Emerging Drug – Resistance and Guidelines for Treatment of Malaria

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The increasing prevalence of multi-resistant Plasmodium falciparum malaria worldwide is a serious public health threat to the global control of malaria, especially in poor countries like Pakistan. In many countries choloroquine-resistance is a huge problem, accounting for more than 90% of malaria cases. In Pakistan, resistance to choloroquine is on the rise and reported in up to 16-62% of Plasmodium falciparum. Four to 25% of Plasmodium falciparum is also reported to be resistant to sulfadoxine-pyrimethamine and several cases of delayed parasite clearance have been observed in patients with Plasmodium falciparum malaria treated with quinine. In this article we have introduced the concept of Artemisinin-based Combination Therapy (ACT) and emphasize the use of empiric combination therapy for all patients with Plasmodium falciparum malaria to prevent development of drug resistance and to obtain additive and synergistic killing of parasite.

Key words: Malaria, drug resistance, artemisinin-based combination therapy, guidelines, Pakistan

INTRODUCTION

More than 2 billion people around the world are at-risk for malaria infection. The estimated annual global incidence of malaria is 300 to 500 million clinical cases, and about 20 million deaths occur worldwide each year.[1] Malaria is hyperendemic in Pakistan, with the majority of infections caused by Plasmodium vivax, although infections with P. falciparum are increasing and account for about 35%–40% of cases. While a number of economic, political, behavioral, and biological obstacles exist, the development of drug resistance is one of the major threats to the global control of malaria. The increasing prevalence of multidrug-resistant P. falciparum malaria worldwide has serious public health implications for poor countries like Pakistan.[2,3] In most of sub-Saharan Africa and Asia chloroquine-resistance is a huge problem, accounting for more than 90% of malaria cases in parts of West Africa and Southeast Asia, including Thailand.[4,5] Resistance to quinine is also emerging.[6]

In Pakistan, the estimated in vitro resistance of P. falciparum to one or more antimalarial drugs is about 40%. In some regions, chloroquine resistance to P. falciparum ranges from 18% to 62% and resistance rates to sulfadoxine-pyrimethamine of 4% to 25% have been documented.[7,8] In addition, several cases of delayed parasite clearance have been observed in patients with falciparum malaria treated with quinine. Among P. vivax, resistance to chloroquine has also been observed but is not presently a major problem. Worldwide, because of this increasing emergence of multidrug resistance among Plasmodium species, current emphasis is on the use of combination antimalarial drug therapy, especially for P. falciparum malaria.[9,10,11]

The aims of combination treatment are twofold: to afford synergistic or additive killing of malaria parasites, and to prevent emergence of drug resistance. Combination drug therapy for malaria is now recommended as first-line treatment in several countries including Thailand, Cambodia, China, Vietnam, South Africa, Malawi, Kenya, and parts of Peru.[12] Artemisinin-based Combination Therapy, or ACT, is most promising in reducing malarial drug resistance, disease transmission and mortality.[13,14,15,16] However, in most parts of the world, combination antimalarial treatment is still not the standard of care and the lack of economical and available new alternative medications is preventing the expanded use of combination treatment. Continued reliance on monotherapy threatens to broaden the malaria pandemic and limit future treatment options against the disease.

The purpose of the treatment guidelines presented here is to assist physicians in standardizing the treatment of patients with malaria, by optimizing individual patient care through more effective use of combinations of antimalarial agents that can help slow the progression of emerging drug resistance and thereby improve public health.

DIAGNOSIS

The gold standard for malaria diagnosis remains the peripheral blood film. Limitations of this technique relate to reader error and lack of proper equipment and to the absence of P. falciparum from the peripheral blood for a portion of its life cycle. In addition, symptomatic parasitemias are sometimes below the limits of microscopic detection.

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For the diagnosis of malaria, a thick blood film is superior to a thin film because it concentrates red blood cells 20- to 40 fold. In contrast, species-specific parasite identification may be difficult using thick films and is more easily accomplished using thin films. Symptoms may precede detectable parasitemia by 1 to 2 days, and serial peripheral blood smears may be necessary in order to identify malaria parasites.[1] Obtaining daily blood films is much more important than the timing of smears with respect to fever spikes.

