# Drugs Used in the Treatment of Inflammatory Bowel Diseases

## Goals of Pharmacotherapy
- Controlling acute exacerbations of the disease and induce remission.
- Maintaining remission.
- Treating specific complications such as abscess, fistulas.
- Correct nutritional deficiencies

## Drugs of Choice

<table>
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<tr>
<th>Crohn’s Disease</th>
<th>Ulcerative Colitis</th>
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<tr>
<td><strong>Drugs for Controlling Acute Exacerbation</strong></td>
<td><strong>Drugs for Maintaining the Remission</strong></td>
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<td>Moderate to Severe</td>
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<tr>
<td>- Glucocorticoid</td>
<td>- Antimetabolites</td>
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<tr>
<td>o Prednisolone</td>
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<td>Severe</td>
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| **Drugs for Controlling Acute Exacerbation**                                 | **Drugs for Maintaining the Remission**              |
| Mild                                                                          | Mild                                                 |
| - Sulfasalazine                                                              | - Sulfasalazine                                      |
| Moderate to Severe                                                           | Moderate to Severe                                   |
| - Antimetabolites                                                            | - Glucocorticoid                                     |
|   o Azathioprine                                                             |   o Prednisolone                                     |
| - 6-Mercaptopurine                                                           |   o Calcineurin Inhibitor                            |
| - Methotrexate                                                               |   o Cyclosporine                                     |
| - TNF-α Antibodies                                                           |                                                      |
|   o Infliximab                                                               |                                                      |

## Treatment for Complications

**Inhibit Formation and Stimulate Closure of Fistulas**
- Antimetabolites
  - Azathioprine
  - 6-Mercaptopurine
- TNF-α Antibodies
  - Infliximab

**Abscess Formation**
- Broad spectrum Antibiotics
  - Eliminate any opportunistic infection secondary to immunosuppressive therapy
- Used in
  - Specific complications of Crohn’s Disease
  - Severe Ulcerative Colitis

## Supportive Treatment
- Analgesics
- Anticholinergic
- Antidiarrheal
- Oral iron
- Oral folate and vitamin B12
Drugs | Mechanism of Action | Clinical Uses | Adverse Effects
--- | --- | --- | ---
**Sulfasalazine** 1. The Sulfapyridine and 5-Aminosalicylic acid are bounded with Azo bond  
   a. This bond resists digestion in the stomach  
   b. Only digested in the Colon by colonic bacteria  
2. Sulfasalazine is being metabolized into  
   a. **Sulfapyridine**  
      i. Being absorbed  
      ii. Not active in IBD  
   b. **5-aminosalicylic acid**  
      i. Excreted through feaces  
      ii. Active for IBD  
3. 5-Aminosalicylic acid acts by  
   a. **Inhibit COX**  
      i. Reduce production of Prostaglandin  
   b. **Inhibit Lipooxygenase**  
      i. Reduce the production of Interleukin  
   c. **Inhibit production of TNF-a and NK-kB**  
   d. Scavenge for  
      i. Free radicals  
      ii. Oxidants  
   | • Mild ulcerative colitis  
      o Relief of acute attack and induction of remission.  
      o Maintenance of remission.  
      o Topical preparations (enema/suppository) for disease limited to distal colon or rectum  
      Not useful in Crohn’s Disease  
   | It is one type of sulfonamide group of drugs, therefore susceptible to produce  
      1. Hypersensitivity reaction  
         a. Steven Johnson Syndrome  

**Glucocorticoid**  
1. Prednisolone – oral  
2. Hydrocortisone – enema  
   The idea is, when we ↓the inflammation, this will ↓ hyperreactivity in which will therefore ↓ responsiveness to stimuli  
   So be clear that this drug  
   1. Can’t stop disease progression  
   2. Only provides symptomatic relieve  

**Inflammatory mediators**  
1. Inhibits Phospholipase A2 in which involve in the formation of Arachidonic Acid; precursor of  
   a. Cyclooxygenase, in return will form  
      i. Prostaglandin  
   b. Lipooxygenase, in return will from  
      i. Leukotriene  

**Inflammatory cells**  
1. Inhibits neutrophils migration  
2. ↑distribution of lymphocytes and monocytes to lymphoid tissue  
3. Inhibit release of proteolytic enzyme by macrophage  
   1. All of these inflammatory mediators formation and action of inflammatory cells will be halted; therefore will ↓ inflammation  

   | • Moderate to severe IBD.  
   • To relieve acute exacerbations  
   Given for short duration. Therapy is terminates by tapering the dose.  
   Response of Steroid  
   • Steroid Responder (remission)  
      o Sulfasalazine  
      o Azathioprine  
      o 6-Mercaptopurine  
   • Steroid Dependent  
      o Azathioprine  
      o 6-Mercaptopurine  
   • Steroid Non-responder  
      o Methotrexate  
      o Cyclosporine  

| Prolonged usage will lead to  
1. **Systemic effect**  
   a. Cushing syndrome  
   b. Osteoporosis  
   c. Cataract  
   d. Glaucoma
### Antimetabolites

