the children's hospital at Westmead

ANTI-MALARIAL THERAPY

PRACTICE GUIDELINE ©

DOCUMENT SUMMARY/KEY POINTS

- Malaria remains an important cause of illness and death in children in countries in which it is endemic.
- Malaria must be considered in any patient who has visited a malarious area and presents with a febrile illness.
- Malaria should be considered if there is history of recent travels within past 12m.
- The severity of symptoms depends on infecting species, the level of parasitaemia and the immune status of the patient.
- Early diagnosis and prompt, effective treatment of malaria within 24-48h of the onset of malaria symptoms is crucial.
- All patients suspected to have malaria should have blood film and malaria antigen testing done in addition to the other investigations to assess the severity of the disease.
- Artemether +lumefantrine (Riamet®) is the 1st line for treatment of uncomplicated malaria.
- Artesunate is the first line for treating severe malaria
- Prophylaxis is strongly recommended for children travelling to high-risk areas.

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READ ACKNOWLEDGEMENT

- All medical officers evaluating children with fever and administering anti-malarial therapy should read and acknowledge this document.

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Introduction

Malaria remains an important cause of illness and death in children in countries in which it is endemic. Malaria is caused by Plasmodium parasites, which are transmitted to humans through the bites of infected mosquitoes. Malaria must be considered in any patient who has visited a malarious area and presents with a febrile illness.

Of the five Plasmodium species that infect humans (*P. falciparum*, *P. vivax*, *P. knowlesi*, *P. malariae* and *P. ovale*), *P. falciparum* and *P. knowlesi* are the most pathogenic and *P. falciparum* is the most resistant to standard anti-malarials. *P. knowlesi* has recently been recognized as an important cause of malaria in parts of Southeast Asia.

Who is at risk for malaria?

Anyone can get malaria. Most cases occur in people who live in countries with malaria transmission. People from countries with no malaria can become infected when they travel to countries with malaria (Figure. 1) or through a blood transfusion (although this is very rare). An infected mother can transmit malaria to her infant before or during delivery.

