



Epidemiology of Malaria

- **41% of world population live in malaria endemic areas in 99 countries**
- **Most of them are in Africa**
- **500 million episodes of clinical infection every year**
- **2.7 million deaths per year due to malaria**
- **3.5 million low birth weight infants due to malaria**
- **In Kenya specifically there are 8.2 million reported cases every year**

EPIDEMIOLOGY CONT

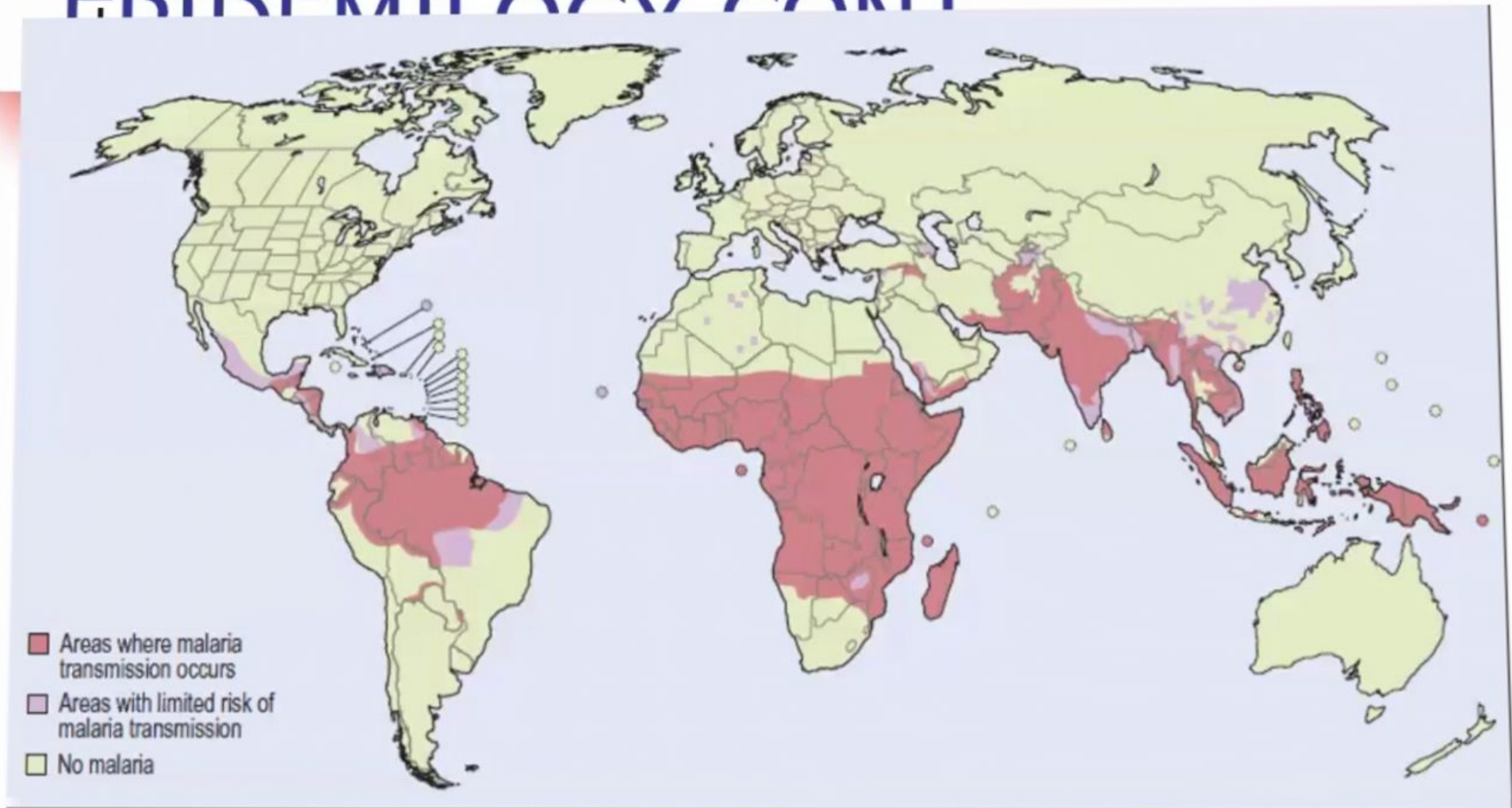


Figure 96.1 Areas of the world where malaria is transmitted, with differentiation between high- and minimal-risk areas. (Reproduced from World Health Organization. Available online at: <http://gamapserver.who.int/mapLibrary/default.aspx>.)



