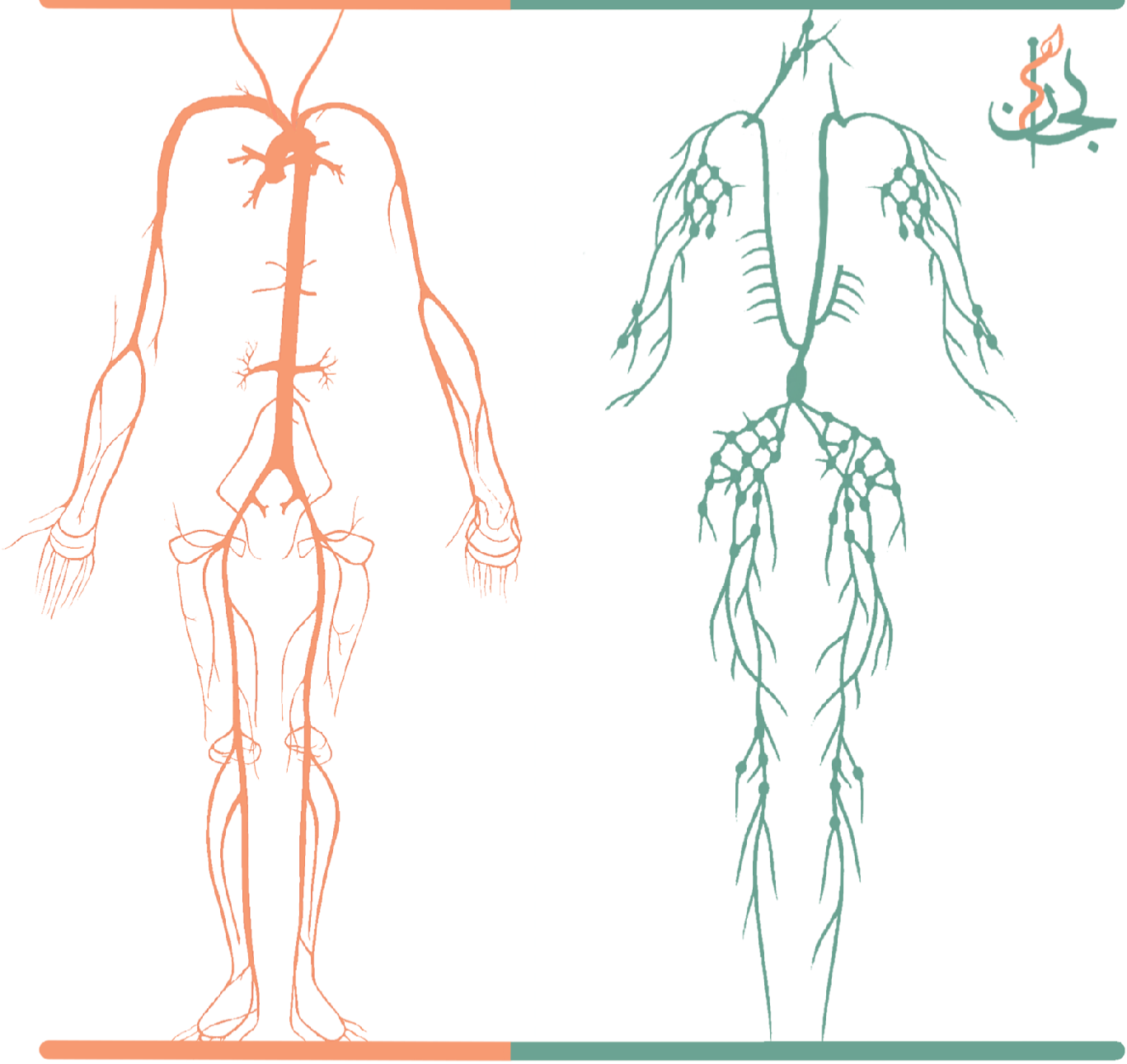
Pharmacology

HematoLymphatic



Title: Sheet 5 –Antimalarial Drugs

Writer: 018 - Updated by 019

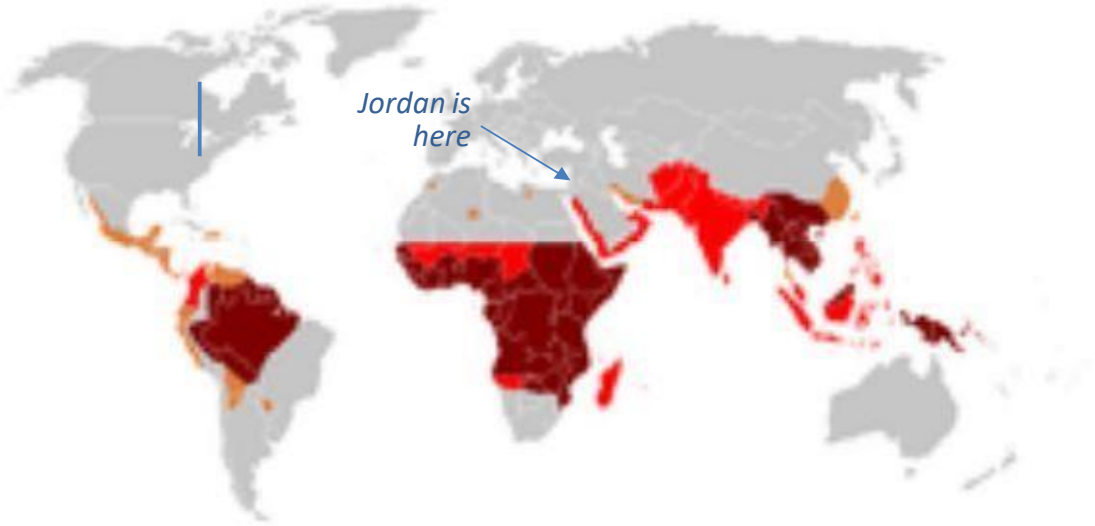
Scientific Correction: Yazeed hanbali

Final Correction: Anas mahseeri

Doctor: Munir Gharabiah

MALARIA

Malaria is a serious and sometimes fatal disease, in 2019, there were an estimated 229 million cases of malaria (296 million in 2015) which resulted in an estimated 409,000 deaths all over the world. (The countries in red are endemic for malaria).
-Children under 5 years old are the most affected, accounting for 67% of malaria deaths.



