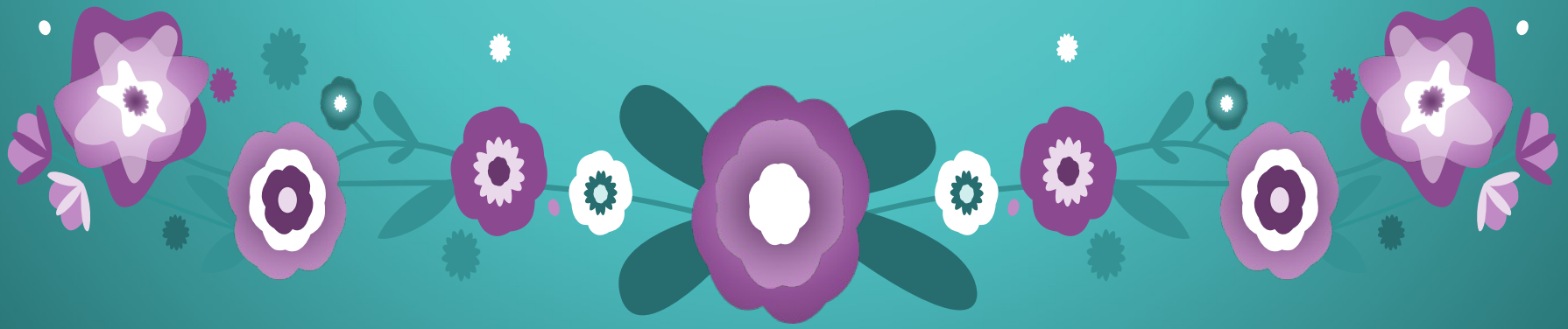
ANTIMALARIAL DRUGS.



MALARIA.

Malaria is an infective disease characterized by high grade fever, rigors and chills.

It is caused by five species of protozoal genus plasmodia.

Types of plasmodia

Plasmodium falciparum.

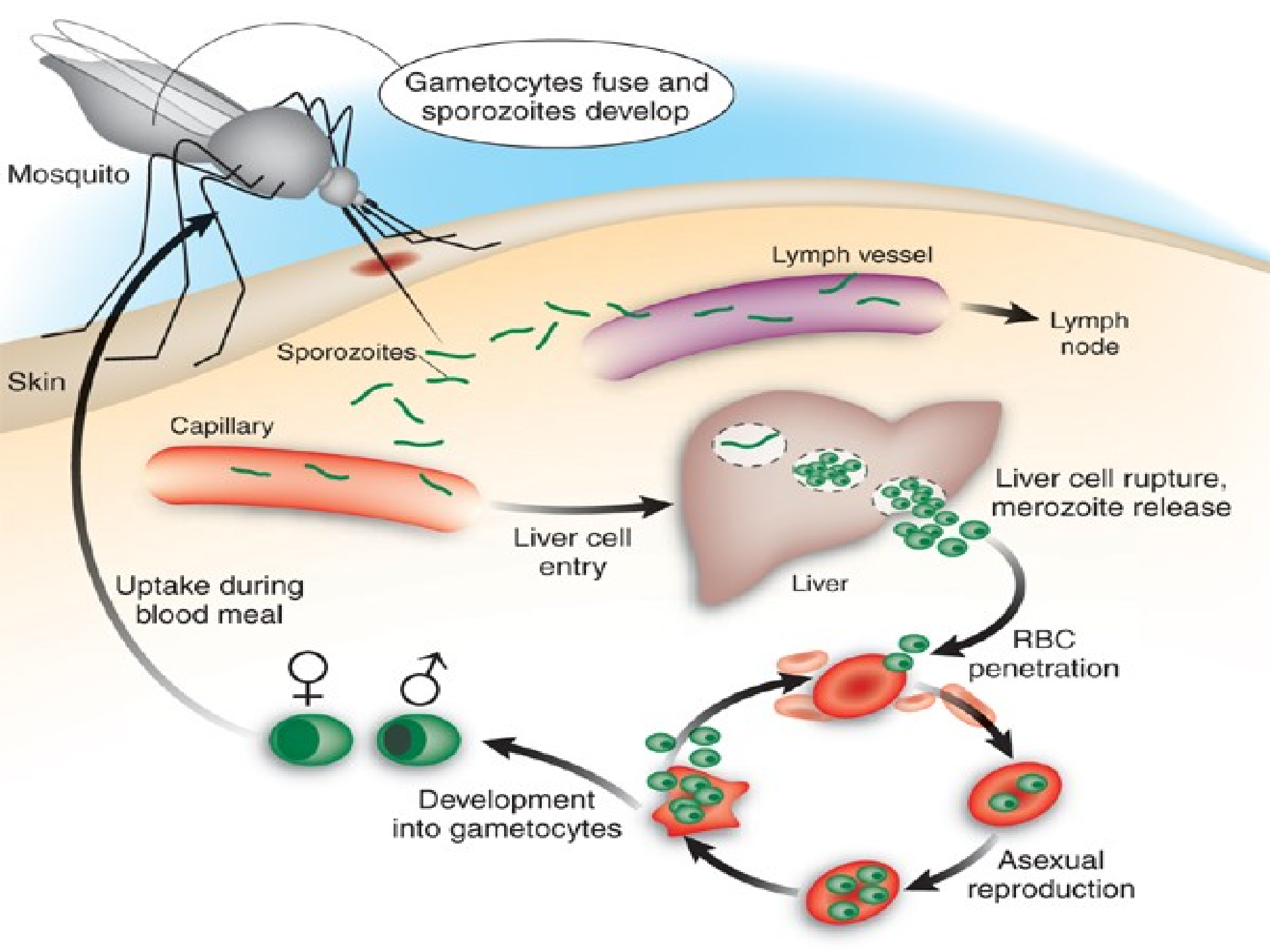
Plasmodium ovale.

