

Malaria

What's New in the Management of Malaria?



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KEYWORDS

• Malaria • Plasmodium • Management • Antimalarials • Resistance

KEY POINTS

- Intravenous artesunate for severe malaria and oral artemisinin-based combination therapies for uncomplicated malaria are first-line treatment for all *Plasmodium* species causing disease in humans.
- Species-specific diagnosis is important to guide appropriate primaquine administration for gametocytocidal treatment of falciparum malaria to reduce transmission in endemic areas, and for radical treatment of vivax and ovale malaria to prevent relapse.
- Severe malaria management requires early renal replacement therapy for acute kidney failure and cautious fluid resuscitation to prevent lethal pulmonary edema.
- Post-artesunate delayed-onset hemolysis of once-infected red blood cells is an expected consequence of the removal of pyknotic ring form parasites through splenic pitting after artesunate treatment.
- Artemisinin and partner drug resistant falciparum malaria is spreading in the Greater Mekong Subregion, and increasingly causes treatment failure of artemisinin-based combination therapies.

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INTRODUCTION

Malaria affected an estimated 216 million people causing 445,000 deaths in 2016.¹ This reduced burden of disease and death is a result of more than a century of worldwide effort and research aimed at improving prevention, diagnosis, and management of malaria.

Since the first description of a protozoan parasite causing malaria,² it is now recognized that 6 *Plasmodium* species cause infection in humans living in tropical and subtropical regions. *Plasmodium falciparum* and *Plasmodium vivax* cause the most infections worldwide with differing geographic distributions. The contribution of *Plasmodium malariae*, and sympatric species *Plasmodium ovale curtisi* and *Plasmodium ovale wallikeri* to the global burden of disease is low. The zoonotic *Plasmodium knowlesi*, jumping species from Macaque monkeys, is predominantly found in Southeast Asia. Molecular diagnostics have recently identified human cases of zoonotic *Plasmodium simium* and *Plasmodium cynomolgi*; however, the prevalence and clinical impact of these species are unclear.^{3,4}

Plasmodium infections result in a spectrum of clinical effects, including asymptomatic parasitemia, uncomplicated malaria, severe malaria, and death. Severe and fatal malaria are predominantly caused by *P falciparum* principally due to endothelial cytoadherence causing sequestration of mature-staged infected red blood cells in vital organs. This results in microcirculatory obstruction and end-organ dysfunction. Although *P vivax* and *P knowlesi* infection can cause severe malaria,^{5,6} cytoadherence-mediated sequestration has not been clearly observed. Understanding factors related to the infecting parasite species and host immunity is critical to optimizing treatment and preventing death. This review highlights recent developments in our understanding of malaria pathophysiology and the translation to new aspects of management.

DIAGNOSIS

Appropriate species-specific management of malaria requires early confirmation of the diagnosis. All febrile travelers, particularly visiting friend and relative travelers, returning from malaria-endemic areas should be considered to have malaria until proven otherwise. Febrile patients living in or recently immigrating from endemic regions should have malaria ruled out. The clinical features of severe and uncomplicated malaria are nonspecific; therefore, a parasitologic diagnosis is required by microscopy or a rapid diagnostic test (RDT). Regardless of species, a diagnosis of severe or uncomplicated malaria can be made based on specific diagnostic criteria (**Box 1**).

Microscopic analysis of stained thick and thin blood smears is the diagnostic reference standard. Thick-smear diagnosis allows sensitive parasitemia quantification (as low as 30 parasites per microliter), and thin-smear diagnosis permits speciation and prognostic assessment via parasite staging and proportion of pigment-containing neutrophils. In severe falciparum malaria, the presence of late-stage parasites and/or more than 5% of neutrophils containing pigment predict poor outcomes.^{7,8} In unstable transmission regions, nonimmune patients with signs of severity and low parasitemia may reflect a high sequestered parasite biomass and should not falsely reassure the treating physician.⁸ A high parasitemia in the absence of signs of severity is associated with increased mortality. Large differences between the number of peripheral blood infected cells and number of sequestered infected cells may exist, such that rapid increases in parasitemia can occur in synchronous infections.⁹ In regions of high transmission, diagnosis is challenging because partially immune parasitemic individuals are asymptomatic. RDTs detecting *P falciparum* histidine-rich protein 2

Box 1**Diagnostic criteria for severe malaria****I. Falciparum malaria**

Clinical criteria

- Prostration
- Convulsions (>2 within 24 hours)
- Coma (Glasgow Coma Scale <11 in adults or Blantyre Coma Scale <3 in children)
- Respiratory distress (acidotic breathing)
- Shock (capillary time ≥ 3 s, with or without systolic blood pressure <80 mm Hg [adults], less than 70 mm Hg [children])
- Pulmonary edema (confirmed radiologically)
- Abnormal bleeding
- Jaundice
- Anuria
- Hemoglobinuria (blackwater)
- Repeated vomiting

Laboratory criteria

- Anemia (hemoglobin <70 g/L in adults, <50 g/L in children)
- Acidosis (base deficit >8 mEq/L or bicarbonate <15 mmol/L, or venous lactate >5 mM)
- Hypoglycemia (blood glucose <2.2 mmol/L or <40 mg/dL)
- Renal impairment (creatinine >265 μ mol/L [3 mg/dL] or blood urea >20 mmol/L)
- Jaundice (bilirubin >50 μ M [3 mg/dL] and parasite count >100,000/ μ L)
- Hyperparasitemia >10%

II. Knowlesi malaria

Clinical criteria

- Criteria as per falciparum malaria
- Inability to tolerate oral therapy

Laboratory criteria

- Criteria as per falciparum malaria with modified parasitemia cutoffs as follows
- Jaundice and parasitemia >20,000/ μ L
- Parasitemia >100,000/ μ L

III. Vivax malaria

- Criteria as per falciparum malaria excluding parasite density thresholds

Data from World Health Organization. Severe malaria. Trop Med Int Health 2014;19 Suppl 1:7–131.

(PfHRP2) have a detection threshold of approximately 200 parasites per microliter but new ultrasensitive PfHRP2 RDTs can detect parasitemias as low as 2 to 4 parasites per microliter.¹⁰ However, PfHRP2-based RDTs are not quantitative, remain positive for up to 1 month, exhibit prozone effect at high parasitemias, and may be falsely negative in individuals with PfHRP2 gene deletions, which is reported mainly from South America as well as increasingly from Africa.^{11–14}

In Southeast Asia, speciation may be challenging, as young ring stages of *P knowlesi*, *P falciparum*, and *P vivax* look similar, whereas mature trophozoites of *P knowlesi* and *P malariae* also may be confused. In Africa, *P vivax* is sporadically being diagnosed in Duffy-negative populations, suggesting alternative mechanisms of red blood cell invasion.¹⁵ In absence of a peripheral blood smear, an RDT with a panspecific or species-specific lactate dehydrogenase (pLDH) or aldolase is required for diagnosing nonfalciparum infections. In high resourced regions, diagnosis by polymerase chain reaction should be pursued for accurate species-specific diagnosis and treatment of exported malaria, particularly from Africa and Southeast Asia.

