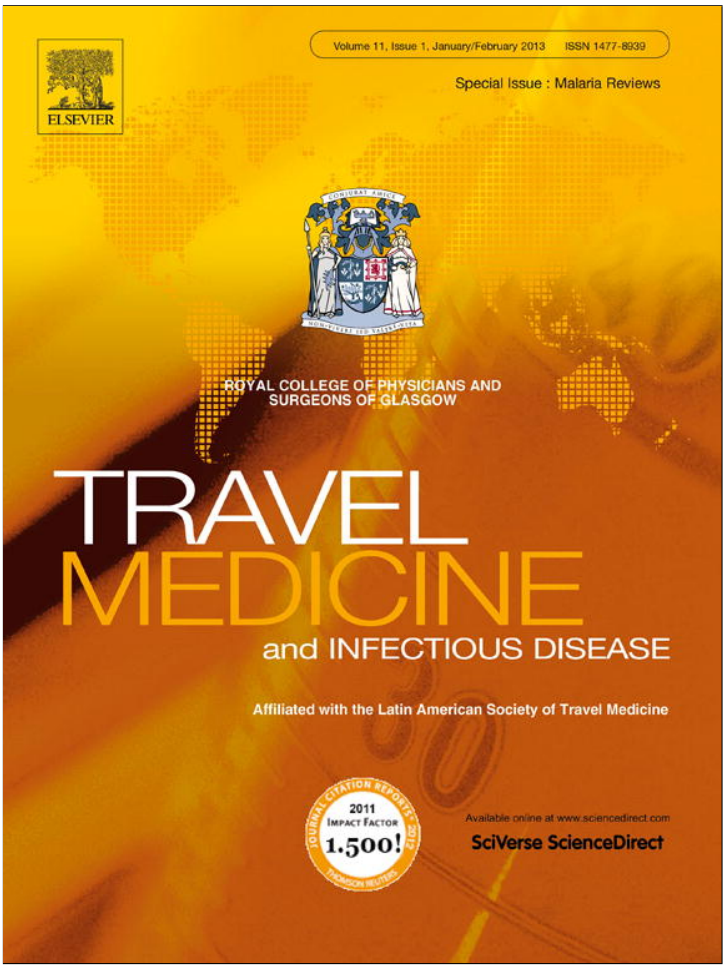

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REVIEW

Artemisinin based combination therapy in travel medicine

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Summary A steadily increasing number of Western travellers are exposed to malaria. Also, numbers of migrants from malarious areas are increasing. Fast and effective treatment options are needed to ensure effective malaria treatment in these groups in the future. Artemisinin combinations are well tolerated and have shown high efficacy in malaria endemic areas. Since 2001, 42 malaria endemic countries, 23 of them in Africa, have adopted artemisinin based combination therapies recommended by WHO. An additional 14 countries are in the process of changing their malaria treatment policy. Studies in non-immune travellers confirm a rapid parasite clearance time and very low rate of side effects. Outpatient clinics and hospitals in non-endemic countries should have standard operating procedures for diagnosing and managing patients with malaria. In this setting, artemisinin combinations should be available for treatment of uncomplicated malaria as they are clearly superior to any other oral antimalarial in their fast reduction of parasite biomass and in decreasing clinical symptoms. Also, they are the drugs of choice for travellers who are advised to carry stand-by emergency treatment during their journey.

Introduction

Malaria is one of the most important global public health challenges. The disease arises from the infection of red blood cells with Plasmodia. The species that infect humans are *Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale, Plasmodium malariae,* and the recently in South East Asia detected *Plasmodium knowlesi*. Severe manifestations are mainly due to *P. falciparum* but *P. knowlesi* and in exceptional circumstances *P. vivax* are also capable of causing lethal disease. Malaria caused an estimated 225 million clinical cases and more than 655.000 deaths in 2011, mainly in children aged less than five years old from sub-Saharan Africa.[1–3] Consequently, malaria

