HLS

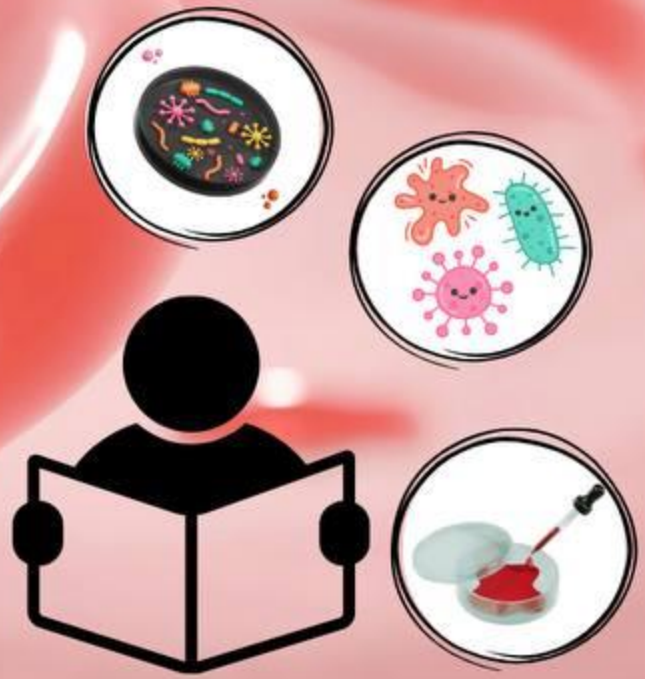
MODIFIED NO. 1

MICROBIOLOGY

كتابة: شهد الأحمد

تدقيق: ريناس الخريسات

الدكتور: د.نادر العرايضة



Blood protozoa : Plasmodium & Babesia

Plasmodium is the causative agent of malaria, while Babesia is responsible for babesiosis.

These two diseases are quite similar, but they have important differences, which will be discussed

Color code

- Slides
- Doctor
- Additional info
- Important
- What Dr mentioned from slides

Ass. Prof. Nader Alaridah MD, PhD

Overview

- A parasite is an organism that lives on or in a host organism and gets its food from or at the expense of its host.
- Protozoa are unicellular eukaryotes that form an entire kingdom.
  - The protozoa that are infectious to humans can be classified into four group based on their mode of movement:

- Sarcodina – the ameba
- Mastigophora – the flagellates, *Giardia*, *Leishmania*
- Ciliophora – the ciliates, e.g., *Balantidium*

The first three classes are(Asexual production,motile), while the fourth class, the sporozoa, is (with alternating sexual and asexual reproductive phases ,non-motile), especially in the adult stage

- Sporozoa – organisms whose adult stage is not motile e.g., *Plasmodium*, *Cryptosporidium* undergo a complex life cycle with alternating sexual and asexual reproductive phases. The human parasites Cryptosporidium, Cyclospora, and Toxoplasma and the malarial parasites (Plasmodium species) are all intracellular parasites.

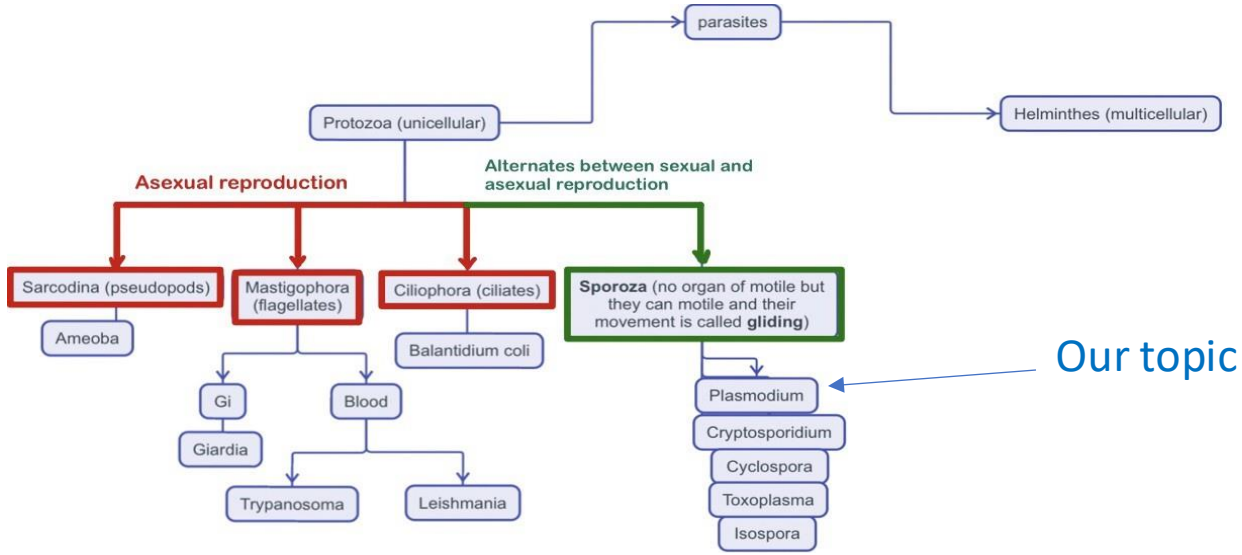
Biologically, parasites are divided into four classes based on two features:

1. their organs for locomotion and 2. their mode of reproduction.. Today, we will focus on sporozoa, which are unique because their life cycle alternates between sexual and asexual reproduction. Sporozoa are intracellular, parasites. This class includes organisms such as Plasmodium and Toxoplasma, as well as other members of the coccidia family.

According to their organs for locomotion

Sarcodina, the first class, includes amoebas –we discussed in GIS-. The second class, **Mastigophora**, includes organisms with flagellar movement, such as Giardia and Leishmania. 3rd class is the Balantidium coli, a large ciliate found in the GIT. Ciliates use tiny hair-like structures called cilia for locomotion.4th class The **sporozoa** "usually can't move", such as Plasmodium species, which follow their cycle in both their mosquito vector and their human host.

Additional Image



Our topic today

Epidemiology

- Over 2 billion (41% world population) lives in malaria-risk area.
- Infects 300-500 million people per year, 90% of whom are in sub-Saharan Africa.
- Kills over 1 million people each year and some estimate as many as 2.5 million. Mainly in children less than 5 years
- Leading protozoan Infectious killer of children. Worldwide a child dies of malaria every 30 seconds.
- Disease Burden increasing due to: weakening public health, agricultural practices, global warming, lack of vaccine, drug resistance in parasite and vector, population growth in endemic areas, increased travel. Migration , floods , all are causes for infection.

- ***Plasmodium*** is a genus of parasitic alveolates, many of which cause malaria in their hosts.
- The parasite always has two hosts in its life cycle: Dipteran "ثنائية الجناح"insect host and a vertebrate host.

- **Species**:

*1.**P. Falciparum*** This is the most dangerous and common species responsible for the highest mortality rates in malaria cases worldwide. Severe complications and fatal outcomes makes it a major concern in malaria-endemic regions , the most serious complications is cerebral malaria (most seen in pts with ***P. Falciparum)***

2.P. Malariae :this is the most ancient species among the human malaria pathogens. It typically has a longer incubation period and a characteristic fever pattern every 72 hours (3 days)

3. P. Vivax This is the most widespread form, often referred to as benign tertian malaria. It has a global distribution, particularly in Asia and Latin America

4. P. Ovale This species is less common than Plasmodium vivax and usually causes milder infections. Although less severe and less frequent, it shares similarities with P. vivax in terms of the disease's presentation

5. Plasmodium knowlesi a new strain, identified about 20 years ago, primarily causes malaria in monkeys, but in regions where humans live in close proximity to these monkeys, it can also infect humans.

- ⚠ ***Plasmodium falciparum*** *is the major species associated with* deadly infections throughout the world. The most serious complication caused by P. falciparum is cerebral malaria, which can be fatal if not treated promptly.

Mechanism of Infection

- The **vector** for malaria is the female anopheline mosquito.
- When the vector takes a blood meal, **sporozoites** contained in the salivary glands of the mosquito are discharged into the puncture wound.

