



Management and prevention of imported *Plasmodium falciparum* malaria: recommendations for clinical practice 2007

(revision of the Consensus conference 1999)

SHORT TEXT

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Every year, close to 5,000 cases of imported malaria due to *Plasmodium falciparum*, including 80% contracted in inter-tropical Africa, are reported in France and cause around twenty deaths.

Question 1: How can the diagnosis of *Plasmodium falciparum* malaria be made earlier?

Most cases of imported *P. falciparum* malaria are diagnosed in the 2 months following a trip to an endemic zone, some 6 months after, especially in migrants. An early diagnosis and the adequacy of treatment are key factors for the prognosis. Most severe or fatal cases occur because of a delayed management, due to negligence of patients or of their relatives and/or because of diagnostic mistakes. Thus, given the risk of a rapid evolution to a severe form, it is mandatory to increase the awareness of travelers and healthcare professionals as to this infection and to the preventive measures to implement before leaving for, during the stay in, and after returning from the endemic zone.

1.1 Traveler's information

Around 70% of patients presenting with imported malaria are native of an endemic country. The information must especially target this population of migrant travelers, through messages distributed by their associations, hosting organisms, travel agencies, medias (Internet, etc.), healthcare professionals and especially those dealing with small children.

1.2 Training healthcare professionals

Knowing about epidemiology and clinical signs leading to the diagnosis must be an essential part of initial and continuing education for healthcare professionals [general practitioners emergency specialists, hospital physicians, pediatricians, public health physicians, biologists, pharmacists, nurses...].

95% of *P. falciparum* malaria cases are simple forms. Fever is the main symptom. Any fever alone or associated to general, digestive, respiratory, or neurological symptoms, after staying in an endemic zone, requires an urgent medical assessment and implementing a parasitological diagnosis in emergency.

1.3 The parasitological diagnosis is an emergency

Blood sampling must be made immediately without waiting for shivering or a pyretic peak. The ideal diagnosis must associate thick and thin blood smear microscopic examination. In case of diagnostic doubt or of previous antimalarial treatment, in a clinical context, this direct examination will be followed by a rapid test (HRP-2 + pLDH) (Fig. 1). The results must be available in a maximum of 2 hours, with immediate interaction between the biologist and the clinician.

PCR may be useful in some cases but it is not used in emergency and cannot be a substitute for classical method. Thrombopenia is frequent in adults as well as in children and is a good indicator in an epidemiological and clinical context.

1.4 Can malaria be treated without parasitological confirmation?

When there is a strong epidemiological and clinical suspicion of malaria in a patient presenting with severity signs, the non-availability of parasitological diagnosis in emergency (thin smear + thick smear) should not delay the onset of treatment. Nevertheless, this should no longer be the case in metropolitan France. It is recommended to obtain parasitological confirmation in every case, as soon as possible.

Question 2: How can emergency be assessed and how should management for *Plasmodium falciparum* malaria be organized?

2.1 What is the pertinence of severity criteria defined by the WHO in 2000?

In adult patients

The definition of severe malaria defined in 1990 by the WHO was revised in 2000. Severe malaria is defined by the presence of *P. falciparum* parasitemia (asexual forms) and by one or several clinical or biological manifestations defined in the original WHO table available in the long text. These criteria were determined by studies carried out in endemic zones. Their pertinence concerning severe imported malaria remains controversial.

Table 1 gives the criteria of severe imported malaria in adults, more adapted to travelers and management in European healthcare settings. This table, built on the WHO model, also gives the frequency and the prognostic value of each criterion. Data in the course of imported malaria is insufficient for the pertinence of some criteria (especially for hyperparasitemia and icterus), and the chosen thresholds were determined according to medical expert agreement.

In children

The WHO severity criteria are the same for children and adults, except for arterial hypotension and renal insufficiency, defined according to the child's age (arterial hypotension: SAP < 60 mmHg under 5 years of age, SAP < 80 mmHg over 5 years of age; renal insufficiency: diuresis < 12 ml/kg/24h, or elevated creatinemia for the age). Isolated hyperparasitemia has no prognostic value.

2.2 Who should be hospitalized in intensive care?

Adult patients

Any *P. falciparum* malaria with at least one of the Table 1 criteria (especially those rated ++ and +++ in terms of prognostic value) must immediately be assessed with the IC specialist for a transfer to the ICU without delaying the onset of specific and symptomatic treatment. After this assessment, the patient will be hospitalized either in «acute» ICU, or in a unit for the management of post-ICU patients, or in a medical unit depending on the local organization.

Parasitemia above 4% in the non-immune adult is considered by the WHO as dangerous enough to justify severe form type of management. Nevertheless, in the absence of sufficient data in the course of imported malaria, the parasitemia thresholds suggested to choose the management level can only be determined on expert agreement.

- a) The patients presenting with at least one of the following Table 1 items will be initially managed in the «acute» ICU: coma (Glasgow score < 11), repeated convulsions, any respiratory failure, any cardio-circulatory failure, metabolic and/or hyperlactatemia acidosis, severe hemorrhage, renal insufficiency making hemodialysis mandatory, hyperparasitemia (> 15%) alone.
- b) The less severe cases but presenting with a risk of rapid worsening will be managed in a unit dedicated to post-ICU patients: simple or mild confusion, convulsion alone, minor hemorrhage, marked jaundice alone, hyperparasitemia (usually from 10 to 15%) alone, moderate renal insufficiency, well tolerated anemia alone. Fragile patients but without severity signs *stricto sensu* will be initially managed in his type of unit: aged patients, patients with comorbidities, associated bacterial infection, patients requiring a IV quinine treatment whatever the reason (emesis, pregnancy...). A pregnant patient will be jointly managed with an obstetrician.
- c) Depending on local specificities and the experience of units in the management of malaria, the patients mentioned above (in paragraph b) as requiring management in a post-ICU unit, can probably also be managed in some medical units (infectious diseases, internal medicine interne, ambulatory emergency units, gynecology-

obstetrics), especially in case of emesis, hyperparasitemia (up to 10%), or jaundice alone. In this case, the proximity of an ICU is essential, to be able to transfer the patient immediately to that unit if his condition deteriorates.

In children

There is no available data in France on the prognostic value of each severity criterion, and it seems prudent to transfer to the ICU any child presenting with one of the clinical severity criteria defined by the WHO in 2000, especially in case of prostration, any organ dysfunction leading to consciousness disorders, convulsions, dyspnea or cardio-circulatory failure, or hypoglycemia. Without one of these severity signs (especially in case of isolated hyperparasitemia), the child may be treated in a post-ICU unit or in a general pediatric unit, as long as permanent surveillance is maintained.

