Lecture 5 : GI PHARMACOLOGY (chp. 78-80)

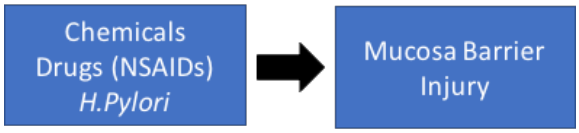
Legend

SECTION HEADER	Sub-topics	Important information
Concepts/topics	Drugs	Nursing capsules

See glossary of abbreviations at the end of the document

WHEN IT BURNS FROM WITHIN: DRUGS FOR PEPTIC ULCERS (CH. 78)

Pathophysiology Review Slides

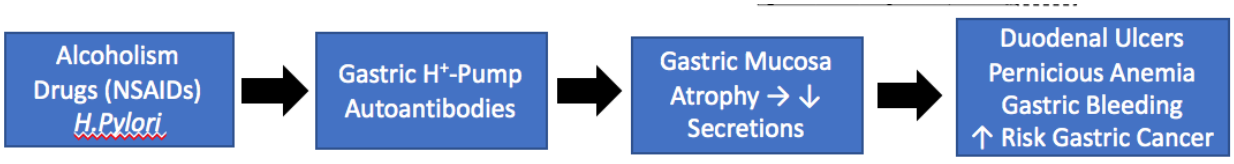


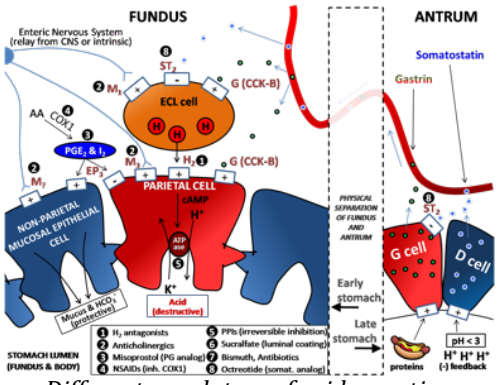
Acute Gastritis

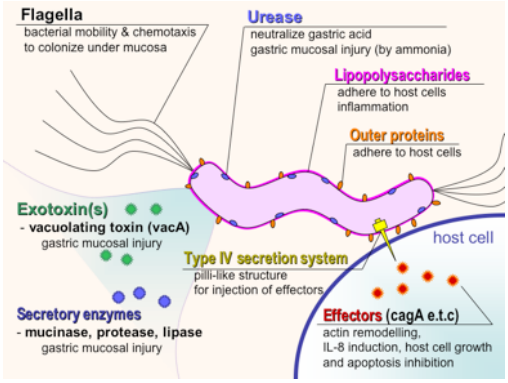
- Diffuse or Localised Gastric Mucosa Inflammation
- Remove Source of Harm or Antacids or ↓ HCl secretions
- Erosion of Gastric Mucosa → Abdominal Discomfort & Bleeding
    - Infection with H.pylora detrucs gastric mucosa = acid starts eating some of GI cells = ulcers, bleeding
    - Sx are painful initially

Chronic Gastritis

- Chronic Inflammation + Mucosal Atrophy + ↑ Cancer Risk
- If left untreated, can lead to significant GI hemorrhage (but usually managed at first bcs painful)
- MUST REVIEW THIS SLIDE – shows all the regulators (ex: proton pump inhibitor)







Different regulators of acid secretions

Peptic Ulcers

- Peptic Ulcer = Break in GI Mucosa extending to the Muscle Layers & Blood Vessels
- Chronic NSAIDs + *H.Pylori* → Acidic Output & Mucosal Defense Imbalance → Inflammation + Autodigestion
- Psychological Stress Ulcers → Unknown Mechanism

Duodenal Ulcers

- Most Common; Affects Younger Individuals (20-50)
- Acid Secretion or Muscle Spasm → Chronic Intermittent Pain
- Meal or antacids relieve Pain

Main Manifestations:

