Drugs for Inflammatory Bowel Disease

RECOMMENDATIONS

**Ulcerative Colitis:** An aminosalicylate is generally used first for induction and maintenance of remission in mild to moderate disease. Azathioprine or mercaptopurine is used for maintenance of remission in patients with moderate to severe disease. Corticosteroids are used to induce remission in patients with severe disease, or with moderate disease refractory to other drugs. Patients with corticosteroid-refractory disease may respond to a TNF inhibitor.

**Crohn’s Disease:** Corticosteroids are used to induce remission. Azathioprine or mercaptopurine is used for maintenance of remission. A TNF inhibitor alone or in combination with azathioprine or mercaptopurine can be used for both induction and maintenance of remission in patients with moderate to severe disease.

AMINOSALICYLATES

Aminosalicylates are effective for induction and maintenance of remission in mild to moderate ulcerative colitis. They are not recommended for treatment of Crohn’s disease.

**FORMULATIONS** — Oral mesalamine is rapidly absorbed in the small intestine and most of the drug does not reach the colon. Pentasa releases mesalamine gradually throughout the gastrointestinal tract. Delzicol, Asacol HD, Lialda, and Apriso delay the release of the drug until it reaches the distal ileum and colon. Sulfasalazine (Azulfidine, and generics), balsalazide (Colazal, and others), and olsalazine (Dipentum) are prodrugs; mesalamine is azo-bonded to a second moiety and released in the colon following bacterial cleavage of the bond. Mesalamine is also available as an enema (Rowasa, and generics) and as a rectal suppository (Canasa).

**EFFICACY** — Aminosalicylates generally induce remission in about 35-50% of patients with mild to moderate ulcerative colitis and maintain the remission for ≥6 months in 55-75%. In distal ulcerative colitis and proctitis, mesalamine suppositories or enemas may be more effective than oral formulations at both inducing and maintaining remission. Combination therapy with oral and rectal mesalamine may be more effective for distal ulcerative colitis than either formulation used alone.

ADVERSE EFFECTS — The most common adverse effects of mesalamine have been nausea, vomiting, diarrhea, headache, and abdominal pain. Nephrotoxicity can occur. Pancreatitis, hepatotoxicity, pericarditis, pneumonitis, and a lupus-like syndrome have been reported.

PREGNANCY — Most formulations of aminosalicylates are classified as category B (no evidence of harm in animals; no adequate human studies) for use during pregnancy. Asacol HD is classified as category C (risk cannot be ruled out); in animal studies, dibutyl phthalate, an ingredient in its enteric coating, was associated with fetal malformations and adverse effects on the male reproductive system. Olsalazine is also classified as pregnancy category C (embryofetal toxicity in animals; no adequate human studies).

DRUG INTERACTIONS — Mesalamine inhibits thiopurine methyltransferase *in vitro* and may interfere with the metabolism of azathioprine and mercaptopurine, which could increase their toxicity, but seldom does except in patients with an inherited deficiency of thiopurine methyltransferase. Extended- and delayed-release mesalamine formulations with pH-sensitive coatings (Delzicol, Asacol HD, Lialda, Apriso) should not be coadministered with antacids because premature dissolution of the coating could occur. Theoretically, a similar interaction could occur with proton-pump inhibitors (PPIs), such as omeprazole (Prilosec, and others), or with H2-receptor antagonists, such as ranitidine (Zantac, and others).
Corticosteroids are effective in both ulcerative colitis and Crohn’s disease for induction of remission in persistent disease. Because of their severe adverse effects, they are used systemically only until acute inflammation is under control, and then are tapered and discontinued.

**Efficacy** – Not all patients with inflammatory bowel disease respond to systemic corticosteroids. In one retrospective study in 146 patients who required treatment with corticosteroids, 51% of patients with ulcerative colitis and 40% of those with Crohn’s disease had a complete response at 30 days; 31% and 35% had a partial response.¹ Most patients who respond to corticosteroids relapse if not given maintenance therapy.

**Adverse Effects** – Corticosteroids can cause fluid retention, increased risk of infection, osteoporosis, osteonecrosis, cataracts, glaucoma, impaired skin healing, acne, insomnia, mood disorders, Cushing’s syndrome, hyperglycemia, and hypothalamic-pituitary-adrenal (HPA) axis suppression.

**RECTAL CORTICOSTEROIDS** – Rectally administered corticosteroids are effective for treatment of distal ulcerative colitis. Enemas can reach the splenic flexure, while foam coats only the last 15-20 cm of the colon.

**Budesonide** – A synthetic corticosteroid with a strong affinity for glucocorticoid receptors and a high ratio of local anti-inflammatory to systemic effects, budesonide has been used orally in an ileal-release formulation (Entocort EC, and generics) to induce remission in mild to moderate Crohn’s disease of the ileum and/or ascending colon. While also approved for maintenance, it does not appear to be effective for preventing relapse beyond 6 months of use.

Budesonide is also available in an extended-release formulation (Uceris) that distributes the drug throughout the colon and is FDA-approved for induction of remission in mild to moderate ulcerative colitis. In patients with active mild to moderate ulcerative colitis for at least 6 months, remission occurred more frequently with Uceris (17.9%) than with Asacol (12.1%) or placebo (7.4%).² Budesonide enemas are effective for distal ulcerative colitis; they are available in Canada, but not in the US.

