

Malaria

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Introduction

- Protozoan disease
 - Vector borne
 - Transmitted by the bite of infected *Anopheles* mosquitoes
- Transmission
 - Common in the tropics
 - in 107 countries containing 3 billion people 1–3 million deaths each year

In Ethiopia

- Major public health concern in Ethiopia
- Among the leading causes of morbidity and mortality irrespective of age group
- Approximately 60% of the Ethiopian population lives in malaria risk areas

Malaria transmission pattern

- Stable (endemic) : not subjected to annual fluctuations, and population immunity is high (pregnant and under 5 children has weaker immunity)
- Unstable (epidemic): subject to marked annual fluctuations and the population immunity is low

In Ethiopia

- Malaria transmission in Ethiopia mainly occurs below 2000m elevation.
 - Occasionally affects areas up to 2300m elevation
- the peak periods of malaria incidence occur from **September to December**
- Goals of the national strategic plan for Malaria are
 - By 2020, to achieve near zero malaria deaths in Ethiopia
 - By 2020, to reduce malaria cases by 40 percent from baseline of 2016
 - By 2030, to eliminate malaria from Ethiopia.

Etiology

- Malaria is caused by five species of Plasmodium parasites: *P. falciparum*, *P. vivax*, *P. malariae* and *P. ovale* and *P. Knowlesi*
- The most dominant ones in Ethiopia: *P. falciparum* and *P. vivax*
- *P. falciparum* represents about 77 percent or more of the total reported malaria cases in Ethiopia
- Malaria is transmitted by the bite of an infected *Anopheles* mosquito that introduces the sporozoites of the plasmodia into blood stream

Etiology

1. **Sporozoites** from the salivary gland of a female *Anopheles* mosquito are injected under the skin
2. They then travel through the blood stream to the liver within 30 minutes
3. The sporozoites invade parenchymal hepatocytes, multiply in stages (exoerythrocytic stages) and become **schizonts**
4. Schizonts rupture to release daughter cells, or **merozoites**, that then infect erythrocytes (around 10,000-30,000 merozoite released to blood stream)
- Merozoites produce symptomatic infection as they invade and destroy red blood cells. However, some parasites remain dormant in the liver as **hypnozoites**

