MALARIA

- Major health problem
- Endemic protozoal disease
- 70-100 million cases per year
- P. Falciparum responsible for half of the cases
- P. Falciparum accounts for 90%of deaths caused due to malaria
- Treatment of malaria has been revolutionized with use of artemisinin

- Mal-Bad ,Aria-Air –occurrence-associated with bad air
- Sir Ronald Ross-Parasitologist
- **Caused by protozoa – Plasmodium**
- **Plasmodium is of 4 species**
- **Vivax, Falciparum. Malariae, ovale**
- **Life cycle of the parasite**

Two stages

Asexual — **Sexual**

Human being — **Female**

Anopheles mosquito

Infected Anopheles mosquito bite

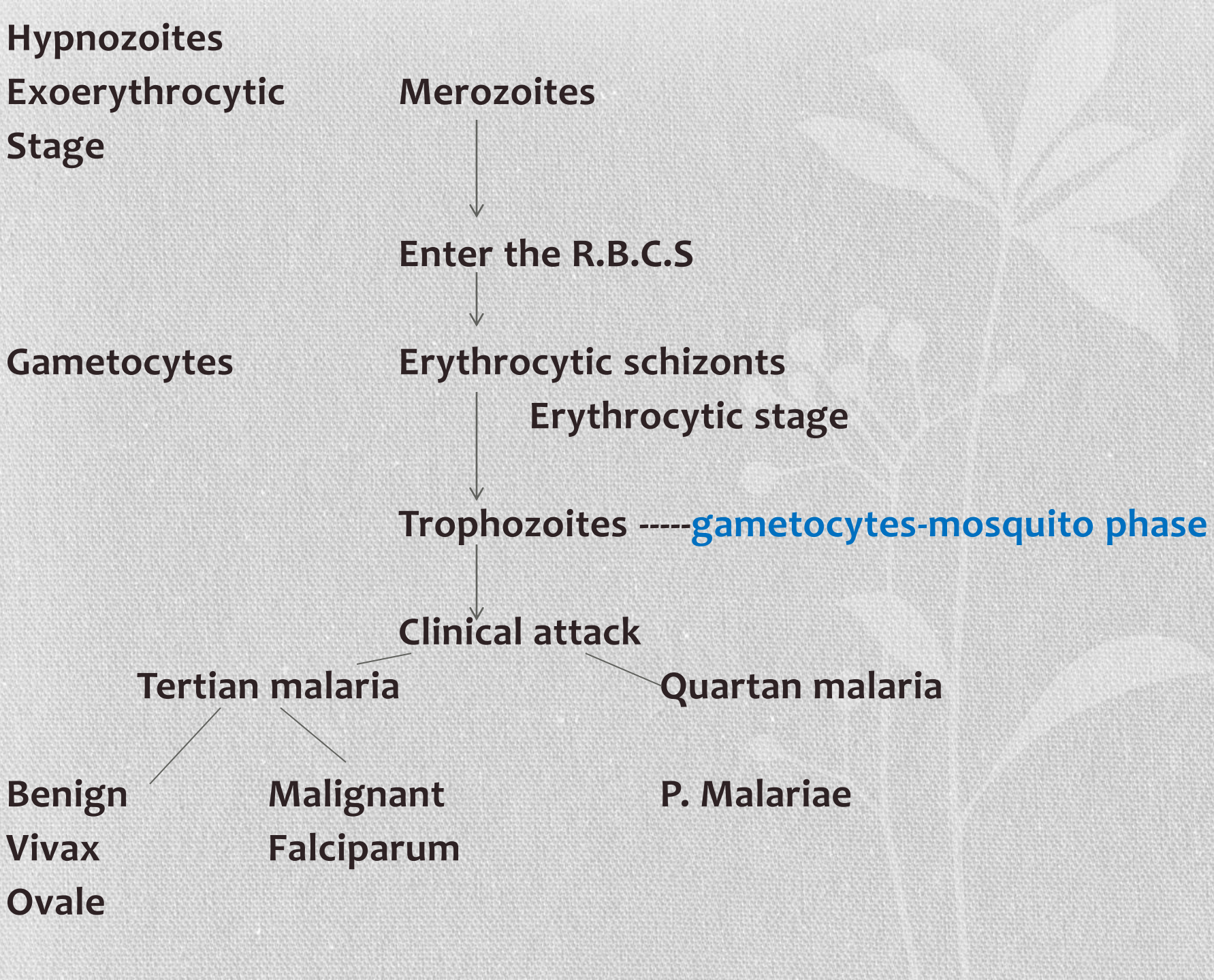
↓

Sporozoites

↓

Liver – Tissue schizonts

Pre – erythrocytic stage

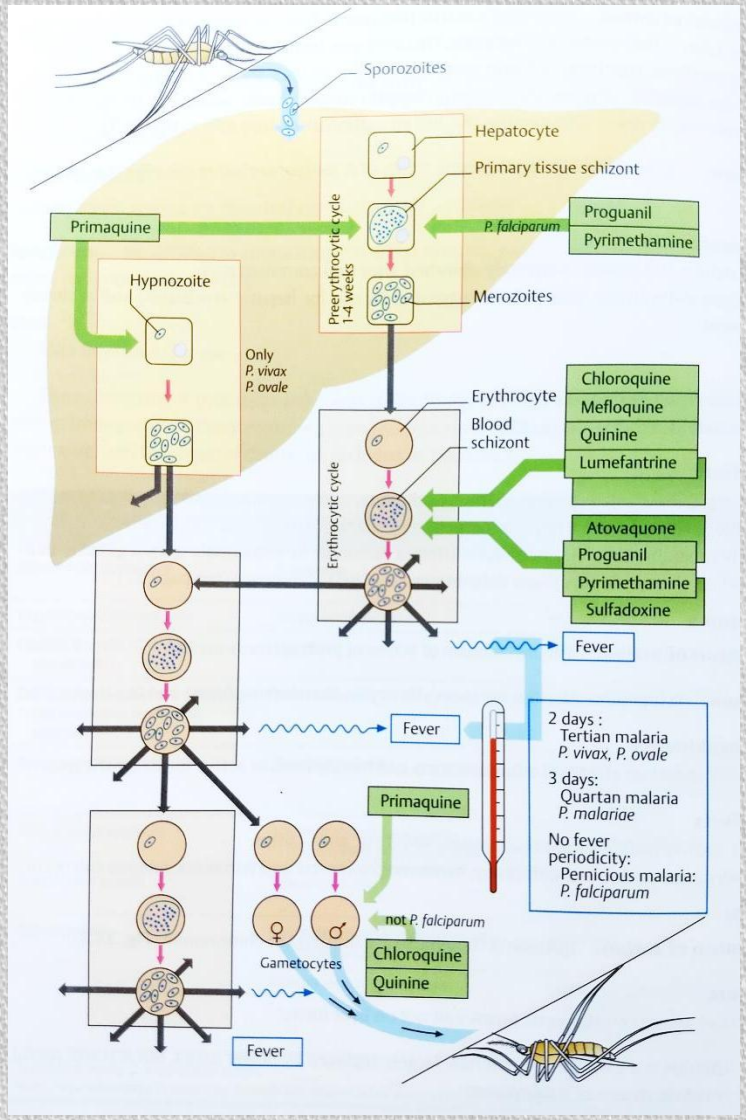

Hypnozoites
Exoerythrocytic
Stage
Merozoites
Enter the R.B.C.S
Gametocytes
Erythrocytic schizonts
Erythrocytic stage
Trophozoites -----gametocytes-mosquito phase
Clinical attack
Tertian malaria
Quartan malaria
Benign
Vivax
Ovale
Malignant
Falciparum
P. Malariae

- Difficult to eradicate malaria

1.resistance to drugs

2. resistance to insecticides

Plasmodium Life Cycle and Drugs' Sites of Action



Classification

According to stage of life cycle at which they act.

No drug is effective against sporozoites

