ANTIPROTOZOAL

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Antiprotozoal drugs

- Protozoal infections are common among people in underdeveloped tropical and subtropical countries due to Poor :-
  - 1.sanitary conditions and hygienic practices, and
  - 2.control of the vectors of transmission.
- However, with increased world travel, protozoal diseases, such as malaria, amebiasis, leishmaniasis, trypanosomiasis, trichomoniasis, and giardiasis, are no lon-ger confined to specific geographic locales.

Antiprotozoal drugs

- Because they are eukaryotes, the unicellular protozoal cells have metabolic processes closer to those of the human host than to prokaryotic bacterial pathogens.
- Therefore, protozoal diseases are less easily treated than bacterial infections, and many of the antiprotozoal drugs cause serious toxic effects in the host

Examples of protozoal infections

- Malaria
- Amebiasis
- Leishmaniosis
- Trypanosomiasis,
- Trichomoniasis
- Giardiasis

Summary of the anti-protozoal agents

AMEBIASIS

Chloroquine ARALEN
Dehydroemetine DEHYDROEMETINE
Emetine IPECAC SYRUP
Iodoquinol YODOXIN
Metronidazole FLAGYL
Paromomycin HUMATIN
Tinidazole TINDAMAX

MALARIA

Artemisinin ARTEMISININ
Chloroquine ARALEN
Mefloquine LARIAM
Primaquine PHOSPHATE TABLETS
Pyrimethamine DARAPRIM
Quinine/Quinidine QUALAQUIN, QUINIDINE GLUCONATE

TRYPANOSOMIASIS

Benznidazole RADANIL
Melarsoprol MELARSOPROL
Nifurtimox NIFURTIMOX
Pentamidine NEBUPENT
Suramin GERMANIN

LEISHMANIASIS

Sodium stibogluconate SODIUM STIBOGLUCONATE

TOXOPLASMOSIS

Pyrimethamine DARAPRIM

GIARDIASIS

Metronidazole FLAGYL
Nitazoxanide ALINIA
Tinidazole TINDAMAX

Amebiasis Chemotherapy

- Amebiasis (also called amebic dysentery) is an infection of the intestinal tract caused by Entamoeba histolytica.
- The disease can be acute or chronic, with patients showing varying degrees of illness, from no Symptoms to mild diarrheal to fulminating dysentery.

Amebiasis Chemotherapy

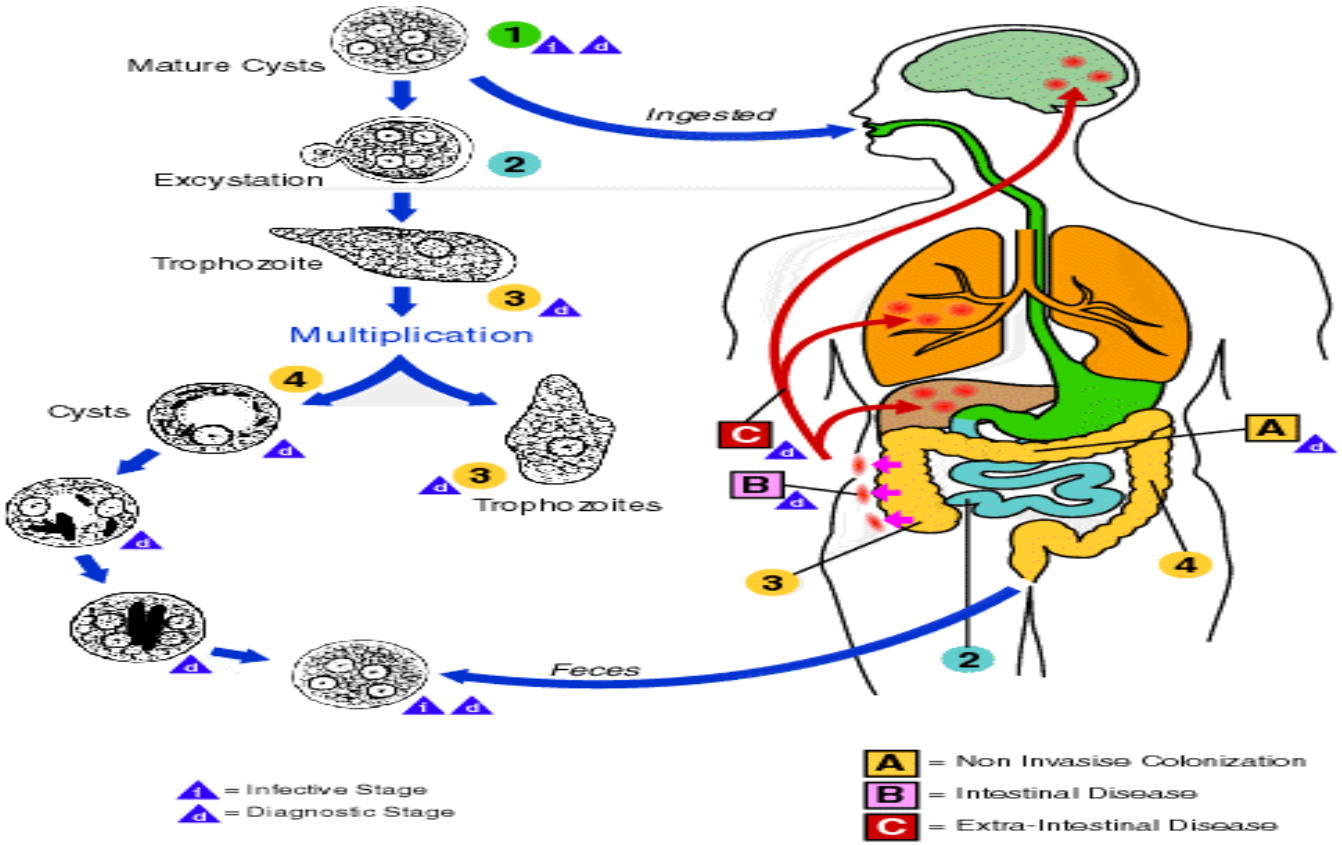
- The diagnosis is established by isolating E. histolytica from fresh feces.
- Therapy is aimed not only at the acutely ill patient but also at those who are asymptomatic carriers, because dormant E. histolytica may cause future infections in the
- carrier and be a potential source of infection for others

