

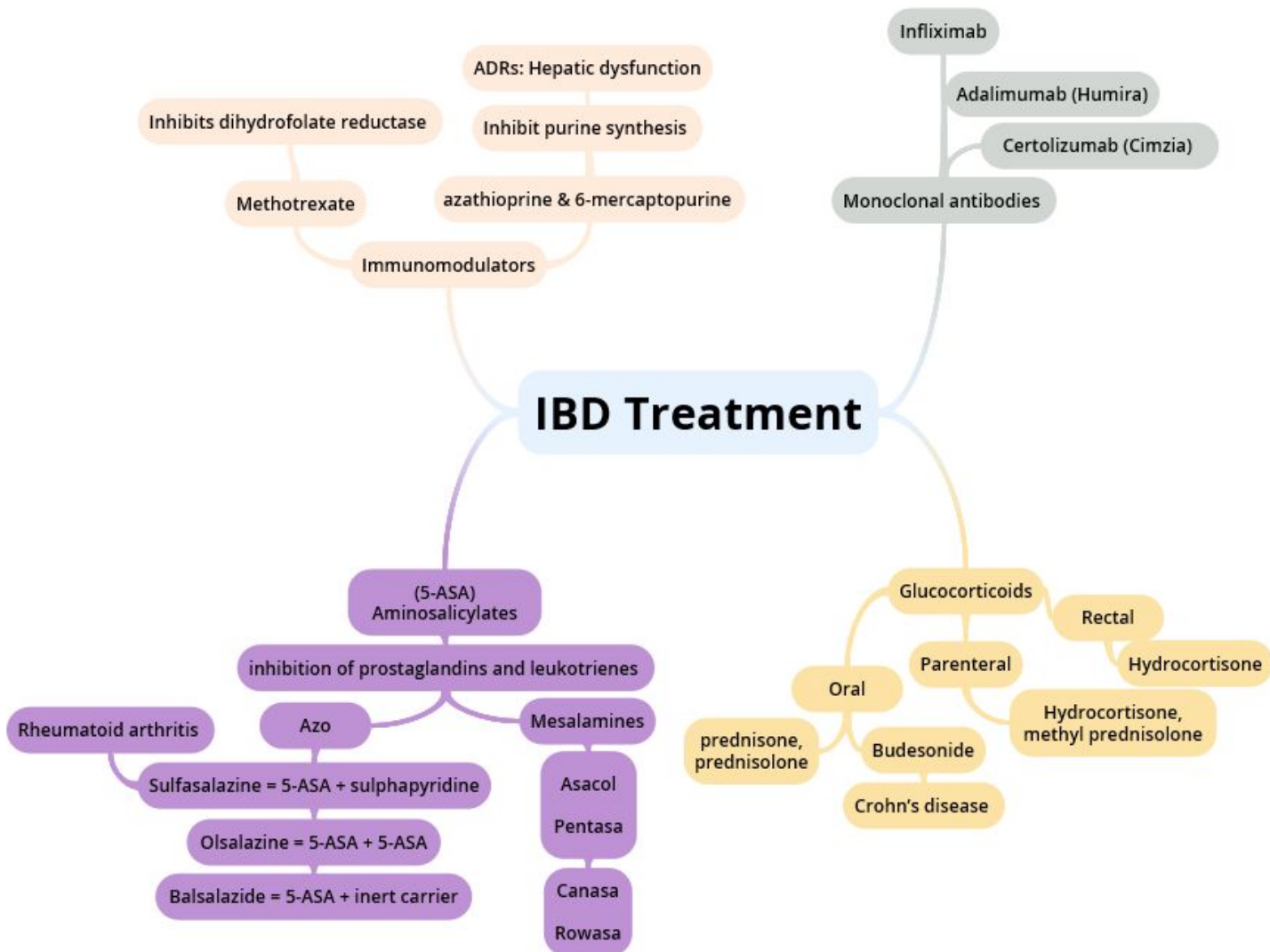
Drugs and biological and immune therapy in inflammatory bowel disease (IBD)