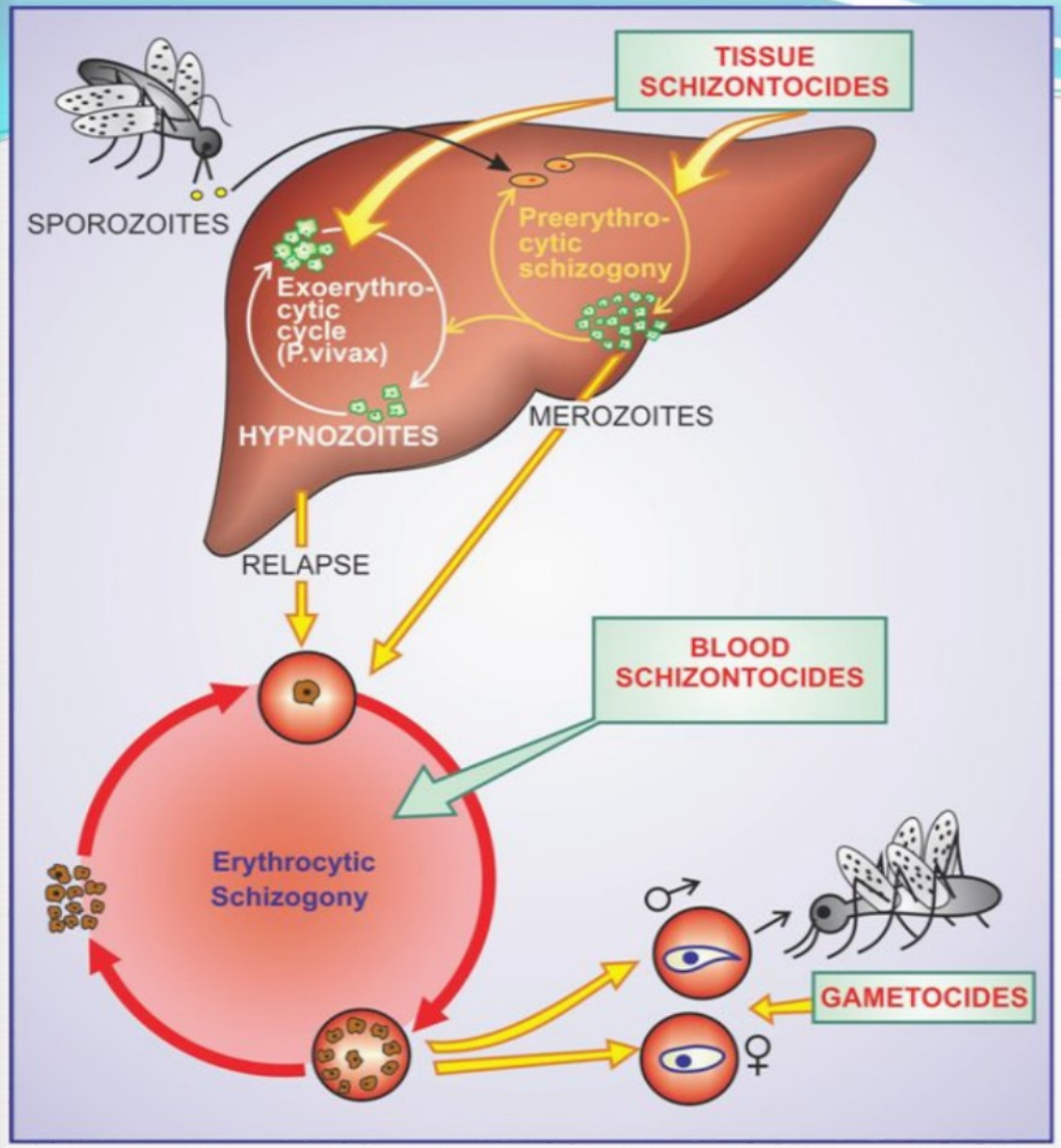
Plasmodium vivax .

Plasmodium malarie .

Plasmodium knowlesi.

Very **F**amous,
Knowledgeable
Medical **O**fficer


Gametocytes fuse and sporozoites develop
Mosquito
Skin
Lymph vessel
Lymph node
Sporozoites
Capillary
Liver cell entry
Liver cell rupture, merozoite release
Liver
Uptake during blood meal
RBC penetration
Development into gametocytes
Asexual reproduction

