

Conventional Medical Management of Inflammatory Bowel Disease



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Conventional therapies for ulcerative colitis and Crohn's disease (CD) include aminosalicylates, corticosteroids, thiopurines, methotrexate, and anti-tumor necrosis factor agents. A time-structured approach is required for appropriate management. Traditional step-up therapy has been partly replaced during the last decade by potent drugs and top-down therapies, with an accelerated step-up approach being the most appropriate in the majority of patients. When patients are diagnosed with CD or ulcerative colitis, physicians should consider the probable pattern of disease progression so that effective therapy is not delayed. This can be achieved by setting arbitrary time limits for administration of biological therapies, changing therapy from mesalamine in patients with active ulcerative colitis, or using rescue therapy for acute severe colitis. In this review, we provide algorithms with a time-structured approach for guidance of therapy. Common mistakes in conventional therapy include overprescription of mesalamine for CD; inappropriate use of steroids (for perianal CD, when there is sepsis, or for maintenance); delayed introduction or underdosing with azathioprine, 6-mercaptopurine, or methotrexate; and failure to consider timely surgery. The paradox of anti-tumor necrosis factor therapy is that although it too is used inappropriately (when patients have sepsis or fibrostenotic strictures) or too frequently (for diseases that would respond to less-potent therapy), it is also often introduced too late in disease progression. Conventional drugs are the mainstay of current therapy for inflammatory bowel diseases, but drug type, timing, and context must be optimized to manage individual patients effectively.

Keywords: Ulcerative Colitis; Crohn's Disease; Treatment; Mesalamine; Corticosteroids; Anti-TNF Therapy.

We review conventional therapies for ulcerative colitis (UC) and Crohn's disease (CD), focusing on timing of treatment and specific dilemmas. Algorithms (Figures 1-4) are included for guidance, although treatment of patients is influenced by external factors such as comorbidities, drug intolerance, patient preferences, and the occupational context of the illness. In practice, treatment is also regulated by health care jurisdiction (certolizumab pegol, for example, is not licensed for the treatment of CD in Europe) or remuneration (especially for anti-tumor necrosis factor [TNF] therapy or steroids, such as budesonide). Detailed practice guidelines have been published in the United States, Asia, and Europe for UC and CD.¹⁻⁵ In this article, conventional therapy means aminosalicylates, corticosteroids, thiopurines, methotrexate, and anti-TNF agents.

Approach to Care

The choice of treatment depends on disease activity and extent, as well as patient acceptability and mode of drug delivery. Disease activity is best confirmed (and infection excluded) before therapy is initiated or when response to therapy is slow. To optimize conventional therapy, it is important to carefully time the steps of treatment and explain the strategy to the patient.

Inducing Remission in Patients With UC

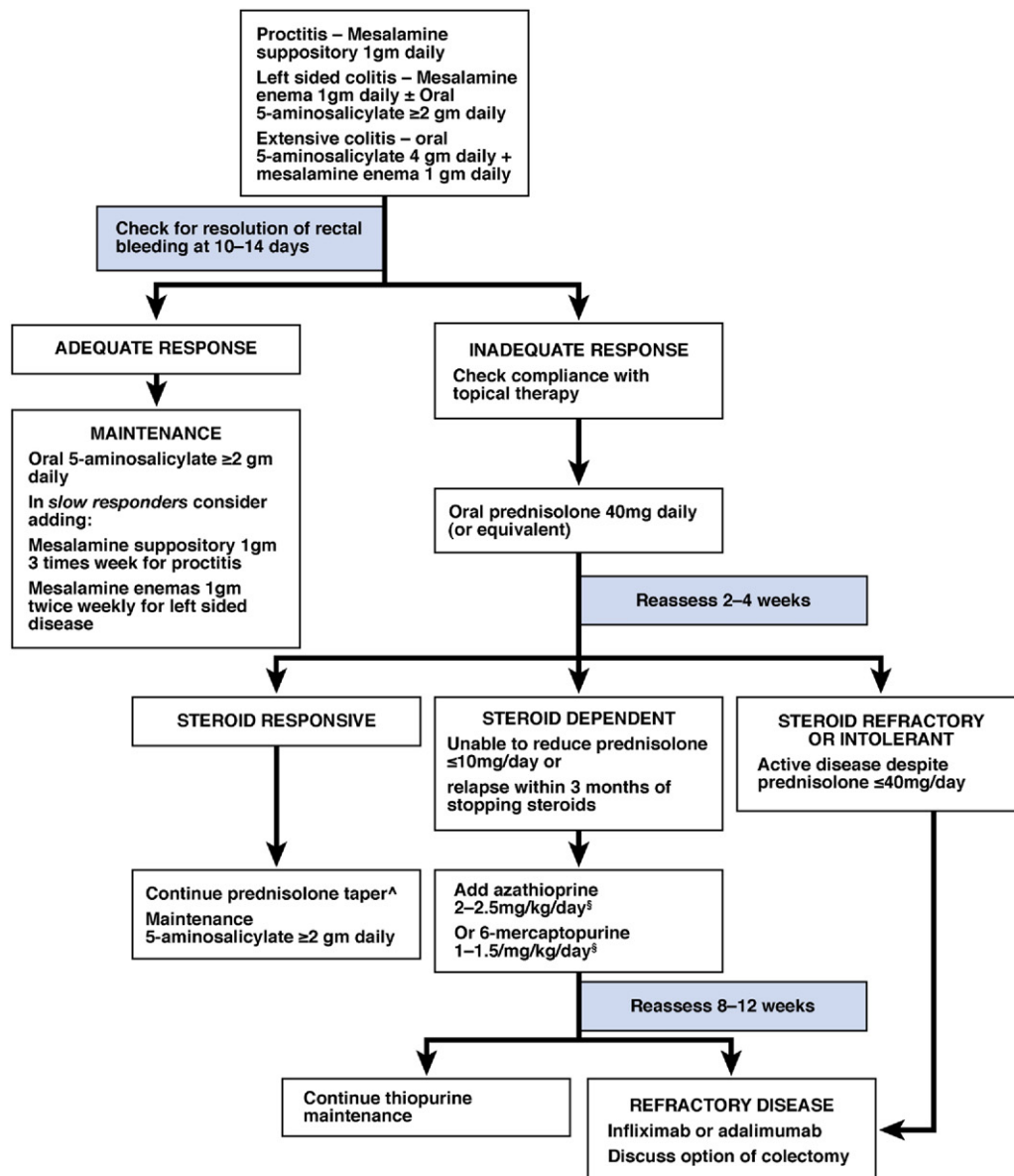
5-Aminosalicylates are the most common treatment for patients with mild (≤ 4 bloody stools/d) or moderately active disease (>4 bloody stools/d without systemic toxicity).⁶ Absorption must be prevented to achieve colonic delivery, either by administration of a

