histologic follow-up of these patients demonstrated that anastomotic recurrence in CD represented de novo disease activity rather than activation of latent microscopic inflammation.

Besides endoscopic disease, other consistent predictors of recurrence include smoking, prior intestinal surgery, fistulizing disease behavior, small bowel involvement, and extensive resection. Studies have demonstrated conflicting results regarding gender, patient age, and disease duration.

Medical Prophylaxis Against Recurrence

As discussed earlier, changing the technique of resection has yet to demonstrate broad reduction in postoperative recurrence, thus generating interest in postoperative medical prophylaxis. Traditional therapies for luminal CD include 5-ASA derivatives such as mesalamine, antibiotics, and thiopurines which have demonstrated modest postoperative utility but limited patient tolerance. Randomized trials are limited by small numbers, relatively short follow-up periods, and high dropout rates. Small trials of TNF-inhibitors have demonstrated large effect sizes relative to these traditional therapies, but their optimal postoperative use remains a matter of study and debate. Multiple RCTs have investigated the effects of the available agents versus placebo or alternate medical regimens and are summarized in Table 3.

Table 3 Randomized trials of postoperative medical prophylaxis

Study	*N*	Control	Treatment	Metric	Follow-up (months)	Outcome	
						Control	Treatment
Brignola 1995[51]	87	Placebo	ASA	Severe ER	12	*56%*	*24%*
Florent 1996[52]	126	Placebo	ASA	ER	3	63%	50%
Lochs 2000[53]	324	Placebo	ASA	CR	18	31%	24%
McLeod 1995[54]	163	Placebo	ASA	CR	72	*41%*	*31%*
Rutgeerts 1995[55]	60	Placebo	Metronidazole	ER	3	75%	52%
Rutgeerts 2005[56]	80	Placebo	Ornidazole	ER	12	*79%*	*54%*
Ardizzone 2004[57]	142	ASA	AZA	CR	24	20%	12%
D'Haens 2008[58]	81	Metronidazole	AZA + metronidazole	Severe ER	12	*44%*	*69%*
Hanauer 2004[59]	131	ASA or placebo	6MP	CR	24	*77%*[a], 58% ASA	*50%*
Nos 2000[60]	39	ASA	AZA	CR	24	37%	36%
Reinisch 2010[61]	78	ASA	AZA	Failure[b]	12	11%	22%
Armuzzi 2013[62]	22	AZA	Infliximab	ER	12	40%	9%
Reguierio 2009[63]	24	Placebo	Infliximab	ER	12	*85%*	*9%*
Savarino 2013[64]	57	ASA/AZA	Adalimumab	ER	24	*83%/65%*	*6%*
Yoshida 2012[65]	31	ASA	Infliximab	ER	36	*79%*	*9%*

Significant differences ($p < 0.05$) indicated in italics

ASA aminosalicylate derivative, *ER* endoscopic recurrence, *CR* clinical recurrence, *6MP* 6-mercaptopurine, *AZA* azathiopurine

[a] 6MP versus placebo significant, but not versus ASA

[b] Failure defined by clinical recurrence or intolerance of medication

5-ASA Derivatives

Compared to other traditional medical therapies, 5-ASA derivatives offer a favorable cost and side effect profile. Meta-analysis of six placebo-controlled RCTs including 652 patients demonstrated a significant, albeit modest, reduction in clinical (RR 0.76, 95% CI 0.62–0.94, NNT = 12) and severe endoscopic (RR 0.50, 95% CI 0.29–0.84, NNT = 8) postoperative recurrence.[66] Most studies used mesalamine 3 g/day as the patient dose. Treatment and follow-up duration were heterogeneous.