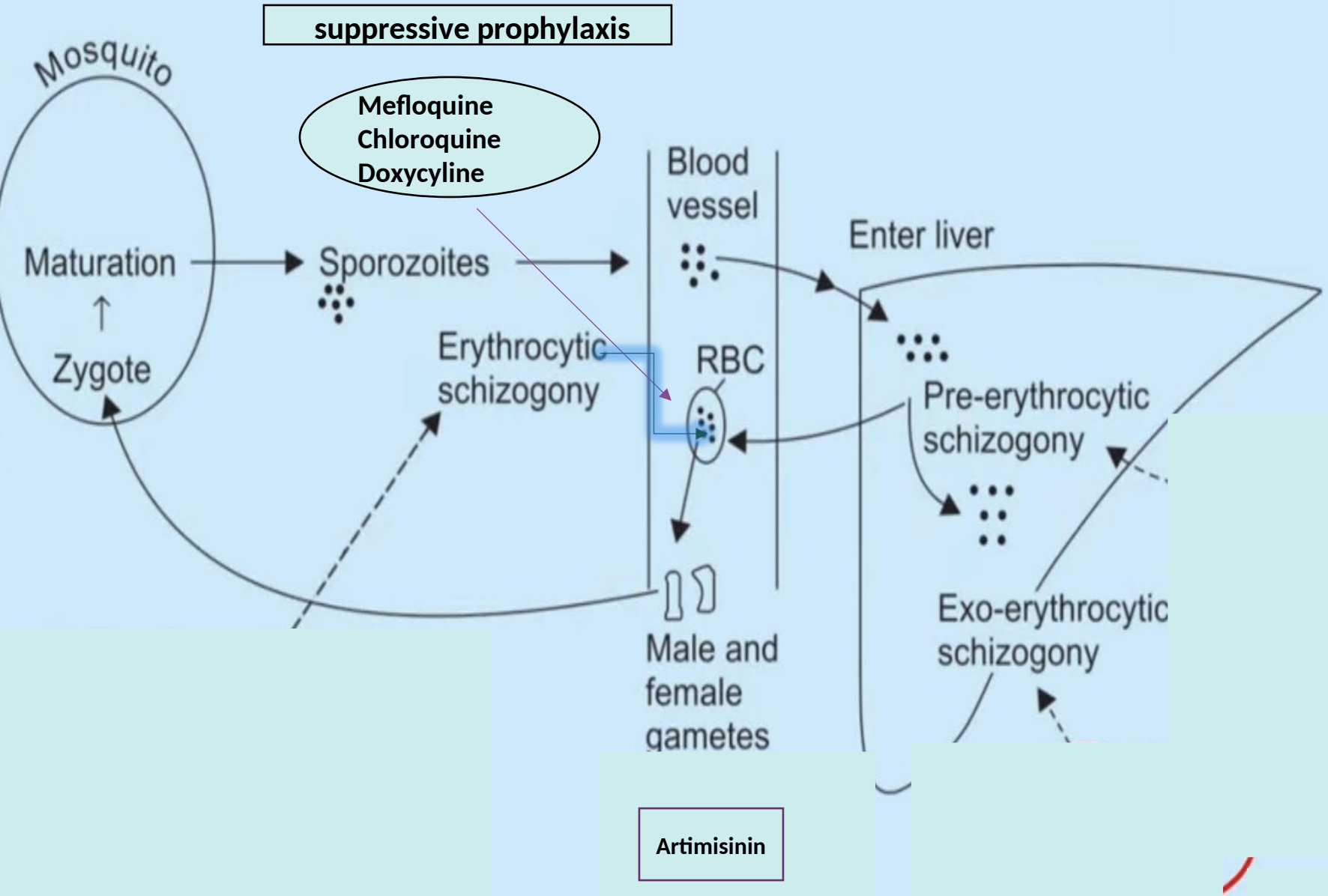


The life cycle of malarial parasite in man.

Antimalarials that act on erythrocytic schizogony are called ***erythrocytic (blood) schizontocides***

Those that act on preerythrocytic as well as exoerythrocytic (*P. vivax*) stages in liver are called ***tissue schizontocides***

Those which kill gametocytes in blood are called ***gametocides.***


suppressive prophylaxis
Mosquito
Mefloquine
Chloroquine
Doxycyline
Blood vessel
Enter liver
Maturation
Sporozoites
Zygote
Erythrocytic schizogony
RBC
Pre-erythrocytic schizogony
Exo-erythrocytic schizogony
Male and female gametes
Artimisinin

CLASSIFICATION OF ANTIMALARIAL DRUGS

1. **Cinchona Alkaloid** – Quinine, Quinidine
2. **4-Aminoquinolines** – Chloroquine, Amodiaquine, Piperaquine
3. **Diaminopyrimidines** – Pyrimethamine
4. **8-Aminoquinoline** – Primaquine, bulaquine
5. **Sulfonamides & Sulfone** – Sulfadoxine, sulfamethopyrazine, Dapsone
6. **Sesquiterpine Lactones** – Artesunate, artemeter, arteether
7. **Quinoline -Methanol** – Mefloquine
8. **Tetracyclines** – Tetracycline, Doxycycline
9. **Amino Alcohols** – Halofantrine, Lumefantrine
10. **Mannich base** – Pyronaridine
11. **Naphthoquinone** – Atorvaquone
12. **Biguanides** – Proguanil, chlorproguanil

