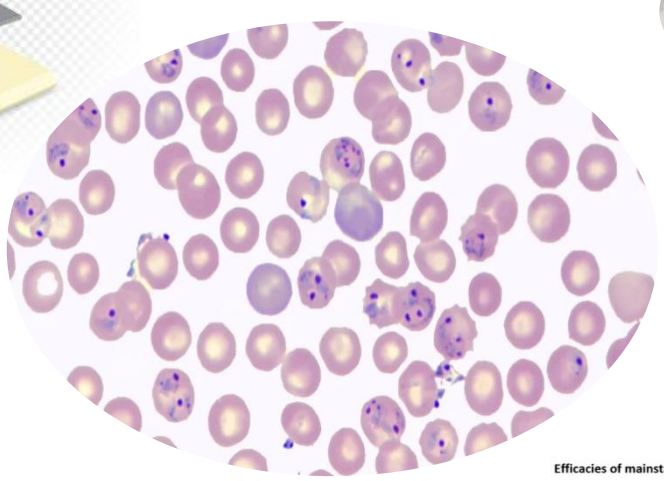
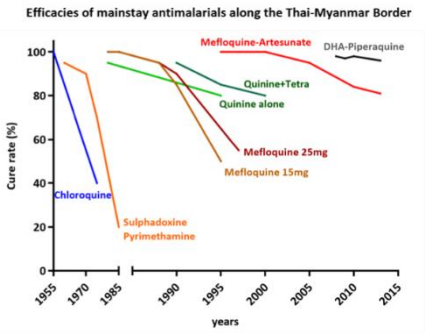
SMRU.
Shoklo Malaria Research Unit

Malaria Guideline

25th edition 2024





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MALARIA GUIDELINE

25th Edition

August - 2024

Introduction

This is the 25th 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 is now resurging along the border, where majority of the cases are vivax malaria. In recent years, many patients have limited access to malaria treatment due to COVID-19 pandemic and the armed-conflicts. The risk of outbreaks may be higher, therefore outbreak management will become important. If there is lower immunity, patients may be sicker. 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*. It is very important that health care workers maintain knowledge about malaria diagnosis, and treatment. Early case management will also prevent severe malaria and deaths.

Artemisinin Combination Therapy ACT resistance is established in this region and the treatment options for malaria are now limited. For resistant P. *falciparum* cases, triple artemisinin combinations therapy is under trial.

Effective management of *P. vivax* necessitates adherence to primaquine treatment after quantitative G6PD deficiency testing. Tafenoquine (single dose) is not currently deployed but is likely to become an essential tool in malaria elimination efforts. In case someone presents with side effects saying they took tafenoquine see 3.3.6.

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

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Glossary

1st line:	Best choice for treatment	2nd line:	not best choice but acceptable
A/AS:	Artesunate	AE	Adverse Effects
AFB:	acid fast bacilli	AKI:	acute kidney injury
BBG	Burma Border Guidelines	BCS:	Blantyre Coma Score
BD:	twice daily	BP:	Blood pressure
C:	Clindamycin	cc:	cubic centimetre =millilitres
CI:	Contraindication	COA:	Artemether-Lumefantrine
CQ	Chloroquine	CSF:	cerebrospinal fluid
D:	Doxycycline	DP:	dihydroartemisinin-piperaquine
D5W:	dextrose 5% in water	G6PD:	glucose-6- phosphate dehydrogenase
GCS:	Glasgow coma score	H:	hour
Hb:	haemoglobin	Hct:	haematocrit
IM:	Intramuscular	IV:	Intravenous
IRBC:	Infected RBC	kg:	kilogram
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	PM:	Plasmodium malariae
PMQ	Primaquine	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		

SMRU Malaria treatment guidelines summary

Uncomplicated *P. falciparum* malaria: See 1.1		
Diagnosis:	RDT or malaria smear	Definition: Presence of PF trophozoites (PFT) (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 (with fat) **2nd line**: ACT, if ACTs are not available, Quinine PLUS doxycycline or tetracycline 7 days, No Doxycycline in children <8 years and pregnant women unless there is no other available option **AND Single low dose 0.25 mg/kg PMQ on the first day of treatment** **if no contraindications***: pregnant women, mothers breast feeding < 1 month old baby, infants < 6 months	
Treatment notes for special groups 1.1.4, 1.1.5, 1.1.6		
	• Very young children and congenital malaria, even when malaria is uncomplicated, may need 1st dose to be IV/IM, due to unknown absorption and vomiting. • Pregnant women have a high risk for treatment failure with COA 3 days at the Thai-Myanmar border and should receive COA 5 days; or DP if available.	

Transmission blocking 0.25mg/kg single primaquine dose for *P. falciparum*

- Primaquine given as a single dose (reduces gametocytes and can reduce transmission)
- G6PD testing is NOT needed for this dose
- ***Contraindications**: pregnant women, mothers breast feeding < 1 month old baby, infants < 6 months

***P. falciparum* malaria not responding to the treatment – day 1 to 14, See 1.2.**		
Diagnosis:	If only RDT is available	Definition: RDTs can stay positive for 2 weeks even with complete treatment. It is not possible to interpret repeat RDT positive result in the first 14 days.
	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:	<u>If only RDT available</u> (i.e. at malaria post): *Ask the patient: Was treatment supervised/completed as instructed without vomiting?* • If No, repeat the same treatment but it must be a <u>supervised</u> treatment. • If Yes, and there are concerns the patient is becoming severe malaria. → **Refer** to a hospital/facility with microscopy (for malaria smear). *Communicate* with receiving clinic. • The patient might also have a non-malaria cause of fever.	
	<u>If malaria smear available</u>: If hyperparasitaemia and/or severe malaria (See 1.3). If uncomplicated: • Repeat the same treatment but it must be a <u>supervised</u> treatment; and check malaria smear until negative	

***P. falciparum* malaria reappearance – day 14 to 28, 42 or 63, See 1.2.3**		
Diagnosis: If RDT or malaria smear available	Definition	malaria infection 14 to <28 days after artemether-lumefantrine malaria infection 14 to <42 days after DHA-Piperaquine malaria infection 14 to <63 days after Mefloquine-Artesunate
Management and Treatment:	*Ask the patient: Was treatment supervised/completed as instructed without vomiting?* • If the previous treatment was incomplete or vomited it can be taken again, <u>supervised</u>. • If the previous treatment was complete and an ACT, then give a different ACT or a quinine-based treatment (Q7C7, Q7T7 or Q7D7), <u>supervised</u>. • If the previous treatment was not an ACT or don't know, then try DP, COA or MAS3 **<u>AND</u> Single low dose 0.25 mg/kg PMQ on the first day of treatment** **If** no contraindications: pregnant women, mothers breast feeding < 1 month old baby, infants < 6 months	

<table>
<tr><th colspan="3">P. falciparum malaria with hyperparasitaemia, See 1.3.2</th></tr>
<tr><td>Diagnosis:</td><td>Malaria smear ONLY
(RDTs cannot give this diagnosis).</td><td>Definition:
Presence of ≥4% of RBC PF trophozoites (PFT) (asexual parasitaemia) on malaria smear (≥PFT 40/1000 RBCT)</td></tr>
<tr><td>Treatment</td><td colspan="2">Same as Severe malaria (below)</td></tr>
<tr><th colspan="3">P. falciparum malaria with severe malaria, See 1.3</th></tr>
<tr><td>Diagnosis:</td><td>Malaria smear or RDT
Clinical and laboratory results can give the diagnosis.</td><td>Definition:
Patients with malaria (P. falciparum, P. vivax, P. malariae, P. ovale, P. knowlesi)
AND severe signs, symptoms or laboratory findings</td></tr>
<tr><td>Treatment</td><td colspan="2">• Artesunate (AS) IV plus Quinine (Q) IV for a minimum of 24 hours. IV is preferred. If IV line is not possible, AS and Q can be given by IM route.
THEN
ACT oral 3 days (Avoid MAS if patient had neurological symptoms)
Minimum length of treatment is a total of 4 days e.g. 24 hr IV and 3 days ACT.
If the patient cannot eat and drink continue IV AS and IV Q until the patient can.
Then give ACT over 3 days (length of treatment likely 5-7 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.</td></tr>
</table>

