

# Current Medical Therapy for Chronic Inflammatory Bowel Diseases

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Chronic idiopathic inflammatory bowel disease (IBD) is a term for Crohn's disease (CD), ulcerative colitis (UC), and colonic IBD type unclassified (IBDU) [1]; the latter was referred to previously as indeterminate colitis (IC). The full spectrum of IBD may include disorders such as lymphocytic colitis, collagenous colitis, diverticular disease-associated colitis, and others. This article focuses upon current medical therapies for adult CD and UC. Detailed management issues, treatment of extraintestinal manifestations of IBD, and therapies not yet shown effective through large clinical trials are not reviewed here. Because the pathophysiology is characterized by an overactive immune response at the gut level, almost all currently accepted therapies are anti-inflammatory or immunosuppressive by design. Newer "biologic" agents achieve potent, targeted blockade of specific aspects of intestinal and systemic immune dysregulation, such as tumor necrosis factor  $\alpha$  (anti-TNF- $\alpha$  agents). Although this has improved the lives of patients suffering from severe IBD dramatically, knowledge of the impact of such immunosuppression (even from corticosteroids) continues to evolve. Therefore, the clinician who uses these therapies should be well versed in their pharmacology, clinical indications, contraindications, and complications and be committed to routine surveillance for all of these issues.

Optimal medical management of IBD is multifaceted and individualized. Except for mild cases (primarily UC), most patients require combination therapy to achieve sustained response or remission. Fine-tuning of treatment is based upon clinical, biochemical, endoscopic, and histologic responses that depend upon considerations of drug doses, routes, and timings and drug-drug synergies. Despite advances in our ability to predict clinical course in specific patients, the individual response to IBD therapy

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often is idiosyncratic. There also are many well-known factors influencing response, including adherence with difficult medication regimens [2], pharmacogenetics [3], clinical phenotype of IBD, drug–drug interactions, drug tolerances, tachyphylaxis, toxicities, and adverse reactions. In addition, the clinician should be aware of commonly occurring infectious complications (eg *Clostridium difficile* or cytomegalovirus colitis intra-abdominal abscesses) and malignancies that may mimic an IBD “flare-up.”

Specific goals of medical therapy for IBD include the reduction of: abdominal pain, diarrhea, fatigue, anemia, nutrient deficiencies, mucosal inflammation, extraintestinal manifestations, hospitalizations, operations, and complications, such as abscesses, fistulae, infections, and malignancy. Improved quality-of-life also has been an important outcome measured in clinical trials. Several clinical indices have been used to measure these outcomes in research trials, but they are difficult to use in day-to-day practice. The correlation between symptoms of IBD and endoscopic appearances is controversial [1].

This article has categorized medical therapy for IBD into agents for inducing remission and those for maintaining remission. Ideally, an overlap occurs between the two, transitioning from sometimes highly aggressive combination therapy induction phases to less complex maintenance regimens, hopefully while avoiding relapse. Best medical management for IBD over the long-term requires a solid physician–patient relationship and explicit agreement upon its shared responsibilities. Adverse effects of the medical therapies described in this article are listed in [Appendix 1](#).

## **Crohn’s disease**

### *Induction of remission*

The initial presentation of active CD or a subsequent “flare-up” implies adverse change from baseline. Because CD may affect any portion of the gut from mouth to anus, symptoms vary widely and may present diagnostic challenges. Most commonly, CD affects the colon, terminal ileum, or both, which may lead to abdominal pain, cramping, diarrhea with or without blood, nausea, vomiting, fever, malaise and fatigue, anorexia, or weight loss. Upper gastrointestinal (GI) tract involvement (esophagus, stomach, and duodenum) may produce heartburn, dysphagia, dyspepsia, early satiety, nausea and vomiting, or epigastric abdominal pain. Extraintestinal manifestations may be present. If clinically indicated, abscess should be ruled out with abdominopelvic CT or MRI, especially before initiating corticosteroids or immunomodulators/anti-TNF- $\alpha$  agents. Therapy should be instituted as early as possible, and, ideally, after colonoscopy or sigmoidoscopy with biopsies, and possibly upper esophagogastroduodenoscopy. This is especially important at initial disease presentation, such that therapy may be tailored to disease location and severity, and to avoid diagnostic confusion after

partially treated IBD. If infectious colitis is suspected (eg, in those already taking immunosuppressors), early colonoscopic biopsy review is helpful before therapy. The Crohn's Disease Activity Index (CDAI) score, derived from a 1-week diary [4], has been used as a guide to distinguishing mild, moderate, and severe disease in clinical trials (Box 1). CDAI scores between 150 and 220 are "mild" and scores between 221 and 400 are "moderate"; more than 400 points is considered "severe" disease, and remission is defined as CDAI score less than 150.

### *Mild disease*

The most commonly used agents include sulfasalazine, oral or topical mesalamine (topical for colonic disease), oral antibiotics, and the topically active oral corticosteroid budesonide (for terminal ileal and right-sided colonic disease). Sulfasalazine was the earliest 5'-aminosalicylate (5'-ASA) drug to be used in IBD; it is made up of a mesalamine moiety linked to sulfapyridine by an azo-bond (Table 1), which is cleaved by the action of colonic bacteria to release the clinically active mesalamine component. Early studies showed 40% to 50% remission rates with sulfasalazine at dosages of 3 to 5 g/d in CD at 16 weeks in patients with some colonic involvement [5–7]. Because the active moiety in sulfasalazine is mesalamine [8], and therapeutic doses

#### **Box 1. Crohn's Disease Activity Index**

- Number of liquid/very soft stools (weighting 2)
- Abdominal pain (0 = none, 1 = mild, 2 = moderate, 3 = severe) (weighting 5)
- General well-being (0 = well, 1 = slightly below par, 2 = poor, 3 = very poor, 4 = terrible) (weighting 7)
- Extraintestinal features (1 per finding): perianal disease (fissure/fistula/abscess), external fistula, mucocutaneous or cutaneous lesions, iritis/uveitis, arthritis/arthralgia, fever (weighting 20)
- Use of antidiarrheal drugs, yes = 1, no = 0 (weighting 30)
- Abdominal mass: none = 0, equivocal = 2, definite = 5 (weighting 10)
- 47 – current hematocrit (men); 42 – current hematocrit (females) (weighting 6)
- $100 \times (1 - \text{body weight/standard weight})$  (weighting 1)

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Total score between 0 and 750, sum score based on a 7-day aggregate of each item scored daily and current hematocrit measurement. Total CDAI = sum (individual scores  $\times$  weighting factor). (From Best WR, Beckett JM, Singleton JW. Rederived values of the eight coefficients of the Crohn's Disease Activity Index (CDAI). *Gastroenterology*. 1979;77(4 Pt 2):843–6; with permission.)

