The GI System

Pharmacology

☑ Sheet ☐ Slide ☐ Handout

Number: 6

Subject: Treatment of IBD

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Treatment of IBD (Inflammatory Bowel Disease)

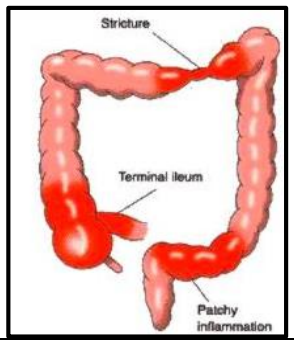
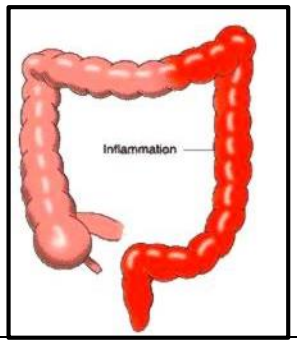
❖ Introduction

- **IBDs** are inflammatory conditions that affect the small and large bowel mainly. *(keep in mind that different types of IBDs differ in the site involved in inflammation).*

- **Major types of IBDs:**
  - Crohn's disease (CD) and Ulcerative Colitis (UC).
  - IBDs are a spectrum of diseases. We have Crohn's disease at one end, and ulcerative colitis at the other end, but in between, there is what we call intermediate colitis. (certain criteria are assigned for Crohn's, and certain criteria are assigned for UC, but in many situatons, we can't decide if the patient has Crohn's or UC).

- They are autoimmune disorders.
- They are inflammatory: characterized by inflammation in the small intestine or the colon.

- The table in the next page contains the major differences between Crohn's disease and ulcerative colitis.

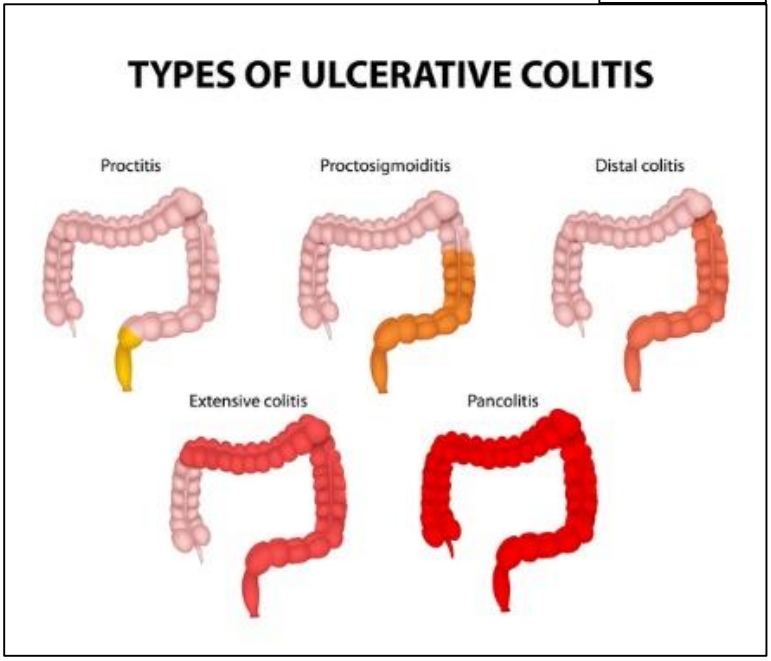
	Crohn's Disease	Ulcerative Colitis
Affected site	Any site in the GI tube that starts from the mouth and ends at the anus.	The inflammation starts from the rectum and moves in an ascending pattern, the maximum point it can reach is the cecum. *Usually, it does not involve the small intestine, stomach, or esophagus.*
Most common site	Terminal ilium	Rectosigmoid
Type of lesion	Patchy (skip lesions) For example, a lesion could be found in the ascending colon and other lesions in the descending colon with normal regions between them.	Continuous lesion
Figure		
Depth of inflammation	Transmural (Deep) ulcerations.	Mucosal (Superficial) ulcerations.
Complications	Strictures (see the figure above), and Fistulas.	Megacolon Rectal bleeding
Presentation (the patient comes with…)	Abdominal pain, weight loss, anemia, symptoms of intestinal obstructions. **Sometimes**, bloody diarrhea	Bloody diarrhea.