CASE MANAGEMENT

Uncomplicated falciparum malaria can progress rapidly to severe disease and death, particularly in nonimmune individuals. Physicians must be alert to the fact that decreasing transmission in Africa will result in older age groups being at risk for severe malaria as premunition (protection from disease despite presence of peripheral blood parasites) is lost (Fig. 1). Thus, it is important that a malaria diagnosis is made soon after onset of malaria symptoms and antimalarial treatment started without delay. If severe malaria is suspected, particularly in high-risk groups, but parasitologic diagnosis is delayed antimalarial treatment should be started immediately. Treatment requires combination therapy with at least 2 effective antimalarials with different mechanisms of action to prevent drug resistance. Antimalarial dosing must be weight-based to ensure necessary drug concentrations; population specific age-based derived schedules can be more practical to implement. Goals of care are to prevent progression of disease and death by ensuring rapid clinical cure and parasite clearance. In malaria-endemic regions, treatment also aims to reduce transmission of a treated infection. In low transmission areas additional gametocytocidal therapy is added to further reduce transmission potential. In malaria caused by *P vivax* or *P ovale*, additional hypnozoitocidal therapy is indicated to prevent relapse infection.

SEVERE MALARIA

Severe malaria is mainly caused by *P falciparum*, but also observed in *P vivax* and *P knowlesi* infections. It is rarely seen with the other *Plasmodium* species. Severe malaria caused by any *Plasmodium* species is a medical emergency requiring prompt administration of an effective antimalarial and supportive management, ideally in an intensive care unit. In resource-limited settings, transfer to higher-level facilities should be considered if mechanical ventilation, renal replacement therapy (RRT) or hemodynamic monitoring are required. Mortality from severe malaria is still 10% to 20% despite optimal treatment and reaches 100% if left untreated.^{16,17} Mortality in pregnant women is approximately 50%. Coma, kidney dysfunction and acidosis independently predict mortality in both non-pregnant adults and children with severe falciparum malaria.^{18–20} Severe malaria is more likely in pregnant women in the second and third trimesters compared to other adults and is more often complicated by pulmonary edema and hypoglycemia. Severe knowlesi malaria is associated with hyperparasitemia due to its 24-h erythrocytic cycle, shock, acute kidney injury (AKI) and respiratory failure.^{21,22} Severe vivax malaria is most commonly associated with respiratory failure, AKI and severe anemia.²³

Antimalarials

Immediate antimalarial treatment

Intravenous artesunate is first-line treatment for severe malaria worldwide caused by any *Plasmodium* species. All adults and children with severe malaria, including infants, lactating women, and pregnant women in all trimesters should receive intravenous artesunate for at least 24 hours until oral medication is tolerated (Box 2).¹⁷ Two landmark randomized controlled trials (RCTs) showed that intravenous artesunate is superior to intravenous quinine, reducing mortality by 35% (95% CI 18.5–47.6) in Southeast Asian adults and by 22% (95% CI 8.1–36.9) in African children.^{24,25} Artesunate is well-tolerated and rapidly metabolized to its active metabolite dihydroartemisinin, reaching peak concentrations within 10 minutes and is rapidly eliminated (half-life 45 minutes).²⁶ It has broad stage specificity, killing young circulating ring-staged parasites up to late-staged sequestered parasites (Fig. 2).^{9,27} This activity against circulating ring-

