Postoperative Complications after Ileocecal Resection in Crohn's Disease: A Prospective Study From the REMIND Group

Mathurin Fumery, MD[1], Philippe Seksik, MD, PhD[2], Claire Auzolle, MD[3,4], Nicolas Munoz-Bongrand, MD[5], Jean-Marc Gornet, MD[3], Gilles Boschetti, MD, PhD[6], Eddy Cotte, MD, PhD[7], Anthony Buisson, MD[8], Anne Dubois, MD[9], Benjamin Pariente, MD, PhD[10], Philippe Zerbib, MD, PhD[11], Najim Chafai, MD[12], Carmen Stefanescu, MD[13], Yves Panis, MD, PhD[14], Philippe Marteau, MD, PhD[15], Karine Pautrat, MD[16], Charles Sabbagh, MD, MhD[17], Jerome Filippi, MD[18], Marc Chevrier, MD[19], Pascal Houze, MD[19], Xavier Jouven, MD, PhD[4], Xavier Treton, MD, PhD[13] and Matthieu Allez, MD, PhD[3] for the REMIND study group investigators[20]

OBJECTIVES: **We sought to determine the frequency of and risk factors for early (30-day) postoperative complications after ileocecal resection in a well-characterized, prospective cohort of Crohn's disease patients.**

METHODS: **The REMIND group performed a nationwide study in 9 French university medical centers. Clinical-, biological-, surgical-, and treatment-related data on the 3 months before surgery were collected prospectively. Patients operated on between 1 September 2010 and 30 August 2014 were included.**

RESULTS: **A total of 209 patients were included. The indication for ileocecal resection was stricturing disease in 109 (52%) cases, penetrating complications in 88 (42%), and medication-refractory inflammatory disease in 12 (6%). A two-stage procedure was performed in 33 (16%) patients. There were no postoperative deaths. Forty-three (21%) patients (23% of the patients with a one-stage procedure vs. 9% of those with a two-stage procedure, *P*=0.28) experienced a total of 54 early postoperative complications after a median time interval of 5 days (interquartile range, 4–12): intra-abdominal septic complications (*n*=38), extra-intestinal infections (*n*=10), and hemorrhage (*n*=6). Eighteen complications (33%) were severe (Dindo–Clavien III–IV). Reoperation was necessary in 14 (7%) patients, and secondary stomy was performed in 8 (4.5%). In a multivariate analysis, corticosteroid treatment in the 4 weeks before surgery was significantly associated with an elevated postoperative complication rate (odds ratio (95% confidence interval)=2.69 (1.15–6.29); *P*=0.022). Neither preoperative exposure to anti-tumor necrosis factor (TNF) agents (*n*=93, 44%) nor trough serum anti-TNF levels were significant risk factors for postoperative complications.**

CONCLUSIONS: **In this large, nationwide, prospective cohort, postoperative complications were observed after 21% of the ileocecal resections. Corticosteroid treatment in the 4 weeks before surgery was significantly associated with an elevated postoperative complication rate. In contrast, preoperative anti-TNF therapy (regardless of the serum level or the time interval between last administration and surgery) was not associated with an elevated risk of postoperative complications.**

