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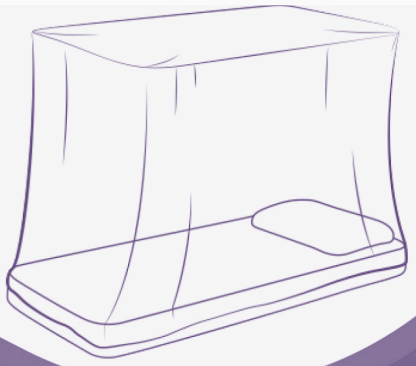
Malaria

Diagnosis and Treatment Guidelines

Version 2.0



MINISTRY OF HEALTH
NATIONAL UNITY GOVERNMENT OF MYANMAR

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1. Abbreviations

AL	Artemether-lumefantrine
BCS	Blantyre coma scale
COVID-19	Coronavirus disease 2019
CQ	Chloroquine
DHA-PPQ	Dihydroartemisinin – Piperaquine
G6PD	Glucose 6 Phosphate Dehydrogenase
GCS	Glasgow coma scale
HRP2	histidine-rich protein 2
LDH	lactate dehydrogenase
PQ	Primaquine
RDT	Rapid Diagnostic Test
SBET	Standby emergency treatment
WHO	World Health Organization

2. Background

Myanmar has made a significant achievement in reducing malaria burden over the past decade. The number of malaria cases has reduced from more than 690,000 in 2010 to just over 56,000 in 2019, and 58,000 in 2020 despite the COVID-19 disruption to health services, putting the country on the path to malaria elimination by 2030[1]. However, the military coup in 2021 and the following events of conflicts and displacements have derailed the achievements the country has made. The reported number of malaria cases has increased to more than 79,000 in 2021 and more than 157,000 in 2022[1]. The reported figures are most likely an under-representation of the actual situation since WHO has estimated north of 580,000 malaria cases in 2022 which is 423,000 cases more than the reported figures[1]. Testing for malaria has also decreased drastically – from 3.7 million and 3.6 million testing in 2019 and 2020 respectively to only 1.9 million and 2.6 million testing in 2021 and 2022 respectively[1]. Despite a slight recovery of testing in 2022, the malaria positivity rate keeps going up, 4.5% in 2021 and 5.9% in 2022 compared to just 1.5% in 2019[1], underscoring the continued under-testing, under-reporting and under-treatment of malaria cases.

Malaria is caused by a parasite of the genus *Plasmodium* that are carried by female *Anopheles* mosquitoes and transmitted to humans through their bites feeding on human blood. *Plasmodium falciparum, Plasmodium vivax, Plasmodium malariae*, and *Plasmodium ovale* are the common species that infect humans. In Myanmar and in the Greater Mekong Subregion, *Plasmodium falciparum* and *Plasmodium vivax* are the most commonly detected species. *Plasmodium falciparum* is notorious for causing severe malaria infection that has a high fatality rate and *Plasmodium vivax* for recurrent clinical episodes. Infections due to *Plasmodium knowlesi* have been reported more commonly in the Southeast Asia, particularly in Malaysia, however, its diagnosis requires molecular tools[2].

Malaria, known as a disease of forest, puts certain population, such as forest goers, mobile migrant population, people who live at forest fringes and development project sites, and displaced or uprooted people, at risk of infection. Displacement poses a unique challenge to malaria control and elimination. When people from geographic areas with little or no malaria are displaced to malaria-endemic areas, there is an increased risk for malaria outbreaks among them. On the other hand, when people originally from malaria-endemic areas are displaced to low or eliminated areas, the risk is re-introduction of malaria and malaria outbreaks in the host community. Such factors should be considered when managing malaria suspects during conflicts and emergencies.

[1] World Health Organization, World Malaria Report, 2023

[2] Zaw MT, Lin Z. Human Plasmodium knowlesi infections in South-East Asian countries. J Microbiol Immunol Infect. 2019 Oct;52(5):679-684. doi: 10.1016/j.jmii.2019.05.012. Epub 2019 Jul 6. PMID: 31320238.

3. Target audience and suggested use

This set of malaria guidelines is a revision to the Version 1.0 released in June 2022, and is intended for medical personnel working in limited-resourced setting of conflicts and emergencies.

4. Summary of changes from the Version 1.0

Section	Version 1.0	Version 2.0
Malaria suspect definition	A person with fever or history of fever within 7 days, with or without other accompanying signs and symptoms, has either history of malaria or had stayed at night in areas where there is malaria transmission, and has no obvious signs and symptoms of any other febrile disease.	Every patient presenting with a history of fever or body temperature of ≥ 37.5 degree C without any obvious reason should be regarded as a “malaria suspect”.
Definition for probable malaria	A suspected case of malaria but not confirmed positive by parasitological test (either by microscopy and/or RDT) and is treated with full course of anti-malaria drugs.	Removed since the terminology no longer appears in WHO's 2023 malaria guidelines.
Definition for confirmed malaria	A case of febrile illness with malaria parasites confirmed by either microscopy and/or RDT.	Removed since the terminology no longer appears in WHO's 2023 malaria guidelines.
Definition for uncomplicated malaria	A case of malaria, either suspected, probable or confirmed, without signs of severity and/or evidence of vital organ dysfunction.	A malaria-suspect with or without parasitological confirmation and with no features of severe malaria is defined as a case of uncomplicated malaria.
General principles for treatment of malaria		Poor adherence to anti-malarial drugs is a major cause of treatment failure, a driving force for development and spread of drug resistance which is already an issue in Myanmar and the Greater Mekong Sub-region. Healthcare providers should ensure that adequate explanation is provided to patients for treatment completion.
Primaquine for P. vivax and P. ovale infections	Primaquine (0.25 mg base/kg/day for 14 days) should be given for confirmed Plasmodium vivax and Plasmodium ovale infections with precautions. If the patient has G6PD deficiency, 0.75 mg/kg is given once weekly for 8 weeks.	Primaquine can be provided at 0.25 mg/kg for 14 days without G6PD test result or at 0.75 mg/kg once a week for 8 weeks when G6PD deficiency is present or in doubt about the G6PD deficiency status. Primaquine can also be given at 0.5 mg/kg for 7 days when G6PD testing is available, and the patient is non-deficient for G6PD test. Primaquine is not required for *P. malariae* infections.