**Adverse Effects** – Budesonide causes less short-term corticosteroid toxicity than prednisone. Whether it is safer in the long term is not clear.

**Pregnancy** – Budesonide is classified as category C (evidence of toxicity in animals; no adequate human studies) for use during pregnancy.

**Drug Interactions** – Budesonide is a CYP3A4 substrate and should be used with caution or avoided in combination with drugs that inhibit CYP3A4, which could increase its toxicity.³ Drugs that change the pH of the gastrointestinal tract (antacids, PPIs, H2-receptor antagonists) may affect the release and absorption of oral budesonide.

**IMMUNOMODULATORY AGENTS**

**Azathioprine and Mercaptopurine** – The thiopurines azathioprine (Imuran, and generics) and mercaptopurine (6-MP; Purinethol, and generics), which is the active metabolite of azathioprine, are effective for maintaining remission in both ulcerative colitis and Crohn’s disease. Since they can take 3-6 months to achieve their maximal effect, they are primarily used for long-term therapy and not for immediate suppression of active inflammation.

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**Table 1. Drugs for Ulcerative Colitis**

<table>
<thead>
<tr>
<th><strong>Recommended Drugs</strong></th>
<th><strong>Some Alternatives</strong></th>
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</thead>
<tbody>
<tr>
<td><strong>Mild to Moderate</strong></td>
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<tr>
<td>Induction of Remission</td>
<td>Budesonide</td>
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<tr>
<td>Mesalamine, oral</td>
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<tr>
<td>Balsalazide</td>
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<tr>
<td>Olsalazine</td>
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<tr>
<td>Mesalamine, rectal</td>
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<tr>
<td>Hydrocortisone, rectal</td>
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<tr>
<td>Maintenance of Remission</td>
<td>Azathioprine</td>
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<tr>
<td>Mesalamine, oral</td>
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<tr>
<td>Balsalazide</td>
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<tr>
<td>Olsalazine</td>
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<tr>
<td>Mesalamine, rectal</td>
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<tr>
<td>Hydrocortisone, rectal</td>
<td></td>
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<tr>
<td><strong>Moderate to Severe</strong></td>
<td></td>
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<tr>
<td>Induction of Remission</td>
<td>Infliximab</td>
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<tr>
<td>Prednisone</td>
<td></td>
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<tr>
<td>Methylprednisolone</td>
<td></td>
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<tr>
<td>Hydrocortisone</td>
<td></td>
</tr>
<tr>
<td>Maintenance of Remission</td>
<td>Sulfasalazine</td>
</tr>
<tr>
<td>Azathioprine</td>
<td></td>
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<tr>
<td>Mercaptopurine</td>
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<tr>
<td>Adalimumab</td>
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<tr>
<td>Pouchitis</td>
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<tr>
<td>Induction of Remission</td>
<td>Rifaximin</td>
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<tr>
<td>Ciprofloxacin</td>
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<tr>
<td>Metronidazole</td>
<td></td>
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<tr>
<td>Maintenance of Remission</td>
<td></td>
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<tr>
<td>Probiotics: VSL #3</td>
<td></td>
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<tr>
<td>Metronidazole</td>
<td></td>
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<tr>
<td>Ciprofloxacin</td>
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</tbody>
</table>
Efficacy – In controlled trials, azathioprine and mercaptopurine have been significantly more effective than placebo in maintaining remission in both ulcerative colitis and Crohn’s disease.4,5

In a study in patients with moderate to severe Crohn’s disease not previously exposed to immunosuppressive or biologic therapy, the combination of azathioprine plus infliximab was more effective than either drug alone; after 26 weeks of therapy, 56.8% of patients receiving combination therapy were in steroid-free clinical remission, compared to 44.4% of patients receiving infliximab alone and 30% of those receiving azathioprine alone.6 The results of another study suggest that the combination of infliximab plus azathioprine is also superior to either agent alone in the treatment of ulcerative colitis.7

Adverse Effects – Azathioprine and mercaptopurine can cause myelosuppression, infection, nausea, vomiting, diarrhea, hepatotoxicity, rash, pulmonary edema, pancreatitis, and a hypersensitivity reaction. Long-term use has been associated with a small increase in the risk of non-melanoma skin cancer and lymphoma. Hepatosplenic T-cell lymphoma has been reported in patients taking azathioprine or mercaptopurine both alone and in combination with a TNF inhibitor.

Pregnancy – Azathioprine and mercaptopurine are both classified as category D (positive evidence of fetal harm) for use during pregnancy.

Drug Interactions – Allopurinol (Zyloprim, and generics) and febuxostat (Uloric) inhibit the metabolism of azathioprine and mercaptopurine by xanthine oxidase and can cause bone marrow depression with pancytopenia; the dose of azathioprine or mercaptopurine should be reduced if allopurinol is used concurrently, and concomitant use of febuxostat is contraindicated. Mesalamine inhibits thiopurine methyltransferase and may decrease the metabolism of azathioprine and mercaptopurine, which theoretically could also increase their myelotoxicity, but seldom does except in patients with an inherited deficiency of thiopurine methyltransferase.

