Pharmacology – HLS

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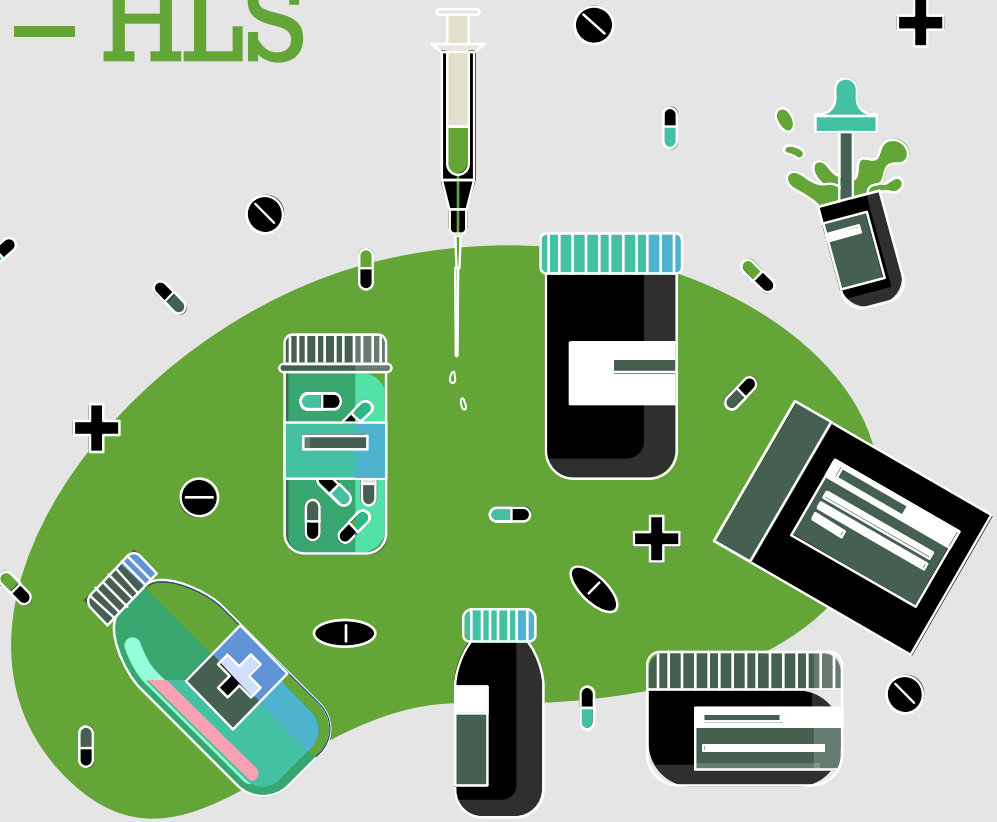

النادي الطلابي
كلية الطب

Antimalarial Drugs

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Malaria

- Malaria is a very important disease, and it causes a lot of mortality.
- 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 figure shows the distribution of malaria, and it is a disease present in Africa, south America as well as south-east Asia, India.
- Fortunately, it is not endemic in Jordan, but we have recorded cases, especially people coming from or going to these countries, so we will have to deal with and treat these patients, or to give them pro

