Current Malaria Management: Guideline 2009

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ABSTRACT

Malaria is still a health problem in the world, particularly in Indonesia with high morbidity and mortality rate. Increased mortality rate due to malaria has been reported and it may occur because of the raising in anti-malarial resistance. Chloroquine-resistant P. vivax and P. falciparum have been reported in almost all over the country. Various dose administrations of anti-malarial treatment, instead of the standard dose and single dose treatment is probably one of possible causes. Another problem in Indonesia includes the shortage in diagnostic facilities as well as various kinds of treatment available.

In 2009, Ministry of Health, Republic of Indonesia has declared the program of Malaria Elimination 2009 to overcome the problems. The policy includes diagnosis and treatment of malaria. It is expected that diagnosis should be established based on the gold standard by confirmation of blood smears. Moreover, first line treatment of malaria shall include the Artemisinin Combination Therapy (ACT). Artemisinin is selected as it has some advantages and it should be combined to prevent resistance.

Principles of severe malaria management are preventing and minimizing the risk of death. Adequate treatment includes supportive and causal (anti-malarial) treatment as well as treating complication. Parenteral artemisinin is given for severe malaria and continued with oral combination of artemisinin treatment once the patient can take oral therapy.

Key words: malaria, malaria elimination 2009, artemisinin combination therapy, severe malaria.

INTRODUCTION

Malaria is still a major health problem in the world and it occurs in 107 countries. It is estimated that 500 millions of people are infected by malaria with mortality rate over 1,000,000 cases each year. In Indonesia, 424 of 576 municipalities/cities (73.6%) are endemic area; therefore, almost forty-five percent of Indonesia citizen are having risk for malaria infection. Malaria cases are concentrated in the outer islands such as Papua, Maluku, Nusa Tenggara, Sulawesi, Kalimantan and Sumatera. The endemic rate in Java and Bali is low and tend to decrease in the past five year period; however, there is possibility of increased number of cases or even become epidemic. In 2009, about 1,143,204 cases of positive malaria has been reported. The number might be smaller than the exact number since malaria cases mainly occurs in remote area which do not have any diagnostic facilities.

In 2009, the Ministry of Health of the Republic of Indonesia has declared the program of Malaria Elimination 2009 to overcome the problems. The policy of Malaria Elimination Program is an endeavor to gradually eradicate malaria in Indonesia, starting with liberating the Special Capital District (DKI) Jakarta, Bali, Barelang Binkar in 2010, liberating Java, Nangroe Aceh Darusalam (NAD), Kepri districts in 2015, liberating Sumatera, NTB, Kalimantan, Sulawesi districts in 2020, and liberating Papua, West Papua, NTT, Maluku, North Maluku in 2030.

The Program of Malaria Elimination 2009 has some specific aims. In 2010, it is expected that the number of villages with positive malaria of ≥5 per 1000 citizen (HCl) will decrease as much as fifty percent. All municipalities/cities shall also be able to conduct the blood smears confirmation for malaria as well as giving appropriate and affordable treatment.
Furthermore, in 2020, all districts in Indonesia shall be able to conduct intensification and integration in controlling malaria. The importance of conducting diagnostic test in keeping with the gold standard by using the blood smear (thick and thin) confirmation test or RDT (rapid diagnostic test) should be taken into concern. It is hoped that there will be no diagnosis which only based on clinical judgment.

In the past few years, increased mortality due to malaria has been reported, which is assumed as the result of the raising in anti-malarial resistance. Chloroquine- and sulfadoxine-pyrimethamine-resistant \( P. \text{vivax} \) and \( P. \text{falciparum} \) have been reported in almost all area in Indonesia. One of the possible causes may include using different anti-malarial doses, instead of the standard dose and single dose treatment. Therefore, the program of Malaria Elimination suggests the Artemisinin Combination Therapy (ACT) for every person with positive blood smears of plasmodium (falciparum, vivax, ovale or mixed infection) for 3 days. For severe malaria/complicated malaria, injection of Arthemeter or Arthesunate is recommended until the patient can take oral therapy (ACT tablet).

