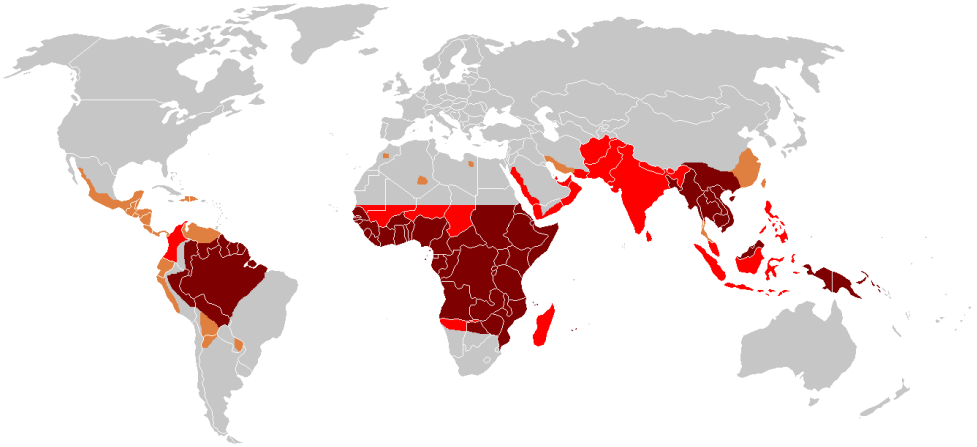
Anti-Malarial Drugs

Dr. Asma Inam

MALARIA



Mosquito's borne and is one of the major killer disease of the world.

Over 90 million cases of malaria occur every year _____ so most important of the transmissible parasitic disease _____ causing 2.7 million deaths annually.

Causative Pathogen

- Caused by unicellular parasites in genus *Plasmodium*
  - *Plasmodium vivax,*
  - *Plasmodium ovale,*
  - *Plasmodium malariae*
  - *P. falciparum* cause of most fatalities
- Spread by bite of female *Anopheles* mosquito

Plasmodium Falciparum

most dangerous

causing acute, rapidly fulminating disease

persistent high grade fever, orthostatic hypotension, and massive erythrocytosis

Capillary obstruction and death if treatment is not given in time

Plasmodium Vivax

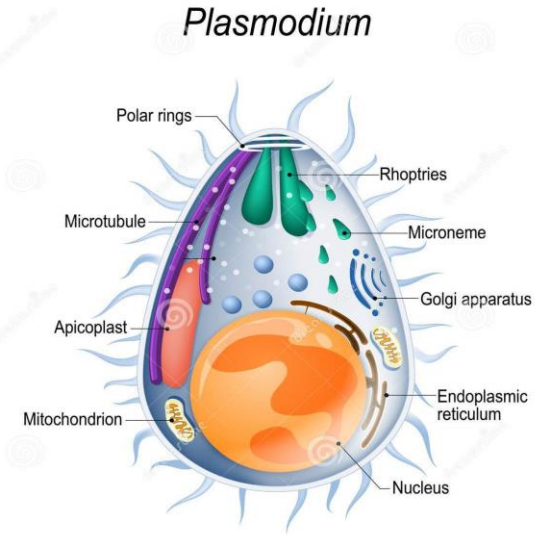
mild disease

Plasmodium Malariae

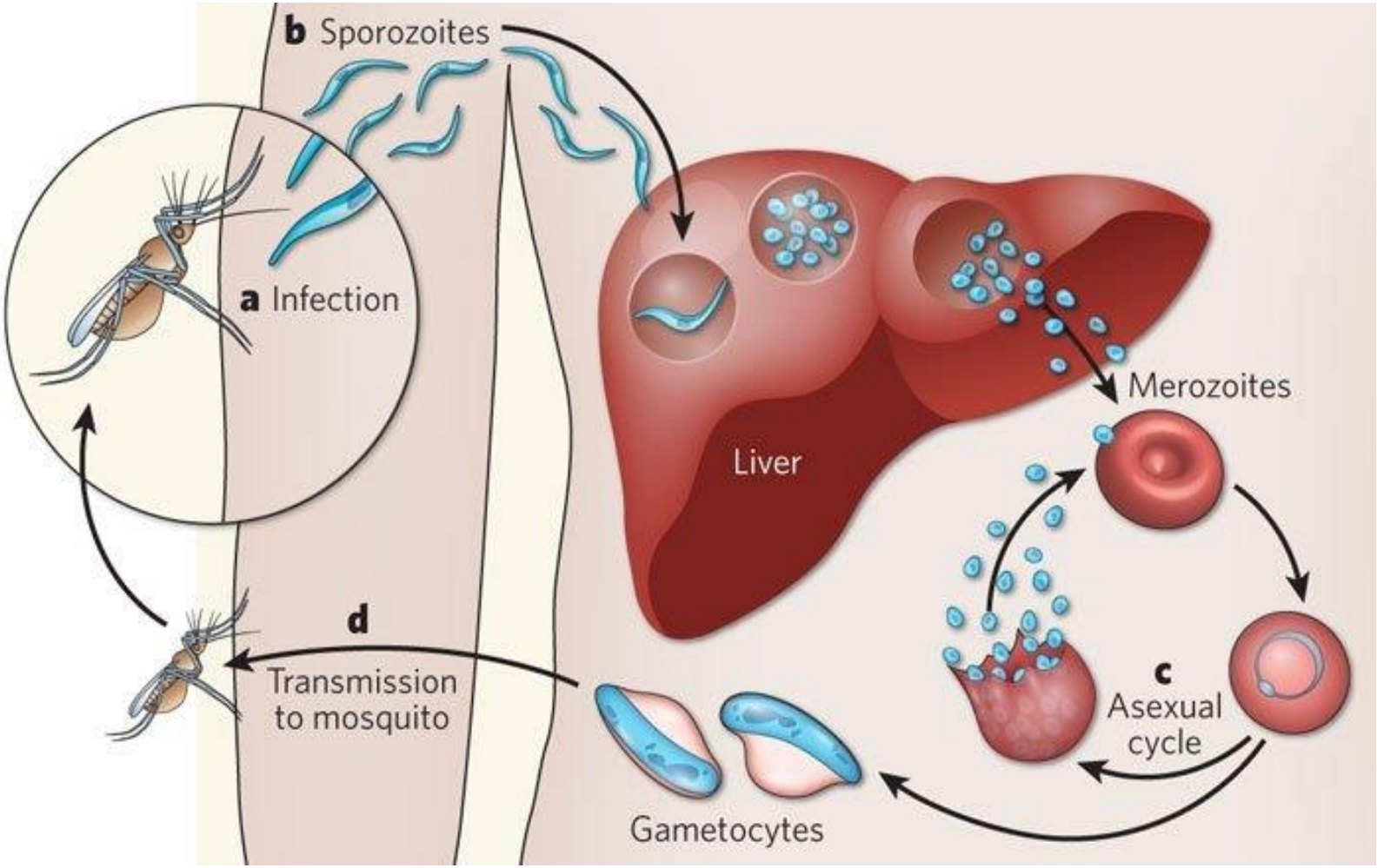
most common

Plasmodium Ovale

rare



Life cycle of plasmodium



Sexual ____ in mosquito

Asexual ____ in human being

1. Asexual:

Hepatic Cycle

Erythrocytic Cycle

1.Female anopheles _____ inject salivary secretion containing sporozoites in humans.

2.Sporozoite Disappear from blood stream

Enter liver cells.

