An Evidence-Based Systematic Review on Medical Therapies for Inflammatory Bowel Disease

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Crohn's disease (CD) and ulcerative colitis (UC) are chronic inflammatory disorders of the gastrointestinal tract. Collectively they are termed inflammatory bowel disease (IBD) and it is estimated that 1.5 million Americans (1) suffer from UC and CD. Their etiologies are unknown, although both are thought to arise from a disordered immune response to the gut contents in genetically predisposed individuals (1). The characteristics of the inflammatory response are different, with CD typically causing transmural inflammation and occasionally associated with granulomas, whereas in UC the inflammation is usually confined to the mucosa. Both UC and CD exhibit a relapsing and remitting course and there is a significant, often dramatic, reduction in quality of life during exacerbations of the disease (2). This has an impact on psychological health, with active IBD patients experiencing greater levels of distress and feelings of lack of sense of self-control compared with the normal population and patients with inactive IBD (3,4).

Extrapolation from US administrative claims databases suggests that IBD is responsible for 2.3 million physician visits (5), 180,000 hospital admissions (6), and costs $6.3 billion (7) annually. There have been recent guidelines on the management of both UC (8) and CD (9) that direct the clinician on diagnosis and treatment. Approximately 33% of the cost of IBD is due to medical therapy (7), and given the substantial clinical burden and economic cost of IBD it is important to establish the effectiveness of current medical therapies in both UC and CD. Although there have been several systematic reviews on the efficacy of therapy (10,11), this is a rapidly changing field and there is a need for a comprehensive review of the literature. The American College of Gastroenterology IBD Task Force developed a protocol for systematically reviewing the data on currently available therapies for UC and CD, both in inducing remission and in preventing relapse of the disease. Evidence-based statements were then developed and the strength of recommendation for each was graded according to standard criteria.

Section 1 Epidemiology of IBD

Multiple studies have evaluated the epidemiology of IBD in adults from various geographic regions; most studies are from Western countries, where the incidence of IBD is highest, the existence of comprehensive databases is more common, and identification of adequately sized populations is easier (12). We have reviewed the literature on population estimates of CD and UC incidence over the past 20 years. Where there was more than one study we have taken the study with the largest population, which is most representative of the country. In the case of two studies of similar size we have evaluated the most recent data. We identified 35 studies (13–47) that provided data on incidence of CD and/or UC. In the US estimates of CD, incidence varies between 6 (13) and 8 (14) per 100,000, with a prevalence of 100 (13) to 200 (12) per 100,000. For UC, the incidence in the United States ranges between 9 (14) and 12 (13), with a prevalence of 205 (13) to 240 (12) per 100,000. Incidence estimates for other countries are given in **Table 1**. Geographical variation suggests that CD has a higher incidence in industrialized countries and higher rates in the West than in the East (**Figure 1a**). There also appears to be a North–South gradient with a strong correlation between degrees latitude and CD incidence when the Western Hemisphere and Western Europe are evaluated (**Figure 2a**). This North–South gradient also exists within an individual country, with CD being less common in the southern United States (12) and in the south of France (32). CD

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Table 1. Incidence of CD and UC by country

Country	CD incidence/10^5 (ref)	UC incidence/10^5 (ref)
North America		
Canada	13.4 (20)	11.8 (20)
US (California)	6.3 (13)	12.0 (13)
US (Minnesota)	7.9 (14)	8.8 (14)
Europe		
Iceland	5.5 (22)	16.5 (22)
Denmark	10.1 (27)	16.8 (32)
Sweden	8.9 (30)	
UK	8.0 (33)	11.0 (33)
Germany	6.6 (34)	3.9 (34)
Netherlands	6.9 (36)	10.0 (36)
Belgium	5.5 (39)	3.5 (39)
France	8.2 (32)	7.2 (32)
Italy	3.4 (40)	7.0 (40)
Spain	7.5 (35)	9.1 (35)
Portugal	3.7 (17)	5.5 (17)
Greece	2.2 (24)	3.7 (24)
Bosnia and Herzegovina	4.15 (23)	
Romania	0.5 (26)	0.97 (26)
Croatia	5.7 (28)	5.9 (28)
Hungary	4.68 (29)	11.01 (29)
Czech Republic	1.5 (28)	1.5 (28)
Poland	0.1 (28)	1.8 (28)
Estonia	1.4 (37)	1.7 (37)
Central/South America and Caribbean		
French West Indies	1.9 (15)	2.44 (15)
Barbados	0.61 (19)	3.32 (19)
Puerto Rico	1.96 (21)	3.32 (21)
Brazil	3.5 (41)	4.48 (41)
Middle East		
Lebanon	1.4 (16)	4.1 (16)
Israel	4.3 (17)	8.5 (17)
Saudi Arabia	1.66 (18)	
Oman		1.35 (47)
Kuwait		2.8 (38)
Turkey		0.74 (45)
Asia		
China (Hong Kong)	1.0 (31)	
China	0.28 (44)	
South Korea	1.34 (42)	3.08 (42)
Japan	1.2 (43)	
Singapore	3.6 (38)	6.0 (38)
India		6.02 (46)
Oceania		
New Zealand	16.5 (25)	7.6 (25)

CD, Crohn's disease; UC, ulcerative colitis.

also has a high incidence in New Zealand, suggesting that the disease may get more common the further the geographical location is from the equator. There may therefore be an environmental agent predisposing to CD that is more prevalent in a more temperate climate. A similar epidemiological pattern exists for UC (**Figure 1b**), although the North–South gradient is not as pronounced (**Figure 2b**).

CD has been increasing in incidence over time in most countries (**Figure 3a**), although it seems to have reached a plateau in the United States (14), Sweden (30), and the UK (48). Incidence rates are also increasing over time for UC, although the degree of change is less significant (**Figure 3b**). Again, rates appear to have reached a steady state in the United States (14). This could be due to wider availability of diagnostic tests such as colonoscopy, but is more likely to represent a change in the environment that predisposes subjects to develop CD. The nature of this environmental agent or agents remains unclear.

The peak age of onset for CD has consistently been reported at around 15–30 years (49), although the disease can be diagnosed at any age. The first diagnosis of UC also occurs most commonly at 15–30 years of age and then the incidence plateaus. Some Western studies suggest that CD is more common in women, with a ratio of around 3:2 (48), and a sex hormone influence on risk of CD is supported by a meta-analysis showing an association between oral contraceptive pill use and CD in women (50). However, the increased risk in women is not a consistent finding in the West (30), and in the East CD may be more common in men (43). The incidence of UC does not have a consistent sex difference (20). Caucasians are reported to have a higher risk of IBD than other races, but a systematic review suggests that the incidence in African Americans is approaching that of Whites, and that in Asian Americans and Hispanics the incidence rate is likely higher than was previously thought (51). Other epidemiologic risk factors include cigarette smoking and appendectomy. Systematic review data (52) confirm that smoking is a risk factor for CD (9 studies, odds ratio (OR) = 1.76; 95% confidence interval (CI): 1.40–2.22) but is protective for UC (13 studies, OR = 0.58; 95% CI: 0.45–0.75). Passive smoking data are less clear, with one study suggesting no impact on either CD or UC (53) and another study reporting an increased risk of CD with passive smoking in children under the age of 12 (54). A meta-analysis (55) reported that appendectomy was significantly associated with risk of CD, but there was

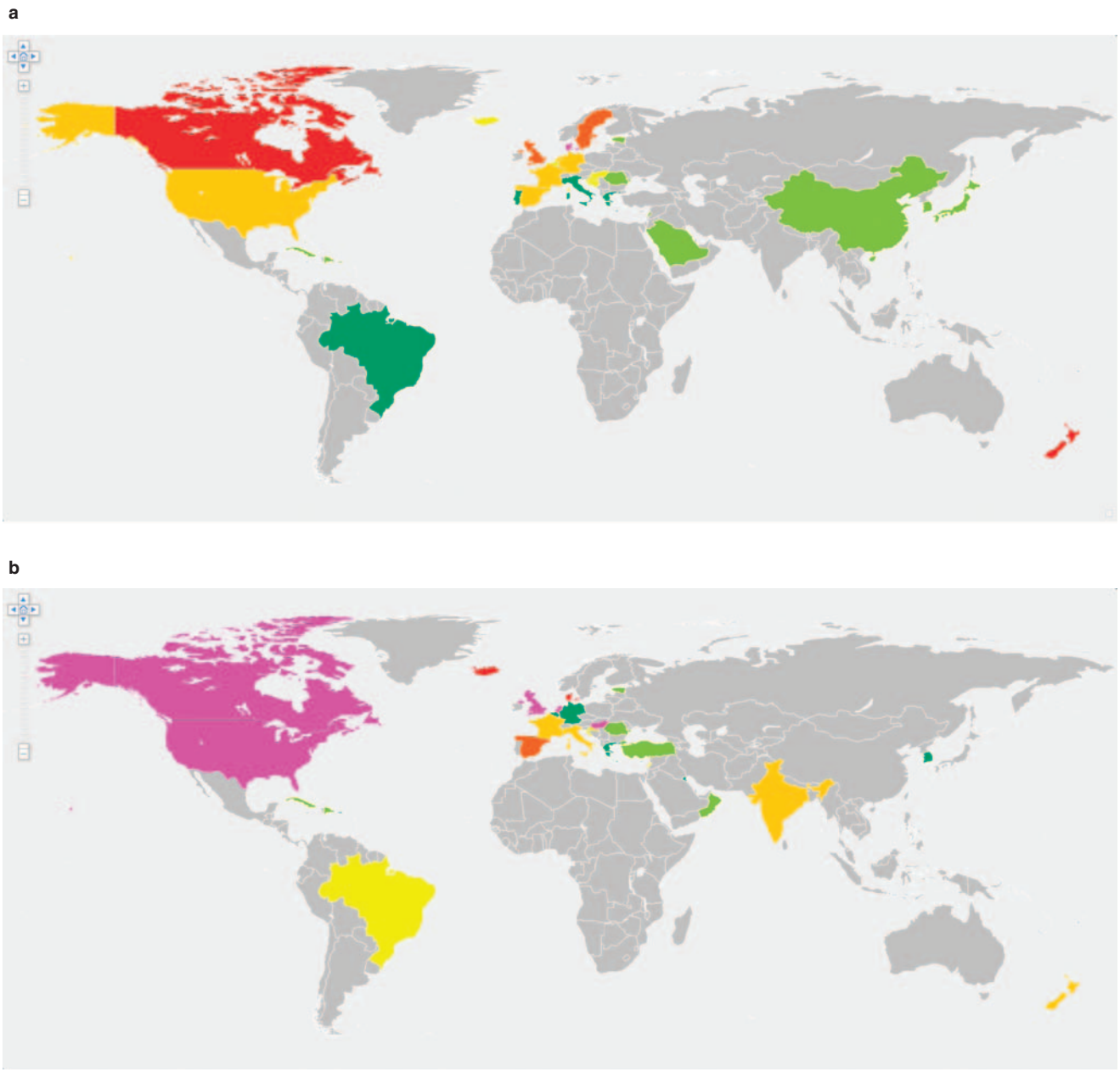

Figure 1. Global variation in incidence rates for inflammatory bowel disease. (**a**) Incidence rates for Crohn's disease. (**b**) Incidence rates for ulcerative colitis. Key: gray = no data, light green 0–1.9, dark green 2–3.9, yellow 4–5.9, light orange 6–7.9, dark orange 8–9.9, pink 10–12, red >12 per 100,000 population.

