ANTIPROTOZOAL /ANTIMALARIAL DRUGS

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ANTIMALARIAL DRUGS

ILOS

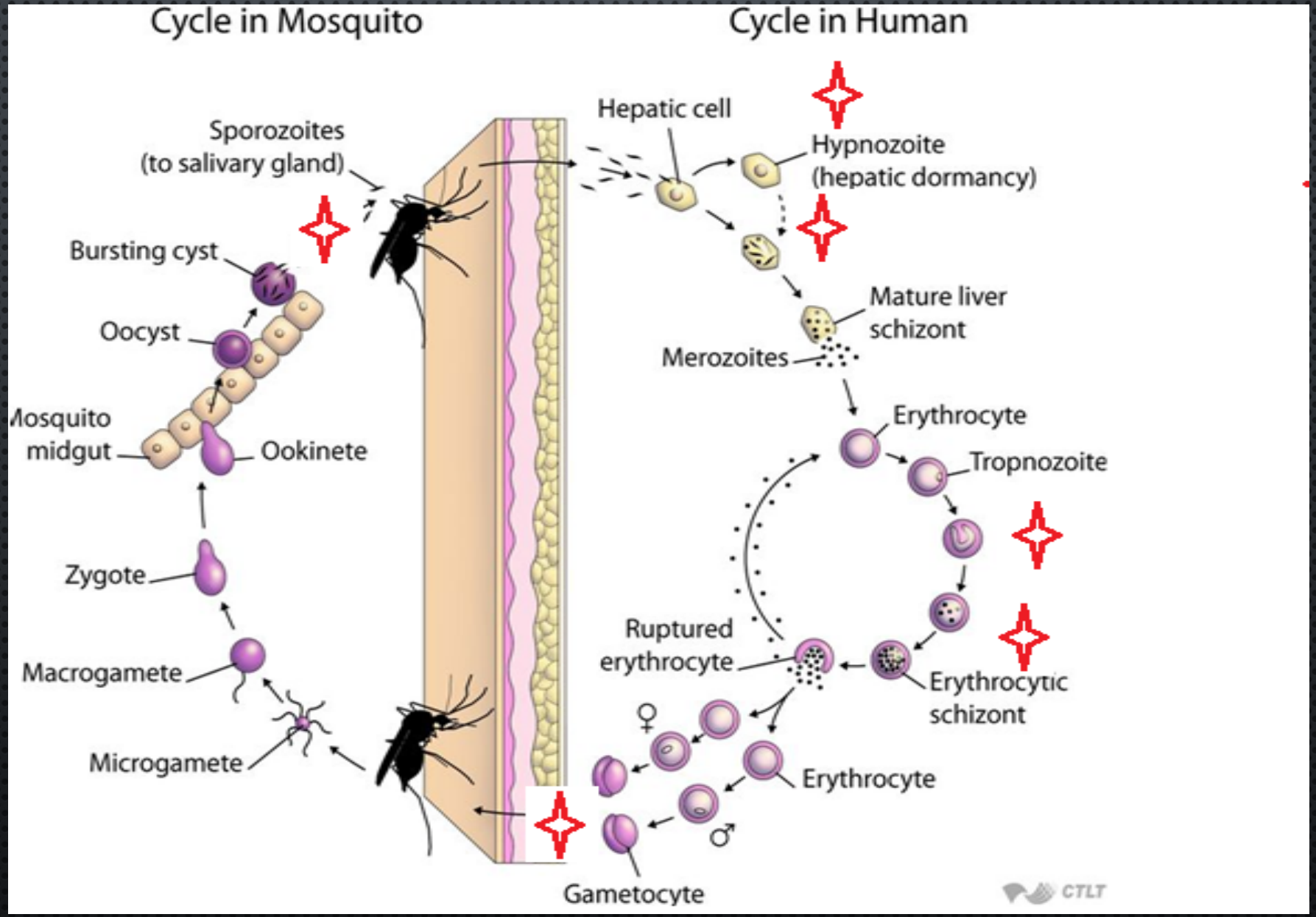
- Classify the main antimalarial drugs depending on their goal of therapy
- Detail the pharmacokinetics & dynamics of main drugs used to **treat** attack or **prevent** relapses
- State the **WHO** therapeutic strategy for treatment
- Hint on the **CDC** recommendations for prophylaxis in travelers to endemic areas.

According to WHO:
212 million cases of malaria worldwide in 2015 & 429,000 deaths.
90% of malaria cases & deaths occur in **Africa**.
Children under 5 are most at risk.

