Drugs Used in Treatment of Malaria

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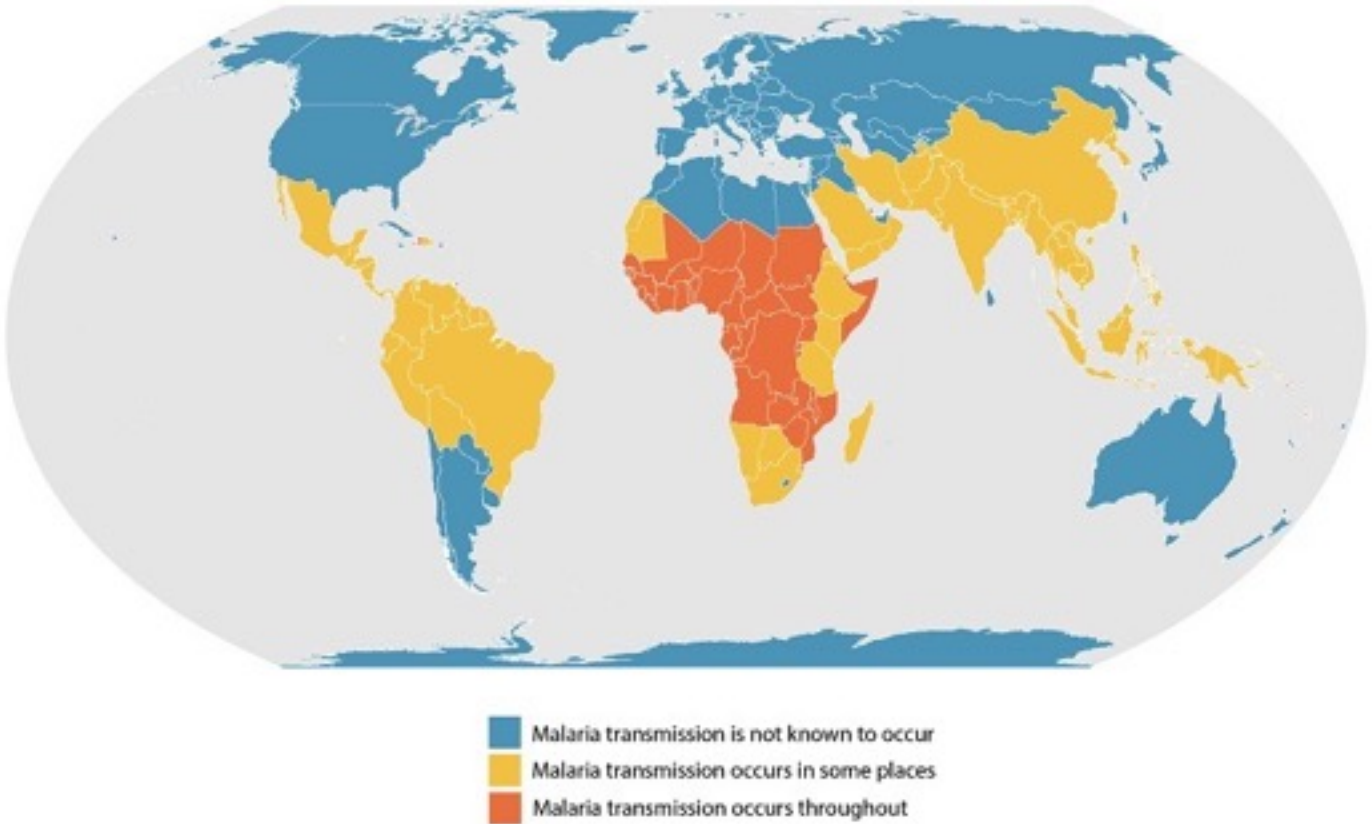
Malaria