substantial heterogeneity in the data. When the reasons for this were explored, it was found that risk of CD was particularly related to the first year after the operation and gradually decreased over the following 5 years. After this period appendectomy was not significantly associated with risk of CD. This raises the possibility that the apparent association between CD and appendectomy is due to incipient CD being misdiagnosed as appendicitis. In contrast, a meta-analysis (56) of the association between appendectomy and UC identified 13 case–control studies and found a strong and consistent protective effect (OR = 0.31; 95% CI: 0.25–0.38), with no significant heterogeneity between results.

The rapidly increasing rates of CD and UC seen over the past 20 years point to environmental factors being important in the cause of IBD. Nevertheless, most diseases are due to the interplay between genes and the environment and IBD is no exception. Identical twin studies have shown a concordance rate of 50–60% (57,58). Since the description of the association between NOD2 polymorphisms and CD (59), there has been a plethora of genes

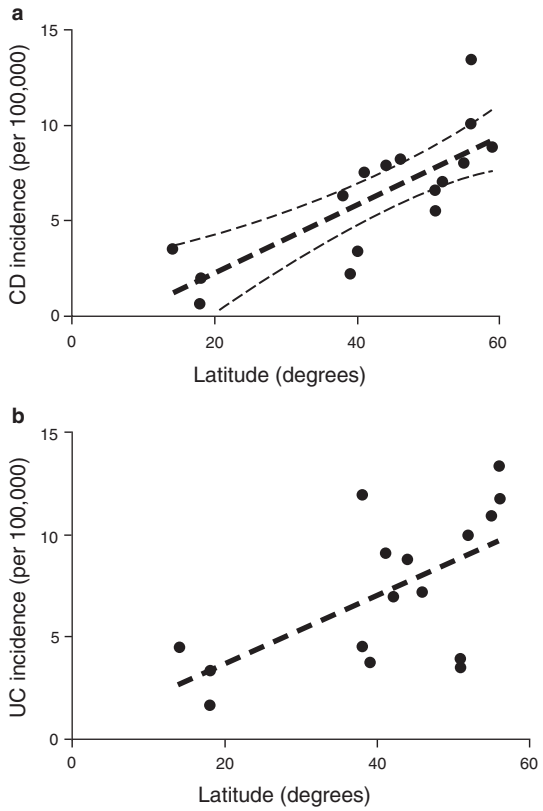

Figure 2. Variation in inflammatory bowel disease incidence rates with degrees latitude from the equator. (**a**) Variation in Crohn's disease incidence rates. R^2=0.62, P=0.0002. (**b**) Variation in ulcerative colitis incidence rates. R^2=0.38, P=0.011.

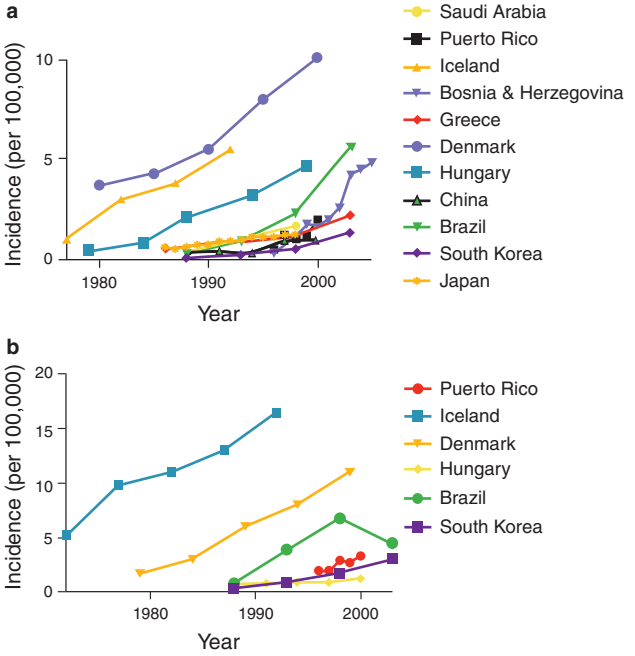

Figure 3. Changes in inflammatory bowel disease incidence rates over time. (**a**) Incidence of Crohn's disease over time. (**b**) Incidence of ulcerative colitis over time.

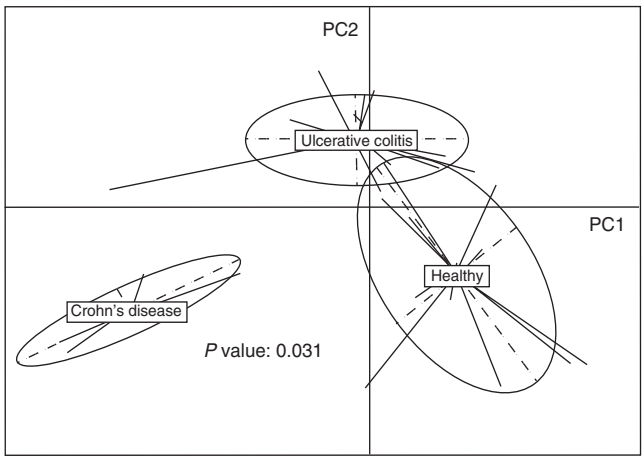

Figure 4. Gut microbiome in Crohn's disease, ulcerative colitis, and healthy subjects (reproduced with permission from ref. (63)).

linked to the increased risk of IBD. Most of these genes relate to immune system function. CD is associated with genes that regulate the innate immune system (NOD2, ATG16L1, IRGM), involved in the interleukin-23/Th17 pathway (IL23R, IL12B, STAT3, CCR6), as well as other immune-related genes (e.g., PTGER4—prostaglandin E receptor 4, PTPN2—T-cell protein tyrosine phosphatase, and MST1—macrophage stimulating 1) (1). UC is also associated with genes involved in the interleukin 23/Th17 pathway (IL23R, IL12B, STAT3), although it has not been associated with genes regulating the innate immune system (1). UC has also been shown to be associated with interleukin-10 and interferon-γ genes (1).

Although those with certain immune function predispositions are more likely to develop IBD, the environmental antigen that triggers the aberrant immune response remains unclear. The most likely candidate may reside within the gut microbiome. Human gut bacteria outnumber human somatic cells by at least 10-fold (60). Perturbation of the gut flora has been associated with an increased risk of IBD in two population-based studies from the United Kingdom (61) and Denmark (62). These studies (61,62) involved over 132,000 subjects, and both reported a two-fold risk of developing IBD even if those diagnosed within 1 year of the infection were excluded (to minimize the diagnostic bias as the explanation for the association). The risk seemed to be similar for UC and CD and for *Salmonella* and *Campylobacter* infections. There is a risk of case ascertainment bias in these studies, as subjects who are known to have these infections are likely to get more follow-up investigations than those who do not have these infections. The Metagenomics of the Human Intestinal Tract Consortium has obtained fecal samples from 124 Danish and Spanish subjects and sequenced their gut flora (63). Microbial genes in these samples were 150-fold greater than the human genome and over 99% were bacterial. This group found that UC, CD, and healthy controls all had distinct bacterial patterns (63) (**Figure 4**). CD patients had a less diverse microbial flora and although the number of patients evaluated was small, this

was consistent with a previous study (64). Whether this is the cause or consequence of IBD cannot be determined from this type of analysis. However, a prospective cohort study is ongoing to evaluate whether differences in gut flora predispose to the development of CD (http://www.gemproject.ca/home).

Dietary factors are also associated with the emergence of IBD, particularly in countries where industrialization has led to a change in eating patterns and types of foods consumed. An increased intake of refined sugar has been consistently identified as significantly associated with CD (65–68). A prospective cohort study (69) carefully assessing the dietary habits of 67,500 French middle-aged women over 10 years has found that dietary protein, particularly from meat and fish, is associated with a threefold increase in risk of IBD when the highest tertile of intake was compared with the lowest. The risk seemed to be similar for UC and CD (69). It is possible that the food consumed could have a direct antigenic stimulus to the immune system, but it is more likely that changes in dietary habits have important implications for the composition of the gut microbiome. An increase in refined sugar, decrease in complex carbohydrates, and increase in animal protein intake might cause shift in gut flora, which could affect the incidence of IBD.

The "hygiene hypothesis" has been proposed to explain the interaction between the immune system and the change in environment in industrialized countries. The hypothesis was proposed to explain the rise in allergic disorders seen in developed nations (70). The zeal to assure a clean environment may have led to a lack of exposure to certain infectious illnesses, particularly in early childhood, and this could lead to a faulty regulation of the Th1/Th2 components of the immune system. There could be excess activity of the Th2 system, which is important in many atopic conditions such as eczema, asthma, and food allergy, or an overexpression of the Th1 system, which is important in CD (71). An alternative explanation for the hygiene hypothesis is that, rather than the loss of contact with potentially injurious organisms that can induce immunological tolerance within the intestinal tract, there is a loss of saprophytic microorganisms that can help in the development of regulatory T cells. This could be the underlying explanation for why risk of IBD is associated with increasing socioeconomic status (72,73) and with urban vs. rural settings (74,75). Certainly there seems to be a fairly consistent association with increased risk of IBD in those living in a cleaner environment (73). However, the hygiene hypothesis is far from proven as the explanation for the increased incidence of IBD in industrialized nations (76). Unraveling any impact of childhood living conditions on the immune system with changes in the gut microbiome is extremely challenging. Although the hygiene hypothesis is interesting as a possible explanation for the rise of IBD in developed countries, the main message from these data is that our understanding of the pathogenesis of these disorders will be achieved through further study of both the immune system and the gut flora (77). Therapies that modulate the immune system have been the current mainstay of IBD therapy to date, but therapies that modulate the gut flora may prove to be quite fruitful in treating IBD.

Section 2 Methodology of the ACG Task Force on medical therapies for IBD

There are a variety of medical therapies available to treat both UC and CD, including 5-aminosalicylic acid (5-ASA) drugs, corticosteroids, immunosuppressive agents, biological therapies, and antibiotics. These agents can heal active disease, prevent relapse, and improve the quality of life (78,79), but the relative efficacy of these competing therapies is unclear. There have been a number of systematic reviews (10,11,80–96) that have evaluated randomized controlled trials (RCTs) of these interventions, but some need updating and some used end points that are poorly defined (e.g., "response to therapy"). Furthermore, we have shown that errors were made in identifying RCTs, assessing eligibility, and extracting data in all previous systematic reviews of irritable bowel syndrome (IBS) (97) when evaluating the evidence for an updated ACG monograph on medical therapies for IBS (98). It is possible that similar errors have been made in some systematic reviews of IBD therapies. We therefore completed a series of systematic reviews evaluating the efficacy of medical therapies for CD and UC in inducing remission and preventing relapse using a similar methodology to the previous ACG monograph on IBS management (98).

Systematic review methodology

Full details of the methodology and results of the systematic reviews are given in individual papers that accompany this monograph (99–104). Only parallel-group RCTs or the first phase of crossover randomized trials were eligible for inclusion in the review. Studies needed to have evaluated adult patients with either active or quiescent CD or UC.

The following interventions were considered:

(a) Oral 5-ASA drugs (e.g., sulfasalazine, mesalamine)
(b) Oral traditional corticosteroids (e.g., prednisone or prednisolone)
(c) Oral budesonide
(d) Immunosuppressive therapy (e.g., azathioprine, 6-mercaptopurine (6-MP), methotrexate)
(e) Biological therapies (e.g., infliximab, adalimumab, etanercept, certolizumab)
(f) Antibiotic therapy (e.g., antimycobacterial drugs, metronidazole)

These interventions were compared with placebo or with no intervention. The minimum duration of therapy was 14 days for treatment of active disease and 6 months for prevention of relapse, and any dose of drug was considered eligible.

Trials evaluating medical therapy in *active* CD were included if they reported evidence of clinical remission or healing of fistula as an outcome. Remission was defined according to a prospectively agreed hierarchy, and in the event that more than one outcome was reported the outcome that was most stringent according to our protocol was selected. The hierarchy agreed among the group was as follows:

(a) Crohn's Disease Activity Index (CDAI) <150 (or other validated index)

(b) Endoscopic evidence of complete remission (most stringent definition available)
(c) Clinical assessment of complete remission
(d) Other author-defined definition of remission

Trials evaluating medical therapy in *quiescent* CD were included if they reported evidence of disease relapse as an outcome. CD relapse was defined according to the following hierarchy:

(a) CDAI > 150
(b) Endoscopic/radiological evidence of relapse (most stringent definition available)
(c) Other CDAI cut-off to define relapse
(d) Clinical assessment of relapse
(e) Other author-defined definition of relapse

Again, in studies that reported one outcome, we chose the most stringent definition according to this predefined hierarchy.

Trials evaluating medical therapy in *active* UC were included if they reported evidence of clinical remission as an outcome according to the following hierarchy:

(a) Endoscopic evidence of complete remission (most stringent definition available)
(b) Clinical assessment of complete remission
(c) Recognized scoring system of complete remission (e.g., Truelove and Witt)
(d) Other author-defined definition of remission

Trials evaluating medical therapy in *quiescent* UC were included if they reported evidence of disease relapse as an outcome according to the following hierarchy:

(a) Endoscopic evidence of relapse (most stringent definition available)
(b) Clinical assessment of relapse
(c) Recognized scoring system of relapse (e.g., Truelove and Witt)
(d) Other author-defined definition of relapse

The hierarchy was different for UC and CD, reflecting the variation in approaches to assessing disease activity in these disorders. For UC a normal colonoscopy (or sigmoidoscopy) establishes disease remission, whereas this is not possible for CD if small-bowel involvement extends beyond the terminal ileum. Furthermore, the CDAI is more extensively validated than UC scoring systems.

Reports of adverse effects were also collected. These included overall numbers with any adverse event in each group, as well as individual adverse events such as upper gastrointestinal disturbances (nausea, vomiting), dermatological problems (rash), systemic effects (myalgia, fever, headache, lethargy), infection and neoplasia.

We recognize the stringency of these criteria and that the majority of clinical trials utilized alternative primary end points such as "clinical improvement" or "maintenance of clinical response" based on various reductions in the Crohn's Disease Activity Index or "reduction in fistula drainage" for CD (105) or Disease Activity Index for UC (106). Furthermore, we realize that the duration of placebo-controlled trials for induction and maintenance of IBD may be insufficient to evaluate longer-term risks of serious infections, immunological events, and malignancies. Thus, we attempted to interpret and analyze the more stringent, systematic remission and adverse-event data within the context of a broader clinical perspective.

Relevant RCTs were identified using MEDLINE (1966 to December 2010), EMBASE (1984 to December 2010), Cochrane Central Register of Controlled Trials (Issue 4, 2010), and the Cochrane Inflammatory Bowel Disease Group Specialized Trials Register. No language restrictions were used. We conducted a recursive search of the bibliography of all relevant trials and papers identified by the electronic search strategy and evaluated abstracts from DDW 2002–2010 and UEGW 2002–2010.

Each potentially eligible paper was evaluated by two independent investigators according to pre-stated eligibility criteria, and where disagreements occurred the opinion of a third investigator was obtained. Papers that were not eligible are outlined in the **Supplementary Appendix** online. Each eligible study was evaluated for seven components of risk of bias as described in the Cochrane handbook (107), including method of randomization, concealment of allocation, and implementation of masking. Data were extracted on specially developed electronic forms by two independent reviewers and any discrepancy was resolved by consensus.

Analyses were conducted separately for CD, UC, treatment of active disease, and prevention of relapse. Each drug class was compared with placebo. The last time point of assessment was used for analysis. For trials that evaluated treatment of active disease, benefit was expressed in terms of the relative risk (RR) of remaining with active disease (with 95% CIs) as the summary outcome statistic, while trials that assessed prevention or relapse were expressed in terms of the RR of relapse. Intention-to-treat data were used, with any drop-outs/withdrawals from the randomized groups being assumed to be treatment failures. Data were synthesized using a fixed-effects model, but if significant heterogeneity was found ($I^2 > 20\%$ and/or chi-squared $P > 0.15$) a random-effects model (108) was used. Adverse effects were summarized with RRs, comparing the incidence rates of the (as well as overall proportion with) adverse effect(s). Number needed to treat (NNT) and number needed to harm (NNH) were calculated using the following formula:

$$NNT = \frac{10}{RRR \times BR}$$

(RRR = relative risk reduction, BR = baseline risk).

This was checked by inversing the pooled risk difference from the meta-analysis.

Funnel plots were produced for the principal outcome for each comparison, and Egger's test (109) of funnel plot asymmetry was used, to investigate whether publication or other bias may have adversely affected the results.

Heterogeneity was assessed using χ^2 statistic and I^2. A value of $I^2 > 20\%$ was considered to indicate heterogeneity and the reasons were explored using subgroup analyses.

Evaluating the evidence

The American College of Gastroenterology Task Force on IBD was mainly selected based on their expertise in the epidemiology and therapy of IBD. The Chair of the Task Force (NJT) and the systematic review lead (PM), however, did not have specific expertise in IBD. This was intentional, so that a different perspective on the data might be obtained. The Task Force developed a protocol for the systematic reviews and were given the data prior to a face-to-face meeting. Statements were created based on the data provided, and the Task Force voted on these statements at the meeting using the jury method to develop consensus. The recommendation and the quality of evidence were voted on according to the GRADE system (110). A recommendation was considered strong if the benefits of therapy clearly outweighed the risks. The implication of this recommendation is that most patients would be prescribed this medication in a given clinical setting. For this reason, statements usually reflected the severity of disease where the intervention was appropriate. When this was not specified, the group felt the intervention was appropriate for all severities of disease. A weak recommendation was made if the benefits of treatment were more closely balanced with possible harms. In this circumstance, the decision as to whether to treat or not would depend on the clinical setting as well as the patient's values and preferences. The quality of the evidence was also graded as high, moderate, low and very low. The quality of the data was reduced if there were inconsistencies between trials, serious flaws in the trials that would increase the risk of bias, the effect measured was indirect, the estimate of the effect was imprecise and/or there was evidence of publication bias (110). The more limitations the evidence had, the lower the quality of evidence grade. The quality of the evidence was assessed using GRADEpro (http://www.gradeworkinggroup.org/), a software developed by the GRADE working group to facilitate evaluation of study quality. Assessment of the quality of evidence given by this software was reviewed by the group and voted on. In all cases there was unanimous agreement on the strength of recommendation and quality of evidence.

Section 3 Efficacy of 5-ASA therapies in IBD

5-ASA preparations are the first drugs to be used for UC and, like many medical discoveries, this was mainly discovered through serendipity. In the earlier part of the twentieth century, rheumatoid arthritis was thought to be due to a bacterial infection. Nanna Svartz, a Swedish professor, had the idea of combining the antibacterial properties of sulfonamides with the anti-inflammatory effects of salicylates. She combined a sulfapyridine moiety with the 5-ASA mesalamine using an azo bond to create sulfasalazine (SASP) and found that it did indeed improve the course of rheumatoid arthritis. In the early 1940s she noted that rheumatoid patients with coincidental UC also had a reduction in the severity of their bowel symptoms (111,112). The main limitation of SASP is that the sulfa-moiety induces dose-related and hypersensitivity side effects, including reduction in male fertility and the rare risk of blood dyscrasias (111). In the late 1970s UK researchers demonstrated that enemas containing 5-ASA were as efficacious as SASP at healing distal UC, but disease remained active with sulfapyridine (113). The beneficial effects of SASP on UC may therefore be due to the mesalamine moiety and this has led to other 5-ASA formulations and delivery systems (114,115). The precise mechanism of action of these drugs is unclear, but they are believed to act as anti-inflammatory agents, as they inhibit nuclear factor kappa B and chemoattractant leukotrienes and alter prostaglandin metabolism (116). The systematic availability of 5-ASA for all preparations is low (117), so adverse events are generally no greater than placebo in RCTs (99,100,118). However, there are very rare serious adverse effects of 5-ASA, such as interstitial nephritis, pancreatitis, pneumonitis, pericarditis, and hepatitis (119).

Section 3.1 Efficacy of 5-ASA therapies at inducing remission in active UC

5-ASA therapies are effective at inducing remission in mild-to-moderately-active UC

Recommendation: strong. Quality of evidence: moderate.

The systematic review is described in detail elsewhere (99). There were 11 RCTs evaluating 2,086 patients (120–130) that compared 5-ASA therapies vs. placebo. The majority of studies evaluated mesalamine and enrolled patients with mild-to-moderately-active UC. There was a strong effect in favor of 5-ASA therapy, with a NNT of 6 (95% CI: 5–8) (99), and with 40% of patients achieving remission overall in the active treatment group compared with 20% in the placebo group. The quality of the studies was graded as moderate, as there was some heterogeneity in the data, some funnel plot asymmetry suggesting publication bias or other small study effects and only two studies (121,123) having a low risk of bias. This would normally have made the quality of evidence low, but the grading was increased to moderate as the effect of 5-ASA on active UC was strong and the heterogeneity was largely explained by duration of therapy and definition of treatment success, with studies using the most stringent definition of success (mucosal healing) showing least heterogeneity. There was no difference in efficacy between the different 5-ASA preparations using either direct (data not shown) or indirect comparisons. There were two trials (120,121) involving 84 patients evaluating SASP with an NNT of 3 (95% CI: 2–10) and seven trials (123–128,130) involving 1,722 patients evaluating mesalamine with an NNT of 6 (95% CI: 5–9).

The optimum dose for 5-ASA therapies appears to be 2.4 g per day of mesalamine or equivalent, with no apparent benefit from increasing the dose. There were 10 trials involving 2,414 patients (124,126–128,130–135) that compared high-dose (defined as more than 2.5 g per day) with standard-dose (defined as 2–2.5 g per day) 5-ASA in treating active UC (99). The majority of patients had mild-to-moderate UC with treatment durations of 4–8 weeks. There was no statistically significant difference between the two groups, with 31% achieving remission in the high-dose compared with 30% in the standard-dose group. Clinicians may still wish to increase the dose of 5-ASA beyond 2.4 g per day in patients on maintenance therapy with a mild relapse of UC, but it is possible that any response obtained is due to the placebo effect or regression to the mean.

Section 3.2 Efficacy of 5-ASA therapies at preventing relapse in quiescent UC

5-ASA therapies are very effective at preventing relapse in quiescent UC
Recommendation: strong. Quality of evidence: high.

We identified 11 RCTs (136–146) with a total of 1,502 participants that compared 5-ASA vs. placebo in patients with quiescent UC (99). There was a strong effect in favor of 5-ASA with a NNT of 4 (95% CI: 3–7) (99). Overall 40% of patients on 5-ASA relapsed compared with 63% of patients taking placebo over 6–12 months. Although there were only two low-risk-of-bias trials (138,144), the quality of evidence was graded as high, as the effect of 5-ASA therapies in preventing UC relapse was strong and consistent between trials. There was some heterogeneity between studies, although this disappeared when only trials with the most rigorous of definitions of combined endoscopic and symptomatic remission were considered and the strong treatment effect remained (99). There was no evidence that efficacy varied between different preparations of 5-ASA either with direct or with indirect comparisons. There were four trials (136–138,140) involving 204 patients that evaluated SASP in quiescent UC with an NNT of 4 (95% CI: 3–7) and five trials (142–146) involving 1,096 patients that evaluated mesalamine with an NNT of 4 (95% CI: 3–8).

The optimum dose of 5-ASA required to prevent UC relapse appears to be the equivalent of mesalamine 2.0–2.4 g per day. Seven trials (147–153) have compared a daily dose of <2 g of 5-ASA with a dose of ≥ 2 g per day, and there was a statistically significant effect in favor of the higher dose of drug (NNT = 10; 95% CI: 5–33) (99). There was only one trial (147) that compared high- (>2.5 g per day) vs. standard-dose (2–2.5 g per day) 5-ASA in 113 quiescent UC patients and found no difference between the two doses. Current evidence therefore supports using the equivalent of mesalamine 2.4 g per day, although further research is needed to establish whether increasing the dose further would have any additional efficacy in preventing relapse.

Section 3.3 Efficacy of 5-ASA therapies at inducing remission in active CD

*5-ASA therapies are **not** recommended for inducing remission in active CD*
Recommendation: weak. Quality of evidence: low.

We conducted a systematic review of the literature for this monograph (100). This included data from the Crohn's II study (154) that had previously been unavailable. This identified six RCTs (154–159) involving 910 patients that compared 5-ASA with placebo. The majority of patients were treated for 6–17 weeks and had ileal or ileocolonic disease. There was a statistically significant effect of 5-ASA therapies when remission was used as the outcome, although the effect was modest, with 32% achieving remission in the 5-ASA group and 26% in the placebo group (NNT = 11; 95% CI: 6–100) (100). When SASP and mesalamine were evaluated separately, SASP had a borderline statistically significant result, while the effect of mesalamine was not statistically significant (100). A planned secondary analysis was remission or improvement in CD activity, and in this analysis mesalamine demonstrated a statistically significant effect in improving CD (NNT = 7; 95% CI: 4–20). Overall we recommended against using 5-ASA to induce remission in active CD. The reason for this was that the data were equivocal and this did not include the Crohn's III trial (160) involving 310 patients. Data on CD remission or improvement were not available for this trial, but the mean CDAI scores were similar between 5-ASA and placebo arms (160), suggesting that this trial is likely to be negative. Given that this trial represents 33% of all the patients in the meta-analysis, we felt that it was likely that 5-ASA was not effective at inducing remission in active CD. 5-ASA therapies are likely to be maximally effective in the colon and yet the majority of patients in the studies analyzed had either ileal or ileocolonic disease. The quality of evidence was categorized as low as there was only one trial (159) with low risk of bias, results were heterogeneous, and conclusions were different depending on what outcome measure was chosen.

Section 3.4 Efficacy of 5-ASA therapies at preventing relapse in quiescent CD

*5-ASA therapies are **not** recommended for preventing relapse in quiescent CD*
Recommendation: weak. Quality of evidence: low.

There were 16 RCTs (155,159,161–174) assessing 2,496 patients comparing 5-ASA with placebo or no therapy in quiescent CD for 6 to 48 months. The majority of patients had ileal or ileocolonic disease and there was no significant difference in relapse rates between the two groups. The overall relapse rate was 56% with 5-ASA therapies and 57% in the control group (100). In the 11 trials that evaluated mesalamine, there was a trend toward benefit of 5-ASA, but this was not statistically significant (100). There were only three trials (155,165,170) that had low risk of bias and a subgroup analysis of these studies suggested a small but statistically significant benefit of 5-ASA at preventing CD relapse (NNT = 13; 95% CI: 6–100). The evidence was of low quality as there was a paucity of trials that had a low risk of bias, there was unexplained heterogeneity between studies and conclusions differed in those with unclear vs. low risk of bias. Overall the evidence available was not sufficient to recommend 5-ASA therapies to prevent CD relapse. Unlike the recommendation of the Cochrane review (91), we concluded that further trials might be helpful in determining whether 5-ASA therapies have a role in colonic CD.

Section 4 Efficacy of corticosteroid therapies in IBD

Corticosteroids are another example of drugs that were first developed for rheumatoid arthritis that then were applied to IBD. Philip Hench and Edward Kendall from the Mayo clinic announced the development of "compound E" (175) that, when injected into a rheumatoid arthritis joint, allowed the patient a miraculous recovery. This wonder drug is today known as cortisone and the medical establishment greeted this discovery so

enthusiastically that Hench and Kendall were awarded the Nobel prize two years later (176). One of the first RCTs described in modern medicine evaluated the efficacy of cortisone in UC in 1954 (177). Since then corticosteroids have been widely used for acute exacerbations of UC and CD. As with any "wonder drug," initial enthusiasm gave way to a realization that these drugs had significant short-term adverse effects such as increased risk of infection (178–181) and psychiatric disorders and even more serious long-term consequences such as loss of bone mineral density and diabetes mellitus (182). This led to the development of budesonide that has an extensive first-pass metabolism, maximizing the amount of corticosteroid available locally to the distal ileum and proximal colon but minimizing the systemic availability (183,184).

Corticosteroids inhibit almost every aspect of the immune response through their interaction with glucocorticoid receptors in the nucleus. Corticosteroids inhibit expression of adhesion molecules and trafficking of inflammatory cells to target tissues including the intestine (185,186). Corticosteroids also induce apoptosis of activated lymphocytes and decrease inflammatory cytokine expression (187–189). There was no evidence of harm of standard corticosteroids vs. placebo in the systematic review (101), but the harmful effects of corticosteroids are well described (183). For this reason we only considered standard corticosteroids for the treatment of acute CD and UC and did not evaluate maintenance therapy (179). We did, however, evaluate maintenance therapy of CD with budesonide, as systemic adverse effects are lower with this preparation.

Section 4.1 Efficacy of corticosteroid therapies at inducing remission in active UC

Corticosteroid therapies are effective at inducing remission in active UC
Recommendation: strong. Quality of evidence: low.

A systematic review (101) performed for the monograph identified five RCTs (177,190–193) involving 445 patients. Corticosteroids were effective at inducing remission in active UC with a NNT of 3 (95% CI: 2–9) (101). Overall 46% achieved remission with corticosteroids in these trials compared with 21% in the placebo arm after 2–8 weeks. Most preparations of oral corticosteroid were more effective than placebo, with the exception of oral fluticasone, which is poorly absorbed and therefore acts mainly topically (190). Indeed, if corticosteroids that were thought to act mainly topically were excluded, there were three remaining trials (180,191,192) with a NNT = 2 (95% CI: 1.4–6). An additional study (194) also found intravenous corticosteroids to be successful at inducing remission, although this was not included in the meta-analysis due to the short duration of therapy and route of administration. Data available were not sufficient to evaluate the efficacy according to severity of disease. The quality of evidence was low as there were a relatively small number of patients studied and so the estimate of effect was imprecise. There was also heterogeneity between studies and only one trial (191) that had a low risk of bias although this trial reported the strongest treatment effect.