Antimalarial Treatment

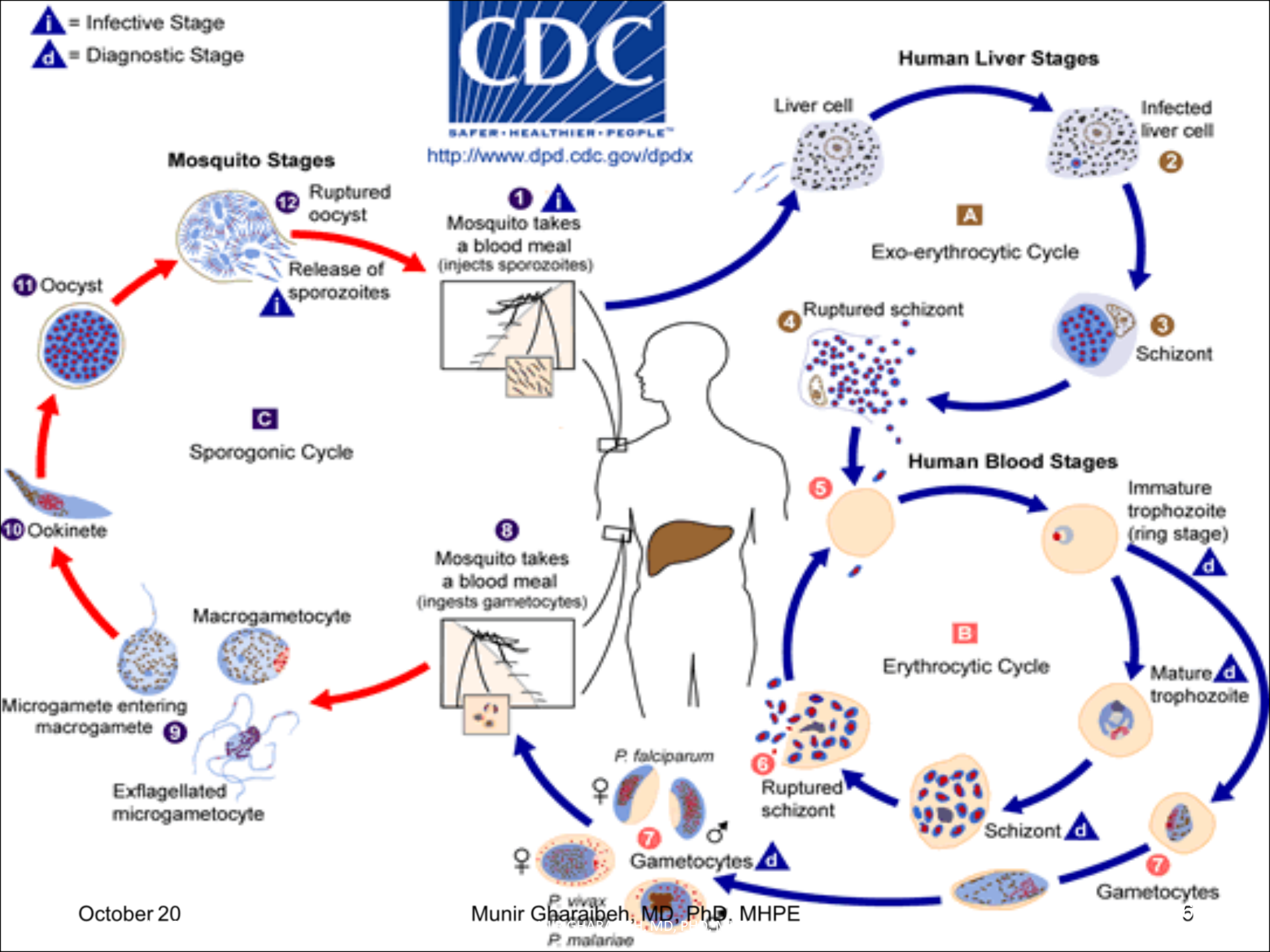
- There are three types of antimalarial treatments:
- **SuppressiveTreatment المعالجة القمعية=Clinical Cure:**
  Chloroquin, Quinine, Quinidine , Doxycyline, Clindamycin, Mefloquine, and Halofantrine.

- **Radical Cure (المعالجة الجذرية)** **Chloroquin followed by Primaquine, required for P vivax and P ovale**

- **Prophylaxis** **Chloroquin, Mefloquin, "Malarone", and Doxycycline.**
- For patients going to endemic areas.

Malarial Parasites

- Malaria is caused by the plasmodium species and there are four species:
- **Plasmodium falciparum**
- **(only erythrocytic, serious, resistance).**It is the most serious one because it does not have exoerythrocytic cycles, it only has an erythrocytic cycle, this is a very serious condition and it might lead to death, and it can also usually show resistance to many of the drugs used in the treatment of malaria.
- **Plasmodium vivax.**
- **Plasmodium malariae.**
- **Plasmodium ovale.**


i = Infective Stage
d = Diagnostic Stage
CDC
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Human Liver Stages
Liver cell
Infected liver cell
2
A
Exo-erythrocytic Cycle
3
Schizont
4
Ruptured schizont
Human Blood Stages
5
Immature trophozoite (ring stage)
d
Mature trophozoite
B
Erythrocytic Cycle
6
Ruptured schizont
Schizont
d
7
Gametocytes
d
P. falciparum
P. vivax
P. malariae
Mosquito Stages
1
i
Mosquito takes a blood meal
(injects sporozoites)
12
Ruptured oocyst
Release of sporozoites
i
11
Oocyst
C
Sporogonic Cycle
10
Ookinete
8
Mosquito takes a blood meal
(ingests gametocytes)
Macrogametocyte
Microgamete entering macrogamete
9
Exflagellated microgametocyte

