PASSION ACADEMIC TEAM

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Sheet# 3

YU - MEDICINE

GASTROINTESTINAL SYSTEM

Lec. Title : Treatment of IBD & IBS .

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Treatment of Inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS)

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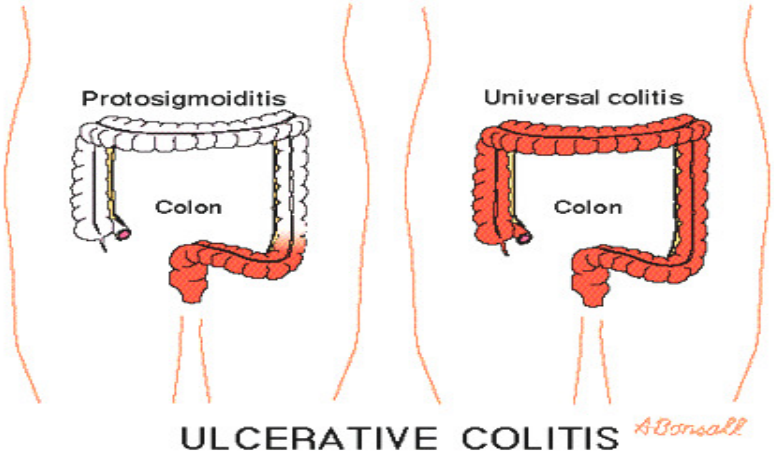
التفريغ يشمل السلايدات ومحاضرات
اليوتيوب ومحاضرات الزوم

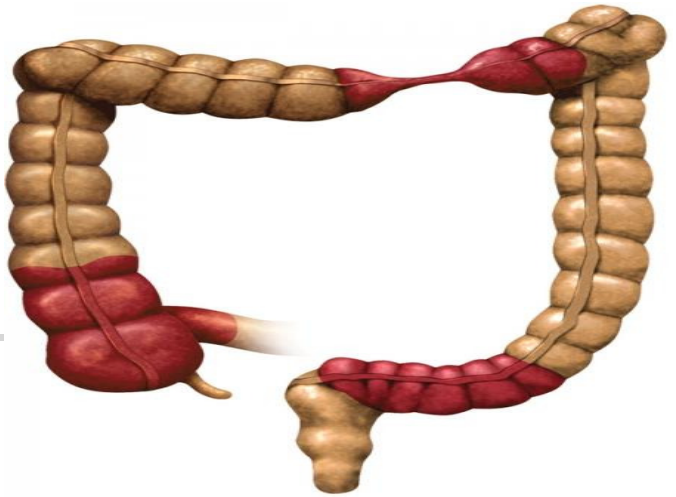
Differences between Crohn's disease and UC

	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	deep into tissues	Shallow, mucosal
Complications	Strictures, Obstruction (Obstruction of intestine which sometimes needs surgery) Abscess, Fistula	Toxic mega colon (Enlargement of the colon) Colon cancer

Regarding to the previous slide

- **They are both called IBD which is an inflammation caused by immune system or mediated by it (mainly T cells), so anti-inflammatory drugs plus immunosuppressants are used to suppress T cells and stop cytokines production.**
- **These drugs are either antibodies against cytokines or act on the receptors that cytokines bind to.**
- **The lesions are most commonly located in the terminal small intestine and the large intestine.**





Ulcerative colitis

Crohn's disease

Note that:

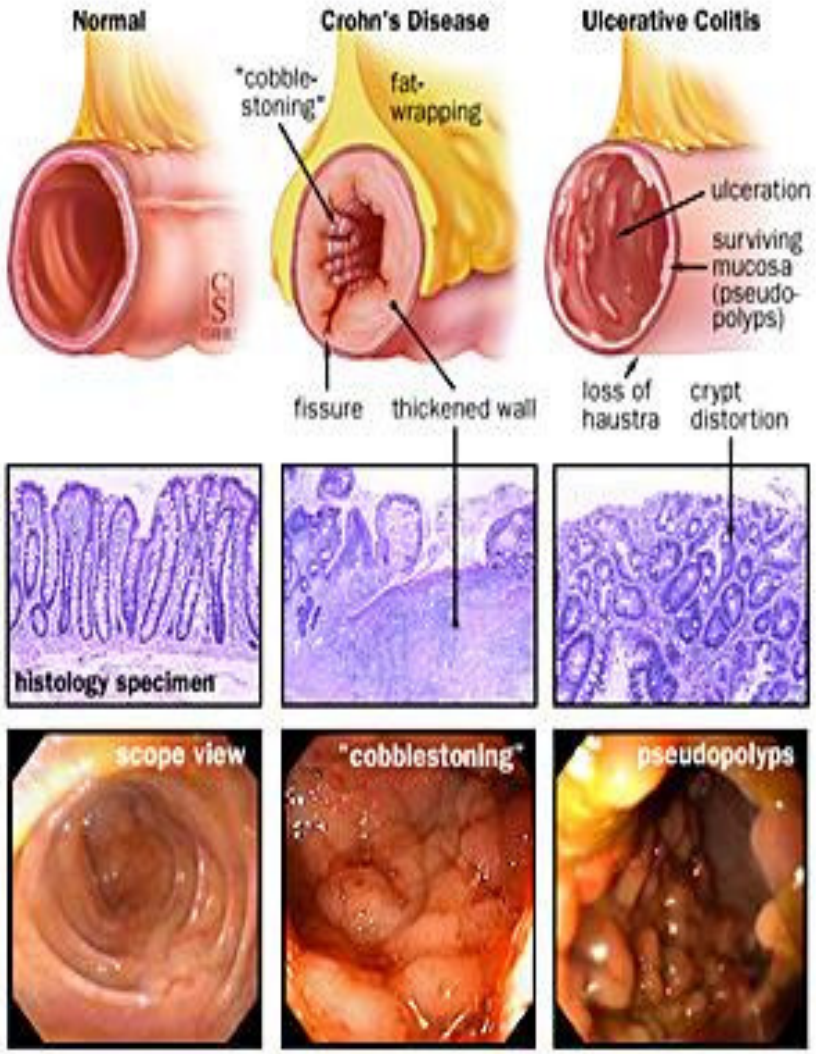
- **ulcerative colitis is only located in colon with continues area of inflammation:**

1. **If it's located in the rectum it's called ulcerative prochtitis**
2. **If it's located in sigmoid colon it's called sigmoid colitis**
3. **If it's located in both it's called proctosigmoiditis**

- **while Crohn's disease could occur in all portions of GIT with a patchy form**

SUMMARY- CROHN'S *VS.* UC (3)

- Crohn's disease: has distinctive appearance which is cobble stoning, with a hall thickening involvement of the wall.
- While ulcerative colitis involves only the mucosa. That is the reason of absent of thickening in the wall



Symptoms and complications

Symptoms

- Vomiting
- Abdominal pain
- Diarrhea
- Rectal bleeding.
- Weight loss

Complications

- Anemia
- Abdominal obstruction (Crohn's disease)
- Mega colon
- Colon cancer

Treatment of IBD

There is no cure for IBDs but treatment options are restricted to controlling symptoms, maintaining remission (either the reduction or disappearance of the signs and symptoms of the disease as long as possible), and preventing relapse (recurrence of the symptoms).

Treatment of IBD

1- 5-amino salicylic acid compounds (5-ASA).

- The most important because it's anti-inflammatory.

2- Glucocorticoids

- For active state with very severe symptoms

3- Immunomodulators

- Control proliferation of T cells by taking away DNA and folic acid.

4- Biological therapy (TNF-α inhibitors).