Section 4.2 Efficacy of corticosteroid therapies at inducing remission in active CD

Standard corticosteroids therapies are effective at inducing remission in active CD
Recommendation: strong. Quality of evidence: low.

We identified two RCTs (155,159) involving 267 patients that compared oral corticosteroids with placebo in active CD. Each trial reported a statistically significant effect in favor of corticosteroids, with results varying between a NNT = 2 (95% CI: 1.6–3) (159) and a NNT = 5 (95% CI: 3–14) (155). Overall 60% achieved remission with corticosteroid therapy compared with 31% in the placebo group. As the estimate of effect was so different and the number of patients studied was modest, this meant that when the two trials were combined the effect of corticosteroids was not statistically significantly different from placebo in a random effects model using RR. When risk difference was used as the summary statistic in the meta-analysis, there was a significant effect of corticosteroid (NNT = 3; 95% CI: 2–11). There were no trials evaluating intravenous therapy and data available were not sufficient to evaluate the efficacy according to severity of disease. The evidence quality was very low as there was a paucity of evidence, heterogeneity between the two studies and neither study was at low risk of bias. We did, however, make a strong recommendation that standard corticosteroids were effective in active CD as there is evidence that budesonide is more effective than placebo at inducing remission in CD and there is also evidence from RCTs that systemic corticosteroids are more effective than budesonide (see below).

Budesonide therapy is effective at inducing remission in mild-to-moderately-active CD
Recommendation: strong. Quality of evidence: low.

There were two RCTs (195,196) involving 458 patients that compared budesonide with placebo in active CD. Patients had terminal ileal and/or right-sided colonic disease. Budesonide was more effective than placebo at inducing remission with a NNT = 5 (95% CI: 3–9) (101). Overall 45% of CD patients achieved remission with budesonide compared with 24% on placebo. Both trials gave similar results with no heterogeneity between the two studies. However, the evidence quality was low as neither trial had a low risk of bias and the number of patients studied was modest.

Standard corticosteroids are more effective than budesonide at inducing remission in mild-to-moderately-active CD
Recommendation: weak. Quality of evidence: low

The systematic review (101) identified six trials (197–202) evaluating 669 patients that compared standard corticosteroids vs. budesonide in active CD. The majority of patients had terminal ileal or right-sided colonic disease. Trials evaluated treatment after 8–10 weeks, with 62% achieving remission in the standard corticosteroid group vs. 53% in the budesonide group. The NNT for standard corticosteroids over budesonide at inducing remission was 11 (95% CI: 6–50). Data on overall adverse events were only

provided by three trials with 274 patients in total (198,199,201). Sixty two percent of patients using standard corticosteroids had an adverse event believed to be associated with steroid use compared with 37% on budesonide. The number needed to harm was 4 (95% CI: 3–6). Hence budesonide was not quite as effective as standard corticosteroids at bringing active disease into remission but was less harmful. The recommendation was only weak, as the clinician would need to balance the modest extra benefit of treating with standard corticosteroids with the increased risk of short-term adverse events and thus the decision of which corticosteroid preparation to prescribe is likely to vary on a case-by-case basis. There was no heterogeneity between studies, but the grade of the evidence was considered low as the treatment effect was modest with wide CIs and there was no trial that had a low risk of bias.

Section 4.3 Efficacy of budesonide at preventing relapse in quiescent CD

*Budesonide is **not** recommended at preventing relapse in quiescent CD*

Recommendation: weak. Quality of evidence: low.

There were five trials (203–207) that evaluated 559 patients comparing budesonide with placebo at preventing relapse in quiescent CD. There was an effect in favor of budesonide, with 63% relapsing with active treatment and 70% with placebo, but this did not reach statistical significance (RR = 0.93; 95% CI: 0.83–1.04). Trials evaluated patients for 52 weeks and used 3–9 mg of budesonide daily. One trial that was not in this analysis specifically included patients with corticosteroid-dependent CD that had been weaned off corticosteroids in the 13 weeks prior to the start of the trial (208) and followed patients up for a further 13 weeks. The trial was excluded due to insufficient follow-up for a remission study, but it did show the strongest treatment effect, and when this study was added the results did reach statistical significance (NNT = 11; 95% CI: 6–50). Data on overall adverse events were provided by three trials (204–206). These trials evaluated 394 patients, with complaints of adverse events in the budesonide group of 53 vs. 52% for placebo. However, corticosteroid-associated adverse events were higher in budesonide-treated patients with an NNH of 6 (95% CI: 4–25). While budesonide has less systemic adverse events than systemic corticosteroids, there is still the risk of long-term corticosteroid-related problems. However, budesonide may be considered an alternative in patients who have become dependent on systemic corticosteroids. The grade of evidence was considered low, as there were no low-risk-of-bias trials and the estimate of treatment effect was uncertain.

Section 5 Efficacy of immunosuppressant therapies in IBD

During the same year that the first RCT of corticosteroids in UC was reported, there was also a description of the first successful live kidney transplant (209). This was made possible through the development of immunosuppressants such as the thiopurine analogs (6-MP and its pro-drug azathioprine), methotrexate, and the calcineurin inhibitors (cyclosporin and more recently tacrolimus). These drugs had already been used in inflammatory conditions once the medical community realized that the dramatic effects of corticosteroids were often transient or required long-term therapy with serious adverse consequences. Again, rheumatologists led the way with descriptions of the benefits of methotrexate on rheumatoid arthritis in the early 1950s (210). Gastroenterologists followed suit with case reports of azathioprine and 6-MP improving IBD (211–214). Although the mechanism of action differs between these three classes of medications, collectively they are referred to as immunosuppressants due to their direct or indirect effects on immune cell number or function. The specific role of immunosuppressants in IBD as induction agents and as maintenance therapy needs to be re-addressed, as systematic reviews assessing their efficacy have been limited by use of ambiguous end points (clinical response), vague search and inclusion criteria, or other potentially problematic methodologies. We therefore conducted an updated systematic review (102) of RCTs of azathioprine, 6-MP, methotrexate, tacrolimus, and cyclosporin compared with placebo with clear end points for induction of remission or maintenance of remission in UC and CD. Owing to the differences in their mechanism of action, we elected to perform separate analyses for thiopurines, methotrexate, and the calcineurin inhibitors (102).

Adverse effects are poorly described in randomized trials, which are also not the best design for determining rare but serious long-term complications. Observational data provide more information on adverse effects. Azathioprine and 6-MP are associated with nausea, allergic reactions, acute pancreatitis, hepatitis, increased risk of infection, malignancy, and bone marrow suppression (215). As bone marrow suppression can occur at any point during therapy, it is recommended that patients have regular blood counts to monitor for leucopenia. The adverse effects of methotrexate include hepatotoxicity, pneumonitis, increased risk of infection, malignancy, alopecia, stomatitis, and myelosuppression. Hepatotoxicity risk increases when the accumulated dose of methotrexate exceeds 1.5 g (215), but seems to be minimal at doses less than 5 g (216). The main adverse effect of cyclosporin and tacrolimus is renal toxicity and drug levels should be monitored (215). Other side effects include hypertension, hirsuitism, headache, opportunistic infections, seizures, and paresthesia (215).

Section 5.1 Efficacy of immunosuppressant therapies at inducing remission in active UC

*Azathioprine and 6-MP are **not** recommended for inducing remission in active UC*

Recommendation: weak. Quality of evidence: very low.

A systematic review of the literature (102) for this monograph revealed only two RCTs (217,218) evaluating 130 patients. Both RCTs (217,218) were negative, and although there was a trend to benefit in the meta-analysis this was not statistically significant. There was no heterogeneity between studies, but neither RCT had a low risk of bias. We felt azathioprine and 6-MP should not be generally used to induce remission in UC, but the recommendation was weak as it was recognized that only a small number of

patients had been enrolled in RCTs and results could change substantially with more information.

*Methotrexate is **not** recommended for inducing remission in active UC.*
Recommendation: weak. Quality of evidence: very low.

There was only one RCT (219) involving 67 patients with active UC. The trial had an unclear risk of bias and reported similar remission rates in placebo and methotrexate groups at 4 months.

IV cyclosporin is effective at improving symptoms in hospitalized patients with severely active UC not responding to corticosteroids. Tacrolimus is not recommended in mild-to-moderately active UC
Recommendation: weak. Quality of evidence: very low.

There was only one RCT (220) involving 20 participants with severely active hospitalized UC patients who were refractory to corticosteroid therapy. This trial compared IV cyclosporin 4 mg/kg for 7 days followed by oral cyclosporin vs. placebo. Remission rates were not provided, but there was a strong effect for "treatment response," with 9/11 patients in the cyclosporin group "responding" vs. 0/9 in the placebo group (NNT = 1.2 for "response"; 95% CI: 1–2). The end point used in this trial to define "response" was not standard and may not be clinically meaningful (221). Nevertheless, this is the only RCT that has specifically evaluated the severe UC group and we felt that although the data were weak, this is a possible alternative to colectomy in this patient group to be decided on a case-by-case basis. There was another RCT (222) that compared 4 mg vs. 2 mg/kg of IV cyclosporin in 73 severe UC patients. Approximately 85% of the patients responded in each group, although there was no placebo control. A further RCT (223) compared IV cyclosporin with IV corticosteroids in 30 severe UC patients. There were more responders in the cyclosporin group, but this did not reach statistical significance and remission rates were not given.

There was one RCT (224) evaluating 63 patients that compared oral tacrolimus (randomized to either 5–10 or 10–15 ng/ml trough levels) vs. placebo for 2 weeks in mild-to-moderate UC. There was a statistically significant effect in UC symptom improvement with a dose response (68% reporting an improvement in symptoms in the high-trough group), but no patient achieved UC remission. At 10 weeks of follow-up, similar numbers of patients were in remission in each group.

Section 5.2 Efficacy of immunosuppressant therapies at preventing relapse in quiescent UC

Azathioprine and 6-MP are effective at preventing relapse in quiescent UC.
Recommendation: weak. Quality of evidence: low.

