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What a Cardiologist Should Know About Malaria

Richard E. Katholi[1*] and Marcella R. Ervin[2]

[1]*Prairie Educational and Research Cooperative, Department of Pharmacology, Southern Illinois School of Medicine Springfield, IL USA*

[2]*Prairie Educational and Research Cooperative, Springfield, IL USA*

Abstract

Delay in diagnosis and treatment is the leading cause of death from malaria in patients in the United States. Malaria should be suspected based on a patient's recent international travel. Besides diagnosing malaria infection, determining the Plasmodium species is important so proper treatment is given. With careful clinical and electrocardiographic monitoring, most cardiovascular complications of malaria and its treatment are fully reversible.

Keywords: *malaria, Plasmodium falciparum, P. vivax, P. ovale, P. malariae, P. knowlesi, hypnozoite, female Anopheles mosquito, chloroquine, artemisinin, monoclonal antibodies, long QTc*

Introduction

In 2017, there were 2161 reported cases of malaria in the United States [1]. This was the highest number since the withdrawal of troops from Vietnam in 1975. This recent increase in cases of malaria appears to be due to increasing tourist travel. Over 86% of cases were associated with travel to Africa, mainly West Africa, and *Plasmodium falciparum* caused 76% of infections. Virtually all of the patients became ill within three months of return to the United States; 93% had not taken chemoprophylaxis as advised; severe illness occurred in 14% of cases, and seven people died [1].

With increasing international travel as COVID-19 restrictions are lifted, with increased efforts to improve health care via doctors volunteering through many organizations, including Doctors Without Borders and with increased immigrants and refugees, physicians in the United States must now consider malaria among the differential diagnoses of patients with an acute febrile illness [1]. Malaria is a potential medical emergency and should be treated accordingly. Delay in diagnosis and treatment is the leading cause of death from malaria in patients in the United States. Malaria can be suspected based on a patient's travel history, so recent international travel questions are an important part of the initial patient workup.

Perspective

Malaria is a scourge of humankind and continues to devastate the health and livelihoods of people worldwide. In 2020, roughly 4 billion people in 87 countries were at risk for malaria, and there were an estimated 241 million cases with 627,000 resulting in deaths, most of which were children younger than 5 years of age and pregnant women in sub-Saharan Africa. The risks of travel resulting in acute and chronic malaria infection are illustrated in a 30-year study of great reed warblers [2]. This bird migrates and winters across sub-Saharan Africa, and roughly 40% of the birds that return to nest in Southern Sweden are infected with one or more species of malaria parasite picked up in their winter habitat. After an initial acute phase of the disease, in which birds are anemic, lethargic and lose their appetite, survivors recover but often remain infected with a low level of parasites in their blood. The research team over the years of study found no significant differences in annual breeding success between infected or uninfected birds. However, chronic malaria infection appears to erode telomeres in blood cells and reduce life spans. Telomeres are strands of DNA that cap the ends of chromosomes and protect them during cell division. In many species, shorter telomeres are associated with aging and shorter life span. On average, uninfected birds lived 2.5 years and raised more than eight offspring to fledglings. Infected birds lived an average of 1.6 years and raised just four offspring. It is not clear whether the shorter telomeres are the result of the extra red blood cells infected birds have to make (telomeres typically shrink with every cell division) or whether they are more of a general consequence of the body's efforts to fight the chronic infection.