Table 1  
Oral sulfasalazine, mesalamine and its second generation derivatives

Drug (brand)	Compound	Release mechanism	Site of action	Available in United States
Sulfasalazine (Azulfidine)	5'-ASA + sulfapyridine, diazo bond	Diazo-bond cleavage by colonic bacterial azoreductase enzyme	Colon	Yes
Mesalamine (Asacol)	mesalamine (5'-ASA), Eudragit-S coated	Coating dissolution at pH > 7	(Ileum <sup>a</sup> ), colon	Yes
Mesalamine (Pentasa)	mesalamine (5'-ASA), ethylcellulose coated	Time- and pH-dependent slow release	(Jejunum <sup>a</sup> ), ileum, colon	Yes
Mesalamine (Mesasal)	mesalamine (5'-ASA), Eudragit-L coated	Coating dissolution at pH > 6	Ileum, colon	No
Olsalazine (Dipentum)	2 mesalamines (5'-ASA + 5'-ASA), diazo bond	Diazo-bond cleavage by colonic bacterial azoreductase enzyme	Colon	Yes
Balsalazide (Colazal)	Mesalamine (5'-ASA) + 4-aminobenzoyl-β-alanine	Diazo-bond cleavage by colonic bacterial azoreductase enzyme	Colon	Yes

<sup>a</sup> Questionable site of significant therapeutic action.

of sulfasalazine often are tolerated poorly, a variety of mesalamine derivatives without sulfapyridine have been developed. These drugs differ in their site of active drug release (see Table 1). The effectiveness of sulfasalazine only in the subgroups of patients who have colonic CD supports this “targeted” design for various azo-bonded formulations. The influence of diarrhea or malabsorption on luminal pH and transit time likely affects drug release for the other types of 5'-ASA formulations; however, these formulations often provide higher doses of 5'-ASA than sulfasalazine because of their better tolerance. One large randomized, placebo-controlled study showed an advantage of Pentasa, 4 g/d for 8 weeks, over placebo for inducing remission (CDAI < 150) in ileal and ileocolonic CD [9]. A meta-analysis of Pentasa studies in active CD [10] also concluded that there was a modest improvement with Pentasa, 4 g/d, versus placebo; however, the clinical significance was less impressive. A similar CDAI remission rate of 45% was shown with Asacol, 3.2 g/d for 16 weeks, in ileocolonic CD [11]. Collectively, these studies suggest modest benefits (≤50% remission) from

sulfasalazine at dosages greater than 3 g/d in colonic CD and for ileocolonic CD at dosages of more than 4 g/d (Pentasa) or 3.2 g/d (Asacol) versus placebo when used for minimum 8 weeks. Because sulfasalazine inhibits absorption of folic acid, the latter usually is coadministered at dosages of 1 to 2 mg/d.

Bacteria play a central role in the pathophysiology of animal models of IBD [12] and are considered important in CD. Thus, antibiotics have often been used; however, few randomized controlled therapeutic trials have been performed, limiting the available evidence. In one 6-week study, oral ciprofloxacin, 1 g/d, induced remission rates (55%) similar to mesalamine, 4 g/d, in mild-moderate CD [13]. Metronidazole seems to be ineffective in uncomplicated CD. At 400 mg orally twice daily for 16 weeks, remission was induced in 25% of patients who had CD (mean CDAI = 261) [7,14], which is not different from placebo remission rates in other studies. Although the result was similar to sulfasalazine, 3 g/d, no placebo group was used in this study, and no benefit was seen in the subgroup with small bowel disease. Another study also suggested the ineffectiveness of metronidazole for small bowel CD at dosages up to 20 mg/kg/d [15]; however, several open-label studies suggested metronidazole's effectiveness in perianal CD, and its use for this indication remains popular (see "Special situations" below). Also of interest in IBD is rifaximin: a new, broad-spectrum antibiotic that is not (<0.4%) absorbed from the GI tract, making it an attractive candidate for targeting intestinal flora or bacterial pathogens that may be associated with CD. Rifaximin has established itself for the treatment of GI disorders, such as traveler's diarrhea, irritable bowel syndrome, small-bowel bacterial overgrowth, and hepatic encephalopathy [16]. One double-blind, placebo-controlled study in 83 patients who had mild-moderate CD found that rifaximin, 800 mg twice daily for 12 weeks, induced remission in 52% of patients versus 33% for placebo ( $P =$  not significant). In the subgroup with an elevated C-reactive protein, however, remission rates were significantly better with rifaximin (63%) than with placebo (21%) [17]. Most 5'-ASA or antibiotic studies referenced above did not stratify responses of mild versus moderate CD, but overall, therapeutic gains are modest. Thus, it is recommended that if sulfasalazine or mesalamine is used for induction of remission in CD at all, they should be limited to mild cases. Patients started on these agents require close observation for nonresponse or clinical deterioration, either of which warrants a switch to more aggressive therapy (usually within 2–3 weeks). Treatment of rectal or left-sided colonic CD with topical mesalamine or corticosteroid agents is discussed in the section on UC.

### *Moderate disease*

Sulfasalazine or mesalamine derivatives should not be used as monotherapy if colonoscopy reveals deep or long ulcerations, edema, fissures, or

fistulae or if there is significant transmural inflammation. Clinical findings may include persisting abdominal pain, diarrhea, tenderness, fever, weight loss, right lower quadrant mass, leukocytosis, or anemia, but most patients with moderate disease remain ambulatory and do not exhibit signs of hypovolemia or systemic toxicity. In some, mesalamine may have been tried but with disease progression. The mainstays of induction treatment in this subset are corticosteroids, either as topically acting oral budesonide or systemically in the form of oral prednisone or equivalent. Corticosteroids exhibit multiple effects, including inhibition of proinflammatory cytokines, such as interleukin (IL)-1, -2, -6, and -8, interferon-gamma, and TNF- $\alpha$ . The challenge is to achieve remission without early relapse following a steroid taper, while minimizing adverse effects that are duration- and dose-dependent (see [Appendix 1](#)). Recent studies have shown that complications following corticosteroid treatment in CD are at least as great as those associated with more “potent” immunomodulator therapies [18]. One exception may be budesonide, an oral, topically acting steroid similar in structure to 16 $\alpha$ -hydroxyprednisolone. It is formulated as a delayed “controlled ileal release” capsule (Entocort-EC in North America), with acid-resistant microcapsules. The external Eudragit-L coating is designed to release at pH greater than 5, along with a second time-release ethylcellulose coating making it aimed at the distal small bowel. Presumably because of budesonide’s high (90%) first-pass hepatic metabolism, traditional corticosteroid-related adverse effects are less common; however, hypothalamic-pituitary-adrenal-axis suppression still does occur with budesonide. Several studies have demonstrated its efficacy in ileal/ascending colonic CD, as well as confirming its fewer steroid-related side effects. A placebo-controlled trial [19] in mild-moderate CD showed remission rates of approximately 50% at 8 weeks of treatment with 9 mg/d. Another study found a difference in remission versus placebo at 2 weeks, but not at 8 weeks [20]. A third study [21] showed that over 16 weeks, budesonide, 9 mg/d, had a higher remission rate (62%) than mesalamine, 4 g/d (36%). Budesonide is not superior to traditional corticosteroids for induction of remission, so it is best reserved for mild-moderate ileal/ascending colonic CD. Similarly, combining mesalamine with any type of corticosteroid for the induction therapy of moderate-severe CD is not superior to steroid treatment alone. The treatment of moderate Crohn’s colitis is similar to that for moderately active UC, and the reader is referred to that section for further details.

