Recommendations

Diagnosis and Management of Malaria in Children

Recommendations and IAP Plan of Action

Writing Committee:
Ritabrata Kundu
Nupur Ganguly
Tapan Kr. Ghosh
Panna Choudhury
Raju C. Shah

Background

Malaria is a major public health problem of developing countries. Approximately, 2.48 million malaria cases are reported annually from South Asia of which 75% cases are contributed by India alone(1). The magnitude of the problem is further enhanced by P. falciparum resistance to standard antimalarial drugs particularly chloroquine. Important contributing factors of drug resistance are population movement, infrastructure defi-ciency, deforestation, unplanned development, drug pressure and haphazard use of drugs. It has been found drug pressure is the singlemost important factor in the development of resistance following presumptive antimalarial treatment. Malaria which was a rural problem of the past has now emerged in different forms namely, urban and forest malaria. These new addition is becoming an increased burden to

Correspondence: Dr. Ritabrata Kundu, Institute of Child Health, 11 Dr. Biresh Guha Street, Kolkata 700 017, India.

our country. Indian Academy of Pediatrics has set up a National Task Force to form a uniform guideline on diagnosis and management of malaria which can be followed by all members of IAP in general. The list of the members who took part in the workshop is given in Annexure I.

SECTION I

1. Diagnosis of Malaria

Diagnosis of malaria in our country is mainly based on symptoms due to lack of proper infrastructure. As per national antimalarial drug policy all fever cases, both in high and low risk areas, without any other obvious causes are to be treated with antimalarials(2). Even in Integrated Management of Childhood Illness (IMCI) strategy all fever cases are given antimalarials(3). This indiscriminate use of antimalarial is constantly increasing the overall drug pressure. The greatest decrease in antimalarial drug use could be achieved through improving the diagnosis of malaria atleast at the places where diagnostic facilities are available. With the development of rapid antigen tests which are cost effective and does not require expertise considerable reduction of unnecessary treatment is possible.

To reduce the increasing drug resistance, in all cases of fever all out efforts should be given to diagnose malaria with all possible means before commencing treatment. However, in complicated malaria or malaria with danger signs presumptive treatment may be started before confirmation after collecting blood for examination.

1.1. *Microscopic diagnosis*

Light microscopy of well stained thick and thin films by a skilled microscopist has

remained the "gold standard" for malaria diagnosis. Thick films are nearly 10 times more sensitive for diagnosis of malaria as larger amount of blood are there in a given area as compared to thin films(4). Species identification is better with thin films as morphology of the parasite and RBC are well preserved.

1.1*a*. COLLECTION OF BLOOD SAMPLE

Timing of sample collection should be as soon as malaria is suspected. It can be collected any time irrespective of fever and not necessarily only at the height of fever(5). Collection should be before administration of antimalarials which causes detection of parasites difficult due to its morphologic alteration.

Smears should be prepared soon after collection which enables better adherence of films to the slide and cause minimal distortion of parasites and red cells. In blood collected with anticoagulants films should be prepared within 2 hours for best results(4).

1.1*b*. EXAMINATION OF BLOOD FILM

Smear should be examined with 100X oil immersion objective. A minimum of 100 fields should be examined before concluding the slide to be negative. Once negative, samples may be examined for at least three consecutive days where clinical suspicion of malaria persists.

1.1*c*. ADVANTAGE OF MICROSCOPY

1. Skilled microscopist with proper infrastructure can pick up parasite as low as 5-10 parasite per μl of blood(6). However, in actual field conditions with limited resources detection capability reduces to 100 parasite per μl of blood(7).

2. Species identification along with characterization of the stage of parasite is possible thereby helping in adequate treatment and prognostication. In falciparum malaria early ring stages has relatively good outcome in contrast to later stages like trophozoites and schizonts(8).

3. It offers the advantage of determining the parasite density. The parasite load in utilized to determine the severity of malaria along with prognosis and assessing the response to treatment.

4. In profound anemia parasite in peripheral blood are often absent but presence of malaria pigment in polymorphonuclear leukocytes (PNM) and monocytes points out the diagnosis and if more than 5% of PNM contains visible pigment it denotes poor prognosis(8).

