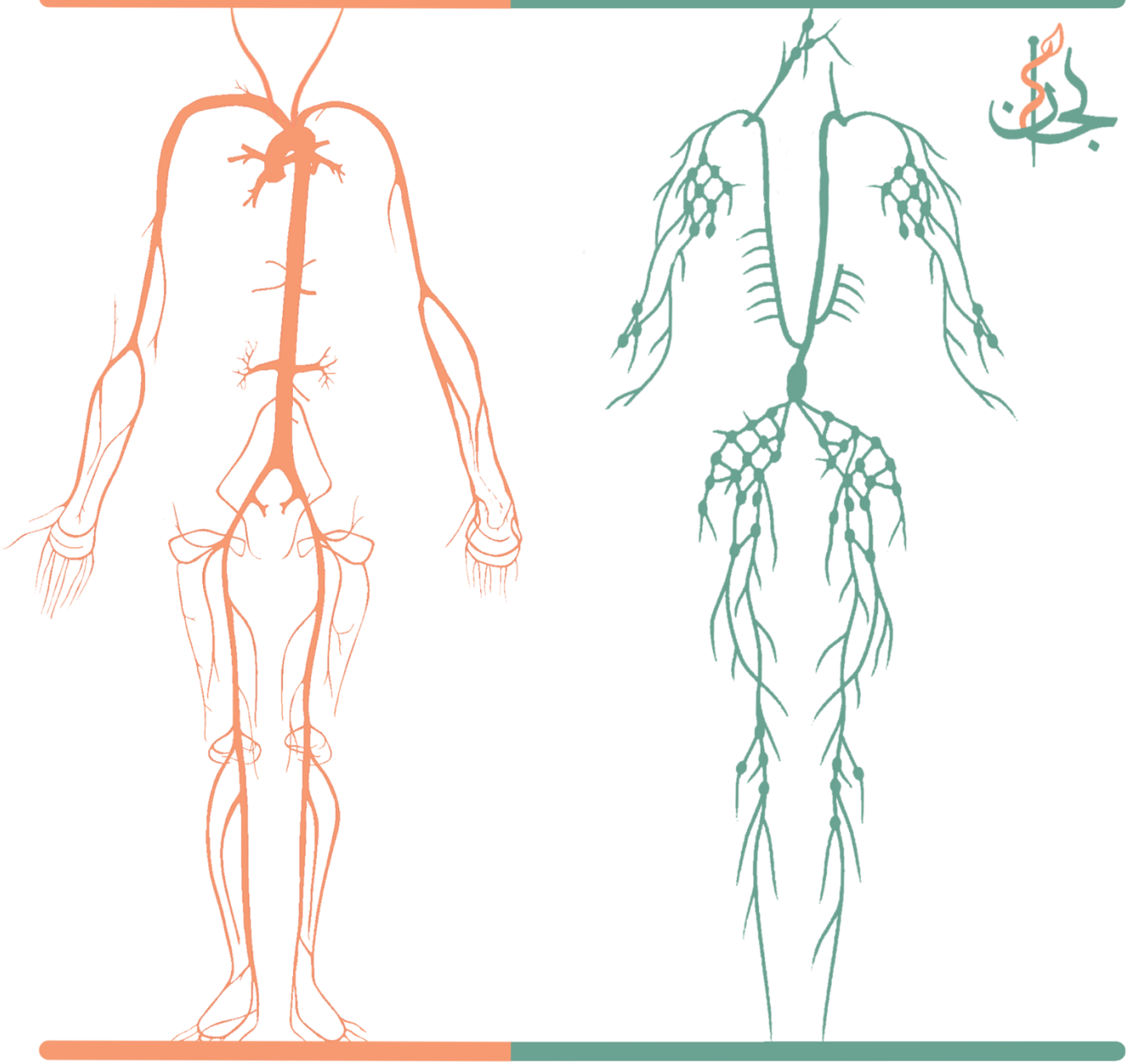
Pharmacology

HematoLymphatic



Title: Sheet 5 –Antimalarial Drugs

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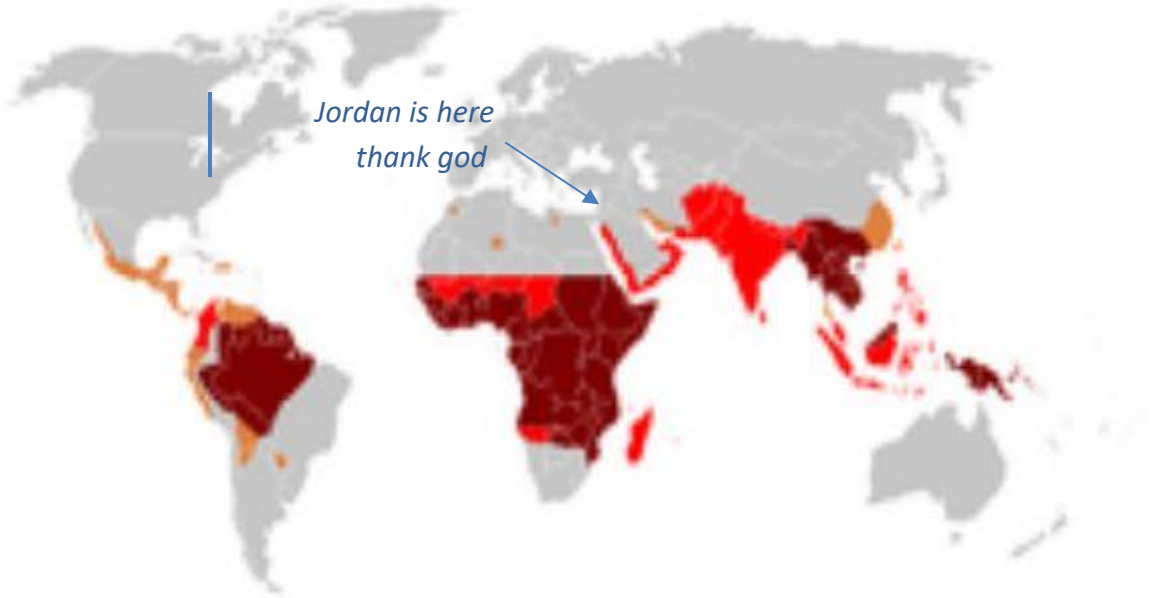
MALARIA

Malaria is a serious and sometimes fatal disease, in 2017, there were an estimated 219 million cases of malaria (296 million in 2015) which resulted in an