Risk of Postoperative Infectious Complications From Medical Therapies in Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis

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Objective: To assess the impact of inflammatory bowel disease (IBD) medications on postoperative infection risk within 30 days of surgery.

Methods: We searched multiple electronic databases and reference lists of articles dating up to August 2018 for prospective and retrospective studies comparing postoperative infection risk in patients treated with an IBD medication perioperatively with the risk in patients who were not taking that medication. Outcomes were overall infectious complications and intra-abdominal infections within 30 days of surgery.

Results: Sixty-three studies were included. Overall infectious complications were increased in patients who received anti–tumor necrosis factor (TNF) agents (odds ratio [OR] 1.26; 95% confidence interval [CI], 1.07-1.50) and corticosteroids (OR 1.34; 95% CI, 1.25-1.44) and decreased in those who received 5-aminosalicylic acid (OR 0.63; 95% CI, 0.46-0.87). No difference was observed in those treated with immunomodulators (OR 1.08; 95% CI, 0.94-1.25) or anti-integrin agents (OR 1.06; 95% CI, 0.67-1.69). Both corticosteroids and anti-TNF agents were associated with increased intra-abdominal infection risk (OR 1.63; 95% CI, 1.33-2.00 and OR 1.46; 95% CI, 1.08-1.97, respectively), whereas no impact was observed with 5-aminosalicylates, immunomodulators, or anti-integrin therapy. Twenty-two studies had low risk of bias while the remaining studies had very high risk.

Conclusions: Corticosteroids and anti-TNF agents were associated with increased overall postoperative infection risk as well as intra-abdominal infection in IBD patients, whereas no increased risk was observed for immunomodulators or anti-integrin therapy. Although these results may result from residual confounding rather than from a true biological effect, prospective studies that control for potential confounding factors are required to generate higher-quality evidence.

Key Words: inflammatory bowel disease, infection, postoperative, biologic

BACKGROUND

Inflammatory bowel diseases (IBD), including Crohn disease (CD) and ulcerative colitis (UC), are chronic and incurable disorders characterized by inflammation of the gastrointestinal tract. More than 1.2 million individuals in North America are affected by IBD, and the worldwide prevalence is projected to increase exponentially over the next decade.[1]

The aim of medical therapy in IBD is to decrease inflammation, hence alleviating symptoms and allowing mucosal healing.[2] Depending on the severity of inflammation and symptoms, medications including 5-aminosalicylates (5-ASA), corticosteroids, immunomodulators, small molecules, and biologics can be used.

The expansion of the therapeutic armamentarium for IBD has improved physicians' ability to manage these diseases medically and often delay or avoid surgery.[3–5] Despite these advances, a meta-analysis found that nearly half of CD patients and 16% of UC patients required surgery within 10 years of diagnosis.[5] Furthermore, many medications commonly used to treat IBD are recognized to increase risk of infection because of their immunosuppressive effects.[2] Hence, concerns have been raised that preoperative treatment with these medications could theoretically impair wound healing and in turn increase postoperative infections and other complications.[6–8]

Of particular concern are biologic medications. Tumor necrosis factor alpha (TNF-α) and leukocytes are important for wound healing and their blockade by biologics has been associated with impaired wound healing in rat models.[7, 9, 10]

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Studies evaluating this topic have yielded conflicting results.[10–16] Therefore, a systematic review of the literature would be valuable to study the impact of perioperative IBD medications on the risk of postoperative infectious complications.

METHODS

This is an abridged version of a Cochrane Review.[17] This systematic review and meta-analysis is reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[18]

Data Sources and Search Strategy

We searched the following databases from inception up to August 30, 2018: MEDLINE, Embase, the Cochrane Library, the Cochrane IBD Group Specialized Register, Clinicaltrials.gov, and the World Health Organization International Clinical Trials Registry Platform. The search strategies for each database are reported in the Appendix. The bibliographies of applicable systematic reviews were also recursively searched.

Study Selection

Manuscripts and abstracts of randomized controlled trials, quasi-randomized controlled trials, nonrandomized controlled trials, prospective cohort studies, retrospective cohort studies, case-control studies, and cross-sectional studies were considered for inclusion. Meta-analyses, systematic reviews, case series, and case reports were excluded. Studies lacking a comparison or control group were also excluded. Studies reporting complications that occurred more than 30 days after surgery were excluded.

Patients needed to have a diagnosis of CD, UC, or indeterminate colitis and have undergone any type of surgery, including both abdominal and nonabdominal surgeries. The majority of patients in each study were required to be adults (≥ age 18). We included studies comparing patients treated with an IBD medication preoperatively or within 30 days postoperatively with patients who were not taking that medication. The following classes of medications were examined: 5-ASAs, corticosteroids, immunomodulators, anti-TNF medications, anti-interleukin medications, anti-integrin medications, and small molecules.

Two investigators (Law and Bao) independently screened the titles and abstracts identified by the literature search. Potentially relevant articles were reviewed in full to determine eligibility for inclusion. Any disagreements were resolved through consensus and evaluation by a third investigator (Narula).

Outcomes of Interest

The primary outcome was overall postoperative infectious complications within 30 days of surgery. The secondary outcome was intra-abdominal infectious complications. Prespecified subgroup analyses were also performed for patients with CD and UC only, studies conducted before and after 1998 (when infliximab was approved by the U.S. Food and Drug Administration), and studies in which patients' last dose of biologic was within 8 weeks of surgery versus more than 8 weeks.

Data Extraction

Two investigators (Law and Narula) performed data extraction independently. In cases where data were missing, we contacted authors for additional information. Study characteristics, patient and IBD disease characteristics (IBD subtype, type of surgery, perioperative IBD medication[s], last dose of medication prior to surgery), and outcome assessment (length of follow-up, rate of overall postoperative infections, rate of intra-abdominal infections) were collected.