Explanation of the previous image

- The mosquito bites the human and takes sporozoites from already-infected people to reinfect other people.
- It goes into the circulation of the mosquito and its stomach and the infective sporozoites can then be injected into another victim and then they will circulate in the victim's circulation.
- They will then go to the liver, where they develop further into schizonts which are released into the human blood.
- In the blood they will develop into trophozoites and then the gametocytes, which is the infective stage of malaria and can infect the mosquito and then the mosquito can transfer these gametocytes in its body and convert them to sporozoites which can reinfect humans. (we restarted the cycle).

Chloroquine

- This is a very important drug, it is **very effective and specific** in the treatment of malaria.
- **Synthetic 4-Aminoquinolone**
- **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.** You can find it everywhere in the body including the circulation.

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Chloroquine

- **Schizonticide for all four types of malaria.**
- **Drug of choice in the treatment of nonfalciparum and sensitive falciparum malaria.** Here we are implying that malaria can develop drug resistance and Chloroquine is only effective if it is sensitive to it (doesn't have resistance). But it is effective in the elimination of all other types of falciparum malaria.
- **Does not eliminate dormant liver forms of P. vivax and P. ovale, so, Primaquine** (it affects the liver forms of the drug) **must be added for their radical cure.**
- Chloroquine only causes suppressive treatment of the erythrocytic cycle of the parasite, it will not affect the liver form, so we will need to add another drug which will eliminate the liver form.

Chloroquine

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 .** This pump pumps out the drug from the parasite.

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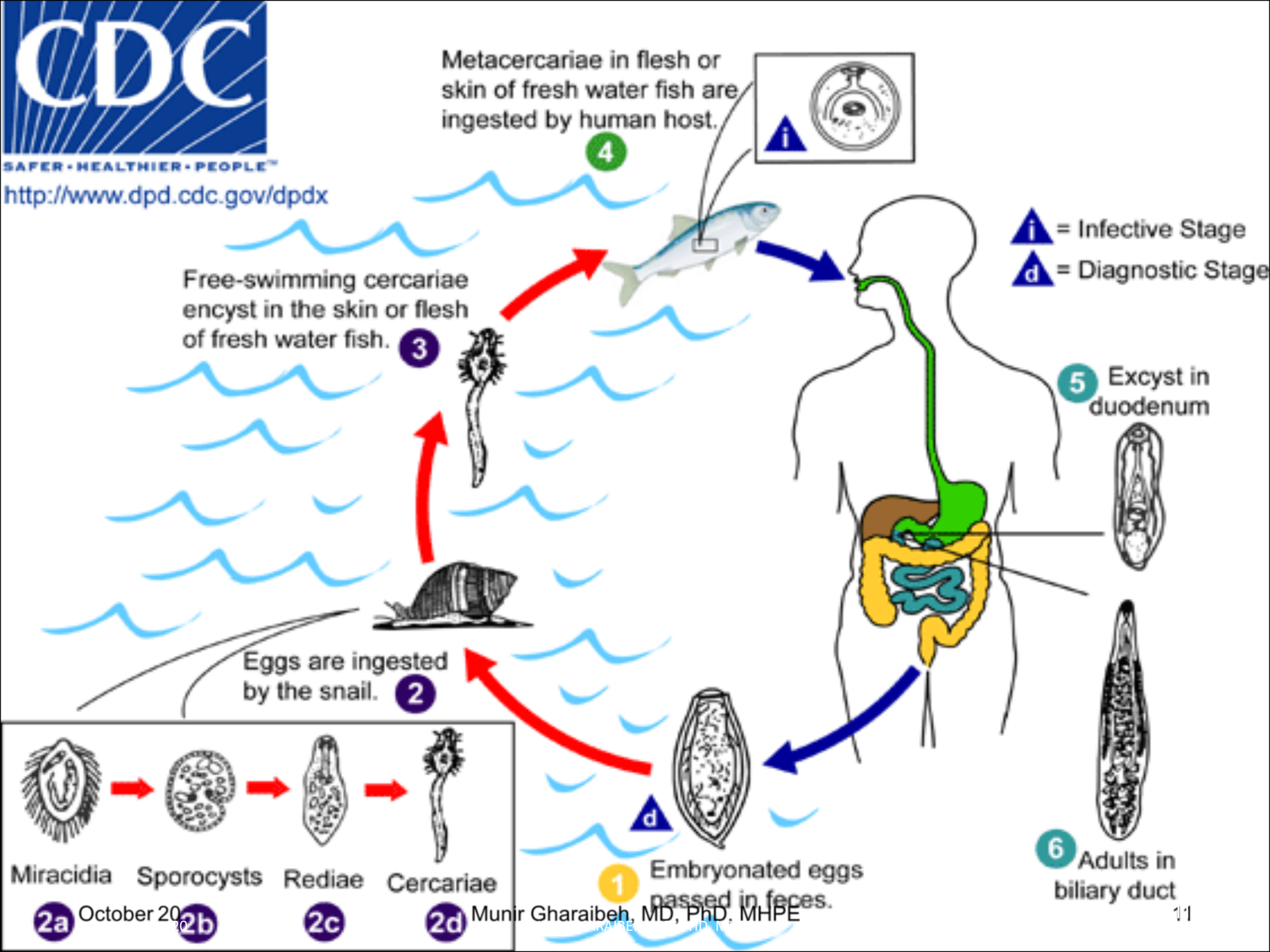
Chloroquine