Antibiotics

Antibiotics are effective at delaying clinical and endoscopic recurrence but are poorly tolerated by patients. Two trials studied the efficacy of antibiotics in preventing postoperative recurrence. Clinical and endoscopic recurrence were significantly decreased at 1 year after ileal resection in patients taking 12 weeks of postoperative metronidazole versus placebo (52% endoscopic recurrence and 4% clinical recurrence in the metronidazole arm versus 75 and 25%, respectively, in the placebo arm), but the groups were equivalent at postoperative years 2 and 3,[55] and 7 of 30 patients taking metronidazole withdrew from the study. Similar results were obtained in a RCT of ornidazole.[56] Clinical and endoscopic recurrences were significantly reduced by 1 year of antibiotic therapy, but 12 of 38 patients in the ornidazole arm discontinued therapy due to side effects.

Thiopurines

Thiopurines (azathioprine (AZA) and 6-mercaptopurine (6-MP)) demonstrate modest efficacy versus placebo, but patient tolerance is limited. Two studies compared AZA/6MP to placebo.[58,59] Pooled analysis of these trials ($n = 168$) found at 1–2-year follow-up that 48% of patients treated with purine analogues suffered clinical recurrence as compared to 63% of patients treated with placebo (RR 0.74, 95% CI 0.58 to 0.94).[66] Side effects include pancreatitis, leukopenia, GI distress, and elevated liver enzymes.

The superiority of thiopurines to 5-ASA derivatives has not been conclusively demonstrated.[67] Five RCTs have assessed thiopurine versus mesalamine prophylaxis against postoperative recurrence. Reinisch et al. performed a 1-year, double-blinded RCT of AZA versus mesalazine in patients with endoscopic recurrence following ileocolonic anastomosis. They demonstrated equal rates of treatment failure. At 1 year, 9 of 41 AZA patients had developed intolerable adverse drug reactions and 4 of 37 mesalazine-treated patients had developed clinical recurrence. Treatment failure rates of 22% for AZA and 11% for mesalazine were equivalent, $p = 0.19$.[61] Ardizzone et al. enrolled 142 patients and compared clinical (CDAI >200) and surgical recurrence following limited resection or strictureplasty between groups treated over 24 months with AZA or mesalamine. There was no difference in either intention-to-treat or per protocol analysis of either outcome: 12% of AZA- versus 20% of mesalamine-treated patients had a clinical relapse ($p = 0.2$) and 5.8% of AZA- versus 9.9% of mesalamine-treatment patients required repeat operation ($p = 0.5$).[57] The only RCT to employ 6-MP, Hanauer and colleagues randomized 131 patients to 6-MP, mesalamine, or placebo for 24 months with clinical, radiologic, and endoscopic assessment.[59] Ultimately, only 57 patients completed the 2-year protocol. 6MP was superior to placebo, but not mesalamine, for prevention of clinical and endoscopic recurrence. A fourth RCT of AZA versus mesalamine was published in letter format after failing to accrue enough participants at interim analysis.[68] The most recent trial included 51 patients randomized to AZA, mesalamine, or adalimumab.[64] Comparison between the AZA and mesalamine groups found no difference in clinical or endoscopic recurrence at 2 years.

A recent Cochrane meta-analysis of these five RCTs ($n = 425$) found no evidence for the superiority of AZA/6MP over 5-ASA derivatives in terms of clinical or severe endoscopic recurrence and continued the concerns for patient tolerance and adverse events.[66] Note was made of low and very low quality data due to open label studies, small trial size, and heterogeneity.

TNF-Inhibitors

TNF-inhibitors demonstrate early promise in prevention of postoperative recurrence. Small trials with large effect sizes have generated enthusiasm for an opportunity to alter the natural history of postoperative CD. In 2009, Reguiero and colleagues randomized 24 patients to infliximab or placebo following ileal resection.[63] At 1 year, endoscopic recurrence was decreased significantly in the infliximab group (9.1 versus 84.6%, $p = 0.0006$). There was no difference in clinical recurrence at 1 year. Follow-up analysis of these patients was performed at a mean of 6.5 years. After the initial 1-year trial period, almost all patients were treated with infliximab at some point. Those patients who were initially randomized to infliximab had longer intervals of endoscopic remission and longer time to repeat operation (1798 versus 1058 days, $p = 0.04$).[69] Patients on infliximab for >60% of the follow-up period had significantly fewer surgical relapses (20 versus 64.3%, $p = 0.047$).