Severe leukopenia has been reported during concomitant therapy with angiotensin-converting enzyme (ACE) inhibitors or trimethoprim/sulfamethoxazole (Bactrim, and others). Azathioprine and mercaptopurine may decrease the anticoagulant effect of warfarin (Coumadin, and others).

METHOTREXATE – In Crohn’s disease, methotrexate can be used as an alternative to azathioprine or mercaptopurine to maintain remission and permit withdrawal of corticosteroids. It has not been clearly shown to be effective in ulcerative colitis.

Efficacy – Several studies have found methotrexate effective in maintaining remission in patients with Crohn's disease.6 In one study, a combination of methotrexate and infliximab was no more effective than either drug alone.9

Adverse Effects – Methotrexate can cause myelosuppression, alopecia, rash, stomatitis, vomiting, diarrhea, gastrointestinal hemorrhage, hepatotoxicity, renal failure, interstitial pneumonia, liver failure, toxic epidermal necrolysis, Stevens-Johnson syndrome, hypotension, blurred vision, headache, nephropathy, and hyperuricemia.

Pregnancy – Methotrexate is contraindicated for use during pregnancy (category X). Pregnancy should be avoided if either partner is receiving the drug.

Drug Interactions – Trimethoprim and other drugs that interfere with folate metabolism may increase bone marrow suppression caused by methotrexate. Drugs that diminish renal function, particularly NSAIDs, may increase serum concentrations of methotrexate and possibly its toxicity.

CYCLOSPORINE – The calcineurin inhibitor cyclosporine (Sandimmune, and others) is used as rescue therapy to avoid colectomy in patients with severe steroid-resistant ulcerative colitis. Use of cyclosporine in Crohn's disease has been limited.
Efﬁcacy – One open-label randomized trial comparing cyclosporine to infliximab for treatment of patients with an acute severe flare of ulcerative colitis refractory to IV steroids found the two drugs equally effective.10

Adverse Effects – Cyclosporine can cause diarrhea, nausea, vomiting, infection, gingival hyperplasia, pruritus, headache, seizures, tremors, visual disturbances, hypertension, hepatotoxicity, nephrotoxicity, paresthesias, and anaphylaxis.

Pregnancy – Cyclosporine is classiﬁed as category C (embryofetal toxicity in animals; no adequate human studies) for use during pregnancy.

Drug Interactions – Nephrotoxic effects may be additive when cyclosporine is used in conjunction with other nephrotoxic drugs such as aminoglycoside antibiotics. Concurrent use of potassium-sparing diuretics such as spironolactone (Aldactone, and generics) may increase the risk of hyperkalemia. Cyclosporine is both a substrate and an inhibitor of CYP3A4 and P-glycoprotein; CYP3A4 inhibitors may increase its toxicity and CYP3A4 inducers may decrease its effectiveness.3

TACROLIMUS – Tacrolimus (Prograf, and generics), another calcineurin inhibitor, has been used as an alternative to cyclosporine to treat patients with refractory ulcerative colitis. Data are limited on its use in Crohn’s disease.