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

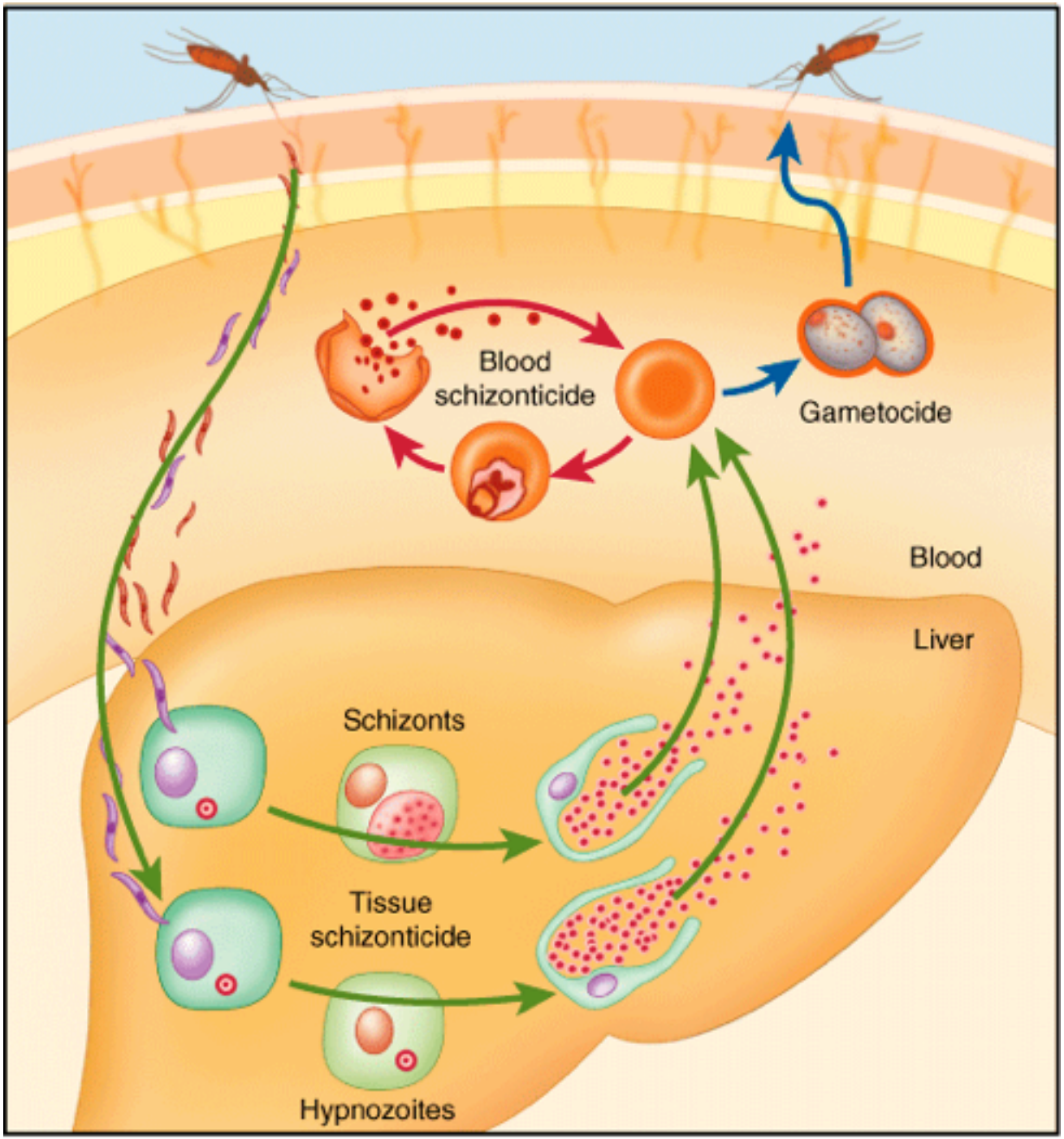


Malarial Parasites

- ***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


Blood schizonticide
Gametocide
Blood
Liver
Schizonts
Tissue schizonticide
Hypnozoites

Antimalarial Drugs

- **SuppressiveTreatment (Clinical Cure): Chloroquine, Quinine, Quinidine , Doxycyline, 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:

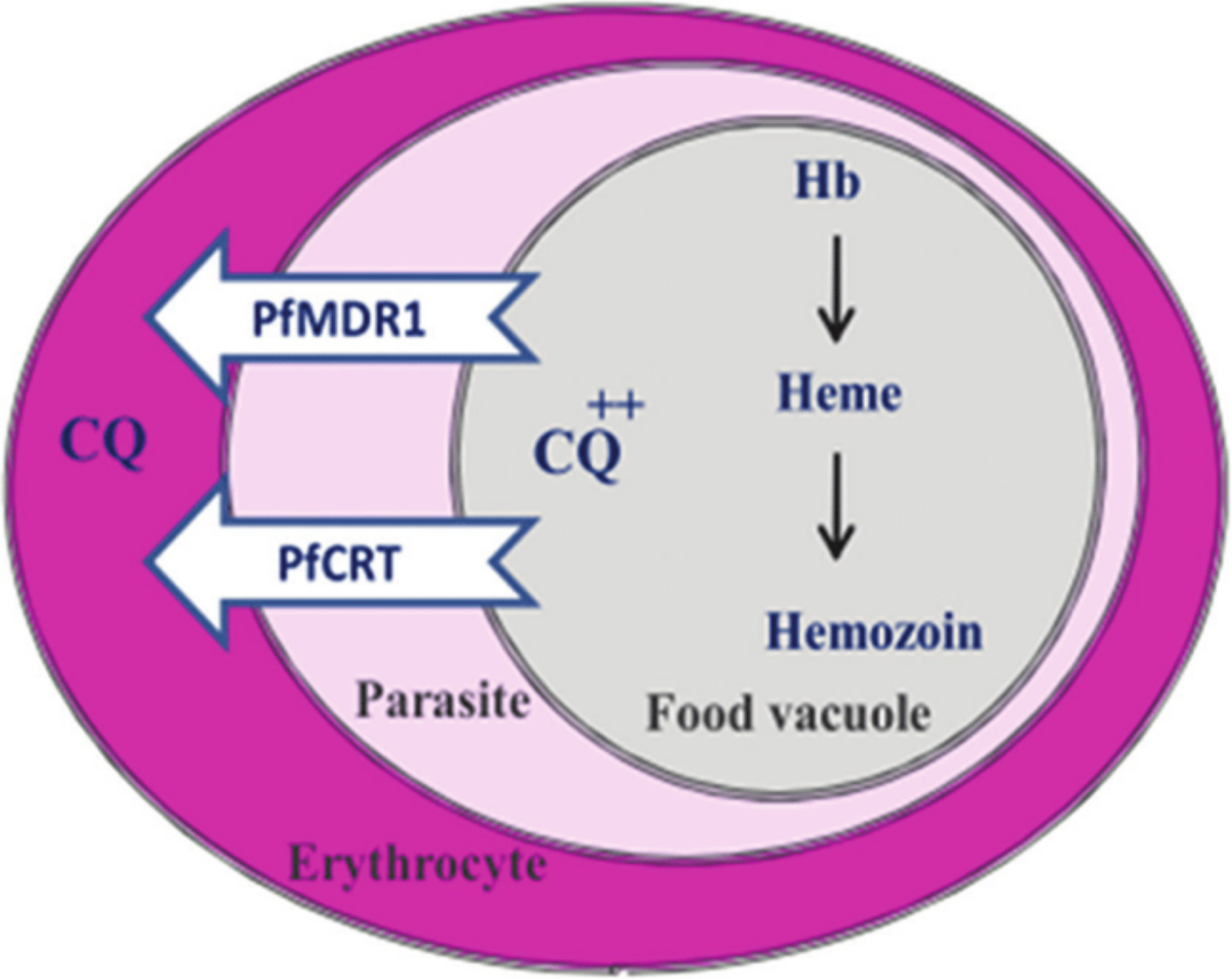
- *P. falciparum* resistance is widely spread all over the world, and is due to enhanced efflux of the drug from the parasite due to increased expression of a transporter.

