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REVIEW ARTICLE

Preoperative use of anti-TNF therapy and postoperative complications in inflammatory bowel diseases: A meta-analysis

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Anti-TNFα;
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Abstract

Background and aims: About one-third of inflammatory bowel disease (IBD) patients still require surgery. A growing number of them receive anti-tumor necrosis factor (TNF) therapy before surgery. The present meta-analysis studied the risk of postoperative complications in IBD patients treated with anti-TNF.
Methods: MEDLINE was searched (up to January 2012) to identify observational studies reporting the prevalence of postoperative complications in IBD patients. The prevalence of overall, infectious, and non-infectious postoperative complications was extracted for all studies, and according to preoperative anti-TNF treatment where reported. Pooled prevalence, as well as odds ratios (ORs), with 95% confidence intervals (CIs) was calculated.
Results: The search identified 86 citations. Twenty-one studies, containing 4251 subjects, reported the prevalence of postoperative complications according to preoperative anti-TNF treatment. Pooled prevalence of any postoperative complication was 21%, 35%, and 26% in Crohn's disease (CD), ulcerative colitis (UC) or inflammatory bowel disease unspecified (IBD-U) and IBD, respectively. The prevalence of any postoperative complication was increased in IBD patients who underwent preoperative anti-TNF therapy (OR: 1.25; 95% CI: 1.02–1.53). Pooled prevalence of infectious postoperative complications was 16%, 17%, and 15% in CD, UC/IBD-U and IBD, respectively. The prevalence of infectious postoperative complications was increased

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in CD patients who underwent preoperative anti-TNF therapy (OR: 1.45; 95% CI: 1.03–2.05). The confounding effect of concomitant therapies could not be studied.
Conclusions: Preoperative anti-TNF use slightly increases the occurrence of overall postoperative complications in IBD patients, and particularly infectious complications in CD patients. Postoperative complications are not increased in UC.
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1. Introduction

Nearly one-third of Crohn's disease (CD) patients still require a major abdominal resection in the 5 years following disease diagnosis in the era of biologic therapy.[1,2] About one-tenth of patients still require colectomy for UC at 5 years in the era of biologics.[3,4] Anti-tumor necrosis factor (TNF) agents are increasingly used in inflammatory bowel disease (IBD) patients. Up to 60% of CD patients received an anti-TNF before first abdominal surgery.[2] Almost one-third of CD patients receive an anti-TNF treatment in the 6 months preceding a small bowel resection.[5] A recent study showed that between ulcerative colitis (UC) diagnosis and colectomy, 30% of patients received at least one anti-TNF agent.[4] The influence of biologic agents on postoperative outcomes is therefore of particular interest in clinical practice.

Most studies focusing on CD patients have failed to demonstrate that preoperative anti-TNF therapy could alter postoperative outcomes.[6–14] However, the largest study has shown that infliximab use within the 3 months before surgery is associated with increased postoperative sepsis and abscess in CD patients.[15] In UC, a meta-analysis found that infliximab is associated with an increased risk of overall short-term post-operative complications.[16] Subsequent studies failed to show a negative impact of anti-TNF therapy on postoperative outcomes.[17–22] As a result, there remains controversy as to whether exposure to anti-TNF therapy prior to surgery is associated with higher rates of postoperative complications.

We have therefore performed a systematic review and a meta-analysis of the existing studies exploring the association between pre-operative anti-TNF treatment and early postoperative complications in patients with IBD. The aims of our study were to determine if preoperative anti-TNF use affects overall postoperative complications, infectious complications, or non-infectious complications in IBD patients, and for CD or UC patients separately.

2. Methods

2.1. Search strategy and study selection

A search of the medical literature was conducted in MEDLINE indexed literature using the PubMed search engine from the National Center for Biotechnology Information (http://www.pubmed.gov) (January 1966 to January 2012). Observational studies evaluating the effect of preoperative anti-

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Table 1 Eligibility criteria.

Observational studies
Adults (>50% of patients aged >16 years)
Inflammatory bowel disease patients: Crohn's disease, ulcerative colitis, and/or inflammatory bowel disease unspecified
Patients undergoing abdominal surgery
Compared patients preoperatively treated or not treated with anti-TNF [a]
Assessment of early overall, infectious, or non-infectious postoperative complications [b]

[a] Infliximab, adalimumab or certolizumab.
[b] Within 30 days postoperatively.

TNF therapy on postoperative complications in patients with CD and/or UC and/or inflammatory bowel disease unspecified (IBD-U) requiring abdominal surgery were eligible for inclusion. Only studies assessing short-term postoperative complications were included (within 30 days after surgery). Studies could report the total number of complications, or infectious, or non-infectious complications. Studies evaluating any type of anti-TNF therapy (infliximab, adalimumab, or certolizumab) were considered eligible. Studies evaluating only pediatric patients were excluded (Table 1).

Studies were identified using the following search terms: "*postoperative complications*" as medical subject headings (MeSH) as well as *postoperative* and *perioperative* as free text terms. These were combined using the set operator AND with studies identified with the search term "*tumor necrosis factor-alpha/antagonist and inhibitors*" as MeSH, as well as *anti TNF*, *infliximab*, *adalimumab*, or *certolizumab* as free text terms. Finally, these were combined using the set operator AND with studies identified with the search terms "*inflammatory bowel disease*", "*colitis, ulcerative*" and "*Crohn disease*" as MeSH, as well as *inflammatory bowel disease*, *ulcerative colitis* and *Crohn's disease* as free text terms. The literature search was restricted to English language articles. Manual searches of reference lists from potentially relevant papers were used to identify any additional studies that may have been missed using the electronic search. We also conducted a manual search of abstracts from the European Crohn's and Colitis Organisation, the American Gastroenterological Association Digestive Diseases Week, and the United European Gastroenterology Week (all from 2008 to 2011 inclusive) congresses.

