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Perioperative Management of Ulcerative Colitis: A Systematic Review

Kate E. Lee, M.D., M.S.[1] • Adam S. Faye, M.D., M.S.[2]
Séverine Vermeire, M.D., Ph.D.[3] • Bo Shen, M.D.[4]

1 Department of Medicine, Duke University Medical Center, Durham, North Carolina
2 Division of Gastroenterology, NYU Grossman School of Medicine, New York, New York
3 Division of Gastroenterology and Hepatology, University Hospital Leuven, Leuven, Belgium
4 Center for Inflammatory Bowel Diseases, Digestive Disease and Surgery Institute, Department of Surgery, New York-Presbyterian/Columbia University Irving Medical Center, New York, New York

BACKGROUND: Patients with ulcerative colitis may require colectomy for severe disease unresponsive or refractory to pharmacological therapy. Managing ulcerative colitis is complicated because there are many factors at play, including patient optimization and treatment, as the guidance varies on the ideal perioperative use of corticosteroids, immunomodulators, biologics, and small molecule agents.

OBJECTIVE: A systematic literature review was performed to describe the current status of perioperative management of ulcerative colitis.

DATA SOURCES: PubMed and Cochrane databases were used.

STUDY SELECTION: Studies published between January 2000 and January 2022, in any language, were included. Articles regarding pediatric or endoscopic management were excluded.

INTERVENTIONS: Perioperative management of ulcerative colitis was included.

MAIN OUTCOME MEASURES: Successful management, including reducing surgical complication rates, was measured.

RESULTS: A total of 121 studies were included in this review, including 23 meta-analyses or systematic reviews, 25 reviews, and 51 cohort studies.

LIMITATIONS: Qualitative review including all study types. The varied nature of study types precludes quantitative comparison.

CONCLUSION: Indications for colectomy in ulcerative colitis include severe disease unresponsive to medical treatment and colitis-associated neoplasia. Urgent colectomy has a higher mortality rate than elective colectomy. Corticosteroids are associated with postsurgical infectious complications and should be stopped or weaned before surgery. Biologics are not associated with adverse postoperative effects and do not necessarily need to be stopped preoperatively. Additionally, the clinician must assess individuals' comorbidities, nutrition status, and risk of venous thromboembolism. Nutritional imbalance should be corrected, ideally at the preoperative period. Postoperatively, corticosteroids can be tapered on the basis of the length of preoperative corticosteroid use.

KEY WORDS: Endoscopy; Inflammatory bowel disease; Perioperative; Postoperative; Preoperative; Resection; Surgery; Ulcerative colitis.

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Correspondence: Bo Shen, M.D., Center of Inflammatory Bowel Diseases, Department of Surgery, Digestive Disease and Surgery Institute, Columbia University Irving Medical Center, Herbert Irving Pavilion, Suite 843, 161 Fort Washington Ave, New York, NY 10032. E-mail: bs3270@columbia.edu

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Patients with ulcerative colitis (UC) often present with diarrhea, abdominal pain, urgency, tenesmus, and blood/mucus in their stool. Severe UC as defined by the Montreal classification involves the passage of at least 6 bloody stools daily, heart rate of ≥90 beats per minute, temperature of ≥37.5°C, hemoglobin of <10.5 g/100 dL, and erythrocyte sedimentation rate (ESR) of ≥30 mm/h.[1] The advent of biologics and small molecule agents has enhanced the armamentarium of therapy for UC. However, when patients have severe UC that does not respond to intravenous corticosteroids or is refractory to current biologic or small molecule therapy, they may require colectomy. Restorative proctocolectomy (RPC) with IPAA is the preferred surgical treatment modality for patients with UC who require colectomy for medically refractory disease or colitis-associated neoplasia. The underlying inflammatory disorders, nutrition status, and perioperative use of immunosuppressive medications, as well as the complexity of the bowel-altering, reconstructive nature of RPC and IPAA, all make patients at risk for the development of postoperative infectious complications, such as anastomotic leaks and surgical site infections. For example, in a multicenter study of 640 patients undergoing proctocolectomy and IPAA, 96 patients (15.0%) developed anastomotic leaks.[2] In a large cohort study of 3707 patients with proctocolectomy and IPAA, including 2953 patients with UC, 63 with indeterminate colitis, 150 with Crohn's disease (CD), and 97 with colorectal neoplasia, 33.5% of patients developed perioperative complications with bleeding and anastomotic leaks and other complications.[3] Just as the surgeon tailors operations to disease severity, the gastroenterologist tailors medical management to changes in disease severity before and after surgery. Because of the complex nature of managing UC and increased pharmacological options, it is important to delineate how to manage UC before, at, and after colectomy. In this review, we outline the current discussion on the perioperative management of UC.

METHODS

We performed a literature search for articles using PubMed and Cochrane databases. Search criteria included "perioperative," "management," "ulcerative colitis," "preoperative," and "postoperative" in titles and abstracts published in English from January 2010 to June 2022. Searches with Boolean operators were used to find more relevant articles (eg, "ulcerative colitis" AND "preoperative"). Duplicates were removed. Initially, we included all articles with titles and abstracts that were relevant to aspects of the perioperative management of UC. These articles were read in full to screen for relevancy. References of relevant articles were scanned to identify additional articles of interest to our review in a snowball search. All article types were included: systematic reviews, reviews, and original articles. Exclusion criteria included abstracts and articles regarding pediatric or endoscopic management.

RESULTS

Search results identified 49 articles and a snowball search identified an additional 72 articles. In total, 121 articles were included in this review (Fig. 1). These articles included 18 meta-analyses, 5 systematic reviews, 25 reviews, 51 cohort studies, 5 randomized trials, and 10 guidelines. Given that the articles extracted were highly heterogeneous, no meta-analysis was performed.

