Management of Biological Therapy Before Elective Inflammatory Bowel Disease Surgeries

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Increasing uptake of biologic therapy has contributed to declining surgical rates for inflammatory bowel disease (IBD). However, a significant number of patients on biologic therapy will go on to require surgery. The literature is conflicted with regard to the preoperative management of biologic therapy before urgent or elective IBD surgery. This article reviews the available data on postoperative complications following preoperative treatment with anti-tumor necrosis factor alpha therapy, anti-integrin therapy, and anti-interleukin therapy.

Key Words: biologic, surgery, Crohn's disease, ulcerative colitis, complications

CASE 1

A 38-year-old female with a 5-year history of Crohn's disease (CD) is referred to your office for obstructive symptoms. She initially presented with ileocolonic inflammation that has been well controlled on 700 mg of infliximab (10 mg/kg) every 6 weeks. However, over the past 8 months, she has been experiencing progressive postprandial nausea, vomiting, and abdominal pain. Cross-sectional imaging shows a terminal ileal stricture measuring 15 cm in length extending proximally from the ileocecal valve with 4-cm small bowel dilation. Lab evaluation demonstrates therapeutic drug levels with no antibodies. She is referred for an elective ileocecal resection. Should her infliximab be discontinued before surgery, and if so, how soon before the surgery date?

CASE 2

You are following a 24-year-old male with a 3-year history of ulcerative colitis (UC) who is a secondary nonresponder to adalimumab with high antibody levels. He travels for work and feels that his disease interferes with his ability to function. He has a cousin with an ileal pouch-anal anastomosis (IPAA) and is now interested in surgery. After meeting with the surgeon, an elective proctocolectomy with ileal pouch-anal anastomosis is planned. Should his surgery be delayed in order for the adalimumab to wash out?

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BACKGROUND

Anti-tumor necrosis factor alpha (anti-TNFα) therapy has revolutionized the management of inflammatory bowel disease (IBD). Since the late 1990s, increasing uptake of anti-TNFα use has paralleled decreasing surgical rates for ulcerative colitis and Crohn's disease.[1–4] Retrospective data suggest that early commencement of anti-TNFα therapy may delay time to surgical intervention in patients with CD. Despite this, it is estimated that one third of CD patients will require surgery within 5 to 10 years of diagnosis.[5–7] In similar fashion, approximately 10% of UC patients will require colectomy within 10 years of diagnosis.[4] Since medical management is the preferred initial approach to controlling disease, a significant proportion of IBD patients on biologic therapy will go on to require surgical management. However, there is a lack of consensus on how to manage patients in the preoperative period as there is controversy on the impact of biological exposure on postoperative morbidity.[8] The current literature consists of heterogeneous studies that have reported conflicting results.[9–12] This field is only expected to become more complex with the introduction of new molecules and disease phenotypes that are resistant to multiple therapeutic modalities.[13] In this article, we aim to discuss the impact of biologic exposure on postoperative complications and propose an algorithm on management of patients who need either urgent or elective surgery.

SURGERY, BIOLOGIC THERAPY, AND THE ASSOCIATED RISKS

Serious complications related to CD surgery include anastomotic leak, abscess development, surgical site infections, intra-abdominal sepsis, bowel obstruction, and fistula formation. Rates of surgical site infections and intra-abdominal sepsis are approximately 5%–%18%[14, 15] and 3%–12%,[10, 16, 17] respectively. When indicated, a laparoscopic surgery performed by a skilled surgeon is preferred. Advantages of the laparoscopic approach include faster recovery and decreased rates of small bowel obstructions.[18, 19] Even with improvements

in perioperative management and the introduction of laparoscopic techniques, rates of overall postoperative complications are still estimated to be 21%–44%.[20–24] For individuals undergoing repeated surgeries, rates of complications such as anastomotic leakage are thought to be higher in subsequent operations.[25]