Life History of Entamoeba histolytica

- Entamoeba histolytica exists in two forms: cysts that can survive out-side the body and labile but invasive trophozoites that do not persist outside the body.
- Cysts, ingested through feces-contaminated food or water, pass into the lumen of the intestine, where the trophozoites are liberated.
- The trophozoites multiply, and they either invade and ulcerate the mucosa of the large intestine or simply feed on intestinal bacteria.

- The trophozoites within the intestine are slowly carried toward the rectum, where they return to the cyst form and are excreted in feces.
- [Note: One strategy for treating luminal amebiasis is to add antibiotics, such as tetracycline, to the treatment regimen, resulting
- in a reduction in intestinal flora, the ameba’s major food source]

Life Cycle of Amebiasis



Complications

- Liver abscess
- Pleuropulmonary disease
- Peritonitis
- Pericarditis
- Brain abscess
- Genitourinary disease

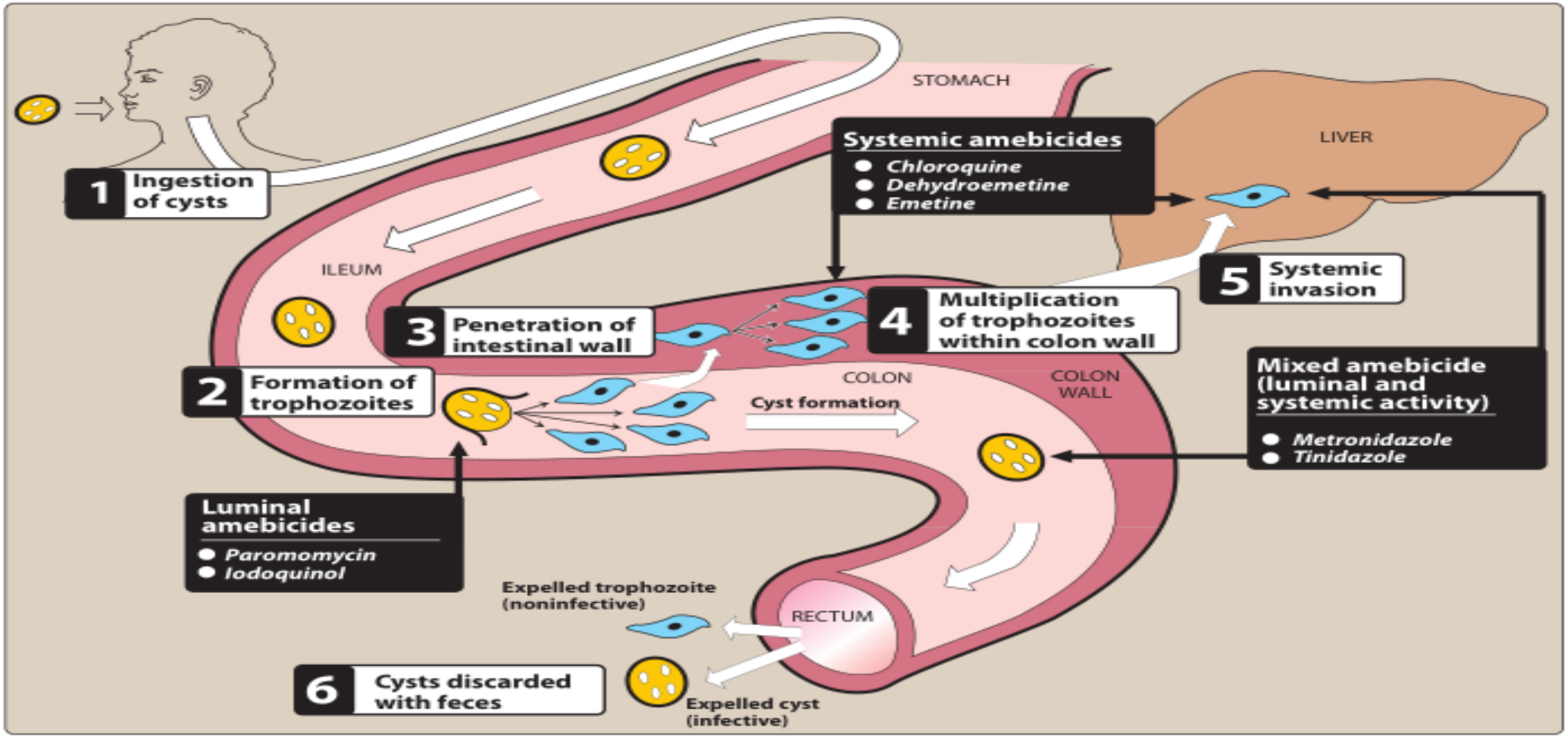
Classification of amebicidal drugs

- Therapeutic agents are classified as luminal, systemic, or mixed (luminal and systemic) amebicides according to the site where the drug is effective
- Luminal amebicides act on the parasite in the lumen of the bowel.
- Systemic amebicides are effective against amebas in the intestinal wall and liver.

