Life Cycle

Has 2 hosts: vertebrate (**intermediate**) and mosquito (**definitive**)

Definitive Host: Sporulating Cycle (Sporogony)	Intermediate Host: Asexual Cycle (Schizogony)

EXO-ERYTHROCYTIC CYCLE

1. Anopheles mosquito (definitive host), inoculates **sporozoites** into human host (intermediate)	Sporozoites are the infective stage to man
2. Sporozoites infect **liver parenchymal cells** and mature into **schizonts**, which produce merozoites	*P. vivax* and *P. ovale* assume a dormant stage (**hypnozoites**), and can persist in the liver

3. Infected cell ruptures and releases **merozoites**

ERYTHROCYTIC CYCLE

4. Merozoites infect **RBCs** and become **trophozoites** (ring stage)	Merozoites are the infective stage for RBCs

Life Cycle (cont)

5. Trophozoites mature into **schizonts**, which rupture and release **merozoites**	Some differentiate into **gametocytes**, which are ingested by the mosquito looking for a blood meal

6. Ruptured schizonts are responsible for the **clinical manifestations** of the disease

SPOROGONIC CYCLE

7. The **gametocytes** are ingested by an anopheles mosquito and make their way into the **stomach** of the mosquito

8. While in the stomach, the **microgametes** (male) penetrate the **macrogametes** (female), which generate **zygotes**	Microgametocyte exflagellates and produces 8 sperm-like microgametes
9. The zygotes become **motile** and **elongated**	These are called **ookinetes**

10. The ookinetes invade the **midgut wall** of the mosquito, where they develop into **oocysts**

11. The **oocysts** grow, rupture, and release **sporozoites**, which makes their way into the **salivary glands** of the mosquito

Life Cycle (cont)

12. Inoculation of the sporozoites into a new human host perpetuates the malaria life cycle

The **merozoite** recognizes a **specific receptor site** on the **RBC** and exposes several organelles for attachment. The red cells becomes **deformed** and the merozoite enters through an invagination of the RBC membrane

For *P. vivax*, the receptor site on the RBC is associated with the *Duffy Blood Group Antigen.* ***Over 90% of*** *Africans* ***are*** *Duffy Negative* and are **resistant** to Vivax Malaria

Pathogenicity and Virulence

Pathological process is the result of **erythrocytic cycle**

1. **Hemolysis**

RBC invasion by merozoites induces changes in **cytoskeleton** and decreases in **deformability**

Pathogenicity and Virulence (cont)

Increased capillary permeability, which allows fluid to lead into surrounding tissues, causing congestion in blood vessels and **tissue infarction and necrosis**

2. **Liberation of Metabolites**

Rupture of RBCs bring on **malarial paroxysm** and **increased hemosiderin** in the **liver, spleen**, and other organs, which become **black** in color

Pathogenicity and Virulence (cont)

Lysis of cells & phagocytosis of cell remnants, debris, and hemozoin congest the **kupffer cells** of the liver, resulting in **hepatosplenomegaly**. Tears of splenic capsule may occur due to trauma or coughing & may require surgery

3. **Immunologic Response**

Antigens of *P. falciparum* induces **cytokines**, which stimulate the release of **TNF** or **Cachexin**, which causes **fever, paroxysms, HA, pains, and prostration**

TNF produces **neurologic symptoms**, which play a role in **cerebral malaria**

Repeated attacks of malaria produce **anemia**

Pathogenicity and Virulence (cont)

Immune complexes are formed and may be deposited in the **kidney**

4. **Formation of Malarial Pigment**

In infected RBC, **Hgb** is **digested** forming the pigment **hemozoin**, which can get deposited to various organs

Hemozoin formation **depletes iron stores**, which leads to **anemia**

VIRULENCE FACTORS

Knobs develop for **adhesion** to parasitized and non-parasitized cells and platelets

***P. falciparum* erythrocyte membrane Pr1** (**PfEMP1**) is the **most adhesive protein** among the knobs

Knobs contain **Histidine-Rich Pr** (**HRP**)

Pathogenicity and Virulence (cont)

In Falciparum, **cytoadherence** causes plugging of **small vessels** by masses of parasitized RBCs and RBCs sticking to **endothelium** causing: **ischemia of the brain, heart, kidney, lungs, and GIT**

PREFERENCE

Vivax and Ovale	Only reticulocytes and young RBC
Malariae	Senescent cells

infections with these 3 parasites (vivax, ovale, and malariae) limits number of RBCs that can be parasitized to less than 3% of all erythrocytes

Falciparum and Knowlesi	All ages of RBC

Results in increased parasitemia, early anemia, and increased severity of complications and mortality