- **Figure (1):** types of ulcerative colitis,

  Pancolitis: starts from the rectosigmoid and ascends to involve the entire colon.

  Notice the types; proctosigmoditis and proctitis as they will be mentioned later in the lecture.

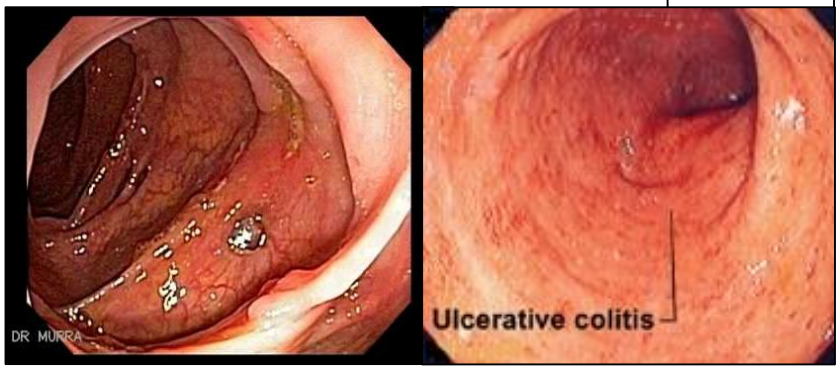
Figure (1)



- **Note:** usually, the last part that ulcerative colitis can affect is the cecum, but in rare cases, UC can involve the terminal ilium when we have **pancolitis** and something called **"Backwash ileitis"**. In this case, inflammation involves the entire colon and extends to a small part of the terminal ilium.
  However, in general, ulcerative colitis does not involve the terminal ilium.

- **Figure (2):** colonoscopy
  - Ulcerative colitis to the right – superficial ulcers
  - Crohn's disease to the left – deep ulcers (and remember, we find normal areas next to abnormal ones).

Figure (2)



- **The cause of IBD:**
  The exact cause is still not fully understood, but usually, two main components contribute to the disease:
  Impaired immunity & Genetic predisposition (familial predisposition).

- **Complications:**
  They were mentioned in the table in page 2, but it is important to mention that colon cancer is one of the complications that might occur in IBD patients, particularly, those with UC.
  - After 8-10 years, patients with ulcerative colitis should have yearly colonoscopy examination to take multiple biopsies to know if colon cancer has developed or not.

❖ Treatment of IBD

- In IBD, the disease is characterized by relapsing and remitting course, meaning that a relapse occurs and then diminishes, another relapse later forms and so on.

- In treatment of IBD, we focus on two main points:
  1. **Induction of remission** (the absence of symptoms) – to remove the relapse.
  2. **Maintain remission** (prevention of flare-ups).

- In all the drugs we will talk about in this lecture, we have to focus on:
  - Whether the drug is used for induction of remission, maintenance, or both.
  - Whether the drug is used to traet UC or Crohn's disease.

- Ways of treatment of IBD:

  A) medications (the topic of this lecture)

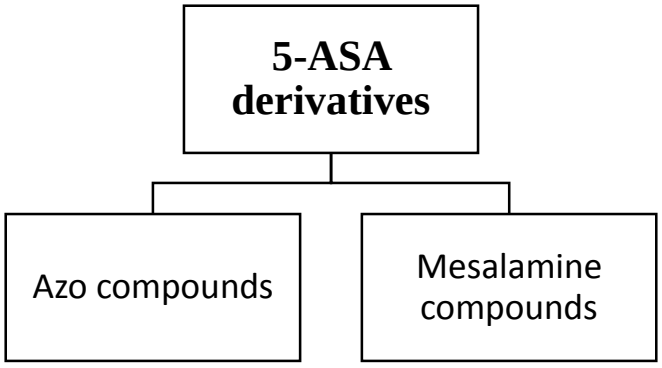
  1. **5- AminoSalicylic Acid compounds (5-ASA compounds)**
  2. **Steroids**
  3. **Immunomodulators**
  4. **Biological therapy (anti- TNF therapy)**

  B) Surgery –if needed (our last resort).

Group 1: 5- Aminosalicylic Acid compounds (5-ASA compounds)

- Topical
  These drugs are given orally but they act topically, meaning that they only act on the colon and their systemic absorption is minimal.

- If 5-ASA compounds are given orally in their original structure –without certain modification- they will be absorbed in the small bowel then go to the systemic circulation without reaching the colon.
  →There are certain methods used during the synthesis of these medications to minimize absorption, enabling the drug to act on the colon without being absorbed into the systemic circulation, where there's no need for it.
- There are two main groups that fall under the title of 5-ASA compounds:

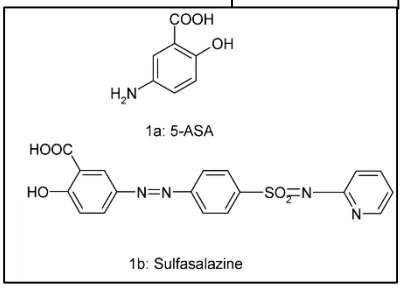


A) Azo compounds

- Their old prototype was sulfasalazine.
  Sulfasalazine was used in the old days but it is not that much used currently.

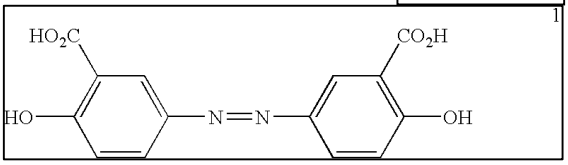
- The structure of sulfasalazine (figure (3))
  It's composed of 5-ASA attached to sulfapyridine moiety through a bond called Azo bond (the reason behind the name "azo compounds" is the azo bond).

Figure (3)



- Azo compounds: 5-ASA molecule connected to "something" via an azo bond.
- Azo compounds include:
  1. Sulfasalazine
  2. Olsalazine: 5-ASA molecule connected to another 5-ASA molecule via an Azo bond. (figure (4)).

Figure (4)



3. Balsalazide: 5-ASA molecule connected to an inert carrier (that does not get absorbed).

- They have low systemic absorption (we want the drug to act locally on the colon as an anti-inflammatory drug).

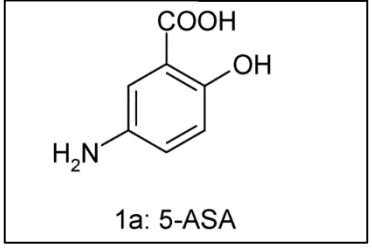
- The role of the azo bond in these compounds:
  - The bacteria found in the colon has an enzyme called Azo reductase.
  - When the Azo compound reaches the colon, the Azo reductase produced by colonic flora will destroy the azo bond, thus, releasing the 5-ASA moiety and the other part.
    → In the case of the balsalazide, the other part is the inert carrier, and when released, it will not be absorbed.
    →In the case of sulfasalazine, the other part is the sulfapyridine that will be absorbed and it has systemic effects.

- Note 1: Sulfapyridine is responsible for most of the side effects associated with sulfasalazine. (the side effects will be discussed later).
  →10-20% of patients who start taking sulfasalazine stop the medication due to its side effects that are *mostly* related to the sulfapyridine.

B) Mesalamine compounds

- Mesalamine structure (figure (5)):
  It is composed of 5-ASA alone.
  There are certain ways in coating it so that it will be absorbed only in the colon.

Figure (5)



1a: 5-ASA

- Types of mesalamine compounds: *(both are delayed-release tablets)*

1. **Asacol →** <u>pH dependent</u>
   The 5-ASA compound is coated with a pH sensitive coating (acrylic based resin) that dissolves in pH that is equal to or higher than 7.
   →The drug reaches the colon without being absorbed in proximal areas.

2. **Pentasa**
   <u>Time- dependent</u> (delayed release in the colon).

   The coating: ethyl cellulose coating.