Four species of plasmodium typically cause human malaria:

- *Plasmodium falciparum,*
- *P vivax,*
- *P malariae, and*
- *P ovale.*

Cycle & Drugs site of action



ANTIMALARIAL DRUGS

THERAPEUTIC CLASSIFICATION:

Causal prophylaxis	Destroys parasite in **liver** cells & prevent invasion of erythrocytes	Primaquine
Suppressive prophylaxis	Suppresses the **erythrocytic** phase & thus attack of malaria fever	Chloroquine, mefloquine, doxycycline

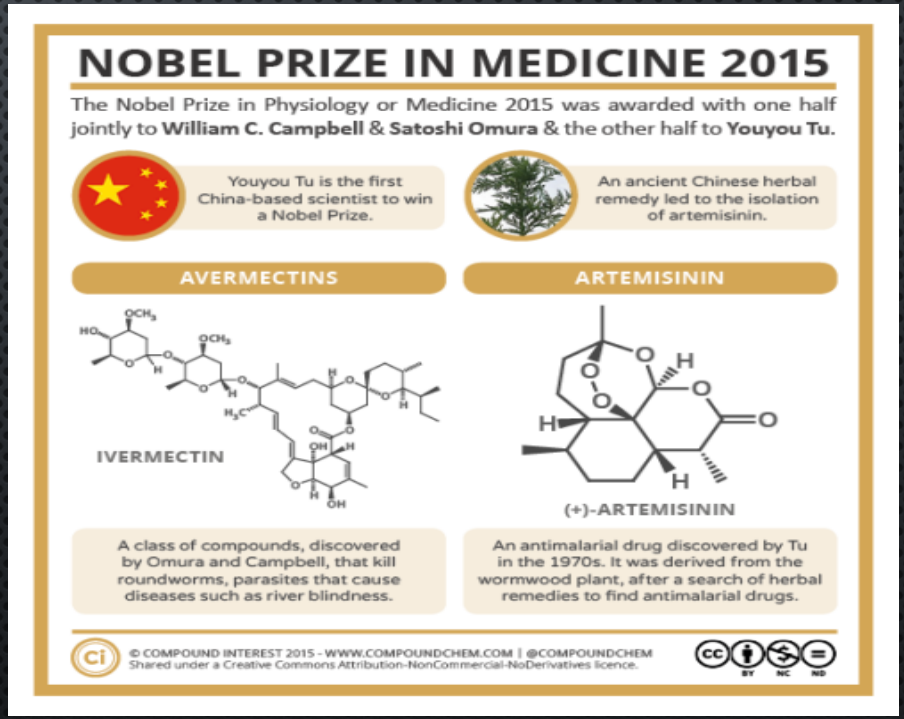
ANTIMALARIAL DRUGS

THERAPEUTIC CLASSIFICATION:

Radical cure (**Erythrocytic** schizonticide)	Eradicate all forms of vivax from the body	Suppressive drug + hypnozoitocidal
Gametocidal high efficacy	Destroys gametocytes & prevent transmission	Chloroquine, quinine against vivax artemisinin
Slow acting low efficacy		Primaquine, all species
Sporozoitocides	Destroys sporozoites	Proguanil, pyrimethamine

ARTEMESININ

- Artemisinin is the active principle of the plant *Artemisia annua* **(qinghaosu)**
- Fast acting **blood** Schizontocide
- Affect all forms including multi-drug resistant *P. falciparum*
- **Short** duration of action
- High recrudescence rate after short-course therapy
- Poorly soluble in water & oil, can only be used orally.



PHARMAKOKINETICS

- Rapidly biotransformed in liver into di-hydroartesiminin ➔ active metabolite
- Artemisinin, artesunate, artemether are **prodrugs**
- Derivatives are rapidly absorbed orally & Widely distributed
- Artemisinin t½ ➔ 4 hrs

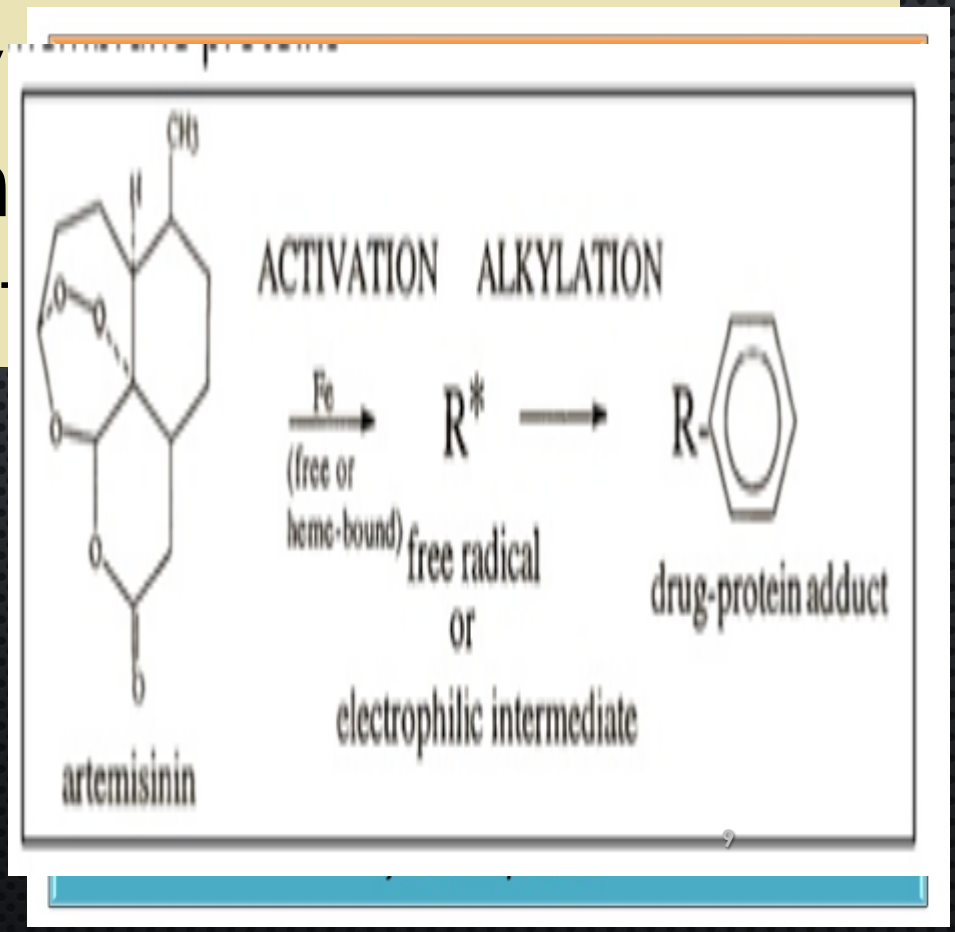
- **Artesunate** t½ 45 min (water-soluble; oral, IV, IM, rectal administration)
- Artemether t½ 4-11 hrs, (lipid-soluble; oral, IM, & rectal administration). Induce its own CYP-mediated metabolism→ ↑ clearance 5 fold.

