PATHOPHYSIOLOGY OF MALARIA

Disease Severity and Duration

	vivax	ovale	malariae	falciparum
Prepatent Period (days)	8-12	8-12	15-18	6-9
Incubation Period (days)	8-27	8-27	16->40	6-25
Severity of Initial Paroxysms	moderate to severe	mild	mild to moderate	severe
Average Parasitemia (per mm^3)	20,000	9,000	6,000	50,000-500,000
Maximum Parasitemia (per mm^3)	50,000	30,000	20,000	2,500,000
Typical Symptom Duration (untreated)	3-8 weeks	2-3 weeks	3-24 weeks	2-3 weeks
Maximum Infection Duration (untreated)	5-8 years*	12-20 months*	20-50 years	6-17 months
Anemia	++	+	++	++++
Other Complications			renal	cerebral

*Includes relapses

Cerebral Malaria

- complication of severe falciparum malaria
- associated with sequestration in microvasculature
- a diffuse encephalopathy with loss of consciousness
  - consciousness ranges from stupor to coma
  - onset can be gradual or sudden
  - unresponsive to pain, visual, and verbal stimuli

Complications

- cerebral malaria
- anemia
- hyperpyrexia
- hypoglycemia
- acidosis
- GI and liver syndromes
- pulmonary edema
- blackwater fever
- algid malaria (shock)

Severe Malaria Features

- impaired consciousness
- repeated convulsions
- respiratory distress
- shock
- acidosis/hyperlactemia
- hypoglycemia
- jaundice or other liver malfunctions
- renal impairment
- high parasitemia (>500,000/mm3)

Increased morbidity and mortality of *P. falciparum*:

- higher parasitemia
  - all erythrocytes invaded
  - large # of merozoites
- sequestration of trophozoites and schizont infected erythrocytes
  - complications in specific tissues
  - immune evasion (avoidance of spleen)
  - low oxygen tensions in deep tissues (better growth)
  - better invasion

Knobs and Cytoadherence

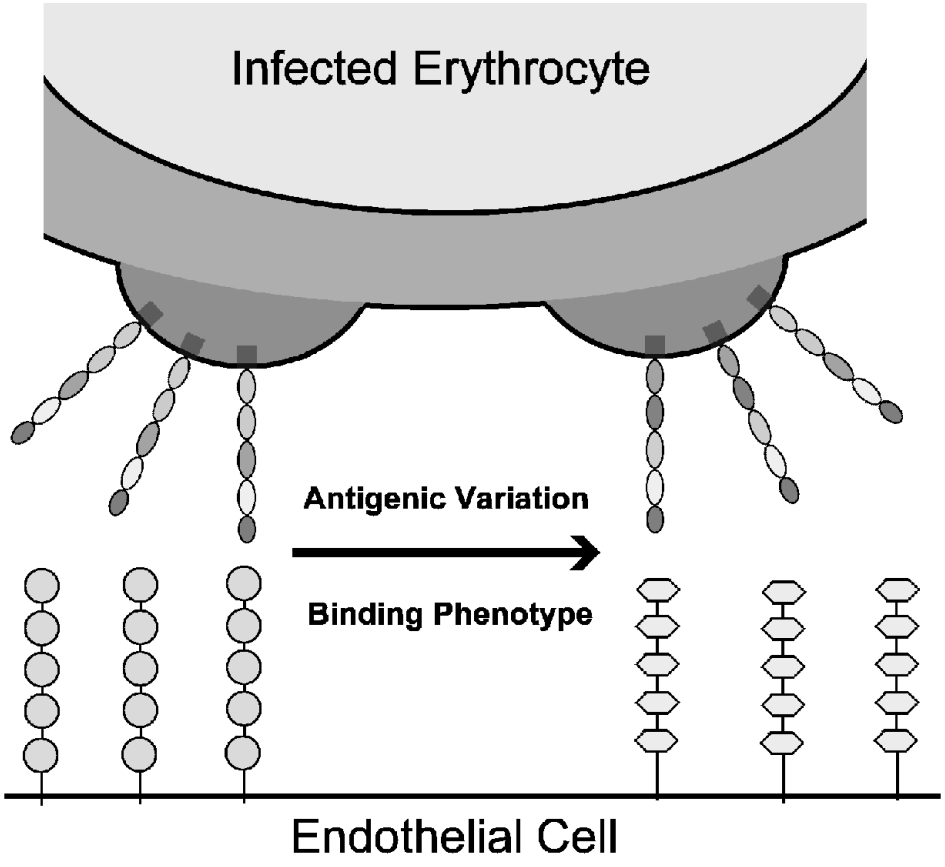
- knobs expressed on surface of infected erythrocytes medicate cytoadherence to host endothelial cells
- several parasite proteins are associated with knobs and knob formation
  - knob associated histidine rich protein
  - *Pf* erythrocyte membrane proteins 1 and 2
- *Pf*EMP-1 is exposed on outer surface of infected erythrocyte

Pf EMP1 Structure

- family of 40-50 *var* genes
- conserved intracellular C-terminus
  - acidic terminal segment (ATS)
  - binds cytoskeleton + KAHRP
- transmembrane domain
- variable extracellular domain composed of modules
  - 2-7 copies of Duffy-binding like domains
  - 5 sequence types (a, b, g, d, e)
  - 1-2 cys-rich interdomain regions
  - all have DBL1a + CIDR
- participates in cytoadherence

Possible Host Receptors

- CD36
- Ig super-family
  - **ICAM-1**
  - VCAM-1
  - PECAM-1
- E-selectin
- thrombospondin
- chondroitin sulfate A
- Rosetting Receptors
  - CR-1
  - glycosaminoglycan
  - blood group A



Sequestration Hypothesis

cytoadherence
↓
cerebral ischemia
↓
hypoxia/metabolic effects
↓
coma
↓
death

Neurological sequelae among survivors of cerebral malaria:

23.3%	at discharge
8.6%	at 1 month
4.4%	at 6 months

van Hansbroek *et al*. (1997) J. Pediatr. 131:125

Cytokine Theory

exoantigens
↓
TNFα + IL-1
↓
±nitric oxide
↓
coma
↓
death