Mechanism of action of 5-ASA derivatives

- They affect arachidonic acid metabolism.
  They are COX-2 inhibitors and lipoxygenase inhibitors.
- They inhibit cytokines, most importantly, TNF, IL-1, and NF-kB.
- They inhibit leukocytes chemotaxis.
- 5-ASA derivatives work as antioxidants (free radicals scavengers).
- They induce apoptosis.

Free radicals have toxic effects on the colonic mucosa and cause its injury

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Adverse effects

- In general, adverse effects are of two types:

  1. **Dose dependent**
     The higher the dose, the higher the likelihood of developing the side effect.

     Examples: GI upset, some mild hematologic disorders like folic acid deficiency.

  2. **Idiosyncratic adverse effects**
     Not related to the dose and might develop even from the first dose.
     Usually, idiosyncratic side effects are blood disorders and skin rash.

- Generally, aminosalicylate **(mesalamine)** compounds are well tolerated, not related to a high degree of GI upset, and rarely associated with interstitial nephritis. Watery diarrhea can occur in some patients.

- On the other hand, **sulfasalazine *has several side effects:***
  - Idiosyncratic side effects include:
    1. ***Agranulocytosis***
       (These patients may develop severe bone marrow suppression → Leukopenia, thrombocytopenia, aplastic anemia)

    2. ***Stevens- Johnson syndrome***
       An idiosyncratic reaction, characterized by erythematous skin rash with target appearance affecting a high percentage of the body. It can be fatal.

If a patient develops Stevens-Johnsons syndrome as a side effect to certain medication – including sulfasalazine-, he must stop that medication immediately, and never take it again.

If a patient starts treatment with sulfasalazine, he must be told to inform his doctor in case he developed fever, petechial skin rash, thrombocytopenia, symptoms of anemia ,… (side effects)

- Other side effects of sulfasalazine:
  1. ***Folic acid deficiency***
     That's why patients who start taking sulfasalazine must be given folic acid supplements along with the drug.
  2. ***Oligospermia***
     This side effect is reversible. It diminishes once the medication is stopped.
  3. ***Interstitial nephritis***
     Related to the 5-ASA moiety, not the sulfa moiety.

Contraindications

- Hypersensitivity
- G6PD (glucose -6-phosphate dehydrogenase) deficiency is a contraindication when it comes to the use of sulfapyridine-sulfasalazine.

Rectal 5-ASA compounds

All the previous was about oral 5-ASA derivatives, but these compounds can be given rectally as:

- Suppositories → cover 5-8 cm proximal to the anus.
  Or
- Enema → can reach up to the splenic flexure.

5-ASA derivatives are given rectally in the cases of proctosigmoditis in which the inflammation is distal or proctitis. (figure (2)).

<u>The use of 5-ASA derivatives when it comes to IBD:</u>

- 5-ASA derivatives are usually NOT used to treat patients with Crohn's disease.
  (In the old days, they were used to treat Crohn's, but the new guidelines nowadays have restricted the use of 5-ASA derivatives to include only **<u>mild</u>** cases of **<u>colonic</u>** Crohn's disease. Moreover, they are NOT used for induction of remission in Crohn's disease).

- In general, when we talk about 5-ASA derivatives, do not think of Crohn's, instead, think of ulcerative colitis.

Remember: Crohn's disease can affect the terminal ilium, colon, small bowel….

Only in colonic Crohn's, we can use 5-ASA derivatives.

- In UC, 5-ASA derivatives are used for **both**; <u>induction of remission and maintenance of remission</u>.
  They are the first line treatment in mild to moderate cases, but if the patient came with severe UC, we can't use 5-ASA derivatives as the first line therapy.

Note: there are other uses for 5-ASA derivatives. For example, sulfasalazine can be used in treatment of rheumatoid arthritis.

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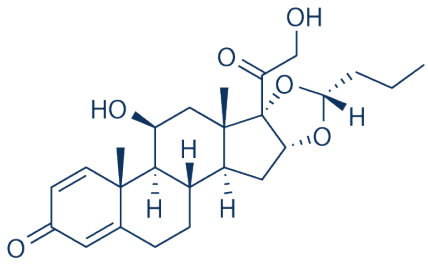
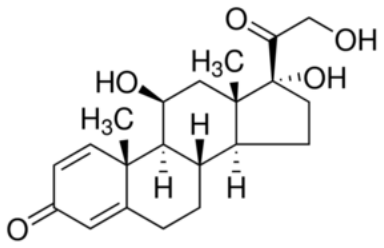
Group 2: Steroids



Budesonide



Prednisolone

- Steroids are known for being used as anti-inflammatory drugs, by inhibiting pospholipase A_2, the enzyme responsible for the ultimate foramtion of prostaglandins, lipoxins, and thromboxanes. So, it's expected that steroids may be used for treatment of IBD.