Rapid immunochromatography-based antigen detection of P. falciparum and P. vivax is available in Pakistan. These rapid antigen detection kits are currently feasible in various field settings and have sensitivities and specificities that range from 75% to 95%.[17,18] Polymerase Chain Reaction (PCR)-based assays that use species-specific primers have also been developed and while technique is highly sensitive and specific it is expensive, not readily available and less useful for individual case detection than antigen detection.

COMPLICATIONS OF MALARIA

The degree and severity of various complications of malaria depend upon multiple factors including the species of Plasmodium, degree of parasitemia, and immune status of the patient (Table 1). Although infections with P. vivax, P. ovale, and P. malariae are very rarely fatal, infection caused by P. falciparum may progress rapidly to lethal multi-system disease.[19,20,21,22,23] P. falciparum is the only malaria species associated with parasitemia above 5% and can reach 75% or more with overwhelming infection. Most life-threatening complications of malaria occur in non-immune patients with falciparum malaria.[19,20]

Table 1: Major complications of malaria

- Severe anemia
- Hypotension
- Hypoglycemia
- Acute tubular necrosis (including 'Blackwater fever')
- Cerebral malaria*
- Algid malaria
- Bacterial infections
- Non-cardiogenic pulmonary edema+
- Disseminated intravascular coagulation
- Immune complex glomerulonephritis
- Nephrotic syndrome°
- Premature labour, abortion, low birth weight, congenital malaria

* *Due to P. falciparum > P. Vivax*
\+ *Acute Respiratory Distress Syndrome (ARDS)*
o *Especially due to P. malariae*

Table 2: Poor prognostic features in severe malaria

Clinical features:
- Impaired consciousness*
- Repeated convulsions (>3 in 24 hours)
- Respiratory distress (rapid, deep, labored, stertorous breathing)
- Substantial bleeding
- Shock

Laboratory features:
- Renal impairment (serum creatinine >3 mg/dL)+
- Metabolic acidosis (plasma bicarbonate <15 mmol/L)
- Jaundice (serum bilirubin >2.5 mg/dL)+
- Hyperlactatemia (venous lactate >45 mg/dL)
- Hypoglycemia (blood glucose <40 mg/dL)
- Elevated aminotransferase levels (>3 times normal)
- Parasitemia >500,000 parasites/mm^3 or >10,000 mature trophozoites and schizonts/mm^3
- >5% of neutrophils containing malaria pigment

* *The deeper the coma the worse the prognosis*
\+ *The combination of deep jaundice and renal failure is particularly grave*
3 *Trophozoites are mature parasites in which pigments is visible under light microscopy*

GENERAL TREATMENT PRINCIPLES

Antimalarial treatment should be started orally unless the patient has vomiting or altered consciousness. Combination therapy should be empirically used for all patients with malaria (especially those requiring hospitalization), except for documented infection due to P. vivax, P. ovale, or P. malariae (Figure 1).

For uncomplicated cases, the goal of combination therapy is largely to prevent recrudescence and transmission by decreasing the development of drug resistance; for severe or complicated cases, the intended benefit of combination treatment is additive or synergistic killing of parasites. Patients should be hospitalized if they are seriously ill, unable to take oral medications or non-immune to malaria (especially those from non-endemic areas) (Table 2). Supportive measures in the management of complicated malaria are important and include administration of IV fluids, oxygen, blood transfusions, exchange transfusion (if parasitemia > 15%), diuretics, and dialysis.

Some of the newer and commonly used antimalarial agents are reviewed below:

Artemisinins

Artemisinins are the most-recently marketed antimalarial medicine and are derivatives of the qinghaosu plant (Artemisia annua) that have been used as a herbal remedy for fever in China for more than 2000 years.