Haemolysis due to primaquine		Close medical supervision should be made to detect and manage primaquine-induced haemolysis at an early stage. Particular attention should be paid to those with G6PD deficiency or those who are native of areas with high G6PD deficiency prevalence.
Definition for mixed infections		Mixed infections are infections with more than one species of Plasmodium. In Myanmar, mixed infections are either *P. falciparum* plus *P. vivax* infection or *P. falciparum* plus *P. ovale* infection.
Treatment of malaria suspects when parasitological diagnosis is not available		When malaria species is unknown, treatment should follow the *P. falciparum* treatment regimen.
Treatment of uncomplicated malaria caused by P. falciparum during pregnancy	In first trimester of pregnancy: Quinine plus clindamycin is the treatment of choice.	Artemether – lumefantrine can be provided to pregnant women with *P. falciparum* infections at all stages of pregnancy and during lactation. The dosage and duration should follow the same as in non-pregnant patients.
Definition for severe malaria	A case of malaria, either suspected, probable or confirmed, with signs of severity and/or evidence of vital organ dysfunction.	A malaria-suspect with or without parasitological confirmation AND with one or more features of severe malaria is defined as a case of severe malaria. Absence or delay of parasitological diagnosis should not be the reason for delay in immediate start of parenteral antimalarial treatment among patients with suspected severe malaria.

Features of severe malaria	Clinical features of severe malaria - Impaired consciousness (GCS <11) - Prostration – generalized weakness (cannot sit, stand or walk without assistant) - Failure to feed or persistent vomiting - Multiple convulsions (more than 2 episodes within 24 hr) - Acidotic breathing (rapid, deep, laboured breathing) - Circulatory collapse or shock (compensated: capillary refill ≥3 s or temp gradient on leg with no hypotension; decompensated: systolic pressure <80 mmHg with cool peripheries or prolonged capillary refill.) - Jaundice plus other vital organ dysfunction - Haemoglobinuria - Abnormal spontaneous bleeding - Pulmonary oedema Laboratory findings - Hypoglycaemia - (blood glucose <2.2 mmol/l or <40 mg/dl) - Metabolic acidosis - (plasma bicarbonate <15 mmol/l) - Severe malarial anaemia: Haemoglobin concentration ≤5 g/dL or a haematocrit of ≤15% in children <12 years of age (<7 g/dL and <20%, respectively, in adults) - Haemoglobinuria - Hyperparasitaemia - >2% low transmission areas, >5% high transmission area, >10% in all settings. - Hyperlactataemia - (lactate >5 mmol/L) - Renal impairment - (serum creatinine >265 µmol/L).	1) Impaired consciousness: Glasgow coma score < 11 in adults or Blantyre coma score < 3 in children 2) Prostration: to the extent that the patient is not able to sit, stand or walk without assistance 3) Multiple seizures: more than 2 episodes within 24 hours 4) Acidosis: clinical features of severe acidosis manifested by respiratory distress such as rapid, deep, laboured breathing or laboratory diagnosis of acidosis such as base deficit of > 8 mEq/L or, if not available, a plasma bicarbonate level of < 15 mmol/L or venous plasma lactate ≥ 5 mmol/L 5) Hypoglycaemia: blood or plasma glucose level of < 2.2 mmol/L 6) Severe malarial anaemia: Haemoglobin concentration ≤ 5 g/dL or a haematocrit of ≤ 15% in children < 12 years of age (< 7 g/dL and < 20%, respectively, in adults) with a parasite count > 10,000/µL 7) Renal impairment: Plasma or serum creatinine > 265 µmol/L (3 mg/dL) or blood urea > 20 mmol/L 8) Jaundice: Plasma or serum bilirubin > 50 µmol/L (3 mg/dL) with a parasite count > 100,000/µL (> 20,000/µL among severe P. knowlesi infection) 9) Pulmonary oedema: Radiologically confirmed or oxygen saturation < 92% on room air with a respiratory rate > 30/min, often with chest indrawing and crepitations on auscultation 10) Significant bleeding: recurrent or prolonged bleeding from the nose, gums or venepuncture sites; haematemesis or melaena 11) Shock: Compensated shock is defined as capillary refill ≥ 3 s or temperature gradient on leg (mid to proximal limb), but no hypotension. Decompensated shock is defined as systolic blood pressure < 70 mm Hg in children or < 80 mmHg in adults, with evidence of impaired perfusion (cool peripheries or prolonged capillary refill). 12) Hyperparasitaemia: P. falciparum parasitaemia > 10% among

