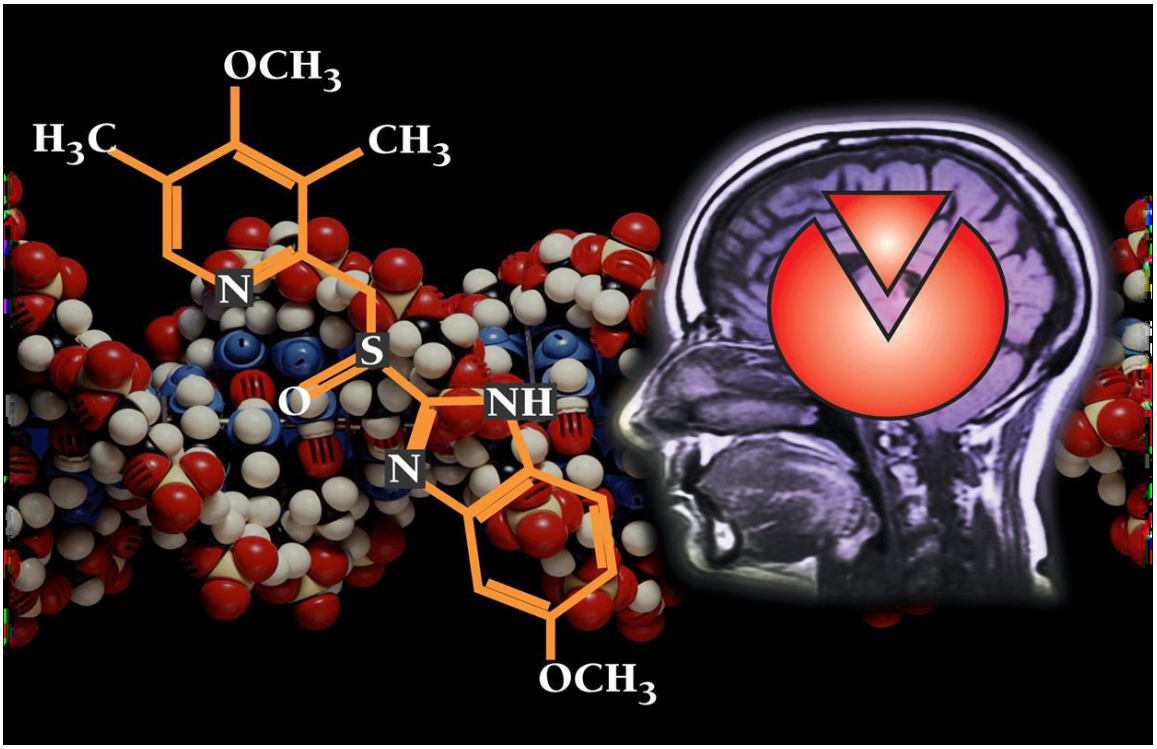
King Saud University
College Of Medicine
Pharmacology Team 430
GIT Block

Drugs Used in IBD



Note: Texts written in green are **team notes, and** textboxes in **thick green margins** are additional info.

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Chronic inflammatory bowel diseases (IBD)

