Malaria – Treatment

Malaria – Treatment 3
Specific anti-malaria drugs 3
Blood schizonticides 5
Antifolates 5
Antimitochondrial products 5
Redox reactions 6
Current treatment of malaria 6
Anti-malaria drugs 7
Drug resistance 20

Malaria – Treatment

Specific anti-malaria drugs

General

Most people are not very interested in the history of a particular medicine. Quinine, however, is rather different and occupies a special place. For 300 years this was the only specific treatment for malaria. The story of its discovery, the important part which quinine has played in the colonization of the tropics, its role in both World Wars and during the Vietnam war, and the present come-back of this product all make it unique. At present quinine and related products are used in the treatment of *P. falciparum* malaria, as an antiarrhythmic, as a muscle relaxant and as a flavouring (Schweppes!)[1]. There are also some minor applications such as the treatment of babesiosis. Quinine is obtained from the bark of Cinchona trees.

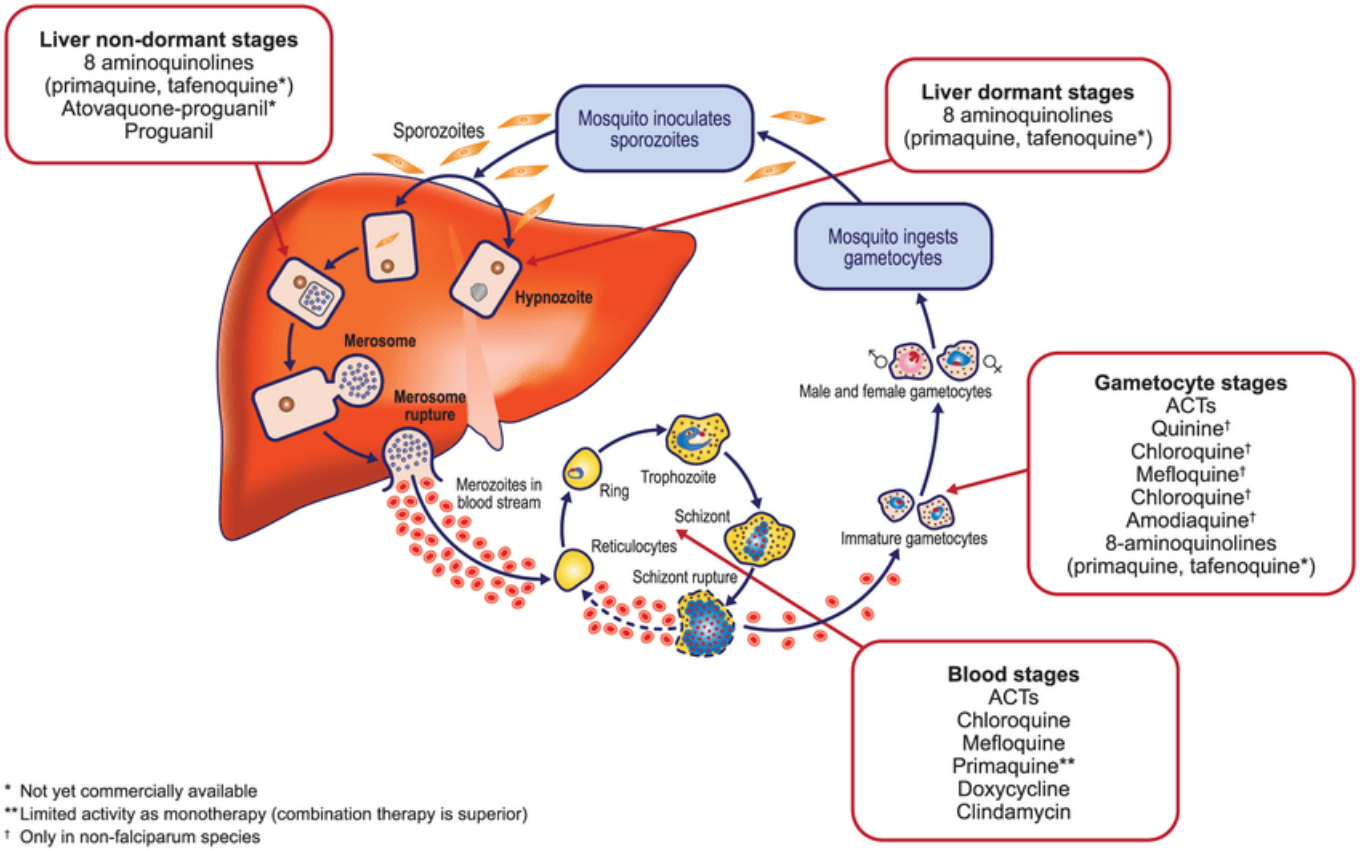
In 1934 resoquine was discovered by the German H. Andersag. Only after the allies took North Africa there was renewed interest in the product. It was renamed chloroquine. Preparation in the laboratory was also economically viable. It quickly became the first choice agent and quinine was pushed into the background. In 1950 in Brazil, Mario Pinotti introduced the strategy of adding chloroquine to cooking salt (as was also done with iodine).

