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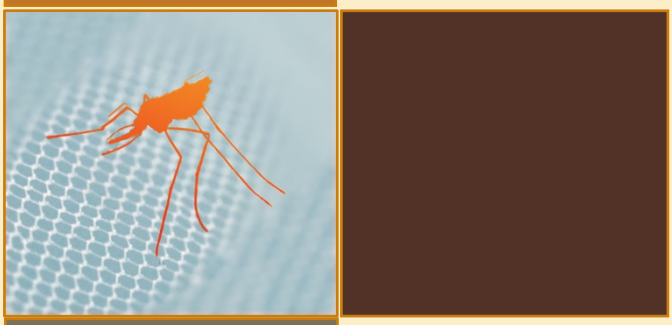
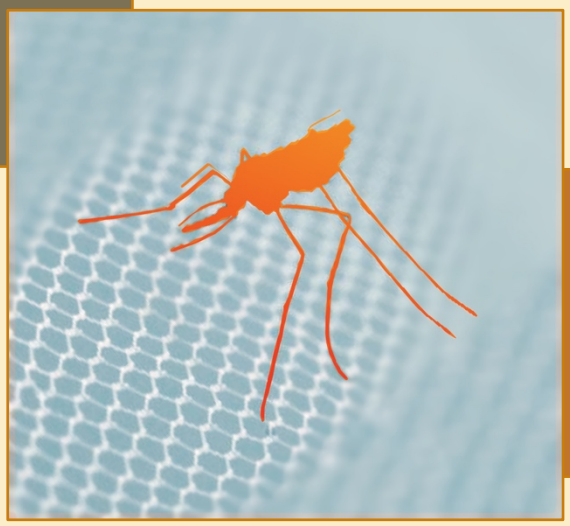


Malaria Guidelines

24th Edition
November 2022



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MALARIA GUIDELINE

24th Edition

Version 2.3

November 2022

Introduction

This is the 24th Edition of the Malaria guideline. It is for healthcare workers along the Thai-Myanmar border who encounter malaria. It is a simple, evidence-based document aimed at providing a practical guide to malaria treatment.

Malaria incidence is now very low along the border. Most of the malaria infections we see now are vivax malaria. In recent years, many patients have limited access to malaria treatment. Because of this, there are increasing vivax cases and now there are more falciparum malaria cases being seen. It is very important that health care workers maintain knowledge about malaria diagnosis, management and treatment. Risk of outbreaks may be higher, therefore, outbreak management will become important. If there is lower immunity, patients may be more sick. Early correct diagnosis (within 48 hours) and treatment with an ACT + single dose primaquine are the most important part for the elimination of *P. falciparum*. Time is critical. Early diagnosis and treatment will also prevent severe malaria and deaths.

There is artemisinin resistance in this region and the treatment options for malaria are limited. For resistant P. *falciparum* cases, triple combinations may be needed, and the treatment may be longer (≥7 days). The treatment and management of *P. vivax* with primaquine or tafenoquine is also important for malaria elimination.

The treatment guidelines can also be downloaded in SMRU website. To help us keep this document useful, please contact us. You may also visit our website: http://www.shoklo-unit.com.

Table of Contents

SMRU Malaria treatment guidelines summary

i. *P. falciparum* resistance to artemisinin is spreading so treatment failures may become more common (1). This guideline will explain how to manage malaria that is not responding to treatment with either RDT (cannot monitor parasite clearance) or malaria smear (can monitor parasite clearance)

ii. Primaquine is an important drug in the treatment of malaria. However, the treatment regimen and the risk for adverse effects are very different between the doses used for *P. falciparum* and *P. vivax*.

   a. Primaquine decreases *P. falciparum* transmission by killing gametocytes, so patients with *P. falciparum* infection should receive single low dose primaquine given as a single dose.

   b. Primaquine decreases *P. vivax* transmission by killing hypnozoites (dormant stage in the liver) and preventing relapses, so patients with *P. vivax* infection should receive daily high dose primaquine for radical cure for 14 days.

Single low dose primaquine for *P. falciparum* should not be given to:
Pregnant women
Infants < 6 months

Daily high dose primaquine for *P. vivax* should not be given to:
G6PD deficient or unknown (use the weekly regimen)
Pregnant women
Infants < 6 months (including congenital malaria)
Women breastfeeding infants < 1 month old
If the patient has a history of haemolysis with primaquine

iii. There is now evidence in *P.falciparum* research that pregnant women can receive the same treatment (ACT) as non-pregnant adults. There are a few exceptions:
   a. Do not give primaquine or doxycycline in pregnant women (2). Doxycycline may be used with quinine only if there are no other options (3).
   b. Pregnant women have high risk for treatment failure with COA (4,5) and should receive a longer course (5 days).

iv. For *P. vivax* in pregnancy, after completing the treatment for the acute infection, give CQ prophylaxis to prevent relapses. Multiple *P. vivax* episodes during a pregnancy increase the adverse effects to the fetus such as miscarriage, preterm birth, and small for gestational age (6)

v. Tafenoquine, a new single dose anti-relapse treatment against *P. vivax* and *P. ovale* has been approved in Thailand but is not easily available.

Malaria treatment summary

Uncomplicated *P. falciparum* malaria in adults, children and infants ≥ 1 month (pg. 2)			
Diagnosis:	RDT or malaria smear	Definition:	Presence of asexual parasitaemia
			Can sit, eat or drink alone without signs of severity or evidence (clinical or laboratory) of vital organ dysfunction.
Treatment:	1st line: DP or COA 2nd line: ACT, or quinine or artesunate-based treatment	AND	Single low dose PMQ on the first day of treatment when possible

- If the patient has another *P. falciparum* infection ≤63 days (treatment failure), use a <u>different ACT</u> from before or use a quinine or artesunate-based treatment

- No Doxycycline in children <8 years unless there is no other available option

Treatment of *P. falciparum* malaria in pregnancy, post-partum and congenital malaria (pg. 5)	
Treatment:	Uncomplicated, hyper and severe malaria treatment is the same as for non-pregnant persons.

- Pregnant women have high risk for treatment failure with COA (4,5). Use COA 5 days

- Do not give doxycycline or tetracycline in pregnant women unless there is no other available option

- Do not give single low dose PMQ in pregnant women or infants <6 months including neonates with congenital malaria

Transmission blocking primaquine dose for *P. falciparum* (pg. 2 and 29)

- Primaquine given as a single dose
- G6PD testing is not needed for this dose
- Do not give primaquine to pregnant women or infants < 6 months (including congenital malaria)

P. falciparum malaria not responding to the treatment ("treatment failure" pg. 9)			
Diagnosis:	If only RDT is available	Definition:	Clinical situation is not improving while on treatment OR the patient comes back within 1-2 weeks with fever and the RDT is still positive (may be positive for 2 weeks from the acute infection so cannot know if parasite was cleared)
	If malaria smear is available	Definition:	While on treatment the parasite count is increasing, or the parasite count is not being cleared
Management and Treatment:	If only RDT available (i.e. at malaria post): New or worsening clinical signs may not be from resistance. Consider other causes. Confirm that the patient finished the full treatment. If you are not certain the patient completed a full treatment, give it again but supervise the treatment. **If you suspect the patient is not responding normally to supervised treatment, refer to the hospital. You may also call SMRU for advice.**		
	If malaria smear available: <u>Increasing parasitaemia</u>: If parasite count after 48h is more than on admission, change to a second anti-malarial that is different from the current treatment and ADD quinine IV/IM (if signs of severe infection) or oral if uncomplicated. Add tetracyclines or doxycycline or clindamycin if oral treatment possible. <u>Decreasing parasitaemia but not clearing after 3 days</u>: Change to a second anti-malarial that is different from the current treatment and ADD quinine oral (or IV/IM if oral not available) and tetracycline or clindamycin. When *P. falciparum* is not responding to artemisinin-based treatments, consider quinine because it is likely that the *P. falciparum* will be sensitive to quinine (Q7T7 or Q7C7).		

- WHO malaria treatment guidelines define treatment failure for *P. falciparum* malaria as malaria infection < 28 days after a treatment for malaria (7). SMRU guidelines define treatment failure as malaria infection ≤63 days after treatment (8). Consider using a different medication combination if you suspect treatment failure.

P. falciparum malaria with hyperparasitaemia (pg. 11)			
Diagnosis:	Malaria smear ONLY RDTs cannot give this diagnosis	Definition:	Presence of asexual parasitaemia ≥4% IRBCs on malaria smear

AND/OR

Severe malaria (pg. 11 and 15)			
Diagnosis:	Malaria smear or RDT	Definition:	Patients with malaria (*P. falciparum, P. vivax, P. malariae, P. ovale, P. knowlesi*)
	Clinical or laboratory results can give the diagnosis		Any severe signs, symptoms or laboratory findings

Treatment:	AS IV or IM plus Quinine IV then change to oral ACT	AND	Single low dose PMQ on the first day of treatment when oral administration is possible

- Do not give mefloquine to severe malaria patients who have neurologic symptoms because it can make neurologic symptoms worse.

- If the patient has hyperparasitaemia confirmed by malaria smear, you may need to continue IV or IM doses even after the patient can tolerate oral medications. The total anti-malarial treatment may be longer than 7 days. *Treatment should be continued until the malaria smear is negative two times and consecutively.*

- If there is clinical deterioration and the patient is already on AS IV plus quinine IV, look for other causes (sepsis, renal failure, hypoglycaemia) and consider hospital referral.

Treatment of *P. vivax* malaria (pg. 23)			
Diagnosis:	Malaria smear or RDT (either pan or Pv specific)	Definition:	Presence of asexual parasitaemia
Treatment:	1st line: CQ 2nd line: DP or COA	AND	Radical cure primaquine or tafenoquine after G6PD testing

If the patient has another *P. vivax* infection:

- if > 28 days after first treatment, repeat CQ
- If ≤ 28 days give a different treatment such as an ACT (preferably DP)

** CQ is still good for *P. vivax* but evidence of resistance is slowly increasing along the Thailand Myanmar border (9)**

Radical cure of *P. vivax* (pg. 24 and 29) or single dose tafenoquine (pg. 24):

1. If G6PD status is deficient or unknown use only the weekly primaquine dose, pg. 43
2. Do not give primaquine or tafenoquine to:
   - Pregnant women
   - Infants < 6 months (including congenital malaria)
   - Women breastfeeding infants < 1 month or infant is G6PD deficient. Primaquine excretion into breast milk is minimal [12]
   - Patients with a history of haemolysis or anaemia with primaquine
3. Do not give tafenoquine if <16 years old (this may change in the future)

- Repeat primaquine treatment if a second *P. vivax* infection occurs >14 days from the previous *P. vivax* infection. If the primaquine treatment is ongoing (i.e. weekly primaquine dose in G6PD deficiency) then continue until finished (no need to repeat).
- If a primaquine dose is missed do not take a double dose the next day. Continue the normal daily dose until the full course is completed. Finishing the full 14 doses is the most important even if it takes 15 days or longer.
- Tafenoquine is not widely available in Thailand. It is a single dose.

If a pregnant woman has current or history of *P. vivax* infection during the current pregnancy, do not give primaquine but consider chemoprophylaxis, pg. 27:

- Confirm that the malaria smear is negative.
  - If no acute *P. vivax* infection, start CQ (2 tabs) weekly
  - If she has acute *P. vivax* infection while on CQ prophylaxis and you are not sure of adherence, treat with supervised CQ for 3 days then after treatment is

completed, between day 14 and 28 start CQ (2 tabs) weekly (supervised if possible).

- If she has *P. vivax* infection while on CQ prophylaxis and you are confident of adherence, give an ACT and restart CQ prophylaxis between day 14 and 28 start CQ (2 tabs) weekly (supervised if possible).
- Continue until 4 weeks postpartum or until radical cure can be given, if possible.

1. Checklist before administrating antimalarials

1	**Confirmed** positive result: malaria smear or RDT	☐ Pf	☐ Other	☐ Neg
2	**Pregnancy** status: urine pregnancy test if any doubt		☐ Pregnant (see pg. 5)	☐ Not pregnant
3	**Breastfeeding** status (Lactation)		☐ No	☐ Yes
	If yes, what is the age of the breastfeeding infant?		_____	
4	**Severity** of malaria if <u>have</u> malaria smear:			
	a. Uncomplicated malaria (<4% IRBC and can sit or drink alone) (if yes, see pg. 2)		☐ No	☐ Yes
	b. Hyper-parasitaemia (≥4% IRBC) and/or severe malaria (cannot sit or drink alone) (if yes, see pg. 11)		☐ No	☐ Yes
4	**Severity** of malaria if <u>not have</u> malaria smear:			
	a. Uncomplicated malaria (can sit or drink alone) (if yes, see pg. 2)		☐ No	☐ Yes
	b. Severe malaria (cannot sit or drink alone) (if yes, see pg. 11)		☐ No	☐ Yes
5	Did the patient have malaria before?		☐ No	☐ Yes
6	Antimalarial use in the last two months?		☐ No	☐ Yes
7	Any history of allergy to antimalarials?		☐ No	☐ Yes
8	Patient already treated for fever?		☐ No	☐ Yes
9	If you intend to treat with mefloquine, check if the patient has a history of:			
	a. Neuropsychiatric disorder		☐ No	☐ Yes
	b. Epilepsy		☐ No	☐ Yes
	c. Other mefloquine reactions		☐ No	☐ Yes
	d. recent Yabba (amphetamine) use		☐ No	☐ Yes
10	Patient weight on the scale:		_____	kg
11	Patient febrile?		_____	◦C

Proceed to the treatment guidelines when you know the answer to all of the above

2. Uncomplicated P. falciparum malaria in adults, children, and infants ≥ 1 month

Please do the checklist first (pg. 1)

2.1 Uncomplicated *P. falciparum* in adults, children, and infants ≥1 month

The first line ACT treatment of uncomplicated *P. falciparum* malaria in pregnant women is the same as for non-pregnant. ACTs have recently been shown to be safe in the first trimester (2). For more information on malaria in pregnancy see pg.5, and for treating infants <1 month see pg. 7.

