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Anti-Tumor Necrosis Factor-α Antibody Therapy Management Before and After Intestinal Surgery for Inflammatory Bowel Disease: A CCFA Position Paper

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Abstract: Biologic therapy with anti–tumor necrosis factor (TNF)-α antibody medications has become part of the standard of care for medical therapy for patients with inflammatory bowel disease and may help to avoid surgery in some. However, many of these patients will still require surgical intervention in the form of bowel resection and anastomosis or ostomy formation for the treatment of their disease. Postsurgical studies suggest up to 30% of patients with inflammatory bowel disease may be on or have used anti–TNF-α antibody medications for disease management preoperatively. Significant controversy exists regarding the potential deleterious impact of these medications on the outcomes of surgery, specifically overall and/or infectious complications. In this position statement, we systematically reviewed the literature regarding the potential risk of anti–TNF-α antibody use in the perioperative period, offer recommendations based both on the best-available evidence and expert opinion on the use and timing of anti–TNF-α antibody therapy in the perioperative period, and discuss whether or not the presence of these medications should lead to an alteration in surgical technique such as temporary stoma formation.

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Key Words: inflammatory bowel disease, Crohn's disease, ulcerative colitis, surgery, colectomy, proctectomy, complications, biologic therapy, infliximab, ileal pouch–anal anastomosis, anti–TNF-α antibody

In 1998, a new class of medications starting with infliximab emerged for the treatment of inflammatory bowel disease (IBD).[1] Biologic therapy with anti–tumor necrosis factor (TNF)-α antibody therapy (anti–TNF-α Ab) and other antibodies are increasingly used in patients with IBD, which includes Crohn's disease (CD) and chronic ulcerative colitis (CUC). However, patients with IBD frequently require surgical intervention in the form of bowel resection with anastomosis or ostomy formation for the treatment of their disease, and referral center studies suggest >30% of IBD patients may have used these types of medications preoperatively.[1,2] Given the immunosuppressive effects of anti–TNF-α Ab, controversy exists as to the impact of this class of medications on the outcomes of surgery. In this position statement, we systematically review the literature regarding the potential risk of anti–TNF-α Ab use in the perioperative period in patients with IBD undergoing abdominal surgery. We offer recommendations on the use and timing of anti–TNF-α Ab therapy in the perioperative period based both on evidence and expert opinion and discuss whether or not the presence of these medications should lead to an alteration in surgical technique. Figure 1 depicts the possible confounding variables for attributing anti–TNF-α Ab use to postoperative surgical complications. In this article, we have systematically reviewed the literature, with an emphasis on postoperative overall and infectious complications, which has accumulated regarding this subject and offer evidence-based expert opinions for recommended management strategies.

METHODS

Subcommittee of the CCFA Professional Education Committee discussed potential topics and selected 3 for the full committee to discuss. The committee unanimously selected "Anti–TNF therapy management around IBD surgery." A statement subcommittee was independently selected to develop the content of the statement; this was made up of 4 primary authors with varied expertise with the

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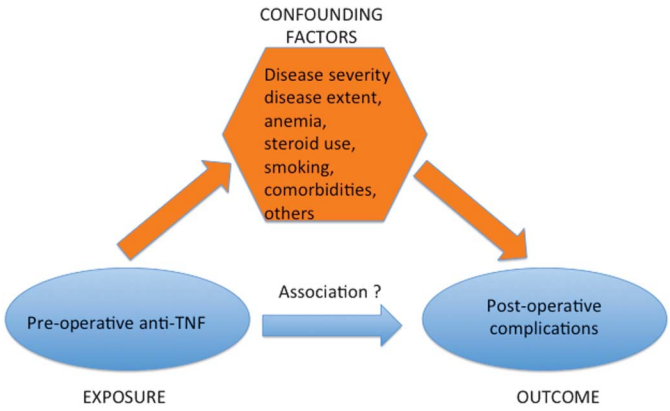

FIGURE 1. Confounding variables for direct association of anti–TNF-α Ab to postoperative complications.

assistance of a research librarian. The subcommittee did an extensive literature review whereby each author reviewed a portion of the literature and analyzed the information. They then reviewed another author's review to cross review the information. Once the manuscript was drafted, 2 independent reviewers from the Professional Education Committee were selected to review the developed statement and methodology and make recommendations to improve/edit consensus recommendations. Additionally, several surgical IBD specialists were invited to review the developed statement and methodology and make recommendations to improve/edit consensus recommendations based on their expertise on the topic. The final draft manuscript was then presented to the remainder of the Professional Education Committee with a request for approval of the position statement. The final statement was then sent to the NSAC chair for review and final approval before submission for publication.

TABLE 1. Summary of Recommendations

For patients with CD, preoperative anti–TNF-α antibody therapy may be associated with an increased risk of postoperative complications after surgery for CD. Level of Evidence: III; Grade of Recommendation: C

For patients with CD on anti–TNF-α antibody therapy, fecal diversion should be left to the surgeon's discretion. Level of Evidence: IV; Grade of Recommendation: D

For patients with CD in the immediate postoperative period, anti–TNF-α antibody therapy should not be resumed until absence of infectious complications. Level of Evidence: III; Grade of Recommendation: D

For patients with CUC, preoperative anti–TNF-α antibody therapy may be associated with an increased risk of postoperative complications after surgery for CUC. Level of Evidence: III; Grade of Recommendation: C

For patients with CUC receiving anti–TNF-α antibody therapy, it is safe to perform a subtotal colectomy (i.e., 3-stage IPAA). Level of Evidence: III; Grade of Recommendation: B

For patients with CUC, anti–TNF-α antibody therapy may increase risk of postoperative complications after 2-stage IPAA; thus, the decision to perform 2-stage versus 3-stage IPAA should be left to the surgeon's discretion. Level of Evidence: III; Grade of Recommendation: C

For patients with CUC, anti–TNF-α antibody therapy is an absolute contraindication for a 1-stage IPAA procedure. Level of Evidence: IV; Grade of Recommendation: D

TABLE 2. Levels of Evidence

I	Meta-analysis of multiple well-designed, controlled studies; randomized trials with low false-positive and low false-negative errors (high-power)
II	At least one well-designed experimental study; randomized trials with high false-positive or high false-negative errors or both (low-power)
III	Well-designed, quasi-experimental studies, such as nonrandomized, controlled, single-group, preoperative–postoperative comparison, cohort, time, or matched case-control series
IV	Well-designed, nonexperimental studies, such as comparative and correlational descriptive and case studies
V	Case reports and clinical examples

