Inflammatory bowel disease represents chronic idiopathic disorders which involve either the colon exclusively (ulcerative colitis) or any part of the gastrointestinal tract (Crohn's disease). The course of these entities is typified by periods of symptomatic exacerbation interspersed with clinical remissions. Management is based upon regimens which decrease mucosal inflammation. Colonic disease distal to the splenic flexure may be treated with topical therapy, but other regions generally necessitate oral therapy. Currently used medications include the aminosalicylates, glucocorticoids, antibiotics and immunomodulators. The immunomodulator class of medications includes azathioprine, 6-mercaptopurine, cyclosporine A and methotrexate. Newer agents include short-chain fatty acids, ω-3 fatty acids and antibodies directed to tumor necrosis factor. Medical management...
also occasionally involves optimizing nutritional status with the addition of elemental diets or total parenteral nutrition. Management of specific clinical presentations is discussed.

Definition

Inflammatory bowel disease (IBD) is composed of the distinct entities ulcerative colitis (UC) and Crohn's disease (CD). These disorders are of unknown etiology and pathogenesis and display great variability in clinical presentation. They are defined by the chronic nature of typical symptoms associated with specific pathologic findings.

UC typically presents with persistent bloody diarrhea and abdominal pain. It is a diffuse mucosal and submucosal disease involving only the colon and is characterized by congestion, superficial ulcers, inflammatory infiltrate and crypt abscesses. It virtually always involves the rectum and may extend proximally in a continuous fashion to involve some or all of the colon. Patients occasionally present with fulminant colitis or toxic megacolon and are at risk for acute perforation. UC typically spares the colonic wall (serosa) and does not extend into the terminal ileum. In some cases of pancolitis, however, the most distal terminal ileum may have evidence of chronic inflammation, often referred to as "backwash ileitis".

CD is a chronic transmural disease causing inflammation in any segment of the alimentary tract. Approximately 75% of patients have small bowel involvement and 90% of these patients have disease in the terminal ileum (1). CD presents usually with pain and diarrhea and may be complicated by fistulization, obstruction and perineal disease. Intestinal involvement characteristically is segmental and interrupted by intervening normal "skip" areas.

Prevalence, Etiology and Pathology

UC is most prevalent in North America, Northern Europe and Australia, affecting 50-80 people per 100,000 population (2). The prevalence is roughly 10 times lower in Southern and Eastern Europe, Africa, Asia and South America. Although it may present at any age, it primarily presents in the second to fifth decades of life, though some series have demonstrated a second peak incidence between 55 and 65 years of age. IBD seems to affect the genders equally, though some studies have suggested a female predominance. Both UC and CD appear to be more prevalent in Ashkenazi Jews. The incidence of CD has reportedly risen during the past 40 years (unlike UC, which appears to have a stable incidence) and has a similar geographic variation as UC (1).

The etiology of IBD has not been determined, but available evidence points both to genetic (particularly for CD) and environmental causes. Twin studies have demonstrated a particularly high concordance rate for CD among monozygotic twins (58% for CD, 6% for UC) (3). Genetic studies have suggested CD associations with HLA-A2, HLA-DR4 and HLA-DR1-DQ5, and inverse associations with HLA-A11 and HLA-DR3 (4). Environmental influences such as diet, smoking, oral contraceptives and infection appear to affect IBD activity, but they do not consistently point to one specific etiology.

The colon in patients with UC macroscopically appears edematous and erythematous and may have superficial erosions or deep ulcers, depending on severity. The mucosa in UC may display inflammatory "pseudopolyps" on its surface. With longstanding disease the colon may become featureless and atrophic. Biopsies in areas of chronic colonic inflammation display a chronic inflammatory infiltrate associated with crypt destruction and crypt architecture distortion. The bowel in CD becomes thickened from transmural inflammation, the mesentery may likewise become edematous, and fat may extend onto the serosal surface of the intestine (so-called "fat-wrapping"). Linear mucosal ulcers may be interspersed with normal intervening areas and over time these normal areas can take on a cobblestone appearance. Granulomas are a classic finding on biopsy and may occur in extraintestinal locations as well, but they are not always detected. Biopsies also demonstrate chronic inflammatory infiltration and distortion of the normal mucosal architecture.

Aims of Medical Therapy

The primary goals of medical therapy for treatment of IBD are severalfold and include: (i) providing symptomatic relief (i.e., induction of disease remission), (ii) maintaining adequate nutritional status, (iii) abatement of inflammation in the intestine, and (iv) reducing the incidence of recurrent flares (i.e., maintenance of disease remission).
while improving the patient’s quality of life. The ideal medication should be safe (i.e., have a low side effect profile), simple to administer and affordable.

