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Malaria in the 21st century – still a threatening problem

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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 World Health Organization 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-based combinations. Since malaria occurs in Europe as an imported (though rarely also autochthonous and a hospital-borne infection), the objective of this paper is to point out current problems and attitudes in the diagnosis and treatment of malaria, without entering the data field significant for professionals (infectologists, epidemiologists, intensivists).
Keywords: malaria; antimalarials; chemoprophylaxis; laboratory diagnostics

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, 91 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 European Union and the European Economic Area (EU/EEA) from 2008 to 2012 ranged 5,000–7,000 [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 EU [3].

The last autochthonous case of malaria in former Yugoslavia was registered in 1964. Since then, malaria has been recorded only as an imported, tropical disease. In the 1990–2001 period, 158 cases of imported malaria were registered in the Republic of Serbia, while in the 2001–2009 period, malaria was diagnosed in 102 patients, mainly from the Afro-Asian region [4]. In 2016, 24 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 relatively small in our community [6, 7].

ACCEPTED DIAGNOSTIC PROCEDURES

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

Parasitological diagnostics, a classic overview of thin and thick blood smear colored according to Giemsa, remain 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 the thick blood smear allows a more efficient detection of parasites even in small numbers (increased sensitivity). Morphology and the ratio of parasites to 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, and enough time to review are preconditions for quality performance reviews [8].

Rapid diagnostic tests detect specific antigens (proteins, enzymes) of malaria parasites. Some of the 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

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parasite-specific lactate dehydrogenase. Some studies have found that the sensitivity was 86.7–93.4%, while the specificity was estimated at 98.2–99.3% [8–11].

Quantitative buffy coat method uses a fluorescence technique to detect parasites stained with acridine dye. For precise diagnosis, a check with a classic scanning technique is always recommended [12].

Molecular diagnostics most commonly use 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, in which 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, and 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 sesquiterpene lactones, while atovaquone is hydroxynaphthoquinones. Various antibiotics – primarily tetracyclines and clindamycin – have antimalarial effects [15]. Current WHO recommendations for the treatment of uncomplicated *P. falciparum* malaria are presented in Table 1 [16].

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 treatment ACT regimens should provide a 3-day 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 of body weight per day of dihydroartemisinin and 20 mg/kg of body weight per day of piperaquine daily for 3 days *Strong recommendation based on pharmacokinetic modelling*

ACT – artemisinin-based combination therapy

According to Table 1, uncomplicated *faciparum* malaria should be treated with artemisinin-based combination therapy (ACT). Artemether–lumefantrine, dihydroartemisinin–piperaquine, artesunate–amodiaquine, artesunate–mefloquine, and artesunate–sulfadoxine–pyrimethamine are currently the most used combinations. Eighteen treatment regimens were reported (2003–2009 period) 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 cases of severe malaria in adults, children/infants, pregnant and lactating women, or inpatients with relatively high parasitemia (> 2%). It is best to treat such patients in 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.

ACT is the mainstay of modern therapeutic protocols. Artemisinin and its semisynthetic derivatives, such as artesunate, artemether, and arteether dihydroartemisinin, are obtained from the plant *Artemisia annua*. They are sesquiterpene lactone containing an unusual peroxide bridge. Artemisinins are considered prodrugs 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 ACT (artemether, artesunate, or dihydroartemisinin) drastically reduces the number of parasites during the first three 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. This is why drugs from other antimalarial groups are added, 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 the 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 hemolysis 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 two to three weeks following the initiation of IV artesunate, after complete parasite clearance, but this phenomenon is also described after oral administration of artemisinin 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 found more often [22].

According to Centers for Control and Disease Prevention recommendations, chloroquine (or hydroxychloroquine) remains an effective choice for *P. vivax* and *P. ovale* infections. After the treatment of *P. vivax* / *P. ovale* infection, primaquine should be used, or recently introduced tafenoquine, due to the effects on hypnozoites in the liver, left after treatment, thus preventing malaria relapses [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 is a newer synthetic peroxide resembling the artemisinin derivative. Arterolane maleate and piperaquine effectively cures *P. falciparum* malaria by day 28 in pediatric patients, which justifies the clinical application of this combination [24, 25].

The US Food and Drug Administration approved tafenoquine for the prevention of relapse of *vivax* malaria on July 20, 2018. Tafenoquine, an 8-aminoquinoline, is used as a 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

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 as follows: doxycycline 100 mg once daily (started one day before traveling, and continued for four weeks after returning); mefloquine 250 mg once weekly (started 2.5 weeks before traveling, and continued for four weeks after returning); atovaquone/proguanil one tablet daily (started one day before traveling, and continued for one week after returning) [27].

Among the recommended drugs, the atovaquone–proguanil combination is the most justified one, especially in regions where there is a multi-resistant malaria. The impact of substituting atovaquone–proguanil for all mefloquine use 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 Medicines Agency gave a positive opinion for the "candidate vaccine" Mosquirix. The vaccine is awaiting the final response from the WHO and African health authorities, with whose approval 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 Phase III clinical trial [30].

Conflict of interest: None declared.

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Маларија у 21. веку – и даље претећи проблем

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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 су регистрована 24 оболела од маларије (учесталост 0,33/100.000). У складу са препорукама *WHO*, свака сумња на маларију треба да се потврди микроскопијом или брзим дијагностичким тестом пре лечења. Главни ослонац антималаричне терапије треба да буду комбинације са артемисинином. 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