### *Severe disease*

In addition to severe signs and symptoms, this subgroup of patients can, for the purpose of therapeutic decision-making, include those who are steroid dependent (immediate or frequent relapse upon tapering) and steroid refractory (little or no response to oral corticosteroids). Perianal fistulizing CD is considered separately. For this article, only remission rates for the

various agents are reported. The reader is reminded that when reading the literature, partial improvement (as measured by higher “response” rates) may be an equally important clinical outcome in this subset of patients for whom first-line therapies fail. Nonetheless, remission rates in moderate-severe CD with inductive systemic corticosteroids approach 80%. Two large studies [5,6] have confirmed this using prednisone, 0.5 to 0.75 mg/kg/d, or 6-methylprednisolone, 48 mg/d (dosage equivalent 60 mg/d prednisone) for at least 4 months. No head-to-head studies comparing various doses have been performed, but higher doses of prednisolone, up to 1 mg/kg/d, have slightly higher remission rates at the expense of additional adverse effects. A typical induction regimen used in North America is oral prednisone, 40 to 60 mg/d, with tapering to discontinuation over 8 to 16 weeks. Other investigators recommend 12 weeks as the maximal extent of steroid induction therapy. This period is best viewed as a “bridge” to longer-term immunomodulator maintenance therapies (Fig. 1) that require 12 weeks or more to effectively modulate inflammatory T-cell subsets [22]. Although it may minimize toxicity, premature tapering is associated with early relapse and possibly the later development of steroid refractoriness. For similar reasons, initial dosages of prednisone less than 40 mg/d generally are not recommended if a decision has been made to use this drug. Patients who respond usually begin to do so within 3 weeks. If no meaningful response or clinical deterioration is seen by this time (“steroid refractory”) at full doses, the traditional therapeutic “step-up” model (Fig. 2) would suggest addition of immunomodulators, infliximab, or both. One example of a prednisone tapering schedule reduces the dosage by 10 mg/d every week at dosages greater than 40 mg/d, then reduces by 5 mg/d each week between dosages of 20 and 40 mg/d, then reduces by 2.5 mg/d each week between dosages of 10 and 20 mg/d, and then reduces by 1 mg/d each week once at less than 10 mg/d. Faster tapers have been used. Some clinicians advise a routine corticotrophin-stimulation test for adrenal insufficiency before steroid discontinuation, but this seldom is necessary unless considerable difficulty in weaning is encountered or if steroid withdrawal symptoms may mimic disease relapse.

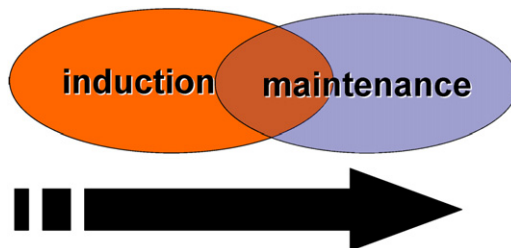


Fig. 1. Overlapping induction and maintenance therapy in IBD. Goal of IBD Therapy: Remission.

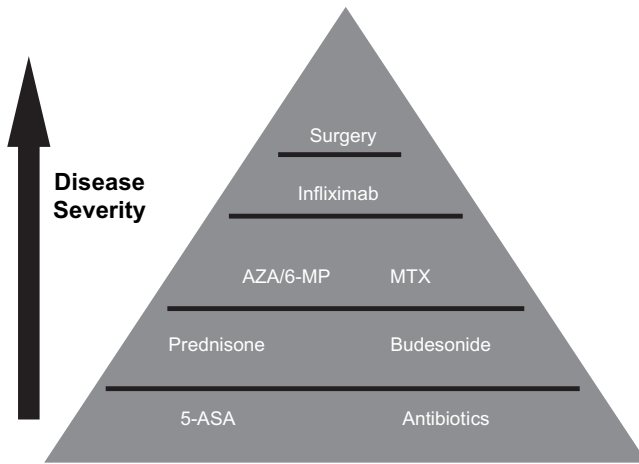


Fig. 2. Crohn's disease: traditional "step-up" therapeutic pyramid.

If the presentation is more fulminant with hypovolemia or other indications for hospitalization, intravenous (IV) steroids usually are administered (eg, methylprednisolone, 48–60 mg/d, or hydrocortisone, 300–400 mg), although the incremental benefit of the IV route over oral steroids for severe CD is unclear. One study showed equal therapeutic effectiveness (82% and 93% response, respectively) for corticotrophin, 120 units/d IV, and hydrocortisone, 300 mg/d [23].

Enteral nutritional therapy has been proposed as a safer and equally effective alternative to induce remission in moderate-severe CD. It has been more popular in Europe than in North America. A meta-analysis of randomized trials showed remission rates using this approach to be approximately 60% [24], which mainly included studies using elemental diets (amino acids); however, polymeric diets also have been used. The rationale for such therapies has been that patients who have CD often exhibit significant nutritional deficiencies, regular diets may present antigenic stimuli responsible for continued inflammatory responses, and traditional induction therapy with corticosteroids is associated with significant adverse effects. Most of the evidence for the elemental diet approach is from the pediatric population, but there is evidence of its effectiveness in adults [25–28]. Incremental benefit is obtained from using specifically defined, low-fat elemental diets [29,30]. Low-fat elemental diets are a valuable alternative to corticosteroid induction therapy, especially in patients who have highly active small bowel CD in whom steroid therapy has higher risks (eg, the elderly; those with concomitant infection, possible intra-abdominal abscess, or a history of steroid-related adverse effects [eg, avascular osteonecrosis]). Because most patients find elemental diets unpalatable, this usually requires temporary insertion of a feeding tube.

The thiopurine antimetabolites, azathioprine and 6-mercaptopurine (6-mp), have long been used in severe CD as induction and maintenance agents and have a large body of evidence supporting their use. These drugs also have well-known metabolic pathways (Fig. 3). Both agents are effective at inducing “response” (~55% with azathioprine, 2–3 mg/kg/d or 6-mp, 1.0–1.5 mg/kg/d) in CD, although the onset of action is slower than for corticosteroids: With continued therapy, response rates increase after 17 weeks [31]. Remission rate definitions differ among various studies, but there is consensus that using azathioprine or 6-mp as an induction agent enables better adherence to a fixed schedule of steroid tapering and the ability to maintain remission at daily steroid dosages less than 10 mg/d (the “steroid-sparing” effect). See [Appendix 1](#) for the adverse effects of thiopurine metabolites. Thiopurine S-methyltransferase (TPMT) is an enzyme involved in metabolizing 6-mp to clinically inactive metabolites 6-thiouric acid, 6-methylmercaptopurine (6-mmp), and 6-mmp ribonucleotides (see Fig. 3). Approximately 89% of the population shows high levels of enzyme activity, approximately 11% have intermediate levels of activity, and 0.1% have low levels of activity. This latter group is at risk for severe leukopenia that is due to toxic accumulations of 6-thioguanine nucleotides whose concentrations correlate with clinical efficacy and leukopenia. Thus, it is recommended by leading IBD experts that a TPMT enzymatic assay be checked routinely before thiopurine

