Review Of Clinical Features Of Malaria

By
Belonwu M. Onyenekwe[1] and Gilbert N. Adimora[2]
[1]Department of Medicine, Faculty of Medical Sciences and Dentistry, College of Medicine, University of Nigeria Enugu Campus.
[2]Department of Pediatrics, Faculty of Medical Sciences and Dentistry, College of Medicine, University of Nigeria, Enugu Campus.

INTRODUCTION

Malaria has had a major impact on the life and economies of affected populations since antiquity. Ancient Assyrian, Chinese and Indian religious and medical texts made references to intermittent and seasonal fevers. Hippocrates in 500Bc first described the clinical features of malaria and some of its complication.[1,2] Association of fever with stagnant water and swamps, led to the drainage of such waters by the Greeks and Romans in the 4th, 5th and 6th century BC. In the early 17th century, the "Peruvian Bark" or Jesuits Powder" was discovered to be of value in the treatment of certain fevers. The tree was later to be named cinchona from which quinine was extracted in 1820. Such fever was known as the agues in England, in Italy as mal'aria and in France as Palludisme due to their association with the fetid air of marshlands. Malaria was an effective obstacle to the colonization of the African heartland by the European Powers in the 16-19th centuries; till quinine chemoprophylaxis was introduced in 1850[2]. Significant progress was made in the understanding of malaria with the description by Laveran of malaria parasites in blood film in 1880. Ronald Ross in 1891 demonstrated the development of malaria parasites in mosquitoes. Patrick Mansion in a series by field experiments confirmed the transmission of malaria by the bite of Anopheles mosquitoes in 1900.

The worldwide distribution of malaria peaked by the end of the 19th and beginning of the 20th country. Apart from the tropics and subtropics, it was common in the temperate lands including the USA, Europe, Northern Eurasia and Asia. In the early part of the 20th century larvicidal and natural methods were engaged to control vector breeding. The ravages of malaria during the World Wars, and the scarcity of quinine stimulated research into discovery of synthetic antimalarials. This resulted in the introduction of pamaquine in 1924 (Germany), mepecrine 1930 (Germany), chloroquine1934 (Germany), proguanil 1944 (England) amodioquine 1946, primaquine 1950 and pyrimethamine in 1952 (USA). DDT, (dichlorodiphenyl –trichloroethane) with residual insecticidal action was discovered in Switzerland in late 1940 raising great hopes for the prospect of global malaria eradication. In 1957 the world health organization launched the Global Malaria Eradication Campaign. The programming went on for the next 15 year with excellent results in North America, Europe, Former USSR, part of Asia and Australia. The result in tropical countries was less dramatic.

Malaria continues to be a major cause of human morbidity and mortality. It is the world's largest killer of all parasitic diseases and a major public health problem. Although malaria has been eradicated in most temperate zones, it still affects 40% of the world population living in endemic zones of the tropics and subtropics namely; Central and South America, Hispaniola,

Correspondence Address
Belonwu M. Onyenekwe, Department of Medicine,
Faculty of Medical Sciences and Dentistry
College of Medicine, University of Nigeria
Enugu Campus

Sub-Saharan Africa, the Indian subcontinent, South East-Asia, Middle East and Oceania [Fig. 1][3, 4]. Current malaria facts and figures are daunting: worldwide, 2.4 million people are at risk of malaria, with 300 to 500 million people affected annually[5, 6, 7]. Malaria results in 1 to 3 million deaths annually with 90% of the deaths occurring in sub-Saharan Africa. Most of the deaths are of under 5-year old children. In Africa, malaria is the leading cause of under 5 mortality as it kills an African child every 30seconds. It makes up 10% of the disease burden, contributing 30% to 50% of inpatient admissions and 50% of outpatient consultation. Malaria accounts for 40% of public health expenditure and reduces the annual GDP by 1-4%.

MALARIA CHALLENGES IN AFRICA

Africa disproportionately bears the brunt of malaria in comparison to the rest of the world due to number of factors: *Plasmodium falciparum* which causes the most severe form of the disease, is the predominant parasite strain; African malaria vectors are the most efficient in parasite transmission; Most countries lack the necessary resources and infrastructure to mount an effective and sustainable campaign against malaria; Increasing resistance to chloroquine and Sulfodoxine Pyrimethamine (SP) has made malaria treatment less effective and more expensive resulting in a 2-3 fold increase in malaria deaths[8].

Malaria is a disease of poverty and perpetuates the cycle of poverty. Malaria causes poverty through: slow economic growth [chronic fatigue, low productivity, illnesses and premature death]; medical costs; diversion of savings and investments; impaired school and social development [absenteeism and permanent neurological deficits].

MALARIA: A RESURGENT DISEASE

The last two decades have noted an appreciable increase in malaria in several tropical countries where eradication measures had major impact. Indeed malaria has returned in full force to North Africa, India, Southeast Asia, China, South America and the Caribbean. There have been outbreaks of malaria in Europe and United States where locally transmitted malaria has appeared in California, Texas, among other states. The problem is compounded by a rapidly growing resistance to available drugs used for treatment and prophylaxis.[10,11] Other contributing factors include: deforestation, road building ,mining ,and massive agricultural and irrigation projects[The Amazon and Southeast Asia]; mass movement of refugees due to armed conflicts; and imported malaria from international travel.[7]

THE MALARIA PARASITE

Malaria is caused by protozoan parasites of the genus *Plasmodium*. They are also termed 'malaria' parasites. These parasites affect a wide range of creatures including humans, primates, rodents, birds and reptiles. The human malaria parasites belong to two sub genii: subgenus *Plasmodium* and subgenus *Levarania*. Of the sub genus *Plasmodium* 3 groups affect man. Of the group Vivax the species *Plasmodium vivax* is important. In the groups Ovale and Malaria the species *Plasmodium ovale* and *Plasmodium malaria* respectively are important. The specie *plasmodium falciparum* belong to the subgenus *Levarania*.

The geographical distribution of the various parasites is as in table 1.

Table 1   Geographical Distribution of Malaria Parasites

Parasite Specie	Geographical Distribution
Plasmodium falciparum	Africa, Hispaniola, New Guinea, East Asia, South America, Oceania
Plasmodium vivax	Indian subcontinent, Southeast Asia, South America, Oceania
Plasmodium malaria	All endemic areas
Plasmodium ovale	Africa.

Plasmodium falciparum and *Plasmodium vivax* cause 95% of all malaria infections worldwide, while *Plasmodium vivax* causes 55% of malaria infections in the subtropics. Transmission of infection occurs through the bite of the female anopheline mosquitoes. Occasionally, infection has been transmitted through the placenta, blood transfusion, or contaminated syringes. Parasites remain viable in stored blood for up to 2 weeks. The parasite life cycle is complex and consists of an asexual cycle in man and a sexual cycle in mosquitoes [Fig 2]. The sporozoites from mosquito saliva enter the circulation and within 30-60 minutes invade host liver cells, a process facilitated by the parasites apical organelles [rhoptries and mironemes]. Asexual exo erythrocytic or pre-erythrocytic schizogony proceeds in liver cells. Rupture of swollen infected liver cells release merozoites into the circulation which invade erythrocytes[13].The parasite ligand is the Erythrocyte Binding Antigen [EBA 175] for *Plasmodium falciparum*, and the Duffy Binding Protein [DB P] for *Plasmodium vivax*. The erythrocyte receptors are glycophorin A [*Plasmodium falciparum.*], and the Duffy antigen [*Plasmodium vivax.*].[14] In *Plasmodium vivax* and *Plasmodium ovale* infection, some sporozoites differentiate into dormant forms in the liver as hypnozoites. An erythrocytic schizogony proceeds and terminates with rupture of erythrocytes containing mature schizonts and release of Merozoites which re-invade erythrocytes to start another cycle. Some Merozoites terminally differentiate into micro- and macro- gametocytes which, when taken up by mosquitoes in a blood meal, leads to gametogenesis and sporogony the mosquito.

CLINICAL FEATURES OF MALARIA

Malaria is characterized by acute febrile illness. Typically, there are febrile paroxysms occurring every 48 – 72 hours with asymptomatic intervals, relapses and recrudescence over days to months to years. The clinical course and severity of attacks are modified by a number of factors; illness modifying factors, parasite specie and-strain, genetic make-up, state of immunity, general health, nutritional status, chemoprophylaxis, and chemotherapy. The typical febrile paroxysm is preceded in the first 2-3days by prodromal flu-like symptoms. These include headache, mild fever, aches and pains in joints, muscles, bones, abdomen; anorexia, nausea, malaise, dizziness. The ensuing febrile paroxysm lasts 4-8 hours and sequentially goes through the cold, hot and sweating stages (Table 2)[15,16].

