HEMATO LYMPHATIC SYSTEM

MICROBIOLOGY

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Introduction :

Protozoa are unicellular eukaryotes, that are classified according to their mode of reproduction & locomotion "movement" into:

	locomotion	reproduction
Sarcodina	Pseudopods Ex: ameba	Asexual [binary fission]
Flagellates (mastigophora)	Flagella Ex: Giardia . Leshmania	Asexual [binary fission]
Ciliates (ciliophoran)	Cilia Ex: Balantidium	Asexual [binary fission]
Sporozoa	Gliding movement Ex : Plasmodium , cryptosporidium	Sexual & Asexual

- About malaria:

✓ **Malaria** is an **intracellular** protozoal infection.

✓ 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.

✓ 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.

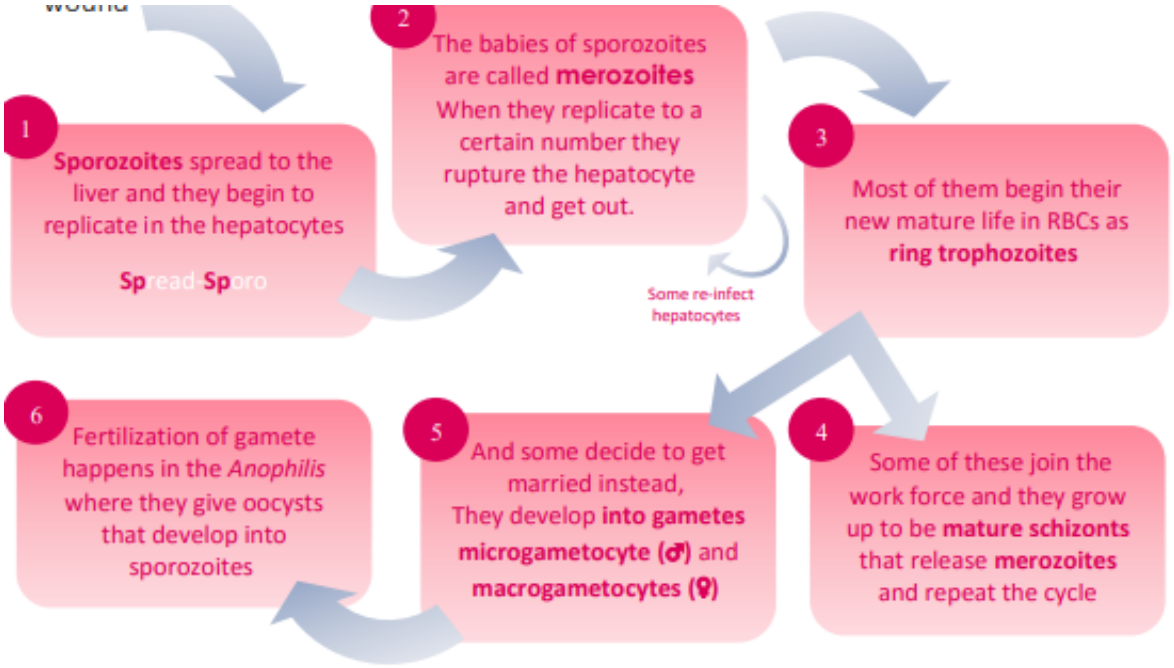
✓ The parasite always has two hosts in its life cycle: Dipteran insect host (sexual cycle)and a vertebrate (in humans).

- Five plasmodium species cause malaria:

1) P. malariae → **Quartan malaria , classical malaria**
2) P. vivax → **most common , Benign Tertian malaria**
3) P. ovale → **second moat common after P. vivax , Benign Tertian malaria**
4) P. falciparum → **most serious, highest mortality rate , Malignant Tertian malaria**
5) P. knowlesi → aka Simian Malaria , mainly infected monkeys & people live with monkeys.

Mechanism of infection:

- ✓ There are 2 phases in the life of plasmodium
  - I. The first is in the mosquito, it includes sexual reproduction that's called (**sporogony**) and it produces sporozoites
  - II. The second is in the human and it includes **ASEXUAL reproduction** that's called (schizogony)
- ✓ The vector for malaria is the female anopheline (anophilis) mosquito, 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 **Exo-erythrocytic cycle** (it's a malarial characteristic to differentiate from babesiosis).
- ➢ Once the RBCs and reticulocytes have been invaded, the parasites grow and feed on hemoglobin →causing hemolysis.
- ➢ The excess protein & hematin from the metabolism of Hb combine to malaria pigment [cause **pigmentation** of RBCs]
- ➢ The mature schizont contains merozoites whose number depends on the species* which are released into the bloodstream.
- ➢ In extra-erythrocytic cycle: 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.
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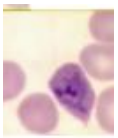
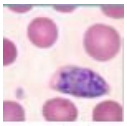
Now let us talk about each one of malaria species :

Type of malaria	description	Characteristics & pathogenesis	stages
P. Vivax	- the most wide spread form of malaria -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. -Tends to relapse	-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. -**splenomegaly** occurs during the first few weeks of infections. - **Characteristics**: -Schuffner's dots appear in the beginning./ multiple & pinkish. -Mature schizont contain an average of **12-24** metrozoites(daughter cells). -Infected RBCs get enlarged . -delicate ring	1.  2.  3. 
P.ovale	-Benign **tertian** malaria. -Infects only reticulocytes which makes the state. -Less common than vivax and also the severity is way down. -**Tends to relapse** less frequently and usually ends with spontaneous recovery. -forms dormant schizogony (hypnozoites) in the liver	**- Characteristics:** -Schuffner's dots appear in the beginning. -Mature schizont contain an average of 8 metrozoites. -Infected RBCs get enlarged - smaller ring than ovale. -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.	1.  2.  3.  4. 

