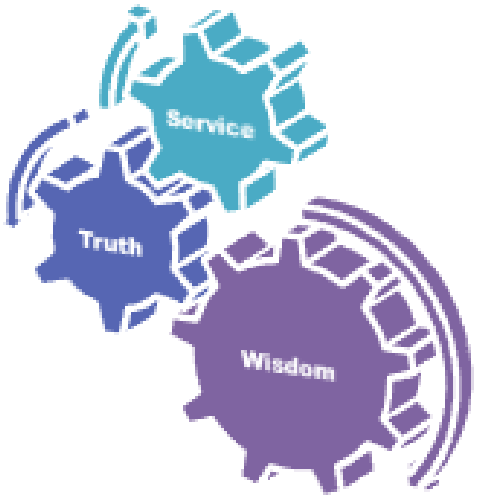
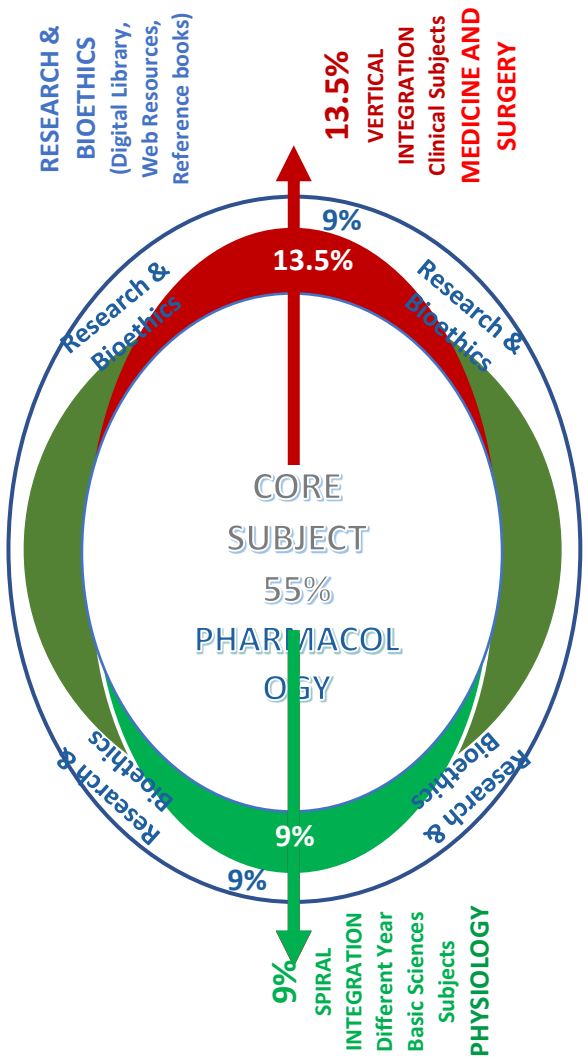

بسم الله الرحمن الرحيم

MOTTO AND VISION



- To impart evidence based research oriented medical education
- To provide best possible patient care
- To inculcate the values of mutual respect and ethical practice of medicine

Prof. Umar's Clinically Oriented Integration Model
For Basic Sciences Interactive Lectures



