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American Gastroenterological Association Institute Technical Review on the Medical Management of Microscopic Colitis

Darrell S. Pardi,[1] William J. Tremaine,[1] and Alonso Carrasco-Labra[2,3]

[1]Department of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota; [2]McMaster University, Hamilton, Ontario, Canada; and [3]Evidence-Based Dentistry Unit, Faculty of Dentistry, Universidad de Chile, Santiago, Chile

Podcast interview: www.gastro.org/gastropodcast. Also available on iTunes.

Microscopic colitis (MC) is a cause of chronic diarrhea, and there are 2 subtypes: collagenous colitis (CC) and lymphocytic colitis (LC). The clinical features, symptoms, and responses to treatment are similar for both CC and LC. All meta-analyses conducted for this technical review tested for interaction (or a subgroup effect), and in every case there was no evidence of a subgroup effect. Therefore, in this review, the 2 subtypes are combined and considered together as MC. Information on pathophysiology was considered outside the scope of this review.

The prevalence of MC has been reported in recent studies to be 48 per 100,000 in Spain, 123 per 100,000 in Sweden, and 219 per 100,000 in Minnesota. MC is more common in people 60 years of age and older, and there is an apparent female preponderance.[1] The clinical course of MC is variable; symptoms range from mild (a few loose stools daily) to severe (incapacitating watery diarrhea and abdominal pain). Symptoms can persist for months to years or spontaneously remit and then recur after months to years.

Diagnosis of MC is based on compatible histology from colonic mucosal biopsy specimens obtained during colonoscopy or flexible sigmoidoscopy. The distribution of colonic involvement can be patchy or segmental, so multiple random biopsy specimens are often required for diagnosis.

Quality of life is impaired in patients with MC in proportion to the degree of diarrhea, abdominal pain, urgency, and incontinence and to a similar degree to that reported for active irritable bowel disease. A diagnosis of MC does not increase mortality or the risk of colorectal cancer and only rarely requires surgery.

The goal of treatment of MC is to induce remission while minimizing potential adverse effects of therapy. Some patients remain asymptomatic after induction of remission and after discontinuing therapy and do not need maintenance treatment for MC. However, many patients have a symptomatic recurrence after discontinuation of treatment and should be considered for maintenance therapy. Medications that are used to treat MC include loperamide (an antidiarrheal agent); bismuth subsalicylate (an antimicrobial, anti-inflammatory agent); colesevelam, cholestyramine, and colestipol (bile acid binders); mesalamine (an anti-inflammatory agent); prednisone and budesonide (corticosteroids); azathioprine and methotrexate (immune suppressants); infliximab and adalimumab (biologic agents); and surgical interventions (diverting ileostomy and proctocolectomy with ileal pouch–anal anastomosis). Several of these therapies are used in clinical practice but have not been studied in clinical trials. These therapies are therefore not addressed directly in this technical review.

Methods

Focused Questions

The methods used to identify, select, and summarize the evidence are described at a question level. This technical review is not intended to be a review of all aspects of MC. Rather, it summarizes the evidence related to the following questions.

Question 1. What is the prevalence of MC? How many colon biopsy specimens should be obtained and from which areas of the colon? This question is for information and not a recommendation, and therefore it was not framed as a PICO (population, interventions, comparisons, and outcomes) question. The content of this question is included in the guideline only for information.

Question 2. In patients with MC (either LC or CC), which treatments are effective and safe for inducing remission of the disease, measured as clinical response, histological response, quality of life, and adverse events?

The population is adult patients with MC (either LC or CC). The interventions include bismuth subsalicylate, budesonide, cholestyramine, sulfasalazine, mesalamine, prednisone, azathioprine, metronidazole, methotrexate, infliximab, adalimumab,

Abbreviations used in this paper: **CC, collagenous colitis; CI, confidence interval; GIQLI, Gastrointestinal Quality of Life Index; GRADE, Grading of Recommendations Assessment, Development and Evaluation; LC, lymphocytic colitis; MC, microscopic colitis; MD, mean difference; PICO, population, interventions, comparisons, and outcomes; RR, relative risk; SIBDQ, Short Inflammatory Bowel Disease Questionnaire.**

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or any other medication described. The comparisons include any of the medications described as an intervention, compared in a head-to-head fashion or compared with placebo or no treatment. The outcomes include clinical response, histological response, quality of life, and adverse events according to the outcome description in the included studies.

Question 3. In patients successfully treated for MC (either LC or CC) and in remission of symptoms, which treatments are effective and safe for maintaining clinical remission of the disease, measured as maintenance of clinical response, maintenance of histological response, time to relapse, quality of life, and adverse events?

The population is adult patients successfully treated for MC (either LC or CC) and in remission of symptoms. The interventions include budesonide, a thiopurine agent (azathioprine), or any other intervention described in the literature for maintaining remission of MC. The comparisons include head-to-head comparisons among any of the interventions identified, placebo, or no treatment. The outcomes include maintenance of clinical response, maintenance of histological response, time to relapse, quality of life, and adverse events, as described in the included studies.

A summary of the focused questions and PICO components is shown in Table 1.

Definition of the Relative Importance of Outcomes

After defining the included outcomes for each focused question, an online survey was circulated among panel members participating in this review. In this survey, participants were asked to rank the outcomes according to their relative importance. The process was conducted individually and independently. In the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, the relative importance of an outcome is defined on a scale from 1 (least important) to 9 (most critical); those rated from 1 to 3 are defined as of limited importance, from 4 to 6 as important, and from 7 to 9 as critical.[2] The panel was not aware of the quality of the evidence for each of the outcomes at the moment of assessing their importance. The results of the determination of the relative importance of the outcomes are shown in Table 2.

Study Selection Criteria and Search Strategy per Question

Question 1. What is the prevalence of MC? How many colon biopsy specimens should be obtained and from which areas of the colon?

Study selection criteria. We included studies recruiting patients with both LC and CC. For estimation of the prevalence of the disease, we selected studies based on populations of patients with chronic diarrhea. These studies also provided a description of the diagnostic test used, number of biopsy specimens obtained, and areas of the colon from which biopsy specimens were obtained. We excluded editorial letters, comments, notes, or case reports.

Search strategy and databases. We searched Ovid MEDLINE, Ovid EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), and the Cochrane Database of Systematic Reviews from inception to August 2014. The search strategy included terms such as "microscopic colitis," "colonoscopy," and "biopsy," among others. There was no restriction by language or status of publication. For more details about the search strategy, see Appendix 1.

Question 2. In patients with MC (either LC or CC), which treatments are effective and safe for inducing remission of the disease, measured as clinical response, histological response, quality of life, and adverse events?

Study selection criteria. We included studies that recruited participants with a confirmed diagnosis of MC, irrespective of whether the patients had CC or LC. In addition, the studies provided information about the effectiveness and safety profile of any medication to treat these conditions compared with other interventions in a head-to-head comparison or placebo. For this question, we excluded studies reporting on the effect of interventions for maintaining remission of MC, because these studies are covered in question 3. Given that we were anticipating scarce evidence to answer this question, we included both randomized controlled trials and observational studies during the initial screening process. Good-quality observational studies were included in the review along with the controlled trials.

Search strategy and databases. We searched Ovid MEDLINE from 1946 to July week 4 2014, Ovid EMBASE from 1980 to 2014 week 31, the Cochrane Central Register of Controlled Trials (CENTRAL) to June 2014, and the Cochrane Database of Systematic Reviews from 2005 to June 2014. The search strategy included terms describing the disease and all medications available for inducing remission of MC. There was no restriction by language. We excluded editorial letters, comments, notes, or case reports. For more details about the search strategy, see Appendix 2.

Question 3. In patients successfully treated for MC (either LC or CC) and in remission of symptoms, which treatments are effective and safe for maintaining clinical remission of the disease, measured as maintenance of clinical response, maintenance of histological response, time to relapse, quality of life, and adverse events?

Study selection criteria. We included treatment trials for patients with a confirmed diagnosis of MC, including both CC and LC, who were in clinical remission. Studies were selected that included information about the effectiveness and safety profile of any medication to maintain remission. We included interventions for maintaining remission compared with other

Table 1. Focus Review Questions and PICO Description

	Question	Population	Intervention or new test	Comparison or gold standard	Outcome
1	What is the prevalence of MC? How many colon biopsy specimens should be obtained and from which areas of the colon?	Patients with both LC and CC; for estimation of the prevalence of the disease, we selected studies based on populations of patients with either nonspecific chronic watery diarrhea or chronic diarrhea refractory to treatment	Colonoscopy with mucosal biopsy specimens in patients with chronic diarrhea	Not applicable	Number of biopsy specimens required and areas of the colon selected
2	In patients with MC (either LC or CC), which treatments are effective and safe for inducing remission of the disease, measured as clinical response, histological response, quality of life, and adverse events?	Adult patients with MC (either LC or CC)	Bismuth subsalicylate Budesonide Cholestyramine Sulfasalazine Mesalamine Prednisone Azathioprine Metronidazole Methotrexate Infliximab Adalimumab Other medication reported in the literature	Head-to-head comparison, placebo/no treatment	Clinical response (decreased fecal frequency and/or stool weight), histological response, quality of life, adverse events
3	In patients successfully treated for MC (either LC or CC) and in remission of symptoms, which treatments are effective and safe for maintaining clinical remission of the disease, measured as maintenance of clinical response, maintenance of histological response, time to relapse, quality of life, and adverse events?	Adult patients successfully treated for MC (either LC or CC) and in remission of symptoms	Budesonide Thiopurine agent (azathioprine)	Placebo/no treatment (observation)	Maintenance of clinical response (number of patients with a maintained clinical response or lack of clinical relapse), maintenance of histological response, time to relapse, effect on quality of life, adverse events

Table 2. Relative Importance of Outcome per Comparison

Question	Outcomes	Rating score	Relative importance
In patients with MC (either LC or CC), which treatments are effective and safe for inducing remission of the disease, measured as clinical response, histological response, quality of life, and adverse events?	Clinical response	9	Critical
	Histological response	6	Important
	Adverse events	7	Critical
	Quality of life	7	Critical
In patients successfully treated for MC (either LC or CC) and in remission of symptoms, which treatments are effective and safe for maintaining clinical remission of the disease, measured as maintenance of clinical response, maintenance of histological response, time to relapse, quality of life, and adverse events?	Maintenance of clinical response	9	Critical
	Maintenance of histological response	6	Important
	Time to relapse during maintenance therapy	8	Critical
	Time to relapse after maintenance therapy	8	Critical
	Adverse events	7	Critical
	Quality of life	7	Critical

interventions or placebo. We excluded studies reporting on the effect of interventions for inducing remission of MC because those studies were addressed in question 2. Because we anticipated scarce evidence to answer this question, we initially included both randomized controlled trials and observational studies. Good-quality observational studies were included in the review along with the controlled trials.

Search strategy and databases. We searched Ovid MEDLINE from 1946 to July week 4 2014, Ovid EMBASE from 1980 to 2014 week 31, the Cochrane Central Register of Controlled Trials (CENTRAL) to June 2014, and the Cochrane Database of Systematic Reviews from 2005 to June 2014. The search strategy included terms describing the disease and all medications available for maintaining remission of MC. There was no restriction by language. We excluded editorial letters, comments, notes, or case reports. For more details about the search strategy, see Appendix 2.

Study Selection Process

After removing duplicates, 2 researchers independently assessed the retrieved references for eligibility using the title and abstract. References that showed potential eligibility were assessed again in duplicate and independently, this time using full text. A piloted form including the main eligibility criteria helped to document this process. When there was disagreement, a third person arbitrated to make the final inclusion decision.

Data Extraction and Analysis

Using a piloted form, data extraction was conducted by one researcher and a second reviewer checked for accuracy. The information retrieved from primary studies included their main features, type of design, patient characteristics, clinical and histological definition of MC, risk of bias assessment, and outcomes measured.

When feasible, contingency tables were created for each dichotomous outcome, and the relative risk (RR) and its 95% confidence interval (CI) was calculated. When data from intention-to-treat analysis were shown, this was preferred over per-protocol analysis. The only exception to this was the outcome of adverse events, for which per-protocol analysis was performed. For continuous outcomes, the mean difference (MD) and its 95% CI was calculated. To facilitate decision making, the data from studies reporting clinical relapse during the maintenance period were transformed from the number of patients free from relapse to the number of participants having the event. When aggregated data such as standard deviation for a group were missing, the exact *P* value was used to approximate it. A random effects model was chosen a priori given that different dosages and methods of administration of medications were expected, representing a distribution of results of effectiveness. Review Manager 5.3 software (Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark) was use to conduct the meta-analyses.

Risk of Bias Assessment of Included Studies

To determine the risk of bias of included studies, the Cochrane Risk of Bias Tool for randomized controlled trials[3] and diagnostic test accuracy studies[4] were used. For randomized controlled trials, the following domains were considered: (1) Was the random sequence adequately generated? (2) Was the allocation adequately concealed? (3) Were participants blinded to the intervention received? (4) Were personnel blinded to the intervention administered? (5) Were outcome adjudicators blinded to the intervention administered? (6) Was the study affected by incomplete outcome data? (7) Was the study affected by selective outcome reporting? (8) Was any other additional bias identified? The domains considered to assess the risk of bias of diagnostic test accuracy were as follows: (1) Was the spectrum of patients representative of the patients who will receive the test in practice? (2) Is the reference standard likely to classify the target condition correctly? (3) Is the time period between the reference standard and the index test short enough to be reasonably sure that the target condition did not change between the 2 tests? (4) Did the whole sample, or a random selection of the sample, receive verification using the intended reference standard? (5) Did patients

receive the same reference standard irrespective of the index test result? (6) Was the reference standard independent of the index test (ie, the index test did not form part of the reference standard)? (7) Were the results of the reference standard interpreted without knowledge of the results of the index test? (8) Were the results of the index test interpreted without knowledge of the results of the reference standard? (9) Were the same clinical data available when test results were interpreted as would be available when the test is used in practice? (10) Were withdrawals from the study explained? This assessment was conducted in duplicate by 2 independent evaluators.

Evaluation of the Quality of the Body of Evidence

The quality of the body of evidence (also known as confidence or certainty in the evidence) across outcomes was assessed using the GRADE approach.[2] In this approach, randomized controlled trials start as high-quality evidence; however, the confidence in the estimates of effect can be downgraded from high to moderate, low, or very low when serious or very serious issues related to risk of bias, imprecision, indirectness, inconsistency, and publication bias are identified. For diagnostic test accuracy studies using a cross-sectional design, the quality of the evidence starts as high and the same domains were assessed to determine whether downgrading was necessary.[5] Results were tabulated using evidence profiles and evidence to decision tables. The Guideline Development Tool (GDT) software was used to assess and record judgments related to the quality of evidence assessment and move from the evidence to decisions (www.guidelinedevelopment.org).

Results

Systematic Search Retrieval and Study Selection

Question 1. What is the prevalence of MC? How many colon biopsy specimens should be obtained and from which areas of the colon?

The search strategy retrieved 1239 articles, of which 402 were duplicates. The remaining 837 references went to the title and abstract screening stage. Then, 51 were included for full-text screening. A total of 29 primary studies proved eligible (Figure 1).

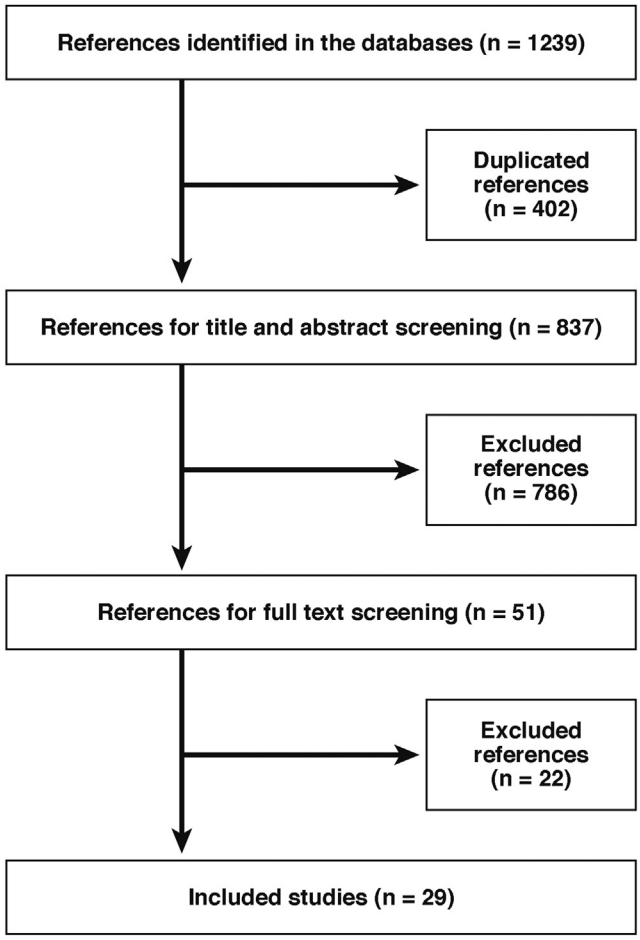

Figure 1. Flow chart retrieval and study selection for the prevalence and biopsy characteristics of patients with MC.

Question 2. In patients with MC (either LC or CC), which treatments are effective and safe for inducing remission of the disease, measured as clinical response, histological response, quality of life, and adverse events?

The search strategy retrieved 592 articles, of which 162 were duplicates. The remaining 430 references went to the title and abstract screening stage. Then, 76 were included for full-text screening. A total of 12 primary studies proved eligible (Figure 2).

Question 3. In patients successfully treated for MC (either LC or CC) and in remission of symptoms, which treatments are effective and safe for maintaining clinical remission of the disease, measured as maintenance of clinical response, maintenance of histological response, time to relapse, quality of life, and adverse events?

The search strategy retrieved 592 articles, of which 162 were duplicates. The remaining 430 references went to the title and abstract screening stage. Then, 80 were included for full-text screening. A total of 3 primary studies proved eligible (Figure 3).

Description of Included Studies

Studies included in question 1. The purpose of this question was to inform clinicians about the prevalence of the disease and the number of biopsy specimens that should be taken along with the areas from the colon that need to be considered. This question was not framed as a PICO question linked to a recommendation because this was classified

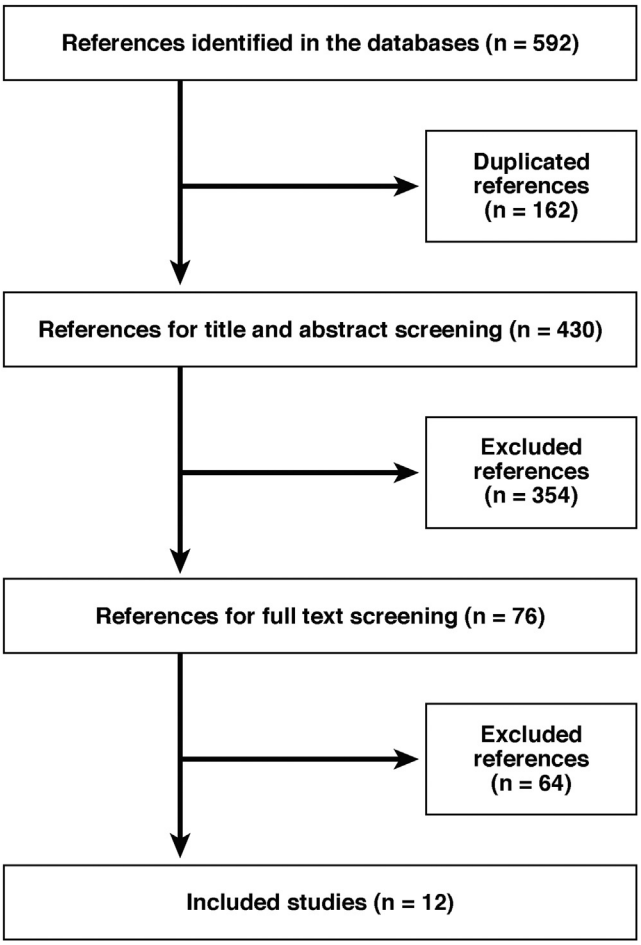

Figure 2. Flow chart retrieval and study selection for inducing remission of MC.

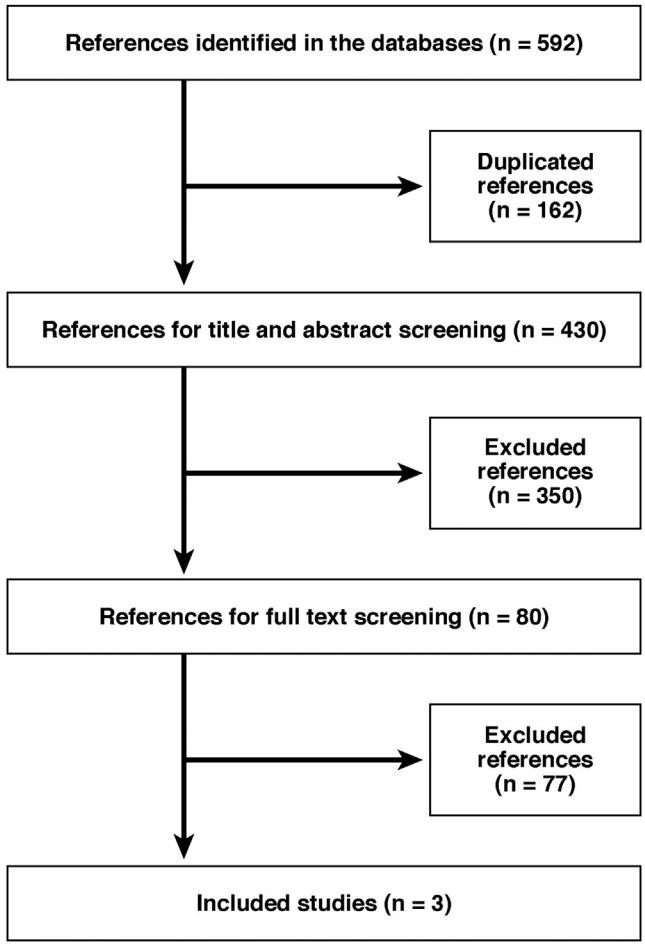

Figure 3. Flow chart retrieval and study selection for maintaining remission of MC.

as a background question. Its content is included in the guideline (these studies are not included in the current review).

Studies included in questions 2 and 3. Table 3 shows a detailed description of the included studies. These studies were published between 1999 and 2014 and conducted in Belgium, Germany, Denmark, Lithuania, and Italy. The proportion of female participants ranged from 67% to 93%. The mode for the age was 60 years. Follow-up ranged from 2 to 25 weeks. For more details about these studies and their characteristics, interventions, and comparisons, see Table 3.

Risk of Bias Assessment of Included Studies

Randomized controlled trials. Of the 15 included randomized controlled trials, 7 were assessed as unclear for the domain related to the way the random sequence generation was created.[6–12] In the allocation concealment domain, 10 of 15 trials were assessed as unclear risk of bias due to limited information regarding the methods used to protect the sequence at the moment of randomization. The domain that had the highest risk of bias classification was the one asking whether selective outcome reporting was present.[6,8–14] Frequently, the investigators did not provide numerical data for outcomes when the study failed to show statistical significance and did not report measures of variability for continuous outcomes; some of the investigators did not report relevant outcomes such as histological response and quality of life. Three trials showed low risk of bias overall[15–17] (Figure 4).

Effect of the Interventions and Assessment of the Quality of the Evidence

Question 1. What is the prevalence of MC? How many colon biopsy specimens should be obtained and from which areas of the colon?

This question is not about the effect of any intervention. The results of these studies are included in the guideline.

Question 2. In patients with MC (either LC or CC), which treatments are effective and safe for inducing remission of the disease, measured as clinical response, histological response, quality of life, and adverse events?

Table 3. Characteristics of Included Randomized Controlled Trials

Author (year)	n	Type of colitis	Female (%)	Mean age (*y*)	Age range or SD (*y*)	Treatment and comparator	Duration of follow-up	Inclusion criteria	Exclusion criteria
Baert et al, 2002[6]	28	CC	71	56	15	Budesonide one 9-mg dose daily vs placebo	8 wk	Clinical: 2 mo of chronic watery diarrhea (at least 3 semi-loose or loose stools per day) and no other cause for diarrhea on history and full clinical examination Histological: subepithelial collagen band with feathery appearance of the inferior border exceeding 10 μm; increased mixed inflammatory cell infiltrate in mononuclear lamina propria	Stool examination with pathogens, parasites, and *Clostridium difficile* toxin; significant gastrointestinal disease
Bonderup et al, 2003[7]	20	CC	80	54	40–80	Budesonide 9 mg/4 wk, 6 mg/2 wk, 3 mg/2 wk vs placebo	8 wk	Clinical: Older than 18 y with clinically active CC (stool frequency >4 daily or stool wt >200 g/day) Histological: collagen layer >10 mm beneath the surface epithelium in colonic mucosa	Treatment with anti-inflammatory drugs within the past 3 mo; chronic gastrointestinal diseases; stool samples positive for pathogens, parasites, and ova; clinically significant renal or hepatic disease; pregnant or breast-feeding women
Bonderup et al, 2009[22]	34	CC	79	Treatment: 62.8 Comparator: 58.4	Treatment: 42–81 Comparator: 33–82	Budesonide 6 mg/day vs placebo	25 wk	Older than 18 y with histologically confirmed CC (diffuse lymphocytic inflammation and evidence of a collagenous band >10 mm, at least focally)	Treatment with Salazopyrine, 5-aminosalicylic acid, budesonide, or a systemic glucocorticoid during the past 3 mo or ketoconazole during the past 7 days
Calabrese et al, 2007[21]	LC: 41 CC: 23	LC, CC	LC: 71 CC: 74	LC: 40.4 CC: 41.6	LC: 13.7 (19–65) CC: 12.5 (28–68)	Mesalazine 800 mg vs mesalazine 800 mg + cholestyramine 4 g	25 wk	Clinical: Chronic or recurrent watery nonbloody diarrhea Histological: increased chronic inflammatory infiltrate in the lamina propria, increased number of IELs and damage of surface epithelium, with flattening of epithelial cells and/or epithelial loss and detachment and minimal crypt architecture distortion	Clear correlation between symptoms and treatment with medication (ie, NSAIDs, ticlopidine, and proton pump inhibitors)

Table 3. Continued

Author (year)	n	Type of colitis	Female (%)	Mean age (*y*)	Age range or SD (*y*)	Treatment and comparator	Duration of follow-up	Inclusion criteria	Exclusion criteria
Fine et al, 1999[18]	9	CC	NR	NR	NR	Bismuth subsalicylate (nine 262-mg chewable tablets daily in 3 divided doses) vs placebo	25 wk	Clinical: 8 wk of nonbloody watery diarrhea (without steatorrhea) Histological: excess of mononuclear inflammatory cells in the lamina propria and surface epithelium without significant neutrophilia or eosinophilic inflammation, numerous crypt abscesses, or granuloma	No evidence of Crohn disease
Latella et al, 2010[8]	46	LC	NR	NR	NR	Beclomethasone dipropionate 5 mg/day vs beclomethasone dipropionate 10 mg/day vs mesalazine 2.4 mg/day	8 wk	Clinical: NR Histological: LC	NR
Madisch et al, 2007[14]	31	CC	BS: 87 Pl: 80	Median BS: 64.5 Pl: 53	NR	*Boswellia serrata* 400 mg per capsule 3 times daily vs placebo	6 wk	Clinical: 5 liquid or soft stools daily on average per week Histological: histologically confirmed diagnosis of CC	Treatment with budesonide, salicylates, steroids, prokinetics, antibiotics, ketoconazole, or NSAIDs within 4 weeks before randomization, other endoscopically or histologically verified causes for diarrhea, infectious diarrhea, pregnancy or lactation, previous colonic surgery, known intolerance to *B serrata* extract
Miehlke et al, 2002[15]	51	CC	76	BS: 60 Pl: 60	BS: 32–78 Pl: 36–75	Budesonide one 9-mg dose daily vs placebo	6 wk	Clinical: 18–80 y of age and use of effective contraception, at least 5 liquid or soft stools daily on average per week Histological: histologically confirmed diagnosis of CC	Evidence of infectious diarrhea; treatment with budesonide, salicylates, corticosteroids, prokinetics, antibiotics, ketoconazole, or NSAIDs within the past 4 wk before randomization; endoscopic-histological findings that may have caused diarrhea; known intolerance to budesonide, pregnancy, or lactation; history of partial colonic resection

Table 3. Continued

Author (year)	n	Type of colitis	Female (%)	Mean age (*y*)	Age range or SD (*y*)	Treatment and comparator	Duration of follow-up	Inclusion criteria	Exclusion criteria
Miehlke et al, 2008[9]	46	CC	73	57.5	34–78	Budesonide 6 mg once daily for 6 mo vs placebo	25 wk	Older than 18 y with symptomatic and histologically proven CC; 3 watery/loose stools daily on 4 of the previous 7 days and a history of diarrhea for 4 wk	Diarrhea with an infectious cause; other chronic inflammatory disease of the bowel; celiac disease; malignancy; major organ disease; previous surgery of the large bowel; current treatment with 5-aminosalicylates, salicylates, systemic corticosteroids, antibiotics, or NSAIDs; use of budesonide within 14 days of enrollment; hypersensitivity to budesonide; pregnancy or lactation; alcohol/drug abuse
Miehlke et al, 2009[16]	42	LC	67	Median: 61	BS: 36–80 PI: 23–76	Budesonide one 9-mg dose daily vs placebo	6 wk	Clinical: 18–80 y of age, 3 watery or loose stools daily within 7 days before random assignment Histological: histologically confirmed LC (20 IELs/100 epithelial cells)	Other types of bowel disease, CC, Crohn disease, ulcerative colitis or ischemic colitis, celiac disease, malignancy or any severe concomitant disease, partial colonic resection, intolerance to budesonide, pregnancy and lactation; patients treated with budesonide, aminosalicylates, corticosteroids, or antibiotics during the 4 wk before random assignment

Table 3. Continued

Author (year)	n	Type of colitis	Female (%)	Mean age (*y*)	Age range or SD (*y*)	Treatment and comparator	Duration of follow-up	Inclusion criteria	Exclusion criteria
Miehlke et al, 2014[17]	92	CC	82.6	58.8	12.9	Budesonide one 9-mg dose daily vs mesalamine one 3-g dose daily vs placebo	8 wk	Clinical: >4 watery/soft stools on at least 4 days during the week before baseline; >3 stools per day on average within the 7 days before baseline, chronic diarrhea for at least 3 mo before baseline Histological: histologically confirmed CC (thickness of collagen band >10 mm, degeneration of surface epithelium)	Other significant colonic diseases, partial colonic resection, infectious diarrhea, celiac disease, diarrhea caused by other organic diseases of the gastrointestinal tract, treatment with budesonide, *Boswellia serrata* extract, salicylates, corticosteroids, antibiotics, cholestyramine, NSAIDs, or other immunosuppressant drugs within the wk before baseline, malignant disease, severe comorbidity, abnormal hepatic function or cirrhosis, renal insufficiency, active peptic ulcer disease, known intolerance or resistance to study drugs, pregnancy, breast-feeding
Munch et al, 2014[10]	84	CC	85	58.8	11	Low-dose budesonide (Budenofalk 3-mg capsules) vs placebo	Placebo	Patients with CC still in remission after 12 mo	NR
Munck et al, 2003[11]	12	CC	83	Pr: 60 Pl: 63	Pr: 42–75 Pl: 61–73	Prednisolone 50 mg once daily for 2 weeks and then 37.5 mg for one week vs placebo	2 wk	Clinical: Older than 18 y reporting at least 3 mo with diarrhea without blood or pus and with stool volume of 350 g/day or 200 g/day and stool frequency of 5 times daily Histological: mixed but predominantly chronic inflammatory infiltrate in the lamina propria and either a lymphocytic infiltration of at least 20% of epithelial crypt cells (LC) and/or a subepithelial collagen bond exceeding 10 m in a well-oriented biopsy (CC)	Bile acid malabsorption and/or no response to cholestyramine, steatorrhea, celiac disease, other gastrointestinal diseases or previous gastrointestinal surgery with the exception of cholecystectomy, other serious diseases, abnormal laboratory test results, treatment with immunosuppressive drugs within 3 mo or use of medications with a known effect on gastrointestinal function including antiulcer medication, antacids, antibiotics, and NSAIDs

Table 3. Continued

Author (year)	n	Type of colitis	Female (%)	Mean age (*y*)	Age range or SD (*y*)	Treatment and comparator	Duration of follow-up	Inclusion criteria	Exclusion criteria
Pardi et al, 2009[12]	15	LC	80	59.7	NR	Budesonide one 9-mg dose daily vs placebo	8 wk	Clinical: adults Histological: histologically confirmed LC (20 IELs/100 epithelial cells)	NR
Wildt et al, 2006[13]	29	CC	93	Pro: 61 Pl: 57	Pr: 36–73 Pl: 26–79	AB-Cap-10, a mixture of *L acidophilus* strain LA-5 and *B animalis* subsp *lactis* strain BB-12 vs placebo	12 wk	Clinical: older than 18 y and presence of active untreated disease for at least 4 wk (>21 liquid or soft stools per week or stool weight >200 g/day) Histological: histological diagnosis of CC	Pregnancy or breast-feeding, chronic liver or kidney disease, severe chronic disease of vascular or cardiopulmonary origin, malignancies, immunosuppressive disease or treatment, known inflammatory bowel disease besides CC, evidence of infectious diarrhea, former surgical procedures involving the gastrointestinal tract except for appendectomy, malabsorption syndromes, celiac disease

IELs, intraepithelial lymphocytes; NSAIDs, nonsteroidal anti-inflammatory drugs; NR, not reported; BS, *Boswellia serrata*; Pl, placebo; Pr, prednisolone; Pro, probiotic.

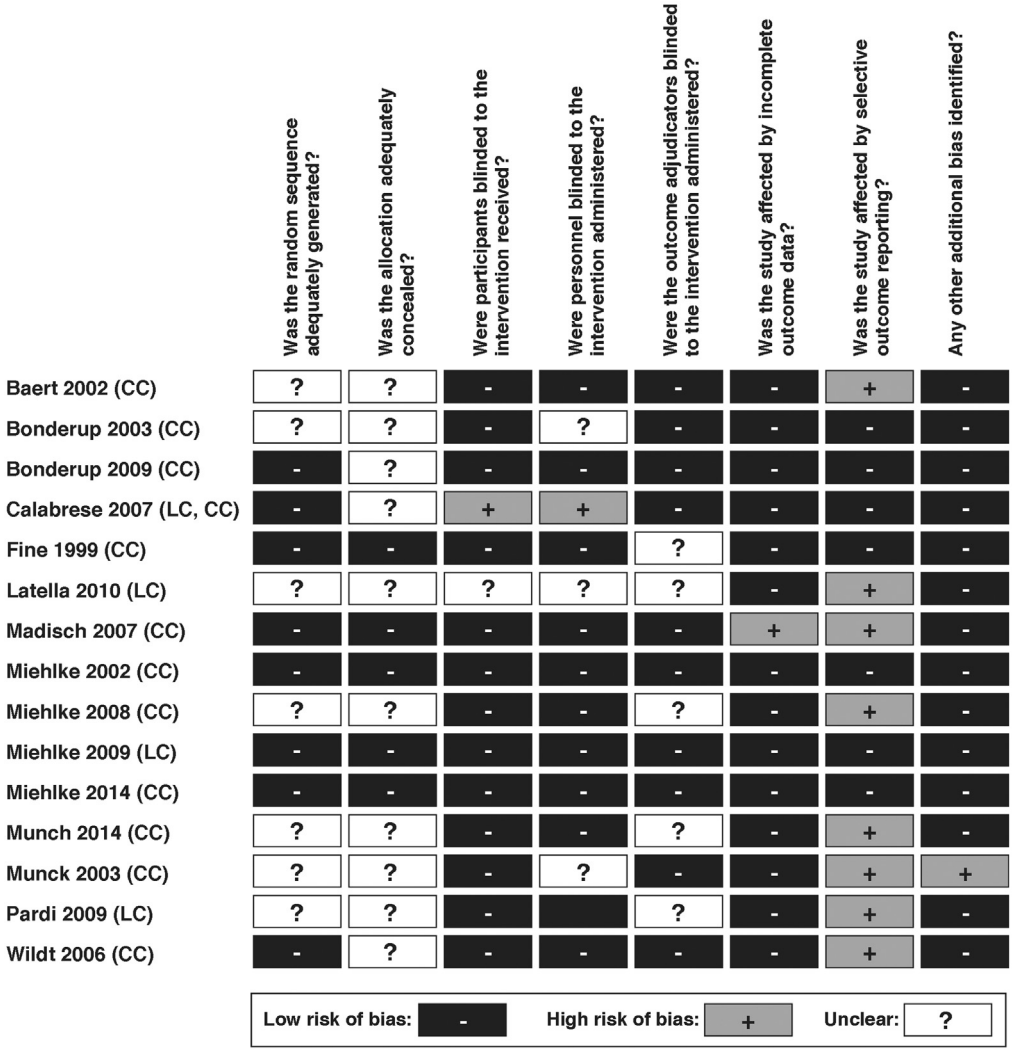

Figure 4. Risk of Bias Assessment of the Included Randomized Controlled Trials.

Bismuth subsalicylate versus no treatment for inducing remission. Only one randomized controlled trial reported results comparing bismuth subsalicylate (eight 262-mg chewable tablets [Pepto-Bismol; Procter & Gamble, Cincinnati, OH] per day for 8 weeks in 3 doses: 3 tablets in the morning, 2 at midday, and 3 in the evening) with placebo (Table 4).[18] This small trial included 14 participants and has only been published as an abstract. Because there were no events in the control arm for the clinical response and adverse events outcomes, it was not possible to calculate absolute and relative estimates.[19] There was a 206% increase in the histological response of participants receiving the intervention after 8 weeks of follow-up; however, this difference was not statistically significant (RR, 3.06; 95% CI, 0.3–30.97). No participants experienced adverse events. Quality of life was not measured in the context of this study. The quality of the evidence for all reported outcomes was low due to very serious imprecision.

Prednisolone versus no treatment for inducing remission of MC. Only one trial reported data comparing the effect of prednisolone (50 mg once daily for 2 weeks and then 37.5 mg for 1 week) with placebo (Table 5).[11] This small trial included 12 participants. Because there were no events in the control arm for the outcome of clinical response, it was not possible to calculate absolute and relative estimates.[19] The quality of evidence for this outcome was assessed as very low due to serious issues of risk of bias and very serious issues of imprecision. Adverse events associated with the intervention included the typical adverse effects related to the use of a corticosteroid and were not severe enough to cause participants to withdraw from the study. The quality of the evidence for this outcome was low due to serious issues of risk of bias and imprecision. Histological response and quality of life were not reported in this trial.

Budesonide versus no treatment for inducing remission of MC. The effect of budesonide (9 mg once daily [three 3-mg capsules]) was based on 6 studies and one additional report published separately (Table 6).[6,7,12,15–17,20] In total, 218 participants informed the outcome of clinical

Table 4. Bismuth Subsalicylate Versus No Bismuth Subsalicylate for Inducing Remission of MC[18]

Quality assessment							No. of patients		Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bismuth subsalicylate	No treatment	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Clinical response (follow-up: 8 wk)												
1	Randomized trials	Not serious	Not serious	Not serious	Very serious[a]	None	7/7 (100.0%)	0/7 (0.0%)[b]	Not estimable	Not estimable	⊕⊕ Low	Critical
Histological response (follow-up: 8 wk)												
1	Randomized trials	Not serious	Not serious	Not serious	Very serious[a]	None	6/7 (85.7%)	1/7 (14.3%)	RR, 3.06 (0.3–30.97)	294 more per 1000 (from 100 fewer to 4281 more)	⊕⊕ Low	Important
Adverse events (follow-up: 8 wk)												
1	Randomized trials	Not serious	Not serious	Not serious	Very serious[c]	None	0/7 (0.0%)	0/7 (0.0%)	Not estimable	Not estimable	⊕⊕ Low	Critical
Quality of life (not reported)												
—	—	—	—	—	—	—	—	See comment	Not estimable	See comment	—	Critical

[a]Only 7 events in total. Because all participants in the intervention group and no participants in the control group experienced the outcome, the RR and absolute risk reduction could not be estimated.
[b]Zero events in the placebo arm prevented estimation of absolute effect.
[c]Zero adverse events in both arms prevented estimation of absolute and relative effects.

remission. In relative terms, budesonide increased the probability of experiencing clinical remission by 152% after 6 to 8 months of follow-up (RR, 2.52; 95% CI, 1.45–4.4), which in absolute terms implies that 572 more patients per 1000 would experience remission when receiving budesonide. The quality of the evidence for clinical remission was assessed as moderate due to serious inconsistency. Histological response was informed by 5 randomized controlled trials including 161 patients.[6,7,15–17] Patients receiving budesonide were 150% more likely to have histological remission after 6 to 8 weeks of follow-up (RR, 2.5; 95% CI, 1.56–3.99). In absolute terms, 421 more patients per 1000 would experience this outcome. The quality of the evidence for this outcome was determined to be moderate due to serious issues of inconsistency. Two studies informed about the time to induce clinical remission.[15,17] Given that the authors of one of the studies did not provide measures of variability, a meta-analysis was not possible. Seven to 13 days was the range of estimated mean days to induce clinical remission (range, 2–30 days). This outcome had moderate-quality evidence due to risk of bias. Five studies[6,12,15–17] reported data on adverse events after 6 to 8 weeks of follow-up, but only 3 of them contributed to the meta-analysis.[15–17] In relative terms, participants receiving budesonide have a 16% increase in the risk of experiencing mild or minor adverse events; however, the difference between groups was not statistically significant (RR, 1.16; 95% CI, 0.45–3). Two additional studies reported adverse events but were not included in this meta-analysis. In 2002, Baert et al[6] reported only minor adverse events related to study medications but did not report them separately for the budesonide and placebo groups (viral infection [n = 3], rash [n = 2], hypertension [n = 1], slight cushingoid face [n = 3], and depression [n = 1]). In 2009, Pardi et al[12] (abstract only) stated that no significant adverse effects occurred, but no numerical data were provided. This outcome is informed by low-quality evidence due to serious issues of inconsistency and imprecision. Finally, 2 trials reported data on the effect of budesonide on patients' quality of life.[16,20] One study showed an increase in quality of life measured with the Gastrointestinal Quality of Life Index (GIQLI) of 23 points, although this increase was not statistically significant (MD, 23; 95% CI, −7.49 to 53.5). One additional study reported quality of life using the SF-36 instrument. In 2009, Miehlke et al[16] reported an increase in the mean change in the physical sum score of 3.5 points and in the mental sum score of 3.1 points. Serious issues of imprecision warrant a determination of moderate-quality evidence for this outcome. Interaction testing showed no difference in treatment response or other outcomes when comparing patients with CC or LC.

Budesonide versus mesalamine for inducing remission of MC. One trial provided evidence of the effect of budesonide (9 mg once daily [three 3-mg capsules]) compared with mesalamine (3 g once daily [2 sachets each containing 1.5 g mesalamine presented as a granule formulation; Salofalk; Dr. Falk Pharma, Freiburg, Germany]) (Table 7).[17] Only 55 patients informed the outcome of clinical remission. Those receiving budesonide had an 82% increase in the probability of experiencing the outcome (RR, 1.82; 95% CI, 1.13–2.93) compared with those receiving mesalamine. This finding is supported by high-quality evidence. For the outcome of histological response, patients receiving budesonide showed a 96% increase in the probability of experiencing the outcome (RR, 1.96; 95% CI, 1.14–3.36), which in relative terms corresponds to 427 more people per 1000 experiencing the benefit. This finding is supported by high-quality evidence. Regarding adverse events, patients receiving budesonide had a lower risk of experiencing these compared with those receiving mesalamine; however, this difference was not statistically significant (RR, 0.69; 95% CI, 0.43–1.1). This finding is supported by moderate-quality evidence due to serious issues of imprecision. Quality of life was not reported. Interaction testing showed no difference in treatment response or other outcomes when comparing patients with CC or LC.

Mesalamine versus no treatment for inducing remission of MC. One study reported on the effect of mesalamine versus placebo in 62 participants (Table 8).[17] Patients receiving mesalamine (3 g once daily [2 sachets each containing 1.5 g presented as a granule formulation; Salofalk]) had a lower risk of experiencing clinical remission compared with those receiving placebo after 8 weeks; however, this difference was not statistically significant (RR, 0.74; 95% CI, 0.44–1.24), and it is supported by moderate-quality evidence due to serious imprecision. Regarding histological response, mesalamine seems to reduce the possibility of experiencing histological remission compared with placebo; however, this difference was not statistically significant (RR, 0.89; 95% CI, 0.46–1.73). The quality of the evidence was determined as moderate for this outcome due to serious imprecision. For the outcome of adverse events, 68% of the patients experienced mild or minor adverse events compared with 54% in the control group; however, this difference was not statistically significant (RR, 1.26; 95% CI, 0.84–1.88). This estimate is supported by moderate-quality evidence. No evidence for quality of life was reported.

Mesalazine plus cholestyramine versus mesalazine for inducing remission of MC. One trial reported evidence on the effect of cholestyramine in addition to mesalazine (mesalazine 800 mg, one capsule after breakfast, lunch, and dinner [2.4 g daily], and cholestyramine 4 g after dinner for 6 months) compared with mesalazine alone (mesalazine 800 mg, one capsule after breakfast, lunch, and dinner [2.4 g daily]) (Table 9).[21] In this trial, which included 64 patients, those receiving mesalazine plus cholestyramine experienced a 9% increased probability of clinical remission when comparing with those receiving mesalazine

Table 5. Prednisolone Versus No Prednisolone for Inducing Remission of MC[11]

Quality assessment							No. of patients		Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prednisolone	No treatment	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Clinical response (follow-up: 2 wk)												
1	Randomized trials	Serious[a]	Not serious	Not serious	Very serious[b]	None	2/9 (22.2%)	0/3 (0.0%)	Not estimable	Not estimable	⊕ Very low	Critical
Histological response: not reported (follow-up: 2 wk)												
—	—	—	—	—	—	—	—	See comment	Not estimable	See comment	—	Important
Adverse events (follow-up: 2 wk)												
1	Randomized trials	Serious[a]	Not serious	Not serious	Serious[c]	None			Typical corticosteroid-related side effects were common in the prednisolone group, but none were severe enough to cause patient withdrawal from the study (headache [n = 5], abdominal pain [n = 3], sleep disturbance [n = 8], change of mood [n = 4], weight gain [n = 5])		⊕⊕ Low	Critical
Quality of life: not reported												
—	—	—	—	—	—	—	—	—	—	See comment	—	Critical

[a]High risk of bias due to selective outcome reporting (no histological response reported) and stopping early due to lack of effectiveness. It is unclear how the randomization scheme was created and the allocation sequence concealed.
[b]The study included only 2 events, with zero events in the control group, which prevents estimation of absolute effect. Given that there were no events in the control group, the RR and absolute risk reduction could not be estimated.
[c]The study included only 12 participants; 9 received prednisolone.

Table 6. Budesonide Versus No Budesonide for Inducing Remission of MC[6,7,12,15–17,20]

Quality assessment							No. of patients		Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Budesonide	No treatment	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Clinical response (follow-up: range, 6–8 wk)												
6	Randomized trials	Not serious	Serious[a]	Not serious	Not serious	None	90/109 (82.6%)	41/109 (37.6%)	RR, 2.52 (1.45–4.4)	572 more per 1000 (from 169 more to 1279 more)	⊕⊕⊕ Moderate	Critical
Histological response (follow-up: range, 6–8 wk)												
5	Randomized trials	Not serious	Serious[b]	Not serious	Not serious	None	65/85 (76.5%)	23/82 (28.0%)	RR, 2.5 (1.56–3.99)	421 more per 1000 (from 157 more to 839 more)	⊕⊕⊕ Moderate	Important
Time to induce clinical remission (follow-up: 6 wk)												
2	Randomized trials	Serious[c]	Not serious	Not serious	Not serious	None			7–13 days (range, 2–30 days) to initial clinical remission		⊕⊕⊕ Moderate	Important
Adverse events (induction therapy) (follow up: range, 6–8 wk)												
3[d,e]	Randomized trials	Not serious	Serious[f]	Not serious	Serious[g]	None	26/75 (34.7%)	26/77 (33.8%)	RR, 1.16 (0.45–3)	54 more per 1000 (from 186 fewer to 675 more)	⊕⊕ Low	Critical
Quality of life (follow-up: 6 wk; assessed with GIQLI[h])												
1[i,j]	Randomised trials	Not serious	Not serious	Not serious	Serious[k]	None	17	12	—	MD, 23 higher (7.49 lower to 53.49 higher)	⊕⊕⊕ Moderate	Critical

[a]Unexplained heterogeneity among included studies (χ^2 P value = .007; I^2 = 68%).
[b]Unexplained heterogeneity among included studies (χ^2 P value = .17; I^2 = 38%).
[c]High risk of bias due to selective outcome reporting. No measure of variability was reported.
[d]Two additional studies reported adverse events but were not included in this meta-analysis. Baert et al[6] (2002) reported only minor adverse events related to study medications but did not report them separately for the budesonide and placebo groups (viral infection [n = 3], rash [n = 2], hypertension [n = 1], slight cushingoid face [n = 3], depression [n = 1]). Pardi et al[12] (2009, abstract) only describe that no significant side effects occurred; no numerical data were provided.
[e]The most common adverse events listed in the studies were nausea, headache, abdominal pain, and skin rash.
[f]Unexplained heterogeneity among included studies (χ^2 P value = .08; I^2 = 60%).
[g]The lower and upper boundaries of the CI suggest both large benefit and harm.
[h]The GIQLI score consists of 4 dimensions (symptoms, physical functioning, emotional functioning, and social functioning). The overall score ranges from 0 to 144 (the higher the score, the better the quality of life). Healthy volunteers have been reported to have a mean score of 121–126 using the GIQLI. These values compare with previously reported mean scores of 104 in patients with anal fissures, 94 in those with severe chronic constipation, 93 in those with fecal incontinence, and 87 in those with gastroesophageal reflux disease requiring surgery.[29]
[i]One additional study reported quality of life using the SF-36 instrument. Miehlke et al[16] (2009) reported an increase in the mean of the change for the physical sum score of 3.5 points and for the mental sum score of 3.1 points.
[j]There was a large difference in baseline quality of life between patients in the budesonide arm (67 points) and those in the control group (86 points).
[k]The lower and upper boundaries of the CI suggest small harm and large benefit.

Table 7. Budesonide Versus Mesalamine for Inducing Remission of MC[17]

Quality assessment							No. of patients		Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Budesonide	Mesalamine	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Clinical response (follow up: 8 wk)												
1	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	24/30 (80.0%)	11/25 (44.0%)	RR, 1.82 (1.13–2.93)	361 more per 1000 (from 57 more to 849 more)	⊕⊕⊕⊕ High	Critical
Histological response (follow-up: 8 wk)												
1	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	20/23 (87.0%)	8/18 (44.4%)	RR, 1.96 (1.14–3.36)	427 more per 1000 (from 62 more to 1049 more)	⊕⊕⊕⊕ High	Important
Adverse events (induction therapy) (follow-up: 8 wk)												
1	Randomized trials	Not serious	Not serious	Not serious	Serious[a]	None	14/30 (46.7%)	17/25 (68.0%)	RR, 0.69 (0.43–1.1)	211 fewer per 1000 (from 68 more to 388 fewer)	⊕⊕⊕ Moderate	Critical
Quality of life: not reported												
—	—	—	—	—	—	—	—	See comment	Not estimable	See comment	—	Critical

[a]The CI includes both potential benefit and large harm.

Table 8. Mesalamine Versus No Mesalamine for Inducing Remission of MC[17]

Quality assessment							No. of patients		Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mesalamine	No treatment	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Clinical response (follow-up: 8 wk)												
1	Randomized trials	Not serious	Not serious	Not serious	Serious[a]	None	11/25 (44.0%)	22/37 (59.5%)	RR, 0.74 (0.44–1.24)	155 fewer per 1000 (from 143 more to 333 fewer)	⊕⊕⊕ Moderate	Critical
Histological response (follow-up: 8 wk)												
1	Randomized trials	Not serious	Not serious	Not serious	Serious[a]	None	8/18 (44.4%)	11/22 (50.0%)	RR, 0.89 (0.46–1.73)	55 fewer per 1000 (from 270 fewer to 365 more)	⊕⊕⊕ Moderate	Important
Adverse events (induction therapy) (follow-up: 8 wk)												
1	Randomized trials	Not serious	Not serious	Not serious	Serious[a]	None	17/25 (68.0%)	20/37 (54.1%)	RR, 1.26 (0.84– 1.88)	141 more per 1000 (from 86 fewer to 476 more)	⊕⊕⊕ Moderate	Critical
Quality of life: not reported												
—	—	—	—	—	—	—	—	See comment	Not estimable	See comment	—	Critical

[a]Small number of events. The CI suggests both important benefit and large harm.

Table 9. Mesalazine Plus Cholestyramine Versus Mesalazine for Inducing Remission of MC[21]

Quality assessment							No. of patients		Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mesalazine + cholestyramine	Mesalazine	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Clinical response (follow-up: 6 mo)												
1	Randomized trials	Serious[a]	Not serious	Not serious	Serious[b]	None	30/33 (90.9%)	26/31 (83.9%)	RR, 1.09 (0.89–1.32)	75 more per 1000 (from 92 fewer to 268 more)	⊕⊕ Low	Critical
Histological response (follow-up: 6 mo)												
1	Randomized trials	Serious[a]	Not serious	Not serious	Serious[b]	None	26/31 (83.9%)	30/33 (90.9%)	RR, 0.92 (0.76–1.12)	73 fewer per 1000 (from 109 more to 218 fewer)	⊕⊕ Low	Important
Adverse events (induction therapy) (follow-up: 6 mo)												
1	Randomized trials	Serious[a]	Not serious	Not serious	Serious[b]	None	2/33 (6.1%)[c]	0/31 (0.0%)	RR, 4.71 (0.23–94.31)	0 fewer per 1000 (from 0 fewer to 0 fewer)[d]	⊕⊕ Low	Critical
Quality of life: not reported												
—	—	—	—	—	—	—	—	See comment	Not estimable	See comment	—	Critical

[a]Neither participants nor personnel or researchers were blinded during the study. It is unclear how the random allocation was concealed.
[b]The CI includes both appreciable harm and benefit.
[c]Two patients in the mesalazine plus cholestyramine group experienced nausea.
[d]Absolute effect not estimable due to zero events in the control group.

alone (RR, 1.09; 95% CI, 0.89–1.32) after 6 months of follow-up. Regarding histological response, the effect was the opposite, showing an 8% reduction in the probability of experiencing this outcome for patients receiving combination therapy (RR, 0.92; 95% CI, 0.76–1.12). Finally, participants receiving cholestyramine plus mesalazine experienced 6% more adverse events compared with those receiving mesalazine only (RR, 4.71; 95% CI, 0.23–94.31). None of the outcomes show statistically significant differences between the 2 groups. In addition, the quality of evidence was assessed as low for all outcomes due to serious imprecision. The outcome of quality of life was not reported for this comparison. There are no clinical trials assessing the efficacy of cholestyramine or other bile acid–binding medication alone.

Boswellia serrata *versus treatment for inducing remission of MC.* One trial reported data on 31 patients for the effect of *B serrata*, 400 mg per capsule 3 times per day (21.2 mg 11-keto-β-boswellia acid, 27.3 mg α-boswellia acid, 50.9 mg β-boswellia acid, 11.3 mg acetyl-11-keto-β-boswellia acid, 9.8 mg acetyl-α-boswellia acid, and 28.7 mg acetyl-β-boswellia acid), versus placebo (Table 10).[14] Participants receiving *B serrata* showed a 64% increase in the probability of experiencing a clinical response after 6 weeks (RR, 1.64; 95% CI, 0.60–4.49); however, this difference was not statistically significant. This finding is supported by moderate-quality evidence due to serious imprecision. For the outcome of histological response, the investigators only declared that there was no statistically significant difference between groups, supported by moderate-quality evidence due to serious risk of bias. Participants receiving *B serrata* experienced more adverse events compared with those in the placebo group; however, this difference was not statistically significant (RR, 1.88; 95% CI, 0.19–18.6). Low confidence in the estimates of effect was determined for this outcome due to very serious issues of imprecision. Finally, the investigators reported that at the end of 6 weeks of therapy, there were no significant changes in quality of life scores in the *B serrata* or placebo groups when comparing baseline with posttreatment or between groups after treatment was completed. No numerical data were provided for this outcome. Serious risk of bias due to selective outcome reporting led to a determination of moderate-quality evidence.

Probiotics versus no treatment for inducing remission of MC. One trial, which included 29 participants, informed about the effect of a probiotic (AB-Cap-10, a mixture of *Lactobacillus acidophilus* strain LA-5 and *Bifidobacterium animalis* subsp *lactis* strain BB-12) compared with placebo for inducing remission of MC (Table 11).[13] The use of the probiotic increased the probability of experiencing clinical remission after 12 weeks by 129% (RR, 2.29; 95% CI, 0.32–16.13); however, this difference was not statistically significant. These findings are supported by moderate-quality evidence. Regarding histological response, no numerical data were reported, but the investigators declared "no differences in histopathological changes between or within groups were observed after 12 weeks." This finding is supported by low-quality evidence. For the outcome of adverse events, the probiotic group experienced worsening of diarrhea, abdominal pain and constipation, stomach burning, nausea, and flatulence after 12 weeks of follow-up; these findings are supported by moderate-quality evidence. Finally, quality of life was assessed using the Short Inflammatory Bowel Disease Questionnaire (SIBDQ) after 12 weeks. An increase in the instrument score of 3% (no information on variability for this estimate was reported) was observed. This finding is supported by low-quality evidence.

Beclomethasone versus mesalazine for inducing remission of MC. One trial, which included 33 participants, reported data for this comparison.[8] Two doses of beclomethasone dipropionate, 5 mg/day and 10 mg/day, were compared with mesalazine 2.4 mg/day. *Although the interaction test showed no* statistically significant differences between the 2 doses, the results are reported separately for convenience. For both doses, beclomethasone showed a reduction in the probability of experiencing clinical remission of 4% for the 5-mg dose and 2% for the 10-mg dose when compared with mesalazine after 8 weeks. Regarding the outcome of adverse events, the authors only reported that beclomethasone and mesalazine were well tolerated with no serious side effects (no numerical data were provided). Low confidence in estimates of effect was determined for all these outcomes due to serious imprecision and very serious risk of bias. Neither histological response nor quality of life were reported (Table 12).

Question 3. In patients successfully treated for MC (either LC or CC) and in remission of symptoms, which treatments are effective and safe for maintaining clinical remission of the disease, measured as maintenance of clinical response, maintenance of histological response, time to relapse, quality of life, and adverse events?

Budesonide versus no treatment for maintaining remission of MC. Three randomized controlled trials, including a total of 80 participants, reported data for this comparison (Table 13).[9,10,22] Two doses of budesonide were studied to maintain clinical remission: 6 mg once a day (two 3-mg capsules for 6 months)[9,22] and 4.5 mg/day (two 3-mg capsules every other day alternating with one 3-mg capsule every other day for 12 months).[10] The 6-mg dose reduced the risk of clinical relapse at 6 months by 66% (RR, 0.34; 95% CI, 0.19–0.6), which in absolute terms means that 495 relapse events can be avoided per 1000 people. This finding is supported by high-quality evidence. The 4.5-mg dose also showed a reduction in the risk of experiencing a relapse of 54% (RR, 0.46; 95% CI, 0.31–0.69) compared with placebo after 13 months of

Table 10. *Boswellia serrata* Versus No Boswellia for Inducing Remission of MC[14]

Quality assessment							No. of patients		Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*Boswellia serrata*	No treatment	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Clinical response (follow-up: 6 wk)												
1	Randomized trials	Not serious	Not serious	Not serious	Serious[a]	None	7/16 (43.8%)	4/15 (26.7%)	RR, 1.64 (0.60–4.49)	171 more per 1000 (from 121 fewer to 512 more)	⊕⊕⊕ Moderate	Critical
Histological response (follow-up: 6 wk)												
1	Randomized trials	Serious[b]	Not serious	Not serious	Not serious	None			Slight reduction in the thickness of the subepithelial collagen band and inflammation score in both the *B serrata* and placebo groups at the end of 6 weeks of therapy, but no statistically significant difference compared with baseline or between the groups; no numerical data were provided		⊕⊕⊕ Moderate	Important
Histological response (follow-up: 6 wk)												
1[c]	Randomized trials	Not serious	Not serious	Not serious	Very serious[d]	None	2/16 (12.5%)	1/15 (6.7%)	RR, 1.88 (0.19–18.6)	59 more per 1000 (from 54 fewer to 1173 more)	⊕⊕ Low	Critical
Quality of life (follow-up: 6 wk; assessed with: SF-36 instrument)												
1	Randomized trials	Serious[b]	Not serious	Not serious	Not serious	None			At the end of 6 weeks of therapy, there were no significant changes in quality of life scores in either the *B serrata* or placebo groups compared with baseline or between groups; no numerical data were provided		⊕⊕⊕ Moderate	Critical

[a]The study included only 11 events. The lower and upper limits of the CI suggest both appreciable harm and important benefit.
[b]High risk of bias. No numerical data were reported. The investigators declared that there was no statistically significant difference compared with baseline or between groups.
[c]Adverse events included hypoglycemia, dizziness, anorexia, and bacterial enteritis.
[d]Only 3 events are reported in the study. The CI includes appreciable benefit and harm in both extremes and for relative and absolute effects.

Table 11. Probiotics Versus No Probiotics for Inducing Remission of MC[13]

Quality assessment							No. of patients		Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Probiotics	No treatment	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Clinical response (follow-up: 12 wk)												
1	Randomized trials	Not serious	Not serious	Not serious	Serious[a]	None	6/21 (28.6%)	1/8 (12.5%)	RR, 2.29 (0.32–16.13)	161 more per 1000 (from 85 fewer to 1891 more)	⊕⊕⊕ Moderate	Critical
Histological response (follow-up: 12 wk)												
1	Randomized trials	Serious[b]	Not serious	Not serious	Serious[c]	None			No differences in histopathological changes between or within groups were observed at 12 weeks; numerical data were not reported		⊕⊕ Low	Important
Adverse events (induction therapy) (follow-up: 12 wk)												
1	Randomized trials	Not serious	Not serious	Not serious	Serious[c]	None			In the probiotic group, worsening of diarrhea (n = 1), abdominal pain and constipation (n = 2), stomach burn (n = 1), nausea (n = 1), and flatulence (n = 1) were reported; in the placebo group, 4 patients had nausea; in 1 patient, development of constipation and abdominal pain led to discontinuation of study drug for 6 wk		⊕⊕⊕ Moderate	Critical
Quality of life (follow-up: 12 wk; assessed with the SIBDQ)												
1	Randomized trials	Serious	Not serious[d]	Not serious	Serious[c]	None	21	8	—	MD, 3 higher (0 higher to 0 higher)	⊕⊕ Low	Critical

[a]The study included only 7 events. Both limits of the CI show an important harm and a large benefit.
[b]High risk of bias due to selective outcome reporting. No numerical data regarding histological response were reported.
[c]The study included only 29 participants and 7 events.
[d]High risk of bias due to selective outcome reporting. Only ranges were reported as a measure of variability between groups.

Table 12. Beclomethasone Versus Mesalazine for Inducing Remission of MC[8]

Quality assessment							No. of patients		Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Beclomethasone	Mesalazine	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Clinical response: beclomethasone 5 mg (follow-up: 8 wk)												
1	Randomized trials	Serious[a]	Not serious	Not serious	Serious[b]	None	15/18 (83.3%)	13/15 (86.7%)	RR, 0.96 (0.72–1.28)[c]	35 fewer per 1000 (from 243 fewer to 243 more)	⊕⊕ Low	Critical
Clinical response: beclomethasone 10 mg (follow-up: 8 wk)												
1	Randomized trials	Serious[a]	Not serious	Not serious	Serious[b]	None	11/13 (84.6%)	13/15 (86.7%)	RR, 0.98 (0.72–1.32)[c]	17 fewer per 1000 (from 243 fewer to 277 more)	⊕⊕ Low	Important
Histological response: not reported												
—	—	—	—	—	—	—	—	See comment	Not estimable	See comment	—	Critical
Adverse events (induction therapy) (follow-up: 8 wk)												
1	Randomized trials	Very serious[a]	Not serious	Not serious	Not serious	None			Both beclomethasone and mesalazine were well tolerated with no serious side effects; no numerical data were provided		⊕⊕ Low	Critical
Quality of life: not reported												
—	—	—	—	—	—	—	—	See comment	Not estimable	See comment	—	Critical

[a]Most of the risk of bias domains assessed were evaluated as unclear. High risk of bias due to selective outcome reporting.
[b]Small number of events. The CI includes both appreciable harm and benefit.
[c]Test for interaction showed no differences between these 2 doses.

Table 13. Budesonide Versus No Budesonide for Maintaining Remission of MC[9,10,22]

Quality assessment							No. of patients		Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Budesonide	No treatment	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Maintenance of clinical response: budesonide 6 mg (follow-up: 6 mo)												
2	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	10/40 (25.0%)	30/40 (75.0%)	RR, 0.34 (0.19–0.6)[a]	495 fewer per 1000 (from 300 fewer to 608 fewer)	⊕⊕⊕⊕ High	Critical
Maintenance of clinical response: budesonide 3 mg (follow-up: 13 mo)												
1	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	17/44 (38.6%)	40/48 (83.3%)	RR, 0.46 (0.31–0.69)[a]	450 fewer per 1000 (from 258 fewer to 575 fewer)	⊕⊕⊕⊕ High	Critical
Maintenance of histological response: budesonide 6 mg (follow-up: 6 mo)												
2	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	21/40 (52.5%)	34/40 (85.0%)	Odds ratio, 0.21 (0.08–0.54)	307 fewer per 1000 (from 96 fewer to 538 fewer)	⊕⊕⊕⊕ High	Important
Time to relapse during maintenance therapy (follow-up: 6 mo; assessed with days)												
1	Randomized trials	Not serious	Not serious	Not serious	Serious[b]	None	17	15	—	MD, 161 higher (7.83 higher to 314.17 higher)	⊕⊕⊕ Moderate	Critical
Time to relapse after maintenance therapy (follow-up: 6 mo; assessed with days)												
1[c]	Randomized trials	Not serious	Not serious	Not serious	Serious[d]	None	17	15	—	MD, 1 higher (4.1 lower to 6.1 higher)	⊕⊕⊕ Moderate	Critical
Adverse events (maintenance therapy): budesonide 6 mg (follow-up: 6 mo)												
2[e]	Randomized trials	Not serious	Not serious	Not serious	Serious[f]	None	13/40 (32.5%)	16/40 (40.0%)	RR, 0.81 (0.45–1.47)	76 fewer per 1000 (from 188 more to 220 fewer)	⊕⊕⊕ Moderate	Critical
Adverse events (maintenance therapy): budesonide 3 mg (follow-up: 13 mo)												
1[g]	Randomized trials	Not serious	Not serious	Not serious	Serious[f]	None	7/44 (15.9%)	5/48 (10.4%)	RR, 1.53 (0.52–4.46)	55 more per 1000 (from 50 fewer to 360 more)	⊕⊕⊕ Moderate	Critical

Table 13. Continued

Quality assessment							No. of patients		Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Budesonide	No treatment	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Quality of life (follow-up: range, 6–13 mo; assessed with SF-36, SIBDQ, and the Short Health Scale)												
2	Randomized trials	Serious[h]	Not serious	Not serious	Not serious	None			Miehlke et al[9] (2008): Physical and mental SF-36 scores in patients receiving budesonide increased to levels similar to those observed in "normal" subjects after induction, and these changes were maintained during maintenance therapy; no numerical data were reported Munch et al[10] (2014): Quality of life was unchanged after 1 y in the budesonide group but showed clinically relevant deterioration in the placebo group; no numerical data were provided		⊕⊕⊕ Moderate	Critical

[a]Test for interaction between the 2 doses of budesonide showed no statistically significant differences.
[b]The CI includes negligible benefit and a large benefit.
[c]Munch et al[10] (2014), not included in the meta-analysis, reported a mean of 40 days to relapse after maintenance therapy (range, 27–57 days).
[d]Unexplained heterogeneity between the 2 studies reporting this outcome. Results differ considerably.
[e]Among budesonide recipients, Miehlke et al[9] (2008) reported adverse events, including headache (2), urinary infection (1), respiratory infection (1), back pain (1), abdominal pain (1), increased body weight (1), and hypertension (1). Among patients who withdrew from the study, adverse events included dizziness (1), sleep disturbance (1), muscle pain (1), gastric ulcer (1), and skin erythema (1). Bonderup et al[22] (2009) reported worsening of diabetes (2), dyspepsia (1), bruising (1), and subarachnoid hemorrhage (1). The latter adverse event, which occurred after 22 weeks of active treatment (ie, 6 weeks of induction plus 16 weeks of maintenance therapy), was considered to be serious and the patient was withdrawn from the study.
[f]Limits of the CI include both appreciable benefit and large harm.
[g]The investigators did not report adverse events in detail (described as an adverse drug reaction).
[h]High risk of bias due to selective outcome reporting. No numerical data were provided.

follow-up. In absolute terms, 450 relapse events can be avoided per 1000 people. The quality of the evidence for this outcome was also assessed as high. Regarding maintenance of histological response, the meta-analysis showed that budesonide 6 mg reduces the risk of histological relapse by 79% (RR, 0.21; 95% CI, 0.08–0.54). In absolute terms, this means that 307 histological relapse events can be avoided per 1000 people. The quality of the evidence for this outcome was also assessed as high. After 6 months of follow-up, the time to relapse during maintenance therapy was on average 161 days longer for the patients in the budesonide group compared with those receiving placebo (MD, 161; 95% CI, 7.8–314.2). This finding is supported by moderate-quality evidence. The time to relapse after maintenance therapy was completed (without medication) was 1 day longer in patients receiving budesonide compared with placebo (MD, 1; 95% CI, −4.1 to 6.1); however, this difference was not statistically significant. The 2014 study by Munch et al,[10] which was included in the meta-analysis, reported a mean of 40 days to relapse after maintenance therapy (range, 27–57 days). This outcome was assessed as having moderate-quality evidence due to serious inconsistency. Adverse events were also analyzed separately for both doses to facilitate decision making. For both the 6-mg and 3-mg doses of budesonide, there were no statistically significant differences between the 2 groups. However, there is no evidence regarding long-term toxicity in patients treated with budesonide for more than 6 months. It has been recommended that these patients be monitored for corticosteroid-related adverse effects.[23] Quality of life was measured in 2 trials. Miehlke et al[9] reported that physical and mental SF-36 scores in patients receiving budesonide increased to levels similar to those observed in "normal" subjects after induction, and these changes remained stable during maintenance therapy. However, no numerical data were reported. Munch et al[10] reported that quality of life did not change after 1 year of treatment with budesonide; however, participants receiving placebo showed a clinically relevant deterioration. No numerical data were provided. The quality of the evidence for this outcome was assessed as moderate due to serious risk of bias issues.

The pooled treatment effects for all outcomes and for all comparisons are presented in Appendix 3.

Discussion

Summary of the Main Results

This review summarizes the best available evidence related to the medical management of MC and clinical features to diagnose celiac disease in this type of patient. A total of 17 primary studies contributed to the body of evidence. The medical interventions identified covered both induction and maintenance of remission of MC. The most promising intervention identified for both purposes was budesonide, supported by moderate- to high-quality evidence. The results for other interventions were too imprecise to draw meaningful conclusions. The selection criteria and outcome definition were consistent across trials. The main risk of bias identified was for the question "Was the study affected by selective outcome reporting?" In this case, 8 of 15 studies were classified as "high risk of bias" due to the fact that the investigators did not provide numerical data for their results but only stated a lack of statistical significance.

Quality of the Evidence

The quality of the evidence ranged from high to very low across outcomes. The main reasons for downgrading were issues of serious imprecision due to the small number of participants per trial and risk of bias mainly due to selective outcome reporting. Investigators tended to avoid reporting numerical data when the trial showed results that were not statistically significant, making it impossible to include these data in the meta-analyses.

Comparison With Previous Systematic Reviews

To our knowledge, this is the most updated systematic review on interventions to treat MC. Previous reviews included fewer studies and had less precise results but came to similar conclusions regarding the role of budesonide as the most studied medication for treating MC.[24–28] The inclusion of 3 new randomized controlled trials[10,16,17] with 218 patients increased the number of participants compared with the previous reviews such that imprecision is no longer an issue for many outcomes. In particular, this review increased the certainty about the role of budesonide for both inducing and maintaining clinical remission.

Strengths and Limitations of This Review

The strengths of this review include the comprehensive search strategy that included multiple databases. In addition, the absence of restriction by language or status of publication allowed us to include key abstracts from conferences and other meetings that have not been published in full version. Screening for articles was conducted independently and in duplicate, while a second reviewer checked the data extraction process. A limitation was that, for many interventions identified, serious imprecision did not allow more definitive conclusions. In general, the trials included few participants and events that affected the precision of the CIs.

Conclusions

Implications for clinical practice. The most important finding of this review for clinical practice is the

effectiveness of budesonide and the role of this medication for inducing and maintaining remission of MC.

Implications for research. Multicenter, high-quality, randomized controlled trials of new treatments should be conducted, particularly of noncorticosteroid medications and comparing budesonide with other interventions. More interventions to manage MC should be investigated, particularly to identify effective alternatives to budesonide. Additional research into the mechanism(s) and natural history of MC is warranted.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2015.11.006.

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Reprint requests
Address requests for reprints to: Chair, Clinical Guidelines Committee, AGA National Office, 4930 Del Ray Avenue, Bethesda, Maryland 20814. e-mail: msiedler@gastro.org; telephone: (301) 941-2618.

Conflicts of interest
All members were required to complete disclosure statements. These statements are maintained at the American Gastroenterological Association Institute headquarters in Bethesda, Maryland, and none of the disclosures were potentially related to the content of this guideline.

Appendix 1. Literature Search Strategy: Prevalence and Biopsy Characteristics of Patients With MC

#	Searches	Results
1	exp Colitis, Microscopic/ use mesz,cctr,coch,clhta	436
2	exp microscopic colitis/ use emez	588
3	((microscopic or collagenous or lymphocytic) adj2 colitis).ti,ab.	3015
4	or/1-3	3161
5	exp Colitis, Microscopic/di [Diagnosis]	298
6	exp Colonoscopy/	67846
7	(colonoscop* or (colon adj endoscop*)).ti,ab.	52968
8	exp Biopsy/ use mesz,cctr,coch,clhta	229496
9	exp intestine biopsy/ use emez	18651
10	(biopsy or biopsied or biopsies).ti,ab.	674022
11	or/5-10	874623
12	4 and 11	1881
13	limit 12 to (editorial or letter or note or case reports or comment) [Limit not valid in CCTR,CDSR,CLHTA,Embase,Ovid MEDLINE(R),Ovid MEDLINE(R) In-Process; records were retained]	359
14	Case Report/	3579331
15	12 not (13 or 14)	1239
16	remove duplicates from 15	837

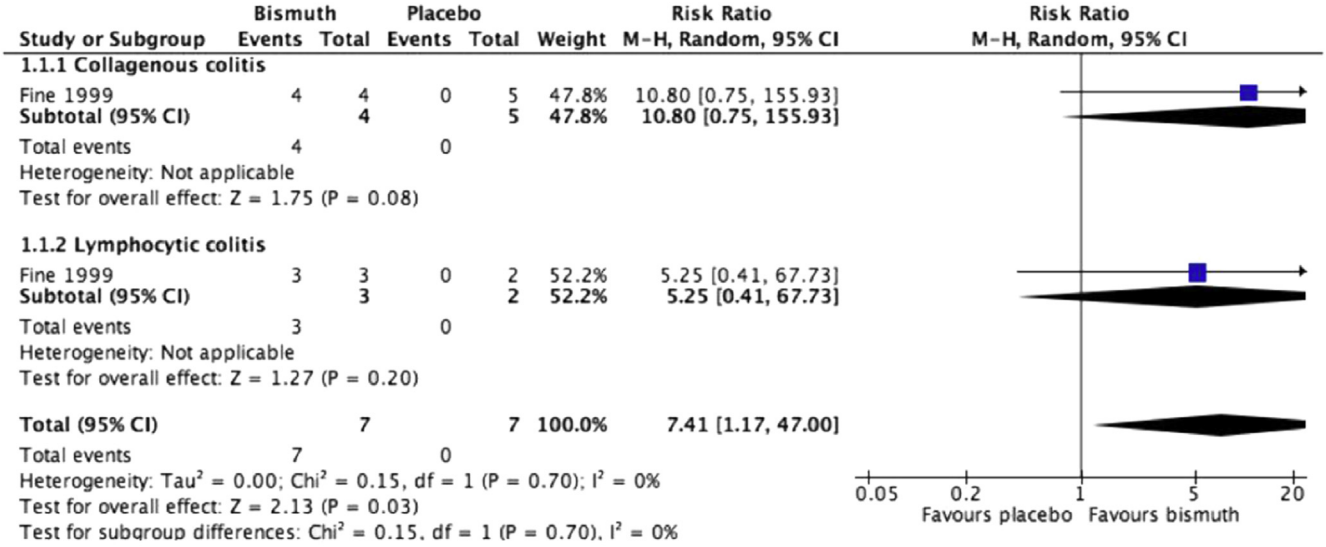
Appendix 2. Literature Search Strategy – Induction and Maintenance of Remission of MC

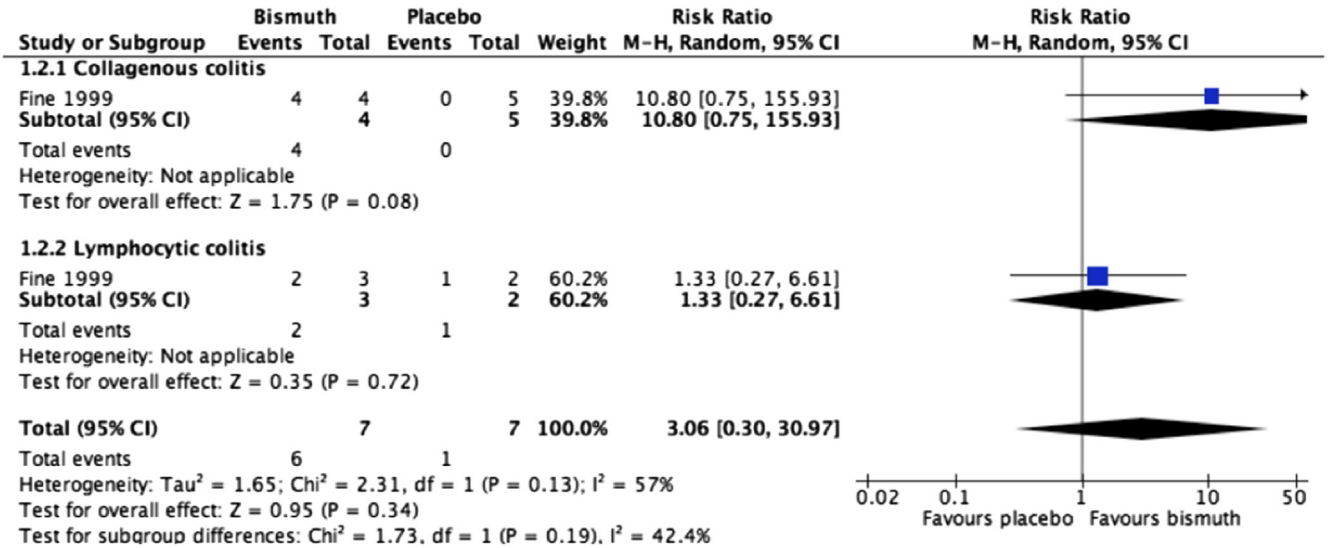
Search date: August 3, 2014

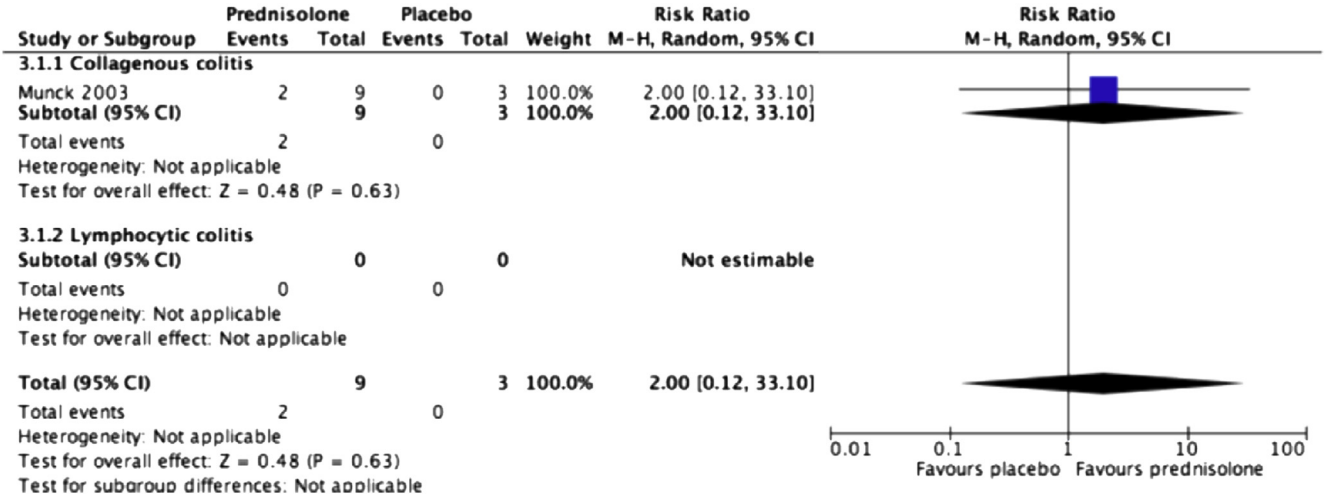
EBM Reviews - Cochrane Central Register of Controlled Trials June 2014, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to June 2014, EBM Reviews - Health Technology Assessment 2nd Quarter 2014, Embase 1980 to 2014 Week 31, Ovid MEDLINE(R) 1946 to July Week 4 2014, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations August 01, 2014

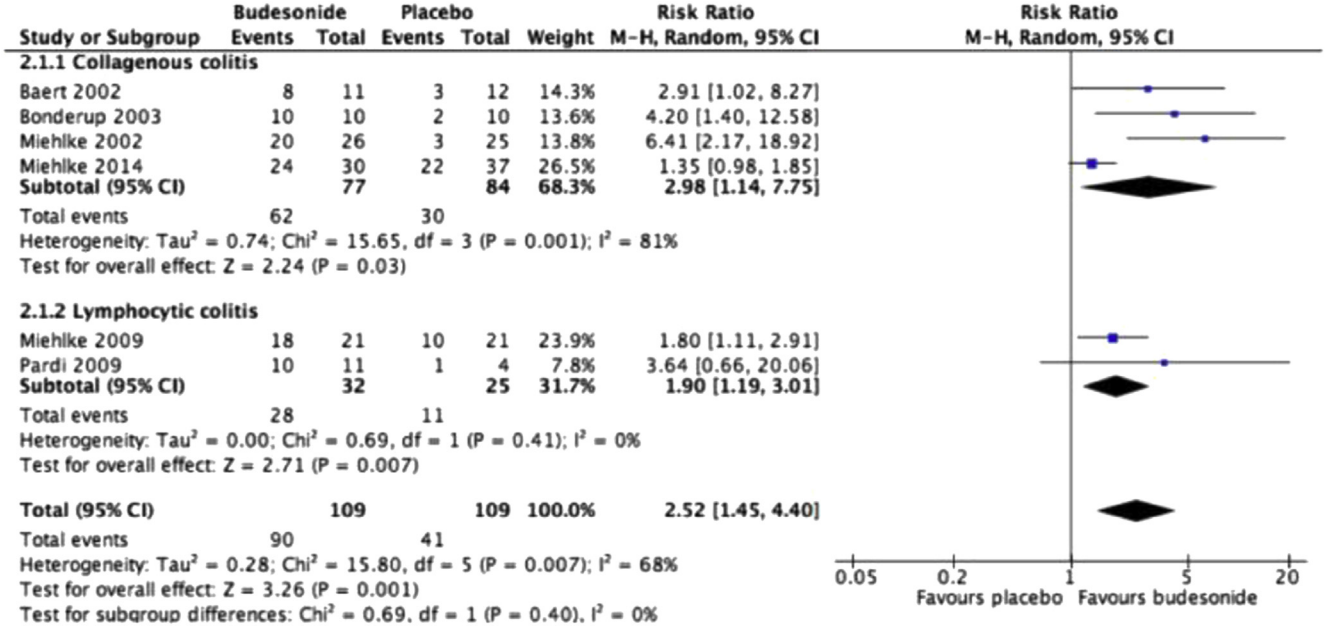
#	Searches	Results
1	exp Colitis, Microscopic/ use mesz,cctr,coch,clhta	437
2	exp microscopic colitis/ use emez	589
3	((collagenous or microscopic or lymphocytic) adj2 colitis).ti,ab.	3015
4	or/1-3	3161
5	exp Bismuth/ use mesz,cctr,coch,clhta	5262
6	exp Salicylates/ use mesz,cctr,coch,clhta	66277
7	exp bismuth salicylate/ use emez	1744
8	bismuth.ti,ab.	12662
9	exp Budesonide/	20193
10	(pulmicort or horacort or rhinocort or budesonide).ti,ab.	12016
11	exp Cholestyramine Resin/ use mesz,cctr,coch,clhta	2793
12	exp colestyramine/ use emez	8760
13	(Cholestyramin* or colestyramin* or Questran or Cholybar or Olestyr).ti,ab.	4960
14	exp Sulfasalazine/ use mesz,cctr,coch,clhta	4007
15	exp salazosulfapyridine/ use emez	19164
16	(Sulfasalazine or salazosulfapyridine or Azulfidine or Salazopyrin or Sulazine).ti,ab.	7031
17	exp Mesalamine/ use mesz,cctr,coch,clhta	3076
18	exp mesalazine/ use emez	12461
19	(Mesalazine or mesalamine or 5-aminosalicylic acid or 5-ASA or Asacol or Pentasa or Salofalk or Mezavant or Canasa or Rowasa or Delzicol or Lialda or Apriso).ti,ab.	9266
20	exp Prednisone/	164408
21	(Cortan or Deltasone or Orasone or Prednisone or Sterapred).ti,ab.	53584
22	exp Azathioprine/	84699
23	(Azasan or Azathioprine or Imuran or Thiopurine*).ti,ab.	33945
24	exp Metronidazole/	62112
25	(Flagyl or Metronidazole).ti,ab.	29405
26	exp Methotrexate/	159974
27	(methotrexate or MTX or Rheumatrex or Trexall or Amethopterin).ti,ab.	81072
28	exp Antibodies, Monoclonal/ use mesz,cctr,coch,clhta	185494
29	(Infliximab or Remicade).ti,ab.	21308
30	exp Infliximab/ use emez	29701
31	exp Adalimumab/ use emez	15571
32	(Humira or Adalimumab).ti,ab.	10327
33	exp Ileostomy/	14297
34	ileostom*.ti,ab.	11256
35	exp Colectomy/ use mesz,cctr,coch,clhta	15635
36	exp Anastomosis, Surgical/ use mesz,cctr,coch,clhta	69526
37	exp proctocolectomy/ use emez	3850
38	exp anastomosis/ use emez	119978
39	(anastomosis or Proctocolectomy).ti,ab.	100208
40	or/5-39	1031152
41	4 and 40	985
42	limit 41 to (editorial or letter or note or case reports or comment) [Limit not valid in CCTR,CDSR,CLHTA,Embase,Ovid MEDLINE(R),Ovid MEDLINE(R) In-Process; records were retained]	213
43	Case Report/	3581344
44	41 not (42 or 43)	592
45	remove duplicates from 44	430

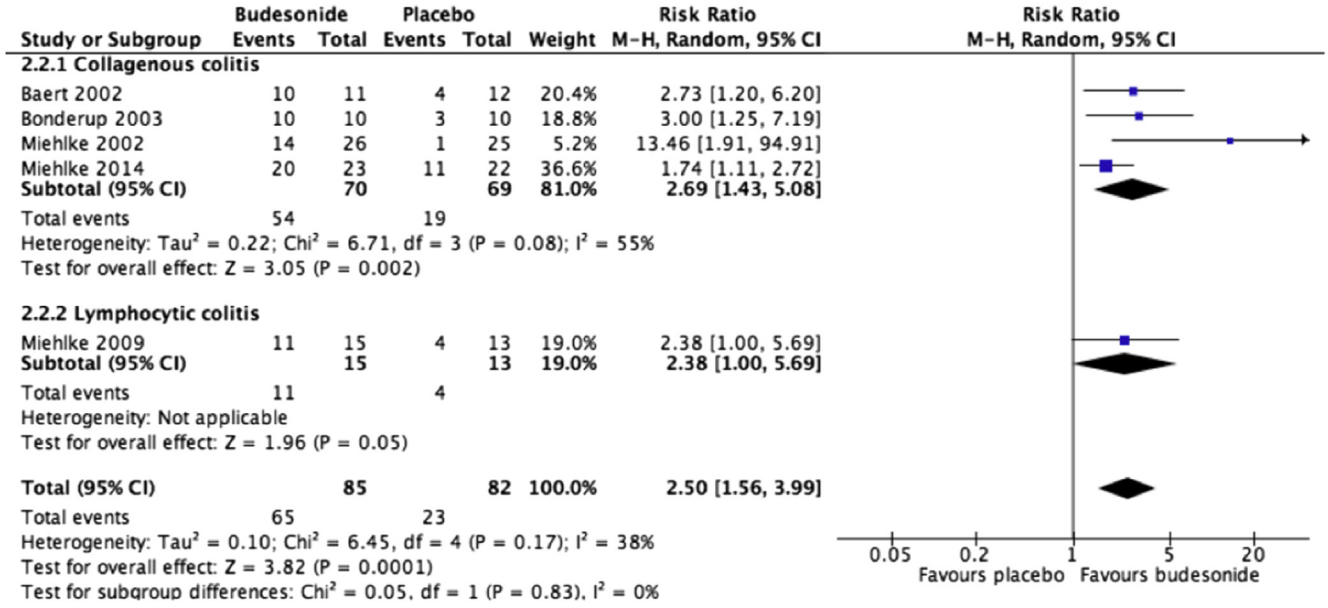
Appendix 3. Forest Plots for the Cited Comparisons

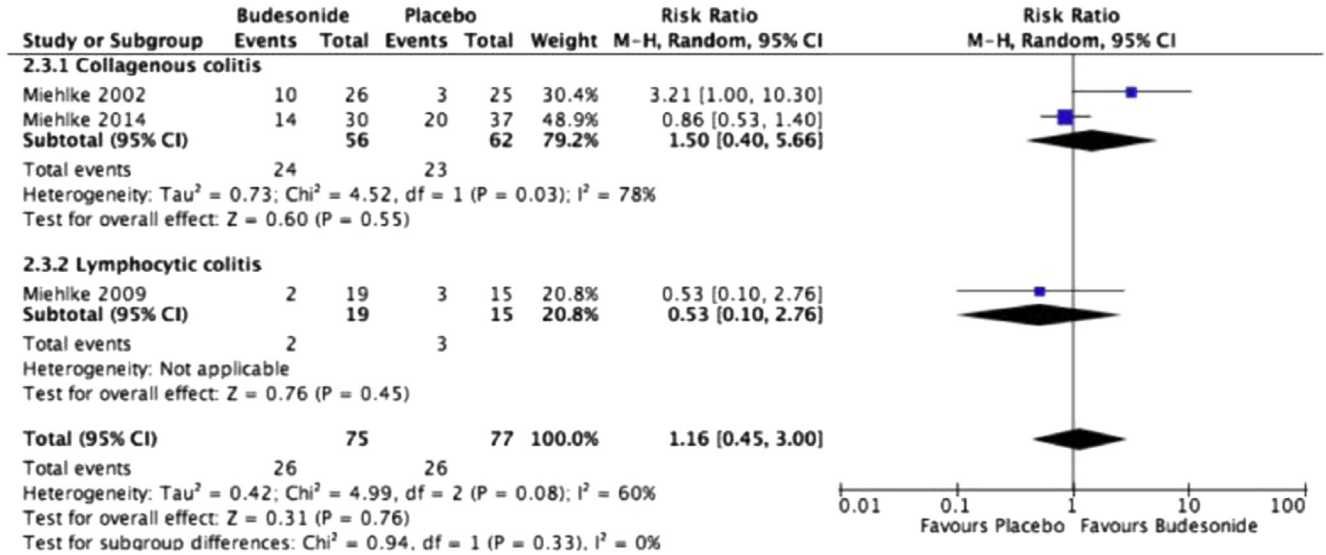


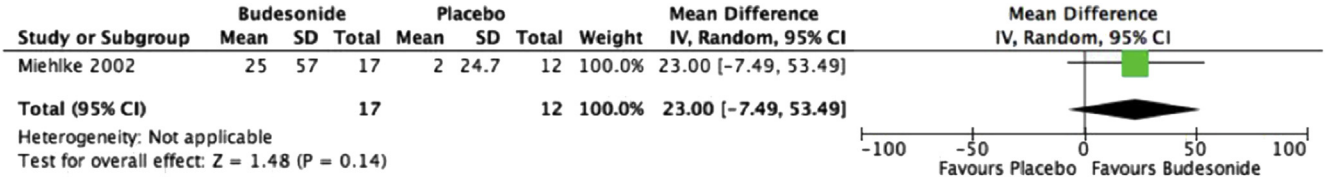


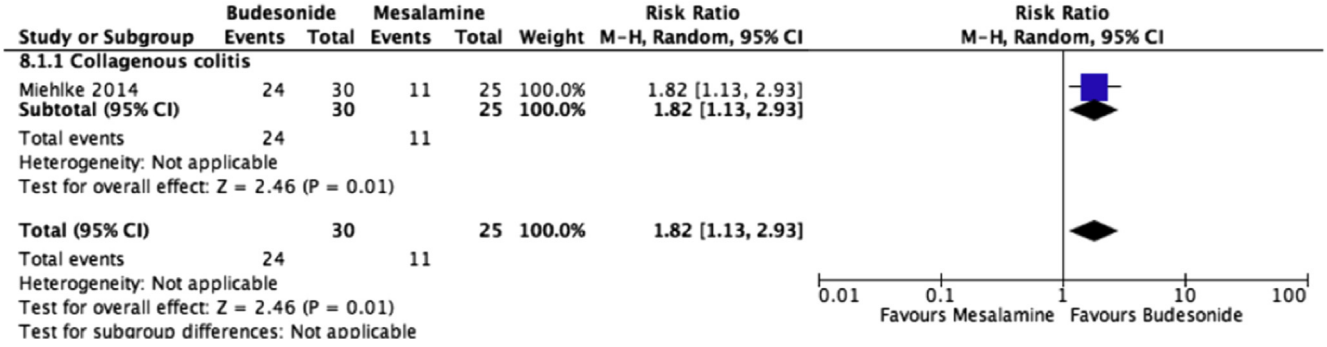

Prednisolone
Placebo
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
3.1.1 Collagenous colitis
Munck 2003 2 9 0 3 100.0% 2.00 [0.12, 33.10]
Subtotal (95% CI) 9 3 100.0% 2.00 [0.12, 33.10]
Total events 2 0
Heterogeneity: Not applicable
Test for overall effect: Z = 0.48 (P = 0.63)
3.1.2 Lymphocytic colitis
Subtotal (95% CI) 0 0 Not estimable
Total events 0 0
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Total (95% CI) 9 3 100.0% 2.00 [0.12, 33.10]
Total events 2 0
Heterogeneity: Not applicable
Test for overall effect: Z = 0.48 (P = 0.63)
Test for subgroup differences: Not applicable
0.01 0.1 1 10 100
Favours placebo Favours prednisolone

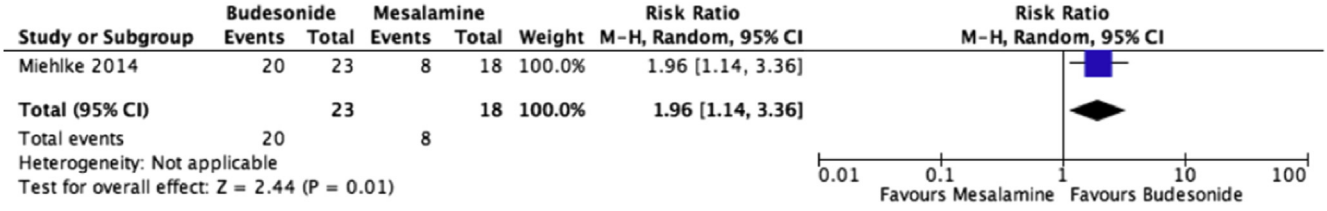

Budesonide
Placebo
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
2.1.1 Collagenous colitis
Baert 2002 8 11 3 12 14.3% 2.91 [1.02, 8.27]
Bonderup 2003 10 10 2 10 13.6% 4.20 [1.40, 12.58]
Miehlke 2002 20 26 3 25 13.8% 6.41 [2.17, 18.92]
Miehlke 2014 24 30 22 37 26.5% 1.35 [0.98, 1.85]
Subtotal (95% CI) 77 84 68.3% 2.98 [1.14, 7.75]
Total events 62 30
Heterogeneity: Tau² = 0.74; Chi² = 15.65, df = 3 (P = 0.001); I² = 81%
Test for overall effect: Z = 2.24 (P = 0.03)
2.1.2 Lymphocytic colitis
Miehlke 2009 18 21 10 21 23.9% 1.80 [1.11, 2.91]
Pardi 2009 10 11 1 4 7.8% 3.64 [0.66, 20.06]
Subtotal (95% CI) 32 25 31.7% 1.90 [1.19, 3.01]
Total events 28 11
Heterogeneity: Tau² = 0.00; Chi² = 0.69, df = 1 (P = 0.41); I² = 0%
Test for overall effect: Z = 2.71 (P = 0.007)
Total (95% CI) 109 109 100.0% 2.52 [1.45, 4.40]
Total events 90 41
Heterogeneity: Tau² = 0.28; Chi² = 15.80, df = 5 (P = 0.007); I² = 68%
Test for overall effect: Z = 3.26 (P = 0.001)
Test for subgroup differences: Chi² = 0.69, df = 1 (P = 0.40), I² = 0%
0.05 0.2 1 5 20
Favours placebo Favours budesonide

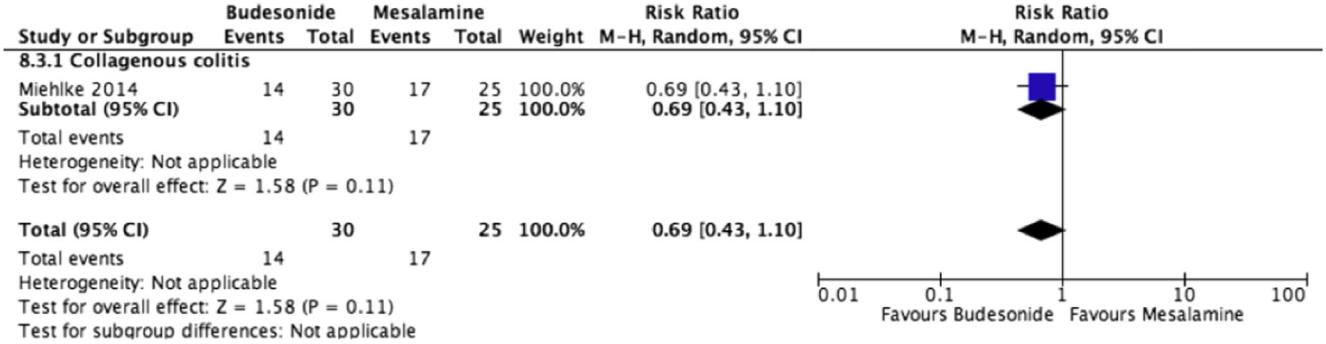

Budesonide
Placebo
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
2.2.1 Collagenous colitis
Baert 2002 10 11 4 12 20.4% 2.73 [1.20, 6.20]
Bonderup 2003 10 10 3 10 18.8% 3.00 [1.25, 7.19]
Miehlke 2002 14 26 1 25 5.2% 13.46 [1.91, 94.91]
Miehlke 2014 20 23 11 22 36.6% 1.74 [1.11, 2.72]
Subtotal (95% CI) 70 69 81.0% 2.69 [1.43, 5.08]
Total events 54 19
Heterogeneity: Tau² = 0.22; Chi² = 6.71, df = 3 (P = 0.08); I² = 55%
Test for overall effect: Z = 3.05 (P = 0.002)
2.2.2 Lymphocytic colitis
Miehlke 2009 11 15 4 13 19.0% 2.38 [1.00, 5.69]
Subtotal (95% CI) 15 13 19.0% 2.38 [1.00, 5.69]
Total events 11 4
Heterogeneity: Not applicable
Test for overall effect: Z = 1.96 (P = 0.05)
Total (95% CI) 85 82 100.0% 2.50 [1.56, 3.99]
Total events 65 23
Heterogeneity: Tau² = 0.10; Chi² = 6.45, df = 4 (P = 0.17); I² = 38%
Test for overall effect: Z = 3.82 (P = 0.0001)
Test for subgroup differences: Chi² = 0.05, df = 1 (P = 0.83), I² = 0%
0.05 0.2 1 5 20
Favours placebo Favours budesonide