PREOPERATIVE PERIOD

Patients with UC often present with diarrhea, abdominal pain, urgency, tenesmus, and blood/mucus in their stool. Acute severe UC (ASUC) involves the passage of at least 6 bloody stools daily, heart rate of ≥90 beats per minute, temperature of ≥37.5°C, hemoglobin of <10.5 g/100 mL, and ESR of ≥30 mm/h.[1]

Endoscopically, erythema, increased mucosal granularity, friability, pseudopolyps, erosions, and ulcers may be present.[4] Signs of severe UC on endoscopy can include obliteration of vascular patterns, spontaneous bleeding with frank blood in the lumen or visible oozing from the mucosa, and deeper excavated ulcers.[5,6] Severe UC often affects a particular distribution in the colon: proctitis, left-sided colitis, or pancolitis.

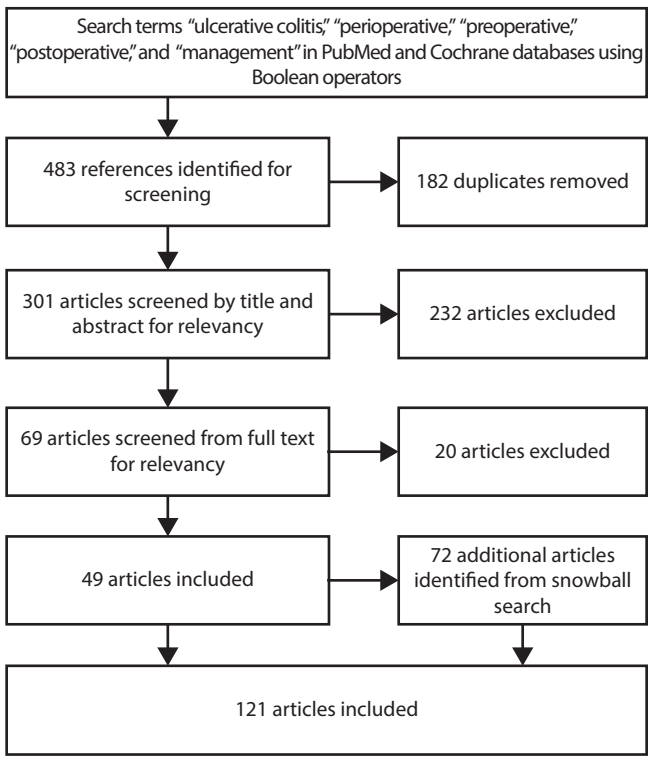

FIGURE 1. PRISMA flow diagram. PRISMA = preferred reporting items for systematic review and meta-analysis.

On histology, the strongest predictor of treatment failure is severe eosinophilic infiltration.[4,7] Histologic findings also include abnormalities of the crypt, abscesses, branching, shortening, disarray, and atrophy, as well as mucin depletion, Paneth cell metaplasia, increased cellularity or eosinophils in the lamina propria, as well as basal plasmocytosis or lymphoid aggregates.[4] In severe UC with deep ulcers, transmural inflammation may be present that can make the distinction between UC and CD difficult. The phenotype is termed indeterminate colitis.

The severity of UC can also be monitored by laboratory abnormalities. Patients with severe UC have elevated inflammatory markers, including ESR, C-reactive protein, and fecal calprotectin and lactoferrin.[4,7] Fecal calprotectin in particular can help assess the degree of inflammation and detect disease relapse.[8] Low serum albumin in patients with UC can demarcate poor nutritional status and more severe disease and is a predictor of colectomy.[9] Additionally, an anemia workup, including iron studies and vitamin B_{12} levels, can help assess nutritional status.[4] Patients with severe disease should be assessed for stool *Clostridium difficile* infection and CMV infection on blood polymerase chain reaction as well as histology when appropriate; increased CMV-stained histiocytes on histology is associated with severe inflammation and higher risk of requiring colectomy, and immunohistochemistry results were correlated with blood polymerase chain reaction results.[10]

When disease persists, patients may eventually require colectomy. This includes patients who present to the hospital with ASUC and do not respond to intravenous corticosteroids, infliximab, or Janus kinase inhibitor (Fig. 2A–C). Approximately 30% of patients fail corticosteroid therapy and require colectomy.[11,12] Additionally, there is a subset of patients who are refractory to current biological and small molecule therapy, necessitating dependence on corticosteroids.[4,11] Both groups eventually require colectomy. The number and severity of complications in colorectal surgery are closely related to preoperative functional capacity, nutritional state, psychological state, and smoking status.

Elective Versus Urgent Colectomy

Up to 25% of patients with UC require surgery in their lifetime for medically refractory disease or colitis-associated neoplasia, and those who undergo urgent colectomy have a significantly higher mortality rate than those who undergo elective surgery (13.2% versus 3.7%; $p < 0.001$).[4,11,13] Emergent surgery is associated with older age, open surgery, greater comorbidities, increased risk of postoperative complications, and longer hospital stays.[14] However, some clinicians argue that the threshold for emergent colectomy in UC is currently too high and that more patients should undergo surgery sooner rather than later.[4,11]

The current indications for elective surgery include failed medical management as outpatients and colitis-associated neoplasia that cannot be endoscopically removed.[15,16] Patients with UC have a higher rate of colorectal cancer than the general population.[17] Meanwhile, indications for emergent colectomy include perforation, uncontrolled bleeding, toxic megacolon, and fulminant disease uncontrolled by medical therapy.[4]

Preoperative Use of Corticosteroids

Corticosteroids have been the mainstay of acute therapy in UC when patients present with moderate to severe disease flares.[18,19] Intravenous corticosteroids are the standard initial therapy for ASUC.[11] According to the European Crohn's and Colitis Organisation (ECCO) guidelines, after 5 to 7 days without significant improvement, surgical intervention is highly recommended to avoid the perioperative complications associated with emergent procedures.[11,13,20,21] Thus, patients with severe UC often require corticosteroid therapy; however, the requirement of systemic corticosteroids is associated with an increased risk for colectomy. Severe disease at baseline is a predictor of colectomy.[22] Patients with UC on corticosteroids preoperatively are at higher risk of both postoperative infectious and noninfectious complications.[23] Other studies have corroborated that corticosteroids are an independent predictor of short-term infectious complications in patients with UC.[24,25] In a retrospective cohort study, patients receiving corticosteroids had higher odds of any complication (OR = 3.69; 95% CI, 1.24–10.97) and infectious complication

