National Malaria Treatment Guideline

June, 2014
Summary
Prompt diagnosis and effective treatment remains one of the key strategies for controlling and eliminating malaria. The National Treatment Guidelines ensures that the best evidence based treatment is provided for management of malaria in the country.

**Diagnosis**
All probable cases of malaria should be parasitological confirmed by microscopy or RDT before treatment. Therefore it is necessary to scale-up malaria diagnostics facilities to ensure the feasibility of parasitological diagnosis.

**Treatment of Malaria**

**UNCOMPLICATED MALARIA**

**First line treatment**
- **Confirmed falciparum malaria**: Sulphadoxine-pyramethamine (25 mg/kg sulphamethoxazole component, maximum of 3 tablets) single dose plus artesunate (4mg/kg, maximum 200mg) daily for 3 days with a single 0.25 mg base/kg primaquine dose on the first day of treatment.
- **Confirmed vivax malaria**: Chloroquine (25mg/kg, maximum 1500mg) over 3 days plus primaquine (0.25mg/kg, maximum 15mg) daily for 14 days or (0.75mg/kg, maximum 45mg) weekly for 8 weeks.
- **Clinically diagnosed malaria**: Chloroquine (25mg/kg maximum 1500mg) over 3 days. Refer patient to facility for confirmation of diagnosis and follow-up treatment.

**Second line treatment**
Quinine (10mg salt/kg orally three times daily) plus Doxycycline (3.5mg/kg once a day) or Clindamycin (10mg/kg twice a day); all drugs to be given for 7 days. All cases must be parasitologically confirmed before treatment.

**Malaria in Pregnancy**
Second and third trimesters: Treat as above, except for Primaquine and Doxycycline which should not be used in pregnancy.
First trimester: Quinine (10mg salt/kg orally three times daily) plus Clindamycin (10mg/kg twice a day); all drugs given for 7 days

**SEVERE MALARIA**

**Health center**
Artemether 3.2 mg/kg (maximum 160mg) by intramuscular injection on day1, then 1.6 mg/kg (maximum 80mg) daily for 5 days, Or Artesunate 2.4mg/kg by intramuscular or diluted intravenously in the admission (0 hour), second dose will be giving after 12 hour of first dose and third dose will be giving after 24 hours after first dose, it will continue one dose a day for 7 day.
However, once a patient can tolerate oral treatment, give a complete treatment course of AS+SP orally. All pregnant women with severe malaria should be referred to hospital.
Quinine IV 20mg/kg (maximum 1200mg in adults) as loading dose, then 10mg/kg (maximum 600mg in adults) three times a day. Once can tolerate oral medication give a complete treatment course of AS+SP orally, or continue with oral quinine 10mg salt/kg (maximum 600mg in adults) three times a day plus Clindamycine (10mg/kg twice a day) or Doxycycline (3.5mg/kg daily); all drugs given for a total of 7 days.

Or Artesunate 2.4mg/kg by intramuscular or diluted intravenously in the admission (0 hour), second dose will be giving after 12 hour of first dose and third dose will be giving after 24 hours after first dose, Once can tolerate oral medication give a complete treatment course of AS+SP orally or it will continue one dose a day for 7 days. As per strong recommendation of WHO artesunate should be used in preference to quinine for the treatment of severe malaria.
Acknowledgments

I would like to extend my immense gratitude to Dr Peter Olumese, Global Malaria Programme, WHO, Geneva for the guidance and support he has given in revising the National Treatment Guideline protocol. Special thanks to all participants who attended and contributed to the workshop on updating the National Treatment Guideline.

Note:
This national treatment protocol reprinted in 2014, in the new printed version there are two amendments after conducting national workshop on May, 2014, based on national malaria control program needs, malaria program performance review and WHO recommendations as below:
1. Consider the effectiveness of injectable Artesunate for treatment of severe malaria at health facility and hospital levels, now Artesunate is preference to quinine for the treatment of severe malaria.
2. Addition of a single dose of primaquine (0.25 mg base/kg) to artemisinin combination treatments (ACTs) for uncomplicated falciparum malaria as a gametocytocidal medicine

Complete revision of this version will be done after anti malaria drug efficacy study finding.

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# Acronyms

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
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<tbody>
<tr>
<td>ACTs</td>
<td>Artmesinin-based Combination Therapies</td>
</tr>
<tr>
<td>AS</td>
<td>Artesunate</td>
</tr>
<tr>
<td>CHW</td>
<td>Community Health Worker</td>
</tr>
<tr>
<td>Combo</td>
<td>combination</td>
</tr>
<tr>
<td>CQ</td>
<td>Chloroquine</td>
</tr>
<tr>
<td>G6PD</td>
<td>Glucose 6 phosphate dehydrogenase</td>
</tr>
<tr>
<td>CBMM</td>
<td>Community Based Management of Malaria</td>
</tr>
<tr>
<td>HRP</td>
<td>Histamine - rich protein</td>
</tr>
<tr>
<td>IDPs</td>
<td>Internally Displaced Persons</td>
</tr>
<tr>
<td>IMCI</td>
<td>Integrated Management of Childhood Illnesses</td>
</tr>
<tr>
<td>NMSP</td>
<td>National Malaria Strategic Plan 2013 – 2018</td>
</tr>
<tr>
<td>PLDH</td>
<td>Plasmodium Lactate Dehydrogenase</td>
</tr>
<tr>
<td>RDT</td>
<td>Rapid diagnostic test</td>
</tr>
<tr>
<td>SP</td>
<td>Suphadoxine-Pyrimethamine</td>
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</tbody>
</table>
1. INTRODUCTION