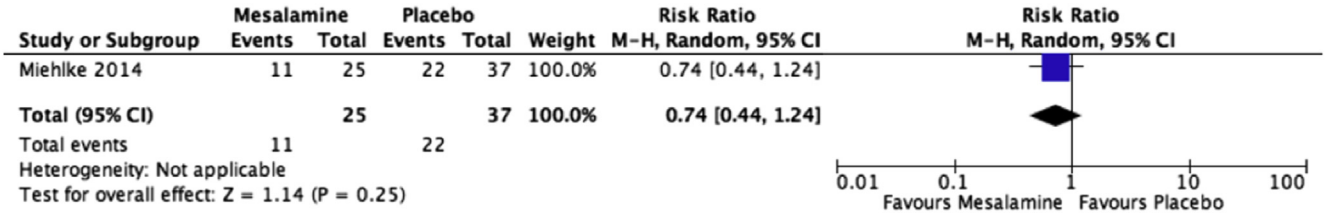

Budesonide
Placebo
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
2.3.1 Collagenous colitis
Miehlke 2002 10 26 3 25 30.4% 3.21 [1.00, 10.30]
Miehlke 2014 14 30 20 37 48.9% 0.86 [0.53, 1.40]
Subtotal (95% CI) 56 62 79.2% 1.50 [0.40, 5.66]
Total events 24 23
Heterogeneity: Tau² = 0.73; Chi² = 4.52, df = 1 (P = 0.03); I² = 78%
Test for overall effect: Z = 0.60 (P = 0.55)
2.3.2 Lymphocytic colitis
Miehlke 2009 2 19 3 15 20.8% 0.53 [0.10, 2.76]
Subtotal (95% CI) 19 15 20.8% 0.53 [0.10, 2.76]
Total events 2 3
Heterogeneity: Not applicable
Test for overall effect: Z = 0.76 (P = 0.45)
Total (95% CI) 75 77 100.0% 1.16 [0.45, 3.00]
Total events 26 26
Heterogeneity: Tau² = 0.42; Chi² = 4.99, df = 2 (P = 0.08); I² = 60%
Test for overall effect: Z = 0.31 (P = 0.76)
Test for subgroup differences: Chi² = 0.94, df = 1 (P = 0.33), I² = 0%
0.01 0.1 1 10 100
Favours Placebo Favours Budesonide

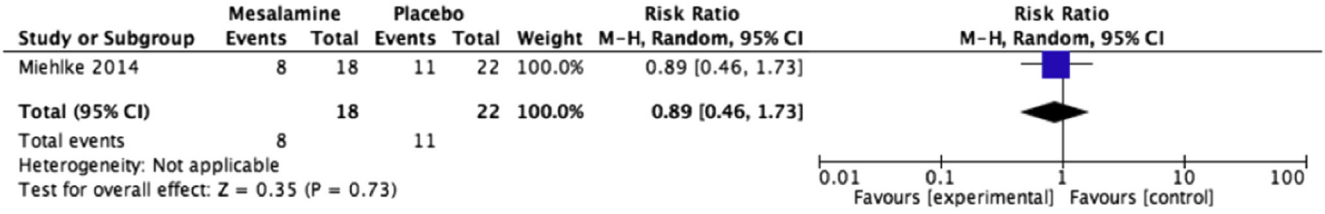

Budesonide
Placebo
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
Miehlke 2002 25 57 17 2 24.7 12 100.0% 23.00 [-7.49, 53.49]
Total (95% CI) 17 12 100.0% 23.00 [-7.49, 53.49]
Heterogeneity: Not applicable
Test for overall effect: Z = 1.48 (P = 0.14)
-100 -50 0 50 100
Favours Placebo Favours Budesonide

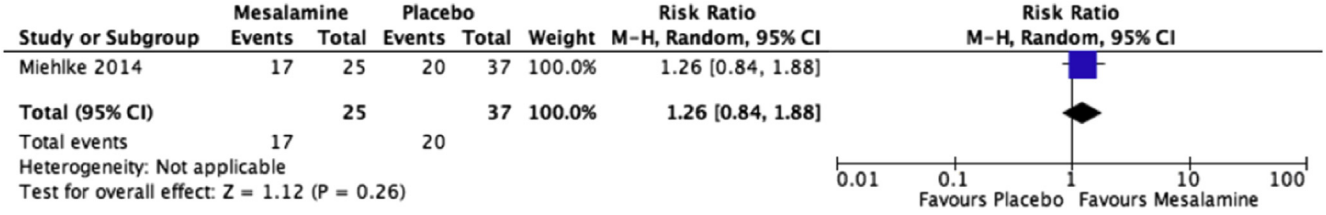

Budesonide
Mesalamine
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
8.1.1 Collagenous colitis
Miehlke 2014 24 30 11 25 100.0% 1.82 [1.13, 2.93]
Subtotal (95% CI) 30 25 100.0% 1.82 [1.13, 2.93]
Total events 24 11
Heterogeneity: Not applicable
Test for overall effect: Z = 2.46 (P = 0.01)
Total (95% CI) 30 25 100.0% 1.82 [1.13, 2.93]
Total events 24 11
Heterogeneity: Not applicable
Test for overall effect: Z = 2.46 (P = 0.01)
Test for subgroup differences: Not applicable
0.01 0.1 1 10 100
Favours Mesalamine Favours Budesonide

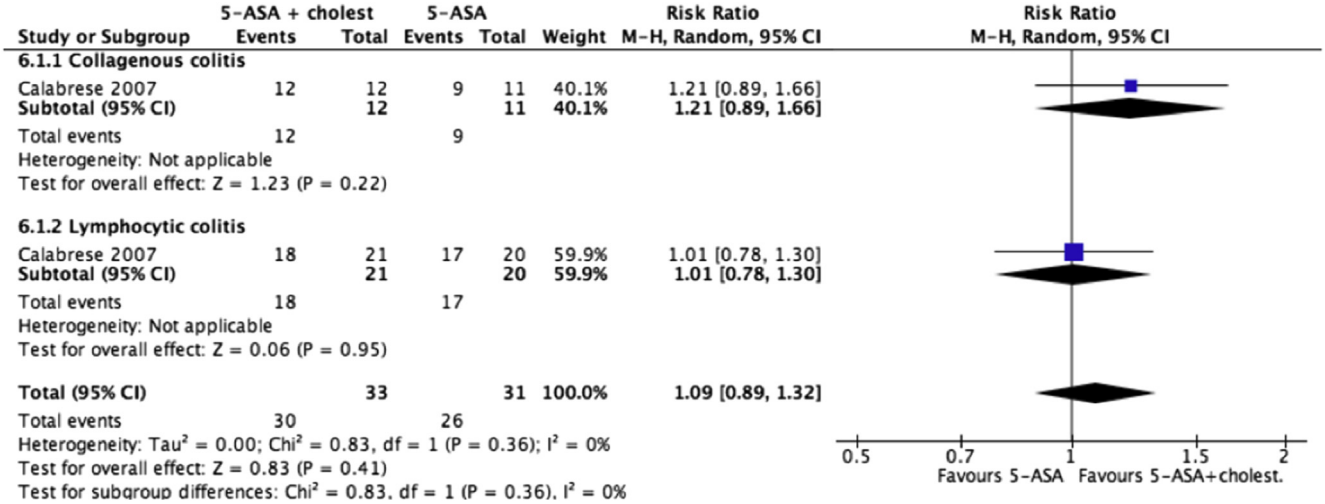

Budesonide
Mesalamine
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Miehlke 2014 20 23 8 18 100.0% 1.96 [1.14, 3.36]
Total (95% CI) 23 18 100.0% 1.96 [1.14, 3.36]
Total events 20 8
Heterogeneity: Not applicable
Test for overall effect: Z = 2.44 (P = 0.01)
0.01 0.1 1 10 100
Favours Mesalamine Favours Budesonide

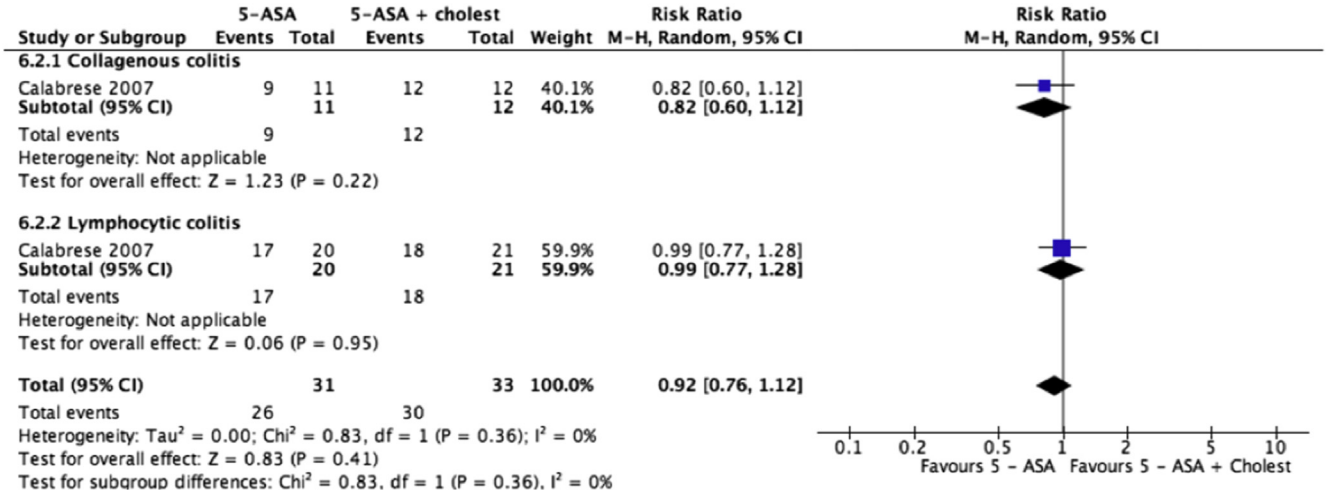

Budesonide
Mesalamine
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
8.3.1 Collagenous colitis
Miehlke 2014 14 30 17 25 100.0% 0.69 [0.43, 1.10]
Subtotal (95% CI) 30 25 100.0% 0.69 [0.43, 1.10]
Total events 14 17
Heterogeneity: Not applicable
Test for overall effect: Z = 1.58 (P = 0.11)
Total (95% CI) 30 25 100.0% 0.69 [0.43, 1.10]
Total events 14 17
Heterogeneity: Not applicable
Test for overall effect: Z = 1.58 (P = 0.11)
Test for subgroup differences: Not applicable
0.01 0.1 1 10 100
Favours Budesonide Favours Mesalamine

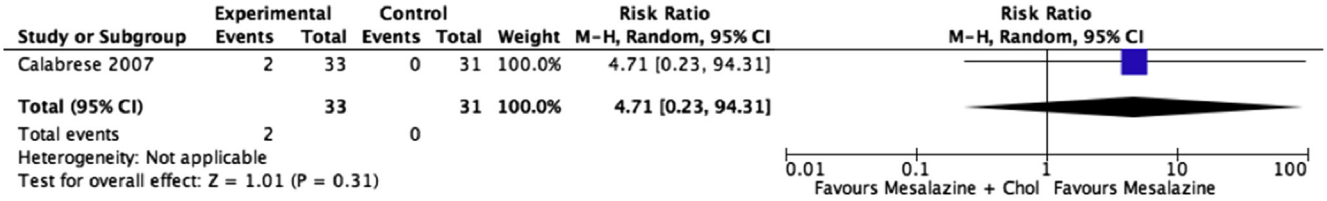

Mesalamine
Placebo
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Miehlke 2014 11 25 22 37 100.0% 0.74 [0.44, 1.24]
Total (95% CI) 25 37 100.0% 0.74 [0.44, 1.24]
Total events 11 22
Heterogeneity: Not applicable
Test for overall effect: Z = 1.14 (P = 0.25)
0.01 0.1 1 10 100
Favours Mesalamine Favours Placebo

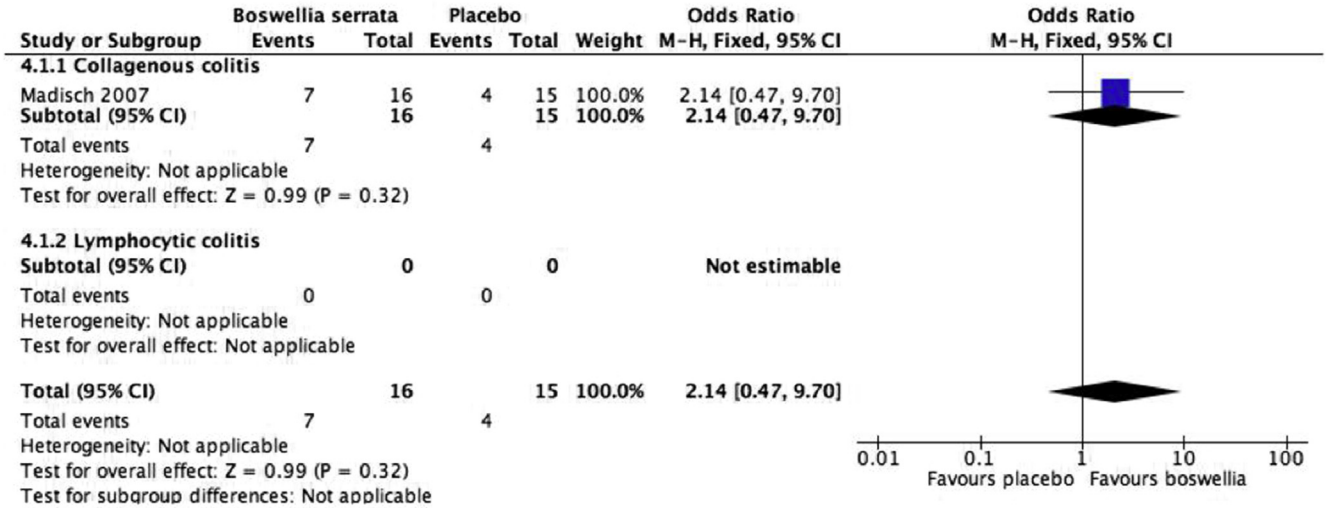

Mesalamine
Placebo
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Miehlke 2014 8 18 11 22 100.0% 0.89 [0.46, 1.73]
Total (95% CI) 18 22 100.0% 0.89 [0.46, 1.73]
Total events 8 11
Heterogeneity: Not applicable
Test for overall effect: Z = 0.35 (P = 0.73)
0.01 0.1 1 10 100
Favours [experimental] Favours [control]

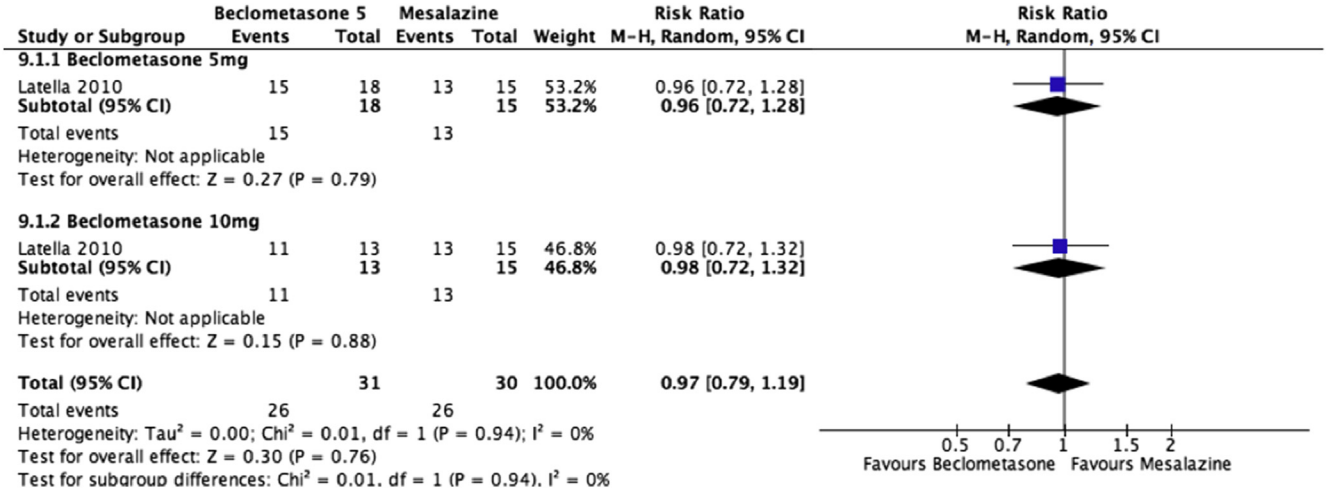

Mesalamine
Placebo
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Miehlke 2014 17 25 20 37 100.0% 1.26 [0.84, 1.88]
Total (95% CI) 25 37 100.0% 1.26 [0.84, 1.88]
Total events 17 20
Heterogeneity: Not applicable
Test for overall effect: Z = 1.12 (P = 0.26)
0.01 0.1 1 10 100
Favours Placebo Favours Mesalamine