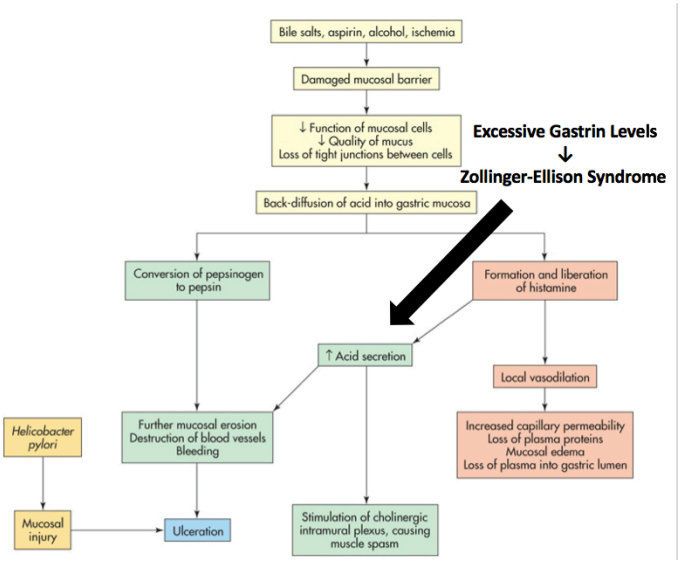
- Intestinal Hemorrhage/Perforation
- Common Nocturnal Pain
- No ↑ Cancer Risk
- Remission-Exacerbation Pattern

Gastric Ulcers (see image)

- ↑ HCl Secretions ≠ 1◦ defect
- Older Onset (55-65)

Main Manifestations:

- Similar to Duodenal
- Vomiting/Nausea & Anorexia
- No Remission-Exacerbation Pattern
- ↑ Gastric Cancer Risk



Stress Ulcers

- Severe Physiological Stress → Acute Mucosal Disease
- Several Ulcers along Gastric & Duodenal Wall

Complication of Severe Illness/Multisystem Organ Failure:

- Ischemic Ulcers → Within Hours
- Curling Ulcers → Following Severe Burn Injuries
- Cushing Ulcers → ↑↑ Vagal Activity Following Brain Surgeries or Head Trauma

Main Manifestations:

- Severe Bleeding
- Exacerbated by concomitant Coagulopathy

Antiulcer Drugs Classification

Classification of Antiulcer Drugs

Class	Drugs	Mechanism of Action
ANTIBIOTICS	Amoxicillin [Amoxil] Bismuth [Pepto-Bismol] Clarithromycin [Biaxin] Metronidazole [Flagyl] Tetracycline (generic only) Tinidazole [Tindamax]	Eradicate *H. pylori*
ANTISECRETORY AGENTS		
H_2 receptor antagonists	Cimetidine [Tagamet] Famotidine [Pepcid] Nizatidine [Axid] Ranitidine [Zantac]	Suppress acid secretion by blocking H_2 receptors on parietal cells
Proton pump inhibitors	Dexlansoprazole [Dexilant] Esomeprazole [Nexium] Lansoprazole [Prevacid] Omeprazole [Prilosec, Zegerid, Losec ◆] Pantoprazole [Protonix, Pantoloc ◆] Rabeprazole [Aciphex, Pariet ◆]	Suppress acid secretion by inhibiting H^+, K^+-ATPase, the enzyme that makes gastric acid
MUCOSAL PROTECTANT	Sucralfate [Carafate, Sulcrate ◆]	Forms a barrier over the ulcer crater that protects against acid and pepsin
ANTISECRETORY AGENT THAT ENHANCES MUCOSAL DEFENSES	Misoprostol [Cytotec]	Protects against NSAID-induced ulcers by stimulating secretion of mucus and bicarbonate, maintaining submucosal blood flow, and suppressing secretion of gastric acid
ANTACIDS	Aluminum hydroxide Calcium carbonate Magnesium hydroxide	React with gastric acid to form neutral salts

- Antibiotics (only use them if you are sure that H pylori is the cause of the ulcers)
    - Must test prior to prevent resistance
    - In the meantime, use something else: antisecretory agents
- Antihistamines agents
    - H2 receptor antagonist VS H1
    - Remember H1 = allergies– don't mix! (more specificity with H2 = less toxicity)
    - H2: subset type in the GI (H1 receptors located in the CNS)
- Proton pump inhibitors: preferred
- Non target agents
    - They don't necessarily block a function of an enzyme/protein but still have a benefit on ulcers)
- Mucosal protectant:
    - Forms a protective coat on ulcer (not blocking acid, just protects by filling the mucosa to prevent further damage)
- Antisecretory:
- Antacids: neutralize ions