Uncomplicated P. *falciparum* is defined as presence of asexual parasitaemia *(<4% IRBC)* on malaria smear or a patient with a positive RDT who is not clinically severe. The patient can sit, eat or drink alone without signs of severity or evidence (clinical or laboratory) of vital organ dysfunction.

If the parasitaemia is decreasing but not clearing OR increasing, this may be from resistant parasites. Please see pg. 9 for further treatment.

2.1.1 First line treatment

First line treatment is ACT (COA or DP) plus single low dose primaquine.

2.1.1.1. Artemether-lumefantrine (COA), Coartem®

Each COA tablet contains 20mg artemether and 120 mg lumefantrine
Treatment is twice daily for 3 days (Dosage table pg. 32)

- The absorption of oral lumefantrine is significantly better with co-administration of fat. Each dose must be taken with some fried or oily food or a carton of milk. Amount of fat required to obtain 90% of maximum effect of Coartem® is 1.2g (10) (50 ml whole milk or 1.2 ml cooking oil).

2.1.1.2. Dihydroartemisinin and piperaquine (DP)

Adult DP tablets contain 40mg of dihydroartemisinin (DHA) and 320 mg piperaquine.
Paediatric DP tablets contain 20mg of DHA and 160 mg piperaquine. Be careful to check which tablets you are using and the number of tablets you give to the patient. Treatment is once daily for 3 days (1.6 mg/kg/day of DHA and 12.8 mg/kg/day of piperaquine) (Dosage table pg. 32)

2.1.1.3. Single low dose primaquine (PMQ) to block transmission

Primaquine tablets contain 5mg, 7.5mg or 15mg of primaquine. It is better to use the 5 or 7.5mg tablet if possible because the dose you need to give is very low (0.25 mg/kg for one dose), and you may need to cut tablets to ¼ or ½. Use a tablet cutter.

Give single dose primaquine on the first day of ACT, when possible. Testing for G6PD deficiency is NOT needed. (Dosage table pg. 40)

- Single low dose primaquine should be supervised, if possible.
- This is important to decrease *P. falciparum* gametocyte carriage (reduce transmission) (11,12), especially because the rate of artemisinin resistant *P. falciparum* is increasing.

Transmission blocking primaquine dose for *P. falciparum* should <u>not</u> be given to:

- Pregnant women
- Infants <6 months (including congenital malaria)

For more information on primaquine safety and adverse effects, see pg. 29

2.1.2 Second line treatment

If DP or COA are not available any other anti-malarial can be used (see examples below). AS only tablets may not be available. We still provide the dosing information so you can use if you need.

2.1.2.1. Mefloquine-artesunate (MAS3)

Each mefloquine tablet contains 250 mg. You may use a combination MAS tablet if available. Treatment is once daily (Dosage table pg. 33 and 34). For contraindications see pg. 28.

First day - Artesunate 4 mg/kg
Second day - Artesunate 4 mg/kg + Mefloquine 15 mg/kg
Third day - Artesunate 4 mg/kg + Mefloquine 10 mg/kg

- Mefloquine is better tolerated when given in split doses of 8 mg/kg per day over 3 days
- *In patients with a 2nd episode of P. falciparum within 63 days of treatment with MAS3, do not give mefloquine again because of increased risk of neurological side effects*.

2.1.2.2. Quinine and clindamycin (Q7C7) or tetracycline (Q7T7) or doxycycline (Q7D7)

Each quinine tablet contains 60 mg quinine sulphate salt
Each tetracycline capsule contains either 250mg or 500
Treatment regimens are below (Dosage table pg. 35 and 36). For adverse effect see pg. 28.

Total 7 days - Quinine 10 mg/kg/dose TID + Clindamycin 5mg/kg/TID
or
Total 7 days - Quinine 10 mg/kg/dose TID + Tetracycline 16mg/kg/TID
or
Total 7 days - Quinine 10 mg/kg/dose TID + Doxycycline 4 mg/kg/day OD

2.1.2.1. Artesunate and doxycycline (AS7D7) or clindamycin (AS7C7)

Each artesunate tablet contains 50 mg
Each doxycycline capsule contains 100 mg
Each clindamycin tablet contains 150 mg
Treatment regimens are below (Dosage table pg. 33 and 36)

Total 7 days - Artesunate 2 mg/kg OD + Doxycycline 4 mg/kg/day OD
or
Total 7 days - Artesunate 2 mg/kg OD + Clindamycin 5 mg/kg/TID

Do not give doxycycline to pregnant women and children younger than 8 years unless there are no other available drugs (adverse effects, pg.28).

2.2 Treatment of anaemia

Patients with *P. falciparum* malaria will usually develop anaemia, but not everyone will need treatment. If you worry about the patient, you can check haemoglobin or haematocrit, and malaria smear. Use the guideline below if you have those tests available. If you do not have tests available, follow up clinically or refer to a hospital.

Definition:

	Hb (mg/dL)	Hct (%)
Males	<13.5	<36
Non-pregnant females	<12	<33
Pregnancy (1st trimester)	<11	<33
Pregnancy (2nd & 3rd trimesters)	<10	<30
Children < 15 years	<11	<33

* Hb thresholds are based on SMRU guidelines

Treat with ferrous sulphate and folic acid if below the threshold, especially pregnant females and children <2 years. (Dosage table pg. 45).

- Anaemia is a common complication of malaria but tends to resolve quickly with treatment (2 weeks).
- Start ferrous only when the patient is trophozoite negative.
- Review the patient in 2 weeks. If still anaemic give an additional 2 weeks treatment.
- Think of other causes of anaemia: worms, thalassaemia, or G6PD deficiency. Make a stool test and deworm if necessary. Refer to the BBG for more information.
- Monitor for severe anaemia (pg. 21)

2.3 Considersations for treatment in infants (≥ 1 month old) and children

Infants can present to the clinic very sick or develop severe symptoms very quickly.

2.3.1 Recommendations to decrease the risk of vomiting

1. Treat the fever. Vomiting is more common if the child has fever.
2. Wait until the child is calm. Explain to the mother the importance of her help.
3. Crush the tablets and dilute exactly as guidelines recommend
4. Give the medicine to the child with the syringe.

   Do not fight with the child or pinch the nose.

5. Give sugar or breast milk.
6. Supervise 1 hour for vomiting (the risk is highest in the first hour)
7. Some medicines can be very difficult to tolerate because they taste bitter
8. If you have tried twice and are not successful, give IV or IM artesunate.

2.3.1 Consider IV or IM artesunate for the first dose if you are worried

Give Artesunate IV or IM (Dosage table pg. 37) for the first dose if:

If PFS (schizonts) are seen on the malaria smear
If you are not sure about the infant's condition
If the patient cannot tolerate oral medication

When the patient is stable, change to oral treatment (Dosage table pg. 33)

2.4 *P. falciparum* (Uncomplicated, hyperparasitaemia and severe) in pregnancy

Morbidity and mortality from malaria in pregnancy is increased (anaemia, post-partum hemorrhage, hypoglycaemia, pulmonary edema). Pregnant women with malaria should be managed with close attention. Infant morbidity and mortality is also increased (small for gestational age, preterm birth, stillbirth) if the mother has malaria in pregnancy.

For *P. vivax* in pregnancy, refer to Chapter 9.3 "Treatment of uncomplicated *P. vivax*" (pg.27)

2.4.1 Points to include when malaria in pregnancy is diagnosed

- Before giving any anti-malarial, ask about pregnancy. If not sure, confirm by pregnancy testing.
- Confirmation of gestation: last menstrual period, measure fundal height (pg. 48) or do an ultrasound if available.
- Check for anaemia.

Pregnant women can have the same malaria treatment in all trimesters (same as non-pregnant, pg. 2) <u>except</u>:

DO NOT give primaquine, tetracycline or doxycycline to pregnant women
Doxycycline may be used only if there are no other options

- If possible supervise treatment until the woman is malaria smear negative.
- DP is preferred in pregnant women because COA has a higher failure rate in pregnancy (20% PCR confirmed) (5).

2.4.2 Management of malaria complications in pregnancy

- Treat anaemia (pg. 4) or severe anaemia (pg. 21)
- Treat fever because it is associated with premature labour.
    a. Give paracetamol QID for at least 72 hrs (pg. 44). This also can help the kidneys (pg. 19)
    b. Premature labour can still develop even after fever better and patient on treatment.
    c. Give dexamethasone and nifedipine (if the BP is stable) as part of the normal management of confirmed preterm labour (<35 weeks gestation).
- Hypoglycaemia is a common problem in pregnant women with severe malaria.
    a. When IV quinine is used for treatment 50% of pregnant women will develop hypoglycaemia.
    b. Quinine given in the 2nd and 3rd trimesters of pregnancy increases the risk of hypoglycaemia even when malaria is uncomplicated (pg. 28).
- Maternal fever and hypoglycaemia may cause marked fetal bradycardia, tachycardia, and other signs of fetal distress.
- Pulmonary oedema is a common complication in severe malaria in pregnancy. This may be present on admission or develop suddenly. It can develop immediately after delivery and may occur at any time in the 1st week post-partum.
- Bacterial sepsis is a concern in pregnant and postpartum women with fever and should be treated appropriately. Look for a source of infection e.g. UTI. If no source is identified, follow the recommendations for severe malaria shock (pg. 18)

2.4.3 *P. falciparum* at the time of delivery

Malaria can be transmitted while the infant is in utero. When we treat the mother, the fetus will be treated by transfer of drug across the placenta.

The highest chance for infection in the neonate is when the mother has malaria at the time of delivery and the risk is higher when malaria smear of the cord and/or placenta blood are positive.

2.4.4 Management if mother is malaria positive (any species) at delivery

1. Find a stand-by blood donor because the risk of PPH is increased.
2. Do a malaria smear of the baby after delivery (cord and placenta smear are optional).
3. Smear of the baby on day 2-3 if the cord blood malaria smear is positive.
4. Do weekly malaria smear and haematocrit of mother and baby.
5. Follow-up to day 63. Malaria parasites do not grow well in fetal red blood cells, so the infection may not be found at birth. Instead, it may occur in the first months of life.

How to collect cord specimens

-Cord specimens are taken before the placenta is delivered.
-Hold the clamped end of the cord attached to the placenta
-Wipe the cord clean
-Puncture the cord with a syringe and needle (small gauge)
-Withdraw blood from the vessel (0.2 ml is plenty)
-Re-clamp the cord above the puncture site.
-The blood obtained needs to go directly onto the glass slide before it clots.

How to collect placenta blood

-Place the placenta maternal surface (red colour) upward.
-Choose a site midway between the edge of the placenta and the cord
-Wipe it clean with gauze
-Make an incision about 1 cm deep and 3-4 cm in length with a scalpel blade. Do not pierce the fetal surface (white colour).
-Use a syringe and needle (or haematocrit tube) to withdraw blood that pools in the incised area.
-Place this blood onto the glass slide before it clots.

Label all samples clearly (e.g. mother, cord, placenta or baby before sending to the laboratory).

3. Congenital and neonatal malaria

3.1 Definitions

Congenital malaria is defined as a positive malaria slide in the newborn within 7 days of birth. Any malaria in a neonate (<28 days old) should be considered a serious infection.

3.2 Clinical features of congenital and neonatal malaria

There may be no symptoms of malaria in the neonate, if present they are non-specific and include:

- Fever ≥ 38 °C on one occasion or > 37.5 °C on two occasions separated by at least one hour
- Hepatosplenomegaly
- Anaemia
- Poor perfusion – shock: Cold hands and feet, CRT > 2s, Mottled, Tachycardia,
- Respiratory distress: Fast RR > 60 per minute, Chest indrawing
- Abdominal distension
- Bile from the NGT
- Hypothermia that doesn't improve with treatment
- Seizures
- Jaundice
- Apnoeas or slow respiratory rate
- Very sleepy or unconscious

P. falciparum malaria can cause neonatal death

3.3 Differential Diagnosis:

Neonatal sepsis
Congenital infections (CHEAP TORCHES):

C Chicken pox and shingles
H Hepatitis C, D and E
E Enteroviruses
A Acquired immunodeficiency syndrome (HIV)
P Parvovirus B19
T Toxoplasmosis
O Other (Candida)
R Rubella
C CMV
H Herpes simplex virus
E Everything else sexually transmitted (N. gonorrhea, Chlamydia, HPV)
S Syphilis

3.4 Management of malaria in neonates

Neonates with malaria can be very sick or become very sick quickly!

ABC- stabilize first
Suspect the diagnosis
Take the investigations
Malaria smear/ Blood glucose/ Hct or HB
or other tests if available (e.g. CBC, CRP, blood culture)

Give MACHO care: M–milk, A–antibiotics, C–cord care, H–heat control, O–oxygen.

3.5 Treatment of congenital or neonatal malaria

3.5.1 *P. falciparum* treatment

Give:
Artesunate IV or IM 2.4.mg/kg for the first dose because the clinical condition can worsen quickly in neonates and infants.