Information about malaria parasites

There are over 200 species of malaria parasites, but only five infect humans: *Plasmodium falciparum*, *P. vivax*, *P. ovale*, *P. malariae* and *P. knowlesi*. *Plasmodium ovale* is endemic to tropical Western Africa where *P. vivax* is almost absent because of the high prevalence of the Duffy blood group-negative phenotype. Unique to the pathogenesis of *P. vivax* infection is the need for the human host to have the Duffy antigen, a protein on the surface of red blood cells, that *P. vivax* uses to invade the cells [3]. The parasite cannot spread effectively in populations in which most people are "Duffy-negative." Most people in sub-Saharan Africa are Duffy-negative, which provides natural immunity to *P. vivax*. *Plasmodium falciparum*, *P. vivax* and *P. malariae* infect humans worldwide with varying distributions. *Plasmodium falciparum* makes up 80-90% and *P. ovale* makes up 8% of cases in Africa; *P. vivax* makes up 70-90% of cases in Asia and South America. The prevalence of *P. malariae* is 1-2% compared to *P. falciparum* and *P. vivax*. Until recently, *P. knowlesi*, which primarily infects macaques, had not been identified as a parasite that infects humans. It is becoming more prevalent in humans in Southeast Asia in recent years as, due to deforestation of areas, the macaques are living closer to humans. Monkey malaria transmission to humans via mosquitoes was confirmed in 2016 [4]. There are three stages of malaria life cycle which require two hosts: human or other mammalian host and the mosquito vector. It has been speculated that bats may have been the first mammalian host of malaria. The female *Anopheles* mosquito is the only known carrier of malaria. Male mosquitoes eat nectar. Only female *Anopheles* mosquitoes, which are known as "night-biting" mosquitoes because they most commonly bite between dusk and dawn, feed on blood or bite and are easily recognized in their resting position on a mammal in which proboscis, head and body are held in a straight line to each other but at an angle to the surface in order to penetrate the skin. Thus, a female mosquito takes a blood meal (bites), and she injects sporozoites into the human host which go to the liver (exoerythrocytic cycle). Fever occurs when the parasite enters red blood cells (erythrocytic cycle). Also, when the female mosquito takes a blood meal (blood meals are required to mature their eggs), she ingests gametocytes so the sporogenic cycle occurs in the mosquito. The "gold standard" for diagnosing malaria is seeing the parasite in red blood cells using a light microscope. Whereas *P. falciparum* attacks red blood cells of all ages, *P. vivax* targets immature red blood cells (reticulocytes) that are relatively rare, which can make *P. vivax* infection harder to diagnose [3]. Until recently, blood smears prepared with Giemsa stain taken during fever episodes was the only diagnostic approach. There are now Rapid Diagnostic Tests (RDT's) to assist in

the diagnosis of malaria by detecting evidence of malaria parasites (antigens) in human blood. These tests require a drop of peripheral blood from a finger or heel prick. Visual readouts are available typically within 20 minutes or less. They require no apparatus and can be used at the point-of-care, including in very remote areas. RDT's work by capturing dye-labelled antibodies bound to specific parasite antigens. Antibodies anti-aldose and anti-pLDH recognize all Plasmodium species. Antibodies anti-Pf-pLDH and anti-PfHRP2 recognize *P. falciparum*. Antibody anti-Pv-pLDH recognizes *P. vivax* but has shown relatively poor performance so far compared to the antibodies to specifically detect *P. falciparum* [1]. Since 2010, the World Health Organization (WHO) recommends all suspected cases of malaria be confirmed by positive blood smears or by RDT's before treatment to avoid overuse of new generation "wonder drugs" to avoid the development of drug resistance [5].

The parasites infecting and killing red blood cells cause the symptoms of malaria. *Plasmodium falciparum* causes the majority of deaths globally. When *P. falciparum* invades red blood cells, it makes them rigid which is thought to lead to blocked capillaries and is a factor in the deadly cerebral malaria. Blood group 0 appears to protect patients against severe *P. falciparum* through the mechanism of reduced rosetting (less ability of *P. falciparum*-infected red blood cells to bind with uninfected red blood cells). If red blood cells are infected by *P. vivax*, the red cells seem to remain pliable which might explain why it is not quite as lethal [3]. Of note, patients with red blood cells containing hemoglobin S (sickle cell trait) or hemoglobin C trait appear to have a reduced incidence of malaria suggesting some natural immunity. In contrast, malaria is the most common cause of sickle cell crisis in Africa in patients with sickle cell disease, and these patients are susceptible to the lethal effects of malaria. Malaria makes sickle cell patients' anemia more severe, and these patients' spleens are less effective (hyposplenism) in combating parasite-infected red blood cells.

Other rare mechanisms for transmission of malaria include congenitally-acquired disease, blood transfusions, sharing of contaminated needles, organ transplantation and nosocomial transmission.

