Recommendations

Diagnosis of malaria

All cases of suspected malaria should have a parasitological test (microscopy or Rapid diagnostic test (RDT)) to confirm the diagnosis.

Both microscopy and RDTs should be supported by a quality assurance programme.
Good practice statement

Treating uncomplicated *P. falciparum* malaria

Treatment of uncomplicated P. falciparum malaria

Treat children and adults with uncomplicated *P. falciparum* malaria (except pregnant women in their first trimester) with one of the following recommended artemisinin-based combination therapies (ACT):

- artemether + lumefantrine
- artesunate + amodiaquine
- artesunate + mefloquine
- dihydroartemisinin + piperaquine
- artesunate + sulfadoxine–pyrimethamine (SP)

Strong recommendation, high-quality evidence

Duration of ACT treatment

ACT regimens should provide 3 days' treatment with an artemisinin derivative.
Strong recommendation, high-quality evidence

Revised dose recommendation for dihydroartemisinin + piperaquine in young children

Children < 25kg treated with dihydroartemisinin + piperaquine should receive a minimum of 2.5 mg/kg body weight (bw) per day of dihydroartemisinin and 20 mg/kg bw per day of piperaquine daily for 3 days.
Strong recommendation based on pharmacokinetic modelling

Reducing the transmissibility of treated P. falciparum infections

In low-transmission areas, give a single dose of 0.25 mg/kg bw primaquine with ACT to patients with *P. falciparum* malaria (except pregnant women, infants aged < 6 months and women breastfeeding infants aged < 6 months) to reduce transmission. Testing for glucose-6-phosphate dehydrogenase (G6PD) deficiency is not required.
Strong recommendation, low-quality evidence

Treating uncomplicated *P. falciparum* malaria in special risk groups

First trimester of pregnancy

Treat pregnant women with uncomplicated *P. falciparum* malaria during the first trimester with 7 days of quinine + clindamycin.
Strong recommendation

Infants less than 5kg body weight

Treat infants weighing < 5 kg with uncomplicated *P. falciparum* malaria with ACT at the same mg/kg bw target dose as for children weighing 5 kg.
Strong recommendation

Patients co-infected with HIV

In people who have HIV/AIDS and uncomplicated *P. falciparum* malaria, avoid artesunate + SP if they are being treated with co-trimoxazole, and avoid artesunate + amodiaquine if they are being treated with efavirenz or zidovudine.
Good practice statement

Non-immune travellers

Treat travellers with uncomplicated *P. falciparum* malaria returning to non-endemic settings with ACT.
Strong recommendation, high-quality evidence

Hyperparasitaemia

People with *P. falciparum* hyperparasitaemia are at increased risk for treatment failure, severe malaria and death and should be closely monitored, in addition to receiving ACT.
Good practice statement

Treating uncomplicated *P. vivax*, *P. ovale*, *P. malariae* or *P. knowlesi* malaria

Blood stage infection

If the malaria species is not known with certainty, treat as for uncomplicated *P. falciparum* malaria.
Good practice statement

In areas with chloroquine-susceptible infections, treat adults and children with uncomplicated *P. vivax*, *P. ovale*, *P. malariae* or *P. knowlesi* malaria with either ACT (except pregnant women in their first trimester) or chloroquine.
Strong recommendation, high-quality evidence

In areas with chloroquine-resistant infections, treat adults and children with uncomplicated *P. vivax*, *P. ovale*, *P. malariae* or *P. knowlesi* malaria (except pregnant women in their first trimester) with ACT.
Strong recommendation, high-quality evidence

Treat pregnant women in their first trimester who have chloroquine-resistant *P. vivax* malaria with quinine.
Strong recommendation, very low-quality evidence

Preventing relapse in *P. vivax* or *P. ovale* malaria

The G6PD status of patients should be used to guide administration of primaquine for preventing relapse.
Good practice statement

To prevent relapse, treat *P. vivax* or *P. ovale* malaria in children and adults (except pregnant women, infants aged < 6 months, women breastfeeding infants aged < 6 months, women breastfeeding older infants unless they are known not to be G6PD deficient, and people with G6PD deficiency) with a 14-day course (0.25-0.5 mg/kg bw daily) of primaquine in all transmission settings.
Strong recommendation, high-quality evidence

