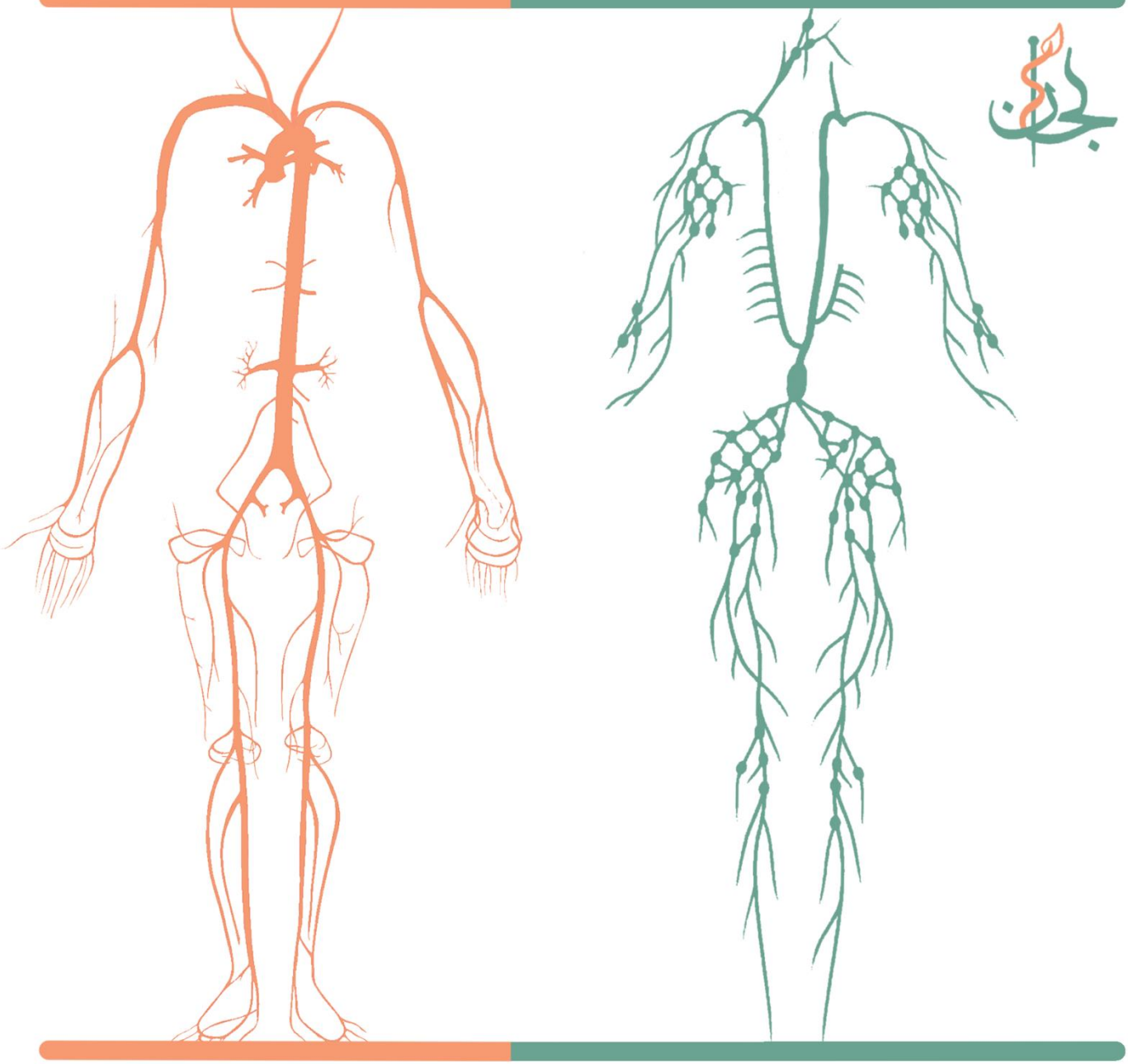
Microbiology

HematoLymphatic



Title: Sheet 3 – Malaria and babesiosis

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Note: In this sheet I didn't include everything in the slides, I tried to focus on what's important, what the doctor highlighted and all the (أنا بهمني تعرف) information, if you want a more comprehensive sheet you can check out 017's, it's truly beautifully written.

