

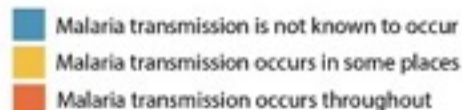
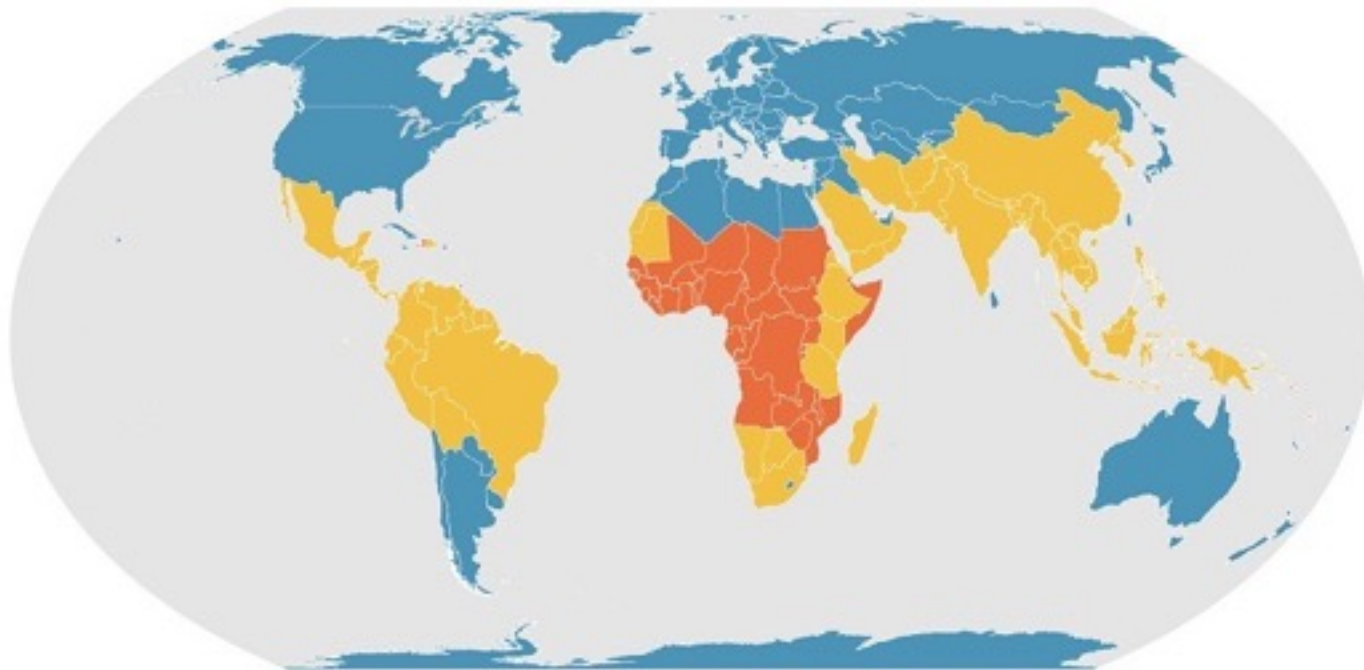
Drugs Used in Treatment of Malaria

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Malaria

Malaria is the most important parasitic disease of humans and causes hundreds of millions of illnesses per year.



Malarial Parasites

- ***Plasmodium falciparum***
(only erythrocytic, serious, resistance).
- ***Plasmodium vivax***
- ***Plasmodium malariae***(erythrocytic)
- ***Plasmodium ovale***

A fifth species, *P knowlesi*, is primarily a pathogen of monkeys, but has recently been recognized to cause illness, including severe disease, in humans in Asia

