GI Pharmacology -5
Inflammatory Bowel Disease

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Drugs used in Inflammatory Bowel Disease

• Ulcerative Colitis.
• Crohn’s Disease.
  – Unknown etiology.
  – Drugs have different nonspecific antiinflammatory actions.
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**Aminosalicylates:**

- Used for decades.
- All contain 5-aminosalicylic acid (5-ASA).
- Believed to work topically.
- 80% of 5-ASA is absorbed from the small intestine and does not reach the lesions.
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**Aminosalicylates:**

**Azo Compounds:**
- **Sulfasalazine.**
- **Balsazide.**
- **Olsalazine.**
  - All contain 5-ASA bound by an azo bond (N=N).
  - In the intestine, bacteria cleave the bond to release the active 5-ASA.

**Mesalamine Compounds:**
- **Pentasa:** time release 5-ASA formulation.
- **Asacol:** enteric coated in a pH sensitive resin.
- **Rowasa:** enema.
- **Canasa:** suppository.
Stomach

Small Intestine
Jejunum

Ileum

Small Intestine

5-ASA delayed-release capsules (Pentasa)

5-ASA pH-dependent release (Asacol, Lialda)

Colon
Proximal

Distal

Rectum

Sulfasalazine

Balsalazide

5-ASA enema (Rowasa)

5-ASA suppository (Canasa)
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**Aminosalicylates:**

**Pharmacodynamics:**

- Modulates inflammatory mediators derived from both COX and lipooxygenase pathways.

- Interfere with the production of inflammatory cytokines:
  - Inhibits nuclear factor κB (NF-κB).

- Inhibits cellular functions of natural killer cells, mucosal lymphocytes, and macrophages and may scavenger reactive oxygen metabolites.
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Aminosalicylates:

Clinical Uses:

– First line drugs for the treatment of mild to moderate active ulcerative colitis.
– Can induce and maintain remission in ulcerative colitis.
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Aminosalicylates:

Adverse Effects:

- Attributable to systemic absorption:
- especially in slow acetylator:
  - Nausea
  - headache
  - arthralgia
  - myalgia
  - bone marrow suppression
  - malaise
- Also allergic reactions, oligospermia, and folate deficiency.
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**Glucocorticoids:**

- **Prednisolone and Prednisone:**
  - Oral
- **Hydrocortisone:**
  - Enemas, foam or suppositories.
- **Budesonide:**
  - Controlled release oral formulation.

Inhibit production of cytokines (TNF-α, IL-1) and chemokines (IL-8), inflammatory cell adhesion molecules, nitric oxide synthase, phospholipase A₂, Cyclooxygenase-2 and NF-KB.
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Glucocorticoids:

Clinical Uses:

- Moderate to severe active IBD.
  - Prednisolone orally or IV.
  - Hydrocortisone, rectally, preferred for rectal and sigmoid involvement.
  - Budesonide for ileal and proximal colon involvement.
  - Not useful for maintenance.
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Antimetabolites:

- **Azathioprim**
- **6-Mercaptopurine.**
  - Are purine analogs; which produce thioguanine nucleotides.
  - Immunosuppressive.
  - Inhibit purine nucleotide metabolism and DNA synthesis and repair, resulting in inhibition of cell division and proliferation and may promote T-lymphocyte apoptosis.
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**Antimetabolites:**

- **Clinical Use:**
  - Onset delayed for 17 weeks.
  - Used in induction and maintenance of remission.
  - Allow dose reduction or elimination of steroids.
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Antimetabolites:

Adverse Effects:
- Nausea, vomiting, bone marrow suppression, hepatic toxicity and allergic reactions (fever, rash, pancreatitis, diarrhea and hepatitis).
- Allopurinol increases levels of the drugs.
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Methotrexate:

- Antimetabolite.
- Can be given orally, subcutaneously and intramuscularly.
- Work by inhibiting dihydrofolate reductase (DHFRase) enzyme which is important in the synthesis of thymidine and purines.
- At high doses it inhibits cellular proliferation.
- At low doses used in IBD, it interferes with the inflammatory actions of interleukin-1, stimulates adenosine release, apoptosis and death of activated T lymphocytes.
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**Methotrexate:**

- Used in cancer chemotherapy, rheumatoid arthritis and psoriasis.
- Used for induction and maintenance of remissions of Crohn’s Disease.
- At high doses, can cause bone marrow depression, megaloblastic anemia, alopecia and mucositis.
- Renal insufficiency may increase risk of hepatic accumulation and toxicity.
- Side effects counteracted by folate supplementation.
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Anti-Tumor Necrosis Factor:

- TNF-α is a key proinflammatory cytokine in the TH1 response in IBD.