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<td>1. Azathioprine – prodrug</td>
<td>1. Azathioprine is converted to 6-MP.</td>
<td>• Delayed onset of actions (weeks/months)</td>
<td>• Bone marrow suppression</td>
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| 2. 6-Mercaptopurine (6-MP) – pro-drug | 2. 6-MP is then converted into 6-Thioinosine-5-monophosphate (TIMP)  
3. TIMP inhibits enzyme that involves in the purine metabolism  
   a. This will therefore inhibit the DNA and RNA synthesis  
Drug drug Interaction  
With Allopurinol – Xanthine Oxidase Inhibitor  
Only if the cancer pts is having a Azathioprine or Mercaptopurine regime:  
1. Azathioprine → Mercaptopurine → Inactive metabolite  
Conversion of mercaptopurine into inactive metabolite requires xanthine oxidase, therefore inhibition of xanthine oxidase activity will lead to ↑ in mercaptopurine toxicity which is pancytopenia  
Not useful for Acute condition due to its late onset of action | • Equally effective in Crohn’s disease and ulcerative colitis.  
• Can treat fistulas in Crohn’s disease.  
• Maintain remission in both diseases. | • Impaired hepatic functions  
• Increased risk of infections |
| Folate Antagonist Methotrexate (MTX) | MTX acts by  
1. ↓direct inhibition towards cellular proliferation  
2. Stimulates apoptosis in immune inflammatory cells  
3. ↓chemotaxis of inflammatory cells  
4. Inhibition in the synthesis of inflammatory cytokines  
These are achieved through the  
1. Irreversible inhibition of Dihydrofolate reductase (DHFR)  
   a. This enzyme requires for the conversion of Folic acid → Dihydrofolate and Dihydrofolate → Tetrahydrofolate  
2. Partially reversible inhibiton of Thymidylate synthetase  
   a. This enzyme requires for the conversion of Tetrahydrofolate → Purine/Pyrimidine  
3. Inhibition of Aminoimidazolecarboxamide Ribonucleotide Transformylase (AICAR)  
1. These steps are essential in the synthesis of DNA | • Response is more rapid than that seen with mercaptopurine or azathioprine.  
• Severe Crohn’s disease.  
• Used in steroid non responders | • Mucosal toxicity  
• Myelosuppression  
• Nephrotoxicity  
• Hepatotoxicity |
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<td><strong>TNF-α Antibodies</strong>&lt;br&gt;Humanized&lt;br&gt;- Adalimumab&lt;br&gt;  o Fully human IgG1 anti-TNF monoclonal antibody</td>
<td>1. Form complex with soluble TNF-α&lt;br&gt;2. Therefore prevents its interaction with p55 and p75 receptors on various tissues&lt;br&gt;3. This will then ↓function of&lt;br&gt;  a. Macrophages&lt;br&gt;  b. Lymphocytes</td>
<td>• Decreases the frequency of acute flares in patients with moderate to severe Crohn's disease.&lt;br&gt;• Maintains remission.&lt;br&gt;• Facilitates the closing of fistulas.&lt;br&gt;• Not effective in ulcerative colitis</td>
<td>1. Opportunistic infections&lt;br&gt;  a. Urinary tract infection&lt;br&gt;b. Upper respiratory tract infection&lt;br&gt;c. Tuberculosis&lt;br&gt;Infliximab is more immunogenic</td>
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<td><strong>Chimeric</strong>&lt;br&gt;- Infliximab&lt;br&gt;  o 25% mouse and 75% human IgG1 anti TNF monoclonal antibody</td>
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<td><strong>Calcineurin Inhibitor</strong>&lt;br&gt;<strong>Cyclosporine</strong>&lt;br&gt;<strong>Drug Drug Interaction</strong>&lt;br&gt;- Cyclosporine alters the activity of CYP450 enzymes through&lt;br&gt;  o Inducing&lt;br&gt;  o Inhibiting</td>
<td>- <strong>Calcineurin</strong> is a Phosphatase enzyme required to Dephosphorylate cytosolic Nuclear Factor of Activated T cells (NFATc)&lt;br&gt;  o Dephosphorylation of NFATc will allow it to enter nucleus&lt;br&gt;  o This will then a promote reaction that requires for cytokine synthesis&lt;br&gt;  - Cyclosporine will bind to a binding protein called <strong>Immunophilin</strong>&lt;br&gt;  o Cyclosporine-Immunophilin complex will further bind to Calcineurin forming another complex of Cyclosporine-Calcineurin complex&lt;br&gt;  o This complex is dysfunctional which therefore inhibits&lt;br&gt;  - Transcription of IL-2 gene&lt;br&gt;  - Cytokine expression&lt;br&gt;  - IL-3&lt;br&gt;  - Interferon Gamma</td>
<td>- A potent immunomodulator used most frequently after organ transplantation.&lt;br&gt;  - Effective in severe ulcerative colitis to relieve acute attack in steroid non-responders&lt;br&gt;  - Not effective for maintenance therapy</td>
<td>1. Nephrotoxicity&lt;br&gt;2. Hepatotoxicity&lt;br&gt;3. Hirsutism&lt;br&gt;4. Neurotoxicity</td>
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