Introduction

◆ Protozoa are unicellular eukaryotes, that are classified according to their mode of movement into: [movement helps in pathogenesis]

I. **Sarcodina**, e.g. Amoeba. [They use pseudopods]
II. **Flagellates** (Mastigophora), e.g. Giardia, Leishmania.
III. **Ciliates** (Ciliophora), e.g. Balantidium.
IV. **Sporozoites**:an example is our star 'plasmodium'
    - ↳ The adult stage of these organisms is **(non-motile)**.
    - ↳ Instead of relying on movement, they alternate between sexual and asexual phases and this thing will be of great significance

❖ About malaria:

› Malaria is an intracellular protozoal infection.
› It's the most important parasitic disease, the no.1 killer of all of them (1 million annualy)
› The infection requires a vector (the female anopheline mosquito) which is why it is endemic to some areas like Sub-Saharan Africa
› Tropism[favorite cell target]: RBCs

❖ About Plasmodium: [a sporozoan]

› Plasmodium is a genus of parasitic alveolates (characterized by the presence of sacs of fluid under the cell membrane), they cause malaria in their hosts.
› The parasite always has **two hosts** in its life cycle: Dipteran insect host (sexual cycle)and a vertebrate (in humans)

› **Five plasmodium species cause malaria:**
- *P. malariae*→ causes Quartan malaria.
- *P. vivax* **most common**
- *P. ovale*

Both cause **Benign Tertian malaria** 48 hr cycles

- *P. falciparum*

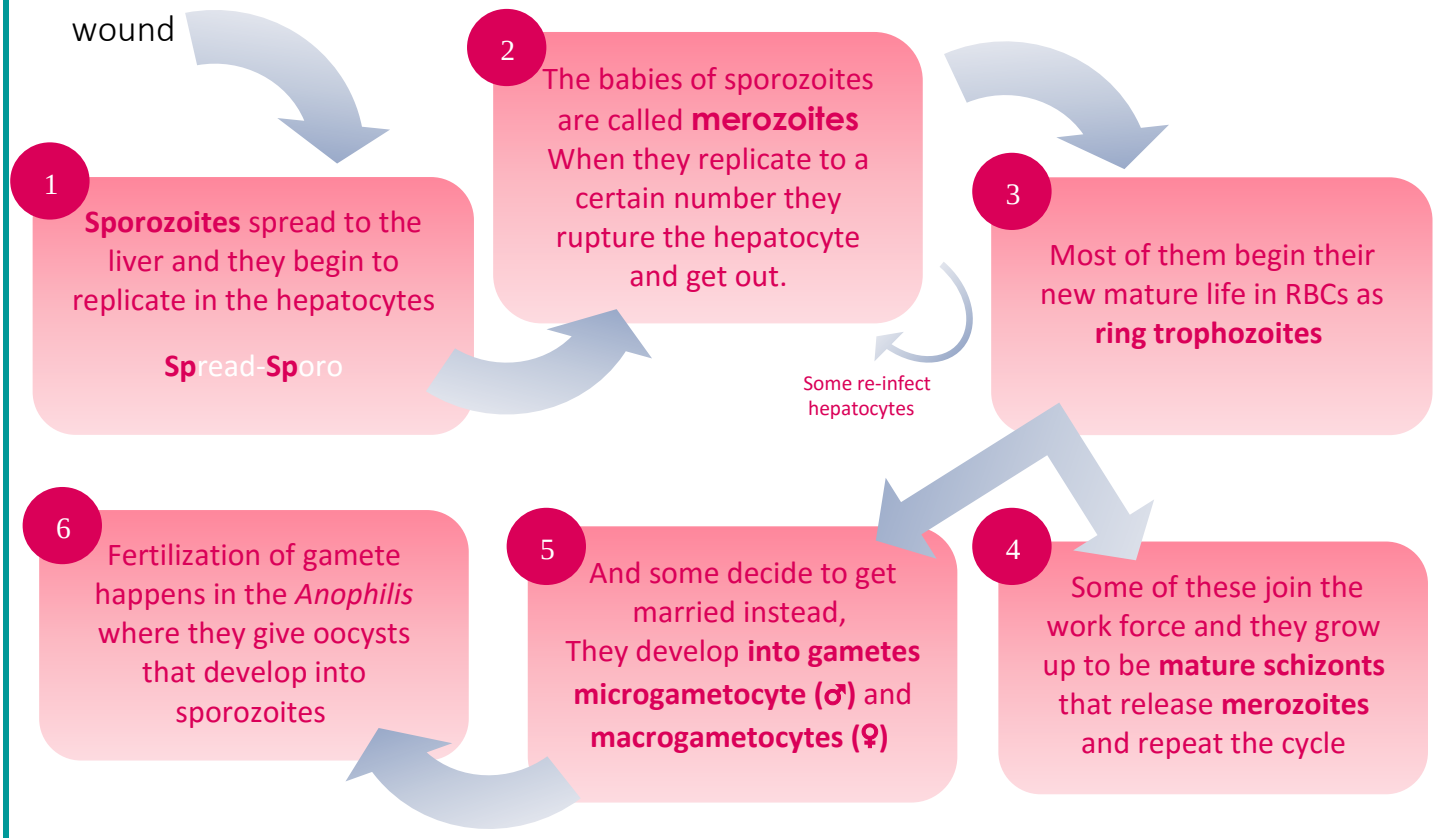
↳ Most common plasmodium associated with deadly infections throughout the world, it causes Malignant Tertian malaria. [most serious, highest mortality rate]
- *P. knowlesi* [aka Simian Malaria]

