Severe Tropical Malaria with Acute Kidney Injury: A Case in a Remote Area

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ABSTRACT

Background: Malaria remains a major health problem in Indonesia; *P. falciparum* is responsible for the majority of severe cases and malaria-related deaths. This report presents a case of severe tropical malaria complicated with acute kidney injury treated in a remote area with limited resources. **Case:** A 25-year-old male with a 9-day history of fever presented to the emergency department with severe headache, nausea, jaundice, abdominal pain, and hemoglobinuria. Microscopic examination of the blood revealed *P. falciparum* parasites. Laboratory results also showed anemia and thrombocytopenia, bilirubinuria, proteinuria, elevated liver enzymes, and pre-renal azotemia. The patient received antimalarial treatment (dihidroartemisinin/piperaquine once daily for 3 days and a single dose of primaquine) and supportive therapy. He was discharged in a stable condition on the fifth day of hospitalization. **Conclusion:** Early detection and management is crucial for the patient's prognosis.

Keywords: Acute kidney injury, malaria, *plasmodium falciparum*.

ABSTRAK

Latar Belakang: Malaria masih menjadi masalah kesehatan utama di Indonesia, *P. falciparum* bertanggung jawab atas sebagian besar kasus berat dan kematian terkait malaria. Laporan ini menyajikan kasus malaria tropika berat yang mengalami komplikasi gagal ginjal akut di daerah terpencil dengan sumber daya terbatas. **Kasus:** Pria berusia 25 tahun dengan riwayat demam selama 9 hari datang ke unit gawat darurat dengan nyeri kepala berat, mual, kuning pada mata dan kulit, nyeri perut, dan hemoglobinuria. Pemeriksaan mikroskopis darah menunjukkan parasit *P. falciparum*. Hasil laboratorium juga menunjukkan anemia dan trombositopenia, bilirubinuria, proteinuria, peningkatan enzim hepar, dan azotemia prerenal. Pasien mendapat antimalaria (*dihydroartemisinin-piperaquine* satu kali sehari selama 3 hari dan *primaquine* dosis tunggal) serta terapi suportif. Pasien dipulangkan dalam kondisi stabil pada hari kelima perawatan di rumah sakit. **Simpulan:** Deteksi dan penanganan dini sangat memengaruhi prognosis pasien. **Prayoga Adinawer Sirait. Malaria Tropika Berat dengan Gagal Ginjal Akut: Tata Laksana di Daerah Terpencil.**

Kata Kunci: Gagal ginjal akut, malaria, *plasmodium falciparum*.

INTRODUCTION

Malaria is a mosquito-borne disease caused by the Plasmodium parasite. It remains a major health problem in tropical countries, including Indonesia.[1] According to WHO, the incidence of malaria in Indonesia was 3 per 1000 population in 2021, the second highest cases in Asia after India.[2] *P. falciparum* is responsible for most severe malaria cases and deaths, including in Indonesia.[2,3,14]

Malaria eradication in Indonesia is still plagued with many problems, such as ineffective mosquito vector control, limited access to health facilities, and resistant parasite strains.[4,5] Another important, factors are challenge to diagnosis and effective treatment, especially in limited resources areas.[4] Berau District in East Kalimantan Province is a low-endemic malaria area; two districts in East Kalimantan (Paser and Penajam Paser Utara) contributed to malaria-related deaths in 2022.[3]

A case of severe tropical malaria complicated with acute kidney injury in a remote area with limited resources is presented.

CASE

A 25-year-old male came to the Emergency Department of a Community Health Center with a fever for 9 days, which subsided only for 3-4 hours in the afternoon. It was accompanied by severe headaches described as stabbing and disturbed sleep, also nausea, and weakness. The patient also reported reddish-yellow urine with decreased volume in the past few days. No history of nosebleeds or bleeding gums. The patient came from a malaria endemic area Mahakam Ulu District, East Kalimantan, but he had no history of malaria. The patient had not taken any medication (including malaria prophylaxis). Currently, the patient works as a gold miner in a remote area of East Kalimantan (Punan Mahakam Village, Berau District).

