Malaria

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A. Situational Awareness
B. Avoid Mosquito Bites
C. Compliance with Chemoprophylaxis
D. Seek early Diagnosis and Treatment
• Haldane’s hypothesis explains human abnormal red cell enzymes (G6PD), hemoglobins (Hb C, Hb E, Hb S) and red cell surface proteins (loss of Duffy antigen) as balanced polymorphisms in the context of malaria.

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Nobel Prizes in Malaria

On November 6, 1880, a French army surgeon stationed in Constantine, Algeria, was the first to notice parasites in the blood of a patient suffering from malaria.

In 1907, Alphonse Laveran was awarded the prize, "in recognition of his work on the role played by protozoa in causing diseases"

On August 20, 1897, a British army surgeon in Secunderabad, India first discovered the mosquito transmission of malaria.

In 1902, Ronald Ross was awarded the prize "for his work on malaria, by which he has shown how it enters the organism and thereby has laid the foundation for successful research on this disease and methods of combating it"
"Doctor," he said, "this will be a long war if for every division I have facing the enemy I must count on a second division in hospital with malaria and a third division convalescing from this debilitating disease!"

GEN Douglas MacArthur 1943

In November 1942, U.S. hospital admissions for malaria reached 178 per 100 men per month at Guadalcanal.

In Vietnam, malaria was the leading cause of disease non battle injuries for U.S. military for missed duty days.
Malaria in Ia Drang Valley, Vietnam 1965

In 1965, Army Vietnam rate = 98/1000 per year

Ia Drang Valley rates reached 600/1000 per year

Ia Drang Valley - 2 Maneuver battalions inoperative due to malaria

By 1969, *P. vivax* patients were being returned to duty in 5 to 8 days, and *P. falciparum* patients in 17 to 19 days.

1LT Rick Rescorla, Platoon Leader, B Co 2/7 Cav in Bayonet Attack on the morning of 16 Nov 1965 at LZ X-Ray, Ia Drang Valley
Joint Task Force Liberia 2003

- 225 Marines in Monrovia, Liberia < 2 weeks
  - Attack rate = 36% (80/225)
  - Evacuated to USA = 19% (43/225)
  - Severe = 2% (5/225)
    - 5 in intensive care unit
    - 4 on ventilators

- Prevention for military
  - Difficult in operational areas
  - Requires consistent, reliable use of:
    - Mosquito repellants
    - Bed nets
    - Treated uniforms
    - Antimalarial drugs (drug-resistance, side-effect & compliance)

- Diagnostic / treatment delay = high risk severe disease

WRAIR’s Development of the Artemisinins
Science, Clinical Trials & Registration

• 1st laboratory outside of China to purify and characterize drug from plants

• Co-developed combinations for MDR falciparum (ACTs)

• Supported registration of artemisinin suppositories for severe malaria by WHO

• Conducted 1st FDA-approved Phase 1 & 2 studies with intravenous artesunate

• Safety Trials in U.S.

• Treatment trials in Kisumu, Kenya

• Needed replacement for IV quinidine

• Anticipate licensure soon

• Available for compassionate use

Reference:
Falciparum Malaria Becomes Resistant to Antimalarial Drugs
Continuous Drug Development and Licensure is Required

<table>
<thead>
<tr>
<th>Drug</th>
<th>Introduced</th>
<th>First Reported Resistance</th>
<th>Difference (Years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinine</td>
<td>1632</td>
<td>1910</td>
<td>278</td>
</tr>
<tr>
<td><strong>Chloroquine</strong></td>
<td>1945</td>
<td>1957</td>
<td>12</td>
</tr>
<tr>
<td><strong>Proguanil</strong></td>
<td>1948</td>
<td>1949</td>
<td>1</td>
</tr>
<tr>
<td><strong>Sulfadoxine-pyrimethamine</strong></td>
<td>1967</td>
<td>1967</td>
<td>0</td>
</tr>
<tr>
<td><strong>Mefloquine</strong></td>
<td>1977</td>
<td>1982</td>
<td>5</td>
</tr>
<tr>
<td><strong>Malarone</strong></td>
<td>1997</td>
<td>2002</td>
<td>5</td>
</tr>
<tr>
<td>Artemisinin/ Proguanil (Coartem)</td>
<td>~2000</td>
<td>?</td>
<td></td>
</tr>
</tbody>
</table>
What is Malaria?