Question 3: Treatment regimen for uncomplicated *P. falciparum* malaria

Uncomplicated *P. falciparum* malaria is an acute episode of malaria, without any severity sign. This definition excludes sub acute visceral presentations. Malaria in specific settings (pregnancy, young child, aged patient, underlying disease, splenectomy) is classified as uncomplicated when there are no severity criteria but these patients must be followed-up carefully.

Four antimalarial drugs are recommended for adults (Table 2 and Fig. 2):

- atovaquone-proguanil or artemether-lumefantrine as first-line treatment;
- quinine or mefloquine as second-line treatment;

Halofantrine must be used only in specific settings and only during hospitalization.

The very few cases of *P. falciparum* malaria susceptible to chloroquine (Caribbean zone) may be treated with this molecule according to the WHO recommendation (10 mg/kg at H0 and H24, 5 mg/kg at H48, or a total dose of 25 mg/kg in 3 days).

In case of emesis, using IV quinine infusion (8 mg/kg every 8 hours) initially is necessary, then switching to relay treatment as soon as possible with an oral antimalarial drug at a curative dose. The combination for 3 days of quinine infusion at a usual dose and clindamycin (10 mg/kg/ every 8 hours, in 3 one hour IV infusions) is an alternative therapy validated for imported malaria in adults. It has the advantage of being a full treatment in 3 days and may be prescribed during pregnancy.

3.1 Criteria for ambulatory management in adults and children

In adults

In the following situations, ambulatory treatment may be prescribed by a general or a hospital practitioner in adults, all the criteria must be checked:

- availability of a reliable parasitological diagnosis (immediate interaction between the physician and the biologist),
- absence of a first treatment failure,
- uncomplicated malaria, without any clinical or biological severity sign,
- absence of digestive disorders (emesis, severe diarrhea, etc.) which could compromise the success of oral treatment,
- parasitemia below 2%,
- platelets $> 50,000/\text{mm}^3$, hemoglobin $> 10 \text{ g/dl}$, creatinemia $< 150 \mu\text{mol/L}$,
- absence of risk factors: physiologically aged patient, fragile patient due to an underlying disease, especially cardiopathy, and splenectomized patients,
- absence of pregnancy (higher severity for the mother and for the fetus),
- presence of patient support (anxiogenic aspect of pyrexia in malaria and no possibility of alert in case of unfavorable evolution if the patient is alone),
- confidence in the good observance and understanding of the treatment regimen (intellectual deficit, linguistic difficulties, etc.),
- guarantee of immediate treatment delivery at the pharmacy (economic assessment of patient, availability of antimalarial drug stock in neighborhood pharmacies),
- living close to a hospital institution (possible referral in case of unfavorable evolution after informing the patient and his relatives),
- possibility of telephone follow-up consultation de at H72 (D3), D7 and D28 (or, possibility to call to check on the evolution).

In difficult socio-economic situations, hospitalization of an adult may be prevented by starting the treatment in hospital, in the emergency unit or in tropical medicine consultations without appointment, with a minimal observation period of 2 hours after the first intake of antimalarial drugs, and giving the patients all the scheduled drugs. This protocol should be

supported by detailed explanations on treatment regimen, making sure they are well understood, and a formal consultation appointment at H72 (D3).

In children

In children and especially young children, the higher frequency of digestive disorders does not leave the option of complete ambulatory management. Hospitalization for the course of treatment is recommended most of the time. Nevertheless, in older children, and for treatments lasting more than 24 h, after an initial management in a short stay hospitalization unit, the remaining treatment may be given at home. This procedure is possible only if the first intakes for treatment were uneventful, if the family is able to give the treatment and observe the clinical evolution, and if the child can be seen in consultation at 72 hours (D3), D7 (in case of parasitemia still weakly positive at 72 hours), and D28, as long as all the previously mentioned criteria for ambulatory management of adults are respected.

3.2 Special cases

- **pregnancy:** only quinine has proved completely innocuous. The atovaquone-proguanil combination is not contra-indicated and may be used when necessary if there is no alternative. Mefloquine should be used only when quinine is contra-indicated, or if the plasmodium is resistant to quinine. Halofantrine is contra-indicated. The artemether-lumefantrine combination is contra-indicated during the first trimester of pregnancy. Obstetrical surveillance is mandatory.
- **travelers coming back from Amazon region (including Guyana), or border zones between Thailand, Myanmar, Laos and Cambodia:** in these zones in which resistance to mefloquine and halofantrine is high, the therapeutic alternatives are the atovaquone-proguanil combination, the artemether-lumefantrine combination, or quinine combined with doxycycline, 200 mg once a day for 7 days, or with clindamycin, 10 mg/kg every 8 h for 7 days. Intramuscular artemether could also be used, even though it would not be easy to use it as emergency treatment because a temporary approval for a given patient would be required.

3.3 Should chemoprophylaxis be maintained after treatment?

There is no reason to prescribe chemoprophylaxis after a curative treatment with any of the 5 drugs mentioned, except in the case of a new stay in an endemic zone.

3.4 Surveillance modalities

Clinical and biological surveillance including a thick blood smear is recommended at H72 (D3) (parasitemia must be inferior to 25% of the initial value), and D7 (parasitemia must be negative). Daily assessment of parasitemia is not useful. Checking at D28 is also recommended.

3.5 Therapeutic scheme for children

The first line drugs are:

- mefloquine, often preceded by an antiemetic drug such as domperidone,
- or atovaquone-proguanil,
- or artemether-lumefantrine, approved for hospital institutions.

Halofantrine, given its cardio toxicity and the risk of relapse after a single course, is a second line treatment, despite its presentation as a suspension, easy to use with children. It is indicated only when strictly necessary and with close observation by an experienced team. If a second course is not administered, the child's follow-up must be very reliable. In case of relapse after a single course, another antimalarial drug must be used. If a second course is administered, it will require hospitalization, as for the first course, the strict observance of contra-indications and precautions of use, and repeated electrocardiographic surveillance.

Quinine *per os*, which requires a perfect compliance to a long treatment, is also a second line drug (Table 3, Fig. 3). In the symptomatic neonate, treatment begins with IV quinine, then relay to a single course of halofantrine.