Nursing Capsule: Ulcer Treatment Overview

Drug Therapy

⇨ Goals: Alleviate Sx + Promote healing + Prevent complications & relapse

Drug Selection

Drug selection depends on cause (If not H pylori, forget about the antibiotic)

- H.pylori-induced ulcers: Antibiotics + PPI or H2AR
- NSAIDs-incuded ulcers prophylaxis: PPI or Misoprostol
- NSAIDs-incuded ulcers treatment: PPI + NSAID discontinuation

Evaluation:

- Pain alleviation & ulcer healing often do not correlate
    - Not because the patient feels better that the ulcer is healing → Make sure ulcer is healed before d/c meds
- H.Pylori test to determine eradication
- Radiologic or endoscopic exam for ulcer healing

Nondrug Therapy

- Diet: Consumption of 5-6 small meals (instead of 3 large) →↓ stomach acidity fluctuation
    - Larger the meal the more acid is released
    - No evidence of efficacy of 'ulcer diet' or exacerbation by coffee and tea
- Other measures: Avoid ulcer-inducing agents
    - Ex.: NSAIDs (except low-dose aspirin) / Smoking / Anxiety-Stress / Alcohol (debated evidence, but take no chance and should avoid it)
    - OK to take aspirin to prevent cardiovascular events (benefit outweighs the risk)

Antibiotic Regimens

- Only use the drugs below & NEVER ALONE
- Only use when H.pylori positive
- Eradication rate shows efficacy of tx
- Most of them last for about 2 weeks. Need to retest after 2 weeks to check if H pylori is still present

First-Line Regimens for Eradicating *H. pylori*

Drug	Duration	Eradication Rate	Comments
CLARITHROMYCIN-BASED TRIPLE THERAPY 1 Standard-dose PPI* Clarithromycin (500 mg twice daily) Amoxicillin (1 gm twice daily)	10–14 days	70%–85%	Consider in non–penicillin-allergic patients who have not previously received clarithromycin or another macrolide
CLARITHROMYCIN-BASED TRIPLE THERAPY 2 Standard-dose PPI* Clarithromycin (500 mg twice daily) Metronidazole (500 mg twice daily)	10–14 days	70%–85%	Consider in penicillin-allergic patients who have not previously received a macrolide or are unable to tolerate bismuth quadruple therapy
BISMUTH-BASED QUADRUPLE THERAPY Bismuth subsalicylate (525 mg 4 times daily) Metronidazole (250 mg 4 times daily) Tetracycline (500 mg 4 times daily) Standard-dose PPI* or ranitidine (150 mg twice daily)	10–14 days	75%–90%	Consider in penicillin-allergic patients and in patients with clarithromycin-resistant *H. pylori*
SEQUENTIAL THERAPY Standard-dose PPI* + amoxicillin (1 gm twice daily) for 5 days, followed by: Standard-dose PPI* + clarithromycin (500 mg once daily) + tinidazole (500 mg twice daily) for 5–7 days	10 days	Over 90%	Efficacy in North America requires validation

Antibacterial Drugs

- Only use once presence of H.pylori is established (see next slide)

Clarithromycin:

- Very effective but high resistance

Amoxicillin:

- Highly efficient & Low resistance
- ↑ efficacy at neutral pH (ex. with meal or PPI)

Bismuth:

- Risk of stool discoloration misdiagnosis as gastric bleeding
- Avoid long-term use (neural injuries)

Tetracycline:

- Very low resistance
- Avoid in pregnant women
    - Teratogenic: baby will have teeth discoloration

Metronidazole & Tinidazole:

- Very effective but high resistance
- Disulfiram-like reaction with alcohol
    - to prevent abuse of alcohol (when scared of relapsing): drinks alcohol = get sick right away (to scare them from drinking alcohol)

H.Pylori Test

Radioactive carbon urea breath test

1) After fasting for 1 hour, breathe into a blue collection bag
2) Drink a solution your HCP gives you
   The solution = make H.pylori go up in the air (like blowing on dust)
3) Wait 15 minutes
4) Breathe into a second, pink collection bag