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Recommendations were formulated based on a systematic review of the literature (Table 1). The criteria we used to assess the level of evidence are shown in Table 2, and the grade and the strength of recommendations are shown in Table 3.[3] A summary of the physical properties of considered biologic agents is shown in Table 4; however, the available literature was limited to anti–TNF-α Ab treatment. The following databases were searched without date restrictions on March 20, 2014: MEDLINE (PubMed), Cochrane Library (Wiley), and Web of Science. The search included indexed terms and text words to capture the concepts of *inflammatory bowel diseases, biologic therapies, and the perioperative period.* Results were limited to articles published in English; however, 3 CD abstracts, which contributed significant findings, were included. The search strategy was adjusted for the syntax appropriate for each database (see Appendix, Supplemental Digital Content 1, http://links.lww.com/IBD/B122 for full search strategies). In an iterative process, 2 dyads authors (2 for CD and 2 for CUC) each reviewed 50% of the resultant 2015 abstracts. Of those, we identified a total of 125 (6.2%), which were relevant, and the original manuscripts were obtained for all. For CUC, 2 studies

TABLE 3. Grade of Recommendation

A	Evidence of Type I or consistent findings from multiple studies of type II, III, or IV
B	Evidence of Type II, III, or IV and generally consistent findings
C	Evidence of Type II, III, or IV but inconsistent findings
D	Little or no systematic empirical evidence

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TABLE 4. Characteristics and Half-lives of Biologic Agents FDA-Approved for Use in IBD

Agent	Route	Indication	Standard Dosing Interval	Half-life
Infliximab (Remicade)[a]	IV	CD and UC	8 weeks	Median, 7.7–9.5 days
Adalimumab (Humira)[b]	SC	CD and UC	2 weeks	Approximately 14 days
Certolizumab pegol (Cimzia)[c]	SC	CD	4 weeks	14 days
Golimumab (Simponi)[d]	SC	UC	4 weeks	Approximately 14 days

[a]Available at: http://www.remicade.com/shared/product/remicade/prescribing-information.pdf. Accessed 9/2015.
[b]Available at: http://www.rxabbvie.com/pdf/humira.pdf. Accessed 9/2015.
[c]Available at: http://cimzia.com/assets/pdf/Prescribing_Information.pdf. Accessed 9/2015.
[d]Available at: http://www.simponi.com/shared/product/simponi/prescribing-information.pdf. Accessed 9/2015.

of pediatric CUC were included, but given the lack of pediatric-specific data, our recommendations are limited to adults aged 18 years or older. Each recommendation was formulated by 4 authors, and then reviewed by members of the CCFA Professional Education Committee. The opinions expressed below are those of the individual authors based on best-available evidence and do not represent the opinion of the CCFA. A summary table of the available literature for CD is shown in Table 5 and for CUC in Table 6.

Biologic Therapy Management Before and After Surgery for CD

A summary of the literature assessing possible associations between anti–TNF-α Ab therapy and postoperative complications in CD is shown in Table 5. Twenty-six studies were reported over a 13-year period, 3 of which were in abstract-only form. Only 2 studies reported prospective data: one a referral-based cohort and the other a post hoc analysis of a 24-patient randomized controlled trial. One population-based retrospective cohort analysis was identified. Finally, with the exception of 4 multicenter retrospective referral cohort analyses, the remaining were all retrospective single-center referral cohort analyses. Population sizes ranged from 24 to 2293 patients with CD, with 14 (54%) reporting on <250 patients.

There was great heterogeneity between the studies meeting criteria for inclusion on several important variables. Five studies (19%) included both CD and CUC in their cohort. Some studies were limited to specific surgeries (such as ileocecal resection with anastomosis), others included any CD resection regardless of anastomosis or diverting stoma, and some included all abdominal surgeries; a select few also included perianal surgeries. Infliximab was the biologic therapy most often analyzed, although 65% of studies had <33% of their total cohort exposed to anti–TNF-α Ab therapy and half of studies had <25% of their cohort exposed. Timing of anti–TNF-α Ab therapy also varied greatly, ranging from 6 months preoperatively to 1 month postoperatively. Most studies were limited to preoperative exposures, one to postoperative and 3 allowed preoperative and postoperative exposure. Half of the studies defined exposure as the 12 preoperative weeks whereas another 4 defined exposure within the 8 preoperative weeks. Twenty studies (77%) used a complication window of 30 days, whereas 3 studies failed to define their outcome timeline. Complication definitions were also varied, with some studies reported only wound or infectious complications, whereas others used a more comprehensive classification. Fifteen studies performed multivariate analyses attempting to control for confounding factors, although only 1 study used an accepted disease severity metric.

In these studies, control patients represent patients with CD not on anti–TNF-α Ab agents but who may be on other widely variable medical regimens including no medication, high-dose steroids, and immunomodulators (azathioprine/6MP). In the experimental arm, the use of other immunomodulators or high-dose steroids in addition to anti–TNF-α Ab agents may also have been used and influenced postoperative outcomes. Numerous studies failed to control these exposures; thus, it is difficult to analyze the effects that additional therapies may contribute to anti–TNF-α Ab agents in the setting of patients with CD. Other potential confounding variables include preoperative anemia, transfusion, patient disease severity, other medical comorbidities, and tobacco use. Although many studies compared some of these factors between the patient cohorts, most often at least some of these variables were not reported (Figure 1).

For Patients with CD, Preoperative Anti–TNF-α Antibody Therapy May be Associated with an Increased Risk of Postoperative Complications After Surgery for CD. Level of Evidence: III; Grade of Recommendation: C

Most individual studies did not report a significant association between anti–TNF-α Ab therapy and postoperative complications. Only 5 studies (Lau, Lau, Syed, Appau, and Serradori) reported a positive association and therefore an increased risk of complications.[7,9,40–42] However, all 5 studies reporting increased complications are very important to consider as they analyzed only patients with CD and used multivariate analysis to control for other factors, although none directly controlled for disease activity or severity. These 5 studies were also more permissive in surgeries analyzed by including all ileocolic resections (Appau

TABLE 5. Summary of Literature of the Possible Association of Anti–TNF-α Ab with Postoperative Complications in CD

