ICU management of malaria cases

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Introduction

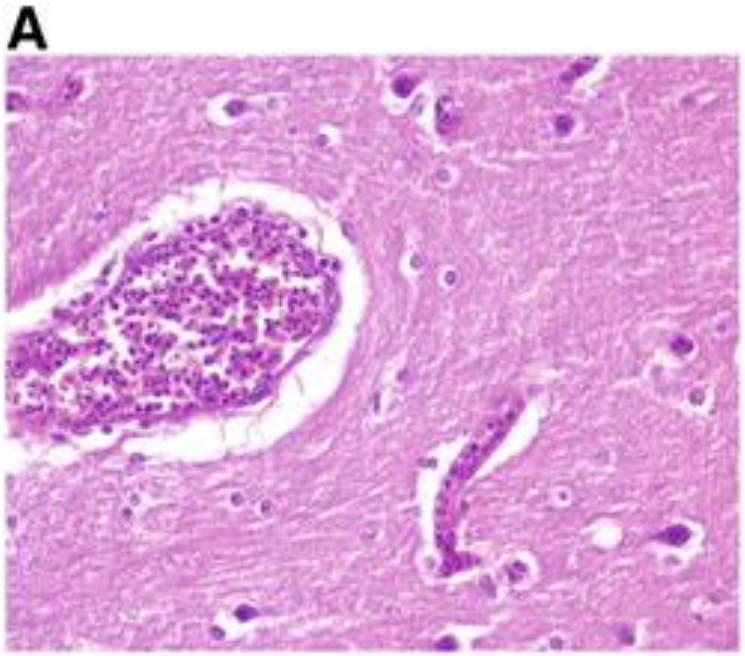
- Most important cause of febrile illness in a returning traveller
- Particularly vulnerable groups
  - Non-immune travellers / migrants
  - Pregnant women
  - Post splenectomy
- Most severe cases by *P. falciparum*, occasionally *P. vivax* or *P. knowlesi*
- CDC 2017: 14.4% severe malaria; 91.4% P. falciparum; 1.9% died

Pathophysiology of severe malaria

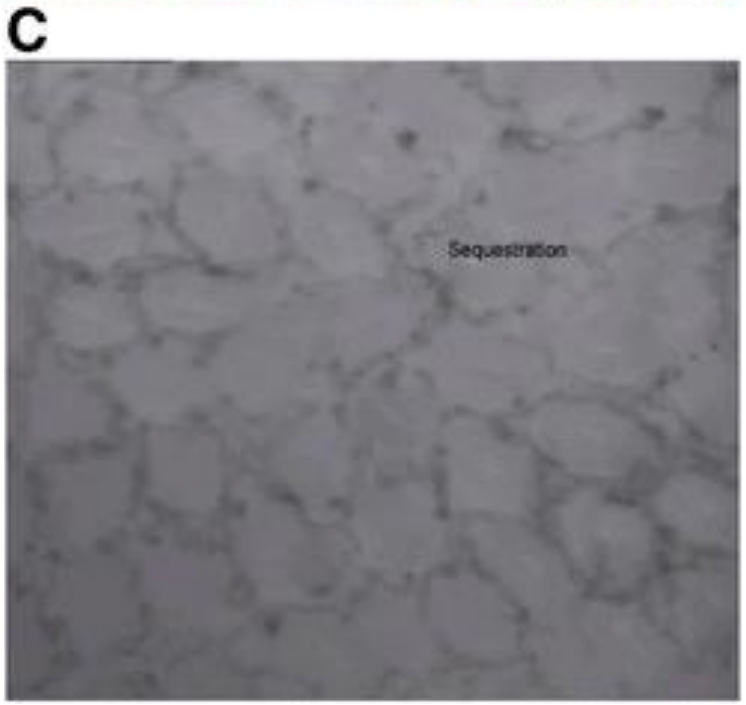
- **Microvascular obstruction**
  - Cytoadherence; Sequestration; Rosetting
  - Impaired tissue oxygenation and **organ dysfunction**

