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Prospective Cohort Study to Investigate the Safety of Preoperative Tumor Necrosis Factor Inhibitor Exposure in Patients With Inflammatory Bowel Disease Undergoing Intra-abdominal Surgery

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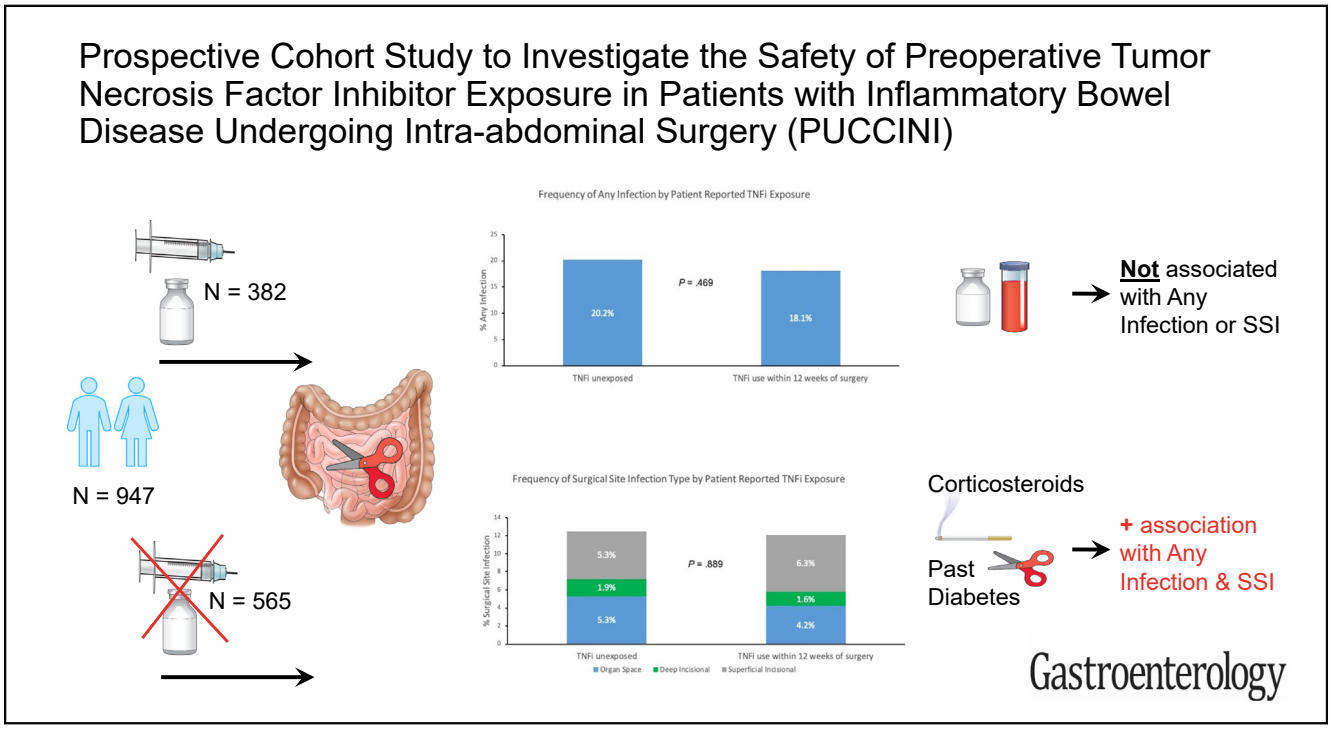

See editorial on page 44.

BACKGROUND & AIMS: Whether preoperative treatment of inflammatory bowel disease (IBD) with tumor necrosis factor inhibitors (TNFis) increases the risk of postoperative infectious complications remains controversial. The primary aim of this study was to determine whether preoperative exposure to TNFis is an independent risk factor for postoperative infectious complications within 30 days of surgery. **METHODS:** We conducted a multicenter prospective observational study of patients with IBD undergoing intra-abdominal surgery across 17 sites from the Crohn's & Colitis Foundation Clinical Research Alliance. Infectious complications were categorized as surgical site infections (SSIs) or non-SSIs. Current TNFi exposure was defined as use within 12 weeks of surgery, and serum was collected for drug-level analyses. Multivariable models for occurrence of the primary outcome, any infection, or SSI were adjusted by predefined covariates (age, sex, preoperative steroid use, and disease type), baseline variables significantly associated ($P < .05$) with any infection or SSI separately, and TNFi exposure status. Exploratory models used TNFi exposure based on serum drug concentration. **RESULTS:** A total of 947 patients were enrolled from September 2014 through June 2017. Current TNFi exposure was reported by 382 patients. Any infection (18.1% vs 20.2%, $P = .469$) and SSI (12.0% vs 12.6%, $P = .889$) rates were similar in patients currently exposed to TNFis and those unexposed. In multivariable analysis, current TNFi exposure was not associated with any infection (odds ratio, 1.050; 95% confidence interval, 0.716–1.535) or SSI (odds ratio, 1.249; 95% confidence interval, 0.793–1.960). Detectable TNFi drug concentration was not associated with any infection or SSI. **CONCLUSIONS:** Preoperative TNFi exposure was not associated with postoperative infectious complications in a large prospective multicenter cohort.

Keywords: Crohn's Disease; Ulcerative Colitis; Surgery; Infection; Tumor Necrosis Factor Inhibitor.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

The postoperative infectious risk of preoperative tumor necrosis factor inhibitor use has been controversial due to the lack of large prospective cohort studies allowing for control of confounding risk factors and limited studies exploring exposure defined by serum drug concentrations.

NEW FINDINGS

In the largest multicenter prospective surgical cohort on the topic, PUCCINI (*P*rospective Cohort of *U*lcerative *C*olitis and *C*rohn's Disease Patients Undergoing Surgery to Identify Risk Factors for Post-Operative *IN*fection *I*) showed that neither patient-reported use of tumor necrosis factor inhibitors within 12 weeks of surgery nor detectable serum drug concentrations were independent risk factors for any postoperative infection or surgical site infection.

LIMITATIONS

Study limitations include nonconsecutive patient enrollment and that the observations may already reflect prejudice in surgical decision making such as approach and timing of surgery.

IMPACT

Preoperative use of tumor necrosis factor inhibitors should not affect surgical decisions in most patients with inflammatory bowel disease.

Current therapies for inflammatory bowel disease (IBD) focus on immunosuppression, and studies have shown combination therapy using both tumor necrosis factor inhibitors (TNFis) and thiopurines is one of the most effective approaches for both moderate to severe ulcerative colitis (UC) and Crohn's disease (CD).[1,2] Despite the use of more effective therapies, the risk of requiring surgery remains high in the biologic era.[3–5] Data from referral center cohorts have shown that up to 50% of patients are exposed to TNFis before their first surgery.[6] There is concern that preoperative treatment with immunosuppressive medications, including TNFis, increases the risk of potential postoperative infectious complications. While the literature is consistent in showing that corticosteroid use before surgery increases the risk of postoperative infectious complications,[7–9] the evidence regarding TNFis remains inconsistent.