First Author	Institution	Year	Population/Setting	Anti–TNF-α Ab Exposed (%)[a]/Unexposed	Exposure
Myrelid et al[4]	6 university hospitals in Western Europe	2014	All patients with CD treated with anti–TNF-α Ab who underwent CD surgery with 1+ anastomoses from 2008 to 2011	111 (37%)[a]/298 (all received anti–TNF-α Ab; unexposed stopped >2 mo before or started >6 wk postoperatively)	2 mo preoperatively
Waterman et al[5]	Mt. Sinai (Toronto)	2013	All IBD abdominal surgery, 2000–2010	IBD: 195/473; CD: 122, (43%)[a]/286	180 d preoperatively
Uchino et al[6]	Hyogo (Japan)	2013	Consecutive patients with CD undergoing laparotomy, 2008–2011	79 (20%)/405	12 wk preoperatively
Serradori et al[7]	3 university hospitals (France)	2013	All CD ileocolonic resections, 2000–2010	42 (19%)[a]/217	12 wk preoperatively
Norgard et al[8]	University of Southern Denmark	2013	CD-related abdominal surgeries, 2003–2010	214 (9%)[a]/2293	12 wk preoperatively
Lau et al,[41] abstract only	Cedars-Sinai	2013	Consecutive CD surgeries; single surgeon; timeline not stated	213 (47%)[a]/458	Not defined
Lau et al[40]	Cedars-Sinai	2013	Patients with CD and serum available within 7 days before abdominal surgery; timeline not stated	123 (100%)[a]/123, 73/123 (59%) had detectable anti–TNF-α Ab levels	Not defined; however, anti–TNF-α Ab levels checked within 7 d preoperatively
Syed et al[9]	University of Maryland	2013	All abdominal surgeries in patients with CD	150 (46%)[a]/325	8 wk preoperatively (97% within standard dosing interval of anti–TNF-α Ab preoperatively)
Bafford et al[10]	Mt. Sinai (New York)	2013	All CD intestinal surgery, 1999–2010	35 (18%)/196	12 wk preoperatively
Krane et al[11]	University of Chicago	2013	Consecutive IBD laparoscopic surgeries, 2004–2011 with at least 6 months of follow-up	IBD: 142/518; CD: 63, (26%)/244	12 wk preoperatively
Desai et al,[12] abstract only	Medical College Wisconsin	2012	All IBD bowel resections, 2005–2010	76 (67%)/114	Not stated
El-Hussuna et al[13]	4 university hospitals, Copenhagen (Denmark)	2012	All CD resection with anastomosis or stricturoplasty, 2000–2007	32 (8%)[a]/417	12 wk preoperatively
Mascarenhas et al[14]	Michigan State University	2012	All ileocolic resections, 2003–2010	19 (3%)/693	12 wk preoperatively
Kasparek et al[15]	Ludwig Maximilian University of Munich (Germany)	2011	All CD abdominal surgery, 2001–2008	48 (50%)/96	12 wk preoperatively
Kotze et al,[16] abstract only	Several hospitals, Sao Paolo (Brazil)	2011	All major CD resections, 2007–2010	19 (25%)/76	4 wk preoperatively
Regueiro et al[17]	University of Pittsburgh	2011	24 ileocolic resections	11 (46%)/24	2–4 wk postoperatively
Rizzo et al[18]	Rome (Italy)	2011	All CD and UC surgery, 2004–10	IBD: 54/114; CD: 37 (49%)[a]/76	12 wk preoperatively for IFX, 4 wk for ADA and CP
Holubar et al[2]	Mayo Rochester	2010	All CD laparoscopic colectomy at Mayo, 1997–2008	32 (35%)[a]/92	8 wk preoperatively
Nasir et al[44]	Mayo Rochester	2010	All CD surgery, 2005–2009	119 (32%)[a]/370	8 wk preoperatively to 4 wk postoperatively

TABLE 5 (*Continued*)

First Author	Institution	Year	Population/Setting	Anti–TNF-α Ab Exposed (%)[a]/Unexposed	Exposure
Canedo et al[19]	Cleveland Clinic, Florida	2010	All CD resection surgery, 2000–2008	65 (29%)/225	12 wk preoperatively
Indar et al[20]	Mayo Arizona	2009	All CD intestinal surgery, 1999–2007	17 (15%)[a]/112	8 wk preoperatively
Kunitake et al[21]	Massachusetts General Hospital	2008	All surgery for CD, UC, or IC, 1993–2007	101/413 (CD = 57 [44%]/131)	12 wk preoperatively
Appau et al[42]	Cleveland Clinic, Ohio	2008	All ileocolic resections (before and after 1998)	60 (15%)/389 and 60 (47%)/129	12 wk preoperatively
Marchal et al[43]	University of Leuven (Belgium)	2004	All IFX, 1998–2002	40 (51%)/79	Variable; 78% within 12 wk preoperatively
Colombel et al[22]	Mayo Rochester	2004	All CD surgery, 1998–2001	52 (19%)/270	8 wk before to 4 wk after OR
Tay et al[23]	Medical College Wisconsin	2003	All CD resection, 1° anastomosis, or stricturoplasty, 1998–2002	2 (2%)/100	8 wk leading up to OR

First Author	Surgery	Outcome	Anti–TNF-α Ab Associated with Postoperative Morbidity?	Adjusted for Disease activity?	Comments
Myrelid et al[4]	CD resections without a temporary stoma	30 days or end of surgical hospitalization	No	No	81% open; 4% emergent
Waterman et al[5]	Various IBD abdominal surgeries	30 days	No	No	No CD-specific subanalysis; exposure-surgery stratified by time ≤14 d preoperatively, 15–30 d preoperatively, 31–180 d preoperatively
Uchino et al[6]	Various; site (small bowel, colon, both), stoma or proctectomy specified	30 days	No; in subanalysis of penetrating CD, IFX was protective of SSI (OR: 0.06; 95% CI: 0.01–0.46)	No	Vienna classification used; preoperative steroid/thiopurine exposure was within 1 wk preoperatively
Serradori et al[7]	CD ileocolonic resections without stoma	Not stated	Yes; increased SSI in anti–TNF-α Ab + steroids	No	Only outcome was interabdominal septic complication; 42 excluded due to misclassification of type of surgery; 41 excluded due to temporary stoma.
Norgard et al[8]	CD resections and stricturoplasties	30 days and 60 days	No	No	Subanalyses of first-time surgery, time since anti–TNF-α Ab, compared IFX-exposed to all unexposed and unexposed with exposure to prednisone or thiopurine within 12 wk preoperatively
Lau et al,[41] abstract only	Not specified	30 days	Yes; in IFX-alone group, increased abdominal abscess, length of stay, and time to diet tolerance	No	Anti–TNF-α Ab group stratified as IFX alone, IFX + other biologic, or other biologic alone

TABLE 5 (*Continued*)

