CASE REPORT

Case Report: Managing the Coinfection of Cerebral Malaria and Dengue in the Intensive Care Unit

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ABSTRACT

Background: Dengue and malaria are the two most common arthropod-borne illnesses, but cases of multiple infections are extremely uncommon. The mortality rate for individuals with dengue and malaria was higher than the death rate for those with malaria alone.

Case: An intubated 53-year-old male was referred from a class B hospital because of severe malaria with suspected cerebral malaria, dengue fever (day-11), septic shock and acute kidney injury. His initial laboratory investigation showed increasing pattern of WBC, thrombocyte, anemia, peripheral blood smear normochromic normocytic erythrocyte, poikilocytosis (ovalocytes (+), teardrop cells (+)), normoblasts (+), presence of *Plasmodium malariae* trophozoite and schizont stage parasites, positive result of IgM and IgG anti dengue, increased liver function test, increased BUN and creatinine serum levels, hyperbilirubinemia, hypoalbuminemia, and normal result of blood gas analysis. On the sixth day of ICU admission, the patient gradually regained consciousness with appropriate responsiveness and showed clinical improvement. The patient was discharged after one month of hospital care with the last peripheral blood smear showing no parasites detected.

Discussion: Mono-infection with malaria and dengue, two mosquito-borne diseases endemic to tropical and subtropical regions, often carries a high risk of fatality. The risk becomes even more pronounced when co-infection occurs. The early diagnosis and management in the ICU are crucial for cases of coinfection involving cerebral malaria and dengue. The primary focus is on both definitive and supportive therapies.

Conclusion: The prognosis for coinfection of cerebral malaria and dengue is generally poor, but in this case, the patient showed improvement and was able to be discharged without any sequelae.

Keywords: cerebral malaria; coinfection; dengue; intensive care unit; septic shock

INTRODUCTION

In the tropics, dengue and malaria are the two most common arthropod-borne illnesses, but cases of multiple infections are extremely uncommon. Concurrent infections of malaria and dengue are when both the diseases occur simultaneously in an individual. There appears to have been a rise in the frequency of concurrent dengue and malaria infections during the past ten years, according to published data from Asian nations, particularly India. A meta-analysis in Africa showed that the prevalence of co-infection with plasmodium falciparum and dengue virus significantly increased over 14 years. It started at 0.9% in 2008, then rose to 3.8% over 11 years, and further increased to 5.5% in just 3 years from 2018.[2] Another study conducted during the 2012 dengue outbreak in Pakistan found that co-infection rates among cases of dengue fever and malaria were high. Other than the lower incidence of jaundice in co-infected patients, there were no appreciable differences in the clinical and laboratory parameters related to the severity of the illness. However, another study found that a prolonged fever with a normal to low hematocrit and a significant thrombocytopenia were concurrent infection manifestations.[1]

Malaria and dengue co-infections may be misdiagnosed or misinterpreted as mono-infections due to similarities in their clinical characteristics, which include fever, headache, myalgia, arthralgia, rash, nausea, diarrhea, vomiting, and stomach discomfort. A strong predictor of dengue fever, thrombocytopenia is associated with an increased risk of malaria. Anemia, which is a primary symptom of malaria infections, is caused by the blood stages causing severe intravascular hemolysis. This is not remarkable when it comes to dengue cases. A significant decrease in platelets and hemoglobin content, along with elevated alanine aminotransferase and decreased aspartate aminotransferase levels, are also linked to concurrent infections.[2]

It is generally observed that concurrent infection results in more severe outcomes compared to single infections, despite the paucity of early reports on the effects of concurrent infection on morbidity and mortality.[3-5] A clinical study conducted by Saurabh Pandey in Eastern India between 2017 and 2018 found that 9.2% of patients with malaria also had concurrent dengue infections, and 10% of these patients also had concurrent chikungunya, enteric fever, lower respiratory tract infections (LRTIs), urinary tract infections (UTIs), and leptospirosis patients. According to this study, the mortality rate for individuals with dengue and malaria was 15.4%, which was significantly higher than the 2.4% death rate for those with malaria alone. Additionally, there were no deaths among those with malaria who also had other concurrent infections. Notably, the patients' less severe outcomes might have been influenced by early diagnosis and treatment of the infections.[5]