Antimalarial Treatment: (you don't have to memorize them now as we will talk about each one in details)

1- Suppressive Treatment المعالجة القمعية (Clinical Cure/ Apparent cure: Chloroquine, Quinine, Quinidine, Doxycycline, Clindamycin, Mefloquine, andHalofantrine.

2- Radical Cure المعالجة الجذرية :Chloroquine followed by Primaquine, required for P.vivax and P.Ovale. (remember that they form hypnozoites which are associated with latency)

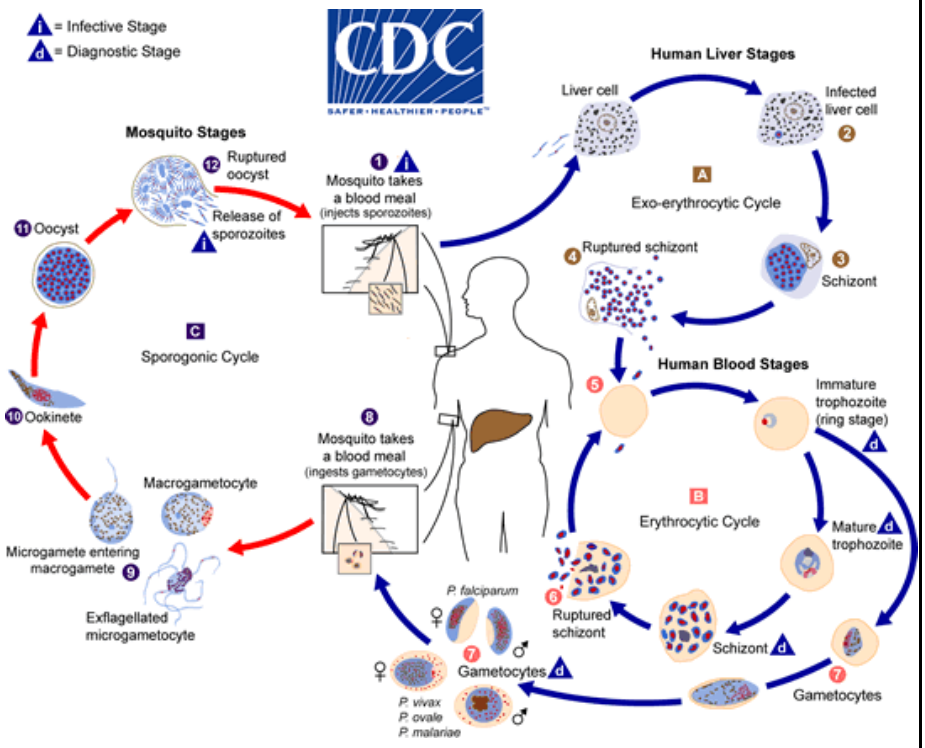
3- Prophylaxis (for people going for endemic areas): Chloroquine, Mefloquine," Malarone", and Doxycycline.