2. Sexual Cycle:

In RBCs, 

merozoites ♀ ♂ gametocytes

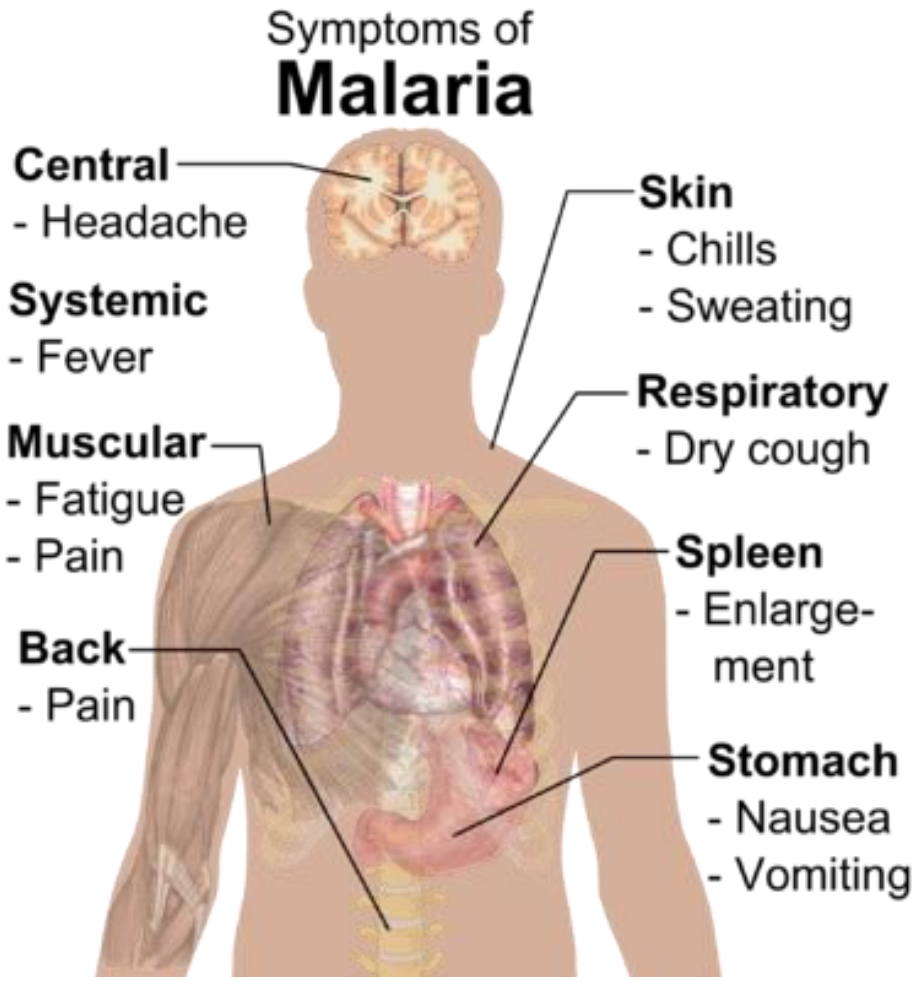
Mosquito 

Male **Female**

gametocyte

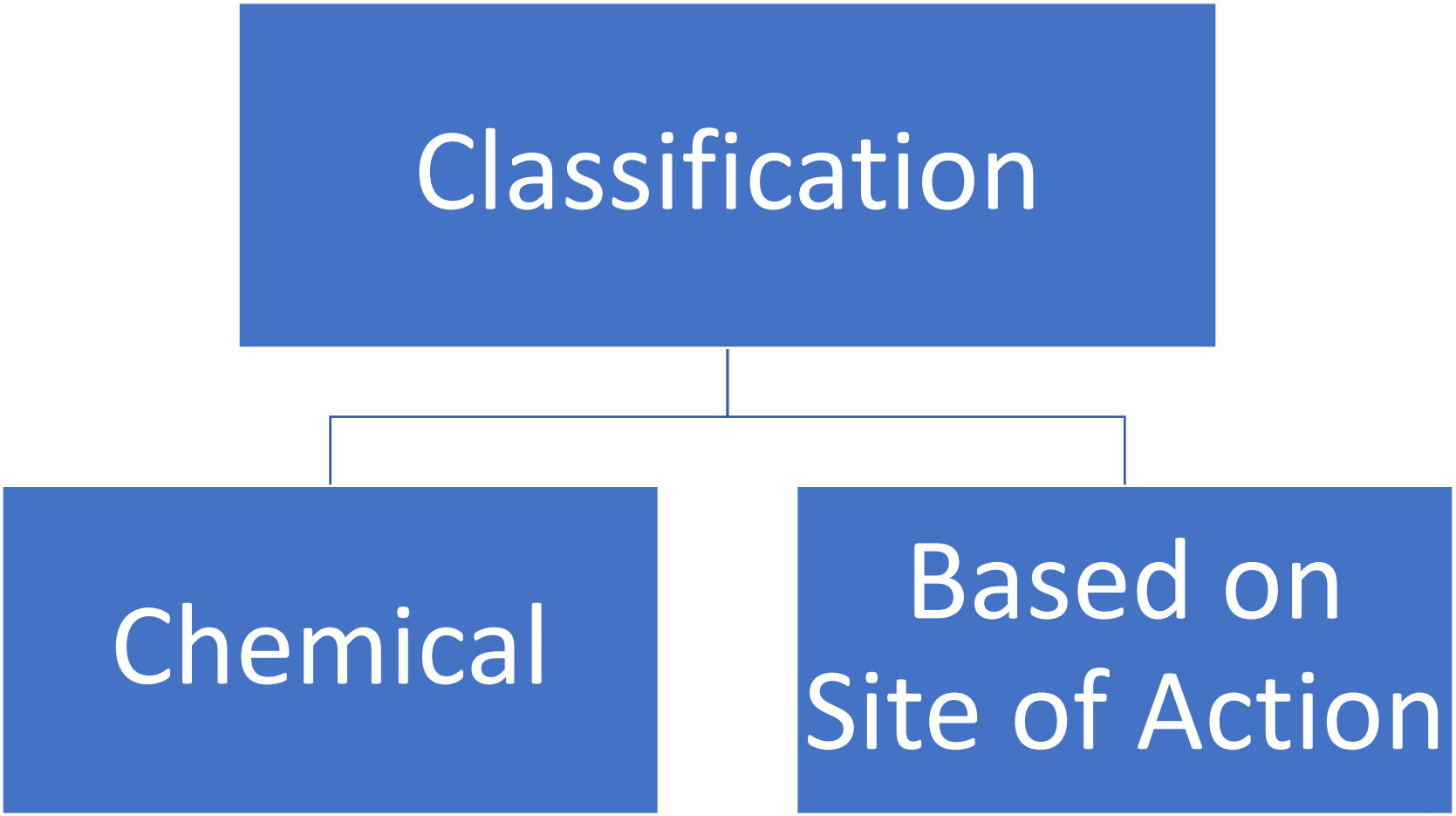
zygote ← **oocyst** ← **Sporozoites**

Gametocytocides ⊖ →


Symptoms of
Malaria
Central
- Headache
Systemic
- Fever
Muscular
- Fatigue
- Pain
Back
- Pain
Skin
- Chills
- Sweating
Respiratory
- Dry cough
Spleen
- Enlarge-
ment
Stomach
- Nausea
- Vomiting

Antimalarial drugs

- Antimalarials are antiprotozoal drugs that are primarily used to treat malaria.
- Certain antimalarials are useful in treating other conditions as well, including quinine for leg cramps and hydroxychloroquine for severe cases of rheumatoid arthritis .


