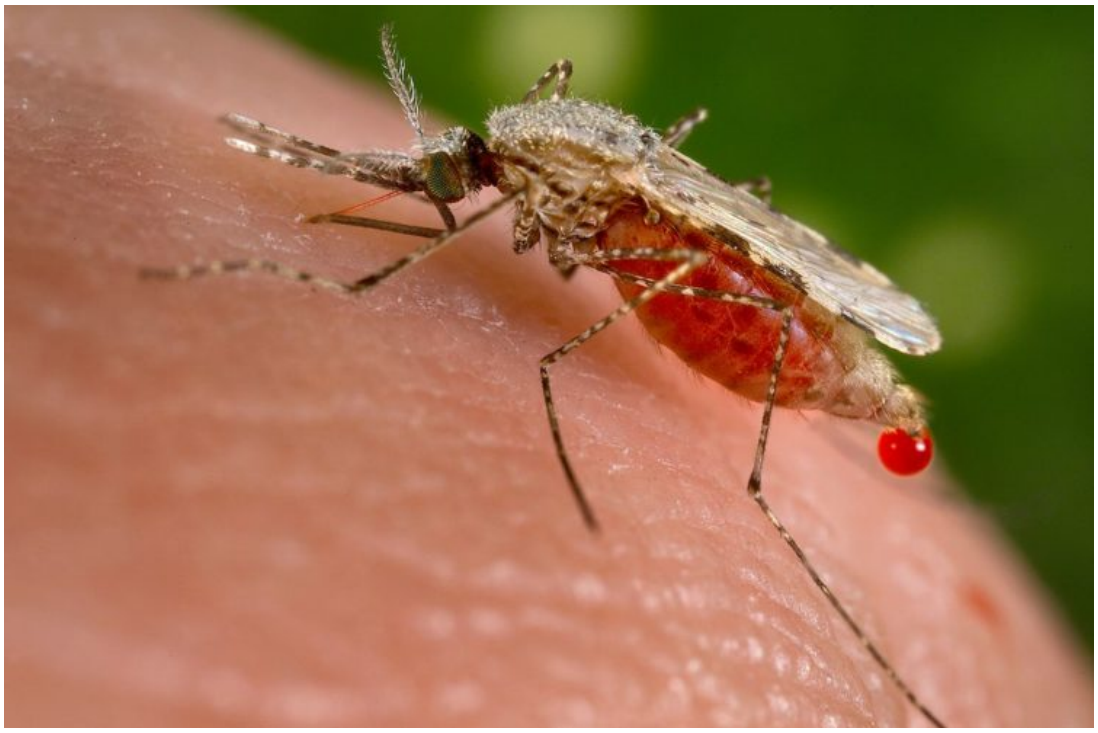
Antimalarial Drugs — Quinine, Quinidine, Sulfonamides, Chloroquine and More

See online here

Malaria is a protozoan infection, caused by the bite of the female Anopheles mosquito. This article reviews the various antimalarial drugs, mechanisms of action, adverse effects/toxicity, and drugs of choice. Important therapeutic aspects of individual drugs will also be covered.



Overview of Malaria

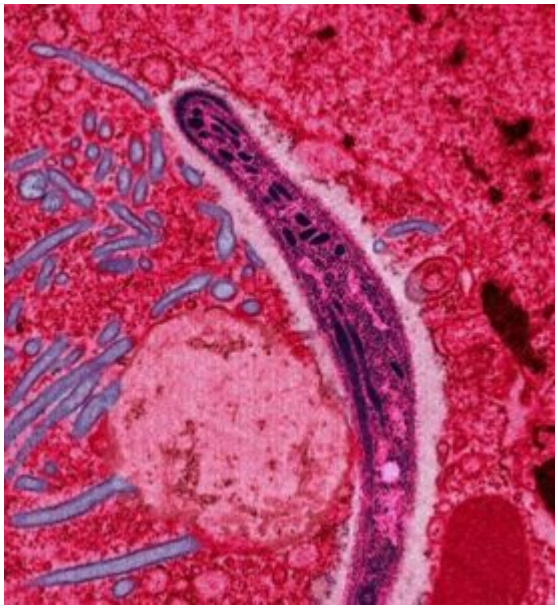


Image: “Malarial sporozoites develop inside oocysts and are released in large numbers into the hemocoel of Anopheles stephensi mosquitoes.” by image by Ute Frevert; false color by Margaret Shear. License: CC BY 2.5

