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National Protocol For Malaria Treatment During Pregnancy

Dr. Abdul Rahman Abdul Hafeez

Each year more than 1.2 million women become pregnant in the Sudan, of those 750,000 are in areas with high malaria transmission: intense perennial, high seasonal transmission or in areas of irrigation.

Malaria in Africa is estimated to cause 15% of maternal anaemia; about 10,000 maternal deaths / year and 35% of preventable low birth weight. Best practices of malaria control during pregnancy include effective case management of malaria for all women in the reproductive age in malarious areas and using of insecticide treated nets (ITNs) and adopting of intermittent preventive treatment (IPT) with SP. The programme and the partners are targeting 60% coverage with these interventions as Abuja Declaration call for by the end of 2005.

4.1 Malaria in pregnancy:

Malaria in pregnancy (**MIP**) is a peculiar disease in many ways:

- The mortality and morbidity of MIP is higher than in non-pregnant women. The risk is even more increased in primigravidae.
- There is evidence of maternal immuno-suppression in the second half of pregnancy which is caused by many factors: hormonal, placental and lymphocyte. The malaria infection itself has a marked immunosuppressive effect.
- Reduced immunity in pregnancy leads to more relapses of malaria and more parasitaemia and so worsens clinical manifestations.
- MIP is the risk to both mothers and baby /ies:
    - For mothers: in particular primigravidae and HIV positive women are at greater risk of malaria and therefore anaemia, svere malaria and death. ○ For infants: placental infection leads to low birth weight, a major risk for malaria and therefore in infant illness and deaths.
- *P. falciparum* is the commonest and can lead to acute renal failure or cerebral malaria with convulsions and coma.
- Transplacental infection to the foetus can occur.
- The risks of MIP are severe so prompt chemotherapy for malaria is mandatory.

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4.1.1 Clinical features of MIP:

Atypical manifestations of malaria are common in pregnancy, particularly in the second half of pregnancy. The woman can present with **fever** with more paroxysms in the second half of pregnancy due to immuno-suppression. **Anaemia** is a common presentation and it could be due to: haemolysis of parasitized RBCs; increased demands of pregnancy; or profound haemolysis that may aggravate folate deficiency. Anaemia is more common and severe between 16 -29 weeks, and pre-existing iron and folate deficiency can exacerbate it and vice versa. Anaemia increase the risk of perinatal mortality and maternal morbidity and mortality, the risk of pulmonary oedema, and the risk of postpartum haemorrhage is also higher.

Splenomegaly may be present but variable in size; and pre-existing large spleen may regress in size in pregnancy.

Acute pulmonary oedema is a more common and serious complication of MIP compared to non-pregnant population. It is more common in the second and third trimesters. However, it can occur immediately postpartum due to: the auto-transfusion of placental blood with high proportion of parasitized RBCs and the sudden increase in the peripheral vascular resistance after delivery.

Hypoglycaemia is another complication of severe malaria and is due to:

- increased demand of hypercatabolic state and infecting parasite,
- hypoglycaemic response to starvation, and
- increased response of pancreatic islets to secretary stimuli.

Hypoglycaemia presents with symptoms similar to those of malaria. Abnormal behaviour, convulsions and sudden loss of consciousness are also symptos of cerebral malaria.

Secondary infections such as urinary tract infection, pneumonias …ect are more common due to immuno-suppression.