In people with G6PD deficiency, consider preventing relapse by giving primaquine base at 0.75 mg/kg bw once a week for 8 weeks, with close medical supervision for potential primaquine-induced haemolysis.
Conditional recommendation, very low-quality evidence

When G6PD status is unknown and G6PD testing is not available, a decision to prescribe primaquine must be based on an assessment of the risks and benefits of adding primaquine.
Good practice statement

Pregnant and breastfeeding women

In women who are pregnant or breastfeeding, consider weekly chemoprophylaxis with chloroquine until delivery and breastfeeding are completed, then, on the basis of G6PD status, treat with primaquine to prevent future relapse.
Conditional recommendation, moderate-quality evidence

Treating severe malaria

Treat adults and children with severe malaria (including infants, pregnant women in all trimesters and lactating women) with intravenous or intramuscular artesunate for at least 24 h and until they can tolerate oral medication. Once a patient has received at least 24 h of parenteral therapy and can tolerate oral therapy, complete treatment with 3 days of ACT (add single dose primaquine in areas of low transmission).
Strong recommendation, high-quality evidence

Revised dose recommendation for parenteral artesunate in young children

Children weighing < 20 kg should receive a higher dose of artesunate (3 mg/kg bw per dose) than larger children and adults (2.4 mg/kg bw per dose) to ensure equivalent exposure to the drug.
Strong recommendation based on pharmacokinetic modelling

Parenteral alternatives where artesunate is not available

If artesunate is not available, use artemether in preference to quinine for treating children and adults with severe malaria.
Conditional recommendation, low-quality evidence

Treating cases of suspected severe malaria pending transfer to a higher-level facility (pre-referral treatment)

Pre-referral treatment options

Where complete treatment of severe malaria is not possible but injections are available, give adults and children a single intramuscular dose of artesunate, and refer to an appropriate facility for further care. Where intramuscular artesunate is not available use intramuscular artemether or, if that is not available, use intramuscular quinine.
Strong recommendation, moderate-quality evidence

Where intramuscular injection of artesunate is not available, treat children < 6 years with a single rectal dose (10mg/kg bw) of artesunate, and refer immediately to an appropriate facility for further care. Do not use rectal artesunate in older children and adults.
Strong recommendation, moderate-quality evidence

Chemoprevention for special risk groups

Intermittent preventive treatment in pregnancy

In malaria-endemic areas in Africa, provide intermittent preventive treatment with SP to all women in their first or second pregnancy (SP-IPTp) as part of antenatal care. Dosing should start in the second trimester and doses should be given at least 1 month apart, with the objective of ensuring that at least three doses are received.
Strong recommendation, high-quality evidence

Intermittent preventive treatment in infants

In areas of moderate-to-high malaria transmission of Africa, where SP is still effective, provide intermittent preventive treatment with SP to infants (< 12 months of age) (SP-IPTi) at the time of the second and third rounds of vaccination against diphtheria, tetanus and pertussis (DTP) and vaccination against measles.
Strong recommendation

Seasonal malaria chemoprevention

In areas with highly seasonal malaria transmission in the sub-Sahel region of Africa, provide seasonal malaria chemoprevention (SMC) with monthly amodiaquine + SP for all children aged < 6 years during each transmission season.
Strong recommendation, high-quality evidence

Treating severe malaria

Treat adults and children with severe malaria (including infants, pregnant women in all trimesters and lactating women) with intravenous or intramuscular artesunate for at least 24 h and until they can tolerate oral medication. Once a patient has received at least 24 h of parenteral therapy and can tolerate oral therapy, complete treatment with 3 days of an ACT (add single dose primaquine in areas of low transmission).
Strong recommendation, high-quality evidence

Revised dose recommendation for parenteral artesunate in young children

Children weighing < 20 kg should receive a higher dose of artesunate (3 mg/kg bw per dose) than larger children and adults (2.4 mg/kg bw per dose) to ensure equivalent exposure to the drug.
Strong recommendation based on pharmacokinetic modelling

Parenteral alternatives when artesunate is not available

If parenteral artesunate is not available, use artemether in preference to quinine for treating children and adults with severe malaria.
Conditional recommendation, low-quality evidence

