REVIEW ARTICLE

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RECENT ADVANCES IN CHILDHOOD ANTIMALARIA CHEMOTHERAPY

Ernest, S. K., Mokuolu, O. A.

Department of Child Health, College of Medicine, University of Ilorin, PMB 1515, Ilorin, Nigeria

Correspondence to: Dr. S. Kolade Ernest (E-mail: skernest2003@yahoo.com)

As malaria continues to kill many people in our world and spreading into areas that were never known to have it before, it becomes necessary to make occasional reviews of what therapeutic measures are effective in areas of malaria endemicity. There is a global concern as to reducing malaria morbidity and mortality worldwide. Malaria eradication had been viewed as impossible with the mechanisms used against it and the world has settled for just a control. One of the critical areas of this control is effective case management. As it was the case with tuberculosis, leprosy and bacterial infections, there is a paradigm shift from the monotherapy that have been used for nearly three centuries (Quinine) and nearly 60 years after other drugs were discovered (Chloroquine, since early 1940s and subsequently others) with no remarkable drop in the global morbidity and mortality. The World Health Organization (WHO) now advocates combination therapy, which are mainly Artemisinin-based. We in this article made an extensive review of the combination chemotherapeutic possibilities and advocacy for it to achieve increase survival, reduced disease burden through effective parasitaemic clearance with reduced chance of early recrudescence. A necessary overview has been made of the life cycle and clinical presentation of malaria which has not changed significantly over the years. Also the combination chemotherapy including Artemisinin-based, Sulphadoxine/Pyrimethamine-based and the non-Artemisinin non-Sulphadoxine/Pyrimethamine-based chemotherapy have all been reviewed and concluded that their use will lead to effective case management and reduced mortality. We therefore advocate for a therapeutic paradigm shift to these combination therapy.

Keywords: Combination chemotherapy, antimalaria, childhood, review

INTRODUCTION

About 300-500 million clinical episodes of malaria occur each year globally, resulting in about one million deaths (1). Figure 1 shows the global malaria distribution. Majority of the deaths occur among the people who did not intervene, intervened incorrectly/ wrongly or intervened too late that such intervention could not salvage their lives. More than 90% of the deaths occur in the sub-Saharan Africa and greater percentage being children.

In 1998, the World Health Organization (WHO) launched the Role Back Malaria (RBM), with the goal to halve malaria deaths worldwide by 2010 (2). To achieve this requires prevention interventions (ITNs, Household spraying) and appropriate case management, which is directly linked with death prevention. To achieve mortality reduction, malaria cases must be promptly and accurately diagnosed and well treated with effective antimalaria drugs. Presently, progress on effective treatment seems so inadequate that RBM seem to be failing to reach its targets. The reason given for this is the fact that RBM is acting on the background of increasing global malaria burden (3).

One of the major reasons why malarial mortality may increase is case management failure. Management failure can either be due to no treatment or treatment failure. Treatment failure will usually be due to inadequate treatment, fake drug syndrome, delayed treatment or multi-drug resistance of the deadly species, *Plasmodium falciparum*.

Presently, WHO said the global malaria control is being threatened on an unprecedented scale by the continued use of outdated drugs such as chloroquine which was said to be ineffective in most part of Africa and Sulphadoxine/Pyrimethamine (SP) which is also becoming less useful (4). For instance, in West Africa, a 12 year community-based study showed that the

onset of chloroquine (CQ) resistance doubled childhood malaria mortality risk and that in some sites, the risk increased 11-fold especially in young children (5, 6).

In the East and Southern African countries, the childhood mortality from malaria double as CQ and later SP resistance started from 1980s to the 1990s even when mortality from other causes declined. In all other African countries, the proportion of admission to hospital increased significantly and the deaths attributed to malaria increased by 2 to 4 folds (7). The link between drug resistance, treatment failure and deaths from malaria are well established and WHO agrees that CQ resistance is the most likely reason why there is increased mortality in Africa (2).

Sequel to the non-usability status of CQ and SP due to treatment failure, it becomes necessary to find alternate drugs for treating malaria. Artemisinin class combination therapy readily comes up as the best option for treatment. A large meta-analyses of close to 6000 patients showed that combining existing antimalaria drugs with an artemisinin reduces patient's risk of treatment failure by 75% and reduces the pool of infectious parasites that transmit the disease. Between year 2000 and now, studies (9, 10, 11) have been conducted in virtually every continent of the world which showed that artesunate combination therapy successfully treated greater than 90% of patients, hence its recommendation by the WHO.