Abbreviations used in this paper: CD, Crohn's disease; CDAI, CD Activity Index; CRP, C-reactive protein; IBD, inflammatory bowel disease; TNF, tumor necrosis factor; UC, ulcerative colitis.

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[^]Prednisolone tapering typically 5mg/week to complete withdrawal.

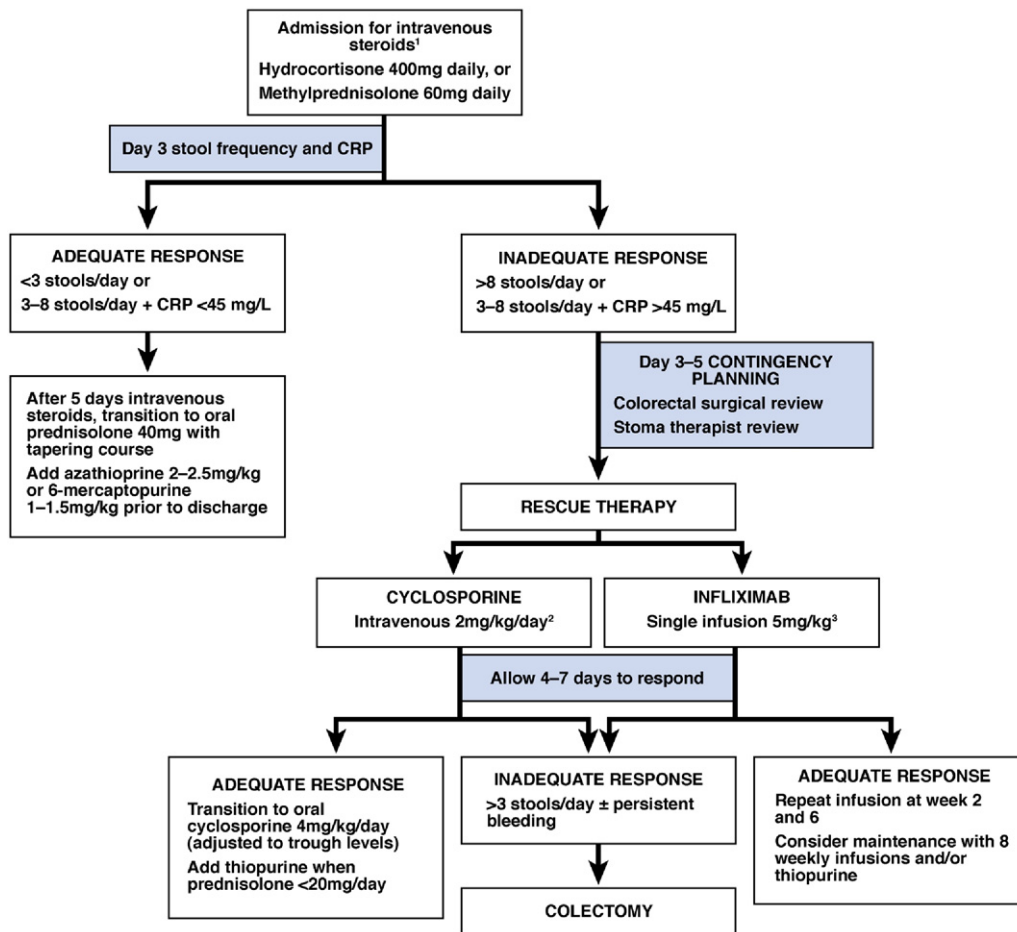
[§]Regular monitoring for toxicity with complete blood count and liver function tests, consider TMPT measurement prior to initiating therapy and thiopurine metabolite monitoring for dose optimization.

Figure 1. Management algorithm for mild-to-moderately active ulcerative colitis (UC). UC activity is defined as mild (≤ 4 motions/d) or moderate (≥ 4 bloody motions/d) when there are no signs of systemic toxicity (pulse < 90 beats per minute, temperature $< 37.5^\circ\text{C}$, hemoglobin > 10.5 g/dL, or erythrocyte sedimentation rate < 30 mm/h). Oral 5-aminosalicylates include sulfasalazine 2–6 g daily, mesalamine 1.5–4.8 g daily, balsalazide 2–6.75 g daily, or olsalazine 1.5–3 g daily.

prodrug (balsalazide, olsalazine, or sulfasalazine), a drug with a gastroresistant, pH-dependent coating (eg, Asacol, Salofalk), or a drug with a slow-release mechanism (eg, Pentasa).⁷ Nevertheless, the asymmetrical, right-to-left gradient of drug delivery in the gastrointestinal tract means that only 9% of oral Asacol is delivered to the distal colon during active distal colitis.⁸ Therefore, enemas or suppositories should be used to optimize mucosal concentrations of mesalamine in patients with distal UC.²