Classification of amebicidal drugs

- Mixed amebicides are effective against both the luminal and systemic forms of the disease,
- Although luminal concentrations are too low for single-drug treatment.
- Mixed amebicides (metronidazole and tinidazole) Metronidazole is the mixed amebicides of choice for treating amebic infections and kills the E. histolytic atrophozoites and also effective against by Giardia lamblia, Trichomonas vaginalis, anaerobic cocci, and anaerobic gram-negative bacilli

Life Cycle Entamoeba histolytica
Site of action of Drugs



Metronidazole
Mechanism of action

- Metronidazole is a prodrug.
- Unionized metronidazole is selective for anaerobic bacteria due to their ability to intracellularly reduce metronidazole to its active form. This reduced metronidazole then covalently binds to DNA, disrupt its helical structure, inhibiting bacterial nucleic acid synthesis and resulting in bacterial cell death.

Metronidazole: Pharmacokinetics

- Metronidazole is completely and rapidly absorbed after oral administration
- For the treatment of amebiasis, it is usually administered with a luminal amebicide, such as iodoquinolor paromomycin. This combination provides cure rates of greater than 90 percent.
- Metronidazole distributes well throughout body tissues and fluids.
- Therapeutic levels can be found in vaginal and seminal fluids, saliva, breast milk, and cerebrospinal fluid (CSF).

Metronidazole: Pharmacokinetics

- Metabolism of the drug depends on hepatic oxidation of the metronidazole side chain by mixed-function oxidase, followed by glucuronylation. Therefore, concomitant treatment with inducers of this enzymatic system, such as phenobarbital, enhances the rate of meta-bolism.
- Conversely, those drugs that inhibit this system, such as cimetidine, prolong the plasma half-life of metronidazole. The drug accumulates in patients with severe hepatic disease.
- The parent drug and its metabolites are excreted in the urine.

Adverse Effects

- The most common adverse effects are those associated with the gastrointestinal tract, including
- nausea
- Vomiting
- Epigastric distress
- abdominal cramps
- Metallic taste is commonly experienced
- Disulfiram-like effect occurs due to alcohol interaction

Tinidazole

- Tinidazole is a second-generation nitro-imidazole that is similar to metronidazole in spectrum of activity i.e
- Absorption
- Adverse effects and
- drug interactions
- Used in treatment of amebiasis, amebic liver abscess, giardiasis, and trichomoniasis
- Tinidazoleis as effective as metronidazole, with a shorter course of treatment.

Commonly used therapeutic option for the treatment of Amoebiasis

CLINICAL SYNDROME	DRUG
Asymptomatic cyst carriers	*Iodoquinol* or *paromomycin*
Diarrhea/dysentery Extraintestinal	*Metronidazole* plus *iodoquinol* or *paromomycin*
Amebic liver absess	*Chloroquine* plus *metronidazole* and/or *diloxanide furoate*

Luminal Amebicides

- After treatment of invasive intestinal or extra intestinal amebic disease is complete,
- a luminal agent, such as IODOQUINOL, OXANIDEFUROATE, OR PAROMOMYCIN should be administered for treatment of the symptomatic colonization state.

Iodoquinol

- Iodoquinol a halogenated 8-hydroxy quinolone, is amebicidal against E. histolytica and is effective against the luminal trophozoite and cyst forms.
- Side effects
- Rash
- Diarrhea and
- Dose-related peripheral neuropathy, including a rare optic neuritis.
- Long-term use of this drug should be avoided

Paromomycin

- Paromomycin an aminoglycoside antibiotic, is only effective against the intestinal (luminal) forms of E. histolytica and tapeworm, because it is not significantly absorbed from the gastrointestinal tract.
- It is an alternative agent for cryptosporidiosis.
- Paramomycin is directly amebicidal and also exerts its anti-amebic actions by reducing the population of intestinal flora.

- Its direct amebicidal action is probably due to the effects it has on cell membranes, causing leakage.
- Very little of the drug is absorbed on oral ingestion, but that which is absorbed is excreted in urine.
- Gastrointestinal distress and diarrhea are the principal adverse effects.

Systemic Amecides

- These drugs are useful for treating
- Liver abscesses
- intestinal wall infections caused by amebas.
- These include:-Ementine and Chloroquine

Chloroquine

- Chloroquine is used in combination with metronidazole and diloxanide furoate to treat and prevent amebic liver abscesses.
- It eliminates trophozoites in liver abscesses, but it is not useful in treating luminal amebiasis.

