MALARIA & TRAVEL MEDICINE

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EDUCATIONAL OBJECTIVES

At the end of this lecture students are expected to know:

- Epidemiology & Etiology
- Clinical presentation
- Risk to travelers
- Malaria and pregnancy
- Diagnostic work up
- Treatment & prophylaxis

ETIOLOGY

4 plasmodia:

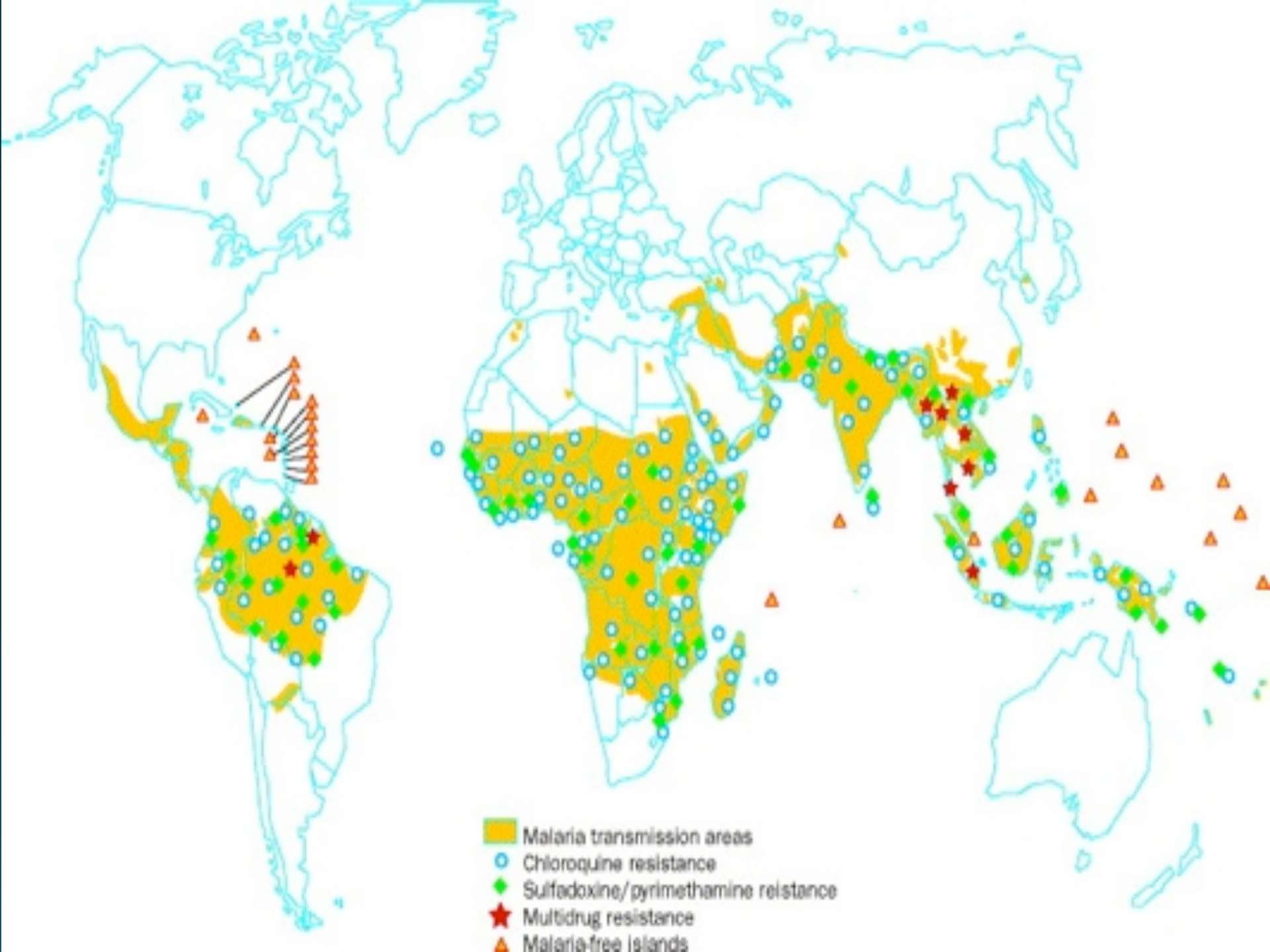
- P. Falciparum
- P. Vivax
- P. Ovale
- P. Malariae

EPIDEMIOLOGY

- Endemic disease
- Usually does not occur at altitudes – 1500 m
- World wide ease of travel
- Most important parasitic disease of humans
- Transmitted in over 100 countries
- Affecting more than 3 billion people world wide
- Causing 1-2 billion deaths per year


Atlantic Ocean
Pacific Ocean
Indian Ocean
Russia
UK
Germany
Poland
Belarus
Ukraine
France
Italy
Romania
Bulgaria
Azerbaijan
Armenia
Georgia
Kazakhstan
Mongolia
Uzbekistan
Kyrgyzstan
Tajikistan
Turkmenistan
Portugal
Spain
Turkey
Greece
Cyprus
Syria
Iraq
Iran
Afghanistan
Pakistan
China
North Korea
South Korea
Japan
Nepal
Bhutan
Bahrain
Kuwait
Qatar
UAE
Saudi Arabia
Oman
Yemen
India
Burma
Taiwan
Laos
Macau SAR (China)
Thailand
Vietnam
Philippines
Cambodia
Brunei
Malaysia
Singapore
Sri Lanka
Bangladesh
Tunisia
Morocco
Algeria
Libya
Egypt
Western Sahara
Senegal
Cape Verde
The Gambia
Guinea-Bissau
Guinea
Sierra Leone
Liberia
Côte d'Ivoire
Ghana
Togo
Benin
Burkina Faso
Mauritania
Mali
Niger
Nigeria
Chad
Eritrea
Sudan
Djibouti
Ethiopia
Somalia
Central African Republic
Cameroon
Equatorial Guinea
Gabon
Republic of the Congo
Democratic Republic of the Congo
Uganda
Kenya
Rwanda
Burundi
Tanzania
Malawi
Angola
Zambia
Zimbabwe
Mozambique
Namibia
Botswana
Madagascar
Swaziland
South Africa
Lesotho
Papua New Guinea
Indonesia
Timor-Leste
Australia
Malaysia
Singapore
Indonesia
China
Macau SAR (China)
Malaria-endemic countries
Malaria endemic
Not malaria endemic


United States
Bermuda
Atlantic Ocean
The Bahamas
Mexico
Cuba
Dominican Republic
Jamaica
Belize
Haiti
Honduras
Guatemala
El Salvador
Panama
Guyana
Nicaragua
Venezuela
French Guiana
Costa Rica
Colombia
Suriname
Ecuador
Brazil
Peru
Pacific Ocean
Bolivia
Paraguay
Argentina
Chile
Uruguay
Malaria-Endemic Countries
Malaria Endemic
Not Malaria Endemic


Malaria transmission areas
Chloroquine resistance
Sulfadoxine/pyrimethamine reistance
Multidrug resistance
Malaria-free islands

PATHOGENESIS

- P.F. invades RBC at all ages
- P. Mal: only old RBC
- P. ovale and P. vivax invade young RBC's.
- Microvascular pathology: secondary Ischemia Adherence of
- Non-deformable parasitezed RBC to endothelium
- Renal failure: *hemalysis, Ischemia secondary microvascular pathology*
- Deep Coma: *hypoglycemia, microvascular adherent parasitized RBC*
- Pulmonary edema; *2 o: Capillary leak Synd (without C.C.F.)*
- Immune complex Neph. Syndrome 2 o P. Malariae

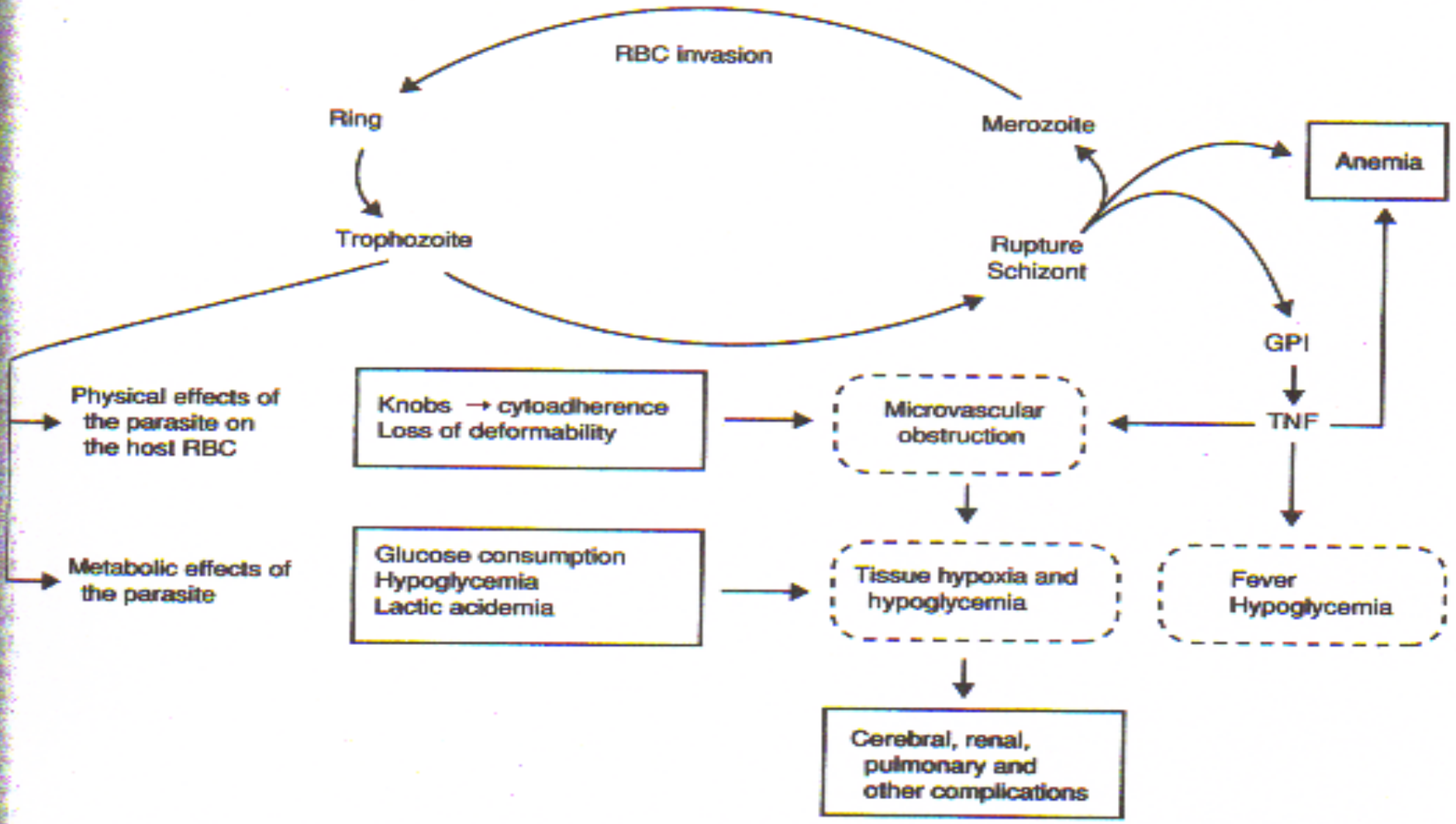


FIG. 4. Pathogenesis of severe, complicated, and cerebral *P. falciparum* malaria. *Plasmodium falciparum* malaria is a microvascular disease with a strong metabolic component. It is a microvascular disease because cytoadherence of *P. falciparum*-infected RBCs to endothelial cells in capillaries and postcapillary venules,[8–10] plus the nondeformable nature of those cells[27,40] 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]

CLINICAL FEATURES

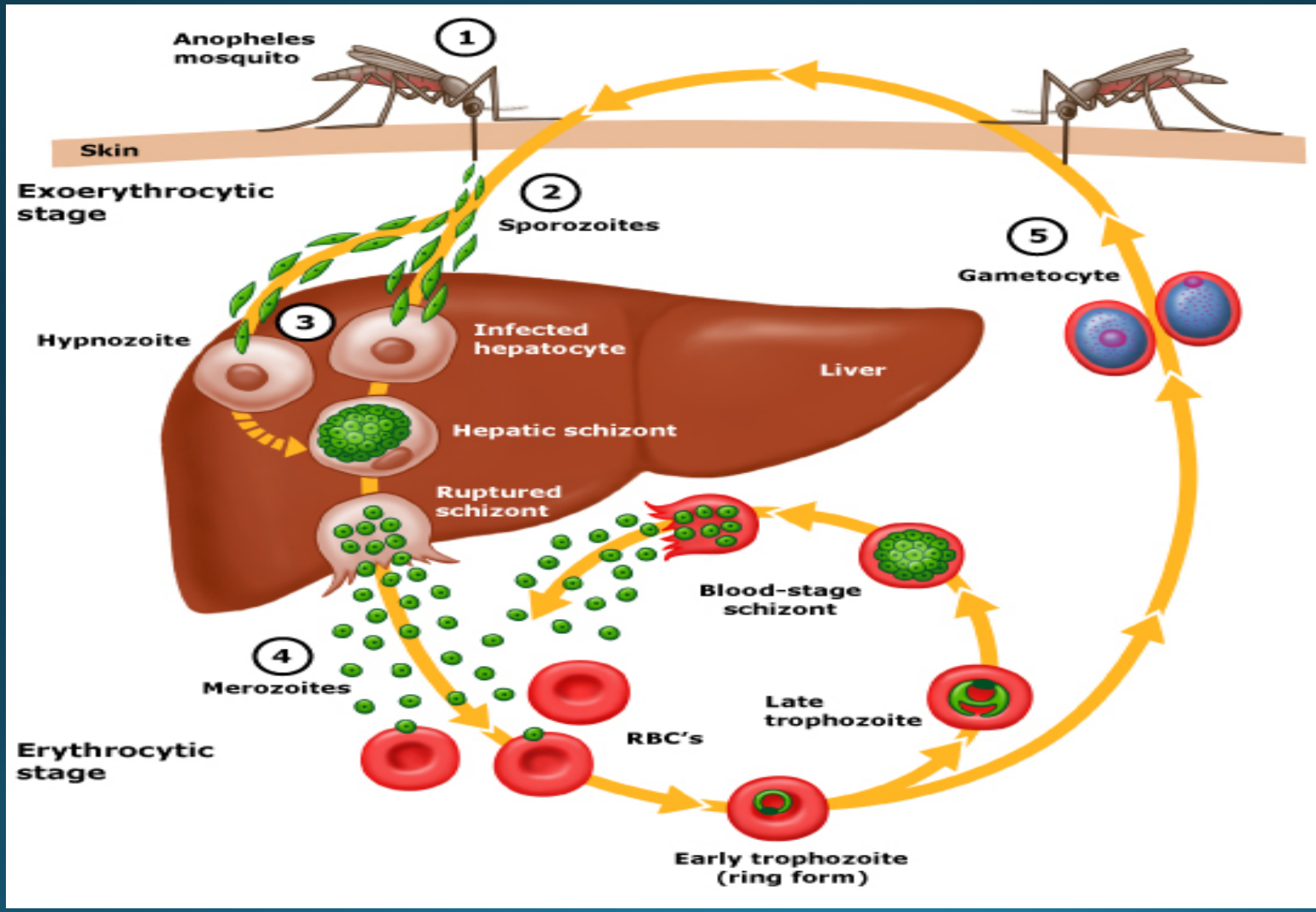
CF vary with:

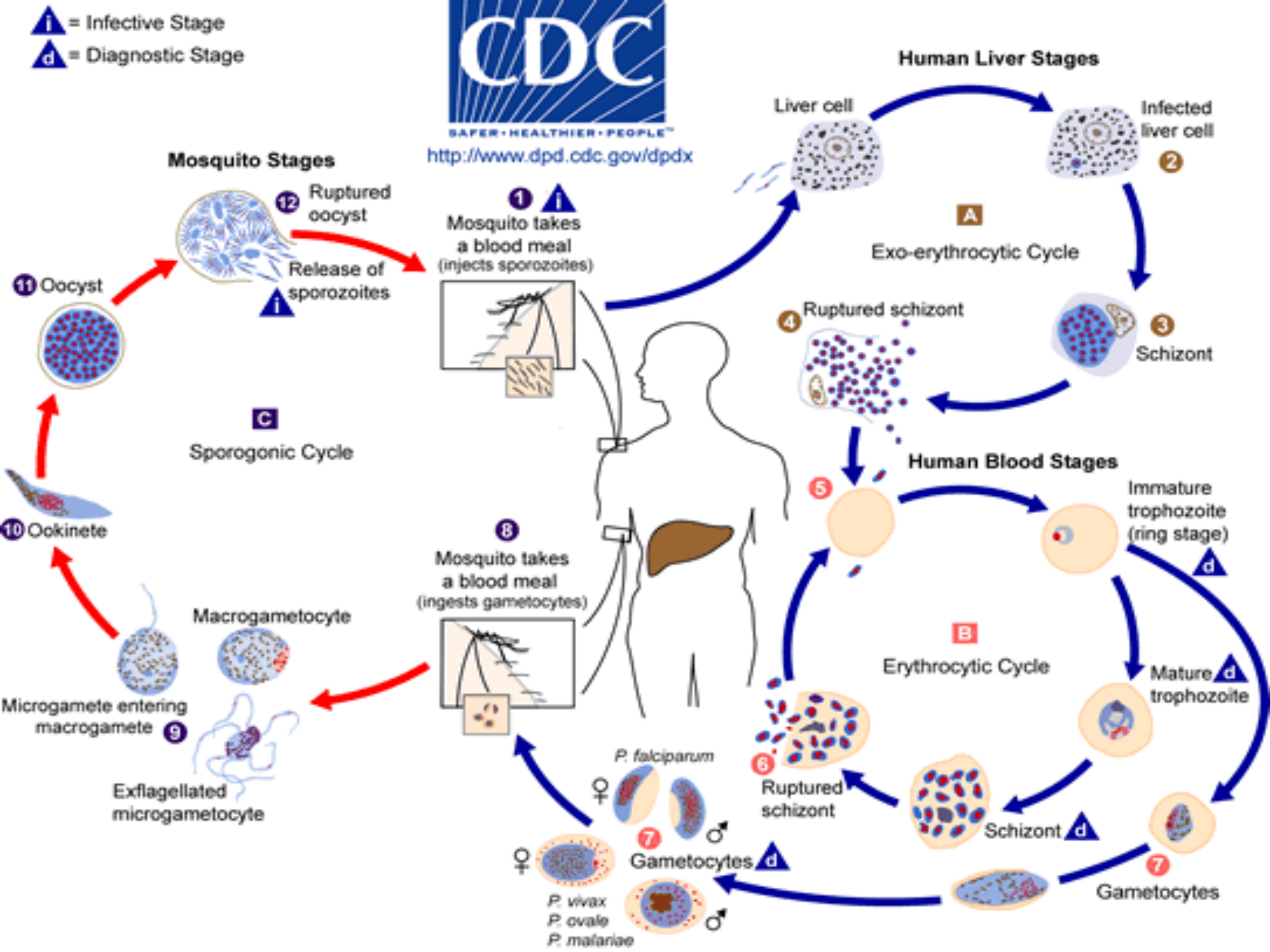
- Geography
- Epidemiology
- Age
- High risk includes
  - Children
  - Pregnant women
  - Non-immune travelers to malarious areas

INCUBATION PERIOD

- Sporozoites reach the liver within 1-2 hours following female Anopheles mosquito bite.
- Pt. asymptomatic for 12-35 days until RBCs stage of parasite life cycle.

LIFE CYCLE


Anopheles mosquito
1
Skin
Exoerythrocytic stage
2
Sporozoites
5
Gametocyte
Hypnozoite
3
Infected hepatocyte
Liver
Hepatic schizont
Ruptured schizont
Blood-stage schizont
4
Merozoites
Late trophozoite
RBC's
Erythrocytic stage
Early trophozoite (ring form)


i = Infective Stage
d = Diagnostic Stage
CDC
SAFER · HEALTHIER · PEOPLE™
http://www.dpd.cdc.gov/dpdx
Human Liver Stages
Liver cell
Infected liver cell
2
A
Exo-erythrocytic Cycle
4 Ruptured schizont
3 Schizont
Human Blood Stages
5
Immature trophozoite (ring stage)
d
Mature trophozoite
d
B
Erythrocytic Cycle
6 Ruptured schizont
Schizont
d
7 Gametocytes
d
Gametocytes
P. falciparum
P. vivax
P. ovale
P. malariae
8 Mosquito takes a blood meal (ingests gametocytes)
Macrogametocyte
Microgamete entering macrogamete
9
Exflagellated microgametocyte
10 Ookinete
11 Oocyst
12 Ruptured oocyst
Release of sporozoites
i
Mosquito Stages
1 i
Mosquito takes a blood meal (injects sporozoites)
C
Sporogonic Cycle

CLINICAL FEATURES

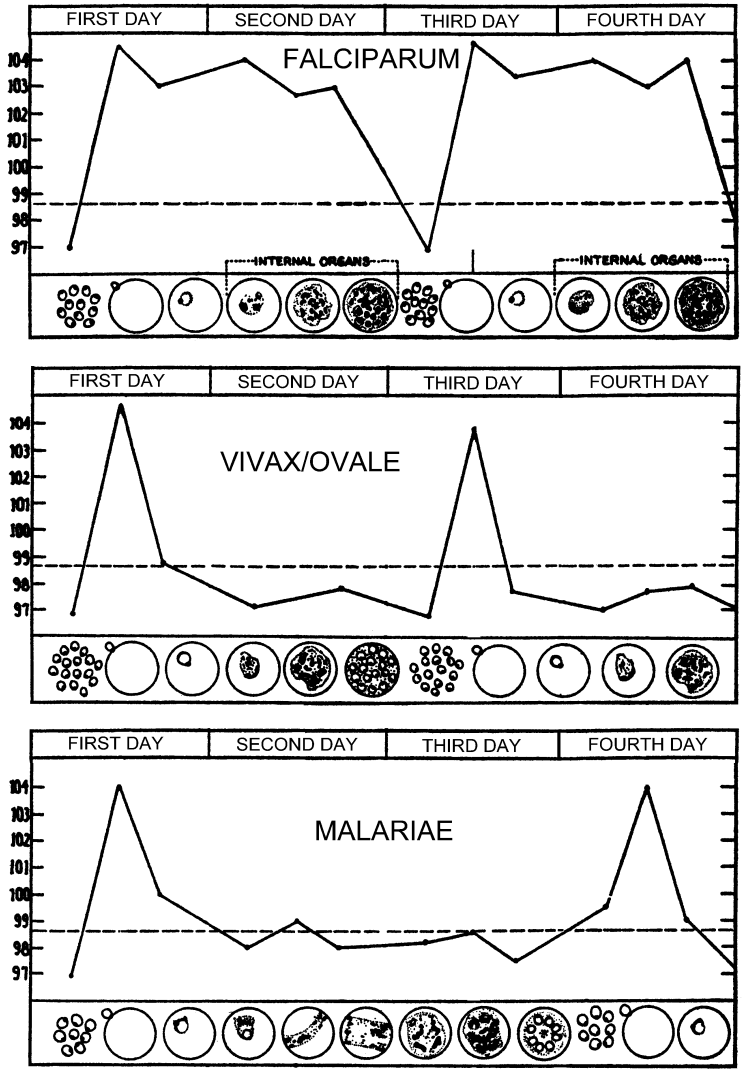
1) **Major**

- Recurring fevers
- Chills (Assoc. RBC lysis – *mature zchisonts)*

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 Paroxysm

- paroxysms associated with synchrony of merozoite release
- between paroxysms temperature is normal and patient feels well
- falciparum may not exhibit classic paroxysms (continuous fever)

tertian malaria
quartan malaria

CLINICAL FEATURES

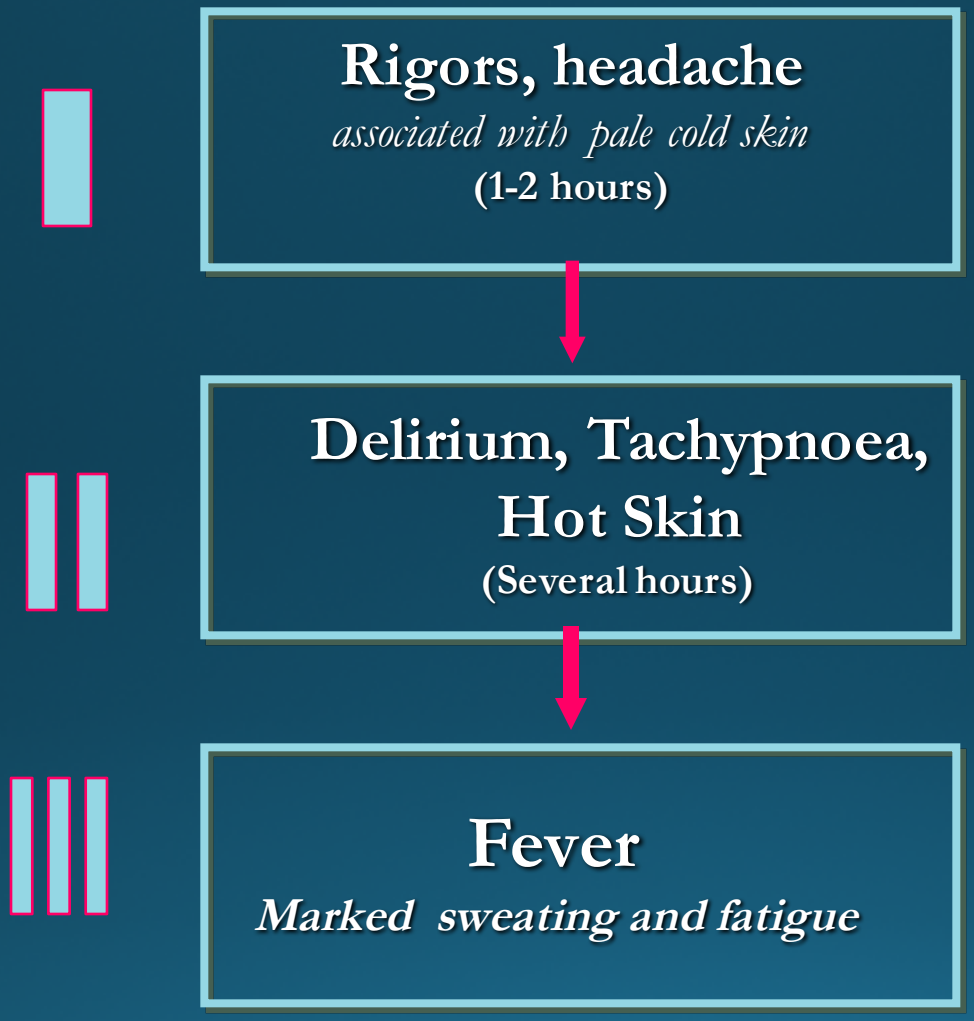
1) Severe P.F. (≥ 10 parasite/ mcl): AC Complications

- Renal failure
- Coma 2 o: hypoglc; TNF, or microvascular pathology
- Pul. Edema
- Thombrocytopenia
- G. Enteritis – *especially diarrhea*
- Ch. P. Falcuparum infection

•Splenomegaly – typically resolves after treatment with anti-malarial meds. 6-12 mon.

