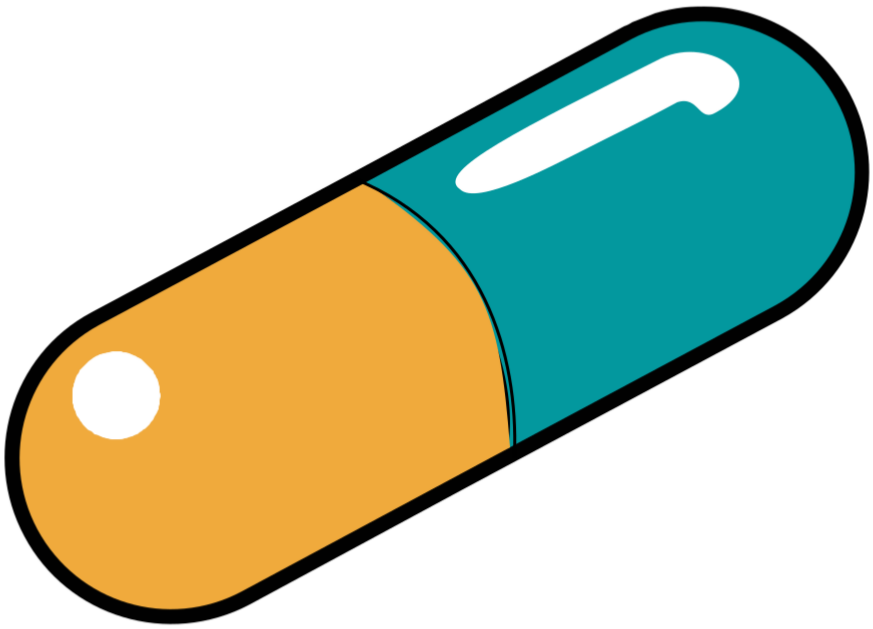
GIS

Sheet no.5

Pharmacology



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Before we start here are some notes regarding this sheet:

- The black colour for what was wrote in the slides.
- The blue colour for what the doctor said.
- The purple colour for things we add to extra illustration.

Emetic Agents

- Purpose:
  - People would, sometimes, accidently, swallow toxic substances, years ago, inducing vomiting was the only viable solution. **Nowadays**, it's no longer recommended.
- Many drugs
  - Hypertonic saline
  - Apomorphine
    - Derivative of morphine, as to lower the possibility of addiction.
    - It works by directly acting on the chemoreceptor trigger area in the medulla, rapidly inducing emesis.
  - Ipecac syrup
    - Action:
      - Emetic agent
      - Expectorant agent (مضاد للبلغم)
    - It's no longer used, indicated or even approved => At higher doses, it causes **cardiovascular toxicity.**

Drugs used in **Irritable** Bowel Syndrome (IBS)

IBS is an **idiopathic**, **non-inflammatory,** chronic relapsing disorder, **characterized** by:

- Abdominal discomfort **(Cramps, bloating, distention** and the pain associated with them.)
- Associated with alterations in bowel habits (Diarrhea, constipation or **both**)

- It's so common in our region, that, sometimes, it's called "Mediterranean bowl syndrome"
- Antispasmodic or anticholinergic agents:

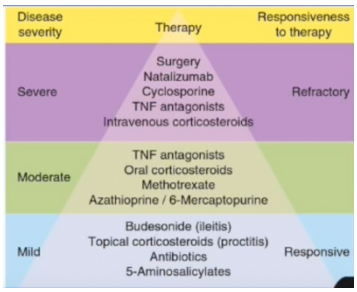
- **Dicyclomine**
- **Hyoscyamine**
  - Purpose:
    - Relaxing the abdominal muscles ➔ ↓ spasms and distention ➔ ↓ Pain
  - Mechanism of action:
    - They are atropine-like drugs, muscarinic blockers ➔ They inhibit muscarinic cholinergic receptors in the enteric plexus and on smooth muscles ➔ Ach secretion ↓ ➔ GI motility ↓ ➔ Cramping ↓ and to lesser extent (Diarrhea ↓)
  - Given at usual **low** doses, have minimal side effects.
  - Spasm is not an important symptom in IBS. (I think, IT'S **pain**.)
- Serotonin 5-HT 4- Receptor agonists:
  - **Tagaserod**
    - Purpose:
      - Approved for **short treatment** of women with IBS who ((predominantly have constipation)) ➔ **Inducing diarrhea**.
      - Reducing pain, bloating and hardness of stool
      - ➔ GI motility & Colonic secretions ↑
  - Mechanism of action:
    - By agonizing 5-HT4 ➔ ↑ Ach release ➔
      - Gastric emptying ↑, Colonic and Small bowel's secretion ↑, GI motility ↑➔ Stool's liquidity ↑ ➔ Diarrhea ↑
  - Problems:
    - Can only be used for **short term** and only **women** could use it.
    - There had been reports of cardiovascular side-effects exclusive to men users.
    - Expensive
  - Conclusion of Problems:
    - Antispasmodic drugs seem to be the better choice.
- The "Irritable" bit of "IBS" indicates psychology taking part.
  - It was shown that **anxiety** can worsen IBS's symptoms.

        - Tx: Either by,
            - Talk therapy (Ex: Reassurance)
            - Anti-anxiety drugs
                - **Benzodiazepines**
                    - **Lorazepam**
                    - **Diazepam**
                    - **Chlordiazepoxide**
- **Conclusion of IBS**
    - **Tx: A combination of anti-cholinergic drugs and anti-anxiety drugs is preferred.**

Drugs used in Inflammatory Bowel disease (IBD)

- **IBD** is a chronic, relapsing **inflammation** of bowel.
    - It's exact etiology is unknown.
    - Subclassified into 2 pathologies:
        - Ul**cer**ative colitis
            - It begins in **rec**tum and can extend, continuously to cecum.
        - Crohn's disease
            - Can begin anywhere from mouth to anus. **Terminal ileum** being the most common site for lesions, rectum is spared here.
        - Pathologically, they are different. Pharmacologically, they are (nearly)the same.
    - Drugs have different nonspecific anti-inflammatory actions. Because, we don't know the causative agent, we don't know when and where would the remission state end or simply **because of its unpredictable chronicity**. Therefore, every drug in the following pages is temporary management, according to IBD's severity, different types would be given, accordingly.
    - On severe cases, surgical intervention may be crucial ➔ colectomy.

Pyramid of treatment, Mild ➔ Severe



- Purpose of Drugs' treatment:
    - Either to, act as an **anti-inflammatory agent** or to directly **suppress immunity**

- Aminosalicylates (**Anti-inflammatory**)
  - Used for decades.
  - All contain 5-Aminosalicylic acid(5-ASA) -Which is, the actual anti-inflammatory agent-
  - Believed to work topically.
    - Meaning, only when the active agent reaches the surface of the damaged mucosa, it works.
  - But 80% of 5-ASA is absorbed from the small intestine and ONLY 20% does reach the lesions in Colon.
    - This is the problem with using oral tablets, much of it would get absorbed before reaching the central cite of inflammation, the Colon.
  - Mission: Preservation of tablets till reaching "certain" locations in Colon. It's done by **2 methods:**
    - Azo compounds
      - **Sulfasalazine**
        - **Sulphapyridine+5-ASA**
      - Balsazide
      - Olsalazine
      - "Azo" indicating the Azo bond (N=N) connecting two compounds. One of them is 5-ASA.
        - It's important because its cleavage only happens in the intestine (Proximal colon) by colonic bacteria, releasing the active 5-ASA.
    - Mesalamine Compounds
      - Active substance (5-ASA), only to be of different formulations.
        - **Pentasa**: Time release 5-ASA formulation.
        - **Asacol**: Enteric coated in pH sensitive resin.

