# MALARIA

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# LECTURE OUTLINE

- Epidemiology
- Life cycle
- Pathogenesis
- Clinical features
- Management
- Prophylaxis
- Vaccine

# RISK GROUPS

- Pregnant women (primi gravida) are most susceptible due to lack of immunity against
- The susceptibility is highest during the 2$^{nd}$ and 3$^{rd}$ trimesters of pregnancy and early post-partum period

- The placenta is preferably susceptible to infection with *P. falciparum*

- HIV infection suppresses antibody responses to malarial antigens during pregnancy.

# PLASMODIUM SPECIES

- ***P. falciparum***
  - Responsible of 90% of parasitemia in Africa
  - It causes malaria associated with a lot of morbidity and mortality
  - This parasite can infect any age group of cells resulting in very heavy parasitemia (> 10%)
  - Another attack is called: **recrudescence**

- ***P. vivax***
  - Not a major problem in Africa
  - Duffy blood group; most Africans are Duffy negative
  - Liver phase (hypnozoites) can result in **relapse**
  - Infects young RBCs (reticulocytes; therefore parasitemia does not exceed 2%): less severe than falciparum

- ***P. ovale***
  - Liver phase can result in relapse
  - Infects young RBCs

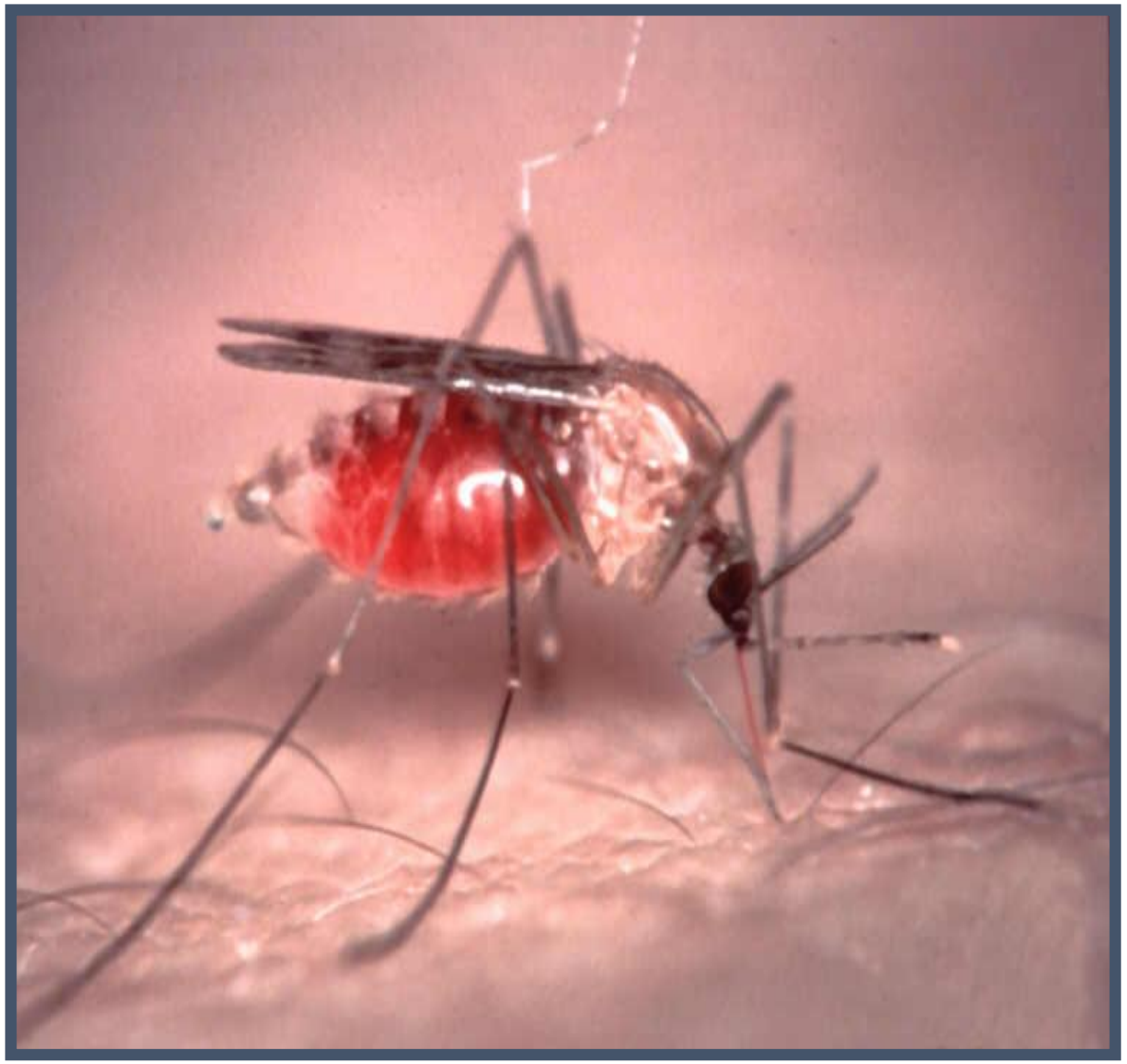
- ***P. malariae***
  - Can persist sub-clinically for extended periods of time
  - Infects old RBCs