Over the last 2 decades, numerous retrospective studies have been published, with some showing an increased risk of postoperative complications or infection associated with preoperative TNFi exposure[10–19] and others showing no increased risk.[20–43] In addition to a retrospective design, limitations of these studies have included being mostly single-institution experiences, difficulty controlling for disease severity, confounding effect of concomitant immunosuppressive therapy, including steroids, variable complications studied, and differing definitions of TNFi exposure. A 2020 Cochrane review of the available literature found an association of preoperative TNFi use with postoperative total infection (odds ratio [OR], 1.60; 95% confidence interval [CI], 1.20–2.13), but the certainty of evidence was very low, and the authors stated that no firm conclusions could be drawn about their safety in the perioperative period.[44]

Two prospective French cohorts, Groupe d'Etude Thérapeutique des Affections Inflammatoires du Tube Digestif (GETAID) Chirurgie cohort and Groupe de **Re**cherche sur les **M**aladies **in**flammatoires **d**igestives (REMIND), have assessed for an association of preoperative TNFi use with

Abbreviations used in this paper: **ADA, adalimumab; CD, Crohn's disease; CI, confidence interval; IBD, inflammatory bowel disease; IFX, infliximab; GETAID, Groupe d'Etude Thérapeutique des Affections Inflammatoires du Tube Digestif; LLoQ, lower limit of quantitation; OR, odds ratio; PUCCINI, *P*rospective Cohort of *U*lcerative *C*olitis and *C*rohn's Disease Patients Undergoing Surgery to Identify Risk Factors for Post-Operative *IN*fection *I*; SSI, surgical site infection; TNFi, tumor necrosis factor inhibitor; UC, ulcerative colitis.**

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postoperative infectious complications after ileocolic resection for CD, with conflicting results.[45,46] The larger GETAID Chirurgie cohort found an association of TNFi use <3 months before ileocolic resection for CD with 30-day postoperative morbidity and mortality as well as intra-abdominal septic morbidity, but did not assess serum drug exposure. TNFi serum drug exposure association with postoperative complication has only been assessed in 2 retrospective studies[43,47] and 1 prospective study (n = 76 exposed).[46]

We sought to determine whether preoperative TNFi exposure is an independent risk factor for infectious complications in patients with IBD undergoing intra-abdominal surgery. The secondary aim was to explore the association of serum TNFi drug exposure with postoperative infectious complications.

Materials and Methods

Study Design

The *P*rospective Cohort of *U*lcerative *C*olitis and *C*rohn's Disease Patients Undergoing Surgery to Identify Risk Factors for Post-Operative *IN*fection *I* (PUCCINI) was a multicenter prospective observational study that enrolled patients undergoing intra-abdominal surgery for IBD with the primary aim to determine whether preoperative exposure to TNFis is an independent risk factor for postoperative infectious complications within 30 days of surgery (ClinicalTrials.gov, number NCT02054533).

Study Setting and Participants

Patients with confirmed IBD were enrolled between September 2014 through June 2017 from 17 participating sites among the Crohn's & Colitis Foundation Clinical Research Alliance. The participating sites were academic centers diverse in size, geography, and patient population. The inclusion criteria were as follows: (1) age ≥18 years at entry; (2) diagnosis of CD, UC, or indeterminate colitis by standard criteria; (3) planned to have intra-abdominal surgery or underwent intra-abdominal surgery in the preceding 4 days; and (4) ability to provide written informed consent. Exclusion criteria included (1) current enrollment in a clinical trial of an investigational therapy for IBD; (2) surgery performed to repair a complication from a recent surgery within 90 days; and (3) inability or unwillingness to provide informed consent. Institutional Review Boards at each site approved the study, and written informed consent was obtained.

Data Collection

Patients were screened between 1 month before surgery and up to 4 days postoperatively to ensure capture of patients who may have had urgent or emergent operations. Demographic information, disease history, preoperative medication use, comorbidities via the Self-Administered Comorbidity Questionnaire,[48] and other relevant medical information was obtained through both structured patient interview and medical record abstraction at baseline. Additional medical record abstraction was performed for operative details, postoperative risk factors, and infectious and noninfectious outcomes at patient discharge and 30 days postoperatively. Patients were also contacted by structured telephone interview at 30 days postoperatively to assess for outcomes, including infections that may not have been captured in the medical record. The subsites obtained supportive documentation as needed to confirm infectious outcomes.

Serum Collection and Testing

Serum was obtained from patients at their baseline visit and stored locally at the sites at −80°C until the conclusion of the study. Serum drug concentrations and antidrug antibody concentrations were measured for infliximab (IFX) and adalimumab (ADA) with a drug-tolerant homogenous mobility shift assay (Prometheus Laboratories Inc, San Diego, CA). Serum drug concentration testing was performed in patients with current IFX or ADA use (≤12 weeks from surgery) and in some patients with past use of IFX or ADA (≤6 months of surgery). Testing was not available for certolizumab or golimumab concentrations.

Outcomes

Surgical site infections (SSIs) were defined by Centers for Disease Control and Prevention criteria and classified as superficial incisional, deep incisional, or organ/space infections.[49] All other postoperative infections were defined as non-SSIs and classified as sepsis, bacteremia, pneumonia, urinary tract infection, fever >101.5°F without an identifiable source, or other. The primary outcome was occurrence of any infection (SSI or non-SSI) within 30 days of surgery. Secondary outcomes included SSI, hospital readmission within 30 days of surgery, reoperation within 30 days of surgery, 30-day postoperative mortality, duration of postoperative hospitalization, thrombotic complication within 30 days of surgery, and hypomotility complication (ileus >5 days or small-bowel obstruction). Outcomes were assessed by review of the medical record at discharge and 30 days postoperatively as well as by telephone interview with the patient 30 days postoperatively.

Tumor Necrosis Factor Inhibitor Exposure Definitions

The prespecified primary definition of TNFi exposure was patient-reported use of a TNFi within 12 weeks before surgery. Patients with TNFi exposure >12 weeks from surgery or never having used a TNFi were considered unexposed in the primary analysis. Secondary analyses were performed to examine the effects of perioperative serum TNFi drug levels on the outcomes of interest. Serum TNFi exposure was explored by using the commercial assay lower limit of quantitation (LLoQ) for IFX and ADA assays as detectable and also separately by using a level >0 μg/mL as detectable. Patients were classified as having an undetectable serum TNFi drug level using the commercial assay LLoQ if their IFX level was <1 μg/mL, ADA level was <1.6 μg/mL, or they had not used any TNFi within 180 days of surgery. In a second definition, serum TNFi exposure definition was defined as having an undetectable serum TNFi drug level if the measured level was 0 μg/mL or no administration of a TNFi within 180 days of surgery. Patients with past use of a TNFi >180 days from surgery were considered to have undetectable levels for the analyses even if serum levels were not available for analysis. The 180-day cutoff was chosen, based

on a reported median half-life of 7.7 to 9.5 days for IFX[50] and a mean of 2 weeks for ADA,[51] to avoid any potential misclassification of an exposure as undetectable. Sensitivity analyses were performed using a 120-day cutoff.