Two RCTs compared infliximab therapy to mesalamine or AZA. Yoshida et al. randomized 31 patients to 36 months of mesalamine treatment with or without infliximab therapy.[65] Endoscopic recurrence was assessed at 12 months and found to be significantly less likely in infliximab-treated patients (18.8 versus 78.6%, $p = 0.004$). At 36 months, the groups showed no difference in CDAI. A small ($n = 22$) RCT

comparing infliximab to AZA found a substantial, but insignificant, decrease in endoscopic recurrence at 12 months in patients receiving infliximab (9%) as compared to AZA (40%), $p = 0.14$.[62] Clinical outcomes were equivalent.

The fully human monoclonal antibody adalimumab has also been assessed in the postoperative setting. Savarino and colleagues randomized 57 patients to adalimumab, AZA, or mesalamine for 2 years. At the conclusion of the study, significantly fewer patients showed endoscopic relapse in the adalimumab (6.3%) compared to the AZA (64.7%) and mesalamine groups (83.3%).[64] Clinical relapse was also significantly less common in the adalimumab (12.5%) compared to the AZA (64.7%) and mesalamine groups (50%) and quality of life was significantly higher in adalimumab-treated patients.

While trials of TNF-inhibitors in the postoperative setting have been of low quality due to short follow-up, small numbers, open label design, and lack of blinding, the large effect size in comparison to other postoperative regimens and their success in non-operative settings has generated enthusiasm for their adoption postoperatively. Aggressive, early use of TNF-inhibitors has been successful in the non-operative setting. The traditional "step up" strategy of reserving TNF-inhibitor therapy for patients late in their disease course has been demonstrated to be less effective than up-front, "top down" biologic therapy.[70] Additionally, TNF-inhibitor treatment may be more efficacious in patients with shorter duration of disease,[71] a potential argument for its early use. However, up-front biologic therapy for postoperative patients is expensive, risks both short- and long-term adverse events, and over-treats low risk patients who will have prolonged postoperative remission without treatment. Conversely, withholding TNF-inhibitor therapy until clinical recurrence becomes apparent may miss a window of treatment opportunity. Given these concerns, postoperative patients with surveillable anastomoses may be offered a more tailored approach to prophylaxis, guided by endoscopic recurrence.[72] Determining a strategy for active, effective surveillance and implementing appropriate personalized therapy is the real-world challenge facing the surgeon and gastroenterologist.

One recently published study trialed a recurrence-prevention strategy tailored to the individual patient and found this to be more successful than uniform treatment of postoperative patients.[73] De Cruz et al. risk-stratified 174 postoperative patients into high- and low-risk groups and then performed a 2:1 randomization into "active care" versus 'standard care' arms. All patients received 3 months of metronidazole. High risk patients additionally received thiopurine or biweekly adalimumab therapy if thiopurine intolerant. "Active care" patients underwent colonoscopy at 6 months with a step up in therapy if endoscopic disease more severe than Rutgeerts i1 was detected. Step up for low risk patients was thiopurine treatment. For high risk patients already receiving a thiopurine, step up therapy was adalimumab, and for those already on adalimumab, the frequency was increased. Endoscopic disease at 18 months postoperatively was the primary endpoint. Before randomization, 83% of patients were considered high risk based on smoking, history of prior surgery, and penetrating disease phenotype. At the outset of the trial, 28% of patients in the "active care" group and 31% of patients in the "standard care" group received adalimumab based on high risk disease and thiopurine intolerance. At 6 months, 39% of patients stepped up therapy in the "active care" group due to endoscopic recurrence, and after 6 months, 50% of patients in the active care group were treated with adalimumab. At 18 months, endoscopic recurrence >i1 was present in 49% of the active care group and 67% of the "standard care" group ($p = 0.03$). Significantly more patients were in endoscopic remission at 18 months in the active care than in the standard care group (22 versus 7%, $p = 0.03$). There was no significant difference in rates of severe (i3 and i4) endoscopic recurrence, patient withdrawal, or CDAI between groups at 18 months. This well-designed trial is not flawless. Delay of endoscopy to 6 months might miss a window of disease responsiveness. The risk stratification allocating the vast majority of patients to a "high risk" group might have missed a subset of very high risk patients who might have benefited from up-front adalimumab therapy. Furthermore, while many patients in both arms were treated with adalimumab immediately, the study was not powered to assess the important question of whether immediate TNF-inhibitor treatment is superior to step up treatment. Nonetheless, the trial supports an aggressive approach to identifying recurrence and tailoring treatment to individual disease process.