- P. Malariae assoc. Immune compl. N. Synd.
- P. Vivax – late splenic rupture with trauma 1-3 mon. after initial infection

MALARIA FEVER PAROXYSMS



Patient often symptoms free between paroxysms

DIAGNOSIS

- Detailed targeted history including travel hx and clinical examination together with:

- High Index of Suspicion (HIS)

DX: Blood film stained with

- Giemsa stain or wright's stain
- Correct identification of malarial Spp is essential for treatment because of P. Falciparum R to Chloroquine&others
- On Giemsa stain – Cytoplasm: light blue, nucleus: dark blue
- In P.F

  (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

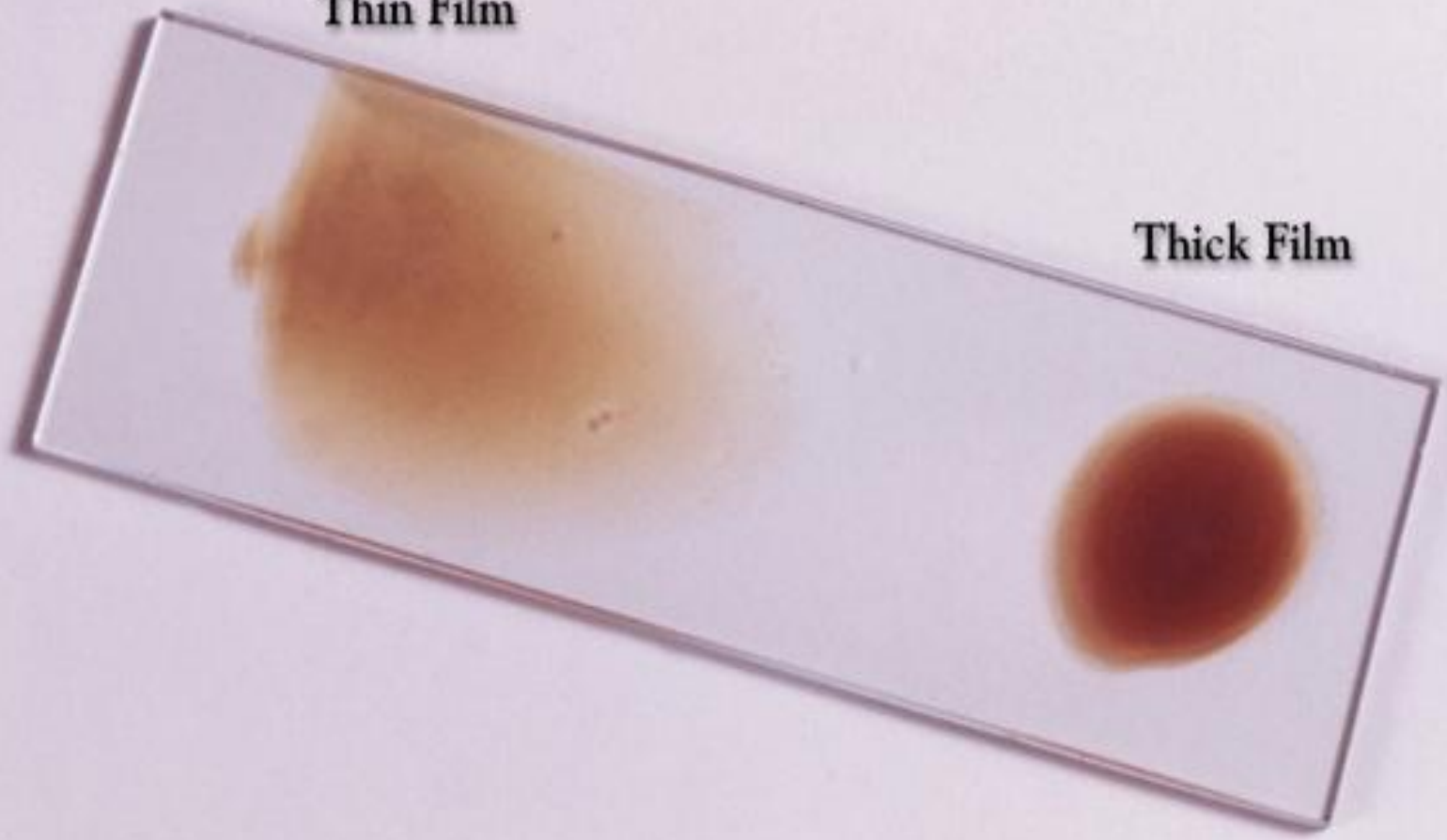
  DDX: P.F. vs P. Vivax, because

  (a) P. Ovale – Vivax – clinical, morphological

  (b) P. malariae - ch. Infeciton

Blood Films

(for microscopic analysis)



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

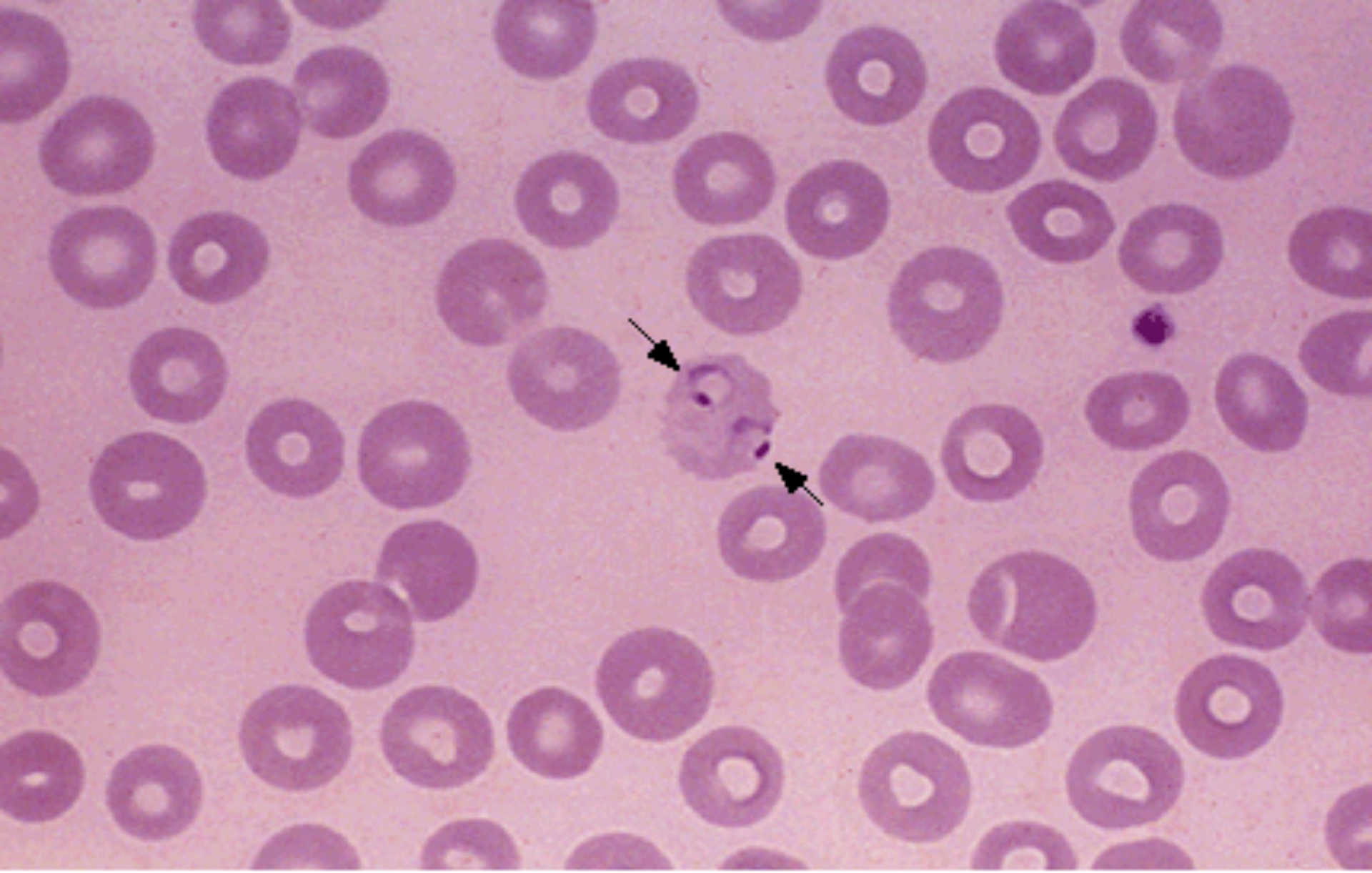
Infection with more than one parasite spp: 5-7%

Thick Blood Film (RBC lysed)

- You may examine 10X. Blood more than in thin film
- More diagnostic in lower degree of parasitemias

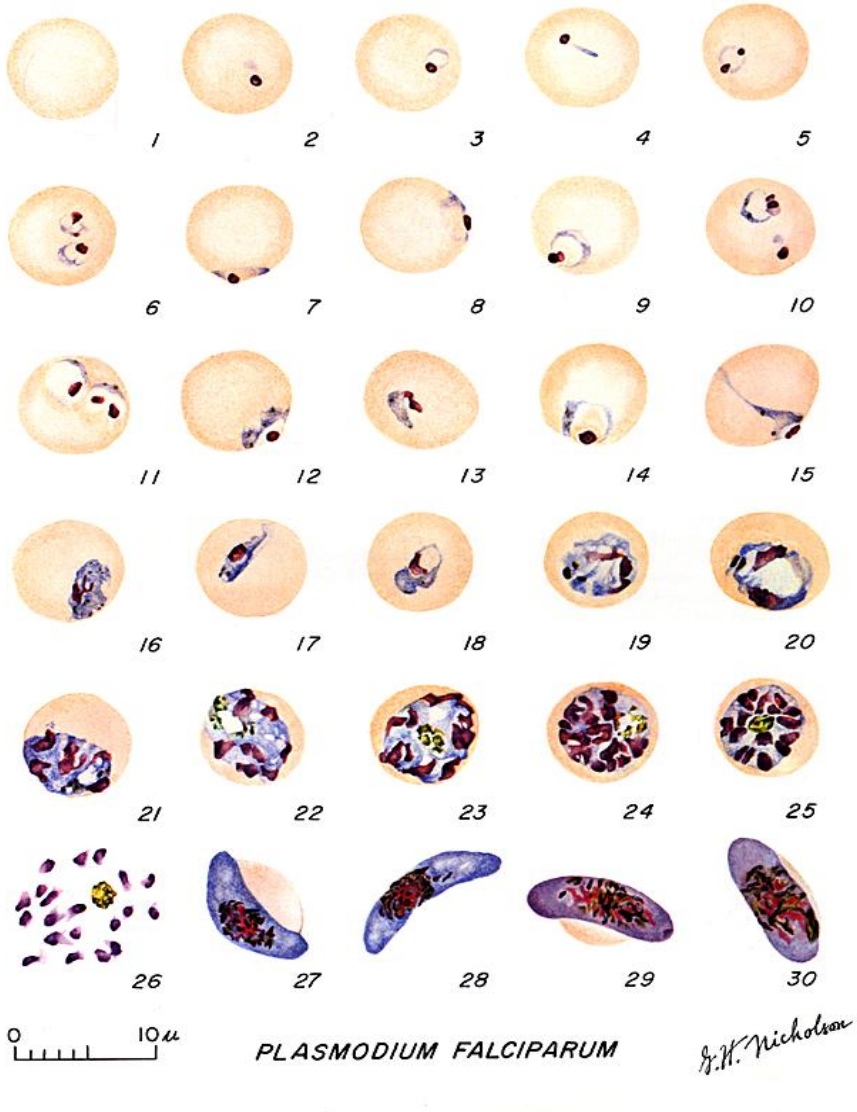
Serology: not useful in managing acutely ill patient

DNA probe: similar thick film sensitivity



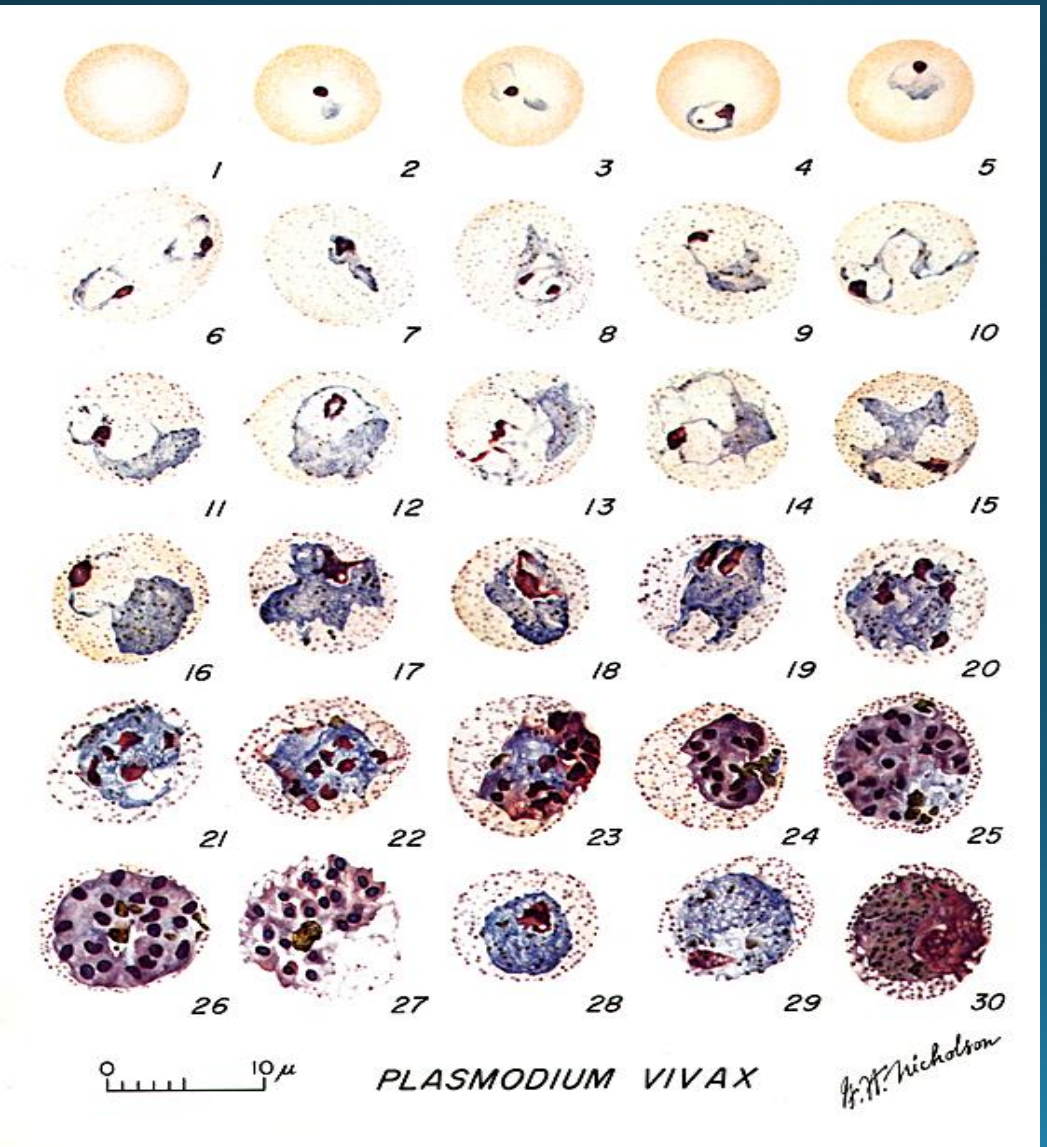
Malaria Peripheral smear from a patient with malaria shows intraerythrocytic ring forms (trophozoites) (arrows). Courtesy of Carola von Kapff, SH (ASCP).

