Revised & Approved

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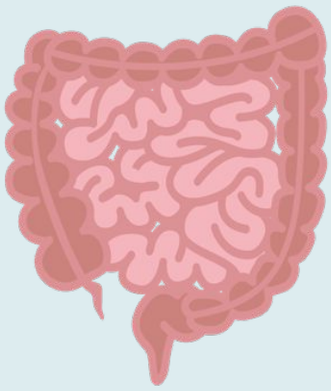
Pharmacology 439

MED439
KING SAUD UNIVERSITY



Gastrointestinal Block

Pharmacology Team 439

Color index:

Main Text

Important

Dr's Notes

Female Slides

Male Slides

Extra

Drugs used in IBD & biological & immunotherapy of IBD

Editing file | Summary

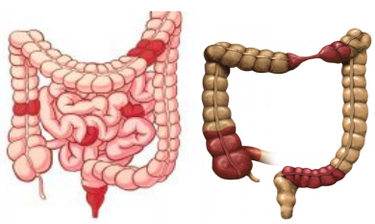
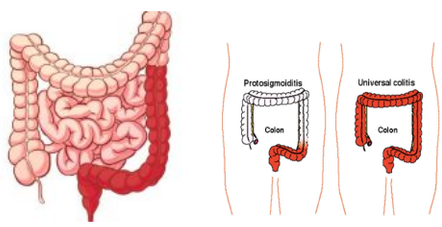
Inflammatory Bowel Disease (IBD)

- 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

The Major Types of IBD

	Crohn's disease	Ulcerative Colitis
Definition	Chronic transmural inflammation of gastrointestinal tract	Chronic mucosal inflammation of the colon
Location	Affects any part of the GIT, From mouth to anus	Restricted to colon & rectum
Distribution	Patchy areas of inflammation (skip lesions)  -Diseased area is followed by a normal area.	Continuous area of inflammation 
Depth of inflammation What layer it can affect	May be transmural, deep into tissues	Shallow, mucosal
Complications	Strictures, Obstruction, Abscess, Fistula	Toxic megacolon, Colon cancer
Females slides only	**Presentation**	
Bleeding	Occasional	Very common
Obstruction	Common	Uncommon
Fistulae		None
Weight loss		Uncommon
Perianal disease		Rare

Main differences in presentation are:

- Weight loss is common in crohn's disease.
- Bleeding is common in ulcerative colitis.

Symptoms of IBD

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

Complications

If the patient was left untreated

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

Treatment

There's no cure for IBD (patient can't return to normal) but what we can do:

Treatment objectives

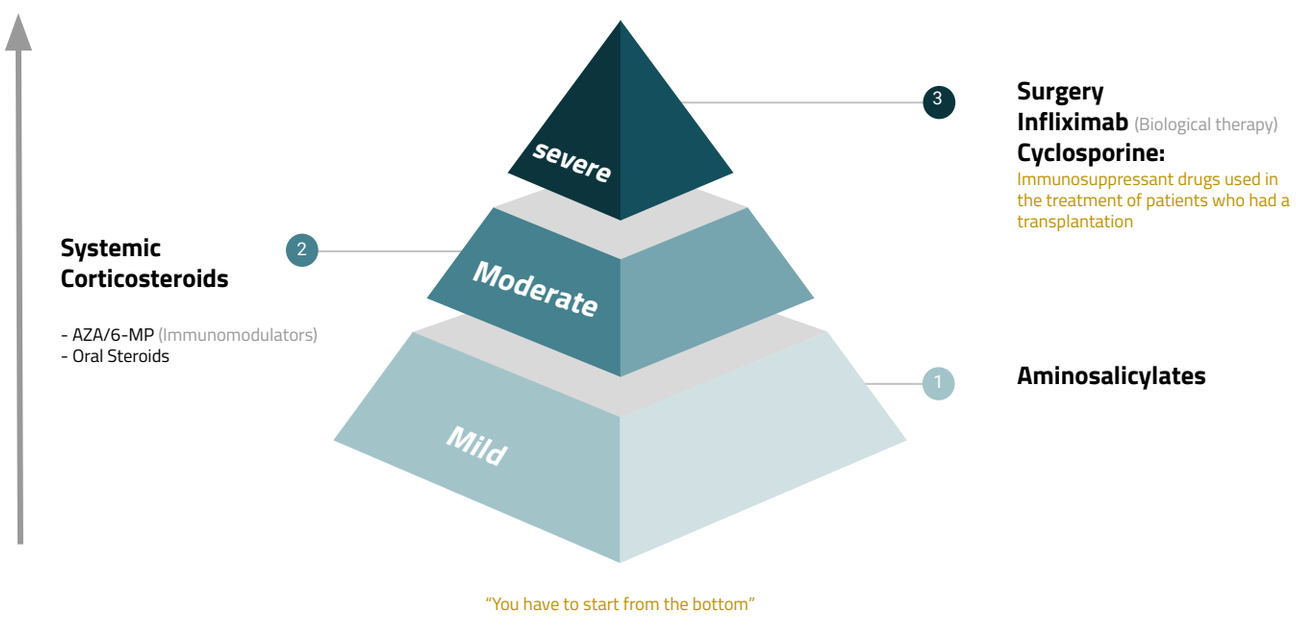
- Achievement of remission (Induction) stop progression of active disease (inflammation)- patient has symptoms ⟶ anti-inflammatory drugs.
- Prevention of disease flares (maintenance) (prophylaxis, after remission of symptoms).
- Normalize bowel function.
- Maintain nutritional status.
- improve quality of life.

Stepwise therapy

(the order in which we prescribe the drugs. only go from a step to the next if the patient has no response to therapy)

1. First step: 5-aminosalicylic acid compounds (5-ASA) or aminosalicylates (cornerstone of IBD treatment) (derivative from salicylic acid).
2. Second step: Glucocorticoids
3. Third step: Immunomodulators
4. Fourth step: Biological therapy (TNF-α inhibitors)
5. Fifth step: Surgery in severe condition

Stepwise therapy For IBD



"You have to start from the bottom"

1- 5-Aminosalicylic acid AKA Aminosalicylates (5-ASA)

class	Azo Compound	Mesalamines
Drugs	(prodrugs), 3 formulations: • Sulfasalazine • Olsalazine • Balsalazide	(5-ASA with coat) • Asacol. • Pentasa • Canasa • Rowasa All have asa (=aminosalicylic acid) in them
	• The major differences are in mechanism and site of delivery (same MOA, different mechanism of delivery)	
MOA	• Have **TOPICAL** anti-inflammatory action due to: ○ inhibition of prostaglandins and leukotrienes. ○ Decrease neutrophil chemotaxis ○ Antioxidant activity (scavenging free radical production) Topical means that for it to work it needs to have a direct contact with the inflammatory tissue. So if you give the drug orally it must be kept in intact form until it reaches the site of inflammation (this is achieved by a certain formulation).	
P.K	• 5-ASA itself is absorbed from the proximal small intestine & stomach (Acidic drugs are best absorbed in acidic medium & Basic drugs are best absorbed in basic medium because they'll exist in the lipid soluble form). • Different formulations (Azo component & Mesalamines) are used to overcome rapid absorption of 5-ASA from the proximal small intestine so it can reach inflamed area only, without systemic effects • **All aminosalicylates are used for induction** (treatment) **and maintenance** (prophylaxis) **of remission *Very Important***	
Uses	• Induction and maintenance of remission in mild to moderate IBD (First line of treatment) • Use azo compound or mesalamines depending on whether the patient has sulfa sensitivity or not. • Rheumatoid arthritis (Sulfasalazine only) • Rectal formulations are used in distal ulcerative colitis, ulcerative proctitis and proctosigmoiditis **Ulcerative proctitis** is an idiopathic mucosal inflammatory disease involving only the rectum and is therefore an anatomically limited form of ulcerative colitis **Proctosigmoiditis** is a form of ulcerative colitis that affects the rectum and sigmoid colon	

A) Azo Compound

One nitrogen atom is from the 5-ASA and the other from a different compound that is not toxic to humans.
These compounds contain (5-ASA) that is connected by azo bond (N=N) into:

- **1- sulfapyridine moiety (Sulfasalazine)** → Sulfasalazine:= 5-ASA + sulphapyridine
- **2- another molecule of 5-ASA (Olsalazine)** → Olsalazine:= 5-ASA + 5-ASA

A way to remember it: ol= all of the compound is 5-ASA.

- **3- inert compound (Balsalazide)** → Balsalazide:=5-ASA + inert carrier

An inert compound is a compound that doesn't have a positive nor a negative effect, its only purpose is to bind to 5-ASA and decrease its absorption.

- **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*** (this means that if crohn's disease affects the upper part of GIT you can't use these medications).

A) Azo Compound

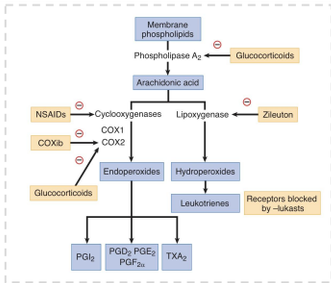
Drug	Sulfasalazine (Azulfidine)
MOA	• First line of treatment • Have **TOPICAL** anti-inflammatory action due to: ○ inhibition of prostaglandins and leukotrienes. ○ decrease neutrophil chemotaxis ○ Antioxidant activity (scavenging free radical production)
P.k	• Pro-drug • A combination of 5-ASA + Sulfapyridine • Given orally (enteric coated tablets, an additional layer of protection from being absorbed in the stomach). • Little amount is absorbed (10%) • In the terminal ileum and colon, sulfasalazine is broken by azoreductase Into: 1- **5-ASA** (not absorbed in the basic medium because it's in the ionized form, active moiety, acting locally) 2- **Sulphapyridine** (absorbed, causes most of side effects)
ADRs	Mainly due to sulphapyridine: (whenever you hear Sulfa, think about ADRs 1. Crystalluria → deposits in the kidney → advise to drink a lot of water. 2. Folic acid (B9) deficiency (Folic acid should be provided as supplements) 3. Megaloblastic anemia 4. Bone marrow depression 5. Impairment of male fertility (oligospermia) low sperm count. • **Due to 5-ASA:** Interstitial nephritis (rare)

B) Mesalamine Compound

- Formulations that have been designed to deliver 5-ASA **in terminal small bowel & large colon**.
- The physician chooses whether to give an oral or rectal formulation based on the case (location of inflammation).

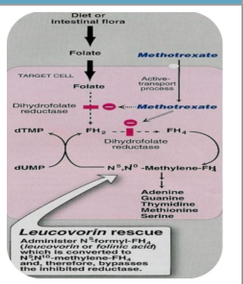
Features of Mesalamine compounds are:	• Well tolerated (meaning it has favorable kinetics and administration- ADRs are not so prominent) • Sulfate free • Less ADRs than sulfasalazine • Useful in patient sensitive to sulfa drugs (in this case we use mesalamine instead of sulfasalazine)
Oral Formulations	• Asacol: Releases 5-ASA **in the distal small bowel** (ileum) 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 tablet) at the beginning of the duodenum • **Pentasa:** micro granules that release 5-ASA throughout the small intestine, stomach, colon. (sustain released) (time sensitive) Notes: - Asacol: release of 5-ASA depend on pH. - Pentasa: starts to release of 5-ASA **depending on time elapsed** since administration of drug (2h). - Must tell the patient NOT to break the tablet, and take it as it is in order to be maintained by the coat. If the coat was broken large amounts of the drug will get absorbed in the stomach → go to the circulation and won't get in contact with the inflamed area (distal ileum + colon) to give its effect.
Rectal Formulations	• Release 5-ASA in the **distal colon.** • **Canasa:** Rectally (suppositories i.e. تحميلة صلبة), rectum. • **Rowasa:** (suspension as enema i.e. تحميلة سائلة), rectum (ignore the word suspension)

2- Glucocorticoids

Route Depends upon the condition	**Oral preparation** P.O	**Parenteral preparation**	**Rectal preparation**
MOA	• Inhibits phospholipase A2 → inhibition of all inflammatory pathways • Inhibits gene transcription of NO synthase, cyclooxygenase-2 (COX-2) • Inhibit production of inflammatory cytokines • Have immunosuppressant & antiemetic action		
Drugs	**Prednisone** **Prednisolone**	**Hydrocortisone** **Methylprednisolone**	**Hydrocortisone**
PK	good oral bioavailability	• Higher rate of absorption • More adverse effects compared to rectal administration	• As enema or suppository, give topical effect. • Less absorption rate than oral. • Minimal side effects & maximum tissue effects
Uses	• Oral glucocorticoids is commonly used in active condition.		• Rectal glucocorticoids are preferred in IBD involving rectum or sigmoid colon
	• Indicated for acute flares of disease (**active moderate to severe IBD**). • **Not useful in maintaining remission (not effective as prophylactic therapy).** **Important** **Other uses:** • Asthma • Rheumatoid arthritis • Immunosuppressive drug for organ transplants • Antiemetic during cancer chemotherapy		

Drug	**Budesonide** A potent synthetic prednisolone analog
PK	• Given orally (controlled release tablets) so release drug in ileum and colon. • Low oral bioavailability (10%); Good oral bioavailability → more of the drug will reach the systemic circulation (undesirable effect). Low oral bioavailability → low rate of absorption. • Extensive first pass metabolism: even if part of the drug was absorbed it will get broken down, and only the part that didn't get absorbed will have effect (topical). • Low bioavailability
Uses	Used in treatment of **active** **mild to moderate** Crohn's disease involving ileum and proximal colon, **Not allowed to be used as prophylaxis**

3- Immunomodulators

Drug	Methotrexate	Purine analogs: **Azathioprine, 6-mercaptopurine**
M.O.A	• Folic acid antagonist • Inhibits **dihydrofolate reductase** required for folic acid activation (tetrahydrofolate) FH4 • Impairs DNA synthesis (impair proliferation of immune cells)  1- when folate enters the cell it has to get converted to FH4 (the active form of folic acid). 2- this conversion needs 2 steps to happen: a) dihydrofolate reductase converts folate to FH2 b) dihydrofolate reductase converts FH2 to FH4 3- polyglutamate will be added to FH4 in the liver	• Azathioprine is **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	Orally, I.M tetrahydrofolic acid polyglutamate is the active form.	
Uses	• **Induce and maintain** remission in **IBD** in active **moderate to severe** conditions or steroid dependent or steroid resistant patients (refractory patients)	
	• Inflammatory bowel disease • Rheumatoid arthritis • Cancer	
ADRs	• Bone marrow depression • Megaloblastic anemia • Teratogenic	• Bone marrow depression: leucopenia, thrombocytopenia. • Hepatic dysfunction • CBC & LFTs are required in all patients • Gastrointestinal toxicity. ما نركز عليها

4- Monoclonal antibodies used in IBD (TNF-α inhibitors)

Mab = monoclonal antibody, and so:
- NOT given orally, only by injection.
- Biological treatment. Focus on the differences between the monoclonal antibodies

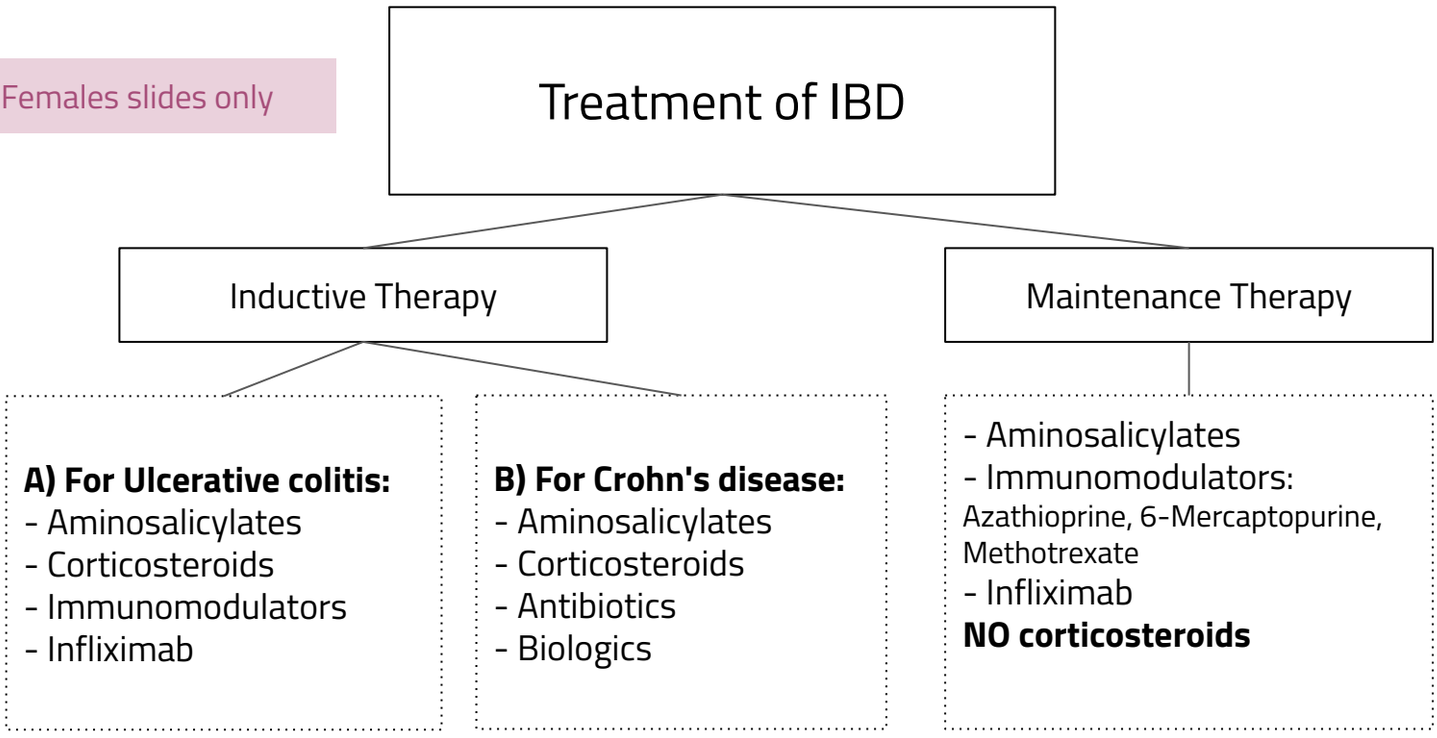
Drug	Adalimumab (Humira)	Certolizumab pegol (Cimzia) pegol= polyethylene glycol
M.O.A	• Act by binding to TNF-α thus preventing its binding to cell surface receptors, and prevent its inflammatory effects. • Increase apoptosis of T-lymphocytes and monocytes.	
P.k	• Fully **humanized** IgG antibody to TNF-α (TNF-α inhibitor) (no antigenicity) • It binds to TNF-α, preventing it from activating TNF receptors • Has an advantage in that it is given by **subcutaneous injection** (the patient takes a subcutaneous bolus and leaves)	• **Fab fragment** of a **humanized** antibody directed against TNF-α (no antigenicity and is more specific) • Attached to polyethylene glycol to increase its half-life in circulation by decreasing the release **(longer duration of action than adalimumab)**. • Given subcutaneously
Uses	• Moderate to severe Crohn's disease • Rheumatoid arthritis • Psoriasis (الصدفية) a skin disease marked by red, itchy, scaly patches.	• Crohn's disease • Rheumatoid arthritis

4- Monoclonal antibodies used in IBD (TNF-α inhibitors), cont.

Drug	**Infliximab** (Remicade)
M.O.A	• Act by binding to TNF-α thus preventing its binding to cell surface receptors and so prevent its inflammatory effects. • Increase apoptosis of T-lymphocytes and monocytes.
Overview	• A chimeric mouse-human monoclonal antibody, 25% murine – 75% human and so it HAS antigenicity. • Inhibits soluble or membrane –bound TNF-α located on activated T lymphocytes. • Given intravenously as **infusion** (patient needs stay on that bed for the duration of the infusion, unlike adalimumab and certolizumab pegol) (5-10 mg/kg). • has long half life (8-10 days) • 2 weeks to give clinical response. Male Dr: Use it for maintenance not induction
Uses	• In **moderate to severe active** Crohn's disease and ulcerative colitis. • Patients NOT responding to immunomodulators or glucocorticoids. • Treatment of rheumatoid arthritis. • Psoriasis (الصدفية). a skin disease marked by red, itchy, scaly patches.
ADRs	• Acute or **early** infusion ADRs **(Allergic reactions or anaphylaxis** in 10% of patients) Type 1 allergic reaction • **Delayed** type hypersensitivity reaction (**serum sickness- reaction**, in 5% of patients). • **Pre-treatment** with diphenhydramine, acetaminophen, corticosteroids is recommended to reduce the previous two side effects. • **Loss of response to infliximab** over time due to the development of antibodies to infliximab. • ↑ risk of opportunistic infection (Latent TB, sepsis, hepatitis B, fungal infection) (make sure your patient doesn't have these diseases because once they takes this medication these diseases will flare up). • Severe hepatic failure. • Rare risk of lymphoma .

***Important Dr's note*: it is very important to know which drugs are used for maintenance and which drugs are used for treating active disease or both**

Females slides only



Drugs used in IBD (Dr's Summary)

- **5-aminosalicylic acid compounds**
  - Azo compounds: Sulfasalazine, Olsalazine, Balsalazide
  - Mesalamines: Asacol, Pentasa, Canasa, Rowasa
- **Glucocorticoids**
  Prednisone, Prednisolone, Hydrocortisone, Budesonide
- **Immunomodulators**
  - Methotrexate
  - Purine analogues: Azathioprine & 6-mercaptopurine
- **TNF-α inhibitors (monoclonal antibodies)**
  - Adalimumab
  - Certolizumab
  - Infliximab

Summary

Class	Drug	M.O.A	Uses	ADRs
5-Aminosalicylic acid (Aminosalicylates) (5-ASA)	**Azo Compound** - Sulfasalazine - Olsalazine - Balsalazide	Have TOPICAL anti-inflammatory action	- Induction and maintenance of remission in mild to moderate IBD (First line of treatment) - Rheumatoid arthritis (Sulfasalazine only)	
	Mesalamines -Asacol - Pentasa -Canasa - Rowasa			
Sulfasalazine (Azulfidine) First line of treatment	- Sulfasalazine - Olsalazine - Balsalazide	A combination of 5-ASA+sulfapyridine	-	Impairment of male fertility (oligospermia)
Glucocorticoids	**Oral** - Prednisone - Prednisolone	- Inhibits phospholipase A2 - Gene transcription of NO synthase (COX-2) - Production of inflammatory cytokines	- Indicated for ACUTE flares of disease (moderate to severe active IBD). -Are NOT useful in maintaining remission	More adverse effects compared to rectal
	Parenteral - Hydrocortisone - Methylprednisolone			
	Rectal Hydrocortisone			Minimal side effects and maximum tissue effects
	Budesonide	A potent synthetic prednisolone analog	- Used in treatment of active mild to moderate crohn's disease involving Ileum and Proximal colon	
Immunomodulators	Methotrexate	A folic acid antagonist	- Induce and maintain remission in IBD in active moderate to severe conditions or steroid dependent or steroid resistant patients.	Megaloblastic anemia
	Purine analogs: Azathioprine 6-mercaptopurine	Inhibit purine synthesis and inhibits synthesis of DNA, RNA, and proteins.		- Bone marrow depression - Hepatic dysfunction
Monoclonal antibodies (TNF-α inhibitors)	Adalimumab (Humira)	Act by binding to TNF-α thus preventing its binding to cell surface receptors.	- Crohn's disease - Rheumatoid arthritis	
	Certolizumab (Cimzia)			
	Infliximab (Remicade)	Inhibits soluble or membrane –bound TNF-α located on activated T lymphocytes.	Patients NOT responding to immunomodulators or glucocorticoids.	- Acute or early infusion ADRs -Loss of response to infliximab over time

MCQs

Q1: Is a complication of IBD			
A- Anemia	B- Rectal bleeding	C- diarrhea	D- Abdominal pain
Q2: A combination of 5-ASA+sulfapyridine			
A- Sulfasalazine	B-Azulfidine	C-Methotrexate	D-Rowasa
Q3: it is a micro granules that release 5-ASA throughout the small intestine			
A- Asacol	B- none	C- A & D	D-Pentasa
Q4: patient come to the ER with Patchy areas of inflammation , what is the diagnosis?			
A- Ulcerative Colitis	B-Crohn's disease	C- A & B	D- none
Q5: which of the following drug is NOT useful in maintaining remission of IBD?			
A- Methotrexate	B-Azathioprine	C- 6-mercaptopurine	D-Prednisone
Q6: A patient came to the ER with ACUTE flare IBD, what is the appropriate drug that should be administered?			
A- Hydrocortisone	B-Methotrexate	C-Infliximab	D-Adalimumab
Q7: A patient with IBD was maintained under a certain drug after a while he developed leukopenia, Hepatic dysfunction what drug that most likely caused these ADRs effects?			
A- Infliximab	B-Azathioprine	C-Budesonide	D-Hydrocortisone
Q8: patient with IBD disease was not responding to Methotrexate and Hydrocortisone what is the appropriate action should be done ?			
A- Increase the dosage of the drug	B-decrease the dosage of the drug	C-change to Budesonide	D-change to Infliximab
Q9: Depending on your answer in the previous question, The patient would have high risk of developing			
A- Fungal infection	B- Megaloblastic anemia	C-Bone marrow depression	D-Oligospermia

1	2	3	4	5	6	7	8	9
A	A	D	B	D	A	B	D	A

SAQ

Q1) 25 lady come to the ER complaining of rectal bleeding , abdominal pain and patchy area of inflammation, what drug you recommend for her & list the ADRs of it?

Q2) list the complications and symptoms of IBD?

Q3) list the features of Mesalamine Compound?

A 35 years old patient Recently diagnosed with IBD:

Q4) mention two drugs with a different route of administration that can be used in the management of acute flares of this disease?

Q5) mention two drugs that use to control the remission of the disease and one side effect for each?

Q6) mention the mechanism of action of the previous drugs that have been mentioned?

Answers

A1) Sulfasalazine , 1-Folic acid deficiency (should be provided) 2. Impairment of male fertility (oligospermia)
3. Megaloblastic anemia

A2) Symptoms: Abdominal pain,Vomiting, Weight loss, Diarrhea ,Rectal bleeding
Complications: Anemia, Megacolon, Colon cancer, Abdominal obstruction (Crohn's disease)

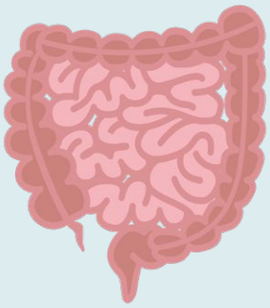
A3) Well tolerated, Sulfate free, Less ADRs than sulfasalazine,Useful in patient sensitive to sulfa drugs

A4) Oral Budesonide, Rectal: Hydrocortisone

A5) Sulfasalazine: Oligospermia, Methotrexate: megaloblastic anemia

A6) Sulfasalazine: Topical anti inflammatory effect, methotrexate: A folic acid antagonist

Feedback Form



Gastrointestinal Block

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