CLINICAL MANIFESTATIONS, DIAGNOSTIC TECHNIQUES, AND MANAGEMENT OF MALARIA OVALE WITH SECONDARY DENGUE INFECTION: A CASE REPORT

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KEYWORDS

Acute fever, Co-infection, Malaria Ovale, Dengue fever, Dengue hemorrhagic fever.

ABSTRACT

Aims: Malaria and Dengue Fever (DF) or Dengue Hemorrhagic Fever (DHF) are infectious diseases that are both transmitted through mosquito bites. Both have a similar clinical presentation of acute fever, and because of that, the possibility of malaria-dengue co-infection is often overlooked and is commonly misdiagnosed as malaria alone or dengue alone. This case study report aims to demonstrate a rare case, the difficulty of diagnosis and management in a peripheral hospital.
Methodology and results: Reported an adult male with initial suspicion of dengue fever infection only, but after re-anamnesis a history of the patient returning from Papua was obtained. Peripheral blood smear examination confirmed that the patient was also infected with malaria (Plasmodium Ovale). The diagnostic challenge of this case is the initial complaint of fever not accompanied by local symptoms (non-specific), thus raising questions about the cause of the fever in this patient. Malaria and dengue are rare co-infections even in endemic areas. Co-infection of both increases morbidity and mortality in patients, and can be more severe if the patient is treated with only one of them.
Conclusion, significant and impact of study: Malaria and DF/DHF are infectious diseases with similar symptoms, namely acute fever, which makes it difficult to determine the diagnosis, especially in peripheral hospitals. Structured anamnesis, supported by blood smears and routine blood tests, may be a reference for establishing a diagnosis. Proper treatment depends on a correct and quick diagnosis

1. INTRODUCTION

Malaria and Dengue Hemorrhagic Fever (DHF) are infectious diseases caused by parasites and viruses. Both are transmitted to humans through the bite of infected mosquitoes, namely the Anopheles and Aedes mosquitoes.(Mon et al., 2022) Malaria is caused by the plasmodium parasite with a prevalence in the world according to the World Health Organization (WHO) in 2022 of 249 million cases and an estimated death toll of 608,000.(World Health Organization, 2023) The cases that occurred in Indonesia are estimated to be around 800,000 cases in 2021, and are the second highest in Southeast Asia after India. With relatively high transmission in eastern Indonesia.(Sugiarto et al., 2022) The intensity of malaria symptoms is determined by the type of plasmodium that infects. The cause of malaria is the female Anopheles mosquito, which transmits the infection through bites. There are 5 types of parasites that cause malaria (plasmodium), namely: Plasmodium Palciparum/ P. Falciparum (the type of plasmodium most commonly found in Indonesia); Plasmodium Vivax/ P. Vivax and Plasmodium Malariae/ P. Malariae (can be found in several provinces such as Lampung, East Nusa Tenggara, and Papua); Plasmodium Ovale/ P. Ovale (some come from the Eastern Indonesia region); and finally Plasmodium Knowlesi/ P. Knowlesi. The Indonesian Ministry of Health through the Directorate of Prevention and Control of Infectious Diseases in 2022, said that there were 399,666 confirmed cases of malaria in Indonesia, with prevalence based on the type of plasmodium being: 51.3% caused by P. falciparum, 33.4% by P. vivax, and 15.3% or the rest by other types of Plasmodium.(Fitriani Kahar, Yuwono Setiadi, SY Didik Widiyanto, Depri Ardiyansyah, 2024)(Fitri et al., 2023) Meanwhile, the discussion turned to dengue infection. Dengue fever is a disease caused by a virus, namely the dengue virus (DENV). Which is divided into types (serotypes) DENV-1, DENV-2, DENV-3, and DENV-4. Which according to world data in 2023, the number of cases affected more than 80 countries which was the highest record with more than 6.5 million cases and more than 7,300 deaths related to dengue fever.(Mon et al., 2022)(World Health Organization, 2024) In Indonesia, from the beginning of the year to July 2024, there were 149,866

confirmed cases of dengue fever in Indonesia. The reported figure is about three times higher than the same period in 2023 (the previous year). It was reported that dengue fever cases had occurred in 465 districts in 38 provinces in Indonesia, with an incidence of 884 deaths.(World Health Organization Indonesia, 2024) Malaria and Dengue Fever, both of these diseases are life-threatening diseases. Both of these diseases attack (endemic) in subtropical and tropical countries such as Southeast Asia and the Asia Pacific region, so both are also often found and can be called endemic in Indonesia.(Mon et al., 2022)

Having the similar symptoms as acute fever or usually this is diagnosed with Acute Undifferentiated Febrile Illness (AUFI). AUFI is a condition where the disease has non-specific symptoms such as sudden fever (which rarely becomes a prolonged fever), accompanied by headache, chills, myalgia, which can also involve certain organs. Malaria and dengue fever are the main causes of this AUFI disease. Both are major causes of acute fever, and may occur together. However, due to similar clinical manifestations, the diagnosis may be either malaria alone or dengue alone, and this may lead to misdiagnosis and missed diagnosis of both possible diseases.(Gebremariam et al., 2023) In areas endemic for malaria and dengue fever, concurrent infections can complicate diagnosis and are sometimes associated with higher severity/morbidity or associated with changes in the clinical pathophysiology of the disease. Although malaria and dengue fever can occur together, the fact that both infections occur together is still a rare and rarely reported case. DHF has severe complications in the form of bleeding (39.6%), jaundice (19.8%), and shock/hypotension (17.9%). While Malaria has complications in the form of severe malaria, with signs and symptoms that are once again similar to DHF with bleeding (47.9%), jaundice (32.2%), and impaired consciousness (7.43%).(González-Macea et al., 2023)(Kotepui et al., 2020) Malaria Ovale caused by P. Ovale is a type of plasmodium with the mildest symptoms of all types of plasmodium that cause malaria. P. Ovale has an incubation period of 11 to 16 days, and can reach a latent period of up to 4 years. Symptoms can last for 3-4 days without treatment, and rarely more than 10 days, symptoms also often occur at night.(Fitriani Kahar, Yuwono Setiadi, SY Didik Widiyanto, Depri Ardiyansyah, 2024) In addition to having similar clinical manifestations, the complications that can be found are almost the same for malaria and DHF. This makes it difficult to distinguish whether the infection that occurs is only dengue fever or malaria fever or both.

2. METERIALS AND METODS

A. CASE ILLUSTRATION

A 19-year-old man with the initials M came to the Emergency Room of Batang District Hospital on May 26, 2024 with complaints of fever and chills. The patient came with complaints of fever since approximately 1 month before being admitted to the hospital. The fever was felt to be fluctuating in temperature, the fever was also felt during the day with a duration of around 1-2 hours. The fever was accompanied by chills, sweating and headache. The fever did not go down with medication. Other complaints were nausea and decreased appetite. Vomiting complaints were denied. there were no complaints related to defecation and urination.

B. PHYSICAL EXAMINATION

On physical examination, abnormal results were obtained at a patient temperature of 38 degrees Celsius.

C. SUPPORTIVE EXAMINATION

Table 1. Complete Blood Examination in the Emergency Room (May 26, 2024)

Type of Examination	Result	Normal Reference Values
Leukocytes	7.800	3.800-10.600 /uL
Erythrocytes	3.030.000	4.400.000-5.900.000 /uL
Hemoglobin	9,3	13,2-17,3 gr/dL
Hematocrit	25,5	40,0-52,0 %
Thrombocytes	117	150.000-450.000 /uL
MCV	84,2	80-100 fL
MCH	30,7	26,0-34,0 pg
MCHC	36,5	32,0 – 36,0 gr/dL
RDW-SD	44	37 – 54 fL
RDW-CV	14,1	11 - 16 %

D. INITIAL WORKING DIAGNOSIS
- Obs febris suspected DHF dd/ Typhoid Fever

E. INITIAL THERAPY
Patient Responsible Physician (Internal Medicine Specialist)
- Ringer Lactate infusion plus Ondansetron 1 ampoule -> 20 drops per minute
- Pantoprazole injection 1 amp every 12 hours
- Paracetamol injection 500 mg every 6 hours
- Methylprednisolone injection ½ ampoule every 12 hours
- Psidii 3x1 capsule
- Recheck laboratory: repeat routine blood tomorrow

F. FOLLOW UP ON PATIENT PROGRESS
- Day 1 (May 27, 2024): the patient complained of fluctuating fever. Routine blood laboratory tests and anti-salmonella IgM were performed. Abnormal results were obtained erythrocytes 2,970,000/uL, Hb 9.3gr/dL, Hemetocrit 25.8%, Thrombocytes 127,000/uL, and anti-salmonella IgM results 2 (within normal limits).
- Day 2 (May 28, 2024): the patient complained of a fever that was still fluctuating. Routine blood laboratory tests and anti-dengue IgG and IgM were performed. The result were abnormal: erythrocytes 2,560,000/uL, Hb 8.4gr/dL, Hemetocrit 23.3%, Thrombocytes 127,000/uL, and positive IgG (normal negative) and negative IgM (normal negative).
- Day 3 (May 29, 2024): Complaints of fever that still fluctuate. Re-anamnesis was performed, it was found that the patient had previously worked in Papua since 11 months ago. When the patient went to Papua and while there, the patient did not take malaria prophylaxis medication. The patient had just returned to Batang district about 9 days before being admitted to the hospital. When in Papua, he had been treated and was only given medication to reduce fever. A similar history of previous illnesses was denied, but many of the patient's co-workers had similar complaints. Then a thick and thin blood smear examination was performed for malaria. With the results of the peripheral blood smear examination, the results found malaria parasites plasmodium ovale ring stage, schizonts and gametocytes. Therapy for the patient changed to:
  - Ringer Lactate infusion plus Ondansetron 1 ampoule -> 20 drops per minute
  - Pantoprazole injection 1 amp every 12 hours
  - Paracetamol injection 500 mg every 6 hours
  - Methylprednisolone injection ½ ampoule every 12 hours
  - Ceftriaxone injection 1 gram every 12 hours
  - Psidii 3x1 capsule
  - Routine blood test repeat, thick and thin blood smears for malaria
  - DHP 1x3 tablets (days 1-3)
  - Primaquine 1x1 tablet (days 1-14)
  - PRC transfusion 2 kolf, extra injection of furosemide 1 ampoule per kolf
- Day 4 (May 30, 2024): complaints of fever have decreased. Therapy for the patient is continued.
- Day 5 (June 1, 2024): complaints of fever are gone. Routine blood laboratory tests are carried out after the transfusion. The results obtained: leukocytes 16,260/uL, erythrocytes 3,700,000/uL, Hb 10.9gr/dL, Hemetocrit 31.8%, Thrombocytes 179,000/uL. The patient was allowed to go home in the afternoon by continuing malaria treatment and control in the internal medicine polyclinic.

3. RESULTS AND DISCUSSION

A. CLINICAL MANIFESTATION
A 19-year-old male patient was reported to the Emergency Room of Batang District Hospital on May 26, 2024, with chief complaints of fever and chills. Fever since approximately 1 month. Worsening since the last 3-4 days. Fever goes up and down. Fever accompanied by chills, sweating and headache. Fever does not go down with medication. History of nosebleeds, bleeding gums, and red spots on the body is denied. Other complaints are nausea, and decreased appetite. There are no complaints of defecation and urination. On physical examination, abnormal results were found temperature 38 C. On routine blood laboratory examination, abnormal results Hemoglobin 9.3 gr / dL and Thrombocytes 117,000 / uL. The initial working diagnosis in the patient is observation of febrile suspected DHF dd / Typhoid Fever.

In patients with initial complaints of fever and chills can be a sign of various conditions of a disease. Acute fever (fever less than 3-4 days) is a common symptom of diseases that can be caused by various infections. Some diseases are accompanied by local symptoms (eg: respiratory tract infections, urinary tract infections, gastrointestinal infections), and some are not accompanied by local symptopms (eg: Unspecified Fever or Fever of Unknown Origin). Febrile diseases due to infection require slightly different patient management than other fevers, because the pathogens that cause fever can vary. These pathogens include parasites (Plasmodium), bacteria (Salmonella, Rickettsia or Leptospira) and viruses (dengue, chikungunya or zika viruses). Therefore, misinterpretation of non-specific fever and empirical diagnostic practices alone can lead to inadequate treatment. Inadequate treatment can result in a high risk of death, continued transmission of the disease, and increased resistance to antimicrobial treatment.(Sebastian Hin, Benjamin Lopez-Jimena, Muhammed Bakheit, Vanessa Klein, Seamus Stack, Cheikh Fall, Amadou Sall, Khalid Enan, Mohamed Mustafa, Liz Gillies, Viorel Rusu, Sven Goethel, Nils Paust, Roland Zengerle, Sieghard Frischmann, Manfred Weidmann, 2021)
The patient was initially diagnosed with dengue fever with a differential diagnosis of typhoid fever. In theory, dengue virus infection is divided into dengue fever (DF) infection and dengue hemorrhagic fever (DHF) infection. The main clinical symptoms of dengue fever are such as sudden high fever, headache, pain in the retro-orbital area, pain in the joints, and myalgia (muscle pain). Meanwhile, dengue hemorrhagic fever is a more severe form of dengue fever which is characterized by clinical manifestations in the form of bleeding phenomena, hepatomegaly, and circulatory failure. Bleeding manifestations that can be found in DHF patients include a positive tourniquet test, petechiae and ecchymosis on the skin, epistaxis and bleeding gums, and even gastrointestinal bleeding in severe DHF conditions.(Alvinasyrah, 2021) However, considering the absence of bleeding manifestations, the patient's clinical course leads to a temporary diagnosis of typhoid fever. Typhoid fever is an acute infectious fever that attacks the digestive system and is caused by the bacteria: Salmonella Typhi and/or Salmonella Paratyphi. Transmitted through food or drink contaminated by bacteria. The classic clinical manifestations of typhoid fever include fever, malaise, abdominal pain and constipation. Blood culture examination is the gold standard examination for a definite diagnosis of typhoid fever, but this examination is rarely performed due to the high cost and long examination time.(Yelvi Levani, 2020)
With the possibility of the two infections above, the patient actually missed the possibility of being infected with malaria fever. Lack of anamnesis from the beginning regarding travel history, and the similarity if the fever is experienced for more than 1 week with typhoid fever makes malaria fever missed. Malaria sufferers usually experience high fever, chills, and flu-like illness. Generally, the diagnosis is made based on symptoms and clinical signs. Even in areas where malaria is not endemic, a differential diagnosis of malaria needs to be considered, especially if there is a history of repeated high fever accompanied by the triad of malaria symptoms, such as: fever, splenomegaly, and anemia. And although in some cases the diagnosis of malaria is the result of clinical considerations, laboratory tests are still needed for rapid diagnosis (such as RDT) to confirm the diagnosis of malaria before treatment. This is because malaria can cause many complications and death, if not given adequate treatment. (Weny Rinawati, 2019)

B. DIAGNOSTIC CHALLENGES

When following up the patient's condition in the ward, the results of IgM anti-salmonella were normal (May 27, 2024), then there was a decrease in Hb to 8.4 gr/dL and thrombocytopenia 127,000/uL and positive IgG anti-dengue (May 28, 2024). Then a re-anamnesis was carried out on the patient and information was obtained that the patient had a history of traveling from Papua, and at the time of re-anamnesis (May 29, 2024) it was the 11th day after returning from Papua, then with suspicion of malaria infection, a peripheral blood smear examination was carried out and malaria parasites were found with the type Plasmodium ovale with ring, schizont, and gametocyte stages. The patient's diagnosis changed to Malaria Ovale coinfection with Dengue Fever with moderate anemia.
The patient was found to have biscytopenia with anemia 8.4 and thrombocytopenia 127,000, accompanied by positive IgG anti-dengue. Positive/appearing IgG indicates a secondary infection from dengue fever, which can appear on the 2nd to 7th day and last a long time or even forever. Dengue virus infection is characterized by IgG/IgM examination results, in the form of IgG (+) and IgM (+) or IgG (+) and IgM (-). However, in reality, many examination results in the field do not match the patient's clinical condition and Thrombocytes count, such as sometimes decreasing Thrombocytes but IgG (-) and IgM (-).(Gela Setya Ayu Putri, Hikmayanti, Erma Lestari, 2024) However, if it is only caused by dengue virus infection, there is an oddity where anemia also occurs without any signs of bleeding. So when re-anamnesis was carried out, a history of travel from Papua was found, and an additional diagnosis was confirmed to be malaria when microscopic examination was

performed with peripheral blood smear examination. Also in this patient, an uncommon malaria (non-falciparum) was found in the form of ring stage, schizont and gametocytes from plasmodium ovale. In this patient, two infections occurred, namely malaria with dengue fever.

Typical symptoms of malaria are chills, fever, and excessive sweating, which are characteristic of paroxysms (malaria attacks). These typical symptoms consist of three consecutive stages, namely: cold stage, hot stage, and sweating stage. However, the clinical manifestations may not be specific and are often mistaken for other diseases such as flu infections. Many diseases also have fever as the main clinical manifestation, therefore accurate laboratory parameters are very important in endemic areas. Cases that are clinically suspicious/ suggestive of malaria infection must be confirmed by laboratory diagnostic tests such as microscopic tests, rapid diagnostic tests (RDTs), and/or polymerase chain reaction (PCR) tests.(Santos-Reis & Nina, 2022) False positive results will lead to inappropriate use of anti-malarial therapy, while in undiagnosed cases it causes increased morbidity and mortality from malaria infection, and causes resistance to antimalarial treatment. The most commonly used method for early detection of malaria infection and remains the gold standard for laboratory confirmation of malaria is microscopic testing (thick and thin blood smear tests) which are easy to use and inexpensive. However, some disadvantages of microscopic testing include subjective identification and counting of parasites according to the examining microscopist, the inability to detect mixed species infections and distinguish P. ovale from P. vivax, and a lower detection limit of parasites that is difficult (between 4–20 parasites/μl). Despite these disadvantages, microscopic testing remains the gold standard for diagnosis because it can identify individuals with active malaria and provide information on parasite density, which is useful for monitoring the effectiveness of treatment. The latest guidelines for the treatment of malaria by the World Health Organization (WHO) require parasitological confirmation with malaria RDT (mRDT) and/or microscopic testing (thick and thin blood smears).(Oboh et al., 2021) Various techniques are currently available to aid in the diagnosis of malaria, ranging from the earliest conventional methods using microscopy to newer methods using rapid molecular methods. In the last decade, the basic concept of immunoassay kits has been discovered and applied to diagnostic methods such as the Malaria Rapid Diagnostic Test (RDT) for detecting Plasmodium species and Flow Cytometry Test, and Enzyme-Linked Immuno Sorbent Assay (ELISA). Other methods are molecular methods such as Polymerase Chain Reaction/PCR (real-time PCR, nested PCR, and Multiplex PCR), and Loop-Mediated Isothermal Amplification (LAMP), are other alternatives that have begun to be widely used in malaria research and diagnosis.(Fitri et al., 2022)

In this patient, clinical symptoms are similar between dengue fever and malaria. Both are life-threatening diseases and are indeed endemic in Indonesia which is an area with a Subtropical and Tropical climate. Both have clinical symptoms in the form of thrombocytopenia, and even in dengue fever can also be accompanied by bleeding which can cause complications in the form of anemia. Malaria and dengue fever are difficult to distinguish only by characteristics of the anamnesis and general supporting examinations. The risk of hematologic changes such as thrombocytopenia, in dengue and malaria infections is associated with various clinical factors (e.g., immune status, level of endemicity, demographic factors, individual hemoglobinopathies, and nutritional status of the patient). The clinical presentation of patients with dengue and malaria can resemble and even overlap with many other common tropical infectious diseases.(Mon et al., 2022)

Malaria and dengue fever are endemic diseases in tropical climates, so they can be transmitted and occur simultaneously. Co-infection of malaria and dengue fever is a condition when both diseases occur simultaneously in one person. However, the problem is that because there are similarities in clinical characteristics between these two infections, the diagnosis can be wrong or considered a single infection. This error can increase morbidity and mortality if there is a delay in diagnosis and a delay in adequate treatment. Co-infection of malaria and dengue is not related to age group and is not related to gender. It was observed that co-infection of malaria and dengue increased the occurrence of fatigue, joint and muscle pain. And other findings were associated with fatigue, joint pain and chills. These findings will facilitate early diagnosis and proper treatment of patients infected with malaria and dengue. Co-infection of malaria and dengue can cause severe clinical conditions such as decreased Thrombocytes and hemoglobin levels. Malaria and dengue infections usually show asymptomatic or non-specific symptoms such as fever, headache, fatigue and malaise. (Khider Alsedig, Mawahib H. Eldigail, Adel Hussein Elduma, Arwa Elaagip, Omnia Altahir, Hanaa Adlli Siam, Ypusif Ali, 2023)

From this patient, it is known that it is important to conduct a structured and systematic anamnesis, and re-anamnesis can be conducted if a patient has a history of fever accompanied by chills and supporting examinations that are not specific to a causative disease. As in this case, the patient who was initially diagnosed with dengue fever with a differential diagnosis of typhoid, changed to malaria coinfection with dengue fever.

Delay or inaccuracy in establishing a diagnosis can cause a bad condition and may possibly worsen the condition.

C. TREATMENT MANAGEMENT

The management of patients when the diagnosis changes to malaria ovale is to become Ringer Lactate Infusion plus Ondansetron 1 ampoule dose 20 tpm; Pantoprazole injection 1 amp per 12 hours; Paracetamol injection 500 mg per 6 hours; Methylprednisolone injection ½ ampoule per 12 hours; Ceftriaxone injection 1 gram per 12 hours; Per oral psidii 3x1; Routine blood checks, Thick and thin smear malaria; DHP 1x3 tablets (days 1-3); primaquine 1x1 tablet (days 1-14); Packed Red Cell transfusion 2 kolf, extra furosemide injection 1 ampoule per kolf. The patient was discharged on 1-6-2024 with lab results of Hb 10.9 gr / dL; Thrombocytes 179,000 / uL and brought home malaria medication to be continued at home.

The main strategy for malaria treatment is rapid and accurate diagnosis followed by effective treatment. According to WHO guidelines, all patients suspected of having malaria should be confirmed by blood smear microscopy or malaria-specific Rapid Diagnostic Tests (RDTs) before antimalarial treatment is started. Presumptive diagnosis based on clinical features and history alone without laboratory confirmation for blood-stage markers of infection is only permissible if blood smear microscopy or RDTs are not available.(Otambo et al., 2022) First-line therapy for P. falciparum malaria is combination therapy that includes artemisinin. When artemisinin-based combination therapy (ACT) is not available, atovaquone-proguanil or quinine plus clindamycin is used for chloroquine-resistant malaria. P. vivax, P. ovale, P. malariae, and P. knowlesi are usually sensitive to chloroquine, and treatment with artemisinin-based combination therapy or chloroquine for areas with chloroquine-susceptible infections for uncomplicated malaria is recommended. For severe malaria, intravenous artesunate is the first-line therapy.(Daily et al., 2022) It would be potentially dangerous to give only the first dose of treatment to patients with suspected but unconfirmed malaria, with the aim of providing complete treatment if the diagnosis is confirmed. This practice is unsafe and may lead to resistance, and is not recommended.(World Health Organization, 2022)

Table 2. Malaria treatment guidelines.(World Health Organization, 2015)

Treatment of uncomplicated P. Falciparum malaria	• Treatment of children and adults (except pregnant women in the first trimester) can take one of the recommended artemisinin-based combination therapies (ACT): - Artemether + lumefantrine - Artesunate + amodiaquine - Artesunate + mefloquine - Dihydroartemisinin + piperaquine - Artesunate + sulfadoxine-pyrimethamine (SP) *strong recommendation • Duration of ACT treatment => ACT regimen is given 3 days of treatment with artemisinin derivatives • Treatment of children => Children <25 kg are treated with dihydroartemisinin + piperaquine given a minimum of 2.5 mg / kg BW daily for dihydroartemisinin and 20 mg / kg BW per day for piperaquine, each for 3 days.
Treatment of malaria P. Vivax, P. Ovale, P. Malariae, P. Knowlesi, without complications	• If the type of malaria is not known for certain, treat as for uncomplicated P. falciparum malaria. • In areas with chloroquine-sensitive infections, treat adults and children with ACT or chloroquine. (except pregnant women in the first trimester) *strong recommendation • In areas with chloroquine-resistant infections, treat adults and children with ACT alone. (except pregnant women in the first trimester). *strong recommendation • Treat pregnant women in the first trimester who have chloroquine resistance with quinine. *strong recommendation
Treatment of Severe Malaria	• Treat adults and children with severe malaria (including infants, pregnant women in all trimesters and lactating mothers) with intravenous or intramuscular artesunate for at least 24 hours and until they can tolerate oral therapy. When patients have received at least 24 hours of parenteral therapy and can tolerate oral therapy, complete treatment with 3 days of ACT (add a single dose of primaquine in areas where transmission is rare). *strong recommendation • • Children weighing <20 kg should receive a higher dose of artesunate (3 mg/kg per dose) than adults (2.4 mg/kg per dose) to ensure equal exposure to treatment.*strong recommendation

Meanwhile, for the management of dengue fever infection, if the case is detected early and given proper medical treatment, then most cases of dengue fever can heal well on their own and have a low mortality rate (only <1%). Only a few patients develop and become severe diseases (including DHF/DSS) with a mortality rate of around 2%-5% after receiving treatment; and if not treated, the mortality rate will increase to reach 20%. Infants and those with secondary DENV infections are the groups most often affected by severe dengue fever. The most common explanation for this phenomenon is the increase in Antibody Dependent Enhancement (ADE). When the immune response produces antibodies that recognize and attach to pathogens but cannot stop the infection, this is known as ADE. As a result, pathogens can enter cells and worsen the immune response because the antibodies behave uncontrollably. The increase in virus entry into host cells, especially dendritic cells and macrophages, is made possible by this virus-antibody complex. Once ADE has formed, infection and spread of the virus increases which will then trigger more cytokine production by immune cells, called a cytokine storm and eventually become severe disease.(Khan et al., 2023)

If there is no therapeutic target for dengue fever (eg: laboratory results and vital signs are still within normal limits), then good supportive care (eg: medication for clinical symptom management and fluid administration) is the cornerstone of therapy for dengue fever. According to WHO Guidelines, acetaminophen or paracetamol is recommended as an antipyretic at a dose of 10 mg/kg/dose (maximum for adults is 4 grams/day and frequency ≥6 hours). And aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) are contraindicated because of their antiplatelet activity and increased risk of bleeding. Proper and adequate fluid administration to ensure adequate peripheral tissue perfusion during the critical phase of the disease is the most important thing in the management of dengue fever. Oral rehydration is recommended in cases of mild dengue fever and in patients with adequate oral intake. Hospitalization and therapy in the form of fluid administration via infusion/intravenous (IV) are recommended in cases of inadequate oral intake, vomiting, persistent increase in hematocrit (HCT) of 10–20% despite oral rehydration, and the presence of warning signs, and in cases of dengue fever with impending shock/ seizures. In the case of DSS (Dengue Shock Syndrome) Randomized clinical trials (RCT) showed that in pediatric patients with DSS there was no difference between resuscitation groups with colloids or crystalloids and no difference in shock recurrence. However, in severe shock, colloids are preferred because they have been shown to restore cardiac index and hematocrit faster than crystalloids. Fluid resuscitation with isotonic crystalloid solution of 10 ml/kg over 1 hour for patients with compensated shock and 20 ml/kg bolus over 15 minutes for severe decompensated hypovolemic shock followed by a reduction in fluid dose supplemented with colloid bolus solution as needed. However, it should be noted that longer duration of IV fluid therapy results in a greater amount of IV fluid therapy and the risk of respiratory distress due to fluid accumulation. In red blood cell transfusion therapy, transfusion of 10 ml/kg of whole blood or 5 ml/kg of red blood cells to treat bleeding due to thrombocytopenia may be necessary according to transfusion indications. Meanwhile, platelet concentrate (TC) transfusion for bleeding prophylaxis has not been shown to be superior to supportive care in preventing bleeding and in fact may increase adverse reactions. The last therapy is the use and development of a dengue vaccine, which is currently facing obstacles. The obstacle to developing a dengue vaccine is that the vaccine has not been able to provide "effective and balanced" protection against all four dengue serotypes. In addition, the existence of ADE poses a significant challenge in the development of a dengue vaccine.(Palanichamy Kala et al., 2023)

Management of malaria and dengue fever is almost the same: focusing on fluid support, treating clinical symptoms and preventing worsening. However, malaria has a more specific therapy in the form of an ACT regimen, and the rest is also supportive: intravenous fluid administration (in the form of colloid or crystalloid fluids, but avoid bolus infusion), blood transfusion (in high transmission blood transfusion if Hb <5 gr/dL/ HT <15%, and in low transmission if Hb <7gr/dL/ HT <20%), use of antibiotics (given only if indicated, especially in pediatric patients with malaria in areas with high transmission).(World Health Organization, 2015)

4. CONCLUSION

Malaria and dengue fever (DF)/ Dengue Hemorrhagic Fever (DHF) are infectious diseases caused by the Plasmodium Parasite and the Dengue Virus, both of which are transmitted through the bite of an infected mosquito to humans. Both of these infectious diseases have similar symptoms, such as acute fever (which rarely becomes a prolonged fever). The fever that appears is also accompanied by headache, chills, and myalgia, which can then also affect certain organs of the body. Because of the similar symptoms or clinical manifestations, the possibility of malaria co-infection with dengue fever is often overlooked and is generally misdiagnosed as just malaria or just dengue fever.

An adult male has been examined with an initial suspicion of only dengue fever infection, but after a re-anamnesis because of slightly unusual clinical and laboratory results, a history of the patient traveling from Papua was obtained. Examination of peripheral blood smears confirmed that in addition to the patient suffering from dengue fever infection, he also suffered from plasmodium ovale malaria infection. The diagnostic challenge here is the similar complaints between these two infectious diseases. And the course of the disease is almost similar, and often occurs together in endemic areas. And it becomes a problem when patients are only treated for dengue fever/dengue hemorrhagic fever, without treating malaria, or vice versa. Both can worsen each other's morbidity when they occur together.

The right management is to know the cause of the infection that occurs in the patient through systematic anamnesis and specific supporting. So that treatment can be given appropriately and treatment time can be reduced, this also reduces patient morbidity and mortality.

5. REFERENCES

1. Alvinasyrah. (2021). Nilai Trombosit Dan Hematokrit Dalam Manifestasi Perdarahan Pasien Demam Berdarah Dengue. Jurnal Penelitian Perawat Profesional, 3(1), 153–158. Https://Doi.Org/10.37287/Jppp.V3i1.358
2. Daily, J. P., Minuti, A., & Khan, N. (2022). Diagnosis, Treatment, And Prevention Of Malaria In The Us: A Review. Jama, 328(5), 460–471. Https://Doi.Org/10.1001/Jama.2022.12366
3. Fitri, L. E., Pawestri, A. R., Winaris, N., Endharti, A. T., Khotimah, A. R. H., Abidah, H. Y., & Huwae, J. T. R. (2023). Antimalarial Drug Resistance: A Brief History Of Its Spread In Indonesia. Drug Design, Development And Therapy, 17(Null), 1995–2010. Https://Doi.Org/10.2147/Dddt.S403672
4. Fitri, L. E., Widaningrum, T., Endharti, A. T., Prabowo, M. H., Winaris, N., & Nugraha, R. Y. B. (2022). Malaria Diagnostic Update: From Conventional To Advanced Method. Journal Of Clinical Laboratory Analysis, 36(4), E24314. Https://Doi.Org/Https://Doi.Org/10.1002/Jcla.24314
5. Fitriani Kahar, Yuwono Setiadi, Sy Didik Widiyanto, Depri Ardiyansyah, N. Q. (2024). Malaria: Penularan, Diagnosis, Pengobatan Dan Pencegahan Di Indonesia. Intechterbuka. Https://Doi.Org/10.5772/ Intechopen.112982
6. Gebremariam, T. T., Schallig, H. D. F. H., Kurmane, Z. M., & Danquah, J. B. (2023). Increasing Prevalence Of Malaria And Acute Dengue Virus Coinfection In Africa: A Meta-Analysis And Meta-Regression Of Cross-Sectional Studies. Malaria Journal, 22(1), 300. Https://Doi.Org/10.1186/S12936-023-04723-Y
7. Gela Setya Ayu Putri, Hikmayanti, Erma Lestari, A. H. (2024). Hubungan Hasil Pemeriksaan Igm Dan Igg Anti-Dengue Terhadap Jumlah Trombosit Pasien Dengue Di Rsud Dr. Gondo Suwarno Semarang. Bornei Journal Of Medical Laboratory Technology (Bjmlt), 7(1), 531–536. Https://Journal.Umpr.Ac.Id/ Index.Php/Bjmlt/Article/Download/7384/4706/31425
8. González-Macea, O., Martínez-Ávila, M. C., Pérez, M., Tibocha Gordon, I., & Arroyo Salgado, B. (2023). Concurrent Dengue-Malaria Infection: The Importance Of Acute Febrile Illness In Endemic Zones. Clinical Medicine Insights: Case Reports, 16, 11795476221144584. Https://Doi.Org/10.1177/11795476221144585
9. Khan, M. B., Yang, Z.-S., Lin, C.-Y., Hsu, M.-C., Urbina, A. N., Assavalapsakul, W., Wang, W.-H., Chen, Y.-H., & Wang, S.-F. (2023). Dengue Overview: An Updated Systemic Review. Journal Of Infection And Public Health, 16(10), 1625–1642. Https://Doi.Org/Https://Doi.Org/10.1016/J.Jiph.2023.08.001
10. Khider Alsedig, Mawahib H. Eldigail, Adel Hussein Elduma, Arwa Elaagip, Omnia Altahir, Hanaa Adlli Siam, Ypusif Ali, T. A. (2023). Prevalence Of Malaria And Dengue Co-Infections Among Febrile Patients During Dengue Transmission Season In Kassala, Eastern Sudan. Plos Negl Trop Dis, 17(10), E0011660. Https://Doi.Org/10.1371/Journal.Pntd.0011660
11. Kotepui, M., Kotepui, K. U., Milanez, G. D. J., & Masangkay, F. R. (2020). Prevalence Of And Risk Factors For Severe Malaria Caused By Plasmodium And Dengue Virus Co-Infection: A Systematic Review And Meta-Analysis. Infectious Diseases Of Poverty, 9(1), 134. Https://Doi.Org/10.1186/S40249-020-00741-Z
12. Mon, N. T. S., Tangpukdee, N., Charunwatthana, P., Boonnak, K., Krudsood, S., Kano, S., Wilairatana, P., & Leowattana, W. (2022). Mimicking Platelet Indices In Patients With Malaria And Dengue Hemorrhagic Fever: Characteristics And Clinical Applications. Tropical Medicine And Health, 50(1), 76. Https://Doi.Org/10.1186/S41182-022-00467-8
13. Oboh, M. A., Oriero, E. C., Ndiaye, T., Badiane, A. S., Ndiaye, D., & Amambua-Ngwa, A. (2021). Comparative Analysis Of Four Malaria Diagnostic Tools And Implications For Malaria Treatment In Southwestern Nigeria. International Journal Of Infectious Diseases, 108, 377–381. Https://Doi.Org/Https://Doi.Org /10.1016/J.Ijid.2021.05.049
14. Otambo, W. O., Olumeh, J. O., Ochwedo, K. O., Magomere, E. O., Debrah, I., Ouma, C., Onyango, P., Atieli, H., Mukabana, W. R., Wang, C., Lee, M.-C., Githeko, A. K., Zhou, G., Githure, J., Kazura, J., & Yan, G. (2022). Health Care Provider Practices In Diagnosis And Treatment Of Malaria In Rural Communities In Kisumu County, Kenya. Malaria Journal, 21(1), 129. Https://Doi.Org/10.1186/S12936-022-04156-Z
15. Palanichamy Kala, M., St. John, A. L., & Rathore, A. P. S. (2023). Dengue: Update On Clinically Relevant Therapeutic Strategies And Vaccines. Current Treatment Options In Infectious Diseases, 15(2), 27–52.

