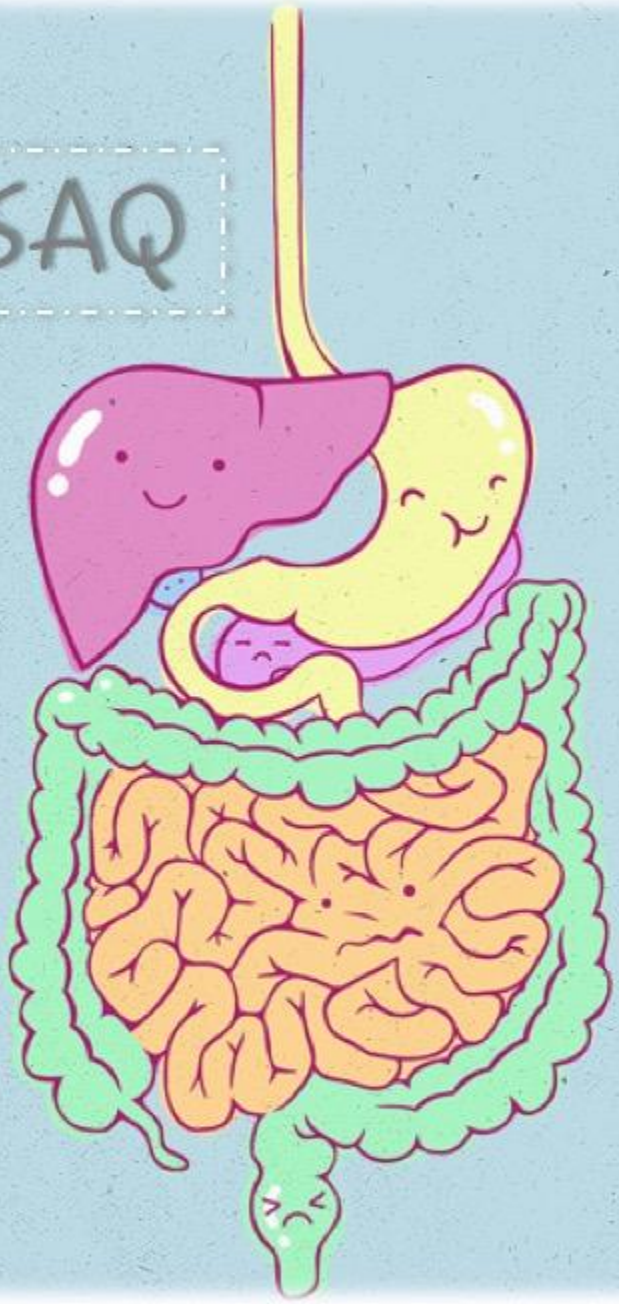
GIT SAQ

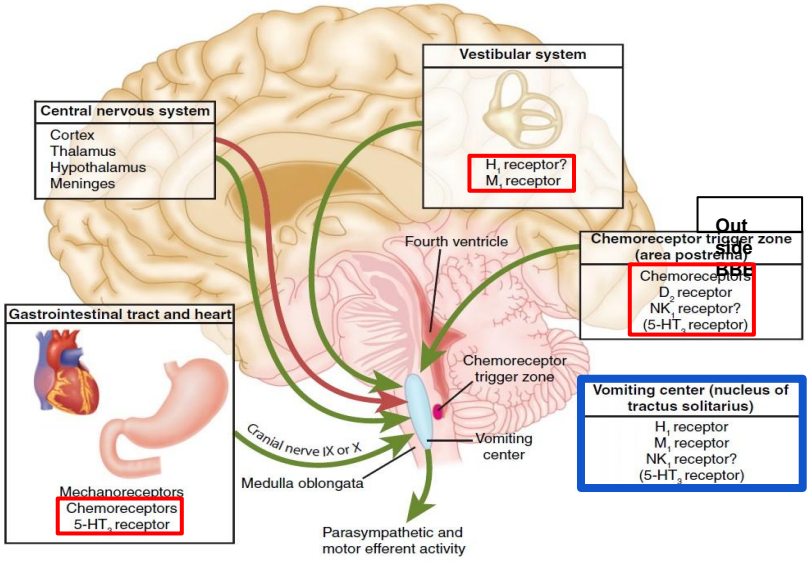


Pharmacology

Editing File

Antiemetics

Pathophysiology: The vomiting center is in the brainstem.its afferent input is as following:



Neurologic pathways involved in pathogenesis of nausea and vomiting

Drugs list:

5-HT3 antagonists	Ondansetron , Granisetron
NK1 antagonists	Aprepitant
Glucocorticoids	Dexamethasone , Methylprednisolone
D_2 antagonists	Prokinetics: Domperidone, Metoclopramide
	Antipsychotics:Chlorpromazine,droperidol
H_1 antagonists	Diphenhydramine , Promethazine , Meclizine , Cyclizine
M_1 antagonists	Hyoscine (scopolamine)

Drugs uses

-Cytotoxic drugs vomiting
-CINV
-Motion sickness
-Vomiting with pregnancy
-Drug- induced vomiting
-Uremia
-Gastritis

Drugs in peptic ulcer

What its complications in long term use H2 receptor blockers?
1-vitamin B12 deficiency 2-increase risk of hip joint fractures

What are the side effects that specific of Cemitidine?
1-CYT-P450 inhiption 2-glactorrhea 3-gynecomastesia&impotence

What should we give in condition of NSAID-indused peptic ulcer?
Prostaglandin analogues (not used in pregnancy)

Drug group	Drug names	Mechanism of action	NOTES
Proton pump inhibitors	Omeprazole, lansoprazole, Pantoprazole, Raprozaole	Irreversible inhibition of (H+/K+ atpase) proton pump.	-**Most potent inhibitors** of acid secretion. -Hypersecretory conditionsas Zollinger Ellison syndrome and gastrinoma. **(first choice.)**
H2 receptor blockers	Cimetidine, Rantidine, Famotidine, Nizatidine	Reversible & competitive blocking at H2 receptors on parietal cells	**Famotidine** is the most potent drug. **Nizatidine** has the greatest bioavailability.
Prostaglandin analogues	Misprostol	-Decreases HCL secretion -Increase protective measures.	-
Antacids	Inorganic salts	acts by direct checmical neutralization of HCL.	-

Treatment Of dysentery and amoebiasis

The two most common cause are:
Amebic dysentery: protozoal infection mainly by Entameba Histolytica
Bacillary dysentery (or shigellosis):bacterial infection mainly by shigella

Drug	Luminal amebicides	Tissue or systemic amebicides
Act on	Acts on the parasites in the lumen of the bowel.	Act on ameba in tissues e.g. the intestinal wall and/or other extra-intestinal tissues as liver, brain and lung.
Uses	Treatment of asymptomatic amebiasis (carriers).	Treatment of systemic form of the disease (invasive amebiasis) e.g. intestinal wall infection or liver abscesses
Include	❑ Diloxanide furoate ❑ Iodoquinol ❑ Paromomycin	❑ Metronidazole/ tinidazole ❑ Emetine / dehydroemetine ❑ Chloroquine (liver only)

Name two lumenal and two tissue (systemic) anti-Amebic drugs?
Luminal amebicides : (Treatment of asymptomatic amebiasis)
❑ Diloxanide furoate ❑ Iodoquinol ❑ Paromomycin

Tissue or systemic amebicides :(Treatment of systemic form of the disease)
❑ Metronidazole/ tinidazole ❑ Emetine / dehydroemetine ❑ Chloroquine

What is the MOA of Mitronidazole? ❑ **Metronidazole inhibits DNA replication.**

What are the ADRs of mitronidazole?
1- GIT disturbance 2- CNS involvement 3- dark urine 4-Disulfiram-like effect if taken with alcohol
What is the major side effect that is caused by emetine dihydroemetine? cardiotoxicity
What is the only use of chloroquine and its ADRs?
use : amebic liver diseases
ADRs:pruritus , blurred vision ,hemolysis
What are the side effects of iodoquinol?
1- optic neuritis 2- enlarged thyroid gland 3- iodine sensitivity
What are the signs of iodine toxicity? dermatitis,urticaria, pruritus, fever