Malaria is a disease caused by the parasite *Plasmodium*. Malaria infection is usually transmitted by the bite of an infected female *anopheles* mosquito. Of the four human species, *P.vivax* and *P.falciparum* are the two most common species in Afghanistan, with *P. vivax* accounting for more than 90% of cases.

In Afghanistan, malaria occurs at altitudes below 2000 meters, with a seasonal pattern of transmission mainly from June to November; however *P.vivax* infections relapse during the spring season (May to July) and this may give rise to a second vivax peak around July.

National Program and its partner update the previous malaria stratification by province to new district level malaria stratification, based on HMIS 2009 – 2010 data, Malaria risk mapping 2006 and other data, verified in the field.

The definition of “risk stratum” is as below:

<table>
<thead>
<tr>
<th>Stratum</th>
<th>Risk of Transmission</th>
<th>Transmission Status</th>
<th>Number Of Districts</th>
<th>Estimated Population</th>
<th>Number confirmed cases</th>
<th>Number Pf</th>
<th>Confirm Incidence /1000</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>High</td>
<td>Active</td>
<td>63</td>
<td>2,944,800</td>
<td>112427</td>
<td>8168</td>
<td>38</td>
</tr>
<tr>
<td>2</td>
<td>Medium</td>
<td>Medium (Malaria is ntrolled but receptive to reintroduction)</td>
<td>138</td>
<td>12,133,500</td>
<td>19097</td>
<td>1580</td>
<td>1.6</td>
</tr>
<tr>
<td>3</td>
<td>Low</td>
<td>Low with risk of epidemics / outbreaks</td>
<td>96</td>
<td>5,023,200</td>
<td>1965</td>
<td>268</td>
<td>0.4</td>
</tr>
<tr>
<td>4</td>
<td>Very low or Malaria free</td>
<td>Nil / Very low</td>
<td>103</td>
<td>4,168,400</td>
<td>727</td>
<td>151</td>
<td>0.2</td>
</tr>
</tbody>
</table>
The overall Goal of malaria control in Afghanistan is “to contribute to the overall improvement of the health status in Afghanistan through reduction of morbidity and mortality associated with malaria”, with the following impact indicators:

- To reduce malaria morbidity by 85% in all malaria stratum by the end of 2017 (baseline total cases (confirmed plus clinical) = 19.5 cases per 1000 population; 5.5 estimated confirmed cases per 1000 population, 2011 data)
- To reduce malaria mortality to 99% by the end of 2017 (nationally malaria reported deaths 40, in 2011)
- To reduce the incidence of P. falciparum malaria to sporadic cases by the end of 2017 with a vision to completely interrupt transmission of Pf by 2020
- To reduce malaria morbidity in high risk (stratum one districts) by 80% by the end of 2017 (baseline total cases [clinical plus confirmed] = 146.7 per 1000; estimated confirmed cases, 38 per 1000 from 2009-2010 figures)

One key strategy necessary to achieve this goal, which is been indentified for strengthening is prompt and effective treatment of malaria in endemic rural areas. Areas targeted for improvement are increased coverage and quality of laboratory services including the introduction of RDTs, wide-scale implementation of CBMM through the extensive CHW network; and an increased awareness of the general population regarding the prompt recognition, appropriate care-seeking behavior and effective prevention of malaria through community-level and mass media support.

This National Malaria Treatment Guidelines has been revised and updated to ensure that health care workers are provided with clear evidence-based recommendations on the diagnosis and treatment of malaria adapted to the specific malaria epidemiology and drug profile in Afghanistan.

2. Diagnosis of Malaria

2.1 Clinical Diagnosis

The clinical course of malaria may present as uncomplicated non severe disease or as severe life threatening disease.

2.1.1 Uncomplicated malaria

This is usually characterized by fever in the presence of peripheral parasitaemia. Other features may include chills, profuse sweating, muscle pains, joint pains, abdominal pain, diarrhea, nausea, vomiting, irritability and refusal to feed. These features may occur singly or in combination.

2.1.2 Severe malaria

This is a life threatening manifestation of malaria, and is defined as the detection of *P. falciparum* in the peripheral blood in the presence of any of the life threatening clinical or laboratory features (singly or in combination) listed below or any life threatening condition requiring hospital admission\(^2\).