- ***P. knowlesii***
  - Malaria research has been transformed by the use of molecular genetic techniques (PCR-based)
  - A cluster of cases in Kapit (Sarawak, Malaysia) were caused by infection with the monkey parasite *P knowlesi*, and not with the morphologically similar *P malariae* (in later stages) as had been previously thought
  - Resembles PF in early stages
  - More aggressive than PM clinically

# TRANSMISSION

- Done by an infected anopheles mosquito
- Other modes of transmission include:

1. **Blood transfusion**
2. **Contaminated needle**
3. **Organ transplant**
4. **Congenital**
5. **“Airport malaria"**



# PATHOGENESIS

- Parasite-derived toxins
- Host-induced cytokines
- Sequestration – cyto-adherence and rosseting
- ***P. falciparum*** **erythrocyte membrane protein 1** (pfemp 1) → ligand responsible for majority of binding interactions
- Antigenic variation also a major feature of pfemp1

# CYTOKINES

- Macrophages secrete TNF alfa & IL-1 that interact with hepatocytes rendering them resistant to parasite; TNF alfa correlates with disease severity
- CD8+ cells produce IFN-gamma which inhibits multiplication of parasites in hepatocytes and/or destroys them;CD8+ do not affect blood stage parasites because RBC do not express MHC-1
- Infection of hepatocyte by sporozoites can be prevented by IL-2 & IFN-gamma,& limit the development in the Kuppfer cell

# CYTOADHERENCE

- In the *P. falciparum* infection, membrane histidine-rich ‘knobs’ appear within 24 hour of asexual cycle-these knobs extrude PfEMP1 protein ,a high molecular wt. antigenically variant strain-specific adhesive protein that mediate cytoadherence
- Cytoadherence is facilitated by:
  - ICAM-1 in the brain
  - Chondroitin sulfate in the placenta
  - CD36 receptors in other organs
- *P. falciparum* infected RBCs can adhere to normal RBC, producing rosettes and also to other infested RBCs (Agglutination)
- Agglutination and cytoadherence are central to pathogenesis of *P. falciparum*
- Sequestered continue to develop out of reach of host defense, with some being filtered in the spleen; only young forms of asexual parasites are seen predominantly

# SITE SPECIFIC SEQUESTRATION

- Brain
  - Measurable reduction in blood flow
- Intestines
  - Diarrhea
- Placenta
  - Intervillus space