CASE

An intubated 53-year-old male was referred from a class B hospital because of severe malaria with suspected cerebral malaria, dengue fever (day-11), septic shock and acute kidney injury. Before he was referred, he was hospitalized for ten days with the chief complaint of persistent fever (day-6 when admission) and other symptoms such as nausea, decreased appetite, myalgia, arthralgia, headache, decreased consciousness (one day before he was referred), followed by

three episodes of generalized seizures (duration of 30–60 seconds and 2-3 hours interval between seizures) and apnea. His medical history includes dengue hemorrhagic fever in March'23 and he traveled to the West of Nusa Tenggara and Sumba in March'23. Additionally, in May 2022, he underwent sphincterotomy surgery in Penang.

After being referred, a physical examination revealed that the patient appeared pale, had icteric sclera and showed no signs of bleeding on the skin or mucous membranes. His body weight, height, and BMI were 60 kg, 180 cm, and 18.5 kg/m^2, respectively, with blood pressure 102/70 mmHg on norepinephrine 0.2 mcg/kg/min, slight tachycardia heart rate (HR) 103–118/min regular, axillary temperature 39.6^oC, peripheral pulse oximetry 99% on pressure control ventilation mode, fraction of inspired oxygen 40%, inspiratory Pressure 21 cmH_2O ~ tidal volume 440–500 ml, frequency 16/min, inspiratory : expiratory ratio of 1:2, positive end expiratory pressure 5 cmH_2O. The patient was in deep sedation, with both pupils exhibiting isocoricity and a diameter of 2 mm. Positive pupillary and corneal reflexes were present, while pathological reflexes, meningeal signs (Brudzinski and Kernig sign), and motor lateralization were not found. Additionally, no hepatosplenomegaly was observed.

His initial laboratory investigation showed increasing pattern of white blood cells (WBC) in six days (from 3.880/µL to 11.560/µL), increasing pattern of thrombocyte (from 10.000/µL to 37.000/µL), anemia (Hb 11 g/dl), peripheral blood smear normochromic normocytic erythrocyte, poikilocytosis (ovalocytes (+), teardrop cells (+)), normoblasts (+), presence of Plasmodium malariae trophozoite and schizont stage parasites, positive result of IgM and IgG anti dengue, increased liver function test (SGOT 751 U/L, SGPT 311 U/L, ALP 251 U/L), increased BUN and creatinine serum levels (BUN 31.4 to 56.4 mg/dl, Cr 1.88 to 2.16 mg/dl, with last CCT 38.91 ml/min), hyperbilirubinemia (total bilirubin 3.6 mg/dl, direct bilirubin 2.41 mg/dl, indirect bilirubin 1.19 mg/dl), hypoalbuminemia (1.8 g/dl), prolonged aPTT (50.1 s), hyponatremia (128 mmol/L), hyperkalemia (5.39), hypoalbuminemia (Alb 1.8 g/dL), normoglycemia (BS 98 mg/dl), normal result of blood gas analysis with PaO2/FiO2 ratio 335.

The results of the radiological examination of the head CT scan without contrast indicate that there were no signs of space-occupying lesions (SOL), infarction, or intracerebral and intracerebellar bleeding. Initially, the X-ray impression of the chest (AP view) showed normal findings. However, on the 5th day of tracheostomy, CXR revealed a presentation of pneumonia with visible consolidation in the lower right lung zone and normal bronchovascular markings. Even though PaO2/FiO2 and SpO2 remained normal, rales were auscultated bilaterally at the paracardial regions, with more prominent findings at the right paracardial region. Additionally, the bacterium Klebsiella pneumoniae ssp had been isolated from the patient's sputum specimen, showing a high level of resistance to third-generation cephalosporins (suspected extended spectrum beta (ESBL) lactamase or AmpC producer). This led to an additional diagnosis of ventilator-associated pneumonia.