First Author	Surgery	Outcome	Anti–TNF-α Ab Associated with Postoperative Morbidity?	Adjusted for Disease activity?	Comments
Lau et al[40]	Abdominal surgery	30 days	Yes; increased infectious complications, readmissions in group with 7-day preoperatively, anti–TNF-α Ab levels >8 μg/mL	No	Banked serum within 7 d preoperatively was used to obtain anti-TNF Ab levels; stratified as undetectable, >0–3 μg/mL, 3–8 μg/mL, and >8 μg/mL; all comparisons were made to undetectable level cohort
Syed et al[9]	Various CD-related and unrelated abdominal surgeries	Greater of 30 days versus time to discharge	Yes; increased overall infectious and SSI complications	No	—
Bafford et al[10]	Various small bowel and colonic resections (included diversion surgeries)	30 days	No	No	Per-procedure analysis; biologic use not primary exposure variable
Krane et al[11]	Various IBD laparoscopic small bowel and colonic resections	30 days and "long-term"	No	No	Excluded emergent, primary diversion, stricturoplasty, and other surgeries
Desai et al,[12] abstract only	Various small bowel and colon resections (99 in CD)	30 days	No	No	Exposure stratified as < or > 50% of dosing interval preoperatively
El-Hussuna et al[13]	Various small bowel and colon resections (9 stricturoplasties)	30 days	No	No	—
Mascarenhas et al[14]	Ileocolic resections	30 days	No	No	Did not use Lennard–Jones criteria (biopsy was gold standard); analysis compared patients with CD to patients with non-CD for outcomes
Kasparek et al[15]	Various small bowel and colon resections	Not stated	No	No	No difference in complications in anti–TNF-α Ab group stratified by time from last dose
Kotze et al,[16] abstract only	Various small bowel and colon resections	30 days	No	No	—
Regueiro et al[17]	Ileocolic resections	≤ 8 weeks postoperatively; 9–54 weeks postoperatively	No	No	22/24 surgeries were for penetrating disease, 2 for obstruction
Rizzo et al[18]	Any IBD resection	30 days	No	No	CD and UC analyzed together
Holubar et al[2]	MIS colectomy	30 days	No	No	Anti–TNF-α Ab's not included in multivariable analysis
Nasir et al[44]	Only CD operations with an anastomosis	30 days	No	Yes	Excluded emergent and proximally diverting surgeries; more "severe disease" in anti–TNF-α Ab group
Canedo et al[19]	Any CD surgery with resection	30 days	No	No	Excluded stoma reversal, adhesiolysis, and stoma creation without resection
Indar et al[20]	Small bowel resection, ileocolic resection, total abdominal colectomy (totaling 75%), + various others	30 days	No	No	Anti–TNF-α Ab's not analyzed separately

TABLE 5 (*Continued*)

First Author	Surgery	Outcome	Anti–TNF-α Ab Associated with Postoperative Morbidity?	Adjusted for Disease activity?	Comments
Kunitake et al[21]	Any abdominal surgery for IBD complication	30 days or index admission	No	No	>95% surgery elective; more in anti–TNF-α Ab group had stricture as indication; longer stay (2d) in anti–TNF-α Ab group ($P < 0.0001$)
Appau et al[42]	Ileocolic resection	30 days	Yes; for readmit, sepsis, abdominal abscess, strong trend for reoperation	No	Perianal disease excluded; rates of sepsis lower with protecting stoma in IFX group (0 versus 28%); no difference if anti–TNF-α Ab given 3 versus 2 mo preoperatively
Marchal et al[43]	Small bowel resection, ileocolic resection, left colectomy, abdominoperineal resection	Early (10 days); late (3 months)	Not major complications	No	Only perianal loaded 0, 2, 6; luminal had 0, on-demand; increased number of early total infections in anti–TNF-α Ab (8 versus 1; $P = 0.03$); trend for infected patients (6 versus 1, $P = 0.10$)
Colombel et al[22]	CD resection, stricturoplasty, bypass	30 days	No	No	Multivariable analysis only for IFX and steroid versus outcome
Tay et al[23]	First resection with anastomosis or stricturoplasty	4 weeks	N/a	No	

[a]Included IFX and ADA.
ADA, adalimumab; CI, confidence interval; CP, certolizumab pegol; IFX, infliximab; MIS, minimally-invasive surgery; NA, not available; OR, odds ratio; SSI, surgical.

and Serradori),[7,42] consecutive CD surgeries (Lau), and all abdominal surgeries in patients with CD (Syed and Lau).[9,41]

The first analysis to suggest (but not clearly detect) possible increased postoperative risk was in 2003 by Marchal et al,[43] who compared 40 patients with CD treated with infliximab before small bowel resection to 39 patients with CD small bowel resection never treated with infliximab. They found a trend to increased early (<10 d) infections and also significantly more overall infectious events in the infliximab group (8 versus 1; $P = 0.03$). However, a greater number of patients treated with infliximab also received corticosteroids or immunomodulators (29 versus 16; $P < 0.0002$), therefore limiting decisive conclusions.

In a 2008 retrospective single referral-center analysis, Appau et al[42] reported that infliximab use in patients with CD within 12 weeks before ileocolic resection was independently associated with increased 30-day postoperative sepsis, anastomotic leak, and readmissions when compared to both contemporary surgical controls and a control group from the prebiologic era. They also found a trend to more abdominal abscess after infliximab exposure compared with infliximab naive contemporary controls. Moreover, they noted that all sepsis episodes in the infliximab group were in patients without formation of a protecting stoma at the time of resection. The authors controlled for multiple covariates, including preoperative exposures to immunomodulators and corticosteroids and presence of preoperative abdominal abscess. Subsequently, 4 additional 2013 analyses reported a significant association between anti–TNF-α Ab therapy and postoperative complications.[7,9,40] In a retrospective single referral-center analysis, Syed et al noted increased overall infectious and surgical site complications in patients with CD treated with anti–TNF-α Ab therapy ≤8 weeks before surgery. All intraabdominal surgeries were included in the analysis (63% were bowel resection), and authors controlled for multiple potentially confounding covariates.[9] The analysis by Lau et al[41] was also a retrospective referral-center analysis of patients with CD undergoing any abdominal surgery but by a single surgeon. This study was unique in that it is the only one verifying preoperative levels of anti–TNF-α Ab therapy. They found that compared to those with undetectable anti–TNF-α Ab levels, patients with CD and detectable anti–TNF-α Ab levels 7 days before surgery had trends toward increased 30-day postoperative morbidity, infectious complications, and readmissions. Furthermore, when stratified by preoperative serum anti–TNF-α Ab level, they found significantly increased frequencies of both infectious complications and readmissions in patients with levels >8 μg/mL compared with those with undetectable preoperative levels.[40] A concurrent abstract by

TABLE 6. Summary of Literature of the Possible Association of Anti–TNF-α Ab with Postoperative Complications in CUC