Erythrocytic stage

Pre- Erythrocytic stage

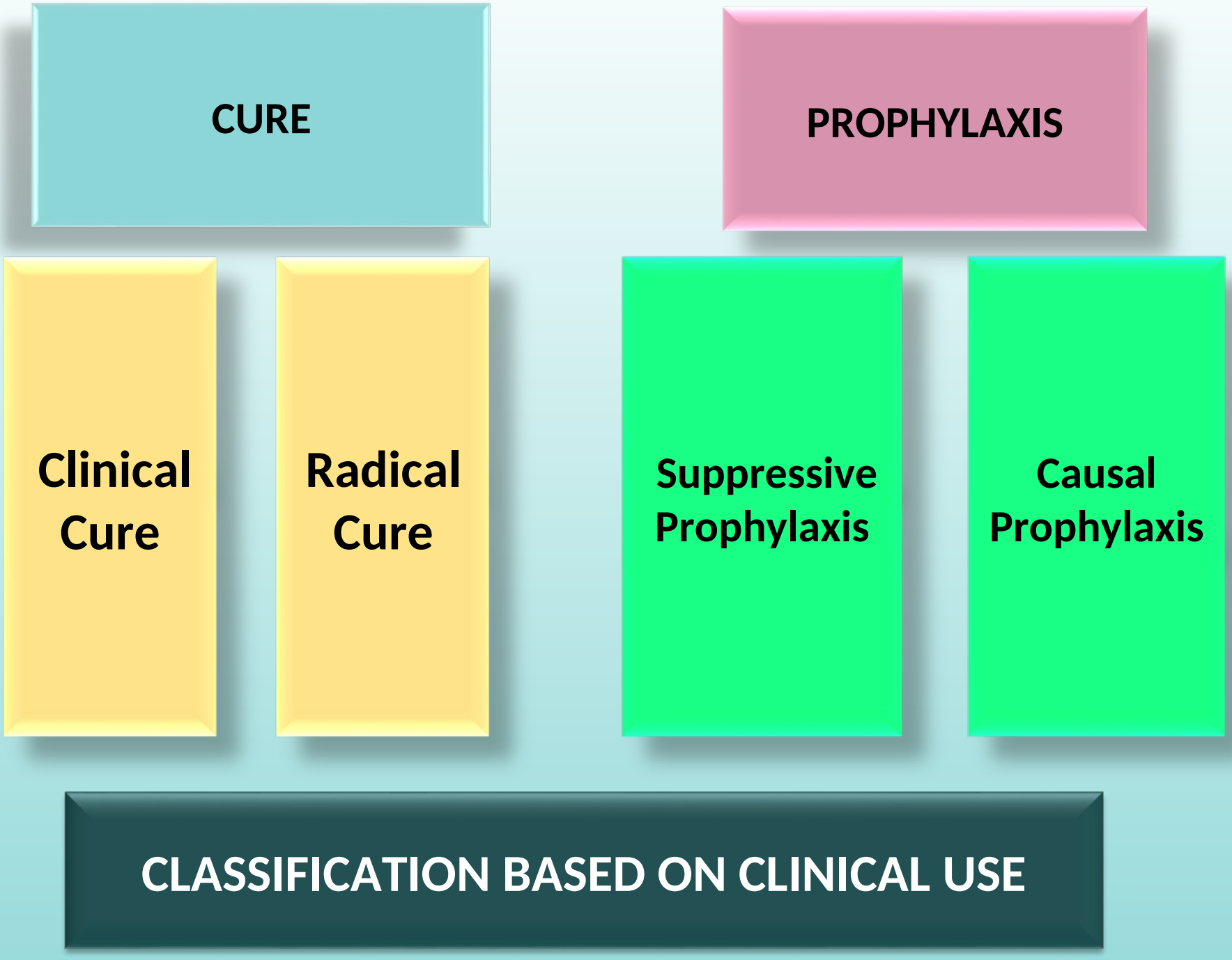
Gametogony stage

Exo-Erythrocytic stage

STAGES OF PARASITE

Stages	Hepatic stages		Blood stages	
	Primary tissue(pre-erythro)	Latent tissue (exoerythro	Asexual	Sexual Gametocidal
Drugs	Primaqiune Proguanil 100mg + Atovaquone 250mg =**Malarone** Pyrimethamine 25mg + Sulphadoxine 500mg = **Fensidar**	**Primaquine**	**M**efloquine **A**rtimisnin **C**hloroquine **H**alofantrine Atovaquone Amodiaquine **Q**uinine Fensidar Proguanil Clindamycin	Artimisinin Primaquine Chloroquine Quinine **vivax**

CLASSIFICATION BASED ON STAGES OF MALARIAL PARASITE IN HUMANS


CURE
PROPHYLAXIS
Clinical Cure
Radical Cure
Suppressive Prophylaxis
Causal Prophylaxis
CLASSIFICATION BASED ON CLINICAL USE

CAUSAL PROPHYLAXIS

SUPPRESSIVE PROPHYLAXIS

pre-erythrocytic stage in the liver

Suppress the erythrocytic stage Before rupture of RBCs

PRIMAQUINE =covers all
PROGUANIL =P. falciparum
Fensidar
Melarone

Chloroquine

Mefloquine

Doxycycline

CLASSIFICATION BASED ON CLINICAL USE

CLINICAL CURE

FAST ACTING

MACHAAR

Mefloquine

Artimisinin

Chloroquine

Halofurantoin

Atovaquone

Amodiaquine

Res –Quinine

SLOW ACTING

Proguanil

Pyrimethamine + Sulphadoxine (fensidar)

Doxycycline

Clindamycin

RADICAL CURE EXO-ERYTHRO HYPNOZOITS

PRIMAQUINE

(ALL SPEIECES)

CLASSIFICATION BASED ON CLINICAL USE

Gametocidal
Inhibits Transmission

PRIMAQUINE

ARTIMISININ

CHLOROQINE

QUININE

CLASSIFICATION BASED ON CLINICAL USE

CHLOROQUINE
4-Amino-quinolones
(BLOOD SHIZONTICIDE)

CHLOROQUINE

- ***Mechanism of action:***
  - Accumulates in the food vacuole of plasmodia
  - Prevents polymerization heme to ***Hemozoin***

    (Heme → hemoglobin breakdown product)
  - Intracellular accumulation of heme is toxic to the parasite