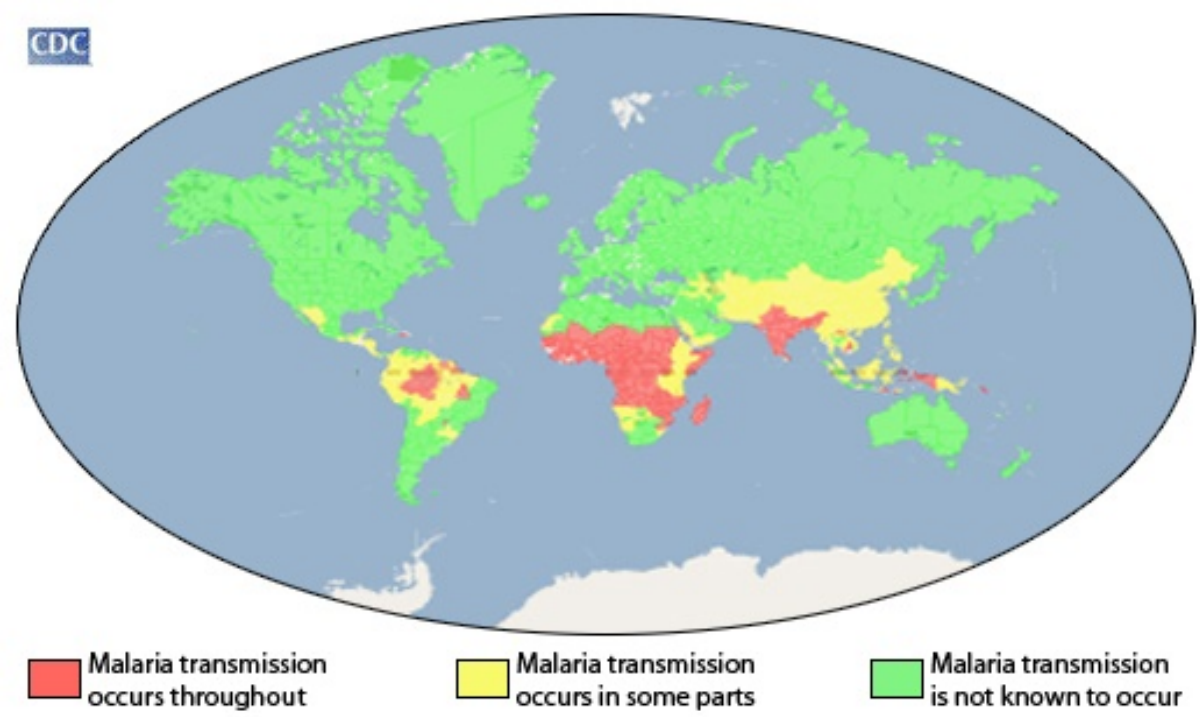


Figure. 1: Approximate parts of the world where malaria transmission occurs
http://www.cdc.gov/malaria/about/distribution.html

Who is most at risk of getting very sick and dying from malaria?

1. People infected with *P. falciparum* who have a high parasitaemia are most at risk of dying from malaria.
2. People who have little or no immunity to malaria, such as young children and pregnant women or travellers coming from areas with no malaria, are more likely to become very sick and die.

Incubation Period

Incubation period is 7 to 30 days, shorter periods with *P. falciparum* and longer with *P. malariae.* Incubation period can last for weeks or months, especially with *P. vivax* and *P.ovale* if the patient has been on prophylaxis. Malaria should be considered if there is history of recent travels within past 12 months.

Clinical Manifestations

The severity of symptoms depends on infecting species, the level of parasitemia and the patient's immune status of the patient.

Uncomplicated Malaria:

- The first symptoms of malaria are non-specific and similar to those of a minor systemic viral illness including: headache, lassitude, fatigue, abdominal discomfort, and muscle and joint aches.
- These symptoms usually followed by fever, chills, perspiration, anorexia, vomiting and worsening malaise.
- Malaria may also present with lethargy, poor feeding and cough in young children.

Severe Malaria:

- Delayed treatment or giving ineffective or poor quality medicine, particularly with *P. falciparum* malaria, result in potentially lethal severe malaria within hours to days.
- Severe malaria defined as one or more of the following, occurring in the absence of an identified alternative cause and in the presence of *P.faciparum* asexual parasitaemia. usually manifests with one or more of the following complications:
  - Altered mental state OR
  - Jaundice (serum bilirubin >50umol/L), OR
  - Renal impairment OR

- Multiple convulsions OR
- Oliguria OR
- Unable to sit, stand or walk unaided OR
- Respiratory distress OR
- Severe anaemia (Hb<50mg/dl or haematocrit <15%) OR
- Hypoglycaemia (plasma glucose <2.2 mmol/L), OR
- Acidosis (base deficit of >8mEq/L or plasma bicarbonate level <15mmol/L) OR
- Hyperparasitaemia *P.falciparum* parasitaemia >10%.

Diagnosis

1. All patients suspected to have malaria should have the following investigations:

   Investigations to confirm diagnosis
   - Microscopy: thick and film films
   - Malaria antigen test

2. Investigations to assess the severity of malaria
   - Full blood count to detect anaemia and thrombocytopenia
   - Electrolytes, Urea and Creatinine (EUC) to detect renal impairment
   - Blood glucose to detect hypoglycaemia
   - Blood gas to detect metabolic acidosis
   - Liver function tests (LFT)

Note:

- A single negative blood film or negative antigen test does not exclude the diagnosis of malaria, particularly if the patient has recently taken anti-malarial drugs.
- 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.
- If both the slide examination and the malaria antigen results are negative, malaria is extremely unlikely, and the other causes of the illness should be sought and treated.