First Author	Institution	Year	Population/Setting	Anti–TNF-α Ab Exposed Subjects (%)[a]/ Total Subjects	Exposure
Nelson et al[24]	University of Chicago	2014	UC (hospitalized only)	24 (32%)/74	During hospitalization
Hicks et al[25]	Massachusetts General Hospital	2014	UC	43 (24%)/179	NA
Hicks et al[26]	Massachusetts General Hospital	2013	UC	39 (27%)/144	NA
Waterman et al[5]	Mt. Sinai (Toronto)	2013	UC (87%) and CD (13%)	51 (47%)[a]/108	24 wk
Gu et al[27]	Cleveland Clinic Ohio	2013	UC	167 (28%)[a]/588	12 wk (4 for ADA/CP)
Uchino et al[29]	Hyogo, Japan	2013	UC	22 (11%)/196	12 wk
Krane et al[11]	University of Chicago	2013	UC and CD	71 (30%)/237	12 wk
Eshuis et al[30]	Netherlands	2013	UC	38 (53%)/72	28 wk
Norgard et al[31]	Danish Nationwide	2012	UC	199 (12%)/1629	12 wk
Bregnbak et al[32]	Hvidovre Hospital (Denmark)	2012	UC	20 (28%)/71	12 wk
Schaufler et al[33]	Connecticut Children's Medical Center	2012	UC (pediatric)	33 (65%)/51	12 wk
Kennedy et al[34]	Mayo Rochester	2012	UC (pediatric)	11 (29%)/38	8 wk
Gainsbury et al[35]	Boston University	2011	UC	29 (36%)/81	12 wk
de Silva et al[36]	University of Calgary	2011	UC (hospitalized only)	24 (4%)/666	During hospitalization
Coquet-Reinier et al[37]	University of Mediterranean (France)	2010	UC	13 (50%)/26	6 wk
Ferrante et al[38]	University of Leuven (Belgium)	2009	UC	22 (15.6%)/141	12 wk
Kunitake et al[21]	Massachusetts General Hospital	2008	UC and CD	26 (21%)/126	12 wk
Mor et al[28]	Cleveland Clinic, Ohio	2008	UC	85 (16%)/523	13.5 wk
Schluender et al[39]	Cedars Sinai	2007	UC (hospitalized only)	17 (11%)/151	NA
Selvasekar et al[1]	Mayo Rochester	2007	UC	47 (16%)/301	24 wk

First Author	Surgery	Outcome	Anti–TNF-α Ab Associated with Postoperative Morbidity?	Adjusted for Disease Activity?	Comments
Nelson et al[24]	3 stage only	30 d	No	Yes	All patients received steroids
Hicks et al[25]	2 stage, 84%; 3 stage, 16%	30 d, long-term NOS	No	Yes	Overlap with Hicks et al[26]
Hicks et al[26]	2 stage, 81%; 3 stage, 19%	30 d, long-term NOS	No	Yes	Overlap with Hicks et al[25]
Waterman et al[5]	3 stage, 100%	30 d	No	No	—
Gu et al[27]	2 stage, 31%; 3 stage, 69%	30 d, 1 yr	Yes: 2-stage only, pelvic sepsis; 1 yr outcome	Yes	Possible overlap with Mor et al[28]
Uchino et al[29]	1, 2, and 3 stages	30 d	No	Yes (surgical site infection only)	—
Krane et al[11]	2 and 3 stages (all laparoscopic)	30 d and 45 mo	No	Yes	—
Eshuis et al[30]	1, 2, and 3 stages	30 d	Yes: 1-stage only[b], pelvic sepsis, noninfectious complications	No	—

TABLE 6 (*Continued*)

First Author	Surgery	Outcome	Anti–TNF-α Ab Associated with Postoperative Morbidity?	Adjusted for Disease Activity?	Comments
Norgard et al[31]	2 stage, 9%; 3 stage, 91%	60 d	No	No	Danish Nationwide cohort
Bregnbak et al[32]	3 stage only	30 d	No	No	—
Schaufler et al[33]	2 stage, 24%; 3 stage, 76%	60 d	No	No	—
Kennedy et al[34]	1 stage, 2%; 2 stage, 74%; 3 stage, 24%	Variable[c]	Yes: Small bowel obstruction after initial surgery	No	—
Gainsbury et al[35]	2 stage, 93%; 3 stage, 7%	30 d	No	No	—
de Silva et al[36]	1 stage, 4%; 2 stage, 59%; 3 stage, 37%	Through discharge	No	Yes	Calgary administrative database
Coquet-Reinier et al[37]	2 stage, 54%; 3 stage, 46%; (all laparoscopic)	30 d	No	No	—
Ferrante et al[38]	1 stage, 30%; 2 stage, 41%; 3 stage, 29%	30 d	No	No	—
Kunitake et al[21]	NA	Not specified	No	No	—
Mor et al[28]	2 stage, 54%; 3 stage, 46%	Early and late NOS	Yes: 2-stage only, early complications (sepsis, leak); late complication (pouchitis)	Yes[d]	Possible overlap with Gu et al[27]
Schluender et al[39]	2 stage, 74%; 3 stage, 26% (all mucosectomy)	30 d	Yes: IFX + cyclosporine only, overall and infectious complications	No	All patients received IV steroids
Selvasekar et al[1]	2 stage, 86%; 3 stage, 14%	30 d	Yes: infectious complications	Yes	—

[a]Included IFX and ADA.
[b]Proctocolectomy with IPAA (with or without diverting ileostomy).
[c]Period 1 (initial surgery to ileostomy takedown), period 2 (30 d after final surgery), and period 3 (1 yr after final surgery).
[d]Used hemoglobin and platelet counts as marker of severity.
ADA, adalimumab; CP, certolizumab pegol; IFX, infliximab; NA, not available; NOS, not otherwise specified.

the same group reported significantly increased postoperative intraabdominal infections, time to hospital discharge, and time to tolerance of diet in patients preoperatively exposed to infliximab monotherapy when compared with patients unexposed to preoperative anti–TNF-α Ab therapy. Finally, Serradori et al[7] described increased rates of intraabdominal infection on univariate analysis, but multivariate analysis only found those patients treated with both anti–TNF-α Ab agents and steroids to be at increased risk for intraabdominal infections.

Nevertheless, most individual studies did not demonstrate a significant adverse effect of anti–TNF-α Ab on postoperative complications. In one of the largest single institution series to date, the Mayo Clinic analyzed 119 patients exposed to anti–TNF-α Ab compared to 251 unexposed patients.[44] No differences were noted in total complications or intraabdominal infectious complications; however, other individual infectious complications were not separately analyzed. Norgard et al[8] performed a large nationwide cohort study from Denmark and found no difference in anastomotic leak rates, abscess drainage, or bacteremia between groups. Yet when evaluating these and the remaining individual studies, there are numerous limitations to the design of each. For example, anti–TNF-α Ab may have been one of the only 2 factors analyzed for multivariate regression analysis or may not have been included at all. Some studies included patients with postoperative exposure to anti–TNF-α Ab, thus complicating the analysis of those exposed preoperatively to anti–TNF-α Ab. Also, the incidence of severe complications such as anastomotic leak requiring operative intervention is low overall. As it is difficult to discern whether complications such as intraabdominal abscesses are related or unrelated to an anastomotic complication, the true presence of an anastomotic leak could be higher than is reported. Anastomotic complications may result in an abscess without sepsis and therefore not require further operative intervention. Thus, there may be variability in reporting these anastomotic complications as an anastomotic complication or as an infectious complication. Furthermore, in larger meta-analyses, it

is even more difficult to discern specific types of complications given the limitations and variability of reporting in individual studies. However, when complications are grouped as total complications or infectious complications, greater conclusions can likely be drawn.

