Team Medicine

21#

Malaria and travel medicine

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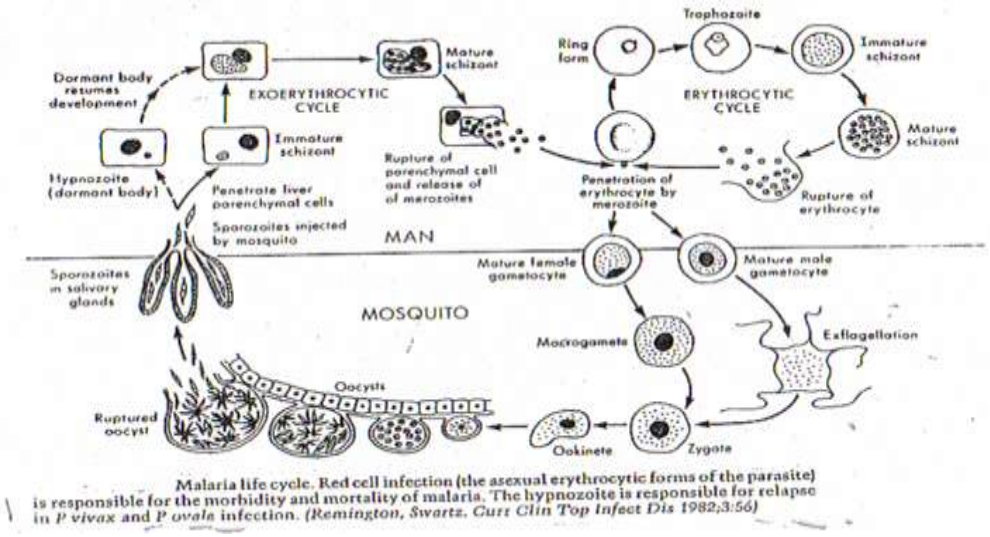
■ Slides ■ Doctors notes ■ Additional ■ IMP

431 Teams

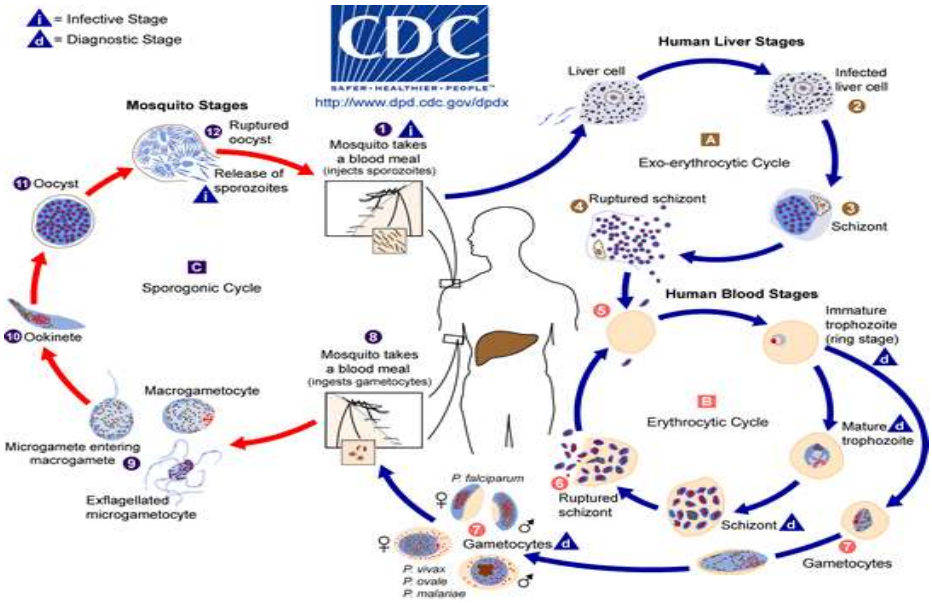
Malaria

4 plasmodia

- *P. Falciparum (is the mostdangerous)*
- *P. Vivax*
- *P. Ovale*
- *P. Malariae*



Malaria life cycle. Red cell infection (the asexual erythrocytic forms of the parasite) is responsible for the morbidity and mortality of malaria. The hypnozoite is responsible for relapse in *P vivax* and *P ovale* infection. *(Remington, Swartz. Curr Clin Top Infect Dis 1982;3:56)*