		patients with severe P. falciparum malaria; parasite density > 100,000/µL among patients with severe P. knowlesi malaria.
Artesunate injection dosage among children with severe malaria		Among children that weigh less than 20 kg, artesunate should be given at a higher dose of 3 mg/kg/dose.
Quinine infusion dosage among specific patient group with severe malaria		Adjustment of quinine dosage is required in patients with acute kidney injury or patients with no clinical improvement in 48 hours. The dose should be reduced to 10mg/kg every 12 hours.
Pre-referral treatment for severe malaria	Considering the risk of dying from severe malaria, either intramuscular artesunate, artemether, or quinine should be given without delay before referral. Another option is to give rectal artesunate when these parenteral treatments are not feasible.	In the event that referral to higher facility is needed, the patient should be provided with a first dose of one of the recommended treatments for pre-referral. Among children under 6 years, the options in descending order of preference are intramuscular artesunate, rectal artesunate, intramuscular artemether and intramuscular quinine. Among children above 6 years and adults, the recommendations in descending order of preference are intramuscular artesunate, intramuscular artemether and intramuscular quinine.
Supportive care and management of complications among severe malaria patients		Refer to relevant section of the revised guidelines for details.
Treatment of severe malaria during pregnancy and lactation	Quinine is not contraindicated in pregnancy.	All the recommended parenteral drugs for severe malaria are suitable for pregnancy and lactation. Treatment regimen and choices should follow the same as in non-pregnant population.

New section: Defining first line anti-malarial failure		**Defining first line anti-malarial failure** Treatment failure should be suspected if fever does not resolve or is recurrent within 28 days of first line treatment. Treatment failure can be due to one or more of the following reasons: drug resistance, sub-optimal dosage, poor adherence, vomiting, sub-standard drugs, unusual pharmacokinetics of an individual. Treatment failure must have parasitological confirmation, either with microscopy or LDH-based RDTs. However, since currently available RDTs in Myanmar also detects HRP2 in addition to LDH, they are not useful for detection of treatment failure. Patients presenting with fever after 28 days of first line treatment should be regarded as a new infection and treated with appropriate first line anti-malarial drugs.
New section: Treating first line anti-malarial failure		**Treating first line anti-malarial failure** If patient reports or is suspected of incomplete treatment, or consuming sub-standard drug, or vomiting, first line antimalarials can be repeated but it needs to be a supervised treatment. If patient does not report or is confirmed not having any of these, AND the parasitological confirmation is made on treatment failure, second line antimalarials should be provided. The recommended second line anti-malarial in Myanmar is Dihydroartemisinin – Piperaquine (DHA-PPQ) once a day for 3 days. DHA-PPQ is safe in pregnancy and lactation.

New section: Standby emergency treatment		Standby emergency treatment (SBET) may be provided to travellers going to remote areas where prompt and effective health care may be difficult. Travellers bring a full course of first line antimalarial treatment for self-administration, i.e., drugs used for treatment of malaria suspects when parasitological diagnosis is not available. Travellers should be provided with a clear and concise written instruction on SBET, and it should include how to recognize symptoms, when to take treatment, how to take treatment, potential side-effects, and importance to complete treatment. They should be made aware of the SBET as a first-aid measure and the need for medical advice as soon as possible. If patient vomits within 30 minutes of taking the drug, a second full dose should be taken. If vomiting is 30-60 minutes after a dose, patient should take an additional half-dose.
Chemoprophylaxis	Chemoprophylaxis should be provided to international travellers going to high-risk areas in and outside of the Greater Mekong Subregion. it is particularly important in the elimination phase. Because of the multi-drug resistance problem in malaria, chemoprophylaxis is not encouraged in Myanmar. Instead, personal protective measures are prescribed for travellers with holding RDT and ACT+PQ as standby treatment.	Removed since it is not encouraged in the context of artemisinin drug resistance.
New section: choices of anti-malarial drugs: summary		Refer to relevant section of the revised guidelines for details.
New section: Side effects of antimalarial drugs		Refer to relevant section of the revised guidelines for details.

New section: Glasgow coma scale		Refer to relevant section of the revised guidelines for details.
New section: Blantyre coma scale		Refer to relevant section of the revised guidelines for details.

5. Diagnosis of malaria

5.1 Malaria suspect

Every patient presenting with a history of fever or body temperature of ≥ 37.5 °C without any obvious reason should be regarded as a "malaria suspect".

Rationale: WHO recommends that in malaria-endemic areas, anyone presenting with a history of fever or measured body temperature of ≥ 37.5 °C without other obvious reason should be considered as "malaria suspect".[3] Although regular update to malaria stratification is an ideal approach to determine the level of malaria-endemicity in an area, such approach is not feasible in conflict and emergency setting that Myanmar is now in. Given a substantial rebound in malaria cases post-2020 and internal displacement that potentially shifts the malaria burden of a geography, it would be wise to take a safer approach by considering every fever case, when no other obvious reason is present, as "malaria suspect".

5.2 Parasitological diagnosis

Whenever available, every malaria suspect should be tested with either microscopy or rapid diagnostic tests (RDTs).[3] Owing to limited resources in conflict areas, the main and perhaps sole parasitological diagnosis will likely be with RDTs. Early diagnosis and effective treatment of malaria within 24-48 hours of the symptom onset is essential.[3]

If RDTs are not available, malaria suspects may be treated with anti-malarial drugs without a parasitological confirmation. Such approach is considered practical in conflict and emergency settings.[3]

Currently available RDTs detect histidine-rich protein 2 (HRP2), an antigen released by *P. falciparum*, and *Plasmodium* lactate dehydrogenase (pLDH) released by *P. vivax* and/or *P. falciparum*. Since HRP2 can be detected in the blood for 1 to 5 weeks after treatment, the test is not useful in distinguishing new *P. falciparum* infections from old infections.

[3] WHO guidelines for malaria, v7.1, published on 16 October 2023

6. Treatment of malaria

6.1 General principles

Use of monotherapy must be avoided at all times.

Poor adherence to anti-malarial drugs is a major cause of treatment failure, a driving force for development and spread of drug resistance which is already an issue in Myanmar and the Greater Mekong Sub-region. Healthcare providers should ensure that adequate explanation is provided to patients for treatment completion.