As single-study sample sizes are typically underpowered to detect differences in low-incidence complications such as anastomotic leak, several systematic reviews/meta-analyses have been published in abstract or manuscript form to attempt to clarify the presence and nature of any association between preoperative anti–TNF-α Ab therapy and postoperative complications in patients with CD.[45–50] Interestingly, all but one of these publications noted an increase in at least one postoperative complication in patients with CD undergoing surgery, who were preoperatively treated with anti–TNF-α Ab therapy. Yang et al noted significant increases in pooled odds of total, infectious, and noninfectious complications, whereas the analysis by Koplov *et al* found significant increases in infectious complications with trends toward increased total and noninfectious complications.[48,49] Finally, El-Hussuna et al[47] noted significantly increased odds of nonanastomotic, major (noninfectious) medical, and minor medical complications. Conversely, Rosenfeld et al[50] did not detect differences in major complications (including sepsis, peritonitis, local abscess, wound infection, and several noninfectious complications), minor complications, 30-day mortality or reoperations. However, these same authors noted significantly increased major complications and a trend toward increased odds of major complications in 2 serially preceding abstracts using equivalent methodology and greater numbers of analyzed patients.[45,46] The reason for the attenuated findings over time with smaller cohorts is unclear. Another pair of meta-analyses analyzed patients with IBD overall but performed sub-analyses of patients with CD.[51,52] Both reported significantly increased odds of postoperative infectious complications in patients with CD treated preoperatively with anti–TNF-α Ab therapy, whereas Naurla et al additionally reported increased odds of total complications and a trend toward increased noninfectious complications.[51] Only one systematic review specifically analyzed anastomotic complication rates and did not demonstrate an increased rate in patients on anti–TNF-α Ab therapy.

Across analyses and depending on the endpoint analyzed, much of the pooled data had moderate-to-significant heterogeneity, limiting broad and consistent conclusions. Nevertheless, most of the meta-analyses seem to demonstrate at least some increased risk of infectious complications in patients with CD on anti–TNF-α Ab therapy who undergo major abdominal surgery. Furthermore, the individual retrospective studies demonstrating an association with adverse events were often better designed, by controlling for other covariates. As prospective, large, postmarketing registry analyses have concurrently reported independently increased risks of serious infections in patients with CD on anti–TNF-α Ab therapy (independent of surgery), the effect is likely real.[53]

Therefore, no strong conclusions can be made regarding the risk of complications in patients with CD treated with anti–TNF-α Ab therapy preoperatively. Patients starting anti–TNF-α Ab therapy should enter an informed discussion with their physician that anti–TNF-α Ab therapy may slightly increase the risks of postoperative complications, although the research to date is not definitive. Overall, the authors favor an individualized approach to perioperative counseling of risks and to surgical management. Finally, if elective surgery is planned, the gastroenterologist and surgeon should consider timing surgery when anti–TNF-α Ab medication levels are lowest (Table 4). However, such a decision would have to weigh against the potential negative effects of gaps in therapy, which include immunogenicity and flare of disease.

For Patients with CD on Anti–TNF-α Antibody Therapy, Fecal Diversion Should be Left to the Surgeon's Discretion. Level of Evidence: IV; Grade of Recommendation: D

Limited data support or refute the need for fecal diversion in patients with CD. Nevertheless, data can be extrapolated from the reoperation and anastomotic leak rates in these patients in combination with the known estimated inherent surgical procedural risk. Appau et al[42] revealed a protective effect of proximal fecal diversion with a protective diverting ileostomy in patients treated with infliximab compared to those not diverted. Fecal diversion may offer a protective effect on serious intraabdominal complications by diverting the fecal stream and limiting contamination and thus mitigating the deleterious effects of the leak. Some intestinal anastomoses are at higher risk for anastomotic leak such as colorectal, coloanal, and ileoanal anastomoses with anastomotic complication rates of 5% to 24%.[54] Therefore, diversion for these high-risk anastomoses should be strongly considered if it is not routinely performed (low colorectal, coloanal, and ileoanal). Although colocolonic anastomoses have lower leak rates (in general 2%–5%) than colorectal anastomoses (up to 10% or higher), they are still considered moderate risk. Therefore, fecal diversion for colocolonic anastomoses should be considered but depends on other risk factors and the clinical scenario. However, a small bowel anastomosis to small bowel or colon has a much lower risk for anastomotic leak (approximately 1%–2%). Therefore, diversion for small bowel anastomosis to small bowel or colon should be considered on a case-by-case basis but depends on other risk factors and the clinical scenario.

Another limitation of these series was that rates of proximal fecal diversion with protective loop ileostomies were also not routinely published. As ileostomy rates may be higher in the subset of patients with more aggressive disease on more aggressive medical therapy, the sequelae of serious intraabdominal infectious complications may be decreased. Fecal diversion with protective ileostomy may, in fact, protect against severe intraabdominal infection not by preventing anastomotic leaks but rather by mitigating the clinical impact of the anastomotic leak.[42] Unfortunately, simply comparing patients who received ileostomies to those who did not is also inadequate given the difference

in disease characteristics, medication regimens, and surgeon preferences and biases.

For Patients with CD in the Immediate Postoperative Period, Anti–TNF-α Antibody Therapy Should not be Resumed Until Absence of Infectious Complications. Level of Evidence: III; Grade of Recommendation: D

Most postoperative complications occur within 30 days, whereas most but not all infectious complications, including anastomotic leakage, occur within the first 14 days.[55] Recovery from surgery is typically considered to be 4 to 8 weeks. Only one study examined early postoperative use of infliximab after surgical resection for CD. In a study from the University of Pittsburgh by Regueiro et al,[17] patients with CD undergoing intestinal resection were randomized to infliximab or placebo within 2 to 4 weeks of surgery. This study demonstrated similar adverse events within 8 weeks of surgery with no increases in infectious or wound complications, suggesting that early resumption of infliximab (defined as 14 days) is likely safe. However, anti–TNF-α Ab therapy should not be redosed or initiated in the presence of active infection because of the presumed negative effects of immunosuppression. Therefore, it is our recommendation that anti–TNF-α Ab agents should not be instituted until infectious complications have been adequately treated. This delay should however be limited because of the potential for loss of responsiveness and development of autoantibodies to anti–TNF-α Ab therapy.