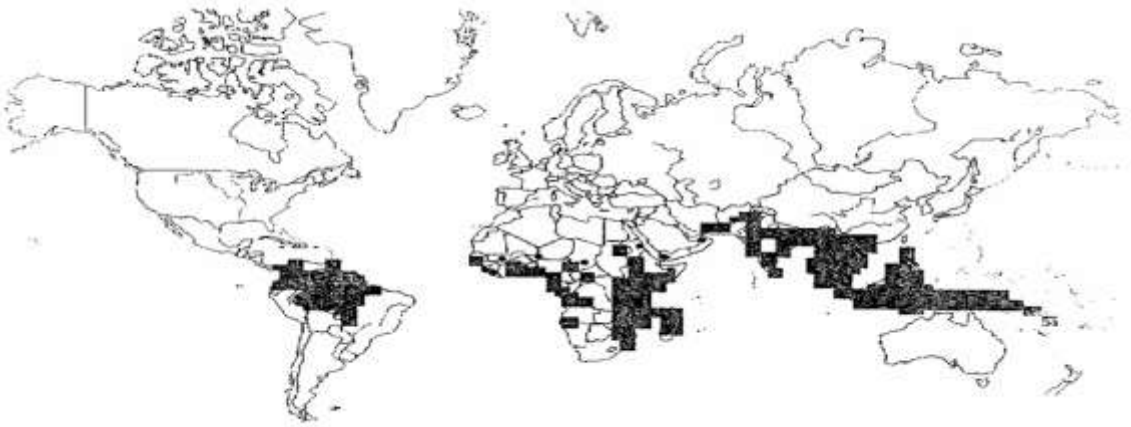


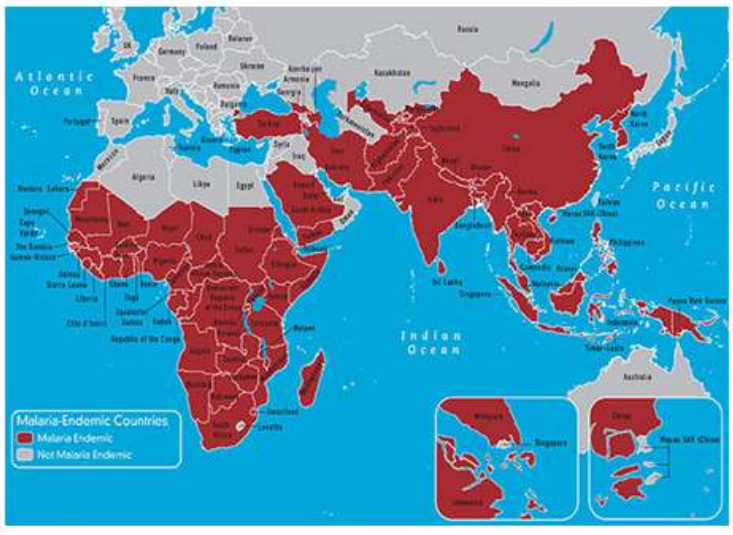
FIG. 6: Areas with chloroquine resistant P. falciparum. Areas of greatest interest to American physicians that do not have chloroquine-resistant *P. falciparum* are in Central America and the Caribbean, especially Haiti. 69 70 Resistance is uncommon in the Middle East, although it is present. Although transmission is much less intense in Southeast Asia than in sub-Saharan Africa. 69 70 drug resistance is quite prevalent and includes resistance to chloroquine, pyrimethamine-sulfadoxine, nefloquine and halofantrine82 –86, 95

EPIDEMIOLOGY

Endemic disease

Usually does not occur at altitudes – 1500 m

World wide ease of travel



To show you how much the disease is endemic

Pathogenesis: m & m degree of parasitemia

P. Falciparuminvades RBC at all ages - 10^6 2500/mcl

P. Malariae: only old RBC – 10,000/mcl

P. ovale and P. vivax invade young RBC's.

· Micro vascular pathology: secondary Ischemia Adherence of non-deformable parasitized RBC to endothelium

· Renal failure: hemolysis, Ischemia secondary micro vascular pathology

· Deep Coma: hypoglycemia, micro vascular adherent parasitizedRBC ((You could have coma either because reduction of blood supply or also because of hypoglycemia))

· Pulmonary edema*; 2 o: Capillary leak Syndrome (without* congestive cardiac failure.*)*Happen because of hypoxemia

· Immune complexNeph. Syndrome 2 o P. Malariae

if you want to forget everything .. just remember this :

* First remember that RBCs have the ability to deform ..meaning that they can go from the aorta the biggest artery to smallest capillaries .. in Malaria .. this deformity is lost therefore the RBCs are not be able to cross.. so there will be obstruction >> when blood supply is interrupted you will suffer from hypoxemia, metabolic acidosis and cell death.

* Sometimes you might treat your patient properly, but he will still die from hypoglycemia. So make sure that you give your patient a good supply of glucose ..

*Pulmonary edema : because of obstruction of pulmonary vasculature you get a lot of ischemia .. a lot of hypoxemia and a lot of metabolic acidosis complications and then you will have non–cardiopulmonary edema or called " acute respiratory distress syndrome " this is because of leak of fluid to the interstitium of the lung ..

