Inflammatory Bowel Disease

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Pharmacist Learning Objectives:  
1. Identify the two predominant forms of inflammatory bowel disease (IBD).  
2. Compare and contrast the pathophysiologies of ulcerative colitis (UC) and Crohn’s disease (CD).  
3. Explain the health complications associated with IBD.  
4. Discuss the different treatment options for UC and CD.

Introduction  
Inflammatory bowel disease (IBD) describes a collection of chronic, idiopathic, and reoccurring inflammatory disorders located in the gastrointestinal (GI) tract.¹ There are 2 predominant forms of IBD known as ulcerative colitis (UC), a mucosal inflammation located in the rectum and colon, and Crohn’s disease (CD), a transmural inflammation that can take place in any section of the GI tract from the mouth to the anus. Inflammatory bowel disease is more common throughout developed (Westernized) countries.² It is estimated that ulcerative colitis occurs in approximately 500,000 people and Crohn’s disease approximately 480,000 people in the United States.³,⁴ The actual prevalence of IBD is considered to be underestimated due to asymptomatic/mild symptoms of the disease, which lead to less medical attention being sought for these conditions. The peak onset occurs between the ages of 15 to 30 years of age.³ While gender does not seem play a role in IBD, ethnicity can influence the incidence of IBD. Jews of European decent have a 4 fold increased incidence of IBD. Additionally, whites have a higher...
incidence compared with Asians and blacks.\(^1\) The exact etiology of both CD and UC are unknown, but they are believed to have similar factors that contribute to these conditions.\(^3\) The major theories consist of a combination of infectious, genetic, and immunologic factors with psychological and environmental factors having a minor role. Microorganisms are a likely possibility for the initiation of inflammation seen in IBD as patients tend to have alterations in their intestinal flora. Genetic factors may also play a role with data showing a high concordance rate with monozygotic twins.\(^5\)

First degree relatives of patients with IBD have a 20 times higher risk of the disease. It is also proposed that IBD can be initiated by the immune system due to an inappropriate reaction. Potential mechanisms include both auto- and non-autoimmune responses. The autoimmune response may be directed towards the mucosal epithelial cells or neutrophil cytoplasmic elements. Anti-neutrophilic antibodies, mostly in ulcerative colitis, potentiate the response. Some individuals with IBD have abnormal structural features in their colonic epithelial cells that become targeted by autoantibodies as well.

Endoscopic pictures of IBD can be seen below in Figure 1.

**Figure 1:**


**Pathophysiology**

UC and CD have similar theories of etiology but their pathophysiologies differ in anatomic site and depth of involvement within the bowel wall. Common clinical features of UC are rectal bleeding, rectal involvement, and crypt abscesses (abscesses located in the mucosa of the large intestine). Common clinical features that are more indicative of CD include malaise, fever, rectal bleeding, linear ulcers, and abdominal tenderness, mass, pain, and internal fistulas.
Ulcerative Colitis

A hallmark feature of UC is that it is not found throughout the GI tract and is limited to the rectum and colon. It only affects the mucosa and submucosal layers of the intestinal wall. For this reason, fistulas, perforations, and obstructions are not common due to inflammation being confined to only these intestinal layers. The damage to the mucosal layers in ulcerative colitis may lead to prominent diarrhea and/or bleeding.

The complications associated with UC can be local, such as in the colon or rectum, or systemic, such as in certain joints. Hemorrhoids, anal fissures, or perirectal abscesses are relatively minor complications and are more likely to be present during active colitis. A more serious complication that can occur is toxic megacolon which is a life-threatening problem that causes accelerated dilation of the large intestine within a few days. It can be segmental or consist of total colonic distension of greater than 6 centimeters accompanied by acute colitis and systemic signs of inflammation such as fever, tachycardia, and abdominal distension.

Patients with UC have a greater risk of colon cancer compared to other individuals. The risk of cancer increases 10 – 15 years after being diagnosed with ulcerative colitis. After 35 years, the absolute risk may be up to 30% and for patients that have a long history of the disease, or had a diagnosis before the age of 15, the risk can be as high as 49%.

In UC, the inflammatory response can give rise to systemic complications including fatty liver, chronic active hepatitis, and cirrhosis. Complications such as scarring of the bile duct, cancerous growths on the bile duct connecting the liver to the small intestine, and gallstones are some of the biliary complications and occur in around 11% of patients. Arthritis is also associated with ulcerative colitis although the exact mechanism relating the two hasn’t been established. Unlike rheumatoid arthritis, it is asymmetric and migratory. It typically involves few joints and the most affected joints are the knees, hips, ankles, and wrists. The arthritis is generally correlated with the severity of the disease. Resolution of these arthritic symptoms typically occurs with proctocolectomy (removal of rectum and all/part of the colon). Even after multiple episodes, this type of arthritis is not deforming or destructive as seen in rheumatoid arthritis.