Classification
Chemical
Based on Site of Action

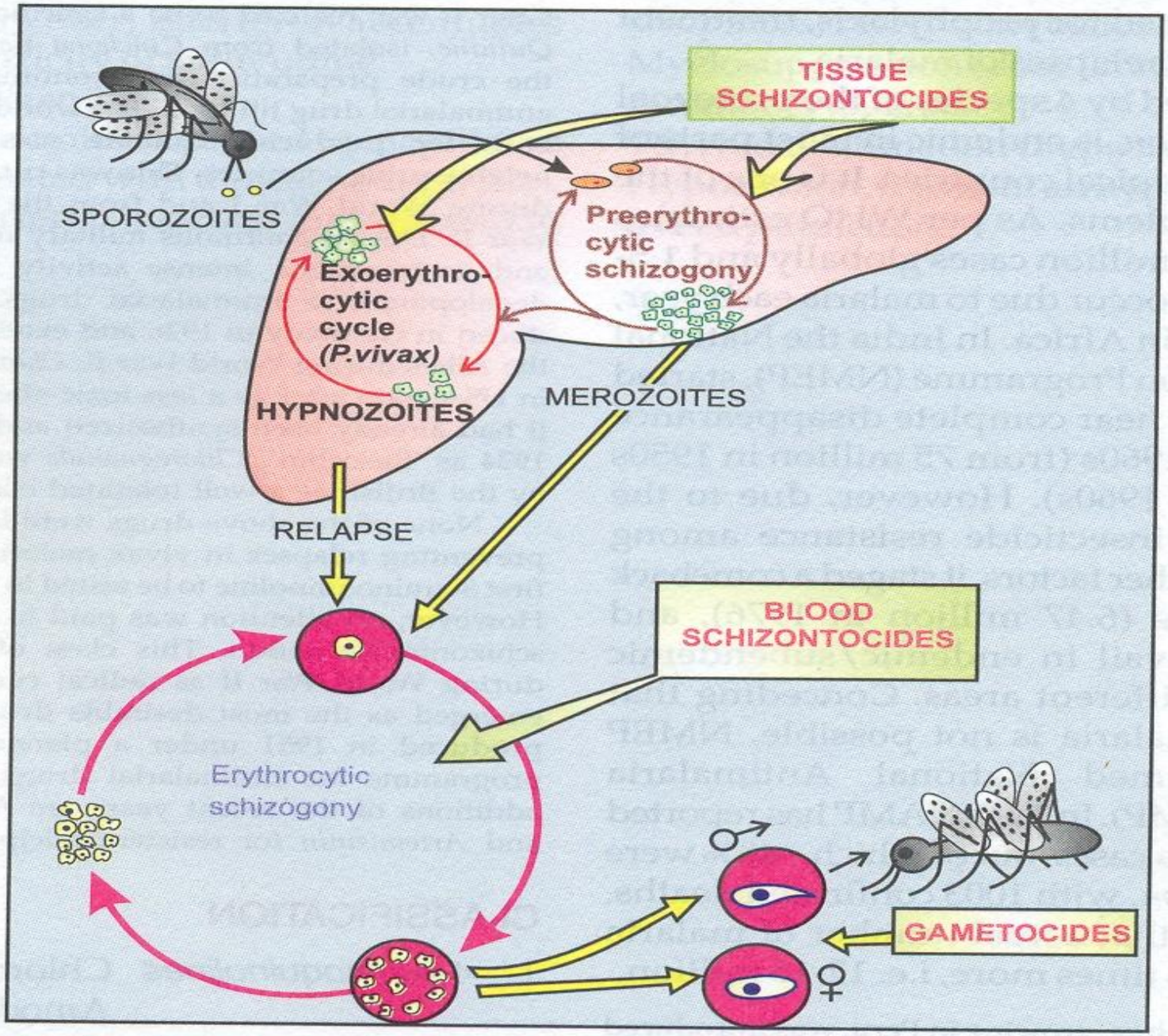


Fig. 57.1: The life cycle of malarial parasite in man. Stages and forms of the parasite at which different types of antimalarial drugs act are indicated.

1. Classification according to Site of action

1.Tissue Hepatic Schizonticides /Acting on Hepatic cycle/ Pre-erythrocytic stage

a. Against primary tissue forms/ **for Causal prophylaxis**

. *Proguanil*

b. Against latent tissue forms/ **for Terminal prophylaxis or Radical cure**

. *Primaquine*

2.Blood Schizonticides /Acting on Erythrocytic Cycle/ for Suppressive cure

a. **Rapidly acting Blood schizonticides**

- ❖Chloroquine
- ❖Amodiaquine
- ❖Quinine
- ❖Mefloquine
- ❖Halofantrine
- ❖Artemisinin (Qinghaosu) & its derivatives i.e. Artemether, Artisunate.

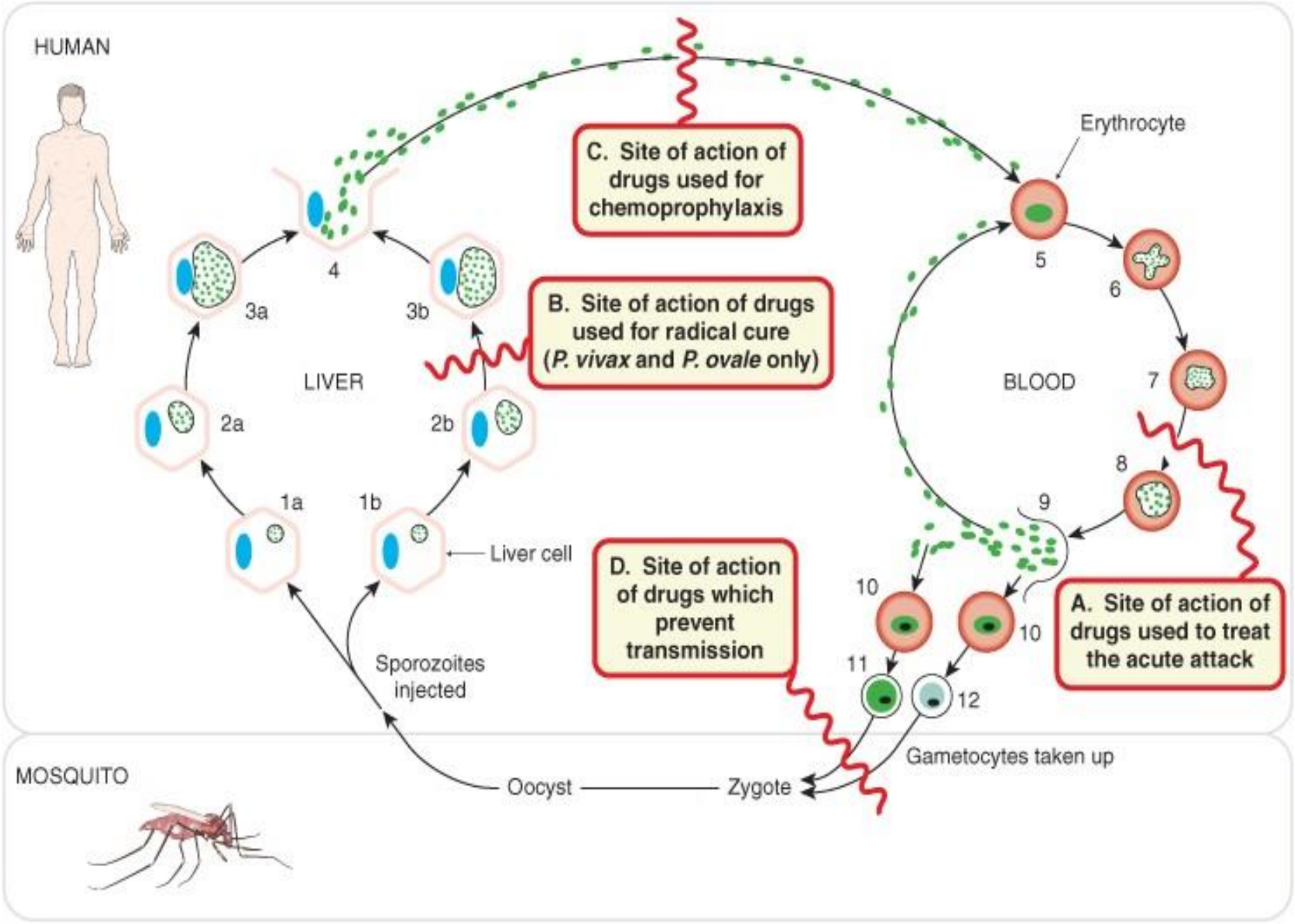
b. **Slower acting Blood schizonticides**