Malaria is caused by four different species of the protozoan parasite *Plasmodium*: *P. falciparum*, *P. malariae*, *P. ovale*, and *P. vivax*. These are transmitted by the bites of female Anopheles mosquitoes. Malaria caused by the *P. falciparum* species is severe; it can cause anemia and cerebral malaria. This parasite has a **complex life cycle** and is active in both the blood (erythrocytic schizonts) and the tissues, mainly the liver (exoerythrocytic forms of **schizonts**).

Treatment of malaria is aimed at killing the schizonts by one or more mechanisms. Resistance occurs when the parasite develops mechanisms that reduce the effects of the antimalarials or bypasses the mechanisms of the drug. Resistance is a major problem in some parts of the world, e.g., Africa and Southeast Asia; therefore, newer drugs are utilized. Monotherapy should be avoided to prevent drug resistance.

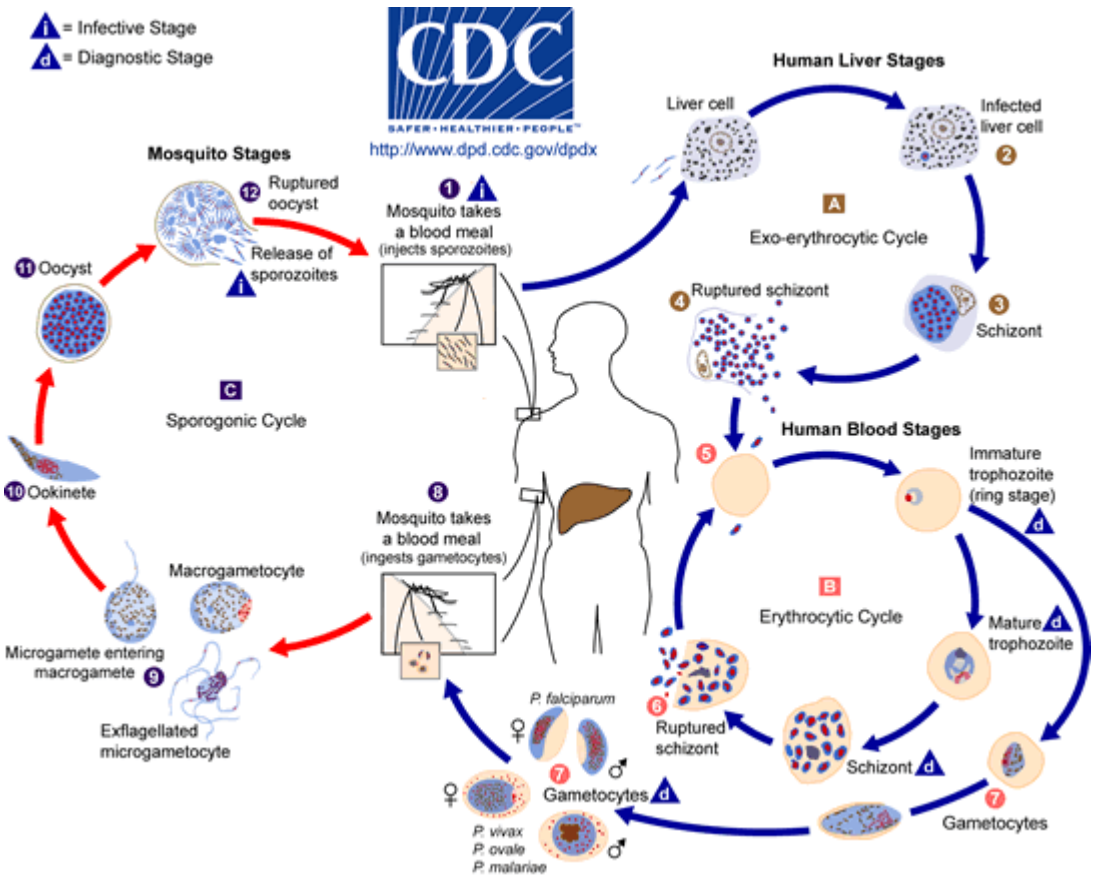


Image: “A chart showing the lifecycle of the malaria parasite.” by Centers for Disease Control and Prevention (CDC).
License: Public Domain