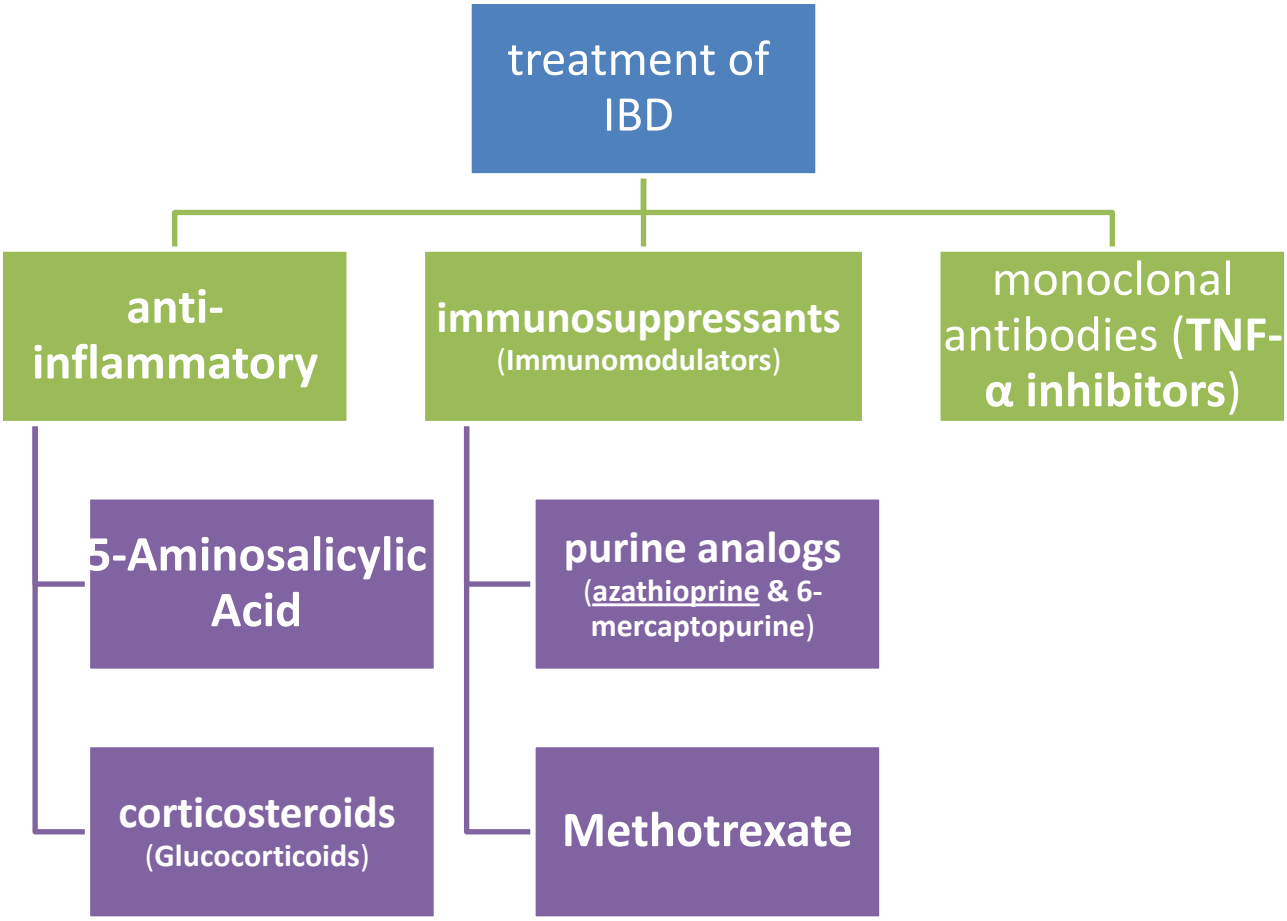
- **IBD is a group of auto-immune disorders in which the intestines become inflamed.**
- **Are chronic inflammatory bowel diseases which have relapsing and limiting course.**
- **The major types of IBD are Crohn's disease and ulcerative colitis (UC).**

	Crohn's disease	Ulcerative colitis
Location	affect any part of the GIT, from mouth to anus	Restricted to colon & rectum
Distribution	Patchy areas of inflammation *(Skip lesions)*	Continuous area of inflammation
Depth of inflammation	May be transmural, deep into tissues	Shallow, mucosal
Complications	Strictures, Obstruction Abscess, Fistula	Toxic megacolon

Differences between Crohn's disease and UC

Ulcerative colitis	Crohn's disease
Limited to colonic mucosa and may reach proximal part of the colon.Bloody diarrhea	Effect the entire thickness of the wall and involve any part of GIT. No blood

Signs and symptoms	Crohn's Disease	Ulcerative Colitis
Defecation	Often porridge-like, sometimes steatorrhea	Often mucus-like and with blood
Tenesmus	Less common	More common
Fever	Common	Indicates severe disease
Fistulae	Common	Seldom
Weight loss	Often	More seldom



Summary of drugs used in IBD

- ✓ **5-aminosalicylic acid compounds:**
- Azo compounds:
  sulfasalazine, olsalazine, balsalazide.
- Mesalamines :
  Pentasa, Asacol, Rowasa, Canasa.