**Oral Treatment**

**Aminosalicylates**

There are several classes of medication available for oral treatment of IBD. Aminosalicylates were the first class of drug shown to provide benefit. The first aminosalicylate used to treat patients with IBD was sulfasalazine in the 1930s. Though first reported in 1941, the first placebo-controlled study proving benefit was reported in 1962 (5). Sulfasalazine is a frequently prescribed medication for IBD and is formed by sulfapyridine bonded covalently via an azo bond to an aspirin analog, 5-aminosalicylate (5-ASA). The sulfasalazine molecule is cleaved by the bacterial enzyme azo-reductase to yield 5-ASA and sulfapyridine. The 5-ASA portion confers the antiinflammatory properties of the molecule. The sulfapyridine moiety serves as the carrier and is also responsible for the majority of the side effects. Approximately 15% of patients taking sulfasalazine have side effects significant enough to require discontinuation of the medication. Observed side effects occurring in a dose-related fashion include nausea, vomiting, anorexia, folate malabsorption, headache and alopecia. Nondose-related side effects include hypersensitivity rashes, hemolytic anemia, agranulocytosis, hepatitis, fibrosing alveolitis, male infertility and colitis. In 1977 Khan et al. (6) demonstrated that it was the 5-aminosalicylate portion that is responsible for the antiinflammatory properties, precipitating the development of newer drugs that delivered the 5-aminosalicylate moiety without using the sulfapyridine carrier molecule (Table I). Approximately 80-90% of people who are intolerant to sulfasalazine are tolerant of other mesalamine derivatives. Several principles have been used to deliver the 5-aminosalicylate to the bowel, including the following: i) enema formulation that allows the direct application of 5-aminosalicylate topically to the left colon (up to the splenic flexure), ii) foam formulation that permits the delivery of 5-aminosalicylate to the colon, iii) the linkage of 5-aminosalicylate to either a molecule that is less toxic to patients than sulfapyridine via an azo bond, or iv) oral delayed release preparations of 5-aminosalicylate that either permit absorption of the 5-aminosalicylate in the proximal intestinal tract (e.g., Pentasa), or allow delivery of the compound to the ileum and/or the colon (e.g., Asacol) for absorption (Table I).

In individuals with mild to moderately active ulcerative colitis, sulfasalazine will induce remission in 35-80% of patients when taken at a dose of 4-6 g/day. Sulfasalazine is also superior to placebo for maintaining remission. It is generally accepted that the oral aminosalicylates are equivalent for treatment of mild to moderately active ulcerative colitis and for maintenance of remission. A meta-analysis (7) estimated that the rate of induction of remission is about twice that seen to occur on placebo, and a dose-response effect was observed as well. There is no evidence which suggests that any of the 5-aminosalicylate derivatives are superior to sulfasalazine. However, most trials have shown significantly fewer side effects with the newer 5-aminosalicylates. The use of any of the aminosalicylates, including sulfasalazine, for severely active ulcerative colitis has not been evaluated in controlled clinical trials.

**Corticosteroids**

Corticosteroids are well established as being efficacious for the treatment of active UC and CD regardless of disease distribution, and historically they have been the mainstay of treatment of acute flares of inflammatory bowel disease. In severe flares of IBD corticosteroids in doses equivalent to 40-60 mg/day of prednisone should be considered in the first line of therapy. However, approximately 20-30% of patients with acute UC or CD will not respond to corticosteroids. Based on data from controlled studies, corticosteroids have not been shown to be beneficial for maintenance of remission in either disease. The beneficial effects are counterbalanced, however, by the side effects that are frequently seen with their use, so other medications with less toxic side effects are often chosen as initial therapy. Important irreversible side effects associated with the use of corticosteroids include: i) avascular osteonecrosis (has also been reported in Chron’s disease prior to initiation of therapy with corticosteroids, ii) posterior subcapsular cataracts, iii) abdominal striae, iv) osteoporosis, v) growth retardation, and vi) myopathy. Other side effects include acne, moonface, hypertension, dyspepsia, mood/disturbances and glucose intolerance. Strategies which have been employed to
minimize the risk of developing these side effects include use of rapid well-defined tapering regimens, every other day dosing, topically applied corticosteroids (suppositories, foam, enemas) and rapidly metabolized “first-pass” steroids. Many clinicians routinely give multivitamins (including vitamin D) and calcium carbonate to their patients on corticosteroids. The use of bisphosphonates has not been critically evaluated in a controlled fashion in IBD patients on corticosteroids, but hormone replacement has been shown to be beneficial for prevention of bone loss (8).

Budesonide is the best studied of the newer corticosteroids. Oral budesonide in a controlled ileal-release preparation has been shown to be effective in treating active ileal and ileocecal CD (9). A recent trial comparing oral budesonide with prednisolone showed comparable efficacy with significantly fewer side effects and less morning plasma depression (10). Oral fluticasone propionate, when given in a dose of 20 mg/day, has been shown to be as efficacious as prednisolone for UC, without suppression of the cortico-adrenal axis (11). It should be noted that studies on newer corticosteroids have been relatively short and the long-term effects on bone, the adrenal axis and other corticosteroid-related side effects are not yet known.

<table>
<thead>
<tr>
<th>Drug and trade name</th>
<th>Constituents</th>
<th>Release area</th>
<th>Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfasalazine</td>
<td>Sulfapyridine, 5-ASA</td>
<td>Colon</td>
<td>Tablets</td>
</tr>
<tr>
<td>Azulfidine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Pharmacia Labs., Piscataway, NJ)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olsalazine</td>
<td>5-ASA dimer</td>
<td>Colon</td>
<td>Gelatin capsules</td>
</tr>
<tr>
<td>Dipentum</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Pharmacia Labs., Piscataway, NJ)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mesalamine</td>
<td>5-ASA</td>
<td>Ileum, colon, pH&gt;7</td>
<td>Eudragit S cover</td>
</tr>
<tr>
<td>Asacol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Proctor &amp; Gamble Pharmaceuticals, Norwich, NY)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pentasa</td>
<td>5-ASA</td>
<td>Duodenum, jejunum, ileum colon (pH, time)</td>
<td>Ethylcellulose microgranules</td>
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<tr>
<td>(Marion Dow, Kansas City, MO)</td>
<td></td>
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<td>Claversal*</td>
<td>5-ASA</td>
<td>Ileum</td>
<td>Eudragit L cover</td>
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<td>(SmithKline Beecham, Philadelphia, PA)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salofalk*</td>
<td>5-ASA</td>
<td>Ileum, pH&gt;6</td>
<td>Eudragit L cover</td>
</tr>
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<td>(Interfalk Canada, Mont-Saint Hilaire, PQ, Canada)</td>
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<td>(Dr. Falk, GmbH &amp; Co., Freiburg, Germany)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Rowasa*</td>
<td>5-ASA</td>
<td>Ileum, pH&gt;6</td>
<td>Eudragit L 100 cover</td>
</tr>
<tr>
<td>(Reid-Rowell Labs., Baudette, MN)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Interfalk Canada, Mont-Saint Hilaire, PQ, Canada)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Balsalazine*</td>
<td>5-ASA + 4 amino-benzoyl + B-alanine</td>
<td>Colon</td>
<td>Capsule</td>
</tr>
<tr>
<td>Colazide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Biorex, UK/Salix Pharmaceuticals, Palo Alto, CA)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ipsalazine*</td>
<td>5-ASA + 4-amino-benzoylglycine</td>
<td>Colon</td>
<td>Capsule</td>
</tr>
<tr>
<td>(Biorex, UK)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poly-ASA*</td>
<td>Sulfanilamidoethy polymer + 5-ASA</td>
<td>Colon</td>
<td>Capsule</td>
</tr>
<tr>
<td>(Wellcome, UK)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Currently not available in the United States; 5-ASA = 5'-aminosalicylate
Antibiotics