Bacillary dysentery caused by shigella
Treated by :
Fluoroquinolones such as ciprofloxacin (can cause Arthropathy)
Cotrimoxazole in traveller's diarrhea
Oral cefixime or parenteral ceftriaxone are safe and effective.(They are 3rd generation cephalosporin)

Constipation and IBS

What are the General Measures in treatment of Constipation?

1. Adequate **fluid intake**. 2. **High fiber** contents in diet. 3. Regular exercise
4. Regulation of bowel habit. 5. Avoid drugs causing constipation. 6. Use drugs (laxatives or purgatives)

How are laxatives classified and mention the mechanism of each?

These drugs are generally classified by simplified mechanism of action, that is,
- as stimulants Act by direct stimulation of nerve endings in colonic mucosa → ↑ peristalsis & purgation
- osmotic: ↑ water content in large intestine.
- Bulking: ↑ volume of non-absorbable solid residue ↑ bulk of intestinal contents by water retention.
- stool softeners Alter the consistency of feces → easier to pass

Give some examples of stimulant laxatives.

1- Castor oil 2- Anthraquinone derivatives *(senna, cascara, aloes)* 3- Bisacodyl

What are the side effects of stimulant laxatives?

Prolonged use → dependence & destruction of myenteric plexus leading to atonic colon.

Name some members of Bulking group?

These agents, which are usually insoluble during the digestive process, include:
- From indigestible parts of fruits and vegetables)
- Hydrophilic colloids (Methylcellulose, Bran powder , Psyllium seed Carboxymethyl cellulose (CMC))

List some osmotic Laxatives?

1.Sugars : e.g. lactulose 2.Salts (Saline laxatives) → • Mg sulphate or hydroxide •Na or K phosphate.
3.Polyethylene glycol (PEG)

What is the mechanism of lactulose ? and why is commonly used in liver cirrhosis?

- mechanism: increases the H^+ concentration in the gut, This favors the formation of the non-absorbable NH_4^+ from NH_3, trapping NH_3 in the colon and reducing its back diffusion into blood.
- because Lactulose → Lactic acid + Acetic Acid acidification of the colon ↓ ammonia absorption (**NH_4^+**)

Stool Softeners . How do these agents work and Name some ?

By emulsification stool, these agents soften it and make its passage easier.
include mineral oil, glycerin suppositories, and detergents such as dioctyl sodium sulfosuccinate (docusate)

Mention some Symptomatic treatment of IBS.

1- Antispasmodics e.g. mebeverine 2- Alosetron (IBS-D) 3-Tegaserod (IBS-C)

What are the mechanism of Alosetron and Tegaserod ?

Aloserton: Selective *$5HT_3$ antagonist* of the enteric nervous system of the GIT
Tegaserod : *$5HT_4$ agonist*. Stimulation of $5HT_4$ of enteric nervous system of GIT → increases peristalsis

What is the main side effect of ***Aloserton*** that make it used in limited emergency situation?

Constipation and ischemic colitis.

Cytochrome system and drug metabolism

What is the rate limting oxidase cytochrome system? CYTP450

Where can we found the CYT P450?
1/ attached to the smooth endoplasmic reticulum of hepatocytes
2/ nterocytes of the small intestine have the principal extra-hepatic source.
3/ Very small quantities in kidneys, lungs, & brain

What is the structure of CYT P450? They are heme-containing isoenzyme

What are the function of CYT P450?
1. Endogenous substances : steroid hormones, prostaglandins, lipids.
2. Exogenous compounds : diet (food & beverages) / Drugs / environmental xenobiotics