The synthetic preparation of primaquine was perfected after the war. The British war programme led to the development of proguanil, which itself served as a model for the development of pyrimethamine. Pyrimethamine in combination with sulphadoxine was introduced in 1970 under the name Fansidar®. After World War II it was hoped that malaria would be definitively eradicated. The use of chloroquine and the world-wide campaign to eradicate malaria by the World Health Organization, led initially to a considerable reduction in malaria infections all over the world. After the anti-malaria campaign vanished due to various circumstances, the resistance of *Anopheles* to various insecticides and the development of chloroquine-resistant and multi-resistant *P. falciparum*, malaria once more became one of the major problems.

Whereas World War II led to the discovery of some new anti-malaria agents, the Vietnam war stimulated a huge programme for the discovery of new drugs. The Walter Reed Army Institute of Research of the United States army investigated thousands of constituents. This research resulted in

mefloquine (Lariam®) and halofantrine (Halfan®). Research in China produced artemisinin, pyronaridine and benflumetol.

Treatment overview



P. vivax life cycle and site of action for different antimalarials. Source: Quique Bassat, PLoS Neglected Tropical Diseases 5(12):e1325, dec 2011

Broadly speaking, anti-malaria drugs can be divided into four major classes

- Blood schizonticides
- Antifolates
- Antimitochondrials
- Redox process-based agents

Blood schizonticides

When the malaria parasite leaves the liver and penetrates an erythrocyte, it can begin a haemoglobin diet. Chloroquine, quinine, mefloquine and halofantrine interfere with the detoxification of haemin in the digestive vacuole of the parasite, so that haemin can generate free radicals and parasitic membrane damage follows. It is therefore logical that the drugs are not active against the parasitic stages which precede the blood forms (sporozoites, liver forms) and which do not consume haemoglobin.

Antifolates

Folic acid is an important metabolic factor. Humans obtain this vitamin from the food they eat. The malaria parasite must produce it for itself. Para-aminobenzoic acid (PABA) is used at an early stage of the biosynthesis of folic acid by the enzyme dihydropteroate synthetase. This step is inhibited by structural analogues of PABA, such as sulphonamides and sulphones, e.g. sulphanilamide, sulphadoxine and dapsone.

The next synthesis step is catalysed by dihydrofolate reductase. This step is prevented by pyrimethamine, trimethoprim and cycloguanil (prodrug = proguanil), to such an extent that tetrahydrofolate – the end product – is not formed. The combination of these two sequential inhibitors forms the basis of Fansidar® (similar to cotrimoxazole). Resistance to both antifolates easily develops. A specific point mutation in each gene (dhps and dhfr) is sufficient.

Antimitochondrial products

Although artemisinin derivatives and 8-aminoquinolines (primaquine and tafenoquine) cause mitochondrial swelling, this organelle is not their chief target. Some antibiotics such as tetracycline and clindamycin prevent protein synthesis by mitochondrial ribosomes (these are similar to the ribosomes found in bacteria). They are slow-acting.

Atovaquone is a naphthoquinone which specifically destroys the electron transport chains of Apicomplexa. The molecule is similar to ubiquinone (coenzyme Q) which plays a role in the energy transfer between cytochrome B and C1. The enzymes of *Plasmodium falciparum* are 1000 times more sensitive to atovaquone than the corresponding enzymes in humans. Resistance can easily develop if used in monotherapy.

Redox reactions

Primaquine and tafenoquine exercise their action via redox-active quinone metabolites. They are selectively toxic for the pre-erythrocytic stages and are the only medicaments which kill hypnozoites. Tafenoquine has in addition a pronounced blood schizonticidal action.

Current treatment of malaria

A summary of the WHO recommendations in 2020 is provided first in these notes for clarity. For detailed dosages and special groups, see additional information in “Guidelines for the treatment of malaria: WHO; third edition, 2015.

All drugs used currently or in the recent past are described in detail below the summary.

- Complicated malaria (whatever the species, and also in all risk groups)
  - First choice: Artesunate IV (2.4 mg/kg in adults and children > 20 kg; 3 mg/kg in children < 20 kg)
  - Second choice (only if artesunate not available): quinine IV (see dosage below)
- Uncomplicated malaria (whatever the species)
  - Artemisinin-based combination treatment (ACT); five ACTs are currently accepted; all are in fixed-dose combination (FDC) nowadays and consist of 3-day regimen:
    - Artemether-lumefantrine
    - Artesunate-amodiaquine
    - Artesunate-mefloquine
    - Artenimol (dihydroartemisinin)-piperaquine
    - Artesunate + sulfadoxine-pyrimethamine (SP)

NB1: In low-endemic countries, a single dose of primaquine (0.25 mg/kg) should be added at the end of the ACT to decrease transmission (no need of G6PD determination)

NB2 : Chloroquine (see dosage below) is a good alternative for uncomplicated *P. vivax*, *P. ovale*, *P. malariae* and *P. knowlesi* in areas where no resistance is reported

NB3 : Primaquine (30 mg/day for 14 days) should be administered in case of *P. vivax* and *P. ovale* infections, after determination of the G6PD activity (alternative regimens available in case of low activity)

Anti-malaria drugs

Qinghaosu and Artemisinin derivatives


© CD-ROM ILLUSTRATED LECTURE NOTES ON TROPICAL MEDICINE

Artemisia annua in Vietnam. This plant is harvested in order to extract artemisinin from the leaves. Copyright Charles Lugt (with special thanks to prof Kager).

