

Malaria in South Sudan 4: treatment of uncomplicated *P. Falciparum* malaria

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In the February 2011 issue of SSMJ we covered the pathophysiology, and clinical and laboratory diagnosis of malaria (1, 2, 3). In this article we deal with the treatment of uncomplicated malaria. Management of malaria among pregnant women and children, and treatment of severe malaria will be published in future issues of this journal.

Uncomplicated malaria is “symptomatic malaria without signs of severity or evidence (clinical or laboratory) of vital organ dysfunction”. Cure is defined as “the elimination from the body of the parasites that caused the illness. This prevents progression to severe disease, and additional morbidity associated with treatment failure (4)”.

The primary aim of treatment is to cure the infection as rapidly as possible so it does not deteriorate into severe malaria. The public health (or secondary) aim is to reduce transmission to others and prevent the emergence and spread of resistance to anti-malarial medicines.

Anti-malarial drugs

Anti-malarial drugs can be classified by their action on different stages of the malaria parasite:

1. Tissue schizonticide (primaquine)
2. Blood schizonticide (chloroquine, sulphadoxine-pyrimethamine, quinine, mefloquine and artemisinins)
3. Gametocytocide (artemisinins and primaquine).

Anti-malarial combination treatments

Anti-malarial combination treatments are the simultaneous use of two or more blood schizonticidal drugs with independent modes of action and unrelated biochemical targets in the parasites (i.e. the partner drugs in a combination must be independently effective). They are recommended by World Health Organization (WHO) because they have the potential to:

- delay the development of resistance to the individual anti-malarials in the combination
- improve treatment outcomes

- overcome the threat of resistance of plasmodium falciparum to monotherapies.

Artemisinin derivatives should be one of the drugs in a combination.

Artemisinin based combination therapies (ACTs)

ACT is a combination therapy where one of the components is artemisinin or its derivative (artesunate, artemotil, artemether, dihydroartemisinin). Artemisinin derivatives are rapidly acting schizonticidal drugs capable of reducing parasite biomass by a factor of 104 each asexual life cycle. Another advantage of artemisinin derivatives is their ability to kill gametocytes, hence interrupting malaria transmission.

To eliminate at least 90% of the parasitaemia, a 3-day course of the artemisinin is needed to cover up to three post-treatment asexual cycles of the parasite. This leaves a much smaller number of parasites (10%) for the partner drug to kill while its concentration in plasma remains high.

ACTs recommended by WHO are:

- Artesunate + amodiaquine
- Artemether + lumefantrine
- Artesunate + mefloquine
- Artesunate + sulfadoxine-pyrimethamine
- Dihydroartemisinin + piperaquine

For the treatment of uncomplicated malaria in South Sudan:

- The recommended first line medicine is Artesunate/Amodiaquine.
- The recommended second line medicine is Artemether/Lumefantrine (Coartem®)

ACTs are available as:

- Two medicines contained in one tablet i.e. they are fixed-dose artemisinin based combination treatments.
- Separate medicines packaged together (co-packaged or co-blistered). However, the public ACT supply has shifted from co-blistered to co-formulated or Fixed Dose Combination of ASAQ.

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Table 1. Artesunate Amodiaquine Fixed Dose Combination (Winthrop®)

Age	Infant 2 months – 11 months	Toddler 1 – 5 yrs	Child 6yrs – 13 yrs	Adolescent/Adult ≥14 yrs
Weight	>4.5 – <9 kg	>9 – <18 kg	>18– <36 kg	Over 36 kg
Tablet	25mgAS/67.5mgAQ	50mgAS/135mgAQ	100mgAS/270mgAQ	100mgAS/270mgAQ
Day 1	1 tablet	1 tablet	1 tablet	2 tablet
Day 2	1 tablet	1 tablet	1 tablet	2 tablet
Day 3	1 tablet	1 tablet	1 tablet	2 tablet

the dose should be repeated and the patient should receive a replacement dose from the health worker.

The presence of malaria parasites should be confirmed in all suspected cases. If there is no means of confirmation (RDT or microscopy) or if

the tests are negative, but the clinician (after history and physical exam and other investigations) is still convinced that malaria is the cause of illness, the patient should be given a full course of treatment with follow up 24-48 hours later.

Treatment regimes

The WHO recommended treatment for treating uncomplicated *P. falciparum* malaria in non-pregnant adults is to give an artemisinin based combination therapy (ACT) for at least 3 days. The regimes for the anti-malarials recommended in South Sudan are (5, 6):

First line: Artesunate + amodiaquine

The total recommended treatment is 4 mg/kg body weight of Artesunate (AS) and 10 mg base/kg body weight of Amodiaquine (AQ) given once a day for 3 days. (Table 1)

The tablets for each age group have different strengths, so they cannot be interchanged, combined or broken down as this can lead to overdosing or under dosing a patient.

Patients must finish all 3 days of treatment. Always give the first dose of the treatment in the clinic and observe the patient swallowing the medicine.

