

Antimalarial Drugs

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Malaria

- Annual Global Incidence:
- 219 million in 2010.



- Annually, in Africa, 1 million children die.
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Antimalarial Drugs

- Suppressive Treatment (المعالجة القمعية) = Clinical Cure: Chloroquin, Quinine, Quinidine , Doxycycline, Clindamycin, Mefloquine, and Halofantrine.
- Radical Cure (المعالجة الجذرية): Chloroquin followed by Primaquine, required for *P vivax* and *P ovale*.
- Prophylaxis: Chloroquin, Mefloquin, "Malarone" and Doxycycline

Malarial Parasites

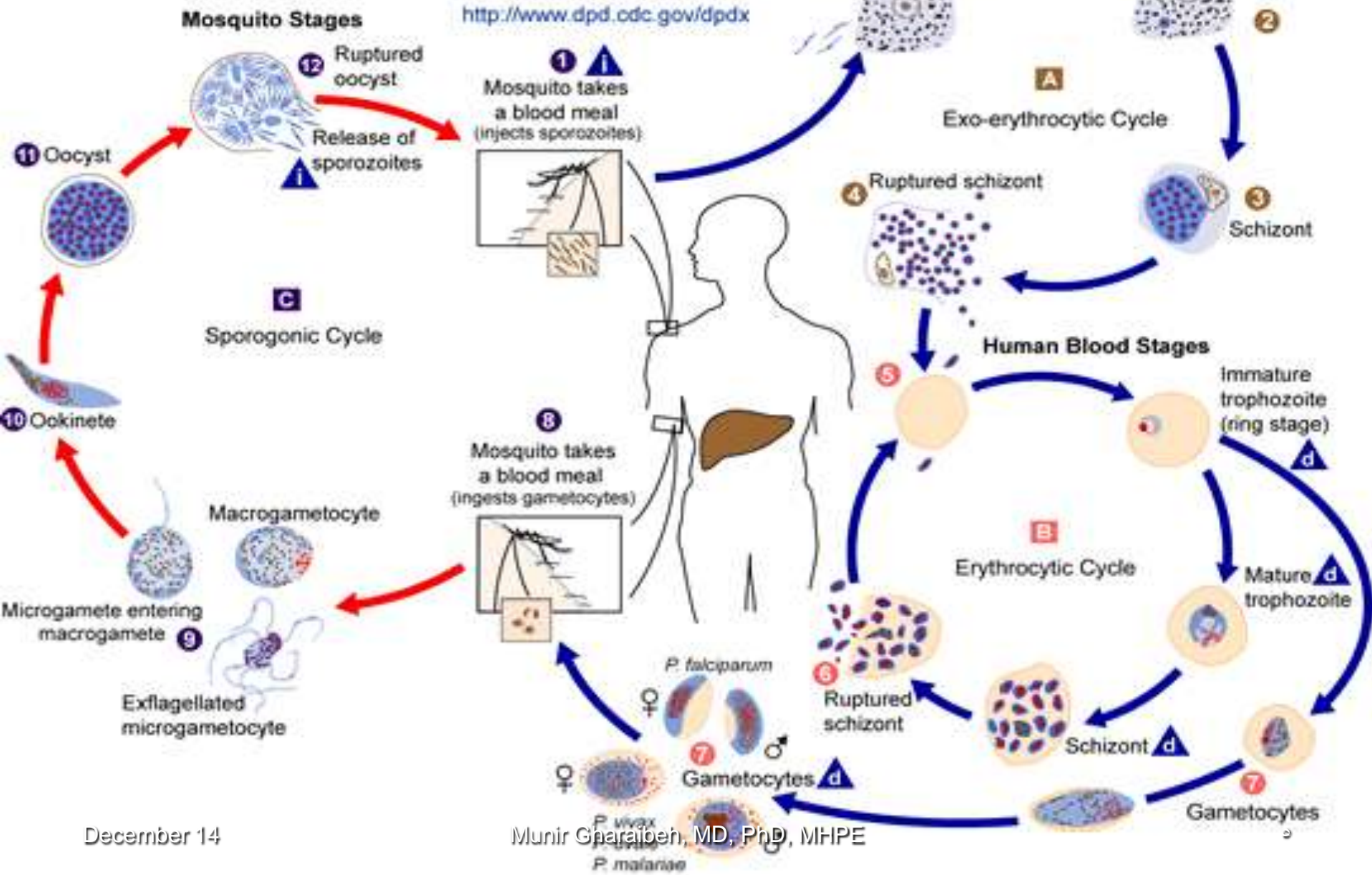
- *Plasmodium falciparum*
(erythrocytic, serious, resistance).
- *Plasmodium vivax*
- *Plasmodium malariae* (erythrocytic)
- *Plasmodium ovale*

i = Infective Stage
d = Diagnostic Stage



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<http://www.dpd.cdc.gov/dpdx>



Chloroquine

Synthetic 4-Aminoquinolone

Specific uptake mechanism is present in the parasite, the drug accumulates in the parasite food vacuoles to inhibit polymerization of heme into hemozoin and thus parasite is poisoned by heme.