The most commonly performed surgeries for UC are proctocolectomy with ileal pouch-anal anastomosis (PC-IPAA) and total proctocolectomy with end-ileostomy (TPC-EI).[26] Other surgical procedures that leave the rectum in situ are less frequently performed because of long-term complications such as proctitis and rectal stump malignancy.[27, 28] Both PC-IPAA and TPC-EI can be performed with open or laparoscopic techniques. Long-term outcomes are equivalent; however, the laparoscopic technique is associated with improved short-term outcomes such as decreased hospital stay, infection rates, and lower infertility rates in women.[29–31] Early complications of IPAA can occur in up to one third of patients, with rates of anastomotic leaks and small bowel obstructions estimated to be 6.5%–7.3% and 13%–25%, respectively.[32, 33] Multistep procedures may decrease the risk of pelvic sepsis; however, these benefits are tempered by stoma complications such as peristomal herniation or prolapse.[31, 33]

Tumor necrosis factor alpha (TNFα) and T cells are essential in the early response to tissue injury.[34] Anti-TNFα therapy interferes with the cytokine cascade responsible for the recruitment of local and systemic immune cells to the wound site.[35–37] Vedolizumab (anti-integrin) and ustekinumab (IL-12/23 inhibitor) interfere with the localization and differentiation of T cells, an important step in the healing of intestinal epithelium.[38, 39] There are theoretical concerns that exposure to biologic therapy could have deleterious effects on anastomotic and surgical site healing. Other risk factors for poor postoperative outcomes are reviewed in Table 1.

Varying definitions of drug exposure have been used across studies. Drug administration within 12 weeks of surgery has most commonly been used to determine exposure status; however, drug levels[40] and exposure durations of 8 to 12 weeks before surgery have also been used.[9, 11, 40–44] From a pharmacokinetic perspective, models suggest that the half-life of anti-TNFα therapies is approximately 2 weeks, whereas ustekinumab and vedolizumab have 3-week half-lives[45–47]

Using the last dose of biologic to determine drug exposure may be insufficient to predict the real risk of postoperative infections as pharmacokinetics are influenced by elements such as severe inflammation, low albumin, immunomodulator use, and antidrug antibodies.[48] There is also no data to show that the same ranges used for therapeutic drug monitoring, predicting clinical response, and guiding management of secondary loss of response can be used to predict postoperative complications. As for vedolizumab and ustekinumab, therapeutic targets have not been definitively established.[47]

TABLE 1. Known Risk Factors for Postoperative Complications and Infections

Risk Factors	Complication
Smoking	• Increased likelihood of postoperative disease recurrence[49–51] • Increased risk of postoperative cardiovascular, pulmonary, infectious, and wound complications[52–54]
Hypercoagulabiilty	• IBD patients at moderate to high risk of a venous thromboembolic episode postoperatively[55, 56]
Malnutrition	• Albumin <21g/L associated with 29% risk of mortality at 30 days after noncardiac surgery[57] • Albumin <25 associated with 9% risk of intra-abdominal septic complications postoperatively[58]
Anemia	• Increased risk of postoperative wound complications, longer hospital stay, and mortality[59, 60]
Corticosteroids	• Higher likelihood of all postoperative complications and postoperative infectious complications[61–66]

ANTI-TUMOR NECROSIS FACTOR THERAPY AND POSTOPERATIVE COMPLICATIONS

Crohn's Disease

Colombel et al were one of the first to describe their experience with anti-TNFα therapy and postoperative morbidity.[67] Most procedures were open resections with no differences in outcome observed between patients treated with steroids, immunosuppressants, or anti-TNFα therapy. Subsequent small single-center trials have reported negative associations or no correlation between preoperative biologic therapy and postoperative outcomes.[9, 58, 67–74]

Population-based data on postoperative complication rates in anti-TNFα-exposed CD patients are available from Europe.[10, 75] Using the national Danish Registry, Norgard et al retrospectively evaluated 214 anti-TNFα-exposed persons and 2079 controls.[75] Ileocolic resection with right hemicolectomy was the most common surgery performed in their population. The 30-day mortality and reoperation rates were 2.4% and 9.3%, respectively. Rates of bacteremia, anastomotic leak, reoperation, and death did not differ between exposed and nonexposed groups. Furthermore, the interval between the last anti- TNFα dose and surgery (≤14 days to 84 days) did not seem to influence postoperative outcomes.[75] More recently, conflicting results were reported by a prospective study. Brouquet et al found significantly higher overall postoperative morbidity (odds ratio [OR], 1.99; 95% CI, 1.17–3.39; $P = 0.011$) and intra-abdominal septic complications (OR, 2.22; 95% CI, 1.22–4.04; $P = 0.009$) among anti-TNFα patients undergoing ileocolonic resections for CD.[10] However, the timing of the last

drug administration in relation to the operative date did not have an effect on morbidity. Meta-analyses have also reported increased rates of postoperative infections in persons exposed to anti-TNFα preoperatively (Table 2).[17, 20, 21, 76–79]