Statistical Analysis and Quality Assessment

We conducted separate analyses for corticosteroids, immunosuppressive agents, anti-TNF agents, anti-integrin agents, anti-interleukin agents, and small molecules, provided that at least 2 studies were available for each type of medication. Data were analyzed using Review Manager 5.3. Odds ratios (OR) with corresponding 95% confidence intervals (95% CI) were calculated. The generic inverse variance method was used for obtaining overall pooled OR estimates. We assessed heterogeneity by visual inspection of forest plots and by calculating the $\times^2$ and I^2 statistics. For the $\times^2$ test, we considered a P value < 0.10 to be statistically significant. I^2 values of greater than 50% were considered to indicate substantial heterogeneity. A random-effects model was used if substantial heterogeneity was present. Otherwise, a fixed-effect model was used.

Three investigators (Law, Koh, and Bao) independently assessed the methodological quality of included studies using the Newcastle-Ottawa Scale.[19] The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach was used to assess the certainty of evidence in the review.[20] Certainty of evidence for the primary and secondary outcomes were determined to be high, moderate, low, or very low. Publication bias was assessed using funnel plots if at least 10 studies were included.

RESULTS

Search Results

We conducted a literature search on August 30, 2018, which identified 12,248 citations. Two additional studies were identified through other sources. After duplicates were removed, 9709 studies remained for screening. We excluded 9594 studies after review of the titles and abstracts. We retrieved the full text of the remaining 115 studies. Of these, 52 studies were excluded and 63 studies were included in the review (Fig. 1).

Included Studies

All included studies were observational studies. There were 4 prospective studies[21–24] and 59 retrospective studies. Of

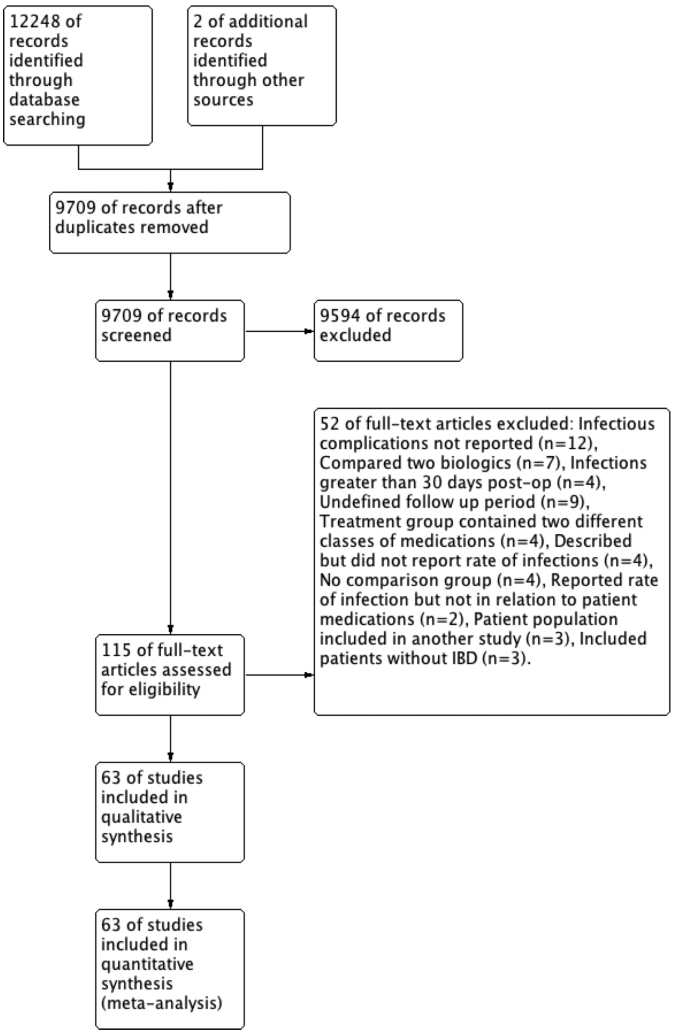


FIGURE 1. Study flow diagram.

these, 57 were manuscripts and 6 were abstracts. The included studies had heterogenous patient selection criteria. Some included only CD or UC patients, while others involved both. Patients underwent elective or emergent abdominal surgeries.

With regard to the type of preoperative medication studied, 35 studies examined corticosteroids,[23–56, 66] 5 examined 5-ASAs,[24, 25, 30, 55, 57] 26 examined immunomodulators,[21, 24–32, 34–36, 38, 42, 47, 52, 54–61, 66] 49 examined anti-TNF agents,[6, 22–30, 32, 34, 36–39, 42, 44, 47–48, 51–57, 61–82] 8 examined anti-integrin agents[28, 37, 45, 55, 62, 69, 70, 73] and only 1 study examined ustekinumab.[28] There were no studies assessing small molecules.

A variety of doses were used in studies examining preoperative corticosteroids. There was also significant variation in the timing of the last dose of anti-TNF medication before surgery. In particular, 17 studies considered a patient to have been treated preoperatively with an anti-TNF agent only if the patient had received a dose within 8 weeks before surgery. Twenty-nine studies used a longer cutoff time, and the remaining 3 did not specify the time of last dose of anti-TNF medication.

All postoperative infectious outcomes occurred within 30 days of surgery. A diverse array of infections was reported by each study. While some studies grouped infections into categories such as intra-abdominal infections and extra-abdominal infections, others studies reported each type of infection individually. Some studies also provided an overall rate of infection. When this information was not available, we estimated the overall rate of infections by combining the rates of individual infections reported in a study.