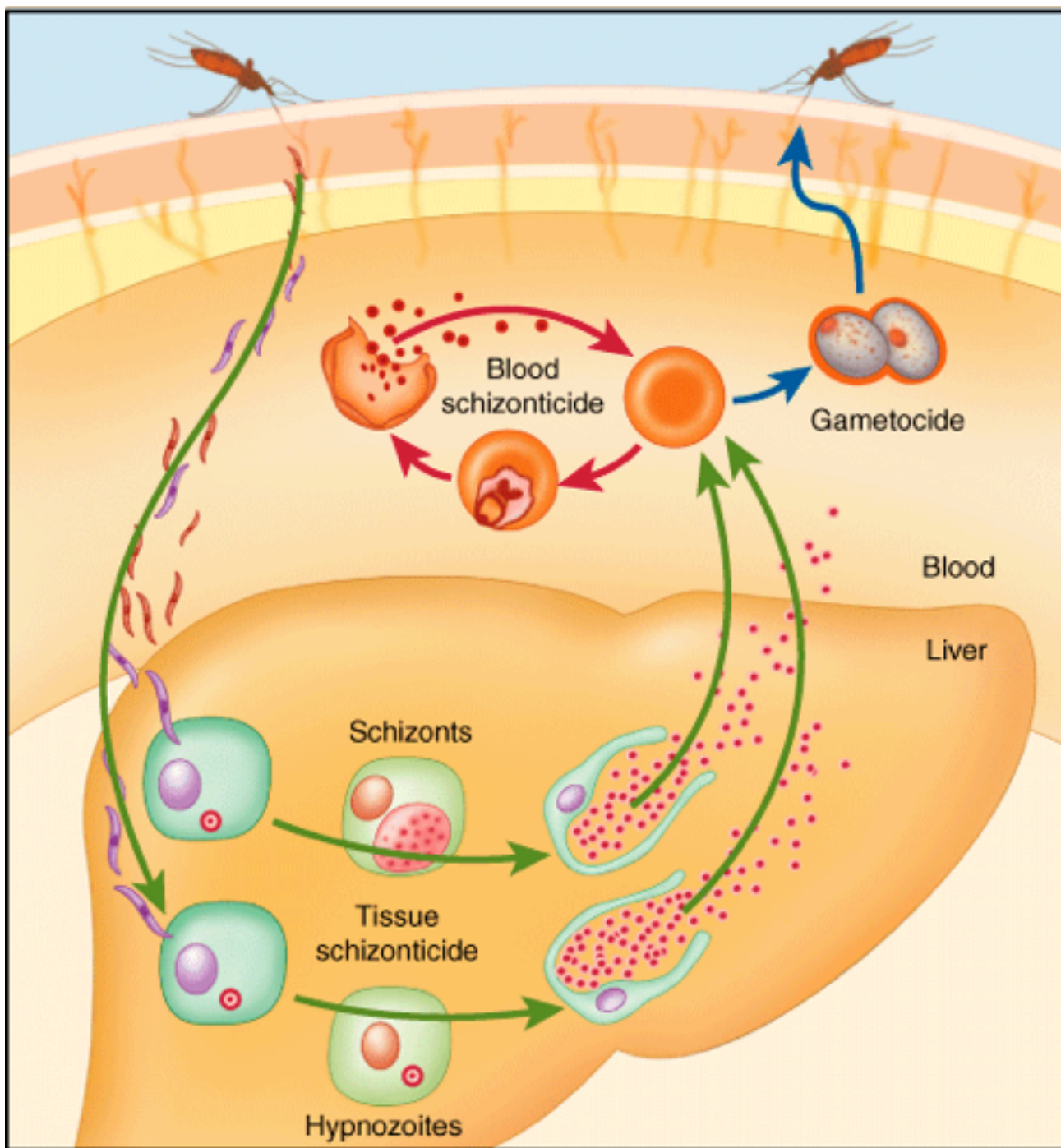


Figure 11.10. Life cycle of a parasite in a vertebrate host. (a) The parasite enters the blood and develops into a blood schizonticide. (b) The parasite develops into a gametocyte, which is taken up by a mosquito during a blood meal. (c) The parasite enters the liver and develops into schizonts. (d) The parasite develops into tissue schizonticide. (e) The parasite develops into hypnozoites, which can remain dormant in the liver.

Antimalarial Drugs

- **Suppressive Treatment (Clinical Cure):** Chloroquine, Quinine, Quinidine , Doxycycline, Clindamycin, Mefloquine, and Halofantrine.
- **Radical Cure:** Elimination of both hepatic and erythrocytic stages of the malaria parasite. No one drug can do this. Ex. Chloroquine followed by Primaquine, required for *P vivax* and *P ovale*.
- **Causal prophylaxis:** Prevention of erythrocytic infection. Can be done by prophylactic agents. Chloroquine, Mefloquine (Malarone), and Doxycycline
- **Terminal prophylaxis:** Eradication of dormant hepatic stages of *Plasmodium vivax* and *P. ovale*..

Chloroquine

Chloroquine is a highly effective blood schizonticide.

It is also moderately effective against gametocytes of *P vivax*, *P ovale*, and *P malariae* but not against those of *P falciparum*.

However, does not eliminate dormant liver forms of *P.vivax* and *P.ovale*.

Primaquine must be added for their radical cure.

Chloroquine

Mechanism of action:

- **Controversial.**
- **It diffuses into, and concentrates in the food vacuole of the parasite and inhibits heme polymerase which converts heme into hemozoin.**
- **Heme is toxic to the parasite.**

Chloroquine

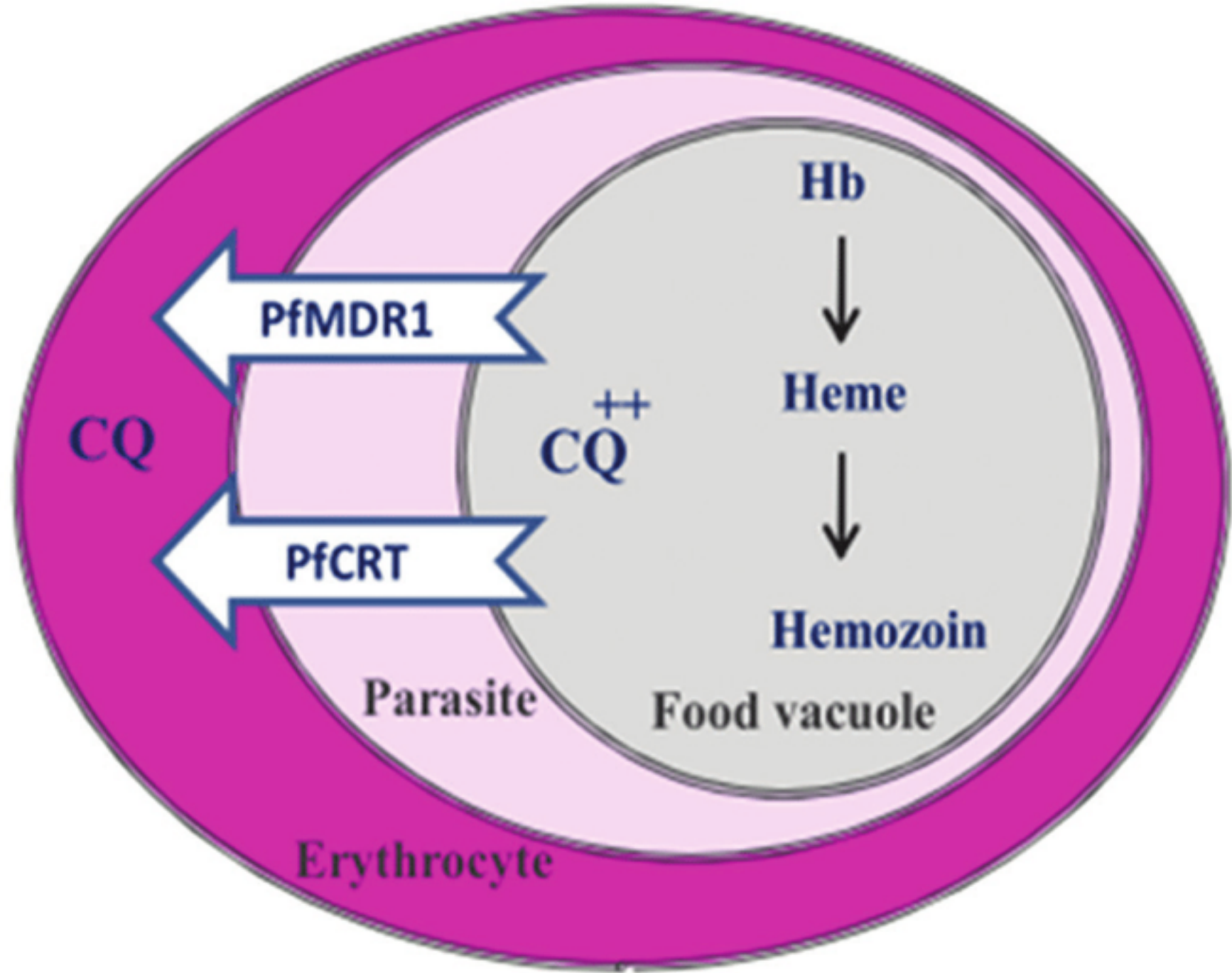
Mechanism of resistance:

- *P. falciparum* resistance is widely spread all over the world, and is due to enhanced efflux of the drug from the parasite due to increased expression of a transporter.
- *P. vivax* resistance (not common) to chloroquine but is increasing.

Resistance:

Very common with *P. falciparum* and increasing with *P. vivax*.

Mutation in a glycoprotein (PfCRT) works as a drug-transporting pump mechanism . Also *MDR 1* protein



Chloroquine

Pharmacokinetics:

- Given orally.
- Kaolin, and Calcium- and magnesium containing antacids interfere with absorption.
- Can be given IM or by slow IV infusion.
- $V_d \sim 100-1000L/kg$
- Eliminated slowly by renal excretion (70%) and hepatic metabolism.
- Half-life of elimination $\sim 1-2$ months.

Chloroquine

Clinical uses:

- 1. Acute attacks of non-falciparum and falciparum-sensitive malaria (2-3 days)**
- 2. Chemoprophylaxis in areas without resistance**
- 3. Amebic liver abscess that fails initial treatment with metronidazole**

Chloroquine

Adverse effects:

- 1. Nausea, vomiting, abdominal pain and anorexia**
- 2. Pruritus**
- 3. QRS and T wave abnormalities**
- 4. Respiratory and cardiac arrest - arrhythmias**
- 5. Visual field abnormalities, retinopathy, blurring of vision.**
- 6. Peripheral neuropathy and myopathy**

Chloroquine

6. Psychosis and seizures
7. Ototoxicity and hearing impairment
8. Hemolysis in patients with G6PD deficiency
9. Agranulocytosis
10. Exfoliative dermatitis
11. Alopecia, bleaching of hair

Quinine⁽¹⁸²⁰⁾ and Quinidine

Cinchona tree.



General protoplasmic poison: will affect the feeding mechanism of the parasite.

Resistance is uncommon.

Effective rapid schizontide therapy for severe falciparum, chloroquine-resistant malaria, usually in combination with another drug (e.g. Doxycycline or Clindamycin) to shorten duration of use.

Quinine⁽¹⁸²⁰⁾ and Quinidine

Adverse Effects:

Cinchonism: Tinnitus, headache, nausea, dizziness, flushing, visual disturbances. Later, auditory abnormalities, vomiting, diarrhea, and abdominal pain.

Blood dyscrasias.

Hypersensitivity, hypoglycemia, uterine contractions.

Hypotension, QT prolongation.

Blackwater fever (hemolysis, hemoglobinemia, hemoglobinuria, and renal failure)

Primaquine

the drug of choice for the eradication of dormant liver forms of *P vivax* and *P ovale* and can also be used for chemoprophylaxis against all malarial species.

Primaquine

8-aminoquinolone

Unknown mechanism.

Drug of choice; the only available one, for eradication of exoerythrocytic forms of malaria after treatment with chloroquin.

Hemolysis in G6PD deficient patients.

Also, nausea, distress, headache, pruritis, leukopenia and agranulocytosis.

Primaquine

- Active against **hypnozoites** of all plasmodia → effects radical cure and causal prophylaxis.
- Has **gametocidal** action in all plasmaodia, and thus, prevents transmission of disease.
- Mechanism of action is unknown.
- Well absorbed after PO, widely distributed and rapidly metabolized.
- $t_{1/2}$ ~ 3-8 hours.

Primaquine

Adverse Effects:

1. Hypotension if used parenterally.
2. Nausea, abdominal pain.
3. Headache.
4. Hemolysis in G6PD deficient individuals.
5. Methemoglobinemia
6. Leukopenia, agranulocytosis
7. Cardiac arrhythmias.
8. Should NOT be given during pregnancy because it may cause hemolysis in the fetus.