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On examination, the patient appeared moderately ill with full consciousness (CGS E4V5M6), blood pressure of 100/60 mmHg, heart rate of 96 beats per minute, respiratory rate of 20/per minute with oxygen saturation of 99%, and body temperature of 38.8° C. Anemic conjunctiva and icteric sclera were observed. Jaundice was observed in the face, body, and extremities. No visible enlargement of cervical lymph nodes. Lung and heart examinations were within normal limits. Hepatomegaly and splenomegaly were found with tenderness in the upper left and right quadrants. The extremities are dry and warm with no edema. Peripheral blood examination results were hemoglobin 8.8 g/dl and platelets 70 x 10^3/µL. A complete urine examination showed blood/hemoglobin 5+, bilirubin 3+, urobilinogen 3+, and protein 1+. Rapid Malaria Test showed positive for *P.falciparum*. Microscopic examination on thick and thin blood smears revealed *P.falciparum* parasites in trophozoite (ring form) and gametocyte stages **(Figure 1).**

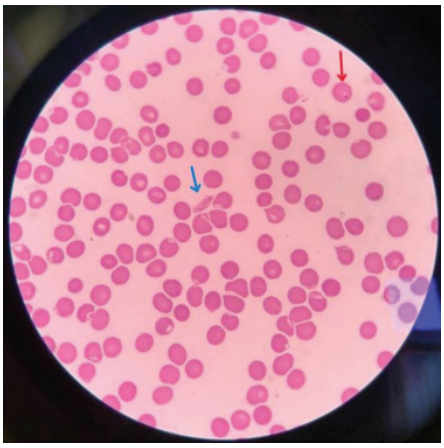

Figure 1. Microscopic examination revealed *P. falciparum* in the ring form trophozoite (red arrow) and gametocyte stages (blue arrow).

The diagnosis is severe tropical malaria; managed with NaCl 0.9% 20 drops per minute, paracetamol tablet 4 x 500 mg, dihydroartemisinin-piperaquine (DHP) 40/320 mg 4 tablets daily for 3 days, and single dose of primaquine 15 mg. The patient was then referred to a level II hospital for further treatment.

Further examination at the hospital revealed slight elevation of liver enzymes: SGOT 76 U/L and SGPT 56 U/L. Creatinine level increased to 5.3 mg/dl and urea level to 235 mg/dl, indicating acute kidney injury (pre-renal azotemia). Serum electrolyte test revealed mild hyponatremia (134 mmol/L) and normal potassium levels.. Abdominal ultrasound showed hepatomegaly and gallbladder sludge indicating acute hepatitis and bile stasis. The patient was closely monitored for fluid intake and was given symptomatic treatment, including intravenous lansoprazole 30mg per 24 hours, betahistine mesylate 2 x 12 mg , and ursodeoxycholic acid 2 x 250mg. Transfusion of 1 unit of packed red blood cells was also planned.

The patient's condition improved, and urine production returned to normal. The patient was discharged on the 5th day of hospitalization.

DISCUSSION

Quick and accurate diagnosis is necessary in every case of malaria to prevent life-threatening complications. Malaria should be suspected in patients with non-specific fever complaints who have a history of travel or living in endemic areas.[5,6] Other factors to consider including history of staying or residing in forest, history of malaria illness, history of taking malaria medication in the past month, or history of receiving blood transfusions.[4,6,8]

Since fever in malaria is often non-specific, possible differential diagnoses such as dengue virus infection, leptospirosis, typhoid fever, acute hepatitis, or meningitis should be assessed.[5,6] Malaria presents with fever (37,5°C axillae temperature); tropical (*P. falciparum)* malaria presents with irregular high fever, while in tertian (*P.ovale and P.* vivax) malaria and quartan (*P. malariae)* malaria, there is 48 hours and 72 hours of defervescence between fever episodes.[5] It can also be accompanied with headache, abdominal pain, muscle pain, nausea and vomiting, diarrhea, conjunctival pallor, and hepatomegaly and/or splenomegaly in a more chronic condition.[5] Patients may also present with a more severe headache, jaundice, oliguria with/without hemoglobinuria, or seizures to coma, indicating cerebral malaria.[5]