***P. vivax* malaria, See 2.2**	
Diagnosis:	Malaria smear or RDT (either pan or Pv specific)
Treatment:	**1st line**: CQ3* **2nd line**: Any ACT (DP or COA with fat, or MAS) …**AND Radical cure with:** Primaquine^ (dose according to G6PD activity) **If** there are no Contraindications‡
Notes	*CQ is still good for treatment of *P. vivax* at the Thailand Myanmar border ^Good adherence to primaquine reduces risk of recurrence. †Biosensor only valid if no severe anaemia ‡**Contraindications** to PMQ or TFQ: ‡Patient Hb <7 (hct <21%) invalid for Biosensor ‡Pregnant women and Infants aged < 6 months ‡Breastfeeding women: if breastfeeding infants **<1 month** old ‡History haemolysis/anaemia with any drug
	Important points on primaquine for Radical cure of *P. vivax*: 1. If a primaquine dose is missed do not 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 longer than 14 days. 2. If a 2nd *P. vivax* infection occurs >14 days from the previous *P. vivax* infection the primaquine treatment can be repeated (check for anaemia and repeat Biosensor) 3. If the primaquine treatment is ongoing (i.e. weekly primaquine dose in G6PD deficiency) and the patient has a 2nd *P.vivax* infection then continue until finished (no need to repeat), as well as treating the acute vivax.

***P. vivax* malaria pregnancy, See 2.3**	
#Pregnancy	• Primaquine is contraindicated • Prevent recurrent *P. vivax* in pregnancy with CQ prophylaxis • Treat acute *P. vivax* with CQ3 and follow-up 14 to 28 day later. • Confirm that the malaria smear is negative. • If negative start CQ 300 mg base (2 tabs) **weekly**, until 1-month post-partum. • A *P. vivax* infection while on CQ prophylaxis is most likely from is non-adherence. Treatment of *P. vivax* recurrence must be *supervised*. Give CQ3 if >28 days after last CQ3 treatment dose). Restart CQ prophylaxis 2 tabs weekly, between day 14 (preferably) and 28, *supervised* if possible. • At 1-month post-partum, provide radical cure.

<table>
<tr><th colspan="3">P. vivax malaria recurrence, See 2.2.5, 2.3</th></tr>
<tr><td>Diagnosis:</td><td colspan="2">Malaria smear or RDT (either pan or Pv specific)</td></tr>
<tr><td>Treatment:</td><td>Assume radical cure was not provided or was not completed.
If >28 days after first treatment:
repeat: CQ3
If ≤ 28 days after first treatment:
give a different treatment such as an ACT (preferably DP or MAS)</td><td>AND Radical cure with:
Primaquine^‡ (Dose according to G6PD activity)
… IF there are no contraindications‡</td></tr>
<tr><td>Notes</td><td colspan="2">^Good adherence to primaquine reduces risk of recurrence.
‡Contraindications to PMQ:
‡Patient does not have severe anaemia:Hb <7 (hct <21%) invalid for Biosensor
‡Pregnant women and Infants aged < 6 months
‡History haemolysis/anaemia with any drug
‡Breastfeeding women:
◦ PMQ is contraindicated if breastfeeding infants <1 month old</td></tr>
</table>

Note: SMRU welcomes calls or referrals if there are any concerns or questions about malaria patients and their treatment, at any time.
Shoklo Malaria Research Unit Facebook message
Clinic Wang Pha 081 973 0750
Clinic Maw Ker Thai 087 307 1314

Complete the checklist (See 4.1) before providing treatment

1 Treatment of *P. falciparum*

1.1. Uncomplicated *P. falciparum*

Uncomplicated P. falciparum is defined as presence of asexual parasitaemia, <4% infected red blood cells (IRBC), on malaria smear or a patient with a positive RDT; and 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. For *P. falciparum* not responding to treatment (See 1.2).

1.1.1. First line treatment for *P. falciparum*

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

- *Artemether-lumefantrine (COA), Coartem®*

Each COA tablet contains 20mg artemether and 120 mg lumefantrine. Treatment is twice daily for 3 days (Dosage Table 4.3.1)

The absorption of 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. Fat required to obtain 90% of maximum effect of Coartem® is 1.2g (=50 ml whole milk or 1.2 ml cooking oil).

- *Dihydroartemisinin and piperaquine (DP)*

Be careful to check which tablets are available: adult or paediatric DP tablets.

Adult DP tablets contain 40mg of dihydroartemisinin (DHA) and 320 mg piperaquine.

Paediatric DP tablets contain 20mg of DHA and 160 mg piperaquine.

Treatment is once daily for 3 days (1.6 mg/kg/day of DHA and 12.8 mg/kg/day of piperaquine) (Dosage Table 4.3.2)

***Plus** Primaquine (PMQ), single dose, 0.25mg/kg,*

Give on the first day of ACT, *supervised* if possible. G6PD testing is NOT needed

Primaquine tablets contain 5mg, 7.5mg or 15mg of primaquine. (Dosage table 4.3.14)

It is better to use the 5 or 7.5mg tablet if possible because of the dose is low. Cut tablets to ¼ or ½: use a tablet cutter.

Single dose primaquine (PMQ) is aimed at blocking transmission (decreases gametocytes).
PMQ single dose is contraindicated for pregnant women, infant <6months.
G6PD testing is not needed.

1.1.2. Second line treatment for *P. falciparum*

Second line treatment **plus** single low dose primaquine.

- *Mefloquine-artesunate (MAS3)*

Each artesunate tablet contains 50mg (Dosage Table 4.3.4). Treatment is once daily. For AE/CI See 3.2.2.

Each mefloquine tablet contains 250 mg (Dosage Table 4.3.5). Treatment is once daily.

For AE/CI See 3.3.3.

Combination MAS3 tablet (Dosage Table 4.3.3) best if available.

Total 3 days - Artesunate 4 mg/kg + Mefloquine 8 mg/kg per day

- Mefloquine is better tolerated at 8 mg/kg per day over 3 days
- If a 2nd episode of *P. falciparum* occurs within 63 days of treatment with MAS3, do not repeat MAS because of increased risk of MFQ neurological side effects.

- *Quinine **and***

  *clindamycin (Q7C7) **or** tetracycline (Q7T7) **or** doxycycline (Q7D7)*

  Treatment below. For quinine (Dosage Table 4.3.6, 4.3.7). AE/CI See 3.3.1.
  Partner drug (Dosage Tables, Clinda 4.3.8, Doxy 4.3.9, Tetra 4.3.10), AE/CI 3.3.2 and 3.3.4

  Total 7 days - Quinine 10 mg/kg/dose TID + Clindamycin 5mg/kg/TID or

  Total 7 days - Quinine 10 mg/kg/dose TID + Doxycycline 4 mg/kg/day OD

  Total 7 days - Quinine 10 mg/kg/dose TID + Tetracycline 16mg/kg/TID or

- Doxycycline and tetracycline are contraindicated in pregnant women and children younger than 8 years unless there are no other available drugs (See 3.3.2).

1.1.3. Treatment of Anaemia

- Patients with *P. falciparum* malaria frequently develop anaemia.

  Check the haemoglobin or haematocrit for age and sex (table below).

  Clinical indicators include (pale sclera, pale mucous membranes).

- Anaemia tends to resolve quickly with treatment.
- Start ferrous (Dosage table 4.3.20 and 4.3.21) when the patient is smear negative
- Folic acid can start on the first day of treatment

Anaemia Definition by category:

	Hb (mg/dL)	Hct (%)
Males	<12	<36
Non-Pregnant females	<11	<33
Pregnancy (1st trimester)	<11	<33
Pregnancy (2nd and 3rd trimester)	<10	<30
Post-partum (up to 7 days)	<10	<30
Children < 15 years	<11	<33

- Review the patient in 2 weeks. If still anaemic give an additional 2 weeks treatment.
- Think of other causes of anaemia: worms, thalassaemia.(Refer to the BBG)

1.1.4. Treatment in infants and children

Infants can present as very sick or develop severe symptoms very quickly.