Table 2 Stages of the Malaria Febrile Paroxysm

	Cold Stage	Hot Stage	Sweating Stage
Symptoms and Signs	Feeling Of Intense Cold	Feeling Of Intense Heat	Drenching Sweat
	Vigorous Shivering	Throbbing Headache	Rapid Decline Of Fever
	Pale, Cold Skin	Palpitation And Tachypnea	Symptoms Subside
	Goose Pimples	Nausea And Vomiting	Exhaustion
	Vomiting	Fatigue And Dizziness	Sleep
	Febrile Convulsions (In Children)	Confusion, Delirium (In Severe Cases) Flushed Skin	
Duration	15 to 60 Minutes	2 to 6 Hours	2 to 4 Hours

The febrile paroxysm occurs every alternate day (tertian) in *Plasmodium vivax* and *Plasmodium ovale*, and every third day (quartan) in *Plasmodium malaria*. In *Plasmodium falciparum* infection, classical febrile paroxysms are not a feature. What obtains is rather a continuous or remittent fever. Febrile paroxysms when they occur may be daily (quotidian), tertian or sub tertian. Patients tend to be prostrated with postural hypotension,

tender hepatosplenomegaly and cold sores. In non-immune individuals, the disease run a rapid course and become very severe and life threatening. Deaths have been reported within 48hours of onset of symptoms. A primary attack consists of a number of febrile paroxysms that wane in time as the untreated patient develops immunity. Relapses can occur in *Plasmodium vivax* and *Plasmodium ovale* from reactivation of hypnozoites in the liver: such relapses are precipitated by cold, fatigue, trauma, pregnancy, infections, and other illnesses. Recrudescence of *Plasmodium falciparum* and *Plasmodium malaria* arise from exacerbation of erythrocytic stages. A summary of the characteristics of the human malaria parasites are shown in Table 3[15,16].

Table 3 Main features of human malarias.

Feature	Specie			
	P. vivax	*P. ovale*	*P. malariae*	*P. falciparum*
Erythrocytic Stage (days)	6-8	9	14-16	5-7
Pre-patent period (days)	11-13	10-14	15-16	9-10
Incubation Period (days)	15 (12–17) to 6–12 m	17 (16–18) or longer	28 (18–40) or longer	12 (9–14)
Erythrocytic Cycle (Hrs)	48	50	72	
Parasitaemia/mm³				
Average	20000	9000	6000	20000-500000
Maximum	50000	30000	20000	2000000
Primary attack	Mild-Severe	Mild	Mild	Severe in non-immune individuals
Febrile Paroxysm (hours)	8-12	8-12	8-10	16-36 or longer
Relapses	++	++	-	-
Period of Recurrence	Variable	Variable	Very long	Short
Duration of untreated infection (years)	1½-5	1½-5	3-50	1-2

Simultaneous infection with two or more parasite species occurs frequently in endemic areas. However, one parasite species tends to predominate. Common combinations are; *Plasmodium falciparum. + Plasmodium vivax.* [subtropics], *Plasmodium falciparum. + Plasmodium malaria.* and *Plasmodium falciparum. + Plasmodium ovale* [Africa], *Plasmodium falciparum. + Plasmodium vivax+ Plasmodium ovale* [rare]. The severity of infection and the degree of parasitaemia are greatly influenced by the individual's immune responses. A clinical malaria episode is classified as either uncomplicated or severe (complicated). In uncomplicated malaria there is no life threatening manifestation.

Severe or complicated malaria is accompanied by vital organ dysfunction or high parasitemia (>3%) with threat to life. Severe malaria needs to be recognized because it causes avoidable deaths.

Persons at risk of developing severe malaria are: children <5years of age (high endemic areas); all ages (low endemic areas); returnees to high endemic areas; pregnant women, especially primigravidae; sickle cell disease patients; internally displaced persons; splenectomized patients, and non-immune travelers to endemic areas. Several features indicate that a malarial episode has progressed to complications[15,16,17,19]. These features, summarized in table 4, include: -

Table 4 Indicators of severe malaria

Clinical and Laboratory Index	Frequency	
	Children	Adults
Prostration	+ + +	+ + +
Impaired Consciousness	+++	++

Respiratory Distress	+++	+
Multiple Convulsions	+++	+
Jaundice	+	+++
Severe Anaemia	+++	+
Hypoglycaemia	++	++
Hyperparasitaemia	++	+
Hyperpyrexia	++	+
Persistent Vomiting	++	+
Renal Failure	±	++
Circulatory Collapse	+	+
Pulmonary Oedema	±	+
Abnormal Bleeding	±	+
Haemoglobinuria	±	+

Hypoglycemia [plasma glucose level <2.2mmol/L or <40mg\ dL]: Symptoms include anxiety, breathlessness, dizziness, impaired consciousness, extensor posturing and seizures. These symptoms may be attributable to other features of severe malaria such as cerebral malaria, and heart failure. It occurs in more than 50% of children with severe malaria.

Lactic acidosis (Arterial pH<7.25 or plasma bicarbonate level <15mmol/L, venous lactate level>15mmo/L): It manifests as labored deep breathing and is referred to as respiratory distress. Lactic acidosis frequently co-exists with hypoglycemia and is compounded by the presence of renal failure. It has a very poor prognosis.

Jaundice/hepatic dysfunction (serum bilirubin >50mmol/L or >3.0mg/dl): Mild hemolytic jaundice is common. Severe jaundice occurs more in adults than in children. Hepatic dysfunction contributes to hypoglycemia, lactic acidosis and impaired drug metabolism. Hepatic failure does not occur except there is concomitant viral hepatitis.

Anemia (hematocrit of >20%, or hemoglobin level of <50g/L [<5g/dL], with parasitemia of>100000/μL): In sub-Saharan Africa, malaria induced anemia causes as much mortality as cerebral malaria. Children aged 1-2years are at the greatest risk. Anemia frequently results in heart failure. Anemia is also associated with retinal hemorrhages hepatic and renal dysfunction and secondary bacterial sepsis. *Plasmodium falciparum* infection is the most common cause of anemia worldwide.

Non-cardiogenic pulmonary edema (adult respiratory distress syndrome) may present at any stage of the disease and may be precipitated by over hydration. The patient is tachypneic, dyspneic, with rales on chest auscultation, and other features of adult respiratory distress syndrome. The mortality rate is very high, greater than 80%. It is a common terminal event.

Renal failure (24 hour urine output < 400ml in adults or 12ml/kg in children, no improvement with rehydration, serum creatinine level > 265 mmol/L or > 3.0 mg/dL): Renal dysfunction is commoner in adults than in children. Biochemical evidence of renal dysfunction is found in up to a 3rd of non-immune individuals with severe malaria.

Contributing factors include; hypoglycemia, jaundice, prolonged coma, pulmonary edema, hypovolemia and hyperparasitemia. Progression to renal failure however occurs in few cases [10%]. Mortality is high in the initial phase of hyper catabolic renal failure. Recovery tends to be rapid.

Black water fever / malarial hemoglobinuria (macroscopic black, brown, or red urine not due to effect of oxidant drugs and G6PD deficient erythrocytes): The condition was typically found in expatriates residing in malaria endemic areas of Africa who had had several attacks of malaria with intermittent quinine treatment and prophylaxis. It results from severe intravascular hemolysis in absence of hyperparasitemia. The illness presents with the usual malaria symptoms that progresses to abdominal and loin pain, bilious vomiting, diarrhea, oliguria or anuria. There is pyrexia, tachycardia, tender hepatosplenomegaly, severe anemia, jaundice and prostration. Renal failure supervenes with hypertension and coma. Most cases of hemoglobinuria today arise from the use of oxidant drugs in persons with G6PD deficiency. Black water fever has been reported in a subgroup of children who suffered recurrent attacks of malaria and were treated with quinine[20].

Hypotension /shock/algid malaria (systolic blood pressure <50 mm Hg in children aged 1-5years or <80mn Hg in adults; core/skin temperature difference of >10 °C): Most patients with malaria will experience some lowering of the blood pressure. Mild supine hypotension with postural drop is due to hypovolemia and vasodilatation. Hypotension and shock (algid malaria) occurs in patients who develop pulmonary edema, metabolic acidosis, gastrointestinal hemorrhage, ruptured spleen or concomitant gram-negative sepsis.

Bleeding abnormalities occur in less than 5% of adults. Significant bleeding is rare in children. Thrombocytopenia is frequent and may be profound [<50,000/mm^3], but rarely causes spontaneous hemorrhage. Serum levels of clotting factors are depressed. There may be petechiae on skin and mucus membrane, spontaneous hemorrhage from the nose, gums and gastrointestinal (GI) tract. Upper GI bleeding may be due to stress ulcers or erosive gastritis. Disseminated intravascular coagulation is rare.