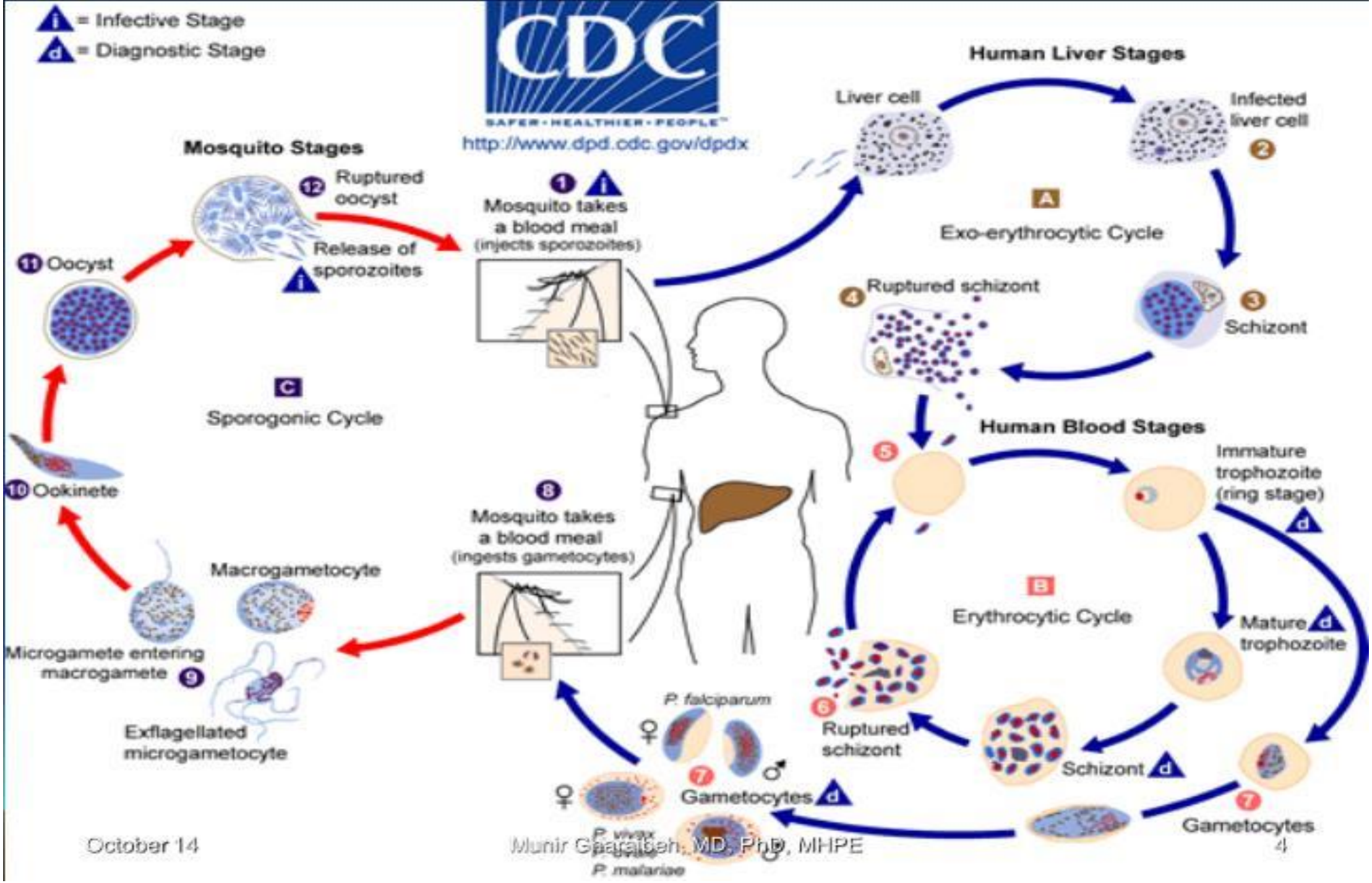
Model 3rd Year Pharmacology CBL (22 slides)	
Core Subject – 70%	
Horizontal Integration – 10%	
Vertical integration (Clinical Subjects)	• Medicine (10 %)
Spiral Integration – 15%	
Different Year Basic Sciences Subjects	
Research & Bioethics 5%	

ANTI MALARIAL DRUGS

LIFE CYCLE OF PLASMODIUM

- Incubation period ; 10-35 days
- Sexual Replication….Sporogony…..In mosquito
- Asexual Replication……Schizogony…..In humans
- Female anopheles mosquito inject salivary fluid in host containing sporozoites(No drugs are effective against sporozoites)
- **EXOERYTHROCYTIC CYCLE: HEPATIC CYCLE:**
- **Sporozoites** → Enter liver cells → Tissue/**Hepatic Stage** → **Schizonts(Hypnozoites)**
- **Merozoites** → Into circulation
- **ERYTHROCYTE CYCLE:**
- Merozoites enter into RBCs Ring form **Trophozoites** **Blood Stage Schizonts** Burst and release 8-32 → **Merozoites** → Re enter the RBCs →
- Some Merozoites convert into **Gametocytes** (Infective to mosquitoes)
- **Gametocytes** → **Gametes** → **Zygotes** → **Ookinetes** → **Oocysts** → **Sporozoites IN MOSQUITO** →