Perspective about mosquitoes

Malaria is caused by injection of plasmodium parasites into the human bloodstream via the bites of female *Anopheles*. Some 60-100 female *Anopheles* mosquito species can serve as a vector for five distinct species of *Plasmodium* that produce varying degrees of illness. While mosquitoes can seem irritating and concerning because of being a vector of disease transmission, mosquitoes play a substantial role in the ecosystem [6]. Mosquitoes form an important source of biomass in the food chain serving as food for fish as larvae and for birds, bats and frogs as adults, and some mosquito species are important pollinators. Out of the more than 3500 mosquito species, only around 400 can transmit diseases like malaria, yellow fever, dengue fever, West Nile virus, Zika virus and chikungunya virus to humans, and most mosquitoes don't feed on humans at all [6].

The mosquito that infects untold millions with malaria every year, female *Anopheles gambiae*, has received much study as part of the global efforts to limit disease transmission. Studies showed that as *Anopheles* mosquitoes evolved, so have the traits that affect interactions between the sexes and likely also their capacity as vectors of human malaria [7]. These traits include evolution of a "mating plug" that allows males to transmit not only sperm, but also the steroid hormone 20-hydroxyecdysone (20E) to females. In the female's reproductive tract, 20E sets off a cascade of processes that increase egg production. As the main vector of malaria, *A. gambiae* proteins that interact with 20E that stimulate egg production also are known to decrease female innate immunity which increases the susceptibility of female mosquitoes to infection by the *Plasmodium* that causes malaria. Studies also suggest that *P. falciparum* expresses a surface protein that enables the single-celled protozoa to escape detection by the mosquito immune system [8].

Travel guidelines

Precautions for travelers to the developing world to prevent malaria may include minimizing outdoor evening and night activity, use of an insecticide-treated mosquito bed net unless the bedroom is protected against mosquitoes and use of insecticide spraying in the bedroom at night [1,9]. People living in malaria-free countries with no spleens (i.e., lost in accidents or in treatment of Hodgkin's disease) who plan to travel internationally should be warned to take extra precautions. The spleen plays an important role in combating malaria. The spleen is the major organ that generates an immune response to the malaria parasite. The spleen also plays a central role in malaria parasite clearance during the red blood cell stage of infection. Malaria prophylaxis depends on a traveler's destination. For areas of the world with chloroquine sensitivity, chloroquine phosphate 300 mg once per week is used beginning one to two weeks before entering malarial areas and continuing until four weeks after leaving [1,9]. For areas of the world with chloroquine resistance, weekly mefloquine 250 mg salt or doxycycline 100 mg weekly can be used.

Additional interventions are needed to reduce the morbidity and mortality caused by malaria. A monoclonal antibody for malaria prevention has been developed called CIS43LS with an extended efficacy against infection with P. falciparum [10]. In a phase 1 clinical trial involving 25 adults who had never had malaria infection or vaccination, administration of the long-acting monoclonal antibody against the circumsporozoite protein covering the surface of the infecting sporozoite prevented malaria for up to 6 months. This trial provides a potential pathway toward passive prevention against malaria when people travel to or transiently work in malaria-endemic areas of the world.

Since then, a phase 1 clinical trial has tested the safety, pharmacokinetics and protective efficacy of L9LS, a next generation antimalarial monoclonal antibody against *P. falciparum*, which is approximately three times more potent than CIS43, the parent antibody of CIS43LS in preclinical models [11]. L9LS targets the circumsporozoite protein on the surface of the parasite during the sporozoite stage when infection is transmitted to establish infection in the liver after a bite from an infected female Anopheles mosquito. The L9LS monoclonal antibody binds to highly conserved regions of this major surface sporozoite antigen which is also the target of the RTS,S/AS01 malaria vaccine [12].

The phase 1 clinical trial participants were healthy adults in the United States who had not previously had malaria or had received a vaccine for malaria. No serious adverse events were reported in the participants who received L9LS, either intravenously or subcutaneously, at a dose of 1 mg, 5 mg or 20 mg per kilogram of body weight [11]. Two to six weeks after they received L9LS, 17 participants were infected with P. falciparum, and outcomes were compared with those of 6 control participants who also had undergone controlled human malaria infection. The primary outcome was the detection of parasitemia by means of a polymerase-chain reaction test through 21 days after the controlled infection. All 6 control participants had parasitemia, as compared with 2 of the 17 L9LS recipients ($p<0.001$). None of the participants who received L9LS intravenously at a dose of 5 mg or 20 mg per kilogram became infected. All of the participants received atovaquone-proguanil antimalarial therapy on day 21 or on detection of parasitemia.

