Mastery of IBD Surgery

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Dr. Fleshner
I dedicate this book to my three kids (Alex, Niki and Jake) and my wife (Shelley). The four of you will always be my everything in life.

Dr. Hyman's Dedication:
With boundless love to my sons EJ and Seth, the two finest men I know.

"Bear in mind that the measure of a man is the worth of the things he cared about"

Dr. Strong
My contributions are dedicated to my wife and best friend, Mary, and daughters, Mallory and Martha, who are my greatest source of joy.

—Marcus Aurelius

Preface

The surgeon managing a patient with inflammatory bowel disease (IBD) must be thoroughly grounded in key management principles to achieve optimal outcomes and provide an individualized treatment plan. The IBD surgeon commonly considers many factors to assess when it is or not appropriate to operate and the best operation for each unique patient. The IBD surgeon considers many factors such as nutritional status, immunomodulatory medications and degree of local sepsis when deciding on the timing and extent of surgery and how the patient may be optimized to make surgery safer. Adequate (but not excessive) imaging, properly interpreted, is often critical to preoperative planning. As legendary UCLA basketball coach John Wooden once pointed out: "failing to prepare is preparing to fail."

An expert pool player not only converts the shot on the table, but engages with a considered touch to ensure the cue ball ends up in optimal position for the next attempt. Similarly, the IBD surgeon should understand the natural history of the disease and anticipate what is likely to be coming next. For example, an ileocolic anastomosis performed for fistulizing disease should not be left in contact with a bared duodenum. In UC, the expert IBD surgeon must have an armamentarium of techniques to get themselves out of trouble when there is a problem with the pouch-anal anastomosis. IBD management is a team sport; surgeons should work hand in hand with GI colleagues, in an environment of collaboration, communication and mutual respect. Our patients deserve this and have a right to expect it.

We are grateful to our teachers, the master surgeons who inculcated a love and appreciation of IBD surgery and let us behind the curtain, showing how a solid understanding of the disease processes can enable a thoughtful approach for each patient. We hope that our colleagues, trainees and students can benefit from the collective experience and world-class expertise of the international authorities who have been kind enough to share their expertise in the chapters to follow.

Finally, we pay particular tribute to the late Dr. Victor Fazio, Dr. David J Schoetz and Dr. Randy Steinhagen who have had such a powerful influence on our careers and our commitment to the care of the patient with IBD.

Chicago, IL — Neil Hyman
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Contents

Nutritional Repletion in the Surgical Patient

1

Tarik Yuce and Michael F. McGee

Introduction

Patients with Crohn's disease (CD) and ulcerative colitis (UC) are prone to high rates of malnutrition [1]. There are several factors inherent to inflammatory bowel disease (IBD) that affect nutritional status including hypermetabolism associated with chronic inflammation, anorexia, and malabsorption [2] as well as intestinal obstruction and ileus. Assessing malnutrition in this patient population can be challenging as there is no gold-standard test available to evaluate a patient's nutritional status [1]. However, managing the preoperative nutritional status of IBD patients is of critical importance due to the high risk of postoperative complications associated with nutritional deficits.

Patients with IBD requiring surgical intervention often present with multiple signs of malnutrition, including anemia, electrolyte abnormalities, low levels of surrogate nutritional markers (albumin, prealbumin, transferrin), and infection [3]. All of these have been shown to increase the risk of poor surgical outcomes [4]. Attempting to augment IBD patients' nutritional status, via enteral or parenteral routes, prior to operative intervention may serve as a key step in improving postoperative outcomes. The role of preoperative parenteral nutrition (PN) versus early surgery in IBD patients requiring surgery is investigated below.

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Table 1.1 PICO table

Patients	Intervention	Comparator	Outcome
Patients with inflammatory bowel disease	Preoperative parenteral nutrition	Early surgical intervention	Postoperative complications

Search Strategy

A literature search of PubMed, MEDLINE and the Cochrane Database of Collected Research was completed to find English-language publications associated with Crohn's disease, ulcerative colitis, nutritional status, parenteral nutrition, and postoperative outcomes from 1988 to 2018. Key search terms used were: "inflammatory bowel disease", "nutritional status," "total parenteral nutrition," "postoperative outcomes." "Crohn's disease," and "ulcerative colitis." Studies that were non-English, or failed to compare PN to early surgery were excluded as well as those involving oral nutritional supplements, intravenous vitamin and mineral infusions, and postoperative nutritional therapy. Preference was given to randomized controlled trials, large randomized observational studies, cohort studies and meta-analyses. The references of each study were analyzed to search for additional articles that may be suitable for inclusion (Table 1.1).

Results

A thorough review of the literature showed a paucity of studies examining the role of preoperative PN in IBD patients. Aside from one meta-analysis, all identified studies examining the role of PN in IBD patients are retrospective, nonrandomized, case series and cohorts. The studies that addressed the role of preoperative PN in IBD patients are detailed below.

Jacobson [5] retrospectively studied the effect of preoperative PN on the rate of 30-day postoperative complications in patients with CD undergoing bowel resection. PN patients (n = 15) received a mean of 45 days (range 18–90) of preoperative PN. Controls (n = 105) were matched 7:1 by disease location, patient sex and age. The author found PN patients were associated with a significant reduction in early postoperative complications. PN patients also experienced an increase in weight and serum albumin concentrations during the preoperative period. Given these findings, the author concluded that a course of preoperative PN should be considered for patients with CD who require bowel resection. The largest limitation of the study arises from an assignment bias since the authors did not include steadfast indications for preoperative PN. Moreover, small sample size, variations in PN formulation and duration, and lack of information regarding the nutritional status of the control group further limit broader applicability of the study findings.

A retrospective review by Salinas et al. [6] found that UC patients receiving at least 7 days of preoperative PN had higher rates of postoperative complications

when compared to those undergoing early surgery. However, when the authors excluded central line related complications, there was no difference in postoperative complications between the two groups. Logistic regression analysis showed that TPN use, even when accounting for perioperative risk factors, was associated with a non-significant trend toward increased rates of complications compared to non-TPN patients (postoperative complication OR = 1.42). Given this information, the authors concluded that there is no indication for routine use of preoperative PN in patients with UC compared to expeditious total abdominal colectomy. The authors acknowledged there may be an empiric role of PN for the most severely malnourished patients, but recognize their study does not support such a practice. Limitations of this study include lack of steadfast inclusion criteria for PN use, unknown PN composition, and variable PN duration.

Grivceva Stardelova et al. [7] retrospectively compared a heterogeneous group of CD and UC patients receiving preoperative PN (n = 29) to controls (n = 61) before undergoing unspecified surgery. PN patients trended toward an improvement in preoperative Crohn's Disease Activity Index (CDAI) scores and BMI, although neither finding reached significance. Additionally, there was no difference in length of stay between the two groups. The authors argue that there may be a role for preoperative PN in patients with severe disease and malnutrition, while acknowledging the many limitations of their study.

Yao et al. [8] studied severely malnourished patients (BMI < 15 kg/m^2) with CD who received PN (n = 16) versus those who received intravenous fluids (n = 16) prior to surgery. There was no significant difference in postoperative complications; however patients in the PN group experienced a significant increase in BMI and a higher rate of convalescence (returning to work) within 6 months. Limitations of this study include small sample size, lack of randomization, and limited and inconsistent description of methods, results, and statistical data.

Lashner et al. [9] retrospectively examined the effect of preoperative PN on patients with CD undergoing small bowel resection, ileocecectomy and segmental/total colectomy. Despite having more extensive disease, PN patients had a shorter segment of bowel resected in small bowel and ileocecectomy groups at the expense of a longer hospital stay. PN use was not associated with outcome differences in segmental or total colectomy patients. Study limitations include patient selection bias for PN and inability to determine the minimum effective duration of PN.

Li et al. [10] authored the largest study to date investigating preoperative PN in which 498 patients underwent 708 intestinal surgeries for Crohn's disease. The authors retrospectively stratified patients based on preoperative immunosuppressant exposure and PN use, and then analyzed surgical outcomes. A 4 week period of preoperative PN afforded patients a longer preoperative immunosuppressant-free interval and was associated with reductions in urgent surgery and fecal diversion when compared to non-PN groups. Notably, preoperative PN was associated with decreases in both infectious and non-infectious postoperative complications.

Another analysis by the same author [11] examined a 123 patient subset of the above study limited to CD patients with enterocutaneous fistulas, revealed that 3 months of preoperative TPN increased patients' serum albumin levels and

decreased C reactive protein at the time of surgery when compared to controls. Moreover, rates of postoperative intra-abdominal septic complications was significantly reduced in PN patients when compared to controls (3.6% vs. 17.6%, OR = 5.7, p = 0.02). Both studies are limited by their retrospective nature, heterogeneity of resection types and locations, and assignment biases arising from lack of randomization.

A recent meta-analysis performed by Brennan et al. [12] examined the differential surgical outcome effects of preoperative PN in CD patients. In a pooled group of 5 studies comprised of 280 patients, there was a trend toward lower complications in PN patients when compared to non-PN patients; however differences were not significant (15% vs. 24.4%, OR = 0.65, p = 0.43).

Study	Patient population	Outcome classification	Results	Quality of evidence
Jacobson [5]	CD patients undergoing surgery, n = 120	Postoperative complications	Reduced postoperative complications in PN group	Low
Salinas et al. [6]	UC patients undergoing surgery, n = 235	Postoperative complications	Increased postoperative complications in PN group due to line infections	Low
Grivceva Stardelova et al. [7]	IBD patients undergoing surgery, n = 90	CDAI score, preoperative BMI, length of stay	Preoperative BMI and CDAI/AI scores improved in PN group, no difference in postoperative length of stay	Low
Yao et al. [8]	IBD patients with BMI <15 kg/m^2 undergoing surgery, n = 32	Postoperative complications, BMI	Preoperative BMI increased in PN group, no difference in postoperative complications	Low
Lashner et al. [9]	CD patients undergoing surgery, n = 103	Length of bowel resection, duration of hospital stay	PN increased length of stay, but decreased length of small bowel resection, no difference for colectomy patients	Low
Li et al. [10]	CD patients undergoing surgery n = 498 patients, 708 surgeries	BMI, postoperative complications, re-admission, stoma creation rate	PN patients had a longer immunosuppressant-free preoperative interval, required less emergent surgery, decreased stoma creation, and had less infectious and non-infectious complications	Low
Brennan et al. [12]	Meta-analysis of CD patients undergoing bowel resection with or without preoperative PN, n = 280 patients	Postoperative outcomes	PN patients had a trend toward lower complication rates but failed to reach significance	Moderate

Recommendations

Malnourished patients with small bowel or ileocolic Crohn's disease requiring resection likely benefit from preoperative PN compared to early surgery (Evidence: low; Recommendation: weak). Malnourished ulcerative and Crohn's colitis patients requiring simple colectomy likely benefit from prompt colectomy without anastomosis compared to preoperative PN (Evidence: low; Recommendation: weak).

The literature regarding PN versus early surgery for IBD patients lacks the robust data provided by randomized controlled trials and hinders the ability to make strong recommendations. The available studies over the past 30 years, while low in quality, show that delaying surgery for selected IBD patients in lieu of preoperative PN may reduce postoperative complications. Cost, patient preference, and long-term follow-up data are strikingly absent. Moreover, the utility of preoperative PN in the contemporary setting of modern-day IBD medicines, minimally invasive surgery, and enhanced recovery programs is untested.

Personal View

It is logical to believe that better nourished patients fare better than malnourished patients; however the retrospective studies only weakly support delaying IBD resections for preoperative PN; and this is conditional based upon etiology and location of the diseased segment. Several hindrances challenge interpretation of the literature. Foremost, variation arising from disease location can be substantial between UC and CD, which introduces significant heterogeneity in studies and obfuscates treatment effect. Since studies are small, authors are forced to pool together patients to please statisticians. But study cohorts can be quite diverse with regard to disease severity, chronicity, and location. Second, most retrospective studies lack steadfast inclusion criteria for preoperative PN treatment rendering treatment allocation discretionary. Lastly, most studies also lack patient nutritional stratification, so it is plausible to believe that patient selection and assignment biases may play just as large of a role in influencing outcomes as PN treatment does.

Nonetheless, where there is smoke, there is fire. Despite relatively low quality data and only a glimmer of evidence-based guidance in IBD, several non-IBD studies have shown a beneficial role of preoperative PN that may be extrapolated to IBD surgery. The Veterans Affairs Total Parenteral Nutrition Cooperative Study Group trial found a 7–15 day course of pre-operative PN reduced postoperative complications from 43% to 5% for severely malnourished patients undergoing laparotomy and non-cardiac thoracotomy [13]. In contrast, for mildly malnourished patients, the overall complication rate was similar regardless of PN use, and infection-specific complications was actually higher in PN patients (14.1% vs. 6.4%). However, the study comes from an era where the detrimental effects of hyperglycemia was not well understood and overfeeding was commonplace. A dated, but thorough, review of over 1300 pooled malnourished surgical patients showed preoperative PN reduced the risk of postoperative complications by an estimated 10% [14].

The authors espouse a judicious policy of an approximately 7 day course of preoperative PN for severely malnourished small bowel CD patients intolerant of enteral supplementation, commensurate with recent European societal guidelines [15]. Patients with severe nutritional risk have been defined as those with at least one of the following criteria: (a) weight loss > 10–15% within 6 months (b) BMI < 18.5 kg/m^2 (c) serum albumin < 3.0 g/dL absent hepatic or renal dysfunction or (d) Subjective Global Assessment (SGA) Grade C or Nutrition Risk Screening Score > 5 [15]. Regardless of nutritional state, ulcerative colitis patients typically will undergo timely colectomy, ileostomy, and rectal stump closure without preoperative PN since minimally invasive techniques are typically successful and anastomoses are avoided. The authors do not typically perform restorative proctocolectomy in the malnourished state and instead advocate for a 3-stage procedure. Patients with isolated Crohn's colitis amenable to laparoscopic colectomy are typically not offered preoperative PN, and instead undergo prompt minimally invasive surgery and liberal use of fecal diversion. Patients with complicated colonic Crohn's disease (e.g. fistula, abscess, phlegmon) that requires extensive surgery or runs the risk of collateral organ damage may be considered for preoperative PN on a conditional basis that accounts for surgical urgency, immunosuppressant use, and other patient comorbidities.

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Preoperative Bowel Prep

2

Benjamin D. Shogan

Introduction

Preoperative preparation of the colon prior to surgical resection was first introduced in 1966 [1]. The strategy employs the use of a mechanical bowel prep with or without oral antibiotics to reduce the bacterial biomass in the intestine as an empirical method to decrease infectious complications.

The literature on the utility of preoperative bowel prep is dominated by patients undergoing surgery for malignancy or benign disease, rather than patients undergoing surgery for inflammatory bowel disease (IBD). Patients requiring surgery for IBD represent a specific subset of patients with a relatively high risk of postoperative complications [2]. Additionally, preoperative anatomic considerations such as intestinal stenosis or enterocutaneous fistulas, and previous infections with or without opportunistic microorganisms often associated with IBD patients will give the IBD surgeon pause when prescribing a preoperative prep. In this chapter, we will review the available data on the utility of mechanical bowel prep and preoperative oral antibiotics in surgical patients, paying particular attention to the unique considerations for patients undergoing surgery for IBD.

Search Strategy

We performed a comprehensive literature search of Medline, PubMed, and Google Scholar to identify all of the English-language publications related to preoperative bowel prep and postoperative complications between 1970 and 2018. Key search terms included: ('mechanical bowel prep' or 'MBP' or 'preoperative bowel prep')

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Table 2.1 PICO table

Patients	Intervention	Comparator	Outcome
IBD patients requiring surgery	1. Mechanical bowel preparation 2. Oral antibiotic preparation	No bowel preparation	Post-op complications

and (‘oral antibiotics’ or ‘preoperative antibiotics’ or ‘preoperative PO antibiotics’) and (‘colorectal’ or ‘colorectal surgery’) and (‘inflammatory bowel disease’ or ‘IBD’ or ‘ulcerative colitis’ or ‘Crohn’s’). References of each relevant publication were reviewed. Because of the paucity of studies investigating the effect of bowel prep specifically on IBD patients, each article was reviewed to determine if subset analysis was conducted for the IBD cohort. Retrospective, prospective, observational, and randomized studies were included (Table 2.1).

Results

Mechanical bowel prep (MBP) and oral antibiotics are the two primary modalities in which the practicing surgeon can prepare the bowel for surgery. Investigators have studied the effects of MBP and oral antibiotics independently as well as in a combined approach to reduce infectious complications, particularly surgical site infections (SSI) and anastomotic leak.

Mechanical Bowel Prep Alone

MBP using a purgative, given via enema or orally, is used to rid the colon of its fecal burden preoperatively. Despite its ubiquitous use for generations, the utility of using MPB alone in preventing complications is largely unfounded**.** Since 1990, at least fifteen randomized controlled trials (RCT), encompassing all colorectal operations for all indications, have shown that preoperative MBP does not significantly reduce the incidence of superficial or deep SSI, or anastomotic leak in patients undergoing elective colorectal surgery [3–16]. The Cochrane Collaboration has published four updates on this topic, most recently in 2011 encompassing 18 trials, concluding that prophylactic MBP given orally or via enema is of no value to patients [17–20].

Most recently in 2018, a meta-analysis analyzed 23 RCT’s and 13 observational trials, including a total of 21,568 patients undergoing colorectal surgery for all indications [21]. Similar to the previous reviews, they reported that MBP was not associated with any significant differences in SSI, anastomotic leak rate, intra-abdominal infections, or hospital length of stay.

There is also evidence that the use of MBP may cause harm. In addition to patient discomfort while taking the purgative, the diarrhea from MBP can cause dehydration, electrolyte dysfunction, and is associated with postoperative intestinal dysmotility [8, 22, 23]. These concerns are particularly important in IBD patients, who

are often at baseline malnourished from their chronic disease. Further, incomplete MBP may actually cause increased stool spillage at surgery, resulting in increased deep pelvic infections [24].

While these results are overwhelmingly compelling, the majority of the included patients in these studies underwent surgery for malignancy or diverticular disease. Of the 36 studies in 2018 meta-analysis, only 12 studies included IBD patients and of these, IBD patients generally made up only 5% of the study group. In fact, to the best of our knowledge, there has been no RCT trials and only a few observational studies specifically investigating the impact of MBP alone in IBD patients.

Review of the few investigations that include only IBD patients provide contradictory conclusions. Barker et al. in 1971 found that patients undergoing a segmental or total colon resection for either Crohn's colitis or ulcerative colitis with complete emptying of their colon after a MBP were significantly less likely to get an SSI, compared to patients found to have residual intraluminal stool [25]. More recently, Lesalnieks et al. retrospectively reviewed 549 patients who underwent elective colorectal resections in patients with Crohn's disease [26]. They found that intraabdominal septic complications (anastomotic leak, intraabdominal abscess, peritonitis) was reduced from 26% to 12% in patients whom received a MBP. When stratified by disease phenotype, MBP did not have an effect on patients with stricturing disease, but did have a beneficial effect in reducing infectious complications in patients with penetrating disease (12% vs. 26%; $p = 0.003$) and colonic resection for colonic Crohn's disease (14% vs. 32%; $p = 0.043$). The authors commented that the number of patients in the stricturing cohort may have been too low to detect a significant difference. Alternatively, it maybe that given the potential obstructive symptoms in patients with stricturing disease, they were unable to complete the MBP thus limiting its effect.

While these results are intriguing, and may represent insight into how MBP differentially effects patients with IBD, the retrospective nature of this study severely limits the confidence of the results. The MBP group consisted mostly of patients operated between 1992 and 2004, whereas nearly all surgeries in the no MBP were performed after 2005. As IBD surgery has evolved over the last three decades, this creates significant demographic differences between the two cohorts; the patients in the MBP group had significantly more open surgeries, were more likely to be on high-dose steroids, and less likely to be using a TNF-alpha inhibitor.

Preoperative oral Antibiotics with or without MBP

While the benefit with MBP alone is not supported by the literature, the addition of preoperative oral antibiotics is more compelling. In 1973, Nichols et al. reported that the addition of oral neomycin and erythromycin to a MBP completely prevented SSI in patients undergoing colon surgery, compared to a 30% incidence of SSI in the MBP alone cohort [27]. Shortly after his landmark paper, a handful of studies published in the 1970s confirmed that oral antibiotics protected against SSI, making its use routine [28–31].

In the decades that followed, there seemed to be a steady trend to omit the oral antibiotics and focus exclusively on IV antibiotic prophylaxis. However, there has been a renewed interest in the addition of oral antibiotics (most commonly neomycin, erythromycin, and/or metronidazole) to the preoperative bowel prep regimen. A meta-analysis compiled 16 RCT's and a total of 2669 patients comparing the addition of oral antibiotics to MBP [32]. Patients undergoing surgery with a diagnosis of IBD were in the minority, encompassing only 129 patients (4.8%) of the total cohort. Regardless, the authors reported that oral antibiotics significantly decreased the risk of SSI (RR: 0.57; 95% CI: 0.43–0.76), but showed no effect on the risk of anastomotic leak (RR: 0.63; 95% CI:0.28–1.41).

More recent RCT's have offered conflicting results. In an noninferiority study, Yamaguchi et al. found that intravenous perioperative prophylaxis alone is not inferior to combined prophylaxis with preoperative oral kanamycin and metronidazole in patients undergoing laparoscopic colon surgery for colorectal cancer [33]. In a more recent RCT, Anjum et al. found that oral metronidazole and levofloxacin conferred a significantly decreased risk of SSI and anastomotic leak in 190 patients undergoing colon surgery [34]. Although a subset analysis was not conducted, patients with the diagnosis of IBD represented 20% of the cohort.

Database studies have also favored the use of oral antibiotics. Using the American College of Surgeons National Surgical Quality Improvement (NSQIP) database, 8442 patients undergoing elective colorectal resection were queried [35]. MBP with oral antibiotics was associated with reduced anastomotic leak (OR = 0.57, 95% CI: 0.35–0.94), SSI (OR = 0.40, 95% CI: 0.31–0.53), and postoperative ileus (OR = 0.71, 95% CI: 0.56–0.90). While there were no significant differences in demographics, the authors did not report how many patients were undergoing surgery for IBD. Using NSQIP data from the similar time period, a different group investigated the effect of the addition of oral antibiotics to MBP stratified by procedure [36]. They found that MBP plus oral antibiotics showed a benefit in the reduction of SSI infections that was most significant in patients undergoing ileocolic resections compared to other procedures, potentially a proxy for patients undergoing surgery for IBD.

Shwaartz et al. focused a NSQIP database study of 3679 patients undergoing colorectal surgery only for IBD [37]. After controlling for demographics, clinical, and procedural variables, MBP plus oral antibiotics was protective against ileus, anastomotic leak, SSI, deep space infection, and septic shock. MBP alone or oral antibiotics alone did confer a benefit for any postoperative complication. Unfortunately, they did not do a subset analysis on the effect of each regimen stratified by the type of surgical procedure.

The fact that the addition of oral antibiotics to MBP reduces complications, while MBP alone has no efficacy, begs the question of whether oral antibiotics are the critical component of combined preoperative bowel preps. While it has long been thought that orally administered antibiotics would only be effective if the bowel is first cleansed of its stool burden, there is little known regarding the potential benefits of oral antibiotics alone. To shed light on this topic, in 2017 Garfinkle et al. utilized the NSQIP database to analyze the effects of oral antibiotics alone in

40,446 patients undergoing elective colorectal surgery [38]. IBD patients were in the minority, comprising only 10.2% of the entire cohort. Oral antibiotics alone offered a protective benefit for SSI (OR = 0.63; 95% CI: 0.45–0.87), anastomotic leak (OR = 0.60; 95% CI: 0.34–0.97), and ileus (OR = 0.79; 95% CI: 0.59–0.98). Oral antibiotics with MBP offered no superiority compared to oral antibiotics alone. These results are similar to a retrospective review of 9940 Veterans Affair patients, showing that the use of oral antibiotics alone was associated with a 67% decrease in SSI (OR = 0.33, 95% CI: 0.21–0.50) whereas oral antibiotics plus MBP was associated with a 57% decrease in SSI's (OR = 0.43, 95% CI: 0.34–0.55) [39]. This line of inquiry is in its infancy and these studies have set the stage for multiple active RCT's containing an oral antibiotic only cohort to help determine the role of oral antibiotics without MBP in a preoperative prep regimen [40, 41].

The efficacy of oral antibiotic alone to prevent complications is highly relevant to the practicing IBD surgeon. It seems likely that patients would benefit from oral antibiotics alone even when undergoing procedures in which the colon is already resected or diverted (i.e. diverting loop ileostomy takedown, ileal pouch anal anastomosis; IPAA). Further, if oral antibiotics are effective alone, surgeons could selectively forego MBP in patients that are at high risk of intolerance of MBP such as those with stricturing or penetrating disease. While almost nothing is known about the efficacy of oral antibiotics in these groups, Oshima et al. randomized 195 patients undergoing open IPAA to receive preoperative kanamycin and metronidazole verses no antibiotics [42]. They reported that the addition of oral antibiotics significantly decreased the SSI rate compared to those patients not receiving antibiotics (6.1% vs. 22.4%; p = 0.0024). Further, on multivariate analysis lack of oral antibiotics was independently associated with the development of SSI (OR 0.178; 95% CI 0.057–0.552). Anastomotic leak was not assessed between the groups. Further studies are needed, but extrapolation of these results to other procedures such as diverting loop ileostomy takedown are intriguing.

Finally, the benefit of oral nonabsorbable antibiotics has to be weighed against the potential for bacterial resistance and opportunistic infections. In most studies, the addition of oral antibiotics to a MBP has not been shown to increase the incidence of *C. diff* infections, and contrary to expectations has been associated with a decreased risk [43]. In the previously mentioned study by Oshima of ulcerative colitis patients, oral antibiotics alone did not influence *C. diff* rates concluding that it can be safely given (Table 2.2).

Recommendations Based on Data

While the retrospective study by Lesalnieks et al. showing a benefit of MBP alone in IBD patients is of interest, the abundance of evidence from high quality RCT's, albeit with limited inclusion of IBD patients, strongly refutes the benefit for the use of MBP alone. Thus based on the available data, we do not recommend the routine use of MBP alone as a preoperative strategy. *Strength of recommendation: strong, level of evidence: high*

Table 2.2 Studies investigating preoperative bowel prep specific to IBD patients

Study (year)	Patients Studied	Study design	Intervention (*n*)	Outcome	Quality of evidence
Lesalnieks (2018)	CD	Retrospective	MBP (232) No MBP (262)	Intraabdominal septic complications 12% MBP vs. 24% ($p < 0.001$)	Low
Shwaartz (2016)	CD (70.8%) UC (29.2)	Retrospective	No prep (1563) MBP alone (791) Oral antibiotics (325) MBP + oral (1000)	MBP + oral antibiotics had lower rates of SSI, anastomotic leak, ileus ($p < 0.05$) No prep, MBP alone, oral antibiotics alone had similar rates of complications	Moderate
Tsutomu (2013)	UC	RCT	Oral antibiotic (100) No oral antibiotic (100)	SSI 6.1% oral antibiotic vs. 22.4% (p = 0.004)	High

There is high quality evidence for both non-IBD and IBD patients that the utilization of preoperative oral antibiotics in combination with a MBP on the day before surgery is beneficial in reducing postoperative complications. Because the majority of investigations combine different classes of antibiotics, a specific regimen cannot be strongly recommended. Thus based on the available data, we recommend the routine use of preoperative MBP and nonabsorbable oral antibiotics for patients undergoing bowel resection for IBD.

Strength of recommendation: strong, level of evidence: high.

There is limited moderate and high quality evidence that preoperative oral antibiotics alone is beneficial in reducing postoperative complications. Thus based on the available data, we recommend oral antibiotics alone in IBD patients that might not tolerate a MBP or if there colon is resected or diverted. *Strength of recommendation: weak, level of evidence: low.*

Personal View

The lack of efficacy of MBP in preventing infectious complications is supported by biological data. Low-tech culture dependent methods have shown that MBP alone does not influence the bacterial counts within stool, nor reduce the mucosal colonization of the common GI organisms *E. coli* or *Bacteroides* [15, 44]. On the other hand, 48 h of oral neomycin and metronidazole significantly decreases *E. coli* and *Bacteroides* recovered from feces [44]. Particularly for anastomotic leak, animal models have lent support to oral antibiotics. Even in the presence of ischemia, oral antibiotics completely protected against anastomotic leak in dogs, whereas MBP alone had no effect on intestinal healing in an experimental rat model [45, 46].

While it has generally be taught that decreasing infection complications following bowel prep is simply a consequence of the reduction of the bacterial fecal load, this simplistic view has been outweighed by the recent explosion in advances in microbial sciences demonstrating the enormous diversity, redundancy, and functional importance that resides within the intestinal microbiome. Advanced non-culture based techniques (i.e. 16 s rRNA sequencing) have let us gleam the first insights into the influence of preoperative interventions on intestinal communities. Recent studies demonstrate that bowel prep is associated with a reduction in certain potentially pathogenic phyla (i.e. Firmicutes) while at the same time causing a reduction in potentially beneficial organisms (i.e. Lactobacillaceae) [47–49]. Because we do not fully understand the bacterial mediated mechanism of SSI, anastomotic leak, or ileus, we are currently unable to predict how this balance actually impacts potential offending organisms.

Therefore, empirical use of decades old bowel prep studies betrays the complexity of the microbial communities and their vast functional diversity in the gut. Each patient can maintain their own unique (yet overlapping) compliment of bacterial species, whose metabolism can influence immune, endocrine, and metabolic functions. This personalized microbial milieu means that the effects of a preoperative prep are likely patient dependent, associated with their preoperative microbiome, and therefore not generalizable across populations [48]. It may stand to reason that in selected patients, MBP and/or antibiotic administration may inadvertently enrich pathogenic organisms that cause postoperative complications, whereas in others it eradicates them. This is especially true in the IBD population who at baseline contain an altered microbiome. Malnourishment, high-dose steroids, and chronic antibiotics, all common in IBD patients, can each have an independent effect on the microbiome; how these variables influence the efficacy of a bowel prep is unstudied. Trials that not only analyze clinical outcomes after bowel prep, but that seek to understand the compositional and functional changes of the microbiome are critical as a path forward in developing the next generation bowel prep.

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3 Extended Venous Thromboembolism Prophylaxis After Surgery for Inflammatory Bowel Diseases

Chun Hin Angus Lee and Stefan D. Holubar

Introduction

Surgical patients with inflammatory bowel disease (IBD) bring unique risk factors for venous thromboembolism (VTE), including Virchow's triad of inflammation-associated hypercoagulability, stasis (ex. bed-rest from fatigue between frequent trips to the bathroom, prolonged operations), and the obvious trauma of surgery [1–3]. In this population, we are all aware that VTE includes not only lower extremity deep vein thrombosis (DVT) and pulmonary embolism (PE), but for IBD patients we must also keep in mind upper-extremity DVT related to central access for enteral nutrition, post-operative portomesenteric vein thrombosis (PMVT), and rarely cerebral venous sinus thrombosis [4, 5]. All of these can present silently or symptomatically, both before and after surgery.

According to "Big Data" studies, the average risk of post-operative VTE after surgery for IBD is approximately 4%, likely higher for ulcerative colitis (UC, 4–6%), and lower for Crohn's disease (CD, 2–3%) [6–9]. At a national level, this translates to >40,000 surgical IBD patients in the United States who develop VTE per year, with an estimated annual added cost of over $17 million dollars per year [10]. In addition to the financial burden posed to healthcare system in relation to readmission and treatment, patients also can suffer from the short- and long-term sequelae of VTE and its treatment, including acute mortality (from PE), therapeutic anticoagulation (AC) related bleeding complications including intracranial hemorrhage, and lower extremity post-thrombotic syndrome. Thus, many IBD surgeons find the above rates unacceptable, and several strategies may be used to decrease the rate of post-operative VTE. The first two are early detection and risk-stratification, both of which we will briefly discuss. The third strategy, which is the focus of this

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Table 3.1 PICO questions

P (Patients)	I (Intervention)	C (Comparator)	O (Outcomes)
IBD patients requiring major abdominopelvic surgery	Extended VTE prophylaxis	Standard VTE prophylaxis	Venous thromboembolism complications, bleeding complications, costs

chapter, is extended post-operative, specifically post-discharge, chemoprophylaxis. We will review the literature supporting the efficacy of extended prophylaxis, bleeding associated with various medications, and the costs and cost-effectiveness of various strategies.

Search Strategy

Relevant PICO (Population, Intervention, Comparator, Outcome) questions were generated (Table 3.1). A comprehensive literature search of Cochrane Database of Collected Research, EMBASE, MEDLINE, and PubMed was performed to identify all of the English-language publications between January 2000 and March 2018 using the following search terms: ('inflammatory bowel disease' or 'IBD' or 'ulcerative colitis' or 'Crohn's') and ('colorectal' or 'colorectal surgery' or 'surgery' or 'surgical' or 'operation' or 'operative' or 'perioperative' or 'pre-operative' or 'post-operative') and ('venous thromboembolism') and ('prophylaxis' or 'chemoprophylaxis'). Retrospective, prospective, observational, randomized controlled trials (RCTs), systematic reviews, and meta-analyses were included. In addition, we searched the reference section of each relevant article to identify additional articles pertaining to this topic which included the most recent revision of the American College of Chest (ACCP) Physicians VTE Prophylaxis Guideline [1] which is an excellent resource. Given the lack of RCTs of VTE prophylaxis for IBD patients undergoing colorectal surgery on this topic, a second search substituting the IBD diagnostic terms for 'cancer' and substituting 'abdominopelvic surgery' for 'colorectal surgery,' limited to RCTs, systematic reviews, meta-analyses, was performed. A supplemental manual search of guidelines was included.

Results

Preoperative Screening and Risk Stratification for High Risk Patients

The incidence of *preoperative* VTE before major colorectal surgery in IBD patients is approximately 4.2% as shown by Zaghiyan et al. [11]. In addition, hospital transfer status and preoperative hospitalization have both been shown to be associating with higher rate of VTE [12, 13]. Hence, our department has protocolized surveillance duplex ultrasound for all colorectal patients transferred from another hospital to screen for lower extremities DVT.

Given the numerous clinical risk factors for VTE, several risk stratification instruments have been developed to estimate the predicted risk of postoperative VTE [14, 15]. The most widely used is the Caprini score, which has been validated in a surgical cohort which included a subset of IBD patients [16]. The caveat of using such system is that most patients undergoing IBD surgery are *a priori* classified as high to highest risk group (IBD + major surgery = VTE risk >3%), hence the Caprini score seldom changes our decision-making in regards to the use of postoperative VTE chemoprophylaxis.

Although most patients with symptomatic VTE are diagnosed in the early postoperative period while hospitalized, > 1/3rd are diagnosed post-discharge [17]. This highlights the importance of developing a novel risk stratification model in identifying at-risk individuals who may benefit from extended VTE chemoprophylaxis [18]. Recent data suggests biochemical hypercoagulability profiling may have a role in risk stratification in addition to traditional clinical risk stratification in this regard [19].

Efficacy of Extended Prophylaxis for After Surgery for IBD

To date, no randomized data exists regarding the efficacy of extended chemoprophylaxis after surgery for IBD.

Retrospective Cohort Studies of VTE Rates After Colorectal Surgery for IBD

Although no RCTs have been performed specifically for IBD, multiple "Big Data" studies have demonstrated that IBD patients have an equivalent or higher risk of postoperative VTE than colorectal cancer patients, and a substantial amount of circumstantial evidence supports extended chemoprophylaxis for IBD patients [6, 17, 20–22]. Results from these studies are presented in Table 3.2. This is exceptionally important because if the rate of VTE after IBD surgery (4% overall) is equal to or higher than that of colorectal cancer, then one may extrapolate the findings of the available RCTs after surgery for abdominopelvic cancer to the IBD surgical patient population.

Quality Improvement Study

In the senior author's previous colorectal practice, with an >50% IBD and >30% colorectal cancer patient case-mix, a quality improvement project was performed which used the NSQIP platform with 100%-sampling for all colectomy and proctectomy cases. We implemented routine enoxaparin for a total of 28-days post-operatively and went from the tenth (highest) decile to the first (lowest) decile (before/after VTE rate of 4.5 vs. 0.5%), becoming a low outlier with exemplary designation for VTE after colorectal surgery [24].

Table 3.2 Retrospective cohort studies evaluating VTE rates after colorectal surgery for IBD

First author (year)	Patients studied	Intervention	Study design	Data Source	N	VTE rates (30-days unless noted)	Quality of evidence
Wallaert (2012) [6]	UC vs. CD	SOC	RC	NSQIP PUF	10,431	3.3% vs. 1.4%, p < 0.001	Low
Gross (2014) [17]	IBD vs. CRC	SOC	RC	NSQIP PUF	45,964	2.7% vs. 2.1%, p < 0.001	Low
Wilson (2015) [20]	IBD vs. non-IBD	SOC	Matched RC	NSQIP PUF	96,999	UC vs. CRC vs. CD: 2.7%, 1.7%, 1.2%, p < 0.001 Propensity score matching: UC 2.7% vs. controls 0.6%, p = 0.009	Low
Brady (2017) [21]	UC vs. CD	SOC	RC	Optum Labs Data Warehouse	7,078	Post-discharge 90-days: 5.8% vs. 2.3%, p = <0.0001 (Post-discharge chemoprophylaxis in only 0.6%)	Low
McKenna (2017) [22]	IBD vs. non-IBD	SOC	RC	NSQIP PUF	18,833	Overall 3.8%, no difference based on diagnosis. High- (4.4%) vs. medium- (1.6%) vs. low-risk (0.7%) surgery; emergent (6.9%) vs. elective (3.1%)	Low
Ali (2018) [23]	UC vs. CD IBD vs. CRC	SOC	RC	ExplorSys Platform	75,620	UC vs. CD: 4.1% vs. 2.1%, p < 0.0001 IBD vs. CRC (90-days): 4.3% vs. 4.3%	Low
Holubar (2018)[a]	IBD vs. non-IBD	SOC	RC	Single institution NSQIP	2,237	UC 5.3% vs. CD 4.1%; IBD 4.9% vs. non-IBD 3.8%, p = NS	Low

PUF participant user file, *SOC* standard of care, *RC* retrospective cohort, *CRC* colorectal cancer, *NSQIP* National Surgical Quality Improvement Program
[a]Un-published data, 2018

Randomized Studies

To date, as relevant to our population, extended prophylaxis has only been studied in RCTs for abdominal pelvic cancer [8, 25–27]. These studies, which are presented in Table 3.3, confirmed that extended prophylaxis is efficacious in decreasing 30-day VTE for abdominopelvic cancer patients. The main caveat/limitation of these three studies is that they all used routine imaging to detect the DVTs, and detection of PE's was clinical. This strategy was used because in order to adequately power a study based on clinical VTE rates, as many as 3000 patients may need to be enrolled which is essentially cost-prohibitive. This is likely why so few randomized studies exist on this topic overall, and why this has not yet been studied in the IBD surgical population.

Table 3.3 Relevant RCTs evaluating extended VTE chemoprophylaxis after abdominal surgery

First author (year)	Patients studied	Intervention	N	VTE rates	Secondary outcome	Quality of evidence
Bergqvist (2002) [8]	Major abdominopelvic cancer surgery	Inpatient enoxaparin only vs. enoxaparin for 28-days	332	*Routine venography* 12% vs. 4.8%, p = 0.02	Bleeding: 4.8% vs. 6.1%, p = NS	Moderate
Rasmussen (2006) [25]	Major abdominal surgery	Dalteparin 7-days vs. 28 days	343	*Routine venography* 16.3% vs. 7.3%, p = 0.01 (**NNT = 12**)	Major bleeding: 1.8% vs. 0.5%[a]	Moderate
Kakkar (2010) [26]	Major abdominopelvic cancer surgery	Bemiparin 8-days vs. 28 day	625	*Routine venography* 4.6% vs. 0.8%, p = 0.01	Major bleeding: 0.6% vs. 0.3%[a] Minor bleeding: 0.3% vs. 0.3%[a]	Moderate
Vedovati (2014) [27]	Laparoscopic colorectal cancer surgery	SQH 1-week vs. 4 weeks	225	*Routine Ultrasound* 30-days: 9.7% vs. 0, p = 0.001; 90-days: 9.7% vs. 0.9%, p = 0.005; **relative risk reduction 91%**	Major bleeding (30-days): 0.9% vs. 0.9%[a]	Moderate

SQH subcutaneous heparin, *NNT* number needed to treat
[a]*p*-value not reported

Some argue that one does not need to give prophylaxis to prevent clinically silent VTEs. On the other hand, one cannot predict when a clinically silent VTE will become symptomatic, and in the worst case result in a patient dying. Studies have proven that extended prophylaxis is both efficacious for preventing VTEs and safe in terms of bleeding. These results have been confirmed by several meta-analyses [28, 29].

Guidelines Recommendations for Extended VTE Chemoprophylaxis after Surgery for IBD

As of 2012, the American College of Chest Physicians (ACCP) Prophylaxis Guidelines for non-orthopedic surgery recommended that highest-risk patients (VTE risk ~6%) who have cancer receive 4 weeks of chemoprophylaxis. As of 2018, the American Society of Colorectal Surgeons Clinical Practice Guidelines Committee recommended that extended prophylaxis be considered for surgical IBD patients [2]. Thus extended chemoprophylaxis can now be considered part of the standard of care for IBD patients.

Outcomes of Extended VTE Chemoprophylaxis

Risk of Bleeding

The risk of bleeding secondary to VTE chemoprophylaxis is low. In a retrospective study of 974 IBD patients, the rate of major postoperative bleeding in patients who had VTE chemoprophylaxis was 0.4%, vs. 0%, p = NS in those with no prophylaxis, whereas the rate of minor bleeding was 5.4% vs. 0%, p = NS [30], with and without prophylaxis, respectively. According to the ACCP VTE Prophylaxis Guidelines for non-orthopedic surgery, which are drawn from a wide-variety of operations, the risk of major bleeding with the use of *any* postoperative chemoprophylaxis is approximately double compared to those without *any* chemoprophylaxis, however as seen above the absolute rates remain small [1]. In addition, there was no difference in wound hematoma and major bleeding requiring reoperation between the use of low molecular weight heparin (LMWH) and unfractionated heparin (UFH) [1]. Bleeding rates reported from RCTs are shown in Table 3.3. In summary, patients should be risk-stratified for both risk of VTE and the risk of bleeding from chemoprophylaxis [1].

Cost-Effectiveness

Currently, there is minimal data regarding the cost-effectiveness of extended VTE chemoprophylaxis for IBD patients underwent surgery. However, there is some evidence suggesting the use of extended VTE chemoprophylaxis in major abdominal and pelvic surgery is indeed cost-effective. In a decision analysis model of pelvic

surgery patients, from a healthcare system perspective, the use of UFH for one month is the most effective and least costly (mean cost of $1,611) strategy in preventing postoperative VTE, whereas LMWH for 1 month is equally effective but more expensive (mean cost of $2,197) [31]. Furthermore, 2 cost-effective analyses demonstrated that the use of LMWH for extended VTE chemoprophylaxis would be cost-effective only when the probability of VTE exceed 2.4% and 2.1% respectively, rates which are below the typical rate seen in IBD patients postoperatively [32, 33]. In contrast, based on results from a decision model constructed to compare the use of UFH, LMWH, and 325 mg of aspirin versus no extended prophylaxis after cancer surgery, UFH was found to be the most cost-effective, potentially saving $30 million per year in the United States; however, the decision-analysis suggested that aspirin could be considered as an alternative strategy when compliance is low (*i.e.* fear of self-injection) [34]. Given wider availability of lower cost generic LMWH since that study (2010), a more recent cost-minimization decision analysis suggests that using LMWH as extended therapy is cost-effective in the current cost environment [35].

Recommendation Based on Data

We recommend that IBD patients undergoing major colorectal surgery be managed with extended VTE chemoprophylaxis with LMWH for 28 days post-operatively (moderate evidence quality; strong recommendation).

Personal View of Data

Despite a present lack of level 1 evidence for post-operative IBD patients, the short- and long-term risks of VTE *far outweigh* the risks of extended chemoprophylaxis. For actively inflamed IBD patients undergoing major abdominopelvic surgery, evaluation begins with a screening lower extremity duplex, and upper extremity duplex if a PICC line if present, for the majority of emergency, transferred, or hospitalized patients. Prior to the induction of anesthesia, we confirm VTE chemoprophylaxis with either SQH 5000 units or enoxaparin 40 mg and the application of sequential compression boots as part of the preoperative checklist; for malnourished, underweight patients below 60 kg of body weight, we dose-adjust to 30 mg of enoxaparin.

Postoperatively, chemoprophylaxis is integrated into the colorectal post-operative order-sets as a hard-stop in the electronic medical record. If a patient is not receiving risk-stratified chemoprophylaxis, then the healthcare provider must document the reason, also as a hard-stop. Sequential compression devices are continued postoperatively until the patient is fully ambulatory. Patients are encouraged to ambulate on the day of surgery and as much as possible thereafter.

The SQH or enoxaparin is continued until hospital discharge. After major abdominopelvic operations for IBD (not including ileostomy closures), we

recommend extending the VTE chemoprophylaxis with enoxaparin for a total of 28 days after discharge. In the circumstance of insurance denials, or unaffordable insurance co-pays/out-of-pocket expense, we first ask the Care Managers for their assistance is cost-reduction mechanism such as coupons; a minority will need to seek charity funding. Although low-dose aspirin may be an alternative in general surgery patients at high-risk of VTE when LMWH or UFH are contraindicated or unavailable, the efficacy for *extended* prophylaxis has not yet been studied [1, 36].

There are multiple caveats regarding the use of LMWH. The first is that LMWH is associated with a lower rate of heparin induced thrombosis and thrombocytopenia (HITT). Prophylactic dose LMWH does *not* need to be held for 24 h before surgery, as this practice is associated with an increased risk of VTE [3]. Also, LMWH cannot be given 12 h before or after an epidural catheter insertion or removal. LMWH is also contraindicated in those with renal dysfunction (*i.e.* creatinine clearance <30 cc/mL), those at increased risk of perioperative bleeding, and in those with heparin allergies and HITT. Finally, two surgical adages to remember: "*It is easier to treat bleeding that to treat clotting*", and "*prophylactic heparin does not cause bleeding, surgeons cause bleeding*".

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4 The Use of Enhanced Recovery Pathways in Patients Undergoing Surgery for Inflammatory Bowel Disease

Lisa Marie Cannon

Introduction

First described in the 1990s by Henrik Kehlet, perioperative care protocols have replaced traditional inpatient convalescence standards in colorectal surgery [1]. At their core, they aim to standardize the care process with evidence-based recommendations for the pre-, intra-, and postoperative phases of care as well as the patient's transition home. These protocols function under several names, including fast-track pathway, accelerated care program, enhanced recovery pathway (ERP), and the Enhanced Recovery After Surgery (ERAS) program. Herein the author refers to this care paradigm exclusively as an enhanced recovery pathway.

Though they vary slightly across institutions, the key components of the multimodal ERP include preadmission counseling, minimizing preoperative fasting, carbohydrate loading, multimodal opioid sparing analgesia, avoidance of excess fluid administration, antibiotic prophylaxis, prophylaxis against post-operative nausea and vomiting and venous thromboembolism, early discontinuation of urinary catheter, early oral feeding, early ambulation, and defined discharge criteria with daily discharge planning. ERPs require that patients become active participants in their care. Informed patients who understand the benefits of an ERP are more likely to be compliant with elements that require a motivated patient, such as early ambulation and readiness for discharge. Lack of consensus about process standardization, increased number of protocol elements, and lack of commitment on behalf of the team stakeholders can all affect protocol adherence.

ERPs within colorectal surgery have repeatedly demonstrated a reduction in length of stay and complications without increasing readmission rate through multiple institutional studies, meta-analysis, and a Cochrane review [2]. Further,

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Table 4.1 PICO table

P (Patients)	I (Intervention)	C (Comparator)	O (Outcomes)
IBD patients requiring surgery	Enhanced recovery protocol	Conventional care	Length of stay 30-day readmission 30-day morbidity

they result in increased patient satisfaction particularly through improved pain-control, and are cost-effective [3]. Given that the ERP framework aims to reduce surgical stress and minimize physiologic disturbance, utilization of a minimally invasive approach is a natural extension of an ERP. A minimally invasive approach is known to be synergistic with ERPs in reducing morbidity and length of stay [4–7].

Currently, enhanced recovery pathways are demonstrated to be efficacious for patients with benign or malignant conditions undergoing colorectal surgery. While a minimally invasive approach is known to be beneficial in patients with Crohn's disease or ulcerative colitis undergoing intestinal resection, little has been reported on the use of enhanced recovery protocols in this population [8–12].

Using the PICO format, inflammatory bowel disease (IBD) patients undergoing surgery and receiving perioperative management on a defined enhanced recovery protocol were compared to those receiving conventional perioperative care (Table 4.1). The outcomes evaluated were length of stay, morbidity, and readmission.

Search Strategy

A systematic literature search was performed of MEDLINE and PubMed to identify English language publications related to utilization of enhanced recovery protocols in IBD in adults published from January 2000 through June 2018. Combinations of key words were constructed and applied to these databases. The search strategy used in MEDLINE included both MeSH subject headings when possible and/or keyword mapping alias operator commands for the terms 'inflammatory bowel disease' or 'ulcerative colitis' or 'Crohn's,' AND 'enhanced recovery,' 'ERAS,' 'fast-track, or 'accelerated care.' Similar combinations were then applied to PubMed. The biographies of all the original articles were then explored for any additional germane publications. Case reports, letters, systematic reviews, and duplicate articles were excluded.

Because the above search yielded only six relevant studies [13–18], a similar search was performed that was limited to 'colorectal,' AND 'enhanced recovery,' 'ERAS,' 'fast-track, or 'accelerated care,' AND 'conventional care' within the same time-frame in adult patients, and then further limited to 'length of stay,' AND 'post-operative complications.' Further limiting by 'readmission' was too restrictive and this limit was lifted. These studies were then individually assessed to determine if they contained any IBD patients in their study population, and in this manner a further seven studies were identified [3, 19–24].

Results

Thirteen English language studies were identified. Using the GRADE system approach to developing practice guidelines, all 13 studies were rated either low or very low quality; reasons for this included small sample size, allocation concealment, surgeon bias, lack of blinding, and lack of reporting on important metrics such as surgical approach, conversion rate, level of adherence to the ERP protocol, or 30-day readmission rate. Most studies did not provide important IBD-specific demographic information such as preoperative use of biologic therapy, steroids, or immune modulation. Some studies did not describe utilizing defined discharge criteria or otherwise discuss discharge readiness even though this parameter is known to influence one of the outcomes of interest, length of stay [25]. There is partial indirectness of study outcomes in regard to IBD in the studies that include other disease populations such as neoplasia or diverticulitis patients. Some studies employed a 'before and after' format of their study populations, recognizing that it is difficult to simultaneously conduct two postoperative care paradigms on the same surgical ward with the same nursing staff; but this does introduce bias. Most of the included studies had more than one of these limitations. Two studies did not have a comparator group [13, 15], and in one study the comparator group was not conventional care, but a different disease population— neoplasia— employing the same ERP. In this study only the IBD arm was considered in the data [14]. These studies are summarized in Table 4.2. One study patient population from Thiele appears to be entirely included within a more recent study from the same institution by Shah [3, 17].

The studies are heterogeneous in regard to the specific components of the pathway, with use of mechanical or oral antibiotic bowel preparation and use of epidural or other neuraxial anesthesia being the most variable. Discussion of the use of mechanical and/or oral antibiotic bowel preparation is a controversial and evolving topic and outside the scope of this chapter; but recent evidence highlights the importance of oral antibiotics as adjunct therapy in reducing surgical site infection [26]. Studies that employed thoracic epidural anesthesia also had increased or exclusive utilization of an open approach; this is consistent with data that does not support the use of epidural anesthesia after laparoscopy in the setting of an enhanced recovery program [27, 28]. Almost all studies included only elective colorectal resections.

All studies adhered to well-established practice parameters for antibiotic prophylaxis and venous thromboembolic prophylaxis. Avoidance of fasting generally meant allowance of clears until 2 h prior to induction of anesthesia. Carbohydrate loading was accomplished through a variety of beverages. Opioid-sparing multimodal analgesia usually included a non-steroidal anti-inflammatory medication and acetaminophen.

There are a total of 3463 intestinal surgeries represented by these studies. Of these 2249 were placed on an enhanced recovery protocol, and 2140 are presumed unique cases. Of these 2140 intestinal surgeries, only 28.9% were performed with a stated indication as IBD. This relatively low proportion sets the framework by which any IBD-specific recommendation must be considered. 71% of the

Table 4.2 Evidence on enhanced recovery pathways in inflammatory bowel disease[a]

Study (period)	N	% IBD	% Minimally invasive approach (% Conversion)	LOS		Defined discharge criteria	30-day Readmission		30-day Morbidity	
Andersen et al. [13] ('00–'03)		+ epidural, restrictive fluid regimen, early mobilization, early PO, early urinary catheter removal, MMA, MagOx								
IBD ileocolic resections on ERP	32[b]	100	0	Mean 3.0 day (Range 2–20)		Yes	6%		25%[c]	
Dai et al. [14] ('12–'15)		Pre-op education, no bowel prep, avoidance of fasting, minimally invasive preferred, Restrictive fluid regimen, early mobilization, early PO, early urinary catheter removal, MMA								
IBD patients on ERP	259	100	52.5 (10.4)	7.9 ± 5.3 day		NR	NR		34.2%	
Delaney et al. [15]		Pre-op education, avoidance of fasting, early mobilization, early PO, early urinary catheter removal, MMA								
Colorectal surgery on ERP	1000	13.2	100 (5.8)	Mean 4.1 ± 3.2 day		Yes	6%		20.3%	
Delaney et al. [19]	64	Pre-op education, early mobilization, early PO								
Colorectal surgery on ERP	31	54.8	0	5.2 ± 2.5 day	NS	Yes	9.7%[e]	NS	22%[e]	NS
Conventional care	33	78.8	0	5.8 ± 3 day			18.2%[e]		30%[e]	
Keane et al. [20] ('07–'09)	240	Pre-op education, ± bowel prep, avoidance of fasting, carbohydrate loading, ± epidural, early HLIV, Early mobilization, early PO, early urinary catheter removal								
Colorectal surgery on ERP	80	12.5	NR	Median 6 day (Range 1–63)	p 0.0004	Yes	21.3%	NS	40.0%	NS
Conventional care	160	4.4	NR	Median 7 day (Range 3–125)			11.9%		42.5%	
Lee et al. [21] ('12–'13)	190	Pre-op education, prehabilitation, ± bowel prep, avoidance of fasting, carbohydrate loading, ± epidural, avoid overhydration, early mobilization, early PO, early urinary catheter removal, MMA								
Colorectal surgery on ERP	95	12.6	75 (NR)	Mean 5.7 ± 5.5 day	p 0.007	NR	13%[d]	NS	40%[d]	NS
Conventional care	95	8.4	45 (NR)	Mean 9.4 ± 11.8 day			11%[d]		43%[d]	

Study (period)	N	% IBD	% Minimally invasive approach (% Conversion)	LOS		Defined discharge criteria	30-day Readmission		30-day Morbidity	
Lovely et al. [22] ('06–'10)[f]	132	Pre-op MMA, avoid overhydration, no epidural, early mobilization, Early PO, MMA								
Colorectal surgery on ERP	66	25.8	100 (NR)	Median 3 day (IQ range 2–3)	p < 0.001	Yes	15.2%	NS	45.5%	NS
Colorectal surgery on FTP	66	33.3	100 (NR)	Median 3 day (IQ range 3–5)			7.5%		36.3%	
Olivares et al. [16] ('15–'17)[f]	256	Pre-op education, no bowel prep, avoidance of fasting, carbohydrate loading, restrictive fluid regimen, Early mobilization, early PO, early urinary catheter removal								
Colorectal surgery on ERP	121	3.3	38.8[c] (4.3[c])	Median 9.8 ± 3.7 day[g]	p 0.018	NR	9.9%	NS	31.4	NS
Conventional care	135	0	22.2[c] (10[c])	Median 11 ± 3.8 day[g]			11.1%		36.3	
Shah et al. [17] ('11–'15)[f]	707	Pre-op education, + bowel prep, avoidance of fasting, carbohydrate loading, pre-op MMA, Goal-directed fluid, early mobilization, early PO, early urinary catheter removal, MMA								
Colorectal surgery on ERP	324	17	54 (NR)	Median 4 day (IQ range 3–5)	p < 0.0001	Yes	12%	p 0.009	22%	p 0.002
Conventional care	383	18	31 (NR)	Median 5 day (IQ range 4–7)			19%		33%	
Serclová et al. [23] ('05–'07)	103	Pre-op education, ± bowel prep, avoidance of fasting, carbohydrate loading, + epidural, Early mobilization, early PO, early urinary catheter removal								
Colorectal surgery on ERP	51	90.2	0	7.4 ± 1.3 day	p < 0.001	Yes	0%	n/a	21.6%	p 0.003
Conventional care	52	82.7	0	10.4 ± 3.1 day			0%		48.1%	

(continued)

Table 4.2 (continued)

Study (period)	N	% IBD	% Minimally invasive approach (% Conversion)	LOS		Defined discharge criteria	30-day Readmission		30-day Morbidity	
Spinelli et al. [18]	90	Pre-op education, no bowel prep, avoidance of fasting, restrictive fluid regimen, early mobilization, Early PO, early urinary catheter removal, MMA								
IBD ileocolic resections on ERP	20	100	100 (0)	Mean 5.3 ± 1.6 day	p 0.04	NR	0%	NS	25%[c]	NS
Conventional care	70	100	100 (0)	Mean 6.8 ± 3.1 day			2.8%		24.3%[c]	
Teeuwan et al. [24] ('03–'08)[f]	183	Pre-op education, avoidance of fasting, carbohydrate loading, + enema, + epidural, neutral fluid regimen, Early mobilization, early PO, early urinary catheter removal, MMA								
Colorectal surgery on ERP	61	23	0	Median 6 day (Range 3–50)	p 0.021	Yes	3.3%	NS	14.8%	p 0.008
Conventional care	122	21.3	0	Median 9 day (Range 3–138)			1.6%		33.6%	
Thiele et al. [3] ('12–'14)[f]	207	+ bowel prep, avoidance of fasting, carbohydrate loading, pre-op MMA, + spinal, goal-directed fluid, Early mobilization, early PO, early urinary catheter removal, MMA, MagOx								
Colorectal surgery on ERP	109	18	43 (NR)	Mean 4.6 ± 3.6 day	p 0.0002	Yes	10%	NS	16%	p 0.007
Conventional care	98	13	31 (NR)	Mean 6.8 ± 4.7 day			17%		30%	

ERP enhanced recovery pathway, *FTP* fast-track pathway, *IBD* inflammatory bowel disease, *IQ* interquartile, *MagOx* magnesium oxide, *MMA* multimodal analgesia, *NR* not reported, *NS* not significant, *PO* per os

[a]Shaded study patients are represented within a more current study in the table

[b]29 patients undergoing 32 ileocolic resections over the study period

[c]Value inferred from the text/data

[d]60-day readmission/complication rate

[e]Time-frame of readmission/complication rate not specified

[f]Study group is not contemporary with comparator group

[g]LOS includes Day -1 and Day 0

procedures were performed through a minimally invasive approach; it is not possible to know what proportion of these was within the IBD subset of the data.

In studies with a conventional recovery comparator group, 9 of 10 demonstrated a significantly decreased length of stay for the ERP group. Eight studies report that readmission rate is not increased after discharge on an ERP and one study demonstrated a significant decrease in the rate of readmission as compared to conventional recovery. One study with 103 patients reported no 30-day readmissions and one study did not report on this outcome metric. Two studies without a comparator group reported a 6% rate of readmission after discharge on an ERP, which is well within the range reported by other studies.

For this review, each author's determination of morbidity was taken at face value, but no standard scheme was used across all studies. Some studies, but not all, reported morbidity using the Clavien-Dindo classification scheme. Total morbidity ranged from 20% to 48%; but because different classifications were used, these percentages are not directly comparable. Most studies showed no difference in the rate of morbidity of ERP compared to conventional recovery. Four studies demonstrated a significant decrease in morbidity for patients recovering on an ERP.

Recommendations Based on the Data

Enhanced recovery pathways can be safely applied to patients with inflammatory bowel disease undergoing colorectal resection. (**Recommendation:** Strong; **Quality of Evidence:** Low).

Available evidence suggests that application of ERPs to patients undergoing colorectal surgery for IBD is safe, and likely leads to decreased length of stay without an increase in the rate of readmission, or morbidity. The quality of the evidence is low, and applicability to the IBD population can be questioned due to the low proportion of IBD patients in the study groups. However, there are no studies to date that offer any opposing data to challenge a recommendation for ERPs as the preferred perioperative approach in IBD. In other words, there is no parameter for which conventional care is superior.

Personal View of the Data

Very little disease-specific data exists supporting the application of ERPs after colorectal resection in IBD. Be that as it may, there is overwhelming literature demonstrating the benefit of ERPs in colon or rectal resection for neoplasm, diverticular disease, and other benign disease. The far-reaching embrace of enhanced recovery in our current surgical climate extends to virtually every imaginable subspecialty including pediatric, cardiothoracic, vascular, orthopedic, bariatric, hepatobiliary, pancreatic, endocrine, breast, and plastic surgery. At this time, there is no patient group that does not stand to benefit from an enhanced recovery approach. We as a surgical community have clearly carried the enhanced recovery paradigm past the

ostensible event horizon, and the author cannot conceive of a sequence of events that would turn us back toward conventional care paradigms, ill defined as they may be. With that in mind, in the author's opinion, it is unnecessary at this juncture to perform further comparative studies of ERP versus conventional care in IBD patients to formally validate the benefit of ERPs in a disease-specific manner. Research efforts should instead be directed to clarify which ERP elements lead to the greatest benefit in IBD patients, and what modifications may be appropriate.

There is insufficient data to recommend modifying or withholding the enhanced recovery approach in any subset of IBD patients undergoing colorectal resection. The data presented herein was almost exclusively collected on patients undergoing elective intestinal surgery. In practice, however, many patients with IBD requiring surgery find themselves needing colorectal resection urgently or on a semi-elective timeline. This can be due to intermittent partial obstruction, recalcitrant disease, bleeding, obstipation, severe pain, abdominal sepsis, symptomatic fistula, or malnutrition due to protein wasting enteropathy. Only three of the above studies made any comment on steroid use, level of immune suppression, or preoperative nutritional status. Dai noted that preoperative steroid use, hypoalbuminemia, and systemic inflammatory response syndrome status were independent risk factors for post-operative ileus and increased length of stay, but do not have an appropriate comparator group to determine how these patients would fare in a conventional care paradigm [14]. It is already established that IBD is a risk factor for prolonged length of stay and this should be taken into account when educating IBD patients about their post-operative expectations for recovery [29]. In the author's view, ERPs are at their core simply quality improvement initiatives that aim to provide the best care and support to a patient undergoing any manner of colorectal surgery. With this in mind, discretionary use of ERPs in higher risk IBD populations is probably safe, pending further data to support this notion.

Further direction should include analysis of extended prophylaxis for venous thromboembolism, use of enhanced nutritional support including immune nutrition, application of ileostomy pathways, enhanced support for non opioid-naïve IBD patients, and formalized efforts to reconcile divergent time-to-readiness-for-discharge versus length-of-stay as indices of recovery.

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5 Perioperative Steroid Management in IBD Patients Undergoing Colorectal Surgery

Adam Truong and Karen Zaghiyan

Introduction

Thoughtful perioperative preparation for patients with inflammatory bowel disease (IBD) is pivotal, as their underlying disease and associated comorbidities introduce several challenges. Colorectal surgeons must be familiar and confident with perioperative steroid management in this complicated patient population. Historically, standard practice has included stress-dose or high-dose perioperative steroids in any steroid-dependent patient undergoing surgery to prevent adrenal insufficiency (AI), cardiovascular collapse, and potentially death. Stress-dose steroids typically consist of hydrocortisone 100 mg intravenous (IV) preoperatively then every 8 hours postoperatively for the first 24 hours followed by a taper down to the basal preoperative dose over the subsequent 2–3 days [1]. This practice is anecdotal and is largely derived from case reports from the 1950s demonstrating cardiovascular collapse and death upon sudden cessation of preoperative steroids [2, 3]; current guidelines do not typically elaborate beyond suggesting individualized steroid dosing [4].

While suppression of the hypothalamic-pituitary adrenal (HPA) axis is known to occur with chronic steroid supplementation [5], the dosage or duration of steroid exposure required to suppress an appropriate endogenous response to surgical stress is unknown. Further, the duration of time to recover from HPA axis dysfunction is also not known [6]. The resolution of HPA axis dysfunction was traditionally thought to take up to 1 year [7], thus stress-dose steroids have been recommended in patients treated with corticosteroids within the past year. However, perioperative high-dose steroids are not without consequence and have been associated with hyperglycemia, impaired wound healing, hypertension, electrolyte imbalance, immunosuppression and psychological impairments [5]. These risks are further

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potentiated and associated with increased perioperative morbidity if accompanied by malnutrition, advanced age, or concomitant use of immunosuppressive medications [8].

Despite the potential for AI and perioperative cardiac decompensation, a standardized preoperative evaluation algorithm for adrenal insufficiency has not been established. Furthermore, the clinical utility of diagnostic tests for adrenal insufficiency is currently debated [9]. Over the past 6 decades, several large case series have been conducted in both IBD and non-IBD patients challenging the practice of stress-dose steroid administration. Recent recommendations lean towards avoiding perioperative stress-dose steroids [10]. Still, there remains great variability in perioperative steroid dosing for IBD patients undergoing colorectal surgery [11] with a recent Twitter poll revealing that 69% (out of 88 respondents) of surgeons using stress-dose steroids in IBD surgery with only 31% maintaining patients on their preoperative steroid or steroid dose-equivalent [12]. In this chapter, we review the literature and evidence surrounding perioperative steroid dosing followed by our recommendations for steroid management in patients with IBD undergoing colorectal surgery.

Search Strategy

Relevant PICO (Population, Intervention, Comparator, Outcome) questions were generated (Table 5.1). A Medline and PubMed search was conducted for publications in the English language between January 1952 and July 2018 using the following search terms: ('inflammatory bowel disease' or 'IBD' or 'ulcerative colitis' or 'Crohn's' or 'organ transplant' or 'transplant' or 'steroid-treated') and ('corticosteroid' or 'steroid') and ('colorectal' or 'colorectal surgery' or 'surgery' or 'surgical' or 'operation' or 'operative' or 'perioperative') and ('stress-dose' or 'high-dose' or 'low-dose' or 'dosing' or 'previous steroid') and ('adrenal insufficiency' or 'hemodynamic' or 'outcome' or 'complication' or 'morbidity' or 'mortality'). We additionally searched the reference section of each relevant article to identify additional articles pertaining to this topic and screened them based on title and abstract.

Table 5.1 PICO questions

P (Patients)	I (Intervention)	C (Comparator)	O (Outcomes)
Steroid-treated patients with or without IBD undergoing colorectal or non-colorectal surgery	Low-dose perioperative steroids	High-dose or stress-dose perioperative steroids	Perioperative hemodynamic instability, adrenal insufficiency, morbidity, mortality, infectious complications
Patients with or without IBD, previously treated with steroids within 1 year undergoing colorectal or non-colorectal surgery	No corticosteroids	High-dose or stress-dose perioperative steroids	Perioperative hemodynamic instability, adrenal insufficiency, morbidity, mortality, infectious complications

Retrospective and prospective, observational and randomized studies were included. Given the paucity of studies investigating IBD patients undergoing colorectal surgery, the search was expanded to include organ transplant recipients and other non-IBD steroid treated patients undergoing non-colorectal surgery.

Results

Several studies have been performed over the past 60 years to assess the clinical utility and optimal dosage of perioperative steroids in steroid-treated or steroid-dependent patients undergoing surgery (Table 5.2). The concept of reducing or omitting high-dose or stress-dose steroids in steroid-treated patients is not novel, particularly given serious concerns about surgical wound healing. In the early trials, steroid-treated patients underwent surgery without perioperative steroids and clinical parameters and HPA function were tested. In 1962, Solem and Lund reported on 30 patients whose steroids were stopped more than 4 weeks before a variety of surgical procedures (IBD undergoing major colorectal surgery, n = 4) without perioperative steroid dosing; no severe hemodynamic collapse to suggest clinically relevant AI was observed in any of these patients [13]. Two studies from the 1970s further investigated the consequence of perioperative steroid omission in steroid-treated patients undergoing surgery. They similarly implemented HPA axis testing and correlated them with clinical parameters and found hypotension attributed to AI in only 4 out of 125 patients combined [14, 15]. In a series of 104 patients, Kehlet and Binder followed steroid-treated patients undergoing major and minor operations. Home-dose steroids were stopped 48 hours before surgery and restarted 24 hours after minor cases and 48 hours after major cases. Clinical adrenal insufficiency was minimal, with only 3 patients exhibiting unexplained hypotension and abnormal adrenocorticotropin hormone (ACTH) testing. Each of these patients recovered spontaneously without the administration of steroids [15].

The utility and clinical relevance of preoperative ACTH testing has been an area of interest in an attempt to distinguish patients who may require perioperative steroids from those whose HPA axis has recovered and do not require steroids. In a prospective study, 48 steroid-treated patients undergoing elective surgery (colorectal, n = 7) without perioperative steroids were analyzed for HPA axis dysfunction. While only 17 of the 48 steroid-treated patients exhibited a normal response to both ACTH stimulation and postoperative HPA axis testing, none exhibited any symptoms consistent with AI or hemodynamic instability and none required steroid administration including the 31 patients with abnormal ACTH responses [16].

Knudsen et al. performed a retrospective study evaluating 250 steroid-treated IBD patients undergoing major colorectal surgery [17]. The study included 3 groups of patients: (1) patients on steroids at the time of surgery (n = 48); (2) patients whose steroids were stopped 1 week to 2 months before surgery (n = 76); and (3) patients with steroid cessation greater than 2 months before surgery (n = 126). Intraoperative hypotension occurred in 29 patients overall (11.6%), and was less common in the in the 126 patients with more than 2 months of steroid cessation

Table 5.2 Studies evaluating perioperative steroid dosing

First author (year)	Patients studied	Intervention	Study design	N	Outcome	Quality of evidence
Solem (1962) [13]	Patients previously treated with steroids/various surgeries (n = 4 IBD/CRS)	No periop steroids	R	30	No unexplained death attributed to AI	Very low
Jasani (1968) [14]	RA/anterior synovectomy	No periop steroids	PO	21 steroid-treated vs. 20 controls	1 patient with abnormal preop ACTH had hypotension responsive to steroids	Very low
Kehlet (1973) [15]	Steroid-treated patients undergoing various major/minor operations	No periop steroids	PO	104	3 patients with hypotension and low cortisol thought to be AI	Low
Knudsen (1981) [17]	IBD/CRS	n = 200 with no periop steroids, n = 50 received steroids	R	250	11 cases of hypotension treated with steroids/possible AI	Very low
Lloyd (1981) [18]	RA/Orthopedic surgery	Stress-dose vs. usual daily dose	PO	61	No difference in periop steroid supplementation between the 2 groups	Very low
Symreng (1981) [19]	Various patients (n = 7 IBD, n = 16 CRS)	If impaired ACTH stimulation test: HC 25 mg IV preop then 100 mg IV/24 h. If normal ACTH stim test: No periop steroids. Return to usual daily dose postop.	PO	14 steroid-treated patients and 8 steroid-naïve controls	No hemodynamic instability	Very low
Bromberg (1991) [21]	Renal transplant patients admitted w/ significant physiologic stress	Usual daily dose	PO	40	No unexplained hemodynamic instability	Very low
Bromberg (1995) [22]	Renal transplant patients/various surgeries	Usual daily dose	PO	52	No clinical or laboratory evidence of adrenocortical insufficiency	Very low

Friedman (1995) [23]	Renal-transplant or RA/ major orthopedic surgery	Usual daily dose	PO	28	All patients with endogenous adrenal function. No unexplained hemodynamic instability.	Very low
Mathis (2004) [24]	Organ transplant/ lymphocele drainage	Stress-dose vs. no steroid. Return to usual daily dose postop	R	58	No hypotension, arthralgia, ileus, mental status changes. Blood glucose higher with stress-dose	Very low
Glowniak (1997) [25]	Various (colorectal n = 2) with positive ACTH stimulation test	Stress-dose vs. placebo. Return to usual daily dose postop	RCT	18	No episodes of AI. One in each group with hypotension	Very low
Thomason (1999) [26]	Organ transplant/gingival surgery	Stress-dose vs. placebo. Return to usual daily dose postop	RCT	20	No hemodynamic instability	Very low
Zaghiyan (2012) [27]	IBD/CRS previously on steroids within 1 year	No periop steroids	R	49	No difference in hemodynamic instability	Low
Zaghiyan (2012) [28]	IBD/CRS	HDS vs. LDS	RO	32	No unexplained hemodynamic instability	Very low
Zaghiyan (2011) [29]	IBD/CRS	HDS vs. LDS	R	97	No difference in hemodynamic instability	Moderate
Aytac (2013) [30]	IBD/CRS	Stress-dose vs. usual daily dose	R	235	More tachycardia with stress-dose otherwise no difference in hemodynamic instability	Moderate
Zaghiyan (2014) [31]	IBD/CRS	HDS vs. LDS	RCT	92	Non-inferiority of LDS vs. HDS with respect to postural hypotension; no difference in hemodynamic instability. More infections with HDS.	High

IBD inflammatory bowel disease, *CRS* colorectal surgery, *RA* rheumatoid arthritis, *ACTH* adrenocorticotropic hormone, *HDS* high-dose steroids, *LDS* low-dose steroids, *R* retrospective, *PO* prospective observational, *RO* retrospective observational, *RCT* randomized controlled trial

(5.6%). In 9 patients, intraoperative rescue hydrocortisone was given, however none of these patients had biochemically proven AI. These early studies elaborated on the inconsistency between positive ACTH testing and clinically significant AI and reinforced the need for perioperative steroids in some patients, though the appropriate patient cohort and steroid dose remained unclear.

Subsequent studies evaluated various perioperative steroid dosing regimens consisting of low-dose steroids or maintaining patients on their preoperative steroid dose without the addition of a stress-dose steroid. In 1981, Lloyd completed a prospective observational trial of 61 arthritic patients requiring orthopedic surgery comparing a single preoperative stress-dose of steroids (hydrocortisone 100 mg) against omission of any stress-dose steroids [18]. They found no significant difference in the need for perioperative rescue steroids in patients treated with perioperative stress-dose steroids (24%) compared to those patients managed without steroids (17%), providing evidence that steroid-treated patients may not require rescue medication despite receiving no stress-dose steroids. Furthermore, they showed that the physiologic requirement for perioperative steroid supplementation may be lower than expected. Further justification for low-dose perioperative steroid safety was evidenced by Symreng in a small study of 14 steroid-treated patients (IBD, n = 7) compared to 8 steroid-naïve controls undergoing various operations (major colorectal surgery, n = 16) [19]. They report that steroid-treated patients with abnormal preoperative ACTH-stimulation testing (n = 6) may be managed with low-dose steroids (hydrocortisone 15 mg IV upon induction of anesthesia followed by 100 mg IV over the next 24 h) followed by reinstitution of the preoperative dose, whereas patients with normal ACTH- stimulation testing may be managed without steroids on the day of the surgery.

In the 1990s, Shapiro et al. prospectively observed 13 pediatric transplant patients whose home-dose steroid regimen was either weaned or abruptly stopped before allograft nephrectomy [20]. The range of overall steroid treatment duration was broad (range: 21 days to 5 years) and although 6 patients, close to half of the observed cohort had evidence of HPA-axis dysfunction on preoperative ACTH testing, no patient in the entire series developed signs or symptoms of AI.

Bromberg et al. later performed two prospective cohort studies evaluating renal transplant recipients admitted with significant physiologic stress (n = 40) or for various operations (n = 52), both managed with only continuation of their home-dose steroid [21, 22]. Almost all patients had normal urinary cortisol levels and no clinical expression of hemodynamic compromise; ACTH-stimulation testing appeared to overestimate adrenal dysfunction in a majority of patients. Friedman et al. prospectively evaluated 28 renal-transplant or rheumatoid arthritis patients on an average prednisone dose of 10 mg/day undergoing major orthopedic surgery [23] and similarly found that all patients had evidence of endogenous adrenal function with no episodes of clinically significant adrenal insufficiency. Further, another retrospective study of 58 pancreas and kidney transplant recipients undergoing lymphocele drainage showed no difference in hypotension, arthralgia, mental status changes, ileus, or wound healing in patients treated with stress-dose steroids or not; patients treated with stress-dose steroids had more hyperglycemia [24].

Several years later, Glowniak and Loriaux conducted a randomized double-blind study of 18 steroid-treated patients with positive ACTH stimulation tests undergoing various surgical procedures (colorectal, n = 2) managed with either stress-dose steroids or placebo plus the patient's baseline steroid dose and observed only two episodes of hypotension (one in each group) both related to bleeding or hypovolemia [25]. Their conclusion was that patients with secondary AI do not manifest symptoms consistent with cardiovascular collapse when given their preoperative steroid dose. Another randomized double-blind crossover study of 20 organ transplant recipients on prednisone (5–10 mg) undergoing gingival surgery showed similar results [26]. Patients were randomized to hydrocortisone 100 mg IV or placebo preoperatively during their first surgery and then received the opposite for the second surgery; there were no symptoms consistent with AI in any patients despite several cases of abnormal ACTH stimulation testing. Despite obvious sample size limitations, these studies provide data against the routine use of stress-dose steroids. Further, these studies suggest that steroid-treated patients may be continued on their preoperative corticosteroid dose during the perioperative period despite abnormal ACTH stimulation testing without risk of clinically significant adrenal insufficiency.

Despite increasing evidence against stress-dose steroids during the perioperative period for steroid-treated patients, colorectal surgeons managing perioperative steroid dosing in IBD surgery remained reluctant to change their practices [1, 11, 12]. Amidst a paucity of colorectal surgery-specific data, our group performed several studies comparing low-dose steroids (LDS) to high-dose steroids (HDS) in steroid-treated IBD patients undergoing major colorectal surgery. Our LDS protocol consisted of one-third of the daily preoperative steroid dose in hydrocortisone intravenous equivalents (IVED) given at the time of surgical incision followed by one-third IVED every 8 hours postoperatively, followed by a taper. For patients off steroids at the time of surgery, no perioperative steroids were given. HDS entailed hydrocortisone 100 mg IV administered preoperatively followed by 100 mg IV every 8 hours postoperatively for 24 hours then a taper to oral prednisone over 3 days. On hospital discharge, steroids were either discontinued or tapered.

In 2012, we performed a retrospective pilot study evaluating 32 steroid-treated IBD patients (10 patients on steroids up until surgery and 22 patients treated with steroids within the past year) managed with LDS [27]. Hypotension occurred in 16% of patients, but all cases resolved spontaneously with no patients requiring fluid bolus, blood transfusion, vasopressors, or high-dose corticosteroid rescue for AI. We later compared LDS (n = 54) versus HDS (n = 43) in IBD patients who were actively receiving steroid treatment (n = 48) or who had previously received steroid treatment (n = 49) undergoing major colorectal surgery [28, 29]. For patients previously treated with steroids, the median duration since last steroid dose was 4 months (range: 0.1–12 months) and median maximum steroid dose in the past year was equivalent to prednisone 25 mg/day (range: 5–60 mg/day). Aside from a higher incidence of tachycardia in patients previously treated with steroids managed with HDS [29], we found no significant difference in hemodynamic instability between the two patient groups and no patients required high-dose steroid rescue for AI.

Aytac et al. performed a large volume IBD-specific retrospective analysis of IBD patients on steroids (n = 48) compared to IBD patients off steroids (n = 187) at the time of proctocolectomy [30]. Eighty-nine patients were treated with stress-dose steroids and 146 without. There was a higher incidence of sinus tachycardia in patients managed with stress-dose steroids. While no episodes of adrenal crisis occurred, one patient in the stress-dose group was readmitted with hypotension, fatigue and bloating and diagnosed with AI. Another patient in the stress-dose group died on postoperative day 25 due to an anastomotic leak.

In 2014, our group performed a prospective, randomized non-inferiority study evaluating 92 steroid-treated IBD patients undergoing major colorectal surgery randomized to HDS or LDS [31]. LDS was non-inferior to HDS with respect to our primary outcome, absence of postural hypotension on postoperative day 1, which occurred in 95% of patients randomized to HDS versus 96% of patients assigned to LDS, $p = 0.007$. This study included 41 patients previously treated with steroids (median duration since last steroid dose of 4 months; interquartile range: 2–6 months), of which 25 were randomized to LDS (no perioperative steroids given). There was no difference in hemodynamic instability between the 2 patient groups and no patients were treated with rescue HDS for AI. There was, however, an insignificant trend toward more infectious complications in HDS (16%) versus LDS-treated patients (4%); $p = 0.11$.

Current practice still lags behind the growing evidence against perioperative stress-dose steroids in IBD surgery. While current anesthesia guidelines reference the growing body of evidence against perioperative stress-dose steroid administration for patients at low-risk for HPA axis suppression, they continue to recommend stress-doses of up to 100 mg hydrocortisone IV for patients with documented HPA axis dysfunction by ACTH stimulation test or those at "high-risk" for HPA axis suppression such as patients on prednisone 20 mg/day for more than 3 weeks despite evidence stating otherwise [32]. These recommendations reflect the 2016 Endocrine Society Clinical Practice Guidelines [33] prioritizing adrenal crisis prevention over the potential adverse effects of short-term overtreatment with stress-dose steroids [32]. On the other hand, a recent review article and practice recommendations for steroid management in IBD surgery has recommended a gradual wean off steroids in patients undergoing IBD surgery with a goal to have patients off steroids for 1 week before surgery [10]. If this is not possible, the authors recommended continuing the preoperative daily dose without the need for additional steroids.