Classifications of Antimalarial Drugs

Chemical classification of antimalarials

4–Aminoquinoline derivatives: Chloroquine

4–Quinoline derivatives: Mefloquine

8–Aminoquinoline derivatives: Primaquine, Bulaquine

Cinchona alkaloid: Quinine, Quinidine

Biguanides: Proguanil

Diaminopyrimidines: Pyrimethamine

Sulfonamides and sulfones: Sulfadoxine, Dapsone

Sesquiterpene lactones: Artemisinin derivatives

Functional classification of antimalarials

Schizonticide: a drug that selectively kills **schizonts** of a sporozoan parasite (in this case, the malarial parasite).

- **Tissue schizonticides** kill exoerythrocytic forms of schizonts, such as those in the liver (e.g., primaquine).

- **Blood schizonticides** kill schizonts only in the erythrocyte (e.g., chloroquine, quinine).

Sporonticide: a drug that prevents **sporogony** and multiplication in the mosquito (e.g., proguanil, pyrimethamine).

Individual Antimalarial Drugs

Chloroquine

This drug is rapidly and completely absorbed following oral administration. It concentrates in the erythrocytes, liver, spleen, kidney, lung, melanin-containing tissues, and leukocytes. Chloroquine also penetrates the central nervous system (CNS) and crosses the placenta.

Mechanism of Action

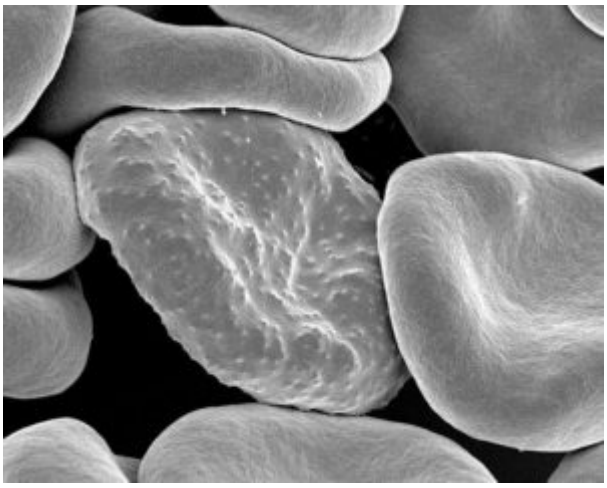


Image: "Electron micrograph of a Plasmodium falciparum-infected red blood cell (center), illustrating adhesion protein "knobs"." by Rick Fairhurst and Jordan Zuspann. License: CC BY 2.0

Free heme is generated by the parasite while digesting the host cell's **hemoglobin**. The parasite polymerizes the heme to **hemozoin** to avoid the toxic effects of the free heme; however, chloroquine accumulates in the **food vacuoles** of plasmodia and prevents polymerization of heme. Consequently, free heme causes the **lysis of the parasite** along with the **red blood cells**.

Note: Free heme is a **cytotoxic agent**. It causes damage to proteins, DNA, cell membranes, and cell organelles via oxidation and lipid peroxidation.

Clinical uses of Chloroquine

Chloroquine is the drug of choice for treatment and prophylaxis of all forms of malaria:

- Non-resistant *P. falciparum* malaria prophylaxis and treatment
- Vivax malaria treatment
- Ovale malaria treatment

Adverse effects/toxicity

- Gastrointestinal (GI) symptoms include nausea and vomiting.
- Other symptoms include pruritus (mostly in the African population, lasting for

48–72 hours), headaches, blurred vision, and **prolonged QT interval.**
- Severe adverse effects are rare.