3.6 Detection of chemoresistance, drug dose: therapeutic consequences

Considering the impact on *P. falciparum* malaria management, research on resistance to antimalarial drugs and antimalarial drug dose (except for quinine) is not rapidly available, except on specific demand and direct contact with the rare specialized laboratories. It currently has an essentially epidemiological interest for the assessment of prophylactic and therapeutic failures and to recommend new preventive strategies.

Question 4: Treatment regimen for severe *P. falciparum* malaria

4.1 In adults

Severe imported malaria is an emergency which may become rapidly lethal. It can only be treated in an ICU.

4.1.1 Treatment with quinine and specific surveillance

Treatment

Injectable quinine remains the reference antimalarial schizonticide drug for this indication. To prevent any confusion and risk of under or overdose, dosage must be expressed in quinine-base when using quinine alone, or alkaloid-base when using combinations of alkaloid salts.

In France, the following drugs are available:

- Quinimax[®], for intravenous infusion in 1, 2, or 4 ml phials corresponding respectively to 125, 250, and 500 mg. It contains 125 mg of alkaloid-base/1 ml.
- Surquina[®], in 1 ml and 2 ml phials, containing 245 mg of quinine-base /1 ml. Quinine is under its hydrochloride formula.

To prevent mistakes, it is preferable for the institution to have only one commercial presentation available.

Using a loading dose during severe imported malaria is still recommended in adults so as to obtain an earlier efficient quinine serum level on *P. falciparum*. The loading dose is 16 mg/kg infused for 4 hours in serum glucose at 5 or 10%. The maintenance dose is 24 mg/kg/24 hours and initiated 4 hours after ending of the loading dose infusion. It should be administered either discontinuously (8 mg/kg in a minimum of 4 hours, every 8 hours), or continuously (24 mg/kg over 24 hours with an automatic electric syringe). It should be combined with a serum glucose infusion (5 or 10%) containing the adequate electrolytes. The total treatment should last 7 days; relay treatment *per os* may be initiated at the 72nd hour, if possible. It is not necessary to begin any further chemoprophylaxis after a complete quinine treatment.

Any previous treatment before hospitalization with quinine at a curative dose (in the previous 2 days), with halofantrine or mefloquine (if the last dose was taken less than 12 hours before), as well as an increased corrected QT interval (QTc) > 25%, are contra-indications for a loading dose because of an increased risk of cardiotoxicity. During pregnancy, quinine must be used with the same doses but there is an increased risk of hypoglycemia. Quinine has no abortive effect. There is no available data for obese patients (> 120 kg) so as precautionary measure; the loading dose should not be superior to 1,500-1,800 mg and the total daily maintenance dose 2,500-3,000 mg .

The only strict contra-indications to quinine use are a documented history of biliary hemoglobinuric fever, hyper sensibility to quinine, and severe rhythm/conduction disorders (these conditions can ideally benefit from parenteral treatment with artemisinin derivatives).

Specific surveillance

A daily assessment of total plasma quinine level for a minimum of 72 hours is recommended, especially for the more severe presentations. Sampling is performed at the end of infusion in case of discontinuous administration. Efficient plasma quinine level should range between 10 and 12 mg/L (30 to 36 mmol/L). The 72nd hour assessment is mandatory to detect under or overdose. The arbitrary dose reduction at the 72nd hour in case of renal insufficiency can only be accepted when quinine serum level surveillance is not available. Quinine serum level surveillance is recommended during the entire treatment course in case of hepatic and renal insufficiency.

An electrocardiogram including QRS and QTc assessment should be performed before the onset of treatment and daily during the complete course. Electrocardioscopic monitoring

should also be implemented. The following risk factors should lead to especially careful monitoring: aged patient, underlying cardiopathy, hypokaliemia, concomitant intake of a drug lengthening the QT interval, of a diuretic or antihypertensive drug.

Glycemia should be assessed every hour during the charge-dose, then every four hours.

Monitoring parasitemia is recommended until its negativation. Parasitemia may increase during the first 24 hours of a well-managed treatment. This increase is not meaningful for the prognosis.

4.1.2 Use of parenteral artemisinin derivatives (artemether and artesunate) in monotherapy

Large studies of severe malaria conducted over the last 10 years in Asia in adults showed that IV artesunate was superior to IV quinine and better tolerated. Nevertheless, artesunate is not available in Europe and IM artemether is available only with a specific nominative temporary authorization of use. The current indications for artemisinin derivatives remain very limited for severe imported malaria: contra-indications for quinine (see above) and patient coming back from a zone of resistance to quinine. Thus, it would be good to see those derivatives and especially IV artesunate, become rapidly available.

4.1.3 Symptomatic treatment of visceral failure and surveillance

The management of coma includes screening for hypoglycemia, an early orotracheal intubation, preventing cerebral edema and secondary lesions, especially by correcting any hyponatremia. An EEG and brain imaging should be performed in case of a focal sign or unexplained coma. The interest of continuous surveillance with a trans-cranial Doppler should be confirmed. A systematic preventive anticonvulsant treatment is not recommended.

Dehydration should be compensated with crystalloid solutes. Managing shock should be made according to recent recommendations on septic shock (including the use of hydrocortisone hemisuccinate). In case of shock and/or metabolic acidosis, screening for a bacterial co-infection (present in 30 to 50% of the cases) and very early initiation of a probabilistic broad-spectrum IV antibiotherapy (3rd generation cephalosporins, piperacillin-tazobactam, etc.) are mandatory. Using activated protein C should be discussed for each case.

The management of lesional pulmonary edema is identical to that of acute respiratory distress syndrome recommended recently.

Oligoanuric renal insufficiency persisting after rehydration requires implementing sequential or continuous extra-renal filtration. Rapid high volume rehydration and/or IV furosemide and/or weak dopamine doses is not recommended.

Infusion of globular concentrates should be suggested according to recent French recommendations. Infusion of fresh frozen plasma is recommended in case of hemorrhage associated to DIVC. Infusion of platelets is indicated for significant bleeding in case of thrombopenia. When there is no hemorrhage, infusion should be discussed for every case with thrombopenia < 10 to 20,000/mm³.

Apart from specificities linked to treatment with IV quinine, surveillance in ICU is not specific, keeping in mind that during the first 72 hours of treatment the evolution is very unpredictable.

4.1.4 Use of antibiotics and adjuvant treatments

Antibiotics

In adults, doxycycline (or clindamycin during pregnancy), should only be used when there is a suspicion of strains with decreased susceptibility to quinine (jungles in the Amazon region and the Far-East).

Other adjuvant treatments

There is currently no argument justifying the use of exsanguino-transfusion in severe imported malaria.