Statistical Analysis

The primary analysis was to determine the independent contribution of TNFi exposure during the preoperative period (patient-reported TNF use within 12 weeks of surgery) to the development of any infection (dichotomized as yes/no) within 30 days after surgery. The secondary analysis was to determine the independent contribution of TNFi exposure to development of a SSI. A logistic regression of the binary response variable, rate of any infection (yes/no), on the binary independent variable, patient-reported TNFi exposure (yes/no), with a sample size of 821 observations (of which 60% are in the TNFi-unexposed group and 40% are in the TNFi-exposed group) achieves 80% power at a 0.05 significance level to detect a change in the probability of infection at 30 days from the baseline value of 10% to 17%. While the literature was conflicted on the true infectious risk associated with TNFi exposure, these estimates were based on 2 of the more commonly quoted studies at the time the study was conceived.[16,38] For the multivariable models, at least 10 patients with infection were estimated to be needed for each covariate in the multivariable model to maintain validity.[52–54]

Continuous variables are reported as the mean (range) or the median (interquartile range [IQR]), and categorical variables are reported as the number (percentage). Continuous variables were compared using the Wilcoxon test. Categorical variables were compared using the χ^2 or Fisher exact test, as appropriate.

Univariable logistic regression was performed to identify predictors of the primary outcome, any infection, as well as SSI. Multivariable models for occurrence of any infection or SSI were adjusted by predefined "core" covariates (age, sex, preoperative corticosteroid use, and disease type), any baseline variable found to be significantly associated ($P < .05$) with any infection or SSI separately, as well as patient-reported TNFi exposure status. Separate exploratory models were created using TNFi exposure based on serum drug concentration as outlined in the TNFi exposure definitions. Final models were selected through a machine learning (random forest) method. In the serum analyses, dose effect was assessed by comparing serum drug concentration quartiles.

All analyses were performed using R 4.0.3 software (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient Characteristics

The cohort's demographic and clinical characteristics at the time of intra-abdominal surgery are described in Table 1. A total of 947 patients, including 453 women (47.8%), were enrolled from September 2014 through June 2017. As expected, the patients were young and had few comorbid conditions, most commonly anemia or other blood disease or depression. More than two-thirds of the cohort had a diagnosis of CD. The median disease duration was 10 years (IQR, 4–18 years). Prior bowel resection was reported by 326 patients (34.4%), with an additional 166 patients (17.5%) reporting prior abdominal surgery without a bowel resection. Active smoking at the time of surgery was reported by 94 patients (9.9%). The median body mass index was 24.28 kg/m^2 (IQR, 21.43–27.70 kg/m^2). Poor preoperative nutritional status, defined as weight loss of >10% of body weight, was present in 128 patients (13.5%), and 54 patients (5.7%) were on total parenteral nutrition preoperatively.

Medication Exposures

Medication exposures of the cohort are summarized in Table 2. Notably, 387 patients (40.9%) had used systemic corticosteroids within 2 weeks of surgery. Thiopurine use was reported by 235 patients (24.8%) and methotrexate use by 74 patients (7.8%) in the month before surgery. Antibiotics were used within 2 weeks of surgery by 401 patients (42.3%). Vedolizumab and ustekinumab were approved for treatment of IBD during the study and used within 12 weeks of surgery by 136 patients (14.4%) and 21 patients (2.2%), respectively.

Tumor Necrosis Factor Inhibitor Exposures

A total of 382 patients (40.3%) reported use of at least 1 TNFi within 12 weeks of surgery. Most of the patients exposed to a TNFi before surgery used ADA (n = 183) or IFX (n = 165), with far fewer using certolizumab (n = 44) or golimumab (n = 10). Among patients not using TNFis within 12 weeks of surgery, 224 patients (23.7%) were TNFi naïve and 341 patients (36.0%) reported past use of TNFis. Patients exposed to TNFis within 12 weeks of surgery differed significantly from unexposed patients in age (39 vs 43 years, $P < .001$), disease duration (11 vs 14 years, $P < .001$), prior bowel resection (28% vs 39%, $P = .001$), prior hospital admission within 30 days (22% vs 15%, $P = .009$), Self-Administered Comorbidity score (1.10 vs 1.39, $P = .001$), and preoperative albumin (3.62 vs 3.79 g/dL, $P = .001$).

Serum TNFi drug concentrations were checked in 322 patients, of whom 280 patients had reported TNFi use within 12 weeks of surgery. The commercial assay LLoQ threshold for detectability showed 213 patients (22.5%) had a detectable TNFi level perioperatively. When any drug concentration >0 μg/mL was used as the threshold for detectability, 244 patients (25.8%) had a detectable TNFi level perioperatively. Among the 280 patients reporting TNFi use within 12 weeks of surgery in whom serum drug levels were available, 208 (74.3%) had detectable levels perioperatively when the commercial assay LLoQ threshold for detectability was used, and 234 (83.6%) had detectable levels perioperatively when any drug concentration >0 μg/mL was used as the threshold for detectability. Serum drug levels were unavailable for 102 patients who had reported TNFi use within 12 weeks of surgery. In patients with past use of a TNFi >12 weeks before surgery for whom perioperative drug levels were available, 5 patients had detectable levels when the commercial assay LLoQ threshold for detectability was used, and 10 patients had

Table 1. Demographic and Disease Characteristics of Cohort

Variable	Overall (N = 947)	CD		UC	
		TNFi use within 12 weeks of surgery		TNFi use within 12 weeks of surgery	
		No (n = 368)	Yes (n = 272)	No (n = 197)	Yes (n = 110)
Age, *y*	39 (29–53)	39 (30–52)	35 (27–49)	45 (33–57)	35 (27–53)
Male sex	494 (52.2)	187 (50.8)	135 (49.6)	113 (57.4)	59 (53.6)
Disease duration, *y*	10 (4–18)	13 (6–20)	10 (4–18)	9 (4–18)	4 (2–11)
UC disease location		…	…		
Proctitis	18 (1.9)			16 (8.1)	2 (1.8)
Left side	55 (5.8)			33 (16.8)	22 (20.0)
Extensive	233 (24.6)			148 (75.1)	85 (77.3)
Not available	1 (0.1)			0 (0.0)	1 (0.9)
CD disease location				…	…
Ileum	242 (25.6)	125 (34.0)	117 (43.0)		
Colon	89 (9.4)	65 (17.7)	24 (8.8)		
Ileum and colon	305 (32.2)	175 (47.6)	130 (47.8)		
Not available	4 (0.4)	3 (0.8)	1 (0.4)		
Upper gastrointestinal tract CD	36 (3.8)	21 (5.7)	15 (5.5)	0 (0.0)	0 (0.0)
Perianal CD	108 (11.4)	71 (19.3)	37 (13.6)	0 (0.0)	0 (0.0)
CD disease behavior					
Nonstricturing, nonpenetrating	385 (40.7)	51 (13.9)	27 (9.9)		
Stricturing	285 (30.1)	164 (44.6)	121 (44.5)		
Penetrating	109 (11.5)	65 (17.7)	44 (16.2)		
Stricturing and penetrating	165 (17.4)	85 (23.1)	80 (29.4)		
Not available	3 (0.3)	3 (0.8)	0 (0.0)		
Prior abdominal surgery					
No prior abdominal surgery	453 (47.8)	130 (35.3)	123 (45.2)	113 (57.4)	87 (79.1)
Abdominal surgery without bowel resection	166 (17.5)	59 (16.0)	48 (17.6)	43 (21.8)	16 (14.5)
Prior bowel resection	326 (34.4)	177 (48.1)	101 (37.1)	41 (20.8)	7 (6.4)
Not available	2 (0.2)	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Current smoker	94 (9.9)	56 (15.2)	26 (9.6)	7 (3.6)	5 (4.5)
ASA status					
I–II	529 (55.9)	222 (60.3)	145 (53.3)	101(51.3)	61(55.5)
III–V	417 (44.0)	146 (39.7)	126 (46.3)	96 (48.7)	49(44.5)
Not available	1 (0.1)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)

Table 1. Continued

Variable	Overall (N = 947)	CD		UC	
		TNFi use within 12 weeks of surgery		TNFi use within 12 weeks of surgery	
		No (n = 368)	Yes (n = 272)	No (n = 197)	Yes (n = 110)
Body mass index, *kg/m²*	24.28 (21.43–27.70)	23.73 (21.09–27.38)	24.28 (21.44–27.44)	24.68 (22.32–28.00)	24.27 (21.14–27.87)
Weight loss >10% body weight	128 (13.5)	55 (14.9)	29 (10.7)	23 (11.7)	21 (19.1)
Pre-op median length of stay					
0 days	722 (76.2)	304 (82.6)	203 (74.6)	156 (79.2)	59 (53.6)
1-3 days	90 (9.5)	30 (8.2)	28 (10.3)	18 (9.1)	14 (12.7)
≥4 days	132 (13.9)	34 (9.2)	39 (14.3)	23 (11.7)	36 (32.7)
Not available	3 (0.3)	0 (0.0)	2 (0.7)	0 (0.0)	1 (0.9)
Transfer from another hospital	36 (3.8)	10 (2.7)	12 (4.4)	4 (2.0)	10 (9.1)
Prior hospital admission within 30 days	167 (17.6)	67 (18.2)	50 (18.4)	17 (8.6)	33 (30.0)
Associated comorbidity					
Anemia or other blood disease	251 (26.5)	115 (31.2)	52 (19.1)	51 (25.9)	33 (30.0)
Depression	160 (16.9)	64 (17.4)	48 (17.6)	29 (14.7)	19 (17.3)
Hypertension	114 (12.0)	38 (10.3)	25 (9.2)	34 (17.3)	17 (15.5)
Osteoarthritis/degenerative arthritis	86 (9.1)	37 (10.1)	24 (8.8)	18 (9.1)	7 (6.4)
History of deep vein thrombosis	54 (5.7)	15 (4.1)	11 (4.0)	19 (9.6)	9 (8.2)
Heart disease	38 (4.0)	9 (2.4)	8 (2.9)	16 (8.1)	5 (4.5)
Rheumatoid arthritis	37 (3.9)	21 (5.7)	6 (2.2)	9 (4.6)	1 (0.9)
Diabetes	34 (3.6)	10 (2.7)	7 (2.6)	12 (6.1)	5 (4.5)
Kidney disease	31 (3.3)	14 (3.8)	2 (0.7)	11 (5.6)	4 (3.6)
History of cancer	30 (3.2)	12 (3.3)	6 (2.2)	12 (6.1)	0 (0.0)
Lung disease	24 (2.5)	8 (2.2)	6 (2.2)	5 (2.5)	5 (4.5)
Liver disease	21 (2.2)	9 (2.4)	2 (0.7)	6 (3.0)	4 (3.6)
History of pulmonary embolus	20 (2.1)	4 (1.1)	5 (1.8)	8 (4.1)	3 (2.7)
Self-Administered Comorbidity score					
0	327 (34.5)	120 (32.6)	114 (41.9)	54 (27.4)	39 (35.5)
1–2	465 (49.1)	175 (47.6)	123 (45.2)	110 (55.8)	57 (51.8)
≥3	154 (16.3)	72 (19.6)	35 (12.9)	33 (16.8)	14 (12.7)
Not available	1 (0.1)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Pre-op disease features/intervention					
Total parenteral nutrition	54 (5.7)	20 (5.4)	22 (8.1)	5 (2.5)	7 (6.4)
Fever	33 (3.5)	6 (1.6)	14 (5.1)	2 (1.0)	11 (10.0)
Clostridium difficile infection	27 (2.9)	9 (2.4)	4 (1.5)	3 (1.5)	11 (10.0)
Nonabdominal infection	44 (4.6)	18 (4.9)	14 (5.1)	6 (3.0)	6 (5.5)
Abscess	98 (10.3)	55 (14.9)	40 (14.7)	2 (1.0)	1 (0.9)
Abscess drainage	43 (4.5)	26 (7.1)	15 (5.5)	0 (0.0)	2 (1.8)
Toxic megacolon or free perforation	28 (3.0)	14 (3.8)	7 (2.6)	4 (2.0)	3 (2.7)

Table 1. Continued

Variable	Overall (N = 947)	CD		UC	
		TNFi use within 12 weeks of surgery		TNFi use within 12 weeks of surgery	
		No (n = 368)	Yes (n = 272)	No (n = 197)	Yes (n = 110)
Pre-op laboratory values					
Hemoglobin, *g/dL*	12.3 (10.78–13.83)	12.5 (10.90–13.90)	12.4 (10.90–13.90)	12.2 (11.20–14.00)	11.4 (9.65–12.90)
White blood cells, */mm*^{3}	7900 (6100–10,300)	8100 (6200–10,300)	7600 (6000–10,190)	8039 (6100–10,450)	8699 (6700–11,100)
Platelets, */mm*^{3}	308,500 (240,000–389,000)	304,000 (244,250–373,000)	291,000 (234,500–371,750)	312,000 (231,000–395,000)	381,000 (281,000–471,500)
Albumin, *g/dL*	3.8 (3.30–4.20)	3.9 (3.40–4.20)	3.85 (3.40–4.20)	3.95 (3.42–4.30)	3.5 (2.80–3.98)
Creatinine, *mg/dL*	0.8 (0.70–1.00)	0.8 (0.70–1.00)	0.8 (0.70–0.90)	0.8 (0.70–1.00)	0.8 (0.70–0.95)

NOTE: Data are presented as median (quartile 1–quartile 3) or as n (%).
ASA, American Society of Anesthesiologists Physical Status Classification; Pre-op, preoperative.

detectable levels perioperatively when any drug concentration >0 μg/mL was used as the threshold for detectability. Detectable antibodies to IFX or ADA were identified in 28 patients.

Surgical Factors

Characteristics of the surgery are described in Table 3. Surgery was performed on an urgent/emergent basis within 24 hours of admission in 14 patients (1.5%). The surgical approach was laparoscopic in 605 patients (63.9%). Bowel resection was performed in 905 patients (95.6%), with a bowel anastomosis created in 584 patients (61.7%). A total colectomy was performed in 330 patients (34.8%), with an ileoanal pouch created in 78 patients (8.2%). A stoma was created or revised in 454 patients (47.9%). Surgical blood loss was >250 mL in 115 patients (12.1%), with 53 patients (5.6%) requiring at least 1 unit of blood transfused.

Postoperative Infectious Outcomes

There was no difference in the primary outcome of any postoperative infection between patients reporting TNFi use within 12 weeks of surgery and those not using a TNFi preoperatively (18.1% vs 20.2%, $P = .469$). Similarly, there was no difference in SSI between patients reporting TNFi use within 12 weeks of surgery and those not using TNFi preoperatively (12.0% vs 12.6%, $P = .889$). No significant differences were present in the distribution of SSIs by preoperative TNFi use (Figure 1*A* and Supplementary Table 1).

