

## CURRENT THERAPEUTIC EVIDENCE BASED APPROACHES TO PATIENTS WITH FALCIPARUM AND NON-FALCIPARUM MALARIA

A.S. Sydoruk, V.D. Moskaliuk

HSEE of Ukraine «Bukovinian State Medical University», Chernivtsi

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E-mail:  
sidorchuk@bsmu.edu.ua

Malaria is a major concern for international health authorities and potentially life-threatening disease because of millions of people suffer every year in the world due to a parasite of the Plasmodium genus transmitted by an infective female Anopheles mosquito vector. Due to the complexity of the parasite biology and genetics, there is currently no vaccine. Individuals with malaria may present with fever and a wide range of symptoms. The second half of the 20th century saw the emergence of strains of malaria parasites (mainly P.falciparum) resistant to chloroquine, which was the most commonly used drug for treatment of the disease. While resistance spread geographically, it also evolved chemically including to other antimalarial drugs like quinine, sulfadoxine, pyremethamine, and proguanil.

**The aim of research.** To describe modern aspects of etiology and epidemiology of malaria, caused by different species of parasite; and to highlight clinical peculiarities with analysis of the best evidence based recommendations of its chemotherapy.

**Methods.** We had used scientific paper searching in Scopus, Cochrane databases, and NCBI library (Pubmed) by key words as "malignant tertian malaria treatment", "benign tertian malaria", benign quartana malaria", "malaria and pregnancy", "resistance to antimalarials".

**Results.** Nowadays there are six known genetically different species of Plasmodium caused malaria disease in human worldwide. This vector-borne infection may transmit via mosquito, blood products, a liver transplantation and through placenta from pregnant to fetus. If suspected any malaria type, promptly therapy should be suggest accounted travel anamnesis and WHO as well as national recommendations. Therapy contained arthemisin in combination with lumefantrine or mefloquine is better and more effective than monotherapy. In case of P.ovale and P.vivax primaquine phosphate is essential to preclude recrudescences.

**Conclusions.** Ukraine is the eastern European country with annual morbidity because of exotic cases connected with travels and employment. In case of fever, chills, sweats, hepatosplenomegaly patient should be tested for parasite presence by methods of parasitology of thick drop and thin smear of blood. Chemoprophylaxis within all duration in endemic country by available antimalarial should be obligatory before planning to subtropical and tropical regions.

**Ключові слова:**  
лікування, плазмодії,  
рецидив, тяжка ма-  
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## СУЧАСНІ ПІДХОДИ ДО ЛІКУВАННЯ РІЗНИХ ВИДІВ МАЛЯРІЇ З УРАХУВАННЯМ ЗАСАД ДОКАЗОВОЇ ІНФЕКТОЛОГІЇ

A.S. Sydoruk, V.D. Moskaliuk

Малярія викликає велике занепокоєння міжнародних інстанцій охорони здоров'я та є потенційно небезпечною для життя хворобою мільйонів людей, які щороку страждають у світі через цього збудника – паразита роду плазмодіїв, які передаються самкою комара роду Anopheles. Через складну біологію і генетику паразита, на даний час вакцини не існує. Хворі на малярію можуть мати лихоманку та широкий спектр симптомів. У другій половині ХХ століття з'явилися штами паразитів малярії (переважно P. falciparum), які є стійкі до хлорохіну, що найчастіше використовується для лікування захворювання. Резистентність поширилася географічно, однак вона також «еволюціонувала хімічно», охопивши інші протималярійні препарати, такі як хінін, сульфадоксин, піреметамін та прогуаніл.

**Мета дослідження.** Проаналізувати сучасні аспекти хіміотерапії малярії з огляду на тип плазмодія, його географічний нозоареал, вікові та гендерні особливості, клінічний перебіг та лабораторні показники з урахуванням міжнародних рекомендацій в ухваленні правильних клінічних рішень.

**Матеріал і методи.** Проведено огляд релевантних наукових публікацій баз даних Scopus, Cochrane та бібліотеки NCBI (Pubmed) за такими ключовими словами: «лікування злоякісної третинної малярії», «доброякісна третинна малярія», «доброякісна чотириденна малярія».

**Результати.** На сьогоднішній день у світі відомо шість генетично різних видів плазмодія, які здатні спричинити хворобу в людини. Ця трансмісивна інфекція може передаватися через укуси комара, через препарати інфікованої крові, трансплантацію печінки та через плаценту від вагітної до плоду та новонародженого. Якщо підозрюється будь-який тип малярії, слід негайно запропонувати терапію з урахуванням анамнезу подорожей, рекомендацій ВООЗ та національних рекомендацій. Терапія, що містить артемізин у комбінації з люмефантрином або мефлохіном є кращою та ефективнішою за монотерапію. У випадку малярії, спричиненої *P. ovale* та *P. vivax* призначення примахіну фосфату є необхідним, оскільки запобігає ймовірності рецидивів.

**Висновки.** Україна є східноєвропейською країною з щорічною захворюваністю через завізні випадки, пов'язані з поїздками та працевлаштуванням. У разі лихоманки, ознобу, поту, гепатоспленомегалії пацієнт повинен бути перевірений на наявність паразитів методами мікроскопії товстої краплі та тонкого мазка крові. Хіміпрофілактика доступними антималярійними препаратами повинна бути обов'язковою перед плануванням візиту, упродовж усього періоду перебування в ендемічній країні та місяць після повернення із субтропічних та тропічних регіонів.

## СОВРЕМЕННЫЕ ПОДХОДЫ К ЛЕЧЕНИЮ РАЗЛИЧНЫХ ВИДОВ МАЛЯРИИ С УЧЕТОМ ОСНОВ ДОКАЗАТЕЛЬНОЙ ИНФЕКТОЛОГИИ

**А.С. Сидорчук, В.Д. Москалюк**

Малярия вызывает большое беспокойство международных инстанций здравоохранения и является потенциально опасной для жизни болезнью миллионов людей, которые ежегодно страдают в мире из-за этого возбудителя - паразита рода плазмодиев, которые передаются самкой комара рода *Anopheles*. Из-за сложной биологии и генетики паразита, на данное время вакцины не существует. Больные малярией могут иметь лихорадку и широкий спектр симптомов. Во второй половине XX века появились штаммы паразитов малярии (в большинстве *P.falciparum*), которые являются стойкими к хлорохину, что чаще всего используется для лечения заболевания. Резистентность распространилась географически, но она также «эволюционировала химически», охватив другие противомаларийные препараты, такие как хинин, сульфодоксин, пиреметамин и прогуанил.

**Цель исследования.** Проанализировать современные аспекты химиотерапии малярии с учетом типа плазмодия, его географического нозоареала, возрастных и гендерных особенностей, клиническое течение и лабораторные показатели и с учетом международных рекомендаций в принятии правильных клинических решений.

**Материал и методы.** Проведён обзор релевантных научных публикаций баз данных Scopus, Cochrane и библиотеки NCBI (Pubmed) со следующими ключевыми словами: «лечение злокачественной третичной малярии», «доброкачественная третичная малярия», «доброкачественная малярия».

**Результаты.** На сегодняшний день в мире известно шесть генетически различных видов плазмодия, которые могут вызвать болезнь у человека. Эта трансмиссивная инфекция может передаваться через укусы комара, через препараты инфицированной крови, трансплантацию печени и через плаценту от беременной к плоду и новорожденному. Если подозревается любой тип малярии, стоит немедленно предложить терапию с учетом анамнеза путешествий, рекомендаций ВООЗ и национальных рекомендаций. Терапия, состоящая из артемизина в комбинации с люмефантрином или мефлохином является лучшей и более эффективной чем монотерапия. В случае малярии, вызываемой *P. ovale* и *P. vivax* назначение примахина фосфата является необходимым, поскольку предупреждает возможность рецидивов.

**Выводы.** Украина является восточно-европейской страной с ежегодной заболеваемостью из-за завезенных случаев, связанных с поездками и трудоустройством. В случае лихорадки, озноба, пота, гепатоспленомегалии пациент должен быть проверен на наличие паразитов методами микроскопии толстой капли и тонкого мазка крови. Химиопрофилактика доступными антималярійними препаратами должна быть обязательной перед планированием визита, во время всего периода пребывания в эндемической стране и месяца после

**Ключевые слова:**  
лечение, плазмодии,  
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## Introduction

Malaria is undoubtedly remains a scourge of mankind from very ancient times. Evolutionary biologists suggest that Plasmodium parasite was causing human disease for the last 100,000 years. Malaria now is still ranked the third leading cause of death due to an infectious agent after HIV and tuberculosis [1].

By WHO report, there are 219 millions of malaria cases in the world and 435 000 deaths at the end of 2017 [2]. Totally, the risk to have malaria have 3.3 billion of Earth population, moreover, for third part of them risk are very high because they live in countries with annual morbidity around thousand people [3].

Notably, that now the list of endemic malaria countries consist of 91 now in comparison with 87 five years ago, perhaps due to climate changes. Spreading and morbidity of malaria depend on unique insect – a vector of Plasmodium parasite – female mosquito of Anopheles genus. Nevertheless, social and economic development of country, free access for medical care and poverty of population are also factors of crucial importance [2].

Malaria is a transmissible parasitic infectious disease that is characterized by periodical fever paroxysms, liver and spleen enlargement, hemolytic anemia and jaundice. In human host it caused by six plasmodium types: *P. vivax*, *P. malariae*, *P. ovale*, *P. falciparum* and *P. knowlesi* and less known and geographically restricted *P. simium*. Tropical malaria is caused by *Plasmodium falciparum* parasite, which is the most severe one with high risk of cerebral malaria development and correlated with it the highest lethality. Such parasites as *Plasmodium vivax* and *Plasmodium ovale* are able to persist in the human host up to three years and then as dormant forms in the liver may reactivate and lead to early or late relapses.

In Europe, malaria was endemic till 1970. Recent Annual report of European Center for Disease Control (ECDC) report about 8349 cases in 2018, and 99,8% of them are travel-related cases. Malaria season in a few European countries like Italy, France, Spain and Greece lasted from July to September. Interestingly, that the overall rate of confirmed malaria cases was higher among men than women (1.6 cases and 0.7 cases per 100 000 population, respectively; male-to-female ratio 1.9:1) [4].

In Ukraine, most cases of malaria are exotic, and occurred after travelling to endemic Asian and African countries in people who did not follow preventive chemoprophylaxis there within all the time of being in zone of malaria spreading.

Annually, in Ukraine there were up to 50 cases of disease, and near tenth part of them, unfortunately, with fatal outcome. All cases connected with touristic trips and, rare – in foreign students from endemic countries [5].

## Results

Current review of modern scientific papers about malaria in Ukraine had evidenced few important conclusions from both epidemiologic and clinical points of view. Moderate and severe malaria mainly occurred

within two weeks (maximum – 47 days) upon arrival from endemic country. Tropical malaria has polymorphic clinical presentation, that's why physicians should be more attentive when questioning in details epidemic and occupational anamnesis (cases in geologists, sailors, aircraft staff, military staff). It's necessary to understand, that the diagnosis may be missed if a history of travel is not elicited.

Infected typically present with non-specific symptoms such as fever, chills, sweats, headache, and myalgia. Differential diagnosis due to these non specific symptoms include leptospirosis, influenza, viral hepatitis, yellow fever etc. It should be remembered that clinical symptoms of malaria in country with moderate climate as Ukraine can appear in any time because this disease is mainly travel related tropical illness. Examination of a Giemsa-stained blood film remains the diagnostic test of choice and should be repeated few times. Once the diagnosis of malaria is confirmed, treatment should be started urgently, as a delay may be associated with disease progression, complications and death.

Infection may also occur through infected blood transfusion [6-8]. Cases of vertical transmission are also happened especially in hyperendemic countries.

The geographical distribution of parasite species is dependent on ecological and social, behavioral factors affecting the ability of mosquitoes to transmit Plasmodium [9].

✓ *P. falciparum* is widespread in the tropic zones of Sub-Saharan Africa, areas of Southeast Asia, Oceania, and the Amazon basin of South America [1].

✓ *P. vivax* is predominantly found in most of Asia, the Americas, parts of Eastern Europe, and North Africa [10]. Nevertheless, about 80% of all cases occur in Ethiopia, India, and Pakistan. If compare these two parasites, *P. vivax* has a much wider distribution, as it can develop in the insect at lower temperatures and cooler climates. Both with *P. ovale*, it has a dormant liver stage and can reactivate within 3 years, causing a late relapse.

✓ *P. ovale* is occurring primarily in central and western Africa and islands in the West Pacific [11].

✓ *P. malariae* has a same distribution like *P. falciparum* but a lower prevalence [12-13].

✓ *P. knowlesi* is spread in certain forested areas of Southeast Asia.

✓ *P. simium* is spread in the Rio-de-Janeiro territory, genetically is different from the rest species, can cause malaria in human.

Treatment will depend on the infecting species, the appearance of the blood smear (% parasitaemia, presence of pre-schizonts or schizonts), and the clinical status of the patient. Consideration should be given to the likely susceptibility of the parasite to the treatment used, based on known epidemiology relating to the geographical area where the infection was acquired. Consequently, the goal of therapy is to eradicate infection; to reduce the risk of complications by reducing the parasite burden as soon as possible; and to avoid selecting resistance by using multiple agents.

Severity of *P. falciparum* malaria is explained by sequestration, rosetting, impaired red cell deformability, cytokine responses, and high levels of parasitaemia [5].

*Plasmodium falciparum* malaria is potentially fatal if not treated immediately, because life-threatening complications can develop rapidly in patients who initially appear well, and even short delays increase mortality risk [5].

Clinical and laboratory findings of severe malaria, caused by *P. falciparum*. Patients are considered as having severe malaria if they have one or more next features [15]. Clinical features: impaired consciousness (i.e., Glasgow coma score <11 in adults or Blantyre coma score <3 in children); clinical signs of jaundice; multiple convulsions (more than 2 episodes in 24 hours); prostration (generalised weakness so that the patient is unable to walk or sit up without assistance); significant bleeding (recurrent or prolonged bleeding from nose, gums, venepuncture sites, haematemesis, melaena); deep breathing, respiratory distress (acidotic breathing); pulmonary oedema (radiological finding, or oxygen saturation <92% on room air with a respiratory rate >30 breaths/minute often with crepitations on auscultation); circulatory collapse or shock - systolic blood pressure <80 mmHg in adults and <70 mmHg in children (decompensated shock); capillary refill  $\geq$ 3 seconds or temperature gradient on leg (mid-to-proximal limb) without hypotension (compensated shock).

Laboratory features: hyperparasitaemia (from above 2 % to >10%); hypoglycaemia (blood glucose <40 mg/dL [ $<2.2$  mmol/L]); serum bilirubin >3 mg/dL [ $>50$  micromol/L] with a parasite count >100,000/microlitre; renal impairment (serum creatinine >3 mg/dL [265 micromol/L]); metabolic acidosis (plasma bicarbonate <15 mEq/L [ $<15$  mmol/L]); severe malarial anaemia (children <12 years of age: Hb  $\leq$ 5 g/dL or haematocrit of  $\leq$ 15%; adults: Hb <7 g/dL or haematocrit of <20%) with a parasite count >10,000/microliter.

In non-immune patients (travelers from European countries) and people in low-transmission settings, parasitaemia above 2% is associated with increased risk of severe disease [13].

Supportive therapy is essential and vital with purpose of correcting the all above-mentioned complications. This includes correct fluid management, often with renal support; breathe support, control of convulsions, and transfusion of blood products. Hypoglycaemia as one of significant laboratory findings of severe disease may be worsened by quinine-induced hyperinsulinaemia [14].

Recommended therapeutic scheme for severe *falciparum* infection is:

- artesunate (parenteral) should be given until the patient is able to take oral treatment (at least 24 hours) and parasitaemia has fallen to less 1% (usually a minimum of three doses), followed by one of the following oral schemes: a full course of locally available ACT; atovaquone/proguanil; doxycycline or clindamycin, with or without quinine; or mefloquine [15, 16].

The WHO recommends alternative regimen like intramuscular artemether (preferly than quinine) if parenteral artesunate is not available. Also, a single dose of rectal artesunate may be administered to children

less 6 years of age [17]. A Cochrane review found that artemether is more effective than quinine in children and adults with severe malaria, and is less effective to artesunate in adults [18].

Therapeutic scheme to non-*falciparum* malaria infection. *P. malariae*, *P. vivax*, *P. ovale*, or *P. knowlesi* infection should be treated with oral chloroquine (preferred) or oral hydroxychloroquine for a total of three doses. *P. knowlesi*, which is found in parts of Southeast Asia, replicates every 24 hours, therefore, quick diagnostics and correct treatment of parasitic infection is essential [19]. *P. vivax* and *P. ovale* therapy schemes should be followed by oral primaquine for 14 days to eliminate the hypnozoite stages that are dormant in the liver tissue. The hypnozoiticidal activity of primaquine is predominantly a function of the total administered dose. The WHO recognises that a higher dose is needed in Southeast Asia, where there is a higher rate of relapse than in other areas [20]. Alternative schemes have been suggested (a shorter seven-day course, once-weekly dosing) to improve patient compliance [21, 22].

### Conclusions

Essential to understand, that uncontrolled self-treatment during stay in endemic areas can lead to long lasted persistence and late relapses [23]. There are often occur more severe cases of *Falciparum* malaria among military staff of Caucasian race, as in the study were described about Ukrainian soldiers after mission in Liberia. The most effective in treatment was scheme that include arthemeter parenteral (1<sup>st</sup> day 160 mg, next four days – 80 mg, plus doxycycline 100 mg twice a day followed by fansidar three pills at once [24]. In endemic and hyperendemic areas the administration of primaquine is precluding *P. falciparum* transmission and is suggested for travelers of a long stay there [25].

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#### Відомості про авторів:

Сидорчук А.С. – доктор філософії, доцент кафедри внутрішньої медицини та інфекційних хвороб Вищого державного навчального закладу України «Буковинський державний медичний університет», м. Чернівці, Україна. ORCID ID: <https://orcid.org/0000-0002-1959-6612>

Москалюк В.Д. – д.мед.н., професор, професор кафедри внутрішньої медицини та інфекційних хвороб Вищого державного навчального закладу України «Буковинський державний медичний університет», м. Чернівці, Україна. ORCID ID: <https://orcid.org/0000-0001-6206-1210>

#### Сведения об авторах:

Сидорчук А.С. – доктор философии, доцент, доцент кафедры внутренней медицины и инфекционных болезней Высшего государственного учебного заведения Украины «Буковинский государственный медицинский университет», г. Черновцы, Украина.

Москалюк В.Д. – д.мед.н., профессор, профессор кафедры внутренней медицины и инфекционных болезней Высшего государственного учебного заведения Украины «Буковинский государственный медицинский университет», г. Черновцы, Украина.

#### Information about authors:

Aniuta Sydorchuk – doctor of philosophy, associate professor, associate professor of department of internal medicine and infectious diseases Higher state educational establishment of Ukraine “Bukovinian state medical university”, Chernivtsi, Ukraine.

ORCID ID: <https://orcid.org/0000-0002-1959-6612>

Vasyl Moskaliuk – doctor of medicine, professor, professor of department of internal medicine and infectious diseases Higher state educational establishment of Ukraine “Bukovinian state medical university”, Chernivtsi, Ukraine.

ORCID ID: <https://orcid.org/0000-0001-6206-1210>

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