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[1]Department of Gastroenterology, Amiens University Hospital, University Picardie Jules Verne, Amiens, France; [2]Sorbonne Universites, UPMC Univ Paris 06, Ecole Normale Superieure, CNRS, INSERM, ERL 1157, LBM, APHP, Gastroenterology Unit, Saint Antoine Hospital, Paris, France; [3]Department of Gastroenterology, Saint-Louis Hospital, APHP, INSERM U1160, University Denis Diderot, Paris, France; [4]INSERM U970, Paris, France; [5]Department of Digestive Surgery, Saint-Louis Hospital, APHP, Paris, France; [6]Department of Gastroenterology, Hospices Civils de Lyon and University Claude Bernard Lyon 1, Pierre-Benite, France; [7]Department of Digestive Surgery, Hospices Civils de Lyon and University Claude Bernard Lyon 1, Pierre-Benite, France; [8]Departmernt of Gastroenterology, Estaing University Hospital, M2iSH, UMR 1071 INSERM/Université d'Auvergne, USC-INRA 2018, Clermont-Ferrand, France; [9]Department of Digestive Surgery, Estaing University Hospital, Auvergne University, Clermont-Ferrand, France; [10]Department of Gastroenterology, Huriez Hospital, Lille 2 University, Lille, France; [11]Department of Digestive Surgery and Transplantation, Huriez Hospital, Université Lille Nord de France, Lille, France; [12]Department of Digestive Surgery, Saint Antoine Hospital, APHP, Paris, France; [13]Department of Gastroenterology, IBD and Nutrition Support, Beaujon Hospital, APHP, University Paris 7 Denis Diderot, Clichy, France; [14]Department of Colorectal Surgery, Beaujon Hospital, APHP, University Paris 7 Denis Diderot, Clichy, France; [15]Department of Gastroenterology, Lariboisiere Hospital, APHP, University Paris 7 Denis Diderot, Paris, France; [16]Department of Digestive Surgery, Lariboisiere Hospital, APHP, Paris, France; [17]Department of Digestive and Oncologic Surgery, Amiens University Hospital, University Picardie Jules Verne, Amiens, France; [18]Department of Gastroenterology and Clinical Nutrition, Nice University Hospital, University of Nice Sophia-Antipolis, Nice, France; [19]Biochimie, Saint-Louis Hospital, APHP, Paris, France; [20]List of REMIND study group investigators is provided before Acknowledgments section. **Correspondence:** Matthieu Allez, MD, PhD, Department of Gastroenterology, Saint-Louis Hospital, APHP, INSERM U1160, University Denis Diderot, Paris 75010, France. E-mail: mathurinfumery@gmail.com
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INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory bowel disease (IBD) that can affect segments of the gastrointestinal tract and may lead to major complications such as strictures, fistulas, or abscesses. Despite improvements in medical care, the frequency of surgery in CD remains high; about half of all patients undergo surgery in the 10 years after diagnosis (1,2). According to the literature, between 10 and 37% of CD patients experience postoperative complications after surgery (3–7). Most of the data on postoperative complications in IBD come from retrospective studies of single referral centers; the latter often feature heterogeneous populations with an association of CD and ulcerative colitis patients and different types of surgical resection (3–7). Ileocecal resection is the most frequent surgical procedure in CD. Several risk factors for postoperative complications after ileocecal resection have been identified in retrospective referral center studies; these include the presence of abscesses at the time of surgery, corticosteroid therapy, and impaired nutritional status (6,7). In practice, a growing number of patients are being exposed to an anti-tumor necrosis factor (TNF) agent before their first surgical procedure. Recent meta-analyses have shown a small but significant increase in the risk of infectious postoperative complications in CD after preoperative exposure to anti-TNF agents (8–10). However, most of these meta-analyses failed to take account important confounding factors such as disease activity and prior or concomitant corticosteroid therapy. Thus, the impact of anti-TNF agents on the risk of postoperative complications is still subject to debate, and the safe interval of anti-TNF windows remains to be determined (11,12).

Prospective studies are, therefore, required in order to (i) evaluate the true burden of postoperative complications after ileocecal resection and (ii) reliably identify risk factors and thus improve postoperative outcomes.

A nationwide prospective study performed by the REMIND group was designed to identify predictors of the postoperative endoscopic recurrence of CD after ileocecal resection. Taking advantage of this nationwide study, we then performed an ancillary study of the early (30-day) postoperative complications after ileocecal resection and sought to identify associated risk factors.

METHODS

The REMIND group performed a nationwide study in 9 French university medical centers. Adult CD patients (18 years of age or older), affiliated to the national health system, undergoing ileocecal resection between 1 September 2010 and 30 September 2014 were included in the study. Patients with dysplasia on surgical specimen and pregnant women were excluded.

Data collection

Data were collected prospectively in a standardized format by a gastroenterologist with expertise in CD. They included demographic data (age, gender, age at diagnosis, age at surgery, and smoking status at surgery), clinical data (disease phenotype and behavior at the time of surgery, according to the Montreal classification (13), history of intestinal resection, Harvey–Bradshaw score at surgery, and the indication for surgery), data on medications (exposure to antibiotics in the 4 weeks before surgery, exposure to 5-aminosalicylic acid in the 3 months before surgery, exposure to corticosteroids (prednisone, prednisolone, hydrocortisone ,or budesonide) in the 3 months before surgery and the 4 weeks before surgery, exposure to immunosuppressants (azathioprine, 6-mercaptopurine, or methotrexate) in the 3 months before surgery, exposure to anti-TNF agents in the 3 months before surgery and the date of the last administration of an anti-TNF agent, the type of anti-TNF agent (infliximab (IFX), adalimumab (ADA), or others)), and nutritional data (weight, height, body mass index (BMI), and oral or parenteral nutritional support before surgery). Biological data (including serum hemoglobin, albumin and C-reactive protein levels, and leukocyte, lymphocyte, neutrophil and platelet counts) were always collected on the day of surgery. Trough serum levels of IFX and ADA and anti-drug antibody titers were determined for all patients using specific ELISA kits (LISA-TRACKER, Theradiag, Marne La Vallée, France).