Effects of Intervention

Analysis 1: Corticosteroids versus control Pooling of data from the 35 studies comparing preoperative corticosteroid use with no corticosteroid treatment demonstrated a significantly increased risk of overall infectious complications (OR 1.34; 95% CI, 1.25-1.44) with moderate heterogeneity in the overall analysis (I^2 = 44%) (Fig. 2). Nine studies included only patients with UC (OR 1.37; 95% CI, 1.22-1.53), and 20 studies included only those with CD (OR 1.27; 95% CI, 1.14-1.40). Fourteen of the 35 studies adjusted for other factors such as age, sex, and concomitant medications.[27–29, 35, 38–40, 44, 46–48, 50, 56, 66] Significantly increased risk was seen in studies performed before 1998 (OR 1.74; 95% CI, 1.26-2.41) and after 1998 (OR 1.32; 95% CI, 1.23-1.42). Data from 24 studies reporting rates of intra-abdominal infections demonstrated increased risk (OR 1.63; 95% CI, 1.33-2.00).

Analysis 2: 5-ASA versus control Pooling of data from the 5 studies comparing preoperative 5-ASA with no 5-ASA demonstrated a significantly decreased risk of overall postoperative infectious complications (OR 0.63; 95% CI, 0.46-0.87). Low heterogeneity was observed in the overall analysis (I^2 = 6%) (Fig. 3). One study included only patients with UC, and 4 studies included only patients with CD (OR 0.68; 95% CI, 0.47-0.99). None of the studies reported adjusted analyses. Studies performed before 1998 (OR 1.08; 95% CI, 0.47-2.51) demonstrated no difference in postoperative infection risk whereas studies post-1998 (OR 0.57; 95% CI, 0.40-0.81) found significantly decreased risk. Three studies reported on intra-abdominal infections (OR 0.77; 95% CI, 0.45-1.33).

Analysis 3: Immunomodulators versus control Pooling of the 26 studies comparing preoperative immunomodulators with no immunomodulators demonstrated no difference in the risk of overall infectious complications (OR 1.08; 95% CI, 0.94-1.25). There was low heterogeneity (I^2 = 0%) (Fig. 4). Nine studies included only patients with UC (OR 1.07; 95% CI, 0.83-1.39), and 11 included only patients with CD (OR 1.06; 95% CI, 0.83-1.36). Seven studies adjusted for other factors such as age, sex, and concomitant medications.[27, 29, 35, 38, 47, 56, 58] Studies pre-1998 showed an increased risk (OR 1.85; 95% CI, 1.14-3.01), while studies performed after 1998 demonstrated no difference in risk

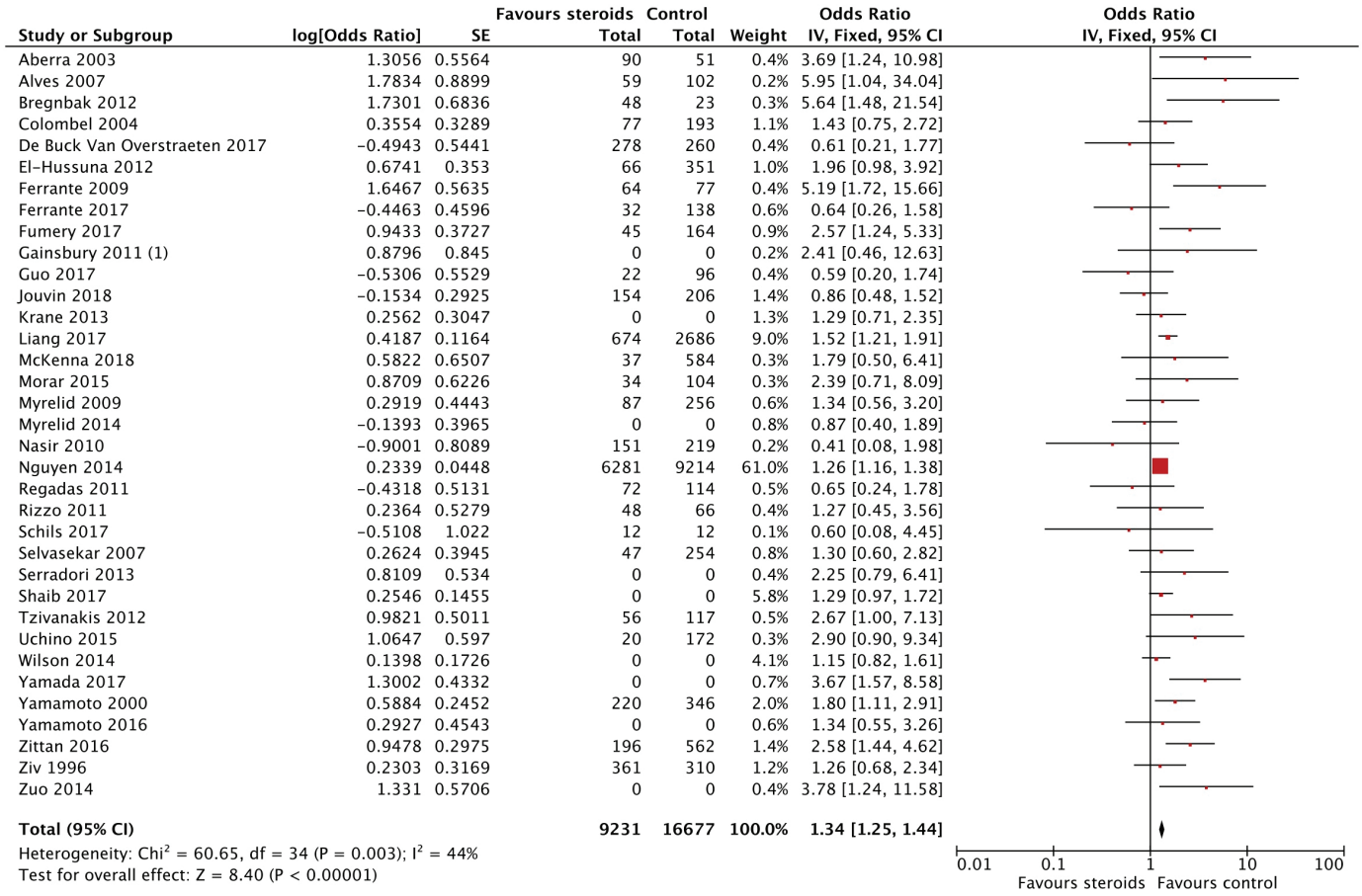


FIGURE 2. Postoperative infection within 30 days of surgery (corticosteroids vs no corticosteroids).