4.1.3 Complications and effects of MIP:

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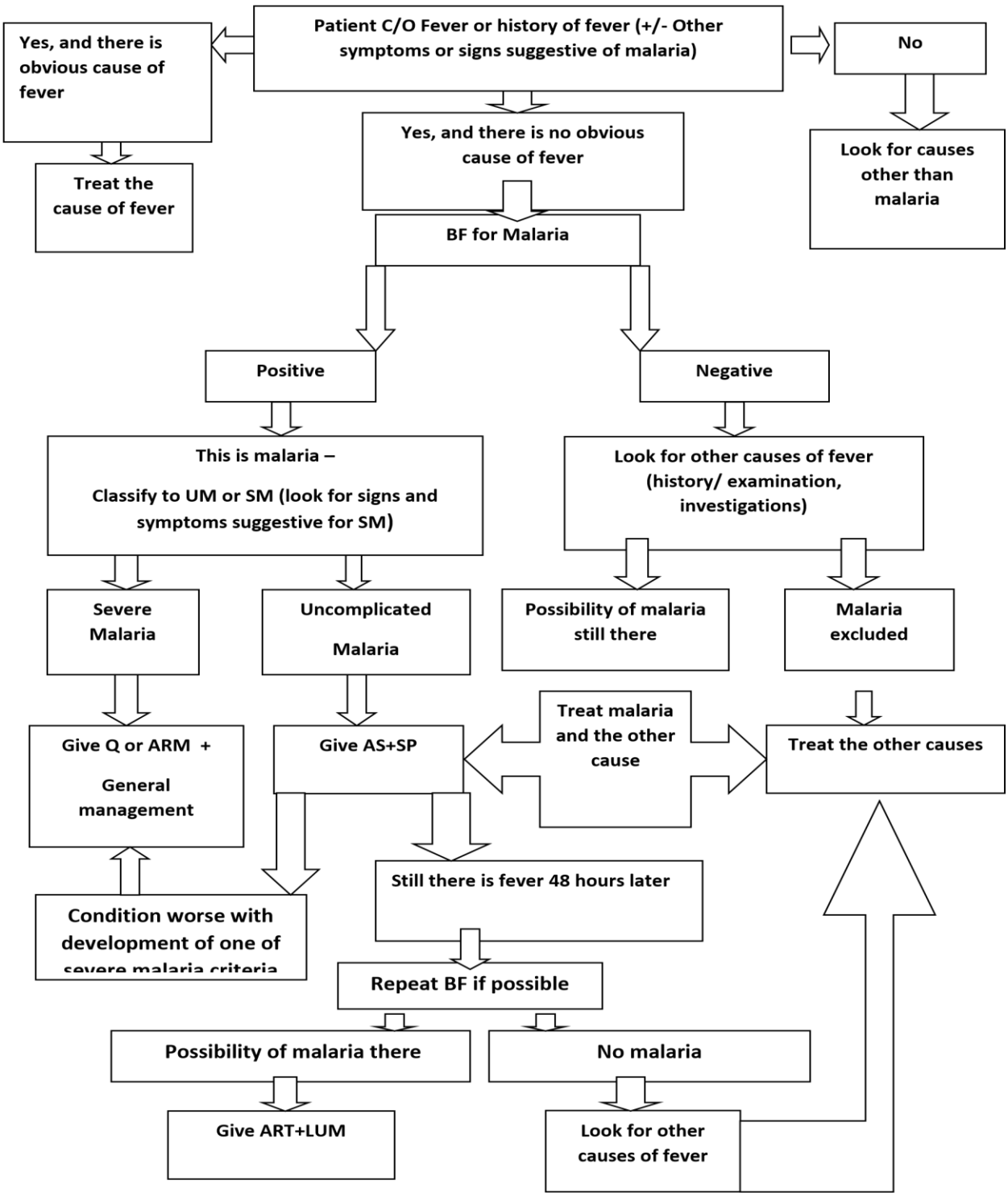
General plan for malaria diagnosis and treatment



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- During pregnancy:
  - Frequency and severity are greater than in non-pregnant
  - Severe anaemia is common
  - Hyperpyrexia leading to abortion, preterm labour, intra-uterine foetal death and macerated still birth. ○
  Hypoglycaemia
  - Transplacental infection leading to congental malaria and neonatal death. ○ Spontaneous abortion, premature birth, still birth, placental insufficiency and IUGR, low birth weight and faetal distress.
- **During labour:**
  - Precipitate labour ○
  Postpartum haemorrhage ▪
  Puerperium:
  - Puerperal pyrexia ○
  Difficulty in lacatation.
- **Risks to the foetus:** high grade fever, placental insufficiency, hypoglycaemia, anaemia and other complications can adversely affect the foetus. Spontaneous abortions, premature birth, still birth, placental insufficiency and IUGR, low birth weight, and faetal distress are problems observed during faetal growth. Transplacental spread to the foetus can result in **congenital malaria**, which is very rare. The placental barrier and maternal IgG antibodies, which cross the placenta, may protect the foetus to some extent. Congental malaria is more common in the non-immune population and the incidence goes up during the epidemic of malaria. Faetal chloroquine and quinine levels are about one third of simultaneous maternal levels and this subtherapeutics drug level does not cure the infection in the fetus. All four species can cause congental malaria but it is proportionately common with P. malariae. The new born can present with fever, irritability, feeding problems, hepatosplenomegally, anaemia, and jaundice. The diagnosis can be confirmed by smear for malaria parasite from cord blood or heel prick. Febrile illness in the first week newborn is mostly bacterial, however think about malaria.

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Treatment of Uncomplicated Malaria Treatment of falciparum Malaria:

(The following guide lines are for non pregnant women. The guide lines for malaria in Pregnancy are described under 4.1.4 management of malaria in pregnancy. The information bellow is expected to add more details in the 4.14. management of malaria in pregnancy)

Falciparum malaria can present as uncomplicated (including drug resistant malaria) or severe (complicated) malaria. Treatment for uncomplicated (UM) as well as severe malaria (SM) in Sudan does not vary with regions i.e. the same recommended drugs applied all over the Sudan. The treatment of UM in Sudan has changed from mono-therapy to combination therapy.

