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Risk of postoperative infectious complications from medical therapies in inflammatory bowel disease (Protocol)

Law CCY, Koh D, Bao Y, Jairath V, Narula N

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[Intervention Protocol]

Risk of postoperative infectious complications from medical therapies in inflammatory bowel disease

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

The primary objective of this review is to assess the impact of perioperative IBD medications on the risk of postoperative infections within 30 days of surgery.

BACKGROUND

Description of the condition

Inflammatory bowel disease (IBD), which includes Crohn's disease (CD) and ulcerative colitis (UC), is a chronic and incurable disorder characterized by inflammation of the gastrointestinal tract. Inflammation in UC is limited to the mucosa of the colon and rectum while Crohn's disease is associated with transmural inflammation in any portion of the gastrointestinal tract. In addition, Crohn's disease is also associated with extraintestinal manifestations in areas such as the skin, joints, and eyes. Over 1.2 million individuals have a diagnosis of IBD in North America and the worldwide prevalence of this disease is projected to increase exponentially over the next decade (Kaplan 2015).

The goal of IBD treatment is to achieve remission of clinical symptoms and resolution of gut inflammation. A plethora of pharmacological and, if necessary, surgical options are available for the treatment of IBD. Traditionally, depending on the severity of inflammation and symptoms, 5-aminosalicylates, corticosteroids, immunomodulators and biologic medications have been used. In recent years, biosimilars and small molecules have also been incorporated into the treatment algorithm for IBD.

Description of the intervention

A diverse array of medications are available for the treatment of IBD. These medications can be categorized into several broad categories: aminosalicylates, corticosteroids, immunomodulators, biologics, and small molecules.

Some of the oldest drugs used for the treatment of IBD are aminos-

alicylates. Aminosalicylates refers to a group of drugs that contain the active ingredient 5-aminosalicylic acid (Sales-Campos 2015). Commonly used aminosalicylates include mesalamine, balsalazide, olsalazine and sulfasalazine and these drugs can be administered orally in pill form or topically as suppositories and enemas. Aminosalicylates are mainly used for the induction and maintenance of remission in mild to moderate UC. Evidence for the use of aminosalicylates in CD is limited.

Another category of medication used to treat IBD are corticosteroids. Commonly prescribed corticosteroids include prednisone, prednisolone, methylprednisolone and budesonide. Corticosteroids can be administered orally, intravenously or rectally. Corticosteroids are effective at inducing remission of CD and UC but are less suitable as long-term therapy due to numerous adverse effects such as increased risk of infection, hyperglycemia, osteoporosis, and hypertension (Sales-Campos 2015).

Immunomodulators include thiopurines, methotrexate, cyclosporine and tacrolimus. Thiopurines are comprised of 6-mercaptopurine and its prodrug, azathioprine. Thiopurines are commonly used maintenance therapies for UC and CD but are not suitable for induction of remission given the slow onset of action of these drugs (Zenlea 2014). Patients treated with thiopurines require regular monitoring for serious adverse effects such as hepatotoxicity and bone marrow suppression. Patients are also at increased risk of infections and malignancies such as non-melanoma skin cancers (Zenlea 2014).

Methotrexate is a folic acid antagonist that can be used for the induction and maintenance of remission of CD. Its role in UC is controversial (Sales-Campos 2015). Uncommon but important adverse effects include opportunistic infections, hypersensitivity pneumonitis, leukopenia and hepatotoxicity (Zenlea 2014). Methotrexate should also be used cautiously in women of childbearing age as it is a teratogen.

There is limited literature on the use of calcineurin inhibitors such as cyclosporine and tacrolimus for the treatment of IBD. Tacrolimus has been used for the treatment of fistulizing CD and refractory UC but data are limited to small studies (Triantafillidis 2011). Cyclosporine is associated with serious adverse effects such as seizure and permanent nephrotoxicity, and has a narrow therapeutic range. Thus, it is reserved as a rescue therapy for steroid resistant, acute severe UC (Zenlea 2014).