Five of the 17 participants in this trial received L9LS at a dose of 5 mg per kilogram subcutaneously [11]. Subcutaneous administration is simpler to perform and less costly than intravenous infusion. Four of the five participants who received L9LS subcutaneously were protected from infection. L9LS has a long serum half-life of 56 days, and the authors predict that a single subcutaneous injection could provide protection for up to 6-12 months.

The major strengths of monoclonal antibody therapy are that it can provide a reliable level of antibodies, regardless of the host immune status, and that its level can be achieved within 24 hours of administration. In contrast to RTS, S/AS01 malaria vaccine, the L9LS monoclonal antibody does not trigger a host memory immune response [13]. Thus, repeated administration would be necessary to maintain

protective antibody levels. Larger clinical trials to test L9LS and other antimalarial monoclonal antibodies in regions where malaria is endemic are underway.

There is also ongoing research to develop a monoclonal antibody against *P. vivax*. Since *P. vivax* shows a strict host tropism for immature red blood cells (reticulocytes), investigators have identified a transferrin receptor 1 (TfR1) as the reticulocyte membrane receptor specific for *P. vivax*. Investigators have also determined that the *P. vivax* protein which binds to TfR1 is PvRBP2b [14]. Development of monoclonal antibodies to binding protein PvRBP2b inhibited *P. vivax* entry into human reticulocytes, thus, inhibiting *P. vivax* blood stage infection.

Despite existing drugs and now the concept of monoclonal antibodies for travellers to endemic areas, there is ongoing work screening for chemical leads for next generation chemoprotective antimalarials [15]. From 2016 to 2018, over 500,000 compounds were tested for their ability to inhibit liver-stage development of malaria. A drug that blocks parasite replication in the liver works on a much lower parasite burden. In addition, a chemical that targets the early liver stage has a lower chance of encountering and selecting for a rare parasite with a resistant mutation than do blood stage active compounds. A substantial number of new chemicals with potent liver-stage antimalarial activity were identified. These results are available to all investigators and can now be tested by scientists seeking to accelerate malaria elimination through the drug development pipeline for chemoprotection [16].

Historical background

Antimalarial drug production increased greatly during World War II because malaria was a leading cause of disease among soldiers, especially those deployed to the South Pacific. Quinacrine, the first antimalarial widely used, had numerous side effects including yellowing of the skin. Research efforts to develop an alternative led field testing to one of its derivative compounds, chloroquine phosphate, by the US Army in 1943. Continued chemical modification resulted in hydroxychloroquine sulfate, introduced in 1955. A consequence of the mass use of antimalarials during World War II was the observation that they had a beneficial effect on lupus and rheumatoid arthritis in US soldiers. Hydroxychloroquine is now the most commonly prescribed antimalarial for treatment of autoimmune disease. Hydroxychloroquine is approved by the US FDA for treatment of discoid lupus, systemic lupus erythematosus and rheumatoid arthritis. While also approved to treat malaria, only *P. falciparum* can still be cured by hydroxychloroquine, and growing resistance limits the geographic location where the drug can be used effectively. On another front, chloroquine and hydroxychloroquine after careful study have failed to demonstrate any antiviral benefit in patients with the novel coronavirus responsible for COVID-19 [17].

Treatment concepts

One bright spot in the global campaign against malaria is that acute uncomplicated infections caused by *P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae* and *P. knowlesi*, if diagnosed properly, are treatable and curable [1]. Parasites infecting and killing red blood cells cause the symptoms of malaria. The most potent and clinically useful antimalarial drugs rapidly eliminate parasites growing in red blood cells. In fact, *P. vivax* has so far developed less resistance to common drugs [3]. Chloroquine which destroys parasites in red blood cells has lost most of its potency against *P. falciparum* but can still effectively treat acute infections of *P. vivax* in most regions. The development of chloroquine resistance by *P. falciparum* has spread to nearly all areas of the world. Studies show an association between pfcrt T76 mutation in *P. falciparum* and the development of chloroquine resistance during the treatment of malaria. This mutation is now used as a marker in surveillance for chloroquine-resistant *P. falciparum*. If a patient acquires uncomplicated *P. falciparum* infection in the areas of chloroquine resistance, artemether-lumefantine is the first choice, followed by atovaquone-proguanil or quinine sulfate plus doxycycline, tetracycline or clindamycin. If an acute P. falciparum infection is confirmed by a clinical laboratory, it should be reported to the state health department as part of the CDC surveillance efforts.