- ✓ **Glucocorticoids:**
  prednisone, prednisolone, hydrocortisone, budesonide.

- ✓ **Immunomodulators:**
- Methotrexate.
- Purine analogues: Azathioprine&6mercaptopurine.

- ✓ **TNF-alpha inhibitors (monoclonal antibodies):**
  Infliximab – Adalimumab – Cetrolizumab.

Drugs Used for Rx and maintenance of I.B.D

I) Anti-inflammatory Drugs

1 5-Aminosalicylic Acid:

MOA: inhibits prostaglandin and leukotriens synthesis; decreases neutrophil chemotaxis and decreases free radicle production. scavenging free radical production.

Note: since it is an irritant to GIT, this drug should not be given orally as such.

Remember: NSAIDs makes IBD worse (not used in its treatment).

Note: 5-ASA differs from salicylic acid only by the addition of an amino group at the 5 (meta) position. Aminosalicylates are believed to work topically (not systemically) in areas of diseased gastrointestinal mucosa. Up to 80% of unformulated, aqueous 5-ASA is absorbed from the small intestine and does not reach the distal small bowel or colon in appreciable quantities. To overcome the rapid absorption of 5-ASA from the proximal small intestine, a number of formulations have been designed to deliver 5-ASA to various distal segments of the small bowel or the colon.

Formulations:

a)Sulpha containing 5-Aminosalicylic Acid

(e.g: Sulphasalazine).

Sulphasalazine is a Prodrug, given orally (enteric coated tablets) (20-30 %) absorbed by intestine, secreted in the bile and hydrolysed in ileum and colon by isoreductase into: 5-ASA (not absorbed, active moiety) and Sulphapyridine (absorbed, side effects)

Sulfapyridine + 5- ASA (Linked by Azo group) ----------> Hydrolyzed by bacteria in ileum and colon

Prodrug used in maintenance therapy, less effective in acute attack; Used for U.colitis; Crohn's colitis but not Crohn's of small intestine Why?

Because the bacteria that hydrolyses the drug are present in the distal ileum and colon, the places where the drug gives its therapeutic action.

Note: Nowadays it is seldom to be used for Crohn's disease (new 5-ASA are preferred but still use for UC).

Side Effects :

- **Muscular pain 29% caused by sulpha , N/V(nausea or vomiting), Diarrhea**
- **Crystalluria and interstitial nephritis.**
- **Hypersensitivity reactions as: skin rash, fever, aplastic anemia. caused by sulpha.**
- **Inhibit absorption of folic acid (megaloplastic anemia)**
- **Infertility in man (decrease sperm counts). However, it is save in pregnancy .**
- **Bone marrow depression**

B. **Non-sulpha containing 5-Aminosalicylic Acid**

1. Mesalamines Compounds.

- **Formulations that have been designed to deliver 5-ASA in small & large colon.**
- **e.g. pentasa (orally): time release microgranules that release 5ASA through the small intestine**
- **e.g. Asacol 5-ASA coated in pH sensitive resin that dissolved at pH 7 (controlled release).**

- e.g. Rowasa (enema) or Canasa (suppositories)
- Treat and maintain remission in mild to moderate ulcerative colitis.
- Well tolerated, less side effects (sulfa free), useful in patient sensitive to sulfa drugs.