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represents a serious health hazard to travellers to endemic areas. According to the World Tourism Organization, there were approximately 940 million travel-related arrivals worldwide in 2010, of which approximately 180 million were arrivals in malarious areas.[4] Imported malaria is seen in travellers returning from endemic countries or in migrants. Latter group consists in a large proportion of migrants living in Europe and returning from visiting friends and relatives (VFR) in a malarious area. VFRs travelling to sub-Saharan Africa have more than eight times the risk of being diagnosed with malaria compared to tourists, and more than twice the odds of being diagnosed of malaria after travel to Asia.[5] VFR children are particularly at risk. As international air travel to tropical destinations becomes more and more popular, the last decades have brought a steady increase of imported cases in non-endemic countries.[6-9] After some years of declining numbers, latest data from Europe[3,10] show increasing trends in imported malaria and US statistics show an increase of 14% in imported malaria for 2010.[11] One study found that the crude risk of malaria infection for travellers varied from 1 per 100,000 travellers to Central America and the Caribbean to 357 per 100,000 in Central Africa.[12]

Clinical presentation of malaria in travellers

Health practitioners in the Western world face a broad spectrum of patient characteristics when encountering malaria, from the moderately compromised individual with few symptoms up to the critically ill patient with organ failure. The majority of imported cases remain uncomplicated.[5,6] The mortality of imported *P. falciparum* malaria cases varies from 0.4% in a large cohort from France up to 5% in a recent cluster of cases imported from the Gambia.[13,14] Most patients with *P. falciparum* infections become symptomatic within 30 days after return from the malaria endemic area. Longer incubation periods are seen with the other *Plasmodium* species and are prolonged by incomplete malaria chemoprophylaxis which may reduce parasitaemia without achieving full protection. Prodromal symptoms, which may precede the fever for up to two days are fatigue, loss of appetite, headache and body pains.

In non-immune patients, malaria usually starts suddenly with a severe feeling of sickness and fever—often reaching 39 °C and higher.[15] Not all patients show typical fever paroxysms and absence of fever does not remove the suspicion of malaria in an ill patient. If present, the frequency of the febrile episodes depends on the parasite species, occurring every 48 h (tertian) for *P. vivax* and *P. ovale*, every 72 h (quartan) for *P. malariae* and 24 h (quotidian) for *P. knowlesi*. In *P. falciparum* malaria the fever usually lacks a regular pattern. Common symptoms are headache and myalgia, nausea is frequent. Other symptoms may include vomiting, dry cough, icterus, confusion and respiratory distress. Compromised circulation leads to renal failure and impaired tissue perfusion resulting in acidosis. Gastrointestinal complaints unrelated to treatment, including vomiting and diarrhoea are less frequent. Clinical examination is non-specific since it often takes some time before anaemia or hepatosplenomegaly develop.

As an effect of previously acquired semi-immunity, malaria in adult migrants is characterized by a milder clinical presentation, lower levels of parasitaemia, shorter parasite clearance time after treatment and shorter fever duration compared to malaria in non-immune travellers.[16—18] A high proportion of migrants have few symptoms and present long after arrival in the host country,[19] with periods of months up to several years recorded.[19—23] If semi-immunity is lost after living two or more years in non-endemic areas, travelling migrants have a risk of clinical malaria approaching that of non-immune travellers.[24,25]

Malaria diagnosis and rapid diagnostic tests (RDT)

Early and fast diagnosis is crucial to prevent uncomplicated malaria progressing to complicated disease. Microscopic examination of Giemsa-stained thin and thick blood films remains the gold standard. In expert hands, the method is simple, rapid, and sensitive[26] with a sensitivity reaching five parasites per μl.[27] More sensitive thick blood films are combined with thin blood films for determination of parasitaemia and species identification. However, expert microscopy is frequently not available when patients need to be diagnosed quickly, thus reducing the use of this method significantly. Even after the start of specific treatment, there is a lag-phase before the parasite density begins to decline[28] and there may even be an increase of parasitaemia in the first 24 h after onset of therapy. Rapid diagnostic tests (RDTs) based on the detection of parasite-specific antigens by monoclonal antibodies have been developed to make the first assessment of a potential malaria patient simpler and potentially more reliable. Antigens commonly used are histidine rich protein 2 (HRP2), pan plasmodial aldolase, and parasite-specific LDH. Assays are available that detect all species i.e. *P. falciparum, P. vivax, P. ovale,* and *P. malariae*.[29] *P. knowlesi* infections can be detected by rapid tests which include the pan plasmodial aldolase or LDH antigens.[30] For falciparum malaria, many RDTs show 100% parasite detection score down to a parasite density level of 200 parasites per μl, equivalent to a parasitaemia of approximately 0.004%.[31] However, there are limitations. Rapid tests cannot determine the parasite density. False negative RDTs in patients with very high parasite densities have been described, probably due to the so-called "pro-zone" effect.[32,33] Mutations in the HRP2 gene may also result in false negative tests[34,35] and rheumatoid factor may lead to false positives.[36]

Results of a WHO multi-centre evaluation of different rapid diagnostic tests show that the best performance was found with tests based on a combination of the HRP2 and pan plasmodial proteins.[31] Clinicians using rapid tests need to be aware that no RDT test so far is 100% reliable and that they should be used in parallel to and not instead of blood film examination.