Mechanism of infection:

- There are 2 phases in the life of plasmodium, the first is in **the mosquito,** it includes **sexual reproduction** that's called **(sporogony)** and it produces **sporozoites**, the second is in **the human** and it includes **ASEXUAL**reproduction that's called **(schizogony)**

let's follow their journey inside the human

The vector for malaria is <u>the female anopheline (anophilis) mosquito</u>, when this very evil lady feeds on the blood, the **sporozoites** in its salivary glands are discharged into the wound



- Steps 1 and 2 are known as the **exo-erythrocytic** cycle and steps 3 and 4 are known as the **erythrocytic cycle** (which is the clinical symptoms phase)
- Keep In mind the term <u>exo-erythrocytic cycle</u> (it's a malarial characteristic to differentiate from babesiosis)
- Check appendix A (at the end) for more less important info on the cycle.
- Once the RBCs and reticulocytes have been invaded, the parasites grow and feed on hemoglobin →causing <u>hemolysis</u>
- The **mature schizont** contains merozoites <u>whose number depends on the species*</u> which are released into the bloodstream.

*this is important later in the differentiation between the different species

➲ In <u>extra-erythrocytic cycle</u>: dormant schizogony may occur in *P. vivax* and *P. ovale* organisms, which stay in the liver. They're termed **hypnozoites** (sleeping plasmodium) and they lead to a true relapse if not killed (>.<)