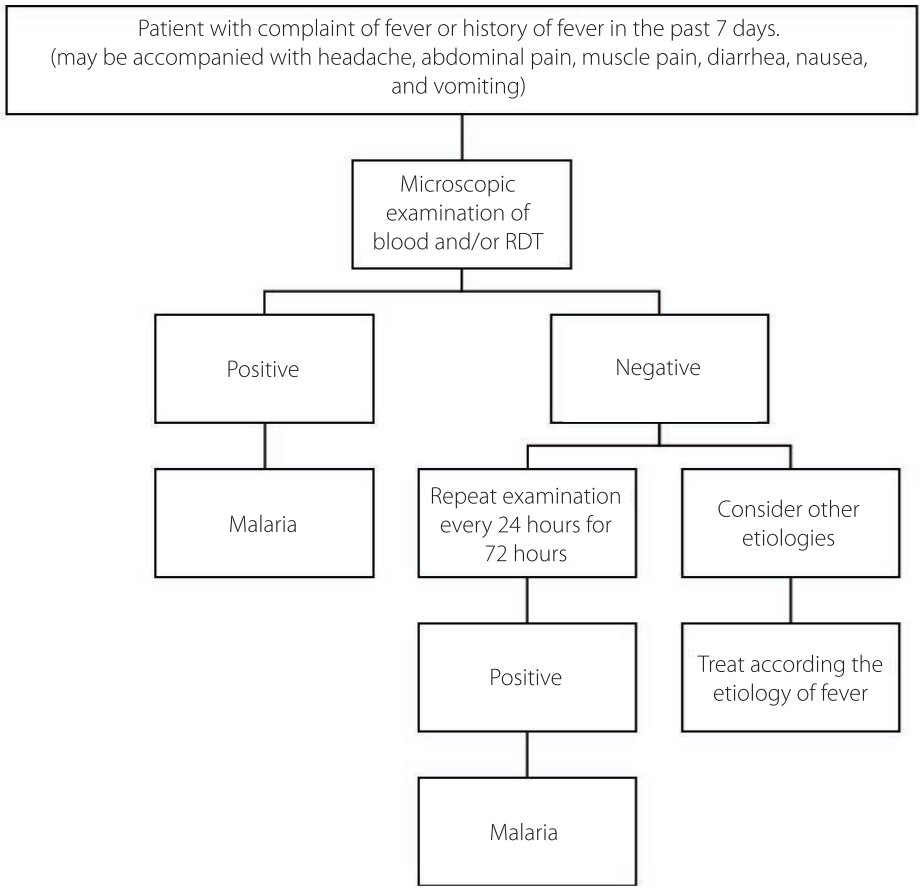

Figure 2. Diagnosis algorithm of suspected malaria patients.[5,14]


For a quick early diagnosis, a Rapid Diagnostic Test (RDT) device can be used in emergency conditions, during malaria outbreaks, and in healthcare facilities with limited microscopic examination and malaria screening capabilities.[5] This test is based on detection of malaria parasite antigens using immunochromatographic methods. Ideally, all RDT (Rapid Diagnostic Test) examinations should be followed by microscopic examination of thick and thin blood smears to identify malaria parasites. If no malaria parasites are found, microscopic examination can be repeated within 72 hours, especially if malaria (anticipation of *P.vivax infection*) is highly suspected.[5,6]

Delay in diagnosis and treatment of malaria may increase the risk of severe malaria. The most common parasite in severe malaria is *Plasmodium falciparum*; *Plasmodium vivax* or *Plasmodium knowlesi* may also be found.[7] Severe malaria is defined as presence of *Plasmodium falciparum*, *Plasmodium vivax* or *Plasmodium knowlesi* asexual parasite with the evidence of vital organ dysfunction, either clinically or through laboratory tests.[5,14] Risk factors for severe malaria include residing in an endemic area without prophylaxis, children or elderly individuals, migrants or tourists, pregnant women, and immunocompromised state.[5,8] Several factors influence the prognosis of severe malaria, including the timing of initiating treatment since disease onset, age (<65 years), gender (females are at higher risk, especially when pregnant), immune status, comorbidities, prophylactic therapy, and the patient's condition upon arrival at the healthcare facility.[6]