Combination therapy (CT) is the simultaneous use of two or more blood schizonticidal drugs with independent modes of action and different biochemical targets in the parasite (AS+SP / Q+AS+SP / Artemether+lumefantrine). There are two form of CT currently: Nonartemisinin and artemisinin-based combination therapy (ACT). WHO recommends the use of ACT.

The advantages of ACT relate to the unique properties and mode of action of artemisinin component, which include the following:

- Rapid substantial reduction of the parasite biomass
- Rapid resolution of clinical symptoms
- Effective action against multidrug-resistant *P. falciparum*
- Reduction of gametocyte carriage, which may reduce transmission of resistant alleles
- No parasite resistance documented as yet with the use of artemisinin and its derivatives
- Few reported adverse clinical effects.

2.1 Treatment for uncomplicated falciparum malaria:

Treatment for uncomplicated malaria will be presented in two distinct sections:

- Recommended malaria treatment: This is the most safe and cost-effective malaria treatment.

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- Treatment not recommended: This includes the use of antimalarial drugs not included in the above section and adjuvant antibiotics for malaria treatment.

2.1.1 Recommended treatment for uncomplicated malaria:

As it is the safest and effective treatment, the national malaria control programme in Sudan strongly recommends the use of the following drugs as a 1st, 2nd and a 3rd line treatment with the dosage and regimens indicated.

First-line treatment:

The "first-line treatment" in Sudan has been changed from *chloroquine* alone to *Artesunate* plus *Sulfadoxine- Pyrimethamine*.

Artesunate (AS) is a water soluble hemisuccunate derivative of dihydroartemisinin. It is effective against *P. falciparum* which resistant to all other operationally used antimalarial drugs. It is a potent schizontocidal drug but it should be administered in combination with another effective schizonticidal drug to prevent recrudescence and delay the selection of resistant strain. AS also reduces the gametocyte carriage rate. The drug is available in Sudan in form of tablets with two concentrations: 50 mg for children and 100 mg for adult. Side effects of AS are not common, transient rise in transaminases and transient reduction in reticulocyte count has been reported.

Sulfadoxine- Pyrimethamine (SP) is a fixed dose combination of two antifolate compounds, which have schizonticidal activity against *P. falciparum* but less effective against other species. SP is available in Sudan in a form of tablets (500 mg Sulfadoxine +25 mg Pyrimethamine) and injection. Side effects of SP are mild and reversible such as gastro-intestinal disturbance, visual disturbance, cutaneous reaction (common), anorexia and insomnia.

The total recommended dose for this combination is: □
AS: 4 mg / kg body weight once a day for 3 days.

□ SP: 25 mg/ kg body weight Sulfadoxine +1.25 mg/ kg body weight Pyrimethamine as a single dose.

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The dose and regimen of this combination should be as follow:

- First dose: both AS + SP simultaneously.

(4 mg / kg AS) + (25 mg / kg Sulfadoxine + 1.25 mg / Kg Pyrimethamine).

- Second dose: only AS

4 mg / kg of body weight (after 24 hours from the first dose).

- Third dose: AS only

4 mg / kg of body weight (after 24 hours from the second dose)

For the dose per age group see the table (Table 1) on the cover of the booklet….

Presentation:

The combination of (AS+SP) is available in Sudan in form of tablets. For each age group (range of weight) a specified number of tablets were recommended, as an example for adult (6) tablets of artesunate 100 mg each and (3) tablets of sulfadoxine-pyrimethamine constitute the full dose (See Table 1).

Health care providers should give advice to the caretakers (e.g. mothers) as it is found to increase the compliance. It worth also to spend time on drawing the attention of caretakers about signs of cure as well as for treatment failure, which is an indicator for coming back to the health facility.

Treatment failure:

It is expected to see patients whose condition did not improve. In such cases, take proper history and re-examine the patient to know exactly the cause/s of treatment failure (check the adequacy of AS+SP dose and regimen, other causes of fever, type and quality of the drug if possible……). If still there is doubt about malaria, check the presence of asexual form of the parasite (trophozoite) in his peripheral blood film. Go for the 2nd line if still it is malaria.

4.1.4 Management of MIP:

This includes: treatment of malaria, management of complications and management of labour.