In human


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

Core subject – Pharmacology

CHEMICAL CLASSIFICATION

- **4 – Aminoquinolines**
  - *Chloroquine, amodiaquine*
- **8 – Aminoquinoline**
  - *Primaquine*
- **Hydroxynaphthoquinine**
  - *Atovaquone*
- **Quinoline methanol**
  - *Mefloquine*
  - *Quinine, quinidine(cinchona alkaloids)*
- **Diaminopyrimidine**
  - *Pyrimethamine*

- **Lactone Endoperoxide**
  - Artemisinin & derivatives
- **Phenantherine**
  - Lumefantrine, Halofantrine
- **Tetracyclines**
  - Doxycycline
- **Biguanides**
  - Proguanil
- **Sulfonamides & Sulfones**
  - Sulfadiazine, sulfadoxine, dapsone

THERAPEUTIC CLASSIFICATION

BLOOD SCHIZOTICIDES

- Chloroquine
- Pyrimethamine
- Amodiaquine
- Lumefantrine
- Quinine
- Artemisinin
- Mefloquine
- Atovaquone

TISSUE SCHIZONTICIDES

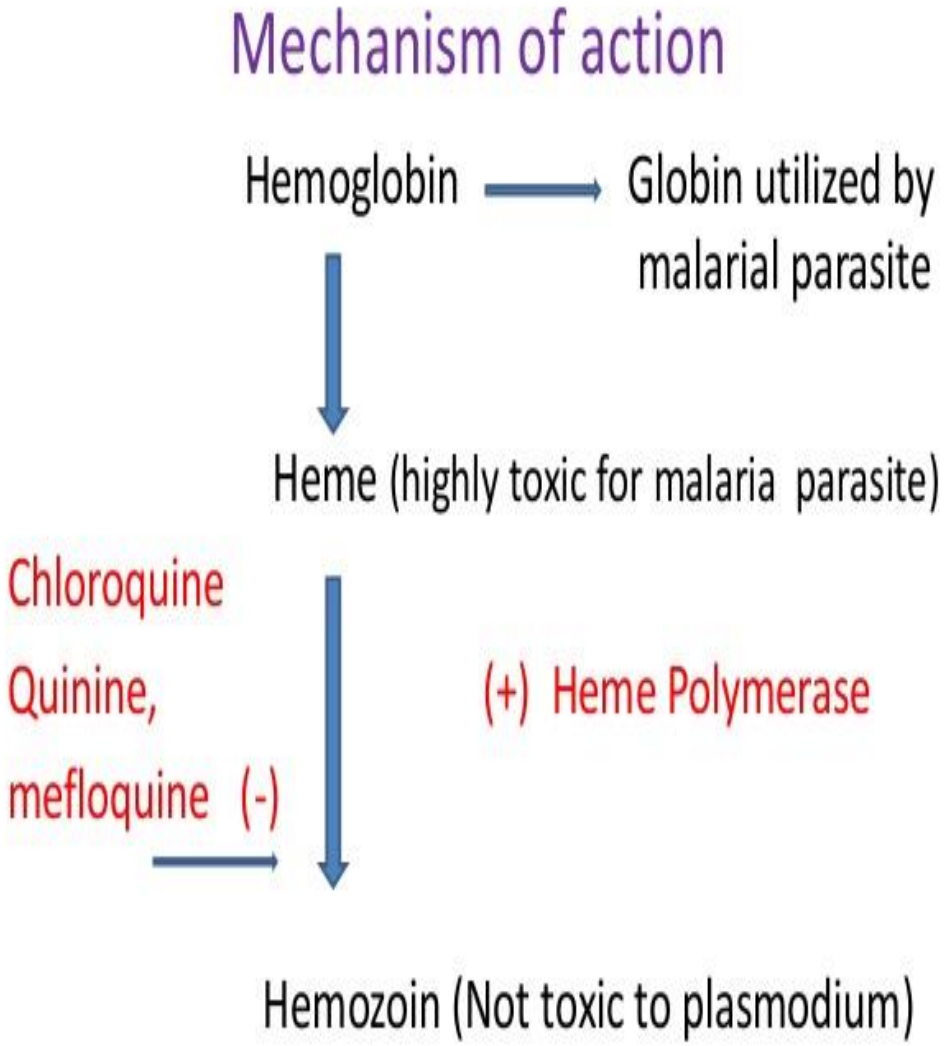
(**Radical curatives-** for vivax & ovale)

