

Malaria is a parasitic infection transmitted by the *Anopheles* mosquito that leads to acute life-threatening disease and poses a significant global health threat. Two billion people risk contracting malaria annually, including those in 90 endemic countries and 125 million travelers, and 1.5 to 2.7 million people die in a year.

The *Plasmodium* parasite has a multistage lifecycle, which leads to characteristic cyclical fevers. With timely treatment, most people experience rapid resolution of symptoms; however, significant complications may occur, including cerebral malaria, severe malarial anemia, coma, or death. Preferred antimalarial therapeutic and chemoprophylactic regimens get dictated by species, geography, susceptibility, and patient demographics. Latent or reactivating infections may be reported years following exposure.

## **Etiology**

The incubation period, and therefore time to symptom development, varies by species: 8 to 11 days for *P. falciparum*, 8 to 17 days for *P. vivax*, 10 to 17 days for *P. ovale*, 18 to 40 days for *P. malariae* (though possibly up to several years), and 9 to 12 days for *P. knowlesi*. The periodicity of the *Plasmodium* life cycle creates the classic “malarial paroxysm” of rigors, followed by several hours of fever, followed by diaphoresis, and a drop to normal body temperature (*P. vivax* infection establishes a 48-hour cycle), though this is less commonly seen today due to rapid identification and treatment.

## **Epidemiology**

Forty percent of the global population resides in or visits malaria-endemic regions annually. *P. falciparum* is present in Western and sub-Saharan Africa and displays the highest morbidity and mortality of the *Plasmodia* species. *P. vivax* is present in South Asia, the Western Pacific, and Central America. *P. ovale* and *P. malariae* are present in Sub-Saharan Africa. *P. knowlesi* is present in Southeast Asia. As many as 500 million malaria cases occur annually, with 1.5 to 2.7 million deaths. Ninety percent of fatalities occur in Africa. Those at highest risk include children under age 5, pregnant women, and disease naïve populations,

including refugees in Central and Eastern Africa, nonimmune civilian and military travelers, and immigrants returning to their place of origin.



Of the 125 million travelers who visit endemic locations each year, 10000 to 30000 develop malaria, and 1% of these will die from complications of their disease. Rising average global temperatures and changes in weather patterns are projected to expand the burden of malaria; a rise of 3 degrees Celsius is postulated to increase malaria incidence by 50 to 80 million.

### History and Physical

In taking a history, it is essential to inquire about the location of residence, recent travel and use of chemoprophylaxis, exposures (including sick contacts, fresh water, caves, farm/wild animals, insects/arthropods), HIV status, history of current or recent pregnancy, history of

G6PD deficiency, history of sickle cell disease, history of anemia, history of blood or other cancers, and history of prior malarial infections (including successful or failed treatments).

Fever is the dominant symptom of malaria—fever, especially for seven or more days, in a patient residing in or with recent travel to an endemic region is highly suspicious and should prompt evaluation. Adults may exhibit headaches, malaise, weakness, gastrointestinal distress, upper respiratory symptoms, and muscle aches; severe cases may include jaundice, confusion, seizures, and dark urine. Children are more likely to present with non-specific or gastrointestinal symptoms such as fever, lethargy, malaise, nausea, vomiting, abdominal cramps, and somnolence. They are more likely to develop hepatomegaly, splenomegaly, and severe anemia without major organ dysfunction than adults. In the case of severe malaria, they present with more frequent seizures (60 to 80%), hypoglycemia, and concomitant sepsis but are less likely to develop pulmonary edema and renal failure than adults.

**In Pregnant Women:** The clinical features of infection in pregnancy vary from asymptomatic to severe, depending on the degree of (incomplete) immunity that a woman had acquired by the time she got pregnant. In semi-immune pregnant women, only a few infections result in fever or other symptoms. Malaria in pregnancy has a devastating effect on maternal health and has been associated with increased infant mortality due to low birth weight caused by either intrauterine growth restriction or preterm labor, or both. *P. falciparum* infections are associated with complications such as maternal anemia, low birth weight, miscarriage, stillbirths, and congenital malaria. It is more likely for a pregnant woman in the second or third trimester to develop severe malaria with complications such as hypoglycemia and pulmonary edema compared to non-pregnant adults.

## Evaluation

Initial evaluation of undifferentiated fever in stable patients with possible malaria exposure includes a complete blood count, comprehensive metabolic panel, coagulation panel, blood culture, urinalysis, chest radiograph, and thick and thin blood smears. In patients with altered mental status, when cerebral malaria is suspected, a lactate level, arterial blood gas, and

lumbar puncture may also be indicated.

In patients with malaria, complete blood count reveals thrombocytopenia in 60-70% of all cases and varying degrees of anemia in 29% of adults and 78% of children. Anemia is more severe in *P. falciparum* due to invasion of all aged erythrocytes and capillary and splenic erythrocyte sequestration secondary to decreased flexibility and cytoadherence. Anemia is typically moderate with *P. vivax* and *P. malariae* due to preferential invasion of reticulocytes and older erythrocytes, respectively. A comprehensive metabolic panel may reveal hepatocellular injury secondary to parasitic invasion, indirect hyperbilirubinemia due to hemolysis, electrolyte abnormalities secondary to the release of intracellular contents, concomitant dehydration, and kidney injury secondary to glomerular damage. The coagulation panel may reveal coagulopathy concerning bleeding risk in patients with severe thrombocytopenia or liver dysfunction. Urinalysis may show proteinuria indicative of nephrotic syndrome.

The gold standard for malaria diagnosis is a microscopic evaluation of Giemsa-stained thick and thin smears of a free-flowing venipuncture blood specimen. An initial negative smear does not rule out malaria, as infected erythrocytes may become intravascularly sequestered; if clinical suspicion of malaria is high, smears require repetition in 12 and 24 hours. The malarial pigment in monocytes and neutrophils may also manifest on the blood smear, particularly in patients with cerebral malaria.

Other diagnostic modalities include rapid diagnostic testing (RDT), microhematocrit centrifugation, and polymerase chain reaction (PCR). For RDTs, sensitivities approach 100%, though microscopy is still a recommendation at the time of presentation and 12 and 24 hours. Limitations of RDTs include the detection of *P. falciparum* species only, the inability to quantify parasitic burden, and false-positive results occurring weeks after infection due to persistent blood antigens. Microhematocrit centrifugation isolates infected erythrocytes, then binds to acridine in the collection tube, causing the fluorescence of parasites. PCR is useful in low-level parasitemia detection and speciation.

## Treatment / Management

Treatment for patients diagnosed with malaria includes schizonticidal medications, supportive care, and hospitalization for high-risk patients. Naïve adult and pediatric patients receiving active antimalarial treatment should remain inpatient for at least 24 hours to ensure adequate and correctly timed medication dosing and to trend parasitemia to evaluate treatment response. Higher initial parasitemia and poor downtrend are associated with fluid imbalance, renal dysfunction, and respiratory distress syndrome. Unstable patients, particularly those with cerebral malaria or significant respiratory sequelae, require intensive care.

Treatment involves combination therapy targeting both the hepatic and erythrocytic forms. The chief antimalarials are chloroquine, hydroxychloroquine, primaquine, artemisinin-based combination therapy (ACT), and atovaquone-proguanil. Chloroquine and hydroxychloroquine are synthetic forms of quinine. They disrupt the erythrocytic stage by interfering with parasitic hemoglobin metabolism and increasing intracellular pH. They generally require two days of treatment, allowing for better tolerance and shorter admissions. However, chloroquine may enhance gametogenesis, contributing to resistance, which is a concern, particularly in South Asia. Primaquine is a hypnozoontocidal agent added for *P. vivax* or *P. ovale* infection for the eradication of liver parasites and the prevention of dormancy and relapse.

Primaquine is contraindicated in pregnant and G6PD deficient patients due to fetal teratogenicity and hemolytic reaction (will see bite cells and Heinz bodies on blood smear), respectively. Artemisinins are active against all parasite life cycle stages. Atovaquone targets the cellular electron transport chain inhibiting ATP production; proguanil enhances atovaquone's effect by sensitizing parasitic mitochondria. Atovaquone-proguanil is active against the erythrocytic and extraerythrocytic forms.

## Differential Diagnosis

The differential for undifferentiated fever is extremely broad and varies based on geographic location and age. In a 2017 review of fever in returning travelers, 77% had protozoal malaria, 18% had a bacterial enteric fever (*Salmonella enterica*, *typhi*, or *paratyphi*), and 5% had another infection. In patients presenting with fever and significant somnolence or seizures, viral or bacterial meningitis or meningoencephalitis must remain on the differential and prompt consideration of lumbar puncture.

Viral etiologies include avian influenza, Middle East respiratory syndrome coronavirus, hemorrhagic fever (Ebola virus, Lassa fever, Marburg hemorrhagic fever, Crimean-Congo hemorrhagic fever), yellow fever, dengue, Japanese encephalitis, Rift Valley fever, hepatitis virus (A or B), viral gastroenteritis, and rabies. Bacterial etiologies include anthrax, epidemic typhus, ehrlichiosis, leptospirosis, melioidosis, murine (endemic) typhus, spotted fever group rickettsioses, Q fever, and *Yersinia pestis*.

The differential in children varies by region, with the most likely etiology being a viral or bacterial infection. In a 2014 study of febrile children in a tropical region, 10.5% were diagnosed with malaria, 62% were diagnosed with a respiratory infection, 13.3% with a systemic bacterial infection (usually *staphylococcus* or *streptococcus* bacteremia), and 10.3% with gastroenteritis (viral or bacterial). Urinary tract infection and typhoid may also be considerations. Meningitis must be ruled out in somnolent children.

The significant complications of malaria are cerebral malaria, severe malarial anemia, and nephrotic syndrome (NS).

## Consultations

Recommended consultations for non-infectious disease experts in the management or prevention of malaria include infectious disease and preventive or travel medicine.

## Management, Education and Recommendation

The recommendation is that patients schedule a pre-travel appointment with a preventive



medicine or infectious disease physician for education regarding malaria deterrence. Malaria prevention centers around vector control and chemoprophylaxis while exposed to mosquito-ridden environments.

Vector control is the prevention of mosquito bites by way of insecticide-impregnated bed nets, permethrin treatment of clothing, and DEET application to the skin. The three main prophylactic agents for *Plasmodium falciparum* are atovaquone-proguanil, doxycycline, and mefloquine. Atovaquone-proguanil is taken once daily during and one week after travel to an endemic region; it suppresses the hepatic stage and does not have approval for pregnancy. Doxycycline is taken once daily during and one month after travel; it suppresses the blood stage. Doxycycline has the added benefit of prophylaxis against Rickettsial disease, Q fever, leptospirosis, and travelers' diarrhea; however, it may cause gastrointestinal distress, photosensitivity, and increased risk of candida infection. Mefloquine is taken once weekly during and one month after travel; it suppresses the blood stage. It has the benefit of safety in the second and third trimester of pregnancy; however, it has a far higher risk of neuropsychiatric side effects. The US military primarily utilizes doxycycline if susceptibilities are equal. For pregnant women in the first trimester or breastfeeding women, chloroquine or mefloquine prophylaxis are preferable; data regarding the safety of atovaquone-proguanil prophylaxis in pregnancy is limited.

The timely care of patients diagnosed with malaria and clinically relevant research regarding advancing diagnostic techniques and treatment requires interprofessional teamwork and communication between clinicians, infectious disease experts, pharmacists, nurses, and global health professionals.

Any clinician treating malaria will initiate treatment as outlined above. Still, it is good policy to include an infectious disease specialist and involve an infectious disease board-certified pharmacist, who can also examine the regimen and agents chosen, as well as verify dosing and drug interactions. A nurse with infectious disease specialty training can also help by answering patient questions, serving as a bridge to the treating clinician, and monitoring

treatment progress and potential adverse drug reactions. All team members must keep accurate and updated records, so everyone involved in treatment has the same information on the patient's case. If there are any concerns, each team member must be free to communicate with other team members so that appropriate interventions can be started or therapeutic modifications can be implemented. This collaborative interprofessional approach can optimize outcomes for malaria patients.

**Source:**

Buck E, Finnigan NA. Malaria. [Updated 2023 Jan 22]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK551711/>

**End Note:** This article was written to mark the World Malaria Day 2023.

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