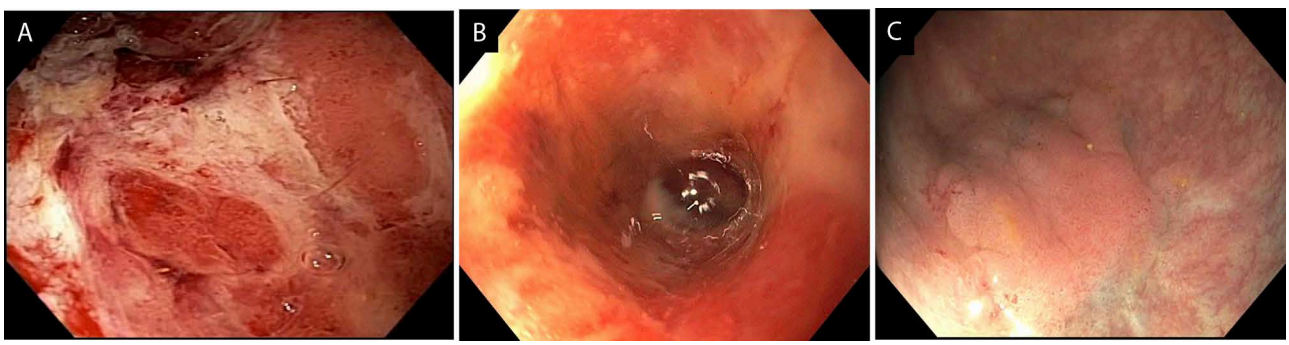

FIGURE 2. Indications for colectomy. A, Acute severe UC. B, UC with stiff colon. C, UC-associated neoplasia. Flat lesion with high-grade dysplasia. UC = ulcerative colitis.

(OR = 5.54; 95% CI, 1.12–27.26) than patients not receiving corticosteroids.[26] A systematic review and meta-analysis of 63 studies of medical therapies in IBD showed that the use of corticosteroids increases the risk of postoperative infectious complications (OR = 1.34; 95% CI, 1.25–1.44).[27] Infectious complications included wound infections and dehiscence, sepsis, pneumonia, peritonitis, abdominal abscess, urinary tract infections, and fever >101.5°F without an identifiable source.[26] Studies included in our review are outlined in Table 1.[24–57] Hence, the ECCO guidelines recommend weaning steroids before surgery, and if weaning is not possible, postponing elective surgery or pouch construction.[11]

Preoperative Immunomodulators

Immunomodulators, such as azathiopurine, 6-mercaptopurine, and methotrexate, have been used in maintenance as monotherapy or part of combination therapy with anti-tumor necrosis factor (TNF). The preoperative use of immunomodulators does not seem to increase the risk for postinfectious complications in IBD;[27] however, the role of immunomodulators in the management of ASUC and in patients with refractory UC undergoing colectomy is limited.

Preoperative Use of Biologics

Biologics, including TNF drugs (eg, infliximab and adalimumab), the anti-integrin (vedolizumab), and the interleukin-12/interleukin-23 inhibitor ustekinumab, have revolutionized disease control in UC. They are becoming first-line therapies for treating moderate to severe UC, and unlike corticosteroids, they are used to induce not only remission but also as maintenance therapies.[58–60] Per the active ulcerative colitis trials I and II (ACT I and ACT II), infliximab has a clinical remission rate of 33% to 39% by week 8 with a clinical remission rate of 20% by week 54.[61] The ULTRA 2 trial showed that adalimumab achieved a clinical remission rate of 17% by week 8 and 17% by week 52.[62] The GEMINI I trial showed that vedolizumab had a clinical remission rate of 17% at week 6 and 42% at week 52.[63] Finally, the UNIFI trial showed that ustekinumab had a clinical remission rate of 16% at week 8 and 38% to 44% at week 44.[64] It is important to note that these trials are difficult to compare given different study designs because some are responder rerandomization studies and others are treat-through designs. In a recent systematic review and meta-analysis, vedolizumab was found to have the lowest rate of adverse events compared to other biologic drugs.[58]

Multiple meta-analyses have tried to characterize the effect of preoperative biologics on postoperative outcomes, with conflicting results.[31–33,65–68] A systematic review and meta-analysis of 63 studies of medical therapies in IBD showed that the use of anti-TNF biologics increases the risk of postoperative infectious complications (OR = 1.26; 95% CI, 1.07–1.50).[27] The ECCO guidelines listed that patients on biologics might be at increased risk of developing early and late pouch-specific complications.[11] Recently, the PUCCINI trial was the first large prospective study examining preoperative anti-TNF therapy on surgical outcomes and showed that preoperative use of anti-TNF drugs in patients with IBD is not an independent risk factor for postoperative infections.[34] In this study, 947 patients were enrolled, of whom 382 were treated with anti-TNF drugs preoperatively.[34] The investigators found no significant difference in rates of infection (18.1% vs 20.2%; $p = 0.469$) or surgical site infections (12.0% vs 12.6%; $p = 0.889$) between patients exposed to TNF inhibitors and those unexposed.[34] Multivariable analysis also found no significant differences in rates of infections. The investigators also measured serum anti-TNF levels preoperatively and found that detectable drug levels were not associated with infection or surgical site infection.[34] Serum levels of anti-TNF agents and preoperative anti-TNF agent use were not found to be associated with colectomy morbidity or postoperative complication rates.[35,36] A retrospective case-control study matching patients with IBD with and without exposure to preoperative anti-TNF biologics found that preoperative anti-TNF inhibitors and the time interval from the last dose of anti-TNF inhibitor were not associated with most early postoperative complications.[37] Furthermore, a recent meta-analysis on postoperative infection with anti-TNF inhibitors found that the risk of postoperative infection was increased in patients with CD on anti-TNF agents but not for patients with UC on anti-TNF agents.[38]