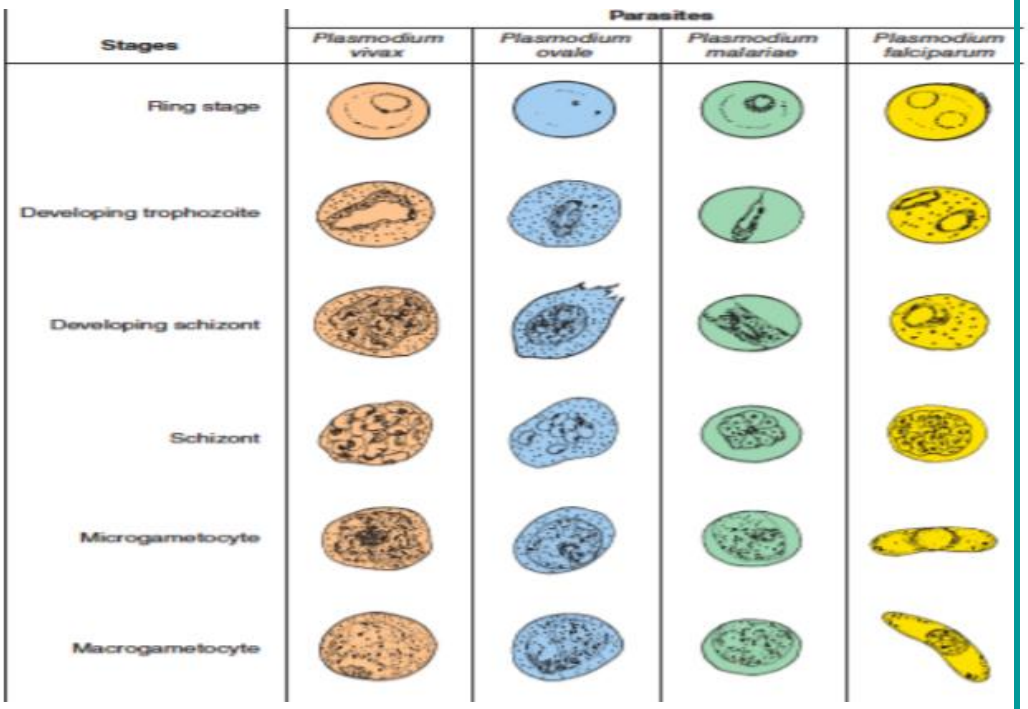
Why should I know this about *vivax* and *ovale*?

Because when I treat them I should give them treatment for those dormant ones too, we don't want any sneakers later on.

Some morphological features:

- *ovale* and *vivax* have granulation in the cytoplasm called Schüffner's dots
- *P.falciparum:* Ring stage: double rings and each ring is **double dotted**.
- All plasmodia are intracellular

we'll refer back to this graph when we explain each species:



Each plasmodium on its own:

side note: All these species have selectivity towards the RBCs they invade [reticulocytes, old RBCs, all ages of RBCs]

1- Plasmodium Vivax (benign tertian malaria)

- Infects only **reticulocytes** which makes the state benign because it means the parasitemia will be low unlike falciparum
- **Benign:** the complications are much less frequent and less severe than falciparum
  Tertian: the cycle of fever repeats itself every 48 hrs ---> 1 day of fever followed by 2 days of feeling ok. [This cyclic fever is caused by the erythrocytic cycle]
- Forms dormant schizogony (hypnozoites) in the liver

➔ we rely on the number of merozoites inside the mature schizont in erythrocytes in asexual reproduction to differentiate it from ovale[more than 8 merozoites can be observed within the mature schizont]

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

› developmental stages of *vivax*:

› Pathogenesis and Spectrum of Disease:

• In patients who have never been exposed to malaria: Symptoms such as headache, photophobia, muscle aches, anorexia, nausea, and sometimes vomiting may occur before organisms can be detected in the bloodstream.

• In other patients with prior exposure to the malaria: The parasites can be found in the bloodstream several days before symptoms appear.

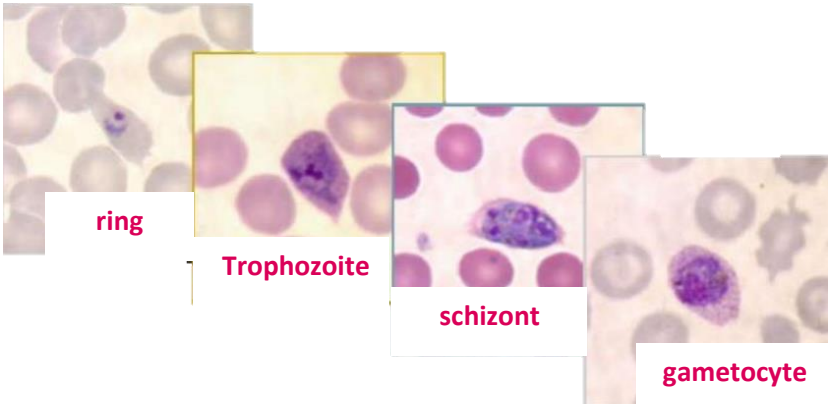
Ovale and vivax are like BFFs that like to do everything the same