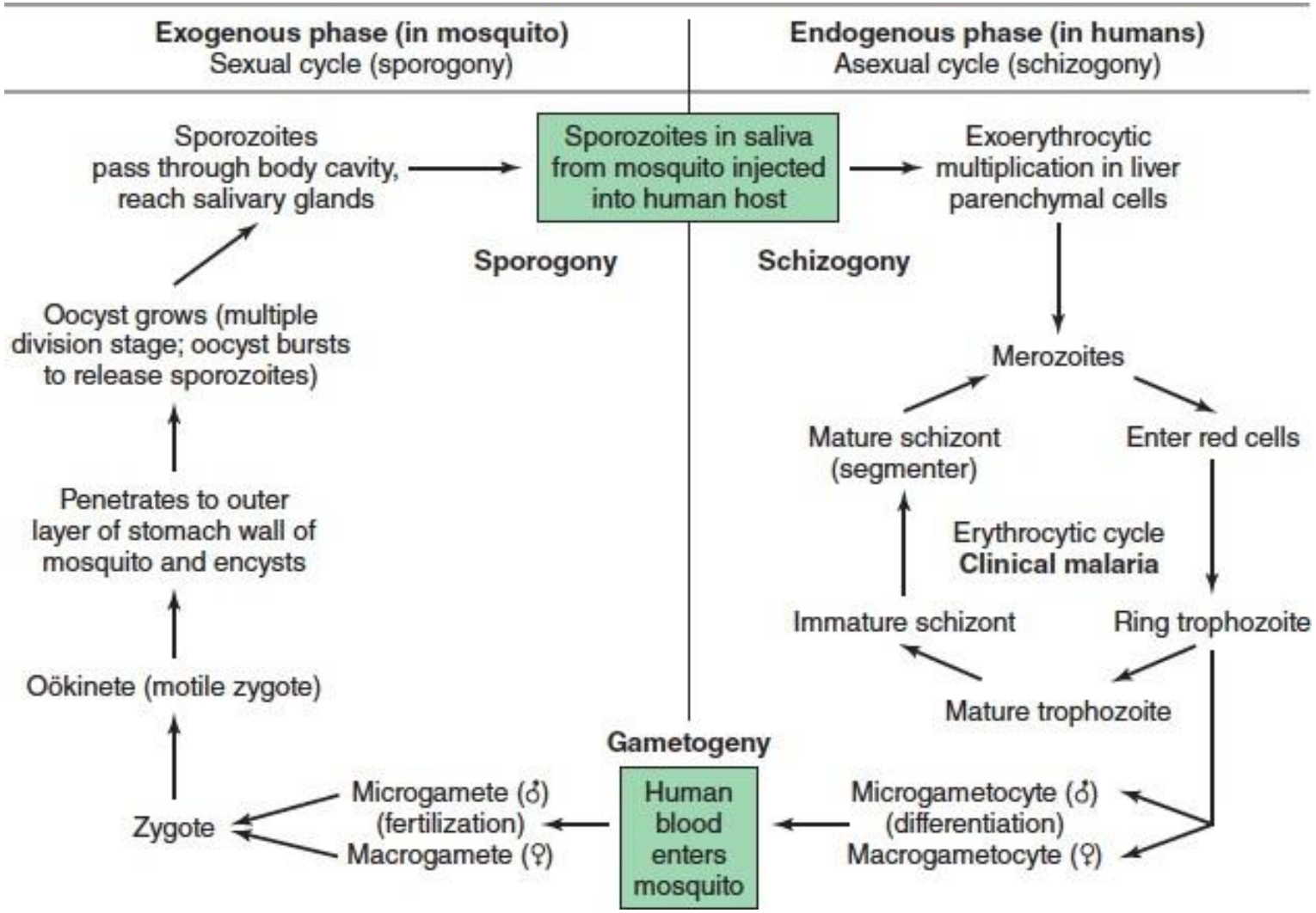
  However, there are other transmission modes (as it's a blood-born), including blood transfusion, organ transplantation, sharing syringes or needles, and congenital transmission from an infected mother
- Within an hour, these infective **sporozoites** are carried via the blood to the liver, where they penetrate hepatocytes and begin to grow, initiating the **pre-erythrocytic** or **primary exoerythrocytic cycle.**

- **The sporozoites** become round or oval and begin dividing repeatedly.

- **Schizogony results in** large numbers of exoerythrocytic merozoites.

- Once these **merozoites** leave the liver, they invade the red blood cells (RBCs), initiating the **erythrocytic cycle.**

Malaria life cycle



Let's break it !

First of all, The lifecycle of *Plasmodium* involves both asexual (schizogony) shown in the pic

and sexual (sporogony) which we will talk about in next slide .

sporozoites enter the liver, undergo *schizogony* to release *merozoites* that infect RBCs (asexual), and some develop into *gametocytes* (sexual), which undergo *sporogony* in mosquitoes.

•But how ?

1.Infected Mosquito Bites Human

Injects *sporozoites* into the bloodstream.(infective stage)

2.Liver Stage (Asexual)

Sporozoites travel to the liver.

Infect liver cells and mature into *schizonts*.

Schizonts rupture, releasing *merozoites* into the bloodstream.

3.Blood Stage (Asexual)

Merozoites infect red blood cells (RBCs).

Develop into *trophozoites* (ring stage), then *schizonts*.

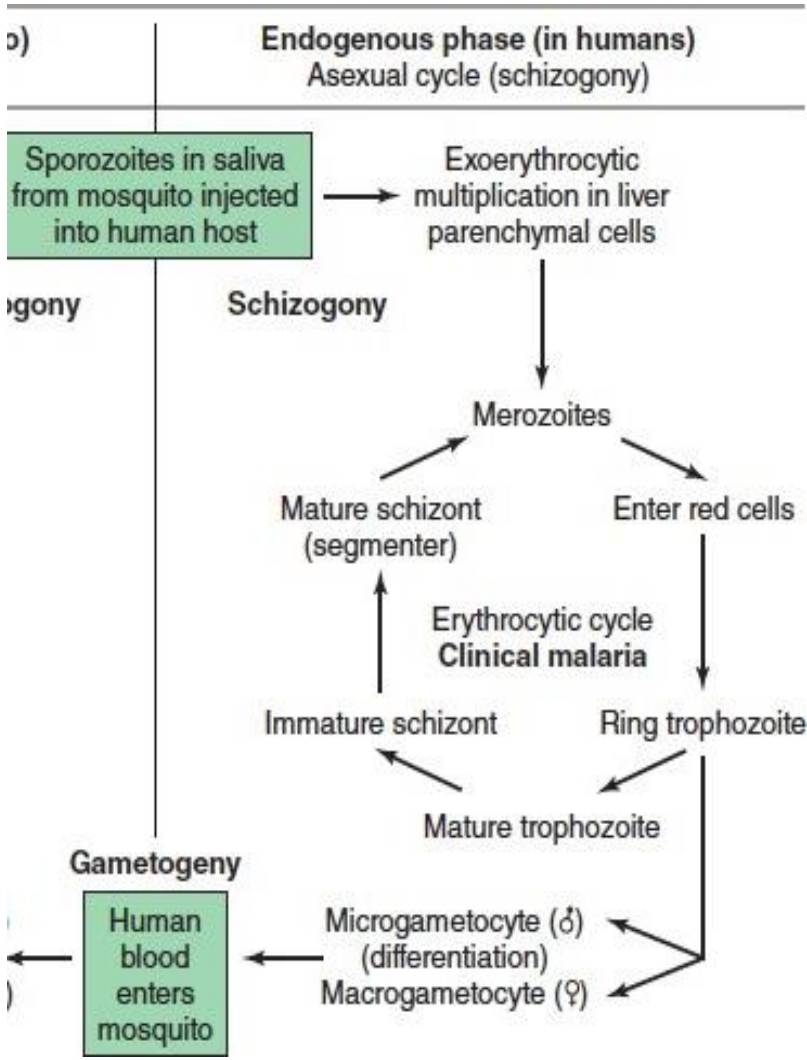
Schizonts rupture, releasing more *merozoites* to infect other RBCs.

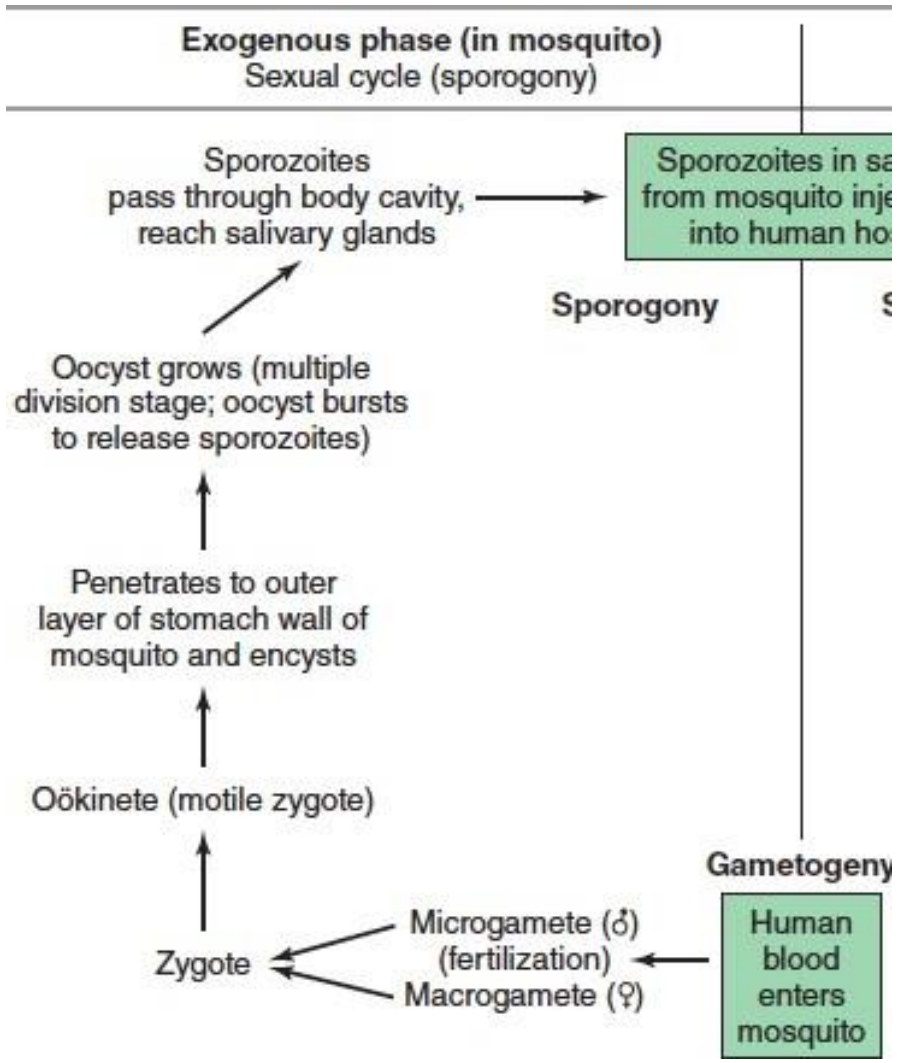
This cycle repeats, causing the symptoms of malaria.