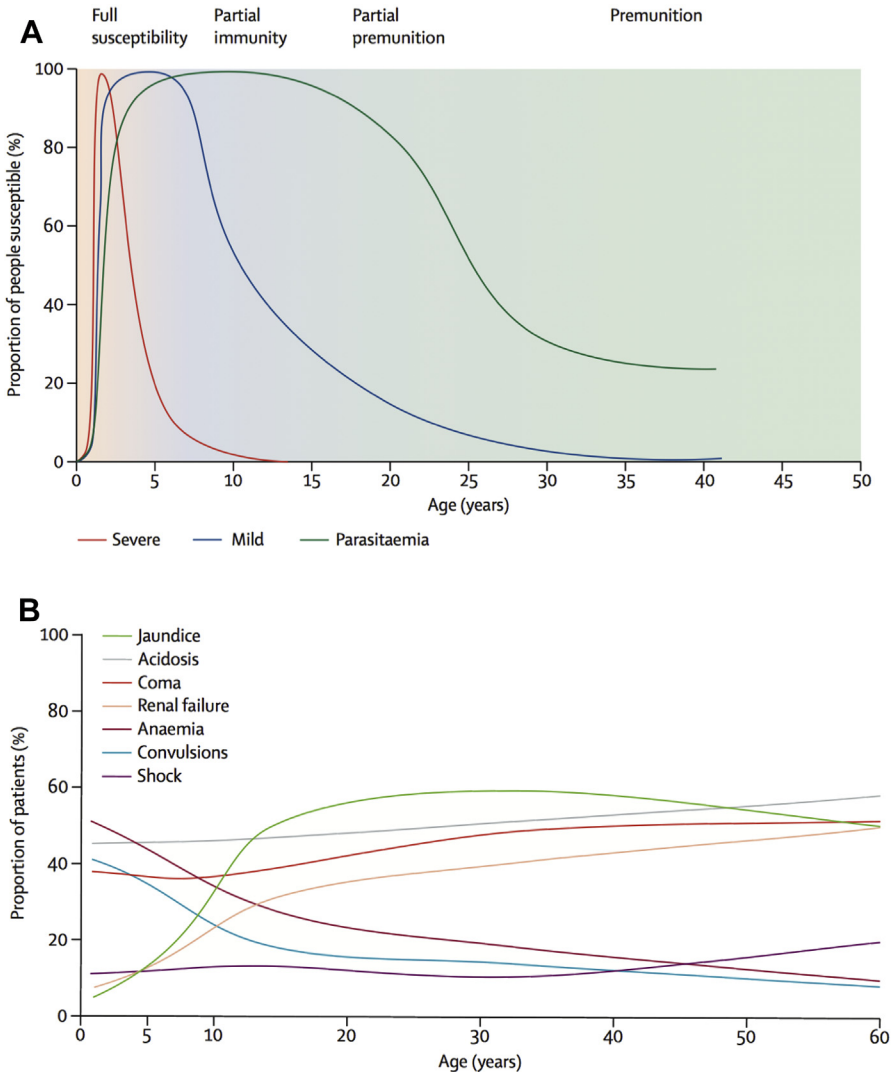


Fig. 1. Relationship between age and malaria severity in moderate transmission intensity regions. (A) Repeated exposures lead to acquired protection against severe malaria then against illness from malaria then in adulthood protective against microscopy-detected parasitemia.¹⁸ With decreasing transmission intensity protection against illness and parasitemia (*blue and green curves*) will be lost and older age groups will be at risk of severe disease (*red curve shifting to right*). (B) Manifestations of severe falciparum by age in unstable transmission regions. (From White NJ, Pukrittayakamee S, Hien TT, Faiz MA, Mokuolu OA, Dondorp AM. *Malaria*. *Lancet* 2014; 383:723-35. Reprinted with permission from Elsevier (*The Lancet*, 2014; 383:723–35)

stage parasites is considered its critical advantage over quinine, as artesunate kills parasites before they can mature and sequester in the microvasculature.²⁸ Quinine has more adverse drug effects, including hypoglycemia, hyperinsulinemia, cardiotoxicity, and hypotension, particularly if given as a rapid injection rather than infusion.²³ Artemether showed a smaller survival benefit than does artesunate, likely due to its

Box 2**Antimalarial treatment of severe malaria**

Adults, pregnant women, and children

First-line initial therapy

- Artesunate intravenously 2.4 mg/kg per dose at hour 0, 12, and 24, then every 24 hours^a
 - If <20 kg: artesunate intravenous 3.0 mg/kg per dose

Alternative initial therapy

- Quinine dihydrochloride intravenous infusion 20 mg/kg loading dose (over 4 hours) then maintenance dose 10 mg/kg (over 2 hours) every 8 hours^b
- Artemether intramuscular^c injection 3.2 mg/kg loading dose, then 1.6 mg/kg every 24 hours

After 24 hours and able to eat and drink^d

- Artemisinin-based combination therapy orally for 3 days (not mefloquine^e)

Travel history to countries with artemisinin resistance

- Intravenous artesunate PLUS intravenous quinine (expert opinion, no evidence)

If intravenous artesunate is not available, use artemether in preference to quinine in adults and children.

^a Artesunate dose does not need to be adjusted if renal impairment or liver dysfunction present.

^b Quinine requires dose adjustment according to renal dysfunction after 48 hours of full dosage. Dose adjustments are not required if receiving dialysis but quinine should be given post-RRT dosing if on dialysis.

^c Intramuscular injections administered to anterior thigh.

^d See uncomplicated malaria treatment (see **Box 3**) for oral artemisinin-based combination therapy options and alternatives.

^e Mefloquine increases risk of postmalaria neurologic syndrome and is contraindicated in patients with epilepsy or neuropsychiatric disorders.

Data from World Health Organization guidelines for the treatment of malaria. 3rd edition. 2015. Available at: <http://www.who.int/malaria/publications/atoz/9789241549127/en/>. Accessed April 24, 2017.

erratic intramuscular absorption.²⁹ Pre-referral rectal formulated artesunate given to severely ill children younger than 6 unable to take oral medications may reduce mortality.³⁰ Parasite clearance with artesunate typically occurs within 72 hours and should be documented by assessing thick and thin smears every 6 to 12 hours.

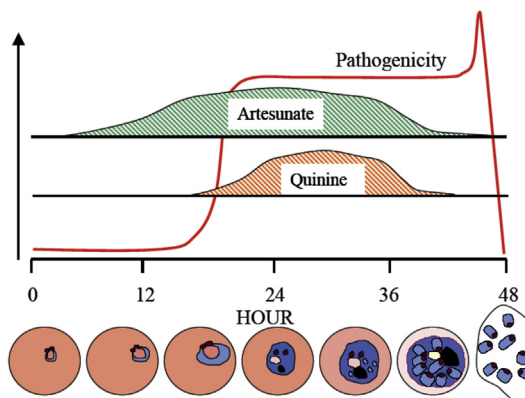


Fig. 2. Stage of parasite development and pathogenicity with rough estimates of stage specificity and “time windows” of antimalarial drug effects. (Adapted from White NJ, Krishna S. Treatment of malaria: some considerations and limitations of the current methods of assessment. *Trans R Soc Trop Med Hyg* 1989;83:767–77; with permission.)

Follow-on antimalarial treatment

After a minimum of 24 hours of intravenous antimalarial treatment and when oral medication can be tolerated, treatment must be completed with an effective, full course of an oral artemisinin-based combination therapy (ACT) (Box 3). If an ACT is not available, then a non-ACT regimen can be used. Mefloquine should not be given as

Box 3

Antimalarial oral treatment of uncomplicated malaria

Uncomplicated *Plasmodium falciparum*, and *Plasmodium knowlesi* malaria

Artemisinin-based combination therapy (ACT): 3-day regimens

- Artemether-lumefantrine (1.4–4.4/10–16 mg/kg) by mouth (PO) twice daily x 3 days (with fat-containing food)**
- Dihydroartemisinin-piperaquine (4/18 mg/kg) PO daily for 3 days
 - If <25 kg: Dihydroartemisinin 4 (2.5–10) mg/kg and Piperaquine 24 (20–32) mg/kg PO daily for 3 days
- Artesunate (4 mg/kg) plus mefloquine (8 mg/kg) PO daily for 3 days^a
- Artesunate (4 mg/kg) plus amodiaquine (10 mg/kg) PO daily for 3 days^a
- Artesunate (4 mg/kg) PO daily for 3 days plus single-dose sulfadoxine-pyrimethamine (25/1.25 mg/kg)^b

ACT: 7-day regimens

- Artesunate (2 mg/kg) PO daily plus tetracycline (4 mg/kg) PO every 6 hours for 7 days^c
- Artesunate (2 mg/kg) PO daily plus doxycycline 100 mg PO twice daily for 7 days^c
- Artesunate (2 mg/kg) PO daily plus clindamycin (20mg/kg) PO divided 2 times daily for 7 days^d

Non-ACT regimens

- Atovaquone-proguanil (15/6 mg/kg) PO daily for 3 days
- Quinine (10 mg/kg) plus EITHER tetracycline OR doxycycline OR clindamycin for 7 days^{c,d}

Uncomplicated *P. falciparum*, and travel to countries with artemisinin resistance^f

- Atovaquone-proguanil (15/6 mg/kg) PO daily for 3 days
- Quinine (10 mg/kg) plus EITHER tetracycline OR doxycycline OR clindamycin for 7 days^{c,d}

Uncomplicated chloroquine-sensitive *Plasmodium vivax*, *Plasmodium ovale*, or *Plasmodium malariae*^e

- Chloroquine (10 mg base/kg) per day at hour 0 and hour 24 then 5 mg base/kg at hour 48

Uncomplicated chloroquine-resistant *P. vivax*^e

- Oral ACT (except sulfadoxine-pyrimethamine) for 3 days
- Quinine (10 mg/kg) plus EITHER tetracycline OR doxycycline OR clindamycin for 7 days^{c,d}

^a World Health Organization prequalified fixed-dose tablets preferable to loose tablets.