A high dose corticotherapy with an anti-edematous and/or anti-inflammatory aim is not recommended.

None of the other adjuvant treatments (anti-TNF antibodies, iron chelator, pentoxifyllin, cyclosporine A, N-acetyl cysteine, etc.) has proved its clinical efficiency.

4.2 Managing severe malaria in children

Severe malaria in children should be managed in a pediatric ICU. IV quinine remains the reference treatment for severe malaria in children. The loading dose, discussed in 1999, is not recommended in children because no benefit was demonstrated for the prognosis, and because of the risk of toxicity.

The standard dose is 24 mg/kg/d of quinine-base or alkaloid-base, corresponding to an 8 mg/kg infusion every 8 hours. IV quinine is administered in infusions lasting a minimum of 4 hours, in serum glucose at 5%, preferably with an automatic electric syringe, with permanent ECG surveillance. Quinine serum level should be assessed after the 24th hour. Glycemia should be carefully assessed. Relay treatment per os is initiated as soon as the child's state allows it.

Hyperparasitemia ranging between 4 and 10%, with no other sign of severity, may be treated with an oral antimalarial drug, preferably in a post ICU unit. Very strict surveillance is mandatory in children under 30 months of age, because of the increased risk of worsening.

Question 5: How can imported malaria be prevented?

More than 90% of imported malaria cases occur in travelers who did not follow, or badly followed the 2 groups of efficient and complementary preventive measures:

- protection against mosquito bites
- and chemoprophylaxis.

5.1 How can access to prevention and its observance be improved?

5.1.1 Who should recommend this prevention?

All the general practitioners, pediatricians, in hospital, private practice, or working in institutions dealing with preventive care of children and mothers, and occupational physicians should recommend this prevention. The prescription of antimalarial drugs for prophylaxis is a medical act.

Centers for advice to travelers are reference structures and preventive measures against malaria should be given when a person comes in for yellow fever vaccination. Consultation in these centers should be reserved first for travelers with risk factors.

The pharmacist participates in giving information and has an important role as a counselor.

The role of travel agents is limited to raising awareness of travelers for the risk of contracting malaria. Travel destination fliers must mention clearly the risk of malaria in the concerned destinations and the need to consult with a physician before departure, so as to learn how to use preventive measures.

5.1.2 What are the obstacles to giving advice and delivering prescriptions and how should these be dealt with?

No awareness of the need for prophylaxis in travelers.

It is important to increase the travelers' awareness as to the risk of malaria, through healthcare professionals, travel agents, and in airports, especially for migrants.

Strengthening continuous medical education.

Teaching preventive measures for malaria must be included in the physicians' initial training and must be a main goal of continuous medical education.

Heterogeneity of data.

The recommendations are published every year in the "Bulletin Epidemiologique Hebdomadaire (BEH)" by the Institut de Veille Sanitaire (French CDC, www.invs.sante.fr), under the aegis of the Conseil Supérieur d'Hygiène Publique de France, now called the Haut Conseil de la Santé Publique (HCSP French committee for public health). The mandatory use of computerized data in medical offices should give access to reliable and easy to use data for all physicians, especially on the Internet site of the Institut de Veille Sanitaire.

Socio-economic obstacles.

Some populations, especially migrant families, do not go to consultations for prevention. Reimbursing this type of consultation, as well as antimalarial drugs, would open access of prevention to the poorest people. When choosing a type of prevention, this economic dimension should be taken into account, to prevent delivering prescriptions too expensive for some travelers.

5.2 Individual anti-vectorial prophylaxis in children and adults

Three measures of anti-vectorial protection, alone or combined, have proved their efficacy for the prevention of malaria, transmitted by anopheles, night-time mosquitoes: the mosquito

bednet impregnated with insecticides, garment protection wearing clothes impregnated with insecticides, and skin repellents.

5.2.1 The mosquito bednet impregnated with pyrethrinoids

This is recommended during sleep, at any age. Before a child can walk, this is also recommended when the child is awake. As a matter of precaution, the young child should be washed before being put under the mosquito net, to remove the repellent applied previously.

5.2.2 Clothes impregnated with permethrin

Wearing large clothes impregnated with permethrin, covering as much of the skin as possible, is recommended at any age.

5.2.3 Skin repellents

The recommendations are those of the Agence française de sécurité sanitaire des produits de santé (AFSSAPS French agency for drug approval), published in BEH n° 24 June 12, 2007 (Table 4). The HCSP thinks that it is possible, when at risk of a severe disease, to follow recommendations of CDC which allows using DEET as soon as two months of age, as long as used concentrations are weak (30%) and given contra-indications and precautions of use are taken into account.

The Groupe de Pédiatrie Tropicale de la Société Française de Pédiatrie (French pediatric Society, Tropical diseases committee) recommends using the following for children less than 30 months of age:

- below 6 months of age, no repellent should be used, because of the immaturity of the hematoencephalic barrier;
- from 6 to 30 months of age: DEET from 10 to less than 30%, citriodiol between 20 and 30%, IR 3535 20% (above 12 months of age).

The repellent should be applied on the smallest non-covered skin area without lesion, away from the eyes, lips, and hands, no more than once a day in children under than 30 months of age.

5.3 Chemoprophylaxis

Chemoprophylaxis (CP) can be used only as a physical and chemical complementary measure of protection against mosquitoes.

5.3.1 What is the required information for a prescription of CP?

Some concern the traveler and history or underlying diseases, contra-indications, drug interaction with other ongoing treatments, as well as the traveler's solvency and his financial capacity for access to healthcare during the stay and once back. The high cost of some chemoprophylaxis (atovaquone-proguanil, mefloquine) limits its use in some travelers (migrants, young people, associations) and requires informing these people before they leave. The prescribing physician should collect all elements allowing the assessment of the real risk of exposure to transmission of malaria during the trip.

A physician should be able to contra-indicate the trip in some settings: pregnancy, child too young to be able to receive the adequate prophylaxis in a zone of strong resistance.

5.3.2 Is chemoprophylaxis still necessary?

A CP (chemoprophylaxis) is not necessary in some countries, regions, or cities the list of which is regularly updated.

For all the other destinations, especially intertropical Africa, CP is still necessary and the following recommendations may be made.

Stay \geq 7 days: CP is always necessary

Stay < 7 days:

- zone with a high risk of transmission:

CP is always necessary.

- zone with a low risk of transmission:

CP is not absolutely necessary. The decision not to prescribe CP depends on:

- (i) the conditions of the stay,
- (ii) the strict observance of anti-mosquito protection rules,
- (iii) and the possibility, in the months following the stay to consult in case of fever, mentioning the trip to an endemic zone for malaria.