1.1*d*. DISADVANTAGE OF MICROSCOPY

1. It is time consuming usually requiring at least 60 minutes from specimen collection to result(9).

2. It needs skilled technician with proper infrastructure which are often unavailable at periphery, weekends, holidays and at odd hours.

3. Microscopy cannot detect parasite sequestered deep in the vascular compartment.

4. In case of mixed infection often one species suppresses the other thereby making detection of the suppressed one difficult(10,11).

1.2. *Rapid diagnostic tests (RDTs)*

These are immunochromatographic test (ICT) to detect plasmodium specific antigens in blood sample. Test employ monoclonal antibodies directed against targeted parasite antigens.

1.2*a*. TARGETED ANTIGENS IN CURRENTLY AVAILABLE RDTS

Histidine rich protein II (HRP-II) is actively secreted by asexual stages and young gametocytes of P falciparum but not by mature gametocytes(12).

A metabolic enzyme Parasite lactate dehydrogenase (pLDH)(13) is produced by all four species of plasmodia, both asexual and sexual (gametocytes) stages provided they are viable(14). Following successful treatment the enzyme is rapidly cleared from the blood and the test become negative within days of treatment. Monoclonal antibodies produced against this antigen are of three groups. One specific for *Plasmodium falciparum* and the second specific for *P. vivax*. The other is pan specific antibody which reacts with all the four species of plasmodia *i.e.*, vivax, falciparum, ovale and malarie but unable to separate them individually. Commercially available kit can detect falciparum, vivax and other malaria but cannot differentiate ovale and malarie malaria.

1.2*b*. PERFORMANCE CHARACTERISTIC OF RDTs

Performance of these kits are evaluated extensively in both endemic and non endemic regions but with newer kits (which detect both falciparum and vivax), the assessment of performance are few that too with small sample size. Instruction guidelines provided by the manufacturer should be followed. Care should be taken to maintain temperature and humidity as recommended. Faulty technique may give false results.

The sensitivity to detect *P. falciparum* HRP-II with parasite density above 100 parasite per μl of blood is above 90%(15). With low level of parasitemia *e.g.*, with 10 parasites per μl of blood the sensitivity decreases to 74.6% and with 10-100 parasites per μl of blood it is 81.3%(16). pLDH kit to detect falciparum and vivax malaria has a sensitivity comparable to that of HRP-II(17) but number of studies are much less to comment for its superiority over

older HRP-II tests. Some investigations have shown specificity of these test are also above 90%.

HRP-II tests can remain positive for 7-14 days following successful malaria treatment even when blood doesn't show parasitemia by microscopy(18). On the other hand as pLDH is produced by only viable parasite so the tests detecting this antigen becomes negative within 3-5 days of treatment(17).

Of all the malaria diagnostic tests RDTs are easiest to perform.

1.2c. ADVANTAGES OF RDTs IN COMPARISON TO MICROSCOPY

1. They are simple, straight forward and less time consuming requiring no special equipment or skill/training. Test result vary little between individual performance.

2. They can detect *P. falciparum* infection even when the parasite is sequestered in the deep vascular compartment.

3. This test can exclude mixed falciparum and vivax malaria where the former may not be evident microscopically(19).

1.2d. DISADVANTAGE OF RDTs IN COMPARISON TO MICROSCOPY

1. RDTs that target HRP-II of *P. falciparum* shows antigenemia to persist longer than parasitemia. Hence, this test is unsuitable for assessment of treatment failure and monitoring of drug resistance. Newer test that target pLDH, which is elaborated only by live parasite has the possibility to monitor treatment. As studies with this test are few they are not recommended at present for monitoring treatment.

2. As they do not quantify the parasite load so neither they have prognostic value nor they can detect therapeutic efficacy of antimalarial drugs.

3. Under optimal conditions an expert microscopist can detect even 5-10 parasite per µl of blood(6). Whereas for all practical purpose detection threshold of RDTs are 40-60 parasite per µl of blood(15).