The association between anti-TNFα drug levels and surgical outcomes has also been investigated. Lau et al used frozen serum taken within a week before surgery to measure anti-TNFα levels in 217 individuals (123 CD and 94 UC).[40] In the CD cohort, no statistically significant differences in postoperative morbidity or complications were found between those with detectable and undetectable anti-TNFα levels. Significantly increased complication rates related to morbidity (OR, 2.5; $P = 0.03$) and infection (OR, 3.0; $P = 0.03$) were found in persons with drug levels ≥3 μg/mL. However, after adjusting for the albumin level, there was no association between drug levels and postoperative complications.[40] Furthermore, only 3 individuals had anti-TNFα levels <3 ug/mL; thus, the morbidity and readmission findings may be biased by small numbers. Conversely, a study by Fumery et al[44] did not find a correlation between postoperative complications and anti-TNF drug levels. Of the 93 (44%) individuals exposed to infliximab or adalimumab, 76 (82%) had drug levels drawn within 3 months before surgery. The median time from last adalimumab and infliximab administration to surgery was 18 days (range: 9 to 31 days) and 42 days (range: 23 to 78 days), respectively. Anti-TNFα exposure and trough levels were not significantly associated with postoperative complications or morbidity.

Ulcerative Colitis

In general, meta-analysis data suggest that anti-TNFα therapy does not appear to have a significant impact on the postoperative course of UC patients (Table 3).[11, 80, 81] However, the influence of anti-TNFα therapy on IPAA outcomes is ongoing. Some reports suggest that any IPAA procedure (primary vs 2-step) can be negatively impacted by exposure to anti-TNFα, whereas others caution against primary IPAA procedures in persons exposed to anti-TNFα agents.[82–85] Kulaylat et al retrospectively evaluated 2476 index UC operations and found higher rates of 90-day postoperative complications after IPAA procedures among anti-TNFα-exposed patients (45.2% vs 37.6%, $P = 0.02$).[11] Zittan et al compared outcomes of 2-step and 3-step IPAA procedures in persons using anti-TNFα and did not report any advantages to performing 3-step IPAAs with regard to early or late complications. This finding has been reported by other studies.[40, 86] When evaluating the 2-step procedures, the authors stratified the patients via the duration of preoperative biologic exposure (classified as ≤14 days, 15 to 30 days, and 31 to 180 days) and did not find any differences in the likelihood of developing an anastomotic leak. Furthermore, there were no differences seen in the complication rate between those with detectable anti-TNFα levels (mean 5.4 μg/mL) and those with undetectable anti-TNFα levels.[87] Lau et al reported similar findings in their UC cohort.[40] Norgard et al used the Danish National Patient Registry to identify the index surgeries of 1226 UC patients. Of those, 199 individuals were exposed to anti-TNFα within 12 weeks before colectomy with ileostomy (predominantly). No differences in death, reoperation, anastomotic leakage, or abscess drainage at 30 and 60 days were noted between treatment groups.[41] Similar results were seen in a more recent English study that evaluated 6225 UC patients who underwent subtotal colectomy between 2006 and 2015.[88] Anti-TNFα-exposed patients were more likely to be younger,

TABLE 2. Meta-Analysis Data Reporting Overall and Infectious Complications in CD Patients Who Did Versus Did Not Receive Anti-TNFα Before Surgery