Another complication with approximately 10% prevalence is ocular abnormalities. Problems including iritis, uveitis, episcleritis, and conjunctivitis are the most common. There are also dermatologic and mucosal complications that include erythema nodosum, pyoderma gangrenosum, and aphthous ulceration. Approximately 10% of patients develop these complications. Erythema nodosum are raised, red, tender nodules that are typically located on the surfaces of the legs and arms. Pyoderma gangrenosum are discrete skin ulcerations that contain a necrotic center with a violet hue surrounding it. They can occur anywhere on the body, but they tend to be located on the legs. Oral lesions, such as aphthous ulcerations, are found in both patients with Crohn’s disease and ulcerative colitis, but they are more common in patients with Crohn’s disease.

Crohn’s Disease

Crohn’s disease is best described as a transmural inflammatory process in which the terminal ileum is the most common site of the disease; however, it can occur in any part of the GI tract. Focal intestinal inflammation is the hallmark sign of
Crohn’s disease and unlike UC, patients often have normal healthy bowel separating portions of inflamed bowel. Approximately 2/3 of patients have colonic involvement and a smaller percentage (15 -25%) only have the colonic disease. In patients with CD, bowel wall injury can be extensive. The mesentery (fold of tissue that attaches the small intestine to the back of the abdominal wall) becomes thickened and edematous. Eventually, it becomes fibrotic which leads to narrowing of the intestinal lumen. The ulcers associated with Crohn’s tend to be deeper, elongated, and extend along the bowel. The nature of the findings/depth of inflammatory changes usually depend on the chronicity of the inflammation.

Problems related to CD can affect not only the intestinal tract, but other organs as well. Small bowel strictures leading to occlusion is a serious condition that may require surgical intervention. Unlike UC, patients with CD are more likely to develop fistulas. They usually occur in areas of frequent inflammation and may be enterocutaneous (connects a segment of the GI tract to the skin), enteroenteric (connects 2 segments of the GI tract together), or enterovesicular (connects a segment of the GI tract to the bladder) fistulas. These complications usually require surgical intervention. The risk of bleeding and developing carcinomas is increased with CD, but it is not as high as with UC. Just as with UC, arthritis, ocular, skin, and liver complications accompany CD. Approximately 10% of patients develop renal stones caused by fat malabsorption. Because CD can affect the entire length of the GI tract, nutritional deficiencies are common. Complications such as weight loss (40 – 80%), stunted growth in children (15 – 88%), iron deficiency (25 – 50%), vitamin B₁₂ deficiency (20 – 37%), folate deficiency (13 – 37%), hypoalbuninemia (25 – 76%), hypokalemia (33%), and osteomalacia (36%).

Clinical Presentation

Patients with IBD present with a wide variety of complications. Some patients can experience a single episode that will resolve and not reoccur; however, most patients experience recurrent episodes of acute exacerbations. As the severity increases, so does the duration of these complications. Systemic complications can occur before GI symptoms occur. Approximately 10% of cases may not be able to categorize as ulcerative colitis or Crohn’s disease. Table 1 summarizes the common signs and symptoms of these conditions.

<table>
<thead>
<tr>
<th>Table 1: Clinical Presentation and Diagnosis of IBD²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signs</td>
</tr>
<tr>
<td>Fever</td>
</tr>
<tr>
<td>Dehydration</td>
</tr>
<tr>
<td><strong>Hemorrhoids</strong>*</td>
</tr>
<tr>
<td>Perirectal abscesses</td>
</tr>
<tr>
<td>Symptoms</td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>Abdominal pain</td>
</tr>
<tr>
<td>Malnutrition</td>
</tr>
<tr>
<td><strong>Urge to constantly defecate</strong></td>
</tr>
<tr>
<td>Laboratory Tests</td>
</tr>
<tr>
<td>Leukocytosis</td>
</tr>
<tr>
<td>Decreased hematocrit/hemoglobin</td>
</tr>
<tr>
<td>Increased erythrocyte sedimentation rate (ESR) or</td>
</tr>
</tbody>
</table>
### Increased C-reactive protein (CRP)
- Guaiac-positive stool
- Positive perinuclear antineutrophil cytoplasmic antibodies

### Signs
- Fever
- Dehydration
- **Abdominal mass & tenderness**
- **Perianal fissure/fistula**
- Tachycardia
- Arthritis

### Symptoms
- Diarrhea
- Abdominal pain
- Malnutrition
- Rectal bleeding
- Weight loss
- Fatigue

### Laboratory Tests
- Leukocytosis
- Decreased hematocrit/hemoglobin
- Increased ESR or CRP
- Guaiac-positive stool
- **Positive anti-Saccharomyces cerevisiae antibodies**
- **Hypoalbuminemia with severe liver disease**