Plasmodium falciparum: Blood Stage Parasites Thin Blood Smears



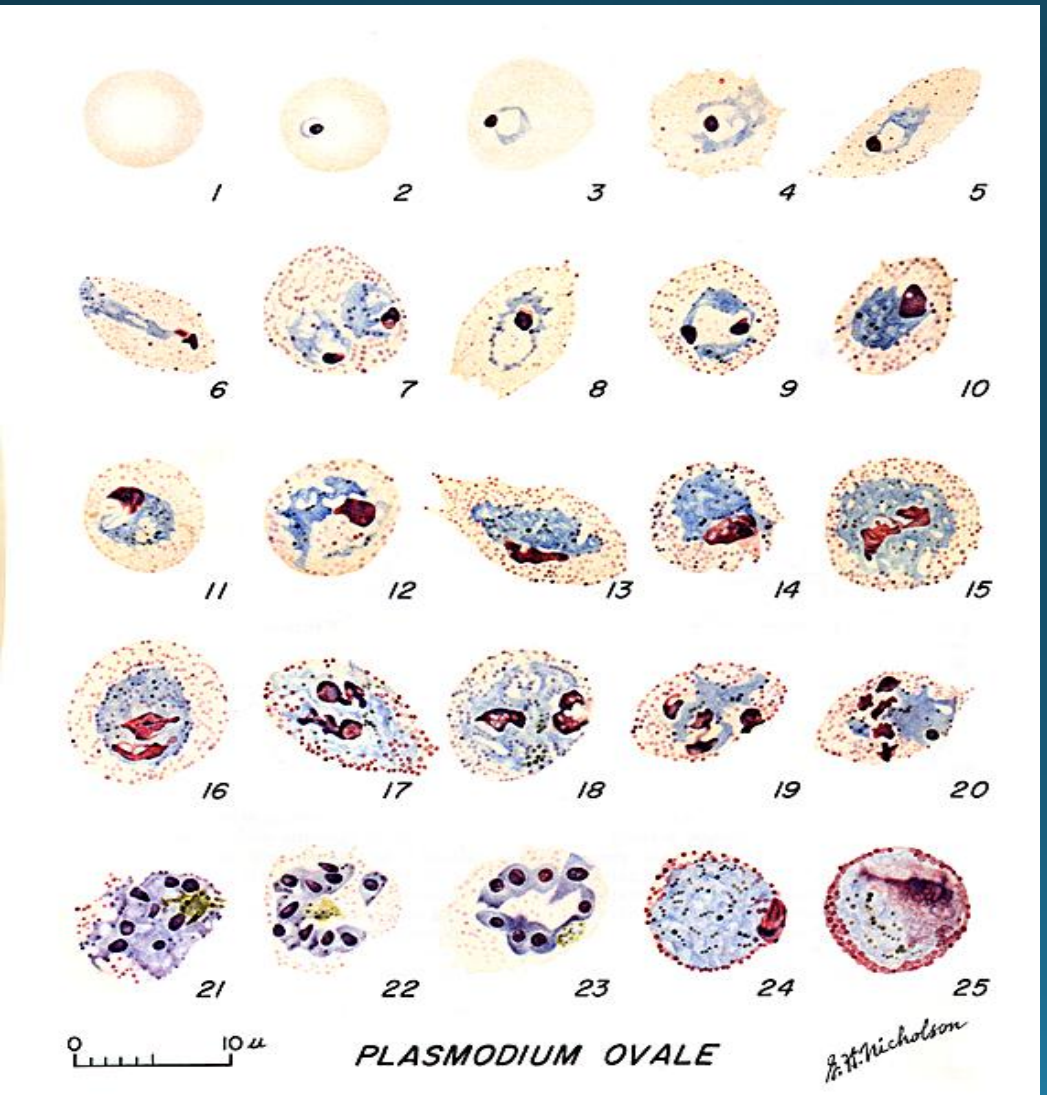
- 1: Normal red cell
- 2-18: Trophozoites
  (2-10: ring-stage trophozoites)
- 19-26: Schizonts (26 is a ruptured schizont)
- 27, 28: Mature macrogametocytes (female)
- 29, 30: Mature microgametocytes (male)

Plasmodium vivax: Blood Stage Parasites Thin Blood Smears



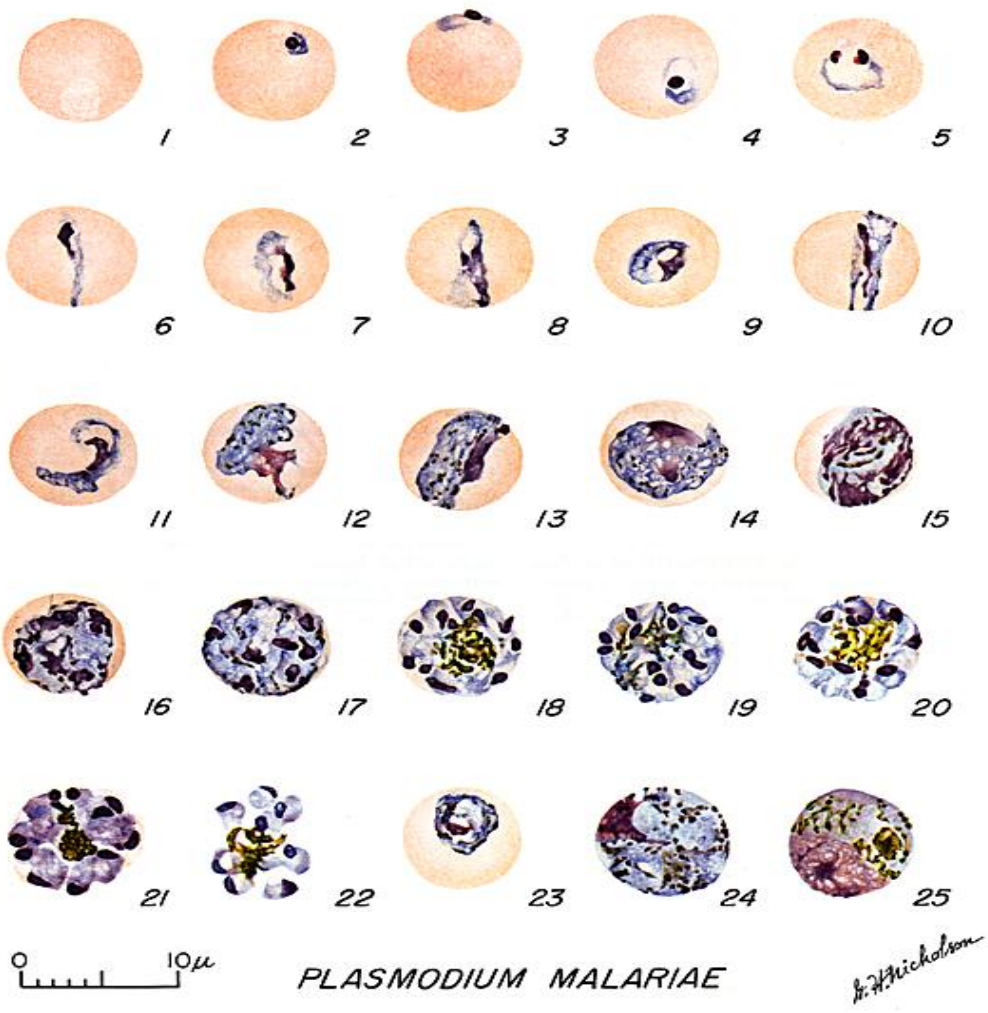
1: Normal red cell
2-6: Young trophozoites (ring stage parasites)
7-18: Trophozoites
19-27: Schizonts
28,29: Macrogametocytes (female)
30: Microgametocyte (male)

Plasmodium ovale: Blood Stage Parasites
Thin Blood Smears



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



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

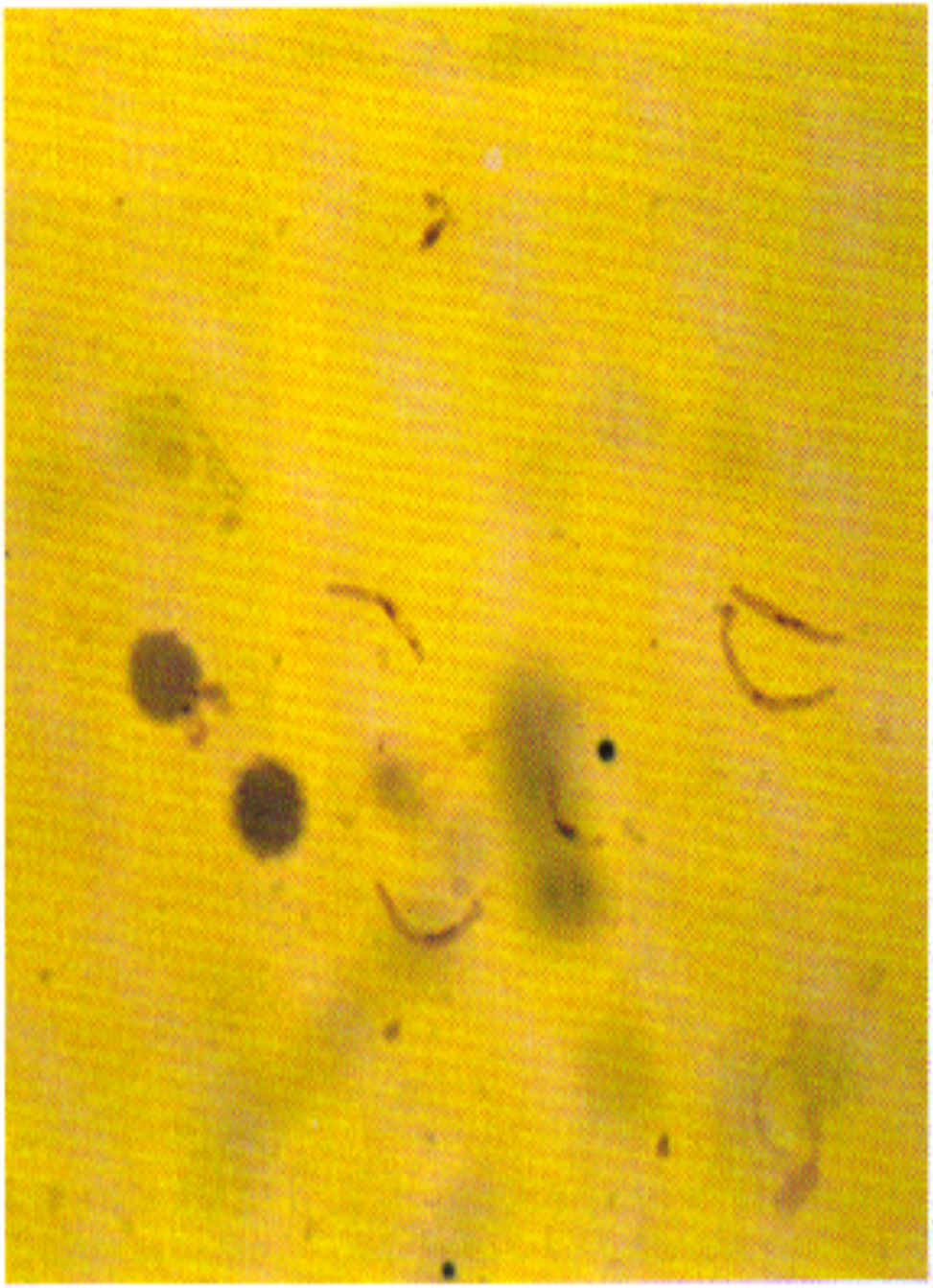


Fig. 13.20 Sporozoites, from an infected mosquito.

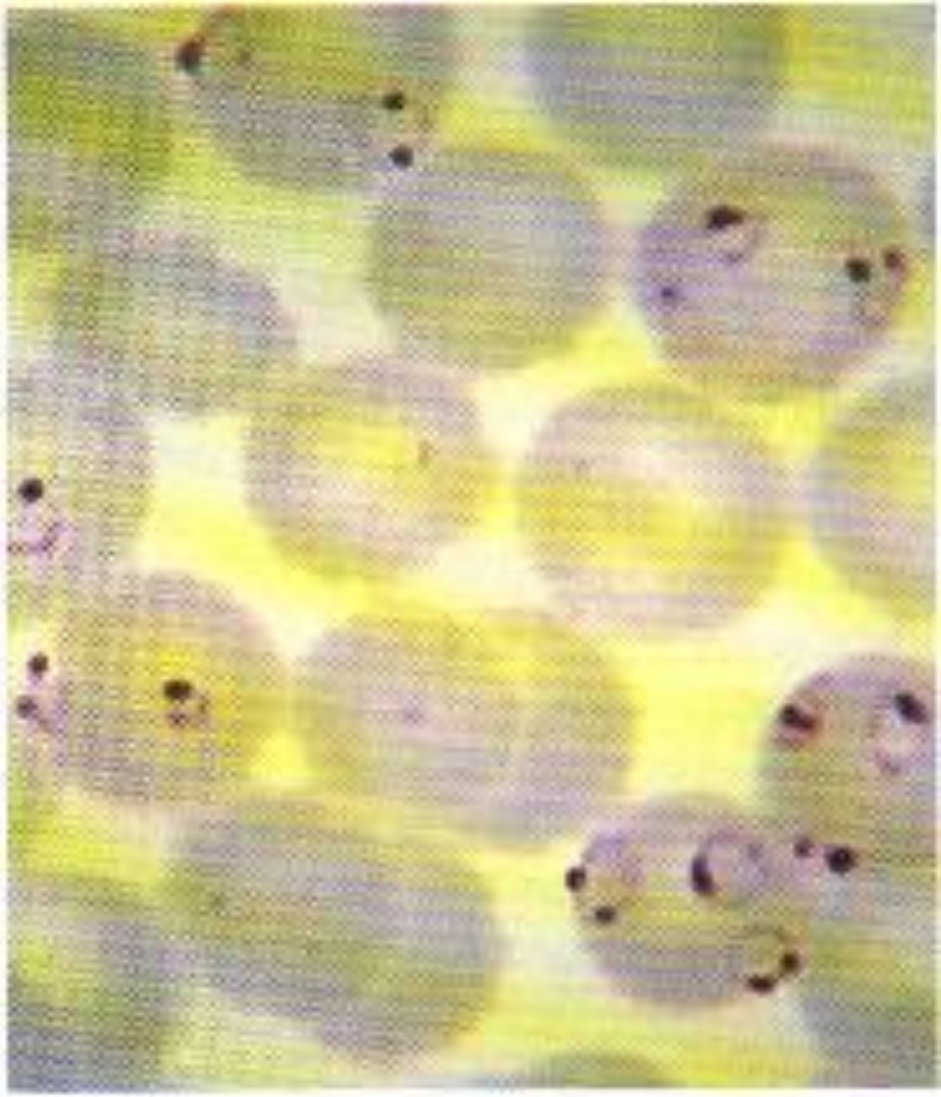


Fig. 13.21 Malaria. Thin blood film showing trophozoites (ring forms) of P. falciparum. Note two parasites within the same red cell and double chromatin knobs. Giemsa stain. By courtesy of Department of Tropical Medicine, Mahidol University, Bangkok.