- **Very practical, convenient (oral), rapid action, low cost, and safe.**
- **Started immediately after diagnosis.** Diagnosis is done after having a blood smear which can be done very easily in any health facility and especially in endemic areas, the health personnel are trained for performing blood smears and if they see the parasite, treatment with chloroquine is started immediately.
- **Other doses are given after 6 hours, 24 hours and last dose after 48 hours.** 4 doses can eliminate the erythrocytic forms of the parasite except in the falciparum resistant species.
- **However, does not eliminate dormant liver forms of P.vivax and P.ovale.**

Chloroquine

Also effective in:

- **Rheumatoid arthritis.**
- **LE.** *Lupus erythromatosus*
- **Amebic liver abscess.**
- **Photoallergic reactions.**
- ***Clonorchis sinensis*.** Another protozoal agent which can cause disease, but it is not as famous as malaria, and it is not common in Jordan, but it present nonetheless and an indication for chloroquine.


CDC
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http://www.dpd.cdc.gov/dpdx
Metacercariae in flesh or skin of fresh water fish are ingested by human host.
4
i
i = Infective Stage
d = Diagnostic Stage
Free-swimming cercariae encyst in the skin or flesh of fresh water fish.
3
5 Excyst in duodenum
Eggs are ingested by the snail.
2
d
1 Embryonated eggs passed in feces.
6 Adults in biliary duct
Miracidia
Sporocysts
Rediae
Cercariae
2a
2b
2c
2d

Chloroquine

Side Effects:

- **Headache**
- **Dizziness**
- **Itching and rash**
- **Nausea**
- **Vomiting**

- **Anorexia**
- **Unmasking of LE**
- **Psoriasis and porphyria**
- **Corneal deposits**
- **Blindness**
- **Blurring of vision**

These side affects are not very serious, or not lethal at least

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Quinine (1820) and Quinidine

The origin of quinine was known in 1820, and it was discovered from

Cinchona tree from South America. The settlers used to chew the leaves of this tree and they thought that will drop the blood pressure, and that it helped with reducing the symptoms of malaria (such as fever) and giving relief from the disease, they didn't know yet that mosquitoes were transmitting the disease of malaria