- These chemical structures are just to show you that the two drugs are steroids.

- In this discussion, we will talk about two major steroids used in the treatment of IBD.
1- **Prednisolone, prednisone.**
2- **Budesonide**

- **Prednisolone** has a high rate of absorption, so it shows a lot of **side effects**.
- **Budesonide** has low bioavailability, as a result of **extensive first-pass effect**. Hence, it's less associated with side effects.

- **Mechanism of Action:**
Generally, these drugs have anti-inflammatory effect, through the following mechanisms:
1- inhibition of phospholipase A_2.
2- reducing the production of cytokines.
3- Drecreasing antigen-antibody reaction.

- Very important note:
Steroids are used for induction of remission, rather than maintenance.

- It's inappropriate to give your patient steroids for a long time, that's why they are only used for induction of remission but not for maintenance.

- Steroids are inappropriate for long-term therapy because of their side-effects.

- 5-ASA derivatives are used for induction and maintenacne of remission in patients with ulcerative colitis.

- In crohn's disease patients, we use steroids or biological agents for induction of remission and then other drugs may be used for maintenance.

Group 3: Immunomodulators.

1- Methotrexate

2- Purine analogs:
Azathioprine (AZA) & 6-mercaptopurine (6-MP).

- We use purine analogs more than methotrexate, but methotrexate may be used when the side-effects of purine analogs cannot be tolerated. Therefore, we will focus now on purine analogs.

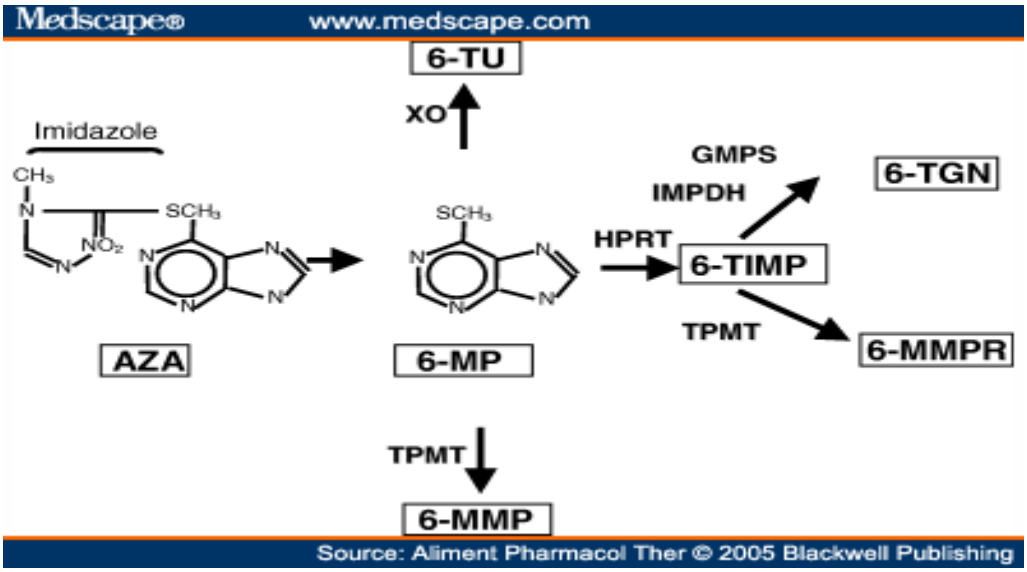
- Azathioprine and 6-mercaptopurine are very similar to each other, in the mechanism of action, side effects, and uses.
- They are different in the following aspects:
1- Azathioprine is a prodrug that's converted by a non-enzymatic reaction to 6-mercaptopurine.
2- 6-mercaptopurine dose = half the dose of azathiprine.

- **Mechanism of action:**
inhibition of purine synthesis.

- They are used for maintenance of remission. They can't be used for induction of remission because they need 6 weeks to start acting, and it's inappropriate to leave the patient without treatment for 6 weeks. Hence, steroids are better used for induction of remission and then we should stop steroids and use purine analogs for maintenacne of remission.

- Rhematoid arthritis and IBD are characterized by inflammation driven by white blood cells, that's why treatment should inhibit proliferation of these cells.

The effect of metabolizing enzymes and their levels on dosing and using purine analogs: (This is very important, clinically and for the purpose of the exam as well)



If you want to understand the whole story, see this
http://www.medscape.com/viewarticle/499922_3

- **AZA is non-enzymatically converted to 6-MP.**

  - Then, 6-MP can be acted on by three different enzymes. The one we want to focus on here is TPMT (Thiopurine methyltransferase). This enzyme converts 6-MP to the active form 6-MMP (6-methylmercaptopurine).
  - In 11% of individuals, there's a partial deficiency in TPMT. So, 6-TGN will be produced more than the normal level. 6-TGN causes bone marrow suppression. In this case, we give the patient a lower dose.
  - In 1% of individuals, there's complete deficiency in TPMT , resulting in higher level of 6-TGN and thus more likelihood of side effects. In this case, we don't use purine analogs at all.

  - Since bone marrow suppression is a dangerous, we screen for TPMT mutations before starting treatment with purine analogs.

- 6-TGN (6-thioguanine) is the active metabolite. Normally, when TPMT is active, it doesn't go up, but when TPMT is deficient, we will get higher levels of 6-TGN and this is associated with bone marrow toxicity.

- Shortly, TPMT deficient patient show a higher risk of developing bone marrow suppression if treated with purine analogs (AZA and 6-MP).

Don't be confused with the names of metabolites. Just understand the concept.

Adverse effects:
1- Bone marrow supression
That's why CBC (complete blood count) is needed after using the drug.
2- Hepatitis
3- Elevation of liver enzymes
4- Pancreatitis

Methotrexate
- DHFR inhibitor
- Has a lot of side effects
- Uses: RA, IBD, cancer
- It inhibits T and B-cell proliferation

Side effects:
1- Bone marrow suppression.
2- Megaloblastic anemia, resulting from folic acid deficiency

Group 4: Biological agents (Anti-TNF therapy).

Monoclonal antibodies directed against TNF-alpha can be used in the treatment of IBD:
We'll talk about three drugs:

TNF-alpha Antagonists:
Infliximab – a murine chimeric monoclonal antibody directed against TNF-alpha
Adalimumab – a fully human IgG1 anti-TNF-alpha monoclonal antibody
Certolizumab pegol – a humanized anti-TNF Fab' monoclonal antibody fragment linked to polyethylene glycol

- Infliximab and adalimumab are complete antibodies directing against TNF-alpha (i.e. they contain F_{ab} and F_c).

- Certolizumab is not a complete antibody. It just consists of the antigen binding fragment (F_{ab}) linked to polyethylene glycol.

- Infliximab is chimeric (part of it is humanized and the other is from a mouse).

- Adalimumab is fully humanized.

- Infliximab is given as IV infusion, necessitating hospitalization.

- Infliximab is used for severe cases of CD and UC for induction and maintenance of remission.

- **Side effect**s:

1- Anaphylaxis

This drug is given as IV infusion, and the patient needs to be prepared for this drug to avoid anaphylaxis. This preparation involves giving Chlorpheniramine maleate (Alerfin) and steroids before taking Infliximab, that's why this drug requires hospitalization.

2- Reactivation of tuberculosis, and hepatitis. Hence, TB and hepatitis screening is required before starting treatment with these biological agents.

- **Adalimumab:**
- Fully humanized
- Given subcutaneously (Remember: Infliximab is given as IV infusion). Being given subcutaneously makes its use easier than infliximab.
- Given for induction and remission for patients with UC and CD.

- **Certolizumab**:
- It's not a complete antibody. It's just an F_{ab}.