Objectives:

1. Define inflammatory bowel disease.
2. Differentiate between ulcerative colitis and Crohn' disease.
3. Define the stepwise treatment of IBD.
4. Discuss the pharmacokinetics, pharmacodynamics, uses and adverse effects of 5-amino salicylic acid compounds (5-ASA), glucocorticoids, immunomodulators and biological therapy (TNF- α inhibitors).
5. Compare between drugs used for induction of remission and those used for maintenance of remission.

[Editing File](#)

Mind Map and introduction



Inflammatory Bowel Diseases (IBD)

- is a group of inflammatory conditions of the small intestine and colon.
- The major types of **IBD** are Crohn's disease and ulcerative colitis (UC).

Causes:

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

Inductive Therapies

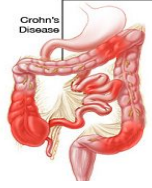
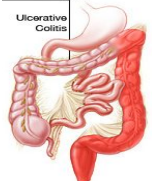
For Ulcerative colitis Aminosalicylates, Corticosteroids, Immunosuppressants, Infliximab

For Crohn's disease Aminosalicylates, Corticosteroids, Antibiotics, Biologics

Maintenance Therapies

Aminosalicylates Immunosuppressants, Azathioprine 6-MP Methotrexate, Infliximab, NO corticosteroids

The major types of IBD

	Crohn's disease	Ulcerative colitis
Location	affect any part of the GIT, From mouth to anus	Restricted to colon & rectum
Definition	Chronic transmural inflammation of gastrointestinal tract 	Chronic mucosal inflammation of the colon 
Distribution	Patchy areas of inflammation (Skip lesions) not Continuous	Continuous area of inflammation
Depth of inflammation	May be transmural, deep into tissues	Shallow, mucosal
Complications	Strictures, Obstruction, Abscess, Fistula	Toxic megacolon, Colon cancer

Presentation

Bleeding	Occasional	Very common
Obstruction	Common	Uncommon
Fistulae	Common	None
Weight loss	Common	Uncommon
Perianal disease	Common	Rare

Symptoms of IBD

Complication

- Abdominal pain - Diarrhea - Rectal bleeding.	- vomiting - Weight loss	- Anemia - Megacolon - Abdominal obstruction (Crohn's disease).	- Colon cancer
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Treatment

There are two goals of therapy

- 1- Achievement of remission (**Induction**) .Suppress the inflammation
- 2-Prevention of disease flares (**maintenance**).
- 3- Normalize bowel function.
- 4- Maintain nutritional status.
- 5- Improve quality of life.

Continue.. Treatment

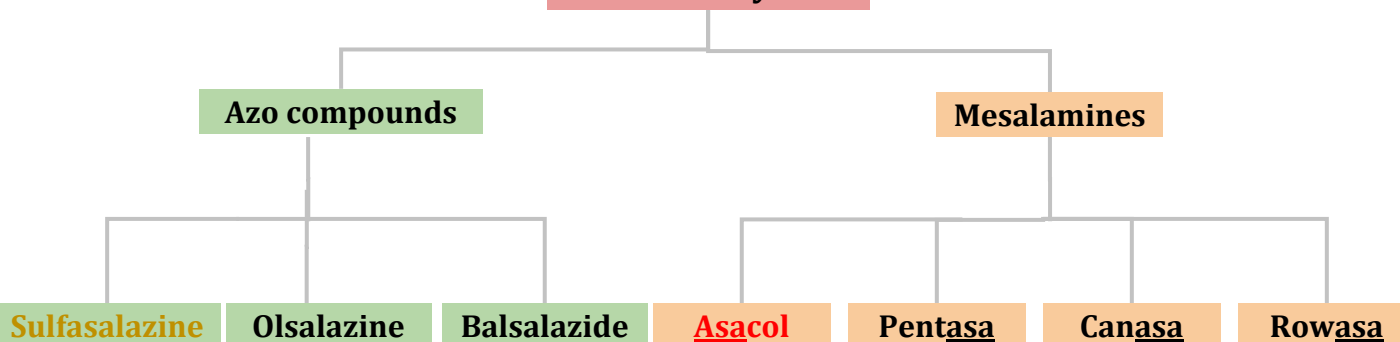
Stepwise therapy: (in order we start from less ADRs to the ones that have more ADRs)