5.4 What are the drugs and doses recommended?

cf. Tables 5 and 6

During pregnancy, chloroquine and proguanil may be prescribed with no restriction. Atovaquone-proguanil and mefloquine may be used during pregnancy. Doxycycline is not advised during the first trimester of pregnancy and is contra-indicated after the second trimester.

5.5 Place of the stand-by treatment

The recommendations are to limit the use of stand-by treatment:

- ⇒ to situations of isolation putting the traveler at more than 12 hours of a healthcare structure,
- ⇒ to stays during which patients do not take chemoprophylaxis (close and repeated stays, prolonged expatriations),

and making sure that the requirements, indications, and modalities of this treatment are well understood.

Even if he has to take a stand-by treatment, the traveler must be informed of the need to consult rapidly with a physician, for the assessment of treatment efficacy, and possibly to supplement it or change it, and to screen for another possible cause of fever than malaria.

Despite their high sensitivity, the rapid diagnostic tests for malaria available on the market are not recommended for self-diagnosis. Several studies reported that many travelers are not able to use these tests correctly or to interpret the results.

The stand-by treatment should be very restricted in children, especially since it has not been assessed for this condition.

What molecules may be used for stand-by treatment?

The efficacy, the mode of administration, and tolerance make atovaquone-proguanil (Malarone[®]) and artemether - lumefantrine (Riamet[®] and Coartem[®]) a good choice for stand-by treatment in adults.

There is a risk for counterfeit or inadequately dosed drugs which may not be adapted to stand-by treatment when buying outside of France.

There is no ideal stand-by treatment for children. Mefloquine or artemether - lumefantrine, and even atovaquone-proguanil may be prescribed for children above 5 kg of body weight. Halofantrine is no longer indicated because of its cardiotoxicity.

Figure 1. Protocol for the parasitological diagnosis of malaria.

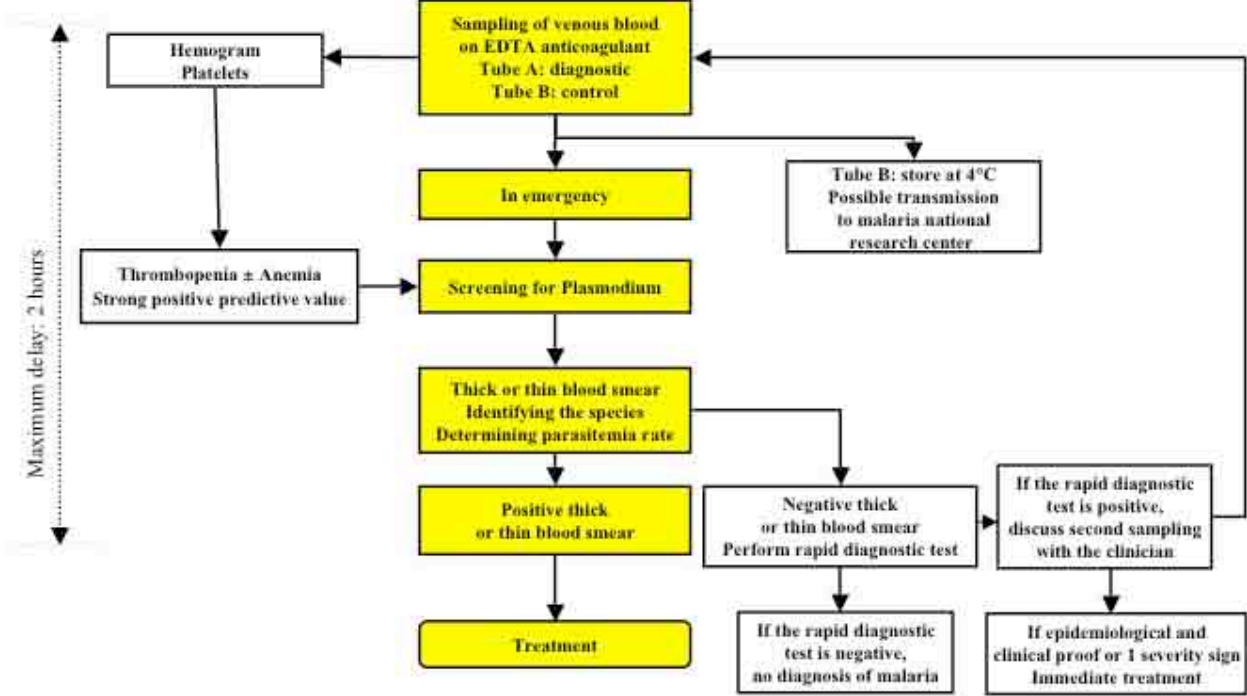


Table 1.
Criteria for the definition of severe imported malaria in adults

Prognosis	<i>Biological or clinical criteria</i>	Frequency
+++	Any neurological failure including: - obtundation, confusion, somnolence, prostration - coma with a Glasgow score < 11	+++
+++	Any respiratory failure including: - if MV or NIPPV: PaO ₂ /FiO ₂ < 300 mmHg - if no ventilation PaO ₂ < 60 mmHg and/or SpO ₂ < 90% in ambient air and/or RF > 32/mn - radiological signs: interstitial and/or alveolar image	+
+++	Any cardiocirculatory failure including: - systolic arterial pressure < 80 mmHg and signs of peripheral circulatory insufficiency - patient treated with vasoactive drugs whatever his arterial pressure - signs of peripheral circulatory insufficiency without hypotension	++
++	Repeated convulsions: at least 2 per 24h	+
++	Hemorrhage: clinical definition	+
+	Jaundice: clinical or total bilirubin > 50 µmol/L	+++
+	Macroscopic hemoglobinuria	+
+	Severe anemia: hemoglobin < 7 g/dl, hematocrit < 20%	+
+	Hypoglycemia: glycemia < 2.2 mmol/L	+
+++	Acidosis: - plasma bicarbonates < 15 mmol/L - or acidemia with a pH < 7.35 (close surveillance when bicarbonates < 18 mmol/L)	++
+++	Any hyperlactatemia: - when superior to the upper limit of normal - <i>a fortiori</i> if plasma lactate > 5 mmol/L	++
+	Hyperparasitemia: when parasitemia > 4%, especially in the non immune patient (according to the clinical context severity thresholds range from 4 to 20%)	+++
++	Renal insufficiency: - creatinemia > 265 µmol/L or blood urea >17 mmol/L - and diuresis < 400 ml/24h despite rehydration	+++