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

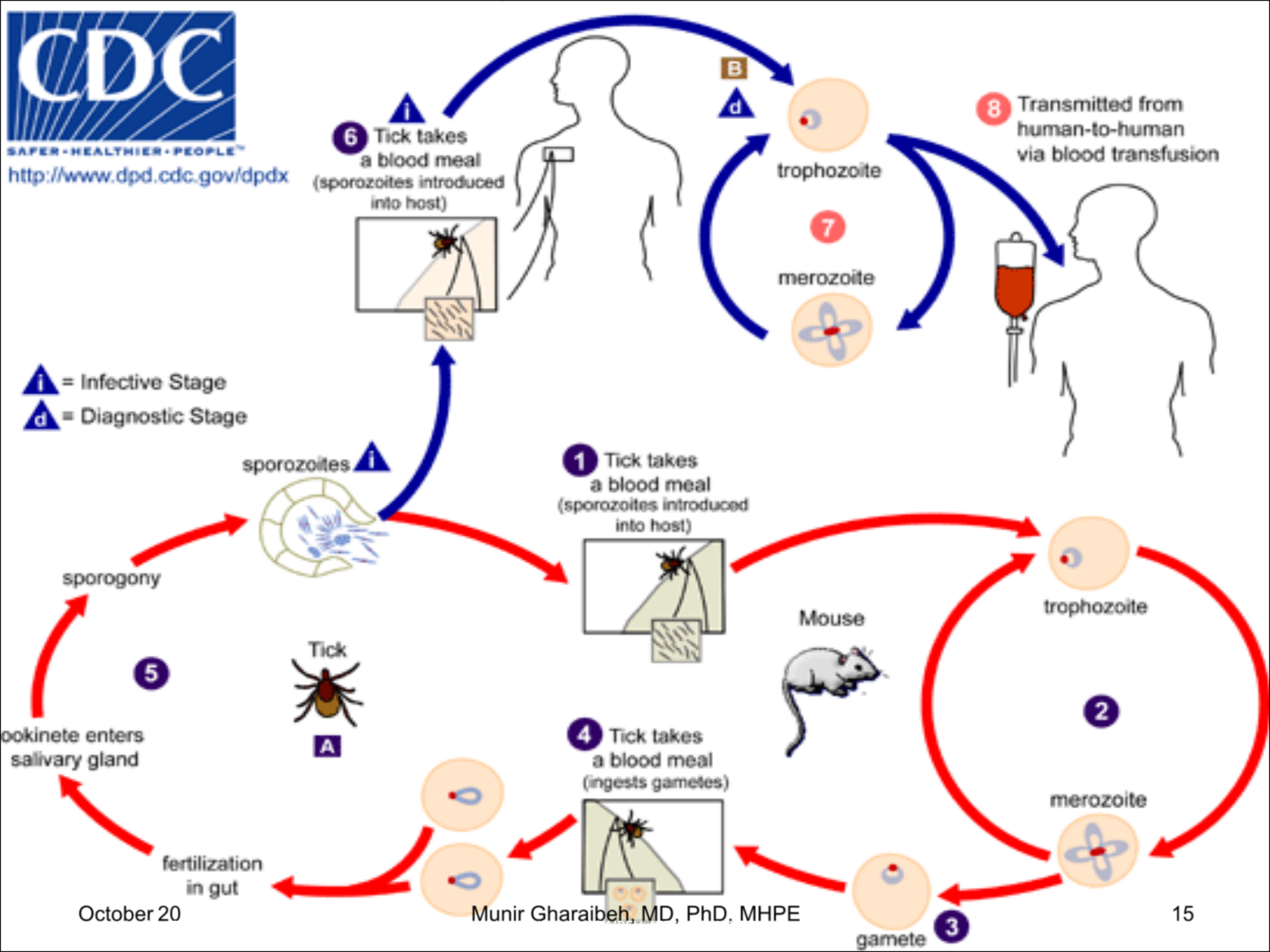
Resistance is uncommon. Even though it is an old drug, but resistance is uncommon.

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 duration of treatment and this might expose the patient to more side effects.

Quinine and Quinidine

- **Also effective for Babesia microti infection.** Another parasitic protozoal disease that is transmitted by **ticks** which takes the parasite from mice and transmits it to humans.
- **Also, for nocturnal leg muscle cramps** (troublesome benign complaint and they accompany some of these diseases) **(Arthritis, DM, thrombophlebitis, arteriosclerosis, varicose veins)**
- This condition can be treated by other drugs such as anti-epileptic drugs and drugs used for the treatment of Parkinson's disease.