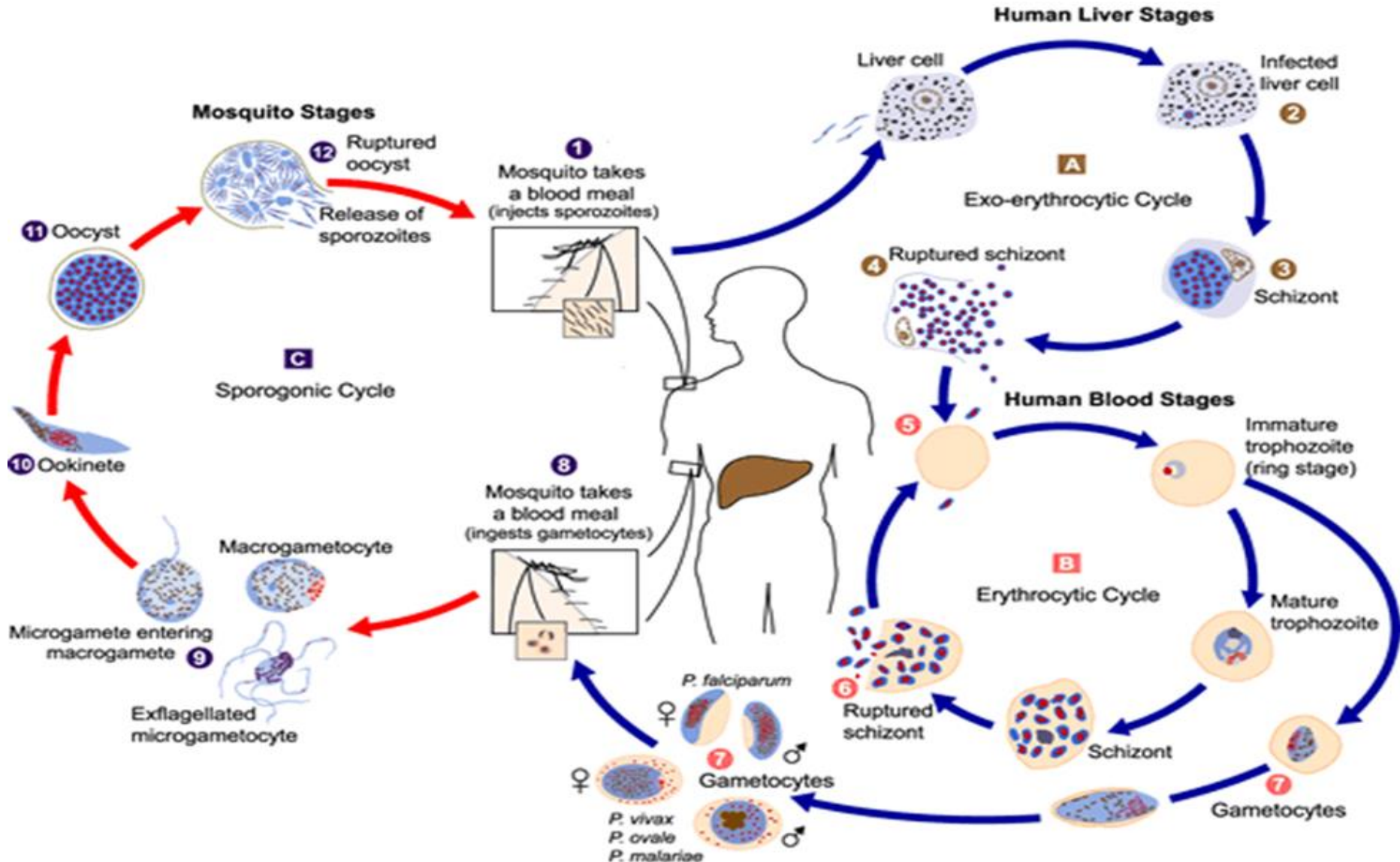
Etiology

- *P. falciparum* and *P. malariae* remain in exoerythrocytic stage in the liver for about 4 weeks before invading erythrocytes
 - *P. vivax* and *P. ovale* can exist in the liver in the latent exoerythrocytic form for extended periods (relapse)
5. the asexual cycle starts with merozoite invasion (merozoite → ring stage → trophozoite → schizont)
 6. Schizonts lyse their host red blood cells as they mature and release the next generation of merozoites
 - invade previously uninfected red blood cells

Etiology

7. Within the red blood cell, some parasites differentiate to sexual forms (male and female gametocytes)
- 8,9 When taken up by a female *Anopheles* mosquito, the gametocytes mature to male and female gametes,
10. Fertilization of female gamete produce zygote which mature to ookinetes
11. The zygote invades the gut of the mosquito and develops into an oocyst
12. Mature oocysts produce sporozoites, which migrate to the salivary gland of the mosquito

Life cycle of malaria parasite



Pathophysiology

- Erythrocyte Changes in Malaria
- Malarial parasite progressively consumes and degrades intracellular proteins, principally hemoglobin (anemia and splenomegaly)
- *P. falciparum* infections complications are primarily due to
 1. its ability to produce high parasitism (up to 80%) of red cells of all ages
 2. the ability of the parasites to sequester in postcapillary vessels of organs such as brain, liver, kidney and lung
- Tissue hypoxia from anemia, together with *P. falciparum* parasitized RBC adherence to endothelial cells in capillaries, likely contribute to extensive vascular disease and severe metabolic effects

Pathophysiology

- In the brain and the placenta, and in most other organs.
 - infected erythrocytes stick inside and eventually block capillaries and venules
- sequestration of RBCs containing mature forms of the parasite in vital organs (particularly the brain), where they interfere with microcirculatory flow and metabolism
- only the younger ring forms of the asexual parasites are seen circulating in the peripheral blood in falciparum malaria

Pathophysiology

- The other malarias, sequestration does not occur, and all stages of the parasite's development are evident on peripheral blood smears
- *P. vivax*, *P. ovale*, and *P. malariae* show a marked predilection for either young RBCs (*P. vivax*, *P. ovale*) or old cells (*P. malariae*)