Today, artemisinin and its derivatives are cornerstones of malaria treatment worldwide. Traditional Chinese medicine herbal fever remedies often included sweet wormwood (*Artemisia annua*). Extract from the plant led to the discovery of artemisinin by Professor Tú Yōuyōu of the China Academy of Traditional Chinese Medicine in Beijing. For her discovery of a novel therapy for malaria, Yōuyōu received one-half of the Nobel Prize for Medicine in 2015 [18]. However, by 2016, recent gains in reducing the global burden of malaria were threatened by the emergence of *P. falciparum* resistance to artemisinin [19]. The discovery that mutations in portions of the *P. falciparum* gene encoding Kelch 13 (K13)-propeller domains are the major determinant of resistance has provided opportunities for monitoring such resistance on a global scale [20]. Thus far, studies show that mutations slow the rate at which drug treatment eliminates a parasite from patients' bodies. Fortunately, despite observed delay in parasite clearance, artemisinin used in combination with other antimalarial therapy remains effective.

Malaria infection can be categorized as uncomplicated or severe (complicated). Severe malaria which is usually caused by *P. falciparum* occurs when infections are complicated by serious organ failures or abnormalities in the patient's blood or metabolism. Manifestations of severe malaria include the following: Cerebral malaria with abnormal behavior, impairment of consciousness, seizures, coma or other neurological abnormalities. Other clinical indicators of severe malaria include acidosis with rapid and deep labored breathing and venous plasma lactate equal to or greater than 5 millimoles per liter, serum bilirubin greater than 3 mg/dL and *P. falciparum* parasitemia count greater than 2.5%. Initial recommended treatment in the United States for severe malaria due to *P. falciform* is intravenous artesunate 2.5 mg/kg over 1-2 minutes at zero, 12 and 24 hours and then once daily until the patient can tolerate oral antimalarial therapy [21]. Artesunate for injection, a semisynthetic artemisinin derivative, is the recommended treatment of choice by the FDA in the United States for induction treatment of severe malaria in children and adults. It has been shown to reduce mortality compared to parenteral quinine in children and adults. After intravenous administration, artesunate is rapidly converted to the active metabolite dihydroartemisinin (DHA). Artesunate and DHA, which are both active against the blood stage parasites of Plasmodium species, including chloroquine-resistant strains, can clear parasitemia within 48-72 hours. They do not prevent relapses of *P. vivax* or *P. ovale* parasitemia which can arise from the dormant hypnozoite stage in the liver. Artesunate and DHA have limited activity against the mature sexual gametocytes of *Plasmodium* species, which circulate in the peripheral blood, and are ingested by the female *Anopheles* mosquito. Resistance has been reported, however, in some parts of Southeast Asia. Initial use of intravenous artesunate should always be followed by a complete course of treatment with an oral antimalarial regimen, preferably artemether-lumefantrine. Other oral follow-up regimens are atovaquone-proguanil, quinine plus doxycycline, tetracycline or clindamycin or mefloquine. If malaria occurred while the patient was taking one of these oral antimalarial drugs for prophylaxis, that drug should be excluded from the treatment regimen unless no other options are available. Relapses can occur in patients treated with intravenous artesunate monotherapy who are not subsequently treated with a complete oral regimen.

Chloroquine still effectively treats acute uncomplicated infections of *P. vivax* and *P. ovale* in most regions. Besides treating acute *P. vivax* and *P. ovale* infection, additional treatment of *P. vivax* and *P. ovale* dormant liver stage called "hypnozoites" (the name derived from "sleeping parasites") is needed and remains a challenge. Hypnozoites may remain inside a liver cell for weeks, months and even years waiting until chances are good that a recipient mosquito will be available to pass sexual stages onto the next victim [3]. The dormant liver stage for *P. vivax* can last up to 2 years, and the dormant liver stage for *P. ovale* can last up to 4 years. The hypnozoites allow the *P. vivax* and *P. ovale* parasite to survive in more temperate zones where mosquitoes bite only part of the year. Hypnozoites cannot be detected by blood tests, and so, theoretically, the best strategy to eliminate the