Resistance: The parasite develops a membrane pump to flush out heme and transporter to flush out chloroquine. A mutation in the gene encoding for **chloroquine resistance transporter protein (PfCRT)** has a role in the development of resistance by *Plasmodium*.

Drug interactions

Antacids may decrease the oral absorption of chloroquine.

Contraindications

- Presence of **psoriasis** and **porphyria** are contraindications for chloroquine.
- Chloroquine should be avoided concomitantly with other drugs that prolong QT interval.

Mefloquine

The **mechanism of action** of mefloquine is unknown. The drug has a long half-life (20 days).

Clinical uses

- Resistant *P. falciparum* treatment
- Falciparum malaria prophylaxis (once a week)

Adverse effects/toxicity

- At high doses: nausea, vomiting, dizziness, disorientation, hallucinations, and depression
- Prolonged QT interval and may precipitate torsade de pointes
- Rare: **pneumonitis**

Drug interactions

- Resistance to mefloquine confers cross-resistance to quinine and halofantrine.
- ECG abnormalities and **cardiac arrest** can occur when taken with quinine or quinidine.

Contraindications

- Neurologic and psychiatric disorders
- Family history of seizures

Artemisinin derivatives

Artesunate, Artemether, and Arteether are artemisinin derivatives. These **blood schizonticides** are considered a superior antimalarial drug to quinine. Artemisinin clears the parasitic load in less time compared to other antimalarial drugs. It kills young parasites before they enter into the deep microvasculature.

To prevent the development of **resistance,** artemisinin derivatives should not be used as monotherapy. Possible combinations include artemether with lumefantrine; artesunate with mefloquine, clindamycin, etc.

The drugs have short half-lives; therefore, they cannot be used for prophylaxis. They are

available as **intravenous preparations**.

Mechanism of action

- Artemisinin derivatives accumulate in the protozoan's **food vacuoles** and get metabolized to release **toxic free radicals.**
- Additional possible action includes binding to and damaging certain parasite proteins.

Clinical uses

- Artemether + lumefantrine: acute, uncomplicated malaria infections in adults and children > 5 kg
- **Multidrug-resistant *P. falciparum*** treatment: They are the only drugs effective against quinine-resistant strains.
- **Severe malaria**: Sometimes intravenous artesunate is used instead of quinine. This treatment is available for severe malaria in the United States and is the drug of choice in low-transmission areas and in the second and third trimesters of pregnancy.

Adverse effects/toxicity

- Usually mild GI symptoms, such as nausea, vomiting, and diarrhea
- Prolong QT interval
- Hypersensitivity reactions and rash

Quinine

This blood schizonticide is usually administered in combination with clindamycin, doxycycline, or tetracycline. It is available in oral and intravenous formulations.

Mechanism of action: As with chloroquine, quinine interferes with heme polymerization.

Clinical uses

- Multidrug-resistant malaria treatment
- Severe malaria, including cerebral malaria (intravenous quinine is the drug of choice.)
- Quinidine, a stereoisomer of quinine, is the only non-oral drug approved by the United States Food and Drug Administration (U.S. FDA) for the treatment of severe malaria.
- To avoid resistance development, quinine should not be given for prophylaxis.

Adverse effects/toxicity

- Quinine is a cardiotoxic drug causing ventricular tachycardia, arrhythmia, hypotension, etc.
- Prolonged QT interval and may precipitate torsade de pointes
- **Cinchonism**: a syndrome of nausea, vomiting, tinnitus, and vertigo; however, this is reversible so therapy can continue.
- Rarely **hemolysis** (blackwater fever), which can lead to hemolytic anemia, hemoglobinuria, and renal damage

Drug interactions

- Enhances the activity of neuromuscular blockers

- Increases digoxin levels
- Absorption decreased with antacids containing aluminum hydroxide

Contraindications

- Known hypersensitivity
- Pregnancy

Primaquine

This tissue schizonticide and gametocide is the only agent that prevents the relapse of *P. vivax* and *P. ovale* malaria. It is **not effective against blood schizonts.**

Mechanism of action

Primaquine forms quinoline-quinone metabolites, which act as cellular oxidants. Its mechanism of action is not clearly understood; however, it is believed to damage the DNA structure and mitochondrial membranes of the parasite.

