

Guideline

Malaria - Assessment and management in children

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Applicable to	All Children's Health Queensland staff				
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Purpose

This guideline is to provide a standardised approach to the initial assessment and management of malaria in children.

Scope

This guideline provides information for Children's Health Queensland staff caring for paediatric patients.

Related documents

- [CHQ-PROC-01035 Antimicrobial Restrictions](#)
- [CHQ Antimicrobial restrictions list](#)
- [CHQ-PROC-01001 Medication – Prescribing](#)
- [CHQ-PROC-01039 Medication - Administration](#)

Acronyms

ARDS	Acute respiratory distress syndrome
CHQ	Children's Health Queensland
ECG	Electrocardiogram
Esp	Especially
FBC	Full blood count
G6PD	Glucose-6-phosphate dehydrogenase
GCS	Glasgow Coma Scale
Hgb	Haemoglobin
ICU	Intensive care unit
ID	Infectious diseases
IV	Intravenous
LDH	Lactate dehydrogenase
LFT	Liver function tests
QCH	Queensland Children's Hospital
RBC	Red blood cells
SAS	Special access scheme
TGA	Therapeutic Goods Administration - Australia
U&E	Urea and electrolytes

Guideline

1. Background

- Malaria, particularly that due to *P. falciparum*, is a medical emergency, and management includes immediate treatment and close follow-up.
- If the species is not unequivocally identified, the case should be treated as *P. falciparum* until further identification.
- Unless there is a strong reason to indicate otherwise, malaria should be treated as chloroquine resistant.
- Unless special circumstances prevail (see [Section 3.3](#)), and consultation with an infectious diseases physician has taken place, all patients with malaria due to *P. falciparum* should be admitted to hospital to receive initial treatment under observation to ensure tolerance of treatment and to confirm with a response treatment.
- Whenever feasible, children should be admitted to hospital for at least the first 24 hours of treatment. However, it is recognised that this will not always be feasible.
- Severe or complicated disease (see [Section 3.6 for "Chemotherapy of severe OR complicated P. falciparum malaria"](#)) requires parenteral therapy and close clinical monitoring, preferably in an intensive care unit.

2. Algorithm for the initial assessment and management of malaria in children

Triage

All febrile or ill patients with a history of travel to a malaria-endemic area in the prior 6 months should be assessed urgently. Early diagnosis and assessment of severity is vital to avoid malaria deaths.

Urgent investigations – all patients should have:

- Thick & thin blood films and malaria rapid antigen tests. Send to laboratory immediately **and ask for a result within 1 hour**.
- Full blood count (FBC), urea & electrolytes (U&Es), liver function tests (LFTs) and blood glucose.
- Blood culture(s) for typhoid and/or other bacteraemia, serum for dengue serology etc.
- Urine dipstick (for haemoglobinuria) and culture. If the patient has diarrhoea, send a stool for microscopy and culture.

- If falciparum malaria is confirmed, do the following: ask the laboratory to estimate the parasite count – e.g. % of RBCs parasitised
- Clotting screen, arterial blood gases and 12-lead ECG – required in **complicated** infection (see below).

Blood tests show:

- Vivax
- Ovale
- Malariae

Outpatient therapy may be appropriate depending on clinical judgement.

Blood tests show:

- Falciparum
- Mixed infection or species not characterised

Consider admission of all cases to hospital
Urgently assess severity
 See text for discussion of criteria for outpatient management

Blood tests show:

No malaria
 A negative film and/or antigen test does not exclude malaria.
Consider other travel-related and non-travel related illness

Empirical therapy for malaria should be avoided unless the patient is severely ill. Seek expert advice before commencing this.

Blood films daily for 2 more days. Malaria is unlikely with 3 negative blood films.