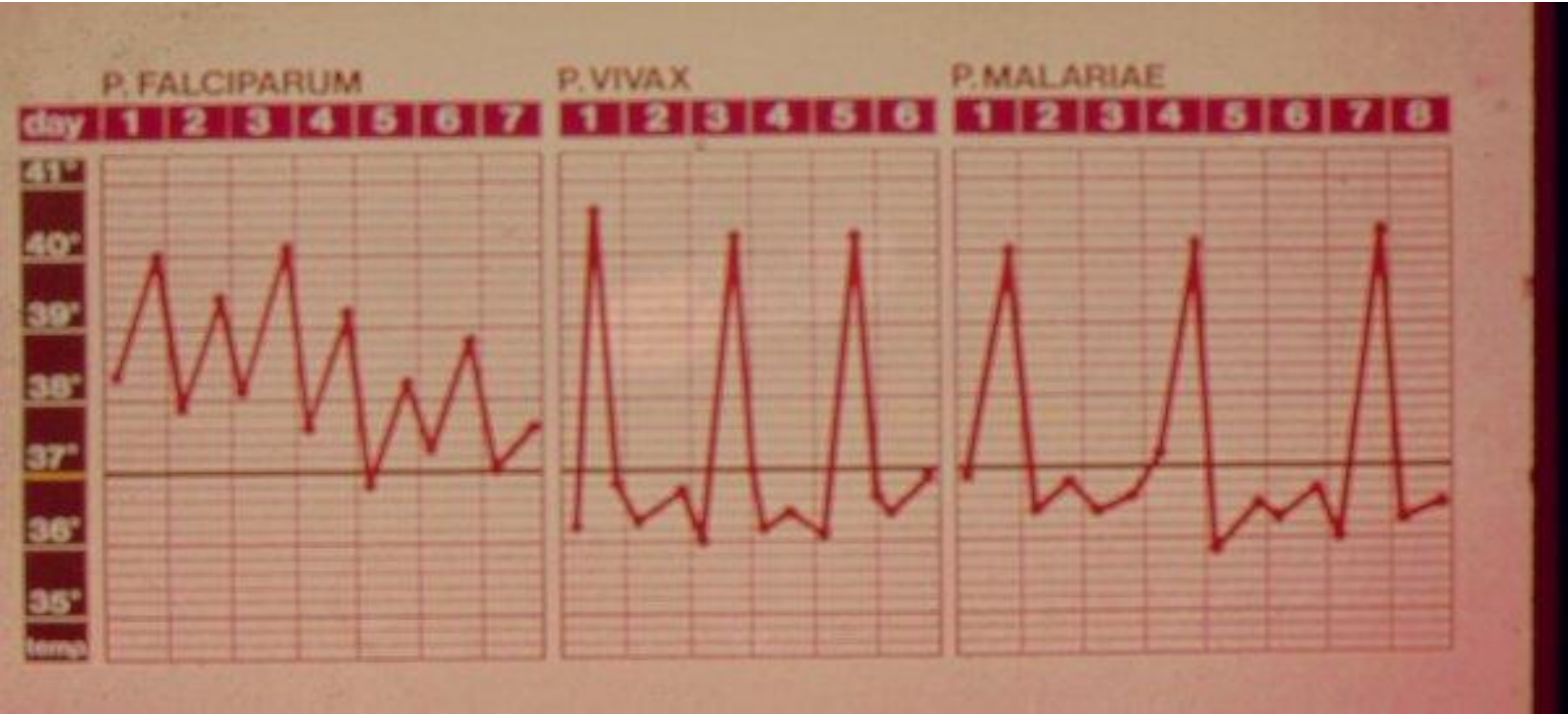
# CLASSIFICATION OF MALARIA

- **Uncomplicated**
  - Travel history in the past 10 days e.g. Coast or Nyanza
  - Initial phase (cold) – 3 hours
    - Chills
    - Temperature rising
  - Hot phase (1-2 hours)
    - Very high fever (39-41)
    - Headache, nausea, vomiting
  - Sweating phase
    - Profuse sweating
    - Temperature comes down
    - Nausea disappears
  - Cycle repeats itself; It corresponds to the rupture of merozoites.

- **Severe (in-patient treatment)**
  - Hyper-parasitemia > 5%
    - Depends with a person's immunity and previous exposure to malaria.
  - Hyperpyrexia >41$^{o}$C
    - At such high temperatures, enzyme systems are deranged and this can be fatal.
  - Anemia (Hb < 5g/dL)
  - Hypoglycemia (BS < 2.2 mmol/L)
  - Acute renal failure
    - More common in adults
  - Also: Jaundice; Respiratory distress syndrome and pulmonary edema; Haemoglobinuria; Algid malaria (shock and gram negative septicemia); Electrolyte disturbances; DIC; Spontaneous bleeding and bloody diarrhea; Mental confusion and coma (cerebral malaria)

- **Treatment failure**
  - Persistent symptoms 2-3 days after initiation of drug therapy

# FEVER CHART FOR DIFFERENT PLASMODIUM SPP.



# DIAGNOSIS

- Light microscopy
  - Stained fixed blood smear
    - Thick film – presence/absence
    - Thin film – morphology/species

-You should suspect malaria in any febrile patient with a history of possible exposure to infected mosquitoes, whether they've been on chemoprophylaxis or not. One of the most important concepts to understand is: when to do a malaria blood smear on a patient?—and the answer is…WHENEVER malaria is suspected or possible.

-The Giemsa-stained blood smear is considered the "gold standard" for lab diagnosis of malaria.