	Odds Ratios Comparing Those Treated With Anti-TNFα Before Surgery Versus No Anti-TNFα Before Surgery (95% CI)	
Reference	**Total Complications**	**Infectious Complications**
Kopylov et al, 2012[17]	1.72 (0.93–3.19)	1.50 (1.08–2.08)* (Finding unrelated to local complications such as intra-abdominal sepsis or anastomotic leak)
Narula et al, 2013[21]	2.19 (1.69–2.84)*	1.93 (1.28–2.89)*
Rosenfeld et al, 2013[76]	(OR for major complications including sepsis, anastomotic leak, peritonitis, local fistula or abscess, wound infection) 1.59 (0.89–2.86)	
Billioud et al, 2013[20]	1.31 (0.96–1.77)	1.45 (1.03–2.05)*
El-Hussuna et al, 2013[77]	Fixed effects meta-analysis: 1.25 (1.10–1.43)* Random effects meta-analysis: 1.18 (0.86–1.62)	1.15 (0.86–1.53)
Ahmed et al, 2014[79]	1.16 (0.97–1.40)	1.29 (1.07–1.55)*
Yang et al, 2014[78]	1.45 (1.04–2.02)*	1.47 (1.08–1.99)*

*Denotes a statistically significant finding

TABLE 3. Meta-Analysis Data Reporting Overall and Infectious Complications in UC Patients Who Did Versus Did Not Receive Anti-TNFα Before Surgery

	Odds Ratios Comparing Those Treated With Anti-TNF Before Surgery Versus No Anti-TNFα Before Surgery (95% CI)	
Reference	**Total Complications**	**Infectious Complications**
Billioud et al 2013[20]	UC/IBD-U: 1.32 (0.94–1.84)	UC/IBD-U: 1.31 (0.55–3.07)
Narula et al 2013[21]	1.10 (0.81–1.47)	1.39 (0.56–3.45)
Silvaggi et al 2015[89]	Any surgery type: 1.19 (1.00–1.42) IPAA-related complications: 2.27 (1.27–4.05)*	Any surgery type: 1.12 (0.87–1.45)
Yang et al 2012[90]	1.09 (0.87–1.37)	1.10 (0.51–2.38)

IPAA: Ileal pouch-anal anastomosis (IPAA)
*denotes a statistically significant finding

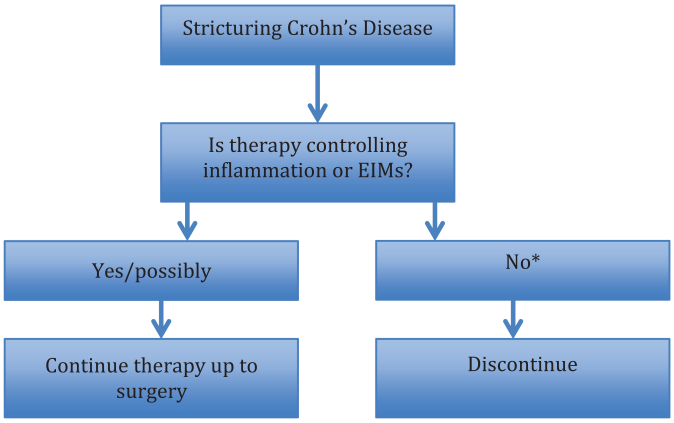

FIGURE 1. Proposed algorithm for the preoperative management of stricturing Crohn's disease. This group would include individuals with primary or secondary nonresponse. In such cases, therapy should be discontinued (drug and antidrug antibody levels may help to establish reason for drug failure).[101]

healthier, and undergo urgent procedures. Complication rates at 4 (12.4% vs 12%, $P = 0.696$) and 12 (12.9% vs 12%, $P = 0.571$) weeks did not differ between treatment groups. Unplanned procedures (OR 1.38; 1.18–1.62) and positive smoking status (OR 1.60; 1.13–2.26) were identified as risk factors for postoperative complications on multivariate analysis.[88] Overall, this information is derived from complete and validated registries, suggesting that postoperative morbidity may be a function of other factors such as nutrition or timing of the procedure rather than rather than anti-TNFα exposure.

Preoperative Vedolizumab and Ustekinumab

Vedolizumab is an α4β7 integrin antibody that blocks trafficking of lymphocytes to the gut. It has shown clinical efficacy in the management of UC and CD.[91, 92] As the α4β7 integrin receptor is only found in the gut endothelium, vedolizumab theoretically may have fewer negative systemic effects but may impact the function of lymphocytes that are integral to wound healing.[93–95] Therefore, there is a theoretical risk that preoperative vedolizumab may increase postoperative morbidity.

Lightner et al retrospectively compared outcomes of 94 IBD patients (22 UC and 71 CD) who received vedolizumab with those receiving anti-TNFα or no biological therapy in the preoperative period and found higher rates of postoperative infections in the vedolizumab group.[96] Specifically, vedolizumab was found to be a significant predictor of skin and soft tissue infections during the 30 days postsurgery ($P < 0.001$). This population was included in a later multicenter retrospective study of 146 vedolizumab-treated patients (46 UC and 97 CD) that found similar results.[42] The increased rates of complications in vedolizumab-treated patients could be reflective of disease severity as these individuals likely had longer durations of refractory disease.[42, 96] Conversely, a growing body of literature does not show an increase in postoperative complications in the vedolizumab group when compared with anti-TNFα users or those naïve to biologic therapy. Most recently, a propensity-matched analysis did not find a significant difference between anti-TNFα and vedolizumab exposed individuals with regard to surgical site infections.[97] Ferrante et al also reported no difference in the rate of postoperative complications between UC persons exposed to anti-TNFα agents and those having received vedolizumab in the preoperative period. All patients exposed to vedolizumab (n = 34) underwent pouch construction (first stage: n = 3; second stage: n = 31). Only 1 stage pouch construction was independently associated with short-term and overall postoperative complications.[12] These data are supported by a study by Yamada et al who did not find significantly different complication rates among patients treated with vedolizumab, anti-TNFα agents, or nonbiologic therapy preoperatively (UC, $P = 0.40$; CD, $P = 0.35$).[98]

According to the systematic review and meta-analysis performed by Law et al,[99] vedolizumab-treated IBD patients are not at significantly increased risk of postoperative infectious or overall complications when compared with individuals unexposed to biologic therapy. Similar findings were also found when comparing anti-TNFα-exposed persons with

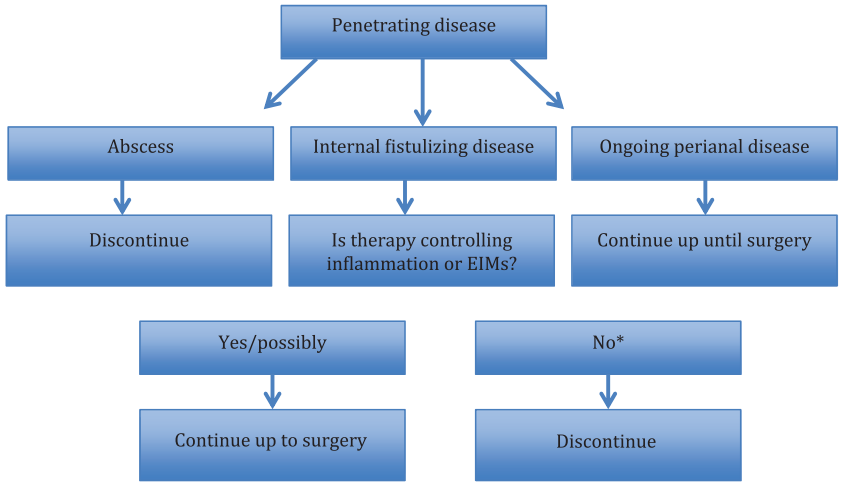

FIGURE 2. Proposed algorithm for the preoperative management of penetrating Crohn's disease. This group would include individuals with primary or secondary nonresponse. In such cases, therapy should be discontinued (drug and antidrug antibody levels may help to establish reason for drug failure).[102]

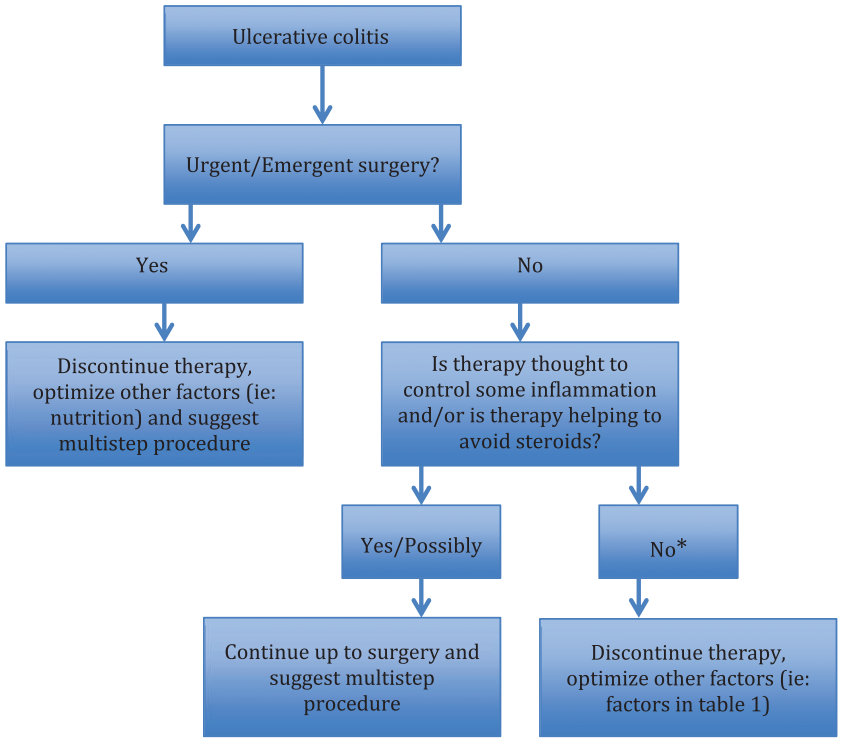

FIGURE 3. Proposed algorithm for the preoperative management of ulcerative colitis. This group would include individuals with primary or secondary nonresponse. In such cases, therapy should be discontinued (drug and antidrug antibody levels may help to establish reason for drug failure).[102]

vedolizumab-exposed persons. A second meta-analysis has confirmed these findings and even suggests that the risk of overall complications in UC patients treated with vedolizumab may be lower when compared with those with anti-TNFα exposure (OR, 0.35; 95% CI, 0.14–0.85).[100]

As for ustekinumab, Lightner et al are the only group to have reported post-operative outcomes among ustekinumab treated patients.[43] They retrospectively compared 44 ustekinumab-treated and 169 anti-TNFα-treated CD patients and did not find any difference in postoperative surgical site infections

between groups (13% vs 20%, respectively). More data on ustekinumab are eagerly awaited.

Recommended Preoperative Management of Cases

The CD patient in case 1 has long segment fibrostenotic disease that will not improve with further drug administration. Although it can be difficult to ascertain the degree of fibrotic to inflammatory disease, the prestenotic small bowel dilation does suggest a fixed stricture that would only be amenable to resection. Thus, infliximab could be discontinued before surgery. Similiarly, in case 2, the patient is a secondary nonresponder who would not derive any benefit from continued adalimumab administration.[102] In this instance, the biologic should be discontinued once the decision for surgery has been made to minimize any potential consequences of drug exposure. However, biologic therapy could be continued up until surgery in individuals with EIMs. There are also patients where surgery is indicated but the biologic therapy has controlled inflammatory disease in other intestinal sites. This may be another situation where the biologic therapy is continued up until surgery. The preoperative management of CD and UC are outlined in Figs. 1–3.

SUMMARY AND CONCLUSIONS

Use of preoperative biologic therapy has not been consistently established as a cause of increased postoperative complications, though it is physiologically plausible that biologics could interfere with the healing process.[93–95, 103, 104] It is clear that interrupting biologic therapy is an appropriate strategy when elective surgery is planned and there is no additional benefit of continuing the biologic. For Crohn's disease, there may be a benefit to continuing therapy in patients with an inflammatory component to their disease or ongoing perianal involvement (Figs. 1 and 2). In such cases, controlling inflammation may assist with improving other factors such as nutrition and anemia, thereby decreasing the risk of complications. As many CD patients will require therapy after surgery, it could be beneficial to schedule surgery in the middle of an 8-week dosing interval. In ulcerative colitis, patients are generally going to surgery only after failure of biologic treatment, and there may not be time to allow the biologic to wash out because of the need for urgent surgery. We would not delay surgery because of biologic exposure and would recommend a multistep IPAA in this scenario (Fig. 3). Furthermore, individuals deriving benefit from biologics before surgery can be maintained on therapy before a multistep IPAA.

Discussions regarding surgery and managing expectations of medical therapy are integral to the patient's care plan and should be discussed earlier in the disease course. Late communication regarding the need for surgery can hinder timely access to operations. Ultimately, decisions regarding medical management preoperatively cannot be made in isolation and require close collaboration between the patient, gastroenterologist, and surgeon.

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