Epidemiology of Malaria

- **Major cause of death equal with HIV/AIDS and tuberculosis**
(Drugs 2002;62(9):1315-1329)
- **Malaria is a leading cause of death in children under 5 years of age in Africa**



Risk groups for malaria

- **Children below the age of 5 years**
- **Sickle cell disease and those having splenectomy**
- **Elderly and immunocompromised**
- **Non-immune –visitors to endemic areas of malaria and tourists**
- **Mortality is determined by patient's genetic and acquired immunity as well as the genetics of the parasite**



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Risk groups for malaria

- **Pregnant women [primigravidae]. The susceptibility highest during the 2nd and 3rd trimesters of pregnancy and early postpartum period**
- **Placenta is preferably susceptible to infection with *P. Falciparum***
- **HIV infection suppresses antibody responses to malarial antigens during pregnancy**



Malaria

- **All four species in Kenya**
- ***P.falciparum* - more than 90%**
- **Infect all ages of RBC**
- ***P.ovale* – young cells**
- ***P.vivax* – young cells**
- ***P.malariae* – old cells**



Species Infecting Humans

- ***Plasmodium falciparum*** Common & Severe
 - Malignant tertian (Cerebral)
- ***Plasmodium vivax***
 - Tertian
- ***Plasmodium ovale***
 - Tertian
- ***Plasmodium malariae***
 - Quartan
- ***Plasmodium knowlesi***



Rare & Mild



Plasmodium Species

- ***P. falciparum***
 - **Most severe and prevalent**
 - **90% of cases in Africa**
 - **Infects RBCs of all ages—Heavy parasitemia**



Plasmodium Species

- ***P. vivax***

- Not a major problem in Africa
- Duffy blood group
- Liver phase
- INFECTS YOUNG RBCs: LESS SEVERE THAN FALCIPARUM

- ***P. ovale***

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- ***P. malariae***

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P knowlesi

- **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**



Modes of Transmission of Malaria

- **By female Anopheles mosquito. Female mosquito need blood for egg production**
- **At 23⁰c. The gonotropic cycle takes 48 hrs. Blood meal every 2-3 nights**
- **In Africa the most important vector is Anopheles Gambiae**
- **Altitude: rarely exists above 2000 metres**