6.2 Treatment of uncomplicated malaria

A malaria-suspect with or without parasitological confirmation and with no features of severe malaria is defined as a case of uncomplicated malaria.

Rationale: WHO defines uncomplicated malaria as "a patient who presents with symptoms of malaria and a positive parasitological test (microscopy or RDT) but with no features of severe malaria is defined as having uncomplicated malaria".[3] In the current context of Myanmar, where parasitological diagnosis is not available, those who are not confirmed with microscopy or RDTs but are considered malaria suspect and do not have severe malaria features will be defined as having uncomplicated malaria.

6.2.1 Treatment of uncomplicated *P. falciparum* malaria

Artemether-lumefantrine (AL) for 3 days is the recommended first line drug for *P. falciparum* malaria in Myanmar.

Primaquine (PQ), without a need for G6PD testing, should be given as a single low dose (0.25 mg/kg body weight) on the first day of treatment.[3]
Primaquine should be avoided among pregnant women, children under 6 months and breastfeeding mother of children under 6 months.[3]

Rationale[3]: When administered over 3 days, artemether clears parasites of the two asexual cycles, leaving only a small number of parasites that can be cleared by the partner drug, lumefantrine. Combining artemether with lumefantrine hence reduces the likelihood of partner drug resistance. Primaquine, on the other hand, can quickly reduce the infectivity of gametocytes to mosquitoes, hence, reduce transmission.

Lumefantrine absorption is increased when co-administered with fat. Hence, AL should be taken immediately after food or fat containing drinks such as milk, especially on the second and third day.[3]

Dosing schedule based on available formulation in Myanmar - Dispersible or standard tablets containing 20 mg artemether and 120 mg lumefantrine.

Age group (years)	Artemether-Lumefantrine + Primaquine						
	Day 0			**Day 1**		Day 2	
	1st Dose	**+ PQ**	**2nd Dose**	**1st Dose**	**2nd Dose**	**1st Dose**	2nd Dose
<1	½	-	½	½	½	½	½
1 – 4	1	3.75 mg	1	1	1	1	1
5 – 9	2	7.5 mg	2	2	2	2	2
10 – 14	3	11.25 mg	3	3	3	3	3
15+ above	4	15 mg	4	4	4	4	4

* PQ = Single low dose (0.25 mg/kg body weight)

Note: Dose interval of artemether and lumefantrine – Given at 0, 8, 24, 36, 48, and 60 hours.

6.2.2 Treatment of uncomplicated *P. vivax, P. malariae* and *P. ovale* malaria

Chloroquine (CQ) for 3 days is still a drug of choice for treatment of *P. vivax, P. malariae* and *P. ovale* malaria in Myanmar. The dosage for CQ is 10 mg/kg on day zero, followed by 10 mg/kg on day one, and 5 mg/kg on day two.

Primaquine can be provided at 0.25 mg/kg daily for 14 days without G6PD test result OR at 0.75 mg/kg once a week for 8 weeks when G6PD deficiency is present or in doubt about the G6PD deficiency status. Primaquine can also be given at 0.5 mg/kg for 7 days when G6PD testing is available, and the patient is non-deficient for G6PD test. Primaquine is not required for P. malariae infections.

Primaquine should be avoided among pregnant women, children under 6 months and breastfeeding mother of children under 6 months.

Rationale: P. vivax is still sensitive to CQ in Myanmar.[4] It can cure the blood stage parasite. Primaquine is intended for radical cure of *P. vivax* and *P. ovale* as the drug can clear

[4] Therapeutic Efficacy Studies (TES) or integrated Drug Efficacy Surveillance (iDES) in Myanmar, slides presented at the WHO workshop on malaria surveillance and malaria elimination in the Greater Mekong Subregion, 15-17 November 2023.

hypnozoites that are dormant in the liver, hence, prevent frequent relapses that can happen over weeks or years after initial infection.[3] *P. malariae* does not produce hypnozoites in the liver, hence, primaquine is not required for *P. malariae*.[3]

Close medical supervision should be made to detect and manage primaquine-induced haemolysis at an early stage. Particular attention should be paid to those with G6PD deficiency or those who are native of areas with high G6PD deficiency prevalence.

Rationale[2]: Primaquine is known to cause haemolysis in G6PD deficient patients. Once a week primaquine for 8 weeks reduces the risk of haemolysis, however, close supervision is still necessary.

Dosing schedule based on available formulation - chloroquine phosphate and hydroxychloroquine.

250 mg of chloroquine phosphate ≈ 150 mg of chloroquine base

200 mg of hydroxychloroquine ≈ 155 mg of chloroquine base

Age groups	Chloroquine tablets (150 mg base tablet)		
	Day 0	**Day 1**	Day 2
<1	⅓	⅓	⅓
1 – 4	1½	1½	1
5 – 9	2	2	1
10 – 14	3	3	1½
15+above	4	4	2

6.2.3 Treatment of uncomplicated mixed infections

Mixed infections are infections with more than one species of *Plasmodium*. In Myanmar, mixed infections are either *P. falciparum* plus *P. vivax* infections or *P. falciparum* plus *P. ovale* infections.

Mixed infections should be treated with AL as in *P. falciparum* infection along with primaquine regimen as in *P. vivax* or *P. ovale* infection.

6.2.4 Treatment of malaria suspects when parasitological diagnosis is not available.

When malaria species is unknown, treatment should follow the *P. falciparum* treatment regimen.[3]

6.3 Treatment of uncomplicated malaria during pregnancy and lactation

6.3.1 Treatment of uncomplicated *P. falciparum* infections during pregnancy and lactation

Artemether – lumefantrine can be provided to pregnant women with *P. falciparum* infections at all stages of pregnancy and during lactation. The dosage and duration should follow the same as in non-pregnant patients.