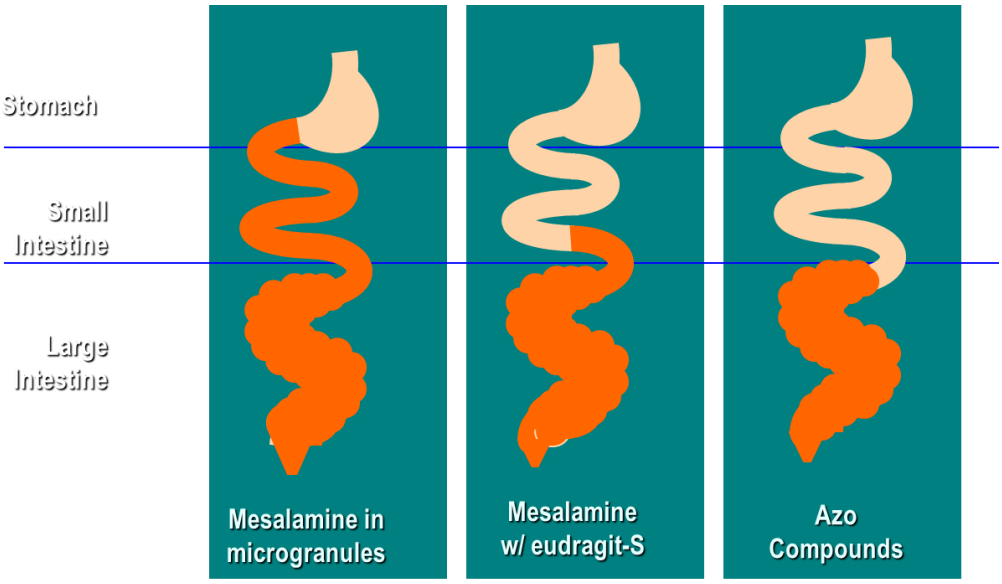
2. Azo compounds.

- Compounds contain 5-ASA and connected by azo bond tosulfapyridine moiety, another molecule of 5-ASA or to inert compound
- Azo structure (N=N)
  - ✓ reduces absorption in small intestine
  - ✓ Bacteria release azoreductase that cleave the azo dye and release 5-ASA in terminal ileum and colon

Examples:

- Olsalazine (Two molecules (dimer) of 5-ASA linked together by diazo bond which pass small intestine to ilium and colon).
- Balsalazide 5-ASA + inert carrier (Colazal).

Oral 5-ASA Release Sites



Clinical uses of 5-amino salicylic acid compounds

- Induction and maintenance of remission In mild to moderate ulcerative colitis & Crohn's disease (First line of treatment).
- Are NOT useful in actual attack or severe forms of IBD.
- Rheumatoid arthritis, psoriasis *(Sulfasalazine only)*
- Rectal formulations are used in *ulcerative* proctitis and proctosigmoiditis.

Ulcerative proctitis: Ulcerative Proctitis is the least severe form of inflammatory bowel disease. Proctitis: inflammation of the rectum and anus.

Proctosigmoiditis: inflammation of the sigmoid colon and rectum.

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2. Corticosteroid

***MOA:**

- **Inhibits phospholipase A2, inhibit gene expression of NO synthase, COX-2.**
- **Inhibit inflammatory cytokines (TNF-a).**

Prednisone, prednisolone (orally)

- **Higher rate of absorption**
- **More adverse effects compared to rectal administration**

Hydrocortisone (enema or suppository):

- **Less absorption rate than oral.**
- **Minimal side effects & Maximum tissue effects.**

Budesonide:

- **A potent synthetic prednisolone analog**
- **Given orally *(controlled release tablets)* so release drug in ileum and colon.**
- **Low oral bioavailability (10%).**
- **Is subject to *first pass metabolism***
- **Used in treatment of active mild to moderate Crohn's disease involving ileum and proximal colon.**

***Indications:**

- **Treat moderate – severe ulcerative colitis. (Prednisone P.O. 40-60 mg/day for 2 weeks).**
- **Less effective as prophylactic (maintaining remission).**
- **Budesonide as controlled release oral (9 mg/day) formulation (Entocort).**
- **Oral glucocorticoids is commonly used in active condition.**
- **Hydrocortisone enema or suppository for rectum or sigmiod colon.**
- **Used also for extracolonic manifestations such as ocular lesion, skin disease, peripheral arthritis. Asthma, immunosuppressive drug for organ transplants , and antiemetics during cancer chemotherapy**

II) Immunosuppressive Agents (Immunomodulators):

Are used to induce remission in IBD in active or severe conditions or steroid dependent or steroid resistant patients.