Cerebral malaria is defined by unarousable coma in a patient with malaria not attributable to convulsions, sedatives, hypoglycemic or non-malarial causes. Onset may be gradual or sudden or follow a convulsion (coma persisting for more than 30 minuets after a seizure). It manifests as a diffuse encephalopathy. Focal deficits and signs of meningial irritation are usually lacking. Muscle tone, deep tendon reflexes and planter response are variable. Convulsions occur in up to 50% of affected adults. Seizures are generalized and recurrent. However, focal seizure may occur. Patients may be immobile or restless. Various involuntary movements, muscle spasms and ophthalmoplegias have been described. Extensor posturing may be decorticate or decerebrate. Corneal reflex is preserved until late. Retinal hemorrhages are found in about 15% of cases. Mortality occurs in 15 – 20% of cases. Neurological sequelae are rare in survivors.

In children cerebral malaria is most common in those aged 2 – 3 years. Initial symptoms include fever, failure to feed, irritability or apathy, cough vomiting and convulsions. Coma supervenes rapidly, usually within 1–2 days of onset of symptoms. Seizures are very common and are generalized, tonic-clonic, focal or bilateral clonic. Absences and tonic eye deviation occur. Pupillary light reflexes are normal, but the corneal reflex is abnormal. Muscle hypotonia is common. Intracranial pressure is raised. Recovery is rapid with treatment, but more than 10% of cases will show persistent neurological deficits which

improve with time. Some of the deficits following cerebral malaria are; hemiplegia, cerebral palsy, cortical blindness, mutism, cerebellar ataxia, tremors, extensor posturing, generalized spasticity or hypotonia, psychosis, mental retardation and abnormal behavior.

High risk factors of neurological deficits are: hypoglycemia, severe anemia, repeated seizures and deep coma.[15, 16,17,18,19]

Malaria in Pregnancy

In semi immune individuals infected with *Plasmodium falciparum*, symptoms and parasitemia are more severe in primigravidae. Malaria contributes to the severe anemia of pregnancy which may result in heart failure in late pregnancy. The heart failure increases the risk of maternal mortality. Maternal anemia has been estimated to cause as much as 10,000 maternal deaths each year in Africa. Maternal malaria causes 8 – 14% of all low birth weight babies, and 3 – 8% of infant deaths in endemic areas of Africa. Other complications include; abortion, stillbirths, and premature delivery. Hypoglycemia is common and tends to be asymptomatic. It is markedly exacerbated by quinine administration. In non – immune individuals, malaria in pregnancy results in severe disease. They are especially prone to hyperparasitemia, anemia, hypoglycemia and pulmonary edema. Fetal distress, premature labor, stillbirths and low-birth weight result.[15.21]

Congenital and neonatal malaria

All four human plasmodia species can cause congenital and neonatal malaria: *Plasmodium falciparum* and *Plasmodium vivax* in endemic areas and *Plasmodium malaria* outside such areas. Parasitemia occurring within 7 days of birth (if there are no mosquito bites or blood transfusion) indicates vertical transmission. In endemic areas, the incidence was described as rare. It occurs in fewer than 5% of babies born to non- immune mothers with malaria. The clinical features include fever, irritability, feeding problems, anemia,

hepatosplenomegaly and jaundice[15, 19]. It was believed that babies did not suffer malarial attacks until 4-6 months of life because of placentally transferred maternal antimalarial antibodies. Recent observations show that a significant number of neonates suffer malaria, the symptoms being similar to those of septicemia. In some cases, recurrent fever at particular periods of the day may be the only symptom. In other cases babies of 6 weeks to 2 months have presented with poor weight gain. Investigations often reveal only malaria parasitemia. Proper antimalarial treatment resolves the diagnostic problem. Thus congenital and neonatal malaria are occurring more frequently than before. This may be as a result of the rising antimalarial drug resistance.

Malaria in children

Early symptoms of malaria in children are drowsiness, headache, and refusal of feeds, nausea and fever. Initially there may be increased thirst with pyrexia. The distinct phases of the febrile paroxysms are not observed. The temperature is variable; vomiting is common and may be bile-stained. Diarrhea is frequent. Febrile convulsions occur even at moderate pyrexia. Loss of consciousness is transient (less than 30 minutes] Abdominal pain is a frequent complaint. The skin is flushed. The spleen becomes enlarged. In endemic areas symptomology is very variable. Children experience severe attacks of malaria until the age of 5years when they would have developed significant protective immunity. Many die from the complications of the disease. Many children on the other hand are asymptomatic with parasitemia, some degree of anemia, and hepatosplenomegaly.[15] Infestation with intestinal worms was reported to increase malaria morbidity.[22] HIV infection does not predispose to severe malaria attacks in persons who have developed immunity to malaria but may do so in non-immune individuals.[23]

Transfusion malaria

This is malaria transmitted by - blood transfusion, needle stick injury or sharing of needles by injection drug users [IDM]. The incubation period is short. The clinical profile and management are as for the naturally acquired infection. *Plasmodium falciparum* infection tends to be severe in IDMs.[16]

Hyperactive malarial syndrome (HMS)/Tropical Splenomegaly Syndrome [TSS]

In some residents of endemic areas, the immunological response to malaria is abnormal resulting in the HMS. This is characterized by massive splenomegaly, hepatomegaly, high serum titres of IgM and malarial antibody, hepatic sinusoidal lymphocytosis and peripheral B-cell lymphocytosis. Affected patients present with a dragging sensation in the abdomen or an abdominal mass or occasional sharp abdominal pain of periplenitis. Anemia and some degree of pancytopenia may coexist[16, 17, 19].

Quartan Malaria Nephropathy (QMN)

The incidence of QMN has dropped in recent times. It presents as nephrotic syndrome in children that is notoriously resistant to steroid treatment. The prognosis is poor. Most patients develop hypertension and renal failure within 5 years. The prevalence has dropped over the years[23].

Lymphomas

Some cases of hyperactive malaria syndrome that resist treatment may result in clonal proliferation and evolve into malignant lymphoproliferative disorder. The immunosuppression of malaria, it has been suggested, promotes infection with the lymphoma virus. This may be why the prevalence of Burkitts lymphoma which is associated with the Epstein–Barr virus is high in malaria endemic areas[16, 19].

PATHOGENESIS AND PATHOLOGY

Malaria parasites contain double-stranded DNA and messenger and ribosomal RNA. Nutrient requirements are obtained from infected red blood cells and plasma. Hemoglobin is the major source of protein. Hemoglobin is digested in parasite food vacuole and the heme moiety detoxified to the pigment hemozoin. Malaria parasite synthesizes folic acid de novo and requires the presence of para-amino benzoic acid (PABA). Energy is derived by the metabolism of glucose to lactate. Oxidative processes are maintained by oxyhemoglobin. While *Plasmodium vivax* and *Plasmodium ovale* infect young erythrocytes, and *Plasmodium malaria* mature cells, *Plasmodium falciparum* infects all cells. All the pathological and clinical abnormalities result exclusively from the blood stage parasites. The erythrocyte cycle results in disease due to their primary effect on infected erythrocytes and secondary changes on the host. In the infected erythrocyte, transport proteins are altered, surface cryptic antigens exposed and parasite induced neoantigens expressed. The erythrocyte thus becomes more permeable, antigenic, irregular and less deformable with shortened life span. The secondary changes are due to stimulation of host immune response to neo and altered erythrocyte surface antigens and parasite antigens, regional blood flow changes, tissue hypoxia, lactic acidosis, hypoglycemia, anemia and cytokine production. Fever is a result of the release of cellular debris at schizont rupture, activation of macrophages, and release of endogenous pyrogens, interleukin (IL-I) and especially tumor necrosis factor (TNF- α). High temperatures damage mature parasites in untreated infection and serve to synchronize the parasites cycle to produce the regular febrile paroxysms. *Plasmodium falciparum* can cause severe diseases due to a number of virulence factors unique to it, including the fact that it infects erythrocytes of all ages; has high reproductive capacity, cytoadherence, sequestration and resetting properties.