(OR 1.03; 95% CI, 0.88-1.20). Data from 16 studies reporting rates of intra-abdominal infections also demonstrated no difference in risk (OR 0.89; 95% CI, 0.67-1.17).

Analysis 4: Anti-TNF agents versus control Pooling of data from the 49 studies comparing preoperative anti-TNF with no anti-TNF demonstrated an increased risk of overall infectious complications (OR 1.26; 95% CI, 1.07-1.50) with substantial heterogeneity (I^2 = 51%) (Fig. 5). Sixteen studies included only patients with UC (OR 1.05; 95% CI, 0.79-1.41) and 25 studied patients with CD only (OR 1.48; 95% CI, 1.11-1.97). Fourteen studies adjusted for other factors such as age, sex, and concomitant medications.[6, 22, 26, 27, 29, 30, 38, 39, 42, 47, 56, 72, 75, 79] Of these, 10 studies[6, 22, 27, 29, 38, 39, 42, 47, 72, 75] specifically controlled for corticosteroid use. In the 17 studies that included patients treated with anti-TNF therapy within 8 weeks of surgery, a significantly increased risk of infectious complications was found (OR 1.44; 95% CI, 1.08-1.93). This risk was no longer significant in patients receiving their last dose of anti-TNF therapy more than 8 weeks before surgery (OR 1.15; 95% CI, 0.93-1.43). Data from 36 studies reporting rates of intra-abdominal infections also demonstrated increased risk in patients treated with anti-TNF agents (OR 1.46; 95% CI, 1.08-1.97).

Analysis 5: Anti-integrin agents versus control Pooling of data from the 8 studies comparing preoperative anti-integrin therapy with no anti-integrin treatment demonstrated no difference in the risk of overall infectious complications (OR 1.06; 95% CI, 0.67-1.69). Again, there was substantial heterogeneity (I^2 = 58%) (Fig. 6). Two studies included only patients with UC (OR 0.61; 95% CI, 0.28-1.36), and 4 exclusively studied patients with CD (OR 1.32; 95% CI, 0.51-3.42). One study[70] adjusted for factors including age, sex, number of prior surgeries, preoperative steroid use, smoking, and indication for surgery. Data from 5 studies reporting rates of intra-abdominal infections also demonstrated no difference in risk (OR 0.40; 95% CI, 0.14-1.20).

Analysis 6: Anti-interleukin agents versus control Only 1 study on anti-interleukin agents met the inclusion criteria, so no meta-analysis was performed. Liang et al[28] reported no difference in the risk of overall postoperative infection (OR 0.98; 95% CI, 0.58-1.66).

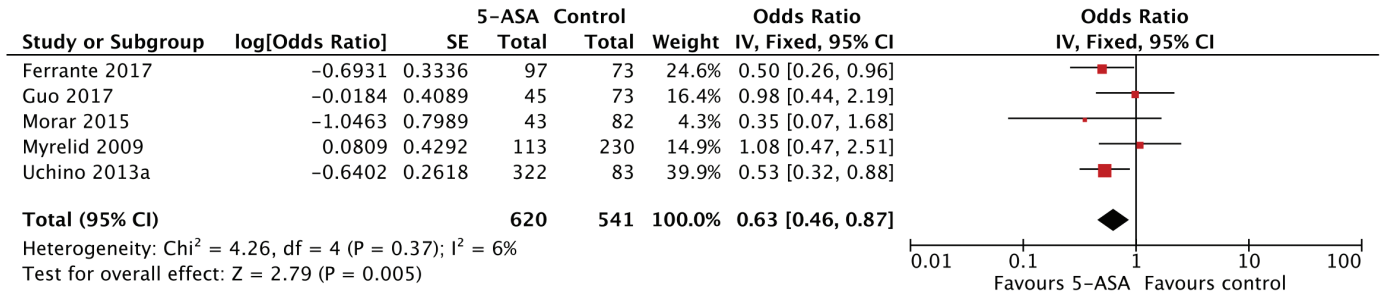
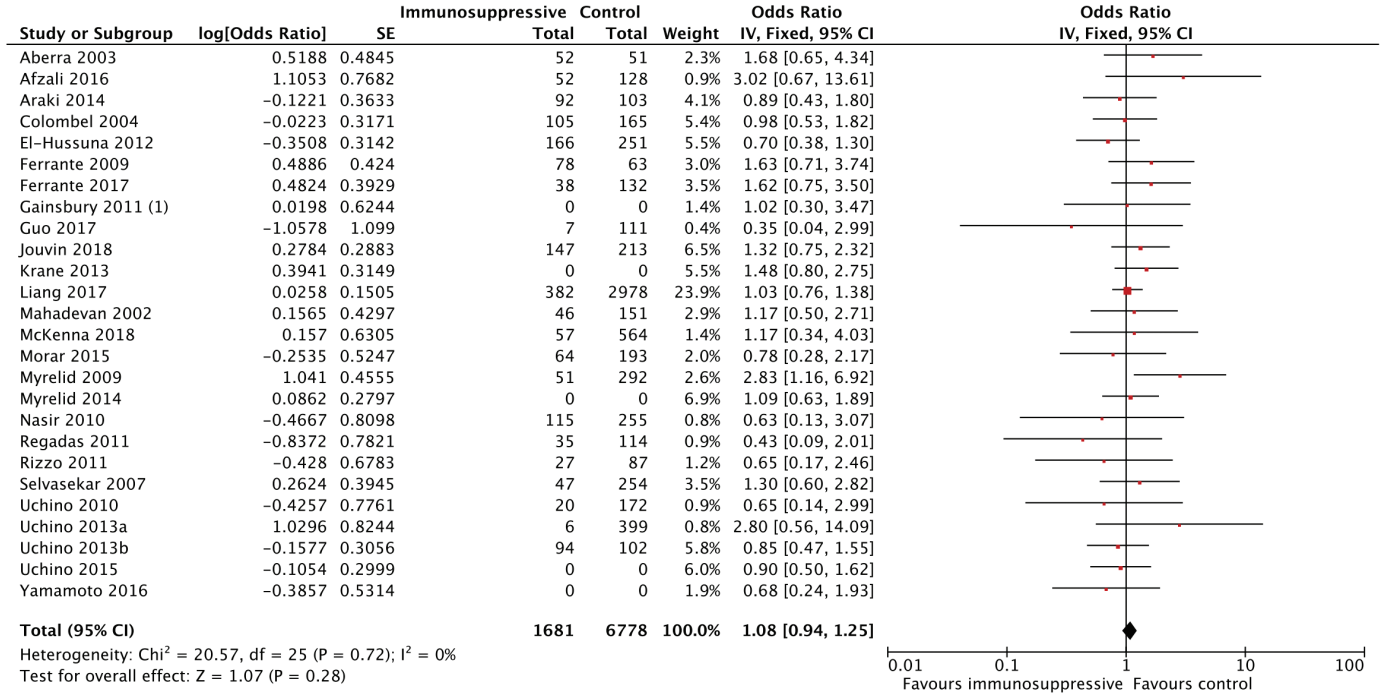