        - "Enteric", as to dissolve only in the intestines, specifically the Colon (Proximal Colon ➔ Distal ileum)
    - **Rowasa**: Enema.
        - For cases of lesions being in a specific location, like being at the distal/descending colon.
    - **Canasa**: Suppository.
- **Pharmacodynamics**:
    - COX synthesis ↓ Modulate inflammatory mediators derived from both COX and lipoxygenase pathways.
    - Cytokine synthesis ↓ Interfere with the production of inflammatory cytokines.
        - **Inhibit nuclear factor κB (NF-κB)**
        - Therefore, can inhibit cellular functions of natural killer cells, mucosal lymphocytes and macrophages.
            - It does, therefore, have immunosuppression effects.
    - Antioxidant effects. May scavenge reactive oxygen metabolites.
- **Clinical uses**:
    - **First line** drugs for the treatment of **mild to moderate** active **ulcerative colitis. (Unproven efficacy for treating Crohn's disease)**
    - Can **induce** and maintain remission in ulcerative colitis.
- **Adverse effects:**
    - Attributable to systemic absorption: Especially in slow acetylators. (Pharmacogenetic differences are playing here, in **fast acetylators** (Ex: Jordan and USA, due to their diverse backgrounds), only Liver, the main site for metabolism would be affected. Whereas in **Slow acetylators** (Ex: Japan), OF COURSE would

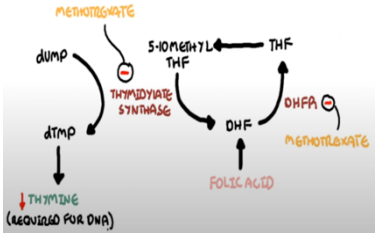
make the drug accumulates in the systemic circulation ➔ Possibly, even reaching toxicity.)
    - **Folate deficiency**
        - **Mainly due to sulphapyridine in sulfasalazine.**
        - **They, therefore, CAN lower the white blood cells count and do have the potential to be immunosuppressants**
    - **Bone marrow suppression**
    - **Oligospermia**
    - **Allergic reactions**
    - Arthralgia, myalgia, malaise, headache and Nausea.
- **Moderate ➔ Severe** active IBD
    - Glucocorticoids (**Anti-inflammatory + Immunosuppressant)**
        - Hormones, that, mimic the structure of cortisone and stimulate gluconeogenesis. (More in Endocrine module)
        - Prednisolone and Prednisone
            - Oral (Seems silly a bit, I think of "pre" as beginning of GIT➔Mouth~Oral)
        - Hydrocortisone
            - Enema, foam and suppositories. (Hydro➔IDK but I think of hydrogen which is gas? ➔Foam)
                - In another words, it's close to Rectum.
                - It's used in severe cases of rectal inflammation where the patient can't withstand enema or suppository.
        - Budesonide
            - **Controlled release** oral formulations.
                - "Controlled release" **doesn't indicate** that nothing is absorbed, in the contrary, most of the drug is absorbed in the Stomach or Small intestine, BUT, through certain mechanism, enough gets released in the colon. (Specifically, the distal ileum and proximal colon.)
        - We need something to act locally, rather than depending on Systemic release drugs ➔**Hydrocortisone** is better.

- **Pharmacodynamics**
  - **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.
- Clinical uses
  - **Moderate ➔ Severe active IBD**
  - Prednisolone orally or **IV (Pre➔I think of it as, to be as early as possible.)**
  - Hydrocortisone, rectally, preferred for **rectal** and **sigmoid** involvement. (Suitable for **Ulcerative colitis.)**
  - Budesonide, for **ileal** and **proximal colon** involvement. (Suitable for **Crohn's disease**)
  - Not useful for long term maintenance therapy. (Low dose for short period ONLY.)
    - Why? They, seriously, have a lot of side effects, **at long term.**
      - Short term's side effects: Nausea or vomiting.
      - Long term's side effects: The symptoms of constantly high serum's cortisol level; Cushing's syndrome, diabetes, obesity, hypertension, etc.
        - Actual pathophysiology: GCs mimic the cortisone's structure ➔ Its high levels would elicit negative feedback from pituitary gland by it sending inhibitory signals to the Adrenal Gland ➔ Exo. Cortisone still increasing ➔ Eventual Suppression of both, Pituitary and Adrenal gland ➔ ↑ Gluconeogenesis ➔Cushing's syndrome

- Antimetabolites
  - Azathioprine
  - 6-Mercaotopurine
  - Both are **PRO-drugs**, they aren't considered active until being turned into **Thioguanine nucleotides**, which mimic **purine**, hence the name, Purine analogs.
    - Summarized pathway:

        - Azathioprine ➔ 6-Mercatopurine
            - 6-Mercatopurine ➔Thioguanine nucleotides.
            - 6-Mercatopurine ➔ Inactive products (**By Xanthine oxidase**)
    - Being a false purine base, it certainly would cause
        - **Defect in purine metabolism** due to it taking part.
        - **Mutation** ➔ Stopping the cell's cycle, leaving it with **2 options**: Repair or Apoptosis. You think that's the end? **Thioguanine nucleotides** ALSO induce apoptosis! 😂 ➔ Ultimately, affecting cells' proliferation ➔ **Immunosuppression/Antimetabolic**
- Inhibit purine nucleotide metabolism and DNA synthesis and repair, resulting in inhibition of cell division and proliferation and may **promote T-lymphocyte apoptosis.**
- Immunosuppressive.
- **Clinical use**:
    - Onset delay of **17 weeks**! (Remember their initials (A6), just turn "A" to Arabic "Allef" ➔ 16, deal with that one difference yourself.)
    - Used in induction and maintenance of remission. (You give antimetabolites when the patient isn't responding to GDs as you can't give high doses of the latter.)
    - Allow **dose reduction** or **elimination of steroids**.
- **Adverse effects:**
    - **Bone marrow suppression (Due to white blood cells apoptosis.)**
        - **Therefore, checking CBC (Complete blood count) is required.**
    - **Hepatic toxicity**
        - **Therefore, checking LFT (Liver functions test) is required.**

    - **Allergic reactions**
        - **(Hepatitis,** Pancreatitis, Diarrhea and diarrhea)
    - Nausea and vomiting
    - **Allopurinol increases levels of the drugs.**
        - Allopurinol is known to inhibit Xanthine oxidase. We know Xanthine oxidase is required to turn MET-6 into the inactive form. For the former to be lost means accumulation of drugs ➔ ↑ Toxicity
- **Methotrexate**
    - It has **2 main functions**
        - Immunosuppression/Antimetabolite (**High dose**)
            - Works by inhibiting **Dihydrofolate reductase** enzyme, which is important in the synthesis of **Purines** and **Thymidine** **➔Ultimately, disrupting DNA synthesis and cells' proliferation.**
            - **➔ONLY at high doses it can inhibits cellular proliferation.**

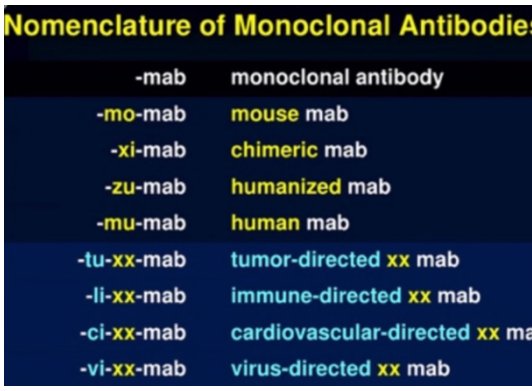


        - Anti-inflammatory (**Low dose**)
            - Through certain mechanism, it causes the accumulation and release of Adenosine ➔ Anti-inflammatory agent.
            - It interferes with the inflammatory actions of interlukin-1 (The main player in RA)
            - Causes the apoptosis and death of Activated T-lymphocyte
            - At low doses used in IBD.
    - Can be given **subcutaneously** and **intramuscularly**.
    - **Clinical uses**
        - Used in
            - Cancer chemotherapy
            - Rheumatoid arthritis
            - Psoriasis
        - Used in
            - Induction and maintenance of remissions of **Crohn's disease.**
        -

Adverse effects:

- **Bone marrow depression,** connected to folic acid depletion ➔ Why? ➔ Because of MTX inhibiting DHFRase, making the body gets rid of more folate as a waste ➔ Possible **Folate deficiency**.
- **Megaloblastic anemia ➔ Folate deficiency**
- **Alopecia ➔** Again, an antimetabolite, it **SHOULD stop** cells **growth**, including hair.
- **Mucositis ➔** It is suggested that upon DNA damage, cytokine release happens to direct the inflammation to the damaged site to repair it. ➔ Cytokines damage epithelium ➔ Disrupting its integrity ➔ **Bacterial growth**
- **Renal insufficiency** may increase risk of hepatic accumulation and toxicity.
- **Most of these side effects are counteracted by folate supplementation.**