The data on vedolizumab on postoperative morbidity were conflicting. A single-center, retrospective review compared vedolizumab-exposed patients with CD with patients on anti-TNF or biologic-naive patients and found vedolizumab to be an independent predictor of postoperative surgical site infection.[39,69] However, another single-center retrospective review found that perioperative vedolizumab did not influence short-term outcomes of surgery, including infectious complications.[40] A systematic review and meta-analysis showed that the use of vedolizumab did not increase the risk for postoperative infectious complications in IBD (OR = 1.06; 95% CI, 0.67–1.69).[27] A separate meta-analysis found that patients with UC taking preoperative vedolizumab were not found to have significantly different rates of postoperative complications compared to patients taking preoperative anti-TNF drugs or no biologics.[41] Another meta-analysis found that patients with UC taking vedolizumab actually had a lower overall postoperative complication rate than those taking anti-TNF but did not find

any differences with respect to infectious, surgical site, or major complications.[42]

As for ustekinumab, a multicenter study showed no difference in postoperative complications between those with preoperative ustekinumab use and those with preoperative anti-TNF use.[70] Additionally, no differences in postoperative surgical site infections or hospital readmissions were found between those with preoperative ustekinumab use and those with preoperative anti-TNF use.[71]

Hence, the use of biologic therapy does not have to delay colectomy in patients who are refractory to medical therapy and have ongoing disease. In addition, biologics need not be stopped or timed beforehand in non-IBD surgery (eg, knee replacement). Studies on biologics and steroids included in our review are outlined in Table 1.[24–57]

Preoperative Use of Small Molecule Agents

Small molecule agents such as tofacitinib and upadacitinib (Janus kinase inhibitors) and ozanimod (a sphingosine 1-phosphate receptor 1 and 5 modulators) are newer drugs for the treatment of IBD. Tofacinitib was approved for moderate to severe UC in 2018. A systematic overview of meta-analyses has shown tofacitinib to be more effective than placebo in achieving clinical remission and mucosal healing in the induction and maintenance phases.[72] Additionally, meta-analyses have shown tofacitinib to be superior to adalimumab when assessing clinical response and mucosal healing in both the induction and maintenance phase.[72–74] There are even data demonstrating that tofacitinib at a dose of 10 mg 3×/d in ASUC is effective in preventing colectomy at 90 days.[75] However, a retrospective review of 53 patients exposed to tofacitinib preoperatively found 90-day postoperative complications of ileus (13.2%), superficial surgical site infection (7.5%), intra-abdominal abscess (3.8%), and venous thromboembolism (VTE; 13.2%).[76] The high rate of VTE was most striking. Tofacitinib has a Food and Drug Administration black-box warning for VTE after an interim analysis of a clinical trial of tofacitinib for rheumatoid arthritis identified 19 pulmonary embolisms out of 3,884 patients compared to 3 of 2,982 in patients treated with anti-TNF inhibitors.[76] Preoperative tofacitinib exposure may present an increased risk of postoperative VTE events. Additionally, in 2 recent systematic reviews and meta-analyses, upadacitinib was found to be significantly superior to other biologics for induction of clinical remission; however, it also had the highest rate of adverse events.[58,59]

The impact of the use of newly Federal Drug Administration–approved agents, upadacitinib and ozanimod, on postoperative infectious complications is not clear.

Preoperative Use of Calcineurin Inhibitors

Recent studies have assessed the efficacy of using cyclosporine as induction therapy versus biologic agents such as vedolizumab and ustekinumab. A multicenter study of 10 patients with ASUC treated with a combination regimen of ustekinumab and a calcineurin inhibitor was associated with no colectomies at 6 months, significantly decreased median partial Mayo score and C-reactive protein levels, and good tolerance to treatment.[77] Several studies assessed the efficacy of calcineurin inhibitor induction therapy with vedolizumab maintenance therapy, finding similar colectomy-free survival rates of over two-thirds at 1 year.[78,79]

Data are limited on the impact of the use of calcineurin inhibitors on postoperative complications after colectomy. However, preliminary data suggest that calcineurin inhibitors do not increase the rate of postoperative complications.[80,81] A study in children showed no difference in postoperative complications in children with UC taking calcineurin inhibitors.[82,83]

Preoperative Anticoagulation

Patients with IBD have a 2- to 3-fold higher risk of developing a VTE than the general population.[84,85] IBD is an independent predictor of VTE.[86,87] Additionally, VTE is a well-known complication of surgery, including colorectal surgery.[88,89] A meta-analysis of 38 studies showed that patients with IBD undergoing colorectal surgery were at higher risk of postoperative VTE than patients without IBD undergoing colorectal surgery.[84,90] Several studies have shown that UC compared to CD presents a higher postoperative VTE risk.[90,91]

With regard to the timing of surgical events among patients with IBD, over 60% of postoperative VTEs occur within 2 weeks of hospital discharge.[92] Although data are limited on the impact of postdischarge VTE prophylaxis, there is evidence that 4 weeks of postdischarge VTE prophylaxis in patients with IBD would be effective and prevent 1 postdischarge VTE among 78 patients with IBD.[93] Thus, postdischarge VTE can be considered in those at particularly high risk (ie, limited mobility, concurrent cancer, pregnancy).

Preoperative Nutrition/Exercise

Malnutrition affects up to 70% of patients with IBD and up to 85% of patients with IBD awaiting surgery.[94,95] This is important because malnutrition is an independent risk factor for adverse postoperative outcomes.[94,95] A multicenter propensity score–matched analysis of 73,843 inpatients with various medical conditions showed that 21.9% of patients were at nutritional risk.[96] Patients at nutritional risk had higher odds of dying in the hospital (OR = 1.56; 95% CI, 1.37–1.76), dying within 30 days of admission (OR = 1.62; 95% CI, 1.45–1.81), and being readmitted within 4 months after discharge (OR = 1.12; 95% CI, 1.07–1.18).[96] Poor nutrition increases the risk of infectious

TABLE 1. Effects of preoperative of biologics or steroids on postoperative complications in ulcerative colitis from major publications