Primaquine should be avoided during pregnancy and breastfeeding mother of children under 6 months.

Rationale[3]: In 2022, WHO recommends use of AL during first trimester of pregnancy, which replaces quinine-based regimens that is recommended until 2022. The recommendation was based on research findings that showed insignificant side effects, very low risk of adverse pregnancy outcomes, and a large magnitude of treatment efficacy compared to quinine-based regimens.

6.3.2 Treatment of uncomplicated *P. vivax, P. ovale* and *P. malariae* infections during pregnancy and lactation

Chloroquine can be provided as in non-pregnant patients. Primaquine should be avoided during pregnancy and breastfeeding mother of children under 6 months.

6.3.3 Treatment of uncomplicated mixed infections or malaria suspects during pregnancy and lactation where parasitological diagnosis is not available.

The treatment regimen for mixed infections and malaria suspects without parasitological diagnosis is the same as for non-pregnant patients. Primaquine should be avoided during pregnancy and breastfeeding mother of children under 6 months.

6.4 Treatment of severe malaria

A malaria-suspect[5] with or without parasitological confirmation AND with one or more features of severe malaria is defined as a case of severe malaria.

Among patients with suspected severe malaria, absence or delay of parasitological diagnosis should not be the reason for delay in immediate start of parenteral antimalarial treatment.

[5] Every patient presenting with a history of fever or body temperature of >= 37.5 degree C without any obvious reason should be regarded as a “malaria suspect”.

Rationale[3]: Severe malaria is most commonly due to *P. falciparum,* but it is also reported with *P. vivax* and *P. knowlesi*. WHO defines severe malaria as "having one or more of the features of severe malaria, in the absence of an identified alternative cause and in the presence of *P. falciparum* or *P. vivax* or *P. knowlesi* parasitaemia". In conflict and emergency setting that Myanmar is in, where parasitological diagnosis may not be universally available, identifying severe malaria may have to be based on clinical suspicion. WHO also emphasizes that in suspected severe malaria patients, absence of or delay in parasitological diagnosis should not hinder an immediate start of parenteral antimalarial treatment.

6.4.1 Features of severe malaria[3]

In the context of limited-resource setting, not all laboratory investigations mentioned below will not be available. The diagnosis of severe malaria will likely be clinical.

1) Impaired consciousness: Glasgow coma score < 11 in adults or Blantyre coma score < 3 in children
2) Prostration: to the extent that the patient is not able to sit, stand or walk without assistance
3) Multiple seizures: more than 2 episodes within 24 hours
4) Acidosis: clinical features of severe acidosis manifested by respiratory distress such as rapid, deep, laboured breathing or laboratory diagnosis of acidosis such as base deficit of > 8 mEq/L or, if not available, a plasma bicarbonate level of < 15 mmol/L or venous plasma lactate ≥ 5 mmol/L
5) Hypoglycaemia: blood or plasma glucose level of < 2.2 mmol/L
6) Severe malarial anaemia: Haemoglobin concentration ≤ 5 g/dL or a haematocrit of ≤ 15% in children < 12 years of age (< 7 g/dL and < 20%, respectively, in adults) with a parasite count > 10,000/µL
7) Renal impairment: Plasma or serum creatinine > 265 µmol/L (3 mg/dL) or blood urea > 20 mmol/L
8) Jaundice: Plasma or serum bilirubin > 50 µmol/L (3 mg/dL) with a parasite count > 100,000/µL (> 20,000/µL among severe P. knowlesi infection)
9) Pulmonary oedema: Radiologically confirmed or oxygen saturation < 92% on room air with a respiratory rate > 30/min, often with chest indrawing and crepitations on auscultation
10) Significant bleeding: recurrent or prolonged bleeding from the nose, gums or venepuncture sites; haematemesis or melaena
11) Shock: Compensated shock is defined as capillary refill ≥ 3 seconds or temperature gradient on leg (mid to proximal limb), but no hypotension. Decompensated shock is defined as systolic blood pressure < 70 mm Hg in children or < 80 mmHg in adults, with evidence of impaired perfusion (cool peripheries or prolonged capillary refill).
12) Hyperparasitaemia: P. falciparum parasitaemia > 10% among patients with severe P. falciparum malaria; parasite density > 100,000/µL among patients with severe P. knowlesi malaria.

6.4.2 Treatment regimen for severe malaria

Initial parenteral treatment[3]

Severe malaria is a medical emergency and patients should be started on parenteral antimalarial drugs immediately. Parenteral drug should be given at least 24 hours regardless of patients' ability to swallow oral drug.

The treatment of choice is intravenous or intramuscular artesunate injection at 2.4 mg/kg/dose for a minimum of 24 hours (at zero, 12 and 24 hours and then once daily) as in the schedule below and until patients can tolerate oral drugs. Among children that weigh less than 20 kg, artesunate should be given at a higher dose of 3 mg/kg/dose.

If artesunate injection is not available, intramuscular artemether injection at 3.2 mg/kg/dose can be given as an initial dose followed by a maintenance dose of 1.6 mg/kg/dose daily.

Artemether injection is preferred to quinine injection.