*Bolded information represents differences between ulcerative colitis and Crohn’s disease.*

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**Non-pharmacological Treatment of IBD**

OTC medications may provide supportive care to prescription medications in IBD. Fiber supplements such as psyllium powder (Metamucil®) or methylcellulose (Citrucel®) help to relieve mild to moderate diarrhea by adding bulk to the stool. Loperamide (Imodium®) may be more effective in patients with severe diarrhea. Swelling may cause intestines to narrow that can result in constipation. Acetaminophen (Tylenol®) can be used for mild pain. Patients should avoid aspirin, ibuprofen (Advil®, Motrin®) and naproxen (Aleve®) as these can worsen symptoms by irritating the gastrointestinal tract. Iron supplements may help restore iron levels since patients with inflammatory bowel disease can experience melena (bloody stools). Vitamin B-12 is absorbed in the terminal ileum, which is often affected by Crohn’s disease, therefore vitamin B-12 shots may be needed to help prevent anemia and promote normal growth/development. Calcium and vitamin D supplements are needed in patients who are treated chronically with corticosteroids.

Inflammation of the small bowel can prevent proper absorption of nutrients. Many of the inflammatory mediators involved in the disease progression are also responsible for muscle wasting and protein loss. Many patients with moderate to severe IBD are malnourished making nutritional support a vital component of treatment. This support can come in the form of enteral or parenteral nutrition depending on the severity of the disease and degree of inflammation. Additionally, many patients with IBD have to undergo multiple bowel resections, resulting in “short gut” syndrome, a condition associated with poor digestion and diarrhea, which can have a detrimental effect on quality of life.
Probiotics could potentially be effective in ulcerative colitis unlike Crohn’s disease. A study involving the E. coli Nissle 1917 strain found that it was just as effective as sulfasalazine in maintaining remission. A study involving the probiotic VSL #3 found that when used with sulfasalazine, it can help to induce remission in mild to moderate ulcerative colitis.

General Approach to Treatment of Crohn’s Disease

It is important to note when approaching the treatment of Crohn’s that there is no cure for the disease. Crohn’s is characterized as a chronic, relapsing disease, cycling between disease flares and remission of symptoms. About half of all patients with Crohn’s will be in remission at any one time. Current therapies are targeted at inducing remission or maintaining remission. The majority of Crohn’s patients will require chronic treatment in order to maintain remission. A patient is said to be in symptomatic remission when they have responded to medical or surgical therapy with total resolution of symptoms and no residual disease activity.

The selection of agents for the treatment of Crohn’s requires the appropriate staging of the disease. The three stages of disease are:

- **Mild to moderate:** These patients are able to tolerate oral nutrition, and lack abdominal tenderness, intestinal obstruction, dehydration, or >10% weight loss.
- **Moderate to severe disease:** This stage of disease is characterized by a failure to respond to mild to moderate treatment options, symptoms of fever, weight loss, abdominal pain or tenderness, nausea and vomiting, or anemia.
- **Severe or fulminant disease:** These patients have persistent disease despite treatment with steroids or biologic agents. Often these patients will appear as though they are wasting away and have symptoms of high a fever, persistent vomiting, or intestinal obstruction.

Induction of Remission of Crohn’s Disease

The goal in mild to moderate active Crohn’s is the complete remission of symptoms with a return to normal daily activities and reduced corticosteroid use. First line agents used in this stage of disease are sulfasalazine and mesalamine derivatives. Sulfasalazine is most beneficial for patients that have disease involving the ileum, colon, or perianal area. Mesalamine derivatives have utility in decreasing inflammation in all areas of the gastrointestinal tract. The mesalamine product formulation determines the agent’s site of action, therefore product selection varies depending on the areas of the bowel that are affected. Although corticosteroids are mostly reserved for moderate to severe disease, budesonide has demonstrated efficacy in disease involving the small bowel. Some patients may also require certain antibiotics as adjunctive agents in disease involving the perianal area.

The goals of therapy in moderate to severe active Crohn’s are the minimization of symptoms and the induction of remission while reducing corticosteroid dependence. Steroids, thiopurines, biologic agents, methotrexate, or metronidazole are the
agents of choice for moderate to severe disease. Steroids are first line therapy in this stage due to their ability to produce remission in 70% of patients.\(^3\) Biologic agents are used in patients contraindicated to steroids or who have failed thiopurine or steroid therapy. Methotrexate is used for patients that are steroid dependant or have not responded to azathioprine or mercaptopurine.

In severe fulminant Crohn’s, IV corticosteroids are given first line to control symptoms.\(^15\) Patients that respond to IV steroids should be switched to oral steroid therapy until symptoms resolve, then have the steroid tapered down. If a patient fails to respond to IV corticosteroids within 10 days, the next treatment option is cyclosporine. Patients that do not respond to drug therapy are then candidates for surgical intervention.