When TNFi drug exposure was defined as having a serum drug concentration above the commercial assay LLoQ threshold, there was no difference between TNFi-exposed vs TNFi-unexposed patients in the rate of any infection (18.8% vs 19.7%, $P = .873$) or SSI (12.7% vs 11.8%, $P = .814$). Similarly, when TNFi drug exposure was defined as having a serum drug concentration >0 μg/mL, there was no difference between TNFi-exposed vs TNFi-unexposed patients in the rate of any infection (18.0% vs 20.1%, $P = .861$) or SSI (11.9% vs 12.1%, $P = .998$). Distributions of SSIs by TNFi exposure using serum drug concentrations were similar (Figure 1*B* and *C* and Supplementary Table 1). Any infection and SSI outcomes by TNFi exposure type are summarized in Supplementary Table 1. Sensitivity analyses including patients with last use of TNFi >120 days from surgery defined as undetectable when drug concentration results were unavailable yielded similar results (Supplementary Table 2).

Univariable and Multivariable Analyses for Any Infection

Results of univariable logistic regression for any infection are available in Supplementary Table 3. Important covariates not associated with any infection postoperatively in univariable analysis include the study site, preoperative weight loss >10% body weight, preoperative albumin, preoperative hemoglobin, immunomodulator or methotrexate use in the last month, antibiotic use within 2 weeks of surgery, preoperative abscess, creation of an ileal pouch-anal anastomosis, type of bowel resection, creation of an

Table 2. Preoperative Medication Exposures

		CD		UC	
		TNFi use within 12 weeks of surgery		TNFi use within 12 weeks of surgery	
Variable	Overall (N = 947)	No (n = 368)	Yes (n = 272)	No (n = 197)	Yes (n =110)
Budesonide	108 (11.4)	46 (12.5)	36 (13.2)	18 (9.1)	8 (7.3)
Corticosteroids	387 (40.9)	128 (34.8)	92 (33.8)	91 (46.2)	76 (69.1)
Stress dose corticosteroids	566 (59.8)	208 (56.5)	156 (57.4)	125 (63.5)	77 (70.0)
Thiopurines	235 (24.8)	84 (22.8)	87 (32.0)	37 (18.8)	27 (24.5)
Methotrexate	74 (7.8)	23 (6.2)	28 (10.3)	13 (6.6)	10 (9.1)
Natalizumab	4 (0.4)	4 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)
Cyclosporine	10 (1.1)	3 (0.8)	1 (0.4)	4 (2.0)	2 (1.8)
Ustekinumab	21 (2.2)	15 (4.1)	3 (1.1)	3 (1.5)	0 (0.0)
Vedolizumab	136 (14.4)	71 (19.3)	6 (2.2)	50 (25.4)	9 (8.2)
Opioid pain medications	321 (33.9)	129 (35.1)	100 (36.8)	56 (28.4)	36 (32.7)
Antibiotics	401 (42.3)	171 (46.5)	130 (47.8)	59 (29.9)	41 (37.3)

NOTE: Data are presented as n (%).

anastomosis, or formation of a stoma. Results of multivariable logistic regression for any infection, including the primary definition of TNFi exposure (patient-reported use within 12 weeks of surgery), are reported in Table 4.

TNFi use was not independently associated with any infection. Covariates independently associated with any infection included age, preoperative corticosteroid use, history of bowel resection, current smoking, history of anemia or other blood disorders,[48] diabetes,[48] depression,[48] rheumatoid arthritis,[48] genitourinary fistula, ureteral stent placement, and preoperative nonabdominal infection. Preoperative budesonide use was inversely associated with any infection. Sensitivity analyses of current and past TNFi use compared with those who were TNFi naïve did not find any association of current or past TNFi use with any infection on univariable (Supplementary Table 3) or multivariable analysis.

Detectable serum TNFi concentration using the commercial assay LLoQ threshold for detectability or any level >0 μg/mL was not independently associated with any infection postoperatively (Supplementary Tables 4 and 5). A separate multivariable analysis comparing quartiles of serum TNFi drug concentration exposure (undetectable, 0.1–4.4 μg/mL, 4.5–11.7 μg/mL, and >11.7 μg/mL) did not demonstrate any independent association of drug level with any infection (Supplementary Table 6). Detectable antibodies to IFX or ADA were not associated with any infection on univariable analysis (Supplementary Table 3).

Univariable and Multivariable Analyses for Surgical Site Infection

Results of univariable logistic regression for SSI are available in Supplementary Table 7. Important covariates not associated with SSI postoperatively in univariable analysis include study site, preoperative weight loss >10% body weight, preoperative albumin, preoperative hemoglobin, immunomodulatory or methotrexate use in the last month, antibiotic use within 2 weeks of surgery, preoperative abscess, creation of an ileal pouch-anal anastomosis, type of bowel resection, creation of an anastomosis, or formation of a stoma.

Covariates independently associated with SSI include preoperative corticosteroid use, history of bowel resection, diabetes,[48] hypertension,[48] and current smoking (Table 5). Sensitivity analyses of current and past TNFi use compared with those who were TNFi naïve did not find any association of current or past TNFi use with SSI on univariable (Supplementary Table 7) or multivariable analysis. Detectable serum TNFi concentration using the commercial assay LLoQ threshold for detectability or any level >0 μg/mL was not independently associated with any infection postoperatively (Supplementary Tables 8 and 9). A separate multivariable analysis comparing quartiles of serum TNFi drug concentration exposure (undetectable, 0.1–4.4 μg/mL, 4.5–11.7 μg/mL, and >11.7 μg/mL) did not demonstrate any independent association of drug level with SSI (Supplementary Table 10). Detectable antibodies to IFX or ADA were not associated with SSI on univariable analysis (Supplementary Table 7).

Secondary Noninfectious Postoperative Outcomes

Noninfectious postoperative outcomes are reported in Table 6. More patients reporting TNFi use within 12 weeks of surgery developed a postoperative venous thromboembolism (3.7% vs 1.4%, $P = .024$). When the analysis