Type of malaria	description	Characteristics & pathogenesis	stages
P. malariae	-Classical malariae. -Quartan malaria Quartan: 72 hrs for the cycle to be repeated [that's mean long incubation period . -Tends to infect old RBCs	-**Proteinuria** is common in P. malariae infections and may be associated with clinical signs of nephrotic syndrome. [protein in urine] -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. **- Characteristics** -No stippling of the cytoplasm (no Schüffner's dots). -Has Zema dots. -thick ring , large nucleus . -Trophozoite tends to form " bands" across the cell. -Mature schizont contains 6-12 merozoites. -normal size of RBCs.	----
P. falciparum	-Malignant tertian fever -Tends **to invade all ages and sizes of RBCs.** -**High parasitemia** - **Malignant Tertian malaria**: It has a 36-48 hour cycle. (high fever and more complications) -Irregular cycles in addition to high fever (+ 42 C) conjunction with tachycardia and sometimes delirium. -Schizogony occurs in the spleen, liver, and bone marrow rather than in the circulating blood. 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 - Two Rings have 2 chromatin dots (in peripheral blood) and show Applique'/Accole' forms (The ring attaches itself to the margin or the edge of erythrocytes). - Gametocytes are crescent 'banana' in shape.	**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(in kidney)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**	1.  2.   3.   4.  5.   6.   

Type of malaria	description	Characteristics & pathogenesis	stages
P. 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 -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. -These infections are often misdiagnosed as the relatively benign P. malariae; however, infections with P. knowlesi can be fatal..	---

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

A. 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.

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

C. Molecular Diagnostics:
   - PCR for detection pf specific genes

D. Automated Instruments.

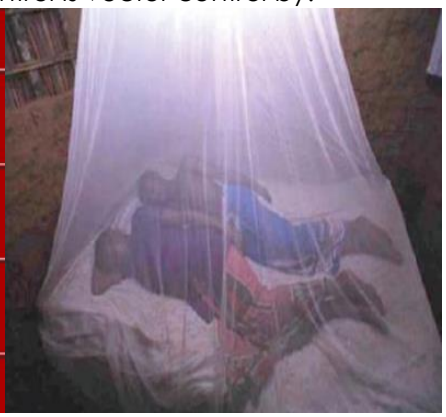
Therapy:

- **Quinolones** are the choice of therapy for the treatment of malaria EXCEPT falciparum (cuz it high resistance to Quinolones).
- 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.
- Tetracycline, doxycycline, and clindamycin are used increasingly in combination with other antimalarials to improve their efficacy.

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.
- Newly introducing / recommending vaccine called RTS . (about 4 doses)

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:
    1. B. microti: the deer tick (**Ixodes scapularis**)
    2. 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** (it's target) and their mainstay of pathogenesis is hemolysis(anemia).
    - 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.

PATHOGENESIS

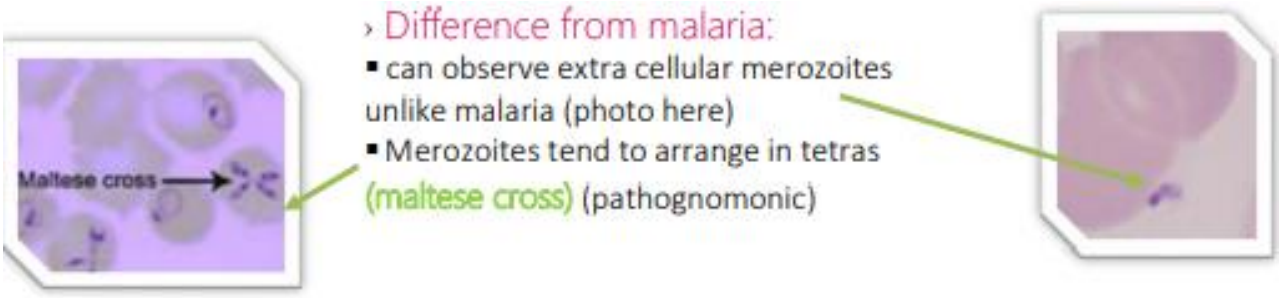
- Anemia is a key feature of the pathogenesis of babesiosis. Hemolytic anemia caused by rupture of infected RBCs generates cell debris that may accumulate in the kidney and cause renal failure
- Anemia also results from the clearance of intact RBCs as they pass through the splenic
- red pulp and encounter 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.

Treatment:

- Quinolones, artimisin-based combination.
- **Atovaquone plus azithromycinis** the recommended antibiotic treatment combination for mild to moderate babesiosis.
- Clindamycin plus quinonesis 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 .



مبروك عليكم اقصر شيت مايكرو بكل مسيرتكم الدراسية

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