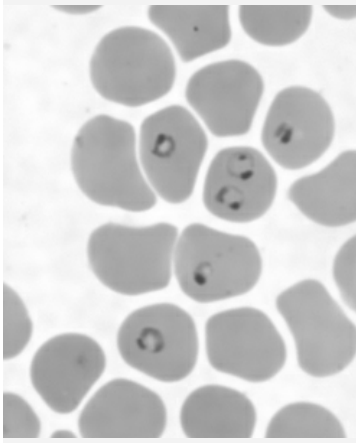
Morphology

Ring Form (Early Trophozoite)

Morphology (cont)

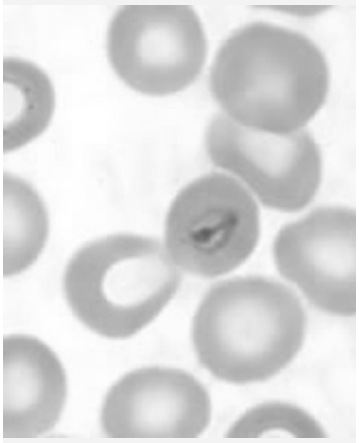
Earliest stage after invasion of RBC. The ring has a dot-like nucleus of **red chromatin**	Falciparum ring: headphone type with a **double chromatin dot**.

Plasmodium Falciparum Ring Form



Headphone type is also seen in *P. knowlesi*

Plasmodium Malariae Bird's Eye Ring Form



Malaria Cheat Sheet

by Paularbear01 via cheatography.com/96492/cs/22456/

Mature Trophozoites

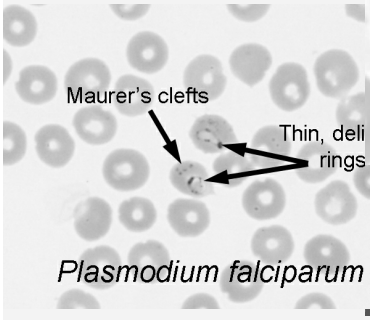
The erythrocyte hemoglobin is metabolized to produce a darkly staining pigment **hemozoin**

Maurer's Clefts: *P. falciparum* infections containing older ring-form trophozoites and asexual stages

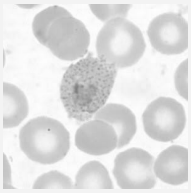
Schüffner's Dots: seen in *P. vivax* and *P. ovale*

Parasite nutrition is hemoglobin and the metabolite is hemozoin or hematin

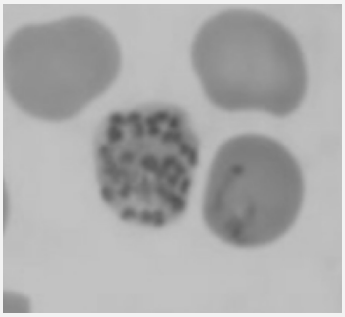
Maurer's Clefts



Schüffner's Dots



Schizont



When parasite divides and shows multiple masses of **nuclear chromatin**. Mature schizonts contain **merozoites**.

Rarely seen in peripheral blood of *P. falciparum* except in severe

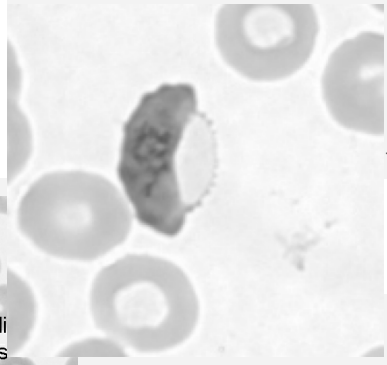
Gametocytes

Sexual form ingested by the mosquito (**infective stage for mosquito**)

Macrogametocyte: nucleus is **dense** and **compact**

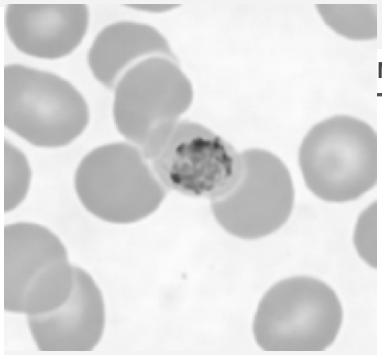
Microgametocyte: nucleus is a **pale, loose network**

Falciparum Gametocyte



Banana shaped

Knowlesi Gametocyte



Gametocytes of **vivax, ovale, malariae**, and **knowlesi** are similar, except that **malariae** is **smaller** and **darker**

Diagnosis

MICROSCOPIC IDENTIFICATION

Gold standard

Specimens can be taken any time

Giemsa stain is preferred for visualization of certain structures (ex. Maurer's Clefts)

If high degree of synchrony exist, late developmental stages can be demonstrated in the repeated smears every 4-6hrs (**not recommended for falciparum**)

Repeated testing is not recommended if parasites are not found initially

Blood smears are obtained to monitor response to treatment

Thick Film: reveals if parasite is **present** and is most efficient method of detection

Thin Film: **identification** of species

MALARIAL RDT

Diagnosis (cont)

	Uses Immunochromatography to detect Plasmodium specific antigens in a finger prick blood sample
	Antigens utilized are: HRP II, pLDH, Plasmodium Aldolase
	HRP II: produced by **trophozoites** and young **gametocytes** of *P. falciparum*
	pLDH: produced by both **sexual and asexual** stages, and can distinguish between falciparum and non-falciparum. Sensitive for severe malaria
	Plasmodium Aldolase: PA + HRP II = PMA which has 90% specificity and can be performed in 30 minutes
SEROLOGY	Cannot differentiate past from current infection
	Indirect Hemagglutination (IHA)
	Indirect Fluorescent Antibody Test (IFAT)
	ELISA
PCR	low parasitemia or mixed infection

infections

Falciparum schizonts stay in capillaries of organs and muscles. If schizont **spills into general circulation**, indicates **bad prognosis**

Plasmodium Falciparum

MALIGNANT TERTIAN MALARIA

Also known as subtertian or Aestivoautumnal Malaria

Deadliest species of plasmodium

Causes **50%** of all malaria cases

Erythrocytic cycle of **48hrs**

Found in tropics, subtropics, and sub saharan Africa

Infected cell is **same size** as normal RBC

Associated with the development of **Burkitt's Lymphoma**

RING-FORM TROPHOZOITES

Headphone Type: Rings may possess 1 or 2 chromatin dots

They may be found on the **periphery** of the RBC (**accolé, appliqué**) and **multiply-infected RBCs** may be seen.

Usually **no enlargement** of infected RBC

Plasmodium Falciparum (cont)

Maurer's Clefts: can be seen in infections w/ older ring-form trophozoites, and resembles **the Schüffner's dots** but are **larger** and **coarser**

DEVELOPING AND OLDER TROPHOZOITES

Remain in ring-form, but may become **thicker and more compact**

Amount of **pigment** and **chromatin** may also **increase**

SCHIZONTS

Schizogony **DOES NOT** take place in the **peripheral blood**, but in **capillaries** of **organs** and **muscles**.

The only stages seen in peripheral blood are **rings** and **gametocytes**

Contain anywhere from **8-24 merozoites**

Mature schizont usually fills 2/3 of infected RBC

GAMETOCYTES

Crescent or **sausage** or **banana** shaped

Pigment is **more coarse and concentrated** in **macrogametocyte** than microgametocyte

Laveran's Bib: **remnants** of host RBC

Plasmodium Ovale

OVALE MALARIA

Has an erythrocytic cycle of **48hrs**

Has a **hypnozoite** stage in the liver, which is the cause of relapse

Infected RBC is **slightly enlarged** compared to normal RBC

Found in Tropical Africa, West Africa, South America, and Asia

RING-FORM TROPHOZOITES

Contains **single chromatin dot**. Difficult to differentiate from vivax.

Multiply-Infected RBC may be see

MATURE TROPHOZOITES

As trophozoite matures, infected RBCs may exhibit **fimbriation** and **Schüffner's dots**

SCHIZONTS

Similar to *P. vivax*, though tend to contain fewer merozoites **(4-16, on average 8**)

Elongation to an **oval shape** and **fimbriation** are common

Plasmodium Ovale (cont)

Schüffner's dots can be observed with proper staining

GAMETOCYTES

Difficult to distinguish from *P. vivax*

Slight enlargement of infected RBC

Plasmodium Vivax

BENIGN TERTIAN MALARIA

Erythrocytic cycle of **48 hours**

Hypnozoite: persistant dormant stage in the liver, which is the cause of **relapse**

Predominant malarial species

Infected **RBC** is **enlarged** due to affinity for **young RBCs or reticulocytes**

RING-FORM TROPHOZOITES

Has a **thick cytoplasm w/ single, large chromatin dot**. Difficult to distinguish from *P. ovale*

Cytoplasm becomes **ameboid** and **Schüffner's dots** may appear as trophozoites mature

LATE TROPHOZOITES

Plasmodium Vivax (cont)

Developing trophozoites become **amoeboid**, with **pseudopodial processes** and **large vacuoles**. Schüffner's dots are visible with proper staining

band-form appearance of trophozoite may occur

May be mistaken for *P. Malariae* or *P. knowlesi*

SCHIZONTS

Pigment is organized in **1-2 clumps**

Mature schizonts contain **12-24 merozoites**, each of which contains a **dot of chromatin** and a **mass of cytoplasm**

GAMETOCYTE

Macrogametocyte: **round to oval** and usually fill host cell. Infected RBC is larger and **cytoplasm** is usually a **darker blue** with **fine brown pigments** throughout

Microgametocyte: usually the size of an **uninfected RBC** and has a **paler blue, pink or grey cytoplasm**

Plasmodium Knowlesi

KNOWLESI MALARIA

Vector is ***A. balabacensis*** **&** ***A. maculatus***

Primate malaria in macaques in South East Asia

Infects **ALL** stages of **RBC**, and causes **severe malaria**

Erythrocytic cycle has **quotidian** pattern (every **24hrs**)

Non-relapsing due to absence of hynozoites

Microscopically **indistinguishable** from ***P. malariae*** (Use PCR to distinguish)

Quotidian pattern results in **high levels of parasitemia** and **severe disease** with **fatal consequence**

TREATMENT

Chloroquine

Primaquine

Should be treated aggressively and urgently

RING-FORM TROPHOZOITES

Normal to 0.75x smaller than uninfected RBC

Rings may show **double chromatin dots**

Plasmodium Knowlesi (cont)

Appliqué forms may be seen as well as rectangular rings harboring one or more **accessory chromatin dots**

RBC may be **Multiply-infected**

OLDER, DEVELOPING TROPHOZOITES

Band forms may appear similar to *P. malariae*

Sinton and Mulligan's stippling may appear

SCHIZONTS

Sinton and Mulligan's stippling may appear

10-16 merozoites

Gametocytes

Mature Macrogametocyte: usually **spherical** and fill the host RBC. **Cytoplasm** stains **blue** and **eccentric nucleus** stains **red**

Microgametocyte: **smaller** and **cytoplasm** stains **pale pink**, while **nucleus** stains a **darker red**

Plasmodium Malariae

QUARTAN MALARIA

Erythrocytic cycle of **72hrs**

Found in **subtropical** and **temperate** areas

Plasmodium Malariae (cont)

Infected cells are **normal to smaller** in size than most RBCs

Old cells are preferentially infected**

RING-FORM TROPHOZOITES

Have **1 chromatin dot** and a **cytoplasm ring that is thicker than** ***P. falciparum***.

Infected RBC is **normal to smaller**

Bird's-eye forms may appear

MATURE TROPHOZOITES

Rounded chromatin and **compact cytoplasm**

As the trophozoite matures, the cytoplasm may **elongate** across the host RBC, forming a **band-form**

Pigment granules become larger and tend to have a more **peripheral** arrangement

Zeimann's stippling may be present

SCHIZONTS

6-12 merozoites, often arranged in a **rosette** or irregular cluster

Mature schizonts nearly fill the normal-sized host

Plasmodium Malariae (cont)

GAMETOCYTES

Compact and *fills** host RBC

Sometimes, there is a **reduction in size** of the infected RBC

Cytoplasm stains **blue** and the **chromatin is pink to red**.

Abundant dark pigment may be scattered throughout the cytoplasm

Band forms are present in *malariae, vivax*, and *knowlesi*

Clinical Manifestations

PRE-PATENT PERIOD	Interval from **sporozoite injection** to **detection of parasites in blood**
	P.falciparum: 11-14 days
	vivax: 11-15 days
	ovale: 14-26 days
	malariae: 3-4 weeks
	knowlesi: 9-12 days
INCUBATION PERIOD	time between **sporozoite injection** and appearance of **clinical symptoms** (8-40)
	falciparum: 8-15 days
	vivax: 12-20 days
	ovale: 11-16 days
	malariae: 18-40 days
	knowlesi: 5 days- few weeks
PRODROMAL SYMPTOMS	Weakness, exhaustion, aching bones, limbs, and back; loss of appetite; nausea; vomiting
	malaise, backache, diarrhea, and epigastric discomfort

MALARIAL PAROXYSM

1. Cold Stage

	Sudden feelings of coldness and apprehension
	Mild shivering quickly turns to violent teeth chattering and shaking of entire body
	Vomiting may occur
	Rigors last for 15min-1hr, then stops

2. Hot Stage or Flush Phase

Patient becomes hot (41° C), with headache, palpitations, tachypnea, epigastric discomfort, thirst, nausea, and vomiting

Skin is hot and flushed, patient is confused and delerious

Lasts 2-6hrs

3. Sweating Stage

Defervesence and diaphoresis or profuse sweating occurs

Temperature lowers in the next 2-4hrs and symptoms diminish accordingly

Total duration is 8-12hrs

Periodicity of attack only occurs if patient is left untreated

Interval length is determined by length of erythrocytic cycle

falciparum, vivax and ovale – 48 hours

malariae – 72 hours

knowlesi – 24 hours

COMPLICATIONS

Vivax, ovale and quartan malaria are relatively **benign**

Knowlesi

Severe thrombocytopenia, jaundice, deranged liver enzymes.