Author, journal, year	*Therapy*	*No. patients, N*	*Outcome*	*Postoperative complications*
Narula et al, *Aliment Pharmacol Ther*, 2013[32]	Anti-TNF-α agents	Systematic review and meta-analysis of 18 studies with 4659 patients with IBD	Infectious complications	Patients with UC did not have significant increases in infectious (OR = 1.39; 95% CI, 0.56–3.45), noninfectious (OR = 1.40; 95% CI, 0.68–2.85), or total complications (OR = 1.10; 95% CI, 0.81–1.47)
Billioud et al, *J Crohns Colitis*, 2013[31]	Anti-TNF-α agents	Meta-analysis of 21 studies with 4251 patients with IBD	Any or infectious postoperative complication	Prevalence of any postoperative complication was increased in patients who received preoperative anti-TNF (OR = 1.25; 95% CI, 1.02–1.53)
Yang et al, *Aliment Pharmacol Ther*, 2012[33]	IFX	Meta-analysis of 13 studies involving 2933 patients	Total complication rate, infectious and noninfectious complication rate	No significant association between preoperative IFX and total (OR = 1.09; 95% CI, 0.87–1.37; $p = 0.47$), infectious (OR = 1.10; 95% CI, 0.51–2.38; $p = 0.81$), and noninfectious (OR = 1.10; 95% CI, 0.76–1.59; $p = 0.61$) postoperative complications
Cohen et al, *Gastroenterology*, 2022[34]	Anti-TNF-α agents (PUCCINI Trial)	947 patients with IBD	Any infection, SSI or non-SSIs	No significant difference in rates of infection (18.1% vs 20.2%; $p = 0.469$) or SSIs (12.0% vs 12.6%; $p = 0.889$) between patients on anti-TNF and those not on anti-TNF agents. Multivariable analysis also found no significant difference. Detectable preoperative serum anti-TNF levels were not associated with infection or SSI
Kulaylat et al, *JAMA Surg*, 2017[35]	Anti-TNF-α agents	2476 patients with UC	90-d complications	Increased postoperative complications in patients who received anti-TNF agents preoperatively vs those who did not ($p = 0.02$)
Lau et al, *Ann Surg*, 2015[36]	Anti-TNF-α agents	217 patients, of whom 123 patients had CD and 94 patients had UC, looking at differences by serum level of TNF-α agents	30-d postoperative morbidity, infectious complications	Postoperative morbidity (OR = 2.5, $p = 0.03$) and infectious complications (OR = 3.0; $p = 0.03$) were significantly higher in the ≥3 μg/mL group
Waterman et al, *Gut*, 2013[37]	Anti-TNF-α agents	473 procedures consisting of 195 patients with exposure to biologics and 278 matched controls	Postoperative wound infection	Patients with detectable preoperative IFX levels had similar rates of wound infection compared with those with undetectable levels (3/10 vs 0/9; $p = 0.21$)
Zanelli et al, *Therap Adv Gastroenterol*, 2020[38]	Anti-TNF-α agents	Meta-analysis of 20 studies with 12494 patients with UC, of whom 2254 received preoperative biologic therapy	Overall and infectious complications	Pooled OR for infectious complications was 0.98 (95% CI, 0.66–1.45) and pooled OR for overall complications was 1.14 (95% CI, 1.04–1.28); no significant association between preoperative biologic therapy and postoperative complications
Uchino et al, *Int J Colorectal Dis*, 2013[43]	IFX	196 patients with UC	Postoperative infectious complications	IFX was not associated with infectious complications
Shwaartz et al, *J Gastrointest Surg*, 2016[44]	Anti-TNF-α agents	282 patients with IBD	30-d anastomotic leak, intra-abdominal abscess, wound infection, extra-abdominal infection, readmission, and mortality	Anti-TNF agents were not associated with increases in anastomotic leak, intra-abdominal abscess, wound infection, extra-abdominal infection, readmission, or mortality
Rizzo et al, *Int J Colorectal Dis*, 2011[45]	Anti-TNF-α agents	114 patients with IBD	Short-term postoperative cumulative and infectious complications	Preoperative anti-TNF agents did not increase the rate of postoperative complications
Regadas et al, *Colorectal Dis*, 2011[46]	IFX	249 patients with IBD	Comorbidity, diagnosis, intraoperative and postoperative morbidity, and length of stay	No significantly increased postoperative complications in patients with preoperative IFX compared with patients who did not receive IFX
Krane et al, *Dis Colon Rectum*, 2013[47]	IFX	518 patients with IBD	Short-term and long-term morbidity and mortality	IFX not associated with increased rates of postoperative complications, including conversion rate to laparotomy, morbidity, mortality, anastomotic leak, infection, and thrombotic complications

