MALARIA TREATMENT GUIDELINES

Ministry of Health and Wellness
MAURITIUS

Approval Form

Version: 2.0 **Effective date:** 8 February 2025

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This document is mostly contextualized material taken directly from the World Health Organization – see the references for details.

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PEER REVIEW

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Date of next review: December 2029

Treatment Guidelines for Malaria

Case management

Uncomplicated falciparum malaria can progress rapidly to severe forms of the disease, especially in people with no or low immunity, and severe falciparum malaria is almost always fatal without treatment. Therefore, national programmes should ensure access to early diagnosis and prompt, effective treatment within 24–48 hours of the onset of malaria symptoms.

To reduce the spread of drug resistance, limit unnecessary use of antimalarial drugs and improve the identification of other febrile illnesses in the context of changing malaria epidemiology; antimalarial medicines should be administered only to patients who truly have malaria. Adherence to a full treatment course must be promoted. Easy access to parasitological diagnosis of malaria is now possible with the use of quality-assured rapid diagnostic tests (RDTs).

Preventing or delaying resistance is essential for the success of both national and global strategies for control and eventual elimination of malaria. To help protect current and future antimalarial medicines, all episodes of malaria should be treated with at least two effective antimalarial medicines with different mechanisms of action (combination therapy).

To prolong their useful therapeutic life and ensure that all patients have an equal chance of being cured, the quality of antimalarial drugs must be ensured, and antimalarial drugs must be given at optimal dosages. Treatment should maximize the likelihood of rapid clinical and parasitological cure and minimize transmission from the treated infection. To achieve this, dosage regimens should be based on the patient's weight and should provide effective concentrations of antimalarial drugs for a sufficient time to eliminate the infection in all target populations.

In patients with suspected severe malaria and in other high-risk groups, such as patients living with HIV/AIDS or pregnant women, absence or delay of parasitological diagnosis should not delay an immediate start of antimalarial treatment.

All cases of malaria should be admitted to a hospital (private or public) in Mauritius for an initial assessment. In addition, all cases of severe malaria should preferably be treated in the ICU setting. Moreover, all patients who have malaria must be placed under mosquito precautions i.e., under a mosquito net with an insect-repellent in the room – such precautions should be continued until such a time that the blood smears are negative.

Since Mauritius is a malaria-free country, an important goal of treatment is to ensure that no autochthonous transmission occurs in the community.

Roles and responsibilities

The following table describes the duties of each cadre in the case management of malaria.

Cadre	Responsibility
Triage nurse	Know and apply the case definition of malaria systematically to reduce the risk of missing cases
Casualty doctor	Stabilize / resuscitate the patient rapidly, take a good history (including travel history), perform a physical examination, admit the patient to the right ward and order the correct tests

Laboratory technician	Complete tests for malaria within 24 hours and notify the Regional Public Health Superintendent (RPHS) if the test is positive; the treating doctor or RPHS should contact the lab to get results within 2h if the patient is severely ill
Specialist doctor	Oversee treatment of the patient, manage complications and take responsibility for the patient as long as the patient is admitted in the hospital and is under his / her service[†]
Hospital nurse	Ensure patients get their medications and other treatments at the right time in the right way
Infection Prevention and Control nurse or doctor	Ascertain that the patient is correctly isolated as per current guidelines
Regional Public Health Superintendent (RPHS)	Distribute anti-malarial drugs promptly to the hospitals that need them, assist with the stock management of anti-malarial drugs, order blood films, prescribe the correct dose of anti-malarial medications, ensure compliance with anti-malarial medications, guide the treating specialist with respect to the risk of contagiousness when discharging the patient and follow up the patient after discharge
Pharmacist	Ensure anti-malarial drugs do not go out of stock and confirm that medications that are purchased are of good quality

Table 1: † – specialists should contact the RPHS or go through the Public Health Department's guidelines for details regarding discharge criteria of malaria patients.

Currently, anti-malarial drugs (with the exception of hydroxychloroquine) can only be procured and stocked by the Ministry of Health and Wellness. Private institutions have to contact the Regional Public Health Superintendent to gain access to these drugs.

Risk groups

Travelers to malarious areas generally have had no previous exposure to malaria parasites or have lost their immunity if they left the endemic area; they are at very high risk for severe disease if infected with *Plasmodium falciparum*. For this reason, it is important to consider malaria in all febrile patients with history of travel to malarious areas.