2-Plasmodium ovale (benign tertian fever)

› Less common than vivax and also the severity is way down
› 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.
› P. ovale infects only the reticulocytes.
› After a few days of irregular periodicity, a regular 48-hour fever cycle is established. Over time, the paroxysms (fever attacks) become less severe and more irregular in frequency and then they 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

- Forms dormant schizogony (hypnozoites) in the liver
- number of merozoites released is less than 8
- vivax and ovale have the same treatment
- stages of development:



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.

3-P. malariae: (classical malariae, quartan malaria)

Quartan: 72 hrs for the cycle to be repeated

- tends to infect all RBCs
- No stippling of the cytoplasm (no Schüffner's dots)
- Mature schizont contains 6-12 merozoites.

Pathogenesis and Spectrum of Disease:

- Proteinuria is common in P. malariae infections and may be associated with clinical signs of nephrotic syndrome.
- 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.

4- P. falciparum: (malignant tertian fever)

- tends to invade all ages and sizes of RBCs (high parasitemia), and the proportion of infected cells may exceed 50%, thus severe infections may result.

Complications:

- 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 (like kidneys, liver, spleen etc)
- cerebral malaria is a result of the previous points. And it's considered the most serious complication and the major cause of death with P. falciparum.
- Another complication is known as blackwater fever which is a complication of malaria that is a result of red blood cell lysis, releasing hemoglobin into the bloodstream and **urine**, causing **discoloration.**
- Although childhood febrile convulsions may occur with any of the malarias, generalized seizures are specifically associated with falciparum malaria and may cause the **development of encephalopathy**
- Malignant Tertian malaria: It has a 36-48 hour cycle. (high fever and more complications)

Features:

- Shows NO Schüffner's dots(no stippling). Instead Large, single, bluish dots may show later on (Maurer's dots).
- RBCs can be seen in all sizes after the infection.
- The fever caused by falciparum sometimes NEVER becomes regular
- Rings have**2 chromatin dots** and show Applique'/Accole' forms (The ring attaches itself to the margin or the edge of erythrocytes).
- Gametocytes are crescent 'banana' in shape.
- Extreme fevers, 41.7° C (107° F) or higher

↳ See appendix B (page 12) for a larger graph of developmental stages

5-Plasmodium knowlesi:[AKA the Simian Malaria or the 5th human Malaria]

- All sizes of RBCs are seen, but most tend to be normal. It has a 24-hour cycle.
- In the early blood stage, it resembles falciparum
- In the Late blood stage and gamytocytes, it resembles: malariae
- P. knowlesi infects any RBC regardless of age, thus heavy infections may result.
- Mature schizont contains 16 merozoites.
- Shows no Schüffner's dots (no stippling). However, Faint, clumpy dots may show later in the cycle.

↳ Unfortunately, these infections are often misdiagnosed as the relatively benign P. malariae; however, infections with P. knowlesi can be fatal..

Things about Malaria

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

➔ we don't compare the thousands of merozoites (as seen in the table), we compare the RBC/hepatocyte released number
➔ we use blood sample or liver biopsy to count them.
➔ Incubation period for all is from 1 week to 5 weeks

Clinical features of all malaria:

- 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.
- Symptoms like prominence of headache, chest pain, abdominal pain, cough, arthralgia, myalgia, or diarrhea may suggest another diagnosis. But we exclude the others by their specific symptoms.

- Then patterns start (cycles of 48-72 hrs)
  - ➲ The fever that comes on the third to forth day has 3 stages (cold stage with chills and rigors -hot stage -sweating stage) then there are two days of feeling well, then the fever attacks again.
- Anemia can show (due to hemolysis) but mostly in falciparum due to high parasitemia.