Treating cases of suspected severe malaria pending transfer to a higher-level facility (pre-referral treatment)

Pre-referral treatment options

Where complete treatment of severe malaria is not possible but injections are available, give adults and children a single intramuscular dose of artesunate, and refer to an appropriate facility for further care. Where intramuscular artesunate is not available use intramuscular artemether or, if that is not available, use intramuscular quinine.
Strong recommendation, moderate-quality evidence

Where intramuscular injections of artesunate are not available, treat children < 6 years with a single rectal dose (10 mg/kg bw) of artesunate, and refer immediately to an appropriate facility for further care. Do not use rectal artesunate in older children and adults.
Strong recommendation, moderate-quality evidence

Mortality from untreated severe malaria (particularly cerebral malaria) approaches 100%. With prompt, effective antimalarial treatment and supportive care, the rate falls to 10–20% overall. Within the broad definition of severe malaria some syndromes are associated with lower mortality rates (e.g. severe anaemia) and others with higher mortality rates (e.g. acidosis). The risk for death increases in the presence of multiple complications.

Any patient with malaria who is unable to take oral medications reliably, shows any evidence of vital organ dysfunction or has a high parasite count is at increased risk for dying. The exact risk depends on the species of infecting malaria parasite, the number of systems affected, the degree of vital organ dysfunction, age, background immunity, pre-morbid, and concomitant diseases, and access to appropriate treatment. Tests such as a parasite count, haematocrit and blood glucose may all be performed immediately at the point of care, but the results of other laboratory measures, if any, may be available only after hours or days. As severe malaria is potentially fatal, any patient considered to be at increased risk should be given the benefit of the highest level of care available. The attending clinician should not worry unduly about definitions: the severely ill patient requires immediate supportive care, and, if severe malaria is a possibility, parenteral antimalarial drug treatment should be started without delay.

7.1 | DEFINITIONS

7.1.1 | SEVERE FALCIPARUM MALARIA

For epidemiological purposes, **severe falciparum malaria** is defined as one or more of the following, occurring in the absence of an identified alternative cause and in the presence of *P. falciparum* asexual parasitaemia.

- *Impaired consciousness:* A Glasgow coma score < 11 in adults or a Blantyre coma score < 3 in children
- *Prostration:* Generalized weakness so that the person is unable to sit, stand or walk without assistance
- *Multiple convulsions:* More than two episodes within 24 h
- *Acidosis:* A base deficit of > 8 mEq/L or, if not available, a plasma bicarbonate level of < 15 mmol/L or venous plasma lactate ⩾ 5 mmol/L. Severe acidosis manifests clinically as respiratory distress (rapid, deep, laboured breathing).
- *Hypoglycaemia:* Blood or plasma glucose < 2.2 mmol/L (< 40 mg/dL)
- *Severe malarial anaemia:* Haemoglobin concentration ⩽ 5 g/dL or a haematocrit of ⩽ 15% in children < 12 years of age (< 7 g/dL and < 20%, respectively, in adults) with a parasite count > 10 000/µL
- *Renal impairment:* Plasma or serum creatinine > 265 µmol/L (3 mg/dL) or blood urea > 20 mmol/L
- *Jaundice:* Plasma or serum bilirubin > 50 µmol/L (3 mg/dL) with a parasite count > 100 000/ µL
- *Pulmonary oedema*: Radiologically confirmed or oxygen saturation < 92% on room air with a respiratory rate > 30/min, often with chest indrawing and crepitations on auscultation
- *Significant bleeding:* Including recurrent or prolonged bleeding from the nose, gums or venepuncture sites; haematemesis or melaena

- *Shock:* Compensated shock is defined as capillary refill ⩾ 3 s or temperature gradient on leg (mid to proximal limb), but no hypotension. Decompensated shock is defined as systolic blood pressure < 70 mm Hg in children or < 80 mm Hg in adults, with evidence of impaired perfusion (cool peripheries or prolonged capillary refill).
- *Hyperparasitaemia: P. falciparum* parasitaemia > 10%.

7.1.2 | SEVERE VIVAX AND KNOWLESI MALARIA

Severe vivax malaria is defined as for falciparum malaria but with no parasite density thresholds.