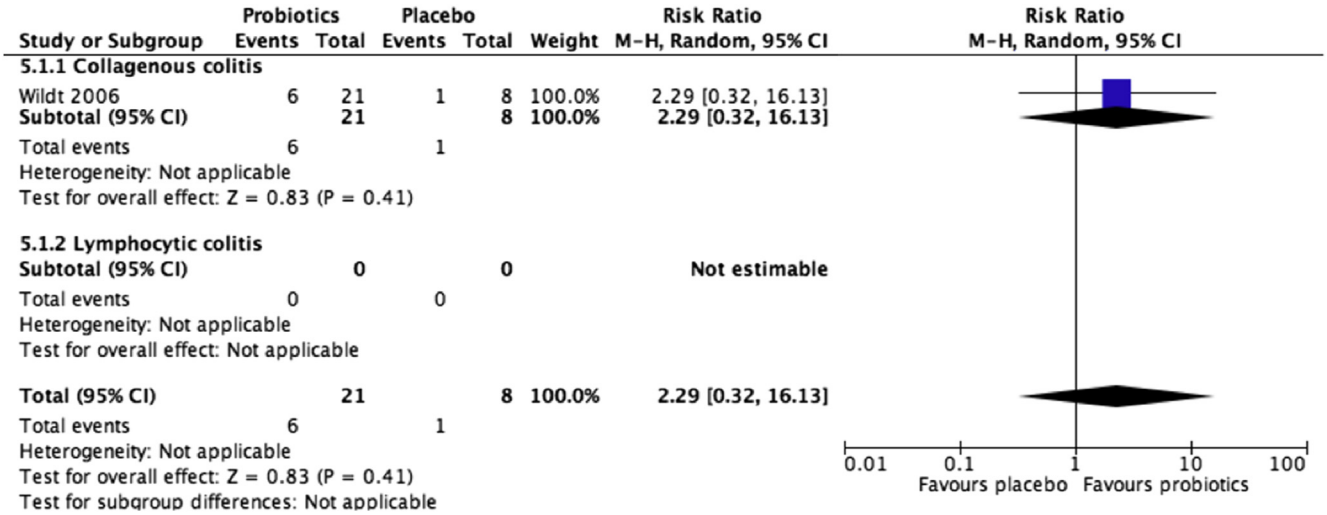

5-ASA + cholest
5-ASA
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
6.1.1 Collagenous colitis
Calabrese 2007 12 12 9 11 40.1% 1.21 [0.89, 1.66]
Subtotal (95% CI) 12 11 40.1% 1.21 [0.89, 1.66]
Total events 12 9
Heterogeneity: Not applicable
Test for overall effect: Z = 1.23 (P = 0.22)
6.1.2 Lymphocytic colitis
Calabrese 2007 18 21 17 20 59.9% 1.01 [0.78, 1.30]
Subtotal (95% CI) 21 20 59.9% 1.01 [0.78, 1.30]
Total events 18 17
Heterogeneity: Not applicable
Test for overall effect: Z = 0.06 (P = 0.95)
Total (95% CI) 33 31 100.0% 1.09 [0.89, 1.32]
Total events 30 26
Heterogeneity: Tau² = 0.00; Chi² = 0.83, df = 1 (P = 0.36); I² = 0%
Test for overall effect: Z = 0.83 (P = 0.41)
Test for subgroup differences: Chi² = 0.83, df = 1 (P = 0.36), I² = 0%
0.5 0.7 1 1.5 2
Favours 5-ASA Favours 5-ASA+cholest.

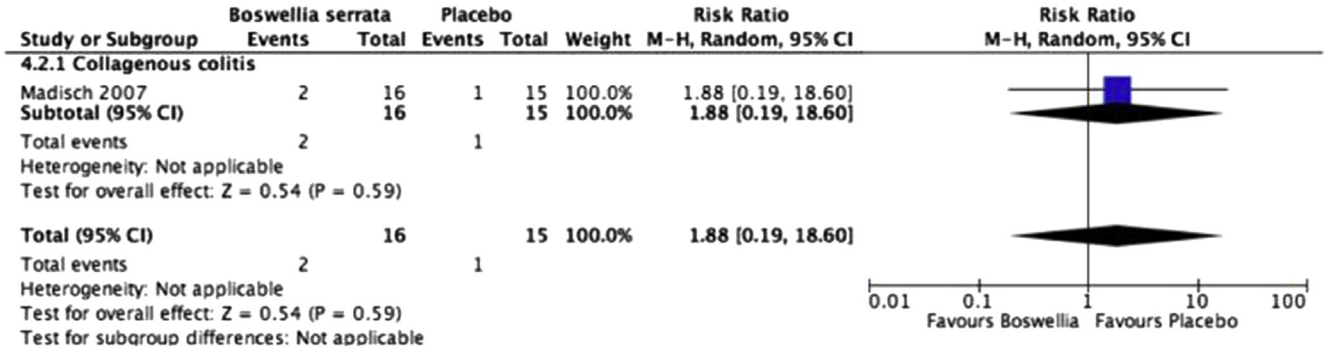

5-ASA
5-ASA + cholest
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
6.2.1 Collagenous colitis
Calabrese 2007 9 11 12 12 40.1% 0.82 [0.60, 1.12]
Subtotal (95% CI) 11 12 40.1% 0.82 [0.60, 1.12]
Total events 9 12
Heterogeneity: Not applicable
Test for overall effect: Z = 1.23 (P = 0.22)
6.2.2 Lymphocytic colitis
Calabrese 2007 17 20 18 21 59.9% 0.99 [0.77, 1.28]
Subtotal (95% CI) 20 21 59.9% 0.99 [0.77, 1.28]
Total events 17 18
Heterogeneity: Not applicable
Test for overall effect: Z = 0.06 (P = 0.95)
Total (95% CI) 31 33 100.0% 0.92 [0.76, 1.12]
Total events 26 30
Heterogeneity: Tau² = 0.00; Chi² = 0.83, df = 1 (P = 0.36); I² = 0%
Test for overall effect: Z = 0.83 (P = 0.41)
Test for subgroup differences: Chi² = 0.83, df = 1 (P = 0.36), I² = 0%
0.1 0.2 0.5 1 2 5 10
Favours 5 - ASA Favours 5 - ASA + Cholest

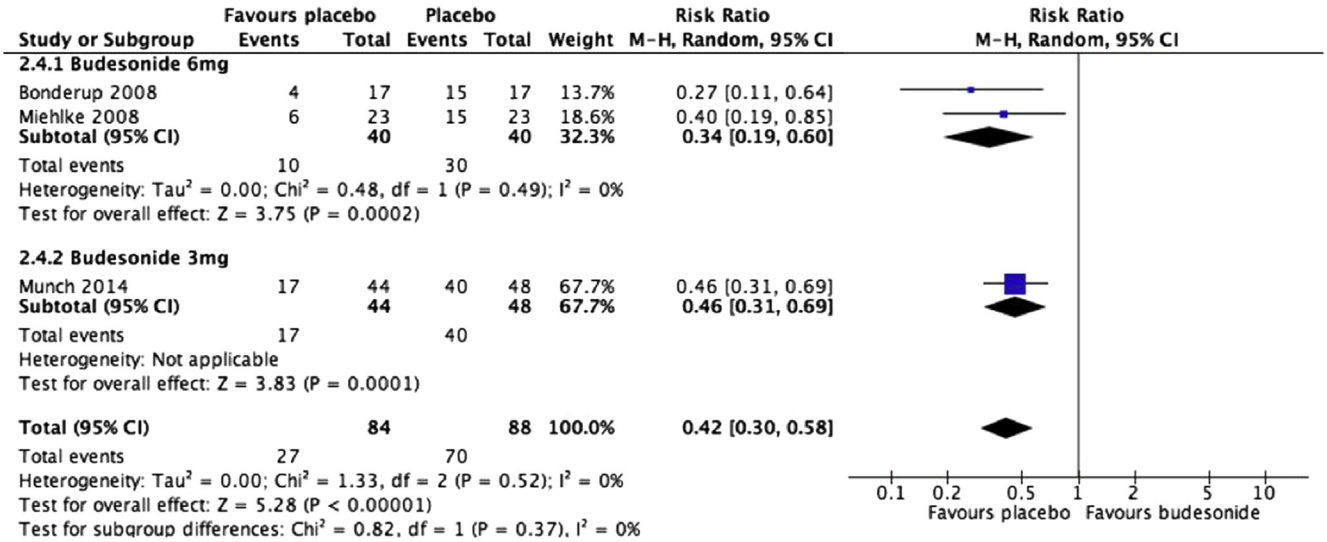

Experimental
Control
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Calabrese 2007 2 33 0 31 100.0% 4.71 [0.23, 94.31]
Total (95% CI) 33 31 100.0% 4.71 [0.23, 94.31]
Total events 2 0
Heterogeneity: Not applicable
Test for overall effect: Z = 1.01 (P = 0.31)
0.01 0.1 1 10 100
Favours Mesalazine + Chol Favours Mesalazine


Boswellia serrata
Placebo
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
4.1.1 Collagenous colitis
Madisch 2007 7 16 4 15 100.0% 2.14 [0.47, 9.70]
Subtotal (95% CI) 16 15 100.0% 2.14 [0.47, 9.70]
Total events 7 4
Heterogeneity: Not applicable
Test for overall effect: Z = 0.99 (P = 0.32)
4.1.2 Lymphocytic colitis
Subtotal (95% CI) 0 0 Not estimable
Total events 0 0
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Total (95% CI) 16 15 100.0% 2.14 [0.47, 9.70]
Total events 7 4
Heterogeneity: Not applicable
Test for overall effect: Z = 0.99 (P = 0.32)
Test for subgroup differences: Not applicable
0.01 0.1 1 10 100
Favours placebo Favours boswellia


Beclometasone 5
Mesalazine
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
9.1.1 Beclometasone 5mg
Latella 2010 15 18 13 15 53.2% 0.96 [0.72, 1.28]
Subtotal (95% CI) 18 15 53.2% 0.96 [0.72, 1.28]
Total events 15 13
Heterogeneity: Not applicable
Test for overall effect: Z = 0.27 (P = 0.79)
9.1.2 Beclometasone 10mg
Latella 2010 11 13 13 15 46.8% 0.98 [0.72, 1.32]
Subtotal (95% CI) 13 15 46.8% 0.98 [0.72, 1.32]
Total events 11 13
Heterogeneity: Not applicable
Test for overall effect: Z = 0.15 (P = 0.88)
Total (95% CI) 31 30 100.0% 0.97 [0.79, 1.19]
Total events 26 26
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.94); I² = 0%
Test for overall effect: Z = 0.30 (P = 0.76)
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.94), I² = 0%
0.5 0.7 1 1.5 2
Favours Beclometasone Favours Mesalazine

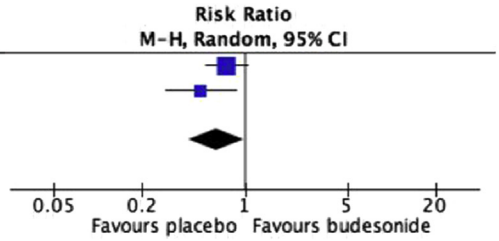

Probiotics
Placebo
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
5.1.1 Collagenous colitis
Wildt 2006 6 21 1 8 100.0% 2.29 [0.32, 16.13]
Subtotal (95% CI) 21 8 100.0% 2.29 [0.32, 16.13]
Total events 6 1
Heterogeneity: Not applicable
Test for overall effect: Z = 0.83 (P = 0.41)
5.1.2 Lymphocytic colitis
Subtotal (95% CI) 0 0 Not estimable
Total events 0 0
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Total (95% CI) 21 8 100.0% 2.29 [0.32, 16.13]
Total events 6 1
Heterogeneity: Not applicable
Test for overall effect: Z = 0.83 (P = 0.41)
Test for subgroup differences: Not applicable
0.01 0.1 1 10 100
Favours placebo Favours probiotics


Boswellia serrata
Placebo
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
4.2.1 Collagenous colitis
Madisch 2007 2 16 1 15 100.0% 1.88 [0.19, 18.60]
Subtotal (95% CI) 16 15 100.0% 1.88 [0.19, 18.60]
Total events 2 1
Heterogeneity: Not applicable
Test for overall effect: Z = 0.54 (P = 0.59)
Total (95% CI) 16 15 100.0% 1.88 [0.19, 18.60]
Total events 2 1
Heterogeneity: Not applicable
Test for overall effect: Z = 0.54 (P = 0.59)
Test for subgroup differences: Not applicable
0.01 0.1 1 10 100
Favours Boswellia Favours Placebo


Favours placebo
Placebo
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
2.4.1 Budesonide 6mg
Bonderup 2008 4 17 15 17 13.7% 0.27 [0.11, 0.64]
Miehlke 2008 6 23 15 23 18.6% 0.40 [0.19, 0.85]
Subtotal (95% CI) 40 40 32.3% 0.34 [0.19, 0.60]
Total events 10 30
Heterogeneity: Tau² = 0.00; Chi² = 0.48, df = 1 (P = 0.49); I² = 0%
Test for overall effect: Z = 3.75 (P = 0.0002)
2.4.2 Budesonide 3mg
Munch 2014 17 44 40 48 67.7% 0.46 [0.31, 0.69]
Subtotal (95% CI) 44 48 67.7% 0.46 [0.31, 0.69]
Total events 17 40
Heterogeneity: Not applicable
Test for overall effect: Z = 3.83 (P = 0.0001)
Total (95% CI) 84 88 100.0% 0.42 [0.30, 0.58]
Total events 27 70
Heterogeneity: Tau² = 0.00; Chi² = 1.33, df = 2 (P = 0.52); I² = 0%
Test for overall effect: Z = 5.28 (P < 0.00001)
Test for subgroup differences: Chi² = 0.82, df = 1 (P = 0.37), I² = 0%
0.1 0.2 0.5 1 2 5 10
Favours placebo Favours budesonide

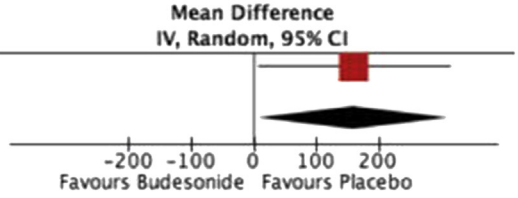
Study or Subgroup	Budesonide Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bonderup 2008	12	17	16	17	62.6%	0.75 [0.54, 1.04]
Miehlke 2008	9	23	18	23	37.4%	0.50 [0.29, 0.87]
Total (95% CI)		**40**		**40**	**100.0%**	**0.64 [0.42, 0.99]**
Total events	21		34			

Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 1.90$, df = 1 (P = 0.17); $I^2 = 47\%$
Test for overall effect: Z = 2.01 (P = 0.04)



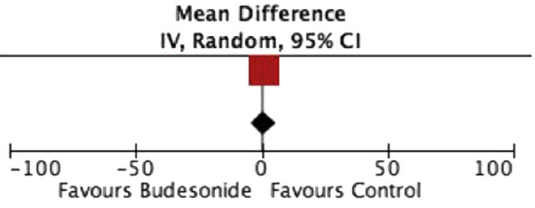
Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Random, 95% CI
Bonderup 2008	161	78.15	100.0%	161.00 [7.83, 314.17]
Total (95% CI)			**100.0%**	**161.00 [7.83, 314.17]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.06 (P = 0.04)



Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Random, 95% CI
Bonderup 2008	1	2.6	100.0%	1.00 [-4.10, 6.10]
Total (95% CI)			**100.0%**	**1.00 [-4.10, 6.10]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.38 (P = 0.70)



Study or Subgroup	Budesonide Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.6.1 Budesonide 6mg						
Bonderup 2008	5	17	8	17	33.7%	0.63 [0.26, 1.53]
Miehlke 2008	8	23	8	23	42.9%	1.00 [0.45, 2.21]
Subtotal (95% CI)		**40**		**40**	**76.6%**	**0.81 [0.45, 1.47]**
Total events	13		16			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.60$, df = 1 (P = 0.44); $I^2 = 0\%$
Test for overall effect: Z = 0.68 (P = 0.49)

2.6.2 Budesonide 3mg						
Munch 2014	7	44	5	48	23.4%	1.53 [0.52, 4.46]
Subtotal (95% CI)		**44**		**48**	**23.4%**	**1.53 [0.52, 4.46]**
Total events	7		5			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.77 (P = 0.44)

Total (95% CI)		**84**		**88**	**100.0%**	**0.94 [0.56, 1.58]**
Total events	20		21			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.63$, df = 2 (P = 0.44); $I^2 = 0\%$
Test for overall effect: Z = 0.23 (P = 0.82)
Test for subgroup differences: $Chi^2 = 1.02$, df = 1 (P = 0.31), $I^2 = 1.7\%$