A successful therapy for severe malaria accompanied by malaria-related acute kidney injury (MAKI) complications: a case report

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Abstract. Indonesia is an endemic malaria country with high levels of morbidity and mortality. In Aceh, by the end of 2016, based on the data from Annual Parasite Incidence, the incidence rate was 0.1 per 1,000 population at risk of malaria. One of severe malaria complications is malaria-related acute kidney injury (MAKI). The death increases threefold by the presence of MAKI. A 56 years old male farmer was a resident in Buketmeuh village, Meukek, South Aceh, Indonesia, which was an endemic malaria area. He had fever for seven days, chills, sweating, joint pain, headache, nausea, vomit, yellow eyes and raved. Concentrated tea-colored urine during four days before hospital admission with a small amount of urine of 200 cc in 24 hours. The diagnosis established based on the Plasmodium vivax trophozoite finding in the blood smear examination, and the severe malaria clinical descriptions such as black water fever (BWF) with MAKI complications. Artemether injection therapy followed by oral primaquine, dihydroartemisinin and piperaquine phosphate (DHP) and hemodialysis provide a good outcome.

1. Introduction
Malaria is a parasitic infectious disease caused by protozoa of Plasmodium genus transmitted to humans through the bite of an infected female Anopheles mosquito that attacks the erythrocytes, characterized by an asexual form finding in blood. Malaria infection may be acute or chronic, without or followed by a systemic complication known as severe malaria. The severe malaria infection was more often caused by Plasmodium falciparum than Plasmodium vivax.¹,²,³ According to WHO’s latest estimate (September 2015), there were 214 million malaria cases in 2000-2015 with 439,000 deaths, malaria incidence decrease about 37% globally, during the same period, malaria mortality decrease about 60%. An estimated number of 6.2 million deaths from malaria since 2000. Among the most severe complications, MAKI was the cause of 45% deaths with an overall prevalence of 1-60%. Of MAKI total incidence, there were 1-4.8% patients living in endemic areas, and 25-30% patients were migrants.⁴,⁵,⁶,⁷ Malaria is a common cause of death in tropical countries. Cerebral malaria is the most deadly complication. Death has increased threefold with the presence of MAKI. This case was raised because of the high mortality and frequent delays in diagnosis.²
2. Case Presentation

A 56-year-old man, a farmer, living in Buketmeuh village, Meukek, South Aceh, Indonesia, an area that was still malaria-endemic. The patient with chief complaint high fever for seven days, and additional complaints of chills, sweating, joint pain, headache, nausea, vomiting, and yellow eyes. Urinating concentrated tea-colored urine during four days before hospital admission with a small amount of urine as much as 200 cc in 24 hours. The patient had treated for one day at Yulidin Away Tapaktuan Public Hospital with a positive blood smear examination for *Plasmodium vivax* trophozoites.

He was comatosus, blood pressure 120/70 mmHg, pulse 86 beats/minute (regular, sufficient volume, strong lift), breathing 20 times/minute, temperature 38.3°C, height 168 cm and weight 70 kg. Physical examinations found pale conjunctiva palpebral inferior, sclera icteric, liver was not palpable, and lien was palpable in Schuffner 1. On laboratory finding; Hemoglobin level 6.6 g/dL, hematocrit 18%, leukocytes 14800/mm³, platelet 125,000/mm³, and normocytic-normochromic peripheral blood morphology. Total bilirubin 20.27 mg/dL, direct bilirubin 17.33 mg/dL, SGOT 101 U/L, SGPT 38 U/L, albumin 2.98 g/dL, Glucose level 101 mg/dL, urea 330 mg/dL, creatinine 11 mg/dL, and the thin blood smear showed a finding of *Plasmodium vivax* trophozoites. The electrocardiography showed a sinus rhythm, thoracic photo examination in normal limit, the abdominal ultrasonography showed pleural effusion and cholecystitis with gallbladder sludge.

On the second day of admission, the patient had a small urine production of 400 cc/24 h and increased amount of urea and creatinine. The patient diagnosed with severe malaria with complications of MAKI, cholestaticis and anemia. Patient received IVFD NaCl 0.9% 20gtt/minute, intramuscular injection artemether 3.2 mg/kg body weight/24 hours (day 1), then followed intramuscular injection 1.6 mg/kg body weight/24 hours on day 2 to day 5, iv ceftriaxone 2 gr/ 24 hours, Paracetamol tablet 3x 500 mg, curcuma tablet 3x1, hemodialysis three times a week and patient also received a PRC transfusion 4 x 250 ccs. After arteremether therapy completed, then followed by oral therapy using primaquine 3 tablet (45 mg) /day for 14 days, DHP 3 tablets/day (each tablet contain dihydroartemisinin 40mg, piperazine phosphate 320mg) for three days. The patient had hemodialysis three times a week with the indication of increased urea and creatinine levels.

The patient’s treatment evaluation performed by a peripheral blood smear. The parasites found on the first and second day of treatment, then not found on the third day until the fifth day of treatment. The examination repeated on day 4, 7, 14, 21 and 28 after the treatment, no parasites were found on the examination. Hemodialysis stopped after normal urea and creatinine levels achieved, and sufficient dieresis obtained. Before hemodialysis, the levels of urea, creatinine, and urine were 330 mg/dL, 11 mg/dL and 200 cc/24 h, after six times hemodialysis the levels of urea, creatinine, and urine were respectively 44 mg/dL, 1.9 mg/dL and 2200 cc/24 hours. After two days of artemether
therapy, the patient's eyes were no longer yellow, and the urine was not concentrated-colored anymore.