Table 3. Surgery Characteristics of the Cohort

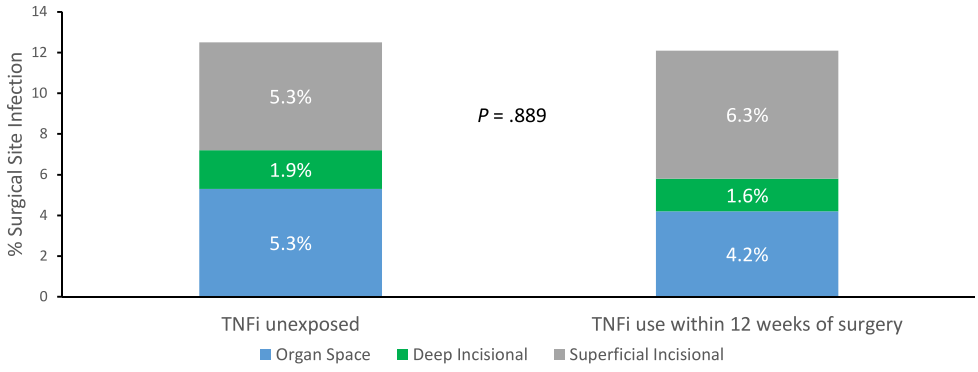
Variable	Overall (N = 947)	CD		UC	
		TNFi use within 12 weeks of surgery		TNFi use within 12 weeks of surgery	
		No (n = 368)	Yes (n = 272)	No (n = 197)	Yes (n =110)
Surgery duration, *min*	180 (124-250)	173 (120-240)	164 (120-221)	210 (140-300)	207 (148-270)
Surgical timing					
Elective/staged	760 (80.3)	308 (83.7)	217 (79.8)	169 (85.8)	66 (60.0)
Semiurgent	170 (18.0)	56 (15.2)	49 (18.0)	24 (12.2)	41 (37.3)
Urgent/emergent	14 (1.5)	3 (0.8)	5 (1.8)	4 (2.0)	2 (1.8)
Not available	3 (0.3)	1 (0.3)	1 (0.4)	0 (0.0)	1 (0.9)
Surgical approach					
Laparoscopic	605 (63.9)	197 (53.5)	164 (60.3)	153 (77.7)	91 (82.7)
Laparoscopic converted to open	110 (11.6)	61 (16.6)	33 (12.1)	10 (5.1)	6 (5.5)
Open	231 (24.4)	110 (29.9)	74 (27.2)	34 (17.3)	13 (11.8)
Not available	1 (0.1)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Bowel preparation used	510 (53.9)	200 (54.3)	143 (52.6)	107 (54.3)	60 (54.5)
Surgical wound protector used	638 (67.4)	244 (66.3)	186 (68.4)	127 (64.5)	81 (73.6)
Bowel resection performed	905 (95.6)	354 (96.2)	254 (93.4)	190 (96.4)	107 (97.3)
Anastomosis created	584 (61.7)	275 (74.7)	218 (80.1)	70 (35.5)	21 (19.1)
Anastomosis type					
None	363 (38.3)	93 (25.3)	54 (19.9)	127 (64.5)	89 (80.9)
Hand-sewn	173 (18.3)	78 (21.2)	68 (25.0)	21 (10.7)	6 (5.5)
Stapled	410 (43.3)	197 (53.5)	149 (54.8)	49 (24.9)	15 (13.6)
Not available	1 (0.1)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Ileocolic resection	446 (47.1)	242 (65.8)	195 (71.7)	8 (4.1)	1 (0.9)
Segmental small bowel only or colon resection only	185 (19.5)	98 (26.6)	65 (23.9)	19 (9.6)	3 (2.7)
Colectomy	330 (34.8)	46 (12.5)	17 (6.2)	164 (83.2)	103 (93.6)
Pouch created	78 (8.2)	1 (0.3)	1 (0.4)	58 (29.4)	18 (16.4)
Genitourinary fistula repair	25 (2.6)	12 (3.3)	12 (4.4)	1 (0.5)	0 (0.0)
Internal fistula repair	77 (8.1)	42 (11.4)	34 (12.5)	0 (0.0)	1 (0.9)
Cutaneous fistula repair	28 (3.0)	18 (4.9)	8 (2.9)	2 (1.0)	0 (0.0)
Surgical abscess drainage	70 (7.4)	31 (8.4)	36 (13.2)	3 (1.5)	0 (0.0)
Stricturoplasty performed	32 (3.4)	16 (4.3)	16 (5.9)	0 (0.0)	0 (0.0)

Table 3. Continued

Variable	Overall (N = 947)	CD		UC	
		TNFi use within 12 weeks of surgery		TNFi use within 12 weeks of surgery	
		No (n = 368)	Yes (n = 272)	No (n = 197)	Yes (n =110)
Stoma formed or revised	454 (47.9)	120 (32.6)	66 (24.3)	167 (84.8)	101 (91.8)
Incidental appendectomy	292 (30.8)	83 (22.6)	81 (29.8)	78 (39.6)	50 (45.5)
Surgical blood loss					
≤ 50 mL	459 (48.5)	170 (46.2)	144 (52.9)	88 (44.7)	57 (51.8)
51-250	373 (39.4)	148 (40.2)	98 (36.0)	78 (39.6)	49 (44.5)
> 250 mL	115 (12.1)	50 (13.6)	30 (11.0)	31 (15.7)	4 (3.6)
Perioperative blood transfusion , *units*					
0	894 (94.4)	352 (95.7)	254 (93.4)	187 (94.9)	101 (91.8)
1-3	46 (4.9)	14 (3.8)	15 (5.5)	8 (4.1)	9 (8.2)
≥4	7 (0.7)	2 (0.5)	3 (1.1)	2 (1.0)	0 (0.0)
Intraoperative hypotension	357 (37.7)	144 (39.1)	108 (39.7)	69 (35.0)	36 (32.7)
Highest intraoperative heart rate, *beats/min*	110 (97–120)	110 (96–120)	110 (95–120)	108 (95–120)	112 (100–122)
Ureteral stent placed	115 (12.1)	51 (13.9)	29 (10.7)	27 (13.7)	8 (7.3)
Postoperative blood glucose ≥200 mg/dL	47 (5.0)	11 (3.0)	15 (5.5)	11 (5.6)	10 (9.1)
Foley catheter >24 h postoperative	411 (43.4)	166 (45.1)	95 (34.9)	101 (51.3)	49 (44.5)

NOTE: Data are presented as median (quartile 1–quartile 3) or as n (%).

A



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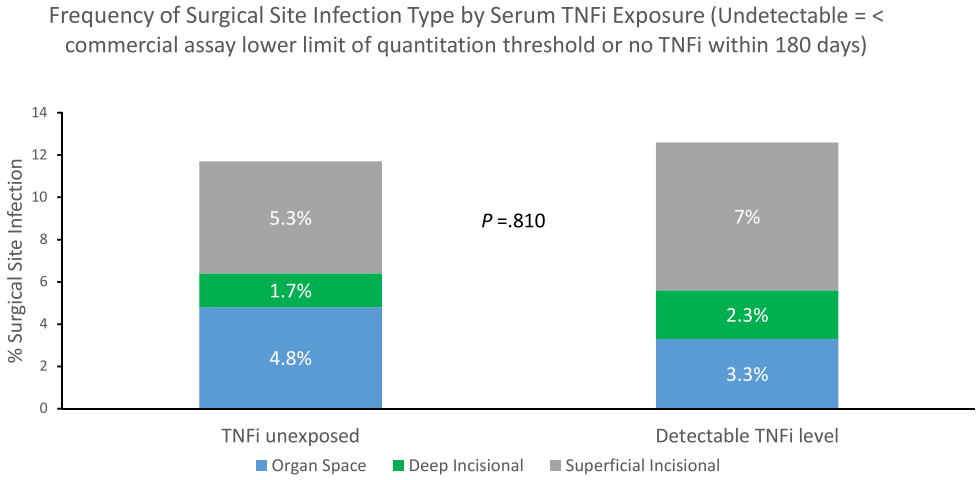

