

Anti-Malarial drugs and Management of Malaria

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Learning Objectives

- Antimalarial agents: Principles of treatment
 - Classification of Anti-Malarial agents
 - Individual Antimalarial agents
 - Regimens for Chemoprophylaxis of Malaria
 - Management of uncomplicated/complicated malaria
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Case Study

5-year-old American girl presents with a 1-week history of chills, fever, and sweats. She had returned home 2 weeks earlier after leaving the US for the first time to spend 3 weeks with her grandparents in Nigeria.

Child was seen in an OPD. Examination reveals lethargic child, with temperature of 103.6°F and splenomegaly. She has no skin rash or lymphadenopathy. Initial laboratory studies are remarkable for hematocrit 29.8%, platelets 45,000/mm, creatinine 2.5 mg/dL, mildly elevated bilirubin & transaminases.

A blood smear shows ring forms of *Plasmodium falciparum* at 1.5% parasitemia. What treatment should be started?



Aim of using Anti-Malarial Drugs

1. To **prevent clinical attack** of malaria.
2. To **treat clinical attack** of malaria.
3. To completely **eradicate** the parasite from the patient's body.
4. To reduce the **human reservoir** of infection - cut down transmission to mosquito.



1. Chemical Classification

4-Aminoquinolines

- Chloroquine , Amodiaquine

8-Aminoquinolines

- Primaquine

Quinoline methanol

- Mefloquine

Alkaloids

- Quinine, Quinidine

Antifolates

- Pyrimethamine, Sulfadoxine

Antibiotics

- Tetracyclines, Doxycycline, Clindamycin

Hydroxynaphthoquinone

- Atovaquone

Quinghaosu comp.

- Artemisinin, Artemether, Artesunate

2. Clinical Classification:

A: Stage of parasite they affect

Tissue schizonticidal

Primaquine, Atovaquone, Proguanil

Blood schizonticidal

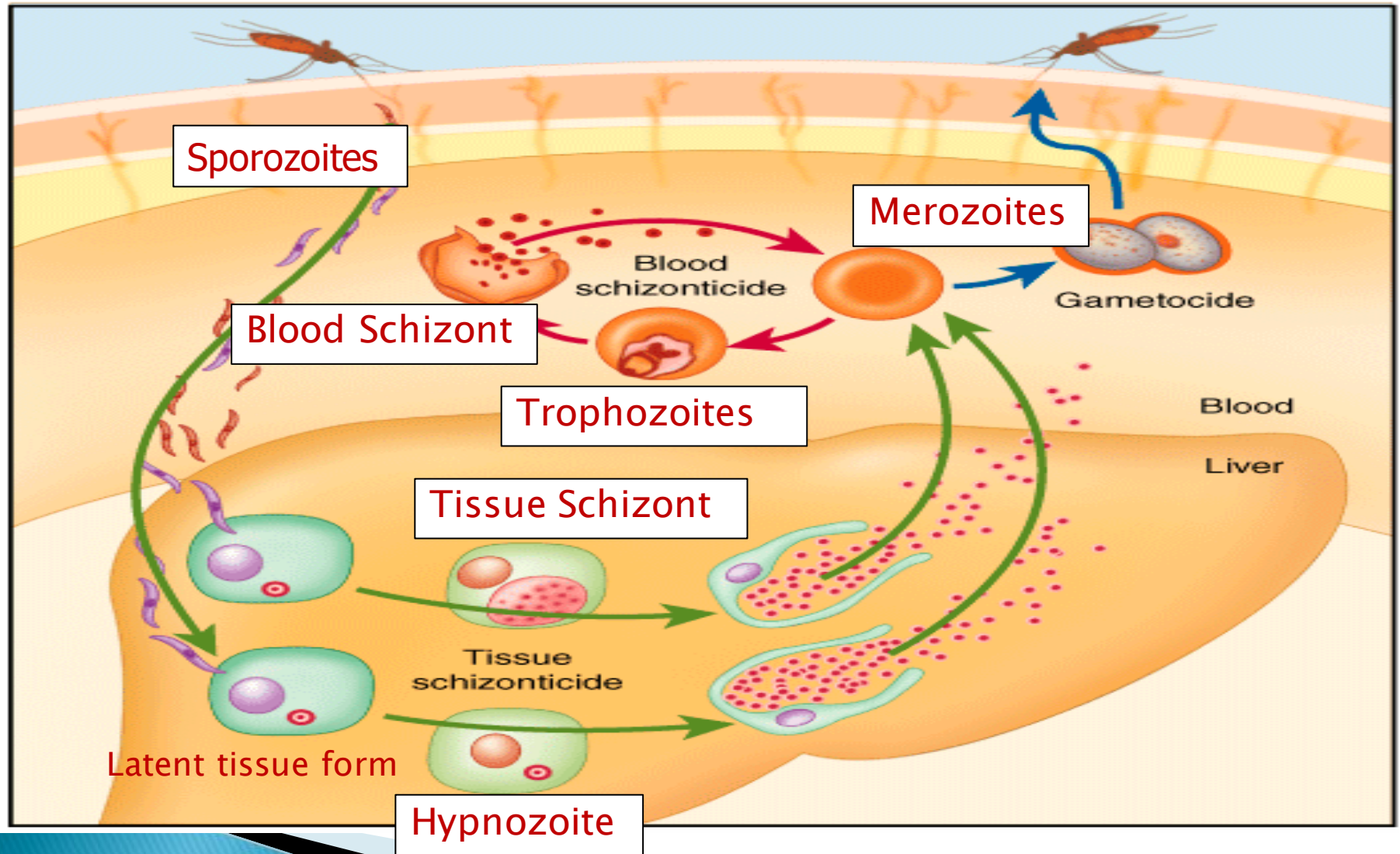
Rapidly: Chloroquine, Artemisinin, Quinine, Mefloquine