Diagnosis of malaria:

Definitive diagnosis is: seeing plasmodium in the peripheral blood,

1.Routine Methods:

- Thick (you look at a drop) and thin (spread the drop then look) blood films.
  - 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.
- The Blood is collected using (EDTA) anticoagulant.

2.Serologic Methods:

- Several rapid malaria tests (RMTs):

1. Some of which use monoclonal antibodies against the histidine-rich protein 2 (HRP2). (there's an antibody in the kit that detects the plasmodium)
2. Whereas others detect species-specific parasite lactate dehydrogenase (pLDH).
   - These procedures are based on an antigen capture approach in **dipstick** or **cartridge** formats.

3. Molecular Diagnostics:

• PCR for detection pf specific genes

4. Automated Instruments

Therapy:

- **Quinolones** are the choice of therapy for the treatment of malaria EXCEPT falciparum
- Quinolones ARE NOT used alone in the treatment of vivax and ovale (remember the hypnozoites phase) They require additional drugs (primaquine) to kill hypnozoites
- Artemisinins (mainly for P. falciparum) and Quinolones

Prevention and control:

It's a vector borne disease so, the main mean of control is vector control by:

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

- Avoid the feeding time of the mosquito from dusk till dawn
- No vaccine currently, but for prophylaxis you can take quinolones if you're travelling to endemic areas like mefloquine.
- Quwat hifth Assalam are the most commonly infected group in JO (I don't feel like switching the keyboard)

To help you with it, watch the sketchy video on plasmodia, it's really good

Babesiosis:

- 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).
  - Commonest causative agent: *Babesia microti* (commonest worldwide and in the USA) and in Europe is *B. divergens. [*another species is B. duncani]
  - Vector:
    - B. microti: the deer tick (Ixodes scapularis)
    - B. divergens: Ixodes dentatus
  - It has symptoms and signs **very similar to malaria** but they differ in that there's no pattern in the fever (NO CYCLES)
  - Life cycle highlights: in humans there's NO EXO-ERTHROCYTIC CYCLE, they go directly to RBCs and their mainstay of pathogenesis is **hemolysis**

↳ ASEXUAL reproduction in humans, the sexual reproduction in the definitive host

- Reservoir for these parasites is white footed mouse
- Humans get infected accidentally

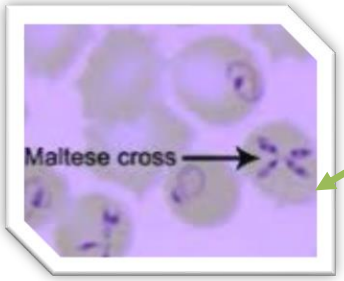
↳ They can get infected through blood transfusions.

Clinical manifestations:

- It mimics malaria starting with non specific symptoms similar to viral illnesses and then later on fever becomes the chief complaint (no cyclic pattern)
- Patients experience a **gradual onset** of malaise, fatigue, and weakness. Fever can reach 40.9˚C and is accompanied by one or more of the following: chills, sweats, headache, myalgia, arthralgia, nausea, anorexia, and dry cough.**[non specific]**
- Mild to Moderate B. microti Illness symptoms typically develop following an incubation period of 1–4 weeks after tick bite and 1–9 weeks after transfusion of blood products.

Complications following RBC hemolysis→ anemia, jaundice, hepatomegaly, splenomegaly

- 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.



Difference from malaria:

- can observe extra cellular merozoites unlike malaria (photo here)
- Merozoites tend to arrange in tetras (maltese cross) (pathognomonic)

Treatment:

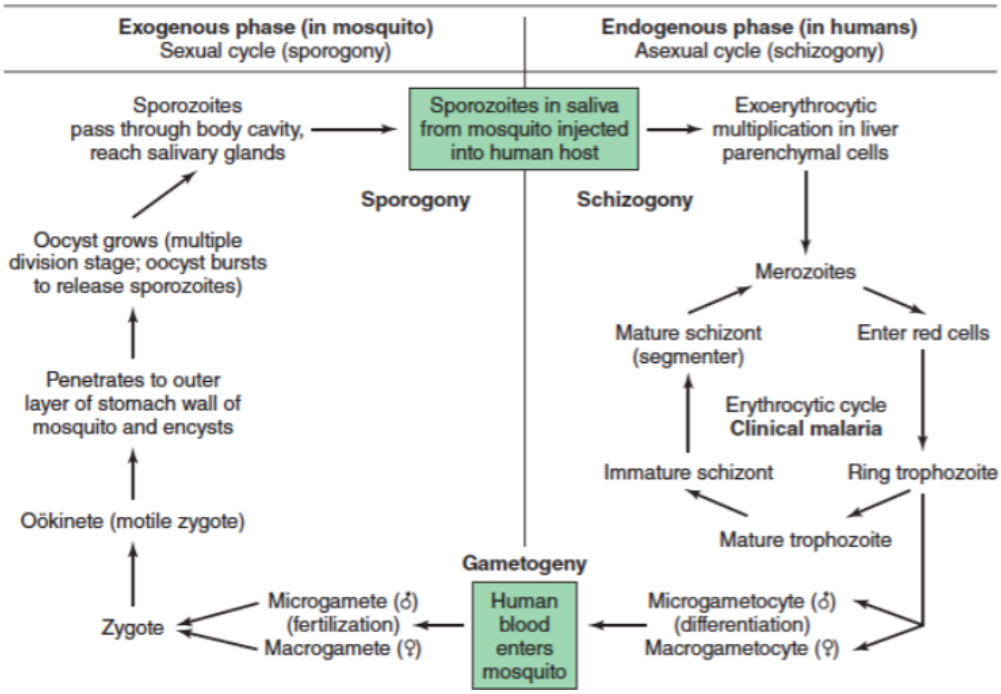
- Quinolones, artimisin-based combination
- **Atovaquone plus azithromycin**is the recommended antibiotic treatment combination for mild to moderate babesiosis.
- **Clindamycin plus quinones**is the choice for severe infections.

Prevention:

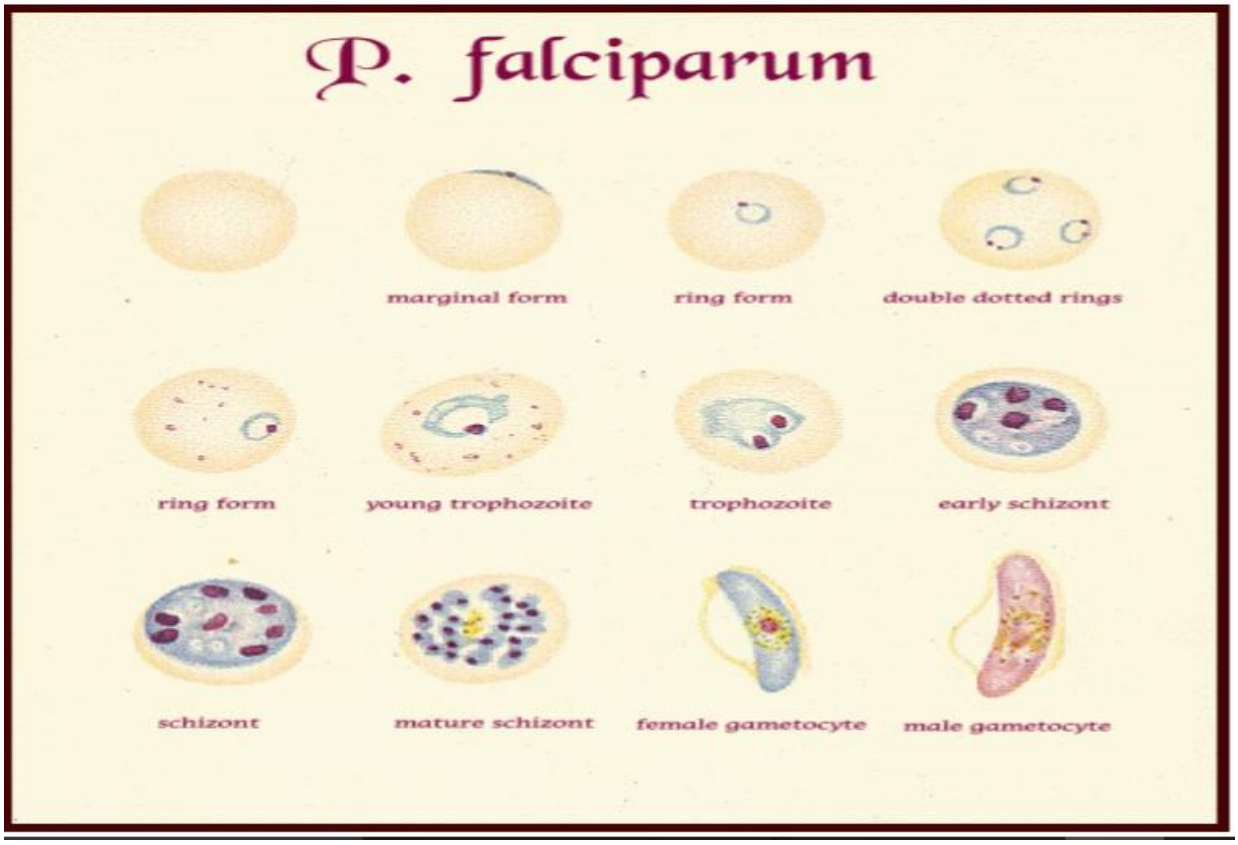
Wear clothing that covers the lower part of the body, apply tick repellents (such as DEET) to clothing, and limit outdoor activities where ticks may abound