Pathophysiology

- Initial host response to plasmodial infection
 - activating nonspecific defense mechanisms
 - Splenic immunologic and filtrative clearance functions are augmented in malaria
 - removal of both parasitized and uninfected erythrocytes is accelerated.
 - The parasitized cells escaping splenic removal are destroyed when the schizont ruptures
 - The material released induces the activation of macrophages and the release of Proinflammatory mediators and cytokines, which cause fever and exert other pathologic effects

Clinical presentation

- **Initial presentation**
- fever, chills, rigors, diaphoresis, malaise, vomiting, orthostatic hypotension, electrolyte abnormalities
- **Erythrocytic Phase**
 1. Prodrome: Headache, anorexia, malaise, fatigue, and myalgia
 2. Nonspecific complaints include abdominal pain, diarrhea, chest pain, and arthralgia
 3. Paroxysm: High fever, chills, and rigor
 4. Cold phase: Severe pallor, cyanosis of the lips and nail beds

Clinical presentation

5. Hot phase: Fever between 40.5°C (104.9°F) and 41.0°C (with *P. falciparum*)
6. Sweating phase: Follows the hot phase by 2 to 6 hours
7. When fever resolves, it is followed by marked
 - fatigue and drowsiness, warm dry skin, tachycardia, cough, headache
 - N/V, abdominal pain, diarrhea and delirium, anemia, and splenomegaly

Clinical presentation

- **Severe malaria**
- Coma/cerebral malaria
- Prostration, i.e. generalized weakness so that the patient is unable to walk or sit up without assistance
- Multiple convulsions – more than two in 24 hours;
- Acidosis
 - Arterial pH <7.25 or plasma bicarbonate level of <15 mmol/L; venous lactate level of >5 mmol/L;
 - Manifests as labored deep breathing, often termed "respiratory distress"
- Pulmonary edema/adult respiratory distress syndrome

Clinical presentation

- Circulatory collapse or shock, systolic BP < 70mmHg in adults and < 50mmHg in children;
- Hypoglycemia (blood glucose < 40mg/dl);
- Severe normocytic anemia (Hb < 5g/dl, packed cell volume < 15%);
- Hemoglobinuria (dark color of urine/cola color urine in the absence of hematuria)
- Hyperparasitemia (>2% of red blood cells parasitized or >100,000 parasites per μ L);
- Acute kidney injury (serum creatinine \geq 3 mg/dl).

Risky groups for severe falciparum malaria

- People of all ages in areas of low endemicity (like most malaria endemic places in Ethiopia);
- Residents of areas where there is little or no falciparum malaria who travel to a high transmission area.
- pregnant women
- Children of ages 6 months to 5 years
- Patients who have had a splenectomy

Diagnosis

- **Clinical diagnosis**
- a patient from malaria endemic area has fever or history of fever in the last 48 hours or
- if a patient from non-malaria endemic area has fever in the last 48 hours and
- has a history of travel to malaria-endemic areas within the last 30 days
- However, treatment based on clinical diagnosis must be the last option if parasitological test can't be done

Diagnosis

- **Parasitological diagnosis**
- Rapid diagnostic test (RDT)
 - detect parasite antigens that may also persist in the blood for sometime even when the parasites are cleared by chemotherapy
 - Should only be used at health post
- Light microscopy
 - the parasite is demonstrated on a properly stained blood film
 - Used in health center and hospitals
 - Patients with negative microscopic result don't need antimalarial medication

Treatment

- **Desired Outcome**
 - To eradicate the infection within 48 to 72 hours
 - To avoid complications such as hypoglycemia, pulmonary edema, and renal failure that are responsible for increased mortality in malaria

Management of uncomplicated malaria

- **P. falciparum positive**
- Artemether lumefantrine (AL) and single dose primaquine is the recommended first line drug
- The first dose should be given under direct supervision
- A fatty meal improves its absorption
- If vomiting occurs within 1/2hr after the patient swallows the drug, the dose should be repeated
- AL is available in co-formulated tablets containing artemether 20 mg and lumefantrine 120 mg per tablet (coartem)

Management of uncomplicated malaria

- primaquine at dose of 0.25 mg/kg is given to reduce the transmission of *P. falciparum* infection
- Contraindication for primaquine
 - pregnant women, infants aged < 6 months
 - Breastfeeding women and
 - testing for G6PD deficiency

Artemether lumiefantrine Dose

Wt in Kg	Age	Day 1		Day two		Day three	
		Immediate	After 8 hr	Morning	Evenin g	Morning	Evenin g
<14kg	≤ 2 years	1 tablet	1 tablet	1 tablet	1 tablet	1 tablet	1tablet
15-24kg	3 to 7 yrs	2 tablet	2 tablet	2 tablet	2 tablet	2 tablet	2tablet
25-34kg	8 to yrs	3 tablet	3 tablet	3 tablet	3 tablet	3 tablet	3 tablet
>35kg	≥ 10yrs	4 tablet	4 tablet	4 tablet	4 tablet	4 tablet	4tablet

Management of uncomplicated malaria

- **P. vivax, and others positive (except P.falciparum)**
- chloroquine plus 0.25mg/kg primaquine radical cure for 14 days
- Chloroquine preparation is 150 mg base tablet OR chloroquine syrup 50 mg base
- A tablet of 250 mg chloroquine phosphate (“salt”) is the same as chloroquine 150 mg base.
- The dose is 10 mg base/kg (Day 1), followed by 10 mg base/kg (Day 2), and 5mg base/kg (Day 3)

Chloroquine dose

Wt (Kg)	Age	Day 1	Day 2	Day 3
5-6	< 4 month	1/2 tablet OR 5ml syrup	1/2 tablet OR 5ml syrup	1/2 tablet OR 2.5ml syrup
7-10	4-11 month	1/2 tablet OR 7.5ml syrup	1/2 tablet OR 7.5ml syrup	1/2 tablet OR 5ml syrup
11-14	1-2yrs	1 tablet OR 12.5ml syrup	0.5 tablet OR 12.5ml syrup	0.5 tablet OR 7.5ml syrup
15-18	3-4yrs	1 tablet OR 15ml syrup	1 tablet OR 15ml syrup	1 tablet OR 15ml syrup
19-24	5-7yrs	1 ½ tablets OR 20ml syrup	1 ½ tablets OR 20ml syrup	1 Tablet OR 15ml syrup
25-35	8-11yrs	2 ½ tablets OR 20ml syrup	2 tablets	1 tablet
36-50	12-14yrs	3 tablets	2 tablets	2 tablets
51+	≥ 15 yrs	4 tablets	4 tablets	2tablets

Primaquine dose

Weight in kg	Age (years)	Number of tablets	
		7.5mg tablet	15mg tablet
8 to 18	7 month- 4 years	$\frac{1}{2}$	$\frac{1}{4}$
19 to 24	5 - 7	$\frac{3}{4}$	$\frac{1}{2}$
25 to 35	8 - 10	1	$\frac{1}{2}$
36 to 50	11- 13	1 $\frac{1}{2}$	$\frac{3}{4}$
50+	14+	2	1

Management of uncomplicated malaria

- **Mixed infection (P . falciparum and P . Vivax)**
- The recommended treatment is AL and single dose primaquine
- Pregnant women in first trimester should be treated with oral quinine when mixed infection or P . falciparum infection present

Management of uncomplicated malaria

- **Supportive treatment**
- antipyretics (children: acetaminophen 15 mg/ kg every 4 hours)
- fanning and tepid sponging

Treatment failure

- **Causes**
- drug resistance,
- poor adherence
- inadequate drug exposure (i.e. from under-dosing or vomiting)
- drug interaction,
- misdiagnosis or
- substandard medicines

Treatment failure

- **Treatment failure within first 28 days:**
- treatment failure within 28 days of receiving AL is very unusual (owing to its potency)
- wherever possible, treatment failure should be confirmed parasitologically
- if cause is identified (e.g. anti-malarial drug is vomited), such cause must be addressed
- If parasites are detected on microscopy , the treatment should be changed to the second-line drug, i.e. quinine tablets