Artemisia annua in Vietnam. This plant is harvested in order to extract artemisinin, used for malaria treatment. Copyright Charles Lugt (with special thanks to prof Kager).

Artemisinin and its derivatives have become essential components of antimalarial treatment. ACTs are now recommended by WHO as the first-line treatment for all falciparum malaria in malaria endemic countries. These plant-derived peroxides are unique among antimalarial drugs in **killing the young intra-erythrocytic malaria parasites**, thereby preventing the more pathogenic mature stages. Huang hua hao or qinghaosu ("essence of qinghao") originates from a Chinese plant, Artemisia annua (sweet wormwood). The antimalarial properties of the traditional Chinese medicine qinghaosu were discovered and developed by Chinese scientists in 1971 (secret "project 523"). This research effort was prompted by the requests of Ho Chi Minh to Zhou En Lai for antimalarial drugs for the Vietnamese troops (cfr the efforts of the American forces to develop halofantrin and

mefloquin).

Artemisinin has the derivatives artesunate (the hemisuccinate; -CO(CH2)2COOH), arteether (the ethyl ether; -OCH2CH3), artemether (the methyl ether; -OCH3) and the reduced substance artenimol, syn. for dihydroartemisinin. Their plasma half-life is very short: 1 hour, both in healthy volunteers and in patients with active malaria.

Artemisinins are not active upon liver stages, but upon both the immature sexual and the all asexual blood stages. Their broad stage specificity (as opposed to quinine) has several therapeutic consequences. Killing young circulating ring-shaped trophozoites results in a more rapid reduction in parasitaemia as compared to other antimalarials and reduces the number of parasites that mature and sequester in the post-capillary venules. Quinine does not stop sequestration since it acts on the mature parasite stages, which have already adhered to the vascular endothelium. Since artemisinin reduces the number of gametocyte carriers, it helps to prevent malaria transmission, although artemisinin does not kill mature gametocytes of *P. falciparum*. In low-transmission areas, where symptomatic infection constitutes the main source of transmission, ACTs reduce gametocyte carrier rate, and if widely employed is expected to reduce the incidence of malaria. Artemether, artesunate and dihydroartemisinin reduce the number of parasites by a factor of approximately 10,000 for each asexual cycle. After two cycles (3-day treatment) there is a 10^8-fold reduction of the parasitaemia. The longer acting partner drug will then eliminate the remaining low numbers of parasites.

The medication is best avoided during the first trimester of pregnancy, if a good alternative is available (quinine + clindamycin). Recent large studies (PREGACT) have demonstrated the safety of ACT administered during the second and third trimesters on pregnancy and infant outcome. In observational studies of pregnant women treated with artemisinin derivatives during the first trimester, no differences were noticed in the risk of miscarriage, stillbirth or congenital anomalies when compared to quinine treatment. Although data are limited, the use of ACTs is probably safe throughout gestation, especially if alternatives are not available.

Artemether (Paluther®, Arteminth®, Cotexcin®, Artenam®) is an oil-soluble derivative that can be used for IM administration.

Artesunate (Artenam®, Artesunate®, Arsumax®, Artemax®, Arinate®, Plasmotrim®) is the fastest-acting artemisinin derivative. It can be administered parenterally (IV, IM), rectally or orally. For IV use the dose is 2.4 mg/kg as start dose. This dose is repeated at least after 12 hours and 24 hours. The side-effects are mild and are difficult to distinguish from the effects of malaria itself. However, delayed onset haemolytic anaemia has been observed in about 20% of travellers who receive

artesunate after about 2 weeks. This post-artesunate delayed haemolysis is also described in endemic countries. Haemoglobin monitoring 1 and 2 weeks after artesunate administration is strongly recommended for this reason, particularly after an episode of severe malaria.
There is now strong pharmacological and clinical evidence that artesunate is superior over quinine for treating severe malaria (35% reduction of fatalities in Asian adults and 22% reduction of fatalities in African children). If patients with severe malaria cannot be treated orally and transport to a hospital for IV therapy will take more than 6 hours, a single inexpensive artesunate suppository at the time of referral substantially reduces the risk of death or permanent disability. A single dose of artesunate, given rectally (by e.g. parent), can provide parasiticidal blood concentrations within 10–20 min and can already halve parasitaemia numbers within 6–12 h.

Artenimol (more commonly named dihydroartemisinin) is obtained by reduction (hydrogen addition) of artemisinin. Together with piperaquine it is available as a fixed drug combination known as Eurartesim®. Artenimol has a short half-life, as opposed to piperaquine which has a long half-life.

After a decade of use in monotherapy in Southeast Asian countries, it has become clear that monotherapy would quickly lead to resistance to artemisinin derivatives (5-10% recrudescence after 7 days of monotherapy). Since 2005, to protect this “last-line” drug, WHO has strongly recommended to systematically combine artemisinin with another, partner drug with a longer half-life to treat all falciparum malaria in endemic countries. “Accepted” partner drugs are amodiaquine, pyrimethamine/sulphadoxine, lumefantrine, piperaquine or mefloquine (see other drugs). New ACT compound are emerging such as pr

Artemisinins also have some activity against other parasites, for example they kill the young stages of trematodes such as schistosomes and Fasciola. They are studied also in animal models of clonorchiasis.

