Management of Malaria in Children : Update 2008

INFECTIOUS DISEASES CHAPTER, INDIAN ACADEMY OF PEDIATRICS

ABSTRACT

***Justification**: The first guideline on diagnosis and management of malaria in children was formulated by Infectious Diseases Chapter of IAP in 2005. In subsequent year WHO proposed artemisinin based combination therapy in all cases of uncomplicated falciparum malaria. The number of falciparum malaria as well as multidrug resistant falciparum malaria cases are constantly on the rise. So there was need to revise the existing guideline. **Process**: The first recommendations on the diagnosis and management of malaria in children were formulated in 2005. The same protocol was revised on 12 October 2007 in NIMHANS, Bangalore in the light of various recommendations of WHO, where all the members of the Task Force Committee on Malaria in Children were present. **Objective:** To revise and update treatment guidelines for malaria with special reference to artemisinin based combination therapy. **Recommendations**: The need for Artemisinin based combination therapy (ACT) is emphasized in chloroquine resistant falciparum malaria. Monotherapy with artesunate will further increase the resistance. Once malaria treatment is initiated it should be completed. In severe malaria the maintenance dose of artesunate is revised.*

Key words : *Artemisinin based combination therapy, Chloroquine resistant falciparum malaria, Multidrug resistant malaria, Guidelines, Recommendations.*

INTRODUCTION

Malaria is one of the leading cause of morbidity and mortality in developing countries. Nearly 2.48 million malaria cases are reported annually from South Asia of which 75% cases are contributed by India alone(2). It is heartening to know the total number of laboratory confirmed cases have declined from 3 million reported in 1997 to 1.84 million in early 2000(3). At the same time, it is perplexing that the number of falciparum cases is constantly on the rise and in recent years they contribute nearly 50% of the total cases(3).

Falciparum malaria resistant to chloroquine (CQ) was identified in the districts of North East along the International border from 2003 onwards. According to National Vector Borne Disease Control Program, high treatment failure to CQ has been detected in 44 districts of 18 states in the country for which second line treatment with sulphadoxine – pyrimethamine (SP) was suggested(4). Resistance to SP combination at various levels has also been reported in the districts of seven North Eastern States. It has been seen that the introduction of a single new drug leads to rapid development of resistance. To overcome this, WHO has recommended Artemisinin based combination therapy (ACT) for the treatment of uncomplicated falciparum malaria(5).

We had previously provided a detailed guideline on diagnosis and management of malaria(1). The present update incorporates our policy on ACT on the treatment of falciparum malaria, in addition to providing the standard treatment protocol. A full course of effective treatment should always be given once it is decided to give antimalarial treatment(6).

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RECOMMENDATIONS

Artemesinin Combination Therapy

Antimalarial combination therapy is simultaneous use of two or more blood schizontocidal drugs with different mode of action in unrelated biochemical targets in the parasite. According to WHO, one of the partner in combination therapy should be an artemisinin derivative due to its high killing rate (reduces parasite number 10,000 fold per cycle whereas other antimalarial reduces 100 to 1000 fold per cycle), lack of serious side effects, relatively low level of resistance and rapid elimination rate, which ensures that the parasites are not exposed to subtherapeutic levels of the drug. When administered in combination with rapidly eliminated antimalarials (clindamycin, tetracycline), a seven days course of treatment is required and adherence to treatment is usually poor. If artemesinin derivatives are combined with slowly eliminated antimalarials [SP, mefloquine (MQ), lumefantrine], shorter courses of treatment (3 days) are effective which ensures better treatment adherence. These combinations also protect against emergence of drug resistance despite the fact that they do leave the slowly eliminated tail of long acting drugs unprotected. Resistance could arise within the residual parasite that have not yet been killed by the artemisinin derivative. However, number of parasites exposed to long acting drug alone is a tiny fraction (less than 0.00001%) of those present in the acute infection. Furthermore, these residual parasites are exposed to relatively high levels of long acting drugs and even if susceptibility was reduced, these levels may be sufficient to eradicate the infection.

Uncomplicated Malaria

Treatment regimes are to be tailored specifically according to the resistance pattern of the region under consideration (***Tables* Ia, Ib, Ic, Id**).