- Primaquine

- **PROPHYLACTIC DRUGS**
  - *Pyrimethamine*
  - *Proguanil*
  - *Primaquine*
  - *Mefloquine*
  - *Doxycycline*
  - *Chloroquine*
- **GAMETOCIDAL DRUGS**
  - ***For vivax and ovale***
  - *Primaquine*
  - *Chloroquine*
  - *Quinine*
  - ***For Falciparum***
    - Primaquine

CHLOROQUINE

- **MECHANISM OF ACTION**
  - Being a weak base it concentrates in the highly acidic parasite food vacuole and raises vesicular pH
  - Inactivation of haem – polymerase prevents polymerization of haemoglobin breakdown product, haem into hemozoin
  - Haem accumulates & elicits parasite toxicity
  - Failure to inactivate toxic haem into non toxic hemozoin kills parasite
  - Damage to biological membranes
- **RESISTANCE**
  - Mutation in transporter
  - Efflux



CHLOROQUINE

- **PHARMACOKINETICS:**
  - Oral, I/M, S/C (Safer when given orally)
  - Large Vd → Large loading doses are required
  - Half life : 3-5 days, excreted in urine
- **Dose**
- For chloroquine sensitive Falciparum and Malaria give 1g followed by 500mg stat at 6, 24 and 48 hour

CHLOROQUINE

CLINICAL USES

- Blood schizontocide against all species of plasmodia
- Moderately effective against gametocytes of vivax, Ovale & Malariae
- NOT ACTIVE against dormant liver stage of vivax and Ovale
- Chemoprophylaxis of malaria 500mg weekly

- Antipyretic properties
- Amoebic liver abscess
- Rheumatoid arthritis
- SLE
- Sarcoidosis

Anti-inflammatory properties because of accumulation in Lysosomes

CHLOROQUINE

ADVERSE EFFECTS

- Pruritis, Urticaria, Agranulocytosis
- Rash, Exfoliative dermatitis, alopecia, bleaching of hair
- GIT: N/V, abdominal pain, anorexia
- Corneal deposits, Blurring of vision
- Impaired hearing
- Haemolysis in G6PD-deficient patients

- **CNS:** Confusion, psychosis, seizures
- **CVS:** Hypotension, QRS widening, Cardiac arrhythmias

LONG -TERM USE

High dose for rheumatological diseases can result in

- Irreversible ototoxicity
- Irreversible Retinopathy
- Myopathy
- Peripheral neuropathy

QUININE & QUINIDINE

- Quinine – chief alkaloid of Cinchona bark
- Quinidine - dextrorotatory stereoisomer of Quinine. More potent & toxic
- Rapid Oral absorption
- I/V route
- Widely distributed- loading dose
- Quinidine has shorter half life than quinine(decreased protein binding)
- **ANTIMALARIAL ACTION & RESISTANCE**
- Rapidly acting blood schizontocide (all four species)
- Gametocidal against Vivax & Ovale
- NOT ACTIVE against hepatic stage

- **RESISTANCE**
- Un common

QUINIDINE & QUINIDINE

- **OTHER PHARMACOLOGICAL EFFECTS**
  - Oxytocic action
  - Atropine like effects
  - Alpha blocking effect
  - Insulin releasing action
  - Local anesthetic action
  - Antipyretic action
  - Curare like action- blocking of NMJ

QUININE & QUINIDINE

- **MOA:**
- Exact Mechanism unknown. May be the same as chloroquine.
- **CLINICAL USES**
- QUINIDINE----Parenteral treatment of drug resistant and severe falciparum malaria, cerebral malaria
- Oral treatment of uncomplicated falciparum
- Used with a second drug like doxycycline or clindamycin to shorten duration of use
- Babesiosis (Quinine+ clindamycin)
- Nocturnal leg cramps