I. Tissue schizontocides

- **Act at pre- erythrocyte stage**
- **Against hepatic schizonts – Preventing R.B.C.S. invasion**
- **Used for causal prophylaxis**

Proguanil, primaquine

II. Tissue schizontocides to prevent relapse

- **Act at exoerythrocytic stage**
- **Against hypnozoites**
- **For radical cure**
- **Prevent relapse**
- **Primaquine**

III. Blood schizontocides

- Act at erythrocytic stage
- Most antimalarials act at this stage
- For clinical cure – treatment of acute attack
- For suppressive prophylaxis – Preventing acute attack

Fast acting (High efficacy)	Slow acting (Low efficacy)
Chloroquine	Sulfadoxine
Quinine	Pyrimethamine
Mefloquine	Doxycycline
Artemisinin	Proguanil
Lumefantrine	
Atovaquone	

IV Gametocidal

- Eliminate male and female gametes
- No benefit to the patient
- ↓Transmission

  Primaquine
- Recrudescence
- Relapse

Chloroquine

Rapid acting erythrocytic scizontocide

High efficacy

- Mechanism of action
- Actively concentrated in infected RBCS
- Alkaline in nature
- Accumulates in acidic food vacuoles of parasite

a. **Damage mediated by accumulated heme**
b. **Alkalinization of food vacuole** -Food vacuole is acidic ,chloroquine is basic-accumulates in it-alkalinization of organells-inability to carry out HB digestion-decrease supply of amino acids