Evaluated outcomes

An early postoperative complication was defined as a surgical or other medical event within 30 days of surgery. Data on postoperative complications were collected in a standardized format and reviewed in detail. The complications were classified into four groups; (i) extra-abdominal infectious complications (including pneumonia and urinary tract infections), (ii) abdominal infectious complications (including wound infections, anastomotic leakage/anastomotic fistula, and intra-abdominal abscess), (iii) hemorrhagic complications, and (iv) other complications (including thromboembolic complications). The severity of each complication was graded as I, II III, IV, or V, according to the Dindo–Clavien classification (14). Grades III–V were considered to be severe postoperative complications. Prolongation of hospitalization, readmission to hospital, and further surgery or secondary stomy due to postoperative complications were also noted.

Statistical analysis

Quantitative variables were quoted as the mean (range) or the median (interquartile range (IQR)), and qualitative variables were quoted as the number (percentage). The comparison of quantitative variables with normal distribution was realized by the Student's *t*-test and the Mann–Whitney's *U*-test or with the Wilcoxon test for variables with non-normal distribution. For qualitative variables, a X^2-test or Fisher's exact test was used, as appropriate. The cumulative incidence curve was plotted using the Kaplan–Meier method. If a given patient had experienced several postoperative complications, the time to event was defined as the time interval between surgery and first of these complications. A logistic regression model was used to identify factors associated with an elevated risk of postoperative complications, expressed as the odds ratio (OR) (95% confidence interval (CI)). In a sensitivity analysis, to address the possibility of treatment selection bias, we used propensity score for

preoperative treatment statistically associated with postoperative complications. To calculate the propensity score, all variables that may influence the decision to have a preoperative treatment were included in a multivariable logistic regression analysis. We used covariate adjustment using propensity score as propensity score method (15). All statistical tests were two-tailed, and the threshold for statistical significance was set to $P<0.05$. All analyses were performed using R software (version 3.2.2, Vienna, Austria). The study was approved by the investigational review board at Saint-Louis Hospital (Paris, France; reference 2007/17).

RESULTS

Demographic and clinical characteristics at the time of surgery

The study population's demographic and clinical characteristics at the time of the first intestinal resection are summarized in **Table 1**. A total of 209 patients were included between 1 September 2010 and 30 August 2014 (median (IQR) number of inclusions per center: 23 (11–38)), including 105 males (50%). The mean age at surgery was 34 years (range, 18–71), and 71 patients (34%) were smokers at the time of surgery. Thirty-six patients (17%) had previously undergone intestinal resection. The indication for surgery was stricturing disease in 109 (52%) cases, penetrating complications in 88 (42%) and medication-refractory inflammatory disease therapies in 12 (6%). Abscesses were observed at the time of surgery in 34 (16%) patients, and the median Harvey–Bradshaw score at surgery was 5 (3–7).

Medications at the time of surgery

The medications being taken at the time of surgery are specified in **Table 1**. Twenty-two (11%) patients were being treated with 5-aminosalicylic acid, and 61 (30%) had been treated with immunosuppressants in the 3 months before surgery. Seventy-one (34%) patients and 45 (22%) patients had taken oral corticosteroids in the 3 months before surgery and the month before surgery, respectively. Ninety-three (44%) patients and 44 (21%) patients had been treated with an anti-TNF agent in the 3 months before surgery and the month before surgery, respectively (with 34 on IFX and 57 on ADA). The median time interval between the last administration of an anti-TNF agent and surgery was 42 days (23–78) for IFX and 18 days (9–31) for ADA.

Nutritional, anthropometric, and biological data at the time of surgery

Nutritional data at the time of surgery are summarized in **Table 1**. The median (IQR) weight, height, and body mass index were, respectively, 62.5 kg (53–71.2), 1.70 m (1.64–1.78) and 21.5 kg/m^2 (18.8–23.7). Thirty-two (15%) and 30 (14%) patients received enteral or parenteral nutritional support before surgery, respectively. The median hemoglobin level was 12.4 g/dl (11.4–13.3), the median leukocyte count was 8000/mm^3 (6000–10,000), and the median platelet count was 314×10^9/l (260–382). The median C-reactive protein level at surgery was 15 (3–55) mg/dl and the median albumin level was 34 (30–40) g/dl.

