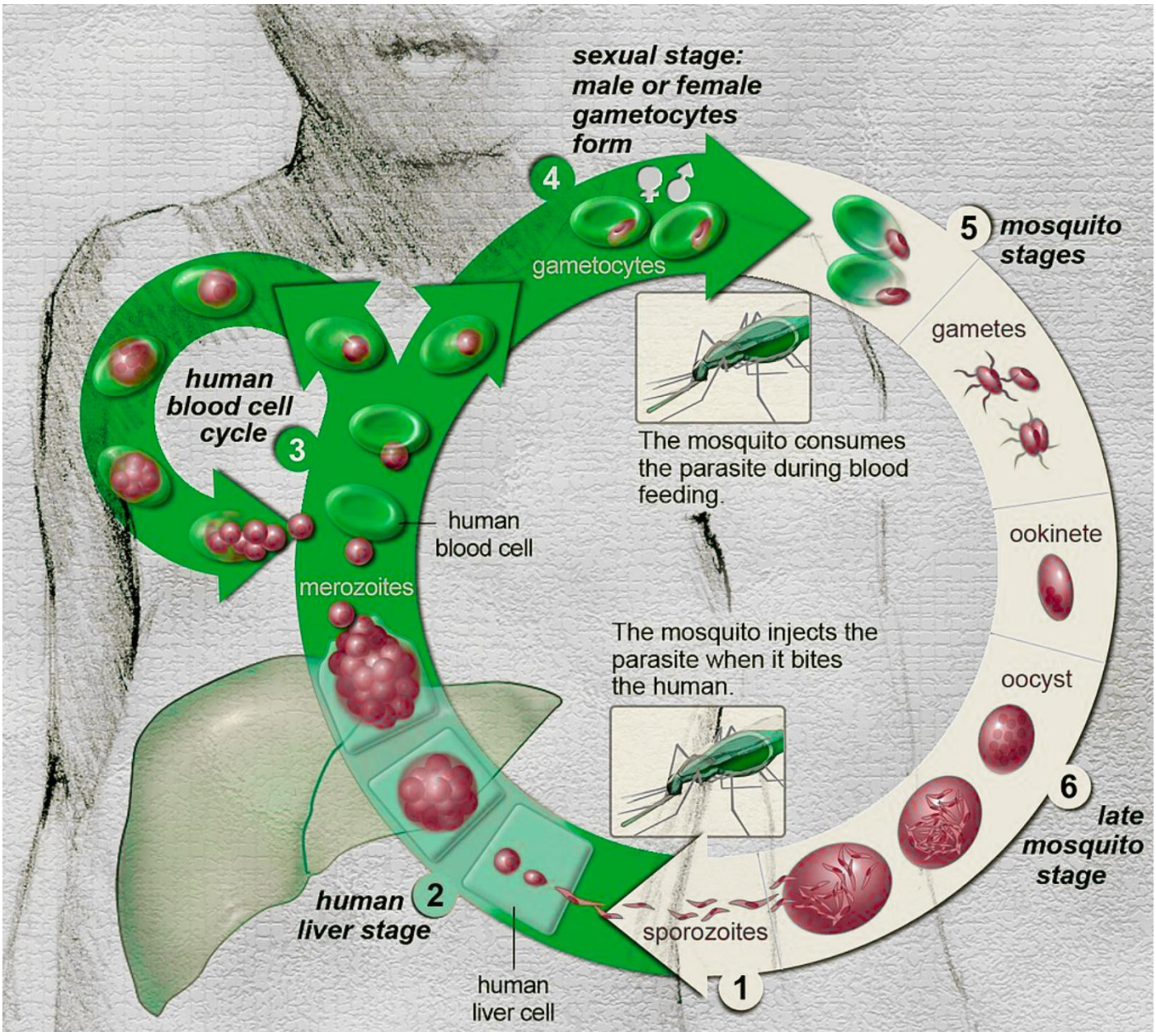
Antimalarials

Etiology (Causes) of Malaria

- Malaria is caused by **Plasmodium** parasites, transmitted by female **Anopheles mosquitoes**.
- The main species causing malaria in humans are:
    1. **Plasmodium falciparum**: Most severe, can cause cerebral malaria.
    2. **Plasmodium vivax**: Causes relapses due to liver hypnozoites.
    3. **Plasmodium ovale**: Similar to P. vivax, but less common.
    4. **Plasmodium malariae**: Can cause chronic infection.
    5. **Plasmodium knowlesi**: Zoonotic malaria, found in Southeast Asia.

Transmission & Life Cycle



1. Mosquito Stage

- The mosquito injects **sporozoites** into the human bloodstream during a bite.