4.Gametocyte Formation (Sexual)

•Some *trophozoites* differentiate into male and female *gametocytes*.

•*Gametocytes* circulate in the blood, awaiting ingestion by a mosquito





Let's continue . . .

Mosquito Stage (Sexual)

- A mosquito bites an infected human, ingesting *gametocytes from the human to its gut*
- In the mosquito's gut, *gametocytes* mature into *gametes*.
- Male and female *gametes* fuse to form a *zygote*.
- *Zygote* develops into an *ookinete*, which penetrates the mosquito gut wall, forming an *oocyst*.
- *Oocyst* ruptures, releasing *sporozoites* that travel to the mosquito's salivary glands, completing the cycle.

- Plasmodium go into 1. sexual 2. asexual …. sexual reproduction takes place in the Anopheles mosquito, while in humans, only asexual multiplication occurs, (divided into two stages 1.exoerythrocytic cycle (hepatocytes) and 2.erythrocytic cycle (RBCs).

- Let's revise our story from the beginning

- The Anopheles mosquito transmits malaria by taking a blood meal and introducing the infective stage which is **sporozoite**, into the human host. These sporozoites travel through the bloodstream to the liver, where they invade hepatocytes. Once inside, they undergo a process called asexual multiplication, or schizogony where they mature into **schizonts**.
- , the sporozoites multiply inside the hepatocytes, leading to the release of daughter cells called **merozoites**. , the released merozoites begin infecting red blood cells (RBCs) multiply, and consume hemoglobin, leaving behind them malarial pigments known as hemozoin. As the parasites replicate within RBCs, they cause hemolytic anemia The repeated invasion and rupture of RBCs lead to a characteristic cycle of symptoms known as paroxysms, marked by periodic fever.

Anyways, some **merozoites** inside red blood cells (RBCs) develop into sexual forms called gametocytes. These include **macrogametocytes (female**) and **microgametocytes (male**). When an *Anopheles* mosquito takes a blood meal containing these gametocytes, the sexual phase of the cycle begins inside the mosquito.

During this sexual phase, known as sporogony, the gametocytes fuse to form a **zygote**, which then transforms into an **ookinete**. The ookinete develops into an oocyst, and after further development, the **oocyst** releases **sporozoites**. When the mosquito bites another host, it injects these **sporozoites**, continuing the malaria transmission cycle

Some Notes (all will be discussed later in the lec)

During the infection process In infections caused by Plasmodium vivax or Plasmodium ovale , some of the merozoites can remain dormant inside the liver cells and are referred to as hypnozoites مهمة جدًا هاي المعلومة

The term "hypno-" signifies their latent or dormant nature. This has clinical significance because if a patient is diagnosed with malaria caused by P. vivax or P. ovale, specific medication must be administered to target and eliminate these hypnozoites. Failure to do so may lead to a relapse.

In contrast, infections caused by P.falciparum and P.malariae do not exhibit this relapse pattern. Instead, they are associated with a different phenomenon called recrudescence, where the infection can persist at low levels in the blood and re-emerge later.

It is important to note that in cases of bloodborne transmission (e.g through blood transfusions), the exoerythrocytic stage does not occur. Therefore, there are no hypnozoites (dormant forms) .. meaning no potential for relapse.

P.vivax and *P. ovale* primarily infect young (RBCs) or reticulocytes, which leads to a lower level of parasitemia. In contrast, *P. falciparum* can infect RBCs of all ages and sizes, resulting in a much higher parasitemia level. higher parasitemia levels correlate with more severe disease manifestations.

feature of the presence of hemozoin dye in RBCs differentiates malaria from babesiosis, as hemozoin is unique to malaria.

Also , in benign tertian malaria caused by *Plasmodium vivax* and *Plasmodium ovale*, symptoms recur every 48 hours, with fever on the first day, followed by a fever-free day, and then recurrence on the third day. In quartan malaria caused by *Plasmodium malariae*, the cycle lasts 72 hours, with fever on the first day, absence on the second and third days, and recurrence on the fourth day. These distinct fever patterns are characteristic of malaria and help differentiate it from babesiosis, which does not show regular fever cycles. The erythrocytic cycle and periodic release of pyrogens from ruptured RBCs are responsible for the typical fevers seen in malaria.

- **A dormant schizogony** may occur in *P. vivax and P. ovale organisms,* which remain quiescent in the liver. Relapse is common in 2-5 years

- These resting stages have been termed **hypnozoites** and lead to a true relapse, often within 1 year or up to more than 5 years later. most of them after 2 years

- Once the RBCs and reticulocytes have been invaded, the parasites grow and feed on hemoglobin.
- Within the RBC, the merozoite (or young trophozoite) is vacuolated, ring shaped, more or less ameboid, and uninucleate.
- The excess protein and hematin present from the metabolism of hemoglobin combine to form malarial pigment.
- Once the nucleus begins to divide, the trophozoite is called a **developing schizont.**
- The mature schizont contains merozoites (whose number depends on the species), which are released into the bloodstream.
- Sporozoites (injected by mosquito) → Liver cells → Schizogony → Merozoites → Blood

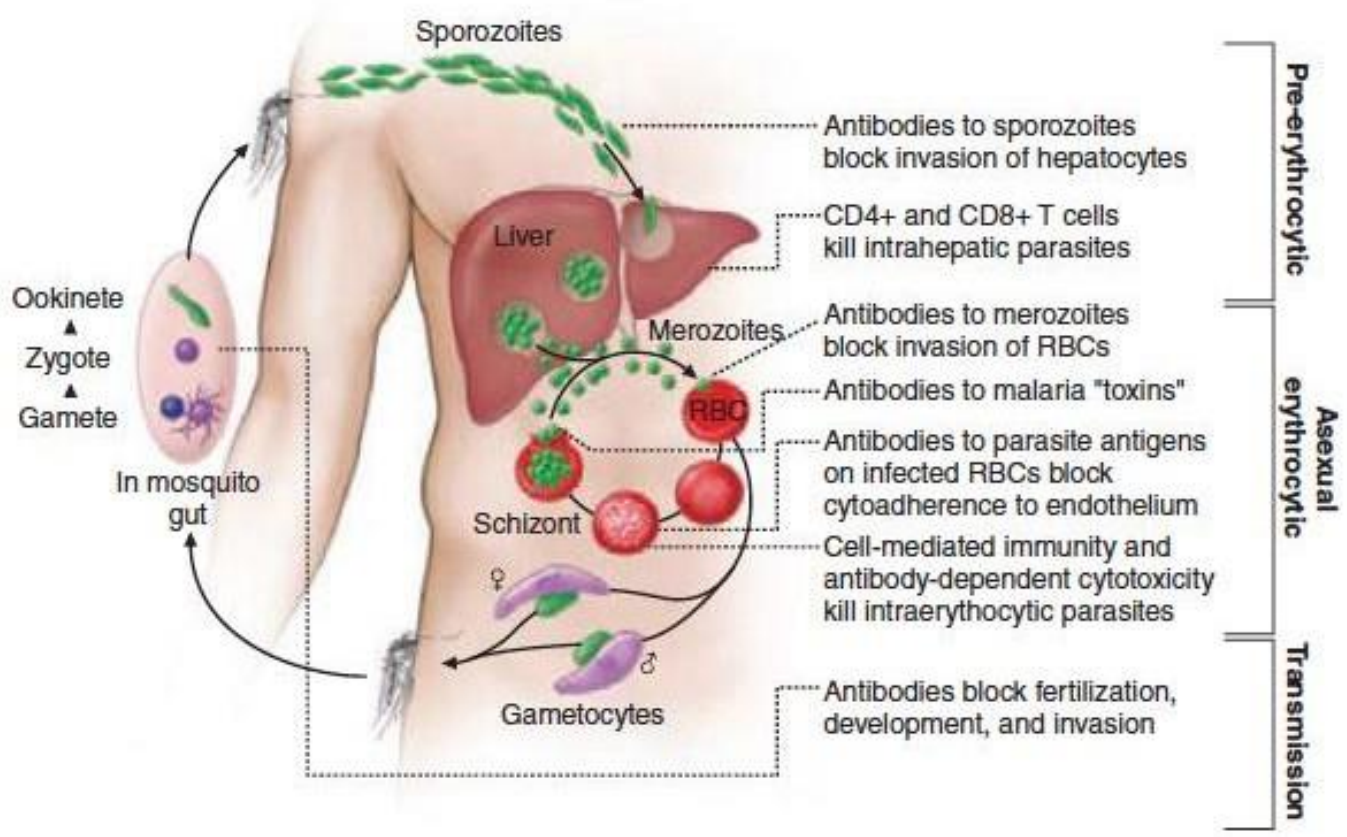
Revision, again and again ✨

- Sporozoites (injected by mosquito) ➞ Liver cells➞ Schizogony ➞ Merozoites ➞Blood(RBCs) ➞ Schizogony ➞ More Merozoites ➞ New Merozoites ➞ Infect More RBCs