Change to oral if condition is good and the parasite count decreases after the first dose:
DP for 3 days (Dosage table, pg. 32)

OR

A7C7 oral artesunate 2 mg/kg/daily for 7 days PLUS clindamycin (5 mg/kg/TID) for 7 days (Dosage table, pg. 33 and 36); if artesunate is not available then give an ACT – refer to Chapter 2 "Treatment of uncomplicated *P. falciparum*" (pg. 2)

3.5.2 *P. vivax* treatment

See pg. 27

4. *P. falciparum* malaria not responding to treatment

There is increasing evidence of artemisinin resistance in Cambodia, Thailand and Myanmar (13). Even as malaria is decreasing, more and more of the *P. falciparum* cases we see will be resistant. It is very important to follow the parasite clearance.

There is some evidence to suggest infections which are truly recrudescent (failure of the drug treatment and not a new infection) will have higher cure rates with a 7-day treatment (14). In the SMRU experience, some patients will be on treatment for as long as 10 days before parasite is cleared. If you need advice on treatment, please call SMRU.

4.1 Definition of anti-malarial resistant *P. falciparum*

SMRU defines treatment failure for *P. falciparum* as ≤ 63 days. For your knowledge, WHO malaria treatment guidelines define treatment failure for *P. falciparum* malaria as malaria infection < 28 days after a treatment for malaria (7).
Slow parasite clearance or malaria smear never becomes negative
Parasite count increasing while on treatment

4.2 Diagnosis of resistant *P. falciparum*

Some RDTs stay positive for approximately 2 weeks after the acute infection, so these *RDT tests cannot tell you if the parasite is clearing.*

If you only have RDT available and you suspect that the patient is not responding to treatment:

1. Confirm that the patient had supervised treatment. If treatment was not supervised, repeat the same treatment but you *must supervise the treatment*.

2. If you can confirm that the previous treatment was supervised, you will need to use your clinical judgement.
    a. Is the patient unwell? Consider other causes (dengue, sepsis) and refer to the hospital.
    b. Is this a common cold or viral infection? If yes, then do not give anti-malarial again. Follow closely.
    c. Can you palpate a spleen? If yes, maybe more likely to be malaria.

3. If you decide <u>not</u> to treat with anti-malarial again, then follow the patient every 1-2 days to see if they become worse.

4. If you decide to treat with anti-malarial again AND you can confirm that the previous treatment was supervised AND malaria smear is available, go to the next section (4.3).

5. If you decide to treat with anti-malarial again AND you can confirm that the previous treatment was supervised, but malaria smear is not available, send the patient to a clinic where a malaria smear can be done. Be sure to communicate the situation with the clinic so that the proper treatment can be given. **If you need further advice, calll SMRU.**

4.3 Treatment of artemisinin resistant *P. falciparum*

4.3.1 Treatment failure ≤ 63 days

ALWAYS confirm that the patient completed the full course of treatment for the previous infection. If this cannot be confirmed, then you can repeat the same treatment, but *you must supervise the treatment.*

If you have confirmed that the previous treatment was fully completed, try to find out what the treatment was.

- If the previous treatment was an ACT, then give a quinine-based treatment (Q7C7, Q7T7 or Q7D7, pg. 3).
- If the previous treatment was not an ACT or don't know, then try DP, COA or MAS3.

4.3.2 While on treatment the parasitaemia is increasing or patient is unwell

Replace with another anti-malarial that is different from the current treatment. We recommend the following order of drugs: DP → COA → MAS3 → quinine (Q7T7 or Q7C7)

AND

Add Quinine IV (Dosage table, pg. 38), only if not already using oral quinine treatment

- If the malaria smear is still positive at the end of the treatment course, change again to another oral treatment.
- Quinine can be continued even when the oral treatment has changed
- If the parasitaemia continues to increase even after you have changed treatment, call SMRU for advice or refer to a hospital.

4.3.3 Parasitaemia is decreasing but not clearing after 3 days of treatment

Add or replace with another anti-malarial that is different from the current treatment. We recommend the following order of drugs: DP → COA → MAS3 → quinine (Q7T7 or Q7C7)
AND

Add Quinine oral (Dosage table, pg. 35), except when using an oral quinine-based treatment

- Use quinine IV or IM if oral not available.

Important points for the management of resistant malaria

If you can do a malaria smear, continue all antimalarial treatment until the *malaria smear is negative 2 consecutive times*. Longer treatment courses may be needed. In some cases, up to 10 days anti-malarial treatment is needed. This recommendation is based on the experience at SMRU. Always keep quinine and tetracycline in the pharmacy as this treatment will be effective against malaria if administered properly.

5. Severe and hyperparasitaemia *P. falciparum* malaria

Please do checklist first, pg. 1.
In an area of established artemisinin resistance (such as in Cambodia, Thailand, and Myanmar (1,13)) these patients should be hospitalized and treated with both IV artesunate and IV quinine.

5.1 Definitions

Hyperparasitaemia is defined as patients with a high parasitaemia (≥4% IRBC) on malaria smear. RDTs cannot give the parasite count so they cannot be used to diagnose hyperparasitaemia.

Severe malaria is defined as patients with any malaria (*P. falciparum, P. vivax, P. malariae, P. ovale, P. knowlesi*) who have any severe signs or symptoms at presentation (i.e. cannot sit/stand/walk alone, difficulty breathing, very low blood pressure, bleeding). WHO severity criteria, pg. 15.

- Some patients can be very sick even if the parasitaemia is not very high. This can be based on clinical observation or laboratory result.
- If a patient with severe symptoms has *P. vivax* or *P. ovale*, use the same management guidelines as below. But the treatment is slightly different, see pg. 24.

5.1.1 First line treatment – IV artesunate PLUS quinine then ACT

For all IV or IM doses, change to tablets after the patient can tolerate oral medications.

Important notes:

- As malaria decreases, health care staff will have less experience managing hyperparasitaemic and severe cases. Please contact someone at SMRU if you have questions. It is better if you contact us early during the management, because these patients are at higher risk to die.

- If a patient has hyperparasitaemia or resistant parasites, management may be different (i.e. choice of oral ACT, duration of treatment). If the patient does not fit to this guideline, you can call SMRU for advice.

- If the patient has hyperparasitaemia confirmed by malaria smear, you may need to continue IV or IM doses until the parasite count decreases even after the patient can tolerate oral medications. If you suspect hyperparasitaemia and do not have access to malaria smear, you should think about referring the patient to a clinic or hospital where a malaria smear can be done.

5.1.1.1. Intravenous (IV) artesunate (can also give IM)

One vial of AS IV contains 60 mg/ml
AS IV or IM (Dosing table pg. 37)

Hour 0 AS 2.4 mg/kg
Hour 12 AS 2.4 mg/kg
Hour 24 AS 2.4 mg/kg
Then continue AS 2.4 mg/kg daily every 24 hours for a total of 4 days or until the patient can tolerate oral medications

- AS can be given intra-muscularly in the same dose as IV

PLUS

5.1.1.2. Intravenous (IV) quinine

One vial of Quinine IV contains 600 mg/2ml
Quinine IV (Dosing table pg. 38)
Hour 0 to H4 Quinine 20 mg/kg given over four hours (preferably in a Metroset /burette)
Hour 8 Quinine 10 mg/kg given over 2 hours
Repeat this dose every 8 hours (Hours 16, 24 etc.) in combination with AS IV

- The total daily dose is 30 mg/kg

THEN

5.1.1.3. ACT oral

When you stop IV treatments, start an ACT – see pg. 2.
For patients that improve rapidly, IV treatment may be stopped after 24 hours. Then give an ACT for 3 days (in this case treatment will be a total of 4 days). If the patient responds slowly to the IV or IM treatment, give a minimum 48 hours of IV treatment then change to an oral ACT for 3-5 days to complete a total of *at least 7 days treatment* because of longer parasite clearance rates along the border (14–16). In some cases, up to 10 days anti-malarial treatment is needed. Call SMRU for advice if you think treatment longer than 7 days is needed.

- See below for details of management of hyperparasitaemia and severe malaria.
- Do not give mefloquine for patients recovering from severe malaria. It increases the risk or post malaria neurologic syndrome, pg. 29.
- Dihydroartemisinin-piperaquine is not associated with significant prolonged QT interval on ECG, or risk of sudden death. (17)

If the patient becomes worse during AS IV plus Quinine IV:

- First check a malaria smear. If you cannot do a malaria smear, you will need to refer.
- Check that the doses are correct and that the drugs are not expired.
- Look for complications or other diagnoses such as typhoid, dengue fever, sepsis, meningitis, etc.
- Consider referral to a hospital. There are no other IV antimalarials that can be used.

5.1.2 Second line treatment

If AS IV or Quinine IV are not available, you can replace with either artemether IM or quinine IM. If both AS IV or Quinine IV are not available, you must give both artemether IM and quinine IM or refer. Continue the IV or IM treatment for 4 days, then change to oral ACT (section 6.1.1.3 above)

Note: If you are not sure how to proceed, refer the patient or contact SMRU

5.1.2.1. Intramuscular (IM) Artemether (if injectable AS is not available)

One vial of Artemether injectable contains 80 mg/ ml
(Dosing table pg. 39)

Hour 0 Artemether 3.2 mg/kg
Hour 24 Artemether 1.6 mg/kg
Then continue Artemether 1.6 mg/kg every 24 hours for 4 days

5.1.2.2. Intra muscular (IM) Quinine (if IV line is not available)

You can use the quinine intravenous solution for IM injection
(Dosing table pg. 38)

Hour 0 Quinine 20 mg/kg
Hour 8 Quinine 10 mg/kg
Repeat this dose every 8 hours (Hours 16, 24 etc.) for 4 days

- To give quinine IM: dilute with same volume of sterile water and give 2 injections in the 2 antero-lateral thighs. (Example: If give 2.8 ml quinine, add 2.8 ml sterile water. Total 5.6 ml will be given as IM injection).
- IM quinine can cause muscle necrosis so check the injection sites daily, pg. 28
- Respect very strict aseptic injection rules because if the risk of abscess.

5.1.3 Combination with transmission blocking primaquine dose

Give the single low dose primaquine when the patient can tolerate oral medications
(Dosage table, pg. 40)

5.2 Important points on management of hyperparasitaemia and severe malaria

5.2.1 Routine observations

On admission check: temperature (Temp), respiratory rate (RR), pulse (PR), blood pressure (BP), consciousness using the Glasgow or Blantyre coma score (pg. 47), glucose, haematocrit (haemoglobin), quantity and colour of urine.

- Do observations every 4-6 hours depending on the condition of the patient. When the patient is eating and drinking observations can be done less often.
  Haematocrit (haemoglobin) can be done daily or more often if there is concern of bleeding or anaemia (i.e colour of urine is like tea)

Very young patients can become very sick more quickly. Take careful observations in these patients and consider other infections if the clinical condition is getting worse or not improving.

5.2.2 Parasite clearance time (PCT)

1. Check parasite count every 4-6 hours.
   - If the parasitaemia does not respond to AS IV plus quinine IV, this may be evidence of artemisinin resistance. See chapter 6 for management of "*P. falciparum* not responding to treatment", pg. 9). Having a lot of schizonts can also increase the parasitaemia.
   - If malaria smear is not available, refer the patient to the hospital.

5.2.3 Patients with schizonts (PFS):

If PFS is reported on the baseline smear of patients with hyperparasitaemia the patient is likely to have a sharp rise in parasitaemia. Check parasite count every 4-6 hours.

- If the patient condition becomes worse or the parasitaemia does not respond to treatment, this may be evidence of artemisinin resistance. Refer to chapter 6 "*P. falciparum* not responding to treatment" (pg. 9).

5.2.4 Very high parasitaemia >20%

These patients are at high risk for poor outcomes. Follow the parasite clearance time (see above section 7.2) and consider referral for cases that do not respond to treatment.

Other points for hyperparasitaemia

Admit patient to the ***inpatient*** department (IPD) for observation since the risk of death is higher in hyperparasitaemia: It is 3% in this area compared to 0.15% with uncomplicated non-hyperparasitaemia[11].

Patients have a higher risk of severe anaemia and need for blood transfusion (pg. 21)

Need longer duration of treatment (at least 7 days). They have greater risk of failure because there are more parasites to kill [12,13]. Sometimes up to 10 days anti-malarial treatment is needed.

5.3 Important points on complications of hyperparasitaemia and severe malaria

Severe malaria is a medical emergency. Most of the deaths are due to delay in treatment or inappropriate therapy. Along the Thailand-Burmese border and in much of Asia severe malaria is seen in all age groups. *The two groups most at risk are children under five years and pregnant women.*

6. Severe malaria

WHO defines severe falciparum malaria as one or more of the following, occurring in the absence of an identified alternative cause and in the presence of *P. falciparum* asexual parastaemia" (18). Severe malaria has been described in non-*falciparum* malaria patients (for example *P. knowlesi* or *P. vivax*). The WHO severe criteria are used for any malaria species.

Clinical features

- Impaired consciousness or coma (GCS <11 in adults or BCS <3 in children)
- Prostration, i.e. generalized weakness so that the patient is unable walk or sit without assistance
- Failure to feed (Drink from a cup by themselves, breast feed in infants)
- Multiple convulsions – more than two episodes in 24 hours
- Deep breathing, respiratory distress (acidotic breathing)
- Circulatory collapse or shock, systolic blood pressure < 80 mmHg in adults and < 70 mmHg in children, capillary refill time ≥ 3 seconds.
- Clinical jaundice plus evidence of other vital organ dysfunction
- Haemoglobinuria
- Abnormal spontaneous bleeding
- Pulmonary oedema (oxygenation <92% on air, RR > 30/min, abnormal examination)

Laboratory findings:

- Hypoglycaemia (blood glucose < 2.2 mmol/l or < 40 mg/dl)
- Metabolic acidosis (base deficit >8 mEq/L or plasma bicarbonate < 15 mmol/l or venous lactate ≥ 5mmol/L)
- Severe normocytic anaemia (Hb <6 g/dl or Hct <20%)
- Haemoglobinuria
- Hyperparasitaemia with other signs of severity
- Renal impairment (serum creatinine > 265 µmol/l (3 mg/dL) or BUN >20 mmol/L (56 mg/dL)
- Bilirubin >50 µmol/L (3 mg/dL) with parasite count >100,000/µL)
- Radiologically confirmed pulmonary oedema

6.1 Management of complications related to severe malaria

Management depends on the level of health care that is available.