Studies were assessed independently by two investigators (VB, XR), according to the pre-defined eligibility criteria. Any disagreements in eligibility assessment were resolved by consensus. This manuscript follows the criteria of the 'Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group'.[23]

2.2. Data extraction

Data were extracted independently by two investigators onto a Microsoft Excel spreadsheet (XP professional edition; Microsoft, Redmond, WA), with discrepancies resolved by consensus. The following data were collected for each study: total number of CD and UC patients treated with anti-TNF prior to surgery, total number of patients not treated with anti-TNF prior to surgery, and the number of CD and/or UC patients who experienced at least one overall and/or infectious and/or non-infectious postoperative complications in both the anti-TNF and the non anti-TNF group. In addition, the following

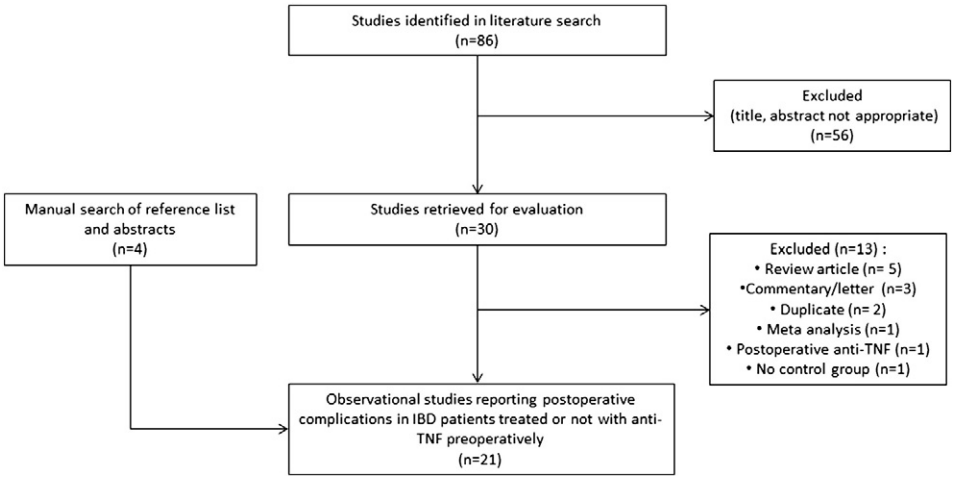

Figure 1 Flow diagram of assessment of studies identified in the systematic review.

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Table 2 Characteristics of studies included in the meta-analysis.

Study (author, year)	Type of study	Type of disease	Inclusion period	Study population (N)	Patient treated with anti-TNF(n)
Tay et al., 2003[14]	Retrospective	CD	1998–2002	100	22 (IFX: 22)
Marchal et al., 2004[11]	Case–control	CD	1998–2002	79	40 (IFX: 40)
Colombel et al., 2004[7]	Retrospective	CD	1998–2001	270	52 (IFX:52)
Appau et al., 2008[15]	Retrospective	CD	1998–2007	389	60 (IFX: 60)
Indaar et al., 2009[8]	Retrospective	CD	1999–2007	112	17
Nasir et al., 2010[12]	Retrospective	CD	2005–2009	370	119 (IFX: 69, ADA: 47, CTZ: 3)
Canedo et al., 2011[6]	Retrospective	CD	2000–2008	225	65 (IFX: 65)
Kasparek et al., 2011[9]	Case–control	CD	2001–2008	96	48 (IFX: 48)
Syed et al., 2011[31]	Retrospective	CD	2004–2010	266	126 (IFX: 126)
Schluender et al., 2007[29]	Retrospective	UC	2000–2005	151	17 (IFX: 17)
Selvasekar et al., 2007[30]	Retrospective	UC	2002–2005	301	47 (IFX: 47)
Mor et al., 2008[33]	Case–control	UC (44) IBD-U (2)	2000–2006	92	46 (IFX: 46)
Coquet-Reinier et al., 2009[19]	Case–control	UC	1999–2008	26	13 (IFX: 13)
Ferrante et al., 2009[27]	Retrospective	UC (134) IBD-U (7)	1998–2008	141	22 (IFX: 22)
Gainsbury et al., 2011[20]	Retrospective	UC	2005–2009	81	29 (IFX: 29)
Bregnbak et al., 2011[18]	Retrospective	UC	2005–2010	71	20 (IFX: 20)
De Silva et al., 2011[22]	Retrospective	UC	1996–2009	666	34 (IFX: 34)
Eshuis et al., 2010[32]	Retrospective	UC	2006–2009	39	17 (IFX: 17)
Kunikate et al., 2008[10]	Retrospective	CD (188) UC (156) IBD-U (69)	1993–2007	413	101 (IFX: 101)
Regadas et al., 2011[28]	Retrospective	UC (224) CD (21) IBD-U (4)	2001–2008	249	28 (IFX: 28)
Rizzo et al., 2011[13]	Retrospective	CD (76) UC (38)	2004–2010	114 [d]	54 (IFX:41, ADA:12, CTZ:1)

Note: CD: Crohn's disease; UC: ulcerative colitis; IBD-U: inflammatory bowel disease unspecified; IFX: infliximab, ADA: adalimumab, CTZ: certolizumab; IS: immunosuppressor, Cyclo: cyclosporin; S: steroids; IPAA: ileal pouch anal anastomosis; na: non avalaible.