The patient is a migrant worker in Punan Mahakam Village, Berau Regency, works as a gold miner in the mostly forested upstream area of the river. Berau Regency is malaria endemic area; 324 new malaria cases were recorded in Berau Regency in 2020.[9] This high incidence may be due to its geographical conditions, which consists mostly of rainforests; and many people living around rivers or swamps, which are the perfect habitats of the malaria parasite vector, *Anopheles* mosquitoes.[4]

The presence of asexual *Plasmodium*

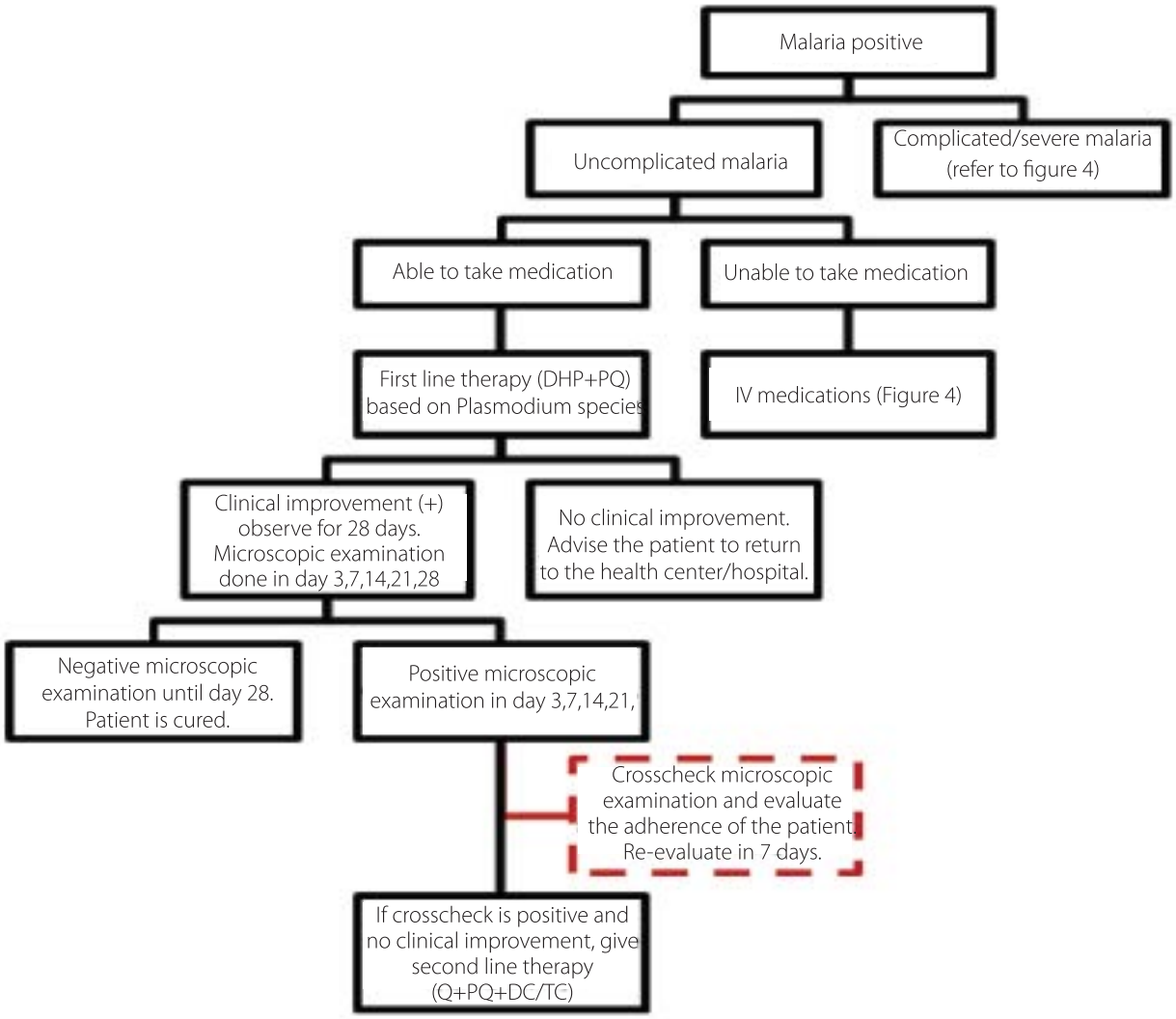

Figure 3. Treatment algorithm of malaria.[14]