Gu et al, *Dis Colon Rectum*, 2013[48]	Anti-TNF-α agents	407 and 181 patients with UC or indeterminate colitis	Postoperative infectious complications	Multivariate analysis showed that preoperative anti-TNF (HR = 2.62; $p = 0.027$) was an independent risk factor for postoperative pelvic sepsis after total proctocolectomy
Gainsbury et al, *J Gastrointest Surg*, 2011[49]	IFX	81 patients with UC	Overall postoperative and infectious complications	Preoperative IFX was not associated with an increased risk of short-term postoperative complications
Coquet-Reinier et al, *Surg Endosc*, 2010[50]	IFX	13 patients	Mean operative time, complication rate, mean hospital stay	No significant difference between patients treated with IFX and those treated without IFX for any outcome, including mean operative time, complication rate, and mean hospital stay
Zittan et al, *Inflamm Bowel Dis*, 2016[51]	Anti-TNF-α agents	773 patients with UC and IPAA surgery, of whom 196 had preoperative anti-TNF therapy and 562 did not	Postoperative infectious and noninfectious complications	No significant differences in postoperative IPAA leaks between those exposed to anti-TNF agents and controls ($p = 0.44$). No significant differences in postoperative 2-stage IPAA leak rate in those operated on within 15 d from the last anti-TNF dose, within 15–30 d, or 31–180 d ($p = 0.43$). No differences based on the presence of detectable IFX serum levels
Ward et al, *Colorectal Dis*, 2018[52]	Anti-TNF-α agents	6225 patients with UC	Any postoperative complication	No association between preoperative anti-TNF agents and postoperative complications
Nørgård et al, *Aliment Pharmacol Ther*, 2012[53]	Anti-TNF-α agents	1226 patients with first surgery for UC	Postoperative reoperation, anastomosis leakage, intra-abdominal abscess, bacteremia, and death	No significant difference in reoperation, anastomosis leakage, intra-abdominal abscess, bacteremia, and death between patients with preoperative anti-TNF agents and those without
Eshuis et al, *J Crohns Colitis*, 2013[54]	IFX	72 patients, of whom 33 had 1-stage surgery (IPAA, with or without temporary diversion) and 39 had 2-stage surgery (emergency colectomy and completion proctectomy with pouch, with or without temporary diversion)	Postoperative complications, infliximab use, and time between last infliximab administration and restorative surgery	1-stage surgery: more patients with preoperative IFX had pelvic sepsis (risk difference 24%; 95% CI, 6–42; $p = 0.067$) and noninfectious complications (risk difference 30%; 95% CI, 4–56; $p = 0.065$). Two-stage surgery: similar rates of all, infectious and noninfectious complication rates, and pelvic sepsis rates between infliximab and noninfliximab groups
Bregnbak et al, *J Crohns Colitis*, 2012[55]	IFX	71 patients with UC	All postoperative and infectious complications	IFX is not associated with an increased risk of short-term postoperative complications
Yamada et al, *Am J Gastroenterol*, 2017[56]	Vedolizumab	443 patients, of whom 64 had vedolizumab, 129 had anti-TNF agents, and 250 had nonbiological therapy	30-d postoperative complications	Risks of postoperative complications similar among patients with preoperative vedolizumab, anti-TNF agents, or nonbiological therapy ($p = 0.40$ for UC)
Novello et al, *J Crohns Colitis*, 2020[57]	Vedolizumab	980 patients, of whom 141 received vedolizumab	Postoperative morbidity, infectious complications, surgical site infections	Multivariable analysis showed preoperative vedolizumab was associated with increased overall morbidity ($p < 0.001$) but not infections ($p = 0.30$). Case-matched comparison of patients treated with vedolizumab vs patients treated with anti-TNF agents did not show any difference in overall morbidity ($p = 0.32$), infectious complications ($p = 0.15$), or surgical site infections ($p = 0.12$)
Lightner et al, *J Crohns Colitis*, 2017[39]	Vedolizumab	94 patients received vedolizumab within 12 wk of an abdominal operation	All postoperative complications, infectious, surgical site infections	Patients on vedolizumab had significantly higher rates of any postoperative infection ($p < 0.001$) and SSI ($p < 0.001$). On multivariate analysis, preoperative vedolizumab significantly predicted postoperative SSI ($p < 0.001$)
Ferrante et al, *J Crohns Colitis*, 2017[40]	Vedolizumab	170 eligible patients, of whom 34 received preoperative vedolizumab	30-d postoperative complications	Preoperative vedolizumab did not significantly influence short-term complications, including pouch-related infectious complications, SSI, nonsurgical site infectious complications, all infectious complications, or noninfectious complications

(continued)

TABLE 1. Continued

Author, journal, year	*Therapy*	*No. patients, N*	*Outcome*	*Postoperative complications*
Law et al, *J Crohns Colitis*, 2018[41]	Vedolizumab	Systematic review and meta-analysis of 5 studies with total of 307 patients with IBD treated with vedolizumab	Postoperative overall and infectious complications	Patients with UC taking preoperative vedolizumab did not have significantly different rates of postoperative infectious complications or overall postoperative complications compared to patients receiving no preoperative biologic. Postoperative infectious complications and overall postoperative complications were not significantly different between the vedolizumab and anti-TNF groups
Yung et al, *Inflamm Bowel Dis*, 2018[42]	Vedolizumab	Systematic review and meta-analysis of 4 studies with 1080 patients total	Overall postoperative complications, infectious complications, SSI, need for repeat surgery, and major postoperative complications	Patients with UC on vedolizumab had lower overall postoperative complication rates than those taking anti-TNF (OR = 0.35; 95% CI, 0.14–0.85). No differences in infectious, SSI, or major complications
Ferrante et al, *Inflamm Bowel Dis*, 2009[24]	Corticosteroids	22 patients who received IFX before (procto)colectomy and 119 patients who did not	30-d short-term infectious complications	A moderate to high dose of corticosteroids (≥20 mg methylprednisolone for ≥2 mo, OR = 5.19, $p = 0.003$) was an independent predictor of postoperative infectious complications
Nguyen et al, *J Crohns Colitis*, 2014[25]	Corticosteroids	8260 patients with CD and 7235 patients with UC	Postoperative complications and 30-d mortality	Steroids were associated with higher risk of any postoperative complication in patients with UC (aOR = 1.44; 95% CI, 1.28–1.61) as well as infectious complications ($p < 0.0001$)
Aberra et al, *Gastroenterology*, 2003[26]	Corticosteroids	159 patients, of whom 56 received steroids alone, 52 received 6-MP/AZA alone or with steroids, and 51 received neither steroids nor 6-MP/AZA	Major and minor postoperative infectious complications	Patients on corticosteroids had higher rates of complications (OR = 3.69; 95% CI, 1.24–10.97) and infectious complications (OR = 5.54; 95% CI, 1.12–27.26) than patients not receiving corticosteroids
Uchino et al, *Int J Colorectal Dis*, 2019[28]	Corticosteroids	301 patients with UC	Surgical site infections	Total prednisolone dose ≥9000 mg (OR = 2.7) was an independent risk factor for incisional SSI
Liang et al, *JGH Open*, 2018[30]	Corticosteroids	3360 patients with IBD	Postoperative infection	Preoperative corticosteroids (OR = 1.52; 95% CI, 1.21–1.92) were associated with postoperative infection
Rahal et al, *Acta Gastroenterol Belg*, 2018[29]	Corticosteroids	5049 patients with IBD	Postoperative mortality, anastomotic leak, and reoperation	Preoperative steroids increased the rate of reoperation (OR = 1.66; 95% CI, 1.26–2.19) and anastomotic leak (OR = 1.81; 95% CI, 1.34–2.45). 30-d mortality was significantly lower among patients on steroids (OR = 0.41; 95% CI, 0.19–0.86)
Law et al, *Cochrane Database Syst Rev*, 2020[27]	All, including corticosteroids, anti-TNF, vedolizumab	Systematic review and meta-analysis of 63 studies of medical therapies in IBD	Postoperative infectious complications	Anti-TNF agents increase the risk of postoperative infectious complications (OR = 1.26; 95% CI, 1.07–1.50). Vedolizumab did not increase the risk for postoperative infectious complications. Preoperative corticosteroids increases risk of postoperative infectious complications (OR = 1.34; 95% CI, 1.25–1.44)