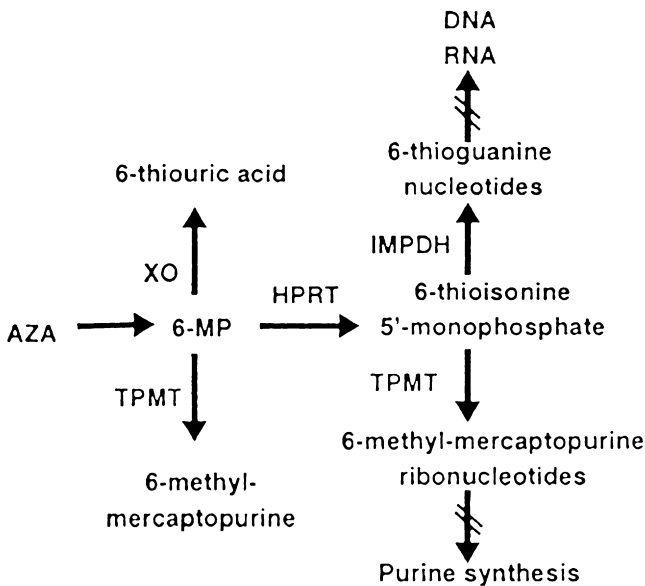


Fig. 3. Metabolic pathways of thiopurine antimetabolites. (From Colombel JF, Tamboli CP, Hugot, JP. Clinical genetics of inflammatory bowel diseases: genetic epidemiology, genotype-phenotype correlations and pharmacogenetics. In: Sartor RB, Sandborn WJ, editors. Kirsner's inflammatory bowel diseases, 6th edition. Elsevier Publishing Inc.; 2004. p. 273.)

metabolite therapy, with low metabolic activity being a contraindication to therapy [32]. TPMT enzyme testing does not obviate the need for routine complete blood cell counts and hepatic enzymes for as long as a patient uses these medications. Frequent checks are required initially. Nonadherence is a contraindication to using these drugs. For a review of thiopurine antimetabolite pharmacotherapy in IBD see Ref. [33]. Another antimetabolite, methotrexate, has been used extensively in rheumatoid arthritis and psoriasis, and, more recently, in CD. It is a dihydrofolate reductase inhibitor, blocking DNA synthesis, but likely possessing additional unknown anti-inflammatory mechanisms in IBD. When given as 25 mg intramuscularly (IM) every week for 16 weeks, it is effective at inducing remission (39% versus 19% with placebo) in steroid-refractory CD [34]. Usually, methotrexate is used as a “third-line” agent following steroid failure and thiopurine metabolite failure or intolerance, but there have been no large head-to-head trials comparing the induction efficacy of methotrexate with thiopurine metabolites. Oral methotrexate is ineffective for inducing remission in active CD, so parenteral administration is required. Some European centers have used subcutaneous (SC) methotrexate as an alternative. Methotrexate is coadministered with folic acid, 1 to 2 mg/d, to reduce nausea and stomatitis.

Infliximab, a chimeric immunoglobulin given intravenously that neutralizes TNF- $\alpha$ , has revolutionized the therapy of severe CD. Besides binding and neutralization of TNF- $\alpha$ , infliximab also fixes complement and induces inflammatory T-cell apoptosis, both of which may contribute to its therapeutic efficacy in IBD [35]. In those who are unresponsive to steroid induction or with the need for rapid induction, improvement of symptoms may be seen within several days of the first infusion. A single IV dose of infliximab, 5 mg/kg, had remission rates of 33% at week 4 in patients who had CD with CDAI greater than 220, most of whom were steroid and thiopurine metabolite resistant [36]. Subsequent to this study, considerable additional research and clinical experience showed that single-dose infusions, which are repeated after a long interval “on-demand” for relapses, are associated more with infusion reactions, loss of therapeutic response, and development of antibodies to infliximab (ATI) [37]. Additionally, ATI are more common when infliximab is given without the patient being on long-term immunomodulators or having preinfliximab treatment with corticosteroids [38]. Therefore, current guidelines discourage infliximab as monotherapy. A standard induction protocol for most forms of severe CD is infliximab, 5 mg/kg IV over several hours, which is repeated at weeks 2 and 6. If response is seen following the second dose, maintenance infusions are given every 8 weeks following the 6-week induction period. Mean time to loss of response is approximately 1 year [39]. Dosage escalation to 10 mg/kg for each infusion has been used to overcome drug “resistance” that develops in many individuals over time, but at the possible expense of increased complications. Intra-abdominal abscesses are a contraindication to commencing infliximab, until definitively managed by drainage or resection. Similarly, screening for latent

pulmonary tuberculosis (TB) is mandatory before initiation of therapy; severe reactivations of TB were described in the early infliximab experience [40]. Surveillance for complications, including infection and malignancy, also demands periodic clinical and laboratory follow-ups. Details regarding clinical prediction of responses to infliximab are beyond the scope of this article, but the fibrostenosing CD phenotype (usually of terminal ileum) does not respond to infliximab; those patients are managed best with surgical resection or strictureplasty of affected segments if obstruction is occurring.

Adalimumab (Humira) is now the second TNF- $\alpha$  inhibitor to be approved by the US Food and Drug Administration (FDA) as induction and maintenance therapy for moderate-severe CD in those having inadequate response to conventional therapy. It is a recombinant human IgG1 monoclonal antibody that shares similar mechanisms of action with its predecessor, infliximab. Unlike infliximab, however, adalimumab does not contain mouse (chimeric) protein fractions, rather it is made up solely of human-derived heavy and light chain variable regions. Theoretically, this should reduce patient antibody formation toward the drug and associated drug reactions, with better sustained efficacy over time; however, further study and experience with adalimumab is required to corroborate this concept. In a large randomized controlled trial, adalimumab was effective at inducing remission (36% remission at week 2) when given as 160 mg SC initially, followed by 80 mg SC at week two [41]. Lower doses were less effective. Patients had moderate-severe active CD and already were on steroids or immunosuppressors (eg, azathioprine), but were “TNF- $\alpha$  blocker naive.” This 36% remission rate result is similar to that for infliximab found in other studies; however, it is unclear whether adalimumab should supersede infliximab as the first “step-up” agent to induce remission in severe CD after failing corticosteroids.

There has been debate over choosing a “top-down” versus “step-up” approach for treatment of CD [42]. The “top-down” approach advocates aggressive therapy with TNF- $\alpha$  blockers before corticosteroids, because many patients eventually progress to the need for surgery, have frequent hospitalizations, and a poor quality of life. It is proposed that similar to rheumatoid arthritis therapy, a “disease-modifying” approach adopted early on in the course of disease may prevent future complications; however, no large trials have been published examining initial therapy with infliximab. Because concerns principally remain about long-term toxicities, the top-down approach has not become the standard of care. This will continue to be a topic of great interest in CD pharmacotherapeutics over the next several years.

