



To Study On Causes, Manifestations, Diagnosis And Pharmacological Treatment Of Malaria

MELAM.YESURATNAM¹ KANDIMALLA.PHANI KUMAR²

NANDIPALLI.PREVANTH³, PERAM.HARISCHANDRA REDDY⁴, SHAIK.ASMA⁵.

1. MELAM.YESURATNAM. Assistant Professor, Department of Pharmacy Practice, A.M Reddy Memorial college of Pharmacy, Petlurivaripalem, Narasaraopeta, Palnadu Dist, Pin:522601, A.P.

2,3,4,5,Pharm.D Students, A.M.Reddy Memorial College of Pharmacy,Petlurivararipalem,
Narasaraopet, Palnadu-522601, Andhra Pradesh.

ABSTRACT

Malaria is a mosquito-borne infectious disease that affects humans and other vertebrates. Human malaria causes symptoms that typically include fever, fatigue, vomiting, and headaches. In severe cases, it can cause jaundice, seizures, coma, or death. Symptoms usually begin 10 to 15 days after being bitten by an infected Anopheles mosquito. If not properly treated, people may have recurrences of the disease months later. In those who have recently survived an infection, This partial resistance disappears over months to years if the person has no continuing exposure to malaria.

Human malaria is caused by single-celled microorganisms of the Plasmodium group. It is spread exclusively through bites of infected female Anopheles mosquitoes. The mosquito bite introduces the parasites from the mosquito's saliva into a person's blood. The parasites travel to the liver where they mature and reproduce. Five species of Plasmodium commonly infect humans. The three species associated with more severe cases are *P. falciparum*, *P. vivax*, and *P. knowlesi*. *P. ovale* and *P. malariae* generally cause a milder form of malaria. Malaria is typically diagnosed by the microscopic examination of blood using blood films, or with antigen-based rapid diagnostic tests.

KEYWORDS:- Malaria, parasites, mosquitoes. Protozoa, ovale.

Malaria

Malaria is a life-threatening disease spread to humans by some types of mosquitoes. It is mostly found in tropical countries. It is preventable and curable.

The infection is caused by a parasite and does not spread from person to person.

Symptoms can be mild or life-threatening. Mild symptoms are fever, chills and headache. Severe symptoms include fatigue, confusion, seizures, and difficulty breathing.

Infants, children under 5 years, pregnant women, travellers and people with HIV or AIDS are at higher risk of severe infection.



Causes:-

Malaria is caused by infection with parasites in the genus *Plasmodium*. In humans, malaria is caused by six *Plasmodium* species: *P. falciparum*, *P. malariae*, *P. ovale curtisi*, *P. ovale wallikeri*, *P. vivax* and *P. knowlesi*. Among those infected, *P. falciparum* is the most common species identified (~75%) followed by *P. vivax* (~20%).

Although *P. falciparum* traditionally accounts for the majority of deaths, recent evidence suggests that *P. vivax* malaria is associated with potentially life-threatening conditions about as often as with a diagnosis of *P. falciparum* infection. *P. vivax* proportionally

is more common outside Africa. Some cases have been documented of human infections with several species of Plasmodium from higher apes, but except for *P. knowlesi*—a zoonotic species that causes malaria in macaques—these are mostly of limited public health importance.

