Current Treatments for Malaria

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Abstract

Antimalarial drug therapy is the recommended measure for malaria patients. In the chapter, the treatment for uncomplicated malaria, severe and cerebral malaria, and drug-resistant plasmodium parasites was described. Meanwhile, population prophylaxis for malaria is also reviewed.

Keywords

Malaria · *Plasmodium* · Antimalarial drug · Treatment · Drug resistant · Artemisinin-based combination therapies

At present, there is a wide range of antimalarial drugs available for the clinical treatment of malaria, and the effectiveness of drug treatment is gradually improving, but the situation of malaria treatment and prevention and control still has a relatively prominent seriousness. Effective malaria management is based on early and accurate diagnosis and treatment. The discovery of artemisinin changed the challenge of malaria treatment from quinoline-based therapies to artemisinin-based combination therapies (ACTs) (Su and Miller 2015). Currently, ACTs are recognized as the most effective drug for the treatment of malaria worldwide, whether for the treatment of uncomplicated malaria or severe falciparum malaria. Artemisinin and its derivatives, including dihydroartemisinin (DHA), artesunate (AS), and artemether, have shown outstanding therapeutic efficacy and research value in the treatment given their speed, potency, and safety.

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10.1 Management of Uncomplicated Malaria

All signs and symptoms of uncomplicated malaria, like other febrile symptoms, are nonspecific and can appear early or late in the course of the disease. Hepatosplenomegaly, thrombocytopenia, and anemia are clearly associated with malaria in endemic areas, especially in children. Fever, cephalgias, fatigue, malaise, and musculoskeletal pain are the most common clinical features of malaria (Grobusch and Kremsner 2005). The main objectives of the treatment of uncomplicated malaria are to prevent progression to severe disease and death, reduce clinical symptoms and cure the infection as quickly as possible. The main advance in the treatment of uncomplicated falciparum malaria has been the replacement of the failed monotherapies chloroquine (CQ) and sulfadoxine-pyrimethamine (SP) with ACTs, a change that has significantly reduced malaria morbidity and mortality worldwide. Current recommendations state that children and adults with uncomplicated *Plasmodium falciparum* malaria (except pregnant women in the first trimester) should be treated with one of the following ACTs: artemether-lumefantrine (AL), artesunate+amodiaquine (AS+AQ), artesunate+mefloquine (AS+MQ), artesunate +sulfadoxine-pyrimethamine (AS+SP), or dihydroartemisinin+piperaquine (DHA + PPQ). The advantage of ACTs is that they combine two active drugs with different mechanisms of action and different half-lives. Two or more drugs with different modes of action make the probability of parasite resistance at the same time much lower than that of parasite resistance to a single drug. ACTs are administered orally in regimens that must in all cases cover a 3-day full course (World Health Organization 2015).

The choice of malaria treatment depends on the infected species, drug resistance, severity of the disease, whether the patient can take oral drugs, and whether he or she belongs to a special risk group (e.g., pregnant women and children) (World Health Organization 2015). If the species of infection is not known or if the infection is caused by more than one species, *P. falciparum* should be treated first, as this parasite causes disease is likely to develop rapidly and have the highest mortality (Lalloo et al. 2007). The patient's travel history provides useful clues for selecting an effective antimalarial drug in terms of the risk of drug resistance. Parenteral treatment is indicated for all patients with severe or complicated malaria, those at high risk of developing the severe disease (e.g., those with over 2% of infected red blood cells; pregnant women), or those unable to take oral medicines.

The use of different treatment options for different species of infections. For *P. ovale, P. vivax,* and *P. malariae* infections, CQ is a recommended treatment to kill the intraerythrocytic stage of the parasite and reduce the fever rapidly, which should be followed by a radical cure with a drug with a specific effect on the liver hypnozoites. Thus, the combination of CQ and primaquine (PQ) is commonly used (Chu and White 2016). ACTs are currently recommended as first-line treatment for all patients with *P. falciparum* infection, including in pregnant women (Hanboonkunupakarn and White 2022). They are an alternative to CQ for infections caused by other malaria species, allowing a single treatment to be deployed for all malaria infections.