Plasmodium falciparum's splenic and immune evasions are also important virulence factors. *Plasmodium falciparum* infected erythrocytes develop surface knobs containing a high molecular weight variant, strain specific adhesive protein, the *Plasmodium falciparum* Erythrocytes Membrane Protein (PfEMP-I). This serves as the parasites ligand for a number of endothelial receptor molecules such as intercellular adhesion molecules (ICAM-1, VCAM-I, PE-CAM], E-selectin and, thrombospondin (TSP), CD36, chondroitin sulfate A (CSA)] resulting in cytoadherence of *Plasmodium falciparum* parasitized erythrocytes to endothelial cells of capillaries and post capillary venules. *Plasmodium falciparum* parasitized erythrocytes form rosettes with unparasitized cells. Possible rossetting receptor is CR-I and glycosaminoglycan. Both phenomena result in sequestration of parasitized cells in the peripheral microvasculature of the brain, lungs, kidneys, placenta, gut and other organs. In addition, the endothelial receptors are inducible by cytokines such as TNF, which is increased in fever of *Plasmodium falciparum* infection, thus enhancing cytoadherence and compounding the micro vascular pathology. Sequestrated parasitized cells evade splenic destruction with resulting hyperparasitemia.[14, 16, 19,25,26,27]

Hyperparasitemia (> 250,000/μL or >5% parasitemia) caries a considerable risk of death in non-immune individuals. The contributing factors include more extensive micro vascular disruption, severe metabolic derangements and high levels of cytokine production.

The observed hypoglycemia is accounted for by depletion of liver glycogen, poor oral intake, anaerobic glycolysis and glucose depletion by large number of parasites, hypoglycemic effect of TNF-α, and pancreatic insulin release during quinine and quinidine therapy.

A combination of factors is responsible for the development of lactic acidosis; anaerobic glycolysis due to hypoxia in micro vascular beds with sequestrated parasitized erythrocytes; lactate production by parasites, and failure of hepatic and renal clearance of lactate.

The pathogenesis of adult respiratory distress syndrome, renal failure, cerebral dysfunction, hepatic dysfunction and rarely malabsorption and enterocolitis is unclear. The sequestration hypothesis fails to explain the pathogenesis of cerebral malaria. Sequestration would suggest a mechanical blockage cerebral ischemia tissue hypoxia in addition to the local metabolic effect of hypoglycemia and lactic acidosis; all eventuating in coma and death. However, coma due to cerebral malaria reverses rapidly on treatment, leaving few permanent damage. Sequestration also occurs in non-cerebral malaria. These suggest that coma is probably mediated by short –lived molecules, hence the cytokine theory. The very high levels of TNF-α, IL-I, TNF-β found in severe malaria may play a more direct role on cells. TNF-α, induces nitric oxide formation. Nitric oxide causes vasodilatation resulting in intracranial hypertension and cerebral edema. It also acts as in inhibitory neurotransmitter leading to coma. The two mechanisms in all likelihood are working in concert, because TNF- α, induces increased expression of adhesion molecules (e.g. 1 CAM-1) on the surface of brain endothelial cells. This will amplify the binding and sequestration of more parasitized erythrocytes.[27]

Multiple mechanisms are implicated in the anemia of malaria infection. Cytokines [TNF-α and IL-6] inhibit erythropioesis. Other factors include; hemolysis [direct red cell invasion, splenic sequestration, immune destruction], hemodilution [from splenomegaly], and the anemia of chronic disease.[28]

Neutropenia and thrombocytopenia are results of splenic sequestration.

HMS is associated with the production of cytotoxic IgM antibodies to suppressor (CD8+) T-cells and increase in the ratio of CD4+ to CD8+ T-cells. This imbalance, results in uninhibited B-cell production of IgM, formation cryoglobulins, false positive

biological tests, mononuclear macrophage hyperplasia and clearance activity, and finally splenomegaly. [16, 19]

QMN results from immune-complex injury to renal gromeruli.

The histological features associated with malaria are rather sparse. Post mortem specimens have documented macro vascular congestion, interstitial edema and hyaline membrane formation (pulmonary edema); micro vascular congestion of cerebral grey matter, perivascular edema, ring hemorrhages, and rarely glial reaction (cerebral malaria); renal cortical ischemia and acute tubular necrosis (renal failure). Some of these findings may be post mortem changes   QMN is a focal or segmental gromerulonephritis. Electron microscopy and immunofluorecence studies, show renal sub endothelial deposits in a granular, diffuse or mixed pattern.

The spleen is enlarged with congestion of the red and white pulp containing large numbers of parasitized erythrocytes. There is a heavy mononuclear infiltration of the splenic cords and sinuses and lymphocytes in the red pulp. Lymph nodes show a similar picture. The liver displays Kupffer cell hypertrophy, macrophage infiltration, sinusoidal dilatation and sludge of infected erythrocytes.

MALARIA IMMUNOLOGY

Immunity to malaria is both innate and acquired

Innate immunity

Certain diseases and genetic polymorphisms confer some protection to invasion by malaria parasites. These include Duffy negative status, ovalocytosis, sickle cell anaemia, Thalassemia and G6PD deficiency. The ovalocyte cell membranes are more rigid and resist penetration by parasites. The Duffy blood group antigen serves as the membrane receptor for *Plasmodium vivax*. It is rare in the populations of the West African sub region and is responsible for the absence of *Plasmodium vivax* infection in this region. The other

erythrocyte defects in combination with parasites invasion result in premature lysis of infected erythrocytes. It has been observed that nutritional deficiency lowers susceptibility to malaria. Kwashiorkor and marasmus, iron deficiency and low riboflavin levels may give some protection. Diet low in PABA is protective in animal models[27, 29].

Acquired immunity

Persons living in endemic areas slowly develop immunity to malaria. The immunity is short -lived unstable and non-sterilizing. Parasitemia is better tolerated (anti-disease immunity), and tends to be lower (anti-parasite immunity). The presence of parasites is necessary to maintain immunity (premunition). Thus, healthy individuals harbor parasites. In endemic areas, the new born is relatively protected in the first 3-6

months of life due to the presence of maternal antimalarial antibodies. Subsequently, the child experiences, increasingly severe attacks of malaria and is at risk for complications. This susceptibility peaks about the 3rd year of life. Even within this period, the majorities of children carries parasites but are healthy. By the 4th year of life, the severity of attacks begins to wane. Malaria related deaths become infrequent after the 5th year of life. Immunity continues to increase with age and may take more than a decade to reach optimal levels, a fact inversely proportional to the intensity of transmission.

The life cycle of malaria parasites is complex and multistage, involving many changes in parasite morphology and antigenic determinants. Large numbers of stage specific antigens appear at each developmental stage. They are classified as listed below.[30]

Pre-erythrocytic stages: Circumsporozoite Protein (CSP); Liver Stage Antigens-1 (LSA-1).

Merozoites and erythrocytes: Erythrocyte Binding Antigen (EBA-175), Merozoites Surface Antigen 1 & 2 (MSA–1&2); Ring Infected Erythrocyte Surface Antigen (RESA); Serine Repeat Antigen (SERA); Rhoptry

Associated Protein (RAP); Histidine Rich protein 2[HRP-2]; Knob Associated- Histidine Rich Protein (KAHRP); *Plasmodium falciparum* Erythrocyte Membrane Protein 1 (PfEMP--1). Mature Parasite infected Erythrocyte Membrane Antigen (MESA / PfEMP -- 2); Glutamate Rich Protein (GLURP).

Gametocytes and gametes: Gametocyte antigens Pf25, 48/48k, Pf230.

Malaria infection is accompanied by a polyclonal B-cell activation, a brisk rise in antibody production many of which lack anti-plasmodial specificity and are responsible for biologic false positive serologic tests.[13] There is chemokine induced hyperplasia of the mononuclear phagocytic system, and recruitment of blood monocytes to the spleen and liver. Recent studies have linked protective immunity to immune response to certain parasite antigens [antibodies to PfEMP-I, PfMSP-I], IFN-Y production to LSA-I, antibody dependent inhibitions to MPS, GLURP.31 Explanations have been sought for the observed pattern of malaria immunity. The antigens are poor immunogens and /or are polymorphic and variable. Variability of antigens will entail that the host accumulate immunological memory to a large number of antigenic epitopes before significant protection can be achieved. It has been observed that in areas with seasonal malaria transmission, while the prevalence of clinical malaria fluctuates, the prevalence of parasitemia remains stable. The clinical episodes then are due to mosquito-mediated exchange of new parasite strains that thrive and multiply disproportionately causing disease, while the old parasites remain under check. Immune responses involving PfEMP-I appear to be central to this breakthrough malaria attacks. PfEMP-I is one of the few parasite antigens expressed on the surface of intact infected erythrocytes. It is hyper variable, and plays a central role in the cytoadherence of parasitized erythrocytes to host microvasculature, and therefore parasite survival. Field studies have linked clinical episodes of malaria in Kenyan

children to variant PfEMP-1. It has been known that women living in endemic areas tend- to loose their protection when pregnant to a degree disproportionate to the general immunosuppression of pregnancy. Again the parasitized erythrocytes sequestrated in the placentas of primigravidae have been found to have adhesion specificity for chrodroitin sulfate A (CSA) present on placental syncitiotrophoblast. The ligand is a variant PfEMP-1. Parasites with this variant antigen are rapidly eliminated in non-pregnant females, but find a safe haven in primgravidae where they multiply unchecked causing disease. With subsequent pregnancies, protective immunity is developed to this strain, and clinical malaria attacks reduce.[31]

DIAGNOSIS OF MALARIA

Malaria is suspected when a person living in an endemic area or having been to an endemic area presents with suggestive symptoms. A careful history is taken and the patient clinically evaluated for presence of features of severe malaria and other differential diagnoses. Some of the differential diagnoses to consider are as follows: [14, 18]

Acute fever with or without paroxysms: other infections such as lobar pneumonia, ascending cholangitis, pyelonephritis and other infections of the urinary tract, uterus, adnexae, and breast [in pregnant women].

