Malariology Overview

History, Lifecycle, Epidemiology, Pathology, and Control

David Sullivan, MD
Malaria History

• 2700 BCE: The Nei Ching (Chinese Canon of Medicine) discussed malaria symptoms and the relationship between fevers and enlarged spleens.
• 1550 BCE: The Ebers Papyrus mentions fevers, rigors, splenomegaly, and oil from Balantines tree as mosquito repellent.
• 6th century BCE: Cuneiform tablets mention deadly malaria-like fevers affecting Mesopotamia.
• Hippocrates from studies in Egypt was first to make connection between nearness of stagnant bodies of water and occurrence of fevers in local population.
• Romans also associated marshes with fever and pioneered efforts to drain swamps.
• Italian: “aria cattiva” = bad air; “mal aria” = bad air.
• French: “paludisme” = rooted in swamp.
Cure Before Etiology: Mid 17th Century - Three Theories

• PC Garnham relates that following: An earthquake caused destruction in Loxa in which many cinchona trees collapsed and fell into small lake or pond and water became very bitter as to be almost undrinkable. Yet an Indian so thirsty with a violent fever quenched his thirst with this cinchona bark contaminated water and was better in a day or two.

• Alternatively, Indians working in mountain mines drank cinchona tea to stop shivering.

• Subsequent story is administration of bark to Countess of Cinchon by Jesuits
Malaria and Military

- Revolutionary War: US Congress bought cinchona bark from South America to treat soldiers with malaria.
- Civil War: 1,200,000 cases 8,000 deaths.
- WWI: Almost 5,000 cases with 7 deaths in US Navy and Marines; more than 100,000 cases in British and French soldiers.
- WWII: 500,000 cases in US Army; more than 110,000 cases with 90 deaths in US Navy and Marines.

"This will be a long war, if for every division I have facing the enemy, I must count on a second division in the hospital with malaria, and a third division convalescing from this debilitating disease.“ - General Douglas MacArthur
Malaria: The Trail of Pigment

• 1847: Meckel identified pigment in blood of insane person.
• 1848: Virchow pictured and described pigmented bodies in blood of malarial patient
• 1850: Hischl connected presence of pigment and intermittent fever
• 1880: Laveran identified pigment in body of living parasite in 26 patients. He is credited with describing the etiologic agent of malaria.
• In the 1890's British scientist Patrick Manson theorized that mosquitoes may be involved in malaria transmission. Manson had recently found that mosquitoes could vector filarial worms that caused elephantiasis.

• Two Johns Hopkins medical students Opie and MacCallum who were the first to describe sexual reproduction of *Plasmodium* in birds and man.

• Manson to Ross, 3/22/1898: “Don’t forget MacCallum’s discovery of the flagellum impregnation of halteridium spheres … I think I mentioned to you what I thought was the explanation, if MacCallum is right, of the mosquito pigmented cell.
Ronald Ross comments on cells outside the stomach of the *Anopheles* mosquito:

"but what now arrested attention was the fact that each of these bodies contained a few granules of black pigment absolutely identical in appearance with the well-known and characteristic pigment of the parasite of malaria (large quartans and crescent-derived spheres)."

Ross, Ronald *British Medical Journal* 1:1786-1788 (1897)

Manson to Ross, 4/29/1898

“It is a delight to watch how the thing is panning out. What a frightful shock it would have been to us had the Yanks done this.”

Source: CDC
1948: Shortt and Garnham Describe Exoerythrocytic Stages of Human Malaria Parasites

Malarial sporozoites in mosquito salivary gland smear.
Source: BIODIDAC/J. Houseman

Histopathology of malaria exoerythrocytic forms in liver.
Source: CDC
Definitive host mosquito

Ingests 3 ul of blood
With 100-300 gametes

Gametocytes
Viable for 28 days

Oocysts on gut wall

28 days In mosquito

100’s

Sporozoites

Within hours invades 1-2 liver cells

Merozoites in liver for seven to 10 days. P. vivax & ovale hypnozoite for Months.

Gametocytes
Viable for 28 days

Plasmodium
Life Cycle

Clinical signs and symptoms in erythrocytic stages of ring, trophozoite and schizont

1,000’s released

1-2 liver cells

48-72 hrs

schizont

trophozoite

ring

Definitive host mosquito

Ingests 3 ul of blood
With 100-300 gametes

Gametocytes
Viable for 28 days

Plasmodium
Life Cycle

Clinical signs and symptoms in erythrocytic stages of ring, trophozoite and schizont
## Malaria Species