**ARTEMISININ COMBINATION THERAPY**

Various studies and recommendation by the Malaria Expert Commission or Komisi Ahli suggest that chloroquine-resistant \( P. \text{Falciparum} \) and \( P. \text{Vivax} \) has been observed. A question emerges, i.e. why we should use artemisinin combination therapy. One of the reasons that artemisinin has some advantages over other anti-malarial drugs. It is generally more effective and has wide specificity toward various stage of malarial parasites, including inhibit the production of gametocytes. Moreover, it needs no adjustment dose for patients with liver and kidney dysfunction and no drug interactions and side effects that clinically significant has been reported.

However, artemisinin has a very short life-time and therefore, when it is used as a single treatment, \( P. \text{Falciparum} \) will have a chance to grow and lead to parasite resistance. As a result, artemisinin treatment shall be combined with other anti-malarial drugs that have long life-time with different mechanism of action. Such combination has a very high effectiveness and may prevent the development of resistance.

ACT preparations which are available in Indonesia can be read on Table 1.

<table>
<thead>
<tr>
<th>Drugs Composition Preparations</th>
<th>Preparations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artemether + lumefantrine (Coartem®)</td>
<td>20 mg + 120 mg Fixed dose tablets</td>
</tr>
<tr>
<td>Artesunate + amodiaquine (Arsuamoon®)</td>
<td>25 mg + 67.5 mg Fixed dose tablets</td>
</tr>
<tr>
<td></td>
<td>50 mg + 135 mg</td>
</tr>
<tr>
<td></td>
<td>100 mg + 270 mg</td>
</tr>
<tr>
<td></td>
<td>50 mg + 150 mg (base)</td>
</tr>
<tr>
<td>Artesunate + mefloquine*</td>
<td>200 mg + 250 mg Co-blistered tablets</td>
</tr>
<tr>
<td>Dihydroartemisinin + piperaquine</td>
<td>40 mg + 320 mg Fixed dose tablets</td>
</tr>
<tr>
<td>Artesunate + sulfadoxine / pyrimethamine</td>
<td>50 mg + 500/25 mg Co-blistered tablets</td>
</tr>
</tbody>
</table>

* not available in Indonesia

**CURRENT MALARIA TREATMENT**

**Treatment of Uncomplicated Malaria**

Treatment of uncomplicated malaria treatment includes four infection cases, i.e.: vivax malaria, malariae malaria, mild-moderate falciparum malaria and or mixed infection of falciparum and vivax/ovale malaria.

a. Treatment of vivax or ovale malaria cases. The treatment of choice is ACT preparation single dose each day for 3 days and primaquine given at a dose of 0.25 mg/kgBW/day for 14 days (adult dose 1 tablet equal to 15 mg). There are some preparations of ACT which can be used and selected based on needs and availability. The first is combination of Artesunate (4 mg/kgBW, daily dose 3-4 tablets equal to 120-160 mg) and piperaquine (16-32 mg/kgBW, dose: 3-4 tablets equal to 960-1,280 mg base). Another ACT regimen is combination of dihydroartemisinin (2-4mg/kgBW, daily dose 3-4 tablets equal to 120-160 mg) and piperaquine (16-32 mg/kgBW, daily dose for adult: 4 tablets ~ 600 mg base). Other alternative malarial drug includes quinine at dose of 3 x 400-600mg/day for 7 days, added with primaquine at dose of 0.25mg/kgBW/ day for 14 days.

b. Treatment of malariae malaria cases. The main choice is one of ACT preparations single dose daily for 3 days. Different from the treatment of vivax/ovale malaria cases, the malariae malaria does not need primaquine. Furthermore, another alternative drug may include quinine at dose of 3 x 400-600mg/day for 7 days.

c. Treatment of mild-moderate falciparum malaria cases. The main choice is one of ACT preparations single dose daily for 3 days and single dose...
primaquine at dose of 0.75mg/kgBW. Adult dose for primaquine is 2-3 tablets (30-45 mg base), single dose. Another alternative drug includes quinine at dose of 3 x 400-600mg/day for 7 days and single dose primaquine at dose of 0.75mg/kgBW. Primaquine is intended to eradicate gametocytes in order to cut off the transmission chain rapidly.

d. Treatment of mixed falciparum and vivax/ovale malaria cases. The treatment is the same with vivax or ovale malaria cases.

