

Chemotherapy of Malaria

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Malaria

Malaria: a protozoal disease transmitted by the bite of infected female Anopheles mosquito, bit infrequently by infected blood transfusion and congenitally.

Site of infection : Liver parenchymal cell and RBC.

Fundamentally the clinical manifestations are results of mechanical events followed by biochemical changes triggered by immunological mediators

CAUSATIVE ORGANISMS

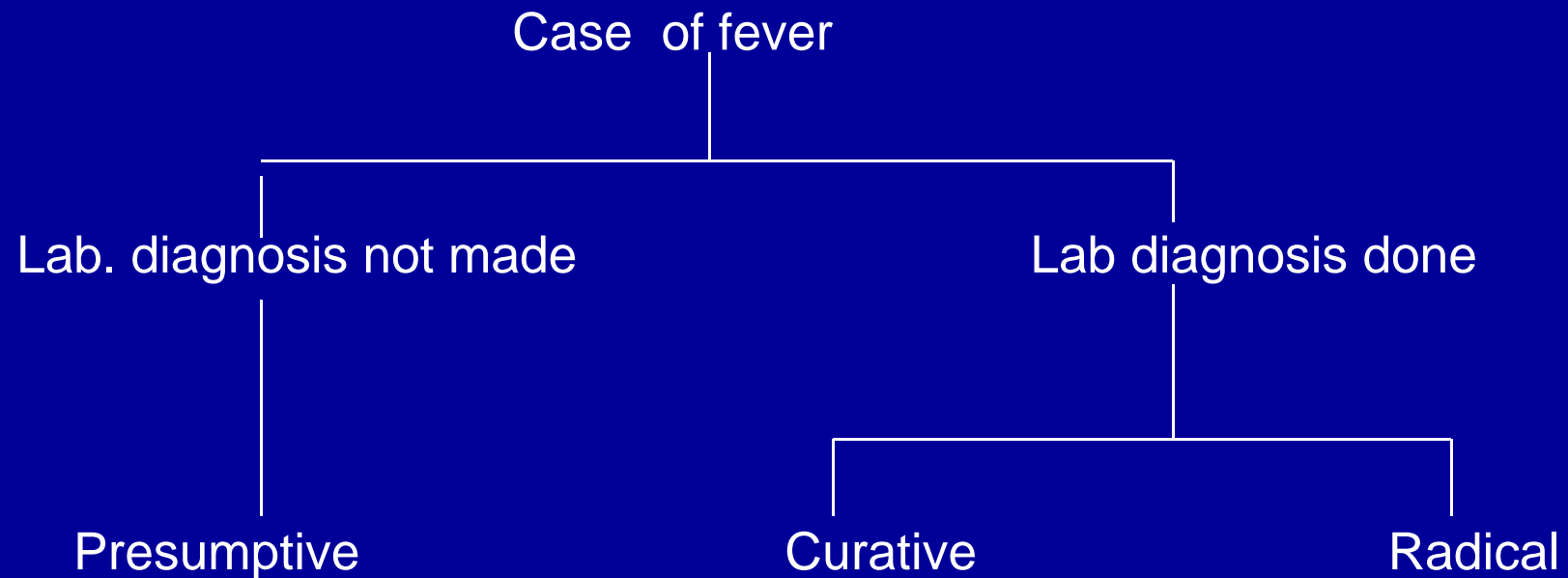
Malaria in man : causative agents

- i. *P. vivax*
- ii. *P. Falciparum*
- iii. *P. malariae*
- iv. *P. ovale*

CHEMOTHERAPY

- 1 Chloroquine sensitive uncomplicated malaria**
- 2 Chloroquine resistant uncomplicated malaria**
- 3 Complicated or severe malaria**
- 4 Treatment of Recrudescence**
- 5 Chemoprophylaxis**

Chemotherapy principle



Presumptive treatment: A case of fever treated for malaria without parasitological diagnosis with an aim to prevent death due to delay in treatment.

Radical treatment: Therapy after parasitological confirmation to eliminate all the forms of the parasite from all possible host tissue is known as Radical Treatment.