Table 3. Drugs for Inflammatory Bowel Disease

<table>
<thead>
<tr>
<th>Drug</th>
<th>Some Formulations</th>
<th>Usual Adult Dosage</th>
<th>Cost1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aminosalicylates</strong>&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mesalamine – delayed- or extended-release</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apriso (Salix)</td>
<td>375 mg ER caps</td>
<td>Maintenance: 1.5 g once/d</td>
<td>$348.00</td>
</tr>
<tr>
<td>Delzicol&lt;sup&gt;2&lt;/sup&gt; (Actavis)</td>
<td>400 mg DR caps</td>
<td>Induction: 800 mg tid</td>
<td>430.20</td>
</tr>
<tr>
<td>Asacol HD (Actavis)</td>
<td>800 mg DR tabs</td>
<td>Induction: 1.6 g tid</td>
<td>445.50</td>
</tr>
<tr>
<td>Lialda (Shire)</td>
<td>1.2 g DR tabs</td>
<td>Induction: 2.4 or 4.8 g once/d</td>
<td>405.00</td>
</tr>
<tr>
<td>Pentasa (Shire)</td>
<td>250, 500 mg ER caps</td>
<td>Induction: 1 g qid</td>
<td>876.00</td>
</tr>
<tr>
<td>Mesalamine – prodrugs</td>
<td></td>
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<tr>
<td>Balsalazide – generic</td>
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<tr>
<td>Colazal (Salix)</td>
<td>750 mg caps</td>
<td>Induction: 2.25 g tid</td>
<td>76.10</td>
</tr>
<tr>
<td>Giazo (Salix)</td>
<td>1.1 g tabs</td>
<td>Induction: 3.3 g bid</td>
<td>864.00</td>
</tr>
<tr>
<td>Olsalazine – Dipentum (Meda)</td>
<td>250 mg caps</td>
<td>Induction: 1.5-3 g daily in 2 divided doses</td>
<td>1087.20</td>
</tr>
<tr>
<td>Sulfasalazine – generic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azulfidine (Pfizer)</td>
<td>500 mg tabs</td>
<td>Induction: 1 g qid</td>
<td>49.20</td>
</tr>
<tr>
<td>Azulfidine En-tabs (Pfizer)</td>
<td>500 mg enteric-coated DR tabs</td>
<td>Induction: 3-4 g daily in divided doses</td>
<td>41.40</td>
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<tr>
<td>Mesalamine – rectal generic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rowasa (Meda)</td>
<td>4 g/60 mL enema</td>
<td>Induction: 4 g rectally once/d at bedtime</td>
<td>370.40&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>SF Rowasa (Meda)</td>
<td></td>
<td>Maintenance: 2-4 g rectally once/d at bedtime</td>
<td>1096.30&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>Canasa (Aptalis)</td>
<td>1000 mg rectal suppository</td>
<td>Induction and maintenance: 1000 mg rectally once/d</td>
<td>709.20</td>
</tr>
<tr>
<td><strong>Corticosteroids</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisone – generic</td>
<td>1, 2.5, 5, 10, 20, 50 mg tabs; 5 mg/5 mL oral solution</td>
<td>Induction: 40-60 mg once/d</td>
<td>15.90</td>
</tr>
<tr>
<td>Rayos (Horizon)</td>
<td>1, 2.5 mg DR tabs</td>
<td>Induction: 40-60 mg once/d</td>
<td>7464.00</td>
</tr>
<tr>
<td>Budesonide – generic</td>
<td>3 mg caps</td>
<td>Induction: 9 mg once/d</td>
<td>1263.00</td>
</tr>
<tr>
<td>Entocort EC (AstraZeneca)&lt;sup&gt;3&lt;/sup&gt;</td>
<td>extended-release</td>
<td>Maintenance: 6 mg once/d&lt;sup&gt;4&lt;/sup&gt;</td>
<td>2070.90</td>
</tr>
<tr>
<td>Uceris (Santarus)&lt;sup&gt;2&lt;/sup&gt;</td>
<td>9 mg ER tabs</td>
<td>Induction: 9 mg once/d</td>
<td>1333.80</td>
</tr>
<tr>
<td>Hydrocortisone&lt;sup&gt;2&lt;/sup&gt; – generic</td>
<td>100 mg/60 mL enema</td>
<td>Induction: 1 enema nightly</td>
<td>182.90</td>
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<tr>
<td>Colocort (Paddock)</td>
<td>10% rectal foam</td>
<td>Induction: 1 application once/d or bid</td>
<td>255.80</td>
</tr>
<tr>
<td>Cortifoam (Meda)</td>
<td></td>
<td></td>
<td>544.60&lt;sup&gt;7&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

ER = extended-release; DR = delayed-release

1. Approximate wholesale acquisition cost (WAC) for 30 days’ treatment at the lowest induction dosage. Prices for Apriso, azathioprine, and mercaptopurine are based on the lowest maintenance dosage. Source: AnalySource® Monthly (Selected from FDB MedKnowledge™) July 5, 2014. Reprinted with permission by FDB, Inc. All rights reserved. ©2014. www.fdbhealth.com/policies/drug-pricing-policy. Actual retail prices may be higher.


3. Delzicol has replaced Asacol due to reproductive safety concerns associated with dibutyl phthalate, a plasticizer in the enteric coating of Asacol. Delzicol does not contain dibutyl phthalate.


6. FDA-approved for up to 3 months.

7. Cost of two 15-gram aerosol containers (each contains ~14 applications).

ER = extended-release; DR = delayed-release
Efﬁcacy – Tacrolimus appears to be effective in producing clinical improvement in some patients with corticosteroid-refractory ulcerative colitis. In one double-blind, randomized trial, clinical response occurred after 2 weeks in 16 of 32 such patients treated with tacrolimus, compared to 4 of 30 taking a placebo.11 One retrospective study found that about 60% of patients with steroid-refractory ulcerative colitis treated with tacrolimus had a clinical remission or showed clinical improvement and that 33% achieved mucosal healing.12

In one small retrospective study in 24 patients with severe Crohn’s disease refractory to TNF inhibitors, tacrolimus treatment resulted in clinical response in 16 (67%) patients and steroid-free remission in 5 (21%).13