❖ Recommendations to decrease the risk of vomiting

- Treat the fever. Vomiting is more common if the child has fever.
- Wait until the child is calm. Explain to the mother the importance of her help.
- Crush the tablets and dilute exactly as guidelines recommend.
- Give the medicine to the child with the syringe.
- Do not fight with the child or pinch the nose.
- Give sugar or breast milk.
- Supervise 1 hour for vomiting (the risk is highest in the first hour)
- Some medicines can be very difficult to tolerate because they taste bitter
- If two tries are not successful (See 3.1).

❖ Recommendations concerning the first dose

IV or IM artesunate (Dosage table 4.3.11) for the first dose can be considered:

- If there are concerns about the infant's condition
- If PFS (schizonts) are seen on the malaria smear
- Repeat vomiting (See 3.1)

1.1.5. Congenital malaria

- Congenital malaria is defined as a positive malaria slide in a neonate within 7 days of birth.
- Congenital malaria is a serious.
- Neonates with malaria can be very sick or become very sick quickly!
- Consider cord and placental malaria smears when mother has malaria at birth (See 4.3.27)
- The main reason babies get very sick or die from congenital malaria is because the diagnosis is missed.

➢ <u>Clinical features congenital malaria</u>:

Symptoms (if present), are non-specific, and include:

Fever ≥ 38 °C on one occasion or > 37.5 °C on 2 occasions separated by at least 1 hr

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 not responding to treatment
Seizures
Jaundice
Apneas or slow respiratory rate
Very sleepy or unconscious

Differential diagnosis**:**

think of malaria and review other causes of neonatal fever (See 4.3.28)

Management

- ABC- stabilize first
- Investigate: malaria smear / dextrose / Hct or Hb / CBC, and other if available
- Do **MACHO** care: **M**–milk, **A**–antibiotics, **C**–cord care, **H**–heat control, **O**–oxygen.
-

<u>Treatment</u>

- ***1st dose****: Artesunate IV or IM 2.4.mg/kg* (Dosage table 4.3.11).

Change to oral ACT (DP or COA) if the condition is good and the parasite count decreases: DP (Dosage table 4.3.2), or COA (Dosage table 4.3.1), for 3 days

- Follow-up baby by malaria smear every 2 to 4 weeks for 2 months or if the infant becomes symptomatic with fever or anaemia.

1.1.6. Uncomplicated *P. falciparum* treatment in pregnancy

- In all trimesters pregnant women can have the same malaria treatment as non-pregnant patients, with few exceptions:
    - **No** tetracycline or doxycycline (but Q7D7 is OK if other options)
    - **No** single dose PMQ
- DP is preferred In *P. falciparum* in pregnancy because 3 days COA even with fat has a higher failure rate in pregnancy. If COA is the only available ACT, give 4 tabs twice per day for 5 days (every dose with fat) for higher cure rates.
- Treatment should be *supervised* to reduce *P. falciparum* morbidity: in the mother where anaemia is very common; and in the fetus: miscarriage, stillbirth, preterm birth ("born too early") and small for gestational age ("born too small").
- Screen actively and frequently and treat anaemia (See 1.1.3) or severe anaemia (See 1.4.9), as pregnant women are more susceptible to anaemia than non-pregnant patients
- Treat fever because it is associated with premature labour. Give paracetamol (See Dosing table 4.3.19).
- Malaria at the time of birth is a risk factor for congenital and neonatal malaria 1.1.4.3. and cord and placental blood samples can provide a guide to congenital infection especially when the cord blood is positive (See.4.3.27)

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

- There is artemisinin resistance in Cambodia, Thailand and Myanmar.
- Even as malaria is decreasing, *P. falciparum* resistance to artemisinin is spreading so treatment failures may become more common
- In these cases, it is BEST to follow the parasite clearance by malaria smear. RDT is not a suitable test for resistance because some of them stay positive for up to 2 weeks after infection.

1.2.1. Definition of antimalarial resistant *P. falciparum*

- It is not possible to quickly know if the patient presenting is carrying a drug resistant *P. falciparum* parasite. It is also not possible to know easily if the patient's parasite is resistant to artemisinins, not just the partner drugs.
- When *P. falciparum* is not responding to artemisinin-based treatments, consider quinine combinations because it is likely that the *P. falciparum* will be sensitive to quinine e.g. Q7T7 or Q7C7.

- The partner drug to artemisinin in ACTs stay in the body for different amounts of time: if they stay for a short time (Lumefantrine) treatment failures will be seen earlier than if they stay for a long time (Piperaquine, Mefloquine). Proving treatment failure requires genotyping but infection before <28 days after artemether-lumefantrine, <42 days after DHA-Piperaquine; and <63 days after Mefloquine-Artesunate should be considered as potential failure.

1.2.2. *P. falciparum* not responding to treatment - day 1-14

❖ Presenting Day 1 to 14

- **Only RDT available**:

  Some RDTs stay positive for approximately 2 weeks after the acute infection, so these RDT tests cannot tell if the patient has acute malaria.

  If only RDT is available and there are concerns the patient is not responding to treatment ask this question:

  Was treatment supervised/completed as instructed without vomiting?

  If No, repeat the same treatment but it must be a *supervised* treatment.

  If Yes, and there are concerns the patient is becoming severe malaria

  → **Refer** to a hospital/facility with microscopy (for malaria smear). **In referred cases** be sure to communicate the situation with the referral clinic so that the proper treatment can be given.

  The patient might also have another cause of fever, a non-malaria fever.

- **Malaria smear available**
- If hyperparasitaemia and/or severe malaria See 1.3.
- If uncomplicated:
  - Repeat the same treatment but it must be a supervised treatment
  - Check malaria smear daily until negative

1.2.3. *P. falciparum* malaria reappearance (day 14 to 28, 42 or 63)

❖ Presenting Day 14 to 28, 42 or 63.

Find out what the last treatment was. Confirm with the patient that treatment was completed as instructed without vomiting, and for COA, every dose taken with fat.

If the previous treatment was **incomplete** or vomited it can be taken again, *supervised*.

If the previous treatment was **complete** and an ACT, then give a different ACT or a quinine-based treatment (Q7C7, Q7T7 or Q7D7), supervised if possible.
If the previous treatment was not an ACT or don't know, then try DP, COA or MAS3.

Important points for the management of resistant malaria

If malaria smear is possible, continue all antimalarial treatment until the *malaria smear is negative 2 consecutive times*. Longer treatment courses may be needed.

Up to 10 days anti-malarial treatment may be needed when we rely on quinine-based treatment.

Always keep quinine and doxycycline/tetracycline or clindaymycin in the pharmacy as this treatment will be effective against malaria if administered properly.

1.3. Severe and hyperparasitaemic *P. falciparum* malaria

In areas of established artemisinin resistance, such as in Cambodia, Thailand, and Myanmar these patients should be hospitalized and treated with both IV artesunate and IV quinine.

1.3.1. Definitions hyperparasitaemia and severe malaria

Hyperparasitaemia is defined as a high parasitaemia (≥4% IRBC) on malaria smear. RDTs cannot give the parasite count: they cannot diagnose hyperparasitaemia. Patients can have hyperparasitaemia and still eat and drink by themselves.

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, See 1.4.

- 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 treatment is slightly different, See 2.2.4.

1.3.2. First line treatment severe and hyperparasitaeamia

- *IV Artesunate **PLUS** IV Quinine **THEN** ACT*

Important notes:

- As malaria decreases, health care staff will have less experience managing hyperparasitaemic and severe cases.
- If a patient has hyperparasitaemia or resistant parasites, management may be different (i.e. choice of oral ACT, duration of treatment, addition of IV quinine).