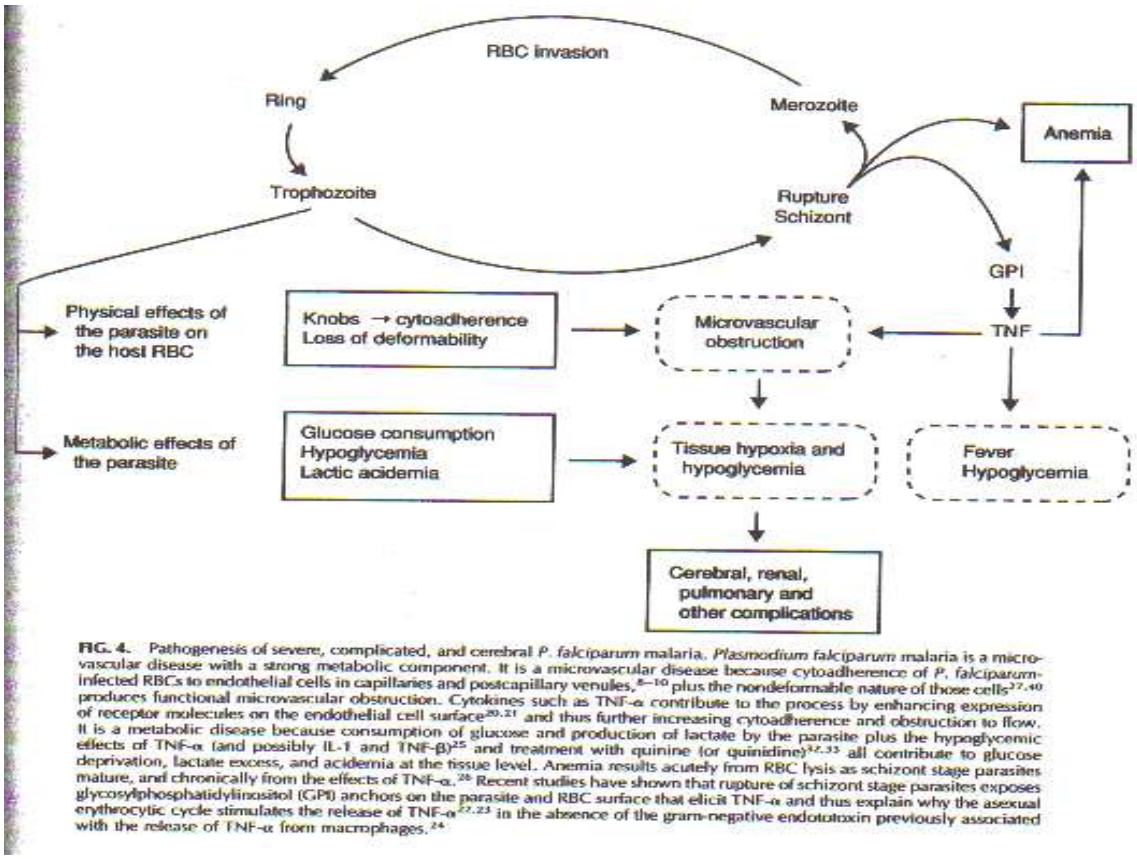


FIG. 4. Pathogenesis of severe, complicated, and cerebral *P. falciparum* malaria. *Plasmodium falciparum* malaria is a microvascular disease with a strong metabolic component. It is a microvascular disease because cytoadherence of *P. falciparum*-infected RBCs to endothelial cells in capillaries and postcapillary venules,[8–10] plus the nondeformable nature of those cells[37,40] produces functional microvascular obstruction. Cytokines such as TNF-α contribute to the process by enhancing expression of receptor molecules on the endothelial cell surface[20,21] and thus further increasing cytoadherence and obstruction to flow. It is a metabolic disease because consumption of glucose and production of lactate by the parasite plus the hypoglycemic effects of TNF-α (and possibly IL-1 and TNF-β)[25] and treatment with quinine (or quinidine)[32,33] all contribute to glucose deprivation, lactate excess, and acidemia at the tissue level. Anemia results acutely from RBC lysis as schizont stage parasites mature, and chronically from the effects of TNF-α.[26] Recent studies have shown that rupture of schizont stage parasites exposes glycosylphosphatidylinositol (GPI) anchors on the parasite and RBC surface that elicit TNF-α and thus explain why the asexual erythrocytic cycle stimulates the release of TNF-α[22,23] in the absence of the gram-negative endotoxin previously associated with the release of TNF-α from macrophages.[24]

The image shows you threethings :

1- Physical effects of the parasites on the host RBC >> parasites will attach to the surface of the RBC by cytoadherence causing loss of deformability (traveling of the RBC through vessels) and this will lead to micro vascular obstructions, tissue hypoxia and hypoglycemia causing all the complications (so here the parasite is interfering with the mobility of RBCs)

2- Metabolic effect of the parasite >> once the organ is not receiving an adequate blood supply it will be hypoxic.
Increased consumption of glucose by the host and by growing parasites will lead to hypoxemia leading to other complications ..

3- RBC parasites will rapture and this will lead to the following

- Anemia
- Release of GP (glycoprotein) and cytokines which is inflammatory mediator >> causing fever
- MORE micro vascular obstructions

CLINICAL FEATURES

depends on :

- where does the patient live .. they can develop immunity if they live in an endemic area.
- age (younger patients are more prone to complications) the older the better
- Pregnant women >> mortality could reach up to 50% ..you should be very cautious if you have a pregnant woman with malaria
- Non-immune travelers >> they must take the prophylaxis 1-2 weeks before travel

Note :It can start just like any other illness .. headache , fever , generalize fatigue .. so it can mimic any other simple viral infection in the beginning .. (1-2 hours)
In few hours the pt will start to have tachypnea, tachycardia, deliriumand hot skin ..this indicates a CNS infection (this type of patients usually die) if u don't treat him properly ..
Then he will have fever, marked sweating and fatigue ..between attacks the patient will be symptom free(this what differentiates it from other febrile illnesses) before the second begins.
Remember :Clinical features depend on the amount of parasite in your body if you have severe infection or you have parasitemia (parasitic index) you could have renal failure, coma , hypoglycemia because of micro vascular problems

1) Major

· Recurring fevers

· Chills (Assoc. RBC lysis – mature zchisonts)When RBC lyses parasites spread into circulation causing fever

2) Periodicity S/O

· 48 hours: P. Vivax&Ovale

· 72 hours: P. Malaria

· Non-regular/hectic in P.F. especially in non-immune

· Patients (*who are at highest risk of complications and death)*

MALARIA FEVER PAROXYSMS

1- Rigors, headache *associated with pale cold skin*(1-2 hours)
2- Delirium, Tachypnea, Hot Skin (Several hours)
3- Fever *Marked sweating and fatigue*

Complications : Severe P.Falciparum (> 10 parasite/ mcl):

- Renal failure due to micro vascular pathology
- Coma due to :hypoglycemic ; TNF, or micro vascular pathology
- Pulmonary Edema (you have to know what type is it ," non – cardiac ")
- Thrombocytopenia(parasite does not affect the platelets but there is an immune complex which can effect non effecting RBCs and platelets, this might lead to bleeding.)
- G. Enteritis – especially diarrhea(watery diarrhea)
- Chronic P. Falciparum infection
- Splenomegaly – typically resolves after treatment with anti-malarial meds. 6-12 mon.
- P. Malariaeassoc. Immune compl. N. Synd.
- · P. Vivax – late splenic rupture with trauma 1-3 mon.after initial infection
-

Diagnosis:

Detailed history!!! Including targeted travel history and clinical examination together with High Index of Suspicion.