Treatment of uncomplicated malaria (all types):

a) **First choice:** Artemether/ Lumefantrine 20+120 mg (Riamet®) for all cases
 Dose:
 Infant 0 to 14 kg: 1 tablet;
 Child 15 to 24 kg: 2 tablets;
 Child 25 to 34 kg: 3 tablets;
 Child > 34kg: 4 tablets.
 Best taken with fatty food e.g. glass of milk or biscuit.
 Give dose orally at 0, 8, 24, 36, 48 and 60 hours.

b) **Second choice:**
 Atovaquone/ Proguanil (Malarone®) 250/100 mg orally
 Child 10 to 20 kg: 1 tablet;
 Child 21 to 30 kg: 2 tablets;
 Child 31 to 40 kg: 3 tablets;
 Adult : 4 tablets.
 Give dose orally once daily for 3 days.

If slow response to artemether/lumefantrine e.g. parasitemia at 72 hours, follow with atovaquone/proguanil course.

Give patients with vivax (0.5 mg/kg) or ovale (0.25 mg/kg) or mixed infection primaquine daily for 14 days to eradicate liver phase. Commence primaquine with last dose of artemether/ lumefantrine after excluding G6PD deficiency.

Complicated malaria = 1 or more of:

- Extreme weakness (e.g. inability to walk or sit).
- Impaired consciousness (measure GCS) or seizures **check blood glucose urgently**.
- Hypoglycaemia.
- Parasite count **more than or equal to 2%** (Note: lower counts do not exclude severe malaria and cases with prior immunity (from endemic countries) may tolerate higher parasite counts. Discuss with ID).
- Haemoglobin less than 80 g/L.
- Spontaneous bleeding/disseminated intravascular coagulation.
- Haemoglobinuria (without G6PD deficiency).
- Renal impairment or electrolyte/acid-base disturbance (pH less than 7.3).
- Pulmonary oedema or respiratory distress syndrome.
- Shock (algid malaria); may be due to Gram negative bacteraemia.

Essential features of general management

- Commence antimalarials immediately (see "Severe or complicated malaria" box on the right)
- Treatment must be started within 1 hour of the diagnosis and the first dose supervised by a medical officer using antimalarials from the emergency department imprest

Complicated (Severe) malaria

- Admit to ICU
- Monitor blood glucose regularly (esp. if using IV quinine)
- Consider ECG monitoring if using IV quinine
- Transfuse if Hgb <5g/dL
- If hypotensive, give broad spectrum empiric antibiotic cover - start IV Cefotaxime
- To reduce the risk of haemolytic acute kidney injury, give paracetamol 15 mg/kg (up to 1 g) orally or enterally, 6 to 8 hourly for 72 hours.

Severe or complicated malaria:
Artesunate IV 3mg/kg (if >20kg 2.4mg/kg) stat, then repeat at 12 hours and 24 hours and then daily until oral therapy can be given.

If malaria acquired from Mekong Delta area (Thailand, Vietnam, Cambodia, Laos, Myanmar) give Artesunate IV with Quinine IV.

Loading dose: Quinine 20mg/kg IV infusion in 5% glucose over 4 hours (no loading dose if patient taking quinine or mefloquine already)

and then Maintenance dose: 10mg/kg IV infusion (over 4 hours) every 8 to 12 hourly. See text for sequential oral therapy. Seek expert advice as soon as possible.

After artesunate course, check FBC, LFT, Urea and electrolytes (plus LDH and haptoglobin if >10% drop in Hgb) at 1, 2, 3 and 4 weeks.

3. General principles of management

Initial management depends on many factors, including the infecting species of malaria, the severity of infection, the patient's age, pre-existing immunity, the pattern of drug resistance in the area of acquisition as well as the safety, availability, and cost of antimalarial drugs.

Clinicians should address the following questions in order to initiate effective treatment:

- **Is this infection caused by *P. falciparum*?**
 - This is critical, as treatment varies according to the species of malaria.
- **Is this a severe or complicated infection? (see [Section 1](#))**
 - Severe or complicated malaria requires parenteral therapy and sometimes an exchange transfusion.

3.1 Criteria for severe Falciparum Malaria

Any one or more of the following 11 features:	
1	Impaired consciousness or coma
2	Severe normocytic anaemia
3	Renal failure
4	Pulmonary oedema or acute respiratory distress syndrome (ARDS)
5	Hypoglycaemia
6	Circulatory collapse, shock
7	Spontaneous bleeding/disseminated intravascular coagulopathy
8	Repeated generalized convulsions
9	Acidaemia/ acidosis
10	Haemoglobinuria
11	Parasitemia of greater than 2 % (greater than 100 000/microlitre)

3.2 Management of Falciparum Malaria

All *P. falciparum* malaria in Australia should be treated as chloroquine resistant.

