Antimalarial Drugs

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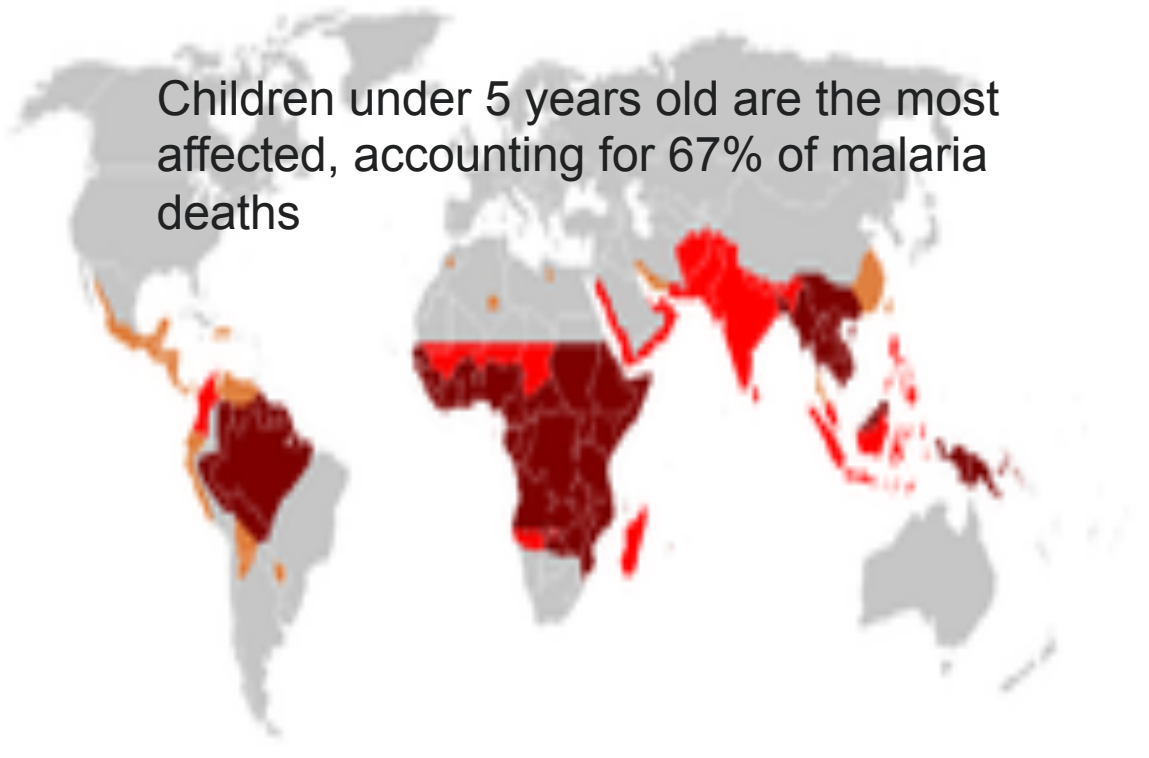
Malaria

- In 2019, there were an estimated 229 million cases of malaria(296 million in 2015) which resulted in an estimated 409,000 deaths.



Antimalarial Treatment

- **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*.