Lumefantrine or Benflumetol

Lumefantrine (= benflumetol) was registered in China in 1987 for the treatment of *P. falciparum* malaria. The half-life in the blood is approximately 4 days. The product is not active on the liver stages or gametocytes. Lumefantrine, like chloroquine, probably destroys heme polymerization (a detoxifying pathway for the parasite). It is synergistic with artemether. The combination artemether-lumefantrine is known as co-artemether (AL; Riamet®, Coartem®: artemether 20 mg/lumefantrine 120 mg, adult dose 2×4 tablets/d for 3 days). The combination artemether-lumefantrin is probably the most used ACT worldwide.

The possibility of drug-interaction and QTc-prolongation needs to be studied further, especially if this product would be used as stand-by medication in travellers to the tropics who also might take certain quinolones, azoles, macrolides or prokinetics (domperidone).

Absorption in the intestine is highly variable from person to person and is greatly increased (up to 16-fold) by fatty food. Since people who are ill generally do not eat much, this has important consequences. Early in the treatment very little lumefantrine is absorbed. In combinations, such as Co-artem, the artemether is responsible for the initial important reduction in the number of parasites and the low residual numbers of parasites is then cleared up by lumefantrine.

In HIV-infected children, lopinavir-ritonavir-based ART (Kaletra) was associated with a decreased incidence of recurrent malaria (reinfection) as compared to an NNRTI-based regimen, largely because of an interactions that increases drug levels of lumefantrine.

Piperaquine

Piperaquine is a Chinese synthetic drug belonging to the bisquinolines. Half-life of piperaquine is 9 days. Piperaquine is a highly lipid-soluble drug. The combination dihydroartemisinin (artenimol) 40 mg with piperaquine 320 mg per tablet (Artekin®, Eurartesim®, Duo-cotecxin®, adult dose: 1×4 tablets/day for 3 days) is increasingly used in first-line in many endemic countries.

In 2006 Papua New Guinea became the first country to implement dihydroartemisinin-piperaquine treatment for *P. falciparum* and *P. vivax* infection in pregnant women during the second and third trimesters as well as its first-line therapy for any case of malaria. Because of the slow elimination of piperaquine, this treatment provides up to 6 weeks posttreatment prophylaxis against new infections and relapsing *P. vivax* infection (better than all other ACTs). It is recommended in travel medicine to check first an ECG to exclude an underlying QTc prolongation in people with serious liver, kidney or heart diseases or in people taking other QTc prolongating medication (macrolides, fluoroquinolone, domperidone, …). It is contra-indicated if > 500 msec and to be used withcaution if QTc > 450 msec.

Amodiaquine

Amodiaquine is closely related to chloroquine. Long-term use causes grey skin pigmentation in white people. Sometimes there are severe side effects (agranulocytosis in approximately 1/2000, liver toxicity in approximately 1/15,000). Amodiaquine (Camoquine®, Flavoquine®, Malarid®) had been rarely used in monotherapy. There is therefore less resistance to amodiaquine than to chloroquine.

Since the product is eliminated slowly, a single dose of 600 mg was (and is) sufficient.

Amodiaquine is nowadays the partner drug of artesunate in one of the 5 recommended ACTs. This therapy exists now in fixed-drug combination (Coarsucam®, ASAQ: 100 mg artesunate/270 mg amodiaquine, adult dose: 1×2 tablets/d on 3 consecutive days) and because of its low price, has become the first-line ACT for P. falciparum in many African countries.

Mefloquine

Mefloquine (Lariam®) is a long-acting product. After 2 to 3 weeks half of the dose is still present in the body. Mefloquine has a rather slow onset of action. For curative use, mefloquine is always combined with other antimalarials, and its use in monotherapy for treatment is now strongly discouraged (major side effects, while effective alternatives exist). The combination mefloquine + pyrimethamine + sulphadoxine is known as Fansimef®. Now, mefloquine is used with artesunate in a fixed-drug combination and is one of the first-line therapies of Pf malaria in many countries: artesunate 100 mg/mefloquine 220 mg (ASMQ), 1×2 tables/d for 3 consecutive days (adult dose).

Mefloquine plays an important (although decreasing) role in prophylaxis: cfr. infra.

Quinine

Quinine has long been a first line anti-malarial drug and was for a long time one of the only parenteral treatment options. More recent studies however, showed clinical benefit of parenteral Artesunate and oral artemisinin combination treatment over quinine, together with less side effects. Quinine is still a powerful product, which acts upon the schizonts of the parasites in the blood (it is a schizonticide). It thus acts **chiefly in the second half of the maturation cycle**: on the parasites which are sequestered in the small blood vessels (not on the young ring forms in the peripheral circulation). Quinine also possesses gametocytocidal activity against *P. vivax, P. malariae* and *P. ovale* (but not against gametocytes of *P. falciparum*). As for chloroquine, quinine causes an inhibition of hemozoin biocrystallization in the heme detoxification pathway, which facilitates the aggregation of cytotoxic heme. Free cytotoxic heme accumulates in the parasites causing their deaths.