In the previous hospital treatment, the patient had already received symptomatic therapy and fluid resuscitation from the 3rd to the 5th day of fever. Because the fever persisted (on the 8th day of fever), and the presence of plasmodium malariae was confirmed in the peripheral blood smear, dihydroartemisinin-piperaquine PO therapy was initiated. On the first day in the ICU, this patient was administered Artesunate IV at a dose of 2.4 mg/kg (administered at hours 0, 12, 24, and then every 24 hours thereafter). After the patient's enteral intake improved (on the 7th day of treatment), the therapy was changed to dihydroartemisinin-piperaquine, with 4 tablets taken orally every 24 hours. Based on sputum culture recommendations, cefoperazone-sulbactam was administered (on the 5th day of tracheostomy) at a dose of 1 g every 12 hours intravenously for one week. This was then replaced with meropenem at a dose of 1 g every 8 hours intravenously.

Euvolemic status was sustained by a combination of enteral nutrition and intravenous fluid administration, with guidance from inferior vena cava ultrasonography (IVC USG) measurements. Norepinephrine was titrated based on the minimal mean arterial pressure (MAP) 65 mmHg to ensure tissue perfusion. However, oliguria-anuria was observed for the first 16 hours in the ICU. To treat this condition, he was given furosemide 80 mg IV bolus at the initial 6 hours of oligo-anuria and maintenance intravenous continuous (IV) furosemide at a rate of 15 mg/hr. Improved urine output was gradually achieved after the next 12 hours, and the administration of furosemide was tapered off and stopped after normal urine output was achieved.

The patient still experienced a fever with temperature fluctuations, reaching a maximum of 39.5 degrees Celsius despite the routine use of a cooling blanket, cold compresses on the neck, axillary region, and groin, as well as intravenous paracetamol at a dose of 1 gram every 8 hours if the temperature was above 38.3^{o}C. Other supportive therapies were implemented to ensure adequate oxygen delivery by maintaining airway patency and a lung-protective strategy. Analgo-sedation was provided using midazolam at a rate of 5-15 mg/hr, fentanyl at a rate of 50 mcg/hr, with target RASS -3 and daily sedation vacation was starting from the 3rd day of intubation. An early tracheostomy was performed on the 5th day of intubation. Measures were routinely taken to prevent nosocomial respiratory infections through head bed elevation, oral care with chlorhexidine, airway suctioning and chest physiotherapy. Side-to-side position changes were performed every 4 hours to prevent pressure ulcers.

On the sixth day of ICU admission, the patient gradually regained consciousness with appropriate responsiveness and showed clinical improvement. Hemodynamics, respiratory, kidney, and liver functions also improved day by day, allowing the patient to be transferred to an intermediate ward after ten days of close monitoring in the ICU. No post-recovery phase sequelae symptoms were identified, and the patient was discharged after one month of hospital care with the last peripheral blood smear showing no parasites detected.

DISCUSSION

Mono-infection with malaria and dengue, two mosquito-borne diseases endemic to tropical and subtropical regions, often carries a high risk of fatality. The risk becomes even more pronounced when co-infection occurs. The typical symptoms of acute dengue virus infection, such as high fever, arthralgia, myalgia, decreased appetite, nausea, and acute headache, as well as a drop in platelet count during the acute phase of fever and a positive IgM antidengue serology, supported the initial diagnosis.[2,6,7] The presence of positive IgM and IgG antidengue serology in this patient indicated a history of previous dengue infection, but a new dengue infection (with a different serotype) still cannot be ruled out.[7] However, given the patient's history of travelling to a malaria-endemic region in Indonesia (Sumba), and the fact that there was no improvement in fever after the fifth day of fever onset despite an increase in platelet count, suspicion of malaria coinfection arose. Despite the absence of any signs of worsening anaemia, which is a hallmark of malaria and is caused by Plasmodium sp. destructing off red blood cells, a peripheral blood smear examination was still carried out.[2] The results confirmed the presence of Plasmodium malariae, leading to the initiation of oral dihydroartemisinin-piperaquine therapy.[8]