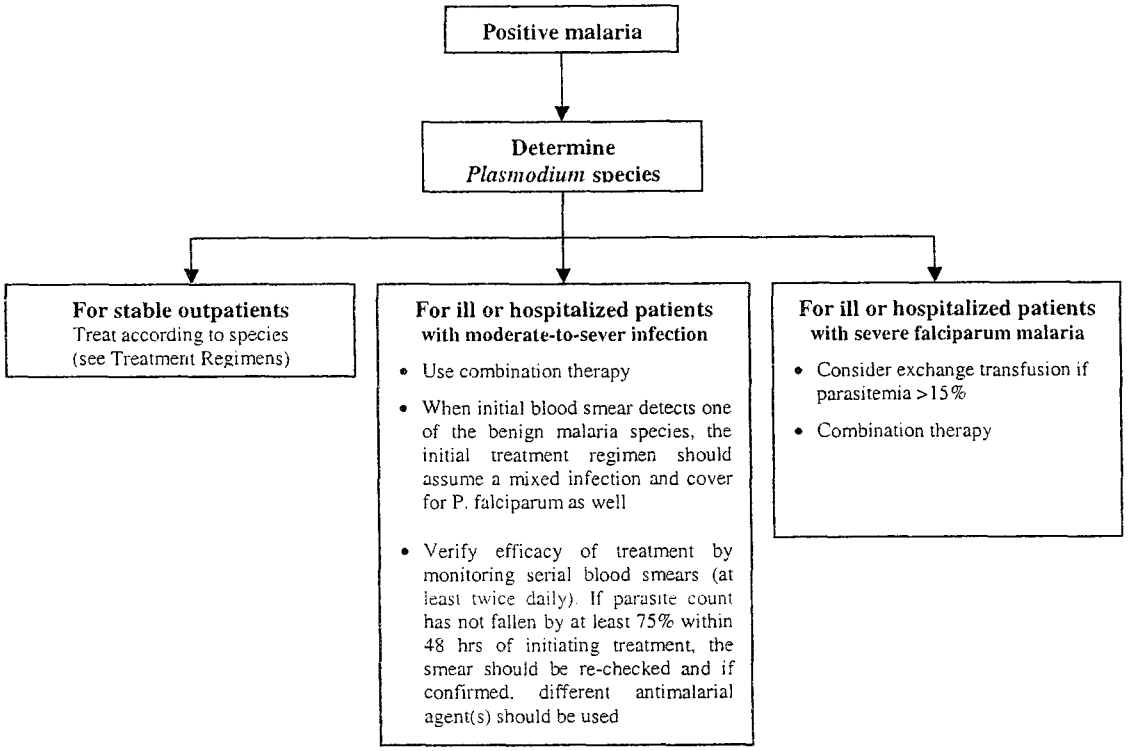


Figure 1: Simplified malaria treatment algorithm

Artesunate and artemether are the main derivatives and they are pro-agents that are metabolized to the active compound dihydroartemisinin artesunate. Artesunate is unstable in solution and is therefore, dispensed as a powder and given parenterally mixed with 5% sodium bicarbonate solution and further diluted with normal saline or 5% dextrose water, as either intravenous or intramuscular injections. Artemether is more stable than artesunate, is formulated in peanut oil and is administered intramuscularly. Artesunate is available orally, per rectum, intrvascular and intravenous formulations and is absorbed rapidly from the gastrointestinal tract. Rectal suppositories of artemisinins have proven as effective as parenteral medicines.[24,25]

Artemisinins have the shortest half-life and provide the most rapid clearance of Plasmodia parasitemia of all antimalarial agents. Artemisinins have a broader 'window period' of effectiveness than other antimalarial agents during the 48-hr asexual cycle of the parasite. Antiparasitic effect on younger ring-form parasites leads to their clearance and prevents development to the more mature pathogenic forms that induce parasitized erythrocytes to adhere to uninfected cells (rosetting) or to vascular endothelium (cytoadherence). Parasitic clearance times (from blood) are consistently more rapid in patients treated with artemisinin drugs than in patients treated with other antimalarials.[26,27,28]

Artemisinins are extremely useful in settings where P. falciparum has developed multidrug resistance, but artemisinin-based combination therapy is now widely recommended to prevent the development of drug resistance.[13,14,15,16] These compounds reach concentrations in P. falciparum-infected erythrocytes 100 to 300 times higher than in uninfected erythrocytes.[29] Their pharmacokinetic and pharmacodynamic properties make them especially useful components of combination treatment. In vitro studies and large clinical field trials support their use with a number of other antimalarials including quinine, mefloquine, lumefantrine, sulfadoxine-pyrimethamine, amodiaquine, and chloroquine. Because of their short half-lives, recrudescence of infection and development of drug resistance may be more common when these drugs are used alone for

treatment periods <7 days. Mefloquine is an excellent drug to use with an artemisinin derivative because of its longer half-life and more sustained antimalarial effect.