ARTEMESININ & ITS DERIVATIVES

MECHANISM

They have endoperoxide bridges
Haem iron cleaves this bridge to yield carbon-centered free radicals in parasite, that will➔

- Alkylate membranes of parasite's **food vacuole** & mitochondria➔ no energy
- Irreversibly bind & inhibit sarco-endoplasmic reticulum **Ca^{2+}-ATPase** of the parasite, thereby inhibiting its growth
- Inhibiting formation of **transport vesicles** ➔no food vacuoles.



ARTEMESININ

CLINICAL USES

Because **artemisinin derivatives** have short t½,

(1) Monotherapy should be extended beyond disappearance of parasite to prevent recrudescence or

(2) by combining the drug with long- acting antimalarial drugs (Ex. mefloquine)

PREPARATIONS

Artesunate IV or IM preparations for severe complicated cases as cerebral malaria (24 h) followed by complete course of ACT.

ARTEMESININ

PREPARATIONS

- Artemisinin-based combination therapies (ACTs):
  - ➢Artemether + lumefantrine
  - ➢Artemether + amodiaquine
  - ➢Artemether + mefloquine
  - ➢Artemether + sulfadoxine- pyrimethamine.

ARTEMESININ

ADRs

- Transient heart block
- ↓ Neutrophil count (rare)
- Brief episodes of fever

Resistance ➔ was reported recently in Cambodia- Thailand border.

ANTIMALARIAL DRUGS

CHLOROQUINE

Potent **blood** Schizontocide

Active against all forms of the schizonts (exception is chloroquine-resistant *P.f.* & *P.v.*)

Not active against tissue shizonts

Gametocide:-Against all species except *P. falciparum*.

CHLOROQUINE

PHARMACOKINETICS

- Rapidly & completely absorbed from the GIT, given po
- Has high volume of distribution (100-1000 L/kg);