Recommendations Based on Data

Based on various retrospective and observational studies and few randomized prospective studies, stress-dose steroids appear to be unnecessary and potentially harmful in IBD patients undergoing major colorectal surgery. Several studies in both IBD and non-IBD patients have suggested that steroid-treated patients can be maintained on their usual preoperative steroid dose in the perioperative period. For patients previously treated with steroids within the past year, perioperative steroids may be

avoided altogether. While preoperative ACTH stimulation and perioperative plasma cortisol levels may be evaluated, these tests tend to overestimate adrenal insufficiency with a majority of patients not exhibiting clinically significant hemodynamic instability even when perioperative steroids are held altogether. Thus, a low-dose perioperative steroid protocol consisting of the patient's preoperative dose appears to not only be sufficient, but may avoid complications associated with high-dose steroids. **Based on the available data, we recommend that steroid-treated IBD patients undergoing major colorectal surgery be managed with low-dose perioperative steroids equivalent to their preoperative steroid dose in the perioperative period (*evidence quality high; strong recommendation*).**

Personal View of the Data

In our view, high-dose perioperative steroids are unnecessary and may increase perioperative risk. In our practice we maintain patients on their preoperative steroid dose in the perioperative period. Our perioperative protocol entails hydrocortisone one-third IVED given at the time of surgical incision, followed postoperatively by oral prednisone equivalent to the patient's preoperative steroid dose or in patients unable to tolerate perioperative oral medications, hydrocortisone equivalent to the preoperative steroid dose is administered followed by a taper. For patients off steroids at the time of surgery, no perioperative steroids are given. Patients are monitored closely in the perioperative period and any unexplained hemodynamic instability is followed by ACTH stimulation testing. Patients are initially managed conservatively and high-dose steroids are added only if the patient remains unresponsive to conservative measures and ACTH stimulation testing is positive. However, in our experience no patients have required additional high-dose steroids for AI with this protocol.

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Managing Immunomodulators Perioperatively

6

David R. Rosen and Radhika K. Smith

Introduction

With the westernization of industrialized societies, the incidence of inflammatory bowel disease (IBD) has drastically increased globally. With this rise in incidence, there has been a resultant rise in the number of patients on immunosuppressive medications [1]. Colorectal surgeons, therefore, must be well prepared for the potential perioperative complications associated with these medications. Immunomodulators (thiopurines, calcineurin inhibitors, and methotrexate) are one class of medication that is used quite frequently in the medical treatment of IBD. Intuitively, as these medications alter immune system function, they raise a theoretical concern of increased perioperative complication rate, particularly related to wound infection, anastomotic healing, and other infectious complications. In this chapter, we examine the literature pertinent to the timing of surgery in patients on immunomodulators and provide our recommendations for the management of these medications in the perioperative period.

Search Strategy

A PICO (Population, Intervention, Comparator, Outcome) question was generated (Table 6.1). The following search was performed in Medline and PubMed of publications in the English language from January 1952 to March 2018: ('inflammatory bowel disease' or 'IBD' or 'ulcerative colitis' or 'Crohn's') and ('immunomodulator' or 'thiopurine' or 'purine analogue' or 'mercaptopurine' or 'azathioprine' or

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Table 6.1 PICO question

P (Patients)	I (Intervention)	C (Comparator)	O (Outcomes)
IBD patients on immunomodulators who require surgery	Delay in surgery	Continue as scheduled	Post-op complications (also consider when to restart)

'methotrexate' or 'cyclosporine' or 'tacrolimus') and ('operative' or 'perioperative' or 'postoperative'). This search yielded 573 studies, which were then examined for relevance to the PICO question. We then also searched the reference section of all relevant articles to identify any studies that were not identified during our initial search.

Results

There have been few studies over the years that have examined immunomodulator use in patients with IBD (see Tables 6.2, 6.3, and 6.4).

Thiopurines (6-Mercaptopurine/Azathioprine/6-Thioguanine)

In 2003, Aberra retrospectively examined a group of 159 patients with IBD undergoing elective bowel surgery who preoperatively were taking corticosteroids, 6 mercaptopurine/azathioprine (6-MP/AZA), or a combination of the two [2]. While the group taking corticosteroids had an increased rate of postoperative complications, this did not hold true for the group taking 6-MP/AZA. Furthermore, the addition of 6-MP/AZA to corticosteroids did not worsen the complication rate. Similarly, in 2013, Bafford retrospectively analyzed 196 patients with IBD who underwent intestinal surgery with an anastomosis [3]. Of these, 69 patients were on single agent thiopurine and 36 additional patients were taking thiopurine in addition to either a corticosteroid, anti-tumor necrosis alpha agent (anti-TNF), or both. There was not an increase in morbidity or septic complication rate compared to those not on medications.

Canedo retrospectively evaluated 225 patients, 85 of whom were taking either corticosteroids, 6-MP/AZA, or a combination, and were lumped into one group [4]. There was no difference in postoperative complication rate compared to controls. Colombel reported on 270 IBD patients, undergoing abdominal surgery, of whom 105 were taking immunosuppressives (64 AZA, 38 6-MP, 4 methotrexate) [5]. The immunosuppressive group did not have an increase in septic or nonseptic complications. Similarly, El-Hussuna examined 417 patients who underwent surgery for Crohn's disease, of whom 166 were on immunosuppressive medication (147 AZA, 15 methotrexate, 4 6-MP) [6]. The use of immunosuppressive medication did not result in an increase in anastomotic complication. Indar reported a review of 112 patients who underwent intestinal resection for Crohn's disease, of which 39 were taking 6-MP/AZA [7]. Again, there was no increase in perioperative complication rate.

Table 6.2 Studies evaluating thiopurine use

Study	Disease process	Total Patients (patients receiving thiopurine)	Outcome measured	Results	Quality of evidence
Aberra [2]	IBD	159 (52)	Infectious complications	No difference	Low
Bafford [3]	IBD	196 (105)	Infectious complications	No difference	Low
Canedo [4]	Crohn's	225 (85)	Infectious complications	No difference	Low
Colombel [5]	IBD	270 (102)	Infectious complications	No difference	Low
El-Hussuna [6]	Crohn's	417 (151)	Anastomotic complication	No difference	Low
Indar [7]	Crohn's	112 (39)	Perioperative complication	No difference	Very low
Mahadevan [8]	Ulcerative colitis	216 (46)	Perioperative complication	No difference	Low
Page [9]	IBD	105 (33)	Perioperative complication, length of stay	No difference	Very low
Uchino [10]	Ulcerative colitis	181 (65)	Surgical site infection	No difference	Low
White [11]	Crohn's	338 (148)	Readmission rate	No difference	Low
Tay [12]	Crohn's	100 (68)	Infectious complications	Improved with thiopurine	Low
Myrelid [13]	Crohn's	343 (51)	Infectious complications	Worsened with thiopurine	Low

Table 6.3 Studies evaluating calcineurin inhibitor use

Study	Disease process	Total Patients (patients receiving calcineurin inhibitor)	Outcome measured	Results	Quality of evidence
Fleshner [14]	Ulcerative colitis	14 (14)	Perioperative morbidity	No difference	Very low
Hyde [15]	Ulcerative colitis	44 (19)	Perioperative complications	No difference	Very low
Nelson [16]	Ulcerative colitis	78 (23)	Perioperative complications	No difference	Low
Pinna-Pintor [17]	Ulcerative colitis	25 (25)	Perioperative complications	No difference	Very low
Poritz [18]	Ulcerative colitis	41 (29)	Perioperative complications	No difference	Very low
Saito [19]	Ulcerative colitis	88 (50)	Perioperative complications	No difference	Low
White [11]	Crohn's	338 (35)	Readmission rate	No difference	Low
Mahadevan [8]	Ulcerative colitis	216 (6)	Perioperative complications	No difference	Very low
Uchino [10]	Ulcerative colitis	181 (4)	Surgical site infection	No difference	Very low

Table 6.4 Studies evaluating methotrexate use

Study	Disease process	Total patients (patients receiving methotrexate)	Outcome measured	Results	Quality of evidence
Afzali [20]	IBD	180 (15)	Perioperative complications	No difference	Low
El-Hussuna [6]	Crohn's	417 (15)	Anastomotic complication	No difference	Very low
Colombel [5]	IBD	270 (4)	Infectious complications	No difference	Very low
Mahadevan [8]	Ulcerative colitis	216 (6)	Perioperative complications	No difference	Very low
White [11]	Crohn's	338 (57)	Readmission rate	No difference	Low

Mahadevan analyzed 216 patients who underwent restorative proctocolectomy for ulcerative colitis [8]. In this cohort, 46 patients received either 6-MP or AZA. There was no increase in early or late complications associated with this use. Page matched 30 patients age 60 or older who underwent laparotomy for IBD with 75 controls that were younger than 60 years of age [9]. In the younger cohort, 20 patients were on AZA. In the older cohort, 13 patients were receiving AZA. There was no increase in perioperative complication or length of stay in either group. Uchino examined 181 patients who underwent restorative proctocolectomy for ulcerative colitis to see if there was an increase in surgical site infection with immunosuppressive therapy [10]. The authors' multivariate analysis revealed that the use of 6-MP/AZA did not increase the rate of surgical site infection. White retrospectively evaluated if the postoperative readmission rate was higher for patients taking immunosuppressive medication in 338 patients with Crohn's disease undergoing abdominal surgery [11]. The authors concluded that monotherapy with a thiopurine was not associated with increased readmission rate, but the use of multiple immunosuppressive medications (steroids, biologics, immunomodulators) did increase readmission rate.

Tay retrospectively analyzed 100 consecutive patients with Crohn's disease who underwent their first intestinal resection with anastomosis or stricturoplasty [12]. Within this group, 68 patients received 6-MP/AZA, and the authors found that immunomodulator use actually decreased the rate of intraabdominal septic complication (5.6% vs. 25%, $p < 0.01$), though the immunomodulator cohort did include patients receiving infliximab and methotrexate as well.

In contrast, Myrelid retrospectively analyzed 343 consecutive operations on patients with Crohn's disease undergoing either intestinal anastomosis or stricturoplasty [13]. The authors found a significantly increased rate of intraabdominal septic complication (16% vs. 6%, $p = 0.044$) in patients taking 6-MP/AZA.

Calcineurin Inhibitors (Cyclosporine/Tacrolimus)

In 1995, Fleshner reviewed the results of their early experience with cyclosporine [14]. The authors reported 14 patients at two institutions undergoing urgent subtotal colectomy with end ileostomy for severe ulcerative colitis after failing cyclosporine

therapy. In their small sample, they did not find that the use of cyclosporine increased perioperative morbidity. Hyde reviewed 44 patients who underwent urgent total abdominal colectomy with end ileostomy for severe ulcerative colitis [15]. In this group, 25 patients were receiving corticosteroids and 19 were taking both cyclosporine and steroids. The addition of cyclosporine did not result in any increase in perioperative complications.

Nelson reviewed 78 patients who underwent urgent colectomy for ulcerative colitis after failing medical therapy [16]. In this group, 19 were treated with cyclosporine and corticosteroids, and 4 received cyclosporine, corticosteroids, and infliximab. The authors found that there was no increase in perioperative complication from the addition of cyclosporine to intravenous corticosteroids. Pinna-Pintor reviewed 25 cases of failure of cyclosporine treatment for ulcerative colitis that went on to have restorative proctocolectomy [17]. The authors reported a complication rate of 36% and concluded that there is no increase in perioperative complication from the use of cyclosporine.

Similarly, Poritz reviewed 41 cases of steroid-refractory colitis [18]. 29 of these patients received cyclosporine, and 18 went on to require total abdominal colectomy. There was no increase in perioperative complication rate compared to the group that required surgery but did not receive cyclosporine. Saito examined perioperative complications in patients receiving salvage medical therapy in steroid-refractory ulcerative colitis [19]. Of the 88 patients examined, 50 patients received calcineurin inhibitor (cyclosporine or tacrolimus), 30 had been treated with infliximab, and 12 required surgical intervention. Consistent with the findings of the previous studies, their analysis revealed that although corticosteroid use increased perioperative complication rate, there was no increase in complication rate with either cyclosporine or tacrolimus use.

As an aside, the previously mentioned study by White (see thiopurine section, above) included 26 patients receiving cyclosporine and 9 patients receiving tacrolimus [11]. Again, there was no increase in readmission rate with use of these medications. Similarly, the Mahadevan study (see thiopurine section, above) included 6 patients taking cyclosporine; although there was no increase in perioperative complication, this sample was too small to draw a significant conclusion [8]. The study by Uchino discussed earlier did not find an increase in surgical site infection rate related to cyclosporine use, but there was only 4 patients in this cohort [10].

Methotrexate

Studies are sparse regarding the use of perioperative risk with the use of methotrexate. As mentioned previously, the immunosuppressive group in El-Hussuna and Colombel's studies included patients on methotrexate, though no conclusion can be drawn from this [5, 6]. Similarly, the previously mentioned Mahadevan study included 6 patients on methotrexate; although there was no increase in complication rate, this sample size is clearly too small to draw significant conclusion [8]. The study by White discussed earlier included 57 patients receiving methotrexate, and methotrexate use was not associated with an increase in readmission rate [11].

Afzali retrospectively examined 180 patients undergoing abdominal surgery, 15 of whom were on methotrexate [20]. Their analysis revealed no increase in perioperative complication rate. Despite the obvious limitations of this small sample size, the authors point out this finding is in concordance with studies examining perioperative risk of surgery for rheumatoid arthritis in patients taking methotrexate.

Recommendations Based on Data

Based on the retrospective studies cited above, there is no compelling data to support immunomodulatory cessation prior to surgery. With regards to thiopurine use, only one study showed an increase in postoperative intraabdominal septic complications [13]. However, ten other studies showed no increase in postoperative septic complication, and one study showed thiopurine use actually decreased postoperative intraabdominal septic complication [12]. The elimination half-life of 6-MP is 1–2 h and the elimination half-life of AZA is 1 h. The metabolites of both drugs have a half-life of approximately 5 h [21]. These short half-lives would indicate that these drugs are systemically absent in the perioperative period, protecting from long-standing effects. Lastly, there was no study that showed worse perioperative outcomes in patients receiving calcineurin inhibitors or methotrexate.

Personal View of the Data

In our view, discontinuing immunomodulator therapy prior to surgery is unnecessary. In our practice we hold the dose of immunomodulator medication the morning of surgery for all patients with IBD. For those with Crohn's disease, medications are resumed as necessary in the immediate postoperative period. This is typically done on the day of discharge for a patient with a typical postoperative course. There is some evidence that shows a reduction in postoperative symptoms and both endoscopic and clinical recurrence with initiation of thiopurines in patients with Crohn's disease [22, 23].Thus, our practice is to support early resumption of immunomodulator therapy. Management of all IBD medications in the perioperative period is done in conjunction with the treating gastroenterologist when possible, to assure a seamless transition from surgery to prophylaxis.

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Managing Biologics Perioperatively

7

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Approximately 60% of patients with Crohn's disease (CD) [1, 2] and 30% with ulcerative colitis (UC) [3] will undergo a major abdominal operation during their disease course. Since the advent of biologic therapy with the Federal Drug Administration (FDA) approval of infliximab in 1998, biologics have gained an important foothold in the treatment of inflammatory bowel disease (IBD) [4]. Thus, an ever-increasing number of patients are undergoing surgical consultation at the time of biologic exposure. At that time, patients often have a loss of response to biologic therapy, with poor relief of symptoms, increasing disease severity, worsening nutrition, and the addition of concurrent immunomodulators and/or corticosteroids in an attempt to bridge them to surgery. Therefore, whether it's the biologic agents themselves or increased disease severity that increases postoperative morbidity remains difficult to discern. Regardless, it is imperative that surgeons have an increased understanding of the perioperative optimization of biologics in order to more closely work with both their patients and gastroenterologists to optimize outcomes (Table 7.1).

Table 7.1 PICO table

Patients	Intervention	Comparator	Outcome
Patients on biologic therapy peri-operatively	Proceed with surgery	Delay surgery to avoid recent exposure to biologics	Postoperative complications

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Search Strategy

A comprehensive literature search of the Cochrane Database of Collected Research, EMBASE, MEDLINE, and PubMed was performed to identify all the English language publications related to biologic therapy and postoperative outcomes in both CD and UC between 1998 and 2017. Key search terms included the following: 'infliximab,' 'adalimumab,' 'certolizumab pegol,' 'vedolizumab,' 'ustekinumab,' 'post operative,' 'surgical outcomes,' 'post operative infection,' 'pouch outcomes,' 'Crohn's disease,' 'ulcerative colitis.' Case reports, chapters, and review articles were excluded. Of the included retrospective reviews, systematic reviews, prospective reviews, and randomized control trials, papers were excluded if the primary focus was biologic efficacy rather than perioperative outcomes or included pediatric patents. The references of the included studies were searched for additional relevant publications, and included where appropriate.

Results

While a significant number of studies have investigated postoperative complications in the setting of biologic therapy, the literature remains limited by retrospective study design, heterogeneous patient populations, inconsistent primary endpoints, and variability in biologics studied. The most well studied biologics are the class of anti-TNFs (infliximab, adalimumab, certolizumab pegol). Several studies have investigated the effects in both CD and UC with conflicting results.

In CD, numerous retrospective series and three prospective studies have reported no significant increase in postoperative complications in the setting of anti TNF therapy [5–23] (Table 7.2). Rather than anti-TNF therapy, emergent surgery, penetrating disease, high blood loss, malnutrition, and corticosteroids were found to be significantly associated with increased postoperative complications and intra-abdominal septic complications. In contrast, a number of retrospective and prospective have also reported a significant increase in the rate of postoperative infectious complications and intra-abdominal septic complications in patients exposed to anti-TNF therapy [24–35] (Table 7.3). This makes it difficult to definitively conclude whether anti-TNFs in isolation negatively impact postoperative outcomes versus anti-TNFs being a surrogate marker of increased disease severity. What is consistent is that postoperative morbidity increases as the number of risk factors increases [26]. Thus, anti-TNF therapy may be one of many risk factors for postoperative complications which needs to be put into context of other concurrent risk factors, before there is attribution.

In UC, the data is similarly controversial with regard to anti TNF therapy; some studies report no increased risk of postoperative complications while others report a significant increase in the rate of postoperative complications [14, 19, 36–42] (Table 7.4). Importantly, the two largest series looking at ileal pouch anal anastomosis (IPAA) outcomes in the setting of biologic therapy show an increased risk of postoperative pouch sepsis in the setting of anti TNF therapy. This is a

Table 7.2 Studies showing no increased risk of postoperative complications with anti-TNF therapy in patients with Crohn's disease

Author	Journal	Year	Study design	Patients exposed to anti-TNF	Postoperative outcomes studied	What associated with these outcomes?
Colombel [52]	Am J Gastroenterol	2004	Retrospective single-center	52	Postoperative infectious complications	None
Marchal [15]	Alim Pharmacol Ther	2004	Retrospective single-center	40	General complications and length hospital stay	None
Kunitake [14]	J Gastrointest Surg	2008	Retrospective single-center	101	Medical and surgical complications	None
Indar [9]	World J Surg	2009	Retrospective single-center	17	General complications	Emergency surgery, blood loss
Nasir [18]	J Gastrointest Surg	2010	Retrospective single-center	119	General complications	Penetrating disease
Rizzo [20]	Int J Colorect Dis	2011	Retrospective single-center	54	Higher rates of infectious complications	Steroid use
Canedo [6]	Colorectal Dis	2011	Retrospective single-center	65	Pneumonia, surgical site infections, abscesses and anastomotic dehiscence	None
Kasparek [10]	Inflamm Bowel Dis	2012	Retrospective single-center	48	Sepsis, anastomotic complications, time of admission	Malnourished
Mascarenhas [16]	Am J Surg	2012	Retrospective single-center	19	General complications	None
Norgard [19]	Aliment Pharmacol Ther	2013	Retrospective single-center	214	General complications, reoperations, anastomotic dehiscence and bacteraemia; time from last biologic	None
Waterman [22]	Gut	2013	Retrospective single-center	195	UTI and surgical site infections. Time of last dose of biologics; detectable vs. undetect levels	None

(continued)

Table 7.2 (continued)

Author	Journal	Year	Study design	Patients exposed to anti-TNF	Postoperative outcomes studied	What associated with these outcomes?
Bafford [5]	J Clin Gastroenterol	2013	Retrospective single-center	63	General complications	None
Rosenfeld [21]	J Crohns Colitis	2013	Meta-analysis	344	General complications	None
Krane [13]	Dis Colon Rectum	2013	Retrospective single-center	65	General complications, anastomotic dehiscence, TE events and infections, conversions to laparotomy	None
Myrelid [17]	Br J Surg	2014	Retrospective single-center	111	Infectious, general and anastomotic complications	None
Yamamoto [23]	UEG Journal	2016	Prospective Multi Center	231	Overall complication, anastomotic complication	Penetrating disease, previous surgery, blood transfusion
Kotze [12]	Dig Dis Sci	2017	Retrospective Single Center	123	Surgical and medical complications	Steroids, hypoabluminemia
Fumery [8]	Am J Gastro	2017	Prospective Multi-Center	209	Steroid increase rates; no increased anti TNF	corticosteroids
Kotze [11]	Colorectal	2017	Retrospective Multi Center	123	Surgical and medical complications	Steroids, hypoabluminemia

Table 7.3 Studies showing an increased risk of postoperative complications with anti-TNF therapy in patients with Crohn's disease

Author	Journal	Year	Study design	Patients exposed to anti-TNF	Post operative outcomes	What associated with these outcomes other than ant TINF?
Appau [24]	J Gastrointest Surg	2008	Retrospective single-center	60	Higher rates of sepsis, abdominal abscesses, readmissions and anastomotic dehiscence	Steroid use higher in infliximab group
Kopylov [29]	Inflamm Bowel Dis	2012	Meta-analysis	423	Higher rates of infectious complications	None
Serradori [33]	Br J Surg	2013	Retrospective multicenter	42	Higher rates of infectious complications in multivariate analysis, in association with steroids	Steroid use
Syed [34]	Am J Gastroenterol	2013	Retrospective single-center	150	Higher rates of infection and surgical site infections	None
Narula [32]	Alim Pharmacol Ther	2013	Meta-analysis	987	Higher rates of complications in general and infectious complications	None
El-Hussuna [28]	Dis Colon Rectum	2013	Meta-analysis	Undefined	Higher rates of anastomotic complications in low bias studies	None
Billioud [25]	J Crohns Colitis	2013	Meta-analysis	977	Higher rates of Infectious complications	None
Yang [35]	Int J Surg	2014	Meta-analysis	Undefined	Higher rates of complications in general and infectious complications	None
Lau [30]	Ann Surg	2014	Prospective single-center	123	Higher rates of complications in general and infectious complications in patients with detectable IFX levels	None
Morar [31]	JCC	2015	Retrospective single center	165	Higher rates of intra-abdominal sepsis copmlications	Penetrating disease
de Buck van Overstraeten [27]	Br J Surg	2017	Prospective multi-center	538	Higher rates of anastomoic leak	ASA III, increased length of resection
Brouquet [26]	Ann Surg	2017	Prospective multi-center	592	Higher rates of all complications	Anemia, operative time, reoperative CD

Table 7.4 Complications with anti TNF and Ulcerative Colitis

Author	Journal	Year	Study Design	Patients exposed to anti-TNF	Post operative outcomes	Complications with anti-TNF
Selvasekar [41]	J Am Coll Surg	2007	Retrospective	47	Pouch related infectiou complications	Increased
Mor [40]	Dis Colon Rectum	2008	Retrospective	87	Postoperative complications	Increased
Kunitake [14]	J Gastrointest Surg	2008	Retrospective	101	Postoperative complications	No influence
Ferrante [38]	Inflamm Bowel Dis	2009	Retrospective	22	Postoperative complications	No influence
Yang [42]	Aliment Pharmacol Ther	2012	Meta-analysis	516	Total and infectious postoperative complications	Increased
Gainsbury [39]	J Gastrointest Surg	2011	Retrospective	29	Short term postoperative outcomes	No influence
Bregnbak [36]	J Crohns Colitis	2012	Retrospective	20	Total and infectious postoperative complications	No influence
Eshuis [37]	J Crohns Colitis	2013	Retrospective	21	Postoperative complications	Increased
Nørgård [19]	Aliment Pharmacol Ther	2013	Populational	214	Postoperative complications	No influence

significant finding given that it has been well established that peripouch sepsis is associated with worsened long term pouch function [40, 41]. On the other hand, anti-TNF does not appear to increase the risk of complications following a subtotal colectomy. Therefore, delaying the IPAA to a second stage is suggested in the setting of anti TNF therapy to optimize both short and long term pouch outcomes.

Vedolizumab, a humanized monoclonal antibody to a4B7 integrin, approved by the FDA in 2015 for the treatment of moderate to severe UC and CD, has been enthusiastically utilized for its theoretically improved safety profile due to its gut selective mechanism. However, the effect on postoperative outcomes has been the topic of much debate in the literature. The initial study garnering attention regarding the potential risk of veodlizumab was a single center retrospective review of 94 vedolizumab treated patients compared to 126 anti TNF treated patients and 172 non biologic patients [43]. The rate of all postoperative complications was significantly higher in the vedolizumab treated cohort as compared to anti-TNF or no biologic therapy (53% vs. 28% vs. 33%; $p < 0.001$), and on multivariable analysis,

vedolizumab was an independent predictor of postoperative infectious complications when compared to the anti-TNF ($p < 0.01$) and no biologic ($p < 0.01$) cohorts. A subsequent multi-center report of 146 vedolizumab treated patients compared to 289 anti-TNF patients similarly found an increased rate of postoperative surgical site infections (27% vs. 5%), and again found vedolizumab to be an independent predictor of surgical site infections on multivariable analysis ($p < 0.01$) [44]. Due to the perioperative safety concerns generated with this study, several other studies have since been performed with conflicting results. Data from the University of Chicago [45] and University Hospitals Leuven [46] reported no increased risk of postoperative complications, and a systematic review of the literature to date found no increased risk in postoperative complications. And, when the study by the Leuven group looked at the data based on the time interval from vedolizumab exposure to surgical intervention (12 weeks vs. 16 weeks), there was no difference in postoperative outcomes.

However, recent literature suggests there may be a difference in complications with perioperative vedolizumab exposure based on whether a patient has CD or UC. When looking at CD patients alone, there was a significant increase in postoperative complications [47]. However, when analyzing UC patients alone, there was no significant increase in overall rates of early postoperative infectious complications in two reported series [46, 48]. Interestingly, however, when looking at patients who had a IPAA within 12 weeks of vedolizumab exposure, the rate of peripouch abscess was higher than anti-TNF exposed patients (31.3% vs. 5.9%) [48] (Table 7.5).

Table 7.5 Studies of postoperative outcomes with vedolizumab

Author	Journal	Year	Study design	CD/UC/ Both	Patients exposed vedo	Post operative outcomes	Significant increase with vedolizumab
Lightner [43]	JCC	2017	Retrospective single-center	Both	94	30-day post op infectious complications	Yes
Lightner [44]	Inflamm Bowel Dis	2018	Retrospective multicenter	Both	146	30-day post op infectious complications	Yes
Lightner [47]	AP&T	2017	Retrospective single-center	CD	100	30-day post op infectious complications	Yes
Lightner [48]	IBD	2017	Retrospective single-center	UC	88	30-day post op infectious complications	Yes
Yamada [45]	Am J Gastroenter	2017	Retrospective single-center	Both	64	30-day post op infectious complications	No
Ferrante [46]	JCC	2017	Retrospective single-center	UC	34	30-day post op infectious complications	No

Ustekinumab, a humanized monoclonal antibody to interleukin 12 and 23, was only recently approved in 2017 for the treatment of moderate to severe CD. Due to the short window of approval, there are a limited number of patients which have undergone an operation while exposed to ustekinumab. In attempt to overcome this limitation, a consortium of six IBD referral centers was generated with the primary goal of investigating the rate of postoperative complications in the setting of ustekinumab. A total of 44 ustekinumab-treated patients were compared to 169 anti TNF treated patients. There was no significant increase in the rate of postoperative complications in the setting of ustekinumab [49], suggesting this drug may be safe in the perioperative period.

Do Drug Levels Help?

To date, three studies have looked at the association of preoperative serum drug levels and the relationship with postoperative complications. The first by Lau et al. looked at 123 CD patients and 94 UC patients with preoperative anti TNF levels, and found no difference in rate of complications in patients when comparing detectable versus undetectable levels [30]. A subsequent prospective study of 214 Crohn's patients undergoing an ileocecal resection collected serum drug levels on every included patient within 48 h of surgery, and found no difference in complications based on serum trough levels [8]. A recent abstract looking at serum vedolizumab levels also found no association with postoperative complications [50].

Recommendations

CD patients on anti-TNF therapy at the time of the surgery may be at increased risk of postoperative complications. Delaying elective surgery by at least 4 weeks may by optimal to decreased any potential risk from the biologic therapy, allowing for a washout period of two half-lives (anti TNF half life 10–14 days), but only if the patient's overall state of health will not worsen during that time. Otherwise, consideration may be given for the use of intestinal diversion following a primary anastomosis in the setting of 2 or more risk factors, one of which may be anti TNF therapy. CD patients on ustekinumab at the time of surgery are not at increased risk of postoperative complications as compared to patients on anti-TNF therapy. Thus, the same recommendations for anti-TNFs may be followed. CD patients on veodlizumab are likely at increased risk of postoperative complications. Thus, strong consideration should be given to delay elective operations for a washout period of at least two half-lives (50 days), or use of intestinal diversion, especially in the setting of additional risk factors for postoperative intra-abdominal sepsis.

In accordance with the American Gastroenterologic Association (AGA) guidelines, high risk patients (patients younger than 30 years old, actively smoking, $\geq$2 prior resections for penetrating disease) should be restarted on biologic therapy following surgery for postoperative prophylaxis [51]. It is unclear when biologic

therapy can be safely restarted. In patients without any postoperative complications, it seems reasonable to restart biologic therapy 4 weeks after surgery based on the patients preoperative dosing interval. In patients with postoperative complications, all postoperative infectious complications should be resolved for at least two weeks prior to initiation of biologic therapy.

UC patients on anti-TNF or anti-integrin therapy should delay IPAA by utilizing a 3 stage or modified 2 stage approach. There is no need to delay the first stage, a subtotal colectomy, in the setting of biologic therapy. Since biologic therapy is not needed after a subtotal colectomy, patients are afforded a prolonged (~12 week) washout period prior to IPAA.

Personal View

Patients with CD and UC, and operations associated with each, are disparate and therefore require a different approach. Patients with CD, exposed to anti-TNF therapy within the 12 weeks of a major abdominal operation, may be at increased risk of postoperative complications. Therefore, when feasible and safe, it is reasonable to delay elective surgery 4 weeks from the last dose of anti-TNF. When patients are on a Q8 week dosing interval, the perioperative management of anti-TNF can be relatively straightforward: patient receives dose of biologic → wait four weeks for surgery → resume the biologic 4 weeks after surgery. This ensures no dose is missed, and maintains the normal dosing interval. If a primary anastomosis is constructed at the time of surgery, consideration for the use of fecal diversion may be given for patients with two or more risk factors for intra-abdominal sepsis (e.g., corticosteroids, anti-TNF therapy, anemia, malnutrition), but is unnecessary based on anti-TNF therapy alone. We follow this same algorithm for ustekinumab treated CD patients given there is no known increased risk in postoperative complications as compared to anti-TNF therapy.

While the evidence remains controversial regarding the effect of vedolizumab on postoperative outcomes, there is enough mounting data to highlight an increased risk of postoperative complications following major abdominal operations, especially in CD. In fact, one center in the recently published multicenter study had two deaths in young vedolizumab exposed CD patients due to overwhelming postoperative sepsis of unknown etiology, an exceedingly uncommon complication in IBD patients [44]. In addition, our center has a handful of CD patients which have returned to the operating room within two days of surgery for symptoms consistent with an anastomotic leak (febrile, tachycardia, peritonitis), but at the time of exploration, no leak was identified resulting in a negative exploratory laparotomy. When scrutinizing the data which found no increased risk of postoperative complications in the setting of vedolizumab, it is important to note nearly half of the vedolizumab cohort from the University of Chicago study were patients undergoing perianal operations rather than major abdominal operations [45], and the study from Leuven included patients who received vedolizumab within 16 weeks of their operation [46]. Therefore, while we certainly await further evidence to help resolve this

controversy, for now it is reasonable to either delay an elective operation for 6 weeks (approximately two half-lives) to allow for a washout period, or consider diversion of a primary anastomosis in the setting of multiple risk factors associated with intra-abdominal sepsis.

In patients with UC who desire a definitive sphincter sparing restoration with a proctocoletomy and IPAA, there is limited downside with delaying the IPAA of the operation to a later date, allowing the patient to come off immunosuppression, and improve their nutritional status and anemia. Given that the largest pouch referral centers have reported increase pouch complications in the setting of anti TNF and vedolizumab [40, 41, 49], and it has been well described that pouch sepsis is associated with worsened long-term pouch function and increased pouch failure, it is logical to perform the pouch as a second stage operation. This allows a medically refractory patient to be off biologic therapy for a period of at least 12 weeks between their subtotal colectomy and IPAA, allowing for an optimized setting for their pouch operation.

Drug levels do not appear to be associated with postoperative complications, both with anti TNF therapy and vedolizumab. In addition, there is still little understanding as to what drug levels mean with regard to receptor saturation in the setting of vedolizumab. Therefore, we do not utilize serum drug levels to determine optimal surgical timing or assign a level of risk for postoperative complications.

Biologic therapy is one of many reported risk factors for postoperative complications following major abdominal surgery for Crohn's disease. Holding biologics for at least 4 weeks in the elective setting may help obviate the potential increased risk of postoperative complications, and can be timed such that patients remain on a Q8 week dosing interval. Use of diversion may be considered in the setting of two or more risk factors, of which biologic therapy may be one such factor. In UC, IPAA should be delayed to a second stage in the setting of biologic therapy in order to optimize pouch outcomes, and prevent long term sequelae of peripouch sepsis.

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Management of Perianal Skin Tags

8

Emily Steinhagen

Introduction

The incidence of skin tags in Crohn's disease (CD) is likely underreported as few studies consider them to be as significant as other perianal manifestations such as fissure or fistula and may not even consider their existence. Skin tags can be typically classified into two types: "elephant ear" tags which are usually painless and can be soft or firm, broad- or narrow-based, and the more cyanotic, edematous, tender tags that generally arise after healing from another anorectal pathology [1]. Skin tags likely occur more frequently in patients who demonstrate distal disease.

When other forms of perianal disease have been evaluated, the absence of concomitant proctitis suggests a better prognosis—this may also be true of skin tags [2]. These tags may act as a marker of more proximal inflammation as they often swell and become inflamed when intestinal disease is more active [3]. It is hypothesized that Crohn's disease-related skin tags arise from lymphedema secondary to lymphatic obstruction. They are a generally benign entity, but patients may complain of painful, inflamed tags or report that the size and number of the tags make hygiene difficult. In some cases, skin tags may resemble hemorrhoids and may be misclassified as such. The reported incidence of symptomatic hemorrhoids in inflammatory bowel disease (IBD) patients ranges from 3.3% to 20.7% [4]. Nevertheless, excisional hemorrhoidectomy leads to similar surgical wounds as a skin tag excision and therefore the outcomes of the procedure may be used to extrapolate potential strategies of tag excision.

Historically, it was felt that perianal wounds in Crohn's disease patients do not heal so these wounds were avoided at all costs [5]. However, this dogma has been challenged by many; a guide as to when it is appropriate to excise perianal skin tags

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Table 8.1 PICO questions

P (Patients)	I (Intervention)	C (Comparator)	O (Outcomes)
Patients with Crohn's disease who have perianal skin tags	Surgical excision	Expectant management	Complications, symptomatic relief
Patients with Crohn's disease who have hemorrhoids	Surgical excision	Expectant management	Complications, symptomatic relief

in patients with Crohn's disease would aid many surgeons who are frequently faced with requests from patients and referring providers to address this issue. In this chapter, the literature related to the management of perianal skin tags as well as hemorrhoids in Crohn's disease patients will be reviewed and recommendations for the treatment of perianal skin tags will be provided.

Search Strategy

Relevant PICO (Population, Interventional, Comparator, Outcome) questions were generated (Table 8.1). A Medline and PubMed search was conducted for English language publications between January 1975 and July 2018 using the following search terms: ('inflammatory bowel disease' or 'IBD' or 'Crohn's') AND ('skin tag' or 'skin tags' or 'anal tags' or 'hemorrhoid' or hemorrhoids' or 'haemorrhoid' or 'haemorrhoids'). Patients from 1935 to 2011 were included in the studies. The reference section of each relevant article was reviewed to identify additional articles pertaining to this topic. Retrospective, prospective, observational, and randomized studies were included. The inclusion of the literature related to hemorrhoids was due to the paucity of studies examining the role of surgery in the management of anal skin tags in Crohn's disease.

Results

In 1978, Hughes concluded his report about surgery for Crohn's disease patients by stating that "local surgery should be avoided when signs of disease activity are present since healing is likely to be poor." [5] While there have been no studies designed to specifically evaluate the outcome of surgery for anal skin tags in this group, Hughes' caution is still a reasonable place to start in the approach to this benign problem.

The best available information about the topic comes from very limited subsets of already small case series in which this data is incidentally reported. One of the biggest issues in some of the earliest series is that the complications and incidence of proctectomy were not temporally related to skin tag excision [6]. The fissures and fistulas seen afterwards and the need for proctectomy may not have been related to the skin tag excision itself. Rather, the skin tags were incidental to perianal disease severe enough to cause other problems that drove the need for proctectomy.

In one study, skin tags were excised in the office setting under local anesthesia with the goal of histologic evaluation [7]. The authors report that "the procedure

was well tolerated and without complication" but do not comment on healing or other problems that might have developed after the excision. This could indicate that there were no long-term complications, or that the procedure itself was completed without difficulty. Given the nature of the study, the former seems more likely but without careful reading this could be misinterpreted.

No study includes information about overall disease severity at the time of intervention. This information would be useful as most colorectal surgeons would not perform surgery for skin tags in a patient suffering with active inflammation.

Several studies report on outcomes of hemorrhoidectomy in Crohn's disease patients. Unfortunately, the time to complications is not well described across studies. This makes it difficult to infer causation and whether the complications that developed were driven by the disease itself or were truly procedure-related. It is quite likely in some series that the high rate of proctectomy reflects severe perianal disease such as when proctectomy was performed 15 years after the hemorrhoidectomy [8]. When surgery is restricted to hemorrhoids arising in patients with stable intestinal disease without the need for corticosteroids and a Crohn's disease activity index (CDAI) <150, significant complications were infrequent [9].

When studies include patients who were not diagnosed with IBD until after their surgery, patients tend to have higher reported rates of complications [9, 10]. This demonstrates the importance of excluding Crohn's disease prior to proceeding with anorectal surgery. It may also reflect the reluctance and more stringent criteria of surgeons operating on patients with known Crohn's disease. While the heterogeneity in the data limits the ability of practitioners to apply the findings to their patients, it does suggest that patients with well controlled disease will experience better outcomes (Tables 8.2 and 8.3).

Table 8.2 Studies evaluating surgery for perianal skin tags in Crohn's disease patients

First author (year)	Patients studied	Intervention	Study design	N	Complications	Quality of evidence
Buchman (1980) [11]	Patients with skin tags and CD	Observation	RO	37	Resolved in 32%	Very low
Keighley (1986) [6]	Patients with skin tags and CD	Observation Excision	RO	75 2 excisions	Observation: Resolved in 39% of patients with no treatment; 10 had proctectomy due to intestinal disease Excision: 1 (50%) healed; 1 did not and developed stenosis	Very low
Taylor (1989) [7]	Patients with skin tags and CD	Excision	PO	26	0	Very low

R retrospective, *PO* prospective observational, *RO* retrospective observational

Table 8.3 Studies evaluating surgery for hemorrhoids in Crohn's disease patients

First author (year)	Patients studied	Intervention	Study design	N	Complication rate with surgery Complications	Quality of evidence
Jeffery (1977)[10]	Patients with hemorrhoids and CD; included those diagnosed after treatment	Observation; excisional hemorrhoidectomy if observation failed	RO	21 patients; 12 required surgery	66% 1 anal pain 10 fistula/abscess → 6 went on to require proctectomy for fistulas	Very low
Hughes (1978) [5]	Patients with hemorrhoids and CD	Surgery	PO	2	0	Very low
Keighley [6] (1986)	Patients with hemorrhoids and CD	RBL	PO	2	50% 1 stenosis	Very low
Wolkomir (1993) [8]	Patients with hemorrhoids and CD	Surgery	RO	17	29.4% 2 stenosis 2 nonhealing wounds 1 fissure → proctectomy (15y later)	Very low
D'Ugo (2013) [9]	Patients with hemorrhoids and CD; included those diagnosed after surgery	Excisional hemorrhoidectomy or RBL if failed conservative management	PO	17 (2 RBL)	41.2% 3 bleeding 2 fissure 2 abscess/fissure	Very low

RBL rubber band ligation, *R* retrospective, *PO* prospective observational, *RO* retrospective observational

Recommendations Based on the Data

Perianal skin tags in patients with Crohn's disease should generally not be excised. (*Weak recommendation based on very low quality evidence*).

Personal View of the Data

While there is essentially no high-quality data evaluating the outcomes of perianal skin tag excision in Crohn's disease patients, there is certainly common sense that can and should dictate management.

Patients with symptomatic skin tags and active inflammation, particularly in the rectum, should have treatment directed at controlling the inflammation. This will intrinsically help with the inflammation of the tags but will also decrease the number of bowel movements and improve stool consistency; this, in turn, should provide some symptomatic relief. Sitz baths, moistened wipes for hygiene, and careful cleaning also play a role in reducing the symptoms of irritated skin tags. Anorectal surgery in the face of uncontrolled inflammation is a setup for poor healing.

For Crohn's disease patients in remission complaining of hygiene issues and impaired quality of life secondary to large or multiple skin tags, it may be reasonable to consider excision especially if the tags are narrow-based and the resulting defects will be small. However, it is difficult to truly quantify the risk in this situation and a good understanding of the potential complications is critical. The association between skin tag excision and proctectomy is more likely a reflection of natural disease progression than the procedure itself based on the very limited descriptions in the available studies.

Much of the data on this topic is a subset of a smaller series on overall perianal disease, and essentially (or virtually) all of it includes patients treated prior to modern Crohn's disease therapies such as biologic agents. To truly understand the risk of operating for perianal skin tags, anecdotal common wisdom requires quantification. Large databases and registries may enable appropriate data analysis to guide future practice.

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Management of Chronic Anal Fissures in Patients with Crohn's Disease

9

Stewart Whitney and Randolph Steinhagen

Introduction

Anal fissures begin with a tear in the anoderm that often presents with bleeding and pain, and can progress to a chronic fissure in up to 40% of patients [1]. In the general population, the etiology is believed to be related to local trauma and/or ischemia. Most acute fissures heal with stool-bulking, topical medications, and local care. If acute fissures do not heal and become chronic, the treatment algorithm expands. Non-surgical options, including botulinum toxin injection or topical medications such as nitric oxide donors and calcium channel blockers are efficacious, but have been shown to be inferior to lateral internal sphincterotomy (LIS) in promoting healing and preventing recurrence. However, LIS carries a small risk of both transient and permanent incontinence [2].

Management of fissures becomes much more complicated in patients with perianal Crohn's disease, who can develop perianal pathology secondary to chronic inflammation linked to the disease. As a result, the treatment algorithm is much different because the pathophysiology is dissimilar and surgical intervention carries a higher risk of complications related to poor wound healing and incontinence. We will review the literature concerning management of chronic fissures in patients with Crohn's disease with regards to LIS and other surgical procedures, and provide recommendations based on this appraisal.

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Patients	Intervention	Comparator	Outcome
Patients with Crohn's disease with chronic anal fissure	LIS	Non-operative management	Fissure healing, incontinence, symptomatic relief

Search Strategy

A comprehensive literature search of the Cochrane Review Database, Medline and PubMed was performed to identify all publications involving chronic anal fissures and Crohn's disease between 1960 and 2018. Keywords for search included: "anal fissure," "chronic anal fissure," "Crohn's disease." References of these studies were then reviewed to incorporate any other pertinent studies. Outcomes measured and compared were: short-term morbidity, mortality, intra-operative complications, resolution of fissure, recurrence, long-term complications (incontinence).

Results

The management of chronic anal fissures has been well-studied, and multiple Cochrane reviews have examined this topic. The first was comprised of 75 randomized clinical trials that included over 5000 patients who were managed with either medical therapy or surgery [3, 4]. The review showed that topical nitroglycerine was superior to placebo in promoting healing (48.9% vs. 35.5%, $p < 0.0009$) and similar results were found with topical calcium channel blockers (e.g., nifedipine) and botulinum toxin injection making these agents safe and effective as first-line treatment for chronic fissures. However, recurrence was noted in approximately 50% of cases. LIS has been shown to have more enduring cure rates as compared to medical management in the general population. One prospective randomized controlled trial consisting of 142 patients showed healing at 8 weeks in 88.2% of patients in the LIS group and 68.9% of patients in the nifedipine group ($p = 0.007$) [5]. This study also found decreased pain at 3 and 7 days with LIS compared to topical nifedipine. A different randomized controlled trial comparing LIS to botulinum toxin injection plus topical diltiazem showed a significantly higher rate of healing in the LIS group for fissures that had been present for longer than 12 months (86% vs. 23%, $p < 0.001$) [6].

Chronic anal fissures in patients with Crohn's disease have a different etiology when compared to the general population. It is believed that chronic fissures in this group develop as the result of chronic inflammation secondary to the underlying disease rather than local trauma [7]. Another characteristic of anal fissures or ulcerations in Crohn's disease is the variability of their location. In the general population, the posterior and anterior midlines are the most commonly involved sites whereas fissures are often multiple and frequently situated off the midline in patients with Crohn's disease [7]. As a result, a different treatment algorithm should be applied to these patients. One retrospective study looked at a cohort of patients with

Crohn's disease at a single institution [8]. They compared 29 male and 27 female patients who had anal fissures; 41 patients underwent initial medical management and 15 underwent immediate LIS with fissurectomy. They reported short-term healing rates of 50% in the medical group and 67% in the surgical group. In patients who also had severe bowel involvement, only 43% experienced proper healing. After long-term follow-up, 17 of 35 patients in the medical group had healed fissures (49%), while 9 of 15 patients in the surgical group healed (60%). Of the patients with non-healed fissures, 26% developed a fistula leading the authors to propose a more aggressive use of LIS in this population to prevent fistula or abscess formation. Moreover, a statistically higher rate of healing was observed in the surgical patients who did not have concomitant resection of involved proximal bowel compared to those who also underwent intraabdominal surgery (88% vs. 29%, $p = 0.03$) [8].

Another study looked at outcomes for patients previously diagnosed with Crohn's disease presenting with symptomatic hemorrhoids and fissures; 41 patients were diagnosed with fissures and 53.7% of these also manifested intestinal involvement [9]. All patients were initially treated nonoperatively and those with stable intestinal disease who failed conservative management were eligible for surgical intervention. Ultimately, 14 of the 41 patients underwent surgery for their anal fissure (i.e., botulinum toxin injection, botulinum toxin injection plus fissurectomy, LIS), and 8 of 14 patients (57%) suffered one or more complications including poor wound healing, recurrence, and fistula formation (Table 9.1).

As a result of the distinctive etiology of chronic fissures in patients with Crohn's disease, different non-surgical options exist. Topical metronidazole was used in one study and did show some relief in symptoms at 4 weeks [12]. Use of other topical agents, such as tacrolimus, has also been reported. One study showed improvement with topical tacrolimus in 3 out of 4 patients (while also on systemic therapy for Crohn's disease) compared with 0 out of 3 in the placebo group [13]. Systemic agents

Table 9.1 Studies involving anal fissures and Crohn's disease and surgical interventions

First author (year)	Study population	Intervention	N	Healing rate	Quality of evidence
Fleshner (1995) [8]	Patients with fissures and CD	LIS or Fissurectomy vs. Medical management, bowel surgery	56	Medical—19/38 Anal surgery −7/8 Bowel surgery-3/7	Low
Sweeney (1988) [10]	Patients with fissures and CD	Medical management vs. anal surgery	61	Medical—19/24 Surgery—0/6	Low
D'Ugo (2013) [9]	Patients with fissures or hemorrhoids and CD	Medical management vs. anal surgery	41	Medical	Low
Wolkomir (1993) [11]	Patients with fissures and CD	Fissurectomy/ ulcerectomy, LIS, partial LIS, multiple LIS	25	Short term outcomes not reported	Low

have been used in management of fissures or ulcerations in Crohn's disease, but the results are inconsistently reported with none of the studies having primary end-points related to fissures. Cyclosporine, thalidomide, and hyperbaric oxygen have been reported to provide possible benefit, but only in small uncontrolled studies [14–16].

Anti-TNF agents have become increasingly utilized for the management of perianal Crohn's disease. Although many reports have focused on fistulizing disease, some also looked at the efficacy of anti-TNF agents with regards to healing of fissures and ulcerations. One study had patients on systemic infliximab therapy while also performing local injections of infliximab for chronic fissures [17]. Only a trivial potential benefit was reported in this small uncontrolled study. Bouguen examined healing rates of chronic fissures and ulcerations using systemic infliximab [18]. Of 94 patients identified with anal canal ulcers, 40 patients (42.5%) had a complete response following induction of therapy. After a median follow-up of 175 weeks (range 13–459), complete response was seen in 68 of 94 patients (72.3%).

Control of proximal bowel disease has long been known to influence perianal Crohn's disease. The role of fecal diversion has been well described regarding anorectal fistulas in Crohn's disease; however often the diversion becomes permanent [19]. Sweeney reported that most patients with fissures improved with medical therapy alone; 42 of 61 patients who demonstrated disease in the proximal bowel had fissure healing, however 16% developed other perianal lesions [10]. McKee found that outcomes of patients with perianal Crohn's disease were related to the extent and severity of proximal bowel involvement, with patients who had more severe proctitis exhibiting lower rates of perianal disease healing [20]. Fleshner reported that only 3 of 7 patients with fissures who had severe small bowel or colonic disease and underwent an intraabdominal operation healed their fissure [8].

Surgery has long been discussed in the management of fissures in Crohn's disease and its role remains debated. Due to the association of fissures with sphincter hypertonicity, LIS has been a common procedure performed in the general population. In patients with Crohn's disease, fissures are more likely to result from the underlying disease. Accordingly, they are at significant risk for developing chronic non-healing wounds or fistulas after surgical intervention. Additionally, patients with Crohn's disease have higher rates of chronic diarrhea, thus potentially increasing the risk of fecal incontinence after LIS. It is because of these factors that we recommend taking a more conservative approach to anal fissures in the Crohn's disease population with management focused on control of proximal bowel disease and symptoms related to the fissure. LIS can be considered in highly selected cases with quiescent rectal disease and evidence of sphincter hypertonicity.

Recommendation Based on the Data

Surgical management of fissures in patients with Crohn's disease should be approached with great caution due to the high risk of poor wound healing and the possibility of continence issues in these patients with chronic diarrhea. LIS should

be considered only in highly selected patients who demonstrate internal sphincter hypertonicity and fissures that resemble a typical anal fissure without proctitis. (moderate recommendation, low quality evidence)

A personal View of the Data

Despite the lack of high-quality evidence, lateral internal sphincterotomy should be approached with a great deal of caution in patients with Crohn's disease. Fissures complicating Crohn's disease are not commonly associated with hypertonicity of the internal sphincter and LIS in this setting is illogical and potentially harmful because perianal wounds heal very poorly in patients with Crohn's disease, especially when significant proctitis or more proximal intestinal disease is present. If faced with a fissure secondary to hypertonicity of the internal sphincter in a patient with Crohn's disease and significant proctitis, the proctitis should be successfully managed before considering a LIS. Finally, the issue of impaired continence becomes much more important in a patient with Crohn's disease compared to the general population.

The typical patient without Crohn's disease who has an anal fissure and a hypertonic internal sphincter, is more likely to complain of associated constipation. Therefore, the small reduction in sphincter pressure associated with a LIS is more likely to improve their bowel function than cause incontinence. Conversely, Crohn's disease patients often suffer from diarrhea that is either chronic or episodic, and the reduction in sphincter pressure resulting from a LIS is more likely to produce long-term disturbances in continence. Therefore, the only patients with Crohn's disease for whom LIS is considered are those with an internal sphincter that is clearly hypertonic and hypertrophied and a fissure that is single, located in the midline, and uncomplicated by overhanging edges, proctitis, or more proximal disease. The practical result of these rather stringent criteria is that only a very small number of patients with fissure complicating their Crohn's disease are suitable candidates for LIS.

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Management of Simple Anoperineal Fistulas

10

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Introduction

Patients with anoperineal Crohn's disease (CD) are often challenging to treat. They frequently require a combination of medical and surgical treatment to control their disease. More than one-third of patients with Crohn's disease will at some point develop perianal disease, and some patients will have it as their presenting symptom several years before a diagnosis of Crohn's disease is made [1]. Anal fistulas are particularly difficult to treat in patients with Crohn's disease due to the pathophysiologic characteristics of the disease, the high likelihood of recurrence, and the potential for surgical complications [2].

Although medical management of Crohn's disease is crucial to achieve long-term control of perianal disease, surgery is sometimes required as a primary treatment or as an adjunct to other treatments. It is usually reserved for patients who present with active infection or sepsis, or to treat complex or non-healing perianal fistulas. The American Society of Colon and Rectal Surgeons currently recommends no surgical treatment for asymptomatic fistulas, while simple low anal fistulas can be safely treated with fistulotomy [3, 4].

In this chapter, we will address the management of simple perianal fistulas (including superficial, intersphincteric, and low transsphincteric that cross 30% or less of the external anal sphincter), comparing surgical management to medical management, specifically biologics and immunomodulators. We will review the relevant literature, looking at the success rate of treatment, as well as the complications from surgery including incontinence.

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Table 10.1 PICO question

P (Patients)	I (Intervention)	C (Comparator)	O (Outcomes)
Crohn's disease patients with simple fistula-in-ano	Surgical management (fistulotomy, seton, fistula plug/glue)	Medical management (antibiotics, infliximab, tacrolimus)	Healing rates and recurrence, complications (incontinence)

Search Strategy

We performed our literature review using a Medline and Pubmed search for publications in the English language addressing the surgical and medical management of simple perianal Crohn's disease in the last 2 decades. We included studies published between January 1995 and June 2018, and we used the following search terms: "Crohn's," "perianal disease," "simple fistula," "fistula-in-ano," "fistulotomy," "seton," "medical management," "infliximab," "adalimumab," "tacrolimus," "immunomodulator," "biologic," "outcome," "healing rate," "recurrence," incontinence."

We then looked at the reference section of each article to identify additional studies relevant to our review. We included randomized trials, retrospective and prospective studies. We included articles looking specifically at simple perianal fistulas, and excluded studies addressing the management of complex perianal disease and rectovaginal fistulas (Table 10.1).

Results

Over the past few decades, several studies have been published looking at the management of perianal fistulas in patients with Crohn's disease. Only a few of these studies however reported separate outcomes for simple fistulas, and even fewer only included simple fistulas in their study population. Those were all included in Table 10.2. The surgical management of complex anal fistulas in Crohn's disease will be discussed in a different chapter.

The earlier studies were mostly retrospective reviews of patients with Crohn's disease presenting with simple anal fistulas, who were surgically treated. Halme performed a 20-year review of Crohn's disease patients showing 100% healing rate following fistulotomy, compared to 50% following seton placement for simple fistulas [5]. In a similar review with a higher number of patients, Scott described more comparable healing rates between the two techniques (81% vs. 85%) [6]. Both studies reported some degree of anal incontinence in about 20% of patients after fistulotomy [5, 6]. Around that same time, three retrospective reviews looking at fistulotomy in Crohn's disease patients also reported similar outcomes. Williamson, in a 20-year review, reported a healing rate of 85% in 22 patients with

Table 10.2 Studies evaluating management of simple anal fistulas in Crohn's disease patients

First author (year)	Patients (N)	Study design	Treatment modality	Healing rate	Incontinence (post-operative complication)	Quality of evidence
Halme (1995)	18	R	Fistulotomy vs. seton	100% vs. 50%	20% (to some degree) vs. 0%	Low
Scott (1996)	54	R	Fistulotomy vs. seton	81% vs. 85%	19% vs. 0%	Moderate
Williamson (1995)	22	R	Fistulotomy	85%	13%	Low
Sangwan (1996)	47	R	Fistulotomy	N/A	0%	Low
Platell (1996)	34	R	Fistulotomy	91%	0%	Low
Michelassi (2000)	33	PO	Fistulotomy	27/33 (82%)	2/33 (12%)	Moderate
Van Koperen (2009)	28	PO	Fistulotomy	82%	>50% (to some degree)	Low
Witte (2007)	11	PO	Fibrin glue	54%	N/A	Low
Grimaud (2010)	41	RCT	Fibrin glue vs. observation	50% vs. 18%	N/A	High
Senéjoux (2016)	78	RCT	Fibrin plug after seton vs. seton alone	30% vs. 25%	N/A	High
Lowry (1999)	22	R	Oral tacrolimus, and AZA or 6-MP	7 complete response (32%) 4 partial response (18%)	N/A	Low
Thia (2009)	25	RCT	Ciprofloxacin vs. metronidazole vs placebo	40% vs 14.3% vs 12.5%	N/A	Moderate
Topstad (2003)	21	R	Seton followed by infliximab	67% complete response 19% partial response	0%	Low
Park (2017)	20	R	Fistulotomy or seton followed by infliximab	75%	0%	Low

PO prospective, *R* retrospective, *RCT* randomized controlled trial, *AZA* azathioprine, *MP* mercaptopurine

low fistulas [7]. Postoperative incontinence was observed in 13% of patients, but that included cases with complex fistulas [7]. Sangwan reported no postoperative incontinence in his series of 47 patients with anal fistulas, 35 of whom underwent fistulotomy [8]. Platell showed an excellent healing rate of 91% of the 34 patients with simple fistulas [9]. More recently, Michelassi prospectively recorded outcomes of 224 patients with Crohn's disease and perianal disease, 33 of whom had simple fistulas, over a period of 15 years. They reported a healing rate of 82%, with incontinence in two of the patients (12%) [10]. Similarly, van Koperen prospectively studied surgical outcomes following fistulotomy. Out of the 28 patients included in his series, 23 demonstrated complete resolution and healing (82%) [11]. More than one-half of the patients in that series however, reported at least some degree of fecal incontinence [11].

There have also been a few studies looking at the use of fibrin and collagen products in the treatment of simple anal fistulas in patients with Crohn's disease. Witte prospectively looked at the outcomes of patients undergoing fibrin sealant treatment of anal fistulas. The subset of patients with Crohn's disease had a healing rate of 54%, which was similar to the healing rate of patients with simple fistulas and no Crohn's disease [12]. In a multi-center randomized controlled trial (RCT), Grimaud compared outcomes of fibrin sealant treatment compared to no treatment for patients with perianal Crohn's disease. They found a significant increase in healing rate from 18% to 50% in the group of patients with simple fistulas [13]. In another RCT, Senéjoux looked at the use of collagen plug following seton removal in Crohn's disease patients. In the subset of patients with simple fistulas, the healing rate was 30% for patients treated with the plug compared to 25% for patients who merely had their seton removed with no further surgical treatment [14]; this difference was not statistically significant.

Lastly, some authors have reported outcomes with different medical therapies used in Crohn's disease patients with simple fistulas. Lowry retrospectively reviewed the role of oral tacrolimus plus azathioprine or 6-mercaptopurine to treat 22 patients with low simple fistulas; 7 of these patients had complete response, and 4 had partial response (32% and 18% respectively) [15]. Thia studied antibiotic treatment in an RCT, where Crohn's disease patients with simple fistulas were treated with either ciprofloxacin, metronidazole, or placebo. Healing of the fistula was achieved in 40% of patients treated with ciprofloxacin, compared to 14.3% of those managed with metronidazole, and 12.5% for those receiving placebo [16]. However the number of patients was too low in each group, and the study was underpowered to show a significant difference. Topstad retrospectively reviewed 22 patients treated with infliximab, 14 of those underwent seton placement before treatment. The complete healing rate was 67%, with 19% showing partial response [17]. No incontinence was reported in that group. Another retrospective study by Park looked at patients managed with infliximab following either fistulotomy or seton placement. The subset of patients with simple fistulas experienced a 75% healing rate after induction, and 100% with maintenance therapy [18]; no incontinence was reported in that selected group.

Recommendations Based on the Data

To summarize these data, the first seven studies looking at outcomes following fistulotomy consistently revealed excellent rates of healing that ranged from 82% to 100% [5–11]. Furthermore, the incontinence rate following fistulotomy was 0% to 20%, except for one report that showed some degree of incontinence in more than one-half of the patients. This wide range and difference in incontinence rates may reflect differences in the way incontinence was assessed in these patients. But overall, the trend is toward excellent healing rates following fistulotomy for low simple fistulas with acceptable risk for incontinence. Non-cutting seton placement was associated with slightly lower healing rates ranging from 50% to 85% in two of the studies but no incontinence was reported [5, 6]. In comparison, the studies that examined the role for fibrin and collagen products as primary treatment of these patients, showed that these products did not achieve healing rates comparable to fistulotomy, and ranged from 30% to 54% [12–14]. Medical management without surgical therapy achieved even lower healing rates [15, 16]. However, when used in combination with surgery, infliximab was shown in two separate studies to provide healing rates ranging from 67% to 75% [17, 18].

Based on these available data, we recommend that patients with Crohn's disease presenting with symptomatic simple anal fistulas undergo fistulotomy as primary treatment. If there are concerns about significant sphincter muscle involvement or risk for incontinence with fistulotomy, seton placement is a good alternative. Infliximab or other biologics should not be used alone in the treatment of simple anal fistulas, but rather in combination with surgical treatment.

Personal View

Our experience with Crohn's disease patients presenting with perianal disease is consistent with the reviewed published data. Patients who have well controlled disease and present with a simple anal fistula are best treated with an examination under anesthesia, and when no or minimal external sphincter muscle is involved, we perform a fistulotomy if we believe their risk for incontinence from fistulotomy is low. The majority of these patients will have complete resolution of their symptoms. However, if there is any concern about significant sphincter involvement or active proctitis, we usually place non-cutting setons and optimize medical management. These patients tend to have recurrences and several fistulas, and we accordingly avoid dividing any sphincter muscle. Seton placement is a valid and effective alternative to fistulotomy, and in our experience patients tolerate this approach very well.

Most of the recently published data about perianal Crohn's disease mainly focuses on the management of complex fistulas, and on new medical treatments. The optimal surgical management of simple fistulas has been established for decades. These older published studies all report good outcomes following

fistulotomy for Crohn's disease patients with simple fistulas. This is why it is crucial for surgeons treating these patients to know how to assess the disease, and to offer the appropriate surgical treatment.

1. **Patients with Crohn's disease presenting with symptomatic simple anal fistulas should undergo fistulotomy as primary treatment.**
2. **If there are concerns about sphincter muscle involvement, seton placement is a good alternative.**

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Management of Severe Anoperineal Disease

11

Sergey Khaitov and Asya Ofshteyn

Introduction

Perianal involvement can occur in up to 42% of patients with Crohn's disease and has the potential to cause significant life impairment [1, 2]. Close to 90% of patients with anoperineal Crohn's disease require surgical intervention at some point in their lifetime [3, 4], and up to 38% of patients with complex perianal fistulas undergo fecal stream diversion [5, 6]. This chapter focuses on surgical treatment of severe perianal Crohn's disease (pCD) with a goal to compare seton placement with temporary fecal diversion (Table 11.1).

No established definition exists in the literature for what constitutes severe perianal Crohn's disease. Traditionally, fistulas are classified as simple or complex fistulas by criteria described by the American Gastroenterological Association [7]. However, anatomic complexity is only one of the many factors that affects patient experience. The Perianal Disease Activity Index (PDAI) is a disease activity score that uses five sequelae to categorize severity of perianal disease, including levels of discharge, pain interfering with day-to-day activity, restriction of sexual activity, degree of induration, and type of disease [8]. Although useful for clinical trials, the PDAI and other measurements of perianal Crohn's disease activity such as fistula drainage assessment are not routinely used in clinical practice. Additionally, there is

Table 11.1 PICO question

Patients	Intervention	Comparator	Outcome
Patients with severe perianal Crohn's disease	Fecal diversion	Multiple setons	Long-term stoma avoidance, quality of life

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no PDAI threshold for mild versus severe perianal Crohn's disease. Therefore, most gastroenterologists and surgeons focus on individual patient-reported experience and global clinical judgment to define severe disease [9]. For the purposes of this chapter, we have defined severe perianal Crohn's disease as anoperianal involvement with: (1) infectious complications requiring frequent surgical intervention; (2) persistent discomfort and incontinence significantly affecting quality of life.

Search Strategy

We performed a comprehensive search of the Medline, Pubmed, Web of Science, and Cochrane databases using the following search terms: 'Crohn's disease' and ('perianal' OR 'perineal' OR 'anoperineal') and ('management' OR 'seton' OR 'diversion' OR 'stoma' OR 'ostomy'). The search was limited to peer-reviewed English language publications between 1950 and 2018. Any relevant studies found in reference sections of pertinent articles were also included. All abstracts were reviewed and papers evaluating outcomes of either fecal diversion or multiple seton placement were selected. We sought to include randomized, observational, prospective and retrospective studies, but only retrospective and prospective observational studies were available. These are represented in the Table 11.2.

Results

No studies directly compare fecal diversion with seton management in the same patient population. Most of the literature consists of retrospective chart and database reviews that describe a varied patient population with perianal Crohn's disease, a wide range of surgical interventions, and a plethora of outcomes (Table 11.2). For this review, all patients had anoperineal Crohn's disease including simple and complex anorectal fistulas, ano- or rectovaginal fistulas, and differing levels of proctitis or other proximal disease. Surgical interventions were chosen based entirely on the discretion of the treating surgeon and consisted of local therapy including: loose seton placement with or without incision and drainage; definitive treatments including cutting setons, fistulotomy, fistula plug, fistula glue, advancement flap, sphincterotomy, sphincteroplasty, fissurectomy, and soft tissue flaps (local surgical treatment outcomes described in Table 11.2), and; major operations including loop ileostomy, small or large bowel resections, and proctectomy (diversion outcomes described in Table 11.3).

When reported, concurrent medical management was similarly diverse. Some patients received only antibiotics, while others also received immunosuppressants (e.g., methotrexate, thiopurines). Patients enrolled in more recent studies received biologic agents, most commonly infliximab or adalimumab but at different dosages and durations of treatment (combined biologic agent and seton outcomes described in Table 11.4). Reported outcomes also wildly differed, including anoperineal healing, initial versus lasting perianal Crohn's disease improvement, patient

Table 11.2 Studies describing outcomes of seton placement or diversion with and without medical therapy for perianal Crohn's disease

First author (year)	Patients studied	Intervention	Study design	N	Outcome	Quality of evidence
van Dongen (1986) [10]	Patients with pCD	No treatment, local surgery, diversion, proctectomy	R	55	13 no treatment (4 healed), 28 local surgery (2 with setons, 22 healed, 2 proctectomy), 9 diversion (4 healed, 2 stomas closed), 5 proctectomy (2 persisted)	Very low
Bernard (1986) [11]	Patients with pCD	I&D ± seton, fistulotomy, proctectomy	R	102	57% I&D ± seton required fistulotomy; primary fistulotomy for abscess 71% healed; primary fistulotomy for chronic fistula 60% healing; 12% proctectomy	Very low
Radcliffe (1988) [12]	Women with pCD and anovaginal or rectovaginal fistula	Medical management, fistulotomy or I&D, repair of fistula, proctectomy	R	90	12 medical management, 12 fistulotomy or I&D, 12 fistula repair (8 cured, 1 symptomatic, 3 proctectomy), 8 diverted, 46 proctectomy	Very low
Fry (1989) [13]	Patients septic pCD	Perianal intervention, diversion, proctectomy	R	73	After 4.6 years f/u: 38 healed and 17 acceptable condition after one or more EUA; 9 healed with diversion, 9 required proctectomy	Very low
Fry (1989) [13]	Patients with pCD	Seton or fistulotomy	R	73	Mean follow up 4.6 years. 38 healed after one or more local treatment, 17 incompletely healed, 9 healed after diversion, 9 proctectomy	Very low
Williams (1991) [14]	Patients with high anal fistula (23 with pCD)	Long-term seton	R	23	9 recurred, 3 proctectomy	Very low
Scott (1992) [15]	Women with pCD ± RVF	Local surgery, diversion, proctectomy	R	67	13/38 women with anorectal fistula got diversion or proctectomy compared to 18/29 women with RVF	Very low

(continued)

Table 11.2 (continued)

First author (year)	Patients studied	Intervention	Study design	N	Outcome	Quality of evidence
Pescatori (1995) [16]	Patients with pCD ± intestinal involvement	Medical management, surgery	R	225	123 initial medical management (21 healed); 166 anal surgery—18 seton, 8 proctectomy, rest drainage, fistulotomy, excision, sphincterotomy, sphincteroplasty (97 pCD healed or improved)	Very low
Koganei (1995) [17]	Patients with severe pCD	Seton placement	PO	10	Mean follow-up 12.1 months 10/13 improved, one colostomy for intestinal disease, 2 did not improve, 8/13 had some setons removed	Very low
Pescatori (1995) [16]	Patients with pCD	Local surgery, medical management	R	225	Median 6 years follow-up 166 anal surgery—97 (58%) positive outcome. 24.5% recurrence. Medical treatment curative 21/123	Very low
Sangwan (1996) [18]	Patients with pCD	Local surgical intervention	R	66	I&D (57), fistulotomy (35), I&D and seton (24), internal sphincterotomy (6), fissurectomy (1), anal dilation (3). 40/66 have functional anus. 1980–1990	Very low
Scott (1996) [19]	Patients with pCD	Local surgical intervention	R	59	27 fistulotomy (81% success based on pt. satisfaction), 27 loose seton (85% success based on pt. satisfaction)	Very low
Scott (1996) [19]	Patients with pCD	Fistulotomy, seton placement ± diversion	R	59	27 fistulotomy (81% successful), 27 seton (85% successful), 5 diverted as part of primary procedure	Very low
Makowiec (1997) [20]	Patients with pCD	Seton ± I&D, diversion	R	126	8 diverting stoma. 21% recurrence at 1 year, 54% at 2 years, 70% at 3 years. 4 proctectomy	Very low

Regimbeau (1999) [21]	Patients with pCD who underwent any CD surgery	Anal dilation, sphincterotomy, fissurectomy, fistulotomy, I&D, seton placement, advancement flap	R	119	Mean f/u 93 months. 16 (13%) diverted at initial operation. 30 (25%) proctectomy at end of study—9 (56%) permanent stoma. 39/89 with functional anal sphincter (44%) fecal incontinence	Very low
Takesue (2002) [22]	Patients with complex pCD	Seton, fistulectomy, fistulotomy	R	32	62 months median f/u. 10 (31.3%) recurrent abscess. 28 (87.5%) no effect on continence	Very low.
Shinozaki (2002) [23]	Patients with pCD	Seton	R	39	11 (28%) simultaneous bowel and anus operation. 29 (74%) two or more setons. Seton removal 52% at 12 months, 86% at 24 months. 10 (26%) diversion. No proctectomy	Very low
Bell (2003) [5]	Patients with simple or complex pCD	Local surgical and medical tx ± diversion	R	87	68% healed all fistulas at 6 years. 80% fistulas complex, Half required stoma, resection or proctectomy	Very low
Thornton (2005) [24]	Patients with pCD	Seton ± medical therapy	R	28	Median follow-up 13 months. 21% recurrene, 11% another surgery. 32% adjuvant medical therapy. 1 (4%) proctectomy	Very low
Thornton (2005) [24]	Patients with complex pCD	Seton	R	28	Median follow up 13 months. 21% recurrence. 11% further intervention.	Very low
Mueller (2007) [25]	Patients with complicated pCD	Local surgical therapy, medications, diversion	PO	97	Median 16 years f/u. 30 (31%) permanent stoma. 17 (18%) proctectomy. 51 (53%) temporary diversion, removed in 24/51 (47%)	Low
Koperen (2009) [26]	Pateitns with pCD without proctitis or active sepsis	Local surgical intervention	R	61	Median f/u 79 months, seton (24, half reported soiling), fistulotomy (28, recurrence 5, 2/3 reported soiling), mucosal advancement (9, recurrence 5, 3/4 reported soiling)	Very low
Löffler (2009) [27]	Patients with pCD ± RVF	Local surgical intervention, diversion	R	147	29 (20%) proctectomy, complex fistulas 45.6% recurrence rate, 5 years follow-up	Low

(continued)

Table 11.2 (continued)

First author (year)	Patients studied	Intervention	Study design	N	Outcome	Quality of evidence
Lozynskyy (2009) [28]	Patients with pCD	Local surgical therapy, medications, diversion	R	144	Recurrence 65 (45.1%) in 2 years, 128 (88.9%) in 5 years	Very low
Rehg (2009) [29]	Patients with pCD	Local treatment or diversion	R	39	33% fecal diversion (85% complete resolution)—half restored. 67% local treatment (19% complete resolution)	Very low
Galis-Rozen (2010) [30]	Patients with and without pCD	Seton placement	R	17	17 patients with pCD, 40% recurrence after 24 months f/u	Very low
Molendijk (2014) [31]	Patients with simple or complex pCD	Medical treatment and/or surgery (colectomy, fistulectomy, stoma, and rectum amputation)	R	232	Complex fistulas 180 patients: 25% (24) proctectomy, 63.6% (60) overall diverted, 40.3% (73) combo diversion and meds—45% (33) durable remission	Very low
Papaconstantinou (2017) [32]	Patients with high and low pCD fistulas	Seton or fistulotomy	R	59	Mean follow up 1.6 years ± 1.1 year. Incontinence in 3 pts. with setons, 6 fistulotomy, recurrence in 1 with seton	Very low

Table 11.3 Studies describing outcomes of diversion for pCD

Harper (1982) [33]	Patients with severe pCD	Diversion	R	29	Initial improvement after 23 loop ileostomies, 8 reverted. At end 6 reversed, 8 proctocolectomy, 15 diverted	Very low
Grant (1986) [34]	Patients with pCD	Diversion	R	12	7 rectovaginal fistula (1 restored continuity, 1 active fistula after restored continuity, 3 minimal or no symtoms, 2 proctocolectomy); 5 proctitis or anorectal sepsis (1 no symptoms, 1 with symptoms, 3 proctocolectomy)	Very low
Yamamoto (2000) [35]	Patients with severe pCD	Diversion	R	31	13—severe perianal sepsis, 3—recurrent deep anal ulcer, 9—complex anorectal fistula, 6—RVF; 3—restored continuity, 21—proctectomy (30 to 3 years of f/u)	Very low
Edwards (2000) [36]	Patients with severe pCD	Diversion	R	18	15 patients underwent proctocolectomy or remain with stoma at 36 months; 2 with good clinical response	Very low
Regimbeau (2001) [37]	Patients with complex pCD	Diversion	R	17	Mean follow-up 135 months. 9 proctectomy. 8 restored	Very low
Spivak (2006) [38]	Patients with severe pCD	Diversion	PO	10	80% response with median f/u 41 months	Very low
Hong (2011) [39]	Patients with complex pCD	Diversion ± IFX	R	21	4 reversed, 11 proctocolectomy, 6 still diverted at 22 months (<20% restoration); 52% lasting pCD improvement or healing	Very low
Sauk (2014) [40]	Patients with pCD	Diversion	R	49	5 (10%) remained undiverted, and 3 of them required further local procedures	Low
Mennigen (2015) [41]	Patients with colorectal and pCD	Diversion	R	29 (22 with pCD)	19 (76%) had stoma reversal but 10/19 (52.6%) needed resection and 7/19 (36.8%) needed permanent stoma	Very low

(continued)

Table 11.3 (continued)

Gu (2015) [42]	Patients with severe pCD	Diversion	R	138	30 (22%) stoma closure, 45 (33%) stoma with rectum in situ, 63 (45%) proctectomy. 5.7 years follow-up	Low
Singh (2015) [43]	Patients with pCD	Diversion	Meta-analysis	556	Restoration of continuity successful in 16.6%	Low
Martí-Gallostra (2016) [44]	Patients with pCD	Diversion	R	76	Restoration of continuity successful in 27%, complex anal fistulas/ stenosis 10% and 0% respectively	Very low
Bafford (2017) [45]	Patients with pCD	Diversion	R	30	2/3 patients with refractory colonic and/or severe pCD remained diverted at 2 years	Very low

satisfaction, quality of life, PDAI score, intestinal continuity, and presence of an intact rectum. Importantly, no commonly established length of follow-up existed and it ranged from months to years. Studies involving the pediatric population are separately described in Table 11.5. This clinical heterogeneity understandably stems from the fact that anoperineal Crohn's is just one manifestation of a highly complex disease that requires a multidisciplinary and multimodal approach.

Two main clinically relevant trends surfaced from the data. The first is that biologic agent therapy combined with surgical source control is the only treatment for perianal Crohn's disease that has demonstrated a lasting response. Local surgical intervention with or without diversion that is not accompanied by concurrent infliximab or other biologic treatment has a high recurrence rate and low chance of fistula healing over long-term follow-up. The second trend is that once the fecal stream is diverted, even when the intention is a temporary stoma, the likelihood of restoring intestinal continuity is remarkably low.

