Malaria
“Bad Air”

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Malaria: Lecture Goals

• Understand basic principles of malaria pathogenesis in the context of relevance to clinical disease and epidemiology
• Understand the clinical symptoms of malaria
• Understand the difference between uncomplicated and severe malaria
• Understand how to choose an antimalarial
• Understand where to find up-to-date resources for malaria
Outline

• Background
  ▪ Organism
  ▪ Epidemiology
  ▪ Pathophysiology

• Clinical
  ▪ Symptoms
  ▪ Differential diagnosis

• Malaria in a complex emergency
  ▪ Who is at risk
  ▪ How to choose a medication
Malaria

- Caused by a protozoal blood parasite
  - *Plasmodium vivax*
  - *Plasmodium ovale*
  - *Plasmodium malariae*
  - *Plasmodium falciparum*
  - *Plasmodium knowlesi*
    - *Often cause severe malaria*
Malaria

- Transmission: *Anopheles* mosquito
- Wide spectrum symptoms
  - Fever
  - 1927 Nobel Prize: pyrotherapy for syphilis
- Geographical distribution:
  - Tropic / Subtropics
- 350-500 million infections worldwide/year
- 1 million deaths worldwide/year
• **Liver stage**: Asymptomatic. With *P. vivax* and *P. ovale*, has dormant form (hypnozoite) that can relapse much later. This form is not killed by most malaria medications.

• **Blood stage**: Symptomatic. Notice the continuous circle. This will continue until medication or immune system eradicates (1-5+ years untreated). Once cycle 3-4 days, except *P. falciparum*. 
Malaria: Endemicity and Resistance

- Chloroquine-resistant malaria
- Chloroquine-sensitive malaria
- Mefloquine-resistant malaria

POWELL B, FORD C. Cleveland Clinic Journal of Medicine 2010;77:246-254
% Malaria *P. falciparum*

Estimated percentage of malaria cases due to *P. falciparum*, 2006

http://www.who.int/gho/map_gallery/en/
Chloroquine resistance and *P. falciparum* overlap, with exceptions:
- Central America West of Panama Canal
- Haiti/Dominican Republic
- Middle East
- Make easy: Rx *P. falciparum* with ACT

Mixed infection possible
- Asia 20-30%
- Africa usually *P. falciparum*
- Americas usually *P. vivax*
P. falciparum: Dangerous

- Infects various RBC stages
- Makes RBCs “sticky”
- Result:
  - Severe hemolysis
  - Obstruction of microcirculation
  - Obstruction of capillaries
- Holo/hyperendemic
- Good News? Does not have hypnozoite
  - Hypnozoite: dormant liver form that causes relapse with *P. ovale, P. vivax*
  - Does not relapse, but can recrudesce
Malaria in a Complex Emergency: Symptoms

**UNCOMPLICATED**
- Fever
  - Not always cyclic!
- Chills, sweats
- Headache
- Myalgia
- Diarrhea, nausea, emesis
- Anemia (pallor of palms)
- Thrombocytopenia
- Hepatosplenomegaly

**SEVERE**
- > 5% parasitemia
- Severe anemia
- Hemoglobinuria
- Bleeding diathesis
- Shock/Hypotension
- Renal failure
- Hypoglycemia
- Acidosis
- **Neurologic abnormalities**
  - Biggest killer
“The symptoms are fever, the chills, and exciting adventures in the toilet..weak..really just very bad flu conditions with a little food poisoning thrown in to make you the perfect party guest.”

Malaria in a Complex Emergency: Who is at Risk for severe disease?