If the traveler has taken chemoprophylaxis, the same medicine should not be used for treatment. However, treatment of *P. vivax, P. ovale* and *P. malariae* malaria in travellers should be the same as for patients in endemic areas.

Rare instances of transmission of malaria via blood transfusion, needle prick injuries, from contaminated syringes and from organ transplants have been described. Proper infection prevention and control practices should be in place in all health institutions to reduce the risk of nosocomial spread of malaria.

Incubation period

Following the bite of an infected female Anopheles mosquito, the inoculated sporozoites migrate to the liver within one to two hours. Individuals are generally asymptomatic for 12 to 35 days after infection, but symptoms can commence as early as 7 days (depending on parasite species).

The incubation period for the relapsing species, *Plasmodium vivax* and *Plasmodium ovale*, is also about two weeks; however, illness can occur months after initial infection due to activation of residual

hypnozoites in the liver. Relapses generally occur within two to three years of infection, with even longer periods of dormancy being reported.

Clinical manifestations

The initial symptoms are nonspecific and may include fever, tachycardia, tachypnea, chills, malaise, fatigue, diaphoresis, headache, cough, anorexia, nausea, vomiting, abdominal pain, diarrhea, arthralgias, and myalgias.

Physical findings may include manifestations of anemia (lethargy, pallor) and a palpable spleen in some cases; splenic enlargement supports the diagnosis if present but may also reflect other conditions.

Laboratory evaluation may demonstrate anemia, thrombocytopenia, elevated transaminases, mild coagulopathy, and elevated blood urea nitrogen (BUN) and creatinine.

Severe malaria is defined as one or more of the criteria in table 1.

Notably, uncomplicated hyperparasitaemia is considered to be present in patients who have ≥ 4% (≥ 200,000/μL) parasitaemia but no signs of severity. They are at increased risk for severe malaria and for treatment failure and are considered an important source of antimalarial drug resistance. However, in low-transmission settings, mortality already starts to rise when the parasite density exceeds 100,000/μL (~2% parasitaemia).

Manifestations	**Definitions**
Impaired consciousness	Glasgow coma score <11 in adults or Blantyre coma score <3 in children; inability to swallow
Prostration	Generalized weakness so that a person is unable to sit, stand, or walk without assistance
Multiple convulsions	More than two episodes within 24 hours
Acidosis	A base deficit of >8 mEq/L, a plasma bicarbonate level of <15 mmol/L, or venous plasma lactate ≥5 mmol/L. Clinical indicators include rapid, deep, labored breathing.
Hypoglycemia	Blood or plasma glucose <40 mg/dL (<2.2 mmol/L) for children ≥5 years and adults; blood or plasma glucose <54 mg/dL (<3 mmol/L) for children <5 years
Severe anemia	Hemoglobin concentration ≤5 g/dL or hematocrit ≤15% in children <12 years of age (<7 g/dL and <20%, respectively, in adults) with parasite count >10,000 parasites/μL
Renal impairment	Plasma or serum creatinine >3 mg/dL (265 μmol/L) or blood urea >20 mmol/L
Jaundice	Plasma or serum bilirubin >50 μmol/L (3 mg/dL) with one of the following: • *Plasmodium falciparum* parasite count >2.5% parasitemia • *Plasmodium knowlesi* parasite count >20,000 parasites/μL
Pulmonary edema	Radiographically confirmed or oxygen saturation <92% on room air with respiratory rate >30/minute, often with chest indrawing and crepitations on auscultation
Significant bleeding	Includes recurrent or prolonged bleeding (from the nose, gums, or venipuncture sites), hematemesis, or melena
Shock	Compensated shock: capillary refill ≥3 seconds or temperature gradient on leg (mild to proximal limb), but no hypotension. Decompensated shock: systolic blood pressure <70

	mmHg in children or <80 mmHg in adults, with evidence of impaired perfusion (cool peripheries or prolonged capillary refill).
Hyperparasitemia	*P. falciparum*: • In non-immune travelers: parasitemia ≥5% • All patients: parasitemia >10% *P. knowlesi*: • Parasite density >100,000 parasites *Plasmodium vivax*: • No established parasite density threshold

Table 2: Criteria for severe malaria.

Diagnosing malaria

The signs and symptoms of malaria are non-specific. Malaria is suspected clinically primarily on the basis of fever or a history of fever in the correct epidemiological context. There is no combination of signs or symptoms that reliably distinguishes malaria from other causes of fever; diagnosis based only on clinical features has very low specificity and results in overtreatment. Other possible causes of fever and whether alternative or additional treatment is required must always be carefully considered. The focus of malaria diagnosis should be to identify patients who truly have malaria, and to guide rational use of antimalarial medicines.