Plasmodial food vaccuole

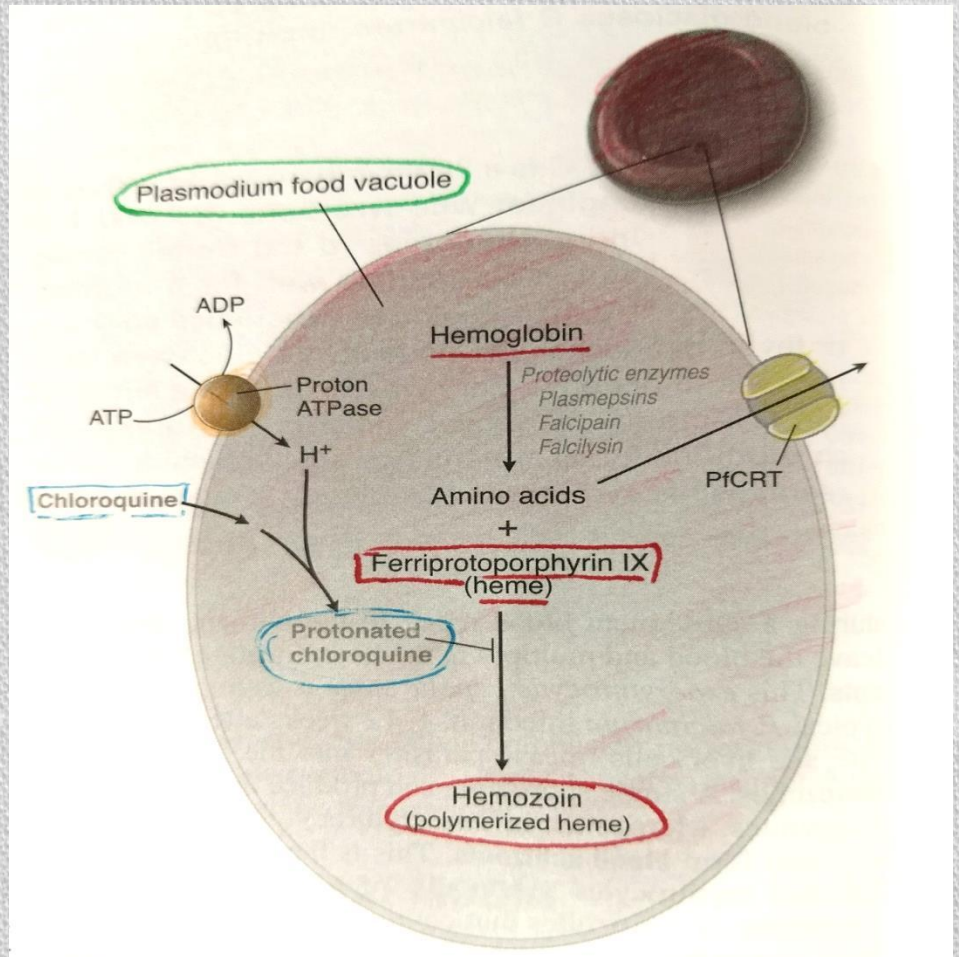


FIGURE 37-2. **Proposed mechanisms of heme metabolism in the plasmodial food vacuole.** Malarial plasmodia possess a specialized food vacuole that maintains an acidic int

Chloroquine

Mechanism of action

i. The parasite digests the host cell's hemoglobin to obtain essential amino acids

ii. The process releases large amounts of heme, which is toxic to the parasite

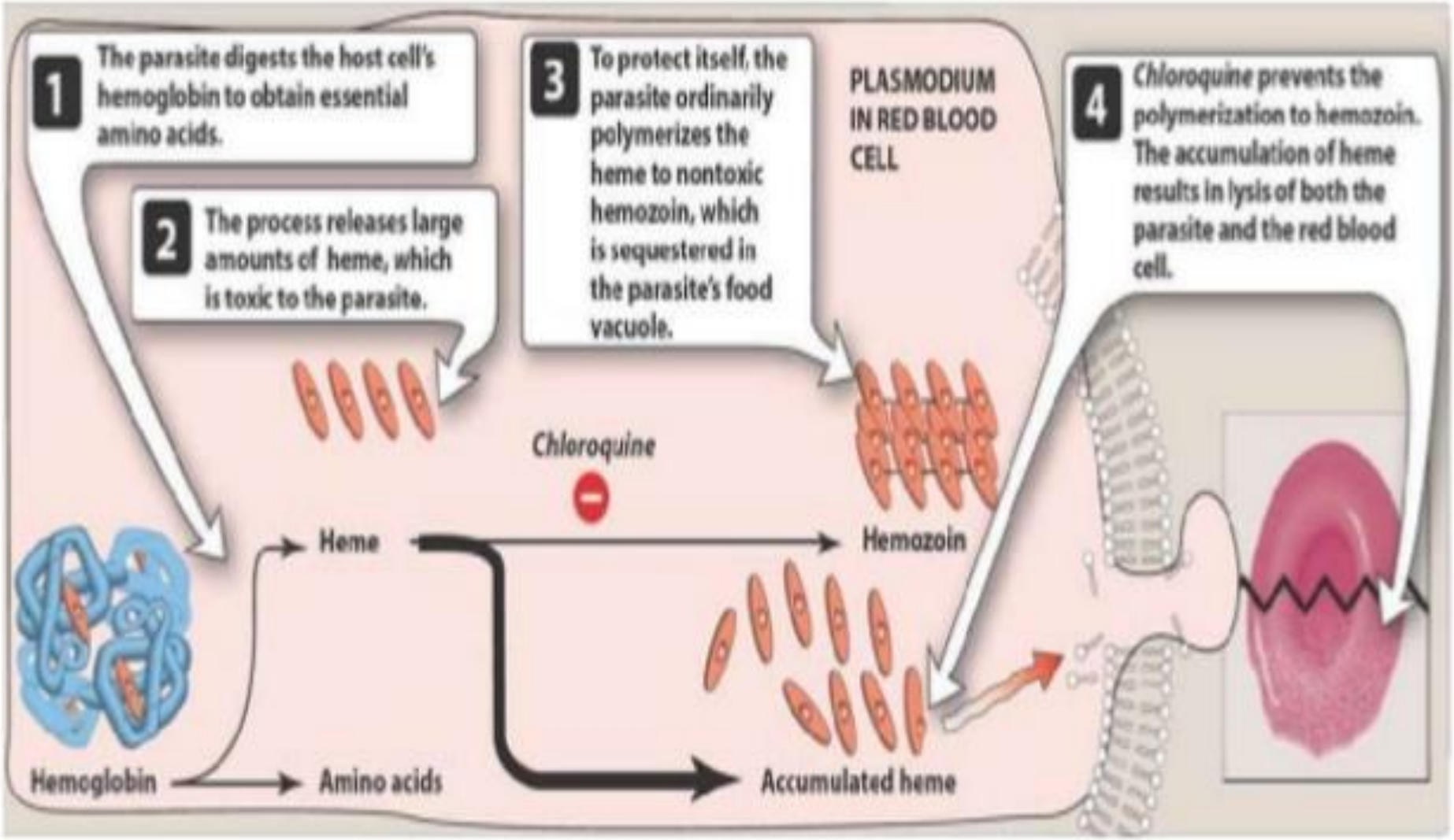
iii. To protect itself the parasite ordinarily polymerizes the heme to nontoxic hemozoin, which is sequestered in the parasite's food vacuole