Mild-to-Moderately Active Proctitis

The best way to induce remission in patients with proctitis is with mesalamine suppositories because $< 10\%$ of liquid and only 40% of foam from enemas remain in the rectum after 4 hours. Mesalamine suppositories (1 g/d) induced clinical remission in 64% patients with proctitis within 2 weeks.⁹ For patients who do not respond to topical mesalamine, a combination of topical corticosteroid and mesalamine leads to better clinical,



¹General management – Obtain complete blood count, urea, creatinine, electrolytes (including magnesium), liver enzymes, albumin, C-reactive protein, erythrocyte sedimentation rate, fasting cholesterol, and blood culture (if febrile), stool cultures for enteric pathogens and C. difficile toxin. Flexible-sigmoidoscopy to confirm activity and biopsy to exclude cytomegalovirus. Abdominal radiology on admission to exclude colonic dilation (≥6 cm) and repeated in patients who are slow to respond. Thromboembolism prophylaxis should be prescribed. Daily stool chart, correct electrolyte imbalances, avoid anti-cholinergics and opiates.

²Ensure magnesium >0.55mmol/L and serum cholesterol >3 mmol/L

³Check contra-indications – tuberculosis, congestive heart failure, demyelinating disease

Figure 2. Management algorithm for acute severe ulcerative colitis (UC). Acute severe colitis is defined by Truelove and Witts' Criteria as ≥6 bloody stools/d in the presence of 1 or more of the following criteria: pulse of >90 beats per minute, temperature >37.8°C, hemoglobin <10.5 g/dL, or an erythrocyte sedimentation rate >30 mm/h.

endoscopic, and histological improvements than either drug alone.² Other topical therapies (eg, arsenic, lidocaine) can be used, more in hope than with expectation.² Oral corticosteroids are often used, but there have been no clinical trials of prednisone for isolated proctitis. In a review of 420 patients treated with infliximab for UC, 13 of 420 had refractory proctitis; 11 of 13 responded to infliximab and 9 of 11 maintained response during a median 17 months.¹⁰

Mild-to-Moderately Active Distal Colitis

For distal or left-sided colitis, rectal mesalamine is better than steroids for inducing remission (odds ratio = 1.65).¹¹ The combination of oral and rectal mesalamine is better at stopping rectal bleeding (89%) than rectal (69%) or oral (46%) monotherapy.¹² Sulfasalazine cannot be justified as a first-line therapy because of side effects,

although mesalamine drugs are no more effective than sulfasalazine (odds ratio = 0.83), yet are 4-fold the price.¹³

Mild-to-Moderately Active Extensive Colitis

Combining oral mesalamine (4 g) with enemas (1 g) is better than oral monotherapy for mild-to-moderately active, extensive UC—the combination induces 64% remission within 8 weeks, compared to 43% with oral monotherapy.¹⁴ This combination is appropriate for initial therapy as long as there is no delay in escalating treatment for slow responders.

Timing Treatment Escalation in Patients With Mild-to-Moderately Active Colitis

Oral mesalamine without enemas is generally preferred by patients with active UC and can work

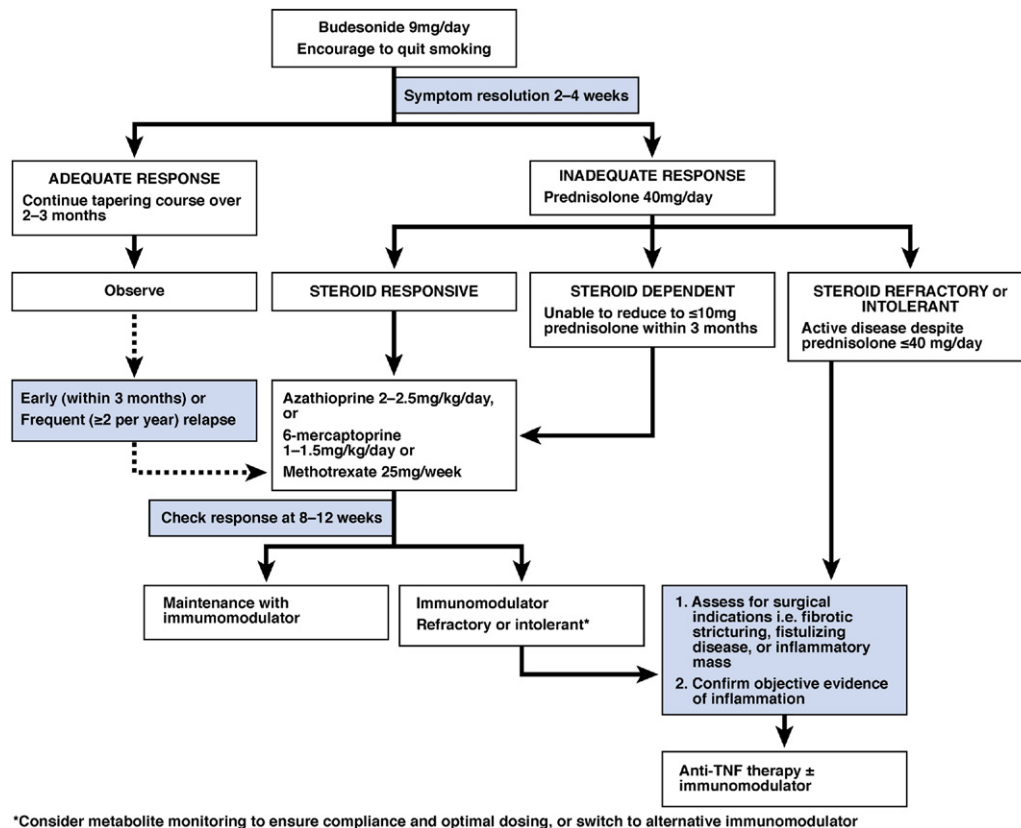
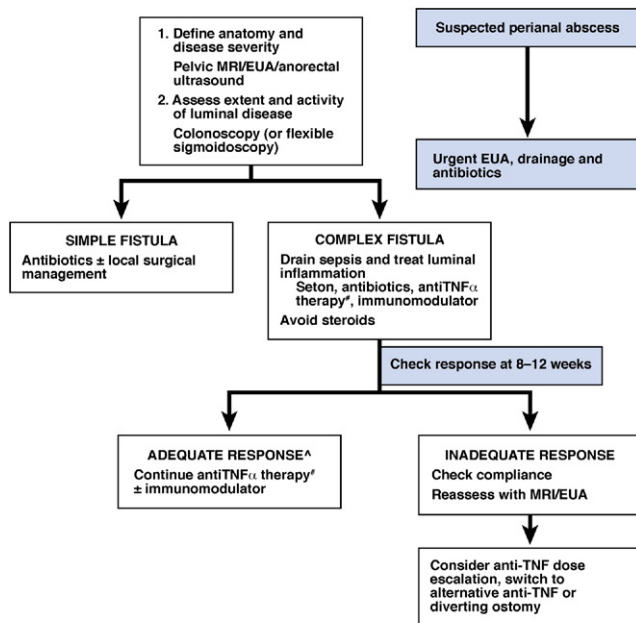


Figure 3. Management algorithm for mild-to-moderate ileal Crohn's disease. Mild-to-moderate disease activity refers to intestinal inflammation in the absence of systemic symptoms (fevers, dehydration, and rigors), obstruction, painful mass, or >10% weight loss.

rapidly. Median time to cessation of rectal bleeding in patients with moderately active UC treated with mesalamine was 9 days for 4.8 g/d and 16 days for 2.4g/d.¹⁵ This can guide the time to escalate therapy; if rectal bleeding persists after 10–14 days, then patients are slow responders to mesalamine and treatment escalation is generally appropriate.² Alternative strategies of waiting 3–4 weeks to escalate therapy in those with relatively mild symptoms, or simply increasing the dosage of mesalamine at 10–14 days and waiting an additional 14 days before committing to steroids are also reasonable, but the decision depends on the views of the patient. The optimal starting dosage of prednisone is 40 mg/d; higher dosages increase side effects with limited therapeutic gain. No randomized trials have compared tapering regimes, but most physicians reduce the dosage by 5 mg each week. However, of 84% patients who initially responded to steroids (remission rate 54%), only 49% were steroid- and surgery-free 1 year later.¹⁶ Moving straight from mesalamine to infliximab is an effective option that avoids steroids; 33.9% of patients achieved remission after 8 weeks of therapy with 5 mg/kg infliximab, compared with 5.7% given placebo.¹⁷ However, infliximab is generally reserved for those who do not respond to or cannot tolerate steroids.^{1,2}

Acute Severe UC

Acute severe UC is defined as a bloody stool frequency $\geq 6/d$ and a tachycardia (>90 beats per minute), temperature $>37.8^\circ\text{C}$, anemia (hemoglobin <10.5 g/dL), or an increased erythrocyte sedimentation rate (>30 mm/hr).^{1,2} Flexible sigmoidoscopy is used to confirm active disease and exclude cytomegalovirus infection,¹⁸ along with stool sample analysis for *Clostridium difficile* toxin and plain abdominal radiography to exclude colon dilatation. Administration of intravenous corticosteroids (methylprednisolone 60 mg or equivalent) should not be delayed while waiting for results from microbiology testing. Higher dosages are no more effective, but lower dosages are less effective.² Fluid and electrolyte replacement, with heparin thromboprophylaxis, are considered to be essential, but neither intravenous nutrition nor antibiotics have altered outcomes in controlled trials.² *C difficile* infection is associated with worse outcomes in patients hospitalized with UC. Based on the Nationwide Inpatient Sample, the prevalence of *C difficile* in patients with UC (37.3/1000) was 3-fold higher than in those with CD (10.9/1000), was associated with greater mortality (odds ratio = 3.79), and resulted in a 65% longer length of hospital stay.¹⁹ Oral dosages of vancomycin should be given if *C difficile* infection is suspected. The response to



*Infliximab – evidence of benefit from randomized controlled trial, adalimumab and certolizumab – evidence from sub-group analysis of randomized trials
^Adequate response considered as cessation of drainage despite pressure in >50% of fistulas
MRI – magnetic resonance imaging, EUA – examination under anaesthetic

Figure 4. Management algorithm for fistulizing perianal Crohn's disease. Simple fistulae do not involve the sphincter complex or branch to form multiple openings, and are not complicated by abscess formation, rectovaginal fistulization, or anal stricturing. The assessment modality is determined by local expertise.

corticosteroids has remained unchanged for decades: in 32 trials involving 1991 patients from 1974 to 2006, the overall response was 67%; 29% required colectomies.²⁰ Treatment is usually given for about 5 days; extending therapy beyond 7 days has no benefit.

