


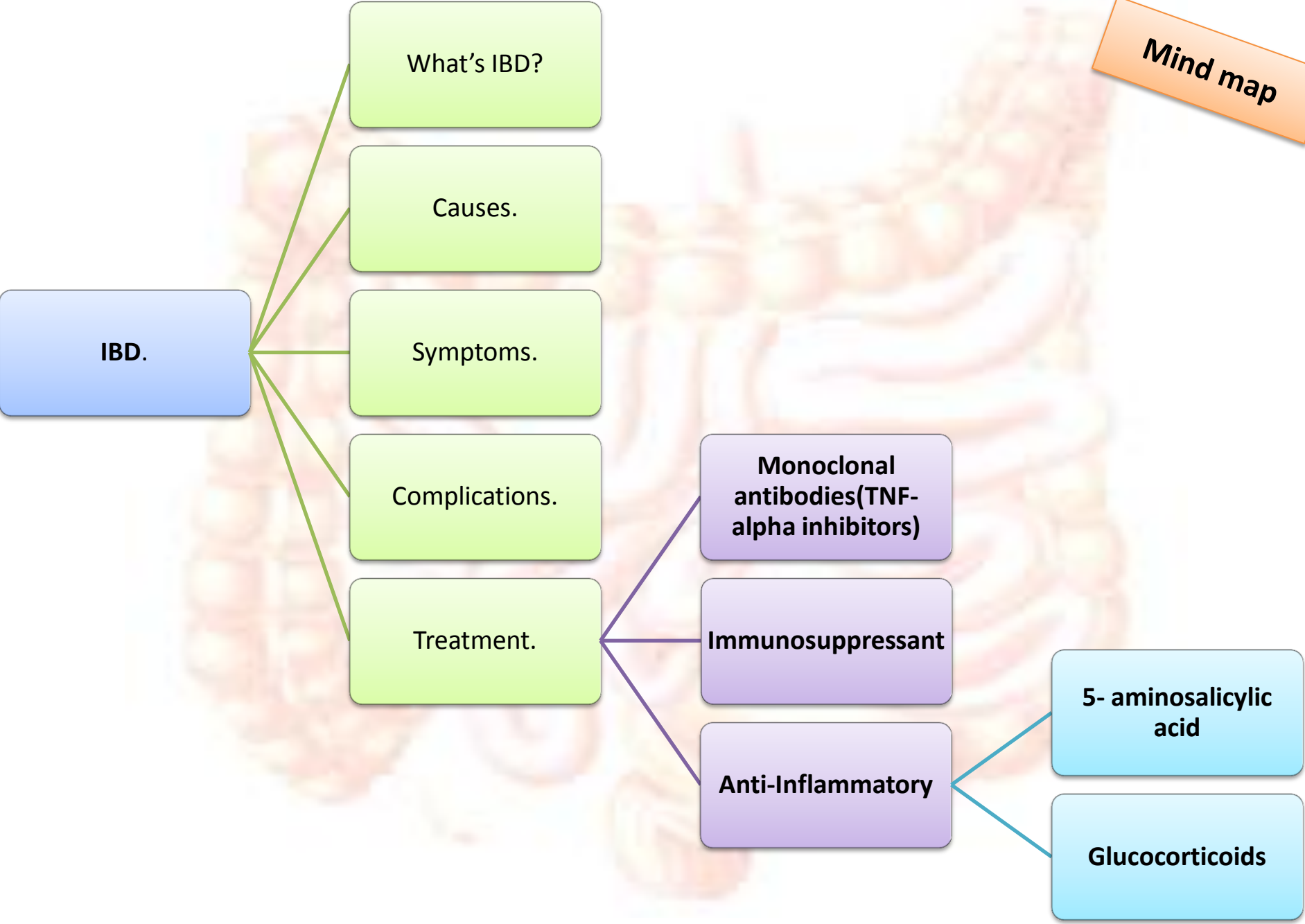
King Saud University  
College of Medicine  
2nd Year, 2nd Block

# GIT BLOCK



**L5: Drugs used in  
inflammatory bowel disease  
and biological and immune  
therapy of IBD**

Mind map



slide

doctor's note

important

explanation

## What is IBD ?

is a group of inflammatory conditions of the small intestine and colon. auto-immune disorders. 1-crohn's and 2-ulcerative colitis (UC).

	<b>Crohn's disease</b>	<b>Ulcerative colitis</b>
<b>Location</b>	affect any part of the GIT, from mouth to anus	Restricted to colon & rectum
<b>Distribution</b>	Patchy areas of inflammation (Skip lesions)	Continuous area of inflammation
<b>Depth of inflammation</b>	May be transmural, deep into tissues	Shallow, mucosal
<b>Complications</b>	Strictures, Obstruction Abscess, Fistula	Toxic megacolon Colon cancer

### Causes:

1-Not known.

2-Abnormal activation of the immune system.

3-The susceptibility is genetically inherited.

**Symptoms:**

1. **Abdominal pain**
2. **Vomiting**
3. **Diarrhea**
4. **Rectal bleeding.**
5. **Weight loss**

**Complications:**

1. **Anemia**
2. **Abdominal obstruction (Crohn's disease)**
3. **Mega colon**
4. **Colon cancer**

**goals of therapy:**

- **No complete recovery, only suppression of the inflammation.**
1. **Achievement of remission (Induction).**
  2. **Prevention of disease flares (maintenance).**

**Stepwise therapy:** ( we use them step by step e.g; if the 1<sup>st</sup> is not efficient we move to the next and so on ...)

1. **5-amino salicylic acid compounds (5-ASA) or aminosalicylates.**
2. **Glucocorticoids**
3. **Immunomodulators**
4. **Biological therapy (TNF- $\alpha$  inhibitors).**
5. **Surgery in severe condition.**

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

**M.O.A :** Have **topical anti-inflammatory\*** action due to: \*( at the site of inflammation )

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

**Pharmacokinetic :**

1-5-ASA itself is absorbed from the proximal small intestine.

2-Different formulations are used to overcome rapid absorption of 5-ASA from the proximal small intestine.\*(change the form to be activated )

3-All aminosalicylates are used **for induction (acute) and maintenance (prophylaxis) of remission**

# Different formulations of aminosalicylates are:

## 1-Azo compounds\*

- A. Sulfasalazine
- B. Balsalazide
- C. Olsalazine

\*(azo is 2 nitrogen bind together)

## 2-Mesalamines

- A. Asacol
- B. Pentasa
- C. Canasa
- D. Rowasa

**Azo structure reduces absorption of 5-ASA in small intestine.**

**A.Sulfasalazine :5-ASA + sulphapyridine \*(to prevent the absorption in the intestine )**

**B.Balsalazide: 5-ASA + inert carrier ( خامد )**

**C.Olsalazine: 5-ASA + 5-ASA**

**azoreductase enzyme produced by bacterial flora cleaves the azo bond and releases 5-ASA in terminal ileum and colon.**

# 1. Aminosalicylates

Groups	1-Azo compounds	2-Mesalamines
drugs	Sulfasalazine (Azulfidine)	Asacol ,Pentasa ,Canasa ,Rowasa
pharmacokinetics	<p>Pro-drug., A combination of 5-ASA + sulfapyridine, given orally (enteric coated tablets).</p> <p>Little amount is absorbed (10%).</p> <p><u>In the terminal ileum and colon, sulfasalazine is broken by azoreductase into:</u></p> <ul style="list-style-type: none"> <li>▪5-ASA (not absorbed, active moiety acting locally).</li> <li>▪Sulphapyridine (absorbed, <u>causes most of side effects</u>)</li> </ul>	<p><b>Oral formulations:</b></p> <p><b>Asacol:</b> 5-ASA coated in pH-sensitive resin that dissolve at pH 7 (<b>controlled release</b>).</p> <p><b>pentasa:</b> time-release microgranules that release 5-ASA throughout the small intestine (<b>delayed release</b>).</p> <p><b>Rectal formulations</b></p> <p><b>Canasa</b> (suppositories)</p> <p><b>Rowasa</b> (enema)</p>
Side effect	<p><b>Side effects of sulfasalazine:</b> (Crystalluria, Bone marrow depression, Megaloblastic anemia, Folic acid deficiency (should be provided), <b>Impairment of male fertility (Oligospermia)</b>).</p> <p><b>Side effect of 5-ASA:</b> Interstitial nephritis.</p>	<p><b>Sulfa free</b> → useful in patient sensitive to sulfa drugs</p> <p><b>well tolerated</b> → have less side effects compared to sulfasalazine</p>
Clinical uses	<ul style="list-style-type: none"> <li>- 1-Induction and maintenance of remission in <u>mild to moderate IBD</u> (First line of treatment).</li> <li>- 2-Rheumatoid arthritis (Sulfasalazine only)</li> <li>- 3- Rectal formulations are used in ulcerative proctitis and proctosigmoiditis</li> </ul>	

# 2. Glucocorticoids

preparation	drugs	pharmacokinetics	MOA	Uses
Oral	-prednisone -prednisolone -Budesonide*	Higher rate of absorption. More adverse effects compared to rectal administration. Budesonide* (A potent synthetic prednisolone analog - .Given orally (controlled release tablets) so	-Inhibits phospholipase A2.  -Inhibits gene transcription of NO synthase, cyclo-oxygenase-2 (COX-2).	-acute flares of disease (moderate & severe active IBD) → not effective as Prophylactic. <b>Oral glucocorticoids:</b> is commonly used in <u>active condition</u> <b>Rectal glucocorticoids:</b> are preferred in IBD involving <u>rectum or sigmoid colon</u> .
Parenteral	-hydrocortisone -methyl prednisolone	release drug in ileum and colon. - Low oral bioavailability (10%) if the bioavailability lower → that means it is breakdown fast -Is subject to extensive first pass metabolism)	-Inhibit production of inflammatory cytokines.	Budesonide*(treatment of active mild to moderate Crohn's disease involving ileum and proximal colon). <b>Extra:</b> -Asthma. -Rheumatoid arthritis. -immunosuppressive drug for organ transplants. -Antiemetic during cancer chemotherapy.
Rectal	-Hydrocortisone	As enema or suppository. give topical. Less absorption rate than oral. Minimal side effects & maximum tissue effects.		

slide

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# 3. Immunomodulators

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

drugs	Purine analogs: (azathioprine & 6-mercaptopurine)	Methotrexate:
MAO	Azathioprine is <b>pro-drug</b> of 6-mercaptopurine Inhibit purine synthesis	(a <b>folic acid antagonist</b> ) Inhibits dihydrofolate reductase required for folic acid activation (tetrahydrofolate)
Indication	<b>Induction and maintenance remission in IBD</b>	Used to induce and maintain remission. <b>*Inflammatory bowel disease.</b> <b>*Rheumatoid arthritis.</b> <b>*Cancer.</b>
Side effect	<ul style="list-style-type: none"> <li>- <b>Bone marrow depression:</b> (leucopenia, thrombocytopenia. )</li> <li>- Gastrointestinal toxicity.</li> <li>- Hepatic dysfunction.</li> <li>- <b>Routine 'Complete blood count &amp; liver function tests are required in all patients</b></li> </ul>	<ul style="list-style-type: none"> <li>- <b>Megaloblastic anemia</b></li> <li>- Bone marrow depression</li> </ul>

# 4. Monoclonal antibodies used in IBD (TNF- $\alpha$ inhibitors)

## (last line of treatment) A- Infliximab

PHARMAKINETICS	USES	ADVERS EFFECT
<ul style="list-style-type: none"><li>▪ a chimeric mouse-human monoclonal antibody</li><li>▪ 25% murine – 75% human. (because that we can not give it orally because the protein that come from mouse lead to allergy.)</li><li>▪ TNF-<math>\alpha</math> inhibitors</li><li>▪ Inhibits soluble or membrane –bound TNF-<math>\alpha</math> located on activated T lymphocytes.</li><li>▪ Given intravenously as infusion (long term) (5-10 mg/kg).</li><li>▪ has long half life (8-10 days)</li><li>▪ 2 weeks to give clinical response</li></ul>	<ul style="list-style-type: none"><li>▪ In moderate to severe active Crohn's disease and ulcerative colitis.</li><li>▪ Patients not responding to immunomodulators or glucocorticoids.</li><li>▪ Treatment of rheumatoid arthritis</li><li>▪ Psoriasis</li></ul>	<ul style="list-style-type: none"><li>- Acute or early adverse infusion reactions (<b>Allergic reactions</b> or <b>anaphylaxis</b> in 10% of patients)</li><li>- Delayed infusion reaction (<b>serum sickness-like reaction</b>, in 5% of patients).<ul style="list-style-type: none"><li>▪ And these advers effect because mouse protein of drugs.</li></ul></li><li>- This reaction can be reduced by Pretreatment with diphenhydramine, acetaminophen, corticosteroids is recommended.</li><li>- Infection complication (Latent tuberculosis, sepsis, hepatitis B)<ul style="list-style-type: none"><li>▪ all of these disease will show because the drugs is suppressent for immunity.</li></ul></li><li>- Loss of response to infliximab over time due to the development of antibodies to infliximab.</li><li>- Severe hepatic failure.</li><li>- Rare risk of lymphoma</li></ul>

# 4. Monoclonal antibodies used in IBD (TNF- $\alpha$ inhibitors)

## B- Adalimumab , C. Certolizumab pegol

DRUGS	PHARMAKINETICS	USES
<p><b>B- Adalimumab (HUMIRA)</b></p>	<ul style="list-style-type: none"> <li>- Fully humanized IgG antibody to TNF-<math>\alpha</math> (no or little allergy).</li> <li>- Adalimumab is TNF-<math>\alpha</math> inhibitor.</li> <li>- It binds to TNF-<math>\alpha</math>, preventing it from activating TNF receptors.</li> <li>- Has an advantage that it is given by subcutaneous injection.</li> </ul>	<ul style="list-style-type: none"> <li>- is approved for treatment of, moderate to severe Crohn's disease.</li> <li>- rheumatoid arthritis.</li> <li>- Psoriasis.</li> </ul>
<p><b>C. Certolizumab pegol (Cimzia)</b></p>	<ul style="list-style-type: none"> <li>- Fab fragment of a humanized antibody directed against TNF-<math>\alpha</math></li> <li>- Certolizumab is attached to polyethylene glycol to increase its half-life in circulation</li> </ul>	<ul style="list-style-type: none"> <li>- Given subcutaneously for the treatment of Crohn's disease</li> <li>- rheumatoid arthritis</li> </ul>

# Summary

Drug	Uses	Side effect
1-Aminosalicylates	<p>1-Induction and maintenance of remission in <u>mild to moderate IBD</u> (First line of treatment).</p> <p>2-Rheumatoid arthritis (Sulfasalazine only)</p> <p>3- Rectal formulations are used in ulcerative proctitis and proctosigmoiditis</p>	<p>Crystalluria, Bone marrow depression, Megaloblastic anemia, Folic acid deficiency (should be provided), <b>Impairment of male fertility (Oligospermia)</b>).</p>
	Asacol ,Pentasa ,Canasa ,Rowasa	less side effects
2-Glucocorticoids:	<p>acute flares of disease (<b>moderate &amp; severe active IBD</b>) → <b>not effective as Prophylactic.</b></p> <p><u>Oral glucocorticoids:</u> is commonly used in <u>active condition</u></p> <p><u>Rectal glucocorticoids:</u> are preferred in IBD involving <u>rectum or sigmoid colon</u>.</p> <p>Budesonide (treatment of active mild to moderate Crohn's disease involving ileum and proximal colon).</p>	-----
3-Immunomodulators:	<p><b>*Purine analogs:</b> (azathioprine &amp; 6-mercaptopurine).</p>	<p>Induction and maintenance remission in IBD</p> <ul style="list-style-type: none"> <li>-Bone marrow depression: (leucopenia, thrombocytopenia. )</li> <li>- Gastrointestinal toxicity.</li> <li>- Hepatic dysfunction.</li> <li>- Routine Complete blood count &amp; liver function tests are required in all patients</li> </ul>
	<p><b>*Methotrexate</b></p> <p>Used to induce and maintain remission.</p> <ul style="list-style-type: none"> <li>*Inflammatory bowell disease.</li> <li>*Rheumatoid arthritis.</li> <li>*Cancer</li> </ul>	<ul style="list-style-type: none"> <li>- <b>Megaloblastic anemia</b></li> <li>- Bone marrow depression</li> </ul>
5-TNF-α inhibitors	<p>A- Infliximab</p>	<p>Patients not responding to immunomodulators or glucocorticoids</p>
	<p>B- Adalimumab (HUMIRA)</p>	<p>treatment of, moderate to severe Crohn's disease.</p>
	<p>C. Certolizumab pegol (Cimzia)</p>	<p>Given <b>subcutaneously</b> for the <b>treatment of Crohn's disease</b></p>

