

Jorge Hidalgo, Pedro Arriaga,
and Gloria M. Rodriguez-Vega

Case Presentation

A 25-year-old male presented to the emergency department with a history of abdominal pain in the right hypochondrium, jaundice, fever, and a decrease in consciousness. He was businessman who had recently returned from Nigeria, where he had spent 3 weeks. Laboratory tests at presentation showed WBC: 20,650 Neu:88 Lymph:12 Platelets: 38,000 SGOT: 88 SGPT: 120 Billirubins: T: 4.3 mg/dl I: 29 mg/dl, severe metabolic acidosis, thrombocytopenia, a creatinine of 5.6 mg/dl, and dark urine (macroscopic hemoglobinuria see Fig. 57.1). His APACHE II score was 37, with an estimated risk of death of 88%. The patient was admitted to the intensive care unit with septic shock. A thick blood smear revealed *P. falciparum* malaria. The patient was initiated with anti-malaria IV drugs: quinidine gluconate plus doxycycline. Despite antimalarial drug administration and supportive care the patient developed acute respiratory distress syndrome, acute renal failure requiring renal replacement therapy, and an Important Thrombocytopenia (Fig. 57.2).

J. Hidalgo
Adult Intensive Care, Critical Care Division, Karl
Heusner Memorial Hospital, Belize City, Belize

P. Arriaga
Internal Medicine, Karl Heusner Memorial Hospital,
Belize City, Belize

G.M. Rodriguez-Vega (✉)
Department of Critical Care Medicine, Hospital
Hima – San Pablo – Caguas, Rio Piedras, PR, USA
e-mail: glorie68@gmail.com

Question What are the challenges in the diagnosis and management of the returning traveller with severe malaria?

Answer People now move across the world with great facility, whether on vacation or business. Endemic diseases, such as malaria, can affect the travelers upon return to home. Malaria.com maps the regions of the world where *Plasmodium falciparum*, the type intensivists might encounter, may be transmitted [1].

In a returning traveler, fever can be a benign and self-limiting infection, but initially must be considered seriously. Table 57.1 displays the top illnesses encountered in returning travelers. In order to make a diagnosis a comprehensive history with details regarding places visited, duration, purpose, activities undertaken, any chemoprophylaxis taken before or while traveling is critical for the initial work-Up. Knowledge of incubation period and disease risk by geographic are helps in making a differential diagnosis. Table 57.2 displays various diseases potentially encountered by the returning traveler by the duration of incubation period.

Principles of Management in Severe Falciparum Malaria

Patients with severe malaria usually present with a high level of parasitemia and/or major signs of organ dysfunction. Populations at

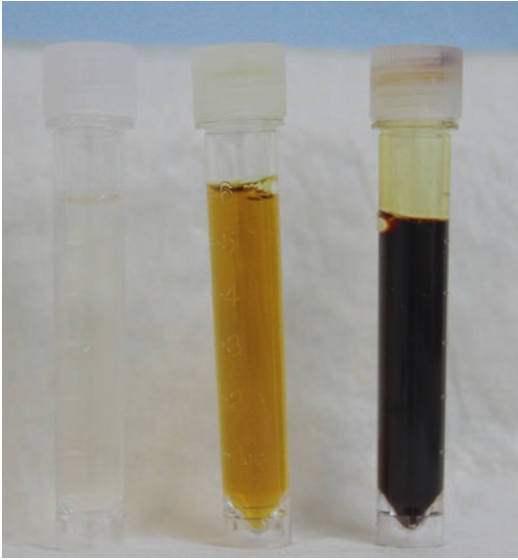


Fig. 57.1 “Blackwater Fever” – Urine sample showing dark urine due to hemoglobinuria (right tube)

greatest risk for severe falciparum malaria are young children, pregnant women and travelers to endemic areas. In endemic areas, elder children and adults develop partial immunity after repeated infections and are at relatively low risk for severe disease. Travelers to areas where malaria is endemic generally have no previous exposure to malaria parasites and are at high risk for severe disease. Pregnant women are more likely to develop severe *P. falciparum* malaria than other adults, particularly in the second and third trimesters. Complications such as hypoglycemia and pulmonary edema are more common than in non-pregnant individuals. Maternal mortality can approach 50 %, and fetal death and premature labor are common [2].

Patients with severe malaria represent a clinical challenge for the clinician given the complex pathophysiology of the infection involving multiple organ systems. Seizures and severe anemia are relatively more common in children, whereas hyperparasitemia, acute renal failure, and jaundice are more common in adults. Cerebral malaria (with coma), shock, acidosis, and respiratory arrest may occur at any age [2-4].

Definition of Severe Malaria

Severe malaria is generally defined as acute malaria with high levels of parasitemia (>5 %) and/or major signs of organ dysfunction

1. Altered consciousness with or without convulsions
2. Use of accessory muscles, nasal alar flaring, Tachypnea.
3. Metabolic acidosis (plasma bicarbonate M 15 mmol/L or whole blood lactate >5 mmol/L)
4. Circulatory collapse
5. Pulmonary edema or acute respiratory distress syndrome (ARDS)
6. Renal failure, hemoglobinuria (“Blackwater Fever”)
7. Jaundice
8. Disseminated Intravascular coagulation
9. Severe Anemia
10. Hypoglycemia

Diagnosis

The clinician must have a high index of suspicion for malaria in travelers presenting with fever and a history of travel to malaria endemic regions within the previous year and especially in the prior 3 months. In uncomplicated malaria apart from fever, patients usually present with nonspecific clinical features. If the diagnosis of falciparum malaria has been delayed, a seemingly well-appearing patient may rapidly deteriorate and present with jaundice, confusion, or seizures and have a high fatality rate. Hence, it is critical to make a rapid and accurate diagnosis when malaria is suspected clinically [3, 4].