- Antibodies against cytokines from T cells

5- Surgery in severe condition

- mainly in Crohn's disease due to intestinal obstruction

5-amino salicylic acid compounds (5-ASA)

Aminosalicylates

first line of induction and maintenance of remission

- **Topical (local) anti-inflammatory drugs**
- **5-ASA itself is absorbed from small intestine.**
- **Different formulations are used to overcome rapid absorption of 5-ASA from the proximal small intestine**
  - **Azo compounds**
  - **Mesalamine compounds**

Regarding to the previous slide

- **We need these drugs to be local and act in the lumen of the gut in colon and rectum for example, and not to be absorbed from the small intestine so we do different formations of it to stop the absorption:**

1. **Azo compound : ASA + sulfa compound attach to each other by azo bond (bond produced by attachment of nitrogen from each compound). In the terminal ilium and colon the microbial flora release enzymes (azo reductase enzyme) that break the bond between them and the effect starts.**

2. **pharmaceutical formations and controlled release formations are also used.**

Azo compounds

Compounds that contain 5-ASA and connected by azo bond (N=N) to sulfapyridine moiety, another molecule of 5-ASA or to inert compound.

Sulfasalazine: 5-ASA + sulphapyridine

Olsalazine: 5-ASA + 5-ASA

Balsalazide: 5-ASA + inert carrier

Regarding to the previous slide (important note)

- How many ASA is released from each compound?
- Sulfasalazin: 1 ASA
- Olsalazine: 2 ASA
- Balsalazide: 1 ASA

Azo compounds

- **Azo structure reduces absorption in small intestine**
- ***In the terminal ileum and colon*, bacterial flora release azoreductase that cleaves the azo bond (N=N) and releases 5-ASA.**

Sulfasalazine (Azulfidine)

- **Pro-drug**
- **A combination of 5-ASA and sulfapyridine**
- **Is given orally.**
- **Little amount is absorbed (10%)**
- ***In the terminal ileum and colon*, sulfasalazine is broken by azoreductase into:**
- **5-ASA (not absorbed, active moiety)**
- **Sulphapyridine (absorbed, side effects)**

Mechanism of action of sulfasalazine

5-ASA has anti-inflammatory action due to:

- **inhibition of prostaglandins (cyclooxygenase pathway)and leukotrienes (lipooxygenase pathway).**

  (Pay attention that aspirin prevents only cyclooxygenase)

- **decrease neutrophil chemotaxis.**
- **Antioxidant activity (scavenging free radical production).**

Side effects of sulfasalazine (most of them are caused by sulphapyridine)

- **Crystalluria.** (It is deposited in the urine)
- **Bone marrow depression**
- **Megaloblastic anemia.** (due to folic acid deffenciacy)
- **Folic acid deficiency (should be provided** with the drug**).**
- **Impairment of male fertility (*Oligospermia*).**
- **Interstitial nephritis due to 5-ASA.**
- **Allergy, hypotension, little bronchospasm, aplastic anemia, destruction of RBC's which causes hemolytic anemia**
- **All of them occur even in normal doses so we have to use another compound with lower side effects** (next slide)

Mesalamine compounds

Formulations designed to deliver 5-ASA in terminal small bowel & large colon

Mesalamine formulations are

- **Sulfa free (only 5-ASA)**
- **well tolerated**
- **have less side effects**
- **useful in patient sensitive or allergic to sulfa drugs.**

Mesalamine compounds

Oral formulations

Asacol: 5-ASA coated in pH-sensitive resin that dissolved at pH 7 (*controlled release*). Take a look to the next slide to understand it clearly

Pentasa: time-release microgranules that release 5-ASA throughout the small intestine (*delayed release*).

Rectal formulations

Canasa (suppositories)

Rowasa (enema)

Regarding to the previous slide

- pH-sensitive resin is an excipient (an inactive substance that serves as the vehicle or medium for a drug or other active substance and has no side effect) which are sensitive to alkaline pH, when the drug reaches this area(alkaline area) resin will dissolve and starts to release ASA.
- Important notes:
- Mesalamin compound is ASA itself but it includes:

1. Resin which is the capsule
2. Pentasa which is granules

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).**
- **Rheumatoid arthritis *(Sulfasalazine only)***
- **Rectal formulations are used in active distal UC *ulcerative* proctitis** (rectum only , in this case use rowasa and canasa) **and proctosigmoiditis.** (rectum + sigmoid colon)

Glucocorticoids

(Only for moderate to sever cases after failure of ASA)

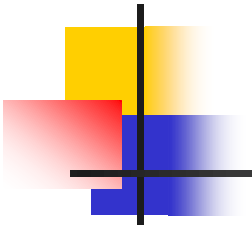
Prednisone, prednisolone (orally)

- **Higher rate of absorption**
- **More adverse effects** (especially on the endocrine system) **compared to rectal administration** (rectal way is the favorable one if the inflamed organ is rectum or sigmoid colon)

Hydrocortisone (enema or suppository): (produced by the body)

- **Less absorption rate than oral.** (more better)
- **Minimal side effects & Maximum tissue effects.**

Budesonide:



- **A potent synthetic compound**
- **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 forms of moderate to severe UC & Crohn's disease involving ileum and proximal colon.**

Regarding to budesonide

- The upper part of the rectum drainage is into superior mesenteric vein then to portal vein
- The lower 2/3 drainage is into inferior mesenteric vein (systemic circulation)
- So rectal preparations can expose to first pass metabolism

Mechanism of action of glucocorticoids

- **Inhibits phospholipase A2**
- **Inhibits gene transcription of NO synthase** (**NO increase the inflammation**), **cyclooxygenase-2 (COX-2)** (see the next slide)
- **Inhibit production of inflammatory cytokines**
- **Decrease antigen-antibody reaction (it has effect on B and T cells)**

Regarding to the previous slide

How does glucocorticoids work?

Phospholipase A2 in cell membrane → breaking down of phospholipids in the membrane→ arachidonic acid formation→ lipooxygenase pathway →leukotrienes

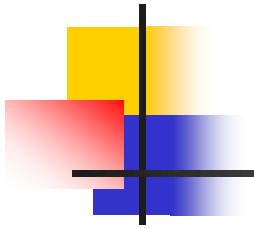
Cyclooxygenase pathway (cox-1 or cox-2) → prostaglandin synthesis.

Glucocorticoids will block cox-2 (more abundant during inflammation) and prevent prostaglandins synthesis. Also it blocks lipooxygenase pathway

Uses of glucocorticoids

- **Induction of remission in moderate & severe active IBD.**
- **Not used for maintaining remission.** (just for a few period of time) **(very important point : it has no role in remission state)**
- **Oral glucocorticoids is commonly used in active condition.**
- **Rectal glucocorticoids are preferred in IBD involving rectum or sigmoid colon**

Uses of glucocorticoids



- **Asthma**
- **Rheumatoid arthritis**
- **immunosuppressive drug for organ transplants**
- **Antiemetics during cancer chemotherapy**

Regarding to corticoids

- It's used as anti-inflammatory agent by reducing expression of NO synthase enzyme (enzyme that induced in inflammatory cases to produce NO) which in turn reduces NO releasing and leads to reduction of oxidative stress.
- Now what do we mean by mild , moderate and sever UC? Is it related to severity of inflammation it self or to the extent of the inflammation?

Cont.

- Actually it's related to the extent:
- Mild: rectum and sigmoid : in this case use ASA
- Moderate: left colon and ascending colon, if the ASA fail use steroids
- Sever: entire colon , corticoids
- If corticoids fail start with Immunomodulators

Immunomodulators

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

Immunomodulators include:

- **Methotrexate (inhibits folic acid → inhibition of purine and pyrimidine synthesis→ inhibition of T cells DNA synthesis → weakness of immune system)**
- **Purine analogs:**

(azathioprine & 6-mercaptopurine).

Purine analogs (azathioprine & 6-mercaptopurine)

Azathioprine

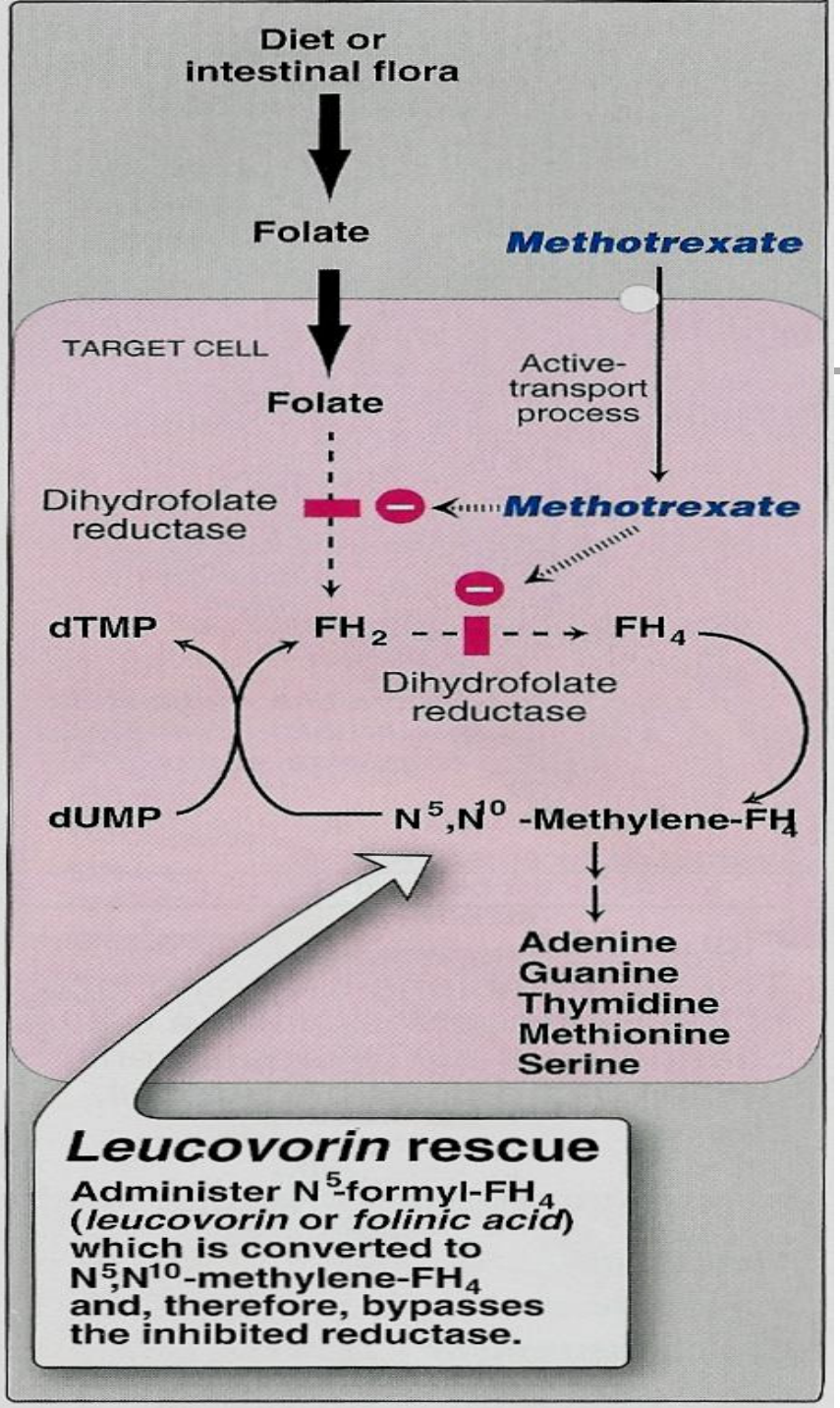
- is a pro-drug of 6-mercaptopurine
- Inhibits purine synthesis
- Induction and maintenance of remission in IBD