  - **Infliximab “Remicade”**:  
    - Is a chimeric mouse-human monoclonal antibody to human TNF-α.
    - Given IV.

  - **Adalimumab**:  
    - Fully humanized IgG antibody, given SC.

  - **Certolizumab**:  
    - Polyethylene glycol Fab fragment of humanized anti-TNF-α, also given SC.
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Anti-Tumor Necrosis Factor:

- Half life 8-10 days with persistence of antibodies in plasma for 8-12 weeks.
- Binds to cell surface as well as to membrane-bound TNF-α receptors, preventing the cytokine from binding to its receptors.
- The Fc portion of human IgG₁ region promotes complement activation and antibody-mediated apoptosis and cellular cytotoxicity of activated lymphocytes and macrophages.
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**Anti-Tumor Necrosis Factor:**

- Used in acute and chronic treatment of patients with moderate to severe IBD.
- Given in repeated doses at 0, 2, and 6 weeks for induction.
- If response is adequate, infusions are repeated every 8 weeks.
- Response might be lost due to development of antibodies to infliximab.
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Anti-Tumor Necrosis Factor:

- Serious Adverse effects:
  - Infection due to immunosuppression, occur in 6% of patients on infliximab, e.g. reactivation of TB or dissemination, pneumonia, sepsis, pneumocystis, listeriosis, and reactivation of hepatitis B.
  - Antibody formation against the murine epitope of infliximab develops in 1/3rd of patients leading to loss of response or infusion reactions.
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Anti-Tumor Necrosis Factor:

- **Acute Infusion Reactions**: fever, headache, dizziness, urticaria, chest pain, and dyspnea, hypotension, shortness of breath, muscle spasm and chest discomfort.

- **Delayed Reactions or Serum Sickness-like Reactions**: occur after retreatment with infliximab include myalgia, arthralgia, jaw tightness, fever, rash, urticaria, and edema.
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Anti-Tumor Necrosis Factor:

Disease severity

Therapy

Responsiveness to therapy

Severe
- Surgery
- Natalizumab
- Cyclosporine
- TNF antagonists
- Intravenous corticosteroids
- Refractory

Moderate
- TNF antagonists
- Oral corticosteroids
- Methotrexate
- Azathioprine / 6-Mercaptopurine

Mild
- Budesonide (ileitis)
- Topical corticosteroids (proctitis)
- Antibiotics
- 5-Aminosalicylates
- Responsive
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- Treatment choice is predicated on both the severity of the illness and the responsiveness to therapy.
- Agents at the bottom of the pyramid are less efficacious but carry a lower risk of serious adverse effects.
- Drugs may be used alone or in various combinations.
- Patients with mild disease may be treated with 5-aminosalicylates (with ulcerative colitis or Crohn’s colitis), topical corticosteroids (ulcerative colitis), antibiotics (Crohn’s colitis or Crohn’s perianal disease), or budesonide (Crohn’s ileitis).
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- Patients with moderate disease or patients who fail initial therapy for mild disease may be treated with oral corticosteroids to promote disease remission; immunomodulators (azathioprine, mercaptopurine, methotrexate) to promote or maintain disease remission; or anti-TNF antibodies.

- Patients with moderate disease who fail other therapies or patients with severe disease may require intravenous corticosteroids, anti-TNF antibodies, or surgery.

- Natalizumab is reserved for patients with severe Crohn’s disease who have failed immunomodulators and TNF antagonists.

- Cyclosporine is used primarily for patients with severe ulcerative colitis who have failed a course of intravenous corticosteroids.
Natalizumab is a humanized monoclonal antibody against the