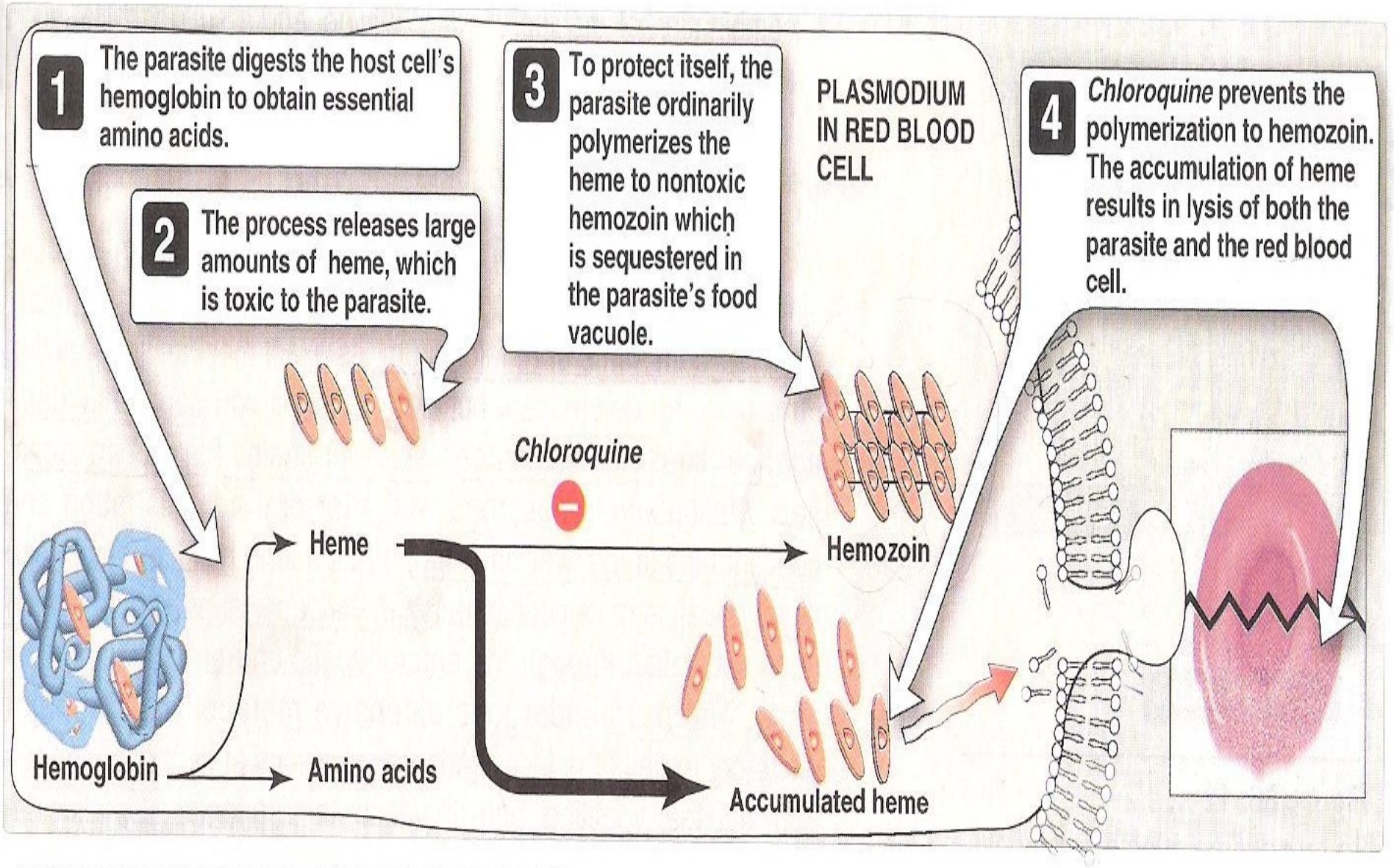


Figure 36.10

Action of *chloroquine* on the formation of hemozoin by Plasmodium species.

MECHANISM OF RESISTANCE TO CHLOROQUINE

Multigenic alterations mainly mutation in putative transporter[PfCRT], confers high level resistance to chloroquine.

Pharmacokinetics

Chloroquine is administered orally and parentrally.

Affinity for melanin rich tissues.

Extensive tissue binding

Loading dose given to achieve therapeutic concentrations.

Tendency to concentrate in liver, spleen, kidneys, lungs & skin

etc.

Metabolized in liver and slowly excreted in urine.

THERAPEUTIC USES OF CHLOROQUINE

MALARIA

P.Vivax

P. Ovale

P. Malariae

P. Falciparum

(sensitive strains)

P.Knowlesi.

Amoebiasis

Lepra reactions

Rheumatoid Arthritis

Infectious

mononuecleosis

Autoimmune disease

ADVERSE EFFECTS OF CHLOROQUINE

anti-malarial dose	parenteral doses	prolonged use Large dose(RA)
nausea **Vomiting headache** **itching, skin rash,** **visual disturbances.**	**Hypotension,** **Cardiac arrhythmias** **Cardiac arrest** **Confusion** **Convulsions.**	**Irreversible** **Retinopathy** **Ototoxity**

QUININE & QUINIDINE

Blood schizonticide

(alkaloid derived from Cinchona bark)

Causes the death of the plasmodial parasite by preventing the formation of **hemozoin** from heme.

THERAPEUTIC USES OF QUININE

Malaria:

P.falciparum Resistant malaria.

In combination with **clindamycin** or **tetracycline** its antimalarial activity is enhanced.

BABESIOSIS;

caused by bebesi microti,treated by quinine+clindamycin, tic borne malaria like illness.

ADVERSE EFFECTS OF QUININE

At therapeutic doses;

CINCHONISM;

Headache,tinnitis,
nausea ,vomiting, flushing ,
visual and auditory disturbances.

HYPERSENTIVITY REACTIONS

Urticaria,Agioedema,Broncospasm,Hypoglycemia.

BLACK WATER FEVER.

_Also_a hypersensitivity reaction (acute intravascular hemolysis classically occuring after the re-introduction of quinine in long-term residents in Plasmodium falciparum endemic areas and repeatedly using the product.)

Cramps :

due to decrease in sensitivity of the receptors to ACH by quinine.

ADVERSE EFFECTS OF QUININE

I/V infusions if rapidly infused can lead to severe hypotention.

ECG ;abnormalities [QT Interval prolonged]

Arrythmias.

CONTRA -INDICATIONS

Cinchonism ,hemolysis, hypersentivity reactions,

- Should be suspended if there is +ive coombs test for hemolysis.
- Cardiac conduction disorders.
- In renal insufficiency
- In hepatic insufficiency
- In visual disorders
- In auditory disorders