[a] 10 day complications included in the analysis only.

[b] Some patients received anti-TNF up to 30 days postoperatively.

[c] Overall and infectious complication rate not available for one stage IPAA.

[d] A group of control patients (anti-TNF therapy more than 12 months preoperatively) was not included in the analysis.

clinical data were extracted for each study where available: type of study, inclusion period, overall study population, type of anti-TNF therapy, anti-TNF treatment duration, time since last anti-TNF injection/infusion, concomitant medications, type of surgery, and duration of follow-up after surgery.

To calculate overall postoperative complication rates, infectious and non-infectious complications were not pooled, as one patient could suffer from more than one complication. Similarly, infectious complications were not subtracted from the total number of complications in order to determine the non-infectious complication rate. In studies providing major and minor complication rates separately, the two data were not pooled and only major complications were included in the analysis.

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Anti-TNF treatment duration (median/mean number of infusions (IQR/SD))	Time since last anti-TNF treatment (weeks)	Concomitant medication in the anti-TNF group (n(%))	Concomitant medication in the non-anti-TNF group (n(%))	Type of surgery	Postoperative follow-up duration (days)
na	na	IS:20 (91)	IS: 50 (64)	First resection with anastomosis or strictureplasty	28
4 (1–10)	12 (78%)	IS: 24 (60) S: 12 (30)	IS: 11 (29) S: 12 (30)	Small bowel resection, ileo-colonic resection, eft colectomy or abdomino-perineal rectal excision	90 [a]
1 (1–2)	8 [b]	na	na	Surgical resection, stricturoplasty, intestinal bypass	30
na	12	IS: 37 (62) S: 39 (65)	IS: 55 (17) S: 253 (77)	Ileocolonic resection	30
na	8	IS: 8 (47) S: 10 (59)	IS: 31 (32.6) S: 37 (39)	Instetinal resection	30
na	8 [b]	IS: 32 (27) S: 37 (31)	IS: 83 (33) S: 114 (45)	Operations resulting in some form of suture or staple line at risk	30
na	12	na	na	Intestinal or colorectal resection	na
na	12	IS: 35 (73) S: 45 (94)	IS: 35 (73) S: 45 (94)	Abdominal surgery	5
na	8	na	na	Intra-abdominal surgery	na
2 (1–9)	2 (median)	IS: 16 (94) Cyclo: (29) S: 17 (100)	IS: 59 (44) Cyclo: 56 (42) S: 134(100)	Subtotal colectomy or IPAA	30
na	24	IS: 43 (92) S: 42 (89)	IS: 112 (44) S: 218 (88)	IPAA	30
3 (2–4)	13.5 (median)	IS: 18 (39)	IS: 13 (28)	Two stage IPAA	30
5 (+/−3.5)	1.5 (median)	IS: 7 (54) Cyclo: 2 (15) S: 6 (46)	IS: 1 (8) Cyclo: 7 (54) S: 5 (38)	Laparoscopic RPC with IPAA	30
2.5 (2–3)	12	IS: 13 (59) S: 14 (64)	IS: 65 (59) S: 82 (69)	Restorative proctocolectomy	30
na	12	IS: 24 (82.8) S: 27 (93.1)	IS: 28 (53.8) S: 36 (69.2)	IPAA	30
1.7 (1–2)	12	IS:5 (25) S: 15 (75)	IS: 16 (31.4) S: 33 (64.7)	Colectomy	30
na	na	na	na	Total abdominal colectomy, subtotal colectomy, or proctocolectomy	na
na	na	na	na	Two stage IPAA [c]	na
na	12	IS: 37 (37) S: 76 (75)	IS: 81 (26) S: 240 (77)	Abdominal surgery	30
na	8	IS: 15(53.6) S: 18(64.3)	IS: 35 (16) S: 107 (49)	Ileostomy reversal	30
na	12 (IFX) 4 (ADA, CTZ)	IS: 21 (39) S: 19 (35)	IS: 13 (22) S: 29 (48)	CD- or UC-related abdominal surgery	30

2.3. Data synthesis and statistical analysis

The proportion of individuals with overall, infectious and non-infectious postoperative complication in each study was combined to give a pooled prevalence of postoperative complication for studies including CD, UC/IBD-U or IBD patients. Heterogeneity between studies was assessed using the I^2 statistic with a cutoff of 50%,[24] and the χ^2 test with a P value$<$0.10, used to define a statistically significant degree of heterogeneity. Data were pooled using a random effects model,[25] to give a more conservative estimate of the prevalence of postoperative complication and the odds of a postoperative complication in these various groups. StatsDirect version 2.7.2 (StatsDirect, Sale, Cheshire, UK) was used to

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Table 3 Postoperative complications in anti-TNF treated patients.