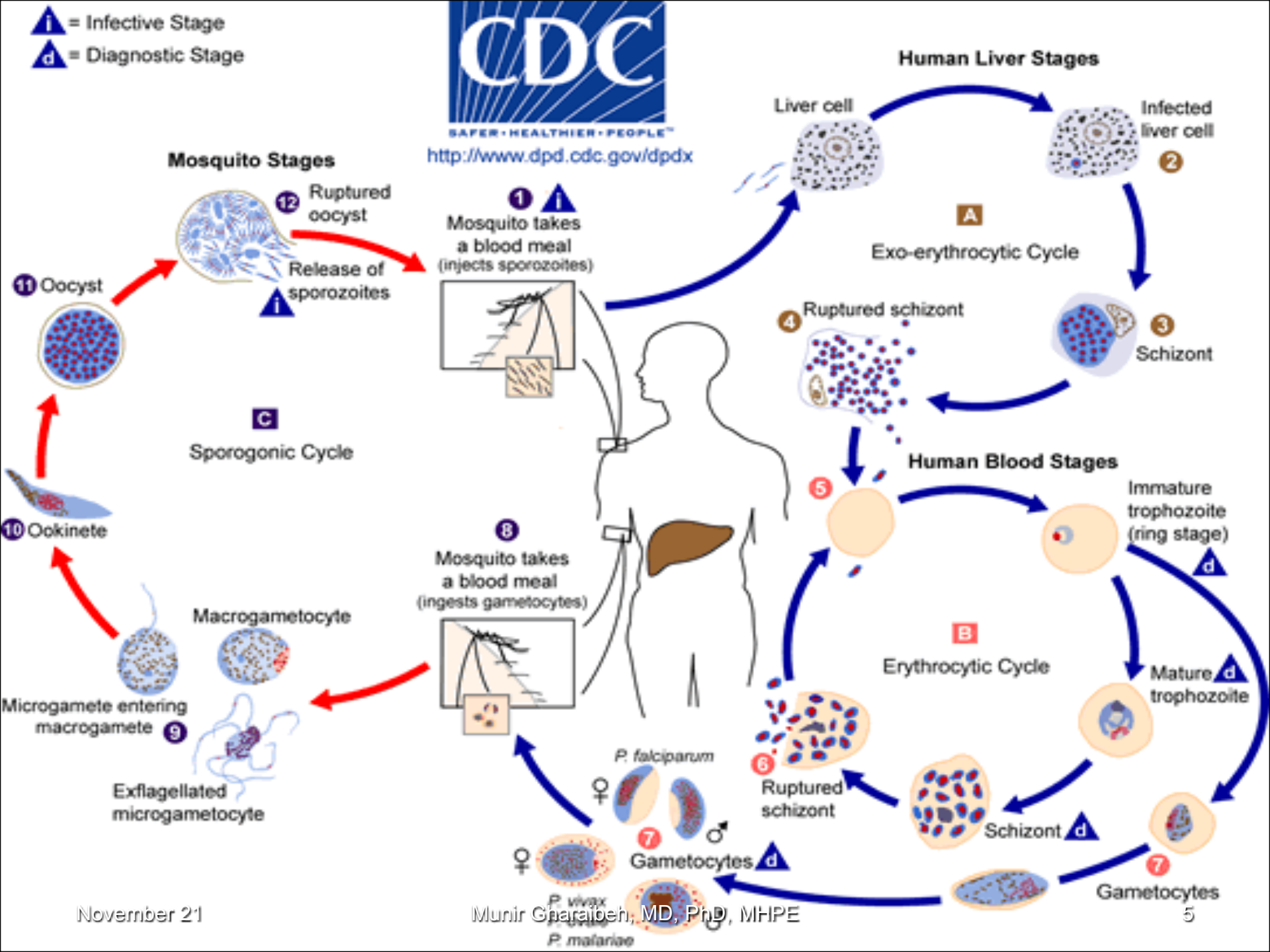
- **Prophylaxis**: Chloroquin, Mefloquin, "Malarone", and Doxycycline.

Malarial Parasites

- ***Plasmodium falciparum***

  (only erythrocytic, **serious, resistance*).***

- ***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
8
Mosquito takes a blood meal
(ingests gametocytes)
Macrogametocyte
Microgamete entering macrogamete
9
Exflagellated microgametocyte
10
Ookinete
11
Oocyst
12
Ruptured oocyst
Release of sporozoites
Mosquito Stages
1
Mosquito takes a blood meal
(injects sporozoites)
C
Sporogonic Cycle

Chloroquine

- 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.

Chloroquine

Schizonticide for 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.*
- Due to mutation in P170 glycoprotein (PfCRT) works as a drug-transporting pump mechanism .