MV: mechanical ventilation; NIPPV: non invasive positive pressure ventilation; RF: respiratory frequency

Table 2. Major antimalarial drugs used in adults for the treatment of uncomplicated imported *P. falciparum* malaria and choice criteria

Antimalarial drugs	Line of treatment	Arguments «for»	Arguments «against»	Contra-indications	Main adverse effects	Dose
Atovaquone + proguanil Malarone®	1 st line	- short treatment - well tolerated	- emesis - weak bioavailability (atovaquone)	- none unless allergy to one of the constituents	- nausea and emesis	- 4 tablets in 1 intake qd for 3 days during a meal (for a total of 12 tab. over 48 h) - above 40 kg of body weight
Artemether + lumefantrine Riamet® Coartem®	1 st line	- rapidly efficient - short treatment - well tolerated	- weak bioavailability (lumefantrine)	- not recommended during pregnancy and breast feeding - high grade intra-ventricular conduction disorders	- headaches, vertigo - digestive disorders	- 4 tablets in 1 intake at H0, H8, H24, H36, H48 and H60 (2 times/d for 3 d) with food or drink and fatty product (for a total of 24 tablets in 60h) - above 35 kg of body weight
Quinine - Quinimax® cp at 500 and 125 mg - Quinine Lafran® cp at 500 and 250 mg - Surquina® cp at 250 mg	2 nd line	- may be used during pregnancy	- not too well tolerated - long treatment	- no ci except for a history of biliary hemoglobinuric fever or allergy (rare) - high grade intra-ventricular conduction disorders	-cinchonism* : digestive disorders, headaches, tinnitus ++ (≅D2) - rhythm disorders (overdose)	- 8 mg/kg /8 hours for 7 days (= 1 tablet at 500mg x3/d in the adult of average weight; no more than 2.5 g/d) - IV infusion if emesis (same dose)
Mefloquine Lariam® cp at 250 mg	2 nd line	- short treatment	- badly tolerated	- history of neuro-psychic diseases (including convulsions), intolerance to mefloquine, and biliary hemoglobinuric fever - treatment with valproic acid - severe hepatic insufficiency - relay with halofantrine*** - not recommended during pregnancy	- digestive disorders, headaches, vertigo (frequent) - neuro-psychic diseases (including convulsions) : rare but potentially severe	- 25 mg/kg in 3 intakes every 8 hours - usually: 3 tablets then 2 tablets (the 1 tablet if > 60 kg)

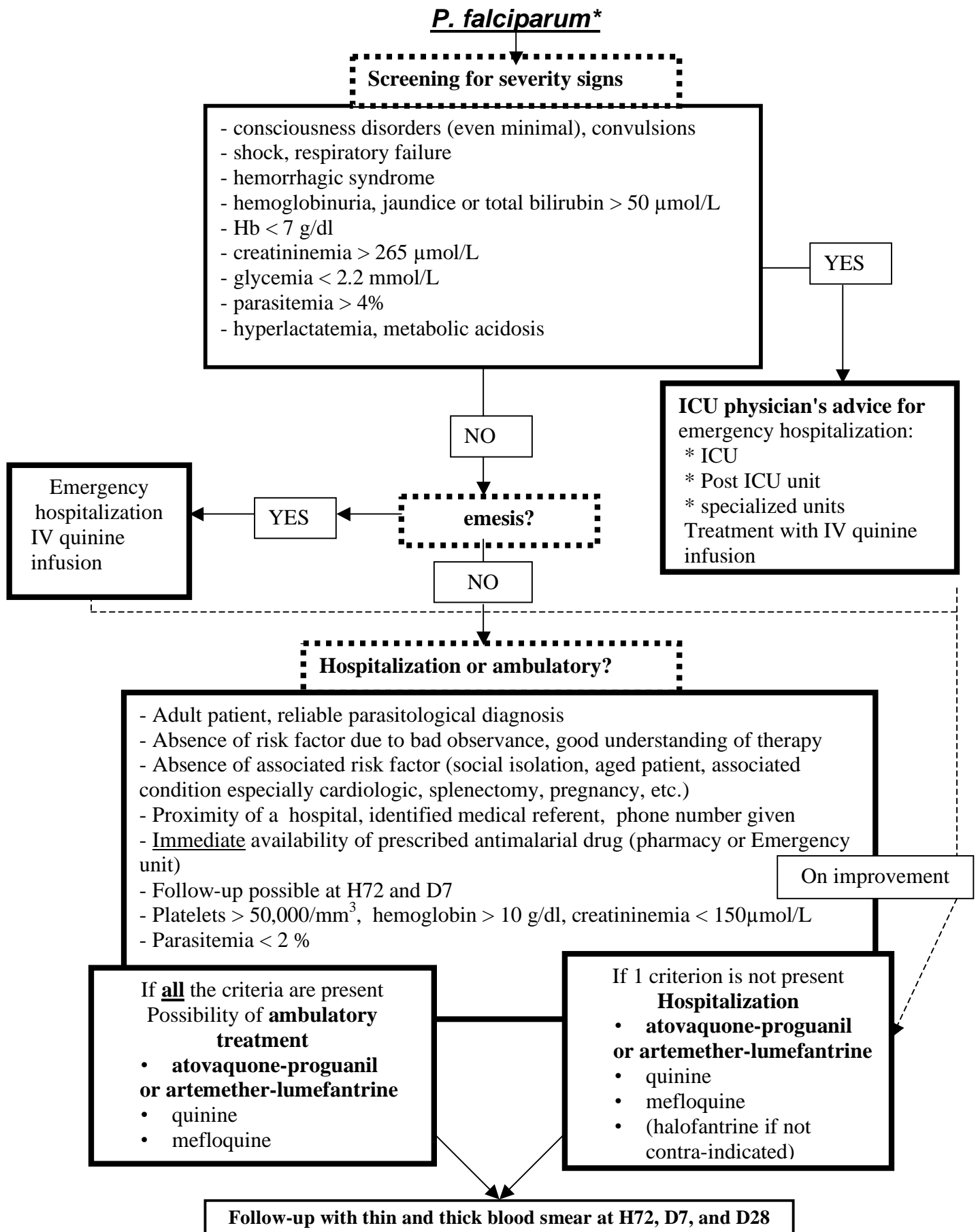
Halofantrine Halfan® 250 mg tablets and suspension at 100mg/5ml	3 rd line (if specific situation)	- rapid action - short treatment - well tolerated	-cardiotoxicity - weak and variable bioavailability (possible rare failure)	- history of rhythm disorders and biliary hemoglobinuric fever - hypokaliemia, - drug increasing the QT interval - increased QTc - cardiac insufficiency - relay with mefloquine*** - pregnancy	- cardiotoxicity: very frequent increased QTc; rhythm disorders (rare/severe)	- 25 mg/kg in 3 intakes every 6 hours, fasting (usually 2 tablets x 3) + 2 nd course at D7-D10 in the non immune (at reduced doses**) - in hospital settings (ECG surveillance especially between the 2 nd and 3 rd intake)
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* the occurrence of cinchonism and especially tinnitus is not a sign of overdose but one of high level tissue concentration of quinine: it should not lead to decreasing the doses

** non validated dose, increased risk of cardiotoxicity at full doses

*** potentiation of cardiotoxicity

Figure 2. Therapeutic management of imported malaria in adults.