The ideal approach for preventing, detecting, and treating postoperative recurrence is yet to be determined. Surgeon and patient are confronted with the dilemma that established treatments have limited efficacy and patient tolerance, and TNF-inhibitors, while rapidly accruing data, are expensive and have a comparatively limited track record. Further research is required to answer the real-world dilemmas facing the surgeon and gastroenterologist: which drug, which patient, when to initiate, how often to surveil, and how long to treat.

Conclusions

What is the place of surgery within the modern treatment algorithm for CD? Is it the last resort of the patient failing medical therapy or is it first-line treatment? Does it produce early, frequent recurrence, or long-lasting clinical remission? Are its outcomes improved or undermined by biologic therapy? The fact that these critical questions remain unanswered speaks to the challenge in studying and treating an idiopathic disease that runs an unpredictable relapsing and recurring course across the lifetime of affected individuals. The

evidence base to guide the surgeon is composed largely of small, retrospective, single-institution studies that often mutually conflict. The apparent equivalence of two therapeutic options may be due to real clinical phenomena or may reflect selection bias, shorter follow-up for the novel technique, or type II statistical error. Meta-analysis increases the sample size, but cannot overcome bias. In the small bowel in particular, therapeutic efficacy, or lack thereof, is even more difficult to study due to the challenge in endoscopic evaluation.

The multidisciplinary integration and patient risk stratification that is integral to clinical care of CD patients is often lacking in research. Patients in surgical studies often demonstrate variability in medical therapy, and surgical details and outcomes are lacking in medical studies. In this setting, studies such as that of De Cruz et al. represent the vanguard, integrating medical treatment, endoscopic assessment, and risk stratification with surgery.

Decades of research have yielded two bowel-preserving surgical innovations: strictureplasty and minimizing surgical margins. These strategies should be in the armamentarium of any surgeon operating on the small bowel for CD. Adoption of laparoscopy and stapled anastomoses minimizes the surgical burden to the patient and puts more tools in the hands of the surgeon, but may not alter the natural history of the disease. The Kono-S anastomosis holds early promise for reducing anastomotic recurrence. Interventions such as EBD for stricturing disease and PD for abscess are surgery-sparing for some patients, but determining ideal candidates is a work in progress. TNF-inhibitors are powerful tools against recurrence, but questions persist about patient selection, initiation and duration of therapy, cost, and long-term safety and efficacy. Increasingly sophisticated imaging, endoscopy, and biomarkers may hold promise for tailoring therapy to disease activity.

To rigorously study new therapies and diagnostics in surgical patients, clinicians require of researchers a greater focus on randomized, prospective trial designs, multidisciplinary integration, and multi-institutional collaboration. Furthermore, increasing collaboration with basic scientists may identify genetic or molecular markers indicative of aggressive disease, novel experimental models of individuals' gut epithelia,[74] and may prove useful for personalization of biologic or surgical therapy. The nature of CD being idiopathic, variable, recurrent, and chronic makes it challenging to study, but only by incorporating the surgeon's understanding of these difficulties and nuances into rigorous scientific study, will this challenge be surmounted.

Compliance with Ethical Standards

Conflict of Interest L.B., L.H.M., A.M.K., K.A., P.E.W., and R.S. have no disclosures.

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