Clinical uses

- Eradication of liver schizonts (liver hypnozoites)
- Prophylaxis of *P. vivax* and *P. ovale* malaria

Adverse effects/toxicity

- Usually well tolerated
- GI distress symptoms, pruritus, headache, **methemoglobinemia**
- Primaquine and its metabolites have oxidative activity and may be associated with **methemoglobinemia**, especially when the daily dose exceeds 60 mg

Contraindications

- **G6PD deficiency** leads to hemolysis
- Pregnancy

Antifolate Drugs

Proguanil, pyrimethamine, sulfadoxine, and dapsone are blood schizonticides. Pyrimethamine has a **sporonticide** action as well. Proguanil has a shorter half-life (12–16 hours) than others (> 100 hours).

Mechanism of action

- Proguanil (a prodrug, biotransformed to **cycloguanil**) and pyrimethamine inhibit protozoan **dihydrofolate reductases**, which are needed for the synthesis of **tetrahydrofolate**, a cofactor that plays a role in the synthesis of nucleic acids.
- Sulfonamides (sulfadoxine and dapsone) block **folic acid synthesis** by inhibiting **dihydropteroate synthase**.
- Pyrimethamine and sulfadoxine (Fansidar) act by both of the above mechanisms, leading to a synergistic effect.

Clinical uses

- Multidrug-resistant *P. falciparum* prophylaxis and treatment
- Pyrimethamine and sulfadoxine (Fansidar): chloroquine-resistant *P. falciparum* treatment and toxoplasmosis treatment

- Proguanil with atovaquone (Malarone): chloroquine- and mefloquine-resistant *P. falciparum* prophylaxis
- Dapsone is used to treat leprosy in combination with trimethoprim. Like primaquine, it is also used to treat **pneumocystis pneumonia.**

Adverse effects/toxicity

- Pyrimethamine may cause a folic acid deficiency in high doses, and **megaloblastic anemia**, which can be reversed with leucovorin.
- Sulfonamides may cause skin rashes, GI symptoms, hemolysis, and kidney damage.

Drug Interactions: Carbamazepine increases doxycycline metabolism.

Doxycycline

Doxycycline is a blood schizonticide.

Mechanism of action

Doxycycline inhibits protein synthesis in the bacteria by interfering with the binding of **aminoacyl-tRNA** molecules to bacterial ribosomes.

Clinical uses

- *P. falciparum* malaria prophylaxis, including chloroquine-, mefloquine-, or multidrug-resistant malaria
- *P. falciparum* malaria treatment in combination with quinine
- Other clinical uses: **gonorrhea**, community-acquired pneumonia, **Lyme disease**, **amebiasis**, and others

Adverse effects/toxicity

- Dizziness and vertigo, which are dose-dependent and reversible
- **Candidal vaginitis**
- Photosensitivity

Drug interactions

- Carbamazepine and barbiturates increase doxycycline metabolism.
- Phenytoin decreases doxycycline levels by stimulating its metabolism.

Contraindications: Younger children and pregnant women

Amodiaquine

This drug is similar to chloroquine but less metallic/bitter in taste and somewhat faster acting.

Mechanism of action: S**imilar to that of chloroquine**

Clinical uses

- Uncomplicated *P. falciparum* malaria treatment
- Not used for prophylaxis

Adverse effects/toxicity

- Similar to chloroquine

- Neutropenia in pediatric patients

Drug interactions: Similar to chloroquine

Contraindications: Similar to chloroquine

Atovaquone

Atovaquone is a rapidly acting blood schizonticide.