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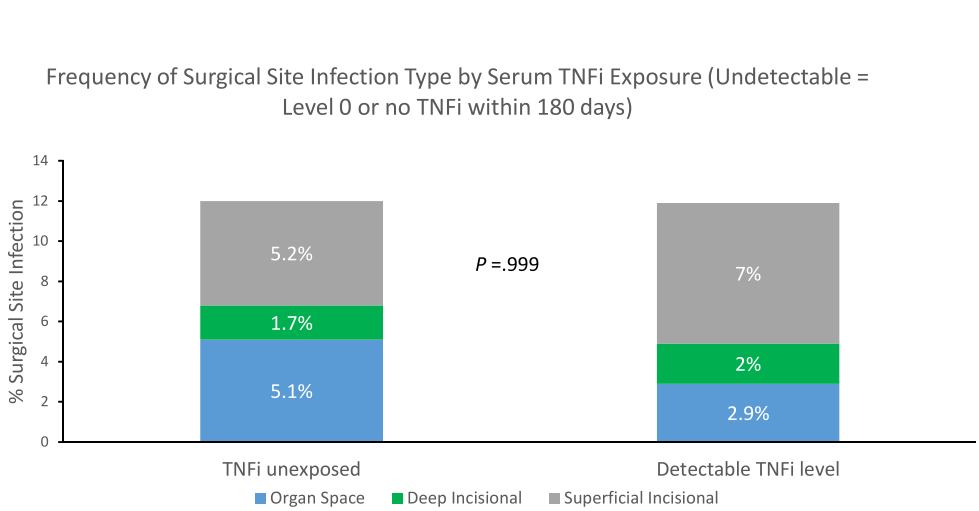

Figure 1. Frequency of surgical site infection types by (*A*) patient-reported TNFi exposure; (*B*) serum TNFi exposure with undetectable defined as below commercial assay LLoQ threshold, never on a TNFi, or no TNFi within 180 days of surgery; and (*C*) serum TNFi exposure with undetectable defined as level = 0 μg/mL, never on a TNFi, or no TNFi within 180 days of surgery.

Table 4. Multivariable Analysis of Risk Factors for Any Infection Postoperatively Using Patient-Reported Tumor Necrosis Factor Inhibitor Exposure

Predictor	OR for any infection	95% CI	*P* value
TNFi use within 12 weeks of surgery	1.05	0.716–1.535	.8
Age	1.014	1.001–1.027	**.034**
Male sex	0.878	0.604–1.275	.49
Pre-op corticosteroids	1.836	1.258–2.687	**.002**
Pre-op budesonide	0.403	0.189–0.785	**.012**
UC/indeterminate colitis	0.883	0.564–1.369	.58
Prior bowel resection			
No prior abdominal surgery	Reference	Reference	
Abdominal surgery without resection	0.665	0.356–1.192	.18
Yes bowel resection	2.614	1.653–4.169	**<.001**
Genitourinary fistula	3.654	1.394–9.335	**.007**
Current smoking	1.976	1.147–3.352	**.013**
Anemia or other blood disorder	1.775	1.187–2.641	**.005**
Ureteral stent	1.994	1.194–3.282	**.007**
Diabetes	3.31	1.448–7.425	**.004**
Pre-op total parenteral nutrition	1.967	0.977–3.829	.051
Pre-op nonabdominal infection	2.397	1.158–4.824	**.016**
Depression	1.697	1.070–2.661	**.023**
Rheumatoid arthritis	2.538	1.062–5.774	**.03**
Surgical approach			
Laparoscopic	Reference	Reference	
Laparoscopic convert to open	1.354	0.768–2.345	.29
Open	0.626	0.382–1.013	.06

NOTE: Bold *P* values are statistically significant ($P < .05$).
Pre-op, preoperative.

controlled for corticosteroid use, the association of TNFi use within 12 weeks of surgery with postoperative venous thromboembolism remained significant (OR, 2.641; 95% CI, 1.096–6.367). There was no other difference in secondary outcomes of 30-day readmission, 30-day reoperation, postoperative ileus, or length of stay by patient-reported TNFi exposure status. No differences were found in the in incidence of any noninfectious postoperative outcomes by TNFi serum drug concentration detectability using the commercial assay LLoQ threshold or >0 μg/mL as the cutoff for exposure. No deaths occurred within 30 days of surgery. Detectable antibodies to IFX or ADA were not associated with any of the secondary outcomes.

Discussion

In this prospective cohort of patients with IBD undergoing intra-abdominal surgery, the use of TNFis within 12 weeks before surgery was not associated with occurrence of any infection or SSI 30 days postoperatively. Secondary analyses also did not find any association of detectable serum TNFi drug concentrations with any infection or SSI postoperatively. Risk factors found to be independently associated with both any infection or SSI included preoperative corticosteroid use, current smoking, prior bowel resection, and diabetes.

PUCCINI is the largest prospective study to assess risk factors for postoperative infection after intra-abdominal surgery in patients with IBD. Two prospective French cohorts previously reported on risk factors for postoperative complications, including infection after surgery for ileocolonic CD, with conflicting results. The GETAID Chirurgie Group found TNFi use <3 months before surgery was independently associated with overall postoperative morbidity (OR, 1.99; 95% CI, 1.17–3.39) and intra-abdominal septic morbidity (OR, 2.22; 95% CI, 1.22–4.04). However, TNFi exposure in this cohort was defined by patient-reported use, and the effect of serum drug concentrations at the time of surgery was not explored. Similarly, the authors did not find a significant difference in the rate of postoperative complication or infection by timing of the last dose of a TNFi. Only 24% of the GETAID Chirurgie cohort was on TNFis preoperatively compared with >40% of the PUCCINI cohort, suggesting differences in practice patterns

Table 5. Multivariable Analysis of Risk Factors for Surgical Site Infection Postoperatively Using Patient-Reported Tumor Necrosis Factor Inhibitor Exposure

Predictor	OR for SSI	95% CI	*P* value
TNFi use within 12 weeks of surgery	1.249	0.793–1.960	.34
Age	1.01	0.994–1.027	.22
Male sex	1.172	0.744–1.856	.49
Pre-op corticosteroids	2.525	1.587–4.056	**<.001**
UC/indeterminate colitis	0.65	0.282–1.576	.32
Prior bowel resection			
No prior abdominal surgery	Reference	Reference	
Abdominal surgery without resection	0.971	0.465–1.933	.94
Yes bowel resection	2.465	1.410–4.358	**.002**
Diabetes	3.491	1.403–8.358	**.006**
Hypertension	1.956	1.011–3.702	**.042**
IBD disease behavior			
Neither stricturing nor penetrating	Reference	Reference	
Penetrating only	1.768	0.741–4.412	.21
Stricturing only	0.847	0.385–1.975	.69
Stricturing and penetrating	0.542	0.216–1.388	.19
Surgical approach			
Laparoscopic	REF	REF	
Laparoscopic converted to open	1.809	0.929–3.436	.075
Open	0.884	0.487–1.578	.68
Current smoking	2.695	1.431–4.936	**.002**
Anemia or other blood disorder	1.469	0.892–2.385	.12
Ureteral stent	1.825	0.978–3.300	.051
Pre-op ustekinumab	2.585	0.800–7.571	.093

NOTE: Bold *P* values are statistically significant ($P < .05$).
Pre-op, preoperative.