Malaria

- Malaria is an acute infectious disease caused by four species of the protozoal Genus. Plasmodium
- The parasite is transmitted to humans through the bite of a Female Anopheles mosquito with P Falciparum infection leading to capillary obstruction and death if treatment not commenced on time
- P Falciparum is the most dangerous species causing an acute fulminating disease characterised by Fever, Orthostatic hypotension, Erythrocytosis

Species

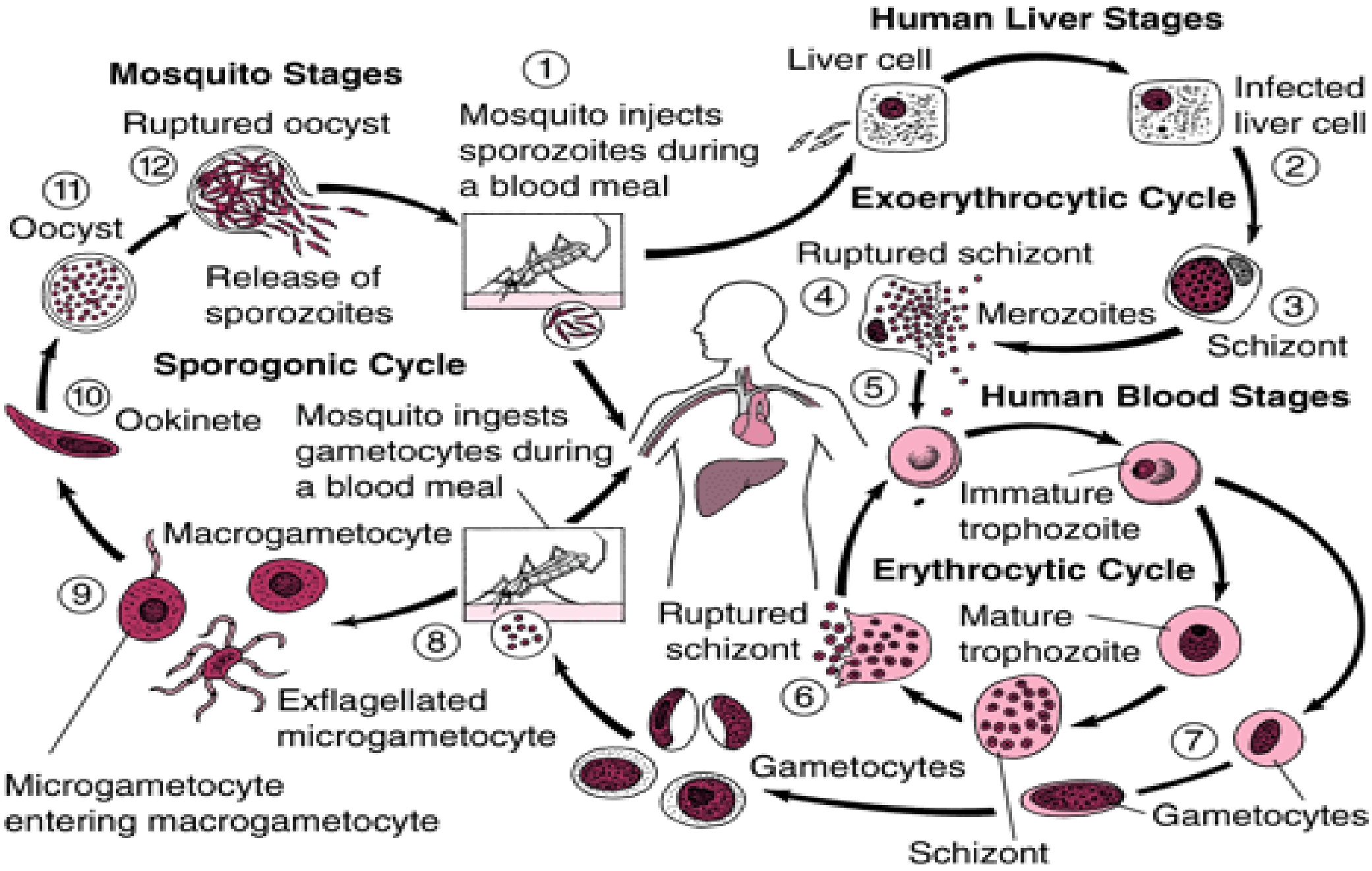
- *P Falciparum* is the most dangerous
- *P Vivax* causes a milder form of the disease
- *P Ovale is rarely encountered.*
- *P Malariae* common to many tropical regions.
- *Mosquitoes* have acquired resistance to Insecticides and other parasite drugs has caused therapeutic challenges.