Table 3. Drugs for Inflammatory Bowel Disease (continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Some Formulations</th>
<th>Usual Adult Dosage</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immunosuppressants</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azathioprine – generic</td>
<td>25, 50, 75, 100 mg tabs</td>
<td>Maintenance: 2-2.5 mg/kg once/d</td>
<td>$36.70</td>
</tr>
<tr>
<td>Imuran (Prometheus)</td>
<td>50 mg tabs</td>
<td>Maintenance: 1-1.5 mg/kg once/d</td>
<td>$567.90</td>
</tr>
<tr>
<td>Mercaptopurine – generic</td>
<td>50 mg tabs</td>
<td>Maintenance: 1-1.5 mg/kg once/d</td>
<td>$170.30</td>
</tr>
<tr>
<td>Purinethol (Teva)</td>
<td>50 mg tabs</td>
<td>Maintenance: 1-1.5 mg/kg once/d</td>
<td>$543.30</td>
</tr>
<tr>
<td>Methotrexate** – generic</td>
<td>50 mg/2 mL ampule</td>
<td>Induction: 25 mg IM/SC11 once/wk</td>
<td>$8.80</td>
</tr>
<tr>
<td>Otrexup (Antares)</td>
<td>15 mg/0.4 mL; 25 mg/0.4 mL</td>
<td>Maintenance: 15-25 mg IM/SC11 once/wk</td>
<td>$548.00</td>
</tr>
<tr>
<td>Rasuvo (Medac)</td>
<td>15 mg/0.3 mL; 25 mg/0.5 mL</td>
<td>Maintenance: 15-25 mg IM/SC11 once/wk</td>
<td>N.A.</td>
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<tr>
<td>Cyclosporine – generic</td>
<td>50 mg/mL ampule</td>
<td>Induction: 2-4 mg/kg IV daily</td>
<td>$91.60</td>
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<tr>
<td>Sandimmune (Novartis)</td>
<td>50 mg/mL ampule</td>
<td>Maintenance: 150 mg/mL once/wk</td>
<td>$173.90</td>
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<tr>
<td>Tacrolimus – generic</td>
<td>0.5, 1, 5 mg caps</td>
<td>Induction: 0.05-0.2 mg/kg/d in 2 divided doses14</td>
<td>$398.40</td>
</tr>
<tr>
<td>Prograf (Astellas)</td>
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<td>$522.00</td>
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<tr>
<td><strong>TNF Inhibitors</strong></td>
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<tr>
<td>Adalimumab – Humira (Abbvie)</td>
<td>40 mg/0.8 mL prefilled syringe;</td>
<td>Induction: 160 mg SC at wk 0, then 80 mg at wk 2</td>
<td>$5400.60</td>
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<tr>
<td></td>
<td>40 mg/0.8 mL single-use pen</td>
<td>Maintenance: 40 mg SC every other wk starting at wk 4</td>
<td>$5538.40</td>
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<tr>
<td>Certolizumab pegol – Cimzia** (UCB)</td>
<td>200 mg vial (lyophilized powder);</td>
<td>Induction: 400 mg SC at wks 0, 2, and 4</td>
<td>$6234.20</td>
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<td></td>
<td>200 mg/mL prefilled syringe</td>
<td>Maintenance: 400 mg SC q4 wks</td>
<td>$4819.00</td>
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<tr>
<td>Golimumab – Simponi** (Janssen)</td>
<td>50 mg/0.5 mL, 100 mg/1 mL auto-</td>
<td>Induction: 200 mg SC at wk 0, then 100 mg SC at wk 2</td>
<td>$3539.50</td>
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<tr>
<td></td>
<td>injector; 50 mg/ 0.5 mL, 100 mg/1 mL prefilled syringe</td>
<td>Maintenance: 100 mg SC q4 wks</td>
<td>$3539.50</td>
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<tr>
<td>Infliximab – Remicade (Janssen)</td>
<td>100 mg vial (lyophilized powder)</td>
<td>Induction: 5 mg/kg IV at wks 0, 2, and 6</td>
<td>$3539.50</td>
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<td>Maintenance: 5-10 mg/kg IV q8 wks</td>
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<tr>
<td><strong>Integrin Receptor Antagonists</strong></td>
<td>300 mg/15 mL vial (lyophilized powder)</td>
<td>Induction and maintenance: 300 mg IV q4 wks</td>
<td>$32.00</td>
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<tr>
<td>Natalizumab – Tysabri1,2 (Elan/Biogen)</td>
<td>300 mg/20 mL vial (lyophilized powder)</td>
<td>Induction: 300 mg IV at wks 0, 2, and 6</td>
<td>$422.10</td>
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<td>Vedolizumab – Entyvio (Takeda)</td>
<td>300 mg/20 mL vial (lyophilized powder)</td>
<td>Maintenance: 300 mg IV q8 wks</td>
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<td>Antibiotics**</td>
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<tr>
<td>Metronidazole – generic</td>
<td>250, 500 mg tabs; 375 mg caps</td>
<td>250 mg tid16</td>
<td>$4819.00</td>
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<tr>
<td>Flagyl (Pﬁzer)</td>
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<tr>
<td>Ciprofloxacin – generic</td>
<td>100, 250, 500, 750 mg tabs</td>
<td>500 mg bid</td>
<td>$344.20</td>
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<td>Cipro (Bayer)</td>
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<tr>
<td>Rifaximin – Xifaxan (Salix)</td>
<td>200, 550 mg tabs</td>
<td>600-2000 mg daily in divided doses</td>
<td>$1202.40</td>
</tr>
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N.A. = Not available
1. Not FDA-approved for inflammatory bowel disease.
2. Cost based on a 75-kg patient.
3. Use of supplements containing folic acid (1-4 mg daily) or folinic acid (2.5-10 mg weekly 24 hours after the methotrexate dose) may decrease some of methotrexate’s adverse effects.
4. Natalizumab and Infliximab are for subcutaneous injection only.
5. Natalizumab has been approved by the FDA, but is not yet available.
7. Adjust dose to maintain target trough levels of 5-15 ng/mL.
8. Cost for 8 weeks’ treatment at the lowest maintenance dosage.
9. 250 mg tid for induction and maintenance of remission in pouchitis; 10-20 mg/kg daily in divided doses for induction of remission in Crohn’s disease; 500 mg tid for induction of remission in perianal and fistulizing disease.