* if biparasitism or species not identified, treat as *P. falciparum*

Table 3.
Oral treatments for uncomplicated *Plasmodium falciparum* malaria in children in France

Molecule	Galenic presentation	Dose	Advantages	Drawbacks	Precautions of use
Mefloquine	Lariam® Tablets at 250 mg	25 mg/kg Scheduled as: 15 mg/kg H0 and 10 mg/kg H12 or 8 mg/kg H0, H6-8, H12-16	One course in one day Cardiac tolerance	No adapted galenic presentation for the infant and young child Digestive intolerance	Antipyretic treatment first Antiemetic treatment before oral intake Repeat oral intake if emesis within the following hour
Atovaquone-proguanil	Malarone® Tablets for adults at 250 mg/100 mg Tablets for children at 62.5 mg / 25 mg	20/8 mg/kg/d for 3 days (single daily intake) 5-< 9 kg: 2 tabs child / d 9-< 11 kg: 3 tabs child / d 11-< 21 kg: 1 tab adult / d 21-< 31 kg: 2 tabs adult / d 31-< 40 kg: 3 tabs adult / d ≥ 40 kg: 4 tabs adult / d	Cardiac tolerance	No adapted galenic presentation for the infant and young child Treatment length Digestive intolerance	Intake during a meal or milk feeding Repeat oral intake if emesis within the following hour
Artemether-lumefantrine	Riamet® or Coartem® Tablets at 120 mg / 20 mg	6 oral intakes H0, H8-12, H24, H36, H48, H60 5-< 15 kg: 1 tab / by intake 15-< 25 kg: 2 tabs / by intake 25-< 35 kg: 3 tabs / by intake ≥ 35 kg: 4 tabs / by intake	Cardiac tolerance	No adapted galenic presentation for the infant and young child Treatment length	Repeat oral intake if emesis within the following hour
Halofantrine	Halfan® Suspension at 100 mg / 5 mL Tablets at 250 mg	1 st course: 24 mg/kg or 8 mg/kg at H0, H6, H12 2 nd course at D7 (if prescribed, use a reduced dose)	Adapted galenic presentation Digestive tolerance	Cardiac toxicity Requires 2 courses Modalities of the 2 nd course not well documented	Strict observance of contra-indications ECG before and after treatment for both courses Do not repeat oral intake if emesis whatever the timing
Quinine per os	Quinimax® Tablets at 500 and 125 mg Surquina® Tablets at 250 mg	8 mg/kg three times a day for 7 days	Long-term documentation	Cinchonism Risk of intoxication Treatment length	Total compliance mandatory

Before 6 years of age, tablets must be crushed

Figure 3. Modalities of treatment for *P. falciparum* malaria in children in France.

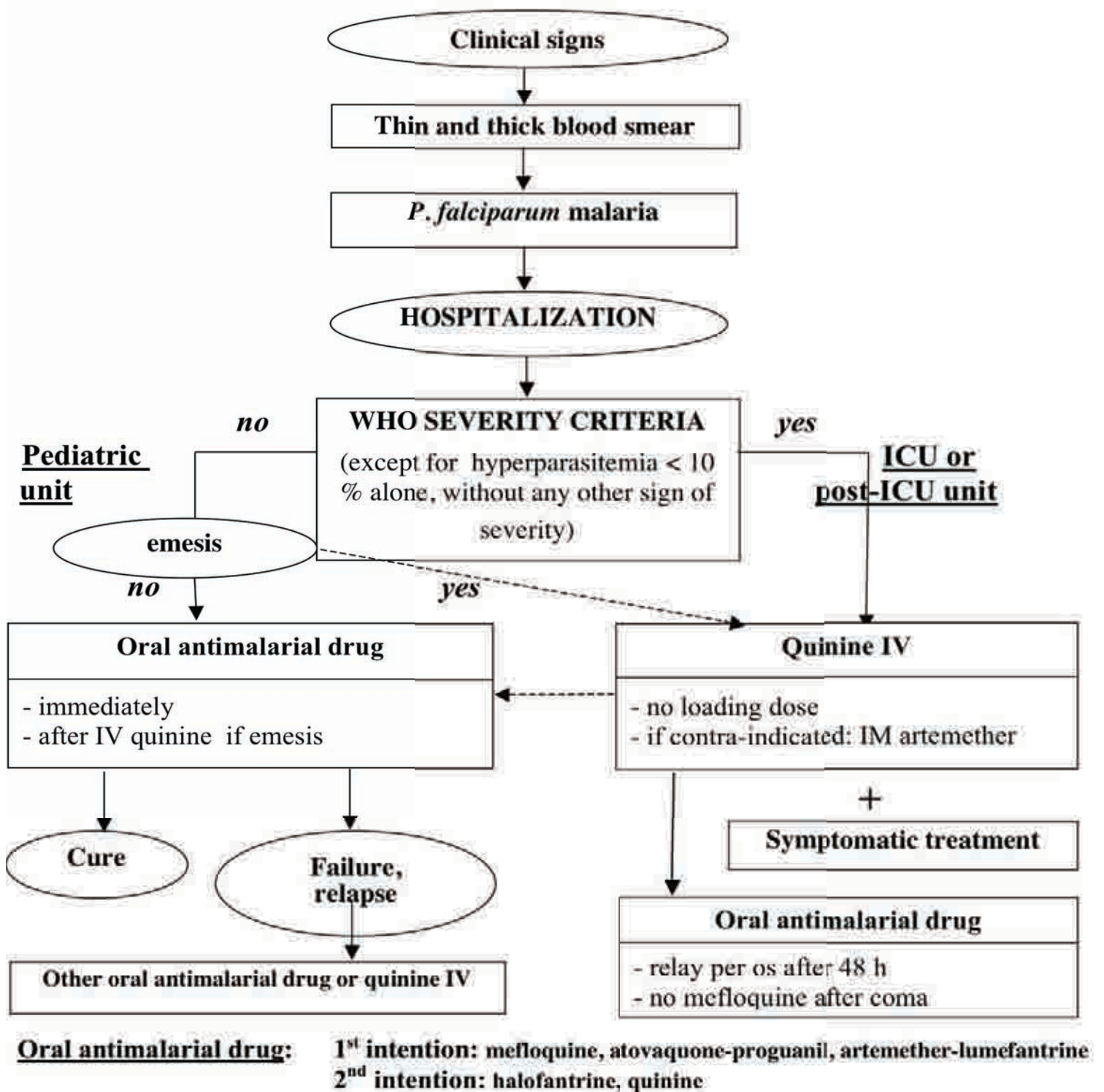


Table 4.
AFSSAPS Recommendations for the use of skin repellents (BEH 2007)

Age range / state	Active substance	Concentrations	Example of commercial formulations
From 30 months to 12 years	Citriodiol ^a	20 to 50%	<i>Mosiguard (spray)</i> <i>Antimosquitospray</i>
	IR 3535	20 to 35%	<i>Akipic (gel)^d</i> , <i>Cinq sur cinq Tropic lotion^e</i> <i>Duopic lotion for adults</i> , <i>Manouka citronella lotion tropical zones</i> , <i>Mouskito (spray or roller)</i> , <i>Prebutix tropical zones (gel or lotion)</i>
	DEET ^b	20 to 35%	<i>Mouskito Tropic^f (spray or roller)</i> , <i>Mouskito Travel^f stick</i> , <i>Mouskito Tropical spray^f</i>
	KBR 3023 ^c	20 to 30%	<i>Insect skin screen, child</i>
>12 years	Same substances than in the previous category	same concentrations except for DEET: from 20 to 50%	All the previously mentioned + <i>Insect skin screen adult (gel or spray)</i> , <i>King</i> , <i>Mouskito tropical spray</i> , <i>Pikpa adults</i> , <i>Repel insect adults</i>
	+ KBR 3023 ^c	20 to 30%	<i>Insect screen special tropic</i>
Pregnancy	IR 3535	20 to 35%	<i>Akipic (gel)</i> , <i>Cinq sur cinq Tropic lotion</i> , <i>Duopic adult lotion</i> , <i>Manouka citronella lotion tropical zones</i> , <i>Mouskito (spray or roller)</i> , <i>Prebutix tropical zones (gel or lotion)</i> ,

^a unless there is a history of convulsions ;

^b unless there is a history of convulsions; prevent contact of diethyl toluamide (DEET) with plastics, varnish, watch glass, and glasses; caution DEET decreases the efficacy of sunscreens (by 1/3).

^c limit consecutive use to one month

^d the manufacturer recommends using it above 4 years of age

^e the manufacturer recommends using it above 36 months of age

^f the manufacturer recommends using it above 5 years of age

Precautions of use: no more than 3 applications/ day. Avoid contact with the eyes. Do not apply on mucosa or extensive skin lesions. Do not apply if there is a history of skin allergy.

Table 5.
Prophylactic scheme recommended in adults (except during pregnancy) according to travel destination

<i>Travel destination</i>	<i>Prophylactic scheme</i>	<i>Length</i>
Group 1 countries	Chloroquine 100 mg (Nivaquine®) Once a day	Stay + 4 weeks after
Group 2 countries	Chloroquine 100 mg + proguanil 200 mg (Nivaquine® + Paludrine®) or Savarine® Once a day during a meal	Stay + 4 weeks after
or	Atovaquone 250 mg + proguanil 100 mg (Malarone®) Once a day during a meal	Stay + 1 week after Limited to 3 consecutive months
Group 3 countries	Atovaquone 250 mg + proguanil 100 mg (Malarone®) Once a day during a meal	Stay + 1 week after Limited to 3 consecutive months
or	Mefloquine 250 mg (Lariam®) Once a week	10 d before+ stay + 3 weeks after
or	Monohydrate de doxycycline 100 mg (Doxypalu® , Granudoxy®Ge) Once a day, in the evening	Stay + 4 weeks after

Table 6.
Antimalarial drug chemoprophylaxis in children in France in 2007

<i>Molecule</i>	<i>Presentation</i>	<i>Dose</i>	<i>Comments, length, indications</i>
Nivaquine® (chloroquine)	Syrup at 25 mg = 5 ml Breakable tablets at 100 mg	1.5 mg/kg/d < 8.5 kg: 12.5 mg/d ≥ 8.5-16 kg: 25 mg/d ≥ 16-33 kg: 50 mg/d ≥ 33-45 kg: 75 mg/d	Beware of accidental intoxication Stay + 4 weeks after Group 1 countries (and 2 in combination with proguanil)
Paludrine® (proguanil)	Breakable tablets at 100 mg	3 mg/kg/d 9-16 kg: 50 mg/d ≥ 16-33 kg: 100 mg/d ≥ 33-45 kg: 150 mg/d	Only in combination with chloroquine Stay + 4 weeks after Group 2 countries
Lariam® (mefloquine)	Breakable tablets at 250 mg	5 mg/kg/week 15-19 kg: 1/4 tab/week > 19-30 kg: 1/2 tab/week > 30-45 kg: 3/4 tab/week	Contra-indications: convulsions, SCUBA diving 10 d before + stay +3 weeks after Group 3 countries
Malarone for children® (atovaquone- proguanil)	Tablets at 62.5 mg/25 mg	5-< 7 kg: ½ tab/d (no approval) 7-< 11 kg: ¾ tab/d (no approval) 11-< 21 kg: 1 tab/d 21-< 31 kg: 2 tab/d 31-≤ 40 kg: 3 tab/d	Take during a meal or with milk feeding Stay + 7 days after Length: 3 consecutive months maximum Group 2 & 3 countries
Malarone® (atovaquone- proguanil)	Tablets at 250 mg/100 mg	1 tab/d weight > 40 kg	
Doxypalu® (doxycycline) Granudoxy®Ge (doxycycline)	Tab at 50 mg Tab at 100 mg Tab at 100 mg	< 40 kg: 50 mg/d ≥ 40 kg: 100 mg/d	Contra-indication: age < 8 years Take with the evening meal Stay + 4 weeks after Group 3 countries

Before 6 years of age, tablets must be crushed.