Absolute indications for referral to well-equipped hospital:
Acute renal failure (needs dialysis)
Respiratory insufficiency (Needs intubation and mechanical ventilation)
Shock not responding to fluid resuscitation

Points to remember for the care of the patient with severe malaria.

- aspiration in unconscious patient (Keep upright as close as possible to 45 degrees and insert a nasogastric tube to empty the stomach)
- bedsores (change position every 2 hours)
- corneal ulceration (irrigate eyes with saline, artificial tears or lubricant / ointment). Keep eye lids kept closed with eye pads.
- malnutrition

Avoid these mistakes in severe malaria:

- Fail to diagnose severe signs
- Missing hypoglycaemia
- Inappropriate fluid management
  (may lead to pulmonary oedema OR renal failure)
- Delay in blood transfusion

6.1.1 Coma Management (Steps A-K)

The arrival of the comatose/unconscious patient requires medical staff to be skilled in basic life support (BLS) and to operate quickly to reduce morbidity and mortality. See Coma management (pg. 49).

6.1.2 Hypoglycaemia

Blood glucose must be confirmed with a glucometer or glucose sticks.

Treatment for hypoglycaemia: 5ml/kg of 10% dextrose (D10W) over 10 minutes.

- 10% dextrose (D10W) can be made by removing 50ml from a 500ml bag of 5% dextrose (D5W) and adding 50ml of 50% dextrose.
- It is important to follow the D10W bolus with a continuous infusion of 10% dextrose. The rate is adjusted according to blood sugar and it can be run at the same time (in a different IV site) as normal maintenance fluids (pg. 46)

The risk of hypoglycaemia is higher in:

- Children
- Pregnant women
- With quinine treatment

Always check blood glucose if there is decreasing consciousness.
Check plasma glucose every 4 hours in the unconscious patient.
Consider other causes of decreased consciousness like shock, or meningitis.

6.1.3 Evaluate for meningitis

If not sure about the diagnosis of cerebral malaria, a lumbar puncture should be performed to rule out bacterial meningitis (if there are no contraindications, see below).

Contraindications for lumbar puncture
Do not perform if any of the following are present:

- signs of raised intracranial pressure such as unequal pupil size, non-reactive pupils, a very slow heart rate (<50 bpm in adults)
- focal neurological signs
- irregular breathing or severe respiratory distress
- low platelets or bleeding
- convulsions (seizure or fitting)

The following symptoms are uncommon in cerebral malaria, so meningitis must be considered if:

- Stiff neck (a sign of meningeal inflammation)
- Malaria slide is negative for asexual forms of *P. falciparum*
- Shock
  - Septic shock: low BP, high pulse rate (can look similar to hypovolemic shock, but septic shock does not respond as well to IV fluids)
  - Neurogenic shock: low BP, variable pulse rate, low respiratory rate.
- Leucocytosis and/or a left shift (elevated band cells) in the white cell count
- Cloudy cerebrospinal fluid (CSF) when lumbar puncture done

6.1.3.1. First line treatment for meningitis

Ceftriaxone: Adults 2gm IV BD
Children 50mg/kg IV BD

Continue treatment for 10-14 days. Refer to the SMRU medical guidelines for more information. Most 3rd generations cephalosporins (in the same class as ceftriaxone) can be used to treat meningitis.

- If possible, the CSF should be sent for cell count, glucose and protein level, Gram stain (for bacteria) and AFB stain (for tuberculosis), and culture. The Gram stain and cultures (CSF and blood) are the most helpful for diagnosis and should be prioritized.

6.1.4 Convulsions (Seizure or Fitting)

Observe for convulsions, these may be very subtle. Convulsions should be treated.
Check the blood glucose level. Hypoglycaemia can also cause convulsions.

6.1.4.1. Acute treatment

Diazepam: Adults 5-10 mg IV over 5 minutes (maximum 30 mg)
Children 0.3 mg/kg IV over 5 minutes (maximum 10 mg)

The same dose of IV solution may be given per rectum if an IV line is not available.
May repeat diazepam dose every 5 - 10 minutes for total of 3 doses

- If the patient continues to have convulsions (>10 min) the diagnosis is status epilepticus. Refer to the hospital.

> IV diazepam will stick to PVC so don't inject it in the giving set.
> Seizures are more common in children than adults with severe malaria.
> Prophylaxis for convulsions is not recommended[9].

Phenobarbitone is not recommended for prophylaxis of recurrent convulsion because it is related to increased mortality in cerebral malaria (19).

6.1.5 Shock

Shock (systolic blood pressure below 70 mm Hg in adults, capillary refill time > 2 seconds in children) is an uncommon finding in severe malaria. If a malaria patient has shock, you should also suspect bacterial sepsis.

6.1.5.1. Management of shock

1. Do blood cultures before antibiotics, if possible. But, do not delay if the patient is very sick.
2. Start fluid bolus: Adults 1 L NSS, Children 20 ml/kg NSS
   If the blood pressure does not improve, refer to the hospital. The patient may need IV medicines to increase blood pressure.

> Always use NSS or Ringers bolus for shock or dehydration. *Do not use D5W for bolus.*

6.1.5.2. Treatment of shock

Start empirical antibiotic therapy with:
Ceftriaxone: Adults 2gm IV OD, Children 50 mg/kg IV OD (give BD if suspect meningitis)

OR

Cefotaxime: Adults 1gm IV TID, Children 50 mg/kg IV QID

- A single dose of Gentamicin (7 mg/kg) can be given if there is no improvement while on Ceftriaxone or Cefotaxime in suspected septic shock.
- Continue fluid resuscitation until mean blood pressure is > 60-70 mmHg.

> **Mean BP = diastolic BP + 1/3*(systolic BP-diastolic BP)**

6.1.6 Fluid management and renal failure

This is one of the most difficult parts of caring for a comatose/unconscious malaria patient. *Paracetamol has been shown to protect the kidneys against damage from malaria* (20). *Give scheduled paracetamol every 6 hours for 72 hours starting from admission*. Continue the scheduled paracetamol even if the patient does not have fever. Consider paracetamol IM or crushed tablets by NG tube if possible. Paracetamol is an extra treatment to help the kidneys so give it if you can.

Be careful with fluid and blood transfusions

Volume overload (pulmonary oedema) can be dangerous and can cause death. Check for dyspnoea, orthopnoea (dyspnea when prone) lung crepitations and low SpO2. Between boluses and during blood transfusions, check respiratory rate, SpO2 (if available) and lung exam.

6.1.6.1. Management of renal failure

1. Insert urinary catheter
    - Monitor fluid input and output, check urine stick (if available)
    - Give IV fluids if there are signs of dehydration or urine output< 0.5 ml/kg/hr (see below)
    - Observe for signs of pulmonary oedema
    - Check BUN and creatinine if possible. Many patients with Acute kidney injury (AKI) with malaria may have normal urine output but the kidney tests will be abnormal.

2. If there is no pulmonary oedema increase maintenance IV fluids to 5 ml/kg/hour for 4 to 6 hours.

3. If urine output does not improve with IV fluids after 6 hours, the patient may have AKI. **Test** for AKI with a Furosemide Stress Test:
    a) Give IV furosemide 1mg/kg. Furosemide IV can cause deafness if given as a bolus. It is better to give an infusion by mixing 1mg furosemide with 1ml IV fluid. In children, the infusion should be no more than 0.5 mg/kg/minute. In adults, give <4mg/minute.
    b) Monitor urine output *strictly*. After an IV furosemide dose, urine output should be >100 ml each hour (i.e. 50ml in 30 minutes) or approximately 2ml/kg/hour.
    c) If no response in 30 minutes, give IV furosemide 2mg/kg. If no response in 30 minutes, give 3 mg/kg. If no response in 30 minutes, give 4 mg/kg.
    d) If poor or no response to furosemide, the kidney failure is *severe* and *the patient should be referred to a well-equipped hospital for dialysis.*
    e) If the patient does not need referral for dialysis, continue to monitor urine output and pulmonary oedema. *Continuing furosemide will not treat the AKI and should only be used if there is pulmonary oedema.*
    f) You may need to refer the patient if the urine output decreases again. Early blood transfusion does not improve AKI and can cause pulmonary oedema.

4. Other management if signs of pulmonary edema:
    - The patient should be in a sitting position
    - Oxygen therapy (nasal catheter or face mask

5. If there are no symptoms of pulmonary oedema after 4-6 hrs of 5 ml/kg/hr IV fluids, start maintenance fluid with close monitoring.

6.1.6.2. Maintenance fluid rate calculation

Adults: 100 ml/hr alternating D5W and NSS.
The rate of infusion may be slower or faster depending on the patient.

Children >5 years: First 10 kg body weight, give 4 ml/kg/h, next 10 kg bodyweight, give 2ml/kg/h, and for each additional kg body weight, give 1 ml/kg/h.

Example: 27 kg = 40 + 20 + 7 = 67 ml/hr

6.1.6.3. Maintenance fluid in small children (age 4 weeks to ≤ 5 yr)

Use 0.81% saline and 5% dextrose

- How to make: Take out 50ml from 500ml of NSS then put in 50ml of 50% dextrose.
- Infusion rate (pg. 46)
- For the fluid management of infants less than 4 weeks refer to the SMRU Neonatal Guidelines.

6.1.6.4. Monitor closely during maintenance IV fluids

Close monitoring of the fluid balance is important in severe malaria, because dehydration can cause to renal failure and volume overload can cause to pulmonary oedema

- Urine output should be > 0.5 ml/kg/hr.
  Example: Weight = 40kg, urine volume 120 ml in last 3 hours
  = 120 ÷ 3 ÷ 40 = 1 ml/kg/hr. Urine output is enough.
- If urine output is < 0.5 ml/kg/hr see renal failure protocol (pg. 19)

Points to check for dehydration:
Skin turgor
Dry lips and mouth
No tears in eyes
Urine stick Specific Gravity (SG) >1.020

Points to check for fluid overload (pulmonary oedema):
Dyspnea, increased RR, crepitation or low oxygenation (low SpO2)
Jugular venous distension (can be difficult to assess)
Patient cannot breathe when they lie down (orthopnoea)

6.1.7 Management for Respiratory Failure

Pulmonary oedema with Acute Respiratory Distress Syndrome (ARDS) is mainly a complication in adults and pregnant women. It can still develop in the days after admission. It is caused by capillary leakage in the lung because of malaria. Fluid overload is an important risk factor.

6.1.7.1. Differential diagnosis

Metabolic acidosis (deep breathing called Kussmal breathing)
(https://www.youtube.com/watch?v=brZi9-FRHWk)
Severe anaemia (pallor)
Pneumonia (lung crepitation on one side)

6.1.7.2. Investigations (if available):

Peripheral white blood count (WBC). High WBC may be from other infection, not malaria.
Chest X-ray may show diffuse shadowing of the lung fields in ARDS. It may be normal or show an infiltrate in pneumonia.

When to refer to the hospital:
Severe dyspnoea (high RR, increased work of breathing)
Cyanosis (if pulse oximetry not available)
Pulse oximetry (SpO2<90%) if available

6.1.8 Check parasitaemia

Severe malaria patients should be monitored with regular malaria smear (4-6 hourly) until negative 2 consecutive times (pg 14).

6.1.9 Management of severe anaemia

Check the haemoglobin or haematocrit on admission and every 24 hours.
Give blood transfusion for all patients with Hct < 20% (Hb ≤ 6 g/dL).

- Dehydration can cause high haematocrit then anaemia is more difficult to diagnose
- If an anaemic patient has severe symptoms (i.e shock), *blood transfusion can be given early* even if Hct is not below 20%.

6.1.9.1. Blood Transfusion

Screen donor blood: blood group and Rhesus, cross-match, HIV and Hepatitis B, (Hepatitis C and syphilis if available), malaria smear, and Hct (or Hb).

Whole blood or packed red cells can be given. Packed red cells should be given if the patient has pulmonary oedema or risk for pulmonary oedema (i.e. suspect renal failure).

- How to prepare packed red cells: Let the blood bag hang and the clear plasma fluid will rise to the top of the bag. Only give the red cells during transfusion. You can discard the plasma.

  Adults: give 1-2 units
  Children: give 20 ml/kg

- Give transfusions over 4 hours or 6 hours if pulmonary oedema is a concern.

Monitor during blood transfusion

Every 15-30 minutes:

- Temp, HR, RR, BP
- Check for rash or itching
- Check for lung crepitations (Volume overload)
- Check for lung wheezing (Anaphylaxis)

If an allergic reaction develops:

- Stop transfusion

If severe:

- Give Adrenaline STAT
- Give chlorpheniramine
- Over the next 24-48 hours, hydrocortisone (IV) or another steroid should be given regularly

6.1.10 Jaundice

Patients with severe malaria can be severely jaundiced, due to intravascular haemolysis of parasitized (and unparasitized) red cells and hepatic dysfunction. Jaundice is a poor prognostic sign. There is no specific therapy.

6.1.11 Blackwater fever

Haemoglobinuria is caused by massive intravascular haemolysis. It is associated with quinine therapy and G6PD deficiency. Give blood transfusion to maintain a Hct > 20% (Hb >6g/dL). There is no specific therapy.