Slow: Proguanil, Doxycycline, Pyrimethamine

Gametocidal

Artemisinin, Primaquine (all), Quinine,
Chloroquine (P. vivax)

Life cycle of Malarial Parasite



2. Clinical Classification:

Clinical indication for use

Causal prophylaxis
(Pre-erythrocytic)

- Primaquine, Proguanil

Suppressive prophylaxis
(Erythrocytic)

- Chloroquine , Mefloquine, Doxycycline

Clinical Cure
(Erythrocytic)

- Chloroquine, Quinine, Mefloquine, Artemisinin, Doxycycline

Radical Cure
(Erythrocytic + Hypnozoites)

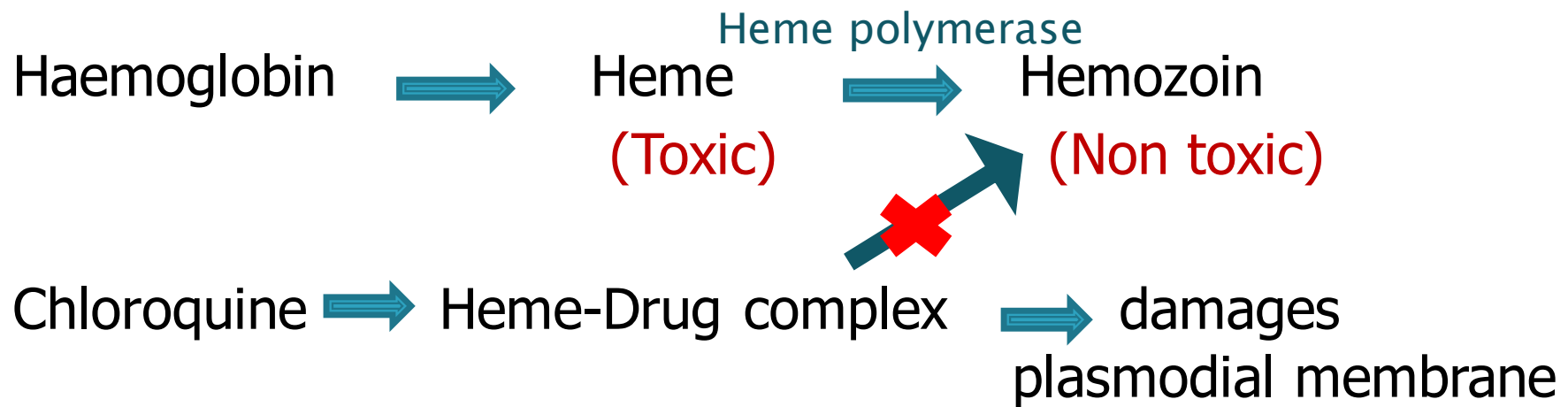
- Chloroquine + Primaquine

Gametocidal
(Gametes)

- Primaquine

Chloroquine

Mechanism of action: Plasmodium derive nutrition by digesting haemoglobin in their acidic vacuoles



▶ Antimalarial actions:

- Blood schizonticidal
- Gametocidal
- No activity against liver forms

Chloroquine

Pharmacokinetics: $t_{1/2}$ of 3-10 days

Adverse reactions

- ▶ **GI intolerance:** Nausea, vomiting, abdominal pain, headache, anorexia, malaise, and urticaria are common.
 - ▶ **Prolonged adm:** ototoxicity, retinal damage.
 - ▶ **IV administration:** hypotension, arrhythmias, seizures
 - ▶ Safe in **pregnancy** and for young **children**
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Chloroquine