Immunomodulators include:

- **Purine analogs: (azathioprine & 6-mercaptopurine).**
- **Methotrexate**

The bioavailability of azathioprine (80%) is superior to 6-MP (50%). After absorption azathioprine is rapidly converted by a non-enzymatic process to 6-MP.

1)Azathioprine:

Is pro-drug of 6-mercaptopurine that Inhibit purine synthesis (purines ,along with pyrimidines, make up the nitrogenous bases in our DNA and RNA. Inhibiting purine synthesis will inhibit cells proliferation, especially leukocytes, therefore these agents are used as immunosuppressants.)

M.O.A: Suppress the body's immune system.

*** Clinical indications: for Rx and maintenance of remission of severe conditions and steroids dependent or resistant (ulcerative and Crohn's disease).**

*** Side Effects:**

- **nausea and vomiting.**
- **bone marrow depression (leading to leukopenia, macrocytosis, anemia, or thrombocytopenia).**
- **LFT changes (it can cause hepatic toxicity).**

Routine laboratory monitoring with complete blood count and liver function tests is required in all patients. Leukopenia or elevations in liver chemistries usually respond to medication dose reduction. Severe leukopenia may predispose to opportunistic infections; leukopenia may respond to therapy with granulocyte stimulating factor.

- **Hypersensitivity reactions Why? (in 5% of patients. usually include fever, rash, pancreatitis, diarrhea, and hepatitis.)**

Azathioprine is composed of a nitroimidazole attached to 6-mercaptopurine. It is proposed that the imidazole component causes hypersensitivity, while the 6-mercaptopurine may cause haematological side effects. However, there are conflicting reports about the component of the drug to which the hypersensitivity reaction can be attributed.

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2. Methotrexate:

*** MOA: (folic acid antagonist) dihydrofolate reductase inhibitor (an enzyme important in the production of thymidine and purines), Works as antimetabolite. (plus other MOAs mentioned in the box coming after the one below).**

Antimetabolite: A drug that is similar enough to a natural chemical to participate in a normal biochemical reaction in cells but different enough to interfere with the normal division and functions of cells. So named because the drug inhibits a normal metabolic process. Examples of antimetabolites include 6-mercaptopurine (6MP), methotrexate, and hydroxyurea.

*** Clinical indications: Cronn's disease (to induce and maintain remission); Rheumatoid Arthritis and cancer.**

At the high doses used for chemotherapy, methotrexate inhibits cellular proliferation. However, at the low doses used in the treatment of inflammatory bowel disease (12–25 mg/wk), the anti-proliferative effects may not be evident. Methotrexate may interfere with the inflammatory actions of interleukin-1. It may also stimulate increased release of adenosine, an endogenous anti-inflammatory autacoid. Methotrexate may also stimulate apoptosis and death of activated T lymphocytes.

***Side effects: Bone marrow suppression and megaloblastic anemia**

At higher dosage, methotrexate may cause bone marrow depression, megaloblastic anemia, alopecia, and mucositis. At the doses used in the treatment of inflammatory bowel disease, these events are uncommon but warrant dose reduction if they do occur. Folate supplementation reduces the risk of these events without impairing the anti-inflammatory action.

III) Monoclonal antibodies used in IBD, (TNF-α inhibitors).

- **Infliximab (source: chimeric: human/mice) 75% human**
- **Adalimumab (source: purely human) 100% human**
- **Certolizumab (source: humanized from mice) 95% human**

Actions of TNF: Binding of TNF to TNF receptor initially activates components including NF-(kappa)B that stimulate transcription, growth, and expansion. Biologic actions ascribed to TNF receptor activation include release of pro-inflammatory cytokines from macrophages, T-cell activation and proliferation, fibroblast collagen production, up-regulation of endothelial adhesion molecules responsible for leukocyte migration, and stimulation of hepatic acute phase reactants. Activation of TNFR may later lead to apoptosis of activated cells.