Intravenous (IV or IM) artesunate (Dosing table See 4.3.11)

Hour 0, 12, 24 and then continue every 24 hours until the patient can tolerate oral medications

PLUS

Intravenous (IV) quinine (Dosing table See 4.3.12)

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.

For patients that improve rapidly, IV treatment may be stopped after 24 hours.

When IV treatments are stopped:

***PLUS** Oral ACT* (COA - Dosing table 4.3.1, DP – Dosing table 4.3.2)**.**

If IV stopped at 24 hours with ACT for 3 days treatment will be a total of 4 days.

If IV is ongoing as 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 (COA - Dosing table 4.3.1, DP – Dosing table 4.3.2)**.**. Try to complete a total of *at least 7 days treatment. Why? B*ecause of longer parasite clearance rates along the border, a longer treatment works better than a short course treatment. In some cases, up to 10 days anti-malarial treatment is needed.

- Do not give mefloquine for patients recovering from cerebral malaria. It increases the risk or post malaria neurologic syndrome.

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

- First check a malaria smear. If malaria smear is not possible: 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.

1.3.3. Second line treatment severe and hyperparasitaeamia

Consider early referral if first line treatment is not available. **Treat before referral**.

If either, or both, AS IV or Quinine IV are not available, or there is no IV line, replace with IM route as soon as possible.

If it is possible, give two antimalarials (AS **or** artemether) **and** Quinine. If two (IV/IM) antimalarials are not available just give one and refer as soon as possible.

- *IM Artemether **PLUS** IM Quinine **THEN** ACT*
  - *Intramuscular (IM) Artemether* (if injectable AS is not available) (See 4.3.13)
  - *Intra muscular (IM) Quinine* (if IV line is not available) (Dosing table See 4.3.12)

Quinine intravenous solution can be given as IM injection

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, See 3.3.1
- Respect very strict aseptic injection rules because if the risk of abscess.

*Continue the IV or IM treatment for 4 days, **PLUS** Oral ACT (COA Dosing table 4.3.1, DP Dosing table 4.3.2).*

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 the Thai-Myanmar border area compared to 0.15% with uncomplicated non- hyperparasitaemia.
- Patients have a higher risk of severe anaemia and need for blood transfusion (See 1.4.9)
- ***A longer duration of treatment (at least 7 days).*** They have greater risk of failure because there are more parasites to kill. Sometimes up to 10 days antimalarial treatment is needed.

1.3.2. Monitoring

❖ Routine observations

On admission check: temperature (Temp), respiratory rate (RR), pulse (PR), blood pressure, consciousness using the Glasgow (See 4.3.23) or Blantyre coma score (See 4.3.24), 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 dark)

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.

❖ Parasite clearance time (PCT)

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, and for management for to "*P. falciparum* not responding to treatment", See 1.2.2). Use parasite clearance graph in first 24 hours See 4.2.
- If malaria smear is not available, refer the patient to the hospital.

❖ Patients with schizonts (PFS)

If a lot of schizonts (PFS) are 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, and for management go to "*P. falciparum* not responding to treatment" (See 1.2.2).

❖ Very high parasitaemia >20%

These patients are at high risk for poor outcomes. Follow the parasite clearance time (Use 4.2, parasite clearance graph in first 24 hours) and consider early referral for cases that do not respond to treatment, or first dose as IV.

❖ Severe and hyperparasitaeamia in pregnancy

- In *P. falciparum* vital organ dysfunction (coma, hypotension, respiratory failure) are associated with highest risk of mortality. If possible, supervise treatment until malaria smear negative (admit if needed).

Beware of:

- Hypoglycaemia is a common problem in pregnant women with severe malaria: up to 50% of pregnant women develop hypoglycaemia on IV quinine (See 1.4.2.1).
- Fever and hypoglycaemia may cause marked fetal bradycardia, tachycardia, and other signs of fetal distress but usually responds to maternal antimalarial treatment.
- Pulmonary oedema is a common complication in severe malaria in pregnancy and may occur suddenly and at any time including in the 1st week post-partum (See 1.4.2.7).
- Confirm gestation: last menstrual period, measure fundal height (See 4.3.26) if no ultrasound. Premature labour can still develop even when afebrile and malaria is treated. Be prepared to provide dexamethasone and nifedipine (if the BP is stable) if indicated.
- Bacterial sepsis is a risk so fevers are an indication to check for more than must malaria. Look for a source of infection e.g. UTI. If no source is identified, follow the recommendations for severe malaria shock (See 1.4.2.4).

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.

1.4. WHO criteria for 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 parasitaemia".

Severe malaria has been described in non-*falciparum* malaria patients, for example, *P. knowlesi* and rarely *P. vivax* (except in young infants).

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, 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 examiation)

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 3 mg/dL or BUN > 56 mg/dL (20 mmol/L)
- Bilirubin >50 µmol/L (3 mg/dL) with parasite count >100,000/µL
- Radiologically confirmed pulmonary oedema

1.4.1. 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

❖ 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 4.3.25.

❖ 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 (See 1.4.2.5).

The risk of hypoglycaemia is higher in: ●Children, ●Pregnant women, ●With IV quinine.

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.

❖ 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
- 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.

❖ Convulsions (Seizure or Fitting)

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

Acute treatment malaria Convulsions (Seizure or Fitting)

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.

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

❖ 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, consider suspected bacterial sepsis.

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.*

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)

❖ 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. Give scheduled paracetamol every 6 hours for 72 hours starting from admission (See Dosing table 4.3.18 and 4.3.19). 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 available.

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.

❖ Fluid Management

If the patient can tolerate oral hydration, ORS is the safest.

- Close monitoring of the fluid balance is important in severe malaria, because dehydration can cause renal failure and volume overload can cause pulmonary oedema.
- If the patient requires IV fluids (no symptoms of pulmonary oedema) start 5 ml/kg/hr maintenance fluid with close monitoring.
- Talk to the family – an unconscious patient may not have had a prolonged time without any fluid intake. *When was the last drink?* Also ask if the know *When was the last urine?*
- If there are confirmed signs of dehydration start resuscitation with a fluid bolus.

Dehydration: Points to check for dehydration:

Skin turgor

Dry lips and mouth

No tears in eyes

Urine stick Specific Gravity (SG) >1.020

Pulmonary oedema: Points to check for fluid overload (pulmonary oedema):

Dyspnea, increased RR, crepitation

Low oxygenation (low SpO2)

Jugular venous distension (can be difficult to assess)

Patient cannot breathe when they lie down (orthopnoea)

Edema in legs or buttocks

- Fluid Bolus
    - Use normal saline or ringers lactate as the bolus IV fluid

Adults: 20 ml/kg or 1000 ml; be cautious to avoid fluid overload, e.g. 2 times 500 ml

Children 10-20 ml/kg See 4.3.22

- Maintenance fluid rate calculation

Adults: 100 ml/hr alternating with NSS or Ringers preferred if no hypoglycaemia.

Children 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

- 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 maintenance (See 4.3.22)
- For the fluid management of infants <4 weeks refer to the SMRU Neonatal Guidelines.
- 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 (below)

❖ Renal failure

All severe malaria patients need a urinary catheter to monitor fluid input and output

- Measure the first urine after insertion of catheter, check urine stick (if available) and discard this volume of urine
- Low urine output in the first 1 hour raises suspicion of Acute Kidney Injury (AKI)
- Low urine out

  Adults< 0.5 ml/kg/hr in adults

  Children < 1.0 ml/kg/hr,
- 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.

Test for AKI with a Furosemide Stress Test:

a) The patient needs to be **euvolaemic** (adequate hydration) **before this test is started by following the Fluid Management guideline (See Above)**.

b) Set the urine catheter bag to zero

c) 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.

d) 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.

e) If poor or no response to furosemide (e.g. <200 ml in 2 hours in 50kg adult), the kidney failure is *severe. **Refer** the patient to a well-equipped hospital for dialysis.*

f) 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.*

g) ***Refer*** the patient if the urine output decreases again. Early blood transfusion does not improve AKI and can cause pulmonary oedema.