Rationale[3]: Death rate from untreated severe malaria is almost 100%. However, with prompt and effective anti-malarial treatment along with supportive treatment, the mortality rate falls to 10-20%. Artesunate injection being the first choice in severe malaria treatment is based on the largest randomized clinical trial results that showed a substantial fall in death rate with artesunate injections as compared to quinine injections. Given intramuscularly, absorption of water-soluble artesunate is faster than oil-based artemether. Among young children, the dosage requirement of artesunate is higher due to underexposure among them, which is based on pharmacokinetic modelling data. Studies of the artesunate dosage between 1.75 mg/kg and 4 mg/kg also do not show any toxicity. According to a systematic review of trials conducted in Asia where artemether was compared with quinine for severe malaria treatment, artemether was shown to prevent more deaths. Hence, intramuscular artemether is preferred over quinine.

Follow-on oral treatment[3]

Once the parenteral treatment has been given for at least 24 hours and the patient can tolerate oral drugs, a full 3-day course of oral anti-malarial drugs should be provided.

Oral drugs are artemether + lumefantrine along with single low dose primaquine in severe malaria caused by *P. falciparum*, and chloroquine in severe malaria due to *P. vivax*. Primaquine radical cure for *P. vivax* should be provided only after patient has recovered.

When AL is not available, artesunate + clindamycin, artesunate + doxycycline, quinine + clindamycin or quinine + doxycycline can be considered for follow-on oral treatment. Doxycycline should not be used in children and pregnant women.

Parenteral anti-malarial drug dosing schedule

Antimalarial drug	Dosage and Administration
Artesunate injection	2.4 mg/kg body weight/dose administered at zero hour, 12 hour and 24 hour, followed by once a day until the patient can tolerate oral drugs. Note 1: parenteral drugs should be given at least 24 hours. Note 2: For children < 20kg, parenteral artesunate dose is 3mg/kg. Route: intravenous or intramuscular into anterior thigh
Artemether injection	3.2 mg/kg body weight/dose at zero hour and then 1.6 mg/kg body weight/dose daily until the patient can tolerate oral drugs. Route: intramuscular into anterior thigh
Quinine infusion	Loading dose*:* 20mg/kg body weight dose of quinine diluted in 10 ml/kg body weight of 5% Dextrose Water or Dextrose Saline administered by intravenous infusion over 4 hours. Maintenance dose*:* 10 mg/kg body weight dose of quinine diluted in 10 ml/kg body weight dose of 5% Dextrose Water or Dextrose Saline administered by intravenous infusion over 4 hours at an interval of every 8 hours until the patient can tolerate oral drugs. Note: parenteral drugs should be given at least 24 hours. Note: quinine infusion rate should not exceed 5 mg/kg per hour. Adjustment of quinine dosage is required in patients with acute kidney injury or patients with no clinical improvement in 48 hours. The dose should be reduced to 10mg/kg every 12 hours.

Pre-referral treatment[3]

In the event that referral to higher facility is needed, the patient should be provided with a first dose of one of the recommended treatments for pre-referral.

Among children under 6 years, the options in descending order of preference are intramuscular artesunate, rectal artesunate, intramuscular artemether and intramuscular quinine.

Among children above 6 years and adults, the recommendations in descending order of preference are intramuscular artesunate, intramuscular artemether and intramuscular quinine.

Rationale: Probability of death from severe malaria is highest in the first 24 hours. The transit time during referral can be quite long especially in the current context of Myanmar. Hence, it is imperative to provide pre-referral treatment to patients with severe malaria. Rectal artesunate is feasible and easy to administer at the community level, however, the only research trial available on rectal artesunate as pre-referral treatment showed an increased death rate among older children and adults while the death rate was reduced among young children. Hence, rectal artesunate is recommended only for younger children and only when intramuscular artesunate is unavailable.

Among younger children (under 6 years of age), when intramuscular artesunate is not available, a single dose of 10 mg/kg/dose of artesunate should be given rectally. If it is expelled within 30 minutes of insertion, another dose should be inserted while holding up the buttocks for 10 minutes to retain the dose.

Treatment regimen during pregnancy and lactation

All the recommended parenteral drugs for severe malaria can be used during pregnancy and lactation. Treatment regimen and choices should follow the same as in non-pregnant population.

6.4.3 Supportive care and management of complications[3]

Frequent monitoring of vital signs, coma score, urine outputs, and blood glucose (every 4 hours) is necessary.

The followings are the immediate management measures of complications as appeared in WHO guidelines. Not all of them will be feasible in the context of Myanmar.

Manifestation or complication	Immediate management
Coma (cerebral malaria)	Maintain airway, place patient on his or her side, exclude other treatable causes of coma (e.g. hypoglycaemia, bacterial meningitis); avoid harmful ancillary treatments, intubate if necessary.
Hyperpyrexia	Administer tepid sponging, fanning, a cooling blanket and paracetamol.
Convulsions	Maintain airways; treat promptly with intravenous or rectal diazepam, lorazepam, midazolam or intramuscular paraldehyde. Check blood glucose.

Hypoglycaemia	Check blood glucose, correct hypoglycaemia and maintain with glucose-containing infusion. Although hypoglycaemia is defined as glucose < 2.2 mmol/L, the threshold for intervention is < 3 mmol/L for children < 5 years and <2.2 mmol/L for older children and adults.
Severe anaemia	Transfuse with screened fresh whole blood.
Acute pulmonary oedema	Prop patient up at an angle of 45°, give oxygen, give a diuretic, stop intravenous fluids, intubate and add positive end-expiratory pressure or continuous positive airway pressure in life-threatening hypoxaemia.
Acute kidney injury	Exclude pre-renal causes, check fluid balance and urinary sodium; if in established renal failure, add haemofiltration or haemodialysis, or, if not available, peritoneal dialysis.
Spontaneous bleeding and coagulopathy	Transfuse with screened fresh whole blood (cryoprecipitate, fresh frozen plasma and platelets, if available); give vitamin K injection.
Metabolic acidosis	Exclude or treat hypoglycaemia, hypovolaemia and septicaemia. If severe, add haemofiltration or haemodialysis.
Shock	Suspect septicaemia, take blood for cultures and sensitivity; give parenteral broad-spectrum antimicrobials, correct haemodynamic disturbances.