Well absorbed, distributed, bound to tissues (VDL 100-1000L/Kg, Liver 500x).

Chloroquine

Destroys the blood stages of all four types of malaria.

Drug of choice in the treatment of nonfalciparum and sensitive falciparum malaria.

Does not eliminate dormant liver forms of *P. vivax* and *P. ovale*, so, Primaquine must be added for their radical cure.

Chloroquine

Resistance:

Very common with *P. falciparum* and increasing with *P. vivax*.

Mutation in P170 glycoprotein (PfCRT) works as a drug-transporting pump mechanism .

Chloroquine

- Very practical, convenient, rapid action, low cost, and safe.
- Stat.
- After 6 hours
- After 24 hours
- After 48 hours
-

However, does not eliminate dormant liver forms of *P.vivax* and *P.ovale*.

Chloroquine

Also effective in:

Rheumatoid arthritis.

LE.

Amebic liver abscess.

Photoallergic reactions.

Clonorchis sinensis.

Metacercariae in flesh or skin of fresh water fish are ingested by human host.



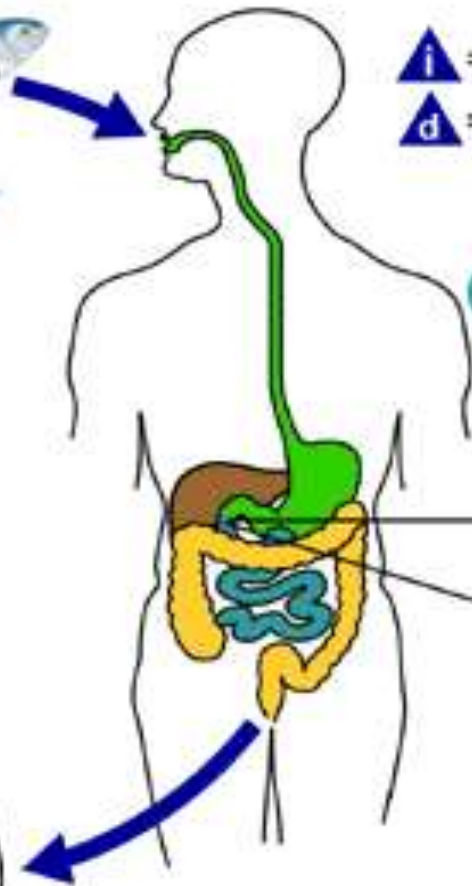
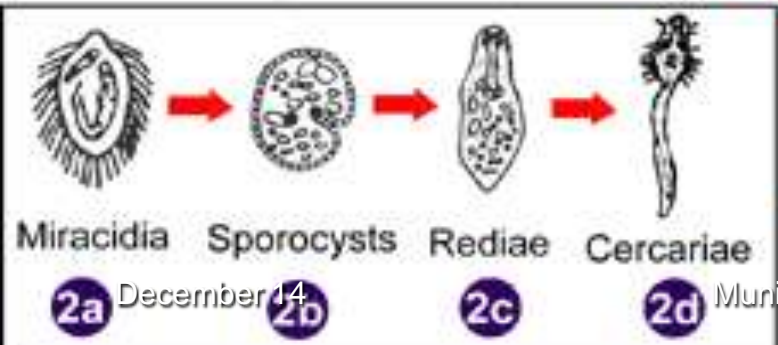
Free-swimming cercariae encyst in the skin or flesh of fresh water fish.



i = Infective Stage
d = Diagnostic Stage

Eggs are ingested by the snail.

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5 Excyst in duodenum



6 Adults in biliary duct



4



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Embryonated eggs passed in feces.



Chloroquine

Side Effects:

Headache, dizziness,

Itching and rash,

Nausea, vomiting, anorexia

Unmasking of LE, psoriasis and porphyria.

Corneal deposits, blindness, blurring of vision,

Hydroxychloroquin

Amodiaquin

Quinine⁽¹⁸²⁰⁾ and Quinidine

Cinchona tree.



General protoplasmic poison: will affect the feeding mechanism of the parasite.