Released slowly from tissues & metabolized in liver

Concentrated into parasitized RBCs

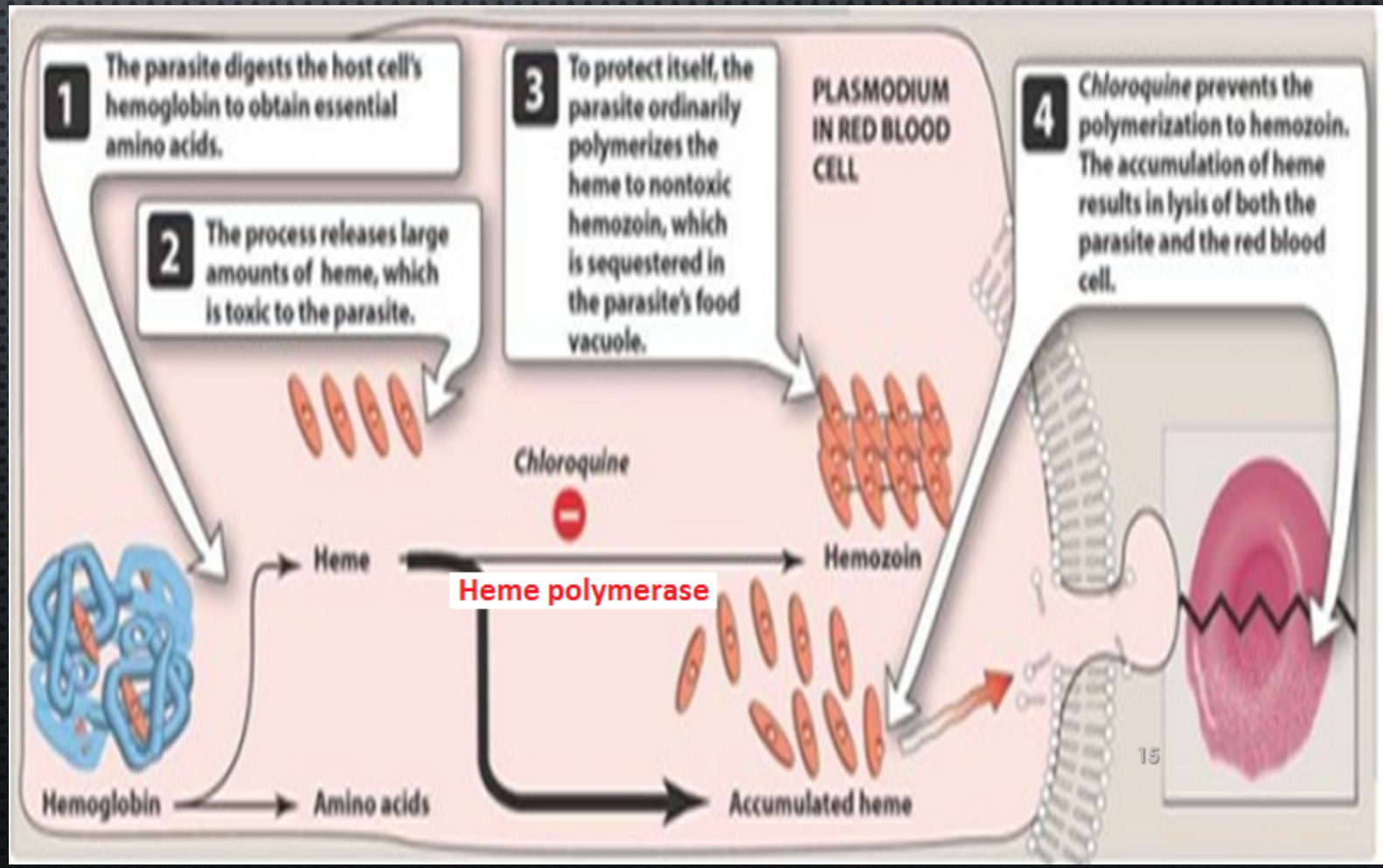
- Excreted in the urine 70% unchanged
- Initial t½ = 2-3 days & terminal elimination t½=1-2 months.

CHLOROQUINE

MECHANISM OF ACTION

Malaria Parasite digest host cell's Hb to utilize globin & obtain amino acids

Heme is released ➔ Toxic
So parasite detoxifies it by *heme polymerase* ➔ Hemozoin (NonToxic) & traps it in food vacuoles.