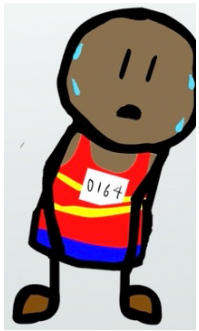
- **Anti-Tumor necrosis factor:**
  - TNF-α is a key proinflammatory cytokine in the TH1 response in IBD.
  - Basic terminology:



- With that out of the way,
  - **Infliximab "Remicade"**
    - Is chimeric(**xi**), mouse-human monoclonal antibody to human TNF-α.
    - Given **IV** (Infliximab) (**SC**والباقي)
  - **Adalimumab**
    - Fully humanized(mu) **IgG** antibody, given **SC**
  - **Certolizumab**
    - Polyethylene glycol Fab fragment of humanized anti-TNF-α, also given **SC.** (Not fully humanized, **Fc portions IS MISSING.**)
  - Half-life 8-10 days with the persistence of **antibodies in plasma** for 8-12 weeks.
  - **How do they work?** Binds to cell surface as well as to membrane-bound TNF-α receptors, preventing the cytokine from binding to its receptors.
  - **Significance of Fc portion of** human IgG1 region.
    - Promotes complement activation
    - Antibody-mediated apoptosis

- Cellular cytotoxicity of activated lymphocytes and macrophages.
- Certolizumab would, then, miss these features.

- **Clinical uses:**
  - 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**, infusion is repeated every **8 weeks** **(**This might be the silliest thing of this sheet, count the number of letters in "Anti-tumor necrosis factor ➔ That's 4, an even number ➔ 0 – 2 – 4 – 6 **– 8)**
  - Response might be lost due to development of **antibodies to infliximab**. (Obviously, due to its chimeric nature)
- **Serious Adverse effects:**
  - Infections due to immunosuppression, occur in 6% of patients on **infliximab**, e.g.
    - **Reactivation of TB or dissemination**
    - **Reactivation of Hepatitis B**
    - Pneumonia
    - Pneumocystis
    - Listeriosis
  - Antibody formation against the murine epitope of **infliximab** develops in 1/3rd of patients ➔ Loss of response or **infusion reactions** (Literally the two of them are hypersensitivity reaction, they could share several allergic features, like, **urticaria**)
    - **Acute infusion reaction** (Visualize this, and you are set! "acute"➔Emergent!)
      - Chest pain and discomfort.
      - Shortness of breath and dyspnea.
      - Hypotension and muscle spasm.
      - Headache and dizziness.



- **Delayed reactions or serum sickness-like reactions** ("Delayed" indication for the formation of infliximab antibodies.) (Mom: Why are you late? Me: My jawwwww. So, yea, remember kids, don't be like Big jaw tommy!)

- Occur after retreatment with infliximab. Includes,
  - Myalgia, arthralgia and jaw tightness.
  - Fever rash, **urticaria** and edema.

▪ **<u>Other adverse reactions</u>**:

- **+ Antinuclear anti-bodies, anti-double stranded DNA**, **<u>Lupus like syndrome</u>**, severe hepatic reactions, lymphoma, multiple sclerosis and congestive heart failure.
- **Remember, that the purpose is not to memorize all the side effects, just know that they have a long list possible side effects + whether the side effects happen, immediately, later, or after repeated administration.**

Test your knowledge

1- Which of the following is wrong about methotrexate?

a) Used in cancer chemotherapy
b) can be used to induce and maintain the remission of crohns disease
c) iron supplement could be used to counteract the side effects
d) at high doses it inhibits cellular proliferation and at low doses it treats IBD
e) all of the above are correct

2- A 17 year old boy with a history of sulfa allergy is diagnosed with left side ulcerative colitis after 3 week history of bloody diarrhea and tenesmus. The appropriate drug therapy to institute initially is which of the following ?

a. Metronidazole
b. Sulfasalazine

c. Mesalamine
d. Dicyclomine
e. None of the above

3- Which of the following drugs is contradicted in patients with congestive heart failure?

a. Infliximab
b. Adalimumab
c. Certolizumab
d. Natalizumab
e. All of the above

4- Wrong about IBD drugs:

a. Corticosteroids aren't used for maintenance
b. Methotrexate is a second line maintenance therapy for Crohn's disease.
c. Azathioprine is used for induction of UC

Answers: 1-c, 2-c, 3-A,4-c