Study (author, year)	Overall complications				Infectious complications					Non-infectious complications				
	Study population n(%)	Definition	Non-anti-TNF group n (%)	Anti-TNF group n (%)	Study population n (%)	Definition	Non-anti-TNF group n (%)	Anti-TFN group n (%)	Anti-TFN group, details (n)	Study population n (%)	Definition	Non-anti-TNF group n (%)	Anti-TFN group n (%)	Anti-TFN group, details (n)
Tay et al., 2003[14]	na	na	na	na	11 (11)	Intra-abdominal septic complications: abscess, fistula, and anastomotic leak which required intravenous antibiotics, a drainage procedure, or reexploration	8 (10)	3 (14)	Abscess (2) Leak (1)	na	na	na	na	na
Marchal et al., 2004[11]	8 (10)	Early major complications[b] (sepsis, anastomotic leak, peritonitis, local fistula or abscess, wound infection, wound failure, severe anemia, bulbar ulcer bleeding)	3 (8)	5 (13)	7 (9)	Catheter infection Wound infection Upper airway infection Infectious diarrhea Yeast infection (both major and minor complications)	1 (3)	6 (15)	Catheter sepsis (2) Wound infection (1) Upper airway infection (1), Infectious diarrhea (2) Oral–pharyngeal candidiasis (2)	na	na	na	na	na
Colombel et al., 2004[7]	63 (23.3)	na	51 (23)	12 (23)	52 (19)	Wound sepsis Intra-abdominal infection Extra-abdominal infection	43 (20)	9 (17)	na	18 (7)	CD recurrence Small bowel obstruction Gastrointestinal bleeding Thromboembolism	na	na	na
Appau et al., 2008[15]	46 (12)	na	33 (10)	13 (22)	45 (12)	Wound dehiscence Sepsis	33 (10)	12 (20)	Intra-abdominal abscess (6) Anastomotic leak (6)	1 (1)	Urinary complication	0 (0)	1 (1)	Urinary complication (1)
Indaar et al., 2009[8]	33 (29.5)	Anastomotic leak Enterocutaneous fistula Gracilis flap necrosis Intra-abdominal abscess Intraoperative bleeding Myocardial infarction Pneumonia rectal stump leak Wound dehiscence Postoperative	27 (28)	6 (35)	na	na	na	na	na	na	na	na	na	na

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		bleeding Wound infection Non-oliguric renal failure Thrombosis upper limb Prolonged ileus Urinary tract infection												
Nasir et al., 2010[12]	106 (28.6)	na	70 (28)	36 (30)	9 (3)	Intra-abdominal abscess Anastomotic leaks	5 (3)	4 (2)	na	na	na	na	na	na
Canedo et al., 2011[6]	na	na	na	na	57 (25)	Wound infection Pulmonary infection Abscess Anastomotic leakage [a]	41 (26)	16 (25)	Wound infection (9) Pulmonary infection (1) Abscess (2) Anastomotic leakage (2)	na	na	na	na	na
Kasparek et al., 2011[9]	25 (26)	Major complication [b] (anastomotic leak, intraabdominal abscess, small bowel leakage, stoma complication, postoperative hemorrhage, enterocutaneous fistula)	12 (25)	13 (27)	na	na	na	na	na	na	na	na	na	na
Syed et al., 2011[31]	na	na	na	na	87 (33)	na	38 (27)	49 (39)	na	na	na	na	na	na
Schluender et al., 2007[29]	43 (28)	Pneumonia Deep vein thrombosis Pancreatitis Acute renal failure Cerebrovascular accident Dehydration Superficial thrombophlebitis Pyoderma gangrenosum Urinary retention Readmission for small-bowel obstruction Large peristomal abscess Rectal stump leak	37 (28)	6 (35)	14 (9)	na	11 (8)	3 (18)	na	na	na	na	na	na

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Table 3 (*continued*)

Study (author, year)	Overall complications				Infectious complications					Non-infectious complications				
	Study population n(%)	Definition	Non-anti-TNF group n (%)	Anti-TNF group n (%)	Study population n (%)	Definition	Non-anti-TNF group n (%)	Anti-TFN group n (%)	Anti-TFN group, details (n)	Study population n (%)	Definition	Non-anti-TNF group n (%)	Anti-TFN group n (%)	Anti-TFN group, details (n)
		Superficial wound infection Ileus Bleeding requiring transfusion or reoperation												
Selvasekar et al., 2007[30]	153 (50.8)	na	124 (49)	29 (62)	38 (13)	Anastomotic leak Pelvic abscess Wound infections	25 (10)	13 (28)	na	na	na	na	na	na
Mor et al., 2008[33]	23 (50)	na	7 (15)	16 (35)	11 (24)	Pelvic sepsis	1 (2)	10 (28)	na	na	na	na	na	na
Coquet-Reinier et al., 2009[19]	8 (31)	Small bowel obstruction Pelvic abscess Pneumoperitoneum Anastomotic leak Pleural effusion Anastomotic Hemorrhage Small bowel perforation	5 (39)	3 (23)	2 (8)	Pelvic abscess Anastomotic leak[a]	1 (8)	1 (8)	Pelvic abscess (1)	6 (23)	Small bowel obstruction Pneumoperitoneum Pleural effusion Anastomotic Hemorrhage Small bowel perforation[a]	4 (31)	2 (15)	Small bowel obstruction (1) Pneumoperitoneum (1)
Ferrante et al. 2009[27]	na	na	na	na	31 (22)	Anastomotic leak Pelvic abscess Wound infection Nonsurgical site infectious	29 (24)	2 (9)	Wound infection (1) Nonsurgical site infection (1)	na	na	na	na	na
Gainsbury et al 2011[20]	36 (44)	Pouch/anastomotic leak Pelvic/ intraabdominal abscess Pouch-related complications Wound infection Others (thrombosis, small bowel obstruction, ileus, and one episode of wound dehiscence)	23 (44)	13 (45)	19 (24)	Pelvic/ intraabdominal abscess wound infection	14 (27)	5 (17)	Pelvic/ intraabdominal abscess (4) wound infection (1)	28 (35)	Pouch/anastomotic leak, pouch-related, other	16 (31)	12 (41)	Other (12)