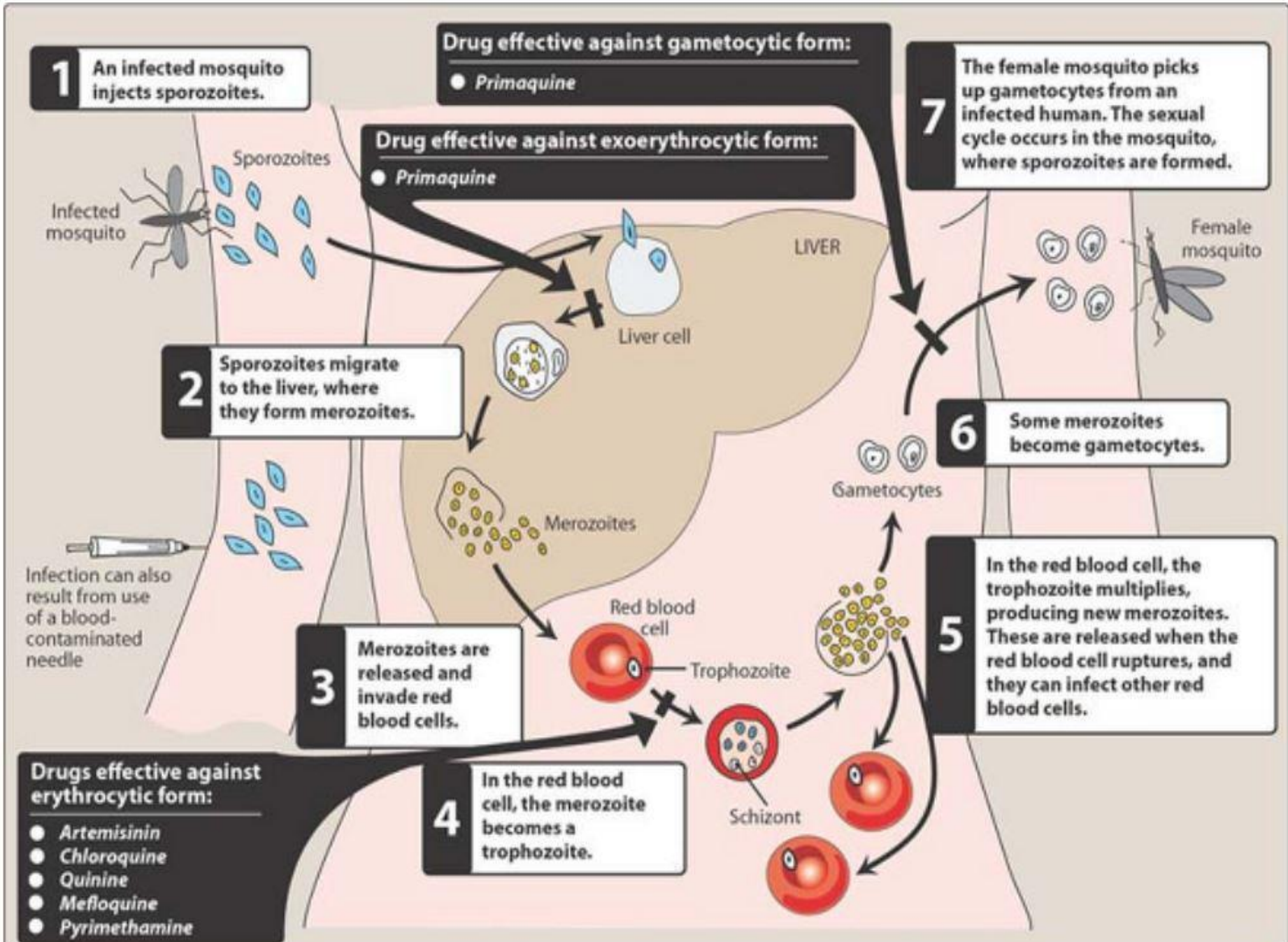
- ❖ Proguanil
- ❖ Doxycycline
- ❖ Pyrimethamine

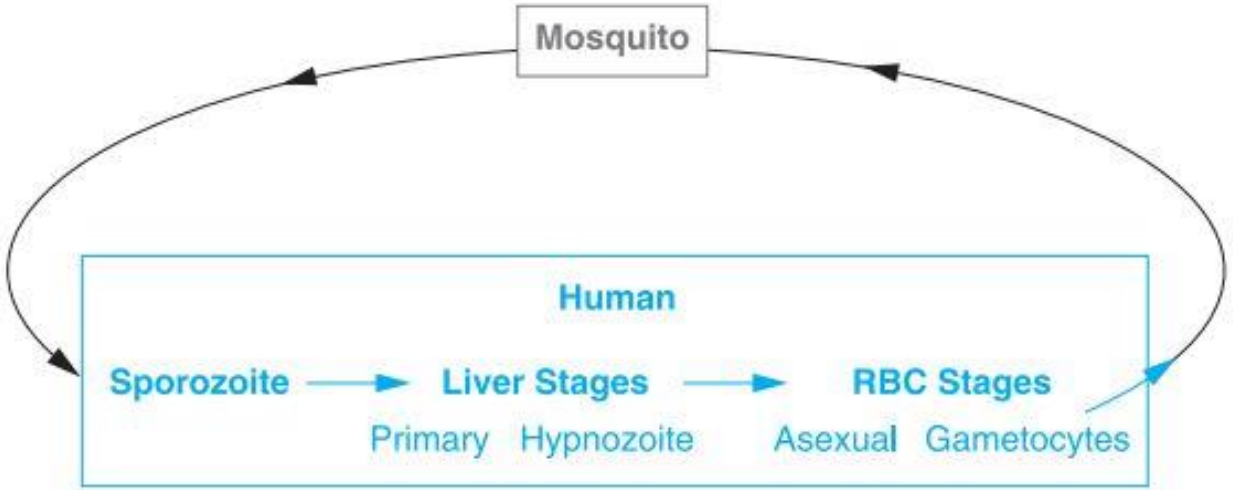
3. Gametocides/ Against sexual Erythrocytic forms

Primaquine --- Against P Falciparum

Chloroquine, Quinine --- Against P Vivax, P Ovale


HUMAN
C. Site of action of drugs used for chemoprophylaxis
Erythrocyte
4
3a
3b
5
6
B. Site of action of drugs used for radical cure (P. vivax and P. ovale only)
LIVER
BLOOD
7
2a
2b
8
9
1a
1b
Liver cell
D. Site of action of drugs which prevent transmission
10
10
A. Site of action of drugs used to treat the acute attack
11
12
Sporozoites injected
Gametocytes taken up
MOSQUITO
Oocyst
Zygote


1 An infected mosquito injects sporozoites.
Drug effective against gametocytic form:
Primaquine
Drug effective against exoerythrocytic form:
Primaquine
7 The female mosquito picks up gametocytes from an infected human. The sexual cycle occurs in the mosquito, where sporozoites are formed.
Sporozoites
Infected mosquito
LIVER
Liver cell
Female mosquito
2 Sporozoites migrate to the liver, where they form merozoites.
6 Some merozoites become gametocytes.
Gametocytes
Merozoites
Infection can also result from use of a blood-contaminated needle
Red blood cell
Trophozoite
5 In the red blood cell, the trophozoite multiplies, producing new merozoites. These are released when the red blood cell ruptures, and they can infect other red blood cells.
3 Merozoites are released and invade red blood cells.
Drugs effective against erythrocytic form:
Artemisinin
Chloroquine
Quinine
Mefloquine
Pyrimethamine
4 In the red blood cell, the merozoite becomes a trophozoite.
Schizont



Class I						
	Chloroquine	–	–	–	+	(±)
	Mefloquine	–	–	–	+	–
	Quinine, Quinidine	–	–	–	+	(±)
FANSIDAR	Pyrimethamine / Sulfadoxine	–	±	–	+	–
	Tetracyclines	–	–	–	±	–
Class II						
MALARONE	Atovaquone / Proguanil	–	(+)	–	+	–
Class III						
	Primaquine	–	+	+	–	+

2.Chemical Classification

1. **Cinchona Alkaloids:** Quinine
2. **4-Aminoquinolines:** Chloroquine
   Amodiaquine
3. **8-Aminoquinolines:** Primaquine
4. **Quinoline Methanols:** Mefloquine , Quinidine
5. **Folate antagonists:** Proguanil
   Pyrimethamine
6. **Sulfonamides:** Sulfadoxine
7. **Sulphone:** Dapsone

8. Antibiotics: Doxycycline
Clindamycin

9. Miscellaneous

- Halofantrine & Lumefantrine
- Atovaquone
- Artemisinin (Qinghaosu) & its derivatives i.e. Artemether, Artisunate.