Adverse effects:

- **Bone marrow depression: leucopenia, thrombocytopenia.**
- **Gastrointestinal toxicity.**
- **Hepatic dysfunction.**
- **Complete blood count & liver function tests are required in all patients**

Methotrexate

- a folic acid antagonist
- Inhibits dihydrofolate reductase required for folic acid activation
- Orally, S.C., I.M. (7.5 mg/week)
- Used to induce and maintain remission in inflammatory bowel diseases.
- Rheumatoid arthritis
- Cancer



MOA:

- Folic acid is taken by cells and then converted into FH2 by dihydrofolate reductase, then dihydrofolate form is converted into FH4 which produce Methylene-FH4 which in turn produces purine and pyrimidine.
- When methotrexate inhibit dihydrofolate reductase the purine and pyrimidine synthesis is blocked.
- To protect other body cells we give leucovorin along side with methotrexate(which means methotrexate has a selective toxicity on lymphocytes)

Adverse effects of methotrexate

- Bone marrow depression(patient mat need blood transfusion)
- Megaloblastic anemia
- Ulcers because it affects the mucus membrane of the entire gut
- Liver fibrosis

Monoclonal antibodies used in IBD (TNF-α inhibitors)

- **Infliximab**
- **Adalimumab**
- **Certolizumab**

It is important to differentiate between Infliximab and adalimumab like is it against human or animal TNF ? which one causes allergy ? route of administration and antigenicity for each one.

Infliximab

- a chimeric mouse-human monoclonal antibody
- 25% murine – 75% human.
- TNF-α inhibitors
- Inhibits soluble or membrane –bound TNF-α located on activated T lymphocytes
- Given intravenously as infusion (5-10 mg/kg).
- has long half life (8-10 days) (very slow effect and long duration)
- 2 weeks to give clinical response

Regarding to infliximab for easer remembering

- Inf : IV infusion
- F: فأر (mouse) chimeric mouse-human monoclonal antibody . It’s a mix between antibodies against mouse and human TNF which means it may cause allergic reaction (because of 25% antibodies against mouse TNF)

Uses of infliximab

- **In moderate to severe active Crohn's disease and ulcerative colitis** (if the 3 drugs that was mentioned before fail)
- **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).***
- **Delayed infusion reaction *(serum sickness-like reaction, in 5% of patients).***
- **Pretreatment with diphenhydramine (antihistamin), acetaminophen, corticosteroids is recommended.**

Side effects (Cont.)

- **Infection complication *(Latent tuberculosis, sepsis, hepatitis B).***
- **Loss of response to infliximab over time *due to the development of antibodies to infliximab***

و دي بتحدث لما بتبئى دكتور مكلكع و ألبك أسود أوي

- **Severe hepatic failure.**
- **Rare risk of lymphoma.**
- **It’s only used when the patient is under monitoring**

Adalimumab (HUMIRA)

- Fully humanized (no allergy) IgG antibody to TNF-α
- Adalimumab is TNFα inhibitor
- It binds to TNFα that located in the blood only, preventing it from activating TNF receptors
- Has an advantage that it is given by subcutaneous injection
- is approved for treatment of, moderate to severe Crohn's disease, rheumatoid arthritis, psoriasis.