iv. Cholroquine prevents the polymerization to hemozoin

v. The accumulation of heme results in lysis of both the parasite and the red blood cell

Chloroquine

Mechanism of action



PK

1. Oral absorption – Good
2. Highly tissue bound
3. High volume of distribution
4. Gets accumulated in retina - Sequestration
5. High con. in liver
6. Loading dose of chloroquine
7. Safe in pregnancy

A/E

- Gastric irritation, nausea, Vomiting- Antiemetic
- Never given I.V.-Cardiac depression, Hypotension, arrhythmias
- Long term administration - Retinopathy

Uses

1. Treatment of acute attack of P.vivax malaria

Chloroquine sulphate – 200 mg

Chloroquine phosphate – 250 mg = 150mg base

4 Tablets stat (600 mg)

2 tablets after 6 hrs (300mg)

1 Tablet (150mg) BD- 2 days

Total – 10 tablets

Fever subsides -1-2 days

Parasites disappear from blood – 1-3-days

Chloroquin Resistance

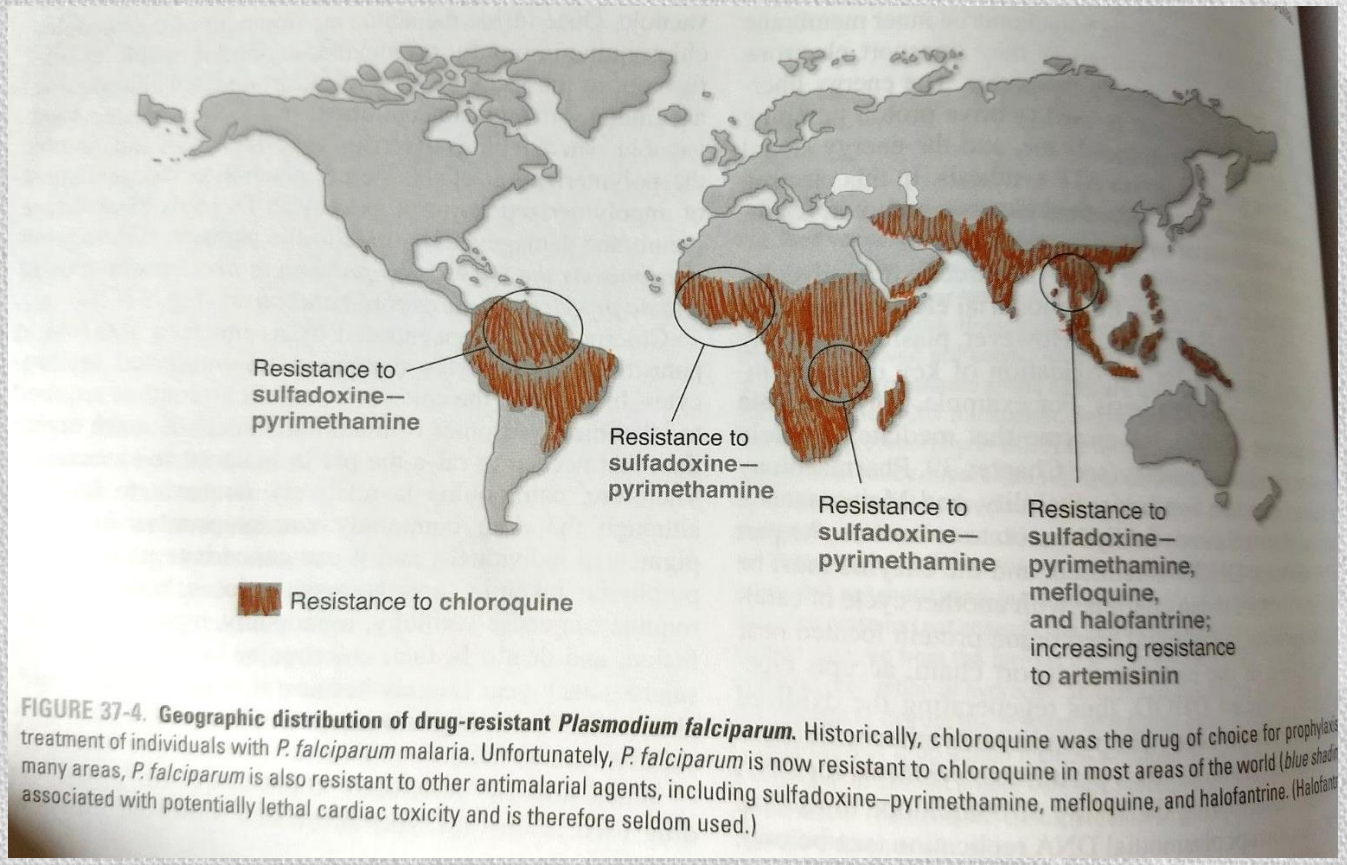


FIGURE 37-4. **Geographic distribution of drug-resistant *Plasmodium falciparum*.** Historically, chloroquine was the drug of choice for prophylaxis treatment of individuals with *P. falciparum* malaria. Unfortunately, *P. falciparum* is now resistant to chloroquine in most areas of the world (*blue shadi* many areas, *P. falciparum* is also resistant to other antimalarial agents, including sulfadoxine–pyrimethamine, mefloquine, and halofantrine. (Halofantr associated with potentially lethal cardiac toxicity and is therefore seldom used.)

2. Prophylaxis of malaria –NOT USED

Chloroquine – 150 mg base

2 tablets wkly – to be started 1 wk before entering in endemic area and continued 4 wks after leaving.

3. Extra intestinal amoebiasis

600 mg / day – 2 days

300 mg/ day – 2 weeks

4. Treatment of RA

5. Lepra reaction-150mg TDS-2 weeks

- Presumptive treatment of malaria with a single dose of chloroquine has been stopped.

- In all cases of suspected malaria which cannot be immediately confirmed by tests, full treatment with chloroquine for 3 days should be given.

- **Amodoquine**
- Agranulocytosis, hepatotoxicity