4. Gametocytes of *P. falciparum* can persist even after successful chemotherapy which are non pathogenic. RDTs in such situation will give rise to false positive result with chances of unnecessary treatment.

5. Currently, available RDT kits are required to store up to or under 30ºC. In remote areas without electricity temperature often reaches 40ºC or more.

1.2*e*. ROLE OF RDTS IN OUR COUNTRY WITH LOW TO MODERATE MALARIA TRANSMISSION

In comparism to high transmission areas, malaria in our country occurs less frequently, in all age groups and almost always symptomatic. Drug resistance including multidrug resistance has started developing in our country so laboratory confirmation of malaria is an essential component of disease management. Expert microscopic diagnosis is available in central levels of health care system like metro cities but it is often unreliable or unavailable in remote areas with poor health facilities. So RDTs will be useful in the following situations in our country:

(*a*) In far away communities where patient has poor access to health care facilities and microscopic diagnosis is not available. Also in areas where laboratory service is inadequate, of an unacceptable standard or not available at odd hours.

(*b*) All malaria patients due to low levels of immunity, are at high risk of developing serious disease if there is delay in diagnosis and treatment. RDT can be helpful in such situation.

(*c*) In areas of multidrug resistance treatment with drug or drug combinations are more expensive than the diagnostic test.

(*d*) In severe and complicated malaria peripheral parasitemia may be negative due to sequestration but RDTs are expected to provide evidence of antigenemia.

(*e*) If blood smear is positive for malaria parasite there is no need to do RDTs. In case of strong clinical suspicion negative RDTs are to be confirmed by microscopy. In complicated malaria bed side RDT can provide results within 30 minutes.

1.2*f*. CONCLUSION

RDTs permit on the spot confirmation of malaria even at the peripheral health care system, by unskilled health workers with minimal training. Rational use of RDTs as a complement to microscopy might offer following benefits :

1. Early treatment will reduce morbidity and mortality.

2. In multidrug resistant areas expensive drugs and drug combination are targeted to high risk population.

3. Avoidance of unnecessary treatment will reduce drug pressure and delay progress of drug resistance.

1.3. *Other methods of diagnosis*

Other diagnostic methods namely microscopy using fluorochromes and on centrifused blood specimens, molecular probes, polymerase chain reaction (PCR) and serology are available. Unfortunately, they are not suitable for routine disease management and do not have wide field application. Their use is currently for only research and epidemiological purpose.

SECTION 2

2. **Management of uncomplicated malaria in children**

Treatment of malaria may be presumptive, curative and radical.

Presumptive

A case of fever treated for malaria without parasitological diagnosis with an aim to prevent mortality and morbidity due to delay in treatment.

Curative

Treatment given after diagnosis but without 8 aminoquinolines because of contraindication.

Radical

Therapy after parasitological confirmation to eliminate all the forms of parasite from all possible host tissues.

2.1. *Basis of antimalarial treatment*

Malaria in children has some unique features. Young children below 5 years whose passive immunity wanes and as yet to develop sufficient immunity of their own are most vulnerable.

Falciparum malaria can be rapidly progressive and can develop rapid clinical deterioration hence this group needs constant monitoring

Children can tolerate antimalarial drugs better than adults and their symptoms resolve more quickly following successful treatment.

The main aim of antimalarial treatment in children, which is also the basis of National Antimalarial Program, is to prevent morbidity and death by early diagnosis and prompt treatment (EDPT). Unfortunately, in our country prompt treatment is mostly presumptive based on clinical diagnosis. It is interesting to note that in the year 2000 out of 86.46 million blood smear examination throughout the country on presumptive diagnosis of malaria slide positivity rate (SPR) was found to be only 2.32% (21). Extrapolating

from these data it is evident that the use of presumptive treatment of malaria has the potential for facilitating resistance by greatly increasing the number of patients who are treated unnecessarily.

Hence, all efforts should be given to treat malaria after diagnosis by microscopic examination, rapid diagnostic tests or both as facilities and circumstances dictate. In situation where such facilities are not available one should make atleast clinical diagnosis of malaria following clinical algorithmic approach.