think host-vector-parasite

- Potentially lethal parasitic disease (Plasmodium falciparum, P. vivax, P. ovale, P. malariae, P. knowlesi)

- Transmitted between humans (reservoir) by mosquitoes (the vector, Anopheles)

- **Initial malaria**: fever, chills, muscle aches, headaches, fatigue, rigors
  
  **ACUTE ILLNESS**

- **Untreated**: severe anemia, kidney failure, coma, convulsions, respiratory distress
  
  **DEATH**

- **Treated**: Watch out for relapses!
  - *P. falciparum* - inadequate treatment ~ within 1 month
  - *P. vivax* - hypnozoites - weeks to months later
Malaria is still a big deal

- Every day, 3000 children die of malaria
- Malaria is the #1 cause of death of young African children
- Malaria is resurgent: more cases now than ever in history
- Inadequate prevention:
  - Bed nets save lives - but not widely used
  - DDT/insecticides save lives – but not adequately used
- Inadequate treatment
  - Poor diagnosis -
  - Drug resistance:
    - affordable drugs not effective
    - effective drugs not affordable
- No malaria vaccine yet licensed

Child with severe malaria
In 1900; 53% land area malarious; 890,000,000 people at risk
In 2002; 27% land area malarious; 3,400,000,000 people at risk
The Host (Reservoir) of Malaria

New Guinean 10 month old with severe malaria and older brother

African children with large spleens due to malaria

Asian boy with malaria and family

Indian malaria patients

U.S. military

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The Vector of Malaria

*Anopheles gambiae*, the most common species of mosquito transmitting malaria

Without the female *Anophelene* mosquito, there would be no malaria
**Plasmodium falciparum** Life Cycle and Disease

**NO SYMPTOMS**

Sporozoite Stage (minutes)
- From Mosquito - To Liver:
  - 1-10 sporozoites

Liver Stage (6 days)
- Enter Liver - Leave Liver
  - 30-300,000 merozoites

**DISEASE & DEATH**

Blood Stage (days - weeks)
- Enter RBCs - Leave RBCs
  - 100,000,000 iRBCs = mild
  - 1,000,000,000,000 iRBCs = moderate
  - 100,000,000,000,000 iRBCs = severe
  - >$10^{14}$ iRBCs = death
Malaria Anemia
Severe Red Cell Destruction // Suppressed Red Cell Production

Plasmodium falciparum can infect > 25% of red cells, & destroy them

Pale palm of Kenyan child with severe malaria anemia held in the palm of his mother

Mother with malaria in 1st pregnancy at high risk for severe anemia, death, low birth weight and infant death

Pale eyelids in Gambian child with severe malaria anemia

Figure 5: Gambian child with severe malaria anemia
Clinical findings

Uncomplicated
- fever
- non-specific flu-like symptoms
- GI (nausea, diarrhea, vomiting)
- not rash, not upper respiratory symptoms

Severe
- prostration
- mental status changes leading to unconsciousness (cerebral malaria)
- acute respiratory distress syndrome
Cerebral Malaria - Long Term Burden

- 10% death rate for cerebral malaria
- Brain damage in survivors
- Acute and long term disability
  - Deficits in
    - Attention
    - Memory
    - Visual-spatial skills
    - Language
  - Educational impairment
Prevention
A – B – C – D

A. Situational Awareness
B. Avoid Mosquito Bites
C. Compliance with Chemoprophylaxis
D. Seek early Diagnosis and Treatment

• pre-travel preparation
• assess malaria risk in geographic location
• length of stay
• urban vs rural
Prevention
A – B – C - D

A. Situational Awareness

B. Avoid Mosquito Bites

C. Compliance with Chemoprophylaxis

D. Seek early Diagnosis and Treatment

• personal protection
  • shirt sleeves rolled down
  • DEET (concentrations 30-50%)

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Prevention
A – B – C - D

A. Situational Awareness

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D. Seek early Diagnosis and Treatment

- insecticide-treated bed nets (ITNs)
- military use depends upon pre-treatment with permethrin and deployability
ITNs - Insecticide Treated Nets

- ITNs versus no nets // protective effect
  - 50% reduction in malaria attacks
  - 45% reduction in severe malaria attack
  - 17% reduction in death