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1 National Malaria Strategic Plan 2013 - 2017, MOH Afghanistan

Clinical features
- Impaired consciousness or unrousable coma (Glasgow Coma Scale <10) Prostration i.e. generalized weakness so that the patient is unable walk or sit up without assistance. Child is unable to feed.
- Multiple convulsions – more than two episodes in 24 hours
- Deep breathing, respiratory distress (acidotic breathing)
- Circulatory collapse or shock, systolic blood pressure <70mmHg in adults and <50mmHg in children
- Jaundice with evidence of other vital organ dysfunction
- Haemoglobinuria/ (coca cola-like urine)
- Abnormal spontaneous bleeding (Disseminated Intravascular Coagulopathy)
- Pulmonary oedema (radiological)

Laboratory findings
- Hypoglycaemia, (blood glucose <2.2mmol/L or <40mg/dl)
- Metabolic acidosis, (plasma bicarbonate <15mmol/L)
- Severe normocytic anaemia (Hb < 5g/dl, packed cell volume < 15%)
- Haemoglobinini
- Hyperparasitaemia (parasitaemia of >200,000/µl - in high transmission areas, or 100,000/µl in low transmission areas)
- Hyperlactataemia, lactate >5mmol/L
- Renal impairment, serum creatinine >265mol/L

2.2 PARASITOLOGICAL DIAGNOSIS OF MALARIA
The commonly used confirmatory tests to detect the presence of malaria parasites in blood are microscopy or rapid diagnostic tests (RDTs). Quality assurance of microscopy and RDTs is vital to ensure high sensitivity and specificity of results.

2.2.1 MICROSCOPY
Microscopy is the “gold standard” method for parasitological diagnosis of malaria. This is done by examining a stained thick and/or thin blood film for the presence of malaria parasites.
Thick films are recommended for parasite detection and quantification and can be used to monitor response to treatment.
Thin films are recommended for species identification and can also be used for parasite quantification.

2.2.2 RAPID DIAGNOSTIC TESTS
RDTs are immunochromatographic tests based on detection of specific parasite antigens, either *Plasmodium* lactate dehydrogenase (pLDH) activity or the presence of Histamine-Rich Protein (HRP).
Most RDT tests available are specific for P. falciparum; however, there are a few tests with the ability to differentiate between P. falciparum and non-P. falciparum malaria (vivax, malaria and oval). 

RDTs are simple to use but are not sensitive in detecting low parasitaemia. Use of RDTs is not recommended for follow-up assessment after an initial antimalarial treatment, as most tests, especially HRP based tests, remain positive for up to two weeks following effective antimalarial treatment and clearance of parasites. RDTs also cannot be used for parasite quantification.

3. CASE DEFINITIONS

3.1 Probable uncomplicated malaria

A patient with fever (auxiliary temperature \( \geq 37.5^\circ C \)) or history of fever within the last 24 hours in whom there is no other obvious cause of the fever, or using the IMCI criteria in children:
- The absence of,
  - Cough with fast breathing, which is:
    - Breathing 50 or more times per minute for infants aged 2 months to 1 year;
    - Breathing 40 or more times per minute for children aged 1 to 5 years
  - Rash
  - Runny nose
  - Tonsillitis (sore throat plus tonsillar exudates and tender cervical lymphadenopathy)
  - Abscess or other localized infection
  - Ear discharge
  - General danger signs:
    - Inability to drink or breast feed
    - Inability to sit or stand unaided
    - Witnessed convulsions
    - Coma
    - Neck stiffness
    - Bloody diarrhea

3.2 Confirmed uncomplicated falciparum malaria

A patient with fever (auxiliary temperature \( \geq 37.5^\circ C \)) or history of fever within the last 24 hours, with parasitological confirmation of \( P \) falciparum infection (whether or not other species are present), either by microscopy or rapid diagnostic test, and no symptoms or signs of severe malaria.

3.3 Confirmed uncomplicated vivax malaria

A patient with fever (auxiliary temperature \( \geq 37.5^\circ C \)) or history of fever within the present illness with parasitological confirmation of \( P \) vivax, either by microscopy or rapid diagnostic test, and no symptoms or signs of severe malaria.
3.4 Confirmed uncomplicated mixed infection
A patient with fever (auxiliary temperature $\geq 37.5^\circ$C) or history of fever within the present illness with parasitological confirmation of $P$. falciparum and $P$. vivax, either by microscopy or rapid diagnostic test, and no symptoms or signs of severe malaria.

3.5 Probable severe malaria
A patient with probable clinical malaria (fever or history of fever, with no other obvious cause of the fever) presenting with one or more of the features of severe malaria or requiring hospitalization in whom there is no parasitological confirmation.