<table>
<thead>
<tr>
<th></th>
<th>P. falciparum</th>
<th>P. vivax</th>
<th>P. ovale</th>
<th>P. malariae</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hepatic Development</strong></td>
<td>5-6</td>
<td>8</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td><strong>Phase</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Erythrocytic Cycle (days)</strong></td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td><strong>Hypnozoites (relapses)</strong></td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Merozoites per schizont</strong></td>
<td>30,000</td>
<td>10,000</td>
<td>15,000</td>
<td>2,000</td>
</tr>
<tr>
<td><strong>RBC preference</strong></td>
<td>All; prefers younger cells</td>
<td>Retics</td>
<td>Retics</td>
<td>Older RBCs</td>
</tr>
</tbody>
</table>
*Plasmodium falciparum*: High percent rings  
Source: Thomas Spahr and David Sullivan JHMRI

*Plasmodium vivax*: Enlarged erythrocytes  
Source: CDC/Dr. Mae Melvin

*Plasmodium malariae*: Band forms  
Source: CDC/Steven Glenn, Lab & Consultation Division

*Plasmodium ovale*: Oval or comet shape  
Source: CDC/Dr. Mae Melvin
Classical Malaria:
Hippocrates 5th Century BCE

- Fever
- Splenomegaly
- Anemia
Pyrogenic density is parasite density at time of fever.

*P. vivax* pyrogenic density is 100 parasites /µl

*P. falciparum* pyrogenic density ranges from 0 to 10,000/µl in nonimmunes

Semi-immune can have up to 100,000 par/µl without fever
Clinical Complications of Malaria

**P. falciparum**
1. Cerebral coma
2. Anemia
3. Pulmonary edema
4. Renal Failure
5. Shock
6. Lactic acidosis
7. Hypoglycemia
8. Tropical splenomegaly
9. Pregnancy
   a. Maternal death
   b. Stillbirth
   c. Low birth weight
   d. Anemia

**P. vivax (P. ovale)**
1. Splenic rupture
2. Anemia (mild)
3. Debilitating fevers
4. Higher TNF-α per parasite

**P. malariae**
1. Immune complex
2. Glomerulonephritis, leading to nephrotic syndrome
Edema brought on by nephrosis associated with malaria.

Source: CDC/Dr. Myron Schultz
Why do we see predominately rings only in peripheral circulation with *P. falciparum*?
Placental Malaria

Unstable epidemiology
Maternal death, abortion, stillbirth, premature delivery, low birthweight

Stable (Holoendemic) epidemiology
Clinical symptoms and parasitemia is higher in primigravida
Low birthweight

Non-immunes
Higher mortality
Progressive anemia
Quinine induced hypoglycemia
The Numbers

- 70 kg person X @70 ml / kg = 4.9 liters of blood @ 5 liters = \(5 \times 10^3\) ml = \(5 \times 10^6\) µl

- \(5 \times 10^6\) RBCs per µl of blood

- \(2.5 \times 10^{13}\) RBCs

- 1% parasitemia (50,000 ul) = 1 in 100 iRBCs = \(2.5 \times 10^{11}\) parasites per person

- A million people each day have this symptomatic burden = \(2.5 \times 10^{17+1}\) total parasites in world
Recrudesence & Relapse

Recrudesence
Renewed manifestation of infection due to survival of erythrocytic forms

Relapse
Renewed manifestation of infection arising from survival of exoerythrocytic forms (hypnozoites)

*P. vivax* or *P. ovale* only
### Table: Days to Onset of Illness for all US cases in 4 yrs

<table>
<thead>
<tr>
<th>Interval (days)</th>
<th>P. vivax</th>
<th>P. falciparum</th>
<th>P. malariae</th>
<th>P. ovale</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-29</td>
<td>750</td>
<td>1,542</td>
<td>103</td>
<td>27</td>
<td>2,422</td>
</tr>
<tr>
<td>30-89</td>
<td>562</td>
<td>157</td>
<td>35</td>
<td>28</td>
<td>782</td>
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<tr>
<td>90-179</td>
<td>554</td>
<td>35</td>
<td>37</td>
<td>34</td>
<td>660</td>
</tr>
<tr>
<td>180-364</td>
<td>605</td>
<td>21</td>
<td>28</td>
<td>33</td>
<td>687</td>
</tr>
<tr>
<td>&gt;365</td>
<td>127</td>
<td>7</td>
<td>6</td>
<td>11</td>
<td>151</td>
</tr>
<tr>
<td>Total</td>
<td>2,598</td>
<td>1,762</td>
<td>209</td>
<td>133</td>
<td>4,702</td>
</tr>
</tbody>
</table>
• 100 countries in malaria endemic areas.
• half in sub-Saharan Africa.
• 2.4 billion at risk.
• 300 to 500 million cases each year.
• 1.0 to 2.7 million deaths in children.
• Malaria constitutes 25% of child mortality in Africa.
• 90% of all malaria mortality is in under children under 5.
• Low birth weight, preterm delivery, cerebral malaria, and severe malarial anemia are major causes of mortality.
• Sequelae from severe clinical complications include cognitive impairment, behavioral disturbances, spasticity, and epilepsy as well as vision, hearing, and speech impairments.
Relationship Between Age and Clinical Presentations of Severe Falciparum Malaria at Different Levels of Malaria Transmission