ARTIMISININS & ITS DERIVATIVES

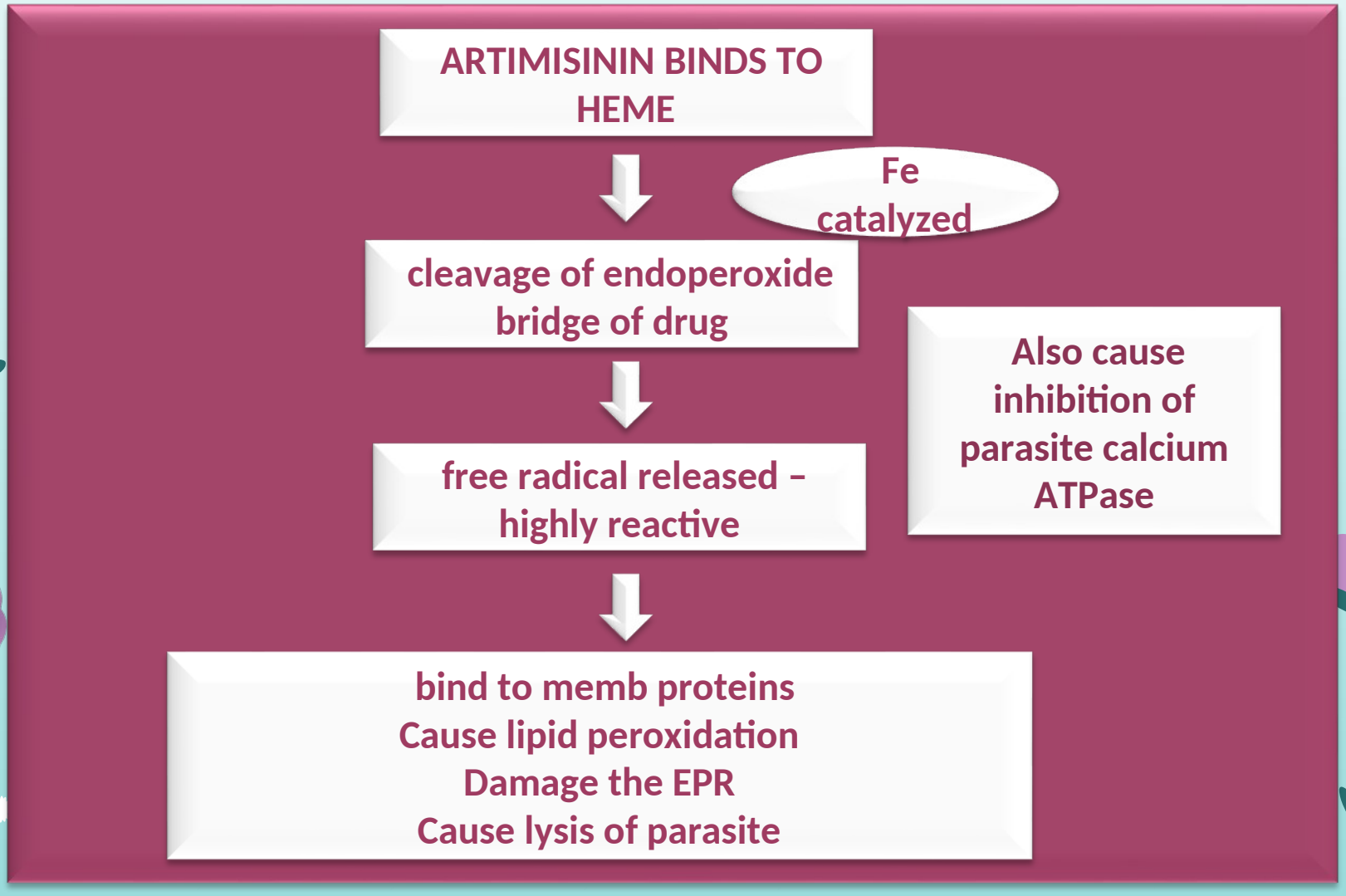
[SESQUITERPENE LACTONE ENDOPEROXIDE]
[QUNGHAOSU]

Blood shizonticide

DERIVATIVES OF ARTMISINS/PHARMACOKINETICS

Dihydroartimisinin Water sol Used orally	**Artmether** Lipid sol Orally,I/M, per rectal	**Artesunate** (Water sol) Used orally,I/V,I/M,Rectally

MECHANISM OF ACTION OF ARTIMISININ



THERAPEUTIC USES

1. Uncomplicated chloroquine resistant falciparum malaria.
2. It is also used to prevent transmission of malaria by having gametocidal activity against all the species of plasmodia.
3. In case of severe malaria caused P.falciparum., **artesunate** is the drug of choice and preferred over quinine bcz
   - Decreased risk mortality
   - Rapid parasite clearance
   - No toxic effect of heart
   - Doesn't require rate controlled I/V infusion
   - No cross resistance with other antimalarial drugs

Treating uncomplicated *P. falciparum* malaria

Treatment of uncomplicated P. falciparum malaria

Treat children and adults with uncomplicated *P. falciparum* malaria (except pregnant women in their first trimester) with one of the following recommended artemisinin-based combination therapies (ACT):

- artemether + lumefantrine
- artesunate + amodiaquine
- artesunate + mefloquine
- dihydroartemisinin + piperaquine
- artesunate + sulfadoxine–pyrimethamine (SP)

Strong recommendation, high-quality evidence

ACT should be given for 3 days.

ADVERSE EFFECTS

LOW DOSE; Nausea vomiting dizzyness.

LARGE DOSE, ECG abnormalities [QT interval prolonged].

Neurotoxicity.

Antibiotics: Tetracycline/Doxycycline, Clindamycin

- Slow acting erythrocytic schizontocides
  - Active against all plasmodial species, including CQ, MQ and S/P resistant P. falciparum
- Mechansim of Action:
  - Delayed death mechanism resulting from their inhibition of protein translation in the parasitic plastid
- Used in combination with quinine or artesunate for uncomplicated and severe falciparum malaria

MEFLOQUINE

It is a synthetic quinoline methanol.
Very effective blood schizonticide.
Only active against the erythrocytics stage of parasite.

MEFLOQUINE MECHANISM OF ACTION

Causes the death of the plasmodial parasite by preventing the formation of hemozoin from heme.

MEFLOQUINE USES

mainly acts on erythrocytic stage

Also used for the suppressive prophylaxis

Chemoprophylaxis of chloroquine resistant

p.falciparum and vivax.

MEFLOQUINE ADVERSE EFFECTS

Nausea

Vomiting

Dizzyness

Neurotoxicity

Seizure

(shouldn’t be used with quinine,preg, children

Or those with the H_x OF Psychiatric disease.)

Atovaquone

- Synthetic napthoquinone
- Rapidly acting erythrocytic schizonticide for plasmodium falciparum & other plasmodia
- MOA: Collapses mitochondrial membrane & interferes ATP production
- Proguanil potentiates action of atovaquone and prevents development of resistance
- Also used in *P. Jivoreci* & *Toxoplasma gondii infections*

synergizes

The constituents of MALARONE, atovaquone and proguanil hydrochloride, **interfere with 2 different pathways involved in the biosynthesis of pyrimidines required for nucleic acid replication**. Atovaquone is a selective inhibitor of parasite mitochondrial electron transport

PRIMAQUINE
8-AMINO QUINOLINE]

TISSUE SCHIZONTICIDE

RADICAL CURE

PRIMAQUINE MECHANISM OF ACTION

Metabolic compounds released are oxidants which has schizonticidal action also resulting in hemolysis and methemoglobinemia

PRIMAQUINE

Used in pre-erythrocytic stage of all the plasmodia

Used in ex-oerythrocytic phase of all the plasmodia

Has gemetocidal activity against all the four types of parasites

Leads to Radical cure of mainly Vivax & Ovale.