- With artesunate-TOXICITY LESS
- Approved in India

Quinine

- Obtained from bark of cinchona tree
- Fast acting
- As compared to chloroquine
  - More toxic
  - Less effective
- Mechanism of action same as chloroquine

- A/E

1. I. V –1. hypotension – arteriolar dilatation, cardiac depression I.V – fluids

   2. Hypoglycemia- stimulates beta cells – insulin release, 5% Dextrose along with quinine drip

2 Gastric irritation

3 Chinchonism

4 Black water fever

Uses

- Chloroquine resistant falciparum malaria
- Multidrug resistant falciparum malaria

Quinine 600 mg TDS -7 days -along with doxycycline-100mg/day-7days /Clindamycin-600mg BD

If used alone , chances of recrudescence

-Narrow TI,toxicity,7 days course used only when ACT can not be used

- **Cerebral malaria, severe, complicated P. Falciparum malaria**

I.V. Quinine

Monitor . B.P., BSL

Not used for prophylaxis - Toxicity

Mefloquine

- **Fast acting, erythrocytic Schizontocidal**
- **Pk**
- **Slow oral absorption**
- **Long t1/2 – Protein + tissue bound**
  Enterohepatic circulation
- **No parenteral preparation – Not in complicated**
- **P. Falciparum malaria, cerebral malaria**
- **Use restricted – Toxicity**
  cost
  Long t ½

A/E

. 50 % patients GIT disturbances

To be taken with meal

Large amount of water

Can be ↓ed by splitting the dose

- Neuropsychiatric reactions

Ataxia, hallucination

Use

- Chloroquine resistant P. Falciparum malaria
- Multidrug resistant P. Falciparum malaria

Combined with artesunate to prevent resistance to Mefloquine –Not preferred ACT-due to toxicity

- 250 mg tab.
- 750 mg on 2nd day, 500 mg 3rd day
- Prophylaxis of malaria

Doxycycline

- Slow acting
- Used with quinine for chloroquine, multidrug resistant P .falciparum malaria.
- Prophylaxis

- **Short term chemoprophylaxis (up to 6 weeks)**
- **Doxycycline : 100 mg once daily for adults and 1.5 mg/kg once daily for** children(contraindicated in children below 8 years). The drug should be started 2 days before travel and continued for 4 weeks after leaving the area.