Uses

Malaria

Amoebiasis

Lepra reaction

AR } Rheumatoid arthritis

Infectious mononucleosis

Autoimmune disorder – discoid lupus erythematosus

Quinine

- ▶ Obtained from Cinchona bark
 - ▶ **Antimalarial actions:**
 - Blood schizonticidal
 - Gametocidal (*P. vivax*, *P. Malariae*)
 - No activity against liver forms
 - ▶ **Other Actions**
 - **GIT:** Increases gastric acid
 - **CVS:** hypotension, cardiac depressant
 - **Skeletal muscle:** depresses skeletal muscle contraction
 - **CNS:** disturbances of hearing and vision
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Quinine

▶ Adverse effects:

- Cinchonism: tinnitus, deafness, blurred vision, N,V
- Hypoglycemia (common with IV adm)
- Hypotension, cardiac arrhythmias, A-V block
- **Black water fever:** haemolysis, haemoglobinuria, haemoglobinemia

▶ Uses

Malaria:

- Chloroquine resistant *P. falciparum* malaria
- Cerebral malaria (Vs ACT)
 - **ACT Preferred:** Faster acting, more effective better tolerated more conveniently administered

Mefloquine

▶ Antimalarial actions:

- Blood schizonticidal
- No Gametocidal activity, No activity against liver forms

▶ Pharmacokinetics:

- Orally adm., Not suitable for parenteral administration
- $t_{1/2}$: 3 weeks

▶ ADR:

- Sinus bradycardia, prolongation of QT interval
- Neuropsychiatric disorder

▶ Clinical uses: Reserve drug for Chloroquine resistant *P. falciparum* and *P. vivax* malaria. Used in comb. with artesunate

Primaquine

▶ Antimalarial actions:

- Activity against liver forms (primary and latent forms)
- Gametocidal activity

▶ ADR:

- Nausea, vomiting, epigastric distress, headache
- Haemolytic anaemia (Glucose 6 PD deficiency)
- Contraindicated in pregnancy

▶ Clinical uses:

- **P. vivax** : Radical cure : 15 mg OD, 14 day course
- **P. falciparum malaria**: single 45 mg with CQ/ACT

Artemisinin derivatives

Antimalarial actions:

- Potent and rapid blood schizonticidal action
- Kill early stage malarial gametes
- Do not kill hypnozoites



**Artemisia annua
(Qinghaosu)**

Mechanism of action:

- Cleavage of endoperoxide bridge-heme interaction: free radicals generated
- Lysis of parasite

Artemisinin derivatives

Artesunate:

- ▶ Adm oral, i.m, i.v

Artemether

- ▶ Oral, i.m. not i.v.

Arteether

- ▶ $t_{1/2}$ of 23 hours

Dihydroartemisin and Arterolane

- ▶ Oral use only

Adverse effects

- GIT
- CVS

Artemisinin based combination therapy

- ▶ **WHO recommendation:** cases of acute uncomplicated malaria : artemisinin comp+ erythrocytic schizontocide
 - ▶ Selection criteria of schizontocide : elimination $t_{1/2}$
 - ▶ **Rationale:** Short $t_{1/2}$ (artemisinin comp) + long $t_{1/2}$ erythrocytic schizontocide
 - ▶ Effective conc. maintained for 6-8 days to exhaust the parasite burden
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Artemisinin based combination therapy

Advantage over other antimalarial's

- ▶ Rapid clinical and parasitological cure
- ▶ High cure rates (>95 %) and low recrudescence rates
- ▶ Absence of parasite resistance
- ▶ Good tolerability profile

ACT Regimens for uncomplicated falciparum malaria

- ▶ **Artesunate** (100 mg BD, 3 days) – **Sulfadoxine** (1500 mg + **Pyrimethamine** (75 mg)
- ▶ **Artesunate** (100 mg BD, 3 days)-**Mefloquine** {750 mg (2nd day) , 500 mg (3rd day)}
- ▶ **Artemether** (80 mg BD) + **Lumefantrine** (480 mg BD) x 3 days
- ▶ **Artesunate** (200 mg) - **Amodiaquine** (600 mg) x 3 days

Clinical uses

Uncomplicated falciparum malaria:

- Artemisinin's as ACT
- DCGI prohibited use of oral artemisinin's as monotherapy

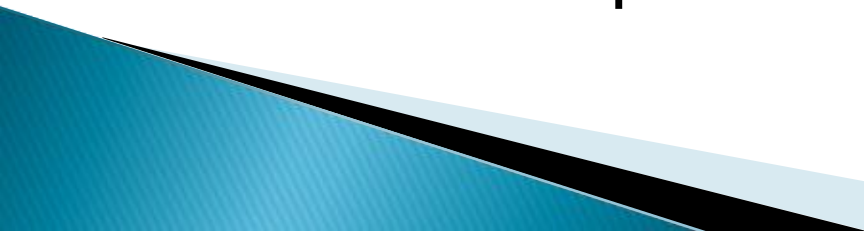
Uncomplicated vivax malaria:

- ACT if CQ/Quinine + doxycycline /clindamycin resistant
- Single dose Primaquine to kill circulating gametes

Severe and Complicated falciparum malaria

- Parenteral Arterminsins (IV/IM) DOC
 - Quinine (I.V.) DOC 1st trimester of pregnancy
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Advantages of Artesunate (I.V.)

- ▶ Faster parasite clearance than IV Quinine
 - ▶ Safer and better tolerated than IV Quinine
 - ▶ Its dose schedule is simpler
 - ▶ Higher efficacy and lower mortality
 - ▶ Risk of hypoglycaemia is lower
 - ▶ Does not require cardiac monitoring
 - ▶ Does not require rate controlled infusion
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Regimens for Chemoprophylaxis of Malaria

Primary Prophylaxis (Chloroquine sensitive)

- **Chloroquine** 500 mg (300 mg base) once weekly during stay x 4 weeks

Primary Prophylaxis (Chloroquine resistant *P. falciparum*)

- **Mefloquine** 250 mg salt (228 mg base) once weekly x 4 weeks
- **Doxycycline** 100 mg OD + stay x 4 weeks after
- **Atovaquone** (250 mg) + **Proguanil** (100 mg) + stay x 4 weeks after

Terminal prophylaxis

- **Primaquine** (15 mg) daily x 2 weeks

Treatment of Uncomplicated Malaria (Chloroquine sensitive)

P. vivax, *P. ovale*,
P. malariae

Chloroquine

- **Day 1:** 600 mg base foll. 300 mg 6h
- **Day2:** 300 mg base
- **Day 3:** 300 mg base: **Total dose:** 1500mg +

Primaquine

Day 4-14: 15 mg base orally

P. falciparum

Chloroquine (As above) +

Primaquine 45 mg single dose

Treatment of Uncomplicated Malaria

Chloroquine resistant *P. falciparum*

ACT

- **Artesunate** (100 mg) BD x 3 days+ **Sulphadoxine** (1500 mg)+ **Pyrimethamine** (75 mg) single dose day
- **Artesunate** (100 mg) BD x 3 days+ **Mefloquine** (750 mg, 2nd day)+ **Mefloquine** (500 mg, 3rd day)
- **Artemether** (80 mg) + **Lumefantrine** (480 mg) BD x 3 days

Alternative

- **Quinine** (600 mg) TDS x 7 days + **Doxycycline** (100 mg) BD x 7 days / Clindamycin 600 mg BD x 7 days

Treatment of Severe/Complicated Malaria

Cerebral malaria

ACT

- **Artesunate** (2.4 mg/kg iv, im) repeat at 12 and 24 h then once daily for 7 days + 3 day oral ACT
- **Artemether** (3.2 mg/kg im, 1st day) + 1.6 mg/kg for 7 days.
- **Arteether** (150 mg im for 3 days) + + 1.6 mg/kg for 4 days.

Alternative

- **Quinine dihydrochloride** (20 mg/kg) IV dil in 500 ml of 5 % dextrose over 3-4 hr 10 mg/kg repeat 4-8 hr +
Quinine sulphate (640 mg) TDS 7 days + **Doxycycline** (100 mg) OD x 7 days

Summary

- **Principles of Treatment:** clinical attack, eradicate, transmission
- **Classification of Anti-Malarial agents:** chemical, clinical use
- Individual Antimalarial agents
- **Regimens for Chemoprophylaxis of Malaria:**
 - **Primary** (CQ/MQ)
 - **Terminal** (Primaquine)
- **Management of Malaria**
 - **Uncomplicated** (CQ+ Primaquine / Quinine+ Doxy /ACT)
 - **Complicated Malaria** (Parenteral Artemisinin/Quinine)

Case Study

5-year-old American girl presents with a 1-week history of chills, fever, and sweats. She had returned home 2 weeks earlier after leaving the US for the first time to spend 3 weeks with her grandparents in Nigeria.

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