Malaria species:

- **Plasmodium falciparum** (The most serious one as it **doesn't** have an Exo-erythrocytic cycle , **only erythrocytic cycle** which might lead to death and usually P.falciparum exhibit drug-resistance to many of the drugs used in the treatment of malaria)
- **Plasmodium vivax.**
- **Plasmodium malariae.**
- **Plasmodium ovale.**

Both cycles (erythrocytic and exoerythrocytic)

As you see in the figure :
The life cycle of malaria starts with a mosquito bite and transmit the **Sporozoites** to human.
It will go through the circulation reaching the liver and develop to **Schizont** that will rupture and release its content to the blood and becoming **Trophozoites.**
Most Trophozoites will begin a cycle
(Trophozoites ->Schizoint -> rupture of the schizoint relesing more trophozoites)



Some Trophozoites will further develop to **Gametocytes** (infective stage of malaria that infect the mosqutio, inside the mosquito body the gametocytes will be converted to sporozoites, which can reinfect the human)

Drugs used in malaria :

- **Chloroquine** (Well absorbed, distributed, bound to tissues)

a) Synthetic 4-Aminoquinolone

b) **Mechanism of action** (MOA):Has a specific uptake mechanism is present in the parasite, the drug accumulates in the parasite to inhibit polymerization of heme into**hemozoin** and thus parasite is poisoned by heme.

*Well absorbed, distributed, bound to tissues

c) **Schizonticide** for all four types of malaria, drug of choice in the treatment of non- falciparum and sensitive falciparum malaria. (Because there are drug-resistant P.falciparum)

d) Does **not** eliminate dormant liver forms of P. vivax and P. ovale, so, **Primaquine** mustbe added for their radical cure.(so we conclude that Chloroquine causes suppressive treatment of the erythrocytic cycle of the parasite)

e) **Resistance:** Very common with P. falciparum and increasing with P.vivax ; Due to mutation in **P170 glycoprotein** (PfCRT) works as a drug-transporting pump mechanism) pumps thedrug out of the parasite).

f) Very practical, convenient(oral), rapid action, low cost, and safe . Started **immediately** after diagnosis (we diagnose through the blood smear).

g) Other subsequent doses of chloroquine are given after 6 hours,24 hours and last dose after 48 hours. (4 doses)

However, Chloroquine does not eliminate dormant liver forms of P.vivax and Provable(so we use primaquine)

h) Chloroquine also effective in:

Rheumatoid arthritis/Lupus Erythematosus(LE)/ Amebic liver abscess/ Photoallergic reactions/Clonorchis sinensis(another protozoal agent)*the professor skipped the life cycle*

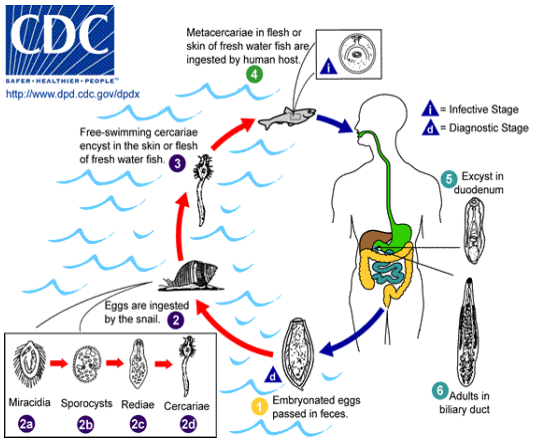
Side Effects:(safe drug in general, side effects not lethal)

Headache, dizziness, Itching and rash.

Nausea, vomiting, anorexia.

Unmasking of LE, psoriasis and porphyria.

Corneal deposits, blindness, blurring of vision.



Time=10:18

Quinine (1820) and Quinidine:

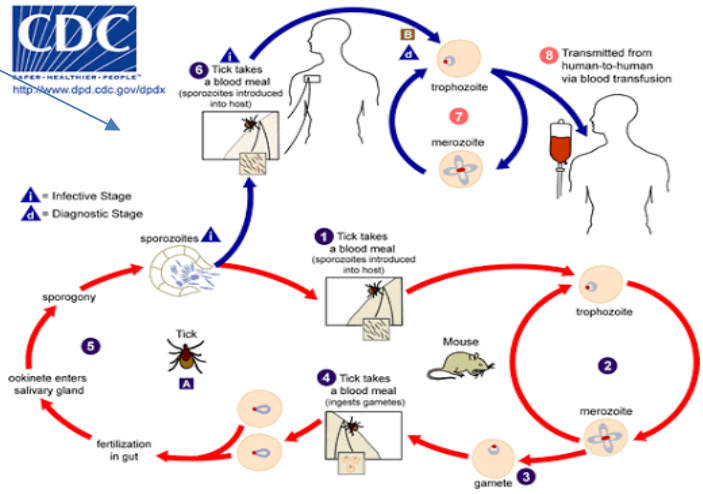
a) Discovered in the **Cinchona tree** from south America(شجرة الصفاف)

b) **MOA**: General protoplasmic poison(will affect the feeding mechanism of the parasite).

c) Although it's an old drug , resistance is **uncommon**.

d) Effective rapid schizonticide therapy for severe falciparum, **chloroquine-resistant** malaria, usually in combination with another drug (e.g. Doxycycline or Clindamycin) to **shorten** duration of use(if we depend only on quinine , we need a longer period of treatment and this might expose the patient for more severe side effects).

e) Also effective for **Babesia microti** infection(another protozoal disease transmitted by the mouse as well as the tick) and for nocturnal leg muscle cramps which might be due to disease like: Arthritis, DM, thrombophlebitis, arteriosclerosis, varicose veins.