Blood film stained with:

· Giemsa stain or wright's stain.

· Correct identification of malarial Spp is essential for treatment because of P.Falciparum is resistant to Chloroquine.

· On Giemsa stain – Cytoplasm: light blue, nucleus: dark blue

· In P. Falciparum :

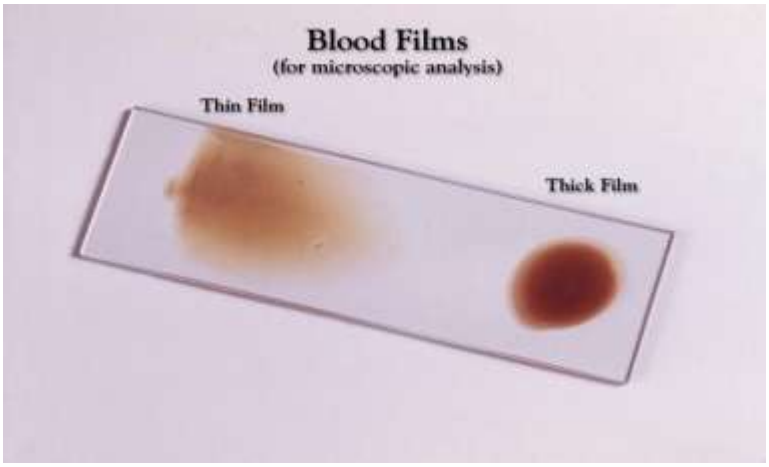
(a) only ring stage a sexual parasite and gametocytes seen in periph. Blood.
(b) While RBC with Trophozoites or Schixonts stage – sequestered in peripheral, Microvasculature, and NOT circulating P-blood.

· All asexual erythrocytic stages of P. Vivax, Ovale&malariae circulate in peripheral blood, thus seen on Blood Smear

· Acutely ill patients

DDX: P.F. vs P. Vivax, because

(a) P. Ovale – Vivax – clinical, Morphological.
(b) P. malariae - ch. Infection.



In blood film when u see RBC with a group of parasitesthey're usually Falciparum

inVivax and Ovale u will see mature trophozite ..

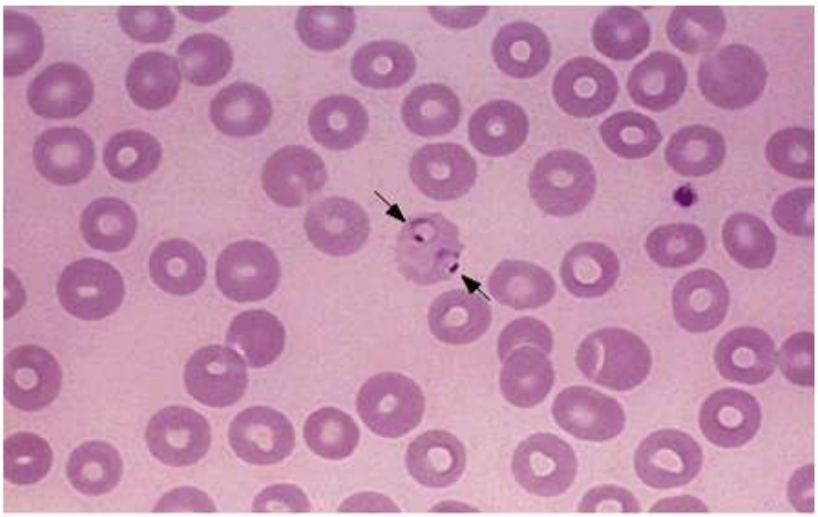
Vivax and Ovale behave exactly the same and have the same treatment.

How to you diagnose ?

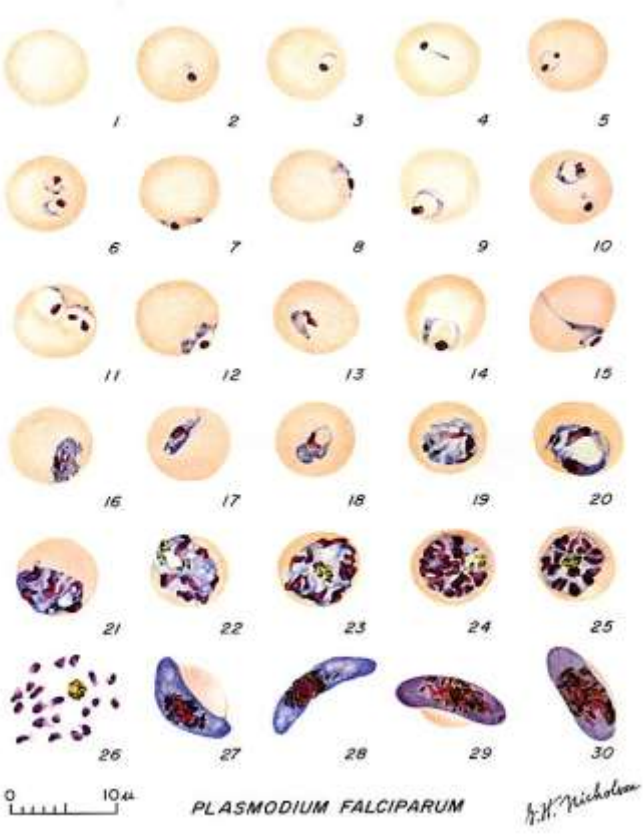
First you need to take a detail history that must include (travel history and what was he doing ?) and then completed examination ..