SEVERE AND COMPLICATED MALARIA

The main objective of treatment is to prevent death. Prevention of recrudescence, transmission or emergence of resistance and prevention of disabilities are of secondary importance. Untreated severe malaria has a mortality of 100% but with proper treatment it can be reduced to 15-20%. As death due to severe malaria often occurs within hours of admission it is essential to ensure therapeutic concentration of antimalarial drugs as soon as possible. Hence, antimalarial drug should

TABLE Ia RECOMMENDED TREATMENT IN CHLOROQUINE SENSITIVE MALARIA

Drug sensitivity	Recommended treatment
P. vivax and	*Chloroquine 10 mg base/kg stat followed by 5mg/kg at 6, 24 and 48 hours.
chloroquine sensitive	OR
P. falciparum	Chloroquine 10mg base/kg stat followed by 10mg/kg at 24 hours and 5mg/kg at 48 hours (total dose 25mg base/kg).
	†In case of vivax malaria, to prevent relapse, primaquine should be given in a dose of 0.25 mg/kg once daily for 14 days. In case of falciparum malaria, a single dose of primaquine (0.75mg/kg) is given for gametocytocidal action.

* *Chloroquine should not be given on an empty stomach and in high fever. Bring down the temperature first. If vomiting occurs within 45 minutes of a dose of chloroquine, that particular dose is to be repeated after taking care of vomiting by using antiemetic (domperidone/ondansetron).*

† *According to National Anti Malarial Program, a 5 days course of primaquine is advocated because of risk of toxicity and operational feasibility. Whereas other authorities advocate 14 days course of primaquine due to lack of evidence to support shorter courses(7). As primaquine can cause hemolytic anemia in children with G6PD deficiency, they should be preferably screened for the same prior to starting treatment. As infants are relatively G6PD deficient, it is not recommended in this age group and children with 14 days regime should be under close supervision to detect any complication. In cases of borderline G6PD deficiency, once weekly dose of primaquine 0.6 – 0.8 mg/kg is given for 6 weeks.*

TABLE Ib RECOMMENDED TREATMENT IN CHLOROQUINE RESISTANT *P. FALCIPARUM*

Artesunate 4mg/kg of body weight once daily for 3 days and
a single administration of SP as 25mg/kg of sulfadoxine and 1.25 mg/kg of pyrimethamine on day 1
or artesunate as above and mefloquine 25mg/kg of body weight in two (15 + 10) divided doses on day 2 and day 3.

OR

Co-formulated tablets containing 20 mg of artemether and 120 mg of lumefantrine can be used as a six dose regimen twice a day for 3 days. For 5-14 kg body weight 1 tablet at diagnosis, again after 8 hours and then twice daily on day 2 and day 3. For 15 to 24 kg body weight same schedule with 2 tablets. For 25-35 kg body weight and above same schedule with 3 and 4 tablets, respectively.

(*i*) *Under the previous National Drug Policy, SP monotherapy in a single dose was used in areas of chloroquine resistance. Countries where SP was introduced following CQ resistance showed its rapid decline in efficacy within few years.*

(*ii*) *Currently there are insufficient safety and tolerability data on mefloquine at its recommended dosage of 25 mg/kg body weight in children. Mefloquine shares cross resistance with quinine which is still a effective drug in our country. Health planners of our country do not advocate use of menfloquine.*

(*iii*) *Advantage of artemether lumefantrine combination is that lumefantrine is not available as monotherapy and has never been used by itself for the treatment of malaria. Lumefantrine absorption is enhanced by coadministration with fatty food like milk.*

TABLE Ic RECOMMENDED TREATMENT OF MULTIDRUG RESISTANT *P. FALCIPARUM* (BOTH TO CHLOROQUINE AND SULFADOXINE-PYRIMETHAMINE)

Quinine, 10mg salt/kg/dose 3 times daily for 7 days.
+
Tetracycline (above 8 years) 4mg/kg/dose 4 times daily for 7 days
OR
Doxycycline (above 8 years) 3.5mg/kg once a day for 7 days
OR
Clindamycin 20mg/kg/day in 2 divided doses for 7 days.
In case of cinchonism,
Quinine, 10mg salt/kg/dose 3 times daily for 3-5 days
+
Tetracycline (above 8 years) 4mg/kg/dose 4 times daily for 7 days
OR
Doxycycline (above 8 years) 3.5mg/kg once a day for 7 days
OR
Clindamycin 20mg/kg/day in 2 divided doses for 7 days.
A single dose of primaquine above 1 year age (0.75mg/kg) is given for gametocytocidal action.
OR
Artemether lumefantrine combination as in ***table 1b.***