Acute Respiratory Distress Syndrome with tachypnea, hypoxemia, and pulmonary infiltrates on CXR.

Acute Renal Failure with elevated serum creatinine

Hypotension

Acidosis

Chronic Malariae

immune-complex deposition on the glomerular walls, leading to **nephrotic syndrome** in children

Falciparum

Clinical Manifestations (cont)

Cerebral Malaria (requires prompt administration of **quinidine IV** and then **quinine PO**)

Anemia

Acute Renal Failure (tubular necrosis and nephrotic syndrome)

Blackwater fever: from massive intravascular hemolysis and hemoglobinuria

Dysenteric Malaria

Algid Malaria: rapid development of hypotension and impairment of vascular perfusion

Pulmonary Edema

Tropical Splenomegaly Syndrome

Hyperparasitemia (>10-20% of RBC mean high mortality rate)

Hypoglycemia

Treatment

Proper use of the antimalarial drugs is based on knowledge of their effects on the parasite at **various stages of the life cycle**

Suppressive therapy:	destroy the parasites as they enter the bloodstream; effective against the **erythrocytic stages**.
Clinical Cure:	full and rapid elimination of plasmodiumfrom the blood to prevent complications
Radical cure:	elimination of not only the bloodstream infection but the tissue stages in the liver as well.

BLOOD SCHIZONTICIDES

Clinical cure of an acute attack, no effect on pre-erythrocytic and gametocyte stage

Treatment (cont)

1. Quinine	blood schizonticide against all five species of human malarial parasites. Side effects of treatment include tinnitus and headache, vertigo
2. Quinidine	
3. Chloroquine	
4. Amodiaquine	
5. Mefloquine	effective against both chloroquine--sensitive and –resistant strains of P. falciparum and P. vivax. It is also effective against P. malariae and P. ovale
6. Doxycycline	
7. Proguanil	Prevents development of oocysts in mosquito
8. Halofantrine	

Treatment (cont)

9. Artemisinin	effective against P. falciparum , P. knowlesi and P. vivax, and in patients with cerebral malaria
TISSUE SCHIZONTICIDES	destroy the developmental stages in the liver
1. Primaquine	effective against the hypnozoites of P. vivax and P. ovale.
**GAMETOCYTICIDES*	
1. Primaquine	gametocyticidal for all five species of malaria parasites and acts to render the patient noninfectious to the mosquito

UNCOMPLICATED P. FALCIPARUM

1. Atovaquone-Proguanil	(Malarone™) 4 adult tabs po qd x 3 days

Treatment (cont)	
2. Artemether-Lumefantrine	(Coartem™) 1 tablet = 20mg artemether and 120 mg lumefantrine . 4 tabs initial dose, followed by 4 tabs as second dose 8 hours later, then 4 tabs po bid for the following 2 days.
3. Quinine Sulfate	plus one of the following: Doxycycline, Tetracycline, or Clindamycin (for pregnant)
4. Mefloquine	
CHLOROQUINE-SENSITIVE FALCIPARUM OR UNCOMPLICATED P. MALARIAE	
1. Chloroquine phosphate	
UNCOMPLICATED P. VIVAX OR OVALE	
1. Chloroquine phosphate plus Primaquine phosphate	
CHLOROQUINE RESISTANT VIVAX	
1. Quinine sulfate plus either Doxycycline or Tetracycline plus Primaquine phosphate	
SEVERE MALARIA	
1. Quinidine gluconate plus one of the following: Doxycycline, Tetracycline, or Clindamycin	

Treatment (cont)
2. Exchange transfusion has been recommended for very severe falciparum malaria associated with high parasitemia (>10% of RBCs)
P. KNOWLESI
Uncomplicated
1. Chloroquine
2. Primaquine
Severe
1. Quinine
2. Artemether-Lumefantrine
MALARIA PROPHYLAXIS
1.Atovaquone/Proguanil
2. Doxycycline
3. Chloroquine
4. Mefloquine
5. Primaquine