Transmission

Mosquito vector: *ANOPHELES*

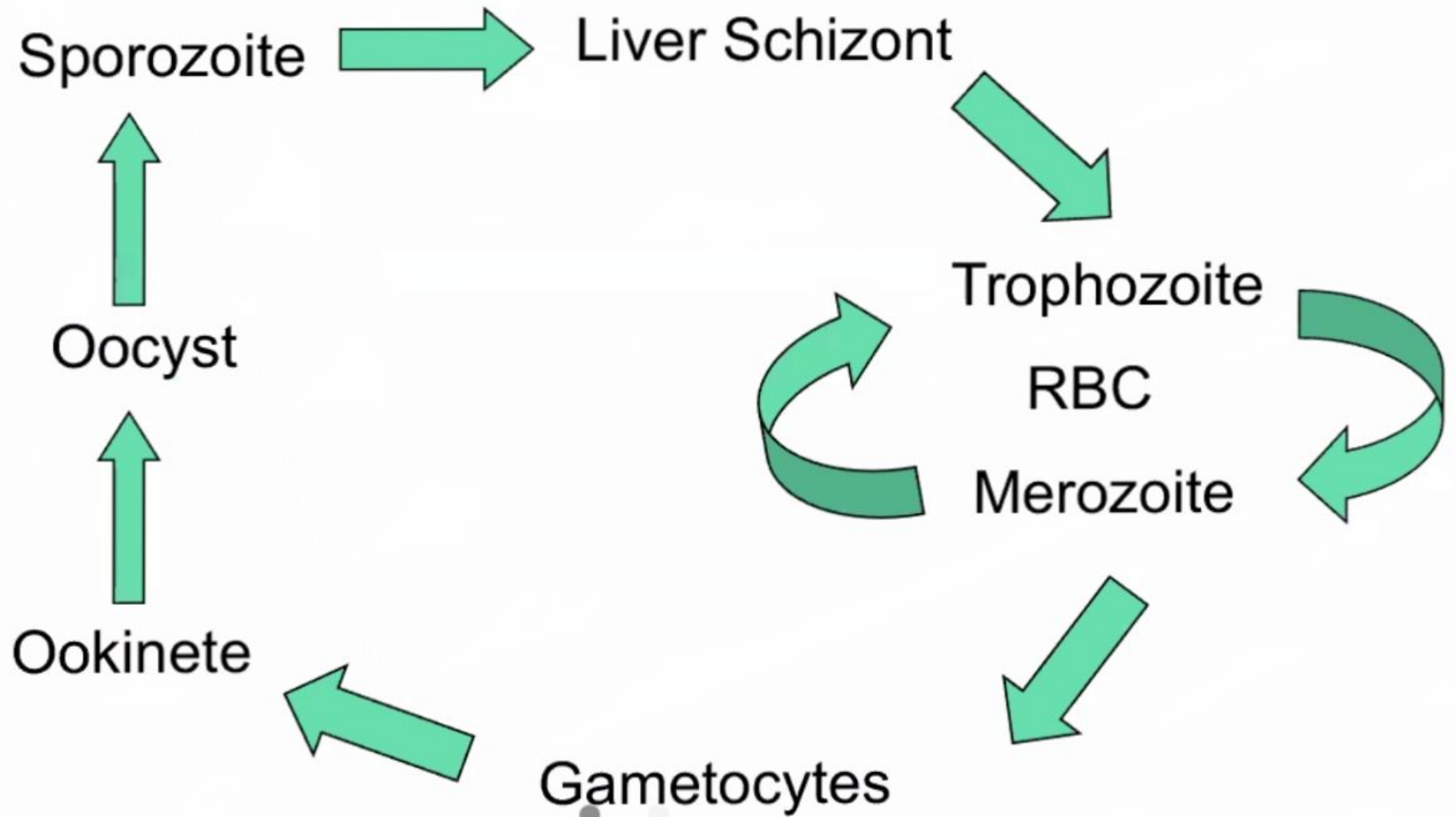
Transmission also possible through:

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





Life Cycle





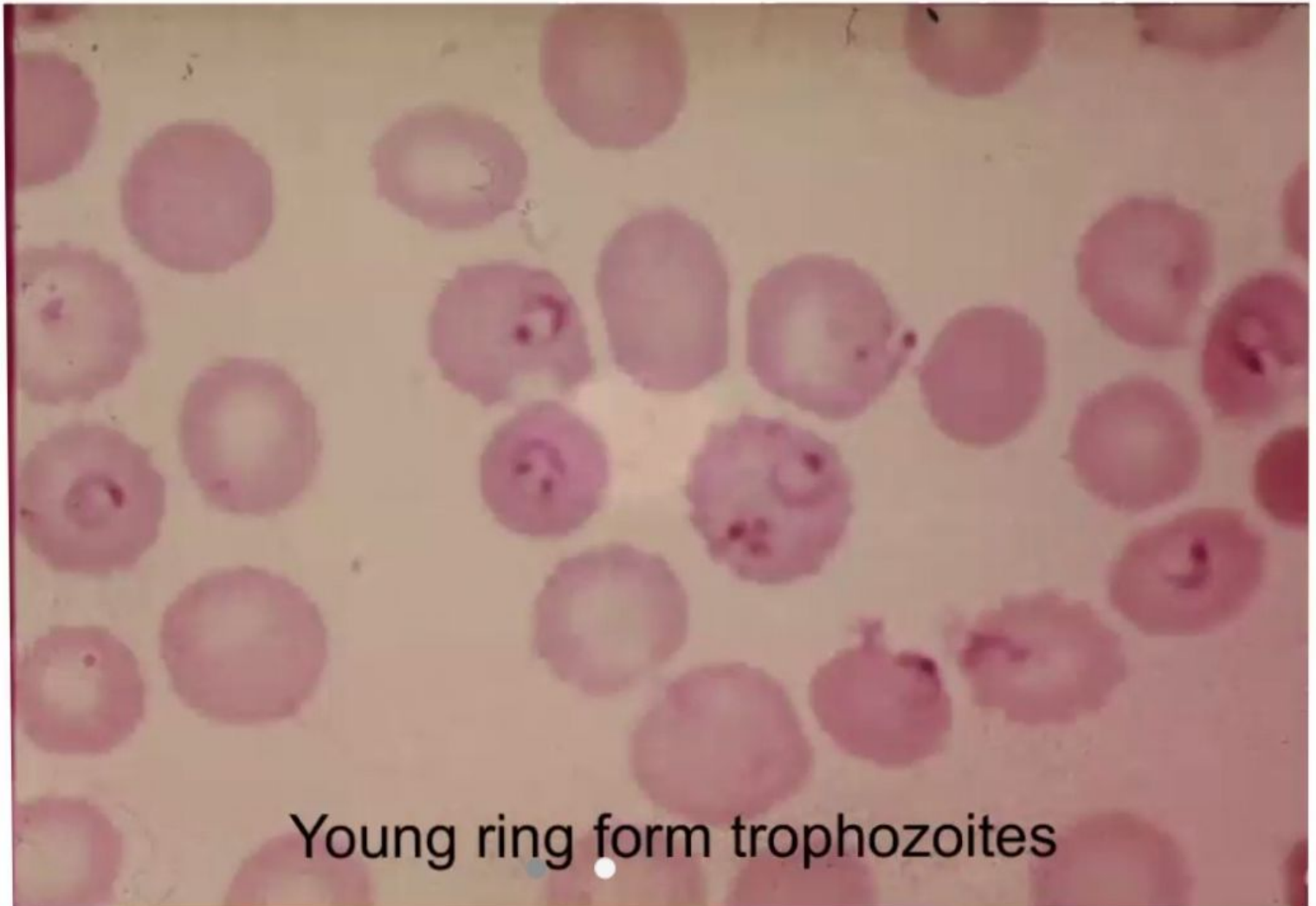
Transmission and Life Cycle

- **Sporozoites – circulation time 30 mins.**
- **Hepatic stage – sporozoites enter the kupffer cells – hepatic schizont – release of merozoites into circulation**
- **Hypnozoites – p.vivax & P.ovale**
- **Erythrocytic or blood stage responsible for symptoms**
- **Gametocytes – sexual reproduction in mosquito**