Table 1. Characteristics of patients at surgery in the overall study population

Male gender (*n* %)	105 (50)
Age at diagnosis (mean-range, years)	26 (1–63)
Age at surgery (mean-range, years)	34 (18–71)
Smoker at surgery (*n*, %)	71 (34)
Previous intestinal resection (*n*, %)	36 (17)
Disease location	
Ileal (L1) (*n*, %)	119 (57)
Colonic (L2) (*n*, %)	2 (1)
Ileocolonic (L3) (*n*, %)	85 (41)
Anoperineal lesion (*n*, %)	48 (23)
Granuloma (*n*, %)	56 (27)
Harvey–Bradshaw score (*n*)	5 (3–7)
Indication for surgery	
Stricture (s) (*n*, %)	109 (52)
Penetrating complication (fistula/abscess) (*n*, %)	88 (42)
Both stricturing and penetrating complication (*n*, %)	12 (6)
Absecess at surgery (*n*, %)	34 (16)
Medications at surgery	
Antibiotics<4 weeks (*n*, %)	128 (62)
5-ASA<3 months (*n*, %)	22 (11)
Corticosteroids <3 months (*n*, %)	71 (34)
Corticosteroids <4 weeks (*n*, %)	45 (22)
Immunosuppressants <3 months (*n*, %)	61 (30)
Anti-TNF <3 months (*n*, %)	93 (44)
Anti-TNF <4 weeks (*n*, %)	44 (21)
ADA (*n*)	57
IFX (*n*)	34
Median time interval between the last administration of an anti-TNF agent and surgery (days)	
IFX	42 (23–78)
ADA	18 (9–31)
Median anti-TNF level	
Anti-TNF level>1 µg/ml	40 (53)
Anti-TNF level>3 µg/ml	36 (37)
Nutritional and anthropometric data at surgery	
Weight (mean-s.d., kg)	63 (13)
Height (mean-s.d., cm)	171 (9.5)
BMI (mean-s.d., kg/m^2)	21.6 (4.0)
Preoperative enteral nutrition (*n*, %)	32 (15)
Preoperative parenteral nutrition (*n*, %)	30 (14)
Biological data at surgery	
Hemoglobin (mean-s.d., g/dl)	12.4 (1.7)
Leukocytes (mean-s.d.,/mm3)	8.4 (3.8)

Table 1 continued on following page

Table 1. Continued

Neutrophils (mean-s.d.,/mm3)	6.1 (3.6)
Platelets (mean-s.d.,*1000/mm3)	328 (103)
CRP (median-IQR, g/l)	15 (3–55)
Albumin (median-IQR, g/l)	34 (30–40)
Type of surgery	
Laparotomy	45
Laparoscopy	96
Laparoscopy and conversion to laparotomy	20
Missing data	48
Emergency surgery	23
Missing data	35

ADA, adalimumab; ASA, 5-aminosalicylic acid; BMI, body mass index; CRP, C-reactive protein; IFX, infliximab; IQR, interquartile range; TNF, tumor necrosis factor.

Anti-TNF drug levels at the time of surgery

Serum anti-TNF drug levels were assayed for the 76 patients exposed to anti-TNF agent in the 3 months before surgery. The anti-TNF level was >1 µg/ml in 40 patients and >3 µg/ml in 36 patients.

Surgical procedures

A two-stage procedure was performed in 33 (16%) cases. In a multivariate analysis, a penetrating phenotype (P=0.002), the presence of abscesses (P=0.005), BMI<18 kg/m^2 (P=0.018), and previous resection (P=0.024) were significantly associated with the decision to perform a two-stage procedure. Surgery was performed in emergency 23 patients (missing data: 35); laparoscopy in 116 patients (missing data n= 48), and a conversion in laparotomy was necessary in 17% of them.

Postoperative complications

Fifty-four postoperative complications were observed in 43 patients (20.5%) (**Table 2**). The median (IQR) time interval between surgery and the occurrence of a complication was 5 (4–12) days. **Figure 1** shows the Kaplan–Meier curve for the cumulative risk of postoperative complications in the 30 days after surgery for patients having undergone a one-stage procedure and for those having undergone a two-stage procedure (P=0.28). No deaths or thromboembolic complications were observed.

Postoperative complications in patients having undergone a one-stage procedure (n=176)

When considering the 176 patients having undergone a one-stage procedure, 40 (22.8%) experienced a total of 51 complications (9 extra-abdominal infectious complications, 6 abdominal hemorrhages, and 36 abdominal infectious complications). The abdominal infectious complications included wound abscesses (n=17), anastomotic leakage without intra-abdominal collection (n=5), anastomotic leakage with intra-abdominal collection (n=6), and intra-abdominal collections (n=8). The postoperative complications' severity grades (according to the Dindo–Clavien classification) were distributed as follows (**Table 3**): grade I, 20% (n=8); grade II, 35% (n=14); grade III, 40% (n=16); grade IV, 5% (n=2); grade V, 0%. Hospitalization was prolonged or required in 30 cases (75% of the patients with postoperative complications). The occurrence of all types of postoperative complication (including parietal abscesses) was significantly correlated with the length of hospital stay. Reoperation for complications was necessary in 14 patients (33% of the patients with postoperative complications), and secondary stomy was performed in 8 patients (19% of the patients with postoperative complications and 4.5% of the overall study population). The median time spent with a temporary stoma was 3.7 (3.1–6.7) months.