I wish you the best of luck

Appendix A:

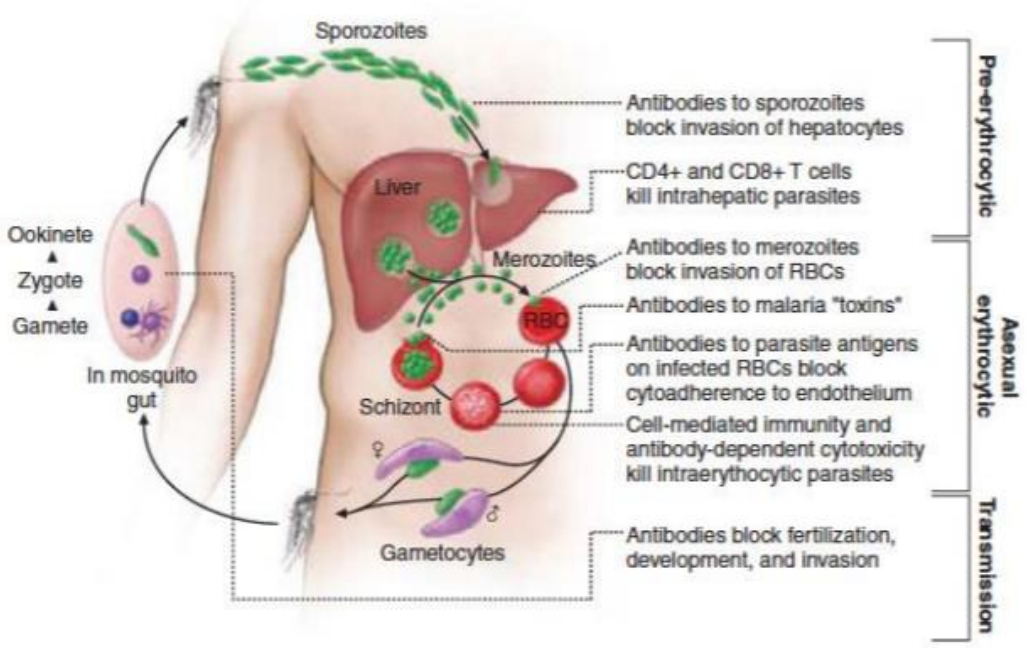


Appendix B:



Appendix C: things the doctor didn't focus on, but mentioned, if you want to know more:

Antigenic targets:



Life cycle of babesia: