

INFLAMMATORY BOWEL DISEASES[®]

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Clinical Scenarios in IBD: Optimizing the Use of Conventional and Biologic Agents

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ACTIVITY OVERVIEW

With improved understanding of the pathophysiology and natural history of inflammatory bowel disease (IBD), new treatment goals are evolving and therapeutic strategies continue to be refined. This supplement summarizes the discussions regarding the natural history of IBD, strategies for optimizing both conventional and biologic agents, and the relevance of various therapeutic end points that were featured in a recent symposium and explores issues of high relevance to clinicians who treat patients with IBD.

Target Audience

This activity has been designed to meet the educational needs of gastroenterologists and other health care professionals involved in the care of patients with IBD.

Learning Objectives

After completing this activity, participants should be able to:

- Compare clinical and endoscopic end points for treatment of ulcerative colitis and Crohn's disease
- Recognize predictors of disease course in IBD
- Develop treatment plans that utilize clinical predictors to optimize therapy for individual patients
- Design treatment plans that incorporate the appropriate selection and timing of conventional agents or biologic agents for ulcerative colitis or Crohn's disease

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Azathioprine	Imuran	Prevention of rejection in renal homotransplantation Severe, active rheumatoid arthritis (RA) that is unresponsive to rest, aspirin, or other nonsteroidal anti-inflammatory drugs (NSAIDs) or to agents in the class of which gold is an example	Induction and maintenance of remission in IBD; mucosal healing, and disease modification in IBD
Balsalazide	Colazal	Treatment of mildly to moderately active UC	Mucosal healing in UC
Budesonide, controlled-release	Entocort-EC	Treatment and maintenance of mild to moderate CD involving the ileum and/or ascending colon for up to 3 months	Treatment of CD for >3 months
Certolizumab	Cimzia	Reducing signs and symptoms and maintaining response in CD patients with inadequate response to conventional therapy Moderately to severely active RA	Mucosal healing and disease modification in IBD
Corticosteroids	Various	UC and regional enteritis, endocrine disorders, rheumatic disorders, collagen disorders, dermatologic diseases, allergic states, ophthalmic diseases, respiratory diseases, hematologic disorders, neoplastic diseases, edematous states, nervous system disorders (acute exacerbations of multiple sclerosis), and miscellaneous disorders (tuberculosis meningitis, trichinosis)	CD; mucosal healing and disease modification in IBD
Cyclosporine	Sandimmune, Neoral	Kidney, liver, and heart transplantation; RA; psoriasis	IBD
Infliximab	Remicade	CD, UC, RA, ankylosing spondylitis, psoriatic arthritis, plaque arthritis	Mucosal healing and disease modification in IBD
6-Mercaptopurine	Purinethol	Remission induction and maintenance therapy of acute lymphatic leukemia	Induction and remission, mucosal healing, and disease modification in IBD (adult and pediatric)
Mesalamine	Asacol	Treatment of mildly to moderately active UC Maintenance of remission of UC	CD; mucosal healing in UC
Mesalamine	Asacol HD	Treatment of moderately active UC	Treatment of mildly active UC; maintenance of remission of UC; CD; mucosal healing in UC
Mesalamine	Lialda	Induction of remission in patients with active, mild to moderate UC	CD; mucosal healing in UC
Mesalamine	Pentasa	Induction of remission and for the treatment of patients with mildly to moderately active UC	Maintenance of remission of UC; CD; mucosal healing in UC
Methotrexate	Rheumatrex	Treatment of neoplastic diseases Symptomatic control of severe, recalcitrant, disabling psoriasis that is not adequately responsive to other forms of therapy Management of selected adults with severe, active, RA (ACR criteria), or children with active polyarticular-course juvenile RA who have had an insufficient therapeutic response to, or are intolerant of, an adequate trial of first-line therapy including full dose NSAIDs	Maintenance of remission of CD, mucosal healing and disease modification in CD
Metronidazole	Flagyl	Trichomoniasis, amebiasis, treatment of <i>T. vaginalis</i> in asymptomatic consorts, anaerobic bacterial infections, intra-abdominal infections, skin and skin structure infections, gynecologic infections, bacterial septicemia, bone and joint infections, CNS infections, lower respiratory tract infections, endocarditis	CD
Olsalazine	Dipentum	Maintenance of remission of UC in patients who are intolerant of sulfasalazine	Treatment of active UC, mucosal healing in UC
Sulfasalazine	Azulfidine	Treatment of mild to moderate UC and as adjunctive therapy in severe UC Prolongation of the remission period between acute attacks of UC	CD; mucosal healing in UC
Sulfasalazine	Azulfidine-EN	Treatment of mild to moderate UC and as adjunctive therapy in severe UC Prolongation of the remission period between acute attacks of UC Treatment of patients with RA who have responded inadequately to salicylates or other NSAIDs Treatment of pediatric patients with polyarticular-course juvenile RA who have responded inadequately to salicylates or other NSAIDs	CD; mucosal healing in UC

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CAN WE PREDICT THE COURSE OF ULCERATIVE COLITIS AND CROHN'S DISEASE?

Crohn's disease (CD) and ulcerative colitis (UC)—known collectively as inflammatory bowel disease (IBD)—are chronic, inflammatory disorders that can become disabling over time. CD, in particular, is a generally progressive and luminally destructive disorder: most patients with CD eventually develop enteric structural complications that require (multiple) hospitalizations and surgeries.^{1,2} Prospective longitudinal data indicate that although most patients

with CD present initially with inflammatory disease, ≈80% of patients develop stricturing or penetrating complications within 20 years.¹ Further, approximately half of patients require surgical resection within 10 years of diagnosis, with a similar number of patients experiencing postoperative recurrence after 10 years.²

Despite the progressive course of the disease, however, the clinical course of IBD and the rate at which patients develop complications vary markedly, with about half of patients with either CD or UC in remission at any

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TABLE 1. Prognostic Factors in IBD

Age of onset
Duration of disease
Extent and location of disease
Severity of disease
Disease behavior
Prior treatment
Endoscopic appearance
Pharmacokinetics
Biomarkers
Genetic markers
Patient adherence
Smoking
<i>Clostridium difficile</i>

given time.^{3,4} Given the variability in clinical course, the ability to predict which patients are likely to develop complicated disease—and how they might respond to conventional or biologic agents—would be invaluable in guiding therapeutic decisions. To that end, an increasing number of clinical, serologic, and biologic factors that affect patient outcome have been identified (Table 1).