Adverse Effects – Tacrolimus can cause tremors, renal dysfunction, gastrointestinal discomfort, headache, infection, hypomagnesemia, hypertension, insomnia, and seizures. It has been associated with an increased risk of lymphoma.

Drug Interactions – Additive nephrotoxicity may occur if tacrolimus is used in combination with other nephrotoxic drugs such as aminoglycosides. Tacrolimus is a substrate of CYP3A4 and P-glycoprotein; CYP3A4 inhibitors may increase its toxicity and CYP3A4 inducers may decrease its effectiveness.3 Tacrolimus can cause QT interval prolongation; it should be used with caution when other drugs that prolong the QT interval are taken concurrently.
TNF INHIBITORS

Three tumor necrosis factor (TNF) inhibitors – infliximab (Remicade), adalimumab (Humira), and certolizumab pegol (Cimzia) – are used for treatment of moderate to severe Crohn’s disease. Infliximab is the only one of the three approved by the FDA for use in children. Infliximab, adalimumab, and golimumab (Simponi) are approved by the FDA for treatment of moderate to severe ulcerative colitis not responsive to conventional therapies. Drug and antibody levels may sometimes be helpful in the use of these agents.

EFFICACY – Crohn’s Disease – Infliximab has been effective for the treatment of moderate to severe Crohn’s disease that has not responded to other drugs, including systemic corticosteroids. It has been more effective than placebo in inducing and maintaining remission and in producing closure of fistulas. Infliximab has also been shown to reduce Crohn’s disease recurrence after ileocolonic resection. In an open-label 5-year follow-up study, 22% of patients treated with infliximab had recurrences, compared to 94% of untreated patients. The rates of response and remission in Crohn's disease treated with other TNF inhibitors appear to be comparable to those with infliximab. In one study, a response to induction with adalimumab occurred in 499 of 854 patients (58%). Among responders who received adalimumab every other week for maintenance, 62 of 172 (36%) were in remission after 12 months. In a study with certolizumab pegol, 428 of 668 patients (64%) responded to induction, and after maintenance treatment for 26 weeks, 103 of 215 (48%) responders were in remission.

Head-to-head comparisons of TNF inhibitors are lacking. Adalimumab has been effective in some patients who had become refractory to infliximab. Certolizumab pegol has also been effective in some patients who had become refractory or intolerant to infliximab. In general, however, the rate of response to a second TNF inhibitor has been lower than the rate of response to the first.

Use of a TNF inhibitor in combination with azathioprine or mercaptopurine may be more effective than either drug alone (see page 61).

Ulcerative Colitis – TNF inhibitors have also been effective for treatment of ulcerative colitis. Infliximab, adalimumab, and golimumab have all been shown to be significantly more effective than placebo in inducing and maintaining remission in patients with moderate to severe ulcerative colitis. In a meta-analysis of clinical trials of biologic agents including infliximab, adalimumab, golimumab, and the integrin receptor antagonist vedolizumab, there was no conclusive evidence that any one of these was more effective than any other in maintaining clinical remission in moderate to severe ulcerative colitis.

ADVERSE EFFECTS – Patients treated with TNF inhibitors are at increased risk for serious infections, including reactivated and disseminated tuberculosis, invasive or disseminated fungal infection, and other opportunistic infections, such as those caused by Legionella and Listeria. Tuberculin skin testing and chest radiography are recommended before starting and periodically during therapy. Inhibition of TNF has also been associated with reactivation of hepatitis B virus in patients who are chronic carriers; serologic testing for active hepatitis B infection is recommended before treatment. Anti-TNF therapies have also been associated with injection and infusion reactions and with new onset psoriasis, hematologic cytopenias, non-ischemic congestive heart failure, demyelinating disorders, and induction of a lupus-like syndrome.

An increased risk of cancer, including lymphoma, melanoma, and non-melanoma skin cancers, has been reported with use of TNF inhibitors, but a cause-and-effect relationship has not been established. A nationwide study in Denmark found that patients with inflammatory bowel disease treated with TNF inhibitors and followed for a median of 3.7 years did not have an increased risk of cancer.

PREGNANCY – Adalimumab, certolizumab pegol, golimumab, and infliximab are all classified as category B (no evidence of harm in animals; no adequate human studies) for use during pregnancy. Placental transfer of anti-TNF antibodies may be higher during the late second and third trimesters, especially with infliximab, adalimumab, and golimumab.

DRUG INTERACTIONS – Concomitant administration of a TNF inhibitor with another biologic may increase the risk of serious infections and neutropenia. Patients being treated with TNF inhibitors should not receive live vaccines.