Second line: Artemether+lumefantrine

Patients must finish all 3 days of treatment. (Table 2) Always give the first dose of the treatment in the clinic and observe the patient swallowing the medicine. Explain that this ACT should be taken with food or fluids (fatty meals or milk) to improve its absorption, particularly on the second and third days of treatment. If vomiting occurs within half an hour of swallowing the medicine,

Treatment failures

Causes

Recurrence of *P. falciparum* malaria can result from re-infection or treatment failure - although it may be difficult to know the cause. Treat it as treatment failure if fever and parasitaemia have not resolved or recur within two weeks of treatment. Treatment failures may result from:

- drug resistance
- poor adherence or inadequate drug exposure (e.g. due to under-dosing, vomiting) or
- substandard medicines.

Find out if the patient vomited the previous treatment or did not complete a full course of treatment. If possible, confirm treatment failure by examining a blood slide.

In many cases, failures are missed because patients who present with malaria are not asked whether they have received anti-malarial treatment within the preceding 1–2 weeks. This should be a routine question in patients who present with malaria.

Table 2. Dosage of Coartem® tablets (Artemether 20mg & Lumefantrine 120mg)

Weight kg	Age	Day 1	Day 2	Day 3	Colour code of package
5 - 14 kg	From 4 months to 3 years	1 tablet 12 hourly	1 tablet 12 hourly	1 tablet 12 hourly	Yellow
15 - 24 kg	From 3 years to 7 years	2 tablets 12 hourly	2 tablets 12 hourly	2 tablets 12 hourly	Blue
25 - 34 kg	From 7 years to 12 years	3 tablets 12 hourly	3 tablets 12 hourly	3 tablets 12 hourly	Brown
>35	From 12 years and above	4 tablets 12 hourly	4 tablets 12 hourly	4 tablets 12 hourly	Green

MAIN ARTICLES

PREGNANT WOMEN AND YOUNG INFANTS

Pregnant women should not take Artesunate/Amodiaquine or Artemether/Lumefantrine in the first trimester. Artemether/Lumefantrine is contraindicated for children below 5kg body weight. Such patients should be treated with oral Quinine (at a dose of 10mg/kg). In very young infants it is important to exclude other causes of fever.

Management

- Treatment failure within 14 days of receiving an ACT is unusual, but if it occurs treat with a 2nd-line antimalarial (i.e. Artemether /Lumefantrine).
- Treatment failure after 14 days of initial treatment should be considered as a new infection and treated with the first-line ACT (i.e. Artesunate/Amodiaquine).

Other aspects of management

Incorrect approaches to treatment

Do not:

- use artemisinins as monotherapy as this promotes resistance.

Patients who cannot take oral medicine

Some patients need parenteral or rectal administration for 1–2 days until they can swallow and retain oral medication reliably. Although such patients may never show other signs of severity, they should receive the same initial anti-malarial dose regimens as for severe malaria followed by a full 3-day course of ACT.

Antipyretics

Fever is a key sign of malaria and is associated with tiredness, weakness, headache, anorexia and often nausea. Treat with antipyretics and, if necessary, fanning and tepid sponging. Antipyretics should be used if core temperatures $\geq 38.5^{\circ}\text{C}$.

Paracetamol (acetaminophen) 15 mg/kg every 4 hours given orally or as a suppository is safe and usually well tolerated. Do not give acetylsalicylic acid (aspirin) to children because of the risks of Reye's syndrome.

Antiemetics

Vomiting is common in acute malaria and may be severe. It is not known if antiemetics are effective but there is no evidence that they are harmful, though they can mask severe malaria. Patients that vomit everything, including anti-malarials, should be managed as severe malaria.

Health education

Public education should be given at health facilities and schools, and by pharmacists and anyone prescribing and dispensing anti-malarials. This can:

- improve the understanding of malaria
- improved adherence to full treatment
- minimize the use of inappropriate anti-malarials.
- promote the use of malaria prevention tools especially insecticide-treated bed nets (ITNs).

HIV infection

Worsening HIV-related immunosuppression may lead to more severe manifestations of malaria. In stable endemic areas, HIV-infected patients with partial immunity to malaria may suffer more frequent and higher density infections. It is recommended that:

- patients with HIV infection who develop malaria should receive prompt, effective anti-malarial treatment regimens as recommended in the relevant sections of the WHO guidelines (1).
- intermittent preventive treatment with sulfadoxine-pyrimethamine should not be given to HIV-infected patients receiving cotrimoxazole (trimethoprim plus sulfamethoxazole) prophylaxis.
- treatment in HIV-infected patients on zidovudine or efavirenz should, if possible, avoid amodiaquine-containing ACT regimens.
- the use of malaria prevention tools like insecticide-treated bed nets should also be promoted in HIV-infected individuals.

References

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Note: This article is based on the powerpoint presentation 'Drug treatment of malaria' by Jane Achan