For *P. vivax* and *P. ovale* infections, CQ plus PQ is preferred. If CQ treatment is ineffective, PPQ, pyronaridine, or ACTs plus PQ can be used. For *P. malariae* infection, CQ is the first choice. When CQ does not respond to treatment, PPQ, pyronaridine or ACTs can be used. For infection with *P. falciparum*, ACTs or pyronaridine are used. PPQ was used in pregnant women suffering from *P. falciparum* within 3 months of pregnancy. Patients with multiple mixed plasmodium parasite infections, such as *P. falciparum* and *P. vivax*, *P. falciparum* and *P. ovale,* are ACTs or pyronaridine plus PQ. Patients with *P. falciparum* and *P. malariae* coinfection should receive ACTs or pyronaridine (Epelboin et al. 2020; Lalloo et al. 2016; Imbert and Laurent 2002) (Table 10.1).

10.2 Management of Severe and Cerebral Malaria

In 2011, the WHO recommended Artesunate (AS) instead of quinine (QN) as the first-line treatment for severe malaria (Le et al. 2018). The largest random clinical trial of severe malaria to date has shown that intravenous or intramuscular AS significantly reduces mortality compared to parenteral QN, in addition to being simpler and safer to administer (Checkley and Whitty 2007). As of April 1, 2019, patients who meet one or more of the following criteria for severe malaria should receive treatment with intravenous AS according to the Centers for Disease Control and Prevention's (CDC's): impairment of consciousness/coma, severe normocytic anemia (hemoglobin < 7), renal failure, acute respiratory distress syndrome, hypotension, disseminated intravascular coagulation, spontaneous bleeding, acidosis, hemoglobinuria, jaundice, repeated generalized convulsions, and/or parasitemia exceeding 5% (CDC's). Considering the relative effectiveness of AS as a substitute for QN in the treatment of severe malaria, based on evidence from current practice, the WHO recommends a second-line therapy: AS plus tetracycline, doxycycline, or clindamycin and recommends that artemisinin and its derivatives should not be used as monotherapy in the treatment of malaria (World Health Organization 2015). If intravenous artesunate is not available, use artemether in preference to QN in adults and children (Table 10.2). Parenteral treatment must be shifted to oral treatment when the patient improves and is able to eat and drink. AS is also indicated in its rectal form as a prereferral option for children under 6 years of age living in remote areas waiting for immediate transfer to a higher level (Okebe and Eisenhut 2014).

Cerebral malaria (CM) is the most common severe malaria with a high mortality rate. There are currently no effective therapeutic drugs available for the eradication of CM. The two types of treatments are available for CM include antimalarial chemotherapy, QN, and adjuvant therapy (Purohit et al. 2021). Treatment options for CM were studied, and it was found that intravenous AS was superior to intravenous QN in the treatment of CM, but antimalarial drugs alone are insufficient to prevent death and neurological deficits in patients with severe malaria. The currently available antimalarial drugs lack lipophilicity and are thus unable to reach the brain tissue. Therefore, safe, cost-effective agents with improved lipophilicity possessing the potential to target brain tissues are needed to fight CM worldwide. Among

Table 10.1 Main regimens for the drug treatment of malaria (Ashley and Poespoprodjo 2020; D'Alessandro et al. 2018; Plewes et al. 2019)

