Approach to the Patient With Malaria

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KEY POINTS

- Malaria often occurs in returning travelers and people who visit friends and relatives in malaria-endemic areas.
- Acute malaria of any species is a medical emergency.
- A febrile illness in a patient returning from travel in a malaria-endemic area should be presumed to be malaria until proven otherwise.
- Five species of plasmodial parasites infect humans causing essentially similar febrile illnesses.
- Uncomplicated malaria resembles many other infections and its diagnosis requires laboratory confirmation.
- Uncomplicated malaria may progress to a severe, multisystem, life-threatening disease within hours, if not diagnosed and treated promptly.

- Several chemotherapeutic options exist for treating uncomplicated malaria and are guided by the parasite species and local drug resistance patterns.
- Artemisinin-based combinations are the most potent antimalarial drugs.
- For severe and complicated malaria, intravenous or intramuscular artesunate is the first line treatment for all patients, including all trimesters in pregnant women.
- *Plasmodium vivax* and *Plasmodium ovale* are relapsing malarias and require radical cure with primaquine.

INTRODUCTION

Malaria in a traveler poses a highly complex and potentially dangerous clinical challenge. Five species of plasmodial parasites routinely infect humans and each may progress to complicated and severe disease if not promptly diagnosed and effectively treated. The notion of malignant and benign species of plasmodia should be considered a dangerous fallacy. Managing a patient with malaria requires navigating many diagnostic and therapeutic options and potential pitfalls. This chapter guides the approach to patients who may have malaria and the successful management of those having confirmed malaria. This chapter sets aside management of patients resident in endemic areas and focuses on the traveling patient population.

THE THREAT

Endemic malaria occurs globally across most of the tropics and some subtropical countries, even on the temperate Korean peninsula. Thousands of travelers each year are diagnosed with acute malaria and treated but some do not survive.[1,2] Data from 40 nonendemic countries show that mean number of imported cases per year from 2005 to 2015 is nearly 10,000, led by France (~2000), the United Kingdom (~1900), and the United States (~1500). *Plasmodium falciparum* is the predominant species from Africa, especially western Africa; and *P. vivax* is more common from eastern Africa, Asia, and the Americas (where *P. vivax* is most common).[3] The case fatality rates (CFRs) for imported severe malaria typically range between 2% and 10%. Deaths generally occur among those not taking antimalarial chemoprophylaxis and in those facing delayed diagnosis and treatment by geographic isolation/travel, reluctance to seek medical attention, misdiagnosis, or inappropriate/

ineffective therapy.[4–6] Promptly diagnosed and treated uncomplicated malaria very rarely progresses to life-threatening severe malaria.

THE MALARIAS

Malaria is not one disease but a number of diseases. Except in rare instances such as congenital or transfusion/transplant malaria, the malarias are acquired by the bite of particular species of mosquito in the genus *Anopheles* carrying any of the five species of sporozoan parasites in the genus *Plasmodium* known to routinely infect humans (Table 17.1). Each species typically causes an undifferentiated febrile illness characterized by periodic fevers, chills, headache, muscle aches, malaise, and sometimes nausea and vomiting. Symptoms are essentially the same across all five species and so have no discriminating value. Each species may also progress to a severe and complicated systemic illness (*P. falciparum* may do so more often and with greater rapidity) comprising cerebral, pulmonary, renal, hepatic, or circulatory dysfunction. Although not species specific, the dominant syndromes do tend to vary with species and age of the patient (see Table 17.1).

Each species and its clinical presentation thus represent a particular malaria and are given appropriate terms (e.g., acute uncomplicated ovale malaria, severe vivax malaria [global description of the unwell patient], cerebral malaria due to *P. falciparum*, *P. knowlesi*–induced acute respiratory distress syndrome [ARDS]). Therefore clinicians should make the species diagnosis, define the illness, and understand the vulnerability of the patient. These then inform clinical management.