Table 6. Noninfectious Postoperative Outcomes by Tumor Necrosis Factor Inhibitor Exposure Type

	Patient-reported TNFi use			Serum TNFi detectable (below commercial assay LLoQ threshold, never on a TNFi, or no TNFi within 180 days of surgery)			Serum TNFi detectable (level = 0, never on a TNFi, or no TNFi within 180 days of surgery)		
Outcomes	No	Yes	*P* value	No	Yes	*P* value	No	Yes	*P* value
Readmission	110 (19.5)	65 (17.0)	.340	98 (18.0)	31 (14.6)	.315	93 (18.1)	36 (14.8)	.307
Reoperation	32 (5.7)	15 (3.9)	.227	32 (5.9)	7 (3.3)	.208	30 (5.8)	9 (3.7)	.285
Thrombosis	8 (1.4)	14 (3.7)	**.024**	13 (2.4)	6 (2.8)	.931	10 (1.9)	9 (3.7)	.234
Hypomotility	60 (10.6)	39 (10.2)	.840	63 (11.6)	22 (10.3)	.731	58 (11.3)	27 (11.1)	1
Length of stay, mean (SD), *d*	5.82 (4.03)	6.06 (5.12)	.451	5.98 (4.25)	6.08 (5.35)	.808	5.94 (4.18)	6.13 (5.37)	.631

NOTE: Data are presented as n (%) unless indicated otherwise. The bold *P* value is statistically significant ($P < .05$).
SD, standard deviation.

or characteristics of the study population. Surgery for stricturing disease was performed in >60% of the GETAID Chirurgie cohort compared with only 30% of the PUCCINI cohort. While PUCCINI was a mixed IBD cohort, controlling for diagnosis along with many other factors related to disease activity, severity, and phenotype did not alter the TNFi findings.

In contrast to the GETAID Chirurgie Group findings, the REMIND Group did not find TNFi use within 3 months of surgery or serum TNFi drug concentrations to be associated with overall postoperative complications or intra-abdominal septic complications after ileocolic resection for CD. However, this cohort consisted of only 209 patients, of whom 76 were TNFi exposed. Although not specifically designed to control for risk factors for postoperative complications, our results are also supported by the findings of large nationwide Danish registry studies that did not find an association of TNFi use within 14 days or 12 weeks of CD surgery or 12 weeks of UC surgery with postoperative complications, including infections such as anastomotic leak, intra-abdominal abscess, or bacteremia.[55,56]

Confirming the findings of our primary analysis through secondary analyses defining TNFi exposure by perioperative serum drug concentrations differentiates PUCCINI from the other studies evaluating TNFi risk. Most previously published studies have used varying definitions of TNFi exposure, with the most common being last use within 12 weeks of surgery. However, patients with active IBD are known to have increased clearance of TNFi, potentially leading to misclassification of exposure when defining by last use alone.[57] Among patients having used IFX within 12 weeks of surgery, 18% had undetectable levels perioperatively, and among patients having used ADA, 9% had undetectable levels perioperatively. A smaller percentage of patients with the last dose of a TNFi >12 weeks from surgery in whom drug level analyses were available had detectable levels. Commercial drug assays may report small but detectable amounts of drug as undetectable, and therefore, we evaluated serum drug concentrations defining detectable by a level of >0 μg/mL and separately as greater than the commercial laboratory LLoQ for the assay.

TNFi was not associated with any infection or SSI by either definition of detectability. Lau et al[58] previously reported detectable serum TNFi levels were not associated with postoperative infections in CD or UC in a cohort including 143 patients exposed to TNFis preoperatively. However, when using a cut point of $\geq$3 μg/mL vs <3 μg/mL, the authors found significantly more infectious complications in the patients with CD with higher levels of a TNFi. Owing to the smaller size of the cohort with CD, the authors were limited in their ability to control for multiple risk factors in the analysis, and a Cochrane Armitage trend analysis did not demonstrate significant results. Our sensitivity analysis defining serum drug concentration exposure by quartiles did not show any range of TNFi exposure to be associated with infectious complications compared with patients with undetectable TNFi.

It has been reported that patients taking corticosteroids preoperatively may have double the risk of infectious complications compared with those not taking corticosteroids.[59] Both PUCCINI and the REMIND cohort found preoperative systemic corticosteroid use was associated with postoperative infectious complications, confirming the findings of prior studies.[46] In patients undergoing elective surgery, attempts to minimize corticosteroid exposure should be made. Randomized studies have previously shown no benefit to using stress dose corticosteroids for IBD surgery in the absence of confirmed adrenal insufficiency.[60] Uncontrolled retrospective studies have suggested benefits to preoperative nutritional optimization and corticosteroid weaning, but this needs to be studied prospectively.[61]

Although the data are limited, most studies have shown that treatment with azathioprine, 6-mercaptopurine, or methotrexate before surgery is not a risk factor for postoperative complications.[7,8,24,62] Neither thiopurine use nor methotrexate use were associated with postoperative infections in our cohort. On the basis of the totality of the evidence, surgery does not need to be delayed on account of taking these medications, and decisions on whether to hold thiopurines or methotrexate should be made based on other factors besides infectious risk.

Current smoking preoperatively was a significant risk factor for both any infection and SSI in our cohort. Smoking represents one of the most important modifiable risk factors for postoperative complications, and its association with postoperative infection, particularly wound infection, has been established in other non-IBD surgical cohorts.[63–67] Wound inflammation and fibroblast proliferation have been shown to be attenuated in smokers, potentially decreasing wound healing.[68] Investigators from the Mayo Clinic recently showed that stopping smoking even if only on the day of surgery was associated with decreased frequency of SSI in a large mixed cohort of patients, including those undergoing gastrointestinal surgery.[69] Low-intensity smoking cessation interventions have been shown to stop perioperative smoking in 20% of patients.[70] Despite the known risks of smoking both to postoperative outcomes and CD disease activity, perioperative smoking cessation interventions have not been specifically studied in IBD. While integration of smoking cessation strategies into the normal workflow of perioperative care may be challenging, implementation science may guide us in incorporating evidence-based approaches into routine care.[71]

Preoperative TNFi use was not associated with any of the secondary outcomes with the notable exception of postoperative venous thromboembolism. Prior studies have demonstrated an association of corticosteroid use, but not TNFi use, with venous thromboembolism.[72–75] However, the association of preoperative TNFi use within 12 weeks of surgery with postoperative venous thromboembolism persisted after adjusting for preoperative corticosteroid use. When TNFi exposure was defined as having detectable serum drug concentrations, the association was no longer significant, suggesting other factors may be at play. The absolute number of thromboembolic events in the cohort

was small, making it difficult to explore how much of this association is due to the TNFi exposure vs other risk factors such as severe disease, malnutrition, or postoperative deconditioning.

Strengths of our study include its prospective enrollment of a large number of patients with IBD from a geographically diverse group of centers in the United States among the Crohn's & Colitis Foundation Clinical Research Alliance as well as the incorporation of serum drug concentrations into the analyses. The size of the cohort enabled controlling for a larger number of concomitant risk factors than was possible in other studies of TNFi association with postoperative infections.

Limitations of our study include nonconsecutive patient enrollment, participation of largely academic centers, which may affect the generalizability of our findings, potential for missed infections diagnosed at other centers not accounted for in our medical record review or telephone follow-up, and that our observations may already reflect prejudice in surgical decision making such as approach and timing of surgery.

In the largest multicenter prospective surgical cohort studying the association of preoperative TNFi use with 30-day postoperative infectious complications, neither patient-reported use of TNFi nor detectable serum TNFi levels were independent risk factors for any postoperative infection or SSI. Therefore, preoperative use of TNFi should not affect surgical decisions in most patients with IBD. Instead, focus should be placed on modifiable risk factors such as smoking and preoperative systemic corticosteroid use.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://dx.doi.org/10.1053/j.gastro.2022.03.057.

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