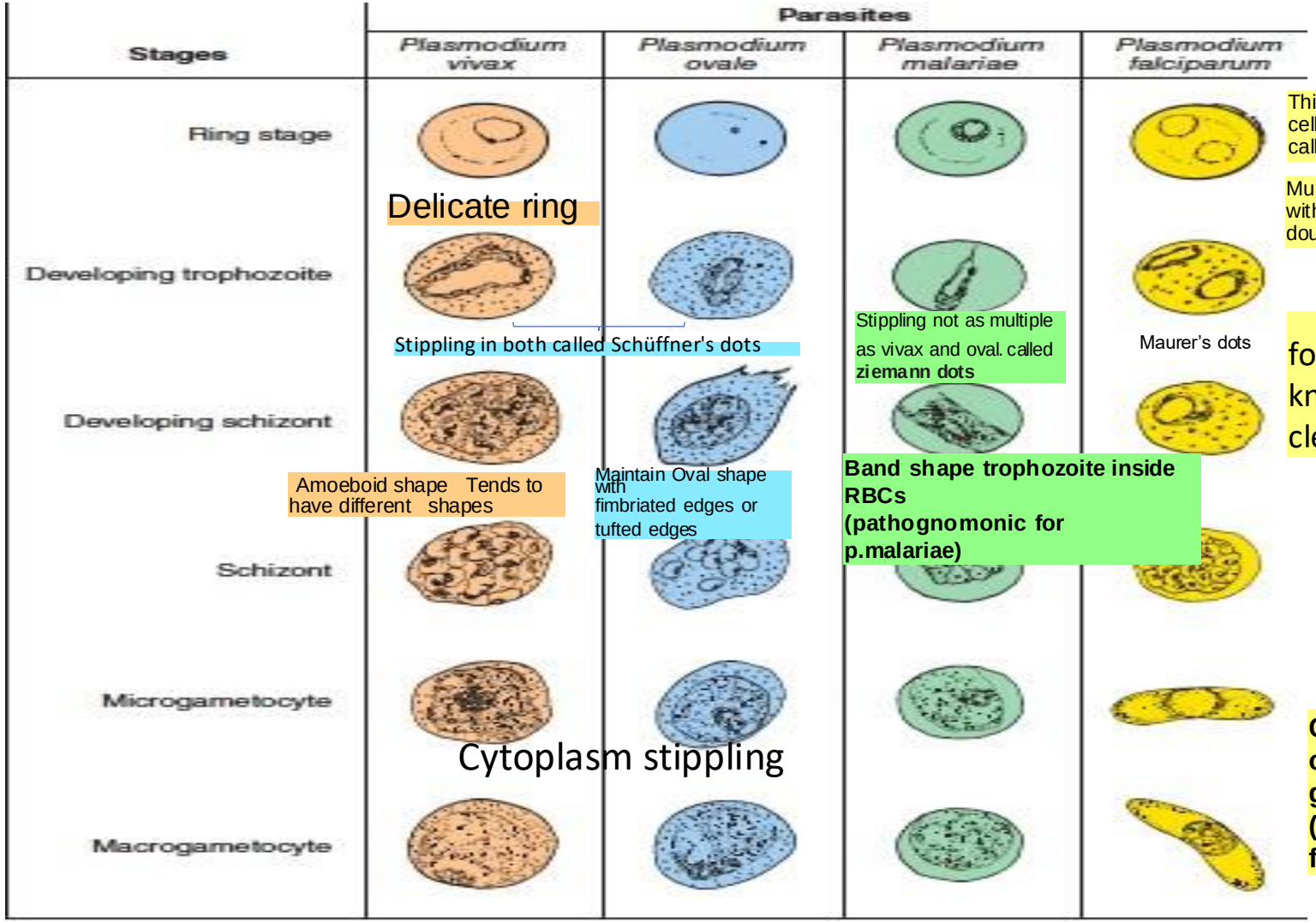
Here (New Merozoites) stage,**it can go into 2 fates**

Gametocytes (in RBCs) ➞ Mosquito (during blood meal) ➞ Fuse to Form Zygote (in mosquito) ➞ Ookinete ➞ Oocyst (in mosquito gut wall) ➞ Sporozoites ➞ Injected into Human Host (during next bite)

Malaria transmission cycle



Developmental stages of malarial parasites



PLASMODIUM VIVAX (BENIGN TERTIAN MALARIA)

The most common one

- *P. vivax infects **only** the reticulocytes. Young RBCs*

- **Splenomegaly** occurs during the first few weeks of infection, and the spleen will progress from being soft and palpable to hard, with continued enlargement during a chronic infection.

- If the infection is treated during the early phases, the spleen will return to its normal size.
- A secondary or **dormant schizogony** occurs in *P. vivax and P. ovale, which remain quiescent in the liver.*

- *These resting* stages have been termed ***hypnozoites.***

- After a few days of irregular periodicity, a regular 48-hour cycle is established.

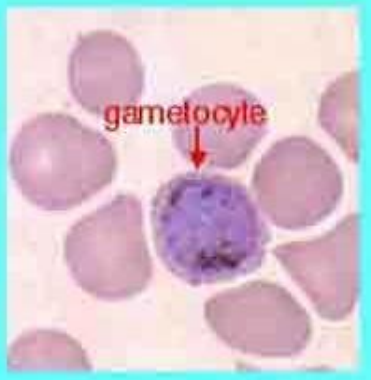
Type of Malaria	Characteristics
Plasmodium vivax (benign tertian malaria)	1. 48-hour cycle 2. Tends to infect young cells 3. Enlarged RBCs 4. Schüffner's dots (true stippling) after 8-10 hours 5. Delicate ring 6. Very ameboid trophozoite 7. Mature schizont contains 12-24 merozoites

In the RBCs. While in liver hepatocytes there're thousands of merozoites

Plasmodium vivax

trophozoite

schizont



gametocyte

Pathogenesis and Spectrum of Disease:

- In patients who have never been exposed to malaria:

non-specific Symptoms such as headache, photophobia, muscle aches, anorexia, nausea, and sometimes vomiting may occur before organisms can be detected in the bloodstream. These initial symptoms are common in all malaria patients and do not point to a specific cause, making early diagnosis challenging, As the infection progresses, paroxysms (periodic fever spikes) develop, usually starting around the third or fourth day. fever in malaria follows a cyclical pattern. After the release of parasites from infected RBCs, the fever spikes and then subsides, only to recur when the parasites undergo another cycle of reproduction

In other patients with prior exposure to the malaria:(patients in endemic areas)

The parasites can be found in the bloodstream several days before symptoms appear.

In endemic areas, there is a phenomenon known as "premonition," where individuals harbor a low level of parasites that are subclinical or even undetectable microscopically. This low-level parasitemia can provide some protection against superinfection but does not prevent reinfection,

as there is **no long-lasting immunity to malaria.**

PLASMODIUM OVALE

has a more limited range and is uncommon relatively to p.vivax

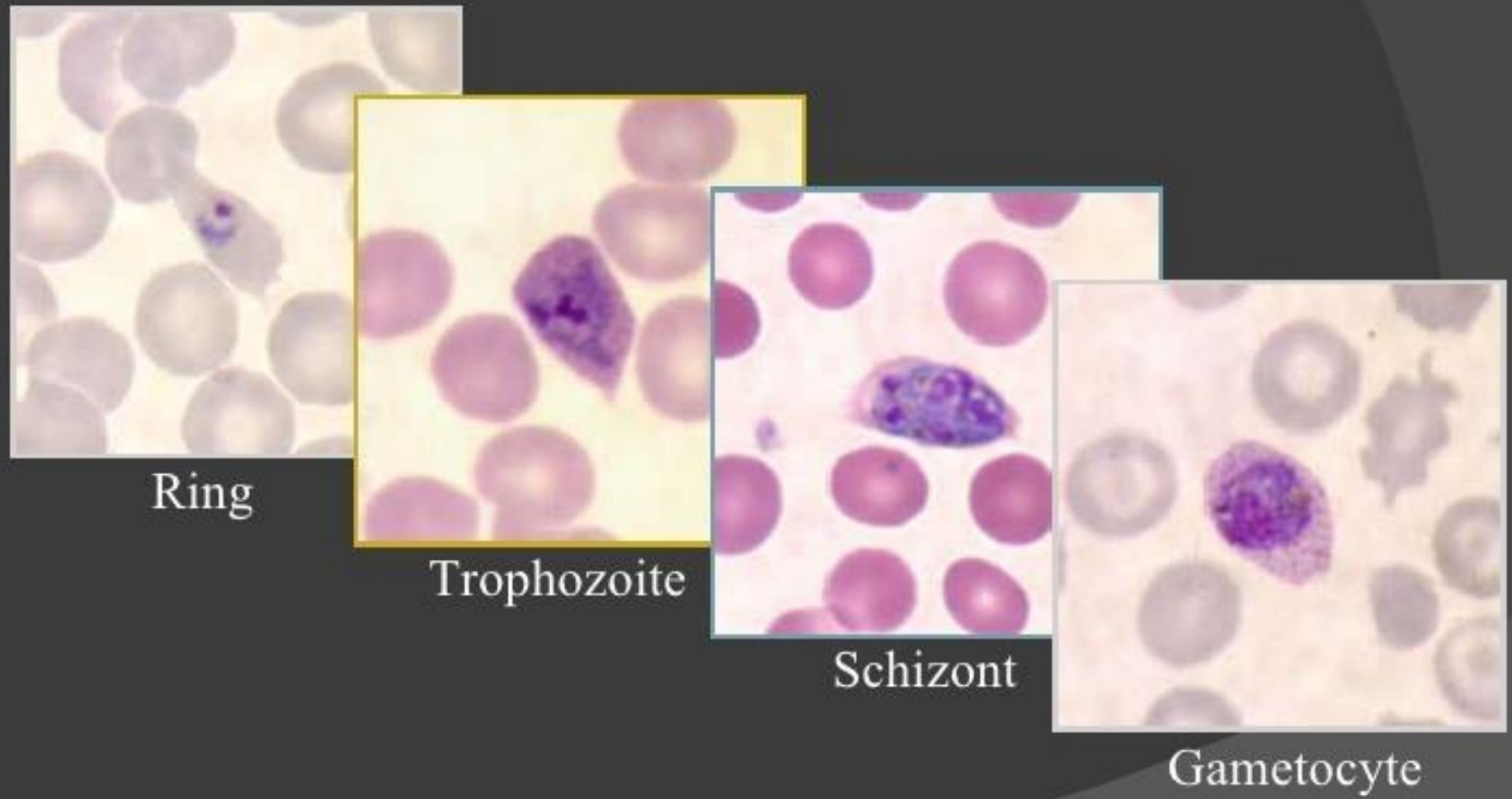
- Although *P. ovale and P. vivax infections are clinically* similar, *P. ovale malaria is usually less severe, tends to* relapse less frequently, and usually ends with spontaneous recovery even without treatment