**Maintenance of Remission of Crohn’s Disease**

Once an agent is selected, the patient’s response should be evaluated within several weeks of initiating therapy.\(^13\) Clinical response should be evident within 2-4 weeks and a maximal response should be seen by 12-16 weeks. Maintenance therapy should be considered for patients that are able to achieve remission. Those patients that are unable to achieve remission should be treated with an alternative therapy if they have mild to moderate disease or advanced to moderate to severe treatment options.\(^3\)

Many of the agents that are able to induce remission are continued into the maintenance phase of treatment, with the exception of steroids, which are tapered off.\(^1\) Maintenance therapy options vary depending upon the agent used to induce remission, the patient’s exposure to corticosteroids, and the agent’s long-term efficacy and side effect profile.\(^3,13\)

Table 2 summarizes the available options for the treatment of Crohn’s and the stage of disease each agent is used.
## Table 2: Pharmacotherapy Treatment Options for Crohn’s Disease

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Dose, Route, and Frequency</th>
<th>Stage Used</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immuno-suppressant</strong></td>
<td>Cyclosporine</td>
<td>4 mg/kg IV daily</td>
<td>Severe, fistulizing disease</td>
<td>Long-term risks of renal toxicity and infection limit utilization</td>
</tr>
<tr>
<td>Anti-folate</td>
<td>Methotrexate</td>
<td>15-25 mg SC or IM weekly</td>
<td>Induction in moderate to severe</td>
<td>More commonly used in maintenance than in the induction phase</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15 mg SC or IM weekly</td>
<td>Maintenance in moderate to severe</td>
<td></td>
</tr>
<tr>
<td>Amino-salicylates</td>
<td>Mesalamine (Pentasa®)</td>
<td>1 g PO QID</td>
<td>Induction in mild to moderate</td>
<td>Targets the small bowel and colon; can be given with or without food; capsule can be opened</td>
</tr>
<tr>
<td></td>
<td>Mesalamine (Asacol®)</td>
<td>800 mg PO BID</td>
<td>Maintenance mild to moderate</td>
<td>Targets the ileum and colon; do not break outer coating</td>
</tr>
<tr>
<td></td>
<td>Sulfasalzine (Azulfidine®)</td>
<td>1-2 g PO TID</td>
<td>Mild to moderate disease</td>
<td>Targets the colon; high pill burden associated with use</td>
</tr>
<tr>
<td><strong>Steroids</strong></td>
<td>Budesonide (Entocort®)</td>
<td>9 mg PO daily for 8 weeks</td>
<td>Induction in mild to moderate disease</td>
<td>Targets the ileum or colon; therapy beyond 3 months has no clinical benefit</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 mg PO daily for 3 months</td>
<td>Maintenance in mild to moderate disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prednisone</td>
<td>40-60 mg PO daily</td>
<td>Induction or maintenance in moderate to severe</td>
<td>Treatment duration for induction phase 2-28 days; if response is observed, prednisone should be tapered over 2-4 weeks</td>
</tr>
<tr>
<td></td>
<td>Hydrocortisone</td>
<td>100 mg IV q 6-8 H</td>
<td>Severe, fistulizing disease</td>
<td>Patients should be switched to oral steroids once response is seen</td>
</tr>
<tr>
<td><strong>Antibiotics</strong></td>
<td>Metronidazole</td>
<td>400 mg PO BID or 1 g PO daily</td>
<td>Induction in mild to moderate disease</td>
<td>Adjunctive agent that can be used with or without ciprofloxacin (more effective when in combination); used in refractory perianal disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>500 mg PO BID</td>
<td>Induction in mild to moderate</td>
<td>Adjunctive agent used in refractory perianal disease</td>
</tr>
<tr>
<td><strong>Thiopurines</strong></td>
<td>Azathioprine (Imuran®)</td>
<td>2-3 mg/kg PO daily</td>
<td>Induction and maintenance of moderate to severe</td>
<td>Requires a minimum of 3-4 months to see maximum benefits</td>
</tr>
<tr>
<td></td>
<td>Mercaptopurine</td>
<td>1.5 mg/kg</td>
<td>Maintenance of moderate to severe disease, steroid</td>
<td>Requires a minimum of 3-4 months to see maximum benefits; patients with certain</td>
</tr>
<tr>
<td>Biologic Agents</td>
<td>Infliximab (Remicaide®)</td>
<td>Adalimumab (Humira®)</td>
<td>Certolizumab pegol (Cimza®)</td>
<td>Natalizumab (Tysabri®)</td>
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<td>-----------------</td>
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</tr>
<tr>
<td>Dosage</td>
<td>2 mg/kg IV at weeks 0, 2, and 6</td>
<td>160 mg SC on day 1 (as four 40 mg injections), then 80 mg on day 15</td>
<td>400 mg SC at weeks 0, 2, and 4</td>
<td>300 mg IV every 4 weeks</td>
</tr>
<tr>
<td>Description</td>
<td>Induction in moderate to severe disease</td>
<td>Induction in moderate to severe disease</td>
<td>Induction in moderate to severe disease</td>
<td>Induction and maintenance of moderate to severe disease</td>
</tr>
<tr>
<td>Maintenance</td>
<td>5 mg/kg IV every 8 weeks</td>
<td>40 mg SC every other week starting day 29</td>
<td>400 mg SC every 4 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Maintenance of moderate to severe disease</td>
<td>Maintenance of moderate to severe disease</td>
<td>Maintenance of moderate to severe disease</td>
<td></td>
</tr>
<tr>
<td>Toxicity</td>
<td>Dependant patients, and fistulizing disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testing</td>
<td>Genetic testing may be utilized before initiation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Side Effects</td>
<td>Patients can develop antibodies to infliximab, decreasing efficacy; doses can be increased to 10 mg/kg if efficacy is lost at 5 mg/kg; helps minimize steroid dependency</td>
<td>May be particularly useful in patients that have lost response to infliximab</td>
<td>Only requires SC injections every 4 weeks during remission</td>
<td>Patients must be enrolled in the CD TOUCH Prescribing Program</td>
</tr>
</tbody>
</table>
General Approach to Ulcerative Colitis