Confusion/Coma/Convulsions:
meningoencephalitis (viral, bacterial, fungal, protozoal), cerebral abscess, intoxications, poisoning, metabolic conditions (such as hypoglycemia, uremia, liver failure, hyponatremia, diabetes mellitus), eclampsia [in pregnant women] and febrile convulsion [in children].

Jaundice: viral hepatitis, yellow fever, septicemia, hemolysis, biliary obstruction, toxic hepatic necrosis, leptospirosis, relapsing fever, acute fatty liver and cholestasis [in pregnant women], Rh incompatibility and intrauterine infections [in neonates].

Acute renal failure: septicemia, drug intoxication and prolonged hypotension.

Abdominal pain: ruptured spleen, enteric fever, amebic liver abscess, acute pancreatitis, peritonitis, perforated viscus and ruptured ectopic pregnancy [in pregnant women].

Shock: septic, hemorrhagic or hypovolemic shock and myocarditis.

Hemoglobinuria: G6PD deficiency, oxidant stress, transfusion reaction and other pigments (myoglobin, urobilinogen, porphobilinogen).

Hyperpyrexia: heat stroke, other causes of pyrexia and infections.

The gold standard for the diagnosis of malaria is the demonstration of parasites in blood. Both thick films (parasite diagnosis) and thin films (species identification] are used. Several negative blood films a day for 3 days are required to exclude the diagnosis[18]. Rapid diagnostic tests are now available using immuno-chromatographic methods. The tests detect malarial antigens present in peripheral blood. Available tests detect the histidine rich protein II (HRP II Pf) or the parasite lactate dehydrogenase (pLDH) of the 4 human malarias, or both. The tests can therefore only tell *Plasmodium falciparum* from non-*Plasmodium falciparum* infections. The test sensitivity is low, but specificity is high (>90%). While pLDH disappears from plasma quickly with chemotherapy, HRP II persists for up to 2 weeks.[32] Tests are available for detecting malarial antibodies, but are used mainly for epidemiological studies, and screening of blood donors. Patients with severe disease need to be further evaluated to confirm the presence of complications, assess severity, and exclude other possible differentials. The choice of tests will be judged by the manifestations present and include full blood count, blood sugar level, urinalysis, lumber puncture, renal and liver function tests, chest x-ray, blood group blood and blood gases. Experience in malaria endemic areas, however, indicate that demonstration of malaria parasites in an individual's blood, even in the presence of clinical symptoms, allows

only a presumptive diagnosis, as the symptoms could still be explained by other clinical conditions.

TREATMENT OF MALARIA AND DRUG RESISTANCE

Chemotherapy remains the primary means of treating malaria. Chemotherapy exploits the unique metabolic peculiarities of the parasite. The drugs available and their mechanisms of actions presented below[19, 27, 33].

Food vacuoles/heme polymerase inhibitors

4 –aminoquinolines: chloroquine [CQ], amodiaquine [AQ].

Quinoline-methanols: quinine [Q], Mefloquine [MQ].

Phenanthrene-methanols: halofantrine [HAL], lumefantrine [LUM]Antifolates

Dihydropteroate synthase [DHPS] inhibitors: sulfonamides [sulfodoxine, sulfalene] sulfones [dapsone].

Dihydrofolate reductase [DHFR] inhibitors: pyrimethamine, proguanil [PR]

Redox mechanisms

Peroxide [sesquiterpene lactones]: Quinghaosu (Artemisinin)/related compounds: artemesinin [ATM], artesunate [ASU], artemether, arteether Ribosomal inhibitors: antibiotics; tetracycline [T], doxycycline [D], clindamycin[C].

8-Aminoquinolines

Primaquine (PQ)

Naphthoquinones: atovaquone [AT]

Iron chelating agents

Desferroximine

Chinese drugs

Pyronaridine

Daphnetin

Chloroquine is the prototype of drugs acting on the parasite food vacuole where it is concentrated 1000 fold. It inhibits heme polymerase that converts heme to hemozoin. Accumulation of heme results in parasites death. Antifolates sequentially inhibit the de novo synthesis of folic acid. Since the parasite cannot utilize pre-formed folates, amino acid and

nucleotide synthesis is inhibited. The artemisinin group of drugs participates in futile redox cycling, increase the level of oxidant stress, and overwhelm parasite reactive oxygen intermediate (ROI) defenses causing parasite death. Antibiotics inhibit protein synthesis. Primaquine binds DNA and may disrupt parasite mitochondria. Atovaquone inhibits mitochondrial electron transport chain. The mechanism of action of the other drugs is not clear.[19, 27]

Antimalarial Drug Resistance

Drug resistance is defined by treatment failure leading to recrudescence of disease level. Drug resistance was traditionally defined as Sensitive (no recrudescence); R1 [delayed recrudescence); R11 [early recrudescence]; and RI11 [minimal or no anti-parasite effect). This protocol was fraught with many problems in endemic areas.

The WHO introduced a modification based on clinical outcome in 1996: adequate clinical response [ACR]; late treatment failure [LTF]; and early treatment failure [ETF].

Selection of parasites with decreased sensitivities to anti malarial drugs under drug pressure leads to the emergence of drug resistance. Decreased drug sensitivity arises from genetic mutation(s) or polymorphisms in parasite population. Factors contributing to the emergence of drug resistance are: sub therapeutic doses of drugs, incomplete treatment, mass treatment, long drug half-life, and high transmission intensity. The most susceptible parasites are eliminated allowing the less susceptible ones to multiply at low drug levels.

After its introduction, chloroquine rapidly became the first choice antimalarial because of its effectiveness, low cost and low toxicity. In late 1950 foci of chloroquine resistant *Plasmodium falciparum* appeared in Columbia and the Cambodia-Thailand border. By 1970, resistant strains have spread throughout South America, Southeastern Asia and India. In Africa, resistance was first reported in East

Africa in 1978, and spread to the rest of the continent during the 1980s. Chloroquine resistance now exists in all areas except North America, Central America north of the Panama Canal, Hispaniola and the Middle East. *Plasmodium vivax* resistance appeared in Papua New Guinea in 1989, and several foci have appeared in Southeast Asia. Resistance of *Plasmodium falciparum* to other antimalarials has been reported: to AQ [in E. Africa, New Guinea, Amazon basin]; to SP [in S. America, SE. Asia, India, E. Africa]; to Q [in SE. Asia and S.America]; to MQ [in SE. Asia, the Amazon basin, West and Central Africa]. No resistance has been reported to artemisinin monotherapy, although it is associated with a high recrudescence rate. Table 5 shows mutations associated with drug resistance. Chloroquine resistance is associated with efflux of the drug from the parasite food vacuole[16, 19, 27].

Table 5 Mutations associated with Drug Resistance

Drug	Gene
Chloroquine	Chloroquine Resistance Transporter, Multi drug Resistance Gene 1
Mefloquine	Multi Drug Resistance Gene 1, Dihydropteroate Synthatase
Sulfodoxine/Pyrimethamine	Dihydrofolate Reductase

Anti malarial Treatment Polices

Within the context of WHO global strategy for malaria control, antimalarial treatment aims to provide rapid and long lasting clinical cure; reduce morbidity; prevent progression to severe malaria; and minimize the development of resistant parasites.

There has been a marked drop in the efficacy of most affordable antimalarials. Many endemic areas experience problems with access, availability, suitability and proper choice of antimalarials. The problem is compounded by the proliferation of fake drugs. This informed the initiative for the development of National Antimalarial Treatment Polices [NATP] to

provide countries with a framework for the safe and effective treatment of uncomplicated and severe malaria and chemoprophylaxis for travelers and vulnerable groups. Many countries have subscribed to this initiative including Nigeria. NATP selects and makes available to the population at risk safe, effective, good quality, affordable antimalarials to achieve treatment objectives[34].

Drug treatment [16,17,19,34]

The end point of antimalarial treatment is clinical cure in high transmission areas and radical cure in areas of low transmission. The choice of drugs used is determined by the severity of the infection and drug sensitivity of local parasites.