Remember : Exposure to mosquites is commonly before sunrise ..

Remember :Falciparum is acute illness while malariae takes time ..



Malaria Peripheral smear from a patient with malaria shows intraerythrocytic ring forms (trophozoites) (arrows). Courtesy of Carola von Kapff, SH (ASCP).



Plasmodium falciparum

Blood Stage Parasites
Thin Blood Smears

**** This is just for your knowledge

1: Normal red cell

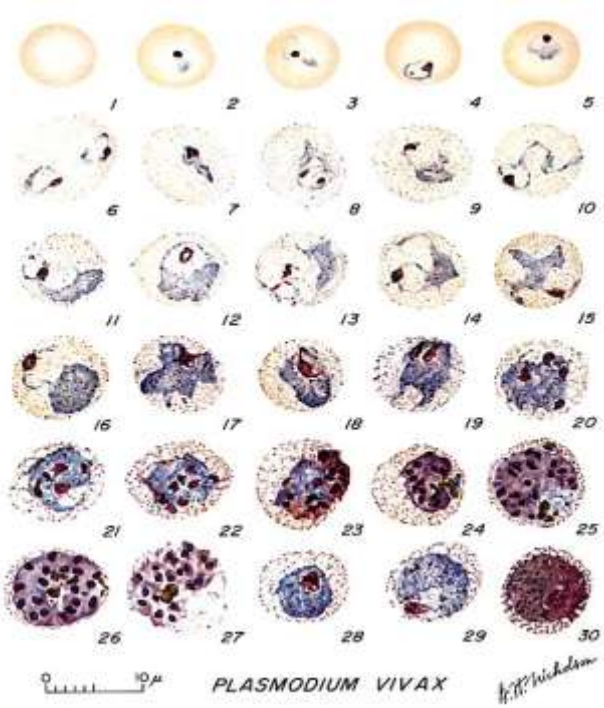
2-18: Trophozoites

(2-10: ring-stage trophozoites)

19-26: Schizonts(26 is a rupturedschizont)

27, 28: Mature macrogametocytes(female)

29, 30: Mature microgametocytes(male)



Plasmodium vivax:

Blood Stage Parasites

Thin Blood Smears

**** This is just for your knowledge

1: Normal red cell

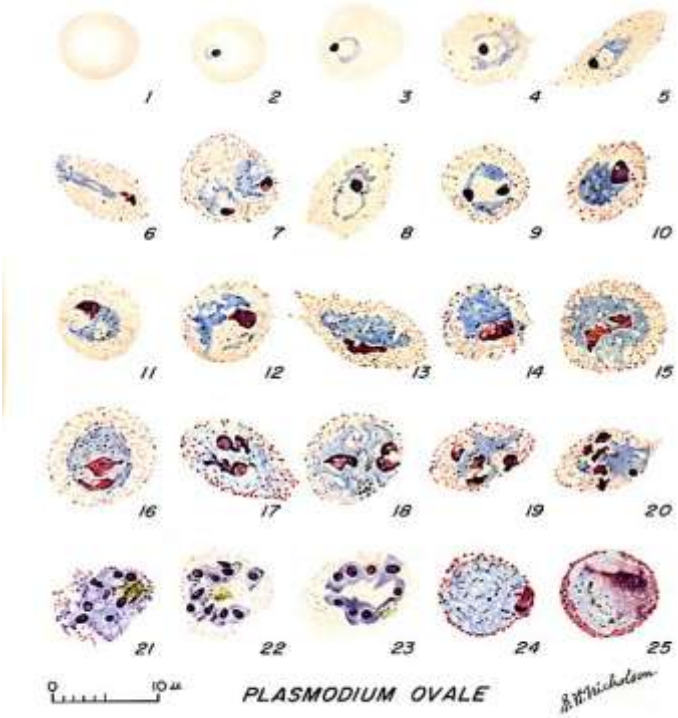
2-6: Young trophozoites (ring stage parasites)

7-18: Trophozoites

19-27: Schizonts

28,29: Macrogametocytes (female)

30: Microgametocyte (male)



Plasmodium ovale:

Blood Stage Parasites

Thin Blood Smears

**** This is just for your knowledge

1: Normal red cell

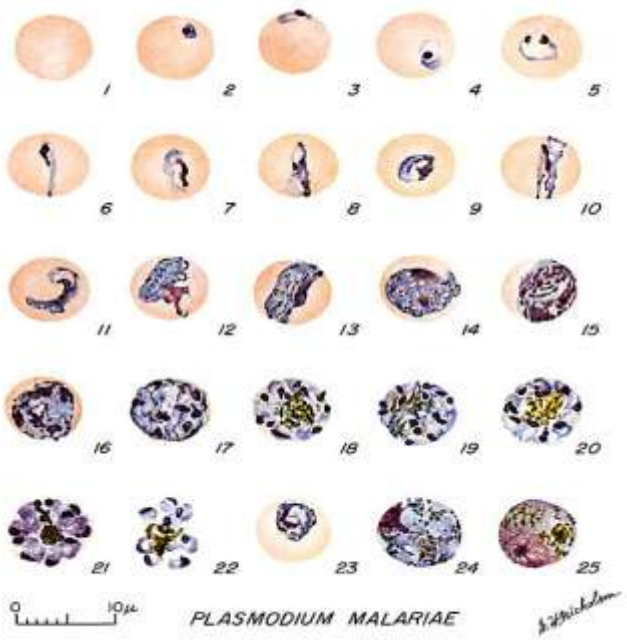
2-5: Young trophozoites

6-15: Trophozoites

16-23: Schizonts

24: Macrogametocytes (female)