RDTs also are a potential option for travellers without access to qualified medical care. However, rapid tests may be difficult to perform and interpret by untrained persons, particularly those in distress[37,38] Emphasis should be placed on proper instructions and training if tests are recommended to travellers. An evaluation of self-diagnosis and treatment in oil service employees showed that provision of a malaria kit with diagnostic tests and treatments was useful in expatriates.[39]

Stand-by emergency treatment (SBET)

Stand-by emergency treatment (SBET) is described as the self-administration of antimalarial drugs by travellers. The older term stand-by prophylaxis is no longer used. SBET has been developed in German-speaking countries and is increasingly used. With this strategy, travellers are prescribed antimalarial medication which they carry during their journey. They are advised to use the medication when malaria is suspected and prompt medical attention is unavailable within 24 h of onset of symptoms. This strategy is indicated as a potentially life-saving measure since malaria poses an emergency situation.[40] SBET is not intended to replace chemoprophylaxis at high-risk destinations such as sub-Saharan Africa or to detract from the importance of medical consultation when suspected malaria occurs. However, the worldwide increasing issue of counterfeit medication is of great importance for travellers. The concept of SBET ensures the availability of safe and effective medication when it is needed since carriage of an antimalarial bought prior to travel from a safe source ensures reliable quality of medication in contrast to locally bought medication that could be counterfeit.[41]

SBET can be recommended for travellers[4,42–44]

- visiting an area with a minimal malaria risk and/or a remote area far from medical attention,
- expatriates or long-term travellers who are likely to have gaps in chemoprophylaxis adherence,
- travellers who are likely to have a changing itinerary with different malaria risks (e.g., backpackers),
- short-stay, frequent travellers (e.g., aircrews and business travellers),
- travellers visiting destinations without qualified medical services and/or with high likelihood to encounter counterfeit antimalarials.

According to WHO guidelines,[40] drug options indicated for SBET are the same as the treatment options for uncomplicated malaria: artemether/lumefantrine, dihydroartemisinin/piperaquine, mefloquine, atovaquone/proguanil, quinine with doxycycline or clindamycin or chloroquine (in areas without chloroquine resistance). Due to their fast acting mechanism with resulting rapid parasite clearance and disappearance of symptoms, artemisinin based combinations are highly preferable in this setting.

Therapy: artemisinin based combinations

Treatment of malaria should provide rapid clinical and parasitological cure. WHO recommends oral Artemisinin based combination therapy (ACT) as standard treatment of uncomplicated malaria.[45] Artemisinin or Qinghaosu is an extract of the medical plant Qinghao (*Artemisia annua*), which together with its derivatives, artesunate and artemether are the most effective antimalarial compounds to date.[46–48] The use of a drug combination with different mechanisms of action will dramatically reduce the likelihood of a resistant parasite surviving. Artemisinin derivatives are highly potent and capable of reducing the parasite biomass by a factor of 10^4 per asexual life-cycle (approximately every 48 h). This will leave a much smaller number of parasites for the partner drug to kill while its concentration in plasma remains high. Another advantage of artemisinin derivatives is their ability to kill gametocytes, thus interrupting malaria transmission and making them the drugs of choice in epidemics. The artemisinin derivatives have a rapid onset of therapeutic effect which makes their use particularly desirable in non-immune patients who may develop complicated malaria within very short time. However, they have a very short terminal elimination half life of less than 2 h.[47,48] Thus, monotherapy should be avoided and combination therapy (ACT) is recommended as standard treatment of uncomplicated malaria in order to avoid parasite recrudescence.[45]