3.3 Inpatient or outpatient management?

- All non-immune patients (e.g. patients who have only visited a malaria endemic country or patients who have been out of an endemic country for more than three (3) months) with *P. falciparum* malaria, whether severe or not, should be admitted to hospital in order to ensure tolerance of antimalarial drugs and to detect complications or early treatment failure.
- Patients who may have some immunity to malaria (e.g. have been living in an endemic country for years and have recently arrived in Australia) may be treated as outpatients provided the following criteria can be filled:
 - No features of complicated or severe malaria are present.
 - Parasite count is less than 2%.
 - No vomiting.
 - Patient is not pregnant.
 - Patient older than 12 months / weighs more than 10kg.

- Careful instructions regarding dosing schedules, side effects and what action to take if therapy is not tolerated or the patient deteriorates, can be given to the patient or their guardian, in a language they understand.
- The first dose of medication is supervised in hospital.

3.4 Severe infection with *Plasmodium falciparum*

- Severe *P. falciparum* infections, as defined by the criteria in [Section 3.1 'Criteria for severe falciparum malaria'](#) may have a mortality rate of 20 % or higher. Patients with these infections require immediate hospitalisation and urgent, intensive medical management. They are at risk of all the complications defined in [Section 3.1 'Criteria for severe falciparum malaria'](#) as well as permanent neurologic deficits, chronic renal insufficiency, and death.
- When managing a patient with severe or complicated falciparum malaria, consultation with an infectious or tropical disease expert is strongly recommended.
 - All patients with severe *P. falciparum* infections and those who are unable to tolerate drugs orally should receive intravenous artesunate ([Section 3.7 – dosing recommendations](#)).
 - If artesunate is not available, intravenous quinine may be given as an alternative.
 - When quinine is administered to a patient who has taken mefloquine or halofantrine in the previous two (2) weeks, there is a risk of drug-induced cardiac arrhythmia; such patients should be monitored electrocardiographically.
 - Once infection is under control the patient should be changed to oral therapy.
 - Clinicians should avoid the use of steroids to treat severe or cerebral malaria as it has been associated with worse outcomes.
 - Many ancillary treatments have been suggested for the treatment of severe malaria, but few have been objectively shown to improve outcome. Only antipyretic drugs (paracetamol) and anticonvulsants have been supported by sufficient evidence to warrant their use. In cases of complicated *P. falciparum* infection ([Section 3.1 'Criteria for severe falciparum malaria'](#)), or if there is high parasitemia (10%), exchange transfusion has been used but it has not been subjected to good control trials.

3.5 Uncomplicated *Plasmodium falciparum*

Uncomplicated cases of *P. falciparum* can progress to life threatening infection over 12 to 24 hours if not treated and monitored properly.

***P. falciparum* malaria seen in Australia should be treated with: -**

First choice (for all cases):

- Artemether / lumefantrine 20+120 mg (Riamet Dispersable tablets®) to be taken orally with fatty food (e.g. glass of milk or biscuit), at 0, 8, 24, 36, 48 and 60 hours.
 - infant 0 to 14 kg: 1 tablet
 - 15 to 24 kg: 2 tablets
 - 25 to 34 kg: 3 tablets
 - Adult or child greater than 34kg: 4 tablets

- Clinicians should be aware of the following information regarding administration:
 - If a dose of Artemether / lumefantrine is required to be given to an infant, it would be appropriate to crush the tablet and mix with some water close to the time of administration.
 - Alternative method: Crush the tablet and mix with a spoonful of yoghurt or ice cream before administering.
 - Whenever possible, it should be given with food (milk is fine but preferably with a fatty meal) as this significantly improves absorption of the Artemether and lumefantrine.
 - A repeat dose should be given if the child vomits within one (1) hour after administration.