In all settings, suspected malaria should be confirmed with a parasitological test. The results of parasitological diagnosis should be available within a short time (e.g., < 2 h) of the patient presenting. In settings where parasitological diagnosis is not possible within this time frame, a decision to provide antimalarial treatment must be based on the probability that the illness is malaria.

The two methods used routinely for parasitological diagnosis of malaria are light microscopy and immunochromatographic RDTs. The latter detect parasite-specific antigens or enzymes that are either genus or species specific.

RDTs for detecting PfHRP2 can be useful for patients who have received incomplete antimalarial treatment, in whom blood films can be negative. This is particularly likely if the patient received a recent dose of an artemisinin derivative. If the initial blood film examination is negative in patients with manifestations compatible with severe malaria, a series of blood films should be examined at 6–12 h intervals, or an RDT (preferably one detecting PfHRP2) should be performed.

Current RDTs are based on the detection of histidine-rich protein 2 (HRP2), which is specific for *P. falciparum*, pan-specific or species-specific Plasmodium lactate dehydrogenase (pLDH) or pan-specific aldolase. However, RDTs have a limit of detection >100 to 200 parasites/microL and do not allow determination of parasitemia level or life cycle stages.

Light microscopy not only provides a highly sensitive, specific diagnosis of malaria when performed well but also allows quantification of malaria parasites and identification of the infecting species. A skilled microscopist can detect asexual parasites at a density of < 10 per μL of blood, but under typical field conditions, the limit of sensitivity is approximately 100 parasites per μL.

Sequestration is well known to occur with *P. falciparum* and as a result, the parasite densities measured in blood films (reflecting circulating parasites only) variably underestimate the total malaria parasite biomass. Hence, parasite count should not be the main determinant of disease severity.

Two types of blood smears are used in malaria microscopy: thin and thick smears. Thin smear preparation maintains the integrity and morphology of erythrocytes so that parasites are visible within red blood cells. Thin smears allow identification of the infecting parasite species and can be used to measure parasite density. Thick smear preparation involves mechanical lysis of red blood cells so that malaria parasites can be visualized independent of cell structures. Thick smears allow the microscopist to review a relatively large quantity of blood and are typically used to screen for the presence or absence of parasites and to estimate parasite density.

RDTs are also available for the detection of *P. vivax* malaria; however, they are relatively insensitive for detecting *P. malariae* and *P. ovale* parasitaemia. Rapid diagnostic antigen tests for human Plasmodium species show poor sensitivity for *P. knowlesi* infections in humans with low parasitaemia. Light microscopy remains the preferred method to diagnose these infections.

While the theoretical limit of detection for nucleic acid tests has been estimated at 0.02 to 1 parasite/μL (which is better than light microscopy), nucleic acid tests are not currently used routinely to diagnose malaria. Nevertheless, genomic sequencing can help to distinguish recrudescence from reinfections.

Treatment of uncomplicated malaria from *P. falciparum*

A patient who presents with symptoms of malaria and a positive parasitological test (microscopy or RDT) but with no features of severe malaria is defined as having uncomplicated malaria.

The clinical objectives of treating uncomplicated malaria are to cure the infection as rapidly as possible and to prevent progression to severe disease. “Cure” is defined as elimination of all parasites from the body. The public health objectives of treatment are to prevent onward transmission of the infection to others and to prevent the emergence and spread of resistance to antimalarial drugs.

Some patients cannot tolerate oral treatment and will require parenteral or rectal administration for 1–2 days, until they can swallow and retain oral medication reliably. Although such patients do not show other signs of severity, they should receive the same initial antimalarial treatments recommended for severe malaria. Initial rectal or parenteral treatment must always be followed by a full 3-day course of artemisinin-based combination therapy (ACT).

Adults and children with uncomplicated *P. falciparum* malaria (including infants, pregnant women in their second and third trimesters and breastfeeding women) should be treated with artemether-lumefantrine for 3 days.

A 3-day course of the artemisinin component of ACTs covers two asexual cycles, ensuring that only a small fraction of parasites remain for clearance by the partner drug, thus reducing the potential development of resistance to the partner drug.