How the regulation of CYT P450 occures?
1. Directly : through the enzyme itself.*drug activate cyt-p450 direct*
2. Indirectly : by expression or repression of its relevant genes by activation or inhibition of the responsible transcription factors

What are the type of regulation by <u>drugs</u>?
Enzyme Inducer : if activate the enzyme.
Enzyme inhibitor : if inactivate the enzyme

Polymorphism in CYP2C19 showes increased & prolonged action of its substrates as **omeprazole**. - This has been an advantage as in those variants cure rates in peptic ulcer patient with Helicobacter pylori. Genetic

CYTP2C19

- **Warfarin, phenytoin, & tolbutamide** are examples of drugs with narrow therapeutic index that are metabolized by CYP2C9.
- Clearance of these drugs is impaired in genetic variation of the enzyme

CYP2C9

Substrates	Inhibitors= toxicity	Inducers= no response
Immunosuppressants: Cyclosporine	•Protease Inhibitors: Ritonavir • Cimetidine • Chloramphenicol • Nefazadone • Grape Fruits	•Rifampicin • Phenytoin • Carbamazepine • Barbiturates • Dexamethazone • Progestins
Azole Antifungals: Fluconazole		
Antibiotics: Erythromycin, Clarithromycin		
Ca channel blockers: Amlodepine, Verapamil		
Statins: Atorvastatin		
Antiarrhythmic: Amidarone		
Cancer Chemotherapy: Cyclophosphamide, Tamoxifen		
Non-Sedating Antihistaminics: Astamizole		
Benzodiazipines: Midazolam, Clonazepam		

CYT P450 "3A4"

Metabolism of some drugs	The pro-drugs
neuroleptics, tricyclic antidepressants, antianginals agent **(perihexiline)**, antiarrhythmics **(propafenone & metoprolol)** is suppressed → so side effects & toxicity develop	cannot be converted to their therapeutically active metabolite; e.g poor analgesia with **codeine & tramadole** because they are not transformed into active forms

Neuropathy after therapeutic doses

Severe brady arrhythmias → heart block on therapeutic dose

CYP2D6

Hepatotoxic drugs

Why is the liver considred the major site of ADRs is ?

1-It is the first organ to come in contact with the drug after absorption from the GIT.
2-Being the metabolic clearing house of the body it expresses the highest levels of drug metabolizing enzymes that converts some drugs(PROTOXINS) into intermediate (TOXINS) before being conjugated for elimination

Mention 3 diffrences between intrinsic hepatotoxin and idiosyncratic hepatotoxin ?

1- **Direct while Indirect**
2--SUPERTHERAPEUTIC or CUMULATIVE dose while Normal dose
3-Predictable while Unpredictable / bizzar

Mention the two main types of intrinsic hepatotoxin ?

A. Immunoallergic Idiosyncratic Hepatotoxicity : A drug or its metabolite binds to hepatic membranes or proteins act as hapten to induce a variety of immune reactions
B. Metabolic Idiosyncratic Hepatotoxicity :The metabolite of the offending drug interferes with hepatic metabolism as that of bilirubin or protein synthesis

Mention two drugs the have viral hepatits like pattern , inflammotory cholestasis, interfre with bilirubin metabolism and interfere with protien synthesis ?

1- Viral hepatits like pattern : isoniazed and phenytoin
2-Inflammtory cholithesis : Chlorpropamide. Erythromycin.
3-interfere with bilirubin metabolism : Erythromycin and Rifampicin
4- Interfere with protien synthesis : Corticosteroids and Tetracycline

Patient is taking drug A, after 6 months from taking this drug he developed pruritus, what is drug A?

Oral contraceptives ,Chlorpropamide ,Erythromycin or Rifamycin ((Cholestatic type))

Mention the drugs that cause hepatoceullar type of injury ?

Acetaminophen ,NSAIDs ,Isoniazid or Amiodarone

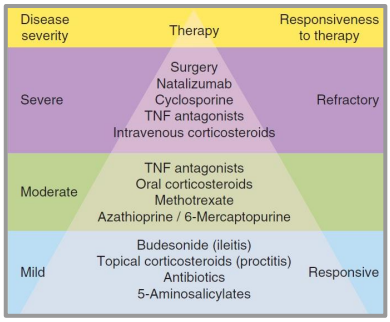
Mention the line of treatment ?

1-Immediate withdrawal : of any suspected drug (If it cause an injury u immediately stop it)
2-Symptomatic : 1-severe allergic reaction USE Corticosteroids 2- pruritus USE Cholestyramine 3-cholestatic liver injury USE Ursodeoxycholic acid (Ursodiol) 4-coagulopathy or encephalopathy develop USE High carbohydrate, moderate protein diet .
3-Specific antidotes :1-acetaminophen toxicity : use N- acetylcysteine (if a child took overdose or someone commit suicide 2-valproate toxicity : use L-carnitine
4- Emergency liver transplantation : for drug induced liver falure

Drugs used in IBD and biological and immune therapy

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

Treatment:



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.

1. 5-amino salicylic acid compounds (5-ASA) or aminosalicylates.

unformulated 5-ASA are 80% absorbed in small intestine So different formulations of aminosalicylates are made:
***Azo compounds (N=N)** -Sulfasalazine: 5-ASA + Sulphapyridine note: Sulphapyridine is the part that causes the side effects
***Mesalamines** ((Beter than Sulfasalazine, Sulfa free)) (Oral : Asacol , Pentasa) , (Rectal:Canasa , Rowasa)
The major differences are in mechanism and site of delivery. The bond will break in the terminal ileum and colon

2. Glucocorticoids.

I)**Oral preparation: e.g. prednisone, prednisolone**
II)**Parenteral preparation: e.g. hydrocortisone, methyl prednisolone**
–Higher rate of absorption –More adverse effects compared to rectal administration
III) Rectal preparation e.g. Hydrocortisone
•As enema or suppository, give topical effect. •Less absorption rate than oral.
•Minimal side effects & maximum tissue effects
Budesonide: Is subject to extensive first pass metabolism
Mechanism of action of glucocorticoids
•Inhibits phospholipase A2
•Inhibits gene transcription of NO synthase, cyclo-oxygenase-2 (COX-2)
•Inhibit production of inflammatory cytokines
Uses of glucocorticoids not effective as prophylactic therapy

3. Immunomodulators

include:
•Methotrexate:
Used to induce and maintain remission
used for Cancer
•Purine analogs:
(azathioprine is pro-drug of 6-mercaptopurine)

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

•Infliximab
-given to Patients not responding to immunomodulators or glucocorticoids
important Side effect Severe hepatic failure
•Adalimumab
-humanized IgG antibody to TNF-α
-advantage subcutaneous injection
-drug of chouse fore **Crohn's disease** ***
•Certolizumab
– Given subcutaneously for the treatment of Crohn's disease & rheumatoid arthritis

Anticoagulants

Parenteral anticoagulants:	Oral anticoagulants:
Direct thrombin inhibitors: Lepirudin.	Vitamin K antagonists: Warfarin
Indirect thrombin inhibitors: Heparin, LMWH, Fondaparinux.	-

Name of Drug / Characteristic	Heparin (UFH)	LMWH (Fondaparinux),enoxaparin , dalteparin)
IV ½ life	2 hours	4 hours
Bioavailability after SC injection	20%	90%
Antidote	protamine sulphate	none
Advantages / disdvantages	Disadvantages - Risk of HIT(Heparin Induced Thrombocytopenia) - NEEDED: aPTT - frequent bleeding, - Allergic reaction (chills, fever…) - Osteoporosis - Anticoagulant response is variable since it binds to plasma proteins.	Advantages -Better bioavailability (Anticoagulant response is predictable) - Binding to platelets & osteoblasts is reduced - can be given once a day - for FondaparinuxLess likely to trigger (HIT) -less bleeding. -less ADR in general. - not needed for aPTT
Mechanism of action	inhibits factors IIa & Xa	inhibits Xa only

Warfarin		
Mechanism of action	**Advantage**	**Disadvantages**
Inhibits synthesis of Vitamin K-dependent coagulation factors II, VII, IX, & X as (not use in pregnancy)	Bioavailability 100%	1- slow onset and offset of action 2-narrow therapeutic window leading to increased risk of severe bleeding 3- numerous interaction with foods (containing Vit. k) and drugs. 4- need Monitoring by measuring PT , expressed International Normalized Ratio.

Why the mechanism of action in Warfarin takes 3-4 days until the effect is seen ?

because Does not have any effect on already-synthesized coagulation factors; therefore, the therapeutic effects are not seen until these factors are depleted

Lepirudin: a direct thrombin inhibitor used as IV anticoagulant in patients with HIT.

Patient has got toxicity because of heparin overuse. Mention the management steps?

1- Stop the drug First 2- use Protamine sulfate

Antiplatelet Drugs

What are the substance that inhibit the platelet aggregation ?
NO & prostacyclin
What is thrombosis ?
is the formation of unwanted clot within the blood vessel
What are the difference between anticoagulants & antiplatelet?
anticoagulants :drugs which prevent clotting by inhibiting **clotting factors**
antiplatelet :drugs which prevent and inhibit **platelet activation and aggression**

calssification of antiplatelet drugs				
	Arachidonic acid pathway inhibitors	**Phosphodiesterase inhibitors**	**ADP inhibitors**	**Glycoprotein IIb/IIIa inhibitors**
Drugs	Aspirin	Dipyridamole	Ticlopidine - Clopidogrel **NEW: Prasugrel Ticagrelor**	Abciximab – Eptifibatide - Tirofiban
MOA	Irreversible inhibition of cyclooxygenase enzyme (COX-1) via acetylation	Inhibits phosphodiestrase thus increases cAMP causing decreased synthesis of thromboxane A2 and other platelet aggregating factors	These drugs specifically and irreversibly inhibit ADP receptor of subtype P2Y12, which is required for platelets activation thus prevent platelet aggregation.	Glycoprotein IIb/ IIIa receptor is required for platelet aggregation with each others and with fibrinogen and von Willbrand factor

Drugs	Aspirin	Dipyridamole	Ticlopidine - Clopidogrel NEW: Prasugrel Ticagrelor	Abciximab – Eptifibatide - Tirofiban
Uses	•Prophylaxis of thromboembolism •Prevention of ischemic events	•Adjunctive therapy for prophylaxis of thromboembolism in cardiac valve replacement (with warfarin). •Secondary prevention of stroke and transient ischemic attack (with aspirin).	Secondary prevention of ischemic complications after myocardial infarction, ischemic stroke and unstable angina	abciximab:is used with heparin and aspirin as adjunct to PCI for the prevention of cardiac ischemic complications. Eptifibatide - Tirofiban: •(act as fibrinogen-mimetic agents). •They are given intravenously for the reduction of incidence of thrombotic complications during coronary angioplasty (PCI)
Disadvantage	•peptic ulcer. •GIT bleeding	•Headache •Postural hypotension	•Sever neutropenia •Bleeding •G.I.T •Allergic reactions	-

What are the clinical use of clopidogrel?

For patients with a history of recent myocardial infarction (MI), recent stroke, or established peripheral arterial disease.

- For patients with acute coronary syndrome

what are the AVD of ticagrelor? dyspnea

Antimalarial drugs

1-name the main 4 drugs that are used for malaria:

a-artemesinin b-chloroquine c-quinene d-primaquine

2-what is the MOA of artemesinin:

They have endoperoxide bridges → - cleaved by **haem** iron to yield carbon- centered free radicals, that will:

Alkylate membranes of parasite's food vacuole and mitochondria- → no energy.

Irreversibly bind & inhibit sarco-endoplasmic reticulum Ca^{2+}-ATPase of the parasite→ - inhibiting its growth.

Inhibiting formation of **transport vesicles** → - no food vacuoles

3-what are the uses of chloroquine:

- **Active against all forms of the schizonts (except chloroquine-resistant P.f. & P.v.)**
- **Effect against all Gametoside species except falciparum**
- **No activity against *liver* shizonts**

what are the main side effect of quinine ?

- ★ **therapeutic dose → poor compliance → bitter taste**
- ★ **Higher doses :**
  - **Cinchonism syndrome : (tinnitus, deafness, headaches, nausea & visual disturbances)**
  - **Abdominal pain & diarrhea**
  - **Hypotension & arrhythmias**
  - **Rashes, fever, hypersensitivity reactions**
  - **Blackwater fever (Most series effect) , a fatal condition in which acute haemolytic anaemia is associated with renal failure**

4-what are the main adverse effects of primaquine ?

At regular doses:

-G6PD deficient patients→hemolytic anemia

At larger doses:

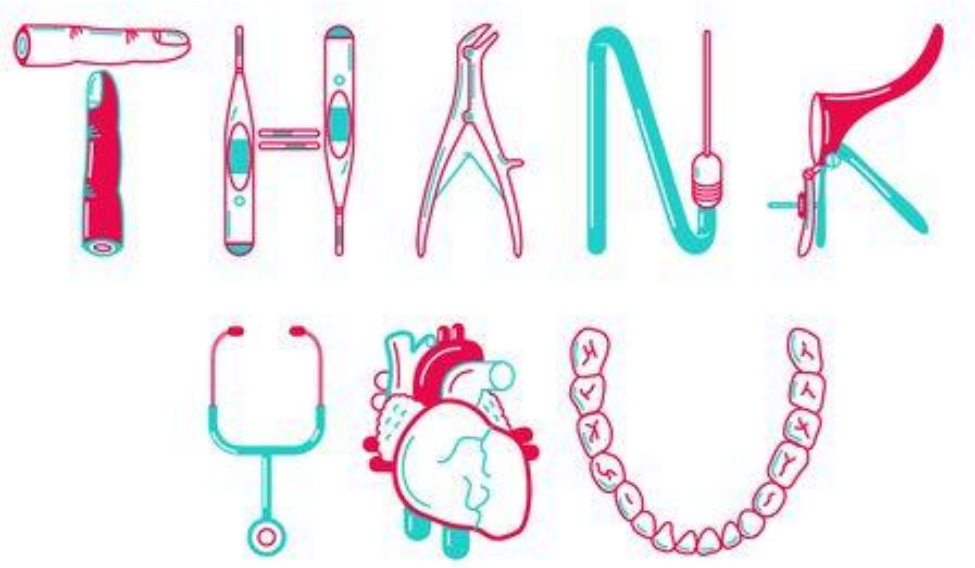
- Epigastric distress, Abdominal Cramps
- Mild Anemia, cyanosis, methemoglobinemia
- Severe Methemoglobinemia >> patients with deficiency of NADH methomoglobin reductase (rare)
- Granulocytopenia, agranulocytosis (rare)

WHO treatment guidelines

In P. Vivax	**Sensitive:** • **Chloroquine**(3 days) • followed by **Primaquine** (14 days)	**Resistant:** • **ACT** (3 days) • followed by **Primaquine** (14 days)	
In Falciparum (all show resistance)	**Uncomplicated :** **-ACT**	**Complicated:** **Artesunate** (IV for 24 hours) followed by:- ***ACT** or **[Artemether/Quinine] + [clindamycin/doxycycline]**	**Special Risk Groups:** **-Quinine + Clindamycin** (pregnancy 1st trimester) **-ACT** (Pregnancy 2nd, 3rd trimesters, lactating women, infants, and young children)

Prophylaxis in travellers

Chloroquine	**Areas without resistant P. Falciparum**	Begin 1-2 weeks before departure (except doxycycline 2 days prior) continue for 4 weeks after leaving endemic area
Mefloquine	**Areas with chloroquine-resistant P. Falciparum**	
Doxycycline	**Areas with multidrug-resistant P. Falciparum**	



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