Second choice:

- Atovaquone / proguanil (Malarone®) 250/100 mg to be taken orally daily for 3 days.
 - Child 10 to 20 kg: 1 tablet
 - Child 21 to 30 kg: 2 tablets
 - Child 31 to 40 kg: 3 tablets
 - Adult or adolescent greater than 40 kg: 4 tablets
- Clinicians should be aware of the following information regarding administration:
 - Food increases absorption, particularly high-fat food.
 - If a dose of Atovaquone / proguanil is required to be given to an infant, it would be appropriate to crush the tablet and mix with some water close to the time of administration.
 - Alternative method: Crush the tablet and mix with a small amount of milk or smooth food such as yoghurt.
 - A repeat dose should be given if the child vomits within one (1) hour after administration.

Third choice:

- Combination of Quinine sulphate **plus either** Doxycycline **or** Clindamycin.
- **Quinine sulphate** to be taken orally, 8-hourly for 7 days
 - Infant and child: 10 mg/kg (up to 600 mg)
 - Adult or adolescent less than 50 kg: 450 mg/dose
 - Adult or adolescent greater than 50 kg: 600 mg/dose

Caution: Risk of QTc prolongation. Assess patient risk and monitor carefully. Please check medication interactions before starting Quinine (CyP3A4 substrate).

PLUS EITHER:

- **Doxycycline:** Child older than 8 years: 2 mg/kg (up to 100 mg) orally every 12 hours for 7 days (which need not commence on Day One (1)).
 - Note: Not to be used in children less than eight (8) years of age.

OR (only for malaria **not** acquired in South-East Asia): **Clindamycin:** Children greater than 5 kg and adolescents: 5 mg/kg (up to 300 mg) orally every 8 hours for 7 days.

For all patients, if oral medication cannot be tolerated, then parenteral Artesunate should be administered.

If there is slow response to artemether / lumefantrine (e.g. persisting parasitemia after 72 hours of therapy), then give atovaquone / proguanil course after artemether / lumefantrine course. This pertains particularly to *M.falciparum* acquired in the Mekong Delta.

3.6 Management of Non-falciparum Malaria (*P.vivax*, *P. ovale*, *P.malariae*)

Due to the emergence of Chloroquine resistance in all species, all species should be treated as for falciparum malaria as above (see [Section 3.4](#) and [Section 3.5](#)).

- As with *P. falciparum* malaria, response to treatment should be documented with a repeat of thick and thin blood films 28 days after therapy, and at any time there is recurrence of symptoms.
- Recurrence after 30 days suggests Primaquine resistance.
- *P. vivax* and *P. ovale* have a persistent liver phase that is responsible for relapses and is susceptible only to treatment with primaquine or related drugs. Relapses caused by the persistent liver forms may appear months and, rarely, up to five (5) years after exposure. None of the currently recommended treatment regimens (e.g. Artemether / lumefantrine or Atovaquone / Proguanil) will prevent relapses due to these two (2) species of Plasmodium. In order to reduce the risk of relapse following the treatment of symptomatic *P. vivax* or *P. ovale* infection, Primaquine is indicated to provide "radical cure".
- The possibility of G6PD deficiency should be excluded before anti-relapse therapy with Primaquine is given. In patients with known or suspected G6PD deficiency, expert medical advice should be sought, since Primaquine may cause haemolysis in such patients. Dose adjustment in some patients with G6PD deficiency is possible.
- Primaquine use is contraindicated in pregnancy. *P. vivax* or *P. ovale* infections occurring during pregnancy should be treated with standard doses of chloroquine. Relapses can be prevented by weekly chemoprophylaxis with chloroquine until after delivery, when Primaquine can be safely used for mothers with normal G6PD levels.
- For *P. ovale* infection, once G6PD deficiency has been excluded, **use concurrently**:
 - Primaquine 0.25 mg/kg (max 15 mg/day, dose expressed as primaquine base) orally once daily for 14 days to eradicate liver phase.
- *P. vivax* isolates with a decreased responsiveness to primaquine are well documented in Southeast Asia and, in particular, Papua New Guinea and Irian Jaya. Recently, Primaquine radical treatment failure has been reported from Thailand and Somalia.
 - Once G6PD deficiency has been excluded, the recommended dosage of Primaquine to prevent relapse has increased to 30 mg (0.5 mg/kg) orally once daily for 14 days.
 - *For patients weighing more than 70 kg*, Primaquine 0.5 mg/kg orally once daily for 14 days or 30 mg orally once daily until 6 mg/kg has been given.
- When *P. vivax* malaria relapses after Primaquine therapy there are two (2) issues to be considered:
 - The treatment of the acute vivax malaria.
 - Prevention of further relapses by a doubling of the standard dose of Primaquine, e.g. 30 mg (0.5 mg/kg) of Primaquine base daily for 14 days (B I - evidence-based medicine recommendation).¹
- WHO Guideline suggests for patients with borderline G6PD deficiency to use weekly dosing of Primaquine for eight weeks (instead of daily dosing) to reduce risk of haemolysis.