**Treatment of Severe Malaria**

It has been known that severe malaria is caused by *P.falciparum*. However, recent data suggests that there is a new plasmodium species found in Kalimantan, i.e. *P.knowlesi* that may cause severe malaria. The microscopic appearance is similar to *P.malariae*, but it frequently manifests as severe malaria. In addition, there are some risk factors for severe malaria including under five years old age, pregnancy, immune-compromised patients, endemic inhabitants who have living the area for a long time and come back to the area, and tourist in hypoendemic area.4

The manifestations of severe malaria are highly varied depend on the involved vital organ. Generally, it includes the mild-moderate falciparum malaria case that did not receive adequate treatment. Diagnosis of severe malaria is made when one of clinical and laboratory findings is found, including muscle fatigue (without neurological disorder), impaired consciousness, acute respiratory distress syndrome, repeated convulsions, circulatory collapse, pulmonary edema (proven by radiograph), spontaneous bleeding, jaundice, hemoglobinuria, hyperpyrexia (adults 40°C, children >41°C), severe anemia (Hb <5 g/dl atau Ht <15), hypoglycemia, acidosis, renal dysfunction, hyperlactatemia, hyperparasitemia >5% in hypoendemic area (non-immune).4,11

Principles of severe malaria management are preventing and minimizing the risk of death. It can be achieved by performing early diagnosis as well as prompt and appropriate treatment. Adequate treatment includes supportive treatment, causal (anti-malarial) treatment and management of complications.11

Supportive treatment requires good intensive facilities. If ICU facilities are available, all severe malaria cases should be handled in intensive care unit to monitor vital signs, JVP, dieresis and the status of parasitemia. Moreover, fluid, acid-base and electrolyte balance as well as nutritional status should also be maintained. Chloroquine treatment is not applied anymore due to its high resistance rate. The main choice for severe malaria treatment is one of artemisinin preparations either parenteral or suppositories. It includes intramuscular artemether, intravenous artesunate or suppositories artemisinin. Dose regimens and instruction for parenteral artemisinin can be seen on Table 2. After the patient has been conscious, parenteral treatment can be stopped and treatment should be continued with combined oral anti-malaria drugs (ACT).

Another alternative for severe malaria treatment that may be used is intravenous quinine drip. Never give bolus injection of quinine since it has toxic characteristic to the heart. If the patient has been conscious and able to take oral therapy, the treatment shall be continued with oral quinine at dose of 10mg/kgBW for every 8 hours in combination with tetracycline/doxicycline/clindamycin. Quinine should be administered maximal for seven days, either given intravenously or orally. Dose and instruction for giving intravenous quinine can be seen on Table 2.

**Table 2. Dose regimen and instructions for using artemisinin and parenteral quinine in severe malaria treatment**

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Instructions</th>
<th>Doses</th>
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| Artemether intra muscular | Day I divided in 3 doses:  
- 0 Hour 2.4mg/kgBW  
- 12 Hour 2.4mg/kgBW  
- 24 Hour 2.4mg/kgBW  
Day II to VII 3.2mg/kgBW/12hr (2x 1.6mg/kgBW/12hr) | 1.6mg/kgBW/day |
| Artemisinin suppositories | Temporary use until definitive therapy received | 7.9-8.5 mg/kgBW/12hr |
| Artesunate intravenous | Loading dose  
Quinine HCl 25% infusion in 250-500 cc 5% Dextrose  
Maintenance, given in 4 or 8 hourly and repeated every 8 hours till day VII | 2.4mg/kgBW  
2.4mg/kgBW  
2.4mg/kgBW/day  
20mg/kgBW in the first 4 hours  
10mg/kgBW (500mg) |

**CONCLUSION**

Malaria is still a major health problem in Indonesia with increasing resistance rate on anti-malaria drugs. According to the program by Ministry of Health, Republic of Indonesia, diagnosis should be made based on the gold standard blood microscopic test (thin and thick). Management of malaria should include ACT which has high effectiveness to prevent resistance. Basically, the treatment should be performed fast and adequate to reduce the morbidity and mortality rate.
REFERENCES