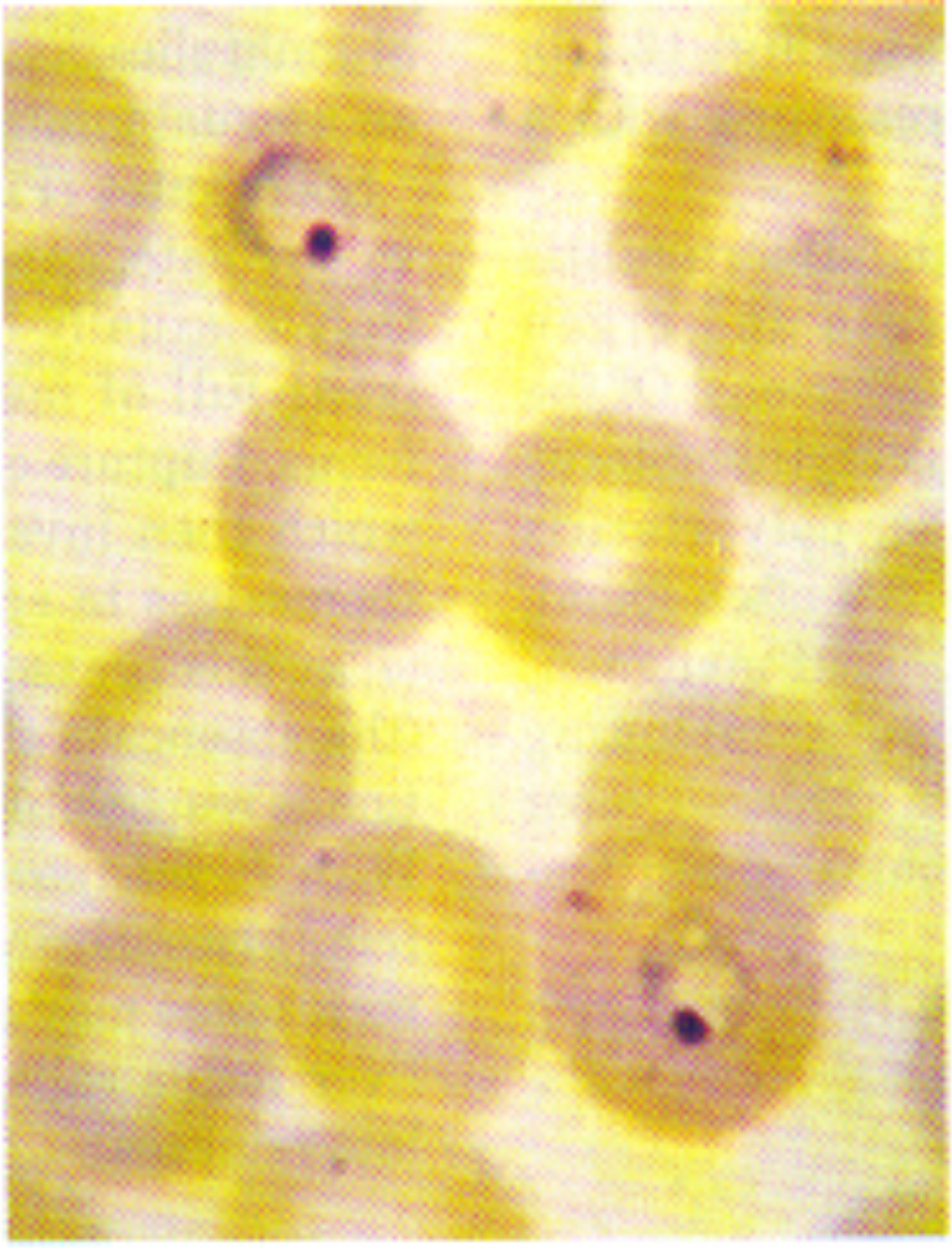


Fig. 13.22 Malaria. Thin blood film showing early trophozoite (ring form) of P. vivax. See fig 13.21 for source.

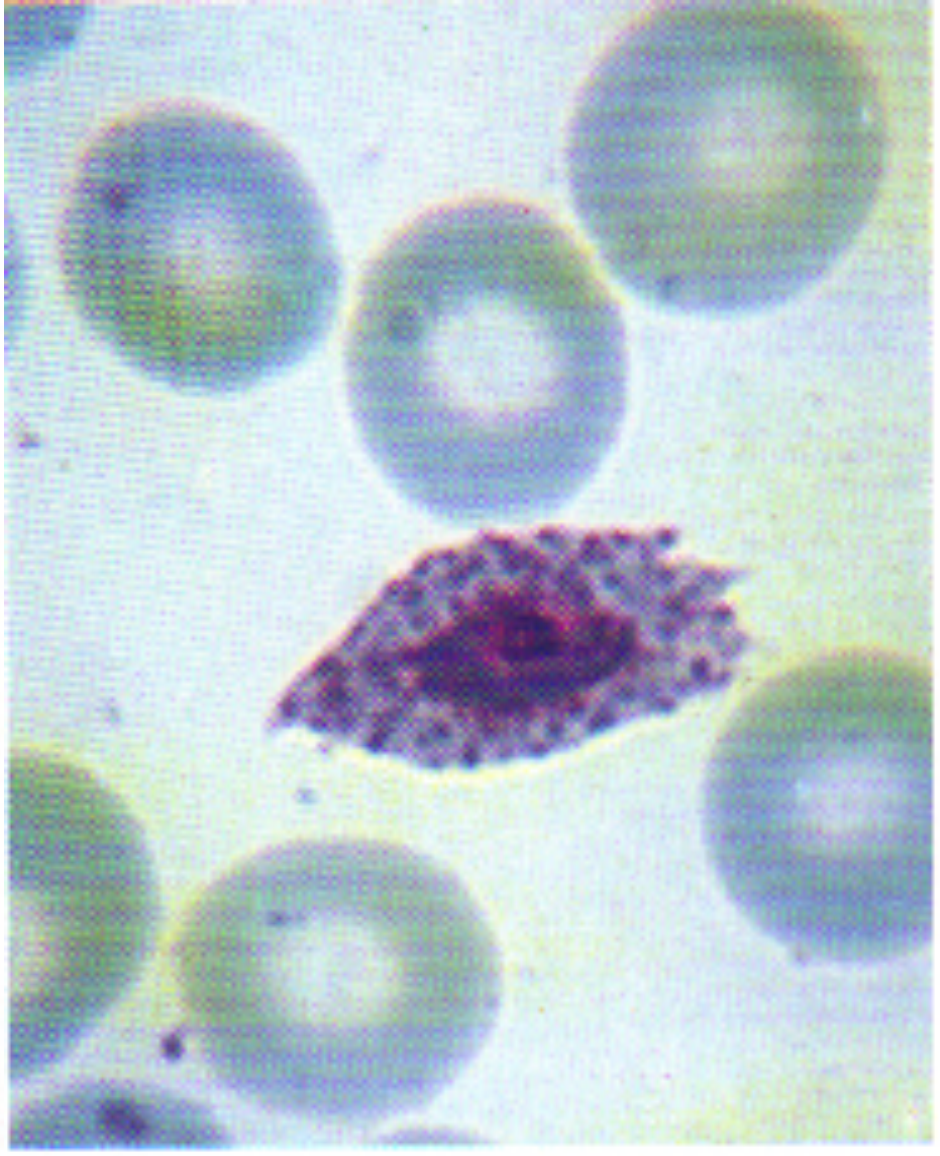


Fig. 13.24 Malaria. Thin blood film showing trophozoite of P. ovale. Note pronounced stippling of red cell and coarse pigment within parasite. Giemsa stain. See fig 13.21 for source.

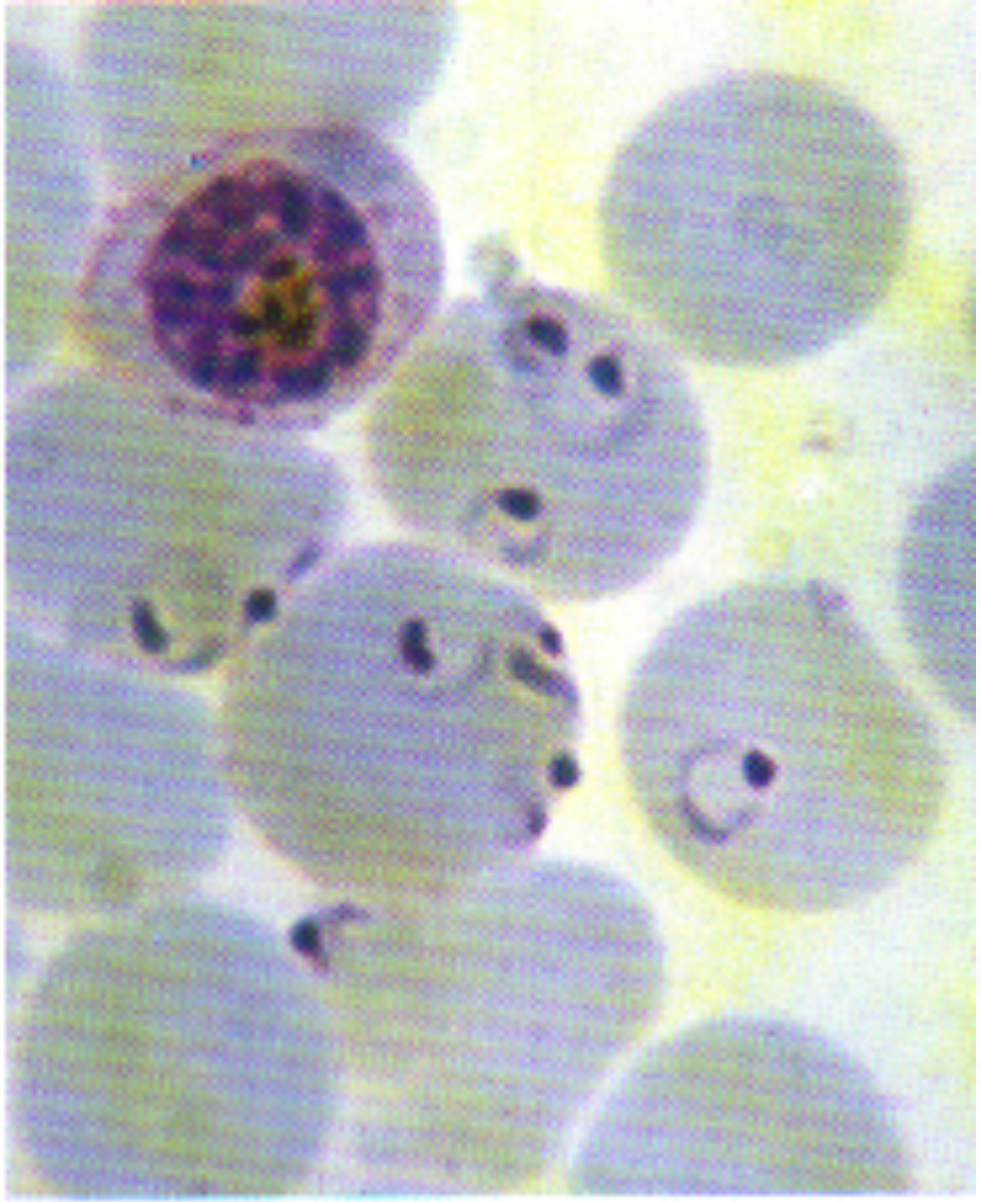


Fig. 13.25 Malaria. Thin blood film showing several ring forms and a schizont of *P. falciparum*. This is only seen in severe cases. Giemsa stain. See fig 13.21 for source.

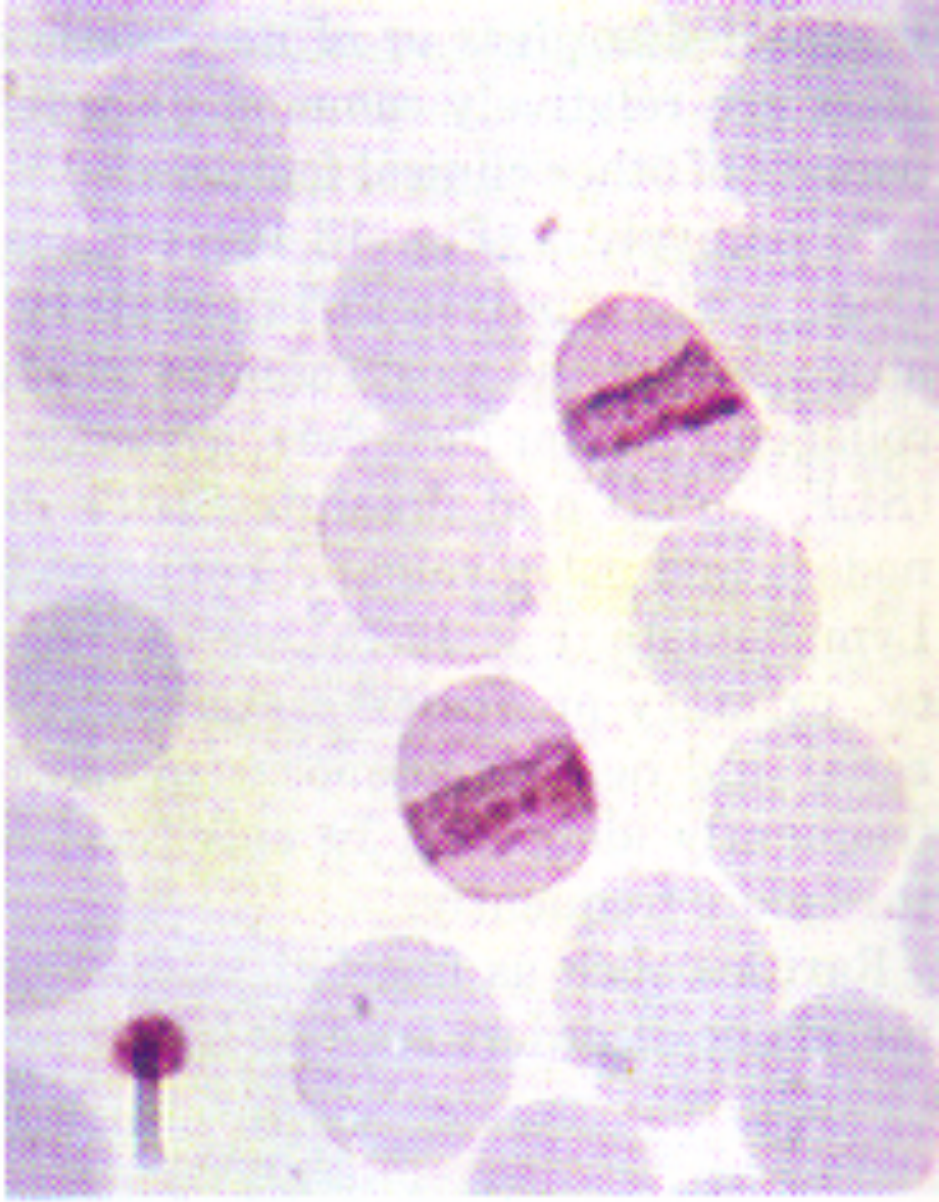


Fig. 13.23 Malaria. Thin blood film showing band forms (trophozoites) of *P. malariae*. This is a characteristic feature of *P. malariae*. Giemsa stain. See fig 13.21 for source.

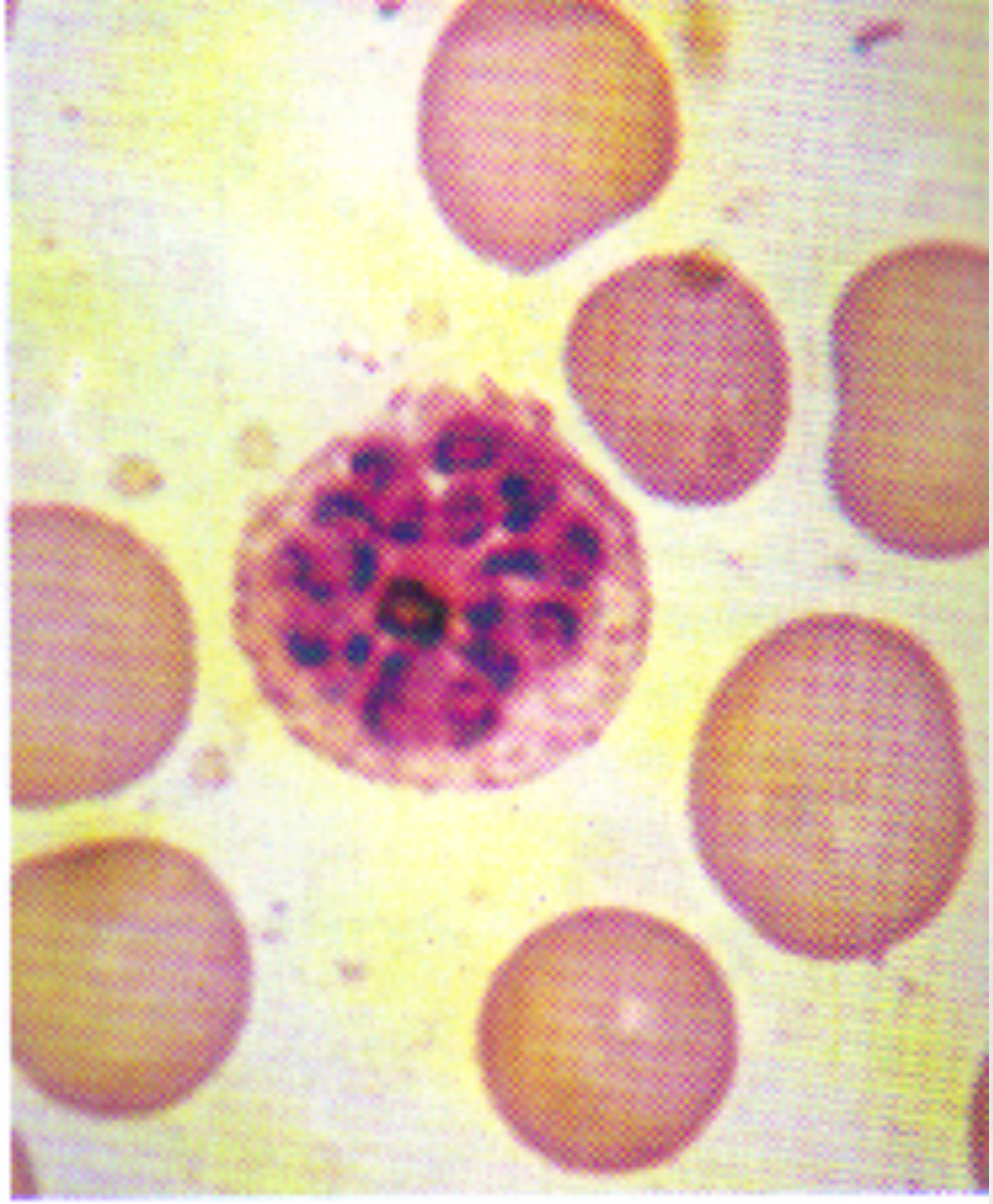


Fig. 13.26 Malaria. Thin blood film showing fully developed schizont of *P. vivax* with merozoites ready to burst out. Giemsa stain. See fig 13.21 for source.

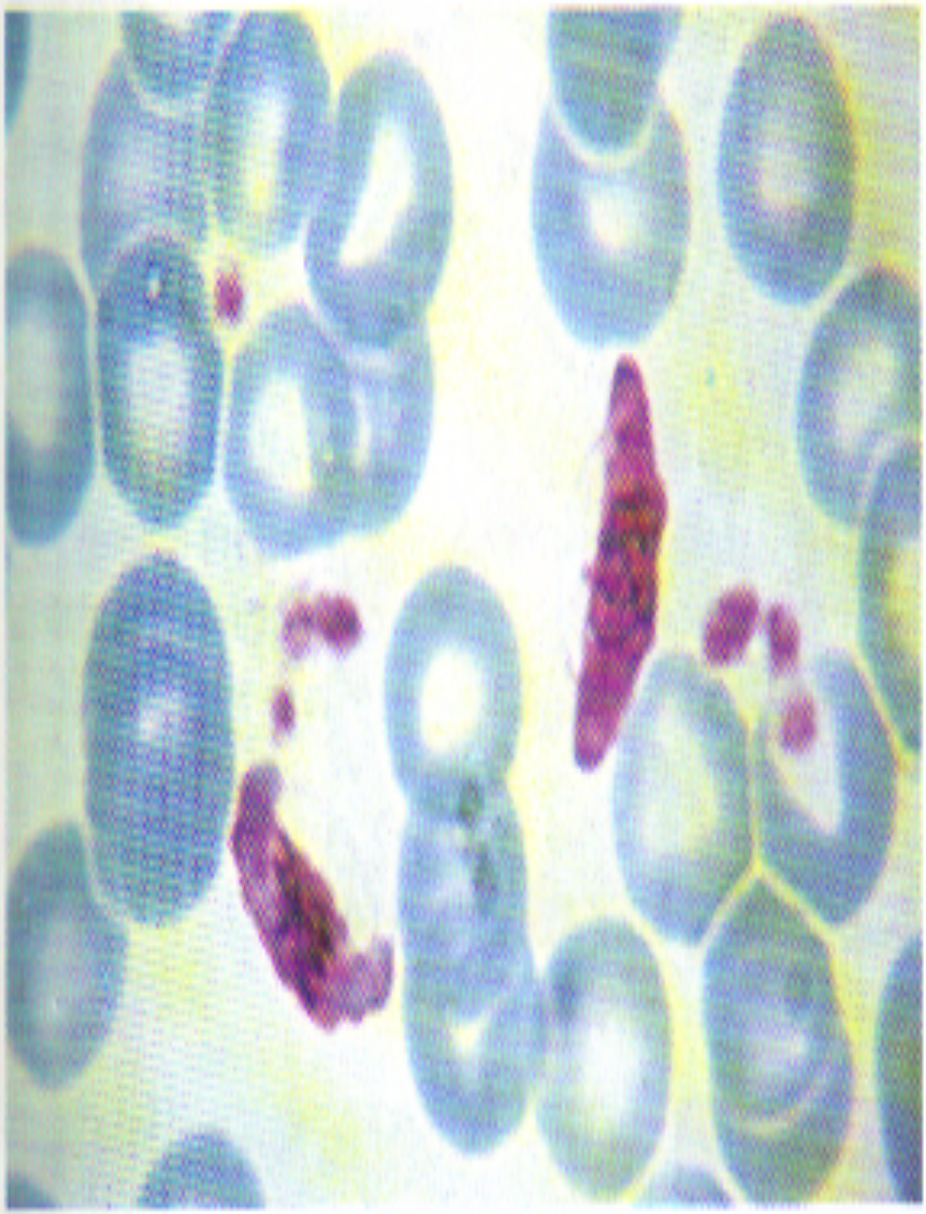


Fig. 13.27 Malaria. Thin blood film showing banana-shaped gametocyte of *P. falciparum*. Note the central mass of pigment. Giemsa stain. See fig 13.21 for source.

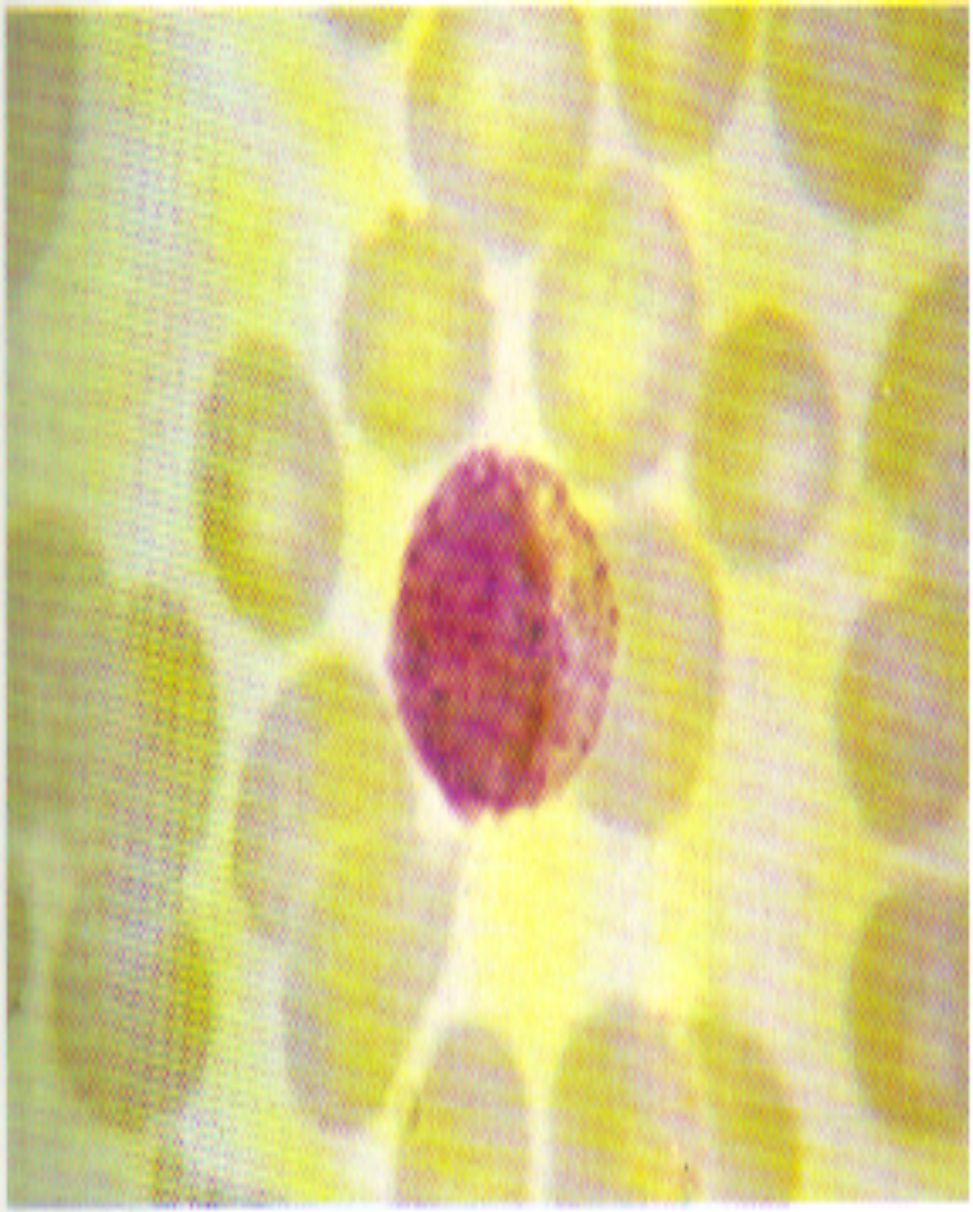


Fig. 13.28 Malaria. Thin blood film showing gametocyte of *P. vivax* with stippling (Schüffner's dots) in the cytoplasm. Giemsa stain. See fig 13.21 for source.

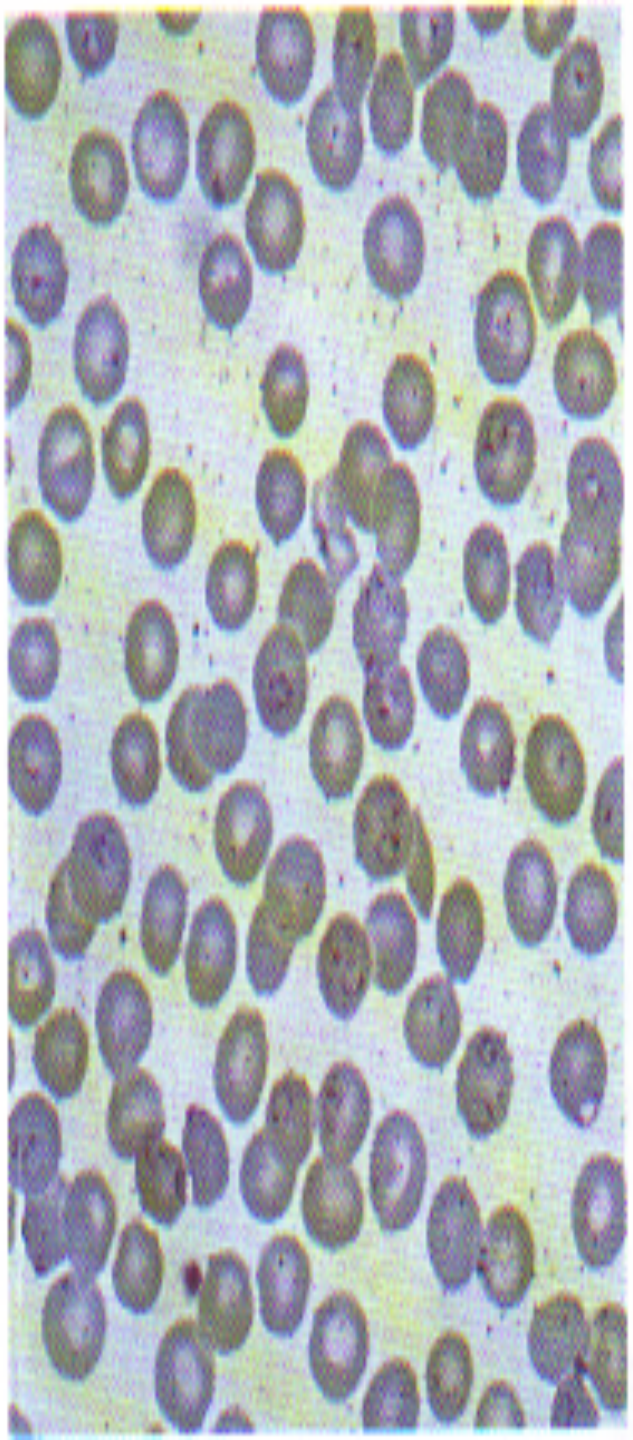


Fig. 13.31 Malaria. Very heavy parasitaemia in a patient with severe *P. falciparum* infection. Despite chemotherapy and exchange transfusion the patient died of cerebral malaria.