Response is best assessed objectively around the third day. Among patients with stool frequencies of 3–8/d and levels of C-reactive protein (CRP) >45 mg/L on the third day of intravenous steroids, 85% needed colectomies.²¹ Surgical options are best considered and discussed at this stage, although “rescue” therapy with either cyclosporine or infliximab is often appropriate. Preliminary results from a randomized controlled trial that compared the effects of cyclosporin and infliximab in 110 patients showed no difference in short-term (7- and 90-day) efficacy.²² A randomized study of 45 patients demonstrated the efficacy of infliximab—24 patients were given 5 mg/kg infliximab and 21 were given placebo with continued intravenous betamethasone; 7 of 24 in the infliximab group and 14 of 21 in the placebo group needed a colectomy within 3 months (odds ratio = 4.9).²³ The difference in outcomes between groups was maintained during 3 years (12 of 24 required a colectomy after infliximab treatment vs 16/21 after placebo), although most patients received a single dose of infliximab.²⁴ In the largest randomized study of cyclosporin, 73 patients received either 2 mg/kg or 4 mg/kg; response rates were

similar between groups at 8 days (86% and 84%, respectively); 9% required a colectomy in the 2 mg/kg group and 13% in the 4 mg/kg group. In patients given 2 mg/kg, the mean cyclosporin concentration on day 4 was 246 ± 64 ng/mL, but in patients given 4 mg/kg, it was 345 ± 146 ng/mL.²⁵ Most of cyclosporin's side effects were dose-dependent, so low-dose (2 mg/kg) intravenous induction is the best option.

Many gastroenterologists are more familiar with infliximab than cyclosporin, but the short half-life of cyclosporin is a potential advantage if infliximab does not work—cyclosporin disappears from the circulation within hours, whereas infliximab circulates for weeks. This could matter if emergency colectomy is necessary because septic complications cause most postoperative morbidity.²⁶ Although steroids (but not infliximab) increased the risk of postoperative infection in one study (odds ratio = 5.19 for ≥20 mg methylprednisolone for ≥2 months), 137 of 141 had elective rather than emergency colectomies, so the safety of infliximab in this context is unresolved.²⁷ The median time to response for cyclosporin is 4 days, based on decreases in stool frequency and levels of CRP—this time is similar to that for infliximab.²⁵ Colectomy is recommended if there is clinical deterioration or no improvement within 4–7 days of rescue therapy.^{1,2,21} Contingency planning to prepare for surgery allows time for rescue therapy to work within the bounds of safety. The worst outcome is not surgery, but the mortality associated with acute severe UC.²⁸

Treatment-Refractory UC

Treatment-refractory UC can be severe in terms of consequences for the patient, but should be distinguished from acute severe UC. For patients with treatment-refractory UC, the disease activity should be confirmed, adherence to treatment evaluated, other causes of persistent symptoms considered (including proximal constipation, defecation disorder, mucosal prolapse, or cancer), and the pattern of disease progression reviewed.^{1,2} Patients with corticosteroid-dependence who are unable to withdraw prednisolone within 3 months of starting, or relapse within 3 months of stopping steroids, should receive therapy with thiopurines. When azathioprine was given to 156 patients with UC, the rate of steroid dependence decreased from 39% to 9%.²⁹ Treatment with infliximab is also appropriate. A Cochrane review analyzed 7 placebo-controlled trials of UC that was refractory to steroids and/or immunomodulators; infliximab was more effective than placebo for inducing clinical (relative risk: 3.22) and endoscopic remission (relative risk: 1.9) at 8 weeks.³⁰ A primary response to infliximab occurred in 78% of 191 patients with UC in a French multicenter study.³¹ Adalimumab is also effective for treatment-refractory UC; 18.5% of patients went into remission and 54.6% responded to 8 weeks of therapy with 160 or 80 mg adalimumab (followed by 40 mg

adalimumab every other week), compared with 9.2% that went into remission and 44.6% that responded to placebo.³² Why these remission rates appear lower than in the ACT 1 (Ulcerative Colitis Treatment) trial is unclear; it may be that the dosage of adalimumab was too low, duration of therapy too short, or a consequence of variability in the scoring of endoscopy or physician's global assessment.³³

Inducing Remission of Patients With CD

The therapeutic strategies are broadly similar in CD and UC, although significant differences exist, including a limited or lack of response to mesalamine or cyclosporin, response to nutritional therapy, and greater need for surgery in CD.^{4,5} Enthusiasm for biological therapy needs to be tempered with recognition that half will have a benign course; in a Norwegian, 10-year, population-based study, just 53% developed stricturing or penetrating disease.³⁴ At diagnosis, it is possible to identify patients with poor prognosis. In a study of 371 patients in Belgium, 37% developed complex perianal disease, colonic resection, ≥ 2 small bowel resections, or a definitive stoma within 5 years.³⁵ Factors associated with poor prognosis included age younger than 40 years, strictures, weight loss >5 kg, initial need for steroid therapy, and perianal disease at diagnosis.³⁵ Two risk factors (stricturing disease and weight loss) had a 78% predictive value. Patients with these risk factors might benefit from early introduction of biological or immunomodulator therapy, even if disease activity is mild or moderate.³⁶

Mild-to-Moderately Active Ileocolic CD

Mesalamine has limited efficacy in patients with CD. A meta-analysis found a statistically significant, 18-point reduction in the CD Activity Index (CDAI) among patients with mild-to-moderately active ileocecal CD given ethylcellulose-coated mesalamine (4 g/d) compared to placebo,³⁷ indicating little clinical benefit. However, a recent study that compared daily doses of budesonide (9 mg) to mesalamine (4.5 g) reported a 100-point reduction in the CDAI score among 89% of patients given budesonide and 79% given mesalamine, indicating equivalent efficacy.³⁸ Budesonide is less effective than prednisone in patients with more severe (CDAI >300) or extensive colonic disease, but causes fewer side effects.³⁹ Consequently budesonide (if available) is recommended for patients with mild-to-moderately active ileocolonic CD, unless there is distal colonic disease, when prednisone is more appropriate. Nutritional therapy remains first-line therapy in children, but is generally not well-tolerated by adults and cannot compete with the efficacy of biologic therapy. Biologic therapy with infliximab, adalimumab, or certolizumab pegol is appropriate when there is objective evidence of active CD and steroids are either inef-

fective or cannot be tolerated.^{4,36} Methotrexate (25 mg/week) is also effective for patients with active CD despite steroid therapy. In a controlled study, 141 steroid-dependent patients with active CD were given either 25 mg/week of intramuscular methotrexate or placebo for 16 weeks. More patients in the methotrexate-treated group were able to withdraw steroids and enter remission, compared with placebo (39% vs 19%)⁴⁰; these findings were confirmed in a systematic review.⁴¹