25: Microgametocyte (male)



Plasmodium malariae:

Blood Stage Parasites

Thin Blood Smears

**** This is just for your knowledge

1: Normal red cell
2-5: Young trophozoites (rings)
6-13: Trophozoites
14-22: Schizonts
23: Developing gametocyte
24: Macrogametocyte (female)
25: Microgametocyte (male)

- **Thin blood film (RBC morphology preserved) :**

  - P. Vivax; infected RBC
  - RBC enlargement with parasite maturation
  - Scuffner's dots (eosinophilic dots in RBC cyto.)
  - May see Maurer's clots in RBC eytoplasm
    - Infection with more than one parasite spp: 5-7%
    - Thick Blood Film (RBC) lysed
  - You may examine 10X. Blood more than in thin film
  - More diagnostic in lower degree of parasitemias
    - Serology: not useful in managing acutely ill patient
    - DNA probe: similar thick film sensitivity

Differential Diagnosis of Malaria in Acutely Ill Patients Based on P.B. Smear

	P. Falciparum	P. Vivax P. Ovale
Multiply Infected RBC	Common	Rare
Mature (Trophozoite and schizont) parasites	Absent	Common
RBC enlargement with lager parasite stages	Absent	Common

- Mature (trophozoites&schizont) stage P. falciparum. Typically sequestered in the peripheral microvasculature.
- RBC enlargement in P. vivax typically occurs with later stage parasites that do not circulate in P. falciparum infection.

M A L A R I A Complications

Depth of coma
Temp
Vomiting
Seizures
Parasite load
Anemia

} Do not modify outcome

✓ HIV infection did not affect clinical or biological presentation of cerebral malaria and appears not to affect outcome.

(Niyongabo et al, Acta TropicaApr 1994)

❖ Risk factors for poor prognosis in cerebral malaria: *very important*

Increased with :

- Creatinine
- Bilirubin "more bilirubin amount means the more parasite in the liver. The liver is destruction"
- Lactates

- Patient WITH rising amount of Creatinine and lactate and bilirubin you should keep your eyes on him why ?it's usually falciparum with end organ involvement

MALARIA COMPLICATIONS :

- Major clinical features of malaria are those of the complications.
- Majority of complications (apart from anemia) associated with P. Falciparum

Majority of complications (apart from anemia) associated with P. falciparum :

* Anemia: presents in most severe infections and parallels parasitaemia
  due to :
    - Hemolysis of infected RBC
    - Delayed reticulocytes release from bone marrow
    - Immune – mediated hemolysis of non-infected RBC

* Non-immune: (primary infection)
    - Haemoglobinuria
    - Black water fever>pt has hemolysis and having hemoglobinuria in his urine > the urine become so dark " black water " this indicate that the pt having sever hemolysis ..he could die
    - Exaggerated haemolytic response to quinine – sensitized RBC
    - Mild unconjugated jaundice common, and parallels hemolysis. Hepatocellular dysfunction may contribute to jaundice.(remember: the higher the bilirubin in the blood the higher the degree of heamolysis>> severe aneamia)

* Tissue hypoxia related complications
    - Hypoxia results from altered microcirculation + anemia.
    - Maturation of erythyrocyteschizontsin P. falciparum takes place in tissue capillaries and venules.

P. falciparum parasitized RBC sequestered in micro circulation because:

- Altered deformability of parasitized RBC
- Adhesion involving parasite – derived proteins within RBC and glycoproteins on vascular endothelium.

❖ Cerebral malaria
- *Most severe common complication*

❖ Renal Failure
- *Most severe common complication*
- *ATN*
- *Dehydration*
- *Hypotension*
- *Hypervescosity (increase risk of ischemia)*

- Pulmonary Edema
  - ARDS – may complicate acute phase of severe malaise. Fluid overload may contribute.

- Hypoglycemia
  - *Glucose consumption*
  - *Lactic acidosis*
  - *Quinine/quinidine --- insulin secretion*

- Bleeding
  - *Thrombocytopenia* (parasite does not affect the platelets but there is an immune complex which can effect non effecting RBCs and platelets, this might lead to bleeding.)
  - *Consumption coagu*lopathy
- Shock: induced endotoxins (Endotoxemia)
- Diarrhea(increase hypotension)
- Hyponatremia (SIADH)

Late Complication :

- *Tropical splenomegaly in P. Falciparum endemic areas.*
- *N. syndrome with P. malariae.*
- *Burkett's lymphoma (PF - EBV)*

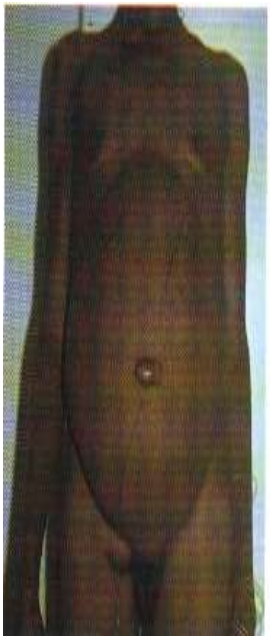


Fig. 13.30 Malaria. Tropical splenomegaly in a patient with evidence of hyperparasitemia living in a *P. falciparum* endemic area.