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

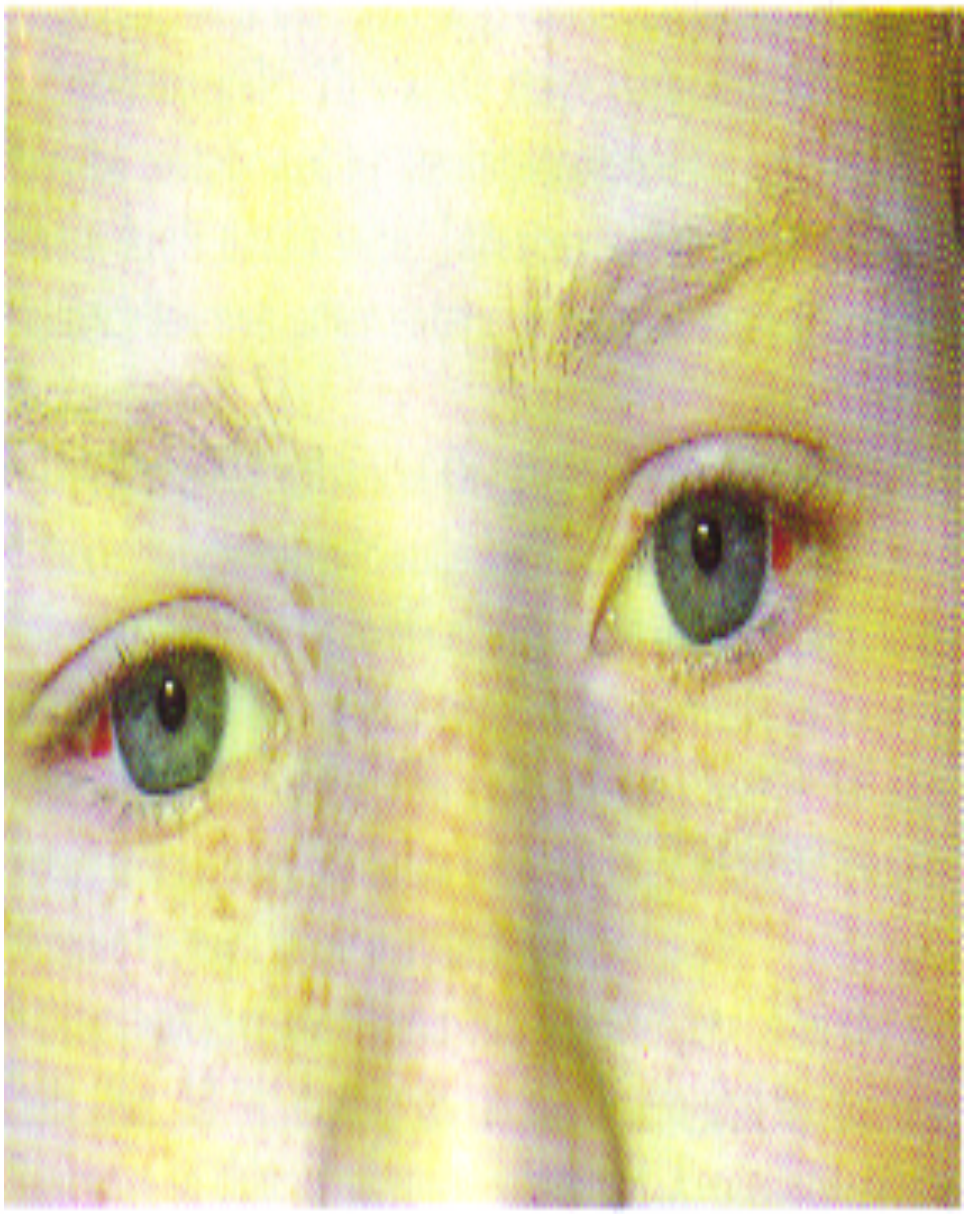


Fig. 13.29 Malaria. Child with mild jaundice, pallor and bilateral conjunctival haemorrhages associated with *P. falciparum* infection.

DIFFERENTIAL DIAGNOSIS OF MALARIA IN ACUTELY III 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 later 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.

MALARIA 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 Tropica Apr 1994)

RISK FACTORS FOR POOR PROGNOSIS IN CEREBRAL MALARIA

- Creatinine ↑
- Bilirubin ↑
- Lactates ↑

MALARIA COMPLICATIONS

Major clinical features of malaria are those of the complications.

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

MALARIA COMPLICATIONS

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

* Anemia: presents in most severe infections and parallels parasitaemia

- Hemolysis of infected RBC
- Delayed retics. release from BM
- Immune – mediated hemolysis of non-infected RBC

MALARIA COMPLICATIONS

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

Non-immune: (primary infection)

- Haemoglobinuria
- Black water fever
- Exaggerated haemolytic response to quinine – sensitized RBC

MALARIA COMPLICATIONS

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

Mild unconjugated jaundice common, and parallels hemolysis. Hepatocellular dysfunction may contribute to jaundice.

MALARIA COMPLICATIONS

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

Tissue hypoxia related complications

Hypoxia results from altered microcirculation + anemia.

Maturation of erythyrocyte schizonts in 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

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
→ Consumption coagulopathy

Shock: Endotoxemia

Diarrhea

Hyponatremia (? SIADH)

LATE COMPLICATION

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

MALARIA & PREGNANCY

- → Mortality
- → Anemia, hypoglycemia, pulmonary edema: > common
- → Abortion
- → Stillbirth
- → Premature delivery high infant mortality
- → LB wt.
- → Placental insufficiency
- → High parasitaemia - ? placenta favorable site for P. falciparum.

CONGENITAL MALARIA

- Transplacental infection
  - Can be all 4 species
  - Commonly *P.v.* and *P.f.* in endemic areas
  - *P.m.* infections in nonendemic 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**
- **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 as *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

-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

TREATMENT

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

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

World Health Organization

وزارة الصحة
Ministry of Health

Kingdom of Saudi Arabia
Ministry of Health
Public Health Agency
Infectious Diseases Control General Directorate
Malaria Department

The national policy of malaria case management in The Kingdom of Saudi Arabia

1. Treatment of simple uncomplicated falciparum malaria:

1.1 First-line Treatment: *Artesunate (AS) + Sulfadoxine – Pyrimethamine* (SP)

Age in years	Weigh in Kgs	Day 1		Day 2	Day 3
		SP (500 S+25 P mg tab)	AS (50mg tab)	AS (50mg tab)	AS (50mg tab)
5 - 11 Months	5 - 10 Kgs	½	½	½	½
1 - 6 years	11 - 24 Kgs	1	1	1	1
7 - 13 years	25 - 50 Kgs	2	2	2	2
> 13 years	> 50 Kgs	3	4	4	4

- A single dose of primaquine (0.25 mg base/kg bw, maximum dose 15 mg) should be added on the first day of treatment to ACT for uncomplicated falciparum malaria as a gametocytocidal medicine.

1.2 Second-line Treatment: *Artemether* 20mg + *Lumefantrine* 120mg

Age in years	Weigh in Kgs	Day1		Day2		Day3	
		AM	PM	AM	PM	AM	PM
< 5		Not recommended					
<3 years	5 - 14	1	1	1	1	1	1
3 - 8 years	15 - 24	2	2	2	2	2	2
9 - 14 years	25 -34	3	3	3	3	3	3
>14 years	> 34	4	4	4	4	4	4

- A single dose of primaquine (0.25 mg base/kg bw, maximum dose 15 mg) should be added on the first day of treatment to ACT for uncomplicated falciparum malaria as a gametocytocidal medicine.

2. Treatment of malaria caused by P. vivax, or P. ovale and malariae:

Chloroquine 25mg base / kg divided over three (3) days, *(Chloroquine 4 tablets day 1, 4 tablets day 2, 2 tablets day 3)* combined with *Primaquine* 0.25 mg / kg bw taken daily with food for 14 days *for vivax and ovale* , *(Primaquine 15 mg tabs daily for 14 days for adult)*

3.Treatment of severe malaria:

Treatment		Day 1		Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
		Time 0	12 hrs						
First option	*Artesunate* I.V / I.M	2.4mg/kg	2.4mg/kg	2.4mg/kg	2.4mg/kg	2.4mg/kg	2.4mg/kg	2.4mg/kg	2.4mg/kg
Second option	*Artemether* I.M	1.6mg/kg	1.6mg/kg	1.6mg/kg	1.6mg/kg	1.6mg/kg	1.6mg/kg	1.6mg/kg	1.6mg/kg
Third option	*Quinine* I.V	20mg/kg in 5% Glucose(loading dose)		After 8hrs of loading dose start the maintenance dose as, 10mg/kg /8 hourly till the patient can take by mouth then shift to the oral.					

4. Treatment of malaria in pregnancy:

N.B. Malaria in pregnancy should be considered severe and treated in hospital

Pregnancy in weeks	Uncomplicated malaria	Severe malaria
0-12 (1st trimester)	*Quinine + Clindamycine*	*Quinine + Clindamycine*
13- delivery (2nd &3rd trimester)	* First option: (AS + SP) * Second option: *Quinine + Clindamycine*	*Artesunate* Or *Quinine + Clindamycine*
Puerperium	AS + SP	*Artesunate* Or *Quinine + Clindamycine*

For any queries; *Please call:* ***0112917743 or 0114738275***

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 travelers

Other Measures in Treating Severe Malaria

1) Antibodies against TNF - ✔

→ they ↓ fever

→ but no effect on mortality & morbidity

→ ? reason

- Effects of other cytokines as IL – 1, TNF-
- On pathogenesis of complicated severe malaria

Other Measures in Treating 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

FUTURE PERSPECTIVE

· ***Success to control or eradicate malaria faced by obstacles:***

- **Increasing drug resistance in P. falciparum and appearing (R) in P. vivax**
- **Basis of protection against infection and disease not understood.**
- **Biologic basis of vector capacity responsible for mosquito-borne malaria transmission is unknown.**
- **Increasing anopheline mosquito resistance to insecticide.**

Further Extra Reading

The following are for interested readers.

Guidelines for treatment of uncomplicated P. falciparum malaria (or species not identified)

Recommended drug and adult dose	Recommended drug and pediatric dose (pediatric dose should NEVER exceed adult dose)
Chloroquine-resistant or unknown resistance*	
All malarious regions except those specified as chloroquine-sensitive listed below. Middle Eastern countries with chloroquine-resistant *P. falciparum* include Iran, Oman, Saudi Arabia, and Yemen.	
A. Artemisinin combination therapy	
Artemether + lumefantrine (Coartem) ♦ Administration consists of combination tablets (1 tablet = 20 mg artemether and 120 mg lumefantrine). A three day treatment schedule with a total of 6 oral doses is recommended based on weight (5 - <15 kg: 1 tablet per dose, 15 - <25 kg: 2 tablets per dose, 25 - <35 kg: 3 tablets per dose, ≥35 kg: 4 tablets per dose). The patient should receive the initial dose, followed by the second dose 8 hours later, then 1 dose po bid for the following two days.	
Artesunate + amodiaquine Administration consists of separate scored tablets containing 50 mg of artesunate and 153 mg base of amodiaquine. The recommended treatment is 4 mg/kg of artesunate and 10 mg/kg of amodiaquine given once a day for three days.	
Artesunate + mefloquine Administration consists of separate scored tablets containing 50 mg of artesunate and 250 mg base of mefloquine, The recommended treatment is 4 mg/kg of artesunate given once a day for three days and 25 mg base/kg of mefloquine (usually split over two or three days to reduce vomiting and optimize absorption). This may be achieved either as 15 mg/kg (usually on the second day) followed by 10 mg/kg one day later, or as 8.3 mg/kg per day for three days.	
Artesunate + sulfadoxine-pyrimethamine Administration consists of separate scored tablets containing 50 mg of artesunate, and tablets containing 500 mg of sulfadoxine with 25 mg of pyrimethamine. The total recommended treatment is 4 mg/kg of artesunate given once a day for three days and a single administration of sulfadoxine-pyrimethamine (25/1.25mg base/kg) on day 1.	
B. Atovaquone-proguanil (Malarone)♦	**B. Atovaquone-proguanil (Malarone)♦**
Adult tab = 250 mg atovaquone/100 mg proguanil 4 adult tabs po once daily x 3 days	Adult tab = 250 mg atovaquone/100 mg proguanil Peds tab = 62.5 mg atovaquone/25 mg proguanil 5 to 8 kg: 2 peds tabs po once daily x 3 days 9 to 10 kg: 3 peds tabs po once daily x 3 days 11 to 20 kg: 1 adult tab po once daily x 3 days 21 to 30 kg: 2 adult tabs po once daily x 3 days 31 to 40 kg: 3 adult tabs po once daily x 3 days >40 kg: 4 adult tabs po once daily x 3 days

Therapeutic options for parenteral treatment of severe malaria*

I. Artemisinin derivative•	
Artesunate	2.4 mg/kg intravenously as first dose, followed by 2.4 mg/kg at 12 and 24 hours, followed by 2.4 mg/kg once daily
II. Quinine or quinidineΔ	
Quinine dihydrochloride◊	16.7 mg base/kg (= 20 mg salt/kg) in 5 percent dextrose loading dose over four hours, followed by 25 mg base/kg/day (20 to 30 mg salt/kg/day) divided into two to three equal administrations of 8.35 mg base/kg (= 10 mg salt/kg) over two hours at 8 or 12 hour intervals (maximum 1800 mg salt/day)
Quinidine gluconate§	6.25 mg base/kg (= 10 mg salt/kg) loading dose intravenously (maximum 600 mg salt) in normal saline over one to two hours, followed by 0.0125 mg base/kg/min (= 0.02 mg salt/kg/minute) continuous infusion for at least 24 hours
	Alternative: 15 mg base/kg (= 24 mg salt/kg) loading dose intravenously in normal saline over four hours, followed by 7.5 mg base/kg (= 12 mg salt/kg) infused over four hours every eight hours, starting eight hours after the beginning of the loading dose
PLUS* one of the following: Doxycycline, Tetracycline, or Clindamycin	
Doxycycline	Adults: 100 mg orally twice daily. Children: 2.2 mg/kg (up to 100 mg) orally twice daily. Intravenous dosing acceptable if oral medication not tolerated; switch to oral dosing once patient is able to swallow. Treatment course is seven days.
Tetracycline	Adults: 250 mg orally four times daily. Children: 25 mg/kg/day (up to 1000 mg) divided into four equal doses. Treatment course is seven days.
Clindamycin¥	Adults and children: 20 mg base/kg/day orally (maximum 1800 mg) divided into three equal doses. Treatment course is seven days.