Management

Core principles:

- Early diagnosis and prompt, effective treatment of malaria within 24-48 hours of the onset of malaria symptoms is crucial.
- Uncomplicated *P. falciparum* malaria can progress rapidly to severe forms of the disease which is almost always fatal without treatment, especially in immunocompromised patients.
- Use of antimalarial treatment should be limited to patients who truly have malaria and the adherence to full treatment course must be promoted to reduce the spread of drug resistance.
- Infectious diseases advice and admission if required

Treatment of uncomplicated malaria

Options	Antimicrobial	Dose	Comments
1st line	Artemether +lumefantrine tablets (Riamet® 20+120 mg)	5-14 kg: 1 tablet 15-24 kg: 2 tablets 25-34 kg:3 tablets >34 kg: 4 tablets **6 doses orally to be given at 0,8,24, 36, 48 and 60 hours**	Give with fatty food of full-fat milk.
2nd line	Atovaquone + proguanil (Malarone Junior ® tablets 62.5 mg+25 mg; Malarone® tablets 250+100 mg)	5-8 kg: 2 Malarone Junior® tablets 9-10 kg: 3 Malarone Junior® tablets 11-20 kg: 1 Malarone® tablets 21-30 kg: 2 Malarone® tablets 31-40 kg: 3 Malarone® tablets >40 kg: 4 Malarone® tablets **Dosed orally once daily for 3 days.**	Give with fatty food of full-fat milk.
3rd line	Quinine sulfate + either: Doxycycline **OR** Clindamycin	-Quinine sulfate 10 mg/kg (max 600 mg) orally, 8 hourly for 7 days -Doxycycline child >8 years: 2 mg/kg (max 100 mg) orally, 12-hourly for 7 days (which can start after day 1 of quinine therapy) -Clindamycin child> 1 month 5 mg/kg (max 300 mg) orally, 8-hourly for 7 days.	

Consider:

A single dose of primaquine 0.25 mg/kg (up to 15 mg) orally with the above combination to patients with *P. falciparum* malaria (except infants < 6months) to reduce transmission of infection. G6PD testing is not required.

Note:

- Artemisinin resistance has been reported in some of Southeast Asia, resulting in reduced efficacy of artemisinin-based combination therapy (1st line treatment) against *P. falciparum*.

- Consider switching to 3rd line treatment (combination of quinine + either clindamycin or doxycycline) in patients with slow response to 1st line therapy (ie persisting parasitaemia after 72 hours of therapy.

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

- To prevent relapse caused by dormant parasites in the liver, treat with a 14-day course of primaquine 0.5 mg/kg (up to 30 mg) orally once daily. If nausea and vomiting are troublesome, give 0.25 mg/kg (up to 15 mg) orally 12-hourly. Primaquine should be given in all transmission settings, except for infants <6 months and children with G6PD deficiency.
- In children with G6PD deficiency, consider preventing relapse by giving primaquine 0.75 mg/kg orally once a week for 8 weeks, with close medical supervision for potential primaquine-induced haemolysis.

Treatment of severe malaria

- **Supportive care:** Severe malaria is associated with a variety of manifestations and complications, which must be recognized promptly and targeted as shown below:

Manifestation or complication	Immediate management
Coma (cerebral malaria)	Maintain airway, place patient on her or his side, exclude other treatable causes of coma (e.g. hypoglycaemia, bacterial meningitis); avoid harmful ancillary treatments, intubate if necessary and avoid aggressive fluid resuscitation.
Hyperpyrexia	Administer tepid sponging, fanning, a cooling blanket and paracetamol
Convulsions	Maintain airways, treat promptly with IV or rectal diazepam or midazolam. Check blood sugar
Hypoglycaemia	Check blood glucose, correct hypoglycaemia and maintain with glucose-containing infusion. Threshold for intervention is <3mmol/L for children <5years and <2.2mmol/L for older children.
Severe anaemia	Transfuse with screened fresh whole blood.
Acute pulmonary oedema	Prop patient up at an angle of 45◦, give oxygen, give a diruretic, stop intravenous fluids, intubate and add positive end-expiratory pressure or CPAP in life-threatening hypoxaemia.
Acute kidney injury	Care to be taken with fluid resuscitation. Exclude pre-renal cause, 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); give Vitamin K injection.

Treatment of severe malaria

Options	Antimicrobial	Dose	Comments
1st line	Artesunate	3 mg/kg if < 20 kg, 2.4 mg/kg if >20 kg IV on admission and repeat at 12 and 24 hours, then once daily until oral therapy is tolerated.	• Orally if parenteral artesunate is not immediately available, • Once a patient has received at least 24 hours of parenteral therapy and can tolerate oral medications, complete treatment with 3 days of oral artesunate.
2nd line	Quinine dihydrochloride	20 mg/kg IV over 4 hours as a loading dose, then 10 mg/kg IV over 4 hours (starting 4 hours after the loading dose is completed), 8 hourly until oral therapy is tolerated.	• If parenteral artesunate is not immediately available • IV loading dose of quinine is not required in all patients (please refer to note below table) • Once a patient has received at least 24 hours of parenteral therapy and can tolerate orally, complete treatment with 3 days of ACT. • Patient needs cardiac monitoring and monitoring of BP and serum glucose.