estimated 453,000 deaths all over the world. (The countries in red are endemic for malaria).



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, and Halofantrine.

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

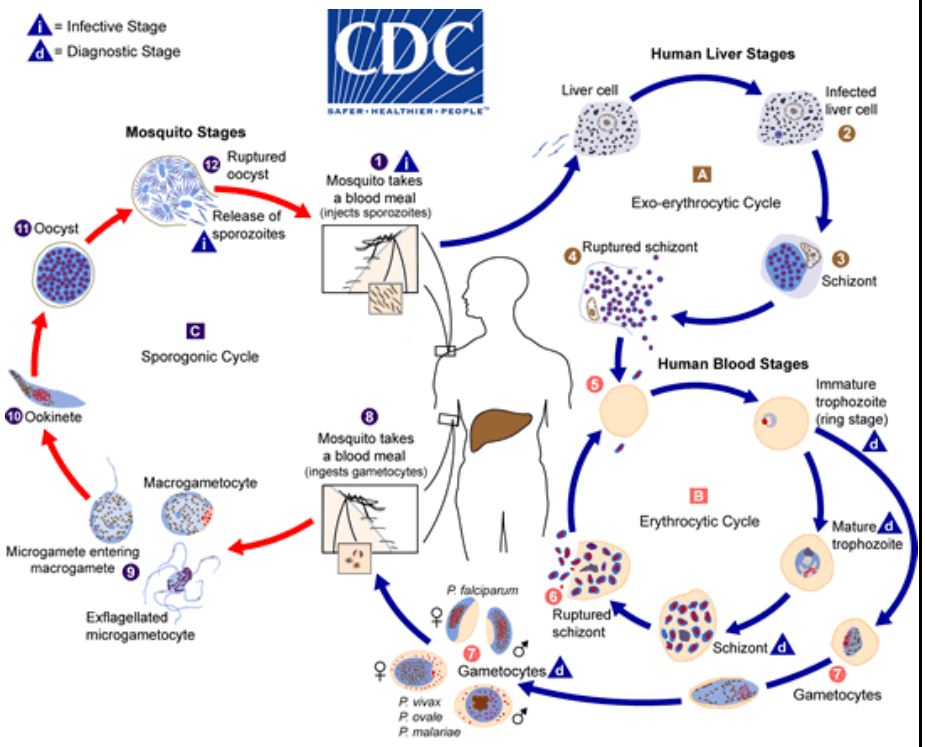
3- Prophylaxis (for people going for endemic areas): Chloroquine, Mefloquine," Malarone", and Doxycycline.