**SEVERE MALARIA MANAGEMENT**

| Patient comes with severe malaria symptoms: |
|-------------------------------------------|
| - High fever                              |
| - Pale severe anemia, Hb <7g/dL           |
| - Jaundice (yellow)                       |
| - Decreased consciousness                 |
| - Shortness of breath                      |
| - Hemoglobinuria                           |
| - General State (KL): Weak                 |
| - Symptoms of shock                       |
| - Seizures                                 |
| - Continuous venous                        |

**Microscopic Blood Examination / Rapid Diagnostic Test**

Results: *Plasmodium falciparum (+) or Mixed (P. Falciparum + P. Vivax)*

**Artesunate injection**

**Or Artesunate injection**

**Artesunate injection 60 mg/vial, Intravenous (IV)/Intramuscular (IM)**

First day: 2.4 mg/kg body weight at 0, 12, and 24 hours

Following day: 2.4 mg/kg body weight daily until patient is conscious

**Artesunate injection 80 mg/ampoule Intravenous (IM)**

First day: 3.2 mg/kg body weight on day 1

Following day: 1.6 mg/kg body weight or 1 ampoule for adults

Intramuscular (IM) 1x a day until patient is conscious

When patient is able to eat and drink: replace with ACT tablet

For 3 days + Primaquine on day 1

If KU worsens refer to hospital

Figure 3. Severe malaria management.

3. **Discussion**

Malaria is a parasitic infectious disease caused by protozoa of *Plasmodium* genus transmitted to humans through the bite of an infected female Anopheles mosquito that attacks the erythrocytes, characterized by an asexual form finding in blood. Malaria infection may be acute or chronic, without complications or followed by a systemic complication known as severe malaria. The severe malaria infection commonly caused by *Plasmodium falciparum* than *Plasmodium vivax*.1,2,3

In this case, a 56-year-old man, a farmer, living in an area malaria-endemic. Come with a positive blood smear examination for *Plasmodium vivax* trophozoites.

According to WHO 2015, severe malaria is a malaria disease with one or more complications such as decreased consciousness, weakness, recurrent seizures, acidosis, hypoglycemia, severe anemia, acute renal failure, jaundice, pulmonary edema, spontaneous bleeding, shock, and hyperparasitemia. MAKI is a sudden change in renal function (48 hours) characterized by an increased serum creatinine of 0.3 mg/dL or higher than the previous value, an increased serum creatinine percentage of 50% or higher than the baseline, a decreased urine production of <0.5 cc/kg body weight/hour for more than 6 hours.18

In this case, the patient with fever for seven days, chills, sweating, joint pain, headache, nausea, vomiting, jaundice, and acute kidney injury characterized by an increased serum creatinine (baseline 1.0 mg/dL increased up to 11 mg/dL in 48 hours), and decreased urine production about 200 cc in 24 hours.
Anti-malarial drug administration in severe malaria cases is different than in common malaria cases. Severe malaria requires a faster parasite-killing power and ability to survive in the blood longer to immediately lower the degree of parasitemia. Therefore, the parenteral (intravenous, per infusion/intramuscular) administration chosen as it had a rapid effect and caused less resistance. Artemether administered with a dose 3.2 mg/kg body weight intramuscularly. Then, artemether given for 1.6 mg/kg body weight intramuscularly once a day until the patient was able to take oral medicines. When the patient was able to take the oral medicines, the treatment continued by dihydroartemisinin-piperaquine regimen or another ACT regimen for three days plus primaquine. The indication of artemether showed a rapid blood schizontocide both \textit{in vitro} and \textit{in vivo}. Therefore, it was used to treat severe malaria. From several clinical trials, it has been shown that artemether rapidly overcome parasitemia in both mild and severe malaria and was the most effective, safe and fast-acting drug for severe malaria cases.

In this case, antimalaria drugs given after malaria diagnosis established. A therapy combination; antimalarial drug and dialysis performed. Patient given intramuscular injection artemeter therapy 3.2 mg/kg body weight/24 hours (day 1), followed by intramuscular artemeter injection 1.6 mg/kg body weight/day on second day until fifth day. After Artemether therapy completed, then followed by oral therapy of primaquine 45 mg (3 tablet) for 14 days, and DHP 120/960 mg (3 tablet) for three days.

Dialysis on MAKI performed if there were anuria for more than 12 hours, uremic encephalopathy symptoms, excessive fluids (pulmonary edema, congestive heart failure) and pericardial rub. Laboratory indicators for dialysis included severe metabolic acidosis (HC03 $<15$ mEq/L), hyperkalemia ($K^+ > 6.5$ mEq/L). Dialysis should be performed daily for a better prognosis in acute renal failure. Death is reduced in patients with dialysis six times per week. Dialysis is performed until the levels of urea and creatinine after the fourth dialysis decrease to 50% of the pre-dialysis levels and the diuresis $> 400$ cc/24 h.

In this case, Hemodialysis was performed six times (three times a week) with the indications of anuria for more than 12 hours and increased urea and creatinine levels. The patient improved after the sixth dialysis with decrease urea and creatinine $> 50\%$ of pre-dialysis value and sufficient diuresis obtained. Furthermore, no longer needed hemodialysis.

The patient’s treatment evaluation performed by a peripheral blood smear test every day, to found the parasite density and to assess the success of therapy, then the examination repeated on day 4, 7, 14, 21 and 28 after the treatment.

In this case, treatment evaluation performed by a peripheral blood smear for five days, the parasites found on the first and second day of treatment, then not found on the third day until the fifth day of treatment. The examination repeated on day 4, 7, 14, 21 and 28 after the treatment, no parasites were found on the examination.

4. Conclusion
Intravenous artemether followed by oral primaquine for 14 days, DHP for three days, and six times hemodialysis provide a good outcome for severe malaria accompanied by malaria-related acute kidney injury (MAKI) complications, clinical and laboratory improvement.

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