

Chronic Bowel Diseases

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- ★ أولى الناس بي
- ★ يوم القيامة
- ★ أكثرهم علي صلاة .
- ★



* Chronic bowel diseases: diseases that affect colon and intestine.

* chronic Inflammatory bowel disease. (caused by inflammation, no exact cause, but it may related to autoimmune mechanism)

structure
Mucosa, submucosa, and muscularis

Malabsorption

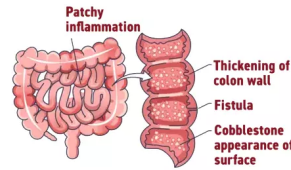
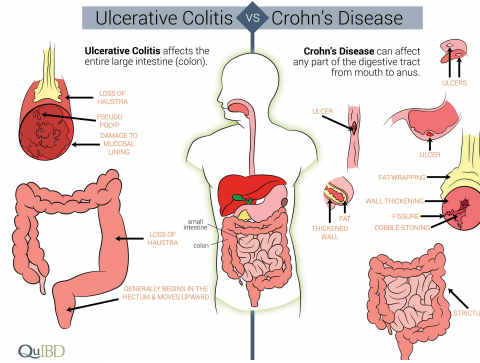
(Some sort of intoxication) + fever + (TNF, IL) \rightarrow cause ulcers or patches in mucosa. Large int. mainly

Ulcerative colitis

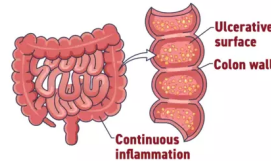
1- Ulcerative colitis: من بداية anal canal and rectum الى السعوم

2- Crohn's disease: from mouth to the terminal part of ileum.

Crohn's disease



Crohn's Disease



Ulcerative Colitis



* Any inflammatory disease caused by autoimmune we give the patient (Cortico Steroids) to suppress the immune response.
كيفية إخماد المناعة يكون على صيغتين رئيسيتين .

* if there is an acute attack by inflammatory bowel..... give them:

- 1- Aminosalicylates
↳ Powerful Anti-inflammatory
↳ Effective like NSAIDs
- 2- Corticosteroids
↳ powerful anti-inflammatory
↳ " immunosuppressant

* to avoid recurrence, give the patient on long run

Immunosuppressive agents like

- azathioprine
- 6mercaptopurine
- tacrolimus

In this lecture, our study will focus on ASA.

Chronic inflammatory bowel disease (IBD) includes: (ulcerative colitis & Crohn's disease).

- **Corticosteroids:** prednisolone.
- **Immunosuppressive agents:** azathioprine , 6mercaptopurine.
- **Aminosalicylates.**



أفوك الصفر (الجراسه أفرن)
لازم أبعث فيه هذا أنا أربع معه عشان
ما يضيح...

Aminosalicylates

Up to 80% of unformulated, aqueous 5-

80% من غير الـ
Absorption

ASA is absorbed from the small intestine & does not reach the distal small bowel or colon in appreciable quantities.

- Azo compounds:

الأخو البجر الذي عاش بالبلاد
like sulfapyridine

5-ASA bound by an azo ($N=N$) bond to an inert compound or to another 5-ASA molecule.

Azo markedly reduces absorption of the parent drug from the small intestine.

In terminal ileum & colon, bacteria cleave the azo bond by azoreductase, releasing the active 5-ASA.

- **Sulfasalazine:** (5-ASA “Active moiety” + Sulfapyridine “side effects”).

- **Olsalazine:** (two molecules of 5-ASA).

- **Balsalazide:** (5-ASA + 4-aminobenzol- β -alanine).

preparations of ASA → pharmaceutical preparations تحفزة

Mesalamine compounds

Package of 5-ASA itself in various ways to deliver it to different segments of the small or large bowel.

Pentasa: ^{بتمفتح بعد ٦ ساعات حتى يكون داخل الـ colon} contains timed-release microgranules that release 5-ASA throughout the small intestine.

Asacol: has 5-ASA coated in pH-sensitive resin that dissolves at pH 7 (the pH of the distal ileum & proximal colon).

Rowasa ^{حقنة شرجية} (enema formulations) &

Canasa (suppositories): To deliver high concentration of 5-ASA to the rectum & sigmoid colon.



Pharmacokinetics:

Mesalamine:

20-30% of 5-ASA is absorbed. So, there will be (80-70)% working at the site of action.
So, has no action → by N-acetyl transferase

5-ASA undergoes N-acetylation in the liver and gut epithelium. *So, becomes active by N-acetyl transferase*

Metabolite is excreted by the kidneys.

Sulfasalazine

هم المذنبين

الاحتكاك فيه تكون في
sulterpyridine

adverse effects: severe reaction

- 10% is absorbed.
- After azoreductase, $>85\%$ of sulfapyridine is absorbed.
- Sulfapyridine undergoes hepatic metabolism.
- Metabolite is excreted by the kidney.

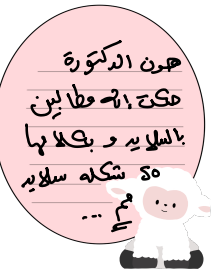
Balsalazide:

- <1% is absorbed.
- After azoreductase, small amount of systemic absorption occurs.

Mechanism of action

- ✓ 5-ASA inhibits inflammatory mediators derived from both the cyclooxygenase & lipoxygenase pathways.
- ✓ Interferes with the production of inflammatory cytokines.
- ✓ Inhibits the activity of nuclear factor- κ_B (NF- κ_B), an important transcription factor for pro-inflammatory cytokines.
- ✓ Inhibits cellular functions of natural killer cells, mucosal lymphocytes, and macrophages.
- ✓ It may scavenge reactive oxygen metabolites.

ASA لا تعمل إلا موضعيًا ... بترجع مكان معين ... يسهل الـ activation وهو مكان آخر له activation في الأمعاء لا
• liver
* لا يسهل active ← بترجع عمل PPAR-gamma (وهو عبارة عن Nuclear rec) جواً إلى فيها (lesion)
(تعللة)



مسؤولة عن inflammatory response .

ASA يثبط suppression له receptor ، وبالتالي يمنع

gene expression of inflammatory mediators . like : 1- NF- κ B 2- Cox, Lox pathway
3- TNF 4- ILs 5- Natural killer cells

کیونکہ بہتر ہے

Therapeutic uses

ASA بڑا ہے severe → corticosteroids

1. First-line agents for treatment of mild to moderate active ulcerative colitis
2. Crohn's disease involving the small bowel
mesalamine compounds, which release 5-ASA in the small intestine, have the advantage over azo compounds.
من ایلائیوم لیباریڈس
cecum
pH = 7
+ time released
3. Ulcerative colitis or Crohn's colitis that extends to the proximal colon, both azo & mesalamine compounds are useful.
ascending + descending + transverse
سگموئیل
4. Ulcerative colitis or Crohn's disease confined to the rectum or distal colon, suppositories or enema are useful.
+ sigmoid

بعد میں داخل ہائیڈروکسی وٹامین ڈی ۵
نفع و شکل اسرار

Adverse effects

Sulfasalazine (→ sulfapyridine) has high incidence of side effects, >40% cannot tolerate therapeutic doses:

1. ^{سبب} **GIT** ^{سبب} **upset**, headache, arthralgia, bone marrow suppression & malaise
2. Hypersensitivity (fever, exfoliative dermatitis, pancreatitis, pneumonitis, hemolytic anemia, pericarditis, or hepatitis).
3. ^{تزداد بآثاره الدواء} **Reversible oligospermia** ^{الرجوع}
4. Impairs folate absorption

Sulfasalazine reduces folate absorption → risk of megaloblastic anemia; folic acid supplementation may be needed.
يقلل امتصاص الفوليك جزئياً، لذا تعويضه
بمكملات فوليك بجرعة أعلى يعوّض النقص



Other aminosalicylate formulations

Are well tolerated:

دفع داء

Olsalazine may cause secretory diarrhea (10%). Hypersensitivity (rare).

Interstitial nephritis (rare, high doses of **mesalamine**).

المقرون الطبي

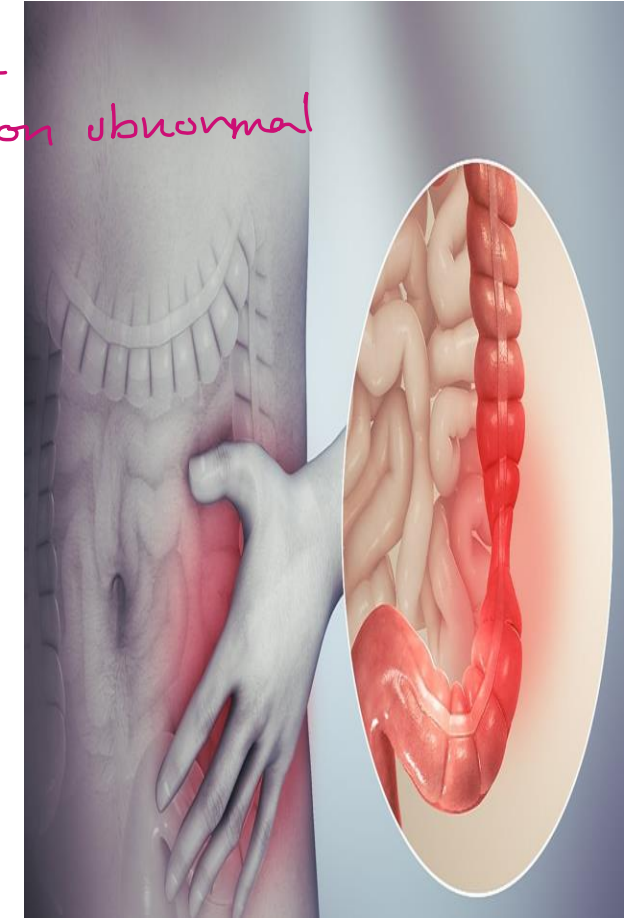
Irritable bowel syndrome: IBS

Idiopathic chronic, relapsing disorder, characterized by:

- ① Abdominal discomfort (pain, bloating, distention, or cramps).
- ② Alteration of bowel habits (diarrhea, constipation, or both).

Goal of therapy: Relieving abdominal pain, discomfort with improving bowel function.

Normal structure but the function abnormal



Non-pharmacological
أهم ما ينبغي أن نأخذ به هذا الشخص - يبعد عن المجهجات ونسكن تناول الألياف
الفيت - بـ fibers ← كمنع د فبر أسير مثلاً (من عندي)

^{dominant} A-Predominant diarrhea (Diarrhea-predominant IBS):

- Anti-diarrheal agents, loperamide. *Agonist opioid, works on μ receptors in GIT and decreasing motility.*
- Alosetron (5-HT₃ antagonist): for women with severe diarrhea-predominant IBS. *لتقليل motility*
- 5-HT₃ antagonist.
- Binds with higher affinity and dissociates more slowly from 5-HT₃ R than other 5-HT₃ antagonists (long duration).
- **Uses:** Women with severe irritable bowel syndrome with diarrhea.
- **Dose :** 1mg once or twice daily.

Side effects of Alosetron:

Rare but serious G.I.T. toxicity may occur:

Constipation (↑30%).

Episodes of ischemic colitis (3 per 1000). Restricted to women with severe diarrhea-predominant IBS.



B-Predominant constipation (Constipation-predominant IBS)

- Fiber supplements (however, ↑gas production may exacerbate bloating and abdominal discomfort).
- Osmotic laxatives, *milk of magnesia*. Never give them stimulant laxatives ... (work on function) في الجزء الثاني
- *Tegaserod* (partial 5-HT₄ agonist). ↑↑ motility ↑↑ motility

For short-term treatment of women with constipation-predominant IBS.

C- Chronic abdominal pain:

- Low doses of Tricyclic antidepressants TCAs (amitriptyline or desipramine, 10-15mg/d). محاولة تغيير function of GIT
- At these doses, these agents have no effect on mood but may alter central processing of visceral afferent information.
- Anti-cholinergic effects → reduce stool frequency & liquidity of stool.
- Alter receptors for enteric neurotransmitters such as serotonin, affecting visceral afferent sensation.

4) Spasmolytics (Antispasmodics):

Parasympathetic depressants:

○ Atropine.

○ Atropine substitutes:

Propantheline.

Hyoscine-N-butyl bromide (Buscopan).

Metixene (Spasmocanulase).

Dicyclomin&hyoscyamine (inhibit M receptors in enteric plexus & on smooth muscle).

anticholinergic effect
↓
reduce spasm
+
هناك
hapi



Direct spasm Volatile

Volatiles oils.

Khellin.

Papaverine.

Aminophylline.

Nitrites.

Mebeverine (Colspasmin).





THANK YOU