❖ Management of 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.

- 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)
- 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.

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

Other management if signs of pulmonary edema:

- The patient should be in a sitting position; help the patient with pillows
- Oxygen therapy (nasal catheter or face mask

❖ Check parasitaemia

Severe malaria patients should be monitored with regular malaria smear (4-6 hourly) until negative 2 consecutive times (See 1.3.2.2).

❖ 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%.

❖ 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: discard the plasma.

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

- Give transfusions over 4 hours or 6 hours and *consider* IV Lasix 1mg/kg if there are signs of pulmonary oedema.

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

❖ Jaundice, Blackwater fever, Disseminated Intravascular Coagulation

◦ 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.

◦ 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

◦ Disseminated Intravascular Coagulation

DIC is relatively rare in severe malaria (5%), but much more common in septicaemia so consider septicemia treatment as well as DIC treatment.

Diagnosis:

Spontaneous bleeding and oozing from venipuncture sites

Management:

Vitamin K 10 mg IV (slowly) every 24h for 3 days
Nursing care & feeding
Avoid trauma

❖ 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. Wait to feed the patient when they are conscious.

2 Treatment of non-*P. falciparum* malaria

2.1. *P. knowlesi*

P. knowlesi had been found in forested regions of SE Asia. *P.knowlesi* is a monkey parasite that can cause infection in humans and reported mostly in people living close to the natural monkey (macaques) hosts. 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*. RDT may give negative result in *P. knowlesi*. PCR genotyping assays can differentiate *P.knowlesi* from *P. malariae* but sometimes confuses with *P.vivax*.

2.1.1. Treatment for *P. knowelsi*

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

- Like *P. falciparum*, *P. knowlesi* can reach high parasitaemias rapidly which can be fatal
- Use the same treatment guideline as for *P. falciparum* (See 1.3.)

2.2. *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 episode even when the patient does not have a new mosquito bite.

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

- **First line treatment**

Chloroquine (CQ) is still effective for treatment at the Thailand-Myanmar border

Each chloroquine tablet contains 250 mg CQ phosphate (approximately 150 mg base)
(Dosage table 4.3.16)

- *First 2 days: CQ 10 mg base/kg once daily*
- *Third day:CQ 5 mg base/kg once daily*
- ***Plus Radical Cure for P. vivax and P. ovale (See 2.2.5)***

- **Second line treatment**

- *DP* - Effective against *P. vivax* in areas where there is chloroquine resistance **OR**
- *COA* - short half-life of lumefantrine compared to piperaquine so earlier recurrence
- ***Plus Radical Cure for P. vivax and P. ovale (See 2.2.5)***

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

2.2.2. Treatment of *P. vivax* recurrence

P. vivax recurring > 28 days	*Can be treated with standard treatment (CQ3), must be supervised **AND** Radical Cure*
P. vivax recurring ≤ 28 days	Maybe due to resistance (exclude non-adherence i.e. check with the patient if they took the full treatment). If not adherent repeat CQ3 *An ACT (COA or DP) should be given and must be supervised **AND** Radical cure*

2.2.3. Treatment of congenital and neonatal *P. vivax*

- Congenital malaria is defined as a positive malaria slide in a neonate within 7 days of birth.
- Any malaria, including *P. vivax,* in a neonate (<28 days old) should be considered a serious.
- The differential diagnosis: includes other causes of neonatal fever (See 4.3.28)
- Symptoms are non-specific and the management is the same as with congenital and neonatal infection with *P. falciparum* (See 1.1.4.3).

Treatment

If infant unwell give

- *Artesunate IV or IM 2.4 mg/kg* (Dosage table 4.3.11) for the first dose, then give Chloroquine (Dosage table 4.3.15)
- ***If well**, give: Chloroquine once daily for 3 days* (Dosage table 4.3.15)

Follow-up baby by malaria smear every 2 to 4 weeks for 6 weeks and explain to the mother if the infant becomes symptomatic with fever, repeat malaria smear, pale, check for anaemia.

Reminder: Radical cure ***is not*** required for congenital malaria (no hypnozoites)

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

In this area, severe malaria caused by *P. vivax* infection is very rare and more likely in very young infants. Underlying medical problems, and coinfection with *P. vivax* can result in more severe symptoms. Make sure to treat both the underlying condition (i.e. sepsis, diarrhea especially typhoid fever, or chronic disease) and acute vivax when patients are unwell.

- *Artesunate IV/IM* (Dosage table 4.3.11) (use the same doses as for *P. falciparum*) **OR** *quinine IV/IM* (Dosage table 4.3.12).

When oral treatment is tolerated, change to CQ once daily for 3 days (Dosage table 4.3.15)

2.2.5. Radical cure for prevention of *P. vivax* and *P. ovale* relapse

- *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 (PMQ) can be used to prevent relapses. PMQ is an 8-aminoquinoline class of antimalarials. WHO recommends that PMQ should be given for *P. vivax* infections.

First line treatment for radical cure

- Before giving PMQ **check G6PD status**, using the quantitative test (if possible)
    - Quantitative tests: e.g Standard G6PD Biosensor Reference Range See Table 4.3.29
- Biosensor is valid when Hb >7g/dL / Hct >21%
- The Biosensor can report the G6PD activity with a range of numbers which is more detailed than the fluorescent spot test (FST) which only reports 'normal' or 'deficient'. If only the Fluorescent Spot Test (FST) is available, normal results in FEMALES could be intermediate but the FST will probably give a 'normal' result.
- **Check PMQ contraindications (cannot use):**

Pregnant women
Infants aged < 6 months
Patient has a history of haemolysis (any drug).
Women breastfeeding an infant < 6 month old*
Follow the patient's G6PD test result to choose the PMQ dose. If G6PD testing is unavailable, give PMQ weekly.

* Data suggests that there is only a very small amount of PMQ in the breast milk and it is safe to give PMQ to women breastfeeding an infant >1 month old.

➢ For non-pregnant adults and children >6 months old:

a. If G6PD status is ≤4.0 U/g Hb (≤ 30%) by "STANDARD G6PD" Biosensor (See Table 4.3.29), or deficient by FST, or G6PD unknown:
    - *PMQ 0.75 mg/kg/dose every week for 8 weeks* (Dosage table, 4.3.17)

b. If G6PD status is ≥ 4.1 U/g Hb (>30%) by Biosensor (See Table 4.3.29), or normal by FST:
    a. *PMQ 0.5 mg/kg/day for 14 days* (Dosage table, 4.3.16)

Notes:

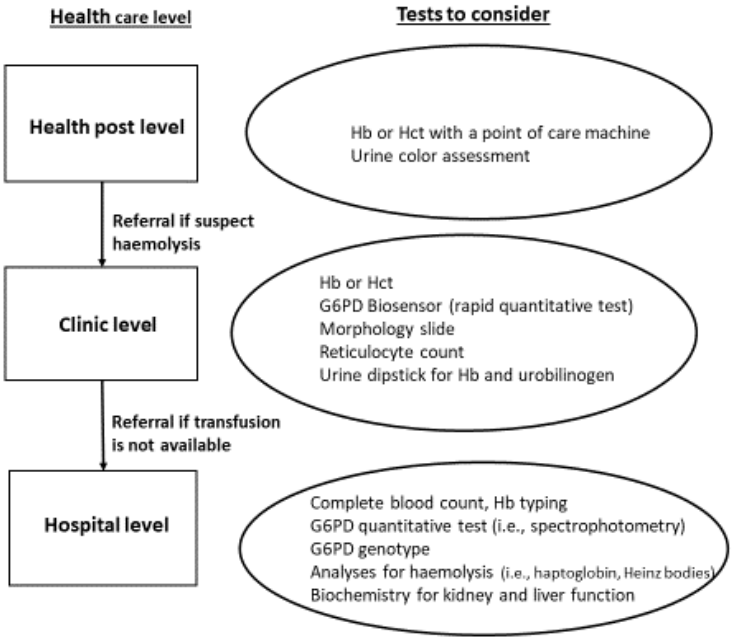
- Follow up at day 3-5 and counselling about haemolysis signs are especially important if the Biosensor result is 4.1-6 U/g Hb (>30-70%, or intermediate)
- We do not yet have normal values for biosensor for infants >1 month and <1 year.
    - The safest choice to avoid hemolysis is to follow the newborn normal values if you need to test babies >6 months old but less than 1 year.
    - This will over diagnose deficiency. G6PD results from 1-11 months of age should be checked again after 1 year of age if the result is borderline (4.1-5 U/g Hb), if possible.