-The thick smears are used for screening to detect the presence of malaria parasites

-The thin smears are used for identifying *which species* is/are present

-Multiple thick smears and thin smears should be prepared—

a) Use venous or capillary blood for the blood smears–

b) If the sample is negative, it should be repeated as often as every 6-8 hours for 24 –36 hours for two reasons—1) because symptoms can precede detectable parasitemia by 24-36 hours; and 2) if the parasites are synchronous, they may be present in the peripheral circulation for only half of the cycle (cycle is 48 h for falciparum, vivax, and ovale).

# CONT.

c) If the sample is positive, then slides should be repeated periodically to determine whether the parasitemia is decreasing in response to treatment –very important, especially with *falciparum.*

- Para-sight F is like a rapid "dipstick" for Plasmodium falciparum only- it doesn't identify the presence of other species. It is a very promising technique, but isn't yet available in the U.S.

-The most common lab findings that can be seen on a CBC are:

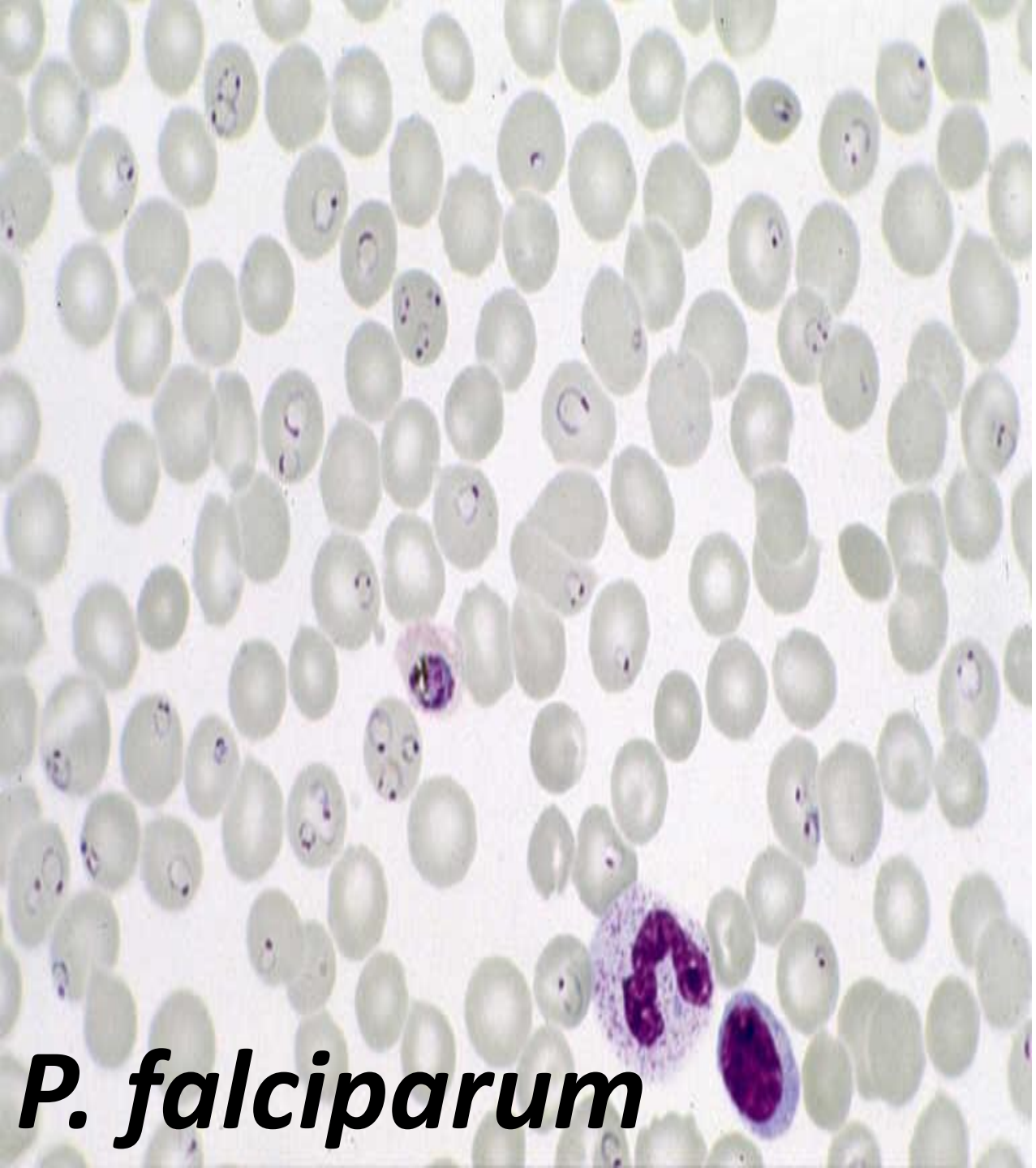
(1) anemia, thrombocytopenia, leukopenia (or leukocytosis), without eosinophilia

-Other lab findings include:

(2) elevated liver enzymes

(3) elevated urinary albumin, urobilinogen, and bilirubin

-The most specific finding, of course, is the presence of parasites on peripheral blood smears.