Severe CD of Any Location

Patients with severe CD are initially treated with oral or intravenous corticosteroids; anti-TNF therapy is reserved for patients who do not respond to initial therapy. Efficacy and adverse events associated with biological therapies have been reviewed in detail.^{36,42} In 14 trials of anti-TNF therapy for severe luminal CD (3995 patients), the mean incremental benefit for inducing remission at week 4 was 11%.⁴³ This might seem to be a modest value, but response is best evaluated at week 12—in a cohort of 614 patients, the primary nonresponse rate was only 10.9%.⁴⁴ Anti-TNF therapy can be used in patients with strictures, but those without objective evidence of active inflammation usually have a poor response. Subanalysis of data from the ACCENT 1 (A Crohn's Disease Clinical Trial Evaluating Infliximab in a New Long Term Treatment Regimen) trial, matched for disease location and severity, showed no increase in symptomatic strictures or obstruction, even among patients who achieved mucosal healing within 10 weeks.⁴⁵ It can be difficult to distinguish active disease from a septic complication, so cross-sectional imaging is appropriate before anti-TNF therapy begins to exclude an abscess if a patient has a fever or focal tenderness.⁵ Management of severe CD also includes nutritional support, treatment of iron deficiency (40% patients have iron or multiple nutrient deficiency⁴⁶), and the psychological consequences of severe CD. Psychological distress was associated with worse outcomes in an observational cohort.⁴⁷ Surgery is part of an appropriate management strategy, especially in localized ileal or ileocecal disease.⁵

Maintaining Remission of Patients With UC

In a population-based study of 1575 patients with UC, 13% had no relapse, 74% had ≥ 2 relapses, and 13% had active disease every year for 5 years after diagnosis.⁴⁸ Oral mesalamine is the first-line maintenance therapy reducing the risk of relapse by 50% (odds ratio = 0.47 for failure to maintain clinical or endoscopic remission vs placebo).⁴⁹ Clinical remission with complete discontinuation of corticosteroid use should be the goal of therapy for UC, but the definition of remission varies, making it a challenge to compare results from different trials.

Maintaining Remission in Patients With Proctitis or Distal Colitis

Topical mesalamine, given 3 or more times a week, is effective for maintaining remission in patients with distal colitis (odds ratio = 16.2 for maintaining remission more than 1 year, compared to placebo) or proctitis.⁵⁰ Although long-term rectal therapy works, 80% of patients surveyed preferred oral treatment alone.⁵¹ Combining topical with oral mesalamine is an option for patients unable or unwilling to take thiopurines or anti-TNF therapies—this combination doubled the 1-year remission rate compared to oral therapy alone.⁵²

Maintaining Remission in Patients With Extensive Colitis

A meta-analysis showed that dosages of mesalamine ≥ 1.2 g/d do not provide additional benefit,⁴⁹ however, 2.4 g/d was more effective than 1.2 g/d at delaying the time to relapse (from 47 to 143 days) in patients with extensive UC.⁵³ Furthermore, more patients who were given 3 g once daily were still in clinical remission after 1 year than those given lower dosages, with no effect on safety.⁵⁴ Remission was also maintained at 12 months in 74.6% of patients given mesalamine 2.4 g/d whose active disease had responded to <8 weeks of therapy, compared to 52.5% who had needed up to 16 weeks to achieve remission. So the dosage of mesalamine required to induce remission might be the best dosage for maintenance therapy.⁵⁵ A shorter time in remission, but not extensive disease, is associated with risk of relapse.⁵⁶ Maintenance mesalamine may also have a chemopreventive benefit, with a 50% reduction in colorectal cancer,⁵⁷ but other studies have not confirmed this value or only shown a trend toward reduced cancer risk,⁵⁸ perhaps because compliance with mesalamine therapy varies.

Maintaining Remission in UC That Relapses Despite Mesalamine Therapy

Patients that relapse in spite of mesalamine therapy can be given thiopurines. Meta-analysis of 7 placebo-controlled trials concluded that the number needed to treat to prevent one recurrence with azathioprine or 6-mercaptopurine was 5, with an absolute risk reduction of 23%.⁵⁹ When azathioprine (2 mg/kg/d) and mesalazine (3.2 g/d) were compared for 6 months in patients with steroid-dependent UC, steroid-free, clinical, and endoscopic remission was achieved in 53% of patients given azathioprine and 21% given mesalamine (odds ratio = 4.78).⁶⁰ Nevertheless, infliximab appears to be most effective for patients with treatment-refractory UC; in the ACT 1 trial, remission rates at week 54 were 35% (5 mg/kg), 34% (10 mg/kg), and 17% (placebo), with response rates that were approximately double these values.¹⁷ Treatment with infliximab reduced the 6–12-month colectomy rate by about 50% (hazard ratio = 0.59); early endoscopic response (determined by complete

mucosal healing at 8 weeks) was associated with 74% vs 10% steroid-free remission and 5% vs 20% colectomy.^{61,62} It is not clear whether the combination of azathioprine and infliximab is better than monotherapy for patients with UC, but there is no reason that results should differ from those of CD.