Clinical Factors

Numerous clinical factors have been associated with poor outcomes in CD. A recent analysis of data from the PRECiSE 2 trial indicated that response to certolizumab pegol was inversely proportional to duration of CD, with response rates 30% higher among patients with disease for less than 1 year compared with those with disease durations of 5 or more years ($P < 0.05$).⁵ Although early age at onset (i.e., age younger than 40 years) has been associated with aggressive CD,^{6,7} other studies have found a slower rate of progression to surgery among patients with childhood-onset CD compared with those who have adult-onset disease.⁸ In another study of patients with colorectal CD, patients with fistulizing disease had a significantly higher probability of requiring a permanent ileostomy over time than did those without fistulizing disease.⁹ Further, a study of 1526 patients with CD identified perianal disease at diagnosis and ileocolonic location as significant predictors of a 5-year disabling disease course.⁶ Additionally, smoking has been found to be associated with a higher risk of developing severe disease among CD patients.¹⁰

Endoscopic appearance may also be useful in predicting which patients will develop an aggressive clinical course in CD. In a retrospective study of 102 patients with active CD followed for a median of 52 months, the presence of deep and severe endoscopic lesions at initial colonoscopy was found to be an independent predictor of the risk of colectomy (relative risk = 5.43, 95% confidence

interval [CI] = 2.64–11.2).¹¹ In addition, all of the six patients who developed penetrating complications during the follow-up period had severe endoscopic lesions at the index colonoscopy.

Although not as well characterized as in CD, disease extent and behavior also appear to influence the clinical course of UC. Patients with UC who presented initially with pancolitis had significantly higher cumulative surgery rates over a 20-year span, in a referral-based series, than patients who presented with proctitis (66.7% versus 12.0%).¹² In contrast to CD, smoking appears to have a protective effect in UC, with smoking cessation significantly associated with more active disease, more hospitalizations, and greater need for corticosteroids or azathioprine in patients with CD.¹³

Biomarkers and Genetic Markers

An increasing number of studies suggest that, in addition to clinical parameters, various laboratory parameters and genetic markers may have prognostic value in IBD. Various laboratory parameters that reflect systemic inflammation have been studied in this regard, including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), platelet count, and white cell count.¹⁴ The best-studied of these markers is CRP, which correlates well with disease activity in CD but less so in UC.¹⁵ In contrast, fecal calprotectin is a stable, noninvasive marker of intestinal inflammation in both CD and UC.¹⁴ This marker may be particularly useful for predicting clinical relapse in IBD, with one study finding that a single fecal calprotectin level over 50 mg/L was highly predictive of clinical relapse in both CD and UC patients.¹⁴

Although they are not considered first-line for making diagnostic or clinical decisions,^{16,17} growing evidence suggests that genetic markers or serologic antibodies directed against microbial antigens may help predict aggressive disease behavior.^{18–20} Longitudinal analysis of 796 pediatric patients with CD demonstrated faster disease progression among children with immune reactivity to various microbial antigens, with the rate of complicated disease behaviors and surgery increasing with both the number and magnitude of immune reactivity.¹⁸ Another study in which 505 CD patients were genotyped found that patients with CARD15 variants at the time of diagnosis had a significantly shorter time to onset of stricturing disease and abdominal surgery over a median follow-up period of 15.6 years.²⁰ Although more studies are needed to characterize how these findings can be used clinically,²¹ these remain active areas of IBD research.

Predicting Response to Medical Therapies

A number of clinical factors may influence patient response to medical therapies in IBD. For many years the need for corticosteroids has been recognized as a poor

prognostic factor in IBD. Nearly a decade ago, population-based data from Olmsted County, Minnesota, demonstrated that 38% of patients with CD and 29% with UC who required steroids to achieve remission underwent surgical resection within 1 year of initiating steroids.²² In another study involving 1123 patients with CD, the need for steroids at the first exacerbation of disease tripled the likelihood of a subsequent 5-year disabling disease course (odds ratio [OR] = 3.1, 95% CI = 2.2–4.4).⁶ Similarly, previous response to medical therapies may help identify patients with UC who have difficult-to-treat disease. Analysis of data from 772 patients with moderately active UC in the ASCEND III (Assessing the Safety and Clinical Efficacy of a New Dose of 5-ASA) study indicated that patients who had previously used two or more UC medications were more likely to benefit from higher doses (4.8 g/day) of mesalamine than from a conventional 2.4 g/day dose.²³ Other characteristics associated with greater response to the higher dose were previous use of steroids, rectal therapies, or oral 5-aminosalicylates (5-ASAs).²³

Not surprisingly, nonadherence with medications has been associated with poor outcomes in IBD patients. Despite the frequent need for lifelong maintenance therapy, nonadherence is a prevalent problem in UC patients; some studies have reported adherence rates as low as 40%.²⁴ In a prospective study of 99 patients with quiescent UC, the risk of clinical recurrence during 24 months of follow-up was 5-fold higher among patients who were not adherent with their maintenance mesalamine compared with adherent patients (hazard ratio = 5.5, 95% CI = 2.3–13, $P < 0.001$).²⁵ Nonadherence is a complex behavior linked to many factors in IBD patients, including disease duration, disease activity, status as a new patient to the clinician, and the quality of the patient–physician relationship.²⁶

Growing evidence suggests that response to antitumor necrosis factor (anti-TNF) therapy may be influenced by various clinical and genetic factors. In a randomized, controlled study of 45 hospitalized patients who received infliximab for steroid-refractory UC, a single dose of infliximab was associated with a reduced rate of colectomy within the first 90 days after treatment (29% colectomy rate with infliximab versus 67% with placebo, $P = 0.017$).²⁷ However, when disease severity was stratified by Seo index, none of the patients with moderate disease activity required colectomy within 90 days of infliximab therapy, compared with 62% of patients with severe disease activity.²⁷ A recent study involving 94 pediatric UC and CD patients identified a combination of certain genetic factors (i.e., known IBD susceptibility loci and genomewide association identified loci), serologic markers, and clinical phenotypes to be an important predictor of increased risk and frequency of primary nonresponse to infliximab.²⁸ Lastly, serum infliximab levels have been found to be useful in predicting