2. Liver Stage (Pre-Erythrocytic Stage)

- Sporozoites invade liver cells, multiply, and form **merozoites**.

3. Blood Stage (Erythrocytic Cycle)

- Merozoites infect red blood cells (RBCs), multiply, rupture RBCs, and cause fever.

4. Gametocyte Formation

- Some parasites develop into **gametocytes**, which are taken up by a mosquito.

5. Mosquito Cycle

- Gametocytes mature into **sporozoites**, completing the cycle.

Symptoms of Malaria

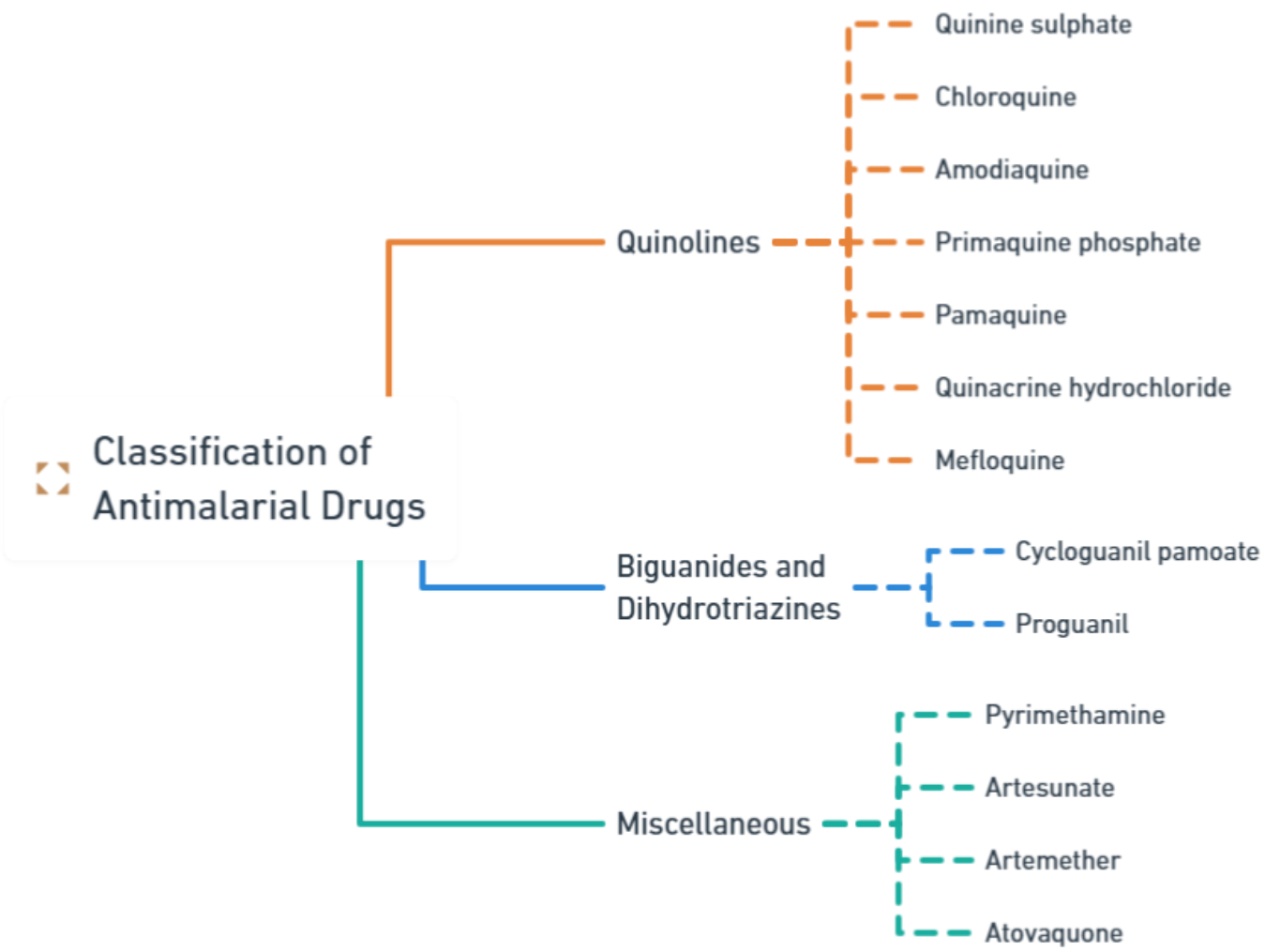
- High fever, chills, sweating (classic **tertian or quartan fever cycles**)
- Headache, muscle pain, fatigue
- Severe malaria (P. falciparum) → Organ failure, coma, death

Prevention & Treatment

- **Prevention:** Mosquito control (nets, repellents), prophylactic drugs (chloroquine, doxycycline).
- **Treatment:** Antimalarial drugs (artemisinin-based combination therapies, chloroquine, mefloquine).

