Malaria

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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. 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

Five *Plasmodium* species possess the ability to infect humans: *P. falciparum*, *P. ovale*, *P. vivax*, *P. malariae*, and *P. knowlesi*. The female *Anopheles* mosquito ingests gametes during a blood meal, which form sporozoites that replicate in the gut. During subsequent bloodmeals, saliva containing sporozoites gets released into a human host's bloodstream. Within 60 minutes, sporozoites reach the liver, invade hepatocytes, and then rapidly divide, forming merozoites. In an active infection, organisms reenter the bloodstream and invade erythrocytes. Within erythrocytes, *Plasmodia* consume hemoglobin and develop from immature trophozoites (ring stage) to either mature trophozoites or gametocytes. Mature trophozoites replicate, forming schizonts, disrupting erythrocyte cell membrane integrity, and leading to capillary endothelial adherence and cell lysis. Untreated malaria lasts 2 to 24 months. *P. vivax* and *P. ovale* infections may display "dormant schizogony," where inactive intrahepatic parasites (hypnozoites) remain until reactivation months to years in the future.

Epidemiology

Forty percent of the total 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 cases of malaria 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 refugee populations 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.

Pathophysiology

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* lifecycle creates the classic "malarial paroxysm" of rigors, followed by several hours of fever, followed by diaphoresis and 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.

History and Physical Examination

Fever is the dominant symptom in 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 headache, malaise, weakness, gastrointestinal distress, upper respiratory symptoms, and muscle aches; severe cases may include jaundice, confusion, seizures, and dark urine. Children may exhibit lethargy, malaise, abdominal pain, nausea, vomiting, and diarrhea; severe cases may include somnolence, seizures, and coma. In taking a history, it is essential to inquire about location of residence, recent travel and use of chemoprophylaxis, exposures (including sick contacts, freshwater, 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).

The physical exam may reveal a febrile, ill-appearing patient with possible hepatosplenomegaly, icterus, jaundice, pallor, or signs of dehydration. Severe cases may display hemodynamic instability, somnolence, or coma, particularly in those with concomitant bacterial infection or malaria-induced adrenal insufficiency. Severe presentation is more common with *P. falciparum* infection.

Diagnosis

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 release of intracellular contents, and concomitant dehydration, and kidney injury secondary to glomerular damage. Coagulation panel may reveal coagulopathy concerning for 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). RDTs detecting parasitic antigens histidine-rich-protein-2, lactate dehydrogenase, and aldolase are increasingly being utilized to diagnose *P. falciparum* infection. 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.

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. 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**.

Per the **2019 CDC Guidelines** below, appropriate treatment depends on the *Plasmodium* species, clinical stability, and age of the patient, and regional antimalarial susceptibility:

- Uncomplicated *P. falciparum, P. malariae* or *P. knowlesi* infections in chloroquine-sensitive regions are treated with a chloroquine phosphate 600 mg (pediatric: 10 mg/kg) loading dose, followed by 300 mg (pediatric: 5 mg/kg) at 6, 24, 48 hours; or a hydroxychloroquine 620 mg (pediatric: 10 mg/kg) loading dose, followed by 310 mg (pediatric: 5 mg/kg) at 6, 24, and 48 hours.

- Uncomplicated *P. falciparum* infections in chloroquine-resistant or unknown regions are treated with atovaquone-proguanil 250 mg/100 mg 4 tabs (pediatric: varied weight-based dosing, 6.5 mg/25 mg tabs) daily for 4 days; or artemether-lumefantrine 20 mg/120 mg 4 tabs (pediatric: varied weight-based tabs) at initial dose, then 8 hours later, then twice daily for 2 days; or quinine sulfate 542 mg (pediatric: 8.3 mg/kg) three times daily for 3 days (7 days if in Southeast Asia) plus either doxycycline 100 mg daily for 7 days (pediatrics 2.2 mg/kg every 12 hours), or tetracycline 250 mg daily for 7 days (pediatric: 25 mg/kg/day divided four times daily for 7 days), or clindamycin 20 mg/kg/day divided three times daily for 7 days (pediatric: same); or mefloquine 684 mg (pediatric: 13.7 mg/kg) loading dose followed by 456 mg (pediatric: 9.1 mg/kg) every 6 to 12 hours for total of 1250 mg (pediatric total: 25 mg/kg).

- Uncomplicated *P. vivax* or *P. ovale* infections in chloroquine-sensitive regions receive treatment with chloroquine phosphate or hydroxychloroquine as per above, plus either

primaquine phosphate 30 mg (pediatric: 0.5 mg/kg) daily for 14 days, or tafenoquine 300 mg once (same in children older than 16 years).

- Uncomplicated *P. vivax* infections in chloroquine-resistant regions (Indonesia, Papua New Guinea) get treated with quinine sulfate as per above plus either doxycycline, primaquine, or tafenoquine as per above; or atovaquone-proguanil as per above plus either primaquine or tafenoquine; or mefloquine as per above plus either primaquine or tafenoquine as per above.
- Uncomplicated infections with any species in pregnant women in chloroquine-sensitive regions require treatment with chloroquine or hydroxychloroquine as per above.
- Uncomplicated infections with any species in pregnant women in chloroquine-resistant regions are treated with quinine sulfate as per above plus either clindamycin or mefloquine as per above in the first, second, or third trimesters; or artemether-lumefantrine as per above in only the second and third trimesters.
- Severe malaria infection in unstable, non-pregnant patients in all regions includes IV artesunate 2.4 mg/kg (pediatric: children greater than 20 kg receive 2.4 mg/kg, children less than 20 kg receive 3.0 mg/kg) at 0, 12, 24, and 48 hours and either artemether-lumefantrine, atovaquone-proguanil, doxycycline, or mefloquine as per above.

References

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