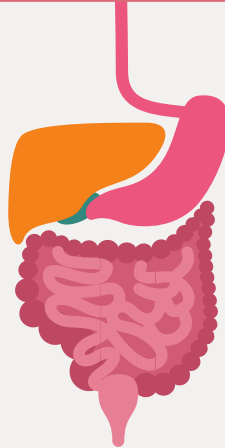


Drugs used in inflammatory bowel disease



Done by:

Editing file

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● Drugs names ● Doctors notes ● Important ● Extra

« **بأدلاً وسعي** في استنقاذها من الهلاك والمرض، والألم والقلق »

Mind map

Treatment of IBD

**5-amino salicylic acid compounds
(5-aminosalicylates)**

Azo compounds:
Sulfasalazin (Azulfidine),
Balsalazide & Olsalazine

Mesalamines:
Asacol, Pentasa, Canasa
& Rowasa

Glucocorticoids

Oral preparation:
Budesonide, prednisone &
prednisolone

Parenteral preparation:
hydrocortisone, methyl
prednisolone

Rectal preparation:
Hydrocortisone

Immunomodulators

Methotrexate

Purine analogs:
azathioprine & 6-
mercaptopurine

**Biological therapy
(TNF- α inhibitors).**

**Infliximab, Adalimumab &
Certolizumab pegol
(Cimzia)**

**Surgery in severe
condition**

To understand better

Inflammatory Bowel Diseases (IBD)

A group of inflammatory conditions of the small intestine and colon.

Symptoms

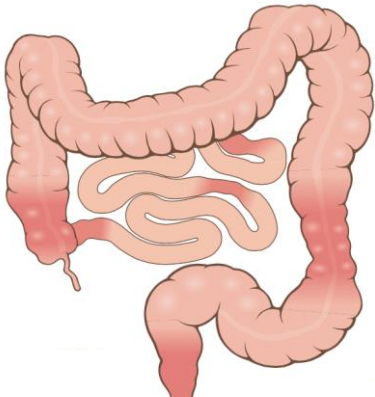
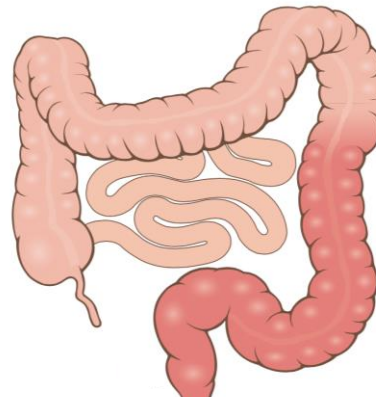
Abdominal pain - Vomiting - Diarrhea - Rectal bleeding - Weight loss

Causes

- Not known.
- Auto-immune disorder due to abnormal activation of the immune system.
- The susceptibility is genetically inherited.

Complications

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

Types of IBD	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	May be transmural, deep into tissues	Shallow, mucosal
Complications	Strictures, Obstruction Abscess, Fistula	Toxic megacolon Colon cancer
		

Treatment of IBD

Goals of therapy

Achievement of remission (**Induction**)

Prevention of disease flares* (**maintenance**)

* Flares: episodic attack

Stepwise therapy:

في طريقة العلاج، لازم نمشي خطوة بخطوة (حسب ما هو مرقم هنا) إذا ما نفع الأول نروح للثاني، وإذا ما نفع الثاني نروح للثالث وهكذا...
ليش طبيب؟ لأننا نمشي من الدواء الأقل ADRs إلى الدواء الأكثر ADRs

1

- 5-amino salicylic acid compounds (5-ASA) or aminosalicylates.

2

- Glucocorticoids.

3

- Immunomodulators.

4

Biological therapy (TNF- α inhibitors).

5

- Surgery in severe conditions. → if all drugs above fail.

5-amino salicylic acid compounds (5-ASA)

1- Aminosalicylates

Mech. of action	<ul style="list-style-type: none">○ Have topical anti-inflammatory action due to:<ul style="list-style-type: none">• Inhibition of prostaglandins and leukotrienes.• Decrease neutrophil chemotaxis.• Antioxidant activity (scavenging free radical production).○ They produce their effect locally (Those drugs have to come in contact with the inflamed area to produce effect)○ The exact mechanism is unknown but overall they inhibit the inflammatory process.○ All aminosalicylates are used for induction and maintenance of remission
P.K	<ul style="list-style-type: none">○ 5-ASA itself is absorbed from the proximal small intestine. → بهذي الحالة ما راح نستفيد من الأكشن حقه لأنه ما سواه على مكان الالتهاب! طيب إيش أسوي؟○ Different formulations are used to overcome rapid absorption of 5-ASA from the proximal small intestine.

aminosalicylates

Different formulations of aminosalicylates

Azo compounds

- Sulfasalazine
- Balsalazide
- Olsalazine

Mesalamines

- Asacol
- Pentasa
- Canasa
- Rowasa

The major differences are in **mechanism** and **site** of delivery.

هنا الغرض من هذي المركبات، إننا زدناها على 5-ASA عشان يقلل أو يؤخر الامتصاص ونوصله لمكان الالتهاب ☺

Aminosalicylates (cont.)

Azo compounds

Characteristics

- These compounds contain (5-ASA) that is connected by **azo bond (N=N)**:
 - To sulfapyridine moiety (**Sulfasalazine**):
 - ✓ **Sulfasalazine** = 5-ASA + **sulphapyridine**
 - To another molecule of 5-ASA (**Olsalazine**):
 - ✓ **Olsalazine** = 5-ASA + **5-ASA**
 - To inert compound (**Balsalazide**):
 - ✓ **Balsalazide** = 5-ASA + **inert carrier** (doesn't have ADRs)
- Azo structure **reduces absorption** of 5-ASA in small intestine.
- In **the terminal ileum and colon**, azo bond is **cleaved** by **azoreductase enzyme** produced by **bacterial flora** releasing **5-ASA** in the terminal ileum and colon.

الأدوية المحتوية على sa
هنا، يعني محتوية على
5-ASA

Sulfasalazine

أشهر واحد في 5-ASA formulations

P.K

- **Pro-drug** → bc it has to be splitted to produce its action.
 - A combination of **5-ASA + sulfapyridine**
 - Is given **orally (enteric coated tablets)**.
 - Little amount is absorbed (10%)
- In the terminal ileum and colon, **sulfasalazine** is **broken** by **azoreductase** into:
- **5-ASA** (not absorbed, active moiety acting locally).
 - **Sulphapyridine** (absorbed, **causes most of side effects**) → bc it is absorbed, it will produce a lot of ADRs.

MOA

- 5-ASA has **anti-inflammatory** action due to: (Again it's the same of 5-ASA)
 - **Inhibition of prostaglandins and leukotrienes.**
 - **Decrease neutrophil chemotaxis.**
 - **Antioxidant activity (scavenging free radical production).**

ADRs

- (1) **Crystalluria.**
- (2) Bone marrow depression
- (3) Folic acid deficiency (**should be provided**) → **Megaloblastic anemia** → That means we give it as supplement.
- (4) **Impairment of male fertility (Oligospermia).**
- (5) **Interstitial nephritis (The only side effect due to 5-ASA).**
→ Others are due to the **sulphapyridine**

Aminosalicylates (cont.)

Mesalamine compounds

- Formulations that have been designed to deliver 5-ASA in **terminal small bowel & large colon**.
- **Mesalamine** formulations are: **Sulfa free**, well tolerated →
 - **Have less side effects compared to sulfasalazine**
 - **Useful in patient sensitive to sulfa drugs.**

ORAL formulation

RECTAL formulations

- Releases **5-ASA** in the **distal small bowel** secondary to **pH** changes. → they release it in alkaline pH, stomach is acidic, therefore they won't release 5-ASA.
- Releases start at the **pylorus** and continues throughout the small bowel and **colon**.
- **Asacol**: 5-ASA coated in **pH-sensitive** resin that dissolves at pH 7 (**alkaline**).



Asacol is **not cool** so it's pH sensitive

- **Pentasa**: micro granules that **release 5-ASA** throughout the small intestine.

→ what is the control factor here (make it release 5-ASA)?

It is the **Time**. يعني هم مسويينه على أساس ما يطعم اللي داخله إلا بعد ٣س مثلا



بنت يعني شيء صغير وكيوت فيعني (micro granules)

- Release 5-ASA in the **distal colon**.

- **Canasa (suppositories)**
*suppository is a solid dosage form that is inserted into the rectum

- **Rowasa (enema)**
*enema is a procedure in which liquid or gas is injected into the rectum.

Clinical uses of 5-amino salicylic acid compounds

- **Induction** (treat acute conditions) and **maintenance** (prophylaxis) of remission in mild to moderate IBD (**First line of treatment**).
- Rheumatoid arthritis (**Sulfasalazine only**).
- **Rectal formulations** are used in **distal ulcerative colitis**, ulcerative proctitis and proctosigmoiditis.

2- Glucocorticoids

Drug	Oral: Prednisone, Prednisolone	Parenteral: Hydrocortisone, Methyl prednisolone	Rectal: hydrocortisone	Budesonide
Characteristics	<ul style="list-style-type: none"> - Higher rate of absorption. - More adverse effects compared to rectal administration. 		<ul style="list-style-type: none"> - As enema or suppository, give topical effect. - Less absorption rate than oral. - Minimal side effects and maximum tissue effects. → preferable. 	<p>A potent synthetic prednisolone analog.</p> <p>P.K</p> <ul style="list-style-type: none"> - Given orally (controlled release tablets) so release drug in ileum and colon. - Low oral bioavailability (10%) → ميزة إذا ما ألبيه يسوي سايد إفكتس كثيرة
MOA	<ul style="list-style-type: none"> - Inhibits phospholipase A2. - Inhibits gene transcription of NO synthase, cyclo-oxygenase-2 (COX-2) - Inhibits productions of inflammatory cytokines. 			
Indications	<ul style="list-style-type: none"> - Acute flares of disease (moderate to severe active IBD) → Used only in the treatment, <u>not</u> prophylaxis! In the prophylaxis use → 2-ASA - NOT useful in maintaining remission (NOT effective as prophylactic therapy) - Asthma → bc it inhibits leukotrienes. - Rheumatoid arthritis. - Immunosuppressive drug for organ transplants. - Antiemetic during cancer chemotherapy. 		<p>Treatment of active mild to moderate Crohn's disease involving ileum and proximal colon.</p>	
	Oral glucocorticoids	Rectal glucocorticoids		
	Commonly used in active conditions.	Preferred in IBD involving rectum or sigmoid colon.		
ADRs	-		<p>Is subject to extensive first pass metabolism. → ميزة إذا ما ألبيه يسوي سايد إفكتس كثيرة</p>	

3- Immuno-modulators

Drug	<p>Methotrexate</p>	<p><u>Purine analogs:</u> Azathioprine, 6-mercaptopurine</p>
Mech. of action	<ul style="list-style-type: none"> ○ A folic acid antagonist. ○ Inhibits dihydrofolate reductase required for folic acid activation (tetrahydrofolate) ○ Impairs DNA synthesis. ○ Diagram explain it 	<ul style="list-style-type: none"> ○ Azathioprine is a pro-drug of 6-mercaptopurine. ○ Inhibit purine synthesis and inhibits synthesis of DNA, RNA, and proteins. ○ It may decrease proliferation of immune cells, which lowers autoimmune activity.
P.K	<ul style="list-style-type: none"> ○ Orally, S.C, I.M. 	
Indications	<ul style="list-style-type: none"> ○ They are used to induce (treat the acute condition) and maintain (prevent) remission in IBD in active and moderate-to-severe conditions or steroid dependent or steroid resistant (refractory=not responding) patients. 	
	<ul style="list-style-type: none"> ○ Inflammatory bowel disease. ○ Rheumatoid arthritis. ○ Cancer 	
ADRs	<ul style="list-style-type: none"> ○ Megaloblastic anemia → bc it inhibits folic acid activation ○ Bone marrow depression. 	<ul style="list-style-type: none"> ○ Bone marrow depression: leucopenia, thrombocytopenia. ○ Gastrointestinal toxicity. ○ Hepatic dysfunction → <u>Complete blood count and liver function tests are required in all patients.</u>

4- Monoclonal antibodies (TNF- α inhibitors)

Drug	Infliximab	Adalimumab (HUMIRA)	Certolizumab pegol (Cimzia)
Drug	<ul style="list-style-type: none"> Mabs is the acronym for monoclonal antibodies (protein) Any drug with suffix mab it is not given orally because antibodies are sensitive to acidity → given by injection! Not used as prophylaxis. 		
Mech. of action	<ul style="list-style-type: none"> A chimeric mouse-human monoclonal antibody (25% murine 75% human) Inhibits soluble or membrane bound TNF-α located on activated T lymphocytes 	<p>Fully humanized IgG antibody to TNF-α</p> <ul style="list-style-type: none"> It binds to TNFα preventing it from activating TNF receptors. (TNFα inhibitor). 	<ul style="list-style-type: none"> Fab fragment (is a region on an antibody that binds to antigen) of a humanized antibody directed against TNF-α Attached to polyethylene glycol to increase its half-life in circulation.
P.K	<ul style="list-style-type: none"> Given intravenously as infusion (infiximab=infusion) (5-10 mg/kg) Has long half life (8-10 days) 2 weeks to give clinical response (delayed onset of action) 	<p>Given by subcutaneous injection (<u>advantage</u>)</p>	<p>Given subcutaneously</p>
Uses	<ul style="list-style-type: none"> In moderate to severe active Crohn's disease and ulcerative colitis Patients not responding to immunomodulators or glucocorticoids. Treatment of rheumatoid arthritis Psoriasis. 	<ul style="list-style-type: none"> Approved for treatment of: moderate to severe Crohn's disease, Rheumatoid arthritis Psoriasis 	<p>for the treatment of: Crohn's disease rheumatoid arthritis</p>

- **Side effects of Infiximab:** (a lot of side effects that's why it is the last choice)

- 1) Acute adverse infusion reactions (**Allergic reactions** or anaphylaxis in 10%) or Delayed infusion reaction (**serum sickness-like reaction** in 5% of patients)
Pretreatment with **diphenhydramine, acetaminophen, corticosteroids** is recommended (to prevent the infusion reaction)
- 2) **Infection complication** (**Latent tuberculosis, sepsis, hepatitis B**)
- 3) Loss of response to **infiximab** over time
(due to the development of antibodies to **infiximab** → لأن جزء من مكوناته حيوانية تختلف عن الإنسان)
- 4) **Severe hepatic failure.**
- 5) Rare risk of **lymphoma** (with all immunosuppressant drugs)

Summary-1

5-aminosalicylic acid compounds	Azo compounds: sulfasalazine, olsalazine, balsalazide
	Mesalamines: Pentasa, Asacol, Rowasa, Canasa
Glucocorticoids	prednisone, prednisolone, hydrocortisone, budesonide
Immunomodulators	Methotrexate Purine analogues: Azathioprine & 6mercaptopurine
TNF-alpha inhibitors (monoclonal antibodies)	Infliximab, Adalimumab, Cetrolizumab

Aminosalicylates (5-ASA)

MOA	Have topical anti-inflammatory action due to: <ul style="list-style-type: none"> inhibition of prostaglandins and leukotrienes. decrease neutrophil chemotaxis. Antioxidant activity (scavenging free radical production). 		
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Formula	Azo compounds	Mesalamines		
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Sulfasalazine (5-ASA+Sulfapyridine)	Asacol	Pentasa	Canasa	Rowasa
oral	oral		rectal	
			suppositories	enema

Site of release	cleaved by azoreductase enzyme releasing 5-ASA in the terminal ileum and colon .	Releases start at the pylorus and continues throughout the small bowel and colon	release 5-ASA in the distal colon.
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ADRs	<ul style="list-style-type: none"> Crystalluria. Bone marrow depression Megaloblastic anemia. Folic acid deficiency (should be provided). Impairment of male fertility (Oligospermia). Interstitial nephritis due to 5-ASA. 	Advantages <ul style="list-style-type: none"> Sulfa free well tolerated have less side effects compared to sulfasalazine useful in patient sensitive to sulfa drugs.
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uses	<ul style="list-style-type: none"> Induction and maintenance of remission in mild to moderate IBD (First line of treatment). Rheumatoid arthritis (Sulfasalazine only). Rectal formulations are used in distal ulcerative colitis, ulcerative proctitis and proctosigmoiditis.
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Summary-2

Glucocorticoids

Budesonide

MOA	<ul style="list-style-type: none">• Inhibits phospholipase A2.• Inhibits gene transcription of NO synthase, cyclo-oxygenase-2 (COX-2).• Inhibit production of inflammatory cytokines.
Indications	<ul style="list-style-type: none">• for acute flares of disease (moderate –to- severe active IBD).• not useful in maintaining remission (not effective as prophylactic therapy).• Oral glucocorticoids is commonly used in active condition.• Rectal glucocorticoids are preferred in IBD involving rectum or sigmoid colon.• Asthma• Rheumatoid arthritis• immunosuppressive drug for organ transplants• Antiemetic during cancer chemotherapy

Immunomodulators

	Purine analogues(azathioprine&6-mercaptopurine)	Methotrexate
MOA	<ul style="list-style-type: none">• Inhibit purine synthesis and inhibits synthesis of DNA, RNA, and proteins.• It may decrease proliferation of immune cells, which lowers autoimmune activity.	<ul style="list-style-type: none">• a folic acid antagonist• Inhibits dihydrofolate reductase required for folic acid activation (tetrahydrofolate)• Impairs DNA synthesis
Indications	<p>Induction and maintenance of remission in IBD</p>	<ul style="list-style-type: none">• Used to induce and maintain remission.• Inflammatory bowel disease• Rheumatoid arthritis• Cancer
ADRs	<ul style="list-style-type: none">• Bone marrow depression: leucopenia, thrombocytopenia.• Gastrointestinal toxicity.• Hepatic dysfunction.• Complete blood count & liver function tests are required in all patients	<ul style="list-style-type: none">• Megaloblastic anemia• Bone marrow depression

Summary-3

Biological therapy (TNF-a inhibitors)

	infliximab	adalimumab	certolizumab
	<p>a chimeric mouse-human monoclonal antibody.</p> <p>(IV infusion)</p>	<p>Fully humanized IgG antibody to TNF-a</p> <p>(Subcutaneous)</p>	<p>Fab fragment of a humanized antibody directed against TNF-a</p> <p>(Subcutaneous)</p>
MOA	Inhibits soluble or membrane –bound TNF-a located on activated T lymphocytes.	It binds to TNF-a, preventing it from activating TNF receptors	
Indications	<ul style="list-style-type: none"> In moderate to severe active Crohn's disease and ulcerative colitis. Patients not responding to immunomodulators or glucocorticoids. Treatment of rheumatoid arthritis Psoriasis 	<ul style="list-style-type: none"> is approved for treatment of, moderate to severe Crohn's disease, rheumatoid arthritis, psoriasis. 	<p>Given subcutaneously for the treatment of Crohn's disease & rheumatoid arthritis</p>
ADRs	<ul style="list-style-type: none"> 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). Infection complication (Latent tuberculosis, sepsis, hepatitis B). 		

MCQs

1- In which drug routine complete blood count and liver function tests are required?

- A- Methotrexate
- B- Azathioprine
- C- Adalimumab
- D- budesonide

2- A patient suffering from prostate cancer and he is also having IBD which one of the following is the drug of choice?

- A- Methotrexate
- B- Infliximab
- C- Azathioprine

3- A 84 years old was diagnosed with IBD, after some investigations the doctor found that his proximal colon and ileum were affected which drug of these is best to be used?

- A- Cimzia
- B- Azathioprine
- C- Budenonide
- D- Pentasa

4- Which of the following drugs that cause allergic reaction?

- A- Adalimumab
- B- Infliximab
- C- Certolizumab

5- Which of the following side effects is a result of treatment rheumatoid arthritis using infliximab?

- A- Glaucoma
- B- Vomiting
- C- Activation of latent tuberculosis

Thank you for checking our team!



Pharmacology 435

 @pharmacology435

Sources:

1. 435's slides.
2. Pharmacology (Lippincotts Illustrated Reviews Series), chapter 39, 5th edition.