Chemoprophylaxis for longer stay (more than 6 weeks)

- **Mefloqiune: 250 mg weekly for adults and should be administered two weeks before ,**during and four weeks after leaving

- These agents kill erythrocytic parasites before they grow sufficiently in number to cause clinical attack

Sulfadoxine + Pyrimethamine

- Same t ½
- Synergistic combination
- Mechanism of action

    Sulfadoxine inhibits folate synthase

    Pyrimethamine inhibits dihydrofolate reductase

Adv – Single oral dose

    Low cost

A/E – Severe cutaneous reactions, Exfoliative dermatitis, Steven – Johnson syndrome

Less common with single dose

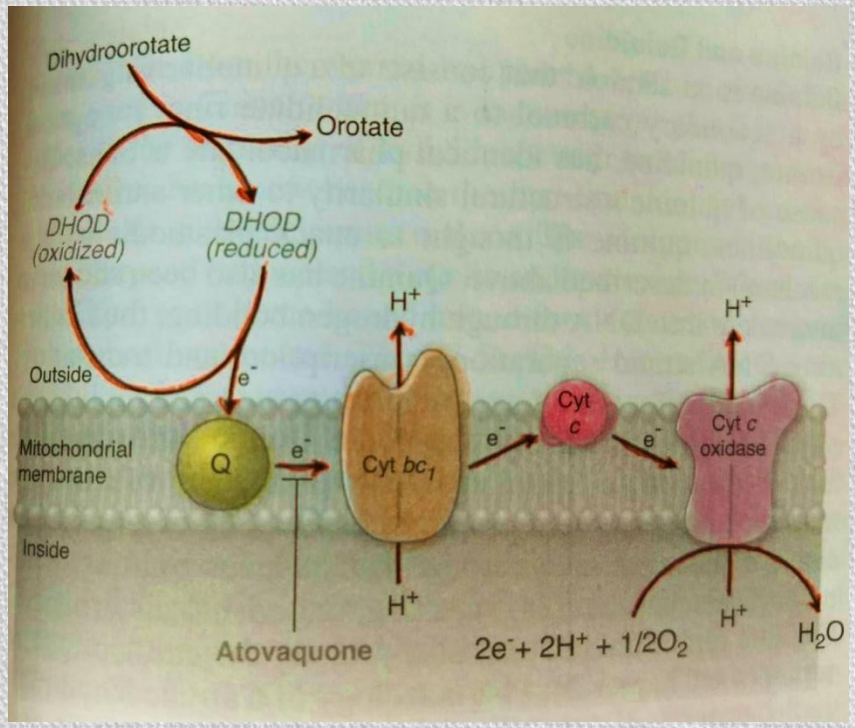
Use

Chloroquine resistant falciparum malaria

    500 mg+25mg-3 tablets stat

To prevent resistant to combination – used with artesunate

Atovaquone MOA



Lumefantrine

- High efficacy erythrocytic schizontoicide
- Long acting
- Combined with artemether
- Administered with fatty food-increase absorption of lumefantrine

Artemisinin derivatives

Artemisinin-plant Artemisia annua

Artesunate –oral, i.m. i.v

Artemether – oral, i.m.

Arteether – i.m. ,Longer half life, developed in India

Prodrugs- dihydroartemisinin

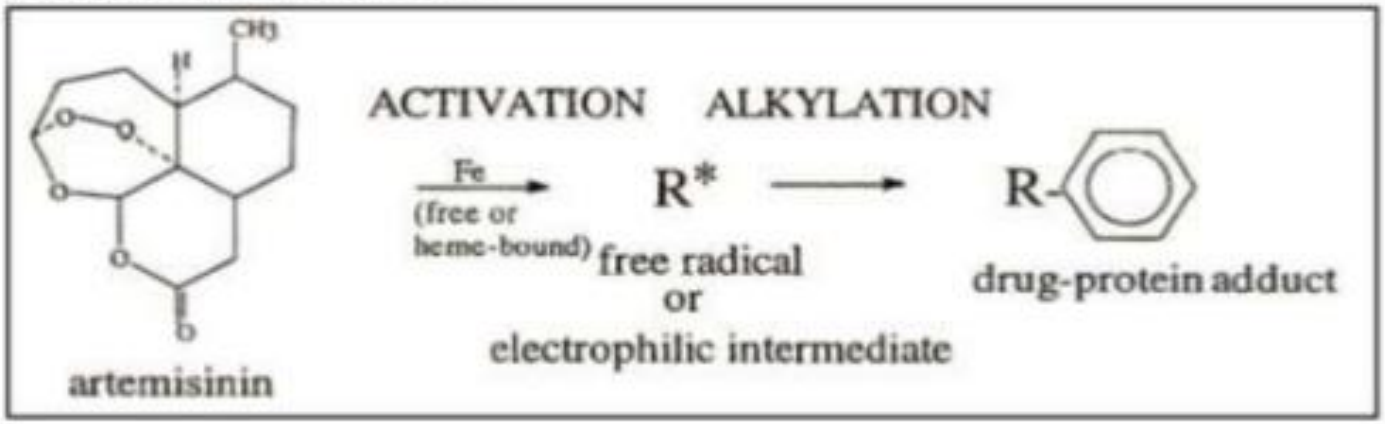
- **Most Rapidly acting – against all malarial parasites**
- **Resistance – Not yet an imp problem**
- **T ½ short – Not used for prophylaxis**

-Recrudescence rate high – to be used with long acting agent.