Quinine sulphate is administered orally. It is absorbed well in the intestines. Quinine bihydrochloride is injected, preferably by slow IV (infusion with glucose because of the risk of hypoglycaemia). IM injections may lead to sterile abscesses but can be used where necessary if there are no alternatives available. For IM injection, it is best to use a diluted solution (60 to 100 mg/ml) instead of the

concentrated solution (300 mg/ml). Quinine administered via IM injection is absorbed well even in severe malaria. Treatment with quinine is unpleasant (bitter taste, cinchonism) and poor compliance after the acute phase is common.

Treatment regimens

The basic regimen is 10 mg salt/kg, every 8 hours, orally or slow IV. Currently, a loading dose of 20 mg/kg IV over 4 to 8 hours is universally recommended for the first administration (followed by 10 mg/kg every 8 hours). This should be continued for at least 4 days, preferably 7 to 10 days (if used in monotherapy). This is an unpleasant treatment. Because there is still a risk of relapse if quinine is used in monotherapy even for > 7 days, another product is generally combined with it, e.g. tetracycline or clindamycin. This allows also to shorten the quinine administration to 4-5 days. Sometimes treatment with Fansidar® is given after a few days, which shortens the treatment period, but only in regions where this drug is still sufficiently effective. If a patient vomits within an hour after swallowing the medication, the whole dose should be repeated. If vomiting occurs longer than one hour after ingestion, no new dose is necessary. In case of repeated vomiting IV administration is required.

Side effects of quinine

Quinine is a substance with highly irritating properties (also for the gastric mucosa: nausea is not uncommon). Capsules are therefore best taken after a meal. Quinine increases the secretion of insulin from the pancreas, increasing the risk of hypoglycaemia. Quinine allergy is not common. What is common is a range of side effects such as tinnitus, temporary deafness for high frequencies, headache, nausea and palpitations. These toxic phenomena are known as cinchonism: quinine was first isolated from the bark of the cinchona tree. This reduces the patient’s compliance.

Quinine increases irritability of the pregnant uterus. In case of need one must not hesitate to use quinine in a pregnant woman with malaria (malaria itself can lead to abortion, preterm labour or death in utero). To prevent an impending premature labour, a tocolytic agent can be given such as the beta 2-mimetic ritodrine, fenoterol or salbutamol. The calcium antagonist nifedipine is as effective a tocolyticum as the beta-mimetics. Prolongation of the PR, QRS and QT intervals may occur during the use of quinine (as with quinidine). If the patient has atrial fibrillation, conversion to sinus rhythm may occur with possibly arterial embolic complications. Atrial fibrillation which has already been present for more than 48 hours is a contra-indication for quinine. Congenital long QT syndrome and Brugada syndrome are equally formal contra-indications for using quinine. ECG monitoring to detect

QTc-prolongation is recommended during quinine therapy, especially in case of kidney failure.

Overdose of quinine may lead to very severe situations such as deafness, delirium, bradycardia, hypotension, respiratory arrest or death (lethal dose approximately 8 gram). Overdose may also lead to blindness via a direct toxic effect on the retina and possibly also due to spasms of the retinal blood vessels and subsequent retinal ischemia.

Quinine and Gin Tonic

Unlike the majority of other bitter products which occur naturally, the bitter taste of quinine is short-acting with no annoying after-taste. It is therefore used as a flavouring to produce tonic water. The British colonialists in India often drank gin and tonic. The present-day tonic water contains approximately 15 mg per litre, however, only enough to give a bitter taste. Copious drinking of gin and tonic in order to prevent malaria, is thus only an excuse for drinking gin.

Why is quinine resistance still rare?

The product has been used for more than 360 years. This is in stark contrast to the resistance to other malaria drugs or antibiotic resistance in bacteria where the “useful life” of a product is measured in years or a few decades. The concept of a standard dose was only developed in the twentieth century. Earlier the duration of treatment and the dosage were left to the discretion of the doctor. This together with the fact that the concentrations of alkaloids varied greatly from plant to plant and that quinine was never pure, meant that malaria was treated with a therapy which must have produced the most varied blood levels. Yet no wide spread quinine resistance has been reported. The answer to the question why there is virtually no quinine resistance, could be very important. Is the target molecule of quinine so special that mutation is not possible? It would then be very helpful to know this target. It could also be that there is quinine resistance, but that it was not, and has not been recognized. However, this is doubtful. Is it that the present recommended dose is much higher than that which was formerly necessary? Is it the fact that “quinine” is actually a mixture of various active products, which prevents resistance developing? Resistance to combined therapy requires multiple, simultaneous mutations which is less readily achieved than that to single products. It is possible that quinine has not previously been used at levels which create sufficient evolutionary pressure. The majority of malaria cases in Europe and America were P. *vivax* infections. Even in British India, *P. vivax* represented the lion’s share of infections. In *P. falciparum* endemic regions, only a few fortunate people were able to take quinine and then only when they had to (because of unpleasant side effects). Few used quinine as a prophylactic agent

(especially among the indigenous population). What is more, quinine has a short half-life, so that the parasite was only exposed to subtherapeutic concentrations for a short time. Probably its limited use is the reason for the absence of resistance, but if used on a larger scale, quinine resistance may yet become a reality in years to come.