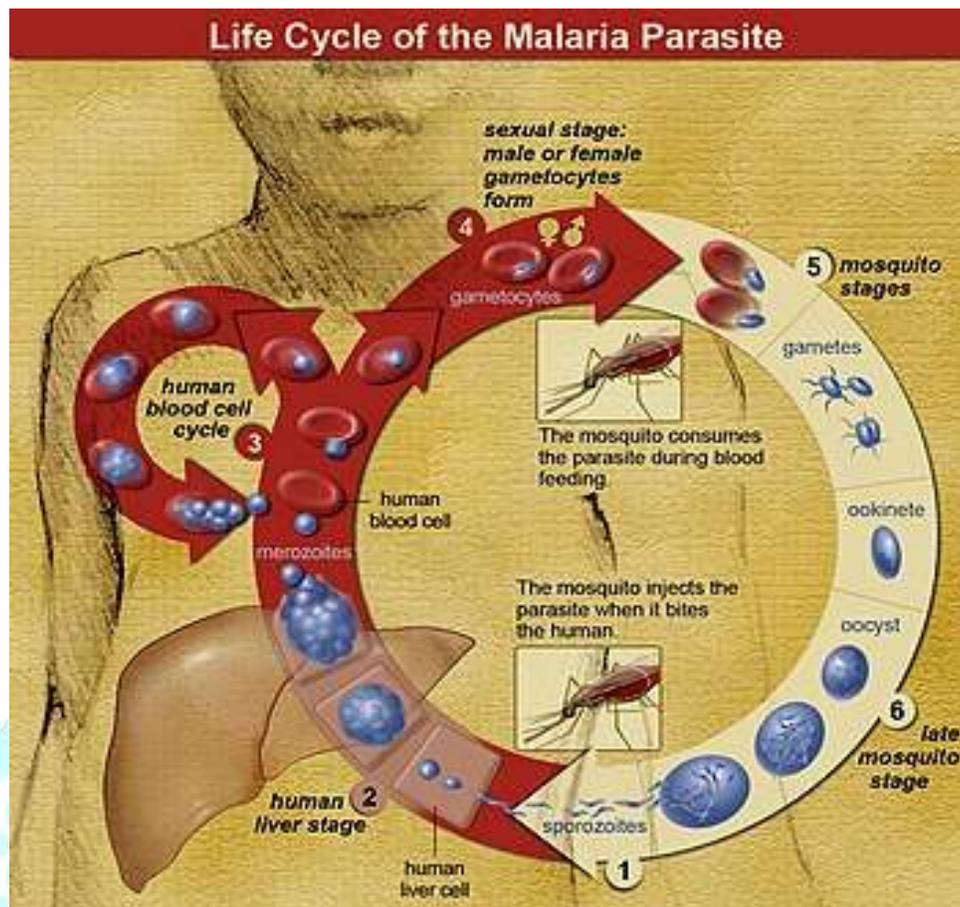
LIFE CYCLE:-

The life cycle of malaria parasites: Sporozoites are introduced by a mosquito bite. When they reach the liver, they multiply into thousands of merozoites. The merozoites infect red blood cells and replicate, infecting more and more red blood cells. Some parasites form gametocytes, which are taken up by a mosquito, continuing the life cycle.

The Anopheles mosquitos initially get infected by Plasmodium by taking a blood meal from a previously Plasmodium infected person. Parasites are then typically introduced by the bite of an infected Anopheles mosquito. Some of these inoculated parasites, called "sporozoites", probably remain in the skin, but others travel in the bloodstream to the liver, where they invade hepatocytes. They grow and divide in the liver for 2–10 days, with each infected hepatocyte eventually harboring up to 40,000 parasites. The infected hepatocytes break down, releasing this invasive form of Plasmodium cells, called "merozoites" into the bloodstream. In the blood, the merozoites rapidly invade individual red blood cells, replicating over 24–72 hours to form 16–32 new merozoites. The infected red blood cell lyses, and the new merozoites infect new red blood cells, resulting in a cycle that continuously amplifies the number of parasites in an infected person.[45] Over rounds of this infection cycle, a small portion of parasites do not replicate, but instead develop into early sexual stage parasites called male and female "gametocytes". These gametocytes develop in the bone marrow for 11 days, then return to the blood circulation to await uptake by the bite of another mosquito. Once inside a mosquito, the gametocytes undergo sexual reproduction, and eventually form daughter sporozoites that migrate to the mosquito's salivary glands to be injected into a new host when the mosquito bites.