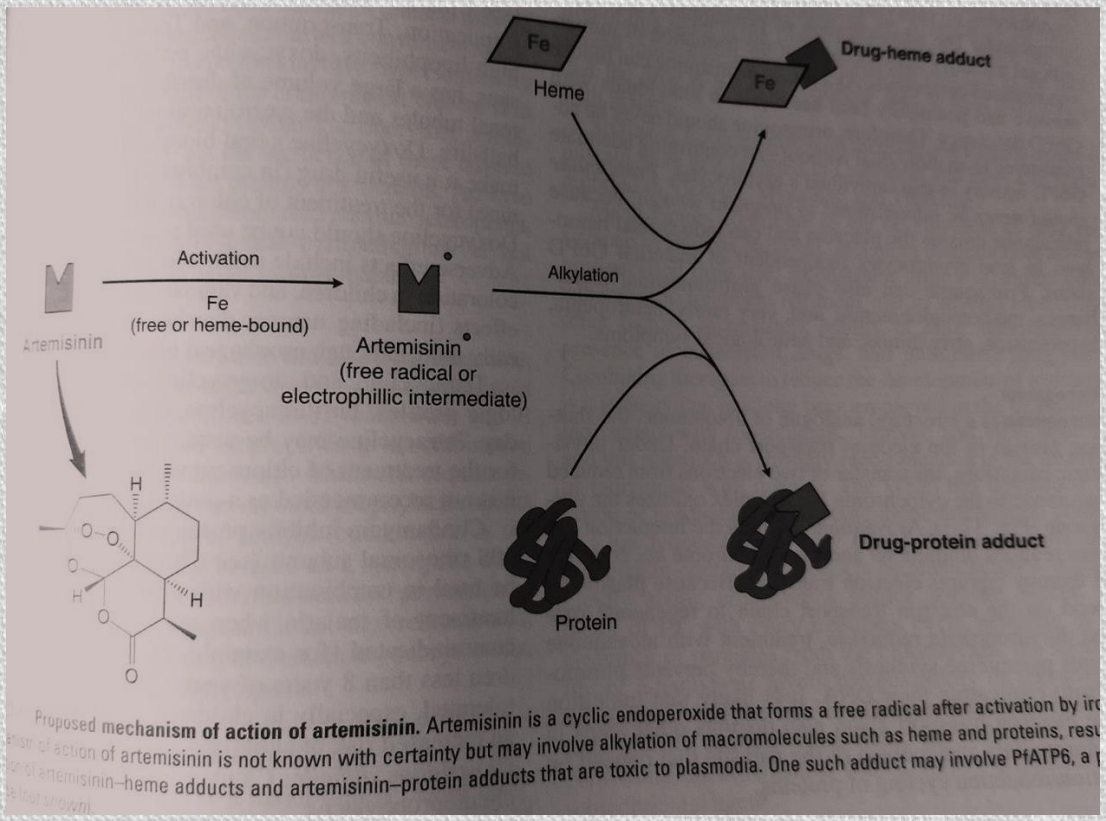
Mechanism of action -Endoperoxide bridge-reacts with heme-release free radicals-damage to membrane, ER

Mechanism of action

- These compounds have presence of endoperoxide bridge
- Endoperoxide bridge interacts with heme in parasite
- Heme iron cleaves this endoperoxide bridge
- There is generation of highly reactive free radicals which damage parasite membrane by covalently binding to membrane proteins



Artemisinin MOA



Proposed mechanism of action of artemisinin. Artemisinin is a cyclic endoperoxide that forms a free radical after activation by ir
ism of action of artemisinin is not known with certainty but may involve alkylation of macromolecules such as heme and proteins, res
of artemisinin–heme adducts and artemisinin–protein adducts that are toxic to plasmodia. One such adduct may involve PfATP6, a
be best shown.

- WHO recommended acute uncomplicated resistant P. Falciparum malaria to be treated only by combining artemisinin with other agents-

- Rapid clinical and parasitological cure
- high cure rate
- Low recrudescence rate
- No Resistance
- Good tolerability profile
- Convenient dosing

Artesunate + sulfadoxine + Pyrimethamine

Artesunate+ mefloquine

Artemether + lumefantrine

Artemether + lumefantrine

ACT-AL Co-formulated tablet of ARTEMETHER(80 mg) - LUMEFANTRINE (480 mg) BD for 3 days

- **(Not recommended during the first trimester of pregnancy)**

- **Primaquine: 0.75 mg/kg body weight on day 2**

- Primaquine (PQ) prevents transmission of falciparum malaria to others by its ability to kill gametocytes

(ACT-SP)-slightly higher efficacy

- Artesunate (AS), 100 mg BD given for three days, and Sulfadoxine-Pyrimethamine (S-P) tablets, containing 1500 mg Sulfadoxine and 75mg pyrimethamine are given for one day. –commonly used-first line therapy

- **Artesunate+ Mefloquine**

Artesunate- 100mg BD-3 days + Mefloquine 750 mg on 2nd day, 500 mg 3rd day

- **Less preferred due to adverse effects**

- Artesunate + amodiaquine
- 200mg+600mg /day-3 days

ARTEROLANE +PIPERAQUINE

150 mg + 750mg per day for 3 days

Dihydroartemisinin+ PIPERAQUINE

120 mg + 960 mg per day for 3 days

- ACT is not to be given in 1st trimester of pregnancy
- **Treatment of uncomplicated *Falciparum cases in pregnancy:***
- **1st Trimester :**

  Quinine salt 10mg/kg 3 times daily for 7 days
  +Clindamycin 600 mg BD for 7 days
- Quinine may induce hypoglycemia; pregnant women should not start taking quinine on an empty stomach and should eat regularly, while on quinine treatment.