***P. falciparum***

-There are several diagnostic features that we look for when examining the thin blood smears under the microscope that help identify the species. In general they include:

a) Which developmental erythrocytic stages are present;

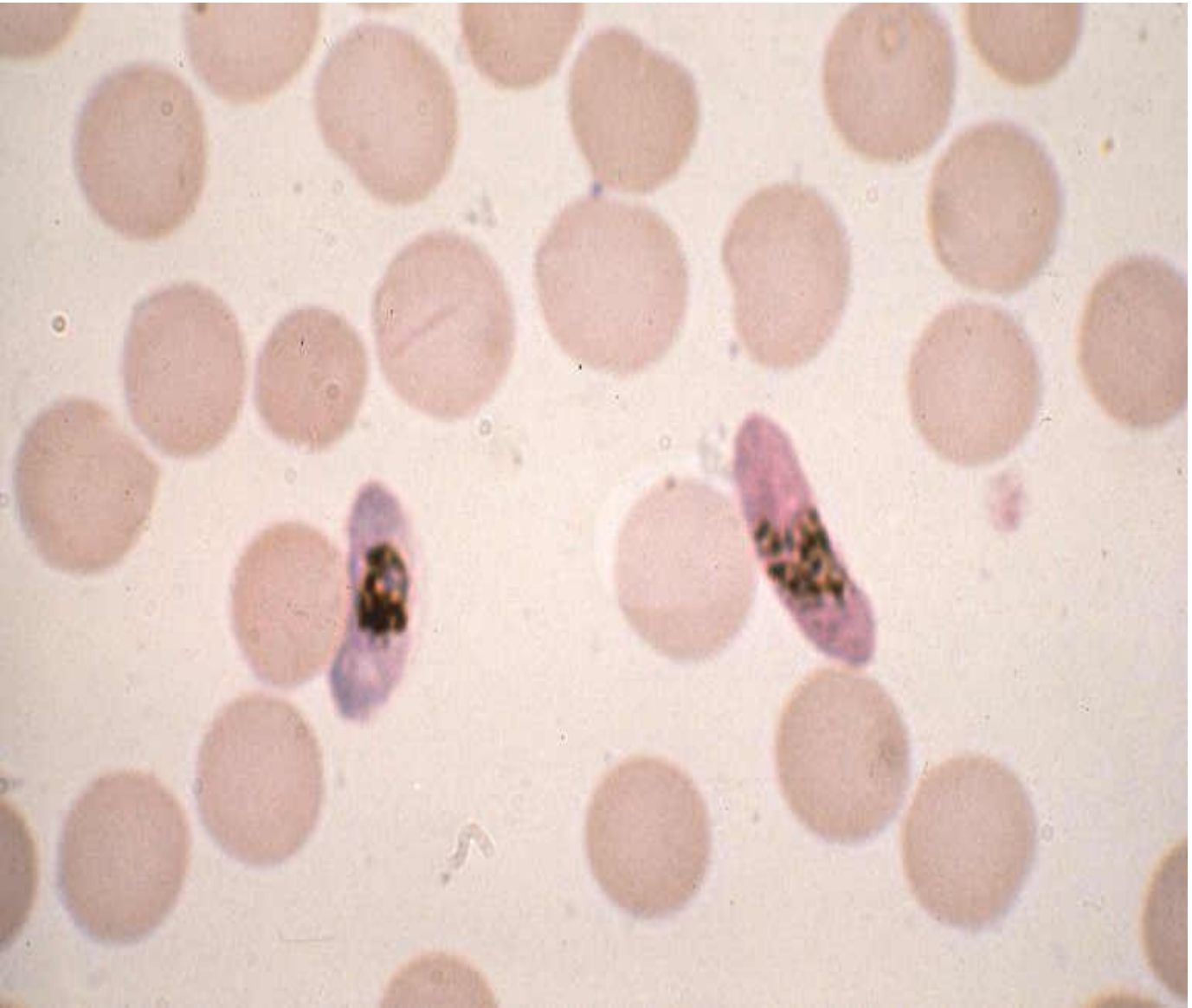
b) The size of the parasitized RBCs- whether they're enlarged, normal (or smaller )

c) The morphology of the RBCs and the parasites

In this slide we see many RBCs with ring forms in them:

-Ring forms are small and delicate (about 1/5 the size of the RBC), and its quite common to see multiple forms in single RBCs

# GAMETOCYTES:
# Pink – Male
# Blue - Female



- This is the banana or crescent-shaped gametocyte- it has a single nucleus.
- If you see this, you know the patient has *P. falciparum*.