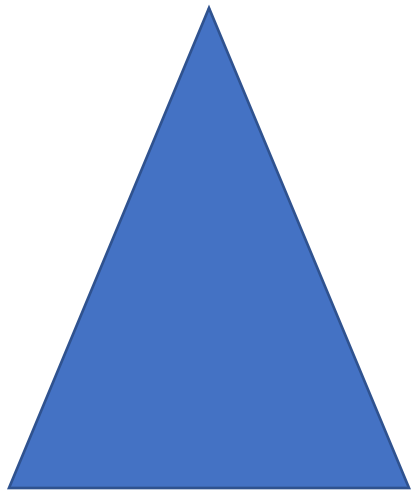
ADVERSE EFFECTS

- **CINCHONISM**
- **Hearing disturbances**– tinnitus, decreased hearing, vertigo
- **Visual disturbances** – blurred vision, disturbed colour perception, photophobia, diplopia, night blindness, mydriasis, blindness
- **GI symptoms** – vomiting, abdominal cramps, diarrhoea
- **Cutaneous** – flushing, sweating, rash, angioedema
- **Cardiac** – Arrhythmias, Torsades de pointes, QT interval prolongation (I/V quinidine)
- **BLACKWATER FEVER** (massive hemolysis, hemoglobinemia, hemoglobinuria leading to anuria and renal failure)
- Thrombophlebitis (I/V)

ADVERSE EFFECTS

Cinchonism

Tinnitus, high tone deafness, headache, nausea, flushing, visual disturbances, hyperthermia



Hypoglycemia

Hypotension

Due to hyperinsulinemia because of stimulatory effect on pancreas

QUININE & QUINIDINE

- **CONTRAINDICATIONS**
- Discontinue if signs of
  - Cinchonism
  - Hemolysis
  - hypersensitivity
- Caution in cardiac abnormalities
- Dosage reduction in renal failure
- Not given subcutaneously- parenteral solutions are highly irritating

- **DRUG INTERACTIONS**
- Mefloquine
- Aluminium antacids(Reduce absorption)
- Warfarin & Digoxin(Increase levels)
- Enhance effect of NMJ blockers & antagonize effect of AChE inhibitors
- Clearance enhanced by urinary acidification & rifampicin

ARTEMISININ & DERIVATIVES

- **Artemisinin**: – oral
  - **Artesunate** – oral I/V, I/M & rectal
  - **Artemether** - oral I/M, rectal
  - **Dihydroartemisinin** – oral

- Standard treatment for uncomplicated falciparum malaria
- Blood schizonticides, weak Gametocidal effect

MOA

- Production of free radicals that follow the iron-catalyzed cleavage of the artemisinin endoperoxide bridge in parasite food vacoule OR inhibition of parasite Calcium ATPase

ARTIMISININ BASED COMBINATION THERAPY: (ACT)

1. Artemether – Lumefantrine (Coartem)
2. Dihydroartemisinin – Piperaquine
3. Artesunate – Mefloquine
4. Artesunate – Amodiaquine
5. Artesunate-Sulfadoxine-Pyrimethamine

Artemisinin has short half life which led to relapse after short therapy so long acting drugs were combined with it to protect against artemisinin resistance

ARTEMISININ & DERIVATIVES

- I/M Artemether efficacy is equal to quinine
- I/V Artesunate superior to I/V quinine esp for cerebral malaria due to
  - Faster parasite clearance time
  - Safer and better tolerance
  - Higher safety lower mortality
  - Simpler dosing schedule
- Cannot be used for chemoprophylaxis of malaria
- Effective against chloroquine and quinine resistant strains
- **Adverse effects:**
  - NVD, dizziness
  - Rarely: neutropenia, anemia, hemolysis, allergic reactions
  - Neurotoxicity and QT prolongation

Use in pregnancy

WHO recommends

- Quinine Plus Clindamycin in first trimester
- ACT for uncomplicated falciparum malaria during second and third trimesters of pregnancy
- I/V Artesunate for treatment of severe malaria(all stages of pregnancy)

- **RESISTANCE**: Not developed yet

AMODIAQUINE

- Closely related to chloroquine
  - Widely used
  - low cost
  - Effective against chloroquine resistant strains of falciparum

ADR:

  - Agranulocytosis, aplastic anemia & hepatotoxicity
  - serious toxicity is rare

- **COMBINATIONS:**
  - Amodiaquine + Artesunate for falciparum malaria resistant
  - Amodiaquine + sulfadoxine-pyrimethamine if artemisinin containing therapies are unavailable)

MEFLOQUINE

- Mechanism unknown but appears to damage parasite's membrane
- Oral administration Only
- Long half life, gets concentrated in liver and lungs

- **ANTIMALARIAL ACTION**
- Blood Schizontocide (P. falciparum, & P. vivax)
- NOT ACTIVE against hepatic stage or gametocytes

- Effective for prophylaxis and treatment of Chloroquine

resistant strains of P. Falciparum & others

- Artesunate + Mefloquine: For treatment of uncomplicated malaria

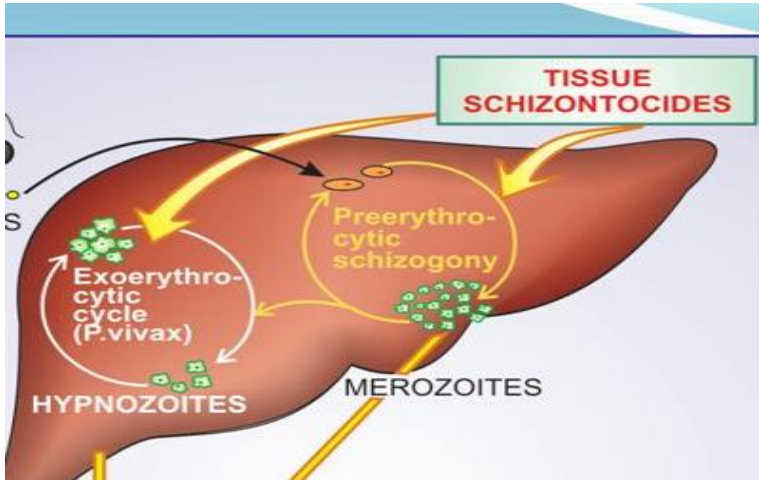
MEFLOQUINE

ADVERSE EFFECTS

- Nausea, vomiting, epigastric pain, dizziness, headache, sleep & behavioural disturbances, rash.
- Neuropsychiatric toxicities like psychosis & seizures (reserved for infections where other agents cannot be used)
- Higher doses: leucocytosis, thrombocytopenia & LFT elevation
- Can alter cardiac conduction - arrhythmias
- **CONTRAINDICATION:** in epilepsy, psychiatric disorders, cardiac conduction defects
- Should not be co-administered with quinine, quinidine

PRIMAQUINE

- Drug of choice for eradication of dormant liver forms of P vivax & P ovale
- Used for chemoprophylaxis of all species
- Well absorbed orally
- Widely distributed to tissues
- **ANTIMALARIAL ACTION**
- Act on exo-erythrocytic stages of plasmodia
- Active against hepatic stage of all species



- **ONLY AGENT** active against dormant **HYPNOZOITE** stage of Vivax & Ovale
- **GAMETOCIDAL** against all four species
- Weakly active against erythrocytic stage. Given in combination with chloroquine and mefloquine
- Mechanism unknown (maybe free radical generation & interfering with parasite's mitochondrial electron transport)

PRIMAQUINE

- **USES** :
- Drug of choice for eradication of dormant liver forms of P vivax & P ovale
- Radical Cure of Acute Vivax & Ovale malaria
- Chemoprophylaxis of all species: Initiated shortly before or immediately after a person leaves an endemic area
- Gametocidal: single dose can render P falciparum gametocytes non-infective to mosquitoes
- Pneumocystosis (Primaquine+Clindamycin)

- **ADVERSE EFFECTS & CONTRAINDICATIONS**

- Mild abdominal discomfort
- Mild anaemia, cyanosis, leucocytosis
- Haemolysis (G6PD deficiency)
- Methemoglobinemia
- Marked hypotension (Never given I/V)
- Arrhythmias, agranulocytosis
- Avoided in pregnancy & lactating mother(foetus is G6PD deficient)

ATOVAQUONE-PROGUANIL

- In combination are used for chemoprophylaxis and treatment of chloroquine resistant P. Falciparum