Factors associated with the occurrence of postoperative complications in patients having undergone a one-stage surgical procedure

Clinical and biological variables. In a multivariate analysis, none of the studied demographic, clinical, or biological variables was significantly associated with the occurrence of postoperative complications.

Preoperative medications. Fourteen patients having been treated with corticosteroids in the 4 weeks before surgery (35%) experienced postoperative complications, compared with only 26 (19%) of the non-treated patients (OR (95% CI)=2.65 (1.19–5.80); P=0.016). This difference was mainly due to a greater incidence of abdominal septic complications (30.6% vs. 14.5% of the treated and non-treated patients, respectively; P=0.046) and overall infectious complications (35.1% vs. 17.4%, respectively; P=0.034). Treatment with corticosteroids in the 3 months before surgery was not associated with any types of complication.

Treatment with anti-TNF agents in the 3 months before surgery was not associated with the risk of postoperative complications. Similarly, postoperative complications were observed in 8 (22.2%) patients treated with anti-TNF agents in the 4 weeks before surgery and 32 (22.3%) patients not exposed to anti-TNF agents. There were no intergroup differences in the incidence of any of the postoperative complications, including abdominal septic complications (16.7% vs. 18.1% in the treated and non-treated patients, respectively). The time interval since the last administration of anti-TNF agents was not associated with the occurrence of postoperative complications. We also analyzed the impact of trough serum levels of anti-TNF (IFX or ADA) at the time of surgery by using two different thresholds (>1 and>3 µg/ml) and found no effect on risks of postoperative complications (**Table 4**).

In a multivariate analysis adjusted for center, gender, age, smoking status, previous intestinal resection, phenotype, the presence of ano-perianal lesions and the Harvey–Bradshaw index at surgery, only exposure to corticosteroids in the 4 weeks before surgery was significantly associated with the overall postoperative complication rate (OR (95% CI)=2.69 (1.15–6.29);

Table 2. Postoperative complications in 176 patients having undergone a one-stage procedure and 33 having undergone a two-stage procedure

	All patients (*n*=209)	Two-stage procedure (*n*=33)	One-stage procedure (*n*=176)
Total number of patients with complications (*n*, %)	43 (20.6)	3 (9)	40 (22.7)
Total number of complications (*n*)	54	3	51
Abdominal septic complications (*n*)	38	2	36
Intra-abdominal collection (*n*)	10	2	8
Anastomotic leakage (*n*)	5	0	5
Both anastomotic leakage and intra-abdominal collection (*n*)	6	0	6
Parietal abscess (*n*)	17	0	17
Extra-abdominal infection (*n*)	10	1	9
Pneumonia/pleurisy (*n*)	4	1	3
Septicemia (*n*)	4	0	4
Urinary infection (*n*)	1	0	1
Catheter infection (*n*)	1	0	1
Hemorrhage (*n*)	6	0	6
Thrombosis (n)	0	0	0
Death (*n*)	0	0	0
Dindo–Clavien classification (14)			
Total number of patients with complications (n)	43	3	40
I: any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions	8 (18.5)	0	8 (20)
II: requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included	15 (35)	1 (33)	14 (35)
III: requiring surgical, endoscopic, or radiological intervention	18 (42)	2 (66)	16 (40)
IIIa: intervention not under general anesthesia	6	2	4
IIIb: intervention under general anesthesia	11	0	11
IV: life-threatening complication	2 (4.5)	0	2 (5)
IVa: single-organ dysfunction	2		2
Ivb: multi organ dysfunction	0		0
V: death of a patient	0	0	0

P=0.022), the occurrence of intra-abdominal septic complications (OR (95% CI)=2.60 (1.05–6.40); *P*=0.035), and the occurrence of extra-abdominal septic complications (OR (95% CI)=2.56 (1.08–6.02); *P*=0.030). We performed a sensitivity analysis with a propensity score for corticosteroid treatment in the 4 weeks before surgery; in our logistic regression model, this modality was still significantly associated with the overall incidence of postoperative complications (OR (95% CI)=2.73 (1.15–6.53); *P*=0.023). In sensitivity analysis on variables with more than 2% of missing data (abscess at surgery, BMI, and type of surgery), results were similar and corticosteroids <4 weeks at surgery was the only variable significantly associated to postoperative complication. Moreover, by including the variable "type of surgery" in the logistic regression model with propensity score corticosteroids <4 weeks was still statistically associated with complications. In bivariate analysis, type of surgery was not associated with complications.

