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Predrag Čanović[1,2], Biljana Popovska-Jovičić[1,2,†], Milorad Pavlović[3]

Malaria in the 21st century – still a threatening problem

Маларија у 21. веку – и даље претећи проблем

[1]Kragujevac Clinical Center, Clinic for Infectious Diseases, Kragujevac, Serbia;
[2]University of Kragujevac, Faculty of Medical Sciences, Department of Infectious Diseases, Kragujevac, Serbia;
[3]Retired Professor, Infectologist, Belgrade, Serbia

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†**Correspondence to:**
Biljana POPOVSKA-JOVIČIĆ
Kragujevac Clinical Center, Clinic of Infectious Diseases, Zmaj Jovina 30, 34000 Kragujevac, Serbia
E-mail: **biljanapop@yahoo.com**

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SUMMARY
There are six parasite species (*P. falciparum*, *P. vivax*, *P. ovale curtisi*, *P. ovale wallikeri*, *P.malariae*, and *P. knowlesi*) that cause malaria in humans. *P. falciparum* is responsible for most malaria-related deaths globally. *P. vivax* is the dominant malaria parasite in most countries outside of the Sub-Saharan Africa. In 2016, 91 countries reported a total of 216 million cases of malaria. The global tally of malaria deaths reached 445,000. In 2016, 24 cases of imported malaria were registered in the Republic of Serbia, with an incidence of 0.33/100,000. According to the WHO recommendations, every suspected malaria case should be confirmed by microscopy or a rapid diagnostic test before treatment. The main stone of antimalarial therapy should be artemisinin-combinations. Since malaria occurs in Europe as an imported (though rarely an autochthonous and a hospital-borne infection), the aim of this paper is to point out current problems and attitudes in the diagnosis and treatment of malaria, without entering into data field significant for professionals (infectologists, epidemiologists, intensivists).
Keywords: malaria; antimalarials; chemoprophylaxis; laboratory diagnostics

САЖЕТАК
Постоји шест врста паразита рода *Plasmodium* (*P. falciparum, P. vivax, P. ovale curtisi, P. ovale vallikeri, P. malariae* и *P. knowlesi*) који узрокују маларију код људи. *P. falciparum* је одговоран за већину смртних случајева везаних за маларију. *P. vivax* је доминантни паразит маларије у већини земаља изван подсахарске Африке. У 2016. години 91 земља је пријавила укупно 216 милиона оболелих од маларије. Број смртних случајева у 2016. години је 445.000. У 2016. години у Србији регистрована су 24 оболела од маларије (учесталост 0,33/100.000). У складу са препорукама *WHO*, свака сумња на маларију треба да се потврдити микроскопијом или брзим дијагностичким тестом пре лечења. Главни ослонац антималаричне терапије треба да буду артемисинин-комбинације. Будући да се маларија у великом броју европских земаља јавља као унесена (мада ретко и као аутохтона и болнички стечена инфекција) циљ овог рада је упознавање са актуелним проблемима и ставовима у дијагностици и лечењу маларије, без упуштања у детаље значајне за професионалце који се овим проблемима посебно баве (инфеколози, епидемиолози, интензивисти). .
Кључне речи: маларија; антималарици; хемопрофилакса; лабораторијска дијагностика

INTRODUCTION

There are six parasite species *(P. falciparum, P. vivax, P. ovale curtisi, P. ovale wallikeri, P. malariae, P. knowlesi*) that cause malaria in humans. *P. falciparum* and *P. vivax*– pose the greatest threat. *P. falciparum* is the most prevalent malaria parasite on the African continent. In 2016 ninety-one countries reported a total of 216 million cases of malaria. The global burden of malaria deaths reached 445,000 victims, mostly children under five years of age [1]. The number of confirmed malaria cases reported in the EU/EEA from 2008 to 2012 ranged between 5,000 and 7,000 [2]. Since the late 1990s autochthonous malaria cases occurred in some European countries (Spain, Germany, Netherlands, France, Italy, and Greece) while between January 2016 and April 2018, six sporadic hospital transmissions of malaria were identified in the European Union.[3]

The lastautochthonous case of malaria in former Yugoslavia was registered in 1964. Since then, malaria has been recorded only as animported, tropical disease.In the period 1990-2001, one hundred and fifty-eight cases of imported malaria in the Republic of Serbia were registered, while, in the period from 2001. to 2009, malaria was diagnosed in 102 patients, mainly from the Afro-Asian region [4]. In 2016, twenty-four cases of imported malaria were registered in the Republic of Serbia, with an incidence of 0.33/100,000 [5].However epidemic potential for malaria transmission is relative small in our community [6, 7].

ACCEPTED DIAGNOSTIC PROCEDURES

According to the WHO recommendations every suspected malaria case should be confirmed by microscopy or a rapid diagnostic test (RDT) before treatment.