Co-artemether is a new fixed-dose combination of artemether and lumefantrine in an oral formulation (1 tablet = 20 mg artemether plus 120 mg of lumefantrine). The drug is well-tolerated, safe in children and adults and highly efficacious in patients with acute, uncomplicated malaria. Artemether produces a rapid reduction of parasites during the initial stages of treatment and lumefantrine has a slower onset of action and prevents recrudescence of parasitemia. The frequencies of QT interval prolongation are similar to or lower than that observed with chloroquine, mefloquine or artesunate plus mefloquine and considerably lower than that seen with quinine or halofantrine.[30] In controlled trials, patients with QT prolongation (7%) receiving co-artemether remained asymptomatic and had no clinically-relevant adverse cardiac events.[30,31,32]

In comparative studies of patients with severe P. falciparum malaria, artemether appears to be a well-tolerated and acceptable alternative to quinine in severe infection and is possibly more effective than IV quinine for severe malaria, including cerebral forms of the disease.[7,33] A meta-analysis of nine trials demonstrated no significant difference between artemether and quinine in terms of mortality rate. Survival was 85.4% for patients treated with artemether compared to 82.4% for patients receiving quinine. Clinical trials in adult patients conducted in sub-Saharan Africa suggest insignificant differences in survival between artemether and quinine, and corroborate the results of an earlier meta-analysis of African children with cerebral malaria.[7,8]

Artemisinin compounds act rapidly against drug resistant P. falciparum but have high recrudescence rates (about 10%–50%) when used as monotherapy for durations of less than seven days.[12] Recent studies have examined a seven-day course of therapy and combinations of qinghaosu derivatives or mefloquine in order to prevent recrudescence.[12,34] In vitro synergy has been demonstrated between artemisinin derivatives, mefloquine, amodiaquine and tetracycline.[35] In Thailand, treatment with oral artesunate for 3–5 days combined with mefloquine (15–25 mg/kg) was more effective than mefloquine or artesunate alone.[12] Combination therapy results in cure rates >90% for primary and recrudescent P. falciparum infections.[12,15,16] Artesunate combined with sulfadoxine-pyrimethamine resulted in more rapid defervescence and parasite clearance, a reduced risk of treatment failure and lower gametocyte carriage compared to monotherapy.[11] All artemisinin preparations are recommended for malaria treatment only and not for prophylaxis.

In conclusion, artemisinins are as, and possibly more effective than quinine in the treatment of severe malaria. Furthermore, these compounds are relatively safe and offer the advantage of lower rates of resistance than quinine. Artemisinin-based combination therapies are the best options for combating drug resistance.

Quinine and Quinidine

Cinchona compounds such as quinine and quinidine have been the mainstay of malaria management for many years. Treatment with oral quinine is not well tolerated. The drug is extremely bitter and often induces cinchonism (i.e., nausea, dysphoria, tinnitus, and high-tone deafness). The combination of quinine plus tetracycline or doxycycline remains more than 85% effective for resistant P. falciparum infection, although compliance with a standard seven-day course of therapy is poor. The combination of quinine plus clindamycin can be safely used in pregnancy, and is extremely efficacious in uncomplicated P. falciparum malaria.[36,37,38]

When quinine was used in conjunction with clindamycin or tetracycline for multidrug-resistant falciparum malaria, the fever clearance time for both of these combination regimens was significantly shorter compared to quinine monotherapy.[37] However, the parasite clearance times were not significantly different compared to quinine-only treatment. The cure rates assessed at 28 days of follow-up were 100% for the combination therapy groups, vs. 87% for quinine alone ($p < 0.04$). Clindamycin plus quinine is a safe and effective treatment for multi-drug resistant P. falciparum malaria. This combination may be of particular value in children and pregnant women in whom tetracycline is contraindicated.[37]