Biologic Therapy Management Before and After Surgery for Chronic Ulcerative Colitis

Surgical approaches to CUC are summarized in Table 7. Before the biologic era, for patients who were ambulatory with medically refractory disease or neoplasia as the indication, not on high-dose steroids, and otherwise judged by their surgeon not to be at increased risk of anastomotic leak, the 2-stage ileal pouch-anal anastomosis (IPAA) was the most common initial operation and procedure of choice. For patients who were hospitalized and refractory to medical therapy (most of whom were on high-dose IV steroids), the current standard of care was to perform a total abdominal colectomy with end-ileostomy. This was recommended because the IPAA construction must be performed at the time of proctectomy, and multiple immunosuppressive medications (including high-dose steroids), anemia, and malnutrition—all of which are more common in hospitalized patients—are relative contraindications to both proctectomy and IPAA construction and increase the risk of pelvic sepsis.[56,57] Pelvic sepsis from an anastomotic leak may result in a noncompliant pelvic floor, precluding long-term optimal IPAA functional outcome, and greatly increased risk of pouch excision; if a leak does occur, the pouch loss rate is as high as 50%.[57]

A summary of the literature of the possible association of anti–TNF-α Ab therapy with postoperative complications in CUC is shown in Table 6. Data were limited to retrospective cohorts; no prospective or randomized trials were available on this topic. Over a 7-year period (2007–2014), there were 20 studies; 18 were single center studies, one was a nationwide retrospective cohort study,[31] and one study was based on a query of a province-wide administrative database.[36] There was likely overlap in patients between studies originating from the same center. Three studies looked at patients with both CD and CUC.[4,19,22] There were 2 studies that looked exclusively at pediatric patients.[33,34] Three studies were limited to hospitalized patients.[24,36,39] The anti–TNF-α Ab exposure was limited to infliximab in all studies, except for 2 that also included adalimumab exposure[22,27]; only one study included 2 patients with certolizumab pegol exposure.[27] The window for infliximab exposure before surgery was variable, ranging from <4 weeks (during hospitalization) to 24 weeks; exposure window was not available in 3 studies.[58–60] Proportion of patients on other immunosuppressants including corticosteroids and thiopurines was variable and not uniformly reported. The breakdown of 1, 2, and 3 stage procedures was variable (Table 6), as was the proportion of cases that were performed laparoscopically; most studies did not report on stapled versus handsewn approaches. Most studies examined short-term (<30 d) and long-term (>30 d) outcomes; most separated complications to infectious and noninfectious. Nine of 20 studies adjusted outcomes for disease severity.

Regarding overall strengths and weakness of these studies, although some studies adjusted for disease severity, variable TNF-α Ab exposure definitions were used. Theoretically, a difference

TABLE 7. Surgical Approaches to Ileal Pouch–Anal Anastomosis for CUC

Operation	1-stage IPAA	2-stage IPAA[a]	3-stage IPAA
First operation	IPAA without diverting ileostomy	TPC, IPAA, DLI	TAC with end ileostomy
Second operation	—	DLI-R	Completion proctectomy with IPAA and DLI
Third operation	—	—	DLI-R

All operations may be performed by traditional (open) or minimally invasive (laparoscopic) techniques according to surgeon expertise.
[a]Modified 2-stage IPAA: TAC with end ileostomy; completion proctectomy with IPAA but *without* DLI.
DLI, diverting loop ileostomy; DLI-R, diverting loop ileostomy reversal; IPAA, ileal pouch-anal anastomosis (also known as J-pouch); TAC, total abdominal colectomy (also known as subtotal colectomy); TPC, total proctocolectomy.

should exist between "ever" history of anti–TNF-α Ab exposure (e.g., last dose 1 year before surgery) versus recent exposure in which serum levels would expected to be detectable and clinically active. Recent evidence supports this concept. Lau et al[61] from Cedars Sinai have demonstrated a positive association between serum levels of anti–TNF-α Ab and postoperative morbidity in CD but not in CUC. Regardless of the serum levels, when critically examining the literature, one must question negative studies that have inappropriately long windows, lack of adjustment for disease activity, or small sample size which is underpowered to detect noncomposite outcomes; all of these characteristics were often observed in the reported retrospective series.

For Patients with CUC, Anti–TNF-α Antibody Therapy May be Associated with Increased Risk of Postoperative Complications After Surgery for CUC. Level of Evidence: III; Grade of Recommendation: C

Six of 20 studies (30%) showed a positive association between preoperative anti–TNF-α Ab therapy exposure and postoperative complications. However, only 9/20 (45%) specifically adjusted for disease severity, such as the Montreal Classification.[58] In 2007, Selvasakar et al[1] were the first study to demonstrate the association of an adverse impact. This study suggested that infliximab is independently associated with an increased risk of postoperative infectious complications after surgery for CUC.

Subsequent to the Selvasakar study, 2 additional studies have confirmed the presence of an association between anti–TNF-α Ab therapy and increased risk of postoperative outcomes.[28,39] Of note, Schluender only found an effect when anti–TNF-α Ab was given in the presence of cyclosporine A, an uncommon combination therapy.[58] Mor et al isolated increased risk of postoperative infection only among patients who underwent 2-stage IPAA procedures.[61]

Because these 3 initial studies demonstrated an adverse effect, most subsequent studies have had discordant results and refuted this association (Table 6).[1,28,39] Of studies that demonstrated increased postoperative complications, one isolated an increased risk of small bowel obstruction only[34] and another study found increased complications only among patients who received 1- or 2-stage IPAA procedures.[26] In 2013, Cleveland Clinic updated their experience and again demonstrated a relationship.[27] This study, one of the largest to date (including 167 anti–TNF-α Ab exposed patients), concluded that a 2-stage approach while exposed to anti–TNF-α Ab therapy was independently associated with an increased rate of pelvic sepsis.