Splenomegaly

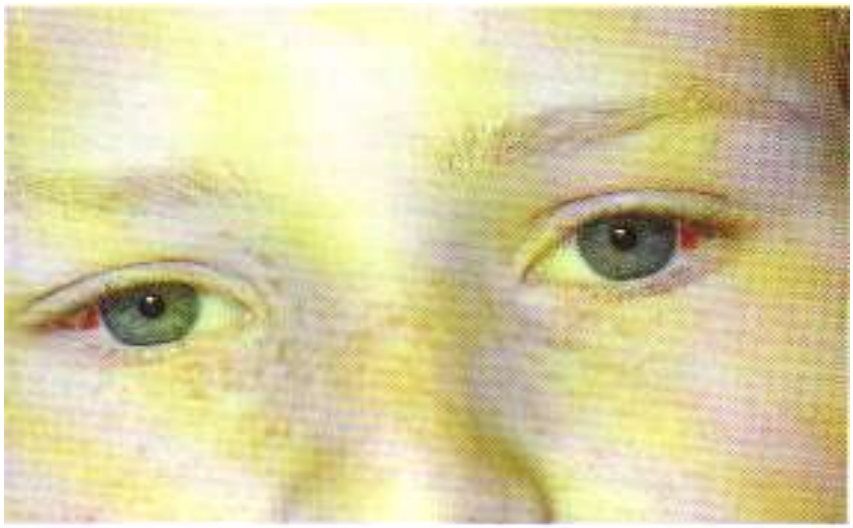


Fig. 13.29 Malaria. Child with mild jaundice, pallor and bilateral conjunctival haemorrhages associated with *P. falciparum* infection.

Subconjunctival hemorrhage because of thrombocytopenia

MALARIA &PREGNANCY :

- Mortality
- Anemia, hypoglycemia, pulmonary edema: >> common
- Abortion
- Stillbirth
- Premature delivery high infant mortality
- Low Birth weight .
- Placental insufficiency.
- High parasitaemia. Why? The parasites have a specialpredilection for the palcenta. (The parasite can cross the placenta).

Congenital malaria :

- Transplacental infection
  - Can be all 4 species
  - Commonly P.v. and P.f. in endemic areas
  - P.m. infections innonendemic areas due to long persistence of species

- Neonate can be diagnosed with parasitemia within 7 days of birth or longer if no other risk factors for malaria (mosquito exposure, blood transfusion)
- Fever, irritability, feeding problems, anemia, hepatosplenomegaly, and jaundice
- Be mindful of this problem even if mother has not been in malarious area for years before delivery

MALARIA AND HEMOGLOBINOPATHIES

- Heterozygous sickle cell train children less likely to contract P. falciparum.

- C.S. disease: no such protection, rather mortality is higher > normal.

- Thalassemics: partially protected (? Fetal Hb).

- G-6-phosphatase RBC : less prone to P. falciparum.

Principles of Treatment

Treatment should be guided by three main factors (CDC):

- The infecting *Plasmodium* species
- The clinical status of the patient (if there's any complications, treat them!)
- The drug susceptibility of the infecting parasites as determined by the geographic area where the infection was acquired and the previous use of antimalarial medicines

- If treatment must be initiated before the species is known treat for *P falciparum,*
- *P falciparum* should be presumed to be chloroquine resistant, except in a few areas of Central America and the Middle East.
- Primaquine should be given if *Plasmodium vivax* or *Plasmodium ovale* is likely.

Resistance patterns " just for reading ..won't ask about it "

-*Chloroquine-resistant P falciparum*:
Eastern Hemisphere: All of sub-Saharan Africa, Saudi Arabia, Yemen, Iran, Pakistan, Afghanistan, China, Nepal, and all of Southeast Asia
Western Hemisphere: Panama, Haiti, Brazil, Peru, Bolivia, Colombia, Venezuela, Ecuador, French Guiana, Guyana, and Suriname
-*Chloroquine-sensitive P falciparum*:
Eastern Hemisphere: Turkey, Iraq, Syria, Georgia, Azerbaijan, Tajikistan, Turkmenistan, and Kyrgyzstan
Western Hemisphere: Argentina, Paraguay, Mexico, Guatemala, Costa Rica, Honduras, Nicaragua, El Salvador, and Dominican Republic
-*Mefloquine-resistant P falciparum*:
Southeast Asia: Regions of Vietnam, Laos, Thailand, Burma, and Cambodia
-*Chloroquine-resistant P vivax*:
Papua New Guinea and Indonesia

Doctor notes :

- THERE IS no place for steroid in the malaria .it makes it worse .. it prolongs the duration of coma.
- If u give diuresis to a malaria pt with pulmonary edema you could kill him ..pt is already dehydrated.
- There is no question about drug doses in the exam.

Treatment Updates

- Uncomplicated P falciparum infection:

- Artemether-lumefantrine or,
- Atovaquone-proguanil or,
- Quinine or,Mefloquine.

- Uncomplicated Plasmodium malariae, Plasmodium knowlesi, or chloroquine-sensitive P falciparum infection:

- Chloroquine phosphate or,
- Hydroxychloroquine.

- Uncomplicated P vivax or P ovale infection, expected to be chloroquine-susceptible:

- Chloroquine phosphate or,
- Hydroxychloroquine.

- Uncomplicated P vivax infection, expected to be chloroquine-resistant:

- Quinine or,
- Atovaquone-proguanil or,
- Mefloquine or,
- Amodiaquine.

Complicated Malaria

- Quinidine gluconate 10 mg/kg loading dose over 1-2h, then 1.2 mg/kg/h for at least 24h
- Once parasitemia is < 1% and patient can take oral medication, switch to quinine 650 mg PO TID to complete 3-d course (7-d course if malaria was acquired in southern Asia)
- In addition, give doxycycline 100 mg IV or PO BID for 7d.
- for pregnant women, instead of doxycycline, give clindamycin 20 mg base/kg/day PO divided TID for 7d

Chemoprophylaxis

IMP .. If you're going to the area of malaria u must take it

- Atovaquone-proguanil or,
- Chloroquine phosphate or,
- Doxycycline or,
- Mefloquine or,
- Primaquine.