❖ Considerations for administering radical cure doses:

- Crushed primaquine tablets are bitter, so mix with sugar water or juice for suspension.
- Give dose after food and/or drink to prevent epigastric pain
- Encourage patient adherence for effective treatment
- Always try to supervise – it is so hard to finish 14 days.
- If 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.

[a] There is point of care G6PD quantitative tests available: contact SMRU for training so 8-aminoquinolines can be prescribed safely. Reference can be accessed at https://doi.org/10.12688/wellcomeopenres.15100.2

If 8-aminoquinoline associated haemolysis is suspected, investigations will depend on the resources available**. Refer to a higher level of care** where G6PD quantitative test[a] is available.



❖ Important follow up issues following PMQ treatment

For adverse effects PMQ See 3.3.5

Check Hb or Hct before giving treatment so if unexpected haemolysis occurs there is a baseline and Hb or Hct can be compared.

Patient Counselling is important:

- Explain to the patient that if they develop pallor, dizziness, difficulty breathing or other signs, they should return to the clinic.
- *Do not share tablets* with other people. Keep away from children. The people living around you may be G6PD deficient and develop serious adverse effects if they take your PMQ tablets.
- **For missed PMQ doses:** If a PMQ 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 treated with PMQ to check for anaemia or unexpected haemolysis.

Treat with blood transfusion if the haemolysis is severe, See 1.4.9.

Refer to the hospital if a patient develops haematuria or severe anaemia.

- **Vivax after 8-aminoquinoline** Repeat the PMQ 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) as well as treating the acute vivax.

2.3. Treatment of *P. vivax* in pregnancy

- Treatment is the same as for non-pregnant: Chloroquine x 3 days (CQ3) (Dosage table 4.3.15)
- *Supervised* if possible followed by CQ prophylaxis
- Primaquine is contraindicated in pregnancy.

AND Prevention of recurrent *P. vivax* in pregnancy with CQ prophylaxis

Reduce the risk of multiple vivax episodes adverse effects (miscarriage, stillbirth, preterm birth, and small for gestational age), by CQ prophylaxis.

Steps for chloroquine prophylaxis pre

1. **At day 14 to 28** after treatment of acute infection check (RDT or malaria smear) that the mother does not currently have *P. vivax* malaria.
2. **If negative, start prophylaxis with CQ 2 tabs weekly** (one 250mg tablet chloroquine phosphate approximately 150mg base). Provide supportive counseling, guidance and encouragement take the CQ weekly.
3. **Check malaria smear** at each antenatal care visit, Screen for anaemia. Revise CQ compliance. It is really hard to remember weekly tablets throughout pregnancy. Don't scold.
4. **After delivery**, continue CQ prophylaxis every week until 4 weeks postpartum or until radical cure can be given.
5. **At 4 weeks postpartum** (the baby should be > 28 days old) provide primaquine after G6PD testing (See 2.2.5) as excretion into breast milk is minimal.

❖ **IF Recurrence of *P. vivax* in pregnancy on CQ prophylaxis**

Check adherence.

^Forgotten or late doses can be enough to have a *P. vivax* breakthrough infection.
^Assist the patient: ask them which day of the week is easy for them to remember.
. Remind: it is good for the baby for the mother to avoid another *P. vivax*.

➢ Treat the acute episodes (See 2.2.2.) This treatment must be *supervised*.

Restart CQ prophylaxis as above (See 2.3.2). Counsel again for compliance. If <28 days DP is a better choice in pregnancy than COA.

3. Adverse effects (AE) and contraindications (CI) of antimalarials

3.1. 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 dose.

If the patient vomits twice IV or IM treatment will be necessary

3.2. Allergy

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

3.2.1. 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.

3.2.2. Allergy to Artesunate

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

3.3. Common serious side effects

3.3.1. 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 (See Dosing table 4.3.18 and 4.3.19) if not already given.

Hypoglycaemia is also a common adverse effect of quinine. Pregnant women are at higher risk for hypoglycaemia (See Hyoglycamia in 1.4.1). IV quinine should be given with a D10W infusion, See 4.3.12.

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 diluted (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.

3.3.2. Tetracycline and Doxycycline

Do not give tetracycline to pregnant women or children < 8 years. It can cause permanent tooth discoloration in the infant and child. Doxycycline can cause this as well, but much less often/less severe.

3.3.3. 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 (methamphetamines) use.

3.3.4. 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.

3.3.5. 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 haemoglobin). At high levels patients can have cyanosis (blue lips and fingers) or have other symptoms like tiredness, difficulty breathing (dyspnea), 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.

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, (See 2.2.5). 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.

Single low dose primaquine (0.25mg/kg) in *P. falciparum* is safe in G6PD deficient patients.

3.3.6. Tafenoquine

If you see a patient who has received Tafenoquine, then these are the common side effects: 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). 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), follow-up regularly for 3 months (because tafenoquine is a long-acting drug).

4. Appendices

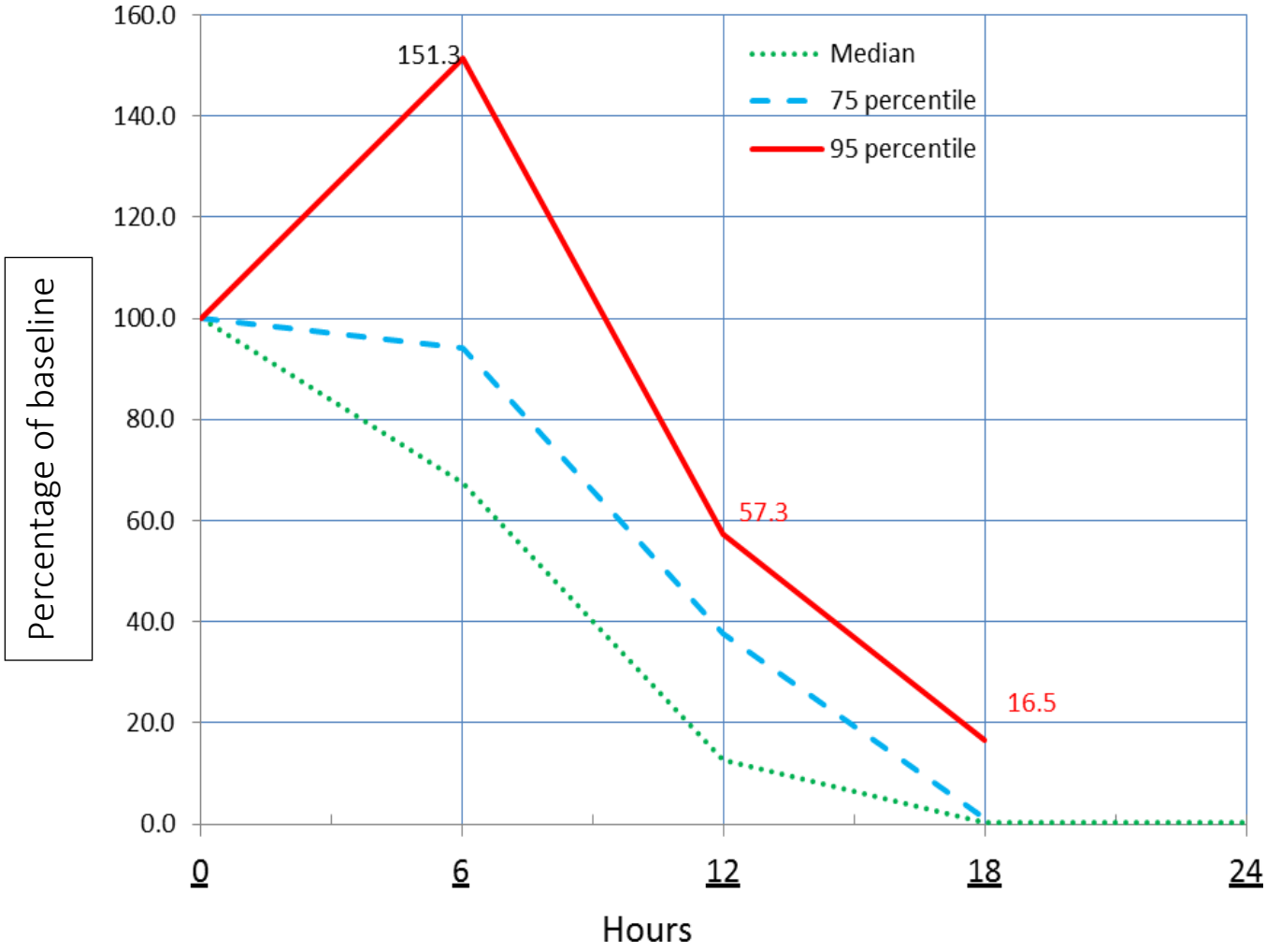
4.1. Checklist before administering antimalarials