There have been two primary uses for antibiotics in the setting of IBD: (i) as primary therapy and (ii) as treatment of intercurrent infections. It should be stressed, however, that infections can lead to subsequent flares of underlying IBD. Metronidazole has been the most extensively studied antibiotic in patients with IBD. Metronidazole is unique in that not only is it an antibiotic, but it also appears to have a direct antiinflammatory effect in CD. Treatment with metronidazole as primary therapy for active CD has been shown to be superior to placebo and equally as efficacious as sulfasalazine, particularly in those individuals with colonic CD (12). Metronidazole may also be beneficial in preventing postoperative recurrence in CD (13). Metronidazole has proven particularly useful in the management of perineal complications in CD. Nonrandomized trials have shown that at least 45% of patients achieve healing/benefit of perineal disease with metronidazole. When using metronidazole for perineal disease, it should be continued for 4-6 months, typically in doses of 1-2 g/day. Although it has not been shown to be beneficial as acute therapy for active UC, it is unclear if it is beneficial in maintenance of remission in UC since there is one trial which has demonstrated benefit (14) (though this has not been reproduced by others). Additionally, Clostridium difficile may precipitate flares of ulcerative colitis, and in this situation metronidazole is the first-line treatment. While most acute flares of UC are not due to infection, it has been recommended that severely ill patients should receive a trial of antibiotics prior to being considered a failure of medical therapy, since some will respond. Controlled trials of antibiotics in UC, however, have failed to demonstrate efficacy. Of note, metronidazole has been shown to be efficacious in patients who develop pouchitis after total proctocolectomy and ileal anastomosis with an ileal reservoir (which occurs in approx. 45% of patients after 15 years). Ciprofloxacin is a second antibiotic which appears to be helpful in active CD and may help fistulae and perianal symptoms in CD as well (15). The quinolones may also have immunomodulating properties. Combining metronidazole and ciprofloxacin has been shown to decrease CD activity (16). Early data suggest that clarithromycin may also be a promising drug for treatment of CD. The role of mycobacteria in the pathogenesis of IBD, particularly CD, has long been suspected but the preponderance of evidence has failed to universally demonstrate organisms in the tissues or a consistent response to antimycobacterial agents.

Immunomodulators

1) Azathioprine and 6-mercaptopurine

The use of immunosuppressant agents such as azathioprine and 6-mercaptopurine (6-MP) appears to be efficacious in the treatment of both UC and CD. It is believed that 6-mercaptopurine and azathioprine have similar actions, efficacy and toxicity. Their exact mechanism of action remains unknown. However, it is known that azathioprine is metabolized to 6-MP in vivo, which is subsequently metabolized to 6-thioinosinic acid, the presumed active metabolite which becomes incorporated into developing strands of DNA. In lymphocytes, this substitution inhibits lymphocyte proliferation. Other antiinflammatory effects may be derived from their action on leukocyte cell membranes. At a low dosage there is a mild decrease in T-, K- and NK-mediated cytotoxicity, whereas at higher doses there is inhibition of T-cell activation and cytokine production.

Azathioprine and 6-MP have been used to treat patients with active CD since their initial use in the late 1960s. They have primarily been considered appropriate for individuals who: (i) have disease unresponsive to aminosalicylates, antibiotics or corticosteroids, (ii) have had fistulous disease not responding to ciprofloxacin or metronidazole, (iv) have had fistulous disease, or (v) require maintenance of remission.

Azathioprine has been shown to be more efficacious than placebo in 5 of 7 (17-23) studies on the treatment of active CD (Table II). Five of 6 studies (24, 25) similarly demonstrated that 6-MP/azathioprine are efficacious for maintenance of remission in patients with CD (Table III). In a retrospective study using 6-MP in 148 patients who had not responded to steroids or other medications (26), 66% of patients eliminated steroids, 65% (32/49) healed or improved internal fistulas (rectovaginal, 6/7; ileorectal and ileosigmoid, 11/15; enteroenteric, 2/5; ileocecutaneous, 6/10; colocolonic, 2/2; ileovesical, 5/10) and 87% had healing or improvement by elimination of pain, tenderness and discharge of perirectal fistulas and abscesses.
Similar results were observed in the only placebo-controlled, randomized study evaluating the efficacy of 6-MP in CD (19). The study was performed in a double-blind, crossover design consisting of 1 year on 6-MP and 1 year on placebo. The crossover data showed a 67% response to 6-MP as compared to an 8% placebo response rate. The mean response time was 3.1 months with 81% (of the 67%) responding at 4 months and the remaining 19% (of the 67%) responding within 6 months. Fifty percent of patients were able to discontinue corticosteroids and another 23% were able to significantly reduce the dosage. Approximately 25% of fistulas healed with 6-MP, while another 50% demonstrated improvement (including perianal, abdominal wall, ileosigmoid, gastroduodenal, and colovesical fistulas).