Artemisinins are used orally in uncomplicated malaria. Once absorbed, artemisinin derivatives are converted primarily to dihydroartemisinin (DHA) and further to inactive metabolites via hepatic cytochrome P-450 and other enzyme systems.[49,50] DHA is itself a potent antimalarial with an elimination half life of about 45 min.[48] The extent of conversion to DHA differs between derivatives. Artemisinin itself is not metabolised to DHA but acts as the primary antimalarial, while artesunate is hydrolysed to DHA within minutes and its antimalarial activity is largely mediated by DHA. Time to maximum DHA concentration is typically one to 2 h.[48] High recrudescence rates (10–15%) are seen with artemisinin monotherapy. This is difficult to reconcile with the high efficacy of this compound against parasites. This poor efficacy of monotherapy is not due to resistance. It is explained by the short half life, which is further shortened by the increased drug clearance that develops during repeat dosing.[49–52] Thus, combination with a long acting antimalarial is crucial for the efficacy of artemisinins.

Artemisinins kill all plasmodium species that infect humans.[45–47] In vitro *P. falciparum* IC50 values (median and range) have been reported as 4.2(0.5–34.6), 4.3(0.5–23.2), and 16.2(1.3–58.3)nM for artesunate, dihydroartemisinin, and artemether respectively.[53] The asexual stages of infection are the most susceptible, with artemisinins inducing up to a 10,000-fold reduction in parasite biomass per asexual cycle. Like other antimalarials, artemisinins are particularly active against the large ring stage of infection when parasites are beginning to become most metabolically active. However, in contrast with other antimalarials, artemisinins also target early ring stages of infection that are present only a few hours after red cells are invaded by merozoite stages.[49,50] This effect results in an early removal of parasites from infected cells, probably by the reticuloendothelial system. These ''pitted'' erythrocytes are returned to the circulation, carrying an immunological marker of the presence of the parasite on its surface (an early stage antigen called RESA).[54] Artemisinins inhibit the metabolism of parasites more quickly than any other antimalarial used to treat severe malaria. This is a pharmacodynamic property that is of immense benefit given that complications of falciparum malaria may develop very fast in non-immune patients. They also reduce cytoadherence of infected red cells and thereby sequestration, a recognised virulence determinant in falciparum malaria.[55] Artemisinins do not interfere with hepatic stages of parasite development and therefore have no causal prophylactic value. Also, their short half life renders them inappropriate

for chemoprophylaxis. They do kill early gametocyte stages of development and have the potential to interfere with mosquito transmission.[56] Artemether/lumefantrine (Riamet®, Coartem®) and dihydroartemisinin/piperaquine (Eurartesim®) are the only artemisinin derivatives licenced for use in Europe.

Artemether/lumefantrine

Artemether/lumefantrine is the most widely-used ACT globally. It is well tolerated and highly efficacious in all endemic regions except for *P. falciparum* infections acquired in Cambodia and the border regions of Thailand with Myanmar, where multidrug resistant *P. falciparum* strains are prevalent.[1,3] Artemether is a methyl-ether derivative of artemisinin. Lumefantrine is a racemic fluorine derivative with high blood schizontocidal activity.[47] This combination is effective and well documented with few adverse events. The recommended treatment is a 6-dose regimen over a 3-day period. The dosing is based on the number of tablets per dose according to pre-defined weight bands (5—14 kg: 1 tablet; 15—24 kg: 2 tablets; 25—34 kg: 3 tablets; and >34 kg: 4 tablets), given twice a day for 3 days. An advantage of this combination is that lumefantrine is not available as a monotherapy, and that it has never been used by itself for the treatment of malaria. Artemether/lumefantrine has to be administered with fatty food to obtain optimal plasma drug concentrations.[46] This might be a disadvantage in a clinical setting, and in particular when the combination is used as SBET, since patients with malaria tend to suffer from nausea and will frequently decline food.

Studies in non-immune travellers confirm a rapid parasite clearance time (PCT) and very low rate of side effects.[57] In one study, direct comparison with atovaquone/proguanil showed a shorter PCT and less relapses in patients treated with artemether/lumefantrine.[57] No significant side effects on ECG or laboratory parameters were observed in observational studies performed with non-immune populations.[57,58]

Dihydroartemisinin/piperaquine

Dihydroartemisinin/piperaquine was approved by the European Medicines Agency in 2011 for the treatment of symptomatic, uncomplicated malaria in adults, children and infants older than 6 months and/or above 5 kg. It has been extensively used in malaria endemic regions since more then 10 years under the name Artekin®. Marketing in European countries has started towards the end of 2012. Dihydroartemisinin/piperaquine has been found to be as effective and safe as artemether/lumefantrine in several trials,[48,59—62] number and type of side effects were comparable to those with artemether/lumefantrine. This combination is currently available as a fixed-dose combination with tablets containing 40 mg of dihydroartemisinin and 320 mg of piperaquine. A target dose of 4 mg/kg/day dihydroartemisinin and 18 mg/kg/day piperaquine once a day for 3 days, with a therapeutic dose range between 2 and 10 mg/kg/day dihydroartemisinin and 16—26 mg/kg/dose piperaquine. Dihydroartemisinin/piperaquine should be taken fasting, a clear advantage since malaria patients are frequently nauseated and anorectic.