- *P. vivax, P. ovale infects only the reticulocytes(young RBCs)*

- After a few days of irregular periodicity, a regular 48-hour cycle is established. Over time, the paroxysms become less severe and more irregular in frequency and then stop altogether.

Plasmodium ovale	1. 48-hour cycle 2. Tends to infect young cells 3. Enlarged RBCs with fimbriated edges (oval) 4. Schüffner's dots appear in the beginning (in RBCs with very young ring forms, in contrast to *P. vivax)* 5. Smaller ring than *P. vivax* 6. Trophozoite less ameboid than that of *P. vivax* 7. Mature schizont contains an average of 8 merozoites

Plasmodium ovale



Pathogenesis and Spectrum of Disease:

- The incubation period is similar to that for *P. vivax* malaria, but the frequency and severity of the symptoms are much less, with a lower fever and a lack of typical rigors.

In the trophozoite stage, *P. ovale* often exhibits an oval shape with fimbriated (fringed) edges, which can make it difficult to distinguish from *P. vivax*.
Expert examination is often needed to accurately identify the species.
Also Malaria fever has three distinct stages:

1.Cold stage
2.Hot stage.
3.Sweating stage

PLASMODIUM MALARIAE *(QUARTAN MALARIA)*

The ancestor of all *Plasmodium* species, it's primarily found in certain African countries.

Plasmodium malariae **(quartan malaria)**	1. 72-hour cycle (long incubation period) 2. Tends to infect old cells 3. Normal size RBCs 4. No stippling To be more accurate it has Ziemann's stippling 5. Thick ring, large nucleus 6. Trophozoite tends to form "bands" across the cell different from the banana shaped gametocytes seen in *falciparum* 7. Mature schizont contains 6-12 merozoites

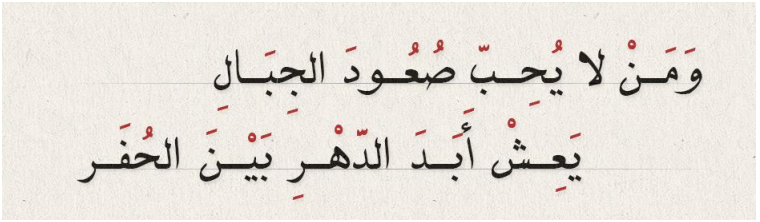
In contrast, *Plasmodium vivax* and *Plasmodium ovale* have shorter cycles, around 48 hours and they predominantly infect young RBCs (reticulocytes), resulting in lower levels of parasitemia.

Pathogenesis and Spectrum of Disease:

- **Proteinuria** is common in *P. malariae infections and may* be associated with clinical signs of nephrotic syndrome., usually we don't see this sign with p.vivax or ovali

- With a chronic infection, kidney problems result from deposition within the glomeruli of circulating antigen antibody complexes.

- A membrane proliferative type of glomerulonephritis is the most common lesion seen in **quartan malaria.**



PLASMODIUM FALCIPARUM (MALIGNANT TERTIAN MALARIA)

most severe form of human malaria and majority of malaria-related mortality. Cerebral malaria cause coma then Death . The cycle repeats itself every 48 h at the 3rd day.

- *Plasmodium falciparum invades all ages of RBCs.*

- Schizogony occurs in the spleen, liver, and bone marrow rather than in the circulating blood.

- Ischemia caused by the obstruction of vessels within these organs by parasitized RBCs will produce various symptoms, depending on the organ involved.

The term "**malignant**" has two implications. **First**, patients often experience very high fevers, with temperatures ranging from 41°C to 42°C (**hyperpyrexia**). This extreme fever is particularly dangerous for young children, who are at risk of febrile convulsions, that can arise from the high temperatures associated with *P. falciparum* infections.

Second, *P. falciparum* causes the most serious complication of malaria: **cerebral malaria, or encephalopathy**. This condition can lead to coma and, if not treated promptly, can be fatal. "tertian" refers to the typical 48 hour cycle of fever recurrence seen with this infection.
In *P. falciparum*, schizogony (asexual replication) primarily occurs in lymphoid organs such as the spleen, bone marrow, and liver, rather than in peripheral blood. In blood smears, the most common observations are the delicate ring forms and banana-shaped gametocytes, which are pathognomonic for this species.

P. falciparum can infect RBCs of all sizes and ages, leading to high levels of parasitemia.

- A decrease in the ability of the RBCs to change shape when passing through capillaries or the splenic filter may lead to plugging of the vessels Also, only *P. falciparum causes cytoadherence, a feature that is associated* with severe malaria.

- In *P. falciparum infections, as the parasite grows,* the RBC membrane becomes sticky and the cells adhere to the endothelial lining of the capillaries of the internal organs.

- Thus, only the ring forms and the gametocytes (occasionally mature schizonts) normally appear in the peripheral blood.

P. falciparum-infected RBCs produce protein projections called "knobs" on their surfaces, which cause the cells to become sticky. This stickiness, known as "cytoadherence," leads the infected RBCs to adhere to each other and to blood vessel walls, particularly in small capillaries. This can obstruct blood flow and cause organ damage, including in the brain, leading to cerebral malaria.

fever pattern may be irregular at first, making it difficult to identify a clear cycle. To diagnose malaria, it's important to ask patients specific questions about the frequency and timing of their fever

Plasmodium falciparum **(malignant tertian malaria)**	1. 36-48-hour cycle 2. Tends to infect any cell regardless of age, thus very heavy infection may result 3. All sizes of RBCs leading to high levels of parasitemia 4. No Schüffner's dots (Maurer's dots: may be larger, single dots, bluish) 5. Multiple rings/cell (only young rings, gametocytes, and occasional mature schizonts are seen in peripheral blood) 6. Delicate rings, may have two dots of chromatin/ring, appliqué or accolé forms 7. Crescent-shaped gametocytes

They take the margin of the RBCs , they aren't specific

Pathogenesis and Spectrum of Disease

- Symptoms such as aches, pains, headache, fatigue, anorexia, or nausea..This stage is followed by fever, a more severe headache, and nausea and vomiting. As the infection progresses, patients develop the classical malaria presentation of periodic fever spikes, known as paroxysms

- Severe or fatal complications can occur at any time and are related to the obstruction of vessels in the internal organs (liver, intestinal tract, adrenal glands, intravascular hemolysis/black water fever, and kidneys).
- The stickiness of infected RBCs leads to blockages in capillaries, causing local hypoxia and ischemia, which are particularly dangerous in the brain. This mechanism explains the brain swelling seen in cerebral malaria, where impaired circulation can lead to coma and death.