Note:

- Mortality from severe *P. falciparum* malaria is lower with IV artesunate than with IV quinine.
- IV loading dose of quinine is not required if the patient has received:
  - ≥3 doses of quinine or quinidine in the last 48 hours
  - Mefloquine prophylaxis in the last 24 hours
  - A treatment dose of mefloquine in the last 3 days.
- Consider combining 1st and 2nd line therapy for patients with slow improvement especially if there was history of travel to South East Asia where there is an increased rate of artemisinin resistance.
- If treatment with IV quinine continues for longer than 48 hours, reduce maintenance doses avoid accumulation and in patients with renal impairment, extend the interval as follows:
  - Normal renal function: 5-7 mg/kg 8 hourly
  - CrCl 10-50 mL/minute: 8-12 hourly
  - CrCl <10 mL/minute: 24 hourly

Additional considerations for clinical management:

1. Patient who can't tolerate oral medications, parenteral antimalarial therapy for severe malaria can be given for 1-2 days but must always be followed by a full 3-day course of artesunate.
2. Anti-emetics are potentially sedative and may have neuropsychiatric adverse effects, which could mask or confound the diagnosis of severe malaria. They should therefore be used with caution.
3. Management of seizures: seizure can be caused by cerebral malaria and can be caused by high fever (febrile convulsion). Patients who have more than two seizures within a 24 hour period should be treated as for severe malaria. If the seizures continue, the airways should be maintained and anticonvulsants given (parenteral/rectal benzodiazepines or intramuscular paraldehyde). There is no evidence that prophylactic anticonvulsants are beneficial in otherwise uncomplicated malaria, and they are not recommended.
4. In patients with suspected severe malaria and in other high-risk groups, such as patients living with HIV/AIDS, absence or delay of parasitological diagnosis should not delay an immediate start of antimalarial treatment.

Criteria for management as an outpatient:

All patients should be admitted for the initial 24-48 hours in hospital. Outpatient management can be considered in consultation with ID team for children WITHOUT any of the following:

- Parasitaemia >1%
- Child <12 months old
- Significant co-morbidity eg: splenectomised patients
- Unable to tolerate oral medication
- All cases of *P. falciparum*, *P. malariae* and *P. knowlesi* malaria and any malaria cases where the species cannot be confirmed within 24 hours require assessment in hospital.
- Severe malaria

Management of co-travellers:

All co-travellers of a malaria case with similar high risk malaria exposure should be tested for malaria.

Follow-up for treatment failure

Patients should be reviewed for clinical and parasitological cure at Day 0, 1, 2, 3,7,14 and 28 day.

A 28-day follow-up is recommended as the minimum standard to allow national malaria control programmes to capture most failures with most medicines.

Patients should be advised that if there is recurrence of fever in the next 3 months they should seek medical advice and repeat blood film.