Further, a complete and successful antimalarial therapy is possible only when the parasite species are known. In case of clinically suspected malaria at times the first smear examination may be negative but it is prudent of avoid the diagnosis of "blood smear negative malaria". In these cases repeated blood smear at 12 to 24 hours interval(19) and RDTs are suggested and all other causes of fever are to be excluded.

One of the major problem in the successful treatment of malaria is the development of resistance of *P. falciparum* to first line drug chloroquine (CQ) in certain areas of our country. Malaria is prevalent in all parts below 5000 feet mean sea level. Before initiating treatment it is desirable to have some idea about the pattern of resistance in our   country.

Transmission of malaria is usually low in most parts of India but intense transmission is seen in North Eastern States and large areas of Orissa, Chattisgarh, Jharkhand and Madhya Pradesh. Year 2004 reveals largest number of cases in our country reported from Orissa followed by Gujarat, Chattisgarh, West Bengal, Jharkhand, Karnataka, Uttar Pradesh and Rajasthan(22).

To combat drug resistant malaria, the

NVBDCP recommends the use of combination therapy *i.e.*, artesunate plus sulfadoxine/pyrimethamine (SP) for *P. falciparum* cases in chloroquine resistant areas.

P. falciparum resistant to chloroquine and sulfadoxine/pyrimethamine are prevalent in the neighboring countries of Bangladesh, Bhutan, Myanmar and Nepal. North Eastern part of our country share international border with the above mentioned countries and reports resistance to sulfadoxine/pyrimethamine at various level in district of seven North Eastern States(23).

Though few reports of emergence of chloroquine resistance *P. vivax* are there but the drug still retains its effectivity against *P. vivax* infection in our country.

Treatment regimes of uncomplicated malaria

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

3. Monitoring of uncomplicated malaria

3.1. Standardized test system for the assessment of *in vivo* drug response in *P. falciparum* malaria were developed by WHO following reports of chloroquine resistance(19).

Sensitive parasite

Parasites are sensitive if clearance of asexual parasitemia by day 6 from the initiation of treatment, without subsequent recrude-scence until day 28 (Day 0 = first day of treatment).

Resistant parasite

Grade I resistance (RI): If clearance of asexual parasitemia for at least 2 consecutive days, latest on day 6, after the initiation of treatment, followed by recrudescence within day 28.

Grade II resistance (RII) : If there is marked reduction of asexual parasitemia to less than 25% of the pretreatment count within 48 hours of the initiation of treatment, but no subsequent disappearance of asexual parasitemia (positive on day 6 after the initiation of treatment).

Grade III resistance (RIII): If there is modest reduction (not less than 25%), no change, or an increase in asexual parasitemia, during the first 48 hours following the implementation of the treatment and no subsequent clearance of asexual parasites.

This system is not practicable in day to day practice due to the need of daily blood examination for 28 days.

3.2. *New system of monitoring*

Subsequently, WHO developed a new system of monitoring with follow up for 14 days where both clinical and parasitological assessment was done(25). Parasitological assessment should include detection of malaria parasite, species determination and parasite density measurement. Patient should also be assessed clinically with examination of body temperature.

Microscopy should be done at day 0, before initiation of treatment, on day 3, 7 and 14 if not indicated more frequently. Parasite count on day 0 is taken 100% for that particular child.

Early treatment failure: The patient will be classified as early treatment failure (ETF) under the following situations :

(*i*) Development of danger sign or severe malaria (*Tables II* and *III*)(25) during the first three days (day 1-3) in presence of parasitemia.

(*ii*) Axillary temperature ≥37.5ºC on day 2 with parasite count greater than that of day 0.

TABLE I*a***:** *Recommended Treatment in Chloroquine Sensitive Malaria.*

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

(*i*)   Chloroquine should not be given in 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 Domperidone/Ondansetron.

(*ii*)   According to National Anti Malarial Program a 5 days course of primaquine is advocated because of toxicity and operational feasibility. Whereas other authorities advocate 14 days course of primaquine due to lack of evidence to support shorter courses(19). As primaquine can cause hemolytic anaemia 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 I*b*– *Recommended Treatment in Chloroquine Resistant P. falciparum.*

Drug sensitivity	Recommended treatment
Chloroquine resistant *P. falciparum*	Artesunate 4 mg/kg of body weight once daily for 7 days followed the next day by SP as 25 mg/kg of sulfadoxine and 1.25 mg/kg of pyrimethamine as a single dose or Mefloquin 25 mg divided in two(15 + 10) doses at 4- 6hrs interval. A single dose of Primaquine (0.75 mg/kg) is given for gametocytocidal action.

Under the previous National Drug Policy SP monotherapy in single dose as mentioned above was used in areas of chloroquine resistance. Countries where SP was introduced following CQ resistance showed its rapid decline in efficacy within few years. WHO recommends in countries experiencing resistance should use combination therapy preferably those containing an artemisimin derivative (ACT - Artemisimin based combination therapy(24). Falciparum resistance to artemisinin is not yet reported. However, artemisimin monotherapy will require 7 days treatment. The objective of the current ACT is for a three days course to act over 2 asexual cycles to substantially reduce total parasite numbers, ensuring a rapid clinical response. The rationale for a combination therapy is the additive action of two drugs to improve efficacy and to delay development of drug resistance to individual drugs if used as monotherapies.

(*iii*)   Axillary temperature ≥37.5°C on day 3 in presence of parasitemia.

(*iv*)   On day 3 irrespective of axillary temperature parasite count is ≥25% of that of day 0.

Late treatment failure: Patient will exhibit late treatment failure (LTF)(25) under following situations:

(*i*)   Development of danger sign or severe malaria on any day between day 4 and day

TABLE I*c–Recommended Treatment of Multidrug Resistant P falciparum (Both to CQ and SP)*

Drug sensitivity	Recommended treatment
Multidrug resistant *P. falciparum* i.e., both to CQ and SP	Quinine, 10 mg salt/kg/dose 3 times daily for 7-10 days. In case of cinchonism, Quinine, 10 mg salt/kg/dose 3 times daily for 3-5 days + Tetracycline (if age >8 yrs) 4 mg/kg/dose 4 times daily for 7-10 days OR Doxycycline (if age >8 yrs) 3 mg/kg/day 2 times daily for 7-10 days OR Clindamycin 20mg/kg/day divided 3 times daily × 7-10 days
	A single dose of primaquine above 1 year age (0.75mg/kg) is given for gametocytocidal action.

(*i*)   Multidrug resistant *P. falciparum* is found in North Eastern parts of our country where transmission of malaria is intense. Use of artesunate SP combination in this area would affect the efficacy of treatment and will be equivalent to use of artesunate monotherapy thereby increasing the potential of resistance to artesunate. Other alternative suggested are artesunate plus amodiaquine has its limitation due to cross resistance of amodiaquine with CQ. Artesunate mefloquine combination will not be suitable in areas of intense transmission due to long half life of mefloquine. In areas of low transmission this combination will be effective (it showed good result in Thailand) with artesunate given in a dose of 4 mg/kg daily for 3 days along with mefloquine 25mg base/kg (15 mg/kg on day 2, 10mg/kg on day3). The other viable option is artemether lumefantrine combination tested is some South East Asian countries but not available in our country.

(*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.

(*iv*) Tetracycline and doxycycline is not recommended in children below 8 years of age.

14 in presence of parasitemia.

(*ii*) Axillary temperature ≥37.5ºC in presence of parasitemia on any day from day 4 to day 14.

3.3. *General Danger signs of malaria (Table II)*

So from practical point of view the therapeutic response is taken as adequate if the patient is afebrile without parasitemia from day 3 onwards. In day to day practice where repeated blood examination is not possible resistance should be suspected in spite of full treatment and no history of vomiting or diarrhea, if patient does not respond within 72 hours parasitologically(2). If the patient shows therapeutic failure then he/she should be given alternative therapy as guided in the treatment section.

According to IAP recommendations, if by

TABLE II.*–General Danger Signs of Malaria.*

Danger signs of malaria :
(*i*)   Not able to drink or breast feed
(*ii*) Vomiting everything.
(*iii*) Recent history of convulsion
(*iv*) Lethargic or unconscious state
(*v*)   Unable to sit or stand up

The parent/guardian should be instructed to bring the child to the doctor if the patient develops any of the danger signs during the follow up.

TABLE III–*Features of Severe Malaria.*

Features of severe malaria
(*i*) Cerebral malaria (Unrousable coma)
(*ii*) Severe normocytic anemia (Hb <5 g/dL)
(*iii*) Renal failure (Serum creatinine >3 mg/100 mL)
(*iv*) Pulmonary edema
(*v*) Hypoglycemia (<40 mg/100 mL)
(*vi*) Circulatory collapse/Shock (Systolic blood pressure less than 50 mmHg in children below 5 years)
(*vii*) Spontaneous bleeding/Disseminated intravascular coagulopathy
(*viii*) Repeated generalized convulsions
(*ix*) Acidemia/Acidosis
(*x*) Macroscopic hemoglobinuria.

Other manifestations :

(*i*) Impaired consciousness but rousable
(*ii*) Prostration, extreme weakness (inability to stand or sit)
(*iii*) Hyperparasitemia (>5% RBC infected)
(*iv*) Jaundice (total serum bilirubin >3 mg/dL)
(*v*) Hyperpyrexia (axillary temperature >39.5ºC)

day 3 of the treatment, there is no clinical improvement, a blood smear is to be repeated. In case it is positive and the level of asexual parasitemia is more than or equal to 25% of the pretreatment value, revise treatment. If less than 25%, follow the patient till 28 days. Continuation of fever till day 5 or reappearance thereafter, but within 28 days, repeat blood smear. If positive, irrespective of the percentage of parasitemia, revise treatment.

3.4. *Feature of severe malaria*

Definition of severe falciparum malaria: One or more of the criteria written in *Table III* in the presence of asexual parasitemia define severe falciparum malaria.

SECTION 4

4. Management of severe malaria in children

Severe life threatening malaria is nearly always due to *P. falciparum*. All cases with severe manifestations are to be treated in the same line of complicated malaria with injectable antimalarials irrespective of the species.

High degree of suspicion of severe malaria is of utmost importance and any delay in initiation of treatment can be fatal. It should be treated as a medical emergency at highest level of medical facility available preferably in a intensive care setting. Confirmation of the diagnosis is preferable but one should not delay the treatment if it needs more than one hour(26). Further, in cases of strong clinical suspicion prompt antimalarial therapy is needed even if parasite are not found in the initial blood examination.

Severe malaria in children differs to certain extent from adults. Progression to cerebral malaria can be very rapid, but again, recovery is also rapid. Most common complications in children are cerebral malaria, severe anemia, respiratory distress (acidosis) and hypoglycemia. Fortunately, common complications in adults like pulmonary edema and jaundice are rare in children. The definition of severe malaria was proposed by working groups convened by WHO in 1990(27) and modified in the year 2000(28) (*Tables II* and *III*). In case of high degree of suspicion physician should not withhold treatment even if the patient do not clearly qualify into any one of the categories.

Effective therapy in children with severe malaria includes antimalarial chemotherapy, supportive management and management of complications. All these three interventions are equally important and to be taken care of simultaneously.

4.1. Antimalarial chemotherapy of severe

and complicated malaria *(Tables IV &V)*

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

After weighing the patient antimalarials should be given according to the body weight. If parenteral injection is not possible, referral is likely to be delayed and artemisinin is not available as suppository form consider crushed

TABLE IV–*Drug and Dosage of Antimalarials in Complicated and Severe Malaria According to NAMP*(2).

Drug	Dosage(26)
Quinine salt	20 mg salt/kg (loading dose) diluted in 10 ml of glucose containing isotonic fluid/kg by infusion over 4 hours. Then 12 hours after the start of loading dose give a maintenance dose of 10 mg salt/kg over 2 hours. This maintenance dose should be repeated every 8 hours, calculated from beginning 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).
	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).

(*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.

(*iii*) If there is no clinical improvement after 48 hours of parenteral therpy 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.

TABLE V–*Alternative Drugs Rather Than Quinine in Severe Malaria.*

Drug	Dosage(26)
Artesunate	2.4 mg/kg IV (loading dose), followed by 1.2 mg/kg at 12 and 24 hours, then 1.2 mg/kg daily for 6 days. If the patient is able to swallow, then the daily dose can be given orally. 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.

(*i*) 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).

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

(*iii*) At the end of the therapy a single dose of SP as 25 mg/kg of sulfadoxine and 1.25 mg/kg of pyrimethamine OR Mefloquine 25 mg/kg (divided into 2 doses of 15 mg/kg and 10 mg/kg 4 to 6 hours apart) is to be given.

antimalarial to be given by nasogastric tube. But it has the risk of causing vomiting and may produce inadequate drug levels in the blood.

According to the National Anti Malaria Programme (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(2). A single dose of primaquine (0.75 mg/ kg) is to be given for gametocytocidal action irrespective of the drug given.

4.2. *Quinine or artemisinin: Which one to use?*

Artemisinin are the most rapidly acting of all known antimalarial drugs, they often produce a 10,000 fold reduction of parasites per asexual cycle. They have the broadest time window of antimalarial effects from ring forms to early schizonts. Thus, they can stop para-   site maturation, particularly from the less pathogenic circulating ring stages to the more pathogenic cytoadherent stages(19).

Artemisinin also has an excellent safety profile and the cost of therapy as compared to quinine is almost similar. There are no reports of resistance to artemisinin at present but declining sensitivity to quinine has been reported from some South East Asian countries like Thailand.

All these theoretical advantages are not reflected in few randomized control trials available. However, most trials are conducted with artemether administered intramuscularly, which has questionable reliability of absorption in severe malaria. More comperative studies with artesunate which can be given intravenously and which does not have the pharmocokinetic disadvantage of artemether are needed for its recommendation.

However, artemisinin should be used when rate controlled intravenous infusion of quinine is not possible, patients have contraindications to quinine use and evidence of inadequate response or resistance to quinine noted. Simultaneous use of quinine and artemisinin is not indicated as it may be harmful and there is no added advantage. In limited studies available artisunate has been found to be better than artemether.

SECTION 5

5. Supportive management

(*i*)   Rapid clinical assessment with respect to level of consciousness (use Blantyre coma scale), blood pressure, rate and depth of respiration, anemia, state of hydration and temperature.

(*ii*) Thick and thin blood films should be made. Minimal investigation should include PCV (hematocrit), blood glucose and lumbar puncture specially in cerebral malaria. If lumbar puncture is delayed proper antibiotic cover for meningitis must be given. Antibiotics may also be considered if any secondary infection is suspected, which is common in severe malaria. Start intravenous antimalarial after drawing blood.

(*iii*) Good nursing care with proper position-ing, meticulous attention to airways, eyes, mucosa and skin should be done. Appropriate fluid therapy is to be given.

(*iv*) For unconscious child nasogastric tube is to be inserted to reduce the risk of aspiration.

(*v*)   Oxygen therapy and respiratory support should be given if necessary.

(*vi*) In case of shock resuscitate with Normal saline or Ringer lactate by bolus infusion. Avoid under or over hydration.

(*vii*) Convulsion should be treated with Midazolam /diazepam. Rectal Diazepam or Buccal Midazolam can be used.

(*viii*) Hyperpyrexia should be treated with paracetamol, tepid sponging, and fanning.

(*ix*) Close monitoring of the vital signs preferably every 4 hours to be done till the patient is out of danger. Also maintain intake output chart and watch for hemoglobinuria.

(*x*) Monitoring of the response to treatment is essential. Detail clinical examination with particular emphasis on hydration status, temperature, pulse, respiratory rate, blood pressure and level of consciousness is to be given. Blood smear examination every 6 to 12 hours for parasitemia for first 48 hours is needed.

(*xi*) In case of quinine parasite count may remain unchanged or even rise in first 18-24 hours which should not be taken as an indicator of quinine resistance. However, parasite count should fall after 24 hours of quinine therapy and should disappear within 5 days(29).