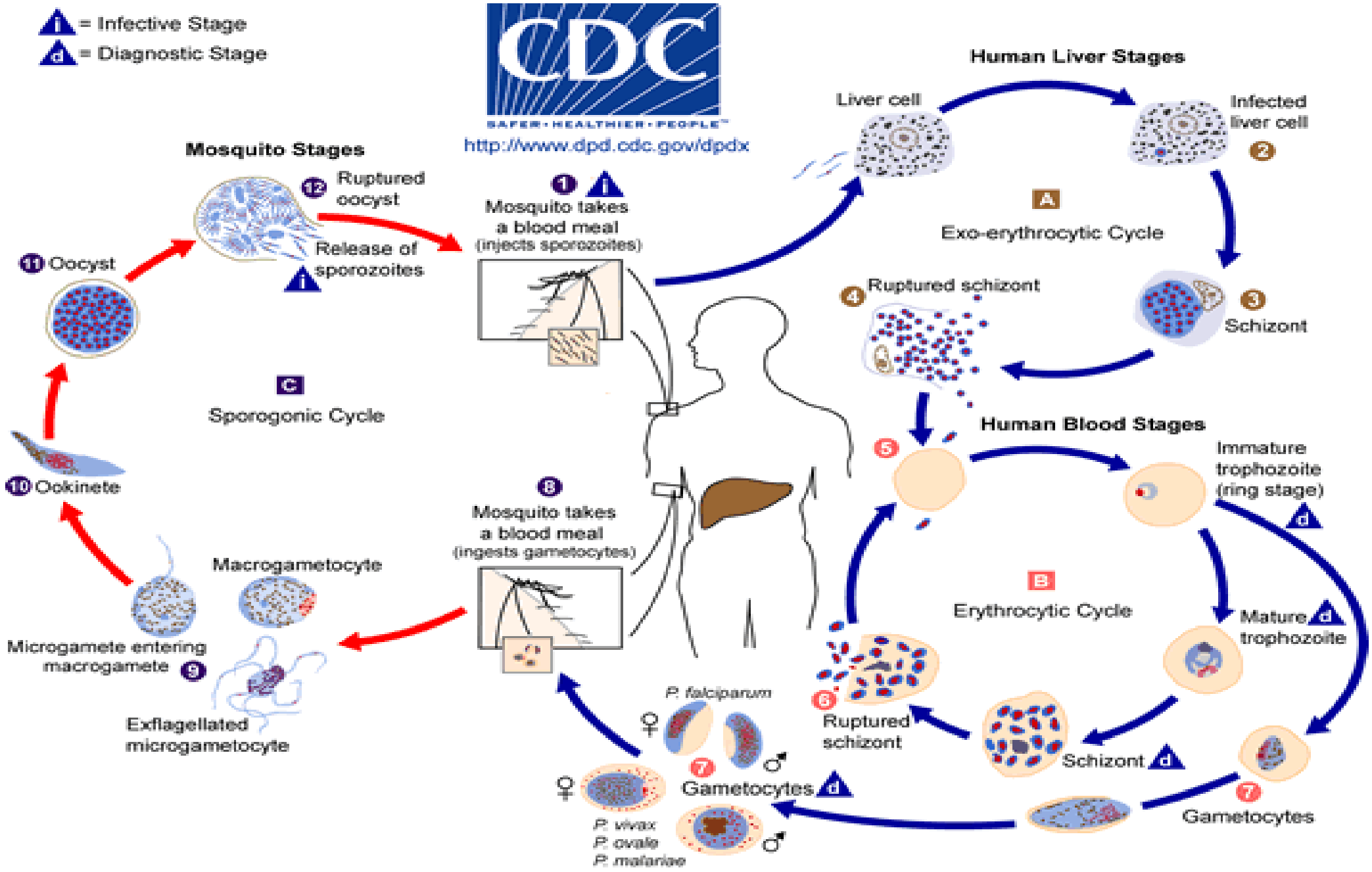
Life cycle of malaria parasite

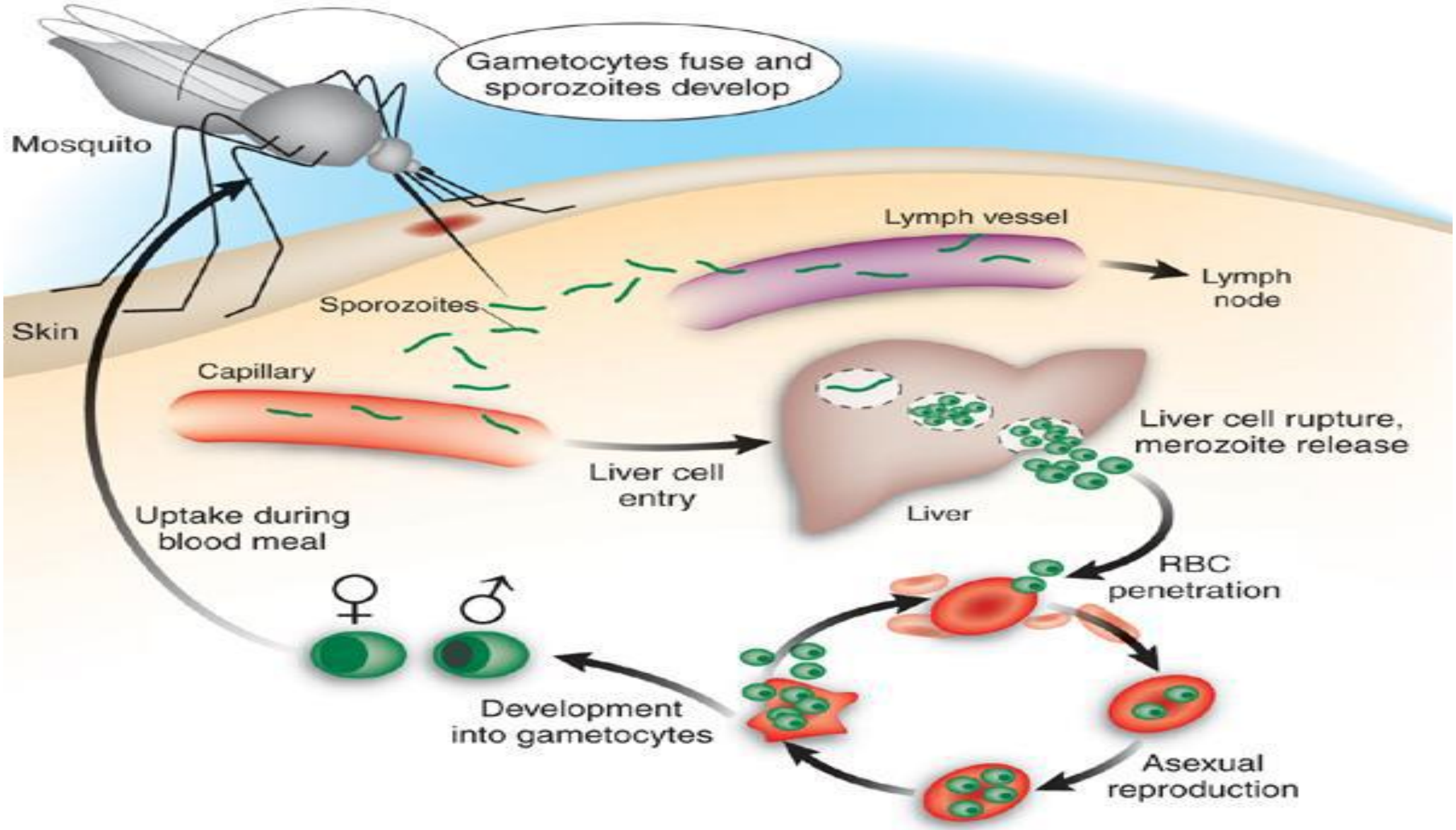
- When an infected mosquito bites, it injects plasmodium sporozoites into the blood stream.
- They migrate through the bloodstream to the liver.
- Where they form cyst like structures containing thousands of merozoites.
- Upon release each merozoite invades a red blood cell becoming a trophozoite using haemoglobin as a nutrient.
- The trophozoites multiply and become merozoites and infected cell raptures