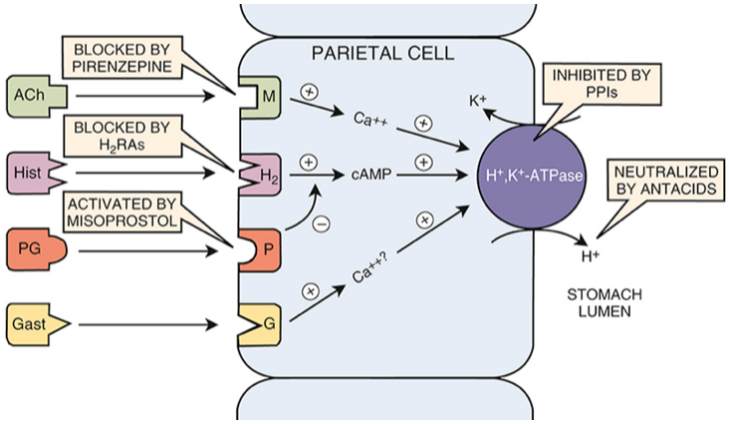
The lab checks for changes between the first and second samples that tell whether you have H.pylori.

Sensitivity/specificity among the highest = good test

Sensitivity: are you able to identify patients that are infected by H pylori – can we detect it when they have an infection

Specificity: are you able to differentiate does that don't have it → (you detect it so well that you're able to « discriminate »)

Antiulcer Drugs Overview



Pirenzepine not studied in class

H2-Antagonists (H2-RA): Cimetidine

Fun Fact: 1st ever 'blockbuster Rx' → 1st to sell over 1 billion $

Action:

- Selective H2 receptor antagonist: binds to H2 receptors and ↓ the stimulation of the acid secretion
- ↓ gastric secretion volume & acidity
- No anti-allergy effects (H1 receptors)

Therapeutic Uses:

- Gastic & Duodenal Ulcer → Treatment + Prevention
- Gastroesophageal Reflux Disease → Sx alleviation only
- Zollinger-Ellison Syndrome (gastrin-secreting tumor)
  - Ulcer formed by gastrin secreting tumor → remember gastrin stimulates acid secretion
  - need higher doses to manage which increases toxicity
- Requires high doses → significant toxicity

Adverse Effects: Low incidence and mostly benign

- Antiandrogenic effects (ex.: ↓ libido)
- CNS excitation & confusion → renal or hepatic impaired mostly
- Small ↑ Pneumonia risk (↑ gastric pH = ↑ bacteria colonies)
    - increasing pH (reducing acid)= increase risk of bacteria surviving = Bacteria in the stomach, can go in circulation (blood stream) and finds a way to the lungs = can colonize lungs = promote pneumonia

Interactions: Most important toxicity factor

- CYP450 inhibition of warfarin, phenytoin & lidocaine (narrow TI)
- Antacids ↓ cimetidine absorption

Better option: **Ranitidine**

- Better, but newer

Similar Drug with 3 Advantages

1. ↑ Potency
2. Fewer ADRs
3. Fewer Interactions

Proton Pump Inhibitors (PPI): Omeprazole

- Superior to H2-RA in HCL ↓ and onset speed
- PPIs are equivalent in terms of safety & efficacy → Selection based on $$

Actions

- Prodrug/Irreversible H+/K+ ATPase inhibitor
    - needs to be activated by CYP enzymes
    - Irreversible inhibitor
- Short T1/2 but long duration
    - Short T1/2 drugs not bound to protein, but those that are bound to protein, they will have a longer effect, once they detach from that protein, they degrade quckly
- Very efficient → 97% ↓ HCl within few hours

Uses:

- Short-term ulcer & gastric reflux Tx
- Long-term Zollinger-Ellison syndrome management

Adverse Effects:

- Minimal with short-term therapy → that's why the drug is preferred
- Rebound acid hypersecretion
- ↑ **risk of C.diff** → Report signs of diarrhea

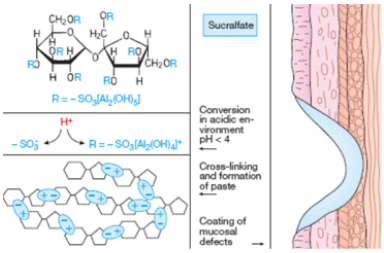
Interactions:

- ↓ absorption of antiviral & antifungal Rx

The Clopidogrel Situation:

- Often given to pts with stents to prevent coagulation (beneficial)
- PPIs can ↓ GI Bleeding risk (beneficial)
- But also ↓ Antiplatelet efficacy (adverse)
- Combine in patients with bleeding risk factors only
    - If pt is not at risk of GI bleeding → better to not put the pt at any risk for the stent (until they become at risk for bleeding)
- (ex.: NSAIDs use; advanced age)

Sucralfate (Sucralfate comes from sucrose)



Sucralfate mechanism of action

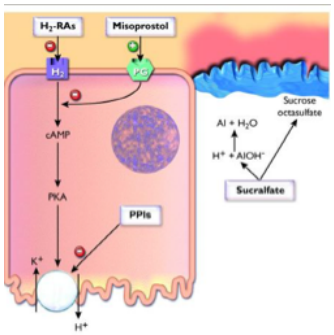
Actions:

- forms a protective layer on the ulcers (physical barrier)
- Orally available acid barrier → Promotes ulcer healing
    - While protecting the ulcer, allows for healing
    - Doesn't decrease the acid environment at all
- Efficacy ≈ H2-RA

Uses:

- Acute + Maintenance therapy of duodenal & gastric ulcers

Toxicity:



- No serious ADRs → Constipation in 2% patients
    - No toxicity bcs doesn't get into the system (doesn't get absorbed – stays in GI)

Interactions:

- Antacids: Efficacy ↓ if pH ≥ 4
    - If pH is higher, sucralfate does not form a protective layer anymore
    - If you give antacids, pH not adequate= decrease sucralfate action
- Possible ↓ absorption of other Rx → Administer 2h apart
    - By forming a layer= more difficult for other drugs to go through (decreased absoprtion)

Misoprostol

Actions:

- Promotes prostaglandin action
- Prostaglandin E analog → ↓ HCL + ↑ cytoprotective mucus
- Also ↑ uterine contractions & cervial ripening
    - Prepares uterus for delivery during pregnancy

Uses:

- USA: NSAIDs-induced ulcer prevention
- World: Peptic ulcer disease therapy
- Misoprotol + Mifepristone for medical abortions

Toxicity:

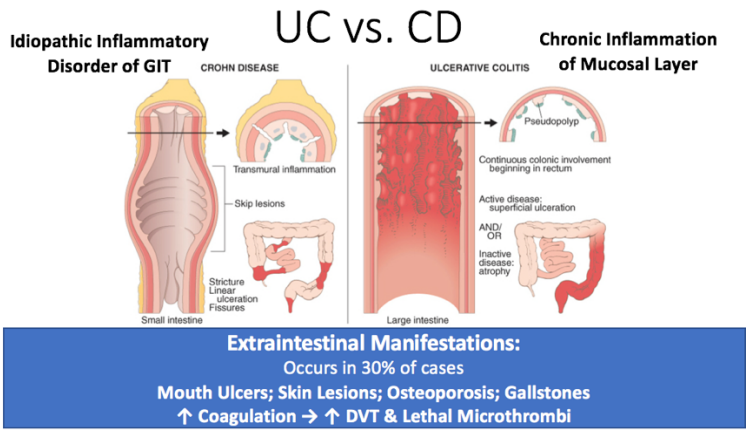
- Diarrhea / Abdominal pain / Dysmenorrhea
- Induced abortion risk → Super contraindicated during pregnancy bcs it can induce abortions as well

Antacids

- Efficacy ≈ H2-RAs but more toxicity
    - They're equivalent to H2RA but +++ toxic = therefore not preferred (rarely used)
- MOA: neutralize H+
- Choose your drug depending on what you're looking for. Some SE include constipation, diarrhea, effect on pH
    - You prefer a drug that doesn't increase systemic pH

OTHER GASTROINTESTINAL DRUGS (Ch. 80)

Pathophysiology review slides



Ulcerative Colitis (UC)

- Only Affects Rectum & Colon
- Continuous Lesion
- Unknown Cause
- Maybe Genetic/Diet/Infection

Autoimmune Disorder

Colonic Antibodies + ↑ Activated B-Cells + Cytotoxic T-Cells & Inflammatory Cytokines → Damaged Mucosa & Edema → Ulcers & Abscess → Hemorrhage, Necrosis & Regenerating Pseudopolyps