INTEGRIN RECEPTOR ANTAGONISTS

Two integrin receptor antagonists – natalizumab (Tysabri) and vedolizumab (Entyvio) – are approved by the FDA for treatment of inflammatory bowel disease. Natalizumab is approved for induction and maintenance treatment of moderate to severe Crohn’s disease. Vedolizumab is approved for use in both Crohn’s disease and ulcerative colitis. Vedolizumab is a humanized monoclonal antibody that binds to α4-β7 integrin and is approved for the treatment of moderate to severe ulcerative colitis.
integrin. Specifically blocking the β-7 integrin is thought to inhibit leukocyte migration in the intestine, but not in the central nervous system, thereby decreasing the risk of progressive multifocal leukoencephalopathy (PML), which has occurred with natalizumab.

**Efficacy** — Natalizumab has been modestly effective in some studies as an induction agent in patients with moderate to severe Crohn’s disease with active inflammation. It appears to be more effective at maintaining response and remission, with significant steroid-sparing effects.

Vedolizumab has been approved by the FDA for treatment of Crohn’s disease and ulcerative colitis in patients who have not responded to or could not tolerate corticosteroids, immunosuppressants, or TNF inhibitors. In a randomized, controlled trial in patients with Crohn’s disease, a clinical remission occurred after 6 weeks of treatment in 14.5% of vedolizumab-treated patients and in 6.8% of those taking placebo. A clinical response occurred in 31.4% of patients treated with vedolizumab and in 25.7% of those randomized to placebo; this difference was not statistically significant. Responders received maintenance therapy with vedolizumab every 4 or 8 weeks, or placebo, for 52 weeks; 36.4% and 39% of patients receiving vedolizumab every 4 and 8 weeks, respectively, were in clinical remission at 52 weeks, compared to 21.6% of those receiving placebo.

In patients with ulcerative colitis, a clinical response occurred in 47.1% of vedolizumab-treated patients after 6 weeks of therapy, compared to 25.5% of those taking placebo. Among responders, continued treatment with vedolizumab every 4 or 8 weeks resulted in clinical remission at 52 weeks in 44.8% and 41.8%, respectively, compared to 15.9% with placebo.

**Adverse Effects** — Use of natalizumab in clinical practice has been limited by the rare occurrence of progressive multifocal leukoencephalopathy (PML) and severe hepatic toxicity.

No cases of PML have been reported with vedolizumab to date. In clinical trials of vedolizumab, hypersensitivity reactions have occurred, including one case of anaphylaxis. Severe infections including tuberculosis, sepsis (sometimes fatal), and meningitis have occurred. Increased transaminase and bilirubin levels have been reported.

**Pregnancy** — Natalizumab is classified as category C (toxicity in animals; no adequate human studies) for use during pregnancy. Vedolizumab is classified as category B (no evidence of risk in animals; no human studies).

**Drug Interactions** — Other biologic agents or immunomodulators may increase the risk of infectious complications with natalizumab or vedolizumab and should not be used concomitantly.

**Antibiotics**

Many experts believe that alterations in the balance of enteric bacteria (dysbiosis) play a role in the development of inflammatory bowel disease, but the evidence that antibiotics are effective in treating Crohn’s disease or ulcerative colitis is limited, and they might make dysbiosis worse. Metronidazole (Flagyl, and generics), ciprofloxacin (Cipro, and generics), and rifaximin (Xifaxan) are used, sometimes together, to treat Crohn’s disease microperforations and fistulas, and to treat pouchitis in ulcerative colitis. They have also been used following resections to prevent recurrence of Crohn’s disease.

**Efficacy** — One meta-analysis found antibiotics more effective than placebo in inducing remission in active Crohn’s disease, particularly in fistulizing disease. A randomized, double-blind trial in more than 400 patients found that 12 weeks of rifaximin 800 mg twice daily induced remission in 62% of patients with moderately active Crohn’s disease, compared to 43% of those receiving placebo. The evidence that antibiotics are effective in maintaining remission in Crohn’s disease is limited.

The use of antibiotics is not recommended for ulcerative colitis, except pouchitis, for which ciprofloxacin, metronidazole, and rifaximin all appear to be effective, but large controlled trials are lacking.

**Adverse Effects** — Metronidazole can cause abdominal discomfort, metallic taste, nausea, vomiting, diarrhea, loss of appetite, ataxia, and peripheral neuropathy. Ciprofloxacin can cause nausea, vomiting, diarrhea, abdominal discomfort, headache, dizziness, QT interval prolongation, altered mental status, lowering of the seizure threshold, spontaneous tendon rupture, and an increased risk of Clostridium difficile infection. Rifaximin is minimally absorbed and has an incidence of adverse effects similar to that of placebo.

**Drug Interactions** — Taken with alcohol, metronidazole can cause a disulfiram-like reaction (flushing, headache, nausea, vomiting, abdominal cramping). It is a moderate CYP2C9 inhibitor and may increase serum concentrations of CYP2C9 substrates such as warfarin.

Ciprofloxacin is a moderate inhibitor of CYP1A2 and may increase serum concentrations of CYP1A2 substrates.
such as tizanidine (Zanaflex, and generics). Antacids and products containing iron, calcium, or magnesium may prevent full absorption of ciprofloxacin and should not be taken within 2 hours before or 6 hours after taking the drug. Taking ciprofloxacin with other drugs that prolong the QT interval may have an additive effect.14

Rifaximin is minimally absorbed and does not appear to cause any clinically significant interactions.