Infliximab

- **Is a monoclonal IgG antibodies.**
- **%25murine – 75% human.**
- **Anti-TNF-α: Inhibits soluble or membrane –bound TNF-α located on activated T lymphocytes.**
- **Given as infusion (5-10 mg/kg).**
- **has long half-life (8-10 days).**
- **2 weeks to give clinical response.**

*Uses

- **In moderate to severe active crohn's disease and ulcerative colitis.**
- **Patients not responding to Immunomodulators or glucocorticoids.**
- **Treatment of rheumatoid arthritis.**
- **Psoriasis.**

*Side effects

- **Acute or early adverse infusion reactions (Allergic reactions or anaphylaxis in 10% of patients), this reaction can be reduced by pretreatment with diphenhydramine, acetaminophen, corticosteroids.**
- **Delayed infusion reaction (serum sickness-like reaction, in 5% of patients). (It consists of myalgia, arthralgia, jaw tightness, fever, rash, urticaria, and edema and usually requires discontinuation of that agent).**
- **Infection complication *(Latent tuberculosis, sepsis, hepatitis B).* (due to suppression of the TH1 inflammatory response)**
- **Loss of response to infliximab over time *due to the development of antibodies to infliximab.* (Anti-body development is most commonly seen in infliximab because it is the least humanized among the three.)**
- **Severe hepatic failure.**
- **Rare risk of lymphoma.**

Lymphoma appears to be increased in patients with untreated inflammatory bowel disease. Anti-TNF agents may further increase the risk of lymphoma in this population, although the relative risk is uncertain. An increased number of cases of hepatosplenic T-cell lymphoma, a rare but usually fatal disease, have been noted in children and young adults, virtually all of whom have been on combined therapy with immunomodulators, anti-TNF agents, or corticosteroids.

Adalimumab (Humira)

- Fully humanized IgG antibody to TNF-α.
- Adalimumab is TNFα inhibitor.
- It binds to TNFα, preventing it from activating TNF receptors.
- Has an advantage that it is given by subcutaneous injection.
- It is approved for treatment of, moderate to severe Crohn's disease, rheumatoid arthritis, psoriasis.

Certolizumab pegol (Cimzia)

- Fab fragment of a humanized antibody directed against TNF-α .
- Certolizumab is attached to polyethylene glycol to increase its half-life in circulation.
- Given subcutaneously for the treatment of Crohn's disease & rheumatoid arthritis.

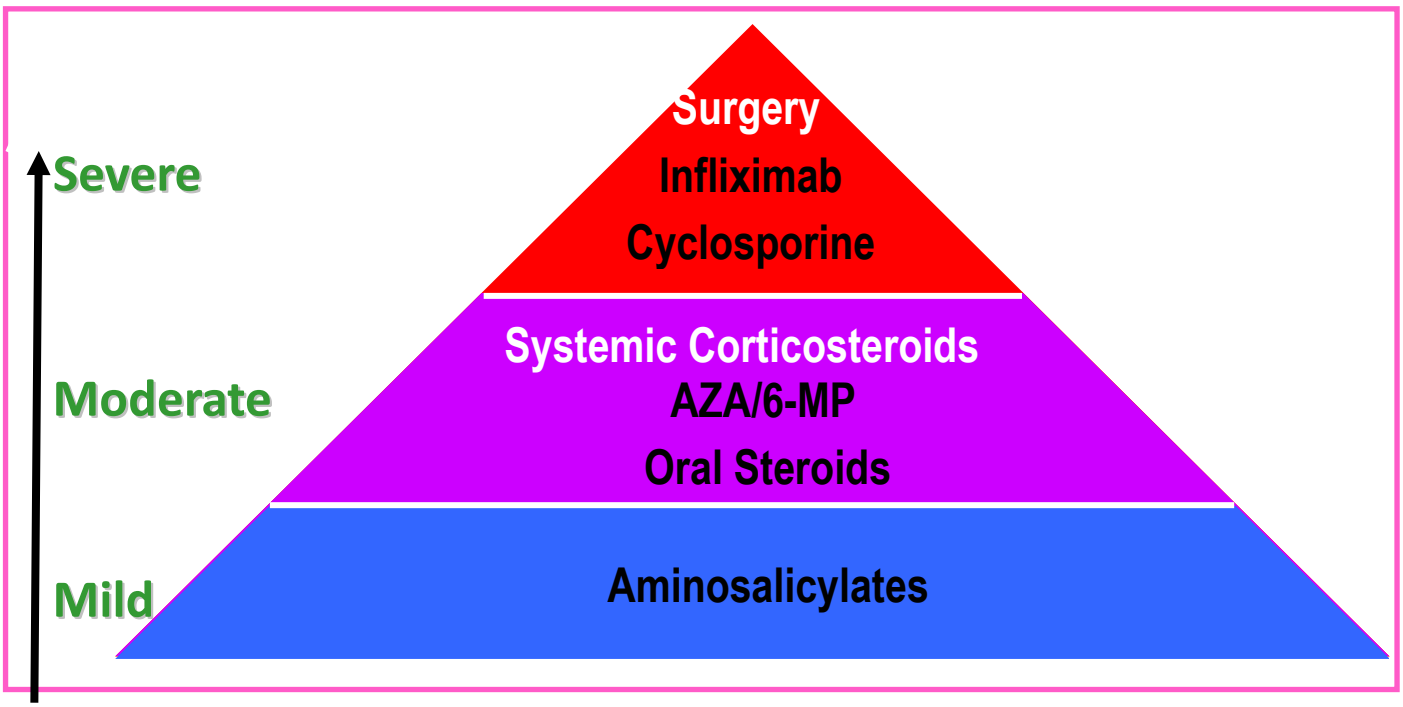
Inductive Therapies

For ulcerative colitis: (ASA/corticosteroids/cyclosporine)

For Crohn's disease: (ASA/corticosteroids/antibiotics/infliximab)

Maintenance Therapies

Immunosuppressors/ASA/infliximab but NO corticosteroids



Summary:

- **IBD is a group of auto-immune disorders in which the intestines become inflamed. (chronic/relapsing).**
- **The major types of IBD are Crohn's disease and ulcerative colitis (UC).**
- **Treatment includes using 5-ASA, corticosteroids, purine analogs, methotrexate, and monoclonal antibodies.**
- **Sulphasalazine (5-ASA) is a Prodrug (20-30 %) absorbed by intestine, secreted in the bile and hydrolysed in ileum and colon by isoreductase .**
- **Sulphasalazine is used in maintenance therapy, less effective in acute attack; Used for U.colitis; Crohn's colitis but not Crohn's of small intestine.**
- **S/E include muscular pain and hypersensitivity reaction because of the sulpha group. Safe in pregnancy.**
- **pentasa (Mesalamine) (oral) it releases microgranules that release 5ASA through the small intestine.**
- **Mesalamines treat and maintain remission in mild to moderate ulcerative colitis.Well tolerated, less side effects (sulfa free).**
- **5-ASA generally are NOT useful in actual attack or severe forms of IBD.**
- **Corticosteroids can treat moderate – severe ulcerative colitis.(prednisone). Less effective as prophylactic (maintaining remission).**
- **Immunomodulators (purine analogs and methotrexate) are used to induce remission in IBD in active or severe conditions or steroid dependent or steroid resistant patients.**
- **Bone marrow depression is one of the most common S/E in immunomodulators.**
- **Monoclonal antibodies (TNF-α inhibitors) include Certolizumab,Adalimumab (100% human), and Infliximab.**
- **Anti-TNF-α Inhibits soluble or membrane –bound TNF-α located on activated T lymphocytes.**
- **Uses include: severe Crohn's disease, patients not responding to Immunomodulators or glucocorticoids.**
- **S/E include: early adverse infusion reactions, serum sickness-like reaction, Infection complication, loss of response to infliximab over time, Severe hepatic failure, rare risk of lymphoma.**
- **Certolizumab is attached to PEG to increase its half-life.**
- **No corticosteroids used in maintenance therapy.**