  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


Hb
Heme
Hemozoin
PfMDR1
PfCRT
CQ
CQ++
Parasite
Food vacuole
Erythrocyte

Chloroquine

Pharmacokinetics:

- Given orally.
- Kaolin, and Calcium- and magnesium containing antacids interfere with absorption.
- Can be given IM or by slow IV infusion.
- Vd ~ 100-1000L/kg
- Eliminated slowly by renal excretion (70%) and hepatic metabolism.
- Half-life of elimination ~ 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, hemoglobinurea, 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.
- t½ ~ 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.

Mefloquine

- **Blood schizonticide, not for liver forms.**
- **Used for prophylaxis**
  Used for resistant *P. falciparum* (single oral dose).

  Also for suppressive in addition to prophylactic treatment (weekly doses).
- **Nausea, vomiting, diarrhea, pain.**
- **Vertigo, dizziness, headache, rashes and visual alterations.**
- **Psychosis, hallucinations, confusion, anxiety, depression.**

Atovaquone and Proguanil

- **Usually in fixed combination = “Malarone”.**
- **Recommended drug for prophylaxis.**

- **Atovaquone also approved for *P. jiroveci* pneumonia, although has lower efficacy than Trimethoprim-sulfamethaxazole combination.**

- **Can cause fever, rash, nausea, vomiting, diarrhea, headache, and insomnia.**

Pyrimethamine

Inhibits DHF Reductase

Slow and long acting drug.

Effective on erythrocytic forms of all species.

Not for severe malaria.

Preferential binding to parasitic enzyme.

Usually combined with Sulfadoxine" Fansidar" or Sulfones which inhibit Dihydropteroate synthase.

No longer recommended for prophylaxis.

Also, for Toxoplasmosis(in higher doses),

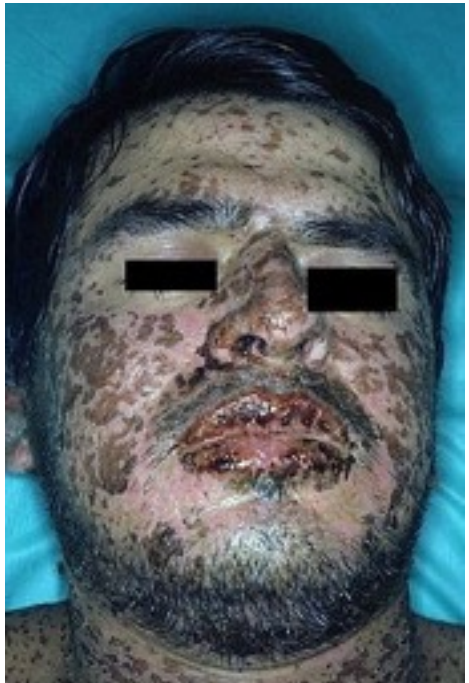
and *P. jeroveci.*

Adverse Effects:

Anorexia, Vomiting, Leucopenia, Thrombocytopenia, glossitis

CNS: Stimulation, Convulsions

Allergic reactions including Stevens-Johnson Syndrome



Antibiotics

- **Tetracycline.**
- **Doxycycline.**
- **Clindamycin.**
- **Azithromycin.**
- **Fluoroquinolones.**

Active against erythrocytic forms of all species.
Usually for chloroquine-resistant strains.
Also effective against other protozoal diseases.

Halofantrine and Lumefantrine

Rapidly effective against erythrocytic forms of all species.

Usually for chloroquine-resistant strains.

Well tolerated, except for cardiac toxicity (QT prolongation)

Artemisnin

- Artesunate.
- Artemether.

- Derivatives of Artemisia(الشيح) used by Chinese since 2000 years.
- Rapidly acting schizonticides against all species.
- No documented resistance.
- Work by free radical formation or ATP inhibition.
- Only drugs reliably effective against quinine-resistant and multi-drug resistant strains.

- N,V,D, and neurotoxicity in animals.