# OTHER DIAGNOSTIC METHODS

- Fluorescent microscopy
- Antigen-capture
  - RDTs; rapid diagnostic tests
    - HPR-2 (histidine rich protein-2; PF only)
    - pLDH (parasite LDH; all species)
- PCR
- Other non-specific lab abnormalities
  - FBC
    - Anaemia
    - Haemolysis
    - Thrombocytopenia
  - LFTS
    - Raised transaminases (mildly)
    - Hyperbilirubinemia
  - Sometimes evidence of DIC

# MANAGEMENT: OPTIMAL TREATMENT APPROACH

- Rapid case identification
- Rapid parasitological classification
- Rapid initiation of therapy
- Rapid initiation of supportive care

# RECOMMENDED ACTs FOR UNCOMPLICATED FALCIPARUM MALARIA

- Artemether – Lumefantrine
  - First line
- Dihydroartemisinin + Piperaquine
  - Second line
- Artesunate + Amodiaquine – significant resistance to amodiaquine in Kenya
- Artesunate + Mefloquine
  - Side effects to Mefloquine are not pleasant
  - Dizziness, mental confusion
- Artesunate + SP – obsolete in Kenya
  - There is a lot of resistance to sulfapyrimethamine (fansidar)

# SUPPORTIVE THERAPY

- Antipyretics
- Anti-emetics
- Hydration
- Electrolytes
- Generalized anti-convulsants
- Organ failure transport
- Nutrition

# TREATMENT OF SEVERE AND COMPLICATED MALARIA

- Parenteral Artesunate at 2.4 mg per Kg stat IV and repeated after 12 hours, 24 hours and then for 6 days daily

- Parenteral quinine
  - Loading dose 20 mg/Kg thereafter 10 mg/Kg 8 hourly (as infusion in 5% dextrose to run over 4 hours)

- Change to oral ACT as soon as the patient can tolerate oral medication

- Read about the drug preparation

# SPECIAL POPULATIONS

- Pregnant women
  - IPT
  - Breast feeding: avoid dapsone and tetracycline
    - Infants and young children: ACTS seem safe
  - Use artemisinin derivatives after 3-4 weeks of pregnancy
  - All pregnant women in malaria endemic areas should receive dose of SP to prevent fetal loss, low birth weight and low HB
  - As a single SP dose in the beginning of 2nd trimester
  - Second dose of SP in the 3rd trimester between 28 and 34 weeks

- Travelers
  - Co-morbidities

- HIV
  - Malnutrition: drug kinetics are changed but no evidence to support modification of therapy
  - In HIV-positive monthly SP from 2nd trimester up to 36 weeks may be more efficacious
  - Mefloquine can also be used

# PREVENTION

- ITN
- Indoor residual spraying
- Repellant cream (Containing DEET 30% and over; in pediatric patients → only 10%)
- Chemoprophylaxis
  - Mefloquine 250 mg once a week 3 weeks before one travels, during the stay in the malaria-endemic zone and 4 weeks after one has left the endemic zone.
  - Malarone (Proguanil - atovaquone); very expensive (5,000 Kshs); take 600 mg daily from just the day before the travel  to a week after one comes back; it has a favorable side-effect profile.
- Environmental management
- Vaccine
  - Sporozoite-based; gives 30%-60% protection
  - Sporozoite is irradiated and injected
  - It is difficult to produce vaccines because of antigenic variation in the malarial parasite

# CHEMOPROPHYLAXIS FOR PREVENTION OF MALARIA IN OTHER RISK GROUPS

- Proguanil-dose 200mg per day
- Mefloquine-dose 250mg once weekly
- Doxycycline-dose 100mg daily, but not for children under 8 years and pregnant women
- Atovaquone + Proguanil [one Malarone daily]
- Chemoprophylaxis be continued for 4 weeks after leaving a malaria endemic area
- No anti-malarial drug can guarantee absolute protection

# ASSIGNMENT

- Review antimalarial pharmacology with a special focus on artemisinin

- Review malaria life cycle

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