10. Combinations

- Pyrimethamine & Sulfadoxine **(Fansidar)**
- Mefloquin , Pyrimethamine & Sulfadoxine **(Fansimef)**
- Atovaquone & Proguanil **(Malarone)**
- Pyrimethamine & Dapsone **(Maloprim)**
- Artemether and lumefantrine. (**coArtem**)

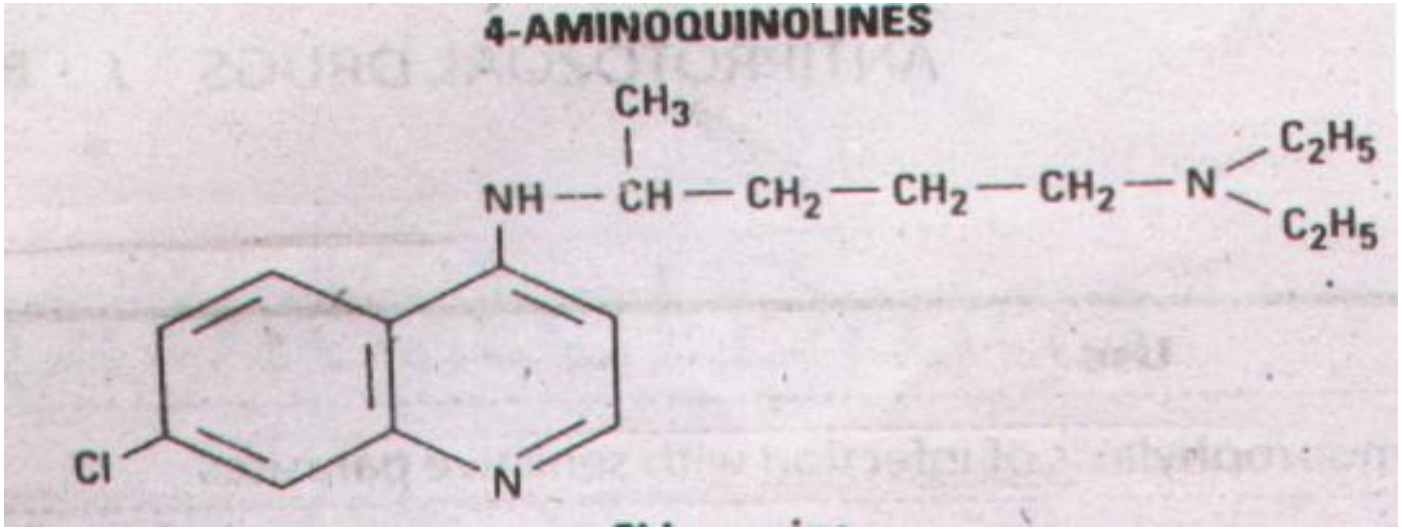
Antimalarial drugs & their Site of action

Parasite organelle	Target	Chemical class	Drugs
Cytosolic compartment	Inhibit or antagonise folic acid metabolism	Diaminopyridines Biguanides	Pyrimethamine Proguanil
		Sulfones	Dapsone
		Sulfonamides	Sulphadoxine
Mitochondrion	Block electron transport energy production	Hydroxynapthoquinones	Atovaquone, tafenoquine, pyridones
Apicoplast	Block protein synthetic machinery	Tetracyclines and others	Azithromycin, doxycycline, clindamycin other antibiotics
Digestive vacuole	Inhibit the detoxification of haem	Quinolones	Chloroquine, amodiaquine, mefloquine, quinine
		Aryl amino alcohols	Lumefantrine
Membranes ?	Inhibition of Ca^{+}-dependent ATPase	Sesquiterpene lactones	Artemisinin derivatives

CHLOROQUINE

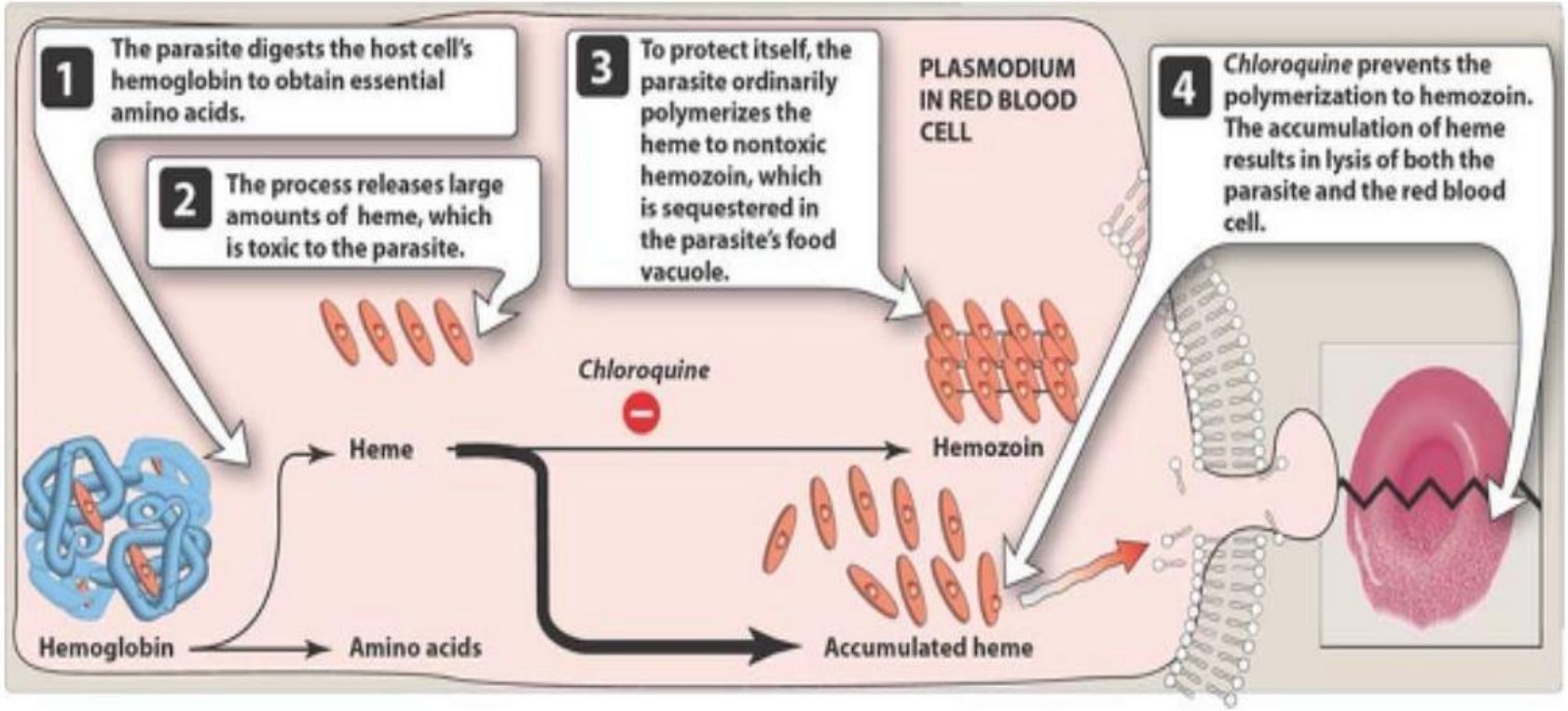
Chloroquine

- Most widely used anti-malarial, blood schizonticide
- **Source:** Synthetic drug.
- **chemistry**: 4-Aminoquinoline.
- **P/K. Vd, PPB** ↑