FIGURE 3. Postoperative infection within 30 days of surgery (5-ASA vs no 5-ASA).



Footnotes
(1) Zeros indicate the study reported the OR rather than the number of participants

FIGURE 4. Postoperative infection within 30 days of surgery (immunomodulators vs no immunomodulators).

Analysis 7: Small molecules versus control No small molecule studies met the inclusion criteria.

Quality Assessment and Publication Bias

Risk of bias was deemed low in 22 studies and very high in 41 studies (Fig. 7). Studies commonly lost points in the comparability section because many studies did not control for important factors such as disease severity and concomitant medications. In addition, many studies did not account for possible pre-existing infections, and in cases where there are known preoperative infections such as abdominal abscess, it may be prudent to adjust for this factor.

Our assessment based on GRADE suggests that the certainty of evidence supporting the outcomes of this review is very low because of the observational nature of the data and the very serious risk of bias. In addition, many outcomes also had substantial levels of imprecision, as demonstrated by wide confidence intervals.

We explored publication bias by creating funnel plots for the primary outcome of each class of medication (Supplemental Figs. 1–3). Funnel plots were not created for the 5-ASA and anti-integrin analyses because of an insufficient (< 10) number of studies. Publication bias was not detected based on visual inspection of these funnel plots.

DISCUSSION

This systematic review included 63 observational studies that evaluated the risk of postoperative infectious complications in patients receiving various classes of medications for treatment of IBD. It is the largest and most comprehensive