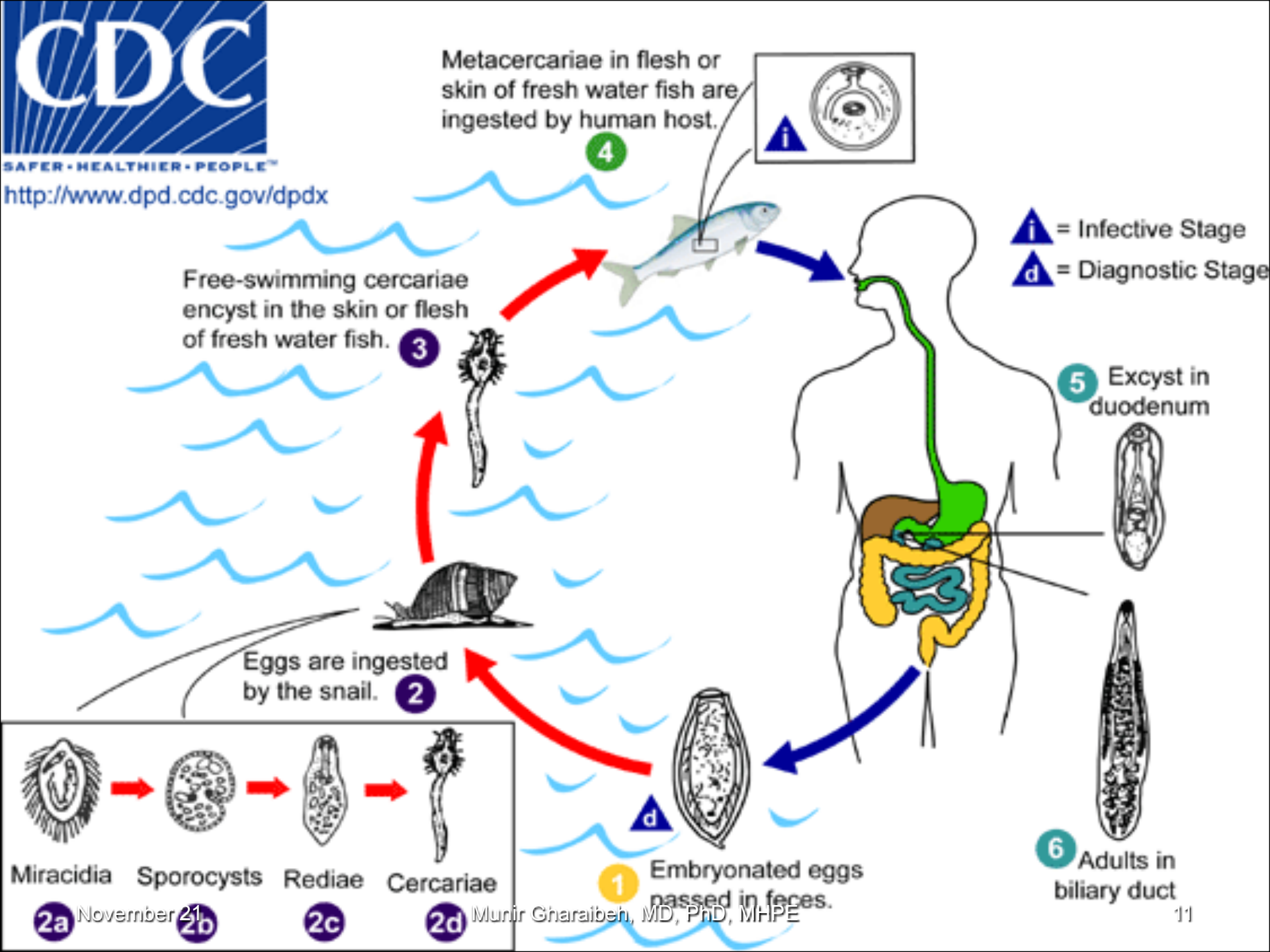
Chloroquine

- Very practical, convenient(oral), rapid action, low cost, and safe.
- Started immediately after diagnosis.
- Other doses are given after 6 hours, 24 hours and last dose 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.*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Metacercariae in flesh or skin of fresh water fish are ingested by human host.
4
i
Free-swimming cercariae encyst in the skin or flesh of fresh water fish.
3
i = Infective Stage
d = Diagnostic Stage
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,

Quinine(1820) and Quinidine

Cinchona tree from

South America.