Maintaining Remission in Patients With CD

Cigarette smoking should be discouraged in patients with CD because it increases the need for steroid therapy and surgery.⁶³ Mesalamine cannot be recommended for patients with CD, as results from meta-analyses are inconsistent. A Cochrane review found no benefit of mesalamine (odds ratio = 1.00 for maintaining medically induced remission over 12 months), but there may be differences among delivery systems.^{64,65} Steroids should not be used to maintain remission either. Budesonide (6 mg) daily was no more effective than placebo over 6 months (relative risk: 1.15) or 12 months (relative risk: 1.13).⁶⁶ Nevertheless, budesonide is approved by the Food and Drug Administration for maintenance of remission for Crohn's disease, based on prolonging the time to relapse by approximately 2 months on 6 mg per day. The disparity in short- and longer-term effects of budesonide may conceivably be a result of a relatively rapid change in disease biology from steroid-responsive to steroid-resistant disease. This would be in contrast to the other drugs. Because budesonide has fewer side effects than traditional steroids, it can be considered as a short-term maintenance therapy in patients whose disease relapses with discontinuation of budesonide and there is reason to delay the introduction of thiopurines, methotrexate, or anti-TNF therapy (such as impending travel, or patient concerns).

Maintaining Medically Induced Remission in Patients With CD

Thiopurines maintain remission in patients with CD, in a dosage-dependent manner (odds ratio = 1.20 for 1 mg/kg/d, 3.01 for 2 mg/kg/d, and 4.13 for 2.5 mg/kg/d).⁶⁷ Methotrexate is also effective. In 76 patients that responded to therapy with methotrexate, steroid-free remission was maintained over 40 weeks in 65% and in 39% of patients given methotrexate (15 mg/week) or placebo, respectively.⁶⁸ Anti-TNF therapy is effective, but best combined with an immunomodulator. In a meta-analysis, infliximab maintained remission in more patients than placebo (relative risk: 2.50), and also increased response (relative risk: 2.19) and spared patients from corticosteroid therapy (relative risk: 3.13); adalimumab has similar effects.⁶⁹ In a study that tested infliximab and azathioprine in 508 patients within 2 years of diagnosis, after 12 months of therapy, 28.2% achieved steroid-free remission from azathioprine, 39.6% from infliximab, and

55.6% from the combination.⁷⁰ However, there was no difference among groups of patients that did not have increased levels of CRP or endoscopic activity at baseline.⁷⁰ It is not clear whether combining azathioprine with adalimumab or certolizumab pegol would also improve outcomes. Response to adalimumab monotherapy was maintained over 3 years in 42% of patients who were given 40 mg every other week, and among 83% of responders after 1 year.⁷¹ The combination of methotrexate and infliximab had a high rate of inducing steroid-free remission (56% at 50 weeks), but no more than with infliximab monotherapy, possibly because methotrexate and infliximab were given along with steroids in this study.⁷²

Maintaining Surgically Induced Remission in Patients With CD

Approximately 50% of all patients with CD have surgery within 10 years of diagnosis, but endoscopic recurrence is common (72% by 12 months after diagnosis), which precedes clinical (32% at 3 years) and surgical recurrence (15% at 5 years).⁷³ Smoking doubles the risk of postoperative recurrence (odds ratio: 2.15).⁷⁴ Mesalamine and thiopurines reduce clinical recurrence (number needed to treat = 12 and 7, respectively, in a Cochrane review).⁷⁵ Mesalamine was less effective than azathioprine or 6-mercaptopurine for preventing endoscopic recurrence (relative risk: 1.46), but had fewer adverse events (relative risk: 0.51). Anti-TNF therapy appears to be very effective; 91% of patients did not have endoscopic recurrence after 1 year compared with 15% of patients given placebo in a small trial.⁷⁶ Postoperative therapy with infliximab is probably best reserved for patients who need surgery again within a short time period for recurrent CD, or if further surgery would carry a high risk of short-bowel syndrome. Therapeutic approaches might change as additional studies are performed.

Special Considerations

Perianal CD

Antibiotics reduce fistula drainage, but in a randomized comparison, only 4 of 10 patients responded to ciprofloxacin, compared to 1 of 8 on metronidazole and 1 of 7 on placebo.⁷⁷ The study was too small to show significant differences, but 5 of 8 could not tolerate metronidazole for 10 weeks. Azathioprine has only been assessed in retrospective studies; fistulae healed in approximately 33% of patients. Complex fistulizing CD warrants early introduction of anti-TNF agents, combined with appropriate surgical drainage. In a randomized study of infliximab, 48% of 305 patients experienced cessation of fistula drainage by 14 weeks; this was maintained for more than 1 year in 36% of patients who received maintenance therapy with

infliximab and 19% who received placebo.⁷⁸ Addition of ciprofloxacin can improve results; 73% of patients responded to infliximab with ciprofloxacin, whereas 39% responded to infliximab alone.⁷⁹ The combination of infliximab and seton placement achieved complete clinical response in 50% of patients at 1 year and was maintained in 42% of patients during a mean follow-up of 4.9 years.⁸⁰ Adalimumab effectively maintains fistula healing, even among those who lost their response to infliximab.^{81,82} The persistence of perianal pain after examination under anesthetic indicates persistent sepsis and the requirement for additional drainage before anti-TNF therapy.