To date, 2 meta-analyses have been reported on this topic in CUC.[51,62] Neither study demonstrated an increased risk of either infectious or noninfectious complications. Specifically, the studies (Table 6) included in the meta-analyses commonly lacked adjustment for disease severity, had a very heterogeneous and often inappropriately long exposure window, and had underpowered sample sizes. Finally, these studies do not include the more recent Cleveland Clinic data that showed an effect in the largest cohort to date.[27]

Presently, surgeon concern over increased risk of postoperative complications in the era of anti–TNF-α Ab therapy, which in the case of IPAA construction can have life-long consequences, has led to increased use of the 3-stage approach. Therefore, total abdominal colectomy (not proctocolectomy) is now the most common initial operation for CUC in the United States.[57,63]

For Patients with CUC Receiving Anti–TNF-α Antibody Therapy, it is Safe to Perform a Subtotal Colectomy (i.e., 3-Stage IPAA). Level of Evidence: III; Grade of Recommendation: B

Although there are limited data to date, no single study has demonstrated an increased risk of postoperative complications after subtotal colectomy for patients on anti–TNF-α Ab agents. The largest study (Gu et al) from the Cleveland Clinic only saw an increased risk for patients who underwent 2-stage IPAA procedures.[28] Even the earliest studies that demonstrated increased overall risk included mostly patients who underwent 2-stage procedures (74%–86% of the patients within the 2 studies).[1,58] In the most recent study, Nelson et al[24] showed that a 3-stage approach (subtotal colectomy without IPAA construction), in the presence of an anti–TNF-α Ab agent, was not associated with increased postoperative complications. Specifically, the authors found that in patients on high-dose steroids for severe, acute CUC, and excluding those who underwent IPAA at the time of their colectomy, the addition of anti–TNF-α Ab therapy or cyclosporine A did not increase postoperative complications relative to those who did not receive those additional medications.

The burden of the additional operative procedure in this more conservative approach is aided by several modern surgical technical developments, namely, laparoscopic surgery and enhanced recovery programs (ERP), both of which lead to shorter lengths of stay and decreased complication rates.[59,64] Presently, patients who undergo a minimally invasive 3-stage IPAA with ERP can be expected to have a cumulative length of stay equivalent to a patient who undergoes an open 2-stage IPAA recovered in the conventional manner.[56] Furthermore, the highest risk surgery, which is the creation of the IPAA itself, can then be performed when patients are off all medications, regardless of the medication regimen before total colectomy, and have recovered from the nutritional and metabolic derangements associated with CUC.

For Patients with CUC, Anti–TNF-α Antibody Therapy May Increase Risk of Postoperative Complications After 2-Stage IPAA; Thus, the Decision to Perform 2- versus 3-Stage IPAA Should be Left to the Surgeon's Discretion. Level of Evidence: III; Grade of Recommendation: C

Limited data exist comparing 2- and 3-stage IPAA approaches. A study by Pandey et al[60] showed that 2-stage patients had a higher rate of infectious complications than those who underwent a 3-stage approach. However, a study by Hicks et al[25] showed that among hospitalized patients, outcomes of 2-stage

IPAA were no worse compared to 3-stage IPAA. The preponderance of available evidence for lack of an association between infliximab and postoperative complications is in nonhospitalized patients. The literature and expert opinion support that it is safe to perform a subtotal colectomy. However, it is unclear whether or not it is safe to perform an IPAA procedure, with most literature suggesting that it is safe. Accumulation of risk factors and surgeon experience may be a more important factor than anti–TNF-α Ab therapy by itself.[26] Thus, patients who are solely on anti–TNF-α Ab without any other risk factors can likely safely be managed with a 2-stage procedure.[26] In addition, a pragmatic and safe approach is to schedule elective 2-stage surgery at the time of nadir plasma levels of the agent. Thus, the half-lives of the individual medications, with the knowledge that these medications may not follow first-order elimination kinetics, should be considered. Although the study by Lau et al. did find that higher levels did not correlate with postoperative complications in CUC, the authors postulated that in CUC, drug levels are confounded by disease activity, with worse inflammation leading to more mucosal drug excretion and lower plasma levels. In addition, the subgroup of patients who underwent 2-stage IPAA was underpowered to show an effect.[61]

For Patients with CUC, Anti–TNF-α Antibody Therapy Is an Absolute Contraindication for a 1-Stage IPAA Procedure. Level of Evidence: IV; Grade of Recommendation: D

The vast majority of literature on IPAA is regarding 2- or 3-stage procedures. In the prebiologic era, 1-stage procedures have been shown to be safe especially in the cases of familial adenomatous polyposis, although other centers have not demonstrated similar results.[65] However, in the United States, the vast majority of IPAA procedures are performed as either a 2- or 3-stage procedure, and very limited data on 1-stage procedures in the biologic era exist on which to base recommendations. One study by Eshuis et al[30] show that for 1-stage procedures, anti–TNF-α Ab use was associated with an increased rate of pelvic sepsis, which was increased by 24% relative to anti–TNF-α Ab naive patients; however, this study classified primary pouches with or without ileostomy as a 1-stage procedure rather than delineating some as modified 2-stage procedures. Further supporting the 2-stage approach, if a leak does occur, the pouch loss rate is significant and as high as 50%.[57] Thus, any potential risk factor that putatively increases the anastomotic leak rate or sequelae of the leak, including anti–TNF-α Ab therapy, should represent an absolute contraindication to primary undiverted IPAA creation.

CONCLUSIONS

Controversy exists regarding the relationship between anti–TNF-α Ab agents and the risk of postoperative complications after surgery for IBD. Evidence supports this adverse association in both CD and CUC, with less evidence supporting this association in CD and more evidence supporting this association in CUC. The summation of our recommendations is that for patients requiring elective surgery, a prudent approach is to time the surgery at the nadir of the anti–TNF-α Ab agent and resume it 2 to 4 weeks postoperatively and/or when the surgical wounds are mostly healed unless delay of re-initiation will result in nonresponsiveness to the medication. This measured approach would also be a logical extension for non-IBD surgeries in patients with IBD on anti–TNF therapy. For elective patients, if the anti–TNF-α Ab agent has not been held, the presence of the medication by itself, in the absence of other clinical risk factors, should not necessarily alter surgical management with the exception of single-stage IPAA in which case a 2- or 3-stage IPAA should be performed. For elective patients in the presence of anti–TNF-α Ab agents and additional risk factors, surgical decision-making should be made in an individualized manner and left to the discretion of the surgeon. For patients with CD who require urgent surgery and also have significant additional risk factors for surgical complications and/or are on additional medical therapy (such as corticosteroids and immunomodulators), fecal diversion with either an end ileostomy or protective diverting loop ileostomy is strongly recommended. The evidence supporting these recommendations is weak; thus, the strength supporting this recommendation is moderate at best. Given heterogeneity of study designs, we recommend that future case series and trials should adjust for disease severity and ideally should report adverse postoperative outcomes according to the standardized Clavien-Dindo system. Also in the case of small sample sizes or single institutional series, composite outcomes, which can increase statistical power, should be used.[66] Prospective observational data from the PUCCINI study are anticipated in the next several years and are sorely needed to clarify these concepts and recommendations to provide optimal care to patients with IBD who may require surgical intervention.

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