In the combination with clindamycin is effective in the treatment pneucystitis jerovecii,.

DRUG RESISTANCE

All plasmodia can develop resistance. [p.vivax]

So double the dose and give for 14 days.

ADVERSE EFFECTS OF PRIMAQUINE

- Hemolytic aneamia in G6PDdefficient pts.
- Abdominal discomfort [larger doses]
- Rarely causes
- Agranulocytosis.
- Granuloctopenia.
- Methemoglobinemia

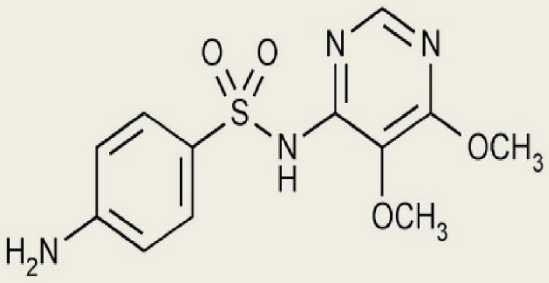
ANTI-FOLATES

- PYRIMETHAMINE
- SULPHADOXINE
- SULPHONES
- PROGUANIL

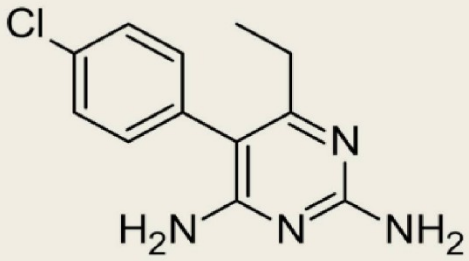
ANTI-FOLATES

- Useful in the pre-erythrocytic stage of malarial parasite (primary tissue phase).
- Slow acting drug of the erythrocytic stage

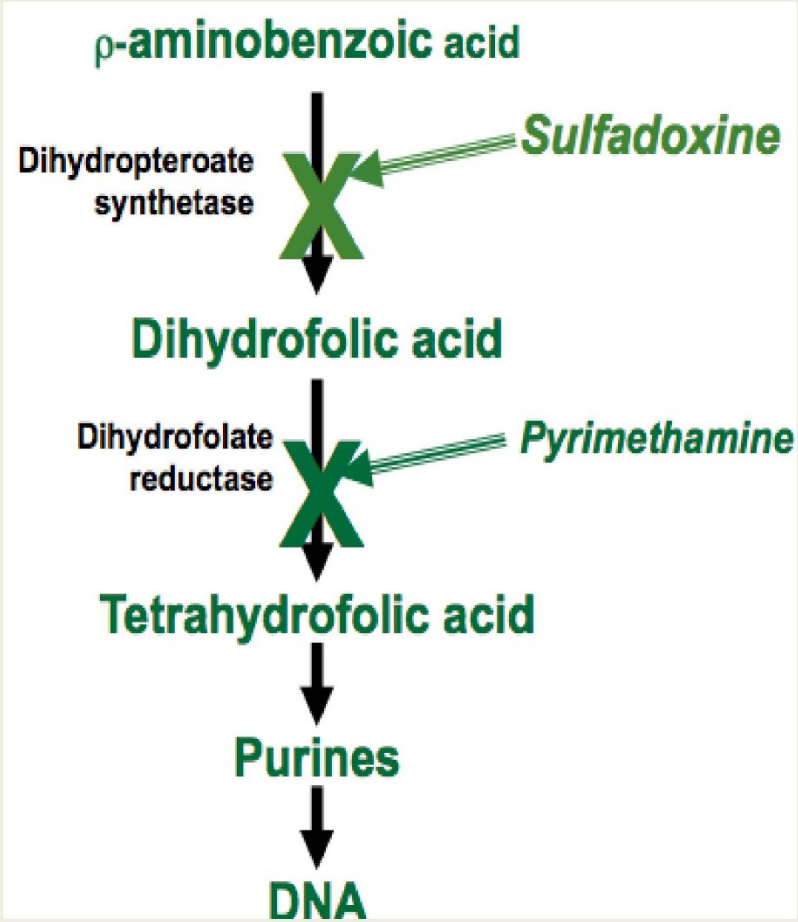
Antifolates: mode of action



Sulfadoxine



Pyrimethamine



PROGUANIL
ANTI-FOLATE

PRODRUG

It is a slow acting blood schizonticide & tissue pre-erythrocitic stage.

It is used for the causal prohylaxis usually in combination with Atovaquone. Majorly effective against P. Falciparum.

ATOVAQUONE/PROGUANIL(MALARONE)

250mg 100mg

Atovaquone/proguanil acts synergistically against the malarial parasite and avoids the rapid selection of atovaquone resistant parasites whenever the parasites are exposed to the action of atovaquone alone. This combination also brings about enzymatic inhibition of pyrimidine synthesis.

TREATMENT OF CHLOROQUINE SENSITIVE P.FALCIPARUM AND P.MALARIAE

Oral Tab Chloroquine phosphate 1gm then at 6hrs, 24hrs,48hrs

Treatment of chloroquine sensitive P.Vivax & P. Ovale

Tab chloroquine (as above)then (if G6PD normal)
Primaquine 52.6mg (30mg) for 14 days

CHLOROQUINE RESISTANT , UNCOMPLICATED P.FALCIPARUM. MALARIA

TAB QUININE SULPHATE 650MG 3 TIMES A DAY X 3-7 DAYS

+(either of the following)

Tab Doxycycline 100mg BD X 7DAYS

OR

Tab Clindamycin 600mg BD X 7 days

ALTERNATIVE REGIMEN

Malarone (4 tabs) (1g. Atovaquone +400mg. Proguanil) daily for 4 days

Mefloquine 15mg/kg once OR 750 mg then 500mg in 6-8 hrs

Coartem(Artemether 20mg +lumifantroin120mg)

4tabs BD X 3days

SEVERE COMPLICATED INFECTION WITH P. FALCIPARUM

a.

a. Artesunate 2.4 mg/kg/IV, 12hrly for 1 Day,

Then BD for 2days, followed by oral doxycycline or clindamycin or full treatment course of malarone of mefloquine x 7 days.