Clinical Manifestations:

- Intermittent Exacerbation-Remission Episodes
- Bloody Diarrhea; ↑ Colon Cancer
- **Pancolitis** = Severe cases involving whole Colon
- Fever; Crampy Pain; ↑ BP
- Edema + Strictures + Fibrosis → Colon Obstruction

Crohn's Disease (CD)

- Hypothesised Pathophysiology: Immune-Related Disorder
- Genetic Vulnerability → Th1-Hypersensitivity Reaction to Microbiota
- Cell-Mediated Cytotoxicity → Skip Lesions
- Severe Ulcers → Transmural Inflammation → Crypts Destruction

Clinical Manifestations:

- Irritable Bowel Phase = Several years
- Abdominal Pain & Diarrhea
- Weight Loss & ↑ Osteoporosis Risk
- Frequent Anal Fissures & Colon Obstruction
- Sx vary with Affected Location
    - Ex.: Ileum → ↓ Vit.B12 → Pernicious Anemia

Appendicitis

- Inflammation of Appendix → Surgical Emergency
- Develops most often 20-30

Theorised Pathophysiology:

- Lumen Obstruction (Stool, Tumors, etc.) → ↑ Intraluminal Pressure → Ischemia → Bacterial Infection & Inflammation

Manifestations:

- Acute Pain (right lower quadrant)
- Fever
- Nausea/Vomiting
- Serious Complications = Abscess & Perforations

Gallstones

- Stones Obstruct Gallbladder Duct
- Most Asymptomatic

Risk Factors:

- Obesity; Low HDL
- Pancreatic/gallbladder/Ileal Disease

Cholesterol Stones (Yellow)

- Supersaturated Bile → Cholesterol Crystal Formation → Cystic or Common Duct Occlusion
- Pigmented Stones (Dark)
- Hemolytic Anemia or Infection→ Hyperbilirubinemia → Cystic or Common Duct Occlusion

Clinical Manifestations

- Upper Abdominal Pain + Intolerance to Fatty Food
- Jaundice = Common bile duct obstruction
- Fever = Cholecystitis

Opioids Used to Treat Diarrhea

Generic Name	Brand Name	CSA Schedule	Antidiarrheal Dosage
Diphenoxylate (plus atropine)†	Lomotil	V	*Adults:* 5 mg, 4 times/day *Children (initial dosage):* Ages 2–5 yr: 1 mg, 4 times/day Ages 5–12 yr: 1–2 mg, 4 times/day
Difenoxin (plus atropine)†	Motofen	IV	*Adults:* 2 mg initially, then 1 mg after each loose stool
Loperamide	Imodium, Pepto Diarrhea Control, others	NR	*Adults* (initial dose): 4 mg *Children (initial dosage):* Ages 2–5 yr: 1 mg, 3 times/day Ages 5–8 yr: 2 mg, 2 times/day Ages 8–12 yr: 2 mg, 3 times/day

Antidiarrheal Agents: Opioids

- Opioids used with the intent of using the « constipation » effect to cancel out diarrhea. Mu receptors are also found in the GIT
- GI Opioid Receptor Effects:
    1. ↓ Intestinal motility
    2. ↓ fluid secretion
    3. ↑ Fluid & Electrolyte Absorption
- Opioid antidiarrheal dosage < Analgesia
- ↓ BBB X-ing → Reduced toxicity & CNS effects
- **Loperamide** : chemically cant cross BBB so you can give it to relieve constipation without affecting the CNS (no sedation)

Nursing capsule: Infectious Diarrhea Management

General Considerations

- Most are mild and self-limiting
    - non threatening and will dicipate on their own once infection is gone
- Only use antibiotics for severe infections (ex.: C.diff / Salmonella) to prevent resistance
- Best Tx: Fluid & Electrolyte formulations + good hygiene

Traveler's Diarrhea: Mostly E.coli

- No Tx needed → Dissipates within few days
- Only treat if prolonged Sx & severe → Preferred = **Ciprofloxacin (Review abx lecture)**
- **Loperamide**: Sx relief but ↑ infection duration
- Effective Prevention: Washing food products + Avoiding local tap water