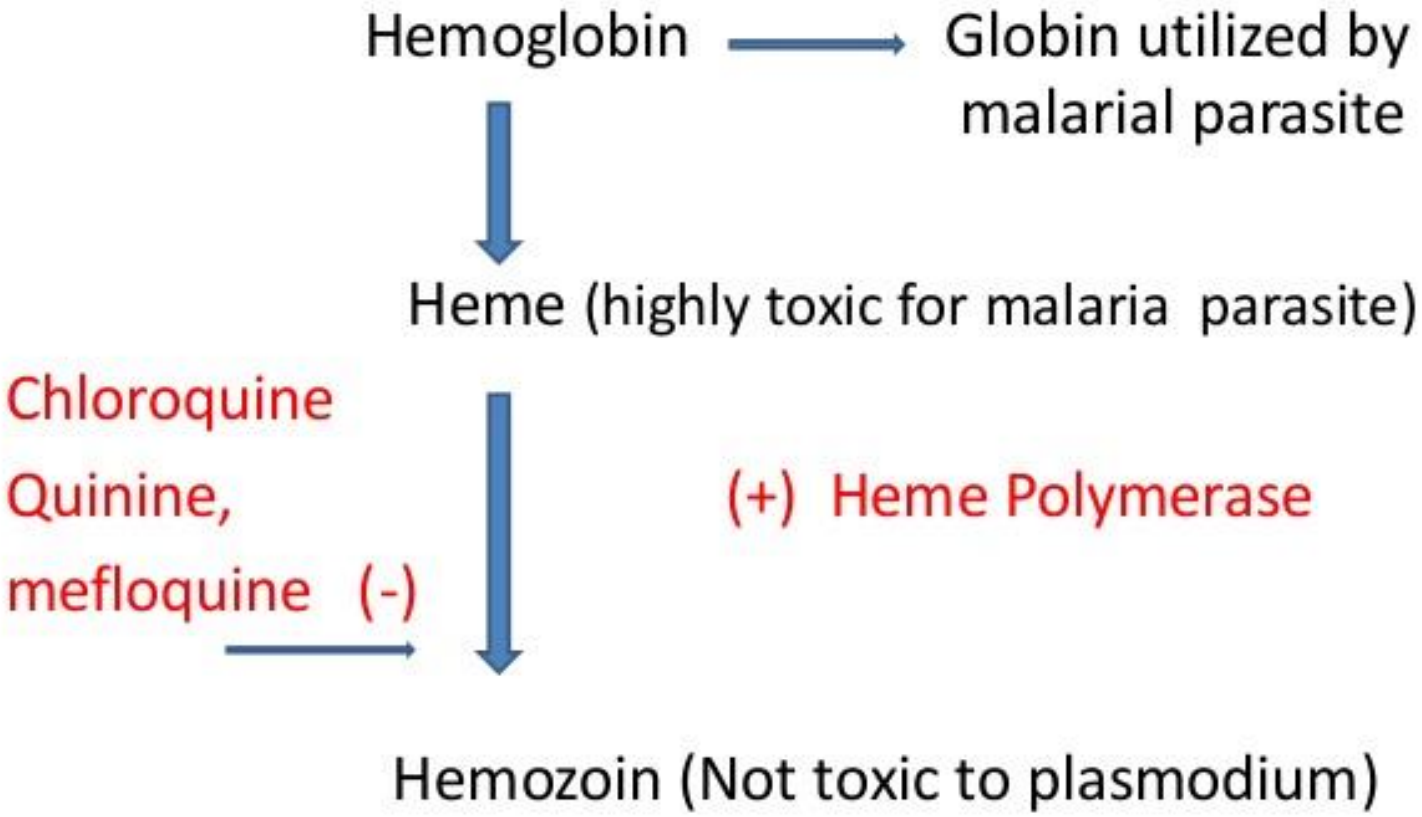


MOA of Chloroquine as Antimalarial

- It is highly effective blood schizonticide for all 4 species.
- Gametocide for P vivax.P ovale & P malariae.
- No effect on liver stages


1
The parasite digests the host cell's hemoglobin to obtain essential amino acids.
2
The process releases large amounts of heme, which is toxic to the parasite.
3
To protect itself, the parasite ordinarily polymerizes the heme to nontoxic hemozoin, which is sequestered in the parasite's food vacuole.
PLASMODIUM IN RED BLOOD CELL
4
Chloroquine prevents the polymerization to hemozoin. The accumulation of heme results in lysis of both the parasite and the red blood cell.
Chloroquine
Heme
Hemozoin
Hemoglobin
Amino acids
Accumulated heme

Mechanism of action



MOA controversial , probably acts as follows:

- Chloroquine is concentrated in parasite' food vacuoles.
- Malarial Parasites utilize hemoglobin as food, it is broken down in to heme which is polymerized into hemozoin.
- Chloroquine prevents polymerization of heme in to Hemozoin ,by inhibiting HAEM POLYMERASE.
- Accumulation of free heme, which is toxic & leads to death of Malarial Parasites.

Therapeutic uses (Safe in pregnancy)

- Acute attack of Malaria
- Chemoprophylaxis of Malaria
- Rheumatoid diseases i.e.

  Systemic lupus erythematosis, Sjogren syndrome

  Rheumatoid Arthritis
- Hepatic amoebiasis / abscess

Adverse Effects

1.After oral doses for Acute attack of Malaria:

Common:

- Pruritis sometimes Urticaria.
- Nausea, vomiting ,Abd. Pain, Anoraxia.(given with..)
- Mild headache.
- Blurring of vision.

Rare:

- **Haemolysis** in G6PD deficiency
- Impaired Hearing , confusion
- Psychosis , Seizures
- Agranulocytosis
- Exfoliative Dermatitis
- Alopecia, Bleaching of Hair
- Hypotension
- ECG Changes: QRS widening & T wave changes

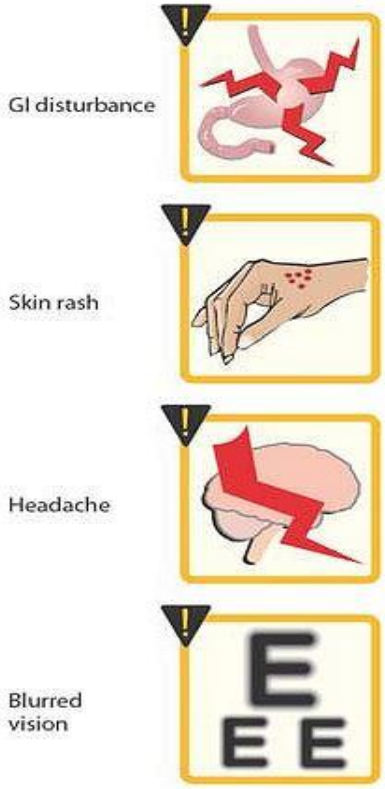
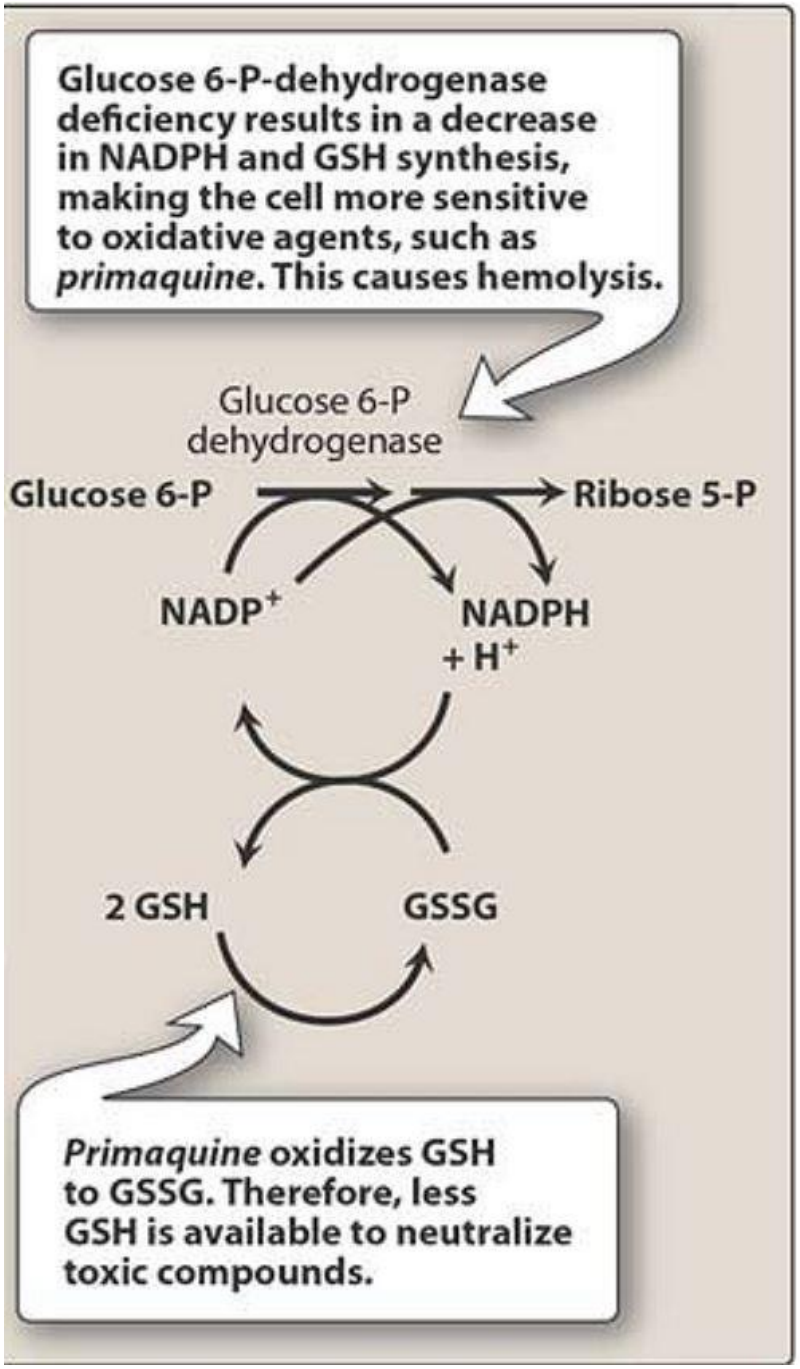


Figure 36.11 Some adverse effects commonly associated with *chloroquine*.