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Bregnbak et al., 2011[18]	35 (49)	na	25 (49)	10 (50)	25 (35)	na	21 (41)	4 (20)	Wound infection (1) Abscess (1) Pneumonia (1) Epididymitis (1)	16 (23)	na	10 (18)	6 (30)	Ileus (6) Wound rupture (1)
De Silva et al., 2011[22]	180 (27)	Unexpected medical events that occurred between the start of the surgery and discharge from the hospital	172 (96)	8 (4)	na	na	na	na	na	na	na	na	na	na
Eshuis et al., 2010[32]	16 (41)	na	8 (36)	8 (47)	11 (28)	na	5 (23)	6 (35)	na	9 (23)	na	3 (14)	6 (35)	na
Kunikate et al., 2008[10]	67 (16)	Infectious Hypomotility Cardiac Hepato-renal Bleeding Anastomotic leak	49 (16)	17 (17)	38 (9)	Pneumonia, sepsis Anastomotic leak Enterocutaneous Fistula Wound infection/ dehiscence Intra-abdominal abscess	32 (10)	6 (6)	na	na	na	na	na	na
Regadas et al., 2011[28]	32 (13)	Infectious complications Small bowel obstruction	31 (14)	1 (4)	22 (9)	Wound infection Anastomotic leak Intra-abdominal abscess Enterocutaneous fistula Clinical sepsis	22 (10)	0 (0)	na	10 (4)	Small bowel obstruction	9 (4)	1 (4)	Small bowel obstruction (1)
Rizzo et al., 2011[13]	24 (21)	Infectious complications Hypomotility complications Thrombotic complications Bleeding requiring re-surgery Anastomotic leak Cardiac and/or hepatorenal failure	10 (17)	14 (26)	17 (15)	Pneumonia Sepsis Wound infection Intra-abdominal abscess	8 (13)	9 (17)	na	na	na	na	na	na

[a] Defined by VB and XR.
[b] Minor complication not included in analysis.

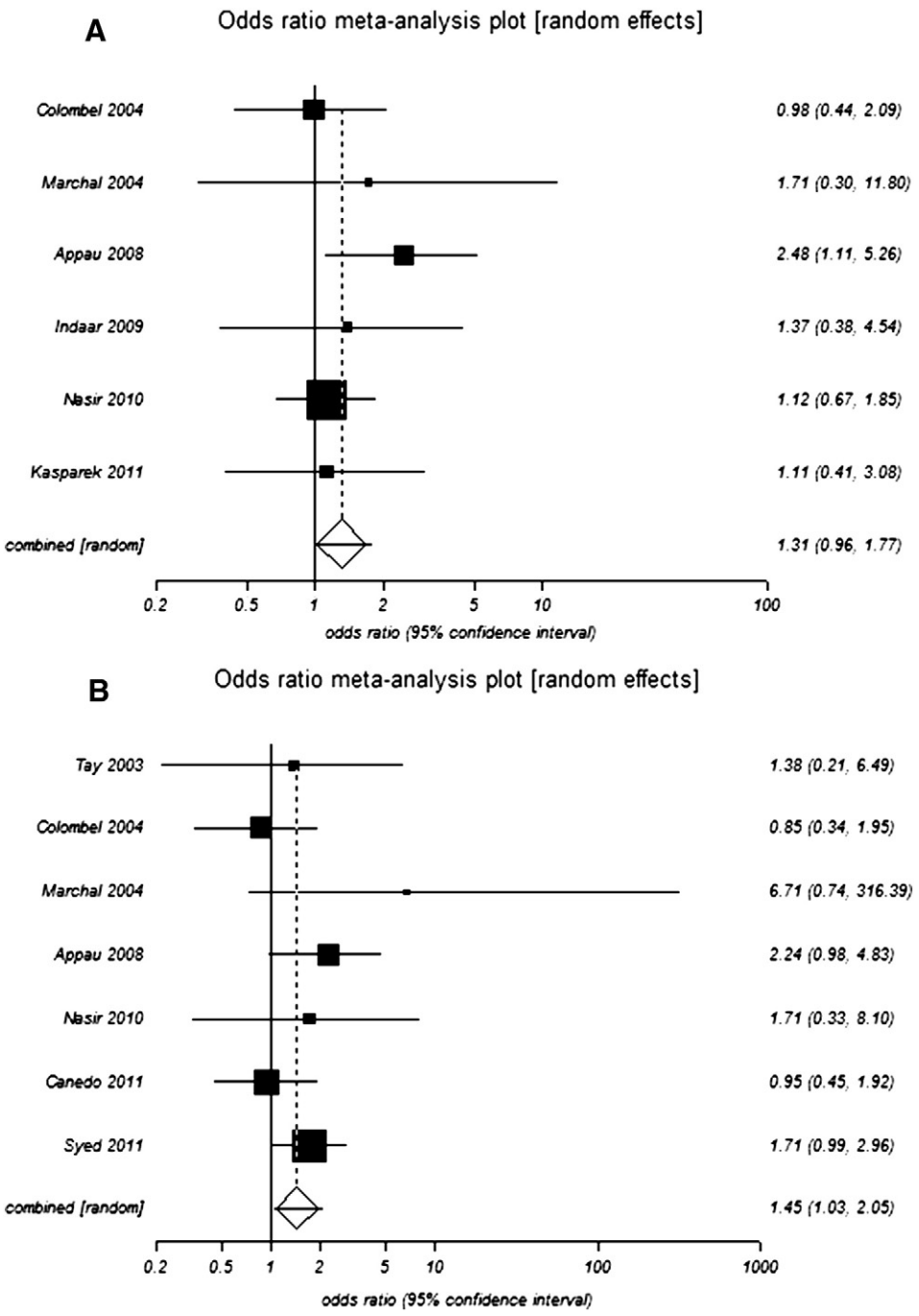

Figure 2 Pooled odds ratio for overall postoperative complications (A) and infectious complications (B) in anti-TNF and non-anti-TNF treated CD patients.