### *Maintenance of remission*

Following successful induction of remission, the natural history of CD is of further relapses and remissions for most patients. At 10 years, relapse rates as high as 76% have been documented for colorectal CD, with median time to relapse following induction being 2 years. It is difficult to interpret the

literature regarding the role of mesalamine in maintaining remission in CD; however, the benefit seems to be greater in the postoperative setting (see “Special situations” below). When remission follows corticosteroid induction (probably implying a more severe CD subset), mesalamine in the form of Pentasa, 4 g/d, is not effective for maintaining remission at 1 year [43]. A meta-analysis of mesalamine as maintenance therapy concurs with the slight benefit in maintaining ileal CD in remission, or for postoperative (but not medically induced) remissions [44]. Oral budesonide, 6 mg/d, prolongs remission in CD up to 6 months, but not at 1 year [45]. It has been used off-label as an alternative to traditional immunosuppressors if necessary. Methotrexate, 15 mg IM once weekly, maintains remission significantly better than placebo (65% versus 39%) when remission is induced by methotrexate, 25 mg IM weekly [46]. Hepatic or significant renal disease is a contraindication to methotrexate. Several studies have shown the benefit of CD remission maintenance using oral azathioprine, 2 mg/kg/d, or 6-mp, 1.5 mg/kg/d, even when remission is induced by corticosteroids [47]. Although the results are less clear when remission follows azathioprine induction, there still seems to be a benefit over placebo [48]. Azathioprine and 6-mp are the most popular options for maintaining remission in moderate CD; however, long-smoldering concerns regarding a potential lymphoma risk associated with thiopurine metabolites have resurfaced recently [49].

In those in whom remission is induced with primary infusions at weeks 0, 2, and 6, infliximab maintains remission in CD for a mean of 40 weeks (versus 14 weeks with placebo) when given as 5 mg/kg infused IV every 8 weeks [50]. Generally, it is advisable to comaintain immunomodulator use, typically with azathioprine, 6-mp, or methotrexate, because this reduces infliximab immunogenicity and may prolong therapeutic responses [37]. In the Crohn’s Trial of the Fully Human Antibody Adalimumab for Remission Maintenance (CHARM) trial, adalimumab was shown to be effective in moderate-severe CD, with up to 41% maintaining remission at week 56 (versus only 12% with placebo) when given as 40 mg SC weekly [51]. Dosing adalimumab at 40 mg SC every other week was just as efficacious (36%). A second smaller trial Clinical Assessment of Adalimumab Safety and Efficacy Studied as Induction Therapy in Crohn’s Disease (CLASSIC II) also confirmed high remission rates with adalimumab, 40 mg SC (79% remission when given every other week or 83% when given weekly), when treatment immediately follows remission induction with adalimumab [52]. The higher remission rates in CLASSIC II compared with CHARM may be due to differences in study design, sample size, and baseline patient characteristics. TNF- $\alpha$  blocker-naïve patients may have higher response rates, and the CHARM trial enrolled many more patients than did CLASSIC II. It is unclear whether coadministration of immunomodulators with adalimumab is necessary or safe over the longer term, but efficacy and safety profiles (including serious infections) within CHARM were similar over 1 year with and without immunomodulators [51].

In summary, effective maintenance of remission has been shown for several of the currently used standard therapies in CD, with the exact drug choice being dictated by previous responses, drug toxicity/intolerance, and disease severity. The greatest clinical challenges for maintenance therapy are those patients with severe disease who become refractory to infliximab, typically after 1 or 2 years of continuous injections, and who already are optimized with traditional immunomodulator therapy. These patients become candidates for adalimumab, for newer experimental therapies in clinical trials, or for using less commonly prescribed agents that were shown to be useful in small studies.

### **Crohn's disease: special situations**

#### *Perianal fistulizing Crohn's disease*

Sulfasalazine, mesalamine, and corticosteroids are ineffective at primarily controlling fistulizing CD [53]. Antibiotics have been used frequently for this indication (most commonly ciprofloxacin or metronidazole), but short-term clinical improvement is likely related to control of local sepsis, rather than to an inherent property for healing fistulous tracts. Azathioprine and 6-mp have been suggested to speed healing of fistulae (54% response rate overall), as shown by examining a pooled subgroup of CD patients within a meta-analysis of all thiopurine antimetabolite trials [54]; however, these results have been challenged by a retrospective study showing much poorer outcomes [55]. Infliximab has been examined specifically for its efficacy in fistulizing CD, both for induction [56] and maintenance settings [50]. These studies show approximately 50% of patients initially had "response," defined as more than 50% closure of draining fistulae with infliximab, 5 mg/kg at weeks 0, 2, and 6, followed by maintenance infusions, 5 mg/kg every 8 weeks for up to 54 weeks. Similar results are obtained with other immunomodulators, such as tacrolimus [57]; however, long-term data are unavailable, and it is well recognized radiologically that fistulous tracts often persist following infliximab, despite reduced drainage [58]. Clinical experience has suggested that adjunctive surgical therapy for complex fistulizing disease (eg, Seton placement, endorectal advancement flap, diversion procedures) achieves better outcomes and avoids infective complications than medical management alone. Therefore, a multimodality, medical-surgical team approach to dealing with most CD fistulae represents the current standard of care.

#### *Medical management of postoperative recurrence*

Historically, more than 70% of patients who have CD require surgery at some point [59]. Whether TNF- $\alpha$  antagonists or other biologic agents will reduce this figure requires further long-term study. Following resection, endoscopic evidence of inflammation is the strictest definition of postoperative recurrence, with the highest anticipated rates from studies using this

definition. Conversely, having reoperation is the most liberal definition of postoperative recurrence and is expected to be much lower. Therefore, postoperative recurrence rates vary greatly among prophylactic studies. Because postoperative recurrence using any definition is high without prophylaxis (up to 100% 3 years postoperatively), it is generally desirable to continue medications in the postoperative setting. Mesalamine has a slightly more established role in CD here. A meta-analysis of several trials has concluded that a subset of patients who have ileal CD may have reduced postoperative recurrence rates when mesalamine is used at 4 g/d [60]. Metronidazole, although effective at up to 1 year in preventing endoscopic postoperative recurrence, is not used generally because of adverse effects during sustained therapy. Azathioprine, 2 mg/kg/d for 24 months, was effective at reducing clinical and surgical postoperative recurrence in those who had a previous *bowel resection* [61], but it had postoperative recurrence rates similar to mesalamine in other postoperative subgroups. Higher postoperative recurrence rates may occur in smokers (especially women), those with perforating or fistulizing disease, and possibly those with younger age at diagnosis or short disease duration before surgery [62]. Thus, it is particularly recommended that these patients undertake medical prophylaxis for postoperative recurrence.