6.5 Treatment of first line anti-malarial failure

6.5.1 Defining first line anti-malarial failure

Treatment failure should be suspected if fever does not resolve or is recurrent within 28 days of first line treatment.[3]

Treatment failure can be due to one or more of the following reasons: drug resistance, sub-optimal dosage, poor adherence, vomiting, sub-standard drugs, unusual pharmacokinetics of an individual.[3]

Treatment failure must have parasitological confirmation, either with microscopy or LDH-based RDTs.[3] However, since currently available RDTs in Myanmar also detects HRP2 in addition to LDH, they are not useful for detection of treatment failure.

Patients presenting with fever after 28 days of first line treatment should be regarded as a new infection and treated with appropriate first line anti-malarial drugs.

6.5.2 Treating first line anti-malarial failure

If patient reports or is suspected of incomplete treatment, or consuming sub-standard drug, or vomiting, first line antimalarials can be repeated but it needs to be a supervised treatment.

If patient does not report or is confirmed not having any of these, AND the parasitological confirmation is made on treatment failure, second line antimalarials should be provided.

The recommended second line anti-malarial in Myanmar is Dihydroartemisinin – Piperaquine (DHA-PPQ) once a day for 3 days.

DHA-PPQ is safe in pregnancy and lactation.

Dosage regimen of DHA-PPQ based on available formulations: 20 mg DHA/160 mg PPQ and 40 mg DHA/320 mg PPQ

Body weight (kg)	20 mg DHA/160 mg PPQ tablet	40 mg DHA/320 mg PPQ tablet
5- <8	1 tab	
8- <11	1 ½ tab	
11- <17	-	1 tab
17-<25	-	1 ½ tab
25-<36	-	2 tab
36-<60	-	3 tab
60-<80	-	4 tab
>80	-	5 tab

6.6 Standby emergency treatment

Standby emergency treatment (SBET) may be provided to travellers going to remote areas where prompt and effective health care may be difficult.[6]

Travellers bring a full course of first line antimalarial treatment for self-administration[6], i.e., drugs used for treatment of malaria suspects when parasitological diagnosis is not available (refer to section 6.2.4).

Travellers should be provided with a clear and concise written instruction on SBET, and it should include how to recognize symptoms, when to take treatment, how to take treatment,

[6] World Health Organization, International Travel and Health, Chapter 7 – Malaria, 2020 update.

potential side-effects, and importance to complete treatment.[6] They should be made aware of the SBET as a first-aid measure and the need for medical advice as soon as possible.[6]

If patient vomits within 30 minutes of taking the drug, a second full dose should be taken. If vomiting is 30-60 minutes after a dose, patient should take an additional half-dose.[6]

Rationale[6]: Studies have shown that RDT self-testing by untrained travellers causes issues with human performance, test interpretation, with an unacceptably high rate of false-negative results.

7. Appendices

7.1 Choices of anti-malarial drugs: summary

Severity of malaria	Species	Drug choice
Uncomplicated malaria	*P. falciparum*	Artemether – lumefantrine + single low dose primaquine
	P. vivax, P. ovale	Chloroquine + 7 days/ 14 days/ 8 weeks primaquine
	P. malariae	Chloroquine
	Mixed	Artemether – lumefantrine + 7 days/ 14 days/ 8 weeks primaquine
	No parasitological diagnosis	Artemether – lumefantrine + single low dose primaquine
Severe malaria	All species	IM or IV artesunate – first choice IM artemether – second choice IV infusion quinine – third choice Follow-on oral treatment as appropriate to the species detected
Standby emergency treatment	No parasitological diagnosis	Artemether – lumefantrine + single low dose primaquine

7.2 Side effects of antimalarial drugs

Artemether – lumefantrine

Artemether – lumefantrine is generally well-tolerated. Reported side effects are nausea, dizziness and headache.

Chloroquine

Chloroquine is well-tolerated in general with reported side effects of pruritus as a common side effect. Less common side effects are headache, hepatitis, increased liver enzymes, skin eruptions, nausea, vomiting and diarrhoea.

Primaquine

Primaquine is generally well-tolerated. It may cause gastrointestinal discomfort such as abdominal pain, nausea and vomiting. In G6PD deficient patients, primaquine can cause haemolysis, the severity of which is dependent on dose, duration of drug exposure and extent of G6PD deficiency.

Artesunate

Artesunate is generally well-tolerated with reported side effects of hypersensitivity reactions, gastrointestinal disturbances, cough, rash, arthralgia, dizziness and delayed haemolysis.

Artemether

Artemether is well-tolerated in general with reported side effects of hypersensitivity reactions, mild gastrointestinal disturbances, dizziness, reticulocytopaenia, neutropaenia and increased liver enzymes.

Quinine

Quinine has frequent side effects. Cinchonism is the terms used for side effects that commonly occur after quinine administration. Mild form of cinchonism includes tinnitus, slight hearing impairment, headache, nausea, dizziness, dysphoria, and disturbed vision. Severe form of cinchonism is manifested by vertigo, vomiting, abdominal pain, diarrhoea, marked auditory loss, and visual symptoms including vision loss. In young children, pregnant women and elderly patients, quinine commonly causes hyperinsulinaemic hypoglycaemia. Quinine causes QT interval prolongation in ECG. Hypotension and cardiac arrest may occur if quinine is administered too rapidly. Hypersensitive reactions are also reported and include urticaria, bronchospasm, skin flushes, fever, antibody-mediated thrombocytopenia, haemolytic anaemia, and haemolytic-uraemic syndrome.