- Antimalarial therapy with *quinine must be continued*.
- STOP primaquine if the patient G6PD status is deficient or unknown

6.1.12 Disseminated Intravascular Coagulation (DIC)

DIC is relatively rare in severe malaria (5%), but much more common in septicaemia. If you suspect DIC, septicaemia should be considered and treated.

Diagnosis:

Spontaneous bleeding and oozing from venipuncture sites

(To test clotting time at the local hospital blood needs to be put into a citrate tube. This is not important in the field situation.)

Management:

Vitamin K 10 mg IV (slowly) every 24h for 3 days

Nursing care & feeding

Avoid trauma

6.1.13 Feeding

Early NGT feeding increases the risk of aspiration pneumonia. There is no clear benefit for enteral feeding in patients with severe malaria. Surviving patients with cerebral malaria frequently recover consciousness over the first 24–72 hours[8]. Wait to feed the patient when they are conscious.

7. Treatment of non-*P. falciparum* malaria

7.1 *P. knowlesi*

P. knowlesi had been observed to occur in forested regions of SE Asia. *P.knowlesi* is human infection with the monkey malaria parasite and reported mostly in people living close to the natural monkey hosts (21). On the malaria smear, ring stages of *P. knowlesi* look like *P. falciparum*, but older forms are similar to the band forms of *P. malariae*. PCR genotyping assays can differentiate between these 2 species correctly.

7.1.1 Treatment for *P. knowelsi*

The treatment for uncomplicated, hyperparasitaemia and severe malaria is the same as for *P. falciparum* (pg. 11)

- Like *P. falciparum*, *P. knowlesi* can reach high parasitaemias rapidly which can be fatal so use the same treatment guideline as for *P. falciparum* (pg. 2 and 11)

7.2 *P. vivax*, *P. ovale* and *P. malariae*

P. vivax and *P. ovale* both have hypnozoites. This means that the parasite has dormant forms in the liver. The hypnozoites can come out of the liver to make a new infection even when the patient does not have a new mosquito bite.

7.2.1 Uncomplicated *P. vivax, P. ovale and P. malariae* treatment

7.2.1.1. First line treatment

Each chloroquine tablet contains 250 mg chloroquine phosphate (approximately 150 mg base) (Dosage table pg. 41)

First 2 days: Chloroquine 10 mg base/kg once daily
Third day: Chloroquine 5 mg base/kg once daily

7.2.1.2. Second line treatment

DP - Effective against *P. vivax* in areas where there is chloroquine resistance (9,22)

OR

COA - Day 42 failure is high due to the shorter half-life of lumefantrine compared to piperaquine (23,24).

- Any ACT can be used. The drug doses are the same as for *P. falciparum* (25).
- Sulfadoxine-pyrimethamine is not effective against *P. vivax* (or *P. falciparum*).

7.2.2 Treatment of *P. vivax* recurrence

P. vivax recurring > 28 days	Can be treated with standard treatment and must be supervised
P. vivax recurring ≤ 28 days	Maybe due to resistance (exclude non-compliance). An alternative treatment with ACT should be given and must be supervised

7.2.3 Treatment of *P. vivax* in patients who are unwell

In this area, severe malaria caused by *P. vivax* infection is rare (26). If patients already have other medical problems, they may get severe symptoms when have a *P. vivax* infection. Remember to treat the underlying condition (i.e. sepsis, diarrhea especially typhoid fever, or chronic disease).

Give Artesunate IV/IM (use the same doses as for *P. falciparum*, pg. 37) or quinine (Dosage table pg. 38). When oral treatment is tolerated, change to CQ once daily for 3 days (Dosage table pg. 41)

7.2.4 Prevention of *P. vivax and P. ovale* relapse with radical cure

P. vivax and *P. ovale* have a hypnozoite stage. Hypnozoites stay in the liver and cause more infections even when there is no new mosquito bite. These repeated infections are called relapses.

Primaquine or tafenoquine can be used to prevent relapses. Both are in the 8-aminoquinoline class of antimalarials. WHO recommends that primaquine should be given for *P. vivax* infections (18). The WHO malaria treatment guideline is not yet updated for the use of tafenoquine.

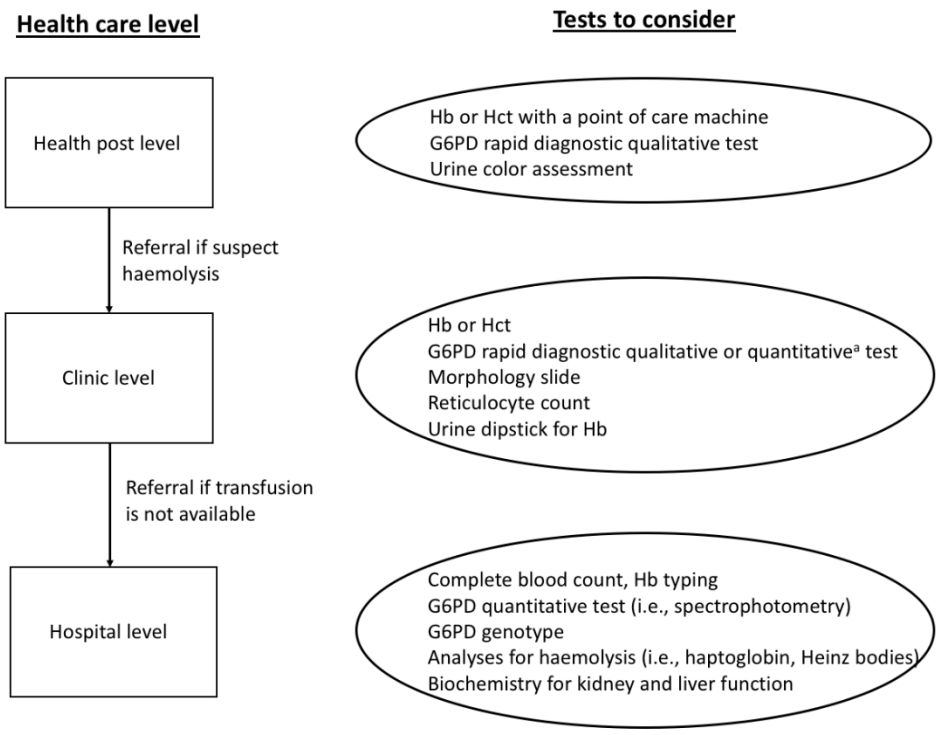
7.2.4.1. First line treatment for radical cure

- Before giving primaquine or tafenoquine you should **check G6PD status**, if testing is available.
- Before primaquine you can use the <u>qual</u>itative tests – the fluorescent spot test (FST). Before tafenoquine, you must check G6PD status with a <u>*quan*</u>*titative* test – G6PD Biosensor. You will need training before using any G6PD tests.
- If pregnant, you cannot give primaquine or tafenoquine. We recommend CQ prophylaxis in pregnant women until radical cure can be given, pg. 27. You can give radical cure treatment at 4 weeks postpartum or later. This information might change in the future, after there are more studies about primaquine in breast milk.
- For non-pregnant adults and children >6 months old:
    a. If G6PD status is deficient or unknown:
    Primaquine 0.75 mg/kg/dose every week for 8 weeks (Dosage table, pg. 43)
    b. If G6PD normal with a qualitative test (e.g., FST):
    Primaquine 0.5 mg/kg/day for 14 days (Dosage table, pg. 42)
    c. If G6PD ≥70% or 6.0IU/gHb with a *quantitative* test (i.e. G6PD Biosensor):
    Primaquine 0.5 mg/kg/day for 14 days (Dosage table, pg. 42)
    OR
    <u>Only for >16 years old</u>: Tafenoquine 300mg stat dose

Considerations for administering radical cure doses:

- Crushed primaquine tablets are very bitter, so mix with sugar water or juice for infants and children.
- Give dose after food and/or drink to prevent epigastric pain
- Try to supervise treatment so you can be sure the patient is taking all the doses to ensure adherence and effective treatment against relapses.
- Try to supervise treatment and follow up to check for anaemia or haemolysis,
- If the patient has moderate anaemia (e.g., Hct <25% or Hb <8g/dL):
    - Do not start radical cure. Follow up in 3-6 days to check symptoms and Hct/Hb and consider starting radical cure treatment when the anaemia is better.
    - Follow closely for clinical signs of worsening anaemia.
- *Do not give primaquine or tafenoquine to:*
    - G6PD deficient individuals (use the weekly dose, pg. 43)
    - Pregnancy
    - Children < 6 months (including congenital malaria) for primaquine, ≤16 years for tafenoquine
    - Women breastfeeding infants who are <28 days old for primaquine, and <6 months old for tafenoquine
    - If the patient has a history of haemolysis with any drug.

If 8-aminoquinoline associated haemolysis is suspected, you may take investigations depending on the resources available at your site(27). If you do not have the resources needed, refer to a higher level of care.



[a] There is one new point of care G6PD quantitative tests available. If you plan to use this test, we suggest that you contact SMRU for training so 8-aminoquinolines can be prescribed safely. Reference can be accessed at https://doi.org/10.12688/wellcomeopenres.15100.2

Important follow up issues during 8-aminoquinoline treatment

For adverse effects, see pg. 29

Check Hb or Hct before giving treatment if there is concern about haemolysis or anaemia in the patient. It is good to have a baseline Hb or Hct so you can compare results.

Educate the patient. If the patient develops pallor, dizziness, difficulty breathing or other signs, the patient should return to the clinic.

Do not share tablets with other people. Keep away from children. We do not know the G6PD status of the people living around you, so if they are G6PD deficient, they can develop adverse effects if they your primaquine or tafenoquine tablets.

For missed primaquine doses:

- Repeat the primaquine treatment if a second *P. vivax* infection occurs >14 days from the previous *P. vivax* infection. If the primaquine treatment is ongoing (i.e. weekly primaquine dose in G6PD deficiency) then continue until finished (no need to repeat).

- If a primaquine dose is missed do not try to take a double dose. *Continue the normal daily dose until the full course is completed.* Finishing the full 14 doses is the most important even if it takes 15 days or longer.

Follow up in 3-5 days to check Hct or Hb in patients who have high risk for haemolysis or anaemia.

Treat with blood transfusion if the haemolysis is severe, pg. 21.

Refer to the hospital if a patient develops haematuria or severe anaemia and you cannot manage the case at your site.

7.3 Treatment of *P. vivax* in pregnancy

7.3.1 If the mother has an acute *P. vivax* infection in pregnancy

Treat the acute infection with the usual dose of CQ
(Dosage table, pg. 41)

THEN

Between days 14 to 28 after starting CQ treatment, start CQ prophylaxis if the malaria smear is negative. (see section 9.3.2 below).

7.3.2 If the mother has a history of *P. vivax* in pregnancy

If the mother has had *P. vivax* during pregnancy, she is at risk of relapses from the hypnozoites in the liver. Prophylaxis with CQ is recommended since pregnancy is a contraindication to use of primaquine.

- First check (RDT or malaria smear) that the mother does not currently have *P. vivax* malaria. Then start prophylaxis with CQ (2 tabs) weekly. After delivery, continue CQ prophylaxis every week until postpartum week 4 or until radical cure can be given.
- At postpartum week 4 (the baby should be ≥ 28 days old) also give the mother primaquine radical cure. Primaquine excretion into breast milk is minimal (28) but we do not yet know about excretion into colostrum.

7.3.3 If the mother has a recurrence of *P. vivax* in pregnancy

- Refer to section 9.3.1 (pg.24, above)

7.4 *P. vivax* treatment for congenital malaria

If unwell, give:
Artesunate IV or IM (2.4 mg/kg) for the first dose

If well, give:
Chloroquine once daily for 3 days (Dosage table pg. 41)

- Follow-up malaria smear weekly until day 63 – this allows early detection and treatment before the infant becomes symptomatic with fever or anaemia.
- Do not give primaquine or tafenoquine for radical cure of *P. vivax* malaria to infants < 6 months old.

8. Contraindications and adverse effects of antimalarials

8.1 Vomiting

Observe the patient for 1 hour after taking antimalarials, for vomiting. Patients who vomit have a higher risk of drug treatment failure. If not using fixed dose tablets, the best way to give the medicines is to give them as separate doses (i.e. artesunate first and after 30 minutes give mefloquine second).

If vomiting:

Within 30 minutes: Repeat the whole dose.
Between 30 minutes and one hour: Repeat half the dose

8.2 Allergy

If there is a history of severe allergy do not give the drug again.

8.2.1 Allergy to Quinine or Chloroquine

Try to give artesunate, artemether or ACT.

If not available, pre-medicate the patient with dexamethasone IM (adults 12 mg; children 0.25 mg/kg) or hydrocortisone sodium succinate (adult 2g; children 2 mg/kg), and oral chlorpheniramine (adult 4 mg; children 0.1mg/kg) before starting.

8.2.2 Allergy to Artesunate

Artesunate allergy can be severe: use quinine (+ doxycycline or clindamycin) or mefloquine.

8.3 Common serious side effects

8.3.1 Quinine

Quinine commonly causes cinchonism. This is a group of symptoms: headache, nausea, tinnitus (ringing ears), blurry vision, and dysphoria (anxiety or unhappiness). The dose should be continued even if the patient complains of cinchonism. Give kind support to the patient and treat pain with paracetamol if not already given.

Hypoglycaemia is also a common adverse effect of quinine. Pregnant women are at higher risk for hypoglycaemia. IV quinine should be given with a D10W infusion, pg. 38.

Quinine should never be given as a bolus injection because it can cause hypotension and death. Only give infusion with a Metroset or burette to control the rate of infusion. Quinine IM should be dilute (ie. 60 mg/ml) to reduce pain with injection. If the IM injection is too concentrated (ie. 300 mg/ml), it can cause muscle necrosis and abscess (29).