parasite from a region would be to mass-treat populations with a drug that could kill the sleeping pathogen. Primaquine daily for 14 days or a single dose of a newer drug, tafenoquine, target liver stage parasites. The oral antimalarial tafenoquine succinate is a long-acting analog of primaquine [22-25]. Brazil has the highest incidence of malaria in South America, with 143,381 endogenous cases of malaria recorded in 2021 of which 84% were due to *P. vivax*. The elimination of *P. vivax* infection, which is critical to eliminating malaria, is challenging because of the ability of *P. vivax* parasite to persist in the liver as a quiescent hypnozoite. Until recently, primaquine was the only licensed antimalarial drug that could kill hypnozoites, but primaquine has now been joined by tafenoquine which has the advantage of being a single dose [24,25]. In 2022, it was reported from Brazil that the administration of primaquine at a total dose of 7 milligrams per kilogram (0.5 milligrams per kilogram per day for 14 days) had higher efficacy in preventing relapse of *P. vivax* malaria than a total dose of 3.5 milligrams per kilogram (0.5 milligrams per kilogram per day for 7 days) through 168 days of follow up [26]. This study shows that when primaquine is administered at the right dose for a sufficient period of time, it is an effective treatment to prevent the recurrence of *P. vivax* malaria in South America. However, it would be difficult to force large numbers of people who don't feel ill to take the treatment [27]. Further, primaquine and tafenoquine are not recommended for use in pregnant women and should not be given to people who have a genetic condition called G6PD deficiency. G6PD stands for glucose-6-phosphate dehydrogenase, an enzyme that is especially important in red blood cell metabolism. In patients with G6PD deficiency, both primaquine and tafenoquine can cause hemolytic anemia. There is no cheap, easy field test to screen for G6PD traits, and so any mass treatment campaign risks severe side effects in some people. The search for other anti-hypnozoite drug candidates is ongoing.

In patients with severe (complicated) malaria due to *P. vivax* or *P. ovale*, intravenous artesunate should be administered with primaquine, which is active against the hypnozoite liver stage form of malaria parasites [21]. Tafenoquine, a long-acting analogue of primaquine, prevents relapses of *P. vivax* parasitemia when used in combination with chloroquine, but one clinical trial found that it lacked efficacy for this indication when used with an artesunate-based drug [21].

Cardiac complications of malaria

The most common strains of malaria are *P. falciparum* and *P. vivax*. Most notably, *P. falciparum* can cause serious complications, such as lung, kidney and cerebral damage. Malaria can be fatal, and the treatment of this disease can be challenging. Although the malaria parasite can affect all organs, cardiovascular (CV) involvement is considered a rare complication [28]. The majority of published data about CV involvement, such as electrocardiographic abnormalities (prolonged QTc), myocarditis or pericarditis, comes from case reports or small studies. However, severe CV complications of malaria may be unrecognized or underreported due to inexperience, lack of diagnostic strategies or overlap with fatal complications, such as pulmonary manifestations and circulatory collapse. In a state-of-the-art review by the emerging leaders' program of the Inter-American Society of Cardiology, an algorithm for appropriate use of diagnostic tools to assess cardiac involvement has been developed [28]. Future research including prospective trials with long-term follow up are recommended to define the spectrum of cardiac complications of malaria.

Because the CV system is quite resistant to the systemic response elicited by malaria infection, treatment focuses on reducing the level of parasitemia. Cardiac complications, such as prolonged QTc, myocarditis or pericarditis, usually resolve once the infection is effectively treated; therefore, there are no specific treatments for CV manifestations other than hemodynamic support when necessary.

Since cardiac involvement of acute malaria infection is rare, the choice of some medicines for treatment of malaria affect risk. In some parts of the world, cost and availability results in use of antimalarial medications which are proarrhythmic. *Plasmodium falciparum* can progress to severe (complicated) malaria and has become more resistant to oral chloroquine. This strain, therefore, has a different treatment regimen. If intravenous artesunate is not available, severe (complicated) *P. falciparum* malaria is treated with intravenous quinidine, and patients require intensive care continuous monitoring [29]. If the level of parasitemia decreases and clinical symptoms begin to resolve, oral quinine with sulfadoxine replaces quinidine. Polymorphic ventricular tachycardia is a known life-threatening complication of quinidine [29].