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.

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** must be 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 the drug 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).

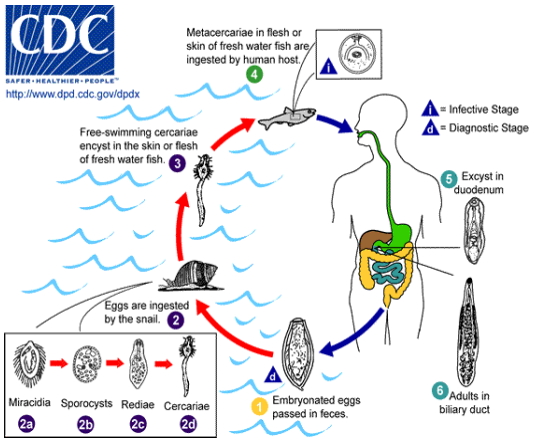
g) Other subsequent doses of chloroquine are given after 6 hours,24 hours and last dose after 48 hours. (4 doses)

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 and Quinidine: (known since 1820)

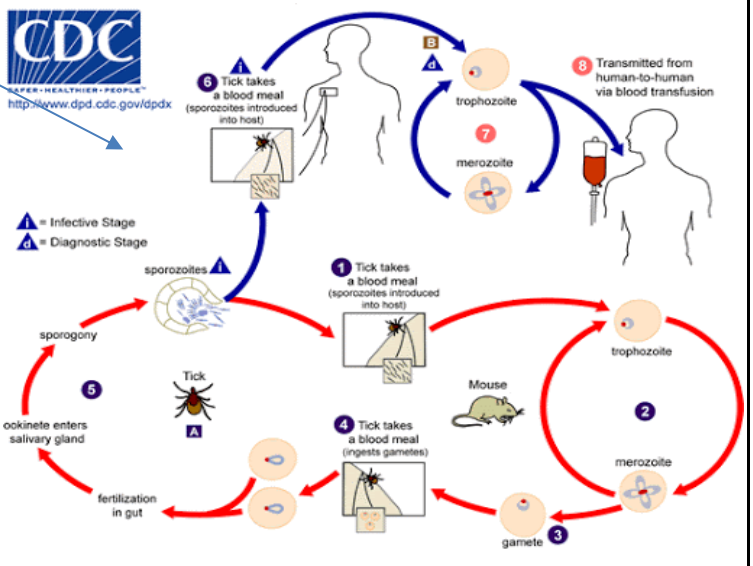
a)Discovered in the **Cinchona tree** (شجرة الصفاف)

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

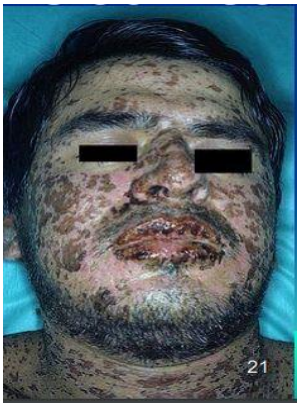
b) Slow and long acting drug, **Not** for severe malaria.