DHP: dihidroartemisinin/piperaquine; PQ: primaquine; Q: quinine; DC: doxycycline; TC: tetracycline.


falciparum parasites accompanied by jaundice and acute kidney injury in this case were signs of severe malaria. Jaundice is a clinical manifestation commonly found in severe malaria.[11] Causes of jaundice in malaria are multifactorial, including intravascular hemolysis of erythrocytes, disseminated intravascular coagulation, liver dysfunction, hemoglobinopathy, cholestasis, drug-induced hemolysis, or G6PD deficiency.[12] Jaundice is generally mild (<5 mg/dL) with indirect bilirubin due to hemolysis or "biphasic" if accompanied by an increase in direct bilirubin due to cholestasis.[11] This case had the evidence of bile stasis as gallbladder sludge from abdominal ultrasonography finding, indicating that the jaundice was associated with both indirect and direct bilirubin, although blood bilirubin level was not measured. Ursodeoxycholic acid (UDCA) orally twice a day was given. UDCA has been proven as effective and safe for biliary sludge treatment[16] and may be beneficial as an adjunctive therapy for malaria-related jaundice, although Treepasertsuk (2009) study did not show statistically significant improvement in liver test result compared to placebo.[17] Jaundice can be accompanied by increase in liver enzymes (3-8 times), although rarely reach the level of acute hepatitis.[12] Hemolysis in severe malaria is also related to other conditions such as thrombocytopenia and splenomegaly, and acute kidney injury.[12]

Acute kidney injury in severe malaria is a medical emergency; it is one of the leading causes of death due to malaria.[8,11] The incidence of acute kidney injury due to malaria is 1%-4% worldwide, and 60% cases are from non-endemic areas.[1] The pathogenesis of acute kidney injury due to malaria is not fully understood, several hypotheses include blockage of renal microcirculation due to sequestration of red blood cells, glomerular injury mediated by the immune system, and fluid deficiency (hypovolemia).[1,6,11] Another contributing factor is liver dysfunction, which can cause hyperbilirubinemia. Excess bilirubin can burden the kidneys and trigger kidney failure (hepatorenal syndrome).[11]

Diagnosis of acute kidney injury is based on clinical signs (oligo-anuria) and laboratory findings (azotemia).[5,13] Management of acute kidney injury in severe malaria includes administration of antimalarial drugs, correction of fluids, and renal replacement therapy if needed.[13] Oliguria with pre-renal azotemia in this case improved after antimalarial therapy and fluid correction without renal replacement therapy. Timely administration of antimalarial drugs and supportive therapy such as fluid correction is crucial in managing acute kidney injury due to severe malaria.[13]

Standard management protocol for malaria is radical treatment with antimalarial drugs to eliminate all stages of parasite, including gametocyte. The goal of radical treatment is to achieve clinical and parasitological cure and to interrupt the transmission chain[5]. National Program in Indonesia uses artemisinin derivatives in combination with aminoquinolines, specifically the fixed-dose combination (FDC) known as Dihydroartemisinin-Piperaquine (DHP) for the first line treatment of uncomplicated malaria.[5,14] Each tablet contains 40 mg dihydroartemisinin and 320 mg piperaquine, administered orally once daily for three consecutive days; the dosage is: dihydroartemisinin 2-4mg/kg/day; piperaquine 16-32mg/kg/day. For children under 25 kgs, dyhidroartemisinin is given at 2,5-4/kg/day and piperaquine at 20mg/kg/day.[5,14]. Primaquine is also used, primarily beneficial as a radical therapy for hypnozoites stages of *P.vivax* and *P.ovale* that can cause

Table 1. First line treatment of uncomplicated malaria.[5]