C.Difficile-Associated diarrhea

- Review antibiotic lecture (week1)
- Vancomycin PO & Mitromidazole IV

Irritable Bowel Syndrome (IBS)

- Hypersensitive & Hyperresponsive bowel without structural or chemical abnormalities
- Associated with diarrhea (IBS-D); constipation (IBS-C) or a mix of both (IBS-M)

Nondrug Interventions:

- Identification & avoiding stressors (foods, events, time of day)
- Frequent small meals vs. Large meals
- ↑ Fluid & fiber diet intake

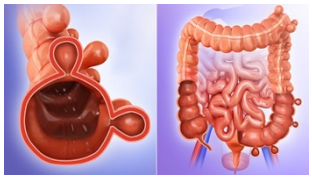
Nonspecific Drugs:

- Old Tx: TCAs or Antispasmodics or Loperamide or Bulk-forming agents
- **Current evidence: Only TCAs seem effective**
- New evidence: significant Sx relief with broad-specturm PO antibiotics or Acid suppressants

IBS-specific drug: Alosetron

- The only 5-HT receptor antagonist approvecd for the tx of women with severe IBS-D (IBS diarrhea)
- Only 5% of IBS-D qualify as severe
- Frequent incontinence or debilitating quality of life
- PO available → Extensive P450 metabolism
- Watch out for interactions

ADRs: Potentially severe



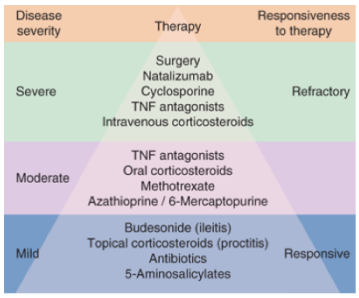
- Constipation leading to Ischemic colitis

Contraindicated if history of:

- Chronic constipation or ischemic colitis
- Inflammatory Bowel Disease
- Diverticulitis (bowel tangle together = pockets of inflammation where stool gets trapped)

Only available under FDA Risk management program involving Patient + Pharmacist + Prescriber

Nursing Capsule: Inflammatory Bowel Disease (IBD) Management



- No curative therapies / Sx relief only
- IBD ≈ Exaggerated immune response
- The more severe the disease, the more aggressive the therapy

5-Aminosalicylates: Sulfasalazine

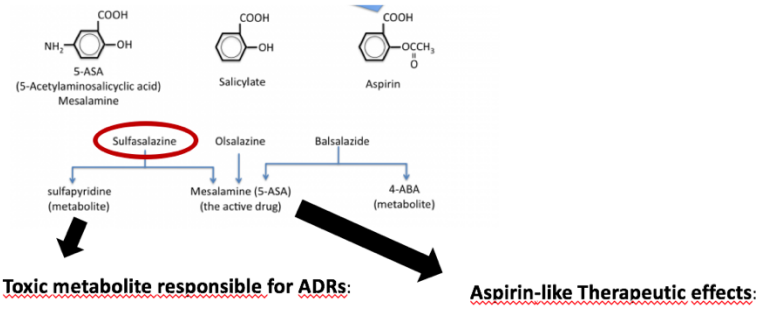
- Very similar in composition to Aspirin
- Crohn and UC have a big inflammatory component in their pathophys

Toxic metabolite responsible for ADRS:

- Nausea & Fever
- Possible agranulocytosis
- Complete blood count (CBC)

Aspirin-like therapeutic effects

- ↓ Inflammatory Prostaglandin synthesis
- Best for mild-moderate acute ulcerative colitis episodes



Immunosuppressants

- All of these drugs are powerful immunosuppressants used for multiple indications.
- Information here is specific for IBD therapy.
- More details in anticancer & immunosuppressant lectures

Glucocorticoids

- PO for mild-moderate cases / IV for severe
- USE SHORT TERM: High systemic toxicity if long-term use

Thiopurines

- High toxicity → Only if aminosalicylates & GCC failed
- Delayed effect onset → Up to 6 months!!