The antimalarials, hydroxychloroquine and chloroquine were approved before the now mandatory evaluation of drugs for QT prolongation risk. Mechanistically, hydroxychloroquine blocks the potassium channels leading to prolongation of the QT interval. This in turn increases the risk of torsades de pointes and sudden death [17,30].

Current recommendations include periodic electrocardiographic measurements during treatment of malaria [31]. Long QTc can result from both the parasitic compromise and from the choice of antimalarial medications. Most vulnerable populations, such as children with severe anemia, often experience long QTc during the recovery phase of malaria. Quinidine can cause QTc prolongation and should be administered only with frequent electrocardiographic monitoring. When treating uncomplicated *P. falciparum* malaria, extended artemisinin-based combination therapy is sometimes used in conjunction with existing drug regimens to prevent resistance. It is important to note reports of cardiotoxicity including the antimalarial drug lumefantrine [32]. Thus, prolonged QTc interval is a concern with this regimen as well.

The recommendations are, if the QTc interval becomes prolonged by greater than 50% of the baseline value, the antimalarial treatment should be stopped [31]. Treatment should only resume once the QTc interval prolongation falls to less than 25% above the baseline value. Concomitant use of beta-adrenergic blocking drugs which shorten the QTc may make antimalarial treatment safer in selected patients and warrants future study in double-blind clinical trials.

Mefloquine, another antimalarial drug, sometimes causes sinus bradycardia and QTc interval prolongation [31]. In general, patients with cardiac conduction system disorders or taking antimalarial medication should be monitored carefully with frequent electrocardiograms.

In conclusion, cardiac involvement during acute malaria infection appears to be rare from the low reported incidence. Further, with careful clinical and electrocardiographic monitoring, most cardiovascular complications of malaria and its treatment are fully reversible.

The malaria-high blood pressure hypothesis

With physicians serving in malaria-endemic developing countries and increased immigration of patients from these countries, the malaria-high blood pressure hypothesis warrants discussion and currently constitutes a major subject of research [33]. Recent studies, particularly in sub-Saharan African countries, have suggested that exposure to malaria parasites during pregnancy or childhood may result in hypertension in adult life. Two key mediators of the malaria-high blood pressure association are: endothelial dysfunction (reduced NO) and increased angiotensin-converting enzyme activity/angiotensin 2 levels. Of note, sickle cell trait is associated with protection against malaria infection, and these patients are less likely to develop hypertension. The link between malaria and high blood pressure warrants continued clinical studies.

Further information in the fight against malaria

Beyond the focus of this paper are efforts coordinated by the World Health Organization (WHO) in the fight against malaria. These initiatives include dealing with mosquitoes and will require combining established approaches with innovative new strategies in development [34]. An update on insecticides, improved bed nets, engineering genes to end malaria and the world's first malaria vaccine are recently reviewed [12,35]. In recent years, the WHO has certified Algeria, El Salvador, Paraguay, Argentina and China free of endemic malaria [36].

Summary and conclusions

There has been an increase in cases of malaria in the Continental United States. Malaria should be considered as a potential medical emergency. Delay in diagnosis and treatment is the leading cause of death from malaria in patients in the United States. Physicians must now consider malaria among the differential diagnoses of patients presenting with an acute febrile illness. Recent international travel questions are an important part of the initial patient evaluation so proper laboratory testing can be done. Besides diagnosing malaria infection, determining the *Plasmodium* species is important so proper treatment is given. *Plasmodium vivax* and *P. ovale* require treatment of the red blood cell infection as well as treatment of the hypnozoite in the liver to avoid relapse. Complications of severe malaria, which are primarily caused by *P. falciparum*, include QTc prolongation and shock. Some of the antimalarial medicines also cause QTc prolongation, and so cardiology consultation in patient management is expected. With careful clinical and electrocardiographic monitoring during therapy, most cardiovascular complications of malaria and its treatment are fully reversible.

With increasing international travel and physicians volunteering with Physicians without Borders to malaria-endemic countries, protective measures against female *Anopheles* mosquito bites in addition to prophylactic chemoprotective medicines are essential. Development of long-acting monoclonal antibodies against malaria infection may be available in the future to make travel to these countries safer.

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[*] ***Correspondence:*** Richard E. Katholi, M.D, Prairie Cardiovascular Consultants, Ltd., P.O. Box 19420, Springfield, IL 62794-9420, USA, E-mail: rkatholi@aol.com

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