^b Chloroquine-resistant *P. vivax* can be treated with any oral ACT except artesunate plus sulfadoxine-pyrimethamine.

^c Doxycycline preferred, as it does not accumulate in renal failure and it can be dosed daily. Contraindicated in children younger than 8 years and pregnant/lactating women (Class D).

^d Recommended in first-trimester pregnant women.

^e *P. vivax* and *P. ovale* should be followed by a course of primaquine for radical cure to prevent relapse. Contraindicated if glucose-6-phosphate-dehydrogenase deficient, pregnant or age younger than 6 months. Primaquine 0.5 mg base/kg daily for 14 days (G6PD normal; East Asia and Oceania); Primaquine 0.25 mg base/kg daily for 14 days (G6PD normal; elsewhere) or 0.75 mg base/kg weekly for 8 weeks (G6PD deficient).

^f Admit patient, monitor clinical and parasitologic response until recovery or parasite clearance, follow-up at 4 weeks to ensure cure.

** Number of tablets per dose according to pre-defined weight bands (5–14 kg: 1 tablet; 15–24 kg: 2 tablets; 25–34 kg: 3 tablets; and > 34 kg: 4 tablets) given twice a day for 3 days.

Data from World Health Organization Guidelines for the treatment of malaria. 3rd edition. 2015. Available at: <http://www.who.int/malaria/publications/atoz/9789241549127/en/>. Accessed April 24, 2017.

follow-on treatment if impaired consciousness was present at diagnosis due to the increased risk of neuropsychiatric complications. In returning travelers, follow-on anti-malarial medication should be different from any prophylactic drug used during travel. In severe vivax malaria, a full course of radical treatment with primaquine should also be given after recovery.

Cerebral Malaria and Convulsions

Cerebral malaria is a clinical malaria syndrome of impaired consciousness characterized by unrousable coma, as defined in **Box 1**, in the absence of hypoglycemia, convulsions, sedative drugs, and nonmalarial meningoencephalitis. Generalized convulsions are observed in approximately 80% of children and 15% of adults and may progress to status epilepticus and coma.^{24,25} Blood cultures should be drawn and glucose should be checked 4-hourly, especially if there is a decline in the coma score. Hypoglycemia is more frequent in children, pregnant women, and patients receiving quinine. In comatose children with suspected cerebral malaria, lumbar puncture does not increase mortality even when swelling on MRI brain or papilledema is present.³¹ Funduscopic examination for malaria retinopathy is specific, but not highly sensitive, for the diagnosis of cerebral malaria and is prognostic in patients with severe malaria.^{32,33} Patients should be positioned in the lateral recovery position, alternating sides every 2 hours.²³ A large randomized controlled trial is currently being conducted to assess whether recovery positioning in acutely comatose adults decreases aspiration pneumonia and improves outcomes ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02427633) NCT02427633). An oropharyngeal airway may be sufficient and/or bridge until endotracheal intubation is possible if the patient cannot maintain a patent airway. Nasogastric tube with suction may protect from aspiration but it should be clearly communicated to avoid early enteral feeding because feeding within 60 hours is associated with an increased risk of aspiration pneumonia.³⁴

Supportive therapies include glucose and acetaminophen to maintain euglycemia and fever control. Mannitol administration to reduce intracranial pressure in patients is not recommended.¹⁷ An RCT of a single dose of mannitol in children with cerebral malaria found no impact on clinical outcomes compared with placebo.³⁵ In adults with cerebral malaria and brain swelling on computed tomography imaging, mannitol prolonged coma recovery time compared with controls not receiving mannitol.³⁶ RCTs of dexamethasone to reduce vasogenic edema in adults³⁷ and children³⁸ found no benefit on coma recovery or survival and is therefore not recommended. Corticosteroids increase the risk for gastrointestinal bleeding, seizures, and prolonged coma resolution times compared with placebo. Seizure prophylaxis with phenobarbital or fosphenytoin has not shown to be beneficial in preventing seizures, where the former was associated with increased mortality likely due to respiratory depression.^{39–41} Therefore, routine seizure prophylaxis is currently not recommended in patients with seizures or cerebral malaria. Witnessed seizures should be treated with up to 2 doses of a benzodiazepine 10 minutes apart with careful respiratory monitoring. Recurrent seizures likely indicate status epilepticus and should be treated with phenytoin or phenobarbital loading, then maintenance dosing in a highly monitored setting.

Shock, Dehydration, and Acidosis

Fluid management is a critical but challenging intervention in the management of severe malaria. Patients present at differing times during their infections with variable degrees of hypovolemia, acidosis, and AKI. Most adult patients have a stable blood pressure in the low-normal range. Thus, fluid therapy should be individualized, as adult patients are at risk of developing pulmonary capillary leakage and subsequent acute respiratory distress syndrome (ARDS), particularly if excess fluids are administered

too rapidly. However, ARDS can develop after admission unpredictably and irrespective of fluid administration. In a study of Bangladeshi adults, 70% of patients were hypovolemic at the time ARDS developed.⁴² Clinical assessment and invasive hemodynamic monitoring at admission do not necessarily reflect effective circulating blood volume nor predict fluid responsiveness or ARDS.^{42–44} Further, correction of fluid deficits has not been shown to improve acidosis or AKI and increases the incidence of ARDS. This is likely due to the sequestration with subsequent microvascular obstruction and tissue hypoperfusion driving the acidosis and acute tubular injury that is not corrected by fluid loading. Aggressive fluid resuscitation in pediatric patients with compensated hemodynamic shock is also harmful. A landmark multinational study in African children with severe febrile illness and compensated shock showed a relative risk for death of 1.45 (95% CI 1.13–1.86; $P = .003$), with fluid bolus therapy (20 or 40 mL/kg of 0.9% saline or 5% albumin).⁴⁵ The case fatality rate of the 1793 children with a positive malaria slide was 9.2% with fluid bolus therapy compared with 5.8% in the control group (relative risk for death of 1.59; 95% CI 1.10–2.31). The increased mortality was suggested to be due to cardiovascular collapse rather than fluid overload in a retrospective analysis.⁴⁶