Life cycle of malaria parasite

- When cell ruptures heme and merozoites are released that can enter other erythrocytes and become gametocytes which are picked up by mosquitoes from the blood they ingest.
- The cycle thus begins again


Human Liver Stages
Liver cell
Infected liver cell
Exoerythrocytic Cycle
Ruptured schizont
Merozoites
Schizont
Human Blood Stages
Immature trophozoite
Erythrocytic Cycle
Mature trophozoite
Gametocytes
Schizont
Gametocytes
Ruptured schizont
Mosquito Stages
Ruptured oocyst
Release of sporozoites
Oocyst
Sporogonic Cycle
Ookinete
Mosquito injects sporozoites during a blood meal
Mosquito ingests gametocytes during a blood meal
Macrogametocyte
Exflagellated microgametocyte
Microgametocyte entering macrogametocyte
1
2
3
4
5
6
7
8
9
10
11
12

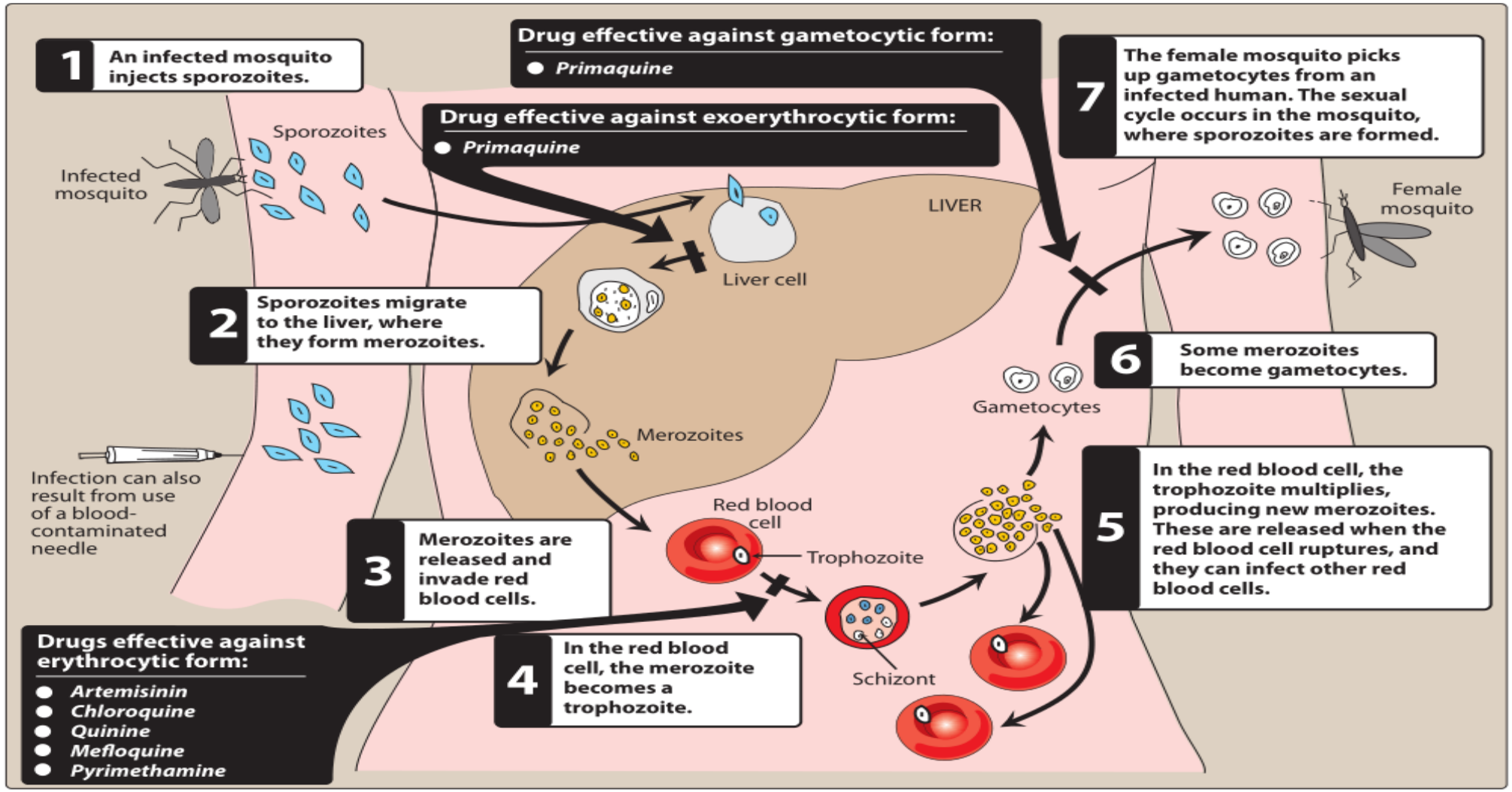

= Infective Stage
= Diagnostic Stage
CDC
SAFER·HEALTHIER·PEOPLE™
http://www.dpd.cdc.gov/dpdx
Human Liver Stages
Liver cell
Infected liver cell
2
A
Exo-erythrocytic Cycle
3
Schizont
4
Ruptured schizont
Human Blood Stages
5
Immature trophozoite (ring stage)
d
Mature trophozoite
d
B
Erythrocytic Cycle
6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