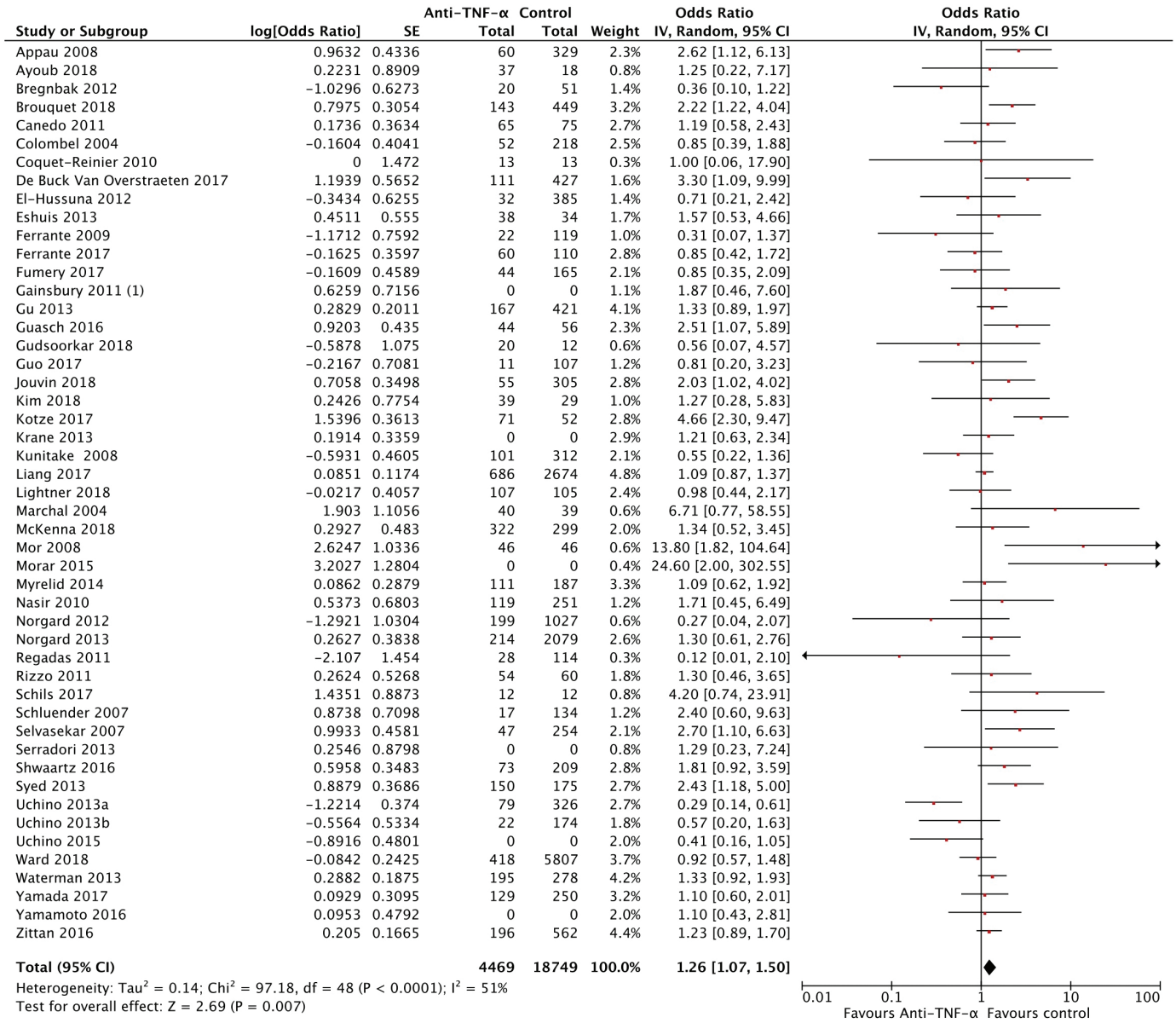


FIGURE 5. Postoperative infection within 30 days of surgery (TNF inhibitors vs no TNF inhibitors).

meta-analysis to date on this topic. Separate analyses were performed for corticosteroids, 5-ASAs, immunomodulators, anti-TNF medications, and anti-integrin medications. Meta-analysis was not performed for anti-interleukin medications and small molecules because of an insufficient number of studies.

We found increased postoperative infection risk in patients treated with corticosteroids. The strength of these findings was bolstered by low heterogeneity and precision of the treatment estimates. Furthermore, the results remained similar in subgroup analyses of UC and CD patients, regardless of study completion before or after 1998. In contrast, we found that treatment with 5-ASA was associated with a decreased risk of postoperative infection. This suggests either a protective effect of 5-ASA against postoperative infections or, more likely, residual confounding or a chance result. We postulate that disease severity was a major source of confounding. Typically, 5-ASAs are used for patients with mild to moderate disease. Comparing patients using 5-ASA to those not using 5-ASA likely was confounded by the presence of milder disease severity in patients treated with 5-ASA. Patients with mild disease have a lower baseline risk for

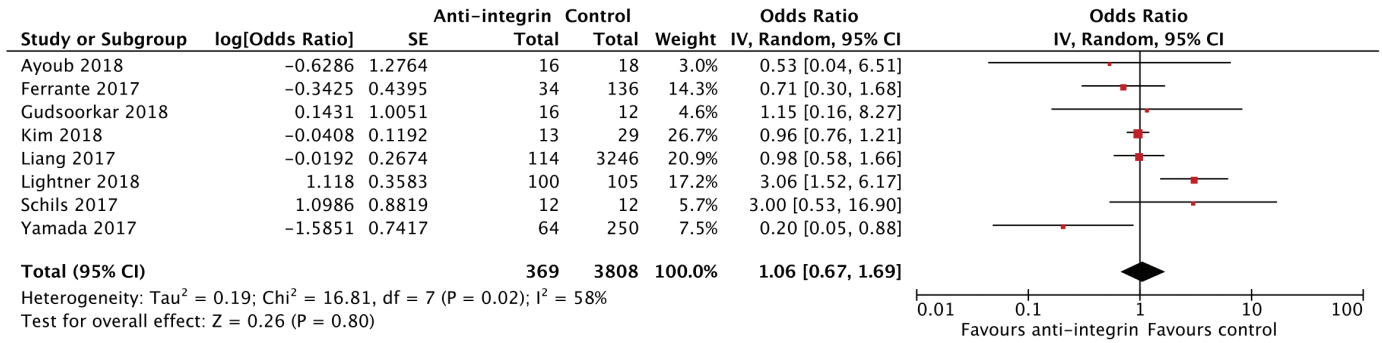


FIGURE 6. Postoperative infection within 30 days of surgery (anti-integrins vs no anti-integrins).

surgical complications because of factors such as improved nutritional status.

There was no significant difference in the risk of postoperative infections in patients treated with immunomodulators. This result was associated with low heterogeneity and low imprecision. The findings remained stable in subgroup analyses of UC and CD patients. Rates of infection were significantly increased in patients treated with perioperative anti-TNF therapy. However, there was substantial heterogeneity. In subgroup analyses, the result remained significant in only CD patients and in patients treated within 8 weeks of surgery. It is unclear why anti-TNF medications are associated with more postoperative infectious complications in CD patients than in UC patients, but this result may reflect differences in pathophysiology and disease severity between the groups. Given the pharmacokinetics of anti-TNF agents, patients who receive anti-TNF therapy more than 8 weeks before surgery are less likely to have therapeutic plasma concentrations. Future studies should also explore whether the risk of postoperative infection in patients treated with anti-TNF agents is higher in those with elevated serum drug levels or is related to specific TNF inhibitors.

No difference in the rates of postoperative infection was noted in patients taking anti-integrin medications. This finding was associated with low heterogeneity but was also imprecise, likely because of a small sample size. Given the assumed gut selective mechanism of vedolizumab, intra-abdominal infections were of particular interest. There was no increased risk of intra-abdominal infections. Our findings are similar to those reported in previous meta-analyses on this topic.