Loss of Response to Therapy in UC or CD

General principles apply when patients with CD or UC no longer respond to therapy. Active inflammation should be confirmed as the cause of symptoms and nonadherence considered; risk of relapse in UC increases 5-fold among patients who take <80% of their prescribed mesalamine.⁸³ Measurement of the drug (anti-TNF agent) or metabolite (thiopurine) can help guide management decisions. Low levels of the drug indicate that compliance should be checked or the dosage increased, whereas appropriate levels of the drug indicate that therapy should be switched. In 614 patients on infliximab, 22% had secondary loss of response and 63% a sustained benefit over a median of 5 years.⁴⁴ About 50% needed an intervention to maintain response. The dose should be optimized before therapy is switched. In ACCENT 1, 88% of patients who lost response to infliximab during maintenance therapy regained response when the dose was increased to 10 mg/kg;⁸⁴ in CHARM (Crohn's Trial of the Fully Human Antibody Adalimumab for Remission Maintenance), 75% who lost response to adalimumab responded again when the dose interval was changed.⁸⁵ It is sometimes possible to regain responsiveness by transient dose escalation. This has been most clearly demonstrated for certolizumab pegol (63% of patients regained responsiveness after a re-induction dose),⁸⁶ but might apply to other anti-TNF therapies. In the GAIN study (Gauging Adalimumab Efficacy in Infliximab Nonresponders), 301 patients with active CD who had failed infliximab were randomized to adalimumab or placebo; 21% of those given adalimumab achieved remission (52% response) compared with 7% of those given placebo (34% response) after just 4 weeks, and the response rate increased in an open-label extension of the study.⁸⁷ In a randomized trial of certolizumab pegol in 539 patients that lost response to infliximab, 62% responded and 39% were in remission at 6 weeks.⁸⁸ A retrospective series of 67 patients found that up to 30% of primary nonresponders to 1 anti-TNF respond to a second or a third agent.⁸⁹ When drugs fail, surgery is often necessary, but it is logical to try an agent with

a different mechanism of action. Natalizumab was equally effective in patients who did not respond to anti-TNF therapy and those who had never been treated with an anti-TNF agent in a subgroup analysis of a trial of 509 patients.⁹⁰

Duration of Conventional Therapy

No medication permanently changes the pattern of CD or UC progression, so treatment that is tolerated and effective is generally continued. In a study of azathioprine withdrawal in patients with CD, 52% relapsed within 3 years, compared to 20% who continued therapy.⁹¹ Of 115 patients in remission who had been treated with infliximab and immunomodulators for at least 1 year and who were off steroids for >6 months, 57% relapsed within 1 year of stopping infliximab therapy. Predictors of relapse included lack of mucosal healing and increased levels of CRP.⁹² These data help patients and physicians make decisions about therapy. Biological therapy has a safety profile at least as good as (and probably better than) undertreated active disease. The standardized mortality of patients with CD who were treated with adalimumab (0.44)⁹³ is lower than that reported in a meta-analysis of epidemiological studies (standardized mortality rates: 1.52).⁹⁴ Potential consequences of discontinuation (relapse, lower response to re-induced therapy, and infusion reactions) should be discussed and decisions should be made based on predicted risks and benefits.

Timing of Treatment

Managing inflammatory bowel disease (IBD) can be compared with a dance. The steps are familiar—mesalamine, steroids, immunomodulators, or anti-TNF therapy and surgery—but it is the timing of the steps that creates the dance. Traditional dose-escalation therapy has been, in some cases, replaced by top-down therapies and more potent drugs. For many patients, an accelerated dose-escalation approach is the best approach. A population-based study from Wales reported lower rates of long-term steroid use (19% vs 44%) and surgery (25% vs 59%) at 5 years in patients given thiopurines within a year compared to patients started 5 years from diagnosis.⁹⁵ Among patients who had mucosal healing induced after early-stage therapy with infliximab, 71% were in steroid-free remission 3 and 4 years after treatment, whereas only 27% of those without mucosal healing were in remission.⁹⁶ Mucosal healing, therefore, clearly seems to be associated with extended steroid-free remission and fewer operations and other complications. This draws on principles established for rheumatoid arthritis, where early use of disease-modifying antirheumatic drugs prevents structural joint damage and, hence, long-term morbidity. Applying this to IBD has been challenged by the lack of objective measures of disease activity or future pattern of

disease. Conventional tools to assess IBD disease activity such as the CDAI rely heavily on subjective assessment. An index to estimate cumulative damage (the Lémann score) is being developed.⁹⁷ These findings provide preliminary evidence that treating inflammation at early stages of IBD reduces structural damage. It is important to evaluate the probable pattern of disease progression at the time of diagnosis so that effective therapy is not delayed.

Conclusions

Common mistakes in conventional therapy include overprescription of mesalamine for CD, inappropriate use of steroids (for perianal CD in patients with sepsis or for maintenance), delayed introduction or underdosing with immunomodulators (azathioprine, 6-mercaptopurine, or methotrexate), and failure to consider timely surgery. The paradox of anti-TNF therapy is that although it is used inappropriately (when there is sepsis or a fibrostenotic stricture) or overused (for disease that would respond to less potent therapy), it is also too often introduced too late in disease progression for those with a poor prognosis. We need to be smarter with conventional therapy. Smart means thinking about timing, checking disease activity, accelerating the introduction of immunomodulators or anti-TNF therapy, monitoring the biological response, avoiding therapies that have minimal efficacy, and measuring drug or metabolite levels. These are ways to tailor conventional therapies to individuals.

Supplementary Material

Note: The first 50 references associated with this article are available below in print. The remaining references accompanying this article are available online only with the electronic version of the article. Visit the online version of *Gastroenterology* at www.gastrojournal.org, and at [doi:10.1053/j.gastro.2011.02.045](https://doi.org/10.1053/j.gastro.2011.02.045).

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Conflicts of interest

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