Https://Doi.Org/10.1007/S40506-023-00263-W
16. Santos-Reis, A., & Nina, J. (2022). A Difficult Diagnosis Of Plasmodium Ovale Malaria. Acta Médica Portuguesa, 35(6 Se-Case Report), 484–487. Https://Doi.Org/10.20344/Amp.15814
17. Sebastian Hin, Benjamin Lopez-Jimena, Muhammed Bakheit, Vanessa Klein, Seamus Stack, Cheikh Fall, Amadou Sall, Khalid Enan, Mohamed Mustafa, Liz Gillies, Viorel Rusu, Sven Goethel, Nils Paust, Roland Zengerle, Sieghard Frischmann, Manfred Weidmann, K. M. (2021). Fully Automated Point-Of-Care Differential Diagnosis Of Acute Febrile Illness. Plos Negl Trop Dis, 15(2), E0009177. Https://Doi.Org/1 0.1371/Journal.Pntd.0009177
18. Sugiarto, S. R., Baird, J. K., Singh, B., Elyazar, I., & Davis, T. M. E. (2022). The History And Current Epidemiology Of Malaria In Kalimantan, Indonesia. Malaria Journal, 21(1), 327. Https://Doi.Org/10.1186/S12936-022-04366-5
19. Weny Rinawati, F. H. (2019). Tinjauan Pustaka : Diagnosis Laboratorium Malaria. Journal Of The Indonesian Medical Asscociation, 69(10), 327–335. Https://D1wqtxts1xzle7.Cloudfront.Net/89871653/114-Libre.Pdf?1660820361=&Response-Content-Disposition=Inline%3b+Filename%3ddiagnosis_Laboratorium_Malaria.Pdf&Expires=1734578589&Signature=Mfack1wfwdu6yih-Teegav1ldipnk-Iopgkum6git~Ocw1kexlkciz4mnups9cpxc2bd
20. World Health Organization. (2015). Guidelines For Treatment Of Malaria-3rd Edition (Third Edit). Who Library Cataloguing. Https://Iris.Who.Int/Bitstream/Handle/10665/162441/9789241549127 _Eng.Pdf?Sequence=1&Is
21. World Health Organization. (2022). Who Guidelines For Malaria (Revision 2). Who Global Malaria Programme.Https://Iris.Who.Int/Bitstream/Handle/10665/354781/Who-Ucn-Gmp-2022.01-Rev.2-Eng.Pdf?Sequence=1
22. World Health Organization. (2023). Malaria. Fact Sheets. Https://Www.Who.Int/News-Room/Fact-Sheets/Detail/Malaria
23. World Health Organization. (2024). Dengue And Severe Dengue. Fact Sheets. Https://Www.Who.Int/News-Room/Fact-Sheets/Detail/Dengue-And-Severe-Dengue
24. World Health Organization Indonesia. (2024). Indonesia Takes Decisive, Pioneering Action To Strengthen Multisource Collaborative Surveillance For Dengue. Surveillance. Https://Www.Who.Int/ Indonesia/News/Detail/30-07-2024-Indonesia-Takes-Decisive--Pioneering-Action-To-Strengthen-Multisource-Collaborative-Surveillance-For-Dengue
25. Yelvi Levani, A. D. P. (2020). Demam Tifoid : Manifestasi Klinis, Pilihan Terapi Dan Pandangan Dalam Islam. Al-Iqra Medical Journal : Jurnal Berkala Ilmiah Kedokteran, 3(1), 10–16. Https://D1wqtxts1xzle7.Cloudfront.Net/70375352/Pdf-Libre.Pdf?1632808 566=&Response-Content-Disposition=Inline%3b+Filename%3ddemam_Tifoid_Manifestasi_Klinis_Pilihan.Pdf&Expires=1734582320&Signature=Fvk~Pp~Ycxurpz8iawdm2ypruj7qwxx6em8u~Kdcpi5olxme6t2~Lx90lji