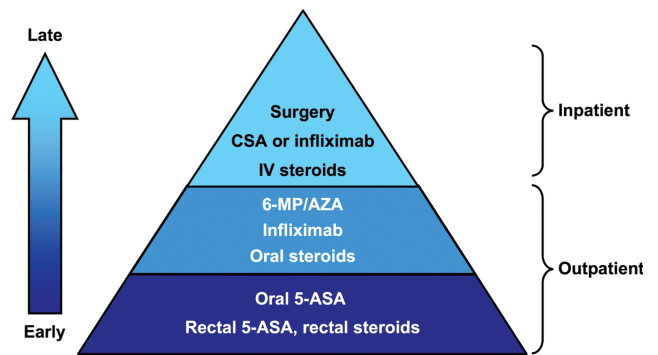


FIGURE 1. Current treatment paradigm for induction of remission in UC.

response to infliximab in CD. Of 105 patients receiving infliximab maintenance therapy, the rate of remission over a median follow-up period of 23 months was 82% among patients with a detectable serum trough infliximab concentration compared with 6% among those without detectable trough concentrations ($P < 0.001$).²⁹

Despite increasing recognition of clinical, biologic, serologic, and genetic factors that may indicate a complicated course of disease, it is not yet possible to reliably predict an individual's prognosis. However, future models are expected to incorporate many sources of information that, combined with clinical judgment, will be useful in estimating an individual's likelihood for aggressive disease and in guiding treatment decisions.

POSITIONING AND OPTIMIZING CONVENTIONAL AND BIOLOGIC AGENTS IN UC

The American College of Gastroenterology (ACG) recommends in its 2010 clinical practice guidelines that the initial approach to UC management be stratified by disease severity and extent.¹⁶ The severity of UC symptoms, not course, is characterized as mild, moderate, severe, or fulminant based on the number of daily stools and the presence of systemic toxicity, whereas disease extent is assessed endoscopically and characterized as distal (disease confined to below the descending colon) or extensive (extending proximal to the descending colon).¹⁶

The 5-ASAs are the cornerstone of therapy for induction and maintenance of remission in patients with mild to moderate disease activity (Fig. 1).^{16,30} Rectal 5-ASAs are superior to rectal steroids or oral 5-ASAs in distal disease and typically have a quicker onset of action than oral therapies.¹⁶ Factors that may influence the choice of rectal formulation include patient preference and extent of disease, as suppositories reach ≈ 10 cm, cortisone foam reaches ≈ 15 cm, and rectal suspension therapies (with either corticosteroids or mesalamine) may reach as far as the splenic flexure.¹⁶

Whereas rectal mesalamine therapies are effective as monotherapy for distal disease, oral aminosalicylates are required for patients with disease extending proximal to the descending colon (i.e., beyond the reach of rectal therapy).¹⁶ All of the oral 5-ASAs have predictable efficacy in achieving and maintaining remission in patients with mildly to moderately active UC.¹⁶ However, given that patients with extensive disease may also have significant distal disease and proctitis symptoms, rectal therapies offer an important therapeutic benefit in combination with oral therapies. Indeed, the combination of rectal mesalamine suspension and oral mesalamine has been shown to achieve earlier and greater relief of symptoms than either agent alone in patients with mildly to moderately active distal UC.³¹ Similarly, combination rectal and oral 5-ASA therapy achieves higher clinical response and remission rates than oral therapy alone in patients with mildly to moderately active extensive disease.³² As in patients with distal disease, the addition of rectal 5-ASA to oral therapy resulted in significantly earlier relief of rectal bleeding ($P = 0.0025$).³² Thus, combination therapy with rectal and oral agents may be an effective strategy for mildly to moderately active UC, regardless of the anatomic extent of disease.

Effective doses of oral 5-ASAs in mildly to moderately active UC range between 4 and 6 g/day for sulfasalazine and up to 4.8 g/day (mesalamine equivalent) for alternative aminosalicylates (olsalazine, balsalazide, mesalamine). Although response to sulfasalazine is dose related,¹⁶ studies have not demonstrated a consistent dose response with the nonsulfa 5-ASAs among UC patients with mildly to moderately active disease.^{33–38} However, as discussed previously, there may be a therapeutic advantage in using higher delayed-release mesalamine doses in certain patients with moderately active disease. Retrospective post-hoc analysis of data from the ASCEND III trial suggests the existence of a subgroup of patients with difficult-to-treat moderate UC who may benefit from higher doses (4.8 mg/day) of delayed-release mesalamine compared with conventional (2.4 g/day) doses.²³ Although no significant treatment difference between doses was observed in the overall population, treatment success at week 6 was significantly higher with the 4.8 mg/day dose among patients who were previously treated with two or more medications ($P = 0.01$), corticosteroids ($P = 0.05$), oral mesalamine ($P = 0.07$), or rectal therapies ($P = 0.06$).²³

When Patients Do Not Respond to First-line Agents in UC

Patients with mildly to moderately active UC who are refractory to rectal therapies and oral 5-ASAs may be candidates for therapy with oral steroids, azathioprine (AZA)/6-mercaptopurine (6-MP), or infliximab.¹⁶ Because

oral corticosteroids are rapidly effective for inducing clinical and endoscopic response and remission in UC,³⁹ they may be useful for patients whose symptoms require rapid improvement.¹⁶ However, steroids are associated with a high rate of steroid dependence²² and significant toxicities affecting multiple organ systems, including cushingoid features, emotional and psychiatric disturbances, metabolic disturbances, bone disease, and increased risk of opportunistic infections.⁴⁰ Further, steroids do not appear to provide “safe and effective” sustained maintenance benefits or alter the natural history of IBD. To the contrary, only one-third of UC patients have continued response to steroids within a year of initiating these agents, and an equal proportion eventually require colectomy.^{22,41} We describe the one-third of patients with continued response as “steroid-dependent” and continue to advocate “steroid-sparing” approaches to minimize their long-term toxicities.