Hemodynamic shock is not common on admission in severe malaria (approximately 16% of adults and 12% of children) and should prompt investigation for an alternative cause of the septic syndrome.^{24,25} Concomitant bacteremia is observed in 6% to 13% of children and adults with malaria, and is frequently associated with increased mortality.^{47–49} The incidence of bacteremia is likely underestimated due to minimal microbiological diagnostics and frequent preadmission antibiotic use in resource-limited settings. Gram-negative organisms are most commonly isolated, particularly nontyphoidal *Salmonella*, followed by *Streptococcus pneumoniae* and *Staphylococcus aureus*.^{47–49} Gram-negative bacteremia complicating malaria is thought to be due to intestinal translocation from sequestration-mediated increased gut permeability, along with macrophage and neutrophil dysfunction.^{47,50,51} Shock and leukocytosis are frequently associated with concomitant bacteremia in malaria; however, there is no reliable clinical or laboratory predictor. The metabolic acidosis in severe malaria is predominantly due to lactic acid from sequestration-induced tissue hypoxia. However, hydroxyphenyllactic and other gut-derived microbial acids are also elevated and predictive of mortality (ClinicalTrials.gov NCT02451904).⁵² Thus, loss of gut integrity likely contributes to acidosis and gram-negative bacteremia in severe malaria; whether these gut-derived acids are predictive biomarkers of bacteremia is yet to be determined.

Given the frequently fatal outcome of ARDS even in settings with mechanical ventilation, the World Health Organization (WHO) recommends individualized restrictive fluid management, keeping the patient slightly dry (Table 1). Isotonic crystalloids (not colloids) are recommended because there is some evidence for harm using colloids in resuscitation.^{23,53} However, fluid type has yet to be trialed in adult malaria. Dextrose-containing fluids should be used in unconscious patients to maintain glucose concentrations greater than 4 mmol/L. Transfusion is recommended for children with a hemoglobin less than 5 g/dL in areas of moderate to high transmission, and less than 7 g/dL in adults and children in low transmission regions.²³ An RCT is currently being conducted to evaluate best transfusion strategies to prevent death in severely anemic African children, as evidence for the recommended threshold is lacking (ISRCTN84086586). As anemia can develop rapidly, hematocrit should be monitored every 6 to 12 hours. Preparation for transfusion should occur at higher thresholds in patients with hyperparasitemia and/or blackwater fever because of the expected drop in hemoglobin. Recently, a more conservative weight-based fluid strategy assessed in adult patients hospitalized with malaria, found that administering

Clinical Status	Adults	Children
1. No severe dehydration, no anuria, no shock	Initial: 0.9% saline intravenous (IV) 2–4 mL/kg per h for 6 h ^c Maintenance: 5% dextrose/0.9% saline IV 2–3 mL/kg per h Monitoring: every 2 h for first 6 h	Initial: 0.9% saline ^b IV 3–5 mL/kg per h for 3–4 h ^c Maintenance: 5% dextrose IV 2–3 mL/kg per h Monitoring: every 2 h for first 6 h
2. Severe dehydration, urine output <0.5 mL/kg per hour ^a	Initial: 0.9% saline IV 10 mL/kg per h for 2 h ^c If no urine output (>0.5 mL/kg per h) response: Repeat: 5% dextrose/0.9% saline IV 5 mL/kg per h for 4 h Monitoring: every 2 h	—
3. Hemodynamic shock	Initial: 0.9% saline IV 20 mL/kg bolus If no blood pressure response: Repeat: 0.9% saline IV 20 mL/kg bolus Monitoring: every 30 min If no response start vasopressor	—

^a Accurate urine output monitored with a urinary catheter is valuable to monitor fluid responsiveness to initial fluid administration; however, is an unreliable marker of kidney perfusion during acute kidney injury and may result in overresuscitation or underresuscitation if used to guide fluid therapy.

^b Alternate resuscitation fluid in children: 0.45% saline/5% dextrose.²³

^c During initial fluid administration, assess for pulmonary crepitations and work of breathing every 2 h and reassess individualized fluid needs.

Data from World Health Organization. Severe malaria. *Trop Med Int Health* 2014;19 Suppl 1:7–131.

2.5 mg/kg per hour in the first 6 hours did not result in any adverse disease complications.⁵⁴ This is reassuring for the treatment of moderately severe patients without anuria, ARDS, or shock, but this strategy needs to be evaluated in a larger cohort with more severe disease. Empiric antibiotics should be initiated in pediatric severe malaria and in all patients with shock in severe malaria.²³ Antibiotic choice should be guided by local hospital susceptibility patterns, source of suspected sepsis, and ideally should be non-nephrotoxic. Inadequate hemodynamic response after initial fluid resuscitation is an indication for vasopressors to be started (see **Table 1**). Norepinephrine is recommended over dopamine and epinephrine, but evidence regarding optimal vasopressor therapy is limited. Epinephrine has been shown to worsen lactic acidosis in severe malaria.⁵⁵ Bicarbonate is not recommended unless blood pH is less than 7.10, based on sepsis guideline consensus and the potential harms with overuse.

Acute Kidney Injury

AKI, defined by WHO criteria, complicates up to 40% of *P falciparum*,²⁴ 55% of *P knowlesi*,²² and 6% of *P vivax*⁵⁶ adult severe malaria and 10% of *P falciparum*²⁵ pediatric falciparum malaria. As the WHO AKI definition is not applicably defined for children, a high index of suspicion is needed because nearly 50% of children with falciparum malaria have AKI⁵⁷ as defined by current nephrology guidelines (creatinine rise ≥ 1.5 times baseline or 26.5 $\mu\text{mol/L}$ increase within 48 hours).⁵⁸ Malaria is a risk

for AKI, therefore all patients should have creatinine and urine output measured from admission. Sequestration contributes to the acute tubular necrosis in falciparum malaria.^{59,60} Cell-free hemoglobin-mediated damage is a common pathophysiological pathway contributing to AKI in falciparum,⁶¹ knowlesi malaria,⁶² and potentially vivax malaria, although the latter has yet to be studied.

