OUT OF AFRICA AND INTO FLORIDA: AN UPDATE ON MALARIA IN 2024

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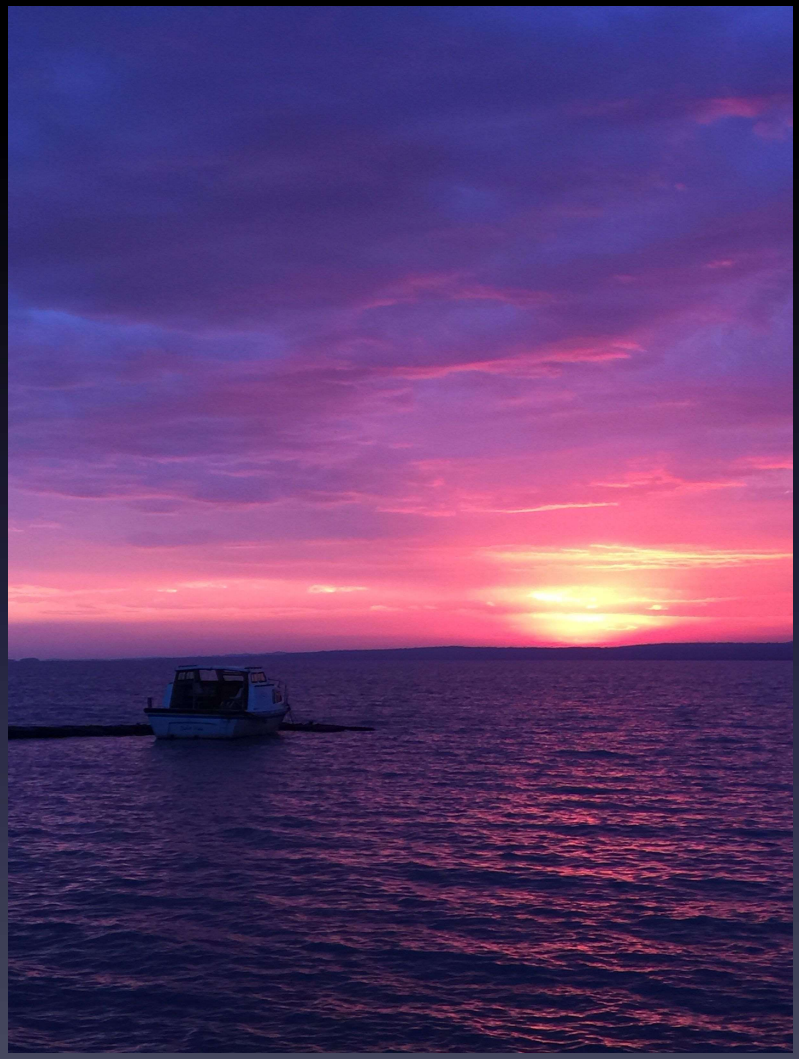
LEARNING OBJECTIVES

- Provide overview of clinical syndromes of malaria
- Discuss pathogenesis of severe malaria
- Discuss current treatments for malaria
- Update recent malaria status in Florida



Disclosures

Ravi Durvasula, M.D., faculty for this educational activity, has no relevant financial relationships with ineligible companies to disclose, and has indicated that the presentation or discussion will not include off-label or unapproved product usage.

CASE HISTORY

- 63 year old man went wilderness hunting in Tanzania for 3 weeks
- Without prophylactic medications
- Returned to US and within week had high fevers and obtundation
- Initial head CT showed no abnormalities
- Admitted to ICU

CASE HISTORY

- Responsive only to pain at admission
- Hgb=12.2 g/dL
- WBC= 17,300/uL
- Platelets= 21,000/uL
- BUN= 52 mg/dL
- Creatinine= 1.36 mg/dL
- Lactate= 8.3 mmol/L
- pH= 7.24

CASE HISTORY

- Blood smear revealed >25% parasitized red cells with ring forms, consistent with Plasmodium falciparum
- CSF revealed ring forms; xanthochromic; normal glucose
- Antimicrobials started empirically: vancomycin, cefipime, acyclovir and doxycycline
- Quinidine gluconate given intravenously
- Artesunate 250 mg IV at 0, 12, 24 and 48 hours

CASE HISTORY

- Very tenuous hospital course
- Parasite load dropped to <1% with Artesunate
- Remained intubated and sedated
- Worsening renal failure requiring hemodialysis
- Massive hemolysis, persistent fevers
- Hgb= 8.1 mg/dL on day 5
- Platelet count= 69,000/uL

CASE HISTORY

- No improvement in mentation
- CT scan on Day 5 revealed multiple areas of hypoattenuation: right and left globus pallidus and right caudate body
- Suggestive of severe ischemic/ toxic insult
- Patient transitioned to comfort care and expired

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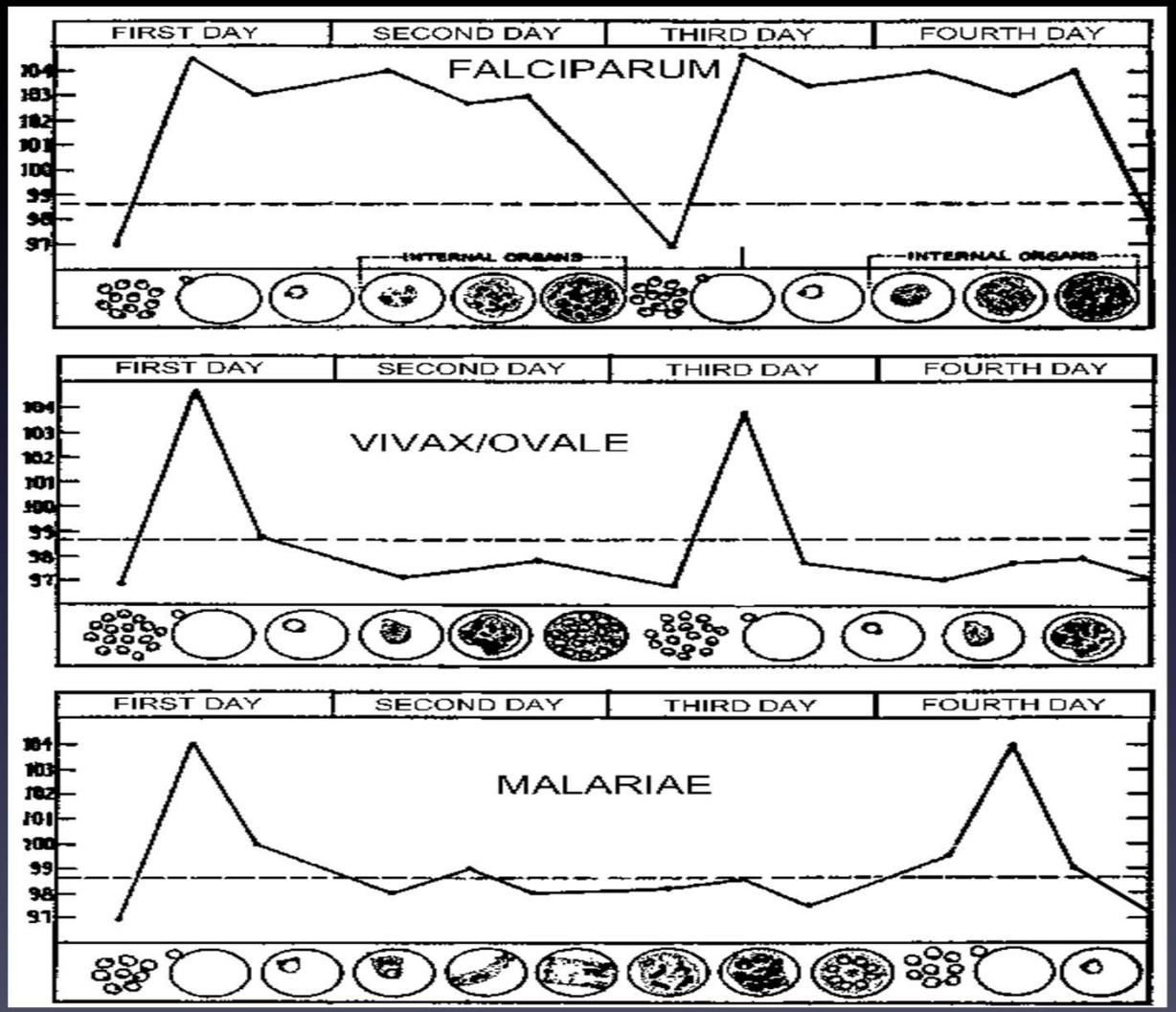
Europe
Central Asia
nerica
Caribbean
Central America
Middle
East and Asia
Africa
South America
Indian
Subcontinent
Australia &
South Pacific


MALARIA IS 100% TREATABLE AND PREVENTABLE
each year
655,000 people die from MALARIA
200,000 of these deaths are NEWBORNS
10,000 MOTHERS DIE
SIMPLE INTERVENTIONS can save LIVES
PREVENTIVE MALARIA MEDICINE & ANEMIA SCREENING DURING PRENATAL CARE
USE OF BED NETS
PROMPT DIAGNOSIS, TREATMENT AND COUNSELING FOR MALARIA ILLNESS & ANEMIA
INVEST IN THE FUTURE
DEFEAT MALARIA
innovating to save lives
Jhpiego
an affiliate of Johns Hopkins University
ROLL BACK MALARIA
Sources: WHO (2012). World Malaria Report. Geneva, Switzerland; http://www.who.int/malaria/high_risk_groups/pregnancy/en/

MAJOR MALARIAL SYNDROMES: GENUS PLASMODIUM



NEWER STRAINS OF PLASMODIUM

- Plasmodium knowelsi transmitted from Rhesus macaques to humans, up to 70% of cases in SE Asia: Thailand, Malaysia, Singapore
- Plasmodium brasilianum, transmitted via New World monkey reservoirs in the Amazonian basin: identified in Venezuela

Research Paper

EBioMedicine (2015)
Published by THE LANCET

Natural infection of *Plasmodium brasilianum* in humans: Man and monkey share quartan malaria parasites in the Venezuelan Amazon

Albert Lalremruata [a], Magda Magris [b], Sarai Vivas-Martínez [b,d], Maike Koehler [a], Meral Esen [a], Prakasha Kempaiah [c], Sankarganesh Jeyaraj [a], Douglas Jay Perkins [c], Benjamin Mordmüller [a], Wolfram G. Metzger [a,b,*]

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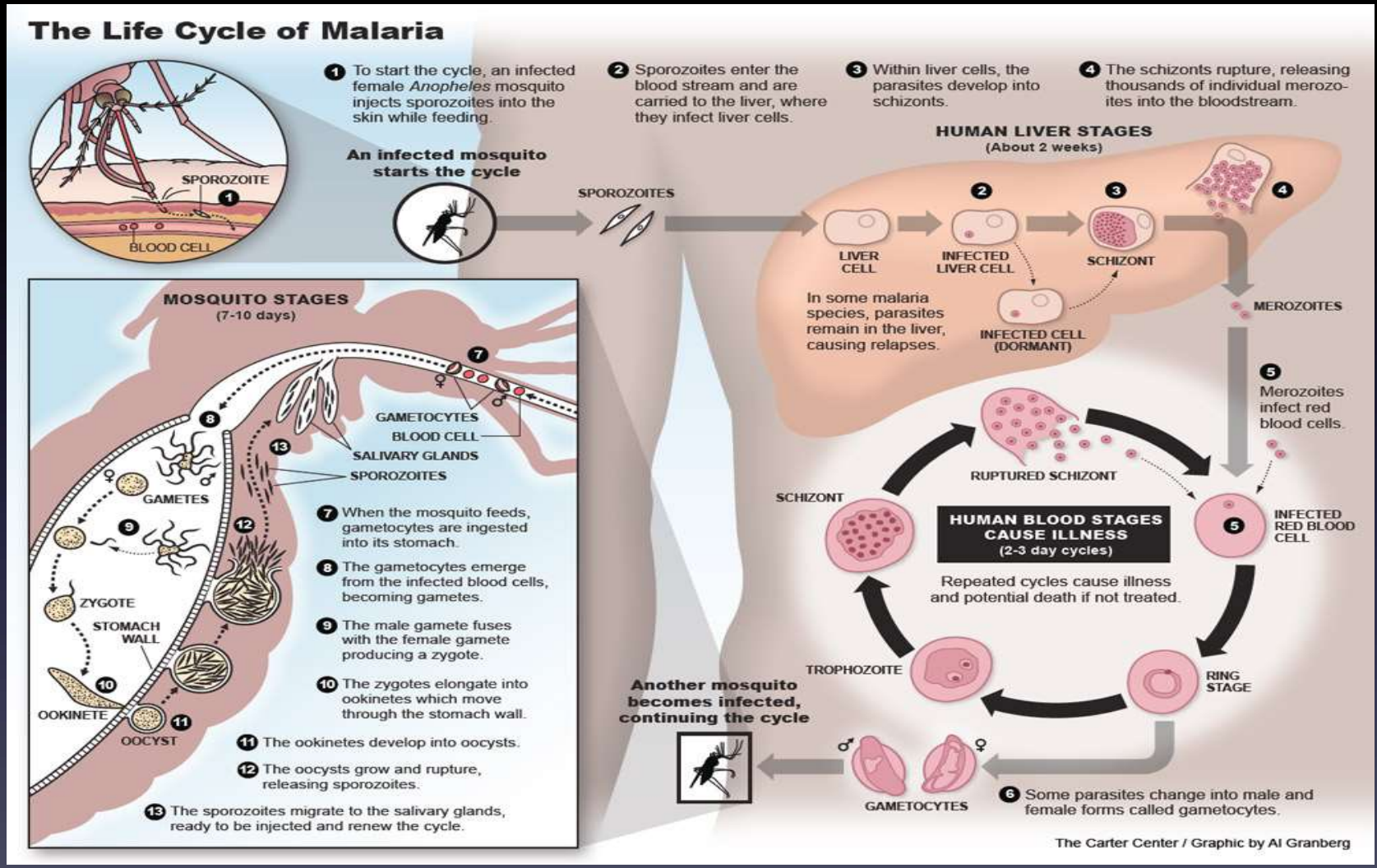
LIFE CYCLE OF PLASMODIUM



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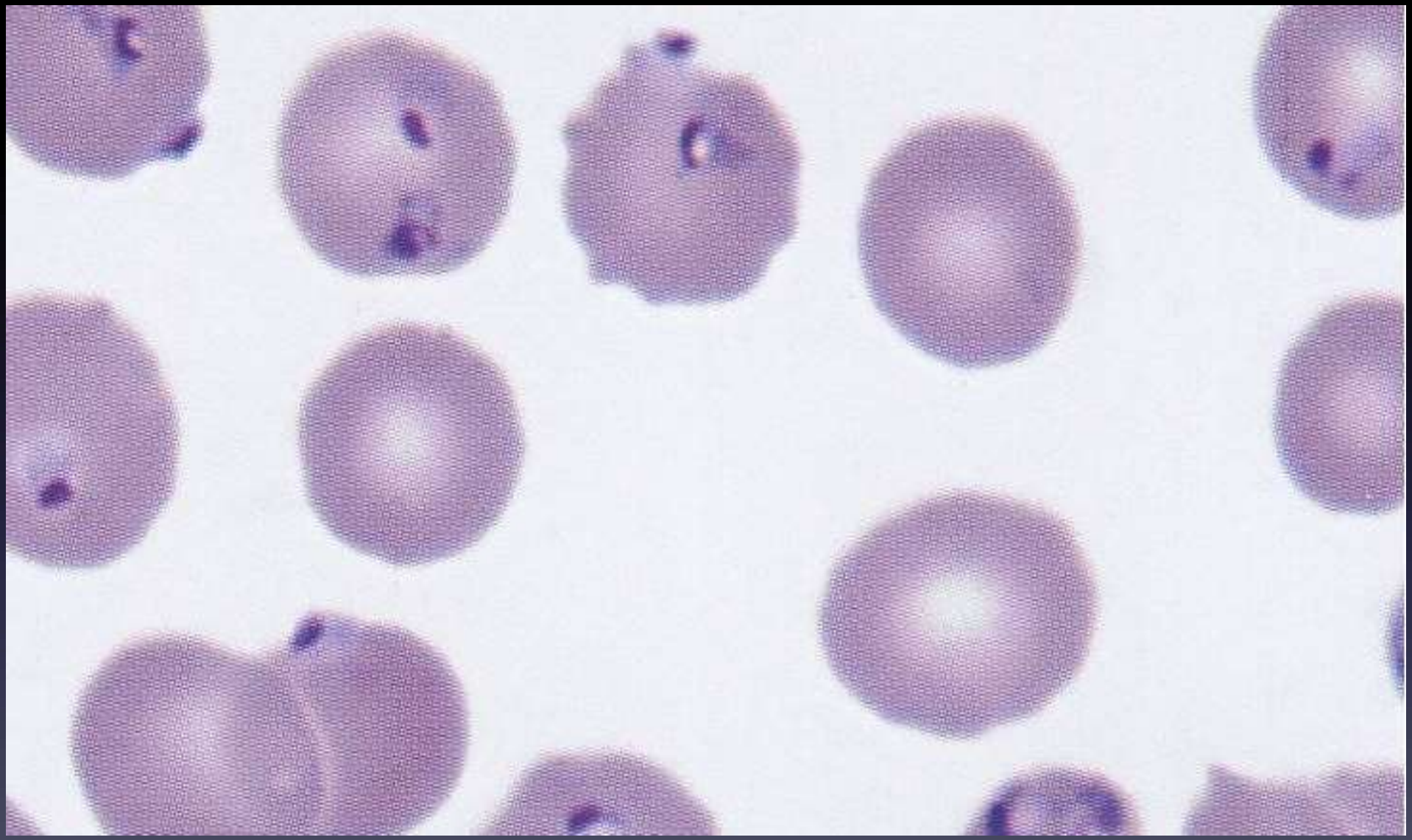

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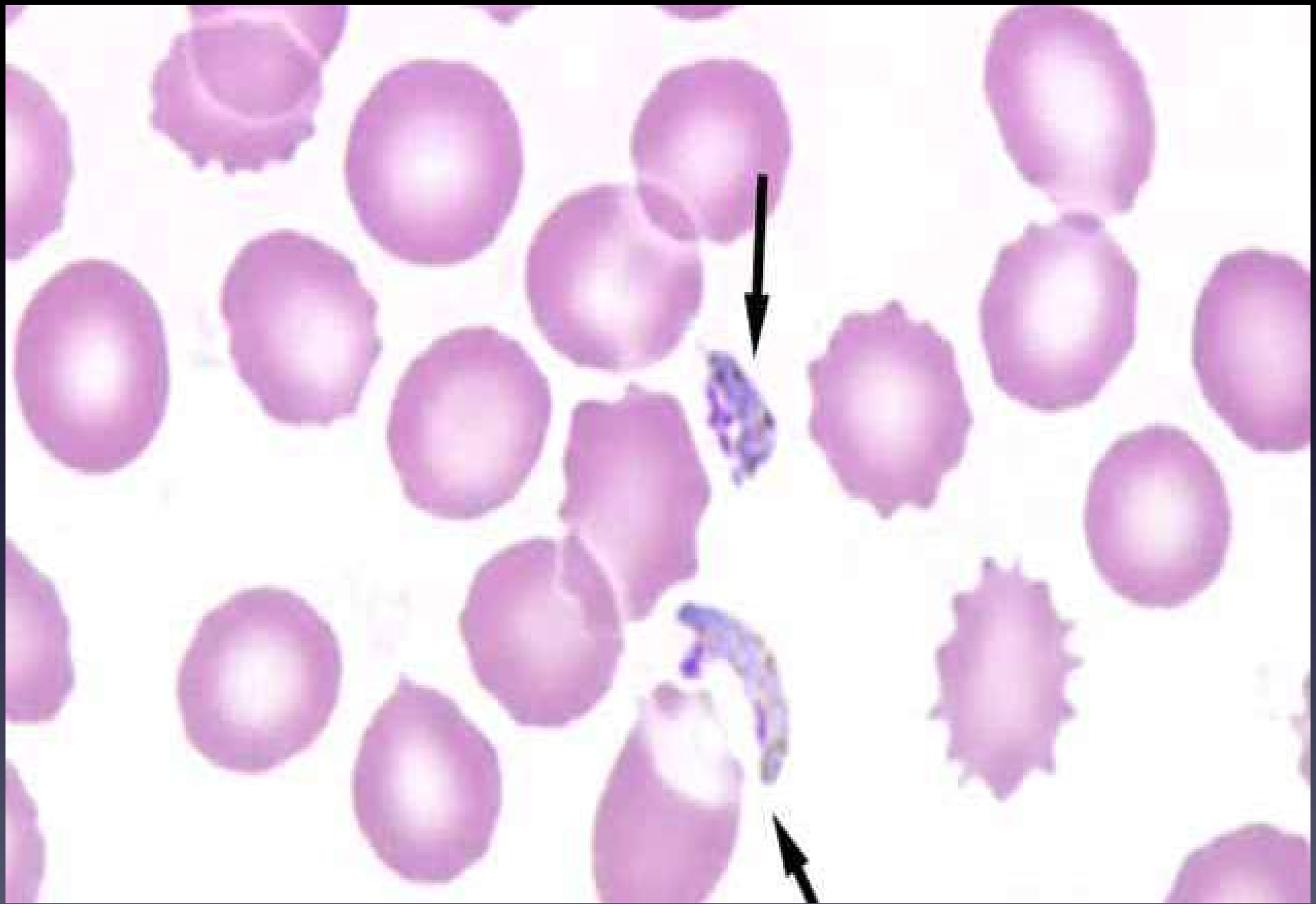
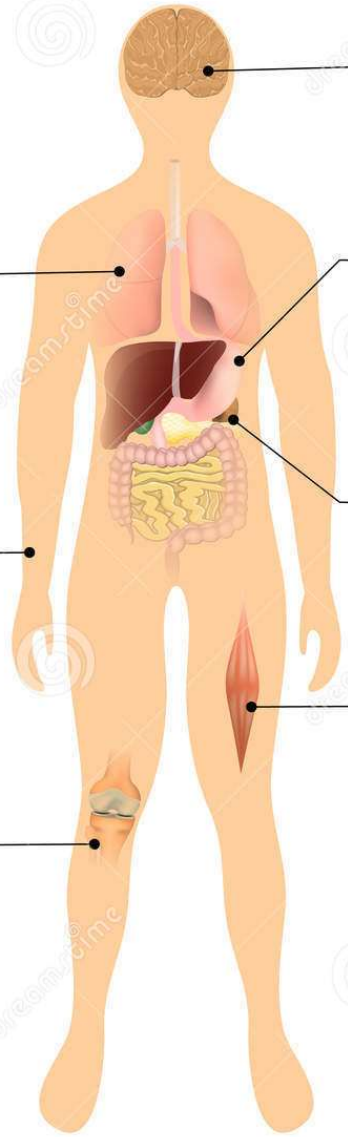


SYMPTOMS OF MALARIA



Headache

Respiratory system
- dry cough

Stomach
- vomiting
- nausea

Spleen
- enlargement

Skin
- fever
- shivering
- jaundice

Muscle
- pain
- fatigue
- convulsions

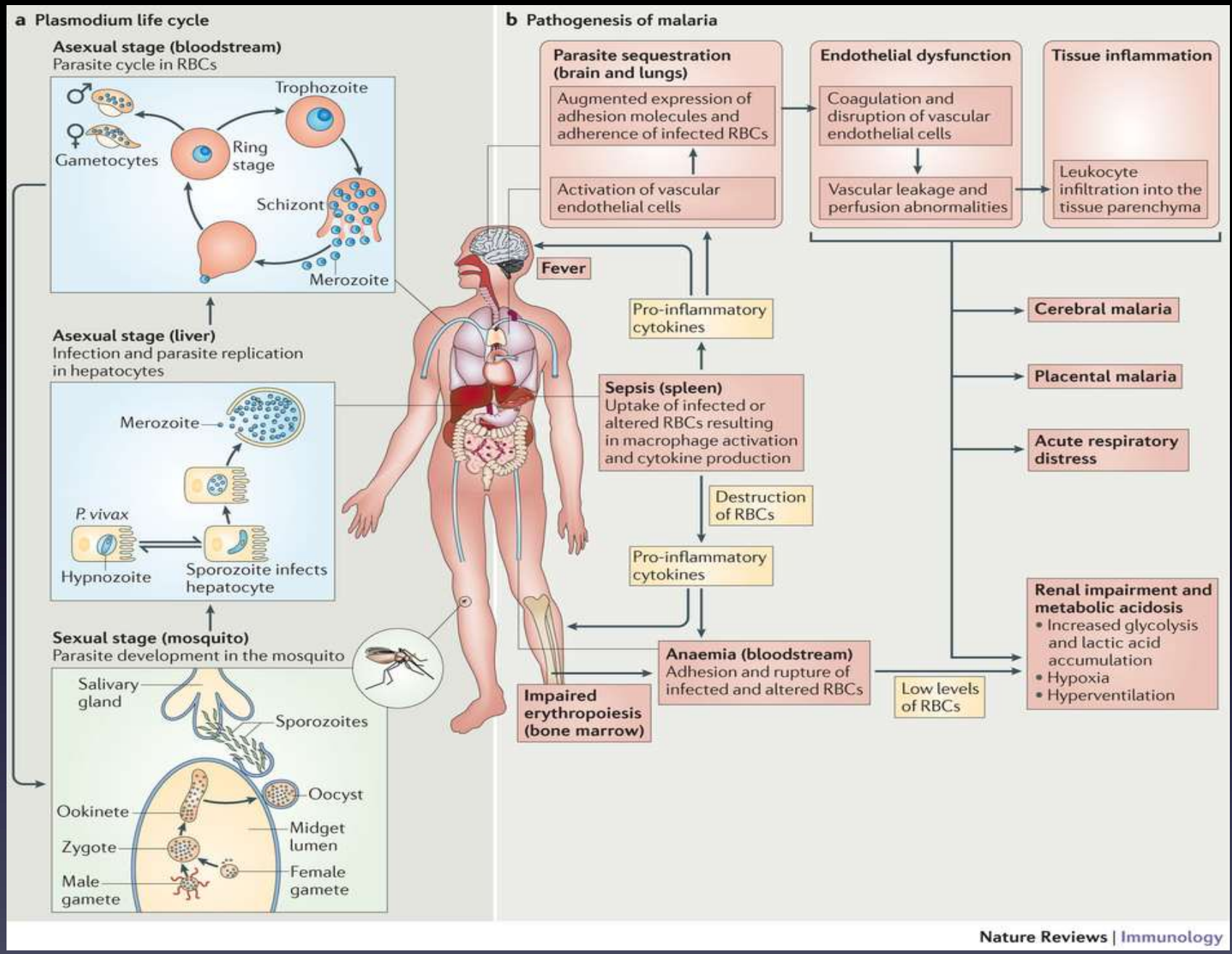
Joints
- pain

Nature Medicine 2013 19:2

Table 1 | **Severe and fatal disease syndromes in malaria**

Syndrome	Clinical features	Possible sequence or mechanism of disease
Cerebral malaria	Sustained impaired consciousness, coma, long-term neurological sequelae	Cerebral parasite sequestration; bioactive GPI; pro-inflammatory cytokine cascade; endothelial-cell activation; natural killer T-cell activation; T_H1/T_H2-cell balance; chemokine production; monocyte, macrophage and neutrophil recruitment; platelet and fibrinogen deposition; $CD4^+$, $CD8^+$ and $\gamma\delta$ T-cell involvement; IFN-γ production; neurological metabolic derangements; possibly hypoxia
Placental malaria	Placental insufficiency, low birth weight, premature delivery, loss of fetus	*Plasmodium falciparum* EMP1-mediated binding to placental endothelium and syncytiotrophoblast through chondroitin sulphate A and hyaluronic acid; cytokine production; chemokine-mediated recruitment and infiltration of monocytes; intravascular macrophage differentiation
Severe malarial anaemia	Pallor, lethargy, haemoglobin level of 4–6 g per 10 ml	Erythropoietic suppression by toxins and cytokines; increased RBC destruction, owing to parasitization, RBC alterations, complement and immune complex or antigen deposition, erythrophagocytosis, splenic hyperphagism, $CD4^+$ T cells, T_H1/T_H2 cytokine balance (TNF and IFN-γ versus IL-10)
Metabolic acidosis	Respiratory distress, deep breathing (Kussmaul breathing), hypovolaemia	Molecular mechanisms unknown. Possibly widespread parasite sequestration; bioactive toxins; increased vascular permeability; reduced tissue perfusion; anaemia; pulmonary airway obstruction; hypoxia; increased host glycolysis; repressed gluconeogenesis. Some overlap with shock-like syndrome
Shock-like syndrome (systemic inflammatory-response-like syndrome)	Shock, haemodynamic changes, impaired organ perfusion, disseminated intravascular coagulation	Bioactive toxins; T_H1 cytokines; acute-phase reactants

EMP1, erythrocyte membrane protein 1; GPI, glycosylphosphatidylinositol; IFN-γ, interferon-γ; IL-10, interleukin-10; RBC, red blood cell; T_H, T helper; TNF, tumour-necrosis factor.


a Plasmodium life cycle
Asexual stage (bloodstream)
Parasite cycle in RBCs
Trophozoite
Gametocytes
Ring stage
Schizont
Merozoite
Asexual stage (liver)
Infection and parasite replication in hepatocytes
Merozoite
P. vivax
Hypnozoite
Sporozoite infects hepatocyte
Sexual stage (mosquito)
Parasite development in the mosquito
Salivary gland
Sporozoites
Oocyst
Ookinete
Midget lumen
Zygote
Female gamete
Male gamete
b Pathogenesis of malaria
Parasite sequestration (brain and lungs)
Augmented expression of adhesion molecules and adherence of infected RBCs
Activation of vascular endothelial cells
Endothelial dysfunction
Coagulation and disruption of vascular endothelial cells
Vascular leakage and perfusion abnormalities
Tissue inflammation
Leukocyte infiltration into the tissue parenchyma
Fever
Pro-inflammatory cytokines
Cerebral malaria
Placental malaria
Acute respiratory distress
Sepsis (spleen)
Uptake of infected or altered RBCs resulting in macrophage activation and cytokine production
Destruction of RBCs
Pro-inflammatory cytokines
Renal impairment and metabolic acidosis
• Increased glycolysis and lactic acid accumulation
• Hypoxia
• Hyperventilation
Anaemia (bloodstream)
Adhesion and rupture of infected and altered RBCs
Low levels of RBCs
Impaired erythropoiesis (bone marrow)
Nature Reviews | Immunology

MECHANISMS of PATHOGENESIS

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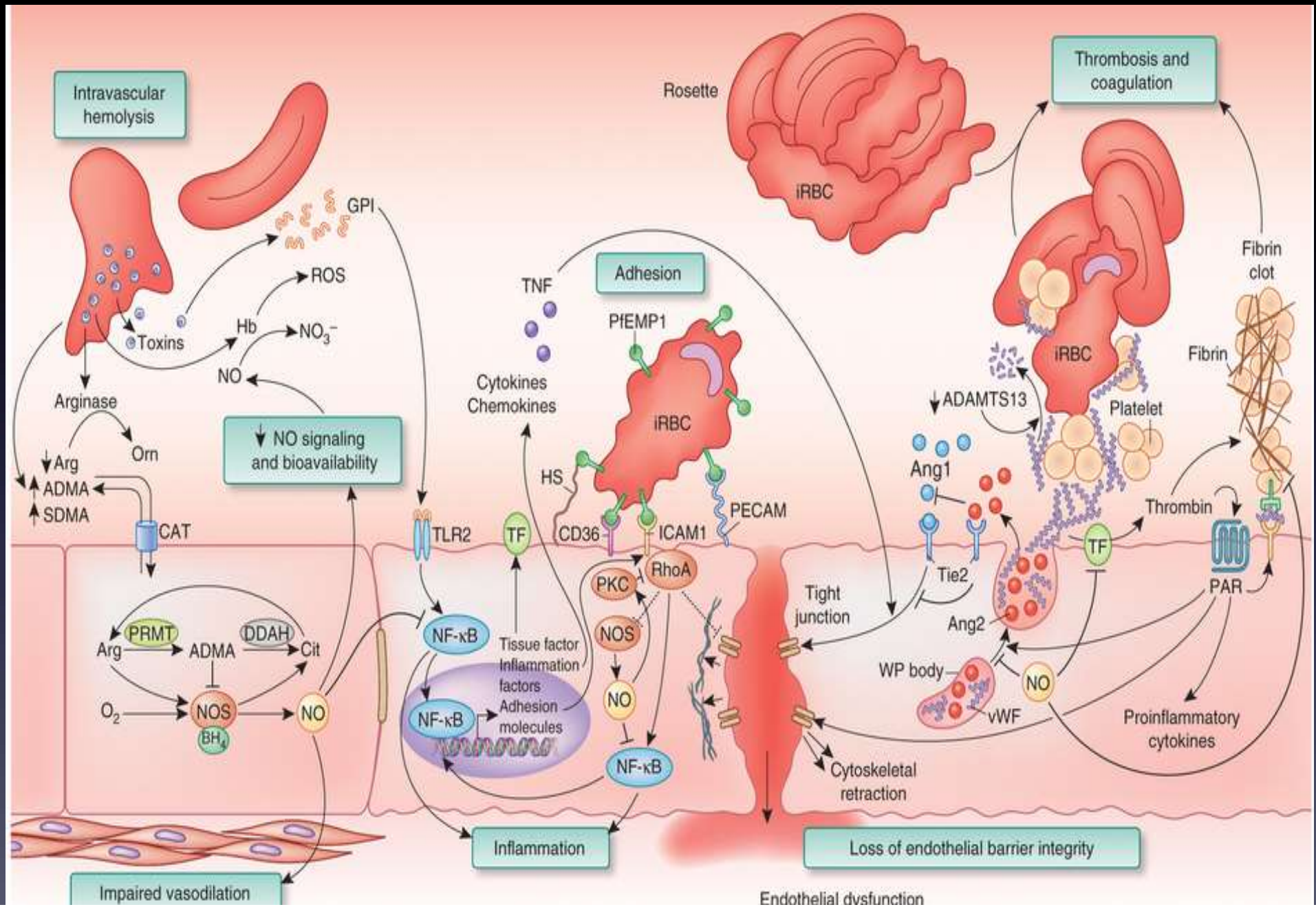
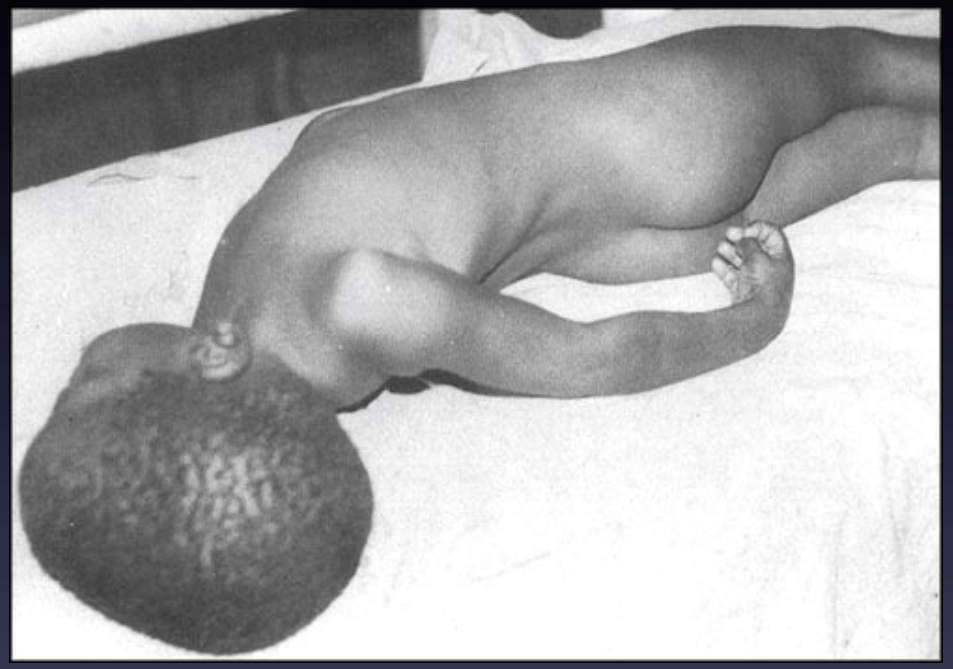
- Increased erythrocyte adhesion
- Enhanced thrombosis and coagulation
- Intravascular hemolysis: decreased nitric oxide bioavailability
- Impaired nitric oxide synthesis
- Loss of barrier integrity
- Inflammation
- Weibel-Palade body exocytosis

Nature Medicine 2013 19:2

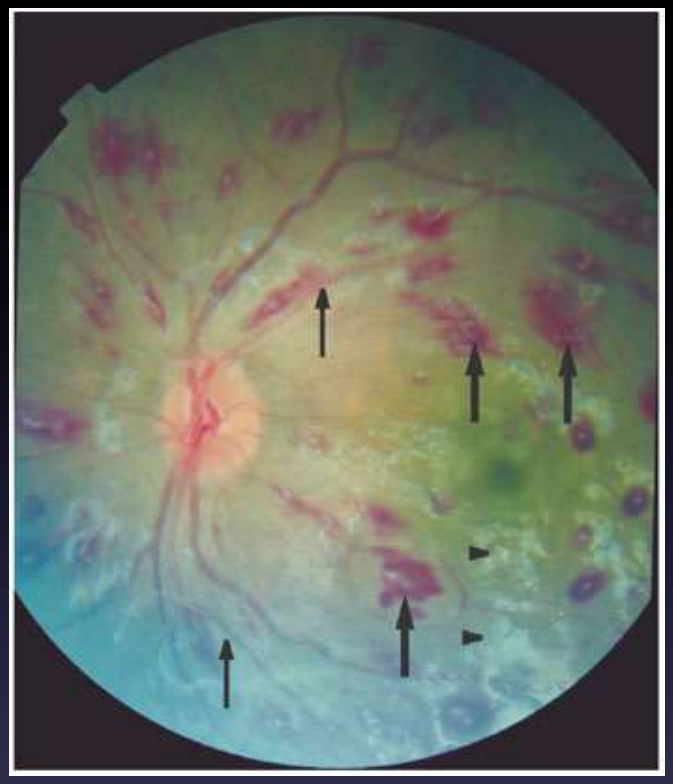


CLINICAL CEREBRAL MALARIA

- Blantyre Coma Scale less than or equal to 2
- Coma persists despite correction of hypoglycemia
- Parasitemia on blood smear
- No other cause of coma: meningitis, metabolic, trauma, post-ictal state
- Characteristic retinal findings may increase sensitivity



MALARIAL RETINOPATHY



Mishra SK and Newton CRJC (2009) Diagnosis and management of the neurological complications of falciparum malaria
Nat Rev Neurol doi:10.1038/nrneurol.2009.23

nature REVIEWS NEUROLOGY

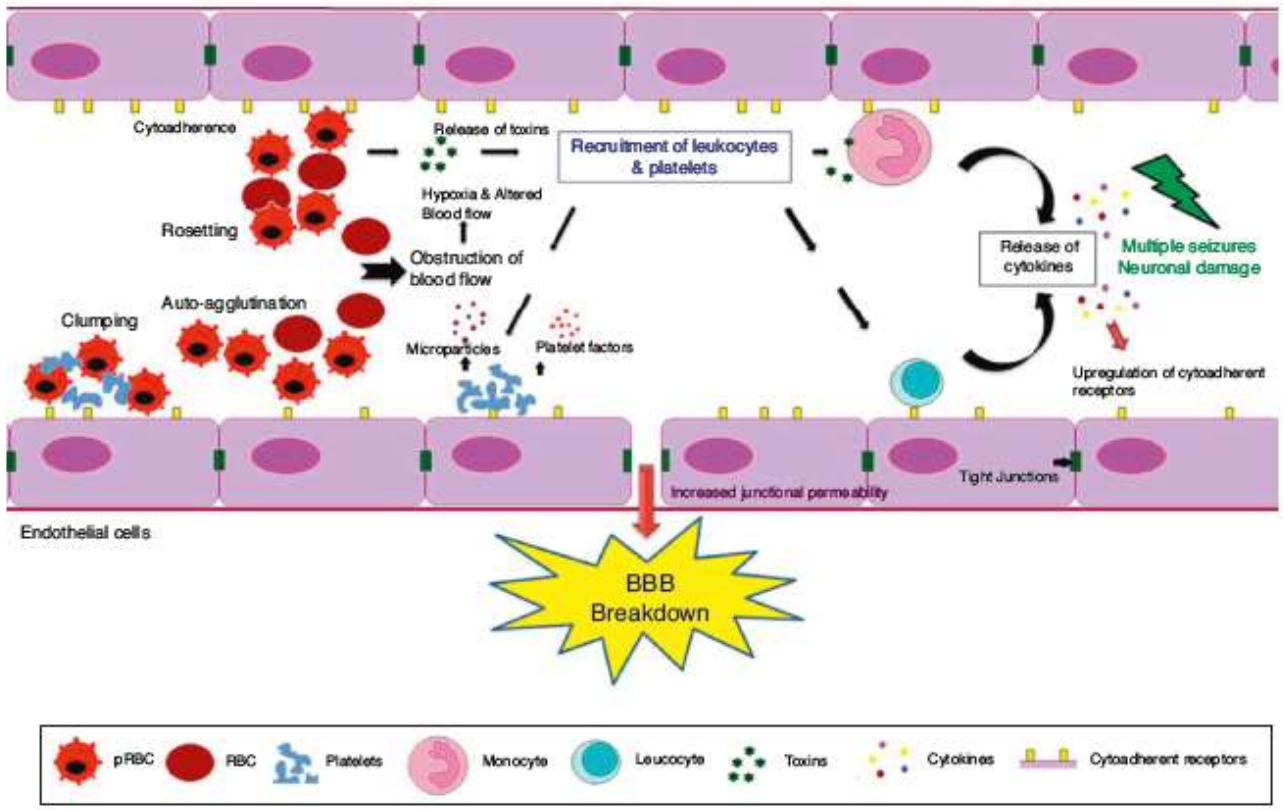
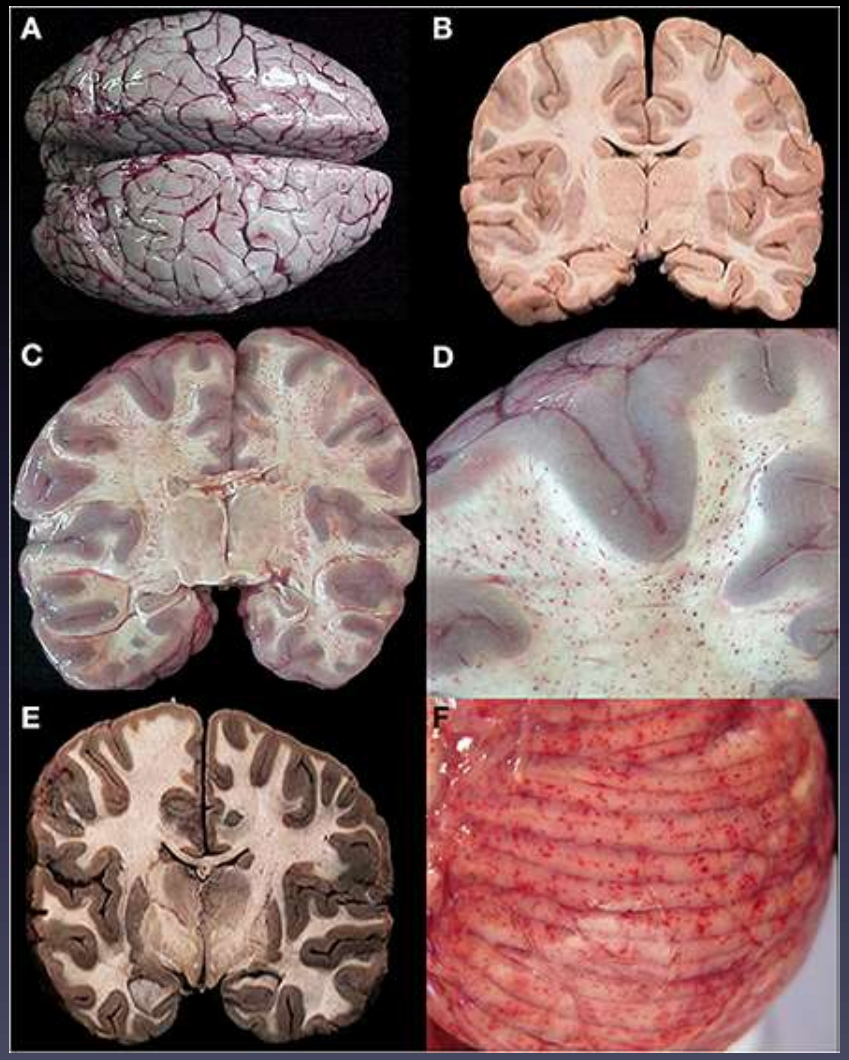
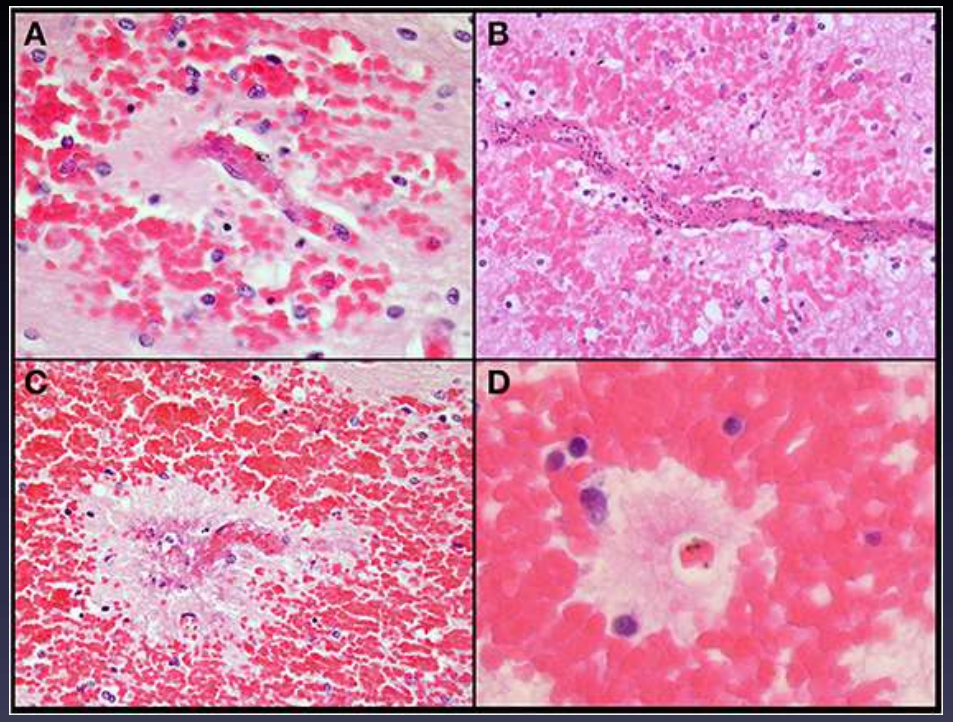
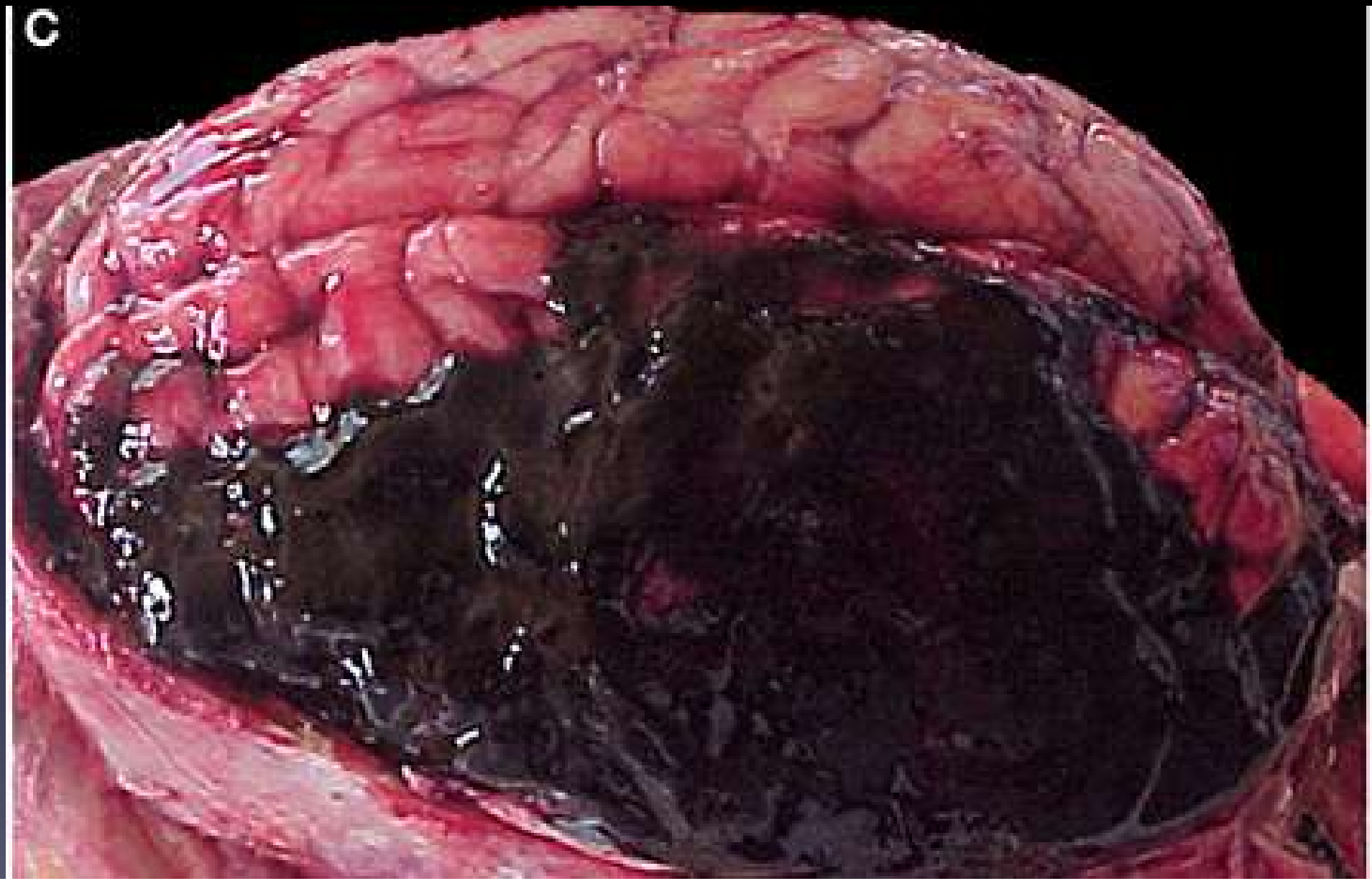


Fig. 1 – The blood–brain barrier (BBB) breakdown during cerebral malaria pathogenesis. The diagram shows the events and the possible mechanisms that play a vital role in CM. The mature forms (trophozoites and schizonts) of parasitized red blood cells (PRBCs), host leukocytes and platelet-fibrin thrombi adhere to the cerebral endothelial cells and sequester in large numbers in the brain. This cytoadherence, combined with other events such as rosetting, auto-agglutination, clumping and decreased RBCs and PRBCs deformability causes altered blood flow leading to impaired tissue perfusion and hypoxia. Further, sequestered parasites produce local toxins which lead to recruitment of leukocytes and platelets followed by the release of inflammatory cytokines (IL-1, IL-6, TNF, LT, and NO) and microparticles. These mediators lead to endothelial cells activation and apoptosis, BBB breakdown, increased junctional permeability, followed by secondary neuropathological events that can lead to cerebral edema or coma. Sequestration of PRBCs within microvasculature increases cerebral volume, which together with increased cerebral blood flow from seizures, anemia and hyperthermia and altered BBB function lead to cerebral edema and raised intracranial pressure. This may result in death or neuronal damage with consequent neurocognitive sequelae in the survivors.

PATHOLOGY



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DRUGS FOR MALARIA

Prophylaxis primarily with Atovaquone/proguanil, Tafenoquine, Mefloquine, Mefloquine, Primaquine for terminal prophylaxis

Uncomplicated malaria:

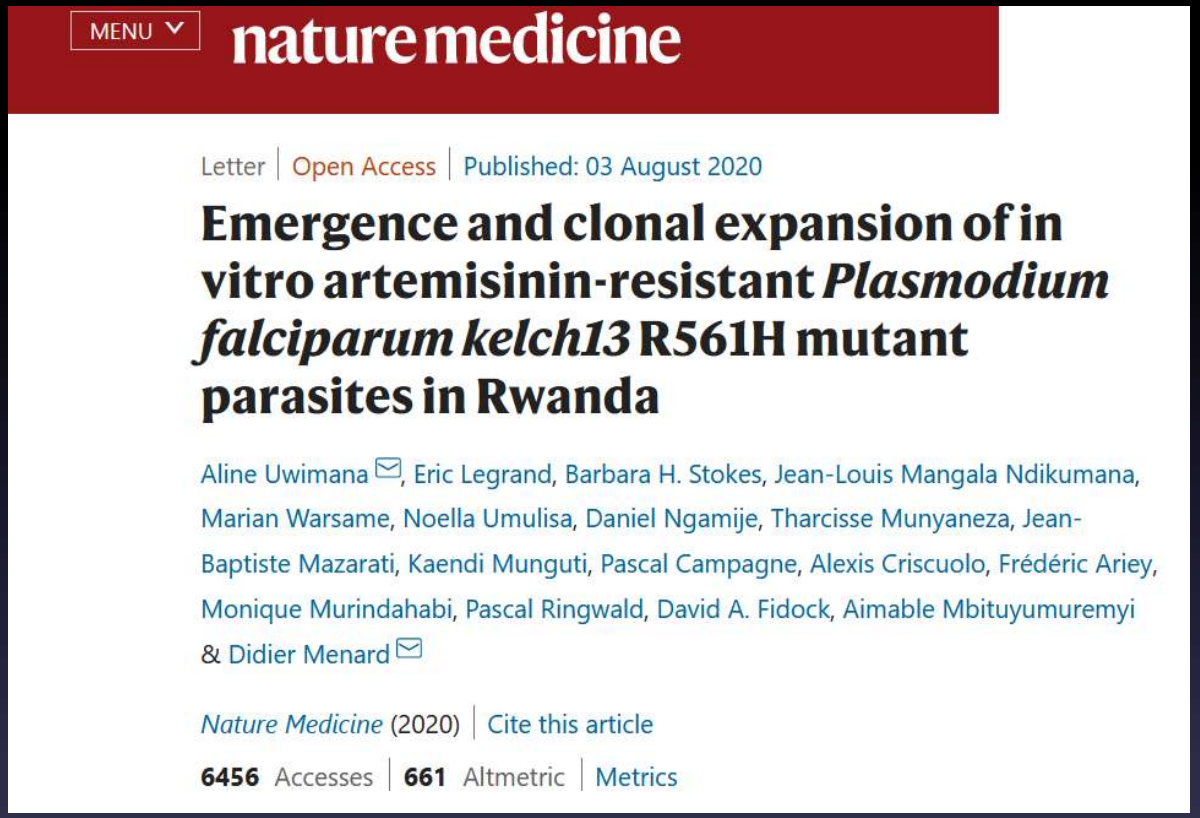
Atovaquone/proguanil x 3 days,

Artemether/lumefantrine x 3 days

Quinine + doxy or tetracycline or clindamycin

Severe P falciparum:

Contact CDC for IV Artesunate for 7 days; may follow with Atovaquone/proguanil, doxycycline or mefloquine



MENU nature medicine

Letter | Open Access | Published: 03 August 2020

Emergence and clonal expansion of in vitro artemisinin-resistant *Plasmodium falciparum kelch13* R561H mutant parasites in Rwanda

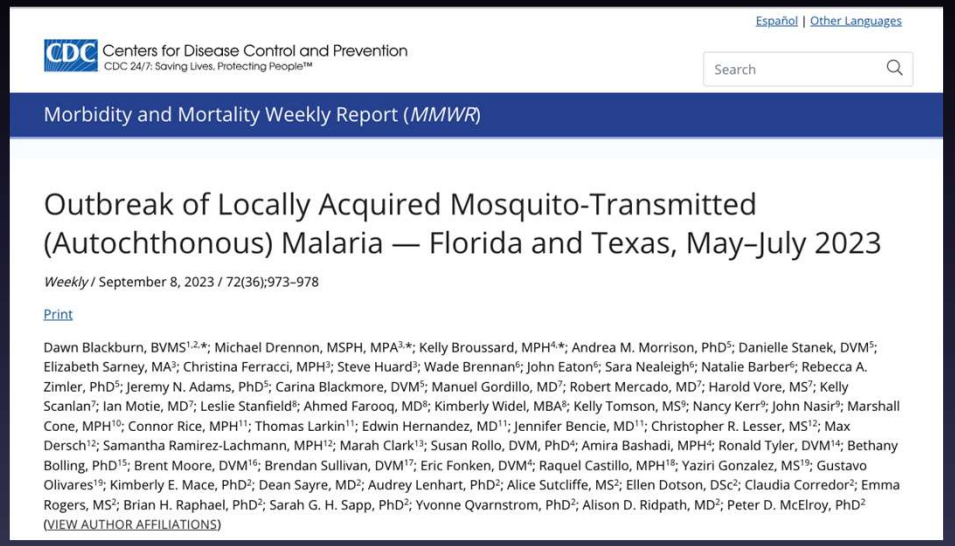
Aline Uwimana, Eric Legrand, Barbara H. Stokes, Jean-Louis Mangala Ndikumana, Marian Warsame, Noella Umulisa, Daniel Ngamije, Tharcisse Munyaneza, Jean-Baptiste Mazarati, Kaendi Munguti, Pascal Campagne, Alexis Criscuolo, Frédéric Ariey, Monique Murindahabi, Pascal Ringwald, David A. Fidock, Aimable Mbituyumuremyi & Didier Menard

Nature Medicine (2020) | Cite this article

6456 Accesses | **661** Altmetric | Metrics

UNCOMFORTABLY CLOSE TO HOME

- 7 autochthonous cases from Florida and 1 from Texas
- No travel risk factors
- All confirmed as P vivax
- All treated with Artemether/lumefantrine or Atovaquone/proguanil + primaquine
- Patients within 4-mile radius in Sarasota County
- No association to imported cases
- Enhanced vector surveillance and eradication efforts



Español | Other Languages

CDC Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

Search

Morbidity and Mortality Weekly Report (*MMWR*)

Outbreak of Locally Acquired Mosquito-Transmitted (Autochthonous) Malaria — Florida and Texas, May–July 2023

Weekly / September 8, 2023 / 72(36);973–978

Print

Dawn Blackburn, BVMS[1,2,*]; Michael Drennon, MSPH, MPA[3,*]; Kelly Broussard, MPH[4,*]; Andrea M. Morrison, PhD[5]; Danielle Stanek, DVM[5]; Elizabeth Sarney, MA[3]; Christina Ferracci, MPH[3]; Steve Huard[3]; Wade Brennan[6]; John Eaton[6]; Sara Nealeigh[6]; Natalie Barber[6]; Rebecca A. Zimler, PhD[5]; Jeremy N. Adams, PhD[5]; Carina Blackmore, DVM[5]; Manuel Gordillo, MD[7]; Robert Mercado, MD[7]; Harold Vore, MS[7]; Kelly Scanlan[7]; Ian Motie, MD[7]; Leslie Stanfield[8]; Ahmed Farooq, MD[8]; Kimberly Widel, MBA[8]; Kelly Tomson, MS[9]; Nancy Kerr[9]; John Nasir[9]; Marshall Cone, MPH[10]; Connor Rice, MPH[11]; Thomas Larkin[11]; Edwin Hernandez, MD[11]; Jennifer Bencie, MD[11]; Christopher R. Lesser, MS[12]; Max Dersch[12]; Samantha Ramirez-Lachmann, MPH[12]; Marah Clark[13]; Susan Rollo, DVM, PhD[4]; Amira Bashadi, MPH[4]; Ronald Tyler, DVM[14]; Bethany Bolling, PhD[15]; Brent Moore, DVM[16]; Brendan Sullivan, DVM[17]; Eric Fonken, DVM[4]; Raquel Castillo, MPH[18]; Yaziri Gonzalez, MS[19]; Gustavo Olivares[19]; Kimberly E. Mace, PhD[2]; Dean Sayre, MD[2]; Audrey Lenhart, PhD[2]; Alice Sutcliffe, MS[2]; Ellen Dotson, DSc[2]; Claudia Corredor[2]; Emma Rogers, MS[2]; Brian H. Raphael, PhD[2]; Sarah G. H. Sapp, PhD[2]; Yvonne Qvarnstrom, PhD[2]; Alison D. Ridpath, MD[2]; Peter D. McElroy, PhD[2]
(VIEW AUTHOR AFFILIATIONS)

Clinical Pearls

- Malaria remains leading cause of pediatric mortality globally with resurgence after COVID pandemic
- P knowlesi is a leading cause of malaria in SE Asia
- Severe malarial syndromes are primarily a result of inflammation and endothelial injury, not level of parasitemia
- Artemesinin is mainstay of treatment for severe disease, but resistance is evolving globally
- Autochthonous cases of P vivax in Florida and Texas in 2023 raise concerns for re-emergence of this disease