PHARMACOLOGY

TEAM 432

Drugs Used In IBD

Objectives

Add the objectives

Color Guide

Slides = Black
Females slides = Green
Males slides= Blue
Explanation=Orange

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Inflammatory Bowl disease(IBD)

Introduction:

- IBD is a group of auto-immune disorders in which the intestines become inflamed.
- Are chronic inflammatory bowel diseases which have relapsing and limiting course.
- The major types of IBD are Crohn's disease and ulcerative colitis (UC).

Causes

-Not known.

-Abnormal activation of the immune system.

-The susceptibility is genetically inherited.

Symptoms

-Abdominal pain

-Vomiting

-Diarrhea

-Rectal bleeding. -Weight loss

Complications

-Anemia

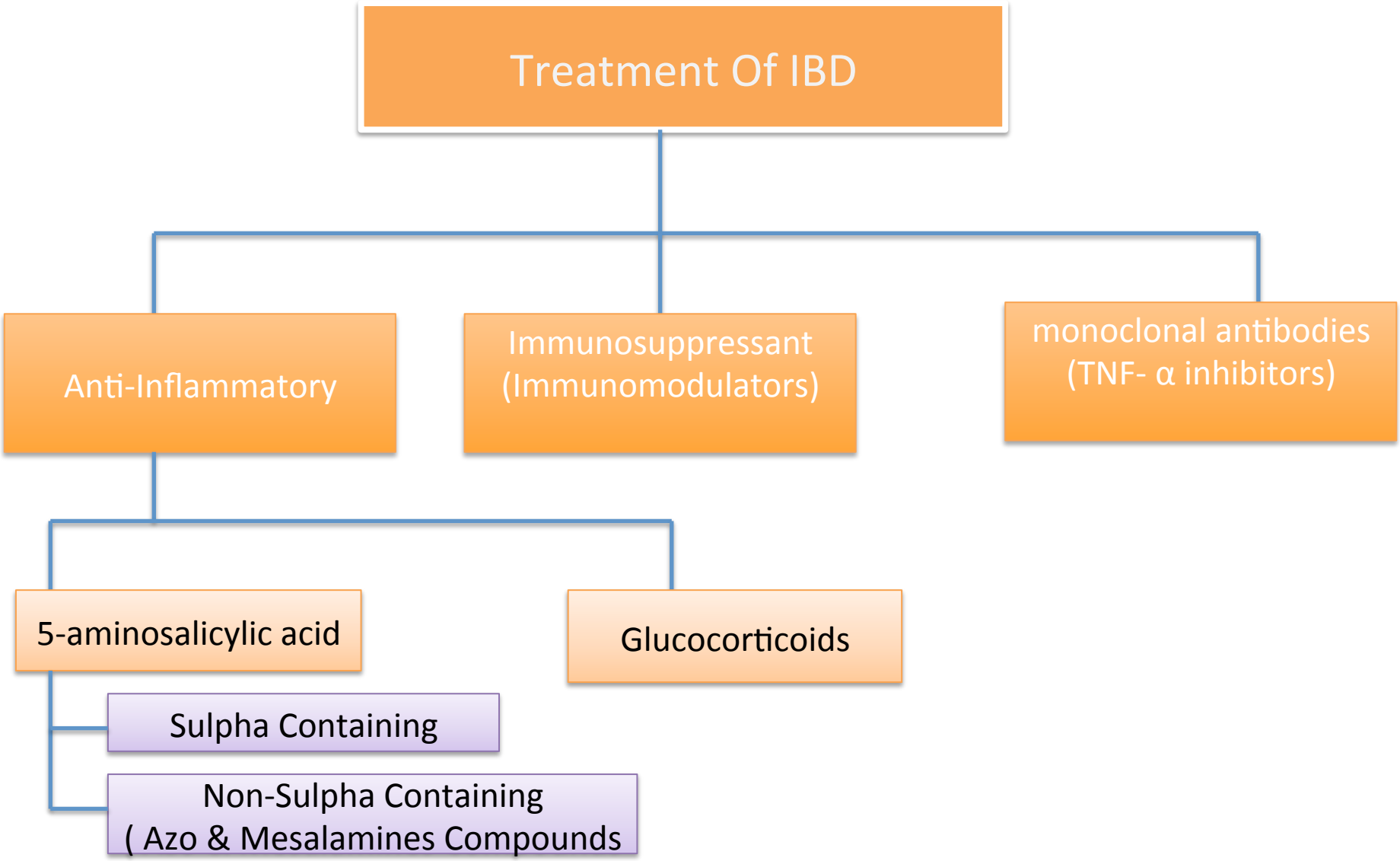
-Abdominal obstruction (Crohn's disease)

-Mega colon

-Colon cancer

	Crohn's Disease	Ulcerative Colitis
Location	Any Part of GI	Colon & Rectum
Distribution	Skip Lesions	Continues
Extent of Inflammation	Transmural(extends to deep tissue)	Shallow,Mucosa
Complications	Strictures, Obstruction Abscess, Fistula	Toxic megacolon Colon cancer
Diarreah	Bloody diahrrea	No blood

Treatment of IBD



Treatment of IBD

There are two goals of therapy

1. Achievement of remission (Induction).(keep the disease under control)

2. Prevention of disease flares (maintenance).prophylaxis

Stepwise therapy:

1. 5-amino salicylic 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

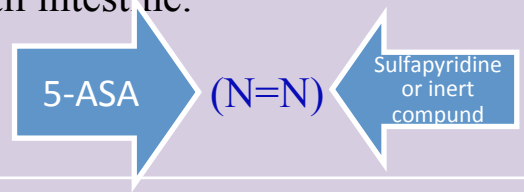
MOA:	**Have topical anti-inflammatory action** (come in contact with the inflammed tissue to produce action)**due to:** •inhibition of prostaglandin and leukotriens synthesis •decrease neutrophil chemotaxis •Antioxidant activity (scavenging free radical production)

Note: since it is an irritant to GIT(especially to the stomach).So, this drug should not be given orally as such.
Remember: NSAIDs makes IBD worse (not used in its treatment).

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

- Azo compounds
  - Sulfasalazine
  - Balsalazide
  - Olsalazine
- Mesalamines
  - Asacol
  - Pentasa
  - Canasa
  - Rowasa

The major differences are in mechanism and site of delivery.

Azo compounds	Mesalamine compounds
These compounds contain (5-ASA) that is connected by azo bond (N=N) to sulfapyridine moiety, another molecule of 5-ASA or to inert compound. Azo structure reduces absorption of 5-ASA in small intestine. 	Formulations that have been designed to deliver 5-ASA in terminal small bowel & large colon. Mesalamine formulations are •Sulfa free (remove all ADS of sulfasalazine) •well tolerated •have less side effects compared to sulfasalazine •useful in patient sensitive to sulfa drugs.
Sulfasalazine : 5-ASA + sulphapyridine **Olsalazine(all):** 5-ASA + 5-ASA **Balsalazide**: 5-ASA + inert carrier (Colazal). In the terminal ileum and colon, bacterial flora release azoreductase enzyme that cleave the azo bond and release 5-ASA in terminal ileum and colon reach colon but not absorbed there. It is more useful in ulcerative colitis than Crohn's D. Inert=has no ADS or action.	**Oral formulations** **Asacol:** 5-ASA coated in pH-sensitive resin that dissolve at pH 7 (controlled release). **pentasa:** time-release microgranules that release 5-ASA throughout the small intestine (delayed release). **Rectal formulations** **Canasa** (suppositories) **Rowasa** (enema)

Clinical uses of 5-ASA compounds :

- Induction and maintenance of remission in mild to moderate IBD (First line of treatment).
- Are NOT useful in actual attack or severe forms of IBD.
- Rheumatoid arthritis *(Sulfasalazine only)*
- Rectal formulations are used in *ulcerative proctitis* and *proctosigmoiditis*

- **Ulcerative proctitis**: It is the least severe form of inflammatory bowel disease.
- **Proctitis**: inflammation of the rectum and anus.
- **Proctosigmoiditis**: inflammation of the sigmoid colon and rectum.

Sulfasalazine

- Pro-drug (it has to be activated) used in maintenance therapy, less effective in acute attack; Used for U.colitis; Crohn's colitis but not Crohn's of small intestine.

Because the bacteria that hydrolyses the drug are present in the distal ileum and colon, the places where the drug gives its therapeutic action.

Note: Nowadays it is seldom to be used for Crohn's disease (new 5-ASA are preferred but still use for UC).

- A combination of 5-ASA + sulfapyridine
- Is given orally (enteric coated tablets).(it would be better if it's given rectally but in Chrin's diesase has to be orally)
- 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).

Mechanism of action of sulfasalazine

5-ASA has anti-inflammatory action due to:

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

Side Effects
(Very Important)

Muscular pain 29% caused by sulpha , N/V(nausea or vomiting), Diarrhea

- Crystalluria (crystals found in the urine) and interstitial nephritis.
- Hypersensitivity reactions as: skin rash, fever, aplastic anemia du to presence of sulfa group. Bone marrow depression
- Inhibit absorption of folic acid(should be provided) (megaloplastic anemia)
- Infertility in man(decrease sperm counts)Oligospermia.However, it is safe in pregnancy.

Note: most of adverse effects of sulfasalazine are attributable to (sulfapyridine)

Glucocorticoids

preparation	Oral	Parenteral	Rectal
e.g.	prednisone, prednisolone	hydrocortisone, methyl prednisolone	Hydrocortisone As enema or suppository,
	Higher rate of absorption More adverse effects compared to rectal administration High absorption=> more ADS		give topical effect. Less absorption rate than oral. Minimal side effects & maximum tissue effects
Common use	active condition.		preferred in IBD involving rectum or sigmoid colon
MAO	Inhibits phospholipase(all inflam mediators are removed) A2, inhibit gene expression of NO synthase, COX-2. Inhibit inflammatory cytokines (TNF-a).		

Budesonide:

- A potent synthetic prednisolone analog
- Given orally (controlled coated release tablets) so release drug in ileum and colon.
- Low oral bioavailability (10%) we don't want it to be absorbed to lower the ADS.
- Is subject to extensive first pass metabolism
- Used in treatment of active mild to moderate Crohn's disease involving ileum and proximal colon.

Indications

- Indicated for acute flares of disease (moderate & severe active IBD).
- not useful in maintaining remission.
- Used also for extracolonic manifestations such as :ocular lesion, skin disease, peripheral arthritis,Rheumatoid arithritis. Asthma, immunosuppressive drug for organ transplants , and antiemetics during cancer chemotherapy

Immunosuppressive Agents (Immunomodulators)

Are used to induce remission in IBD in active or severe conditions or steroid dependent or steroid resistant patients. (we use them when steroids fail to work since steroids have Immunosuppressive action)

Immunomodulators	Purine analogs: (azathioprine & 6-mercaptopurine).	Methotrexate
MAO steroid resistant Exception (satrt with it not stepwise	**Azathioprine** It Is pro-drug of 6-mercaptopurine that Inhibit purine synthesis	(folic acid antagonist) dihydrofolatereductase inhibitor (an enzyme important in the production of thymidine and purines),required for folic acid activation(tetrahydroflate) Works as antimetabolite
indications	Induction and maintenance of remission of severe conditions and steroids dependent or resistant (ulcerative and Crohn's disease).	Cronn's disease (to induce and maintain remission);inflammatory bowel disease, Rheumatoid Arthritis and cancer.
		Orally, S.C., I.M.
Side Effects	•bone marrow depression (leukopenia, macrocytosis, anemia, or thrombocytopenia). •Gastrointestinal toxicity •Hepatic dysfunction So,Routine laboratory monitoring with CBC and liver function tests is required in all patients.	•Bone marrow suppression •megaloblastic anemia.

Note: purines ,along with pyrimidines, make up the nitrogenous bases in our DNA and RNA. Inhibiting purine synthesis will inhibit cells proliferation, especially leukocytes, therefore these agents are used as immunosuppressants

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

- **Infliximab** (source: chimeric: human/mice) 75% human .(may cause hypersensitivity reaction)
- **Adalimumab** (source: purely human) 100% human
- **Certolizumab** (source: humanized from mice) 95% human

Infliximab :

- Is a monoclonal IgG antibodies.
- 25%murine from mouse – 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(. (not given orally cuz it's protein)
- has long half-life (8-10 days(. Delayed onset of action
- 2 weeks to give clinical response.

Uses :

- In moderate to severe active crohn's disease and ulcerative colitis.
- Patients not responding to Immunomodulators or glucocorticoids.
- Treatment of rheumatoid arthritis.
- Psoriasis.

Cont.

Side effects :

- Acute or early adverse infusion reactions (Allergic reactions or anaphylaxis in 10% of patients), this reaction can be reduced by pretreatment with diphenhydramine, acetaminophen, corticosteroids.

- Delayed infusion reaction (serum sickness-like reaction, in 5% of patients). (It consists of myalgia, arthralgia, jaw tightness, fever, rash, urticaria, and edema and usually requires discontinuation of that agent).

- Infection complication (Latent tuberculosis, sepsis, hepatitis B). (due to suppression of the TH1 inflammatory response)

- Loss of response to infliximab over time due to the development of antibodies to infliximab. (Anti-body development is most commonly seen in infliximab because it is the least humanized among the three.)

- Severe hepatic failure.

- Rare risk of lymphoma.

Cont.

Adalimumab (Humira) :

- Fully humanized (so no allergic manifistations) IgG antibody to TNF-α.
- Adalimumab is TNFα inhibitor.
- It binds to TNFα, preventing it from activating TNF receptors.
- Has an advantage that it is given by subcutaneous injection.
- It is approved for treatment of, moderate to severe Crohn's disease, rheumatoid arthritis, psoriasis.

Extra:

Certolizumabpegol (Cimzia) :

- 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 for the treatment of Crohn's disease & rheumatoid arthritis.

Summary for drugs used in IBD

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

Summary

Drugs used in IBD			
Drug	**MOA**	**Pharmacokinetics and Uses**	**ADRs**
5-aminosalicylic acid compounds: Topical anti-inflammatory drugs. 5-ASA itself is absorbed from small intestine. Different formulations are used to overcome rapid absorption of 5-ASA from the proximal small intestine **Uses:** Induction and maintenance of remission in mild to moderate ulcerative colitis & Crohn's disease (First line of treatment). Are NOT USEFUL in actual attack or severe forms of IBD. ▪ Rheumatoid arthritis, psoriasis *(Sulfasalazine only)* ▪ Rectal formulations are used in *ulcerative* proctitis and proctosigmoiditis.			
Azo compounds : Sulfasalazine	5-ASA has anti-inflammatory action due to: ▪ inhibition of prostaglandins and leukotrienes. ▪ decrease neutrophil chemotaxis. ▪ Antioxidant activity (scavenging free radical production).	▪ Pro-drug ▪ A combination of 5-ASA and sulfapyridine ▪ Is given orally (enteric coated tablets). ▪ Little amount is absorbed (10%), secreted in the bile ▪ *In the terminal ileum and colon*, sulfasalazine is broken by azoreductase into: 5-ASA (not absorbed, active moiety) and Sulphapyridine (absorbed, side effects)	▪ Muscular pain 29% caused by sulpha. N/V(nausea or vomiting), Diarrhea ▪ Crystalluria and interstitial nephritis. ▪ Hypersensitivity reactions as: skin rash, fever, aplastic anemia. caused by sulpha. ▪ Inhibit absorption of folic acid (megaloplastic anemia) ▪ Infertility in man (decrease sperm counts). However, it is save in pregnancy . ▪ Bone marrow depression
Mesalamine compounds: Well tolerated, less side effects (sulfa free), useful in patient sensitive to sulfa drugs.	▪ Treat and maintain remission in mild to moderate ulcerative colitis .	• Formulations that have been designed to deliver 5-ASA in terminal small bowel & large colon. • Oral formulations -Asacol: 5-ASA coated in pH-sensitive resin that dissolved at pH 7 (*controlled release*). -pentasa: time-release microgranules that release 5-ASA throughout the small intestine (*delayed release*). • Rectal formulations Canasa (suppositories), Rowasa (enema)	
Glucocorticoids	▪ Inhibits phospholipase A2 ▪ Inhibits gene transcription of NO synthase, cyclooxygenase -2 (COX-2) ▪ Inhibit production of inflammatory cytokines	• Treat moderate – severe ulcerative colitis. (Prednisone P.O. 40-60 mg/day for 2 weeks). • Less effective as prophylactic (maintaining remission). • Budesonide as controlled release oral (9 mg/day) formulation (Entocort). • Oral glucocorticoids is commonly used in active condition. • Hydrocortisone enema or suppository for rectum or sigmiod colon. • Used also for extracolonic manifestations such as ocular lesion, skin disease, peripheral arthritis. Asthma, immunosuppressive drug for organ transplants , and antiemetics during cancer chemotherapy	

Summary

Immunomodulators **Uses:** Are used to induce remission in IBD in active or severe conditions or steroid dependent or steroid resistant patients.			
Purine analogs (azathioprine & 6-mercaptopurine)	Inhibit purine synthesis	Azathioprine is pro-drug of 6-mercaptopurine **Used in** Induction and maintenance of remission in IBD	▪ Bone marrow depression: leucopenia, thrombocytopenia. ▪ Gastrointestinal toxicity. ▪ Hepatic dysfunction. ▪ Hypersensitivity reaction Complete blood count & liver function tests are required in all patients
Methotrexate	▪ a folic acid antagonist ▪ Inhibits dihydrofolate reductase required for folic acid activation (tetrahydrofolate)	▪ Orally, S.C., I.M. **Uses:** ▪ Used to induce and maintain remission. ▪ Inflammatory bowel disease ▪ Rheumatoid arthritis ▪ Cancer	▪ Megaloblastic anemia ▪ Bone marrow depression
Monoclonal antibodies used in IBD (TNF-α inhibitors)			
Infliximab	▪ TNF-α inhibitors ▪ Inhibits soluble or membrane –bound TNF-α located on activated T lymphocytes and	▪ a chimeric mouse-human monoclonal antibody ▪ 25% murine – 75% human. ▪ Given intravenously as infusion (5-10 mg/kg). ▪ has long half life (8-10 days) ▪ 2 weeks to give clinical response **Uses** ▪ In moderate to severe active Crohn's disease and ulcerative colitis ▪ Patients not responding to immunomodulators or glucocorticoids. ▪ Treatment of rheumatoid arthritis ▪ Psoriasis	▪ Acute or early adverse infusion reactions (Allergic reactions or anaphylaxis in 10% of patients), this reaction can be reduced by pretreatment with diphenhydramine, acetaminophen, corticosteroids. ▪ Delayed infusion reaction (serum sickness-like reaction, in 5% of patients).Infection complication (Latent tuberculosis, sepsis, hepatitis B ▪ Loss of response to infliximab over time due to the development of antibodies to infliximabSevere hepatic failure. ▪ Rare risk of lymphoma.

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- Fully humanized IgG antibody to TNF-α.
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- It binds to TNFα, preventing it from activating TNF receptors.
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Certolizumab pegol (Cimzia)

- 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 for the treatment of Crohn's disease & rheumatoid arthritis.

Questions

1- Which of the following is a side effect of Sulfasalazine:

A. Hepatic dysfunction
B. Megaloplastic anemia
C. Predispose to infection

2-Which one of the following is a Clinical use of infliximab :

A. Asthma
B. Crohn's disease C. IBD with diarrhea
D. IBD with constipation

3-What's the first line treatment for IBD:

A. 5ASA
B. Immunosuppressant
C. TNF-α inhibitors

Questions

4-Which of these drugs is safe in pregnancy?:

A. Budesonide
B. Azathioprine
C. Sulphasalazine
D. Infliximab

5- Bone Morrow depression is a side affect of which of the following drugs:

A. Methotrexate
B. Certolizumab
C. Olsalizine
D. Azathioprine

Answers: 1: B, 2:B, 3:A, 4:C, 5:A and D

PHARMACOLOGY

TEAM 432

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