The systematic review (102) identified three RCTs (217,218,225) evaluating 127 patients with quiescent UC and comparing azathioprine with placebo. All studies followed the patients up for 12 months and there was a significant reduction in relapse rate in the azathioprine group compared with placebo, with an NNT of 4 (95% CI: 2–10). The annual relapse rate was 39% in the azathioprine group compared with 66% in the placebo group. There was little heterogeneity between studies, but the evidence was graded as low as there were no low-risk-of-bias trials and the number of patients studied was small and so the CIs were wide. There was one additional RCT (226) that evaluated azathioprine withdrawal in 79 patients who had been maintained on this drug. This study found that relapse occurred in 36% of the patients who continued on azathioprine and in 59% of the patients in the placebo group after 1 year and concluded that thiopurines should be continued for at least 2 years if they appear to be effective.

*Methotrexate is **not** recommended for preventing relapse in quiescent UC.*
Recommendation: weak. Quality of evidence: low.

There were two RCTs (219,227) with a total of only 58 patients that compared methotrexate with placebo in quiescent UC. Both used oral methotrexate at a dose of 12.5 (219) or 15 mg (227) weekly and followed patients up for 9–12 months. Both trials were negative. The meta-analysis (102) demonstrated no statistically significant effect of methotrexate and no trend toward benefit. It is possible that subcutaneous or intramuscular methotrexate and/or a higher dose of 25 mg weekly may be more beneficial in preventing relapse in UC, but with the current evidence the effectiveness of this approach is unproven.

Section 5.3 Efficacy of immunosuppressant therapies at inducing remission in active CD

*Azathioprine and 6-MP are **not** recommended for inducing remission in active CD.*
Recommendation: weak. Quality of evidence: low.

The systematic review identified five RCTs (158,219,228–230) evaluating 380 patients and comparing azathioprine or 6-MP with placebo in active CD. Thiopurines were not statistically significantly better than placebo at inducing remission. One trial evaluated 6-MP (219) and none were at low risk of bias. There was only minor heterogeneity between studies, and all but one (228) was negative. Two RCTs (231,232) were excluded as they only reported symptom improvement rather than CD remission, but including these studies did not alter the result and both studies reported a lack of efficacy of azathioprine. One study (233) evaluating 6-MP in 83 patients was excluded, as it only reported on symptom improvement after 1 year. This trial was very positive in favor of 6-MP, but the relevance of this is unclear as data were only provided at 12 months.

Intramuscular methotrexate is effective at inducing remission in active CD.
Recommendation: weak. Quality of evidence: low.

There were only two RCTs (234,235) involving 193 patients that compared methotrexate with placebo in active CD. Overall there was a strong trend in favor of methotrexate, but this was not

statistically significant (RR of no remission = 0.82; 95% CI: 0.65–1.03, $P = 0.08$). Both trials had an unclear risk of bias. There was heterogeneity between studies, with one trial being positive (235) and another being completely negative (234). The negative study evaluated a lower dose of methotrexate and with an oral route of administration, which may lower the bioavailability (236). Overall, we placed greater emphasis on the larger positive RCT that gave the higher dose of drug intramuscularly. Of note, all patients in this study were given steroids and only those on > 20 mg/day prednisone showed a benefit of methotrexate over placebo. Given the paucity of the data, conclusions may change with more data, but, based on one well-done trial, the group gave a weak recommendation in favor of methotrexate to induce remission in CD.

*Cyclosporin is **not** recommended for inducing remission in active CD*
Recommendation: weak. Quality of evidence: very low.

There was only one trial (237) evaluating 64 patients with definitely active CD that compared cyclosporin with placebo. This trial had an unclear risk of bias and there was no statistically significant effect of active treatment. Another RCT (238) was excluded, as it only described symptom improvement as an outcome. This trial was positive, but currently evidence is not sufficient enough to recommend cyclosporin for active CD. There was another RCT (239) that evaluated tacrolimus vs. placebo for fistulas in CD. There was a statistically significant effect in favor of treatment, so this drug may be useful in treating CD fistulas.

Section 5.4 Efficacy of immunosuppressant therapies at preventing relapse in quiescent CD

Azathioprine and 6-MP are effective at preventing relapse in quiescent CD
Recommendation: weak. Quality of evidence: low.

The systematic review identified two RCTs (158,229) that compared azathioprine with placebo to prevent relapse in 198 patients with quiescent CD. There was one low-risk-of-bias trial (229) and a high degree of heterogeneity between the studies, with one positive (229) and one negative (158) trial. There was an additional trial (240) involving 22 patients that was also positive, but this was excluded as follow-up was only for 24 weeks. Inclusion of this trial did not alter the conclusions of the review. Overall, there was a trend toward benefit of azathioprine (NNT = 3; 95% CI: 1.3 to ∞), but this was not statistically significant. We gave a weak recommendation in favor of azathioprine/6-MP preventing CD relapse as the highest-quality trial was positive (229). There were also three RCTs (241–243) comparing continued azathioprine vs. withdrawal in 163 quiescent CD patients who had been successfully maintained on azathioprine. All of these trials suggested that relapse rates were higher in the placebo group compared with active treatment, with a pooled meta-analysis giving an NNT of 6 (95% CI: 3–14) (102). Another RCT (244) evaluating corticosteroid-dependent CD patients suggested that azathioprine was better than placebo at reducing the need for corticosteroid therapy. Finally there were two RCTs (245,246) of post-operative CD patients that suggested that azathioprine (245) or 6-MP (246) was superior to placebo at preventing post-operative recurrence.

Methotrexate is effective at preventing relapse in quiescent CD
Recommendation: weak. Quality of evidence: low.

There was one trial (247) that compared methotrexate with placebo in quiescent CD. This trial enrolled 76 patients and had an unclear risk of bias. Relapse rates were significantly lower in the methotrexate group (NNT = 4; 95% CI: 2–25). Another trial (248) evaluated methotrexate vs. placebo in 33 corticosteroid-dependent CD patients and found a trend toward lower relapse rates at 1 year as corticosteroids were withdrawn in the methotrexate group.

*Cyclosporin is **not** recommended for preventing relapse in quiescent CD*
Recommendation: weak. Quality of evidence: low.

We identified only one RCT (237) that evaluated cyclosporin vs. placebo to prevent CD recurrence in 118 patients. There was no statistically significant benefit of the active drug, with over 70% relapsing at 1 year in both groups.

Section 6 Efficacy of biological therapies in IBD

Anti-tumor necrosis factor alpha antibodies (anti-TNFα) were originally developed to improve survival from septicemia, but a phase II trial was negative (249). Feldman and Maini at the Kennedy Institute of Rheumatology in London highlighted the importance of cytokines in rheumatoid arthritis and managed to convince the pharmaceutical industry to give them some anti-TNFα antibodies for a small open-label clinical trial. Their results were impressive (250) and, as with previous rheumatological discoveries, they were soon used in IBD. Biological therapies were introduced into the United States, and subsequently the world market, for the treatment of CD in 1998 and eventually for the treatment of UC. These therapies have been incorporated into the recent guidelines for therapy of CD by the American College of Gastroenterology (9), American Gastroenterological Association (251), and The European Crohn's and Colitis Organization (252), and for UC by the American College of Gastroenterology (8). Such guidelines have been formulated on the basis of composite evidence from clinical trials, clinical series, and expert opinions. Previous meta-analyses have examined the benefit of these biological therapies in various situations, but none have synthesized all current available evidence for their role in IBD, and some have important limitations. We have therefore conducted a systematic review and meta-analysis of RCTs to estimate the efficacy and safety of these drugs in IBD as a whole (103) and focused on double-blind, placebo-controlled trials to minimize bias and heterogeneity between trials.

Overall there were no statistically significant differences between adverse events in patients randomized to biological therapy compared with placebo. However, as mentioned previously,

trials did not evaluate enough participants or provide sufficient follow-up to capture rare adverse events. Observational data suggest that patients taking biological therapy are at increased risk of opportunistic infection (182). This risk is not limited to biological therapy and is also seen with corticosteroids and immunosuppressant therapies (182). The risk of infection increases if these agents are used in combination. There are also concerns that the biological therapies may increase the risk of lymphoma (253). Again, these concerns also apply to immunosuppressant therapies and if there is an association with these drugs the absolute risk is low (254).

Section 6.1 Efficacy of biological therapies at inducing remission in active UC

Infliximab is effective at inducing remission in ambulatory patients with moderate-to-severely-active UC
Recommendation: strong. Quality of evidence: moderate.

The systematic review identified three RCTs (255,256) involving 771 patients that compared biological therapy with placebo in moderately active UC. All trials evaluated infliximab, with 6–8 weeks follow-up. Overall infliximab was more effective than placebo with a NNT = 4 (95% CI: 3–10) and 59% of patients achieved remission with active treatment (103). The grade of recommendation was strong given the marked treatment effect, but the quality of evidence was moderate, as trials had an uncertain risk of bias and there was unexplained heterogeneity between studies, with one small trial (255) reporting negative findings and two large trials reported in one paper (256) that were strongly positive.

Infliximab is effective at improving symptoms in hospitalized patients with severely active UC
Recommendation: weak. Quality of evidence: very low.

There were two RCTs (257,258) evaluating 56 patients that compared biological therapy with placebo in severely active UC. Infliximab was used in both trials and follow-up was done for 3 months. There was a trend for infliximab to be superior to placebo, but this was not statistically significant (NNT = 6; 95% CI: NNT 3 to NNH 50, $P = 0.08$). There was no heterogeneity between studies, but both trials had unclear risk of bias. We gave a weak recommendation in favor of infliximab for severely active UC despite the meta-analysis only showing a trend for benefit. This was because the drug is effective in moderately active UC and therefore the effect is likely to be seen in severe disease as well. The magnitude of effect is, however, uncertain, and the role in the management of severe UC needs to be decided on an individual patient basis.

Section 6.2 Efficacy of biological therapies at preventing relapse in quiescent UC

There were no trials performed to examine this issue. Two trials (256) reported relapse rates during extended follow-up (long-term induction). Data available were not sufficient to make a recommendation for biological therapy as maintenance therapy for UC and more studies are required.

Section 6.3 Efficacy of biological therapies at inducing remission in active CD

Anti-TNF antibody therapies (infliximab, adalimumab, and certolizumab pegol) are effective at inducing remission in ambulatory patients with moderate-to-severely-active CD
Recommendation: strong. Quality of evidence: moderate.