Fluid management and avoidance of nephrotoxic drugs are foundations of AKI management. Patients with severe malaria with volume depletion and less severe AKI (moderately elevated creatinine) at admission, show normalization of creatinine with careful volume expansion.⁵⁴ However, patients with severe AKI (creatinine >175–300 $\mu\text{mol/L}$) and/or anuria are not necessarily hypovolemic and are unlikely to respond to fluid administration.^{42,43} There is no predictive model or biomarker to determine which patients will respond to fluid or not. Therefore, in patients with moderate AKI (creatinine >177 $\mu\text{mol/L}$), creatinine should be measured daily after initial cautious fluid administration. A low threshold for early RRT in malaria-associated AKI should be maintained. Early hemodialysis in acute renal failure reduces mortality from 75% to 26%.⁶³ Patients with anuria, rapidly rising creatinine (>220 $\mu\text{mol/L/d}$), or severe metabolic acidosis (pH <7.1) should have prompt RRT because rapid renal recovery is unlikely.^{63,64} All RRT modalities are lifesaving; however, hemodialysis has been shown to be superior to peritoneal dialysis in reducing mortality.^{65–67}

Furosemide has not been studied in malaria, and in nonmalaria, AKI is ineffective in preventing or treating AKI and potentially may be harmful.⁶⁸ Bicarbonate urine alkalinization in blackwater fever has not been trialed and in general is not recommended.⁵⁸ Multiple studies in nonmalaria populations show that there is no benefit of low-dose dopamine in preventing or treating AKI and may cause harm.⁶⁹ In severe malaria, low-dose dopamine was shown to increase renal blood flow but did not improve oxygen consumption or reduce peak creatinine or RRT requirement.⁵⁵ Based on the mechanism of acetaminophen inhibiting hemoprotein-mediated AKI,⁷⁰ a recent RCT in adults with severe malaria found that acetaminophen improved kidney function and reduced AKI development, particularly in patients with high cell-free hemoglobin levels.⁷¹ Larger studies of acetaminophen are being conducted to further assess this renoprotective effect in adults and children with falciparum and knowlesi malaria ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03056391) NCT03056391).

Other Adjunctive Therapies

Various other adjunctive treatments targeting the underlying pathophysiology of malaria have been evaluated without showing benefit, including heparin, desferrioxamine, anti-tumor necrosis factor antibody, levamisole, hyperimmune serum, N-acetylcysteine, and exchange transfusion.^{17,72}

UNCOMPLICATED MALARIA

Plasmodium falciparum

Blood-stage cure

ACT is recommended first-line therapy for uncomplicated falciparum malaria in all populations except in first-trimester pregnancy; this latter exception might be lifted in the near future (see **Box 3**). ACT is also efficacious against nonfalciparum malaria and therefore recommended to treat mixed infections and unspesiated infections. ACT consists of an artemisinin component (artesunate, artemether, or dihydroartemisinin) that rapidly reduces parasitemia, and a second partner antimalarial drug that is slowly eliminated to kill the residual parasites. Oral ACT treatments are reliably effective with few adverse effects⁷³ and are available as fixed-dose combinations

(artemether-lumefantrine, dihydroartemisinin-piperavaquine, artesunate-amodiaquine, artesunate-sulfadoxine/pyrimethamine, artesunate-mefloquine, and recently added artesunate-pyronaridine). The recommended dosing of dihydroartemisinin-piperavaquine was recently revised for children less than 25 kg after it was shown that children were suboptimally dosed resulting in reduced efficacy.^{74,75} A recent meta-analysis and systematic review provides evidence of the low risk of cardiotoxicity of dihydroartemisinin-piperavaquine.⁷⁶ Partner drugs with slow elimination (eg, mefloquine, piperavaquine) provide 4 to 6 weeks' prophylaxis, whereas rapidly eliminated partner drugs (eg, lumefantrine) expose a risk to reinfection within a month. The choice of oral ACT depends on risk of drug resistance of the partner drug and potential for treatment failure, which is increased in regions of Southeast Asia (Fig. 3). Fake and substandard antimalarials are widespread; therefore, quality-assured drugs are required to maintain effectiveness and prevent selecting for drug resistance.⁷⁷

Non-ACT regimens are still recommended in certain circumstances. Atovaquone-proguanil is highly effective for returned travelers without hyperparasitemia and who have not taken the drug as prophylaxis.¹⁷ In endemic countries, it is not recommended for widespread use as high-grade atovaquone resistance emerges from a single point mutation. However, it can be given with artesunate plus primaquine in cases of standard ACT treatment failure. Quinine in combination with clindamycin or doxycycline is poorly tolerated but is recommended as second-line treatment in certain countries with ACT failure, as quinine remains efficacious. Quinine plus clindamycin 7-day treatment is the recommendation for uncomplicated falciparum malaria in first-trimester pregnancy.¹⁷ However, this recommendation will likely be revised in the near future, as safety data of ACT in the first trimester are reassuring.⁷⁸

Patients with uncomplicated malaria can be treated as outpatients if the patient remains clinically stable after confirming that oral therapy is tolerated and parasitemia has declined. If vomiting occurs within 1 hour of the oral antimalarial dosing, then the dose should be repeated. Mefloquine is associated with increased rates of vomiting and all quinolines (quinine, mefloquine, and chloroquine) are associated with

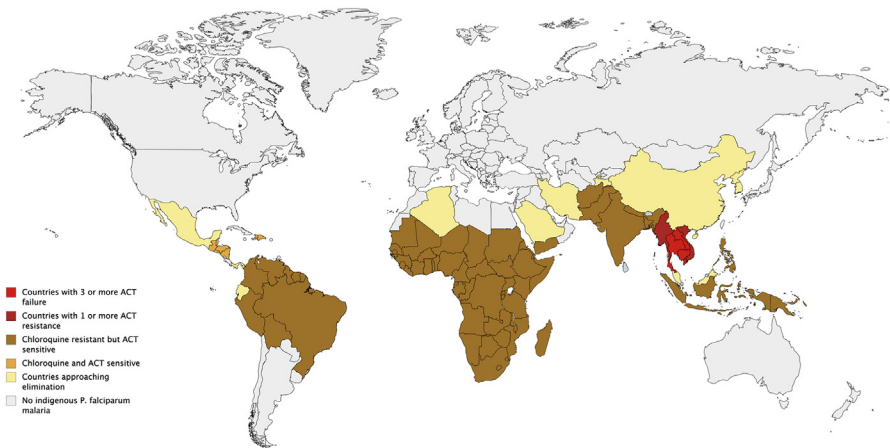


Fig. 3. Global distribution of *P. falciparum* drug resistance. Countries shown by level of antimalarial resistance of local *P. falciparum*. Countries approaching malaria elimination also shown (as defined in Malaria World Report 2016). (From Ashley EA, Phyo AP, Woodrow C. Malaria. Lancet 2018;391:1608–21. Reprinted with permission from Elsevier (The Lancet, 2018;391:1608–21).

orthostatic hypotension, which may result in patients not completing therapy. Higher-risk populations, including pregnant women, infants, nonimmune travelers, individuals infected with the human immunodeficiency virus, patients on tuberculosis therapy, and uncomplicated hyperparasitemic ($\geq 2\%$ nonimmune; $\geq 4\%$ immune) patients should be considered for admission due to increased risks of treatment failure and/or severe disease. Ideally, parasite clearance should be documented in all patients.