Subramanian et al.[83] and Ahmed Ali et al.[84] performed meta-analyses on the risk of postoperative complications in IBD patients treated with corticosteroids, and both reported significant increases in postoperative infection risk. There are no previous meta-analyses examining the association between 5-ASA therapy and postoperative infections in IBD patients. We found two systematic reviews studying preoperative immunomodulator use and postoperative infections,[83, 84] and neither found an increase in postoperative infections. Two other systematic reviews have reported that preoperative anti-integrin medications do not increase postoperative infections, consistent with our findings.[12, 85] Numerous meta-analyses have examined the association between anti-TNF therapy and postoperative infections,[11, 13, 14, 16, 86–90] and while the conclusions are somewhat mixed, most have suggested a mildly increased risk particularly in CD patients, which is consistent with the findings from our study.

We believe this review is comprehensive and reflects the best available evidence. The results of this study are generalizable to UC and CD patients with some caveats. Because most of the studies were performed at tertiary centers, the results may be less applicable to hospitals with less expertise in IBD-related surgeries. In addition, all the surgeries were abdominal procedures, so they may not be generalizable to patients undergoing nonabdominal surgeries. Some studies excluded emergency surgeries and surgeries for the management of dysplasia/malignancy, so applicability of the results of this study to these populations may be limited.

In addition, there were few studies regarding 5-ASA, anti-integrin medications, anti-interleukin medications, and small molecules. More studies are required before firm conclusions can be drawn regarding these medications. There was also a paucity of prospective studies. The prospective PUCCINI trial, which is completed but not yet published, may provide further insight on the perioperative risks associated with anti-TNF medications.[91]

This study was also limited by the quality of evidence. Certainty of evidence supporting the outcomes of this review is very low because of the observational nature of the data, a very serious risk of bias, and imprecision. Prospective studies and studies controlling for potential confounding factors such as disease severity and concomitant medications are required to generate higher-quality evidence. Finally, there were variations between studies as to what constituted an infectious complication. For example, some studies only examined intra-abdominal infections whereas others reported intra-abdominal and extra-abdominal outcomes. Standardization in the method of reporting postoperative infections would facilitate more accurate comparisons between studies.

In summary, we found that overall infectious complications were increased in patients receiving anti-TNF agents and

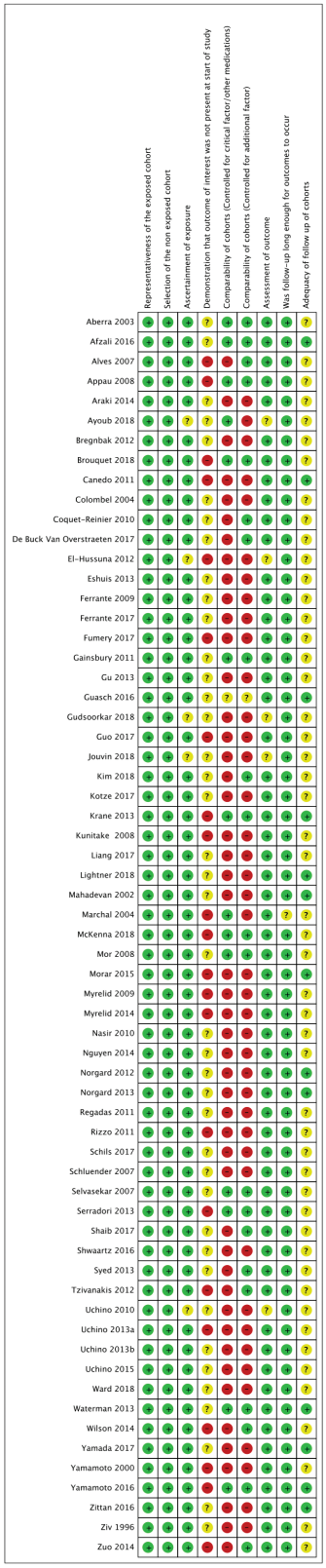


FIGURE 7. Risk of bias summary.

corticosteroids and decreased in those receiving 5-ASA medications. There was no impact in those receiving immunomodulators and anti-integrin agents. Corticosteroids and anti-TNF agents were associated with increased intra-abdominal infection risk, whereas no impact was observed with 5-ASA, immunomodulators, or anti-integrin agents. Because the evidence was very low in certainty, no firm conclusions can be drawn regarding the safety of these medications in the perioperative period. The decision to stop IBD medications before surgery involves potential risks and benefits and should be individualized based upon each patient's circumstances, treatment history, preferences, and values.

SUPPLEMENTARY DATA

Supplementary data are available at *Inflammatory Bowel Diseases* online.

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APPENDIX

RISK OF INFECTIOUS COMPLICATIONS FROM MEDICAL THERAPIES IN POSTSURGICAL PATIENTS: SEARCH STRATEGY, AUGUST 30, 2018

Medline

1. random$.tw.
2. factorial$.tw.
3. (crossover$ or cross over$ or cross-over$).tw.
4. placebo$.tw.
5. single blind.mp.
6. double blind.mp.
7. triple blind.mp.
8. (singl$ adj blind$).tw.
9. (double$ adj blind$).tw.
10. (tripl$ adj blind$).tw.
11. assign$.tw.
12. allocat$.tw.
13. randomized controlled trial/
14. or/1–13
15. exp cohort studies/
16. exp case-control studies/
17. exp retrospective studies/
18. exp Epidemiologic Studies/
19. case-control studies/or longitudinal studies/or follow-up studies/or prospective studies/or cross-sectional studies/
20. (cohort$ or prospective$ or retrospective$).mp.
21. or/15–20
22. 14 or 21
23. Exp Inflammatory bowel disease/
24. (inflammatory bowel disease* or IBD).mp.
25. Exp Crohn disease/or crohn*.mp.
26. Exp ulcerative colitis/or (colitis and ulcerat*).mp.
27. or/23–26
28. (Anti-TNF* OR anti TNF* or Biologic*).mp.
29. Integrin receptor antagonist.mp.
30. (Corticosteroid* or steroid*).mp.
31. (immunosuppress* or immunomodulator*).mp.
32. Antibiotic*.mp.
33. Aminosalicylate*.mp.
34. (Adalimumab or Certolizumab* or Golimumab or Infliximab or Natalizumab or Ustekinumab or Vedolizumab).mp.
35. (Tofacitinib or Ozanimod).mp.