The liver infection causes no symptoms; all symptoms of malaria result from the infection of red blood cells. Symptoms develop once there are more than around 100,000 parasites per milliliter of blood. Many of the symptoms associated with severe malaria are caused by the tendency of *P. falciparum* to bind to blood vessel walls, resulting in damage to the affected vessels and surrounding tissue. Parasites sequestered in the blood vessels of the lung contribute to respiratory failure. In the brain, they contribute to coma. In the placenta they contribute to low birthweight and preterm labor, and increase the risk of abortion and stillbirth. The destruction of red blood cells during infection often results in anemia, exacerbated by reduced production of new red blood cells during infection.

Only female mosquitoes feed on blood; male mosquitoes feed on plant nectar and do not transmit the disease. Females of the mosquito genus *Anopheles* prefer to feed at night. They usually start searching for a meal at dusk, and continue through the night until they succeed. However, in Africa, due to the extensive use of bed nets, they began to bite earlier, before bed-net time. Malaria parasites can also be transmitted by blood transfusions, although this is rare.

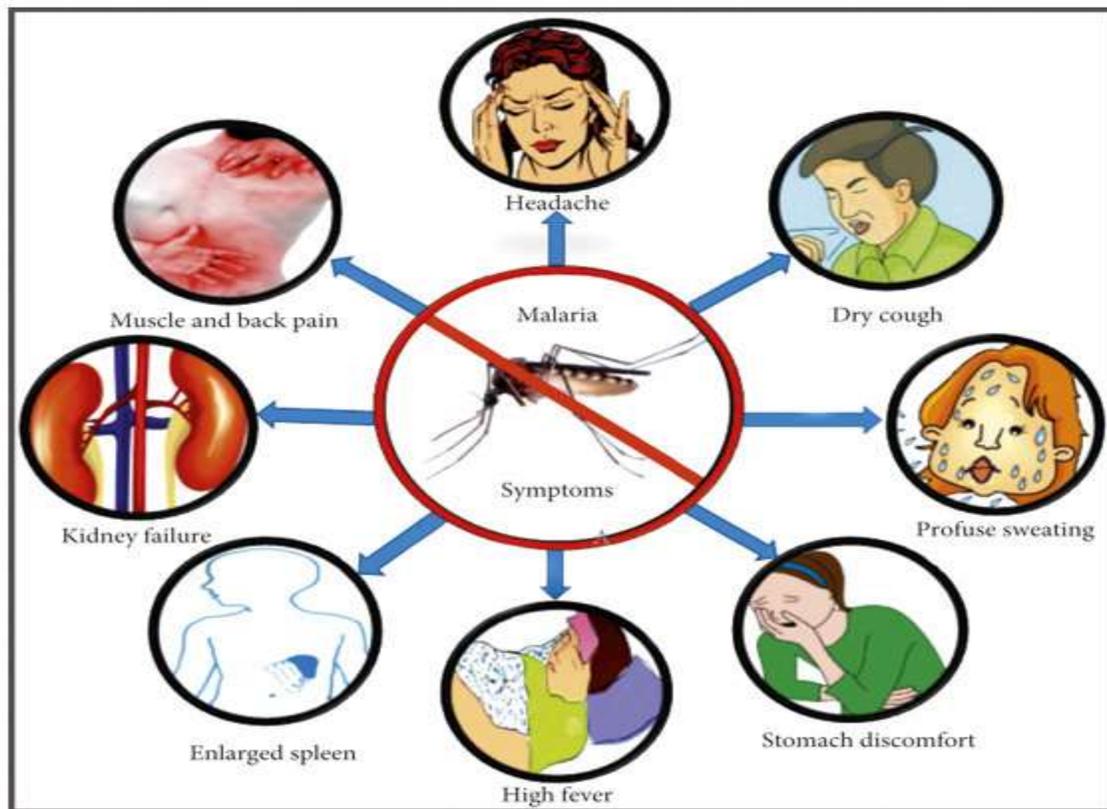


Manifestations:-

A person bitten by an infected *Anopheles* mosquito becomes symptomatic within 10–14 days to several weeks, beginning with flu-like symptoms without a runny nose, followed by fever, chills, sweating, headache, body and muscle aches, nausea, vomiting, and loss of appetite. Symptoms range from mild to severe, depending on the malaria strain and individual body immunity. Some can remain dormant in the liver for years before spreading into the bloodstream, infecting, and destroying red blood cells, and precipitating malaria symptoms. There are three malaria stages as follows:

1. Cold stage malaria, or the first stage of malaria: This stage lasts approximately 15-60 minutes, during which time the parasites invade the red blood cells and destroy them, resulting in fever, shivering with goosebumps, trembling, tooth clenching, coughing, shortness of breath, high blood pressure, rapid pulse, a cold body, nausea, vomiting, and frequent urination. The body temperature gradually rises to the hot stage.