Goals of treatment in ulcerative colitis are treatment of active disease, induction of remission and maintenance of remission. Therapies used are based on stage of disease, extent of disease, and patients’ preferences.

There is no widely accepted criteria for staging ulcerative colitis but the more recent staging tools include Mayo Clinic Index, Sutherland Index (UC Disease Activity Index). These indices calculate a composite score based on number of loose or soft stools, rectal bleeding, sigmoidoscopic appearance (appearance of GI lining) and a global assessment by physicians. Each of these items is given a number from 0 to 3, with 3 being the highest rating for disease activity.

The oldest tool that has been used in staging ulcerative colitis but the more recent staging tools include Mayo Clinic Index, Sutherland Index (UC Disease Activity Index). These indices calculate a composite score based on number of loose or soft stools, rectal bleeding, sigmoidoscopic appearance (appearance of GI lining) and a global assessment by physicians. Each of these items is given a number from 0 to 3, with 3 being the highest rating for disease activity.

The oldest tool that has been used in staging ulcerative colitis is the True-Love Witts Criteria of 1955 which classifies UC as: \(^{21}\)

- **Mild Disease**: less than four stools a day, with or without blood, no signs of toxicity, normal erythrocyte sedimentation rate.
- **Moderate Disease**: more than four stools a day and some signs of toxicity.
- **Severe Disease**: more than six stools a day, melena (blood in stools), elevated erythrocyte sedimentation rate and signs of toxicity such as fever, increased heart rate or anemia.
- **Fulminant Disease**: more than 10 stools a day, continuous melena, requirement for blood transfusion, abdominal tenderness, colon or abdominal plain film, and signs of toxicity.

Oral aminosalicylates, topical mesalamine, or topical steroids are the treatments of choice in patients with mild to moderate distal ulcerative colitis. \(^{19}\) Therapy is determined by patient choice because all therapies are equally effective; however, topical mesalamine is considered superior to topical steroids or oral aminosalicylates. Using topical therapies gives the advantage of less frequent dosing, quicker response time (medication gets to site of action faster) and less systemic absorption (fewer drug interactions). Combining oral and topical aminosalicylates is even more effective than either agent alone. Patients that do not respond to oral aminosalicylates or topical corticosteroids can use mesalamine enemas or suppositories. Patients who do not respond to any of the above agents can be tried on oral prednisone or infliximab, although these agents have not been studied in this population. Maintenance of remission in distal ulcerative colitis can be done using mesalamine (first line), thiopurines and infliximab. \(^{3,11,19}\) The doses used are usually lower than treatment doses. Thiopurines and infliximab are only used if mesalamine does not work. Corticosteroids such as hydrocortisone and budesonide have not proven effective in remission of distal colitis.

In patients with extensive ulcerative colitis the inflammation has spread to the descending colon and so oral therapies are required either solely or in combination with topical therapies. \(^{19}\) First line agents are oral aminosalicylates. If a patient fails aminosalicylates or requires immediate relief, they are placed on corticosteroids such as prednisone or a combination of oral mesalamine and prednisone can also be tried. \(^{3}\) Prednisone has shown a dose response effect, with higher doses being more effective than lower doses; however, using higher doses means more side effects such as cushingoid symptoms, emotional and psychiatric disturbances, infections,
Patients who use steroids long term are prone to gastroduodenal mucosal injury, impaired wound healing, metabolic bone disease (osteopenia or osteoporosis) and metabolic disturbances (hyperglycemia, hypokalemia, sodium and fluid retention, hyperlipidemia, metabolic alkalosis). If steroids are withdrawn or tapered too rapidly, patients are at risk for experiencing adrenal insufficiency. Thiopurines are third line agents used in patients who do not respond to oral corticosteroids but whose disease is not severe enough to require IV therapy. However, these agents can take up to 3-6 months to work fully thus limiting their usefulness. The advantages of using azathioprine long term are steroid sparing, fewer hospital admissions and fewer operations. Some serious adverse events associated with azathioprine are bone marrow suppression, particularly leucopenia. This is dose dependent and usually occurs within the first few weeks to months of therapy. The FDA issued a warning in April of 2011 concerning reports of a rare cancer of white blood cells seen in adolescents and young adults being treated concomitantly with thiopurines and biologic agents for Crohn’s and ulcerative colitis.

**FDA Warning on Thiopurines**

- **WARNING -**
  MALIGNANCY Chronic immunosuppression with IMURAN, a purine antimetabolite increases risk of malignancy in humans. Reports of malignancy include post-transplant lymphoma and hepatosplenic T-cell lymphoma (HSTCL) in patients with inflammatory bowel disease. Physicians using this drug should be very familiar with this risk as well as with the mutagenic potential to both men and women and with possible hematologic toxicities. Physicians should inform patients of the risk of malignancy with IMURAN.

Infliximab is the last line therapy and is used in patients who are steroid refractory/dependent and have received adequate doses of thiopurines but are still seeing no relief. It is given at 8 week dosing intervals to reduce infusion reactions. Most common adverse effects are: autoimmunity, increased infection risk, lymphoma. Rare but serious adverse effects include worsening of congestive heart failure (CHF), worsening of multiple sclerosis, optic neuritis or hepatotoxicity. Infliximab is contraindicated in patients with active infection, inactive TB, demyelinating disorder, moderate to severe CHF and those who have malignancies. A novel treatment for extensive colitis is nicotine. It was shown to be more effective than placebo in achieving remission and improvement of active ulcerative colitis; however, it was not more effective than mesalamine and so its place in therapy is very limited. Maintenance of remission in extensive ulcerative colitis requires the use of aminosalicylates (first line), thiopurines (use only if aminosalicylates fail) and infliximab (last line therapy). Azathioprine has been shown to be superior to 5-aminosalicylates when it comes to remission in steroid dependent patients. Corticosteroids should not be used in chronic maintenance of remission. Uncontrolled severe or fulminant ulcerative colitis requires...
hospitalization. These patients should not receive anything by mouth and most of their therapy is parenteral. Aminosalicylates are not useful in these patients because they are removed from the bowel very quickly due to diarrhea not allowing the bacteria to cleave molecules to activate the drugs. Intravenous corticosteroids such as hydrocortisone or methylprednisolone (preferred due to lower mineralocorticoid activity) are necessary in these patients and can prevent the need for colectomy. If no improvement is seen in the 3-5 days on corticosteroids, the patient may need a colectomy or need to be treated with IV cyclosporine (2 mg/kg). Patients who have had no response to maximal oral treatment with aminosalicylates, prednisone and topical agents can be started on infliximab at a dose of 5 mg/kg if hospitalization is not required. Infliximab may help to prolong the time before a colectomy is needed in patients who fail therapy with IV steroids. Addition of thiopurines may help to maintain long-term remission in these patients and extend the time before a colectomy is needed. Antibiotics such as oral vancomycin, IV metronidazole and IV ciprofloxacin have shown no benefit in severe colitis when added to steroid therapy in patients with toxicity.

Table 3 summarizes the treatment options, stage used, and dosing of agents used in ulcerative colitis.
### Table 3: Pharmacotherapy Treatment Options for Ulcerative Colitis\(^3,11,16,19,22\)