- **Proguanil – (100mg)**
- Antimalarial action due to metabolite-cycloguanil
- Inhibit plasmodial dihydrofolate reductase- thymidylate synthetase-inhibiting DNA synthesis as well as depletion of folate cofactors

- **Atovaquone- (250mg)**
- inhibits mitochondrial processes like electron transport, ATP and pyrimidine synthesis

Pharmacokinetics

- Given orally

- Metabolized by CYP2C9- genetic polymorphism resulting in poor metabolism in some patients

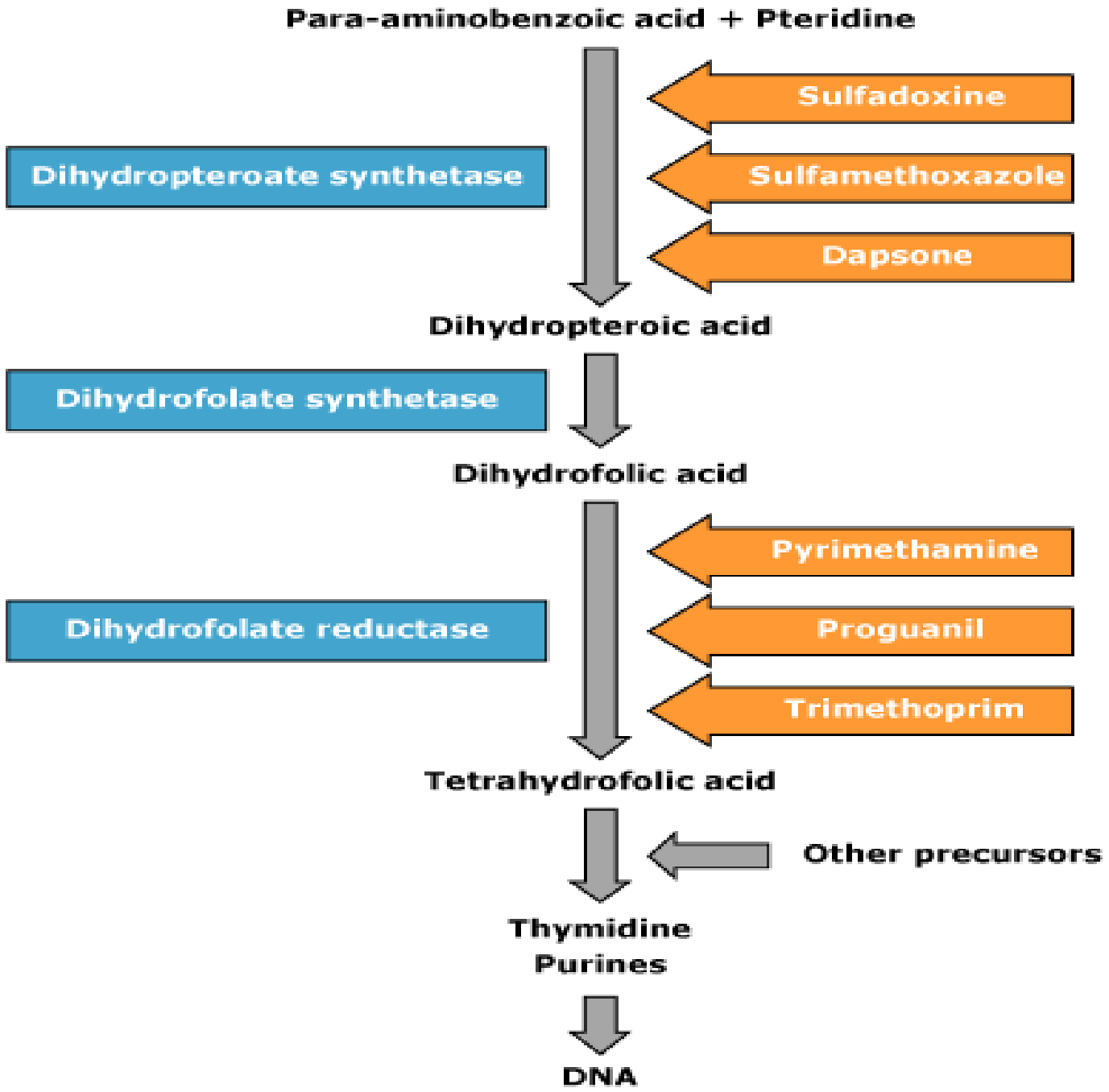
- Combination should be taken with milk or food to enhance absorption