(*xii*) In case of artemisinin derivatives parasite count usually comes down within 5 to 6 hours of starting therapy. Asexual parasitemia generally disappears after 72 hours of therapy(29).

(*xiii*) Poor prognosis is suggested by high parasite densities (above 5% RBC infected or parasite density >250000/µL). At any parasitemia prognosis worsens if there is predominance of more mature parasite stages. If more than 20% of the parasite contain visible pigment (mature trophozoites and schizonts) the prognosis worsens. Poor prognosis is also indicated if more than 5% of the peripheral blood polymorphonuclear leukocytes contain visible malaria pigment(26).

(*xiv*) In follow up cases add iron and folic acid.

5.1. Management of complications of malaria(26)

Of the various complications of falciparum malaria the common and important ones in children are as follows:

(*a*) Cerebral malaria

(*b*) Severe anemia

(*c*) Respiratory distress (acidosis)

(*d*) Hypoglycemia

5.1*a*. CEREBRAL MALARIA

Initial presentation is usually fever followed by inability to eat or drink. The progression to coma or convulsion is usually very rapid within one or two days. Convulsions may be very subtle with nystagmus, salivation or twitching of an isolated part of the body. Effort should be given to exclude other treatable causes of coma (*e.g.*, bacterial meningitis, hypoglycemia). Patients should be given good nursing care, convulsions should be treated with diazepam/midazolam and avoid harmful adjuvant treatment like corticosteroids, mannitol, adrenaline and phenobarbitone.

5.1*b*. SEVERE ANEMIA

Children with hyperparasitemia due to acute destruction of red cells may develop severe anemia. Packed red cell transfusion should be given cautiously when PCV is 12% or less, or hemoglobin is below 4g%. Transfusion should also be considered in patients with less severe anemia in the presence of respiratory distress (acidosis), impaired consciousness or hyperparasitemia (>20% of RBCs infected).

5.1*c*. LACTIC ACIDOSIS

Deep breathing with indrawing of lower chest wall without any localizing chest signs suggest lactic acidosis. It usually accompanies cerebral malaria, anemia or

dehydration. Correct hypovolemia, treat anemia and prevent seizures. Monitor acid base status, blood glucose and urea and electrolyte level.

5.1*d.* HYPOGLYCEMIA

It is common in children below 3 years specially with hyperparasitemia or with convulsion. It also occurs in patients treated with quinine. Manifestations are similar to those of cerebral malaria so it can be easily overlooked. Monitor blood sugar every 4 to 6 hours. If facilities to monitor blood glucose is not available assume hypoglycemia in symptomatic patient and treat accordingly. Correct hypoglycemia with IV dextrose (25% dextrose 2 to 4 mL/kg by bolus) and it should be followed by slow infusion of 5% dextrose containing fluid to prevent recurrence.

5.1*e.* HYPERPYREXIA

High fever is common in children and may lead to convulsion and altered consciousness. Paracetamol 15mg/kg, Tepid sponging and fanning should be given.

5.1*f .* HYPERPARASITEMIA

Specially seen in nonimmune children associated with severe disease. Consider exchange transfusion/cytapheresis if greater than 20% of RBCs are parasitised.

5.1*g.* CIRCULATORY COLLAPSE (ALGID MALARIA)

In case of circulatory collapse suspect gram negative septicemia, send blood for culture before starting antibiotics. Resuscitate with judicious use of fluids.

5.1*h.* SPONTANEOUS BLEEDING AND COAGULOPATHY (DIC)

Usually seen is nonimmune children which should be treated with vitamin K, blood or blood products as required.

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Annexure

List of participants of the Workshop organized by IAP Task Force on Guidelines for Diagnosis and Management of Malaria in Children.

Chairperson: **Raju C. Shah;**
Convenor: **Ritabrata Kundu;**
Members**: Amitava Nandy,
Deepak Ugra,
Nigam P. Narain,
Nitin K Shah,
Nupur Ganguly,
Panna Choudhury,
Shivananda,
Tapan Kr. Ghosh.**