- Additional benefits
  - Improved maternal health & hematocrits

- Cost: about $1

- Cost effective: Yes

- Usage: Less than 10% of children at risk

- Issues:
  - Too expensive for poor users to purchase
  - Requires retreatment with insecticide
  - Requires repair
  - Requires education to promote use

Lengeler C. Insecticide-treated bed nets and curtains for preventing malaria. Cochrane Database Syst Rev. 2004;(2):CD000363.
Indoor Residual Spraying (IRS)
DDT Use and Cumulative Malaria Cases in South America

Cumulative numbers of cases (x 1000)

Sprayed houses per 1000 population
## Prevention

### A. Situational Awareness

### B. Avoid Mosquito Bites

### C. Compliance with Chemoprophylaxis

<table>
<thead>
<tr>
<th>Anti-malarial Drug</th>
<th>Dosage</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxycycline</td>
<td>One tablet (100 mg)</td>
<td>Daily</td>
</tr>
<tr>
<td>Atovaquone-proguanil (Malarone®)</td>
<td>One tablet (250 mg atovaquone plus 100 mg proguanil)</td>
<td>Daily</td>
</tr>
<tr>
<td>Mefloquine (Lariam®)</td>
<td>One tablet (250 mg)</td>
<td>Weekly</td>
</tr>
<tr>
<td>Chloroquine (Aralen®)</td>
<td>One tablet contains 500 mg of chloroquine phosphate USP, equivalent to 300 mg chloroquine base</td>
<td>Weekly</td>
</tr>
</tbody>
</table>
1. Doxycycline
   - Take with food (GI distress)
   - Skin rash (hypersensitivity to sun; wear hat, long sleeves)
2. Malarone
   - Take with food/whole milk
   - Abdominal pain, rash
3. Mefloquine (Larium)
   - Neuropsychiatric reactions
   - No longer first line in U.S. Army (TSG-directive)
4. Chloroquine
   - Retinal changes on long-term prophylaxis
A. Situational Awareness
B. Avoid Mosquito Bites
C. Compliance with Chemoprophylaxis
D. Seek early Diagnosis and Treatment

A. Malaria Blood Film – thick and thin blood smears
   • What do you need?
   • Clean glass slides
   • Giemsa stain
   • Microscope with high power objective (100x)
   • Training
B. Rapid Diagnostic Tests (RDTs)
   • What do you need?
   • RDT card
   • Developing reagents (check expiration, cold storage)
   • Training
C. What to do if first test is negative and you still suspect malaria?
Seek early **Diagnosis** and **Treatment**

- **Thick blood smear**
- **Thin blood smear**
**Species of Malaria**

*Plasmodium falciparum*

Peripheral blood

- Ring stage

Sequestered parasite stage

- Schizont stage
Species of Malaria

*Plasmodium vivax*

1991 Somalia

1997-present, Republic of Korea

2003-present, Afghanistan

2005 Horn of Africa
Factors influencing rapid test performance

- quality of manufacture
- species of parasite
- number, viability, and the strain of parasites present
- condition of the RDT (including storage conditions)
- technique and care used in performing the test
- correct interpretation by the reader.
Mode of action of common malaria RDT format

1. Dye-labeled antibody, specific for target antigen, is present on the lower end of nitrocellulose strip or in a plastic well provided with the strip. Antibody, also specific for the target antigen, is bound to the strip in a thin (test) line, and either antibody specific for the labeled antibody, or antigen, is bound at the control line.

2. Blood and buffer, which have been placed on strip or in the well, are mixed with labeled antibody and are drawn up strip across the lines of bound antibody.

3. If antigen is present, some labeled antibody will be trapped on the test line. Excess-labeled antibody is trapped on the control line.
Diagnostic and Treatment Strategy

Suspected case (clinical criteria)

RDT / microscopy

Positive
- falciparum
  - Severe malaria
    - Treatment protocol
  - Uncomplicated malaria
    - Treatment protocol (ACT)

- Non-falciparum
  - (chloroquine, primaquine)