3.6 Confirmed severe malaria
A patient with parasitological confirmation of falciparum either by microscopy or RDT (whether or not other species are present) presenting with one or more of the features of severe malaria and no other obvious cause of the symptoms.
4. Treatment of Malaria

4.1 UNCOMPROMISED MALARIA

4.1.1 First line drug treatment

4.1.1.1 Probable uncomplicated malaria

**Chloroquine (oral) 10mg base/kg days 1 and 2, 5 mg base/kg day 3**

All cases of probable uncomplicated malaria should be treated as possible vivax malaria and referred to a centre where parasitological confirmation with either microscopy or RDT can be obtained.

Pregnant women should be treated with CQ and referred for parasitological diagnosis. Promptly if malaria is probable.

Give first dose under supervision and observe for half an hour. Repeat if patient vomits within half an hour. Patients with repeated vomiting require admission.

Check for dehydration and treat if necessary.

In children, if auxiliary temperature ≥ 38.5°C, treat fever with paracetamol (10mg/kg orally, maximum 4 times per day) and tepid sponging.

Give second and third dose of CQ for continued treatment at home. Explain how to give the treatment at home.

To prevent dehydration; explain to caregivers that it is important for infants to breastfeed frequently, and older children to drink plenty of fluids.

Explain to caregivers that if someone is abnormally sleepy or difficult to wake, or has convulsions, or has difficult breathing these are danger signs of severe illness. Seek treatment immediately.

Ask the patient to return after 2 days if there is no improvement.

SP monotherapy or in combination with CQ should not be used in the treatment of probable uncomplicated malaria. All cases of probable falciparum malaria should have confirmatory diagnosis and where falciparum is confirmed, the appropriate ACT given.

Children under 2 months of age should be referred for confirmatory diagnosis and treated with the second-line medicine.

4.1.1.2 Confirmed uncomplicated falciparum malaria:

**Sulphadoxine-pyrimethamine (oral) single dose 25 mg/kg sulphadoxine component plus artesunate (oral) 4mg/kg/day for 3 days.**

Do not use SP if history of allergy to sulpha drugs or if patient has received a dose of SP in previous 4 weeks: give the second-line medicine.

Do not use SP in patients under 2 months of age: give the second-line drug.

AS plus SP can be used in second and third trimesters of pregnancy. Pregnant women with malaria can become very sick very quickly and should be treated promptly if malaria is diagnosed.

Give first dose under supervision and observe for half an hour. Repeat if vomits within half an hour. Patients with repeated vomiting require admission.

Check for dehydration and treat if necessary.

In children, if auxiliary temperature ≥ 38.5°C, treat fever with paracetamol (10mg/kg orally, maximum 4 times per day) and tepid sponging.

Give second and third dose of artesunate for continued treatment at home. Explain how to give the treatment at home.
Explain to caregivers that it is important for infants to breastfeed frequently, and older children to drink plenty of fluids, to prevent dehydration. Explain to caregivers that if someone is abnormally sleepy or difficult to wake, or has convulsions, or has difficult breathing these are danger signs of severe illness. Seek treatment immediately. Ask the patient to return after 2 days if there is no improvement.

4.1.1.3 gametocytocid therapy in confirmed uncomplicated falciparum malaria
- A single 0.25 mg base/kg primaquine dose should be given to all patients with parasitologically-confirmed P. falciparum malaria on the first day of treatment in addition to an ACT, except for pregnant women and infants <1 year of age.

Primaquine potentially has a major role in reducing malaria transmission, especially in efforts to eliminate Plasmodium falciparum malaria. The population benefits of reducing malaria transmission by gametocytocidal drugs require that a very high proportion of patients receive these medicines.

WHO has conducted a review of the evidence on the safety and effectiveness of primaquine as gametocytocide of P. falciparum, which indicates that a single 0.25mg base/kg is effective in blocking transmission and is unlikely to cause serious toxicity in subjects with any of the G6PD variants. Based on this review, the Malaria Policy Advisory Committee (MPAC) recommends the following:

In elimination areas which have not yet adopted primaquine as a gametocytocide for P. falciparum malaria a single 0.25 mg base/kg primaquine dose should be given to all patients with parasitologically-confirmed P. falciparum malaria on the first day of treatment in addition to an ACT, except for pregnant women and infants <1 year of age.

4.1.1.4 Confirmed uncomplicated vivax malaria:
Chloroquine (oral) 10mg base/kg days 1 and 2, 5mg base/kg day 3
CQ can be used in pregnancy.
Give first dose under supervision and observe for half an hour. Repeat if vomits within half an hour. Patients with repeated vomiting require admission.
Check for dehydration and treat if necessary.
In children, if auxiliary temperature ≥38.5°C, tepid sponge and treat fever with paracetamol (10mg/kg maximum 4 times per day).
Give second and third dose of CQ for treatment at home. Explain how to give the treatment.
Explain to caregivers that it is important for infants to breastfeed frequently, and older children to drink plenty of fluids, to prevent dehydration.
Explain to caregivers that if someone is abnormally sleepy or difficult to wake, or has convulsions, or has difficult breathing these are danger signs of severe illness. Seek treatment immediately.
Ask the patient to return after 2 days if there is no improvement.