Seton Placement Combined with Biologic Therapy

The era of biologic therapy for perianal Crohn's disease began when Present first reported that infliximab infusion was effective for treating perianal Crohn's disease fistulas in 1999, demonstrating a 68% response rate in draining fistulas with median onset response time of 2 weeks [71]. In 2004, the ACCENT II trial showed that maintenance therapy with infliximab reduced time to loss of response compared to placebo (>40 weeks vs. 14 weeks; $p < 0.001$). Since then, it's been shown that seton placement alone fares worse compared to seton placement combined with biologic agent therapy [72]. A recent systematic review evaluated ten mainly retrospective studies combining data on 305 patients who underwent seton placement with or without concurrent biologic agent treatment [72]. In one study, seton drainage alone

Table 11.4 Studies describing outcomes of seton placement with biologic therapy for pCD

Topstad (2003) [46]	Patients with pCD ± RVF	Seton placement + medical and biologic therapy, diversion	R	29	13 setons, 1 diverting stoma. 24 complete or partial response	Very low
Regueiro (2003) [47]	Patients with pCD	IFX ± EUA with possible seton placement	R	32	At least 3 months follow-up. Combination group vs. IFX alone had lower recurrence rate (44% vs. 79% p = 0.01), longer time to recurrence (13.5 months vs. 3.6 months p = 0.001), better initial response (100% vs. 82.6% p = 0.014)	Very low
van der Hagen (2005) [48]	Patients simple and complex pCD	Setons ± diversion with and without Infliximab	PO	17	7 seton followed by definitive tx—2 recurrence, 2 incontinence; 3 setons with diversion (2 restored continuity) Infliximab group: 7 setons followed by definitive tx, 3 setons with diverting stoma (1 restored continuity)—1 fecal incontinence, 1 recurrence 20 months follow-up	Very low
Hyder (2006) [49]	Patients with pCD	IFX (3 infusions) ± I&D with seton placement	R	22	Median follow-up 21 months. 4 had sustained fistula healing. 5 diverted or proctectoy	Very low
Gaertner (2007) [50]	Patients with pCD	Local surgery ± IFX	R	226	Mean follow-up 30 months. 88 (60%) healed completely with local surgery alone, 47 (59%) healed with combination therapy	Very low
Guidi (2008) [51]	Patients with pCD	Seton and IFX	PO	9	At week 6, CD activity index and perianal disease actity index were both significantly reduced. Complete response 8/9	Very low

(continued)

Table 11.4 (continued)

Tougeron (2009) [52]	Patients with pCD	Seton and IFX	R	26	Mean follow-up 4.9 years. 13 (50%) complete response after induction. 42% in remission at end of follow-up	Very low
Sciaudone (2010) [53]	Patients with complicated pCD	IFX, seton or combination	PO	35	Median follow-up 18.8 months. 11 IFX, 10 seton, 14 combination. Combination had shorter time to healing than surgery alone ($p < 0.05$) and longer time to relapse (0.05) IFX alone	Very low
Tanaka (2010) [54]	Patients with pCD	Seton and IFX	PO	14	Mean follow-up 12.1 months. All improved. 11 patients had setons removed. Reported good QOL	Very low
Sciaudone (2010) [53]	Patients with complex pCD	Infliximab (A), seton (B) placement or both (C)	RCT	35	Time to healing of fistulas shorter in group C than in B ($p = 0.041$), group C had a longer mean time to relapse than groups A ($p = 0.012$) and B ($p = 0.016$)	Low
Alvarez (2011) [55]	Patient's with complex pCD (fistula and sphincter defect)	Setons ± I&D and sphincter defect repair with IFX	PO	10	Wexner's score improved at 12 months (10 vs. 18 $p = 0.003$) and at 48 (9.5 $p = 0.001$). No incontinence to solid stools	Very low
Hotokezaka (2011) [56]	Patients with complicated pCD	Setons and IFX (induction and maintenance)	PO	20	Complete response 15 (75%), worse disease 3	Very low
Gaertner (2011) [57]	Patients with pCD and RVF	Local surgical intervention, ± diversion, ± IFX	R	51	26 had IFX. 10 preop diversion. 38.6 months mean follow-up, 27 healed (60% of diverted), 24 (51% non-diverted) recurred. 14 (27%) had proctectomy	Very low

(continued)

Table 11.4 (continued)

Roumeguere (2011) [58]	Patients with severe pCD ± RVF	Local surgical intervention, IFX and methotrexate	PO	34	Initial response 85% with 74% complete response. At 1 year 50% with some response	Very low
Duff (2012) [59]	Patients with complicated pCD	IFX ± setons	R	52	22 patients received setons. 42 had maintenance after induction. 22 (42.3%) complete response, 23 (44.2%) partial response and 7 (13.5) no response	Very low
Antakia (2013) [60]	Patient's with complex pCD	Setons ± I&D and IFX	R	48	Median follow-up 20 months. 14 (29%) complete response, 20 (42%) partial response, 14 (29%) no response	Very low
Kotze (2014) [61]	Patients with pCD	Setons and IFX or adalimumab	R	78	Median follow-up 48.2 months. 41 complete remission. 4 recurrence	Very low
Bor (2015) [62]	Patients with pCD	Setons ± I&D, IFX	R	68	1-year period of study. 26 full response, 53 partial response. 45% needed another seton placement/I&D	Very low
Haennig (2015) [63]	Patients with pCD	Seton and IFX	R	81	Median follow-up 64 months. Seton 62 (80.5%). Recurrence 29 (41%). Total rate of closure 75.3%	Very low
Yardimci (2016) [64]	Patients with simple and complex pCD	Seton with biologic	R	27	Complete response in 63% (17 months median follow-up). 24/27 complex	Very low
Schwartz (2017) [65]	Patients with simple and complex pCD	Setons with biologics vs. biologics alone	R	1845	No seton group had more hospitalizations (0.41 vs. 0.23) and higher costs ($9711 vs. $1900	Low

compared to combination therapy with an anti-TNF agent had a significantly worse outcome response (17% vs. 45%; p = 0.001) [50]. Another study demonstrated that anti-TNF agent alone also had worse response rates compared with anti-TNF agent combined with setons (82.6% vs. 100%, p = 0.014) [47]. Combined therapy also resulted in significantly improved recurrence rates compared to anti-TNF agent

Table 11.5 Studies describing outcomes of seton placement or diversion for perianal Crohn's disease in pediatric patients

Orkin (1985) [66]	Children (4–18 years) who required intestinal CD resection and had concurrent pCD	Resection intestinal Crohn's disease with anastomosis, diversion, proctectomy	R	38	8 years follow-up after intestinal Crohn's disease operation; 11 diverted; 20 proctocolectomy (11 as initial procedure)	Very low
Rosen (2010) [67]	Pediatric patients with pCD	EUS for monitoring fistula healing after	R	25	Setons more likely to be left in place and patients more likely to be started on biologic after EUS follow-up	Very low
Hukkinen (2014) [68]	Pediatric patients with pCD	Seton placement and IFX	R	13	Fistulas recurred in 23% over 1 year after final response	Very low
Mattioli (2015) [69]	Pediatric patients with complicated pCD	Cone-like resection, fistulectomy, sphincter reconstruction, endorectal advancement and biologics	R	11	3 patients needed second treatment, 2 needed more than two surgeries, 1 temporary colostomy	Very low
Seemann (2016) [70]	Children (0–17 years) with simple or complex pCD	Abscess drainage + seton, loop ileostomy	R	57	43 patients—abscess drainage and seton insertion; 14–loop ileostomy (7 required further surgery)	Very low

CD Crohn's disease, *R* retrospective, *PO* prospective observational, *RO* retrospective observational, *RCT* randomized controlled trial, *IFX* infliximab, *RVF* rectovaginal fistula

alone (44.4% vs. 78.9% p = 0.001) [47]. The timing of seton removal is controversial. In this review, setons were removed between 3 weeks and 40 months after initial surgery [72]. Recent evidence indicates there may be benefit to waiting until anti-TNF induction is complete before removing the seton; however, the decision is primarily based on surgeon evaluation [73].

Temporary Diversion Associated with Permanent Stoma

A recent systematic review and meta-analysis by Singh evaluated 16 cohort studies combining 556 patients and demonstrated that though there is an initial clinical response in perianal Crohn's disease following diversion, the rates of restoring intestinal continuity are ultimately low. Refractory perianal Crohn's disease improved in 63.8% of patients following diversion. Restoration was attempted in 34.5%; however, more than one-half required re-diversion and only 16.6% of patients were reported to be in continuity within the included cohorts. Successful

restoration was most highly associated with lack of rectal involvement. Proctocolectomy was the outcome for 41.6% of all patients. The rate of restoration was not significantly higher in patients treated after the introduction of biologic agent therapy [43].

Recommendations Based on the Data

For patients with severe perianal Crohn's disease, we recommend evaluation with magnetic resonance imaging (MRI) or endoanal ultrasound (EAUS) to assess the complexity of both proximal and perianal disease [74, 75]. All abscesses should be drained and setons should be placed in identifiable fistulas. Proctoscopy should be performed to evaluate the rectum for evidence of disease. Anti-TNF therapy should be strongly considered, especially in the setting of proctitis. Patients should have close surgical follow-up to assess fistula healing, although the exact timing of seton removal is controversial. Generally, setons are removed if there is evidence that anti-TNF therapy is contributing to healing after weeks to months of induction and/or maintenance therapy. Fecal diversion with a loop ileostomy should be discussed with the patient early in the treatment course, especially if recurrent septic complications require frequent returns to the operating room or if the patient's symptoms significantly affect quality of life despite using setons combined with maximal medical therapy.

Current data demonstrates that temporary diversion most often becomes permanent. However, diversion significantly improves the patient's quality of life in the setting of severe perianal Crohn's disease [76]. These decisions are particularly difficult for young patients with severe perianal Crohn's disease with concerns about quality of life and body image with a stoma, and patients with concomitant intestinal Crohn's disease with worry about bowel preservation and avoidance of short bowel syndrome. Therefore, the decision to pursue fecal diversion should be a mutual one between patient, surgeon, and gastroenterologist. Following loop ileostomy construction, surgical therapy with setons and medical therapy with anti-TNF and other agents should continue. Patients should be monitored for fistula healing and symptom improvement with imaging and clinical exams. If there is no evidence of healing after continued biologic therapy, reversal should not be recommended. If septic complications and/or fecal incontinence persist despite best efforts of combined medical and surgical therapy, proctocolectomy with a permanent end ileostomy should be considered. Other indications for proctectomy include concern for malignancy, large nonhealing defects, and comorbidities that increase patient's risk for poor healing. Diversion may be required in patients with persistent perianal Crohn's disease in the setting of severe proctocolitis and distal stenosis. This presentation has a higher risk of permanent diversion or conversion to proctocolectomy if rectal disease persists resulting in severe anorectal stricturing that prevents restoration of continuity.

List of Recommendations

1. Evaluate patients with complex perianal Crohn's disease with MRI or EAUS in conjunction with examination under anesthesia to assess proximal disease and anatomy of the perianal disease (strong recommendation based on moderate quality evidence).
2. For patients with complex perianal Crohn's disease complicated by sepsis, the initial step is to drain all abscesses and place loose setons in identifiable fistulas (strong recommendation based on low quality evidence).
3. Patients with refractory perianal symptoms and septic complications requiring recurrent surgical intervention, and patients with significantly impacted quality of life despite combined seton and medical management should be counseled to consider fecal diversion with a loop ileostomy (strong recommendation based on low quality evidence).
4. Counseling regarding temporary fecal diversion should include discussion about a possible permanent ostomy given low rates of continuity restoration (moderate recommendation based on moderate quality evidence).
5. Discussion about permanent diversion is especially pertinent for patients with proximal disease who have or are at risk for rectal stenosis (strong recommendation based on moderate quality evidence).

Personal View of the Data

In our search, no studies directly compared seton placement with diversion in similar patient populations. Clinically, these surgical strategies are used in a stepwise approach. Drainage of any infectious source and seton placement are the first stage of perianal Crohn's disease treatment. This is completed in conjunction with medical treatment, specifically anti-TNF biologic therapy. If seton placement with concurrent maximized medical management fails, then diversion is considered. The discussion of diversion is based on the severity of complications, including the frequency of surgical interventions for perianal Crohn's disease, fecal incontinence, patient discomfort, and the combined effect of these complications on the patient's quality of life. Proceeding with diversion is a joint decision between patient, surgeon, and the gastroenterologist. The decision is based on exhaustion of combined seton and medical therapy, and the potential for improving quality of life [77].

Diversion with a loop ileostomy is generally discussed as an initial temporizing measure that allows treatment of perianal disease with biologic agents in the absence of continued irritation from the fecal stream. However, temporary diversion has been shown to be reversed in as few as 17% of patients [39, 43]. Therefore, patients should be made aware that a temporary loop ileostomy may result in permanent diversion with or without conversion to proctectomy.

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Management of Ano/Rectovaginal Fistula

12

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Introduction

Fistulas to the vagina from the anus or low rectum are variously called anovaginal and rectovaginal fistula (RVF) and the latter phrase will be used throughout this chapter. RVF's are a devastating problem producing severe symptoms in many cases. They occur more commonly in Crohn's disease than in the general population, with a prevalence of 10% and mean age of onset of 34 years in a series of 886 patients [1]. A population based survey from Minnesota found that 35% of Crohn's disease patients had fistulas and 9% of these were RVF's [2]. RVF's are more commonly associated with colonic (23%) than small bowel (3.5%) Crohn's disease [3, 4]. A variety of techniques are used in managing Crohn's disease related RVF's. In this chapter, the literature pertaining to surgical treatment of an RVF complicating Crohn's disease is reviewed and is followed by recommendations and opinions (Table 12.1).

Table 12.1 PICO question

PICO table	Population	Intervention	Comparator	Outcomes
Management of ano/rectovaginal fistula	Pts with Crohn's disease	repair	stoma	Recurrent fistula, quality of life

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Search Strategy

A comprehensive literature search of the Cochrane, EMBASE and MEDLINE databases was performed to identify all relevant English-language publications over the last 20 years. Key search terms included: 'rectovaginal fistula,' 'anovaginal fistula,' 'Crohn's' and 'surgery' (and variants). Studies were excluded if they reported fewer than 3 patients with Crohn's RVF, or did not study surgical intervention (reparative or ostomy formation), describe outcomes in Crohn's patients separately from other etiologies or consider fistula healing and/or quality of life assessment as outcomes. Conference proceedings were excluded. Only the most recent study was included if similar studies from the same institution were encountered. The references of the included studies were reviewed to identify additional studies.

Results

Almost all published studies are observational and retrospective in nature. No studies directly compare reparative surgery with ostomy formation. Reparative surgical options reported include gracilis interposition, advancement flap repair (i.e. rectal, vaginal), Martius flap, episioproctotomy, abdominal approaches including Soave-type coloanal pull-through, and novel approaches including glue, plug, mesh interposition, stem cell injection and fat injection. Ostomy formation was performed in three situations: temporarily to "protect" a repair; permanently to reduce symptoms by defunctioning the rectum and therefore the fistula, or; as part of an ablative operation (e.g. proctectomy).

Studies either tend to be of a single technique with multiple etiologies, or multiple techniques with a single etiology, or multiple techniques in multiple etiologies. Many studies had only a small number of Crohn's disease RVF's treated by a particular technique and comparison between techniques is therefore difficult. It was not always possible to determine the precise number of Crohn's disease RVF patients undergoing a particular technique. Most studies measured healing of the fistula as an outcome although assessment was performed at various time points using multiple methods. Quality of life scoring was rarely reported. Heterogeneity in etiology, fistula morphology, surgical technique, previous repair attempts, and outcome measurement limits the strength of the recommendations that follow (Table 12.2).

Few series of gracilis interposition contain three or more Crohn's disease RVF patients. Most include recurrent fistulas and utilize fecal diversion. In one study, three of nine patients' RVF healed and one became sufficiently small with reduced symptoms such that no further treatment was required [5]; these four patients had their stomas successfully reversed. Quality of life assessments were not reported. In a study of gracilis interposition for RVF's and rectourethral fistulas, repair of Crohn's disease-related fistulas was reported as "successful" but only one of the three RVF's healed [7]. Another study reporting 11 patients with Crohn's disease RVF's treated with gracilis interposition found that all had healed and had their

Table 12.2 Studies evaluating reparative techniques for Crohn's disease RVF

Study	Patients	Intervention(s)	Outcome(s)	Quality of evidence
Wexner (2008) [5]	9 CD RVF	Gracilis	3/9 (33%) healed	Low
Furst (2008) [6]	11 CD RVF	Gracilis	11/11 healed	Low
Ulrich (2009) [7]	3 CD RVF	Gracilis	1/3 (33%) healed	Low
Lefevre (2009) [8]	5 CD RVF	Gracilis	4/5 (80%) healed	Low
Rottoli (2018) [9]	8 CD RVF	Gracilis	6/8 (75%) healed	Low
Jarrar (2011) [10]	12 CD RVF	Rectal adv flap	5/12 (42%) healed	Low quality
Nosti (2013) [11]	6 CD RVF	5 Vaginal adv flap, 1 rectal adv flap, (4 + Martius/Gracilis)	4/6 (67%) healed	Very low
Songne (2007) [12]	7 CD RVF	Martius flap	8/8 (100%) healed	Very low
Pitel (2011) [13]	8 CD RVF	Martius flap	4/8 (50%) healed	Low
Schwandner (2009) [14]	9 CD RVF	Rectal adv flap & Surgisis mesh	7/9 (78%) healed	Low
Mege (2016) [15]	4 CD RVF	Biological mesh (Strattice)	2/4 (50%) healed	Low
Gajsek (2011) [16]	8 CD RVF	Button plug	4/8 (50%) healed	Low
Garcia-Arranz (2016) [17]	5 CD RVF	Allogeneic stem cell transplant	3/5 (60%) healed	Very low
Norderval (2018) [18]	7 CD RVF	Autologous fat graft injection	6/7 (86%) healed	Low

stoma reversed, although the follow-up interval was just a few months in one-half of the patients [6] and medical treatment was not described.

One study of gracilis interposition for multiple etiologies reported quality of life outcomes in addition to healing, which occurred in 4 of 5 (80%) Crohn's disease patients [8]. Quality of life was reported for all 8 RVF's. Seven of eight women had been sexually active before surgery but only four remained so afterwards. All four had a healed fistula. One noted reduced libido and two complained of dyspareunia, but three of the four said they were satisfied with their sex-related quality of life.

Studies reporting outcomes from advancement flap repair also suffer from heterogeneity. For example, one study with 6 Crohn's disease RVF patients used 5 vaginal advancement flaps and 1 rectal advancement flap [11]. In the vaginal flap patients, one was bolstered by porcine small intestinal submucosa-derived mesh, one by gracilis interposition, and three by Martius flaps, with only one patient having follow-up longer than 4 months. It is difficult in this context to define advancement flap success rates. Several studies include Crohn's disease RVF's but do not report their outcomes separately from the RVF's of other etiologies or anorectal

fistulas to the perineum. One study that carefully described 12 Crohn's disease RVF's found a primary healing rate of RVF managed by rectal advancement flap of 42% [10], rising to 83% after up to 3 attempts. Across the entire cohort, continence and quality of life were similar before and after surgery. However, the "incontinence" associated with the fistula and true anal incontinence associated with the surgical insult to the internal anal sphincter are not disentangled in this study and so the true impact of this surgical technique on continence and any related impact on quality of life cannot be determined.

Two studies analyzed the Martius flap technique in a variety of patients. One study reported 8 Crohn's disease RVF patients and found that the fistula healed in one-half [13]. Fecal incontinence (Wexner score), sexual quality of life [Female Sexual Function Index (FSFI)], and overall quality of life [Short Form-12 (SF-12) Health Survey] were analyzed for the entire group but results in the Crohn's disease RVF group were not separately presented. Fecal diversion was also used in several patients and was maintained in at least one-half of the Crohn's disease patients. An earlier study described healing of all (7/7) Crohn's disease RVF's, but two of the seven patients went on to proctectomy for "non-RVF" indications and the details are unclear [12].

The generally poor outcomes associated with RVF repair, often reported as worse in patients with Crohn's disease, coupled with the morbidity of the operations and postoperative symptoms, have prompted a slew of novel techniques, usually aimed to be less invasive but more effective.

The over the scope clip (OTSC) has been used in Crohn's disease RVF's in two studies of mixed fistulas and etiologies. In one, [19] the success rate in the Crohn's disease RVF group was not described and in the other [20], only two Crohn's disease RVF patients were included and neither healed.

Two studies reported biological mesh interposition in at least 3 Crohn's disease RVF patients. Porcine skin-derived mesh was used in 4 diverted patients in one study [15]. Two patients' RVF's fully healed, one failed to heal, and the other was converted to a rectoperineal fistula. In another study, porcine small intestinal submucosa-derived mesh was used and 7 of 9 (78%) Crohn's disease RVF patients' fistulas were healed at the end of follow up [14].

A submucosal tissue-derived fistula plug specifically designed for fistulas to the vagina was used in 8 Crohn's disease RVF's without fecal diversion [16]. At final follow-up, 4 of 8 (50%) fistulas were healed. Plug dislodgement led to several failures, and repairs in smokers and repeat procedures were always unsuccessful.

Allogeneic stem cells have been used to treat anal fistulas arising in Crohn's disease in a large multicenter randomized controlled trial [21]. A phase I–II study [17] from the same Spanish group found that 3 of 5 (60%) Crohn's disease RVF patients maintained a healed fistula at 1-year follow-up. Autologous fat implantation led to healing of Crohn's disease RVF's in one study, in which 6 of 7 patients (86%) had no fistula at final follow-up [18]. Repeat procedures, fecal diversion, and medical treatment occurred but were not specified.

Several mixed series have been published that include Crohn's disease RVF's treated with several different surgical techniques. In many it is impossible to

determine the primary healing rate of a given procedure. For example, one study reported on 6 different techniques performed 71 times in 52 Crohn's disease RVF patients [22]. Cumulative closure rates after one, two, three, and four attempts at surgery (without specifying which techniques were chosen) were 56%, 75%, 78%, and 81%, respectively. Most operations were rectal or vaginal advancement flaps. Another study identified overall success rates after one, two, three, and four operations (totaling 56 fistulas in 37 patients) of 2/7 (29%) for rectal advancement flaps compared to 70% to 86% of 49 direct, transperineal, or anocutaneous advancement flap repairs [23]. A study including 12 Crohn's disease RVF patients who underwent 21 procedures of varying types resulted in a healed fistula in 6 patients [24]. Fecal diversion did not influence outcome in this small series.

A larger series of 45 Crohn's disease RVF patients in whom 95 operations were performed demonstrated a healed fistula at 5 years in 53% [25]. This and other studies have demonstrated a consistent rate at which proctectomy is required in the complex anal fistula group, including RVF, of approximately 20% [25, 26]. A slightly higher rate of proctectomy (30%) was seen in an older series of 49 patients [27]. Rectal involvement was associated with a higher likelihood of proctectomy. This series also commented on a group of 15 patients with few symptoms who were initially managed with a non-operative approach. None of these needed proctectomy, seven became completely asymptomatic, and three required intervention with fistulotomy or seton insertion. A small series of 10 Crohn's disease RVF patients reported primary healing in 50% rising to 80% after subsequent repairs [28]. Rectal advancement flaps were the most common initial procedure, usually under fecal diversion.

Sexual function and quality of life were assessed in a study of Crohn's disease RVF patients who underwent a variety of different procedures [29]. Thirty of 65 (46%) women had healed at the end of follow-up, and all were offered survey by SF-12, Inflammatory Bowel Disease Quality of Life (IBDQOL), and FSFI. Twenty-eight women (fewer than one-half of the total group) were sexually active at follow-up, approximately one-half with healed fistulas. Only women without healed fistulas had dyspareunia (although it was not reported why those who were not sexually active had stopped). Sixteen of the 28 women completed the FSFI questionnaire. None of the four used surveys demonstrated a difference between the healed and unhealed groups.

Several studies have tried to identify factors that influence outcome in response to Crohn's disease RVF treatment. Immunomodulators have been shown to improve healing [29] and induce healing earlier after surgery [30], whereas smoking and steroid use [29], and multiple Crohn's disease sites [31] are associated with reduced healing. Smoking has been shown to influence advancement flap failure in non-Crohn's disease anal fistulas [32]. One study of 286 procedures in 79 patients with mixed etiology RVF's using several different surgical techniques, found that within the entire cohort (not just Crohn's disease patients), a short interval between diagnosis and first repair, no previous repairs performed elsewhere prior to referral, major procedure, and fecal diversion were independent positive prognostic factors on multivariate analysis [33].

Five studies were identified that specifically examined Crohn's disease RVF's and fecal diversion. One study considered the post-biologic agent era and included 7 patients with Crohn's disease RVF's as their primary indication for diversion [34]. At the end of the study period, one of these patients had their stoma reversed. Fistula healing and quality of life were not assessed. A similar paper in the pre-biologic agent era included 6 patients with Crohn's disease RVF's [35]. All had severe proctitis. Four became asymptomatic after creation of a defunctioning stoma but relapsed and all six ultimately required proctectomy. Another study performed during the post-biologic agent era found that 4 of 8 Crohn's disease RVF patients' fistulas healed following fecal diversion and maintained intestinal continuity at the end of follow-up [36]. Three of them had a local fistula repair in addition to diversion and three-quarters of the whole cohort were managed with biologic agents, although the number in the RVF group was not specified.

These studies examined the diverted perianal Crohn's disease group retrospectively so there is an inherent selection bias at play since simpler fistulas, which settled in response to medical or reparative surgical treatment, might also have responded to diversion, and only refractory fistulas are likely to have been selected for diversion. There has been no study that has examined the use of fecal diversion as a sole or primary treatment in unselected or primary Crohn's disease RVF patients, so its efficacy in this setting cannot be estimated.

A review of consecutive Crohn's disease patients, including 26 patients with RVF's, found two-thirds required temporary fecal diversion and just over one-half ultimately needed a permanent ostomy [37]. A similar study analyzed a database of consecutive patients including 20 women with RVF's of whom 60% required permanent diversion [38]. Neither of these two studies found RVF's to be an independent predictor of the need for permanent fecal diversion. The indication for permanent stoma was said to be RVF for these patients but the reader will recognize that there is usually a constellation of features of luminal and perianal Crohn's disease that will contribute to this decision; disentangling these is difficult and this evidence must be considered within that context.

Recommendations

Several options exist for the surgical repair of a RVF complicating Crohn's disease. Gracilis interposition, rectal and vaginal advancement flaps, and Martius flap represent those approaches with the largest evidence base although it remains small. All are reasonable options for repair of Crohn's disease RVF's in appropriately selected patients when requisite surgical experience is available. (low quality evidence, weak recommendation).

Failure/recurrence, the potential for worsening of symptoms, and the risk of surgical morbidity including dyspareunia and continence impairment, should be thoroughly discussed with the patient when counselling her regarding surgery. (low quality evidence, weak recommendation).

Personal View

Crohn's disease RVF's are a particularly difficult area to review because the evidence supporting a given technique is poor, the studies are almost all observational and retrospective, and the literature is plagued by heterogeneity.

Frequent recurrence and postoperative morbidity have driven innovation and analysis of several techniques.

Gracilis interposition provides a bulky, robust repair, with a large volume of muscle that can be used to fill the rectovaginal septum space and repair the anal sphincter if required. The morbidity associated with incisions outside the diseased area dissuades some surgeons but other are strong proponents. In the Crohn's disease setting, there are very few data on which to base an opinion, particularly given that, as with many of the techniques discussed, the series presented contain many recurrent fistulas. This is a function of the units that tend to publish their data and have sufficient numbers to do so, also being referral centers that will see more recurrent and refractory fistulas, in which repair elsewhere has previously failed.

The rectal advancement flap literature is similarly sparse, but a consistent theme emerges of initial success in around one-half of patients, rising to approximately 80% with repeated attempts at repair. The advancement flap procedures are perhaps some of the simpler RVF repairs to perform.

Rectal advancement flap, regardless of fistula etiology or morphology, is associated with a recognized rate of deterioration of continence, related to dissection or mobilization of the rectal muscle wall or internal anal sphincter. This varies in different series but certainly a figure of 20% is reasonable, and in addition to clinical continence impairment, changes in resting and squeeze pressure have been shown [39]. Techniques such as muscular plication rather than incision may avoid this problem [40]. Patients must be warned about this risk in a technique often considered one of the "sphincter-preserving procedures."

Martius flaps offer a valuable and relatively straight forward option to bolster a repair but are best suited to lower fistulas as the volume of tissue obtained is relatively modest and is superficially tethered. Some authors have argued that the whole technique is simple, but I disagree. As with omental flap, gracilis interposition or direct repair, I find that the initial dissection in the rectovaginal septum space, scarred and often considerably narrowed by the fistula itself, can be very challenging.

Episioproctotomy with immediate [41] or delayed [42] reconstruction is argued by proponents to be particularly useful where there is already significant sphincter injury and associated continence impairment.

Some of the novel techniques used in Crohn's disease RVF's are intriguing, although much further study is required. The fistula plug and OTSC seem least likely to develop in the future but techniques to ameliorate the hostile environment in which Crohn's disease fistulas of all types are encouraged to persist, such as stem cells or fat implantation, may well carry benefit either alone or to augment a reparative technique.

Several authors have discussed the value of a tailored approach to repair of RVF's. An algorithm of technique selection was published from our unit in 2013 [43]. There are several factors that define suitability of a given technique including fistula height, whether the residual anterior sphincter complex is intact, and the quality, pliability and mobility of the local tissues. However, the constellation of features that define the optimal approach in each patient remain subjective and debated by colorectal surgeons.

Little discussion in the literature surrounds the importance of the patient's voice in decision making. First, an RVF producing minimal symptoms can be conservatively managed. There is always potential to worsen symptoms following surgery either with a recurrent but larger fistula, or through postoperative symptoms such as continence impairment or dyspareunia. Second, the risks of these various postoperative symptoms are likely to vary from one procedure to another. For example, a gracilis interposition may impact an athlete, a Martius flap might be more likely to produce dyspareunia, and a risk of even minor continence impairment will be abhorrent to some. Such risks are not yet clearly elucidated. Third, the question of a defunctioning stoma or proctectomy remains highly emotive. Some patients present with their "red line" being stoma formation. The absence of strong evidence supporting their use to improve healing rates does not dissuade surgeons from offering it for that very reason.

Indeed, many of us will employ a stoma when previous attempts have failed. But perhaps those initial attempts carried the best chances of success. It may be preferable to employ a "top-down" approach in patients with significant symptoms. Fourth, proctectomy is rarely a patient's initial choice, but in my view, it should be discussed from the initial consultations for Crohn's disease RVF's. The chance of a patient requiring proctectomy is relatively high (perhaps around 20%), particularly in the presence of rectal disease or anorectal stricturing, and, it is valuable for the patient and her supporters to understand proctectomy may be inevitable. Occasionally, a Crohn's disease patient will sigh with relief at the mention of proctectomy, usually in the presence of additional disease. For the rest, it nevertheless provides important context for the subsequent discussion about reparative options, fecal diversion, risks of failure and surgery, and for management of expectations.

In summary, a tailored approach to procedure selection by an experienced RVF surgeon is likely to produce optimal results. Avoidance of smoking, careful medical optimization, and probably fecal diversion are likely to improve healing rates. Much more attention must be paid to the impact on quality of life of the fistula and recurrence but also the sequelae of even successful surgery.

Key questions to be answered by future studies include whether fecal diversion improves outcome in RVF repair, what outcomes are most important to patients in determining success, and how to measure quality of life in RVF. Augmentation techniques, currently under study in Crohn's disease anal fistulas more than in RVF's, should be assessed for benefit in this area, building on the existing studies described above. Finally, centralization of RVF repair, so the initial attempt at repair occurs by an experienced surgeon using optimized techniques, should enable RVF's

to be studied in greater numbers and lead to more reliable outcome data to guide treatment.

Several options for surgical repair of Crohn's disease RVF exist. Gracilis interposition, rectal and vaginal advancement flaps, and Martius flap represent those techniques with the largest evidence base although it remains small. All of these approaches to Crohn's disease RVF's are reasonable options for repair by an experienced surgeon in appropriate patients. (Low quality evidence, weak recommendation).

Failure/recurrence, the potential for worsening of symptoms and the risk of surgical morbidity including dyspareunia and continence impairment, should be carefully discussed with the patient when counselling her about surgery. (Low quality evidence, weak recommendation).

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Proctectomy in Patients with "Watering Can" Perineum

13

Konstantin Umanskiy

Introduction

Perineal wound complications are common after proctectomy for inflammatory bowel disease (IBD). The failure of initial primary healing of perineal wound ranges from 2% to 45% in ulcerative colitis (UC) and up to 36% in Crohn's disease (CD) [1, 2]. The presence of perineal sepsis due to extensive perineal fistulas, the so-called "watering can" perineum, can further complicate healing after proctectomy and contribute to delay in perineal wound closure. While most perineal wounds heal over time, some result in the development of a chronic perineal sinus. The incidence of perineal sinus formation may be as high as 50% in ulcerative colitis and 62% in Crohn's disease [1, 3, 4].

Several methods have been proposed to reduce perineal wound complications, including flap closure of the perineum [5, 6], vacuum-assisted wound management systems [7], and the use of biologic barriers [8]. Many of these techniques are associated with prolonged operative times, higher early wound complications, and need for additional interventions. An alternative approach in the presence of a "watering can" perineum, is to leave the anorectum *in situ* by performing an ultra-low Hartmann's procedure [9]. Theoretically, by eliminating the inciting factors of the adjacent inflamed rectum and the flow of fecal material, the perineal sepsis can be more effectively managed. Even though most patients treated with this approach may still require surgical removal of the remaining anorectum at a later time, the proponents of this staged method argue that "cooling off" the perineal sepsis and improving the patient's nutrition will result in improved perineal wound healing (Table 13.1).

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Table 13.1 PICO table

Patients	Intervention	Comparator	Outcome
Patients with "watering can" perineum	Complete proctectomy	Ultralow Hartmann's procedure	Unhealed perineal wound, need for operation

Search Strategy

A comprehensive literature search of PubMed, Cochrane Database Library, EMBASE, MEDLINE, and Google Scholar were performed and supplemented by manual search through the references identified in selected publications. We set the search criteria to include all English language publications related to perineal wound healing in inflammatory bowel disease, proctectomy, pelvic sepsis, and non-healing perineal wound after proctectomy from 1980 to 2018. Key search terms included "proctectomy," "watering can perineum," "non-healing perineal wound," "inflammatory bowel disease," "Crohn's disease," and "Hartmann pouch." Studies were excluded if they did not directly address the strategies of managing post-proctectomy perineal wound, as some studies described medical and surgical strategies of managing perineal sepsis, such as fistulizing disease. We were unable to identify publications directly comparing the management of "watering can" perineum in IBD by either complete proctectomy or ultrashort Hartmann procedure. A total of 12 publications addressing the management of complex perineal wounds in IBD and strategies of mitigating its complications were included for analysis. Several publications included patients with both inflammatory bowel disease and malignant conditions. From these publications, a subset of patients specifically addressing inflammatory bowel disease were selected (Table 13.2).

Results

The review of the literature review is summarized in Table 13.1. The quality of evidence was evaluated using the GRADE system. The studies identified in our search were found to be small, retrospective studies with limited power and no standardization of outcomes. Sher [9] proposed a technique of ultrashort Hartmann's pouch as a definitive procedure for severe perineal Crohn's disease. Of the 25 patients included in the study, 10 (40%) went on to require completion proctectomy and 3 (12%) of these never healed their proctectomy wound. There was no comparison group, but the authors argued that ultrashort Hartmann's procedure provides satisfactory outcomes for patients who did not require subsequent excision of the remnant as well as those who did. In a follow-up publication from the same group, the authors caution, however, that the ultrashort Hartmann's pouch in patients with severe perianal Crohn's disease is at risk for malignancy, as experienced in three of their original 15 patients with a retained anal canal and distal rectum [10].

Table 13.2 Literature search summary

Study	Study type	Patients	Intervention	Outcome		Quality of evidence GRADE
				Delayed perineal wound healing	Need for reoperation	
Corman (1977) [1]	Retrospective	UC (90) CD (61)	Complete proctectomy with primary closure	25% UC 48% CD	18% UC 26% UC	Very Low
Lubbers (1982) [17]	Retrospective	UC (23) CD (25)	Complete proctectomy with primary closure or packing (100%)	26% UC 40% CD	22%	Very Low
Scammell (1986) [18]	Retrospective	CD (116)	Complete proctectomy with primary closure or packing (100%)	37%	9%	Very Low
Sher (1992) [9]	Retrospective	CD (25)	Ultralow Hartmann's procedure	NR	40% 12% non-healed	Very Low
Adam (2000) [14]	Retrospective	UC (27) CD (19)	Complete proctectomy with primary closure (89%)	21% CD 18.5% UC	4.3%	Low
Hurst (2001) [5]	Retrospective	CD (12)	Complete proctectomy with myocutaneous flap closure	0%	none	Very Low
Yamamoto (1999) [4]	Retrospective	CD (147)	Complete proctectomy with primary closure or packing (100%)	43% delayed 23% perineal sinus	16.3%	Low
Yamamoto (2000) [3]	Retrospective	CD (103)	Complete proctocolectomy with primary closure (74%) packing (26%)	35%	11.6%	Low
Ip (2012) [13]	Retrospective	IBD	Complete proctectomy with primary closure	54%	NR	Low
Bertucci Zoccali (2015) [20]	Retrospective	IBD (170)	Complete proctectomy (100%)	15.4%	NR	Low
Poylin (2017) [11]	Retrospective	CD (17) UC (50)	Complete proctectomy (12 CD, 17 UC) Ultralow Hartmann's procedure (5 CD, 33 UC)	No difference in complications and wound healing between complete proctectomy and ultralow Hartmann's procedure	0% primary closure vs. 24% ultralow Hartmann's procedure	Low
Li (2017) [12]	Retrospective	CD (136)	Complete proctectomy with primary closure (72%) secondary closure (28%)	35%	20%	Moderate

CD Crohn's disease, *UC* ulcerative colitis, *NR* not reported

A study by Poylin [11] is the sole comparison of primary versus delayed proctectomy in patients with IBD. In their retrospective review, the authors contrasted the outcomes of a heterogeneous group of patients including those with inflammatory bowel disease and rectal cancer. The patients were treated selectively with either complete proctectomy and primary closure of the perineal defect or a short Hartmann's pouch. The authors did not specify the length of the remaining anorectal segment, but they noted that it was quite short, presumably with transection at the level of the pelvic floor. A subset analysis of the 50 patients with ulcerative colitis and 17 patients with Crohn's disease revealed no statistically significant differences in overall perineal wound complications between the complete proctectomy and short rectal stump groups. Patients with a retained anorectum, however, were more likely to develop disease recurrence, anal leakage, irritation, and bleeding. These patients were also more prone to require reoperation or additional interventions, such as drainage of pelvic abscess or completion proctectomy. Even though the IBD cohort in this study was small, particularly for patients with Crohn's disease, the study showed that the ultrashort Hartmann's procedure in this patient population did not provide a benefit with regards to perineal complications or healing of the perineal wound after subsequent proctectomy.

The other studies listed in Table 13.1 address perineal wound healing and complications after complete proctectomy. They are retrospective in design and lack a comparison group. Li [12] addressed the question of which factors could be contributing to poor wound healing or postoperative complications after proctectomy in IBD. On multivariate analysis, only the presence of perineal sepsis at the time of surgery was independently associated with delayed perineal wound healing or nonhealing of the perineal wound after proctectomy. Ip [13] also found that preexisting perineal sepsis was significantly associated with failure of primary healing of the perineal wound after proctectomy.

There is a lack of consistency in the literature with regards to the methods of mitigating the perineal sepsis prior to complete removal of the rectum. Corman [1] found that preoperative fecal diversion with ileostomy resulted in improved wound healing in patients who had proctectomy for ulcerative colitis but appeared to be detrimental for patients with Crohn's disease. Adam and Shorthouse [14] noted that preoperative fecal diversion had no influence on the incidence of postproctectomy major wound breakdown. In fact, there was a 14% incidence of perineal wound breakdown in the fecal diversion group and only a 7.7% incidence in the nondiversion group. Even though these numbers did not reach statistical significance, the data support the notion that fecal diversion does not provide a reduction in the wound complication rates. Similarly, there is no consistency with regards to the correlation between corticosteroid use and wound complications.

None of the publications directly address the role of anorectal abscess drainage, fistulotomy, or seton placement and their effect on perineal wound healing after proctectomy. Several authors have addressed the technical aspects of proctectomy. Most advocate for intersphincteric proctectomy with primary suture closure whenever possible. This technique allows for maximal preservation of the pelvic floor integrity and facilitates closure of the perineal wound without tension.

Perineal sinus, a long-term complication seen in patients whose primary wound fails to heal, is often associated with considerable morbidity. A technique practiced in the 1970s using wound packing has not demonstrated superiority compared to primary closure of the wound. Most of the authors agree that packing of the perineal wound after proctectomy increases the chances of wound complications and development of a postoperative sinus. It has been thought that obliteration of dead space in the pelvis can minimize the risk of a pelvic fluid collection or hematoma that could potentially contribute to disruption of the perineal closure. Several authors proposed filling the pelvis with an omental pedicle flap in combination with temporary placement of a pelvic suction drain. In a study by Thompkins and Warshaw [15] using this approach, 38 of the 47 patients (81%) with IBD primarily healed their perineal wound, and none of the patients developed a perineal sinus. Alternatively, in those patients who do develop a perineal sinus, wound debridement with closure using an omental pedicle flap has been shown to produce acceptable results [3]. Hurst [5] recommended closure of large, complex perineal wounds with myocutaneous flaps to avoid the potential complications of a non-healing wound and perineal sinus. In their study, 12 patients with complex perineal wounds who were treated with myocutaneous flaps completely healed the perineal wound without sinus formation.

Recommendations Based on the Data

For patients with severe fistulizing perianal IBD who require proctectomy or proctocolectomy, the decision must be made whether to remove the distal rectum and anus at the time of initial operation [9, 11, 16]. Leaving the anorectum in place (ultrashort Hartmann's pouch) is a seemingly attractive option because it allows preservation of pelvic floor integrity and eliminates the potential risk of perineal wound complications such as sinus or hernia. Yet, patients with an ultrashort Hartmann's pouch can develop persistent or recurrent disease with symptoms of pelvic abscess due to rectal stump staple line breakdown, leakage of mucus, and anal drainage as well as worsening fistulizing disease. Even though our review did not specifically identify publications comparing the ultrashort Hartmann's procedure and complete proctectomy in patients with severe fistulizing IBD ("watering can" perineum), the available literature did not support the lesser operation in patients requiring proctectomy.

Several publications identified the presence of perineal sepsis as a significant risk factor for perineal wound complications following proctectomy. One would expect that addressing perineal sepsis would improve wound healing. Yet the available data do not support the hypothesis that fecal diversion or perineal debridement prior to proctectomy mitigates perineal wound complications following proctectomy. Most authors recommend complete proctectomy as an initial operation even in the face of pelvic sepsis [16–20]. Avoiding large, complex wounds by performing dissection within the intersphincteric plane whenever possible, with direct suture closure of the wound in a layered fashion is uniformly recommended [14, 21]. Wound

breakdown and infectious complications can be managed by wound packing, vacuum-assisted devices, or myocutaneous flap. While some authors recommend the routine practice of pelvic space obliteration with an omental flap used at the time of initial surgery, most publications recommend employing this approach on an individualized basis and reserve its use for patients with high-risk wounds.

Management of a postoperative perineal sinus remains a difficult problem. Most authors recommend extensive debridement, curettage, or excision of the associated fibrotic tract and its associated biofilm. In some instances, flap closure may be required if more conservative attempts fail.

A personal View of the Data

Proctectomy for patients with IBD, particularly those with perineal sepsis, often results in poorly healed perineal wounds. Frequently, the patients presenting with severe perianal disease are at the nadir of their illness. They are often severely malnourished since they suffer from the effects of chronic inflammation. These effects are exacerbated by the fact that patients intentionally avoid eating to minimize the pain and drainage associated with perineal fistulas and abscesses.

My initial approach aims to optimize nutritional status and overall health. Unfortunately, these patients are unlikely to improve their condition even if offered elemental nutrition and perineal wound care. A course of parenteral nutrition could be helpful, but it is unlikely to significantly affect their nutritional status. Although most patients are clearly in need of surgical intervention, they are reluctant to consider an extensive operation and frequently delay their decision to proceed for fear of a permanent ostomy.

An alternative I employ in my practice is laparoscopic creation of a diverting loop ileostomy. I find that a laparoscopic loop ileostomy as the first step in treatment of severe perianal disease is readily accepted by patients and provides them with a less morbid surgical option that results in a speedy recovery. The construction of a diverting or end colostomy in patients with isolated perineal Crohn's disease seems to result in poor colonic function with watery, malodorous output that is often difficult to manage.

The main objective of this staged approach is to improve the patient's nutritional status over the ensuing 3–6 months. Most patients will be able to discontinue corticosteroids and have a noticeable improvement in their perineal sepsis. Importantly, the patients become comfortable with caring for their ileostomy and are more likely to accept it is as a permanent option. In some patients with a satisfactory nutritional status, a laparoscopic total abdominal colectomy with Hartmann's pouch is a valuable initial option.

In my practice, I do not perform the ultrashort Hartmann's procedure even in the face of severe perineal sepsis as I do not find that this option provides the patient with a better chance of avoiding perineal complications. In agreement with the literature, my experience with the ultrashort Hartmann's pouch is notable for patients who had a breakdown of the staple line which resulted in pelvic abscess, ongoing

fistulizing disease, drainage, and pain. All patients in my series with a retained anorectum required excision of their remnant. The wound healing was prolonged and the wound required packing in some patients.

I perform the proctectomy portion of a total proctocolectomy using a robotic approach and total mesorectal excision technique whenever possible. Any existing loop ileostomy generally does not need to be revised; instead, the distal limb of the loop ileostomy is stapled and divided during the laparoscopic portion of the operation. The patients who have adjusted to the configuration of the ileostomy will be happy to have it unchanged as it becomes permanent. I agree with authors who recommend perineal dissection to be performed in the intersphincteric plane whenever possible, followed by immediate approximation of the pelvic floor and subcutaneous tissues. Depending on the degree of perineal inflammation, the skin may be left open to heal by secondary intention. I selectively leave a 19-French pelvic drain inserted through a separate stab incision on the buttock. In my experience, removing the fluid that can potentially collect in the dependent space of the pelvic cavity increases the likelihood of primary healing. In agreement with most authors, I do not routinely use flap closure of the perineal defect as this procedure significantly increases operative time and morbidity, and it does not always lead to improved wound healing.

The strategies reported by some authors to address the non-healing perineal wound include curettage or excision of the perineal sinus. Some authors report that the perineal sinus can be found to contain entrapped hair. In my practice, I perform meticulous hair removal for the patients with a non-healing perineal wound or persistent sinus.

Abstracted Recommendation

IBD patients with a "watering can" perineum do not benefit from the ultrashort Hartmann's procedure. (moderate recommendation based on low quality evidence).

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Management of Isolated Proctitis/ Proctosigmoiditis

14

Takayuki Yamamoto

Abbreviations

CD	Crohn's disease
PSD	Proctosigmoidectomy
PT	Proctectomy
PTC	Proctocolectomy
UC	Ulcerative colitis

Introduction

Patients who are affected by isolated Crohn's disease of the rectum or rectosigmoid region and do not respond well to medical therapy including biologic agents or immunosuppressants may require surgical intervention [1, 2]. Nonetheless, there have been few reports about the surgical treatment for isolated proctitis/proctosigmoiditis likely because Crohn's disease (CD) confined to the rectum or the rectosigmoid colon is a relatively uncommon clinical entity. Likewise, patients with Crohn's disease of the rectum usually have complex anorectal fistulas and therefore, proctitis without perianal involvement is rare [3].

Until now, an optimized surgical strategy for proctitis/proctosigmoiditis secondary to Crohn's disease has not been established. In this chapter, the indications, outcomes, and limitations of different surgical approaches to the problem in patients with Crohn's disease will be evaluated together with a specific focus on two topics

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Table 14.1 PICO questions

Patients	Intervention	Comparator	Outcomes
Patients with isolated Crohn's proctitis/ proctosigmoiditis	Conventional proctectomy/ proctosigmoidectomy	Restorative proctectomy/ proctosigmoidectomy	Postoperative complications, recurrence, and quality of life
Patients with isolated Crohn's proctitis/ proctosigmoiditis	Proctectomy/ proctosigmoidectomy	Proctocolectomy	Postoperative complications, recurrence, and quality of life

(Table 14.1). First, the role of restorative proctectomy (PT)/proctosigmoidectomy (PSD) with anal sphincter preservation and coloanal anastomosis for isolated proctitis/proctosigmoiditis will be compared to that of conventional PT/PSD with inter- or extra-sphincteric excision of the anorectum plus creation of an end colostomy. Second, the outcomes of PT/PSD with construction of an end colostomy will be contrasted to proctocolectomy (PTC) with creation of an end ileostomy.

Search Strategy

A comprehensive literature search of Medline and PubMed was undertaken to identify publications in the English language between 1985 and July 2018 by using the following search terms: "Crohn's proctitis", "Crohn's proctosigmoiditis", "Anorectal Crohn's disease", "Operation", "Surgery", "Proctectomy", "Proctocolectomy", "Proctosigmoidectomy", "Abdominoperineal resection", "Stoma", "Ileostomy", "Colostomy", "Outcomes", "Complications", "Recurrence" "Reoperation" and "Quality of life". Citations from relevant studies were accessed to identifying additional studies. Conference proceedings relevant to the review topic were also searched.

Results

Only a few studies exist that have reported the outcomes of surgery for proctitis/proctosigmoiditis secondary to Crohn's disease [4–9]. A summary of these studies is presented in Table 14.2. All the studies, except one case report [6] were retrospective, and several included both patients with Crohn's disease and ulcerative colitis (UC) [4, 5], which means the outcomes of surgery for Crohn's disease alone were unclear. Further, patients with concomitant perianal Crohn's disease appeared to have been included making the outcomes of these reports not rigorous enough for studying isolated proctitis/proctosigmoiditis. Additionally, all the above studies had a small sample size and were non-comparative. Accordingly, the quality of evidence in all the above studies [4–9] should be considered as low.

Fasth [4] favored an endoanal mucosal PT with anal sphincter preservation (conservative PT) and creation of an end stoma as an alternative to conventional PT in

Table 14.2 Studies reporting the outcomes of surgery for Crohn's proctitis/proctosigmoiditis

Authors (Year)	Patients studied	Type of surgery	Study design	Major outcomes	Quality of evidence
Fasth et al. (1985) [4]	23 patients with UC or CD	Conservative PT	R	– Relatively low incidence of postoperative complications. – Low incidence of urinary disorders or sexual dysfunction.	Low
Bauer et al. (1986) [5]	388 patients with UC and 39 with CD	Conventional PT	R	– Relatively low incidence of postoperative complications and sexual dysfunction. – Unhealed perineal wound was more frequently observed in CD than in UC.	Low
Lawal et al (2010) [6]	3 patients with rectal strictures (CD)	Restorative PT / PSD for 2 patients	Case report	– Anal sphincteric function was preserved. – A permanent stoma was avoided.	Low
de Buck van Overstraeten et al (2013) [7]	10 with anorectal CD (2 with mild colitis)	Conventional PT	R	Early and severe CD recurrence in the proximal colon occurred in the majority of patients.	Low
Schlegel et al (2015) [8]	15 patients with fistulizing and stenotic Crohn's proctitis	Restorative PT for 12 patients	R	Acceptable rates of healing of fistula or stricture, and stoma avoidance.	Low
Memon et al (2016) [9]	29 with Crohn's proctitis (17 with history of proximal bowel resection for CD, 20 with history of perianal CD)	Restorative PT	R	– A permanent stoma was avoided in half of patients. – Colonic recurrence was observed in one-fourth of patients.	Low

CD Crohn's disease, *UC* ulcerative colitis, *PT* proctectomy, *PSD* proctosigmoidectomy, *PTC* proctocolectomy, *R* retrospective

23 patients with ulcerative colitis or Crohn's disease. Ten patients in whom the anal canal was left open had uneventful postoperative courses. Among the remaining 13 patients in whom the top of the anal remnant was oversewn, four developed pelvic sepsis that was conservatively managed and one developed a pelvic hematoma

requiring repeat laparotomy and removal of the sphincter muscle. Postoperative urinary or sexual dysfunction was not experienced by any of their patients. During a mean follow-up time of 21 months, all patients reported being very satisfied with the outcome of the surgery. Proctoscopic examination revealed an anal remnant measuring approximately 3 cm from the anal verge. The upper end of the remnant had healed with a fibrous scar in one-half of the patients, whereas a small area of friable granulation tissue with or without a short sinus was observed in the remainder. The persistence of such lesions was associated with minor and occasional mucus discharge from the anal canal. Biopsies revealed regeneration of columnar and transitional epithelium. The authors concluded that endoanal mucosal PT could be a relevant alternative to conventional PT because the operation may minimize postoperative complications and enhance postsurgical rehabilitation.

Bauer [5] reported the outcomes of PT either as part of a primary PTC or as a secondary staged operation in 388 patients with ulcerative colitis and 39 patients with Crohn's disease between 1973 and 1984. In all patients, the perineal wounds and pelvic peritoneum were closed after placing a suction drain. There were two deaths in the early postoperative period; one death occurred from pulmonary embolism and the other from sepsis. Three patients required reoperation due to hemorrhage from a branch of the superior hemorrhoidal artery. After surgery, two patients developed a perineal hematoma and four developed perineal abscesses that required reopening of the perineal wound. The perineal wound did not heal in 3 (0.8%) of 388 patients with ulcerative colitis and in 5 (13%) of the 39 patients with Crohn's disease. After PT, one patient was permanently impotent, two experienced temporary impotence, and three were experiencing retrograde ejaculation at the end of the follow-up. However, the incidence of postoperative complications and impaired sexual function appeared to be relatively low. In this study, the outcomes of patients with Crohn's disease alone were not clear, but an unhealed perineal wound was more frequently observed in Crohn's disease than ulcerative colitis.

Lawal [6] used a transanal rectal resection for Crohn's patients with rectal strictures that did not respond to medication, rectal dilation, or balloon dilation. Two patients with isolated proctitis/proctosigmoiditis opted for a transanal sphincter-preserving dissection in the prone position plus transabdominal proctosigmoidectomy with construction of a diverted coloanal anastomosis in the lithotomy position. The authors suggested this operation preserves the sphincteric function of the anal opening and may be a relevant strategy for avoiding a permanent stoma in a subgroup of motivated patients with proctitis.

de Buck van Overstraeten [7] reported the results of a retrospective assessment of 10 consecutive patients who underwent conventional PT with end colostomy for refractory anorectal Crohn's disease between 2007 and 2011. All but one patient was receiving immunosuppressant medications or biologic agents prior to surgery. Although two patients showed mild colitis during preoperative ileocolonoscopy, all other patients had no endoscopic evidence of colitis. During a median follow-up time of 9.5 months (range: 1.9–23.6 months), early and severe endoscopic recurrence in the proximal colon occurred in 9 of the 10 patients. Despite prolonged medical therapy, completion colectomy was required in 5 patients. One patient, who underwent a second segmental colectomy with construction of a new end

colostomy, developed endoscopic recurrence again, and received treatment with biologic agents. These observations suggest that conventional PT with end colostomy might be an ineffective strategy for anorectal Crohn's disease secondary to the high risk of recurrent Crohn's disease in the remaining colon. Therefore, despite a normal appearance of the proximal colon, a PTC with end ileostomy appears to be a suitable surgical approach in these patients.

Schlegel [8] reported a single center experience with an anterior rectal resection for Crohn's disease of the rectum. Twelve of the 15 patients with long-standing fistulizing and stenotic proctitis underwent anterior rectal resection with intersphincteric sphincter-sparing techniques, and creation of a diverted coloanal anastomosis while the remaining 3 patients were treated with primary conventional PT due to malignancy (2 patients) or patient's wish (1 patient). One patient developed an unexpected malignancy, which led to a secondary PT. After anterior rectal resection with coloanal anastomosis, fistulas and stenotic lesions healed in 5 patients (46%), while 4 patients (36%) experienced relapse of their fistula, and 2 (18%) developed restenosis. The diverting ileostomy was closed in 7 patients, of whom 6 were stoma-free at the end of the study. Quality of life and fecal incontinence evaluated according to a standardized scoring system were not significantly changed, while the frequency of bowel movements decreased in patients who had their ileostomy closed. The authors found that anterior rectal resection with intersphincteric sphincter-sparing coloanal anastomosis did not improve patients' quality of life but suggested it was an appropriate procedure for the management of proctitis because of good rates of fistula and stricture healing, or stoma avoidance.

At the 57th Annual Meeting of The Society for Surgery of the Alimentary Tract, Memon [9] described the outcomes on 29 patients who underwent restorative PT for Crohn's disease of the rectum between 1997 and 2015. Seventeen patients (59%) had a prior or concurrent proximal bowel resection for Crohn's disease. Twenty patients (69%) had a prior or concurrent history of perianal Crohn's disease. Seventeen patients underwent a Turnbull-Cutait coloanal anastomosis (59%), 9 patients had a stapled anastomosis, and 3 patients had a hand-sewn anastomosis. After surgery, one patient died from an unrelated cause. With a median follow-up of 21 months (range: 6–192 months), the median duration of stoma-free survival was 59 months. At the most recent follow-up, 15 of the 28 patients (54%) were free from a permanent stoma. Eight patients (28%) developed recurrent Crohn's disease in the colon, of whom 7 required a permanent stoma. Based on these outcomes, the authors concluded that the Turnbull-Cutait technique [10, 11] for coloanal anastomosis has a role in patients with Crohn's disease of the rectum who wish to avoid a permanent stoma. Recurrent colitis is frequent and a potential cause for subsequent permanent stoma formation.

Recommendations Based on the Data

The quality of evidence for the surgical management of isolated proctitis/proctosigmoiditis secondary to Crohn's disease is low. From a clinicopathological viewpoint, there are three types of proctectomy/proctosigmoidectomy: conventional [5, 7]; restorative [6, 8, 9], and; conservative. Among these, there is no convincing

evidence that favors one procedure over the other two. Therefore, the choice of the best surgical procedure for each patient is predicated upon the patient's clinical presentation and desires as well as the surgeon's discretion.

If a patient with Crohn's disease and proctitis/proctosigmoiditis without severe perianal disease is strongly motivated to avoid a permanent stoma, and her/his anal sphincter function is not compromised then restorative PT/PSD with coloanal anastomosis can be a relevant treatment option. Likewise, in patients with Crohn's disease thought to be limited to the distal large bowel, the proximal colon should be thoroughly evaluated prior to surgery. When there is evidence of active Crohn's disease in the proximal colon, PTC with end ileostomy is recommended; and when PT/PSD with end colostomy creation is performed, prophylactic medication should be strongly considered to minimize the risk of recurrent Crohn's disease of the residual colon.

Personal View of the Data

This author's view is that restorative PT/PSD with coloanal anastomosis might be a relevant approach for the rare patient with isolated proctitis/proctosigmoiditis without significant perianal Crohn's disease, intact anal sphincter function, and an expressed desire to avoid a permanent stoma. However, patients should be informed of the potential risk for developing perianal Crohn's disease and subsequent need for excision of the coloanal anastomosis. Additionally, the operation should be carried out by experienced surgeons in specialized hospitals.

Further, conservative PT could be an appropriate procedure for patients with proctitis without perianal Crohn's disease lesions [4]. Indeed, the concept of conservative surgery is based on the rationale that impaired healing of the perineal wound is often observed after conventional PT [12] and this might be eliminated by conservative PT [13–15]. Contrary to this assertion, several studies [16, 17] have suggested that conservative PT does not offer any advantage over conventional PT, and cannot be recommended as a definitive surgery.

One study recently found that conventional PT with end colostomy was associated with a very high rate of recurrent Crohn's disease in the residual colon [7]. The authors accordingly advocated for PTC with end ileostomy as an appropriate surgical approach for patients with anorectal Crohn's disease despite normal preoperative findings in the proximal colon. Similarly, another group has reported a high rate of colonic recurrence after PT with coloanal anastomosis [9]. Nonetheless, favorable outcomes have been reported by one group who found that conventional PT with end colostomy was not associated with a high incidence of recurrent Crohn's disease in the remaining colon [5]. The experience described by these authors should help decision making in therapeutic settings.

Currently, in patients with evidence of active Crohn's disease in the proximal colon, we often opt for PTC rather than PT/PSD. When there is no evidence of Crohn's disease in the proximal colon, PT/PSD with end colostomy should be a favorable option with added prophylactic medication like a biologic agent to

minimize the risk of recurrent Crohn's disease recurrence in the proximal colon. Therefore, we may need to wait for future work, preferably randomized controlled trials involving large cohorts of patients to fully understand the therapeutic benefit of conservative PT/PSD with end colostomy or PTC with end ileostomy in the surgical management of proctitis/proctosigmoiditis secondary to Crohn's disease.

When patients with proctitis/proctosigmoiditis without severe perianal Crohn's disease lesions express a strong desire to avoid a permanent stoma, and their anal sphincter function is normal, restorative proctectomy/proctosigmoidectomy with coloanal anastomosis may be considered. (Weak recommendation based on low quality evidence)

Prior to surgery, in patients with proctitis/proctosigmoiditis secondary to Crohn's disease, the surgeon should carefully evaluate the proximal colon. When there is evidence of active Crohn's disease in the proximal colon, proctocolectomy with end ileostomy is recommended. When proctectomy/proctosigmoidectomy with end colostomy is performed, prophylactic medication should be considered to minimize the risk of recurrent Crohn's disease in the residual colon. (Weak recommendation based on low quality evidence)

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Role of IPAA for Crohn's Disease

15

Gaetano Gallo and Willem A. Bemelman

Introduction

Proctocolectomy and creation of an ileal pouch-anal anastomosis (IPAA), first described by Parks and Nicholls [1], is the preferred and most commonly performed surgical procedure for patients requiring resection of the entire large intestine provided they demonstrate good sphincter function and lack risk factors for postoperative complications or dysfunction. The operation was initially developed for patients with ulcerative colitis or familial adenomatous polyposis to preserve the normal route of defecation and avoid the need for a permanent stoma while ensuring acceptable functional results and satisfactory patient-reported quality of life [2].

In a pioneering study published more than two decades ago, Yves Panis described a series of patients undergoing proctocolectomy and IPAA for known Crohn's disease with favorable results [3]. These patients had Crohn's disease limited to the large intestine without evidence of prior/current small bowel or anoperineal disease. Since that initial report, proctocolectomy and IPAA in Crohn's disease is accepted by many as a valid option for selected patients [4, 5]. However, some debate persists about whether the operation is a good idea for a Crohn's disease patient because the procedure is associated with short- and long-term complications (e.g., anastomotic leakage, pouchitis, pouch dysfunction, pouch failure). Prior anastomotic leakage and recurrent Crohn's disease involving the pre-pouch ileum, ileal pouch, or

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anoperineal region are the most important causes for pouch dysfunction and pouch failure [6].

The alternative operation is a proctocolectomy and creation of an end ileostomy. Apart from living with a stoma, these patients might suffer from an unhealed perineal wound or a presacral sinus. Furthermore, recurrent Crohn's disease can manifest itself in the remaining small bowel [7].

Aside from patients with known Crohn's disease managed by proctocolectomy and IPAA, others undergo the operation for presumed ulcerative colitis and are later diagnosed with Crohn's disease based on histologic features of the excised specimen or later clinical course [8–15]. These patients are not the primary objective of this PICO but will be discussed for completeness.

The research question focuses on patients with known Crohn's disease requiring proctocolectomy and determining which surgical procedure (i.e., IPAA, ileostomy) is the preferred option based on recurrent disease and quality of life (Table 15.1).

Search Strategy

A comprehensive literature search of the Cochrane Library, PubMed, EMBASE, Science Citation Index Expanded, and MEDLINE databases was performed through June 2018 using the following terms: "restorative proctocolectomy", "Crohn's proctocolitis", "ileal pouch-anal anastomosis", "pouch complications rate", "ileostomy", "pouch failure", "recurrence rate", "quality of life", "de novo Crohn's disease of the pouch".

The search process involved articles published in the period between January 1990 and January 2018. The type of eligible studies included RCT, prospective and retrospective observational studies, Case series and Systematic Reviews.

Only articles published in the English language were included for review. No restrictions were made based on publication year or publication status. Duplicate publications and conference abstract were excluded. Comments and letters were also excluded due to the lack of information.

The references of the identified trials were also searched to find additional trials for inclusion.

The following information were extracted from each study: authors, design of the study, number and characteristic of the patients, quality of life, pouch failure rate, pouch complication rate, de novo Crohn's disease, pouch excision rate and follow-up.

Table 15.1 PICO questions

P (Patients)	I (Intervention)	C (Comparator)	O (Outcomes)
Patients with Crohn's proctocolitis	Restorative Proctocolectomy with ileal pouch-anal anastomosis	Proctocolectomy with ileostomy	Disease recurrence
Patients with Crohn's proctocolitis	Restorative Proctocolectomy with ileal pouch-anal anastomosis	Proctocolectomy with ileostomy	Quality of life

The recommendations were defined and graded based on the current levels of evidence and in accordance with the criteria adopted by the American College of Gastroenterology's Chronic Constipation Task Force [16]. Five evidence levels were defined. The recommendations were graded A, B and C.

Results

Disease Recurrence PICO

A good body of literature exists with respect to pouch failure due to Crohn's disease, but the data are limited because many series include few patients, and several were published more than 15 years ago [3, 17, 18]. Most authors do not distinguish between patients with Crohn's disease diagnosed before, immediately after, and months following proctocolectomy and IPAA. For this PICO, the data on patients with known Crohn's disease who intentionally underwent a proctocolectomy and IPAA are of principal interest [3, 9, 17–23]. The data are not consistent with respect to reported failure rates, defined as defunctioning of the pelvic pouch or pouch excision. Patients who had restorative proctocolectomy with a preoperative diagnosis of Crohn's disease did remarkably well with failure rates around 15% (Table 15.2). Conversely, failure rates approaching 45% are derived from the older studies earlier described (Table 15.2).

Melton [19] discriminated between outcomes and the time when Crohn's disease was diagnosed. A preoperative diagnosis was made in 20 patients (10%) whereas a postoperative (histopathological – "incidental") and a delayed diagnosis were made in 97 (47%) and 87 (43%) patients, respectively. Pouch retention rates were 85%, 87%, and 52% respectively (Tables 15.2 and 15.3). Seventy-two percent of the patients who intentionally underwent a proctocolectomy and IPAA despite a diagnosis of Crohn's disease had near-perfect or perfect-continence and 68% had rare or no fecal urgency. Interestingly, patients' quality of life, quality of health, and happiness with IPAA in the same group were 9/10, 9/10, and 10/10, respectively.

A later publication from the same group [22] reported the largest series of IPAA with a median follow-up of 84 months. They compared the outcomes after IPAA in patients with different diagnoses: ulcerative colitis (N = 2959; 79.8%), Crohn's disease (N = 150; 4.1%), indeterminate colitis (N = 63; 1.7%), and familial adenomatous polyposis (N = 223; 6%). The pouch failure rate was highest in the Crohn's disease group compared with the other three groups (Crohn's disease: 13.3%; ulcerative colitis: 5.1%; indeterminate colitis 4.8%; FAP 3.6%). The three most important findings were a pouch retention rate of 82% at 10 years and equivalent functional outcomes and quality of life (dietary, social, work, and sexual restrictions) between the Crohn's disease and ulcerative colitis groups. In fact, all the four patient groups were happy to have undergone the operation (Crohn's disease: 97.1%; ulcerative colitis: 96.3%; indeterminate colitis: 92.6%; familial adenomatous polyposis:

Table 15.2 Patients with preoperative known Crohn's disease

Preoperative known			Recurrent Crohn's				Pouch failure		
Author	Follow up	Number of patients	Overall	Small bowel / prepouch ileum	Crohn's pouchitis	Perianal/ perineal fistula	Overall	Diverting ileostomy	Excision + end ileostomy
Panis (1996) [3]	59 months	18[a]	5 (16%)[a]		2 (6%)[a]	5 (16%)[a]	2 (6%)[a]		2 (6%)[a]
Mylonakis (2001) [17]	122 months	23[a]		7 (30%)[a]	15 (65%)[a]	7 (30%)[a]	12 (52%)[a]		4 (33%)[b]
Regimbeau (2001) [18]	113 months	26[a]			15 (37%)[a]	9 (22%)[a]	3 (7%)[a]		3 (7%)[a]
Brown (2005) [9]	153 months	37[a]		7 (19%)[a]		Abscess 8 (22%)[a] Pouch-fistula 14 (39%)	20 (56%)[a]	3 (8%)[a]	16 (45%)[a]
Melton (2008) [19]	89 months	20[b]			47 (40%)[b]	22 (19%)[b]	15%		
Shen (2010) [20]	60 months	11	7 (63.6%)		7 (63.6%)		1 (9.1%		1 (9.1%)
Grucela (2011) [21]	44 months	13[a]			3 (23.1%)[a]	2 (15.4%)[a]	1 (7.7%)[a]		1 (7.7%)[a]
Fazio (2013) [22]	120 months	150					20 (13.3%)[a]		20 (13.3%)[a]
Le (2013) [23]	60 months	17	7/17 (41%)	4 (23%)	6 (35%)	3 (18%)	1 (6%)		1 (6%)

[a]Pre-operative, peri-operative known and delayed diagnosis
[b]Pre-operative known & Peri-operative know

Table 15.3 Patients with delayed diagnosis of Crohn's disease

Postoperative known			Recurrent Crohn's				Pouch failure		
Author	Follow up	Number of patients	Overall	Small bowel/ prepouch ileum	Crohn's pouchitis	Perianal/ perineal fistula	Overall	Diverting ileostomy	Excision + end ileostomy
Hyman (1991) [11]	38 months	25	8 (32%)		9 (36%)	3 (12%)	9 (36%)	1 (4%)	8 (32%)
Grobler (1993) [12]	48 months	10	4 (40%)		5 (50%)		3 (30%)		3 (30%)
Sagar (1996) [13]	120 months	37		2 (5%)	20 (54%)		46%	7 (19%)	10 (27%)
Peyregne (2000) [8]	89 months	7			1 (14%)	3 (43%)	3 (43%)	2 (28%)	1 (14%)
De Oca (2003) [10]	76 months	12	2 (16%)		1 (8%)	2 (16%)	3 (25%)	2 (16%)	2 (16%)
Braveman (2004) [14]	153 months	32	23 (72%)		16 (50%)	18 (56%)	9 (28%)	2 (6%)	7 (22%)
Tekkis (2005) [15]	56 months	26			4 (15.4%)	16 (61.5%)	58%	1 (4%)	14 (54%)
Melton (2008) [19]	89 months	87			63 (72%)	39 (45%)	47%		

93.6%) 10 years after surgery. Those results were consistent with studies from other referral centers [15, 24].

The results of the alternative operation (i.e., proctocolectomy and permanent ileostomy) for Crohn's disease are difficult to assess. The limited number of publications on proctocolectomy and ileostomy for known Crohn's disease describe a mix of patients varying from patients with Crohn's disease limited to the large intestine to patients with large bowel disease plus severe anoperineal disease. These two completely different phenotypes of Crohn's disease are not separately evaluated with respect to disease recurrence, unhealed perineal wound, persistant presacral sinus, and quality of life. An unhealed perineal wound or persistent presacral sinus is reported in up to 25% of patients after one year of postoperative follow-up [7, 25, 26].

Quality of Life

It has always been suggested that proctocolectomy with IPAA in ulcerative colitis provides a better quality of life than a permanent ileostomy. However, a recent systematic review, considering 1603 patients who underwent a proctocolectomy and ileostomy (N = 820) or IPAA (N = 783) challenged this assumption, concluding that restorative proctocolectomy with either IPAA or ileostomy are associated with equivalent quality of life outcomes [27]. These results must be mentioned during any preoperative discussion with the patient. As stated earlier, no data exist with respect to quality of life in Crohn's disease patients who would have been eligible for either a restorative proctocolectomy or proctocolectomy and permanent ileostomy. The latter group consists of different phenotypes of Crohn's disease with or without small bowel or anoperineal disease.

Peyregne [8] evaluated quality of life using a subjective scale between 1 and 10, in 7 patients submitted to a restorative proctocolectomy and IPAA for ulcerative colitis but with a subsequent delayed diagnosis of Crohn's disease. The associated quality of life was deemed to be satisfactory or very satisfactory (score > 7/10) in six out of seven patients (85%) and poor (score < 4/10) in only one patient (15%). Interestingly, diverted patients were more satisfied than nondiverted patients (9/10 vs 7/10).

Recommendations

Proctocolectomy and IPAA may be offered as an alternative to proctocolectomy and definitive end ileostomy in selected patients with a preoperative diagnosis of Crohn's disease without small bowel or anoperineal manifestations (Strong recommendation based on moderate quality data).

Pouch retention rates are acceptable and function and quality of life are good in patients with Crohn's disease limited to the colon and rectum undergoing the restorative procedure.

Personal View

Inflammatory bowel disease of the large bowel refractory to therapy or complicated by neoplasia generally warrants proctocolectomy. The type of the underlying inflammatory bowel disease is not always easy to discern [28], but endoscopic and pathologic features might point lead to a diagnosis of Crohn's disease. Restorative proctocolectomy and IPAA was traditionally contraindicated in patient with Crohn's disease [29]. Panis [3] challenged this view after publishing more favorable results after proctocolectomy and IPAA surgery for a selected group of Crohn's disease patients. Their observations were confirmed by later data indicating that some patients with pelvic pouches created for Crohn's disease had good pouch retention rates and quality of life scores similar to patients undergoing the procedure for ulcerative colitis. Conversely, the literature indicates that the patients with a pelvic pouch and a delayed diagnosis of Crohn's disease have the worst prognosis in terms of ileal pouch retention [19].

Furthermore, even if Crohn's disease manifests itself in the neo-terminal ileum or ileal pouch, this disease can quite often be medically managed and acceptable function can be preserved [30]. Troublesome are those patients who develop anoperineal fistulas requiring setons in combination with medical therapy. Again, these are mostly the patients with delayed diagnosis of Crohn's disease who might have already enjoyed their pelvic pouch for many years. Patients undergoing proctocolectomy and IPAA in whom the diagnosis of Crohn's disease was preoperatively known or recognized in the resected specimen should be discussed by a multidisciplinary team to decide whether prophylactic therapy is indicated.

Patients with Crohn's disease strictly limited to the large bowel without anoperineal disease should be counseled about the two operative options. On one hand, proctocolectomy and IPAA is associated with an 85% retention rate at 10 years with function that is comparable to that seen in patients with pelvic pouches created for ulcerative colitis. On the other hand, proctocolectomy and ileostomy has a 23% rate of long-term perineal wound problems as well as possible stoma-related complications [31]. An individualized approach with tailored counseling and shared decision making is critical.

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Surgical Options for Neoplasia Complicating Crohn's Disease of the Large Intestine

16

Jeffrey S. Scow and Amit Merchea

Abbreviations

CC	Crohn's colitis
CD	Crohn's disease
CRC	Colorectal cancer
CUC	Chronic ulcerative colitis
HGD	High-grade dysplasia
IBD	Inflammatory bowel disease
IPAA	Ileal pouch-anal anastomosis
LGD	Low-grade dysplasia
STC	Subtotal colectomy
TAC/IRA	Total abdominal colectomy/ileorectal anastomosis
TPC/EI	Total proctocolectomy/end ileostomy

Introduction

Individuals with Crohn's disease (CD) of the large intestine develop colorectal cancer at an increased rate compared to the general population. The exact magnitude of increased risk is unknown. The prevalence of dysplasia at 25 years has been reported to range between 0.5% to 25% [1–5] and the risk for colorectal cancer may be six-fold that of the general population [6–8]. Colorectal cancer in patients with

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inflammatory bowel disease (IBD) appears to develop via a pathway that deviates from the well characterized adenoma-carcinoma sequence of sporadic colorectal cancer and may progress rapidly, skipping steps seen with sporadic colorectal cancer [1, 9–14].

Currently, it is recommended by most professional organizations that patients with Crohn's disease involving at least one-third of the large intestine for 8 or more years undergo surveillance colonoscopy on a regular basis with the goal of intervening, either endoscopically or surgically, prior to the development of colorectal cancer [15–20]. Current guidelines for screening, surveillance, and treatment of dysplasia in patients with Crohn's disease of the large intestine have been predominantly extrapolated from observations and experience with the treatment of dysplasia in patients with ulcerative colitis (UC) [21, 22] which rely on frequent surveillance colonoscopy followed by appropriately timed total proctocolectomy and end ileostomy (TPC/EI) or reconstruction with an ileal pouch-anal anastomosis (IPAA).

Patients with Crohn's disease have typically not been considered eligible for IPAA because of Crohn's disease's variable nature, propensity to affect the entire GI tract, and predilection for involvement of the anoperineal area. Current guidelines, relying on heterogenous data, recommend TPC/EI for patients with Crohn's disease that develop dysplasia [15, 19]. However, some patients with rectal sparing may be candidates for total abdominal colectomy with ileorectal anastomosis (TAC/IRA) if counseled appropriately regarding the requirement for frequent surveillance endoscopy of the rectum and continued potential for development of Crohn's proctitis, rectal dysplasia, and possibly rectal cancer [22–27]. TAC/IRA, as opposed to TPC/EI, has the advantage of not requiring a permanent ileostomy and does not subject a patient to the risk of possible perineal wound healing problems and sexual dysfunction or infertility. The aim of this chapter is to examine the published literature of the past 20 years to guide clinicians counseling patients with Crohn's disease of the large intestine who are facing colectomy in the setting of dysplasia. Our aim was to describe the incidence of synchronous and metachronous neoplasia. We did not examine the risk of recurrent Crohn's proctitis as this is the focus of a different chapter.

Search Strategy

Relevant PICO (Population, Intervention, Comparator, Outcome) questions were generated (Table 16.1). A comprehensive literature search of the Cochrane Database of Collected Research, EMBASE, Google Scholar, PubMed, and SCOPUS and was performed to identify all the English language publications related to dysplasia in

Table 16.1 PICO

Patients	Intervention	Comparator	Outcome
Patients with Crohn's colitis that develop dysplasia requiring resection	Total abdominal colectomy with ileorectal anastomosis	Total proctocolectomy with end ileostomy	Risk of undetected neoplasia or recurrent neoplasia

patients with Crohn's disease of the large intestine for the past 20 years, between 1998 and 2018. Key search terms included: colectomy, Crohn's disease, Crohn's colitis, dysplasia, inflammatory bowel disease, and proctocolectomy. Case reports, chapters, and review articles were omitted. Retrospective, systematic, and prospective reviews and randomized control trials were reviewed. Meta-analyses were reviewed for appropriateness and pertinent publications. Publications that did not evaluate the risk of undetected or recurrent neoplasia as a primary or secondary outcome were excluded. Studies that examined inflammatory bowel disease as a whole and did not specifically delineate results for patients with Crohn's disease were also excluded. References of the included studies were examined for additional publications and included when criteria were met.

Results

Over the past 20 years, no randomized or prospective studies evaluating the risk of undetected or recurrent neoplasia in patients with Crohn's disease of the large intestine and dysplasia have been published. Several retrospective studies have examined synchronous neoplasia at the time of colectomy for neoplasia and a couple of retrospective studies reported on metachronous neoplasia in patients with Crohn's disease of the large intestine in patients who previously underwent procedures sparing portions of the large intestine. Overall these are heterogenous studies with varied inclusion/exclusion criteria, relatively few patients, and performed at large referral centers, such that applicability to the broader population with Crohn's disease of the large intestine may be difficult. Additionally, colonoscopy equipment has dramatically changed over the past decades as high-definition colonoscopes and monitors have become more common and widespread since the mid-2000s. Furthermore, chromoendoscopy has recently been recommended by several organizations to enhance detection and endoscopic treatment of neoplasia and is becoming more universally utilized for the evaluation of patients with IBD [16, 28, 29]. In this review of the data, chromoendoscopy was used in only a limited number of patients. Likely, this technique will become more widepsread to survey and manage inflammatory bowel disease patients at risk for dysplasia in the future.

Undetected Neoplasia

Four studies investigated undetected synchronous neoplasia in patients with Crohn's disease of the large intestine and known dysplasia undergoing some form of colectomy. Friedman examined patients (n = 259) with Crohn's disease of the large intestine undergoing screening and surveillance colonoscopies (n = 1424). Patients discovered to have dysplasia were referred for surgery (22). Patients undergoing colectomy (extent undefined in their study) for low-grade dysplasia (LGD) were found to have high-grade dysplasia (HGD) or colorectal cancer in 54% of cases. Similarly, 50% of patients who underwent a colectomy for high-grade dysplasia

were found to have colorectal cancer. This occurred despite intense surveillance with patients undergoing a median of five previous colonoscopies [5].

In 2012, Kiran reported on 50 patients with Crohn's disease of the large intestine that underwent colectomy for dysplasia. Patients with known colorectal cancer were excluded in this report. No patient with low-grade dysplasia was found to have colorectal cancer but 35% of patients with low-grade dysplasia were found to harbor undetected, synchronous, high-grade dysplasia. Of those with preoperative diagnosis of high-grade dysplasia, 45% were found to have colorectal cancer. High-grade dysplasia was predictive of high-grade dysplasia/colorectal cancer in 73% of patients. Patients with low- or high-grade dysplasia were found to have multifocal dysplasia in 32% and 36% of cases, respectively. Of the patients found to have colorectal cancer, 40% had dysplasia remote from the cancer site [22].

Cleveland retrospectively reviewed 36 patients with inflammatory bowel disease who were undergoing surveillance colonoscopy, discovered to have dysplasia or colorectal cancer, and then proceeded to colectomy. These 36 patients were preoperatively known to have 44 neoplastic lesions. Nearly one-half (47%) of the patients had Crohn's disease of the large intestine and the remaining had ulcerative colitis. Of the 30 low-grade dysplasia lesions preoperatively known to exist, only 11 were identified in colectomy specimens of which one (1/11, 9%) was upgraded to high-grade dysplasia. More significantly, in the group operated on for low-grade dysplasia, 8 previously undiagnosed synchronous lesions were discovered (3 low-grade dysplasia; 4 high-grade dysplasia; one sporadic cancer). Of patients with high-grade dysplasia, 5 of 6 known lesions were identified and one (1/5, 20%) was found to be colorectal cancer. Additionally, one synchronous colorectal cancer was found in the group with high-grade dysplasia. Eight lesions were known to be colorectal cancer and 6 were confirmed in colectomy specimens, none of which were downgraded. In patients with known colorectal cancer, no synchronous lesions were discovered [30].

Most recently, Eluri published a retrospective review of patients with Crohn's disease of the large intestine (21) who were either preoperatively known or found to have high-grade dysplasia or colorectal cancer after "complete abdominal colectomy." All patients had at least one colonoscopy prior to operation. Four patients were known to have high-grade dysplasia and 12 patients were known to have colorectal cancer. At the time of colectomy, 5 patients (24%) were found to have unknown high-grade dysplasia (4) or colorectal cancer (1) [31].

Recurrent/Metachronous Neoplasia

One study specifically examined metachronous neoplasia in patients with known neoplasia in the setting of Crohn's disease of the large intestine undergoing segmental colectomy or subtotal colectomy (STC). Three additional studies made mention of the development of metachronous lesions but did not extensively report on this phenomenon. Kiran (2010) studied 240 inflammatory bowel disease patients undergoing colectomy for colorectal cancer of whom 27% had Crohn's disease of the large intestine. The authors' primary aim was to compare differences between ulcerative colitis and Crohn's disease of the large intestine. Not reported in their results,

but included in the discussion of the manuscript was the comment that "…15% of the [Crohn's disease of the large intestine] patients who underwent segmental colon resection, developed metachronous tumor within 4 years [32]."

Kiran (2012) then examined patients with Crohn's disease of the large intestine and confirmed dysplasia undergoing colectomy. The authors noted that "eleven… patients… underwent procedures that left them at risk of developing cancer or high-grade dysplasia in the retained colorectum during follow-up." One (9%) of these patients developed a metachronous rectal cancer three years after the index operation and died. The authors note that this individual had not complied with surveillance recommendations [22].

Maser looked at the incidence of metachronous dysplasia and colorectal cancer in 75 patients with Crohn's disease of the large intestine who underwent segmental or STC for dysplasia (11 patients) or colorectal cancer (64 patients). Of patients with colorectal cancer, 39% developed metachronous colorectal cancer at an average of 6.8 years after the index operation. Patients with high-grade dysplasia were found to have developed recurrent dysplasia (low-grade dysplasia in 2 patients and high-grade dysplasia in 3 patients) in 46%, at an average of 6.2 years. Notably, none of the patients with an index operation for high-grade dysplasia recurred with a colorectal cancer. 50% of patients with metachronous colorectal cancer died due to the recurrence. When comparing recurrence rates in patients with segmental resection versus STC, no significant difference was found. This led the authors to conclude that, "the lack of detectable benefit in doing a STC over a segmental resection also suggests that leaving even a portion of colon behind puts a patient at risk for a metachronous lesion [23]."

Cleveland noted in their small series that, of the subset of patients who underwent segmental/STC, no metachronous neoplasia was identified. However, their median follow-up and number of colonoscopies were only 6 months (3 months to 81 months) and 2 (1–5), respectively. Furthermore, the bulk of these patients had low-grade dysplasia (5) (Table 16.2) [30].

Recommendations

Because of the high risk for undetected and metachronous neoplasia, TPC/EI should be performed for patients with Crohn's disease of the large intestine found to have low-grade dysplasia, high-grade dysplasia, or colorectal cancer (strongly recommendation, low quality evidence).

Based on the reviewed studies, the incidence of undetected synchronous and/or upgraded lesions was 9–54%. Studies that investigated metachronous neoplasia reported rates of 0–46%. TPC/EI is the procedure of choice because anything less than total extirpation of the colon and rectum continues to subject a patient with neoplasia to these risks. We do acknowledge caveats and exceptions that may sway the surgeon and patient to consider, at least initially, TAC/IRA, and they include rectal sparing and/or desire for preservation of fecundity. However, patients must be strongly counseled about risks of retaining the colon or rectum and commit to stringent follow-up, specifically in the form of surveillance endoscopy.

Table16.2 Studies examining risk of undetected neoplasia and recurrent/metachronous neoplasia in patients with CC and dysplasia

First Author (year)	Design	Patients Breakdown of patients	Results	Notes	Quality of evidence
Friedman (2008)	CC patients undergoing surveillance colonoscopy and surgery	259 Surveillance pathology/# undergoing surgery LGD (flat) 8 LGD (polyp) 5 HGD (flat) 4 CRC 5	5/8 (63%) CRC/HGD 2/5 (40%) CRC 3/4 (75%) CRC/HGD 5/5 (100%) CRC	Primarily a colonoscopy surveillance study	Low
Kiran (2010)	IBD patients undergoing colectomy for CRC (retrospective)	240 Crohn's 64 **Indications** HGD/CRC 84% Colitis 4% Mass/stricture 10% Fistula 2%	"…15% of the CD patients who underwent segmental colon resection, developed metachronous tumor within 4 years" p334	Metachronous data only mentioned in discussion	Very low
Kiran (2012)	CD & confirmed dysplasia undergoing colectomy. Preop CRC excluded	50 LGD 25 HGD 22 IFD 3	Preop:postop LGD: 36% HGD HGD: 45% CRC LGD: 32% MFD HGD: 36% MFD	1/11 patients with intact rectum developed rectal cancer 3 years after surgery (p222)	Low
Maser (2013)	MCRC after segmental or STC for HGD or CRC in CD	75 CRC 64 HGD 11	25/64 (39%) MCRC 5/11 (46%) recurrent dysplasia (no MCRC)	Average time from surgery to MCRC was 6.8 years	Low

Cleveland (2016)	IBD patients with dysplasia/CRC diagnosed at high-definition colonoscopy undergoing colectomy	Patients/lesions 36/44	Upgraded pathology or synchronous CRC	Unable to completely separate Crohn's patients or determine # of patients in each group as # of lesions are reported	Low
		Crohn's 17 (47%)/19 (43%)	LGD: 1/11 (9%) HGD 8 SL: 3 LGD, 4 HGD, 1 SC		
		Ulcerative Colitis 19 (53%)/25 (57%)	HGD: 1/5 (20%) CRC 1 SL: 1 CRC		
		LGD 30 lesions HGD 6 lesions CRC 8 lesions	No metachronous neoplasia in 7 patients undergoing segmental/ STC		
Eluri (2017)	IBD undergoing colectomy with HGD or CRC in postop specimen	70 Crohn's 21	5/21 (24%) undetected HGD/CRC	All patients had prior surveillance colonoscopy	Low

Abbreviations: *CC* Crohn's colitis, *CD* Crohn's disease, *CRC* colorectal cancer, *CUC* chronic ulcerative colitis, *HGD* high grade dysplasia, *IBD* inflammatory bowel disease, *IFD* indefinite for dysplasia, *LGD* low grade dysplasia, *MCRC* metachronous colorectal cancer, *MFD* multifocal dysplasia, *SC* sporadic cancer, *SL* synchronous lesions, *STC* subtotal colectomy

Personal View

In accordance with current guidelines, TPC/EI is our recommendation for patients with Crohn's disease of the large intestine and neoplasia because of the very real risk of undetected synchronous neoplasia and the lifetime risk of metachronous neoplasia with preservation of the colon and/or rectum [19]. As outlined above, in both scenarios the risk is real and unacceptably high for the average patient. However, we acknowledge that there are strong arguments against TPC/EI, at least as the initial operation. Any resectional procedure performed for Crohn's disease must be done by a surgeon cognizant of the fact the patient will still be at risk of sequelae of this disease even when the entire colon and rectum has been resected.

Recently, international consensus guidelines from the Surveillance for Colorectal Endoscopic Neoplasia Detection and Management in Inflammatory Bowel Disease Patients (SCENIC) were published and endorsed by multiple, international gastroenterologic and endoscopic societies. These guidelines recommend complete endoscopic removal of polypoid and nonpolypoid dysplasia followed by further surveillance colonoscopy. For patients with invisible dysplasia, chromoendoscopy with a high definition endoscope is recommended [28]. Critics have pointed out that these guidelines are flawed for three reasons: current poor adherence to endoscopic screening/surveillance guidelines, very low quality evidence, and significant risk of synchronous and metachronous neoplasia as demonstrated by the aforementioned studies [5, 22, 23, 30–33].

Ideally, prospective, randomized studies will be performed to more definitively answer the questions of the relative roles of surveillance colonoscopy, endoscopic resection, and colectomy, including what extent of resection is appropriate. Until the data are more complete, patients should be counseled on the risks of synchronous and metachronous neoplasia and the options available for treatment. One study demonstrated that patients are reticent to agree to colectomy unless the risk of colorectal cancer is 72% [34]. Other than dysplasia [13], risk factors for an increased risk of colorectal cancer in patients with Crohn's disease of the large intestine include young age at diagnosis, duration of disease [7], extent of disease [4], chronic inflammation [35], and concomitant primary sclerosing cholangitis [36]. These risk factors must be considered when counseling patients about options for the treatment of neoplasia in the setting of Crohn's disease of the large intestine.

Ultimately, the best procedure is one that accounts for the risk of undetected synchronous neoplasia, future metachronous neoplasia, and the patient's goals and ability to comply with future surveillance. Factors that may play a role in this decision include: age of the patient, capability to care for and cultural perceptions of an ostomy, desire for children, presence of anoperinal disease, rectal involvement, risk factors for colorectal cancer, and type of work. One of many plausible scenarios would be to perform a TAC/IR in a female of child-bearing age with rectal sparing while planning to perform regular surveillance endoscopy and a completion proctectomy with creation of an end ileostomy when child bearing is complete. While procedures less than TPC/EI may be feasible and appropriate in certain circumstances, our practice is to recommend TPC/EI in accordance with current surgical

guidelines that account for the risk of synchronous and metachronous neoplasia in patients with known neoplasia.

TPC/EI is recommended for patients with Crohn's disease found to have neoplasia because of the high risk for undetected synchronous and the development of future metachronous neoplasia (*evidence quality low; strong recommendation*).

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The Role of Segmental Resection in Crohn's Colitis

17

Luca Stocchi

Introduction

Total abdominal colectomy with ileorectal anastomosis is an accepted alternative to total proctocolectomy and end ileostomy in the surgical management of patients with Crohn's disease of the colon provided that the rectum and anoperineum have minimal or no evidence of active disease [1–3]. Segmental colonic resection for the same scenario is an even more conservative option, which could still remove gross disease while allowing improved functional results. It is uncertain however whether a segmental resection actually results in improved functional outcomes and whether it is associated with an increased risk of disease recurrence.

Patient population	Intervention	Comparator	Outcomes studied
Patients with Crohn's colitis and rectal sparing	Segmental resection	Total colectomy	Recurrence rate, functional results

Search Strategy

A comprehensive literature search of Cochrane Database of Collected Research, EMBASE, MEDLINE, and PubMed was performed to identify all of the English-language publications related to Crohn's disease, colectomy, recurrence and functional results from 1985 to 2015. Key search terms included the following: "Crohn's colitis", "Crohn's disease of the colon", "inflammatory bowel disease," "Crohn's

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disease" "surgical treatment", "colectomy," "subtotal colectomy", "total colectomy", "hemicolectomy", "segmental colectomy", "resection of the colon", "colonic resection". Studies were excluded if they did not directly contrast segmental resection with total colectomy, failed to measure recurrence and functional results, included patients with ulcerative colitis or familial adenomatous polyposis, or included pediatric patients. Only the most recent study was included if similar studies from the same institution were encountered. The references of the included studies were reviewed to identify additional studies that were incorporated as appropriate.

Results

The available evidence indicates that segmental colectomy and total abdominal colectomy for management of Crohn's disease of the colon are comparable with respect to the risk of recurrence. When assessing surgical recurrence, a few studies have been conducted over a long period of time and their quality is moderate to low (Table 17.1). All of the studies are retrospective and not surprisingly patients treated with segmental colectomy were more likely to have disease localized to a single colonic segment while total abdominal colectomy was more frequently performed when two or more colonic segments were involved. An earlier meta-analysis comparing these surgical approaches in patients with two or more colonic segments indicated that patients undergoing total abdominal colectomy and ileorectal anastomosis experienced a lower reoperation rate, although the difference did not reach statistical significance [4]. Angriman conducted a more recent systematic review, which included data on both surgical recurrence and overall recurrence, and found statistically similar rates when comparing the two operations. An additional subset analysis that focused on patients undergoing surgery after the introduction of biologic medications again confirmed equivalence in the risk of either overall or surgical recurrence [5].

Table 17.1 Selected studies comparing surgical recurrence after segmental colectomy vs total colectomy

Author	Year	Patients (N) Segmental resection vs. total colectomy	5-year recurrence (%) Segmental resection vs. total colectomy	Quality of evidence
Sanfey [9]	1983	14 vs. 14	50 vs. 57	Low
Andrews[a] [10]	1989	36 vs. 63	26 vs. 46	Low
Bernell[b] [17]	2001	134 vs. 106	47 vs. 58	Moderate
Andersson [6]	2002	31 vs. 26	55 vs. 41	Moderate
Fichera [7]	2005	54 vs. 49	38 vs. 24	Moderate
Kiran [8]	2011	49 vs. 59	27 vs. 14	Moderate

[a]Data on segmental resection refers to right hemicolectomy
[b]10-year clinical recurrence instead of 5-year surgical recurrence assessed

With respect to functional results, one relevant endpoint assessed in the literature is the risk of permanent stoma. Most studies have indicated that the risk for permanent stoma creation is comparable between segmental colectomy and total colectomy, particularly more recent studies [6–8]. Earlier studies had suggested that the more conservative segmental colectomy is actually associated with a significant reduction in the risk of permanent stoma creation [9–11]. When all eligible studies were evaluated in a systematic review, the incidence of permanent stoma was significantly decreased following segmental colectomy [5].

Despite the putative advantages of preservation of a longer segment of functioning bowel, there is actually limited data on functional outcomes. Andersson reported that patients undergoing segmental colectomy experienced improved anorectal function when assessing a composite score incorporating the ability to pass flatus without leakage, incontinence for loose stools, and soiling [6]. A subsequent study by Kiran assessed the Cleveland Global Quality of Life [12] instrument scores and Short Form Inflammatory Bowel Disease Questionnaire scores, which were both found to be statistically similar between the groups [8].

The management of patients with dysplasia or cancer on the background of Crohn's disease is a particularly daunting problem. In general, the standard of care in this situation is total proctocolectomy with end ileostomy and either a segmental resection or a total colectomy should be avoided [13]. Kiran identified a 40% rate of remote dysplasia in the resected specimen in the presence of cancer and an incidence of multifocal dysplasia of 44% [14]. A more recent study reported that 40% of patients undergoing segmental colectomy for neoplasm and 35% receiving a subtotal colectomy for the same indication developed metachronous cancer over a mean follow-up of 6.8 years [15]. However, there have been reports of selected patients undergoing conservative, sphincter-saving procedures, ranging from segmental resection to subtotal colectomy, which resulted in acceptable oncologic outcomes. This approach remains highly controversial and has been advocated for individualized cases, such as poor-risk patients and/or cases of preoperative low-grade dysplasia [14]. The techniques of endoscopic detection and management of colorectal dysplasia in Crohn's disease of the colon continue to evolve and could lead in the future to a decreased number of patients requiring surgery for this particular indication [16].

Recommendations

In patients requiring surgery for Crohn's disease of the colon, a segmental colectomy is equivalent to a total abdominal colectomy in terms of disease recurrence and risk of permanent stoma creation. If the extent of disease is limited, a segmental resection is therefore preferable. While the preservation of a longer segment of functional large intestine seems to be intuitively desirable, a segmental resection is not associated with substantially documented advantages. For patients requiring surgery for dysplasia, the operation of choice remains total proctocolectomy with end ileostomy.

Personal View

The general management principle describing the surgical approach to colonic disease should be to resect only segments of colon that are grossly involved with Crohn's disease. Therefore, if Crohn's disease is located in a discrete segment of colon, a segmental resection is preferable. The perioperative complication rate is similar to total colectomy and there are possible functional advantages. There is no evidence that the removal of a longer segment of colon through total abdominal colectomy results in either reduced disease recurrence or increased stoma-free survival. The factors independently associated with disease recurrence and risk of permanent stoma creation do not include a particular restorative procedure, whether segmental resection or total colectomy, but are instead disease-related or patient-related variables such as younger age [18], female sex [19], and concurrent perianal disease [8, 17]. The only operation for large bowel Crohn's disease that independently minimizes the risk of disease recurrence is total proctocolectomy with end ileostomy, which is obviously not favored by the majority of patients.

In the case of diffuse Crohn's disease of the colon with rectal sparing or mild proctitis, total abdominal colectomy remains a reasonable surgical option. Under these circumstances segmental colectomy is not feasible. Two segments of disease separated by a short segment of grossly preserved colon should be *de facto* considered as one single area of disease and therefore should be preferentially treated with one long, encompassing segmental resection. However, if the colitis is distributed in two or more distinctive segments, a total abdominal colectomy is preferable to a double segmental colonic resection.

With respect to dysplasia in the background of Crohn's disease of the colon, treatment algorithms are evolving with increasing data supporting the safety of endoscopic management as suggested by the SCENIC guidelines [16]. For those patients requiring surgery for dysplasia, any option more conservative then total proctocolectomy and end ileostomy remains oncologically risky and should be considered only in extraordinary, individualized cases.

Abstracted Recommendation

Patients requiring surgery for Crohn's disease of the large bowel limited to the colon can undergo segmental resection when technically feasible instead of total abdominal colectomy. (strong recommendation based on low and moderate quality evidence).

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Role of Percutaneous Drainage for Disease-Related Abscesses

18

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Introduction

Intra-abdominal abscesses can occur in up to 20% of patients with Crohn's disease, and the management of these abscesses is a complex issue, even for inflammatory bowel disease specialists [1, 2]. A number of treatment modalities have been proposed to manage disease-related abscesses, including surgery, percutaneous drainage (PD), conservative medical management, and various combinations of these approaches. However, the relatively low incidence of this complication provides somewhat of a barrier for prospective trial designs that aim to identify the optimal management for disease-related abscesses. Several small retrospective studies have attempted to describe the incidence of disease-related abscesses and their treatment. The most appropriate management is dependent on multiple factors including abscess size and location and interventional radiology resource availability.

PICO table

Patient Population	Intervention	Comparator	Outcomes Studied
Patients with Crohn's disease requiring surgery presenting with associated abscess	Preliminary percutaneous drainage	Definitive surgery	Postoperative complications, cost effectiveness

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Search Strategy

A literature search of the EMBASE and MEDLINE databases was conducted using the search terms; "Crohn's disease," "abscess," percutaneous drainage," "surgery," "complications", "cost-effective analysis", "mortality", and "morbidity." The Boolean operators "AND" and "OR" were used to define the search. Articles published from 2000 to 2018 were considered for inclusion. No language restrictions were applied. Initially, two hundred and sixty-five articles were identified. Following removal of duplicate articles, conference abstracts, case reports, and pediatric papers, 160 abstracts were screened. Forty-five full texts were analyzed and only articles which directly compared the role of PD versus surgery or "PD plus surgery" versus "surgery alone" were included in analysis below. This included 8 observational studies and 2 meta-analyses. The specific outcomes of interest were those that pertained to post-procedural complications and cost-effectiveness in the management of disease-related abscesses in Crohn's disease. The significance levels adopted by all studies was $p < 0.05$.

Results

The results of the individual studies are summarized in Table 18.1. We present data regarding postoperative complications, length of hospital stay (LOS), and need for subsequent surgery or an intestinal stoma, both for studies comparing PD alone to surgery alone, and then for studies comparing PD combined with subsequent surgery to surgery alone.

Studies Comparing PD Alone to Surgery Alone

1. Postoperative Complications
   Conflicting results exist related to the incidence of postoperative complications. Xie found a significantly increased incidence in the surgery alone group (9/13, 69%) compared to that of the PD alone group (2/10, 20%), $p = 0.036$) [3]. However, Liu found no difference in the incidence of complications between the groups [4].

   Three studies reported the incidence of abscess recurrence following PD or surgery. Two studies found no difference in abscess recurrence [4, 5], but one study reported a significantly lower recurrence rate in the surgery alone group [6]. Garcia grouped "antimicrobial therapy alone" with the "PD alone" in their comparison versus the "surgery alone" group. Four of 7 (57%) of the PD group had a recurrent abscess versus 12% (4/34) in the surgery alone group [6]. However, they found no difference in the time to abscess recurrence between medical management, PD, and surgical intervention groups. Interestingly, Nguyen reported no difference in the incidence of abscess recurrence at 5 years (PD alone 20.3% versus surgery alone 31.2%, $p = 0.25$.) [5]

Table 18.1 Data summary from individual studies

Author	Study type	Comparison	Variable studied	Cost-effectiveness	Newcastle-Ottawa grade
Nguyen et al. (2012) [5][a,b]	O	N = 95 PD (55) vs surgery alone (40)	**LOS:** PD (5 d.) vs Surgery Alone (15.5 d.), **p < 0.001** **Abscess recurrence:** PD (17/55–31%) vs Surgery Alone (8/40–20%) **Abscess recurrence at 5 years:** PD 20.3% vs Surgery Alone 31.2% p = 0.25	Not analyzed	9
Lobatan et al. (2013) [7][a,b]	O	N = 44 PD (22) + rescue surgery (16/22) vs. surgery alone (22)	**Success of initial treatment:** PD (6/22, 27.2%) vs Surgery Alone (21/22, 95.5%); **p < 0.001** **Length of stay:** PD + Rescue Surgery (56.12 ± 35.89 d.) vs Surgery (27.52 ± 15.11d.); **p = 0.017** **Postoperative stay:** PD + Rescue Surgery (44.0 ± 83.7d.) vs Surgery Alone (14.3 ± 30 d.); p = 0.179 **Postoperative Complications:** PD + Rescue Surgery (7/16–43.8%) vs Surgery Alone (12/22–54.5%); p = 0.75 **Need for subsequent surgery:** PD + Rescue Surgery (5/16, 31%) vs Surgery Alone (1/22, 4.5%); p = 0.065	Not analyzed	7
Xie et al. (2012) [3][b]	O	N = 23 PD (10) vs. Initial Surgery (13)	**Post-procedural complications:** Initial PD 2/10 (20%) vs Initial surgery 9/13 (69%), **P = 0.036** **Abscess recurrence:** Initial PD 2/10 (20%) vs Initial surgery 1/13 (8%), Not significant **Subsequent surgery:** Initial PD 6/10 (60%) vs Initial surgery 4/13 (31%), Not significant **Stoma creation:** Initial PD 1/10 (10%) vs Initial surgery 9/13(69%), **P = 0.01**	Not analyzed	8

(continued)

Table 18.1 (continued)

Author	Study type	Comparison	Variable studied	Cost-effectiveness	Newcastle-Ottawa grade
Liu et al. (2014) [4][b]	O	N = 77 Trocar group (21) vs PD (25) vs Surgery alone (31)	**Post-procedural complications:** Trocar (0) vs PD (6/25–24%) vs Surgery (8–25.8%), p = 0.04 (no difference between PD & Surgery Alone) **Post-procedural length of stay:** Trocar (14.0 ± 10.1 d.) vs PD (14.0 ± 18.6 d.) vs surgery (25.0 ± 27.7 d.), p = 0.294 **Abscess recurrence:** Trocar (6/21–28.6%) vs PD (16/25–64%) vs Surgery (18/31–58.1%), p = 0.04 (difference between Trocar vs PD, p = 0.02, no difference between PD and Surgery Alone) **Need for subsequent surgery**: Trocar (10/21–47.6%) vs. PD (17/25–68%) vs. surgery (22/31–71%), p = 0.197 **Stoma creation** Surgery (18/31–58.1%) vs PD (5/25–20%), **p = 0.0061**	Not analyzed	7
Garcia et al. (2001) [6][a,b]	O	N = 51 Medical therapy (10) vs. PD (7) vs. surgery alone (34)	**Abscess recurrence:** Medical therapy 5 (50%) vs PD 4 (67%) vs. surgery alone 4 (12%), **p = 0.016** **Time to recurrence:** Medical therapy (mean, 86 d.; range, 3–245 d.) vs. PD (mean, 27 d.; range, 1–64 d.) vs. surgery alone (mean, 180 d.; range, 25–480 d.), p > 0.05	Not analyzed	6

Da Luz Moreira et al. (2009) [8][a]	O	N = 94 PD+ delayed surgery (48) vs surgery alone (46)	**Septic complications:** PD success (3/31–10%) vs PD failure (1/17–6%) vs Surgery (9/46–20%), p = 0.1 **LOS:** PD successful (median 10 d. (6–31 d.)) vs PD failure (13 d. (10–48 d.)) vs. surgery (median11 d. (5–44 d.)), p = 0.09 **Stoma creation:** PD success (7/31–23%) vs PD failure 10/17–58%) and surgery (24/46–52%), **p = 0.01** **Stoma reversal:** PD success (5/6–83%) vs PD failure (8/9–89%) vs. surgery (14/19–74%), p = 0.7	**PD + surgery ($11,791/QALY) vs. surgery $26,393/QALY) PD success ($10,589/QALY vs. PD failure $13,925/QALY) More cost effective in PD failure vs surgery (data not given)**	8
Bafford et al. (2012) [9][a]	O	N = 70 PD + surgery (38) vs. surgery alone (32)	**Overall complications:** PD + surgery (7/38–20%) vs surgery (10/32–31.3%), p = 0.4 **LOS:** PD + surgery (mean 15.8 d.) vs surgery (mean 12 d.), **p = 0.007** **Postoperative LOS:** PD + surgery (mean 8.2 d.) vs surgery (mean 7.8 d.), p = 0.71 **30-day readmission:** PD + surgery (11/38–28.9%) vs surgery (5/32–15.6%), p = 0.71	Not analyzed	8
Muller-wille et al. (2011) [10][a]	O	N = 25 PD + surgery (12) vs surgery (13)	**Intra-abdominal Septic Complications:** PD + surgery (3/12–25%) vs surgery (9/13–69%), **p = 0.04** **Postoperative LOS:** PD + surgery (mean 11 d. (5–26 d.)) vs Surgery (mean 19 d. (6–91 d.)), **p = 0.04** **1-year recurrence:** PD + surgery (1/12–8%) vs surgery (4/13–33%), **p = 0.046**	Not analyzed	8

O Observational, *LOS* Length of stay, *QALY* quality-adjusted life-years, *ICER* Incremental cost-effectiveness ratio, all times listed in days (d)

[a]Included in He et al. 2015

[b]Included in Clancy et al. 2016

2. Length of Hospital Stay
   Conflicting results with respect to LOS are also found. Three studies reported on the LOS associated with either PD alone or surgery. Nguyen reported a significantly lower median LOS in the PD group (5 days) than in the surgery alone group (16 days) ($p < 0.001$) [5]. Liu in contrast found no difference in the LOS between PD (14.0 ± 18.6 days) and surgery groups (25.0 ± 27.7 days) ($p = 0.294$) [4]. Lobaton reported a significantly increased LOS in the PD (56.12 ± 35.89 days) versus surgery alone group (27.52 ± 15.11) ($p = 0.017$) [7]. It is important, however, to note that only 27% (6/22) of PD cases were successful in the study by Lobaton, and as expected, there was a trend towards more patients in the PD group requiring a second surgical intervention (PD plus surgery: 31% versus surgery plus second surgery: 4.5%, $p = 0.065$) [7].
3. Subsequent Surgery or Need for an Intestinal Stoma
   Three studies reported no significant difference in the incidence of a subsequent surgery between the groups. As previously mentioned, Lobaton indicated a trend towards a secondary intervention in the PD group when compared to surgery alone [7]. Two other studies found no difference in the need for a second surgery between either group [3, 4]. Despite this apparent lack of difference in the incidence of a second surgery, the same two studies including 100 patients found a significant association between stoma creation and "surgery alone." [3, 4]

Studies Comparing PD Combined with Subsequent Surgery to Surgery Alone

1. Postoperative Complications
   There were conflicting individual results with respect to infectious postoperative complications. Two studies found no difference in the incidence of septic complications between the "PD and subsequent surgery" groups versus "surgery alone" group [8, 9]. However, Muller-Wille reported a higher incidence of postoperative infectious complications in the surgery alone group (9/13, 69%) versus PD plus surgery (3/12, 25%, $p = 0.04$) [10].
2. Length of Hospital Stay
   There were conflicting results with respect to LOS. Da Luz Moreira found no difference in the LOS between the "PD and subsequent surgery" group compared to the "surgery alone" group [8]. The authors did a subgroup analysis on the success of the initial PD groups ("initial PD successful" and "initial PD unsuccessful") and found that there was no difference in either group with respect to LOS when compared to "surgery alone" [8]. Muller-Wille found a significantly decreased post-procedural LOS in the "PD plus surgery" group (median 11 days, range 5–26 days) versus the "surgery alone" group (median 19 days, range 6–91 days, $p = 0.04$) [10]. Conversely, Bafford found a significantly increased LOS in the "PD plus surgery" group (mean 16 days) when compared to the "surgery alone" group (mean 12 days, $p = 0.007$) [9] However, when

the authors examined the postoperative LOS, there was no difference between groups.

3. Subsequent Surgery or Need for an Intestinal Stoma
   Data regarding the incidence of stoma creation were conflicting. Two studies compared the rates of stoma creation between the "PD and subsequent surgery" group and the "surgery alone group". Bafford found no difference in the frequency of stoma creation [9]. In contrast, Da Luz Moreira reported a similar frequency of stoma creation, between the "failed PD and urgent surgery" group (10/17, 58%) and the "surgery alone" group (24/46, 52%). However, a significant difference existed compared to the "successful PD plus interval surgery" group (7/31, 23%, p = 0.01) [8]. Interestingly, there was no difference in the frequency of stoma reversal between these groups.

Meta-analyses

Two recent meta-analyses have attempted to aggregate these conflicting studies to identify significant associations between treatment strategies and adverse outcomes (Table 18.2). He included 9 studies and Clancy included 6 studies, of which three were common to both meta-analyses [11, 12]. He specifically investigated associations with a number of morbid outcomes. Interestingly, the initial analysis grouped "PD alone" and "PD and subsequent surgery" together and this was compared to "surgery alone." There was a significant increase in overall complications in the surgery alone as compared to the entire combined PD group (OR = 0.58, 95% CI 0.35–0.96, p = 0.03.) Additionally, there was also an increased likelihood of stoma creation associated with the surgery alone group as compared to the combined PD group (OR = 0.44, 95% CI 0.21–0.91, p = 0.03.) In this meta-analysis, there was no difference in specific complications including development of enterocutaneous fistulae, postoperative wound infections, anastomotic leak, postoperative abscess, LOS, or recurrent abscess. In this study, a recurrent abscess was defined as the development of an abscess at the original abscess site following radiographic resolution of the initial abscess. In the subgroup analysis of overall complications, the authors found a significant increase in complications in the "surgery alone" versus "PD and subsequent surgery" groups (OR = 0.44, 95% CI 0.23–0.83, p = 0.01).

There was no difference in the incidence of overall complications between the "PD alone" versus "surgery alone" groups. In the subgroup analysis of recurrent abscesses, there was a significant increase in the incidence of recurrent abscess in the "PD alone" versus "surgery alone" groups (OR = 2.16, 95% CI 1.03–4.54, p = 0.04).

Similarly, Clancy reported an increased incidence of abscess recurrence in a "PD alone" groups versus "surgery alone" (OR: 6.544, 95% CI: 1.783–24.010, p = 0.005). They also found no difference in the incidence of complications or in the length of stay between the two intervention groups. While He found an increased incidence of stoma creation in the "surgery alone" group, Clancy reported no overall difference in the incidence of permanent stoma requirement.

Table 18.2 Data summary from meta-analyses

Author	Number of cases	Intervention groups	Outcomes	Results	Quality of evidence
He et al. 2015 [11]	513 (9 studies)	Initial PD (both PD alone and PD+ surgery) vs surgery	Overall complications	7 studies (371 patients): Increased complications in surgery vs PD + surgery **(OR = 0.58 95% CI 0.35–0.96, p = 0.03)**	Medium
			Enterocutaneous fistula	3 studies (204 patients): No difference in enterocutaneous fistula, (OR = 1.12 95%CI 0.40–3.16, p = 0.83)	
			Wound infection	3 studies (200 patients): No difference in wound infection, (OR = 0.25, 95%CI 0.05–1.19, p = 0.08)	
			Anastomotic leak	2 studies (164 patients): No difference in anastomotic leak OR = 3.7 95%CI 0.40–33.99, p = 0.25)	
			Postoperative abscess	3 studies (238 patients): No difference in postoperative abscess (OR = 0.47 95%CI 0.16–1.4, p = 0.17)	
			Stoma creation	2 studies (147 patients): Increased stoma creation with surgery vs PD + surgery **(OR = 0.44 95% CI 0.21–0.91, p = 0.03)**	
			Length of hospital stay	4 studies (283 patients)- No difference in hospital stay, (mean difference − 2.65 95%CI -20.71-15.41, p = 0.77)	
			Recurrent Abscess	5 studies (291 patients): No difference in recurrent abscess, (OR = 1.33, 95%CI 0.47–3.76, p = 0.59)	
		Subgroup analyses PD Alone vs, Surgery Alone PD + surgery vs Surgery alone	Overall complications	**PD Alone vs. Surgery Alone** 3 studies (144 patients) - no difference in complications (OR = 0.60 95%CI 0.25–1.44, p = 0.25) **PD + Surgery vs Surgery Alone** 4 studies (227 patients): Increased complications in surgery vs PD + surgery **(OR = 0.44 95% CI 0.23–0.83, p = 0.01)**	
			Recurrence	**PD Alone vs. Surgery** 3 studies (172 patients): Increased recurrence in PD alone vs surgery **(OR = 2.16, 95% CI 1.03–4.54, p = 0.04)** **PD+ Surgery vs Surgery Alone** 2 studies (119 patients): no difference in recurrence (OR = 0.40, 95%CI 0.12–1.39, p = 0.15)	

Clancy et al. 2016 [12]	333 (6 studies)	PD alone vs. Surgery	Complications	3 studies (153 patients) No difference in complications. [OR: 0.657, 95% CI: 0.175–2.476, p = 0.535]	Medium
			Permanent stoma requirement	4 studies (197 patients) No difference in ostomy requirement [OR: 0.557, 95% CI: 0.147–2.111, p = 0.389]	
			Length of hospital stay	4 studies (253 patients) No difference in length of stay [difference in means: −1.006, 95% CI: −28.762–26.749, p: 0.943]	
			Abscess recurrence	6 studies (331 patients) Increased abscess recurrence in PD vs surgery **[OR: 6.544, 95% CI: 1.783–24.010, p = 0.005]**	

Cost-Effectiveness

One study, by Da Luz Moriera, reported on quality of life and cost-effectiveness of PD versus surgery in the management of disease-related abscesses [8]. This utilized quality-adjusted life-years (QALYs) and incremental cost-effectiveness ratios (ICERs). The overall cost of initial surgery alone ($20,032) was greater than that of initial PD ($10,022). Treatment with initial PD was associated with higher QALYs and with increased ICERs, when compared to initial surgery alone (0.850 QALY versus 0.759 QALY, and $11,791/QALY versus $26,393/QALY). As expected, in subgroup analysis, successful PD was associated with a higher QALY and higher ICER as compared to PD failure (0.869 versus 0.829 QALY and $10,589/QALY versus $13,925/QALY). Interestingly, the authors reported that patients who had PD failure still had a higher QALY and ICER than patients initially treated with surgery; however, the exact figures are not reported in the manuscript. The patient heterogeneity in this study was notable, as the authors included patients with peritonitis and abscesses which would be not easily amenable to interventional radiological drainage.

Recommendations Based on the Data

1. A newly presenting Crohn's disease-related abscess should be considered for percutaneous drainage by an interventional radiologist with a view to interval surgical resection of the associated diseased bowel because of the risk of abscess recurrence. (Moderate quality evidence)
2. In patients where surgery is the most appropriate therapy, preoperative drainage of the Crohn's disease-related abscess may reduce the risk of postoperative complications and stoma creation (Moderate quality evidence.)
3. For approximately one-third of Crohn's disease patients, surgical intervention may be avoided in disease-related abscesses, but the characteristics of this cohort is unclear; at present, this should not be a goal of therapy. (Moderate quality evidence)

Personal View

The data presented herein highlight practice changes over the past 20 years. Initial studies examining the use of PD in the management of Crohn's disease-related abscesses were fraught with procedural failure and complications. Current data, however, suggest that some patients may avoid surgical resection in the setting of abscess resolution with PD. Accurate phenotyping of disease is crucial to determine in which patients PD alone will succeed. This is our greatest clinical challenge.

Abscesses in Crohn's disease reflect a perforating phenotype, which typically results from proximal pressure on a Crohn's disease ulcer in the presence of distal obstruction. If this distal obstruction is due to fibrotic disease, the patient will

require surgery for resection of this segment of bowel or the abscess will recur. If the distal obstruction is inflammatory in nature and the patient is treatment naïve, institution of medical therapy, in most cases biologic therapy, may prevent recurrence of the obstruction and abscess reformation. Depending upon which type of Crohn's disease is present, and as PD has become more successful, some authors have reported a significantly increased risk of abscess recurrence in the setting of complete radiological resolution.

The concept of interval surgery, as opposed to urgent/emergent surgery, for abdominal abscesses provides a safer means of resecting diseased (strictured) bowel, which is the "nidus" for abscess recurrence. This again emphasizes the concept that, in the setting of distal bowel obstruction/stenosis, simply draining the abdominal abscess does not address the underlying pathology that led to abscess formation. In these patients, therefore, the optimal treatment is that of a segmental resection of the diseased bowel, following "preoperative" percutaneous drainage of the abscess to decrease contamination and the associated inflammatory reaction in the surgical field. The aforementioned meta-analyses demonstrate the increased risk of stoma formation in the setting of surgery alone as compared to "PD plus surgery." While there is still an increased risk for stoma formation with PD and interval surgery, it is still a safer option for the patient. Operating without an abscess present results is a lesser risk of overall complications as evidenced by the meta-analysis by He referred to above [11].

The selection of patients appropriately treated with PD alone is an area of ongoing study. Many of the studies that have been mentioned are observational, nonrandomized studies, and as such, there is significant selection bias. In these studies, this most likely indicates sound judgement on the part of the operating surgeon, as the surgery alone cases occurred only where abscesses were not amenable to drainage, or where PD was contraindicated, and patients proceeded directly to surgery. In summary, initial PD should be the preferred approach in all cases amenable to interventional radiology abscess drainage, with subsequent interval surgery to treat the underlying pathology. The decision to perform a diverting stoma should be individualized, based on the surgeon's assessment of the residual contamination at the former abscess site, the patient's nutritional status, recent biologic/immunosuppressive therapy, and patient co-morbidities.

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Management After Successful Percutaneous Drainage of Disease-Related Abscess

19

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Introduction

Crohn's disease is characterized by inflammatory, fistulizing, or stricturing behavior. In up to 30% of patients, fistulizing disease can occur that may result in the formation of an intraabdominal abscess [1]. Significant improvements in percutaneous drainage techniques with technical success rates approaching 90% have led to a strong preference for initial treatment of abscesses with percutaneous drainage and antibiotics [2, 3]. This approach allows for the resolution of acute infection, control of inflammation, and medical stabilization. The decision on how to manage patients following successful drainage of an abscess remains controversial.

Traditionally, surgery with resection of the primary disease was performed following successful drainage of an intra-abdominal abscess because removal of the fistulizing segment was thought to prevent abscess or fistula recurrence. However, nonoperative management of the fistulizing disease with biologic agent therapies after abscess resolution has been shown to be successful in some cases, and resultant clinical and endoscopic improvement has been well documented [4, 5]. The question of whether surgery is necessary or should be recommended following successful drainage of intraabdominal abscesses, as well as the timing of initiation or continuation of biologic medications remains unclear. We searched the literature on outcomes of medical versus surgical management following successful percutaneous treatment of Crohn's disease-related intra-abdominal abscesses.

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PICO table

Patients	Intervention	Comparator	Outcomes
Patients after successful percutaneous drainage of Crohn's related abscess	Medical management including biologics	Surgery	Abscess recurrence or surgery

Search Strategy

A comprehensive literature search of Cochrane Database of Collected Research, MEDLINE, and PubMed was performed to identify all of the English-language publications related to Crohn's disease, abscess formation, percutaneous drainage and medical management from 1998 to 2018. Key search terms included the following: [percutaneous OR radiological] AND [aspiration OR drainage] AND [abscess] AND [Crohn's] AND [Biologic]. Studies were excluded if they did not provide information on abscess recurrence rates or surgical resection after initial management. When possible, information on medical management was included. Pediatric studies were excluded. If multiple studies were published from the same institution only the most recent study was included. All articles and reviews were evaluated for additional references and incorporated as appropriate.

Results

The data on outcomes following percutaneous drainage (PD) of Crohn's disease-related abscesses are retrospective case series and lack direct comparison of medical management to surgical outcomes. There are no published studies comparing medical management to surgical treatment following percutaneous drainage and conclusions must be extrapolated from data comparing the short-and long-term outcomes of immediate surgery to PD, as well as a few trials in which the details of medical management are included. In addition, the small sample size of these retrospective case series limit the ability to determine statistical significance among most treatment groups.

The most clinically significant outcomes are recurrence of abscess and need for subsequent surgery. Studies demonstrate intraabdominal abscess recurrence rates of 20–67% following drainage procedures (Table 19.1). Moreover, these rates are statistically higher than those seen in patients undergoing immediate surgical resection [6–9]. Recurrent abscesses often appear within thirty days of draining the index abscess with up to 80% of all recurrences occurring within one month of initial presentation [6, 7]. Gervais found abscess recurrence and short-term failure to be associated with underlying fistula (20% versus 64%) and pretreatment use of corticosteroids (42% versus 62%) [2]. Larger initial abscess size (7.7 cm versus 6.6 cm) and shorter duration of catheter placement (13.4 days versus 16.9 days) were also higher in short-term failures, although these factors did not reach statistical significance [2]. Clancy performed a meta-analysis of surgery versus PD using data from

Table 19.1 Studies showing abscess recurrence rates and need for surgical intervention rates after percutaneous drainage of Crohn's related abscess +/− medical management including biologics

Study author (year)	Patients (N)	Abscess recurrence	Surgical intervention	Quality of evidence
Clancy (2016)	155	OR 6.54	70%	Moderate
Ibanez-Samaniego (2015)	7	2/7 (29%)	3/7 (43%)	Low
Liu (2014)	46	22/46 (48%)	27/46(59%)	Low
Lobatón (2013)	22	6/12 (50%)	16/22 (72%)	Low
Cullen (2012)	13	0/13(0%)	2/13(15%)	Low
Nguyen (2012)	55	17/55 (31%)	12/55 (22%)	Low
Bermejo(2012)	30	22/30(73%)	21/30(70%)	Low
Bafford (2012)	35	9/35 (26%)	32/35 (92%)	Low
Xie (2012)	10	2/10 (20%)	6/10(60%)	Low
Gervais (2002)	32	11/32 (34%)	7/31 (77%)	Low
Garcia (2001)	7	4/6(67%)	4/6(67%)	Low
Jawari (1998)	8	2/8(25%)	5/8 (67%)	Low

six trials and 333 patients. Patients undergoing initial percutaneous drainage were significantly more likely to have recurrence of an abscess than patients undergoing initial surgery (OR: 6.544, 95% CI: 1.783–24.010, p = 0.005) [8].

Liu compared outcomes from conventional PD, trocar drainage, and surgical drainage. Trocar drainage is a novel strategy utilizing a sump drain placed under ultrasound or CT guidance that is subsequently used for irrigation of the abscess cavity. They found this approach was associated with lower rates of abscess recurrence (29% versus 64%) and long-term need for surgery (68% versus 48%) when compared to conventional PD [9].

Interpretation of the data on the long-term need for surgery following intraabdominal abscess drainage must include consideration for whether the operation was performed because of surgeon choice or required for disease recurrence. Five-year surgical recurrence rates may be as high as 25% in some series [10]. Following PD, the need for surgery rates vary greatly from 20% in the Nguyen trial to 92% in a study by Bafford [7, 11]. Bafford recognized that surgeon preference greatly affects this number, with over 38% of patients undergoing elective surgery merely due to surgeon choice following successful abscess drainage [11]. The meta-analysis by Clancy found overall rates of subsequent surgery secondary to failure, disease, or surgeon preference to be 70% in all included trials [8].

Little data is included in the published reports about post-drainage medical management. Nguyen restarted patients on medications at a mean of 9 days following abscess resolution [7]. The authors noted that 7 patients in the PD group were started on biologic agents the day of abscess drainage. Overall, treatment with biologic medications was noted to be protective for recurrence of an abscess when compared to no medical treatment (HR 0.0895% CI, 0.02–0.36) but this was found in both the PD and the immediate surgery group. Bermejo also found that the rate of recurrent abscess did not differ between those who were on immunosuppressive therapy

(73%) and those who were not (80%) [12]. Lobatón noted that of 22 patients who underwent percutaneous drainage, 15 were started on post-intervention therapy [13]. Of the 5 patients in the study that were started on azathioprine after drainage, 60% ultimately required surgery. Three patients were started on biologic agents and two of these also subsequently needed operative intervention.

Two small cases series directly looked at the safety of immediately starting patients on biologic agents following diagnosis with an abscess or phlegmon [14, 15]. In a single institutional study by Ibanez-Samaniego, twelve patients were retrospectively reviewed who were started on biologic medications following presentation. Of these patients, nine were anti-tumor necrosis factor (TNF)-naive and three were previously managed with adalimumab; seven patients underwent percutaneous drainage before anti-TNF therapy was started and five had abscesses too small for drainage. Anti-TNF agents were started once signs of systemic toxicity disappeared and the patients were followed for an average of 37.8 months. Two of seven patients (29%) had abscess recurrence; one patient required surgery whereas the other was treated with antibiotics alone. There were two additional patients that required elective surgery secondary to refractory luminal disease. No patients required urgent intervention or developed signs of sepsis during the study period. Of note, all patients continued antibiotics after initiation of biologic therapy with a mean duration of 72 days.

The second study, a retrospective review by Cullen, reviewed outcomes of intraabdominal phlegmons treated with antibiotics and anti-TNF antibody in Crohn's disease patients. Twelve out of 13 patients had an abscess in addition to a phlegmon and two of these patients underwent percutaneous drainage before anti-TNF treatment. Patients were started on biologic agents a mean of 38 days (30 days to 82 days) after diagnosis and the average C-reactive protein was 51.4 mg/L (19.3 mg/L to 88.3 mg/L) prior to initiation of therapy. Drains were removed before initiation of biologic therapy with either infliximab or adalimumab. Antibiotics, generally metronidazole and a quinolone, were continued for a mean of 45 days after initiation of therapy. There were no recurrences of abscess following initiation of therapy. The median time for follow-up after initiation of anti-TNF therapy was 2.3 years. All patients achieved clinical remission with anti-TNF therapy without development of infection. Two patients did undergo surgery; one had an abscess and phlegmon that resolved, but after 14 months, there was loss of response to adalimumab and the patient chose elective surgery instead of treatment with an alternative biologic medication. The other had resolution of an abscess, phlegmon, and fistula but had a symptomatic ileal stricture that warranted elective resection after 20 months of infliximab treatment.

Recommendations

Not all patients with a Crohn's disease-related abscess require surgical intervention following resolution of symptoms. (Evidence Weak: Recommendation Strong)

It may be safe to initiate biologic treatment in patients following improvement of symptoms while on antibiotics. (Evidence Weak: Recommendation Weak)

Most patients with Crohn's disease will require surgery following successful drainage of an intra-abdominal abscess. Although traditional teaching has held that patients with fistulas are less likely to respond to medical management, there is no good data to support this conclusion. The role of biologic agents in treating fistulizing disease following drainage is not clear. Further studies should focus on whether this provides durable treatment and if surgical intervention may be avoided in selected cases.

Personal View

A key principle for the management of patients with Crohn's disease has always been to minimize resection of bowel whenever appropriate. Patients with Crohn's disease-related abscesses may provide an excellent example of how medical advances may eventually help us better achieve this goal.

Following successful drainage of a Crohn's disease-related abscess, the first step should be optimization of the patient as a whole. Initially, the goal of treatment is complete resolution of sepsis as evidenced by normalization of any leukocytosis or fevers, and hemodynamic stabilization. Early treatment with broad spectrum antibiotics is common practice. Cultures and bacteriology are usually not necessary, as the drainage generally has mixed flora consistent with stool. The exception to this is a patient who does not respond to first-line antibiotics or has a history of multi-drug resistant organisms. Patients who fail to improve with initial therapy should be reimaged to determine whether new areas of abscess, worsening bowel obstruction, or even free perforation have occurred.

For patients experiencing clinical improvement, a transition to oral antibiotics is generally appropriate after 5–7 days. The ideal duration of antibiotics is not well defined and reimaging to confirm resolution of infection may be helpful. Some providers completely stop antibiotics after clinical stabilization, whereas others continue antimicrobial therapy if an abscess cavity remains. There is no data to support continued long-term antibiotics in the setting of a clinically stable fistula. In several studies, metronidazole and fluoroquinolones have been used, but surgeons should be aware there is increasing data regarding potential side effects for fluoroquinolones and consideration of alternatives may be appropriate [16, 17].

Nutritional concerns are also paramount during this time. In some cases, cessation of enteric diet is necessary to control the output from a drain or manage sepsis. This may be temporary for a few days as accompanying sepsis and leukocytosis resolve, or patients may require longer periods of bowel rest such as in cases of intestinal fistulization or bowel obstruction where total parental nutrition may be required. Although no perfect markers exist to assess nutritional optimization, a serum albumin greater than 3.5 g/dL and normalization of the prealbumin level can be helpful. If possible, surgery should be delayed until patients are no longer in a catabolic state and nutritional health has been restored, because surgery on malnourished patients is significantly less likely to be effective [18].

The abscess drain is generally kept in place while output is high; outputs of greater than 20 mL per day are considered too high for drain removal. The nature of the output is also important. Feculent or bilious drainage implies direct and ongoing connection with the bowel, and these drains should be left in place regardless the volume of output. If the drainage is not feculent and less than 20 mL per day, a sinogram should be obtained to exclude occult communication between the drain and bowel. In cases of a demonstrated fistula, slow removal (2 cm per day) of the drain may create a fistula track to the abdominal wall. Other times, drains may be left in place until surgery.

If operative intervention is to be considered, the timing of surgery should be carefully considered. Waiting is generally recommended until the acute inflammatory response has resolved, bowel function has normalized, and nutrition has been optimized. In most cases this is a minimum of 4 weeks to 6 weeks [18]. Reimaging prior to consideration of surgery is appropriate in most cases. Magnetic resonance enterography (MRE) can help elucidate the extent of disease and demonstrate ongoing areas of inflammation, fistulization, or stenosis. In a patient with only mild residual disease, a treatment approach analogous to that used with diverticular disease can be argued. The safety of non-surgical management in diverticular disease following removal of a drain has been demonstrated [19]. Similarly, in a patient with Crohn's disease, surgery may not be necessary if all clinical and radiographic evidence of disease-related activity has resolved.

Theoretically, the medical management of fistulizing Crohn's disease is appealing in the hopes of avoiding surgical intervention. However, evidence related to the use of biologic agents immediately following treatment of an intra-abdominal abscess is lacking. Two small studies demonstrated the efficacy and safety of initiation and early resumption of these medications in this setting, but this data is not robust enough for general extrapolation. It should be noted, that in both reports, patients were maintained on long-term antibiotics to help obviate the risks of recurrent sepsis [14, 15].

Any decisions related to the management of a patient with Crohn's disease and intraabdominal abscess successfully treated by percutaneous drainage should include the gastroenterologist, surgeon, and patient. Close observation is necessary if a nonoperative approach is selected to watch for signs of infection and clinical deterioration while reimaging may provide additional information. Further studies are needed to better assess the appropriateness and optimal features of nonoperative management, including the duration of antibiotics and timing of introducing biologic agent therapy. Ideally a prospective trial with initiation of biologic treatment in a controlled setting might help better elucidate best practice.

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Intraoperative Detection of Upper Gastrointestinal Strictures

20

Thomas G. Barnes and Neil J. Mortensen

Introduction

Stricturing in patients with Crohn's disease is frequently symptomatic and as a result, intervention is often needed to relieve symptomatic intestinal obstruction. Up to one-third of patients will eventually require surgical resection within 10 years of their diagnosis [1–3]. One-quarter of patients with Crohn's disease will have had at least one small bowel stricture [4] and most of these patients require re-operative intervention at least once during their lifetime [5]. Despite advances in medical therapies, no significant decrease in the need for surgery has occurred for stricturing Crohn's disease [6–8].

Surgical intervention should improve the patient's symptoms as well as preserve as much intestine as possible. It is imperative that an intraoperative strategy is adopted to ensure appropriate treatment and identification of additional strictures. Most patients undergoing surgery will have had radiological assessment of their gastrointestinal tract to identify stricturing disease. Whilst sensitivity and specificity for the various radiological modalities is high, intestinal strictures may still be missed and thus intraoperative assessment of the extent of disease is essential when operating on a patient with Crohn's disease (Table 20.1).

Table 20.1 PICO outline

Patients	Intervention	Comparator	Outcome
Patients with Crohn's disease requiring surgery undergoing intraoperative assessment of strictures	Intraoperative palpation	Other modalities	Stricture Identification

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Search Strategy

A comprehensive literature search of Cochrane Database of Collected Research, EMBASE, MEDLINE, and PubMed was performed to identify all of the English-language publications related to Crohn's disease, stricture identification, stricture palpation, intraoperative enteroscopy, intraoperative detection of Crohn's strictures and small bowel calibration from 1985 to 2018. Key search terms included the following: "Crohn's," "Stricture," "intraoperative detection," "enteroscopy", "marble", "calibration", "balloon", and "palpation". Studies were excluded if they did not directly relate to intraoperative stricture detection or were for detection of pathology other than that caused by Crohn's disease. References from identified studies were searched to identify any additional references that were not identified on the initial search. Abstracts of articles were assessed for their relevance followed by full text evaluation of the remaining studies. Reports of single cases and letters to the editor were excluded.

Results

Thirteen studies assessing various techniques for intraoperative Crohn's stricture detection were identified (Table 20.2). Reported techniques included palpation [9–14], passage of a Foley catheter or similar device [12, 13, 15], passage of a calibration ball or similar object, [12] and intraoperative endoscopy (IOE) [9, 10, 11, 14, 16, 17, 18, 19]. Overall, the quality of evidence is poor with most studies being retrospective case series assessing strictureplasty outcomes rather than specifically addressing efficacy of intraoperative stricture identification.

Five studies compared IOE with an additional technique which were case series with patients acting as their own controls [9, 10, 11, 17, 18]. Three studies comparing IOE with preoperative barium radiography demonstrated higher lesion (including stricture) detection with IOE [10, 17, 18]. Lescut [18] and Esaki [17] identified Crohn's disease lesions outside of the resection margin in 36% of patients where preoperative barium radiography was reported as negative. Similarly, Hotokezaka reported identification of an additional 33 lesions with IOE that were not identified on preoperative barium radiography. No studies comparing intraoperative stricture detection with modern diagnostic modalities (i.e., capsule endoscopy, computerized tomography enterography, magnetic resonance enterography) were identified.

Small bowel calibration using a 20-French Foley catheter with the balloon inflated or the use of a solid ball (i.e., rubber, acetyl copolyma) were described in five studies [12, 13, 15, 20, 21]. The diameter of the calibration tool was 20–25 mm with the Foley catheter balloons being fully inflated. In addition to the studies described, other case reports have described calibration balls made of wood [20], steel [22], and marble [23, 24].

Table 20.2 Outline of studies identified

Study	Patients	Technique	Study design	Outcome measure	Key findings	Quality of evidence
Dehn et al. (1989) [15]	30	36-Fr plastic oesophageal tube (22), 20-Fr Foley balloon catheter (8)	Prospective case series	Weight gain at 3 months and recurrence requiring operation	Median weight gain of 4.0 kg. 4 patients undergoing re-do surgery for obstructive symptoms	Low
Arima et al. (1992) [16]	37	IOE	Case series	Postoperative radiological and surgical recurrence	70.3% radiological recurrence; 21.6% surgical recurrence	Low
Fazio et al. (1993) [13]	116	Palpation and if in doubt 20-Fr Foley balloon catheter	Retrospective case series	Relief of obstructive symptoms.Number of new unrelated strictures	95% of patients asymptomatic at 6 months, symptomatic recurrence in 24% (17 underwent re-operation). New strictures in 23 patients.	Low
Lescut et al. (1993) [18]	20	IOE vs preoperative radiography	Case series	Additional Crohn's pathology identification	Lesions in 13 patients identified with IOE, 7 of which had normal radiography.	Low
Smedh et al. (1993) [19]	37	IOE & palpation	Case series	External versus mucosal findings & influence on procedure	IOE influence procedure in 65% of cases	Low
Stebbing et al. (1995) [21]	52	Palpation or esophagogastric tube or 20-Fr balloon catheter	Prospective case series	Reoperation rate	23 (44%) required further operation, 19 of which were complicated Crohn's disease.	Low
Garcia-Granero et al. (1999) [20]	15	Acetal corpolyma sphere	Technical report	Peri-operative complications	No peri-operative complications	Very low
Dietz et al. (2001) [12]	314	Visual inspection, palpation, balloon & rubber ball	Retrospective case series	Recurrence requiring re-operation	37% requiring re-operation, 92% of which were for obstruction	Low

(continued)

Table 20.2 (continued)

Study	Patients	Technique	Study design	Outcome measure	Key findings	Quality of evidence
Esaki et al. (2001) [17]	27	IOE vs double-contrast small bowel radiography	Case series	Recurrence	Small ulcers and inflammatory polyps less frequently detected by radiographs (37 vs 74%). Type or IOE findings not different in recurrence + or −.	Medium
Olaison et al. (2001) [14]	178	IOE & palpation	Case series	Influence on procedure	IOE had significant influence on procedure in 45% of patients.	Low
Otterson et al. (2004) [11]	118	Balloon catheter vs barium radiography	Prospective comparative study	Number of strictures identified with each modality	BR over or underestimated stricture number in 36% of patients.	Medium
Hotokezaka et al. (2007) [10]	30	IOE vs barium radiography	Case series	Stricture identification	45 strictures identified by barium radiography, 78 by IOE.	Low
Almer et al. (2007) [9]	48	Palpation and IOE vs scintigraphy	Prospective case series	Number of pathological lesions	28 identified small bowel strictures with IOE. Leukocyte scintigraphy positive in 19 (18 with positive histology).	Low

Two studies assessed the influence on procedure of intraoperative stricture identification modalities [14, 19]. In both, IOE had an influence on the procedure in 50% of included patients with most being a reduction in planned small bowel resection (48%). IOE led to an increased amount of small bowel resection from the original plan in only 0.04%. Additional strictures identified by IOE in the remaining patients in these studies were managed with strictureplasty.

Recommendations

Patients undergoing resection or strictureplasty for Crohn's disease should have the whole of their gut examined for additional strictures particularly in the small bowel above and below an index lesion. This should entail at least inspection and palpation for additional disease. IOE is likely to increase the diagnostic yield of detection of additional disease and may reduce unnecessary resections in up to 50% of cases (quality of evidence: low).

The size of the calibration device for trawling the small bowel should be 20 to 25 mm (quality of evidence: low).

Personal View

When undertaking operative intervention for Crohn's disease, the aim should be to appropriately treat disease that is (or will be) symptomatic whilst resecting as little small bowel as possible. A secondary aim is to be sure that no stricture is overlooked downstream of an anastomosis, since this could increase the risk of anastomotic leakage. The planned target of resection or strictureplasty is often clear, based on pre-operative modern diagnostics such as capsule endoscopy, computerized tomography enterography (CTE), and magnetic resonance enterography (MRE) [7]. Despite this, there will still be some disease that is not identified using these modalities and it is essential to assess the rest of the gastrointestinal tract during operative intervention to avoid missing occult disease that may soon become symptomatic. Advances in non-invasive diagnostic imaging provide thorough preoperative evaluation of the small bowel. The sensitivity and specificity of CTE and MRE can approach 100%; however, intraoperative location of disease identified on these images can be limited to the terminal ileum or proximal jejunum thus intraoperative stricture identification using the aforementioned techniques is essential.

Once the abdomen is entered, careful inspection of the remaining gastrointestinal tract should occur. Advanced disease is easily recognised with characteristic appearances of thick-walled and indurated bowel segments with fat wrapping and loss of the scalloped appearance of the mesentery. Proximal to strictured segments, the bowel is usually dilated often with the appearance of chronic obstruction resulting in thickening from muscular hypertrophy. Where these findings are absent, careful palpation can allow detection of subtle strictures where there is a thickened mesenteric edge. Even in experienced hands, external changes of the bowel wall often do

not reflect the underlying mucosal inflammation [19] nor do they reflect the degree of stricturing if present.

Where there is uncertainty about remaining disease, 'trawling' the small bowel with a Foley catheter or a "calibration sphere" should then be utilised. As reflected in the literature, the size of such calibration modalities is between 20 mm and 25 mm as most surgeons would correct strictures of this diameter [25]. Foley catheters are cheap, quick, and easy to use and our preferred technique. When passing through fibrotic strictures, the silicone balloon may deform and could miss or underestimate such segments of disease [20] unless the balloon is inflated above the target diameter during the trawl. "Calibration balls" made of steel, marble, or wood are solid and therefore will not pass through strictured segments of a smaller diameter. Furthermore, direct use of diathermy onto the ball can be used in order to open a diseased segment of bowel to resect or perform a strictureplasty which is not possible with a Foley catheter. It is recommended to use a material that can be repeatedly autoclaved when using a calibration sphere.

The main disadvantage of both balloon and ball calibration methods is that the mucosal surface cannot be visualised. From the limited evidence available in the literature, there is certainly more support for IOE as a technique that is superior to inspection and palpation of the bowel [10, 19] versus certain radiological diagnostics [9, 17, 18]. IOE provides information not just about the degree of stricturing, but also the presence of active ulcers which prelude the decrease in diameter of a stricture [26]. A distinction can also be made between segments of bowel obstructed by either phlegmonous Crohn's disease or by fibrotic Crohn's disease. However, surgical indications based on ulcer activity have not been studied. IOE can also allow more accurate measurement of distance between strictures allowing surgical correction of a mild stricture if it is near a severe stricture. It is certainly useful in very complex re-operative cases.

The main drawback of IOE and other stricture detection techniques is conversion of a clean procedure to a contaminated one which may increase the risk of wound or abdominal sepsis [10]. Furthermore, if there are multiple strictures, multiple enterotomies are needed to insert an endoscope, catheter, or ball at several sites.

With the advent of minimally invasive surgery, some of these stricture detection techniques may be more difficult than in open surgery and although still possible, would require delivery of the small bowel through the abdomen [27].

Conclusion

Intraoperative stricture detection is an essential tool for surgeons operating on Crohn's disease patients. Techniques include visualisation, palpation, passage of a Foley catheter or calibration sphere, and intraoperative endoscopy, and each has their own advantages. Evidence surrounding each technique is of low quality and very limited. Intraoperative endoscopy is likely to be most useful to both identify strictures and visualize mucosal disease, and may reduce the need for unnecessary resection.

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Management of Long Segment Small Bowel Crohn's Disease

21

Diane Mege and Fabrizio Michelassi

Introduction

Crohn's disease (CD) is a chronic inflammatory and recurrent disease. Up to 50–60% of Crohn's disease patients will eventually require at least one surgical resection within 10 years of diagnosis, even if recent studies have suggested that the need for surgery is probably lower today due to advances in medical therapy.

Jejunoileitis occurs in as many as 10–15% of patients with Crohn's disease [1], and has been most often managed with an intestinal resection. However, this approach ignores the recurrent nature of the disease and data suggesting that the length of the recurrence is similar to the length of the primary disease [2]. Short bowel syndrome may develop after resection of primary and recurrent disease in the presence of long-segment jejunoileitis. Hence, procedures that spare the intestine should be employed when feasible in the management of long-segment small bowel Crohn's disease.

Bowel-sparing procedures in the surgical treatment of Crohn's disease of the small bowel were first described by Emanoel Lee in 1982 [3]. Since then, several series [4–7] have demonstrated the feasibility and safety of strictureplasties in the treatment of fibrostenotic strictures. Two strictureplasties, the Heineke-Mikulicz and the Finney, have emerged as the two most commonly used techniques, yet they are not suitable for long segments of disease with multiple sequential strictures of jejunum and ileum. To treat these challenging cases, a new strictureplasty, the side-to-side isoperistaltic strictureplasty (SSIS), was described in 1996 [8]. This technique is based on the division of the diseased loop in half and placement of the two

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halves in an isoperistaltic side-to-side configuration to allow for performance of a long side-to-side enteroenterostomy leading to a wider diameter of the diseased bowel, without sacrificing any mucosal absorptive area.

The European Crohn's and Colitis Organisation (ECCO) guidelines state that strictureplasty is a safe alternative to resection in jejunoileal Crohn's disease with similar short- and long-term results. Conventional strictureplasty techniques are advised when the length of the stricture is <10 cm. In extensive disease, with long strictured bowel segments where resection would compromise the effective small bowel length, nonconventional strictureplasties may be attempted (ECCO Statement 7C) [9].

The objective of this chapter is to evaluate postoperative outcomes and recurrence rates after SSIS and resection for long-segment small bowel Crohn's disease.

Search Strategy

Relevant PICO (Population, Intervention, Comparator, Outcome) questions were generated (Table 21.1). A comprehensive literature search of Cochrane Database of Collected Research, EMBASE, MEDLINE, and PubMed was performed to identify all the English-language publications related to long segment small bowel Crohn's disease from 1987 to 2017. Key search terms included the following: "Crohn's disease", "small bowel", "side-to-side isoperistaltic strictureplasty", "intestinal resection", "postoperative outcomes" and "recurrence". Retrospective and prospective, observational and randomized studies were included.

Studies were excluded if they did not directly compare SSIS with resection, or if they included only colonic Crohn's disease. Only the most recent study was included if similar studies from the same institution were encountered. The references of the included studies were reviewed to identify additional studies that were incorporated as appropriate.

Results

Eight studies were identified with patients who underwent SSIS (Table 21.2): four retrospective [10–13] and four prospective [14–17] (one multicentric [17]), two comparing SSIS with small bowel resection [12, 15] and one study including pediatric cases [12]. To date, there is no randomized study comparing SSIS and bowel resection.

Table 21.1 PICO table

Patients	Intervention	Comparator	Outcome
Patients with long segment disease	Isoperistaltic strictureplasty	Resection	Postop complications, recurrence rates

Table 21.2 Studies evaluating the management of long segment small bowel Crohn's disease

Study	Patients (n)	Study design	Outcomes	Quality of evidence
Michelassi (2000) [14]	**21 SSIS**	Prospective 1992–1999	Morbidity: n = 1 (5%) Recurrence: n = 48% at 4 years	Low
Sampietro (2000) [15]	35 Stx vs 54 Res **➔ 12 SSIS**	Prospective comparative 1993–1999	Morbidity*: 1 (3%) vs 5 (9%) Recurrence*: 27% vs 22% at 5 years	Low
Sampietro (2004) [16]	102 Stx **➔ 80 SSIS**	Prospective 1993–2002	Morbidity*: n = 6 (6%) Recurrence: n = 13 (16%) at 3 years	Low
Tonelli (2004) [10]	**31 SSIS**	Retrospective 1996–2002	Morbidity: n = 6 (19%) Recurrence: 19% at 3.6 years	Low
Michelassi (2007) [17]	**184 SSIS**	Prospective multicentric 1992–2004	Morbidity: n = 19 (10.3%) Recurrence: 23% at 5 years	Moderate
Bellolio (2012) [11]	94 Stx **➔ 3 SSIS**	Retrospective 1985–2010	Morbidity*: n = 21 (17.6%) Recurrence*: 29.3% at 5 years	Low
Romeo (2012) [12]	19 Stx vs 20 Res **➔ 11 SSIS** (pediatric)	Retrospective comparative 1996–2011	Morbidity: n = 0 vs n = 2 (10%) Recurrence: 5% at 6 years vs 5%	Low
Fazi (2016) [13]	**91 SSIS**	Retrospective 1996–2010	Morbidity: n = 24 (26%) Recurrence: n = 37/83 (32%) at 4.5 years	Low

Stx strictureplasty, *Res* resection, *SSIS* side-to-side isoperistaltic strictureplasty
Results given for all the strictureplasties

The feasibility of the procedure was first reported by Michelassi in 1996 [8]. A follow-up manuscript reporting the first 21 patients established the safety of the new technique [18]; a subsequent paper reporting on a prospective, multicenter study in 2007 established the reproducibility of the procedure by surgeons at six medical centers in three continents [17]. Six additional papers (Table 21.2) have been published. Postoperative morbidity rates varied from 0% [12] to 26% [13]. The principally reported surgical complications were bleeding (2–3%) [10, 14, 17] and anastomotic leak (4–5%) [11, 17].

Regarding recurrence rates, Michelassi initially reported a rate of 48% at 4 years; however, the follow-up was based on radiographic and endoscopic examinations in only half of the patient cohort [14]. In the international multicentric study, recurrence was noted in 23% of patients after 5 years [17]. This multicenter study included patients previously reported by Sampietro and Tonelli, with similar but lower recurrence rates (16–19% at 3 years, 27% at 5 years) [13, 16]. More recently,

Fazi reported recurrence in 32% of patients at 4.5 years after SSIS. Not surprisingly, some independent predictive factors for recurrence were identified, including young age at diagnosis and at surgery, family history, and smoking habits [11, 13].

In a recent review [19], Michelassi and Mege reviewed the senior authors' experience with 61 SSIS over 25 years. After a median follow-up of 11 years (range: 1 month to 25 years), symptomatic recurrence was observed in 61%; 15 patients at the SSIS and 19 remote from the strictureplasty site. Of 15 recurrences at the SSIS, 11 required surgical treatment and one-half were managed by revision or strictureplasty (revision or strictureplasty in 6; SSIS resection in 5). There was no evidence of neoplastic transformation in any of the SSIS's and 51 patients (86%) maintained the original SSIS at the end of the observation period.

The authors specified that SSIS is best suited for Crohn's disease with multiple fibrostenosing strictures over an extensive segment of small bowel, while it should not be performed in the presence of inflammatory masses, or in cases with very thickened mesentery or with long, tight strictures and a thick, unyielding intestinal wall. In these latter two situations, it is difficult to transect the mesentery and then slide the proximal intestinal loop over the distal one for sufficient length without undue tension. Similarly, a long, severely strictured intestinal segment may not provide enough luminal surface to be incorporated adequately in an SSIS.

Recommendations Based on the Data

Side-to-side isoperistaltic strictureplasty can be safely performed in patients with extensive small bowel Crohn's disease in the absence of inflammatory masses or very thickened mesentery with satisfactory postoperative outcomes and recurrence rates, while avoiding extensive intestinal resection and short bowel syndrome (*evidence quality moderate; strong recommendation*).

The strength of the recommendation is based on the consistency of the data published over the course of the past 25 years and on a recent review of the senior author's experience over the same interval.

Personal View of Data

To summarize, our long-term experience suggests that the SSIS is a safe, effective, and durable bowel-sparing procedure in patients with Crohn's disease demonstrating multiple fibrostenosing strictures over an extensive segment of small bowel. As can be expected by the nature of Crohn's disease, recurrence rates after SSIS increases with the length of the follow-up but the most patients are able to maintain the original SSIS for many years after the index procedure. Surgeons called to operate on patients affected by Crohn's disease need to familiarize themselves with this technique to avoid sacrificing large amount of intestine and achieve optimal short- and long-term outcomes for this cadre of patients with the most aggressive pattern of jejunoileitis.

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Construction of the Ideal Ileocolic Anastomosis in Crohn's Disease

22

Rebecca Brown and Alessandro Fichera

Introduction

Approximately 80% of patients diagnosed with Crohn's disease will ultimately require an intestinal resection for complications relating to their inflammatory bowel disease [1]. Unfortunately, endoscopic recurrence of disease is identified in up to 70% of patients who have undergone surgical resection within one year of the operation [2] and nearly one-third of patients will require additional operative interventions [3]. There is still significant room for improvement in terms of efficacy of medical therapy in preventing recurrence in patients with Crohn's disease in surgical remission [4–7]. Furthermore, recurrence is most often seen at the anastomotic site or in the neo-terminal ileum [8, 9]. These findings indicate that efforts should be made to identify factors associated with recurrence and optimize anastomotic technique as a key proponent in the management of this difficult disease.

Search Strategy

A comprehensive literature search of Cochrane Database of Collected Research, EMBASE, MEDLINE, and PubMed was performed to identify all English-language publication related to ileocolonic resection and anastomosis in patients with Crohn's disease and recurrence and postoperative complications, focusing primarily on anastomotic leak rates from 1985 to 2017. Key terms included: Inflammatory bowel disease, Crohn's disease, ileocolonic resection, anastomosis, recurrence, anastomotic leak. Reference sections of all articles were reviewed to identify additional articles pertaining to this topic. Retrospective and prospective, observational and randomized studies were included.

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Table 22.1 PICO table

Patients	Intervention	Comparator	Outcome
Patients requiring ileocolic anastomosis in Crohn's disease	End-to-end anastomosis	Side-to-side anastomosis	Recurrence rate, anastomotic leak

Results

Over the past 30 years, numerous studies have compared recurrence rates and complications related to ileocolonic resection and type of anastomotic reconstruction in patients requiring resection for Crohn's disease (Table 22.1). With the advent and wide acceptance of the surgical stapler, many of the early studies aimed to compare stapled to sutured anastomotic techniques, but ultimately attributed their results to the anatomic configuration of the anastomosis rather than the material used for its creation.

In 1996, Caprilli [10] reviewed data on 110 patients enrolled in a multicenter trial primarily looking at the effectiveness of 5-aminosalicylic acid in the prevention of postoperative Crohn's disease recurrence (Table 22.2). The authors found that patients with end-to-end anastomoses (n = 55) had a risk of endoscopic recurrence more than three-fold higher than those with other types of anastomotic configuration (n = 20: end-to-side; n = 23: side-to-side, relative risk 3.4). Subsequently, Hashemi [11] retrospectively compared 69 patients undergoing resection for Crohn's disease and determined that wide-lumen stapled side-to-side anastomoses were associated with fewer complication rates than sutured end-to-end anastomoses and, furthermore, may delay reoperations for symptomatic recurrence. The authors attributed the results of their study to the resultant anatomic configuration (wide-lumen side-to-side versus end-to-end) rather than the anastomotic technique (stapled versus handsewn).

Similarly, in 1999, Yamamoto [12] performed a retrospective review of 123 patients undergoing surgical resection for Crohn's disease – 45 patients underwent stapled side-to-side anastomosis and 78 underwent sutured end-to-end anastomosis. They identified a significantly lower rate of complications in the stapled side-to-side group compared to the sutured end-to-end group (7% versus 23%, p = 0.04). Additionally, they reported lower recurrence rates requiring surgery in the stapled side-to-side group at 1-, 2-, and 5-year follow-up (0% versus 5%, 0% versus 11%, 3% versus 27%, respectively, p = 0.007). Tersigni [13] also demonstrated lower rates of recurrence in the side-to-side anastomosis group in their 2003 retrospective review. Additionally, in 2005, Resegotti [14] found a significant reduction in anastomotic leak in patients undergoing side-to-side anastomosis (n = 51) compared to those undergoing end-to-end anastomosis (n = 71; 2% versus 14.1%, p = 0.02).

In 2001, Muñoz-Juárez [15] performed the first case-control comparative analysis of 138 patients undergoing ileocolonic resection for Crohn's disease, divided evenly into stapled, wide-lumen, side-to-side anastomoses and handsewn end-to-end anastomoses. Clinical recurrence occurred in 16 (24%) of the side-to-side anastomosis group and in 39 (57%) of the end-to-end anastomosis patients. The

Table 22.2 Summary of comparative studies

Study	Anastomotic configuration E-E[a] vs S-S[b]	Outcomes	Results E-E[a] vs S-S[b]	Quality of evidence
Caprilli (1996) [10]	55 vs 43[c]	Endoscopic recurrence	3× higher recurrence (relative risk 3.4)	Moderate
Hashemi (1998) [11]	27 vs 42	Complications Reoperation	17% vs 8% 43% vs 2%	Moderate
Yamamoto (1999) [12]	78 vs 45	Overall complications Symptomatic recurrence Re-operation at 5 years	23% vs 7% (p = 0.04) 50% vs 7% 24% vs 3% (p = 0.007)	Moderate
Munoz-Juarez (2001) [15]	69 vs 69	Complication rates Recurrence at 1 year Recurrence at 5 years Reoperation at 5 years	20% vs 7% (p = 0.048) 28% vs 12% 52% vs 32% (p = 0.004) 20% vs 11% (p = 0.017)	Moderate
Tersigni (2003) [13]	76 vs 30[d]	Recurrence rate	2.6% vs 16.7%	Moderate
Resegotti (2005) [14]	71 vs 51	Anastomotic leak Postoperative stay	14% vs 2% (p = 0.02) 12.3d vs 9.7d (p = 0.03)	Moderate
Simillis (2007) [16] [8 studies]	383 vs 329	Anastomotic leak Recurrence	Lower in S-S (OR 4.37) No difference	Moderate
McLeod (CAST) (2009) [19]	86 vs 84	Endoscopic recurrence Symptomatic recurrence	43% vs 38% (p = 0.55) 22% vs 23% (p = 0.92)	Moderate
Guo (2013) [17] [11 studies]	7 studies 4 studies 4 studies	Anastomotic leak Endoscopic recurrence Symptomatic recurrence	No difference No difference No difference	Moderate
Feng (2018) [18] [11 studies]	9 studies 7 studies 7 studies	Anastomotic leak Clinical recurrence Reoperation	No difference Lower in S-S (OR 0.32) Lower in S-S (OR 0.22)	Moderate

(continued)

Table 22.2 (continued)

Study	Anastomotic configuration E-E[a] vs S-S[b]	Outcomes	Results E-E[a] vs S-S[b]	Quality of evidence
Gajendran (2018) [20]	68 vs 60	30-day complications Endoscopic recurrence Quality of life Healthcare utilization	No difference 25% vs 39% (p = 0.112) Higher in E-E (p = 0.007) Lower in E-E (p < 0.01)	Moderate

[a]E-E = End-to-end anastomosis
[b]S-S = Side-to-side anastomosis
[c]23 side-to-side anastomoses + 20 end-to-side anastomoses
[d]Hand-sewn end-to-end or end-to-side isoperistaltic anastomoses

cumulative reoperation rate for recurrence at 5 years was 11% after side-to-side anastomosis and 20% after conventional end-to-end anastomosis (p = 0.017). These promising results suggested that the wider diameter and configuration of the anastomosis could decrease the ischemia-induced recurrence rates, reduce the occurrence of proximal fecal stasis with the resulting modification of the local microbiome, and delay the recurrence of symptoms.

A 2007 meta-analysis [16] comprising eight studies (including five of the studies above) with 661 patients who underwent 712 anastomoses compared the outcomes between end-to-end anastomoses (53.8%) and other types of anastomotic configuration (46.2%)—stapled side-to-side in the vast majority. There were no significant differences between the groups regarding overall complication, anastomotic recurrence, and reoperation needed because of anastomotic recurrence. When comparing only side-to-side and end-to-end anastomosis, a lower leak rate as well as reduction in overall postoperative complications and duration of hospital stay was demonstrated in the side-to-side anastomosis group. However, there was no difference in recurrence or rates of reoperation needed for recurrence.

Two more recent systematic reviews [17, 18], however, demonstrated no difference in anastomotic leak rates between side-to-side and end-to-end anastomotic configurations. Additionally, Guo [17] reported no differences in recurrence rates between the two anastomoses, while Feng [18] found a significant superiority of the side-to-side anastomosis in decreasing risk for clinical recurrence and reoperation. However, the results from these reviews should be interpreted with caution given the retrospective nature of most data included in each analysis.

In 2009, the results of the first randomized study comparing anastomotic type – the CAST trial [19] – were released. In this trial, patients with Crohn's disease who underwent ileocolonic resection were randomized to either wide-lumen stapled side-to-side anastomosis or handsewn end-to-end anastomosis. A total of 139 patients were included and after a mean follow-up of 11.9 months, the endoscopic recurrence rate was 37.9% in the side-to-side anastomosis group and 42.5% in the end-to-end anastomosis group (p = 0.55). The symptomatic recurrence rate was also similar between the two groups (22.7% versus 21.9%, p = 0.92). This study presents the only

level one evidence comparing these two types of anastomoses and questions the benefits of side-to-side anastomoses in preventing disease recurrence; however poor accrual rate lead to early termination which resulted in an underpowered study.

Recommendations Based on Data

Data from the numerous retrospective studies presented above evaluated the effect of anastomotic reconstruction after resection in Crohn's disease and have demonstrated lower complication and recurrence rates associated with creation of a side-to-side anastomosis. These results are consistent with other data suggesting that infectious complications are associated with increased risk of postoperative recurrence of Crohn's disease [21]. These findings have further been supported by meta-analyses of the retrospective studies which confirm a potential superiority in the creation of side-to-side anastomosis after resection for ileocolonic Crohn's disease. The obvious limitations associated with the retrospective nature of these studies, which make up most data on anastomotic reconstruction, make this data difficult to interpret. Unfortunately, the only level one evidence on the subject is an underpowered study that was unable to confirm the retrospective findings.

While there appears to be a trend towards superiority of a side-to-side anastomosis in ileocolonic Crohn's disease requiring resection, this opinion remains controversial based on available literature. One concept, however, that most authors agree on, is that the creation of a wide-lumen anastomosis that prevents fecal stasis while maximizing blood supply to proximal bowel, is a vital component of anastomotic construction to prevent recurrence of Crohn's disease after surgical resection.

Personal View

In our personal experience and based on the data in the literature, the ideal anastomosis for terminal ileal Crohn's disease ought to result in a wide lumen to prevent localized fecal stasis, and is associated with very low postoperative complication and leak rates. Therefore, our preference for anastomotic reconstruction to prevent recurrence in Crohn's disease is a unique antimesenteric functional end-to-end handsewn anastomosis as described by Kono and colleagues in 2003 [22]. They first reported the outcomes of this novel technique comparing 69 patients after Kono-S anastomosis with 73 patients who underwent conventional anastomosis (handsewn end-to-end, handsewn side-to-side, or stapled functional end-to-end). The median endoscopic recurrence score at 5 years was significantly lower after the Kono-S anastomosis (2.6 versus 3.4, $p = 0.008$). Surgical recurrence was also significantly lower with the novel Kono-S anastomosis (0% versus 15%, $p = 0.0013$). These results led to rapid adoption of the Kono-S anastomosis in numerous medical centers in Japan and other countries around the world.

In our own experience [23], we followed 44 patients after 46 Kono-S anastomoses and reported no surgical recurrences during the study period with an average

Rutgeerts score of 0.722 at a mean follow-up of 6.8 months. Similarly, Katsuno [24] evaluated 30 consecutive patients who underwent Kono-S anastomosis and reported no anastomotic leaks or surgical recurrences during a median follow-up period of 35 months. Endoscopic surveillance evidenced an average Rutgeerts score of 0.78 at a mean of 14.5 months postoperatively.

In 2016, an international multicenter study [25] conducted at five hospitals (four in Japan and one in the United States) analyzed 187 patients who underwent a Kono-S anastomosis for Crohn's disease. In the Japanese cohort (144 patients), surgical recurrence occurred in only two patients with a 5-year recurrence-free survival rate of 98.6%. In the United States group (43 patients), no surgical recurrences occurred during the follow-up period of 32 months.

The Kono-S anastomosis is a safe and feasible anastomotic technique suitable for both small and large intestine. International prospective and randomized trials are underway to confirm the benefits and value of this anastomotic technique in reducing surgical recurrence in Crohn's disease.

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Management of Enteroenteric Fistula

23

Cathy Lu and Florian Rieder

The lifetime risk of internal penetrating disease in adult-onset Crohn's disease (CD), encompassing enterocutaneous, enteroenteric, enterovaginal, and enterovesical fistulas has been reported to range from approximately 15% in inception cohorts [1] to 20–40% in tertiary referral center populations [2, 3]. While there is a robust association between internal penetrating disease and perianal fistulizing disease [4], their management is distinct. Internal penetrating disease is classified by the organs from which they originate and terminate [5]. This article focusses only on management of fistulas originating and terminating in the intestine, with its most common forms being enterocolonic (29%), enterosigmoid (17–26%), and enteroenteric (18–24%) [5]. This disease manifestation represents a significant clinical problem and the available evidence of healing rates and cost effectiveness with biologic therapy versus surgery will be investigated.

Search Strategy

A comprehensive literature search of Cochrane Database of Collected Research, EMBASE, MEDLINE, and PubMed was performed to identify all the English-language publications related to Crohn's disease, enteroenteric fistula, surgery, healing rates and cost effectiveness from 1988 to 2018. Key search terms included the following: "Crohn's disease," "inflammatory bowel disease," "fistula,"

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"biologic," "surgery," and "cost effectiveness," "cost utility," or "cost benefit" (Table 23.1). Studies were excluded if they failed to include statements about cost effectiveness or included only pediatric patients. Only the most recent study was included if similar studies from the same institution were encountered (Table 23.2). The references of the included studies were reviewed to identify additional studies that were incorporated as appropriate.

Table 23.1 PICO table

Patient	Intervention	Comparator	Observation
Crohn's disease patients with enteroenteric fistula	Biologic therapy	Surgery	Healing rates, cost effectiveness

Table 23.2 Studies evaluating cost effectiveness of Crohn's disease biologic therapy

Study	Patients (N) with enteroenteric fistula	Medical intervention	Healing rates	Cost effectiveness compared to surgery	Quality of evidence
Cohen [13]	NS	Pharmacotherapy; medication details not provided	Not discussed	No comparison to surgery. Surgical cost/patient with fistula higher than non-fistula cohort.	Low
Lindsay [7]	NS	Markov Model: Infliximab 5 mg/kg at weeks 0, 2, 6 and every 8 weeks thereafter.	Markov model. Week 14 responders defined in ACCENT II [17]	No comparison to surgery for fistulizing disease alone.	Low
Lichtenstein [8]	NS	Infliximab 5 mg/kg at weeks 0, 2, 6 and every 8 weeks thereafter vs placebo (ACCENT II). ≥ Week 22 lost response could be treated with 5 mg/kg q 8 weeks.	Fistulizing CD: significantly reduced hospitalizations and surgeries, $p < 0.05$.	No cost comparisons	Low

Table 23.2 (continued)

Study	Patients (N) with enteroenteric fistula	Medical intervention	Healing rates	Cost effectiveness compared to surgery	Quality of evidence
Pillai [16]	NS	Infliximab 5 mg/kg at weeks 0, 2, 6 and every 8 weeks Adalimumab 160 mg week 0. 80 mg week 2, 40 mg every 2 weeks thereafter.	Not discussed.	No cost comparisons Fistula group: costs for infliximab induction and maintenance versus medication standard care above acceptable cost thresholds.	Moderate
Rubenstein [9]	NS	Infliximab 5 mg/kg at weeks 0, 2, 6. Maintenance infliximab assessed by treating physician.	Fistulizing CD had decreased gastrointestinal surgeries, $p < 0.01$.	No cost comparisons. Assumed that lower cost with decreased surgical rate.	Low

NS – data not stratified into enteroenteric fistula

Results

Based on the published literature, no head to head comparison of surgery versus biologic therapy for enteroenteric fistulizing disease has been conducted. Most studies focus on perianal disease and if enteroenteric (EE) fistulas are included in study populations, they are not separately analyzed. No validated instruments exist to classify enteroenteric fistulas and their response to therapy and no randomized controlled trial is dedicated to enteroenteric fistulas.

Similarly, no direct comparisons have been made between cost effectiveness of surgery versus biologic therapy for enteroenteric fistulas. The often asymptomatic nature of enteroenteric fistulas may be responsible for this lack of data. The presence of enteroenteric fistulas is usually not an indication for surgery, unless there is an obstructing stricture, septic complication, or significant malnutrition from bypass [6]. As a result, extrapolations from current literature need to be used and are described below.

Studies have mainly focused on the cost effectiveness of maintenance biologic therapy for perianal fistulizing Crohn's disease by reducing hospitalizations and surgeries [7–9]. Although infliximab results in a decrease in hospital resource use including hospital admission days and surgeries, and health care costs such as colonoscopies in patients with fistulas, there is a substantial increase in long-term total health care costs once infliximab is added [10, 11] and particularly, where there is a loss of treatment response or intolerance to infliximab [10, 12]. In a study of health care resource use and costs in Crohn's disease before and after infliximab therapy, the health care costs over 2–4 consecutive years following the addition of infliximab therapy was higher [10]. Overall, Crohn's disease patients with fistulas are thought to incur higher health care costs from outpatient hospital visits such as diagnostic imaging, physician visits, and surgery compared to those without fistulas [13]. However, it is unknown in these studies if greater costs also occur with enteroenteric fistulas before and after biologic therapy, as the type of fistula is not specified.

Other studies have also shown that maintenance infliximab significantly reduces surgeries and procedures in patients such as those with fistulizing Crohn's disease enrolled in the ACCENT II study [8]. However, patients enrolled in this landmark clinical trial had to have single or multiple external draining anorectal fistulas; enteroenteric fistulas were not separately analyzed. Similarly, a comprehensive cost effectiveness analysis using a Markov model of Crohn's disease patients with and without fistulas on infliximab incorporated patients with actively draining enterocutaneous and/or anorectal fistulas, but not enteroenteric fistulas. Eight-week scheduled maintenance infliximab therapy was found to be cost effective for those with enterocutaneous and/or anorectal fistulas.

Healing rates of enteroenteric fistulas with both medical therapy and surgery are not well specified. Internal fistulas such as enterovesical fistulas are known to have lower rates of closure in comparison to externally draining fistulas when treated with infliximab [14, 15]. For example, in a study of Crohn's disease patients who received three infliximab infusions with at least 3 months of follow-up thereafter, complete closure of the fistula or cessation of fistula drainage was observed in 69% of patients with external fistulas compared to 13% of those with internal fistulas [14].

Only one systematic review comparing cost effectiveness of biologic and surgical interventions for Crohn's disease with a fistulizing phenotype has been published [16]. In this review, infliximab and adalimumab induction and maintenance regimens were, surprisingly, only cost effective with fewer hospitalizations and surgeries in Crohn's disease patients without fistulas. Overall for fistulizing disease, biologic agents were not cost effective, especially for use as maintenance therapy [16]. Disadvantages of this review are the inclusion of ulcerative colitis data and lack of specification of fistula type making a conclusion about enteroenteric fistulas challenging.

Further analyses on the cost effectiveness and healing rates of surgery versus biologic therapy for enteroenteric fistulas are warranted, particularly with the advent and availability of lower cost biosimilar medications.

Recommendations

Healing rates of internal penetrating disease under biologic therapy are unclear and no trial exists evaluating healing rates separately from perianal disease. Biologic therapy for internal penetrating disease carries the risk of abscess formation and abdominal sepsis [18]. Successful surgery with resection of the affected bowel segments leads to healing of the internal penetrating disease, but comes with associated risk for operative complications and morbidity [6]. There is no head to head trial of biologic therapy compared to surgery for internal penetrating disease.

The LIRIC (Laparoscopic ileocecal resection versus infliximab for terminal ileitis in Crohn's disease) randomized controlled, open-label multicenter trial, studied patients with non-stricturing, non-penetrating ileocecal Crohn's disease where the disease segment measured less than 40 cm and conventional therapy had failed. Patients were randomized to receive an ileocecal resection or infliximab therapy [19]. Quality of life as assessed on the Inflammatory Bowel Disease Questionnaire at 12 months and general quality of life (short form-36) were similar between those patients with and without surgery. Therefore, extrapolating this data to patients with internal penetrating disease, surgical resection may be a reasonable alternative to biologic treatment.

Biologic therapies are the main cost driver in patients with inflammatory bowel disease [16]. Enteroenteric fistulas are often asymptomatic and behave differently from anorectal, enterovesical, and rectovaginal fistulas. Thus, perhaps early surgical intervention of enteroenteric fistulas may be more cost effective than long-term biologic therapy, even though evidence is currently lacking. The recurrence rate of enteroenteric fistulas is unknown and surgical resection may potentially provide patients with a long period of remission with a good quality of life.

Personal View

Subjects with enteroenteric fistulas complicating their Crohn's disease should undergo a thorough work-up with cross sectional imaging and endoscopy to stage the disease activity and delineate the exact anatomy of the enteroenteric fistula. This will also serve to exclude other complications, such as phlegmon or abscess. The accuracy for all three imaging modalities (i.e., ultrasound, computed tomography enterography, magnetic resonance enterography) is high with approximate sensitivities between 70% to 80% and specificities around 95% [20]. The role of endoscopy in the diagnosis is limited and there is no value of fistulograms in enteroenteric fistulas.

Every patient should receive proper hydration and correction of electrolyte abnormalities. Malnutrition is a concern in enteroenteric fistulas that bypass large segments of bowel due to nutrient loss or increased energy demand secondary to significant inflammatory burden. Treatment of malnutrition, including total parenteral nutrition (TPN), is critical to support healing and to optimize patients for a potential surgical resection [21]. In fistulas arising from the proximal small bowel, TPN may also aid healing by reducing fistula output.

Further treatment would depend on the likelihood for spontaneous healing with medical therapy or the necessity for surgery. While most available data relates to perianal fistulizing disease [22], it is believed that spontaneous closure of enteroenteric fistulas is rare and consequently warrants therapeutic intervention [23, 24]. Spontaneous external fistula closure rates in patients on placebo in clinical trials of fistulizing Crohn's disease is about 1 in 6 patients [22]. Predictors of spontaneous closure have been reported in enterocutaneous and enterogastric fistulas and include a lower chance for spontaneous closure in short tracts (less than 2 cm), high fistula output, chronicity, presence of distal obstruction, poor nutritional status, and presence of comorbidities [25–27].

Medical therapy can be attempted in selected patients with the goal to treat the enteric fistula or lessen its severity. Data is available on efficacy of antibiotics in perianal fistulizing disease [28], but not enteroenteric fistula healing. In clinical practice, antibiotics are frequently prescribed for enteroenteric fistulas, but their use should be limited to presence of infection or abscess.

Data supporting use of azathioprine/6-mercaptopurine (MP) for enteroenteric fistulas is limited. In a small study by Present, 31% of patients receiving 6-MP had complete fistula closure versus 6% for the placebo group [29]. Most of these fistulas were anorectal but also included enterocutaneous, enteroenteric, rectovaginal, and vulvar fistulas. A meta-analysis of five randomized controlled trials assessing response or complete fistula healing indicated favorable healing in perianal disease with azathioprine or 6-MP, where 54% experienced healing with an immunomodulator as compared with 21% managed by placebo [30]. However, this data included varied definitions of fistula closure and requires careful interpretation. There is no data on methotrexate in enteroenteric fistulas, but in a case series of 7 patients, including fistulas to bladder, vagina, abdominal wall, and perianal area, 4 out of 7 patients responded to methotrexate [31]. Taken together, the lack of data, side-effect profile, and response rate favor azathioprine/6-MP as co-medication of anti-tumor necrosis factor (TNF) therapy, rather than a standalone treatment. Calcineurin inhibitors (i.e., cyclosporine, tacrolimus) have been used for non-anorectal fistulas only in uncontrolled studies where they demonstrated efficacy, but the side-effect profile was not favorable for long-term therapy [32–34].

Controlled data for the efficacy of biologic therapies on healing of internal fistulas in Crohn's disease are lacking. Healing rates in studies of non-anorectal fistulas treated with anti-TNF vary from 14% to 50% and most studies report mixed populations with the majority being anorectal fistulas [14, 35, 36]. Most of our understanding about healing rates of internal fistulas associated with biologic agent therapy are gleaned from two multicenter randomized, double blind, placebo-controlled trials assessing infliximab response on draining abdominal, anorectal, or rectovaginal fistulas. These two key trials demonstrated that infliximab reduced the number of draining fistulas by ≥50% for at least 4 weeks, with some patients experiencing complete closure of their fistula [17, 23]. This effect (i.e., no draining fistula) was durable in 35% of patients subjected to infliximab maintenance therapy compared to 19% in the placebo group [17]. In the subgroup with rectovaginal fistulas, infliximab was also superior to placebo [37]. The addition of immunomodulators to

infliximab may increase its efficacy [38]. It must be mentioned, however, that extrapolation of these trials to enteroenteric disease should be done with caution as the number of non-anorectal fistulas, in particular enteroenteric fistulas, was exceptionally small in these studies.

In a study assessing the response of 48 patients with an enterocutaneous fistula to anti-TNF therapy, complete fistula closure was achieved in 33% of patients within 3 years [39]. In a retrospective multicenter cohort study by Huguet of 66 patients with internal non-anorectal, non-enterocutaneous fistulas treated with anti-TNF agents, the success rate defined as patients being free from surgery was 56.1% after 43.2 months [18]. Predictors of surgery were anemia, complex fistulas, and hypoalbuminemia. In 62% of patients that did not undergo surgery, the fistulas healed as shown on cross sectional imaging and the mean time to fistula healing was 14 months. A major concern was safety because 16.6% of the patients reported septic complications, 2% cancer (intestinal and colonic adenocarcinoma), and 4% death (cancer and septic shock). This study is only available in abstract form and the manuscript is awaited.

The rate for surgical intervention is high in patients with enteroenteric fistulas because the intervention also leads to healing in most patients. Surgery is further justified by the low rate of healing associated with medical therapy that is paired with a high rate of potential septic complications. Indications for surgical intervention include symptomatic internal penetrating disease, intraabdominal abscesses, and sepsis. In asymptomatic patients with internal penetrating disease, surgery is not generally indicated. At the time of surgery, Crohn's disease fistulas are either managed by proximal intestinal diversion or resection. Complete resection of the diseased bowel segment and fistula tract is recommended to decrease recurrence [40]. The rates of operative morbidity and mortality can be as high as 5–29% and 3%, respectively, for enterocutaneous fistula repair [25]. However, the morbidity and mortality rates for surgical management of enteroenteric fistulas is lower. In any case, surgery should be delayed until the nutritional status is optimized, and intraabdominal sepsis is controlled. Surgery should be performed in specialized centers with a multidisciplinary team that includes medical and nutritional support [41]. The risk-benefit evaluation should include considerations related to comorbidities, overall nutritional status, and presence of infection. Proper cross-sectional imaging should be obtained prior to surgery to assess the exact fistula anatomy, determine any anatomic barriers, and exclude possible distal obstruction.

In summary, medical therapy is frequently unsuccessful in closing the internal fistulas, and the complication rate, including sepsis, cancer, and death appears to be significant. This makes fistula resection a frequent necessity [42]. The optimal timing of surgery is unclear in the absence of data, but the authors of this article feel that early resection in symptomatic internal penetrating disease is preferred to avoid deterioration in nutritional status or the development of abdominal sepsis leading to urgent or emergent interventions and poor outcomes. Asymptomatic internal penetrating disease is a matter of debate and the approach should be thoroughly discussed with the patient. In this situation, the cost effectiveness may also warrant early surgical intervention. Biologic agents are the main cost driver for Crohn's

disease patients with complicated disease courses and early resection may provide patients with long-term remission. In addition, most of these patients must eventually undergo surgery at a later stage.

Recommendations

Patients with symptomatic enteroenteric fistulas should undergo early surgery prior to biologic agent therapy, but after optimization of nutritional status (weak recommendation, low quality evidence).

Early surgery should be discussed in patients with asymptomatic enteroenteric fistulas as it may be cost effective and provide patients with long-term disease remission, but this should be discussed on a case by case basis (weak recommendation, low quality evidence).

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Management of Enterovesical Fistula

24

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Introduction

Crohn's disease (CD) is an idiopathic chronic inflammatory condition affecting the gastrointestinal tract anywhere from the mouth to the anus and is characterized by transmural inflammation that leads to penetrating complications [1–3]. As a result, about one-third of Crohn's disease patients have internal fistulas over the course of their life [4]. Fistulas are abnormal communications between two epithelial surfaces, and patients with Crohn's disease may suffer from different types of fistulas: anorectal, enterovesical or colovesical, enterovaginal or rectovaginal, enteroenteric or enterocolic, and enterocutaneous fistulas, to name a few [5]. Entero-urinary fistulas are a relatively uncommon, yet challenging, complication of Crohn's disease. Our understanding of fistulas to the urinary tract is incomplete, and strategies to manage these fistulas remain somewhat controversial. Epidemiological data on entero-urinary fistulas are contradictory, with published studies reporting highly variable incidence rates, ranging from 1.7% to 7.7% [6, 7]. Entero-urinary fistulas are most commonly diagnosed based on clinical symptoms, although diagnostic tests such as cystoscopy (Fig. 24.1), computerized tomography (CT) scan, magnetic resonance imaging (MRI), upper gastrointestinal contrast studies with small bowel follow-through, barium enema, and colonoscopy are often necessary to confirm the fistula. At present, there is no uniform agreement on the optimal diagnostic algorithm, although certain principles remain.

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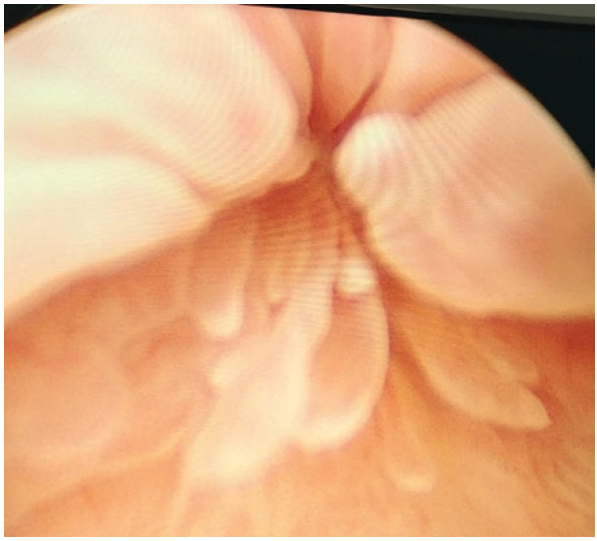

Fig. 24.1 Enterovesical fistula seen on cystoscopy

The optimal management and treatment of entero-urinary fistulas is also under debate. In the case of the enterovesical fistula in a patient with Crohn's disease, surgery is a safe and effective treatment and is the treatment of choice for many people [8, 9]. On the other hand, although the success of medical treatment for entero-urinary fistulas in Crohn's disease has so far been modest, some authors consider medical therapy the first choice [10]. In this review, we will discuss the management of enterovesical fistulas in patients with Crohn's disease.

Search Strategy

A comprehensive literature search of Cochrane Database of Collected Research, EMBASE, MEDLINE, and PubMed was performed to identify all the English-language publications related to management of Crohn's patients with enterovesical fistula and outcomes from 1932 to 2018. Relevant PICO (Population, Intervention, Comparator, Outcome) questions were generated (Table 24.1) based on this review. Key search terms included the following: "Crohn's disease," "inflammatory bowel disease," "entero-vesical fistula," "colo-vesical fistula," "surgical management," "medical management," "biologics," "timing of treatment," "creation of stoma," "morbidity," "mortality," and "fistula recurrence." Only the most recent study was included if similar studies from the same institution were encountered. The references of the included studies were reviewed to identify additional studies that were incorporated as appropriate. We also searched the reference section of each relevant article to identify additional articles pertaining to this topic. Retrospective and prospective, observational and randomized studies were included.

Table 24.1 PICO questions

P (Patients)	I (Intervention)	C (Comparator)	O (Outcomes)
Crohn's patients with enterovesical fistula	Biologics	Surgery	Morbidity, mortality, recurrence, timing (regarding biologics), and stoma rate

Results

The medical treatment of Crohn's disease has rapidly evolved since the introduction of biological anti-TNF agents such as infliximab and adalimumab [11, 12], which have at least some degree of demonstrated efficacy in the treatment of fistulizing Crohn's disease [13]. At present, there is no consensus regarding the appropriate management of enterovesical fistulas in Crohn's disease. Presentation of these fistulas varies widely, ranging from a radiologically identified occult fistula to frank feces passed per urethra, which directs the management strategy. Overall, the evidence available in the literature on the treatment of enterovesical fistulas is limited, without sufficient prospective studies and randomized controlled trials specifically reporting on the management of enterovesical fistulas. The number of patients with enterovesical fistulas reported by the included studies was low. To date, there are no randomized controlled trials reporting on enterovesical fistulas alone, and may be related in part to the relative low incidence of these types of fistulas [14].

In three medically-themed articles reporting on 11 enterovesical fistulas, in which anti-TNF treatment was the principal therapy, 5 of 11 enterovesical fistulas completely responded to treatment (45%), 4 of 11 exhibited a partial response (36%), and 2 of 11 fistulas did not respond to therapy (18%) [15–17] (Table 24.2). In addition, two articles reported on various medical treatments including anti-TNF agent therapy in 4 enterovesical fistulas [18–20]. Anti-TNF therapy alone or used concomitantly with medications such as antibiotics, sulfasalazine, and immunosuppressants, was used to treat enterovesical fistulas in 5 studies [15–19], for a total of 14 fistulas, in which 8 exhibited a complete response to treatment (57%), 5 a partial response (35%), and 1 fistula did not respond to treatment (7%). Response rates of enterovesical fistulas to medical therapy and to anti-TNF agent therapy were much higher than expected. As the majority of enterovesical fistulas included were from surgically-based articles, they may represent a subgroup of patients who do not accurately reflect the entire enterovesical fistula population due to referral bias.

Studies reporting on anti-TNF agent therapy in enterovesical fistulas were of lower quality and reported on a smaller group of patients [15–20]. A recent retrospective study by Zhang [18] contradicts some older studies, by stating that medical therapy alone is the best practice in patients suffering from enterovesical fistula. They suggest that a "step-up" model of treatment may be recommended, where patients are medically treated using combination therapy that includes anti-TNF agent, immunosuppressant, and antibiotics. Although up to 40% complete remission rates have been reported following infliximab and non-surgical management for Crohn's

Table 24.2 Studies evaluating perioperative anti-TNF use vs. surgical management in patients with Crohn's disease complicated with enterovesical fistula

First author (year)	Patients studied	Intervention	Study design	N	Outcome	Quality of evidence
Yamamoto [20] (2000)	Patients w/ CD c/w EVF	Medical vs surgical tx	Retrospective	30	25 pts required surgery with two recurrences later	Low
Afzal [15] (2009)	Pediatric pts. w/ Crohn's disease	Infliximab infusion	Retrospective	5/62	Three of five children healed and closed their fistulas after treatment	Low
Parsi [16] (2004)	Patients w/ fistulous Crohn's disease	Infliximab infusion	Retrospective	2/62	Both patients had partial response	Low
Teitelbaum [17] (2007)	Pediatric pts. w/ Crohn's disease c/w EVF	Infliximab infusion	Retrospective	5	Out of 5 pts, EVF was closed in one pt	Low
Zhang [18] (2014)	Patients w/ CD c/w EVF	Medical tx (including infliximab, or combination)	Retrospective	37	13/37 (35.1%) patients achieved long-term remission over a mean period of 4.7 years and avoided surgery	Moderate
Triantafillidis [19] (2006)	Patients w/ CD c/w ileovesical fistula	Medical and surgical tx	Retrospective	5	All patients were operated eventually	Low
Taxonera [21] (2016)	Patients w/ CD c/w ileovesical fistula	Medical and surgical tx	Multicentric-retrospective	97	More than 80% of patients required surgery. Anti-TNF may induce long-term fistula remission in selected pts	Moderate

Table 24.2 (continued)

First author (year)	Patients studied	Intervention	Study design	N	Outcome	Quality of evidence
Kobayashi [22] (2017)	Patients w/ CD c/w internal fistula	Medical and surgical tx	Multicentric-retrospective	16/93	Cumulative surgery rate was 47.2%, and fistula closure rate was 27.0% at 5 years from the induction of anti-TNF agents	Moderate

Tx treatment, *Pt* patient(s), *c/w* consistent with, *EVF* enterovesical fistula, *TNF* tumor necrosis factor, *CD* Crohn's disease, *w/* with

disease-associated enterovesical fistulas in adults, the success rate has generally been low for nonoperative treatment [17]. In non-responders and in recurring enterovesical fistulas, or if other surgical indications are present (e.g., concomitant symptomatic fistula, obstruction, sepsis), patients should undergo surgical treatment.

In a recent multicenter retrospective study, 6081 Crohn's disease patients were screened, of whom 97 had entero-urinary fistulas (rate: 1.6%). After a median follow-up of 91 months, 96% of patients were in sustained remission. Thirty-three patients (35%) received anti-TNF agent therapy. Of these, 45% achieved sustained remission (median follow-up: 35 months) without needing surgery. Overall, more than 80% of patients eventually required surgery, which induced remission (median follow-up: 101 months) in 99% of them. Only the use of anti-TNF agents was associated with an increased rate of remission without need for surgery (hazard ratio 0.23, 95% confidence interval 0.12–0.44; $p < 0.001$) [21]. In another multicenter retrospective cohort study, a total of 93 Crohn's disease cases were included with a mean follow-up period of 1453 days. Fistula locations were entero-enteric/colonic (77%), enterovesical (17%), or enterovaginal (5%). The cumulative surgery rate was 47%, and the fistula closure rate was 27% at 5 years from the time of induction with anti-TNF agents [22].

Recommendations

The number of patients with enterovesical fistulas reported in the literature to have received successful medical therapy is low. A multidisciplinary, multimodal approach is required to treat these patients and ultimately to improve the management of enterovesical fistulas in Crohn's disease. Medical therapy, alone or in combination with surgery, appears to benefit some patients with enterovesical fistulas. However, given the small size and low quality of the published studies, it is still difficult to draw conclusions regarding treatment. Further, most medically treated patients will either fail to respond or recur, leading to recommendations for other approaches.

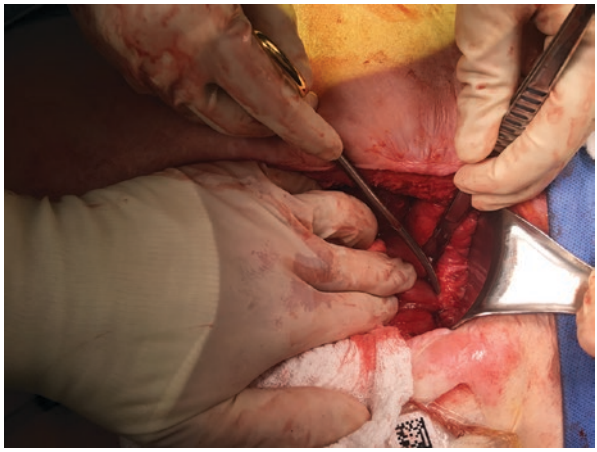

Fig. 24.2 EVF seen at the time of the operation in a patient with Crohn's disease. Scissors pointing to the EVF from the small bowel to the dome of the bladder

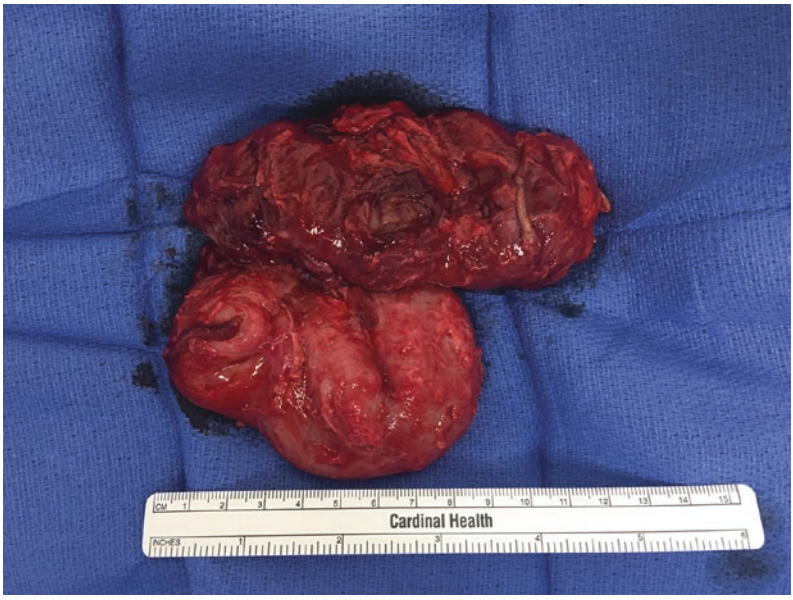

Fig. 24.3 Gross image of the resected segment of small bowel causing an EVF in a patient with Crohn's disease

Based on limited retrospective studies focusing on enterovesical fistulas in patients with Crohn's disease, it appears that many patients initially or eventually undergo surgery for treatment of their fistula (Figs. 24.2 and 24.3). While some smaller studies have shown success with medical treatment alone, particularly in the

pediatric population, a combination of medical and surgical therapy is the most effective approach to keep remission rates low [21]. Only the use of anti-TNF agents had an increased rate of remission without needing surgery, although many of these patients eventually did receive surgery to maintain remission.

More high-quality research is needed to better understand which populations would benefit the most from medical therapy alone.

Personal View

There is a paucity of literature that studies remission rates in patients with medical therapy alone, as many of these patients eventually undergo an operation. In our view, surgery is the recommended treatment for symptomatic enterovesical fistulas. Medical therapy may be an option for patients who are nontoxic and minimally symptomatic. However, many patients who are medically managed often require surgical treatment for sustained remission.

Surgical treatment is the treatment of choice for patients with Crohn's disease-induced enterovesical fistulas. Medical treatment with anti-TNF agents can be reserved for patient populations who cannot undergo surgery (*strong recommendation, evidence quality low).*

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Preventing Postoperative Crohn's Disease Recurrence

25

Erica R. Cohen and Gil Y. Melmed

Although the advent of novel medical therapies has broadened the management options for Crohn's disease, many patients still undergo surgical resection [1, 2]. Management of postoperative Crohn's disease poses a difficult dilemma as disease recurrence is often clinically silent yet progressive and can lead to future complications requiring additional surgery. Off medical therapy, endoscopic disease recurrence approaches 90% at one year and symptomatic recurrence may reach 60% at 3 years [3]. One-half of these patients will require additional surgery within 10 years [4]. The goal of postoperative Crohn's disease management is to prevent clinical recurrence and additional surgical resections. Evaluating the anastomosis and preanastomotic ileum for mucosal healing has emerged as the primary measure of success for postoperative medical treatment and a reliable tool to predict surgical recurrence. The Rutgeerts endoscopic ileal score (i0 to i4) is commonly used to grade recurrence after ileocecal resection and a score of (i2 or greater) in this setting is defined as endoscopic recurrence [5].

When to initiate therapy and which medication to recommend remain important clinical dilemmas. Clinicians should be able to risk-stratify a patient for disease recurrence to determine if and when to initiate medical therapy. A patient's preferences, prior medication history, and disease-related factors should be used to determine the optimal postoperative management for each patient.

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PICO table

P (Patients)	I (Intervention)	C (Comparator)	Outcomes
CD after an ileocecectomy	Empiric medical therapy (within 8 weeks of surgery)	Therapy initiated based on endoscopic findings within 1 year of surgery	Difference in recurrence (both endoscopic and surgical) after surgery
CD patients after an ileocecectomy, treated with early medical therapy empirically (within 8 weeks of surgery)	5-ASA Probiotics Elemental diet Budesonide Thiopurines Antibiotics Anti-TNF Anti-Integrins	Various comparators	Reduction difference in recurrence (both endoscopic and surgical) after surgery

Search Strategy

Relevant PICO (Population, Intervention, Comparator, Outcome) questions were generated (Table 25.1). Medline and PubMed searches were conducted for publications in the English language between January 1952 and May 2018 using the following search terms: "Crohn's disease OR Crohns OR Crohn's," AND "surgery OR surgical OR colorectal, OR postoperative OR post-operative" AND "ileocecum, OR ileocecectomy OR resection OR anastomosis," AND "Colonoscopy OR disease monitoring OR endoscopy OR remission, OR recurrence" AND "pharmacological OR prophylaxis OR medical therapy," AND "natural history," OR "disease course," AND: "mesalamine" OR "budesonide" OR "probiotic" OR "antibiotic" OR "thiopurine" OR "anti-tumor necrosis factor," OR "vedolizumab" Retrospective and prospective, observational and randomized studies were reviewed.

Results

Strong evidence suggests that all patients status post ileocolonic resection with ileocolonic anastomosis should undergo endoscopic evaluation of the anastomosis 6 to12 months later to assess for disease recurrence [6]. However, only one randomized controlled trial exists that aimed to define the benefit of routine early postoperative

Table 25.1 Risk factors for postoperative recurrence of Crohn's disease

	Low-risk	High-risk
Patient characteristics	Nonsmoker	Smoker
Clinical characteristics	Older patient (>50 years) First surgery Short segment of disease (<20 cm) Disease duration >10 years	Younger patient (<30 years) ≥ 2 prior surgeries Penetrating disease type Perianal disease Short disease duration

pharmacological prophylaxis (within 8 weeks) over endoscopic guided therapy initiation (6–12 months) for the prevention of long-term disease recurrence [7]. In that trial, patients were randomized to weight-based azathioprine either routinely within two weeks of surgery (n = 32) or only in the presence of disease recurrence found on endoscopy at 6–12 months (n = 31). Rates of endoscopic remission 102 weeks after surgery were 50% in the empirically-treated group and 58% in the endoscopy-driven azathioprine group (p = 0.521). Fourteen patients in the endoscopically-driven group required azathioprine initiation at the time of first endoscopy. No patients required repeat surgical intervention during the study period.

This study was rated as very low quality of evidence due to high risk for bias, and there were baseline differences in prognostic factors for disease recurrence such as higher rates of smoking in the early prophylaxis group (53% versus 29%), high attrition rate (33%) and early termination of the study due to low recruitment (63 of 200 randomized). Lastly, the use of an immunomodulator rather than a more effective biologic agent for early therapy may limit differences seen between these groups.

Several risk factors have been identified that impact the likelihood of postoperative recurrence [6, 8–11] and should be assessed when considering early empiric therapy (Table 25.1). Tobacco smoking is the only patient-related modifiable risk factor [12]. Several surgery-specific risk factors have been evaluated but none were related to risk for disease recurrence including type of anastomosis and surgical margins [13–15]. One retrospective study comparing side-to-side versus end-to-end anastomoses found that those undergoing an end-to-end anastomosis experienced improved functional status, quality of life, and lower healthcare utilization than those with a side-to-side anastomosis over a 2-year postoperative period [16]. Risk stratification is recommended to guide the postoperative management strategy. Patients considered "low-risk" for recurrence can likely await endoscopic evaluation 6 to 12 months after surgery to determine the need to initiate medical therapy. Those deemed "high-risk" should consider initiation of empiric, prophylactic medical therapy shortly after surgery.

Once the decision is made to start early postoperative pharmacological prophylaxis, the question then focuses on the comparative effectiveness of the variety of medications within the therapeutic armamentarium. Several trials have examined the effect of early postoperative pharmacological prophylaxis compared to placebo (Table 25.2).

Table 25.2 Trials of Endoscopic Recurrence Rates within 1 year

Intervention	Endoscopic recurrence rates (%)	Follow up (months)	Quality of evidence
Placebo	51–81	3–12 months	n/a
Elemental diet (+ASA) [17]	30	12 months	Very low
Probiotics [18, 19]	49–60	6 months	Very low
Mesalamine [20–22]	33–63	12 months	Very low
Antibiotics (Ciprofloxacin, Metronidazole, Nitronidazole) [23–25]	52–65	3–12 months	Low
Budesonide [26, 27]	32–57	12 months	Very low

There does not appear to be a benefit with the use of 5-aminosalicylastes, probiotics, or budesonide in preventing endoscopic disease recurrence. Rates of recurrence with these agents are comparable with placebo-treated patients across the various trials. The quality of this evidence is very low based on imprecision, inconsistency, and concern for publication bias. Further, there is significant heterogeneity in the studies regarding formulations and dosing between trials. Enteral nutrition is a compelling therapy for patients since there is no risk of immunosuppression. One small study (n = 40) found a significant difference in endoscopic recurrence with enteral nutrition plus mesalamine versus mesalamine alone at 12 months (30% versus 70%). However, a follow-up study noted similar surgical reoperation rates between the two groups [28]. This study is limited by a small sample size with marked attrition, bias, and the failure to test complete enteral nutrition as the subjects were allowed low-fat diets. Additional studies are needed to determine the benefit of elemental diet in this setting.

While antibiotic therapy may reduce recurrence rates, anti-tumor necrosis factor (TNF) alpha monoclonal antibody and thiopurine monotherapy yield the most significant reductions in disease recurrence versus placebo. Multiple randomized controlled studies have evaluated the efficacy of immunomodulators and biologic therapies in this setting. In the PREVENT trial, Regueiro compared the efficacy of infliximab to placebo in the prevention of Crohn's disease recurrence at 76 weeks. For inclusion, subjects needed at least one high-risk disease feature for disease recurrence (Table 25.3). Endoscopic recurrence rates were significantly lower in patients receiving infliximab compared to placebo (22% versus 51%; $p < 0.001$).

Table 25.3 Trials of Initiation of Early Postoperative therapy with Immunomodulator or Biologics

Medical Strategy	Study Design	Comparator	Endoscopic Recurrence	Quality of Evidence
Immunomodulator				
D'Haens [29]	Randomized Controlled	AZA + metronidazole or metronidazole alone	55.0% vs 78% (12 months)	Moderate
Hanauer [21]	Randomized Controlled	6-MP 50 mg or 5-ASA 3 g or placebo	43% vs 63% vs 64% (24 months)	Moderate
Anti-Tumor Necrosis Factor				
Regueiro [30]	Randomized Controlled	Infliximab 5 mg/kg or placebo	9.1% vs 84% (12 months)	High
Regueiro [31] (PREVENT)	Randomized Controlled	Infliximab 5 mg/kg or placebo	30.6% vs 60.0% (18 months)	High
Savarino [32]	Randomized Controlled	Adalimumab or AZA 2 mg/kg/d (6-MP 1.5 mg/kg/d) or 5-ASA	6.3 vs 64.7 vs 83.3 (24 months)	Moderate
De Cruz [33] (POCER)	Subgroup analysis	ADA vs Thiopurine	21% vs 45%(6 months)	High
Anti-Integrin Inhibitor				
Yamada [34]	Retrospective	Vedolizumab vs anti-TNF	75% vs 34% (6-12 months)	Low

Those with more than one resection and preoperatively treated with anti-TNF agents were at higher risk for clinical recurrence. Overall, clinical recurrence was numerically lower in the treatment group compared to placebo but this did not reach statistical significance (13% versus 20%; p = 0.097).

The POCER trial assessed the utility of a 6-month postoperative colonoscopy with treatment escalation as indicated by findings at the time of that colonoscopy. All patients postoperatively received metronidazole. If they were deemed to be at high risk for recurrence (83% of cohort), they also received a thiopurine, or adalimumab if intolerant to thiopurines, shortly after surgery. Patients were randomly assigned to undergo colonoscopy at 6 months with treatment escalation or optimization as needed versus no colonoscopy. At 18-month follow-up, patients who underwent a 6-month colonoscopy had significantly lower endoscopic recurrence rates compared to those that did not (43% versus 67%; p = 0.003). A subgroup analysis among high-risk active care patients found that endoscopic recurrence rates at 6 months were lower in those patients receiving adalimumab versus thiopurines (21% versus 45%).

One retrospective trial comparing vedolizumab with anti-TNF agents for postoperative recurrence showed that rates of endoscopic remission at 6 to 12 months were significantly lower in the vedolizumab group compared to the anti-TNF group [34]. Vedolizumab was the only factor associated with increased endoscopic recurrence on univariate (OR 5.58, 95% CI 1.51-24.3; p = 0.005) and multivariate (OR 5.77. 95% CI 1.71-19.4; p = 0.005) analysis. Limitations of the study include its retrospective design, small sample size, and lack of endoscopic data for nearly one-third of patients. Prospective postoperative vedolizumab trials are currently underway.

Recommendations Based on the Data

All patients who have undergone surgically induced remission of Crohn's disease should undergo postoperative endoscopic surveillance at 6 to 12 months. The data suggests a benefit of early pharmacological prophylaxis over endoscopy-guided pharmacological treatment, particularly in those who are at moderate- to high-risk for disease recurrence. The use of mesalamine, budesonide, or probiotics is not recommended to prevent endoscopic recurrence. Anti-TNF agent therapy and thiopurines are currently first-line agents for early pharmacologic prophylaxis based on moderate to high quality of evidence. Nitromidazole antibiotics are likely inferior to both thiopurines and anti-TNF agents but may be considered as second-line alternative agents for patients concerned about the cost or safety of biologic medications. Subsequent colonoscopy at 6 to 12 months should be used to reassess the anastomosis and determine the need to continue or change the current management.

Personal View

Surgically induced remission of Crohn's disease represents an opportunity to prevent Crohn's disease recurrence, rather than to treat active Crohn's disease. On the other hand, patients frequently perceive a clinical "clean slate" which can lead

to reservations about initiating new therapies or even complying with active surveillance. It is during this period that shared decision making is paramount. An individual's patient- and disease-specific risk factors should be assessed before surgery to determine their risk of disease recurrence. Currently, no validated risk-assessment tool exists to guide that discussion. Patients should be counseled that tobacco smoking increases endoscopic and clinical recurrence rates, with a 2.5-fold increased risk for another surgery. Patients with penetrating or fistulizing disease and those who have had prior surgeries are at highest risk of recurrence. These insights aid the clinician in weighing the benefits and risks of early initiated therapy while also considering the patient's personal preferences.

For low-risk patients, it is reasonable to await endoscopic evaluation 6 to12 months after surgery in order to determine the need for medical treatment. If there is evidence of disease recurrence (Rutgeerts score i2 or higher) it is appropriate to start medical therapy. Moderate-risk patients may land between the low- and high-risk categories delineated in the literature. This may include patients with a longer segment of disease or a shorter disease duration. If the patient puts a higher value on prevention of disease recurrence and a lower value of the small risk of medication-related adverse effects, a prophylactic agent should be initiated. Current guidelines recommend that high-risk patients receive early pharmacologic prophylaxis, within 8 weeks of surgery.

The best agent for early prophylactic therapy remains unknown and is likely impacted by several patient- and disease-related factors. It is not recommended to use mesalamine, budesonide, or probiotics for prevention of disease recurrence. Antibiotics, specifically metronidazole and ornidazole, may be of some benefit but have significant side-effects with long-term use. Almost one-half of patients on postoperative thiopurines will have recurrence within one year and many patients are intolerant of the medication. To date, the most efficacious medication to prevent endoscopic recurrence is anti-TNF therapy. There are no studies comparing anti-TNF agent monotherapy to dual anti-TNF agent and immunomodulator therapy. Likewise, we are awaiting prospective studies evaluating anti-integrin inhibitors and anti-IL12/23 inhibitor in this setting.

We employ a shared decision-making process with patients who are at moderate- to high-risk for disease recurrence to weigh the risk of medical prophylaxis versus the risk of disease recurrence. We recommend consideration of a postoperative antibiotic, thiopurine, or biologic agent for moderate-risk patients depending on patient preference and prior history. For patients at high-risk for recurrence, we recommend starting a biologic, with or without an immunomodulator, or for those going in to surgery already on a biologic, to consider an alternative agent or optimized dose. Specific disease characteristics, disease location, and prior medication responses should be assessed to determine the appropriate biologic agent and need for thiopurine use. Subsequent endoscopic surveillance should be used to either optimize a biologic agent or switch to another medication.

The prevention of postoperative Crohn's disease recurrence is a dynamic process that relies on risk stratification, frequent monitoring, and the incorporation of patients' preferences to prevent repeat surgery. Regardless of the treatment strategy, proactive

endoscopic surveillance is critical to identify endoscopic recurrence and proactively alter the treatment course. As newer therapies for Crohn's disease emerge, additional comparative effectiveness trials are needed to guide management algorithms.

Abstracted Recommendations

1. Patients who have undergone a surgically induced remission should undergo postoperative endoscopic surveillance at 6 to 12 months over no monitoring (moderate to high quality of evidence, strong recommendation).
2. There may be a benefit to early pharmacological prophylaxis over endoscopy-guided pharmacological treatment, particularly in patients at moderate- to high-risk for disease recurrence (moderate quality of evidence, conditional recommendation).
3. It is not recommended to use mesalamine, budesonide, or probiotics to prevent endoscopic recurrence (very low quality of evidence, conditional recommendation).
4. Anti-tumor necrosis factor therapy and thiopurines are currently the first-line agents for early pharmacologic prophylaxis (moderate quality of evidence, strong recommendation).

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Role of Minimally Invasive Reoperative Surgery

26

Nuha A. Yassin and Antonino Spinelli

Introduction

The recurrence of Crohn's disease (CD) after surgery is one of the most crucial challenges in the management of this disease [1]. Approximately 50% of patients undergoing an operation for Crohn's disease are likely to need further surgeries within 10–15 years. Relapse of the symptoms and recurrence of the disease within the first 5 years after surgical resections may occur in 30–50% of patients. The chances of recurrence may increase to 50% to 80% within 10 years from the primary resection [1–4].

Minimally invasive surgery, in combination with enhanced recovery programs, offers several advantages compared to conventional open surgery. Patients experience less morbidity, better cosmesis, and reduced lengths of hospital stay. Laparoscopic surgery is currently considered the approach of choice for primary ileocolic Crohn's disease. The benefits have been shown to be an overall reduction in short- and long-term morbidity and mortality, improved quality of life scores, and equivalent recurrence rates. Those data are nevertheless predominantly obtained from Crohn's disease patients undergoing primary resection.

A recent consensus statement by the European Crohn's and Colitis Organisation (ECCO) in conjunction with the European Society of Coloproctology (ESCP) has highlighted the fact that laparoscopic surgery should be the chosen approach for primary ileocolic resection in patients with Crohn's disease, and should be

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performed for recurrent disease when the expertise is available [5–7]. While there is wide consensus for approaching primary ileocolic Crohn's disease with laparoscopy, the adoption of minimally invasive techniques for recurrent Crohn's disease is less common and an object of debate. In this chapter, the literature pertaining to the use of minimally invasive surgery for recurrent ileocolic Crohn's disease is reviewed and followed by our personal views and practice on this subject.

Search Strategy

The published literature was searched through PubMed (January 1966 to July 2018), the Cochrane Database, and EMBASE (January 1947 to July 2018). The MeSH terms used in the search were: Crohn Disease, Crohn's Disease, complex, recurrent, surgery, colorectal surgery, conventional, reoperation, laparoscopy, laparoscopic, open and minimally invasive. A combination of the search terms as well as the search engine operators was employed to ensure comprehensive and full capture of all relevant literature. Searches were limited to human adult studies published in the English language. The abstracts of all potentially relevant studies were consulted to identify studies suitable for inclusion. Studies were excluded if they did not meet the PICO (population, intervention, comparator and outcomes) inclusion criteria set for this search (see Table 26.1). Articles were excluded if they did not focus on surgery for Crohn's disease; focused only on open surgery; focused on only primary surgery for Crohn's disease; focused on all surgery for Crohn's disease with no mention of re-do ileocolic resection; failed to mention post-operative complications or length of in-hospital post-operative stay. The full-texts of all eligible articles were retrieved. Additional search strategies included searching the cited references of selected articles.

Results

Although several publications in the literature describe the use of a minimally invasive approach in the form of laparoscopic surgery for primary ileocolic Crohn's disease [5, 8, 9], data are sparse when it comes to studies focusing in recurrent disease. Very few studies compare laparoscopic surgery for recurrent disease to the conventional open approach, with most studies reporting on the feasibility and outcomes of laparoscopic surgery for recurrent ileocolic disease either as the primary aim or as part of sub-group analyses. Table 26.2 highlights the studies investigating surgery for recurrent ileocolic disease.

Table 26.1 PICO criteria for the literature search strategy and study design

P (Patient Population)	I (Intervention)	C (Comparator)	O (Outcomes Studied)
Crohn's patients requiring re-operative ileocolic resection	Laparoscopic surgery	Open surgery	Post-op complications [8], length of stay

Table 26.2 Studies evaluating laparoscopic surgery for recurrent Crohn's disease

Study	Patient population: recurrent CD (N)	Intervention	Comparator	Study design	Outcomes	Quality of evidence
Wu et al. (1997) [10]	N = 10	VLS	Open surgery (n = 70)	R	*LOS* 3.9 days *Conversion to open* 20% *Morbidity* 10%	Low
Hasegawa et al. (2003) [11]	N = 16	VLS	VLS (n = 52) for primary CD	R	*LOS* (median, range) days 8 (6–14) *Conversion to open* 12.5% *Complications*: (SSI):18.7%	Low
Moorthy et al. (2004) [12]	N = 26	VLS	VLS (n = 57) for primary CD	R	*LOS* (median, range) days 8 (4–47) *Conversion to open* 42.3% (higher after previous open surgery) *Complications* 15%	Low
Uchikoshi et al. (2004) [13]	N = 43	VLS (n = 17) HALS (n = 6)	Open surgery (n = 20) for recurrent CD	R	*LOS* (median, range) days ($p < 0.01$) Open: 42.5 (21–90) VLS: 22.4 (11–34) HALS: 16.4 (9–24) *Complications* (SSI) Open 5 (25%) VLS 3 (18%) HALS 0 *Conversion* 43.4% (VLS)	Low
Lawes et al. (2006) [14]	N = 55	VLS (n = 15) for recurrent CD after primary VLS	VLS (n = 40) for recurrent CD after primary open surgery	R	*LOS* (median, range) days 4·5 (3–13) *Conversion*: 0% if primary VLS; 17.5% if primary open *Complications* p = 1.000	Low

(continued)

Table 26.2 (continued)

Study	Patient population: recurrent CD (N)	Intervention	Comparator	Study design	Outcomes	Quality of evidence
Edden et al. (2008) [15]	N = 34 (31 secondary, 3 tertiary resection)	VLS	VLS for primary CD (n = 133)	R	*LOS* 5.9 days 7.4 days for converted to open ($p<0.05$) *Conversion to open* 61% in recurrence CD *Complications* = no statistically significant difference between redo and primary VLS	Low
Brouquet et al. (2010) [16]	N = 29	VLS	Open (n = 33)	R	*LOS* (median, range) days VLS = 9 (6–63) Open = 9 (6–44) *Conversion* 31% Complications VLS = 38% Open = 30%	Low
Holubar et al. (2010) [23]	N = 40	VLS	VLS converted (n = 10)	R	*LOS* (median, range) days ($p = 0.002$) VLS = 4 (3–10) Converted 7 (5–11) *Conversion* = 25% *Complications* VLS = 10% Converted = 30%	Low

Chaudhary et al. (2011) [24]	N = 30	VLS	VLS for primary CD (n = 29)	P	*LOS* (median, range) days Recurrent 3 (1–7) Primary 3 (1–21) *Conversion* Recurrent 6.6% Primary 10.3% Complications Recurrent 17% Primary 24%	Low
Pinto et al. (2011) [25]	N = 50	VLS	VLS for primary CD (n = 80)	R	*LOS* (mean, SD) days Recurrent 7.4 ± 4.3 Primary 6.7 + 3.8 *Conversion* Recurrent 32% Primary 18.7% *Complications* Recurrent 40% (severe 12%) Primary 36.2% (severe 12.5%)	Low
Bandyopadhyay et al. (2011) [26]	N = 27	VLS	No comparator	R	*LOS* (median, range) days 4 (2–7) *Conversion* 7.4% *Morbidity* 7.4%	Low
Huang et al. (2012) [19]	N = 48	VLS	VLS for primary CD (n = 82)	R	*LOS*—unstated *Conversion* Recurrence 20.8% Primary 17.1% Complications Recurrence 27.1% Primary 15.9%	Low

(continued)

Table 26.2 (continued)

Study	Patient population: recurrent CD (N)	Intervention	Comparator	Study design	Outcomes	Quality of evidence
Aytac et al. (2012) [18]	N = 26	VLS	Open (matched, n = 26)	R	*LOS* (mean, SD) days VLS 6.4 ± 6.2 Open 6.9 ± 3.5 *Conversion* 11.5% Complications VLS 38.4% Open 69.2%	Low
Moftah et al. (2014) [20]	N = 10	SPLS	No comparator	R	*LOS* (median, range) days 6 (3–33) *Conversion* 33% Complications83.3%	Low
Leo et al. (2017) [21]	N = 18	SPLS	SPLS for primary CD (n = 27)	P	*LOS* (median, range) days Recurrent 7 (5–14) Primary 6 (3–28) *Conversion* Recurrent 0.3% Primary 0.3% *Complications* Recurrent 11% Primary11%	Low

Panteleimonitis et al. (2017) [27]	N = 19	VLS	VLS for primary CD (n = 87)	P	*LOS* (median, range) days Recurrent 5 (4.2–7.7) Primary 4 (3–6) *Conversion* Recurrent 5.3% Primary 4.6% *30-day readmission rate*: Recurrent 26.3% Primary 14.9% *30-day reoperation rate* Recurrent 0% Primary 6.9% *Anastomotic leak rate* Recurrent 0% Primary 1.4%	Low
Celentano et al. (2018) [22]	N = 29 (recurrent CD and history of 2 or more previous laparotomies)	VLS	Primary and no previous surgery (n = 90)	P	*LOS* (median, range) days Recurrent 6 (2–49) Primary 5.5 (2–22) *Conversion* Recurrent 3.4% Primary 4.44% Complications Recurrent 24.1% Primary 25.5% *Readmissions* Recurrent 17.2% Primary 17.2% *Reoperations* Recurrent 3.4% Primary 5.5%	Low

CD Crohn Disease, *VLS* video-laparoscopic surgery, *SPLS* single port laparoscopic surgery, *HALS* hand-assisted laparoscopic surgery, *LOS* length of stay
R retrospective; *P* prospective

Initial studies date back to 1997 when Wu reported on 116 patients undergoing laparoscopic and open surgery for primary as well as recurrent Crohn's disease. Ten patients underwent laparoscopic surgery for recurrent ileocolic disease with a conversion rate of 20% to the open approach [10].

Following that initial experience, several studies have continued to show that laparoscopic surgery for recurrent Crohn's disease is both feasible and safe. Specifically, morbidity rates were comparable between primary and recurrent laparoscopic resections and most studies did not report an increased conversion rate. When conversion to the open approach did occur, it was typically associated with the complexity of the disease, with rates widely ranging from 0% to 31% [11–15].

In 2010, Brouquet [16] conducted an elegant study where two groups with recurrent Crohn's disease treated by laparoscopy or conventional open surgery were compared. Overall, 33 procedures were performed in 28 patients. The study included some patients who had previously undergone open surgery. Conversion rates were as high as 31% and abandonment of a laparoscopic approach was mainly due to intestinal injury, intraoperative findings of entero-enteric fistulas, or challenging intraperitoneal adhesions. The complication and postoperative morbidity rates were comparative between the laparoscopic and open approaches. In this study the laparoscopic approach was recommended for selected patients with recurrent Crohn's disease recurrence who had less than three previous abdominal surgeries, no previous history of peritonitis, and non-fistulizing disease.

However, it was still unclear whether previous open surgery increased the risk of conversion from a laparoscopic to open approach when surgery was required for recurrent disease [17, 18]. Huang [19] in 2012 commented on their experience with the laparoscopic management of recurrent Crohn's disease in 130 patients. Prior Crohn's disease-related abdominal surgery was recorded as well as operative times, conversion rates, and complication rates. Thirty-seven percent of the patients who were included in the study had undergone previous open abdominal surgery, which resulted in no statistically significant increase in the subsequent laparoscopic operative times, blood loss, or conversion rates. Postoperative morbidity was also comparable between the two groups. It was concluded from this study that the laparoscopic approach is safe and feasible for patients who had undergone previous open surgery, and may in fact reduce further morbidity in this group of patients, as they might require even more surgery in the future.

With improvements in the learning curves and more of this complex surgery being done in specialty centers, the data has suggested improvement in clinical and surgical outcomes.

Moftah in 2014 reported excellent outcomes using a single-port technique [20] in a series of 33 patients of which 6 were recurrent cases. In a more recent study from 2017 by Leo [21], sixteen patients underwent single-port laparoscopic surgery for recurrent Crohn's disease, 9 of whom had previous open surgery and 7 had laparoscopic surgery. The morbidity was comparable, and the conversion rate was only 0.3%.

Another recently published study iterated the safety and feasibility message about minimally invasive surgery for recurrent Crohn's disease. Celentano [22]

compared patients operated by laparoscopy for recurrent ileocolic Crohn's disease and a history of two or more previous laparotomies, with 90 patients operated for primary ileocolic Crohn's disease and no history of previous abdominal surgery. Morbidity and conversion rates were similar in the two groups, but operative time was longer in recurrent patients with a history of previous abdominal surgery.

Recommendations

Minimally invasive surgery represents a feasible and safe option for patients with recurrent ileocolic Crohn's disease leading to improved short-term outcomes. (Evidence: Low; Recommendation: Moderate).

Personal View

Minimally invasive surgery for recurrent Crohn's disease is feasible and can be safely performed by experts. Although the evidence to support such a practice still relies on cohort studies and case series, we approach most recurrent ileocolic Crohn's disease cases laparoscopically. Furthermore, we use single-port surgery [28] to access the peritoneum in a safe, open technique. In cases with massive entero-enteric adhesions where the operation may not be safely completed by laparoscopy, proceeding with open surgery is made simple by enlarging the single access site. This approach is combined with a low threshold for conversion that does not introduce additional risk or loss of time.

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Extent of Mesenteric Resection

27

Miranda G. Kiernan and J. Calvin Coffey

Introduction

Rates of surgery in Crohn's disease have remained largely unchanged [1]. Indeed, a rather substantial proportion of patients with Crohn's disease continue to require one of more operations. In addition, the proportion requiring re-operation is also significant with rates varying between 4% and 60% [2–19].

Recent clarifications of mesenteric anatomy have identified and clarified the fascial and peritoneal landscape associated with the small and large intestine [20]. In addition, data increasingly points to a pathobiological role for the mesentery in Crohn's disease [2, 21]. Mesenteric-based surgical treatment strategies have become the gold standard in colorectal surgical practice in the management of colon and rectal cancer, but not in management of Crohn's disease [22].

The conventional surgical approach in Crohn's disease is to divide the mesentery flush with the intestine [2]. Alternatively, surgeons divide the mesentery at the first level they regard as safe to divide. The result is that the mesentery is retained. This conservative approach arose mainly from concerns regarding the possibility of intraoperative hemorrhage. In Crohn's disease, the diseased mesentery is often friable and inflamed and bleeds readily on division. This means that in simple

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Table 27.1 PICO table

General IBD	Patient Population	Intervention	Comparator	Outcomes Studied
Extent of mesenteric resection	Crohn's patients requiring resectional surgery	Wide mesenteric excision	Limited mesenteric excision	Recurrence rate, post-op complications

separation of components of a phlegmon, which generally include broad areas of mesentery, bleeding can be extensive [2, 20, 21, 23–26].

Emerging data indicates that pathobiological events primarily occur along two major axes in Crohn's disease. These are the circumferential (i.e., submucosal) and radial (i.e., mesenteric) axes. Whilst disease appears to arise in these locations, spread from here ultimately involves the mucosa whilst also generating the transmural appearance characteristic of Crohn's disease. Where the radial and circumferential axes intersect, inflammation is most intense and results in ulceration. Several observations support this model. For example, mucosal ulceration always commences at the intersection of the mesentery and mucosa (i.e., where axes meet) [21, 27–32]. A detailed review of the data supporting this model is beyond the scope of this chapter, but the concept of circumferential and radial axes of pathobiology is surgically relevant and is the basis for mesenteric resection (Table 27.1).

Search Strategy

A comprehensive literature search of Cochrane Database of Collected Research, EMBASE, MEDLINE, and PubMed was performed to identify all the English-language publications related to wide and limited mesenteric resection, Crohn's disease and outcomes from 1911 to 2018. Key search terms included the following: "mesentery," "Crohn's disease," "convention", "ileocolic", "resection." The references of the included studies were reviewed to identify additional studies that were incorporated as appropriate.

Results

Only two studies were identified that compare different forms of mesenteric resection in Crohn's disease [2, 33]. These, including limitations, will be described in the following:

Our group compared conventional (mesenteric sparing) with extensive (mesentery included) mesenteric resection [2]. In the test arm, the mesentery was mobilized and detached back to the central/root region at the head of the pancreas, and the mesentery was hemostatically divided at a level that approximately corresponded to D2 resection (i.e., at the takeoff of the ileocolic vessel from the superior mesenteric artery). There was a significant reduction in the proportion of patients who progressed to require reoperation in the group in which the mesentery was

Table 27.2 Post-operative complication rates in CD patients undergoing ileocolic resection

Post-op complication/parameter	Cohort A	Cohort B	P-value
Total	19 (63%)	15 (44%)	0.124 (Chi^2 test)
Surgical site infection (including wound infection and wound breakdown/dehiscence)	14 (47%)	9 (27%)	0.093 (Chi^2 test)
Sepsis	3 (10%)	0 (0%)	0.059 (Chi^2 test)
Intra-abdominal/pelvic collection	5 (17%)	3 (9%)	0.344 (Chi^2 test)
Anastomotic leak	3 (10%)	0 (0%)	0.059 (Chi^2 test)
Death	0 (0%)	0 (0%)	N/A
Re-operation	2 (7%)	0 (0%)	0.126 (Chi^2 test)
Drainage of collection	3 (10%)	0 (0%)	0.059 (Chi^2 test)
Revision of abdominal wound	2 (7%)	0 (0%)	0.126 (Chi^2 test)
Washout	0 (0%)	1 (3%)	0.344 (Chi^2 test)

Cohort A = mesentery not included during resection (n = 30), Cohort B = mesentery included during resection (n = 34). MW-U = Mann Whitney-U test

resected. On multivariate analysis this remained significant, as did smoking status at the time of surgery and disease phenotype.

A preliminary analysis of short-term outcomes demonstrated that inclusion of the mesentery as part of the resection was at least as safe as conventional resection (see Table 27.2) and some complications trended towards being reduced in patients in which the mesentery was resected.

We applied the mesenteric-based approach in the setting of ileal disease, ileocolic disease, Crohn's colitis, and in patients requiring ileal pouch resection or proctectomy. This indicates that the approach may be used for a broad range of indications in Crohn's disease. However, the procedure was not always possible at the index procedure. To date, six patients with ileocolic disease were unsuitable for resection at the index operation. These patients underwent defunctioning ileostomy and reoperation after several months. At reoperation it was possible to resect both diseased intestine and mesentery and restore intestinal continuity in five patients. This suggests that a staged approach may be safely adopted in patients in whom extensive disease precludes safe resection at the first operation.

Our study was limited in so far as a single institute was involved, and a prospective group was compared against an historic group. Notwithstanding this, the differential between both control and test groups supports a comprehensive head to head challenge of both approaches in the setting of a randomized, multicenter, controlled, and blinded study. Several such studies are currently in progress [34, 35].

An earlier study by Ewe et al. [33] found that increased surgical radicality was associated with increased rates of surgical recurrence and they recommended that a non-radical approach be adopted in patients undergoing surgery for Crohn's disease. The follow-up was limited to 3 years. It is not possible, based on the publication, to determine the technical basis of their approach (i.e. how much mesentery was resected and how). It is also unclear as to whether the approach was standardized between units involved. Finally, surgeons adopted the conventional model of

mesenteric anatomy during that era. This model has been shown to be erroneous. The importance of mesenteric-based surgery emerged during the 1990's and mesenteric anatomy was updated in tandem. Thus it is unclear as to how radical Ewe *et al.* were in terms of the mesenteric component of their resection.

Recommendations

The findings regarding inclusion of the mesentery as part of a resection in ileocolic Crohn's disease should be considered as preliminary.

They require further investigation in the setting of trials as discussed above. In view of our findings we continue to include the mesentery, where safe to do so, in ileocolic disease and in Crohn's colitis. In the absence of data other than that from our institute, we make the following recommendations if one is including the mesentery as part of the resection in Crohn's disease.

The intestine and mesentery should be detached (but not disconnected) along planes established during embryological development. This should be conducted as far proximally as the head of the pancreas to allow hemostatic division of the mesentery and provide unimpeded access to the mesentery should difficulties with hemostasis arise.

Placement of the proximal intestinal division should be guided by mesenteric rather than intestinal manifestations of disease. The mesenteric transition zone (see below) should be identified and the proximal intestinal division made immediately proximal to this. The distal intestinal and mesenteric margin should be placed at the first level at which both are found to be normal.

The mesentery is best divided between Kocher clamps, and suture ligated by creating an overlapping series of ligature loops using a heavy (0.0) suture. Overlapping suture loops ensures that all mesentery is included in the ligation (i.e., with no gaps in mesentery outside the ligature that could bleed or ooze after).

During mesenteric division it is important not to directly encroach on the central region of the mesentery that contains the superior mesenteric artery and vein because damage to either is potentially fatal. If there is a phlegmon and the components of this cannot be separated without extensive hemorrhage, then resection should be abandoned. It is unlikely that a Kono-S strictureplasty will be possible in this setting. Options at that point include defunctioning loop ileostomy (with a staged resection at a later point) or bypass. Our experience (albeit in a limited cohort) is that following loop ileostomy formation, resection with restoration of intestinal continuity usually becomes possible at a later stage.

Personal View

Mesenteric-based surgical strategies in Crohn's disease require further exploration. As part of this it has been suggested that they be introduced early in the treatment paradigm of Crohn's disease, and not just reserved for when complications arise, or when symptoms are refractory to medical treatment [36].

If a surgeon is to conduct a mesenteric resection it is important to fully mobilize the mesentery back to the central region at the level of the pancreas. This mobilizes the mesentery enough to provide unimpeded access should difficulties arise in relation to hemostasis [37]. An understanding of mesenteric anatomy, and how this dictates the peritoneal landscape is essential and requires the surgeon to depart from the classic model of mesenteric anatomy. The classic model erroneously holds that the small intestinal region of mesentery, transverse mesocolon, and mesosigmoid, all attach directly to the posterior abdominal wall. With recognition of mesenteric continuity from duodenojejunal flexure to anorectal junction it was recognized that no such attachments occur [38–42]. Instead, broad regions of the mesentery (e.g., right and left mesocolon) flatten out against and are anchored to the posterior abdominal wall.

The importance of this anatomical property extends beyond the mesentery. According to the classic model of anatomy, the peritoneal landscape is complex and unpredictable as it is determined by a multiplicity of mesenteries. Mesenteric continuity means this is far from the case and the mesenteric landscape determines the peritoneal blueprint in all cases. The peritoneal landscape is entirely predicated on the anatomy of the mesentery and contiguous organs. Whilst it might seem that we are laboring an anatomical point, one cannot overestimate the importance of these concepts in a disease setting that is anatomically complex and challenging.

We do not recommend the mesentery be divided between arterial clamps or using currently available vessel sealing devices. Whilst there may still be some oozing even with our approach, it is readily controlled provided the mesentery has been fully mobilized. We have rarely encountered a mesenteric hematoma using the approaches mentioned above. When this did occur, it was controlled by mesenteric compression, between two 10×10 swabs, placed flat on either side of the mesentery and gently compressed. It is important that the entire operative team have all equipment available prior to division of the mesentery. Mesenteric hemostatic division can be rendered challenging if adequate numbers of Kocher clamps or heavy sutures are not immediately available throughout the process. Anesthesia staff should be alerted to the fact that the mesentery is about to be divided.

The proximal resection margin should be placed just proximal to the transition zone (i.e., zone where the mesentery changes from normal to abnormal) [2]. As such, mesenteric, rather than intestinal, features of disease should be used to guide positioning of the proximal intestinal division. Mesenteric features include thickening, swelling, fat wrapping (also called creeping fat) and loss of the angle between the mesentery and contiguous intestine.

We do not recommend that one aims to resect all diseased mesentery. As mentioned above it is important not to encroach directly on the central region of the mesentery. The benefits of complete mesocolic excision (CME) are clear-cut in terms of oncological outcome, but they do come at the price of increased short-term complications [43, 44]. A “D3” or “CME-type” exploration of diseased mesentery is not recommended in the setting of Crohn’s disease.

If the mesentery is severely diseased, alternative strategies may be adopted. Accordingly, the diseased region may be taken out of circuit, using a loop ileostomy. After a period of no less than three months, a repeat laparotomy can be

performed, and our experience is that resection with restoration of continuity is often feasible. This should not be considered a surgical failure but rather a strategic option. It is important that patients are aware of that possibility before both index and subsequent operations. We recommend consultation with gastroenterological services to determine whether patients should be placed on adjuvant medical treatment during the interval between operations.

Selected cases may be completed using the laparoscopic approach. The surgeon should not take the technical short-cuts that sometimes are adopted when using minimally invasive techniques (i.e., incomplete mesenteric mobilization). The complications that could arise due to avoidable trauma on damaged mesentery are unforgiving. It is also likely that any case that can be laparoscopically completed can also be achieved using the robotic approach, although this is an area for future investigation.

The question commonly arises as to how one reconciles the excellent results associated with the Kono-S anastomosis or strictureplasty (in which the mesentery is retained) with the results of our series, in which the mesentery was resected [45–50]. In the Kono-S procedure, an intestinal anastomosis is created that is circumferentially free of mesenteric inputs. It is more difficult to reconcile findings associated with strictureplasty (in which the mesentery is retained). As mentioned above, pathobiological events in Crohn's disease occur along two axes. These are the circumferential submucosal axis, and the radial mesenteric axis. Following strictureplasty, the circumferential axis is altered and lengthened. It is likely this alters submucosal inputs, as well as the intensity of inflammatory inputs at the junction between mesentery and intestine.

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Role of Endoscopic Management in Ulcerative Colitis Patients with Dysplasia

28

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Introduction

Ulcerative colitis (UC) patients are at increased risk of developing colorectal cancer (CRC), with multiple surveillance studies demonstrating an incidence rate as high as 10.8% at 40 years from symptom onset [1–4]. In the earliest days of cancer prevention for colitis, there were some who routinely recommended elective colectomy after 20 years of disease in order to avoid cancer entirely.

It was described subsequently that precancerous dysplasia was an important marker for the patient at risk for cancer. Observational studies confirmed that dysplasia in the setting of colitis was a risk factor for both synchronous and metachronous neoplasia, often of higher grades. Additional studies later identified that precancerous dysplasia of chronic UC behaved differently from the polypoid dysplasia found in the non-colitis population, and that there was a high rate of progression from low-grade dysplasia (LGD) to high-grade dysplasia (HGD) or adenocarcinoma.

Due to this risk, practice guidelines from many medical societies recommended that UC patients with any grade or focality of confirmed neoplasia should undergo proctocolectomy. The rationale for this recommendation was based on a secondary prevention strategy and the fact that the available endoscopic technology was unable to "see" dysplasia. Because of this limitation in technology and the challenges in identifying dysplasia, the discovery of *any* dysplasia was considered fortunate and sufficient to trigger surgical intervention. The adage "save a life, not a colon" was a frequent message to patients when this approach was recommended.

Advances in endoscopic technology however, have shown that most dysplasia in chronic UC is actually visible with white light, and that augmented imaging with

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Table 28.1 PICO table

Patients	Intervention	Comparator	Outcomes
UC patients with dysplasia	Surgery	Endoscopic surveillance	Cancer risk, quality of life, cost effectiveness

high definition colonoscopes with or without electronic or dye-spray chromoendoscopy does not miss adenocarcinoma, and can in fact see flat lesions. The so-called "invisible" dysplasia is a rare occurrence when current techniques are applied in a thoughtful surveillance strategy.

As technology improves, so should our comfort to perform "active surveillance" in patients with discrete dysplastic lesions. Surgery is no longer required for all patients who have dysplasia, and updated consensus statements and guidelines allow for risk stratification approaches to follow-up and timing of surgery in these patients. In this chapter, we present the literature of surgical and endoscopic management of dysplasia as it pertains to cancer risk, quality of life and cost effectiveness (Table 28.1).

Search Strategy

A PubMed search was conducted for publications in the English language between January 1994 and April 2018 using the following search terms: ('Ulcerative Colitis' or 'UC' or 'IBD' or 'Inflammatory Bowel Disease') and ('dysplasia' or 'neoplasia' or 'cancer' or 'low-grade dysplasia' or 'high-grade dysplasia' or 'LGD' or 'HGD') and ('endoscopic management' or 'colonoscopy management' or 'endoscopy' or 'colonoscopy') and ('before surgery' or 'after surgery' or 'surgery' or 'operation' or 'procedure') and ('colectomy' or 'total colectomy') and ('quality of life' or 'QALY') and ('cost' or 'cost analysis' or 'cost effectiveness' or 'indirect cost' or 'direct cost') and ('cancer risk' or 'colorectal cancer' or 'CRC'). Additionally, we searched the reference section of every relevant article to obtain additional research pertaining to the topic. Retrospective and prospective studies were included in the literature. Given a scarcity of studies published investigating quality of life and cost effectiveness in individuals with established dysplasia before surgery, the search was expanded to include studies assessing quality of life and cost effectiveness of patients without established dysplasia who have undergone colonic resection.

Results

Cancer Risk

There are no prospective trials comparing endoscopic management to surgery for UC patients with dysplasia. There are also no observational trials with mortality as an endpoint. In the majority of the retrospective, observational trials, the outcome of interest is neoplasia of higher grade. Therefore, recommendations from this level of evidence are of low to moderate quality.

Precancerous dysplasia in the setting of chronic UC is a risk factor for both synchronous and metachronous adenocarcinoma, and the magnitude of the risk is dependent on the grade of the index lesion, the size of the index lesion and additional risk factors which have been identified retrospectively. In an early observational study, Bernstein found that patients with confirmed LGD who underwent proctocolectomy had a concurrent adenocarcinoma 19% of the time [5]. Numerous subsequent studies have revealed that the finding of LGD has a predictable progression of between 16% and 33% to advanced neoplasia (HGD or cancer) in 3–6 years, and that this risk is higher if the index dysplasia was a flat or invisible lesion [1, 5–7]. In one study, there was a concurrent adenocarcinoma found in two patients who had a single biopsy with LGD [6]. These studies are confounded by selection bias by either the managing gastroenterologist or surgeon who chose not to have the patient undergo surgery or by the patient who refused surgical recommendation. Nonetheless, as the risk of missed neoplasia and the high rate of progression of known dysplasia was deemed unacceptable, proctocolectomy was recommended in all such patients [8].

As endoscopic equipment improved, a number of studies demonstrated that most colitis-associated dysplasia is visible using standard definition colonoscopes and with white light examinations [4, 9, 10]. Additionally, possibly due to improved visualization of dysplasia, the rate of progression of LGD to high-grade lesions was found to be lower than previously described [11]. These findings have contributed to a new era of endoscopic, as opposed to surgical, management of dysplasia. One study by Pekow at our institution evaluated patients who had dysplasia but did not undergo immediate proctocolectomy (at either the endoscopists' or the patients' discretion). LGD that was flat or invisible had an incident rate of progressing to advanced neoplasia (HGD or CRC) of 4.3 cases per 100 person-years at risk, while polypoid LGD had a risk of only 1.5 cases per 100 person-years. Importantly, patients with primary sclerosing cholangitis (PSC) had a significantly higher incidence rate of 10.5 cases per 100 years of patient follow-up [12]. The lower incidence rate seen in patients who had polypoid lesions was attributed to complete endoscopic resection of the lesion as well as the theory that raised dysplastic lesions may behave biologically more like sporadic adenomas rather than the traditionally described colitis-associated flat lesions. Numerous other studies have reported similar results. A subsequent systematic review of 10 studies of 376 patients with IBD who had resected polypoid dysplasia, with a mean follow-up of 54 months, reported a low annual incidence of CRC of 0.5% [13].

A larger and later systematic review by Fumery, which included 14 surveillance cohort studies of 671 patients with UC and LGD (both visible and non-visible, resectable and non-resectable), calculated the pooled annual incidence of CRC in this patient population to be 0.8%, and the pooled annual incidence of advanced neoplasia to be 1.8%. These authors also identified the risk factors associated with dysplasia progression in surveillance cohorts to be concomitant PSC (OR = 3.4), invisible dysplasia (OR = 1.9), distal location of the dysplasia (OR = 2.0) and multifocal dysplasia (OR = 3.5). Importantly, patients with invisible LGD had an annual incidence rate of 6.1% compared to those with visible LGD which was only 1.0% [11].

Table 28.2 The incidence of colorectal cancer in UC patients with low grade dysplasia who undergrowing endoscopic surveillance instead of surgery

Study	Patients (N)	Incidence rate of development of CRC	Quality of evidence
Fumery [11]	671	0.8 per 100 person-years	Low
Nguyen [14]	42	0.05%	Low
Wanders [13]	376	2.4%	Low

In 12 surgical cohort studies of 450 patients who underwent colectomy for LGD, the prevalence of a synchronous CRC was 17% [11]. Importantly, the authors postulated that the discrepancy between metachronous CRC (seen in the surveillance cohorts; 0.8%) and synchronous CRC (from the surgical cohorts; 17%) was related to bias and differences in patient populations (the inherent bias selection of patients sent to surgery often being the higher risk group to progress to CRC versus those of low-risk LGD selected for surveillance). Difference in time periods of the studies being conducted may be another explanation for this, as most surgical cohorts were before 2000 and most surveillance cohorts were published after 2000 (Table 28.2).

As opposed to the evolving management of LGD, the approach to HGD (flat or polypoid) has been less controversial due to high rates of synchronous adenocarcinoma; up to 42% of patients at the time of proctocolectomy [5]. On the other hand, none of 9 patients with polypoid HGD that was resected without surgery developed cancer after a median followup of 76.5 months, suggesting that colectomy may be avoided in this subgroup [15]. In our study of 56 patients with polypoid dysplasia in colitis with a median follow-up of 1.7 years, 9 patients had 12 HGD polyps which were removed endoscopically. The presence of HGD in a polyp was associated with a risk of subsequent HGD or cancer of 50%, 60%, and 70% by 1, 3, and 5 years, respectively (hazard ratio, 7.0; standard error, 4.8) [16]. The evidence based on these limited studies suggest that polypectomy and ongoing surveillance may be possible, but that there is a definite risk for future advanced neoplasia in these patients.

An international consensus statement of surveillance for colorectal endoscopic neoplasia detection and management in inflammatory bowel disease (IBD) patients (SCENIC) was published in 2015 [17]. It makes a variety of recommendations for the approach to detection and subsequent management of dysplasia in colitis. UC patients with polypoid or raised dysplastic lesions that can be completely endoscopically resected can have ongoing “active surveillance” colonoscopy instead of colectomy. The members of this consensus statement were unanimous in making this a strong recommendation, but this recommendation was made with very low quality of evidence. For flat dysplastic lesions that were endoscopically removed, ongoing surveillance colonoscopy was also suggested. However, this recommendation was conditional and also based on very low-quality evidence since no studies have compared surveillance colonoscopy to colectomy in patients with nonpolypoid (flat) dysplasia after endoscopic resection.

For endoscopically invisible LGD (found only on random biopsy), the group recommended referral to an endoscopist with experience using dye spray

chromoendoscopy with high definition colonoscopy in an attempt to identify the neoplastic lesion (or others) and to remove it endoscopically. This recommendation was unanimous among the experts, but conditional and supported by very low-quality evidence. Subsequently, two studies have described the experience of identifying dysplasia with chromoendoscopy after referral for prior dysplasia found on white light or random biopsy [18, 19]. Both studies described additional neoplastic lesions found by chromoendoscopy in this setting, sometimes of higher grade than the index lesion(s) that prompted the referral. SCENIC concludes that if an invisible lesion cannot be identified by an expert or if the lesion is not endoscopically resectable, the patient should be referred for surgery.

Quality of Life

While it is clear that proctocolectomy eliminates future risk of colonic neoplasia, patients undergoing ileal pouch-anal anastomosis (IPAA) or a permanent ileostomy may have a distinctly different quality of life than those with an intact non-inflamed rectum. A systematic review evaluating the burden of UC on patients' quality of life investigated a sample of UC patients who had undergone proctocolectomy with an ileostomy or IPAA. They used the SF-36 Health Survey, a generic measure assessing 8 quality-of-life domains, to compare UC patients and matched reference samples. Interestingly, no burden was observed in the post-surgical patients. Similar results were demonstrated by a group in Iceland who were surveying UC patients post colectomy using three validated questionnaires (SF-36v2, EORTC and QOL-questionnaires). Among the patients who had their rectum removed, 37% described changes in urinary habits and 46% had negative changes in their sexual life after surgery. Among the patients with IPAA, 75% reported fecal incontinence. There was no significant difference in QOL of colectomy patients compared to the general population [20].

UC patients whose indication for surgery is neoplasia (rather than medically refractory disease) may have near-normal preoperative bowel function and therefore would be less tolerant of an inferior functional outcome postoperatively. A study looking at quality of life in UC patients who required colectomy with subsequent pouch formation due to neoplasia compared to those whose indication was medically refractory disease, found that the quality of life scores were quite good and that there was no significant difference between the two groups [21]. Good functional results and quality of life was demonstrated by other studies as well [22].

A long-term follow-up of medically refractory UC patients after restorative proctocolectomy for UC assessed reservoir function, mucosal change and quality of life. One hundred eleven patients were followed for 6.8 years. Almost 90% of patients were satisfied with their J-pouch function, while 93.1% had some kind of functional restriction such as food (75.5%), social (28.9%), physical (37%), sexual restriction (15.3), or events of fecal incontinence (18.6%) [20].

Despite these reassuring quality of life results, there are clearly some patients, such as the elderly, who may be poor candidates for proctocolectomy, and in whom

alternative approaches may have value. In such patients, we have offered subtotal or segmental colectomy for proximal colitis-associated dysplasia. At a median 17 months of follow-up (range 3–228 months), we found several new LGD lesions but no subsequent cancers [23].

Cost Effectiveness

There are limited cost effectiveness data to inform a difference of approach between surgery and endoscopy for neoplasia in chronic UC. A study from Oxford published in 2017 evaluated the clinical and cost-effectiveness of colonoscopic surveillance versus colectomy for endoscopically invisible LGD (lesions detected only on random biopsies) in UC patients. For patients undergoing surgery, it was assumed that up to age 60 years, 75% of patients received an IPAA procedure, with the remainder receiving end ileostomy. This proportion decreased to 25% from age 60 to 70 years and to 2% from age 71 years onward. Patients undergoing surveillance were assumed to receive a colonoscopy every year for the first 5 years and every 3 years thereafter, in line with expected clinical practice in the Oxford University Hospitals NHS Foundation Trust. This modeling found that an active surveillance approach was associated with more life years and QALYs compared with surgery from age 61 in patients with no comorbidities or age 51 with one comorbidity. In patients younger than 60 years old, colectomy was found to be more cost-effective [14].

Nguyen compared the relative cost effectiveness of immediate colectomy and colonoscopic surveillance with repeated colonoscopy at 3, 6, 12 months, and then annually for the management of unifocal, flat, low grade dysplasia. Analysis of two simulated cohorts of 10,000 patients found that immediate colectomy was superior to enhanced surveillance in terms of higher QALYs (20.1 vs. 19.9 years) and lower cost ($75,900 vs. $83,900) [24].

Recommendations

1. Patients with UC who have dysplasia identified should be counseled regarding risk for current and subsequent cancer (moderate confidence, low quality of evidence).
2. Patients with colitis who have dysplastic lesions that are not endoscopically resectable should be referred for surgery (moderate confidence, low quality of evidence).
3. Patients with colitis who have low-grade dysplastic lesions that are discrete and can be removed endoscopically may continue surveillance colonoscopies (low confidence, low quality of evidence).
4. Patients with colitis who have HGD, whether invisible or polypoid, should be referred for colectomy (low confidence, low quality of evidence).

5. Patients with colitis who have invisible LGD (found by random or non-targeted biopsies) may be followed with a more intensified surveillance approach (referral to an expert colleague, incorporation of augmented imaging and shorter interval exams) (low confidence, low quality).
6. Patients with colitis and concurrent PSC and any grade of neoplasia should be referred for surgery since the risk of synchronous and metachronous lesions is high (moderate confidence, low quality of evidence).
7. Patients with colitis and dysplasia in whom surgery is needed but who are poor candidates for optimal surgical outcomes or quality of life may undergo segmental resection and ongoing active surveillance (low confidence, very low quality of evidence).
8. When deciding between ongoing surveillance and surgery, if one approach over another is not clear, surgery is favored as a cost-effective option given otherwise similar quality of life outcomes (low confidence, very low quality of evidence).

Personal View

The choice of ongoing surveillance or surgery for UC patients with dysplasia is a complex decision that should take into consideration patient-related risk factors (risk profile, willingness to undergo ongoing procedures, family history of cancer), disease-related risk factors (duration, PSC, extent of inflammation, prior dysplasia), dysplasia-related risk factors (morphology, grade, focality) and the availability of endoscopic and surgical expertise. The ultimate goal of dysplasia management must be kept in perspective while making these decisions. While it is certainly acknowledged that most patients would prefer not to have surgery, appropriate surgical input must be recommended whenever dysplasia is found, and the available data suggesting similar quality of life between IPAA and ongoing surveillance is reassuring.

At our institution, we refer the majority of UC patients with dysplasia to our surgical colleagues for an opinion regarding a surgical approach, and work with our surgical colleagues to make plans for either ongoing endoscopic surveillance or combined endoscopic and surgical management when appropriate and possible. Our equipment is high definition colonoscopes, and we do utilize dye spray chromoendoscopy and advanced resection techniques when dysplasia is visible and endoscopically discrete. However, when a patient has multiple cancer risk factors (especially PSC), repeated findings of dysplasia on multiple exams or unresectable lesions, we strongly recommend surgery. In our older patients who are in stable remission but have dysplasia in their proximal colon, we do offer a segmental (subtotal) colectomy and ileosigmoid or ileorectal anastomosis with ongoing surveillance. This is an option when the UC is truly in deep and durable remission and that ongoing surveillance is possible.

Additional advances in technology for surveillance (like augmented narrow band imaging) are improving our ability to detect dysplasia and to remove it, without concerns for missing other lesions, so this is certainly an evolving field.

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29 Surgical Options for Endoscopically Unresectable Dysplasia in Ulcerative Colitis

Mantaj S. Brar and Anthony de Buck van Overstraeten

Introduction

The management of ulcerative colitis-associated dysplasia (UCAD) has evolved over the last decade. Many have advocated for increased utilization of endoscopic resection of dysplastic lesions, mainly driven by improved endoscopic techniques [1, 2]. This has occurred in spite of significant inter-rater variability with respect to the pathological diagnoses, shifting taxonomy, evidence that low-grade dysplasia may not progress to high-grade dysplasia prior to malignancy, and with heterogeneous reported rates of synchronous and metachronous neoplasia [1–8].

Despite the controversies regarding the appropriate selection of patients for surgery, there is little debate regarding the optimal surgical intervention. Surgical society guidelines recommend a total proctocolectomy with end-ileostomy (TPC) or a restorative proctocolectomy with an ileo-anal pouch anastomosis (RP) for patients with UCAD given the resection of all/most of the at-risk mucosa [9, 10]. However, with the shift towards endoscopic resection of dysplastic lesions, some have advocated segmental colectomy (SC) for endoscopically unresectable dysplasia, suggesting an acceptable risk of metachronous neoplasia while preserving bowel function and quality of life [11]. In this chapter, we will evaluate the body of evidence on segmental vs. total proctocolectomy with respect to the risk of metachronous neoplasia and quality of life.

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PICO table

Patients	Intervention	Comparator	Outcomes
Ulcerative colitis patients with endoscopically unresectable dysplastic lesions	Segmental colectomy	Total proctocolectomy	Risk of recurrent neoplasia Quality of life

Search Strategy

A comprehensive literature search of Cochrane Database of Collected Research, EMBASE, and MEDLINE was performed to identify all of the English-language publications from 1997–2018 using the following search terms: ("IBD" or "Inflammatory Bowel Disease" or "Ulcerative Colitis" or "Colitis) AND ("Neoplasia" OR "dysplasia") AND ("Colectomy" OR "Segmental Colectomy" OR "limited resection" OR "Proctocolectomy" OR "extended resection" OR "Restorative proctectomy" OR "IPAA" OR "Ileo-anal J-pouch" OR "Ileal anal pouch" OR "Pouch"). Based on our clinical question, we initially included only studies that directly compared segmental colectomy to either a total proctocolectomy or ileo-anal pouch anastomosis and reported either rates of metachronous neoplasia, bowel function, or quality of life outcomes. Given the lack of literature on the subject, we expanded the literature search to include patients who underwent subtotal colectomy and ileorectal anastomosis (IRA), and included case-series for which UC patients with dysplasia received either SC, IRA, TPC, or RP and reported rate of metachronous neoplasia or quality of life outcomes. Lastly, we reviewed published guidelines on the surgical management of ulcerative colitis from 2007 to 2018.

Results

Comparative Studies of SC/IRA vs. TPC/RP

There was a paucity of evidence directly comparing SC vs. TPC/RP for the treatment of UCAD in the literature. No reports specifically evaluated patients undergoing only segmental colectomy and therefore we reviewed reports with either SC or IRA vs. TPC or RP. In total, only one comparative analysis evaluating the risk of metachronous neoplasia was found. In a Swedish national cohort study of all UC patients from 1964 to 2010 who underwent colectomy, 70 patients had pre-operative *severe* dysplasia, 36 of whom underwent IRA and 34 who underwent RP [12]. Preoperative dysplasia or cancer was identified as a risk factor for rectal cancer only among patients with a diverted rectum with end-ileostomy (HR 3.67, 95% CI 1.01–13.37, p = 0.049) and not among patients who received IRA (HR 0.99, 95% CI 0.26–3.69, p = 0.98) or RP (HR not reported). Among those who underwent RP for severe dysplasia, none of the patients on follow-up were diagnosed with rectal cancer (0/34, 95% CI 0–10%).

Rates of Metachronous Neoplasia Among SC/IRA Patients

In the absence of direct comparative analyses, we reviewed case-series to estimate the risk of metachronous neoplasia among UC patients with dysplasia undergoing SC/IRA vs. those undergoing TPC/RP (Table 29.1). With respect to UC patients undergoing SC/IRA for dysplasia, only three reports were identified in the literature, each of limited sample size.

Lindberg reported a single-institution retrospective case series of 21 patients who underwent SC/IRA for UC, of whom 3 underwent surgery for dysplasia [13]. Among these three patients, 1 patient underwent surgery for LGD five years after IRA [13]. Cleveland reported a single-institution retrospective case series that included 6 UC patients with quiescent disease who underwent SC/IRA surgery for dysplasia (5 with LGD and 1 with HGD pre-operatively). Over a (limited) median 17 months follow-up, no metachronous dysplasia or carcinoma was identified (0%, 95% CI 0–46%) [11]. Uzzan reported a multicentre retrospective case-series of patients who underwent IRA from 1960 to 2014 at 13 centres. Among the 343 patients included in the series, only 17 patients underwent IRA for dysplasia [14]. Patients were followed for a median 10 years, and 3 patients were found to have metachronous neoplasia during follow-up (17%, 95% CI 4–43%). However, the estimated cumulative incidence of rectal neoplasia was 30% (95% CI 1–61%) and of rectal carcinoma was 25% (95% CI 1–57%) at 10 years for patients with preoperative dysplasia [14].

Table 29.1 Risk of metachronous neoplasia by extent of surgery in UCAD

Author year	Patients studied	Study design	Surgery (N)	Risk of metachronous neoplasia
Abdalla (2017) [12]	Colectomy for UC; subgroup of patients with severe dysplasia	R, O	IRA (36) RP (34)	HR for rectal cancer = 0.99 (95% CI 0.26–3.69, p = 0.98) Rectal cancer: 0/34 (0%, 95% CI 0–10%)
Lindberg (2017) [13]	SC/IRA for UC; subgroup with dysplasia	R, O	SC/IRA (3)	1/3 (33%, 95% CI 1–91%)
Cleveland (2018) [11]	SC/IRA for IBD-associated dysplasia; subgroup with UC	R, O	SC/IRA (6)	0/6 (0%, 95% CI 0–46%) at median follow-up of 17 months
Uzzan (2017) [14]	IRA for UC; subgroup with dysplasia	R, O	IRA (17)	3/17 (17%, 95% CI 4–43%) Cum. risk at 10 years 30% (95% CI 1–61%)
Derikx (2016) [15]	Colectomy for IBD; subgroup with RP for UCAD	R, O, MA	RP (639)	OR for carcinoma 4.38 (95% CI 1.91–10) Pooled risk of carcinoma 1.4% (95% CI 0.8–2.6%) at 5–8 years follow-up
Al-Sukhni (2010) [16]	RP for UCAD or UC and carcinoma	R, O	RP (82)	Carcinoma 2/82 (2.4%, 95% CI 0.2–8.5%)

Retrospective (R), Observational (0), Meta-analysis (MA)

Rates of Metachronous Neoplasia Among TPC/RP Patients

There was no literature reporting the rate of metachronous neoplasia among patients undergoing TPC and end-ileostomy for UCAD. For patients undergoing RP, a meta-analysis by Derikx reported the findings of five retrospective case series and demonstrated that prior colorectal dysplasia was a risk factor for the development of carcinoma following RP (OR 4.38, 95% CI 1.91–10) [15]. However, the crude pooled absolute risk of carcinoma among patients with colorectal dysplasia (n = 639, with median follow-up of 5–8 years) was only 1.4% (95% CI 0.8–2.6%) [15]. Our institution reported our single-centre retrospective case series of 82 patients who underwent RP for UC with a history of dysplasia or cancer [16]. With a median follow-up of 6 years, 2 patients were found to have metachronous carcinoma (2.4%, 95% CI 0.2–8.5%) [16].

Quality of Life Among IRA vs. RP Patients

No comparative analysis was found comparing QOL among patients who received SC/IRA vs. TPC/RP for UCAD. However, three single-centre case-series compare the QOL of patients selected for IRA vs. RP for UC (Table 29.2). Given that the indication for surgery for a majority of the patients is medically refractory disease, these findings may not be generalizable to patients with dysplasia. It is conceivable that in the absence of medically refractory disease, patients with dysplasia alone may have better functional outcomes with IRA than those reported for patients with medically refractory disease. Tonelli reported a matched-pair analysis comparing IRA vs. RP among 98 pairs of UC patients, evaluating bowel function and QOL [17]. In this series, severe dysplasia or carcinoma was a contraindication to IRA. In their analysis, those selected for an IRA had similar number of bowel movements, work restriction, sexual dysfunction, quality of life, quality of health, energy levels and mean Cleveland Global Quality of Life (CGQOL) scores as those selected for RP. However, those with IRA were less likely to have liquid stools (7% vs. 21%), less seepage at day and night (0% vs. 6%, and 6% vs. 26%, respectively), less social restriction (28% vs. 41%), and were more often satisfied with their surgery (98% vs. 88%) [17].

Andresson reported a single centre review of 253 patients who underwent either IRA or RP for UC. The risk of metachronous neoplasia was not presented for patients with dysplasia and no QOL measures were reported. However, patients with IRA had lower mean BMs/day (4 vs. 5, p = 0.03), and cumulative failure rates did not significantly differ between the two groups (at 10 years, 24% vs. 19% for IRA and RP, respectively) [18]. da Luz Moreira reported a single-centre case series on functional and QOL outcomes on 22 IRA patients and 66 RP patients for UC [19]. With respect to bowel function, patients with IRA had less BMs during the daytime (4 vs. 5), less seepage at night (5% vs. 32%), but more urgency (68% vs. 21%) compared to RP patients [19]. With respect to QOL outcomes, energy level, quality of life, quality of health, CGQOL, satisfaction with surgery, social restrictions and sexual function were similar between both groups, but there were more dietary (68% vs. 30%) and work restrictions (27% vs. 8%) among those who received an IRA vs. RP [19].

Table 29.2 Comparison of functional and QOL outcomes between IRA and RP for UC

Author year	Study design	N IRA vs. RP	QOL or functional measure	Results IRA vs. RP
Tonelli (2016) [17]	R, O, matched pairs	98 vs. 98	Bowel movements, daytime (mean) **Liquid stools** **Seepage, daytime** **Seepage, night** Discrimination Work Restriction **Social Restriction** Sexual Restriction Dietary Restriction Current QOL (mean) Current quality of health (mean) **Current Energy level (mean)** CGQoL (mean)	3.2 vs. 4.5—NS **6.7 vs.** **29%—p < 0.01** **0 vs.** **6%—p = 0.01** **6 vs.** **25%—p = 0.03** 100 vs. 95%—NS 6 vs. 7%—NS **28 vs.** **40%—p = 0.03** 1 vs. 2%—NS 41 vs. 57%—NS 7.5 vs 7.3—NS 7.2 vs. 7.5—NS **7.1 vs.** **7.9—p = 0.045** 0.72 vs. 0.75—NS
Andresson (2014) [18]	R, O	105 vs. 148	**Bowel movements, daytime (median)**	**4 vs. 5— p = 0.03**
Da Luz Moreira (2010) [19]	R, O	22 vs. 66	**Bowel movements, daytime (median)** **Urgency** IncontinenceSeepage, daytime Seepage, night Energy level (mean) QOL (mean) Quality of health (mean) CGQoL (mean) Satisfaction with surgery (mean) **Dietary restrictions** Social restrictions **Work restrictions** Sexual restrictions	**4 vs. 5—p = 0.01** **68 vs.** **21%—p < 0.01** 5% vs. 14%—NS 19 vs. 17%—NS 5 vs. 32%—NS 7.5 vs. 7.4—NS 8.4 vs. 8.3—NS 8.0 vs. 8.1—NS 0.80 vs. 0.79—NS 9.4 vs. 9.1—NS **68 vs.** **30%—p < 0.01** 18 vs. 17%—NS **27 vs.** **8%—p = 0.02** 14 vs. 12%—NS

Retrospective (R), Observational (0)

Recommendations

Given the limited data on the risk of metachronous neoplasia after segmental colectomy or subtotal colectomy and ileorectal anastomosis for the treatment of ulcerative colitis-associated dysplasia, patients should be offered total proctocolectomy with end-ileostomy or restorative proctectomy with ileo-anal pouch anastomosis (Strong recommendation based on low quality evidence).

RP offers acceptable rates of metachronous neoplasia (1–2%) with medium-term follow-up, and preserves global quality of life, despite modestly inferior bowel function in comparison to IRA.

Our Personal View

The management of inflammatory bowel disease requires balancing the quality of life of our patients and minimizing the long-term complications of the disease. Patients with endoscopically unresectable dysplasia in the setting of ulcerative colitis have a heterogeneous risk of progression and occult carcinoma based on factors including the morphology, focality, aneuploidy, and grade of dysplasia [2, 7]. Unfortunately, the three small reports in the literature to date do not adequately characterize the dysplastic lesions and the limited sample sizes preclude any meaningful conclusions regarding the safety of limited resection for UC-associated dysplasia. We suspect that subtotal colectomy and ileorectal anastomoses are being employed with increasing frequency in patients with quiescent rectal disease and low risk dysplastic lesions (unifocal low-grade lesion that is visible but endoscopically unresectable), especially in certain jurisdictions, such as Sweden, where IRA is used more frequently for the treatment of UC. As the paradigm shifts towards an increasing role for endoscopic resection and more surgery, data regarding the safety of such practices will begin to accrue. However, although the rates of synchronous occult invasive cancer among patient with low-grade dysplasia has decreased over time, likely due to increased endoscopic detection of invasive disease preoperatively and the increased detection of possibly earlier dysplastic lesions, the rates are still unacceptably high at 3–17% [7, 20]. Therefore, caution needs to be exercised when recommending a limited resection for UC associated dysplasia.

Given the low risk of metachronous neoplasia, the comparable QOL indices, and the low-risk of long-term failure, restorative proctectomy with an ileoanal J-pouch anastomosis remains the treatment of choice when surgery is required for UC associated dysplasia. For patients who do not want to proceed with a pouch reconstruction such as those with distal rectal dysplasia or poor sphincter function, a total proctocolectomy with end-ileostomy provides comparable QOL with no risk of further neoplasia. Interestingly, physician thresholds of acceptable risk differs from our IBD patients; as reported by Siegel, on average, patients with chronic UC would only accept a restorative proctectomy if the risks of synchronous invasive carcinoma were greater than 70% [21]. Therefore, all decisions regarding the management of dysplasia in the setting of UC must involve an informed discussion with the patient about the known (and unknown) current and future risks of neoplasia.

Further study of the surgical options for endoscopically unresectable dysplasia is urgently required to accurately risk stratify these patients; ideally with explicit characterization of the dysplastic lesions preoperatively, characterization of extent of disease, with involvement of expert GI pathologists to review both preoperative and surgical specimens, and defined post-operative endoscopic surveillance.

Recommendation Summary

Ulcerative colitis patients with endoscopically unresectable dysplasia should be offered either a total proctocolectomy with end-ileostomy or restorative proctocolectomy with an ileo-anal pouch anastomosis. (Strong recommendation based on low quality evidence).

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Management of Ulcerative Colitis in Patients with Rectal Cancer

30

Evangelos Messaris and Walter Koltun

Introduction

While medical therapy is the first line of treatment for ulcerative colitis (UC), proctocolectomy can provide a curative option. Approximately 20% of patients with ulcerative colitis will require surgery in their lifetime [1]. Indications for surgery are medically refractory disease, complicated disease, extraintestinal manifestations, toxic colitis, failure to thrive, dysplasia and cancer. In most cases, a restorative proctocolectomy with an ileal pouch-anal anastomosis (IPAA) is the preferred method to provide concurrent cure of ulcerative colitis and reconstruction of the gastrointestinal tract. The risk of developing colorectal cancer with ulcerative colitis over a lifetime is estimated between 5% and 13.5% [2]. In cases of ulcerative colitis complicated by rectal cancer, the choice of operative procedure becomes more challenging. An alternative to IPAA would be a total proctocolectomy with end ileostomy (TPC). In UC patients with rectal cancer, the need for neoadjuvant chemoradiation and adjuvant chemotherapy, in addition to other patient and disease dependent variables, may impact long term outcomes including overall survival and quality of life (Table 30.1).

Table 30.1 PICO table

Patients	Intervention	Comparator	Outcome
Ulcerative colitis with rectal cancer	Total Proctocolectomy with Ileal Pouch Anal Anastomosis	Total Proctocolectomy with end ileostomy	Cancer specific disease free survival and Health Related Quality of Life

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Search Strategy

A relevant PICO (Patients, Intervention, Comparator and Outcome) table was generated. A comprehensive literature search of MEDLINE, PubMed and Cochrane database of Collected Research between 1980 and 2018 was performed to identify articles on rectal cancer and ulcerative colitis, colectomy, IPAA, disease free survival, cancer specific survival and quality of life. Key search terms included the following: ulcerative colitis, colectomy, proctocolectomy, IPAA, rectal cancer, survival, quality of life, ileostomy. Studies that included rectal cancer patients with Crohn's disease or familial adenomatous polyposis were excluded from the analysis. Given the paucity of the literature, some articles that did not compare directly IPAA with total proctocolectomy and end ileostomy were also included.

Results

Very few studies report survival outcomes after surgery for rectal cancer in patients with ulcerative colitis, and no studies report quality of life measures in these patients. In addition, all studies are plagued with very low number of subjects and retrospective design.

The largest study to date measuring the oncologic outcomes of patients with ulcerative colitis and rectal cancer has been reported by Merchea [3]. In this retrospective review of 41 patients, the majority had proctocolectomy with end ileostomy. IPAA was done in 11 patients, abdominoperineal resection with end colostomy in 2 patients and subtotal colectomy with end ileostomy in 1. There was a clear preference for patients with early stage (I and II) rectal cancer to undergo an IPAA while patients with more advanced stage (III and IV) underwent non-restorative operations. Consequently, very few of the IPAA patients received either neoadjuvant (n = 1) or adjuvant treatment (n = 3) (radiation and/or chemotherapy). Half of the IPAA patients received a stapled anastomosis and the rest a handsewn anastomosis. Postoperative morbidity was not related to the type of surgery. Five-year disease free and overall cancer specific survival was 62% and was not found to be related to the type of procedure. As expected, the recurrences and deaths occurred in patients with advanced rectal cancer (stage III and IV). The authors concluded that rectal cancer in ulcerative colitis is rare, usually presents in early stage and that IPAA is feasible and safe for early stage disease.

In an older study from Ziv [4], a mixed group of ulcerative colitis patients with colon (n = 20) and rectal cancer (n = 7) underwent IPAA; local recurrence occurred in 2 patients (7.7%) and 3 died, but none from rectal cancer. The authors noted that most of their patients had early stage cancers, which may have accounted for the high rate of IPAA and the excellent overall outcomes. They concluded that IPAA can be used for curative intent as long as adequate margins are achieved.

In 2003, Remzi [5] reported the outcomes of 70 patients undergoing IPAA for colorectal cancer. Twenty six patients had rectal cancer and more than half of them underwent mucosectomy with a handsewn anastomosis. Most of them were early

Table 30.2 Studies of IPAA and Rectal Cancer

Study	Patients with rectal cancer	5 Year-recurrence	5 Year—survival	Quality of evidence
Merchea [3]	28 TPC vs 11 IPAA	38%	62%	Low
Ziv [4]	7 IPAA	0%	100%	Low
Remzi [5]	26 IPAA	3.8%	96%	Low
Hotta [7]	9 IPAA	0%	100%	Low
Gorfine [8]	14 IPAA	N/A	79%	Low

stage cancer (Stage I and II) and only 7 were stage III. The advanced stage patients received adjuvant chemotherapy without radiation therapy. One rectal cancer patient received adjuvant radiation therapy that was associated with pouch failure and development of cancer recurrence. Only one of the rectal cancer patients died during the average 6.1 years of follow up. This group concluded that IPAA should be considered in patients with coexisting colorectal cancer and UC. Surgery along with chemotherapy, when needed, can provide good prognosis with very good functional outcomes.

Finally, in a study that we did not include in our PICO analysis, McLeod [6] compared IPAA to TPC, but included patients with Crohn's disease and familial adenomatous polyposis. A total of 27 patients had rectal cancer; as in the previous studies, patients with advanced T4 tumors with poor differentiation did not receive an IPAA. Use of radiation was much more common in the TPC group. Overall disease free survival was comparable between the 2 groups and median time to recurrence or death was 14 months for both groups. The authors recommended IPAA as a safe alternative to TPC with end ileostomy, but not in those with T_3 or T_4 lesions, or those with threatened radial margins (Table 30.2).

Although there are several studies comparing the IPAA versus TPC for UC for health related quality of life measures, there are no studies on patients that also have rectal cancer. Although most studies without rectal cancer patients demonstrate comparable quality of life for both groups, in patients with rectal cancer there are two distinct differences in management which can affect overall pouch function: the increased use of handsewn anastomosis (especially for distal rectal tumors) and the need for neoadjuvant chemoradiation or adjuvant chemotherapy.

IPAA with mucosectomy and handsewn anastomosis is a more demanding procedure that consists of stripping the anal transitional zone and suturing the anastomosis. Alternatively, the stapled anastomosis retains the distal rectal mucosa (possibly increasing the risk for local recurrence), but is superior in terms of postoperative defecatory function. It has been shown extensively that the stapled technique has a superior functional outcome and better quality of life than hand-sewn anastomosis with mucosectomy [9]. The oncologic advantage of the hand-sewn technique is challenged in several articles that support the use of a stapled approach. In 2009, Zmora [10] and Cohen [11] demonstrated that for most colorectal cancer patients with ulcerative colitis, the stapled IPAA is a reasonable and safe option.

The use of radiation therapy before or after IPAA has not been analyzed extensively. This is because in all the published studies, it is clearly stated that the

Table 30.3 Studies of the consequence of radiation therapy and IPAA

Study	Rectal cancer	Postoperative radiation	IPAA failure	Quality of evidence
Radice [13]	21	5	3	Low
Remzi [5]	26	1	1	Low
Gorfine [8]	14	2	1	Low
Inoue [14]	1	1	0	Low

majority of the IPAAs were performed for early stage cancers and that most of the patients with advanced rectal cancers declined radiation therapy. Wu [12] reported the largest cohort of patients with rectal cancer with preoperative radiation therapy that received an IPAA (n = 9), and compared their outcomes with patients undergoing IPAA without pelvic radiation. Chronic pouchitis was significantly more common in patients with neoadjuvant chemoradiation. Furthermore, almost half of the rectal cancer radiated patients (43%) lost their pouch during the follow up period, while only 17% of the non-radiated pouches were excised over the same time period. The average time for a radiated pouch to fail was 60 months. The study concluded that pelvic radiation administered prior to IPAA creation appears to be associated with worse pouch outcomes.

Several studies have demonstrated that postoperative radiation is linked to a high chance for pouch failure (see Table 30.3).

Recommendations Based on Data

Patients with ulcerative colitis and early (T_1 or T_2, N_0) rectal cancer can undergo IPAA instead of TPC with end ileostomy and expect comparable oncologic outcomes (Weak Recommendation based on Low Quality Evidence).

Patients with ulcerative colitis requiring neoadjuvant or adjuvant chemoradiation for locally advanced rectal cancer should not be offered IPAA, but rather undergo a TPC with end ileostomy (Strong Recommendation based on Moderate Quality Evidence).

Personal View

Patients with rectal cancer in the setting of ulcerative colitis need to undergo a sound oncologic operation and at the same time, attempt to have a curative resection for their ulcerative colitis. The sequence from dysplasia to cancer in the background of inflammation from ulcerative colitis patients is less predictable, and may occur at a rate faster than what is seen with the traditional adenoma to carcinoma sequence [15]. Thus, patients with ulcerative colitis and colorectal cancer are at higher risk of developing another cancer in the remaining inflamed colon or rectum. This can occur in the remaining rectum when total abdominal colectomy is performed for

either initial colon cancer treatment or severe colitis, and there is a subsequent delay in removing the retained rectum. In those patients undergoing TAC for dysplasia or cancer, close surveillance of the rectum is necessary to avoid the development of a second rectal malignancy, prior to either completion proctectomy or IPAA reconstruction.

Thus, UC patients with a rectal cancer have two options; either an IPAA or a TPC with end ileostomy. The current data is insufficient to support a firm recommendation. While all available data suggests that oncologic outcomes for both procedures are equivalent, it is clear that in all the studies, there was a very strict pre-selection of patients. IPAA can be safely performed as a primary or secondary procedure in conjunction with radical resection of the tumor bearing rectum in most early (T_1, T_2, N_0) rectal cancer patients. As in patients who do not have ulcerative colitis, if the tumor is invading sphincter muscles or reaches the level of the dentate line, radical resection without reconstruction is recommended. In a similar fashion, for symptomatic patients (i.e. bleeding or obstructing tumor) or with metastatic disease, a TPC with an end ileostomy would be the lowest risk procedure to get the patient to chemotherapy as soon as possible.

A significant challenge remains for patients with more advanced rectal cancer who require neoadjuvant chemoradiation or adjuvant chemoradiation. Patients with locally advanced rectal malignancies who undergo IPAA are at greater risk of pouch excision, diversion and death. Preoperative combined chemoradiation for Stage II or III rectal lesions followed by IPAA is theoretically possible; however with the small amount of data presently available, these patients are at significantly increased risk for pouch failure and subsequent pouch excision. In addition, a significant number of colorectal cancers may be found only after the surgical excision is done ostensibly for dysplasia and adjuvant chemoradiation therapy may then be required. Patients with rectal lesions who already received an IPAA and now require postoperative chemoradiation are probably best treated by deferring the radiation and utilizing just chemotherapy. Postoperative adjuvant chemotherapy is compatible with this approach, and does not appear to increase the risk for pouch failure or any other complications. The use of preoperative chemotherapy has recently emerged as an option in the care of patients with locally advanced rectal cancers but has not been studied in IPAA patients.

In conclusion, early stage (T_1, T_2, N_0) upper and mid rectal tumors in the setting of ulcerative colitis can be safely treated with restorative proctocolectomy (IPAA) with acceptable oncologic and functional outcomes when compared to TPC with end ileostomy. Adjuvant chemotherapy if needed is safe. Distal rectal tumors in patients should be considered for TPC with end ileostomy.

Neoadjuvant or adjuvant chemoradiation is associated with high incidence of pouch failure and complications. Thus, IPAA is not recommended in patients with locally advanced tumors that need neoadjuvant radiation therapy. No data exists on the role of neoadjuvant chemotherapy for locally advanced rectal tumors in the setting of ulcerative colitis with subsequent IPAA.

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Surgical Approach to the Older Ulcerative Colitis Patient

31

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Introduction

Ulcerative colitis has a bimodal age distribution; between 10% and 15% of patients are diagnosed with ulcerative colitis after the age of 60 years [1]. A significant proportion of these patients require surgery and the choice between proctocolectomy with end ileostomy or proctocolectomy with ileal pouch-anal anastomosis (IPAA) can be difficult.

Previously, patients over age 50 undergoing surgery for ulcerative colitis were assumed to be poor candidates for IPAA and were more likely to undergo end ileostomy. A study of 3635 patients with ulcerative colitis between 2005 and 2012 using the American College of Surgeons NSQIP database found that the odds of having an end ileostomy decreased by 12% per year in patients 61–70 years compared with patients under age 50 as IPAA became a more acceptable option for older patients [2]. However older patients generally have more comorbidities and may have decreased functional capacity; the risk of complications and their anticipated quality of life should be factored into which procedure is offered and ultimately performed for older ulcerative colitis patients [3] (Table 31.1).

Table 31.1 PICO table

Patients	Intervention	Comparator	Outcome
Surgical approach to the older ulcerative colitis patient	IPAA	Ileostomy	Complication rate, quality of life

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Search Strategy

A comprehensive literature search of Cochrane Database of Collected Research, EMBASE, MEDLINE, and PubMed was performed to identify all of the English-language publications related to ulcerative colitis, colectomy and ileal pouch-anal anastomosis, older patient and complication rate and quality of life (QOL) outcomes from 1985 to 2018. Key search terms included the following: "colectomy," "colitis," "ileal pouch-anal anastomosis," "inflammatory bowel disease," "elderly," "older," "proctocolectomy," and "ulcerative colitis." Studies were excluded if they did not directly address older patients with ileal pouch-anal anastomosis or failed to measure complication rates or any component of health-related quality of life. Due to the small cohorts of older patients undergoing IPAA for ulcerative colitis, studies which included familial adenomatous polyposis patients along with ulcerative colitis patients undergoing IPAA were included. Only the most recent study was included if similar studies from the same institution were encountered. The references of the included studies were reviewed to identify additional studies that were incorporated as appropriate.

Results

The definition of older patient differed among studies. Some studies defined older patient as ≥50 or 55 years and several studies used ≥70 years. There were no studies which specifically compared complications or quality of life between IPAA and ileostomy in older ulcerative colitis patients. However, several studies evaluated complications and quality of life of IPAA patients stratified by age group or focused on a cohort of older IPAA patients. The cohorts of older IPAA patients in published studies are small.

As expected, older patients had more comorbidities and higher ASA scores [4–8]. Complication rates were generally comparable between older patients and younger patients undergoing IPAA (Table 31.2) [5, 6, 9, 10]. However, older patients suffered more from dehydration than younger patients [4, 6, 11]. Small bowel obstruction was more common in younger patients [4, 11]. One study noted that pouch-anal stenosis was significantly more common in older patients with ulcerative colitis compared with younger patients (37% vs. 17%, $p = 0.02$) [10].

Pouch function including stool frequency and incontinence episodes were comparable between older and younger patients in the majority of studies (Table 31.2) [4–6, 10] Pellino [4] found that older patients took significantly more antidiarrheals than the younger group at 1-year follow-up; however, this observation was not confirmed at 3-year follow-up. In a retrospective review of 2002 patients, Chapman [9] reported higher number of stools at night, more frequent day time incontinence for patients ≥55 years compared with patients <45 years (15.2% vs. 4.1% at 1 year, $p = .004$) and more frequent night time incontinence in patients ≥55 years compared with patients <45 years (26.1% vs. 9.4% at 1 year, $p = .001$; 19.6% vs. 9.3% at

Table 31.2 Complications and pouch function for older patients undergoing IPAA

Study	Patients (N) IPAA	Complication rate	QOL measure	QOL results	Quality of evidence (Newcastle-Ottawa quality assessment)
Pellino (2013) [4]	27 Patients over age 70 vs. 81 younger controls	Comparable major complications; older group had more dehydration, younger group more SBO	Pouch function at 1 year/3 years IBDQ at 1 year/3 years	Comparable; older patients took more antidiarrheals at 1 year Comparable	Good
Delaney (2002) [13]	17 Patients ≥ age 70	4 Patients with major complications, 1 death at 6 months post-op	Pouch function CGQL SF-36	Complete continence in 38% Good QOL and health Comparable to healthy individuals ≥65	Fair
Ho (2005) [5]	17 Patients ≥ age 70 vs. 313 patients in younger age groups	Comparable between age groups	Pouch function	No difference in major or minor incontinence. Older patients had more frequent bowel movements	Good
Pinto (2010) [6]	33 Patients ≥ age 65 vs. 33 matched younger patients	Comparable major complications; older group had more dehydration	Pouch function	Comparable	Good
Chapman (2005) [9]	65 Patients ≥ age 55 vs. 1937 patients in younger age groups	Comparable between age groups	Pouch function QOL	Daytime and nighttime incontinence more frequent in patients ≥55 years Comparable	Good
Dayton (1996) [11]	32 Patients ≥55 years vs. 423 patients <55 years	Comparable; older group had more dehydration	Pouch function	Stool frequency, daytime and nighttime incontinence higher in patients ≥55 years	Good

(continued)

Table 31.2 (continued)

Study	Patients (N) IPAA	Complication rate	QOL measure	QOL results	Quality of evidence (Newcastle-Ottawa quality assessment)
Tan (1997) [10]	28 Patients > age 50 vs. 199 patients in younger age groups	Comparable major complications; pouch-anal stenosis more common in older group	Pouch function	Comparable	Good

3 years, p = .03). Delaney, in a study of 1895 patients, also found that incontinence and night time seepage were more common in older patients [12].

Older patients and younger patients with IPAA reported similar restrictions in travel, sports activity, social activity, family relations and work. Severe sexual restrictions were more common in patients ≥55 years compared with patients <45 years at 5 year and 10 year follow-up [9]. Delaney used the Cleveland Global Quality of Life (CGQL) score which encompasses quality of life, health and current energy level. IPAA patients ≥70 years in this study reported good CGQL scores. This study also compared Short Form-36 results between the IPAA patients ≥70 years and the U.S. population norm for healthy individuals ≥65 years and found no significant difference. Importantly, 82% of these patients stated that they would undergo IPAA again and 89% would recommend it to others.

In a separate retrospective review by Pellino of ten IPAA patients >80 years old compared with 30 randomly selected younger controls, older patients had significantly more nocturnal seepage and used antidiarrheal medications more frequently. By 1 year, only nocturnal seepage remained significantly higher in the elderly group. All patients retained their pouch at a median follow up of 7 (range 2–13) years. All patients reported they would undergo surgery again and recommend IPAA to other patients.

Recommendations

1. Ileal pouch-anal anastomosis can be safely performed in older patients who have well-managed comorbidities, adequate anal sphincter function and the ability to understand and manage their pouch function. (Evidence: moderate; Recommendation: strong)
2. Older patients with IPAA are at higher risk of dehydration than younger patients and should be monitored carefully for dehydration. (Evidence: moderate: Recommendation: strong)
3. Older patients with IPAA may have more frequent stools and an increased rate of incontinence, but they are generally satisfied with their pouch function and quality of life.

Personal View

In our view, IPAA is an acceptable and safe option for selected older ulcerative colitis patients. We agree with the American Society of Colon and Rectal Surgeons Practice Parameters for the Surgical Treatment of Ulcerative Colitis and the European Crohn's and Colitis Organisation Consensus guidelines which both state that IPAA can be offered to selected older patients as long as the patient retains good anal sphincter function and has adequate mental and physical function [14, 15].

For our older patients, particularly those with a history of fecal leakage, we recommend anal manometry testing prior to consideration of IPAA. Patients with very low resting anal sphincter pressures should not proceed to IPAA.

We find that many of our older ulcerative colitis patients prefer to have their disease addressed in a single operation with a total proctocolectomy and end ileostomy rather than undergo two or potentially three operations. Still, IPAA is a possibility for patients who wish to avoid permanent ileostomy.

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Role of Minimally Invasive Surgery in Pouch Surgery

32

Stewart L. Whitney and Alexander J. Greenstein

P (Patients)	I (Intervention)	C (Comparator)	O (Outcomes)
Ulcerative colitis patients undergoing ileal pouch-anal anastomosis	MIS	Open	Complication rate, quality of life

Introduction

Ileal pouch-anal anastomosis (IPAA) has undergone a progression of techniques over the last several decades. It was first described in 1978 by Sir Alan Parks in the British Medical Journal [1]. Although other types of pouches have been employed, such as the S-pouch and W-pouch, the J-pouch remains the most common pouch technique employed currently [2]. The creation of the pouch is commonly performed in 2 or 3 stages, although single stage creation has been described [3]. These stages typically include total abdominal colectomy (or subtotal colectomy), followed by restorative proctocolectomy with pouch creation with or without a diverting loop ileostomy, and then closure of the diverting loop ileostomy.

Laparoscopic surgery has been shown to be safe and effective in colorectal surgery in general, and ulcerative colitis in particular [4–6]. These minimally invasive

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approaches were initially used in ulcerative colitis for the total abdominal colectomy portion but are now commonly used during completion proctectomy and IPAA [7–12]. Our goal is to present and examine the data to support the safety, efficacy, and benefits of laparoscopy in surgery for ulcerative colitis by showing the comparisons of outcomes, quality of life and other endpoints.

Search Strategy

A comprehensive literature search of the Cochrane Review Database, Medline and PubMed was performed to identify all publications involving laparoscopy, ileal pouch-anal anastomosis, minimally invasive between 1980 and 2018. Keywords for search included: "ileal-pouch anal anastomosis", "laparoscopy", "minimally invasive". Studies were excluded if a laparoscopic or minimally invasive approach was not employed or was not mentioned in the study. References of these studies were then reviewed to incorporate any other pertinent studies. Outcomes measured and compared were: short-term morbidity, mortality, intra-operative complications, blood loss, operative time, functional outcomes (number of bowel movements per 24 h, night-time frequency, incontinence), quality of life, cosmesis, body image, fertility, incisional hernia rates.

Results

Early studies reporting on laparoscopic or minimally invasive IPAA tended to be single institution case series and cohort studies discussing their experience and outcomes. Over time, this led to several randomized trials with more robust data on long-term and functional outcomes.

Short-Term Outcomes

Short-term outcomes include: operating room time, intraoperative complications, return of bowel function, time to resumption of diet, length of stay, and postoperative complications. Operative time was reported by 10 trials and was noted to be significantly longer for the laparoscopic approach. Median operative time was 133 min with open and 214 min (range 149–400) with the laparoscopic approach ($p < 0.001$). Of note, several trials found that this gap closed over the years as the surgeons became more experienced with the laparoscopic technique [13–16]. Seven trials reported reoperation rates and there was a no significant difference between the laparoscopic and open approaches [14, 16–21]. In the single RCT reported by Maartense, there was 1 intraoperative complication in each group. Major complications were reported as 4/30 (13%) in the laparoscopic group and 5/30 (20%) in the open group ($p = 0.74$) [21].

Length of stay (LOS) is a perceived advantage of the laparoscopic approach, and thus was a primary endpoint in several studies. Many studies showed a statistically significant decrease in LOS when compared to open [22–24], while others showed no statistical difference [21, 25–27]. The RCT showed no difference between the

groups, with mean LOS at 11 days (range 6–28 days) in the open group and 10 days in the laparoscopic group (range 5–24 days; p = 0.76). A Cochrane Review published in 2011 [28] found a small, non-significant decrease in LOS when comparing laparoscopic to open with mean LOS being 11 and 12 days, respectively. Mortality was reported in nine trials, with eight showing 0 deaths in either group. One trial had a single death in the open group: however the Cochrane review showed no significant difference [13, 28] (Table 32.1).

Comparison between laparoscopic and open approaches with regards to time to regular diet were reported by several studies [22, 25, 29–32]. Maartense reported median time to regular diet at 6 days in the laparoscopic group and 7 in the open group (p = 0.6) [21]. Two studies showed a significantly faster return of bowel function in the laparoscopic group. Fichera reported that the laparoscopic group regained bowel function one day faster (p < 0.001) [33], and Marcello showed median days to return of bowel function at 2 days in the laparoscopic group vs. 4 days in the open group (p = 0.03) [22]. However, several other studies have shown no difference in time to regular diet between the two approaches [25, 30, 32].

Long-Term Outcomes

Long-term outcomes were reported by many studies. Functional outcomes included defecation frequency, fecal incontinence, and sexual dysfunction. Fecal incontinence was expanded to daytime episodes, nighttime episodes, soiling and urge incontinence. In these categories of fecal incontinence, no significant difference was found between the laparoscopic and open approaches.

Quality of life (QOL) aspects were reported by several studies. Dunker reported a mean number of defecations during the day at 5.7 (SD 1.3) in the laparoscopic group and 6.3 (SD 2.0) in the open group (p = nonsignificant) [16]. The RCT reported daytime frequency at 6.09 (SD2.29) in the laparoscopic and 5.35 (SD 1.82) in the open group, respectively (p = 0.161). Nighttime frequency was reported by these studies as well. This same study reported a nighttime rate of 1.0 (SD 0.7) in the laparoscopic group compared to 1.3 (SD 0.7) in the open group (p = non-sig). The RCT reported nighttime frequency rate at 2.14 (SD 1.91) in the lap group and 1.78 (SD 1.41) in the open group (p = 0.371). Incontinence rates were reported by 4 trials and all found a no significant difference between the groups. Each study had different parameters and definitions, and as such it is difficult to pool results (Table 32.2).

It is well-studied that laparoscopic surgery offers significant advantage with regards to future development of incisional hernia [34]. This is of particular interest in our cohort of patients given the need for an extraction site during the colectomy stage and the IPAA. Many surgeons now use the stoma site as the extraction site for a perceived decrease in incisional hernia due to the lack of need for a larger extraction incision. Two studies showed a significantly lower rate of incisional hernias in the laparoscopic group [29, 33]. Fichera and colleagues showed incisional hernia rates at 0% and 8.8% in the laparoscopic and open groups respectively (p = 0.011) [33].

Duff reported on their institutional experience with laparoscopic IPAA, and reported a 0% incisional hernia rate in their series of 75 patients [29]. Other studies

Table 32.1 Studies comparing LOS and complications with laparoscopic and open IPAA

First author year	Patients studied	Intervention	Study design	N (lap/open)	LOS (range)	30-Day major complication rate	30-Day reoperation rate
Maartense (2004) [21]	Patients with UC or FAP after IPAA	Laparoscopic or Open IPAA	RCT	30/30	Lap: 10 (5–31) Open: 11 (6–28) p = 0.767	Lap: 16.7% Open: 13.3% p = 0.74	Lap: 10% Open: 13.3% p = 0.72
Marcello (2000) [22]	Patients with UC or FAP after IPAA	Laparoscopic or Open IPAA	P, NR	20/20	Lap: 7 (4–14) Open: 8 (6–17) p = 0.02	Lap: 4 (20%) Open: 5 (25%) p = NS	Not reported
El-Gazzaz (2009) [23]	Patients with UC or FAP after IPAA	Laparoscopic or Open IPAA	P, NR	119/238	Lap: 5 (4–7) Open: 6 (5–8) p = 0.001	Lap: 23.1% Open: 21.5% p = 0.760	Not reported
Fajardo (2010) [25]	Patients with UC or FAP after IPAA	Laparoscopic or Open IPAA	R, NR	55/69	Lap: 8.4 (3–32) Open: 7/8 (3–31) p = 0.55	Lap: 50.1% Open: 59.4% p = 0.34	Lap: 21.8% Open: 20.3% p = NS
Polle (2008) [26]	Patients with UC or FAP after IPAA	Laparoscopic or Open IPAA	P, NR	65/30 (Total lap: 35, Hand-assist: 30)	Total lap: 9 (5–39) Hand-Assist: 10 (5–31) Open: 11 (6–28) p = 0.13	Total lap: 20% Hand-assist: 16.7% Open: 13.3% p = 0.745	Total lap: 20% Hand-assist: 10% Open: 13.3% p = 0.70
White (2014) [24]	Patients with UC or FAP after IPAA	Laparoscopic or Open IPAA	P, NR	76/131	Lap: 6 (4–8) Open: 8 (7–12) P < 0.001	Lap: 16% Open: 11.5% p = NS	Lap: 13.2% Open: 7.6% p = NS

R retrospective, *P* prospective, *NR* non-randomized, *RCT* randomized control trial, *NS* non-significant

Table 32.2 Studies comparing functional outcomes between laparoscopic and open IPAA

First author year	Patients studied	Intervention	Study design	N (lap/ open)	Daytime bowel movement frequency (mean and SD/ range)	Nighttime bowel movement frequency	Incontinence
Dunker (2001) [16]	Patients with UC or FAP after IPAA	Laparoscopic or open IPAA	R, NR	15/17	Lap: 5.7 (1.3) Open: 6.3 (2.0) p = NS	Lap: 1.0 (0.7) Open: 1.3 (0.7) p = NS	Lap: 0 Open: 1 (<1/ week) p = NS
Maartense (2004) [21]	Patients with UC or FAP after IPAA	Laparoscopic or open IPAA	RCT	22/23	Lap: 6.09 (2.29) Open: 5.35 (1.82) p = 0.161	Lap: 2.14 (1.91) Open: 1.78 (1.41) p = 0.371	Not applicable
Larson (2005) [17]	Patients with UC or FAP after IPAA	Laparoscopic or open IPAA	P, NR	33/33	Lap: 7 (3–14) Open: 6 (3–12) p = 0.23	Lap: 1 (1–5) Open: 2 (1–4) p = 0.86	Lap daytime: 70% Open daytime:70% p = 0.96 Lap nighttime: 52% Open nighttime: 45% p = 0.16
Otani (2001) [15]	Patients with UC or FAP after IPAA	Laparoscopic or open IPAA	NR	10/18	Lap: 8 (2.3) Open: 11 (1.0) p = NS (reported as 24 h)	Not applicable	Not applicable

R retrospective, *P* prospective, *NR* non-randomized, *RCT* randomized control trial, *NS* non-significant

have shown there is no difference, however. Benlice and colleagues showed no difference in incisional hernia rates between the groups, with the open group having an incidence of 8.4 while the laparoscopic group had a rate of 5.8% (p = 0.4) [35].

Fewer adhesions after laparoscopic intraabdominal surgeries has long been an argument for laparoscopy. Indar reported their findings after performing a laparoscopic evaluation of pelvic adhesions during the closure of the loop ileostomy following previous laparoscopic IPAA. 68% had no adhesions to the anterior abdominal wall, with the remaining 32% had mild, avascular filmy adhesions to the anterior abdominal wall [36]. No patients were found to have dense adhesions. Adnexal adhesions were also quantified using a standardized method and 15 of 21 (71%) female patients were found to have no adnexal adhesions, 5 of 21 (24%) had filmy adhesions enclosing less than one-third of one adnexa and 1 of 21 (5%) had filmy adhesions enclosing one-third to two-thirds of one adnexa. No patients had adhesions involving both adnexae.

Sexual function was reported by three trials. Each trial had different definitions for sexual function, and none of these studies found a significant different between the groups [16, 17, 21]. Cosmesis was reported by two studies using the same cosmesis scale, showing higher scores in the laparoscopic group compared to the open group [16, 21]. The RCT performed by Maartense found a superior score on the cosmesis scale from 14.7 to 18.5 in the laparoscopic group (p = 0.01) [21]. Dunker found a similar difference with mean score of 16 in the open group and 19.8 in the laparoscopic group (p = 0.03) [16].

Fertility is an important discussion with female patients undergoing IPAA, as these patients have a higher risk of infertility postoperatively. It has been well shown that open IPAA carries a high risk of infertility [37]. Bartels found that those patients who underwent laparoscopic IPAA had significantly lower infertility rates when compared to the open group, which was hypothesized to be secondary to decreased adnexal adhesions in the laparoscopic cohort [38]. This study used a questionnaire sent to female patients who had previously undergone IPAA. 50 patients reported they had attempted to conceive; 23 (46%) had undergone open and 27 (54%) had undergone laparoscopic IPAA. Their analysis showed a higher pregnancy rate in the laparoscopic IPAA group when compared to the open (p = 0.03). Three metaanalyses showed infertility rates in the open group at 48%, 43%, and 63%, respectively [39–41]. Beyer-Berjot found that that 73% of female patients after laparoscopic IPAA who attempted to conceive were able to, with a global infertility rate of 27%, which is much lower than the reported rates for the open groups [42] (Table 32.3).

Table 32.3 Studies evaluating fertility rates after Laparoscopic IPAA

First author year	Patients studied	Intervention	Study design	N (lap/ open)	Spontaneous pregnancy rate
Bartels (2012) [38]	Patients who underwent laparoscopic IPAA	Laparoscopic IPAA	R, NR	27/23	Lap: 19 (70%) Open: 9 (39%) p = 0.023
Beyer-Berjot (2013) [42]	Patients who underwent laparoscopic IPAA	Laparoscopic IPAA	R, NR	63 (only Lap)	73%

R retrospective, *P* prospective, *NR* non-randomized, *RCT* randomized control trial, *NS* non-significant

Personal View

Over the last 10–15 years, laparoscopy has become the primary surgical approach for IPAA. Our experience mirrors that seen in the studies; laparoscopic IPAA has similar functional outcomes when compared to open, can have shorter length of stays, with relatively low rates of conversion to open surgery. Our laparoscopic technique has evolved over the years, beginning with frequent use of hand-assist laparoscopic surgery (HALS) via a Pfannensteil incision. This technique was often employed when the colectomy and IPAA were performed in a single stage. The colon was mobilized laparoscopically and extracted, and the construction of the pouch and IPAA were performed via the hand-assist port.

Now, given the widespread use of biologics in our patients and the high percentage of patients that come for their initial operation after admission through the emergency room, we often create the IPAA in three stages, and perform this purely laparoscopically. We typically use a double staple technique unless there is rectal dysplasia or severe proctitis which would push us more towards mucosal stripping and a handsewn ileoanal anastomosis. Our preferred extraction site for the colon during the subtotal colectomy portion of the procedure is the ostomy site itself, but if the colon is too fatty and/or bulky, a small Pfannenstiel incision can be used. There is typically a 3 month wait between the first and second stages and then a 2–3 month wait between the second and third stages. There is routine use of diverting ileostomy during creation of the pouch and we have moved away from plain film enema studies towards CT pouchogram as the best strategy for evaluating the pouch prior to closure. Using standard 5 mm laparoscopic ports, we have had good results. Our patients are generally discharged on postoperative day 3 following the first and second stages with no change appreciated in either functional outcomes or leak rate.

We have found that we can obtain better visualization and thus a lower dissection in the pelvis with the laparoscopic technique when compared to open, and that subsequent cuff lengths can be significantly reduced. Endo GIA (Medtronic) is our stapler of choice and by using the shorter length staple loads (i.e. 45 and 30 mm) and deploying them through a 12 mm suprapubic port, it is easier to achieve a more flush staple line.

Another notable advantage is the significant decrease in adhesions in the laparoscopically-created IPAAs. We have found that re-operations in patients who underwent open IPAA had have had significantly worse intra-abdominal and pelvic adhesions when compared to the laparoscopic group, especially for those patients who underwent the pure laparoscopic approach without hand-assist.

We have found the laparoscopic approach to be safe with good functional outcomes, quicker return of bowel function and shorter length of stay. Our technique has evolved over the years with a significant learning curve required prior to reduction of operative times and complications.

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How Many Stages Should We Use in Pouch Surgery?

33

Roger D. Hurst

Introduction

For the last three decades restorative proctocolectomy with J-pouch ileoanal anastomosis has been the primary treatment for ulcerative colitis patients who require surgery. While most patients requiring surgery for ulcerative colitis are young and are at baseline in good health, many are at least temporarily debilitated from either severity of disease, infection, malnutrition, obesity or side effects of immunosuppressant medications. These factors greatly increase the risk for poor surgical outcomes, both in the short and long term. Even when conditions are optimized, the ileoanal anastomosis is known to be a high-risk anastomosis with frequent leaks and pelvic sepsis. Leak rates for the procedure are reported to be between 5% and 14% [1].

The high risk for anastomotic dehiscence was recognized early in the development of the procedure and strategies have been implemented in the hopes of diminishing the risks and consequences of poor anastomotic healing. For these reasons, performing the operation in multiple stages was the initial standard approach. However, the absolute need for staging has been questioned, with many advocating for a strategy of omitting the approach of multiple stages in selected cases and others omitting staging in almost all cases [2–4]. This chapter will review current available evidence to support the need for staging of operations in ulcerative colitis.

The ileoanal procedure can be performed in either a single stage, two-step, or three-step approach [5, 6]. The decision points for the number of stages selected center around two separate issues (Tables 33.1 and 33.2).

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Table 33.1 Decision point 1

Pt Population	Intervention	Comparator	Outcomes studied
Ulcerative colitis patients undergoing ileo-anal procedure	Omission of diverting stoma	Diversion of fecal stream	Anastomotic leaks, pelvic sepsis, long-term function, cost, length of hospital stay

Table 33.2 Decision point 2

Pt Population	Intervention	Comparator	Outcomes studied
Ulcerative colitis patients undergoing initial surgery	Total abdominal colectomy as initial operation	Ileoanal anastomosis as initial operation	Anastomotic leaks, pelvic sepsis, long-term function, cost, length of hospital stay

1. When constructing the ileal pouch-anal reservoir and performing the ileoanal anastomosis, should the fecal stream be diverted with a loop ileostomy to enable the pouch and the anastomosis to heal optimally?
2. In patients who are temporarily debilitated, should a total abdominal colectomy with end ileostomy and defunctionalized Hartmann's pouch be performed to allow for physiologic recovery prior to undertaking the riskier reservoir construction and ileoanal anastomosis?

This chapter will review both of these controversies.

Search Strategy

A midline Ovid database search was performed on publications from 1985 through June 2018 comparing ileal pouch-anal anastomosis with or without diverting loop ileostomy. MeSH search headings utilized: restorative proctocolectomy, ileo-anal, ileoanal anastomosis, ileal pouch, ileal reservoir, ileostomy, loop ileostomy and infliximab. References found from these articles were also searched and reviewed. Additionally "Find Citing Articles" function was utilized to further enhance the extent of the search.

Results

Diverting Loop Ileostomy

Multiple reports have been published regarding the value of a diverting loop ileostomy when performing pouch construction and creating the ileoanal anastomosis. No definitive study exists, as each of these studies is flawed by either a lack of adequate numbers, poor study design, or the potential for significant bias. Many studies are retrospective reports comparing only highly selected cases. Case control studies do exist, yet again in most instances these studies involve highly selected patients or insufficient numbers. Add to this, the results of these studies have been

conflicting, with some studies suggesting an increased risk for anastomotic leaks and pelvic sepsis when the diverting stoma is omitted [7–12] while other studies suggest that the presence of the stoma does not affect the rate of anastomotic complications [13–30]. The studies supporting and opposing the use of a temporary diverting stoma are listed in Tables 33.3 and 33.4.

Table 33.3 Studies supporting the use of diverting stomas

Author	Date	Study type	Patients with stoma	Patients without stoma	Quality of evidence
Cohen et al. [7]	1992	Retrospective, selected	87	71	Low
Tjandra et al. [8]	1993	Matched controls	50	50	Moderate
Williamson et al. [9]	1997	Selected	50	50	Low
Kienle et al. [10]	2003	Prospective cohort, Selected	27	32	Low
Weston-Petrus [11]	2008	Meta-analysis			Moderate
Mennigen et al. [12]	2011	Selected, retrospective	89	33	Low

Table 33.4 Studies supporting omission of diverting stoma

Author	Date	Study type	Patients with stoma	Patients without stoma	Quality of evidence
Everett et al. [13]	1990	Selected	35	29	Low
Matikainen et al. [14]	1990	Consecutive	21	25	Low
Galandiuk et al. [15]	1991	Retrospective matched controls, selected	37	37	Low
Grobler et al. [16]	1992	Randomized control study, selected	23	22	Low
Sagar et al. [17]	1992	Consecutive, Selected	28	30	Very low
Gorfine et al. [18]	1995	Retrospective, selected	69	74	Low
Gullberg et al. [19]	1995	Consecutive	7	13	Low
Hainsworth et al. [20]	1998	Selected	30	72	Low
Antos et al. [21]	1999	Selected	20	23	Low
Dolgin et al. [22]	1999	Consecutive, Prospective nonrandomized	14	16	Low
Mowschenson et al. [23]	2000	Retrospective, selectided	28	102	Low
Heuschen et al. [24]	2001	Matched controls, selected	144	57	Moderate
Lepisto et al. [25]	2002	Retrospective	154	332	Moderate
Ikeuchi et al. [26]	2005	Retrospective, selected	92	150	Low
Remzi et al. [27]	2006	Retrospective, selected	1725	277	Low
Joyce [28]	2010	Retrospective	715	120	Low
Gray et al. [29]	2012	Selected	28	22	Low
Sahami et al. [30]	2016	Retrospective	305	316	Low

A common design strategy employed in many of these reports is to allow the operative surgeon to make a judgment regarding the need for the loop ileostomy (those with "selected" study designs as designated in Tables 33.3 and 33.4). This decision is based on the perceived risk for anastomotic complications. The surgeon therefore decides who is at high risk (placing these patients in the diverted group) and patients judged to be at low risk (placing these patients in the undiverted group). While this strategy may well be a reasonable approach in the management of patients undergoing surgery for ulcerative colitis, when applied to a clinical study, this method of patient selection creates obvious bias, such that interpretation of the results can be difficult. Accordingly, when such studies show no difference between the two groups, it is difficult to conclude that there is in fact no benefit from the loop ileostomy.

The absence of a difference between the two groups may result from the loop ileostomy effectively taking high risk patients and decreasing their risk to that of the lower risk group. One can only conclude from these studies that patients judged to be at low risk for anastomotic complications will do as well as a high-risk cohort when the loop ileostomy is omitted. Additionally, it is important to note that there are several studies that indicate that even in patients selected in this manner, those without a loop ileostomy have an inferior outcome [7, 9, 12].

There is only one randomized controlled trial looking at the value of diverting loop ileostomy in restorative proctocolectomy [16]. This study was markedly underpowered, with only 23 patients in the loop ileostomy group and 22 patients in the undiverted group. In each group, there is only one anastomotic leak and patients that were randomized had been preselected by the operating surgeon as having a low risk for anastomotic leak.

Perhaps the best available study to suggest that loop ileostomy may not be necessary is a matched-pair controlled study conducted by Heuschen [24]. In this study, 57 patients in the study group (no diversion) were compared to 114 matched controls. No significant differences were found in early complications, including pouch related septic complications. Conversely, Tjandra reported a study with matched controls with 50 patients in each group and found a 14% risk for anastomotic leak and pelvic sepsis in patients who had not been diverted compared to 4% in the controls [8].

In 2008, Weston-Petrides published a meta-analysis for the data available from 1978 through 2005 from all comparative studies looking at restorative proctocolectomy with or without covering ileostomy [11]. This analysis indicated that restorative proctocolectomy without a diverting loop ileostomy resulted in similar long-term functional results but was associated with an increased risk for anastomotic leak and pelvic sepsis. The conclusion of the authors was that the loop ileostomy should only be omitted in carefully selected patients.

The goal of avoiding an anastomotic leak is worthwhile, as poor anastomotic healing typically has major consequences both in the short and long term. For instance, patients who experience pelvic sepsis are five times more likely to require pouch excision compared to patients who avoided anastomotic leaks and pelvic sepsis [1, 31, 32]. In addition, patients who have pelvic sepsis but are able to retain their pouches are more likely to have anal incontinence [1].

While many of the studies looking at the value of fecal diversion focus on the risk for anastomotic leak, there are other considerations that come into play when deciding which operative strategy is best for the patient. Studies looking at the total length of stay and total costs have favored the approach of performing the ileoanal anastomosis without the loop ileostomy. While performing the operation in a single step tends to lead to a longer initial hospitalization, when the length of hospital stay for the reversal of the loop ileostomy is taken into account, the total hospitalization is shorter with the one step approach [9, 12, 14, 16–18, 20, 21, 26, 28]. Additionally total costs have been shown to be lower in those patients undergoing the procedure without a diverting loop ileostomy [28].

When considering a staged approach, the morbidity associated with the loop ileostomy itself must also be considered [33]. Some have suggested that the overall morbidity associated with loop ileostomy is substantial [34, 35], but others have noted that severe complications are not frequent [36]. Additionally a large study published in 2005 involving 1504 patients from the Cleveland Clinic demonstrated that closure of the ileostomy can be accomplished with an overall complication rate of 11.4% and a risk of intra-abdominal sepsis of only 1% [37]. Additionally an aggressive and coordinated approach of managing stoma patients can greatly diminish the incidence of stoma related dehydration and need for readmission [38].

Initial Colectomy Prior to IPAA

The value of an initial total abdominal colectomy prior to ileal pouch-anal anastomosis in patients with intraabdominal sepsis or severe comorbid disease has not been subject to comparative studies as the risks to these patients would be difficult to justify. However, reports of patients who have undergone either a two or three step approach have identified certain parameters under which a three stage approach would be preferred [39–41]. Traditionally, these have included urgent surgery, sepsis, fulminate disease, anemia, hypoalbuminemia, steroids, and uncertain diagnosis [3, 5, 41, 42].

A more recent and significant controversy surrounds the risks for perioperative complications for patients who are being treated with anti-TNF agents. In 2005, the anti-TNF antibody infliximab, was approved for use in patients with ulcerative colitis [43]. Shortly after the widespread use of infliximab for the treatment of ulcerative colitis, the Mayo Clinic and the Cleveland Clinic both reported a substantial increase in postoperative infectious complications in ulcerative colitis patients treated with infliximab [44, 45]. This finding had not been consistent across all reports, and is somewhat surprising given that infliximab had been used for many years in the treatment of Crohn's disease and no significant increase in perioperative complications has been consistently demonstrated in these patients [46–52]. This may be explained by the fact that the ileal pouch-anal anastomosis is normally a high risk anastomosis even under ideal conditions. It may well be that infliximab generates a relatively small effect on healing in general, but that this effect is magnified in this very delicate anastomosis.

In response to the findings suggesting that anti-TNF therapy increases risk for anastomotic leaks, many surgeons have changed their approach to the surgical management by utilizing a three-step approach in patients treated with anti-TNF agents [53, 54]. In a study from the Cleveland Clinic, Gu looked at patients undergoing surgery for ulcerative colitis without an initial total abdominal colectomy [53]. They found that those patients on anti-TNF therapy had a significantly greater risk for pelvic sepsis (32% versus 16%; $p = 0.01$) when the procedure was not staged with an initial total abdominal colectomy. However, they reported no difference in outcomes between the patients who had been treated with anti-TNF therapy as compared to those who had never been treated with anti-TNF agents when patients initially underwent an initial colectomy. These findings not only indicate that the use of anti-TNF therapy increases the risk for septic complications, they also indicate that utilizing an initial total abdominal colectomy can mitigate the negative effects of the anti-TNF agents.

Recommendations Based on the Data

1. A diverting loop ileostomy may be omitted in highly selected patients undergoing ileal pouch-anal anastomosis. (Weak Recommendation based upon low-quality of evidence)

   From current available data, it is difficult to give strong recommendations as to appropriateness of omitting a diverting loop ileostomy with restorative proctocolectomy. Even investigators intimately involved in the subject have had difficulties with this. For instance, Sagar in 1992 initially reported a comparison of one-stage versus two-stage ileoanal procedures and found no significant difference in the risk for anastomotic leaks or other complications, concluding that omission of the loop ileostomy may be a reasonable option in selected patients [17]. The same group later reported in 1997 that with further experience they found that patients undergoing a one-stage restorative proctocolectomy had significantly higher risk for severe septic complications and cautioned against the routine use of a one-stage proctocolectomy [9]. Additionally, Tjandra in 1994 initially reported a matched control study that found in equally favorable cases, restorative proctocolectomy without diversion was not as safe as with diversion [8]. The same institution later reported a retrospective study indicating no difference in septic complications [27]. The senior author on both of these studies subsequently co-authored a meta-analysis indicating that restorative proctocolectomy without a diverting ileostomy was associated with an increased risk for anastomotic leak [11].

   Even with these difficulties, there is general consensus among experts that the diverting loop ileostomy can be omitted in highly selected patients. Indeed, this has been the recommendation from expert panels from both Europe and North America [55, 56]. Patient selected for omission of loop ileostomy are best not to have any of the risk factors listed in Table 33.5. Despite the recommendation from expert panels that omission of the loop ileostomy is reasonable in selected

Table 33.5 Factors that may increase risk for poor anastomotic healing

1. Severe or Fulminate Colitis
2. Sepsis
3. Malnutrition
4. Hypoalbuminemia
5. Obesity
6. Technical difficulties
7. Steroid use
8. Use of immunosuppressants
9. Technical concerns
10. Tension on anastomosis
11. Fecal contamination
12. Anemia
13. Anti-TNF therapy

patients, many practicing surgeons appear to adopt a very conservative approach to this issue. A recent survey of colorectal surgeons in North America indicated that 73% would perform a diverting loop ileostomy even in low risk patients [57].

2. Ulcerative colitis patients with sepsis, severe comorbid factors, or those treated with anti-TNF therapy should undergo an initial total abdominal colectomy prior to ileal pouch-anal anastomosis. (Weak recommendation based upon low-quality of evidence)

There is little controversy that the sickest of patients should undergo a three-stage approach. At the same time, there is insufficient evidence to accurately delineate the circumstances in which the three-stage approach is the best option. Early evidence suggests that the use of anti-TNF therapy poses a risk for increase in anastomotic leaks and pelvic sepsis and that these risks can be diminished by utilizing a three-stage approach [53]. Further study however is required to confirm the advantage of this approach.

A Personal View of the Data

Unfortunately, the data on the value of staging the surgeries for the ileoanal procedure are conflicting. Thus, it is a difficult decision as to whether to omit the diverting loop ileostomy. In addition, it is also a problem deciding when to perform an initial total abdominal colectomy prior to the ileoanal procedure. Ultimately it is up to the discretion of the experienced surgeon working in concert with the patient's wishes to determine the best approach.

In the past, as many as one third of this author's patients underwent an ileoanal procedure in a single step. With the advent of anti-TNF therapy, this however has changed and now most patients in my practice undergo surgery with a staged approach. The reports of poor anastomotic healing with anti-TNF therapy are concerning. This combined with my antedoctal experience with anastomotic problems in patients receiving anti-TNF therapy has made staging in my practice much more common. Additionally, the decision to stage the operations has become somewhat

more attractive with the advent of laparoscopic surgery. The lower morbidity and enhanced recovery after laparoscopic total abdominal colectomy makes the decision for staging easier to accept as it is much better tolerated than an open procedure [58].

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Optimal Design for Ileal-Pouch Anal Anastomosis

34

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Introduction

Since its description in 1978 [1], the ileal-pouch anal anastomosis (IPAA) has become the most commonly performed procedure for patients with ulcerative colitis requiring surgery. In their initial description of the IPAA, Parks and Nichols constructed a three-limb "S" pouch with a hand-sewn pouch-anal anastomosis. Several years later, Utsunomiya [2] et al. reported on a two-limb "J" pouch; with the advent of the surgical stapler, this generally became the procedure of choice due to its ease of construction. As practice patterns have changed over time, the optimal pouch configuration has been debated in the literature. Both the S-pouch and J-pouch configurations have well described functional and complication profiles. In this chapter, the literature comparing the complication rates and functional results of these pouches is reviewed and followed by our recommendation on the optimal design for IPAA (Table 34.1).

Table 34.1 PICO Table

(P) Patients	(I) Intervention	(C) Comparator	(O) Outcome
Ulcerative colitis patients undergoing ileal pouch-anal anastomosis	J-pouch	S-pouch	Complication rates, functional results

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Search Strategy

A comprehensive literature search of Cochrane Database of Collected Research, EMBASE, MEDLINE, and PubMed was performed to identify all of the English-language publications related to ulcerative colitis and ileal pouch-anal anastomosis complication rates and functional results from 1985 to 2018. Key search terms included the following: "ileal pouch-anal anastomosis," "inflammatory bowel disease," "proctocolectomy," and "ulcerative colitis," "J-pouch," "S-pouch." Studies were excluded if they did not directly compare J-pouch and S-pouch configurations or if they failed to measure any post-operative complications or functional outcomes of interest. Several studies included comparisons of J-pouches and S-pouches, in addition to comparisons to other pouch designs (K-pouch, W-pouch). Only the most recent study was included if similar studies from the same institution were encountered. References of the included studies were reviewed to identify additional studies that were incorporated as appropriate.

Results

After the description of the J-pouch and the development of the end-to-end surgical stapler, many surgeons began to favor J-pouch creation for patients with ulcerative colitis due to ease of construction. Subsequently, a number of studies have compared both post-operative complications and functional outcomes between the J-pouch and the previously described S-pouch. The majority of these studies are limited to retrospective, single-center series of patients undergoing IPAA for either ulcerative colitis or familial adenomatous polyposis. No randomized controlled trials exist and few studies focus solely on patients with UC.

Complications

Pouch Failure

Anastomotic leak and pelvic sepsis have been shown to be important risk factors for pouch failure, defined as the need for permanent ileostomy or pouch excision [3]. A prospective, non-randomized analysis of 23 J-pouches and 15 S-pouches evaluated at 6 months after surgery by DeSilva [4] showed no difference in surgical complications before or after diverting ileostomy closure, including pelvic sepsis, wound infection, anastomotic dehiscence, stricture, and hemorrhage. Macrae [5] and Tulchinksy [6] similarly showed no difference in pouch failure in retrospective single-center studies.

A meta-analysis performed in 2007 of 23 studies found no difference in rates of anastomotic leak, pelvic sepsis or pouch failure [7]. One study by Mukewar [8] focusing on long-term complications evaluated 215 J-pouches at a median of 15 years after pouch creation and 45 S-pouches at a median of 9 years after surgery. Pouch failure was similar between groups at 6.7% and 7.9% respectively. The most

recent large retrospective single-center study of 4525 patients (4098 J and 427 S pouches) in 2017 again found no difference in pouch failure [9]. Interestingly, one study [10] of 502 handsewn IPAAs at a single tertiary care center (68.7% with UC) including 333 J pouches and 169 S-pouches, found a statistically higher rate of complications in J-pouches. Specifically, pelvic sepsis (13.8% vs. 7.7%), pouch fistula (15.8% vs. 9.5%), and pouch-related complications (33.0% vs. 23.1%) were higher in patients with J-pouches. However, anastomotic leak, separation, and pouch failure rates were similar between groups. The authors of that study hypothesized that the S-pouch had more favorable anatomy for a hand-sewn anastomosis due to its extra 1–2 cm of length.

Pouchitis

Pouchitis is the most common long-term complication for patients with IPAA. Several studies have looked at the incidence of pouchitis by pouch design with mixed results. At least six retrospective studies [4, 10–14] and two meta-analyses [7, 15] have found no differences in pouchitis rates between configurations. These studies have a fair amount of heterogeneity in the reported incidences of pouchitis (10–39%), likely due to variable follow up rates and definitions of pouchitis (some studies used clinical diagnosis while others relied on endoscopic evidence). In contrast, at least three studies have found a higher rate of pouchitis in patients with J-pouches. McMullen [16] retrospectively compared 38 J-pouches and 35 S-pouches and found pouchitis rates of 23.7% and 5.7% respectively, and Durno [17] reported pouchitis in 12 out of 41 J-pouches and none of 13 S-pouches. The highest quality data demonstrating an increased risk of pouchitis in J-pouches comes from Mukewar [8], who identified rates of acute pouchitis in 36% of J-pouches and 15.6% in S-pouches. Furthermore, this study reported that chronic antibiotic-resistant pouchitis occurred in 13% of J-pouches and none of the S-pouches (S-pouch vs. J-pouch OR 0.07; 0.001–0.54, $p = 0.001$). The etiology for the potential increased rates of pouchitis in J-pouches is unclear; however, some authors have hypothesized that there is likely a mechanical etiology, such as stretch on the mesenteric vasculature during pouch creation.

Mechanical Complications

Mechanical obstruction in patients with IPAA can present in the form of adhesive small bowel obstruction, pouch-anal anastomotic stricture, or efferent limb syndrome. Two large meta-analyses [7, 15] showed no differences in adhesive small bowel obstruction when the data were viewed in aggregate. A retrospective study [12] of pediatric patients with ulcerative colitis also demonstrated no differences in small bowel obstruction between J-pouches and S-pouches. Wu's comparison of handsewn J-pouch and S-pouch [10] highlighted a higher rate of partial SBO in J-pouches (35% vs. 22%, $p = 0.003$).

Obstruction at the pouch-anal anastomosis itself has been widely studied, as S-pouches appear to be uniquely susceptible to "efferent limb syndrome" in which the segment of ileum that exits the pouch and is anastomosed to the anus prevents spontaneous evacuation. In one of the earliest comparisons between the two designs,

Schoetz [11] reported that two of 20 S-pouches required pouch intubation compared to none of the J-pouches. DeSilva's [4] prospective study of 23 J-pouches and 15 S-pouches at 6 months post-operatively reported the ability to evacuate in all J pouches and only 7 of the 15 S-pouches. Pescatori [14] reported that a small number of S-pouches (4 of 59) required intubation, however none of the 131 J-pouches had difficulty evacuating.

Furthermore, three retrospective single-center studies [17–19] cite spontaneous evacuation rates of 46–75% in S-pouches compared to 88–98% in J-pouches; Lovegrove's [7] meta-analysis calculated a cumulative odds ratio of 6.2 in the need for pouch intubation when comparing S-pouches to J-pouches. Mukewar's study on long term outcomes of pouches reported that S-pouches were more likely to have pouch-related complications than J pouches (44% vs. 9%), with the majority of complications in S-pouch being related to obstruction due to a long distal limb or anastomotic stricture [8].

In contrast, a number of studies comparing J-pouches and S-pouches have demonstrated no difference in pouch intubation or spontaneous evacuation; however, these are often small retrospective studies with lower quality data [20, 21]. Stricture at the pouch-anal anastomosis has been reported in a small number of studies. A retrospective single-center study [12] of pediatric patients with UC reported an incidence of 2.0% in J-pouches compared to 21% in S-pouches. Wu's analysis of hand-sewn anastomosis did not favor S-pouches or J-pouches in regard to anastomotic stricture (21% vs. 26%).

Functional Outcomes

Many studies have examined functional outcomes in J-pouches compared to S-pouches and the two pouch designs therefore have very well described profiles. Several of these studies have focused on pouch anatomy and physiology, attempting to characterize differences in pouch function that may be attributed to the extra volume associated with the third limb of the S-pouch. The earliest review of pouch physiology was conducted by Nasmyth [22] in 1987 and examined 10 J-pouches and 7 S-pouches. The average maximum volume and compliance of S-pouches was 440 mL and 13.3 mL/mmHg respectively, which was higher than the average measurements in the J-pouches (340 mL and 8.8 mL/mmHg). However, this study was possibly confounded by differences in the times from surgery, as S-pouches were measured at a mean of 23 months from time of creation while J-pouches were measured at an average time of 5 months from creation. One other study by Hallgren [23] concluded that S-pouches have greater maximum pouch volume at 1 year compared to S-pouches (420 mL vs. 305 mL). Two other prospective studies [4, 21] and one retrospective study [24] found no difference in maximum pouch volume, but reported greater compliance in

S-pouches (14 mL/mmHg vs. 7–8 mL/mmHg). Interestingly, there was also no difference in resting anal canal pressure between groups. The clinical significance of these parameters is unclear.

Frequency of defecation, urgency, and fecal incontinence have a tremendous impact on patient quality of life. In some of the earliest retrospective analyses in the late 1980s [22, 25, 26], J-pouches were associated with an increase in stool frequency by about one bowel movement over 24 h (5–6 vs. 4–5). One of these studies [25] interestingly found that urgency was increased in J-pouches in the short term, but that this disappeared at 8 months. Schoetz [11] reported an incontinence rate of 10.6% in J-pouches vs. 5% in S-pouches, but no differences in urgency, frequency, or need for absorptive pads. Cohen's retrospective study [20] of 70 J-pouches and 80 S-pouches initially found worse urgency, frequency, and nocturnal awakening with J-pouches, but again these differences disappeared at 8 months.

As technical proficiency in J-pouch creation increased, several studies [4, 14, 23, 24, 27, 28] reported no statistically significant difference in 24-h stool frequency. Of these studies, one [24] demonstrated a significantly higher prevalence of nocturnal bowel movements in J-pouches compared to S-pouches (70% vs. 50%). DeSilva [4], Romanos [18], and Sarigol [12] all reported no differences in overall, daytime or nocturnal incontinence, and Tekkis [27] showed no difference in urgency. In a small prospective single center study of 17 J-pouches and 18 S-pouches, Tuckson [21] reported an increase in median stool frequency over 24 h in J-pouches (6 vs. 5, $p < 0.05$), as well as a higher rate of nocturnal incontinence (53% vs. 28%), nocturnal bowel movements (75% vs. 40%), and lower proportion of patients that were able to defer defecation for greater than 1 h (35% vs. 50%). The groups in this study had no difference in daytime incontinence rates and had similar average duration of deferred defecation.

In Wu's analysis of handsewn pouch-anal anastomoses, J pouches had significantly more bowel movements over 24 h (7 vs. 6, $p < 0.001$), higher prevalence of use of absorptive pads (46% vs. 29%, $p < 0.001$), and higher fecal incontinence severity index scores (26.8 vs. 21.4, $p = 0.02$). Both of the large meta-analyses [7, 15] comparing pouch designs concluded that J-pouches were subject to increased stool frequency with an average of one more bowel movement over 24 h. All other functional outcomes however were equivalent between pouch designs.

The creation of an IPAA inherently results in an increase in diarrhea due to the lack of colonic absorptive capacity. Consequently, many patients require anti-diarrheal agents for symptom management. Studies evaluating necessity for anti-diarrheal agents have shown a clear advantage for the S-pouch design. In Schoetz's earliest analysis in 1986, 51% of J pouches required anti-diarrheal agents compared to 30% of S-pouches [11]. Similarly, three other retrospective studies [4, 18, 21] found a significantly increased need for anti-diarrheal agents and a meta-analysis [7] calculated an aggregate odds ratio of 0.36 for S-pouch compared to J-pouch ($p = 0.01$).

Alternative Pouch Designs

In addition to J and S pouches, several other IPAA designs have been described, in particular the four-loop W-pouch, the H-reservoir, and the ileoanal Kock pouch. While detailed analysis of these designs is outside the scope of this chapter, it should be noted that some groups have reported improved outcomes over the more commonly performed J-pouch. A meta-analysis [15] of studies comparing pouch configurations found that the W-pouch had a lower rate of pouch failure when compared to the J-pouch (OR 2.8, $p < 0.01$) and S-pouch (OR 4.9, $p < 0.01$). Furthermore, the W-pouch had a weighted mean difference of 0.6 bowel movements per 24 h less than the J-pouch ($p < 0.01$) and a lower rate of need for anti-diarrheal medications (J vs. W, OR 2.7, $p < 0.01$), but similar rates of seepage, pad usage, urgency, incontinence, and ability to evacuate spontaneously. This meta-analysis did include three randomized control trials; however close to 50% of W-pouches were created by a single high-volume center and therefore these favorable outcomes may not be generalizable.

Recommendations Based on Data

Surgeons performing restorative IPAA after proctocolectomy for ulcerative colitis should favor creation of a J-pouch configuration over an S-pouch configuration, although both designs have generally good outcomes when performed by experienced surgeons. Although the quality of evidence in the literature is low, a distinct advantage for the J pouch over the S pouch exists when considering the ability to spontaneously evacuate without pouch intubation, as this has been a reported complication of S-pouch creation.

Because the J pouch configuration is associated with slightly increased stool frequency (one BM/day) and higher rates of pouchitis, one can make the case for the S-pouch configuration. However, the difference in stool frequency is small and may decrease with time as the pouch matures. Furthermore, the pouchitis data are heterogenous with a number of studies (including 2 meta-analyses) showing no difference in pouchitis rates and only one retrospective study showing increased pouchitis rates in J-pouches in the long-term. S-pouches may have improved functional outcomes for handsewn pouch-anal anastomosis, however prospective randomized controlled trials are needed to support this practice. (*Evidence quality: low; strength of recommendation: moderate*).

Personal View of Data

Taken together, we continue to favor the J-pouch design over the S-pouch because of relative ease of creation and comparable functional outcomes in terms of stool frequency, continence, etc. There may be slightly less pouchitis with the S-pouch, but we suspect the incidence is probably similar if one were to perform a careful study that included histologic as well as clinical criteria. The main problem with the S-pouch is the association with poor evacuation and need for intubation, difficulties that are virtually absent in the J-pouch patients. However, in patients where extra length is required to reach the anal canal, the S-pouch is a reasonable alternative (Table 34.2).

Table 34.2 Selected studies comparing pouch configurations

Study (year)	Study design	Patients, n J-pouch vs. S-pouch	Outcomes measured	Finding	Quality of evidence
Remzi (2017) [9]	Retrospective, 4525 IPAAs at single institution (66.8% with UC)	4098 vs. 426	Pouch failure	No difference – OR 0.66 (0.37–1.18) for S vs. J pouch	Very low
Wu (2015) [10]	Retrospective, 502 handsewn IPAA from 1983–2012 at single tertiary care center (68.7% with UC)	333 vs. 169 *S-pouch patients tended to be younger (35.5 ± 12 vs. 3.8.9 ± 12), higher BMI (26 vs. 24), fewer extra-intestinal manifestations	*Complications* Ileus Anastomotic leak Wound infection Anastomotic separation Anastomotic stricture Pouch fistula Partial SBO Pelvic sepsis Pouchitis Dehydration Pouch-related hospitalizations Pouch failure *Function* Bowel movements/24 h Use of pads (daytime/nighttime) Fecal incontinence severity index	No difference (13.5% vs. 12.4%, p = 0.73) No difference (1.5% vs. 3.0%, p = 0.32) No difference (6.9% vs. 10.7% p = 0.15) No difference (90.0% vs. 8.3%, p = 0.79) No difference (20.7% vs. 26.0%, p = 0.18) 15.9% vs. 9.5% (p = 0.047) 35.4% vs. 22.5% (p = 0.003) 13.8% vs. 7.7% (p = 0.044) No difference (39.3% vs. 37.9%, p = 0.75) No difference (16.2% vs. 13.0%, p = 0.15) 33.0% vs. 23.1% (p = 0.021) No difference (13.5% vs. 10.1%, p = 0.23) 7.0 vs. 6.0, p < 0.001 45.8% vs. 28.9% (p = 0.001)/55.2% vs. 41.3% (p = 0.001) 26.8 ± 15.5 vs. 21.4 ± 14.8 (p = 0.02)	Moderate

(continued)

Table 34.2 (continued)

Study (year)	Study design	Patients, n J-pouch vs. S-pouch	Outcomes measured	Finding	Quality of evidence
Mukewar (2014) [8]	Retrospective, all patients with UC	215 vs. 45 (36 with continent ileostomies) *J pouches more likely to be male (56% vs. 35%)	Acute pouchitis Chronic-antibiotic resistant pouchitis Pouch related complication Pouch failure	36.3% vs. 15.6%, p = 0.002 13% vs. 0%, S vs. J - OR 0.07 (0.001–0.54); p = 0.001 9.3% vs. 44.4%, S vs. J – OR 8.0 (3.7–17.5), p < 0.001 No difference (6.7 vs. 7.9%)	Moderate
Ozdemir (2014) [13]	Retrospective, tertiary care center. 433 pediatric IPAA patients (78.3% with UC)	371 vs. 62	Pouchitis	No difference (31.8% vs. 32.3%, p = 0.094)	Low
Tekkis (2010) [27]	Retrospective, multi-center study; 2491 patients, (79.9% with UC)	1464 vs. 110 (612 W pouches, 305 unspecified)	Urgency Frequency	No difference No difference	Low
Lovegrove (2007) [7]	Meta-analysis of 23 studies; 1519 IPAA patients	689 vs. 524 (306 W pouches)	Anastomotic leak Anastomotic stricture Wound infection Pelvic sepsis SBO Pouchitis Pouch failure Stool frequency/24 h Seepage Day/night pad usage Urgency Incontinence Anti-diarrheal medications Pouch intubation	No difference No difference No difference No difference No difference No difference No difference S vs. J – Coefficient − 1.48 (−2.10 to −0.85); p < 0.001 No difference No difference No difference No difference S vs. J – OR 0.36 (0.16–0.81); p = 0.01 S vs. J – OR 6.19 (1.12–34.07); p = 0.04	High

Table 34.2 (continued)

Study (year)	Study design	Patients, n J-pouch vs. S-pouch	Outcomes measured	Finding	Quality of evidence
Tulchinksy (2003) [6]	Retrospective, single center (96.5% with UC)	202 vs. 46 (296 W pouches, 90 Kock pouches)	Pouch failure	No difference (15% vs. 22%)** compared to 5% in W pouch, p = 0.001)	Very low
Romanos (1997) [18]	Retrospective, single center (87.5% with UC)	130 vs. 41	Incontinence Urgency Spontaneous evacuation Antidiarrheals	No difference (17.6% vs. 14.6%, p = 0.649) 13.8% vs. 2.4%, p = 0.427 97.7% vs. 46.3%, p < 0.001 36.9% vs. 7.3%, P < 0.001	Low
Macrae (1997) [5]	Retrospective, single center	321 vs. 228	Pouch failure	No difference	Very low
Sarigol (1996) [12]	Retrospective, single center pediatric patients (all with UC)	51 vs. 38	Anastomotic stricture Perineal infection Small bowel obstruction Pouchitis Daytime incontinence Nocturnal incontinence	2.0% vs. 21.1%, P = 0.004 No difference No difference No difference No difference No difference	Very low
Gemlo (1995) [28]	Retrospective, single center, 297 IPAAs 9 months post-op (282 with UC)	68 vs. 229 (50 vs. 30 within non-mucosectomy group)	Frequency/24 h Functional index Night-time pad use	No difference 95.5 vs. 91.8, p = 0.009 Higher in S pouch, p = 0.031	Low

(continued)

Table 34.2 (continued)

Study (year)	Study design	Patients, n J-pouch vs. S-pouch	Outcomes measured	Finding	Quality of evidence
DeSilva (1991) [4]	Prospective, functional pouches 6 months	23 vs. 15 (23 W pouches)	Reoperation and complications Evacuation Pouchitis Frequency Incontinence Anti-diarrheals Pouch capacity	No difference 8 S-pouches could not evacuate ($P < 0.001$) No difference No difference (5 vs. 4) No difference (5 vs. 4) 12 vs. 1 ($P < 0.05$) No difference	Moderate
Tuckson and Fazio (1991) [21]	Prospective, single center (31/35 with UC)	17 vs. 18 (</>6 months)	Anal canal pressure Pouch capacity Compliance Daytime incontinence Night time incontinence Median frequency Nocturnal bowel movement Time to defer defecation % deferring defecation >1 hr. Spontaneous evacuation Anti-diarrheals	No difference No difference (250 vs. 254/275) 7.6 mL/mmHg vs. 14.1/15.4 mL/mmHg No difference (29% vs. 22%) 53% vs. 28%, $p < 0.05$ 6 vs. 5/4 (>6 months $p < 0.05$) 75% vs. 40% No difference (1.7 h) 35% vs. 50%/70% (>6 months $P < 0.05$) No difference 71% vs. 44%/29% (>6 months $p < 0.05$)	Moderate

Table 34.2 (continued)

Study (year)	Study design	Patients, n J-pouch vs. S-pouch	Outcomes measured	Finding	Quality of evidence
Tuckson, McNamara et al. (1991) [24]	Retrospective, single center	69 vs. 47	Frequency Nocturnal bowel movement Pouch volume Compliance	No difference 70% vs. 50% No difference (228 vs. 276) 8.4 vs. 14.4 mL/mmHg ($P < 0.005$)	Low
Pescatori (1990) [14]	Retrospective, 207 IPAAs multiple centers (141 with UC)	131 vs. 59 (13 W and 4 L pouches)	Pouchitis Bowel frequency Evacuation	No difference (13% vs. 11%) No difference (4.4 ± 1.9 vs. 3.9 ± 2.1) 4 S-pouches required intubation, 0 J-pouches	Very low
Hallgren (1989) [23]	Retrospective	11 vs. 11	Pouch volume Frequency	J-pouch significantly less at 1 year (305 vs. 420; $p < 0.05$) No difference	Low
McHugh (1987) [25]	Retrospective, single center 74 patients (2 surveys, 8 months apart)	20 vs. 19	Urgency Frequency Nightime soiling	J > S ($p = 0.0015$) on first survey; no difference on 2nd 6.6 vs. 5.5/6.8 vs. 5.9 No difference	Low
Schoetz (1986) [11]	Retrospective, single center, 91 patients	66 vs. 20	Required intubation Pouchitis Incontinence Urgency Wearing pad Antidiarrheals Frequency	0 vs. 2 (NS) No difference 10.6% vs. 5% No difference No difference 51.5% vs. 30% No difference	Low

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Mucosectomy Versus Stapled Ileal Pouch-Anal Anastomosis

35

Fabian Grass and David W. Larson

Introduction

Ileal pouch-anal anastomosis (IPAA) is the procedure of choice to alleviate the need for permanent ostomy creation in patients with ulcerative colitis (UC) who have exhausted medical therapy. Controversies remain regarding the optimal anastomotic approach. While the original description by Parks and Nicholls in 1978 suggested complete mucosectomy to the dentate line and hand-sewn anastomosis, stapling devices over the last three decades have become the default practice [1–3]. Several historical randomized trials [4, 5] compared mucosectomy and stapled IPAA in the nineties, but none demonstrated the superiority of either technique. Small sample size and single institutional methods may account for such findings.

Better functional results due to less surgical trauma with stapled anastomosis need to be carefully balanced with inherent risks of disease recurrence and dysplasia due to residual mucosa around the anal transition zone (ATZ). In this chapter, consideration of more recent evidence on surgical complications, long-term function and quality of life (QoL) and oncological risks will be reviewed.

Search Strategy

Relevant PICO terms were generated, as outlined in Table 35.1. A comprehensive literature search of Cochrane Database of Collected Research, EMBASE, MEDLINE, and PubMed was performed to identify all English-language publications related to ulcerative colitis, ileal pouch-anal anastomosis (IPAA) and surgical, functional and oncological outcome and quality of life (QOL) from 2000 to 2018. Key search terms included the following: "j-pouch," "ileal pouch-anal

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Table 35.1 PICO table

Patients	Intervention	Comparator	Outcome
Ulcerative colitis patients undergoing proctocolectomy with ileal pouch anal anastomosis	Mucosectomy (hand-sewn anastomosis)	Stapled anastomosis	Complication rate, quality of life

anastomosis," "ulcerative colitis," "mucosectomy," "proctocolectomy," "hand-sewn" and "stapled." Studies were excluded if they did not specifically compare mucosectomy to stapled IPAA, exclusively reported on familial adenomatous polyposis (FAP) patients, included pediatric patients, reported only on specific pouch configurations other than J-pouch, or failed to report on any pertinent outcome as specified above. Cross-referencing of included studies was performed to identify pertinent additional studies that were retained as appropriate.

Results

Technical Considerations

Regardless of pouch configuration, IPAA can be performed by either a hand-sewn technique at the dentate line or to the remaining rectal cuff with a stapling device. Some technical aspects must be considered to recognize potential complications of either technique. Mucosectomy by definition implies removal of the proximal anal mucosa (dentate line) and the distal 3–4 cm of rectal mucosa through a perineal approach [6] before anastomosing the ileal pouch to the dentate line. This approach requires additional pouch mobilization to advance the additional 2–4 cm into the pelvis for the hand-sewn anastomosis [7]. These technically demanding aspects may lead to mechanical trauma to the sphincter mechanisms due to inelastic retractors. Removing anal mucosa may also impair the rich sensory innervation of the ATZ [7, 8].

Stapling on the other hand may decrease tension on the mesentery, which has been directly related to pouch survival [9]. Stapling has hence been labeled "quick and safe" [10], while mucosectomy is more challenging. A learning curve for mucosectomy was quantified for senior staff who attained adequate results following an initial period of 31 procedures [11], and the direct relationship of surgical skills and septic complications was described by a susequent study [12]. These facts clearly suggest the importance of surgical experience when entertaining the more challenging and complex mucosectomy.

Surgical Complications

Short and long-term surgical complications of IPAA are classified as septic complications (e.g., anastomotic leaks, abscesses, fistulas) and non-septic complications (e.g., small bowel obstruction, anastomotic stricture, pouchitis or cuffitis of the retained rectal mucosa, pouch failure). Table 35.2 provides an overview of cohort studies providing complication rates by comparing mucosectomy to stapled IPAA. Anastomotic

Table 35.2 Cohort studies providing surgical complication rates comparing mucosectomy (hand-sewn anastomosis) versus stapled IPAA

First author (year)	Patients per group (hand vs. stapled)	Outcome	Study design	Complication rate (hand vs. stapled)	Quality of evidence
Fukushima (2000) [17]	64 vs. 146 (13 FAP)	Pelvic sepsis	R	15.6% vs. 5.5% ($p < 0.05$)	Low
Gecim (2000) [18]	1358 vs. 99 (153 FAP)	Perianal abscess or fistula	R	7% vs. 3% (ns)	Low (small control group)
Rossi (2002) [19]	41 vs. 34 (7 FAP)	Anal complications:Abscess, fistula, fissure, stenosis	PO	41% vs. 47% (ns)	Moderate (small sample size)
Prudhomme (2003) [26]	Overall 1884 (208 FAP)	Strictures (fibrotic and non-fibrotic)	R	12% vs. 4% ($p < 0.05$)	Low (design, data gathering)
Bednarz (2005) [27]	15 vs. 56 (9 FAP)	Strictures (among others)	R	6.6% vs. 5.3%	Very low (small sample size, endpoints)
Rickard (2007) [16]	167 vs. 334 (53 (FAP)	Anastomotic leak, strictures	R	8.5% vs. 3.3%, 16% vs. 9% ($p < 0.05$ for both)	Moderate (multicenter, web-based data collection, heterogeneous configuration)
Kirat (2009) [14]	474 vs. 2635 (516 non UC)	Septic complications, obstruction, strictures, pouch failure	R	21.3% vs. 16.9%, 23% vs. 18.6%, 21.7% vs. 16%, 11.4% vs. 4% ($p < 0.05$ for all)	Moderate (large sample size, heterogeneous patient groups)
Lian (2009) [15]	437 vs. 2580 (unknown non UC)	Anastomotic leak, pouch failure	R	7.2% vs. 5.5% (ns), 35.3% vs. 12% ($p < 0.05$)	Moderate (heterogeneity, pouch configuration)
Manilich (2012) [31]	521 vs. 3233 (792 non UC)	Pouch failure	R	HR 1.72; 95% CI, 1.23–2.42)	Moderate
Fazio (2013) [13]	386 vs. 2573	Anastomotic leak, strictures, fistula, obstruction	R	9.2% vs. 6.1%, 23% vs. 15.3%, 12.7% vs. 8.5%, 22.7% vs. 17.1% ($p < 0.05$ for all)	Moderate

(continued)

Table 35.2 (continued)

First author (year)	Patients per group (hand vs. stapled)	Outcome	Study design	Complication rate (hand vs. stapled)	Quality of evidence
Helavirta (2016) [28]	283 vs. 69	Strictures	R	17.6% vs. 0% ($p < 0.05$)	Low (small control group)
Sahami (2017) [32]	39 vs. 674	Pouch failure	R	HR 3.01 (1.04–8.64)	Moderate (validation of Cleveland cohort)

R retrospective, *PO* prospective observational, *UC* ulcerative colitis, *FAP* familial adenomatous polyposis

leak rates of up to 6.5% have been reported after IPAA [13]. Among large-scale studies, Fazio [13] and Kirat [14] of the Cleveland group demonstrated slightly higher leak rates after mucosectomy, while no significant difference was observed by Lian [15]. Consistently in these large series, a shift towards stapled anastomosis was described in recent decades, leaving mucosectomy for challenging or high-risk cases, which might represent a selection bias for all studies. Rickard [16] found an increased relative risk of anastomotic leak after hand-sewn anastomosis of 2.6, and emphasized the severe sequelae (pouch removal, strictures and fistulae). Fukushima [17] reported similar results with higher leak rates after mucosectomy that were explained by lack of experience and surgical difficulty. Both studies were limited due to their small sample size.

Anal complications including abscesses or fistulas were not significantly affected by hand-sewn anastomosis in two studies reporting on this outcome [18, 19]. These specific complications may be associated with anastomotic leaks and are more likely in patients with Crohn's disease, according to Nisar [20]. One must keep in mind that sutured anastomoses were often reserved for specific challenging situations including complex pouch configurations or rectal dysplasia. The question of whether or not fistulas are related to technical challenges remains debatable [21, 22]. Several meta-analyses have not demonstrated significant differences in the outcomes based on anastomotic technique [23, 24].

Small bowel obstruction (SBO) represents the most common surgical complication after IPAA with rates of up to 23% [25]. The rate of SBO has been specifically compared between the two types of anastomosis in the study of Kirat [14] and Fazio [13] with higher rates after mucosectomy (Table 35.2). This finding may be partly explained by a greater use of stoma and associated complications after mucosectomy.

Several series [13, 14, 16, 19, 26–28] reported on strictures that may occur early or late, and were consistently higher after mucosectomy. In a recent study by Helavirta [28], a shift towards the stapled technique was described in 2005, and no strictures after stapled anastomosis were observed in this rather small series. The Cleveland group published stricture rates of up to 23% after mucosectomy in contrast to 15% after stapled anastomosis [13]. Independent of the technique, most strictures could be managed conservatively across all studies.

Inflammation of the pouch (pouchitis) is frequent with rates of up to 50% [29]. Pouchitis has not specifically been compared between the two techniques in recent years and might rather be related to patient- and disease-related factors [30]. The risk of pouch failure, on the other hand, was estimated in a large retrospective cohort study including 3754 patients, considering 21 potential preoperative risk factors [31]. Lower pouch survival was associated with completion proctectomy, Crohn's disease, hand-sewn anastomosis and diabetes, factors which were retained in the final prognostic model for pouch failure. The authors explained higher failure rates after hand-sewn anastomosis based on changing patterns of surgery at the institution (pouch configuration, only complex cases undergoing mucosectomy in early experience, longer follow-up time after hand-sewn cases). A recent external validation study [32] retained hand-sewn anastomosis as the only independent predictor in the suggested model (Table 35.2), with further predictors being anastomotic leak and Crohn's disease.

Function and Quality of Life (QoL)

Numerous parameters are available to evaluate pouch function after IPAA, including defecation frequency, nocturnal defecation, continence, soiling and seepage [33]. Surrogate parameters of pouch function include QoL and sexual function, which are highly interdependent. Table 35.3 gives an overview on studies providing data on functional outcome including sexual function and QoL comparing both anastomotic techniques. In summary, throughout most studies, pouch function seems to be better in early follow-up (<5 years) after stapled anastomosis, which is thought to be due to preservation of the ATZ [7]. However, studies providing data on long-term follow up suggest equivalent long-term outcomes [34] including QoL, which was excellent 20 years after IPAA regardless of the anastomotic technique according to the Mayo experience [35]. The only study revealing a better QoL using the Cleveland Global QoL score after stapled anastomosis was the single center large scale study of Kirat [14]. However, the authors acknowledge a potential bias regarding the two patient groups as a hand-sewn anastomosis was reserved for more complex cases. Several studies including a meta-analysis specifically described improved nocturnal continence after stapled IPAA, with improved anorectal physiologic measurements [23, 34, 36, 37]. Contrary data includes the meta-analysis of Schluender, which found no advantage in functional outcome including manometric measures for either group [24].

Dysplasia/Neoplasia Risk

Performing mucosectomy with a hand-sewn anastomosis does not protect entirely from dysplasia or malignancy, since dysplasia may develop in the pouch itself, especially in the setting of chronic pouchitis [38]. A systematic review of Scarpa including 2040 patients concluded that an increased risk of cancer due to chronic inflammation

Table 35.3 Cohort studies providing data on functional outcome and quality of life comparing mucosectomy (hand-sewn anastomosis) versus stapled IPAA

First author (year)	Patients per group (hand vs. stapled)	Outcome	Study design	Main results (mucosetomy)	Quality of evidence
Saigusa (2000) [36]	12 vs. 20 (18 FAP)	Function (manometry)	PO	↓ Resting pressure	Moderate
Michelassi (2003) [43]	274 vs. 117	Long term function, QoL	PO	↓ Continence, improvement over time + good QoL after both techniques	Moderate (emergency procedures included)
Gorgun (2005) [44]	13 vs. 109 (51 non UC)	Male sexual function	S	Improved scores after IPAA in both techniques	Low (small response rate)
Kirat (2009) [14]	474 vs. 2635 (516 non UC)	Urgency, incontinence, QoL	R	↑ Incontinence, ↑ social restrictions, ↓ QoL	Low (large sample size, heterogeneous patient groups)
Lian (2009) [15]	437 vs. 2580 (unknown non UC)	Incontinence, QoL	R	↑ Incontinence (after leak), QoL comparable	Moderate (heterogeneity, pouch configuration)
Kiran (2011) [45]	145 vs. 248 (18 FAP)	Long term (>15 years) function	R	↓ Pouch function in both groups, QoL comparable and high	Moderate (heterogeneous configuration)
Ishii (2015) [46]	23 vs. 35	Bowel movements, soiling, QoL (SF-36, IBDQ)	R/S	Equal functional outcomes after 3 years and long-term QoL	Moderate (small sample size)
Harnoy (2016) [47]	69 vs. 66	Sexuality and fertility (IIEF-5 questionnaire)	R/S	No difference in both techniques for sexuality and fertility	Moderate (policy change during study period)
Tonelli (2016) [37]	60 vs. 273	Function (manometry)	PO	↓ Sphincter tone, ↓ nocturnal continence	Moderate (long study period)
Sunde (2018) [34]	386 vs. 2573	Pouch volume/ sensation Pouchitis	S/ Pouch endo-scopy	No difference in sensation thresholds, ↑ poorly functioning pouches	Moderate

PO prospective observational, *R* retrospective, *S* survey, *UC* ulcerative colitis

exists after either anastomotic technique [39]. The cumulative incidence of pouch-related adenocarcinoma does not exceed 0.4% 20 years after IPAA, according to a more recent systematic review by Selvaggi [40]. Mucosectomy decreased the risk of neoplasia eight-fold according to this last study, with the strongest risk factor for adenocarcinoma being the presence of preoperative dysplasia or cancer. Zmore [41] investigated the oncological outcome in patients with coexisting colorectal cancer or dysplasia who underwent stapled IPAA. While 2 out of 16 patients with preoperative cancer died of metastatic disease, no patient with preoperative dysplasia relapsed at 5 years. The authors concluded stapled IPAA was a reasonable option in patients with cancer/dysplasia at the time of IPAA. Vento [42] did not detect any dysplasia at 10 years in patients who developed chronic pouchitis after mucosectomy and IPAA. Altogether, these ambiguous results suggest that either technique carries a risk of neoplasia, even though the risk after mucosectomy seems to be decreased.

Recommendations

Stapled IPAA can be recommended as standard approach in most circumstances (Evidence: low to moderate; Recommendation: strong).

Recent data is probably biased by the adoption of stapled IPAA as standard approach by most centers in recent decades, leaving mucosectomy for more challenging disease presentations. Technical ease of use and decreased short and long-term morbidity were identified as major advantages of this approach. While some studies reported superiority of short-term functional outcome, long-term function and quality of life seem to be equal. Since the stapled procedure bears an inherent increased risk of disease relapse and/or dysplasia and neoplasia, mucosectomy and hand-sewn anastomosis should remain the procedure of choice for patients with preoperative dysplasia or cancer upon endoscopic evaluation. However, data is scarce, and this approach requires advanced surgical expertise and skills to accomplish effectively.

Personal View

Recent evidence as reviewed in this chapter revealed equal long term functional results comparing both anastomotic techniques, while short-term morbidity was consistently lower after stapled IPAA. Regarding the risk of disease relapse or malignancy, the largest published series [38, 39] did not find a higher rate of neoplasia in either the ATZ or pouch after a stapled procedure; the primary risk factor remains dysplasia or malignancy at the time of IPAA [33]. Thus, in patients presenting with colitis and rectal high-grade dysplasia or adenocarcinoma at the time of surgery, mucosectomy and hand-sewn IPAA should be performed in a high volume center. Stapled anastomosis can be considered as the first choice in all other circumstances.

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Transanal Proctectomy and Ileoanal Pouch Procedure (ta-J Pouch)

36

A. D'Hoore

Introduction

Akin to other minimally invasive surgical colorectal procedures, laparoscopic ileoanal pouch surgery has gained popularity with significant short-term benefits encompassing postoperative recovery, less pain and reduced hospital stay. Long-term favorable effects on the risk of adhesive small bowel, abdominal wall hernia and female fecundability are yet other potential advantages of the laparoscopic approach. Furthermore, improved body image and cosmesis after a laparoscopic pouch procedure should not be underestimated in this frequently young population [1]. Interestingly, pelvic sepsis, including anastomotic leak and ultimate pouch failure, remain equal between laparoscopic and open ileoanal surgery [2].

On the other hand, the learning curve of laparoscopic pouch surgery is significant with a relatively high rate of conversion to an open approach. Some authors therefore advocate a hand-assisted approach [3] or a laparoscopic facilitated approach with use of a Pfannenstiel incision to overcome inherent problems during the pelvic dissection and distal rectal transection [4].

An important, yet technically demanding step in the laparoscopic technique is assuring the distal rectal transection is perpendicular to the pelvic floor. Often the angle for transection is oblique, resulting in the need for multiple stapler firings and an increased risk of anastomotic leak [5]. In addition, inadequate transection of the distal rectum may risk leaving a long rectal cuff behind resulting in an increased occurrence of cuffitis and/or pouch evacuation problems.

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The transanal J pouch (ta-J pouch) was developed in an effort to address technical shortfalls of the laparoscopic ileoanal pouch. The transanal approach nearly completely abolishes the need for conversion to an open approach, and the outcome is independent from patient related features such as obesity and a narrow male pelvis. In contrast to a TME procedure for cancer, close rectal dissection can be performed to avoid autonomic nerve damage. Leaving the mesorectal fat behind resolves the problem of an empty space behind the ileoanal pouch. The key advantage of the transanal approach however is the direct visual control on the level of the pouch-anal anastomosis.

The surgeon can directly decide where to transmurally transect the anorectal junction, just leaving the anal transition zone in place. This in contrast to 'blind' cross-stapling if performed from above. It appears intuitive that this is more accurate than using digital control at stapler closure and avoids leaving behind a longer cuff on the anterior side. Another advantage of this approach is the design of the ileoanal anastomosis, changing from a double staple with the potential creation of "dog ears" at the sides to a single stapled which can be easily reinforced transanally. Finally, the transanal platform allows an ergonomic dissection in a horizontal plane of the most distal and curved part of the rectum.

Methodology

See Table 36.1.

Search Terms

PICO (Population, Intervention, Comparator, Outcome) data were obtained (Table 36.2). A literature search of EMBASE, MEDLINE, and PubMed was conducted to identify all publications associated with ulcerative colitis, ileoanal anastomosis, and post-operative pouch complications from 2013–2018. The following key search terms were queried: 'colitis', 'ulcerative colitis', or 'inflammatory bowel disease'; 'ileoanal anal anastomosis', 'IPAA', 'J pouch'; 'transanal'. All reference lists of the included manuscripts were noted to identify additional publications that were acceptable for inclusion. Publications from the same institution were carefully assessed for overlap and only the most recent study was considered in this circumstance. Observational, prospective, retrospective, and randomized studies were considered for the literature assessment.

Table 36.1 PICO table

Patients	Intervention	Comparator	Outcome
UC patients requiring IPAA	Transanal IPAA	Laparoscopic IPAA	Short-term complications

Table 36.2 Feasibility studies (single center experiences) in ta-J Pouch

	Study	N patients	Conversions	Anastomotic leak	Hospital stay Median, (range)
de Buck van Overstraeten [6] Leuven University Hospital, Belgium	Description of the technique Feasibility study	11	0	0	6 days (4–12)
Leo CA [7] St Marks Hospital London, UK	Feasibility study consecutive May 2013–oct 2015	16	18.7% Due to adhesions	1	6 days (3–20)
Levic Souzani K [8] Hospital Hvidovre Copenhagen, Denmark	Feasibility study consecutive Sept 2017–Feb 2018	11	0	1	7 days (5–37)

Operative Approach

The Ta J pouch is usually performed after the patient has fully recovered from a total colectomy with Brooke ileostomy [6]. The patient is placed in a modified Lloyd-Davis position on a pink pad to allow extreme Trendelenburg positioning. The patient's arms are cushioned along the body to allow free movement of the operating team and a urinary catheter is installed. Intravenous prophylactic antibiotics are given.

Step 1: Ileal Pouch Creation

As a first step, the end ileostomy is completely mobilized. The bowel end is stapled closed. After complete mobilization, a single port device is introduced through the ileostomy site. The abdominal cavity is insufflated with CO_2 and a maximum pressure of 12 mmHg is maintained. The table is tilted to the left allowing a complete mobilization of the mesentery from the retroperitoneal plane to the pancreatic head up to the origin of the superior mesenteric vessels. This is important to gain maximum mesenteric length for ileal pouch construction. Using a vessel sealing device, incisions are made on the anterior surface of the mesentery in a stepladder fashion. Thereafter the terminal ileum is exteriorized through the single port and a classical J-pouch is fashioned. The head of a mechanical circular stapling device is introduced and the purse string knotted. We use a short rubber tube to allow easy grasping from the transanal side (Fig. 36.1).

Step 2: Transanal Pelvic Proctectomy

The patient is now positioned in Trendelenburg position to allow the small bowel and ileal pouch to stay out of the pelvis. If the uterus is in place, temporary suspension can be performed through the round ligaments to allow better pelvic access.

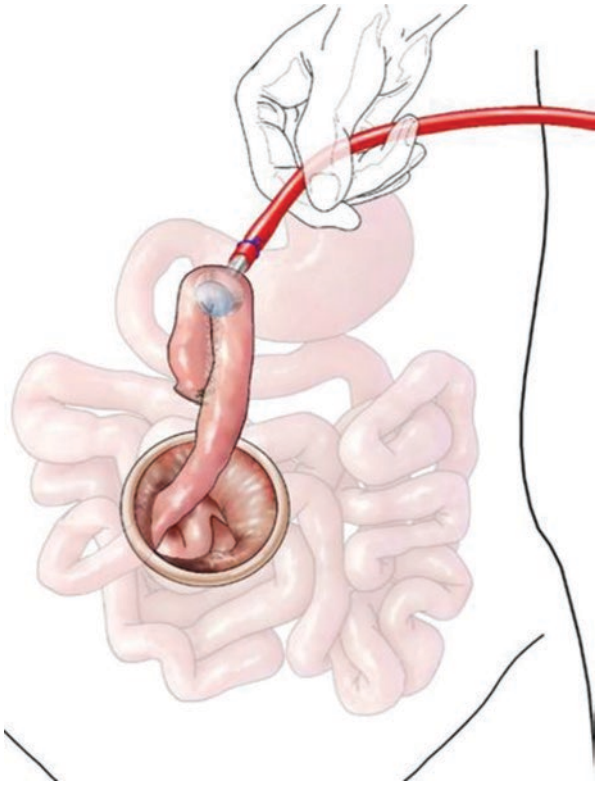

Fig. 36.1 Construction of the ileal pouch after the terminal ileum has been delivered through the single-port device. Mounting a short rubber tube is useful to facilitate grasping the pouch from the transanal side

The rectal stump is grasped and the upper part is dissected. Care is taken to stay close to the rectal tube so the superior rectal artery and the mesorectal fat stay in place. This dissection is advanced to the level of the pouch of Douglas.

In a second phase, the transanal dissection is started. To expose the anal canal, a Lonestar® retractor is used to adequately visualize the dentate line as well as the anal transition zone. An endoanal purse string suture is place at the level of about 0.5 cm above the transition zone, above the desired level for the pouch anal anastomosis. Care should be taken to appreciate that the tissue will be incorporated in the distal doughnut and the stapled anastomosis should not be placed too low in the anal canal.

With traction on the purse string suture, monopolar electrocautery is used to create a transmural incision. Thereafter, the GelPoint® Path transanal port is introduced and an AirSeal® trocar introduced. The Airseal will maintain a stable CO_2 pneumorectum environment and adequate smoke evacuation to optimize visual control during the transanal dissection. Using a sealing device, a close rectal tube dissection is performed cephalad to 'rendezvous' with the abdominal dissection. As the dissection is performed close to the rectal tube, only minor vessels need to be sealed and there is virtually no risk for autonomic nerve damage or injury to the bulbar urethra. After the dissection has been completed, the rectum is fully dismounted and removed through the transanal port or the ileostomy site. Final hemostasis is

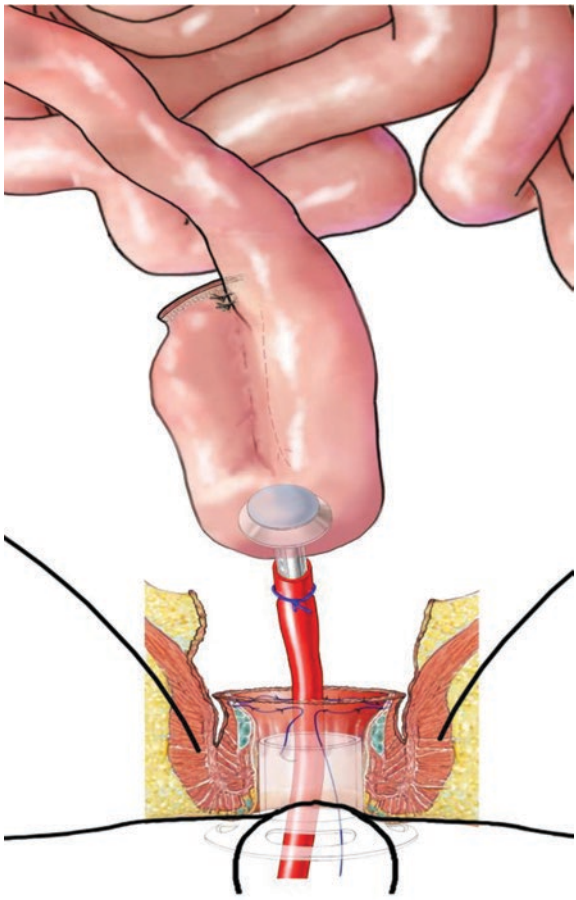

Fig. 36.2 By grasping the rubber tube (18 French) from the transanal position, the pouch is gently maneuvered into the pelvic cavity. There is continuous visual control from the abdomen. It can be helpful to elevate the incised pouch of Douglas to give space for the pouch to descend into the pelvis

performed of the remaining mesorectal fat pad. A laparoscopic clamp is introduced transanally and the rubber tube on top of the anvil of the pouch is grasped. With visual control from the abdominal single port, the pouch is now advanced into the pelvic cavity and guided to the anal canal (Fig. 36.2). This maneuver is critical to avoid inadvertent twisting of the ileal pouch and to avoid internal herniation of small bowel under the mesentery of the pouch.

The transanal platform is now removed and a distal purse string using a 2–0 Prolene® is made. Care should be taken to incorporate all layers of the transmural incised distal rectum. The stapler is assembled and the purse string suture knotted. We routinely leave a plastic obturator within the anal canal to easily introduce the stapling device, avoiding damage to the anorectal mucosa or the internal sphincter of the distal anal canal (Fig. 36.3). After closing of the stapler, a final check of the anatomy is performed from the abdomen, and the vagina is digitally controlled to avoid any dorsal vaginal entrapment within the stapler. The stapler is fired, removed and the donuts inspected. A reverse airleak test should now be performed.

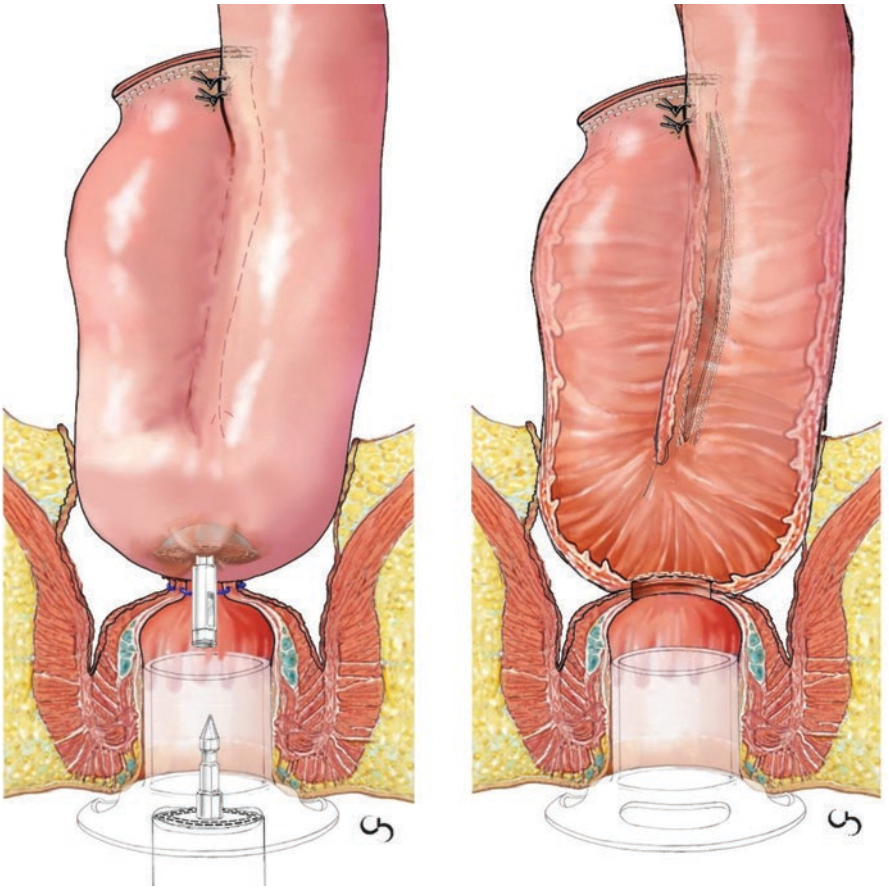

Fig. 36.3 The anvil and stapler head are docked and the distal purse string knotted. The mechanical circular stapler is introduced through a plastic transparent anal obturator to protect the anal canal and mucosa

Pneumoperitoneum is accomplished and the distal anastomosis transanally immersed in saline. We routinely reinforce the stapler line by placing endo-anal 3–0 Vicryl interrupted stitches. A drainage tube is left within the pouch for two days. No pelvic drain is necessary as the pouch is surrounded by the remaining mesorectal fat with little or no dead space. If no technical difficulties have been encountered, a diverting loop ileostomy is omitted and we opt for a modified two stage procedure. The abdominal single port device is extracted and the peristomal fascia and skin closed.

Literature Review

The literature regarding outcomes of ta-J pouch is in its infancy (Table 36.2). De Buck van Overstraeten was the first to publish their technique in a technical note

(with video vignette) to illustrate the step-by step approach of ta-J pouch [6]. The authors reported on a pilot series of 11 patients (median age 34; range 22–66). A close rectal dissection was performed. No conversion to either multiport laparoscopy or laparotomy was needed. No anastomotic leaks were reported. Median hospital stay was 6 days (range 4–12). Feasibility of the technique was demonstrated.

Leo [7] published their experience with 16 patients. In this series, the authors explored the safety and feasibility using a TME-type of dissection. In this prospective, consecutive case series performed between May 2013 and October 2015, only patients having a ta-J pouch with an abdominal approach using a single-incision platform were included. Thirteen patients previously underwent subtotal colectomy. In two patients (19%), intraabdominal adhesions required conversion to laparotomy. One patient developed an anastomotic leak and the overall 30-day surgical complication rate was 37.5%. The authors conclude that ta-J pouch was a feasible alternative to open or multiport laparoscopic surgery for restorative proctocolectomy. Potential advantages included safer dissection of the rectum and a single stapled anastomosis.

Levic Souzani [8] described their first experience in 16 consecutive patients (operations performed between September 2017 and February 2018). All patients had previous subtotal colectomy and end-ileostomy and had a three-stage approach. The authors demonstrate the feasibility of the technique and did not report any perioperative complications or conversions to laparotomy. An anastomotic leak occurred in one patient. The median length of hospital stay was 7 days (range: 5–37). This initial experience demonstrated the feasibility of the technique. Spinelli [9] described the technique of transanal ileal pouch and the use of ICG (indocyanine green) to evaluate bowel perfusion before and after anastomosis.

Studies Comparing ta-J Pouch to Other Surgical Approaches

There are no prospective randomized data available. There is only one comparative study [10], adding data from three referral centers in Europe (Leuven University, Belgium; Academic Hospital Amsterdam, Netherlands and Aarhus University Hospital, Denmark). Ninety-seven patients with ta-IPAA were compared to 119 transabdominal J pouch procedures. The CCI (cumulative complication index) [11] was used as a primary endpoint. The mean CCI score for ta-J pouch was 13.1 compared to 18.2 for the transabdominal approach. The odds for postoperative morbidity were 0.52 times lower in the ta-J pouch group ($p = 0.003$). When complications were present, no differences between groups was observed. Interestingly the mean overall leak rate was 7.4% and not different between the two groups. There was a significant reduction in conversion to laparotomy rates in favor for the ta-J pouch group. Operating time was shorter and overall hospital stay reduced.

Ta-J pouch is safe and feasible (strength of recommendation is moderate based on moderate quality evidence).

Personal View

The safety and feasibility of ta-J pouch has been established. From a theoretical perspective, this new approach could be advantageous over a classical laparoscopic or open approach. With more experience, conversion to laparotomy will probably be significantly reduced. Level of the ileal pouch anal anastomosis may be more precise and therefore the risk of leaving a too long rectal cuff should be minimized. Whether a combination of close rectal dissection and single stapled anastomosis will reduce the risk for anastomotic failure needs to be confirmed. There is also a need to evaluate functional outcomes as the transanal device stretches the anal canal.

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Use of Antiadhesive Barriers in Pouch Surgery

37

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Introduction

Ileal-pouch anal anastomosis (IPAA) is a desired option for many ulcerative colitis (UC) patients since it provides the opportunity for restoration of intestinal continuity. Nonetheless, there is no difference in the overall quality of life between patients who undergo IPAA versus permanent ileostomy as both groups report significant improvement [1]. IPAA reconstruction is associated with a variety of complications which may impact quality of life. Postsurgical adhesions create a significant amount of morbidity for patients after IPAA. Over 20% of patients who undergo IPAA may develop small bowel obstruction (SBO) [2]. Decreased fertility after IPAA has been well-established with approximately 40–50% of female patients in the child-bearing years reporting inability to conceive within 12 months [3–5]. There is great interest in surgical approaches that can minimize the formation of these adhesions.

Numerous commercial barrier agents have been designed to reduce intraabdominal adhesions after surgery [6]. These products prevent contact between raw peritoneal or serosal surfaces. 0.5% Ferric Hyaluronate Gel (Intergel; Lifecore Biomedical Inc., Chaska, MN) was designed to be instilled into the peritoneal cavity following surgery to minimize tissue apposition. This product was subsequently withdrawn due to adverse events. Oxidised regenerated cellulose (Interceed®; Ethicon, Sommerville, NJ, USA) is an absorbable product. Interceed® is not often used due to the requirement for total hemostasis prior to application, as the combination of blood and oxidized cellulose in the peritoneal cavity may promote increased adhesion formation; this is antithetical to the intended purpose. Polytetrafluorethylene (Gore-Tex®, W.L. Gore Corporation, Flagstaff, AZ, USA) is a permanent material that requires suture fixation. Justifiable concerns about leaving permanent material in the intraperitoneal position have decreased enthusiasm for Gore-Tex® as an antiadhesive product. Sodium hyaluronic

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Table 37.1 PICO table

Patients	Intervention	Comparator	Outcome
Patients with UC undergoing IPAA	Anti-adhesion barriers	Standard care	Adhesions Small bowel obstruction Fertility

acid and carboxymethylcellulose membrane (Seprafilm®; Genzyme Corporation, Cambridge, MA, USA) is an absorbable product that can be used without fixation and without a requirement for absolute hemostasis, making it a more popular choice.

This chapter will discuss the role of antiadhesive barriers in IPAA surgery (Table 37.1).

Search Strategy

A comprehensive literature search was performed in MEDLINE, EMBASE and PubMed from inception to June 2018, without language restriction, for any human clinical study assessing the effect of antiadhesive barriers in colorectal surgery with regards to intraabdominal adhesions, small bowel obstruction, or fertility. MeSH descriptors were used that included: "proctocolectomy, restorative" or "colonic pouches" or "surgery, colorectal" or "digestive system surgical procedures" combined with "biocompatible materials" or "membranes, artificial" or "carboxymethylcellulose sodium" or "hyaluronic acid" combined with "tissue adhesions" or "intestinal obstruction" or "fertility". Given the paucity of studies investigating IPAA patients, the search was expanded to include all colorectal surgical patients. Citation tracking was used to identify any additional relevant studies.

Results

Becker [7] was the first to assess the effects of Seprafilm® in a randomized controlled trial. In this study, patients with ulcerative colitis or familial adenomatous polyposis undergoing restorative proctocolectomy with loop ileostomy were randomized to receive Seprafilm® placed under the midline incision or not (n = 85 Seprafilm® vs. n = 90 control). The degree and severity of subsequent adhesions were assessed at the time of ileostomy closure with laparoscopy 8–12 weeks later. Seprafilm® decreased both the incidence (49% vs. 94%, $p < 0.001$) and severity (15% vs. 58% grade 3 severity, $p < 0.001$) of adhesions. There was no significant difference in the incidence of complications, including intraabdominal abscess, between the groups.

Salum [8] conducted a retrospective matched cohort study comparing patients who underwent colorectal surgery and had Seprafilm® placed under the incision (n = 259) to those that did not have Seprafilm® placed (n = 179). Chart review and telephone interviews were used to assess for SBO and complications. There was no significant difference between the Seprafilm® and control group in terms of rate of SBO (4.6% vs. 6.7%, p = NS) or rate of surgery for SBO (1.5% vs. 2.8%, p = NS).

Vrijland [9] performed a randomized controlled trial (RCT) to evaluate the effect of Seprafilm® on patients undergoing Hartmann procedure for diverticulitis or cancer. They randomized 71 patients, but were only able to assess 42 patients undergoing a second operation for anastomosis (21 Seprafilm® vs. 21 control). There was no difference in the incidence of adhesions found at subsequent surgery. They did find a reduction in the severity of adhesions in the group that received Seprafilm® (mean severity score 18 vs. 50, $p = 0.002$). They published a follow-up study assessing the long-term incidence of SBO. They did not find any significant difference between the groups, but the study was underpowered with only 35 patients in this analysis [10].

Fazio [11] performed an RCT to evaluate the effect of Seprafilm® on patients undergoing intestinal resection. This international, multicenter study randomized 1701 patients (840 Seprafilm® vs. 861 control) to receive between 3 and 10 sheets of Seprafilm® at the time of abdominal closure. There was no difference in the primary outcome of overall SBO (12% vs. 12%). However, a subgroup analysis was done for patients who underwent surgery for SBO and were confirmed to have an adhesive cause at the time of operation. There was a lower rate of operatively diagnosed adhesive disease for patients who received Seprafilm® (1.8% vs. 3.4%, $p < 0.05$). It is important to note that the overall rate of surgery for SBO did not differ between the two groups. They also analysed the rate of adverse events and found that patients who received Seprafilm® had higher rates of anastomotic leak (4% vs. 2%, $p < 0.05$), peritonitis (3% vs. 1%, $p < 0.05$) and fistula (2% vs. <1%, $p < 0.05$) [12]. They found that these complications occurred in association with wrapping Seprafilm® around the anastomosis. This has led to a recommendation against placing Seprafilm® in contact with enteric suture lines.

Cohen [13] performed a RCT using sodium hyaluronic acid and carboxymethylcellulose that was chemically modified with glycerol to form G-HA/CMC. This modification aimed to improve membrane flexibility and handling. In this RCT, patients with ulcerative colitis or familial adenomatous polyposis undergoing restorative proctocolectomy with loop ileostomy were randomized to receive G-HA/CMC placed under the midline incision (n = 59 G-HA/CMC vs. n = 61 control). As in prior studies, the degree and severity of subsequent adhesions were assessed at the time of laparoscopic ileostomy closure. G-HA/CMC decreased both the incidence (67% vs. 90%, $p = 0.002$) and severity (6% vs. 33% grade 3 severity, $p < 0.001$) of adhesions. Of note, there was a trend towards increased intraabdominal abscess in patients who received G-HA/CMC (15% vs. 4.9%, $p = 0.07$). After this trial, G-HA/CMC was never brought to the market.

Tang [14] performed an RCT to evaluate the effect of Intergel® instillation on patients undergoing colorectal resection. They initially aimed to recruit 200 patients but the trial was suspended after 32 patients had been recruited due to high morbidity in the treatment group (65% vs. 27%, $p = 0.031$).

Tsuruta [15] retrospectively analyzed all patients who had undergone laparoscopic colorectal surgery (n = 167) at their institution between 2007 and 2012. The primary outcome was short-term postoperative SBO or ileus diagnosed by X-ray or computed tomography (CT). The rate of postoperative SBO was 9.7% (6/62) in the group without any adhesion barrier, 5.0% (1/19) in the group with single layer Seprafilm® and 0% (0/86) in the group with multi-layer Seprafilm® ($p < 0.05$). This

retrospective study has significant limitations with no adjustment in the analysis for possible confounders such as type of surgical procedure or history of previous surgery (Table 37.2).

Table 37.2 Summary of literature search

Study	Population	Intervention	Study design	N	Outcome	Quality of evidence
Becker (1996) [7] Beck (1997) [16]	Patients undergoing restorative proctocolectomy with IPAA	Seprafilm® placed under the midline incision	RCT	90 control vs. 85 Seprafilm®	Reduced incidence of adhesions in Seprafilm® group (49% vs. 94%, $p < 0.001$) Decreased severity of adhesions in Seprafilm® group (15% vs. 58% grade 3 severity, $p < 0.001$)	High
Salum (2001) [8]	Patients who underwent colorectal surgery	Seprafilm® placed under the midline incision and around stoma sites	R	259 Seprafilm® vs. 179 control	No difference in the incidence of SBO (4.6% vs. 6.7%, p = NS) No difference in the rate of surgery for SBO (1.5% vs. 3.9%, p = NS)	Low
Vrijland (2002) [9] Van der Wal (2011) [10]	Patients undergoing Hartmann procedure for diverticulitis or obstructing cancer	Seprafilm® placed under the midline incision and in the pelvis	RCT	21 control vs. 21 Seprafilm®	No difference in the incidence of adhesions Severity of adhesions decreased in Seprafilm® group (mean severity score 18 vs. 50, p = 0.002) No significant difference in long term SBO incidence	Moderate

Table 37.2 (continued)

Study	Population	Intervention	Study design	N	Outcome	Quality of evidence
Beck (2003) [12] Fazio (2006) [11]	Patients undergoing intestinal resection	Seprafilm® placed in 3–10 sheets at the surgeon's discretion	RCT	861 control vs. 840 Seprafilm®	No difference in incidence of SBO (12% vs. 12%)	High
Cohen (2005) [13]	Patients undergoing restorative proctocolectomy with IPAA	G-HA/CMC placed in 2–4 sheets under the midline incision	RCT	61 control vs. 59 G-HA/CMC	Reduced incidence of adhesions in G-HA/CMC group (67% vs. 90%, $p = 0.002$) Decreased severity of adhesions in Seprafilm® group (6% vs. 33% grade 3 severity, $p < 0.001$)	High
Tang (2006) [14]	Patients undergoing colorectal resection	Intergel® instillation	RCT	15 control vs. 17 Intergel®	Terminated early due to high morbidity (anastomotic dehiscence and ileus) in treatment group	Moderate
Tsuruta (2015) [15]	Patients undergoing laparoscopic colorectal surgery	Seprafilm® placed in a single or multi-layer	R	62 control vs. 19 single layer vs. 86 multi-layer	Postoperative bowel obstruction or ileus within 3 months: 9.7% with no adhesion barrier vs. 5% with single layer vs. 0% with multi-layer	Very low

N number, *R* retrospective, *RCT* randomized controlled trial, *NS* not significant

Recommendations Based on Data

While multiple RCTs have demonstrated that antiadhesive barriers (specifically Seprafilm®) reduce both the incidence and severity of adhesions after IPAA and other intestinal surgery, this has not translated into a decreased incidence of SBO. There was no data in our patient population regarding antiadhesive barriers and future fertility. Antiadhesive barriers have also been associated with increased risk of abscess in colorectal surgery, particularly when placed in contact with an anastomosis. However, the question remains as to whether patients who later require reoperative surgery benefit from decreased intraabdominal adhesions.

The clinical benefit of antiadhesive barriers in patients with UC undergoing IPAA is uncertain and its use may be evaluated on a case by case basis.

(Evidence: moderate; Recommendation: moderate).

Personal View of the Data

The senior author was a blind participant in the Becker [7] study where laparoscopy was done at the time of stoma closure to evaluate the presence adhesions to the midline incision. The senior author could correctly guess which patient received Seprafilm® and which patient did not in every case, based on viewing the extent of adhesions, which impressed her. Our institution has not experienced issues with increased anastomotic leaks, but we do not wrap anastomoses in this product. We have seen rare cases of "sterile peritonitis" [17]. That is, the patient presents with an acute abdomen and, upon reoperation, has generalized erythema throughout the abdomen with neither bowel perforation nor abscess. We have not used antiadhesive barriers with the laparoscopic approach in our practice. Laparoscopic IPAA surgery has been shown to cause fewer intraabdominal adhesions as well as adnexal adhesions [18]. Small retrospective series have reported on improved pregnancy rates with laparoscopic IPAA [19, 20]. However, when there is reoperative surgery with an open approach, we strongly consider the use of antiadhesive barriers, particularly if we suspect that there will be further open operations in the future [21].

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Optimal Management of Pelvic Abscess After Pouch Surgery

38

Julia T. Saraidaridis and Peter W. Marcello

Introduction

For patients who undergo ileal pouch anal anastomosis (IPAA), pelvic sepsis is the leading cause of pouch failure. Additionally, it is well-acknowledged that infectious complications following pouch surgery result in worsening function [1–3]. It is estimated that after a septic complication from IPAA, the chance of pouch failure is roughly 25% [3, 4]. Depending on the definition of pelvic sepsis, most studies report a 5–14% incidence of pelvic sepsis (4.8%—Mayo [4], 5%—Lahey [5], 8.2%—Cleveland Clinic [6], 13.3% Mount Sinai, Toronto [3]). Pelvic sepsis is a broad term that encompasses anastomotic leaks, anastomotic separations, pelvic cellulitis, pelvic abscess, and perineal fistulas as the component complications. Pouch abscess, classically, is described as a collection of purulent exudate without demonstrable anastomotic leak [7].

However, for the purpose of this chapter, we will use the term pouch abscess defined as a collection of purulent exudate with or without an evident anastomotic leak. Management of pouch abscess includes a number of potential avenues towards source control. If a patient is overtly septic, they will require operative intervention with drainage of the abscess and fecal diversion (if not already diverted). If the patient is hemodynamically stable, non-operative interventions including percutaneous drainage and trans-anastomotic drainage (including endo-sponge) can be attempted. This chapter investigates whether there is any difference in the outcomes of abscess eradication, pouch function, and pouch loss when comparing percutaneous drainage versus trans-anastomotic drainage to treat pelvic abscess after IPAA (Table 38.1).

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Table 38.1 Pico table

Patients	Interventions	Comparator	Outcome
Patients with pelvic abscess after IPAA	Percutaneous drainage	Trans-anastomotic drainage	Abscess eradication, pouch function, and pouch loss

Search Strategy

A comprehensive literature search was performed of the PubMed and MEDLINE database to identify English-language publications related to ulcerative colitis, ileal-pouch anal anastomosis, pouch abscess, and pelvic sepsis from 1980–2018. Key search terms included "ileoanal pouch", "ileal pouch anal anastomosis", "pouch abscess", "anastomotic leak", and "pelvic sepsis." Studies were excluded if they did not include patients who had treatment of a pelvic abscess with either method specified or did not reflect upon the outcomes above. The reference lists of each article were also searched to identify additional articles relating to this topic. Unfortunately, there is a dearth of publications regarding this issue; however, the articles that do address this topic are included in Table 38.2.

Results

Pelvic abscess as described in the literature is a heterogeneous group of different processes and pathologies including abscesses resulting from anastomotic leak and those without a demonstrable anastomotic leak. Within the category of anastomotic leak, a pelvic or pouch abscess can include abscesses from three anatomic locations: the tip of the J-pouch, the body of the J-pouch, and the ileal pouch-anal anastomosis (Fig. 38.1). Each of these locations lends itself to different treatment paradigms. As a result, we have grouped the studies and reported the outcomes based on the location of the pouch leak (from the tip of the J-pouch, pouch body versus ileoanal anastomosis).

For those with a leak from the tip of the J-pouch, trans-anastomotic drainage is not an option. If there is an associated abscess, patients should undergo an attempt at percutaneous drainage and if unsuccessful, revisional surgery will need to be considered. Leaks from the tip of the J were reported exclusively in a Cleveland Clinic series of 27 patients. Only four were treated initially with percutaneous drainage while 23 underwent immediate salvage surgery. Percutaneous drainage was successful in one patient, while three patients required subsequent surgery. Overall, salvage surgery was successful with eventual stoma closure in 24/26 patients, with functional outcomes similar to those with a primary IPAA. Only one patient had pouch loss and one did not have their ileostomy reversed [8].

Mount Sinai in Toronto, Canada also reported on 23 patients with leakage from the pouch body (not leakage from the pouch-anal anastomosis). Eleven were treated with pouch drainage alone (rectal tube) with healing in nine (82%). Five of 23 had percutaneous drainage, of which three (60%) healed. Seven patients underwent laparotomy and repair of leak, of which four (57%) healed. Of the seven patients in

Table 38.2 Studies evaluating treatment of IPAA associated abscess: percutaneous drainage versus trans-anastomotic drainage

Reference	Year published/pts accrued	Number of patients	Intervention	Abscess eradiation	Pouch loss	Quality of evidence
Farouk (Mayo) [4]	1997 (1981–1994)	73 (pelvic abscess)	– 40 abdominal surgery – 6 trans-anastomotic – 11 antibiotics alone – 16 CT guided percutaneous drainage	– 36/40 (90%) healed – 5/6 (83%) healed – 9/11 (81%) healed – 15/16 (94%) healed	**19 (26%) pouch failure overall** – 14/40 immediate pouch excision – 1/16 prolonged ileostomy – 1/11 prolonged ileostomy	Very low
Kirat (Cleveland Clinic) [8]	2011 (1983–2009)	27 (tip of J-pouch)	– 4/27 CT-guided drainage – 25/27 abdominal surgery	– 1/4 (25%) healed	– 1/27 pouch loss – 17/27 pouch repair – 6/27 pouch repair with repeat IPAA – 2/27 new pouch with repeat IPAA	Very low
Raval (Mt. Sinai Toronto) [12]	2007 (1981–2003)	29 (IAA leak with abscess)	– 17 percutaneous drainage – 8 trans-anastomotic – 3 abdominal surgery – 1 combined drainage	– 16/17 (94%) healed – 6/8 (75%) healed – 3/3 (100%) healed	– 1/3 pouch removal	Very low
Raval (Mt. Sinai Toronto) [12]	2007 (1981–2003)	23 (pouch leak—not IAA)	– 11 pouch drainage – 5 percutaneous drainage – 7 laparotomy	– 9/11 (81%) healed – 3/5 (60%) healed – 4/7 (57%) healed	– 18/23 maintained pouch – 2/23 successful pouch reconstruction	Very low
Kirat (Cleveland Clinic) [9]	2011 (1984–2009)	71 (IAA leak)	– 18 percutaneous drainage – 53 trans-anastomotic	– 15/18 (83%) healed – 40/53 (75%) healed	– 2/18 redo pouch – 6/53 pouch excision – 3/53 redo pouch – 2/53 long-term stoma	Very low

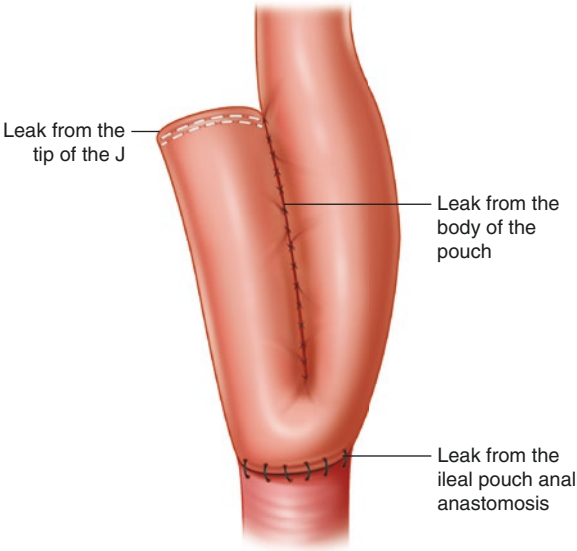

Fig. 38.1 Leaks can arise from (*1*) The tip of the J, (*2*) the body of the pouch, and (*3*) the ileal pouch anal anastomosis

whom the original intervention failed (pouch drainage, percutaneous drainage or laparotomy), five underwent pouch reconstruction of which three (60%) healed. Of these three "successful" salvage patients however, one had poor pouch function and the pouch was removed. While this data is very heterogenous and it is unclear why each treatment methodology was chosen, percutaneous drainage in properly selected patients can be successful in treating leak from the J-pouch and pouch body leak.

For those patients who have an anastomotic leak from the ileoanal anastomosis, there is choice as to whether to pursue trans-anastomotic drainage versus percutaneous drainage. These drainage methods have similar results with regards to abscess eradication, pouch loss, and functional outcomes, but this data is strongly influenced by selection bias. In a series from the Cleveland Clinic, 18 patients underwent percutaneous drainage and 53 underwent trans-anastomotic drainage [9]. Of the 18 patients who had percutaneous drainage, 15 (83%) were successful. Of those having trans-anastomotic drainage as the initial intervention, success was noted in 40 patients (75%). For the three patients who failed percutaneous drainage, two underwent pouch revision and one underwent diversion. Of the thirteen trans-anastomotic failures, only four had successful pouch salvage surgery, while the remaining nine had pouch excision (n = 6), continent ileostomy (n = 1) or proximal diversion (n = 2). In patients in whom the pouch was saved, short and long-term functional outcomes and quality of life were similar between the two initial treatment groups [9].

In a series of 29 ileoanal pouch anastomotic leaks from Mount Sinai of Toronto, 17 patients underwent percutaneous drainage, 8 trans-anastomotic drainage, 3 laparotomy, and one underwent a combination of these methods. Percutaneous drainage was successful in 16/17 (94%) of patients and in 6/8 (75%) of those who underwent

trans-anal drainage. Two of the four patients who underwent laparotomy healed with a functioning pouch. The overall rate of healing of the entire group was 86%. There was no assessment of later pouch function or quality of life. Finally, in one further study from Mayo Clinic, the results of 73 patients with pouch abscess were reported. Eleven were treated with antibiotics alone, sixteen underwent percutaneous drainage, six underwent trans-anastomotic drainage, and forty required laparotomy. Of those treated percutaneously, 15 (94%) were successful and in the trans-anastomotic group 5 (83%) were successful [4]. Taken together, these three studies suggest that both percutaneous and trans-anastomotic drainage are successful in around 80–90% of the population (Table 38.2).

With percutaneous drainage, there is some concern that an extra-sphincteric fistula could arise from the percutaneous drain track. Only one study evaluated this concern, noting that two of their seventeen patients who underwent percutaneous drainage developed a fistula at the CT-guided drainage site. Both healed after conservative therapy/drainage of the associated gluteal abscess [9].

For patients with septic complications following pouch creation, there is a well-founded concern that pouch function will suffer, even if the pouch is salvaged. This is thought to be due to the consequences of chronic inflammation, which results in a woody, fibrotic pouch with poor pouch compliance and discoordinated evacuation. Unfortunately, there are no articles in the literature that directly address function after different treatment modalities for pouch abscess. One study from the Lahey Clinic however did evaluate the functional outcomes of patients suffering perineal (including septic) complications following ileoanal pouch [10]. From a total of 624 pouches, 153 (24%) had perineal complications (including anastomotic stricture, anastomotic separation, pouch fistula, and pelvic sepsis). The functional outcomes and pouch loss in this group were compared to a control group of 277 patients who suffered no significant postoperative complication after pouch surgery. Pouch failure occurred in 16 (10.5%) of patients with perineal complications. For those patients who were able to have pouch salvage, two areas of deterioration in function were noted when the perineal complication group was compared to controls. This included a higher daily frequency of bowel movements: (7.1 versus 5.9, $p = 0.009$) and inability to discriminate between stool and gas (50% versus 77%, $p = 0.02$) [10]. While this study did not specifically address the complication of pouch abscess (these patients were bundled into the category of perineal complications), patients who suffer perineal complications with a resulting inflammatory response can anticipate some adverse effects on their pouch function.

While not a direct outcome measured in our PICO question, the decision whether to divert a patient requiring treatment for pelvic abscess after pouch surgery is a difficult one. It is universally accepted that any patient who presents with septic complications after IPAA with hemodynamic instability should undergo prompt proximal fecal diversion. What to do in the setting of a clinically stable patient who demonstrates an abscess associated with leak identified after ileostomy reversal or in patients who undergo one stage procedures is not well established in the literature. Gorfine has argued that diversion may not be necessary in these scenarios [11]. They initially noted those who underwent IPAA without initial diversion did not have an increase in the likelihood of pelvic sepsis. In a retrospective review of IPAA patients, pelvic

sepsis occurred in 27/344 (7.8%) patients who were diverted versus 24/492 (4.9%) who were not diverted (p = 0.07). For those patients who developed a septic complication, there were 89 salvage procedures performed in 51 patients: 85 underwent trans-anal anastomotic revisions (4 underwent combined abdomino-perineal approaches); 37 (44%) were performed with diversion and 48 (57%) performed without diversion. One-quarter of the 41 diverted repairs succeeded and 21% of the nondiverted repairs succeeded (p = 0.45) [11]. Given this data, the authors argue that diversion is not necessary either for the initial one-stage or multi-staged IPAA associated abscess.

Recommendations Based on the Data

Patients who develop a pelvic abscess after IPAA should undergo diagnostic work-up to determine if the abscess is associated with an anastomotic leak and, if so, where the leak is located. This data will help guide decisions regarding drainage modality.

For patients who are clinically stable and have pelvic abscesses that are either not associated with an anastomotic leak or that stem from the tip of the J-pouch or pouch body, percutaneous drainage should be attempted first. (Evidence: low; Recommendation strong).

For patients with pelvic abscess associated with an ileal pouch-anal anastomotic leak, there is no clear evidence that one drainage technique is preferable to the other. However, it appears that those who underwent percutaneous drainage had slightly better success compared to those with trans-anastomotic drainage. (Evidence: low; Recommendation: weak).

Overall, both modalities did have success in abscess eradication and prevention of pouch loss. About 80–90% of pouches were able to be preserved using either of these methodologies. For all clinically stable patients with pelvic abscess associated with IPAA, attempts should be made to treat the pelvic abscess and preserve the pouch regardless of treatment modality.

The studies used to make these recommendations are small and underpowered to detect real differences. Additionally, they do not delineate why the surgeons chose the treatment modality. These studies also did not control for the size of the anastomotic defect, so there is a selection bias inherent to the comparison. If a patient has a small anastomotic defect, the surgeon was not likely to want to widen the defect with a trans-anastomotic approach and may have preferred a percutaneous drain. On the other hand, patients with large trans-anastomotic defects would be expected to have poor healing, possibly accounting for the association between trans-anastomotic drainage and pouch loss.

A Personal View of the Data

In conclusion, prompt diagnosis and assessment of the patient with a pouch abscess is essential to the successful salvage of the pouch and preservation of pouch function. Imaging and/or endoscopic assessment will assist in the determination of

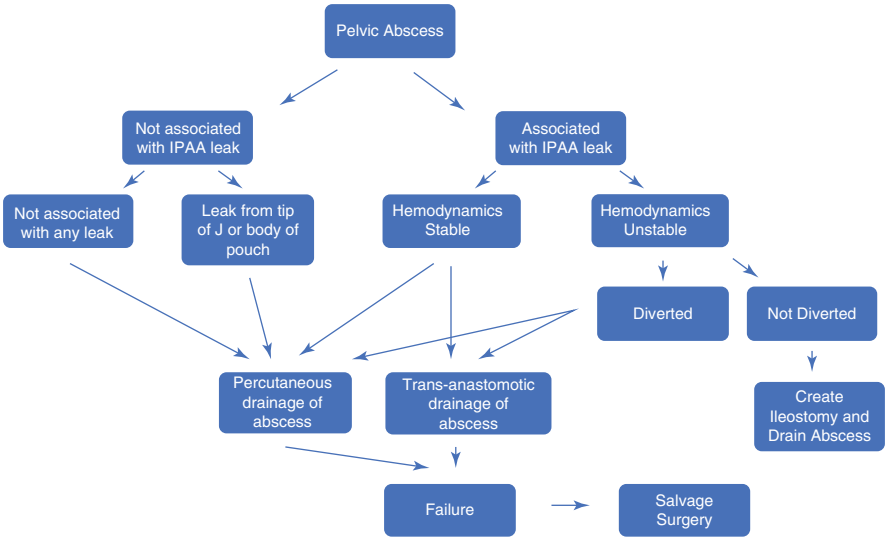

Fig. 38.2 Suggested algorithm for approaching abscess after IPAA

whether a pouch abscess is associated with an anastomotic leak. If the patient is hemodynamically unstable or has peritonitis, they should be brought to the operating room urgently for washout and diversion. If the patient is clinically stable, and is not diverted (either a one-stage IPAA or the development of an abscess following ileostomy reversal), strong consideration should be taken towards diverting the patient. Because of the potential loss of eventual pouch function associated with pelvic sepsis, we believe all steps to resolve the infectious process should be taken promptly (including fecal diversion). In select cases, in which the patient is hemodynamically stable and shows no signs of sepsis, an initial attempt can be made at drainage of pelvic abscess via percutaneous or trans-anastomotic means without diversion, but this is highly unusual and selective in our practice (Fig. 38.2).

For patients who develop a large pelvic abscess associated with an anastomotic leak in the early postoperative period, there should be consideration for both trans-anastomotic and trans-abdominal drainage utilizing diagnostic laparoscopy with washout of the pelvis and placement of drains. Since the majority of elective ileo-anal pouch procedures are performed laparoscopically, early re-intervention laparoscopically is often feasible. This avoids the need to reopen a lower midline or Pfannensteil incision. Utilizing a three-port technique, the abscess cavity can be entered from above, washed out, and drains placed through the trocar sites, along with trans-anastomotic drainage. The abdominal drains are subsequently removed while the trans-anal drain remains in place.

The choice of either percutaneous or trans-anastomotic drainage is dependent upon the size and location of the abscess, the presence and size of an anastomotic disruption, and surgeon preference and experience. For stable patients who have an abscess associated with a leak from the tip of the J pouch or upper body of the

pouch, an initial attempt at percutaneous drainage may be considered. For those patients with an abscess associated with pouch-anal disruption, the choice to proceed with either percutaneous or trans-anastomotic drainage should be based on anatomic features of both the abscess and leak, surgeon experience, and institutional preferences. In our experience, we have utilized both approaches successfully. Both treatment options should be considered, with early intervention of either approach if the pouch is to be salvaged. For the majority of patients, the development of a pelvic abscess following ileoanal pouch surgery can be managed successfully, allowing the patient to keep their pouch with expectation of reasonable function.

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Management of Chronic Pouchitis

39

Emanuelle Bellaguarda and Stephen B. Hanauer

Introduction

Despite improvement and optimization in both medical therapies for ulcerative colitis, as well as endoscopy techniques to detect dysplasia, approximately 30% of UC patients still require colectomy due to refractory disease or dysplastic lesions [1]. Pouchitis, the most common complication of ileal pouch-anal anastomosis (IPAA), can be classified according to duration (acute or chronic), response to medical therapy (antibiotic responsive, dependent, or refractory) or according to etiology (idiopathic versus secondary causes) [2]. The incidence of acute pouchitis is as high as 40% during the first 12 months after ileostomy closure [3]. In contrast, patients undergoing an ileoanal pouch for polyposis syndromes have a cumulative incidence ranging from 0–10% [4, 5]. Most cases of acute pouchitis resolve after a short course of antibiotics, although over 60% are likely to relapse [6]. Furthermore, between 5–19% of patients with acute pouchitis will evolve to chronic pouchitis [7–9]. The development of chronic pouchitis significantly impacts their quality of life and is one of the leading causes of pouch failure [10, 11]. The risk of developing chronic pouchitis is also increased in UC patients with pancolitis, longer length of follow-up, concomitant primary sclerosing cholangitis, extraintestinal manifestations [2] and ex-smokers prior to colectomy [12].

Chronic pouchitis is defined as persistent symptoms of urgency, increased frequency of bowel movements and abdominal pain for more than 4 weeks despite adequate antibiotic therapy [2]. Chronic pouchitis can be subclassified into antibiotic-dependent or antibiotic-refractory pouchitis [2]. While pouchitis is a clinical diagnosis based on a constellation of symptoms, examination of the pouch mucosa and histological findings [13], a validated scoring system, the Pouchitis Disease Activity Index (PDAI), was developed to further define and quantify

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severity of pouchitis. The PDAI takes into consideration stool frequency, rectal bleeding, fecal urgency, fever, endoscopic, and histologic inflammation. A score equal to or greater than seven is used to define pouchitis [14]. It is important to acknowledge that studies have demonstrated a poor correlation between bowel frequency and the endoscopic or histologic appearance of the ileal pouch. For IPAA patients who have asymptomatic inflammation of the pouch, treatment is not advised as the clinical significance of the inflammation is not well defined. In this chapter, we will discuss the management of idiopathic chronic pouchitis, including the comparative utility of antibiotics and biologic therapies.

Search Strategy

A comprehensive literature search of Medline and PubMed was conducted for publications in the English language between January 1975 and June 2018 using the following search keywords: 'pouchitis', 'chronic pouchitis', 'total proctocolectomy with ileoanal pouch anastomosis', 'refractory pouchitis', antibiotic-dependent pouchitis', 'antibiotic-refractory pouchitis', 'IPAA' and 'antibiotics', 'biologics', 'anti-TNF', anti-integrin inhibitor', 'budesonide', 'infliximab', 'adalimumab', 'vedolizumab', 'ustekinumab', 'cost effectiveness', 'steroids', 'remission', and 'resolution'. We also searched the reference section of each relevant article to identify additional articles pertaining to this topic. Data from full papers was extracted. Retrospective and prospective observational studies were included. No randomized controlled clinical trial was identified during our literature search (Table 39.1).

Results

Long-term antibiotic therapy: Patients requiring at least three courses of antibiotics/year are considered to have antibiotic-dependent pouchitis. Prolonged courses of combined antibiotic therapy are often recommended or required to maintain symptomatic control of chronic pouchitis. Several prospective and observational studies have tested different combinations of antibiotics for 2–4 weeks, however there is no long-term followup data to determine their effectiveness.

Abdelrazeq treated eight patients with chronic pouchitis (PDAI > 7) with a combination of ciprofloxacin (1 g per day) and rifaximin (2 g per day) for 2 weeks. Five of eight patients went into remission and two of eight patients improved. The median (range) PDAI scores before and after therapy were 12 (9–18) and 0 (0–15), respectively ($p = 0.018$). At a median follow up of 30 months, 88% of patients who responded "maintained good pouch function" [15].

Table 39.1 PICO table

Patients	Intervention	Comparator	Outcome
IPAA patients with chronic pouchitis	Long-term antibiotics	Biologics	Symptomatic control, cost effectiveness

Gionchetti also reported treating eighteen patients with chronic pouchitis (PDAI score > 7) with ciprofloxacin (1 g/day) and rifaximin (2 g/day) for 15 days. They defined "improvement" as a decrease of ≥3 points in PDAI score and remission as a PDAI score of "0". Sixteen of eighteen patients (88.8%) either improved (n = 10) or achieved remission (n = 6). The median PDAI scores before and after therapy were 11 (range 9–17) and 4 (range 0–16), respectively ($p < 0.002$). There was no long-term followup reported after initial treatment [16].

Mimura treated 44 patients with metronidazole (1 g per day) and ciprofloxacin (1 g/day) for 28 days. Remission was defined as a combination of a PDAI clinical score of ≤2, endoscopic score of ≤1 and total score of ≤4. Thirty-six patients (82%) went into remission. The median PDAI scores (range) before and after therapy were 12 (8–17) and 3 (1–10), respectively ($p < 0.0001$). The study also reported an improvement in quality of life based on a change of the Inflammatory Bowel Disease Questionnaire score from 96.5 (range, 74–183) to 175 (range, 76–215, $p < 0.0001$). No long-term followup data was provided after the 28 day treatment [17].

Shen also reported on sixteen patients with "chronic refractory pouchitis" (defined as symptoms for more than 4 weeks with endoscopic and histological inflammation despite treatment with single or dual antibiotics for more than 4-weeks) treated with ciprofloxacin (1 g per day) and tinidazole (15 mg/kg per day) for 4 weeks and used an historical cohort of patients (n = 10) treated with oral mesalamine (4 g/day), enema (8 g/day) or suppository (1 g/day) as comparator groups. The rate of clinical remission and clinical response for the antibiotic group was 87.5% and 87.5% respectively, versus 50% and 50% respectively in the mesalamine treated patients ($p = 0.069$ for both treatments). Two patients developed peripheral neuropathy and dysgeusia but were able to continue on the study [18]. Again, no long-term outcomes were described.

While the chronic pouchitis studies described above demonstrated short-term benefits, clinical observations demonstrate that maintenance therapy is often required to prevent recurrence of symptoms for patients who respond to a course of antibiotics [19]. In an open-label study of 51 patients administered rifaximin (median dose: 200 mg/day), after 2 weeks of conventional antibiotic therapy, 33 patients (65%) remained in remission for 3 months and 19 (58%) maintained remission at 12 months [20]. A few studies have shown that the probiotic combination VSL#3 is effective for maintenance of remission after antibiotic-induced resolution of acute pouchitis. A randomized controlled trial of 40 patients administered two packets/day of VSL#3 (600 billion bacteria) or placebo showed that VSL#3 was able to prevent a relapse during the study follow-up period of 9 months (15% of VSL#3 had relapse versus 100% placebo, $p < 0.001$) [21].

Recently, Segal published an observational study with long-term follow up of chronic pouchitis patients treated with maintenance antibiotics continuously for 1 year. Main outcome measures were the development of pouch failure (defined by the need for a permanent ileostomy), drug side effects and development of antibiotic resistance. Thirty-nine patients were evaluated retrospectively. Twenty-one percent of patients were able to achieve remission (PDAI <7) over a median follow-up of 102 months (range 9–125). Pouch failure occurred in 18% of patients after a median

follow-up of 8.5 years. Side effects of long-term antibiotic use occurred in 28% of patients, with resistance to antibiotics from at least one stool sample occurring in 78% [22].

The use of long-term antibiotics is also limited by cost. The least expensive antibiotic used to treat chronic pouchitis is metronidazole, however it is associated with numerous side effects including dysguesia, coating of the tongue and more concerning irreversible peripheral neuropathy. Rifaximin and tinidazole, which have a better safety profile, are comparatively more expensive yet frequently not covered by third party payers. [23].

Small studies have shown some efficacy of budesonide in treating refractory pouchitis with reported short-term remission rates of 60–75% [24, 25]. Many clinicians also find systemic corticosteroids to be empirically useful in refractory patients; however there is an absence of long-term treatment effect for short-term responsive patients.

Biologic therapy: Since the advent of biologic therapies for IBD, a few small studies have reported on the efficacy of anti-TNFs (infliximab and adalimumab) as rescue therapy for refractory pouchitis. In one retrospective series, 28 patients received infliximab 5 mg/kg for pouchitis (n = 25) or pouch fistula (n = 7). Complete clinical response was defined as cessation of diarrhea, blood loss, and abdominal pain, and a partial response was defined as marked clinical improvement. Fistula response was defined as "complete" with cessation and "partial" with reduction of fistula drainage. Patients who were diagnosed with Crohn's disease of the pouch were excluded from the study. Eighty-two percent of patients were receiving concomitant immunomodulatory therapy. At week 10, 88% of patients demonstrated clinical response (14 partial, 8 complete) with significant reduction in PDAI scores (9.0 [8–1]) to 4.5 [3–7], $P < 0.001$), while 86% of patients showed fistula response (three partial and three complete). Fifty-six percent of patients had sustained clinical response, and three out of seven fistula patients showed sustained fistula response on follow-up to 20 months. Five patients (18%) required pouch excision with permanent ileostomy [26].