<table>
<thead>
<tr>
<th>Class</th>
<th>Drugs</th>
<th>Dose, Route, and Frequency</th>
<th>Stage Used</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Aminosalicylates | **Sulfasalazine** \((Azulfidine®)\) | 4-6 g/day taken orally QID \((Treatment)\) | Mild to Moderate Ulcerative Colitis | - Least expensive  
- Titrate up due to GI intolerance seen with this medication.  
- Intolerance can result in nausea, vomiting, dyspepsia, headache and anorexia.  
- Severe adverse effects include pancreatitis, hepatotoxicity, bone marrow suppression, interstitial nephritis and hemolytic/megaloblastic anemia.  
- Generally take 2-4 weeks to see effects. |
|                | **Balsalazide** \((Colazal®)\) | 750 mg taken orally TID for 8-12 weeks \((Treatment)\) | Mild to Moderate Ulcerative Colitis | - Causes staining of teeth or tongue if capsule is opened and sprinkled on food.                                                                                                                   |
|                | **Olsalazine** \((Dipentum®)\) | 500 mg taken orally BID \((Treatment)\) | Mild to Moderate Ulcerative Colitis | - Higher doses have been associated with diarrhea.                                                                                                                                                   |
|                | **Mesalamine** \((Pentasa®)\) | 1 g taken orally QID for 3-8 weeks \((Treatment)\) | Mild to Moderate Ulcerative Colitis | - Asacol ® and Mezavant ® are for treatment only.  
- Apriso ® is for maintenance only.  
- Serum creatinine needs to be measured prior to initiating treatment and periodically during therapy with mesalamine as nephrotoxicity has been noticed rarely.  
- Work in all areas of GI tract but site of action is determined by product formulation. |
<p>|                | <strong>Mesalamine</strong> ((Asacol®, Asacol®HD)) | 800 mg taken orally TID for 6 weeks or 1.6 g taken orally TID for 6 weeks ((HD)) ((Treatment)) | Mild to Moderate Ulcerative Colitis |                                                                                                                                                                                                       |
|                | <strong>Mesalamine</strong> ((Lialda®,(2.4-4.8) g taken orally) | 800 mg taken orally BID ((Remission)) | Mild to Moderate Ulcerative Colitis |                                                                                                                                                                                                       |</p>
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Remission</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mesavant®)</strong></td>
<td>TID for 8 weeks (Treatment) 2.4 g taken orally QD (Remission)</td>
</tr>
<tr>
<td><strong>Mesalamine (Apriso®)</strong></td>
<td>1.5 g taken orally in the morning (Remission)</td>
</tr>
<tr>
<td><strong>Mesalamine (Canasa®)</strong></td>
<td>1 g suppository in rectum QD at bed time for 3-6 weeks (Treatment) 500 mg suppository in rectum BID (Remission) 4 g enema retained for 8 hours overnight (Treatment) 4 g enema QD, QOD or every third day (Remission)</td>
</tr>
<tr>
<td><strong>Corticosteroids</strong></td>
<td><strong>Hydrocortisone (A-Hydrocort®, Cortef®)</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Prednisone</strong></td>
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</tbody>
</table>

- Doses of 1-4g are needed to reach higher into the colon and are effective for inducing and maintaining remission in distal colitis.
- Combination of oral and rectal mesalamine is better than either agent alone for remission.
- If no response is seen in 5-7 days with IV hydrocortisone then patient should be switched to cyclosporine.
- When improvement is seen, slowly taper the dose by 5-10 mg every week until a dose of 20 mg a day is reached.
- Yearly DEXA bone scan and an ophthalmic exam
- Bisphosphonate therapy should be considered in patients who are taking steroids for 3 months.
or more and have a T score of -2.5.
- Calcium supplementation (1500 mg/day),
  vitamin D supplementation (800 U/day) and
  estrogen replacement should be considered in
  postmenopausal women.
- Modifiable risks such as cigarette smoking,
  alcohol use and sedentary lifestyle should also be
discussed.
- **Chronic use of corticosteroids is not recommended for remission in any stage.**

<table>
<thead>
<tr>
<th>Table 1</th>
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<tbody>
<tr>
<td><strong>Indications</strong></td>
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<tr>
<td>Methylprednisolone</td>
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<tr>
<td><strong>Thiopurines</strong></td>
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<tr>
<td>Azathioprine (Imuran®)</td>
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<tr>
<td>6-Mercaptopurine (Purinethol®)</td>
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<tr>
<td><strong>Biologics Agents</strong></td>
</tr>
<tr>
<td>Infliximab (Remicade®)</td>
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<tr>
<td><strong>Miscellaneous</strong></td>
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<tr>
<td>Cyclosporine</td>
</tr>
</tbody>
</table>

- Preferred agent due to lower mineralocorticoid activity.
- CBC is recommended frequently during the first few months of therapy.
- Black Box Warning for lymphoma and other malignancies.
- Patients should be premedicated with corticosteroids and antihistamines.
- Patients should be screened for latent TB with a skin test and a chest radiograph.
- Infliximab has also been known to reactivate hepatitis B infections and so patients should be
  screened prior to initiation of this drug.
- Vaccination should be considered in patients at high risk for contracting hepatitis B.
- Once patients are controlled, they can be
| (Gengraf®, Neoral®) | **Treatment** | fulminant ulcerative colitis | switched to an oral cyclosporine taper regimen. They can then be transitioned to thiopurines. |
**Future Therapies for IBD**

The efficacy of anti-TNF-α agents and other biologics has been assessed in ulcerative colitis. A recent study of adalimumab for the induction of clinical remission in moderate to severe ulcerative colitis found that a higher dose of this agent (ADA 160/80 - 160 mg at week 0, 80 mg at week 2, 40 mg at weeks 4 and 6) was successful in inducing remission in these patients. This trial was a randomized, double-blind placebo controlled trial conducted at 94 centers in the U.S. and Europe. It was an 8-week study and involved 186 patients. At week 8, 18.5% of patients in the ADA160/80 group (p=0.031), 10% in the ADA80/40 group (p=0.833) and 9.2% in the placebo group were in remission.