Adverse Effects:

1- Cinchonism(caused by ingesting plenty of the cinchona tree leaves and the drug quinine) which is characterized **primarily** by :Tinnitus, headache, nausea, dizziness, flushing, visual disturbances. **Later**, auditory abnormalities, vomiting, diarrhea, and abdominal pain.

2- Blood dyscrasias (dyscrasia : the presence of abnormal material in the blood)

3- Hypersensitivity, hypoglycemia, uterine contractions(may lead to abortion).

4- Hypotension, QT prolongation(important parameter to test the side effects of drugs)

****QT prolongation** means the heart muscle takes longer than normal to recharge between beats which can be seen on the ECG**

5- Blackwater fever (hemolysis, hemoglobinemia, hemoglobinuria, and renal failure) which causes dark red urine

Mefloquine :

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

b) Also for suppressive and prophylactic treatment (weekly doses).

Side Effects: (mainly CNS effects)

Nausea, vomiting, diarrhea, pain. *general*

Vertigo, dizziness, headache, rashes, visual alterations

psychosis, hallucinations,confusion, anxiety, depression. *CNS*

Primaquine:

a) 8-aminoquinolone

b) MOA: Unknown mechanism.

c) Drug of choice; the **only** available one, for eradication of **exoerythrocytic** forms of malaria after treatment with chloroquine.

Side Effects:

Causes hemolysis **only** in G6PD deficient patients.

Also, nausea, distress, headache, pruritis, leukopenia and agranulocytosis.

Time=20:39

Atovaquone and Proguanil

a) Usually both drugs are in fixed combination called “Malarone”.

b) Recommended drug for prophylaxis(for the people going to endemic areas)

c) Atovaquone also approved for **P. gynoecia** pneumonia, although has lower efficacy than Trimethoprim-sulfamethoxazole combination.

Side Effects:

Can cause fever, rash, nausea, vomiting, diarrhea, headache, and insomnia.

Pyrimethamine: (related to Trimethoprim)

a) MOA: Inhibits DHF Reductase

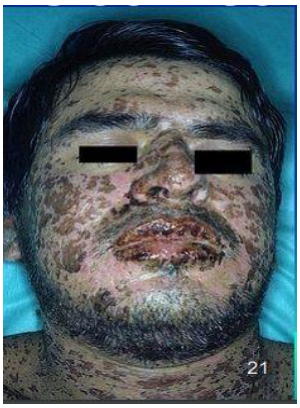
b) Slow and long acting drug, **Not** for severe malaria.

c) Effective on erythrocytic forms of all species.

d) Preferential binding to parasitic enzyme.

e) Usually combined with Sulfadoxine ” **Fansidar**” or Sulfones which inhibit Dihydropteroate synthase.

f) Although it's **no longer** recommended for prophylaxis (for malaria) it's **still** used for Toxoplasmosis (in higher doses) and P. jeroveci



Adverse Effects:

Anorexia, Vomiting, Leucopenia, Thrombocytopenia, glossitis.
CNS: Stimulation, Convulsions
Allergic reactions including Stevens-Johnson Syndrome (severe exfoliation of the skin and the patient might die if there's dehydration or infection)

Antibiotics:

a) Include: Tetracycline, Doxycycline, Clindamycin, Azithromycin , Fluoroquinolones (like **ciprofloxacin)**
b) Active against **erythrocytic** forms of all species. Usually for chloroquine-resistant strains, also effective against **other** protozoal diseases

Halofantrine and Lumefantrine:

a) Rapidly effective against erythrocytic forms of all species, usually for chloroquine-resistant strains.
b) Well tolerated, except for cardiac toxicity (QT prolongation)

Remember that
Quinine and Quinidine also cause QT prolongation

Artemisnin (Qinghaosu)

a) Include : **Artesunate and Artemether.**
b) Derivatives of Artemisia(الشيح)used by Chinese since 2000 years.
c) Rapidly acting schizonticides against all species.
d) No documented resistance.
e) MOA: Work by free radical formation or ATP inhibition.
f) Only drugs reliably effective against quinine resistant and multi-drug resistant strains(because new strains of malaria might also develop resistance to Quinine).
j) High cost, unavailable.
h) Causes N,V,D, and neurotoxicity in animals.