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. jerovecii



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:

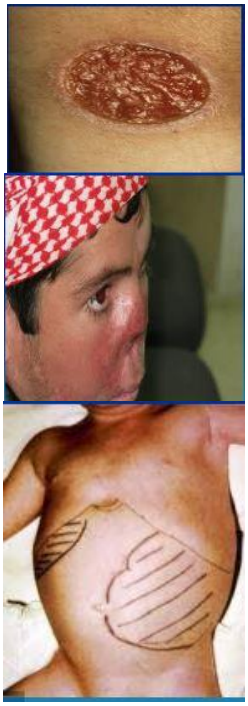
a) Rapidly effective against erythrocytic forms of all species, usually for chloroquine-resistant strains.
b) Well tolerated, except for cardiac toxicity (QT prolongation)

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.

Leishmania:



Caused by three leishmania species :

1-L.tropica :causes Cutaneous leishmaniasis or oriental sore.
(more common in our country)

2-L. brazeliensis : causes Mucocutaneous leishmaniasis.
(common in brazil and south America)

3-L. Donovani : causes Visceral leishmaniasis

Time=30:25

Drugs for leishmania:

- **Sodium Stibogluconate**

  a) derived from :

  Pentavalent Antimony (الأثمد)

b)MOA: Binds to SH groups on proteins.

c) Contains 30% to 34% pentavalent antimony by weight as well as m-chlorocresol added as a preservative.

d) Also, inhibits phosphofructokinase

e) Local, IM or slow IV (irritant). Given for 20-28 days.

f) Drug of choice for **all forms** of leishmaniasis.

j) Resistance is increasing, especially in India (Mucocutaneous and Visceral leishmaniasis)

Side Effects:

Cough, V, D, myalgia, arthralgia, ECG changes, Rash, Pruritus.

Amphotericin B:

- a) Antifungal agent (Usually for systemic fungal disease , used intravenously) , difficult to use, and toxic.

b) Alternative therapy for **visceral** leishmaniasis, especially in areas with high resistance (not drug of choice but an alternative for sodium stibogluconate).

Miltefosine:

- a) For visceral leishmaniasis.
- b) Given orally, for 28 days.
- c) Causes V & D, hepatotoxicity, nephrotoxicity, and teratogenicity.

Pentamidine:

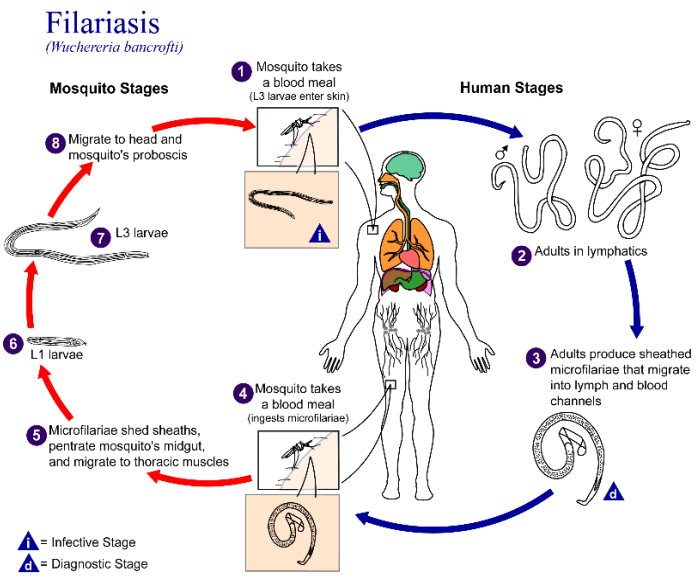
a) MOA: Inhibits DNA replication.
b) Also, DHF reductase inhibitor
c) Given by IM or IV injection and Inhalation
d) Binds avidly to tissues, but not to the CNS.
e) **Used for** :
1- Leishmaniasis: Alternative to Na stibogluconate
2-Pneumocystis jiroveci: Treatment and prophylaxis of patients who cannot tolerate or fail other drugs.
3-Trypanosomiasis: For early hemolymphatic stage