- Blood infection with *P. malariae* may persist for many years, but it is not life-threatening and is easily cured by a standard treatment course of Chloroquine.
- Patients with mixed infection e.g. *M.falciparum* with vivax or ovale should receive primaquine as above.

3.7 Chemotherapy of severe or complicated *P.falciparum* malaria

Note: A switch to oral therapy should be made as soon as possible.

Artesunate

- Dose:
 - Infants and children less than 20 kg: 3 mg/kg IV, on admission and repeat at 12 hours and 24 hours, then once daily until oral therapy is possible.
 - Children more than 20 kg: 2.4 mg/kg IV, on admission and repeat at 12 hours and 24 hours, then once daily until oral therapy is possible.
- IV administration:
 - Reconstitute 60 mg vial with 1 mL of provided sodium bicarbonate 5%. Shake well for 2 to 3 minutes and wait until completely dissolved.
 - Dilute dose to 10 mg/mL with either Glucose 5% or Sodium chloride 0.9% and give over 1 to 2 minutes.
- Delayed haemolysis can occur after artesunate use. Check FBC, LFTs, Urea and electrolytes (plus LDH and haptoglobin if more than 10% drop in haemoglobin) at 1, 2, 3 and 4 weeks following therapy
- When patient is able to tolerate oral therapy, give a full course of artemether / lumefantrine, as for uncomplicated *P. falciparum* malaria.
 - Note: Artesunate does not currently have marketing approval in Australia but the TGA has agreed to allow hospital pharmacies to import and hold Artesunate under the Special Access Scheme (SAS). A small quantity of emergency stock is held in a few identified hospitals. Central pharmacy can provide supplies on presentation of a completed [SAS Category A form](#). As artesunate is not registered the medical practitioner should obtain informed consent from the parent/carer.

OR (if parenteral Artesunate is not immediately available)

Quinine dihydrochloride

- Dose: 20 mg/kg (up to 700 mg) IV diluted in 10 mL/kg glucose 5% by intravenous infusion over 4 hours.

OR

- Dose: 7 mg/kg IV over 30 minutes, followed immediately by 10 mg/kg IV over 4 hours.
 - For maintenance dose, repeat quinine dihydrochloride^b 10 mg/kg (up to 700 mg) IV diluted in 10 mL/kg glucose 5% by intravenous infusion over 4 hours every 8 hours until the patient can swallow.
 - When the patient has clinically improved, continue treatment with oral quinine combined with doxycycline or clindamycin as for uncomplicated *P. falciparum* malaria to complete a total of seven (7) days of treatment with quinine.
 - Note: Parenteral quinidine may be used but only if parenteral quinine is unavailable. Because of increased risk of cardiac toxic effects with quinidine, cardiac monitoring is required.

Comments:

- Loading dose should not be used if the patient has received three (3) or more doses of quinine or quinidine in the previous 48 hours, or mefloquine prophylaxis within the preceding 24 hours or a mefloquine treatment dose within the previous three (3) days.
- Rapid infusion may cause severe and fatal cardiotoxicity. Monitor pulse and blood pressure and slow the rate of infusion if dysrhythmias occur.
- Frequent measurements of blood pressure and blood glucose are required as quinine stimulates insulin secretion and can cause hypoglycaemia
- Switch to oral therapy with quinine as soon as possible. In patients requiring more than 48 hours of parenteral therapy, reduce the quinine maintenance dose by one-third to one-half.