Severe knowlesi malaria is defined as for falciparum malaria but with two differences:

- *P. knowlesi* hyperparasitaemia: parasite density > 100 000/μL
- Jaundice and parasite density > 20 000/μL.

7.2 | THERAPEUTIC OBJECTIVES

The main objective of the treatment of severe malaria is to prevent the patient from dying. Secondary objectives are prevention of disabilities and prevention of recrudescent infection.

Death from severe malaria often occurs within hours of admission to a hospital or clinic, so it is essential that therapeutic concentrations of a highly effective antimalarial drug be achieved as soon as possible. Management of severe malaria comprises mainly clinical assessment of the patient, specific antimalarial treatment, additional treatment and supportive care.

7.3 | CLINICAL ASSESSMENT

Severe malaria is a medical emergency. An open airway should be secured in unconscious patients and breathing and circulation assessed. The patient should be weighed or body weight estimated, so that medicines, including antimalarial drugs and fluids, can be given appropriately. An intravenous cannula should be inserted, and blood glucose (rapid test), haematocrit or haemoglobin, parasitaemia and, in adults, renal function should be measured immediately. A detailed clinical examination should be conducted, including a record of the coma score. Several coma scores have been advocated: the Glasgow coma scale is suitable for adults, and the simple Blantyre modification is easily performed in children. Unconscious patients should undergo a lumbar puncture for cerebrospinal fluid analysis to exclude bacterial meningitis.

7.7 | FOLLOW-ON TREATMENT

The current recommendation of experts is to give parenteral antimalarial drugs for the treatment of severe malaria for a minimum of 24 h once started (irrespective of the patient's ability to tolerate oral medication earlier) or until the patient can tolerate oral medication, before giving the oral follow-up treatment.

After initial parenteral treatment, once the patient can tolerate oral therapy, it is essential to continue and complete treatment with an effective oral antimalarial drug by giving a full course of effective ACT (artesunate + amodiaquine, artemether + lumefantrine or dihydroartemisinin + piperaquine). If the patient presented initially with impaired consciousness, ACTs containing mefloquine should be avoided because of an increased incidence of neuropsychiatric complications. When an ACT is not available, artesunate + clindamycin, artesunate + doxycycline, quinine + clindamycin or quinine + doxycycline can be used for follow-on treatment. Doxycycline is preferred to other tetracyclines because it can be given once daily and does not accumulate in cases of renal failure, but it should not be given to children < 8 years or pregnant women. As treatment with doxycycline is begun only when the patient has recovered sufficiently, the 7-day doxycycline course finishes after the artesunate, artemether or quinine course. When available, clindamycin is preferred in children and pregnant women.

7.8 | CONTINUING SUPPORTIVE CARE

Patients with severe malaria require intensive nursing care, preferably in an intensive care unit where possible. Clinical observations should be made as frequently as possible and should include monitoring of vital signs, coma score and urine output. Blood glucose should be monitored every 4 h, if possible, particularly in unconscious patients.

7.9 | MANAGEMENT OF COMPLICATIONS

Severe malaria is associated with a variety of manifestations and complications, which must be recognized promptly and treated as shown below.

Immediate clinical management of severe manifestations and complications of *P. falciparum* malaria

Manifestation or complication	Immediate management[a]
Coma (cerebral malaria)	Maintain airway, place patient on his or her side, exclude other treatable causes of coma (e.g. hypoglycaemia, bacterial meningitis); avoid harmful ancillary treatments, intubate if necessary.
Hyperpyrexia	Administer tepid sponging, fanning, a cooling blanket and paracetamol.
Convulsions	Maintain airways; treat promptly with intravenous or rectal diazepam, lorazepam, midazolam or intramuscular paraldehyde. Check blood glucose.
Hypoglycaemia	Check blood glucose, correct hypoglycaemia and maintain with glucose-containing infusion. Although hypoglycaemia is defined as glucose < 2.2 mmol/L, the threshold for intervention is < 3 mmol/L for children < 5 years and < 2.2 mmol/L for older children and adults.
Severe anaemia	Transfuse with screened fresh whole blood.
Acute pulmonary oedema[b]	Prop patient up at an angle of 45°, give oxygen, give a diuretic, stop intravenous fluids, intubate and add positive end-expiratory pressure or continuous positive airway pressure in life-threatening hypoxaemia.
Acute kidney injury	Exclude pre-renal causes, check fluid balance and urinary sodium; if in established renal failure, add haemofiltration or haemodialysis, or, if not available, peritoneal dialysis.
Spontaneous bleeding and coagulopathy	Transfuse with screened fresh whole blood (cryoprecipitate, fresh frozen plasma and platelets, if available); give vitamin K injection.