# Quiz yourself

Answers 1-D, 2-C, 3-B, 4-A, 5-C, 6-B, 7-B, 8-A, 9-A

1-patient comes with moderate IBD and he is sensitive to sulfa drugs which drug of the following the best?

- A-Asacol.
- B-Azulfidine
- C-Pentasa.
- D-a&c.

4-A patient was diagnosed with IBD, he developed ulcerative proctitis , which of the following drugs is best used in this case :

- A-Canasa
- B-Sulfasalazine
- C-Asacol
- D-Adalimumab

7-A patient comes with IBD that involving the sigmoid colon which of the following is drug of choice ?

- A-Methotrexate
- B-Hydrocortisone
- C-Budesonide

2-Patient on treatment of IBD comes with Oligospermia, which drug he use?

- A-azathioprine.
- B- Infliximab.
- C- Sulfasalazine.
- D- Canasa.

5-A 84 years old was diagnosed with IBD, after some investigation the doctor found that his proximal colon and ileum was effected , which drug of these is best to be used

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

8- Which one of these drugs is used only to treat Rheumatoid arthritis?

- A-Sulfasalazine
- B-Rowasa
- C-Pentasa

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

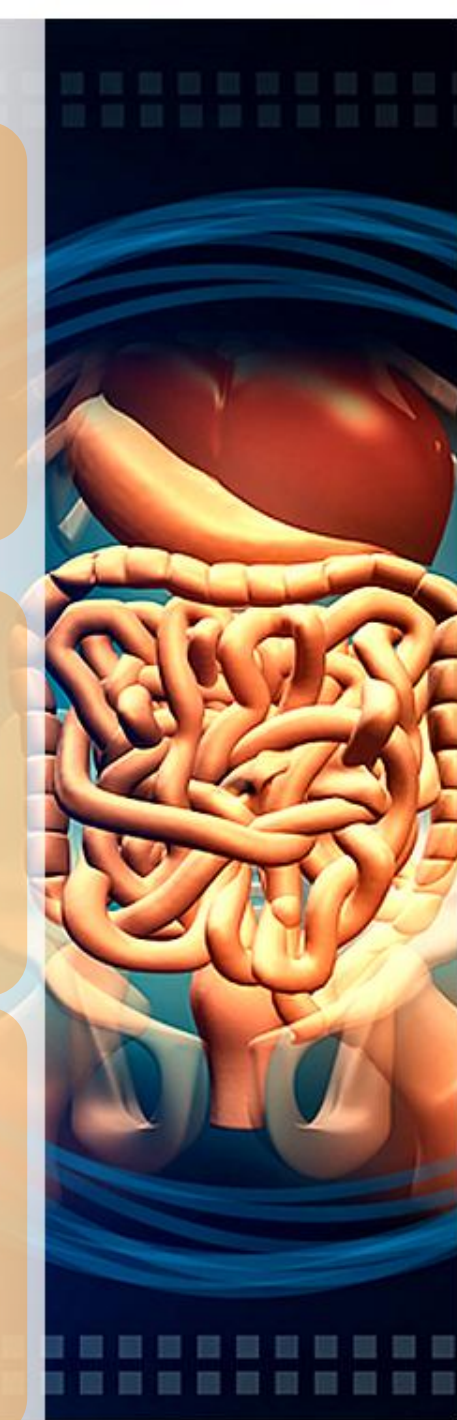
- A- Methotrexate
- B- azathioprine
- C- Adalimumab
- D- Budesonide

6-Which drug of the following use subcutaneously for the treatment of Crohn's disease?

- A- 6-mercaptopurine
- B- Certolizumab pegol
- C-Rowasa
- D- prednisone

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

- A-Methotrexate
- B- Infliximab
- C- azathioprine



*Done by*

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*It always seems impossible until it is done*

**BEST OF LUCK**



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