36. (Budesonide or Methylprednisolone or Prednisolone or Prednisone).mp.
37. (Azathioprine or 6-MP or 6-mercaptopurine or Cyclosporine or Mercaptopurine or Methotrexate or Tacrolimus).mp.
38. (Ciprofloxacin or Metronidazole).mp.
39. (5-ASA or Balsalazide or Mesalamine or Olsalazine or Sulfasalazine).mp.
40. or/28–39
41. (Post-operation or Post-operative or Post-op* or postoperative* or postsurgical* or post-surg*).mp.
42. (operation* or surg* or strictureplasty or resection or colectomy or proctocolectomy).mp.
43. 41 or 42
44. (Infect* or complication* or heal* or re-operation or reoperation or outcome* or adverse* or adverse event* or side effect*).mp.
45. 22 and 27 and 40 and 43 and 44

Results = 2501 Human only (MEDLINE)

Embase

1. random$.mp.
2. factorial$.mp.
3. (crossover$ or cross over$ or cross-over$).mp.
4. placebo$.mp.
5. single blind.mp.
6. double blind.mp.
7. triple blind.mp.
8. (singl$ adj blind$).mp.
9. (double$ adj blind$).mp.
10. (tripl$ adj blind$).mp.
11. assign$.mp.
12. allocat$.mp.
13. crossover procedure/
14. double blind procedure/
15. single blind procedure/
16. triple blind procedure/
17. randomized controlled trial/
18. or/1–17
19. exp cohort studies/
20. exp case-control studies/
21. exp retrospective studies/
22. exp Epidemiologic Studies/
23. case-control studies/or longitudinal studies/or follow-up studies/or prospective studies/or cross-sectional studies/
24. (cohort$ or prospective$ or retrospective$).mp.
25. or/19–24
26. 18 or 25
27. Exp Inflammatory bowel disease/
28. (inflammatory bowel disease* or IBD).mp.
29. Exp Crohn disease/or crohn*.mp.
30. Exp ulcerative colitis/or (colitis and ulcerat*).mp.
31. or/27–30
32. (Anti-TNF* OR anti TNF* or Biologic*).mp.
33. Integrin receptor antagonist.mp.
34. (Corticosteroid* or steroid*).mp.
35. (immunosuppress* or immunomodulator*).mp.
36. Antibiotic*.mp.
37. (Aminosalicylate* or Aminosalicylic*).mp.
38. (Adalimumab or Certolizumab* or Golimumab or Infliximab or Natalizumab or Ustekinumab or Vedolizumab).mp.
39. (Tofacitinib or Ozanimod).mp.
40. (Budesonide or Methylprednisolone or Prednisolone or Prednisone).mp.
41. (Azathioprine or 6-MP or 6-mercaptopurine or Cyclosporine or Mercaptopurine or Methotrexate or Tacrolimus).mp.
42. (Ciprofloxacin or Metronidazole).mp.
43. (5-ASA or Balsalazide or Mesalamine or Olsalazine or Sulfasalazine).mp.
44. or/32–43
45. (Post-operation or Post-operative or Post-op* or postoperative* or postsurgical* or post-surg*).mp.
46. (operation* or surg* or strictureplasty or resection or colectomy or proctocolectomy).mp.
47. 45 or 46
48. (Infect* or complication* or heal* or re-operation or reoperation or outcome* or adverse* or adverse event* or side effect*).mp.
49. 26 and 31 and 44 and 47 and 48

Results = 8676 human only (Embase)

COCHRANE CENTRAL

#1 MeSH: [Inflammatory bowel disease] explode all trees
#2 IBD
#3 Crohn
#4 ulcerative colitis
#5 #1 or #2 or #3 or #4
#6 MeSH: [Biological factors] explode all trees
#7 MeSH: [Receptors, Steroid] explode all trees
#8 MeSH: [Immunosuppressive Agents] explode all trees
#9 MeSH: [Anti-bacterial agents] explode all trees
#10 MeSH: [Aminosalicylic Acids] explode all trees
#11 Adalimumab or Certolizumab* or Golimumab or Infliximab or Natalizumab or Ustekinumab or Vedolizumab
#12 Tofacitinib or Ozanimod
#13 Budesonide or Methylprednisolone or Prednisolone or Prednisone
#14 Azathioprine or 6MP or mercaptopurine or Cyclosporine or Mercaptopurine or Methotrexate or Tacrolimus
#15 Ciprofloxacin or Metronidazole
#16 5ASA or Balsalazide or Mesalamine or Olsalazine or Sulfasalazine
#17 #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16
#18 Post-operation or Post-operative or Post-op* or postoperative* or postsurgical* or post-surg*

#19 operation* or surg* or strictureplasty or resection or colectomy or proctocolectomy
#20 #18 or #19
#21 Infect* or complication* or heal* or re-operation or reoperation or outcome* or adverse* or adverse event* or side effect*
#22 #5 and #17 and #20 and #21

Results = 469 (trials only)

Cochrane IBD Specialized Register

1. Operation and infection
2. Post-opera and outcome
3. Operation and complication (1)
4. Surgery and Crohn's disease (33)
5. Surgery and ulcerative colitis (8)

Results = 42

Clinicaltrials.gov

1. Inflammatory bowel disease and operation/surgery (366)
2. Inflammatory bowel disease and surgical complication (59)

Results = 425

World Health Organization Trials Registry

1. Inflammatory bowel disease and operation/surgery (135)
2. Inflammatory bowel disease and surgical complication (0)

Total results = 12,248

Duplicates = 2528

Results to screen = 9720