Recently, the combined treatment with azathioprine and prednisolone in a study of 42 patients with active CD has been shown to be more efficacious than treatment with prednisolone alone for the induction of remission (7). At the end of the trial (4 months) 16 of 21 (76%) patients treated with combination therapy achieved remission, whereas only 8 of 21 (38%) treated with prednisolone alone achieved remission ($p = 0.03$). No major side effects were seen in this trial. Similar overall clinical improvement rates have been observed in pediatric patients treated with these agents as well. Another recent preliminary trial suggested that high-dose intravenous azathioprine (1800 mg i.v. over 36 h followed by 50-100 mg/day p.o.) achieved remission within 4 weeks compared to the usual 3-6 months (27).

The role of immunosuppressants in the treatment of UC is emerging. The onset of action may require up to 6 months for either CD or UC, and thus patients may require treatment with other agents for acute symptoms until the immunosuppressive agents begin to demonstrate clinical efficacy. There have been 4 controlled studies published to date demonstrating efficacy in the treatment of active UC, with all studies demon-

### Table II: Azathioprine/6-MP versus placebo for active Crohn’s disease.

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Method of Assessing Response</th>
<th>Duration (months)</th>
<th>Response Rate</th>
</tr>
</thead>
</table>
| Negative results
Rhodes et al. (17) 4 mg/kg x 10 days then 2 mg/kg | CDAI Fistula | 2* | Improved-2/15 (13%) Worse-6/15 (40%) No change-7/15 (47%) |
Klein et al. (18) 3 mg/kg | CDAI Fistula | 4* | AZA-6/13 (46%) Placebo-6/13 (46%) |
Positive results
Present et al. (19) 1.5 mg/kg | CDAI Fistula | 12* (total 24) | Placebo-5/36 (14%) 6-MP-26/36 (72%) |
Candy et al. (20) 2.5 mg/kg | CDAI ≤ 150 | 13 weeks | Placebo-20/30 (67%) AZA-25/33 (76%) |
Ewe et al. (21) 2.5 mg/kg | CDAI ≤ 150 | 17 weeks | Placebo-8/21 (38%) AZA-16/21 (76%) |
NCCDS (22) 2.5 mg/kg | CDAI ≤ 150 | 17 weeks | Placebo-20/77 (26%) AZA-21/59 (36%) |
Willoughby et al. (23) 4 mg/kg x 10 days | CDAI | 26 weeks | Placebo-1/6 (17%) AZA-6/6 (100%) |

CDAI= Crohn’s disease activity index; AZA= azathioprine; *crossover trial (similar time on placebo and on active medication).
strating efficacy of azathioprine compared to placebo (25, 28-30) (Table IV). The only published controlled trial using azathioprine for maintenance of remission in UC in patients who initially achieved remission on azathioprine demonstrated a relapse rate of 36% in the azathioprine group compared with a 59% relapse rate for those switched to placebo, suggesting benefit in this scenario as well (31) (Table IV).

The long-term toxicity of 6-MP or azathioprine has been demonstrated to be less than that of corticosteroids. Approximately 10% of patients are intolerant to these immunosuppressants. Side effects commonly seen include bone marrow toxicity (2%), allergic type reactions (2%), pancreatitis (3-4%), infections (2%) and rarely hepatitis (32). There have been 2 reports of CNS lymphoma in patients with CD on immunosuppressants. Myelosuppression is commonly observed and can be lethal; it can take the form of leukopenia, thrombocytopenia and rarely aplastic anemia (in approx. 1 in 3000 patients). Leukopenia is the most common form of myelosuppression and the most important hematologic complication. Regular monitoring of the complete blood count is therefore recommended during treatment. Side effects are uncommonly seen at the usual starting dose of 50 mg for 6-MP or azathioprine, but they are frequent at higher doses. Typically, the dose is increased gradually to a maximum of 1.5 mg/kg daily for 6-MP or 2.0 mg/kg daily for azathioprine, if necessary.

2) Cyclosporine A

Cyclosporine A (CyA) is an immunosuppressant which selectively inhibits cellular immunity and has been extensively used in the arena of a rapid onset of action (about 1-2 weeks) as compared to the 3-6 months typically seen with azathioprine and 6-MP. The benefit of such a rapid onset of action is that the medication needs only to be tested for a short period of time to determine if it will be clinically efficacious. CyA is an unchanged peptide extracted from the soil fungus *Tolypocladium Infatum Gams*, and acts by binding to an endogenous extracellular peptide (cyclophilin) which blocks the entry of activated T-lymphocytes into the S phase of the cell cycle. In addition to its effect on T-lymphocytes, it alters B-cell function by inhibiting the production of B-cell activating factors and interferon-γ by T-helper cells. Granulocyte, monocyte, and macrophage function remain unaltered by CyA therapy.

At present there are four controlled trials evaluating the efficacy of CyA in CD (33-36) (Table V).