Infected Liver Cell Hepatocyte

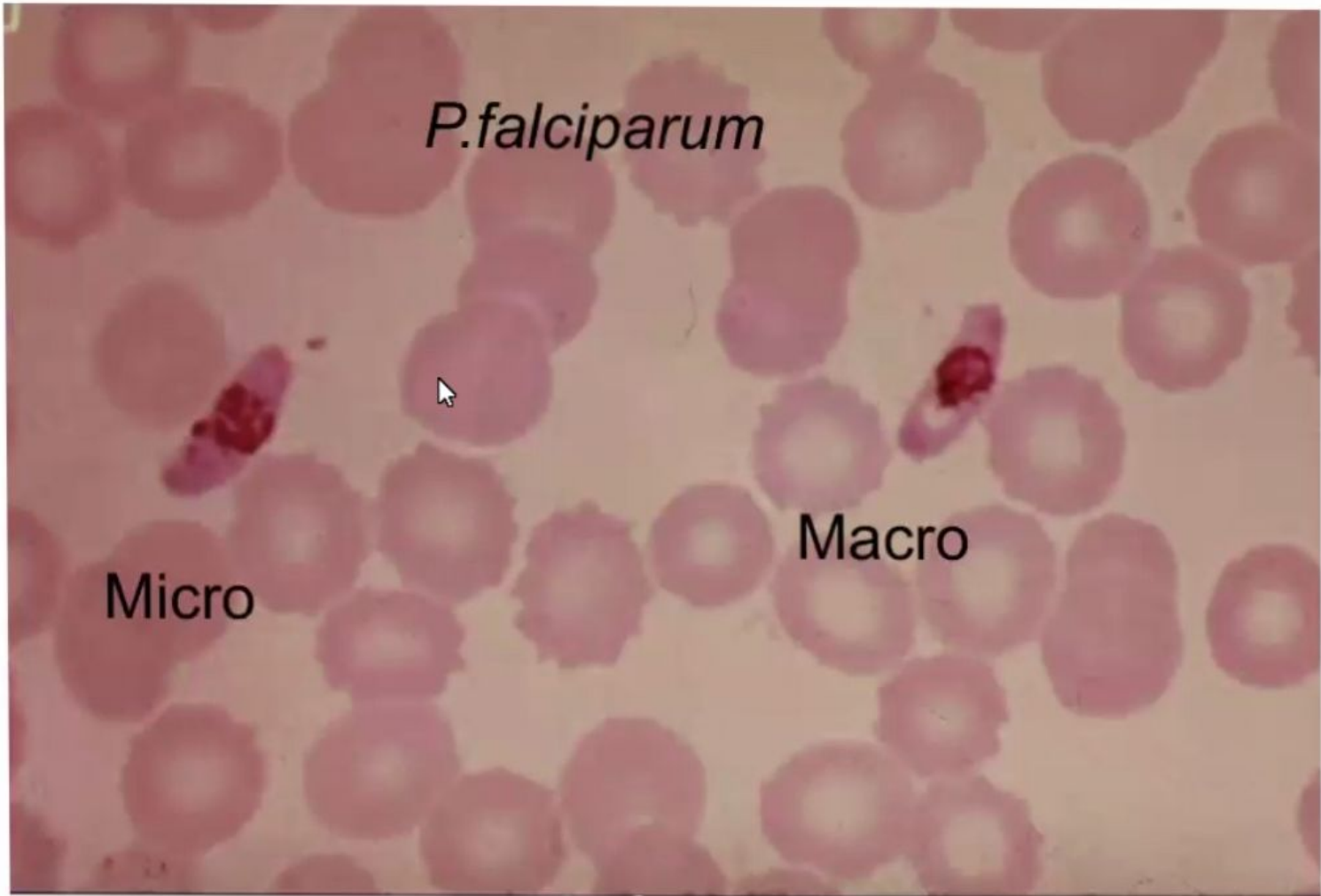


Erythrocytic forms (signet)



Young ring form trophozoites

Gametocytes



Pathogeneses of Severe Malaria

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



Cytokines

- **Macrophages secrete TNFa & IL-1 that interact with hepatocytes rendering them resistant to parasite; TNFa correlates with disease severity**
- **CD8+ cells produce IFN-gamma which inhibits multiplication of parasites in hepatocytes and/or destroys them; CD8+ do not affect bloodstage 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 Kupffer cell**



Cytoadherence

- **In *P. falciparum* infection, membrane histidine-rich 'knobs' appear within 24 hr of asexual cycle-these knobs extrude PfEMP1 protein, a high molecular wt. antigenically variant strain-specific adhesive protein that mediate cytoadherence**



Cytoadherence

- **Cytoadherence is facilitated by:-**
 - **-ICAM-1 in the brain;**
 - **-Chondroitin sulfate in the placenta;**
 - **-CD36 receptors in other organs**
- **P. falciparum infected RBC can adhere to normal RBC, producing rosettes, & also to other infected RBC (AGGLUTINATION)**
- **Agglutination & Cytoadherence are central to pathogenesis of P. falciparum**
- **Sequestered continue to develop out of reach of host defense, with some being filtered in spleen; only young forms of asexual parasites are seen peripherally**



Site Specific Sequestration

- **Brain**
 - **measurable reduction in blood flow**
- **Intestines**
 - **diarrhoea**
- **Placenta**
 - **intervillous space**



Classification of Malaria

- **Uncomplicated Malaria**
- **Severe Malaria**
- **Treatment failure**

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



Clinical Features of Malaria

- **A typical attack of malaria has 3 stages**
 - 1. Cold stage – Temp.↑ patient shivers, lasts 1-2 hrs., infected RBCs burst releasing merozoites and many ring forms in the blood smear**



Clinical Features of Malaria

**2. Hot stage – temp. ↑ to about 40°C,
skin**

**hot and dry, severe headache,
nausea**

and vomiting

Lasts 3-4 hrs.