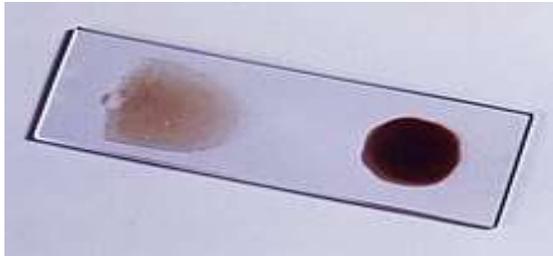
2. Hot Stage Malaria: Approximately 2 hours after the first stage, symptoms include a high fever, a hot body, hot breath, a pale mouth, thirst, a rapid pulse, high blood pressure, a red face, red skin, dry skin, eye socket pain, nausea, vomiting, diarrhea, a severe headache, and restlessness before entering the Sweating stage. Young children may experience convulsions.



3. Sweating stage malaria: The symptoms appear approximately 1 hour after the second stage. The fever begins to subside, followed by sweating, starting in the temples, then throughout the body. The body temperature rapidly drops, and the blood pressure will return to normal, followed by extreme tiredness and falling asleep. If untreated, malaria relapses at the Cold stage and re-enacts through the two succeeding stages, according to the malaria life cycle.

DIAGNOSIS:-

Due to the non-specific nature of malaria symptoms, diagnosis is typically suspected based on symptoms and travel history, then confirmed with a laboratory test to detect the presence of the parasite in the blood (parasitological test). In areas where malaria is common, the World Health Organization (WHO) recommends clinicians suspect malaria in any person who reports having fevers, or who has a current temperature above 37.5 °C without any other obvious cause. Malaria should be suspected in children with signs of anemia: pale palms or a laboratory test showing hemoglobin levels below 8 grams per deciliter of blood. In areas of the world with little to no malaria, the WHO recommends only testing people with possible exposure to malaria (typically travel to a malaria-endemic area) and unexplained fever.



In sub-Saharan Africa, testing is low, with only about one in four (28%) of children with a fever receiving medical advice or a rapid diagnostic test in 2021. There was a 10-percentage point gap in testing between the richest and the poorest children (33% vs 23%). Additionally, a greater proportion of children in Eastern and Southern Africa (36%) were tested than in West and Central Africa (21%). According to UNICEF, 61% of children with a fever were taken for advice or treatment from a health facility or provider in 2021. Disparities are also observed by wealth, with an 18 percentage point difference in care-seeking behaviour between children in the richest (71%) and the poorest (53%) households.

Malaria is usually confirmed by the microscopic examination of blood films or by antigen-based rapid diagnostic tests (RDT). Microscopy – i.e. examining Giemsa-stained blood with a light microscope – is the gold standard for malaria diagnosis. Microscopists typically examine both a "thick film" of blood, allowing them to scan many blood cells in a short time, and a "thin film" of blood, allowing them to clearly see individual parasites and identify the infecting Plasmodium species. Under typical field laboratory conditions, a microscopist can detect parasites when there are at least 100 parasites per microliter of blood, which is around the lower range of symptomatic infection. Microscopic diagnosis is relatively resource intensive, requiring trained personnel, specific equipment, electricity, and a consistent supply of microscopy slides and stains.

In places where microscopy is unavailable, malaria is diagnosed with RDTs, rapid antigen tests that detect parasite proteins in a fingerstick blood sample. A variety of RDTs are commercially available, targeting the parasite proteins histidine rich protein 2 (HRP2, detects *P. falciparum* only), lactate dehydrogenase, or aldolase. The HRP2 test is widely used in Africa, where *P. falciparum* predominates. However, since HRP2 persists in the blood for up to five weeks after an infection is treated, an HRP2 test sometimes cannot distinguish whether someone currently has malaria or previously had it. Additionally, some *P. falciparum* parasites in the Amazon region lack the HRP2 gene, complicating detection. RDTs are fast and easily deployed to places without full diagnostic laboratories. However they give considerably less information than microscopy, and sometimes vary in quality from producer to producer and lot to lot.

Serological tests to detect antibodies against Plasmodium from the blood have been developed, but are not used for malaria diagnosis due to their relatively poor sensitivity and specificity. Highly sensitive nucleic acid amplification tests have been developed, but are not used clinically due to their relatively high cost, and poor specificity for active infections

PHARMACOLOGICAL TREATMENT :-

Malaria is treated with antimalarial medications; the ones used depends on the type and severity of the disease. While medications against fever are commonly used, their effects on outcomes are not clear. Providing free antimalarial drugs to households may reduce childhood deaths when used appropriately. Programmes which presumptively treat all causes of fever with antimalarial drugs may lead to overuse of antimalarials and undertreat other causes of fever. Nevertheless, the use of malaria rapid-diagnostic kits can help to reduce over-usage of antimalarials.

Further information: Cotrifazid

Uncomplicated malaria

Simple or uncomplicated malaria may be treated with oral medications. Artemisinin drugs are effective and safe in treating uncomplicated malaria. Artemisinin in combination with other antimalarials (known as artemisinin-combination therapy, or ACT) is about 90% effective when used to treat uncomplicated malaria. The most effective treatment for *P. falciparum* infection is the use of ACT, which decreases resistance to any single drug component. Artemether-lumefantrine (six-dose regimen) is more effective than the artemether-lumefantrine (four-dose regimen) or other regimens not containing artemisinin derivatives in treating falciparum malaria. Another recommended combination is dihydroartemisinin and piperaquine. Artemisinin-naphthoquine combination therapy showed promising results in treating falciparum malaria but more research is needed to establish its efficacy as a reliable treatment. Artesunate plus mefloquine performs better than mefloquine alone in treating uncomplicated falciparum malaria in low transmission settings.

Atovaquone-proguanil is effective against uncomplicated falciparum with a possible failure rate of 5% to 10%; the addition of artesunate may reduce failure rate. Azithromycin monotherapy or combination therapy has not shown effectiveness in treating Plasmodium falciparum or Plasmodium vivax malaria. Amodiaquine plus sulfadoxine-pyrimethamine may achieve less treatment failures when compared to sulfadoxine-pyrimethamine alone in uncomplicated falciparum malaria. There is insufficient data on chlorproguanil-dapsone in treating uncomplicated falciparum malaria. The addition of primaquine with artemisinin-based combination therapy for falciparum malaria reduces its transmission at day 3-4 and day 8 of infection. Sulfadoxine-pyrimethamine plus artesunate is better than sulfadoxine-pyrimethamine plus amodiaquine in controlling treatment failure at day 28. However, the latter is better than the former in reducing gametocytes in blood at day 7.

Infection with *P. vivax*, *P. ovale* or *P. malariae* usually does not require hospitalisation. Treatment of *P. vivax* malaria requires both elimination of the parasite in the blood with chloroquine or with artemisinin-based combination therapy and clearance of parasites from the liver with an 8-aminoquinoline agent such as primaquine or tafenoquine. These two drugs act against blood stages as well, the extent to which they do so still being under investigation.

To treat malaria during pregnancy, the WHO recommends the use of quinine plus clindamycin early in the pregnancy (1st trimester), and ACT in later stages (2nd and 3rd trimesters). There is limited safety data on the antimalarial drugs in pregnancy.

Severe and complicated malaria

Cases of severe and complicated malaria are almost always caused by infection with *P. falciparum*. The other species usually cause only febrile disease. Severe and complicated malaria cases are medical emergencies since mortality rates are high (10% to 50%).