### Table III: Azathioprine versus placebo for maintenance of remission in Crohn’s disease.

<table>
<thead>
<tr>
<th>Daily dose (ref.)</th>
<th>No. pts.</th>
<th>Study design</th>
<th>Method of assessing response</th>
<th>Duration (months)</th>
<th>Response rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCCDS-Pt II (22)</td>
<td>234 AZA alone</td>
<td>CDAI ≤ 150</td>
<td>12</td>
<td>Placebo-65/101 (64%) AZA-37/54 (69%)</td>
<td></td>
</tr>
<tr>
<td>O'Donoghue et al. (24)</td>
<td>51 AZA withdrawn from stable patients</td>
<td>CDAI</td>
<td>12</td>
<td>Placebo-8/27 (30%) AZA-13/23 (57%)</td>
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</tr>
<tr>
<td>Willoughby et al. (23)</td>
<td>22 Attempt steroid taper</td>
<td>CDAI</td>
<td>6</td>
<td>Placebo-2/5 (40%) AZA-4/5 (80%)</td>
<td></td>
</tr>
<tr>
<td>Rosenberg et al. (25)</td>
<td>20 Attempt steroid taper</td>
<td>Steroid reduction CDAI</td>
<td>6.5</td>
<td>Placebo-7/10 (70%) AZA-4/10 (40%)</td>
<td></td>
</tr>
<tr>
<td>NCCDS - Part I (22)</td>
<td>39 AZA alone</td>
<td>CDAI ≤ 150</td>
<td>35 wks</td>
<td>Placebo-15/20 (75%) AZA-16/19 (84%)</td>
<td></td>
</tr>
<tr>
<td>Candy et al. (20)</td>
<td>45 In remission CDAI &lt; 150</td>
<td>CDAI ≤ 150</td>
<td>12</td>
<td>Placebo-2/20 (10%) AZA-14/25 (56%)</td>
<td></td>
</tr>
</tbody>
</table>

CDAI= Crohn’s disease activity index
One study demonstrated efficacy whereas three studies did not show any benefit over placebo, suggesting no significant utility for CyA in CD either for acute therapy or for maintenance of remission.

A recent article reviewed the 8 published studies on the use of CyA in fistulous CD which has not responded to corticosteroids, metronidazole, or antimetabolites (38). Twenty-eight of 36 patients (78%) had fistula closure initially with 18 of 36 (50%) remaining closed in long-term follow-up. These studies, however are uncontrolled case reports and thus further randomized, placebo-controlled assessment is needed.

Cyclosporin A has been used to treat UC which has been refractory to corticosteroid therapy. Currently there is one published randomized, double-blind, placebo controlled study evaluating the efficacy of CyA in severe UC (38). In 16 patients who failed 10 days of intravenous hydrocortisone at a dose of 300 mg (or its equivalent) daily, 14 (88%) responded favorably to CyA within a mean time of 7.1 days. The initial study protocol was halted because outside reviewers noted a significant difference between treatment and placebo and deemed it was unethical to continue the trial. Uncontrolled literature suggests that CyA is beneficial acutely in 81% of patients with severe UC and is effective for approximately 56% to maintain remission (the mean follow-up was 3.9 years) (39). There have been four uncontrolled studies evaluating the use of CyA enemas for refractory proctosigmoiditis (40-43). Twenty one of 36 patients (58%) responded to initial therapy with 13 of 36 patients (36%) remaining in remission after therapy. There is only one controlled study published suggesting that CyA enemas at a daily dose of 350 mg are not efficacious in the treatment of mildly to moderately active left-sided UC (44). In general, it is felt that topical CyA is not efficacious and thus it is not used.

If CyA is going to be used for long-term treatment of patients, then the potential for long-term...
toxicity needs to be evaluated carefully. Many side effects have been observed in patients, including hypertension, seizures (especially in individuals with low serum cholesterol), paresthesias, tremor, cholestasis, anorexia, vomiting, nausea, gingival hyperplasia, hypertrichosis and renal damage. The most typical renal side effects are an increase in serum BUN and creatinine with a decrease in the glomerular filtration rate subsequent to a decrease in renal blood flow. Tubular dysfunction has also been found with subsequent hypomagnesemia and or hyperkalemia. Dose reduction may decrease toxicity in some patients; however, some may develop irreversible renal dysfunction. Also, therapeutic levels do not protect against renal dysfunction. Careful monitoring for these side effects is critical and familiarity with the use of CyA is recommended for those using it.

3) Methotrexate

Methotrexate is a folic acid antagonist having both antimetabolite and antiinflammatory activity. It inhibits the enzyme dihydrofolate reductase, thymidine synthase and other enzymes involving DNA synthesis. The antiinflammatory properties of this medication resulted in its use as a treatment for rheumatoid arthritis and psoriasis. These experiences led to an open trial of methotrexate in 14 patients with refractory CD and 7 patients with refractory ulcerative colitis in a dose of 25 mg intramuscularly once weekly for 12 weeks (45). Five of the 7 patients with ulcerative colitis and 11 of the 14 patients with CD showed objective signs of improvement. Five of the 14 patients with CD went into complete remission compared to none of the 7 patients with UC. Whereas azathioprine and 6-MP may require 3-6 months for clinical efficacy, methotrexate may work more quickly. In the trial, most responders improved markedly by 8-10 weeks. In a controlled trial using parenteral methotrexate (25 mg/week i.m. or s.c.), steroids were able to be reduced or eliminated while inducing remission in chronically active CD (46). Long-term trials still need to be performed to evaluate efficacy. Oral methotrexate has not been as efficacious for UC or CD as the parenteral formulation.