Microscopy is the gold standard and preferred option for the diagnosis of malaria. In most cases the examination of thin and thick blood films will reveal Malaria parasites (Figs. 57.3 and 57.4).

Thick films are more sensitive to detect low levels of parasitemia. In general the greater the parasite density in the peripheral blood, the higher likelihood that severe disease is present or will develop, especially in immunocompromised

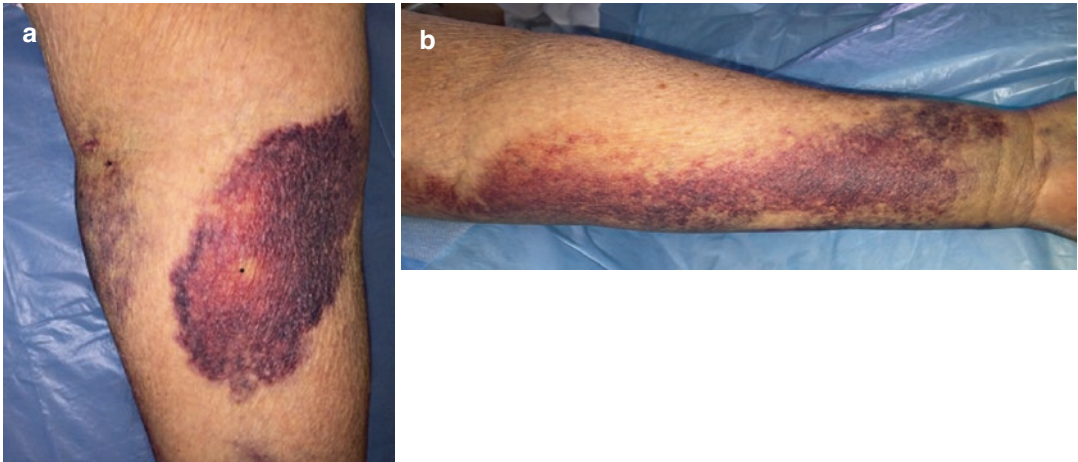


Fig. 57.2 (a, b) Ecchymosis from thrombocytopenia

Table 57.1 Top illnesses in returning travelers

Diagnosis	%
1. Systemic Illnesses	35
Malaria	21
Malaria due to <i>P Falciparum</i>	14
Malaria due to <i>P Vivax</i>	6
Malaria due to other species	2
Dengue	6
Salmonella enterica serovar Typhi or paratyphi	2
Rickettsia	2
2. Acute diarrhea	15
3. Respiratory illness	14
4. Genitourinary diseases	4
5. Gastro intestinal illness	4

From: Wattal and Goel [22]. Reprinted with permission from Elsevier Limited

patients. Thick smears are more sensitive diagnostically but the thin smear subsequently helps in determining the malaria species and the level of parasitemia (the percentage of a patient’s red blood cells that are infected with malaria parasites).

Clinical Management

General Principles

Most of the time uncomplicated malaria have a good prognosis with a fatality case less 0.1%. Uncomplicated malaria caused by *P. ovale*, *P. vivax*, and *P. malariae* can usually be managed

Table 57.2 Incubation period of various diseases potentially encountered in returning travelers

Incubation period	Diseases
<7 days	Common: Malaria, Traveler’s diarrhea, dengue, enteric fever, respiratory tract infection Others: rickettsiosis, leptospirosis, meningitis, yellow fever, arbovirus, meningococcal
7–21 days	Common: Malaria, enteric fever Others: rickettsioses, viral hepatitis, leptospirosis, HIV, Q Fever, brucellosis, African Trypanosomiasis
>21 days	Common: Malaria, Enteric Fever Others: tuberculosis, hepatitis B virus, bacterial endocarditis. HIV, Q fever, brucellosis, amebic liver diseases, melioidosis.

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with oral drugs on an outpatient basis, unless a patient has other comorbidities or is unable to take drugs orally [4, 5].

Due to little immunity against these infections, *P. falciparum* infections in travelers can rapidly progress to severe illness or death in as little as 1–2 days, so prompt assessment and initiation of antimalarial therapy is essential. Patients should be evaluated with attention to findings consistent with malaria as well as additional and/or alternative causes of presenting symptoms. Of primary importance in the

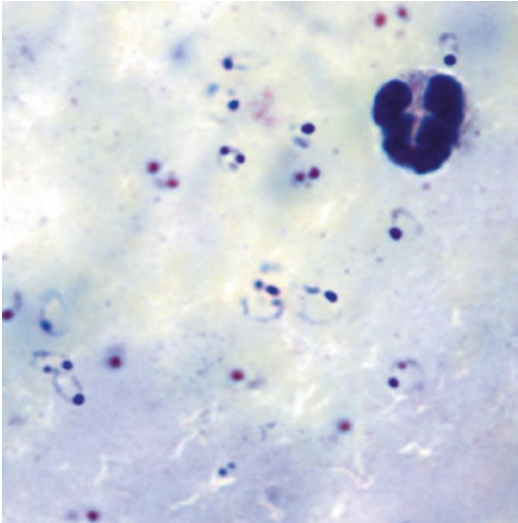


Fig. 57.3 *P. falciparum* on thick smear (From: Centers for Disease Control and Prevention (CDC) [23])