The patient's clinical condition drastically worsened one day prior to being referred, which was contrary to the recovery stage of the patient's dengue disease, as indicated by increasing leukocyte and platelet counts. An acute decline in consciousness, three episodes of seizures within 24 hours followed by apnea and hypotension requiring norepinephrine, persistent hyperpyrexia, hyperbilirubinemia, acute kidney injury, compensated metabolic acidosis, and a SOFA Score of 15 indicated severe malaria, cerebral malaria (Table 1), and septic shock.[8,9,10] Sequestration, characterized by the accumulation of parasites in blood vessels, hinders local blood flow in brain and may result in hypoxic injury. The subsequent harmful insults and epileptogenic parasites can instigate seizures, establishing a cycle of brain injury and heightened seizure occurrence. Severe metabolic imbalance can further worsen the damage. The severity of brain injury depends on factors such as the cause of coma, the extent of microvascular obstruction, the inflammatory response, the duration of exposure, the presence of additional complications like shock, and the accessibility and promptness of interventions.[33] Furthermore, the invasion of liver cells by the sporozoite form of the malarial parasite, leading to organ congestion, sinusoidal blockage, and cellular inflammation, may result in the release of both parenchymal enzymes (transaminases) and membranous enzymes (alkaline phosphatase) from the liver into the bloodstream, as reflected by the increased levels of SGOT, SGPT, and ALP in this case.[11] Hepatosplenomegaly is a common occurrence in severe malaria. The main factor contributing to liver enlargement is sinusoidal dilatation, while reticulo-endothelial hyperplasia and hypertrophy play a relatively minor role.[34] The early stages of malaria infection may not show signs of hepatosplenomegaly. It may manifest as the infection worsens. Therefore, the observation of hepatosplenomegaly may depend on when the examination is performed in connection to the disease's progression. Genetic variables and individual differences in immune response might affect the symptoms, such as

hepatosplenomegaly, present.[36] This may be the cause of the absence of hepatospenlomegaly in this case. The enlargement of the spleen, both in size and weight, is connected to cellular expansion in the red and white pulp, emphasizing their crucial roles during malaria infection. The red pulp becomes congested with red blood cells (RBCs), including both uninfected and parasitized ones. The heightened numbers of macrophages in this region highlight their primary responsibility for removing and destroying damaged and parasitized RBCs from circulation.[35] In some cases, hepatosplenomegaly may not be observed, possibly due to a less fulminant Plasmodium sp. infection as seen in this case.

Table 1. WHO criteria for severe malaria[7]

Manifestation	Definition
Cerebral Malaria	Impaired consciousness or unrousable coma not attributable to any other cause, with a Glasgow score ≤9 Prostration, i.e. generalized weakness so that the patient is unable to walk, or sit up without assistance Failure to feed Multiple convulsions – more than two episodes in 24 h
Severe Anaemia	Haematocrit <15% or haemoglobin <5 g/dl in the presence of parasite count > 10.000 µl
Renal Failure	Urine output <400 ml/24 hours in adults (<12 ml/kg/24 hours in children) and serum creatinine >265 µmol/l (>3.0 mg/dl) despite adequate volume repletion
Pulmonary Oedema and ARDS	The acute lung injury score is calculated on the basis of radiographic densities, severity of hypoxemia and positive end-expiratory pressure
Hypoglycaemia	Whole blood glucose concentration <2.2 mmol/l (<40 mg/dl)
Circulatory Collapse	Systolic blood pressure <70 mmHg in patients >5 years of age (<50 mmHg in children aged 1-5), with cold clammy skin or a core-skin temperature difference >10^{o}C
Abnormal Bleeding and/or Disseminated Intravascular Coagulation	Spontaneous bleeding from gums, nose, gastrointestinal tract, or laboratory evidence of disseminated intravascular coagulation
Repeated Generalized Seizures	≥2 seizures observed within 24 hours
Acidemia/ Acidosis	Arterial pH <7.25 or acidosis (plasma bicarbonate <15 mmol/l)
Macroscopic Haemoglobinuria	Haemolysis not secondary to glucose-6-phosphate dehydrogenase deficiency
Impaired Consciousness	Rousable mental condition
Prostration or Weakness	Generalized weakness so that the patient is unable to walk or sit up without assistance
Hyperparasitaemia	>2% parasited erytrocytes or >250.000 parasites/µl (in non-immune individuals)
Hyperpyrexia	Core body temperature >40^{o}C
Hyperbilirubinaemia	Total bilirubin >43 µmol/l (>2.5 mg/dl)

Hypoalbuminemia was also observed in this case as a result of sepsis. The release of cytokines or anomalies in the inflammatory response brought on by sepsis are likely to be the causes of hypoalbuminemia. TNF-alpha and IL-1 cytokines can suppress serum albumin levels via regulating the gene that produces albumin. The antioxidant properties of albumin may offer biologically significant defence. Albumin, however, is the primary target protein for oxidative stress in extracellular plasma, and a protracted inflammatory response or a severe sepsis might accelerate albumin degradation The redistribution of intravascular albumin in sepsis, which leads to further capillary leak syndrome, also results in decreased albumin levels.[12] These factors, along with clinical research findings that albumin supplements did not reduce the 7-day or 28-day in-hospital mortality of patients with sepsis or septic shock[13], led to the decision to forgo giving this patient an albumin transfusion during the critical illness phase.

The head CT in this case did not reveal any abnormal findings. In fact, it showed an occasional normal head CT result, and there didn't seem to be any connection between this result and the level of parasitemia. However, head MRIs and CT scans can display certain features, such as reduced attenuation in the cerebellar white matter, decreased attenuation in the thalamus associated with infarction, and possible cerebral edema.[14] This edema could be partly cytotoxic, resulting from the release of inflammatory cytokines and other harmful substances due to ischemia, and partly vasogenic due to microcirculation disruption. Other potential factors include reduced venous outflow and increased cerebral blood flow due to factors like fever, anemia, and seizures. Additionally, increased cerebral blood volume could be caused by microvascular congestion due to sequestered RBCs.[15]

Despite adequate fluid therapy and the maintenance of the target mean arterial pressure (MAP) from the beginning of ICU admission, episodes of oligo-anuria persisted during the initial 3 hours of evaluation in this patient. It was related to the changes in red blood cells, including the loss of their typical discoid shape, increased membrane rigidity, elevated permeability, and increased adhesiveness, especially to endothelial surfaces, which result from the progression of the parasite within parasitized red blood cells. As the parasite products accumulate in the kidneys, these altered RBCs become sequestered, activating endothelial cells. This activation was a central pathological event that led to the impairment of endothelial barrier function, dysregulation of blood flow and coagulation cascades, and the secretion of proinflammatory cytokines. These processes further amplified the host's inflammatory response and blocked microvessels, ultimately leading to a reduction or even cessation of blood flow to the kidneys.[16,17,18] The World Health Organization (WHO) criteria for severe malaria can be seen in Table 1.[11]

To evaluate prerenal or renal pathology, an early furosemide stress test was performed in response to the oligo-anuria observed over the preceding six hours. This action was taken in response to clinical data indicating that, even in cases of sepsis, patients might still have abnormal or elevated global renal blood flow due to impairment in the microcirculation of the renal cortex or medulla. Acute kidney injury (AKI)

might arise from this due to hypoxia and the triggering of inflammatory pathways. Because furosemide inhibits the Na-K-2Cl cotransporter (NKCC2 pump) and lowers the glomerular filtration rate and tubular workload, it may be a helpful treatment to lessen the severity of AKI by reducing oxygen consumption and metabolic demands of injured renal tubular cells. By raising prostaglandin E2 release into renal venous blood and urine, it may also prevent ischemia-reperfusion injury to the outermost vulnerable segment of the medullary tubular system, ischaemia-reperfusion-induced apoptosis, and related gene transcription in AKI. Furthermore, this function guards against luminal obstruction caused by necrotic debris for the injured kidneys.[19,20]

Urine output was still less than 200 ml two hours after the Furosemide Stress Test (FST), so a continuous infusion of furosemide (15 mg/hr) was started. As opposed to intermittent dosing, continuous infusion maintained an effective rate of furosemide excretion and inhibited Na+ reabsorption over time. This made it the preferred method after a loading dose. Based on renal function, 40–200 mg of furosemide is the recommended loading dose. The rate of infusion is 10–20 mg/hr, with the option to increase to 40 mg every hour. Urine output did, however, gradually increase after the oligo-anuric episodes continued for the next eight hours. Renal replacement treatment would have been taken into consideration if oligo-anuria had persisted.[21]