3) Methotrexate

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Short-chain fatty acids

Short-chain fatty acids (primarily acetic, butyric and propionic acids) act as a fuel substrate for normal colonic mucosa. Butyrate alone accounts for approximately 70% of the energy for colonocyte oxygen utilization. When segments of the colon are diverted from the fecal stream (such as after a Hartmann’s pouch is created), patients may develop crampy abdominal pain, tenesmus and a purulent or bloody discharge typically 3-6 months after surgery. These findings are due to inflammation in the excluded segment of colon, and the syndrome is referred to as “diversion colitis”. Macroscopically the colon in a patient with diversion colitis

<p>| Table V: Cyclosporine A versus placebo for Crohn’s disease. |</p>
<table>
<thead>
<tr>
<th>Daily dose (ref.)</th>
<th>No. pts.</th>
<th>Study design</th>
<th>Method of assessing response</th>
<th>Duration (months)</th>
<th>Response rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive results</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brynskov et al. (33)</td>
<td>71</td>
<td>CDAI ≥ 150 Chronic active Crohn’s</td>
<td>CDAI Lab</td>
<td>3</td>
<td>Placebo-11/34 (32%) CyA-22/37 (59%) (p = 0.032)</td>
</tr>
<tr>
<td>Negative results</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stange et al. (34)</td>
<td>182</td>
<td>Chronic active</td>
<td>CDAI Lab</td>
<td>12</td>
<td>Placebo-19/93 (20%) CyA-18/89 (20%)</td>
</tr>
<tr>
<td>Feagan et al. (35)</td>
<td>305</td>
<td>CyA while continuing other meds.</td>
<td>CDAI Lab</td>
<td>18</td>
<td>Placebo-80/154 (52%) CyA-91/151 (60%) (NS)</td>
</tr>
<tr>
<td>Jewell et al. (36)</td>
<td>146</td>
<td>Active Crohn’s on AZA or steroids</td>
<td>Harvey-Bradshaw Index Steroid dose</td>
<td>12</td>
<td>Placebo-32/74 (43%) CyA-26/72 (36%)</td>
</tr>
</tbody>
</table>

CDAI = Crohn’s disease activity index; CyA = cyclosporine
may be indistinguishable from the colon of a patient with ulcerative colitis. It has been shown that topical short-chain fatty acids are useful for the treatment of patients who have developed diversion colitis (47). The dose for an acute flare is 60 ml b.i.d. of sodium butyrate. Typically the symptoms can be controlled with less frequent treatment after 2-4 weeks. Based in part on this finding, short chain fatty acid enemas were used and shown to be beneficial for treatment of active distal UC (in the absence of previous surgery) (48), with decreased symptoms and improved histology compared to placebo. Their use in UC also stems from the finding of increased butyrate levels in the colonic lumens of patients with active disease, suggesting that butyrate uptake may be inhibited in patients with ulcerative colitis. A recent review of several trials (49) noted that 35 of 41 (81%) previously resistant patients obtained benefit with butyrate enemas. Additionally, there are reports of benefit in patients with resistant pouchitis following ileal anastomosis (50). It is unclear if the small bowel mucosa in the pouch of these patients has undergone colonic metaplasia, since glutamine (and not short-chain fatty acids) is normally the major energy substrate for the small bowel.

**Omega-3 fatty acids**

Omega-3 fatty acids, such as the eicosapentaenoic acids found in fish oils, are structurally similar to arachidonic acids. Arachidonic acid is a precursor of inflammatory mediators such as leukotrienes and prostaglandins. It has been postulated that by altering the levels of certain subtypes of these inflammatory mediators (such as by shunting arachidonic acid to form leukotriene B₄ preferentially over leukotriene B₂ with leukotriene B₂ having less proinflammatory effect than leukotriene B₄), ω-3 fatty acids may have a beneficial effect on colitis. Early studies have shown ω-3 fatty acids to be beneficial in patients with active ulcerative colitis, though they appear not to be helpful in maintenance of remission (51).

**Topical Therapy**

Topical aminosalicylates are available in the United States in the form of mesalamine enemas (Rowasa®) or mesalamine suppositories (Rowasa®), and are associated with few side effects. A recent meta-analysis reviewing 17 randomized, double-blind controlled trials concluded that topical mesalamine has been shown to be useful for treatment of acute disease (odds ratio of 7.36 compared with placebo) and maintenance of remission (odds ratio of 16.22 compared with placebo) in left-sided UC and ulcerative proctitis (52). Chapman et al. (52) showed that mesalamine enemas reach the splenic flexure in 92% of patients. Approximately 80% of patients with left-sided colitis respond to mesalamine enemas, typically within 3-21 days, and patients should be treated for 3-6 weeks (54). Of those patients with distal colitis who are initially refractory to mesalamine enemas, approximately 50-75% of patients will respond after 4-6 months of additional treatment (54). Topical mesalamine enemas have been shown to be effective in maintaining remission in ulcerative colitis, but there is a high relapse rate once the drug is discontinued. Every other night or every third night dosing is useful in this regard. Mesalamine suppositories are useful in ulcerative proctitis, given for acute flares as a 500 mg suppository twice daily. Mesalamine foam has not been approved in the U.S. as yet. It has a similar distribution to mesalamine enemas and may have a more uniform distribution and longer persistence in the descending and sigmoid colon. One trial indicated that mesalamine foam provided more prompt remission of symptoms in active UC (55).

The first topical steroids used for treatment of active distal UC and proctitis were retention enemas and foam preparations of hydrocortisone and prednisolone. While effective, they are still associated with many of the steroid-related systemic side effects. It should be noted that there is greater absorption from normal mucosa than when it is inflamed, so the dose should be reduced as remission is induced. Recently, a new generation of corticosteroids have been developed that will likely be an important advancement in the management of IBD. These new corticosteroids, such as budesonide and fluticasone propionate, are highly potent and have a high corticosteroid receptor affinity. More importantly, when absorbed they are rapidly and extensively metabolized by the liver cytochrome P450 system (high first-pass metabolism). Table VI compares the features of glucocorticoids used for topical treatment in IBD.