## Ulcerative colitis

In addition to severity, disease location influences therapeutic strategies for UC. Extent of disease follows more predictable patterns in UC than for CD, with well-recognized boundaries of extent being the sigmoid colon (proctitis) and splenic flexure (left-sided or “distal” colitis). For this reason, management strategies are presented here by disease location and severity; however, clinical end points have varied far more across UC clinical trials than for CD. A review of UC clinical trial end points describes 11 instruments that have been used for measuring clinical disease activity, 9 instruments based on endoscopic disease activity, and at least two composite scoring indices, with at least 10 different definitions of remission cited across the studies [63]. This must be considered when interpreting the “remission rates” referenced below. A general guide to assessing disease severity for this article may be given by the Truelove and Witts Severity Index (Box 2) [64], but therapeutic decision making must remain individualized.

### *Induction of remission*

#### *Mild-moderate distal disease*

Usually, but not always, mild disease is restricted to the rectum or left colon. This makes topical therapy with mesalamine suppositories or enemas valuable in UC management. In fact, topical mesalamine is superior to topical corticosteroids for inducing remission in mild-moderate UC extending up to the splenic flexure [65,66]. Typically, mesalamine, 4 g in a 60 mL

**Box 2. The Truelove and Witts Severity Index***Severe*

Six or more bowel movements per day

Mean evening body temperature greater than 37.5°C

Mean pulse rate greater than 90 beats per minute

Hemoglobin less than 10.5 g/dL

Erythrocyte sedimentation rate (ESR) greater than 30 mm/h

*Mild*

Less than four bowel movements per day; scant amounts blood

No fever or tachycardia

Mild or absent anemia

ESR less than 30 mm/h

*Moderate*

Somewhere in between mild and severe

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*Adapted from* Truelove SC, Witts LJ. Cortisone in ulcerative colitis; final report on a therapeutic trial. *Br Med J* 1955;2(4947):1042.

enema suspension, is administered once nightly. Lying on the left side is useful to allow drug migration proximally. Patients usually require encouragement with this treatment, because rectal retention is poor in the early phases when inflammation is greater. A 10% hydrocortisone foam or 100 mg hydrocortisone enema also induces remission and may be tolerated better; however, compared with topical mesalamine these are no more effective for induction, are less effective for maintenance, and carry higher risks for side effects [67–69]. A promising area for drug development is for alternative mesalamine formulations, such as gels and foams with better retention properties. For isolated proctitis, 1000 mg/d mesalamine suppositories are effective at inducing remission in 69% of patients after 4 weeks [70]. This is now available as a 1000-mg single suppository dose in North America. Topical budesonide enemas and foams are as effective as other topical therapies for mild-moderate UC induction, with remission rates up to 66% [71]; however, they are not readily available in North America.

In addition to topical therapy, all oral mesalamine formulations and sulfasalazine are effective in mild-moderate UC [72–75]. More than 40 years ago, sulfasalazine, 4.0 to 6.0 g/d, was shown to be effective [76,77]; however, at these dosages it often is poorly tolerated. Response with sulfasalazine or mesalamine is usually seen within 8 weeks. For mesalamine, typical dosages have ranged between 2.0 and 4.8 g/d. A combination of oral (2.4 g/d) and topical mesalamine (4 g/d rectal enema) is more effective than either drug alone for distal disease [78]. This is a useful strategy for more resistant cases.

*Mild-moderate extensive disease*

Traditionally, mesalamine was always prescribed at 2.4 g/d for inducing remission [75] in mild-moderate UC, but recent studies have considered improved release formulations and more aggressive dosing schedules [79]. Dosages of mesalamine of less than 2.0 g/d are ineffective for inducing remission. It also is probable that pH-dependent-release mesalamine formulations are less reliably effective than other formulations (see Fig. 2). Balsalazide, a newer diazo-bonded mesalamine preparation (mesalamine bonded to an inert carrier), may be more effective at dosages of 6.75 g/d than pH-dependent-release mesalamine at 2.4 g/d [80] for mild UC. There is also a dose-response gradient with pH-dependent mesalamine, however, with induction occurring more effectively at 4.8 g/d than the FDA-approved dosage of 2.4 g/d, or 1.6 g/d, which is no more effective than placebo [81]. A more recent study also suggested that 4.8 g/d of pH-dependent mesalamine is more effective to induce remission in moderately active UC (72% remission) than is 2.4 g/d (59% remission) after 6 weeks of therapy [82]. As with distal colitis, a combination of oral (4.0 g/d) and topical mesalamine is superior to oral mesalamine monotherapy (64% versus 43% remission at 8 weeks,  $P = .03$ ), even when using a reduced-dosage 1.0 g/d rectal mesalamine enema [83]. This again suggests that higher overall doses of mesalamine delivered directly to inflamed colonic mucosa may be more effective at inducing remission. From these studies, it also is clear that remission rates continue to increase for up to 8 weeks of induction therapy; therefore, therapy should not be discontinued prematurely. A new, once-daily high-concentration multi matrix system (MMX) mesalamine formulation may improve patient adherence. When given once daily at 2.4 g/d or 4.8 g/d, MMX mesalamine induced clinical remission in 41% of patients versus 22% with placebo [84]. The FDA has given approval for this formulation as therapy for mild-moderate active UC.

If the initial induction regimen with oral or topical mesalamine is ineffective or clinical deterioration ensues early on, oral corticosteroids may be used. Several studies showed that prednisone, 40 to 60 mg/d, is effective induction therapy [64,85,86]. Remission rates are 55% to 65% at 30 to 35 days [86,87]. The exact timing and method of steroid tapering remains more an art than a science; see the section on induction of remission in moderate-severe CD for typical schedules, which also are used in UC. Although oral budesonide was shown to be effective in active UC, most of these studies did not use the controlled ileal release formulation.

*Severe (usually extensive) and fulminant disease*

As regards refractory distal colitis, it should be remembered that disease severity and disease extent (location) in UC do not always coincide. In other words, severe or refractory chronic ulcerative proctitis may be disabling, and on rare occasion it is an indication for total restorative proctocolectomy. The therapeutic approaches listed above should be tried aggressively first, however. Commonly, these have not been accelerated enough or

maximized before being deemed ineffective, and this is important when making surgical decisions, following discussions of risks/benefits/costs with the patient. A “top-down” therapeutic strategy using TNF- $\alpha$  blockers has not been studied for severe UC naive to other therapies. Notwithstanding these comments, up to 15% of patients who have UC will have severe colitis and are less likely to respond to first-line conventional therapies; it is these patients with whom surgeons will be most acquainted. If the patient presents with a more fulminant course, hospitalization is required and IV corticosteroids should be instituted. IV prednisolone, 60 mg/d, induces remission in 64% of patients after 5 days [88,89]. On average, 50% response rates are seen across all studies [48]. A 10-day trial is considered sufficient to determine response, with little incremental benefit (and possibly toxic complications) beyond this. Bolus infusions fare as well as continuous infusions [90]. If oral and topical mesalamine and oral or IV corticosteroids have failed, traditionally the next step is total proctocolectomy. In selected patients, IV cyclosporine (as rescue therapy in patients failing IV corticosteroids; see later discussion) or infliximab can be considered, but the elderly and those with comorbid conditions, such as chronic cardiovascular or renal disease, are at higher risk from complications. Antibiotics have been studied in small trials, some showing benefit [91] and others showing no benefit [92–94]. One editor’s letter reported no significant remission induction benefit over placebo in severe UC with oral rifaximin, 400 mg twice a day for 10 days [95], but there was some clinical improvement. This study only included 28 patients. No larger studies are available at this time. Despite some negative results (and similar to its use in CD in the absence of robust evidence), clinical intuition suggests that IV antibiotics might help to prevent sepsis in the setting of a severely inflamed colon. Therefore, they are added commonly to the induction regimen for hospitalized patients; however, worsening symptoms also may indicate superinfection with bacteria, such as *Clostridium difficile*, for which broad-spectrum antibiotics, including quinolones, are clearly a risk factor [96]. Repeat stool cultures and toxin assays for *C difficile* should be obtained.