Formulations of artemether-lumefantrine that are currently available include dispersible or standard tablets containing 20 mg artemether and 120 mg lumefantrine, and standard tablets containing 40 mg artemether and 240 mg lumefantrine in a fixed-dose combination formulation. The flavored dispersible tablet pediatric formulation facilitates use in young children.

The target dose range is a total dose of 5–24 mg/kg by weight (bw) of artemether and 29–144 mg/kg bw of lumefantrine. The recommended dosage regimen is artemether + lumefantrine given twice a day for 3 days

(total of six doses). The first two doses should, ideally, be given 8 h apart. Tables 2 and 3 provide necessary details.

In uncomplicated hyperparasitaemia, both giving longer courses of ACT and preceding the standard 3-day ACT regimen with parenteral or oral artesunate may be considered.

Body weight (kg)	Dose (mg) of artemether + lumefantrine given twice daily for 3 days
5 to < 15	20 + 120
15 to < 25	40 + 240
25 to < 35	60 + 360
≥ 35	80 + 480

Table 3: Infants weighing < 5 kg with uncomplicated P. falciparum malaria should be treated with an ACT at the same mg/kg bw target dose as for children weighing 5 kg.

Weight (kg)	***Age*** *(years)*	**No. of tablets at approximate timing of dosing**					
		0 h	**8 h**	**24 h**	**36 h**	**48 h**	**60 h**
5-14	***(<3)***	1	1	1	1	1	1
15-24	***(>3-8)***	2	2	2	2	2	2
25-34	***(>9-14)***	3	3	3	3	3	3
>34	***(>14)***	4	4	4	4	4	4

Table 4: Dose of artemether-lumefantrine in tablets.

In low-transmission areas, a single dose of 0.25 mg/kg bw primaquine should be given with an ACT to patients with *P. falciparum* malaria (except pregnant women, infants aged < 6 months and women breastfeeding infants aged < 6 months) to reduce transmission. G6PD testing is not required. The primaquine can be administered on the first day of ACT therapy. See table 4 for more information.

Body weight (kg)	Single dose of primaquine (mg base)
10[a] to < 25 3.75	3.75
25 to < 50 7.5	7.5
50 to 100 15	15

Table 5: [a]Dosing of young children weighing < 10 kg is limited by the tablet sizes currently available.

Single doses of primaquine > 0.4 mg/kg bw reduced gametocyte carriage at day 8 by around two thirds – however, insufficient data is available for the 0.25 mg/kg bw dose. Analysis of observational data from mosquito feeding studies suggests that 0.25 mg/kg bw may rapidly reduce the infectivity of gametocytes to mosquitoes.

Life-threatening hemolysis is considered unlikely with the 0.25mg/kg bw dose and without G6PD testing.

Recurrent falciparum malaria

Recurrence of *P. falciparum* malaria can result from re-infection or recrudescence (treatment failure). Treatment failure may result from drug resistance or inadequate exposure to the drug due to sub-optimal dosing, poor adherence, vomiting, unusual pharmacokinetics in an individual, or substandard medicines. It is important to determine from the patient's history whether he or she vomited the previous treatment or did not complete a full course of treatment.

Failure within 28 days of treatment may indicate resistance to ACT – if this occurs, consider getting expert advice. An alternative ACT should be used if available.

Failure of treatment after 28 days may suggest a new infection (especially if the patient has travelled once again to an endemic area) and artemether-lumefantrine may be re-used to treat such patients.

Obese adults, pregnant women and young children should be closely monitored after treatment since failure rates are more common in these categories of patients due to difficulties associated with accurate dosing and pharmacokinetics.

Pregnant and lactating women infected with *P. falciparum*

Malaria in pregnancy is associated with low-birth-weight infants, increased anaemia and, in low-transmission areas, increased risks for severe malaria, pregnancy loss and death. The risk of malaria infection is said to be highest in the first and second trimesters of pregnancy.

Pregnant women with uncomplicated *P. falciparum* malaria can be safely treated with artemether-lumefantrine during the first trimester. In a study published in The Lancet, treatment with artemether-lumefantrine in the first trimester was associated with a statistically significant lower risk (42%) of adverse pregnancy outcomes compared to treatment with oral quinine (adjusted hazards ratio: 0.58; 95% confidence interval: 0.36–0.92).[7]

The current assessment of risk–benefit suggests that ACTs should be used to treat uncomplicated falciparum malaria in the second and third trimesters of pregnancy.