Tabulated summary of all studies discussed.

AZA = azathioprine; CD = Crohn's disease; CI = confidence interval; IFX = infliximab; 6-MP = 6-mercaptopurine; aOR = adjusted OR; OR = odds ratio; PUCCINI = Prospective Cohort of Ulcerative Colitis and Crohn's Disease Patients Undergoing Surgery to Identify Risk Factors for Post-Operative Infection I; RR = relative risk; SSI = surgical site infection; TNF = tumor necrosis factor; UC = ulcerative colitis.

complications after surgery in CD and UC. In a case-control study of 70 patients with UC (N = 34) or CD (N = 36) receiving biologic therapy within 8 weeks before undergoing bowel resection versus 70 patients with IBD without biologics, postoperative infectious complications were significantly more common in those with poor nutrition than those without, regardless of the use of biologics.[97]

It is important to assess the nutritional status using tools such as nutritional risk screening.[98] In addition, preoperative correction of nutrition in UC may impact surgical outcomes. A systematic review of studies on preoperative nutrition in patients with CD, albeit not in patients with UC, found that all studies suggested the need for nutritional support in preoperative management. Hence, it is recommended that patients with UC undergoing colectomy have perioperative dietary therapy to correct undernutrition.[99] Oral or enteral nutrition is preferred whenever possible; however, parenteral nutrition could be considered for patients with UC who have malnutrition but are unable to tolerate enteral nutrition.[94] The ECCO guideline on preoperative management of CD recommended that nutritional status should be optimized before surgery via enteral or parenteral routes. If surgery is required in a malnourished patient, a staged procedure is advised.[100] However, there was no evidence to support the routine use of enteral or parental nutrition in preoperative patients undergoing UC surgery. Nonetheless, the ECCO guideline recommended preoperative correction of altered body composition and nutrition imbalances, and iron supplementation for iron deficiency anemia in UC is recommended.[11]

Preoperative Sarcopenia/Frailty

The prevalence of frailty in patients with IBD has increased each year between 2010 and 2014, from 10.20% to 11.45%.[101] A nationwide study showed that frailty in patients with IBD, independent of age, comorbidities, and severity of admission, increased the risk of readmission and mortality. According to a study in patients with UC using the National Surgical Quality and Improvement Program cross-institutional database, on multivariate analysis, the modified frailty index was an independent predictor of septic complications (adjusted OR [aOR] = 31.26; $p = 0.006$), cardiopulmonary complications (aOR = 216.3; $p \leq 0.001$), serious morbidity (aOR = 66.8; $p \leq 0.001$), overall morbidity (aOR = 25.5; $p \leq 0.001$), and return to the operating room (aOR = 14.29; $p = 0.048$).[102] In addition, sarcopenia, defined as loss of skeletal muscle mass, is an independent predictor of poor postoperative outcomes. A retrospective cohort study of 147 patients with IBD who underwent IBD-related major abdominal surgery found sarcopenia to be associated with postoperative anastomotic leak (OR = 11.3; 95% CI, 1.53–83.51), grade IV complications (OR = 6.79; 95% CI, 1.1–43.6), and requirement of total parenteral nutrition (OR = 3.21; 95% CI, 1.3–8.1).[103] Hence, surgery in patients with sarcopenia or frailty should be a more careful decision, weighing risks and benefits, with the potential for preoperative optimization in individuals at higher risk for adverse outcomes.

PREPARATIONS FOR COLECTOMY

Anticoagulants/Antiplatelets

The benefit of anticoagulants and antiplatelets in reducing VTE occurrence in patients with IBD, especially UC, who are at higher risk of VTE, must be balanced by the risk of bleeding in surgery. Severe IBD, hospitalization, and surgery are known major factors that increase the risk of VTE.[84,86,93,104] However, because bowel resection surgery has high bleeding risk, it is recommended that anticoagulants be stopped immediately before surgery.[105] Direct oral anticoagulants (DOACs), including factor Xa inhibitors (eg, apixaban, rivaroxaban), have the benefit of a short half-life and rapid onset of action and may be held for a minimum of 24 hours for lower-risk procedures and at least 48 hours for higher risk procedures such as resection surgery.[105] However, this timeline depends on the patient's renal function and the individual DOAC because these drugs are renally cleared to varying degrees.[105] When deciding on warfarin, it is important to keep in mind that warfarin's half-life depends on the half-lives of the factors it affects and is around 36 to 42 hours.[105–107] Hence, before major surgery such as colectomy, warfarin is held usually for 5 days depending on the patient's international normalized ratio. To bridge the patient before surgery, low-molecular-weight heparin (LMWH) is often started 36 hours after the last warfarin dose. Then, 24 hours before the surgery, the last dose of LMWH is given, albeit at half the normal daily dose, because discontinuing LMWH or heparin drip altogether can increase the risk of thrombosis.[105,108,109]

Reported rigorous data on stopping or continuing aspirin suggest no difference between continuing versus stopping; the clinician should assess individual patient risk for thrombosis, especially when deciding on perioperative aspirin use.[108,110] In general, the clinician should always assess patients' risk for bleeding versus thrombosis, looking at the current antiplatelet/anticoagulation regimen and indications, comorbidities, and baseline laboratory tests, including platelet count, creatinine, and international normalized ratio.