In some areas, clinicians have combined parenteral artesunate and quinine in the belief that the two agents would have additive or synergistic parasite killing in severe malaria. It appears, however, that there is no significant benefit in combining these parenteral agents in the acute phase of malaria treatment.[38]

Halofantrine

Halofantrine (also known as benflumetol) is more active and better tolerated than mefloquine, but its oral bioavailability is poor and variable (although it is increased by consumption of fat). The drug induces a concentration-dependent delay in AV conduction and ventricular re-polarization and therefore, should not be given to patients with cardiac diseases as it is likely to cause QT prolongation. Neither halofantrine

nor mefloquine should be used to treat early recrudescence (within 28 days of treatment) of malaria after primary treatment because their respective cardiac and CNS effects are increased. In a randomized clinical trial conducted on the Thai-Burmese border, a higher dose of oral halofantrine (8 mg/kg every 8 hrs x 3 doses) was more effective and better tolerated than oral mefloquine 25 mg/kg. Failure rates were 3% and 8%, respectively ($p < 0.03$). The rate of failure was higher after re-treatment (44% with mefloquine vs. 15% with high-dose halofantrine) than after primary treatment.[32,39]

Sulfadoxine-Pyrimethamine (Fansidar)

The fixed-dose combination of sulfadoxine-pyrimethamine is recommended for use in chloroquine-resistant areas where P. falciparum is not yet resistant to this two-drug regimen. Surveys of drug-resistant P. falciparum conducted in several Afghan refugee settlements in Pakistan in 1994-95 found resistance to chloroquine and sulfadoxine-pyrimethamine in every settlement.[7] The frequency of chloroquine resistance ranged from 18%– 62% and but occurred at much lower frequencies for sulfadoxine-pyrimethamine, ranging from 4%-25%.[7]

Mefloquine-Sulfadoxine-Pyrimethamine

A fixed-dose triple combination of mefloquine-sulfadoxine-pyrimethamine is available in Pakistan. As for others combinations, the rationale for this formulation is to prevent the development of drug-resistant parasites. Unfortunately resistance to each of the three drug components has been reported.[40]

RECOMMENDED TREATMENT REGIMENS FOR MALARIA

In many parts of the world, the selection of first-line treatment for uncomplicated malaria is extremely difficult because of increasing drug resistance of P. falciparum and, in some areas, P. vivax. At present, chloroquine is still the preferred first-line treatment for malaria caused by any sensitive plasmodium species. In areas with chloroquine–sensitive Plasmodium infection chloroquine phosphate is administered orally as a 1 gram (600 mg base) dose, followed by 500 mg (300 mg base) at 6, 24, and 48 hours. the pediatric dose is 10 mg base/kg, followed by 5 mg base/kg at same intervals as in adults.

Tables 3 and 4 provide some treatment guidelines, employing drugs available in Pakistan, which can be used for the management of uncomplicated and complicated cases of documented or suspected chloroquine-resistant malaria. A combination approach is suggested for both oral and parenteral regimens.

Table 3: Oral treatment for chloroquine-resistant P. falciparum and P. vivax infection*

Drugs of choice:

Quinine sulfate 600 mg tid x 3-7d (*10 mg/kg tid x 3-7d*)

plus

Sulfadoxine-pyrimethamine+ 3 tablets at once on last day of quinine (*1/2 to 1 tablet once*)

or

Clindamycin 900 mg tid x 5d (*20-40 mg/kg/d in 3 doses x 5d*)

or

Doxycycline 100 mg bid x 7d (*2 mg/kg/d x 7d in children aged > 8 yrs*)

Alternatives regimens for chloroquine- resistant parasites:

Mefloquine-sulfadoxine-pyrimethamine@ (250/500/25 mg): 3 tablets as a single dose (>60 kg); 2 tablets as a single dose (<60 kg) (*1/2 to 2 tablets according to age*)

or

Artemether-lumefantrine° 4 tablets at 0,8,24 and 48 hrs (total 4 doses) (*5 to <15kg - one tablet; 15 to <25 kg - two tablets; 25 to <35 kg - three tablets ≥ 35 kg - four tablets*)

Amodiaquine 25-35 mg/kg base over 2 days (600 mg base stat followed by 300 mg base at 6, 24, and 48 hrs)

plus

Sulfadoxine-pyrimethamine+ 3 tablets once on the last day of amodiaquine

or

Clindamycin 900 mg tid x 5d (*20-40 mg/kg/d in 3 doses x 5d*)

or

Doxycycline 100 mg bid x 7d (*2 mg/kg/d x 7d in children > 8 years old - maximum 100 mg total daily dose*)

Halofantrine 500 mg q6 hours x 3 doses (repeat in 1 wk) (*8 mg/kg q6h x 3 doses; repeat in 1 wk*)

* *Pediatric dosages in parentheses and italics.*
\+ *Risk of serious or fatal Stevens-Johnson syndrome.*
o No QT prolongation with lumefantrine.
@ *Plain Mefloquin tablets are not available in Pakistan.*

For patients with features of moderate-to-severe malaria and whose blood smear detects one of the benign malaria species, the initial treatment regimen should assume a mixed infection and cover for P. falciparum as well.

Clinical and parasitological criteria are used to classify the response to treatment as adequate clinical response, early treatment failure (from days 1 to 3), or late treatment failure (from days 4 to 14).

Table 4: Recommended parenteral anti-malarial treatment for hospitalized patients*
Drugs of choice:
Quinine dihydrochloride 20 mg/kg IV infusion over 4 hours, followed by 10 mg/kg over 2-4 hrs q8h (max. 1,800 mg/day) until oral therapy can be started (*same as adult dose*)
plus
Doxycycline 100 mg q12h
or
Clindamycin 900 mg q8h (*20-40 mg/kg/d*)
Alternative regimens:
Artemether 3.2 mg/kg IM, then 1.6 mg/kg/d or 160 mg loading dose, then 80 mg daily x 4-6d (note: maximum total dose 600-700 mg over 3-7 days) (*same as adult dose*)
plus
Doxycycline 100 mg q12h+
or
Clindamycin 900 mg q8h (*20-40 mg/kg/d*)
* *Pediatric dosages in parentheses and italics*
+ *Not recommended in pediatrics*
Note: Parenteral quinidine gluconate is not available in Pakistan

It has been suggested by the World Health Organization (WHO) that national malaria treatment guidelines be revised when treatment fails in 25% of cases (counting both early and late treatment failures).[41] Chloroquine resistance should be assumed in every patient with complicated malaria.

TREATMENT FOLLOW- UP

Follow-up blood smears should be obtained to monitor the efficacy of antimalarial treatment regimens. For moderate-to-severe infections, repeat blood smears should be checked at least twice daily until documentation of parasite clearance. If the parasite count does not fall by at least 75% within 48 hours of starting therapy, a different antimalarial regimen should be prescribed. For prevention of malaria relapse caused by P. vivax and P. ovale, the treatment of choice is oral primaquine 26.3 mg (15 mg base) daily x 14 day, or 79 mg (45 mg base) weekly x 8 weeks (0.3 mg base/kg/d x 14 d). In view of the risk of drug-induced hemolytic anemia, all patients should be screened for glucose-6-phosphate dehydrogenase (G-6PD) deficiency prior to receiving primaquine.

CONCLUSION

In Pakistan, significant chloroquine resistance exists and quinine resistance appears to be emerging. Analogous to the cornerstone of treatment for tuberculosis and HIV/AIDS, combination therapy, especially artemisinin-based combination regimens, is routinely recommended in the management of malaria. Chloroquine may still be a reasonable empiric first choice for the treatment of uncomplicated malaria (proven or presumptive) where severe cost limitations exist. However, for patients with more severe malaria, especially those requiring hospitalization, or those with infection refractory to treatment, combination therapy is preferred.

NOTES ABOUT CONTRIBUTORS

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