Dihydroartemisinin – Piperaquine

Dihydroartemisinin – Piperaquine is generally well-tolerated. Reported side effects include nausea, diarrhoea, vomiting, anorexia, anaemia, dizziness, headache, sleep disturbance and cough.

7.3 Glasgow coma scale

Glasgow coma scale (GCS)[7]: total possible score 3 - 15

Best motor response	Best verbal response	Eye opening
6 Obeying commands	**5** Oriented (time, place, person)	**4** Spontaneous
5 Localizing to pain	**4** Confused conversation	**3** In response to speech
4 Withdrawing to pain	**3** Inappropriate speech	**2** In response to pain
3 Flexor response to pain	**2** Incomprehensible sounds	**1** None
2 Extensor response to pain	**1** None	
1 No response to pain		

7.4 Blantyre coma scale

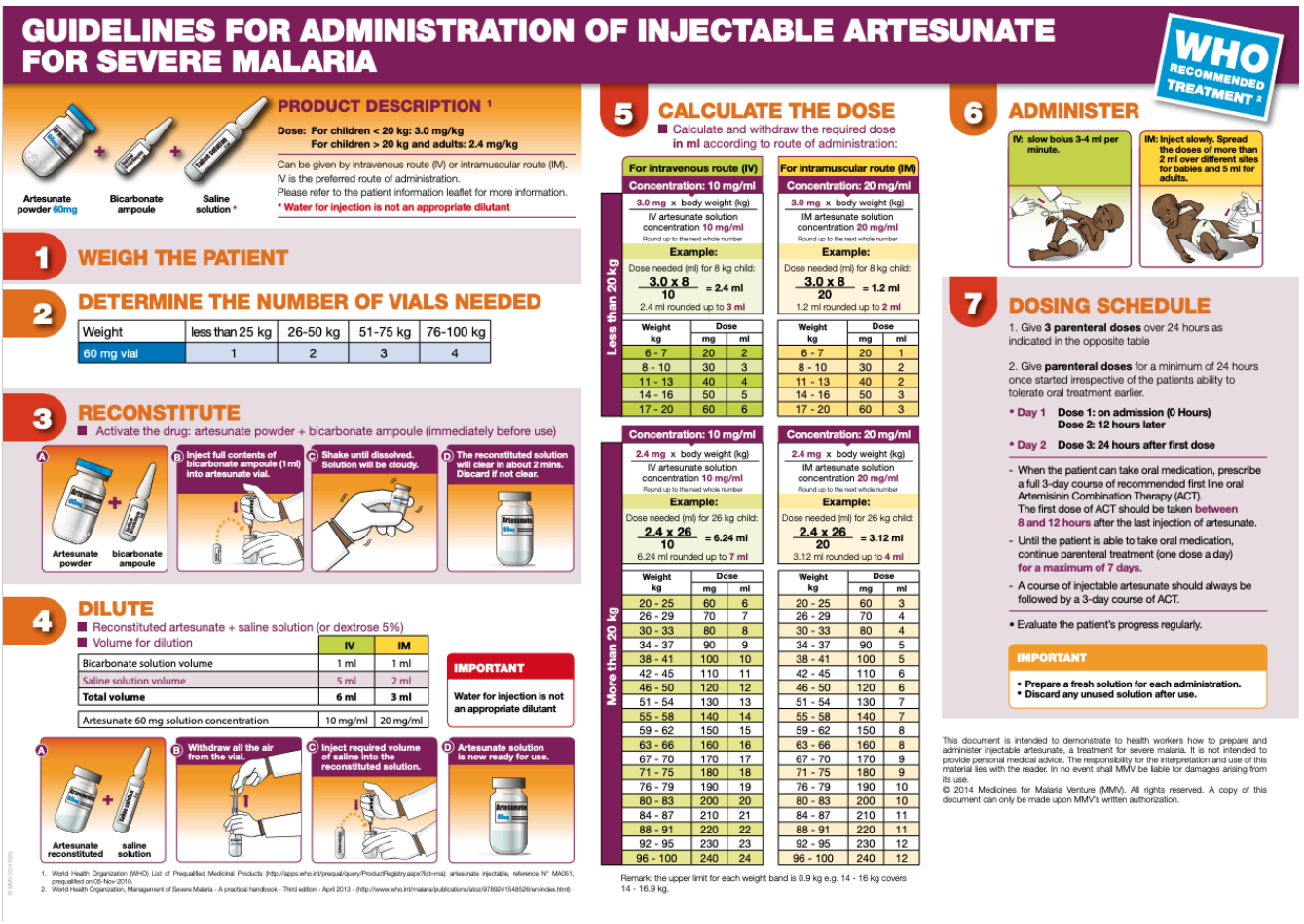
Blantyre coma scale (BCS)[8]: total possible score 0-5

Motor	Verbal	Eye response
2 Localizes pain	**2** Appropriate cry	**1** Directed eye movements
1 Withdraws from pain	**1** Immediate cry/ moan	**0** Not directed
0 No response	**0** No cry	

[7] Oxford Handbook of Clinical Medicine, 10th edition.

[8] Molyneux, M. E., Taylor, T. E., Wirima, J. J. & Borgstein, A. (1989). Clinical features and prognostic indicators in paediatric cerebral malaria: a study of 131 comatose Malawian children. Quarterly Journal of Medicine, 71,441-459.

7.5 Infographic on administration of injectable artesunate for severe malaria



The infographic is taken from Medicines for Malaria Venture website.