Parasitological diagnostics, a classic overview of thin and thick blood smear colored according to Giemsa, remains the "gold standard" of diagnostics. Thin and thick blood smear consists of a thick layer of lysed red blood cells. The blood elements, including parasites, are more concentrated so, thick blood smear allow a more efficient detection of parasites even in small numbers (increased sensitivity). Morphology and the ratio of parasites with erythrocytes are preserved, so the typical forms of individual parasites can be identified. In the thin blood smear, the degree of parasitemia, the appearance of pigments in leukocytes, the number of thrombocytes, and other possible hematological changes can be assessed as well. A well-educated parasitologist, standardized laboratory procedures, enough time to review are preconditions for quality performance reviews [8].

Malaria Rapid Diagnostic Tests [RDT] detect specific antigens (proteins, enzymes) of malaria parasites. Some of tests can detect only one species (*P. falciparum*) while others detect multiple species (*P. vivax, P. malariae* and *P. ovale*). Immunochromatographic tests can target the histidine-rich protein 2 of *P. falciparum*, a pan-malarial plasmodium aldolase, and the parasite specific lactate dehydrogenase. Studies have found that the sensitivity was between 86.7-93.4%, while the specificity was estimated at 98.2% to 99.3% [8–11].

QBC method (Quantitative Buffy Coat Technique) uses a fluorescence technique to detect parasites colored with acridine-color. For precise diagnosis, a check with a classic scanning technique is always recommended [12].

Molecular diagnostics most commonly uses polymerase chain reaction(PCR), providing superior specificity and sensitivity compared to other mentioned methods, which is of particular importance in epidemiological and resistance studies [8, 13].Real-time PCR, may be useful as a method complementary to microscopy, particularly in cases of low parasitemia, and for species determination, especially in non-P. falciparum cases where most instances of misdiagnosis occur [13].

ACTUAL RECOMMENDATIONS FOR THERAPY AND PROTECTION

Actual therapeutic approaches have undoubtedly been marked by new therapeutic protocols. Particularly important items of data are related to the resistance of parasites [14].

Antimalarials come from different chemical structures. The 4- aminoquinolines are chloroquine, quinine, mefloquine, amodiaquine, while the 8-aminoquinolone is primaquine. The antifolates area class of antimetabolite medications such as pyrimethamine, proguanil and sulfadoxine. The artemisinin derivatives (artemisinin, artesunate, artemether, arteether) are sequiterpene lactones, while atovaquone is hydroxynaphthaquinones. Various antibiotics - primarily tetracyclines and clindamycin have antimalarial effects [15]. Current WHO recommendations for the treatment of uncomplicated *P. falciparum* malaria are presented in Figure 1 [16].

According to Figure 1, WHO uncomplicated faciparum malaria should be treated with artemisinin-mixed treatment (ACT). Artemether–lumefantrine, dihydroartemisinin – piperaquine, artesunate– amodiaquine, artesunate–mefloquine and artesunate–sulfadoxine–pyrimethamine are currently the most used combinations. Eighteen treatment regimens were reported (period 2003-2009) in several European countries. Atovaquone-proguanil was predominantly used, followed by older drugs such as mefloquine, or quinine alone or in combination with clindamycin or tetracyclines [17].

Two classes of drugs are available for parenteral treatment of severe malaria: artemisinin derivatives (artesunate or artemether) and the cinchona alkaloids-quinine. Experiences with the treatment of severe malaria give priority to the treatment of artesunate in relation to other therapeutic options [18, 19]. Artesunate should be applied parenterally, best intravenously, in all severe malaria in adults, children/infants, pregnant women in all trimesters and lactating women, or inpatients with relatively high parasitemia (> 2%). It is best to treat such patients in the intensive care units, since severe malaria is associated with a number of complications including acute respiratory distress syndrome, disseminated intravascular coagulation, acute kidney injury, seizures, and severe infections, even with sepsis.

Artemisinin combination therapy (ATC) is the mainstay of modern therapeutic protocols. Artemisinin and its semisynthetic derivatives such as artesunate, artemether, arteether dihydroartemisinin belong to the products of the plant *Artemisia annua*. They are sesquiterpene lactone containing an unusual peroxide bridge. Artemisinins are considered prodrugs that are activated to generate carbon-centered free radicals or reactive oxygen species, and are the most potent antimalarial agents, effective against nearly all asexual and sexual parasite stages [20].

Artemisinin component in artemisinin combination therapy (ACT) (artemether, artesunate, or dihydroartemisinin) reduces the number of parasites drastically during the first 3 days of treatment, but potential disadvantage may be a higher risk of recrudescence when these drugs are used in monotherapeutic regimens. Recrudescence signifies the emergence of a clinical picture of malaria from parasites that persist in erythrocytes after the initial treatment. That is why they are added drugs from another antimalarial groups which eliminate the remaining parasites, and in that way prevent recrudescent malaria [20].