The delayed effect of furosemide in this case is that patients with AKI exhibit significantly different furosemide bioactions. The amount of furosemide protein-bound fraction is significantly reduced in hypoalbuminemic conditions, which consequently reduces tubular secretion and the therapeutic efficacy of the drug. The loss of epithelial polarity that often follows acute tubular injury is caused by the redistribution of Na/K + ATPase from the basolateral membrane to the apical membrane. This compromises the sodium gradient across the tubule and the secondary active transport of organic acids. Furosemide secretion and activity could potentially be restricted due to its competition with uremic organic acids and moderate-to-severe metabolic acidosis at the (Organic Anion Transporter) OAT1/OAT3 site. Furosemide's pharmacodynamics are changed in patients with oliguric AKI, which raises the medication's potentially dangerous plasma levels and reduces the drug's excretion in urine.[22]

For definitive therapy, intravenous Artesunate (ART) followed by oral DHP had been given and routine evaluation parasite detection using blood smear. Artesunate, a water-soluble compound, can be administered intravenously or intramuscularly. Unlike quinine and some other antimalarial drugs, Artesunate demonstrates greater effectiveness in clearing parasites due to its swift action and enhanced tolerance. Its documented efficacy against resistant strains of malaria parasites further supports its effectiveness.[37] Artesunate is administered intravenously at a dose of 2.4 mg/kg of body weight three times at hours 0, 12, and 24 on the first day. Subsequently, it is given intravenously at a dose of 2.4 mg/kg of body weight every 24 hours until the patient is able to take oral medication. In the body, ART gets converted to dihydro-artemisinin, which has a higher half-life of around 45 min. Mechanisms of action for ART (like any other artemisinin) include inhibiting heme polymerization, generating ROS, destabilizing parasite membrane,

alkylating proteins and inhibiting PfATP6 (gene that has been reported to be responsible for the emergence of resistance to artemisinin).[23] Figure 1 shows the comparison of antimalarial drugs usage. For inpatients, treatment evaluation is conducted daily with clinical examinations and malaria blood tests until clinical improvement and microscopic results are negative. Treatment evaluation continues on days 7, 14, 21, and 28 with clinical examinations and microscopic blood examinations.[8] He also had been given antibiotic for Ventilator-associated Pneumonia based on antibiotic sensitivity.[24]

	PRE-ERYTHRO.		ERYTHROCYTIC PHASE			EXO ERYTHRO.	GAMETES		RESISTANCE	TOXICITY GRADING
DRUG	Fal.	Viv.	Activity	Onset	Duration	Viv.	Fal.	Viv.		
1. Chloroquine	–	–	+	Fast	Long	–	–	+	Slow	±
2. Mefloquine	–	–	+	Int	Long	–	–	–	Minor	++
3. Quinine	–	–	+	Int	Short	–	–	+	Minor	+++
4. Proguanil	+	±	+	Slow	Short	–	*	*	Rapid	±
5. Pyrimethamine	–	–	+	Slow	Long	–	*	*	Rapid	+
6. Primaquine	+	+	±	–	–	+	+	+	Minor	++
7. Sulfonamides	–	–	±	Slow	Long	–	–	–	Minor	+±
8. Tetracyclines	+	–	+	Slow	Short	–	–	–	Nil	+
9. Artemisinin	–	–	+	Fastest	Short	–	+	+	Nil	+
10. Lumefantrine	–	–	+	Int	Long	–	–	–	Nil	+

*Do not kill gametes but inhibit their development in mosquito.
Pre-erythro. — Preerythrocytic stage; Exo-erythro. — Exoerythrocytic stage
Fal. — *P. falciparum*; Viv — *P. vivax*; Int — Intermediate

Figure 1. Comparison of antimalarial drugs[23]

Supportive care for this patient included daily routines such as analgosedation with daily sedation vacation, fever control, oral hygiene, prevention of nosocomial infections, and pressure ulcer prevention.[25-30] The patient's response improved with enhanced consciousness and adequate breathing efforts on the 6th day of ICU admission and continued to improve until the patient could be transferred to an intermediate room. Regular examination of sequential blood smears with parasite quantification is advised to monitor the response to therapy, focusing on the reduction in percent parasitemia and eventual parasite clearance. The frequency of monitoring should be determined by the clinical severity of the patient, with daily or more frequent testing initially recommended for severe malaria cases. An increase in parasite loads after 36 to 48 hours may suggest treatment failure due to parasite resistance. Repeat testing is generally recommended, at a minimum, on days 7 and 28 after the onset of illness.[32] Although peripheral blood smear examination on the 7th day still showed positive result for parasites during the patient's ICU stay, consecutive tests on the 14th and 21st day, conducted in the ward, indicated negative results. No post-ICU treatment sequelae were found, and the patient was discharged from the hospital one month after treatment.

CONCLUSION

The early diagnosis and management in the ICU are crucial for cases of coinfection involving cerebral malaria and dengue. The primary focus is on both definitive and supportive therapies. These treatments play a vital role in optimizing the patient's organ function until the infectious parasites are eliminated. The prognosis for coinfection of cerebral malaria and dengue is generally poor. One study conducted in India revealed that the mortality rate for individuals with both dengue and malaria was 15.4%, significantly higher than the 2.4% death rate observed in those with malaria alone. Another study demonstrated sequelae following malaria with common clinical features, including confusion (50%), fever (47.7%), seizure (31.8%), speech abnormalities (18.2%), tremor (18.2%), behavioral abnormalities (16%), impaired consciousness (16%), myoclonus (11.3%), ataxia (11.3%), and headache (6.8%).[31] But in this case, the patient showed improvement and was able to be discharged without any sequelae.

REFERENCES

1. Zaman M, Assir K, Adnan M, Ijaz H. International Journal of Infectious Diseases Concurrent dengue and malaria infection in Lahore , Pakistan during the 2012 dengue outbreak. Int J Infect Dis [Internet]. 2014;18:41–6.
2. Gebremariam TT, Schalling HDFH, Kurmane ZM, Danquah JB. Increasing prevalence of malaria and acute dengue virus coinfection in Africa: a meta-analysis and meta-regression of cross-sectional studies. Malar J [Internet]. 2023;22(1)
3. Carme B, Matheus S, Donutil G, Raulin O, Nacher M, Morvan J. Concurrent dengue and malaria in Cayenne Hospital, French Guiana. Emerg Infect Dis. 2009;15(4):668–671
4. Cox J, Grillet ME, Ramos OM, Amador M, Barrera R. Habitat segregation of dengue vectors along an urban environ ment gradient. Am J Trop Med Hyg. 2007;76(5):820–826
5. Obsomer V, Defourny P, Coosemans M. The Anopheles dirus complex: spatial distribution and environmental drivers. Malar J. 2007;6:26.
6. Marks M, Gupta-Wright A, Doherty JF, Singer M, Walker D. Managing malaria in the intensive care unit. Br J Anaesth. 2014;113(6):910-921.
7. WHO. 2012. Handbook for Clinical Management of Dengue. Geneva, Switzerland: WHO Press
8. Malaria S, Kesehatan K, Indonesia R. Tatalaksana Kasus Malaria. 2019
9. Santos LC, Abreu CF, Xerinda SM, Tavares M, Lucas R, Sarmento AC. Severe imported malaria in an intensive care unit : a review of 59 cases. 2012;1–9.
10. Moreno R, Rhodes A, Piquilloud L, Hernandez G, Takala J, Gershengorn HB, et al. The Sequential Organ Failure Assessment (SOFA) Score : has the time come for an update ? Crit Care [Internet]. 2023;1–5
11. Al-Salahy M, Shnawa B, Abed G, Mandour A, Al-Ezzi A. Parasitaemia and Its Relation to Hematological Parameters and Liver Function among Patients Malaria in Abs, Hajjah, Northwest Yemen. Interdiscip Perspect Infect Dis. 2016;2016:5954394.