Gametocytocidal treatment

In low-transmission areas, primaquine should be given as a single dose (0.25 mg base/kg) with all ACT regimens for the treatment of falciparum malaria, except in pregnancy and infants.¹⁷ This treatment serves to prevent onward transmission by killing mature stage gametocytes thereby sterilizing the infection.⁷⁹ This low dose is considered safe even in glucose-6-phosphate dehydrogenase (G6PD) deficiency, and therefore G6PD testing is not required before administration.

Plasmodium vivax*, *Plasmodium ovale*, *Plasmodium malariae*, and *Plasmodium knowlesi

Blood-stage cure

Unspicuated malaria and *P malariae*-like infections acquired in Southeast Asia should be treated as for uncomplicated falciparum malaria. Uncomplicated *P vivax*, *P ovale*, and *P malariae* acquired in chloroquine-sensitive regions are treated with chloroquine (see **Box 3**). While chloroquine remains efficacious against *P knowlesi*, ACT is recommended in the Malaysian malaria treatment guidelines due to the risk of misdiagnosed falciparum malaria, presence of chloroquine-resistant vivax, and trials confirming efficacy with faster parasite clearance times with ACT compared with chloroquine.^{80–82} In chloroquine-resistant regions (**Fig. 4**), adults and children with uncomplicated *P vivax*, *P ovale*, *P malariae*, and *P knowlesi* should be treated with an ACT containing piperaquine, mefloquine, or lumefantrine (except first-trimester pregnancy).^{17,83} Mixed infections are common in coendemic areas. Microscopy and RDT diagnostics may underestimate mixed infections. ACTs are the treatment of choice for mixed infections.

Liver-stage cure

Radical cure with primaquine is required to kill liver hypnozoites of vivax or ovale malaria to prevent relapse in all settings. Individuals with G6PD-deficiency may experience potentially dangerous dose-dependent primaquine-induced hemolysis. The severity of hemolysis also depends on the G6PD genetic variant. Testing for G6PD deficiency is required before treatment. In most trials, primaquine has been given daily for 14 days if there is no G6PD deficiency, and for 8 weeks as weekly supervised doses if G6PD deficient.⁸⁴ Adherence and hemolysis remain issues for delivery of effective radical cure. A recent trial of a 7-day course of higher-dose primaquine (1 mg base/kg) resulted in significant hemolysis in G6PD heterozygous female individuals compared with a standard 14-day course of primaquine (0.5 mg base/kg).⁸⁵ Tafenoquine is a longer-acting 8-aminoquinoline given as a single dose for radical cure that is currently under review.⁸⁶ However, this new treatment will not obviate the need for primaquine in G6PD-deficient individuals due to the risk of hemolysis.⁸⁷

FOLLOW-ON MANAGEMENT

Post-artesunate Delayed-Onset Hemolysis

Delayed-onset hemolysis after intravenous artesunate can occur in nonimmune travelers returning from malaria-endemic regions, particularly if hyperparasitemia is

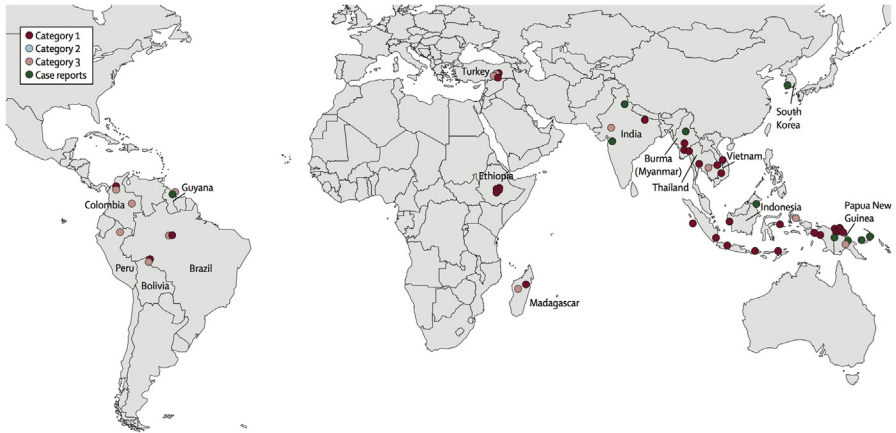


Fig. 4. Global distribution of *P vivax* chloroquine resistance. Chloroquine resistance was categorized according to the strength of evidence⁹⁹: Category 1: greater than 10% recurrence by day, irrespective of confirmation of adequate blood chloroquine concentration; Category 2: confirmed recurrences by day 28 within reported whole-blood chloroquine concentration of greater than 100 nm; and Category 3: greater than 5% recurrences by day 28, irrespective of chloroquine concentration. Chloroquine sensitivity was confirmed if patients had enrolled after a symptomatic clinical illness, fewer than 5% recurrences had occurred by day 28, no primaquine was given before day 28, and studies had a sample size of at least 10 patients. Case reports were observations in individual patients of treatment failure during chloroquine prophylaxis, prolonged parasite clearance or *P vivax* recurrence following treatment. (From Price RN, von Seidlein L, Valecha N, et al. Global extent of chloroquine-resistant *Plasmodium vivax*: a systematic review and meta-analysis. *Lancet Infect Dis* 2014;14:982–91; and Creative Commons Attribution License (CC BY). Available at: [https://doi.org/10.1016/S1473-3099\(14\)70855-2](https://doi.org/10.1016/S1473-3099(14)70855-2). Accessed September 13, 2014; with permission.)

present.⁸⁸ The mechanism of this hemolysis relates to the mechanism of clearance of young ring-stage parasites after artesunate treatment. When artesunate rapidly kills ring-stage parasites, which confers its lifesaving advantage over quinine, the dead parasites become pyknotic. These are then removed from the red cells in the spleen by a process called pitting, leaving the once-infected red cells to be recirculated.⁸⁹ The once-infected red cells retaining PfHRP2 have a shortened life span, resulting in the observed delayed hemolysis and persistently positive PfHRP2 RDT. The PfHRP2 concentration after parasite clearance predicts delayed hemolysis.⁹⁰ This phenomenon is less pronounced in African children living in high-transmission regions,⁹¹ and post-artesunate late anemia in this setting is uncommon and not more frequent than after quinine treatment. Nonimmune patients, including travelers, should be followed up to 2 weeks after parenteral artesunate treatment to monitor hemoglobin levels, along with creatinine if hemolysis is evident.