The systematic review (103) identified 10 RCTs (259–268) that evaluated 2,756 patients and compared anti-TNFα antibody therapy with placebo in active CD. Remission of CD was achieved in 28% of patients randomized to receive anti-TNFα antibodies at 4–12 weeks, compared with 19% of patients randomized to placebo. The NNT was 8 (95% CI: 6–17) (103). The impact of anti-TNFα antibody therapy on active CD appears modest compared with some other therapies described above, but from a clinical perspective the data are impressive considering the "refractoriness" of patients enrolled and the short duration used to assess the response. Clearly, more patients benefited based on the criteria used to assess clinical responses in these trials than achieved clinical remission. Further, based on maintenance of responder trials (see below), many patients may require longer duration of anti-TNF therapy to achieve remissions based on CDAI and, in addition, corticosteroid-free remissions were not assessed in these short-term trials. Based on all these factors, we gave a strong recommendation. The quality of evidence was moderate as there was heterogeneity in the data. This was unexplained but largely driven by one trial (260). Two trials (260,262) had a low risk of bias and both reported a statistically significant effect in favor of biologic therapy, with a similar or smaller NNT than the overall meta-analysis.

There was statistically significant heterogeneity between the three different types of anti-TNFα antibodies and this appeared to be driven by more positive results of infliximab and adalimumab compared with certolizumab pegol trials (103). However, such comparisons may be invalid, as trials were performed sequentially rather than concurrently and assessed induction end points at different time frames, and, although patients with relatively similar disease activities were enrolled, there were potential biases based on subtle differences in concomitant medications and "refractoriness to corticosteroids or immunosuppressives," disease duration, and study sites. The recognition of individual formulations response at any particular time point likely reflects the specific time frames and dosing of individual trials and, in the absence of head-to-head comparisons between agents, should not be interpreted as a "faster onset of action" for any anti-TNF biological agent in luminal CD.

The evidence from this systematic review and meta-analysis (103) supports the use of biological therapies in patients with luminal CD who have failed treatment with first- and second-line agents, or who are corticosteroid-dependent. No head-to-head comparisons between biological agents have been performed and it is important to consider the data from the large clinical trials that were, primarily, designed to obtain regulatory approval as "minimal" estimates of benefits, as, in clinical practice, dose or dose–frequency adjustments are often required to sustain adequate pharmacokinetics of each agent. We also included multiple doses

in the active treatment arm, some of which are not approved and were not demonstrated to be effective.

Anti-α4 integrin antibodies (natalizumab) are effective at inducing remission in ambulatory patients with moderately-to-severely-active CD
Recommendation: weak. Quality of evidence: moderate.

Five RCTs (269–273) assessing 1,771 patients compared anti-α_4 integrin antibodies with placebo in active CD. All trials evaluated natalizumab and evaluated efficacy at 2–12 weeks. Remission was achieved in 35% of patients randomized to receive natalizumab at 2–12 weeks, compared with 23% of patients randomized to receive placebo. The NNT with natalizumab was 11 (95% CI: 7–20). The magnitude of effect was similar to the anti-TNFα antibody therapies, but the recommendation was weak rather than strong, as there is risk of progressive multifocal leukoencephalopathy (PML) associated with natalizumab therapy in approximately 1 in 1,000 patients (274,275). This serious risk has limited the use of natalizumab in clinical practice to patients who have failed anti-TNFα antibody therapy.

Anti-TNFα antibodies (infliximab, adalimumab, certolizumab pegol) are effective in cessation of fistula drainage in CD.
Recommendation: strong. Quality of evidence: low.

Six trials (261,262,266,276–278) evaluated anti-TNFα antibodies vs. placebo in 453 patients with fistulizing CD. Fistula healing occurred in 33% of the patients randomized to receive anti-TNFα antibodies at 4–26 weeks, compared with 22.5% of patients randomized to receive placebo. This difference was not statistically significant in the meta-analysis (103). Only one trial (277) with infliximab was specifically designed to evaluate fistula healing. In that trial, infliximab was significantly better than placebo at healing fistulizing CD (NNT = 3; 95% CI: 2–6). In subgroup analyses of trials with adalimumab and certolizumab pegol, these agents were found to be not effective for fistula healing. It was largely based on the one positive trial involving 94 patients that we recommended the use of anti-TNFα antibodies in fistulizing CD as this is the only trial to specifically assess this group. The recommendation is weak as the quality of evidence is low, with only one small positive trial and negative result in subgroup analyses of other trials.

Section 6.4 Efficacy of biological therapies at preventing relapse in quiescent CD

Anti-TNFα antibodies (infliximab, adalimumab, certolizumab pegol) are effective at preventing relapse in quiescent CD.
Recommendation: strong. Quality of evidence: high.

There were five trials (276,279–282) evaluating 1,390 patients that compared anti-TNFα antibody therapy with placebo in quiescent CD. Relapse occurred in 56% of the patients randomized to receive anti-TNFα antibodies at 26–56 weeks, compared with 78% of the patients randomized to receive placebo. The NNT was 4 (95% CI: 3–5). There were no statistically significant differences in indirect comparisons between infliximab, adalimumab, and certolizumab.

The relapse-preventing potential of the anti-TNFα antibodies is related to the pharmacokinetics of the individual formulation and is influenced by dose, frequency of administration, and immunogenicity (283). Within the confines of controlled clinical trials there is less potential to adjust dosing or dose frequency to "optimize" maintenance therapies. Hence, it is likely that the estimates of benefit reflect minimal effects that can be improved upon in clinical practice (284). In addition, while no apparent difference has been noted for induction of remission in patients receiving concomitant therapy with immunosuppressants, in a recent controlled trial combination therapy with azathioprine and infliximab achieved improved results compared with infliximab monotherapy without increases in adverse effects (268) although methotrexate plus infliximab was not superior to biological therapy alone (285).

The recommendation was strong regarding the benefits of continuing anti-TNFα antibody therapy in patients, in that response to treatment outweighed the risks. The quality of evidence was high, as, although all trials had unclear risk of bias, there was no heterogeneity between studies, the treatment effect was strong, and there were reasonably tight CIs around the estimate.

Anti-α_4 integrin antibodies (natalizumab) are effective in prevention of relapse in quiescent CD.
Recommendation: weak. Quality of evidence: low.

One RCT (271) compared natalizumab with placebo in 250 patients with quiescent CD. Relapse occurred in 61% of patients randomized to receive natalizumab at 60 weeks, compared with 85% of patients randomized to receive placebo. The NNT with natalizumab was 5 (95% CI: 3.5–5). Although the efficacy of natalizumab appears to be similar to anti-TNFα antibody therapies, the risk of PML means that natalizumab is only appropriate for patients who have failed other biological therapies.

Infliximab is effective in prevention of relapse in healed fistulizing CD.
Recommendation: weak. Quality of evidence: low.

One trial (286) compared infliximab with placebo in 195 patients with fistulizing CD. Relapse of healed fistulizing CD occurred in 66% of patients randomized to receive infliximab at 54 weeks, compared with 81% of patients randomized to receive placebo. The NNT was 7 (95% CI: 4–33).

Section 7 Efficacy of antibiotic therapies in IBD

All the above therapies have focused on modulating the immune system to treat IBD. This is a sensible approach given that IBD is thought to arise from a disordered immune reaction to a gut antigen (1). However, the question remains as to what is the antigen or antigens that are generating this immune response? The most obvious answer is the gut flora and it would be logical to try

and modulate this as well as the immune system. One approach to medically modulate the microbial environment would be by using probiotics. However, the science of probiotics is still developing and we prospectively decided not to evaluate these interventions for the monograph. Systematic reviews of probiotics in IBD (287–289) have suggested that current therapies have little efficacy in either UC or CD. The alternative approach is to try and modulate gut flora with antibiotics. Several bacterial species have been suggested to have a role in the pathogenesis of CD, including *Mycobacteria* (290,291), *Listeria* and *Escherichia coli* (292–294). Indeed, almost as soon as CD was described, it was observed that diverting the fecal stream by ileostomy reduced the recurrence of CD in the colon (295). Altering the gut microbiome with antibiotics may have a similar effect and we have evaluated this in a systematic review of randomized trials (104).

Section 7.1 Efficacy of antibiotic therapies at inducing remission in active UC

*A pooled analysis of antibiotic therapies shows a statistically significant effect at inducing remission in UC but these are **not** recommended as no particular class of drug can be recommended in clinical practice.*
Recommendation: weak. Quality of evidence: very low.

There were nine RCTs (296–304) involving 622 patients that compared antibiotics with placebo in active UC. Three RCTs (296–298) evaluated combination antibiotic regimens, three trials ciprofloxacin (299–301), and one trial each of tobramycin (302), vancomycin (303), and rifaximin (304). There was no clear antibiotic that was efficacious in acute UC, but overall there was a statistically significant effect in favor of antibiotics, with an NNT of 7 (95% CI: 4–25) (104). One trial (303) required some assumptions regarding the definition of remission and if this study was excluded there was only a trend to statistical significance ($P = 0.06$), with RR as the summary statistic, but results were still statistically significant if risk difference was used. The quality of the evidence was very low as there was moderate heterogeneity between studies and the appropriateness of combining all antibiotics in the meta-analysis was unclear. There were also no low-risk-of-bias trials. We did give this a weak recommendation against the use of antibiotics in acute UC, as with the current level of evidence we cannot recommend which antibiotic to prescribe. Nevertheless, these drugs may be worth trying in certain cases although risks of *Clostridium difficile* and antibiotic resistance must be weighted against any potential benefits.

Section 7.2 Efficacy of antibiotic therapies at preventing relapse in quiescent UC

There was only one trial (305) that provided follow-up of a previous trial in acute UC (302) to assess whether a 7-day course of tobramycin would have any long-term effect on relapse rate. This trial evaluated 81 patients for 2 years and there was no difference in relapse rates at 1 and 2 years. Therefore, data available are not sufficient to make a recommendation on this topic and more studies are needed.

Section 7.3 Efficacy of antibiotic therapies at inducing remission in active CD

*A pooled analysis of antibiotic therapies shows a statistically significant effect at inducing remission in active CD but these are **not** recommended as no particular class of drug can be recommended in clinical practice.*
Recommendation: weak. Quality of evidence: very low.

There were 10 RCTs (306–315) involving 1160 patients that compared antibiotic therapy with placebo in active CD. There was a statistically significant benefit of antibiotics compared with placebo in active CD (RR of active CD not in remission = 0.85; 95% CI: 0.73–0.99, $P = 0.03$) with an NNT of 11 (95% CI: 5–200) (104). A diverse number of antibiotics were tested either alone or in combination. It is therefore difficult to evaluate whether any particular antibiotic is effective in active CD. One trial (309) did suggest that ciprofloxacin was effective, but this study evaluated only 84 patients. This was, however the only trial (309) with a low risk of bias. Two trials (314,315) evaluated rifamixin in 485 active CD patients, with pooled data suggesting a statistically significant effect in favor of the antibiotic (104).