Recommended treatment for severe malaria is the intravenous use of antimalarial drugs. For severe malaria, parenteral artesunate was superior to quinine in both children and adults. In another systematic review, artemisinin derivatives (artemether and arteether) were as efficacious as quinine in the treatment of cerebral malaria in children. Treatment of severe malaria involves supportive measures that are best done in a critical care unit. This includes the management of high fevers and the seizures that may result from it. It also includes monitoring for poor breathing effort, low blood sugar, and low blood potassium. Artemisinin derivatives have the same or better efficacy than quinolones in preventing deaths in severe or complicated malaria. Quinine loading dose helps to shorten the duration of fever and increases parasite clearance from the body. There is no difference in effectiveness when using intrarectal quinine compared to intravenous or intramuscular quinine in treating uncomplicated/complicated *falciparum* malaria. There is insufficient evidence for intramuscular arteether to treat severe malaria. The provision of rectal artesunate before transfer to hospital may reduce the rate of death for children with severe malaria. In children with malaria and concomitant hypoglycaemia, sublingual administration of glucose appears to result in better increases in blood sugar after 20 minutes when compared to oral administration, based on very limited data.

Cerebral malaria is the form of severe and complicated malaria with the worst neurological symptoms. There is insufficient data on whether osmotic agents such as mannitol or urea are effective in treating cerebral malaria. Routine phenobarbitone in cerebral malaria is associated with fewer convulsions but possibly more deaths. There is no evidence that steroids would bring treatment benefits for cerebral malaria.

Managing Cerebral Malaria

Cerebral malaria usually makes a patient comatose. If the cause of the coma is in doubt, testing for other locally prevalent causes of encephalopathy (bacterial, viral or fungal infection) should be carried out. In areas where there is a high prevalence of malaria infection (e.g. tropical region) treatment can start without testing first. To manage the cerebral malaria when confirmed the following can be done:

Patients in coma should be given meticulous nursing care (monitor vital signs, turn patient every 2 hours, avoid lying the patient in a wet bed etc.)

A sterile urethral catheter should be inserted to help with urinating

To aspirate stomach content, a sterile nasogastric tube should be inserted.

In the occasion of convulsions, a slow intravenous injection of benzodiazepine is administered.

There is insufficient evidence to show that blood transfusion is useful in either reducing deaths for children with severe anaemia or in improving their haematocrit in one month. There is insufficient evidence that iron chelating agents such as deferoxamine and deferiprone improve outcomes of those with malaria falciparum infection.

Monoclonal antibodies

A 2022 clinical trial shows that a monoclonal antibody mAb L9LS offers protection against malaria. It binds the Plasmodium falciparum circumsporozoite protein (CSP-1), essential to disease, and makes it ineffective.

Resistance

Drug resistance poses a growing problem in 21st-century malaria treatment. In the 2000s (decade), malaria with partial resistance to artemisins emerged in Southeast Asia. Resistance is now common against all classes of antimalarial drugs apart from artemisinin. Treatment of resistant strains became increasingly dependent on this class of drugs. The cost of artemisinins limits their use in the developing world. Malaria strains found on the Cambodia–Thailand border are resistant to combination therapies that include artemisinins, and may, therefore, be untreatable. Exposure of the parasite population to artemisinin monotherapies in subtherapeutic doses for over 30 years and the availability of substandard artemisinins likely drove the selection of the resistant phenotype. Resistance to artemisinin has been detected in Cambodia, Myanmar, Thailand, and Vietnam, and there has been emerging resistance in Laos. Resistance to the combination of artemisinin and piperazine was first detected in 2013 in Cambodia, and by 2019 had spread across Cambodia and into Laos, Thailand and Vietnam (with up to 80 percent of malaria parasites resistant in some regions).

There is insufficient evidence in unit packaged antimalarial drugs in preventing treatment failures of malaria infection. However, if supported by training of healthcare providers and patient information, there is improvement in compliance of those receiving treatment

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