Species of plasmodium	Drug	Administration of drugs	Adult dosage	Pediatric dosage
P. vivax *P. ovale*	**Non-ACTs regimens-8-day regimens**			
	Chloroquine (CQ) plus primaquine (PQ)	The total dose of CQ was 1200 mg, divided into 3 oral days; the total dose of PQ was 180 mg, divided into 8 oral days	CQ 600 mg (4 tablets) daily divided 2 times oral doses on the first day; CQ 300 mg (2 tablets) by oral once daily on the second and third day; in parallel PQ 22.5 mg (3 tablets) oral once daily for 8 days	CQ (10 mg/kg) divided 2 times oral daily on the first day; CQ once oral daily on the second and third day, once 5 mg/kg body weight; in parallel, PQ (0.375 mg/kg) oral once daily for 8 days
	Piperaquine (PPQ) plus primaquine (PQ)	The total dose of PPQ was 1200 mg, divided into 3 oral days; the total dose of PQ was 180 mg, divided into 8 oral days	PPQ 600 mg (4 tablets) daily divided 2 times oral doses on the first day; PPQ 300 mg (2 tablets) by oral once daily on the second and third day; in parallel PQ 22.5 mg (3 tablets) oral once daily for 8 days	PPQ (10 mg/kg) divided 2 times oral daily on the first day and once oral daily on the second and third day; in parallel PQ (0.375 mg/kg) oral once daily for 8 days
	Artemisinin-based combination therapies (ACTs)- 8-day regimens			
	Dihydroartemisinin-piperaquine (DHA-PPQ) plus PQ	The total dose of DHA-PPQ 8 tablets, divided into 2 oral days; the total dose of PQ was 180 mg, divided into 8 oral days	The first dose of DHA-PPQ is 2 tablets orally; continue oral drug 2 tablets at 8 h, 24 h, and 32 h. PQ 3 tablets per dose oral once daily for 8 days	According to the age and first dose, 8 h, 24 h, 32 h oral, respectively 7–10 years old: The 1 tablet per dose at first dose, 8 h, 24 h, 32 h oral, respectively 11–15 years old: The 1.5 tablets per dose at first dose, 8 h, 24 h, 32 h oral, respectively PQ: 4–10 years old: 7.5 mg (1 tablet) per dose one time daily for 8 days 11–15 years old: 15 mg (2 tablets) per dose one time daily for 8 days

	Artesunate-amodiaquine (AS-AQ) plus PQ	The total dose of AS-AQ 4 tablets, divided into 2 oral days; the total dose of PQ was 180 mg, divided into 8 oral days	AS-AQ 2 tablets per dose oral once daily for 3 days; PQ 3 tablets per dose oral one time daily for 8 days	AS-AQ: According to the age and take orally on the first, second, third day, respectively 2–11 months:1/4 tablets on the first, second, and third day 1–5 years old: 1/2 tablets on the first, second, and third day 6–13 years old: 1 tablet on the first, second, and third day PQ: 4–10 years old: 7.5 mg (1 tablet) per dose one time daily for 8 days; 11–15 years old: 15 mg (2 tablets) per dose one time daily for 8 days
	Artemisinin-piperaquine (ART-PPQ) plus PQ	The total dose of ART-PPQ 4 tablets, divided into 2 oral days; the total dose of PQ was 180 mg, divided into 8 oral days	ART-PPQ 2 tablets per dose oral once daily for 2 days. PQ 3 tablets per dose oral once daily for 8 days	ART-PPQ: According to the age 2–3 years old: 1/2 tablets on the first and second day 4–6 years old: 3/4 tablets on the first and second day 7–10 years old: 1 tablet on the first and second day 11–15 years old: 1 + 1/2 tablets on the first and second day PQ: 4–10 years old: 7.5 mg (1 tablet) per dose one time daily for 8 days 11–15 years old: 15 mg (2 tablets) per dose one time daily for 8 days

(continued)

Table 10.1 (continued)

Species of plasmodium	Drug	Administration of drugs	Adult dosage	Pediatric dosage
	Pyronaridine phosphate plus PQ	The total dose of pyronaridine phosphate was 1200 mg, divided into 3 oral days; the total dose of PQ was 180 mg, divided into 8 oral days	Pyronaridine phosphate 3 tablets per dose twice per day on the first, interval 4–6 h; 3 tablets per dose oral once daily on the second and third day. PQ 3 tablets per dose oral once daily for 8 days	Pyronaridine phosphate: 6 mg/kg weight oral twice daily on the first day, interval 4–6 h, 6 mg/kg weight oral once daily on the second and third day; PQ: 4–10 years old: 7.5 mg (1 tablet) per dose once daily for 8 days; 11–15 years old: 15 mg (2 tablets) per dose once daily for 8 days
P. malariae	**Non-ACTs regimens-3-day regimens**			
	CQ	Total dose 1200 mg, divided into 3 oral days	CQ 600 mg (4 tablets) daily divided 2 times oral doses on the first day; CQ 300 mg (2 tablets) by oral once daily on the second and third day; in parallel PQ 22.5 mg (3 tablets) oral once daily for 8 days	CQ (10 mg/kg) divided 2 times oral daily on the first day; CQ once oral daily on the second and third day, once 5 mg/kg body weight
	PPQ	Total dose 1200 mg, divided into 3 oral days	PPQ 600 mg (4 tablets) daily divided 2 times oral doses on the first day; PPQ 300 mg (2 tablets) by oral once daily on the second and third day	PPQ (10 mg/kg) divided twice oral daily on the first day and once oral daily on the second and third day
	Pyronaridine phosphate	Total dose 1200 mg, divided into 3 oral days	Pyronaridine phosphate 3 tablets per dose twice per day on the first, interval 4–6 h; 3 tablets per dose oral once daily on the second and third day	Pyronaridine phosphate: 6 mg/kg weight oral twice daily on the first day, interval 4–6 h, 6 mg/kg weight oral once daily on the second and third day

	ACTs			
	DHA + PPQ	The total dose 8 tablets, divided into 2 oral days	The first dose is 2 tablets orally; continue oral drug 2 tablets at 8 h, 24 h and 32 h	According to the age and first dose, 8 h, 24 h, 32 h oral, respectively 7–10 years old: The 1 tablet per dose at first dose, 8 h, 24 h, 32 h oral, respectively 11–15 years old: The 1.5 tablets per dose at first dose, 8 h, 24 h, 32 h oral, respectively
	AS+AQ	The total dose 6 tablets, divided into 3 oral days	AS-AQ 2 tablets per dose oral once daily for 3 days	AS-AQ: According to the age and take orally on the first, second, and third day, respectively2–11 months: 1/4 tablets on the first, second, and third day 1–5 years old: 1/2 tablets on the first, second, and third day 6–13 years old: 1 tablet on the first, second, and third day
	ART+PPQ	The total dose 4 tablets, divided into 2 oral days	ART-PPQ 2 tablets per dose oral once daily for 2 days	ART-PPQ: According to the age 2–3 years old: 1/2 tablets on the first and second day 4–6 years old: 3/4 tablets on the first and second day 7–10 years old: 1 tablet on the first and second day 11–15 years old: 1 + 1/2 tablets on the first and second day
P. Falciparum	**Non-ACTs regimens-3-day regimens**			
	Pyronaridine phosphate	Pyronaridine phosphate total dose 1200 mg, divided into 3 oral days	Pyronaridine phosphate 3 tablets per dose twice per day on the first, interval 4–6 h; 3 tablets per dose oral once daily on the second and third day	Pyronaridine phosphate: 6 mg/kg weight oral twice daily on the first day, interval 4–6 h, 6 mg/kg weight oral once daily on the second and third day

(continued)

Table 10.1 (continued)

Species of plasmodium	Drug	Administration of drugs	Adult dosage	Pediatric dosage
	ACTs			
	DHA-PPQ	The total dose of DHA-PPQ 8 tablets, divided into 2 oral days	The first dose is 2 tablets orally; continue oral drug 2 tablets at 8 h, 24 h, and 32 h	According to the age and first dose, 8 h, 24 h, and 32 h oral, respectively 7–10 years old: The 1 tablet per dose at first dose, 8 h, 24 h, 32 h oral, respectively 11–15 years old: The 1.5 tablets per dose at first dose, 8 h, 24 h, 32 h oral, respectively
	AS+AQ	The total dose of AS-AQ 6 tablets, divided into 3 oral days	AS-AQ 2 tablets per dose oral once daily for 3 days	AS-AQ: According to the age and take orally on the first, second, and third day, respectively. 2–11 months: 1/4 tablets on the first, second, and third day 1–5 years old: 1/2 tablets on the first, second, and third day 6–13 years old: 1 tablet on the first, second, and third day
	ART+PPQ	The total dose of ART-PPQ 4 tablets, divided into 2 oral days	ART-PPQ 2 tablets per dose oral once daily for 2 days	ART-PPQ: According to the age 2–3 years old: 1/2 tablets on the first and second day 4–6 years old: 3/4 tablets on the first and second day 7–10 years old: 1 tablet on the first and second day 11–15 years old: 1 + 1/2 tablets on the first and second day

Table 10.2 Antimalarial treatment regimens in severe malaria (Varo et al. 2020; Plewes et al. 2019; Severe malaria 2014)