Regarding antimetabolite immunomodulators, methotrexate cannot be recommended for UC induction therapy, based only on the results of one negative double-blind placebo-controlled study using 12.5 mg orally per week for 9 months [97]. Azathioprine and 6-mp have been studied more extensively in this role, but there is no consensus of results. These two agents do not improve outcome in the short-run for patients hospitalized with severe UC, but if a response is seen with other medical management, they may be considered for early introduction as maintenance agents [48]. IV cyclosporine was shown to “salvage” up to 82% of severe UC nonresponders to IV corticosteroids [98], averting colectomy and permitting discharge from hospital. Smaller doses may be as effective as larger ones [99]; however, its use does not remain widespread because of the significant potential for toxicities (see Appendix 1) [100] and the fact that colectomy is not averted

over the longer term in many patients [101]. Effective transitioning to maintenance therapy probably requires intensive combination regimens involving simultaneous oral antibiotics (prophylactic for *Pneumocystis carinii*), corticosteroids, azathioprine, and oral cyclosporine.

Infliximab promises to revolutionize therapy for treatment-refractory, but ambulatory patients who have UC. When given as 5 mg/kg infusions at weeks 0, 2, and 6 to patients failing conventional medical management (including corticosteroids), infliximab induced “response” in 64% to 69% of patients at week 8 (versus 29%–37% for placebo,  $P < .001$ ) [102]. Remission occurred in 39% of patients given infliximab at week 8 versus 15% with placebo in “ACT 1” of the study. Infliximab is approved by the FDA for induction therapy in UC. This new evidence is likely to reduce referrals for total proctocolectomy over the short range. Infliximab also has been used as a substitute for IV cyclosporine in hospitalized patients who had severe UC that was refractory to IV corticosteroids. A small series reported 77% clinical response to a single infliximab infusion of 5 mg/kg, with 80% of responders remaining in clinical remission after 2 years [103]. A slightly larger randomized, double-blind, placebo-controlled trial showed that in 45 hospitalized patients who had severe steroid-refractory UC, 67% of the placebo group required proctocolectomy within 1 month versus 29% of those receiving a single infusion of infliximab, 5 mg/kg ( $P = .017$ ) [104]. Follow-up was to 90 days. Although the pretreatment severity details are not directly available for comparison, this result is similar to the IV cyclosporine trials. Thus, it is doubtful that IV cyclosporine, with its considerable potential for toxicities, can remain justifiable as a “last-resort” medical alternative to proctocolectomy in hospitalized patients who have severe UC. How long infliximab might be able to avert proctocolectomy in the long-term is unclear. As a comparison, the mean duration of infliximab efficacy in CD is only about 1 year [39] (see “Maintenance of UC remission” below). As well, the outcome and postoperative complications associated with urgent proctocolectomy following failed infliximab therapy should receive research attention in the combined medical-surgical arena. A small series suggests no increase in postoperative complications with failed IV cyclosporine followed by proctocolectomy [105], and postoperative complications do not seem to be higher using infliximab in CD [106]; however, the total volume of data available in this regard is small.

### *Maintenance of ulcerative colitis remission*

5'-aminosalicylates and sulfasalazine are first-line therapies as maintenance agents for UC. There is strong evidence for this effect from multiple studies. An updated pooled analysis from a Cochrane Collaboration review of the literature showed an odds ratio (OR) for relapse of 0.47 (95% confidence interval [CI]: 0.36–0.62) for mesalamine versus placebo, but also a superior effect of sulfasalazine versus mesalamine, even at sulfasalazine

dosages of 2 g/d [107]. A dosage-dependent effect was not observed for maintenance mesalamine, but this is not as well established because of lower statistical power from existing trials. In distal colitis, topical mesalamine also maintains remission, even when followed for 2 years (for summary of UC maintenance topical mesalamine trials see Ref. [108]). In one study, remission at 2 years was maintained in 74% of patients using 4-g mesalamine enemas every third night versus 32% remission with oral mesalamine, 1.5 g/d [109]. Other studies have confirmed the efficacy of twice or thrice weekly topical mesalamine. Thus, reduced-frequency rectal mesalamine schedules that decrease total medication inconveniences, risks, and costs may be an attractive alternative to maintaining remission in mild-moderate distal UC for those patients who are willing to continue it. As with CD, corticosteroids should not be used for maintenance therapy. In addition to side effects, relapse rates at 10 months are unacceptably high (50%) [110]. The data are not convincing regarding methotrexate as maintenance therapy in UC; therefore, this drug also is not currently recommended. As cited above, a 9-month randomized trial in UC used methotrexate, 12.5 mg/wk orally [97], which is a different route and lower dosage than shown to be effective for maintaining remission in CD [46]. Further studies are required here. There is evidence for a benefit of maintenance therapy with azathioprine, although the evidence is weaker than for its role in CD. A pooled analysis reported a significant OR for likelihood of relapse (OR, 0.41; 95% CI: 0.24–0.70) [111] when compared with placebo, but significant concerns persist because of the weakness of evidence relative to the potential risks of long-term immunosuppression. A recent randomized trial compared azathioprine, 2 mg/kg/d, with mesalamine, 3.2 g/d for 6 months, in patients who had UC and failed corticosteroid tapers [112]. This study strengthens the case for azathioprine. Adverse effects required withdrawal of treatment in only two individuals. Fifty-three percent of the group that received azathioprine treatment achieved clinical and endoscopic remission versus 19% for mesalamine ( $P < .01$ ). TNF- $\alpha$  blockers are also being used for UC maintenance therapy. Infliximab also has found a new role here [102], with remission being maintained at week 54 in 45% of those receiving infusions of 5 mg/kg versus 20% remission rates with placebo. The long-term extent of response to infliximab remains unclear.