In Serbia, malaria is treated in infectious departments of tertiary medical institutions, adapted to the WHO's advice. Unfortunately, due to low consumption, most antimalarial drugs are not registered, so procurement takes place according to special procedures. Artemisinin-mixed treatment is cornerstone for therapeutic approach, while artesunate is the preferred therapy for treatment of severe falciparum malaria.

Side effects of artemisinins occur rarely (3.4 %). However, the greater concern is related to haemolysis which occurs in approximately 10-15% patients, and even more

following intravenous artesunate treatment [21]. Delayed-onset anemia or postartesunate late hemolysis has been observed to occur 2–3 weeks following the initiation of IV artesunate, after complete parasite clearance, but this phenomenon is also described after oral administration of artemisin drugs. Although there is no complete explanation for this phenomenon, it unconditionally requires additional differential diagnostic and therapeutic efforts. Artemisinin resistance is a rare phenomenon, but the releases in the literature are more often found [22].

According to CDC recommendations chloroquine (or hydroxychloroquine) remains an effective choice for *P. vivax* and *P. ovale* infections. After the treatment of *Pl vivax /P. ovale* infection, primaquine should be used, or recently introduced tefanquine, due to the effects on hypnozoites in the liver, left after treatment, thus preventing malaria recidives [23].

It is said that 13 drugs are in advanced research development, two of which are in the advanced, final phase - artefenomel–ferroquine and lumefantrine-KAF156[24].

Arterolane, newer synthetic peroxide resembling the artemisinin derivative. Arterolane maleate and piperaquine effectively cures *P. falciparum*malaria by day 28 in paediatric patients, which justifies the clinical application of this combination [24, 25].

FDA approved tafenoquine for prevention of relapse of vivax malaria on July 20, 2018. Tafenoquine is an 8-aminoquinoline. The final examination, and even authorization by the FDA, was experienced Tafenoquinea single-dose treatment for *Plasmodium vivax* relapse prevention. Administration of this drug, as well as primaquine, follow the same restriction and adverse events (glucose-6-phosphate dehydrogenase deficiency) [26].

CHEMOPROPHYLAXIS

The experiences of European authors show that only 10% of patients with severe malaria had taken antimalarial chemoprophylaxis and very few of them had been fully compliant [17].

The most commonly recommended regimens of chemoprophylaxis are: doxycycline 100 mg once daily (started one day before travel, and continued for four weeks after returning);

mefloquine 250 mg once weekly (started two-and-a-half weeks before travel, and continued for four weeks after returning); atovaquone/proguanil 1 tablet daily (started one day before travel, and continued for 1 week after returning [27].

Among the recommended drugs the combination of atovaquone-proguanyl, is the most justified, especially in regions where there is a multi-resistant malaria. The impact of substituting atovaquone-proguanil for all mefloquine usage resulted in a 2.3% decrease in estimated infections [28].

Advice on the protection from mosquito bites (repellents, insecticide impregnated bed nets, etc.) are certainly an important part of the protection.

The vaccine remains an unfulfilled dream, although work on it is still being carried out with great enthusiasm today. In July 2015, the Committee for Medicinal Products for Human Use of the European Medical Agency gave a positive opinion of the "candidate vaccine" Mosquirix. The vaccine is awaiting the final response by the WHO and the African Health Authorities, with whose approval the phase III of its examination has been conducted [29]. The latest information favors, the vaccine which consists of the central repeat the C-terminal domain of *Plasmodium falciparum* circumsporozoite protein, fused to hepatitis B virus surface antigen (HBsAg) in a 1:4 ratio. This vaccine demonstrated protective efficacy against clinical malaria in a Phase III clinical trial [30].

Conflict of interest: None declared.

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Table 1. Treating uncomplicated *P. falciparum* malaria [16] – reproduced with WHO permission

Treatment of uncomplicated *P. falciparum* malaria. Treat children and adults with uncomplicated *P. falciparum* malaria (except pregnant women in their first trimester) with one of the following recommended ACTs: • **artemether + lumefantrine** • **artesunate + amodiaquine** • **artesunate + mefloquine** • **dihydroartemisinin + piperaquine** • **artesunate + sulfadoxine–pyrimethamine (SP).** *Strong recommendation, high-quality evidence*
Duration of ACT (artemisinin-based combination therapy) treatment **ACT regimens should provide 3 day's treatment with an artemisinin derivative.** *Strong recommendation, high-quality evidence*
Revised dose recommendation for dihydroartemisinin +piperaquine in young children **Children weighing <25 kg treated with dihydroartemisinin + piperaquine should receive a minimum of 2.5 mg/kg bw per day of dihydroartemisinin and 20 mg/ kg bw per day of piperaquine daily for 3 days.** *Strong recommendation based on pharmacokinetic modelling*