1	**Confirmed** positive result: malaria smear or RDT	☐ Pf	☐ Other	☐ Neg
2	**Pregnancy** status: urine pregnancy test if any doubt		☐ Preg	☐ Not Preg
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 1.1)		☐ No	☐ Yes
	b. Hyperparasitaemia (≥4% IRBC) and/or severe malaria (cannot sit or drink alone) (if yes, See 1.3)		☐ No	☐ Yes
	b. Severe malaria (cannot sit or drink alone) (if yes, See 1.3)		☐ No	☐ Yes
5	Did the patient have malaria before?		☐ No	☐ Yes
6	Antimalarial use in the last one to two months?		☐ No	☐ Yes
	a. Supervised or not supervised?		☐ No	☐ Yes
	b. Vomit or not vomit?		☐ No	☐ Yes
	c. If COA was every dose taken with fat?		☐ No	☐ Yes
7	Any history of allergy to antimalarials?		☐ No	☐ Yes
8	Patient already treated for fever?		☐ No	☐ Yes
9	If treatment with mefloquine is needed, check for 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	Does the patient have G6PD card? Did the patient have history of haemolysis after taking primaquine?		☐ No	☐ Yes
11	What is G6PD activity of patient if vivax or ovale?	_____		
12	Does the patient have anaemia? Hb / Hct done _____ result		☐ No	☐ Yes
13	Patient weight on the scale:		_____	Kg
14	Patient febrile?			◦C

Proceed to the treatment guidelines when the answers to all of the above are complete.

4.2. Parasite clearance graph

This graph is here to check parasite clearance, 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.



4.3. Dosage tables

4.3.1. Artemether-lumefantrine (COA) dosing table

1 tablet contains 20mg artemether and 120 mg lumefantrine.

Weight	Tab	Frequency
≤15	1	BID
16-25	2	BID
26-35	3	BID
>35	4	BID

COA must be taken with fat such as fried (samosa, ready-made chips) or oily food (peanuts) or a carton of milk. A large spoonful of oil if there is no food prepared. Small babies can take with breast milk

4.3.2. Dihydroartemisinin + piperaquine (DP) dosing table

1 Adult tablet contains 40mg of dihydroartemisinin (DHA) and 320 mg piperaquine OR

1 Paediatric tablet contains 20 mg of dihydroartemisinin (DHA) and 160 mg of piperaquine

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

Weight	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

4.3.3. Mefloquine-artesunate fixed combination table

1 Paediatric tablet contains: artesunate 25mg + mefloquine 50mg

1 Adult tablet contains artesunate 100mg + mefloquine 200mg

Age range (years	Weight range (kg)	Paediatric dose (tablets /day)	Adult dose (tablets /day	MFQ total dose range mg/kg	Artesunate total dose range mg/kg
<1	5 to < 9 kg$	1		18.9-30.0	9.5-15.0
1 to 6	9 to < 18 kg$	2		17.6-33.3	8.8-16.7
7 to 12			1	20.7-33.3	10.3-16.7
≥13	≥30		2	17.1*-40.0^	8.6*-20^^

$ for these age/weight categories the MFQ will be allowed to disintegrate in water and the drug will be administered in a syringe /on a spoon if necessary; ^ these values are for a 30 kg patient ; * for 70kg patient

4.3.4. 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	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	

4.3.5. 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)	
	tab		tab	(or ml)	tab		tab	
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.

4.3.6. 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/day) x 7 days

Weight	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

4.3.7. Oral quinine dosing table (for young children)

1 ml suspension contains 60 mg quinine sulphate (salt)

Weight	Suspension	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

4.3.8. Clindamycin dosing table

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

Weight	Capsule	Frequency
< 35	1	TID
35 - 69	2	TID
> 69	3	TID

4.3.9. Doxycycline dosing table

One capsule is 100mg; capsules cannot be split or broken.CI: <8 years old and pregnant woman

Dose given once a day for 7 days (4 mg/kg/day)

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

4.3.10. Tetracycline dosing table

Once capsule is 250mg mg. Contraindicated in: children <8y; pregnancy; lactating women

Weight	Nearest cap	Frequency
15 - 37	2	TID
38 - 62	3	TID
> 62	4	TID

4.3.11. IV (or IM) Artesunate dosing table

For hyperparasitaemia or severe malaria: 1 vial contains 60 mg artesunate (60 mg/ml)

Give the dose in the table (3.0 mg/kg for body weight under 20 kg and 2.4 mg/kg for above.) at H0, H12 & H24, then same dosing every 24 hourly for at least 48 hours or until the patient can tolerate oral medication.

Weight	ml	Weight	ml
2.0	0.1	47-48	1.9
3-4	0.2	49-51	2.0
5-6	0.3	52-53	2.1
7-8	0.4	54-56	2.2
9-10	0.5	57-58	2.3
11-12	0.6	59-61	2.4
13-14	0.7	62-63	2.5
15-16	0.8	64-66	2.6
17-18	0.9	67-68	2.7
19-26	1	69-71	2.8
27-28	1.1	72-73	2.9
29-31	1.2	74-76	3.0
32-33	1.3	77-78	3.1
34-36	1.4	79-80	3.2
37-38	1.5	77-78	3.1
39-41	1.6	79-81	3.2
42-43	1.7	82-83	3.3
44-46	1.8	84-85	3.4

*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.**

4.3.12. IV 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 also be given IM 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	

Dilute Quinine in D5W or D10Wto make a maximum dilution of ***10 mg/ml. Consider putting 2 lines if glucose is low.***

4.3.13. Artemether I.M table

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	ml (cc)	Weight	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	ml (cc)	Weight	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		

4.3.14. Primaquine single dose table for *P. falciparum* to block transmission

- Dose: 0.25 mg/kg single stat dose
- No G6PD testing needed for this dose.
- ***A tablet may contain 7.5 mg or 15 mg – confirm this before treatment***

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	# of **7.5 mg** tablets to mix	# of **15 mg** tablets to mix	Mix with sugar water	Single dose
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	# **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 weight 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.

4.3.15. Chloroquine dosing table

1 tablet contains 250 mg chloroquine phosphate (approximately 150 mg base)
Chloroquine phosphate 161mg salt = 100mg base

Dose: D0 & D1 give 10mg/kg, then D2 give 5 mg/kg

Weight	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

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

- Dose: 0.5 mg/kg **DAILY** for 14 days (standard course)
- *Use in **G6PD normal** persons only*
- ***A tablet may contain 7.5 mg or 15 mg – confirm this before treatment***
- Give food before dose to prevent abdominal pain and nausea (take after meals)

Use this table for persons < 13 kg or if <18kg and cannot take tablets.