On assessing the evidence as a whole, we felt the evidence available is not sufficient to recommend that antibiotics were beneficial and hence gave a weak recommendation not to use these in acute CD. The evidence was classified as very low quality given the different antibiotic regimens evaluated, and there was moderate heterogeneity between studies.

Antibiotic therapies are effective at reducing fistula drainage in CD.
Recommendation: weak. Quality of evidence: low.

There were three RCTs (316–318) that evaluated antibiotics vs. placebo in 123 patients with fistulizing CD. Two trials evaluated metronidazole (317,318) and two trials ciprofloxacin (316,318). There was only one study that evaluated fistula resolution (318). This was a small pilot study of 25 patients and had a low healing rate in all three arms, with no statistically significance between metronidazole, ciprofloxacin, or placebo. All studies provided improvement in fistula drainage as an outcome. There was a trend to benefit for both ciprofloxacin and metronidazole, but neither reached statistical significance (104). The meta-analysis of all antibiotics, however, did show a statistically significant benefit in favor of antimicrobials with a NNT of 5 (95% CI: 3–20). There was no heterogeneity between studies and one trial (317) had a low risk of bias. Given the paucity of the data, we could only give a weak recommendation in favor of antibiotics, but there does appear to be some efficacy in treating fistulae with either ciprofloxacin or metronidazole.

Section 7.4 Efficacy of antibiotic therapies at preventing relapse in quiescent CD

*A pooled analysis of antibiotic therapies shows a statistically significant effect at preventing relapse in quiescent CD but these are **not** recommended as no particular class of drug can be recommended in clinical practice.*
Recommendation: weak. Quality of evidence: very low.

Table 2. Recommendations for therapy in active UC to induce remission

Intervention	Severity of disease	No. of trials	No. of patients	NNT (95% CI)[a]	Recommendation
5-ASA	Mild/moderate	11	2,086	6 (5–8)	Yes, 1B
Steroids	All	5	445	3 (2–9)	Yes, 1C
Azathioprine/6-MP	N/A	2	130	N/A	No, 2D
Methotrexate	N/A	1	67	N/A	No, 2D
IV cyclosporin	Severe hospitalized	1	20	1.2 (1–2)[b]	Yes, 2D
Infliximab	Moderate/severe	3	771	4 (3–10)	Yes, 1B
Infliximab	Severe hospitalized	2	56	6 (3–50 NNH)[b]	Yes, 2D
Antibiotics	N/A	9	622	7 (4–25)	No, 2D[c]

A, high-quality evidence; 5-ASA, 5-aminosalicylic acid; B, moderate-quality evidence; C, low-quality evidence; 95% CI, 95% confidence interval; D, very-low-quality evidence; IV, intravenous; N/A, not applicable; NNH, number needed to harm; NNT, number needed to treat; UC, ulcerative colitis; 1, strong recommendation; 2, weak recommendation.
[a]NNT should NOT be compared between therapies, as trials evaluated different severities of disease and used different end points to define remission. [b]NNT for symptom improvement and not remission. [c]Decision was to NOT recommend, as the statistically significant result was achieved by pooling all antibiotics and it is not clear which (if any) class of antibiotic can be recommended clinically.

Table 3. Recommendations for therapy in quiescent UC to prevent relapse

Intervention	No. of trials	No. of patients	NNT (95% CI)	Recommendation
5-ASA	11	1,502	4 (3–7)	Yes, 1A
Azathioprine/6-MP	3	127	4 (2–10)	Yes, 2C
Methotrexate	2	58	N/A	No, 2C
Biological agents	0	0	N/A	N/A[a]
Antibiotics	1	81	N/A	N/A[a]

CI, confidence interval; A, high-quality evidence; B, moderate-quality evidence; C, low-quality evidence; D, very-low-quality evidence; N/A, not applicable; NNT, number needed to treat; UC, ulcerative colitis; 1, strong recommendation; 2, weak recommendation.
[a]Insufficient evidence to make a recommendation.

The systematic review identified three RCTs (306,307,314) involving 186 patients that compared antibiotic therapy vs. placebo in quiescent CD. There was a statistically significant effect of antibiotics in preventing CD relapse compared with placebo, with a NNT of 4 (95% CI: 3–10) (104). All studies evaluated antimicrobials that could be considered to be anti-mycobacterial although all studied different regimens and follow-up was for 9–12 months. The quality of evidence was considered very low, as there was a paucity of data on all trials comparing different antibiotics. All trials also had unclear risk of bias although there was no heterogeneity between studies. We gave a weak recommendation against the use of antibiotics to prevent relapse in CD. Although the evidence available is not sufficient enough to recommend their general use, they may be helpful in individual cases although the risks of *Clostridium difficile* and antibiotic resistance also need to be considered. For both UC and CD more studies are needed to determine which, if any, antibiotic used alone or in combination is effective in IBD.

Section 8 Summary of the efficacy of medical therapies in IBD

This series of systematic reviews performed by methodologists supported by IBD experts provides an authoritative perspective on the efficacy of medical therapies in IBD. The assessment of all trials in both UC and CD using the same criteria by one group of researchers gives a unique overview of the strength and quality of the evidence. This is summarized in **Tables 2–5**. Data suggest that 5-ASA can be recommended to treat mild-to-moderately-active UC and to prevent UC relapse, but these drugs are not recommended for the treatment of CD or to prevent CD relapse. Systemic corticosteroid therapy is effective for acute UC and CD and budesonide may be an alternative for those with terminal ileal CD for whom systemic steroid adverse effects are a concern. These drugs are not recommended for maintenance therapy in IBD. Immunosuppressants are generally not recommended for inducing remission in active UC and CD. The exception to this is that intramuscular methotrexate may be of benefit as an adjunct to steroids in inducing remission in CD and intravenous cyclosporin may be helpful in improving symptoms in hospitalized patients with severe UC. Azathioprine/6-MP is effective for maintenance therapy of UC and CD and methotrexate is also effective as maintenance therapy for CD. Cyclosporin is not recommended for maintenance of IBD. Infliximab is effective at inducing remission in moderate-to-severely-active UC outpatients and may be of benefit in reducing symptoms in severely active hospitalized

Table 4. Recommendations for therapy in active CD to induce remission

Intervention	Severity of disease	No. of trials	No. of patients	NNT (95% CI)[a]	Recommendation
5-ASA	N/A	6	910	11 (6–100)	No, 2C
Steroids	All	2	267	3 (2–11)	Yes, 1C
Budesonide	Mild/Moderate	2	458	5 (3–9)	Yes, 1C
Azathioprine/6-MP	N/A	5	380	N/A	No, 2C
i.m. Methotrexate	All	2	193	Trend	Yes, 2C
Cyclosporin	N/A	1	64	N/A	No, 2D
Anti-TNFα	Moderate/severe	10	2,756	8 (6–17)	Yes, 1B
Anti-TNFα	Fistulizing	1[b]	94[b]	3 (2–6)[c]	Yes, 1C
Antibiotics	N/A	10	1,160	11 (5–200)[d]	No, 2D
Metronidazole/ciprofloxacin	Fistulizing	3	123	5 (3–20)[c]	Yes, 2C

CI, confidence interval; A, high-quality evidence; B, moderate-quality evidence; C, low-quality evidence; D, very-low-quality evidence; N/A, not applicable; NNT, number needed to treat; UC, ulcerative colitis; 1, strong recommendation; 2, weak recommendation.

[a]NNT should NOT be compared between therapies as trials evaluated different severities of disease and used different end points to define remission. [b]More trials evaluated fistulizing CD in subgroup analysis but only one trial evaluated fistulae specifically. [c]NNT is for improvement in fistula drainage. [d]Decision was to NOT recommend as the statistically significant result was achieved by pooling all antibiotics and it is not clear what (if any) class of antibiotic can be recommended clinically.

Table 5. Recommendations for therapy in quiescent CD to prevent relapse

Intervention	No. of trials	No. of patients	NNT (95% CI)	Recommendation
5-ASA	16	2,496	N/A	No, 2C
Budesonide	5	559	N/A	No, 2C
Azathioprine/6-MP	2	198	3 (1.3 to ∞)	Yes, 2C
Methotrexate	1	76	4 (2–25)	Yes, 2C
Cyclosporin	1	118	N/A	No, 2C
Anti-TNFα	5	1,390	4 (3–5)	Yes, 1A
Antibiotics	3	186	4 (3–10)	No, 2D[a]

CI, confidence interval; A, high-quality evidence; B, moderate-quality evidence; C, low-quality evidence; D, very-low-quality evidence; N/A, not applicable; NNT, number needed to treat; UC, ulcerative colitis; 1, strong recommendation; 2, weak recommendation.

[a]Decision was to NOT recommend, as the statistically significant result was achieved by pooling all antibiotics and it is not clear which (if any) class of antibiotic can be recommended clinically.

UC patients. Anti-TNF alpha therapies are effective at inducing remission in moderate-to-severely-active CD and are also effective as maintenance therapy for CD. The anti-α4 integrin antibody, natalizumab, is effective at inducing and maintaining remission in outpatients with moderately-to-severely-active CD, but the rare risk of PML has limited the use of this drug to those who have first failed prior anti-TNF therapy. Although there was a statistically significant effect of antibiotic therapy in inducing remission in active UC and in preventing relapse in quiescent CD, these agents are not recommended, as the classes of antibiotics that were evaluated are diverse and it is not clear which antibiotic to recommend for these conditions. The data do, however, suggest that modulating the gut microbiome could have some influence on the activity of IBD and more trials evaluating this approach are warranted.

These data highlight that there are a paucity of options for patients with mild CD who require maintenance therapy given that 5-ASAs are not recommended in this disease. Although there are a large number of maintenance trials in IBD, follow-up is generally only for 1 year and these are life-long conditions (319). The optimum maintenance therapy in UC and CD therefore remains to be determined and, in particular, there are only a few trials that study the benefit of combinations of therapies to prevent relapse (268,285). There is also a need for more data on whether early aggressive therapy or a "step-up" approach is better for CD (320) and whether early aggressive therapy has any role in altering the natural history of the disease. Despite these limitations, this monograph highlights the wealth of RCT data that can guide the clinician in the medical management of IBD.

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