MALARIA

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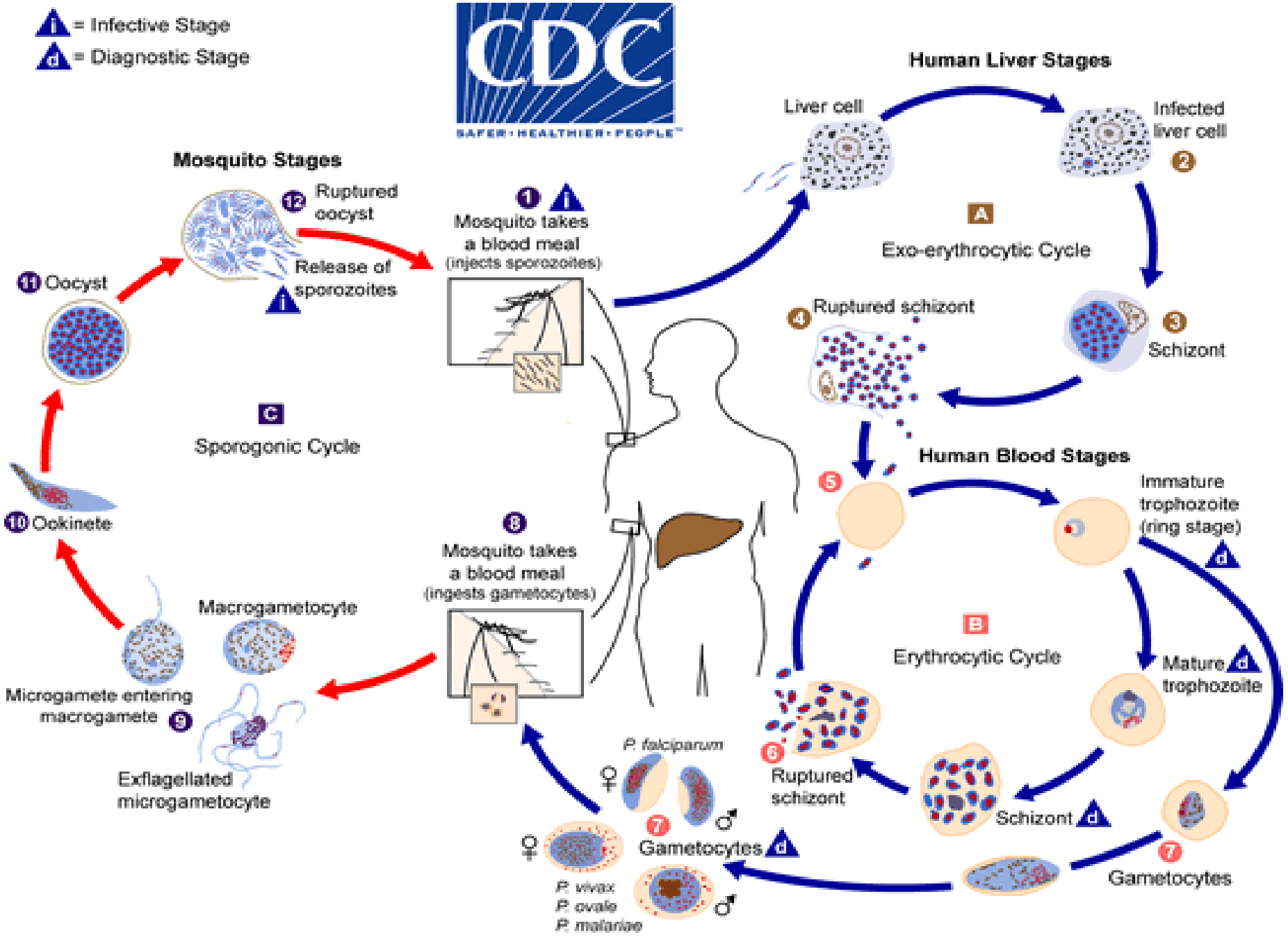
= Infective Stage
= Diagnostic Stage
CDC
SAFER · HEALTHIER · PEOPLE™
Human Liver Stages
Liver cell
Infected liver cell
2
A
Exo-erythrocytic Cycle
3
Schizont
4
Ruptured schizont
Human Blood Stages
5
Immature trophozoite (ring stage)
Mature trophozoite
Schizont
Gametocytes
B
Erythrocytic Cycle
6
Ruptured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