Clinical Features of Malaria

- 3. Sweating stage – Temp. ↓ rapidly,
profuse sweating
Lasts 2-4 hrs.
The patient is relieved but
exhausted**



Severe And Complicated Malaria

- **Hyperparasitaemia $> 5\%$**
- **Hyperpyrexia- temperature $> 41^{\circ}\text{C}$**
- **Anaemia-haemoglobin $< 5\text{g/dl}$**
- **Hypoglycemia-blood sugar < 2.2 mmol/l**
- **Acute renal failure**



Severe And Complicated Malaria

- **Jaundice**
- **Respiratory distress syndrome and pulmonary oedema**
- **Haemoglobinuria**
- **Algid malaria (shock and gram - negative septicaemia)**



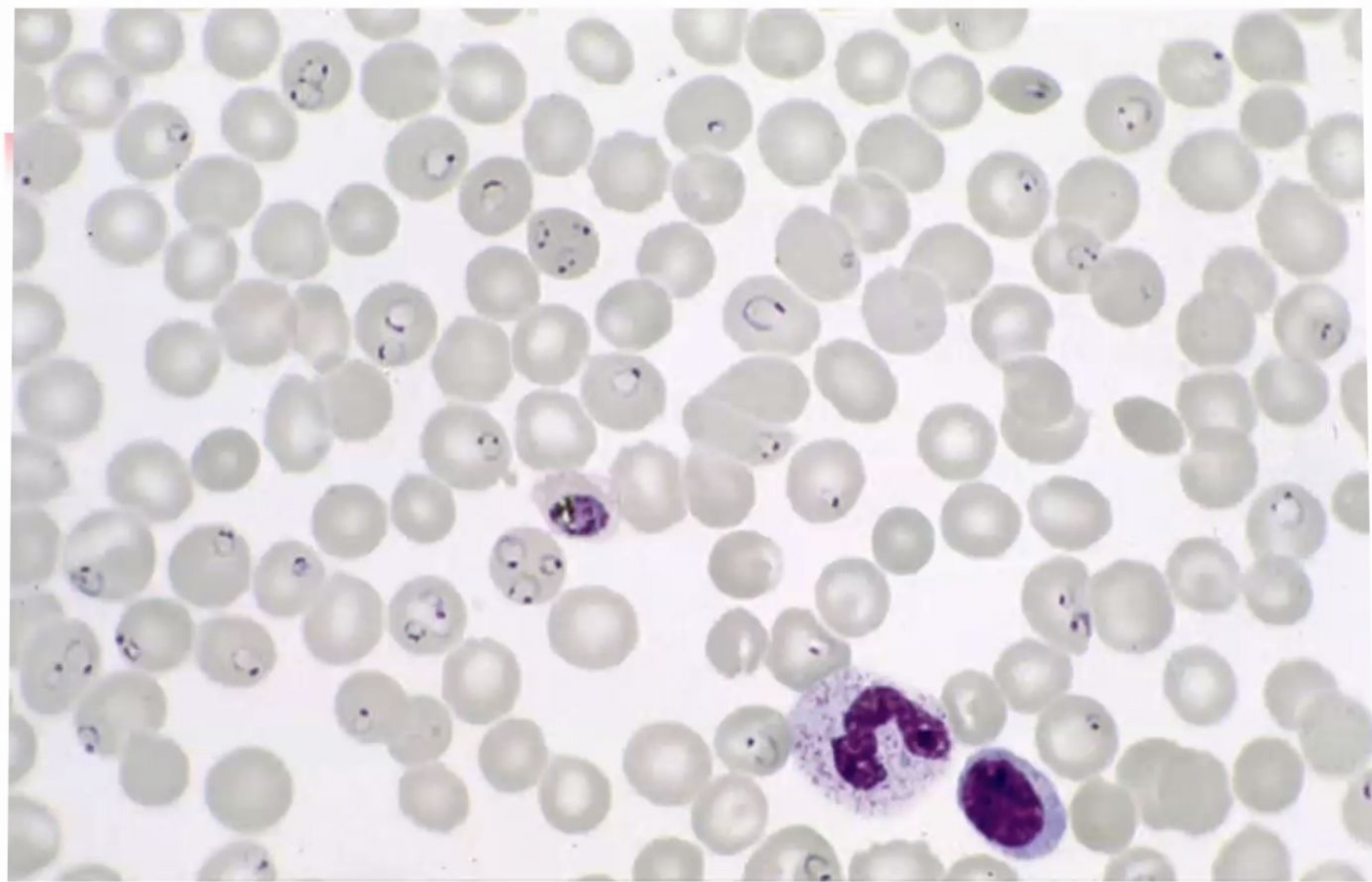
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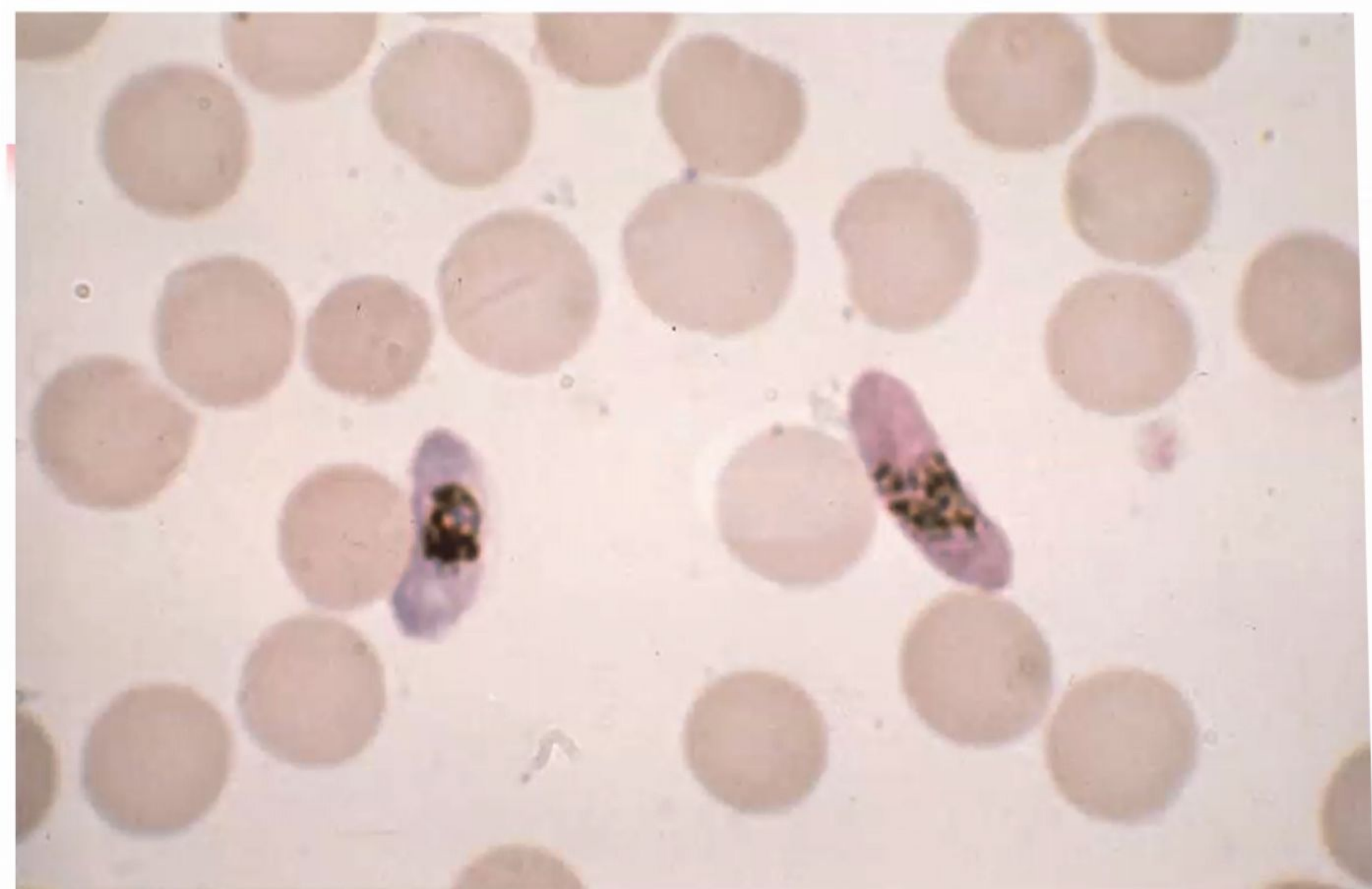
- **Electrolyte disturbances**
- **Dic, spontaneous bleeding, bloody diarrhoea**
- **Mental confusion and comma**