Medication	Daily Dose Based on Bodyweight/Age								
	≤5 kg 0-1 mo	>5-6 kg 2-<6 mo	>6-10 kg 6-11 mo	>10-17 kg 1-4 yrs	>17-30 kg 5-9 yrs	>30-40 kg 10-14 yrs	>40-60 kg >15 yrs	>60-80 kg >15 yrs	>80 kg >15 yrs
DHP (day 1-3)	1/3 tab	1/2 tab	1/2 tab	1 tab	1 1/2 tab	2 tab	3 tab	4 tab	5 tab
Primaquine (day 1 for *P. Falciparum* **or** day 1-14 days for *P. Vivax/Ovale*)	-	-	1/4 tab	1/4 tab	1/2 tab	3/4 tab	1 tab	1 tab	1 tab

Table 2. Second line treatment of uncomplicated malaria.[5]

Medication	Daily Dose Based on Bodyweight/Age									
	≤5 kg 0-1 mo	>5-6 kg 2-<6 mo	>6-10 kg 6-11 mo	>10-17 kg 1-4 yrs	>17-30 kg 5-9 yrs	>30-33 kg 10-14 yrs	>33-40 kg 10-14 yrs	>40-45 kg >15 yrs	>45-60 kg >15 yrs	>60 kg >15 yrs
Quinine	3x 10 mg /kgbw	3x1/2 tab	3x1/2 tab	3x1 tab	3x1 1/2 tab	3x1 1/2 tab	3x2 tab	3x2 1/2 tab	3x2 1/2 tab	3x3 tab
Primaquine (day 1 for *P. Falciparum* **or** day 1-14 days for *P. Vivax/Ovale*)	-	-	1/4 tab	1/4 tab	1/2 tab	3/4 tab	3/4 tab	1 tab	1 tab	1 tab

Medication	Daily Dose Based on Bodyweight/Age				
	<19 kg <8 yrs	>19-29 kg 8-10 yrs	>29-44 kg 10-14 yrs	>44-59 kg >15 yrs	>59 kg >15 yrs
Doxycycyline (day 1-7) **or**	-	2x 25 mg	2x50 mg	2x75 mg	2x100 mg
Tetracycline (day 1-7)	-	4x125 mg	4x125 mg	4x250 mg	4x250 mg


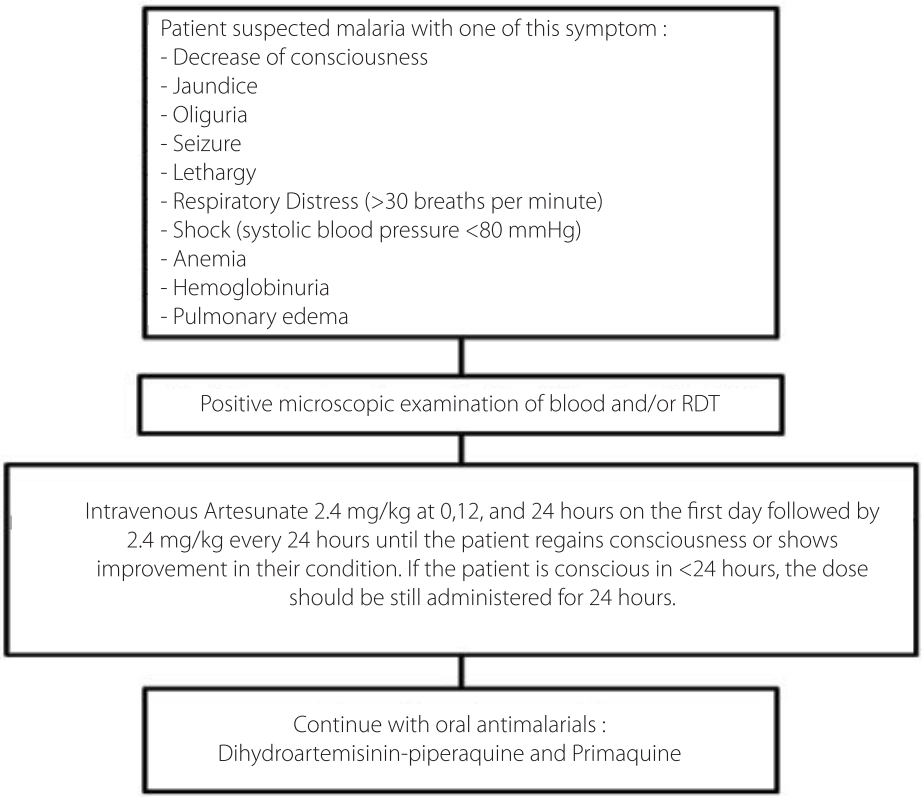

Figure 4. Treatment algorithm of severe malaria.[5,14]

relapse due to reactivation of dormant parasite in the liver cells.[5] In *P. falciparum* infection, it is given at 0,25mg/kg as a single dose in first day of treatment, while in *P.vivax/P.ovale* or mixed *(P.falciparum & P.vivax)* infection, it is continued for 14 days.[5] For first line therapy failure, quinine, doxycycline/ tetracycline, and primaquine combination can be used as second line therapy.[5] Quinine and doxycycline/tetracycline is given for 7 days with the dosage: quinine (as quinine sulphate 222mg) 10mg/kg tid, doxycycline 3,5 mg/kg/ day (>15 years) or 2,2 mg/kg/day (8-14 years) divided in two doses, and tetracycline 4mg/ kg/day divided in four doses.[5] Primaquine is not given in pregnancy due to the risk of G6PD deficiency.[5] Doxycicline and tetracycline is contraindicated in pregnancy and children under 8 years.[5] Clindamycin may be used instead with the dose of 10mg/kg bid for 7 days (maximum dose 300mg/day).[5] In case of treatment failure, it is also important to consider patient adherence and drug resistance possibility.[5,14]

The DHP + Primaquine dosage should be given based on bodyweight. If it is not possible to obtain the bodyweight,the age group based dose may be used.[5]

The Quinine + Primaquine + Doxycycline/ Tetracycline dosage should be given based on bodyweight. If bodyweight is not available, the age group based dose may be used. Doxycycline/Tetracycline is contraindicated in children under 8 years and pregnancy. [5]

Malaria chemoprophylaxis is recommended for individuals traveling to high-risk malaria areas. The recommended regimen is 100 mg doxycycline capsules once daily, started one day before travel and continued during the stay in the high-risk area for up to 4 weeks after leaving the area. It is not recommended for children under 8 years old, personal preventive measures such as wearing long sleeves, using mosquito repellent lotions, or mosquito nets should be taken instead.[5]

Intravenous artesunate is still the preferred and primary treatment for severe malaria.[13] It is given at a dose of 2,4 mg/kg bodyweight at 0, 12, and 24 hours on the first day followed by 2,4 mg/kg every 24 hours until the patient regains consciousness or shows improvement. Another drug of choice is intravenous quinine HCl 25% with a loading dose of 20mg/kg via slow infusion in 4 hours followed 8 hours later with a maintenance dose of 10mg/kg (4 hours slow infusion) every 8 hours until there is improvement. It is then followed by standard oral antimalarial regimen according to causative parasite.[5]

However, intravenous drug was not administered in this patient due to shortage; only 3-day course oral antimalarial consisting dihydroartemisinin-piperaquine (DHP) and single dose primaquine was given. Although the patient showed improvement after oral antimalarial regimen and supportive therapy, the therapy is still suboptimal since intravenous artesunate, as the treatment of choice to rapidly eliminate plasmodium parasite in the blood and thus preventing further complication, is not given, but based on Pedoman Nasional Pelayanan Kedokteran Tata Laksana Malaria,[5] oral antimalarial can be directly given in case of IV drug shortage.

CONCLUSION

Malaria is an disease caused by Plasmodium infection, diagnosed clinically and microscopically. Mortality and morbidity increase with the emergence of complications. A case of *P.falciparum* severe malaria complicated with acute kidney injury was reported. Oral antimalarial immediately initiated after diagnosis is successfully treating this case. Early detection and management is crucial for the prognosis of severe malaria, particularly in limited resources setting.