Postoperative complications in patients having undergone a two-stage procedure (*n*=33)

When considering the 33 patients with a stoma at the time of the ileocecal resection, three patients experienced a total of three postoperative complications (including two cases of intra-abdominal collection and one case of pneumonia). Two of these complications were considered to be severe (both grade III). These patients had a longer length of hospital stay or required readmission but none underwent further surgery. One patient had not undergone stoma closure at last follow-up, and the two others underwent stoma closure after 2.8 and 5.4 months, respectively.

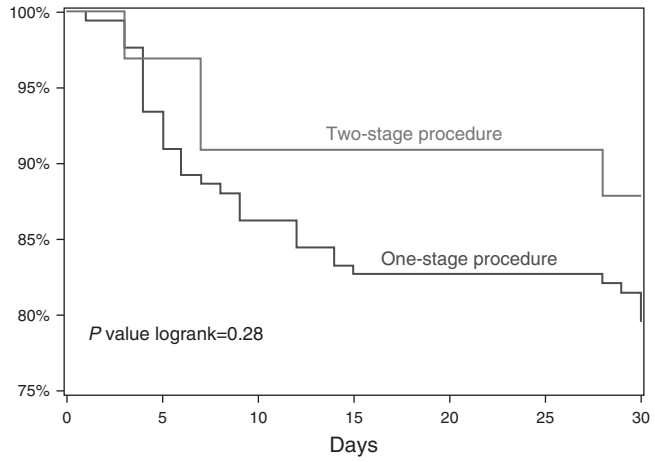

Figure 1. Kaplan–Meier curve of the cumulative risk of postoperative complications in patients having undergone a one-stage surgical procedure (*n*=176) and those having undergone a two-stage surgical procedure (*n*=33).

Table 3. Outcome after postoperative complications

	All patients with postoperative complications (*n*=43)	Two-stage procedure (*n*=3)	One-stage procedure (*n*=40)
Prolongation of hospitalization or readmission (*n*, %)	33 (76)	3 (100)	30 (75)
Further surgery for complications (*n*)	14 (32)	0	14 (35)
Secondary stoma (*n*)	8 (18)	—	8 (20)
Stoma not closed at last follow-up (*n*)	1 (2.3)	1 (33.3)	0
Duration of stoma (median (IQR), days)	3.7 (2.8–6.06)	4.1 (3.4–4.8)	3.7 (3.1–6.7)

IQR, interquartile range.

Table 4. Risk factors for postoperative complications in patients with preoperative exposure to anti-TNF agents and one-stage surgical procedures

	OR (95% CI)
Anti-TNF agent in the month before surgery	1.01 (0.52–2.01)
Combination therapy (immunosuppressants and anti-TNF)	1.38 (0.48–5.15)
Time interval between last anti-TNF administration and surgery	0.99 (0.97–1.02)
Trough serum level >1 μg/ml	0.69 (0.21–2.22)
Trough serum level >3 μg/ml	0.95 (0.28–2.96)

CI, confidence interval; OR, odds ratio; TNF, tumor necrosis factor.

DISCUSSION

Ileocecal resections expose CD patients to a high risk of postoperative complications. In this large, nationwide, prospective study performed by the REMIND group, postoperative complications occurred in 21% of patients—a proportion that is similar to previous reported values (3–7). There were no deaths, although severe complications were observed in 9% of patients and secondary stomy was required in 8%.

The risk of postoperative complications in CD has been assessed in several population-based studies. A study of an adult cohort (*n*=152) in the USA reported an early postoperative complication rate of 37%. One patient died (mortality rate: 0.7%) of sepsis following the occurrence of enterocutaneous fistula with bile leakage. Among the 80 reported complications, 6% were abscesses, 4% were wound infections, 4% corresponded to anastomotic leakage, and 9% were extra-abdominal infections (3). Patients with colonic disease were more likely to develop postoperative complications than patients with ileal or ileocolonic disease. The influence of preoperative treatment was not evaluated. A recent EPIMAD population-based study in northern France evaluated the risk of postoperative complications in 128 children with CD (76% of whom underwent ileocecal resections) (4). Thirty-two (25%) patients experienced at least one early postoperative complication in which 12% of the complications were wound abscesses, 7% were intra-abdominal abscess, 2% corresponded to anastomotic leakage, and 33% corresponded to extra-abdominal infections. No deaths, bleeding episodes, or venous thromboembolic complications were observed. Exposure to corticosteroids in the 3 months before surgery was associated with postoperative complications in a bivariate analysis only. Data on the risk of postoperative complications after ileocecal resection specifically are scarce, and the few available data came from retrospective studies of single referral centers (6,7,16). The reported incidence of intra-abdominal septic complications (anastomotic leakage, intra-abdominal abscess, and enterocutaneous fistula) ranged from 9 to 13%.