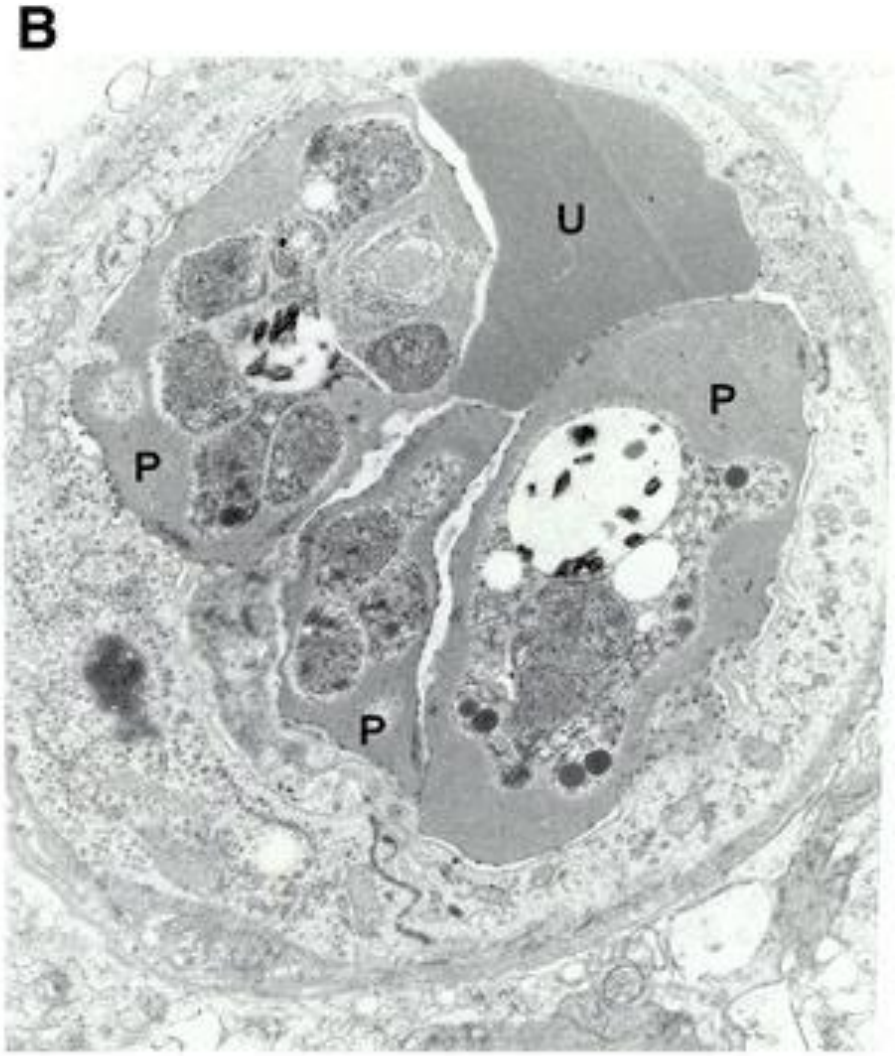
- Haemolysis → anaemia and release of haemoglobin
- Others e.g. cytokine

Cerebral vessel packed with parasitized erythrocytes



Orthogonal polarization spectral imaging of rectal mucosa





Parasitized erythrocytes and uninfected erythrocyte

Hanson J, Anstey NM, Bihari D, White NJ, Day NP, Dondorp AM. The fluid management of adults with severe malaria. Critical Care 2014;18(6).

WHO criteria for severe *P. falciparum* malaria

- **Impaired consciousness** (GCS < 11)
- **Prostration** (unable to sit/stand/walk without assistance)
- **Multiple convulsions** (>= 2 within 24 hours)
- **Acidosis** (BE >= 8mEq/L; lactate >= 5mmol/L)
- **Hypoglycaemia** (< 2.2mmol/L)
- **Severe anaemia** (Hb < 7g/dL; Hct < 20%)
- **Renal impairment (**Cr > 265umol/L or urea > 20mmol/L)
- **Jaundice** (Bilirubin > 50umol/L with parasite count > 100,000/uL)
- **Pulmonary oedema** (Radiology or SpO_2 < 92% on room air with RR > 30/min)
- **Significant bleeding** (recurrent or prolonged bleeding from nose, gums or venepuncture sites; haematemesis or melaena)
- **Shock**
  - Compensated (CRT>= 3 secs or temperature gradient on leg) ; no hypotension
  - Decompensated (SBP < 80mmHg with evidence of impaired perfusion)
- **Parasitaemia > 10%**

Guidelines for the Treatment of Malaria. 2022, World Health Organization, Geneva, Switzerland