generate Forest plots of pooled prevalences and pooled ORs with 95% CIs. We planned to assess for the evidence of publication bias by applying Egger's test to funnel plots of Ors when a sufficient number of studies (more than ten) existed.[26]

3. Results

3.1. Literature search results

The search strategy identified 86 citations. We identified 30 papers that appeared to be relevant to the study question. From these, thirteen studies were excluded. Finally, 17 observational studies reporting short-term postoperative complications in patients treated preoperatively with anti-TNF were included in the analysis. Manual searches of reference list and abstracts identified 4 additional studies resulting in a total of 21 studies including 4251 patients from whom 977 were treated with anti-TNF (Fig. 1).

Seventeen of the studies were retrospective case series.[6–8,10,12–15,18,20,22,27–32] We also identified 4 case–control studies.[9,11,19,33] The study populations included CD patients, UC/IBD-U patients and both UC/IBD-U and CD patients in 9,[6–9,11,12,14,15,31] 9[18–20,22,27,29,30,32,33] and 3[10,13,28]

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studies respectively. The individual study characteristics are provided in Table 2. Individual postoperative complication rate and definitions are provided in Table 3.

3.2. Short-term postoperative complications in CD patients treated with anti-TNF

3.2.1. Overall complications

Six studies assessed overall postoperative complications in CD patients treated or not treated with anti-TNF preoperatively, and included a total of 1316 patients.[7–9,11,12,15] A total of 281 (21%) CD patients experienced any postoperative complication, 85 (25%) among 336 patients receiving anti-TNF compared with 196 (20%) of 980 patients not treated with anti-TNF. There was no statistically significant difference detected between anti-TNF and non-anti-TNF treated CD patients for any postoperative complication (OR: 1.31; 95% CI: 0.96–1.77) (Fig. 2A), with no statistically significant heterogeneity detected between studies ($I^2 = 0\%$, $P = 0.50$).

3.2.2. Infectious complications

Seven studies assessed infectious postoperative complications in CD patients treated or not treated with anti-TNF preoperatively, and included a total of 1699