With a view to improving postoperative outcomes and reducing postoperative complications, it is essential to determine the patient's individual risk prior to surgery (17,18). According to the literature, exposure to corticosteroids in the 4 weeks before surgery is significantly more frequent in patients with postoperative complications. In contrast to previous studies, we found that the presence of abscesses or luminal fistulas at surgery was not associated with a greater incidence of postoperative complications. Hence, the 4 weeks before surgery seems to be a period that critically determines the postoperative outcome. A prospective study showed that (i) adequate nutritional support, (ii) weaning off corticosteroids, and (iii) control of intra-abdominal sepsis were pivotal for preoperative management and were associated with a lower incidence of anastomotic leakage and postoperative complications (19). Several other studies (20–22) have confirmed the positive impact of preoperative nutritional therapy on the postoperative complication rate in patients with poor nutritional status. It has been observed that the risk of postoperative complications increases with the number of risk factors. Before the advent of anti-TNF therapy, Yamamoto *et al.* (7) determined that a low preoperative serum albumin level,

preoperative corticosteroid use, and the presence of intra-abdominal abscess or fistula at the time of laparotomy was associated with a significantly greater the risk of postoperative infectious complications. The risk of septic complications was 29% in a patient with three of these risk factors and 50% in a patient with all four risk factors. Many authors therefore recommend diversion for patients with more than two risk factors (6,7).

The nature of the risk of postoperative complications associated with anti-TNF agents in CD is still subject to debate, and there is no clear consensus. Most studies have not demonstrated a significant association between preoperative anti-TNF therapy and postoperative complications. Appau *et al.* (23) were the first to report that exposure to anti-TNF agents in the 3 months before surgery was associated with an increased risk of postoperative septic complications after ileocecal resection. However, studies showing an association between postoperative complications and anti-TNF therapy have been criticized for not taking account of the disease activity, as anti-TNF treatment might simply be a surrogate marker for severe disease. In line with this hypothesis, a large, a large single-center study (24), demonstrated an increased rate of infectious and surgical site complications in CD patients exposed to anti-TNF therapy (<8 weeks), regardless of disease severity. According to the recently published results of a large UK study of a cohort of CD patients with ileocecal resection, peri-operative use of biologics was an independent predictor (hazard ratio (95% CI)=24.6 (2.0–29)) of postoperative intra-abdominal septic complications after adjustment for smoking status, concomitant upper gastrointestinal involvement, peri-operative anemia, and peri-operative hypoalbuminemia (16). It is noteworthy that the latter analysis did not take account of preoperative corticosteroid therapy or disease activity. Waterman *et al.* (25) compared the postoperative outcomes in 195 IBD patients exposed to anti-TNF agents in the 180 days before surgery vs. controls matched by type of surgical procedure, type of IBD, preoperative corticosteroid exposure (≥20 mg/day) and age at surgery. In a multivariate analysis adjusted for age, type of disease, type of main procedure, preoperative prednisone requirements, BMI, and preoperative treatment with azathioprine or 6-mercaptopurine, there were no significant intergroup differences in any of the outcomes. When the analysis was restricted to patients with small bowel resection (n=69), the frequencies of most of the complications were again similar in the two groups (except for bacteremia and a postoperative requirement for antibiotics). Three meta-analyses have sought to accurately determine the impact of peri-operative anti-TNF agents on outcomes (8–10). The pooled data suggest a modest but significant increase in the risk of septic postoperative complications in CD (with an OR ranging from 1.45 to 1.93); it is noteworthy that a sensitivity analysis of disease severity could not be performed. Furthermore, these meta-analyses evidenced marked heterogeneity with regard to the time interval since the last administration of anti-TNF agents, the type of surgery, the criteria used to define complications and the follow-up time after surgery. Moreover, most of the studies included in the meta-analyses were not able to control for important confounding factors, such as disease severity, the indication and timing of surgery, corticosteroid use, and nutritional status. All these limitations make it difficult to draw definitive conclusions from these studies; elevated postoperative complication rates in patients exposed to anti-TNF agents may in fact reflect the impact of disease severity and a higher likelihood of concurrent corticosteroid use, rather than a direct effect of anti-TNF therapy. The present prospective study is the first to show that neither the preoperative use of anti-TNF agents nor the time interval since the last administration of anti-TNF agents were associated with postoperative complications (after adjustment for disease activity and preoperative corticosteroid use). With a view to better assessment of the impact of preoperative anti-TNF treatment on the postoperative course, it might be useful to assay serum anti-TNF levels. Lau *et al.* (12) recently evaluated the impact of preoperative serum anti-TNF levels in 109 patients with CD. The researchers observed an increase in postoperative morbidity (OR=2.5; P=0.03) and infectious complications (OR=3.0; P=0.03) in the group of patients with a trough serum IFX level ≥3 µg/ml. We assayed serum anti-TNF levels on the day of surgery in patients having been exposed to these drugs in the 3 months before the resection. Thirty-six patients had a trough serum level ≥3 µg/ml; this variable did not appear to be correlated with the frequency of postoperative complications.