1. 5-aminosalicylic acid compounds (5-ASA) or aminosalicylates.
2. Glucocorticoids
3. Immunomodulators
4. Biological therapy (TNF- α inhibitors).
5. Surgery in severe condition.

5-aminosalicylic acid compounds (5-ASA) Aminosalicylates

M.O.A	<ul style="list-style-type: none"> • Have topical anti-inflammatory need to come in contact with inflamed area action due to: <ul style="list-style-type: none"> ○ inhibition of prostaglandins and leukotrienes. ○ decrease neutrophil chemotaxis. ○ Antioxidant activity (scavenging free radical production).
P.K	<ul style="list-style-type: none"> • 5-ASA itself is absorbed from the proximal small intestine. <i>We need it to be intact until it reach the inflamed area</i> • Different formulations are used to overcome rapid absorption of 5-ASA from the proximal small intestine. • All aminosalicylates are used for induction and maintenance of remission
Clinical 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.

Aminosalicylates

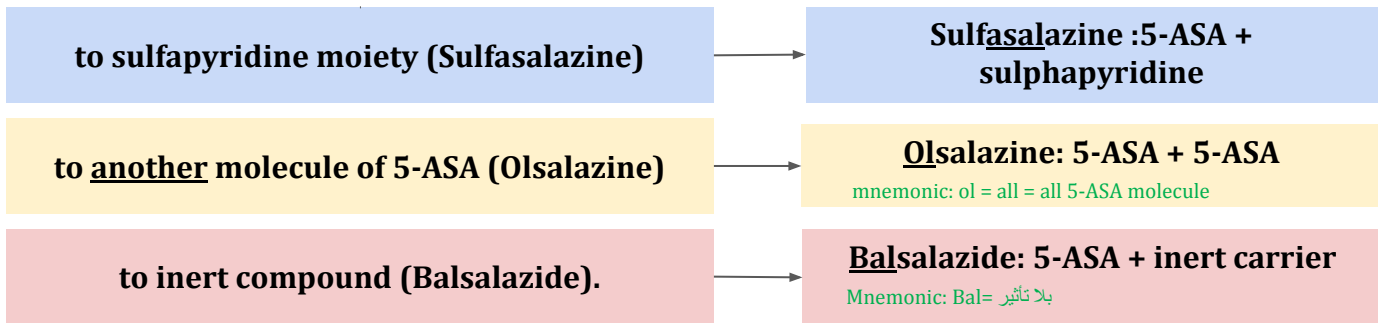


The major differences are in **mechanism** and **site** of delivery.

1-Azo compounds

These compounds contain (5-ASA) that is connected by azo bond (N=N) :

Stabilize it until it reach the colon



Inert compound = a compound that won't produce any additional action

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.**

Azo compounds

Drug	Sulfasalazine (Azulfidine)
General Info	<ul style="list-style-type: none"> <input type="checkbox"/> Pro-drug <input type="checkbox"/> A combination of 5-ASA + sulfapyridine <input type="checkbox"/> In the terminal ileum and colon, sulfasalazine is broken by azoreductase into: <ul style="list-style-type: none"> ● 5-ASA (not absorbed, active moiety, acting locally). ● Sulphapyridine (absorbed, causes most of side effects).
M.O.A	5-ASA has 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).
P.K	<ul style="list-style-type: none"> <input type="checkbox"/> Is given orally (enteric coated tablets). <input type="checkbox"/> Little amount is absorbed (10%)
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.

2-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 formulations

- releases 5-ASA in the distal small bowel secondary to pH changes.
- Release starts at the pylorus and continues throughout the small bowel and colon.

Asacol: 5-ASA coated in pH-sensitive resin that dissolve at pH 7. (delayed release)

Pentasa: micro granules that release 5-ASA throughout the small intestine. (sustained release)

rectal formulations

release 5-ASA in the distal colon.

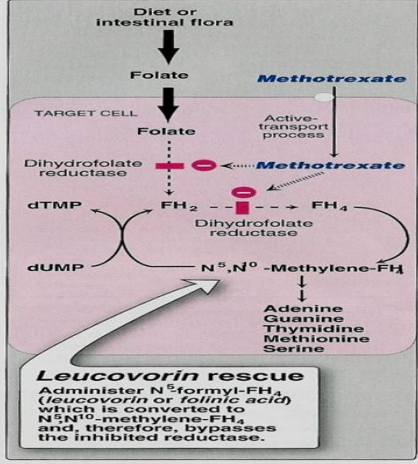
Canasa (suppositories)

Rowasa (enema)

Glucocorticoids

Route of administration	Oral preparation		Parenteral preparation (IV,IM)		Rectal Preparation
Drug	Prednisone	Prednisolone	Hydrocortisone	Methylprednisolone	Hydrocortisone
M.O.A	<ul style="list-style-type: none"> ● Inhibits phospholipase A2 ● Inhibits gene transcription of NO synthase cyclooxygenase-2 (COX-2) ● Inhibit production of inflammatory cytokines 				
P.K	<p>Higher rate of absorption</p> <p>Gradually given</p>				<ul style="list-style-type: none"> ● As enema or suppository give topical effect ● Less absorption rate than oral.
Indications	<ul style="list-style-type: none"> ● Indicated for acute flares of disease (moderate to- severe active IBD). ● Are not useful in maintaining remission . <p style="text-align: center; color: green; font-size: small;">Many ADRs</p> <p><u>Oral glucocorticoids</u> is commonly used in active condition.</p> <p><u>Rectal glucocorticoids</u> are preferred in IBD involving rectum or sigmoid colon.</p> <p>Also used in: Dr mentioned all the ADRs</p> <ul style="list-style-type: none"> ● Asthma ● Rheumatoid arthritis ● immunosuppressive drug for organ transplants ● Antiemetic during cancer chemotherapy 				
ADRs	<p>More adverse effects compared to rectal</p>				<p>Minimal side effects and maximum tissue effects</p>
Drug	<p>Budesonide</p>				
M.O.A	<p>A potent synthetic prednisolone analog</p> <p style="color: green; font-size: small;">Used orally and give action as topical even if a little amount was absorbed won't produce any action because of the first pass metabolism</p>				
P.K	<ul style="list-style-type: none"> ● Given orally (controlled release tablets) so release drug in ileum and colon ● Low oral bioavailability (90% will reach site of inflammation, while the rest are going to cause the ADR'S) ● Subject to extensive first pass metabolism 				
Indications	<p>Used in treatment of active mild to moderate crohn's disease involving Ileum and Proximal Colon.</p>				

Immunomodulators

Drug	Methotrexate	Purine analogs (azathioprine and 6-mercaptopurine)
M.O.A	<ul style="list-style-type: none"> • a folic acid antagonist • Inhibits dihydrofolate reductase required for folic acid activation (tetrahydrofolate) • Impairs DNA synthesis 	<ul style="list-style-type: none"> • Azathioprine (Inactive form) is pro-drug of 6-mercaptopurine (Active form) • Inhibit purine synthesis and inhibits synthesis of DNA, RNA, and proteins. • It may decrease proliferation of immune cells, which lowers autoimmune activity. (suppresses the inflames cell)
P.K	Orally, Subcutaneous, Intramuscular	
Indications	<p>Are used to induce remission in IBD in active moderate-to-severe conditions or steroid dependent or steroid resistant (refractory) Patients and to maintain remission. (Prophylactic therapy)</p> <ul style="list-style-type: none"> • Inflammatory bowel disease • Rheumatoid arthritis • Cancer 	
ADRs	<ul style="list-style-type: none"> • Megaloblastic anemia • Bone marrow depression • Teratogenic contraindicated in pregnant women. 	<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

Monoclonal antibodies used in IBD

(TNF- α inhibitors) **used when others fail**

Drug	Infliximab	Adalimumab (HUMIRA)	Certolizumab (Cimzia)
Overview	<ul style="list-style-type: none"> 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) 2 weeks to give clinical response. <small>delayed</small> 	<ul style="list-style-type: none"> -Fully humanized IgG antibody to TNF-α -Adalimumab is TNFα inhibitor. -Has an advantage that it is given by subcutaneous injection 	<ul style="list-style-type: none"> <small>More specific</small> -Fab fragment of a humanized antibody directed against TNF-α -Certolizumab is attached to polyethylene glycol to increase its half-life in circulation. -Given subcutaneously
Uses	<ul style="list-style-type: none"> In moderate to severe active (maintain and reduce) Crohn's disease and ulcerative colitis. Patients not responding to immunomodulators or glucocorticoids. Treatment of rheumatoid arthritis. Psoriasis. 	<ul style="list-style-type: none"> -moderate to severe Crohn's disease -rheumatoid arthritis -psoriasis 	<ul style="list-style-type: none"> -Crohn's disease -Rheumatoid arthritis
Side Effects	<ul style="list-style-type: none"> • Acute or early adverse infusion reactions (<i>Allergic reactions or anaphylaxis in 10% of patients</i>) Type 1 allergic reaction • Delayed infusion reaction/ <i>delayed type hypersensitivity reaction (serum sickness- reaction, in 5% of patients).</i> • Pretreatment with diphenhydramine, acetaminophen, corticosteroids is recommended <small>Reduce ADRs</small> • Infection complication Reoccurrence <u>Causing</u> decreased immunity "opportunistic infection" (Latent tuberculosis, sepsis, hepatitis B, fungal infection). • Loss of response to infliximab over time due to the development of antibodies to infliximab. • Severe hepatic failure. • Rare risk of lymphoma.. 	-	-

Summary

Stepwise Therapy:

We move to the next step when the previous didn't work

Aminosalicylates "5-ASA"

Drug	Azo compounds Sulfasalazine (Azulfidine)	Mesalamine compounds		
M.O.A	<ul style="list-style-type: none"> - It has anti - Used for induction & maintenance of remission - 1 line of treatment mild to moderate IBD 			
P.K	<ul style="list-style-type: none"> • Azo Bond is cleaved by Azoreductase enzyme produce by bacterial flora releasing 5-ASA in the terminal ileum and colon. • Sulphapyridine is responsible for the ADRS : 	They are formulation designed to deliver 5-ASA in terminal small bowel & large colon		
Indications		Oral formulation	Rectal formulation	
ADRs		<ul style="list-style-type: none"> -Crystalluria -Megaloblastic Anaemia -Impairment if male fertility 	Release 5-ASA in the distal small bowel	Release 5-ASA in distal colon
C.I		<ul style="list-style-type: none"> • 5-ASA ARDS: Interstitial nephritis. 	<ul style="list-style-type: none"> • Asacol "ph sensitive coat" • Pentasa: "time sensitive coat" 	Canasa-suppositories Rowasa- enema

Glucocorticoids

	Oral preparation		Parenteral preparation		Rectal Preparation
Drug	Prednison e	Prednisolon e	Hydrocortis one	Methylpredn isolone	Hydrocortisone
M.O.A	<ul style="list-style-type: none"> • Inhibits phospholipase A2 & Inhibits gene transcription of NO synthase cyclooxygenase-2 (COX-2) • Are not useful in maintaining remission 				

P.K	Higher rate of absorption - <u>Oral glucocorticoids</u> is commonly used in active condition.	<u>Rectal glucocorticoids</u> are preferred in IBD involving rectum or sigmoid colon.
Indications	<ul style="list-style-type: none"> Indicated for acute flares of disease (moderate to- severe active IBD). 	
ADRs	More adverse effects compared to rectal	Minimal side effects and maximum tissue effects

Immunomodulators

Drug	Methotrexate	Purine analogs (azathioprine and 6-mercaptopurine)
M.O.A	<ul style="list-style-type: none"> a folic acid antagonist Inhibits dihydrofolate reductase required for folic acid activation (tetrahydrofolate) 	<ul style="list-style-type: none"> Azathioprine (Inactive form) is pro-drug of 6-mercaptopurine (Active form) Inhibit purine synthesis and inhibits synthesis of DNA, RNA, and proteins. lowers autoimmune activity.
Indications	Are used to induce remission in IBD in active moderate-to-severe conditions or steroid dependent or steroid resistant Patients and to maintain remission.	

Monoclonal antibodies used in IBD

(TNF- α inhibitors) **used when others fail**

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Overview	<ul style="list-style-type: none"> 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) 2 weeks to give clinical response. 	<ul style="list-style-type: none"> Fully humanized IgG -Adalimumab is TNFα inhibitor. -Has an advantage that it is given by subcutaneous injection 	<ul style="list-style-type: none"> -Fab fragment of a humanized antibody directed against TNF-α -Certolizumab is attached to polyethylene glycol to increase its half-life in circulation. -Given subcutaneously
Uses	Used for induction “treating” only		

MCQs

Q1-Which of the following drugs is fully humanized IgG antibody to TNF- α ?

- A-Infliximab
- B-Adalimumab
- C-Certolizumab
- D-Methotrexate

Q2-Which of the following TNF- α inhibitors is given via intravenous route?

- A-Infliximab
- B-Adalimumab
- C-Certolizumab
- D-Methotrexate

Q3-Which of the following 5-ASA drugs is coated in pH-sensitive resin that dissolve at pH 7?

- A-asacol
- B-pentasa
- C-Canasa
- D-Rowasa

Q4-Which of the following is the First line of treatment for Induction and maintenance of remission in mild to moderate IBD?

- A-glucocorticoids
- B-immunomodulators
- C-5-ASA
- D-Biological therapy

Q5- 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
- D-Adalimumab

Q6-In which drug routine Complete blood count & liver function tests are required in all patients?

- A- Methotrexate
- B- azathioprine
- C- Adalimumab
- D- Budesonide

Q7:which one of these drugs is a folate acid antagonist:

- A) methotrexate.
- B) prednisolone
- C) prednisone.
- D) hydrocortisone

Q8)which one of these drugs undergoes first pass hepatic metabolism?

- A) azathioprine.
- B) methotrexate.
- C) hydrocortisone.
- D) Budesonide

D-8
A-7
B-9
A-5
C-4
A-3
A-2
B-1

SAQ:

23 y/o man visited the physician complaining of abdominal discomfort, rectal bleeding and diarrhea for the past month. Endoscopy of the colon showed patchy inflamed areas along the colon.

1- What drug do you recommend for him first?

Sulfasalazine

2- Mention the mechanism of action of the drug?

5-ASA has anti-inflammatory action due to:

- inhibition of prostaglandins and leukotrienes.
- decrease neutrophil chemotaxis.
- Antioxidant activity (scavenging free radical production).

3- Mention three side effect.

1. Bone marrow depression
2. Megaloblastic anemia.
3. Folic acid deficiency

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References:

✓ Doctors' slides and notes



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