In light of these limitations, it is essential that a strategy for discontinuing steroids (i.e., an exit strategy) is implemented at the time of steroid initiation. In addition to a dose taper schedule and optimization of oral and rectal 5-ASAs,¹⁶ immunosuppressants may be valuable in reducing steroid requirement in UC patients. In one randomized study involving 72 patients with steroid-dependent UC, 53% of patients receiving AZA 2 mg/kg/day achieved steroid-free clinical and endoscopic remission compared with 19% of those receiving oral 5-ASA 3.2 g/day ($P = 0.006$).⁴² A subsequent meta-analysis of five small studies in UC patients with steroid-induced remission suggested a trend towards AZA efficacy in maintaining clinical remission or response, although statistical significance was not reached.⁴³ Despite this relatively weak evidence base, AZA/6-MP is considered an important steroid-sparing therapeutic option for patients with UC.¹⁶

The anti-TNF α agent infliximab is an important option for patients who are refractory to or dependent on steroids despite adequate therapy with AZA/6-MP and for patients who cannot tolerate these agents.¹⁶ The Active Ulcerative Colitis Trials 1 and 2 (ACT 1 and 2) demonstrated the efficacy of infliximab in inducing and maintaining remission in outpatients with symptoms of moderate to severe UC despite treatment with conventional therapy.⁴⁴ In these large, randomized controlled trials, infliximab was associated with significantly higher clinical remission rates than placebo at 54 weeks in ACT 1 (34% for infliximab 5 mg/kg and 10 mg/kg versus 17% for placebo, $P = 0.001$).⁴⁴ However, steroid discontinuation rates in the ACT 1 and 2 trials were relatively modest, with fewer than 30% of infliximab patients discontinuing steroids at 30 weeks in each trial and at 54 weeks in ACT 1.⁴⁴ However, because these trials did not permit steroid dosage adjustment or concomitant treatment with rectal therapies or thiopurines, these remission and steroid discontinuation rates

may not be reflective of clinical practice where these conventional strategies are commonly used.

In addition to achieving clinical response and remission, subanalyses of data from the ACT 1 and 2 trials demonstrate that infliximab improves health-related quality of life (HRQoL)⁴⁵ and may have disease-modifying benefits in UC.⁴⁶ In a subanalysis of 728 patients involved in these trials, patients who received infliximab had a 7% reduction in the absolute risk of colectomy through 54 weeks compared with placebo-treated patients (10% versus 17%, $P = 0.02$). Further, infliximab-treated patients had fewer UC-related hospitalizations (40 versus 20, $P = 0.003$) and surgeries/procedures (34 versus 21, $P = 0.03$) compared with placebo-treated patients.⁴⁶

Patients with severe disease who are not responding to maximal doses of prednisone, oral 5-ASAs, or rectal medications should be treated with a course of intravenous (IV) steroids.¹⁶ However, a meta-analysis of 32 studies indicated that $\approx 30\%$ of patients admitted for severe UC required colectomy despite the use of IV steroids.⁴¹ Moreover, retrospective data suggest that certain clinical parameters by day 3 of admission—notably sustained fever, persistence of diarrhea, and CRP elevation—are predictive of steroid resistance.⁴⁷ Thus, patients who do not improve significantly after 3 to 5 days of IV steroids are considered unlikely to respond to this treatment and should be considered candidates for IV cyclosporine or infliximab, or surgery.¹⁶

Several small studies in patients with severe UC indicate that $\approx 80\%$ of patients treated with IV cyclosporine respond and avoid colectomy in the acute phase.^{48–50} The doses used in these studies typically ranged from 2 to 4 mg/kg/day, with the 2 mg/kg/day dose as effective as the higher dose but less likely to induce adverse effects.^{49,51} Despite good efficacy in the short term,^{48–50} however, follow-up studies indicate lower long-term success rates with cyclosporine in severe UC. Studies with mean follow-up periods of 7 years have demonstrated colectomy-free rates ranging from 12%⁵² to 58%.⁵³ Further, cyclosporine is associated with substantial potential toxicities, including nephrotoxicity, seizures, and opportunistic infection.¹⁶ Antibiotic prophylaxis against *Pneumocystis jiroveci* (*carinii*) pneumonia is recommended during cyclosporine therapy.¹⁶ Other antibiotics should be used if signs of toxicity occur. There is an increasing frequency of *Clostridium difficile* infection in UC patients, which is associated with increased morbidity and mortality in this population.

Infliximab may be an effective alternative to cyclosporine in patients who are hospitalized with moderate to severe steroid-refractory UC.^{27,54–57} The largest of these studies found infliximab to be an effective rescue therapy in 45 patients who did not respond to IV steroids, with 29% of the infliximab-treated patients requiring colectomy within 90 days compared with 66% of placebo-treated

patients ($P = 0.017$).²⁷ Preliminary analysis of these data indicate that the benefit of infliximab is sustained over 2 years in nearly half of patients who received infliximab during the initial flare in the hospital.⁵⁸

Although either cyclosporine or infliximab may be beneficial for avoiding colectomy in the short term,^{27,48–50,54–57} as yet there are no trials comparing these two therapies in patients with severe steroid-refractory UC.¹⁶ However, the effect of switching salvage therapies was examined in one study of 19 patients who did not respond to either cyclosporine or infliximab and were then treated with the alternative drug within 30 days.⁵⁹ At 12 months, only $\approx 30\%$ of patients had avoided colectomy and remained in steroid-free remission. Moreover, the incidence of a serious adverse event was 16%, including one death. Another recent study assessed the efficacy and safety of infliximab treatment for 51 patients with steroid-refractory UC who did not respond to cyclosporine therapy. Although treatment with infliximab resulted in avoidance of colectomy for two-thirds of the study participants, the rate of adverse events was 25%, including one death.⁶⁰ Given these outcomes, cyclosporine and infliximab should not be used concomitantly, and the drugs should be used with great caution if used in immediate succession.¹⁶

Surgery is indicated for patients with severe UC who do not respond to, or cannot tolerate, maximal medical therapy.¹⁶ Exsanguinating hemorrhage, perforation, or documented and strongly suspected carcinoma are absolute indications for surgery. Despite the significant risks and morbidities associated with surgery,¹⁶ clinicians and patients alike must bear in mind that restoring the patient's health and well-being, rather than avoidance of colectomy, is the ultimate goal of UC therapy.