Biologics are medications derived partly or completely from living cells (Rawla 2018). The introduction of biologic medications in the late 1990s revolutionized the treatment of IBD. While biologics are effective, these drugs can cause undesired adverse effects such as infections, antibody formation and malignancies. Biologics used for the treatment of IBD include anti-tumor necrosis factor-alpha (TNF-α) antibodies, anti-integrin antibodies (natalizumab and vedolizumab), and anti-interleukin antibodies (ustekinumab). Anti-TNF-α medications approved for use in CD include infliximab, adalimumab and certolizumab pegol. Infliximab, adalimumab and golimumab are approved medications for UC.

Natalizumab and vedolizumab are anti-integrins. Natalizumab's use is limited due to its association with progressive multifocal leukoencephalopathy (PML) (Zenlea 2014). Vedoliuzmab is approved for treatment of moderate to severe CD and UC. As it is more selective than natalizumab, vedolizumab does not carry the same level of risk for PML (Zenlea 2014). However, concerns have been raised that vedolizumab could impair postoperative wound healing because it targets leukocyte migration, a necessary component of wound healing (Law 2018).

Biosimilars are a new and developing category of medications. The three biosimilars available currently for infliximab are infliximab-dyyb, infliximab-abda, and infliximab-qbtx. Biosimilars for adalimumab include adalimumab-atto and adalimumab-abdm (Rawla 2018). Indications for these biosimilars are comparable to infliximab and adalimumab and studies evaluating switching from originator drugs to biosimilars have generally not shown inferiority (Reinglas 2018).

Lastly, small molecules are an emerging class of IBD therapy. Tofacitinib is a new oral medication approved for the treatment of UC in the United States in 2018. Notably, studies of tofacitinib in UC patients reported an elevated risk of herpes zoster (Reinglas 2018).

How the intervention might work

The aim of medical therapy in IBD is to decrease inflammation and hence alleviate symptoms and allow mucosal healing (Rawla 2018). Current medications target different stages of the inflammatory cascade that is believed to underpin IBD pathogenesis. Aminosalicylates topically decrease inflammation in the colon through three main ways: inhibition of macrophage chemotaxis, increase in intestinal epithelial cell proliferation, and activation of peroxisome proliferator activated receptor γ (Sales-Campos 2015). Corticosteroids systemically suppress inflammation by down regulating the transcription of proinflammatory genes involved in cytokine production and inhibiting the recruitment of immune cells (Sales-Campos 2015). Thiopurines inhibit lymphocyte proliferation and induce apoptosis of activated T-lymphocytes (Sales-Campos 2015; Zenlea 2014). Methotrexate is a folic acid antagonist, which increases adenosine, inhibits interleukin-1 and suppresses T cell function (Zenlea 2014). Cyclosporine and tacrolimus are calcineurin inhibitors. These drugs act by suppressing cytokine production and T-cell activation (Triantafillidis 2011; Zenlea 2014).

Biologics work by targeting various pro-inflammatory molecules. Anti-TNF drugs inhibit tumor necrosis factor-α, a key cytokine in the pathogenesis of IBD (Sales-Campos 2015). Infliximab is a chimeric human-mouse monoclonal antibody. It has increased specificity and affinity to the TNF receptor and hence blocks TNF-α from binding (Rawla 2018). Adalimumab is a fully human monoclonal antibody that inhibits TNF-α and its ability to interact with p55 and p75 cell surface receptors (Rawla 2018). Other

anti-TNF medications used to treat IBD include certolizumab, a recombinant antigen-binding fragment antibody against TNF-α conjugated to polyethylene glycol, and golimumab, a fully human monoclonal antibody that binds to and inhibits soluble and transmembrane forms of anti-TNF (Rawla 2018). Ustekinumab functions by blocking the activity of interleukin 12 and interleukin 23, which play a role in the activation of natural killer cells and CD4 T lymphocytes (Rawla 2018; Reinglas 2018). Natalizumab is a humanized monoclonal antibody that is an antagonist to both alpha-4-beta-1 and alpha-4-beta-7 integrins. It works by inhibiting the translocation of leukocytes across blood vessel membranes (Rawla 2018). In comparison, vedolizumab is a monoclonal antibody to only the alpha-4-beta-7 integrin. As a result, vedolizumab is gut-selective. It prevents T cell activation and adhesion through blocking the binding of mucosal addressin cell adhesion molecule-1 to the integrin receptor (Rawla 2018).