Treatment failure

- **Treatment failure after 28 days:**
- All presumed treatment failures after four weeks of initial treatment should be considered as new infection
 - Treatment is AL for *P. falciparum* and CQ for *P. vivax*.
 - Primaquine should be given as appropriate

Management of severe malaria

- **Desired outcome**
- Prevent mortality
- Prevent treatment failure, resistance and disabilities
- **General principles of treatment**
- The patient presenting with severe malaria needs URGENT medical attention.
- Many suspected cases can be managed at either the health center or primary hospital but severe cases need referral
- Antimalarial medicines should be given parental if possible

Management of severe malaria

- **First-line treatment of severe malaria**
- IV or IM artesunate (preferred) (shown to reduce risk of death by 35% compared to iv/im quinine)
- IM artemether (alternative)
- IV quinine infusion (if artesunate or artemether is not available); or
- IM quinine

Management of severe malaria

- **Dose of Artesunate**
- For those weighing >20 kg
 - Artesunate 2.4 mg/kg IV or IM given on admission (time = 0), then at 12 hrs and 24 hrs, then once a day until the patient tolerates po drugs.
- Children weighing < 20 kg
 - Artesunate (3 mg/kg per dose)

Management of severe malaria

- **Artesunate reconstitution (intravenous):**
- The injectable artesunate, which contains 60 mg powder within a 7ml glass vial must be reconstituted with 1ml of 5% sodium bicarbonate solution, and shaken for 2-3 minutes
- then prepare IV infusion of artesunate (10 mg/ml), by adding 5 ml of 5% glucose (D5W) or NS to the just-reconstituted 7 ml vial, and
 - then infuse slowly (i.e. 3-4 ml per minute IV)

Management of severe malaria

- **Artesunate reconstitution (IM):**
- add 2 ml of 5% glucose (D5W) or Normal Saline to the reconstituted 7 ml vial to make 3 ml of artesunate (20 mg/ml) for IM injection
- N:B second vial must be prepared and reconstituted for persons >26 kg, since they will need one full vial and at least a fraction of the second vial

Management of severe malaria

- **IV quinine infusion:** 20mg salt/ kg (LD) diluted in 10ml isotonic fluid/ kg by IV infusion over 4 hours; followed by 8 hourly maintenance dose of quinine 10mg salt/kg over 4 hours,
- **IM quinine:** given in the same dosages by IM injection in the anterior thigh (not in the buttock).
- The dose of quinine should be divided between two sites – half the dose in each anterior thigh
- Rapid administration may cause sudden death due to arrhythmia or refractory hypotension

Adjunctive Management

- Patients in coma should be nursed always in lateral position to avoid aspiration
- A rapid test for hypoglycaemia is important. Give 40% or 50% glucose to all patients with severe manifestations
- Regular lab checks on hematocrit, glucose, urea or creatinine, and electrolytes.
- Regular monitoring of temperature, RR, BP and level of consciousness
- Frequent monitoring of the therapeutic response, both clinical and parasitological should be done

Chemoprophylaxis

- Persons who travel to malaria-endemic areas are at risk of acquiring malaria.
- Health workers should advise all persons traveling to such areas to avoid mosquito bites, by sleeping under long lasting insecticide nets (LLINs)
- **mefloquine** and **atovaquone-proguanil** can be used as anti-malarial chemoprophylaxis in Ethiopia
- mefloquine : should be given 1 weeks before departure, continued throughout stay and 4 weeks after return
- Atovaquone-proguanil : start 1 day earlier continue throughout the stay and for 7 days after returning

Mefloquine dose for chemoprophylaxis

Weight (kg)	Age (approximate)	Number of tablet per week
<9	<3 month	Not recommended
9-19	3 to 23 month	1/4
20-30	2 to 7 years	1/2
31-45	8 to 10 years	3/4
36-50+	11 to 14+ years	1

Atovaquone/proguanil dose for chemoprophylaxis

Weight (kg)	Atovaquone/proguanil HCL	Dosage regimen
11-20	62.5mg/25mg	1 pediatric tablet daily
21-30	125mg/50mg	2 pediatric tablets as single dose daily
31-40	187.5mg/75mg	3 pediatric tablets as single dose daily
>40	250mg/100mg	1 tablet (adult strength) single dose daily