* In general, parenteral therapy is administered for severe disease. Once the patient is able to tolerate oral medications, treatment may be completed orally. Options include: **1.** Parenteral artesunate followed by atovaquone-proguanil (for adults: 4 adult tabs orally for three days), mefloquine (for adults: 750 mg salt orally as initial dose followed by 500 mg salt orally 6 to 12 hrs later), doxycycline or clindamycin. **2.** Parenteral quinine (or quinidine) with doxycycline, tetracycline, or clindamycin (seven days therapy total); this is common practice for patients with malaria acquired in Southeast Asia, if artesunate is not available. **3.** Parenteral quinine (at least three doses) until the patient is able to swallow, followed by oral therapy with an artemisinin combination drug such as artemether-lumefantrine (three days therapy total; see separate table summarizing oral artemisinin combination therapy); this is common practice for children with malaria acquired in Africa, if artesunate is not available.

• Artesunate can also be administered intramuscularly, orally, or via rectal suppository (100 mg for children six months to six years of age; 400 mg for children >6 years). In the United States, intravenous artesunate is not approved by the Food and Drug Administration (FDA) but is available for emergency use under an investigational protocol by enrollment with the Centers for Disease Control (CDC). Artesunate is unstable in solution so is dispensed as a dry powder of artesunic acid together with an ampule of diluent (5 percent sodium bicarbonate solution or sodium phosphate solution as supplied by US CDC). The powder and liquid are mixed to provide a concentration of 10 mg/mL; the artesunate solution should be administered within one hour of preparation. Once the patient has received four doses of intravenous artesunate and is able to swallow, the treatment can be completed with a course of an active oral antimalarial drug based on known susceptibility data.

Δ Important adverse effects include hypoglycemia, QT prolongation, tinnitus, reversible hearing loss, nausea, vomiting, dizziness and visual disturbances. To avoid cardiotoxicity, a loading dose of quinine/quinidine should not be administered to patients who received mefloquine or other quinine derivatives within the previous 12 hours.

◊ Quinine should be given by rate-controlled intravenous infusion and never by intravenous injection (which can be lethal). Quinine can also be administered via intramuscular injection if intravenous infusions cannot be given: two injections of 10 mg/kg quinine (diluted to 60 mL) should be administered four hours apart. The anterior thigh is preferred over the gluteal region to minimize the risk of sciatic nerve damage.

§ In the United States, intravenous quinidine is available for treatment of severe malaria. Quinidine can cause QT prolongation and should be administered by rate-controlled intravenous infusion with continuous electrocardiographic and hemodynamic monitoring in an intensive care unit. Quinidine may be significantly absorbed to PVC tubing; tubing length should be minimized to approximately 12 inches.

¥ Clindamycin should be administered for pregnant women; doxycycline and tetracycline are contraindicated.

CDC Malaria Hotline: (770) 488-7788 Monday-Friday 8a to 4:30p EST; (770) 488-7100 after hours, weekends, and holidays.

C. Quinine sulfate PLUS one of the following: Doxycycline, Tetracycline, or Clindamycin	**C. Quinine sulfateΔ PLUS one of the following: Doxycycline◊, Tetracycline◊, or Clindamycin**
Quinine sulfate: 542 mg base (=650 mg salt)Δ po tid x 3 or 7 days §	Quinine sulfate: 8.3 mg base/kg (=10 mg salt/kg) po tid x 3 or 7 days §
PLUS one of the following:	**PLUS** one of the following:
Doxycycline: 100 mg po bid x 7 days	Doxycycline: 2.2 mg/kg po every 12 hours x 7 days
Tetracycline: 250 mg po four times daily x 7 days	Tetracycline: 6.25 mg/kg po every 6 hours x 7 days
Clindamycin: 20 mg base/kg/day (up to 1.8 grams) po divided tid x 7 days	Clindamycin: 6.7 mg base /kg po every 8 hours x 7 days
Sulfadoxine-pyrimethamine: single dose of 25/1.25 mg base/kg on day 1.	Sulfadoxine-pyrimethamine: single dose of 25/1.25 mg base/kg on day 1.
D. Mefloquine (Lariam and generics) ¥	
Mefloquine + artesunate (dosing as above)	
Mefloquine +/- doxycycline ‡	
Mefloquine: 684 mg base (=750 mg salt) po as initial dose, followed by 456 mg base (=500 mg salt) po given 6 to 12 hours after initial dose. Total dose = 1250 mg salt.	Mefloquine: 13.7 mg base/kg (=15 mg salt/kg) po as initial dose, followed by 9.1 mg base/kg (=10 mg salt/kg) po given 6 to 12 hours after initial dose. Total dose = 25 mg salt/kg.
PLUS	**PLUS**
Doxycycline: 100 mg po bid	Doxycycline: 2.2 mg/kg po every 12 hours
Chloroquine-sensitive	
Central America west of Panama Canal; Haiti; the Dominican Republic; and most of the Middle East. Infections acquired in Korea and the states of the former Soviet Union have been uniformly caused by *P. vivax* to date and should therefore be treated as chloroquine-sensitive infections.	
Chloroquine (Aralen and generics)	**Chloroquine (Aralen and generics)**
600 mg base (=1000 mg salt) po immediately, followed by 300 mg base (=500 mg salt) po at 6, 24, and 48 hours. Total dose: 1500 mg base (=2500 mg salt).	10 mg base/kg po immediately, followed by 5 mg base/kg po at 6, 24, and 48 hours. Total dose: 25 mg base/kg.
OR	**OR**
Hydroxychloroquine (Plaquenil and generics)	**Hydroxychloroquine (Plaquenil and generics)**
620 mg base (=800 mg salt) po immediately, followed by 310 mg base (=400 mg salt) po at 6, 24, and 48 hours. Total dose: 1550 mg base (=2000 mg salt).	10 mg base/kg po immediately, followed by 5 mg base/kg po at 6, 24, and 48 hours. Total dose: 25 mg base/kg.

po: orally; bid: twice daily; tid: three times daily.

* NOTE: There are 4 options (A, B, C, or D) available for treatment of uncomplicated malaria caused by chloroquine-resistant *P. falciparum*. The US Centers for Disease Control (CDC) recommends options A (artemether-lumefantrine), B, and C equally. The World Health Organization (WHO) recommends option A as the first line treatment for uncomplicated malaria. For option C, because there is more data on the efficacy of quinine in combination with doxycycline or tetracycline, these treatment combinations are generally preferred to quinine in combination with clindamycin. In addition, option C has higher incidence of adverse effects than options A or B. Because of a higher rate of severe neuropsychiatric reactions seen at treatment doses, option D (mefloquine) is recommended only when the other options cannot be used.

• Take with food or whole milk. If patient vomits within 30 minutes of taking a dose, then they should repeat the dose. It is also acceptable to take one half of the dose twice daily.

Δ US manufactured quinine sulfate capsule is only available in a 324 mg (salt) strength; therefore 2 capsules should be sufficient for adult dosing. Pediatric dosing may be difficult due to unavailability of non-capsule forms of quinine in the United States.

◊ Doxycycline and tetracycline are not indicated for use in children less than eight years old. For children less than eight years old with chloroquine-resistant *P. falciparum*, atovaquone-proguanil and artemether-lumefantrine are recommended treatment options; mefloquine can be considered if no other options are available. For children less than eight years old with chloroquine-resistant *P. vivax*, mefloquine is the recommended treatment. If it is not available or is not being tolerated and if the treatment benefits outweigh the risks, atovaquone-proguanil or artemether-lumefantrine should be used instead.

§ For infections acquired in Southeast Asia, quinine treatment should continue for seven days. For infections acquired elsewhere, quinine treatment should continue for three days.

¥ Treatment with mefloquine is not recommended in persons who have acquired infections from Southeast Asia due to drug resistance.

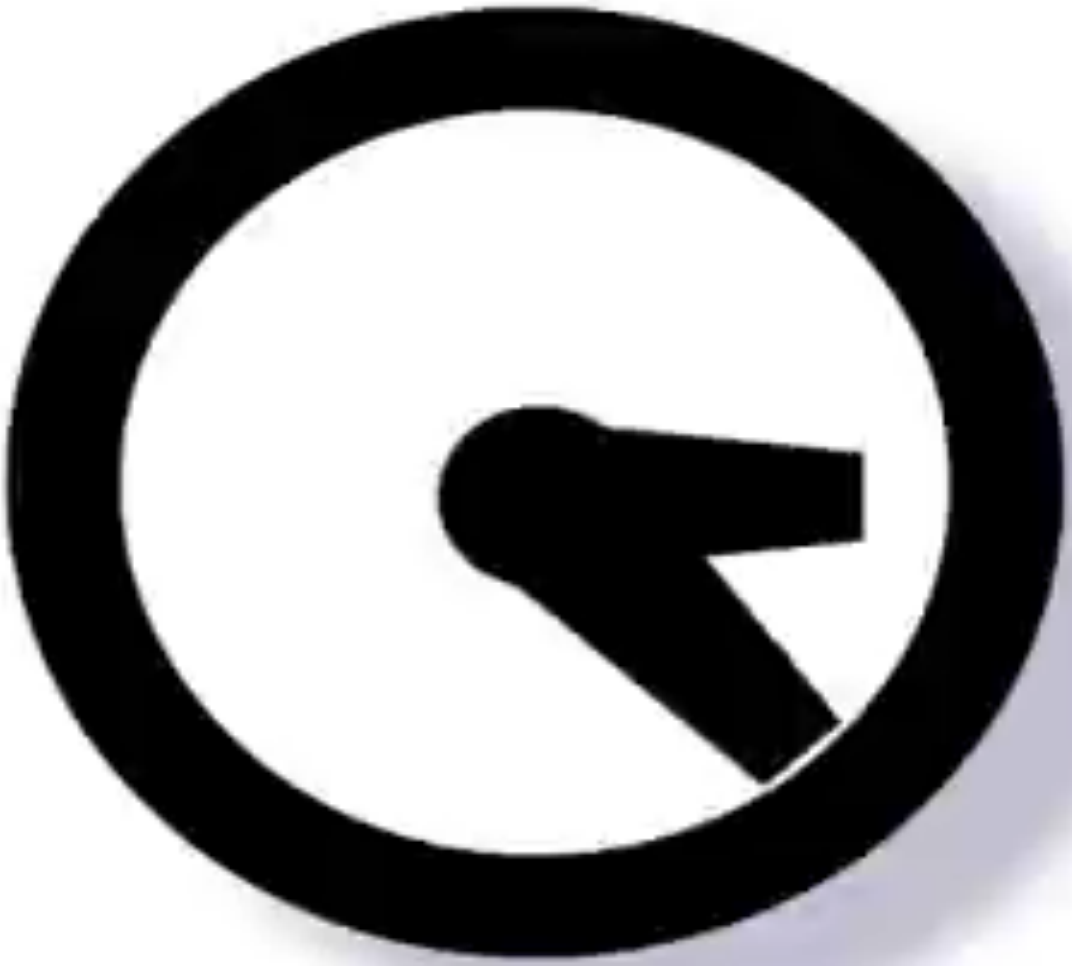
‡ Treatment with mefloquine as a single agent is acceptable in low endemic areas as the likelihood of spread and maintenance of drug resistant parasites is low. However, in highly endemic areas combination therapy is important to prevent emergence of resistance.

Adapted from United States Centers for Disease Control guidelines for treatment of malaria: http://www.cdc.gov/malaria/pdf/treatmenttable.pdf (Accessed June 18, 2009). CDC Malaria Hotline: (770) 488-7788 Monday-Friday 8 am to 4:30 pm EST - (770) 488-7100 after hours, weekends, and holiday.

Drug regimens for prophylaxis against malaria in adults

Drug	Tablet size	Dose	Frequency*	Initiation (time before first exposure to malaria)	Discontinuation (time after last exposure)	Use in pregnancy
Areas with chloroquine-resistant Plasmodium falciparum						
Atovaquone-proguanil (Malarone)	250 mg atovaquone and 100 mg proguanil	One tablet orally	Once daily	1-2 days	7 days	No; insufficient data on use in pregnancy
Mefloquine hydrochloride (Lariam and generic agents)	250 mg salt (228 mg base)	One tablet orally	Once weekly	3 weeks preferable; 2 weeks acceptable	4 weeks	Yes
Doxycycline hyclate (Vibramycin, Vibra-Tabs, other brands, and generic agents); doxycycline monohydrate (Monodox, Adoxa, and generic agents)	100 mg	One tablet orally	Once daily	1-2 days	4 weeks	No; teratogenic
Areas with chloroquine-sensitive Plasmodium falciparum						
Chloroquine phosphate (Aralen and generic agents)	500 mg salt (300 mg base)	One tablet orally	Once weekly	1-2 weeks	4 weeks	Yes
Hydroxychloroquine sulfate (Plaquenil)	400 mg salt (310 mg base)	One table orally	Once weekly	1-2 weeks	4 weeks	Yes
Atovaquone-proguanil (Malarone)	250 mg atovaquone and 100 mg proguanil	One tablet orally	Once daily	1-2 days	7 days	No; insufficient data on use in pregnancy
Mefloquine hydrochloride (Lariam and generic agents)	250 mg salt (228 mg base)	One tablet orally	Once weekly	3 weeks preferable; 2 weeks acceptable	4 weeks	Yes
Doxycycline hyclate (Vibramycin, Vibra-Tabs, other brands, and generic agents); doxycycline monohydrate (Monodox, Adoxa, and generic agents)	100 mg	One tablet orally	Once daily	1-2 days	4 weeks	No; teratogenic
Areas with P. vivax						
Primaquine phosphate (appropriate prophylaxis for short duration travel to areas with principally P. vivax)	26.3 mg salt (15 mg base)	Two tablets orally	Once daily	1-2 days	7 days	No; contraindicated because of potential toxicity for fetal erythrocytes
Chloroquine phosphate (Aralen and generic agents)	500 mg salt (300 mg base)	One tablet orally	Once weekly	1-2 weeks	4 weeks	Yes
Hydroxychloroquine sulfate (Plaquenil)	400 mg salt (310 mg base)	One tablet orally	Once weekly	1-2 weeks	4 weeks	Yes
Atovaquone-proguanil (Malarone)	250 mg atovaquone and 100 mg proguanil	One tablet orally	Once daily	1-2 days	7 days	No; insufficient data on use in pregnancy
Mefloquine hydrochloride (Lariam and generic agents)	250 mg salt (228 mg base)	One tablet orally	Once weekly	3 weeks preferable; 2 weeks acceptable	4 weeks	Yes
Doxycycline hyclate (Vibramycin, Vibra-Tabs, other brands, and generic agents); doxycycline monohydrate (Monodox, Adoxa, and generic agents)	100 mg	One tablet orally	Once daily	1-2 days	4 weeks	No; teratogenic
Presumptive antirelapse therapy (to prevent relapse due to P. vivax or P. ovale)						
Primaquine phosphate	26.3 mg salt (15 mg base)	Two tablets orally	Once daily	As soon as possible following exposure for which another prophylactic drug taken	14 days	No; contraindicated because of potential toxicity for fetal erythrocytes

* Drugs administered once daily should be taken at the same time each day; drugs administered once weekly should be taken on the same day each week.



THANK YOU