Uncomplicated malaria
Chloroquine sensitive areas [*Plasmodium falciparum, Plasmodium vivax, Plasmodium malaria, Plasmodium ovale*]

The first line treatment is chloroquine base administered at a total dose of 25kg/kg body weight in divided doses: 10mg/kg for days 1 and 2, and 5mg/kg on day 3, orally. This is the first line drug in Nigeria. Parenteral chloroquine may be occasionally indicated in the patient who cannot tolerate oral medication due to repeated vomiting. The parenteral dose is 3.5mg base/kg, 8 hourly intramuscularly or subcutaneously, until the individual is able to take the medicine orally to complete 25kg /kg total dose.

The second line treatment is Amodiaquine 25mg/kg total dose. It is an alternative to chloroquine and the dosage schedule is identical. Another second line drug in such areas is Sulfodoxine/Pyrimethamine (SP), 25mg /1.25mg / kg body weight given as a single oral dose.

Chloroquine Resistant Areas

In such areas the first line drug is Sulfodoxine/Pyrimethamine combination administered at a dose of 25mg /1.25mg / kg as a single oral dose.

The second line drugs include Artesunate (12mg/kg), or Artemether (2mg/kg) or Dihydroartemisinin (10mg/kg), all in divided doses over 4 – 7 days. Mefloquine 15mg/kg may be given as a single dose (in Mefloquine sensitive areas),or at a dose of 25mg/kg (in areas with low grade Mefloquine resistance).

Other second line drugs include Halofantrine 8 mg / kg· [children], 500mg [adults] 6 hourly for 3 doses; Quinine 10mg / kg 8 hourly for 7 days combined with Tetracycline [4mg/kg qid] or with Doxycycline [3mg/kg once daily] or with Clindamycin [10mg/kg bid].

Eradication of hypnozoites [*Plasmodium vivax* and *Plasmodium ovale* only]

For the eradication of *P. vivax and P. ovale* Primaquine base, 0.3mg/kg or 15mg is given daily for 14 days [22.5-30mg in SE. Asia and Oceania], in G6PD sufficient persons. In mild G6PD deficiency, the dose is reduced to 0.6mg/kg [45mg] weekly for 8 weeks.

Combination Therapy

Drug combinations have been very successful in the therapy of certain disease such as tuberculosis, HIV and cancer. Declining effectiveness of available antimalarials due to drug resistance has drawn attention to this mode of therapy, to enhance antimalarial effectiveness and delay the emergency of resistant parasites. Antimalarial combination therapy (CT) is defined as the use of 2 or more blood schizonticidal drugs with independent mechanisms of action and different biochemical targets in the parasite. Artemesinin based combination therapy (ACT) is much favored because of the rapid clearance of parasites, resolution of symptoms and its proven effectiveness against multi-drug resistant *Plasmodium falciparum.* In areas with drug resistance, combination therapies are increasingly being advocated and used as first line treatment. Common and potential drug combinations are shown in Table 6[34].

Table 6 Antimalarial combinations[*]

Past and Present Combinations	Trial of Available drugs	Trial of new drugs
CQ + SP	ASU + SP	Chlorguanil + Dapsone
AQ + SP	ASU + AQ	Chlorguanil + Dapsone + ASU
Q + antibiotics	ASU + MQ	Pyronaride + ASU
MQ + ASU	AT + PR + ASU	DHA+PR + trimethoprim (TMP)
ATM + LUM		DHA + PR + TMP + PQ

* AQ = Amodiaquine; ASU = Artesunate; AT = Atovaquone; ATM = Artemisinin; CQ = Chloroquine; DHA = Dihydroartemisinin; LUM = Lumefantrine; MQ = Mefloquine; PQ = Primaquine; PR = Proguanil; Q = Quinine; SP = Sulfodoxine/Pyrimethamine; TMP = Trimethoprim

Treatment of Severe malaria (*Plasmodium falciparum*) [16, 17,19,34,35]

For the treatment of severe malaria, usually caused by *Plasmodium falciparum*, the first line drug is Quinine dihydrochloride. A loading dose of 20mg/Kg base in 10ml/kg of dextrose saline is given as an intravenous infusion over a 4-hour period. In children 12 hours later, or 8 hours later in adults, a maintenance dose of 10mg / kg is started 12 hourly, as intravenous infusions, each time the infusion being made to run over 4 hours (maximum dose 1800mg). If intravenous quinine is required for more than 2 days, or the patient is in acute renal failure, the dose of quinine should be reduced by 30 – 50% (i.e. 5–7mg/kg) to avoid cumulative toxicity. Oral quinine is continued when the patient is able to take it to complete 7 days of treatment. Intramuscular quinine can be used where infusion facilities or capability are not available. The drug is diluted to 60 – 100mg / ml, and given into the anterior part of both thighs. The dosage and dosage schedule are as for the intravenous preparation. Alternatively, treatment can be completed with a singe oral dose of Sulfodoxine/Pyrimethamine.

Quinidine gluconate 10mg/kg [max 600mg] in normal saline may be given over 1-2 hours, followed by continuous infusion of 0.02mg/kg until the patient is able to take orally.

The second line drug for the treatment of severe malaria is Artesunate 2.4mg/kg administered as an intravenous bolus injection; this is reduced to 1.2mg/kg at 12 hours, repeated daily for 6 days or convert to oral therapy when feasible. Artemether, another second line drug, may be given at an initial dose of 3.2mg/kg intramuscularly, then reduced to1.6mg/kg daily for 6 days or convert to oral therapy when feasible. Suppositories of artesunate and artemether can be used as alternatives to the parenteral route with good effectiveness. Mefloquine, Doxycycline, Tetracycline, or Sulfodoxine/Pyrimethamine is often added after the treatment to avoid late recrudescence 3 – 4 weeks later.

MANAGEMENT OF SEVERE MALARIA [13, 14, 16,17,18,35]

Severe malaria needs to be recognized early. Patients should be hospitalized, quickly assessed and investigated, and the appropriate parenteral antimalarial chemotherapy started. Some of the general treatment measures include checking to ensure potency of the airways, weighing the patient, determining the patient's fluid requirements and maintaining an intravenous line. The patient is tepid sponged, bathed or placed under a fan for temperatures greater than 38.5℃. For the pyrexia, paracetamol may be given.

For patients in **Coma (Cerebral malaria)**, it is essential that the airway is maintained. The patient is nursed on his/her side, hypoglycemia is corrected and prophylactic anticonvulsants administered.

If **Convulsions** occur, manage the patient as for a patient in coma. Seizures are controlled in children with rectal diazepam 0.5mg/kg or intramuscular paraldehyde 0.1mg/kg. In the adults, intravenous diazepam 10mg is used. Pyrexia is controlled and hypoglycemia corrected.

For associated **Hypoglycemia**, children should be given 0.5ml/kg of 50% dextrose diluted to 10-15% intravenously. Adults should receive 25-100ml of 50% dextrose. The blood glucose is monitored every 4 – 6 hours. Nasogastric tube feeding may be substituted for intravenous dextrose.

In **Lactic Acidosis**, hyperglycemia, hypovolemia and gram negative sepsis are treated. It may be required to administer oxygen by intranasal tube or face mask. Parasitemia is treated promptly.

For **Severe anemia (PCV < 20%)**, treatment would include transfusion of fresh whole blood or packed cells [10ml/kg children]. Exchange blood transfusion has been used with uncertain benefits. **Exchange blood** transfusion could be indicated in severely ill non-immune individuals with more than 10% parasitemia not responding to conventional therapy. Despite a significant reduction in the level of parasitemia and presumptively the toxic factors, and improvement in blood rheology, exchange blood transfusion did not improve the prognosis in patients with severe anemia[36].One reason could be that parasitized erythrocytes are not affected by exchange blood transfusion. It can be of value in severe anemia with heart failure, especially high output failure of late pregnancy.

Hypovolemia / Shock is treated with intravenous fluids. The blood is cultured and parenteral broad-spectrum antibiotics administered. Monitoring of the patient is aided by Swan-Ganz catheterization [CVP 5mm H_2O, PCWP 15cm H2O].

When **acute Pulmonary edema** complicates malaria, management includes propping such patients up at an angle of 45°, stopping of the administration of intravenous fluids and giving intravenous Frusemide, 2-4mg/kg. positive pressure ventilation with high PEEP and inverted I/E ratio, avoiding high F_iO_2 and tidal volume.

Acute renal failure associated with malaria is managed by adequate rehydration and challenging the individual with Frusemide 1-2mg/kg. A strict fluid balance is maintained aided by accurate monitoring of urine output. Haemodialysis or haemofiltration is done as required.