Malaria in travelers differs in important ways from that in local residents chronically exposed to malaria and having varying degrees of naturally acquired immunity. In heavily endemic areas, the risk of severe and complicated falciparum malaria sharply declines with age

Abstract

Nearly 3 billion people live at risk of malaria across most of the tropics, subtropics, and even some temperate zones. Millions visit these areas, and each year thousands appear in hospitals with posttravel acute malaria. That diagnosis should be managed as a medical emergency. Illness may deteriorate rapidly without prompt diagnosis and effective treatment. Among five species of *Plasmodium* responsible for human malaria, *Plasmodium falciparum* most often deteriorates rapidly, but all species potentially threaten life. Malignant and benign species of malaria parasites is a dangerous fallacy. Clinical malaria mimics other common tropical infections and the diagnosis requires laboratory confirmation, but malaria-like symptoms in a patient exposed to risk should be presumed to be malaria until proven otherwise. Intravenous or intramuscular artesunate is used for severe malaria of any species in any patient, including all trimesters of pregnancy. Primaquine is administered with vivax or ovale malarias after affirming glucose-6-phosphate dehydrogenase (G6PD)–normal status.

TABLE 17.1	Essential Features of the Plasmodia Routinely Infecting Humans				
	P. falciparum	**P. vivax**	**P. malariae**	**P. ovale**	**P. knowlesi**
Relative abundance	Very common	Very common	Rare	Rare	Rare
Natural host	Human	Human	Human	Human	Macaques
Other hosts	• Some African apes	• Some African apes • New World monkeys	• Some New World monkeys	• Some African apes	• Gibbons • Leaf monkeys • Others
Incubation period	7–14 days	10–20 days	15–30 days	11–16 days	9–12 days
Blood schizogonic cycle	48 hours (tertian)	48 hours (tertian)	36 hours (quartan)	48 hours (tertian)	24 hours (quotidian)
Latent hepatic stage	No	Yes	No	Yes	No
Geographic distribution	Subtropical and tropical Americas, Africa, Asia	Temperate, subtropical, and tropical Americas, Africa, Asia	Subtropical and tropical Americas, Africa, Asia	Subtropical and tropical Africa and Asia	Tropical Southeast Asia
Parasitemia	>100,000/μL dangerous	Does not correlate with clinical threat	Almost never high	Almost never high	>50,000/μL dangerous
RBC infected	Any	Youngest reticulocytes	Older erythrocytes	Reticulocytes	Any
Organs infected	Vascular sinuses	Vascular sinuses, spleen, and marrow	Vascular sinuses and unknown	Vascular sinuses and unknown	Vascular sinuses
Salient syndromes in severe disease	• Seizures[a] • Coma • AKI[b] • Jaundice/hepatic dysfunction[b] • ARDS[b] • Anemia[a] • Shock • Metabolic acidosis	• Platelets <50,000/μL • Shock • Jaundice/hepatic dysfunction • Severe anemia • Metabolic acidosis • AKI • Coma • Abnormal bleeding • ARDS • Splenic infarction/rupture	• Rare case reports of AKI and ARDS	• ARDS • Anemia	• ARDS • Jaundice/hepatic dysfunction • AKI • Shock • Metabolic acidosis
Drug resistance problems	• Chloroquine (universal) • Artemisinin (Southeast Asia)	• Chloroquine (Southeast Asia) • Primaquine (Southeast Asia)	One report of chloroquine resistance in southern Sumatra, Indonesia	Unknown	None
Dormancy	Rare	Latent hypnozoites, about 1 month up to 4 years	As long as several decades, mechanism unknown	Latent hypnozoites, but durations unknown	None known

[a]More common in children.
[b]More common in adults.
AKI, Acute kidney infection; *ARDS,* acute respiratory distress syndrome; *RBC,* red blood cell.

whereas that risk in nonimmune patients sharply increases with age.[7] As another example, severe anemia appears commonly in endemic areas with hospitalized malaria, but appears much less often in travelers with the same diagnosis. This chapter sets aside these complexities by considering only the nonimmune traveler.

CLINICAL PRESENTATION OF UNCOMPLICATED MALARIA

Onset of symptoms of uncomplicated malaria in the nonimmune patient not taking chemoprophylaxis is typically within 8–14 days after an infectious anopheline mosquito bite. In most travelers diagnosed with falciparum malaria, clinical attack occurs within 1 month after travel and cessation of suppressive chemoprophylaxis. Vivax malaria, on the other hand, appears 2 months or more later because suppressive chemoprophylaxis does not impact the latent liver stage hypnozoites responsible for delayed attacks. Late falciparum attacks may also occur, but are quite rare.

Fever occurs in almost all patients and is often preceded by a short prodrome of 1–2 days of vague abdominal discomfort, headache, muscle ache, and malaise; cough is surprisingly common (20%–50%). Children may be lethargic, anorexic, and irritable. On the other hand, up to a third of patients with confirmed malaria may present afebrile due to the cyclic nature of paroxysms linked to the asexual reproductive cycle of parasites in the blood. Of those with fever, classic description cycles of 24, 48, or 72 hours according to species (see Table 17.1) rarely appear in the nonimmune patient where daily paroxysm is the rule regardless of infecting species. The paroxysm may begin in the late afternoon with intractable vomiting followed by chills with profound shivering lasting a few hours. Those pass and then quickly progress to a spiking fever (39°–41.5°C) with drenching sweats of several hours. Defervescence by early morning leaves the patient exhausted and finally able to sleep.

Physical signs in uncomplicated malaria are few and nonspecific and include fever (almost always during the illness course), splenomegaly (~25%), hepatomegaly (~11%), and jaundice (~7%). Hematologic findings are noteworthy for the proportions of patients with (i) any degree of thrombocytopenia (40%–80%), (ii) platelet count <50,000/μL (6%–15%), (iii) a total white cell count (WCC, 80%) in the normal range (4–10,000/μL), (iv) similar rates of leukopenia and leukocytosis, and (v) anemia (hemoglobin [HBC] <12 g/dL, 28%). The WCC differential at presentation is variable (e.g., eosinopenia, lymphopenia, neutrophilia, atypical lymphocytes) and should never be used to rule out malaria. Liver enzymes (aspartate transaminase/alanine transaminase [AST/ALT]) are raised in 25% of patients, as is total bilirubin in 38%. A raised lactate dehydrogenase (LDH; liver and red cell origin) is reported in 70% of patients. Many other imported tropical infections share these laboratory abnormalities.

CLINICAL PRESENTATION OF SEVERE AND COMPLICATED MALARIA

Patients presenting with severe malaria are clearly unwell and may exhibit symptoms and signs of a systemic illness that is clinically indistinguishable from other conditions such as sepsis and septic shock. The World Health Organization (WHO) definition of severe malaria has criteria for both adults and children and is based mostly on data from malaria-endemic countries (Table 17.2). In one European series of 185 patients with imported severe malaria (2006 WHO criteria), the main features seen were (i) hyperparasitemia >5% (~71%), (ii) jaundice (44%), (iii) impaired consciousness/coma (25%), (iv) acute kidney injury (19%), (v) shock (15%), (vi) respiratory failure/ARDS (12%), (vii) spontaneous bleeding (7%), (viii) acidosis (5%), (ix) hypoglycemia (3%), and (x) multiple convulsions (2%).[4] The median number of WHO criteria was 2, and some 40% of patients had an underlying comorbidity. These data are broadly consistent with those from an earlier series of 400 patients, reported by Bruneel et al.[5] who highlighted the contribution of

community (7.5% patients) and hospital-acquired (16.6%) bacterial infections to malaria-related morbidity. One important consequence of treating nonimmune, severe malaria patients with intravenous artesunate (IV AS) is delayed (up to ~3 weeks) acute hemolytic anemia (AHA), which may require transfusion; this occurred in 19 (27%) of 70 IV AS–treated patients.[4]

DIAGNOSIS OF INFECTION

The differential diagnosis of acute undifferentiated fever in travelers is very broad. A good history is important to obtain clues of exposure to malaria and other infections, when, where, and how often this may have occurred. Knowledge of the incubation periods is helpful to rule out certain illnesses. A thorough physical examination is mandatory. Malaria has many manifestations and the presenting clinical picture may be one that is dominated by symptoms and signs that favor other diagnoses such as an influenza-like illness, gastroenteritis, pneumonia, encephalitis, and hepatitis. Moreover, the number of pathogens that mimic malaria is also broad (Table 17.3). The key to resolving this diagnostic challenge is laboratory confirmation of malaria as quickly as possible (see upcoming discussion). The diagnosis may be ruled out if three consecutive malaria blood films (preferably in conjunction with rapid tests), examined at 6- to 12-hour intervals, are negative within 24–48 hours. Malaria causes a third of imported fevers and a coinfection with another pathogen should be suspected if patients remain febrile despite effective antimalarial treatment. Thwaites and Day[8] offer an exhaustive review on the causes of imported fevers.

Clinical Diagnosis

A presumptive clinical diagnosis of malaria may be made where there is a high probability of recent exposure to infection and no ability to confirm the diagnosis by laboratory examination within a few hours. Treatment should not await a delayed confirmation where malaria emerges as likely in the differential. Recovery within 48–72 hours of

TABLE 17.2 Differential Diagnosis of Acute Malaria

Undifferentiated Fever	Fever and GI Symptoms	Fever and Jaundice	Fever +/− Arthritis and Rash	Fever and Respiratory Symptoms	Fever and CNS Symptoms	Fever and Abnormal Bleeding
Dengue	Gastroenteritis	Viral hepatitis	Dengue	MERS-CoV	Meningitis	Ebola fever
Zika virus	Infective diarrhea	Yellow fever	Zika virus	Avian influenza	Encephalitis	CCHF
West Nile	Bacterial liver abscess	Relapsing fever	Chikungunya	Seasonal influenza	Rabies	Lassa fever
Chikungunya	Amoebic liver abscess	Leptospirosis	Ross River virus	Atypical pneumonia		Marburg fever
Ross River virus	Pelvic abscess	Q fever	O'nyong'nyong	Q fever		
Acute HIV seroconversion	Appendicitis	Rickettsial disease		Acute schistosomiasis		
Relapsing fever	Diverticulitis	Typhoid/paratyphoid fever	Katayama fever	Acute histoplasmosis		
Leptospirosis		Bacteremia				
Rickettsial disease		Pneumococcal pneumonia				
Typhoid/paratyphoid fever		Ascending cholangitis				
Melioidosis		Bacterial liver abscess				
Brucellosis		Amoebic liver abscess				
African trypanosomasis						
Babesiosis						
Acute schistosomiasis						

CCHF, Crimean Congo hemorrhagic fever; *CNS,* central nervous system; *GI,* gastrointestinal; *HIV,* human immunodeficiency virus; *MERS-CoV,* Middle East respiratory syndrome coronavirus.

TABLE 17.3   **WHO Criteria for Severe Malaria in Adults and Children**

Impaired consciousness	A Glasgow coma score <11 in adults or a Blantyre coma score <3 in children
Acidosis	A base deficit of >8 mEq/L or, if unavailable, a plasma bicarbonate of <15 mmol/L or venous plasma lactate >5 mmol/L Severe acidosis manifests clinically as respiratory distress: rapid, deep, and labored breathing
Hypoglycemia	Blood or plasma glucose <2.2 mmol/L (<40 mg/dL)
Severe malarial anemia	A hemoglobin concentration <5 g/dL or a hematocrit of <15% in children <12 years of age (<7 g/dL and <20%, respectively, in adults) together with a parasite count >10,000/µL
Renal impairment/acute kidney injury	Plasma or serum creatinine >265 µmol/L (3 mg/L) or blood urea >20 mmol/L
Jaundice	Plasma or serum bilirubin >50 µmol/L (3 mg/dL) together with a parasite count >100,000/µL *P. knowlesi:* jaundice as above and parasitemia >20,000/µL
Pulmonary edema	Radiologically confirmed, or oxygen saturation <92% on room air with a respiratory rate >30/min, often with chest indrawing and crepitations on auscultation
Significant bleeding	Including recurrent or prolonged bleeding from nose, gums, or venipuncture sites; hematemesis or melena
Shock	Compensated shock is defined as capillary refill ≥3 s or temperature gradient on leg (mid to proximal limb), but no hypotension. Decompensated shock is defined as systolic blood pressure <70 mm Hg in children or <80 mm Hg in adults with evidence of impaired perfusion (cool peripheries or prolonged capillary refill)
Hyperparasitemia[a]	*P. falciparum* parasitemia >10%, *P. knowlesi* parasitemia >2%

[a]There are no parasitemia limits for *P. vivax.*

initiating effective antimalarial treatment would be consistent with the clinical diagnosis of malaria, but confirmation nonetheless requires laboratory evidence.

Microscopic Diagnosis. In most acutely ill patients, plasmodial parasites may be observed in stained thick blood films examined by oil immersion light microscopy (1000×) by technicians certified as competent and having access to good-quality reagents and microscope. The thin film is most useful for quantifying hyperparasitemia and aiding in identification to species rather than the search for parasites. Guidance for endemic laboratories typically demands examination of at least 200 ocular fields before declaring a slide negative for malaria. In nonendemic clinics seeing nonimmune patients, that search should be much more extensive (e.g., >500 fields and as many as 2000), because nonimmune patients have a far lower threshold of parasitemia for acute febrile illness.

It is often possible for the microscopist to decide upon the species observed employing a variety of visual clues. The banana-shaped gametocytes of *P. falciparum* are pathognomonic, for example. Enlargement of infected red blood cells containing ameboid parasites points to *P. vivax* or *P. ovale.* Mature schizonts may be seen and these offer strong clues to species identity. However, the microscopist also faces limitations in this regard. If only young ring forms are observed, a specific diagnosis may not be possible. If the patient is infected by *P. knowlesi,* the microscopic diagnosis of it is virtually impossible—it is most often mistaken for *P. malariae* but this species characteristically presents with low parasitemia rather than the frequently occurring hyperparasitemia (>50,000/µL) of *P. knowlesi* malaria.

In most patients with malaria, clinical threat correlates with the density of parasitemia, as is proven for *P. falciparum* and *P. knowlesi* malarias with >100,000 and >50,000 parasites/µL blood, respectively, each associated with an increased risk of severe disease. However, this is much less clear in patients with *P. vivax* malaria, where biomass may sequester in the spleen and marrow.[9,10] Any level of parasitemia in vivax malaria should be considered potentially threatening.

Rapid Diagnostic Tests

A wide variety of commercially available immunochromatographic cassettes for the diagnosis of malaria may be applied where competent microscopic diagnosis is not available. Though simple and often effective in endemic settings, the diagnosis is less sensitive than expert microscopy—few of the many available kits detect parasitemia <100/µL, and lower sensitivity for *P. vivax* malaria is typical. No kit reveals parasite counts or stages present. Rapid tests designed to detect only *P. falciparum* histidine-rich protein 2 (HRP-2) will be negative for all other species, including *P. knowlesi.* Non–*P. falciparum* malaria can be detected with rapid tests containing a pan antigen strip but tend to be less sensitive. The problem of some strains of *P. falciparum* in the wild having deleted their HRP genes renders them undetectable by HRP-based rapid diagnostic tests (RDTs).[11]

Nucleic Acid Diagnostic Tests

A wide variety of polymerase chain reaction (PCR) tests for the malarias have been described.[12] Most are sensitive to about one parasite per microliter and may be species specific, and quantitative tests reveal parasite load in examined tissues. PCR testing is far more sensitive to mixed species infection than even expert microscopy. The principal drawbacks are high levels of laboratory expertise, cost, and time required. A laboratory with all specialized reagents on hand typically requires at least several hours and often an entire workday or more to report findings. PCR diagnosis thus typically confirms an early diagnosis that guided immediate therapy.

TREATMENT OF UNCOMPLICATED MALARIA

Several options exist for treating malaria (Table 17.4). Choices depend on drug availability, parasite species, and local resistance patterns. The most powerful antimalarial drugs are the artemisinin-based combinations (ACTs), but some ACTs are unavailable in nonendemic countries. Chloroquine (CQ) is used commonly to treat *P. vivax, P. malariae, P. ovale,* and *P. knowlesi.* However, CQ-resistant *P. vivax* is well documented in Southeast Asia, the Indonesian archipelago, and Papua New Guinea with reported foci in a range of countries. If in doubt, use an ACT. Although CQ is effective against uncomplicated *P. knowlesi,* the ACTs are more rapidly acting and are preferred for an infection with a tendency to produce rapidly severe disease. Atovaquone proguanil is available widely and retains efficacy against *P. falciparum* (failures reported from western Cambodia), *P. vivax,* and *P. knowlesi.* For individuals who have been taking chemoprophylaxis, typically doxycycline, atovaquone proguanil, or mefloquine, treatment should exclude these drugs.

TABLE 17.4	**Treatment of Uncomplicated Malaria**		
		Notes	**Cautions/Contraindications[a]**
Plasmodium falciparum			
First line treatment	Artemether lumefantrine (AL)	Take twice daily with fatty snack/drink to increase lumefantrine absorption. Four dosing bands.	Cautions: AL levels affected by CYP3A4 inducers and antiretroviral drugs. Patients with/on QTc prolongation drugs.
	Dihydroartemisinin-piperaquine (DHAPP)	Once daily dosing. Manufacturer recommends take on an empty stomach because fatty food enhances PP absorption. Eight dosing bands.	PP dose dependent prolongation of the QTc interval. Contraindications: known congenital QTc prolongation in patient or family, on drugs or have a disease with long QTc
	Artesunate amodiaquine	Once daily dosing. Widely used in Africa. Four dosing bands.	Rarely causes transient neutropenia and transaminitis
	Artesunate mefloquine (ASMQ)	Once daily dosing. Most experience in SE Asia. Four dosing bands. Overall tolerability less than other ACTs.	Contraindicated in significant psychiatric disease (depression, anxiety neurosis), epilepsy. No repeat dose ≤2 months.
	Pyronaridine artesunate	Once daily dosing. Pediatric granules available. Four dosing bands for tablets (weight ≥20 kg) and three dosing for granules.	Contraindicated acute liver disease (jaundice and symptoms), severe liver disease (i.e., decompensated cirrhosis, Child-Pugh stage B or C). Severe renal impairment.
Alternative treatment	Atovaquone proguanil (ATV-PG)	Once daily dosing. Take with food or milky drink to increase ATV absorption. Four dosing bands. Not recommended if parasitemia >2%.	Creatinine clearance <30 mL/min. No data in severe liver disease. ATV levels reduced by rifampicin, rifabutin, metoclopramide, tetracycline, efavirenz, and protease inhibitors. PG may enhance the anticoagulant effect of warfarin.
	Mefloquine (MQ)	Total dose 25 mg/kg: 15 then 10 mg/kg over 2 days.	See ASMQ
	Quinine + doxycycline (QN + DOX)	Give both for 7 days. Quinine may be given for 5 days.	QN: Cinchonism common. Bitter taste that children may not like. DOX contraindicated <12 years (United Kingdom), <8 years (United States).
Plasmodium vivax			
No chloroquine (CQ) resistance	CQ	Total dose 25 mg/kg in 48 hours: 10-10-5 or 10-5-5-5. Follow local recommendations.	Reduce dose with creatinine clearance <60 mL/min. Avoid in severe renal disease.
CQ resistance (CQR)	ACTs above or ATV-PG	CQR common in Indonesia, Papua New Guinea, SE Asia. Foci elsewhere.	
Plasmodium ovale; Plasmodium malariae			
First line treatment	Chloroquine		As above
Alternative treatment	ACTs above or ATV-PG		As above
			As above
Plasmodium knowlesi			
First line treatment	ACTs as above	ASMQ, AL, and DHAPP effective.	As above
Alternative treatment	CQ, ATV-PG, MQ	CQ, ATV-PG, MQ effective in travelers.	As above

[a]The main cautions/contraindications are mentioned. Consult the latest manufacturers' package inserts for more details.
ACT, Artemisin-based combination.

One key decision clinicians have to make is whether to admit the patient into hospital for close observation; nonimmune malaria-infected patients can deteriorate rapidly and those with parasite counts >2% (~100,000/μL) are at an increased risk of developing severe disease and death. The UK Malaria Treatment guidelines recommend admission for most falciparum-infected patients unless they are cared for by a specialist unit that has protocols in place for outpatient management.[13]

TREATMENT OF SEVERE MALARIA

Rapid initial assessment followed by rapid treatment is key—use IV AS (Table 17.5). If unavailable, use quinine infusions or intramuscular artemether. All patients with severe malaria should be managed in a high dependency unit or an intensive care unit (ICU). Alert the ICU and renal teams early because rapid deterioration (median time 24 hours) to cerebral malaria (mechanical ventilation needed to protect the airway) and acute kidney injury (AKI) are well documented[2]; ARDS occurs later (median time 3 days) even if patients appear to be improving clinically and the parasite count is falling.[14]

The detailed management of such patients is beyond the scope of this review; however, we highlight key aspects. Good nursing care of the sick patient is crucial. Diligence to fluid balance is important because the risk of fluid overload precipitating pulmonary edema is increased due to increased pulmonary capillary leakage. Patients should

TABLE 17.5 Drug Doses for Severe Malaria		
Drug	**Dose**	**Notes**
Artesunate	2.4 mg/kg at 0 h, 12 h, 24 h	Give for a minimum of 24 h
	2.4 mg/kg daily	Continue treatment until the patient can eat and drink
Artesunate children	3 mg/kg at 0 h, 12 h, 24 h	Treat with an ACT at standard dose
	3 mg/kg daily	
Artemether	3.2 mg/kg IM on 0 h	
	1.6 mg/kg 24 h	
	1.6 mg/kg daily	
Quinine salt	20 mg/kg infused over 4 h	Quinine can be infused in crystalloid (e.g., dextrose 5%, dextrose saline)
	4 h off infusion	Give for a minimum of 24 h
	10 mg/kg infused over 4 h	Monitor glucose every 2 hours during infusion
	4 h off infusion	Continue treatment until the patient can eat and drink
	10 mg/kg infused over 4 h	Treat with an ACT at standard dose
	4 h off infusion, etc.	Give IM into anterior thigh if venous access is challenging

ACT, Artemisinin-based combination; *h,* hour(s); *IM,* intramuscular

be kept "dry" while maintaining adequate perfusion and renal function. An input-output chart is essential, but a central venous–pressure line is not useful in guiding fluid management. Reserve aggressive fluid resuscitation for patients who are shocked but still exercise caution and observe carefully for a response. Limit the number of fluid challenges and seek early ICU advice regarding the use of vasopressors. Shock in severe malaria may be due to a concurrent bacterial infection, which also contributes to metabolic acidosis and the development of ARDS. Take blood and other cultures and treat promptly with a broad-spectrum antibiotic. AKI in severe malaria is hypercatabolic and early renal replacement treatment may be needed. Convulsions should be managed in the standard way; look for and correct hypoglycemia, hypocalcemia, hyponatremia, and hypoxia. Hypoglycemia may occur in severe malaria, particularly in quinine-treated patients even in the recovery phase. Regular blood glucose concentrations by fingerstick are necessary: every 4 hours routinely, every 2 hours during quinine infusions, and at any time a patient has a convulsion and/or reduced level of consciousness. Treat hypoglycemia acutely with 10% dextrose and prevent further episodes with 5% or 10% dextrose infusions as part of fluid maintenance. Full blood counts, clotting, and biochemistry (including calcium, magnesium, and phosphate) should be monitored closely, especially if AKI develops. Daily malaria parasite counts are needed to monitor parasite clearance. Blood transfusion should follow local ICU guidelines. Platelet transfusions are not indicated even with low counts unless there is active bleeding.

TREATMENT OF SEVERE MALARIA IN CHILDREN

Most of the experience of pediatric severe malaria comes from sub-Saharan Africa where the common manifestations are cerebral malaria, severe anemia, and acidotic- and dehydration-driven respiratory distress. Convulsions, hyperpyrexia, and hypoglycemia frequently complicate the clinical course. Maitland et al.[15] have published guidelines for managing nonimmune children.

TREATMENT OF MALARIA IN PREGNANCY

Pregnant women with malaria are prone to severe disease and suffer miscarriages and stillbirths. Involve the obstetric and pediatric teams early. In the second half of pregnancy, malaria can be a fulminant disease associated with a higher mortality than in nonpregnant women. Two features of severe malaria stand out in pregnancy: ARDS and

hypoglycemia (which may be recurrent with quinine treatment). For otherwise uncomplicated disease, malaria in the second and third trimesters should be treated with an ACT; they are effective and safe. In the first trimester, 7 days of quinine combined with clindamycin are recommended. Recent data, however, show similar miscarriage and stillbirth rates for quinine and ACT treatments in the first trimester. For severe malaria, IV AS is the drug of first choice in all trimesters, using the same dose as in nonpregnant adults. Primaquine should not be given to a pregnant woman.

ANTIRELAPSE THERAPY WITH PRIMAQUINE

Presumptive antirelapse therapy (PART) with primaquine poses a complex challenge to the effective treatment of *P. vivax* and *P. ovale*. All patients diagnosed with these infections should be considered at risk of multiple recurrent attacks up to about 2 years following the primary attack. The frequency, timing, and number of secondary attacks varies with geographic origin of the infection, but in general this may occur in at least 30% and often over 80% of patients. Each renewed attack is as debilitating and potentially dangerous as the primary attack. Prescribing PART to prevent relapses is strongly recommended by WHO based on very good evidence.

Primaquine was registered for PART in combination with chloroquine for the radical cure of vivax malaria in 1952 at a dose of 15 mg base daily in adults for 14 days commencing concurrent with chloroquine therapy or within 1–2 weeks of completing it. Most authorities today recommend 30 mg daily in an adult for 14 days because of its high efficacy and the poor efficacy of the 15 mg dose in tropical strains of *P. vivax.*[16] Taken with a snack or meal, the former is remarkably safe and well tolerated in nonpregnant patients aged ≥6 months having normal glucose-6-phosphate dehydrogenase (G6PD) activity (see upcoming discussion).

Some patients prescribed PART and who strictly adhere to it may nonetheless suffer relapses of vivax or ovale malarias as a consequence of relatively poor metabolism of primaquine to its active metabolite by cytochrome P-450 isozyme 2D6 (CYP2D6). That isozyme is highly polymorphic and the extent of primaquine metabolism may be impaired or null according to the CYP2D6 alleles present. Repeated or increased dosing may achieve cure in the former, but not in the latter. The null metabolizer cannot be cured of the latent stages of these malarias. Ascertaining CYP2D6 genotype in patients who fail PART should be undertaken.

PRIMAQUINE AND G6PD DEFICIENCY

In all patients diagnosed with *P. vivax* or *P. ovale* malaria, a laboratory evaluation of G6PD deficiency should be undertaken prior to prescribing primaquine for PART. G6PD deficiency is an ordinarily silent red blood cell abnormality that renders patients vulnerable to AHA caused by primaquine, other drugs, some foods, and infections.[17] Different degrees of G6PD deficiency exist with the more severe variants causing greater primaquine-induced AHA. Accordingly, daily administered primaquine for PART in G6PD-deficient patients may lead to life-threatening AHA and should not be given to patients without ascertaining their G6PD status. Where G6PD screening is not possible, patients may be administered primaquine under clinical supervision with daily hemoglobin measurements and close observation for darkening of urine color. Onset of hemolysis may be observed within 2 days and therapy safely halted. Moreover, PART should not be prescribed to pregnant (risk of fetal hemolysis) or lactating women (risk of hemolysis in G6PD infant), or infants <6 months of age (no safety data).

The diagnosis of G6PD deficiency may be accomplished by qualitative screening using commercially available laboratory or point-of-care kits. Qualitative screening kits of any type suffer the drawback of insensitivity above about 30% of normal G6PD activity. Although this poses no threat to hemizygous males or homozygous females having this X-linked trait, heterozygous females may screen as G6PD normal and yet be vulnerable to significant AHA, especially in the more severe G6PD-deficient variants like G6PD Mediterranean. Female patients should be examined by quantitative spectrophotometric testing and those <70% of normal G6PD activity excluded from primaquine PART.[18]

The early evidence of safety regarding G6PD-deficient patients showed a self-limiting AHA with sustained daily primaquine therapy. Those studies, however, were conducted in otherwise healthy African-American adult male volunteers with the relatively mild African A-variant of G6PD deficiency. Today it is understood that more severe G6PD variants dominate in areas where *P. vivax* is (or has been) most common (i.e., the Mediterranean, Middle East, and all of Asia). Thus G6PD deficiency should be considered a serious threat to any patient of unknown G6PD status.

WHO and other authorities have historically recommended a regimen of 0.75 mg/kg weekly dose for 8 weeks for PART in G6PD-deficient patients. The evidence of the safety of that regimen in other than African A-G6PD-deficient subjects is limited and weak,[19] as is the evidence of its efficacy. Given the risk of significant AHA with the 0.75-mg/kg dose, any patient receiving it should be closely monitored.

MANAGING RELAPSE RISK IN PATIENTS UNABLE TO RECEIVE PRIMAQUINE

Patients with G6PD deficiency who cannot be medically supervised or those of unknown G6PD status, pregnant and lactating women, infants, or CYP2D6 null metabolizers should not receive primaquine therapy. Although some authorities have recommended chloroquine chemoprophylaxis in the months following a primary attack of *P. vivax* malaria, no randomized controlled trials have validated this as safe and effective. WHO makes no recommendation on this matter because of the lacking evidence. Moreover, widespread resistance to chloroquine by this species renders this advice even less useful.

This issue in pregnant women is especially difficult and important. Some providers, wrongly viewing uncomplicated vivax malaria as benign and not threatening, have simply allowed pregnant women to relapse and then treat the acute attack. Large studies in Southeast Asia, however, affirmed that even a single attack of acute vivax (or falciparum) malaria during the first trimester of pregnancy increased the odds of spontaneous abortion, stillbirth, or low birthweight by a factor of 4 compared to uninfected women.[20] Providers should consider any strategy sparing a woman in any stage of pregnancy from often inevitable and multiple relapses in the year or two following a primary attack. One option, for example, may be monthly presumptive therapy with dihydroartemisinin-piperaquine for at least 4 months following the primary attack (i.e., eliminating any blood stages present or those that emerge in the month that follows, by slowly eliminated piperaquine acting as a chemoprophylactic).

CONCLUSION

A febrile illness in a patient with a history of exposure to malaria should prompt immediate diagnostic workup. Where diagnosis within hours is not possible, malaria should be presumed and immediately treated. All five species of plasmodia infecting humans are potentially dangerous without prompt diagnosis and effective treatment.

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