Drug	Administration of drugs	Adult dosage	Pediatric dosage
First-line initial therapy			
Artesunate	Intravenous (i.v.) or intramuscular (i.m.) injection of artesunate. The course of treatment is not less than 7 days. If the patient's clinical symptoms and physical symptoms are relieved and can eat within 7 days, the use of artesunate injection can be discontinued and changed to oral ACTs a course of treatment to continue.	Artesunate (i.v. or i.m.) 2.4 mg/kg immediately, then at 12, 24 h, and daily until oral medication can be taken reliably.	For children ≥20 kg: Give 2.4 mg/kg per dose; for children<20 kg: Give 3 mg/kg per dose. Dose at 0, 12, and 24 h for a total of seven doses.
Alternative initial therapy			
Artemether	The course of artemether (i.m.) treatment is not less than 7 days. If the patient's clinical symptoms and physical symptoms are relieved and can eat within 7 days, the use of artemether injection can be discontinued and changed to oral ACTs a course of treatment to continue	Artemether (i.m.) 3.2 mg/kg initial dose followed by 1.6 mg/kg daily once daily for 7 days until oral medication can be taken reliably.	
Quinine dihydrochloride	Intravenous infusion	Quinine dihydrochloride (20 mg salt/kg) by slow intravenous infusion over 4 h or by i.m. injection split to both anterior thighs, followed by 10 mg salt/kg 8 h until the patient is able to swallow	
Once the patient can tolerate oral therapy. The previously recommended options for follow-on oral treatment are as follows			
Artemether plus lumefantrine Artesunate plus amodiaquine Dihydroartemisinin plus piperaquine Artesunate plus sulfadoxine–pyrimethamine Artesunate plus clindamycin or doxycycline Quinine plus clindamycin or doxycycline			

survivors, further development of adjuvant therapy in combination with antimalarial therapy is needed to compensate for the inadequacy of existing drugs to improve clinical outcomes and/or reduce mortality and prevent long-term neurocognitive deficits. Various other adjunctive treatments targeting the underlying pathophysiology of malaria (Varo et al. 2018), such as corticosteroids, immunoglobulin (rosiglitazone), levamisole, anti-TNF therapies, antiepileptic drugs, agonists peroxisome proliferator-activated receptor-γ (PPAR-γ), mannitol, nitric oxide or exchange blood transfusions (EBTs), and erythrocytapheresis, have been evaluated clinically, but most attempts have failed. Treatments tested in preclinical models are still a potential direction for adjunctive therapy. Through the establishment of an experimental cerebral malaria mouse model, it was found that rapamycin (Gordon et al. 2015; Mejia et al. 2017), HMG-COA reductase inhibitor (statins) (Kumar et al. 2016; Reis et al. 2012), doxycycline (Beeson et al. 2013), Trichoderma matrix (Cariaco et al. 2018), and curcumin (Shikani et al. 2012) could be used as adjuvant treatment strategies for CM to reduce induced death and neurological damage.

10.3 Treatment of Drug-Resistant Plasmodium

Despite the remarkable efficacy of artemisinin and its derivatives in the treatment of malaria, difficulties and challenges remain for the effective treatment of malaria. ACTs are currently the gold standard for antimalarial treatment, in which artemisinin derivatives are commonly used in combination with MQ, PQ, PPQ, and AQ in ACT therapy. The current standard 3-day ACT course is designed to allow pharmacologically distinct drugs to complement each other while reducing the risk of drug resistance. Even though ACTs address most of the shortcomings associated with monotherapies, resistance to antimalarial drugs is a recurring problem. At present, there are ACT treatment failures in the Greater Mekong Subregion. The effective remedy for treatment failure of ACTs is through exchange of partner drugs. The effective remedy for treatment failure of ACTs is through exchange of partner drugs. An effective remedy for the failure of ACT treatment is through the exchange of companion drugs, but this can easily lead to drug resistance to alternative drugs again, so adding more companion drugs to treatment should be considered without other adjustments, perhaps reducing the risk of resistance (Xu et al. 2022; Wang et al. 2021). An interesting new strategy is triple artemisinin-based combination therapies (TACTs), which combine existing combination formulations of ACTs with a second partner drug that is slowly eliminated, could provide effective treatment and delay the emergence of resistance to antimalarial drugs. Based on this idea, van der Pluijm and colleagues (van der Pluijm et al. 2020) conducted an open randomized controlled trial in which uncomplicated patients with *P. falciparum* malaria were recruited from eight countries, and patients were assigned to take DHA + PPQ, DHA + PPQ plus MQ, AS+MQ, AL, and AL plus AQ. The results show that DHA + PPQ plus MQ and AL plus AQ are highly efficacious, well tolerated, and safe treatments for uncomplicated *P. falciparum* malaria. With the increasing failure of conventional ACTs, TACTs may become a new option for the