Bleeding abnormalities may require transfusion with fresh whole blood, Vitamin K injection and platelet cryoprecipitate infusion.

Aspiration pneumonitis requires adequate pulmonary toilet, intravenous antibiotics and oxygen administration.

When a sudden unexpected deterioration occurs, treat hypoglycemia and gram-negative sepsis.

Ancillary measures have been used in managing severe malaria. Among these, TNF-α antibody had no impact on morbidity or mortality. Steroids used for treatment of cerebral malaria were found to increase morbidity. Similarly, heparin and adrenalin were found to be of no useful value.

Nursing care of the unconscious patient include monitoring the vital signs, urine output and level of consciousness. A drug chart is maintained.

The Laboratory should monitor parasitemia (blood smear daily) to assess response to treatment; monitor blood sugar and Packed Cell Volume.

PREVENTION AND CONTROL OF MALARIA

Malaria control and prevention can be achieved through three different approaches.

Reduce human – mosquito contact: This may be achieved by the use of Impregnated Nets (ITNS), repellents, protective clothing, screens, and house spraying with insecticides. ITNS and curtains can reduce child mortality in malaria endemic areas by 15 – 30%.

Reduce vector Population: This involves environmental modification, use of larvicides / insecticides and biological control. The last method, biological control, utilizes fish that eat mosquito larvae or bacteria (e.g. Bacillus thuringiensis) that excretes larval toxins.

Reduce parasite reservoir: This strategy involves case detection and treatment and chemoprophylaxis.

The most appropriate control method will be determined by the epidemiologic, socio-economic, cultural and infrastructural factors of a particular area.

Global initiatives on malaria control

Malaria is the target of several international initiatives to assist in the development of new therapies, coordinating efforts, fostering and integration of basic education programmes for populations at risk[6, 7].

1. WHO Roll Back Malaria [RBM]: Launched in May 1998, with the goal of a 50% reduction in malaria deaths by the year 2010, RBMS four pillars of action are to promote access to treatment, promote insecticide treated mosquito nets (ITN), prevention and control of malaria in pregnant women, and malaria epidemic and emergency response.
2. Malaria Vaccine Initiative (MVI) has the objective of accelerating the clinical development of promising candidate malaria vaccines.
3. WHO New Medicine for Malaria Venture aims to develop antimalarial drugs and drug combinations for distribution in poor countries.
4. The Multilateral Initiative on Malaria facilitates global collaboration and coordination to maximize the impact of scientific research against malaria in Africa.
5. The African Malaria Control Initiative was launched in 1999 and specifically targets malaria control in Africa.
6. Political commitment was made at the highest level in Africa at the Abuja Summit on Malaria in April 2000, where African Heads of State gathered and endorsed the blue print for practical steps to control malaria effectively.

CHEMOPROPHYLAXIS

The objective of chemoprophylaxis is to prevent illness and death in persons exposed to the risk of contracting malaria. Chemoprophylaxis is recommended for travelers to endemic areas, pregnant women and persons with sickle cell disease. No prophylactic regimen gives complete protection.[13, 14, 16,17,19,37]

Travelers From non-Endemic Areas to Malaria Endemic Areas

Protection against Chloroquine susceptible strains (*Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale* and *Plasmodium malaria*) is achieved by the use of Chloroquine base 300mg orally once weekly for short term visitors. Proguanil, 200mg daily is useful in long term visitors.

Protection against Chloroquine resistant strains [*Plasmodium falciparum*] utilizes Mefloquine 250mg orally once weekly or, Doxycycline 100mg orally daily or, Chloroquine 300mg daily in addition to Proguanil 200mg orally daily or, Atovaquone 250mg orally daily added to Proguanil 100mg orally daily.

Whichever drug or drug-combination should be started 2 weeks [at least one week] before departure, continued throughout the duration of the travel, and for 4 weeks after return home.

Protection of Pregnant women

The Intermittent Preventive Treatment (IPT) is advocated. In this strategy, a curative treatment dose of chloroquine is given at the first antenatal attendance. A second treatment is given before delivery. Alternatively, chloroquine can be given at the first visit, followed with 300mg weekly. Sulfodoxine/Pyrimethamine can be used in place of chloroquine: two or more doses may be given in the second and early third trimester.

Protection of Adults and Children with Sickle Cell Disease

Proguanil given at a dose of 100mg daily for children up to15years of age and 200mg daily for adults is recommended.

Adverse Drug Reactions, Cautions and Contraindications of Antimalarials

Chloroquine: This drug is usually well tolerated. In some persons it may cause dizziness, blurred vision headache, postural hypotension and gastro-intestinal upsets. A common reaction among blacks is pruritus [ascribed to anti-microfilarial effect]. Retinopathy may occur after prolonged use: to prevent this, the cumulative maximum adult dose should not exceed 100g.

Sulfodoxine/Sulfalene – Pyrimethamine: This drug may be associated with Erythema Multiforme or Steven – Johnson's syndrome. Megaloblastic anemia may also occur. Rarely bone marrow suppression and hemolysis in G6PD deficient subjects have been reported. This drug is not recommended for malaria prophylaxis, in people with sulfonamide hypersensitivity, premature infants and neonates.

Amodiaquine: This drug is similar to chloroquine but causes less pruritus. It may result in severe leucopenia and agranulocytosis with repeated use.

Quinine and Quinidine: These cinchona alkaloids may cause cinchonism: giddiness, tinnitus, blurred vision, tremors, high tone hearing loss, dysphoria, nausea, vomiting and postural hypotension. They may also cause hypoglycemia and prolonged QT interval on ECG.

Mefloquine: This drug has been known to cause nausea, giddiness, dysphoria, sleeplessness and nightmares. Neuropsychiatric reaction, convulsions and encephalopathy have been reported.

Tetracycline, Doxycycline: These cause gastrointestinal upset, photosensitivity, and overgrowth and proliferation of Candida. Deposition in growing bone and teeth cause yellow discoloration of these structures. They are therefore contraindicated in pregnant women and children less than 8years old, and in persons with severe hepatic dysfunction (tetracycline).

Artemisinin derivatives are associated with fever, allergy and reduction in reticulocyte count.

Halofantrine is known to cause diarrhea, cardiac conduction disturbances such as atrioventricular block and prolongation of QT interval.

Primaquine causes nausea, vomiting, diarrhea, abdominal pain and hemolysis especially in G6PD deficient persons.

Proguanil is well tolerated. It may be associated with mouth ulcers and, rarely, alopecia. Megaloblastic anemia may occur in renal failure.

The side effects of **atovaquone** and **lumefantrine** have not been identified. All drugs are contraindicated in cases of known hypersensitivity to the drug. Halofantrine should not be used in patients with conduction disturbances or in combination with other drugs that cause such disturbances (e.g. quinine, quinidine, Mefloquine, chloroquine, neuropleptics, antiarrythmics, tricyclic antidepressants, terbinafine or astemizole). The resurgence of quinine use makes a case for the closer monitoring of its side effects[38]. ECG monitoring is necessary with quinidine therapy.

MALARIA VACCINE

The last 20 years have witnessed significant progress in malaria vaccine research. The situation is even more urgent due to the difficulty of controlling malaria by other means. The complex life cycle and biology of malaria parasites presents many targets for vaccines [Table 7][27].

Table 7 Potential malaria vaccines

Potential Target	Type of Protection
Sporozoite	Anti-infection
	Anti-parasite
Merozoite	
	Anti-parasite
Infected Red Blood Cells	
	Anti-disease
Exoantigens	
	Anti-transmission
Sexual stages	

The challenge for vaccine development has been to; characterize immune responses that provide protection, define parasite antigens/epitopes that are targets of this protective immune response, and to develop vaccine delivery systems that induce the appropriate immune responses. Vaccines based on a single protein are of very limited value. Most candidate vaccines are multistage and multiantigen. Examples, effectiveness and composition of some candidate vaccines are described[30, 39].

1) CSP Vaccine: did not provide any protection in a Kenyan study.

2] Patorraya vaccine (cocktail vaccine): This synthetic Columbian vaccine [SPF 66] consists of 3 peptide epitopes from 3 blood stage proteins intercalated with NANP sequence. Protection from the vaccine was variable and low in the very young.

3] NYVAC-Pf.7: This vaccine is produced by inserting genes encoding various *Plasmodium falciparum* antigens into the genome of the highly attenuated NYVAC vaccine virus (CSP + SSP + LSA –1 + MSP –1 + SERA + AMA –1 +Pf. 25KDa.]

4) DNA vaccine: Composed of the gene sequences of 21 epitopes of 9 different *Plasmodium falciparum* antigens. Introduction of these genes in the host

leads to the expression of foreign proteins resulting in the stimulation of an immune response. An example is the CDC/NII MLVAC-1 vaccine.