12. Yin M, Si, L, Qin W, Li C, Zhang J, Yang H et al. Predictive value of serum albumin level for the prognosis of severe sepsis without exogenous human albumin administration: A prospective cohort study:J Intensive Care Med. 2016; 33(12):687-94
13. Liu P, Zhi D, Wang Y, Lin J, Zhang M, Duan M. Effects of Albumin Supplements on In-Hospital Mortality in Patients with Sepsis or Septic Shock: A Systemic Review and Meta-Analysis. Evid Based Complement Alternat Med. 2022;2022:2384730.
14. Patankar TF, Karnad DR, Shetty PG et-al. Adult cerebral malaria: prognostic importance of imaging findings and correlation with postmortem findings. Radiology. 2002;224 (3): 811-6.
15. Trivedi, S., Chakravarty, A. Neurological Complications of Malaria. Curr Neurol Neurosci Rep 22, 499–513 (2022)
16. Katsoulis O, Georgiadou A, Cunnington AJ. Immunopathology of acute kidney injury in severe malaria. Front Immunol. 2021;12:651739.
17. Mohandas N, An X. Malaria and human red blood cells. Med Microbiol Immunol. 2012;201(4):593-8.
18. Erwin F. Complications of Kidney in Severe Malaria. 2022;11(3):6–17.
19. Li C, Ren Q, Li X, et al. Association between furosemide administration and clinical outcomes in patients with sepsis-associated acute kidney injury receiving renal replacement therapy: a retrospective observational cohort study based on MIMIC-IV databaseBMJ Open 2023;13:e074046.
20. Billings, F.T., Lopez, M.G. & Shaw, A.D. The incidence, risk, presentation, pathophysiology, treatment, and effects of perioperative acute kidney injury. Can J Anesth/J Can Anesth 68, 409–422 (2021)
21. Oh SW, Han SY. Loop Diuretics in Clinical Practice. Electrolyte Blood Press. 2015;13(1):17-21.
22. McMahon BA, Chawla LS. The furosemide stress test: current use and future potential. Ren Fail. 2021;43(1):830-839.
23. Ruwizhi N, Maseko RB, Aderibigbe BA. Recent Advances in the Therapeutic Efficacy of Artesunate. Pharmaceutics. 2022;14(3):504.
24. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving sepsis campaign : international guidelines for management of sepsis and septic shock 2021. Intensive Care Med [Internet]. 2021;47(11):1181–247.
25. National Clinical Guideline Centre (UK). The Prevention and Management of Pressure Ulcers in Primary and Secondary Care. London: National Institute for Health and Care Excellence (NICE); 2014 Apr. (NICE Clinical Guidelines, No. 179.) 9, Repositioning
26. Aoki Y, Kato H, Fujimura N, Suzuki Y, Sakuraya M, Doi M. Effects of fentanyl administration in mechanically ventilated patients in the intensive care unit: a systematic review and meta-analysis. BMC Anesthesiol. 2022;22(1):323
27. Pasrija D, Hall CA. Airway Suctioning. [Updated 2023 Feb 15]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan

28. Sharma S, Hashmi MF, Valentino III DJ. Sedation Vacation in the ICU. [Updated 2022 Nov 6]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan
29. Dinarello ACA, Porat R. Pathophysiology and treatment of fever in adults. 2023;
30. Pandey S, Rai P, Guha SK, et al. Outcome of Adult Malarial Co-infections in Eastern India. J Glob Infect Dis. 2022;14(2):57-63.
31. Yadava SK, Laleker A, Fazili T. Post-malaria neurological syndrome: a rare neurological complication of malaria. Infection. 2019;47(2):183-193.
32. Mathison BA, Pritt BS. Update on Malaria Diagnostics and Test Utilization. J Clin Microbiol. 2017;55(7):2009-2017
33. Idro R, Marsh K, John CC, Newton CR. Cerebral malaria: mechanisms of brain injury and strategies for improved neurocognitive outcome. Pediatr Res. 2010;68(4):267-274.
34. J.H. Walters, Ian A. McGregor, The mechanism of malarial hepatomegaly and its relationship to hepatic fibrosis, Transactions of The Royal Society of Tropical Medicine and Hygiene, Volume 54, Issue 2, March 1960, Pages 135–145
35. Ghosh D, Stumhofer JS. The spleen: "epicenter" in malaria infection and immunity. J Leukoc Biol. 2021;110(4):753-769.
36. Wilson S, Jones FM, Mwatha JK, Kimani G, Booth M, Kariuki HC, Vennervald BJ, Ouma JH, Muchiri E, Dunne DW. Hepatosplenomegaly associated with chronic malaria exposure: evidence for a pro-inflammatory mechanism exacerbated by schistosomiasis. Parasite Immunol. 2009;31(2):64-71.
37. Adebayo JO, Tijjani H, Adegunloye AP, Ishola AA, Balogun EA, Malomo SO. Enhancing the antimalarial activity of artesunate. Parasitol Res. 2020;119(9):2749-2764.