The present study had some limitations. Despite its nationwide, multicenter design, it was performed in referral centers that managed IBD patients with severe and often complicated disease. However, these centers were staffed by highly experienced and well-trained surgeons and IBD teams. We were not able to determine the level of preoperative corticosteroid exposure that provides an important message for clinicians. The present study also had several strengths. It is the first prospective study to have evaluated the risk of postoperative complications in CD. We focused on ileocecal resection in a well-characterized, homogenous population; this enabled us to analyze factors associated with postoperative complications while taking account of important confounding variables. We were able to accurately evaluate the impact of anti-TNF agents by collecting data on the date of last administration, the type of anti-TNF agent administered, and the serum anti-TNF level on the day of surgery.

In conclusion, the risk of postoperative complications remains high among CD patients undergoing ileocecal resection. Corticosteroid treatment in the 4 weeks prior to surgery was significantly associated with an elevated postoperative complication rate. In contrast, preoperative anti-TNF therapy (whatever the serum drug level or the time interval between last administration and surgery) was not associated with the occurrence of postoperative complications.

REMIND STUDY GROUP INVESTIGATORS:

Pierre Cattan, Mircea Chirica, Hélène Corte, Clotilde Baudry, Nelson Lourenco, My-Linh Tran-Minh, Mariane Maillet, Joelle Bonnet, Leila Chedouba, Lionel Lebourhis, Victor Chardiny, Céline Grand, Andrée Nisard; Laurent Beaugerie, Jacques Cosnes, Loic Brot, Sylvie Rajca, Cecilia Landman, Harry Sokol, Jeremie Lefevre, Magali Svreck, Nadia Hoyau-Idrissi, Leon Maggiori,

Yoram Bouhnik, Olivier Corcos; Xavier Dray, Ulrika Chaput; Marion Goutte, Gilles Bommelaer, Emilie Vazeille, Nicolas Barnich; Maria Nachury, Pierre Desreumaux, Coralie Sommeville; Jean-Louis Dupas, Franck Brazier, Denis Chatelain, Christophe Attencourt, Martine Leconte; Henri Thiebault, Julien Loreau, Stéphane Nancey, Bernard Flourié, Yves François, Anne-Laure Charlois, Peggy Falgon, Driffa Moussata, Marion Chauvenet, Sarah Boyer; Xavier Hebuterne, Paul Hofmann; Carole Margalef, Faycal Djenidi, Patricia Detre.

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CONFLICT OF INTEREST

Guarantor of the article: Matthieu Allez, MD, PhD.

Specific author contributions: Concept and study design, acquisition, and interpretation of data, drafting the manuscript: Mathurin Fumery, Matthieu Allez, Philippe Seksik; critical revision of the manuscript: Philippe Seksik, Claire Auzolle, Nicolas Munoz-Bongrand, Marc Chevrier, Pascal Houze, Xavier Jouven, Matthieu Allez; statistical analysis: Claire Auzolle, Xavier Jouven; performed surgical procedures, critical revision of the manuscript: Jean-Marc Gornet, Eddy Cott, Anne Dubois, Najim Chafai, Leon Maggiori, Karine Pautrat, Charles Sabbagh, Philippe Zerbib; acquisition of data: Jean-Marc Gornet, Carmen Stefanescu; acquisition of data, critical revision of the manuscript: Gilles Boschetti, Anthony Buisson, Benjamin Pariente, Philippe Marteau, Jerome Filippi, Carmen Stefanescu; concept and study design: Carmen Stefanescu, Xavier Treton; biological analysis: Marc Chevrier, Pascal Houze; acquisition and interpretation of data, drafting and critical revision of the manuscript: Xavier Treton.

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Postoperative complications are frequent soon after surgery in patient with CD.
- ✓ Several putative risk factors for postoperative complications after ileocecal resection have been identified: they include the presence of abscesses at surgery, prior corticosteroid therapy, and impaired nutritional status.
- ✓ Anti-TNF therapy may increase the risk of postoperative complications.

WHAT IS NEW HERE

- ✓ This is the first prospective study to show that 23% of patients experienced postoperative complications after one-stage ileocecal resection, and that half of these complications were severe.
- ✓ In a multivariate analysis, only corticosteroid treatment in the 4 weeks before surgery was significantly associated with an elevated postoperative complication rate (OR (95% CI)=2.69 (1.15–6.29); *P*=0.022).
- ✓ Preoperative anti-TNF therapy (regardless of the serum level or the time interval between last administration and surgery) was not associated with an elevated risk of postoperative complications.

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