Negative
- Signs consistent with complicated
  - Anti-malarial treatment while further investigation / referral is underway
- Look for other causes. Review / refer
<table>
<thead>
<tr>
<th>Antimalarial Drug</th>
<th>Dosage</th>
<th>Regimen</th>
<th>Possible Side Effects/contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artemether/lumefantrine (Coartem®, Riamet®)</td>
<td>1 tablet (20 mg artemether plus 120 mg lumefantrine) (take with food/milk)</td>
<td>A 3-day treatment schedule with a total of 6 oral doses Initial dose at Dx followed by the 2\textsuperscript{nd} dose 8 hours later, then 1 dose po bid for the following 2 days. adult: 4 tablets per dose</td>
<td>Hypersensitivity to artemether or lumefantrine</td>
</tr>
<tr>
<td>Atovaquone/proguanil (Malarone®)</td>
<td>1 adult tablet (250 mg atovaquone plus 100 mg proguanil) (take with food/milk)</td>
<td>A 3-day treatment schedule: 4 tablets per dose daily for three consecutive days</td>
<td>Hypersensitivity, abd pain, nausea, skin rash, vomiting, headache, avoid use with creatinine clearance &lt; 30 ml/min</td>
</tr>
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</tr>
<tr>
<td>Quinine sulfate/doxycycline</td>
<td>Quinine: 8 mg base/kg (650 mg tablets (salt)) doxycycline: 100 mg tablets</td>
<td>Quinine: 542 mg base = 650 mg salt 3 times daily for 7 days; US manufactured quinine sulfate capsule is in a 324mg dosage; therefore 2 capsules should be sufficient for adult dosing Doxycycline: 1 tablet q12 hrs for 7 days</td>
<td>Stomach cramps, diarrhea, blurred vision, lightheadedness, dizziness, unusual bleeding, arrhythmias, tinnitus</td>
</tr>
<tr>
<td>Mefloquine (Lariam®)</td>
<td>One tablet (250 mg salt)</td>
<td>3 tablets at Dx and 2 tablets in 6-12 hours (total 1250 mg salt treatment dose)</td>
<td>Neuropsychiatric event, sleep disturbances, vivid dreams, insomnia, dizziness, dysphoria, contraindicated in persons with depression or history of seizures</td>
</tr>
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</table>
## Severe malaria treatment options

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<th>Antimalarial Drug</th>
<th>Dosage</th>
<th>Possible Side Effects/contraindications</th>
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<tr>
<td>Quinidine gluconate plus doxycycline</td>
<td>Quinidine gluconate: 6.25 mg base/kg (=10 mg salt/kg) loading dose IV over 1-2 hrs, then 0.0125 mg base/kg/min (=0.02 mg salt/kg/min) continuous infusion for at least 24 hours. Quinidine/quinine course = 7 days in Southeast Asia; = 3 days in Africa or South America. Doxycycline: Treatment as above. If patient not able to take oral medication, give 100 mg IV every 12 hours and then switch to oral doxycycline (as above) as soon as patient can take oral medication. For IV use, avoid rapid administration. Treatment course = 7 days.</td>
<td>Stomach cramps, diarrhea, blurred vision, lightheadedness, dizziness, unusual bleeding, arrhythmias, tinnitus</td>
</tr>
<tr>
<td>IV artesunate (CDC Hotline, M-F 770-488-7788; after hours, weekends, holidays, 770-488-7100)</td>
<td>Must be done under IND with instructions for preparation and administration by CDC only for hospitalizxed patients within the U.S.</td>
<td></td>
</tr>
</tbody>
</table>
Think of *P. vivax* infections as having both an acute phase and latent asymptomatic phase

Treat acute *P. vivax* infection

**Chloroquine**: 600 mg base (=1,000 mg salt) po immediately, followed by 300 mg base (=500 mg salt) po at 6, 24, and 48 hours  
Total dose: 1,500 mg base (=2,500 mg salt) OR  
**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: 1,550 mg base (=2,000 mg salt)

**AND**

Primaquine (radical cure) **must test for** G6PD deficiency!  
Before starting primaquine  
- if G6PD negative or low levels (< 6%) primaquine causes hemolysis  
  • prescribe 30 mg base (NOT 15 mg) = 2 tablets qd x 14 days
The Situation is Dire

- **Malaria is a personal tragedy**
  - Death in infants and in 1st pregnancies
  - Sickness, long term disability, chronic illness in survivors

- **Malaria is a global health tragedy**
  - Malaria kills 3,000 children a day
  - Malaria hastens spread of HIV infection**

- **Malaria is an economic-political tragedy**
  - Major cause of disability adjusted life years (DALYS)
  - Prevents development in Africa
  - A cause and a consequence of poverty