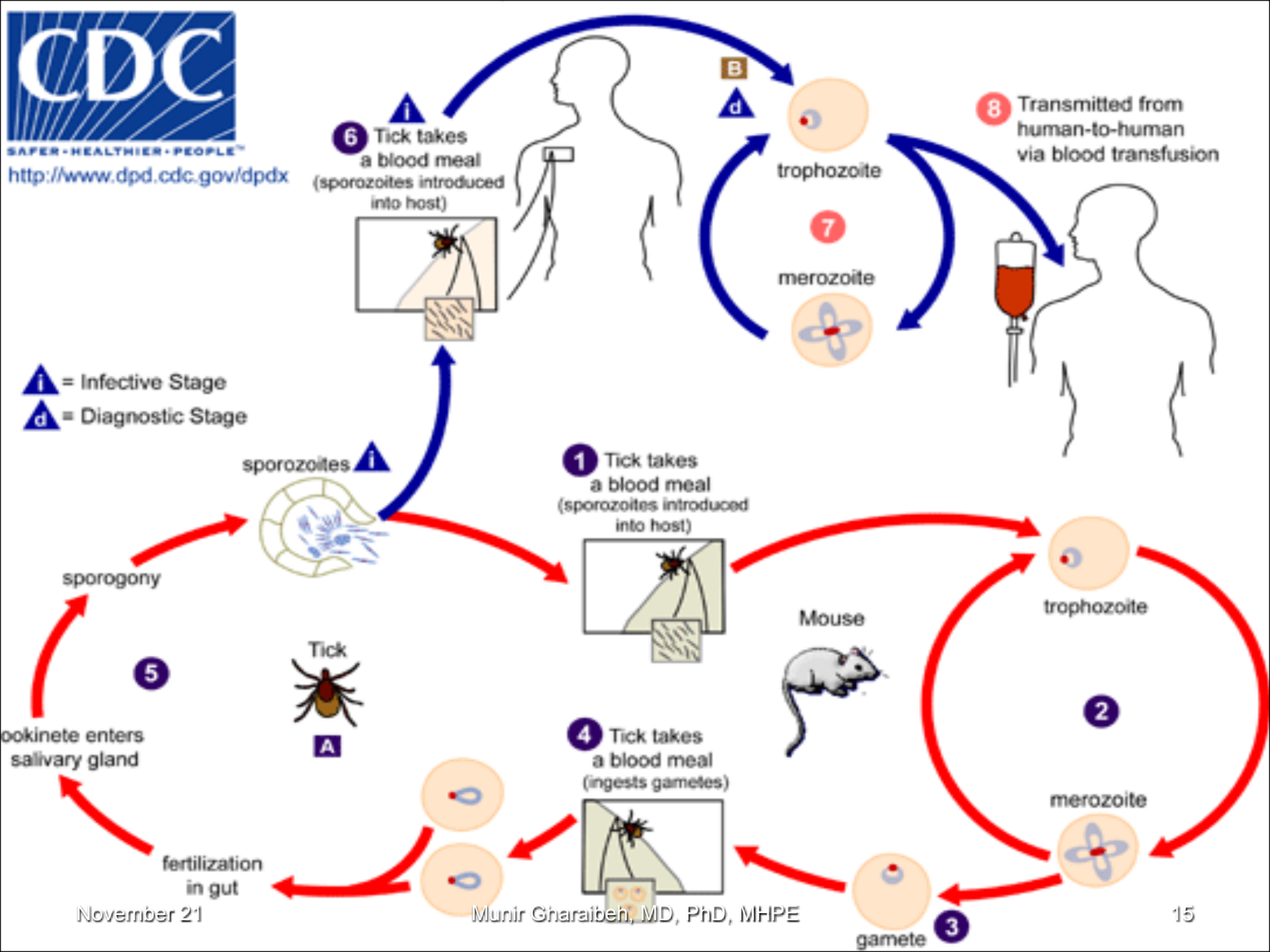
General protoplasmic poison: will affect the feeding mechanism of the parasite.

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.

Quinine and Quinidine

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


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

Quinine 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, hemoglobinurea, 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. jeroveci.*

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)

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.
- High cost.
- N.V.D. and neurotoxicity in animals.