Glucose 6-P-dehydrogenase deficiency results in a decrease in NADPH and GSH synthesis, making the cell more sensitive to oxidative agents, such as *primaquine*. This causes hemolysis.
Glucose 6-P dehydrogenase
Glucose 6-P
Ribose 5-P
NADP+
NADPH + H+
2 GSH
GSSG
Primaquine oxidizes GSH to GSSG. Therefore, less GSH is available to neutralize toxic compounds.

2.High daily doses for prolonged periods in Rheumatoid diseases:-

- Irreversible Ototoxicity , Retinopathy myopathy & Peripheral Neuropathy.
- Bleaching of hair & Alopecia.
- Discoloration of nail beds and M.M.

3. Large I/M or Rapid I/V administration:

- Excessive hypotension.
- Respiratory & cardiac arrest

QUININE & QUINIDINE

Quinine & Quninidine

Blood schizonticides

Source:

Quinine: Natural alkaloid, Bark of Cinchona.

Quninidine: dextrorotatory stereoisomer of quinine.

Chemistry: Quinoline methanol

MOA:

Unknown.(may bind with DNA and block strand separation)

Blood schizonticide:

Rapidly acting, highly effective against four species of human M. Parasites.

Gametocidal: against p vivax and P ovale but not p falciparum.

Not active against liver stage parasites.

Resistance:

- Common in some areas
- It is increasing.

Therapeutic Uses

1. Severe P.falciparum malaria (cerebral Malaria)– **Parenterally**
2. P.falciparum malaria resistant to

   Chloroquine, **orally in combination with other drugs.**
3. Prophylaxis of malaria **– generally not used**
4. Nocturnal leg cramps

ADVERSE EFFECTS

1.Cinchonism: ---- Dose related

a. Mild cases:Tinnitis, headache , Nausea, Dizziness, Flushing , visual disturbances.

b. Severe case: visual & auditory disturbances., Vomiting ,Diarrhoea

2. **Haematological disturbances**

Haemolytic anaemia (in G6PD deficiency)

Leucopenia, agranulocytosis ,thrombocytopenia

3. **Hypersensitivity reactions:**

Skin rashes, urticaria, angioedema , bronchospasm

4. Black Water Fever:

Rare, Serious. Hemolysis & Hemoglobinuria--- hypersensitivity reaction.

5.Hypoglycemia:

6. Abortion– stimulates uterine contractions.

7. Thromophlebitis with I/V inj.

8. Severe hypotension/Cardiac arrhythmias

Hemoglobinuria

Drug interactions:

- Al. containing antacids delay the absorption.
- It may decrease the renal clearance of Digoxin & warfarin --- Increased levels.

Contra indications & cautions:

- Underlying visual & auditory disturbances
- Discontinue on severe Cinchonism.
- G6PD deficient patient.
- Cardiac abnomalities.
- C/I with Mefloquine.
- Dose reduction in renal insufficiency.

PRIMAQUINE

MOA:

Tissue schizonticide against dormant hypnozoit liver forms of P vivax & P ovale.

- Gametocide for all 4 species.
- Exact MOA unknown.

Resistance:

- some strains of P vivax are becoming resistant-- larger repeated doses may be required.

Adverse Effects

GIT upsets

Haemolytic anaemia &

Methaemoglobinaemia

(in G6PD deficiency)

Rarely Leucopenia, agranulocytosis & Cardiac arrhythmias.

Contra indications & cautions:

NEVER given parenterally--- marked hypotension.

Patients with myelosuppression.

Pregnancy.

G6PD status should be checked

Clinical uses of Primaquine

- **Radical cure** of acute Vivax & Ovale Malaria.-- drug of choice provided G6PD status is normal.
- **Terminal prophylaxis** of Vivax & Ovale
- **Gameticidal**. To disrupt transmission , rendering P falciparum gametocytes non-infective.
- **Pneumocystis jiroveci infection** with Clindamycin– mild to moderate cases.
- Not recommended for routine chemoprophylaxis.

PYRIMETHAMINE & PROGUANIL

- Pyrimethamine is related to trimethoprim.
- Proguanil is biguanide derivative.

Combinations

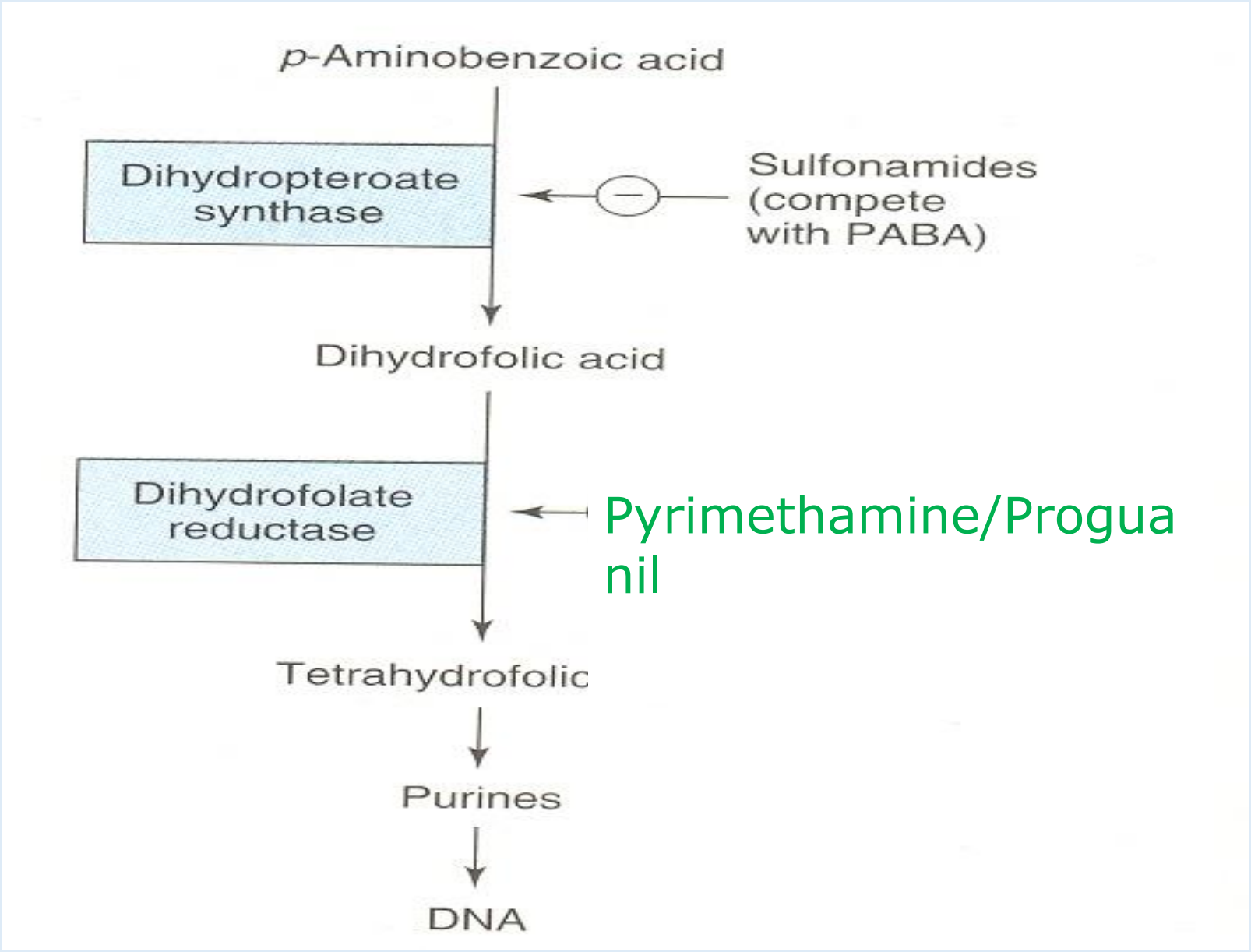
- Pyrimethamine 25 mg & Sulfadoxine 500 mg (Fansidar)
- Mefloquine , Pyrimethamine & Sulfadoxine (Fansimef)
- Atovaquone & Proguanil (Malarone)
- Pyrimethamine & Dapsone (Maloprim)

MECHANISM OF ACTION

- Antifolate drugs
- They selectively inhibit plasmodial DHFR.