MALARIA

- Caused by parasitic protozoa *Plasmodium*.
- Characterized by fever with rigor, anemia and splenomegaly.
- Most seen problem in developing countries.
- Reasons may be due to
  1. Resistance of anopheles mosquitoes to insecticides like DDT.
  2. Increased drug resistance in *P. falciparum.*

➢ 4 major types of plasmodia which infect the man are:

a. P. vivax
b. P. falciparum } *BENIGN TERTIAN MALARIA*

c. P. ovale
d. P. malariae } *BENIGN QUARTAN MALARIA*

➢ Clinically, malarial infections can be controlled by drugs used in the following ways:

➢ **1. True casual prophylactics:** Drugs that destroy sporozoites before their invasion of host reticuloendothelial cells.

➢ **2. Casual prophylactics:** Drugs prevents maturation of or destroy the sporozoites within infected hepatic cells and thus prevents erythrocytic invasion.

➢ Also called as **primary tissue schizonticides**.

MALARIA

- **Primaquine, pyrimethamine and proguanil** acts as casual prophylactic agents against *P.falciparum but not against P.vivax.*
- **3. Suppressives:** Druga inhibit erythrocytic schizogony and prevent rupture of infected erythrocytes. This leads NO PYREXIA OR RIGORS.
- **Eg:** Quinine, 4-amino-quinolones, Mepacrine, Artemesinin, Proguanil, Pyrimethamine, Tetracycline.
- Can cure *P.falciparum* infection. NO effect on *P.vivax.*
- **4. Radical curatives:** Eradication of both erythrocytic and secondary exoerythrocytic schizogony. Treats *P.falciparum*.
- **5. Gametocytocidal drugs:** Chloroquine, Quinine and Artesunate are effective against gametocytes of *P.vivax.* **PRIMAQUINE** is highly effective against gametocytes of all species.

CLASSIFICATION

1. **Cinchona alkaloids** - Quinine, Quinidine
2. **Quinoline derivatives**
   - A. 4-aminoquinolines - Chloroquine, Hydroxyquinoline, Amodiaquine
   - B. 8-aminoquinloines - Primaquine, Bulaquine, Tafeloquine
   - C. Quinoline methanol - Mefloquine, Halofantrine
3. **Antifolates**
   - A. Biguanides - Proguanil
   - B. Diaminopyrimidines - Pyrimethamine
   - C. Sulfonamides
4. **Artemisinin compounds -** Artesunate, Artether, Arthemether
5. **Antimicrobials** - Sulfadoxine, Doxycycline, Clindamycin

CINCHONA ALKALOID- QUININE

- An alkaloid obtained from bark of cinchona tree - Jesuit' bark. Oldest drug.
- Still useful in treating cerebral malaria and chloroquine resistant *P.falciparum.*
- **PHARMACOLOGICAL ACTIONS:**
- **1. Antimalarial action:** It is schizonticidal, useful only as a suppressive.
- It has NO effect on sporozoites, pre-erythrocytic stage and persistent tissue forms.
- MOA similar to chloroquine. But the drug is not effectively concentrated in malarial parasite.
- **2. Local irritant action –** general protoplasmic poison.
- **3. GI tract**
- **4. CVS action**
- **5. Analgesic and antipyretic activity.**
- **PHARMACOKINETICS:** Completely absorbed through small intestine. Crosses placental barrier. Metabolized in liver. Excreted in urine.
- **ADVERSE EFFECTS:**
- **1. CINCHOISM:** Occurs when quinine is administered in higher doses for long time.
- **Symptoms: MILD-** Ringing in ears, nausea, headache, visual impairment.