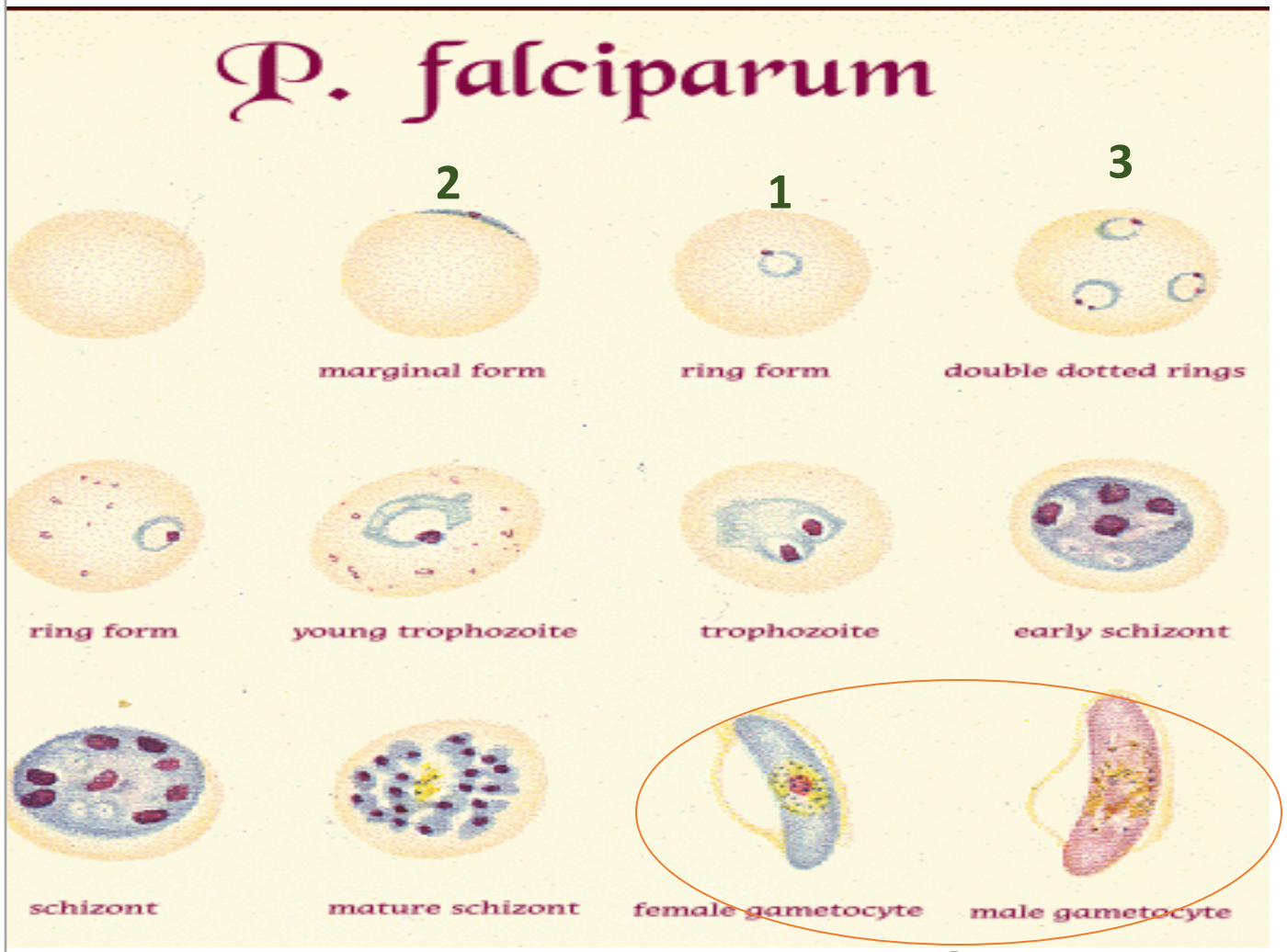
- Blackwater fever is a complication of malaria that is a result of red blood cell lysis, releasing hemoglobin into the bloodstream and urine, causing discoloration.

- Extreme fevers, 41.7° C (107° F) or higher (hyperpyrexia), may occur in an uncomplicated malaria attack or in cases of cerebral malaria. Without vigorous therapy, the patient usually dies.
- Cerebral malaria Due to cytoadherence is considered to be the most serious complication and the major cause of death with *P. falciparum.* مهمة جدًا *cytoadherance ,RBCs become sticky to each other.*

Also, Algid malaria is a severe form of malaria characterized by circulatory shock, often associated with autoimmune hemolysis triggered by the infection. Patients with algid malaria may experience sudden drops in blood pressure, leading to life-threatening complications. This condition requires immediate medical intervention.

In *Plasmodium falciparum* infections, one of the diagnostic features observed in blood smears is the ring stage of the parasite. Typically, these ring forms are found within the cytoplasm of infected RBCs (no.1). Sometimes, the rings can appear near the edge of the RBC, a feature known as the "accolé" or marginal form.(No.2)
A distinctive feature of *P. falciparum* is the presence of multiple ring forms within a single RBC or rings that display two dots (known as "headphone" forms). No.3
Additionally, *P. falciparum* is characterized by its crescent-shaped or banana-shaped gametocytes, which are pathognomonic for this species and help distinguish it from other types of malaria.No.4

These features, including the stereoform (other name to the ring with double dots), are considered classic diagnostic markers of *P. falciparum* malaria, making it easier to identify the infection under a microscope.



PLASMODIUM KNOWLESI (SIMIAN MALARIA, THE FIFTH HUMAN MALARIA)

primarily infects macaque monkeys but can also infect humans, particularly in regions of Southeast Asia where people live in proximity to these monkeys.

- *P. knowlesi invades all ages of RBCs.*
- The early blood stages of *P. knowlesi resemble those of P. falciparum.*
- *Whereas the mature blood stages (late stages) and gametocytes* resemble those of *P. malariae.*
- Unfortunately, these infections are often misdiagnosed as the relatively benign *P. malariae; however, infections with P. knowlesi can be fatal.*

macaque monkeys – Extra pic

Plasmodium knowlesi (simian malaria)*	1. 24-hour cycle 2. Tends to infect any cell regardless of age, thus very heavy infection may result 3. All sizes of RBCs, but most tend to be normal size 4. No Schüffner's dots (faint, clumpy dots later in cycle) 5. Multiple rings/cell (may have 2-3) 6. Delicate rings, may have two or three dots of chromatin/ring, appliqué forms 7. Band form trophozoites commonly seen 8. Mature schizont contains 16 merozoites, no rosettes 9. Gametocytes round, tend to fill the cell Early stages mimic *P. falciparum*; later stages mimic *P. malariae*

The most point the Dr focused in

Characteristic	Finding for Indicated Species[a]			
	P. falciparum	*P. vivax*	*P. ovale*	*P. malariae*
Duration of intrahepatic phase (days)	5.5	8	9	15
Number of merozoites released per infected hepatocyte	30,000	10,000	15,000	15,000
Duration of erythrocytic cycle (hours)	48	48	50	72
Red cell preference	Younger cells (but can invade cells of all ages)	Reticulocytes and cells up to 2 weeks old	Reticulocytes	Older cells
Morphology	Usually only ring forms[b]; banana-shaped gametocytes	Irregularly shaped large rings and trophozoites; enlarged erythrocytes; Schüffner's dots	Infected erythrocytes, enlarged and oval with tufted ends; Schüffner's dots	Band or rectangular forms of trophozoites common
Pigment color	Black	Yellow-brown	Dark brown	Brown-black
Ability to cause relapses	No	Yes	Yes	No

Dr only mentioned last line ..
dormant forms known as **hypnozoites** can remain in the liver. This is crucial for Drs to consider because standard antimalarial treatments may not eliminate these hypnozoites. Therefore, a specific drug, such as primaquine, is required to target and clear these dormant forms to prevent relapse.

CLINICAL FEATURES

- Malaria is a very common cause of fever in tropical countries. The first symptoms of malaria are nonspecific; the lack of a sense of wellbeing, headache, fatigue, abdominal discomfort, and muscle aches followed by fever are all similar to the symptoms of a minor viral illness.in some cases, anemia.
- In infections caused by *P. ovale*, it consumes a significant portion of the red blood cell's hemoglobin: up to two-thirds before the cell bursts (hemolysis), leading to hemolytic anemia.

- In some instances, a prominence of headache, chest pain, abdominal pain, cough, arthralgia, myalgia, or diarrhea may suggest another diagnosis. Although headache may be severe in malaria, the neck stiffness and photophobia seen in meningitis do not occur. While myalgia may be prominent, it is not usually as severe as in dengue fever, and the muscles are not tender as in leptospirosis or typhus. Nausea, vomiting, and orthostatic hypotension are common.

- The classic malarial paroxysms, in which fever spikes, chills, and rigors occur at regular intervals, are relatively unusual and suggest infection with P. vivax or P. ovale.

- The fever is usually irregular at first (that of falciparum malaria may never become regular); the temperature of nonimmune individuals and children often rises above 40C in conjunction with tachycardia and sometimes delirium. Although childhood febrile convulsions may occur with any of the malarias, generalized seizures are specifically associated with falciparum malaria and may herald the development of encephalopathy (cerebral malaria). ALL here mentioned earlier

LABORATORY DIAGNOSIS

(ALL SPECIES)

1.<u>Routine Methods:</u>

Thick and thin blood films. Thick just helps to know if there is *PLASMODIUM or not.*

Thin blood film (specific If you want to know which specie)

- At least 200 to 300 oil immersion fields should be examined on both films before a negative report is issued.

- **Stains:**

1. Giemsa stain.
2. Wright's stain.
3. Fluorescent nucleic acid stains, such as acridine orange.

- Blood collected using (EDTA) anticoagulant.

2.Serologic Methods:

- **Several rapid malaria tests (RMTs):** used in endemic area, such as Africa or in the South-East Asia

1. Some of which use monoclonal antibodies against the histidine-rich protein 2 (HRP2).

2. Whereas others detect species-specific parasite lactate dehydrogenase (pLDH).Much better test than the 1st

- These procedures are based on an antigen capture approach in dipstick or cartridge formats.