Entomologic Inoculation Rate

Years

1 2 3 4 5 10 20 40 60

Holoendemic
Hyperendemic
Mesoendemic
Hypoendemic
Unstable

Severe anemia
Cerebral malaria
Renal failure
Age and Death Rates in Hyperendemic or Holoendemic Area

Risk period for malaria deaths

Parasite Prevalence (%) vs. Age (Years)
Parasite Control

1. Vector control & Sanitation

2. Vaccines?

3. Chemotherapy
   Protective (prophylaxis)
   Curative
   Prevention of transmission
Drug Dependence is Related to Immune Status

- Drug Dependence
- Immunity

Traveler Non-Immune  Endemic Immunity
Sporozoites

Gametocytes

oocysts

Sporozoites

48-72 hrs

merozoites

Primaquine (hypnozoites of \textit{P. vivax} \& \textit{ovale})

Antifolates-proguanil, pyrimethamine

Antibacterials-tetracycline, clindamycin, fluoroquinolone (Cipro)

Atovoquone

48-72 hrs

ring

trophozoite

schizont

Artemisinin

Quinolines- chloroquine, mefloquine, quinine
INNATE RESISTANCE TO MALARIA

Red Cell Polymorphism and Malaria: Polymorphic alternative versions of the same gene coexist in a population at frequencies well above that explained by repeated occurrence of the mutation that produces the variant.

The Malaria Hypothesis
Geographical distribution of red cell polymorphisms due to selective effect of malaria on heterozygote.

Conditions with reasonable evidence to support the malaria hypothesis are: Sickle cell trait and disease, thalassemia's, glucose-6-phosphate dehydrogenase deficiency and, Duffy blood group and hereditary ovalocytosis.
Hemoglobin Variants

**Hemoglobin S:** valine for glutamic acid at AA 6 in beta chain

**Hemoglobin C:** lysine for glutamic acid at AA 6 in beta chain

**Hemoglobin E:** lysine for glutamic acid at AA 26 in beta chain
"Stimulate the Phagocytes. Drugs are a Delusion."
GB Shaw, *The Doctor's Dilemma* 1906

"I myself have been infected with malaria only once in spite of nineteen years' of service in India and thirteen subsequent 'malaria expeditions' to warm climates; and I attribute this to my scrupulous use of the bed net."
Ronald Ross *Studies on Malaria* 1928.

"We must learn to shoot microbes with magic bullets."
Paul Ehrlich in *Microbe Hunters* Paul de Kruif 1926
• How often the mosquito bites influences disease severity.
• Fever corresponds with rupture from erythrocyte.
• In lethal *P. falciparum* rings predominate in circulation because older forms are adhering to tissue capillary beds to cause hypoxia and end organ damage.
• *P. falciparum* malaria is a medical emergency in the nonimmune patient.
• Human genetic polymorphisms such as sickle cell disease, thalassemia’s, glucose 6 phosphate deficiency, and lack of Duffy factor protect from severe disease but not infection.
• *P. vivax* and *ovale* can relapse from liver after effective erythrocyte treatment. Primaquine specifically treats this liver stage.
• *P. falciparum* resistance refers to recrudescence where red blood cell parasites decrease in number before rising again.
• Most current antimalarials do not effect gametocytes, which translates to infectivity to the mosquito.
Johns Hopkins University Malaria Firsts

- Under Osler’s direction, Johns Hopkins Hospital was the first in the world to perform routine malaria blood film analysis on all febrile patients in 1889.
- Two medical students, Opie and MacCallum, were the first to describe sexual reproduction of *Plasmodium* in birds and humans.
- In 1897, Welch actually coined the species name of *falciparum* in contrast to the proposed “falciforme” for the lethal Aestivo-Autumnal fever.
- The WWII wartime Survey of Antimalarial Drugs centered at Johns Hopkins solidly identified SN-7618 (SN = Survey Number) or chloroquine as the drug of choice for malaria. Dr. EK Marshall at Johns Hopkins actually coined the name chloroquine in Nov 1945.
Resources

- CDC Malaria Hotline Number
  - 404-332-4555 (24 hrs a day)
- CDC guidelines for malaria
- CDC guidelines for travel with outbreak information
- Online blood film knowledge testing
    (This web site is presented by the Division of Laboratory Medicine at Royal Perth Hospital)