Biosimilars are biological medications that are highly similar to the reference product and work in the same ways. There are minor differences in clinically inactive components with no clinically meaningful differences in safety and efficacy. (Reinglas 2018). Tofacitinib is an inhibitor of janus kinase enzymes, and functions by suppressing cytokine signaling in mucosal cells (Reinglas 2018).

Why it is important to do this review

The growth of medical treatment options has improved physicians' ability to manage IBD medically and in many cases, delay or avoid surgery (Frolkis 2013; Lichtenstein 2005; Rungoe 2014). However, 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 (Frolkis 2013). Many medications commonly used to treat IBD such as corticosteroids, immunomodulators, and biologics are recognized to increase the general risk of infection (Rawla 2018). However, the impact of these medications on surgical outcomes is controversial. Concerns have been raised that preoperative treatment with these medications could theoretically impair wound healing and in turn, increase postoperative infections and other complications (Appau 2008; Lightner 2017; Magro 2017). Of particular concern are biologic medications, as long-term information on safety, especially with regards to the perioperative setting, is scarce and limited mostly to observational studies. Given the important role TNF-α plays in stimulating dermal fibroblast proliferation and activity, investigators have examined its impact on wound healing in rat models. Lee 2000 demonstrated that continuous suppression of TNF-α decreased wound breaking strength in rats, raising the possibility of a similar outcome in humans treated with anti-TNF medications. Additionally, anti-integrins such as vedolizumab function by blocking leukocyte migration to the gut. However, leukocytes are also critical to wound healing, and thus theoretically could impair anastomotic and stoma healing (Argollo 2018; Lightner 2017). Current studies evaluating this topic have yielded conflicting results (Argollo 2018; Kopylov 2002; Law 2018; Narula 2013; Yang 2012; Yang 2014; Xu 2019). 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.

OBJECTIVES

The primary objective of this review is to assess the impact of perioperative IBD medications on the risk of postoperative infections within 30 days of surgery.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials, quasi-randomized controlled trials, non-randomized controlled trials, prospective cohort studies, retrospective cohort studies, case-control studies and cross-sectional studies will be considered for inclusion. Meta-analyses, systematic reviews, case series, and case reports will be excluded. Studies without a comparison or control group will be excluded. Manuscripts and abstracts will be considered for inclusion.

Types of participants

The majority of patients in each study must be adults (at least 18 years in age) with Crohn's disease or ulcerative colitis as defined by conventional clinical, endoscopic or histologic criteria who have undergone any type of surgery, including both abdominal and non-abdominal surgeries.

Types of interventions

Studies of patients treated with one or more IBD medications perioperatively (preoperatively or within 30 days postoperatively as treatment during this time period could potentially influence rates of early infectious complications) compared to patients who were not using that medication(s) will be considered for inclusion. Comparison groups could include another active medication, placebo, or a no treatment control.

The following is a list of medications that will be examined in this study:

1. Aminosalicylates: 5-ASA, balsalazide, mesalamine, olsalazine, sulfasalazine;

2. Corticosteroids: budesonide, methylprednisolone, prednisolone, prednisone;
3. Immunomodulators: azathioprine, 6-mercaptopurine, methotrexate, cyclosporine, tacrolimus;
4. Biologics: adalimumab, certolizumab, golimumab, infliximab, natalizumab, ustekinumab, vedolizumab; and
5. Small Molecules: tofacitinib.

Types of outcome measures

Primary outcomes

The primary outcome will be postoperative infection within 30 days of surgery.

Secondary outcomes

The secondary outcomes will include:
1. Incisional infections and wound dehiscence;
2. Intra-abdominal infectious complications including anastomotic leak, intra-abdominal abscess and enterocutaneous fistula; and
3. Extra-abdominal infections including pneumonia, urinary tract infection, bacteremia, catheter associated infections and other infections.

Search methods for identification of studies

Electronic searches

An electronic search will be performed of MEDLINE, Embase, the Cochrane Library, the Cochrane IBD Group Specialized Register, Clinicaltrials.gov, and the WHO International Clinical Trials Registry Platform. The search strategies for each database are reported in Appendix 1.

Searching other resources

? To ensure search completeness, we will screen the bibliographies of all available review articles to identify additional relevant publications.