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4.1.5 Treatment of malaria:

- Admit the patient; assess the severity of the condition by general examination: pallor, jaundice, blood pressure, temperature, haemoglobin level and parasite count.
- SGPT, serum bilirubin, serum creatinine and blood sugar may also need to be assessed.
- Monitor the maternal and faetal vital parameters 3-4 hourly and monitor the intake / output daily.
- Choose the drug according to the severity of the disease / sensitivity pattern.
- Avoid over / under dosing of the drugs; avoid fluid overload or dehydration and maintain an adequate intake of calories.

4.1.5.1 Treatment of UM in pregnancy:

Treatment of MIP should only be initiated after confirmation of the diagnosis by the presence of fever and a positive blood film if it is available. It varies according to the gestational age:

In the first trimester:

Oral quinine is safe and is the first line of treatment all throughout pregnancy. The dose is 10 mg salt / Kg body weight, administered 8-hourly for 7 days.

In the second and third trimester:

Oral quinine in the specified dose is the first line of treatment. **Or**

Oral quinine for 3 days in the standard dose followed by sulfadoxine–pyrimethamine in the full treatment dose.

Or

A combination of artesunate tabs (AS) and SP **(AS + SP)**

4.1.5.2 Management of severe malaria during pregnancy:

- In the management of severe malaria in pregnancy especial concern must be paid to: Anaemia, hypoglycemia and pulmonary oedema.

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- Quinine dihydrochloride, quinine hydrochloride or quinine sulphate is the first line of treatment all through during pregnancy. The dose is 10 mg salt / Kg body weight 8-hourly for 7 days. Start with IV quinine in 10% glucose infusion; if for some reason quinine can not be given by infusion, quinine dihydrochloride can be given in the same dosage by IM injection diluted with sterile normal saline to a concentration of 60 mg / ml. the dose should divided into two halves and injected into both medial upper thighs, and shift to oral as soon as possible. In case there is no 10% glucose concentration gives one bottle of 5% glucose before administration of Q.
- Random blood sugar should be done before and after Q administration.
- *Or* **quinine** 10 mg / Kg body weight 8 hourly for at least 3 days (IV or IM) and shift to (AS+SP) as soon as the patient can take orally; this is of course in the second and third trimesters.
- *Or* **Artemether** IM 3.2 mg / Kg body weight in the first day (divided to two doses 12 hours apart) followed by 1.6 mg / Kg daily for the next 6 days.

4.1.6 Management of complications:

- **Pulmonary oedema:** careful fluid management, back rest, diuretics and ventilation if needed.
- **Hypoglycaemia:** 25 -50 % dextrose, 50 -100 ml IV followed by 10% dextrose as a continuous infusion.

  Blood sugar should be monitored every 4 -6 hours.
- **Anaemia:** back cell should transfused if Hb <7 gm.
- **Renal failure:** it could be pre-renal due to unrecognized dehydration or renal due to severe parasitaemia. Management involves careful management, diuretics and dialysis if needed.
- **Septicaemic shock or algid malaria**: administration of third generation of cephalosporins, fluid replacement or monitoring of vital parameters.

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4.1.7 Management in labour:

Falciparum malaria induces uterine contractions, resulting in premature labour. The frequency and intensity of the contractions is related to the degree of the fever. Faetal distress is the common and recognized complication. Lower the temperature by using cold sponging or antipyretics such as paracetamol. Adequate fluid management and careful monitoring in labour are mandatory.

The table below summaries the use of antimalarial drugs for MIP and puerperium.

Pregnancy in weeks	1st line	Severe malaria	Prevention (IPT)	Drugs not recommended in Sudan
0 -12	Q	Q	-	Mefloquine, halofantrine, artimisinin - derivatives, primaquine, SP
13 -36	Q or (Q+ SP) or (AS + SP)	Q or ART	SP	Mefloquine, halofantrine, primaquine
36 –delivery	Q	Q or ARM	-	Mefloquine, halofantrine, primaquine, SP
Puerperium	AS + SP	Q Or ARM	-	Mefloquine, halofantrine, primaquine

AS= artesunate, SP = Sulfadoxine /pyrimethamine, ARM =artemether, Q =quinine

4.1.8 Intermittent preventive treatment (IPT).

This is a new strategy for prevention of malaria and its consequences on mothers and newborns. It entails giving 2 therapeutic doses of **SP**. The first dose of IPT is in the first visit after quickening (week 16- 20) and the 2nd dose is in the next visit at least 4 weeks apart from the first dose. If this not happened the second dose can be given after but should not passed week 30. IPT is recommended only in high transmission areas (south and some irrigated areas in Sudan). In vivax

area and in low to moderate transmission areas, **chloroquine** can be used in a dose of 5 mg/kg weekly till delivery.