Summary for drugs used in IBD

5-aminosalicylic acid compounds

- **Azo compounds:**
  sulfasalazine, olsalazine, balsalazide
- **Mesalamines:**
  Pentasa, Asacol, Rowasa, Canasa

Glucocorticoids

prednisone, prednisolone, hydrocortisone, budesonide

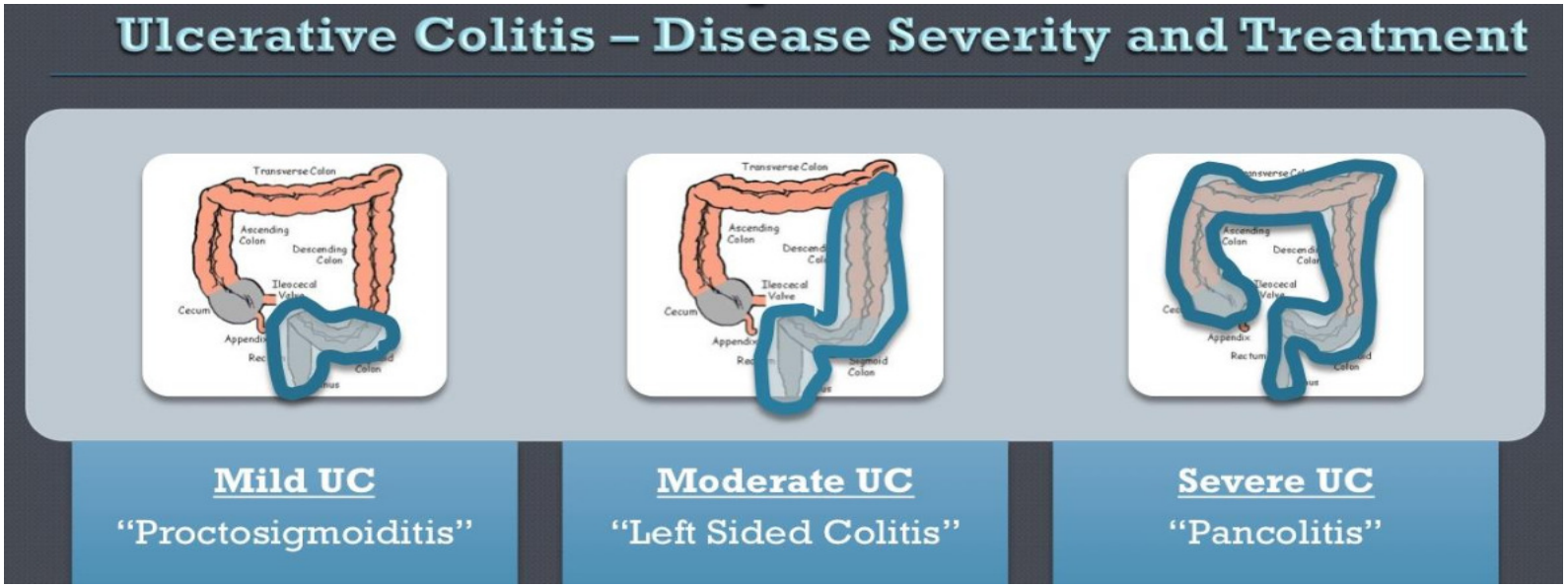
Immunomodulators

- **Methotrexate**
- **Purine analogues:**
  - **Azathioprine &6-mercaptopurine**

TNF-alpha inhibitors (monoclonal antibodies)

- **Infliximab – Adalimumab - Cetrolizumab**

Ulcerative Colitis- Management



a) **Topical** aminosalicylate alone (suppository or enema
b) ?ADD **PO** aminosalicylate to a topical aminosalicylate OR
c) consider an **PO** aminosalicylate alone

a) **PO** Aminosalicylate
- High induction dose of an
b) ?ADD **topical** Aminosalicylate OR **PO** beclometasone dipropionate