POSITIONING AND OPTIMIZING CONVENTIONAL AND BIOLOGIC AGENTS IN CD

The initial management of CD, like that of UC, is based on disease location, severity, and disease-associated complications.¹⁷ The current therapeutic approach outlined in the ACG practice guidelines for CD recommends sequential therapies to induce remission, followed by maintenance therapy to maintain response and remission.¹⁷ Based on this “step-up” approach, patients with mildly to moderately active ileal, ileocolonic, or colonic disease may be treated with oral 5-ASAs, metronidazole, controlled ileal-release budesonide, and oral corticosteroids.¹⁷ In contrast to their well-established role in UC, 5-ASAs for CD remain less supported in controlled clinical trials, and some experts have recently recommended against the use of 5-ASAs for the treatment of CD.

Although sulfasalazine is modestly effective for CD confined to the colon,⁶¹ the current evidence supporting oral mesalamine for the treatment of CD suggests only

minimal efficacy compared with placebo.^{17,62} In contrast, controlled ileal-release budesonide has been shown to be more effective than placebo⁶³ and mesalamine⁶³ and generally comparable to conventional oral steroids^{63,64} in patients with mild to moderate disease involving the distal ileum and/or right colon.¹⁷ Accordingly, this therapy has been recommended as the preferred first-line therapy in patients with mild to moderate disease with ileal and/or right colonic involvement.^{17,64} Conventional oral steroids are a reasonable option for patients not responding to sulfasalazine or controlled ileal-release budesonide.⁶⁴

Maintenance Therapy

Given the high rate of relapse associated with discontinuation of acute therapy or after surgical resection for CD,² most patients require therapy to maintain remission. Neither sulfasalazine or alternative oral 5-ASAs have demonstrated consistent benefit in maintaining remission in CD.^{17,65} Further, despite their significant short-term benefit, neither conventional steroids nor controlled ileal-release budesonide are effective for maintaining remission in the long term or altering the natural history of CD.^{17,65,66} Immunosuppressants (AZA/6-MP, methotrexate) are useful for maintaining steroid-induced remission in CD.⁶⁵ Nevertheless, potential adverse effects of immunosuppressive therapy include short-term intolerance (nausea, fatigue, malaise) or allergy (pancreatitis, fever), and long-term therapeutic monitoring is necessary because of the risks of bone marrow toxicity, hepatotoxicity, infection, and lymphoma.⁶⁵ Taken collectively, the modest long-term efficacy and potential for toxicity of the available agents constitutes an important therapeutic gap for many patients with mild to moderate CD, in whom the optimal maintenance strategy has not been defined.⁶⁵

When Patients Do Not Respond to First-line Agents in CD

Therapeutic strategies for patients who do not respond to first-line agents include steroids (prednisone or controlled ileal-release budesonide), steroids and AZA, an anti-TNF agent, or an anti-TNF agent in combination with AZA. As in UC, the short-term benefits of steroids in CD patients are offset by poor long-term outcomes. Among patients with CD who initially respond to steroids, only one-third have prolonged response at 1 year after steroids are discontinued, while approximately one-third become dependent and nearly 40% require surgery within the year.²² In contrast, AZA achieves steroid-free remission in CD in nearly 40% of patients regardless of whether they receive a concomitant steroid taper.^{61,67} Additionally, the efficacy of biologic agents in inducing and maintaining remission in patients with moderate to severe CD has been well established in randomized, controlled trials.^{68–73}

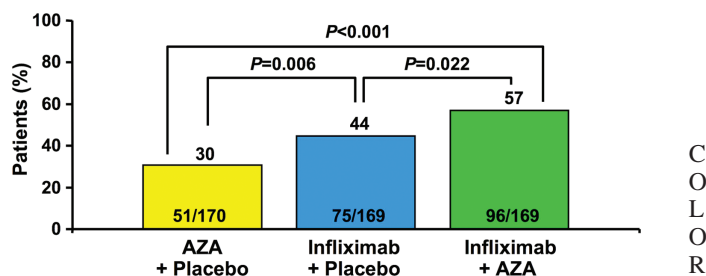


FIGURE 2. Patients with steroid-free remission at week 26 in the SONIC trial. Colombel JF, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med*. 2010; 362(15):1383–1395. Copyright © 2010 Massachusetts Medical Society. All rights reserved.

Most recently, results from the Study of Biologic and Immunomodulator Naïve Patients in Crohn's Disease (SONIC) trial have provided insight into the comparative effectiveness of AZA, infliximab, and the combination of these two agents in CD.⁷⁴ In this randomized, double-blind trial, 508 patients with moderate to severe CD who were naïve to immunomodulators or biologic therapy received AZA 2.5 mg/kg/day, infliximab 5 mg/kg induction therapy followed by maintenance every 8 weeks, or a combination of the two for up to 50 weeks. At 26 weeks, patients receiving combination therapy had higher rates of steroid-free remission (56.8%) than did those receiving infliximab (44.4%) or AZA monotherapy (30.0%) ($P < 0.001$ for combination therapy versus AZA, $P = 0.02$ for combination therapy versus infliximab) (Fig. 2).⁷⁴ These results were similar across all three groups at 50 weeks, suggesting a durable effect of combination therapy. The incidence of adverse effects was similar across treatment groups, and in particular, serious infections developed in a comparable proportion of patients in each treatment group (5.6%, 4.9%, and 3.9% with AZA, infliximab, and combination therapy, respectively).⁷⁴