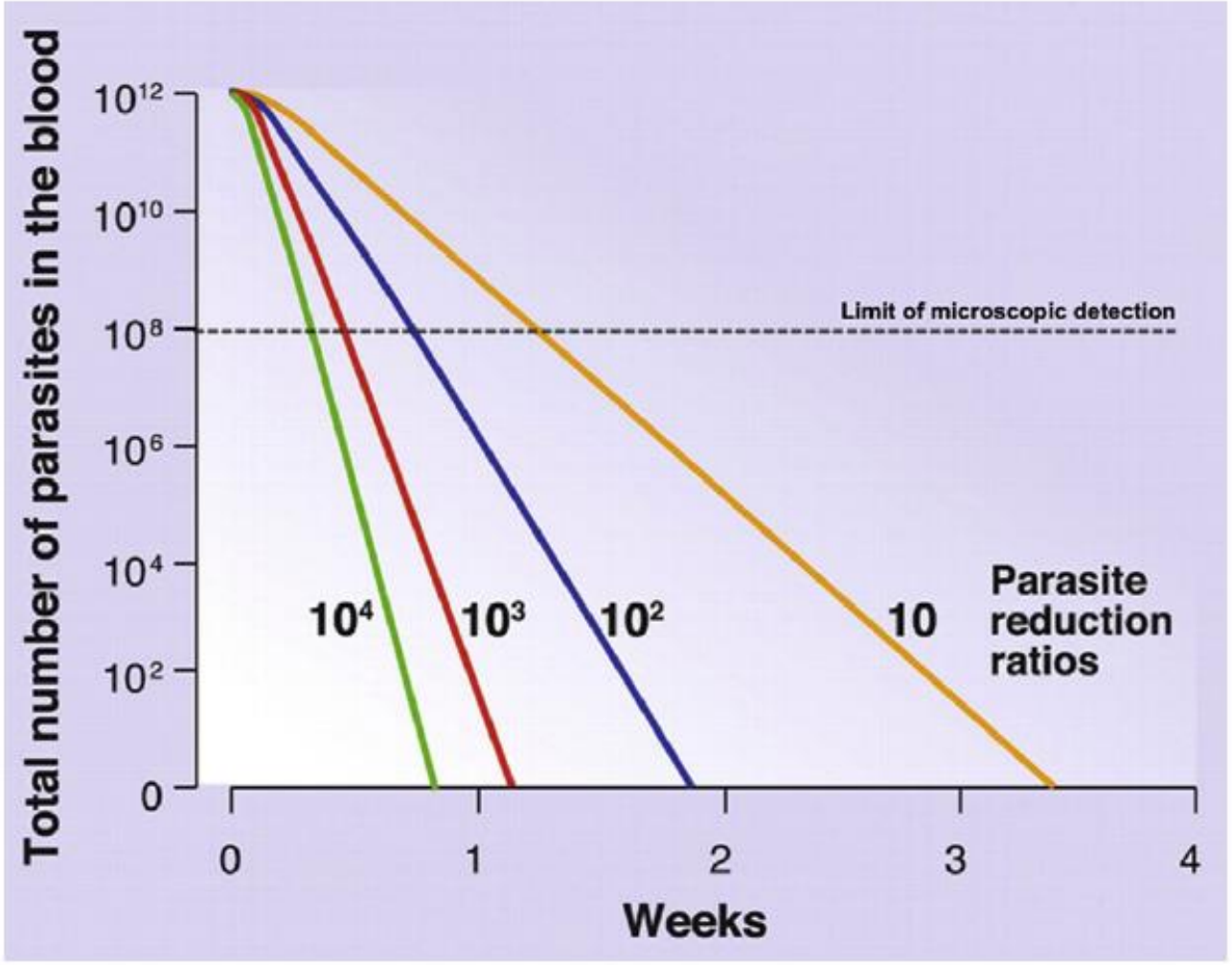
Criteria for severe malaria

- Most severe cases are caused by *P. falciparum*
  - Propensity to cause microvascular obstruction; infects RBCs of all ages
  - *P. vivax* and *P. knowlesi* occasionally cause severe disease
- **Degree of parasitaemia and clinical severity may not correlate**
  - **Sequestrated biomass**
- **Should not worry unduly about definitions**
- **Ill patients → appropriate treatment without delay**
- Empirical treatment if malaria diagnostic test not available promptly

Anti-malarial treatment

- **IV/IM artesunate for all**, including pregnant women in all trimesters
- Most rapid killing (rapidly hydrolyzed in vivo)
- Superior to quinine (RCTs showed mortality benefit)
- No dosage adjustment needed for vital organs dysfunction
- 2.4mg/kg at 0, 12, 24 hours → daily till fit → oral completion therapy
- Usually well tolerated but chance of post treatment haemolysis