CDC
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i = Infective Stage
d = Diagnostic Stage
6 Tick takes a blood meal (sporozoites introduced into host)
i
B
d
trophozoite
8 Transmitted from human-to-human via blood transfusion
7
merozoite
sporozoites
i
1 Tick takes a blood meal (sporozoites introduced into host)
sporogony
Tick
Mouse
trophozoite
5
2
ookinete enters salivary gland
A
4 Tick takes a blood meal (ingests gametes)
merozoite
fertilization in gut
gamete
3

Quinine and Quinidine

- **Adverse Effects:** it is an old and rather toxic agent

- **Cinchonism:** (results from the excessive intake)**Tinnitus, headache, nausea, dizziness, flushing, visual disturbances. Later, auditory abnormalities, vomiting, diarrhea, and abdominal pain.**
  - **Blood dyscrasias.**
  - **Hypersensitivity, hypoglycemia, uterine contractions,** can lead to abortion**.**
  - **Hypotension, QT prolongation** , it is very important parameter nowadays to measure the side effects of drugs, QT prolongation of the ECG (electrocardiogram) exposes the patient to cardiac illness.
  - **Blackwater fever (hemolysis, hemoglobinemia, hemoglobinuria and renal failure),** characterized by very dark red urine.

Mefloquine

- **Blood schizonticide, not for liver forms.**

  Used for resistant P. falciparum (single oral dose). Here resistant indicates it is resistant to chloroquine.

  Also for suppressive and prophylactic treatment (weekly doses).
- It can cause: **Nausea, vomiting, diarrhea, pain.**
- **Vertigo, dizziness, headache, rashes and visual alterations.**
- CNS effects: **Psychosis, hallucinations, confusion, anxiety, depression.**

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Primaquin

- Old drug
- **8-aminoquinolone**
- **Unknown mechanism.**
  Drug of choice; the only available one, for eradication of *exoerythrocytic* (present mainly in the liver) forms of malaria after treatment with chloroquin.

  Hemolysis in G6PD deficient patients, (most common and important effect). Also, nausea, distress, headache, pruritis, leukopenia and agranulocytosis.

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Atovaquone and Proguanil

- **Usually in fixed combination = "Malarone".**
- **Recommended drug for prophylaxis.** Indicated for people travelling to endemic areas.

- **Atovaquone also approved for *P. jiroveci* pneumonia** (the causative agents of pneumonia in HIV patients)**, although has lower efficacy than Trimethoprim-sulfamethaxazole combination.**

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

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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 (other better drugs are now indicated for prophylaxis). Also, for Toxoplasmosis (in higher doses), and P. jeroveci.

Pyrimethamine

Adverse Effects:

Anorexia,

Vomiting,

Leucopenia,

Thrombocytopenia,

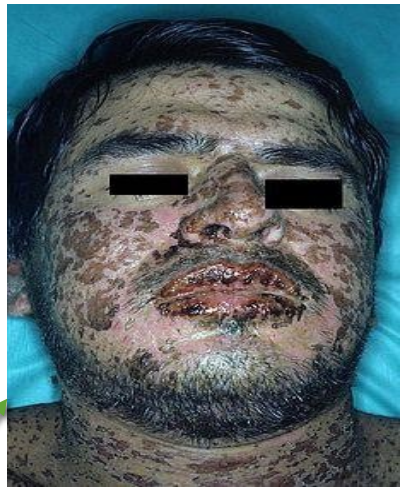
glossitis

CNS:

Stimulation,

Convulsions

Allergic reactions including Stevens-Johnson Syndrome



A severe condition of the skin, with exfoliation and up to 90% of the skin is affected and the patient might die if there is dehydration and infection. It is allergic reaction to this drug.

Antibiotics

- **Tetracycline.**
- **Doxycycline.**
- **Clindamycin.**
- **Azithromycin.**
- **Fluoroquinolones, like ciprofloxacin.**

Active against erythrocytic forms of all species. Usually for chloroquine-resistant strains.

Also effective against other protozoal diseases.

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Halofantrine and Lumefantrine

Rapidly effective against erythrocytic forms of all species.

Usually for chloroquine-resistant strains.

Well tolerated, except for cardiac toxicity (QT prolongation)

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Artemisnin= 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.**
- New strains of malaria are emerging and developing resistance against quinine.
- **High cost, unavailable routinely in the treatment of malaria.**
- **N, V, D, and neurotoxicity in animals**