Danielsson et al. compared budesonide enemas in a dose of 2 g/100 ml with placebo for distal colitis or proctitis (56). No side effects were seen and budesonide was more effective than placebo. A separate study showed that doses up to 4 mg/day of budesonide for 2 weeks had no effect on morning plasma cortisol levels (57). Subsequent trials have shown topical budesonide to be as effi-
cacious as prednisolone enemas, mesalamine enemas and hydrocortisone foam. Tixocortol pivalate also has a high first-pass metabolism, and in comparison with hydrocortisone in the form of retention enemas, was found to be equally effective (58). Prednisolone metasulfobenzoate is a preparation with minimal systemic absorption, and high concentration can be obtained with enemas. It appears to be effective in distal colitis (59).

**Nutrition**

Malnutrition occurs frequently in patients with IBD. Weight loss is seen in approximately 75% of patients with CD and in 18-62% of patients with UC (60). Weight loss may be due to multiple factors including a combination of decreased intake, increased losses, malabsorption, increased requirements and drug interference. Protein-calorie malnutrition in turn contributes to growth retardation in children, as well as poor wound and fistula healing and increased surgical morbidity and mortality. There is a consensus that an effort should be made to maximize the nutritional status of patients with IBD. With regards to specifically treating disease, bowel rest and total parenteral nutrition (TPN) has been shown to be beneficial in inducing remission in patients with active CD (61). Such remissions are generally of short duration, however, and TPN has not been proven to help maintain remission. TPN has not been proven to be superior to medical therapy, and the value of TPN as an adjunct to drug therapy has not been critically evaluated in controlled trials. Thus, TPN use is limited to patients with short bowel syndrome, to malnourished patients preoperatively who cannot tolerate enteral nutrition and to children with growth retardation who cannot tolerate other forms of nutrition.

Table VI: Comparison of glucocorticoids used for topical treatment in IBD.

<table>
<thead>
<tr>
<th>Glucocorticoid</th>
<th>Affinity to receptor</th>
<th>Topical vasoconstriction</th>
<th>Systemic bioavailability</th>
<th>Water solubility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocortisone</td>
<td>1</td>
<td>1</td>
<td>50%</td>
<td>High</td>
</tr>
<tr>
<td>Tixocortol pivalate</td>
<td>1</td>
<td>ND</td>
<td>10-20%</td>
<td>ND</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>13</td>
<td>1</td>
<td>80%</td>
<td>High</td>
</tr>
<tr>
<td>Beclomethasone</td>
<td>80</td>
<td>600</td>
<td>ND</td>
<td>Low</td>
</tr>
<tr>
<td>Fluticasone</td>
<td>ND</td>
<td>1200</td>
<td>&lt;1%</td>
<td>Low</td>
</tr>
<tr>
<td>Budesonide</td>
<td>195</td>
<td>1000</td>
<td>10-15%</td>
<td>Moderate</td>
</tr>
</tbody>
</table>


Management of Specific Clinical Presentations

Exacerbations of inflammatory bowel disease frequently present with diarrhea. However, it is important to emphasize that not all diarrhea in this patient population is due to flares of the underlying disease. A careful history should be obtained to exclude other common causes of diarrhea, as outlined in Table VII. In addition, patients should have...
stool specimens cultured for enteric pathogens and assayed for Clostridium difficile toxin. Finally, pathologic specimens should be carefully reviewed to confirm or refute the diagnosis. In approximately 10% of cases a distinction between UC and CD cannot be made, and hence these are termed “indeterminate colitis”.

There is no “standard” management regimen for all patients. The course, prognosis and clinical presentation varies considerably with patients who have UC and CD. The following represent “guidelines” rather than requisites for the treatment of patients.

### Ulcerative colitis

#### 1) Proctitis
When UC involves the rectum alone it is referred to as proctitis and presents with diarrhea, tenesmus, rectal bleeding, and occasionally constipation. Since the rectal mucosa is accessible to topical therapy (enemas or suppositories), this is often the primary form of treatment. The 5-ASA preparations should be the first choice because of their low side effect profile and proven utility in maintenance of remission. Steroid enemas or foam are an acceptable alternative, though the patient should be substituted to an oral or topical 5-ASA for maintenance. If a patient does not desire topical treatment because of discomfort, anal irritation or due to cost considerations, oral 5-ASA preparations are effective. Oral corticosteroids are less commonly necessary. Proctosigmoiditis is managed similarly to proctitis, except that enemas are preferable to suppositories. The usual starting dose for mesalamine enemas is 4 g (with or without a morning dose). If patients have an incomplete response to topical therapy, oral aminosalicylates can be added. Alternatively, individuals who dislike enemas can have oral therapy instituted initially. Most patients will tolerate sulfasalazine so it is reasonable to start with its use, due to its lower cost (males attempting to conceive should consider other 5-ASA formulations). It is customary to start at a low dose and to check for side effects. But before considering aminosalicylates to have failed, the dose should be pushed to the maximum (sulfasalazine 4-6 g/day, mesalamine (Asacol) 4.8 g/day, mesalamine (Pentasa) 4.75 g/day, olsalazine 3 g/day). Once in remission (maximal effect may take 4 weeks), the dose can be decreased to maintenance levels (sulfasalazine 2 g/day, mesalamine (Asacol) 1.2-2.4 g/day, mesalamine (Pentasa) 2-3 g/day, olsalazine 1 g/day). Patients on long-term sulfasalazine should receive folic acid supplementation. Failure of treatment with aminosalicylates for proctosigmoiditis is managed with topical or oral steroids (prednisone).