8.3.2 Tetracycline and Doxycycline

Do not give tetracycline to pregnant women or children < 8 years. It can cause permanent tooth discolouration in the infant and child. Doxycycline can cause this as well, but much less often/less severe. Avoid in pregnant women and young children unless there are no other medicines available.

8.3.3 Mefloquine

Neuropsychiatric side-effects are the most common severe side-effect. Give diazepam if symptoms are severe. Do not repeat mefloquine within 63 days of previous MAS3 treatment. Do not give mefloquine in patients who have neurologic or psychiatric side effects, a history of epilepsy, previous neuropsychiatric disease or recent Yaba use.

8.3.4 Clindamycin

Antibiotic associated colitis is the most toxic side effect and can be fatal. Explain the risk of developing diarrhoea to the patient before giving the drug. Explain if diarrhoea develops stop the drug immediately. Treat the diarrhoea according to the severity. Severe cases will need IV fluids and metronidazole.

8.3.5 Primaquine

Primaquine commonly causes epigastric or abdominal pain. Give food and / or drink before the dose to prevent pain.

Another common side effect is methaemoglobinaemia (oxidized form of hemoglobin). At high levels patients can have cyanosis (blue lips and fingers) or have other symptoms like tiredness, difficulty breathing (dyspnea), dyspnea on exertion, dizziness, headache. Very high methaemoglobin levels (>40%) can be fatal but are very rare with normal doses. If someone has cyanosis and complains of more symptoms or new symptoms while on treatment, stop the primaquine.

Haemolysis is a serious side effect that can occur in people with G6PD deficiency. <u>The single low dose primaquine for *P. falciparum* is safe when given to G6PD deficient patients.</u> The daily dose primaquine for *P. vivax* is not safe in G6PD deficiency so should not be given. Patients with G6PD deficiency should receive the weekly dose, pg. 43. Stop primaquine if there are signs of severe anaemia or haemolysis. If possible, follow up at day 3-5 to check for haemolysis (red or tea colour urine, pallor/anaemia, other haemolysis symptoms). If unwell refer to hospital immediately because a blood transfusion may be needed.

8.3.6 Tafenoquine

Tafenoquine commonly causes epigastric or abdominal pain. Give food and/or drink before the dose.

Patients can also develop methaemoglobinaemia or haemolysis (see primaquine section above for details). If symptoms develop, tafenoquine cannot be stopped because it is given as a single dose. If possible, follow up at day 3-5 to check for haemolysis (red or tea colour urine, pallor/anaemia, other haemolysis symptoms). Consider follow up every week until stable. If unwell refer to the hospital immediately because a blood transfusion might be needed. There are no other common serious side effects from tafenoquine, but if the patient has vision changes, neuropsychiatric problems (i.e. depression, psychosis, suicide), you should follow regularly for 3 months (because tafenoquine is a long acting drug) (30).

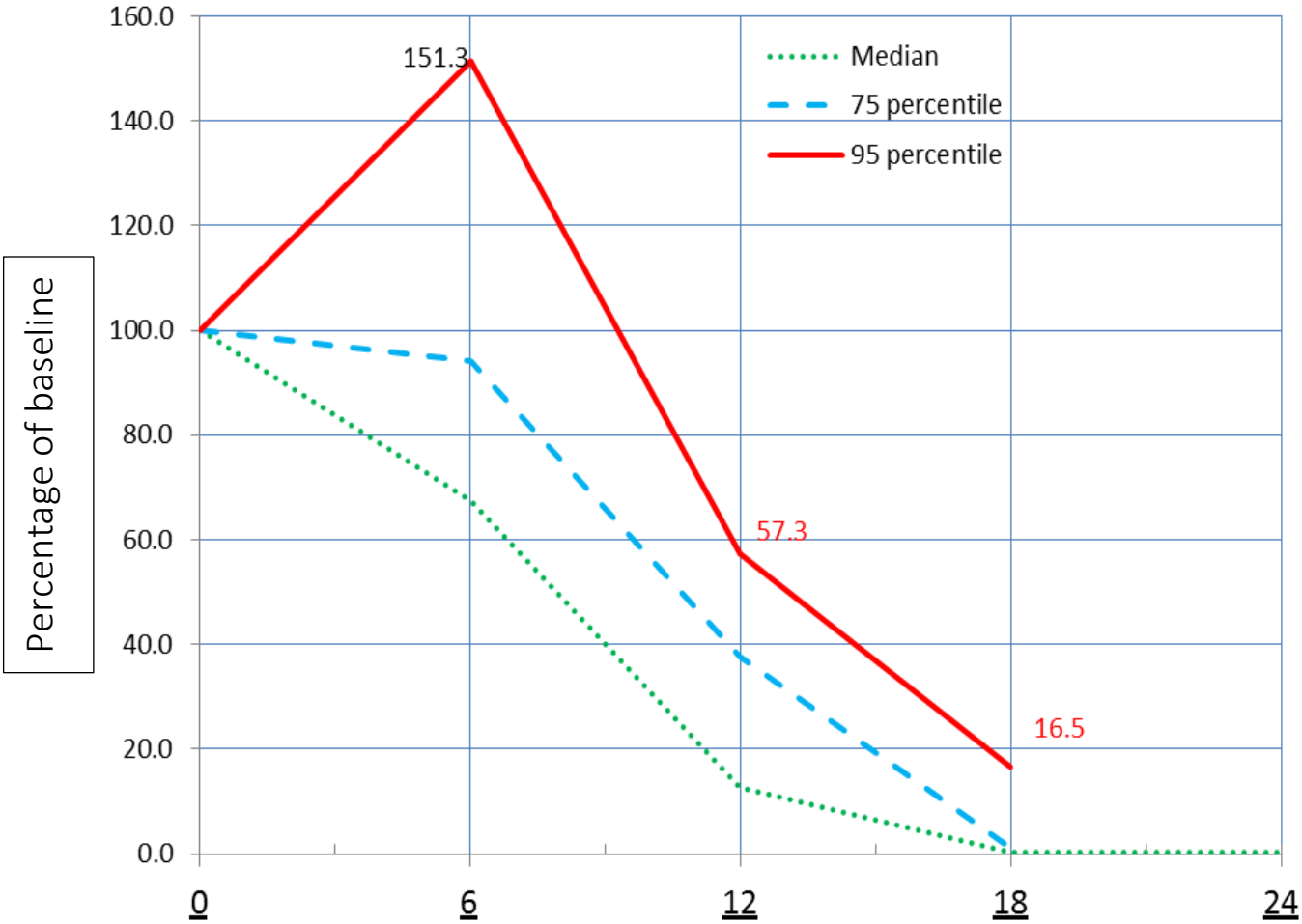
9. Glossary

1st line:	Best choice for treatment	2nd line:	not best choice but acceptable
A/AS:	Artesunate	AFB:	acid fast bacilli
AKI:	acute kidney injury	BCS:	Blantyre Coma Score
BD:	twice daily	BP:	Blood pressure
C:	Clindamycin	cc:	cubic centimetre =millilitres
CSF:	cerebrospinal fluid	D:	day
D:	Doxycycline	DP:	dihydroartemisinin-piperaquine
D5W:	dextrose 5% in water	FCR:	fever clearance rate
G6PD:	glucose 6 phosphate dehydrogenase	GCS:	Glasgow coma score
H:	hour	Hb:	haemoglobin
Hct:	haematocrit	IM:	Intramuscular
IV:	Intravenous	IRBC:	Infected RBC
kg:	kilogram	M:	Mefloquine
MAS:	Mefloquine and Artesunate	mg:	milligrams
NSS:	normal saline solution	OD:	once daily
PCR:	Polymerase Chain Reaction	PF:	Plasmodium falciparum
PCT:	parasite clearance time	PFG:	Plasmodium falciparum gametocytes
PFS:	Plasmodium falciparum schizonts	pg:	page – as in page numbers
PM:	Plasmodium malariae	PO:	Plasmodium ovale
PR:	pulse rate	PV:	Plasmodium vivax
Q:	Quinine	QID:	four times daily
RBC:	red blood cell	RR:	respiratory rate
SG:	Specific Gravity	SpO2:	Oxygen Saturation
T:	Tetracycline	TID:	three times daily
WHO:	World Health Organisation		

10. Appendices

10.1 Parasite clearance

Because of artesunate resistance, we do not monitor parasite clearance for rescue treatment with artesunate. (Giving the rescue dose of artesunate may not decrease the parasitaemia because of drug resistance and may not help the patient.) This graph is here so you can check parasite clearance for your own information, especially at the peak (hour 4-6). The parasite clearance will be much slower (past the red line) and likely still positive after hour 24.



Calculating parasitaemia

Parasite count/500 WBC: Parasitaemia per mcl = $\frac{\text{parasite count * WBC (or 8000)}}{500}$

Parasite count /1000 RBC: Parasitaemia per mcl = parasite count * Hct * 125.6

Hour 0 parasitaemia is 100%
For each malaria smear after Hour 0, calculate the parasitaemia. For percent from baseline:

$$\text{Percent} = \frac{\text{Current parasitaemia} - \text{Hour 0 parasitaemia}}{\text{Hour 0 parasitaemia}} \times 100$$

10.2 DP dosing table

1 adult tablet contains 40mg of dihydroartemisinin and 320 mg piperaquine OR
1 paediatric tablet contains 20 mg of dihydroartemisinin and 160 mg of piperaquine
*A suspension is made by allowing 1 tablet to dissolve in 5ml clean water.

Weight(kg)	Tab (40 mg DHA)	ml (40 mg DHA)	Tab (20 mg) DHA)	ml (20 mg DHA)	Frequency
5	*	1.3 ml	*	2.6 ml	OD
6	*	1.6 ml	*	3.2 ml	OD
7	*	2 ml	*	4 ml	OD
8-12	0.5		1		OD
13-20	1.0				OD
21-30	1.5				OD
31-40	2.0				OD
41-50	2 .5				OD
51-60	3.0				OD
61-70	3 .5				OD
71-84	4.0				OD
85-100	5.0				OD

10.3 Artemether-lumefantrine (COA) dosing table

1 tablet contains 20mg artemether and 120 mg lumefantrine.

Weight (kg)	tab	Frequency
≤15	1	BID
16-25	2	BID
26-35	3	BID
>35	4	BID

Need to take with some fried or oily food or a carton of flavored milk.

10.4 Oral artesunate dosing table

1 tablet contains 50 mg
*A suspension is made by allowing 1 tablet to dissolve in 5ml clean water (10 mg / ml)

Weight (kg)	4 mg/kg (daily dose)		2 mg/kg daily dose)	
	tab	ml	tab	ml
2	*	0.8	*	0.4
3	*	1.2	*	0.6
4	*	1.6	*	0.8
5	*	2.0	*	1.0
6	*	2.4	*	1.2
7	*	2.8	*	1.4
8	*	3.2	*	1.6
9	*	3.6	*	1. 6
10	*	4.0	*	2.0
11	1		1/2	
12	1		1/2	
13 - 14	1		1/2	
15 - 16	1 1/4		1/2	
17 - 20	1 1/2		3/4	
21	1 3/4		3/4	
22 - 23	1 3/4		1	
24 - 26	2		1	
27 - 28	2 1/4		1	
29	2 1/4		1 1/4	
30 - 32	2 1/2		1 1/4	
33 - 34	2 3/4		1 1/4	
35	2 3/4		1 1/2	
36 - 39	3		1 1/2	
40	3 1/4		1 1/2	
41 - 42	3 1/4		1 3/4	
43 - 45	3 1/2		1 3/4	
46	3 3/4		1 3/4	
47 - 48	3 3/4		2	
49 - 51	4		2	
52 - 53	4 1/4		2	
54	4 1/4		2 1/4	
55 - 57	4 1/2		2 1/4	
58 - 59	4 3/4		2 1/4	
60	4 3/4		2 1/2	
61 - 64	5		2 1/2	
65	5 1/4		2 1/2	
66 - 67	5 1/4		2 3/4	
68 - 70	5 1/2		2 3/4	

10.5 Oral mefloquine dosing table

	Single STAT dose		Daily split dose for 2 days				Daily split dose for 3 days	
Weight	25 mg/kg(STAT)		15 mg/kg		10 mg/kg		8 mg/kg(OD)	
(kg)	tab	(ml)	tab	(or ml)	tab	(ml)	tab	(ml)
5	1/2	2.5	1/4	1.5	1/4	1	0.5	0.8
6	1/2	3	1/4	1.8	1/4	1.2	0.5	1.0
7	3/4	3.5	1/2	2.1	1/4	1.4	0.8	1.2
8	3/4	4	1/2	2.4	1/4	1.6	0.8	1.3
9	1	4.5	1/2	2.7	1/2	1.8	1.0	1.5
10	1	5	1/2	3	1/2	2	1.0	1.7
11	1	5.5	1/2	3.3	1/2	2.2	1.0	1.8
12-14	1 1/4		3/4		1/2		1/2	
15-16	1 1/2		1		1/2		1/2	
17-18	1 3/4		1 1/4		1/2		3/4	
19-21	2		1 1/4		3/4		3/4	
22-23	2 1/4		1 1/2		3/4		3/4	
24-26	2 1/2		1 1/2		1		1	
27-28	2 3/4		1 3/4		1		1	
29-31	3		1 3/4		1 1/4		1	
32-33	3 1/4		2		1 1/4		1	
34-36	3 1/2		2		1 1/2		1 1/4	
37-38	3 3/4		2 1/4		1 1/2		1 1/4	
39-41	4		2 1/2		1 1/2		1 1/4	
42-43	4 1/4		2 1/2		1 3/4		1 1/4	
44-46	4 1/2		2 3/4		1 3/4		1 1/2	
47-48	4 3/4		2 3/4		2		1 1/2	
49-51	5		3		2		1 2/3	
52-53	5 1/4		3 1/4		2		1 3/4	
54-56	5 1/2		3 1/4		2 1/4		2	
57-58	5 3/4		3 1/2		2 1/4		2	
59-61	6		3 1/2		2 1/2		2	
62-63	6 1/4		3 3/4		2 1/2		2	
64-66	6 1/2		4		2 1/2		2 1/4	
67-68	6 3/4		4		2 3/4		2 1/4	
69-71	7		4		3		2 1/4	
72	7 1/4		4 1/4		3		2 1/2	
73-77	7 1/2		4 1/2		3		2 1/2	
78	7 3/4		4 3/4		3		2 3/4	
79-81	8		4 3/4		3 1/4		2 3/4	

For the young children, mefloquine can be given by dissolving in sugar water/sweet juices and a suspension is made by allowing 1 tablet (250 mg) to dissolve in 5ml (1ml=50mg), or tablet can be cut and a fraction of tablet is given depending on the compliance.