Treatment Failures

Treatment failure is defined as the “failure to clear parasitemia or resolve clinical symptoms despite use of an antimalarial drug at correct doses,” which does not equate to resistance.¹⁷ Treatment failures can be a result of different factors, including nonadherence, inadequate drug concentrations, poor drug quality, altered pharmacokinetics, host immunity, high initial parasitemia or drug resistance. Artemether-lumefantrine (AL) treatment failures have been reported in nonimmune, returning

traveling men weighing a median of 77 kg, suggesting that AL dosing may need to be optimized in heavier individuals.⁹² Until trials assess optimal dosing, overweight adults should be followed up to assess treatment outcomes.

Primaquine Radical Cure Failures

Failure of primaquine to prevent *P vivax* relapses has been proposed as primaquine tolerance or resistance.⁹³ Similar to failures in treating asexual blood parasitemia, suboptimal dosing and drug concentrations can be an alternative explanation for primaquine failures.⁹⁴ Lower primaquine efficacy and increased risk of relapse has been linked to poor or intermediate metabolism of primaquine in individuals with polymorphisms in the cytochrome P450 CYP isoform CYP2D6.⁹⁵ Tafenoquine efficacy for preventing *P vivax* relapses was not decreased in individuals with decreased CYP2D6 activity⁹⁶; however, prospective studies are still needed to confirm this finding.

RESISTANCE

Plasmodium falciparum

P falciparum resistance to chloroquine and sulfadoxine-pyrimethamine is globally widespread. Artemisinin-resistant falciparum malaria is now prevalent in parts of Cambodia, the Lao People's Democratic Republic, Myanmar, Thailand, and Viet Nam (see [Fig. 3](#)).⁹⁷ Artemisinin resistance affects ring-stage parasites and is characterized by delayed parasite clearance following treatment with an artesunate monotherapy or an ACT. At the population level, artemisinin resistance is confirmed when $\geq 5\%$ of infections carry resistance-related mutations in the Kelch13 gene in combination with a parasite clearance half-life ≥ 5 hours or persistent parasitemia ≥ 3 days after treatment assessed by light microscopy.⁹⁸ With retained full sensitivity to the ACT partner drug, ACT efficacy is largely maintained in the presence of artemisinin resistance; however, reduced efficacy of artemisinins facilitates the selection of partner drug resistance, as was observed with piperazine and mefloquine. Once resistance to both ACT partner drugs appears, treatment failure is high, and spread of resistance accelerates quickly. Kelch13 mutations have been observed at low frequency outside Southeast Asia, including sub-Saharan Africa. However, selection for these mutations has not occurred and there is currently no confirmed artemisinin resistance in Africa.

New antimalarials are not expected within the next 5 years, and the treatment and control of falciparum malaria in the Greater Mekong Subregion (GMS) will become increasingly challenging.⁹⁷ Rotating between different ACTs, sequential treatment with 2 different ACTs or extending the current 3-day regimens have been proposed. A promising approach is deployment of triple artemisinin combinations, combining an artemisinin with 2 matching partner drugs (dihydroartemisinin–piperazine–mefloquine and artemether–lumefantrine–amodiaquine), which are currently being trialed ([ClinicalTrials.gov](https://clinicaltrials.gov/NCT02453308) NCT02453308).

Plasmodium vivax

High-grade resistance to chloroquine in *P vivax* is widespread in Indonesia and Papua New Guinea and resistance has now been reported in more than 10 countries in endemic areas (see [Fig. 4](#)).⁹⁹ However, the geographic extent is unclear due to coadministration of primaquine, or subtherapeutic drug concentrations (inadequate dose or duration), that could mask low-level chloroquine resistance, or accentuate treatment failures, respectively.

SUMMARY

Management of malaria has changed significantly in the past 15 years, both on an individual and population level. ACTs have, together with the widespread distribution of insecticide-treated bednets, contributed to the impressive reduction in malaria transmission globally. ACTs for falciparum malaria have replaced older therapies given the undisputed survival benefit, safety, and tolerance. Further, there has been a shift toward unified ACT treatment for all human malaria infections, given the challenges in speciation and potential rise in chloroquine-vivax malaria infection. Deployment of parenteral artesunate has importantly improved case fatality. Restricted fluid management has become again the standard in severe malaria. Less progress has been made toward developing adjunctive therapies for severe malaria; however, acetaminophen is a first adjunctive treatment showing benefit by reducing AKI. Sevuparin, which inhibits sequestration, has potential to improve the compromised microcirculation in severe malaria. With malaria transmission decreasing in many parts of sub-Saharan Africa, waning immunity will shift symptomatic and severe disease to older children and adults in Africa.

At the same time, the emergence and spread of artemisinin and partner drug resistance in falciparum malaria threatens to undo the progress made in reducing malaria morbidity and mortality. Accelerated elimination of falciparum malaria in the GMS is required to contain further spread of multidrug-resistant parasite strains. This requires a well-coordinated effort to deploy malaria services to the most remote, vulnerable, and often mobile populations. In addition to conventional vector control measures and community-based facilities for early diagnosis and treatment, targeted mass drug administration of ACT and single-dose primaquine have shown potential for rapid elimination of falciparum malaria in eastern Myanmar.¹⁰⁰ In Africa, intermittent preventive therapy in pregnancy and infants, and seasonal childhood chemoprevention in the sub-Sahel region are being scaled up; however, increasing sulfadoxine-pyrimethamine resistance threatens its impact.¹ Enhanced deployment of long-lasting insecticide (pyrethroid)-treated bednets and indoor residual spraying with insecticide significantly reduced morbidity and mortality in high-transmission regions; however insecticide resistance may also threaten this success. Increased use of primaquine to reduce transmission of falciparum malaria may assist toward elimination, whereas increased use of primaquine to prevent relapse of vivax malaria is required for elimination of this species. Limited access to G6PD deficiency testing for safe primaquine administration is a critical issue. The emergence of zoonotic malaria infecting humans from monkey reservoirs increases the complexity of global elimination strategies. To prevent increases in malaria morbidity and mortality, WHO calls for improved access to effective interventions along with an escalation in funding for malaria control programs and research.

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