For LDH antigen detection test (e.g. Optimal®) positive for non-Plasmodium falciparum or a combo test positive for non-falciparum malaria: Treat as for confirmed vivax malaria.
For mixed P falciparum and P vivax infections (confirmed either by microscopy or a combo RDT test): Treat as for confirmed falciparum malaria. Add primaquine (anti relapse treatment) for treatment of liver stages of vivax
4.1.1.5 Anti-relapse treatment for confirmed vivax malaria:
- Primaquine 0.25 mg base/kg, taken with food once daily for 14 days.
- In mild/moderate G6PD deficiency, primaquine 0.75 mg base/kg should be given once a week for 8 weeks.
- In severe G6PD deficiency, primaquine should not be given.

To achieve radical cure, relapses must be prevented using primaquine.
Primaquine should be given only to patients with parasitologically confirmed vivax malaria.

Determine the G6PD status before administration of primaquine.
Where it is not possible or feasible to determine the G6PD status, primaquine should be given at a dose of 0.75mg base/kg once a week for 8 weeks under medical supervision to detect and manage possible cases of haemolysis. At this dose and schedule, severe haemolysis in patient with mild to moderate G6PD deficiency is rare.
In all cases of probable haemolysis, primaquine should be discontinued immediately and the patient referred for further evaluation.
Primaquine is contraindicated in all persons with known severe G6PD deficiency.
Primaquine should not be used in pregnant women, in lactating mothers and in infants.
Primaquine causes abdominal discomfort when taken on an empty stomach; it should always be taken with food.

4.1.1.6 Confirmed uncomplicated mixed infection

Mixed malaria infections (Pf + Pv) are common. Mixed infections can identify by routine microscopy or RDTs. ACTs are effective against all malaria species and they are treatment of choice. In this guideline mixed infection treatment is same as treatment of Confirmed uncomplicated falciparum malaria.


**Treatment Failure**

The use of an alternative ACT as second line treatment other than the first line treatment (AS+SP) should be considered in patients returning with no improvement 2 days after commencement of treatment, or persistent or recurrent symptoms 3 to 28 days after commencement of 1\textsuperscript{st} line treatment, ensure that:

Adequate dose and course of 1\textsuperscript{st} line treatment was given according to the National Guidelines.

Other causes of febrile illness should be excluded.

Parasitological confirmation of malaria whenever possible (whether or not this was confirmed before the initial treatment).

Patients initially treated for falciparum malaria that return with confirmed vivax infections should be treated with CQ as for first line treatment.

Similarly, patients initially treated for vivax malaria that return with confirmed falciparum infections should be treated with SP plus artesunate as for first line treatment. These are not treatment failures and the 2\textsuperscript{nd} line treatment should not be given to these group of patients.

**4.2 SEVERE MALARIA**

Severe malaria is a medical emergency, with a very high fatality if not managed urgently and appropriately. The management involves the use of specific antimalarial medicines and secondly the adjuvant management of the features of severity or accompanying complications\textsuperscript{3}.

\textsuperscript{3} WHO 2006: Guidelines for the Treatment of Malaria, Geneva Switzerland, WHO/HTM/MAL/2006.1108
4.2.1 Antimalarial drug treatment of severe malaria

Antimalarial drug treatment of severe malaria (probable or confirmed)

4.2.1.1 Basic Health Center

Artemether IM

3.2 mg IM day 1 and refer. If referral not possible then 1.6 mg/kg IM once a day from day 2 to complete a total of 6 days. However, once the patient can swallow then give full treatment course of 3 days oral artesunate 4mg/kg daily plus single dose oral SP.

Or Artesunate IM / IV

Or artesunate 2.4mg/kg by intramuscular or diluted intravenously in the admission (0 hour) and refer if referral not possible then, second dose will be giving after 12 hour of first dose and third dose will be giving after 24 hours after first dose, it will continue one dose a day for 7 day.

However, once the patient can swallow then give full treatment course of 3 days oral artesunate 4mg/kg daily plus single dose oral SP.

All pregnant women with severe malaria should be referred to hospital

4.2.1.2 District Hospital, Provincial Hospital

Quinine IV

20mg salt/kg infusion loading dose over 4 hours, then 8 hours after start of loading dose10mg/kg every 8 hours. Omit loading dose if patient has had >40mg/kg quinine over the past 48 hours.

Decrease to 10mg salt/kg every 12 hours if patient still requires intravenous quinine after 48 hours.

Once patient can tolerate oral medication, give a full treatment course of 3 days oral artesunate (4mg/kg daily) plus SP single dose (25mg/kg sulphap component) or continue quinine orally (10mg/kg three times a day) plus doxycycline (3.5mg/kg daily) or clindamycin (10mg/kg twice a day). All medicines should be given for 7 days.

Or Artesunate IV / IM

Evidence has been shown Intravenous arthesunate associated with a lower risk of hypoglycemia. Artesunate is dispensed as a powder of artesunic acid (60mg vials) and before use immediately should activate with sodium Bicarbonate ampoule 5% (1 ml) to form sodium artesunate. Then the solution diluted in approximately with Saline solution or dextrose 5% (Water for injection is not an appropriate diluting) such as 5ml for IV and 2 ml for IM.

Artesunate 60mg solution concentration will come to be 10 mg/ml for IV and 20 mg/ml for IM administrations. Reconstitution and diluting of artesunate powder in Annex 1

Recommended dosage of artesunate is 2.4 mg/ kg by intramuscular or diluted intravenously in the admission (0 hour), second dose will be giving after 12 hour of first dose and third dose will be giving after 24 hours after first dose, Once can tolerate oral medication give a complete treatment course of AS+SP orally or it will continue one dose a day for 7 days. Formula is for calculate dosage by IM and IV in Annex 1
4.2.2 Adjunctive treatment for severe malaria

In an attempt to reduce the unacceptably high mortality of severe malaria, various adjunctive treatments for the complications of malaria have been evaluated in clinical trials. These are summarized in the Table below.

Immediate clinical management of severe manifestations and complications of falciparum malaria

<table>
<thead>
<tr>
<th>Manifestation/complication</th>
<th>Immediate management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coma (cerebral malaria)</td>
<td>Maintain airway, place patient on his or her side, exclude other treatable causes of coma (e.g. hypoglycemia, bacterial meningitis); avoid harmful ancillary treatment such as corticosteroids, heparin and adrenaline; intubate if necessary</td>
</tr>
<tr>
<td>Hyperpyrexia</td>
<td>Administer tepid sponging, fanning, cooling blanket and antipyretic drugs.</td>
</tr>
<tr>
<td>Convulsions</td>
<td>Maintain airways; treat promptly with intravenous or rectal diazepam or intramuscular paraldehyde.</td>
</tr>
<tr>
<td>Hypoglycemia (blood glucose concentration of &lt;2.2 mmol/l; &lt;40 mg/100ml)</td>
<td>Check blood glucose, correct hypoglycemia and maintain with glucose-containing infusion.</td>
</tr>
<tr>
<td>Severe anemia (hemoglobin &lt;5 g/100ml or packed cell volume &lt;15%)</td>
<td>Transfuse with screened fresh whole blood</td>
</tr>
<tr>
<td>Acute pulmonary edema</td>
<td>Prop patient up at an angle of 45°, give oxygen, give a diuretic, stop intravenous fluids, intubate and add positive end-expiratory pressure/continuous positive airway pressure if life-threatening hypoxemia.</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>Exclude pre-renal causes, check fluid balance and urinary sodium; if in established renal failure add haemofiltration or haemodialysis, or if unavailable, peritoneal dialysis. The benefits of diuretics/dopamine in acute renal failure are not proven.</td>
</tr>
<tr>
<td>Spontaneous bleeding and coagulopathy</td>
<td>Transfuse with screened fresh whole blood (cryoprecipitate, fresh frozen plasma and platelets if available); give vitamin K injection.</td>
</tr>
<tr>
<td>Metabolic acidosis</td>
<td>Exclude or treat hypoglycemia, hypovolaemia and septicaemia. If severe add haemofiltration or haemodialysis.</td>
</tr>
<tr>
<td>Shock</td>
<td>Suspect septicemia, take blood for cultures; give parenteral antimicrobials, correct haemodynamic disturbances.</td>
</tr>
</tbody>
</table>
4.3 Malaria in pregnancy

4.3.1 Treatment of probable uncomplicated malaria:
All pregnant women with probable uncomplicated malaria should be treated with CQ and referred for a parasitological diagnosis (Section 4.1.1.1).

4.3.2 Treatment of confirmed uncomplicated falciparum malaria
First trimester: quinine (oral) 10 mg salt /kg (maximum 600mg) three times a day plus clindamycin 10mg/kg 2 times a day. All medicines should be given for seven days.

Second and third trimester: SP plus AS as above (Section 4.1.1.2)

4.3.3 Treatment of confirmed uncomplicated vivax malaria
All trimesters: CQ as above (Section 4.1.1.3). Primaquine is contraindicated and should not be given during pregnancy or to breastfeeding mothers

4.3.4 Treatment of probable or confirmed severe malaria
First trimester: Parenteral quinine as above (Section 4.2.1). Do not withhold other antimalarials if they are the only ones available, as the risk of death and other complications associated with severe malaria is very high.

Second and third trimester: Quinine or artemether / artesunate as above (Section 4.2.1). Parenteral artesunate is preferred over quinine in the second and third trimester.