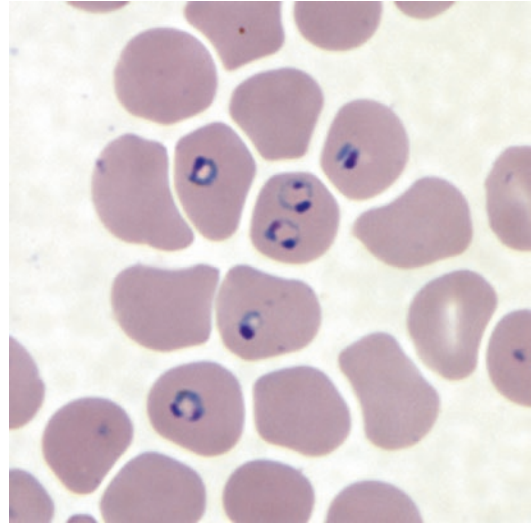


Fig. 57.4 *P. falciparum* on thin smear (From: Centers for Disease Control and Prevention (CDC) [23])

treatment of malaria is the provision of prompt, effective therapy and concurrent supportive care to manage life-threatening complications of the disease. Supportive measures, such as fluid management, oxygen, ventilatory support, cardiac monitoring, and pulse oximetry, should be instituted as needed. During this time, intravenous access should be obtained immediately. Point-of-care testing can be used for rapid determination of hematocrit [packed cell volume (PCV) or hemoglobin (HemoCue)], glucose, and lactate. Parasitemia can also be determined quickly but requires a microscope. Additional tests can be done if/when indicated: electrolytes, full blood count, type and cross, blood culture, and clotting studies. Unconscious patients should have a lumbar puncture to rule out concomitant bacterial meningitis in the absence of contraindications (i.e., papilledema). These tasks should overlap with institution of antimalarial treatment as well as other ancillary therapies as needed (including anticonvulsants, intravenous glucose and fluids, antipyretics, antibiotics, and blood transfusion) [6, 7].

Repeat clinical assessments should be performed every 2–4 h for prompt detection and management of complications in an intensive care setting, if possible. If the Glasgow Coma

Score (or in children the Blantyre coma score [see Table 57.3]) decreases after initiation of treatment, investigation should focus on the possibility of seizures, hypoglycemia, or worsening anemia. Repeat laboratory assessments of parasitemia, hemoglobin/hematocrit, glucose, and lactate should be performed in 6-h intervals. A flow chart summarizing the vital information may be used to guide management decisions [6–8].

Important independent predictors for fatality among African children with severe malaria include acidosis, impaired consciousness (coma and/or convulsions), elevated blood urea nitrogen, and signs of chronic disease (lymphadenopathy, malnutrition, candidiasis, severe visible wasting, and desquamation). Clinical features previously identified as being poor prognostic features that did not correlate with mortality in this study included age, glucose level, axillary temperature, parasite density, and Blackwater Fever [9–11].

Careful observation and thoughtful responses to changes in clinical status are the most important elements in looking after patients with severe malaria. Patients can make remarkable recoveries, and the time and effort to address the components of clinical care described in the following

Table 57.3 Blantyre coma score

Type of response	Response	Score
Best Motor	Localize painful stimulus	2
	Withdraws limbs from pain	1
	Nonspecific or absent response	0
Verbal	Appropriate cry	2
	Moan or innapropriate cry	1
	None	0
Eye movements	Eg: directed (follows mother's face)	1
	Not directed	0
Total		0–5

The Blantyre coma scale is a modification of the Pediatric Glasgow Coma Scale, designed to assess malarial coma in children

It was designed by Drs. Terrie Taylor and Malcolm Molyneux in 1987, and named for the Malawian city of Blantyre, site of the Blantyre Malaria Project

sections can reap tangible rewards in a relatively short period of time.

Clinical evaluation includes full physical exam, a complete neurologic examination, calculation of Glasgow or Blantyre coma score (Table 57.3), and fundusoscopic evaluation. Malarial retinopathy is pathognomonic for cerebral malaria in patients who satisfy the standard clinical case definition (Fig. 57.5).

Patients with altered sensorium should undergo lumbar puncture (in the absence of contraindications) to exclude concomitant bacterial meningitis. If clinical instability or papilledema on ocular fundus examination preclude lumbar puncture, presumptive antibiotic therapy for bacterial meningitis should be initiated. Usual findings are: mean opening pressure about 16 cm of CSF, slightly elevated total protein level and cell count.

Antimalarial Therapy (See Treatment Table 57.4)

Monitoring Parasite Density

Parasitemia should be monitored during treatment to confirm adequate response to therapy. The CDC recommends daily repeat blood smear



Fig. 57.5 Photograph of the retina in patient with malaria, which shows exudates (*arrowheads*), hemorrhages (*thick arrows*) and changes in the color of the blood vessels (*thin arrows*) (From Mishra and Newton [24]. Reprinted with permission from Nature Publishing Group)

to document declining parasite density until negative or until treatment day 7 (if discharged prior to complete parasitemia clearance). During treatment of severe malaria, parasite density should be monitored every 12 h during the first 2–3 days or until negative; some recommendations suggest switching from parenteral to oral therapy as tolerated after parasitemia falls below 1% [10, 11].

Respiratory System

Hypoxemia and rales are not common in the setting of severe malaria; the presence of either should raise suspicion for a concomitant lower respiratory tract infection. Pulmonary edema may develop, particularly in the settings of renal impairment or severe malarial anemia. Acute respiratory distress syndrome (ARDS) can also complicate severe malaria.