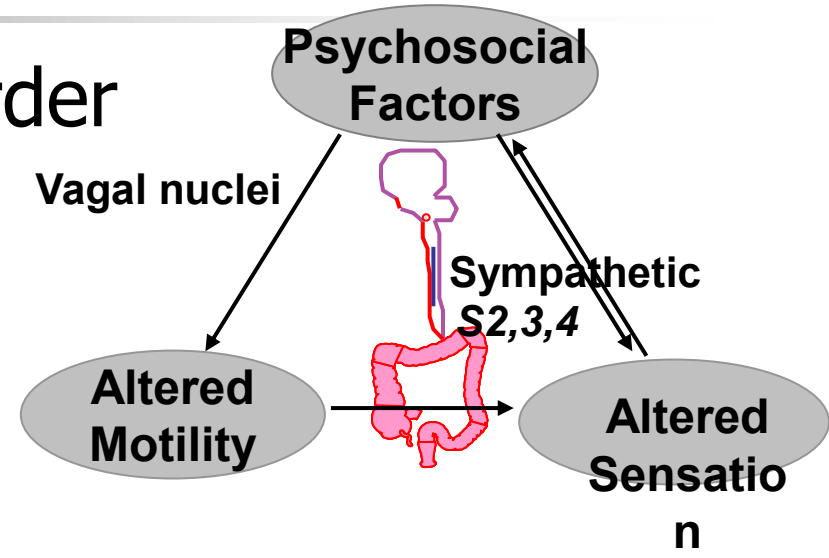
- If no improvement 72 hrs despite **IV** Hydrocortisone OR
-Symptoms worsen to pancolitis:

a) ADD **IV** Ciclosporin (immune suppressive) to **IV** steroids

The colon contains a very sensitive sensory factors causes a colon changes due to bio psychosocial factors

Irritable Bowel Syndrome

- Biopsychosocial Disorder
  - Psychosocial
  - Motility
  - Sensory
  - ? Infectious



- Visceral hypersensitivity

- Increased visceral afferent response to normal as well as noxious stimuli
- Mediators include 5-HT, bradykinin, tachykinins, CGRP, and neurotropins

Regarding to the Mediators

- the most important mediator is serotonin which increases smooth muscle contraction :
- ✓ Give serotonin agonist in constipation state
- ✓ Give serotonin antagonist for diarrheal state

- You can give anticholinergic drugs and sedatives to calm the patient

IBS

Hallmark symptoms of IBS

- **Affects predominantly females (~70% of sufferers) Chronic or recurrent GI symptoms**
  - lower abdominal pain/discomfort
  - altered bowel function (urgency, altered stool consistency, altered stool frequency, incomplete evacuation)
  - bloating
- **Not explained by identifiable structural or biochemical abnormalities**
- **It's not infectious, this was proven by it's non infectious diarrhea (lacks mucus and blood , fever . Only consists of watery diarrhea)**

Currently available Rx treatments for IBS

- Dicyclomine HCl (anticholinergic)
- Hyoscyamine sulfate (± other anticholinergic/sedatives)
- Belladonna(atropine -like) and phenobarbital(sedative)
- Clidinium bromide(anti-cholinergic)with chlordiazepoxide (anxiolytic)… the most commonly used
- Tegaserod (serotonin 4 receptor (5-HT4) agonist) :can cause CVD
- Alosetron (5-HT3 antagonist (serotonin receptor)) can cause ischemic disorders

Multiple medications needed to treat multiple symptoms

	Lower abdominal pain	Bloating	Altered stool form	Altered stool passage	Urgency
Anticholinergics	X	X			
Tricyclic antidepressants and SSRIs	X				
Antidiarrheals			X	X	X
Bulking agents	X		X	X	
Laxatives			X	X	

-Tricyclic is used as pain killer in neurogenic pain

- don't use paracetamol or ibuprophin to relieve the pain even morphine is not used to kill the pain because in this case neuropathy is the cause of this pain , not a side effect

Tegaserod (serotinin 4 receptor agonist)

- Approved for constipation predominant IBS
- 1 pill given twice daily
- Improvement of symptoms in women but not men
- Use up to 12 weeks
- Mild side effects: diarrhea the most prominent side effect


Any Questions ?