Mechanism of action

- Inhibits **mitochondrial electron transport** by interrupting adenosine triphosphate (ATP) production and breaking down mitochondrial membranes
- May also interfere with folate metabolism

Clinical uses

- Mild to moderate **pneumocystis pneumonia**
- Falciparum malaria prophylaxis and treatment in combination with proguanil (Malarone)
- Also used for **toxoplasmosis** (including as a second-line drug in AIDS patients)

Adverse Effects/Toxicity: Coughing, rash, GI symptoms: nausea, vomiting, diarrhea

Contraindications: severe renal impairment

Halofantrine and Lumefantrine

Blood schizonticides

	Halofantrine	**Lumefantrine**
Mechanism of action	Unknown	
Clinical uses	Not used anymore for malaria prophylaxis (effective against all 4 species) because of QT prolongation	In combination with artemether: acute, uncomplicated malaria infections in adults and children > 5 kg
Adverse effects/toxicity	GI symptoms: abdominal pain, diarrhea, vomiting; coughing, rash, headache, pruritus; prolongs QT interval and can precipitate **Torsade de Pointes**	Extremely well tolerated, very mild GI symptoms, headache, etc. may rarely be seen.
Drug interactions	Prior mefloquine therapy worsens QT interval prolongation	
Contraindications	Cardiac conduction defects	

Drugs for Prophylaxis of Malaria in Travelers

Type of malaria	**Therapy**
Chloroquine-sensitive P. falciparum	Chloroquine or mefloquine (weekly)
Chloroquine-resistant P. falciparum	Mefloquine (weekly)
Mefloquine – or multidrug-resistant malaria	Doxycycline or Malarone (daily)
P. vivax and *P. ovale*	Primaquine (daily for 14 days)

Antimalarial Drug Treatment in Severe Malaria

- Intravenous (IV) quinidine (approved by the U.S. FDA)
- IV quinine or IV artesunate (recommended by the World Health Organization, Centers for Disease Control and Prevention, and other sources)
- After initial treatment with one of these drugs, a 1-week course of doxycycline is administered. If doxycycline is contraindicated, e.g., in the pediatric age

group, clindamycin can be used.

Review Questions

The correct answers can be found below the references.

1. Which of the following is the only non-oral drug approved by the U.S. FDA for the treatment of severe *P. falciparum* malaria?

A. Quinine
B. Quinidine
C. Artesunate
D. Mefloquine
E. Proguanil

2. A 35-year-old Belgian man is planning to travel to an Asian country to which to *P. falciparum* malaria is endemic but where malaria resistance has not developed. He has a known case of bipolar II disorder. Which of the following prophylactic drugs or drug combinations is contraindicated in this patient?

A. Mefloquine
B. Chloroquine
C. Doxycycline
D. Malarone
E. Primaquine

3. Which of the following drugs kills the hypnozoites (dormant forms)?

A. Quinine
B. Chloroquine
C. Doxycycline
D. Malarone
E. Primaquine

References

Basso, L. G., Rodrigues, R. Z., Naal, R. M., & Costa-Filho, A. J. (2011). Effects of the antimalarial drug primaquine on the dynamic structure of lipid model membranes. Biochimica et Biophysica Acta (BBA)-Biomembranes, 1808(1), 55-64. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20713019

Centers for Disease Control and Prevention. Malaria Parasites. Availabe at: https://www.cdc.gov/malaria/about/biology/parasites.html

Day, N., & Dondorp, A. M. (2007). The management of patients with severe malaria. The American journal of tropical medicine and hygiene, 77(6 Suppl), 29–35. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18165472

Harvey, R. A., Clark, M. A., Finkel, R., Rey, J. A., & Whalen, K. (2012). Lippincott's illustrated reviews: Pharmacology. Philadelphia: Wolters Kluwer.

Katzung, B. G. (Ed.). (2012). Basic & clinical pharmacology (Vol. 12). New York, NY, USA: Lange Medical Books/McGraw-Hill.

Kumar, S., & Bandyopadhyay, U. (2005). Free heme toxicity and its detoxification systems in human. Toxicology letters, 157(3), 175-188. Available at:

https://www.ncbi.nlm.nih.gov/pubmed/15917143

Travassos M., Laufer M. K. 2016. Antimalarial drugs: An overview. Uptodate. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20713019

Trevor, A. J., Katzung, B. G., Masters, S. B., & Kruidering-Hall, M. (2010). Pharmacology Examination & Board Review. New York: McGraw-Hill Medical.

Tripathi, K. D. (2013). Essentials of medical pharmacology. JP Medical Ltd.

Correct answers: 1B, 2A, 3E

Notes