10.6 Oral quinine dosing table (tablet)

1 tablet contains 300 mg quinine sulphate (salt)
10 mg salt/kg TID (total daily dose is 30 mg salt/kg/d) x 7 days

Weight (Kg)	Tab	Frequency
15-18	1/2	TID
19-26	3/4	TID
27-33	1	TID
34-41	1 1/4	TID
42-48	1 1/2	TID
49-56	1 3/4	TID
57-63	2	TID
64-71	2 1/4	TID
72-78	2 1/2	TID
79-86	2 3/4	TID

10.7 Oral quinine dosing table (for young children)

1 ml suspension contains 60 mg quinine sulphate (salt)

Weight (Kg)	Suspension (ml)	Frequency
4	0.7	TID
5	0.8	TID
6	1.0	TID
7	1.2	TID
8	1.3	TID
9	1.5	TID
10	1.7	TID
11	1.8	TID
12	2.0	TID
13	2.2	TID
14	2.3	TID

A suspension is made by allowing 1 tablet to dissolve in 5ml clean water

10.8 Clindamycin dosing table

Clindamycin cap (150 mg) 5 mg/kg TID for 7 days

Weight(Kg)	Capsule (for 150 mg)	Frequency
< 35	1	TID
35 - 69	2	TID
> 69	3	TID

10.9 Doxycycline dosing table

One capsule (cap) is 100mg; capsules cannot be split or broken
Contraindication: <8 years old and pregnant woman
Dose given once a day for 7 days (4 mg/kg/day)

Weight (Kg)	Nearest cap	Frequency
15 - 37	1	OD
38 - 62	2	OD
> 62	3	OD

10.10 Tetracycline dosing table

One capsule (cap) is 250mg or 500mg; capsules cannot be split or broken
Contraindication: <8 years old and pregnant woman. It can stain teeth in breast feeding infants.
Dose given once daily for 7 days (16 mg/kg/TID)

Weight (Kg)	Nearest 250 mg cap	Frequency
25 - 47	1	TID
48 - 94	2	TID
> 94	3	TID

Weight (Kg)	Nearest 500 mg cap	Frequency
45 - 94	1	TID
> 94	2	TID

10.11 IV artesunate dosing table

For hypermalaria or severe malaria: 1 vial contains 60 mg artesunate (60 mg/ml)
Give the dose in the table (2.4 mg/kg) at H0, H12 & H24, then 2.4 mg/kg every 24 hourly for at least 48 hours or until the patient can tolerate oral medication. See section 6.1.1 for treatment details.

Weight (kg)	ml	Weight (kg)	ml
2-3	0.1	42-43	1.7
4-6	0.2	44-46	1.8
7-8	0.3	47-48	1.9
9-11	0.4	49-51	2.0
12-13	0.5	52-53	2.1
14-16	0.6	54-56	2.2
17-18	0.7	57-58	2.3
19-21	0.8	59-61	2.4
22-23	0.9	62-63	2.5
24-26	1.0	64-66	2.6
27-28	1.1	67-68	2.7
29-31	1.2	69-71	2.8
32-33	1.3	72-73	2.9
34-36	1.4	74-76	3.0
37-38	1.5	77-78	3.1
39-41	1.6	79-80	3.2

A suspension is made by dissolving 1 vial in 1 ml 5% sodium bicarbonate

The solution is light sensitive, prepare directly before injection.
Throw away the excess solution.

10.12 Quinine infusion table

Loading dose = 20mg/kg and Maintenance dose = 10 mg/kg
1 vial of Quinine 2ml = 600 mg
IV fluid using metroset or burette: 1ml = 60 drops
Use D10W for pregnant women and children
Quinine can be given IM if you cannot find an IV, refer to SMRU Malaria Guideline for dosing

Weight Kg	From H0 until H4 Quinine Loading dose Check dextrose hourly		From H8 until H10 Quinine Maintenance dose		From H16 to H18 Quinine Maintenance dose Continue IV Quinine 8 hourly if cannot take oral	
	Amount of Quinine in IV fluid	drop/min	Amount of Quinine in IV fluid	drop/min	Amount of Quinine in IV fluid	drop/min
4 - 5	0.3 ml in 10 ml	Use syringe driver	0.15 in 10 ml	Use syringe driver	0.15 in 10 ml	Use syringe driver
6	0.4 ml in 20 ml	Use syringe driver (give 10ml over 2 hours 2 times)	0.2 ml in 10 ml	Use syringe driver (give 10ml over 2 hours)	0.2 ml in 10 ml	Use syringe driver (give 10ml over 2 hours)
7-9	0.6 ml in 50 ml	12 d/min	0.3 ml in 25 ml	12 d/min	0.3 ml in 25 ml	12 d/min
10-12	0.8 ml in 75 ml	18 d/min	0.4 ml in 40 ml	20 d/min	0.4 ml in 40 ml	20 d/min
13-15	1 ml in 100 ml	25 d/min	0.5 ml in 50 ml	25 d/min	0.5 ml in 50 ml	25 d/min
16-18	1.2 ml in 125 ml	31 d/min	0.6 ml in 65 ml	32 d/min	0.6 ml in 65 ml	32 d/min
19-21	1.4 ml in 150 ml	37 d/min	0.7 ml in 75 ml	37 d/min	0.7 ml in 75 ml	37 d/min
22-24	1.6 ml in 200 ml	50 d/min	0.8 ml in 100 ml	50 d/min	0.8 ml in 100 ml	50 d/min
25-27	1.8 ml in 250 ml	62 d/min	0.9 ml in 125 ml	62 d/min	0.9 ml in 125 ml	62 d/min
28-31	2 ml in 250 ml		1 ml in 125 ml		1 ml in 125 ml	
32-34	2.2 ml in 250 ml		1.1 ml in 125 ml		1.1 ml in 125 ml	
35-37	2.4 ml in 250 ml		1.2 ml in 125 ml		1.2 ml in 125 ml	
38-40	2.6 ml in 250 ml		1.3 ml in 125 ml		1.3 ml in 125 ml	
41-43	2.8 ml in 250 ml		1.4 ml in 125 ml		1.4 ml in 125 ml	
44-46	3 ml in 250 ml		1.5 ml in 125 ml		1.5 ml in 125 ml	
47-49	3.2 ml in 250 ml		1.6 ml in 125 ml		1.6 ml in 125 ml	
50-52	3.4 ml in 250 ml		1.7 ml in 125 ml		1.7 ml in 125 ml	
53-55	3.6 ml in 250 ml		1.8 ml in 125 ml		1.8 ml in 125 ml	
56-59	3.8 ml in 250 ml		1.9 ml in 125 ml		1.9 ml in 125 ml	
>59	4 ml in 250 ml		2 ml in 125 ml		2 ml in 125 ml	

You can dilute Quinine in D5W or D10Wto make a maximum dilution of ***10 mg/ml***
Consider putting 2 IV lines if glucose is borderline
Quinine dosing table version 2_4, 18 August 2012

10.13 IM Artemether dosing table (for hyper and severe malaria management)

Artemether I.M. (1 ml=80 mg). Give H0 dose of 3.2 mg/kg. See section 6.1.2.1 for I.M. Artemether dosing.

Weight (Kg)	ml (cc)	Weight (Kg)	ml (cc)
2-3	0.1	44-46	1.8
4-8	0.2	47-48	1.9
9-11	0.4	49-51	2.0
12-13	0.5	52-53	2.1
14-16	0.6	54-56	2.2
17-18	0.7	57-58	2.3
19-21	0.8	59-61	2.4
22-23	0.9	62-63	2.5
24-26	1.0	64-66	2.6
27-28	1.1	67-68	2.7
29-31	1.2	69-71	2.8
32-33	1.3	72-73	2.9
34-36	1.4	74-76	3.0
37-38	1.5	77-78	3.1
39-41	1.6	79-80	3.2
42-43	1.7		

THEN, give Artemether I.M. H24 dose of 1.6 mg/kg, continue this dose for 4 days.

Weight (Kg)	ml (cc)	Weight (Kg)	ml (cc)
2-3	0.05	43-47	0.9
4-7	0.1	48-52	1.0
8-12	0.2	53-57	1.1
13-17	0.3	58-62	1.2
18-22	0.4	63-67	1.3
23-27	0.5	68-72	1.4
28-32	0.6	73-77	1.5
33-37	0.7	78-80	1.6
38-42	0.8		

10.14 Transmission blocking primaquine dose table for *P. falciparum*

0.25 mg/kg single stat dose

No G6PD testing needed for this dose

A tablet may contain 7.5 mg or 15 mg

YOU MUST KNOW WHAT MG IS IN THE TABLET!

Give food before dose to prevent abdominal pain and nausea

Suspension – Use this table for persons < 11kg (can use up to 19 kg) or if cannot take tablets

A suspension is made with sugar water and/or Vitamin C or breast milk

Weight (kg)	# of **7.5 mg** tablets to mix	# of **15 mg** tablets to mix	Mix with sugar water (ml)	Single dose (ml)
5	1	1/2	3	0.5
6	1	1/2	3	0.6
7	1	1/2	3	0.7
8	1	1/2	3	0.8
9	1	1/2	3	0.9
10	1	1/2	3	1.0
11	1	1/2	3	1.1
12	1	1/2	3	1.2
13	1	1/2	3	1.3
14	1	1/2	3	1.4
15	1	1/2	3	1.5
16	1	1/2	3	1.6
17	1	1/2	3	1.7
18	1	1/2	3	1.8
19	1	1/2	3	1.9

Use a tablet cutter to cut tablets.

Use this table for persons ≥ 20 kg or who can take tablets

Weight (kg)	# **7.5 mg** tablets Single stat dose	# **15 mg** tablets Single stat dose
11 -15	1/2	1/4
16 - 22	3/4	1/2*
23 - 30	1	1/2
31 - 37	1 1/4	3/4
38 - 45	1 1/2	3/4
46 - 52	1 3/4	1
53 - 60	2	1
61 - 67	2 1/4	1 1/4
68 - 75	2 1/2	1 1/4
76 - 82	2 3/4	1 1/2
83 - 90	3	1 1/2
91 - 97	3 1/4	1 3/4
98 - 105	3 1/2	1 3/4

* for persons who weigh 16-19 kg, when giving 1/2 tab the actual dose will be 0.4 to 0.5 mg/kg (not 0.25 mg/kg).

In this group, consider using suspension, because it is too difficult to give the correct dose, which is 1/3 tablet.

10.15 Chloroquine dosing table

1 tablet contains 250 mg chloroquine phosphate (approximately 150 mg base)
Chloroquine phosphate 161mg salt = 100mg base
D0 & D1 give 10mg/kg, then D2 give 5 mg/kg

Weight (kg)	Daily for D0 &D1	Daily on D2
3-5	1/4	1/4
6-9	1/2	1/4
10-11	3/4	1/4
12	3/4	1/2
13-17	1	1/2
18-19	1 1/4	1/2
20	1 1/4	3/4
21-25	1 1/2	3/4
26-27	1 3/4	3/4
28	1 3/4	1
29-33	2	1
34-35	2 1/4	1
36	2 1/4	1 1/4
37-41	2 1/2	1 1/4
42	2 3/4	1 1/4
43-44	2 3/4	1 1/2
45-48	3	1 1/2
49-50	3 1/4	1 1/2
51-52	3 1/4	1 3/4
53-56	3 1/2	1 3/4
57	3 3/4	1 3/4
58-60	3 3/4	2
61-64	4	2
65-66	4 1/4	2
67	4 1/4	2 1/4
68-72	4 1/2	2 1/4
73	4 3/4	2 1/4
74-75	4 3/4	2 1/2
76-79	5	2 1/2
80-82	5 1/4	2 1/2

10.16 Radical cure primaquine DAILY dose for *P. vivax* relapses (liver stage)

0.5 mg/kg DAILY for 14 days standard course

Use in G6PD intermediate or normal persons

A tablet may contain 7.5 mg or 15 mg

YOU MUST KNOW WHAT MG IS IN THE TABLET!