### **Ulcerative colitis: special situations**

#### *Pouchitis*

Pouchitis is an idiopathic, nonspecific inflammation of the ileal pouch reservoir created during an ileal-pouch anal anastomosis (IPAA), usually for medically refractory UC. Endoscopy may reveal erythema, granularity, and friability of the mucosa, erosions, or ulcerations. Histology may reveal acute inflammation with neutrophils, crypt abscesses, and mucosal

disruption superimposed on features of chronic inflammation. There has been great diversity regarding diagnostic criteria for pouchitis, making direct comparisons of therapeutic studies difficult. The etiology of pouchitis remains unknown. Some cases eventually may become diagnosed as CD, but this is uncommon. Following IPAA, about 50% of patients have at least one episode of pouchitis after 8 to 10 years of follow-up [113]. Of these, 10% who experience a single episode will not have further recurrence. Conversely, two thirds of this group experiences more than one episode of acute pouchitis, especially if the first episode occurs within 2 years of IPAA creation. These patients usually respond well to antibiotic treatment [114,115]. Up to one fifth of patients who have pouchitis have a form of "chronic" pouchitis, some of whom are refractory to standard antibiotics; however, a combination of ciprofloxacin plus rifaximin or metronidazole antibiotic therapy may lead to improvement, even in this setting [116,117]. As well, probiotics have a proven role for chronic pouchitis. Of many studies for probiotic therapy in IBD to date, the best evidence is for prevention of chronic pouchitis relapse. A double-blind, randomized, placebo-controlled clinical trial using VSL#3 (VSL#3 in USA Sigma-Tau Consumer Products, Gaithersburg, MD 20877; VSL#3 in Europe: Sigma-Tau Industrie Farmaceutiche Riunite S.p.A., Roma, Italy) was conducted in patients initially in remission after 1 month of antibiotic treatment. VSL#3, 3.0 g twice daily, was given for 9 months. Relapse occurred in 15% of patients who were treated with VSL#3 versus 100% of patients in the placebo group ( $P < .001$ ) [118]. Adverse effects are negligible. An algorithm for the treatment of acute pouchitis has been proposed [119]: if one establishes the diagnosis of acute pouchitis, metronidazole, 250 mg three times daily, or ciprofloxacin, 500 mg two times daily, should be given for at least 2 weeks. The subset of patients who relapse may be treated with prolonged courses of the same antibiotics or with combination antibiotics. Remission should be maintained with probiotics; however, positive randomized clinical trial evidence is only available using the VSL#3 formulation. Similarly, chronic refractory pouchitis may be treated with aggressive antibiotic combinations, then with probiotics once in remission. If no response is seen, topical corticosteroids may be tried. Those remaining refractory to all medical therapy may require pouch revision or excision. A small first study of infliximab plus azathioprine for chronic refractory pouchitis suggests good clinical response [120], but larger positive studies are required before this approach can be recommended.

## Appendix 1

### Adverse effects of medical therapies for inflammatory bowel disease

#### *Sulfasalazine*

Dyspepsia

Nausea, vomiting

Fever, malaise  
Allergy (rash, hives, arthralgia, hemolysis, anaphylaxis)  
Toxic epidermal necrolysis (Stevens-Johnson syndrome)  
Drug-induced lupus syndrome  
Headache  
Oligospermia, male infertility (reversible upon discontinuation)  
Hepatotoxicity  
Nephrotoxicity  
Pulmonary toxicity  
Myelosuppression  
Megaloblastic anemia (folic acid malabsorption)

#### *Mesalamine*

Diarrhea (especially olsalazine)  
Abdominal pain  
Dyspepsia  
Nausea and vomiting  
Rash  
Headache  
Hair loss, alopecia  
Nephritic syndrome, interstitial nephritis (rare)  
Pericarditis, myocarditis (rare)  
Pancreatitis  
Hepatitis

#### *Ciprofloxacin*

Nausea and vomiting  
Headache  
Paresthesiae, seizures  
Rash, photosensitivity, exfoliative dermatitis  
Allergy, hypersensitivity  
Elevated liver enzymes  
Interstitial nephritis  
Anxiety/psychosis  
Diarrhea, pseudomembranous colitis  
Tendon rupture

#### *Metronidazole*

Nausea, vomiting  
Dysgeusia (altered taste, metallic taste)  
Stomatitis, dry mouth, glossitis  
Illness (nausea, vomiting, abdominal pain, fever: 'Disulfiram-like reaction')  
with ethanol coingestion  
Paresthesiae (sometimes irreversible)  
Diarrhea, pseudomembranous colitis

Neutropenia, leukopenia  
Electrocardiogram changes  
Cystitis, dysuria

*Rifaximin*

Diarrhea  
Abdominal pain, cramps  
Nausea, vomiting  
Fatigue

*Corticosteroids (prednisone > budesonide)*

Mood changes, insomnia  
Increased appetite, weight gain  
Cushingoid appearance (“moon face,” “buffalo hump”)  
Edema  
Hyperglycemia, diabetes mellitus  
Acne, striae  
Hirsutism  
Alopecia  
Infection, impaired wound healing  
Osteoporosis  
Avascular bone necrosis  
Cataracts  
Narrow-angle glaucoma  
Adrenal axis suppression (including budesonide)  
Hypertension  
Hypercholesterolemia  
Hypokalemia  
Myopathy  
Growth retardation in children

*Thiopurine antimetabolites (azathioprine and 6-mercaptopurine)*

Allergy (rash, hives, anaphylaxis)  
Pancreatitis (<5%)  
Leukopenia, bone marrow suppression  
Infection  
Elevated liver enzymes, hepatotoxicity  
“Flu”-like symptoms, malaise, myalgia  
Nausea, vomiting  
Malignancy (lymphoma)  
Skin rash  
Arthralgia

*Methotrexate*

Anorexia, malaise, diarrhea  
Fever, chills

Nausea, vomiting  
Stomatitis, gingivitis, pharyngitis  
Rash, photosensitivity  
Toxic epidermal necrolysis (Stevens-Johnson syndrome)  
Leukopenia  
Infection  
Megaloblastic anemia (folate metabolism antagonism)  
Alopecia  
Hepatotoxicity, hepatic fibrosis  
Neuropathy  
Nephrotoxicity  
Interstitial pneumonitis  
Pericarditis  
Pleural effusion  
Malignancy (?)

#### *Cyclosporine*

Opportunistic infection (*eg. Pneumocystis carinii*)  
Hypomagnesemia  
Headache  
Tremor, paresthesiae, seizures  
Hypercholesterolemia  
Hypertension  
Nephrotoxicity - common (sometimes irreversible)  
Hepatotoxicity  
Gingival hyperplasia  
Hirsutism

#### *Infliximab, adalimumab*

Headache  
Fatigue, myalgia  
Acute infusion reactions (local site irritation, rash, fever, arthralgia, back pain)  
Allergy (rash, hypersensitivity, anaphylaxis)  
Delayed infusion reactions (rash, arthralgia, renal dysfunction, lupus-like syndrome)  
Infections (including reactivation tuberculosis), fungal infections  
Reactivated chronic hepatitis B infection  
Respiratory: naso-sinopulmonary infections, dyspnea, bronchitis  
Neurotoxicity (multiple sclerosis, peripheral demyelination, optic neuritis)  
Malignancy (?), lymphoma  
Pancytopenia  
Worsening congestive heart failure

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