Combination produces sequential blockade of steps in Folate synthesis.& synergistic effect

- Slow acting blood schizonticides.
- Proguanil has some activity against primary liver forms.
- Neither Pyrimethamine nor Proguanil is active against dormant / persistent liver forms.
- No gametocidal action.


p-Aminobenzoic acid
Dihydropteroate synthase
Sulfonamides (compete with PABA)
Dihydrofolic acid
Dihydrofolate reductase
Pyrimethamine/Proguanil
Tetrahydrofolic
Purines
DNA

Therapeutic uses

- Chemoprophylaxis:. Proguanil is safe in pregnancy, give Folic acid also. combinations preferred otherwise.

  Pyrimethamine & Dapsone (Maloprim) is first line drug for prophylaxis of chloroquine / Mefloquine resistant malaria

- Treatment of chloroquine resistant P.falciparum Malaria. Pyrimethamine & Sulfadoxine (Fansidar)
- Presumptive treatment of P falciparum in travelers.
- Toxoplasmosis: Pyrimethamine & Sulfadiazine , add folinic acid.

  High doses for immunocompromized patients.
- Pneumocystosis jiroveci :

Pyrimethamine & Sulfamethoxazole.

Adverse Effects

Both drugs can cause:

- Allergic reactions , GIT upsets, Headache.
- Proguanil: mouth ulcers & Alopecia.
- Pyrimethamine: in high doses (used in Toxoplasmosis)----
- Deficiency of Folic acid causes Megaloblastic anaemia, Atrophic glossitis

Fansidar

- With single dose A/E like sulfonamides.
- If used for chemoprophylaxis: severe cutaneous reactions (erythema multiforme) Steven-johnson Syd. & toxic epidermal necrolysis.
- Maloprim: Agranulocytosis

ANTI MALARIAL ANTIBIOTICS

Doxycycline

Clindamycin

Azithromycin

Mechanisms of Antimalarial Action:

Not clear

- May Inhibit protein synthesis, or functions of organelles.
- They are slow acting Blood schizonticides
- Not as single agents for treatment because of much slower action.

CLINICAL USES

- For chemoprophylaxis of chloroquine / Mefloquine resistant malaria
- For treatment of P falciparum malaria with quinine/quinidine.

Clindamycin: slow blood schizonticide used with quinine/quinidine if doxycycline is contraindicated.

Azithromycin: under study for chemoprophylaxis.

HALOFANTRINE
&
LUMEFANTRINE

Halofantrine

- Halofantrine: is related to quinine.
- Effective against most chloroquine resistant P falciparum---**blood schizonticide**
- Limited use because of **cardiac conduction defects** & it is Teratogenic..

Lumefantrine

- Lumefantrine: is related to halofantrine.
- Used in combination with artemether ---Coartem as first line drug for resistant Falciparum malaria.
- **Not cardiotoxic.**

ARTEMISNIN & DERIVATIVES

Artimisinin(Qinghaosu) & its Derivatives

- **Artimisinin:** Sesquiterpene lactone endoperoxide. Active compound of a Herbal medicine used in China.

--- only used orally.

- **Analogs: Artisunate & Artemether.**
- **Artisunate** (Water soluble) useful for oral **I/V ,** I/M & rectal admin.
- **Artemether** (Lipid soluble) useful for oral I/M & rectal admin.

MOA

- Rapidly acting blood schizonticide against all four species of MP.
- No effect on hepatic stages.
- They act by producing free radicals due to iron catalyzed cleavage of the artemisnin endoperoxide bridge in the parasite food vacuole

or

- Inhibition of a parasite calcium ATPase

Therapeutic Uses

- Treatment of multi drug resistant , **specially quinine resistant** P falciparum uncomplicated or severe malaria.

Combination is preferred

Artemether alone or in combination with lumefantrine.

Artisunate in combination with Mefloquine / Amodiaquine / Sulfadoxine / Pyrimethamine.

- Not useful for prophylaxis – short half life.

Adverse effects

Nausea, Vomiting,
Diarrhoea.
Irreversible neurotoxicity in animals at high doses.
Teratogenic in animals.

Antimalarials contra-indicated in pregnancy

- Tetracycline
- Doxycycline
- Halofantrine
- Primaquine
- Tafenoquine

Quinine

- Note: if serious illness, and where limited number of drugs are available, it is necessary to balance the risk of maternal death with the hypothetical risks to the infant

Treatment of Malaria

Clinical setting	Drug Therapy	Alternative Drugs
Chloroquine sensitive p falciparum & p malariae infections	**Chloroquine phosphate, 1 g then 500mg in 6 hrs, followed by 500mg daily for 2 days** **Or** **Chloroquine phosphate, 1g at 0 and 24 hrs, then 0.5 g at 48 hrs**	

Clinical setting	Drug Therapy	Alternative Drugs
P vivax & P ovale infections	Chloroquine (as above), then (if G6PD normal) primaquine, 26.3mg daily for 14 days	

Uncompleted infections with Chloroquine resistant p falciparum	Quinine sulfate, 650 mg 3 times daily for 3-7 days plus one of the following- Doxycycline, 100mg twice daily for 7 days Or Clindamycin, 600mg twice daily for 7 days Or Fansidar, three tablets once.	Mefloquine, 15mg/kg once or 750mg, then 500mg in 6-8 hrs or- Malarone, 4 tablets (total of 1 g atovaquone, 400 mg proguanil) daily for 3 days or- Artesunate or artemether single daily doses of 4 mg/kg on day 0,2 mg/kg on day 2 and 3, 1mg/kg on days 4-7 or- Coartem (coartemether, 20 mg, lumefantrine 120mg), 4 tablets twice daily for 3 days.

Severe or complicated infections with p falciparum	Quinidine gluconate,10mg/kg IV over 1-2 hrs, then 0.02 mg/kg IV/min or- 15 mg/kg IV over 4 hrs, then 7.5 mg/kg IV over 4 hrs every 8 hrs	Artesunate, 2.4mg/kg IV or IM, then 1.2 mg/kg every 12 hrs for 1 day, then every day, Or- Artemether, 3.2 mg/kg IM, then 1.6 mg/kg/d IM.

TABLE 52–1 Drugs used in the treatment of malaria.

Drug	Uses	Adverse Effects
Chloroquine	Prophylaxis and treatment in areas without resistant *P falciparum;* treatment of *P vivax* and *P ovale* malaria	GI distress, rash, headache; auditory dysfunction and retinal dysfunction (high dose)
Artemisinins	Standard of care for all chloroquine-resistant malaria	GI distress, rare neutropenia, anemia, liver enzymes, allergic reactions
Mefloquine	Prophylaxis and treatment in areas with resistant *P falciparum*	GI distress, rash, headache; cardiac conduction defects and neurologic symptoms (high dose)
Quinine[a]	Treatment of multidrug-resistant malaria	Cinchonism, hemolysis in G6PD deficiency, blackwater fever
Primaquine	Eradication of liver stages of *P vivax* and *P ovale*	GI distress, methemoglobinemia, hemolysis in G6PD deficiency
Antifolates	Prophylaxis and treatment of multidrug-resistant *P falciparum* malaria	GI distress, renal dysfunction, hemolysis, folate deficiency
Atovaquone-proguanil (Malarone)	Prophylaxis and treatment of multidrug-resistant *P falciparum* malaria	GI distress, headache, rash hemolysis, folate deficiency

[a]In most cases quinine is used together with doxycycline or clindamycin, or an antifolate. Quinidine gluconate (IV) is used in severe infections or for patients unable to take oral quinine.

THE END.