Treatment of uncomplicated malaria caused by *P. vivax, P. ovale, P. malariae* or *P. knowlesi*

The objectives of treatment of vivax malaria are twofold: to cure the acute blood stage infection and to clear hypnozoites from the liver to prevent future relapses (down to a level < 10% within 28 days). This is known as "radical cure".

For chloroquine-sensitive vivax malaria, oral chloroquine at a total dose of 25 mg base/kg bw is effective and well tolerated. Lower total doses are not recommended, as these encourage the emergence of resistance. Chloroquine is given at an initial dose of 10 mg base/kg bw, followed by 10 mg/kg bw on the second day and 5 mg/kg bw on the third day. This is illustrated in table 5.

Wt (in kg)	***Age***	**No. of tablets**			**Total dose**	**Total tabs**
		150 mg base	**150 mg base**	**150 mg base**		
		Day 1	**Day 2**	**Day 3**		
5 – 6	***< 4 months***	½	¼	1/4	150	1
7 - 10	***4 – 11 months***	½	½	½	225	1 ½
11 – 14	***1 – 2 years***	1	1	½	375	2 ½
15 – 18	***3 – 4 yrs***	1	1	1	450	3
19 – 24	***5 – 7 yrs***	1 ½	1 ½	1	600	4
25 – 35	***8 – 10 yrs***	2 ½	2 ½	1	900	6
36 – 50	***11 – 13 yrs***	3	3	2	1200	8
50 +	***14 + yrs***	4	4	2	1500	10

Table 6: Dose of chloroquine in tablets.

Artemether-lumefantrine should be used to treat vivax malaria in travellers coming from areas known to harbor chloroquine-resistant *P. vivax.*

ACTs are highly effective in the treatment of vivax malaria, allowing simplification of malaria treatment, i.e. all malaria infections can be treated with an ACT.

Resistance of *P. ovale, P. malariae* and *P. knowlesi* to antimalarial drugs is not well characterized, and infections caused by these three species are generally considered to be sensitive to chloroquine. The blood stages of *P. ovale, P. malariae* and *P. knowlesi* should therefore be treated with the standard regimen of ACT or chloroquine, as for vivax malaria.

Chloroquine can be administered to pregnant women – however, discuss with the pediatrician regarding whether breastfeeding can be continued.

Mixed malaria infections (especially with *P. falciparum*) are common in endemic areas. Such infections can be underestimated using both RDTs or light microscopy. ACTs are effective against all malaria species and so are the treatment of choice for mixed infections.

Moreover, if the malaria species is not known with certainty, adults and children should be treated as for uncomplicated *P. falciparum* malaria.

To prevent relapse of *P. vivax* and *P. ovale*, children and adults (except pregnant women, infants aged < 6 months, women breastfeeding older infants unless they are known not to be G6PD deficient, and people with G6PD deficiency) should be treated with a 14-day course of primaquine in all transmission settings. The therapeutic dose is 0.25 mg/kg bw per day of primaquine once a day for 14 days. Tests for G6PD deficiency can be carried out at the Central Health Laboratory.

An alternative is using primaquine 0.5 mg/kg/day for seven days to treat *P. vivax* or *P. ovale* malaria in children and adults since patients are more likely to be adherent to shorter courses of treatment. Primaquine is generally started once the course of chloroquine has been completed. Primaquine causes dose-limiting abdominal discomfort when taken on an empty stomach; it should therefore always be taken with food. Patients on primaquine should be monitored for hemolysis and anemia – a full blood count should be done on the seventh day of treatment.

The G6PD status of patients should be used to guide administration of primaquine for preventing relapse. Consider using 0.75 mg/kg bw primaquine once weekly for 8 weeks for people with mild-to-moderate G6PD deficiency, under close medical supervision.

In women who are pregnant or breastfeeding, instead of using primaquine, weekly chemoprophylaxis with chloroquine can be given until delivery and breastfeeding are completed; then, on the basis of G6PD status, primaquine can be given to prevent future relapse.

Treatment of severe malaria

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.

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.

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.

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.

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.

Severe malaria is associated with a variety of manifestations and complications (like seizures, acute pulmonary edema, acute kidney injury, coagulopathy and shock), which must be recognized promptly and treated.

Fluid requirements should be assessed individually. Adults with severe malaria are very vulnerable to fluid overload, while children are more likely to be dehydrated. Rapid bolus infusion of colloid or crystalloids is contraindicated. If available, hemofiltration should be started early for acute kidney injury or severe metabolic acidosis, which do not respond to rehydration. 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.