treatment of uncomplicated falciparum malaria in the Greater Mekong subregion or other drug-resistant regions in the near future. Hamaluba and colleagues conducted a single-center, open-label, randomized, noninferiority trial using arterolane-based TACTs in treating uncomplicated *P. falciparum* malaria in Kenyan children (Hamaluba et al. 2021). This study demonstrates that arterolane–piperaquine–mefloquine is an efficacious and safe treatment for uncomplicated falciparum malaria in children and may be used to prevent or delay the emergence of resistance to antimalarial drugs.

10.4 Prevention of Malaria

The most important measure to eliminate malaria episodes is to prevent them. Infection can be prevented through vector control or bite prevention, chemoprophylaxis, vaccines, and other interventions to minimize the harm caused by malaria (Varo et al. 2020; Ashley and Poespoprodjo 2020).

Vector control measures included the distribution of long-lasting insecticide-impregnated bed nets and indoor residual spraying. Mosquito nets should be used properly during the mosquito season, and mosquito repellents and equipment should be used during outdoor duty. In addition to the large-scale application of insecticides, the most important anti-mosquito measures are the elimination of stagnant water and the eradication of mosquito breeding sites.

The two main chemoprevention strategies in malaria-endemic countries are seasonal malaria chemoprevention and intermittent preventive treatment. Malaria is highly seasonal, with transmission occurring only in consecutive months of the year. A full treatment course is administered a monthly dose of an artemisinin-free antimalarial (SP + AQ) during malaria-transmission season (usually 3–4 months long), up to four times (Varo et al. 2020; Ashley and Poespoprodjo 2020). Due to concerns about its resistance, DHA + PPQ has been proposed as an alternative to seasonal chemoprophylaxis with a dosing interval of once weekly to maximize protective efficacy (Zongo et al. 2015; Sundell et al. 2015; Chotsiri et al. 2019). Intermittent preventive therapy with SP is recommended by WHO 3,4, provided resistance to SP is not established (<50% prevalence of the Pfdhps 540 mutation). This is a recommendation for many African countries with high *P. falciparum* prevalence and has clear health benefits for pregnant women and newborns. Who currently proposes a minimum of three doses (one month apart) during pregnancy, and infants are given at 10, 14 weeks, and 9 months of age.

Malaria vaccines hold great promise for life-saving benefits, especially for children who bear the brunt of malaria mortality. RTS, S/AS01 is a preerythrocytic vaccine (Draper et al. 2018) that has been shown to give partial protection against falciparum malaria in a large, multicenter trial and has received a favorable opinion from the European Medicines Agency (Efficacy and safety of RTS 2015) and is currently being tested in implementation studies. In parallel, multiple strategies are being advanced to test next-generation malaria vaccines (Laurens 2021), including novel approaches that build on principles learned from RTS, S development,

vaccination with radiation-attenuated sporozoites, and development of monoclonal antibodies targeting immunogenic peptides. Novel vaccine delivery approaches are also being advanced, including self-amplifying RNA vaccine delivery, self-assembling protein nanoparticle methods, circumsporozoite protein-based approaches, whole organism vaccination, and transmission-blocking vaccines. Techniques employed for COVID-19 vaccine development should also be considered for malaria vaccination, including sustained release polymer nanoparticle hydrogel vaccination (Gale et al. 2021) and charge-altering releasable transporters (Haabeth et al. 2021). As vaccine science advances and new approaches optimize knowledge gained, highly effective malaria vaccines that provide sustained protection are within reach.

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