

Malaria Chemotherapy and Drug Resistance

Uses of Anti-malarials

1. **Causal prophylaxis**
To prevent infection from establishing by acting on the tissue stages.
2. **Suppressive prophylaxis**
To prevent an established infection from manifesting itself clinically by using blood schizontocides.
3. **Treatment therapy (or clinical cure)**
To treat an acute attack of malaria in order to relieve the symptoms, to eliminate asexual stages of the parasite, or to completely eliminate the parasites.
4. **Curative therapy (or radical cure)**
To eliminate parasites, whether or not they are causing symptoms.
5. **Anti-relapse treatment**
To eliminate the persisting liver forms (hypnozoites) of the parasite.

Selected Antimalarials

Drug Action	Drugs
Fast-acting blood schizontocide	chloroquine (+ other 4-aminoquinolines), quinine, quinidine, mefloquine, halofantrine, antifolates (pyrimethamine, proquanil, sulfadoxine, dapsone), artemisinin derivatives (quinhaosu)
Slow-acting blood schizontocide	doxycycline (other tetracycline antibiotics)
Blood + mild tissue schizontocide	proquanil, pyrimethamine, tetracyclines
Anti-relapsing	primaquine
Gametocidal	primaquine, 4-aminoquinolines (limited?)
Combinations	Fansidar (pyrimethamine + sulfadoxine), Maloprim (pyrimethamine + dapsone), Malarone (atovaquone + proquanil)

Antimalarial Chemotherapy

- CQ-sensitive (all species)
 - ◆ chloroquine (+ primaquine for radical cure of vivax/ovale malaria)
- CQ-resistant *P. falciparum* (or unknown)
 - ◆ mefloquine, quinine, sulfonamide + pyrimethamine (= Fansidar), or artemisinin derivatives
- severe malaria
 - ◆ i.v. infusion of quinine or quinidine (or chloroquine if sensitive)
 - ◆ artemisinin derivatives (if available)

Chemoprophylaxis

- recommended for transient visits to endemic areas
- non-toxic drugs (eg, chloroquine, pyrimethamine, proguanil) are of limited use because of drug resistance
- presumptive ('standby') treatment often used in conjunction with prophylaxis
 - ◆ person carries Fansidar, mefloquine, or quinine

Mechanisms of Drug Resistance

- mutations in affected gene
- ↑ production of target
- ↓ drug accumulation (including ↑ efflux)
- drug inactivation

Spread of Drug Resistance

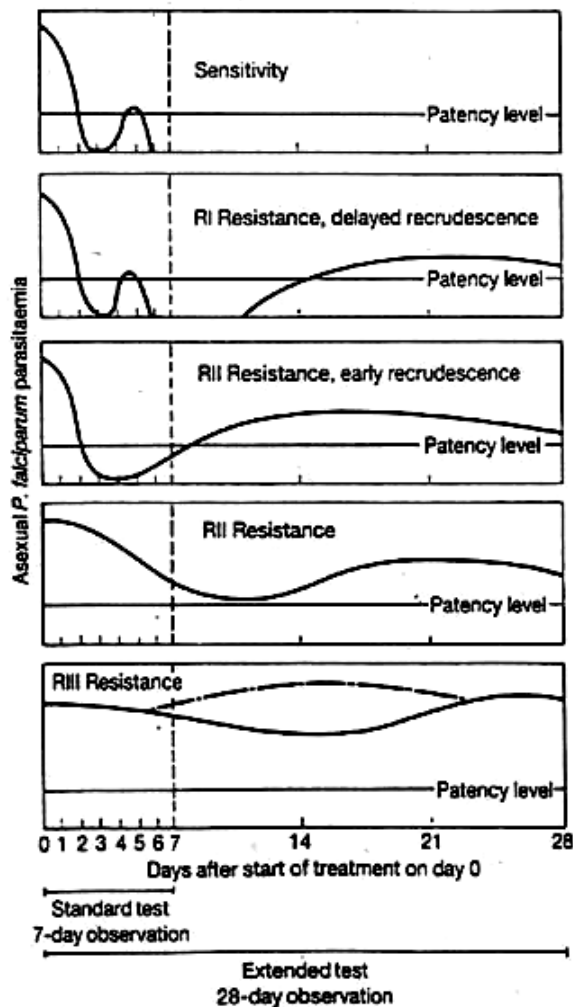
- self treatment
- poor compliance
- mass administration
- long drug half-life

Drug Resistance

- defined by treatment failures
- rule out other factors:
 - non-compliance
 - bad quality
 - wrong dose
 - vomiting
- 28-day or other tests (RI, RII, RIII levels of resistance)

Modified Protocol

- introduced by WHO in 1996
- more practical in areas of intense transmission
 - difficult to distinguish re-infection from recrudescence
 - parasitemia in the absence of clinical symptoms is common
- based on clinical outcome:
 - adequate clinical response (ACR)
 - late treatment failure (LTF)
 - early treatment failure (ETF)



- ACR absence of parasitemia (irrespective of fever) or absence of clinical symptoms (irrespective of parasitemia) on day 14 of follow-up
- LTF reappearance of symptoms in the presence of parasitemia during days 4-14 of follow-up
- ETF persistence of clinical symptoms in the presence of parasitemia during the first 3 days of follow-up