- **2nd and 3rd trimester:**

  ACT

- **Why is it difficult for parasites to develop resistance to ACT?**
- ACT contains three drugs: artesunate, sulphadoxine and pyrimethamine. Each drug acts on a different part of the parasite, in a different manner. It is very, very rare for three simultaneous genetic mutations to occur by chance to produce resistance to such diverse drugs.

- Resistance can be produced in multiple steps, one drug at a time, but this is expected to take many more years. At present, we do not expect resistance to develop to ACT. If resistance develops, it is expected to first develop against sulphadoxine or pyrimethamine, since they have been in use for a longer time.

- In severe, complicated falciparum malaria

Parenteral artesunate preferred over quinine

1. Faster parasite clearance
2. Better tolerated
3. More safe
4. Efficacy more
5. More conveniently administered – dosing schedule simple
6. Mortality less

Cost – high

CI- Pregnancy

Chemotherapy of severe and complicated malaria

- **Initial parenteral treatment for at least 48 hours:**
- **Artesunate: 2.4 mg/kg I.V. or I.M. given on**

admission (time=0), then at 12 h and 24 h, then once a day-7 days-Preferred

or

- **Artemether: 3.2 mg/kg bw I.M. given on**

admission then 1.6 mg/kg per day.-7 DAYS

or

- **Arteether: 150 mg daily I.M. for 3 days**
- Full oral course of ACT:3 days
- **The parenteral treatment in severe malaria cases should be given for minimum of 24 hours once started** (irrespective of the patient's ability to tolerate oral medication earlier than 24 hours).

- **Quinine: 20mg quinine salt/kg body weight**

on admission IV infusion over 4 hrs followed by maintenance dose of 10 mg/kg 8 hourly; infusion rate should not exceed 5 mg/kg per hour.

Quinine:-oral 10 mg/kg three times a day with doxycycline 100 mg once a day **or** clindamycin in pregnant women and children under 8 years of age,to complete 7 days of treatment.

Primaquine

- Effective against exoerythrocytic stage
- Kill hypnozoites
- Radical cure of malaria- 7.5mg BD- 2wks.
- Given with blood scizontocide
- Gametocidal
- A/E –Hemolysis in G6 PD deficiency
- 14 days treatment-hurdle in implementing antirelapse therapy

- Tafenoquine
- Long acting
- Single dose treatment-800 mg

.**Major threat- potential for resistance to arise against artesunate or its partner drug**

Problems with Artemisinin based therapy

1. **Derived from plant source**
2. **So expensive**
3. **Crop depends on weather, harvest varies- Price fluctuations**
4. **Potential for mismatch in demand and supply-Supply constraints**

Ranbaxy launched new anti malarial drug on world malaria day April 25, 2012

8 yrs to develop

ARTEROLANE +PIPERAQUINE (SYNRIAM)

150 mg + 750mg

Mechanism of action of arterolane

- **Rapidly acting Blood schizonticidal**
- **Accumulates in food vacuole(differs from artemisinins)Undergoes reductive cleavage in food vacuole by ferrous iron to generate free radicals which inhibit pfATP6 –a SR calcium ATPase encoded by falciparum**

thus possibly act by perturbing calcium homeostasis of the intracellular parasite.

- The calcium pump of sarcoplasmic reticulum responsible for refilling calcium in the ER stores is critically important for cellular homeostasis and calcium signaling functions

PIPERAQUINE

Complete parasite clearance is dependent on the partner drug being effective and also persist at parasitecidal concentration until most infective parasites are cleared

Mode of action

- Inhibition of heme digestion in parasite food vacuole
- Bulky structure-inhibition of transporters that efflux chloroquine from parasite food vacuole
- Kills residual parasites-prevent recrudescence

PCT- 36 hrs FCT- 18 hrs

Pharmacokinetics

- Orally absorbed
- Peak plasma concentration

  3-5 hrs- Arterolane, 4-6 hrs- Piperaquine
- High protein binding
- Extensive volume of distribution
- Half life-A-1-3 hrs, P- 17-23 hrs
- CYP3A4 –metabolism

Dosage schedule

One tablet once a day for 3days

- Advantages over Artemisinin
- High compliance-better tolerance
- Absorption independent of food intake
- Synthetic source
- Low cost-130/- Rs
- Quick scale up in production can be done

NORTHEASTERN STATES

Arunachal Pradesh, Assam, Manipur, Meghalaya, Mizoram, Nagaland, Tripura

- due to **late treatment failures** to **AS+SP in *P. falciparum***, *the presently* recommended ACT in national drug policy is a FDC of **Artemether-lumefantrine (AL)**
- ACT used in the national programme
  - NE states = AL
  - Rest of India = AS+SP