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

SUSPENSION for 14 day course:			
Weight	Sugar water	# of **15 mg** tab to mix	Daily dose
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

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

One 15 mg tablet is equal to two 7.5 mg tablets.

Example 1: 10kg patient - for suspension, use ½ 15 mg tablet or one 7.5 mg tablet.

Example 2: 15kg patient - one 15 mg table is the same as two 7.5 mg tablets

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

	14 day course	
Weight	# **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

4.3.17. Radical cure primaquine WEEKLY dose for P. vivax relapses

- 0.75 mg/kg **WEEKLY** for 8 weeks
- Use in **G6PD deficient or G6PD unknown persons**
- ***A tablet may contain 7.5 mg or 15 mg – confirm this before treatment***
- Give food before dose to prevent abdominal pain and nausea (take after meals)

Use this table for persons if ≤18kg and cannot take tablets A suspension is made with sugar water and/or Vitamin C or breast milk. Use a tablet cutter to cut tablets

Weight	# of **15 mg** tablets	ml (sugar water)	Weekly Dose
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

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

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

Use this table for persons > 18 kg or who can take tablets

Weight	# **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

** **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 only 15 mg tablets available, follow the patient closely for haemolysis.

4.3.18. Paracetamol dosing table

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. Do not use more than 4 doses (4 grams) every 24 hours

Weight	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

4.3.19. Paracetamol dosing table (suspension)

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

Weight	First dose Stat dose	Following dose 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

4.3.20. Ferrous sulphate suspension dosing (<10kg)

Weight	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

4.3.21. 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)		

4.3.22. Table for maintenance fluid amount and rate

Weight	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%.

4.3.23. 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)

4.3.24. 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.

Eye movement

1 – Watches or follows (mother's face or voice)

0 – Fails to watch or follow

Best motor response

2 – Localizes painful stimulus (patient's ability to remove stimuli)

1 – Withdraws limb from painful stimulus

0 – No response or inappropriate response

Best verbal response

2 – Cries appropriately with pain, or, if verbal, speaks

1 – Moan or abnormal cry with pain

0 – No vocal response to pain

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.

4.3.25. 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

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 lumbar puncture is not available but meningitis is suspected: 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, including:

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

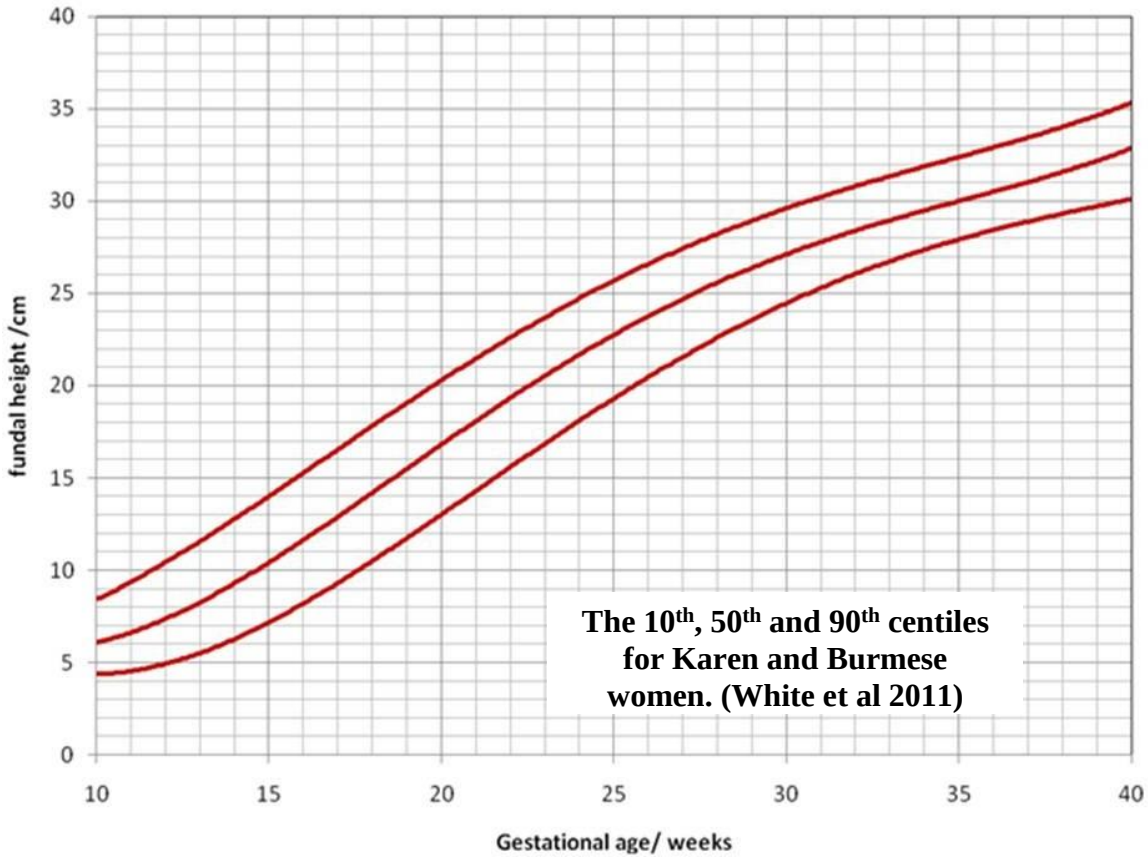
Keep caring - Follow good nursing care (position, eyes, clean, NG)

4.3.26. Karen and Burmese pregnant women estimation of gestational age by fundal height

Fundal Height	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	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	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 migrant 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.

4.3.27. Cord or placenta blood collection to check for malaria at delivery

Consider cord and placental malaria smears when mother has malaria at birth.

How to collect cord specimens

-Cord specimens are preferably taken before the placenta is delivered (if not they must be take as soon as possible after the placenta has delivered).

-Hold the clamped end of the cord attached to the placenta to lengthen the cord

-Wipe the cord clean with gauze

-Use a 21 or 23 gauge (small) needle and syringe

-Withdraw blood from the vessel (0.5 ml is plenty)

-Re-clamp the cord above the puncture site.

-Give the syringe to the person who will prepare a malaria smear as normal onto a glass slide.

-If positive check baby malaria smear, if negative re-smear baby on day 2 to 3, day 28.

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; membranous)).

-Use a syringe and needle 21 or 23 gauge (or haematocrit tube) to withdraw blood pooled in the incision.

-Give the syringe to the person who will prepare a malaria smear as normal onto a glass slide.

-If positive check baby malaria smear, if negative re-smear baby on day 2 to 3, day 28.

4.3.28. Differential diagnosis of congenital malaria

- Neonatal sepsis and other Congenital infections (CHEAP TORCHES):

C Chicken pox and shingles
H Hepatitis C, D and E
E Enteroviruses
A Acquired immunodeficiency syndrome
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) **AND** S Syphilis

4.3.29. Reference ranges of G6PD enzymatic activity in whole blood performed by "STANDARD G6PD" test (SD Biosensor) at SMRU

Age	Sex	Activity	Units	Interpretation
Newborns	M	0.0-4.8	IU/gHb	Deficient
Newborns	M	4.9-21.0	IU/gHb	Normal
Newborns	F	0.0-4.8	IU/gHb	Deficient
Newborns	F	4.9-9.9	IU/gHb	Intermediate
Newborns	F	10.0-21.0	IU/gHb	Normal
Newborns	M & F	HI	--	Normal
>1 years	M	0.0-4.0	IU/gHb	Deficient
>1 years	M	4.1-6.0	IU/gHb	Undefined*
>1 years	M	6.1-21.0	IU/gHb	Normal
>1 years	F	0.0-4.0	IU/gHb	Deficient
>1 years	F	4.1-6.0	IU/gHb	Intermediate
>1 years	F	6.1-21.0	IU/gHb	Normal
>1 years	M & F	HI	--	Normal

* Follow instructions from doctor on how to treat male patients with this level of activity