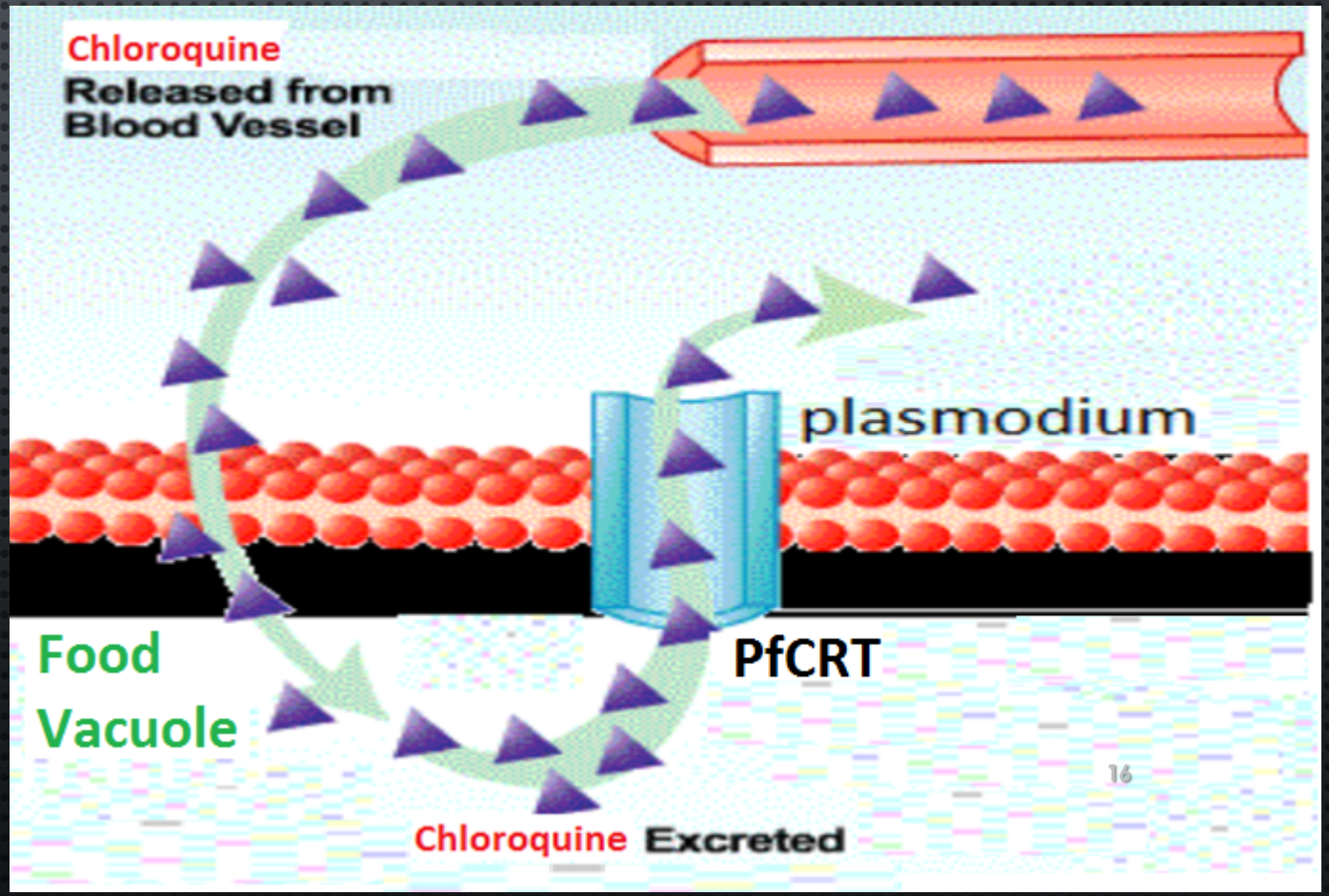


CHLOROQUINE

RESISTANCE

Resistance against the drug develops as a result of mutation of the chloroquine resistance transporter (PfCRT)

PfCRT enhances the efflux of chloroquine from the food vacuole.



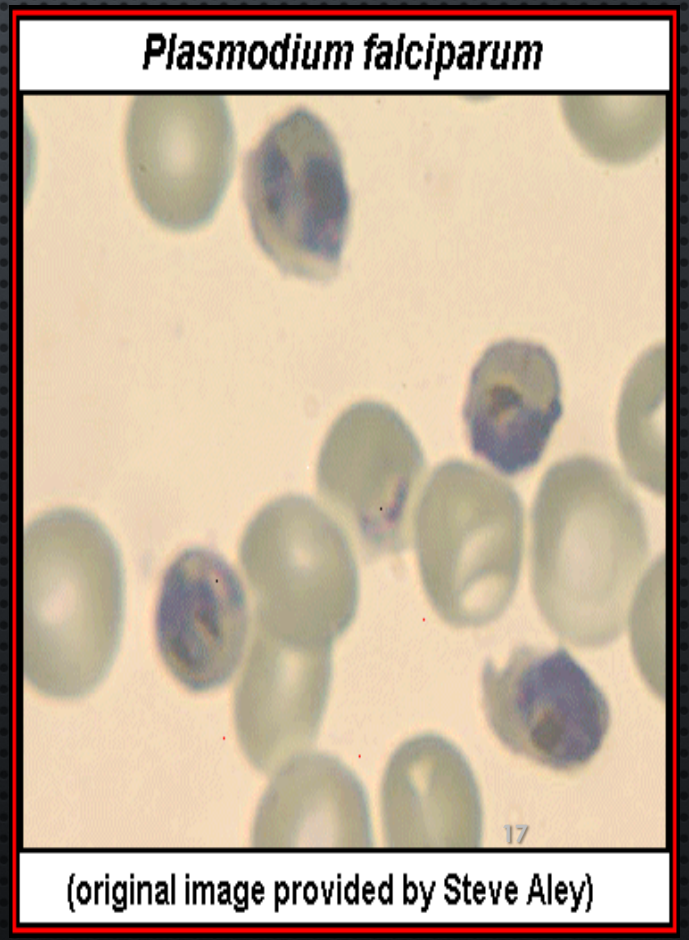
CHLOROQUINE

THERAPEUTIC USES

Used to eradicate **blood** schizonts of *Plasmodium*. It is given in loading dose to rapidly achieve effective plasma conc.

Hepatic amebiasis

Rheumatoid arthritis.



CHLOROQUINE

ADRS

1. Mild headache & visual disturbances
2. GIT upsets; Nausea, vomiting
3. Pruritus, urticaria.

Prolonged therapy & high doses:

Ocular toxicity: Loss of accommodation, lenticular opacity, retinopathy

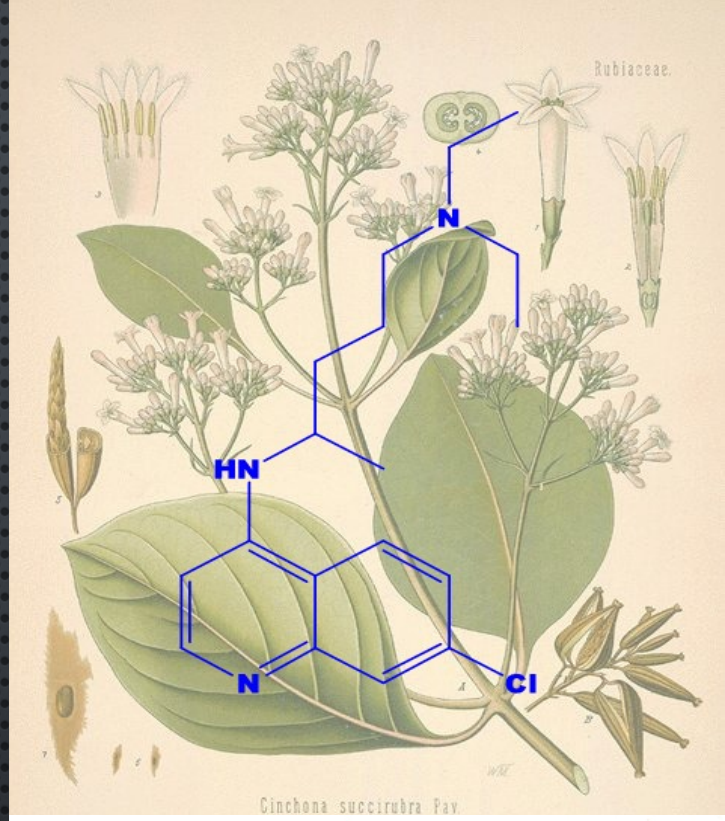
Ototoxicity
Weight loss

Bolus injection → hypotension & dysrrhythmias

Safe in pregnancy

QUININE

- The main alkaloid in cinchona bark
- Potent **blood Schizontocide** of ALL malarial parasites & **gametoside** for *P vivax* & *ovale* but not *falciparum*. It is Not active against liver stage parasites.
- Depresses the myocardium, reduce excitability & conductivity
- Mild analgesic, antipyretic, stimulation of uterine smooth muscle, curare mimetic effect.



QUININE

PHARMACOKINETICS

- Rapidly & completely absorbed from the GIT
- Peaks after 1-3 hours
- Metabolized in the liver & excreted in urine
- 5-20% excreted in the urine unchanged
- $t_{1/2}$ = 10 hrs but longer in sever falciparum infection (18 hrs)

Administered: orally in a 7 day course or by slow IV for severe *P. falciparum* infection.

QUININE

MECHANISM

Same as chloroquine

MECHANISM OF RESISTANCE

Like chloroquine, by mutation of chloroquine resistance transporter, also increased expression of **P-glycoprotein transporter**.

QUININE

CLINICAL USES:

- ✓ Parenteral treatment of severe falciparum malaria
- ✓ Oral treatment of falciparum malaria (schizontocides)
- ✓ Nocturnal leg cramps.

QUININE

ADRS

With therapeutic dose → poor compliance → bitter taste

Higher doses →

- Cinchonism → *(tinnitus, deafness, headaches, nausea & visual*

- Abdominal pain & diarrhea
- Rashes, fever, hypersensitivity reactions
- Hypotension & hypoglycemia
- Blood dyscarasis; anaemia, thrombocytopenic purpura & hypoprothr… …ild)
- Blackwater fever, a fatal condition in which acute haemolytic anae… …ed with renal failure due to a hypersensitivity reaction to th…

IV → neurotoxicity → tremor of the lips & limbs, delirium, fits, stimulation followed by depression of respiration & coma.

Safe in pregnancy

QUININE

CONTRAINDICATIONS

- Prolonged QT Interval
- Glucose-6-Phosphate Dehydrogenase deficiency
- Myasthenia Gravis
- Hypersensitivity
- Optic Neuritis, auditory problems
- Dose should be reduced in renal insufficiency.

Glucose-6-phosphate

↓ G-6-P-D enzyme

6- Phosphoguconate + NADPH + H^+

In case of G-6-P-D

↓ Leads to

Inadequate supply of NADPH

↓ Leads to

Reduced level of Glutathione

↓

Glutathione protects Hb oxidation

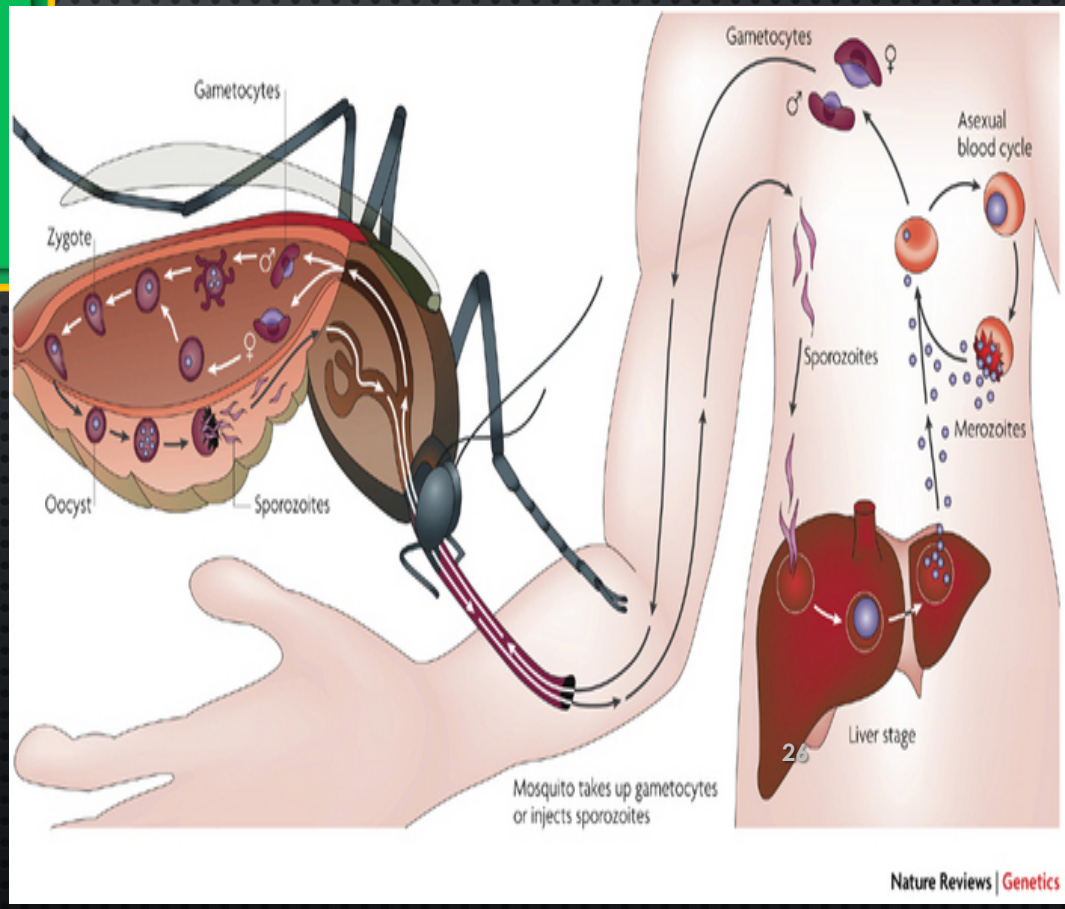
QUININE

DRUG INTERACTIONS

- Antacids: Antacids containing aluminum &/or magnesium may delay or decrease absorption of quinine
- Mefloquine
- Quinine can raise plasma levels of warfarin & digoxin.

PRIMAQUINE

- Hypnozoitocides against **liver** hypnozoites & gametocytocides against the 4 human malaria species
- Radical cure of *P. ovale & P. vivax*
- Prevent spread of ALL forms (chemoprophylaxis)



PHARMACOKINETICS

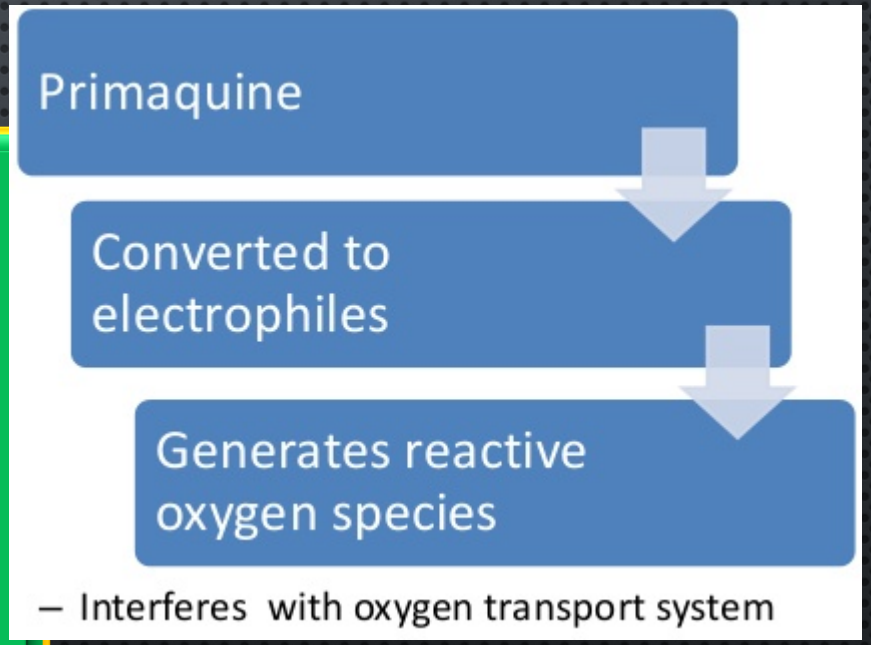
- Well absorbed orally
- Rapidly metabolized to etaquine & tafenoquine ➔ more active forms
- t½ ➔ 3-6 h.

PRIMAQUINE

MECHANISM

Not well understood, It may be acting by:-

- Generating ROS ➔ can damage lipids, proteins & nucleic acids in the parasite
- Interfering with the electron transport ➔ no energy
- Inhibiting formation of transport vesicles ➔no food vacuoles



Resistance; ➔ Rare when primaquine & chloroquine are combined.

ANTIMALARIAL DRUGS

PRIMAQUINE

CLINICAL USES

Radical cure of relapsing malaria, 15 mg/day for 14 days

In falciparum malaria: a single dose (45 mg) to kill gametes & cut down transmission

Should be avoided in pregnancy (the fetus is relatively G6PD-deficient & thus at risk of hemolysis) & G6PD deficiency patients

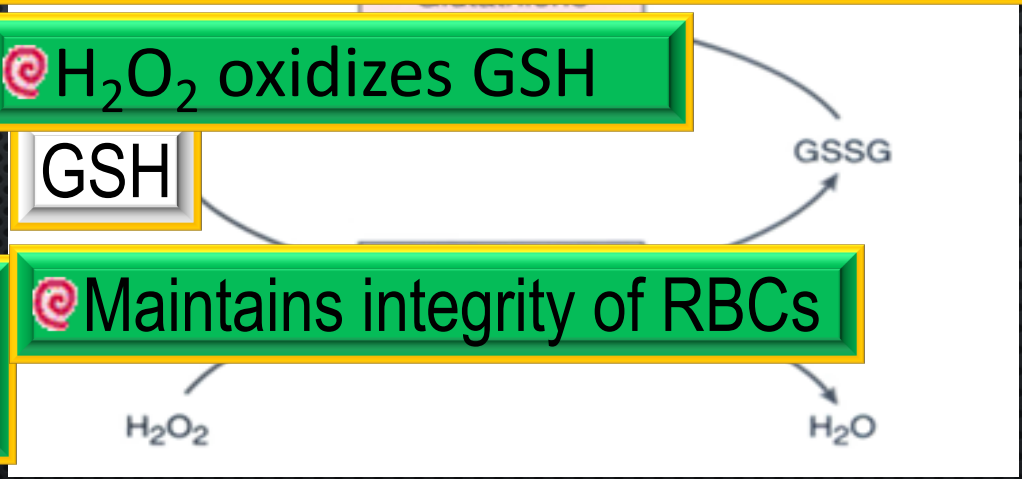
G-6-PD NORMAL	15mg per day x 14
G-6-PD deficiency (Mild African form)	45mg per week for 8
G-6-PD deficiency (More severe Mediterranean variety)	30mg per week for 30 weeks

PRIMAQUINE

ADRS

At regular doses ➔ patients with G-6-PD deficiency ➔ hemolytic anemia.

- Oxidation of primaqune produces free radicals
- Free radicals will cause oxidative damage of RBCs →Hemolysis
- H_2O_2 oxidizes GSH



- Maintains integrity of RBCs

WHO TREATMENT GUIDELINES

In *P vivax*

In *P falciparum*

All show Resistance

RESISTANT

ACT / 3 days followed by Primaquine for 14 days

UNCOMPLICATED

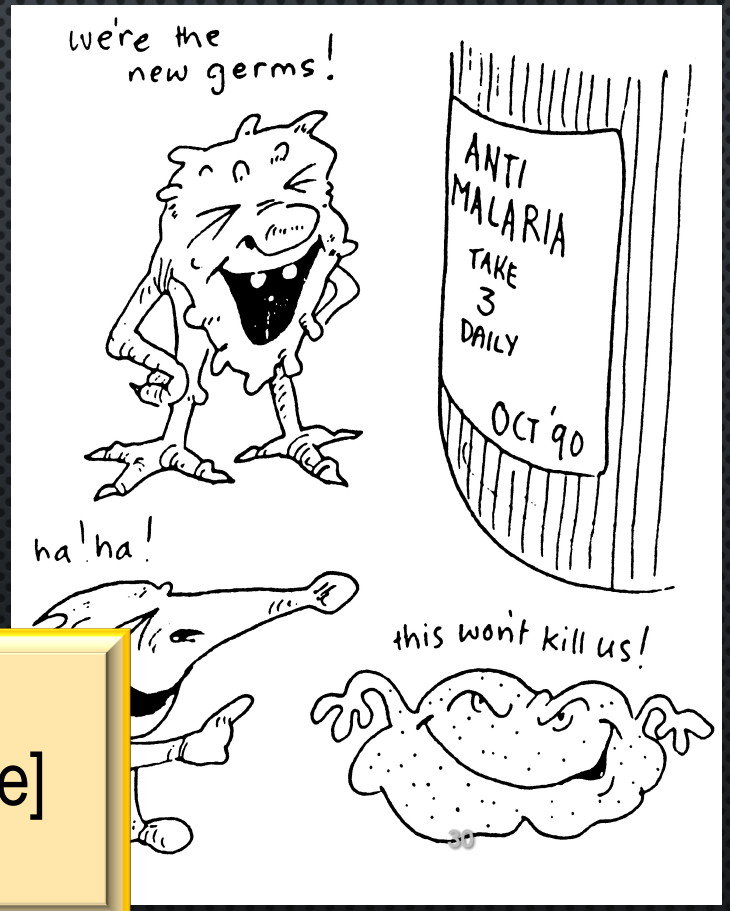
ACT

COMPLICATED

IV Artesunate for 24 hrs followed by ACT

Or Artemether + [Clindamycin / doxycycline]

Or Quinine + [Clindamycin / doxycycline]



WHO TREATMENT GUIDELINES

IN FALICPARUM

SPECIAL RISK GROUPS

Pregnancy; 1st trimester	Quinine + Clindamycin (7 days)
Pregnancy; 2nd & 3rd trimester Lactating women Infants & young children	ACT

PROPHYLAXIS IN TRAVELLERS

CDC RECOMENDATIONS

Chloroquine	Areas without resistant *P falciparum*
Mefloquine	Areas with chloroquine-resistant *P falciparum*
Doxycycline	Areas with multidrug-resistant *P falciparum*

Begin 1-2 weeks before departure (except for doxycycline 2 days) & continue for 4 weeks after leaving the endemic area.

THANK U...!