Other Measures in Treating Severe Malaria

1) Antibodies against TNF - α
→they decrease fever
→but no effect on mortality & morbidity
→ reason ?:
- Effects of other cytokines as IL – 1, TNF- β
- On pathogenesis of complicated severe malaria

2) Steroids
- **Harmful** by controlled trials
- Dexamethasone longer >>duration of coma + worse outcomes than patient receiving quinine alone (NEWJ 1982, Warrel et al)

3) Reducing mosquito – human contact

4) Malaria vaccine

Additional supportive measures

· Blood Tx / Exchange Tx
· Hypoglycemia treatment and prophylaxis especially in pregnant women.
· Avoidance of IVF overload
· Dialysis
· Heparin for consumption coagulation
· Pregnant woman should receive prophylaxis
· Non-immune travellers

· *Halofantrine: Cardiotoxic (can be fatal)*
· *Artesunate:* Reported to be effective for adults with chloroquine (R) P. falciparum
→ 100 mg IV bid x 2 doses, then 50 mg IV bid x 8 doses
→ For total of 600 mg IV over 5 d

· *Success to control or eradicate malaria faced by obstacles:*
o Increasing drug resistance in P. falciparum and appearing (R) in P. vivax
o Basis of protection against infection and disease not understood.
o Biologic basis of vector capacity responsible for mosquito-borne malaria transmission is unknown.
o Increasinganopheline mosquito resistance to insecticide.

ANTI-MALARIA TREATMENT

STAGE IN CYCLE	PURPOSE OF TREATMENT	AGENTS USED
Red cell schizonts	Treats acute infection	Redcellschizonticides · *Quinine* · *Chloroquine* · *Amodiaquine* · *Mefloquine* · *Proquanil* · *Pyrimethamine* · *Suphonamides* · *Sulphones*
Hypnozoites (persistent tissue forms)	Prevents relapse	Tissue schizonticides · *Primaquine* · *Proguanil* · *Pyrimethamine* · *Dapsone*

Summary

*Malaria is a protozoal infection caused by one of four organisms:
***P.falciparum* → only infects RBCs + causes a severe disease**
***P. ovale* → Infect RBCs + infect hepatocytes resulting in relapses**
***P.vivax* →Infect RBCs + infect hepatocytes resulting in relapses**
p.malariae

*It is transmitted via mosquito bite in endemic areas.
Malaria can be suspected based on the **patient's travel history**, **symptoms**, and the **physical findings** at examination. However, for a definitive diagnosis to be made, laboratory tests must demonstrate the malaria parasites or their components.

*The first symptoms of malaria and physical findings are often not specific and are also found in other diseases.

Plasmodium* ***falciparum*,causes severe malaria with clinical findings of **confusion, coma, neurologic focal signs, severe anemia, respiratory difficulties**.

*In addition to ordering the **malaria specific diagnostic tests**, an **initial workup** and a **complete blood count** and a r**outine chemistry panel** should be done.
If someone has a positive malaria test**, the exact organism must be identifiedto know whether the patient has uncomplicated or severe "falciparum results in complications" manifestations** of the malaria infection.
Severe malaria leads to severe anemia, hypoglycemia, renal failure, hyperbilirubinemia, and acid-base disturbances.

***Malaria patients are usually dehydrated and hypoglycemic so it is very important in management to give good amount of fluids and good concentration of glucose.**

***Relapses are treated with primaquine**

*Steroids are very harmful and increase mortality in malaria patients

*There is no vaccine that has been developed yet against malaria

***Pregnant ladies are at an extreme risk of mortality due to malaria**

***Doctor said: Principles of Treatment are very IMP " I want you to remember them" + he also said, "Remember hypoglycemia and those who are pregnant"**

Questions

1-Black water fever is a special manifestation of malaria caused by;
a. P. falciparum
b. P. malariae
c. P. ovale
d. P. vivax

2-Which of the following statement(s) regarding Plasmodium falciparum are true?
a. causes more severe disease in pregnancy
b. is associated with recurrent relapses after initial treatment because of liver hypnozoites
c. is the only malarial parasite causing greater than 20% parasitaemia
d. infection is typically associated with thrombocytopaenia
e. is the only cause of cerebral malaria

3-Symptoms of malaria like fever, chills and sweating are seen when the parasite enters the liver.

a. True
b. False

4-patient with malaria may suffer jaundice

a. True
b. False

5-Relapses of malaria are common following treatment of
a. Plasmodium vivax malaria
b. Plasmodium falciparum malaria
c. Both of the above
d. None of the above

6- *P vivax* infection treated adequately with chloroquine will not show relapses.

a. True
b. False

1-A

2-E

3-B →the malaria parasite initially enters the liver, where it multiplies. The parasites are then released into the circulation and enter red blood cells, where they proliferate and cause the blood cells to rupture. Symptoms coincide with the rupture of the red blood cells and include fever, chills and sweating)

4-A→Jaundice may be present in a patient with malaria. It could be due to rupture of the red blood cells, inflammation of the liver caused by the parasite, or as a consequence of using anti-malarial medication.

5-A → Relapses of malaria may occur following malaria with *Plasmodium vivax* or *Plasmodium ovale*. Relapses occur due to the presence of dormant forms of the parasite in the liver. That is why you should eradicate the organism completely by treating the patient with primaquine

6-B →Chloroquine acts against the parasites in the blood and treats the malarial attack. The dormant forms of *P vivax* from the liver can be eliminated with a complete course of primaquine.