Current evidence does not provide clear direction for managing patients who do not respond to maximal medical therapies with biologic and immunosuppressive agents, but there are several approaches that may be useful in such patients. In addition to magnetic resonance imaging (MRI) enterography and colonoscopy, diagnostic evaluation of such patients may include obtaining blood serum thiopurine metabolite levels as well as serum infliximab and human antichimeric antibody (HACA) levels/antibodies to infliximab (ATIs). Although data are insufficient to recommend routine metabolite monitoring,¹⁷ many retrospective studies have indicated that 6-thioguanine nucleotide (6-TGN) and 6-methylmercaptapurine (6-MMP) levels may be useful in assessing lack of response to AZA/6-MP.⁷⁵

A meta-analysis of 12 trials demonstrated that patients with 6-TGN levels above the threshold value (230–260 pmol/8 × 10⁸ red blood cells) were three times

more likely to be in remission than were those who had levels below the threshold value (OR = 3.3, 95% CI = 1.7–6.3, $P < 0.001$).⁷⁵ Importantly, the dose of AZA/6-MP correlates with 6-TGN production among responders to these therapies, emphasizing the importance of using optimal AZA/6-MP doses in this population.⁷⁶ Methotrexate may be a reasonable alternative for patients who do not respond to optimal thiopurine doses, although controlled data in this setting are not available.

Evaluation of serum infliximab and HACA levels may be helpful in assessing loss of response to infliximab. In the SONIC trial, higher 26- and 50-week rates of steroid-free remission were observed in patients who were negative for HACA than were seen in HACA-positive patients.⁷⁴ However, patients with inconclusive antibody tests (indicating the presence of infliximab in the serum) had higher rates of remission than HACA-negative or HACA-positive patients. When results were stratified by serum infliximab level, remission rates were ≈15%–20% higher in patients with elevated trough serum infliximab levels than they were in those who had very low or undetectable infliximab trough levels.⁷⁴ However, 59% of patients with undetectable infliximab trough concentrations were in steroid-free remission at 26 weeks,⁷⁴ raising the possibility of a clinical carryover effect.

Given these observations, an approach has recently been suggested for managing patients with suboptimal response to infliximab.⁷⁷ Appropriate options include changing to another anti-TNF agent in HACA-positive patients; changing to a drug with a different mechanism of action or investigating alternate etiologies in patients with therapeutic infliximab concentrations; and increasing infliximab dose, reducing infliximab dosing intervals, or changing to a different anti-TNF in patients with subtherapeutic infliximab concentrations.

Surgery is an option for patients with medically intractable disease and is eventually required in up to two-thirds of patients with CD.¹⁷ The functional consequences of bowel resection for CD are significant, however, and tend to increase with the amount of bowel resected. Such complications include bile salt diarrhea, steatorrhea, bacterial overgrowth, and a high incidence of postoperative recurrence.^{17,78} As in UC, however, surgery should not be viewed in a negative light, when in some cases it can be the most rapid and effective route to restoring the patient’s health.¹⁷

CLINICAL VERSUS ENDOSCOPIC END POINTS IN CLINICAL PRACTICE FOR IBD

Treatment goals for IBD have historically been symptom- and laboratory-based end points that focus on the induction and maintenance of clinical remission.^{16,17} A key clinical goal has been to achieve normal bowel function—meaning formed stools without blood, urgency, or

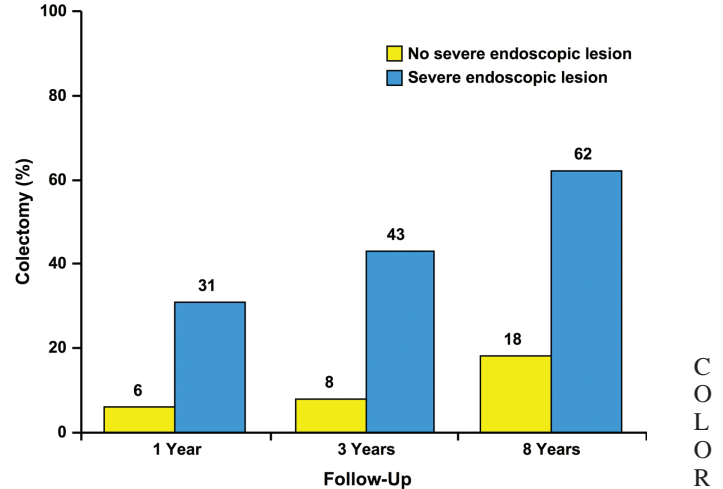


FIGURE 3. Severe endoscopic ulcerations are associated with risk of colectomy in CD.

nocturnal symptoms—and thus improve patients’ quality of life. A particularly important goal for pediatric patients is to achieve clinical response/remission while facilitating appropriate growth and development.⁷⁹ Although these traditional end points remain essential, current goals are evolving to include additional outcomes that may have a more significant, long-term impact on the natural history of the disease. These goals include mucosal healing, disease modification, and prevention of extraintestinal complications such as colorectal cancer.^{17,44,66,80}

Mucosal Healing in CD

The presence of severe mucosal lesions is a poor prognostic factor related to the clinical course of CD. Over 20 years ago, Rutgeerts et al⁸¹ identified the severity of endoscopic lesions as a strong predictor for symptomatic recurrence among 89 patients who had undergone ileal resection for CD. Endoscopic recurrence in this cohort preceded not only symptomatic recurrence but also laboratory and surgical recurrence.⁸¹ More recently, Allez et al¹¹ reached a similar conclusion in a study of 102 CD patients in whom the presence of severe endoscopic lesions at diagnosis was associated with increased risk of colectomy (Fig. 3). Thus, endoscopic assessment may be a useful strategy for identifying patients at increased risk for complications and targeting them for aggressive therapy with biologic agents.