Types of Malaria RDTs:

1.HRP2-based Tests (Parasite F Test):

These tests use chromatographic dipstick assays to detect the presence of HRP2, an antigen produced by *P. falciparum*. The dipstick contains antibodies that bind to HRP2, causing a visible band to appear if the antigen is present.
While these tests are sensitive and can effectively identify *P. falciparum*, they have a limitation: they do not detect other species like *P. vivax*, *P. malariae*, or *P. ovale*.
This specificity means that infections with other *Plasmodium* species could be missed if relying solely on an HRP2 test.

2.LDH-based Tests (Dual Test):

To overcome the limitation of HRP2-based tests, dual tests have been developed that look for two antigens: parasite lactate dehydrogenase (pLDH), which is found in all *Plasmodium* species, and HRP2, specific to *P. falciparum*.
This "sandwich" assay can identify any malaria infection and can also specify whether *P. falciparum* is present.
The dual test offers a broader diagnostic capability, making it better than HRP2-only tests. It ensures detection across different malaria species while still providing information specific to *P. falciparum*.

Both are not that common & need experts

3. Molecular Diagnostics:

- Other methods include direct detection of the five species by using a specific DNA probe after PCR amplification of target DNA sequences.

4. Automated Instruments:

- Using automated flow cytometry hematology instruments, there are potential limitations related to the diagnosis of blood parasite infections.

THERAPY

- Antimalarial drugs are classified according to the stage of malaria against which they are targeted.
- **QUINOLINES , ARTEMISININS**
- *Tetracycline*, *doxycycline*, and *clindamycin* are used increasingly in combination with other antimalarials to improve their efficacy

- **These drugs are referred to as :**

1. Tissue schizonticides (which kill tissue schizonts).
2. Blood schizonticides (which kill blood schizonts).
3. Gametocytocides (which kill gametocytes).
4. Sporonticides (which prevent formation of sporozoites within the mosquito).

1. *Plasmodium vivax*, *ovale*, and Sensitive *P. falciparum*

The first-line treatment for them includes **chloroquine** and **hydroxychloroquine**. These drugs target the blood stages of the parasite, effectively treating the infection.
For *P. vivax* and *P. ovale*, it's also essential to address the **hypnozoites** in the liver. The drug used for this purpose is **primaquine**, which prevents relapses by eliminating the liver stages of the parasites. Without primaquine, the infection is likely to return.

2. *Plasmodium falciparum* and Drug Resistance

Treating *P. falciparum* can be more complex due to resistance to quinolones in certain geographical regions, especially in parts of Africa and Southeast Asia. In these areas, *P. falciparum* has developed resistance to chloroquine, so it is no longer effective as a first-line treatment.
in areas with resistance, the standard treatment is **Artemisinin-based Combination Therapy (ACT)**.

3. Artemisinin-based Combination Therapy (ACT)

ACTs combine derivatives of **artemisinin** (such as artesunate) with other antimalarial drugs, including quinolones, to ensure effectiveness and prevent resistance. The combination approach helps to target different stages of the parasite's life cycle and reduces the risk of the parasites developing resistance to the treatment.
Artemisinin derivatives are potent and fast-acting but should **not** be used as monotherapy because of the risk of resistance. Therefore, they are always given in combination with other drugs to improve efficacy and durability of the treatment. ACTs are considered the best treatment option for *P. falciparum* in regions where resistance to older drugs like chloroquine is prevalent.

CONTROL

Type of control	Measures
Personal protection	Insecticide treated mosquito nets; Mosquito proofing of dwellings; Repellents; Site selection
Environmental management	Drainage & water management; Land reclamation by filling and drainage
Chemical (Insecticides) control	Residual house spraying; larviciding; space spraying
Other measures	Biological control, Genetic control, Zooprophylaxis

Using bed nets treated with insecticides is one of the most effective ways to prevent mosquito bites, especially during the peak feeding times of dusk to dawn, Wearing long-sleeved clothing and pants can minimize skin exposure as well

Babesiosis

higher prevalence in Europe than in the Middle East or Africa.

- Babesiosis is an emerging tick-borne infectious disease caused by protozoan parasites of the genus Babesia that invade and eventually lyse red blood cells (RBCs).

- Most cases are due to Babesia microti. B. microti, a parasite of small rodents, is the most common etiologic agent of human babesiosis

- The primary causative agent of human babesiosis in Europe is B. divergens, but Babesia venatorum and B. microti also have been reported.

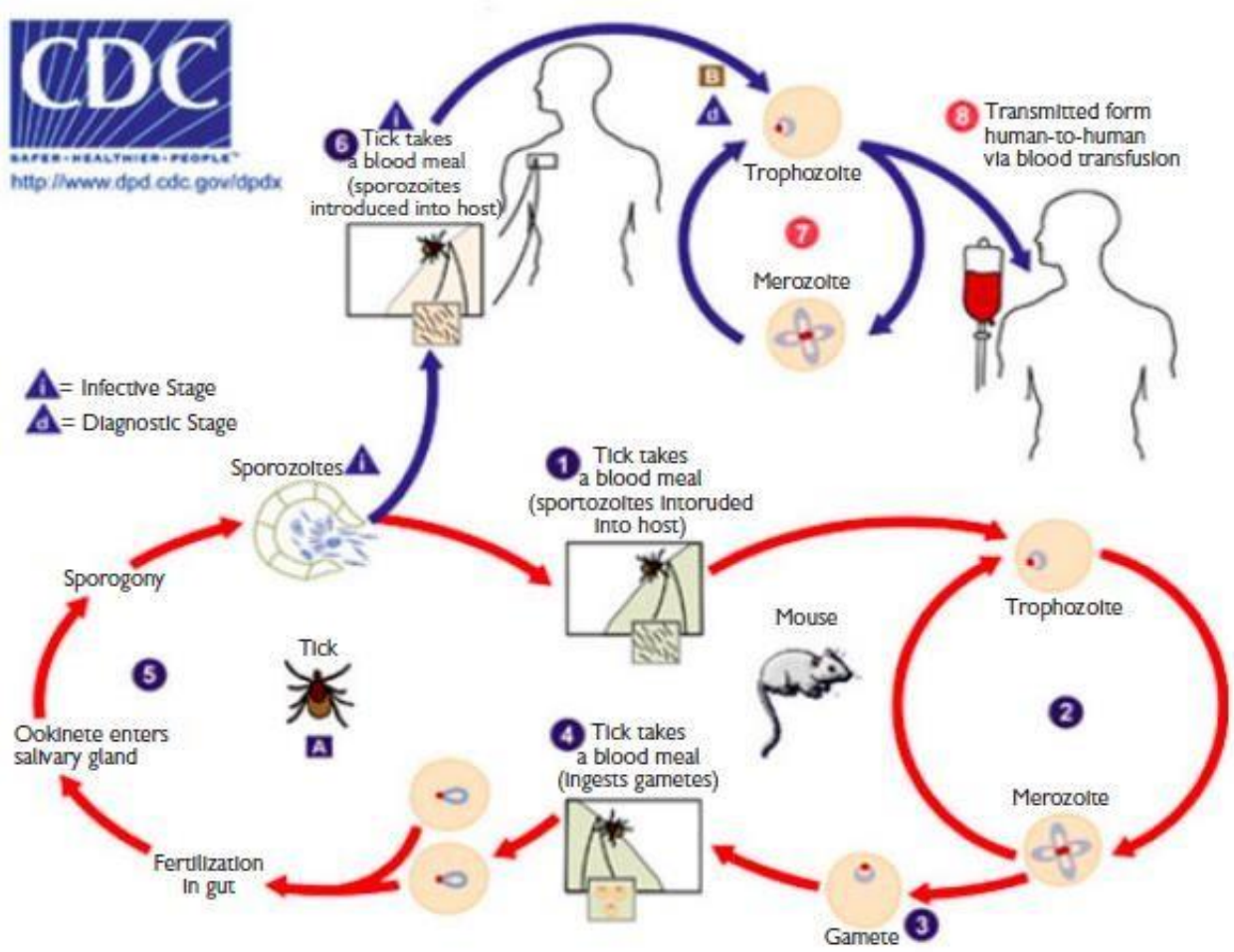
- The infection typically is mild in young and older children and otherwise healthy individuals but can be severe and sometimes fatal in persons >50 years of age and infants and in immunocompromised patients such as HIV. Sporadic cases have been reported in Europe and the rest of the world.

Modes of Transmission

- B. microti is transmitted to humans primarily by the nymphal stage of the deer tick (Ixodes scapularis), the same tick that transmits the causative agents of Lyme disease (which is a tick-born disease)

- The vectors for transmission of B. duncani and B. divergens– like organisms are thought to be Ixodes pacificus and Ixodes dentatus, respectively.

babesia life cycle



babesiosis does not have an exoerythrocytic (liver) stage. Instead, the infection starts directly with the invasion of red blood cells, similar to what occurs in **transfusion-associated malaria.** The merozoites, multiply within the RBCs.

- Wild rodents serve as reservoirs for the *Babesia* species

CLINICAL MANIFESTATIONS

Dr did not mention anything about this page

- Asymptomatic B. microti Infection: At least 20% of adults and 40% of children do not experience symptoms following B. microti infection. There is no evidence of long-term complications following asymptomatic infection; however, people who are asymptomatically infected may transmit the infection when they donate blood.