Data collection and analysis

Selection of studies

Initial screening of titles and abstracts will be performed independently by two investigators (CL and YB). Potentially relevant articles will be reviewed in full to determine eligibility for inclusion according to the above inclusion and exclusion criteria. If necessary, study authors will be contacted for additional information. Disagreement will be resolved through consensus and evaluation by a third investigator (NN).

Data extraction and management

Data extraction will be performed independently by three investigators (CL, DK and YB). The following information will be recorded:
1. Study Characteristics: Author, year of publication, time period of study, country of origin, format (paper/abstract), study design, inclusion and exclusion criteria;
2. Patient and IBD Disease Characteristics: Mean age, gender, number of patients by IBD subtype, type of surgery performed, perioperative IBD medication(s), last dose of medication prior to surgery, emergency versus elective surgery; and
3. Outcome Assessment: Length of follow-up period, rate of overall postoperative infections, rate of incisional infections/wound dehiscence, rate of intra-abdominal infectious complications, rate of extra-abdominal infections.

Assessment of risk of bias in included studies

Three authors (CL, DK and YB) will independently assess the risk of bias of RCTs using the Cochrane risk of bias tool. Each study will be assessed based on sequence generation, allocation sequence concealment, incomplete outcome data, selective outcome reporting and other potential sources of bias. The quality of non-randomized studies will be assessed using the Newcastle-Ottawa Scale (Wells 2019). Studies will be assessed based on the selection of the study groups, the comparability of the groups and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies respectively.
The GRADE approach will be used to assess the certainty of the evidence in the review (Guyatt 2008). Evidence for the primary and secondary outcomes will be evaluated separately and will be reported in Summary of Findings tables. The outcomes that will be included in these tables are overall postoperative infections, incisional infections and wound dehiscence, intra-abdominal infectious complications (anastomotic leak, intra-abdominal abscess and enterocutaneous fistula), and extra-abdominal infections. RCTs start out as high quality evidence and non-randomized studies start out as low-quality evidence. Five domains can lead to lowering the quality of the evidence: risk of bias, inconsistency, indirectness, imprecision and publication bias. Three domains can lead to raising the quality of the evidence: large magnitude of effect, dose response gradient, and a result that opposes any plausible residual confounding (Guyatt 2008). Ultimately, the certainty of the evidence for each outcome will be determined to be high quality (further research is unlikely to change confidence in the estimate of effect), moderate quality (further research is likely to

have an important impact on confidence in the estimate of effect and may change the estimate), low quality (further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate) or very low quality (any estimate of effect is very uncertain). Disagreements will be resolved by discussion and consensus.

Measures of treatment effect

Data will be analyzed using Review Manager 5.3. Data will be analyzed on an intention-to-treat basis. We will calculate the odds ratio (OR) with corresponding 95% confidence internal (95% CI) for count data. For dichotomous outcomes, we will calculate the OR with 95% CI. In cases where only the OR or risk ratio are reported in a study reporting dichotomous outcomes, the generic inverse variance method will be used. For continuous data, we will calculate the mean difference (MD) or standardized mean difference (SMD) with corresponding 95% CI as appropriate. If only the MD is reported by a study, the generic inverse variance method will be used.

Unit of analysis issues

We will analyze count data as dichotomous data by extracting the proportion of participants who experienced at least one infection. For studies with multiple treatment groups, depending on the situation, one of three strategies may be used. If only one of the treatment arms is relevant to the study, the other treatment arms will be ignored and the remaining treatment arm will be compared to the control group. If two or more treatment arms are relevant and are similar (e.g. two types of anti-TNF medications), these treatment arms will be combined into one group. If it is not appropriate to combine the treatment arms, the control group will be divided evenly between the treatment groups. If cross-over studies are encountered, paired analysis using the generic inverse variance method will be used. Cluster-randomized trials are unlikely to be encountered.

Dealing with missing data

For missing dichotomous outcomes, an intention-to-treat analysis will be used. Patients who are lost to follow-up or have missing outcome data will be considered to have experienced an infection. We will also attempt to contact authors to provide missing data. For missing continuous outcomes, the missing value (e.g. standard deviation) will be estimated from other values provided in the study. If this is not possible, the value will be imputed from the mean of the standard deviations of the other studies in the meta-analysis. If possible, we will also perform a sensitivity analysis of per protocol data.