(*i*) *Doxycycline is preferred to tetracycline as it can be given once daily and does not accumulate in renal failure.*
(*ii*) *One of the drawbacks of quinine therapy is its long course. Unsupervised and ambulatory setting may decrease patients compliance and many patients might not complete the full course of prescribed therapy.*
(*iii*) *Fortunately children tolerate quinine better than adults.*

TABLE Id RECOMMENDED TREATMENT IN FAILURE WITH ARTEMISININ COMBINATION THERAPY (ACT)

Quinine + Tetracycline or Doxycycline or Clindamycin for 7 days as in ***Table* Ic.**

(*i*) *Treatment failure within 14 days of receiving an ACT is unusual. It should be confirmed parasitologically by blood slide examination. It is important to determine whether patient has vomited previous treatment or did not complete a full course.*

(*ii*) *Failure after 14 days of treatment can be re-treated with first line ACT.*

TABLE II DRUG AND DOSAGE OF ANTIMALARIALS IN COMPLICATED AND SEVERE MALARIA

Drug	Dosages(5,9)
Quinine salt	20mg salt/kg (loading dose) diluted in 10mL of isotonic fluid/kg by infusion over 4 hours. Then 12 hours after the start of loading dose give a maintenance dose of 10mg salt/kg over 2 hours. This maintenance dose should be repeated every 8 hours, calculated from be ginning of previous infusion, until the patient can swallow, then quinine tablets, 10mg salt / kg 8 hourly to complete a 7 day course of treatment (including both parenteral and oral). Tetracycline or doxycycline or clindamycin is added to quinine as soon as the patient is able to swallow and should be continued for 7 days. Dosage as in table 1c. If controlled IV infusion cannot be administered then quinine salt can be given in the same dosages by IM injection in the anterior thigh (not in buttock). The dose of quinine should be divided between two sites, half the dose in each anterior thigh. If possible IM quinine should be diluted in normal saline to a concentration of 60-100mg salt/ml. (Quinine is usually available as 300mg salt/ml). Tetracycline or doxycycline or clindamycin should be added as above.
Artesunate	2.4 mg/kg IV then at 12 and 24 hours, then once a day for total 7 days. If the patient is able to swallow, then the daily dose can be given orally. Tetracycline or doxycycline or clindamycin is added to artesunate as soon as the patient can swallow and should be continued for 7 days. Dosage as in ***Table 1c.***
	OR
Artemether	3.2 mg/kg (loading dose) IM, followed by 1.6 mg/kg daily for 6 days. If the patient is able to swallow, then the daily dose can be given orally. Tetracycline or doxycycline or clindamycin is added to artemether as soon as the patient can swallow and should be continued for 7 days. Dosage as in ***Table 1c.***

(*i*) *Loading dose of quinine should not be used if the patient has received quinine, quinidine or mefloquine within the preceding 12 hours. Alternatively, loading dose can be administered as 7mg salt/kg by IV infusion pump over 30 minutes, followed immediately by 10mg salt/kg diluted in 10 ml isotonic fluid/kg by IV infusion over 4 hours.*

(*ii*) *Quinine should not be given by bolus or push injection. Infusion rate should not exceed 5 mg salt/kg/hour.*

(*iii*) *If there is no clinical improvement after 48 hours of parenteral therapy, the maintenance dose of quinine should be reduced by one third to one half i.e., 5-7 mg salt/kg.*

(*iv*) *Quinine should not be given subcutaneously as this may cause skin necrosis.*

(*v*) *Previous maintenance dose of parenteral artesunate of 1.2 mg/kg has been modified by WHO to 2.4 mg/kg.*

(*vi*) *Artesunate, 60mg per ampoule is dissolved in 0.6mL of 5% sodium bicarbonate diluted to 3–5 mL with 5% dextrose and given immediately by IV bolus (push injection).*

(*vii*) *Artemether is dispensed in 1 mL ampoule containing 80mg of artemether in peanut oil.*

be given initially by intravenous infusion, which should be replaced by oral administration as soon as condition permits.

According to the National Anti Malaria Program (NAMP), drug policy in all cases of severe malaria is either IV quinine or parentral artemisinin derivatives to be given irrespective of chloroquine resistance status(8). Treatment Guidelines are summarized in ***Table* II.**

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KEY MESSAGES

- Malaria treatment, once initiated, should be completed.
- Artemisinin based combination therapy is recommended in chloroquin resistant falciparum malaria.

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