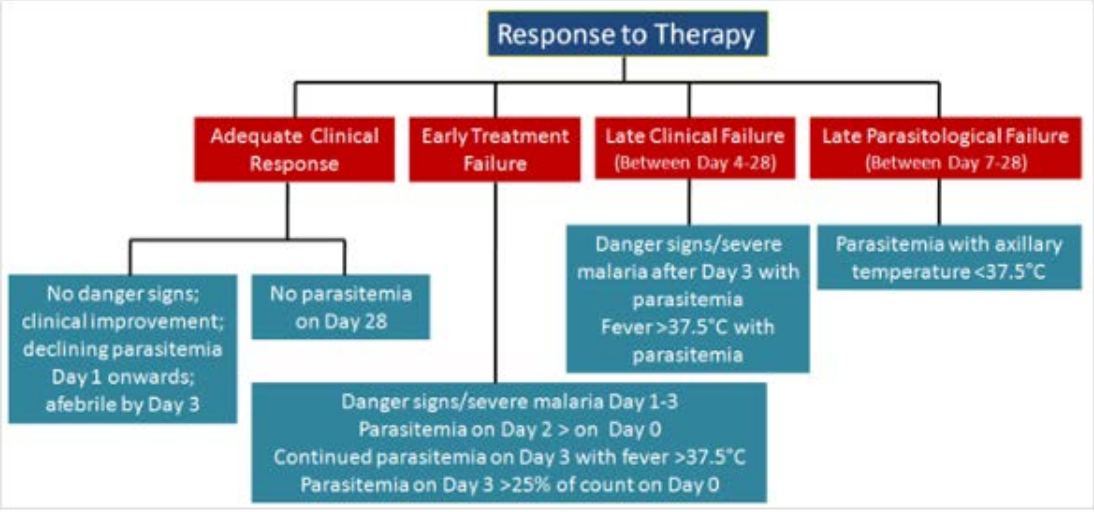


Figure. 2: WHO definitions of malaria treatment failure

Chemoprophylaxis

Prophylaxis is strongly recommended for children, pregnant women, and people staying in malaria-endemic regions for longer than 8 weeks, people with complex travel itineraries, and people travelling to high-risk areas.

The development of widespread multidrug-resistant strains of Plasmodium falciparum throughout the world, but particularly in South-East Asia, complicates recommendations for prophylaxis.

There is considerable variation in the malaria prophylaxis recommendations made by different health authorities and experts. Useful information regarding the malaria risk and the drug susceptibility profile for specific geographical locations is available from:

- World Health Organization. International travel and health 2010. www.who.int/ith/ITH2010chapter7.pdf
- Centers for Disease Control and Prevention. Travelers' health—Yellow book. http://wwwnc.cdc.gov/travel/yellowbook/2010/chapter-2/malaria-risk-information-andprophylaxis.aspx
- Alternatively, travel medicine clinics, advisory services and other experts can provide appropriate information.

Travellers to malarious areas should be advised that chemoprophylaxis is not always effective and any fever while away or after return needs urgent medical consultation and investigation.

There is no drug regimen that is completely safe and effective against malaria. The decision to use chemoprophylaxis must, therefore, be made by balancing the risk of disease against the potential efficacy and toxicity of the drug(s) to be used.

Malaria prophylaxis should be considered when immigrants from malarious areas who are resident in Australia return to a malarious area.

Chloroquine-resistant *P. falciparum* has spread worldwide, so chloroquine is not recommended for prophylaxis.

Areas with chloroquine-resistant malaria

For prophylaxis in areas with chloroquine-resistant malaria (including Pacific Island Nations, South East Asia, Indian subcontinent, China, Africa, South America and the Middle-East).

Options	Chemoprophylaxis	Doses	Comments
1st line	Atovaquone+proguanil (Malarone Junior ® tablets 62.5mg + 25 mg; Malarone® tablets 250+100 mg)	11- 20 kg: 1 Malarone Junior® tablet 21- 30 kg: 2 Malarone Junior® tablets 31- 40 kg: 3 Malarone Junior® tablets >40kg: 4 Malarone® tablets **Dosed orally, once daily**	• Give with fatty food or full fat milk. • Start 1 to 2 days before entering a malarious area, and continue for 7 days after leaving.
2nd line	Doxycycline (Child >8yrs)	Child > 8 years: 2mg/kg up to 100 mg orally, once daily	Start 1 to 2 days before entering, and continuing for4 weeks after leaving the malarious area
3rd line	Mefloquine 250 mg tablet	5- 9 kg: 31.25 mg [= 1/8 tablet]; -10- 19 kg: 62.5 mg [= 1/4 tablet]; 20- 29 kg: 125 mg [= 1/2 tablet]; 30- 44 kg: 187.5 mg [= 3/4 tablet]) **Dosed orally, once weekly.**	• Start 2 to 3 weeks before entering, and continuing until 4 weeks after leaving the malarious area. • Mefloquine is contraindicated in patients with neuropsychiatric disorders, epilepsy or cardiac conduction defects.

Areas with mefloquine-resistant malaria

For prophylaxis in areas with mefloquine-resistant malaria (including parts of South-East Asia), use doxycycline or atovaquone+proguanil. Doses as above.