REFERENCE

1. Boushab BM, Fall-Malick Z, Mamoudou S, Basco L. Acute kidney injury in a shepherd with severe malaria: A case report. Internat J Nephrol Renovascular Dis. 2016;9:249-51.
2. WHO. World malaria report 2022 [Internet]. 2022:21,85,230,285. Available from: https://www.who.int/teams/global-malaria-programme/reports/


world-malaria-report-2022

3. Kementerian Kesehatan RI. Informasi malaria tahun 2022 [Internet]. 2022 [cited 2023 March]. Available from: https://p2pm.kemkes.go.id/publikasi/infografis/informasi-malaria-tahun-2022.
4. Sugiarto SR, Baird JK, Singh B, Elyazar I, Davis TME. The history and current epidemiology of malaria in Kalimantan, Indonesia. Malar J. 2022; 21:327.
5. Menteri Kesehatan Republik Indonesia. Keputusan Menteri Kesehatan Republik Indonesia Nomor HK.01.07/Menkes/556/2019 tentang Pedoman Nasional Pelayanan Kedokteran Tata Laksana Malaria. Jakarta: Menteri Kesehatan Republik Indonesia; 2018.
6. Kurnianingrum N, Ayu N. Severe falciparum malaria with acute kidney injury: A case report. IOP Conference Series: Materials Science and Engineering 2018;434:012316. DOI: 10.1088/1757899X/434/1/012316.
7. Yulita LD, Rahman YA. Laporan kasus pansitopenia pada infeksi malaria falsiparum. Medula 2020;9(4):651-7.
8. Meremo AJ, Kilonzo SB, Munisi D, Kapinga J, Juma M, Mwanakulya S, et al. Acute renal failure in a Caucasian traveler with severe malaria: A case report. Clin Case Rep. 2014;2(3):82-5. DOI: 10.1002/ccr3.65.
9. Badan Pusat Statistik. Jumlah kasus penyakit menurut jenis penyakit dan kabupaten/kota [Internet]. 2020 [cited 2023 March]. Available from: https://kaltim.bps.go.id/indicator/30/333/1/jumlah-kasus-penyakit-menurut-jenis-penyakit-dan-kabupaten-kota.html.
10. Mohanty S, Mishra SK, Pati SS, Pattnaik J, Das BS. Complications and mortality patterns due to Plasmodium falciparum malaria in hospitalized adults and children, Rourkela, Orissa, India. Trans R Soc Trop Med Hyg. 2003;97:69–70.
11. Gowda S, Desai PB, Shetty SJ, Kagwad VS, Ilakal MB. Malarial hepatitis and renal failure: A study of two cases. IJPH. 2011;8(1):19–21.
12. Utama MS, Merati TP. Management malaria with jaundice. Malaria Contr Elimination 2016;5(2): 1000147. DOI: 10.4172/2470-6965/1000147
13. Silva GBD Jr, Pinto JR, Barros EJG, Farias GMN, Daher EF. Kidney involvement in malaria: An update. Rev Inst Med Trop Sao Paulo 2017;59:e53. DOI: 10.1590/S1678-9946201759053
14. Kementerian Kesehatan Republik Indonesia. Buku saku tatalaksana kasus malaria. Direktorat Jenderal Pencegahan dan Pengendalian Penyakit Kementerian Kesehatan Republik Indonesia; 2020.
15. Lüthi B, Schlagenhauf P. Risk factors associated with malaria deaths in travellers: A literature review. Travel Med Infect Dis. 2015;13(1):48-60. DOI: 10.1016/j.tmaid.2014.04.014.
16. Butorova LI, Ardatskaya MD, Osadchuk MA, Drobysheva AE, Zagrebina EA, Kadnikova NG, et. al. Comparative effectiveness of ursodeoxycholic acid preparations in the treatment of biliary sludge. Terapevticheskii arkhiv. 2020;92:60-5.
17. Treeprasertsuk S, Silachamroon U, Krudsood S, Huntrup A, Suwannakudt P, Vannaphan S, et al. Ursodeoxycholic acid and artesunate in the treatment of severe falciparum malaria patients with jaundice. J Gastroenterol Hepatol .2010;25(2):362–8. DOI:10.1111/j.1440-1746.2009.06007.x.