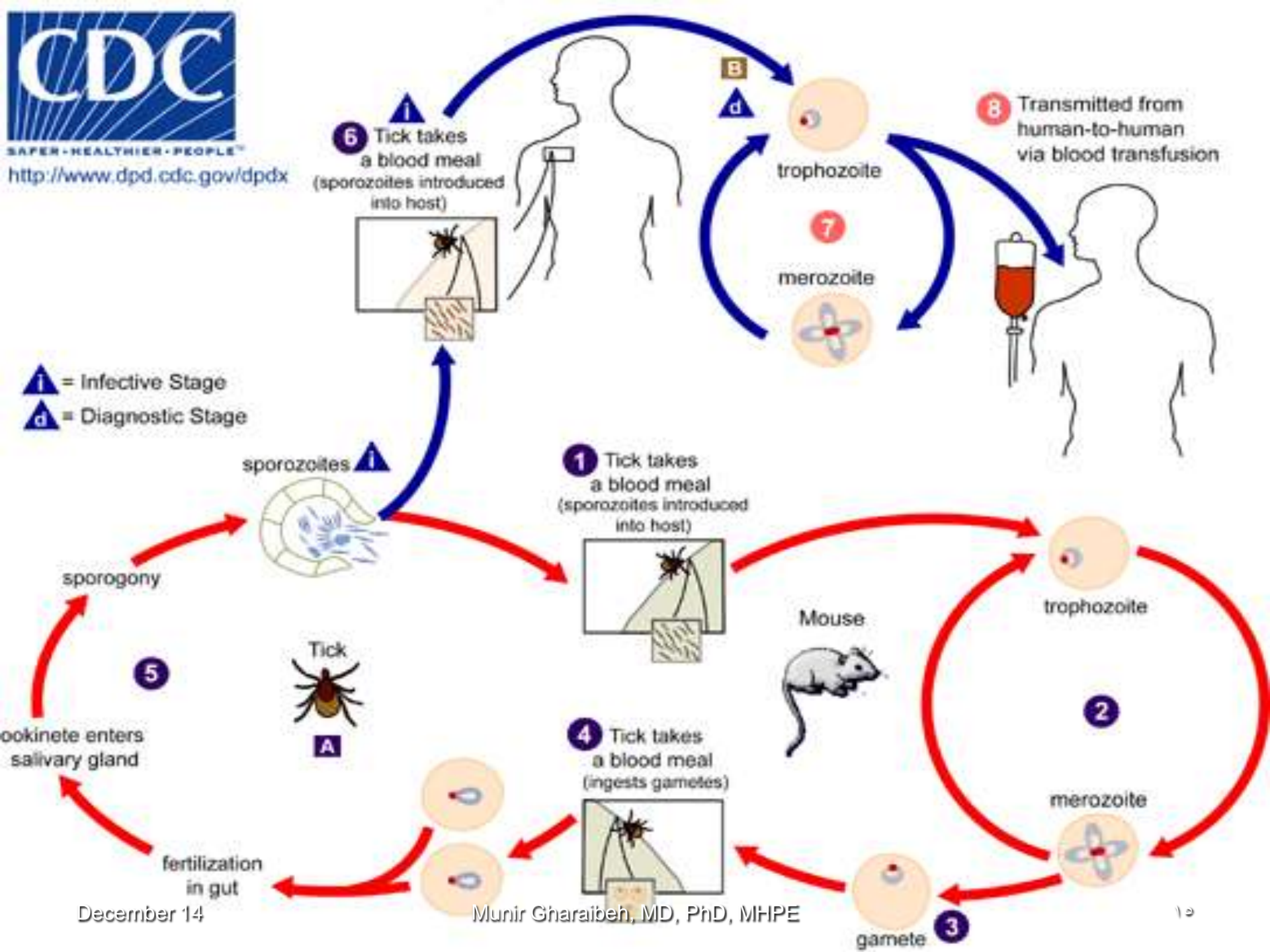
Resistance is uncommon.

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

- Also effective for *Babesia microti* infection.
- Also, for nocturnal leg muscle cramps (Arthritis, DM, thrombophlebitis, arteriosclerosis, varicose veins)

i = Infective Stage
d = Diagnostic Stage



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, hemoglobinuria, and renal failure)

Mefloquine

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

Also for suppressive and prophylactic treatment (weekly doses).

- Nausea, vomiting, diarrhea, pain.
- Vertigo, dizziness, headache, rashes and visual alterations.
- Psychosis, hallucinations, confusion, anxiety, depression.

Primaquin

- 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.

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. jirovecii*.

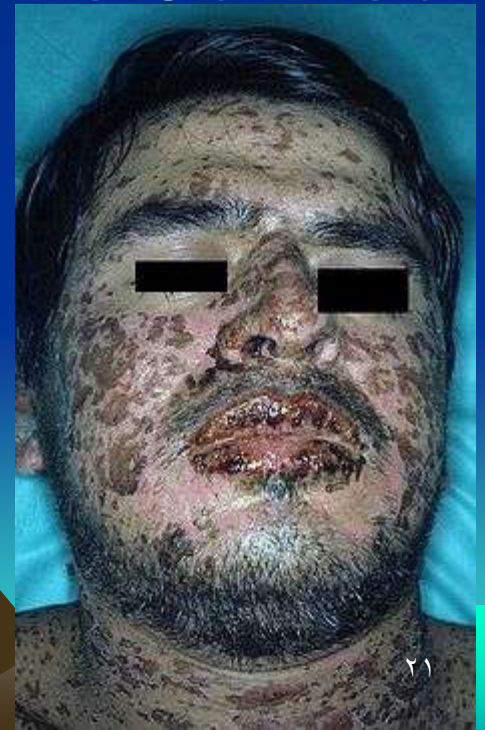
Pyrimethamine

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)

Artemisinin= Qinghaosu



- **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.**
- **High cost, unavailable.**
- **N.V.D. and neurotoxicity in animals.**