- Shorter period of treatment (21 days) than mefloquine and doxycycline but is more expensive

ANTIFOLATE DRUGS

- **Pyrimethamine**
- **Sulfadoxine**
- **Proguanil**
- **Dapsone**

Mechanism of action of antifolates



PYRIMETHAMINE

- Pyrimethamine is related to trimethoprim
- Slow acting blood schizonticide
- Selectively inhibit plasmodial dihydrofolate reductase
- Adequately absorbed – given orally
- Given once weekly
- Pyrimethamine + Sulfadoxine (FANSIDAR)
- Sulfonamides are weakly active so not used alone
- Resistance & toxicity
- **USES**
- **Chemoprophylaxis**
- **Chloroquine Resistant Falciparum Malaria**
- Used in combination only

PYRIMETHAMINE

- **Adverse Effects & Contraindications**
- Well tolerated
- Severe cutaneous reactions – Fansidar
- Agranulocytosis with maloprim (pyrimethamine + dapsone)
- Caution in hepatic & renal disease

HALOFANTRINE & LUMEFANTRINE

- **HALOFANTRINE**
- Effective against erythrocytic stages of all four species
- Cardiac toxicity
- **LUMEFANTRINE**
- Available only with Artemether (COARTEM) – Uncomplicated F. Malaria

ANTIBIOTICS

- **TETRACYCLINE**
- **DOXYCYCLINE**
- Active against erythrocytic schizonts
- Not used alone – slower action
- Used in combination with quinine allowing shorter and better tolerated course of quinine
- Chemoprophylaxis
- **CLINDAMYCIN**
- Slowly acting against erythrocytic schizonts
- After treatment course when doxycycline cannot be given
- **AZITHROMYCIN**
- Under study as an alternative chemoprophylactic drug

Spiral integration – Community medicine

Drug resistant malaria

- Definition:
  - Ability of the parasite species to survive and/or multiply despite the administration and absorption of a drug given in doses equal to or higher than those usually recommended
- MDR Malaria:
  - Resistance to 3 or more antimalarials of different chemical classes of which two are 4-aminoquinolines and diaminopyridine

Treatment of drug-resistant malaria-new policy

- This strategy is based on use of combination therapy based on artemisinin derivatives offers hope to preserving the efficacy of antimalaria drugs and prolonging their useful therapeutic.

1. Artemether+Sulfadoxine/pyrimethamine (1st line)
2. Artesunate +lumefantrine(2nd line)
3. Quinine (3rd line as well a the drug of choice for treatment of severe malaria)

WHO TREATMENT GUIDELINES

IN VIVAX → **Resistance** → ACT / 3 days
followed by Primaquine for 14 days

Sensitive

Chloroquine for 3 days
followed by Primaquine for 14 days

IN FALCIPARUM → **All show Resistance**

Uncomplicated → ACT

Complicated → IV Artisunate for 24 hrs
Followed by; ACT
Or Artemether + [Clindamycin / doxycyline]
Or Quinine + [Clindamycin / doxycyline]

The Four Key Principles of Bioethics

Non-Maleficence

"Do no harm." Minimize any possible risks to the patient.

Autonomy

The patient family retains the right to make treatment decisions with all relevant information presented to them.

Beneficence

The overall needs of the individual must be taken into account with the benefits balanced against the risks.

Justice

Access to treatment and care should be fair and equitable.

How To Access Digital Library

- Steps to Access HEC Digital Library

1. Go to the website of HEC National Digital Library.
2. On Home Page, click on the INSTITUTES.
3. A page will appear showing the universities from Public and Private Sector and other Institutes which have access to HEC National Digital Library HNDL.
4. Select your desired Institute.
5. A page will appear showing the resources of the institution
6. Journals and Researches will appear
7. You can find a Journal by clicking on JOURNALS AND DATABASE and enter a keyword to search for your desired journal.

Thank you