• Highest risk populations:
  - Non-immune
  - Immunocompromised, malnourished
  - Infants, young children, pregnant
  - Infected with *P. falciparum*

• In endemic areas, older children and adults develop partial immunity
  - Can have “asymptomatic” infection
  - Can have subacute or chronic symptoms
Malaria in a Complex Emergency

• Displaced people within malaria endemic areas creates risk for a severe epidemic, particularly if the displaced persons are from less endemic areas (highlands to lowlands)

• Laboratory diagnosis may be impractical

• May become necessary to:
  ▪ Treat some people based on clinical history
  ▪ Do mass fever treatment
Malaria: Practical Aspects of Diagnosis

- Presumptive treatment has been commonplace for decades
  - Problematic, but hard to change
- Even in holoendemic countries, WHO estimates <1/3\(^{rd}\) of febrile episodes due to malaria
- In Africa, <20\% of suspected cases receive a confirmatory diagnostic test
Malaria in a Complex Emergency

• Important, when possible, to at least establish a fever epidemic is due to malaria
  ▪ Do some diagnostics
    • Combination of smears and rapid diagnostic tests
    • To establish malaria as cause
    • To monitor epidemic curve
  ▪ Evaluate for other diseases
  ▪ Monitor clinical response
Malaria: Differential Diagnosis

- Malaria can involve many organs
- Coinfection well described
- Differential diagnosis is broad
  - *Salmonella typhi* and non-typhi
  - *Staphylococcus aureus* with focus (bone, joint, muscle, lung, heart)
  - Dengue, yellow fever, japanese encephalitis
  - Pneumonia
  - Viral and bacterial meningitis/encephalitis
  - Leshmaniasis
  - Schistosomiasis
  - Tuberculosis
  - Liver abscess/cholangitis
  - Oncologic process
Malaria: Diagnostics

- **Rapid diagnostic test (RDT)**
  - Lateral flow test, relies on antibody-antigen interactions
  - Some RDTs specific for *P. falciparum*
  - WHO quality assurance programs underway
    - Clinician/Public acceptance large problem
  - USA: only to confirm species

- **Microscopy**
  - Thick: diagnosis
  - Thin
    - Identification and parasitemia
      - % parasitized RBCs
**Clues to *P. falciparum***:

- Trophozoites most commonly seen, and are small, delicate rings, often multiple per RBC; infect all ages of RBC.
- Gametocytes “banana” shaped.
Malaria: Treatment

MALARIA
CURED BY QUININE
TAKE THE STANDARD TREATMENT
SEE YOUR PHYSICIAN
MISS. STATE BOARD OF HEALTH
CDC Algorithm for Traveler Returned to US

*Not the same as WHO*

Note: CDC now recommending treating severe malaria with artesunate; treat with atovoquone-proquinal until it arrives (5-12 hours). To enroll a patient with severe malaria in this treatment protocol, contact the CDC Malaria Hotline: 770-488-7788 (M-F, 8am-4:30pm, eastern time) or after hours, call 770-488-7100 and request to speak with a CDC Malaria Branch clinician.

http://www.cdc.gov/malaria/diagnosis_treatment/treatment.html
Malaria: Treatment

WHO guidelines and update can be found at: http://www.who.int/malaria/publications/atoz/9789241547925/en/index.html
Malaria: Therapy Options

- ACT (Artemisinin-based combination therapies)
  - **Artemethur + lemefantrine (coartem®)**
  - Artesunate + amodiaquique (coarsucam/ASAQ Winthrop®)
  - Artesunate + mefloquine (AS+MQ)
  - Artesunate + sulfadoxine-pyrimethamine (AS+SP)
    - Not for *P. vivax*
  - Artesunate + doxycycline or clindamycin
  - Dihydroartemisinin plus piperaquine (DHA+PPQ)
  - Quinine + doxycycline or clindamycin
  - Atovaquone + proguanil (malarone®)
  - Mefloquine (larium®)
  - Chloroquine (widespread resistance)
  - Primaquine (kills liver phase for *P. vivax/ovale*)
  - IV and IM: **Artesunate**, artemethur, quinine
  - Rectal: Artesunate
Suspected malaria

Blood films or RDT if available

- Repeat each 12-24 hours for three sets

+ Calculate parasitemia

Evaluate probability based on local epidemiology

- Reassess each 12-24 hours, evaluate alternative causes

+ Categorize as uncomplicated or severe

Not available

Decision to treat

Decision not to treat
Uncomplicated malaria: treatment

*P. falciparum* possible by epidemiology or smear?

