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REVIEW ARTICLE

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Perioperative optimization of Crohn's disease

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Abstract

Crohn's disease (CD) is a chronic inflammatory disease mainly affecting the gastrointestinal tract. With the increased availability of modalities in the last two decades, the treatment of CD has advanced remarkably. Although medical treatment is the mainstay of therapy, most patients require surgery during the course of their illness, especially those who experience complications. Nutritional optimization and ERAS implementation are crucial for patients with CD who require surgical intervention to reduce postoperative complications. The increased surgical risk was found to be associated with the use of corticosteroids, but the association of surgical risk with immunomodulators, biologic therapy, such as anti-TNF mediations, anti-integrin medications, and anti-IL 12/23 was low in certainty. Decisions about preoperative medication must be made on an individual case-dependent basis. Preoperative imaging studies can assist in the planning of appropriate surgical strategies and approaches. However, patients must be informed of any alterations to their treatment. In summary, the management of perioperative medications and surgery-related decision-making should be individualized and patient-centered based on a multidisciplinary approach.

KEYWORDS
Crohn's disease, enhanced recovery after surgery, nutritional support, perioperative care

1 | INTRODUCTION

Crohn's disease (CD) is a chronic relapsing inflammatory disease mainly affecting the gastrointestinal tract. Often characterized by abdominal pain, fever, or diarrhea with blood or mucus passage,[1] CD is primarily treated medically; however, most patients require more than one surgery during the course of their illness and must therefore be evaluated through a multidisciplinary approach.[2,3] The common indications for surgery in patients with CD include abscesses, complex internal fistulas, fibrostenotic strictures, free perforation with peritonitis, and massive hemorrhage unresponsive to other therapies.[4,5] In addition, Crohn's colitis-associated dysplasia and cancer are also indications for surgery in CD patients.[6,7] Surgery for CD carries a high risk of complications. With the increased availability of biologics in the last two decades, the treatment of CD has advanced considerably. However, questions about the surgical trend, rate, and perioperative management of biologics remain. In this review, we compiled up-to-date information about the temporal trend of surgery, nutrition, and medication consideration; enhanced recovery after surgery (ERAS); the perioperative care of CD; image and surgical dilemmas in CD surgery; and finally, recurrence and complications in CD surgery.

2 | TEMPORAL TREND OF CD SURGICAL RATE, INDICATIONS, AND METHODS

The lifetime risk of bowel resection in patients with CD has historically been high, and many patients require several surgeries.[8,9] Approximately 40% to 50% of patients with CD undergo intestinal surgery within 10 years of diagnosis, and the risk of postoperative recurrence was approximately 50% within 10 years.[10] These percentages have improved over time, with patients who received diagnoses in the 1990s having an approximate 14%, 28%, and 39% risk of surgery at 1, 5, and 10 years, respectively, from the initial diagnosis.[11]

The management of CD has changed considerably over the last 20 years. Immunomodulators and biological therapies now play key roles in treating patients with CD. Current reports have indicated that surgery rates at 1 and 5 years in the postbiologic era are lower than those recorded in the prebiologic era (14.8% and 31.2% vs. 12.6% and 24.2%, respectively).[11,12] Although no direct comparison has been made between Eastern and Western countries, the surgical rate is either compatible[13,14] or less in Eastern countries than that in Western countries.[15,16]

During the past decade, several population-based studies have assessed the temporal trends of CD surgery, but results have been conflicting.[12,17] In a Swedish population-based database study, the cumulative incidence of the first abdominal surgical procedure following a CD diagnosis decreased by two-thirds over the past 25 years, whereas the rate of repeat surgery has remained stable despite the introduction of biological therapy.[18] In a Canadian population-based study from 1996 to 2013, surgery rates in a large population of adult patients with CD decreased by 8.4% each year.[19] In addition, a paradigm shift has occurred whereby elective operations have become more common than emergent surgeries.[20] Although anti-tumor necrosis factor (TNF) therapy plays a role, this decrease in surgical trends is likely multifactorial, owing to a decline in smoking trends, earlier diagnosis, earlier treatment, improved patient education, and changes in clinical practice.[19] Because biologics such as vedolizumab (VDZ) and ustekinumab (UST) have been available for less than 10 years, estimating the real effect on the CD surgical rate would currently be difficult.

Surgical resection is the treatment of choice for localized CD of the small bowel or colon that is unresponsive to medical treatment. The uptake of minimally invasive surgery in combination with enhanced recovery programs can reduce both complications and hospital stay.[21] An increased use of laparoscopy and decreased intraoperative blood loss may have contributed to offsetting of the impact of increased comorbidity. The rate of penetrating or complicated cases requiring surgical treatment has increased, preoperative biological therapy is more often used, and extensive surgical procedures are more frequently performed.[22] The need for surgery remains, alongside the earlier use of biologicals, an appropriate therapeutic choice for some CD patients with complications.

Stricture is one of the major complications in CD patients, in up to 50% of patients in European countries and in 20.1% to 39.9% patients in Asian countries.[23] Endoscopic balloon dilatation (EBD) can delay or avoid surgery with either initial or recurrent strictures and is a safe and effective procedure for CD-related stricture.[24] Intestinal strictures longer than 4–5 cm and severely inflamed with ulcers were considered high risk and a potential contraindication to EBD.[23] Surgical treatment, such as strictureplasty, plays an important role in managing the stricture of CD patients, especially when the stricture location is not accessible by endoscopy or the patients were evaluated as high risk/contraindicated for EBD.[25] We also have to be aware of the contraindications for strictureplasty, such as phlegmon or fistula, more than one stricture over a short bowel length, perforation, and any stricture with evidence of dysplasia or malignancy.[26]