Deep breathing (Kussmaul respirations) is a clinical indicator of metabolic acidosis and is

Table 57.4 Treatment of malaria

Clinical diagnosis/ <i>Plasmodium</i> species	Region infection acquired	Recommended drug and Adult dose ^a	Recommended drug and pediatric Dose ^a <i>Pediatric dose should NEVER exceed adult dose</i>
Uncomplicated malaria/ <i>P. falciparum</i> or species not identified If "species not identified" is subsequently diagnosed as <i>P. vivax</i> or <i>P. ovale</i> : see <i>P. vivax</i> and <i>P. ovale</i> (below) re. treatment with primaquine	Chloroquine-resistant or unknown resistance^b (All malarious regions except those specified as chloroquine-sensitive listed in the box below.)	<p>Recommended drug and Adult dose^a</p> <p>A. Atovaquone-proguanil (MalaroneTM)^c Adult tab = 250 mg atovaquone/100 mg proguanil 4 adult tabs po qd x 3 days</p>	<p>Recommended drug and pediatric Dose^a <i>Pediatric dose should NEVER exceed adult dose</i></p> <p>A. Atovaquone-proguanil (MalaroneTM)^c Adult tab = 250 mg atovaquone/100 mg proguanil Peds tab = 62.5 mg atovaquone/25 mg proguanil 5–8 kg: 2 peds tabs po qd x 3 days 9–10 kg: 3 peds tabs po qd x 3 days 11–20 kg: 1 adult tab po qd x 3 d 21–30 kg: 2 adult tabs po qd x 3days 31–40 kg: 3 adult tabs po qd x 3days >40 kg: 4 adult tabs po qd x 3days</p>
		<p>Recommended drug and Adult dose^a</p> <p>B. Artemether-lumefantrine (CoartemTM)^c 1 tablet = 20 mg artemether and 120 mg lumefantrine A 3-day treatment schedule with a total of 6 oral doses is recommended for both adult and pediatric patients based on weight. The patient should receive the initial dose, followed by the second dose 8 h later, then 1 dose po bid for the following 2 days. 5 – <15 kg: 1 tablet per dose 15 – <25 kg: 2 tablets per dose 25 – <35 kg: 3 tablets per dose ≥35 kg: 4 tablets per dose</p>	
		<p>Recommended drug and Adult dose^a</p> <p>C. Quinine sulfate plus one of the following: Quinine sulfate, Tetracycline, or Clindamycin Quinine sulfate: 542 mg base (=650 mg salt)^d po tid x 3 or 7 days^e Doxycycline: 100 mg po bid x 7 days Tetracycline: 250 mg po qid x 7 days Clindamycin: 20 mg base/kg/day po divided tid x 7 days</p>	<p>C. Quinine sulfate^d plus one of the following: Doxycycline^f, Tetracycline^f or Clindamycin Quinine sulfate: 8.3 mg base/kg (=10 mg salt/kg) po tid x 3 or 7 days^e Doxycycline: 2.2 mg/kg po every 12 h x 7 days Tetracycline: 25 mg/kg/day po divided qid x 7 days Clindamycin: 20 mg base/kg/day po divided tid x 7 days</p>
		<p>Recommended drug and Adult dose^a</p> <p>D. Mefloquine (LariamTM and generics)^g 684 mg base (=750 mg salt) po as initial dose, followed by 456 mg base (=500 mg salt) po given 6–12 h after initial dose Total dose = 1,250 mg salt</p>	<p>D. Mefloquine (LariamTM and generics)^g 13.7 mg base/kg (=15 mg salt/kg) po as initial dose, followed by 9.1 mg base/kg (=10 mg salt/kg) po given 6–12 h after initial dose. Total dose = 25 mg salt/kg</p>

Table 57.4 (continued)

<p>Uncomplicated malaria/P. falciparum or Species not identified</p>	<p>Chloroquine-sensitive (Central America west of Panama Canal; Haiti; the Dominican Republic; and most of the Middle East)</p>	<p>Chloroquine phosphate (Aralen™ and generics)^h 600 mg base (=1,000 mg salt) po immediately, followed by 300 mg base (=500 mg salt) po at 6, 24, and 48 h OR Hydroxychloroquine (Plaquenil™ and generics) 620 mg base (=800 mg salt) po immediately, followed by 310 mg base (=400 mg salt) po at 6, 24, and 48 h Total dose: 1,550 mg base (=2,000 mg salt)</p>	<p>Chloroquine phosphate (Aralen™ and generics)^h 10 mg base/kg po immediately, followed by 5 mg base/kg po at 6, 24, and 48 h Total dose: 25 mg base/kg OR Hydroxychloroquine (Plaquenil™ and generics) 10 mg base/kg po immediately, followed by 5 mg base/kg po at 6, 24, and 48 h Total dose: 25 mg base/kg</p>
<p>Uncomplicated malaria/P. malariae or P. knowlesi</p>	<p>All regions</p>	<p>Chloroquine phosphate^h plus Primaquine phosphate Chloroquine phosphate: Treatment as above Primaquine phosphate: 30 mg base po qd × 14 days OR Hydroxychloroquine plus Primaquine phosphateⁱ Hydroxychloroquine: Treatment as above Primaquine phosphate: 30 mg base po qd × 14 days</p>	<p>Chloroquine phosphate:^h Treatment as above OR Hydroxychloroquine: Treatment as above Chloroquine phosphate^h plus Primaquine phosphateⁱ Primaquine phosphate: 0.5 mg base/kg po qd × 14 days OR Hydroxychloroquine plus Primaquine phosphateⁱ Hydroxychloroquine: Treatment as above Primaquine phosphate: 0.5 mg base/kg po qd × 14 days</p>
<p>Uncomplicated malaria/P. vivax</p>	<p>Chloroquine-resistantⁱ (Papua New Guinea and Indonesia)</p>	<p>A. Quinine sulfate plus either Doxycycline or Tetracycline plus Primaquine phosphateⁱ Quinine sulfate: Treatment as above Doxycycline or Tetracycline: Treatment as above Primaquine phosphate: Treatment as above B. Atovaquone-proguanil plus Primaquine phosphateⁱ Atovaquone-proguanil: Treatment as above Primaquine phosphate: Treatment as above C. Mefloquine plus Primaquine phosphateⁱ Mefloquine: Treatment as above Primaquine phosphate: Treatment as above</p>	<p>A. Quinine sulfate plus either Doxycycline^f or Tetracycline^g plus Primaquine phosphateⁱ Quinine sulfate: Treatment as above Doxycycline or Tetracycline: Treatment as above Primaquine phosphate: Treatment as above B. Atovaquone-proguanil plus Primaquine phosphateⁱ Atovaquone-proguanil: Treatment as above Primaquine phosphate: Treatment as above C. Mefloquine plus Primaquine phosphateⁱ Mefloquine: Treatment as above Primaquine phosphate: Treatment as above</p>

(continued)

<p>Uncomplicated malaria: alternatives for pregnant women^{k,l, m}</p>	<p>Chloroquine-sensitive (see uncomplicated malaria sections above for chloroquine-sensitive species by region)</p> <p>Chloroquine-resistant (see sections above for regions with chloroquine resistant <i>P. falciparum</i> and <i>P. vivax</i>)</p>	<p>Chloroquine phosphate: Treatment as above Hydroxychloroquine: Treatment as above</p> <p>OR</p> <p>Quinine sulfate plus Clindamycin Quinine sulfate: Treatment as above Clindamycin: Treatment as above Mefloquine: Treatment as above</p>	<p>Not applicable</p> <p>Not applicable</p>
<p>Severe malaria^{n,o,p}</p>	<p>All regions</p>	<p>Quinidine gluconate^q plus one of the following: Doxycycline, Tetracycline, or Clindamycin Quinidine gluconate: 6.25 mg base/kg (=10 mg salt/kg) loading dose IV over 1–2 h, then 0.0125 mg base/kg/min (=0.02 mg salt/kg/min) continuous infusion for at least 24 h. An alternative regimen is 15 mg base/kg (=24 mg salt/kg) loading dose IV infused over 4 h, followed by 7.5 mg base/kg (=12 mg salt/kg) infused over 4 h every 8 h, starting 8 h after the loading dose (see package insert). Once parasite density <1 % and patient can take oral medication, complete treatment with oral quinine, dose as above. Quinine/quinine course=7 days in Southeast Asia; = 3 days in Africa or South America. Doxycycline: Treatment as above. If patient not able to take oral medication, give 100 mg IV every 12 h and then switch to oral doxycycline (as above) as soon as patient can take oral medication. For IV use, avoid rapid administration. Treatment course=7 days. Tetracycline: Treatment as above Clindamycin: Treatment as above. If patient not able to take oral medication, give 10 mg base/kg loading dose IV followed by 5 mg base/kg IV every 8 h. Switch to oral clindamycin (oral dose as above) as soon as patient can take oral medication. For IV use, avoid rapid administration. Treatment course=7 days. Investigational new drug (contact CDC for information): Artesunate followed by one of the following: Atovaquone-proguanil (MalaroneTM), Doxycycline (Clindamycin in pregnant women), or Mefloquine</p>	<p>Quinidine gluconateⁿ plus one of the following: Doxycycline^d, Tetracycline^e, or Clindamycin Quinidine gluconate: Same mg/kg dosing and recommendations as for adults. Doxycycline: Treatment as above. If patient not able to take oral medication, may give IV. For children <45 kg, give 2.2 mg/kg IV every 12 h and then switch to oral doxycycline (dose as above) as soon as patient can take oral medication. For children ≥45 kg, use same dosing as for adults. For IV use, avoid rapid administration. Treatment course=7 days. Tetracycline: Treatment as above Clindamycin: Treatment as above. If patient not able to take oral medication, give 10 mg base/kg loading dose IV followed by 5 mg base/kg IV every 8 h. Switch to oral clindamycin (oral dose as above) as soon as patient can take oral medication. For IV use, avoid rapid administration. Treatment course=7 days. Investigational new drug (contact CDC for information): Artesunate followed by one of the following: Atovaquone-proguanil (MalaroneTM), Clindamycin or Mefloquine</p>

Source: Malaria Treatment Guidelines from CDC Public Library. July 2013

^aIf a person develops malaria despite taking chemoprophylaxis, that particular medicine should not be used as a part of their treatment regimen. Use one of the other options instead

^bNOTE: There are 4 options (A, B, C, or D) available for treatment of uncomplicated malaria caused by chloroquine-resistant *P. falciparum*. Options A, B, and C are equally recommended. Because of a higher rate of severe neuropsychiatric reactions seen at treatment doses, we do not recommend option D (mefloquine) unless the other options cannot be used. For option C, because there is more data on the efficacy of quinine in combination with doxycycline or tetracycline, these treatment combinations are generally preferred to quinine in combination with clindamycin

^cTake with with food or whole milk. If patient vomits within 30 min of taking a dose, then they should repeat the dose
^dUS manufactured quinine sulfate capsule is in a 324 mg dosage; therefore 2 capsules should be sufficient for adult dosing. Pediatric dosing may be difficult due to unavailability of non-capsule forms of quinine

^eFor infections acquired in Southeast Asia, quinine treatment should continue for 7 days. For infections acquired elsewhere, quinine treatment should continue for 3 days
^fDoxycycline and tetracycline are not indicated for use in children less than 8 years old. For children less than 8 years old with chloroquine-resistant *P. falciparum*, atovaquone-proguanil and artemether-lumefantrine are recommended treatment options; mefloquine can be considered if no other options are available. For children less than 8 years old with chloroquine-resistant *P. vivax*, mefloquine is the recommended treatment. If it is not available or is not being tolerated and if the treatment benefits outweigh the risks, atovaquone-proguanil or artemether-lumefantrine should be used instead

^gTreatment with mefloquine is not recommended in persons who have acquired infections from Southeast Asia due to drug resistance
^hWhen treating chloroquine-sensitive infections, chloroquine and hydroxychloroquine are recommended options. However, regimens used to treat chloroquine-resistant infections may also be used if available, more convenient, or preferred

ⁱPrimaquine is used to eradicate any hypozoites that may remain dormant in the liver, and thus prevent relapses, in *P. vivax* and *P. ovale* infections. Because primaquine can cause hemolytic anemia in G6PD-deficient persons, G6PD screening must occur prior to starting treatment with primaquine. For persons with borderline G6PD deficiency or as an alternate to the above regimen, primaquine may be given 45 mg orally one time per week for 8 weeks; consultation with an expert in infectious disease and/or tropical medicine is advised if this alternative regimen is considered in G6PD-deficient persons. Primaquine must not be used during pregnancy

^jNOTE: There are three options (A, B, or C) available for treatment of uncomplicated malaria caused by chloroquine-resistant *P. vivax*. High treatment failure rates due to chloroquine-resistant *P. vivax* have been well documented in Papua New Guinea and Indonesia. Rare case reports of chloroquine-resistant *P. vivax* have also been documented in Burma (Myanmar), India, and Central and South America. Persons acquiring *P. vivax* infections outside of Papua New Guinea or Indonesia should be started on chloroquine. If the patient does not respond, the treatment should be changed to a chloroquine-resistant *P. vivax* regimen and CDC should be notified (Malaria Hotline number listed above). For treatment of chloroquine-resistant *P. vivax* infections, options A, B, and C are equally recommended

^kFor pregnant women diagnosed with uncomplicated malaria caused by chloroquine-resistant *P. falciparum* or chloroquine-resistant *P. vivax* infection, treatment with doxycycline or tetracycline is generally not indicated. However, doxycycline or tetracycline may be used in combination with quinine (as recommended for non-pregnant adults) if other treatment options are not available or are not being tolerated, and the benefit is judged to outweigh the risks

^lAtovaquone-proguanil and artemether-lumefantrine are generally not recommended for use in pregnant women, particularly in the first trimester due to lack of sufficient safety data. For pregnant women diagnosed with uncomplicated malaria caused by chloroquine-resistant *P. falciparum* infection, atovaquone-proguanil or artemether-lumefantrine may be used if other treatment options are not available or are not being tolerated, and if the potential benefit is judged to outweigh the potential risks

^mFor *P. vivax* and *P. ovale* infections, primaquine phosphate for radical treatment of hypozoites should not be given during pregnancy. Pregnant patients with *P. vivax* and *P. ovale* infections should be maintained on chloroquine prophylaxis for the duration of their pregnancy. The chemoprophylactic dose of chloroquine phosphate is 300 mg base (=500 mg salt) orally once per week. After delivery, pregnant patients who do not have G6PD deficiency should be treated with primaquine

ⁿPersons with a positive blood smear OR history of recent possible exposure and no other recognized pathology who have one or more of the following clinical criteria (impaired consciousness/coma, severe normocytic anemia, renal failure, pulmonary edema, acute respiratory distress syndrome, circulatory shock, disseminated intravascular coagulation, spontaneous bleeding, acidosis, hemoglobinuria, jaundice, repeated generalized convulsions, and/or parasitemia of >5%) are considered to have manifestations of more severe disease. Severe malaria is most often caused by *P. falciparum*

^oPatients diagnosed with severe malaria should be treated aggressively with parenteral antimalarial therapy. Treatment with IV quinine should be initiated as soon as possible after the diagnosis has been made. Patients with severe malaria should be given an intravenous loading dose of quinine unless they have received more than 40 mg/kg of quinine in the preceding 48 h or if they have received mefloquine within the preceding 12 h. Consultation with a cardiologist and a physician with experience treating malaria is advised when treating malaria patients with quinine. During administration of quinine, blood pressure monitoring (for hypotension) and cardiac monitoring (for widening of the QRS complex and/or lengthening of the QTc interval) should be monitored continuously and blood glucose (for hypoglycemia) should be monitored periodically. Cardiac complications, if severe, may warrant temporary discontinuation of the drug or slowing of the intravenous infusion

^pPregnant women diagnosed with severe malaria should be treated aggressively with parenteral antimalarial therapy

associated with a worse outcome in patients with falciparum malaria [10, 11].

Neurologic Involvement

The standard clinical case definition of cerebral malaria includes the following criteria:

1. Blantyre coma score ≤ 2
2. *P. falciparum* parasitemia (any density)
3. No other identifiable cause of coma (e.g., hypoglycemia, meningitis, or a post-ictal state)

The histologic hallmark of cerebral malaria is cerebral sequestration of parasitized erythrocytes.

Establishing whether retinopathy is present is an important marker for cerebral malaria. In the absence of this finding, alternative causes for coma (such as bacterial infection) should be pursued and treated, even in the presence of established malaria infection [11, 12].

Seizure Management

Seizures occur in up to 70% of children with severe malaria; subclinical seizures occur in 15–20% of cases. Seizures may be generalized or focal, and the clinical signs may be subtle (nyctagmus, irregular respirations, hypoventilation, or a drop in the Blantyre coma score). It is also important to evaluate for causes of seizure besides cerebral malaria (e.g., hypoglycemia, fever) and to treat accordingly as outlined in the following sections.

Benzodiazepines are useful first-line agents for seizure treatment. Diazepam (0.4 mg/kg) can be administered intravenously or per rectum; lorazepam (0.1 mg/kg) can be administered intravenously or intraosseously. These doses can be repeated once if seizures do not cease within five minutes of the initial dose. Benzodiazepines should not be combined due to risk of respiratory depression. If seizures are not controllable with benzodiazepines, other options include phenobarbitone (phenobarbital 15–20 mg/kg, slow IV push) or phenytoin (18 mg/kg diluted in 100 mL normal saline, infused over 20 min).

If seizures recur, repeat single doses of benzodiazepine may be administered. Alternatively, maintenance doses of phenobarbital (5–15 mg/kg/day, administered orally, via NG tube, or via slow IV push in divided doses every 12 h) or phenytoin (10 mg/kg/day IV in divided doses every 12 h) may be initiated.

Paraldehyde was used as an intramuscular injection to treat seizures in the setting of severe malaria (0.2–0.4 mL/kg); its chief advantage is that it does not cause respiratory suppression. The cost of this agent has increased dramatically, and it is therefore out of reach for many formularies in malaria-endemic areas.

Patients with severe malaria should not receive routine seizure prophylaxis in the absence of clinical seizure activity [12–14].

Anemia and Coagulopathy

Severe hemolysis, which is mainly extravascular, occurs in hyperparasitemic falciparum malaria. Removal of both infected and uninfected erythrocytes from the circulation, mainly by the spleen, is associated with rapid development of anemia. Patients with severe anemia may present with or without altered consciousness; in addition, severe anemia has been associated with long-term neurocognitive impairment. In endemic areas hemoglobin concentration may decrease gradually over the course of repeated malaria infections. As a result, patients can be fully alert with hemoglobin concentrations of 2–3 g/dL (hematocrit <10%). Evaluation for pallor of the conjunctivae, nail beds, and palms can provide a rough estimate of the degree of anemia, since blood vessels in these areas are close to the surface.

Hemoglobin concentration and hematocrit are routinely measured components of complete blood counts, but this may not be available in resource-limited settings or the results may not be available in a timely manner. In such circumstances the hematocrit can be measured on a fingerprick sample of blood collected into a heparinized capillary tube and centrifuged using a mechanical device. Alternatively, the hemoglobin concentration can be determined from fingerprick samples of blood collected into cuvettes.

This method is more expensive than manually spinning a hematocrit, but can be performed readily near the bedside.

Clinically evident disseminated intravascular coagulation in the setting of severe malaria is rare (<5%), but profound thrombocytopenia is common, and the microcirculation in many organs is occluded by fibrin thrombi [15, 16].

Blood Products

Blood products should be administered in patients with dire prognoses, i.e., patients with altered consciousness, high output heart failure, respiratory distress, a cool periphery, hyperlactatemia, and/or high density parasitemia. Laboratory parameters of concern include low hemoglobin concentration ($\leq 4\text{--}5$ g/dL) or low hematocrit ($\leq 10\text{--}15\%$). The degree of anemia and the level of parasitemia may be useful parameters for predicting the need for a blood transfusion and for determining the volume of blood to transfuse. In general, 10 mL/kg of packed red blood cells or 20 mL/kg of whole blood transfused over 2–4 h is appropriate. Blood should be typed and crossmatched prior to infusion.

Blood transfusions are generally well-tolerated in the setting of severe malaria, since patients are relatively hypovolemic; diuretics are rarely needed. Monitoring of hemoglobin concentration or hematocrit should continue until the parasitemia clears, since repeat transfusion may be required [16].

Hypoglycemia

Defined as blood glucose <40 mg/dL or <2.2 mmol/L, hypoglycemia is a common complication of malaria and a marker of severe disease. It should be suspected in any patient who is comatose or who deteriorates suddenly.

The pathogenesis of hypoglycemia is not fully understood; it may be related to parasite glucose consumption and/or impaired host gluconeogenesis. Malnutrition, adrenal insufficiency, and hyperinsulinemia are not likely causes of hypoglycemia. In addition to primary hypoglycemia, administration of quinine or quinidine (insulin secretagogues) can cause iatrogenic hypoglycemia. Hypoglycemia

with artesunate therapy is less common than with quinine or quinidine.

Patients presenting with normoglycemia can develop hypoglycemia during the course of treatment. When determining maintenance intravenous fluids, the clinician should consider the possibility of hypoglycemia and use glucose containing solutions. In addition, those managed promptly for hypoglycemia at presentation can have subsequent recurrent hypoglycemia. Therefore, blood glucose should be monitored closely during the course of illness with prompt management as outlined above. Patients with recurrent hypoglycemia should receive 10% dextrose. Ten percent dextrose can be prepared quickly by withdrawing 100 mL from a one liter bag of a 5% dextrose solution and replacing it with 100 mL of a 50% dextrose solution [15–17].

Volume Management

Adults with malaria appear to be more vulnerable to fluid overload than children. There is a fine line between under hydration, and thus worsening renal impairment, and over hydration, risking pulmonary and cerebral edema. Hence, fluid requirements should be assessed on an individual basis, using commonly employed tools such as delayed capillary refill, low central venous pressure, and low urine output. Deep breathing, reflecting lactic acidosis, may also be a reasonable indicator of hypovolemia [16, 17].

Nutrition

Nutritional supplementation should be provided by nasogastric tube (NG) for patients with prolonged coma who are unable to eat and drink within 24–48 h.

Fever

High fevers (>38.5 °C) are common in the setting of malaria infection and may reflect the host response to endogenous pyrogens released at the time of schizont rupture. The optimal approach to treatment of fever is uncertain, although use of antipyretics in patients with high fever is

appropriate given the association between high fever and convulsions. Aggressive temperature control may help reduce long-term neurologic outcomes in pediatric patients with retinopathy-positive cerebral malaria.

Paracetamol (acetaminophen); 15 mg/kg every 6 h; maximum dose 1000 mg) is a reasonable antipyretic agent; oral therapy can be used for patients able to swallow. Otherwise, suppository formulations are acceptable. If fever persists, ibuprofen (10 mg/kg every 6 hours; maximum dose 1,200 mg per day) can be administered (orally, via nasogastric tube, or intravenously) alone or on an alternating schedule with paracetamol every 3 h [17–19].

Bacterial Infection

Concomitant bacterial infection is an important contributor to morbidity and mortality in the setting of severe malaria, and severe anemia has been implicated as a primary risk factor for nontyphoidal *Salmonella* septicemia. Bacterial infection should be suspected in patients with severe anemia together with signs or symptoms of sepsis (hypotension, cool extremities, delayed capillary refill, hyperlactatemia). In such cases, blood cultures should be obtained and broad spectrum antibiotic therapy with activity against gram-negative bacilli should be initiated [18, 19].

Evidence Contour

Other Diagnostic Modalities

A major drawback of light microscopy is that the efficiency of the test depends on the type and quality of the smear, skill of the technician, parasite density, and time spent on examining the smear. In addition, mixed infections with *P. malariae* or *P. ovale* are often missed, because their densities are often low in comparison to that of *P. falciparum*. These problems may occur more frequently in non-endemic areas where malaria microscopy is performed infrequently.

Quantitative Buffy Coat

Quantitative buffy coat (QBC) is fluorescent microscopy based on the principle of concentrating the red blood cell-containing parasites within a narrow zone by centrifugation of blood in capillary tubes and staining of malarial parasite nucleic acid with acridine dyes. The sensitivity of QBC almost equals that of Giemsa-stained films. The advantage of QBC is ease of interpretation and rapidity. Species identification and quantification are difficult, however, with this technique and, therefore, thick and thin blood film examination is still required. This technique requires the use of expensive fluorescent microscopy equipment for the interpretation of results. This is an important limitation especially in the poor resource countries [19].

Antigen Rapid Detection Test (RDT)

Antigen detection RDTs detect malaria antigen in blood by immunochromatographic test with monoclonal antibodies directed against the target parasite antigen, which is impregnated on a test strip. The result is usually obtained in 5–20 min. Currently, different combinations of immunochromatographic tests are commercially available, targeting different genus specific or species-specific antigen for malaria diagnosis. Some of the commonly used antigens in RDTs are HRP-2 (*P. falciparum* specific), aldolase (pan-specific), plasmodium lactate dehydrogenase (pLDH) (*P. falciparum* specific), pLDH (*P. vivax*- specific), and pLDH (pan-specific) [19, 20].

Serology

Serology detection of antibodies against malaria parasites, using either indirect immunofluorescence assay or ELISA, does not indicate current infection but rather measures past exposure. Therefore, it has no role in diagnosis of acute infections. Serology may be used to screen donors to prevent transfusion-related malaria, however, and to confirm the diagnosis of malaria in recently treated cases in which the diagnosis could not be confirmed previously [19–21].

Molecular Methods

Molecular technologies have been developed to improve the diagnosis of malaria by detecting specific parasite nucleic acid. The advantage of molecular methods is their exquisite sensitivity down to the level of 5 parasites/mL or 0.0001 % parasitemia [20, 21].

Exchange Transfusion

Exchange transfusion has been proposed as a means of removing infected red blood cells from the circulation, thereby lowering the parasite burden and replacing with unparasitized cells. There is no evidence supporting efficacy of exchange transfusion as adjunctive therapy in severe malaria, and there is no consensus on the indications, approach, benefits, or risks of this procedure.

The CDC no longer recommends exchange transfusion for treatment of severe malaria, based on a review that demonstrated no differences in outcome among patients who underwent exchange transfusion; previously, the CDC recommended exchange transfusion for patients with parasite density of >10% with end organ complications. The WHO guidelines indicate that it is not possible to make any recommendations regarding the use of exchange transfusion based on the available evidence. The American Society for Apheresis (ASFA) supports exchange transfusion as an adjunctive therapy for patients with >10% parasitemia, although its consideration of adverse events associated with exchange transfusion for malaria is limited [19–21].

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