Chloroquine

Despite the presence of this resistance, chloroquine still has a place in treatment. It is still active against non-falciparum plasmodium species almost everywhere and could theoretically still be used against chloroquine-sensitive *P. falciparum* in very limited areas: Central America and the Caribbean. Elsewhere, chloroquine is not recommended any more against *P. falciparum* even in immune patients, who do not usually appear very ill.

The trophozoite in the red blood cell breaks down haemoglobin using lysosomal enzymes. In this digestive process ferriprotoporphyrin IX (haemin) is formed, which is toxic to the parasite and is usually polymerized to non-toxic malaria pigment. Chloroquine binds to ferriprotoporphyrin IX and prevents detoxification.

Since the liver parasite do not feed on haemoglobin this drug is not active at the pre-erythrocytic stages of *Plasmodium sp*.

Chloroquine is available in tablet form as chloroquine sulphate (Nivaquine®) and as chloroquine diphosphate (Resochine®). Hydroxychloroquine sulphate (Plaquenil®) is different and is used in e.g. rheumatoid arthritis, lupus erythematosus and Q-fever. The injectable form is chloroquine dihydrochloride. Nivaquine® tablets contain 100 mg chloroquine, but availability of this drug has decreased over the last years.

Chloroquine is a powerful schizonticide. It has strong affinity for various tissues and organs. It is fast-acting and remains in the blood for many days. A brief treatment (3 days) is therefore possible.

Chloroquine may be given orally, SC, IM or SLOW IV (infusion). Never inject an ampoule of chloroquine IV rapidly as a bolus or rapid infusion (fatal arrhythmia). The injections are not painful.

There are several different treatment regimens. Most of the time it is given orally, 25 mg/kg spread over three days. Parenteral administration should be discontinued as soon as oral administration is possible.

Chloroquine is cheap and not very toxic in normal use.

- Some people are allergic (pruritus, rash) or suffer nausea.
- People with psoriasis are more at risk of side effects.
- A reversible precipitation of chloroquine in the cornea may occur, resulting in small opacities. This may result in seeing haloes around objects, blurred vision or photophobia. This form of keratopathy may become manifest quite rapidly (a few weeks after beginning treatment). After discontinuing the medication it is completely reversible.
- Chloroquine accumulates in melanin-containing tissues. Chronic use may lead to abnormalities of the choroid and retina (chorioretinitis). This toxic retinopathy is not reversible. The abnormalities are always bilateral and symmetrical. Often there is maculopathy (bull's eye lesion) with central and paracentral scotomata, but constriction of the peripheral field of vision may also occur. The total cumulative dose before such problems occur is generally 100 gram chloroquine or more.
- Chloroquine has a narrow safety margin (just 30 mg/kg may be fatal). In case of overdosage myocardial depression, hypotension and severe arrhythmias may occur. ST-segment abnormalities and T-wave inversion occur. Broadening of the QRS complex (>0.12″) and ventricular arrhythmias have a poor prognosis. The patient may become comatose, vomit and aspirate stomach contents. In acute intoxication diazepam is given (Valium® 1 mg/kg) and adrenalin (= epinephrine) or dopamine if these are available.

Pyrimethamine + / – Sulphonamides

Fansidar® is a combination product of pyrimethamine 25 mg and sulphadoxine 500 mg per tablet (Mekalfin® is another commercial name). The curative treatment for an adult is 3 tablets taken as a single dose. Sulphadoxine is a long-acting sulphonamide (t½ = 8 days) which in case of allergy may cause severe skin lesions (erythema multiforme and Stevens-Johnson syndrome). *Plasmodium falciparum* has rapidly developed resistance to this product in many parts of the world. It is not used any more as monotherapy but may be combined to artesunate (at least in regions where no resistance has been observed): Sulfamon®, Artecospe adult® (AS+SP) = artesunate 100 mg + sulphadoxine/pyrimethamine 500/25 mg: 1×2 tablets AS/d for 3 days + 3 tablets SP single dose. This combined treatment is available in co-blister packs (this is not the same as coformulated tablets!). Fansidar is also widely used as intermittent preventive treatment for pregnant woman in Africa (either they present with blood parasite or not, once or twice during pregnancy) and still provide substantial benefit in preventing maternal and infant anaemia and low-weight birth (even in areas with increasing resistance). Though recent studies comparing dihydroartemisine-piperaquine (and other artemisinin-based combination therapies [ACTs]) vs pyrimethamine-sulphadoxine as intermittent preventive treatment during pregnancy (IPTp), showed that ACTs are usually superior in decreasing the malaria

burden during pregnancy. Use of ACT in IPTp is however not yet a WHO recommendation, pending results on the long-term risk of developing resistance.

Halofantrine (Halfan®)

This is fast-acting, effective and has few but potentially lethal side effects. Given a series of casualties, it is no longer used and production has been abandoned. It has been replaced by a similar but non-toxic product: lumefantrin. Halofantrin was very dangerous in people with a long QT interval: reportedly lumefantrin does not present the same toxicity, but this deadly experience with halofantrin makes clinicians very cautious, ordering always an ECG before treatment whenever possible and almost always in high income settings.

Primaquine

Primaquine is an 8-aminoquinoline. It is inactive upon asexual blood forms. It does have an important though only partial causal prophylactic effect (on both *P. falciparum* and *P. vivax*) but only if it is taken 24-48 hours (max. 96 hours) after inoculation with sporozoites. It acts upon the exo-erythrocytic stages of the parasites (liver schizonts). The half-life is relatively short (4 hours). For causal prophylactic use a daily dose of 15-30 mg may be taken. These regimens are not very popular and there has been little experience of them. Chemoprophylaxis with primaquine can be stopped 3 days after leaving a malarious area.

In cases of *P. vivax* or *P. ovale* malaria, hypnozoites remain in the liver after therapy with ACT or chloroquine/quinine. These may be destroyed by primaquine. In the past, 15 mg base per day was used for 14 days [26 mg primaquine biphosphate = 15 mg primaquine base], but current medical opinion favours 30 mg per day for 2 weeks (increasing tolerance of some P. vivax strains). This drug is contra-indicated in pregnant women and in people with a significant deficiency of G6PD (glucose-6-phosphate dehydrogenase), an enzyme in the red blood cells (risk of haemolysis in patient and/or fetus).

Primaquine also acts on *P. falciparum* gametocytes. Therefore, in some circumstances (e.g. refugee camps) it may be given to reduce transmission (single dose of 45 mg). It is nowadays thoroughly investigated (in low dosage) as a potential strategy to decrease/suppress transmission in low-endemic areas contemplating elimination. Detection of underlying G6PD-deficiency is however a major hurdle for its use on a larger scale. Reliable point-of-care tests to detect G6PD deficiency would remediate this problem. Several low-endemic countries have already adopted the systematic administration of

primaquine (0.25 mg/kg) at the end of the course of antimalarials/ACT administered to treat a clinical malaria episode. Mild methaemoglobinemia is often observed with primaquine but rarely with clinical consequences.

Tafenoquine or Etaquine

Etaquine or tafenoquine is a new 8-aminoquinoline, derived from primaquine. It has a half-life of two weeks, which is much longer than the half-life of primaquine. It may be taken orally and has low toxicity. It is active against *P. falciparum* and *P. vivax*. It is an effective schizonticide and is also active on the pre-erythrocytic stages, including the hypnozoites of *P. vivax*. Screening for G6PD deficiency is also required and this is always a limiting factor in low-resource settings. Tafenoquine has been approved in 2018 for the radical (relapse-preventing) treatment of *P. vivax* and *P. ovale* malaria (single dose of 300 mg just after the treatment of the clinical episode) and for malaria chemoprophylaxis (200 mg weekly). The experience of this new drug in not yet that large in clinical practice, but it is expected that replace primaquine soon, due to its much shorter/easier administration.

Proguanil and Chlorproguanil

Proguanil (Paludrine®) and chlorproguanil (Lapudrine®) are biguanides which are converted in the body to the active product cycloguanil.

The combination of chlorproguanil with dapsone is also known as Lapdap®. It is used as a cheap, short-half-life antifolate. It may be combined with artesunate (combination known as “CDA or Chlorproguanil-Dapsone-Artesunate”). In Malarone®, proguanil is combined with atovaquone and both drugs have a synergetic effect explaining its increased efficacy (despite the use of two drugs with moderate activity).

Atovaquone

Atovaquone (Wellvone®, Mepron®) is a lipophilic hydroxynaphthoquinone. Atovaquone is a powerful schizonticide for *P. falciparum* and *P. vivax*. On monotherapy recrudescence occurs very quickly. To avoid this problem, it is combined with proguanil (brand name of the atovaquone + proguanil combination = Malarone®). Atovaquone/proguanil is both used in curative and prophylactic regimen. It cannot be used in renal failure because the blood levels of proguanil/cycloguanil are much higher. Simultaneous use of atovaquone/proguanil and rifampicin is not recommended (blood levels 50%

lower). Most recent data state that it's probably safe in pregnancy, even during the first trimester. The curative dose is 4 tablets of atovaquone/proguanil 250/100 mg for 3 consecutive days.

The product is also being studied in toxoplasmosis, babesiosis, leishmaniasis, microsporidiosis and in Pneumocystis jirovecii pneumonia. In the treatment of babesiosis it proved more active in some animal studies than the combination of clindamycin/quinine.

In general atovaquone/proguanil is very well tolerated. Nausea, diarrhoea and headache are the most frequent side-effects. Stevens Johnson syndrome has also been described. Resistance to atovaquone/proguanil has been rarely described even though a single mutation is enough to substantially decrease its activity. The limited use due to its high price might explain in part the lack of resistance.

Miscellaneous products

Tetracycline, minocycline and doxycycline are antibiotics which are active against malaria parasites but are very slow-acting. For this reason, they are never given as monotherapy, but in combination with quinine. They very much reduce the risk of relapse. Doxycycline has the advantage that it only needs to be administered once daily. Doxycycline is is sometimes used for malaria prophylaxis (cfr. infra).

Clindamycin (Dalacin®) is also active against plasmodia but is a second choice drug (risk of pseudomembranous colitis due to Clostridioides difficile). It is given together with quinine for Pf attack during pregnancy.

Drug resistance

In chloroquine-sensitive *P. falciparum* the drug is concentrated in the parasite. There is slow outflow (t½ = 50 minutes) of chloroquine from the sensitive parasite. In resistant parasites t½ for outflow = 1 to 2 minutes. Resistance is thus not due to inactivation, breakdown or neutralization of chloroquine. The parasite quickly pumps the product away to the blood, so that the concentration of chloroquine within the parasite is low. At present this cannot be counteracted in humans (in vitro reversible with verapamil).