- Use local resistance patterns to choose medication:
  - Chloroquine
  - ACT
  - Hydroxychloroquine
  - Atovoquone-proguanil
  - Mefloquine
  - Quinine + doxycycline
  - * Re-dose if emesis within 30 min

If *P. vivax/ovale* and patient not G6PD deficient, treat with primaquine

Use local resistance patterns to choose medication:

* ACT
  - artesunate plus tetracycline /doxycycline/clindamycin
  - Quinine plus tetracycline /doxycycline/clindamycin
  - Atovoquone-proguanil
  - Mefloquine
  - Quinine + doxycycline
  - * Re-dose if emesis within 30 min

Consider admission to monitor disease progression
Severe Malaria: WHO Criteria

One or more of the following:

- **Clinical features:**
  - Impaired consciousness, prostration
  - Failure to feed
  - Seizures
  - Respiratory distress
  - Circulatory collapse
  - Clinical jaundice plus evidence of other vital organ dysfunction
  - Gross hemoglobinuria
  - Abnormal spontaneous bleeding
  - Pulmonary edema (radiological)

- **Laboratory findings:**
  - Hypoglycemia (blood glucose < 2.2 mmol/l or < 40 mg/dl)
  - Metabolic acidosis (plasma bicarbonate < 15 mmol/l)
  - Severe normocytic anaemia (Hb < 5 g/dl, packed cell volume < 15%)
  - Hemoglobinuria
  - Hyperparasitaemia (> 2%/100 000/μl in low intensity transmission areas or > 5% or 250 000/μl in areas of high stable malaria transmission intensity)
  - Hyperlactatemia (lactate > 5 mmol/l)
  - Renal impairment (serum creatinine > 265 µmol/l).
Severe malaria: Treatment the same regardless of species! Therapy + supportive care:

Intravenous medications available?

- **no**
  - Give oral or rectal until patient can be transferred to referral center:
    - rectal artesunate
    - quinine IM
    - artesunate IM
    - artemether IM
  - If illness is with *P. ovale/vivax*, follow with primaquine if not G6PD deficient

- **yes**
  - Treat IV x 24 hours minimum
    - Artesunate IV or IM
    - Artemether
    - Quinine
  - Ongoing supportive care, including:
    - evaluation for blood transfusion
    - treatment for coinfection
    - treatment of seizures
  - Follow with full course of oral antimalarial:
    - ACT
    - artesunate plus clindamycin or doxycycline
    - quinine plus clindamycin or doxycycline
Malaria: Prevention

• Bed Nets!!!!!!
  ▪ 1000 nets save 5 lives
    • Insecticide impregnated best
  ▪ Cochrane Review, 2009

• Indoor/personal insecticides

• Vaccine: on the horizon?
  ▪ Some candidates reaching clinical trials, with short-lived efficacy
Take Home Points

• Malaria endemicity and seasonality depends on mosquito habits, seasonality, and *Plasmodium spp.*
• Resistance to medications is species and location dependant
  ▪ If *P. falciparum*, assume chloroquine resistant
    • Exception: Island of Hispaniola
• Clinical:
  ▪ Who is at highest risk
  ▪ How to differentiate severe vs. uncomplicated malaria
  ▪ Differential diagnosis
• How to choose an anti-malarial treatment:
  ▪ ACTs are preferred therapies, all species
    • ACT if oral, artesunate if IV
  ▪ Severe malaria treated same regardless of species
• Where to find up-to-date resources on Malaria
Malaria: Resources

- Interactive map on malaria activity:
  - [http://cdc-malaria.ncsa.uiuc.edu/](http://cdc-malaria.ncsa.uiuc.edu/)

- How to do a malaria smear:
  - [C:\Documents and Settings\dr003093\Desktop\MMWR diagnosis of malaria.mht](C:\Documents and Settings\dr003093\Desktop\MMWR diagnosis of malaria.mht)

- How to interpret a malaria smear:
  - [http://dpd.cdc.gov/dpdx/html/Frames/M-R/Malaria/body_Malariadiagfind2.htm](http://dpd.cdc.gov/dpdx/html/Frames/M-R/Malaria/body_Malariadiagfind2.htm)

- How to treat Malaria
  - WHO guidelines: