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Clinical review of malaria for the emergency physician Évaluation clinique du paludisme pour les médecins urgentistes

Laura Janneck [a], **Alex Koyfman** [a,*], **James Kimo Takayesu** [b]

[a] *Department of Emergency Medicine, Brigham and Women's Hospital and Massachusetts General Hospital, Boston, MA, United States*
[b] *Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, 5 Emerson Place, Boston, MA, United States*

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Abstract Malaria is a disease caused by parasites of the Plasmodium genus, and is one of the most prevalent diseases in Africa and around the world. Emergency physicians in both endemic and non-endemic regions often encounter initial presentations of malaria, and knowledge about the pathophysiology, diagnosis, and treatment of this disease is crucial in caring for these patients. This article covers briefly the epidemiology of malaria and the lifecycle of the Plasmodium parasite. This is followed by a discussion of the clinical evaluation, diagnosis, and management of patients with malaria, as pertinent to the African emergency physician.

* Corresponding author. Address: Department of Emergency Medicine, Brigham and Women's Hospital and Massachusetts General Hospital, 75 Francis Street, Neville House, Boston, MA 02115, United States. Tel.: +1 917 658 2802.
E-mail address: akoyfman@partners.org (A. Koyfman).

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Les médecins urgentistes des régions endémiques et non-endémiques sont souvent confrontés à des premières manifestations de paludisme, et les connaissances en matière de physiopathologie, de diagnostic et de traitement de cette maladie sont essentielles à la prise en charge de ces patients. Cet article couvre brièvement l'épidémiologie du paludisme et le cycle de vie du parasite Plasmodium. Ce résumé est suivi d'une discussion sur l'évaluation clinique, le diagnostic et la prise en charge des patients souffrant du paludisme, des éléments pertinents pour le médecin urgentiste africain.

Contents

African relevance:

Very common disease in Africa.
Lots of time dedicated to this topic by WHO.
Area ripe for advances since morbidity/mortality still high; resistance to key medications is rising.

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Introduction

One of mankind's most ancient illnesses, malaria is caused by parasites of the Plasmodium genus. The most virulent of this species is *Plasmodium* falciparum because its case fatality rate can approach 15–20% even when appropriately treated.[1] It can cause severe organ damage including encephalopathy, renal failure, rapidly developing anemia, pulmonary edema, and disseminated intravascular coagulation.[2] *P. falciparum* has developed resistance to multiple anti-malarial drugs over the past several decades.[1] The other three species are *Plasmodium ovale*, *Plasmodium vivax*, and *Plasmodium malariae*. These species differ in their geographic distribution, are rarely fatal, and have lower levels of drug resistance, yet still cause substantial morbidity. *P. ovale* occurs predominantly in sub-Saharan Africa, and *P. vivax* generally occurs throughout the tropics outside of sub-Saharan Africa.[3] *P. falciparum* and *P. malariae* occur globally throughout tropical and subtropical regions, but are less common than *P. falciparum*.[3] Many cases of malaria, in both endemic and non-endemic regions, present first to emergency departments.[4] Patients with malaria can deteriorate quickly, therefore it is important for emergency physicians to be able to diagnose and treat the disease.[4]

Epidemiology

According to the World Health Organization, in 2009 there were approximately 225 million cases of malaria worldwide, resulting in 781,000 deaths.[5] In 2001, the World Health Organization ranked malaria as the eighth largest cause of global disease burden, and the second largest in Africa.[6]

Over 90% of cases occurred in children under 5 years of age in Africa.[5] The burden of malaria is highest in central and Western Africa, and in some regions residents are bitten by at least one infective mosquito per day.[1] Warmer temperatures in some regions of Africa caused by climate change are thought to contribute to increases in malaria prevalence.[7]

Plasmodium life cycle

The Plasmodium parasite is transmitted to humans by mosquitoes in the Anopheles genus when the insects bite and salivate into the blood to prevent clotting. The Plasmodium parasites infect hepatocytes where they rapidly multiply and eventually lyse their host cells. *P. ovale* and *P. vivax* can lie dormant in the hepatocytes for months to years, potentiating recrudescent disease at a later time. When released from infected hepatocytes, the parasites enter red blood cells (RBCs) and feed on

hemoglobin. They eventually reproduce to the point of lysing the RBCs, causing a new infective parasitemia and repeating the life cycle. Some parasites become gametocytes. When male and female gametocytes are both taken up by a biting mosquito, they reproduce in the insect, creating progeny ready to infect a new human host.[2]

Pathophysiology

The lysis of RBCs by parasites can lead to anemia if the parasite burden is high. *P. falciparum* has higher morbidity and mortality due in part to the production of cell surface proteins which are expressed on the RBC membrane.[8] These cell surface proteins mediate adhesion of the erythrocytes to platelets and endovascular cells, causing vessel occlusion and downstream ischemia.[8] Adhesion in the cerebral circulation can cause cerebral malaria, leading to encephalopathy and seizures; adhesion in placental vasculature can lead to miscarriage[8]; and adhesions in other organs can lead to end organ damage.

Because repeated infection by the Plasmodium parasites can lead to partial immunity, most adults in malaria-endemic areas infrequently become ill from malaria, despite regular infection. Patients who are most at risk of death and severe illness from Plasmodium infection are those who have not developed partial immunity. This includes children under the age of five, travelers who have never lived in endemic regions, and people who had lived in endemic regions in the past with waning immunity from loss of repeated exposure.[8] Additionally, primigravidae women experience higher rates of placental malaria than multigravidae women because they produce certain anti-malarial antibodies later in gestation.[9]

Clinical evaluation of the patient with suspected malaria

Malaria can present with a myriad of non-specific signs and symptoms, making the differential diagnosis broad. Symptoms commonly seen in malaria include fever (92%), chills (79%), headaches (70%), and diaphoresis (64%).[10] The earliest symptoms of malaria can also include weakness, myalgias, dizziness, abdominal pain, diarrhea, nausea, vomiting, anorexia, and pruritus.[11] Symptoms can wax and wane, and may be partially relieved by symptomatic treatment including fluids and antipyretics, so one must be cautious to not use symptomatic improvement to rule out malaria from the differential.[10] Malaria should be considered for all patients presenting with fevers in endemic regions, especially those not presumed to have partial immunity. In non-endemic areas, malaria should be considered for all patients with recent travel histories to malaria-endemic regions, noting that the incubation period for *P. ovale* and *P. vivax* can vary widely, and may be as much as several months, especially in patients who have taken chemoprophylaxis.[10]

Once diagnosed, further evaluation is merited with a CBC, electrolytes, coagulation parameters, glucose, hepatic panel, BUN and creatinine, blood cultures, urinalysis, chest X-ray and ECG[4] to assess for signs of severe malaria (see Table 1). The parasitemia level is measured by blood smear (see diagnostic methods below), and is particularly important as there is a correlation between parasitemia and poor prognosis; a 2% parasitemia corresponds to a 1% mortality rate, whereas a 10% parasitemia correlates to a 50% mortality rate.[4]

Other potential causes of the patient's symptoms should be evaluated when appropriate. In the pregnant patient, malaria can be confused with HELLP syndrome (hemolytic anemia, elevated liver enzymes, and low platelet count).[12] Concurrent septicemia is rare, occurring in $< 5\%$ of cases, but should be considered, and blood cultures should be obtained.[13] Likewise, lumbar puncture should be performed in patients with impaired consciousness or repeated seizures to rule out meningitis.[13]

Diagnostic methods

Diagnosis of malaria can be made in several ways. Clinical diagnosis is the most common diagnostic method, especially in resource-poor settings where malaria is endemic.[11] The Integrated Management of Childhood Illness (IMCI) clinical algorithm for malaria diagnosis was shown to have 100% sensitivity, but 0–9% specificity.[11] The lack of specificity in using clinical diagnosis alone can lead to indiscriminate use of antimalarials, which increases rates of drug resistance, and inappropriate treatment of other infectious etiologies.[11]

Whenever possible, laboratory diagnosis of malaria is preferred. The most traditional way, still considered the gold standard, is the thick and thin blood smear, whereby malaria is diagnosed by visualizing parasites microscopically.[2,11] This technique is simple, low-cost, and allows for speciation, however requires trained technicians and can have low sensitivity for low parasite levels.[11] Blood smears allow for both speciation based on RBC morphology and quantification of parasite burden.[8] With observation of 200 oil immersion fields, the sensitivity of peripheral blood smears is 90%.[10]

Another method is the qualitative buffy coat technique, which stains parasite DNA, and thus detects malaria with fluorescent dyes and microscopy.[11] However, it has several disadvantages including greater expense, decreased specificity,[11] lack of speciation or quantification of parasite burden, and inability to differentiate malaria from babesia.[8] There are also a large number of rapid diagnostic tests (RDTs) for malaria on the market, which detect malaria antigens flowing across a membrane of specific anti-malarial antibodies.[11] RDTs have been shown to have widely variable sensitivity, and current recommendations promote their use in conjunction with other methods, but they have potential for wide use in remote settings without laboratory facilities.[1,11]

Severe malaria

The emergency physician should evaluate whether a patient has signs or symptoms of severe malaria since differentiating uncomplicated from severe malaria will help to guide treatment. In a patient with *P. falciparum* parasitemia and no other obvious causes of symptoms, severe malaria is defined as the presence of any of the clinical or laboratory features listed in Table 1.

Management

Initial management of the patient with confirmed or suspected malaria depends upon their clinical stability. There are varying opinions on when malaria should be treated presumptively,[8,10] often depending solely on clinical suspicion. If malaria is confirmed, but speciation cannot be done, patients should be treated for *P. falciparum* presumptively.[8]

Table 1 Assessing for signs of severe malaria.

Evaluation and tests	Signs of severe malaria
History	Failure to feed
	More than two seizures in 24 h
Physical exam	Impaired consciousness or coma
	Prostration (inability to sit or stand)
	Kussmaul breathing
	Circulatory collapse or shock, systolic blood pressure < 70 mm Hg in adults or < 50 mm Hg in children
CBC	Severe normocytic anemia (Hb < 5 g/dl, packed cell volume < 15%)
Electrolytes	Metabolic acidosis (plasma bicarbonate < 15 mmol/l)
Coagulation parameters	Abnormal spontaneous bleeding
Glucose	Hypoglycemia (blood glucose < 2.2 mmol/l or < 40 mg/dl)
Hepatic panel	Jaundice plus evidence of other vital organ dysfunction
Renal function tests	Renal impairment (serum creatinine > 265 micro mol/l)
Blood smears	Hyperparasitemia (> 2%/100,000/microliter in low intensity transmission areas or > 5% or 250,000/microliter in areas of high stable malaria transmission intensity)
Lactate	Hyperlactatemia (lactate > 5 mmol/l)
Urinalysis	Hemoglobinuria
Chest X-ray	Pulmonary edema
ECG	Evidence of ischemia

Most cases of malaria are not severe, and can be treated with supportive therapy including oral fluid resuscitation, antipyretics, nutrition, and antimalarials as elaborated below. In severely ill patients, hydration status should be monitored with central venous pressure catheters, and patients with central nervous system involvement may require airway management and seizure control.[4] Patients with severe anemia should receive RBC transfusion[4]; however platelet transfusions are usually not recommended because malaria-induced thrombocytopenia tends not to be associated with bleeding problems.[13] Procoagulant medications should be avoided.[8] Patients with acute pulmonary edema may require supplemental oxygen, diuresis, and positive pressure ventilation.[4] Hypotension and shock should be treated the same as septic shock, with fluids, vasopressors, and broad-spectrum antibiotic.[4] In capable facilities, red cell exchange or whole blood exchange transfusion may be considered for severe malaria, although there are no clinical trials comparing this therapy with others.[8]

Parasite levels should be re-measured, preferably by peripheral blood smear within 24 h of the initiation of therapy to detect drug resistance and therapeutic failure.[8] Effective therapy should decrease the parasite burden significantly.[8]

Anti-malarial medications

Recommendations for anti-malarial medication regimens are regularly updated due to changing resistance patterns among *P. falciparum*. Emergency physicians unfamiliar with treating malaria should review guidelines before commencing treatment. Up to date recommendations and dosing can be found through the WHO.[14]

The preferred treatment for *P. vivax, P. malariae,* and *P. ovale* (except *P. vivax* from Indonesia or Papua New Guinea) remains chloroquine.[6,13] Intrahepatic latent forms of *P. vivax* and *P. ovale* can be treated only with primaquine, though this drug should be avoided in patients with G6PD deficienc.[4]

Uncomplicated malaria can be treated with oral anti-malarials.[8] For uncomplicated malaria in children, the WHO recommends artemesinin-based combination therapy (ACT) in the face of growing resistance of other previous first-line therapies.[14] When combined with rapidly-eliminated compounds such as tetracyclines and clindamycin, ACT should be given for a 7-day course.[14] Combinations with longer-acting drugs can be prescribed for a 3-day course; these include artemether plus lumefantrine, artesunate plus amodiaquine, artesunate plus mefloquine, artesunate plus sulfadoxine-pyrimethamine, and dihydroartemisinin plus piperaquine.[14]

For severe malaria, the WHO recommends parenteral treatment with IV artesunate for adults and children, in preference to quinine or quinidine.[15] The high doses of quinidine required to treat malaria can cause hypotension and QT prolongation.[12] Quinine can cause cinchonism, a complex of symptoms including tinnitus, high tone deafness, nausea, dysphonia, and visual disturbance.[4] Therefore, treatment with IV artesunate is preferred because it does not require rate-controlled infusion or cardiac monitoring.[14] Patients can be switched to oral agents after their parasitemia levels are below 1% and they are able to tolerate PO medications,[8] and should continue a full course of ACT therapy.[15]

For pregnant women in the first trimester, the first-line treatment for malaria is quinine plus clindamycin for 7 days, or ACT if this fails or is unavailable.[14] For the second and third trimesters, WHO recommends ACT (except dihydroartemisinin plus piperaquine), or artesunate plus clindamycin, for 7 days.[14] Lactating women should receive the recommended antimalarial treatments for adults, except primaquine and tetracycline.[14]

Travelers returning to non-endemic countries with uncomplicated malaria should receive atovaquone plus proguanil, artemether plus lumefantrine, dihydroartemisinin plus piperaquine, or quinine plus doxycycline (not for children under eight) or clindamycin.[14] Severe malaria for travelers should be treated the same as for endemic patients.[14]

Disposition

Patients who are well-appearing with a normal CBC and hepatic panel may be discharged with follow up on their peripheral blood smear results.[10] Admission is recommended if *P. falciparum* is suspected and if the patient is > 65 years, pregnant, not immune to malaria, or if the patient has coexisting medical conditions.[10] All children with confirmed or suspected *P. falciparum* infection should be admitted for at least 24 h because of the risk of rapid progression of disease.[13] Patients with severe malaria should be admitted to an intensive care unit.[10]

Future prophylaxis is important and includes measures to decrease exposure to mosquitoes, including bednets, screened rooms, and insect repellents, and avoiding walking outside at night when Anopheles mosquitoes bite.[8] For non-immune travelers anticipating travel to endemic regions, chemoprophylaxis is recommended. For chloroquine-resistant areas, chemoprophylaxis includes weekly mefloquine starting 1 week before travel to an endemic area and continuing 4 weeks after, or atovaquone and proguanil daily, starting 1–2 days before travel and ending 1 week afterwards.[8] Mefloquine can cause neuropsychiatric side effects and should be avoided in patients with epilepsy and psychiatric illnesses.[16]

Conclusion

Malaria is a widespread disease in Africa and around the world. Emergency physicians are often the first line in medical management of malaria. Early recognition is important as the disease can progress quickly. Proper diagnosis and treatment is also important as part of emergency physicians' stewardship of effective therapies in avoiding development of drug resistance and appropriately treating other diseases on the differential.

Contribution

Laura Janneck: literature search, draft, editing.

Alex Koyfman: literature search, additions to draft, editing.

James Kimo Takayesu: Mentor: literature suggestions, editing, encouragement.

Conflict of interest

None.

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