In low-transmission settings, a threshold of hematocrit of less than 20% (or haemoglobin < 7 g/100 mL) is recommended for transfusion. This recommendation 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.

Refer the patient to the appropriate specialist for further management whenever complications occur.

Parenteral (or intramuscular) artesunate is the treatment of choice for all severe malaria. The dosage of artemisinin derivatives does not have to be adjusted for patients with vital organ dysfunction (renal or hepatic).

It is recommended to give parenteral artesunate for the treatment of severe malaria for a minimum of 24h once started (irrespective of the patient's ability to tolerate oral medication earlier) or until the patient can tolerate oral medication (at 0h, 12h and 24h; then if needed, every 24h for up to 6 days), before giving the oral follow-up treatment.

After initial parenteral treatment, once the patient can tolerate oral therapy and the parasite density is < 1% (< 50,000/µL), it is essential to continue and complete treatment with an effective oral antimalarial drug by giving a full course of effective ACT i.e., 3 days of artemether-lumefantrine.

Artesunate is dispensed as a powder of artesunic acid, which is dissolved in sodium bicarbonate (5%) to form sodium artesunate. The solution is then diluted in approximately 5 mL of 5% dextrose and given by intravenous injection or by intramuscular injection into the anterior thigh. The solution should be prepared freshly for each administration and should not be stored. Tables 6 and 7 provide additional information on two available brand names of artesunate. Contact the RPHS to get access to artesunate and other anti-malarial drugs in Mauritius.

Falcinil*	***Falcinil* Forte***
- 1 vial **Artesunate IP 60 mg**	- 1 vial **Artesunate IP 120 mg**
- 1 ml ampoule $NaHCO_3$ inj. IP 5% w/v	- 2 ml ampoule $NaHCO_3$ inj. IP 5% w/v
- 5 ml ampoule NaCl inj. IP 0.9% w/v	- 10 ml ampoule NaCl inj. IP 0.9% w/v

*Table 7: Extracted from "Communicable Diseases Control Unit, Ministry of Health and Quality of Life, Mauritius. Malaria." * Falcinil = artesunate.*

	I.V. Use	**I.M. Use**
Falcinil*	a) Mix powder for injection with **1 ml of 5% $NaHCO_3$** until *clear solution* is obtained	a) Mix powder for injection with **1 ml of 5% $NaHCO_3$** until *clear solution* is obtained

	b) Add **5 ml of N/S or 5% w/v Dextrose** and mix	b) Add **2 ml of N/S or 5% w/v Dextrose** and mix
Falcinil* Forte	a) Mix powder for injection with **2 ml of 5% $NaHCO_3$** until *clear solution* is obtained	a) Mix powder for injection with **2 ml of 5% $NaHCO_3$** until *clear solution* is obtained
	b) Add **10 ml of N/S or 5% w/v Dextrose** and mix	b) Add **4 ml of N/S or 5% w/v Dextrose** and mix
Final concentration of solution for injection	**10 mg/ml**	**20 mg/ml**
Special precautions	1. Powder for injection should be completely dissolved to form clear solution 2. Solution for injection should be used immediately after reconstitution 3. Discard if solution for injection is cloudy or precipitate is present	

*Table 8: Extracted from "Communicable Diseases Control Unit, Ministry of Health and Quality of Life, Mauritius. Malaria." * Falcinil = artesunate.*

Delayed hemolysis starting >1 week after artesunate treatment of severe malaria has been reported in hyperparasitaemic non-immune travellers. Hence, such patients treated with intravenous artesunate should be monitored for delayed hemolytic anemia, with repeat hemoglobin testing at 7, 14, and 30 days after treatment.

Children weighing < 20 kg should receive a higher dose of artesunate (3 mg/kg bw per dose) than larger children (≥ 20 kg) and adults (2.4 mg/kg bw per dose) to ensure equivalent exposure to the drug. Artesunate may cause hyperbilirubinemia in neonates. While artesunate can be given during pregnancy, discuss with the pediatrician regarding whether breastfeeding should be stopped when it is administered to a breastfeeding woman.

The threshold for administering antibiotic treatment should be low in severe malaria. Septicemia and severe malaria are associated, and there is substantial diagnostic overlap, particularly in children. 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.

Severe malaria in pregnant women

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.

Obstetric advice should be sought at an early stage, a pediatrician alerted, and blood glucose checked frequently.