Corticosteroids

Although biologic drugs do not need to be stopped before surgery in patients with UC, corticosteroids should be stopped at least 30 days before surgery if possible.[25] Patients with ASUC receiving steroids should be monitored for steroid nonresponse, with steroids tapered before

surgery if there is no substantial response.[111,112] If steroids cannot be stopped completely, they should be minimized whenever possible because preoperative prednisone doses of >30 mg/d are associated with adverse postoperative outcomes.[113] Because patients taking >20 mg prednisolone for >6 weeks are at increased risk of early complications and pouch-specific complications, the ECCO guidelines recommended that steroids be weaned before restorative proctectomy or proctocolectomy. If weaning off steroids is not possible, surgery should be postponed or at least a staged procedure should be performed. Preoperative thiopurines or cyclosporine do not increase the risk of postoperative complications.[11]

Biologics

Biologics, including anti-TNF and non–anti-TNF biologics, do not need to be stopped before surgery in patients with UC.[114] Colectomy is needed in almost all cases because of medication failure; hence, there may be no need to continue the medication. Additionally, there is poor systemic bioavailability of biologics in most patients, and if there are detectable anti-TNF levels, there is no clear correlation with adverse surgical outcomes.[114]

There are no clear data that consistently show any class of monoclonal antibodies to be a risk factor for postoperative adverse effects.[27,69] Hence, monoclonal antibody use should not be a deterrent to or delay surgery.[69] If a patient is on a biologic regimen of every 8 weeks, surgery could be performed 4 weeks after the last monoclonal antibody dose to wash out one-half life and resume the antibody 4 weeks postoperatively.[69,115]

The ECCO guideline on surgical management recommended that single-stage restorative proctocolectomy should be avoided in patients receiving biologics because of possible risk for postcolectomy infectious complications.[11] Whether results of the recent PUCCINI trial impact decision-making on surgical strategies in UC remains to be clarified.

Small Molecules

Small molecules are new to the treatment of IBD and have limited data regarding perioperative use. Borrowing from rheumatology guidelines, tofacitinib may be held 7 days before surgery because of the risk of postoperative infection.[116] Similar to recommendations regarding perioperative biologic therapy amid the PUCCINI trial, urgent or emergent surgery should not be delayed because of small molecule use.

IMMEDIATE POSTOPERATIVE PERIOD

Anticoagulants/Antiplatelets

In the postoperative period, DOACs such as apixaban and rivaroxaban can be resumed once there is postoperative hemostasis, around 2 to 3 days after high bleeding risk procedures such as colectomy.[107] The same preoperative dose can be resumed. If resumption of DOACs is delayed for >3 days, LMWH can be administered to provide VTE prophylaxis.[107,108] As for warfarin, warfarin may be restarted 12 to 24 hours after surgery at the same preoperative dose if there are no new postsurgical reasons to suspect increased bleeding risk.[107] If a patient is at a particularly higher risk of VTE, bridging therapy with heparin can be added until warfarin takes full effect (5–10 d).[107] Antiplatelet therapy can be resumed around 24 hours after surgery.[107]

Corticosteroids

Long-term steroid use can suppress the hypothalamic-pituitary-adrenal axis. Thus, the longer the duration of steroids before surgery, the slower the taper. Patients who have been taking steroids for less than a month may stop the corticosteroids abruptly after surgery.[113] Patients who had been taking corticosteroids ≥20 mg/d for 1 to 3 months should have their steroid dose decreased to 5 mg/d/wk after surgery.[113] If patients were on steroids for 3 to 6 months, the taper should be 2.5 mg/d/wk postoperatively.[113] Patients on steroids for >6 months preoperatively should be tapered at a similar rate; then, once at 10 mg/d, it should be reduced more slowly at a rate of ≤1 mg/wk.[113]

Biologics

Patients who develop CD of the pouch can start biologics as soon as they are needed. Studies in CD show that restarting biologic therapy within 4 weeks postoperatively does not increase risk of disease recurrence, and there are limited studies showing that most patients in whom biologics are withdrawn postoperatively experience disease recurrence.[117–120]

Optimizing Functional Exercise Capacity

Rehabilitation, exercise, and lifestyle changes play a key role in the reduction of postoperative complications and disability, shortening of hospital stay, and improvement in outcomes and patients' quality of life. The rehabilitation program may consist of exercise training, smoking sessation, nutritional intervention, and psychological support.[121]

CONCLUSIONS

When patients present to the hospital with severe UC that does not respond to intravenous corticosteroids and/or biologics, or if patients have disease refractory to current biologic or small molecule therapy as outpatients, patients would require colectomy. Urgent colectomies have a significantly higher mortality rate compared to elective colectomies. Indications for elective surgery include failed medical management, intolerance of medical therapy, and colitis-associated neoplasia, whereas indications for emergent surgery include perforation, uncontrolled bleeding,

toxic megacolon, and fulminant disease. For patients with UC undergoing colectomy, it is important to screen for malnutrition, observe and document oral intake, monitor body weight and BMI, obtain nutritional counseling, provide protein-rich diets and even enteral or parental nutrition (if needed), correct deficits, and organize a multidisciplinary team. Corticosteroids have been the mainstay of acute therapy in moderate to severe UC; however, because of their association with infectious complications of surgery, they are recommended to be stopped, weaned, or at least minimized before surgery. Biologics of any class are not a risk factor for postoperative adverse effects and hence do not necessarily need to be stopped before surgery. Limited data are available on the perioperative management of small molecules. In preparation for surgery, patients' comorbidities and risks of venous thromboembolism versus bleeding must be assessed as the clinician decides on when or whether to stop DOACs, warfarin, and antiplatelet regimens. In the postoperative period, corticosteroids can be tapered on the basis of the length of preoperative use of corticosteroid use because of suppression of the hypothalamic-pituitary-adrenal axis. The perioperative management of UC is especially complicated given the many pharmacological considerations for patients with moderate to severe UC.

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