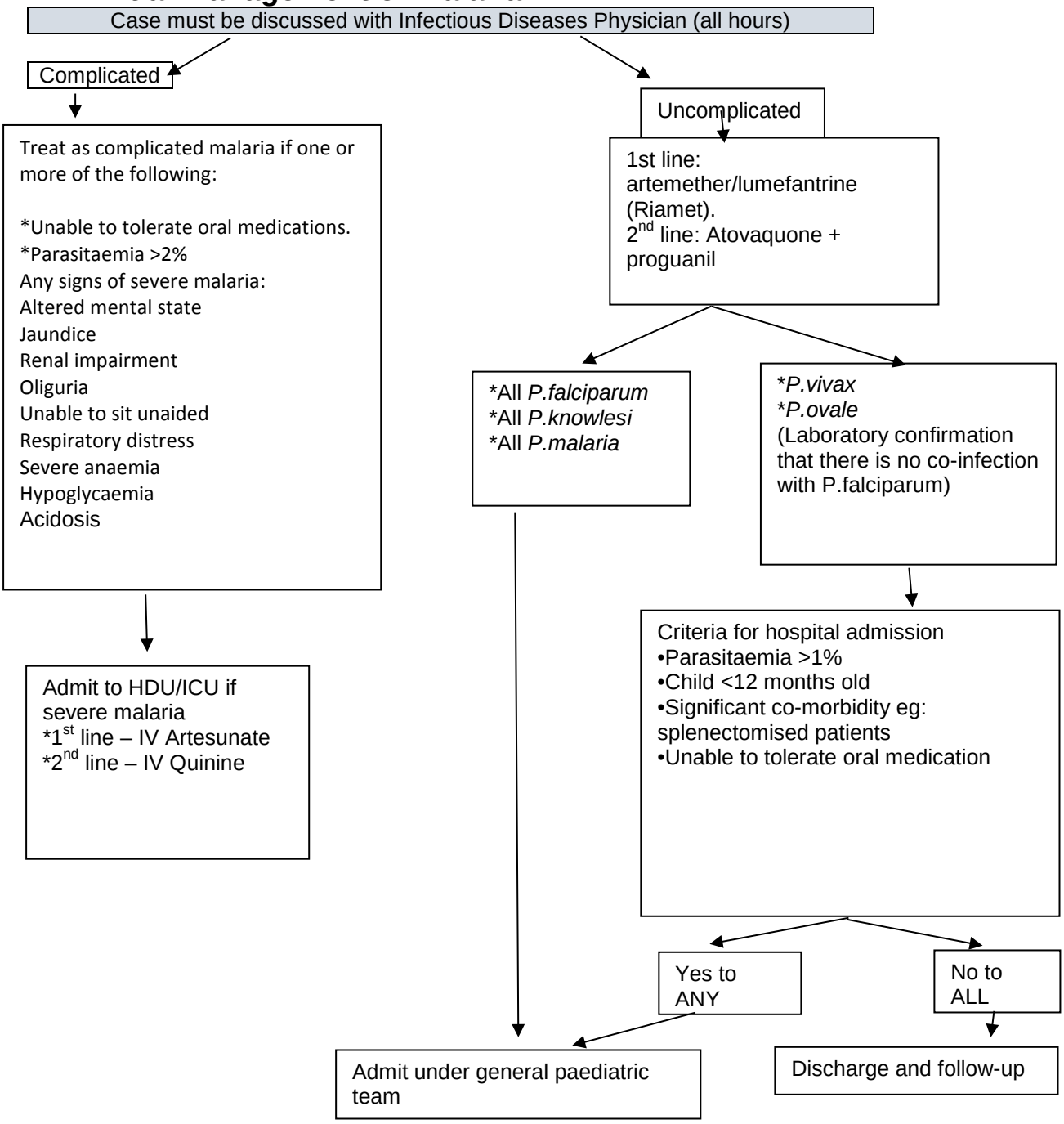
Infection (vector) avoidance

Significant protection is conferred by the simple vector avoidance measures of:

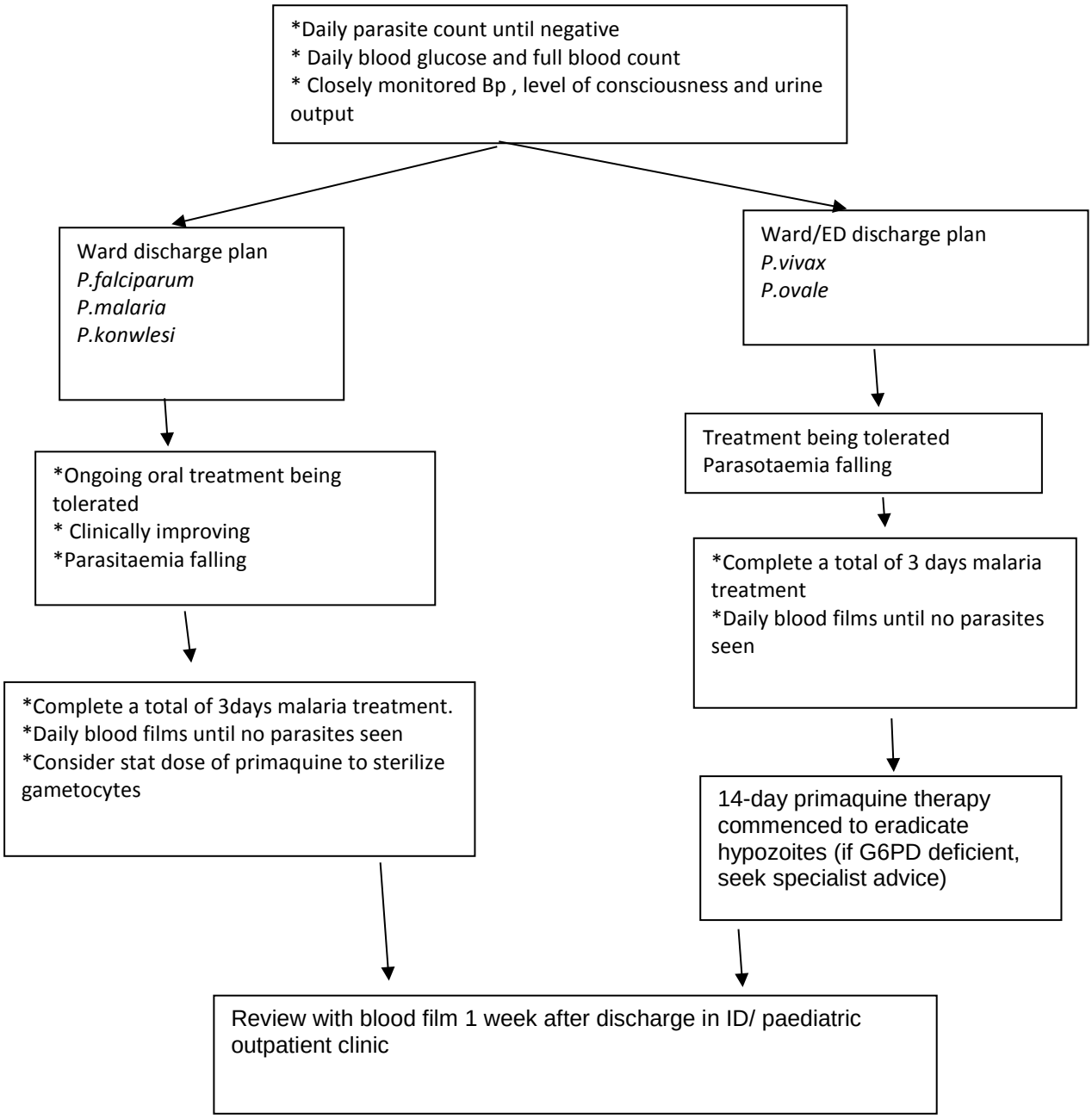
- Using effective personal insect repellent and an insecticide for indoor use
- Wearing light-coloured long trousers and long-sleeved shirts in the evening;
- Sleeping in screened accommodation or using mosquito nets
- Avoiding outside activities between dusk and dawn;
- Avoiding perfume and aftershave.

Appendix

Initial management of malaria



Ward monitoring and discharge plan



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