QUININE

- **Large doses** – Tinnitus, deafness, vertigo, blurred vision, disturbances in colour vision, photophobia.
- Retina becomes pale and arteries are constricted.
- Severe toxicity leads to skin rashes, headache, fever, vomiting, confusion and delerium.
- Skin becomes cold, cyanotic, respiratory depression, B.P falls, death.
- **IDIOSYNCRASY:** Intense flushing. Asthmatic attacks. May lead to thrombocytopenia.
- **CVS TOXICITY.**
- **BLACK WATER FEVER:** Intravascular hemolysis, hemoglobinuria, fever, acute renal failure.
- **HYPOGLYCEMIA**
- **DOSES:**
- Quinine sulfate- tab, 300 – 600 mg.
- Quinine hydrochloride tab- 300-600 mg.
- Quinine sulfate injection – 300 mg of salt/ml. IV or IM route. 300 – 600mg.
- **USES: malaria, myotonia congenita, cramps.**

CHLOROQUINE

- Most frequently used. Diphosphate salt.
- **MOA:**
- Malarial parasites digest Hb in their lysosomes to utilise the aminoacids.
- The released heme is highly reactive.
- So it is converted by parasite polymerase to nontoxic hemozoin by polymerization.
- Chloroquine, being a basic drug, concentrates in the acidic lysosomes and binds to liberated heme.
- The heme-quinoline complex gets incorporated into growing polymer chain, which interrupts the heme polymerization.
- There by leads to damage of parasites.
- **ACTIONS:** CVS, Giardiasis, teniasis, anti-inflammatory, anthistaminic.
- **Antimalarial activity:** NO effect on sporozoites, pre-erythrocytic stage and persistent tissue forms. Kills asexual forms of P. vivax and P.falciparum.
- Effective against gametocytes of P.vivax, P.ovale and P.malariae.
- Resistence to chloroquine by P.falciparum was developed. (efflux mechanism).
- SAFEST DRUG IN PREGNANTS.

- Higher affinity to bind to tissue proteins. So the drug persists in body even after discontinuation of the treatment.

ADVERSE EFFECTS: a relatively SAFE drug in malaria.

- When used in large doses, it causes adverse effects.
- **INTOLERANCE:** Skin rashes, photosensitivity, pigmentation. Long term may lead to bleaching of scalp hair, eyebrows, eyelashes.
- **EYE:** Blurring of vision, diplopia, blue-black pigmentationof retina.
- **CNS:** Insomnia, depression, seizures, neuromyopathy, ototoxicity. **CVS:** Fall in B.P.

DOSES:

- Chloroquine phosphate- 1g followed by 0.5g after 6 hrs and 0.5g daily thereafter for 2 days. Followed by 0.5g once a week for 3 months.
- Chloroquine sulfate tab – 150 mg. similar dose
- Chloroquine injection- contains CH-phosphate or sulfate 40 mg/ml.

USES: Malaria – 1st line treatment against P.vivax.

- Hepatic amoebiasis, giardiasis, rheumatoid arthritis.

AMODIAQUINE: As effective as chloroquine in a single dose. Pharmacological actions are similar to chloroquine. NOT used longer, as it causes hepatitis.

- P. falciparum strains sensitive to chloroquine may be sensitive to amodiaquine also.
- Adverse effects include GI disturbances, headache, photosensitivity.
- **DOSE:** As a suppressive – 0.5 – 0.75g on the 1st day and then 2 tablets daily for 2 days.

8-AMINOQUINOLINES

- **PRIMAQUINE:**
- It is effective against tissue forms of P.vivax and pre-erythrocytic and sexual forms of all species of human malarial parasites.
- **MOA:** Acts by generating toxic, reactive species or by interfering with electron transport in the parasite.
- It exerts NO schizonticidal activity on P.falciparum.
- **KINETICS:** Taken orally. Completely absorbed. Concentrated in liver, lung, brain, heart and skeletal muscle.
- **ADVERSE EFFECTS:**
- Epigastric distress and abdominal cramps. Minimised by taking with food.
- Anemia, leucopenia. In large doses, leads to cyanosis and agranulocytosis.
- In patients with G-6-PD deficiency, causes intravascular hemolysis.
- **DOSES:**
- P.vivax- 15 mg daily for 14 days given along with chloroquine 1 g on 1st day and 500 mg daily for 2 days.
- **Tafenoquine –** achieves cure in 3 days. Under investigation.
- **Bulaquine –** analogue of primaquine. Under evaluation.

