Malaria

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ABSTRACT

Introduction: Malaria is an acute febrile infectious disease caused by protozoa of the genus Plasmodium that are transmitted by the bite of infected female mosquitoes of the genus Anopheles. In 2020, the World Health Organization (WHO) reported 241 million cases and 627 thousand deaths from the disease. This figure represents an increase from an estimated 227 million cases and 558,000 deaths recorded in 2019. In Brazil, the Amazon region is considered an endemic area for malaria, accounting for 99% of autochthonous cases. Objectives: The study of this chapter is to present all the main aspects relevant to the understanding of malaria and its consequences on the individual and society. Etiological Agent: Protozoa of the genus Plasmodium, with the species Plasmodium falciparum, Plasmodium vivax and Plasmodium malariae being the main species found in Brazil. Transmission: Malaria is a disease transmitted to humans through the bite of infected female mosquitoes of the genus Anopheles. Biological cycle: The biological cycle of Plasmodium sp. involves two hosts, the human and the female infected Anopheles mosquito. Clinical manifestations: The interval period between apyretic events varies according to the species of each etiological agent, which presents distinct intervals to complete the schizogonic cycle in red blood cells. The species of P. vivax and P. ovale (found in Africa) have a cycle of approximately 48 hours, the cycles of P. malariae are around 72 hours, while P. falciparum does not show synchronicity between symptomatic events. Diagnosis: The signs and symptoms of malaria are quite nonspecific and can commonly be confused with other infections. Slides stained with Giemsa and observed under light microscopy are widely used and analyzed by thick drop and blood smear. One of the options is rapid tests, currently offered in resource-scarce areas where microscopy services are not feasible or unavailable. Treatment: Treatment of malaria will vary according to the infecting species. Prophylaxis: For individuals who are outside the endemic area, it is necessary that they inform themselves before traveling to these regions. Attention should be paid to the departure time, avoiding being outside the premises during night periods, since the vector usually leaves soon after dusk. Repellents and barrier methods should be used, such as clothing that covers the body area well, as well as mosquito nets and screens on beds and doors. Conclusion: The chapter allows the deepening of the main topics about malaria, thus ensuring greater knowledge about the disease, the care of the infected individual, and the care that society needs to have in the face of this disease.

Keywords: Malaria, *P. falciparum*, *P. vivax*, *P. malariae*.

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INTRODUCTION

Malaria is an infectious, endemic disease that is present in most of the tropics and its transmission occurs continuously in about 85 countries and territories. In 2020, the World Health Organization (WHO) reported 241 million cases and 627 thousand deaths from the disease. This figure represents an increase from an estimated 227 million cases and 558,000 deaths recorded in 2019.

In Brazil, the Amazon region is considered an endemic area for malaria, registering 99% of autochthonous cases, that is, 99% of malaria cases throughout Brazil come from the Amazon region. The region comprises the states of Acre, Amazonas, Amapá, Pará, Rondônia, Roraima, Tocantins, Mato Grosso and Maranhão. In areas outside the Amazon region, more than 80% of the recorded cases are imported from the states belonging to the endemic area and from other Amazonian countries or the African continent. Despite this, there is residual transmission of malaria in states of the extra-Amazon region, mainly in areas of the Atlantic Forest, such as São Paulo, Minas Gerais, Rio de Janeiro and Espírito Santo.

Malaria is an infectious, non-contagious, acute febrile disease caused by protozoa of the genus *Plasmodium* transmitted by the bite of infected female mosquitoes of the genus *Anopheles*, also known as capuchin mosquitoes. The disease is also known as malaria, malaria, malaria, malaria, intermittent fever, benign tertian fever, malignant tertian fever, as well as popular names such as malaria, seezão, tremedeira, mixer or fever.

The mosquitoes that transmit the disease to humans are most abundant at twilight times, that is, at dawn and dusk. However, they are found feeding throughout the night.

ETIOLOGIC AGENT

The parasites that cause malaria belong to the phylum Apicomplexa, family *Plasmodiidae* and the genus *Plasmodium*. There are hundreds of species of plasmodium, but only a few parasitize exclusively on humans. They are: *Plasmodium falciparum*; *Plasmodium vivax*; *Plasmodium malariae; Plasmodium ovale* (species found in Africa) and *Plasmodium knowlesi* (found in Asia)

Plasmodium falciparum is responsible for malignant tertian fever, with fever peaks at intervals of 36 to 48 hours. *Plasmodium vivax* is responsible for benign tertian fever, with 48-hour cycles. *Plasmodium ovale* has a limited distribution to the African continent and is responsible for another form of benign tertian fever, that is, with 48-hour cycles. *Plasmodium malariae* causes quartan fever, promoting fever peaks every 72 hours.

However, another species of plasmodium, *Plasmodium knowesi*, has been linked to clinical cases of malaria on the Asian continent and is closely linked to forested regions.

VECTOR/TRANSMISSION

Malaria is a disease transmitted to humans through the bite of the infected female mosquito of the genus *Anopheles*, popularly known as muriçoca, sovela, capuchin mosquito and boll weevil. In Brazil, 3 main species are involved in the transmission of the disease: *Anopheles darlingi* (main vector species), *Anophleles albitarsis* and *Anopheles aquasalis* (found predominantly in the coastal region of the country). The mosquitoes that transmit the disease to humans are most abundant at twilight times, that is, at dawn and dusk. However, they are found biting throughout the night. The preferred sites chosen by malaria-transmitting mosquitoes to lay their eggs (breeding sites) are collections of clean, shaded and low-flow waters, which are very frequent in the Brazilian Amazon.

The cycle begins when the mosquito bites an individual with malaria, sucking the blood with the parasites (plasmodiums). In the mosquito, plasmodia develop and multiply. The cycle is complete when these infected mosquitoes bite a new individual, infecting the person with the parasites. In this way, the transmission cycle involves: the plasmodium (parasite), the anopheline (mosquito vector) and humans.

The incubation period, i.e., the interval between the acquisition of the parasite by the bite of the female mosquito and the appearance of the first symptoms, varies according to the species of plasmodium. For *Plasmodium falciparum*, minimum of seven days; *P. vivax*, 10 to 30 days and *P. malariae*, 18 to 30 days. There is no direct person-to-person transmission of the disease. Other forms of transmission can also occur in rarer cases by: blood transfusion, use of contaminated syringes, laboratory accidents, and congenital transmission. Malaria is not transmitted through water.

EVOLUTIONARY FORMS OF THE PROTOZOAN AND BIOLOGICAL CYCLE

The main evolutionary forms of *Plasmodium* sp. are:

Sporozoites: Sporozoites are the infective form of the parasite transmitted to humans by the bite of an infected female mosquito. They are inoculated into the bloodstream during the insect's feeding and then go to the liver.

Merozoites: When invading hepatocytes (liver cells), sporozoites transform into rounded structures called merozoites, and are difficult to detect at this stage. In addition to growing, merozoites begin a cycle of asexual reproduction, known as pre-erythrocytic schizogony, as it happens before blood parasitism. This asexual reproduction gives rise to a multinucleated cell, known as a tissue schizont, containing several merozoites inside. Merozoites are released into the blood, either by rupture of hepatocytes or via exocytosis.

Trophozoites: Merozoites invade red blood cells (RBCs), where they transform into young trophozoites. Inside the red blood cells, trophozoites consume the hemoglobin present in red blood cells. The iron present in the molecule is very toxic to the etiological agent and as a protective

measure the crystallization of this substance occurs, generating hemozoin, also known as malarial pigment, which is stored in the vacuole of *Plasmodium*. After their development, they are called mature trophozoites, when they begin the process of asexual reproduction, called blood schizogony. This is followed by the rupture of the red blood cells, with the release of new merozoites that will invade new red blood cells. It is at this time, when several red blood cells rupture simultaneously, that the infected individual presents the fever. Some young trophozoites do not evolve into mature trophozoites, but differentiate into gametocytes, which will continue the cycle in the insect vector.

Gametocytes: Differentiation into gametocytes generates forms known as female gametocytes and male gametocytes, which after ingested by a female *Anopheles*, will give rise to gametes, and sexual reproduction will occur.

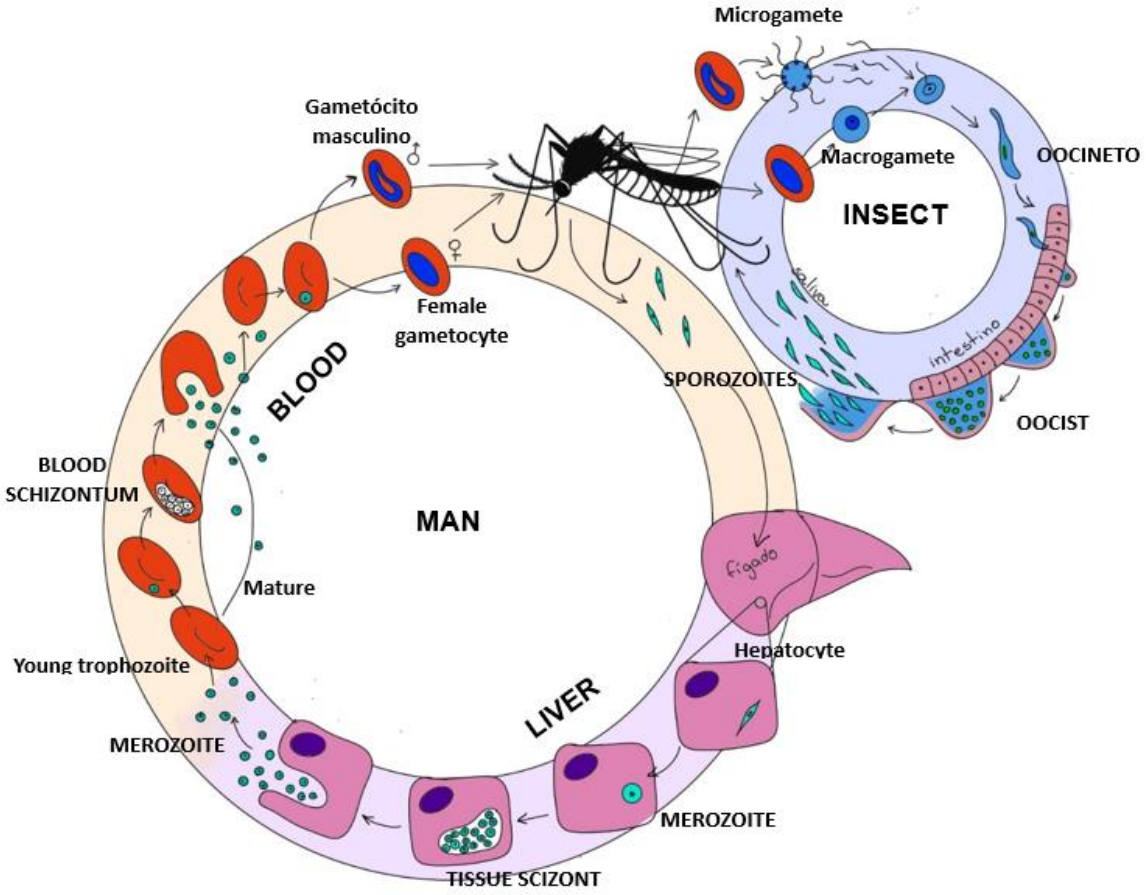
Male and female gametes: Upon reaching the intestine of the insect that has favorable factors, such as high pH and low temperature, gametogenesis begins, the female gametocyte transforms into a macrogamete, and the male gametocyte, after undergoing an exflagellation process, gives rise to eight microgametes, which will fertilize the macrogamete, originating a zygote, or egg cell, known as ookinete.

Ookinete: After one day of the formation of the zygote, it differentiates into an ookinete, which performs contractile movements to move to the wall of the middle intestine of the infected insect, where the cyst is performed, and from this moment on, it is called oocyst.

Oocyst: The oocyst is found within the intestinal epithelium of the infected mosquito. It will do asexual reproduction, called sporogony, producing new sporozoites. The sporozoites, released in the midgut of the mosquito, are transported by the hemolymph to the salivary glands. The cycle is completed when the mosquito bites another individual, transmitting the sporozoites and restarting the cycle.

Figure 1 shows the biological cycle of *Plasmodium* sp. in both hosts.

Figure 1 - Schematic representation of the biological cycle of *Plasmodium* sp. Source: Elaborated



CLINICAL FORMS

The incubation period of the disease varies according to each species of plasmodium. *P. vivax* has an incubation time of around 14 days, *P. falciparum* is approximately 12 days, and *P. malariae* can vary between 18 and 40 days for the onset of the first symptoms.

Malaria is an acute febrile illness and initially the symptoms are nonspecific, and the patient may present fever, headache, tiredness, myalgia and malaise. After this period, the patient may develop malarial access or malarial paroxysm, which occurs suddenly, coinciding with the rupture of the red blood cells. From this moment, which lasts around fifteen minutes to an hour, the patient may present intense cold, chills, paleness, cyanosis, and even intensification of fever. After this period, a high fever is established, which can reach up to 41°C, which can last from 2 to 4 hours. Finally, the symptoms remission occurs with normalization of the temperature, the patient feels relieved and goes through a period of intense sweating.

The interval period between febrile peaks varies according to the species of infecting plasmodium, which has distinct intervals to complete the schizogonic cycle in red blood cells. The species of *P. vivax* and *P. ovale* have a cycle of approximately 48 hours, the cycles of *P. malariae* are around 72 hours, while *P. falciparum* does not present synchronicity between symptomatic events, and febrile attacks can vary from 36 to 48 hours.

In cases of P. *vivax infection*, depending on the treatment performed, the patient may have remission of symptoms and cure. However, due to latent hypnozoites in the liver, after a period, it may present a new symptomatic picture due to the reactivation of the hepatic forms. This phenomenon is called late recurrence of the disease and happens with the species *P. vivax* and *P. ovale*.

Cerebral malaria is the most severe manifestation of the disease and occurs in approximately 2% of non-immune individuals affected by *P. falciparum*, which is responsible for approximately 80% of malaria deaths. During the infection of red blood cells, *P. falciparum* induces the parasitized cell to express proteins of the adhesin class in its cell membrane, leaving the parasitized red blood cell with deformities called "*knobs*" on its surface. Thus, the parasitized cells adhere to other red blood cells, parasitized or not, to other cells and to the vascular endothelium, causing obstruction of the microcirculation with involvement of the adjacent tissue.

Complications that can occur in pregnant patients infected with malaria include miscarriage, prematurity, stillbirth, and maternal death, as well as low fetal birth weight. In rare cases, eclampsia and nephrotic toxemia may occur. Acute renal failure is common in adults, where renal impairment causes reduced urine production, no more than 400ml per day. Jaundice may be present in cases of elevated serum bilirubin due to excess hemolysis and hepatic involvement.

DIAGNOSIS

CLINICAL DIAGNOSIS

The signs and symptoms of malaria are quite nonspecific and can commonly be confused with other infections. Fever, fatigue, arthralgia, headache and vomiting present in the malarial manifestation are also common bacterial and viral infections, which frequently affect humans. This makes it difficult to identify malaria using clinical findings alone. This fact is minimized in endemic areas for the disease, when faced with a febrile condition, the initial suspicion is the disease.

LABORATORY DIAGNOSIS

Microscopic visualization and identification of parasites in the blood of patients is still the gold standard for diagnosing malaria. Slides stained with Giemsa and observed under light microscopy are widely used and analyzed by means of a thick drop (more sensitive) and blood smear (more specific).

An important point to be emphasized is that a negative result does not necessarily mean that the patient is not infected, since the identification of parasites depends on the examiner and his technical skill, as well as the quality of the materials provided. Thus, in socially disadvantaged regions, with few resources and few qualified professionals, there is a need to repeat the technique

and microscopic visualization after a few hours when there is high suspicion and a negative result. Another situation that can hinder diagnosis is in the case of pregnant women with suspected malarial infection. In this case, placental sequestration of parasitized erythrocytes and low levels of parasitic circulation can also lead to a false negative.

Considering the scenarios presented, it is possible that other diagnostic techniques will be employed. One of the options is rapid tests, which do not depend on qualified professionals to perform them, currently offered in areas with scarce resources, where the microscopy service is not feasible. The test is able to identify specific antigens of *P. vivax* and *P. falciparum*, such as histidine-rich protein 2 (HRP2). They also identify mixed infections, which was not possible until a few years ago. However, to date, there are no approved or satisfactory tests to detect infections of *P. malariae*, *P. ovale* and *P. knowlesi*.

Another option for diagnosing malaria is molecular tests, such as polymerase chain reaction (PCR), which has high accuracy. PCR can be useful in cases where there is low parasitemia, but despite having many advantages, the technique is difficult to implement in endemic areas, due to its high cost, need for skilled labor, and delay in releasing results.

Treatment

A complete malarial treatment needs to prevent parasitic reproduction in the bloodstream, aiming at the patient's clinical improvement; It must act on latent forms in the liver, to prevent late recurrences of the disease and also act against gametocytes, as these remain viable in the bloodstream for up to 60 days. In these cases, the patient is clinically cured, but remains a source of infection for the insect vectors.

Uncomplicated malaria:

One of the main goals in the treatment of uncomplicated malaria is to prevent a worsening of the disease, as well as to reduce clinical symptoms. In endemic regions, it is important that treatment prevents transmission to other individuals.

P.vivax *or* P.ovale *malaria*

These two species are responsible for the latent forms of the disease, requiring the use of medication that eliminates the hypnozoites, found in the liver of the infected patient. In this scenario, the combination of two drugs is used: chloroquine and primaquine. Chloroquine is an active drug against the parasitic forms found in the blood, while primaquine will be able to eliminate the parasitic form found in the liver. The patient should use chloroquine for 3 days, with the association of primaquine for 7 days. However, primaquine should not be used by pregnant women and its use

should be carefully monitored in order to avoid unwanted cytotoxic effects in the patient. Another drug being studied for the treatment of this scenario is tafenoquine.

P.falciparum and mixed infections

Unlike other species, *P. falciparum* has a high resistance to chloroquine, thus requiring combination therapy with artemisinin derivatives (ACT). Therapeutic regimens include drugs such as: artesunate and mefloquine; artemether and lumefantrine. ACTs can and should be used by pregnant women, as long as they are accompanied throughout pregnancy.

Complicated malaria

In case of complicated malaria, mainly caused by *P. falciparum*, the patient should preferably be treated in a hospital unit. The faster the diagnosis and treatment occurs, the greater the chances of success. The WHO guideline regarding treatment is the use of artesunate, complemented by another reference treatment (according to the species) and the use of primaquine at the end of the therapeutic regimen.

Prophylaxis

For individuals who are outside the endemic area, it is necessary that they inform themselves before traveling to these regions. Exposure should be avoided at times of greatest activity of the insect vector, which begins at dusk and lasts during the night. Repellents and barrier methods should be used, such as wearing clothing that covers the body areas well, as well as mosquito nets and screens on beds and windows.

Much of this care is also directed to residents of endemic areas, in addition to the use of larvicides and insecticides in their homes, avoiding the accumulation of stagnant water, and health education.

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