It is known that there is increased risk of intestinal cancer in CD patients.[6,27] A meta-analysis, which was based on six Western population studies showed an increased risk of intestinal cancer in CD (SIR 1.9; 95% CI, 1.4–2.5).[28] In Asia, only a few population-based studies have examined the association between IBD and CRC development.[13] A study from Taiwan found that the risk of CRC was not increased significantly in CD (SIR 0.96) compared to the background population.[29] In contrast, a study from Korea found an increased risk of developing CRC in CD patients (SIR: 3.67; 95% CI: 1.58–7.22).[30] Because of the limited number of population-based studies and relatively short follow-up duration in Eastern countries, it is difficult to compare the incidence of colitis-associated intestinal cancer between Western and Asian populations. Intestinal cancer in CD may develop in anorectal regions, especially in CD patients with chronic severe anorectal disease, rectal remnant, and strictures.[31–34] In addition, the incidence of anorectal cancer in CD may be higher in Asia than in Western countries.[35] Therefore, patients with longstanding disease who have chronic non-healing fistula, increase in bloody

discharge, or increasing perianal pain should undergo examination under anesthesia with biopsy and curettage of the fistula track as well as close endoscopic and radiographic surveillance.[36]

3 | IMAGING IN A PERIOPERATIVE SETTING

Cross-sectional imaging is recommended for preoperative evaluation in patients with CD[5,37] to assist in defining the disease extent, assessing disease activity, and detecting complications such as strictures, fistulas, and abscesses.

The three main imaging modalities available are magnetic resonance imaging (MRI), computed tomography (CT), and intestinal ultrasound (IUS). The enterography technique is also used for small bowel distension in MRI and CT. MRI and CT have high and comparable accuracy for the diagnosis and detection of complications in patients with CD.[38,39] IUS is also a reliable diagnostic tool, although its accuracy is lower than that of the other tools for disease proximal to the terminal ileum.[38] Because of the absence of radiation exposure, MRI is preferred over CT in elective settings, especially for young patients. However, in emergency settings, CT is recommended because of its wide availability and short scanning time compared with MRI.[37] In addition, CT is sufficiently sensitive to detect intraperitoneal free gas and should be performed when intestinal perforation is suspected.[40]

Most guidelines recommend biological therapy, in particular anti-TNF, in addition to the antibiotics and/or drainage for patients with complex perianal CD.[41,42] For evaluation of perianal fistulizing CD, pelvic MRI is the preferred first-line test.[40] MRI is superior to CT in terms of its soft tissue contrast for the delineation of fistula morphology and the relationship with the anal sphincter complex (Figure 1). The most commonly used classification is the Parks classification, which includes four types of fistulas: intersphincteric, transsphincteric, suprasphincteric, and extrasphincteric.[43] It can help to determine the complexity of the treatment procedure. Transrectal ultrasonography is an alternative to MRI, though the combined use of these two tools with examination under anesthesia can further improve diagnostic accuracy.[44] Understanding the anatomy of perianal fistula and evaluation of the presence of proctitis are imperative for the selection of appropriate options for surgical repair,[42,45] including loose seton,[46,47] fistulotomy,[41] disconnection procedures (advancement flaps,[48] the ligation of the intersphincteric fistula tract [LIFT] procedure[49]), infill procedures (glues,[50,51] plugs[52]), and ablative procedures (video-assisted anal fistula treatment [VAAFT],[53] fistula tract using laser [FiLaC][54]). Recently, there is still a promising treatment using mesenchymal stem cells to treat CD-related fistula.[55]

Percutaneous image-guided drainage is recommended as the primary treatment for well-defined accessible intraabdominal abscesses in CD (Figure 2).[4] The successful drainage rate is 74% to 100%,[56] which can negate the need for subsequent surgery in 29.3% of patients.[57] Percutaneous drainage can serve as a bridge to elective surgery, during which time medical and nutritional optimization can be implemented.

Detection of small bowel and colorectal cancer in patients with IBD is challenging. The presenting symptoms may overlap with active IBD, and the endoscopic biopsy sometimes could be false-negative and the definite diagnosis is made only after surgery. On imaging, the tumor may present as a soft tissue mass, which is helpful for the diagnosis; but in a substantial number of cases, it may present as stenosis with circumferential wall-thickening, which is difficult to differentiate from inflammation or fibrotic stricture.[58,59] Symptomatic strictures in patients with long-standing IBD after a prolonged remission, or strictures refractory to medical therapy, should be evaluated carefully and may refer for surgical consultation.[60]

Imaging studies assist in the planning of appropriate surgical strategies and approaches. However, studies have reported that unexpected intraoperative findings lead to modification of the planned surgical procedure in 9% and 26% of patients.[61,62] Therefore, surgeons should always search for possible additional lesions intraoperatively, and patients should be informed of the possibility of procedure modification.

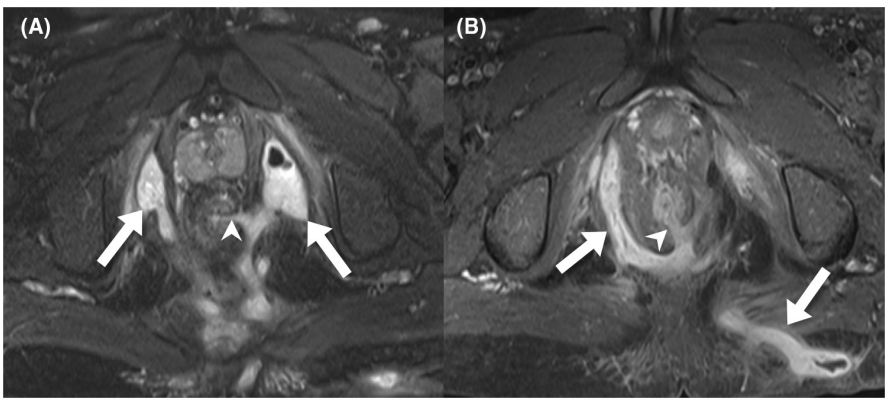

FIGURE 1 Pelvic MRI of a 20-year-old man with CD for preoperative evaluation of the perianal fistula. (A) An axial T2-weighted image with fat saturation presents a suprasphincteric fistula tract at the 3 o'clock position (arrowhead), with branching and abscess formation at bilateral ischioanal fossae (arrows). (B) a postcontrast axial T1-weighted image of another fistula tract (arrowhead), with branching fistulae extending to the right ischioanal fossa and left gluteal region (arrows)

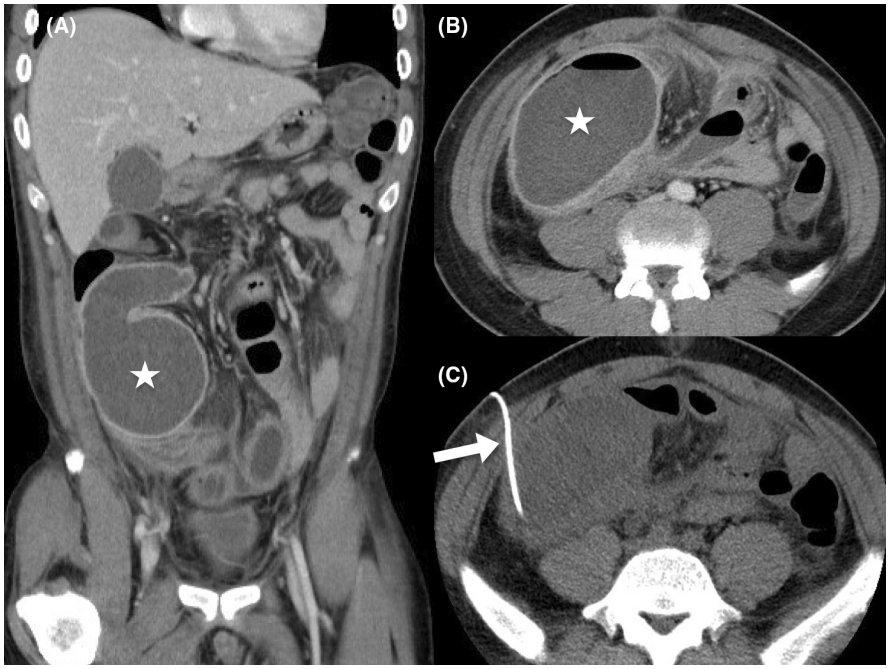

FIGURE 2 Contrast-enhanced CT of a 29-year-old man with CD who presented with right lower quadrant pain that lasted for 3 months. (A and B) coronal and axial images of inflammatory changes of the ileal loops, with a large abscess formation (star) on the lower right abdomen. (C) CT-guided percutaneous drainage of the abscess was performed, and a pigtail catheter (arrow) was inserted into the abscess. The abscess was successfully treated

4 | PERIOPERATIVE NUTRITIONAL MANAGEMENT OF CD

Nutritional optimization is essential for surgical patients to obtain favorable surgical outcomes. Presurgical malnutrition could increase the incidence of complication, such as infection, abscesses, anastomotic leakage, and ineffective wound healing.[63,64] The European Society for Clinical Nutrition and Metabolism guidelines on inflammatory bowel disease (IBD) recommend integration of nutritional support into the overall medical management of patients with IBD requiring surgery. The ERAS guidelines should be applied in perioperative management.[65]

Presurgical nutrition screening should be executed to identify patients with a high risk of malnutrition, such as in patients with enterocutaneous fistula.[66,67] Severe malnutrition is indicated when at least one of the following criteria are met: (1) more than 10% to 15% of unintentional weight loss within 6 months; (2) a body mass index of less than 18.5 kg/m^2; and (3) a serum albumin level of less than 30 g/L (without hepatic or renal dysfunction). Because they are influenced by active disease, serum albumin levels should be carefully interpreted.[68,69] For elective surgical patients with malnutrition, surgery should be postponed in favor of administering an oral nutrition supplement (ONS), enteral nutrition (EN), peripheral parenteral nutrition (PN), or total parenteral nutrition supplementary to EN support for 7 to 14 days. Longer support periods might be necessary for severely malnourished patients.[68,69]

EN is preferred over PN if gastrointestinal function is not contraindicated. Because nutrition requirements cannot be fulfilled through natural food intake, natural food intake with ONS is advised. The nasogastric or nasojejunal feeding routes are alternatives when oral intake is impossible. Because EN support cannot fulfill more than 60% of nutrition requirements, PN support can be considered.[65,68] Protein intake must be increased to 1.2–1.5 g/kg in patients with active IBD.[68] Micronutrient deficiencies, such as in iron, vitamin B_{12}, vitamin D, and zinc should be monitored and corrected in timely manner.[68] Patients should begin natural food intake (gradually progressing form clear liquids, low residue semisolids, and low residue solids to a normal diet) or EN support as early as possible if the gastrointestinal function is not compromised.[68–71] If EN is impossible, PN can be used for nutritional support.[68–70] The perioperative nutritional management is summarized in Figure 3.

5 | PERIOPERATIVE PHARMACOTHERAPY

5.1 | Immunomodulation

Immunomodulators suppress inflammation through T-cell-mediated mechanisms. The suppression of the inflammatory process by T cells may cause impaired collagen synthesis and reduce strength, which may increase the risk of anastomotic dehiscence.[72]

A retrospective international multicenter study[73] enrolled 231 patients undergoing ileocolonic resections for active CD to examine the relationship between preoperative immunosuppressive and biologic agents and postoperative complications. The study revealed that immunosuppressive or biologic therapies prior to surgery did not significantly influence the incidence of overall complications, intraabdominal sepsis, or anastomotic leakage. According to the multivariate analysis, blood transfusions, perforating disease, and previous resections were significant risk factors for overall complications, including intraabdominal sepsis and anastomotic leakage.

A meta-analysis by Huang et al[74] that included six studies with a total of 2146 patients indicated that immunomodulation was not a risk factor for the complication of intraabdominal sepsis, with a pooled odds ratio (OR) of 1.07 (95% CI: 0.66–1.73). A similar result was obtained in another meta-analysis.[75] Although no robust

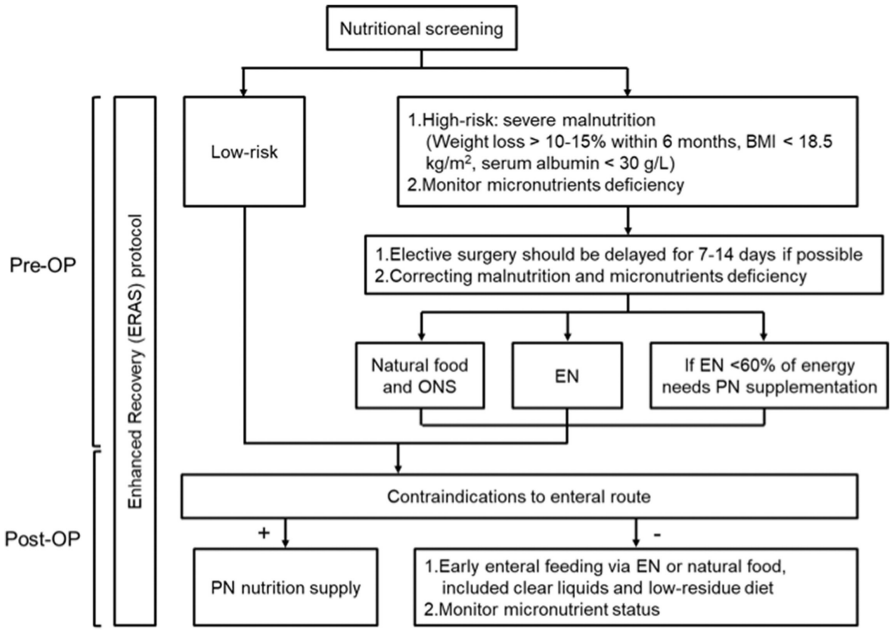

FIGURE 3 Perioperative nutritional management of CD

evidence is yet available, immunomodulation is likely safe to continue perioperatively in patients with CD.[5]

5.2 | Corticosteroids

Systemic corticosteroids (CSs) are recommended for the induction of clinical response and remission, but not maintenance, in patients with CD.[76] In a study pooling data from 71 controlled clinical trials, Stuck et al[77] suggested that the risk of infection was not increased in patients given a daily dose of less than 10 mg or a cumulative dose of less than 700 mg of prednisone. However, for a dosage of 10 mg daily, the overall rate of infection-related complications was 12.7% in 2111 CS-treated patients versus 8% in the 2087 controls (RR: 1.6; 95% CI: 1.3–1.9; $P < 0.001$).

The subgroup analysis of the meta-analysis evaluated whether preoperative CS was a risk factor,[74] revealing that CS administration was associated with a high risk of intraabdominal sepsis complications (OR 1.99; 95% CI: 1.54–2.57). A similar meta-analysis evaluated preoperative CS treatment and the risk of postoperative complications in patients with IBD undergoing abdominal surgery.[78] The results indicated that CS treatment was associated with all postoperative complications (OR 1.41, 95% CI: 1.07–1.87) and an increased risk of postoperative infection complications (OR 1.68, 95% CI: 1.24–2.28). The researchers further concluded that patients who received high doses of perioperative oral steroids (more than 40 mg) had a higher risk of overall complications (OR 2.04, 95% CI: 1.28–3.26).

The European Crohn's and Colitis Organization (ECCO) guidelines[2] stated that a prednisolone dosage of 20 mg daily or equivalent for more than 6 weeks is a risk factor for surgical complications. Therefore, patients must be weaned from CSs when possible. In patients whose high-dose steroids cannot be tapered, a staged surgery with a temporary stoma may be considered.[4]

5.3 | Biologics

Biologic agents, such as anti-TNF, VDZ, and UST, are effective medications for inducing remission in patients with moderate-to-severe CD who have not responded to conventional therapy.[76] However, a significant proportion of patients do not achieve mucosal healing and eventually require surgical intervention after step-up therapy.[79,80] Moreover, surgical intervention is required for 50% of patients with CD within 10 years of diagnosis.[81] The following paragraph details preoperative biologic therapy and the risk of postoperative complications.

5.4 | Anti-TNF agents

The impact of preoperative medical therapy on postoperative surgical complications has been widely studied. Among these therapies, anti-TNF drugs are the most studied biologics with respect to the perioperative management of IBD. Because of the limited heterogeneous data from small retrospective studies, the effects of anti-TNF agents and the risk of perioperative infection in patients with CD remain controversial. No clear consensus has been met as to whether exposure to anti-TNF therapy is associated with an increased risk of postoperative complications.

As reported in the Table 1, several meta-analysis studies have addressed this topic. However, all were based on case–control or cohort studies. For overall complications, several studies[75,82–86] revealed no increase in risk, whereas others[87–91] concluded that anti-TNF is associated with a mildly increased risk of overall postoperative complications in patients with CD. All meta-analyses on patients with CD who received preoperative anti-TNF but two[74,84] have reported an increased risk of infection or sepsis complications.[75,82,83,85,87,89,90,92]

In other studies, the critical risk factors for serious infections are high disease activity and ineffective disease control, CS treatment,

TABLE 1 Meta-analysis studies of postoperative outcomes in patients with CD treated with anti-TNF agents

Authors	Type of complication	No. studies included	Study population	Experiment	Anti-TNF group complication rate (%)	Non-anti-TNF group complication rate (%)	OR (CI)
Kopylov et al[82]	Overall Infectious Noninfectious	6 6 4	1316 1159 834	Anti-TNF-α agents	142/336 (42) 78/287 (27) 39/200 (20)	284/980 (30) 165/872 (19) 60/634 (9)	1.72 (0.93–3.19) 1.50 (1.08–2.08) 1.26 (0.65–2.42)
Billioud, et al[83]	Overall Infectious	6 7	1316 1699	Anti-TNF-α agents	85/336 (25) 99/484 (21)	196/980 (20) 169/1215 (14)	1.31 (0.96–1.77) 1.45 (1.03–2.05)
Narula et al[87]	Infectious Non-infectious Total	15 11 13	3244 2496 3840	Anti-TNF-α agents	214/987 (22) 227/813 (28) 464/1059 (44)	328/2257 (15) 316/1683 (9) 801/2781 (29)	1.56 (1.09–2.24) 1.57 (1.14–2.17) 1.73 (1.23–2.43)
Rosenfeld et al[86]	Major Minor Repeat operation	6 3 3	1129 564 710	Infliximab	99/257 (39) 25/148 (17) 18/173 (10)	223/872 (26) 17/416 (4) 29/537 (5)	1.59 (0.89–2.86) 1.80 (0.87–3.71) 1.33*0.55–3.30
El-Hussuna et al[88]	All anastomotic	13 11	2046 2340	Anti-TNF-α agents	238/419 (57) 45/593 (8)	589/1627 (36) 143/1747 (8)	1.25 (1.10–1.43) 0.91 (0.56–1.47)
Yang et al[89]	Total Infectious	13 10	2538 2116	Infliximab	235/663 (35) 168/626 (27)	479/1875 (26) 280/1490 (19)	1.45 (1.04–2.02) 1.47 (1.08–1.99)
Ali et al[75]	Total Infectious	7 12	1454 3057	Anti-TNF-α agents	235/431 (55) 152/823 (18)	192/1023 (19) 317/2234 (14)	1.16 (0.97–1.40) 1.29 (1.07–1.55)
Huang et al[74]	Septic	6	1833	Anti-TNF-α agents	Not reported	Not reported	1.29 (0.79–2.11)
Waterland et al[92]	Total infectious Abdominal sepsis	8 9	1782 3988	Infliximab	165/548 (30) 60/697 (9)	252/1234 (20) 148/3291 (4)	1.52 (1.14–2.03) 1.22 (0.87–1.72)
Lin et al[90]	Total Infectious	20 15	7159 7063	Anti-TNF agents	476/1673 (28) 272/1625 (17)	1086/5486 (20) 461/5438 (8)	1.53 (1.11–2.09) 2.09 (1.19–3.65)
Xu et al[84]	Overall Infectious	16 14	5498 5179	infliximab	619/1309 (47) 301/1244 (24)	1064/4189 (25) 485/3935 (12)	1.17 (0.82–1.66) 1.23 (0.87–1.74)
Law et al[91]	Total	27	Not reported	Anti-TNF Agents	Not reported	Not reported	1.43 (1.09–1.87]
Hanzel et al[85]	Total Infectious	6 6	1224 1721	Anti-TNF Agents	179/447 (40) 112/694 (16)	207/777 (27) 93/1027 (9)	1.03 (0.71–1.51) 2.05 (1.40–3.01)

and concomitant immunomodulation. In the REMIND study group,[93] a total of 209 patients with CD who underwent ileocecal resection were analyzed. CS treatment 4 weeks before surgery was significantly associated with an elevated postoperative complication rate (OR 2.69; 95% CI: 1.15–6.29; $P = 0.022$). Neither preoperative exposure to anti-TNF agents (n = 93, 44%) nor trough serum anti-TNF levels were significant risk factors for postoperative complications. Yamamoto et al[94] published a case–control study that revealed that malnutrition increases the risk of infection complications after surgery. The detrimental effects of malnutrition on postoperative infection may be enhanced in patients who have received biologic therapy preoperatively.

In 2018, the ECCO-ESCP consensus on surgery for CD indicated that anti-TNF therapy is associated with a high risk of postoperative sepsis complications after abdominal surgery for CD. The safest period for omission of anti-TNF therapy is unknown.[5] In 2020, the ECCO revised this statement, concluding that the current evidence does not support such an association and that cessation of therapy is not mandatory.[4]

5.5 | VDZ

Vedolizumab, a biologic agent that selectively inhibits the migration of leukocytes into the intestinal tract, is an effective medical therapy for IBD.[95] In the clinical trial,[96] complications related to colectomy and bowel surgery and resection were infrequent, with minimal differences observed between VDZ and placebos. Furthermore, the frequency of postoperative complications in a postmarketing setting is low.[97]

Lightner et al[98] performed a retrospective multicenter cohort study to compare preoperative VDZ to anti-TNF therapy in relation to the incidence of postoperative complications. A total of 146 patients received VDZ, and 289 patients received anti-TNF prior to abdominal surgery. In the multivariate analysis, exposure to VDZ was an independent significant predictor of postoperative surgical site infection (OR: 5.78, 95% CI: 2.99–11.76, $P < 0.01$). Another retrospective cohort study by Yamada et al[99] revealed that an age of over 65 years (OR 3.56, 95% CI: 1.30–9.76) and low albumin levels (OR 2.26, 95% CI: 1.28–4) were associated with an increased risk of 30-day postoperative complications, whereas VDZ treatment was not (OR 0.56, 95% CI: 0.28–1.07, $P = 0.08$)

A meta-analysis by Guo et al[100] indicated that, compared with a control group, the incidence of infection complications was reduced after preoperative treatment with VDZ (OR = 0.40, $P = 0.04$). However, VDZ increased the risk of ileus (OR = 2.43, $P = 0.01$), all surgical site infections (SSIs) (OR = 2.97, $P < 0.001$), readmission (OR = 2.74, $P < 0.001$), and return to the operating room (OR = 2.11, $P = 0.04$). However, two other meta-analysis studies have reported no significant difference between VDZ treatment groups and control groups.[91,101] The aforementioned results are summarized in Table 2. In general, VDZ is safe in a surgical setting, although larger randomized studies with perioperative drug monitoring are necessary to draw a solid conclusion.[4]

TABLE 2 Meta-analysis studies of postoperative outcomes in patients with CD treated with vedolizumab (VDZ)

Authors	Type of complication	No. studies included	Study population	Control	Vedo group complication rate (%)	Control group complication rate (%)	OR (CI)
Guo et al[100]	Any complication	2	143	Non-vedolizumab	Not reported	Not reported	2.09 (0.36–12.02)
	Infectious	2	360				0.40 (0.14–0.94)
	All SSI	2	569				2.97 (1.75–5.02)
Guo et al[100]	All SSI	2	343	Anti-TNF-α agents	Not reported	Not reported	3.69 (1.69–8.08)
	ileus	3	343				2.46 (1.16–5.22)
Guo et al[100]	All SSI	2	366	Non-biological agents	Not reported	Not reported	2.47 (1.21–5.04)
	Ileus	2	366				2.40 (1.14–5.07)
Yung et al[101]	All complication	2	343	Anti-TNF-α agents	40/140 (29)	41/203 (20)	1.45 (0.31–6.86)
	Infectious	2	343		33/140 (24)	24/203 (12)	1.00 (0.07–13.86)
	SSIs	2	343		27/140 (19)	18/203 (9)	1.16 (0.08–17.38)
	Major	2	343		13/140 (9)	12/203 (6)	1.16 (0.10–13.90)
Yung et al[101]	All complications	2	366	Non-biological agents	40/140 (29)	55/226 (24)	1.24 (0.21–7.52)
	Infectious	2	366		33/140 (24)	30/226 (13)	0.84 (0.04–15.88)
	SSIs	2	366		27/140 (19)	25/226 (11)	0.91 (0.07–11.58)
	Major	2	366		13/140 (9)	19/226 (8)	0.84 (0.18–3.91)
Law et al[91]	Infectious	4	Not reported	Not reported	Not reported	Not reported	1.32 (0.51–3.42)

5.6 | UST

Ustekinumab, a monoclonal antibody against interleukin-12/23 p40, was approved by the Food and Drug Administration (FDA) in September 2016. Thus, a relatively small number of patients have been exposed to UST compared with anti-TNF therapy, which has been approved since 1998.[95]

A multicenter cohort study of UST-treated patients with CD who underwent abdominal surgery between 2009 and 2016 was performed.[102] Compared with anti-TNF-treated patients, no significant difference in postoperative wound infection or anastomotic leaking was observed. The study concluded that patients with CD treated with preoperative UST did not experience an increase in postoperative complications. A similar result was obtained in another retrospective study.[103] However, a retrospective study based on a single-center series produced contradictory results.[104] Compared with 277 patients with CD who were not treated with biologic therapy in the 12 weeks prior to major abdominal surgery, the 57 patients with CD who received UST had a significantly higher risk of intraabdominal sepsis on multivariable logistic regression.

A systematic review and meta-analysis by Garg et al[105] analyzed the risk of postoperative complications in patients with CD exposed to UST preoperatively. No difference in the rates of intraabdominal sepsis was noted between the UST and the anti-TNF groups (7.2%, 95% CI: 3–16.4 vs 11.9%, 95% CI: 5.9–22.5; $P = 0.4$). A further analysis of three studies directly comparing UST and anti-TNF treatment revealed that the OR of intraabdominal sepsis was 0.41 (95% CI: 0.12–1.23, $P = 0.11$; Table 3). The researchers concluded that the postoperative complication rate in patients with preoperative UST exposure may be similar to that for patients treated with anti-TNF medication. However, studies with a more robust design and larger sample sizes are required to verify these results.

The evidence regarding immunomodulation and biologic therapy, such as anti-TNF and anti-integrin medications and anti-interleukin-12/23, remains weak.[91] An inherent indication bias in the studies revealed a relationship between biologics and postoperative complications. These postoperative complications may be related to the severity of the IBD that served as an indicator for biologic therapy rather than the biologic itself.[106] Thus, whether these medications affect postoperative infectious complications is uncertain, and no firm conclusions can be drawn regarding their safety in the perioperative period.

Each patient's individual case must be taken into consideration when decisions are made about preoperative IBD medications. Complications after surgery can usually be minimized with optimal preparation. CSs and, possibly, anti-TNF agents may increase the risk of infection and septic shock. Therefore, a preoperative drug-free interval, when feasible, could be implemented to reduce this risk.

6 | ADVANCES IN OPERATIVE PROCEDURES

6.1 | Anastomotic techniques

To reduce reoperation rates, various surgical techniques were analyzed. Radical resection of the mesentery can reduce surgical recurrence, as verified through a cohort study.[107] Another frequently discussed surgical technique is anastomosis. The safety and efficacy of types of anastomoses, such as hand-sewn, stapled, end-to-end, end-to-side, or side-to-side anastomoses, were evaluated. However, researchers have failed to determine the optimal anastomotic method for recurrence prevention.[108–110]

In 2003, Kono proposed a novel anastomotic technique, named Kono-S anastomosis,[111] for reducing the recurrence of CD after surgery. The key steps are as follows: First, the bowels are transected using a linear staple cutter such that the mesentery is in the middle of the staple line at a 90° angle. Second, the staple lines are sutured together transversely to create a supporting column for the eventual dimension of the anastomosis. Then, 7-cm long longitudinal enterotomies are created at the antimesenteric aspect, beginning 1 cm from the supporting column; the anastomoses of the bowels are then constructed transversely in a hand-sewn fashion.[111] Several cohort studies and one randomized controlled trial have supported the use of this technique for reducing the postoperative recurrence rate.[112–114]

6.2 | Laparoscopic surgery in CD

Initially, laparoscopic surgery was not used for CD because of the intraoperative characteristics, such as extensive inflammation, enteric fistulae, thickened mesentery, and skipped lesions throughout the bowels. However, the use of laparoscopy in most gastrointestinal procedures has become standard and increasingly accepted for treating patients with CD.[115,116]

For primary uncomplicated ileocolic resection, the benefits of laparoscopic surgery including a quicker return of bowel function, shorter length of hospital stay, fewer short-term postoperative complications, lower incidence of incisional hernia and postoperative

TABLE 3 Meta-analysis studies of postoperative outcomes in patients with CD treated with ustekinumab (UST)

Authors	Type of complication	No. studies included	Study population	Control	UST group complication rate (%)	Control group complication rate (%)	OR (CI)
Garg et al[105]	Intra-abdominal sepsis	3	583	Anti-TNF agent	4/102	47/481	0.41 (0.14–1.23)

small bowel obstruction, and improved cosmesis have been well-documented.[117-119] Even in recurrent complicated cases, several studies have reported that laparoscopic ileocolic resection can be performed in carefully selected patients and has comparable outcomes to primary laparoscopic resection.[120-122] For small bowel resection, a retrospective review revealed that laparoscopic surgery is associated with an equivalent or improved morbidity over open surgery in select patients with small bowel CD.[123]

In summary, retrospective studies and randomized studies have indicated that laparoscopic approaches for patients with CD are both safe and feasible. The choice of laparoscopic or open approaches depends on patient factors, surgeon preference, and equipment availability.

6.3 | Role of the mesentery

Studies of mesenteric anatomy have demonstrated that the mesentery is continuous.[124] Increasing evidence indicates that inflammation in mesenteric adipose tissue, adipocyte hyperplasia, and fibroblast differentiation collectively produces an "outside-in" phenomenon that contributes to bowel inflammation and fibrosis.[125] Based on these related studies, mesenteric resection may also interrupt local recruitment of fibroblast precursors (i.e., fibrocytes[126]), which can differentiate into either adipocytes or fibroblasts.[127]

As mentioned, before surgery, assessing mesenteric and intestinal disease activity for CD through imaging studies is crucial. However, accurately identifying the edge of the lesion during surgery remains a challenge. Studies have reported that the severity of mesenteric inflammation is closely related to the subsequent recurrence probability and can be used as a predicator of disease prognosis.[128-131] The mesenteric thickness tightly and topographically correlates with the area of intestinal inflammation.[132-134] Advanced mesenteric diseases (i.e., fat wrapping) could be regarded as a basis for assessing the need to remove intestinal segments and fat wrapping greater than 50%, which are associated with increased surgical recurrence.[135]

To determine whether the bowel segment has been affected by the disease, the "pinch test" (Figure 4) can be applied whereby two fingertips pinch both sides of the mesentery to detect potential mesenteric thickening. The microscopically positive proximal mucosal margins of postoperative specimens could therefore also be used as a reference. However, more research is required to verify the association between inflammation at the edges of the specimen and subsequent recurrence.[136,137] Therefore, further prospective randomized studies are necessary to clearly determine the role of resection margins in regards to disease recurrence in patients with CD following ileocecal resection.

All these findings support the mesentery's involvement in the pathogenesis of CD and offer a target for future management.[124,133,138] That is, mesentery-based strategies could lead to more favorable outcomes after surgery for CD. However, inclusion of the mesentery during surgery may be associated with reduced surgical recurrence rates in CD, but extended resections are currently not recommended because of the heterogeneous evidence. To answer the question of whether mesocolic excision during primary ileocolonic resection reduces postoperative disease recurrence, an international multicenter randomized trial is currently in progress.[139]

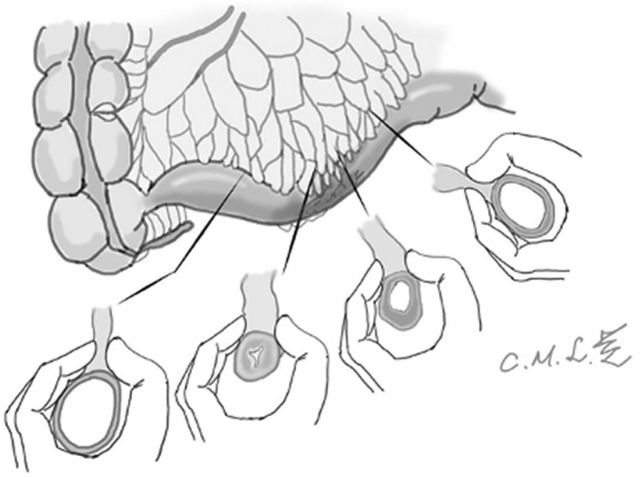

FIGURE 4 Mesenteric thickening can be detected using the "pinch test," which can distinguish the contours of a diseased bowel from a healthy bowel. A healthy bowel has a soft, pliable mesentery, whereas a diseased bowel exhibits obvious fat wrapping and swelling, congestion, and a firm mesentery

6.4 | Short segment of ileocolonic CD

In one-third of patients with CD, gross pathologic changes are limited to the terminal part of the ileum.[140] Approximately 40% of patients have ileocolitis, which is inflammation of the distal ileum and proximal colon.[141] An affected bowel of less than 30 cm in length can be defined as localized or a short segment of ileocolonic CD.[142]

Early surgical intervention in localized CD has been recommended by the British National Institute for Health and Care Excellence,[143] German clinical practice guideline,[144] and updated ECCO guidelines,[4] with institutions recognizing its advantages in terms of reducing disease recurrence and reoperation rates. Significant improvement in quality of life after surgical resection in the treatment of localized diseases has also been noted in multiple trials.[145,146]

Surgeons must consider postoperative recurrence prior to initiating surgery for CD. Many surgical methods, such as Kono-S anastomosis or extensive resection of the mesentery, were discussed and regarded as effective in reducing the rate of recurrence. However, patients with a short segment of ileocolonic CD may have different considerations because of their limited disease entity.

In such situations, a stapled ileocolic end-to-side anastomosis is the preferred technique and has been used extensively at Cleveland

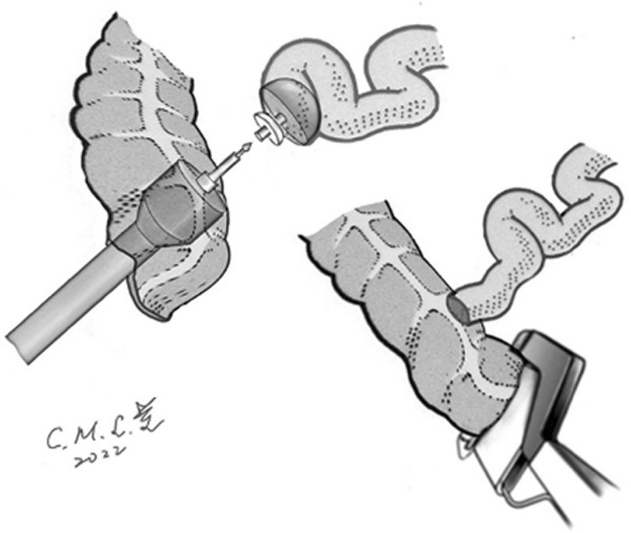

FIGURE 5 Stapled ileocolic end-to-side anastomosis with a circular stapler. The retained stump could be closed using a thoraco-abdominal or gastrointestinal anastomosis linear stapler at approximately 5 cm distal to an ileocolic anastomosis

Clinic in the United States.[147] This technique retains the original physiological angle of 90°, is easier to perform (Figure 5) than stapled side-to-side anastomosis, and facilitates endoscopic manipulation during postoperative follow-up. In addition, more intestinal length may be retained, and the possibility of multiple firing with staple line crossings is reduced.

Although Kono-S anastomosis and extended mesenteric excisions have produced some favorable results,[113,148,149] these surgical procedures are more technically demanding. Taking into account a surgeon's experience and the technical challenges associated with CD-related complications,[150] for ileocolonic CD, performing high-risk procedures may be unnecessary.