MEFLOQUINE

- Exact mechanism of action is not known. It may act like chloroquine.
- It acts on erythrocytic stage. It is highly effective in a single dose against P.falciparum including chloroquine resistant strains.
- Can be given 12 hours after the last dose of quinine. Cardiotoxic. Has no persistent action on tissue forms.
- Eliminated slowly with a plasma t1/2 of about 20 days.
- Parasites can develop resistance to this drug.
- **ADVERSE REACTIONS:**
- **GI tract:** dizziness, nausea, vomiting, diarrhoea, abdominal pain.
- **Neuropsychiatric disturbances:** Anxiety, hallucinations, sleep disturbances, psychosis, loss of concentration, lightheadedness.
- **CVS:** Bradycardia. **Others** like allergic skin reactions, hepatitis.
- **Teratogenecity:** Avoided in first trimester of pregnancy. In non-pregnant women, after drug usage avoid pregnancy for 3 months.
- **DOSES:** A single dose of 750mg (15 mg/kg.p.o). In some areas, same dose should be repeated in 6 hours. 1.5 g dose is effective in case of Multi Drug Resistant (MDR) malaria in 100% patients. But it may cause nausea and vomiting.

- **MEPACRINE:** A suppressive drug, acridine derivative. Once used extensively in malaria, now rarely recommended. Not a drug of choice. Used in giardiasis.
- **PROGUANIL:** Commonly used salt is proguanil Hcl.
- **Mechanism of action:**
- Shows its antimalarial action by converting into cyclic ring triazine metabolite (cycloguanil) in the human body.
- This compound binds to an enzyme DHF-Reductase in malarial parasites which prevents completion of schizogony.
- Sulfonamides synergizes the antimalarial action of proguanil.
- **EFFECT:** It is effective against

a. schizonts of both P.vivax and P.falciparum.

b. Primary erythrocytic forms of P.falciparum. NO action against tissue forms of P.vivax.

c. Prevents development of gametes encysted in the gut wall of mosquito.

- NO HYPOGLYCEMIC action, though it is a biguanide.
- Drug achieves its higher concentration in RBCs, than in plasma.
- **ADVERSE EFFECTS:** NO adverse effects when used in therapeutic doses.
- GI disturbances, stomatitis and mouth ulcers. In large doses, it depresses myocardium.
- Leucopenia may occur rarely.
- **DOSE:** 100 – 200 mg/day. Proguanil 100 mg + atovaquone 250 mg (Malarone) is used in treatment of multiresistant falciparum malaria. Well tolerated. 4 tabs once daily for 3 days. SAFE during pregnancy.

PYRIMETHAMINE

- Selectively toxic to malarial parasite by binding to its DHF-Reductase without effecting the human. More potent than proguanil.
- It is effective against erythrocytic forms of all parasites (slow action), pre-erythrocytic forms (especially P.falciparum).
- It prevents maturation of fertilized encysted gametes within the mosquito.
- INEFFECTIVE against exo-erythrocytic forms.
- CROSS resistance may occur when used with proguanil (due to same MOA).
- The antimalarial activity was enhanced by combination with sulfonamides.
- It is TASTELESS. So useful in case of children.
- **PHARMACOKINETICS:**
- It is completely but slowly absorbed from small intestine.
- Slowly excreted by kidney. Even at low dose of 25 mg, the drug was observed in the body for more than 14 days.
- **ADVERSE EFFECTS:** In therapeutic dose, it is safe. Megaloblastic anemia, thrombocytopenia,agranulocytosis may rarely develop. SAFE in pregnancy.
- **DOSE:** for acute attack of P.vivax – 50 mg on 1st day, followed by 25mg daily for 2 days. Also available in combination with sulfadoxine (3 tablets – FANSIDAR).
- **USES:** In malaria, toxoplasmosis.