Despite all the efforts, malaria vaccines that are effective or suitable for mass production are not available till date.
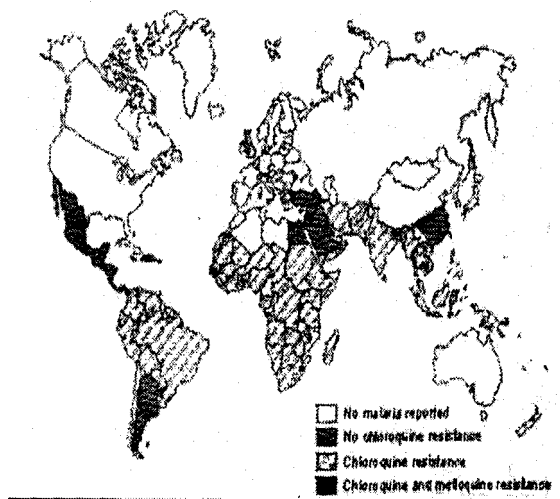

Figure 1 Map showing malaria-endemic zones worldwide*

Fig 1: Map showing malaria-endemic zones worldwide*
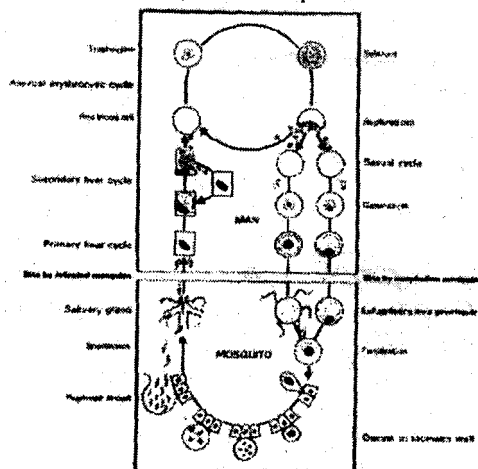

Figure 2. The life cycle of malaria parasite

Fig 2: The life cycle of malaria parasite

CONCLUSION

Malaria remains a formidable disease, taking an enormous toll on lives and lands. Many factors contributed to this of which complacency and laxity in the antimalarial control campaign is important. Malaria is immensely curable. It tends to be taken for granted in endemic areas. Practitioners need to be alert and recognize that it can and does cause severe disease with considerable morbidity and mortality. Much scientific progress has been made in the understanding of the organism but a lot remains to be learnt. The prospects of an effective vaccine will take some years to materialize. New drugs need to be developed to tackle the problem of drug resistance. For now, there is need to resort to simpler less expensive preventive measures to control the disease; personal protection, community measures, early recognition and prompt treatment with simple available and effective drugs.

REFERENCES

1. Giles HM. Historical outline. In Giles HM, Warrel DA, eds. Bruce–Chwatts Essential malariology, 3rd edition Oxford University Press, London 1993: 1 - 11.

2. WHO. EMRO http://www.emro.who.Int/RBM/About Malaria - historicaspects.htm.

3. WHO RBM. What is malaria? http://www.rbm.who.int

4. WHO RBM. Malaria in Africa malaria? http://www.rbm.who.int

5. Committee To Advice on Tropical Medicine And Travel [CATMAT]. Canadian communicable disease report 2000. Canadian recommendations and treatment of malaria among international travelers 2000; 26 (S2): 1-3.

6. WHO RBM. What is roll back malaria? http://www.rbm.who.int

7. Malaria. Nature Biotech 2000; 18: 111 – 112.

8. Trape JF. The public health impact of chloroquine resistance in Africa. Am J Trop Med Hyg. 2001: 64; (1-2suppl): 12 - 17.

9. Sachs J, Meleney P. The economic and social burden of malaria. Nature 2002; 415: 680 – 685.

10. Shell ER. Resurgence of a deadly disease. The Atlantic Online.http://www.theatlantic.com/issues/97aug/malaria.htm.

11. Wyler DJ. Malaria – resurgence, resistance, research. N Engl J Med 1983; 308: 875.

12. Giles GM The malaria parasites. In Giles HM, Warrel DA eds. Bruce-Chwatts Essential malariology. 3rd edition, Oxford University Press London 1993: 12 – 34.

13. Wyler OJ. Plasmodium and babesia. In Gorbach SL, Bartlett JG, Blacklow NR eds. Infections disease. WB Sounders Company Philadelphia, 1992: 1967 – 1978.

14. Krogstad DJ. Plasmodium species (malaria). In Mandel GL, Bennet JE, Dolin R. eds. Principles and practice of infections diseases 4th edition. Churchill Livingstone, London1995: 2415 – 2427.

15. Warrel DA. Clinical features of malaria. In Giles HM, Warrel DA eds. Bruce Chwatts Essential malariology. 3rd edition Oxford University Press, London, 1993: 35-49.

16. White NJ, Bremen JG. Malaria. In Braunwald E, Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL. eds. Harrison's principles of internal medicine. 15th edition volume 1 McGraw–Hill New York 2001: 1203 – 1212.

17. WHO. Severe falciparum malaria. Tran R Soc Trop Med Hyg 2000; 94 (Suppl.1):1 – 90.

18. Mishra SK, Mohanty S. Clinical presentations of severe malaria in India. J. Ind Acad Clin Med 2001; 2:125 – 127.

19.   Bradley D, Newbold CI, Warrel DA. Malaria. In Wetheral DJ, Ledingham GG, Warrell DA. eds. Oxford textbook of medicine. 4th edition Oxford University Press, Oxford 1996: 835-863.

20.   Roginer C, Imbert P, Sakhna C, et al. Epidemiological and clinical aspects of blackwater fever among Africa children suffering frequent malaria attacks. Tran R Soc Trop Med Hyg 2003; 2: 193 – 7.

21.   Malaria in pregnancy. htpp://www.rbm.who.int

22   Spiegel A, Tall A, Raphenon G et al. Increased frequency of malarial attacks in subjects co-infected with intestinal worms and plasmodium falciparum malaria. Tran R Soc Trop Hyg. 2003; 97:198-199.

23   Khasnis AA Karnad DR. Human immunodeficiency virus type 1 in patients with severe falciparum malaria in urban India. J Postgrad Med 2003; 49:114-117.

24.   Adedoyin OT, Adeniyi A. Quartan malaria nephropathy in children. Postgrad Doctor Afr 2001; 23: 72 – 75.

25.   Francis N, Warrel DA. Pathology and pathophysiology of human malaria. In Giles HM, Warrel DA eds. Bruce Chwatts Essential malariology. 3rd edn. Oxford University Press, London, 1993: 50-59.

26.   Kwiatkowski D, Cannon JG, Manoque KR et al. Tumor necrosis factor production in falciparum malaria and its association with schizont rupture. Clin Expt Immunol 1989; 77: 361 – 366.

27.   Wiser MF. Malaria. http://www.tulane.edu/~wiser/prtozoology/malaria.html

28.   Almeida A, Mehta A. Malaria and anemia. Postgrad Doctor Africa Afr 2001; 23: 58-63.

29.   Marsh K Immunology of malaria In Giles HM, Warrel DA eds. Bruce Chwatts Essential malariology. 3rd edn. Oxford University Press, London 1993: 60 – 77.

30.   Venugopalan PP. Malaria vaccine: the last word in malaria prevention – a myth or a reality? http://www.malariasite.com/malaria/malaria_vaccine.htm

31.   Hviid L. Clinical disease, immunity and protection against plasmodium falciparum malaria in populations living in endemic areas.http://www-ermm.cbcu.cam.ac.uk/lhc/txt001lhc.htm

32   WHO. http://www.who.int/tdr/publications/malaria_diagnosis.htm

33.   Pukrittayakamee S, white NJ, New treatment, for malaria. Postgrad Doctor Afr 1995; 17: 14 – 18.

34   Report of an Informal Consultation. The use of antimalarial drugs. http://www.rbm.who.int/cmc

35.   Dondorp A. The treatment of malaria. NNJCC. 2002; 10: 28-30.

36   Burchard GD, Kroger J, Knobloch J et al. Exchange blood transfusion in severe falciparum malaria: retrospective evaluation of 61 patients treated with, compared to 63 patients treated without, exchange blood transfusion.

37.   Balint GA. Possible malaria prophylactic measures in sub-Saharan Africa: focus on tourists. Postgrad Doctor Afr 2003; 25: 46 – 48.

38.   Ologe FE, Sequn-Busari S. Resurgence of quinine in clinical use: the need for audiological monitoring. Postgrad Doctor Afr 2003; 25: 22 – 28.

39   Norman LL, Barry RM, Stephen LH. Prospects for vaccines to protect against AIDS, tuberculosis, and malaria. JAMA 2001; 285: 606-611.