Assessment of heterogeneity

We will assess heterogeneity by visual inspection of forest plots and by calculating the Chi^2 and I^2 statistics. For the Chi^2 test, we will consider a P value of 0.10 to be statistically significant. I^2 values of greater than 50% will be considered to indicate substantial heterogeneity. If any outliers are identified by visual inspection, a sensitivity analysis excluding the study or studies will be performed to attempt to explain the heterogeneity. Preplanned subgroup analyses will also be performed to explore potential sources of heterogeneity.

Assessment of reporting biases

Publication bias will be assessed using funnel plots and Egger's tests provided at least 10 studies are included.

Data synthesis

Data will be pooled by like interventions. We will conduct separate analyses for corticosteroids, immunosuppressive agents, anti-TNF agents, biosimilars of anti-TNF agents, anti-integrin agents, anti-interleukin agents, and small molecules. Additionally, data from individual trials will be pooled for meta-analysis only if the interventions, patient groups and outcomes are sufficiently similar (determined by consensus). Randomized and observational data will be pooled. If applicable, a sensitivity analysis excluding non-randomized studies will be performed to assess the impact on the effect estimate.

For dichotomous outcomes, we will calculate a pooled OR and 95% CI. For continuous outcomes, we calculate the pooled MD or SMD with corresponding 95% CI. A random-effects model will be used if there is substantial heterogeneity present and a fixed-effect model will be used if it is not present. For outcomes reported as count data, the pooled OR and 95% CI will be calculated.

Subgroup analysis and investigation of heterogeneity

If data allow, we plan for the following subgroup analyses:

1. Patients undergoing abdominal surgery versus non-abdominal surgeries;
2. Crohn's disease patients versus ulcerative colitis;
3. Studies conducted prior to 1998 (year of introduction of the first biologic for IBD) versus studies conducted after 1998;
4. Last dose of biologic within eight weeks prior to surgery versus last dose of biologic greater than eight weeks prior to surgery.

Sensitivity analysis

Sensitivity analysis excluding studies of low methodological quality, abstracts, and non-randomized studies are planned. We also plan a sensitivity analysis based on a per protocol analysis.

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REFERENCES

Additional references

Appau 2008

Appau KA, Fazio VW, Shen B, Church JM, Lashner B, Remzi F, et al. Use of infliximab within 3 months of ileocolonic resection is associated with adverse postoperative outcomes in Crohn's patients. *Journal of Gastrointestinal Surgery* 2008;**12**:1738–44.

Argollo 2018

Argollo MC, Kotze PG, Spinelli A, Gomes TNF, Danese S. The impact of biologics in surgical outcomes in ulcerative colitis. *Best Practice & Research Clinical Gastroenterology* 2018;**32-33**:79–87.

Frolkis 2013

Frolkis AD, Dykeman J, Negron ME, Debruyn J, Jette N, Fiest KM, et al. Risk of surgery for inflammatory bowel diseases has decreased over time: a systematic review and meta-analysis of population-based studies. *Gastroenterology* 2013;**145**:996–1006.

Guyatt 2008

Guyatt GH, Oxman AD, Vist GE, Kunz R, Flack-Ytter Y, Aonso-Coello A, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;**336**:924–6.

Kaplan 2015

Kaplan GG. The global burden of IBD: from 2015 to 2025. *Nature Reviews Gastroenterology & Hepatology* 2015; **12**:720–7.

Kopylov 2002

Kopylov U, Ben-Horin S, Zmora O, Eliakim R, Katz LH. Anti-tumor necrosis factor and postoperative complications in Crohn's disease: systematic review and meta-analysis. *Inflammatory Bowel Diseases* 2012;**18**:2404–13.

Law 2018

Law CCY, Narula A, Lightner AL, McKenna NP, Colombel JF, Narula N. Systematic review and meta-analysis: preoperative vedolizumab treatment and postoperative complications in patients with inflammatory bowel disease. *Journal of Crohn's and Colitis* 2018;**12**(5):538–45.

Lee 2000

Lee RH, Efron DT, Tantry U, Stuelten C, Moldawer LL, Abouhamze A, et al. Inhibition of tumor necrosis factor-α attenuates wound breaking strength in rats. *Wound Repair and Regeneration* 2000;**8**(6):547–53.

Lichtenstein 2005

Lichtenstein G, Yan S, Bala M, Blank M, Sands B. Infliximab maintenance treatment reduces hospitalizations, surgeries and procedures in fistulizing Crohn's disease. *Gastroenterology* 2005;**128**:862–9.

Lightner 2017

Lightner AL, Raffals LE, Mathis KL, Cima RR, Tse CS, Pemberton JH, et al. Postoperative outcomes in vedolizumab-treated patients undergoing abdominal operations for inflammatory bowel disease. *Journal of Crohn's and Colitis* 2017;**11**(2):185–90.

Magro 2017

Magro F, Gionchetti P, Eliakim R, Ardizzone S, Armuzzi A, Barreiro-de Acosta M, et al. Third European evidence-based consensus on diagnosis and management of ulcerative colitis. Part 1: definitions, diagnosis, extra-intestinal manifestations, pregnancy, cancer surveillance, surgery, and ileo-anal pouch disorders. *Journal of Crohn's and Colitis* 2017;**11**(6):649–70.

Narula 2013

Narula N, Charleton D, Marshall JK. Meta-analysis: peri-operative anti-TNFα treatment and post-operative complications in patients with inflammatory bowel disease. *Alimentary Pharmacology and Therapeutics* 2013;**37**(11): 1057–64.

Rawla 2018

Rawla P, Sunkara T, Raj JP. Role of biologics and biosimilars in inflammatory bowel disease: current trends and future perspectives. *Journal of Inflammation Research* 2018;**11**: 215–26.

Reinglas 2018

Reinglas J, Gonczi L, Kurt Z, Bessissow T, Lakatos PL. Positioning of old and new biologicals and small molecules in the treatment of inflammatory bowel diseases. *World Journal of Gastroenterology* 2018;**24**(32):3567–82.

Rungoe 2014

Rungoe C, Langholz E, Andersson M, Basit S, Nielsen NM, Wohlfahrt, et al. Changes in medical treatment and surgery rates in inflammatory bowel disease: a nationwide cohort study 1979-2011. *Gut* 2014;**63**:1607–16.

Sales-Campos 2015

Sales-Campos H, Basso PJ, Alves VBF, Fonseca MTC, Bonfa G, Nardini V, et al. Classical and recent advances in the treatment of inflammatory bowel diseases. *Brazilian Journal of Medical and Biological Research* 2015;**48**(2): 96–107.

Triantafillidis 2011

Triantafillidis JK, Merikas E, Georgopoulos F. Current and emerging drugs for the treatment of inflammatory bowel disease. *Drug Design, Development and Therapy* 2011;**5**: 185–210.

Wells 2019
Wells GA Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. www.ohri.ca/programs/clinical_epidemiology/oxford.asp (accessed 28 January 2019).

Xu 2019
Xu YY, Yang LS, An P, Zhou B, Liu G. Meta-analysis: The influence of preoperative infliximab use on postoperative complications of Crohn's disease. *Inflammatory Bowel Diseases* 2019;**25**(2):261–9.

Yang 2012
Yang Z, Wu Q, Wang F, Wu K, Fan D. Meta-analysis: effect of preoperative infliximab use on early postoperative complications in patients with ulcerative colitis undergoing abdominal surgery. *Alimentary Pharmacology and Therapeutics* 2012;**36**(10):922–8.

Yang 2014
Yang ZP, Hong L, Wu Qiong, Wu KC, Fan DM. Preoperative infliximab use and postoperative complications in Crohn's disease: a systematic review and meta-analysis. *International Journal of Surgery* 2014;**12**:224–30.

Zenlea 2014
Zenlea T, Peppercorn MA. Immunosuppressive therapies for inflammatory bowel disease. *World Journal of Gastroenterology* 2014;**20**(12):3146–52.

* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Search strategies

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. (Ciprofloxain 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

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. (Ciprofloxain 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

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 Ciprofloxain 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

Cochrane IBD Group 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)

Clinicaltrials.gov

1. Inflammatory bowel disease and operation/surgery
2. Inflammatory bowel disease and surgical complication

WHO trials registry (ICTRP)

1. Inflammatory bowel disease and operation/surgery
2. Inflammatory bowel disease and surgical complication

CONTRIBUTIONS OF AUTHORS

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Cindy CY Law: None known

Deborah Koh: None known

Yueyang Bao: None known

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