Treatment objectives

A. In uncomplicated malaria

- The objective of treating uncomplicated malaria is to **cure the infection** i.e. eradication of the parasites.
- This is important, as it helps to prevent progression to severe disease and prevent additional morbidity associated with treatment failure.

B. In severe malaria

- The primary objective of anti malarial treatment in severe malaria is **to prevent death**.

Management of malaria

Management options

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graph TD; A[Management options] --> B[Uncomplicated]; A --> C[Complicated]; B --> D["P. vivax/ P. Falciparum"]; C --> E["P. Falciparum"]; D --> F["Chloroquine<br/>Sulphadoxine/Pyrimethamine<br/>Mefloquine<br/>Oral Artemisinin derivatives<br/>Oral Quinine"]; E --> G["Inj. Artemisinin derivatives<br/>Inj. Quinine"]; F --> H["Prevention of relapse in<br/>Vivex- Primaquine"]; G --> H;
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Uncomplicated

P. vivax/ P. Falciparum

- Chloroquine
- Sulphadoxine/Pyrimethamine
- Mefloquine
- Oral Artemisinin derivatives
- Oral Quinine

Complicated

P. Falciparum

- Inj. Artemisinin derivatives
- Inj. Quinine

**Prevention of relapse in
Vivex- Primaquine**

Stage wise action of drugs

Parasite/stage		CQ	SDP	QS	MEF Q	ART	PQ
<i>P.falci parum</i>	Asexual	+	+	+	+	+	Nil
	Sexual	Nil	Nil	Nil	Nil	+/-	+
P. vivax	Asexual	+	+/-	+	+	+	Nil
	Sexual	+	Nil	+	+	+	+
	Hypnozoite	Nil	Nil	Nil	Nil	Nil	+

1 Chloroquine sensitive uncomplicated Malaria

A. Chloroquine

Treatment of uncomplicated CQ sensitive malaria : any species

Dose :

CQ base 25 mg/kg (total dose)

- 10mg stat,5mg/kg at 12h,24h,36h

- 10mg stat,10mg/kg at 24h,5mg/kg at 48h

Toxicity:

GIT – unpleasant taste, N/V, diarrhea,

Pruritis

CNS – convulsion, mental changes

Keratopathy,retinopathy – Chronic use (Rheutoid arthritis,prolonged prophylaxis)

Acute overdose: extremely dangerous, death within few hours

(visual disturbances,convulsion,hypokalaemia,hypotension,cardiac arrest)

Uncommon : myopathy, reduced hearing,alopecia,photosensitivity,aplastic anemia

Drug interactions:

Risk of arrhythmia : with halofantrine

,, “ convulsion: with mefloquine

,, ,, acute dystonic reaction: with metronidazole

Decreased bioavailability of Ampicillin , praziquental

Reduced therapeutic effect of Thyroxin

Antagonistic effect on anti epileptic : CMZ,sod valproate

Increased plasma conc of Cyclosporine

B. Primaquine

For prevention of relapse in *P.vivax*

Dose : 0.25 mg/ kg once daily after food for 14 days

Toxicity :

- * Hemolytic anemia – G6PD def, hemoglobinopathy, defective erythrocytic pentose phosphate pathway
- * abdominal pain – empty stomach
- * Larger doses – Nausea, vomiting, methaemoglobinemia, leukopenia, agranulocytosis

Drug interactions:

avoid drugs that may cause BM suppression

Contraindications :

- * G-6-PD deficiency
 - mild - moderate: 0.75mg/kg once a week x 6 weeks
 - severe : avoid Primaquine
- * Pregnancy
- * Lactation
- * Infants

c. Treatment of uncomplicated malaria
For prevention of transmission in *P. Falciparum*
(Gametocyte stage)

Primaquine : 0.75 mg/ kg(45mg) , single dose after food on day 1 or 2

Contraindications :

G-6-PD deficiency

Pregnancy

Lactation

Infants

2 Chloroquine **resistant uncomplicated** Malaria

Resistant Malaria

[Drug resistance]

R1 (Low grade)	Recrudescence of infection (i.e. reappearance of malaria) between 7 and 28 days of completing treatment following initial resolution of symptoms and parasite clearance.
R2 (High grade)	Reduction of parasitaemia by >75% at 48 hours, but failure to clear parasites within the 7 days.
R3	Parasitaemia does not fall below >75% within 48 hours.

Chemotherapy of **uncomplicated** but **Chloroquine resistant** *P.falciparum* malaria

A. SDP

B. Quinine sulphate

C. Quinine sulphate + Tetra or Doxy

D. Mefloquine

E. Artemisinin compound

i. Artesunate

ii. Artemether

F. Artemisinin combined therapy (ACT)

i. Artesunate + SDP

ii. Artesunate + Mefloquine

iii. Arthemeter + Lumefentrine

iv. Artesunate + Amodiaquin

A. SDP

Dose:

Single dose (2- 3 tab stat)

Sulf : 25mg/kg

Primeth. 1.25 mg/kg

Side effects:

a.Sulfadoxine

*Cutaneous :pruritis,photosensitivity,exfoliative dermatitis,EN,TEN
Steven Johnson syndrome

* Nausea,vomiting,anorexia,diarrhoea

* Crystalluria

* Blood disorders :

agranulocytosis,aplasticanemia,thrombocytopenia,leucopenia
hypoprothrombinemia, Acute hemolytic anemia (rarely)

*Generalized hypersensitivity reaction:

fever, interstitial nephritis, hepatitis,myocarditis,pul eosinophilia,
fibrosing alveolitis, P/Neuritis, systemic vasculitis (PAN)

*Others : Hypoglycemia, jaundice in neonate,aseptic meningitis,
drowsiness, fatigue, headach,ataxia, dizziness, convulsion,
psycosis,pseudomembranous colitis

b.Pyrimethamine: well tolerated

Suppression of hemopoiesis,skin rash, GIT disturbances,CNS stimulation,
Resp & circulated collapse - overdose

A. SDP cont..

Drug interactions (pyrimethamine)

Avoid with folate antagonist

*Cotrimoxazole

*Trimethoprim

*Methotrexate

*Phenytoin

With Benzodiazepines : risk of hepatotoxicity

B. Quinine

Dose : 10mg/kg/dose x 7-10 days

Side effects: * Cinchonism –

a mild : tinnitus, impaired high tone hearing, headache, nausea, dizziness, dysphoria, disturbed vision

b severe: vomiting, abdominal pain, diarrhoea, severe vertigo

* Hypersensitivity – urticaria, bronchospasm, fever, flushing of skin, thrombocytopenia, hemolytic anemia, HUS, Black water fever

* Hypoglycemia

* Cardio toxicity – Hypotension & cardiac arrest – **rapid IV infusion**
arrhythmia, angina, widening of QT interval

Drug interactions

* Avoid drugs that increase QT interval:

a Antiarrhythmic: amiodarone, flecainide

b. antihistamines : terfenadine

c. antimalarial : halofantrine

* Quinine increases plasma conc of Digoxin

* Rifampicin – increases metabolic clearance – therapeutic failure

* Cimetidine inhibits quinine meta – increased Quinine level

C. Mefloquine

Dose : 15 – 25mg/kg
(for 50kg at 25mg/kg – 1250mg = 5 tabs of 250mg)

Dosing patterns:

- A 8.3mg/kg daily for 3 days (1tab BID for 3 Days)
- B 25mg/kg stat (5 tab stat)
- C 15mg/kg on 1st day & 10mg/kg on next day (3tab stat,2tab next day)

Side effects:

Nausea,dizziness,dysphoria,sleep disturbances,neuropsychiatric symptom,
Cardiac : bradycardia,postural hypotension (rarely hypertension, tachycardia)

Contra indication:

h/o epilepsy,psychosis,risk of pregnancy within three months of last dose

Drug interactions:

- *should not be given with halofantrine
- *increased risk of arrhythmia – Beta blocker,amiodarone,CCB,digoxin,antidepressant
- *increased risk of convulsion – Chloroquine, quinine
- *increased mefloquine level – Ampicillin, tetracycline, metoclopramide
- * caution with alcohol

D. Oral Artemisinin

ARTESUNATE TAB(50mg)

Day 1 = 4mg/kg

Day 2 – 5/7 = 2mg/kg/day

ARTHEMETER CAP (40MG)

D1 = 160mg Orally in div doses (3.2mg/kg)

D 2-5/7 = 80mg OD (1.6mg/kg)

Side effects:

Hypersensitivity reaction

GI disturbances, dizziness, tinnitus, neutropenia, reticulocytopenia, inc SGOT/SGPT

Cardiac: bradycardia, prolonged QT interval

Neurotoxicity – high dose IM artemether

Contra indication:

Pregnancy (1st and 2nd trimester)

Drug interactions: not known

*Excellent gametocidal effect : Primaquine (45mg) not to be given in those receiving Artesunate

E. ACT

Artemisinin- based combination therapy

WHO statement (2006)

- WHO has endorsed **ACT** as **first-line treatment for acute uncomplicated malaria**, where the potentially life-threatening parasite *P. falciparum* is the predominant infecting species.



ACT: Artemisinin- based combination therapy

WHO Initiative

Artemether/lumefantrine

Artesunate + amodiaquine

Artesunate + SP

Artesunate + mefloquine

**WHO Technical Consultation on
“Antimalarial Combination Therapy” – April 2001**

ACT (Artesunate + SDP)

Age	Anti Malarial Drug	1st Day No of tabs	2 nd Day No of tabs	3 rd Day
< 1 yr	AS SDP	$\frac{1}{2}$ $\frac{1}{4}$	$\frac{1}{2}$ Nil	$\frac{1}{2}$ Nil
1 – 4 Yrs	AS SDP	1 1	1 Nil	1 Nil
5 – 8 Yrs	AS SDP	2 $1\frac{1}{2}$	2 Nil	2 Nil
9 – 14 yrs	AS SDP	3 2	3 Nil	3 Nil
15 & above	AS SDP	4 3	4 Nil	4 Nil

ACT (Artesunate + Mefloquine)

A

	Day 1	Day 2	Day 3
Artesunate (50mg)	Morn -2 Even - 2	Morn - 2 Morn - 2	Morn - 2 Morn - 2
Mefloquine (250mg)	Morn - 1 Morn - 1	Morn - 1 Morn - 1	Morn - 1 Morn - 1

B

	Day 1	Day 2	Day 3
Artesunate(50mg)	4tabs Single dose	4tabs Single dose	4 tabs Single dose
Mefloquine(250mg)		15mg/kg (3tab)	10mg/kg (2tab)

Mefloquine Dose : for 50kg at 25mg/kg – 1250mg = 5 tabs of 250mg

A 8.3mg/kg daily for 3 days (1tab BID for 3 Days)

B 25mg/kg stat (5 tab stat)

C 15mg/kg on 2nd day & 10mg/kg on next day (3tab stat,2tab next day)

ACT

(ARTHEMETER(20mg) +LUMEFENTRIN(120mg))

	0 hrs	8 hrs	Morning	Evening	Morning	Evening
5 to less than 15 kg	1	1	1	1	1	1
15 to less than 25 kg	2	2	2	2	2	2
25 to less than 35 kg	3	3	3	3	3	3
Adults & children 35 kg & above	4	4	4	4	4	4

Avoid : (for Lumefantrine)

Grape juice

Antiarrhythmic: amiodarone, disopramide, flecainide, procainamide, quinidine

Antibiotics : macrolides

Antifungal : imidazoles, triazole

Antipsychotics, Beta blockers

Antibiotics in Malaria

Antibiotic with antimalarial action

Weak Schizonticidal, synergistic effect with antimalarial

Sulphonamide

Pyrimethamine

Trimetoprim

Tetracycline [4mg/kg qid]

Doxycycline [3.5mg/kg od]

Clindamycin [10mg/kg bid] safe in children & pregnant lady

Macrolide (Azithromycin)

Rifampicin

Chloramphenicol

Fluoroquinolones(cipro, oflox, norf)

Antibiotic with Gr –ve activity

Cephalosporins(3rd & 4th generation)

3 Chemotherapy of severe & complicated malaria

1. Artemisinin derivatives

- a Artesunate IV/IM: 2.4mg /kg stat, 2.4mg/kg 12 hr later [WHO Revised Dose Guideline]
2.4mg/kg 24 hr later, then 2.4mg/kg daily x 2-4 days
- b. Arthemeter IM: 3.2mg/kg in 2 divided doses – 1st day
1.6mg/kg daily – 2 – 7 days
- c. Arthe ether IM: 150mg OD x 3 days (3mg/kg/dose), max up to 5 days

2. Quinine Inj

Loading Dose : 20mg/kg, 10mg/kg 8hourly (infuse over 4hr)
infusion rate should not exceed 5mg/kg/hr
Dose to be reduced to 1/3rd – 1/2th (5-7mg/kg)
if infusion is given > 48/72 hours
[IM : Anterior thigh, dose to be divided between two sites
Dilute in NS – 60mg/ml concentration]

3. Chloroquine inj

Infusion : 5mg/kg in Isotonic over 6hrs – repeat 6Hrly = 5 Doses
10mg/kg in Isotonic over 8Hrs, f/b 15mg/kg over next 24Hrs
IM/SC: 3.5mg/kg every 6Hr (Total dose = 25mg/kg) , a total of 7 doses

4 Treatment of **recrudescent** Falciparum

Treatment of recrudescence Falciparum

Recrudescence following	Treat with
Chloroquine	a . SDP b . Artesunate + mefloquine
SDP	Artesunate + mefloquine
Mefloquine +/- Artesunate	a . Quinine + Doxy/ clinda b . Artesunate + Doxy/ clinda

5 Chemoprophylaxis

Chemoprophylaxis

Chloroquine sensitive areas

CQ : 10mg/kg loading dose f/b 5mg/kg weekly dose

Chloroquine resistant areas

a.CQ + proguanil : weekly CQ + daily 200mg of proguanil

b.Mefloquine : 250mg weekly

c.Doxycycline; 100MG daily

- start chemoprophylaxis one week before arriving ,2nd trimester in pregnancy
- continue till one month after return from endemic area or one month after delivery
- Mefloquine : start CP 3wks before arriving,avoid in those planning to conceive within 3 months of the last dose

Excerpts of National Drug Policy 2008 on Malaria

- Microscopically +ve PF : treat with CQ in therapeutic dose 25mg/kg over 3 days, Primaquine 0.75mg/kg on the first day (CQ with Primaquine Blister pack)
- Microscopically +ve PV : treat with CQ in full therapeutic dose 25mg/kg over 3 days, with Primaquine – 0.25mg/kg daily for 14 days under supervision
- If RDK for only PF is used and found –ve: treat the case as clinical malaria with full dose of CQ
- In place without microscopy & RDK facilities: treat as clinical malaria with full dose CQ over 3 days in low risk areas & with Primaquine 0.75mg/kg on 1st day in high risk areas
- ACT is the first line of anti malaria for Rx of P.Falciparum in CQ resistant areas (Artesunate 4mg/kg OD x 3 days + SDP; SD=25mg/kg,P=1.25mg/kg on 1st day) Artesunate with Primaquine Blister pack
- ACT should be given only to confirmed PF by microscopy or RDK
- Suspect RESISTANCE if inspite of full treatment with no h/o vomiting,diarrhoea patient does not respond within 72 hrs parasitologically – treat with ACT
- Cases resistant to CQ &ACT : oral quinine with Tetracycline/ Doxycycline should be given
- Mefloquine – should only be given to CQ & multi Drug resistant (ACT, Quinine) cases
- Primaquine is C/I pregnant woman and infants

Thankx