The ability of various therapies to heal the mucosa in IBD has been explored in clinical trials, although typically as a secondary end point. Some evidence suggests that AZA/6-MP^{82,83} and methotrexate⁸⁴ heal the mucosa in CD, but inconclusive results have been demonstrated with steroids in this regard.^{66,85} The efficacy of infliximab in achieving mucosal healing at 54 weeks was confirmed in the ACCENT 1 trial, which demonstrated complete

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mucosal healing in over half of patients receiving maintenance infliximab therapy.⁸⁶ Moreover, the Top-Down versus Step-Up trial found that early combination treatment with infliximab and AZA was significantly more effective at achieving mucosal healing than conventional step-up therapy after 2 years of treatment (73% mucosal healing in the early combined immunosuppression group versus 30% with conventional therapy, $P = 0.0028$).⁸⁷ Similarly, combination infliximab/AZA therapy in the SONIC trial achieved higher endoscopic remission rates at 26 weeks than either therapy alone (44%, 30%, 16% with combination therapy, infliximab, and AZA, respectively; $P < 0.001$ for combination therapy versus AZA, $P = 0.06$ for combination therapy versus infliximab).⁷⁴ Preliminary data have also demonstrated efficacy for adalimumab in achieving endoscopic remission at 52 weeks⁸⁸ but the effect of certolizumab pegol in healing the mucosa has not yet been confirmed in a placebo-controlled trial.

Emerging evidence indicates that endoscopic healing is associated with improved outcomes in CD. The results of a Norwegian study indicated that mucosal healing achieved with various agents (5-ASAs, steroids, antibiotics, or AZA) was associated with less inflammation after 5 years ($P = 0.02$) and decreased need for steroid treatment at 5 years ($P = 0.02$).⁸⁰ Subsequently, the endoscopic substudy of the ACCENT 1 trial demonstrated a trend towards fewer hospitalizations among patients who achieved mucosal healing with infliximab.⁸⁶

Follow-up analysis of data from the Top-Down versus Step-Up trial indicated that patients who achieved complete mucosal healing were significantly more likely to achieve sustained steroid-free remission 4 years after the initiation of therapy than were those without complete mucosal healing.⁸⁹ Long-term benefits of mucosal healing associated with infliximab were also demonstrated in a study of 214 CD patients who had received long-term infliximab therapy.⁹⁰ After a median follow-up of 22.3 months, patients who achieved mucosal healing were more likely to have sustained clinical response ($P < 0.001$) and reduced need for major abdominal surgeries than were patients with no or partial healing ($P < 0.0001$).⁹⁰

Most recently, preliminary studies of biologic therapy with infliximab has been shown in a small controlled trial to reduce the rate of endoscopic recurrence in patients who have undergone ileocolonic resection for CD (9.1% recurrence rate with infliximab versus 84.6% with placebo, $P = 0.0006$).⁹¹

Mucosal Healing in UC

Similar to CD, severe endoscopic lesions portend a poor prognosis in UC. In UC, several small studies have demonstrated the efficacy of steroids³⁹ and AZA/6-MP⁴² in achieving endoscopic remission. In short-term induction tri-

als, 69% and 77% of patients receiving delayed-release mesalamine 2.4–4.8 g/day, respectively, achieved mucosal healing (defined as a sigmoidoscopic score ≤ 1),³⁷ whereas up to 80% patients receiving 4.8 g/day in the ASCEND I and II trials achieved mucosal healing (defined as an endoscopy subscore of 0 or 1).⁹² Statistical significance in these trials was reached as early as 6 weeks.⁹² In the ACT 1 and 2 trials, infliximab 5 mg/kg and 10 mg/kg achieved mucosal healing (defined as endoscopy subscore of 0 or 1) in nearly half of patients at 54 weeks.⁴⁴

Although not as extensively studied as in CD, mucosal healing in UC patients has been correlated with a number of improved outcomes. In one study involving 78 UC patients who received combination therapy with oral and rectal 5-ASAs for 6 weeks, cumulative relapse rates at 1 year were significantly lower among patients who achieved both clinical and endoscopic remission than they were in patients who achieved only clinical remission (23% versus 80%, respectively; $P < 0.0001$).⁹³ In the Norwegian study, mucosal healing was associated with a lower risk of future colectomy ($P = 0.02$).⁸⁰ Additionally, the growing association between histologic inflammation and neoplasia^{94–96} suggests that endoscopic and histologic healing may have protective effects against dysplasia.

Is Routine Endoscopic Assessment Ready for Prime Time?

With the increasing recognition of mucosal healing as a therapeutic end point, the use of endoscopy in IBD is expanding from a more diagnostic role to one that includes assessment of disease prognosis and response to therapy. Despite the growing association of mucosal healing with improved outcomes in IBD and its potential prognostic value, however, endoscopic assessment of response to therapy has not yet been adopted into routine clinical practice.

The assessment of mucosal healing in clinical trials has been inconsistent, with significant variation in definition (complete versus partial healing versus improvement by segment), assessment technique (endoscopic versus histologic), and intraobserver and interobserver interpretation. Further, despite intuitive association, mucosal appearance does not correlate well with clinical symptoms or activity indices in IBD.^{87,97} For example, endoscopic remission rates in the ACT and ASCEND III trials were substantially different from the clinical remission rates reported in these trials,^{23,44} underscoring the variable nature of symptoms, and the definitions of mucosal healing used. Practical limitations to the routine use of endoscopic end points in IBD include cost and patient inconvenience. Perhaps most important, there is currently no clear direction on how to use endoscopic information in patient management. This may be particularly challenging when active inflammation is found in asymptomatic patients.

CONCLUSION

Although the natural history of IBD is increasingly recognized as progressive and potentially destructive and carcinogenic, the rate at which an individual patient progresses to complicated disease varies significantly. Accordingly, the ability to predict which patients are likely to develop complicated disease is essential for identifying patients who are most likely to have aggressive disease and thus benefit from aggressive treatment strategies. Studies have identified a number of clinical and environmental factors, and biologic, serologic, and genetic markers that may eventually be useful in predicting complicated disease behavior. It is not currently possible to reliably predict an individual patient's prognosis; however, future models are expected to incorporate these factors and markers in improving clinicians' ability to estimate an individual's likelihood of developing aggressive disease and individualizing treatment.

Consistent with previous guidelines, the 2010 ACG guidelines on UC management emphasize 5-ASAs as the cornerstone of management for patients with mildly to moderately active UC. Prednisone, infliximab, and intravenous steroids may be options for some patients with moderate to severe disease that does not respond to maximal doses of oral and rectal 5-ASAs. Surgery is indicated for patients who do not respond to maximal medical therapies.