Barreiro-de-Acosta led a multicenter retrospective study in Spain, where 33 patients were treated with infliximab 5 mg/kg for chronic pouchitis. Efficacy was evaluated at week 8, 26 and 52. Complete response was defined as cessation of diarrhea and urgency, and partial response as marked clinical improvement but persisting symptoms. After induction doses, 21% of patients had complete response with resolution of diarrhea and 63% had partial clinical response. At weeks 26 and 52, 33% and 27% achieved complete response respectively, while 33% and 18% showed partial clinical response. Thirteen patients withdrew from treatment [27].

Kelly also reviewed the data of 42 patients treated with infliximab for chronic refractory pouchitis. Complete response was defined as a modified (m)PDAI <5. Partial response was defined as mPDAI improvement >2. At week 8, 74% (48% complete) patients were able to achieve response while 62.6% (29.6% complete) had sustained clinical response at 48 weeks. Mean mPDAI and C-reactive protein declined from 8.5 ± 0.3 to 2 ± 3.4 ($p < 0.002$) and from 29.48 ± 6.2 to 5.76 ± 1.6 mg/L ($p < 0.001$), respectively. Predictors of sustained response were pre-treatment

mPDAI <10 ($p < 0.01$), resolution of rectal bleeding ($p < 0.001$) and week 8 endoscopic activity ($p = 0.04$; OR 2.2; 95% CI 1.1–16.5). Sixty-eight percent of patients who had pre-colectomy infliximab exposure required dose optimization, compared with 45% of those who had not been previously exposed ($p = 0.23$) [28].

A small study reporting on eight patients evaluated the efficacy of adalimumab in treating chronic pouchitis. Eight patients received adalimumab loading doses (160 and 80 mg) and continued on 40 mg every other week as maintenance therapy. All patients had been exposed to infliximab in the past. At week 8, 13% of the patients achieved remission and 62% showed a clinical response. At week 26, 13% achieved remission and 38% showed a clinical response. At week 52, half of the patients had undergone a permanent ileostomy and only 25% achieved remission [29].

One retrospective multicenter study of 20 patients looked into the effectiveness of vedolizumab in treating chronic pouchitis. Response was assessed using the Oresland score (OS) at week 2, 6, 10 and 14 and PDAI at week 0 and 14. The mean OS declined from 6.8 (range 2–12) to 3.4 (range 0–11) and the PDAI after 14 weeks declined from 10 (range 5–18) to 3 (range 0–10). Seventeen of nineteen patients were able to stop antibiotic therapy. As the patients were only followed up to 14 weeks, long-term follow up data is unavailable [30]. A large clinical trial evaluating the effect of vedolizumab in chronic pouchitis is currently enrolling patients.

A few case reports have shown the efficacy of ustekinumab to treat chronic pouchitis patients [31, 32]. Ustekinumab is a human immunoglobulin IgG1 monoclonal antibody that binds the p40 subunit of interleukin IL12 and 23 and normalizes IL12- and IL23-mediated signaling. Ustekinumab is known to be effective to treat Crohn's disease as shown in previous studies [33].

Recommendations Based on Data

Prolonged courses of combined antibiotic therapy are usually recommended to treat chronic pouchitis. Several small, randomized clinical trials have tested different combinations of antibiotics such as ciprofloxacin (1 g per day) with rifaximin (2 g per day) [15, 16], metronidazole (1 g per day) [17] or tinidazole (1–1.5 g per day) [18] for 4 weeks. Long-term antibiotic therapy is not without risk and may trigger antibiotic resistance, opportunistic infections such as *C. difficile* and side effects such as peripheral neuropathy (metronidazole) and tendon rupture (ciprofloxacin). Every effort should be taken to minimize antibiotic exposure, and clinicians should consider the use of alternate maintenance therapies such as probiotics to minimize risk. Immunosuppressive agents are considered if patients fail recurrent courses of antibiotics. Small studies have shown some efficacy of budesonide, anti-TNFs and vedolizumab in treating refractory pouchitis [25–30].

Based on the available data, we recommend that patients with chronic pouchitis be treated with a combination of antibiotics for 4 weeks. For patients who are unable to achieve remission, therapy may be escalated to biologic therapy. *(Weak recommendations based on low quality evidence).*

Personal View of Data

The first step in managing chronic pouchitis is to assess and address possible contributing factors to ongoing inflammation. A detailed history should be performed, and the use of NSAIDs should be investigated and avoided. Patients who take NSAIDs are at increased risk for developing pouchitis (OR, 3.24; 95% CI, 1.71–6.13) [34]. Withdrawal of these medications alone can lead to significant improvement in both PDAI and quality of life scores [35].

Diagnosis of chronic pouchitis should be made based on a combined assessment of symptoms, endoscopic and histological features for accurate diagnosis [36]. It is important to perform endoscopic assessment to determine disease activity and to help with the differential diagnosis of chronic pouchitis, including backwash ileitis, CD of the pouch, ischemia, surgical complications such as sinuses, fistulas and strictures, as well as functional changes of the pouch leading to "irritable pouch syndrome". Biopsies should be performed from the pre-pouch ileum, pouch body and rectal cuff. Histological evaluation is important to exclude superimposed infections such as cytomegalovirus (CMV) of the pouch, presence of granulomas, perfusion-associated ischemia [37] or pouch prolapse. For patients with concomitant autoimmune disease, biopsies should be stained for IgG4+ plasma cells in the lamina propria, indicating an autoimmune mediated inflammation [38].

Routine laboratory tests should be performed including complete blood count, iron studies, and complete metabolic panel to evaluate for electrolyte abnormalities. In patients with a long segment of pre-pouch enteritis and elevated alkaline phosphatase, the concomitant diagnosis of PSC should be entertained and investigated. Patients with chronic pouchitis are also susceptible to vitamin B12 and vitamin D deficiencies [39, 40]. Fecal calprotectin or lactoferrin can be used to evaluate disease activity and response to therapy [41, 42], however these tests should not replace endoscopic evaluation. Stool studies should be performed to rule out infection such as *C. difficile*, campylobacter and candida infection.

Treatment for chronic pouchitis remains challenging and is often individualized based on response and tolerance to antibiotics. Due to insufficient clinical trial evidence to guide therapy, management of "refractory" cases remains variable among centers and experts. In our practice, the antibiotic regimen of choice will depend on patient's history and prior exposure/tolerance to antibiotics. Combination of ciprofloxacin and metronidazole or rifaximin for 4 weeks is initially recommended. If patients become antibiotic dependent, low dose antibiotics are usually continued; ciprofloxacin 500 mg daily or metronidazole 500 mg daily are routinely used. Should a patient fail antibiotic course, we will escalate therapy to budesonide 9 mg daily for 8 weeks. If response is achieved, we will attempt to taper budesonide by 3 mg every 4 weeks. Often patients will need a low dose of budesonide to maintain response. Should a patient fail to respond to budesonide, we escalate therapy to biologics (either anti-TNF, vedolizumab or ustekinumab). One should take into consideration prior exposure to these medications during treatment for ulcerative colitis. A detailed

history to investigate possible immunogenicity should be performed and re-exposure should be monitored for immune-related events or rapid drug clearance. Patients are often challenged with biologics invoking the same mechanism of action that they might have failed during their IBD course, as chronic pouchitis may represent a new IBD entity, and response to medications may be different. In our experience, we are often successful achieving a response with biologics and patients retain a good quality of life and pouch function. Biologics are usually continued as a maintenance therapy. For patients with refractory symptoms despite optimization of biologics and no other identifiable treatable secondary causes, referral to a colorectal surgeon for consideration of fecal diversion with or without pouch excision is discussed (Table 39.2).

In summary, chronic pouchitis can be challenging to treat and the evidence-base to guide therapy is limited. It is reasonable to try long course antibiotics and escalate therapy to steroids or biologics if needed. Improved quality of life and decreased morbidity (due to illness or therapies) should be the mainstay goals of patient's treatment. The ultimate "cure" for chronic pouchitis is fecal diversion with or without pouch excision.

Table 39.2 Studies evaluating the use of antibiotics and biologics to manage chronic pouchitis

First author year	N	Intervention	Study design	Duration of treatment	Outcome	Quality of evidence
Gionchetti (1999) [16]	18	Ciprofloxacin 1 g per day + Rifaximin 2 g per day	PO	2 weeks	6/18 (33%) achieved remission	Low
Abdekrazek (2005) [15]	8	Ciprofloxacin 1 g per day + Rifaximin 2 g per day	PO	2 weeks	5/8 (75%) achieved remission with good pouch function at 30 weeks follow up	Low
Mimura (2002) [17]	44	Ciprofloxacin 1 g per day + metronidazole 1 g per day	PO	4 weeks	36/44 (82%) achieved remission	Low
Shen (2007) [18]	16	Ciprofloxacin 1 g per day + tinidazole 15 mg/kg/day	PO	4 weeks	14/16 (80%) achieved remission	Low
Ferrante (2010) [26]	28	Infliximab 5 mg/kg (week 0, 2, 6) for 10 weeks	PO	10 weeks	88% clinical response (14 partial, 8 complete) at 10 weeks and 56% clinical response at 20 weeks follow up	Low

(continued)

Table 39.2 (continued)

First author year	N	Intervention	Study design	Duration of treatment	Outcome	Quality of evidence
Kelly (2016) [28]	42	Infliximab 5 mg/kg (week 0, 2, 6) for 48 weeks	R	48 weeks	74% (48% complete) achieved response at 8 weeks and 62.6% (29.6% complete) achieved response at 48 weeks.	Low
Barreiro-de Acosta (2012) [27]	33	Infliximab 5 mg/kg (week 0, 2, 6) for 52 weeks	R	52 weeks	7/33 (21%) achieved remission at week 8 11/33 (34%) achieved remission at 26 weeks 9/33 (27%) achieved remission at 52 weeks	Low
Barreiro-de Acosta (2012) [29]	8	Adalimumab 160/80 mg induction followed by 40 mg every other week for 26 weeks	R	26 weeks	1/8 (13%) achieved remission at 8 weeks 1/8 (13%) achieved remission at 26 weeks	Very low
Bar (2018) [30]	20	Vedolizumab 300 mg (week 0, 2, 6 and 10)	R	14 weeks	13/20 (65%) achieved clinical response at week 14 with PDAI improvement from 10 to 3	Very low

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Management of Ileal Pouch Vaginal Fistulas

40

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Introduction

Restorative proctocolectomy (RPC) with ileal pouch-anal anastomosis (IPAA) is a safe, accepted surgical treatment for mucosal ulcerative colitis (MUC) and familial adenomatous polyposis (FAP). Pouch vaginal fistula (PVF) formation, first described in 1985 by Wong [1], is an uncommon and difficult to address complication of IPAA. The incidence of PVF has been reported to be between 3.3–16% [2–7]. Contributing factors to the development of PVF include underlying Crohn's disease, pelvic sepsis as well as surgical technique [4–10]. PVFs often require multiple operations, with 20% of patients ultimately requiring pouch excision [7, 11]. This number is much higher in patients with Crohn's disease [4–8].

As PVFs are uncommon, there is limited high quality data with which to firmly guide treatment. Many procedures have been described, ranging from local transanal or transvaginal approaches to pouch excision either with redo IPAA or a permanent ileostomy. In this chapter, we review the evidence from the past two decades with regards to PVF treatment and provide our recommendations for its management (Table 40.1).

Table 40.1 PICO table

Patients	Intervention	Comparator	Outcome
Patient undergoing ileal pouch anal anastomosis with pouch-vaginal fistula	Re-do ileal pouch anal anastomosis/pouch excision	Local procedures	Closure of fistula

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Search Strategy

A comprehensive search of the literature was completed using Medline and PubMed. The search was limited to publications in the English language between January 1998 and June of 2018, using the following search terms: ("ileal pouch anal anastomosis") and ("vaginal fistula") and ("outcome" or "complications" or "healing" or "redo pouch" or "pouch excision" or "pouch advancement" or "local management"). We also searched the reference section of pertinent articles in order to identify any additional articles pertaining to the topic. Studies were excluded if they did not pertain directly to the management of ileal PVF as the primary focus of the study.

Results

Because PVFs are an uncommon complication of a very specific operation, it is not surprising that there have been no randomized prospective studies investigating approaches for PVF repair, and that no one approach has emerged as the best strategy for a successful repair [4]. The studies reported in the literature have been retrospective and observational, however they have provided insight into the etiology of the disease and provided multiple strategies for repair (Table 40.2).

Success of Diversion in Combination with Multiple Local Approaches

In 1989, Wexner et al. reported one of the first multicenter studies conducted in order to determine the incidence of PVF in IPAA as well as its etiology; 304 ileoanal reservoir procedures were performed in women at 11 institutions, and 21 patients developed 22 PVFs (6.9%). In this report, a total of 73 surgical procedures were performed in the 21 patients, indicating that treatment typically requires more than one procedure. Successful PVF closure was higher when local procedures were conducted after diversion. Of the local procedures, endoanal flap and sphincteroplasty had the highest success rates, with an overall local repair success rate of 29.4%. It was recommended that diversion be performed as the initial step in treatment, followed by a local procedure using an advancement flap or sphincterotomy. If these efforts fail, the recommendation was to then proceed with a muscle flap or redo-pouch. Pouch excision was reserved for failure of other approaches [7].

The benefits of an initial approach of diversion and local transanal repair have also been supported by data from multiple subsequent studies. Shah conducted a large retrospective chart review of 993 women who underwent IPAA. In this study, the overall incidence of PVF was 3.3%. The average time to the development of PVF was 21 months after stoma closure (range 1–132 months). Primary treatments studied included local repairs (mostly advancement flaps), redo restorative

Table 40.2 Summary of studies evaluating approaches to the repair of pouch-vaginal fistulas

Study	Study population	Procedure with percent success	Conclusion	Quality of evidence
Wexner et al. (1989) [7]	Total 304 IPAA (21;6.9% PVF)	Transanal closure (29%) Endoanal flap (60%) Sphincteroplasty (75%) Debridement Fistulectomy (6%) Transvaginal closure (27%) Transabdominal closure (100%) Seton (0%) Temporary diversion (13%) Gracilis flap (50%) Bulbocavernosus flap (25%) Redo pouch (100%)	Diversion prior to repair Advancement flap and sphincterotomy Muscle flap or redo pouch Pouch excision	Moderate
Groom et al. (1993) [4]	Total 161 IPAA (17;10.6% PVF)	Fistulotomy (25%) Fistulectomy and sphincter (0%) repair Direct repair (16.6%) Advancement flap (50%) Redo IPAA (0%)	No particular preferable procedure	Low
Burke et al. (2001) [14]	14 PVF	Transvaginal repair (78.6%)	Healing 11/14 patients	Low
Shah et al. (2003) [5]	Total 993 IPAA (33;3.3% PVF)	Advancement flap (44%) Redo IPAA (50%) Seton alone (0%) Diverting stoma (0%) Transabdominal (0%) Endoscopic (0%) Transvaginal (0%)	Advancement flap can be successful with good functional outcomes Redo IPAA can also achieve healing if local repairs fail	Moderate
Zinicola et al. (2003) [16]	Total 460 IPAA (31;6.8% PVF)	Transvaginal repair (not reported) Abdominal pouch advancement (90%, n = 10)	Success rate for treatment of a high fistula by means of an abdominal approach appears better than that of local procedures for a low fistula	Low

(continued)

Table 40.2 (continued)

Study	Study population	Procedure with percent success	Conclusion	Quality of evidence
Johnson et al. (2005) [17]	Total 619 IPAA (24;3.9%)	Fibrin glue (0%) Suture closure (0%) Transvaginal flap (0%) Transanal flap (20%) Anastomotic advancement (11%) Gracilis flap (0%) Pouch advancement (62%) Redo pouch (25%)	Combined abdominoperineal repair offers better results than local procedures (10.5% success vs. 52.9% success)	Moderate
Tsujinaka et al. (2006) [12]	23 PVF	Mean of 2.2 procedures (73.9%) – Diversion – Advancement flap – Seton – Fibrin glue – Redo IPAA	Fecal diversion in combination with local procedures is effective in most patients with IPAA	Moderate
Mallick et al. (2014) [13]	Total 1895 IPAA 152 PVF	Pouch advancement (41.6%) Transvaginal (55.5%) Redo IPAA (40%)	Significantly higher pouch failure rates in Crohn's disease (22.7% vs. 52.7%)	Moderate

proctectomy or pouch excision, with an overall healing rate of 52%. The healing rate of advancement flaps and redo pouches were found to be 44% and 50%, respectively. The overall success rate for local repair was found to be 39% [5]. In this study, most patients (87%) were diverted prior to local repair.

A study by Tsujinaka retrospectively investigated 23 patients with PVF after IPAA and also confirmed the superiority of diversion with local repair. Their data show an overall success rate of 73.9%, with a mean of 2.2 procedures including EUA/observation, diversion, seton placement, fibrin glue, endoileal advancement and redo IPAA [12]. Mallick conducted one of the largest retrospective studies of 152 PVF, reporting a successful healing rate for PVF with advancement flap of 41.6% when performed primarily and 66% when performed secondarily [13]. The majority of these patients were diverted prior to local repair.

The success of diversion followed by local procedures is not limited to the transanal approach. A study of a transvaginal approach to PVF repair found that a transvaginal primary repair was technically simple and achieved healing at a median follow up of 18 months in 11/14 patients (78.6%), in comparison to the approximately 50% overall success rate for transanal procedures reported in the literature. In this study, diversion prior to this local repair was also recommended for symptomatic relief of the patient and to give the repair every chance to heal [14]. A separate study

also reported a transvaginal repair success rate of 55% when performed as the primary procedure and 40% when performed as a secondary procedure [13].

Although most studies recommended proximal diversion prior to repair, one study showed no difference in the rate of healing in transanal repairs between those who were diverted at the time of the local repair and those who were not (29.7% vs. 20.8% success rates respectively) [15].

Influence of Fistula Location on the Approach for Repair

Studies note that the location of the fistula in relation to the anastomosis should be a factor when selecting the appropriate approach for repair. It is thought that approximately 50% of PVF are located below the level of the anastomosis, 25% at the level of the anastomosis, and 25% above the level of anastomosis [12, 13]. Zinicola studied 460 women who underwent a restorative proctectomy with a PVF rate of 6.8%. A subgroup of ten patients who had a high internal opening above the anorectal junction were selected for abdominal pouch advancement to treat the fistula. At a mean follow up of 42 months after diverting ileostomy closure, nine patents were successfully treated (seven by this single procedure, two with one subsequent transvaginal or transabdominal repair). The authors concluded that the success rate for treatment of a high fistula with an abdominal approach appeared to be better than that of local procedures for a low fistula [16]. With regard to a low fistula location, Tsujinaka noted that PVFs at or below the anastomosis were successfully closed with local procedures with an overall success rate of greater than 70% (mean of 2.2 procedures including EUA/observation, diversion, seton placement, fibrin glue, endoileal advancement, and redo IPAA) [12].

A Role for Abdominoperineal Repairs?

Johnson studied 619 women who underwent IPAA with a PVF rate of 3.9%. These authors suggested that a combined abdominoperineal repair offered better results than local repair, with success rates at 10 years of 52.9% and 10.5%, respectively, noting that the majority of the abdominoperineal repairs involved pouch preservation and advancement (77.8%) [17]. The success rate for local repair was substantially lower those previously reported by other studies (29.4–78.6%) [5, 7, 12–14]. This may relate to the fact that proximal diversion prior to local repair was not routinely performed. Abdominoperineal repair is a useful approach, however, it may not necessarily be the first approach attempted as multiple studies have described a better success rate for diversion with local repair.

Influence of Pelvic Sepsis and Anastomotic Technique on Fistula Formation

Understanding the etiology of PVF formation allows for the development of more educated strategies for prevention of PVFs. Based upon multiple studies, pelvic

sepsis is a major determinant of PVF formation [4, 5, 7, 12]. Studies suggest no difference in the incidence of PVF in inflammatory vs. non-inflammatory disease. Furthermore, the severity of the colitis or number of stages in the operation did not seem to influence PVF formation. No difference in the incidence of PVF formation was seen in stapled vs. hand-sewn anastomosis [4]. Based upon these data, there seems to be no preventative measures for PVF formation beyond sound surgical technique in order to prevent pelvic sepsis, regardless of anastomotic approach.

Higher Failure Rates for PVF Repair and Need for Pouch Excision in Crohn's Disease

Although there seems to be no difference in the incidence of PVF formation in inflammatory vs. non-inflammatory disease, there is a clear difference in the healing of PVFs in these two populations. PVFs in Crohn's disease patients have a lower overall healing rate as compared to the non-Crohn's disease cohort (25% vs. 48%) [5]. Furthermore, a diagnosis of Crohn's results in worse treatment outcomes and higher pouch failure rates [5, 13]. PVFs are noted to occur later in patients with Crohn's disease (median of 12 months as compared to 8.2 months in patients without Crohn's disease) [12]; prognosis has also been found to be worse when PVFs occur after ileostomy closure [4].

In summary, approximately 20% of patients have required a pouch excision for cure [7, 11]. Of the 2% of pouch patients ultimately diagnosed with Crohn's disease, the pouch excision rate is approximately 60% as compared to 20% in the remaining cohort [7].

Recommendations Based on Data

Based upon various retrospective and observational data, it is difficult to recommend a firm management algorithm as no single procedure is appropriate for all PVFs. However, the following recommendations are made based upon the current literature:

Advise patients that PVFs generally require multiple attempts at closure with local approaches and ultimately 20% will require pouch excision; an even higher failure rate is expected in patients with Crohn's disease. (Strong recommendation based upon moderate quality evidence)

Fecal diversion should be established prior to attempts at repair of PVFs. (Moderate recommendation based upon moderate quality evidence)

Local transvaginal or transanal (endo-ileal flap) approaches are appropriate to repair PVFs that occur below the anastomosis. (Moderate recommendation based upon moderate quality evidence)

Muscle interposition flap is appropriate if diversion and local repair fails. (Weak recommendation based upon low quality evidence)

An abdominal approach is typically appropriate for repair of high PVFs (Moderate recommendation based upon low quality evidence)

Personal View

PVFs are uncommon and difficult to treat; however, there are several treatment options available. No single treatment is considered successful or unsuccessful, and often times multiple operations are needed to close a PVF. Once a PVF is suspected, the diagnosis is confirmed with a pouchogram and flexible sigmoidoscopy. Biopsies are taken to confirm or exclude Crohn's disease, as PVF repair in this setting will fail at a much higher rate; approximately 60% of patients with PVF in the setting of Crohn's disease will require pouch excision. Knowing this information will allow for appropriate expectations and counseling of the patient.

Prior to any procedures to close the PVF, ileal contents should be diverted and, if needed, debridement and placement of a seton should be undertaken. Diversion for 3–6 months may be considered prior to any further local surgical interventions. This maneuver helps to control sepsis as well as afford patients symptomatic relief. Diversion alone can allow for closure of the PVF in certain cases. Any local procedures to close the fistula prior to diversion are not advised as failure of the procedure may preclude use of that procedure after diversion, if and when it fails. Asymptomatic small fistulas would be an exception to this treatment guideline.

The diverting ileostomy should be placed in a loop of small bowel where that ileostomy can either be subsequently maintained if a redo J-pouch is necessary or where that point would correspond with an appropriate length pouch which would reach the anus. In other words, at the time of loop ileostomy construction, always think about the next potential stage and use a segment of bowel so as not to preclude construction of a second pouch, if necessary.

After diversion, once local infection is treated and sufficient time has elapsed, our personal preference is to utilize healthy fresh tissue in the form of the gracilis muscle as an initial step. If the gracilis muscle fails, consideration could even be given to a contralateral gracilis interposition. Ultimately, pouch advancement is reserved as a final option as transanal pouch advancement is not always possible. It is our preference to commence pouch advancement in the prone jackknife position, yet the patient must be advised that if transanal pouch advancement is not possible, they would be repositioned in the supine modified lithotomy position and prepared for a combination transabdominal transanal pouch advancement. However, if during pouch advancement the pouch becomes ischemic and/or damaged beyond salvage, the fallback position is construction of a second pouch. If a new pouch cannot be constructed, a permanent ileostomy would be necessary. In these instances, either the ileostomy is maintained, or the loop ileostomy may be closed and additional bowel put back into circuit by creating a more distal ileostomy.

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Management of IPAA-Associated Persistent Presacral Sinus

41

Jean H. Ashburn

Introduction

A persistent presacral sinus tract arising after restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) can cause considerable morbidity and is associated with high rates of pouch failure [1, 2]. These sinuses are blind-ending tracts that form as a result of a non-healing leak or suture/staple line dehiscence at the pouch-anal anastomosis. Although many defects remedy themselves with proper drainage and patience, some chronic tracts may persist and lead to significant compromise in pouch function and longevity [3]. A number of interventions have been performed in patients with IPAA-associated persistent sinus tracts, most of which are in a posterior location, with hopes of achieving either symptom relief or complete closure of the tract. The optimal approach must consider the specific characteristics of the persistent sinus tract, and options range from less invasive endoscopic procedures to more extensive pouch revision and redo of the pouch-anal anastomosis (Table 41.1).

Search Strategy

PICO (Population, Intervention, Comparator, Outcome) data were obtained (Table 41.1). A literature search of EMBASE, MEDLINE, and PubMed was

Table 41.1 PICO table

Patients	Intervention	Comparator	Outcome
IPAA patients with persistent presacral sinus	Unroofing of sinus tract	Recreation of IPAA	Healing rate of sinus tract, IPAA loss

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conducted to identify all English-language publications associated with ulcerative colitis, ileal pouch-anal anastomosis, and post-operative pouch complications from 1980–2018. The following key search terms were queried: 'colitis', 'ulcerative colitis', or 'inflammatory bowel disease'; 'ileal pouch-anal anastomosis', 'IPAA', 'J pouch'; 'presacral sinus', 'chronic sinus', 'IPAA sinus', 'chronic anastomotic sinus'. Studies were excluded if they considered sinuses other than those related to the ileoanal anastomosis (i.e. colorectal/coloanal), unless data regarding ileoanal sinuses could be separated and assessed independently. All reference lists of the included manuscripts were noted to identify additional publications that were acceptable for inclusion. Publications from the same institution were carefully assessed for overlap and only the most recent study was considered in this circumstance. Observational, prospective, retrospective, and randomized studies were considered for the literature assessment.

Results

Despite significant morbidity of presacral sinus tracts in IPAA surgery, the optimal management of these persistent sinuses is not well delineated. Reports have not offered direct comparison among the described techniques to confer superiority of one approach over the rest. Large randomized studies are lacking and outcomes from smaller series are varied and limited to retrospective and observational data. Treatment of diverted, asymptomatic sinus tracts found with a water-soluble contrast enema is distinguished from those presenting with symptoms after intestinal continuity is restored in only a few of the available studies.

A common initial approach to the asymptomatic, diverted presacral sinus is observation and delay of ileostomy closure. Observational studies evaluating this treatment describe relatively good healing rates with observation and interval reimaging, followed by ileostomy closure if healing is observed [4]. If sinus tracts persist despite expectant management, patients are more likely to maintain their ileostomy [5].

When a conservative 'watch and wait' strategy is not sufficient to achieve complete healing, several treatments have been reported to surgically correct the presacral sinus tract. The most described method of surgical correction of the IPAA sinus is unroofing, described in 1997 by Whitlow, a method of laying open the sinus tract by incising the common wall between the tract and pouch body, thus incorporating the sinus into the lumen of the pouch. All four patients in their initial report of IPAA sinus who underwent unroofing exhibited complete healing within 12 months of the procedure. There were no IPAA failures in this group [6].

Other retrospective reports have reported success of observation with further intervention for those who do not heal in a timely fashion. One study reported on 22 patients with a persistent sinus tract on contrast imaging after diverted IPAA. Twelve of these patients healed with observation only, and six patients with persistent tracts after the observation period underwent successful debridement (unroofing), with successful closure of the tract. Pouch survival was not reported, but two patients failed treatment and never achieved healing during the study period [7].

One of the largest studies of persistent presacral IPAA tracts reported on 45 patients, with 23 of these patients identified prior to ileostomy closure and 22 after ileostomy closure. Eight of forty-five patients underwent unroofing initially, with 50% healing. Fourteen of forty-five patients underwent unroofing as an additional treatment after one of the following; observation, drainage, sinus closure, or diversion. Seven of these fourteen patients achieved complete healing. Of patients undergoing unroofing for a persistent sinus, 50% showed complete healing, with healing increasing to 81% in sinus tracts that were asymptomatic. Fifteen patients (33%) in the study eventually had pouch failure. Although no patients were initially treated with pouch redo or revision, three patients underwent pouch redo after a failed initial treatment. Two patients achieved a successful redo pouch with good function but one required excision of the redo pouch [8].

Two studies reported on low pelvic anastomotic sinuses, with a few IPAA patients included in each study. In one study, data related only to IPAA sinuses showed complete healing three out of five IPAA sinus tracts with observation (two of five required maintenance of ileostomy for persistent sinus) [5]. The other similar study reported on six patients with an IPAA sinus, all of which were able to undergo successful ileostomy closure after observation or a combination of observation and sinus debridement/unroofing [9].

Finally, the technique of needle-knife sinusotomy (NKSi) is an endoscopic variation of surgical unroofing that has been more recently described [10–12]. Reports from the highest volume NKSi center recently reported on 109 patients with pouch sinus tracts, most of which were symptomatic (93.6%). Complete healing rate was nearly 50% with symptomatic improvement shown in 77.5%. Over half of the group required repeat treatments, and 20% of patients experienced sinus-related IPAA failure [13] (Table 41.2).

Recommendations Based On Data

Patients with an asymptomatic IPAA sinus detected prior to ileostomy closure can be managed initially with a conservative ‘watchful waiting’ strategy in which they are observed and periodically reimaged with water-soluble enema study to check for healing of the sinus. Chronic IPAA sinuses that persist after expectant management may undergo careful surgical unroofing with reasonable hope for healing.

Redo IPAA can be considered for sinus tracts refractory to unroofing, or for patients in whom unroofing of sinuses would significantly interfere with subsequent pouch revision. (Evidence: low; Recommendation: strong).

Personal View

IPAA sinuses occur as a result of anastomotic separation and sepsis after pouch creation. If this occurs, patients should undergo exam under anesthesia and transanal mushroom drain placement every 6–8 weeks with downsizing of the drain until the

Table 41.2 Reported literature

Study	Patients (N) Selection criteria	Treatment/ Healing rate of sinus tract	Pouch failure rate	Quality of evidence
Nyam [4]	**41** Asymptomatic/ diverted	**95% (40/41)** All observation	1/41	Low
van Koperen [5]	**5** All diverted	**60%** 3/5 healed with observation 2/5 required ileostomy	40%	Low
Whitlow [6]	**4** All diverted	**100% (4/4)** All unroofing	NA	Low
Akbari [7]	**22** Asymptomatic/ diverted	**95% (20/21)** Observation ± debridement	0	Low
Ahmed Ali [8]	**45** 25/45 symptomatic 23/45 diverted	**60% (27/45)** Observation 65% (23) Unroofing 50% (8) Drainage 59% (9) Sinus closure 33% (3) Diversion 100% (2)	33%	Low
Zhou [9]	**6** All diverted	**100% stoma closure** Observation ± debridement/ drainage	NA	Low
Lan [13]	**109** 102/109 symptomatic	**49.5% complete** **67.8% complete + partial** All NKSi	20%	Moderate
Swain [14]	**7** Chronic (5/7 diverted)	**100% (7/7)** All debridement + fibrin glue	NA	Low

defect heals. Percutaneous drainage should not be used, as this converts the defect into a fistula tract. With proper management, many of these defects will heal over the course of 9–12 months, while some may develop into a presacral sinus tract.

An asymptomatic sinus tract found on routine contrast imaging, prior to loop ileostomy closure, should be treated initially with a period of watchful waiting, with interval imaging in a few months to confirm sinus healing prior to ileostomy closure. Patience is key during this process, as patients are typically feeling well and eager to experience stoma-free living once again.

Sinuses that persist after watchful waiting, or those presenting with symptoms after intestinal continuity is restored, can be considered for surgical intervention. Further endoscopic and radiographic characterization (i.e. pouchoscopy and pelvic MRI) is helpful here to assess the complexity and length of the sinus tract, and to distinguish from fistulae. Short, superficial sinus tracts should be treated with transanal drain placement (if sepsis persists) or unroofing and debridement of the sinus tract. Sequential treatments may be necessary, with interim imaging to check for healing.

Small sinuses that are present after the above treatment in a diverted IPAA can be offered an attempt at ileostomy closure as long as the patient understands the pathology and possible outcomes of this approach. Fibrin glue injection has been reported

to be successful [14], but in our experience has not consistently contributed to complete healing.

NKSi can be a successful treatment in carefully selected patients. This should be limited to short sinus tracts without signs of sepsis, and should be performed by or in close association with an IPAA surgeon. This treatment is promising, but patients must understand the limitations and limited follow-up available for NKSi, and have reasonable expectations for what this approach can achieve. Repeated treatments may be beneficial but can also compromise the posterior pouch wall in a way that prevents other corrective options if needed.

Some patients with persistent IPAA sinus may be candidates for IPAA revision or redo. Consideration should be given to those who have not achieved symptom relief after transanal treatment (i.e. debridement/unroofing) or those who demonstrate a long sinus tract (over 6 cm) who have not yet undergone unroofing. It is critically important that attempts to unroof longer tracts be approached with great caution. Unroofing rarely leads to complete healing in these longer tracts and can cause major damage to the pouch body. This is important to consider because the ileal pouch can be reused in nearly 2/3 of patients who require revisional pouch surgery, and disruption of the posterior wall of the pouch during an attempted endoscopic intervention may prevent pouch salvage; this, in turn, may make pouch correction much more challenging or not possible at all [15].

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The Management of Patients with Dysplasia in the Anal Transitional Zone

42

Dakshitha Wickramasinghe and Janindra Warusavitarne

Introduction

Sir Alan Parks in 1978 described the first case series of proctocolectomy with ileal-pouch creation [1]. The purpose of the procedure was to remove all disease-prone mucosa in ulcerative colitis (UC) while maintaining intestinal continuity [1]. Of the two main surgical methods of forming ileal pouches, the double-stapled (DS) method may have advantages over the hand-sewn (HS) approach including lower postoperative complications and better functional outcomes [2]. However, an inherent limitation of this technique is the persistence of a length of anal transitional zone (ATZ), the area between colorectal type mucosa above and the squamous epithelium below [3]. Because this mucosa is at risk of chronic inflammation and dysplasia [3, 4], there is a long term risk of perianastomotic malignancy [5]. The management of pouch and ATZ dysplasia take two forms; minimizing the development of dysplasia and treating established dysplasia. To minimize dysplasia, the mucosa left after surgery must be minimized and ensuing inflammation avoided. The former may be achieved by performing a mucosectomy and a HS anastomosis and the latter by treating inflammation of the rectal cuff.

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Table 42.1 PICO table

	Patient population	Intervention	Comparator	Outcomes studied
Minimizing ATZ dysplasia	Ulcerative colitis patients undergoing IPAA surgery	Mucosectomy and hand-sewn anastomosis	Double-stapled anastomosis	Development of dysplasia in the ATZ
Management of patients with ATZ dysplasia	IPAA pts. with dysplasia in the ATZ	Surveillance	Surgery	Persistent/ recurrent neoplasia, quality of life

Search Strategy

We first developed the relevant Patient, Intervention, Comparator, Outcome (PICO) questions (Table 42.1). A comprehensive literature search was performed on MEDLINE, Pubmed, Embase and Cochrane database to identify all articles published in English from 1990 to 2017. The key words are given below.

1. dysplasia
2. transitional ADJ zone
3. "COLONIC POUCHES"
4. 1 AND 2 AND 3
5. (ileal OR ileum) ADJ pouch*
6. 3 OR 5
7. 1 AND 2 AND 6

For the first section, we included all studies that reported on dysplasia in the ATZ in patients who had undergone ileal pouch-anal anastomosis (IPAA). Studies on patients with polyposis were excluded.

In the second section, we confined our analysis to studies which had followed up patients with dysplasia in the ATZ with or without an intervention.

The references of the included studies were reviewed to ensure completeness and any missing studies were included (Table 42.1).

Results

Of the many studies focusing on creating an ileal pouch for UC (Table 42.2), there was a clear trend of surgeons increasingly using the double-stapled technique. Even in the studies with a long inclusion period, the initial cases had been HS while subsequent cases performed using the DS technique.

Table 42.2 Incidence of dysplasia

Study	Patients (UC with pouch)	Intervention	Study design	Number (dysplasia in UC patients)	Quality of evidence
Luukkonen et al. (1994) [6]	179	IPAA – Technique unspecified	Retrospective	No dysplasia in ATZ	Very low quality
Setti Carraro et al. (1994) [7]	60	IPAA – Technique unspecified	Retrospective	No dysplasia in ATZ	Very low quality
Veress et al. (1995) [8]	87	IPAA – Mucosectomy + hand-sewn anastomosis	Retrospective	No dysplasia in ATZ	Low quality
Haray et al. (1996) [9]	109	IPAA – Stapled anastomosis	Retrospective	No dysplasia in ATZ	Low quality
Giebel et al. (1996) [10]	13	IPAA – Mucosectomy + hand-sewn anastomosis	Retrospective	No dysplasia in ATZ	Low quality
Pronio et al. (1997) [11]	38	IPAA – Technique unspecified	Retrospective	No dysplasia in ATZ	Very low quality
Stallmach et al. (1999) [12]	42	IPAA – Technique unspecified	Retrospective	No dysplasia in ATZ	Very low quality
Sarigol et al. (1999) [13]	176	IPAA – Stapled anastomosis	Prospective (Paediatric)	No dysplasia in ATZ	Low quality
Thompson-Fawcett et al. (2000) [14]	113	IPAA – Stapled anastomosis	Retrospective	No dysplasia in ATZ	Low quality
Ettorre et al. (2000) [15]	21	IPAA – Mucosectomy/ rectal eversion and anastomosis	Prospective	No dysplasia in ATZ	Low quality
Tianen et al. (2001) [16]	36	IPAA – Mucosectomy + hand-sewn anastomosis	Retrospective	No dysplasia in ATZ	Low quality
Thompson-Fawcett et al. (2001) [17]	106	IPAA – Mucosectomy + hand-sewn anastomosis	Prospective	No dysplasia in ATZ	Low quality
Sylvester et al. (2002) [18]	48	IPAA – Technique unspecified	Prospective	No dysplasia in ATZ	Very low quality
Coull et al. (2003) [19]	110	IPAA – Stapled anastomosis	Retrospective	No dysplasia in ATZ	Low quality

(continued)

Table 42.2 (continued)

Study	Patients (UC with pouch)	Intervention	Study design	Number (dysplasia in UC patients)	Quality of evidence
Kayaalp et al. (2003) [20]	44	Stapled anastomosis – 22 Hand sewn – 22	Retrospective	Dysplasia in ATZ in 1 (4.5%) patient in stapled group	Low quality
Ståhlberg et al. (2003) [21]	27	IPAA – Technique unspecified	Retrospective	No dysplasia in ATZ	Very low quality
Fruin et al. (2003) [22]	48	IPAA – Technique unspecified	Retrospective	No dysplasia in ATZ	Very low quality
Herline et al. (2003) [23]	164	IPAA – Stapled anastomosis	Retrospective	No dysplasia in ATZ	Low quality
Remzi et al. (2003) [24]	178	IPAA – Stapled anastomosis	Retrospective	ATZ dysplasia in 8 (4.5%)	Low quality
Saigusa et al. (2003) [25]	91	IPAA – Stapled anastomosis	Retrospective	No dysplasia in ATZ	Low quality
Hurlstone et al. (2004) [26]	132	IPAA – Stapled anastomosis	Prospective	No dysplasia in ATZ	Low quality
Börjesson et al. (2004) [27]	45	IPAA – Mucosectomy + hand-sewn anastomosis	Retrospective	No dysplasia in ATZ	Low quality
Elkowitz et al. (2004) [28]	30	IPAA – Technique unspecified	Retrospective	ATZ dysplasia in 1 (3.3%)	Very low quality
Haskell et al. (2005) [29]	200	IPAA – Technique unspecified	Retrospective	No dysplasia in ATZ	Very low quality
Mattioli et al. (2005) [30]	16	IPAA – Stapled anastomosis	Prospective	No dysplasia in ATZ	Low quality
Nilobol et al. (2007) [31]	118	IPAA – Mucosectomy + hand-sewn anastomosis	Prospective	No dysplasia in ATZ	Low quality
Schaus et al. (2007) [32]	2512	IPAA – Technique unspecified	Retrospective	No dysplasia in ATZ	Very low quality
Meléndez Hernández et al. (2009) [35]	38	IPAA – Stapled anastomosis	Prospective	No dysplasia in ATZ	Low quality
Kariv et al. (2010) [33]	3203* some missing data	Stapled anastomosis – 2734 Hand sewn – 451	Retrospective	Dysplasia in pouch (ATZ not separately listed) Stapled – 18 patients Hand sewn – 3 patients	Very low quality

Table 42.2 (continued)

Study	Patients (UC with pouch)	Intervention	Study design	Number (dysplasia in UC patients)	Quality of evidence
Zhu et al. (2013) [35]	109	Stapled anastomosis – 92 Hand sewn – 17	Retrospective	No dysplasia in ATZ	Low quality
Derikx et al. (2014) [36]	1200 (IBD)	Both stapled and hand-sewn	Retrospective	Stapled – 2 patients Hand sewn – 1 patient	Very low quality
Anderson et al. (2014) [37]	253	Stapled anastomosis – 245 Hand sewn – 8	Retrospective	No dysplasia in ATZ	Low quality
Bobkiewicz et al. (2015) [38]	276	Stapled anastomosis – 249 Hand sewn – 27	Retrospective	No dysplasia in ATZ	Low quality
Shannon et al. (2016) [39]	69	Stapled anastomosis – 48 Hand sewn – 21	Retrospective (Paediatric)	No dysplasia in ATZ	Low quality

Most studies did not identify dysplasia in their patient population. Some studies did not document the procedure [28] or the location of the dysplasia [34] and were excluded from this calculation. Scarpa [5] reported a pooled prevalence of 1.55% for dysplasia in rectal cuff and ATZ. Thus, a large patient population would be needed for a statistically significant difference to be identified between the HS and DS procedures.

Of the studies that had clearly documented both the technique and the location of the dysplasia, only one patient had developed dysplasia in the HS group while 11 had dysplasia in the DS group. In a study retrospectively reviewing all pouch procedures done over eight years, Kalaalp [20] identified one patient with dysplasia in the ATZ with the DS technique. Similarly, Elkowitz [28] identified dysplasia in 1 in 30 patients they followed. However, the technique used in the particular patient was not indicated in the article.

Remzi [24] identified dysplasia in 8/178 (4.5%) patients following the DS technique. The authors also noted that dysplasia could spontaneously resolve during follow-up. Similar observations of regression of dysplasia were made by Derikx [36] when they analysed the data of all patients who underwent a pouch creation in the Netherlands between 1991 and 2012. Even though they did not indicate the exact numbers of patients undergoing each technique, they identified ATZ dysplasia in one and two patient(s) after HS and DS techniques, respectively.

Therefore, the results indicate that a DS anastomosis may result in a higher chance of development of ATZ dysplasia. However, there is good evidence to suggest that in a majority of patients, this dysplasia may regress (Table 42.2).

The main concern of a patient developing dysplasia is the possibility of progression to malignancy. As dysplasia may regress in most situations, all patients who develop dysplasia in the ATZ may not warrant surgery. Only three studies have compared mucosectomy or excision of the pouch vs. surveillance in patients who

develop dysplasia. All three are based on the same patient cohort and represent an analysis of different variables and different time points.

In 2010, O'Riordan [40] published the first article on results of long term follow-up on patients after RPC. Their cohort included 210 patients who underwent RPC with preservation of the ATZ and they identified dysplasia in 7 patients. Two patients who had persistent dysplasia for more than 2 years underwent mucosectomy. They did not develop subsequent dysplasia. The remaining patients who had dysplasia did not show persistent dysplasia in subsequent biopsies. None of the patients developed cancer after a follow-up of 5–10 years. Therefore, no additional benefit from mucosectomy was evident.

Remzi [24] reported a retrospective study of patients with UC after RPC and a minimum of 10 years follow-up. Of 289 patients followed up, they identified ATZ dysplasia in eight patients. This also included some of the patients reported by O'Riordan [40]. Additionally, they identified a patient with high grade dysplasia (HGD) which disappeared but was identified again after 10 months. Although mucosectomy with a neo-pouch was planned, due to comorbidities the patient only underwent a partial mucosectomy. The mucosectomy specimen did not show any dysplasia and he had not developed dysplasia in the ATZ after 83 months of follow-up. Therefore, mucosectomy may not provide additional benefits even in patients with HGD.

The most recent paper from this patient cohort was published by Silva-Velazco [41]. The median follow-up was 13.4 years and 73 patients had a follow-up of more than 20 years. Nine patients had developed dysplasia and no new-onset dysplasia was identified after 125 months. They too did not identify any subsequent dysplasia in either patient group (Table 42.3).

Recommendations

The results indicate that a DS anastomosis may result in a higher chance of dysplasia when compared with the HS anastomosis (high quality, moderate confidence).

It is worthwhile noting that this has to be taken in context as the overall incidence of dysplasia in the reported studies is very low. This observation is also supported by a meta-analysis [42] which identified a non-significant increase in dysplasia after the DS technique. Nonetheless this was contradicted by Um [43] who noted that both dysplasia and cancer after restorative proctocolectomy (RPC) were higher in patients who underwent mucosectomy than the DS technique. The persistence of rectal mucosa even after mucosectomy may explain this observation [42].

There is evidence to suggest that in a majority of patients, dysplasia will regress [36] (low quality, low confidence).

There are inherent difficulties in identifying dysplasia conclusively, and this may explain at least partially why some patients diagnosed as having dysplasia subsequently do not show evidence of any future dysplasia. The lack of uniformity in nomenclature for the anatomy after RPC also adds to this confusion [43].

In patients who develop dysplasia in the ATZ after RPC, mucosectomy and pouch advancement did not offer a significant advantage in reducing subsequent

Table 42.3 Interventions for dysplasia in the ATZ

Study	Patients	Intervention	Study design	Number	Outcome classification	Typical risk for therapy A	Relative risk for therapy B	Quality of evidence
Silva-Velazco et al. (2014)	UC patients with pouches (285)	Mucosectomy + perineal pouch advancement + neo-IPAA	Retrospective	Mucosectomy – 4 Observation – 5	Development of dysplasia/ cancer	No further dysplasia/ cancer	3/5 – No further evidence of dysplasia 2/5 – LGD (X2) and HGD (X1) but managed expectantly No cancer	Moderate quality
Remzi et al. (2003)	UC patients with pouches (178)	Transanal excision of ATZ + perineal pouch advancement	Retrospective	Dysplasia – 8/178 • LGD – 6 – Surgery – 2 – Surveillance – 4 • HGD – 2 – Partial mucosectomy – 1 – Surveillance – 1	Development of dysplasia/ cancer	Surgery – No recurrence	Surveillance – no dysplasia	Moderate quality
O'Riordain et al. (2000)	UC patients with pouches (210)	Transanal excision of ATZ + perineal pouch advancement	Retrospective	LGD – 7 • Surgery – 2 • Surveillance – 5 HGD – 1 • Surveillance	Development of dysplasia/ cancer	Surgery – No recurrence	Surveillance – no dysplasia	Low quality

dysplasia or cancer. A perineal surgical intervention of such magnitude can be associated with complications.

As follow-up data indicate that even HGD will regress, a major intervention for ATZ dysplasia cannot be recommended over surveillance alone (moderate quality, moderate confidence).

This is further strengthened by the observation that none of the patients with dysplasia identified in the ATZ developed cancer of the ATZ subsequently.

Surveillance for dysplasia after RPC should begin early because dysplasia was identified as early as 4 months after surgery (moderate quality, low confidence).

The surveillance could be less intense after 10 years because published data indicate no patient developed new-onset dysplasia after 125 months (moderate quality, low confidence).

Personal View

The surveillance strategy for dysplasia after RPC for UC can be contentious and can sometimes be overlooked in the overall treatment algorithm. In some ways, this may not be harmful to the patient as the risk of dysplasia and cancer in the patient without pre-existing colonic or rectal dysplasia is very low. Accordingly, performing routine pouchoscopy to assess the cuff has long been abandoned in most specialist centres and surveillance tends to be targeted to those individuals where there is preexisting rectal dysplasia. Radical excision or removal of the rectal cuff with advancement of the anastomosis are surgical options in the presence of dysplasia but these techniques have not been shown to decrease the risk of pouch cancers in some series. In our institution, patients with dysplasia who have undergone ileoanal pouch surgery have annual surveillance. Should ATZ dysplasia develop, we treat this endoscopically by ablation or submucosal dissection. A multidisciplinary discussion is the key to appropriate decision making in the setting of difficult lesions, but the need for surgery is not common. A risk vs. benefit discussion is also crucial in the decision-making process. Perhaps future research should incorporate time trade off models to ascertain how individuals will value maintaining a pouch over more radical surgery.

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Pouch Excision Versus Diversion for the Failed Pouch

43

P. Ravi Kiran

Ileal pouch-anal anastomosis (IPAA), the gold standard restorative procedure after proctocolectomy in patients with ulcerative colitis and familial adenomatous polyposis [1], is durable, associated with a good quality of life (QOL) and excellent outcomes [2–4]. However, pouch failure occurs in a proportion of patients owing to anastomotic leak or stricture, fistula, pelvic sepsis, recurrent pouchitis, and pouch dysfunction [5–9]. When pouch failure occurs, options include a permanent ostomy, pouch repair, revision or redo pouch, or conversion to a continent ileostomy reservoir if this expertise exists at the particular center. When restoration of intestinal continuity or continence is not pursued, pouch excision is usually undertaken. However, performing a permanent ileostomy above a pouch left in-situ is an alternative to pouch excision.

A permanent diversion that leaves the pouch in-situ with a proximal ostomy has the advantage of being a less invasive procedure within a reoperative abdomen and avoids dissection in the pelvis. However, ongoing symptoms due to drainage from the pouch itself or from the pouch-related complications that led to pouch failure may impact quality of life if the pouch is retained. In addition, the lining of the pouch or residual anorectal cuff mucosa may undergo neoplastic transformation with dysplasia or cancer. While pouch excision eliminates symptoms due to the pouch itself or from its complications that may fester if it were to be retained, the surgery can be far more extensive and technically challenging, associated with risks of reoperation within the pelvis including bleeding, nerve, ureteral and bladder damage, as well as potential problems with perineal wound healing. There is currently minimal information available to highlight the preferable option (Table 43.1).

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Table 43.1 PICO table

Patients	Intervention	Comparator	Outcome
Patients with failed IPAA	Pouch excision	Diversion alone	Complication rate; quality of life (QOL)

Search Strategy

A comprehensive literature search of Cochrane Database of Collected Research, EMBASE, MEDLINE, and PubMed was performed to identify all of the English-language publications related to outcomes after pouch excision as well as permanent diversion when pouch failure occurs from 1985 to 2015. Search was conducted using the following search strategies: ((inflammatory bowel disease) or (IBD) or (ulcerative colitis) or colitis or UC) and ((pouch excision) or (pouch diversion) or (pouch in situ)); (uc or (ulcerative colitis) or IBD or colitis) and (pouch excision); pouch excision and diversion; pouch failure and excision. Studies were excluded if they did not report outcomes after either pouch excision or pouch diversion. Considering the paucity of evidence of literature on the topic, any studies that reported outcomes for either of the procedure, even if there was no direct comparison between the two were included. References of the included studies were reviewed to identify additional studies that were incorporated as appropriate.

Results

There is minimal data comparing the two surgical approaches with only two studies [10, 11] having directly compared outcomes for pouch excision versus permanent diversion with the pouch left in-situ. Two other studies [12, 13] reported outcomes in patients with permanent diversion with pouch in-situ alone without a comparative group of pouch excision patients. Eight studies [14–21], reported outcomes after pouch excision exclusively.

Pouch Excision

Of the eight studies reporting outcomes on pouch excision, the short-term complication rate was 20–77% [14, 16, 17, 19] and the long-term complication rate was 37–53% [14, 19], with surgical site infection being reported as the most frequent. There was also a high occurrence of perineal wound complications (10–43%) and development of a persistent perineal sinus [17].

Four studies [10, 11, 20, 21] reported long-term quality of life after pouch excision. Lepistö [21] suggested that QOL after pouch excision is diminished compared to both the healthy population and patients with a functioning pelvic pouch due to impaired energy and physical role functions. Meanwhile, Tan [20] suggested that while patients who underwent pouch excision had more liquid ileostomy output

than those who underwent a standard proctocolectomy and ileostomy, QOL was similar. The other two studies [10, 11] compared quality of life after pouch excision versus permanent diversion, and are discussed later in the chapter.

Few studies reported information related to sexual and bladder dysfunction [10, 11, 20] with the majority including outcomes for small numbers of patients. Urinary and sexual dysfunction were associated with pouch excision [10, 11, 20] and deemed comparable for pouch excision and permanent diversion [10, 11].

Permanent Diversion

Two studies [11, 13] reported data on residual symptoms from the pouch left in-situ. Bengtsson [13] reported outcomes for 22 patients and found that some patients had minor problems such as mucous discharge and anal pain. However no patients needed further surgery. While Bengtsson [13] reported symptoms only affected a minority of patients, Kiran [11] reported that symptoms related to the pouch can be bothersome when the pouch is left in-situ.

When the pouch is left in-situ after permanent diversion, an important issue to consider is the risk of long-term dysplasia or cancer in the retained pouch. Risk of neoplastic transformation and need for surveillance was evaluated in three studies [11–13]. Bengtsson [13] looked at the morphology of mucosal changes in the pouch left in-situ for 13 patients and found that there was no case of dysplasia and carcinoma after a median follow-up of 8 years. They concluded that indefinite defunctioning of the pouch in asymptomatic patients may be preferable to pouch excision. Das [12] also reported that in 18 patients undergoing permanent diversion with available histology, no dysplasia or cancer was found. Similarly, Kiran [11] found that after a median follow-up of 9.7 years, no dysplasia or cancer was detected in 18 patients with permanent diversion. Although this may suggest that permanent diversion is safe and the risk of pouch neoplasia is small, eight of the patients in the study by Kiran [11] in the pouch excision group had this performed for dysplasia or cancer raising the potential for the development of this condition over the long-term.

Pouch Excision Versus Permanent Diversion

Das [10] compared QOL in patients who underwent permanent diversion with the pouch left in-situ compared to pouch excision for pouch failure following IPAA. They reported that although patients with pouch excision seemed to have a better QOL than those with permanent diversion, this difference was not statistically significant. Male sexual function however was better after permanent diversion. Kiran [11] reported perioperative outcomes and long-term QOL for 136 patients with pouch failure who underwent either pouch excision or permanent diversion. The two groups had similar baseline characteristics, preoperative details and reasons for pouch failure; septic complications following IPAA was the most frequent reason. Time from IPAA to surgery for failure and diagnosis at failure were also

similar between groups. Pouch excision was associated with a greater blood loss but other complications such as ileus, obstruction and septic complications were similar. After a median follow-up period of 9.9 years, patients with pouch excision had significantly better QOL than permanent diversion. Urinary function and related QOL as well as sexual function were also similar between groups. As only a proportion of patients in the two groups responded to the questionnaires pertaining to urinary and sexual function, it was difficult to make definite conclusions. However, based on the information obtained from both male and female patients who responded, urinary and sexual function and QOL appeared similar for patients in both groups (Table 43.2).

Recommendations

Patients requiring an operation for pouch failure can undergo pouch excision or permanent pouch diversion leaving the pouch in-situ. Ongoing pouch-related symptoms and their effect on QOL, potential risk for cancer in the pouch and patient preference for the procedure influence the preferred strategy. The evidence suggests that pouch excision may provide a greater quality of life overall without adversely influencing long-term outcomes when performed safely. (Evidence: moderate; Recommendation: strong).

Patients needing surgery for pouch failure are typically offered pouch excision. Permanent diversion leaving the pouch in-situ is an option for patients who have not entirely decided to forego continence but would like to avoid further surgery after ostomy creation, when intraoperative challenges are encountered and when perineal wound healing may be a concern. Using temporary diversion as a potential long-term or permanent eventual solution may also help decision-making for some patients since this may allow them the comfort of not having to proceed to an irretrievable situation in terms of the possibility of establishing normal intestinal continuity at some point in the future. To some patients, a diversion proximal to the pouch may serve in some cases as a way of determining whether an ostomy provides a better quality of life than their life with a pouch. This may then afford some patients the fallback option of having the ostomy closed to revert to their previous function. Diversion may also allow control of symptoms while patients wait for newer therapies that may eventually allow pouch salvage to emerge, a not uncommon expectation in patients with pouch dysfunction.

Personal View

Pouch excision is a complex procedure due to the need for reoperation within the pelvis, consequent potential for damage to pelvic structures, and also risk for septic complications as a result of the extended surgery that may often be required. In contrast, permanent diversion above a pouch may be technically less formidable and by avoiding pouch excision may obviate the risks associated with pelvic dissection.

Table 43.2 Studies reporting outcomes after pouch excision or permanent diversion

Study	Patients (N) pouch excision	Comparison group		Main complications	Quality of life	Quality of evidence
		Permanent diversion	Other comparators			
Das [10]	31	22		Sexual and urinary dysfunction higher after pouch excision but p value NS	Same but type II error possible	Moderate
Kiran [11]	105	31		Similar ileus, bowel obstruction, wound infection Similar urinary and sexual dysfunction No cancer or dysplasia at 9.7 years after diversion	Better after pouch excision Seepage/ anal pain problematic with permanent diversion	High
Das [12]		20	None	No dysplasia at 3.6 years after diversion (primary outcome)		High
Bengtsson [13]		13	None	No symptoms No dysplasia		Low
Lightner [14]	147		None	57% complication rate; surgical site infection, delayed perineal wound healing		Moderate
Maya [15]	47		None	Perineal wound healing problems (primary outcome)		Moderate
Koleilat [16]	17		None	Surgical site infections; readmissions		Low

(continued)

Table 43.2 (continued)

Study	Patients (N) pouch excision	Comparison group		Main complications	Quality of life	Quality of evidence
		Permanent diversion	Other comparators			
Nisar [17]	110		None	Perineal wound healing (primary outcome)		Moderate
Prudhomme [18]	24		None	Delayed perineal wound healing		Low
Karoui [19]	68		None	At 1 year: readmission 38%, perineal sinus 10%		Moderate
Tan [20]	9		Proctolectomy with end ileostomy		More liquid stoma loss Same QOL	Moderate
Lepistö [21]	21		Functioning pouch		Worse QOL for pouch excision	Moderate

On the other hand, the potential drawbacks with leaving a pouch in-situ include the possibility of ongoing symptoms of anal seepage or pain and the risk of developing cancer in the pouch or residual anorectum over the long-term.

Leaving a pouch in-situ may be associated with ongoing symptoms in up to 50% of patients. Since pouch excision is associated with a significantly better quality of life over the long-term, pouch excision is the preferable option if it can be performed by an experienced surgeon. In particular, patients with incontinence, outlet obstruction or fistulae may be better served by pouch excision rather than permanent diversion since they may continue to experience troubling anal symptoms if the pouch is left in-situ. When a difficult pelvic dissection or prolonged surgery is encountered with the consequent anticipation for adverse perioperative outcomes at laparotomy, permanent diversion with the pouch left in-situ should be considered. Although pouch dysplasia or cancer risk is low, considering that seven patients in our previous study underwent pouch excision for these indications, biopsies of the pouch prior to consideration of permanent diversion and continued endoscopic surveillance of the pouch after ostomy creation seems prudent.

In conclusion, pouch excision with an end ileostomy creation is a better option when pouch failure develops since it is associated with better quality of life over the long-term when compared to a permanent diversion above the failed pouch with the pouch left in-situ. Permanent diversion leaving the pouch in-situ can be chosen in certain circumstances such as technical difficulty at surgery, unclear diagnosis and patient preference, but should be followed up with routine pouch surveillance for neoplasia.

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Pouch Excision vs. Redo IPAA After a Failed Pouch

44

Jean H. Ashburn and Feza H. Remzi

Introduction

Failure of the ileoanal pelvic pouch (IPAA) is an uncommon but disastrous situation for patients motivated to preserve intestinal continuity after restorative proctocolectomy [1]. Patients with IPAA dysfunction unresponsive to local corrective measures have historically been faced with the limited option of permanent fecal diversion +/− excision of the failed pelvic pouch [2]. However, advancements in the understanding of pouch failure have opened avenues for surgical revision of the failed pouch in some instances as an alternative to permanent ileostomy. Carefully selected patients who are decidedly motivated to avoid permanent conventional ileostomy may be considered for surgical pouch salvage, with a high likelihood of safely creating a durable, functional result similar to a de novo pouch [3–6]. Whether to pursue pouch salvage vs. redo IPAA is a challenging decision that is best approached in a multi-disciplinary, patient-centered fashion with input from both patient and experienced IPAA clinicians for best results (Table 44.1).

Search Strategy

PICO (Population, Intervention, Comparator, Outcome) data were obtained (Table 44.1). A literature search of EMBASE, MEDLINE, and PubMed was conducted to identify all English-language publications associated with ulcerative

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Table 44.1 PICO table

Patients	Intervention	Comparator	Outcome
Patients with failed IPAA	Pouch excision	Redo IPAA	Complication rate, quality of life

colitis, ileal pouch-anal anastomosis, and post-operative pouch complications from 1980–2018. The following key search terms were queried: 'colitis', 'ulcerative colitis', or 'inflammatory bowel disease'; 'ileal pouch-anal anastomosis', 'IPAA', 'J pouch'; 'pouch failure, 'pouch excision', 'IPAA failure', 'IPAA/pouch excision', 'IPAA/pouch redo', and 'pouch revision'. Studies were excluded if they considered failure of anastomoses or intestinal pouches (colonic or continent pouches) other than those related to the ileoanal anastomosis (i.e. colorectal/coloanal), unless data regarding ileoanal anastomotic failure could be separated and assessed independently. All reference lists of the included manuscripts were noted to identify additional publications that were acceptable for inclusion. Publications from the same institution were carefully assessed for overlap and only the most recent study was considered in this circumstance. Observational, prospective, retrospective, and randomized studies were considered for the literature assessment.

Results

Whether to perform pouch excision or pouch redo for a failed IPAA is a complex decision with life-altering consequences for the patient. On the one hand, pouch excision offers the opportunity to improve quality of life (QOL), but comes with the risk for postoperative wound healing morbidity and requires the acceptance of a permanent conventional ileostomy. Conversely, pouch revision offers a safe and feasible surgical alternative to maintain continuity of the intestine, but requires a commitment to undergo multiple additional operations over an extended period of time. The literature regarding optimal approach to pouch failure with regard to pouch excision vs. pouch redo is limited (Table 44.2). There are no randomized trials available or studies that directly compare the two approaches. The large majority of available studies are retrospective and descriptive experiences of specialized, high-volume IPAA centers.

The traditional approach to pouch failure has been to offer the patient pouch excision with a permanent conventional ileostomy, often in one operative setting. However, several studies on the topic have reported significant postoperative morbidity after this operation. A retrospective review from the Mayo clinic of 147 patients undergoing pouch excision reported short and long term complication rates of 57% and 37%, respectively, with 11% requiring a return to the operating room due to complications within the immediate postoperative period [2]. This is consistent with a prior study from St Mark's Hospital reporting a 25% and 53.7% early and late postoperative complication rates, respectively. Over half of the patients required readmission, with greater than 50% of these patients requiring reoperation. Persistent perineal wounds were reported in 40% and 10% at 6 and 12 months,

Table 44.2 Current studies evaluating pouch excision vs. redo for failure

Study	Patients (N) Selection criteria	Rate of complication	Quality of life	Quality of evidence
Lightner [2]	**147** **Pouch excision**	**57% Short-term** **37% Long-term**	NA	Low
Maya [8]	**47** **Pouch excision**	**29.8% Perineal complications**	NA	Low
Remzi [3]	**503**	**53% Overall complication rate** **20% IPAA failure**	QOL high; Function nearly comparable to de novo	Low
Karoui [7]	**Pouch excision**	**25% Immediate postoperative** **53% Late postoperative** 40% unhealed wound (6 months)	NA	Low
Lightner [4]	**81** **Pouch revision**	**23% Pouch failure** **36% Postoperative complications** 14% Ileus/bowel obstruction 14% Fistula	NA	Low
Dehni [10]	**19 Transanal** **45 Transabdominal**	**94% Had functional pouch** Complications: Early 6/45 (ileus = 2) Late 11/45 (fistula)	Good to excellent	Low
Pellino [11]	**46**	28.2% Pouch failure	Poorer than de novo	Low
Shawki [6]	**23 Abdominal** **29 Perineal**	**69%/75% Functional IPAA** Complications (descriptive): sepsis	Good to excellent	Low

respectively [7]. Another retrospective report highlighted the difficult challenge of postoperative perineal wound healing in their study of 47 patients undergoing pouch excision. Of these, nearly 30% suffered from perineal wound complications, including perineal wound infections (100%), perineal sinus tracts (28%) and perineal hernia (7%) [8].

The significant morbidity and need for permanent conventional ileostomy are major drawbacks of pouch excision for pouch failure [9], thus making pouch redo an attractive alternative in carefully selected patients. The largest series from Remzi reported outcomes of redo pouch surgery performed in over 500 patients. The large majority suffered from sepsis-related pouch dysfunction. Postoperative complications occurred in 53%, with pelvic sepsis the most common. Ileus/bowel obstruction (16%), anastomotic leak (8%) and wound infection (8%) were most common short-term complications (along with pelvic sepsis). A total of 20% of patients had redo-IPAA failure. Overall, 83% of patients had a functional IPAA at

most recent follow up, with 5- and 10-year pouch survival noted to be 90% and 82%, respectively. This report is one of few that examined QOL and functional outcomes, and reported that more than 90% of patients recommended surgery to others and would undergo the surgery again if needed [3]. Overall, these results strong support the important role of pouch revision surgery in thoughtfully selected patients. Many patients with IPAA failure may have a second chance to achieve stoma-free living with acceptable bowel function and quality of life with the redo pouch.

Other series report similar positive results, albeit with smaller number of patients and more limited follow up. One recent study of 81 patients undergoing pouch revision reported a predicted 5- and 10-year pouch survival of 85% and 65%, respectively, and pouch loss of 23%. The overall (early and late) complication rate was 35.6%, with most common complications being ileus/bowel obstruction and recurrent fistula [4]. Another study described outcomes of 51 patients undergoing pouch salvage, 23 of these undergoing transabdominal redo. Of these, 69% were reported to have acceptable functional results, with septic events described as the most notable and morbid postoperative complication [6]. Others have also reported successful redo IPAA with good functional outcomes and patient satisfaction with acceptable rates of complications [10–13] (Table 44.2).

Recommendations Based On Data

Patients with IPAA dysfunction may be offered the opportunity to undergo comprehensive evaluation in an IPAA center (specializing in revisionary pouch surgery) and discussion of multi-disciplinary management options. (Evidence: low; Recommendation: strong).

A patient's decision to pursue an improved QOL by accepting pouch excision with a permanent lifelong ileostomy should be honored without exception and without persuasion otherwise. For appropriately selected patients desiring an attempt at pouch salvage, pouch revision/redo are good options with a high likelihood of success, and require a thoughtful and honest discussion between patient and clinicians to set mutually agreed-upon goals and expectations for care.

Personal View

Restorative pouch surgery is one of the most important surgical achievements for patients requiring removal of the colorectum who desire a safe and durable method to maintain bowel continuity [1]. This operation was specifically designed with the goal of improving quality of life that may be compromised after proctocolectomy, which itself is curative in many cases but leaves the patient with a permanent lifelong stoma. Contemporary developments have been applied to enhance the operation over the past four decades, but the aims of surgery remain the same: to achieve the best possible QOL for the patient.

The goals of reoperative pouch surgery are no different; it is best to have the patient's QOL as the central core of care. A clear understanding of how the patient defines QOL is important and a solid patient-physician relationship is necessary to ensure a shared vision. After the cause of pouch dysfunction is determined, the patient is given all available options including the risks and benefits of each. Both pouch excision and pouch revision have been shown to have differing but significant risk for postoperative complications, and the patient should be counseled about these if he or she is choosing among these options.

Patients who are only candidates for pouch excision, but have concern about perineal wound issues, might consider a staged approach to minimize risk for complications, beginning with diverting loop ileostomy to cool pelvic sepsis, followed by pouch excision at a later date. Diverting ileostomy is also an option for patients who are candidates for pouch redo but have not been able decide between excision vs. redo. IPAA diversion in this setting allows patients to regain health, and then make a definitive decision when they are feeling better and in a better frame of mind to make this life-altering decision. Preoperative control of pelvic sepsis, when present, is a necessary part of redo pouch surgery, and fecal diversion as a first step is a very effective way of preoperative control prior to pouch revision. In general, a three-stage redo operation is best, beginning with diverting loop ileostomy, then a diverted pouch redo at least 6 months later when sepsis is cleared and the patient is healthy, and finally closure of loop ileostomy when healing is ensured.

It cannot be emphasized enough that a patient who is accepting of a permanent ileostomy should be allowed to pursue this regardless of whether he or she is also a candidate for pouch redo. Humility of the surgeon is mandatory to put the surgeon's own ego and opinions aside to honor the opinions and desires of the patient. Pouch excision is a viable option for any patient who does not have a strong desire for intestinal continuity or who is not a good candidate for attempt at pouch revision (comorbidity, weak sphincter, shortened small bowel, active anal Crohn's disease), and can always be offered as an option. QOL is subjective, and a permanent ileostomy may allow one patient to achieve the same QOL as that seen in a different patient with a functioning redo pouch.

Conversely, and equally important, patients with a failed IPAA who are not accepting of pouch excision with permanent ileostomy should undergo a comprehensive evaluation at a high volume IPAA center where pouch salvage is routinely performed. It is a great disservice to deny a 'pouch failure' patient the opportunity to be assessed by a pouch revision specialist if he or she has a desire to be considered for redo surgery. These decisions are very difficult and require the experience and judgment of specialists who deal with IPAA dysfunction on a daily/weekly basis. Clinicians who do not have the experience or expertise in revisionary pouch surgery should feel comfortable referring these patients to high volume centers without hesitation, as this is the patients last chance to achieve stoma-free living.

If pouch salvage is an option, the patient may be accepting of both the risks for perioperative complications as well as the risk for eventual failure of the salvaged pouch. In addition, patients should be aware of the typical function of a revised pouch, and the possible need for alterations in daily routine to accommodate life

after surgery. Pelvic sepsis as the etiology for pouch failure is of particular importance during this evaluation and discussion. Redo pouch surgery in the setting of chronic pelvic sepsis is commonly more technically challenging, and the presence of pre or postoperative sepsis is a risk factor for poor surgical outcomes. The clinician may consider this and other individualized characteristics around which to build a patient-specific risk profile as well as to set realistic expectations for surgery outcomes.

Crohn's disease as the etiology of pouch failure is a special situation and requires vigilant individualized care. These patients may always be offered the option of pouch excision with a clear understanding of the likelihood of prolonged recovery due to short and long-term perineal wound complications commonly seen in this population. Carefully selected patients with Crohn's disease may be candidates for pouch revision as long as they accept the increased risk for postoperative complications, higher risk for eventual pouch loss, and need for postoperative long-term medical therapy [14]. Many patients are referred to IPAA centers with a diagnosis of IPAA-related Crohn's disease, when the failure is actually due to technical complications at the pouch-anal anastomosis and resultant anoperineal sepsis. These patients are commonly excellent candidates for a redo pouch but were never considered for such due to an incorrect diagnosis of Crohn's disease.

The debate as to how best to approach IPAA failure is multifaceted and ongoing, with limited comparative studies on which to base important decisions. One of the major barriers to studying this topic is the uniqueness of every IPAA failure patient. Each patient is a unique mosaic with a distinctive combination of etiology of pouch dysfunction coupled with personal desires and QOL aspirations. Further studies are necessary to continue to learn how to approach these patients as a population, but an individualized plan of care can be the guiding light to achieve the best outcomes. Instead of posing the question 'Which one is best for *pouch failure* patients?'; rather, we may ask 'Which one is best for *this* patient?'

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Continent Ileostomy After Removal of a Failed IPAA

45

David W. Dietz

Introduction

Ileal pouch-anal anastomosis (IPAA) is considered the reconstructive procedure of choice for patients who require total proctocolectomy (TPC) for treatment of ulcerative colitis (UC) [1, 2]. IPAA is also offered in some centers to highly-selected patients with indeterminate colitis and Crohn's colitis requiring TPC [3–5]. While the vast majority of patients who undergo IPAA report good quality of life and high pouch retention rates [6, 7], approximately 10% will suffer complications leading to pouch excision [8]. These patients are usually presented with standard ileostomy as the only option. However, in a few highly specialized centers throughout the world, creation of a continent ileostomy may be offered as a more palatable alternative to end ileostomy.

Nils Kock initially described the continent ileostomy (CI) in 1969 as an alternative to the Brooke ileostomy [9]. The CI achieved some degree of popularity in the 1970s but was quickly replaced by the IPAA as the best alternative to end ileostomy after its description by Parks and Nicholls in 1978. As time passed, fewer and fewer centers offered CI as an option for patients wishing to avoid a conventional end ileostomy and today only a handful of surgeons adept at the procedure can be found (Table 45.1).

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Table 45.1 PICO table

Patients	Intervention	Comparator	Outcome
Patients with failed Ileal pouch-anal anastomosis (IPAA)	Brooke Ileostomy	Continent Ileostomy	Complication rate & Quality of Life (QoL)

Search Strategy

An exhaustive literature search was performed using Cochran Database, EMBASE, MEDLINE and PubMed to identify all English language publications addressing patients with continent ileostomy vs. Brooke ileostomy after failed IPAA. Keywords searched included the following terms: "Continent ileostomy," "Ileal pouch-anal anastomosis failure," Timeframe reviewed covered 1980–2018. Studies that did not directly address patient quality of life and complication rates after conversion of IPAA to continent ileostomy were excluded. References of sited studies were also used to identify articles relevant to this topic.

Results

We found no studies to date directly comparing the outcome and/or quality of life of patients who have had a failed IPAA converted to continent ileostomy (CI) vs. those with a failed IPAA converted to end ileostomy. It must be noted that CI surgery is performed at very few centers across the country; as such, there is a paucity of data regarding continent ileostomy surgery in general. With that said, there are several studies that provide insight into the questions posed in this chapter.

Complication Rates Following CI vs. Standard Ileostomy

Those complications directly related to takedown of a failed IPAA (e.g., wound infection, pelvic abscess, intra-abdominal bleeding) would be expected to be similar in the two scenarios being compared (creation of standard ileostomy vs. CI). Therefore, the major differences in complication rates between scenarios would likely be related to the complications unique to continent ileostomy surgery that are not present with creation of a standard ileostomy (e.g., pouch suture line leak, fistula, peri-pouch abscess, valve slippage, pouchitis, pouch bleeding). The risk of these relatively unique complications must be carefully considered by the surgeon and patient considering CI creation after IPAA failure, as several are serious in nature and may lead to major reoperative surgeries during the patient's lifetime. Especially important is the risk of CI pouch failure requiring pouch excision, as the loss of the additional ~60 cm of small bowel typically utilized for creation of a CI may put the patient at risk for short bowel syndrome, which can affect both quality and length of life.

Table 45.2 Data on continent ileostomy follow-up

Author	n	Revision (%)	Pouch survival (%)	Mortality	Follow-up (years)
Mullen et al. [23]	510	21	93	0	2[a]
Nessar et al. [21]	216	–	78	1	11[b]
Handelsman et al. [24]	100	11	83	0	2.5[a]
Lepistö and Järvinen [25]	96	59	76	2	18[b]
Litle et al. [26]	85	45	60	0	11.4[a]
Berndtsson et al. [18]	68	65	94	–	31[b]
Wasmuth and Myrvold [27]	63	44	90	0	12[a]
Behrens et al. [13]	42	43	95	0	3.4[a]

[a]Mean
[b]Median

Although a number of complications can occur following continent ileostomy surgery generally speaking, it has been demonstrated that the conversion of failed IPPA to a CI is very feasible and a safe procedure; in fact, most studies have shown a mortality rate similar to other major abdominal surgeries, ranging between 0–2% [10]. Moreover, existing data suggests that patients who have had their IPAA converted to a CI are at no greater risk for CI failure when compared to case matched cohorts who had CI without having an initial restorative procedure [11]. Most studies quote a 30 day complication rate in the 30–35% range. Pouch retention rates have been shown to be around 95% after conversion [12–14].

To date, the largest study that exists looking specifically at the outcomes of patients who have had a failed IPAA converted to CI was reported by Lian. In that study, the authors looked at 64 patients undergoing surgery between the years 1982–2007. Consistent with data from studies looking at de novo creation of CI (Table 45.2), the authors found that the most frequent cause of revision was valve slippage occurring at a rate of almost 30%. The overall complication rate was found to be 60.9% with 45.3% of the patients requiring revisional surgery [12]. This high continent ileostomy retention rate comes at a cost, as the existing data has consistently shown a high need for revisional surgery with rates as high as 66% (Table 45.2). Interestingly, the diagnosis of Crohn's disease did not appear to affect pouch retention, revision, or complication rates. The authors concluded that carefully selected patients with quiescent Crohn's disease could be considered for the procedure [12].

Quality of Life Following CI vs. Standard Ileostomy

It is the improvement in a patient's quality of life that provides the basis for recommending a procedure in which many series have shown that both short-term and long-term complication rates are high, and the majority of patients will require additional surgeries during their lifetime to maintain reasonable function of the CI pouch.

A number of authors have examined the question of quality of life in patients with CI pouch and have found it to be improved in several measures over a Brooke ileostomy [14–19]. However, there is a dearth of information specifically addressing quality of life in patients who have converted their IPAA to CI. It must also be noted that there is no data at this time directly comparing patients with CI vs. patients with Brooke ileostomies after they were converted from a failed IPAA.

It is reasonable to conclude that in the appropriately selected patient, quality of life should improve with CI when compared to Brooke ileostomy. Using the continent ileostomy surgery follow-up questionnaire and the Cleveland Global Quality of Life Scale (CGQL) tool, Nessar, found that patients who had an end ileostomy were 2× more likely to report restrictions in social, work and sexual encounters than their CI counterparts. The CI group also reported better quality of life, health and energy and scored higher on the CGQL scale (0.87 vs. 0.7; $p = 0.006$). Furthermore, more CI patients would undergo the same procedure again and recommend the procedure to someone else compared to end-ileostomy patients [20, 21]. This data was corroborated in another study by Lian, in which the authors found that the median score re quality of life, quality of health and quality of energy were all eight respectively. Moreover, 90% of patients stated they would undergo the procedure again if they had to, and would recommend it to others [12]. Head to head studies comparing CI, EI and IPAA have also been performed. They concluded that patients who had a CI had fewer restrictions in sports and sexual activities compared with those with EI and no differences were seen when comparing social life, recreation, work, and family matters [19, 22].

Recommendations

It is reasonable to recommend a continent ileostomy to patients who have had a failed IPAA. (Evidence: weak; Recommendation: Moderate).

While this procedure can be fraught with short-term morbidity and need for reoperation, carefully selected and motivated patients can achieve very good long-term pouch retention rates and, most importantly, significant improvement in their quality of life.

Personal View

Continent ileostomy provides patients who face the possibility of a permanent ileostomy some reasonable hope of long-term continence. To achieve good outcomes, one must be judicious in the patient selection process. Patients who choose a continent ileostomy should be fully informed of the risks of the procedure, including the possible need for reoperation because of valve-related issues and the risk of short bowel syndrome after multiple surgeries.

The indication for IPAA failure must be assessed and determined. Patients who have Crohn's disease of the small bowel leading to IPAA failure should likely not

undergo CI formation. Available retrospective data indicates that the pouch failure rate in those circumstances is unacceptably high, and as such, patients likely do best with end ileostomy [21]. However the above-mentioned population must be distinguished from patients who have (1) isolated peri-anal Crohn's disease with no small bowel/IPAA involvement or (2) quiescent Crohn's disease. I am of the opinion that this select population can successfully undergo conversion of their failed IPAA to CI provided that they are highly motivated patients and the risks, alternatives and chance of failure have been thoroughly discussed [28, 29].

The issue of short bowel syndrome must also be considered. A continent ileostomy requires approximately 60 cm of small bowel; given the high propensity for revisional surgery and the already utilized bowel for the failed IPAA (if the CI required creation of a new pouch), patients may not have adequate absorptive capacity. Reported data suggests that a CI functions just as well with utilization of already existing J-pouch and conversion to CI, when compared to construction of new CI [12]. Therefore, utilizing the failed pelvic pouch to construct the CI should always be the goal and it is often achievable.

Consideration should also be given to the technical challenges that this procedure presents in the operating room. Because the CI was quickly overtaken with the advent and success of the IPAA in the 1980s, most colorectal surgeons are not adept at performing a CI. Furthermore, it must also be noted that the excision of the IPAA from the pelvis can be very unforgiving, especially when trying to prevent injury to the pelvic pouch and the typical challenges of the reoperative pelvis. In addition to these challenges in the operating room, postoperative management should to include a well-staffed and educated enterostomal therapy team. Their role in the success of the patient is of critical importance as they provide invaluable attention and education to the patient in the perioperative period. While there is no data to show that patients undergoing this procedure should to have it performed at a high volume continent ileostomy center, the combination of these factors would lead one to conclude that this patient population would be best served in such an environment.

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