As with artemether/lumefantrine, possible ECG effects have been discussed prior to licensure. Dihydroartemisinin/piperaquine has the potential to prolong the QT-interval. ECG findings were observed in two pivotal clinical studies conducted in Asia[61] and in Africa[62] in patients with uncomplicated malaria. In both studies, subjects treated with dihydroartemisinin/piperaquine had significantly more borderline or prolonged QTc than those in the control groups. This prolongation was correlated with peak plasma concentrations of piperaquine[60] and was increased when the drug was administered after a meal. In vitro studies on isolated rabbit ventricular wedge preparations showed very low pro-torsadogenic potential of piperaquine when administered alone or in combination with dihydroartemisinin and no arrhythmic events were observed.[63] Similar results were found for artemether/lumefantrine. Chloroquine, used as a control drug in this study, showed markedly higher pro-torsadogenic potential. However, chloroquine has never been associated with significant cardiotoxicity during its many years of use as an antimalarial.[64] On a practical view, the use of dihydroartemisinin/piperaquine as Artekin® in Asia has never been associated with clinically relevant cardiac events. Some patients in the pivotal trials with Eurartesim® had documented QTc prolongation but again, no clinically relevant events occurred.[61,62] For the time being, some national guidelines recommend to record an ECG during treatment initiation and to repeat ECGs subsequently. For this reason, Eurartesim® is not officially recommended as stand-by therapy for travellers by some national regulatory agencies. Safety studies in non-immune travellers have been started together with the marketing of the combination in Europe. Results will not be available before several years.

ACTs in the clinical setting: treating returning travellers with malaria

A steadily increasing number of Western travellers are exposed to malaria. Also, numbers of migrants from malarious areas are increasing. Since 2001, 42 malaria endemic countries, 23 of them in Africa, have adopted artemisinin based combination therapies recommended by WHO. An additional 14 countries are in the process of changing their malaria treatment policy. Returning travellers are not a group who contribute significantly to the spread of drug resistance worldwide. However, artemisinins are so well tolerated and of assured efficacy that they are the drugs of choice for this group of patients, particularly against multidrug resistant infections. If Western countries do not keep pace with changing treatment policies in endemic countries there is a risk that travellers may not be offered appropriate and effective treatment for their malaria. Outpatient clinics and hospitals should have plans for diagnosing and managing patients with malaria.[65] Obtaining a travel history is mandatory for all patients with fever. If rapid diagnostic tests (RDT) indicate the diagnosis of malaria but microscopy cannot be performed locally, adequate treatment should be started immediately and the patient

should promptly be transferred to a health care facility where further diagnosis can be done. If the RDT remains negative, but a clinical suspicion of malaria remains, patients should also be transferred to a centre with expertise in the microscopic diagnosis of malaria. ACT should be available as first line drugs for treatment of uncomplicated malaria.

ACT as SBET option

If the strategy of SBET is employed when counselling travellers to malarious areas, an antimalarial with high antiparasitic capacity should be prescribed as carry-on medication. A strong point in support of equipping travellers with a highly effective antimalarial treatment as part of their travel medical kit is the global proliferation of counterfeit antimalarials. ACT are clearly superior to any other oral antimalarial in their fast reduction of parasite biomass and in decreasing clinical symptoms. Numerous trials and clinical experience have shown that ACT are safe to use and that relevant side effects are exceedingly rare. Although resistance against artemisinins has been described in Sout East Asia, it has no impact on the clinical efficacy of ACT. Thus, they are the drugs of choice for travellers who need to decide upon their symptoms or by self-diagnosis via RDT whether they have to treat themselves against malaria.

Conflict of Interest

The author declares that he has received speakers' honoraria from GlaxoSmithKline, Novartis Vaccines and Sigma-Tau. No writing assistance was utilised for this article.

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