6.5 | ERAS

Enhanced recovery after surgery is an integrated surgical patient care process that allows patients to be assessed in relation to various processes such as outpatient diagnosis, hospitalization waiting periods, preoperative preparation, surgery, postoperative recovery, and discharge tracking. The treatment methods validated through related evidence greatly improve the safety of the surgical anesthesia process and the quality of patients' postoperative recovery, reduce the occurrence of postoperative complications, and significantly enhance the quality of medical care before, during, and after surgery.

The greatest advantage of ERAS is that large investments in hardware are unnecessary; existing professional resources can be used effectively instead. ERAS can be implemented without affecting the operation of existing medical services. ERAS was first used to assist patients who had undergone colorectal cancer surgery. Evidence for its use following surgery for IBD is scarce, with the exception of ileocecal resection in patients with CD, which has been described in several studies.[151,152]

In addition to the high prevalence of malnutrition, anemia, and sepsis, special consideration should be made for ERAS for patients with IBD, such as in the form of stoma team evaluation before and after surgery and before discharge and review of medications including CSs and biologics.[153]

Tailored precision medicine or the establishment of a complete medical model with integrated application continues to be continually developed and refined with increasing evidence.

6.6 | Venous thromboembolism prophylaxis

Inflammatory bowel disease is associated with an increased risk of venous thromboembolic events (VTEs), including deep vein thrombosis and pulmonary embolism, which may lead to significantly high risks of complications and mortality.

The incidence of VTEs in Western countries ranges from 0.73 to 1.82 per 1000 people.[154] Patients with IBD have a 1.5-fold to 4-fold higher risk of VTEs compared with the general population. The overall incidence of VTEs in patients with IBD was reported to be 2.4 to 2.6 cases per 1000 patients per year.[155] The overall incidence of VTEs in Asian populations is lower, ranging from 0.21 to 0.57 per 1000 people.[156] Regarding East Asian patients with IBD, a multinational collaborative study of 2562 hospitalized patients with IBD from South Korea, Japan, and Taiwan indicated that the average incidence of VTEs was 0.72 to 1.38 per 1000 people per year.[157] Moderate-to-severe colitis, IBD flare-ups requiring hospitalization, CS treatment, previous history or family history of VTEs, and previous major abdominal or pelvic surgery are known risk factors for VTEs in patients with IBD.[158]

Current Western guidelines for VTE prophylaxis recommend optimization for all patients with IBD requiring abdominal surgery unless contraindicated. A combination of mechanical and pharmacological prophylaxis should also be considered.[5] The cumulative incidence of VTEs increased from 1.3% at 7 days to 4.3% at 90 days after surgery in patients with IBD. Therefore, extended VTE prophylaxis with 28 days of low molecular weight heparin treatment has been adopted.[159]

Routine thromboprophylaxis before the surgery is infrequently used for Asian patients with IBD because of the relatively low incidence of VTEs; however, no consensus has been reached in this regard. However, a risk-adapted, individualized strategy of VTE prevention is crucial. In patients aged less than 60 years and without other risk factors for VTE, the benefits of routine prophylaxis may not outweigh the risks.[160] VTE prophylaxis is recommended for older patients (aged >60 years) or patients with other associated risk factors. Furthermore, to reduce the risk of VTEs, ambulation should be maintained before and as early as possible after operation, and inflammation must be controlled.

7 | POSTOPERATIVE COMPLICATIONS IN PATIENTS WITH CD

The mortality rate of CD-related surgery is generally low (<1%).[93] The complication rate is approximately 20%, with many complications occurring in the early postoperative period and of a severe nature (Clavien–Dindo classification of >III). The incidence of intraabdominal sepsis complications, including anastomotic leakage and abdominal abscesses, ranges from 9% to 13%.[63,161] Extra-abdominal infection includes pneumonia, bacteremia, urinary infection, and wound infection. Other nonsepsis complications include hemorrhage and VTEs. Patients with colonic disease are more likely to develop postoperative complications than patients with ileal or ileocolonic disease. To improve postoperative outcomes and reduce postoperative complications, determining a patient's individual risk prior to surgery is essential.[162,163] Limiting steroid dosage and duration, adjusting biologic administration, and optimizing preoperative nutrition optimization are also crucial. Urgent surgeries must be avoided when possible, because patients with CD have a higher risk of overall postoperative complications and intraabdominal sepsis following urgent surgeries than following elective surgeries.[164]

8 | POSTOPERATIVE RECURRENCE IN PATIENTS WITH CD

Postoperative recurrences are not uncommon in patients with CD. Rutgeerts et al[165] reported that after 1 year, 73% of patients exhibited recurrence in the neoterminal ileum endoscopically, although only 20% were symptomatic. After 3 years, the endoscopic detection rate had increased to 85%, and the symptomatic rate had increased to 34%.[165] The overall rate of secondary surgery was 28.7%.[166]

The strongest predictor of postoperative recurrence is smoking, with smokers having a 2.5-fold increased risk of surgical recurrence and a 2-fold increased risk of clinical recurrence compared with nonsmokers.[167] Other risk factors related to a higher rate of postoperative recurrence include prior surgical resection, penetrating or perforating disorders, a young age, colonic lesions, and the presence of perianal disease at surgery.[168]

Steroids and probiotics do not assist in the prevention of postoperative recurrence,[169] but azathioprine can delay endoscopic postoperative recurrence.[169,170] Biologics presented the most promising data in terms of reducing postoperative recurrence, but this potential must be verified through large randomized control trials.[171–175]

9 | CONCLUSION

Patients with CD often undergo surgery as part of their treatment, especially those who experience complications. Nutritional optimization and ERAS implementation are crucial for patients with CD who require surgical intervention to reduce postoperative complications. No solid evidence has indicated that perioperative medications have an effect on postoperative complications. Decisions about preoperative medication must be made on an individual case-dependent basis. Preoperative drug-free intervals may reduce the risk of infection, and preoperative imaging studies can assist in the planning of appropriate surgical strategies and approaches. However, patients must be informed of any alterations to their treatment. In sum, the management of perioperative medications and surgery-related decision-making should be individualized and patient-centered.

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