

Chemotherapy of Malaria

Introduction

- **Malaria** is a **mosquito-borne protozoal infection** caused by *Plasmodium* species, primarily:
 - *P. falciparum* (most severe)
 - *P. vivax* (relapsing)
 - *P. ovale*, *P. malariae*, and *P. knowlesi*
- Treatment depends on the species, severity, geographical area (resistance patterns), and whether the infection is complicated or uncomplicated.
- Malaria chemotherapy includes drugs that target:
 - **Liver stages** (pre-erythrocytic)
 - **Blood stages** (erythrocytic)
 - **Hypnozoites** (dormant liver forms of *P. vivax*/*P. ovale*)
 - **Gametocytes** (to prevent transmission)

Classification of Antimalarial Drugs

A. Based on Site of Action

Stage	Drugs
Tissue schizonticides	Primaquine, Tafenoquine
Blood schizonticides	Chloroquine, Artemisinin derivatives, Quinine, Mefloquine, Atovaquone, Lumefantrine
Gametocytocides	Primaquine (most species), Artemisinin (for <i>P. falciparum</i>)

B. Based on Chemical Class

Class	Drugs
4-Aminoquinolines	Chloroquine, Amodiaquine
8-Aminoquinolines	Primaquine, Tafenoquine
Quinoline methanols	Quinine, Mefloquine
Artemisinin derivatives	Artesunate, Artemether, Dihydroartemisinin
Antifolates	Pyrimethamine, Proguanil, Sulfadoxine
Naphthoquinones	Atovaquone
Antibiotics	Doxycycline, Clindamycin (adjunctive)

Mechanism of Action

Drug/Class	Mechanism
Chloroquine	Inhibits heme polymerase → accumulation of toxic heme → parasite death
Artemisinins	Generate free radicals in parasite food vacuole → damage parasite proteins
Quinine/Mefloquine	Interfere with heme detoxification in blood schizonts
Primaquine	Generates reactive oxygen species → disrupts mitochondria of hypnozoites
Antifolates	Inhibit dihydrofolate reductase → block DNA synthesis in parasite
Atovaquone	Inhibits cytochrome bc1 complex → collapse of mitochondrial membrane potential
Doxycycline	Inhibits protein synthesis (delayed parasite death)

Pharmacokinetics (ADME)

Drug	Absorption	Distribution	Metabolism	Elimination	Half-life
Chloroquine	Well absorbed orally	Wide, tissue-bound	Hepatic	Renal	Long (~1–2 months)
Artemisinins	Rapid absorption	Wide	Hepatic (CYP450)	Bile/urine	Short (~1–2 hrs)
Quinine	Good oral	Wide	Hepatic	Renal	11–18 hours
Primaquine	Good oral	Moderate	Hepatic	Renal	~4–6 hours
Atovaquone	Poor (↑ with fat)	High protein binding	Not metabolized	Bile	~2–3 days
Mefloquine	Good oral	Extensive	Hepatic	Bile/feces	Long (~2–4 weeks)

Pharmacodynamics

- Artemisinin-based combination therapies (ACTs) show rapid parasite clearance (used for *P. falciparum*)
- Chloroquine is effective for sensitive strains
- Primaquine and Tafenoquine are the only drugs that eradicate hypnozoites of *P. vivax* and *P. ovale*
- Quinine is still used for severe malaria, often IV

Therapeutic Uses

1. Uncomplicated *P. falciparum* malaria:

- **Artemisinin-based combination therapies (ACTs)** (first-line)
 - Examples:
 - Artemether–Lumefantrine
 - Artesunate–Mefloquine
 - Artesunate–Sulfadoxine–Pyrimethamine
 - Dihydroartemisinin–Piperaquine

2. Uncomplicated *P. vivax/ovale/malariae*:

- **Chloroquine** (if sensitive) + **Primaquine** (for radical cure)
- **ACT + Primaquine** in chloroquine-resistant areas

3. Severe Malaria:

- **IV Artesunate** (preferred)
- **IV Quinine** (alternative where artesunate unavailable)
- Step-down to ACT when patient tolerates oral medication

4. Prophylaxis:

Drug	Use
Mefloquine	Weekly dosing; areas with chloroquine resistance
Atovaquone-Proguanil	Daily dosing; effective against most resistant strains
Doxycycline	Daily; not for children or pregnant women
Chloroquine	Weekly; only in chloroquine-sensitive regions

Adverse Effects

Drug/Class	Major Adverse Effects
Chloroquine	GI upset, pruritus, retinal damage (long-term)
Artemisinins	Nausea, dizziness, rare neurotoxicity, low toxicity overall
Quinine	Cinchonism (tinnitus, dizziness), hypoglycemia, QT prolongation
Primaquine	Hemolysis in G6PD deficiency, methemoglobinemia
Mefloquine	Neuropsychiatric effects, dizziness, sleep disturbances
Sulfadoxine–Pyrimethamine	Rash, Stevens-Johnson syndrome, bone marrow suppression

Atovaquone–Proguanil	GI upset, rash, rare hepatotoxicity
Doxycycline	Photosensitivity, GI upset, contraindicated in pregnancy and <8 years

Contraindications

Drug	Contraindications
Chloroquine	Psoriasis, retinal disease
Primaquine	G6PD deficiency, pregnancy
Mefloquine	History of epilepsy or psychiatric illness
Doxycycline	Pregnancy, children under 8 years
Atovaquone–Proguanil	Severe renal impairment
Quinine	Hypersensitivity, prolonged QT, glucose-6-PD deficiency (caution)

Drug Interactions

- **Chloroquine:** May ↑ digoxin and cyclosporine levels
- **Quinine:** ↑ risk of bleeding with warfarin; interacts with antacids, enhances hypoglycemia with insulin
- **Mefloquine:** Avoid with other QT-prolonging drugs
- **Doxycycline:** Absorption ↓ by antacids, dairy
- **Artemisinins:** Mild CYP3A4 induction; minimal interaction
- **Primaquine:** Additive hemolysis with other oxidant drugs

Dose and Route of Administration

Chloroquine phosphate

- **Treatment dose:** 600 mg base initially, then 300 mg at 6, 24, and 48 hours
- **Route:** Oral
- **Prophylaxis:** 500 mg weekly, starting 1–2 weeks before travel

Primaquine

- **Radical cure:** 15–30 mg base daily × 14 days
- **Route:** Oral
- Test for G6PD deficiency before use

Artemether–Lumefantrine



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