The present approach to malaria control has been the implementation of various strategies. The strategies can be broadly classified into improved case management and disease prevention. The improved case management is our major concern here.

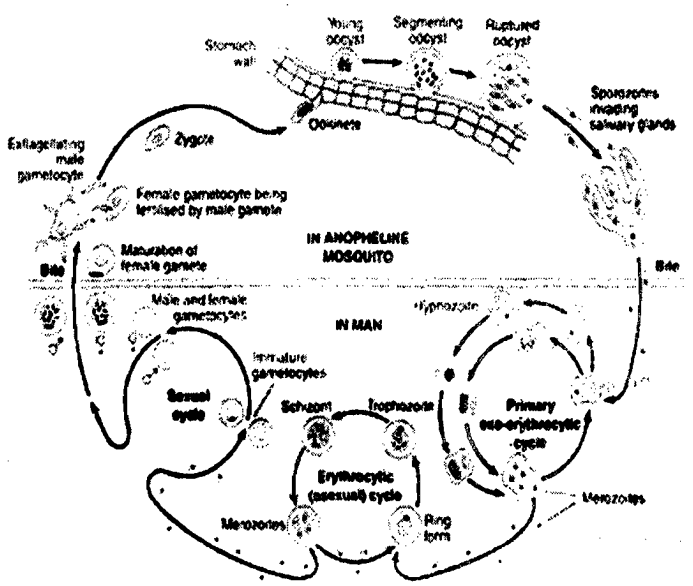


Diagram depicting the life cycle of human malaria ***(Asexual phase in human body and sexual phase in the mosquito)***

LIFE CYCLE OF MALARIA PARASITE

Asexual phase in the human host

Pre-erythrocytic (Tissue) schizogony

This phase starts with the inoculation of the parasite (sporozoites) into the human blood by the bite of a female anopheles mosquito. Some of these reach the liver within half an hour, and invade the liver cells. In the liver cells, the sporozoites multiply asexually (exoerythrocytic schizogony). Eventually, invaded liver cells rupture, releasing thousands of merozoites into the bloodstream.

The time taken for the completion of the tissue phase is variable, depending on the infecting species; (8 - 25 days for *P. falciparum*, 8 - 27 days for *P. vivax*, 9 - 17 days for *P. ovale*, 15 - 30 days for *P. malariae*) and this interval is called pre-patent period. In case of *P. vivax* and *P. ovale*, some sporozoites may go into hibernation, the cryptobiotic or dormant phase, in which they are called as hypnozoites. They can lie dormant for months or years and on reactivation cause clinical relapse.

Erythrocytic schizogony

The merozoites released from the liver cells attach onto the red blood cell (RBC) membrane and by a process of invagination, enter the red cell. Within the RBC, the asexual division starts and the parasites develop into trophozoites. After a period of growth (ring forms, early and late schizont), the trophozoites divide and develop, eventually forming between 8-24 merozoites. The merozoites then invade fresh erythrocytes and another generation of parasites develops in the same manner. This process occurs repeatedly during the course of infection and is called erythrocytic schizogony.

The intra erythrocytic cycle takes about 48 hours in *P. falciparum*, *P. vivax*, and *P. ovale* infections and 72 hours in case of *P. malariae* infection. It occurs synchronously and the merozoites are released at approximately the same time of the day. The contents of the infected cell that are released with the lysis of the RBC stimulate the release of tumor necrosis factor (TNF) and other cytokines, which results in the characteristic clinical manifestations of the disease. A small proportion of the merozoites undergo transformation into gametocytes - male and female. Mature gametocytes appear in the peripheral blood after a variable period and enter the mosquito when it bites an infected individual.

Sexual phase in the mosquito (*Sporogony*)

The male and female gametes fuse and form into a zygote. This transforms into an ookinete which penetrates the gut wall and becomes an oocyst. The oocyst divides asexually into numerous sporozoites which reach the salivary gland of the mosquito. On biting a man, these sporozoites are inoculated into human blood stream. The sporogony in the mosquito takes about 10 - 20 days and thereafter the mosquito remains infective for 1 - 2 months.

CLINICAL PRESENTATION OF MALARIA

Uncomplicated or simple malaria

This is malaria that has no life threatening manifestations. It presents as fever, rigors, vomiting, malaise, diarrhoea and generalized weakness or other non-life threatening manifestations.

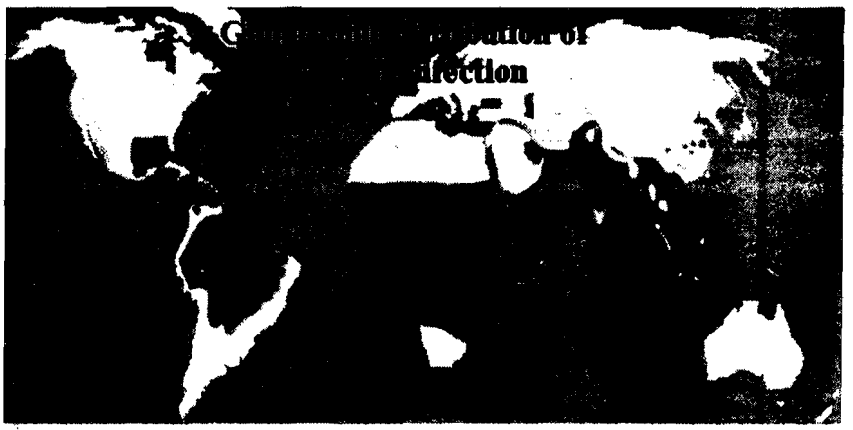
Complicated or severe malaria

This is defined by the demonstration of asexual forms of *P. falciparum* in a patient with a potentially fatal manifestation: clinical or laboratory features, as depicted below (12).

Severe manifestations of *P. falciparum* in children

- Prostration *(i.e. generalized weakness or inability to sit, stand or walk without support)*
- Impaired consciousness *(confusion or drowsiness or coma)*
- Respiratory distress *(difficulty in breathing, fast deep breath)*
- Multiple convulsions *(>2 generalized seizures in 24 hrs with regaining of consciousness)*
- Severe anaemia *(Hb <5 gm/dl)*
- Circulatory collapse *(shock)*
- Pulmonary oedema *(respiratory distress / radiology)*
- Abnormal bleeding *(disseminated intravascular coagulopathy)*
- Jaundice *(yellow discoloration of the eyes)*
- Haemoglobinuria *(Coca-Cola coloured urine)*
- Hyperparasitaemia *Density of asexual forms of P. falciparum in the peripheral smear exceeding 5% of erythrocytes (more than 250,000 parasites per µl at normal red cell counts)*
- Hyperpyrexia *(Rectal temperature above 40°C)*
- Hypoglycaemia *(Blood glucose <2.2mmol/l)*

Figure 1: Showing the global distribution of Malaria



GOALS OF MALARIA MANAGEMENT

There are malaria management expectations at various levels of health care based on the available facilities and staff capabilities.

Level I include all dispensaries and health posts. The cadre of staff at this level includes junior community health extension workers and village health workers and a syndromic approach focusing on disease identification, initiation of appropriate treatment and urgent referral of severe malaria is expected.

Level II include health centres with or without laboratory facilities and most private hospitals without intensive care with staff including medical officers, general practitioners, nurses and community health officers for in-patient care. Basic laboratory support for confirming diagnosis and monitoring of patients is expected at this level.

Level III include teaching, specialist, general hospitals and some private hospitals with specialist physician and highly skilled senior physician. In addition to quality total care, it is expected to provide intensive care for severe disease.

COMMON ANTIMALARIA DRUGS

Antimalarial drugs include several chemical groups (13) and the following gives a brief summary of common anti-malarial drugs.

Quinine

Quinine has been used for more than three centuries and was the only effective medication until the mid 1930's. It is one of the four main alkaloids found in the bark of the Cinchona tree and is the only drug which over a long period of time has remained largely effective for treating the disease. It is now only used for treating multidrug resistant and severe falciparum malaria partly because of undesirable side effects.

Chloroquine

This was one time a very effective 4-amino-quinoline both for malaria treatment and prophylaxis. It was first used in the 1940s shortly after the Second World War and was effective in curing all forms of malaria, with few side effects when taken in the dose prescribed and it was relatively cheap.

Unfortunately, most strains of falciparum malaria are now resistant to chloroquine and more recently, chloroquine resistant vivax malaria has also been reported. Presently it is not useful as antimalarial in most country of the world. The few countries that were still using it have recently discontinued its use.

Proguanil

This is a biguanide antimalarial first synthesized in 1946. It has a biguanide chain attached at one end to a chlorophenyl ring and is very close in structure to pyrimethamine. It is a folate antagonist that destroys the malarial parasite by binding to the enzyme dihydrofolate reductase in much the same way as pyrimethamine. It is still used as a prophylactic in some countries especially in Africa.

Malarone

Malarone is a combination of proguanil and atovaquone released in 1998. Atovaquone became available 1992 and was successfully used for the treatment of *Pneumocystis carinii*. When combined with proguanil, there is a synergistic effect and the combination is at the present time a very effective antimalarial drug. The drug combination

has undergone several large clinical trials and has been found to be 95% effective in otherwise drug resistant falciparum malaria. It has been claimed to be largely free from undesirable side effects but it should be noted that proguanil is an antifolate. At present it is a very expensive drug.

Maloprim

This is a combination of dapsone and pyrimethamine. Resistance to this drug is now widespread and its use is no longer recommended.

Lapdab

This is combination of dapsone and chlorproguanil. Its use has been reduced due to the serious complications of severe haemolysis and anaemia requiring transfusion.

Fansidar

This is a combination drug containing sulphadoxine and pyrimethamine in ratio 20:1 in each tablet. It acts by interfering with folate metabolism. Resistance to Fansidar is now widespread and clinical confidence now dropping.

Mefloquine (Lariam)

First introduced in 1971, this quinoline methanol derivative is related structurally to quinine. The compound was effective against malaria resistant to other forms of treatment when first introduced and because of its long half life was a good prophylactic, but widespread resistance has now developed and this together with undesirable side effects have resulted in a decline in its use. It is not widely approved for use in many African countries.

Halofantrin (Halfan)

This belongs to a class of compound called the phenanthrene-methanols. It is an effective antimalarial introduced in the 1980s, but due to its short half life of 1 to 2 days, is therefore not suitable for use as a prophylactic.

Unfortunately, resistant forms are increasingly being reported and there is some concern about side effects. Halofantrin has been associated with neuropsychiatric disturbances and arrythmias. It is contraindicated during pregnancy and is not advised in women who are breastfeeding. Abdominal pain, diarrhoea, pruritus and skin rash have also been reported. Its use is now restricted in some quarters.

Coartem

This is a combination of Lumefantrin and Artemether. It has proven very effective. However anecdotal experiences are showing early parasitaemic recrudescence.

Artemisinins

This is derived from a Chinese herbal remedy and covers a group of products. The two most widely used are artesunate and artemether. While they are widely used in Southeast Asia, they are not licensed in most of the Western World including Australia. It is a well tolerated drug with little or no side effects.

However due to some treatment failures, it is being combined with several other antimalaria drug for the treatment of falciparum malaria. It has become the base drug for which WHO wants others to be combined for use in the presence of widespread resistant strains of *Plasmodium falciparum* infection.

ANTIMALARIA TREATMENT POLICY (ATP)

Antimalaria Treatment Policy (ATP) is a set of recommendations and regulations concerning availability and rational use of antimalarial drugs in a country. It provides evidence based recommendations and gives clear guidelines for providing

early diagnosis and prompt treatment appropriate to the local context.

The aims or purpose

1. To provide rapid and long lasting clinical cure for individual malaria patients.

2. To prevent the progression of uncomplicated malaria to severe disease and death.

3. To shorten clinical episodes of malaria and reduce the occurrence of malaria related anaemia in the population in Endemic areas.

4. To reduce the unfavourable effects of malaria in pregnancy through chemoprophylaxis or preventive intermittent therapy.

5. To minimize the likelihood and rate of development of drug resistance.

What should be the contents of ATP?

A well written ATP will usually contain information relating to decision on whether a sick patient requires antimalarial treatment or not and the following must be well spelt out;

1. The first and second line antimalarial drugs with their indications and age appropriate dosages for treatment of both uncomplicated and severe malaria.

2. Chemoprophylaxis for various at-risk groups such as children, pregnant women and non-immuned individuals.

3. Distribution and drug delivery.

4. The criteria for changing treatment choice.

How is a National ATP made?

Information available on malaria parasite drug resistance, the current drugs and their roles in malaria management are considered. Using the criteria below the antimalaria drugs are then selected.

1 Efficacy and proven effectiveness against prevalent malaria species
2. Safety profile of drug
3. Simplicity of dosage and route of administration
4. Registered in the country of use
5. Cost

The process of changing ATP policy (14)

The key evidence for the need to change treatment policy is usually

1. The failing therapeutic efficacy of the antimalarial drugs in use assessed by standard WHO protocols.
2. Consumer and provider dissatisfaction with the failing medicines
3. Reports of increasing malarial morbidity and mortality.

Treatment Policy Antimalaria classification

First line drugs are drugs of primary intention for treatment of uncomplicated malaria for example chloroquine. Second line drugs are used when there is clinical failure or intolerance to first line example Fansidar.

Combination therapy, the present focus of discussion, is used for a more efficient case management. Example is Coartem. Adjuvant drugs are those that have antimalaria activities but are not used solely or alone for the treatment of malaria.

Combination therapy (CT)

Principle

The principle was derived from the treatment of tuberculosis, leprosy and bacterial infections where drugs are combined for synergism and reduction in the risk of resistance development

Definition of CT

CT simultaneously uses two or more blood schizonticidal drugs with

independent mode of action and different biochemical targets in the parasite. Multi-drug therapies that include the use of a non-antimalarial drug to enhance the antimalarial effect of blood schizonticidal drug are not included. Also fixed dose combination drugs are operationally considered as single drugs example SP.

Classification

a. Artemisinin based combinations

1. Artesunate+ amodiaquine
2. Artesunate + mefloquine for areas with low transmission
3. Co-artemether (Artemether 20mg + Lumefantrine 120mg/tablets
4. SP + Artemether or Artesunate

b. SP based combinations

1. SP + CQ as separate tablets
2. SP + Amodiaquine as separate tablets
3. SP + Quinine as separate tablets
4. SP + Mefloquine

c. Non-artemisinin/SP based combinations

This combines all other different antimalaria drugs other than Artemisinin or SP. Not necessarily combined in formulation but in drug administration example

1. Quinine + Tetracycline
2. Atovaquone+ Proguanil (Malarone)
3. Dapsone + Pyrimethamine (Use has been discontinued)
4. Dapsone + Chlorproguanil (Haemolysis is a major side effect).

The current WHO recommended treatment policy include all the Artemisinin combination therapies and the combination of Amodiaquine plus Sulfadoxine/Pyrimethamine especially for areas where efficacy of both drugs remain high and mainly in West Africa.

As at March 2004, 32 countries have adopted one of these WHO combination therapies. About 14 countries in Africa have adopted the Artemisinin as either first line or second line. As at now Kenya, Ghana, Equatorial Guinea, Cameroon, Sao Tome and Principe, Comoros, Gabon, Burundi, Zambia, Zanzibar and South Africa moved from using Chloroquine/SP to using Artemisinin. Also, Rwanda, Mozambique and Senegal moved from Chloroquine alone to Amodiaquine/SP. However, Ethiopia, Uganda, Eritrea and Zimbabwe moved from using Chloroquine alone to Chloroquine/SP. Democratic Republic of Congo and Cote d'Ivoire change from using Chloroquine to SP/ Amodiaquine (14). Several changes are taking place in Nigeria and several combinations are been used in different places but still awaiting official policy changes.

CONCLUSION

The effectiveness of the combination therapy has been proven in many countries of the world. These countries wasted no time in making needed changes in their national anti-malarial policies after following standard WHO protocol. The rate at which malaria parasites are becoming resistant to many drugs with increasing treatment failure and increasing case fatality, therapeutic paradigm shift from monotherapy to combination therapy is likely going to become a bride to be embraced by many more countries in the very near future. It is hoped that this will help reduce mortality to the minimum as we anticipate the discovery of effective vaccine for malaria in the near future.

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