Classification of Antimalarial Drugs

- Antimalarial drugs are classified based on their chemical structure and mechanism of action. The main classes include:



1. Quinolines

- These are synthetic or natural compounds that interfere with the parasite's ability to digest hemoglobin.
- **Examples:** Quinine sulphate, Chloroquine, Amodiaquine, Primaquine phosphate, Pamaquine, Quinacrine hydrochloride, Mefloquine.

Structural Feature	SAR Insight
Quinoline nucleus (1- or 4-substituted)	Essential for antimalarial activity. Most active compounds are 4- or 8-aminoquinolines.
Position 4 (4-amino group)	Common in **chloroquine** and **amodiaquine**; important for **blood schizonticidal** activity.
Position 8 (8-amino group)	Seen in **primaquine**, **pamaquine**; responsible for **tissue schizonticidal** and **gametocidal** action.
Side chain on amino group	Chain length (typically 3 C atoms) is critical. Bulky or very long chains reduce activity.

Position 6 (methoxy or other substitutions)	Methoxy or halogen (Cl, Br) often improves lipophilicity and activity (e.g., in primaquine, amodiaquine).
Electron-donating groups on ring	Increase antimalarial activity and reduce toxicity.
Electron-withdrawing groups on ring	Often reduce activity.
Basic nitrogen in side chain	Enhances accumulation in the acidic food vacuole of the parasite. Protonation helps trap the drug.
Hydroxylation or polar groups	May reduce blood stage activity but are tolerated in tissue stage drugs (e.g., primaquine).

2. Biguanides and Dihydrotriazines

- These drugs act by inhibiting dihydrofolate reductase (DHFR), which is essential for the parasite's DNA synthesis.
- **Examples:** Cycloguanil pamoate, Proguanil.

3. Miscellaneous

- This group consists of antimalarial agents with varied mechanisms, such as inhibiting mitochondrial electron transport, disrupting heme detoxification, or acting on parasite protein synthesis.
- **Examples:** Pyrimethamine, Artesunate, Artemether, Atovaquone.

Brand Names Of Important Marketed Products And Their Side Effects.

These drugs are used for the **treatment and prevention of malaria**, caused by *Plasmodium* species.

Drug Name	Brand Name(s)	Formulation	Use
Chloroquine	**Lariago, Aralen**	Tablet, Injection	Treatment/prophylaxis (sensitive strains)
Hydroxychloroquine	**Plaquenil, HCQS**	Tablet	Malaria, rheumatoid arthritis, lupus
Artemether + Lumefantrine	**Coartem, Lumerax**	Tablet	Uncomplicated falciparum malaria
Artesunate	**Falcigo, Malinate**	Tablet, Injection	Severe/complicated malaria
Mefloquine	**Lariam, Mefliam**	Tablet	Prophylaxis and treatment
Quinine	**Quinimax, Quinidine**	Injection, Tablet	Severe malaria

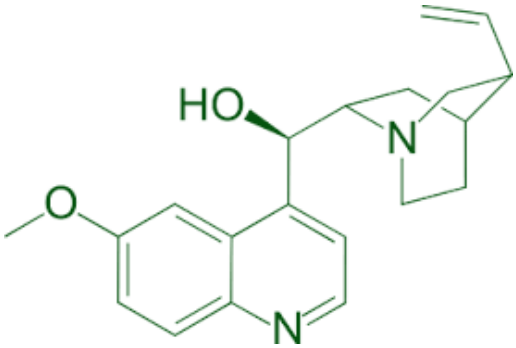
Primaquine	**Primaquine**	Tablet	Radical cure (*P. vivax*, *P. ovale*)
Atovaquone + Proguanil	**Malarone**	Tablet	Prophylaxis and treatment

Various Quinolines drugs

1. Quinine Sulfate

Chemical Structure / Formula

- **Formula:** C20H24N2O2 · H2SO4
- **Structure:** A **quinoline nucleus** with an attached quinuclidine ring.



Mechanism of Action

- Interferes with **heme polymerization** in the malaria parasite, leading to toxic heme accumulation and parasite death.
- Also **interferes with DNA synthesis** in Plasmodium spp.

Uses

- **Severe malaria** (especially against chloroquine-resistant *P. falciparum*).
- **Nocturnal leg cramps** (off-label).

Side Effects

- **Cinchonism** (tinnitus, dizziness, headache, nausea).
- **Hypoglycemia** (stimulates insulin release).
- **Hemolysis in G6PD deficiency** (Blackwater fever).
- **QT prolongation** (cardiac toxicity).

2. Chloroquine*

Chemical Structure / Formula

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