Clinical malaria

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What’s so bad about malaria?

- 40% of world’s population at risk, 90 countries
- Prevalence: 200-300 million cases per year
- ~1 million deaths/year
- *P. falciparum* causes more deaths in children <5y than any other organism
Malaria in the United States

- 1000-2000 cases/year reported to the CDC
- 7 million Americans travel to malaria endemic areas every year
- Isolated cases of locally transmitted malaria have been reported in several states
- *Anopheles* mosquitoes common in the U.S.
Global distribution of malaria
Organisms causing malaria

- *Plasmodium falciparum*
- *Plasmodium vivax*
- *Plasmodium ovale*
- *Plasmodium malariae*
- *Plasmodium knowlesi*  
  (Yes, there is now a fifth species that causes human malaria!)
Malaria life cycle

- Infection
- Transmission to mosquito
- Sporozoites
- Liver
- Macroglobules
- Asexual cycle
- Gametocytes
Clinical Presentation: Adults

- Classic fever pattern
  - Tertian (every 48 hrs): *P. vivax*, *P. ovale*
  - Quartan (every 72 hrs): *P. malariae*
  - “Malignant tertian”: *P. falciparum*
  - This fever pattern occurs after parasites have synchronized (2-3 days); may not be seen on initial presentation

- Three stages of the malaria paroxysm
  - “Cold”: shaking chills
  - “Hot”: temperature to 40°C or higher, systemic symptoms, minimal or no diaphoresis (“dry”)
  - “Sweating”: diaphoresis, fever resolves, fatigue
Clinical Presentation: Adults

- Physical exam findings relate mostly to complications

- May see:
  - tachycardia, diaphoresis, tachypnea, ill appearance
  - pallor (from hemolytic anemia)
  - splenomegaly (less common than in children)
Clinical Presentation: Children

- Often do not have classic malaria paroxysm

- Prominent features include:
  - General malaise, fatigue, listlessness
  - Gastrointestinal: vomiting, nausea, loose stools
  - Fever, generally high (> 40° C)
  - Dehydration, if vomiting and loose stools severe
  - Headache
Clinical Presentation: Children

Physical findings may include:

- Tachypnea, tachycardia, ill appearance
- Pallor (from hemolytic anemia)
- Hepatosplenomegaly (may take days to appear, can be very prominent)
- Jaundice
- Dehydration
- Lethargy
- Respiratory distress (Kussmaul’s respirations)
P. vivax & P. ovale disease

- Symptoms from P. vivax and P. ovale can make children very ill

- Complications: hypersplenism, anemia and relapse

- P. vivax can cause death, primarily from severe anemia – in some areas of Papua New Guinea, P. vivax causes as many deaths as P. falciparum

- Relapse occurs only with P. vivax and P. ovale (only these Plasmodium spp. have liver hypnozoites)
**P. malariae disease**

- Only *P. malariae* causes nephrotic syndrome
- Can cause chronic asymptomatic parasitemia, sometimes for several years after the last exposure
- In general causes milder clinical disease than the other *Plasmodium* species
**P. knowlesi** – something new

- Primate malaria species
- Human disease first described in large scale in 2004
- Occurs in southeast Asia (Malaysia, Thailand, Philippines, Singapore)
- Usually causes mild-moderately severe disease
- Multiplies every 24h, and so, like *P. falciparum*, can cause very high-density parasitemia and death
- Clinical clue: very ill patient, with malaria spp that looks like *P. malariae* on smear, but high density
*P. falciparum* causes most severe disease and deaths from malaria*

*increasing severe disease reported in Southeast Asia with *P. vivax*
P. falciparum: complications

- Cerebral malaria
- Severe malarial anemia
- Acute renal insufficiency ("blackwater fever")
- Pulmonary edema/ARDS
- Metabolic acidosis
- Hypoglycemia
- Vascular collapse/ shock ("algid malaria")
Long-term complications of cerebral malaria

- **Neurologic deficits**
  - Present in ~25% of children at discharge
  - Decreases to 1-4% 6 mo after discharge

- **Cognitive impairment**
  - Present in ~25% of children 2y after episode
  - Primarily attention and language problems
Tropical Splenomegaly Syndrome
Diagnosis

- **Parasitemia on blood smear**
  - Thick smear: more likely to see parasites
  - Thin smear: better for identifying species
  - Level of parasitemia changes; may need 2 or 3 smears

- Hemolytic anemia

- Mild leukopenia (3,000-6,000 WBC/µl)

- Thrombocytopenia
Other diagnostics

- Rapid diagnostic tests (RDTs)
  - LDH or HRP-2 based
  - >95% sensitive and specific for *P. falciparum*
  - >85% sensitive, 95% specific for *P. vivax*
  - Decreased sensitivity with low parasitemia
  - Little data for *P. malariae, P. ovale, P. knowlesi*

- PCR
  - More sensitive than microscopy
  - Generally not available in endemic countries
+ \textit{P. falciparum}
*P. falciparum* gametocyte
$P.\ vivax$
*P. vivax* - Schuffner’s stippling*

*also seen with *P. ovale*
Children in Endemic Areas

- Semi-immune children in an endemic area may have chronic low-level parasitemia.
- Therefore, a “positive smear” in a febrile child does not establish malaria as the cause of the child’s symptoms.
- Level of parasitemia may roughly correlate with level of disease.
- Malaria often causes co-morbidity with other childhood illnesses.
Malaria treatment

- The most effective treatments are more than a thousand years old
  - Quinine
  - Artemisinin derivatives
Treatment

- **Severe malaria**
  - **US:** *quinidine IV* plus either doxycycline or clindamycin
  - **Africa:** *quinine IV* plus either doxycycline or clindamycin
  - **Southeast Asia:** *artesunate IV* plus one of: doxycycline, mefloquine, atovaquone-proguanil or clindamycin
Supportive treatment, severe malaria

- Seizure management
  - Monitor for seizures
  - Watch for respiratory depression with diazepam and phenobarbital combination

- Monitor for hypoglycemia (from disease or quinine treatment)

- Consider exchange transfusion for severe malaria with parasitemia >10%

- Treatment for acidosis is treatment of infection, no evidence of benefit from bicarbonate
Treatment

- Uncomplicated malaria
  - US: *malarone* or *quinine*; *chloroquine* if *chloroquine*-sensitive
  - Africa: artemisinin combination therapy (*ACT*), most common is *Coartem* (artemether-lumefantrine)
  - SE Asia: artemisinin combination therapy (*ACT*), often artemether-mefloquine
Malaria treatment: non-falciparum

- Chloroquine

- Resistant *P. vivax* reported in Oceania, if in risk area, use quinine

- *P. knowlesi* – chloroquine + primaquine; severe – treat like *P. falciparum*
Primaquine

- Give primaquine at the end of *P. vivax* or *P. ovale* treatment to eradicate any liver hypnozoites

- If a person been in a vivax or ovale endemic area, treat with primaquine plus usual treatment, even if only *P. falciparum* is seen on smear

- Check for G6PD deficiency prior to giving – risk of hemolysis with primaquine and G6PD deficiency
“Textbook”

  - Best online summary of clinical malaria
  - “Clearinghouse” for malaria information
- Guerrant’s *Tropical Infectious Diseases*
- Rudolph’s *Pediatrics*
- Nelson’s *Textbook of Pediatrics*