Metabolic acidosis	Exclude or treat hypoglycaemia, hypovolaemia and septicaemia. If severe, add haemofiltration or haemodialysis.
Shock	Suspect septicaemia, take blood for cultures; give parenteral broad-spectrum antimicrobials, correct haemodynamic disturbances.

[a] It is assumed that appropriate antimalarial treatment will have been started in all cases.

[b] Prevent by avoiding excess hydration

7.10 | ADDITIONAL ASPECTS OF MANAGEMENT

7.10.1 | FLUID THERAPY

Fluid requirements should be assessed individually. Adults with severe malaria are very vulnerable to fluid overload, while children are more likely to be dehydrated. The fluid regimen must also be adapted to the infusion of antimalarial drugs. Rapid bolus infusion of colloid or crystalloids is contraindicated. If available, haemofiltration should be started early for acute kidney injury or severe metabolic acidosis, which do not respond to rehydration. As the degree of fluid depletion varies considerably in patients with severe malaria, it is not possible to give general recommendations on fluid replacement; each patient must be assessed individually and fluid resuscitation based on the estimated deficit. In high-transmission settings, children commonly present with severe anaemia and hyperventilation (sometimes termed "respiratory distress") resulting from severe metabolic acidosis and anaemia; they should be treated by blood transfusion. In adults, there is a very thin dividing line between over-hydration, which may produce pulmonary oedema, and under-hydration, which contributes to shock, worsening acidosis and renal impairment. Careful, frequent evaluation of jugular venous pressure, peripheral perfusion, venous filling, skin turgor and urine output should be made.

7.10.2 | BLOOD TRANSFUSION

Severe malaria is associated with rapid development of anaemia, as infected, once infected and uninfected erythrocytes are haemolysed and/or removed from the circulation by the spleen. Ideally, fresh, cross-matched blood should be transfused; however, in most settings, cross-matched virus-free blood is in short supply. As for fluid resuscitation, there are not enough studies to make strong evidence-based recommendations on the indications for transfusion; the recommendations given here are based on expert opinion. In high-transmission settings, blood transfusion is generally recommended for children with a haemoglobin level of < 5 g/100 mL (haematocrit < 15%). In low-transmission settings, a threshold of 20% (haemoglobin,

7 g/100 mL) is recommended. These general recommendations must, however, be adapted to the individual, as the pathological consequences of rapid development of anaemia are worse than those of chronic or acute anaemia when there has been adaptation and a compensatory right shift in the oxygen dissociation curve.

7.10.3 | EXCHANGE BLOOD TRANSFUSION

Many anecdotal reports and several series have claimed the benefit of exchange blood transfusion in severe malaria, but there have been no comparative trials, and there is no consensus on whether it reduces mortality or how it might work. Various rationales have been proposed:

- removing infected red blood cells from the circulation and therefore lowering the parasite burden (although only the circulating, relatively non-pathogenic stages are removed, and this is also achieved rapidly with artemisinin derivatives);
- rapidly reducing both the antigen load and the burden of parasite-derived toxins, metabolites and toxic mediators produced by the host; and
- replacing the rigid unparasitized red cells by more easily deformable cells, therefore alleviating microcirculatory obstruction.

Exchange blood transfusion requires intensive nursing care and a relatively large volume of blood, and it carries significant risks. There is no consensus on the indications, benefits and dangers involved or on practical details such as the volume of blood that should be exchanged. It is, therefore, not possible to make any recommendation regarding the use of exchange blood transfusion.

7.10.4 | CONCOMITANT USE OF ANTIBIOTICS

The threshold for administering antibiotic treatment should be low in severe malaria. Septicaemia and severe malaria are associated, and there is substantial diagnostic overlap, particularly in children in areas of moderate and high transmission. Thus broad-spectrum antibiotic treatment ***should*** *be given* with antimalarial drugs to all children with suspected severe malaria in areas of moderate and high transmission until a bacterial infection is excluded. After the start of antimalarial treatment, unexplained deterioration may result from a supervening bacterial infection. Enteric bacteria (notably *Salmonella*) predominated in many trial series in Africa, but a variety of bacteria have been cultured from the blood of patients with a diagnosis of severe malaria.

Patients with secondary pneumonia or with clear evidence of aspiration should be given empirical treatment with an appropriate broad-spectrum antibiotic. In children with persistent fever despite parasite clearance, other possible causes of fever should be excluded, such as systemic *Salmonella* infections and urinary tract infections, especially in catheterized patients. In the majority of cases of persistent fever, however, no other pathogen is identified after parasite clearance. Antibiotic treatment should be based on culture and sensitivity results or, if not available, local antibiotic sensitivity patterns.

7.10.5 | USE OF ANTICONVULSANTS

The treatment of convulsions in cerebral malaria with intravenous (or, if this is not possible, rectal) benzodiazepines or intramuscular paraldehyde is similar to that for repeated seizures from any cause. In a large, double-blind, placebo-controlled evaluation of a single prophylactic intramuscular injection of 20 mg/kg bw of phenobarbital to children with cerebral malaria, the frequency of seizures was reduced but the mortality rate was increased significantly. This resulted from respiratory arrest and was associated with additional use of benzodiazepine. *A 20 mg/kg bw dose of phenobarbital should* ***not*** *be given without respiratory support.* It is not known whether a lower dose would be effective and safer or whether mortality would not increase if ventilation were given. In the absence of further information, prophylactic anticonvulsants are not recommended.

7.10.6 | TREATMENTS THAT ARE NOT RECOMMENDED

In an attempt to reduce the high mortality from severe malaria, various adjunctive treatments have been evaluated, but none has proved effective and many have been shown to be harmful. Heparin, prostacyclin, desferroxamine, pentoxifylline, low-molecular-mass dextran, urea, high-dose corticosteroids, aspirin anti-TNF antibody, cyclosporine A, dichloroacetate, adrenaline, hyperimmune serum, *N*-acetylcysteine and bolus administration of albumin are not recommended. In addition, use of corticosteroids increases the risk for gastrointestinal bleeding and seizures and has been associated with prolonged coma resolution times when compared with placebo.

7.11 | TREATMENT OF SEVERE MALARIA DURING PREGNANCY

Women in the second and third trimesters of pregnancy are more likely to have severe malaria than other adults, and, in low-transmission settings, this is often complicated by pulmonary oedema and hypoglycaemia. Maternal mortality is approximately 50%, which is higher than in non-pregnant adults. Fetal death and premature labour are common.

Parenteral antimalarial drugs should be given to pregnant women with severe malaria in full doses without delay. *Parenteral artesunate is the treatment of choice in all trimesters.* Treatment must not be delayed. If artesunate is unavailable, intramuscular artemether should be given, and if this is unavailable then parenteral quinine should be started immediately until artesunate is obtained.

Obstetric advice should be sought at an early stage, a paediatrician alerted and blood glucose checked frequently. Hypoglycaemia should be expected, and it is often recurrent if the patient is receiving quinine. Severe malaria may also present immediately after delivery. Postpartum bacterial infection is a common complication and should be managed appropriately.

7.12 | TREATMENT OF SEVERE *P. VIVAX* MALARIA

Although *P. vivax* malaria is considered to be benign, with a low case-fatality rate, it may cause a debilitating febrile illness with progressive anaemia and can also occasionally cause severe disease, as in *P. falciparum* malaria. Reported manifestations of severe *P. vivax* malaria include severe anaemia, thrombocytopenia, acute pulmonary oedema and, less commonly, cerebral malaria, pancytopenia, jaundice, splenic rupture, haemoglobinuria, acute renal failure and shock.

Prompt effective treatment and case management should be the same as for severe *P. falciparum* malaria (see section 7.4). Following parenteral artesunate, treatment can be completed with a full treatment course of oral ACT or chloroquine (in countries where chloroquine is the treatment of choice). A full course of radical treatment with primaquine should be given after recovery.