Cyclosporine

- More powerful than Thiopurines
- IV admin for severe Crohn's & ulcerative colitis
- Watch for nephrotoxicity / neurotoxicity / immunity ↓ = **increase risk of infection**

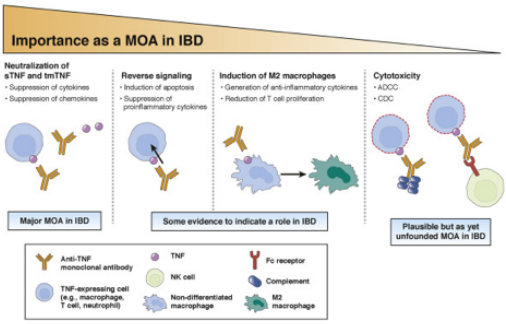
Methotrexate

- Promotes short-term remission when Glucocorticoid Tx is too long
- Dosage much lower than anticancer dosage → Milder toxicity

Immunomodulators

Monoclonal Antibodies against specific molecules

- TNF-α: Infliximab, adalimumab, certolizumab
- α4-Integrins: Natalizumab & vedolizumab
- IL-12 & IL-23: Ustekinumab



Old guidelines: 2nd-line agents for moderate to severe IBD

New guidelines:

- Use as 1st-line to ↑ remission duration
    - Use star player right now!!

Serious toxicity with long-term use:

- Severe ↓ immune functions = ↑ infections, Lymphoma & **Tuberculosis risk**
- Infusion reactions: rash + fever
    - Need to be given IV because they get digested in the stomach if given PO

Prokinetic Agents: Metoclopramide

Actions

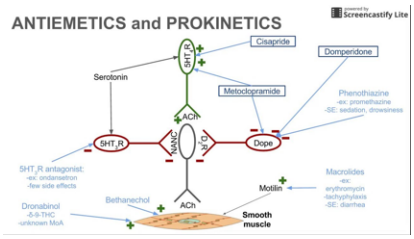
- Antiemetic: 5-HT + DA inhibition at CTZ
    - Prevents CTZ from telling the brain to vomit
- Prokinetic: ↑ Ach release on upper GI smooth muscles
    - Activates Ach = activates smooth muscle = contraction = stimulate the movement of the bowel

Serious toxicity high-dose & long-term use:

- Sedation + Diarrhea
- Irreversible tardive dyskinesia
    - Tardive dyskinesia related to DA inhibiton

Therapeutic Uses

- PO: GERD & Gastroparesis (abnormally slow movement in the bowel)
- IV:
    - ↓ nausea & vomiting (cancer & postoperative)
    - Faciliation of bowel intubation
    - Faciliation radiologic examination



KGF Agonist: Palifermin

Unique Indication:

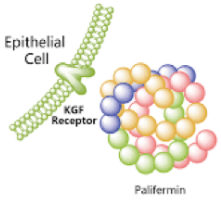
- Severe oral mucositis (OM)
- **only for patients with hematologic cancer on high-dose chemotherapy + whole body irradiation**

Clinical Benefits:

- ↓ OM incidence & duration
    - Decrease incidence of oral mucositis by promoting growth. CA therapy kills cells including cells in the oral mucosa. KGF promotes growth in that region, cancel rate of cell dying.
- ↓ need for opioid analgesia
- ↓ supplemental parenteral nutrition

Adverse Effects:

- Skin rash develops in < 1% patients
- Concern for vision loss but no data yet



Drug Interactions:

- **Reacts with Heparin**
- ↑ severity of OM if administered too close to chemotherapy → minimum 24h apart
    - Opposite effect if given too close to chemotherapy. Keep 24h seperation.

Why only against Hematologic cancers?

- KGF receptors promote growth +Not expressed on blood cells!
- KGF is located on a lot of cells, promotes growth. So dont want to use that on a cancer pt bcs already too much growth. But its not expressed on blood cells so it wont make it worse bcs it wont act on it)

Abbreviations

ADR : adverse reaction

d/c : discontinue

GIT : gastrointestinal tract

IBD : Inflammatory Bowel Disease

IBS-C :Irritable Bowel Syndrome - constipation

IBS-D: Irritable Bowel Syndrome – diarrhea

IBS-M: Irritable Bowel Syndrome – mix

IBS: Irritable Bowel Syndrome

MOA : mechanism of action

OM : oral mucositis

PPI : proton pump inhibitor

Rx : drug

UC: ulcerative colitis

Vit : vitamin

VS: versus