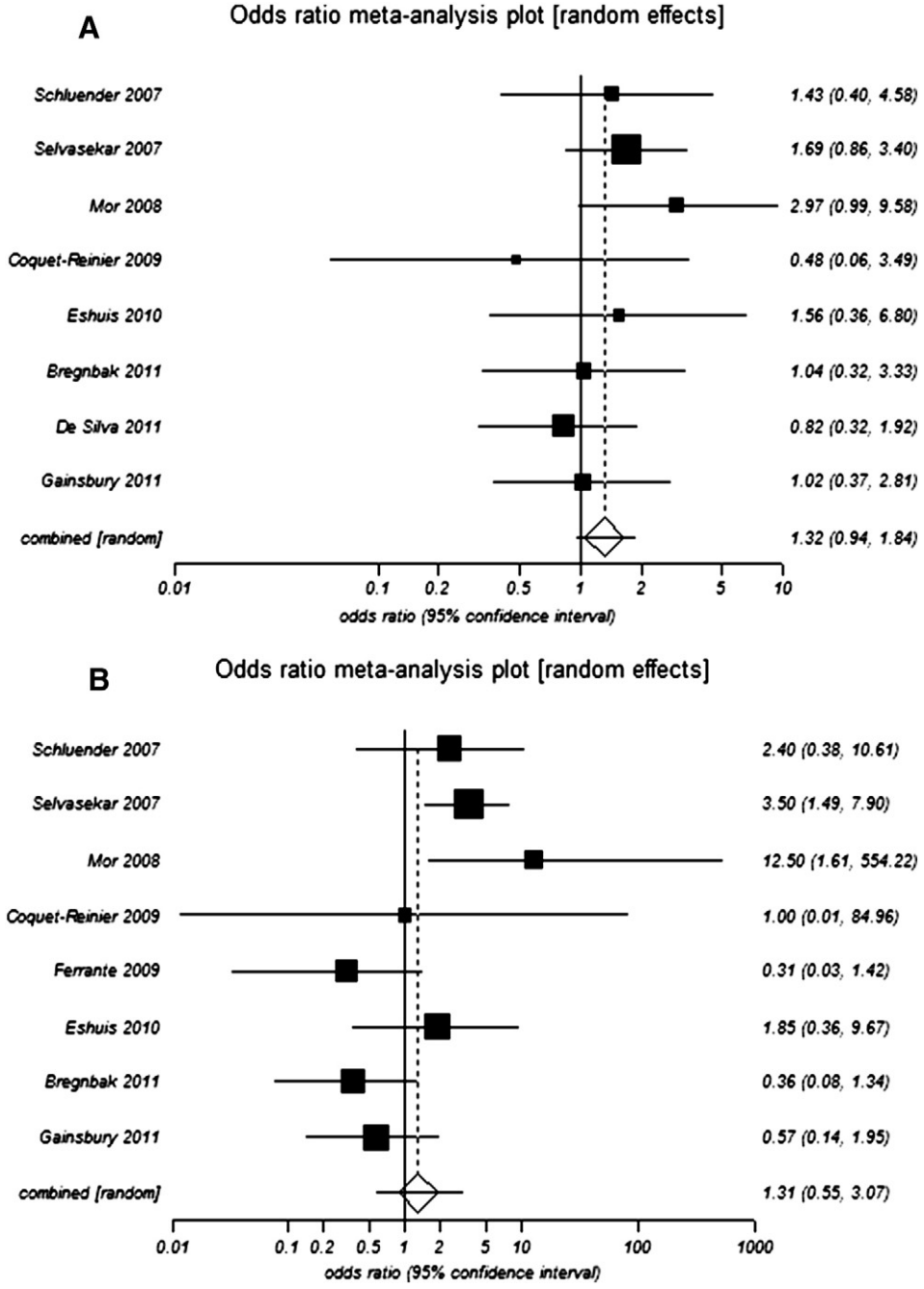

Figure 3 Pooled odds ratio for overall postoperative complications (A) and infectious complications (B) in anti-TNF and non-anti-TNF treated UC/IBD-U patients.

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patients.[6,7,11,12,14,15,31] A total of 268 (16%) CD patients experienced an infectious postoperative complication, 99 (21%) of 484 patients receiving anti-TNF compared with 169 (14%) of 1215 patients not treated with anti-TNF. There was a significantly higher rate of infectious postoperative complications in anti-TNF treated CD patients (OR: 1.45; 95% CI: 1.03–2.05) (Fig. 2B), with no statistically significant heterogeneity detected between studies (I^2 = 14.8%, P = 0.31).

3.3. Short-term postoperative complications in UC or IBD-U patients treated with anti-TNF

3.3.1. Overall complications

Eight studies assessed overall postoperative complications in UC/IBD-U patients treated or not treated with anti-TNF preoperatively, and included a total of 1427 patients.[18–20,22,29,30,32,33] A total of 494 (35%) UC/IBD-U patients experienced any postoperative complication, 93 (41%) of 223 patients receiving anti-TNF compared with 401 (33%) of 1204 patients not treated with anti-TNF. There was no statistically significant difference detected between anti-TNF and non-anti-TNF treated UC/IBD-U patients for any postoperative complication (OR: 1.32; 95% CI: 0.94–1.84) (Fig. 3A), with no statistically significant heterogeneity detected between studies (I^2 = 0%, P = 0.51).

3.3.2. Infectious complications

Eight studies assessed infectious postoperative complications in UC/IBD-U patients treated or not treated with anti-TNF preoperatively, including a total of 902 patients. A total of 151 (17%) UC/IBD-U patients experienced an infectious postoperative complication, 44 (21%) of 211 patients who received anti-TNF compared with 107 (16%) of 691 patients not treated with anti-TNF. There was no statistically significant difference detected between anti-TNF and non-anti-TNF treated UC/IBD-U patients for infectious postoperative complications (OR: 1.31; 95% CI: 0.55–3.07) (Fig. 3B), but with statistically significant heterogeneity detected between studies (I^2 = 67.6%, P = 0.003).

3.3.3. Non-infectious complications

Four studies assessed non-infectious postoperative complications in UC/IBD-U patients treated or not treated with anti-TNF preoperatively, and included a total of 217 patients.[18–20,32] A total of 59 (27%) UC/IBD-U patients experienced a non-infectious postoperative complication, 26 (33%) of 79 patients who received anti-TNF compared with 33 (24%) of 138 patients not treated with anti-TNF. There was no statistically significant difference detected between anti-TNF and non-anti-TNF treated UC/IBD-U patients for non-infectious postoperative complications (OR: 1.60; 95% CI: 0.85–3.00) (Supplementary Fig. 1), with no statistically significant heterogeneity detected between studies (I^2 = 0%, P = 0.41).

3.4. Short-term postoperative complications in IBD patients treated with anti-TNF

3.4.1. Overall complications

Seventeen studies assessed overall postoperative complications in IBD patients treated or not treated with anti-TNF preoperatively, and included a total of 3519 patients.[7–13,15,18–20,22,28–30,32,33] A total of 897 (26%) IBD patients experienced any postoperative complication, 210 (28%) of 742 patients who received anti-TNF compared with 687 (25%) of 2777 patients not treated with anti-TNF. There was a significantly higher rate of any postoperative complication in anti-TNF treated IBD patients (OR: 1.28; 95% CI: 1.04–1.57) (Fig. 4A), with no statistically significant heterogeneity detected between studies (I^2 = 0%, P = 0.58), and no evidence of funnel plot asymmetry (Egger test, P = 0.54).

3.4.2. Infectious complications

Eighteen studies assessed infectious postoperative complications in IBD patients treated or not treated with anti-TNF preoperatively, and included a total of 3377 patients.[6,7,10–15,18–20,27–33] A total of 496 (15%) IBD patients experienced an infectious postoperative complication, 158 (18%) of 878 patients who received anti-TNF compared with 338 (14%) of 2499 patients not treated with anti-TNF agents. There was no statistically significant difference detected between anti-TNF and non-anti-TNF treated IBD patients for infectious postoperative complications (OR: 1.27; 95% CI: 0.87–1.85) (Fig. 4B), but with statistically significant heterogeneity between studies (I^2 = 51.5%, P = 0.006). There was no evidence of funnel plot asymmetry (Egger test, P = 0.67).