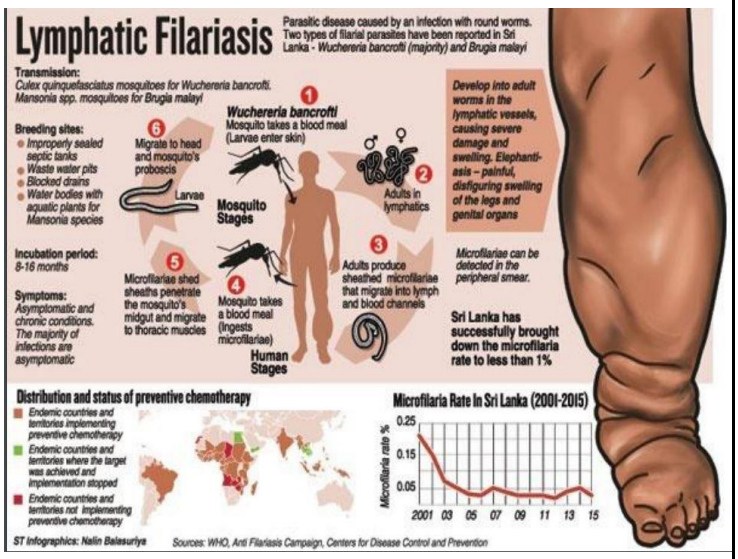
Adverse Effects:

- Rapid Infusion: Hypotension, tachycardia, dizziness.
- Pain at the injection site.
- Others: Pancreatic, Renal, and Hepatic toxicity.

Diethylcarbamazine:

a) The drug of choice in the treatment of filariasis, loiasis(Loa loa), and tropical eosinophilia.
b) May also be used for mass treatment(treating the whole population in area whether they are infected or not) and chemoprophylaxis(for people going to endemic areas).
c) Doesn't directly kill the worm, it Immobilizes microfilariae and alters their surface structure, displacing them from tissues and making them more susceptible to destruction by host defense mechanisms.
d) The mode of action against adult worms is unknown.
e) Plasma half-life is 2–3 hours in the presence of acidic urine but about 10 hours if the urine is alkaline(we alkalinize urine by giving **sodium bicarbonate**).
f) Reactions to dying microfilariae are usually mild in W. bancrofti , more intense in B. malayi , and occasionally severe in Loa loa infections which might cause :
fever, malaise, papular rash, headache, gastrointestinal symptoms, cough, chest pain, and muscle or joint pain, leukocytosis, eosinophilia, proteinuria.(it's not caused by the drug , it's a reaction from the body to the dead worms)
j) In patients with **heavy loads of microfilariae**. Retinal hemorrhages and, rarely, encephalopathy have been described.
h) Antihistamines and corticosteroids might be needed to reduce allergic reactions.





Ivermectine:

a) MOA: Ivermectin appears to paralyze nematodes and arthropods by intensifying γ-aminobutyric acid (GABA).

b) used for :

• Filariasis • Onchocerciasis

•Strongyloidiasis • Also for scabies, lice, and cutaneous larva migrans

c) Occasionally induces severe reactions and appears to be **more dangerous** in this regard than diethylcarbamazine

Doxycycline: (simple , available orally , long half life)

a) Recently shown to have significant macrofilaricidal activity against W. bancrofti , suggesting better activity than any other available drug against adult worms.

b) generally considered old fashioned antibiotics with a lot of inactivates side effects a resistance in bacteria but it's still used for non-bacterial diseases

c)Used for Onchocerciasis. (Acts indirectly, by killing Wolbachia)

d) For both treatment of active disease and in mass chemotherapy campaigns.