American Gastroenterological Association Technical Review on the Management of Crohn’s Disease After Surgical Resection

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eMethods

Search Strategy and Study Selection Criteria

A systematic literature search of multiple electronic databases was conducted by an experienced medical librarian using a combination of controlled vocabulary terms supplemented with keywords. The search was conducted from inception to May 31, 2015, and the databases included Ovid Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Database of Systematic Reviews, and PsychInfo.

Based on our PICOs, randomized controlled trials (RCTs) and observational studies in adults with CD who underwent surgical resection (to achieve surgically induced remission), comparing different management strategies (routine early post-operative pharmacological prophylaxis vs. endoscopy-guided initiation of therapy, only in cases of endoscopic recurrence of CD; routine assessment of endoscopic recurrence of CD after surgical resection vs. no routine endoscopic assessment) or pharmacological interventions (comparative effectiveness of different agents used for luminal CD in preventing recurrence of CD; comparative effectiveness of different agents used for luminal CD for treating asymptomatic endoscopic recurrence of CD), for prevention and/or treatment of recurrence of CD at least 6 months after surgical resection, were included. For questions for which moderate-high quality evidence could be obtained from RCTs, observational studies (which are inherently biased) were not included in evidence synthesis but were used as supporting evidence; when there were insufficient RCTs that offered only low or very low quality evidence, observational studies were reviewed and considered for possible inclusion in evidence synthesis.

Two investigators independently reviewed the title and abstract of studies identified in the search to exclude studies that did not address the focused question, based on pre-specified inclusion and exclusion criteria. The full text of the remaining articles was examined to determine whether it contained relevant information. Conflicts in study selection at this stage were resolved by
consensus, referring back to the original article in consultation with technical review authors. This search was supplemented with a recursive search of the bibliographies of recently published systematic reviews on this topic, to identify any additional studies. Only English language and human studies were included. Filters were applied to exclude conference proceedings, editorials, letters to the editor and case reports. The detailed search strategy is provided below, and a study selection flowchart is provided in eFigure 1.

In addition to systematically reviewing studies informing the quality of evidence for PICOs, a search was conducted of studies evaluating the cost-effectiveness of different strategies and medications, as well as the values and preferences of patients, in relation to outcomes and treatment alternatives for management of CD.

**Data Extraction**

For quantitative synthesis, all outcomes were preferentially assessed at least 18 months after surgical resection, regardless of duration of intervention. When an outcome was reported at multiple time points, preference was given to using 24 months, > 24 months, 18 months, 12 months or 6 months after surgery, in that order. When outcomes were reported for multiple doses of medication, data for all doses were combined. The denominator used in all trials was based on a modified intention-to-treat (mITT) analysis; for clinical recurrence (CR), all dropouts were considered treatment failures, whereas for endoscopic recurrence (ER), only patients with at least one endoscopic follow-up were included in analyses, due to the high attrition in some trials.

**Bayesian Network Meta-Analysis**

The Bayesian network meta-analysis used a contrast-based approach, wherein study data abstracted for each arm (as treatment type, number of events and sample size) are incorporated as log-odds ratios for each comparison in the
included studies for analysis. The statistical outline and WinBUGS code by Dias et al. were used as a primer for analysis. To define the posterior probability distribution for the probabilities of interest, the Markov chain Monte Carlo model was designed with 100,000 simulated draws after a burn in of 10,000 iterations. Multiple chains (i.e., multiple initial values) were evaluated for each analysis. To account for between-arm correlations for multi-arm trials, a correction was performed in estimating the random effect for each multi-arm trial study using a conditional univariate distribution, as described by Dias et al. Model fit was evaluated using the total residual deviance, which indicated good fit if it approximated the number of data points.

To generate summary statistics in analysis, the use of the logit link function allowed for assessment of pairwise log-odds ratios for all treatment comparisons on the linear logit scale, as the difference of probability of the event on the treatment-arm ‘k’ and a control-arm, ‘c’, as described on the logit scale. Similarly, odds ratios were estimable as exponential of the corresponding log-odds ratios.

The use of Bayesian probability distributions allowed for direct estimation of OR with their 95% credible intervals (CrI). The point estimates for the OR were derived from the median of the posterior distribution for their respective functions (as described above), and the corresponding 95% CrI were obtained using the 2.5th and 97.5th percentiles of the respective posterior distribution. The posterior distribution of all parameters was estimated using non-informative priors to limit inference of data derived from the trials at hand (i.e. made no assumptions about the efficacy of these drugs from data external to the trials included in this systematic review). The adequacy of burn-in and convergence reaching a stable equilibrium distribution was tested using visual inspection of parameter fluctuation depicted in trace plots, monitoring the Monte Carlo error, and by estimating the values of the Brooks-Gelman-Rubin statistic.

The above commonly used model for network meta-analysis assumes “consistency” of treatment effects across trials, such that both direct and indirect treatment effects are assumed to be equivalent. This is an extension of the
exchangeability assumption that states that the data for network meta-analysis composed of ‘i’ trials with ‘k’ treatment effects are derived from ‘i’ trials - all with k-arms - among which some of the arms are missing at random. This assumption of network consistency was evaluated by comparing the direct estimates to the indirect estimates for each comparison, using a node-splitting technique.

Estimates of absolute event rates were generated (or absolute risk) by calculating the estimated risk difference (also known as absolute risk reduction) by combining the odds ratio (OR) for each intervention against placebo and the median placebo response rate for the respective outcome across trial as the assumed control risk (ACR), by using the formula: Risk difference = 100 X (ACR-OR X ACR) / (1-ACR+OR X ACR). The risk difference, which represents the difference between the event rates in the intervention and control group, was added back to the assumed control risk to generate an estimate of the absolute risk for each intervention. 95% confidence intervals for the estimates were generated using the 95% credible intervals of the ORs in the above calculations. Estimates of absolute risk were generated using the GRADEpro version 3.6.1 (McMaster University, 2014).
SEARCH STRATEGY

Drugs

*Database: Ovid MEDLINE(R) and Ovid OLDMEDLINE(R)*

1. exp Crohn Disease/su [Surgery]
2. exp crohn disease/
3. ((intestin$ or bowel$ or colon$) adj5 (anastomo$ or resect$ or excis$ or (surg$ adj3 remov$))).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
4. exp reoperation/
5. 3 or 4
6. 2 and 5
7. 1 or 6
8. exp Aminosalicylic Acids/
9. aminosalicylate$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
10. budesonide.mp.
11. exp Anti-Infective Agents/ad, ae, ct, po, tu [Administration & Dosage, Adverse Effects, Contraindications, Poisoning, Therapeutic Use, Toxicity]
12. fluoroquinolone$.mp.
13. metronidazole.mp.
14. rifaximin.mp.
15. exp Probiotics/
16. probiotic$.mp.
17. exp Immunologic Factors/ad, tu [Administration & Dosage, Therapeutic Use]
18. immunomodulat$.mp.
19. azathioprine.mp.
20. mercaptopurine$.mp.
21. methotrexate.mp.
22. exp Tumor Necrosis Factor-alpha/ai [Antagonists & Inhibitors]
23. exp Antibodies, Monoclonal/ad, tu [Administration & Dosage, Therapeutic Use]
24. exp Tumor Necrosis Factor-alpha/
25. 23 and 24
26. 22 or 25
27. anti-tnf.mp.
28. anti-tumor necrosis factor.mp.
29. anti-tumour necrosis factor.mp.
30. infliximab.mp.
31. adalimumab.mp.
32. certolizumab.mp.
33. pegol.mp.
34. exp Integrins/ai [Antagonists & Inhibitors]
35. anti-integrin$.mp.
36. vedolizumab.mp. (natalizumab.mp.
37. pegol.mp.
38. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37
39. 7 and 38
40. random*.mp.
41. (systematic* adj5 review*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
((search* or review*) adj5 (literatur* or MEDLINE or EMBASE or cochrane)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
43 40 or 41 or 42
44 39 and 43 ( exp Epidemiologic Studies/  
45 39 and 45
47 limit 39 to (clinical trial, all or controlled clinical trial or meta analysis or randomized controlled trial or systematic reviews)  
48 44 or 46 or 47
49 limit 48 to english language  
50 limit 48 to abstracts
51 49 or 50

Database: EBM Reviews - Cochrane Central Register of Controlled Trials
1 Crohn$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
2 ((intestin$ or bowel$ or colon$) adj5 (anastomo$ or resect$ or excis$ or operat$ or reoperat$ or (surg$ adj3 remov$))).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
3 1 and 2
4 (crohn$ adj5 (anastomo$ or resect$ or excis$ or operat$ or reoperat$ or (surg$ adj3 remov$))).mp.
5 3 or 4
6 aminosalicylate$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
7 budesonide.mp.
8 (Anti-Infective Agent$ or antibiotic$ or anti-biotic$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
9 fluoroquinolone$.mp.
10 metronidazole.mp.
11 rifaximin.mp.
12 probiotic$.mp.
13 Immunologic Factor$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
14 immunomodulat$.mp.
15 azathioprine.mp.
16 mercaptopurine$.mp.
17 methotrexate.mp.
18 ((tnf or (tumor or tumour)) adj necrosis factor$ adj3 (moncolonal$ adj2 antibod$)).mp.
19 anti-tnf.mp.
20 anti-tumor necrosis factor.mp.
21 anti-tumour necrosis factor.mp.
22 ((tnf or (tumor or tumour)) adj necrosis factor$ adj3 (antagon$ or interfer$ or inhibit$ or block$)).mp.
23 infliximab.mp.
24 adalimumab.mp.
25 certolizumab.mp.
26 pegol.mp.
27 (Integrin$ adj3 (antagon$ or interfer$ or inhibit$ or block$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
28 anti-integrin$.mp.
29 vedolizumab.mp.
30 natalizumab.mp.
31 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
32 5 and 31

Database: EBM Reviews - Cochrane Database of Systematic Reviews
1 Crohn$.mp. [mp=title, abstract, full text, keywords, caption text]
2 ((intestin$ or bowel$ or colon$) adj5 (anastomo$ or resect$ or excis$ or operat$ or reoperat$ or (surg$ adj3 remov$))).mp. [mp=title, abstract, full text, keywords, caption text]
3 1 and 2
4 (crohn$ adj5 (anastomo$ or resect$ or excis$ or operat$ or reoperat$ or (surg$ adj3 remov$))).mp.
5 3 or 4
6 aminosalicylate$.mp. [mp=title, abstract, full text, keywords, caption text]
7 budesonide.mp.
8 (Anti-Infective Agent$ or antibiotic$ or anti-biotic$).mp. [mp=title, abstract, full text, keywords, caption text]
9 fluoroquinolone$.mp.
10 metronidazole.mp.
11 rifaximin.mp.
12 probiotic$.mp.
13 Immunologic Factor$.mp. [mp=title, abstract, full text, keywords, caption text]
14 immunomodulat$.mp.
15 azathioprine.mp.
16 mercaptopurine$.mp.
17 methotrexate.mp.
18 ((tnf or (tumor or tumour)) adj necrosis factor$ adj3 (moncolonal$ adj2 antibod$)).mp.
19 anti-tnf.mp.
20 anti-tumor necrosis factor.mp.
21 anti-tumour necrosis factor.mp.
22 ((tnf or (tumor or tumour)) adj necrosis factor$ adj3 (antagon$ or interfer$ or inhibit$ or block$)).mp.
23 infiximab.mp.
24 adalimumab.mp.
25 certolizumab.mp.
26 pegol.mp.
27 (Integrin$ adj3 (antagon$ or interfer$ or inhibit$ or block$)).mp. [mp=title, abstract, full text, keywords, caption text]
28 anti-integrin$.mp.
29 vedolizumab.mp.
30 natalizumab.mp.
31 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
32 5 and 31

Monitoring

Database: Ovid MEDLINE(R) and Ovid OLDMEDLINE(R)
1 exp Crohn Disease/su [Surgery]
2 exp crohn disease/
3 ((intestin$ or bowel$ or colon$) adj5 (anastomo$ or resect$ or excis$ or (surg$ adj3 remov$))).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
4 exp reoperation/
5 3 or 4
6 2 and 5
7 1 or 6
8 exp colonoscopy/
exp Tomography, X-Ray Computed/
exp Magnetic Resonance Imaging/
(expcapsul* adj5 endoscop*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
((fecal or feces) adj5 calprotect$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
8 or 9 or 10 or 11 or 12
7 and 13
(postop* or post-op* or ((follow* or after*) adj5 (resect$ or excis$ or ((intestin$ or bowel$ or colon$) adj3 (remov$ or surg$))))) adj10 (monitor$ or surveil$ or predict$ or detect* or observ$)).mp.
7 and 16
exp Time Factors/
7 and 18
(postop* or post-op* or ((follow* or after*) adj5 (resect$ or excis$ or ((intestin$ or bowel$ or colon$) adj3 (remov$ or surg$))))) adj10 (monitor$ or surveil$ or predict$ or detect* or observ$)).mp.
7 and 16
exp "Sensitivity and Specificity"/
7 and 20 and 22
exp Biological Markers/
7 and 20 and 24
14 or 17 or 21 or 23 or 25
limit 26 to english language
limit 26 to abstracts
27 or 28
random*.mp.
(systematic* adj5 review*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
((search* or review*) adj5 (literatur* or MEDLINE or EMBASE or cochrane)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
30 or 31 or 32 (exp Epidemiologic Studies/
29 and 33
29 and 34
35 or 36

Database: EBM Reviews - Cochrane Central Register of Controlled Trials

Crohn$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
((intestin$ or bowel$ or colon$) adj5 (anastomo$ or resect$ or excis$ or operat$ or reoperat$ or (surg$ adj3 remov$))).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
1 and 2
(cohn$ adj5 (anastomo$ or resect$ or excis$ or operat$ or reoperat$ or (surg$ adj3 remov$))).mp.
3 or 4
6  (colonoscop$ or sigmoidoscop$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
7  (((x-ray$ or computer$ or electron beam$) adj2 tomogra$) or ((cat or ct) adj2 (scan or scans or scanned or scanning$ or scanner$)) or tomodensitometr$ or (cine adj ct)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
8  (magnetic resonance imag$ or mri or mris).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
9  (capsul$ adj5 endoscop*).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
10  ((fecal or feces) adj5 calprotect$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
11  6 or 7 or 8 or 9 or 10
12  (((postop$ or post-op$ or ((follow$ or after*) adj5 resect$ or excis$ or ((intestin$ or bowel$ or colon$) adj3 (remov$ or surg$)))))) adj10 (monitor$ or surveil$ or detect$ or observ$ or accura$ or predict$ or valid$)).mp.
13  (((biological or biochemi$ or clinical$) adj2 marker$) or biomarker$).mp.
14  5 and 11
15  5 and 12
16  5 and 13
17  14 or 15 or 16

Database: EBM Reviews - Cochrane Database of Systematic Reviews

1  Crohn$.mp. [mp=title, abstract, full text, keywords, caption text]
2  ((intestin$ or bowel$ or colon$) adj5 (anastomo$ or resect$ or excis$ or operat$ or reoperat$ or (surg$ adj3 remov$))).mp. [mp=title, abstract, full text, keywords, caption text]
3  1 and 2
4  (crohn$ adj5 (anastomo$ or resect$ or excis$ or operat$ or reoperat$ or (surg$ adj3 remov$))).mp.
5  3 or 4
6  (colonoscop$ or sigmoidoscop$).mp. [mp=title, abstract, full text, keywords, caption text]
7  (((x-ray$ or computer$ or electron beam$) adj2 tomogra$) or ((cat or ct) adj2 (scan or scans or scanned or scanning$ or scanner$)) or tomodensitometr$ or (cine adj ct)).mp. [mp=title, abstract, full text, keywords, caption text]
8  (magnetic resonance imag$ or mri or mris).mp. [mp=title, abstract, full text, keywords, caption text]
9  (capsul$ adj5 endoscop*).mp. [mp=title, abstract, full text, keywords, caption text]
10  ((fecal or feces) adj5 calprotect$).mp. [mp=title, abstract, full text, keywords, caption text]
11  6 or 7 or 8 or 9 or 10
12  (((postop$ or post-op$ or ((follow$ or after*) adj5 resect$ or excis$ or ((intestin$ or bowel$ or colon$) adj3 (remov$ or surg$)))))) adj10 (monitor$ or surveil$ or detect$ or observ$ or accura$ or predict$ or valid$)).mp.
13  (((biological or biochemi$ or clinical$) adj2 marker$) or biomarker$).mp.
14  5 and 11
15  5 and 12
16  5 and 13
17  14 or 15 or 16

Endoscopy/Strictures

Database: Ovid MEDLINE(R) and Ovid OLDMEDLINE(R)

1  exp Crohn Disease/su [Surgery]
2  exp crohn disease/
3  ((intestin$ or bowel$ or colon$) adj5 (anastomo$ or resect$ or excis$ or (surg$ adj3 remov$))).mp. [mp=title, abstract, original title, name of substance word, subject heading word,
keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
4 exp reoperation/
5 3 or 4
6 2 and 5
7 1 or 6
8 (balloon$ adj5 dilatat$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
9 7 and 8
10 exp Anastomosis, Surgical/
11 7 and 10
12 exp Endoscopy/
13 7 and 12
14 ((endoscop$ or laparoscop$) adj7 (anastom$ or strictur$ or balloon$ or dilatat*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
15 7 and 14
16 9 or 11 or 13 or 15
17 random*.mp.
18 (systematic* adj5 review*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
19 ((search* or review*) adj5 (literatur* or MEDLINE or EMBASE or cochrane)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
20 17 or 18 or 19
21 exp Epidemiologic Studies/
22 16 and 20
23 16 and 21
24 limit 16 to (clinical trial, all or controlled clinical trial or meta analysis or randomized controlled trial or systematic reviews)
25 22 or 23 or 24
26 limit 25 to english language
27 limit 25 to abstracts
28 26 or 27

Database: EBM Reviews - Cochrane Central Register of Controlled Trials
1 Crohn$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
2 ((intestin$ or bowel$ or colon$) adj5 (anastomo$ or resect$ or excis$ or operat$ or reoperat$ or (surg$ adj3 remov$))).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
3 1 and 2
4 (crohn$ adj5 (anastomo$ or resect$ or excis$ or operat$ or reoperat$ or (surg$ adj3 remov$))).mp.
5 3 or 4
6 (balloon$ adj5 dilatat$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
7 anastomo$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
8 ((endoscop$ or laparoscop$) adj7 (resect$ or excis$ or operat$ or reoperat$ or surger$ or surgic$ or strictur$ or balloon$ or dilatat*)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
9 6 or 7 or 8
10 5 and 9
**Database: EBM Reviews - Cochrane Database of Systematic Reviews**

1. Crohn$.mp. [mp=title, abstract, full text, keywords, caption text]
2. ((intestin$ or bowel$ or colon$) adj5 (anastomo$ or resect$ or excis$ or operat$ or reoperat$ or (surg$ adj3 remov$))).mp. [mp=title, abstract, full text, keywords, caption text]
3. 1 and 2
4. (crohn$ adj5 (anastomo$ or resect$ or excis$ or operat$ or reoperat$ or (surg$ adj3 remov$))).mp.
5. 3 or 4
6. (balloon$ adj5 dilatat$).mp. [mp=title, abstract, full text, keywords, caption text]
7. anastomo$.mp. [mp=title, abstract, full text, keywords, caption text]
8. ((endoscop$ or laparoscop$) adj7 (resect$ or excis$ or operat$ or reoperat$ or surger$ or surgic$ or strictur$ or balloon$ or dilatat$)).mp. [mp=title, abstract, full text, keywords, caption text]
9. 6 or 7 or 8
10. 5 and 9

**Cost**

**Database: Ovid MEDLINE(R) and Ovid OLDMEDLINE(R)**

1. exp Crohn Disease/su [Surgery]
2. exp crohn disease/
3. ((intestin$ or bowel$ or colon$) adj5 (anastomo$ or resect$ or excis$ or (surg$ adj3 remov$))).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
4. exp reoperation/
5. 3 or 4
6. 2 and 5
7. 1 or 6
8. exp Economics/
9. ec.fs.
10. 8 or 9
11. 7 and 10
12. ((cost or costs or financ$ or economic$) adj5 (reduc$ or control$ or save$ or saving$ or benefi$ or expens$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
13. ((cost or costs or financ$ or economic$) adj7 (reduc$ or control$ or save$ or saving$ or benefi$ or expens$ or incentiv$ or reimburs$)).mp.
14. ((cost or costs or financ$ or economic$) adj7 (reduc$ or control$ or save$ or saving$ or benefi$ or expens$)).mp.
15. 7 and 14
16. 11 or 15
17. exp Recurrence/
18. Secondary Prevention/
19. 17 or 18
20. 2 and 19
21. 10 and 20
22. 14 and 20
23. 21 or 22
24. 16 or 23
limit 24 to English language
limit 24 to abstracts
25 or 26
eResults

Patients’ Values and Preferences

A key aspect in decision-making and developing recommendations in the management of patients with CD after surgical resection is incorporating patients’ values and preferences. For this technical review, data on patients’ values and preferences were derived from a systematic review on patient preferences for treatment options and process of care in IBD published in 2013, and the search was updated to 2016.2,3

Few studies have evaluated patients’ values and preferences in this setting. In one cross-sectional interview-based study in 127 patients with CD, Kennedy and colleagues observed that about 55% of patients felt that type and severity of medication-related side effects were the most important aspects in determining choice of post-operative maintenance therapy, whereas 36% felt that effectiveness of therapy was most important.4 Additionally, they observed that, even when presented with a hypothetical scenario that a postoperative prophylactic therapy (e.g., 5-ASA) was equivalent to no therapy (i.e., 5-ASA did not decrease the risk of disease recurrence), 10% of participants still preferred 5-ASA over no therapy, because the patients felt that they were actively doing something about their disease or had more control over it.

In a discrete choice experiment study, Bewtra and colleagues observed that patients with prior complicated CD (prior surgery, abscess, fistula or stricture) currently in remission may be willing to accept a 10-year maximum acceptable risk of infection and lymphoma of approximately 23% and 1.3%, respectively, to maintain that state of remission for 5 years.3 Some patients accept greater medication-related risks than their treating physicians, particularly when higher risk is associated with higher treatment efficacy5; conversely, some patients may also accept the risks of surgery more readily than their treating physician and may preferentially choose an ileocolonic resection rather than additional medication.6
Specifically for clinical question #2 on the comparative efficacy of different pharmacologic interventions for preventing the recurrence of CD, one relevant study was identified. In an interview-based cross-sectional study of 127 patients with CD, Kennedy and colleagues evaluated the preferred choice of postoperative prophylactic therapy from 5-ASA, fish oil, budesonide, metronidazole and azathioprine, depending on varying illustrative levels of relative efficacy. When the absolute risk reduction with 5-ASA was >10% versus no intervention (i.e., if risk of 1-year symptomatic recurrence without intervention was 25%, the risk of recurrence with 5-ASA would be <15%), 82% of patients preferred 5-ASA to no treatment. If antibiotics and azathioprine were presented as being as effective as 5-ASA medications, then 29% chose antibiotics and 19% chose azathioprine. When alternative medications decreased the risk of recurrence to 10%, then 90% chose antibiotics and 88% chose azathioprine over 5-ASAs. However, all of these assessments were made with 5-ASAs as the comparator medication and there was limited assessment of patients' values and preferences for other comparisons (for example, choosing between azathioprine vs. antibiotics vs. anti-TNF).

In summary, there is wide variation in the risks that patients accept in reference to disease recurrence or potential medication side effects, with some patients being more likely to accept medication risks and others preferring surgery (to medications). Physicians are not likely to be able to select the most appropriate treatment option for their patient based simply on clinical and demographic data. Shared decision-making regarding the risks and benefits in the context of patients' values and preferences is inherently important in the management of CD after surgical resection.

**Cost-effectiveness**

**Clinical Question #1:** There is limited cost-effectiveness data comparing a strategy of routine early post-operative pharmacologic prophylaxis vs. endoscopy-guided therapy for prevention of CD recurrence after surgical resection. In a decision-analysis, Ananthakrishnan and colleagues evaluated the
comparative cost-effectiveness of five strategies for decreasing the risk of CR 1 year after surgically-induced remission of CD – no treatment, routine early azathioprine monotherapy, routine early antibiotic monotherapy, routine early infliximab, and tailored endoscopy-guided therapy with infliximab, in which there was no early post-operative prophylaxis, but initiation of infliximab only in patients with endoscopic recurrence (≥i2) at 6 months after surgical resection. In a sub-analysis, the investigators observed that, while routine early postoperative prophylaxis with infliximab may be more effective than endoscopy-guided infliximab therapy, it was significantly more expensive, with an incremental cost-effectiveness ratio of $629,500/QALY gained, substantially above standard thresholds for cost-effectiveness. It is unclear whether replacing infliximab with azathioprine, antibiotics, or other medications in either or both management strategies (routine early postoperative pharmacologic prophylaxis vs. endoscopy-guided therapy) would modify the cost-effectiveness relationship.

Clinical Question #2: In a decision-analysis, Ananthakrishnan and colleagues evaluated the comparative cost-effectiveness of five strategies for decreasing risk of CR 1 year after surgically-induced remission of CD – no treatment, routine early azathioprine monotherapy, routine early antibiotic monotherapy, routine early infliximab, and tailored endoscopy-guided therapy with infliximab in which there was no early post-operative prophylaxis but infliximab was initiated only in patients with ER (≥i2) at 6 months following surgical resection. In the base-case scenario, the assumed risk of CR was 24% in the no treatment group, and the relative risk reduction in recurrence with azathioprine, antibiotics and infliximab was 41%, 77%, and 99%, respectively. Of note, the corresponding estimates for relative risk reduction derived from the analysis for azathioprine, antibiotics and anti-TNF monotherapy would have been 65%, 48%, and 49%, respectively.

In their cost-effectiveness analysis, routine early infliximab therapy was the most effective strategy (quality-adjusted life years [QALY], 0.83), followed by antibiotic monotherapy (QALY, 0.82), endoscopy-guided infliximab therapy (QALY, 0.82), azathioprine monotherapy (QALY, 0.81) and no treatment (QALY, 0.80). In a hypothetical low-risk scenario, all strategies were clustered together
within a QALY range of 0.01, whereas the comparative effectiveness of strategies became more divergent, albeit in the same order, with higher hypothetical risks of disease recurrence (1-year risk of recurrence of 50-78%). However, in cost-effectiveness analysis, antibiotic monotherapy was the most cost-effective strategy in all baseline risk categories, except in the low-risk scenario, where azathioprine monotherapy was most cost-effective. Routine early infliximab monotherapy was not deemed cost-effective across the entire spectrum of hypothetical disease recurrence rates ($6,667,000/QALY in low risk, $1,266,801/QALY in high risk, $722,348/QALY in the highest risk group, as compared to antibiotics). However, in sensitivity analysis, extending the time horizon to 3-years in the very high-risk scenario (risk of CR at 1 year, 0.78), the cost per QALY gained with routine early infliximab decreased to $459,158/QALY compared with antibiotic monotherapy.

In sensitivity analysis, when the effectiveness of azathioprine was estimated at a relative risk reduction of 65% (closer to estimates derived from this technical review), azathioprine was more cost-effective than antibiotic monotherapy. The addition of 5-ASA as another treatment option did not significantly alter results – 5-ASA was dominated by (i.e. comparatively not cost-as effective as) antibiotic monotherapy at all levels of baseline risk, and was less effective and more expensive than azathioprine monotherapy as well as endoscopy-guided infliximab therapy.

**Clinical Question #3:** No specific cost-effectiveness analyses comparing a strategy of active management with routine endoscopic evaluation and treatment step-up vs. no endoscopic monitoring in the management of CD after surgical resection were identified. However, a cost analysis that accompanied the study that informed this question reported that the median healthcare cost was non-significantly higher in the active management arm (with endoscopic monitoring and treatment step up) vs. the standard care arm. It was estimated that AU$861 (about US$640) was spent over 18 months to prevent one ER.

**Clinical Question #4:** There are no specific cost-effectiveness analyses pertaining to the comparative effectiveness of different pharmacologic interventions for
reducing risk of disease recurrence in patients in clinical remission but with established ER after surgical resection of CD.

**Effect Estimates and Quality of Evidence – All Interventions vs. Placebo**

**Anti-TNF monotherapy vs. placebo:** Based on direct meta-analysis of two RCTs,\(^9,10\) the odds of CR (anti-TNF vs. placebo, 19/157 vs. 35/163; OR, 0.51; 95% CI, 0.28-0.94) and ER (34/157 vs. 88/163; OR, 0.24; 95% CI, 0.15-0.39) with anti-TNF monotherapy were significantly lower, as compared to placebo. Using these estimates, if one assumes that hypothetical risks of CR and ER in an illustrative lower risk population are 20% and 30%, anti-TNF monotherapy may result in CR and ER in 11.3% (95% CI, 6.5-19.0) and 9.3% (95% CI, 6.0-14.3) of patients, respectively. Corresponding rates of CR and ER with anti-TNF monotherapy in an illustrative higher risk population (hypothetical risks of CR and ER are 50% and 80%) would be 33.8% (95% CI, 21.9-48.5) and 49.0% (95% CI, 37.5-60.9), respectively. Using the GRADE approach, evidence was rated down for serious imprecision due to small number of events (did not reach optimal information size of >300 events); there was no evidence of risk of bias, indirectness, or publication bias. For the outcome of ER, while there was statistical heterogeneity, it was primarily related to magnitude of effect and not direction of effect (very large effect size seen in a small study); hence, evidence was not rated down for inconsistency. Overall, the quality of evidence was rated as moderate.

**Thiopurine monotherapy vs. placebo:** Based on a single RCT comparing standard dose 6-mercaptopurine (50mg/d) with placebo\(^11\), the odds of CR (6-MP vs. placebo, 24/47 vs. 33/44; OR, 0.35; 95% CI, 0.14-0.85) and ER (20/47 vs. 26/40; OR, 0.40; 95% CI, 0.17-0.95) with thiopurine monotherapy were significantly lower, as compared to placebo. Using these estimates, in an illustrative lower risk population, thiopurine monotherapy may result in CR and ER in 8.0% (95% CI, 3.4-17.5) and 14.6% (95% CI, 6.8-28.9) of patients, respectively. Corresponding rates of CR and ER with thiopurine monotherapy in an illustrative higher risk population would be 25.9% (95% CI, 12.3-45.9) and
61.5% (95% CI, 40.5-79.2), respectively. Using the GRADE approach, evidence was rated down for serious imprecision due to small number of events (did not reach optimal information size of >300 events); there was no evidence of risk of bias, indirectness, or publication bias. The overall quality of evidence was rated as moderate.

**Antibiotics alone vs. placebo:** Based on 3 RCTs comparing antibiotics (metronidazole x 3m; ornidazole x 12m; ciprofloxacin x 6m) with placebo\textsuperscript{12-14}, the odds of CR (antibiotics vs. placebo, 22/77 vs. 34/79; OR, 0.52; 95% CI, 0.27-1.02) and ER (36/60 vs. 54/71; OR, 0.46; 95% CI, 0.21-0.99) were considerably lower with antibiotics. Using these estimates, in an illustrative lower risk population, antibiotics may result in CR and ER in 11.5% (95% CI, 6.3-20.3) and 16.5% (95% CI, 8.3-29.8) of patients, respectively. Corresponding rates of CR and ER with antibiotics in an illustrative higher risk population would be 34.2% (95% CI, 21.3-50.5) and 64.8% (95% CI, 45.7-79.8), respectively. Using the GRADE approach, evidence was rated down for serious imprecision due to small number of events (did not reach optimal information size of >300 events); there was no evidence of risk of bias, indirectness, or publication bias; for the outcome of CR, there was serious imprecision because the confidence interval crosses unity. Hence, the overall quality of evidence was rated as moderate.

**5-ASA vs. placebo:** Based on 5 RCTs comparing 5-ASA/sulfasalazine with placebo (813 patients)\textsuperscript{15-19}, the odds of CR (OR, 0.59; 95% CI, 0.43-0.82) and ER (OR, 0.65; 95% CI, 0.33-1.28) were lower with 5-ASA. Using the GRADE approach, evidence was rated down for serious imprecision due to small number of events (did not reach optimal information size of >300 events), and there was suspected publication bias; there was no evidence of risk of bias, or indirectness. For the outcome of ER, there was serious inconsistency with differences in magnitude and direction of effect estimate ($I^2=78\%$) with two of the more recent studies showing no significant beneficial effect of 5-ASA on risk of ER. There was also evidence of serious imprecision in effect estimate for ER outcome. Therefore, the overall body of evidence supporting the use of 5-ASA/sulfasalazine over placebo for decreasing the long-term risk of recurrence of
CD was rated as very low quality. Moreover, there is indirect evidence on the lack of benefit of 5-ASA for inducing or maintaining remission in patients with inflammatory luminal CD, based on several large RCTs and meta-analyses.

**Budesonide vs. placebo:** Based on direct meta-analysis of two RCTs (212 patients)\(^{20, 21}\), the odds of CR (OR, 0.84; 95% CI, 0.46-1.53) and ER (OR, 0.73; 95% CI, 0.41-1.30) were marginally lower with budesonide. Using the GRADE approach, there was serious risk of bias (unclear randomization scheme, unclear blinding of patients/providers), serious risk of indirectness (outcomes in trials assessed at 12m, and findings from these were extrapolated to long-term risk of recurrence) and serious imprecision. Hence, the benefit of using budesonide for decreasing risk of recurrence of CD after surgical resection was uncertain and the overall quality of evidence was rated as very low quality.

**Probiotics vs. placebo:** Based on direct meta-analysis of two RCTs (135 patients)\(^{22, 23}\), the odds of CR (OR, 1.50; 95% CI, 0.45-5.00) were marginally higher with probiotics as compared to placebo, whereas the odds of ER (OR, 0.83; 95% CI, 0.41-1.69) were marginally lower with probiotics. Using the GRADE approach, there was serious risk of indirectness (outcomes in trials assessed at 6-12 months, and findings from these were extrapolated to risk of recurrence at 18 months or beyond), very serious imprecision, and inconsistency for the ER outcome. Hence, the benefit of using probiotics for decreasing risk of recurrence of CD after surgical resection was uncertain, and overall quality of evidence was rated as very low quality.

**Thiopurines combined with antibiotics vs. placebo:** There were no RCTs directly comparing thiopurines in combination with antibiotics vs. placebo for postoperative prophylaxis in CD. The effect estimates and GRADE quality of evidence were derived exclusively from indirect comparisons. Based on network meta-analysis, the odds of clinical (OR, 0.19; 95% CrI, 0.04-0.94) and endoscopic recurrence (OR, 0.17; 95% CrI, 0.03-1.07) were considerably lower with thiopurines in combination with antibiotics. Using the GRADE approach for network meta-analysis, the lower of quality of evidence corresponding to first-order loops contributing to this indirect comparison (antibiotics vs. placebo;
antibiotics vs. immunomodulator + antibiotics) as quality of evidence for this comparison was used. There was no evidence of intransitivity. Hence, the overall body of evidence supporting the use of thiopurines in combination with antibiotics over placebo for decreasing the risk of recurrence of CD after surgical resection was rated as low quality.

**Effect Estimates and Quality of Evidence – Selected Interventions vs. 5-ASA**

**Anti-TNF monotherapy vs. 5-ASA:** Based on 1 RCT comparing anti-TNF with 5-ASA\(^24\), the odds of CR (adalimumab vs. 5-ASA, 1/16 vs. 9/18; OR, 0.07; 95% CI, 0.01-0.62) and ER (1/16 vs. 15/18; OR, 0.01; 95% CI, 0.00-0.14) were considerably lower with anti-TNF therapy. Using the GRADE approach, there was no evidence of risk of bias, indirectness, inconsistency or publication bias; however, due to the very small number of events, there was serious risk of imprecision. Hence, the overall quality of evidence was rated as moderate.

**Thiopurine monotherapy vs. 5-ASA:** Based on 5 RCTs comparing thiopurine monotherapy with 5-ASAs\(^11, 24-27\), the odds of CR (thiopurine vs. 5-ASA, 54/162 vs. 66/168; OR, 0.73; 95% CI, 0.45-1.18) and ER (47/93 vs. 63/97; OR, 0.56; 95% CI, 0.31-1.01) was lower with thiopurine monotherapy, although it did not reach statistical significance. Using the GRADE approach, evidence was rated down for serious imprecision in effect estimate; hence, the overall body of evidence supporting the use of thiopurines over 5-ASA for decreasing the risk of recurrence of CD was rated as moderate quality.

**Thiopurines combined with antibiotics vs. placebo:** There were no RCTs directly comparing thiopurines in combination with antibiotics, or antibiotics alone vs. 5-ASA for postoperative prophylaxis in CD. The effect estimates and GRADE quality of evidence was derived exclusively from indirect comparisons. Based on network meta-analysis, the odds of CR (OR, 0.31; 95% CrI, 0.06-1.65) and ER (OR, 0.28; 95% CrI, 0.04-1.76) were considerably lower with thiopurines in combination with antibiotics, as compared to 5-ASA. Using the GRADE approach for network meta-analysis, the overall body of evidence supporting the use of
thiopurines in combination with antibiotics over 5-ASAs for decreasing the long-term risk of recurrence of CD was rated as very low quality.

**Antibiotics alone vs. 5-ASA:** In the absence of direct comparisons, using network meta-analysis, the odds of CR (OR, 0.87; 95% CrI, 0.31-2.45) and ER (OR, 0.76; 95% CrI, 0.17-3.41) were marginally lower with antibiotics, as compared to 5-ASAs. Using the GRADE approach for network meta-analysis, the benefit of using antibiotics over 5-ASAs for decreasing risk of recurrence of CD was uncertain, and overall quality of evidence was rated as very low quality.

**Effect Estimates and Quality of Evidence – Selected Interventions vs. Antibiotics alone**

**Anti-TNF monotherapy vs. antibiotics alone:** There were no RCTs directly comparing anti-TNF monotherapy or thiopurine monotherapy vs. antibiotics for postoperative prophylaxis in CD. Based on network meta-analysis, the odds of CR (OR, 0.44; 95% CI, 0.09-1.37) and ER (OR, 0.12; 95% CI, 0.02-0.67) were considerably lower with anti-TNF monotherapy, as compared to antibiotics alone. Using the GRADE approach, the overall body of evidence supporting the use of anti-TNF monotherapy over antibiotics for decreasing the risk of recurrence of CD was rated as moderate quality.

**Thiopurine monotherapy vs. antibiotics alone:** In the absence of direct comparison, using network meta-analysis, the odds of CR (OR, 0.90; 95% CrI, 0.29-2.77) and ER (OR, 0.94; 95% CrI, 0.19-4.57) were marginally lower with thiopurine monotherapy, as compared to antibiotics. Using the GRADE approach for network meta-analysis, the benefit of using thiopurine monotherapy over antibiotics alone for decreasing the risk of recurrence of CD is marginal, and the overall quality of evidence was rated as low quality.

**Thiopurines combined with antibiotics vs. antibiotics alone:** Based on 1 RCT comparing thiopurines in combination with antibiotics (40 patients) with antibiotics alone (41 patients),28 the odds of CR (thiopurines + antibiotics vs. antibiotics, 3/40 vs. 7/41; OR, 0.39; 95% CI, 0.09-1.65) and ER (22/40 vs. 32/41; OR, 0.34; 95% CI, 0.13-0.90) was considerably lower with thiopurine + antibiotics. Using
the GRADE approach, evidence was rated down for serious imprecision in effect estimate, as well as indirectness (outcome in trial assessed at 12 months, and findings from extrapolation to long-term risk of recurrence); hence, the overall body of evidence supporting the use of immunomodulators + antibiotics over antibiotics alone for decreasing the risk of recurrence of CD after surgical resection was rated as low quality.

**Effect Estimates and Quality of Evidence – Selected Interventions vs. Thiopurine monotherapy**

**Anti-TNF monotherapy vs. thiopurine monotherapy**: Based on 2 small RCTs comparing anti-TNF monotherapy with thiopurine monotherapy

The odds of CR (anti-TNF vs. thiopurines, 2/27 vs. 13/27; OR, 0.10; 95% CI, 0.02-0.47) and ER (2/27 vs. 15/27; OR, 0.07; 95% CI, 0.01-0.34) were significantly lower with anti-TNF monotherapy. Using the GRADE approach, evidence was rated down for serious imprecision in effect estimate (due to very small number of events); in additional, for the outcome of CR, there was evidence of inconsistency, but primarily due to difference in magnitude, not direction, of effect estimates. Hence, the overall body of evidence supporting the use of anti-TNF monotherapy over thiopurines alone for decreasing the risk of recurrence of CD after surgical resection was rated as moderate quality.

**Thiopurines combined with antibiotics vs. thiopurine monotherapy**: Based on a single small RCT

The odds of CR (thiopurine + antibiotics vs. thiopurine alone, 1/25 vs. 2/25; OR, 0.48; 95% CI, 0.04-5.65) and ER (9/25 vs. 14/25; OR, 0.44; 95% CI, 0.14-1.38) were considerably lower with the combination of an thiopurines and antibiotics, as compared to a thiopurine alone. Using the GRADE approach, evidence was rated down for indirectness (outcome in trial assessed at 12 months, and findings from extrapolation to long-term risk of recurrence); in addition, for the CR outcome, evidence was rated down twice for very serious imprecision (very wide confidence intervals and very small number of events). Hence, the overall body of evidence supporting the use of combination of a
thiopurine with antibiotics, as compared to thiopurine alone, for decreasing the risk of recurrence of CD was rated as very low quality.

**Effect Estimates and Quality of Evidence – Selected Interventions vs. thiopurines combined with antibiotics**

Anti-TNF monotherapy vs. thiopurines combined with antibiotics: There were no RCTs directly comparing anti-TNF monotherapy with the combination of thiopurines and antibiotics for postoperative prophylaxis in CD. The effect estimates and GRADE quality of evidence were derived exclusively from indirect comparisons. Based on network meta-analysis, the odds of clinical recurrence (OR, 1.19; 95% CrI, 0.15-7.14) were marginally higher with anti-TNF monotherapy as compared to thiopurine + antibiotics, whereas the odds of endoscopic recurrence (OR, 0.34; 95% CrI, 0.03-2.56) were significantly lower with anti-TNF monotherapy. Using the GRADE approach for network meta-analysis, the benefit of using anti-TNF monotherapy over the combination of thiopurines and antibiotics for decreasing risk of recurrence of CD was uncertain, and overall quality of evidence was rated as very low quality.
eTables

<table>
<thead>
<tr>
<th>Study</th>
<th>Age [Mean (SD)]</th>
<th>Sex (% males)</th>
<th>Smokers (% current)</th>
<th>Duration of Disease [Mean (SD)]</th>
<th>Penetrating disease (% patients)</th>
<th>&gt;1 CD-related surgery (% patients)</th>
<th>Pre-surgery medications (% on anti-TNF, IMM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferrante</td>
<td>34 (3)</td>
<td>36 (6)</td>
<td>58</td>
<td>32</td>
<td>29</td>
<td>53</td>
<td>5.6 (3.4)</td>
</tr>
</tbody>
</table>

CD, Crohn’s disease; Cont., Control arm; Int., Intervention arm; IMM, immunomodulator; SD, standard deviation; TNF, tumor necrosis factor

**eTable 1.** Baseline patient characteristics in included randomized controlled trials comparing a strategy of routine early postoperative pharmacologic prophylaxis vs. endoscopy-guided therapy for prevention of recurrence of CD after surgical resection (Clinical Question #1)
<table>
<thead>
<tr>
<th>Study, Year of Publication</th>
<th>Study Design</th>
<th>Location; Time period</th>
<th>Timing of intervention after surgery and outcome assessment</th>
<th>Intervention</th>
<th>Control</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mesalamine/Sulfasalazine v. Placebo/No intervention</strong></td>
<td></td>
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<tr>
<td>Brignola, 1995</td>
<td>MC, DB, PC</td>
<td>Italy; 1990-91</td>
<td>&lt;4 weeks; 12 months</td>
<td>Pentasa 3g/day, for 12 months; N=44</td>
<td>Placebo, for 12 months; N=43</td>
<td>Increase of CDAI by 100 points, with score &gt;150</td>
</tr>
<tr>
<td>Caprilli, 1994</td>
<td>MC, OL, no placebo group</td>
<td>Italy; 1990-92</td>
<td>&lt;2 weeks; 24 months</td>
<td>Asacol 2.4g/day, for 12 months; N=55</td>
<td>No intervention; N=55</td>
<td>Increase of CDAI by 100 points, with score &gt;150</td>
</tr>
<tr>
<td>Lochs, 2000</td>
<td>MC, DB, PC</td>
<td>Europe; 1992-96</td>
<td>&lt;10 days; 18 months</td>
<td>Pentasa 4g/day, for 18 months; N=152</td>
<td>Placebo, for 18 months; N=166</td>
<td>Increase of CDAI by 60 points, with score &gt;150</td>
</tr>
<tr>
<td>McLeod, 1995</td>
<td>MC, DB, PC</td>
<td>Canada; 1986-93</td>
<td>&lt;8 weeks; 72 months</td>
<td>Mesalamine 3g/day, for mean 35 months; N=87</td>
<td>Placebo, for mean 29 months; N=76</td>
<td>Clinician diagnosed</td>
</tr>
<tr>
<td>Wenckert, 1978</td>
<td>MC, DB, PC</td>
<td>Europe; NR</td>
<td>&lt;4 weeks; 18 months</td>
<td>Sulfasalazine 3g/day, for 18 months; N=32</td>
<td>Placebo, for 18 months; N=34</td>
<td>Clinician diagnosed</td>
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<tr>
<td><strong>Thiopurines v. mesalamine (v. placebo)</strong></td>
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<tr>
<td>Ardizzone, 2004</td>
<td>SC, OL</td>
<td>Italy; NR</td>
<td>&lt;2 weeks; 24 months</td>
<td>Azathioprine 2mg/kg/day, for 24 months; N=69</td>
<td>Mesalamine 3g/day, for 24 months; N=69</td>
<td>CDAI&gt;200, warranting corticosteroid therapy</td>
</tr>
<tr>
<td>Herfarth, 2006</td>
<td>MC, DB</td>
<td>Germany; NR</td>
<td>&lt;2 weeks; 12 months</td>
<td>Azathioprine 2.5mg/kg/day, for 12 months; N=37</td>
<td>Mesalamine 4g/day, for 12 months; N=42</td>
<td>Not defined</td>
</tr>
<tr>
<td>Nos, 2000</td>
<td>SC, OL</td>
<td>Spain; NR</td>
<td>&lt;4 weeks; 24 months</td>
<td>Azathioprine 50mg/day, for 24 months; N=21</td>
<td>Mesalamine 3g/day, for 24 months; N=18</td>
<td>CDAI&gt;200</td>
</tr>
<tr>
<td>Hanauer, 2004</td>
<td>MC, DB, PC, triple-</td>
<td>USA, Belgium; During index hospitalization</td>
<td>6-mercaptopurine 50mg/day, for 24 months; N=40</td>
<td>Pentasa 3g/day, for 24 months; N=40</td>
<td>Non-validated, 4-point severity</td>
<td>i2-4, Rutgeerts</td>
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<tr>
<td>arm trial</td>
<td>1992-96</td>
<td>24 months</td>
<td>months; N=47</td>
<td>1. Placebo, for months; N=44</td>
<td>24 months</td>
<td>scale</td>
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<tr>
<td><strong>Antibiotics v. Placebo/No intervention</strong></td>
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<tr>
<td>Rutgeerts,13 1995</td>
<td>MC, DB, PC</td>
<td>Belgium; 1988-91</td>
<td>&lt;1 week; 36 months</td>
<td>Metronidazole 20mg/kg/day, for 3 months; N=30</td>
<td>Placebo, for 3 months; N=30</td>
<td>Clinician diagnosed</td>
</tr>
<tr>
<td>Rutgeerts,14 2005</td>
<td>MC, DB, PC</td>
<td>Belgium; NR</td>
<td>&lt;2 weeks; 24 months</td>
<td>Ornidazole 500mg BID, for 12 months; N=38</td>
<td>Placebo, for 12 months; N=40</td>
<td>CDAI&gt;250</td>
</tr>
<tr>
<td>Herfarth,12 2013</td>
<td>MC, DB, PC</td>
<td>USA; 2008-11</td>
<td>&lt;2 weeks; 6 months</td>
<td>Ciprofloxacin 500mg BID, for 6 months; N=17</td>
<td>Placebo, for 6 months; N=16</td>
<td>HBI score &gt;5, or 3-point increase from baseline</td>
</tr>
<tr>
<td><strong>Probiotics v. Placebo/No intervention</strong></td>
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<tr>
<td>Prantera,23 2002</td>
<td>SC, DB, PC</td>
<td>Italy; 1998-2000</td>
<td>&lt;10 days; 12 months</td>
<td>Dicoflor (Lactobacillus GG) 60 BID for 12 months; N=23</td>
<td>Placebo for 12 months; N=23</td>
<td>CDAI &gt; 150</td>
</tr>
<tr>
<td>Marteau,24 2006</td>
<td>MC, DB, PC</td>
<td>France; 2002-2004</td>
<td>&lt;21 days; 6 months</td>
<td>Lactobacillus johnsonii (LA1) BID for 6 months; N=43</td>
<td>Placebo for 6 months; N=43</td>
<td>CDAI &gt; 200</td>
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<tr>
<td><strong>Thiopurines + Antibiotics v. Antibiotics</strong></td>
<td></td>
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<tr>
<td>D’Haens,25 2008</td>
<td>MC, DB, PC</td>
<td>Belgium; 1999-2005</td>
<td>&lt;2 weeks; 12 months</td>
<td>Azathioprine 100mg (wt&lt;60kg) or 150mg (wt&gt;60kg), for 12 months AND metronidazole 250mg TID for 3 months; N=40</td>
<td>Metronidazole 250mg TID, for 3 months AND placebo, for 3 months; N=41</td>
<td>CDAI&gt;250</td>
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<tr>
<td><strong>Thiopurines v. Thiopurines</strong></td>
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<tr>
<td>Manosa,30 2013</td>
<td>MC, DB, PC</td>
<td>Spain; 2004-10</td>
<td>During index hospitalization; 12 months</td>
<td>Azathioprine 2-2.5mg/kg/day, for 12 months AND metronidazole 15-20mg/kg/day for 3 months; N=25</td>
<td>Azathioprine 2-2.5mg/kg/day, for 12 months AND placebo, for 3 months; N=25</td>
<td>HBI score &gt;7</td>
</tr>
<tr>
<td><strong>Budesonide v. Placebo/No intervention</strong></td>
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</tr>
<tr>
<td>Hellers,21 2010</td>
<td>MC, DB, PC</td>
<td>Europe; &lt;2 weeks;</td>
<td>Budesonide 6mg/day,</td>
<td>Placebo, for 12</td>
<td>CDAI&gt;200</td>
<td>i2-4,</td>
</tr>
<tr>
<td>Year</td>
<td>Author</td>
<td>Country</td>
<td>Duration</td>
<td>Drug Details</td>
<td>Comparator</td>
<td>Follow-Up</td>
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</tr>
<tr>
<td>1999</td>
<td>Ewe, MC, DB, PC</td>
<td>Germany; 1992-94</td>
<td>&lt;2 weeks; 12 months</td>
<td>Budesonide 3mg/day, for 12 months; N=43</td>
<td>Placebo, for 12 months; N=40</td>
<td>CDAI &gt;200</td>
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</table>

**Anti-TNF v. Placebo/No intervention**

<table>
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<tr>
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<th>Author</th>
<th>Country</th>
<th>Duration</th>
<th>Drug Details</th>
<th>Comparator</th>
<th>Follow-Up</th>
<th>CDAI Score</th>
<th>Rutgeerts Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>Regueiro, SC, DB, PC</td>
<td>USA; 2005-07</td>
<td>&lt;4 weeks; 12 months</td>
<td>Infliximab 5mg/kg at 0, 2 and 6 weeks, followed by q8 weeks, for 54 weeks (+/- concomitant mesalamine, 9.1% or immunomodulator, 36.4%); N=11</td>
<td>Placebo, for 54 weeks (+/- concomitant mesalamine, 30.8% or immunomodulator, 53.8%); N=13</td>
<td>CDAI &gt;200</td>
<td>i2-4, Rutgeerts score</td>
<td></td>
</tr>
</tbody>
</table>

**Anti-TNF v. Thiopurine (v. Mesalamine)**

<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>Country</th>
<th>Duration</th>
<th>Drug Details</th>
<th>Comparator</th>
<th>Follow-Up</th>
<th>CDAI Score</th>
<th>Rutgeerts Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013</td>
<td>Armuzzi, SC, OL</td>
<td>Italy; 2007-11</td>
<td>&lt;4 weeks; 12 months</td>
<td>Infliximab 5mg/kg at 0, 2 and 6 weeks, followed by q8 weeks, for 12 months; N=11</td>
<td>Azathioprine 2-2.5mg/kg/day, for 12 months; N=11</td>
<td>HBI score &gt;7</td>
<td>i2-4, Rutgeerts score</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>Country</th>
<th>Duration</th>
<th>Drug Details</th>
<th>Comparator</th>
<th>Follow-Up</th>
<th>CDAI Score</th>
<th>Rutgeerts Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013</td>
<td>Savarino, SC, OL, triple-arm trial</td>
<td>Italy; 2008-10</td>
<td>&lt;4 weeks; 24 months</td>
<td>Adalimumab 160mg at week 0, 80mg at week 2, followed by 40mg q2 weeks, for 24 months; N=16</td>
<td>1. Azathioprine 2mg/kg/day, for 24 months; N=17 2. Pentasa 3g/day, for 24 months; N=18</td>
<td>CDAI &gt;200 or using non-validated, 4-point severity scale</td>
<td>i2-4, Rutgeerts score</td>
<td></td>
</tr>
</tbody>
</table>

CDAI, Crohn’s Disease Activity Index; DB, double-blind; HBI, Harvey-Bradshaw index; ITT, intention-to-treat; mITT, modified intention-to-treat; MC, multicenter; NR, not reported; PC, placebo-controlled; OL, open-label; RCT, randomized controlled trial; SC, single center; TNF, tumor necrosis factor

**eTable 2.** Characteristics of included randomized controlled trials comparing different pharmacological interventions for post-operative prophylaxis after surgical resection in Crohn's disease (Clinical Question #2)
<table>
<thead>
<tr>
<th>Study</th>
<th>Age [Mean (SD) or Median (range)]</th>
<th>Sex (% males)</th>
<th>Smokers (% current)</th>
<th>Duration of Disease (in years)</th>
<th>Penetrating disease (% patients)</th>
<th>&gt;1 CD-related surgery (% total or mean [SD])</th>
<th>Pre-surgery medications (% on anti-TNF, IMM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brignola¹⁵</td>
<td>39 (10)*</td>
<td>34 (17)</td>
<td>50</td>
<td>46</td>
<td>48</td>
<td>51</td>
<td>6.2 (6.1)*</td>
</tr>
<tr>
<td>Caprilli¹⁶</td>
<td>36 (16-61)*</td>
<td>34 (16-58)</td>
<td>68</td>
<td>48</td>
<td>NR</td>
<td>3.2 (0-12)*</td>
<td>2.3 (0-10)</td>
</tr>
<tr>
<td>Lochs¹⁷</td>
<td>33 (10)*</td>
<td>34 (10)</td>
<td>47</td>
<td>51</td>
<td>NR</td>
<td>6.5 (6.4)*</td>
<td>6.9 (6.4)</td>
</tr>
<tr>
<td>McLeod¹⁸</td>
<td>39 (13)*</td>
<td>37 (13)</td>
<td>56</td>
<td>64</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Wenckert¹⁹</td>
<td>34</td>
<td>50</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Ardizzone²⁰</td>
<td>&lt;40: 84%</td>
<td>&lt;40: 77%</td>
<td>63</td>
<td>70</td>
<td>39</td>
<td>51</td>
<td>&gt;10y: 37%</td>
</tr>
<tr>
<td>Herfarth²¹</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Nos²²</td>
<td>35 (28)*</td>
<td>33 (28)</td>
<td>53</td>
<td>58</td>
<td>NR</td>
<td>5.5 (3)*</td>
<td>3.5 (1.7)</td>
</tr>
<tr>
<td>Hanauer¹¹</td>
<td>AZA: 35 (11)*</td>
<td>5-ASA: 34 (11); Placebo: 34 (11)</td>
<td>49</td>
<td>43; 45</td>
<td>NR</td>
<td>9.4 (7.8)*</td>
<td>10 (8.7); 10.6 (8.3)</td>
</tr>
<tr>
<td>Rutgeerts²³</td>
<td>33 (10)*</td>
<td>37 (14)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>63</td>
<td>53</td>
</tr>
<tr>
<td>Rutgeerts²⁴</td>
<td>35 (18-70)*</td>
<td>30 (18-68)</td>
<td>42</td>
<td>50</td>
<td>45</td>
<td>47</td>
<td>7 (4-11.8)*</td>
</tr>
<tr>
<td>Herfarth²⁵</td>
<td>33 (19-70)*</td>
<td>27 (18-61)</td>
<td>59</td>
<td>50</td>
<td>23</td>
<td>0</td>
<td>10 (0-51)*</td>
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<tr>
<td>D'Haens²⁶</td>
<td>39 (22-40)</td>
<td>40 (21-40)</td>
<td>51</td>
<td>33</td>
<td>41</td>
<td>NR</td>
<td>50</td>
</tr>
</tbody>
</table>

- * indicates that the data is from a subset of the study population.
- ‡ indicates a comparison group that was not in the study.
- The table presents data on the comparison between mesalamine/sulfasalazine and placebo/no intervention, thiopurines and mesalamine, antibiotics and placebo, as well as thiopurines plus antibiotics versus antibiotics alone.
<table>
<thead>
<tr>
<th></th>
<th>Thiopurines + Antibiotics v. Thiopurines</th>
<th></th>
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</thead>
<tbody>
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<td></td>
<td>Thiopurines + Antibiotics v. Thiopurines</td>
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<td></td>
</tr>
<tr>
<td>Manosa(^{30})</td>
<td>36 (12)*</td>
<td>35 (8)</td>
<td>48</td>
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<td>54</td>
<td>7 (7.8)*</td>
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<td>4.7 (4.7)</td>
<td>40</td>
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<td>52</td>
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<td><strong>Budesonide v. Placebo</strong></td>
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<td>Hellers(^{21})</td>
<td>24 (20-76)(^{¶})</td>
<td>36 (17-81)</td>
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<td>Marteau(^{22})</td>
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<td>&lt;40: 62%</td>
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<td>&gt;10y: 64%</td>
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<td>35 (12)</td>
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<td><strong>Anti-TNF v. Thiopurine (v. Mesalamine)</strong></td>
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<tr>
<td>Armuzzi(^{29})</td>
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<td>36/18</td>
</tr>
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<td>Savarino(^{24})</td>
<td>45 (22-66)(^{¶})</td>
<td>AZA: 49 (24-69); 5-ASA: 46 (25-65)</td>
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</tr>
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<td>53; 44</td>
<td>56</td>
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<td>24; 33</td>
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<td>7.9 (1-17); 6.9 (1-18)</td>
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<td>12; 28</td>
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</tr>
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<td></td>
<td></td>
<td>24/ NR; 6/ NR</td>
</tr>
<tr>
<td></td>
<td><strong>5-ASA, 5-aminosalicylate; AZA, azathioprine; CD, Crohn's disease; C, colon; Cont., Control arm; Int., Intervention arm; IMM, immunomodulator; NR, not reported; SB, small bowel; SD, standard deviation; TNF, tumor necrosis factor</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Mean (standard deviation), ¶Median (range)</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**eTable 3.** Baseline patient characteristics in included randomized controlled trials comparing different pharmacological interventions for prevention of recurrence of CD after surgical resection (Clinical Question #2)**
<table>
<thead>
<tr>
<th>Study</th>
<th>Age [Median (range)]</th>
<th>Sex (% males)</th>
<th>Smokers (% current)</th>
<th>Duration of Disease (in years) [Mean (SD)]</th>
<th>Penetrating disease (% patients)</th>
<th>&gt;1 CD-related surgery (% patients)</th>
<th>Pre-surgery medications (% on anti-TNF, IMM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Cruz²³</td>
<td>36 (24-45)</td>
<td>36 (26-47)</td>
<td>48</td>
<td>37</td>
<td>31</td>
<td>31</td>
<td>9 (3-16)</td>
</tr>
</tbody>
</table>

5CD, Crohn’s disease; Cont., Control arm; Int., Intervention arm; IMM, immunomodulator; SD, standard deviation; TNF, tumor necrosis factor

**eTable 4.** Baseline patient characteristics in included randomized controlled trials comparing a strategy of active management with routine endoscopic monitoring (and treatment step-up) vs. no endoscopic for prevention of recurrence of CD after surgical resection (Clinical Question #3)
References