OTHER DRUGS

- **SULFONAMIDES:** They are effective against the asexual blood forms – too slow action.
- When used in combination with pyrimethamine or proguanil, these compounds increases their action. So these combinations are used against P.falciparum.
- Long acting drugs like **sulfadoxine** is preferred.
- Sulfonamide containing combinations are NOT RECOMMENDED (Stevens-johnson syndrome).
- DDS is used -25mg daily for 4 weeks from the 7^{th} day of illness in combination with quinine/chloroquine and pyrimethamine in case of Chloroquine resistant.
- **DOXYCYCLINE:** exerts slow but potent action against blood schizonts and primary exo-erythrocytic forms of P.falciparum.
- **ARTEMISININ:** Obtained from *Artemisia annua* – a chinese plant.
- It is a sesquiterpene lactone. Lipophilic.
- **Mechanism of action:** These compounds covalently bind to and damages the parasitic proteins by carbon centered molecules.
- These are generated by cleavage of endoperoxide bridge in artemesinin by intraparasitic heme iron.

- Acts as schizonticides and are effective against P.vivax and as well as chloroquine resistant strains of P.falciparum.
- Also used in cerebral malaria.
- Recrudecsence occurs. Exact mechanism is not known. But it may interfere with calcium homeostasis in parasite.
- **ADVERSE EFFECTS:** Nausea, vomiting, abdominal pain, loss of appetite, leucopenia.
- Higher doses causes ECG abnormalities, bradycardia.
- Contraindicated during first trimester of pregnancy, lactation.
- **DOSES:**
- **Artesunate (FALCIGO)–** in chloroquine resistant malaria and cerebral malaria, two doses of 100 mg are taken on 1st day followed by 50 mg twice daily for 5 – 7 days.
- **Artether (E-male) –** Synthetic ethyl derivative of artemesinine. IM inj-150 mg once daily for 3 days.
- **Artemether (PALUTHER) –** 80 mg IM for 6 days.
- Preferred to take along with other drugs to prevent development of drug resistance.

MANAGEMENT OF MALARIA

- **PROPHYLAXIS:**
- Drugs should be started 1-2 week before entering the area and continued for atleast 4 weeks after leaving it.

DRUG REGIMENS FOR MALARIA PROPHYLAXIS

IN CHLOROQUINE SENSITIVE MALARIA	**Chloroquine – 300 mg once a week with or without proguanil 200 mg once daily.**
IN CHLOROQUINE RESISTANT MALARIA	Either mefloquine 250 mg once a week, doxycycline 100 mg daily OR Malorone 1 tablet daily.

DRUGS NOT RECOMMENDED FOR PROPHYLAXIS OF MALARIA

- ❖ Pyrimethamine – Ineffective.
- ❖ Amodiaquine – Long term toxicity.
- ❖ Pyrimethamine + Sulfadoxine combination – Effective but toxic in the form of Stevens-Johnson syndrome.

TREATMENT OF CHLOROQUINE RESISTANT MALARIA

- **IN PATIENTS WHO CAN TAKE ORALLY:**

1. Pyrimethamine + Sulfadoxine – 3 tablets, followed by quinine 600 mg p.o.tid. For 2 days.
2. Quinine 600 mg . TID with Doxycycline 100 mg TID fro 7 days.
3. Mefloquine 750 mg p.o repeated after 6 hours.
4. Atovaquone 250 mg + proguanil 100 mg – 4 tabs daily fro 3 days
5. Sodium artesunate 100 mg p.o- 12 hours on 1st day. Then 50 mg 12 hourly for 4 days.

- **IN PATIENTS WHO CANNOT TAKE ORALLY:**

1. Quinine HCl by IV infusion – 20mg/kg in 500 ml dextrose-saline in 4 hrs, followed by 10 mg/kg in d-saline over 2 hours, every 8 hrs until patient is able to swallow.
2. Artether or artemether IM.

- **MALARIA ERADICATION:**
- Environmental hygeine
- Insecticides
- Larvicides like synthetic pyrethroids
- DDT
- Organophosphates.
- **MOSQUITO REPELLANTS:**
- Citronella oil – vanishing cream. (non-irritant, nontoxic, pleasant)
- A combination of cedar wood oil, citronella oil, spirit of camphor.
- 35% emulsion of dimethyl phthalate.