Studies of antibodies such as PF-00547659 have shown promising results in preventing leukocyte activation in the gut that leads to inflammation. The PF-00547659 study was a randomized double-blind placebo controlled trial of 80 patients with active ulcerative colitis. It was found that this agent has a favorable short term safety profile and efficacy. This has paved a way for future research in the use of unique anti-inflammatory antibodies for ulcerative colitis.

Interleukin-13 has been identified as one of the effector cytokines in ulcerative colitis and therefore, the development of agents that block interleukin-13 production may be extremely beneficial in patients with ulcerative colitis. A recent study testing the suppression of inflammation in ulcerative colitis by interferon-β-1a confirms this. This study showed that interferon-β-1a led to the suppression of interleukin-13 and showed a clinical response in 11 of 16 patients with 4 going into complete remission.

**Conclusion**

IBD is a chronic condition characterized by periods of active disease and symptomatic remission. Assessing disease severity can be challenging due to its subjective nature. Laboratory tests that assist diagnosis include direct endoscopic examination, radiocontrast imaging, fluid and electrolyte status, serum albumin, transferrin, and erythrocyte sedimentation rate. A thorough patient history coupled with physical examination facilitates the appropriate selection treatment regimens. The goal of therapy for all stages of IBD is to induce or maintain disease remission. In addition to the assessment of efficacy and adverse effects, therapeutic outcomes should evaluate patient quality of life.

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References:


INSTRUCTIONS: This page is intended to help participants REVIEW the quiz prior to submitting their answers online. Please take the quiz online using the members section of the website.

1. Ulcerative Colitis is a complication that is primarily found where in the body?
   a. Throughout the GI tract
   b. Limited to the rectum
   c. Limited to the colon
   d. Rectum and colon

2. The exact etiology of irritable bowel disease is
   a. Genetic
   b. Immunologic
   c. Infectious
   d. Unknown

3. Crohn’s Disease is a complication that is primarily found where in the body?
a. Throughout the GI tract  
b. Limited to the rectum  
c. Limited to the colon  
d. Limited to the rectum and colon

4. Some common signs and symptoms found in ulcerative colitis and Crohn’s disease include  
a. Perianal fistula  
b. Abdominal pain  
c. Perirectal abscesses  
d. Constantly have the urge to defecate

5. What stage of Crohn’s disease would IV hydrocortisone be used?  
a. Mild to moderate  
b. Moderate to severe  
c. Severe to fulminant  
d. Not used in Crohn’s disease

6. Of the following agents used to induce remission in Crohn’s disease, which could not be continued into the maintenance phase of treatment?  
a. Infliximab  
b. Prednisone  
c. Methotrexate  
d. Azathioprine

7. What region of the bowel does sulfasalazine target?  
a. Jejunum  
b. Ileum  
c. Small bowel  
d. Colon

8. Which of the following would not be considered a symptom of moderate to severe Crohn’s disease?  
a. Weight loss  
b. Anemia  
c. Intestinal obstruction  
d. Abdominal pain

9. A patient is having about 5 loose stools daily and is experiencing symptoms such as fever, abdominal cramps, and blood in the stool. According to Truelove-Witt criteria they could possibly have  
a. Mild UC
b. Moderate UC
c. Severe UC
d. Fulminant UC

10. A patient with extensive moderate ulcerative colitis has tried oral mesalamine and failed on this therapy. The next best step is to
   a. Add oral methylprednisolone to oral mesalamine
   b. Switch from oral to Mesalamine suppository
   c. Switch to oral azathioprine
   d. Switch to oral prednisone

11. Which class of drugs has a Black Box Warning for malignancies?
   a. Aminosalicylates
   b. Thiopurines
   c. Infliximab (Biologics)
   d. Corticosteroids

12. Which of the following agents is useful in preventing chronic use of steroids (steroid sparing)?
   a. Azathioprine
   b. Infliximab
   c. Mesalamine
   d. Adalimumab

13. Which of the following agents can cause staining of teeth?
   a. Sulfasalazine
   b. Balsalazide
   c. Mesalamine
   d. Olsalazine

14. Which mesalamine formulation is for maintenance of ulcerative colitis only?
   a. Pentasa®
   b. Canasa®
   c. Apriso®
   d. Asacol®