**PROBIOTICS**

Probiotics are live, nonpathogenic microorganisms (usually bacteria or yeasts). They have been tried for prevention and treatment of a variety of disorders, including inflammatory bowel disease.37

Probiotics have been used in ulcerative colitis to maintain remission, particularly in patients with pouchitis after ileoanal anastomosis for severe disease. In small trials in patients with ulcerative colitis and pouchitis, VSL #3 was more effective than a placebo for maintenance of remission.38,39 Probiotics have been less effective for maintenance of remission in Crohn’s disease.

Probiotics can cause bloating, flatulence, diarrhea, and hiccups. Antibiotics can inactivate bacteria-derived probiotics. ■

7. R Panaccione et al. Combination therapy with infliximab and azathioprine is superior to monotherapy with either agent in ulcerative colitis. Gastroenterology 2014; 146:392.
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The mission of The Medical Letter’s Continuing Medical Education Program is to support the professional development of healthcare providers including physicians, nurse practitioners, pharmacists, and physician assistants by providing independent, unbiased drug information and prescribing recommendations that are free of industry influence. The program content includes independent and unbiased reviews of FDA-approved and off-label uses of drugs, their mechanisms of action, clinical trials, dosage and administration, adverse effects, and drug interactions. The Medical Letter delivers educational content in the form of self-study material.

The expected outcome of the CME program is to increase the participant’s ability to know, or apply knowledge into practice after assimilating, information presented in materials contained in The Medical Letter.

The Medical Letter will strive to continually improve the CME program through periodic assessment of the program and activities. The Medical Letter aims to be a leader in supporting the professional development of healthcare providers through Core Competencies by providing continuing medical education that is unbiased and free of industry influence. The Medical Letter is supported solely by subscription fees and accepts no advertising, grants, or donations.

GOAL:
Through this program, The Medical Letter expects to provide the healthcare community with unbiased, reliable, and timely educational content that they will use to make independent and informed therapeutic choices in their practice.

LEARNING OBJECTIVES:
Activity participants will read and assimilate unbiased reviews of FDA-approved and off-label uses of drugs and other treatment modalities. Activity participants will be able to select and prescribe, or confirm the appropriateness of the prescribed usage of, the drugs and other therapeutic modalities discussed in The Medical Letter with specific attention to clinical trials, pathophysiology, dosage and administration, drug metabolism and interactions, and patient management. Activity participants will make independent and informed therapeutic choices in their practice.

Upon completion of this program, the participant will be able to:
1. Explain the current approach to the management of a patient with ulcerative colitis or Crohn’s disease.
2. Discuss the pharmacologic options available for treatment of inflammatory bowel disease and compare them based on their mechanisms of action, efficacy, dosage and administration, potential adverse effects, and drug interactions.
3. Determine the most appropriate therapy given the clinical presentation of an individual patient.

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Questions start on next page
A 23-year-old female patient with severe Crohn's disease saw an advertisement for adalimumab and asks you for some information about TNF inhibitors. You could tell her that:

a. TNF inhibitors have been effective for induction and maintenance of remission in moderate to severe Crohn's disease
b. TNF inhibitors can produce closure of fistulas
c. she should not receive live vaccines while taking a TNF inhibitor
d. all of the above

Adverse events that have been associated with TNF inhibitors include:

a. reactivation of TB
b. injection and infusion reactions
c. new onset psoriasis
d. all of the above

Progressive multifocal leukoencephalopathy (PML) has limited the use of which of the following drugs:

a. vedolizumab
b. natalizumab
c. infliximab
d. all of the above

Which of the following drugs is contraindicated for use during pregnancy?

a. infliximab
b. mesalazine
c. methotrexate
d. vedolizumab

A patient asks you about using probiotics for treatment of ulcerative colitis. You could tell her that:

a. they have been shown to be highly effective for induction of remission in ulcerative colitis
b. probiotics can cause bloating, flatulence, diarrhea, and hiccups
c. they are composed of pathogenic organisms
d. all of the above

A 32-year-old man is hospitalized with severe steroid-resistant ulcerative colitis. Which of the following drugs could be used to avoid colectomy?

a. cyclosporine
b. budesonide
c. metronidazole
d. certolizumab

Aminosalicylates are:

a. generally used first for induction and maintenance of remission in mild to moderate ulcerative colitis
b. generally used first for induction and maintenance of remission in mild to moderate Crohn's disease
c. available only in oral formulations
d. effective in about 90% of patients with mild to moderate ulcerative colitis

Which of the following is an option for maintenance of remission in a 26-year-old male patient with moderate Crohn's disease:

a. golimumab
b. tacrolimus
c. azathioprine
d. cyclosporine

Adverse effects associated with azathioprine and mercaptopurine include:

a. hepatotoxicity
b. myelosuppression
c. rash
d. all of the above

Combining azathioprine with infliximab:

a. has been shown to be more effective than either drug alone in achieving steroid-free remission in Crohn's disease
b. was not more effective than either drug alone in treatment of ulcerative colitis
c. can lower serum concentrations of infliximab
d. all of the above

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