4.3.5 Chemoprophylaxis is not recommended pending further studies; emphasis should be on the promotion of use of ITNs and prompt treatment seeking in pregnancy

5. Malaria treatment during outbreaks
parasitological diagnosis either by the rapid diagnostic tests or microscopy is crucial to confirm the cause of an epidemic of febrile illness is due to malaria, monitor the epidemic curve and confirm the end of an epidemic, and follow progress of patients with severe malaria and probable treatment failures.

Once a malaria epidemic is confirmed, all fever cases should be treated, severe malaria cases in the periphery should be treated with intramuscular artemether or artesunate as an emergency pre-referral care (Section 4.2.1.1)
ANNEX 1

Treatment Charts

1.1 Probable uncomplicated malaria
Fever (auxiliary temperature ≥ 37.5ºC) or history of fever in last 24 hours. Use the IMCI criteria / charts to exclude other causes of fever in children under five years of age. Exclude symptoms and signs of severe disease. Start treatment with Chloroquine as per the chart and refer for confirmatory diagnosis.

Chloroquine tablets (150mg base)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Weight (kg)</th>
<th>DAY 1 (No. of tablets)</th>
<th>DAY 2 (No. of tablets)</th>
<th>DAY 3 (No. of tablets)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>&lt;10</td>
<td>½</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>1-3</td>
<td>10-&lt;14</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>3-5</td>
<td>17-19</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>5-11</td>
<td>20-35</td>
<td>2</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>12+</td>
<td>36+</td>
<td>3</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

1.2 Confirmed falciparum malaria
Fever (auxiliary temperature ≥ 37.5ºC) or history of fever in last 24 hours. Use the IMCI criteria / charts to exclude other causes of fever in children under five years of age. Parasitological confirmation (microscopy or RDTs) of *p.falciparum* malaria (in the presence or absences of other species - mixed infection). Exclude symptoms and signs of severe disease. Treat with SP + AS as per the chart. Advice the patient on taking the medication at home and when to come back if necessary. Fill and send the notification form.

SP (500/25mg Tablet) plus AS (50mg Tablet)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Weight (kg)</th>
<th>DAY 1 (no. of tablets)</th>
<th>DAY 1 (no. of tablets)</th>
<th>DAY 2 (no. of tablets)</th>
<th>DAY 3 (no. of tablets)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>&lt;10</td>
<td>½</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>1-3</td>
<td>10-&lt;14</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>3-5</td>
<td>17-19</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>5-11</td>
<td>20-35</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>12+</td>
<td>36+</td>
<td>3</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>
1.3 Gametocytocide treatment in confirmed falciparum malaria:
A single 0.25 mg base/kg primaquine dose should be given to all patients with parasitologically-confirmed P. falciparum malaria on the first day of treatment in addition to an ACT, except for pregnant women and infants <1 year of age.

**Primaquine (7.5mg base tablet)**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Weight (kg)</th>
<th>SINGLE DOSE (no. of tablets)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-5</td>
<td>14-20</td>
<td>½</td>
</tr>
<tr>
<td>6-11</td>
<td>21-35</td>
<td>1</td>
</tr>
<tr>
<td>11-16</td>
<td>36-50</td>
<td>1 ½</td>
</tr>
<tr>
<td>16+</td>
<td>50+</td>
<td>2</td>
</tr>
</tbody>
</table>

1.4 Confirmed vivax malaria
Fever (auxiliary temperature \( \geq 37.5^\circ C \)) or history of fever in last 24 hours. Use the IMCI criteria / charts to exclude other causes of fever in children under five years of age, Parasitological confirmation (microscopy or RDTs) of *p. vivax* malaria (and the absence of *p.falciparum* parasites). Exclude symptoms and signs of severe disease
Treat with Chloroquine as per chart
Notify for radical cure with primaquine

**Chloroquine (150mg base tablet)**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Weight (kg)</th>
<th>DAY 1 (no. of tablets)</th>
<th>DAY 2 (no. of tablets)</th>
<th>DAY 3 (no. of tablets)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>&lt;10</td>
<td>½</td>
<td>½</td>
<td>½</td>
</tr>
<tr>
<td>1-&lt;3</td>
<td>10-&lt;14</td>
<td>1</td>
<td>1</td>
<td>½</td>
</tr>
<tr>
<td>3 –&lt; 5</td>
<td>14-19</td>
<td>1 ½</td>
<td>1 ½</td>
<td>½</td>
</tr>
<tr>
<td>5-11</td>
<td>20-35</td>
<td>2 ½</td>
<td>2 ½</td>
<td>1</td>
</tr>
<tr>
<td>11-12</td>
<td>36-50</td>
<td>3</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>14+</td>
<td>50+</td>
<td>4</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>
1.4.1 Anti-relapse treatment (radical cure) for confirmed vivax malaria
Parasitological confirmation (microscopy or RDTs) of *p. vivax* malaria (in the absence or presence of *p.falciparum* parasites - mixed infection)
Do not give primaquine to pregnant women, lactating mothers and infants (children less than 1 year of age). Determine G6PD status, if patient is normal treat as per chart
Advice patient on completing treatment and when to come back if necessary

**Primaquine (7.5mg base tablet)**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Weight (kg)</th>
<th>DAILY DOSE FOR 14DAYS (no. of tablets)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-5</td>
<td>14-20</td>
<td>½</td>
</tr>
<tr>
<td>6-11</td>
<td>21-35</td>
<td>1</td>
</tr>
<tr>
<td>11-16</td>
<td>36-50</td>
<td>1 ½</td>
</tr>
<tr>
<td>16+</td>
<td>50+</td>
<td>2</td>
</tr>
</tbody>
</table>

If patient is G6PD deficient (mild or moderate) OR where it is not feasible to determine the G6PD status, use the alternate treatment regimen as shown below in the chart
Monitor and advice patient on completing treatment and when to come back if necessary.

**Primaquine (7.5mg base tablet)**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Weight (kg)</th>
<th>WEEKLY DOSE FOR 8 WEEKS (no. of tablets)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-5</td>
<td>14-20</td>
<td>1</td>
</tr>
<tr>
<td>6-11</td>
<td>21-35</td>
<td>2</td>
</tr>
<tr>
<td>11-16</td>
<td>36-50</td>
<td>3</td>
</tr>
<tr>
<td>16+</td>
<td>50+</td>
<td>4</td>
</tr>
</tbody>
</table>

**Fever treatment**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Weight (kg)</th>
<th>Paracetamol 500mg tabs (max 4 times per day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3</td>
<td>4-&lt;14</td>
<td>½</td>
</tr>
<tr>
<td>3-&lt;5</td>
<td>14-19</td>
<td>½</td>
</tr>
<tr>
<td>5-11</td>
<td>20-35</td>
<td>1</td>
</tr>
<tr>
<td>12+</td>
<td>36+</td>
<td>2</td>
</tr>
</tbody>
</table>
Emergency pre-referral and maintenance treatment of severe malaria
(Artemether / Artesunate)

<table>
<thead>
<tr>
<th>Age</th>
<th>Weight (kg)</th>
<th>DAY 1</th>
<th>Subsequent days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Artemether (ml)</td>
<td>Artemether (ml)</td>
</tr>
<tr>
<td>2 – 4 months</td>
<td>4-&lt;6</td>
<td>0.2</td>
<td>0.1</td>
</tr>
<tr>
<td>4-&lt;12 months</td>
<td>6-&lt;10</td>
<td>0.4</td>
<td>0.2</td>
</tr>
<tr>
<td>1-2 years</td>
<td>10-&lt;12</td>
<td>0.5</td>
<td>0.2</td>
</tr>
<tr>
<td>2-&lt;3 years</td>
<td>12-&lt;14</td>
<td>0.6</td>
<td>0.3</td>
</tr>
<tr>
<td>3 --&lt; 5 years</td>
<td>14-19</td>
<td>0.8</td>
<td>0.4</td>
</tr>
<tr>
<td>5-11 years</td>
<td>20-35</td>
<td>1.4</td>
<td>0.7</td>
</tr>
<tr>
<td>12+ years</td>
<td>36+</td>
<td>2.0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Given by IM injection into the anterior thigh. If referral is not possible, then repeat HALF the dose after 24 hours and again after every 24 hours. Do not continue for longer than 7 days. Once the patient can tolerate oral drugs then give SP single dose plus artesunate as for uncomplicated falciparum malaria.

Recommended dosage of artesunate is 2.4 mg/ kg by intramuscular or diluted intravenously in the admission (0 hour), If referral is not possible second dose will be giving after 12 hour of first dose and third dose will be giving after 24 hours after first dose, Once can tolerate oral medication give a complete treatment course of AS+SP orally or it will continue one dose a day for 7 days. Below formula is for calculate dosage by IM and IV administration:

<table>
<thead>
<tr>
<th>Formula for IV administration</th>
<th>Formula for IM administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.4 mg x body weight (kg)</td>
<td>2.4 mg x body weight (kg)</td>
</tr>
<tr>
<td>IV Artesunate solution</td>
<td>IM Artesunate solution</td>
</tr>
<tr>
<td>concentration 10 mg/ml</td>
<td>concentration 20 mg/ml</td>
</tr>
</tbody>
</table>

Reconstitution and diluting of artesunate powder:

<table>
<thead>
<tr>
<th></th>
<th>IV</th>
<th>IM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bicarbonate solution volume</td>
<td>1 ml</td>
<td>1 ml</td>
</tr>
<tr>
<td>Saline solution volume</td>
<td>5 ml</td>
<td>2 ml</td>
</tr>
<tr>
<td>Total volume</td>
<td>6 ml</td>
<td>3 ml</td>
</tr>
<tr>
<td>Artesunate 60mg solution concentration</td>
<td>10 mg / ml</td>
<td>20 mg / ml</td>
</tr>
</tbody>
</table>
References:
1. World Health Organization (1968), Series of technical Reports No.366