3.4.3. Non-infectious complications

Six studies assessed non-infectious postoperative complications in IBD patients treated or not treated with anti-TNF preoperatively, and included a total of 855 patients.[15,18–20,28,32] A total of 70 (8%) IBD patients experienced a non-infectious postoperative complication, 28 (17%) of 167 patients who received anti-TNF compared with 42 (6%) of 688 patients not treated with anti-TNF agents. There was no statistically significant difference detected between anti-TNF and non-anti-TNF treated IBD patients for non-infectious postoperative complications (OR: 1.65; 95% CI: 0.89–3.06) (Supplementary Fig. 2), with no statistically significant heterogeneity detected between studies (I^2 = 4.7%, P = 0.39).

4. Discussion

The present meta-analysis shows that pre-operative treatment with anti-TNF was associated with a small, but statistically significant, increase in overall post-operative complication rates in IBD in the short-term. We also found a significant association between pre-operative anti-TNF use and short-term infectious complications in CD patients. To our knowledge, to date, no meta-analysis has assessed the impact of anti-TNF therapy in the perioperative setting in CD patients.

Among the 9 studies including a total of 1907 CD patients, only two studies found that preoperative anti-TNF could lead to more postoperative complications.[15,31] By pooling 484 CD patients who received preoperative anti-TNF therapy, we were able to demonstrate that the prevalence of infectious postoperative complications in CD patients is increased, with an OR of 1.45. This is comparable to the risk related to the use of systemic glucocorticosteroids, which has been estimated in a previous meta-analysis as 68%.[34] Interestingly,

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Figure 4 Pooled odds ratio for overall postoperative complications (A) and infectious complications (B) in anti-TNF and non-anti-TNF treated IBD patients.

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this is in line with the largest study included, which showed that infliximab use is associated with 30-day postoperative readmission, sepsis, and intra-abdominal abscess.[18] This study accounted for only 23% of all CD patients included in the calculation of the postoperative infectious complication risk in our meta-analysis.[18]

Interestingly, the present meta-analysis failed to identify an increased risk of overall, infectious or non-infectious complications in UC patients receiving anti-TNF preoperatively. In a previous meta-analysis including 706 patients, Yang et al. found that pre-operative treatment with infliximab increased by 80% short-term total post-operative complications in UC.[16] However, as clearly stated by the authors, their analysis was underpowered due to the small number of studies and high degree of heterogeneity among studies.[16] Five studies have been published since which were all negative.[18–20,22,32] By pooling 1427 UC patients, we were able to show that preoperative anti-TNF therapy is not associated with an increased rate of overall post-operative complications in the short-term. Considering a three-stage IPAA, rather than a two-stage procedure, has been proposed in UC patients receiving anti-TNF close to the time of surgery.[35,36] Our results do not support such a strategy.

The present meta-analysis has several limitations. Most of the studies were retrospective ones. The possible mistakes of the retrospective analysis may add during the meta-analysis and not all the confounding factors can be controlled in these observational studies. For instance, nutritional status and training of the surgeon were not analyzed while they are known to affect postoperative outcomes.[21,37] Concomitant immunomodulator and glucocorticosteroids were used in nearly all groups of anti-TNF patients, but the rates of their use were not similar in anti-TNF treated and control groups in most studies.[10–13,15,20,29,30] The use of such concomitant treatment is missing in five studies.[6,7,22,31,32] Steroid doses are not detailed in most of the studies. Immunosuppressive therapy, such as azathioprine, does not seem to affect postoperative outcomes, whereas glucocorticosteroids increased postoperative complications, particularly infectious ones, in a dose dependant manner.[7,34,38] There was also a lack of adjustment for disease severity. Furthermore, duration of follow-up is unknown in four studies.[6,22,31,32] The duration of follow-up was only 5 days in one study which could be not enough to evaluate postoperative complications.[9] Sensitivity analysis excluding this study was performed (Supplementary Fig. 3). Another limitation of several of these studies is the relatively long pre-operative IFX window, often 12 weeks or more. This should be balanced with pharmacokinetics data, which suggest that the half-life of infliximab is between 7 and 18.5 days.[39] In addition, preoperative anti-TNF duration is not provided in 14 studies and is less than 3 injections in 4 others.[6–10,12–15,18,20,22,27–32] Finally, if patients received induction therapy could not be assessed. This could have underestimated the influence of anti-TNF on postoperative outcomes. The strengths of our meta-analysis are the large number of studies, and hence patients, included in the analysis, the well-described and rigorous methodology, and the analysis of overall, infectious and non-infectious complications.

In conclusion, the present study suggests that preoperative anti-TNF therapy could be associated with a higher rate of overall postoperative complications in IBD patients, with an increased risk of postoperative infections in CD. UC patients receiving preoperative anti-TNF treatment do not seem to be at an increased risk of experiencing postoperative complications. In the present study, the confounding effect of concomitant therapies could not be studied. Further prospective studies about the relationship between anti-TNF and post-operative complications, able to control potential confounding factor and using homogeneous classification of postoperative complications, are keenly awaited before definitive recommendations can be made.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.crohns.2013.01.014.

Conflict of interest

The authors declare the following personal interests:

- VB declares no conflict of interest.
- ACF has received speaker's fees from Shire and MSD.
- EDT declares no conflict of interest.
- JFC has received consulting and lecture fees from Abbott and Merck.
- XR has received consulting and lecture fees from Abbott and Merck.
- LPB has received consulting and lecture fees from Abbott and Merck.

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Specific author contributions:

- VB: acquisition and interpretation of data; and drafting of the manuscript;
- ACF, EDT, XR: acquisition and interpretation of data; and drafting of the manuscript
- LPB: study concept and design; acquisition and interpretation of data; drafting of the manuscript; and study supervision.

The authors did not have writing assistance.

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