The most recent ACG guidelines on CD management identify oral 5-ASAs, metronidazole, controlled ileal-release budesonide, and oral steroids as options for managing ileal, ileocolonic, or colonic disease. In contrast to its well-established role in UC, however, the benefit of 5-ASAs for CD remain less definitive. The biologic agents are highly effective for inducing and maintaining remission in patients with CD, and recent data indicate that combination therapy with infliximab and AZA is superior in maintaining steroid-free remission than either agent alone. Therapeutic strategies for patients who do not respond to maximal therapy with biologic and immunosuppressive agents include further diagnostic evaluation, examining thiopurine metabolite levels, and assessing serum infliximab and HACA levels.

Although the primary treatment goals for IBD have traditionally been the induction and maintenance of clinical remission, mucosal healing is increasingly recognized as an important therapeutic end point in IBD. Recent data have associated mucosal healing with lower relapse rates, reduced need for steroids, and lower risk of surgeries in IBD patients. Further, the recognition that endoscopic recurrence is predictive of clinical recurrence and colectomy suggests that mucosal healing may have prognostic value in IBD. Despite these findings, however, mucosal healing does not correlate with clinical severity of disease, and the

degree to which endoscopic findings should influence treatment decisions remains uncertain.

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POSTTEST

Please record your answers in the spaces provided at the bottom of the Activity Evaluation Form (back cover) or complete the posttest and evaluation online at <http://www.curatiocme.com/posttest/IBDoptimize>.

1. Clinical factors that have been associated with poor outcomes in patients with inflammatory bowel disease (IBD) include
 - a. Early age at disease onset and duration of disease
 - b. Fistulizing disease
 - c. Nonadherence to medical therapy
 - d. All of the above
2. Which of the following has been associated with poor outcomes in patients with IBD?
 - a. Moderate disease activity
 - b. Need for corticosteroid therapy
 - c. Previous mesalamine use
 - d. All of the above
3. Rectal 5-aminosalicylic acid (5-ASA) therapy in patients with mildly to moderately active distal ulcerative colitis (UC)
 - a. Has a slower onset of action than oral therapy
 - b. Is more effective when used in combination with oral 5-ASA therapy
 - c. Is not as effective as oral 5-ASA therapy
 - d. All of the above
4. Which of the following patients with moderately active UC may benefit more from delayed-release mesalamine 4.8 g/day compared with 2.4 g/day?
 - a. Patient who has previously received multiple UC medications
 - b. Patient who has previously received oral mesalamine
 - c. Patient who has previously received steroids
 - d. All of the above
5. Which of the following is true regarding the use of cyclosporine for the management of patients with severe UC?
 - a. Cyclosporine therapy is associated with significant toxicities
 - b. Cyclosporine and infliximab can be used safely as concomitant therapies or in immediate succession
6. The most appropriate first-line agent for patients with mildly to moderately active Crohn's disease (CD) with ileal and/or right colonic involvement is
 - a. Azathioprine
 - b. Controlled ileal-release budesonide
 - c. Delayed-release mesalamine
 - d. Prednisone
7. According to results of the recent SONIC trial, which of the following strategies is most effective for inducing steroid-free remission in patients with moderately to severely active CD?
 - a. Azathioprine monotherapy
 - b. Combination azathioprine-infliximab therapy
 - c. Infliximab monotherapy
 - d. Sulfasalazine monotherapy
8. Which of the following options is appropriate when evaluating patients with CD who have poor clinical response to combination therapy with infliximab and azathioprine?
 - a. Evaluate 6-thioguanine nucleotide levels
 - b. Evaluate for presence of human antichimeric antibody
 - c. Evaluate serum infliximab levels
 - d. All of the above
9. Mucosal healing in IBD has been associated with
 - a. Reduced need for surgeries
 - b. Sustained steroid-free remission
 - c. Trend towards reduced hospitalization
 - d. All of the above
10. The clinical relevance of mucosal healing in daily practice has not yet been clearly defined
 - a. True
 - b. False

Activity Evaluation: *Clinical Scenarios in IBD: Optimizing the Use of Conventional and Biologic Agents*

Number of credits: 1.0 AMA PRA Category 1 Credit™

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EVALUATION

1. Rate the extent to which you agree or disagree.

	Strongly Agree			Strongly Disagree	
• I am satisfied with the overall quality of this activity	5	4	3	2	1
• Participation in this activity changed my knowledge/attitudes	5	4	3	2	1
• I will make a change in my practice as a result of my participation in this activity	5	4	3	2	1
• The activity presented scientifically rigorous, unbiased, and balanced information	5	4	3	2	1

Please list the changes you plan on making in your practice as a result of your participation in this activity:

If you felt the activity was biased, please explain:

2. This activity helped me to achieve the following objectives:

	Strongly Agree			Strongly Disagree	
• Compare clinical and endoscopic end points for treatment of ulcerative colitis and Crohn's disease	5	4	3	2	1
• Recognize predictors of disease course in IBD	5	4	3	2	1
• Develop treatment plans that utilize clinical predictors to optimize therapy for individual patients	5	4	3	2	1
• Design treatment plans that incorporate the appropriate selection and timing of conventional agents or biologic agents for ulcerative colitis or Crohn's disease	5	4	3	2	1

If you felt the learning objectives were not met, please explain:

3. What information remains unclear?

4. Questions or comments regarding this activity:

5. How did you hear about this activity? (Please check all that apply.)

Direct mailing Curatio CME Institute Web site Colleague E-mail Other (Please specify.) _____

6. Suggested topics and/or speakers you would like for future programs:

7. What is/are your preferred format(s) for earning continuing medical education credits? (Please check all that apply.)

Satellite symposium Grand rounds CD-ROM Dinner meetings Internet activities Mobile device
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POSTTEST ANSWERS Please fill in your answers below.

1 _____ 2 _____ 3 _____ 4 _____ 5 _____ 6 _____ 7 _____ 8 _____ 9 _____ 10 _____

Signature _____