Gametocytes fuse and sporozoites develop
Mosquito
Skin
Sporozoites
Lymph vessel
Lymph node
Capillary
Liver cell entry
Liver
Liver cell rupture, merozoite release
Uptake during blood meal
RBC penetration
Development into gametocytes
Asexual reproduction

Drugs used to Malaria

- Therapeutic classification and-chemical classification Therapeutic classification
- **1. Causal Prophylaxis : (Primary Tissue schizonticides)**
- E.gproguanil, primaquine,mefloquine, doxycycline.They Destroy parasites in liver and prevent invasion of erythrocytes
- **2. Clinical cure: erythrocytic schizonticides FAST ACTING HIGH EFFICACY**
- E.gquinine,mefloquine,atovaquone, artemisinin

Life cycle of malaria parasite; Site of Action

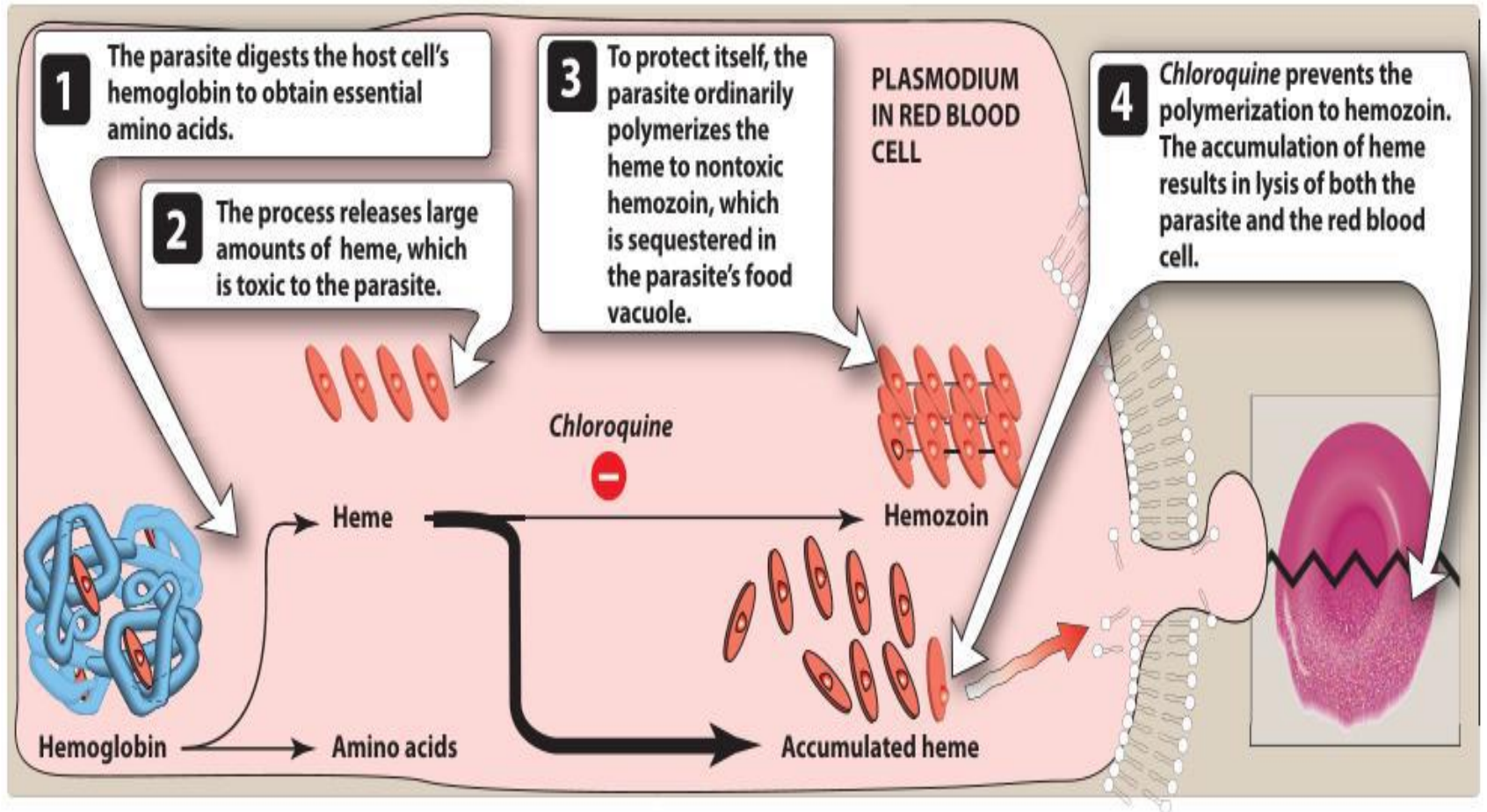


Drugs used to treat Malaria

- **Drugs used to treat malaria can be classified in different ways e.g**
- **SLOW ACTING LOW EFFICACY**
- E.g proguanil, pyrimethamine, sulfonamides, tetracyclines3. Gametocidal
- Destroy gametocytes and prevent transmission E.g primaquine,artemisinin–effective against all plasmodia
- Quinine -P vivax,Proguanil, pyrimethamine-prevent development of sporozoites Chemical classification Antimalarials can be chemically classified in the alphabetical order for us to easily recall

1. 4 aminoquinolines

- e.g amodiaquine, hydroxychloroquine, pyronaridine-8 aminoquinolines e.g primaquine, tafenoquine, bulaquine
- **Mode of action**
- thought to inhibit heme-polymerase activity. This results in accumulation of free heme, which is toxic to the parasites. The drug binds the free heme preventing the parasite from converting it to a form less toxic (hemozoin). This drug-heme complex is toxic and disrupts membrane function and kills the parasite


1
The parasite digests the host cell's hemoglobin to obtain essential amino acids.
2
The process releases large amounts of heme, which is toxic to the parasite.
3
To protect itself, the parasite ordinarily polymerizes the heme to nontoxic hemozoin, which is sequestered in the parasite's food vacuole.
PLASMODIUM IN RED BLOOD CELL
4
Chloroquine prevents the polymerization to hemozoin. The accumulation of heme results in lysis of both the parasite and the red blood cell.
Chloroquine
Heme
Hemozoin
Hemoglobin
Amino acids
Accumulated heme

Adverse effects

- Side effects are minimal at the low doses used in the chemo suppression of malaria.
- At higher doses, many more toxic effects occur, such as
- Gastrointestinal upset, Pruritus, Headaches, blurred vision
- Chloroquine should be used cautiously in patients with hepatic dysfunction or severe gastrointestinal problems and in patients with neurologic or blood disorders
- Chloroquine can cause electrocardiographic (ECG) changes, because it has a quinidine-like effect.

2. Biguanides

- E.g proguanil, chlorproguanil
- Mode of action
- They inhibits the dihydrofolatereductase of plasmodia and thereby blocks the biosynthesis of purines and pyrimidines, which are essential for DNA synthesis and cell multiplication. This leads to failure of nuclear division at the time of schizont formation in erythrocytes and liver.

3. Cinchona Alkaloids

- E.g quinine, quinidine, quinimax
- **Mode of action**
- They interfere with the parasite's ability to break down and digest hemoglobin. Consequently, the parasite starves and/or builds up toxic levels of partially degraded hemoglobin in itself.
- Quinimaxis a combination of four alkaloids (quinine, quinidine, cinchoine and cinchonidine). This combination has been shown in several studies to be more effective than quinine, supposedly due to a synergistic action between the four cinchona derivatives

4.Diamonopyrimidines

- E.g pyrimethamine
- **Mode of action**
- They inhibit the dihydrofolate reductase of plasmodia and thereby blocks the biosynthesis of purines and pyrimidines, which are essential for DNA synthesis and cell multiplication. This leads to failure of nuclear division at the time of schizont formation in erythrocytes and liver.

5.Naphthoquinone

- E.g atovaquone
- **Mode of action**
- Atovaquoneis a hydroxy-1, 4-naphthoquinone, an analog of ubiquinone, with antipneumocystisactivity.
- In Plasmodium species, the site of action appears to be the cytochromebc1 complex (Complex III). Several metabolic enzymes are linked to the mitochondrial electron transport chain via ubiquinone. Inhibition of electron transport by atovaquonewill result in indirect inhibition of these enzymes. The ultimate metabolic effects of such blockade may include inhibition of nucleic acid and ATP synthesis
- The mechanism of action against Pneumocystiscarinii has not been fully elucidated.
- Atovaquone also has been shown to have good in vitro activity against Toxoplasmagondii

6.Phenanthrene Derivatives

- E.g.Halofantrine, lumefantrine
- **Mode of action**
- Acts by forming toxic complexes with ferritoporphyrinIX that damage the membrane of the parasite.

7.Sulphonamides

- E.gsulfadoxine, dapsone
- **Mode of action**
- Sulfadoxine targets Plasmodium dihydropteroate synthase and dihydrofolate reductase.
- They compete with para-aminobenzoic acid (PABA) for incorporation into folic acid.
- The action of sulfonamides exploits the difference between mammal cells and other kinds of cells in their folic acid metabolism.
- Folic acid (as a vitamin) diffuses or is transported into human cells. However, folic acid cannot cross bacterial (and certain protozoan) cell walls by diffusion or active transport. For this reason bacteria must synthesize folic acid from p-aminobenzoic acid.

8.SESQUATERPENE LACTONES

- E.g artesunate, artemether, arteether
- **Mode of action**
- These compounds have presence of endoperoxide bridge which interact with hemein parasite
- hemeiron cleaves this endoperoxide bridge leading to generation of highly reactive free radicals which damage parasite membrane by covalently binding to membrane proteins.

9.Tetracycline

- E.g tetracycline,doxycycline
- **Mode of action**
- Tetracyclines passively diffuses through porinchannels in the bacterial membrane and reversibly binds to the 30S ribosomal subunit, preventing binding of tRNA to the mRNA-ribosome complex, and thus interfering with protein synthesis.

10. Quinoline Methanol

- E.g mefloquine
- **Mode of action**
- Mefloquinehas been found to produce swelling of the Plasmodium falciparum food vacuoles. It may act by forming toxic complexes with free heme that damage membranes and interact with other plasmodial components.