Give food before dose to prevent abdominal pain and nausea

Suspension – Use this table for persons < 13 kg or if cannot take tablets

A suspension is made with sugar water and/or Vitamin C or breast milk

		14 day course	
Weight (kg)	Sugar water (ml)	# of **15 mg** tab to mix	Daily dose (ml)
4	5	1/2	1.3
5	5	1/2	1.7
6	5	1/2	2
7	5	1/2	2.3
8	5	1/2	2.7
9	5	1/2	3
10	5	1/2	3.3
11	5	1/2	3.7
12	5	1/2	4
13	5	1/2	4.3
14	5	1/2	4.7
15	5	1	2.5
16	5	1	2.7
17	5	1	2.8

One 15 mg tablet is equal to two 7.5 mg tablets.
Example 1: for suspension, you can use ½ 15 mg tablet or one 7.5 mg tablet.
Example 2: one 15 mg table is the same as two 7.5 mg tablets

The drug table shows how to mix with a 15mg tablet only

Use a tablet cutter to cut tablets

Use this table for persons ≥ 13kg or who can take tablets

	14 day course	
Weight (kg)	# **7.5 mg** tab Daily dose	# **15 mg** tab Daily dose
11 -12	3/4	Use suspension
13 - 14	3/4	1/2
15 - 17	1	1/2
18 - 20	1 1/4	3/4
21 - 25	1 1/2	3/4
26 - 33	2	1
34- 40	2 1/2	1 1/4
41 - 48	3	1 1/2
49 - 56	3 1/2	1 3/4
57 - 65	4	2
66 - 80	5	2 1/2
81 - 100	6	3

The drug table shows doses for both 7.5mg and 15mg tablets

10.17 Radical cure primaquine WEEKLY dose for *P. vivax* relapses (liver stage)

0.75 mg/kg WEEKLY for 8 weeks

Use in G6PD deficient or G6PD unknown persons

1 tablet may contain 7.5 mg or 15 mg. YOU MUST KNOW THE MG TABLET!
Give food before dose to prevent abdominal pain and nausea
Suspension – Use this table for persons ≤ 18 kg or if cannot take tablets
A suspension is made with sugar water and/or Vitamin C

Weight (kg)	# of **15 mg** tablets	ml (sugar water)	Weekly Dose (ml)
5	1/2	3	1.5
6	1/2	3	1.8
7	1/2	3	2
8	1/2	3	2.4
9	1/2	3	2.7
10	1	3	1.5
11	1	3	1.7
12	1	3	1.8
13-14	1	3	2
15-16	1	3	2.4
17-18	1	3	2.6

Use a tablet cutter to cut tablets. Use this table for persons > 18 kg or who can take tablets

Weight (kg)	# **7.5 mg** tablets Weekly dose	# **15 mg** tablets Weekly dose
12 -13	1 1/4	use suspension
14 - 16	1 1/2	3/4*
17 - 18	1 3/4	use suspension
19 - 22	2	1
23 - 24	2 1/4	1 1/4**
25 - 27	2 1/2	1 1/4
28 - 30	2 3/4	1 1/2
31 - 33	3 1/4	1 1/2
34 - 38	3 1/2	1 3/4
39 - 43	4	2
44 - 46	4 1/4	2 1/4
47 - 50	4 3/4	2 1/2
51 - 55	5 1/4	2 3/4
56 - 60	5 1/2	2 3/4
61 - 66	6	3
67 - 71	6 3/4	3 1/2
72 - 80	7 1/2	3 3/4
81 - 88	8	4 1/4
89 - 95	9	4 1/2
96 - 100	10	5

The drug table shows doses for both 7.5mg and 15mg tablets

* For 14 kg patients, try to use suspension or 7.5 mg tablets, because 3/4 of a 15 mg tablet will give too much primaquine.

** For 23-24 kg patients, 1 1/4 of a 15 mg tablet will give too much primaquine. Try to use the 7.5 mg tablet. If you only have 15 mg tablets available, follow the patient closely for hemolysis.

10.18 Paracetamol dosing table (tab)

1 tablet contains 500 mg.
Give paracetamol every 6 hours for 72 hours, even if there is no fever. This protects the kidneys from damage caused by malaria (20). Do not use more than 4 doses (4 grams) every 24 hours

Weight (kg)	Tab 6 hourly
13-18	0.5 tab
19-26	0.75 tab
27-33	1
34-41	1.25 tab
42-48	1.5 tab
49-56	1.75 tab
57 and above	2

10.19 Paracetamol dosing table (suspension)

5ml of paracetamol suspension contain 120 mg First dose 20 mg/kg and then 15 mg/kg

Weight (kg)	First dose (ml) Stat dose	Following dose (ml) 6 hourly
1.5	1.3	1
2	1.5	1.3
2.5	2	1.5
3	2.5	2
3.5	3	2
4	3.5	2.5
4.5	4	3
5	4	3
5.5	4.5	3.5
6	5	3.5
6.5	5.5	4
7	6	4.5
7.5	6	4.5
8	6.5	5
8.5	7	5.5
9	7.5	5.5
9.5	8	6
10	8.5	6
10.5	9	6.5
11	9	7
11.5	10	7
12	10	7.5

10.20 Ferrous sulphate suspension dosing (<10kg)

Weight (kg)	Dose (mg elemental iron)	ml TID
1	2	0.1
2	4	0.2
3	6	0.2
4	8	0.3
5	10	0.4
6	12	0.5
7	14	0.6
8	16	0.6
9	18	0.7
10	20	0.8

10.21 Ferrous sulphate and folic acid dosing (for anaemia patients)

Age group	Ferrous sulphate	Folic acid
Adult	1 TID	5mg daily
>12 year	1 BID/TID	5 mg daily
5-12 Year	1 ½ OD	5 mg daily
1-5 year	1 OD	5 mg daily
<1 year	½ OD	500 microgram/kg daily
If child under 10 kg (if suspension is available) please see dosing table(above)		

10.22 Table for maintenance fluid amount and rate

Weight (kg)	Drops per minute via metroset
4	17
5	21
6	25
7	29
8	33
9	38
10	40
11	42
12	44
13	46
14	48
15	50
16	52
17	54
18	56
19	58
20	60
21 – 25	65
26 - 30	70
31 – 35	75
36 – 40	80

2 litres per day = **28 drops per minute** with normal giving set
3 litres per day = **42 drops per minute** with normal giving set

If an infant or child has signs of dehydration increase the amount per hour by 10%

10.23 Glasgow Coma Scale (GCS)

	1	2	3	4	5	6
Eyes	Does not open eyes	Opens eyes in response to painful stimuli	Opens eyes in response to voice	Opens eyes spontaneously	N/A	N/A
Verbal	Makes no sounds	Incomprehensible sounds	Utters inappropriate words	Confused, disoriented	Oriented, converses normally	N/A
Motor	Makes no movements	Extension to painful stimuli	Abnormal flexion to painful stimuli	Flexion / Withdrawal to painful stimuli	Localizes painful stimuli	Obeys Commands

Coma is reached at a score of <10. This scale can be used repeatedly to assess improvement or deterioration.

AVPU is also a good quick emergency assessment	A = alert	(GCS = 15)
	V = responds to voice	(GCS = 13)
	P = responds to pain	(GCS = 8)
	U = no response	(GCS = 6)

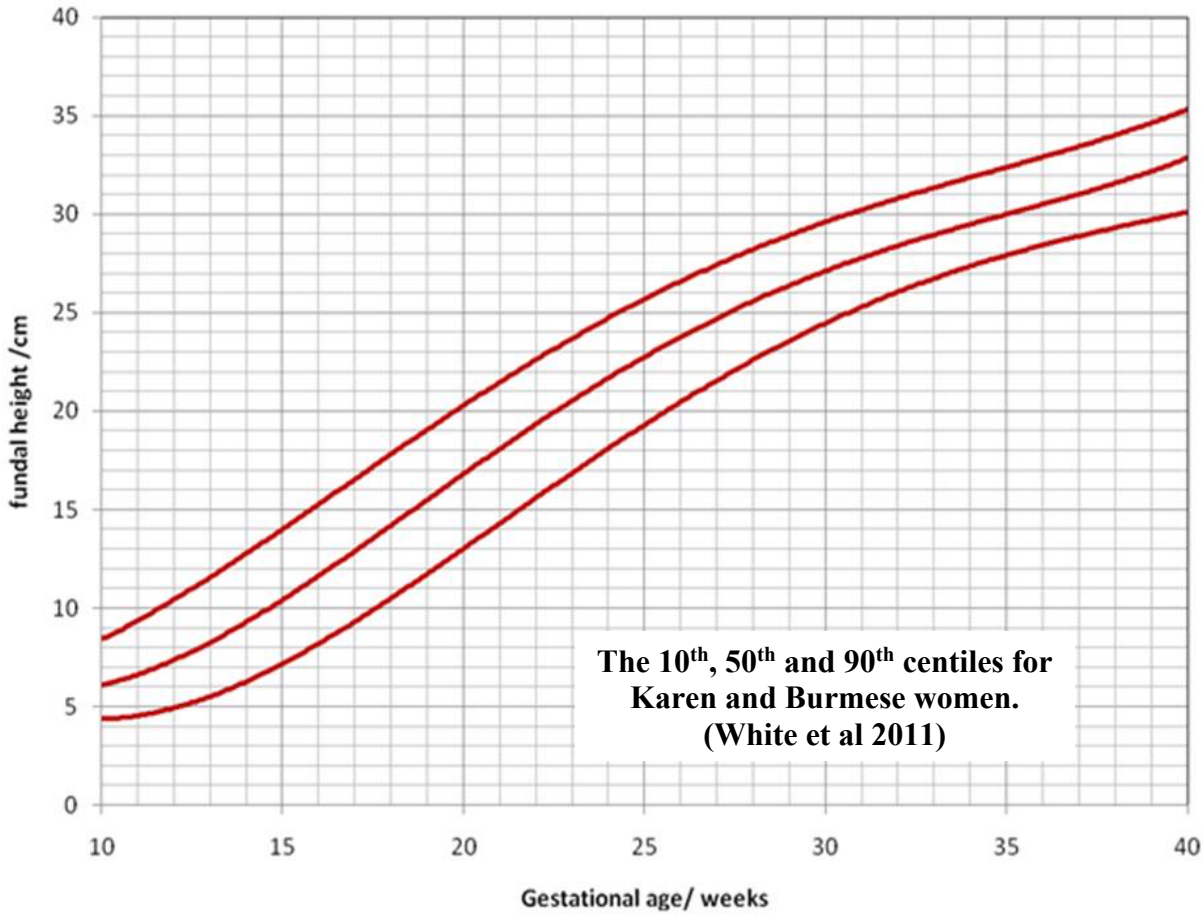
10.24 Blantyre coma scale (BCS) for children

The BCS scale was modified from the widely used Glasgow coma scale (1974), is applicable to children, including those who have not learned to speak.

		Score
Best motor response:	localizes painful stimulus [a]	2
	withdraws limb from pain [b]	1
	nonspecific or absent response	0
Verbal response:	appropriate cry	2
	moan or inappropriate cry	1
	none	0
Eye movements:	Directed (e.g. follows mother's face)	1
	not directed	0
	Total	0–5

A state of unresponsive coma is reached at a BCS score of <3. This scale can be used repeatedly to assess improvement or deterioration. [a] Rub knuckles on patient's sternum. [b] Firm pressure on thumbnail bed with horizontal pencil.

10.25 Karen pregnant women gestation by fundal height



Fundal Height (cm)	EGA (wks)
4	8.1
5	9.3
6	10.4
7	11.4
8	12.3
9	13.2
10	14.1
11	15.0
12	15.8
13	16.6
14	17.4
15	18.3
16	19.1

Fundal Height (cm)	EGA (wks)
17	19.9
18	20.8
19	21.6
20	22.5
21	23.4
22	24.4
15	18.3
16	19.1
17	19.9
18	20.8
17	19.9
18	20.8
19	21.6

Fundal Height (cm)	EGA (wks)
20	22.5
21	23.4
22	24.4
23	25.4
24	26.4
25	27.5
26	28.6
27	29.9
28	31.2
29	32.6
30	34.2
31	36.0
32	38.0
33	40.4

Fundal height is measured from the top of the pubic symphysis to the top of the fundus (when the bladder is empty). This table was produced for refugee and migant women on the Thailand-Burmese border. Pregnant women who had a crown-rump fetal length <60mm by ultrasound and delivered within 5 days of the EDD were included.

10.26 Coma Management STEPS: A to K

A – Airway? – open the airway

B – Is this patient **B**reathing? - look, listen and feel

C – Circulation - Does this patient have a pulse? Assess the pulse

D – Diagnosis of Hypoglycaemia and Malaria.
Perform an urgent: Malaria RDT or malaria smear (MS) and blood glucose
– Hypoglycaemia = < 2.2 mmol/l; < 40 mg/100ml and treat if necessary;
5ml/kg of 10% dextrose (D10W) in 10 mins (repeat blood glucose in 30 mins)
- Malaria positive RDT or MS: IV artesunate 2.4 mg/kg stat

Evaluate for meningitis, such as stiff neck: if present consider performing a lumbar puncture and start IV antibiotics. Do not perform a lumbar puncture if there are signs of raised intracranial pressure such as unequal pupil size, non-reactive pupils, a very slow heart rate (<50 in adults) or irregular breathing. If you cannot perform a lumbar puncture but you are concerned about meningitis start antibiotics.

Fitting? Observe for convulsion, these may be very subtle. Convulsions should be treated.

GCS, **G**lucose and **G**eneral Observations
Hourly observations until the patient is stable and then every four hours,
GCS or BCS – conscious level
Blood glucose
Pulse rate
Respiratory rate
Blood pressure – consider shock

Hydration: Monitor and record fluid input and output. A urinary catheter should be inserted.
If urine output is less than 0.5ml/kg/hr or there are signs of dehydration a fluid bolus should be considered: NSS, initially 1L in adults, 20ml/kg in children. This can be repeated to a maximum of 2L in an adult and 40ml/kg in a child. Observe for signs of oedema, auscultate the chest for crepitations (pulmonary oedema), if present, consider administering furosemide (1mg/kg)

Increasing parasitaemia? Monitor parasitaemia 4-6 hourly until negative

Just confirm haemoglobin or haematocrit (haemoglobin) every 24 hours

Keep caring - Follow good nursing care (position, eyes, clean, NG, food?)

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