#### 2) Left-sided colitis and pancolitis
Left-sided colitis and pancolitis are best managed in a similar fashion to proctitis, except that enemas are preferable to suppositories. The usual starting dose for mesalamine enemas is 4 g (with or without a morning dose). If patients have an incomplete response to topical therapy, oral aminosalicylates can be added. Alternatively, individuals who dislike enemas can have oral therapy instituted initially. Most patients will tolerate sulfasalazine so it is reasonable to start with its use, due to its lower cost (males attempting to conceive should consider other 5-ASA formulations). It is customary to start at a low dose and to check for side effects. But before considering aminosalicylates to have failed, the dose should be pushed to the maximum (sulfasalazine 4-6 g/day, mesalamine (Asacol) 4.8 g/day, mesalamine (Pentasa) 4.75 g/day, olsalazine 3 g/day). Once in remission (maximal effect may take 4 weeks), the dose can be decreased to maintenance levels (sulfasalazine 2 g/day, mesalamine (Asacol) 1.2-2.4 g/day, mesalamine (Pentasa) 2-3 g/day, olsalazine 1 g/day). Patients on long-term sulfasalazine should receive folic acid supplementation. Failure of treatment with aminosalicylates for proctosigmoiditis is managed with topical or oral steroids (prednisone).
in these patients to relieve rectal symptoms (such as urgency and tenesmus). When patients have severe colitis, as defined by severe bloody diarrhea, fever (> 101.5 °C), tachycardia, elevated erythrocyte sedimentation rate and anemia, they should be admitted for bowel rest and parenteral steroids (equivalent of 300 mg i.v of hydrocortisone). Intravenous adrenocorticotropic hormone (120 U/24 h) is an acceptable alternative. In one study, ACTH appeared to be superior to corticosteroids in patients who had not previously received corticosteroids (64). Oral aminosalicylates, which can contribute to diarrhea and nausea, should be stopped when a patient is admitted with a flare of ulcerative colitis. If infectious colitis has been excluded, the use of antibiotics is not standard except in patients with toxic megacolon, peritoneal signs or high fevers. Patients with acute severe ulcerative colitis should be considered candidates for cyclosporine or surgery after 10 days of intravenous steroids (equiv. to 300 mg/day of i.v. hydrocortisone) without clinical improvement. Patients with toxic megacolon should also receive a nasogastric tube put to intermittent suction, should be kept NPO and should have colectomy if not improving within 72 hours. Patients who respond incompletely to corticosteroids or who become chronically dependent upon corticosteroids (despite maximal doses of aminosalicylates), should be considered candidates for azathioprine or 6-MP (starting at a dose of 50 mg/day). Patients with Crohn’s colitis may be treated with sulfasalazine as well. Once remission has been achieved, maintenance therapy with a 5-ASA preparation is advisable for those with frequent flares or significant morbidity (or impaired quality of life) from the disease. In patients who do not respond, the addition of an antibiotic such as metronidazole or ciprofloxacin may be beneficial. Nonresponders should be treated with corticosteroids. Additionally, those who present with severe disease should receive corticosteroids initially. Patients not responding to corticosteroids in active disease will frequently obtain benefit from parenteral nutrition or enteral feeding with an elemental diet. As with UC, patients who do not respond completely to steroids, who become steroid-dependent, or who have steroid-related side effects should be offered azathioprine or 6-MP. These agents are often effective in controlling symptoms and in eliminating the need for chronic steroids. Patients who fail these agents may respond to methotrexate or cyclosporine; however, these medications have additional side effects and may be of only limited benefit, so their usage cannot be considered routine.

Common complications of CD include the development of small bowel obstruction and perineal disease. Obstruction is usually due to stenosis or adhesions, and most patients will respond to bowel rest and decompression and intravenous fluids. Surgical assessment should be requested, however, for those who do not respond. Perineal abscesses and fistulae occur frequently in Crohn’s patients. The initial management is with metronidazole; ciprofloxacin is a viable alternative. Nonresponders may respond to 6-MP or azathioprine; however, surgical intervention may also become necessary or temporary bowel rest. There is evidence that cyclosporine may be beneficial in fistulizing disease as well.

Conclusions
There now exists multiple options for the management of inflammatory bowel disease, both for treatment of acute disease and for maintenance of remission. However, medical management is far from ideal and many patients ultimately require surgery. Yet surgery is virtually never curative for Crohn’s disease. Furthermore, though proctocolectomy does cure ulcerative colitis, these patients are faced with a new set of problems, such as pouchitis in an ileal reservoir or long-term ileostomy care. It is hoped that further understanding of the inflammatory cascade and the etiology of inflammatory bowel disease will lead to more specific and potent treatments for these chronic, debilitating disorders.

Crohn’s disease
CD may affect any segment of the gastrointestinal tract. Gastrointestinal Crohn’s may resemble peptic ulcer disease in clinical presentation, and these patients may respond to gastric antisecretory therapy such as H2 receptor antagonists or proton pump inhibitors (e.g., omeprazole or lansoprazole). Failure of acid suppression therapy should be treated with oral corticosteroids. Ileitis is the most common presentation of CD, and the initial treatment should be with a mesalamine preparation (Pentasa or Asacol). Patients with Crohn’s colitis may be treated with sulfasalazine as well. Once remission has been achieved, maintenance therapy with a 5-ASA preparation is advisable for
References