- Mild to Moderate B. microti Illness Symptoms typically develop following an incubation period of 1–4 weeks after tick bite and 1–9 weeks (but as long as 6 months) after transfusion of blood products. Patients experience a gradual onset of malaise, fatigue, and weakness. Fever can reach 40.9C and is accompanied by one or more of the following: chills, sweats, headache, myalgia, arthralgia, nausea, anorexia, and dry cough.

- Severe B. microti Illness Severe babesiosis requires hospital admission and typically occurs in patients with one or more of the following: age of >50 years, neonatal prematurity, male gender, asplenia, HIV/AIDS, malignancy, hemoglobinopathy, and immunosuppressive therapy.

PATHOGENESIS

- Anemia is a key feature of the pathogenesis of babesiosis. Hemolytic anemia caused by rupture of infected RBCs generates cell debris that may accumulate in the kidney and cause renal failure.
- unlike malaria, *Babesia* infections do not leave behind distinct traces in the blood cells. This is one of the diagnostic differences between babesiosis and malaria, Symptomatically wise, babesiosis can range from mild or subclinical to moderate or severe, depending on the patient's immune status. Patients may experience fever and paroxysms, but unlike malaria, these are not tied to a strict 48-hour or 72-hour cycle.

- Anemia also results from the clearance of intact RBCs as they pass through the splenic red pulp and encounter resident macrophages.

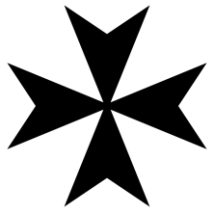
- Babesia antigens expressed at the RBC membrane promote opsonization and facilitate uptake by splenic macrophages. In addition, RBCs are poorly deformable as a result of oxidation generated by the parasite and the host immune response and are filtered out as they attempt to squeeze across the venous vasculature. Bone marrow suppression due to cytokine production may also contribute to anemia.

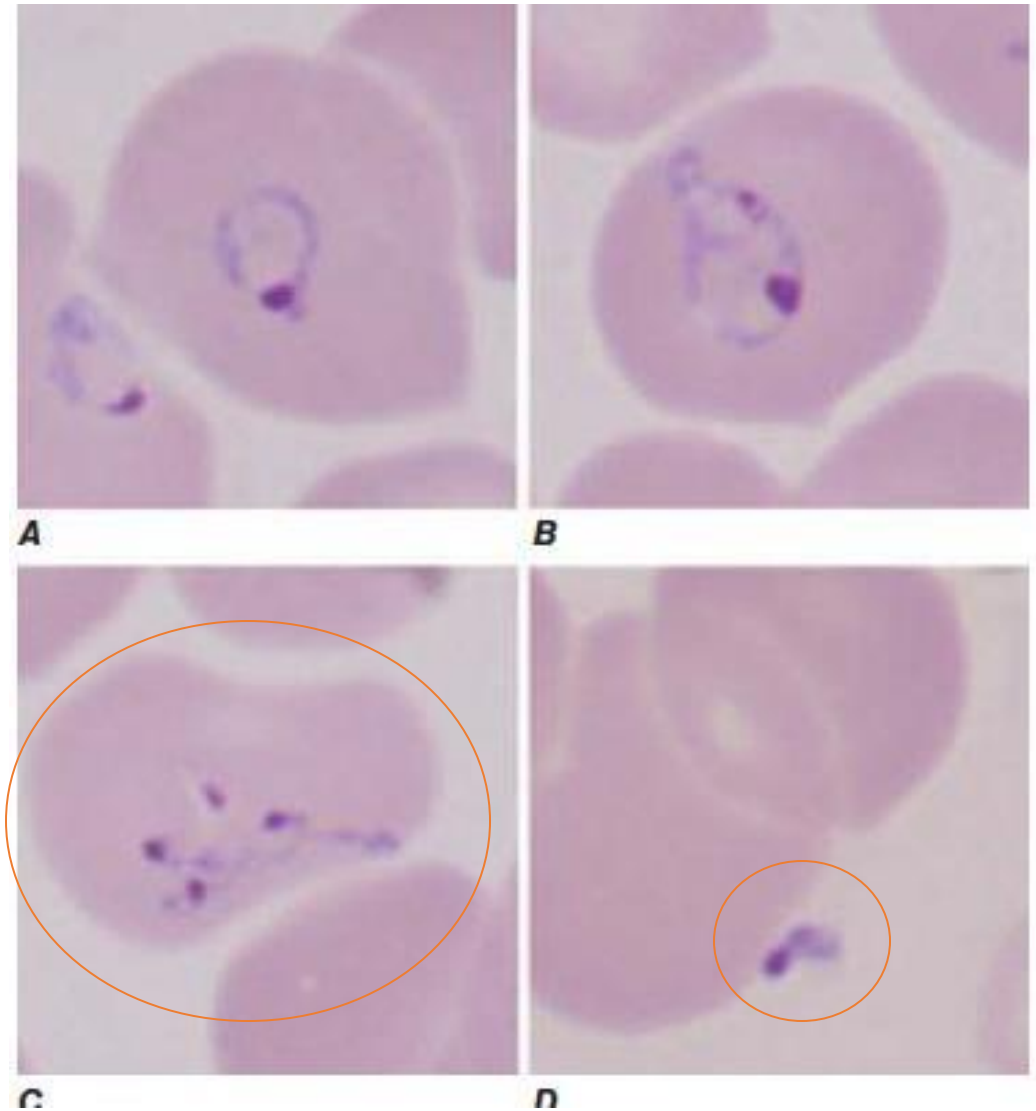
DIAGNOSIS

- Microscopic examination of Giemsa-stained thin blood smears
- Polymerase chain reaction (PCR)
- Serology can suggest or confirm the diagnosis of babesiosis. An indirect immunofluorescent antibody test for B. microti is most commonly used.

Two characteristics are specific to babesiosis and are not seen in malaria.

1. the presence of *Babesia* arranged in tetrads, forming a "Maltese cross”





2. the observation of extracellular *Babesia* in blood smears.

TREATMENT

- Atovaquone plus azithromycin is the recommended antibiotic treatment combination for mild to moderate babesiosis.

- Clindamycin plus quinones is the choice for severe infections.

Prevention

- Wear clothing that covers the lower part of the body, apply tick repellents (such as DEET) to clothing, and limit outdoor activities where ticks may abound from May through October.

Additional Table taken from Dr.21

	P.Malaria	Babesia
target cell	both target RBCs causing their lysis	
vector that mediates the disease	female anopheline mosquito	B.macroti Is transmitted via Ixodes scapularis and B. divergens is transmitted via Ixodes dentatus
life cycle	infective stage: sporozoites intermediate host: human	infective stage: Sporozoites dead-end host: human
symptoms	it shows sign and symptoms with different fever periodicity according to malaria type	asymptomatic to mild symptoms without fever periodicity
fever	it comes in 3 stages: cold stage, hot stage and sweat stage	Is not Regular, you might suffer from it day by day or once a week or once each three days, etc...
diagnosis (microscopic) pathognomonic	differ according to malaria type	Maltese cross as well as extracellular development stag
treatment	Atovaquone (ARTEMISININS derivative) for falciparum. Quinilines for non falciparum infection + primaquine for ovale and vivax	QUINOLINES, ARTEMISININS

Past papers

The highest rate of relapsing in plasmodium species:
P. ovale
P. vivax
P. falciparumm
P. knowlesi

Wrong statement about malignant tertian fever :
shows 2 chromatin dots with crescent gametocytes
Affects RBCs of all ages and shows all sizes
irregular fever with usually episodes
every (36-48) hours
shows Schuffner's dots

Babesia Microti is transmitted by which of the following vectors:
Ixodes scapularis
Ixodes pacificus
Ixodes dentatus
Tsetse fly

Which is not true about P.malariae :
a.chronicity
b.glomeriolonephritis
c.hepnozoites
d.benign
e. band form

Which is wrong about malraia :
sporogony in the liver
it has two cycles
falciparum is the most severe one

The asexual cycle of Plasmodia
occurs in :
vector
RBCs

7. The infectious phase of Plasmodia is :
a. Sporozoites
b. schizont
c. trophozoite

8. Wrong about P. falciparum :
a. it invades all ages of RBCs
b. only has schizogony in the erythrocytes
c. no schuffner's dots

9. Wrong about P. malariae:
a. relapse
b. tends to infect old cells
c. band form

10. Cerebral malaria is seen in:
a. P. falciparum
b. P. ovale
c. P. knowlesi
d. P. malariae
e. Plasmodium vivax

11. Newly produced RBCS are usually the only target for:
a. None of the mentioned
b. P. knowlesi
c. Plasmodium vivax
d. P. falciparum
e. P. malariae

12. wrong about p. malariae:
a. Relapse
b. no Schüffner's dots
c. glomerulonephritis

1.B	7.A
2.D	8.B
3.A	9.A
4.C	10.A
5.A	11.C
6.B	12.A

The End

اللهم نستودعك أهالي غزّة وفلسطين فانصرهم واحفظهم بعينك التي لا تنام، واربط على قلوبهم وأمدهم بجُندك وأنزل عليهم سكينتك وسخر لهم الأرض ومن عليها

VERSIONS	SLIDE #	BEFORE CORRECTION	AFTER CORRECTION
V1→ V2	55	Infective stage: trophozoites	Infective stage: **sporozoites**
V2→V3			

امسح الرمز و شاركنا بأفكارك لتحسين أدائنا !!