PCR technology [polymerase chain reaction] is required to differentiate a recrudescence (or relapse) in an endemic region from a re-infection with the same species. Several polymorphic loci are

analyzed. Every combination of alleles that is tested, is rare and permits differentiation between strains.

The first signs of chloroquine-resistant P*. falciparum* infections occurred in the ’60s, more or less simultaneously in Colombia and Thailand (countries which mixed chloroquine in commercial table salt). This resistance spread progressively and is now a significant problem in most continents. There are three grades of chloroquine resistance (RI, RII, RIII). In RI the parasitaemia after therapy is so low that it falls below the detection threshold, to rise above it again within 28 days. In RII the parasitaemia is reduced by at least 75 %, but the parasites remain detectable in the peripheral blood throughout the treatment. In RIII chloroquine has no effect on the parasitaemia.

In 1991 chloroquine-resistant *P. vivax* strains were discovered in Papua New Guinea. In 2006, already 65% of the Papuan *P. vivax* strains were chloroquine resistant. *P. vivax* chloroquine resistance in other areas, such as Indonesia, India, Brazil, Guyana is spreading. Chloroquine is not the first-choice treatment any more for *P. vivax* in Indonesia and neighbouring islands. To date resistance to chloroquine in *P.ovale* is very rare. The first chloroquine-resistant P. malariae has been reported (Malaysia, 2002).

Resistance also developed against other drugs, including Fansidar®. The situation is evolving rapidly and is a serious threat to the future use of the artemisinins. The highest resistance against anti-malarial drugs is found in some regions in Southeast Asia, including Cambodia, the Thailand-Cambodia border and the Thailand-Myanmar border. It is only a question of time before these resistant strains spread further geographically. There are several reasons for this increasing resistance. Important factors include inadequate individual patient compliance, treatments that are often discontinued prematurely, frequent underdosing, earlier mass-treatment campaigns reaching only part of the population and therapy being sometimes only partly administered, as well as the use of chloroquinated salt [Cambodia, Brazil (the Pinotti method)]. Among the causes of the swift increase in geographical spread are the large-scale migrations of today, and the ability to move rapidly from place to place. Some products are eliminated slowly from the body (e.g. mefloquine t1/2 = 2 weeks) so that for some weeks a subtherapeutic level of the product is present in the body (as what happened with the addition of choloquine to the salt). When malaria parasites are exposed to such low concentrations, partially resistant strains have a selective advantage. The occurrence of subclinical cases (premunition) functions as a source and reservoir for transmission of parasites with reduced sensitivity. Since the cost price of alternative drugs is generally higher than that of traditional treatments, under-dosing with new drugs will become even more important in future.

On the other hand, reversion of chloroquine resistance has been described in areas where chloroquine

was not routinely used for several years. In Malawi, treatment of uncomplicated malaria with chloroquine was 99% effective 12 years after withdrawal due to resistance. This opens possibilities for the use of chloroquine as a partner drug in combination treatments. Stricter control on “fake” drugs (counterfeited medication), some of which contain small amounts of active material will be an essential component in health programs. One idea to combat counterfeit drugs and piracy is to tag individual genuine medication boxes with an authentication number (itemunique code) under a scratch-off label on the wrapping. When revealed just before purchase, this number can be sent toll-free by telephone text message to an independent certifying company (e.g. Sproxil) which then instantly and automatically replies.

In 2008 resistance to artemisinin has been documented for the first time in Cambodia (borders with Thailand and Vietnam) and in the years after it was described in Thailand, Vietnam, Laos and Myanmar. Treatment failures rates after artesunate-mefloquine and artemether-lumefantrine often exceed 10% in these areas, which is worrying, and higher than anywhere else at present. Full resistance seems to be adequately predicted by a failure to clear the parasites after 3 days of combined treatment. This delay in parasite clearance is the best early marker of resistance so far and is therefore scrutinized in all these regions. Resistance to artemisinin is associated with mutations in the kelch protein gene on chromosome 13 (kelch13). It is worrisome that in some regions in Southeast Asia decreased sensitivity to the artemisinin partner drug was found in combination with the kelch13 mutation. High MIC’s (minimal inhibitory concentration) to piperaquine in Cambodia lead to recrudescence in dihydroartemisinin-piperaquine treated patients. Treatment in this region should therefor consist of mefloquine plus artesunate. In 2019, a 15% treatment failure was noted among patients treated with artesunate-sulfadoxine-pyrimethamine due to a mutations in the kelch13 gene combined with resistance to sulfadoxine-pyrimethamine.

In general, six-day courses of ACT still appear to be efficacious if three-day treatments are failing.

Outside of Southeast Asia, only a few cases of artemisinin resistance have been described in Guyana. In Africa, kelch13 mutations where found but it is not clear whether these mutations confer artemisinin resistance. Clinical failure of ACT has not been described in Africa. Ongoing worldwide molecular surveillance and assessment of the efficacy of ACT regimens are warranted to detect resistance and its spreading early.

LAST UPDATED BY ADMIN ON JANUARY 22ND, 2025