Artemisinin-resistant falciparum malaria

The WHO defines clinical artemisinin resistance as delayed parasite clearance following treatment with an artemisinin-based monotherapy or with an artemisinin-based combination therapy. This is also labeled as 'artemisinin partial resistance' and is suspected when 10% (or more) of malaria patients present with parasitemia at day three or have a parasite clearance half-life beyond five hours.

Clinically, any patient that still has a positive blood smear (of > 10 parasites/μL) after 72 hours of ACT therapy may be harboring artemisinin resistance although multiple other factors may contribute to slow parasite clearance and should be ruled out (e.g., obesity, vomiting, poor quality medication or non-compliance to medication).

Artemisinin resistance in *P. falciparum* is now prevalent in parts of Cambodia, the Lao People's Democratic Republic, Myanmar, Thailand and Viet Nam. Mutations in *P. falciparum* that can confer resistance to artemisinin have also been described in some parts of Africa like Eritrea and Uganda. Patients who have travelled to these areas and who fail ACT therapy may be suspected of being infected with artemisinin-resistant *P. falciparum*.

The optimal approach to treatment of artemisinin-resistant malaria is uncertain. For patients with uncomplicated parasitemia, extend the duration of treatment with oral artemether-lumefantrine from 3 days to 5-7 days and follow daily smears until negative.

For severe malaria that is presumed to be partially resistant to artemisinin, combine IV artesunate with IV quinine. The duration of IV therapy is as per the usual protocol for non-resistant severe malaria. Once the IV treatment is over, a three-day course with oral artemether-lumefantrine should be administered. If quinine is unavailable, give artemether-lumefantrine via nasogastric tube together with the IV artesunate for a duration not exceeding 7 days. Consider getting expert advice.

The dosage regimen for quinine is given in table 8.

- Quinine dihydrochloride[†,**] dosed as follows:
  - Loading dose: 20 mg salt/kg (= 16.4 mg base/kg) IV up to a maximum of 1400 mg salt (1150 mg base) in 5% dextrose over 4 hours[†,**].
  - Followed by: 10 mg salt/kg (= 8.2 mg base/kg) IV over 4 hours at 8- or 12-hour intervals (maximum 2100 mg base/day [= 1720 mg salt/day]), starting 8 hours after the beginning of the loading dose[†].

Table 9: Dose of quinine

Each dose of parenteral quinine must be administered as a slow rate-controlled infusion (usually diluted in 5% dextrose and infused over 4 hours). The infusion rate should not exceed 5 mg salt/kg body weight per hour.

Monitor urine output during treatment with quinine. Since quinine can increase insulin level in the blood, monitor blood sugar level 4-hourly in routine cases. Haemoglobin should also be checked regularly.

In patients with cardiac anomalies, since parenteral quinine can cause QTc prolongation, the QT interval should be monitored hourly during infusion, and the infusion should be stopped if the corrected QT interval becomes prolonged by more than 50 percent of the baseline value. The infusion can be renewed (without a bolus) once the QTc falls to <25 percent above the original value.

Important adverse effects of quinine include hypoglycemia, QT prolongation, tinnitus, reversible hearing loss, nausea, vomiting, dizziness, and visual disturbances. To avoid cardiotoxicity, a loading dose of quinine/quinidine should not be administered to patients who received mefloquine or other quinine derivatives within the previous 12 hours.

(This document is largely an extract of text taken directly from reference 1).

References

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ANNEX A

Administration of Artesunate

Adults

IV: 2.4 mg/kg/dose at 0 hours, 12 hours, and 24 hours. Administer additional doses once daily based on treatment recommendations.

Children

<20 kg: IV: 3 mg/kg/dose initially, followed by 3 mg/kg/dose at 12 hours and 24 hours; administer additional doses once daily.

≥ 20kg: IV: As per adult dose.

Remarks

Assess parasite density 4 hours after third dose of artesunate and then, every 24 hours.

After at least 24 hours of parenteral treatment, and when patient is able to tolerate oral medication, initiate a full (eg, 3 days) course of oral artemisinin-based combination therapy to complete treatment.

Kidney Impairment

No dosage adjustment necessary.

Hepatic Impairment

No dosage adjustment necessary.

Administration of Artemether-Lumefantrine

Adults

Artemether 80 mg/lumefantrine 480 mg twice daily for 3 days with the first 2 doses administered 8 hours apart.

Children

See "Table 4: Dose of artemether-lumefantrine in tablets." for details regarding dosage in children.

Remarks

One tablet of Coartem contains artemether 20 mg and lumefantrine 120 mg.

Repeat blood films daily till negative.

Kidney Impairment

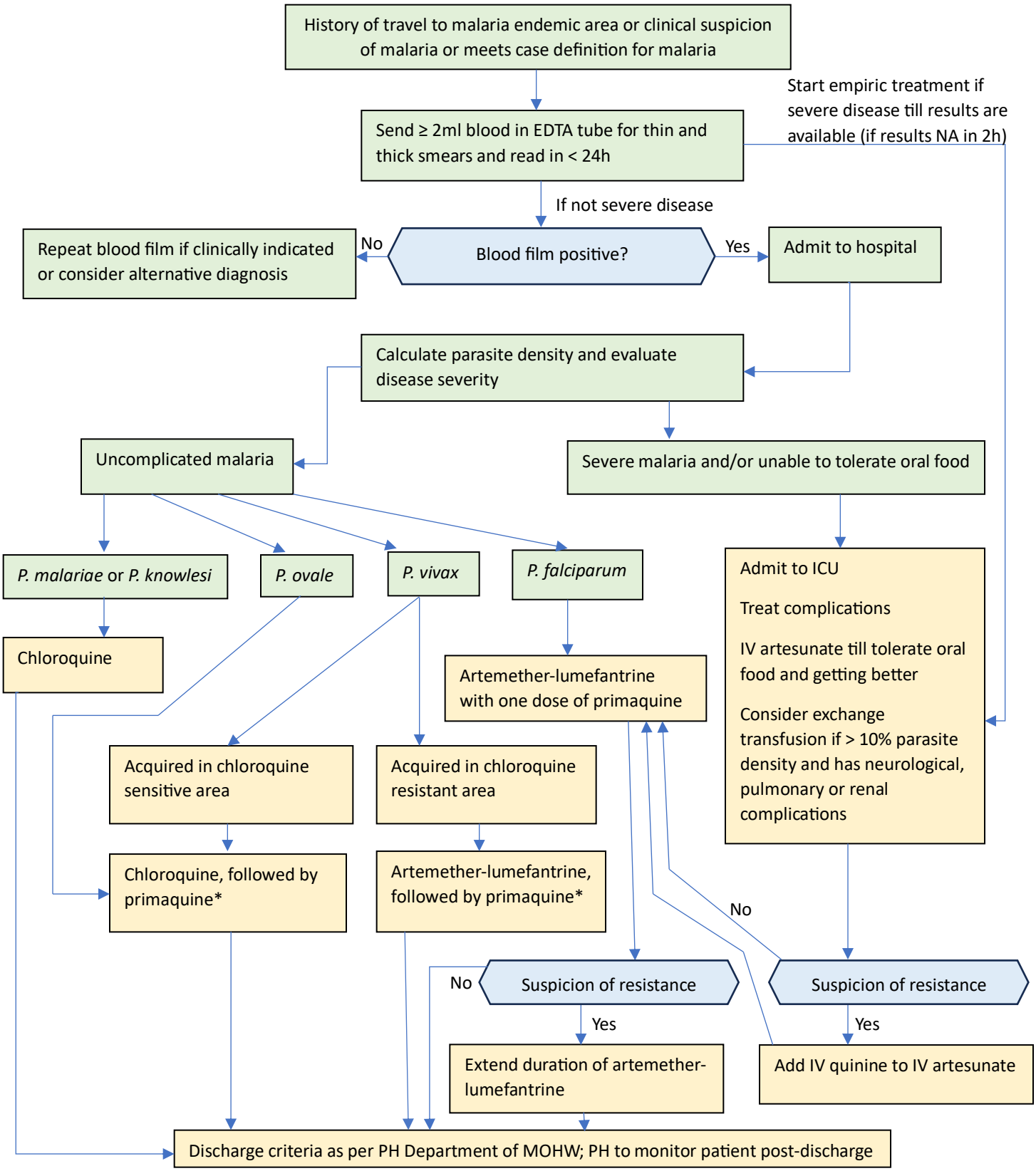
Use with caution in severe impairment.

Hepatic Impairment

Use with caution in severe impairment.

Reference: *Modified from the Drug Information section of UpToDate.*

ANNEX B



*Algorithm for treatment of malaria: PH – public health; MOHW – Ministry of Health and Wellness. * - assess for G6PD deficiency; NA – not available; see further details in main text.*