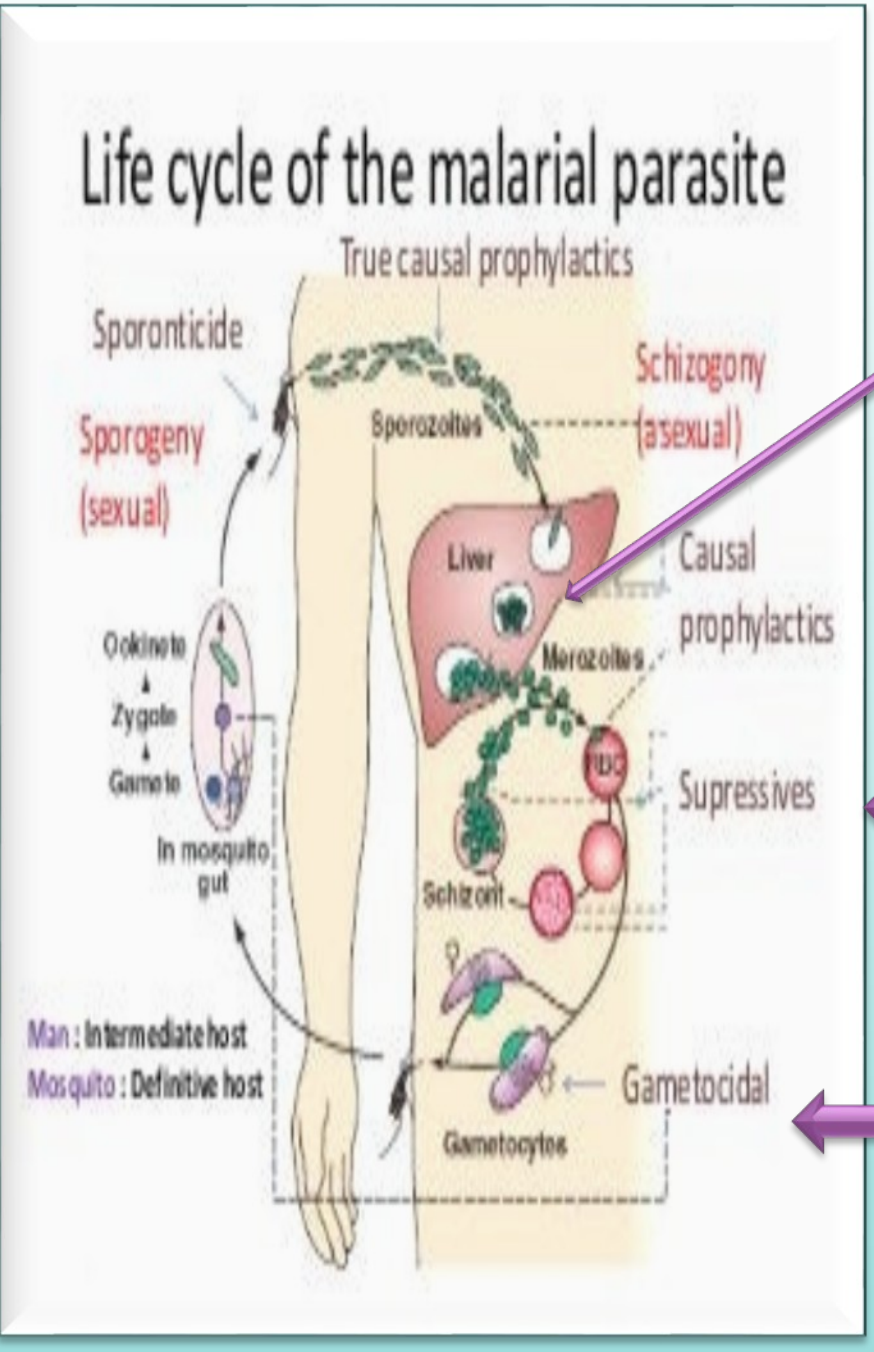
OR

b. Quinidine gluconate 10mg/Kg/IV over 1-2 hr,
Then 0.02mg/Kg/IV/min

OR

c. Quinidine 15mg/kg/IV over 4 hrs, then7.5mg mg/kg/IV over 4 hrs every 8 hrs(TDS)

QUIZ



Primaquine

Exo-erythrocytic stage (relapse phase)

Primaquine
Proguanil
Atovaquone
Fensisar

PRE-ERYTHROCYTIC STAGE)

Doxcycline
Mefloquine
Chloroquineat
atovaquone
Artemisinins
Halofurantoin
Quinine

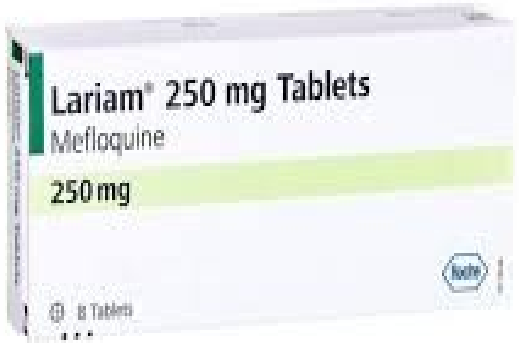
-ERYTHROCYTIC STAGE

Primaquine, Chloroquine, Artimisinin, Quinine.

Gametogony Transmision Phase

Drugs for pre-erthrocytic stage

Mefloquine



suppressive stage

DRUG FOR ALL PLASMODIA SPECIES EXCEPT CHLOROQUINE RESISTANT P-FALCIPARUM?

CHLOROQUINE.


THANK
YOU