Diagnosis

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







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
 - Thrombocytopaenia
 - **LFTS**
 - Raised transaminases (mildly)
 - Hyperbilirubinaemia
 - **Sometimes evidence of DIC**





Management: Optimal Treatment Approach

- **Rapid case identification**
- **Rapid PARASITOLOGICAL classification**
- **Rapid initiation of therapy**
- **Rapid initiation of supportive care**



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Antimalarials

- **No drug acts on all stages of the life cycle currently**
- **Quinoline derivatives**
 - **Chloroquine, Quinine, Quinidine, Amodiaquine, Mefloquine, Halofantrine and *Primaquine*: inhibit heme polymerase activity etc. Intra-erythrocytic phase (NB primaquine)**
- **Antifolates**
 - **Pyrimethamine, sulfonamides, dapsone and proguanil: kill intrahepatic forms but not hypnozoites.**



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- **Artemisinin derivatives**
 - bind iron in the malarial pigment to produce free radicals which damage parasite proteins. All parts of Intra-erythrocytic phase.
- **Antimicrobials**
 - Clindamycin, atovaquone and tetracyclines.
 - Act synergistically with quinolines to kill blood schizonts
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Recommended ACTs For Uncomplicated Falciparum Malaria

- Artemether-lumefantrine
- Artesunate + amodiaquine
- Artesunate + mefloquine
- Artesunate + SP

- **Amodiaquine + SP**

- **No monotherapy use**



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Treatment of Severe and Complicated Malaria

- **parental Artesunate**
- **Parental quinine**
Loading dose 20mg/kg thereafter 10mg/kg 8 hrly (as infusion in 5% dextrose to run over 4 hrs)
- **Change to oral ACT as soon as the patient can tolerate oral medication**



Supportive Therapy

- **Antipyretics**
- **Antiemetics**
- **Generalized seizures**



Special Populations

- **Pregnant women**
- **IPT**
- **Breast Feeding**
 - Avoid dapsonе and tetracycline
- **Infants and young children**
 - ACTs seem safe
- **Travellers**
- **Co-morbidities**
 - **HIV**
 - **Malnutrition: drug kinetics are changed but no evidence to support modification of therapy**



P. Vivax, Ovale And Malariae

- **ACTs can also be used**
- **Vivax and Ovale liver stages (hypnozoites) treated with primaquine: 15mg x od x 14/7**
- **Primaquine is an oxidant and causes variable haemolysis in glucose-6-phosphate dehydrogenase deficiency**



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Mosquito Avoidance

- Anopheline mosquito is a nocturnal feeder
- Screened areas
- Treated mosquito nets
- Cover exposed skin
- Insect repellent e.g DEET, Permethrine



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Chemoprophylaxis

- **Mefloquine:**
- **Once per week (250mg)**
- Neuropsychiatric complications



chemoprophylaxis

- **Artovaquone – Proguanil (malarone)**
- Well tolerated
- Equipotent
- Daily dosing

DEVELOPMENTS IN MALARIA VACCINE



- ◉ The goal of malaria vaccine research is to elicit sterile immunity to sporozoites, before they are transformed into merozoites.
- ◉ Many different antigens have been identified as potential targets for malaria-vaccine development.
- ◉ One of these, the **repetitive sequence of four amino acids in the circumsporozoite antigen** on the surface of the sporozoite of *Plasmodium falciparum*

Refer to NEJM Dec 11 2008 issue



MALARIA VACCINE

- The RTS,S vaccine. i.e. RTS,S/AS01E & RTS/AS02D.-GlaxoSmithKline biologicals
- It is based on the circumsporozoite protein that targets the pre-erythrocytic cycle of *Plasmodium falciparum* in humans
- Induces pre-erythrocytic immunity ,resulting in reduced number of



RTS S VACCINE

- ◉ October 2011 1st results on children aged 5-17 months showed that 3 doses of the vaccine candidate reduced the number of malaria episodes over one year of follow up by 55%.
- ◉ November 2012 data for infants vaccinated aged 6-14 weeks showed estimated overall efficacy over 12 months of follow up was 33% for all malaria episodes.
- ◉ 2013 3rd set of results after 18 months of follow up showed 27% efficacy against clinical malaria in 6-14 weeks and 46% in 5-17 months



Rts s vaccine

- WHO recommendation on use of the vaccine –pilot in Kenya, Ghana and Malawi