Patients with severe malaria acquired in Mekong Delta area

Mortality from severe *P. falciparum* malaria is lower with intravenous artesunate than with intravenous quinine. Although the impact of artemisinin resistance on the efficacy of intravenous artesunate in severe malaria is not yet known; combination therapy with intravenous artesunate plus intravenous quinine is now recommended for patients with severe *P. falciparum* malaria acquired in the Greater Mekong Subregion (Thailand, Vietnam, Cambodia, Laos and Myanmar), where artemisinin resistance is increasing. Do not delay therapy if only one (1) of the two (2) intravenous drugs is immediately available - start treatment with one (1) drug and request urgent shipment of the other.

3.8 Treatment failure

In the case of treatment failure or relapse within 28 days of treatment:

- **Repeat a course of Artemether / lumefantrine (Riamet®) together with a course of Atovaquone / proguanil (Malarone®).**
- **Artemether/lumefantrine 20+120 mg (Riamet®)** to be taken orally with fatty food (e.g. glass of milk or biscuit), at 0, 8, 24, 36, 48 and 60 hours.
 - infant 0 to 14 kg: 1 tablet
 - 15 to 24 kg: 2 tablets
 - 25 to 34 kg: 3 tablets
 - Adult or child greater than 34 kg: 4 tablets

Clinicians should be aware of the following information regarding Artemether / **lumefantrine** administration:

- If a dose of Artemether / lumefantrine is required to be given to an infant, it would be appropriate to crush the tablet and mix with some water close to the time of administration.
- Alternative method: Crush the tablet and mix with a spoonful of yoghurt or ice cream before administering.
- Whenever possible, it should be given with food (milk is fine but preferably with a fatty meal) as this significantly improves absorption of the artemether and lumefantrine.
- A repeat dose should be given if the child vomits within one (1) hour after administration.

- **Atovaquone / proguanil** (Malarone®) 250/100 mg to be taken orally daily for 3 days
 - Child 10 to 20kg: 1 tablet
 - Child 21 to 30kg: 2 tablets
 - Child 31 to 40kg: 3 tablets
 - Adult or adolescent greater than 40kg: 4 tablets
- Clinicians should be aware of the following information regarding administration:
 - Food increases absorption, particularly high-fat food.
 - If a dose of Atovaquone / proguanil is required to be given to an infant, it would be appropriate to crush the tablet and mix with some water close to the time of administration.
 - Alternative method: Crush the tablet and mix with a small amount of milk or smooth food such as yoghurt.
 - A repeat dose should be given if the child vomits within one (1) hour after administration
- If child is older than eight (8) years of age, doxycycline 2 mg/kg (up to 100 mg) orally every 12 hours for seven (7) days can be given instead of Atovaquone / proguanil.

Follow-up and monitoring

Patients should have daily blood smears to check for clearance of parasitemia. Most patients will clear parasites by Day three (3) of treatment.

Follow up blood smears should be arranged for 14 days and 28 days after commencement of therapy to confirm eradication.

References and suggested reading

1. [WHO. Guidelines for the treatment of malaria. In. 3rd ed. Geneva: WHO Press; 2015.](#)
2. Malaria: [revised 2018 Jun]. In: eTG complete [Internet]. Melbourne: Therapeutic Guidelines Limited
3. Plewes K et al. Acetaminophen as a renoprotective adjunctive treatment in patients with severe and moderately severe falciparum malaria: a randomized, controlled, open-label trial. Clin Infect Dis. 2018 Mar 12. doi: 10.1093/cid/ciy213. [Epub ahead of print]
4. SHPA Don't Rush to Crush 2nd edition (2017). Monographs: Artemether/Lumefantrine and Atovaquone/Proguanil [Internet].

Consultation

Key stakeholders who reviewed this version:

- Paediatric Infection Specialist, (CHQ)
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Accreditation references

NSQHS Standards (1-8):

- Standard 3: Preventing and Controlling Healthcare-Associated Infection
- Standard 4: Medication Safety