Artesunate – most rapid killing



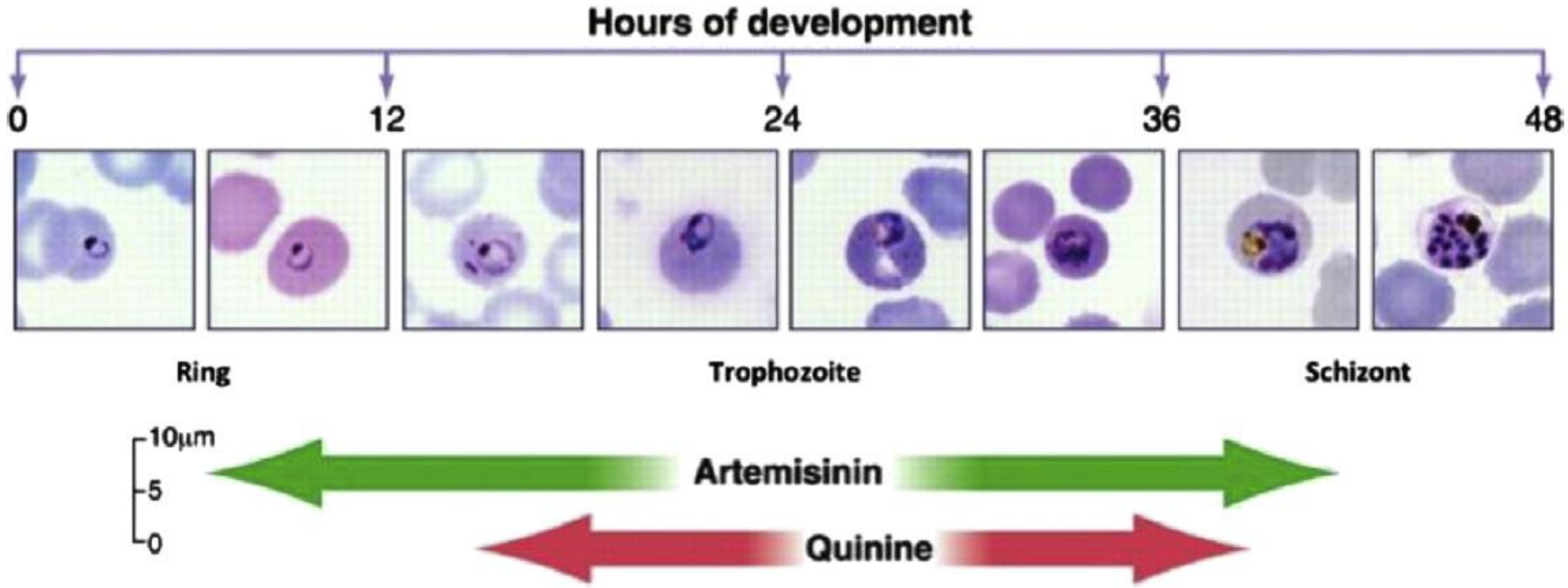
Green – Artemisinins

Red – Quinine

Yellow - Doxycycline

White NJ. Qinghaosu (artemisinin): the price of success. Science 2008;320:330-4

Artesunate – broadest killing



White NJ. Qinghaosu (artemisinin): the price of success. Science 2008;320:330-4

Fluid and cardiac

- Haemodynamic status **different from usual bacterial septic shock**
- Preload mildly ↓, cardiac output and blood pressure maintained
- **Hypotensive in small portion; beware of alternative causes**
  - Concomitant bacterial infection
  - Internal bleeding related to thrombocytopenia; splenic rupture etc.

Aggressive fluid resuscitation not beneficial

- Physical signs and CVP unreliable assessing intravascular volume
- Even guided by transpulmonary thermodilution and pulse contour analysis; no improvement for urine output, acid base & lactate levels
- Hanson JP et al. CCM 2013
  - 28 patients
  - Low GEDVI
  - Median fluid 3230ml first 6 hours
- **Failure to improve microcirculatory problem**

Aggressive fluid may cause harm

- Same study by Hanson JP et al
  - 36% clinical pulmonary oedema; 77% extravascular lung water
  - Despite while hypovolemic/euvolemic
- Maitland K et al NEJM 2011
  - 3141 African children with severe febrile illness; 57% malaria
  - Maintenance fluid with or without boluses of 0.9% saline/ 5% albumin
  - ↑ 4 weeks mortality (No bolus 8.7%; Alb 12.2%, NS 12%)

Restrictive fluid not associated with harm

- Ishioka et al JID 2020
  - 154 patients
  - Prospective observational
  - Median total fluid 3.3ml/kg/hr first 6 hours; 2.2ml/kg/hr first 24 hours
  - Does not worsen kidney function, tissue perfusion, blood pressure

Fluid and cardiac management

- Non hypotensive patients
  - Restrictive approach
  - Maintenance 1-3ml/kg/hour for the first 24 hours without boluses
  - Titrate according to electrolytes, glucose levels
  - Blood products as indicated
- Hypotensive patients
  - Cautious fluid challenge
  - Assess for co-existing pathologies
  - Inotropes and vasopressors as indicated

Respiratory

- Respiratory distress in up to 25% of adults
  - Anaemia; metabolic acidosis; pulmonary oedema; pneumonia etc.
- ARDS in 5 -25% of adults with *P. falciparum*

ARDS in severe malaria

- **Onset time distinct from other complications**; often during recovery phase when parasitaemia begun to decrease
- Krishnan et al CCM 2003
  - 301 patients
  - 6% upon ICU admission; +11% within 48 hours; +12% during >48 hours
- ? endothelial dysfunction / altered capillary permeability related to inflammatory response towards parasitized RBC / antigens
- **Lung protective ventilation** as for non malaria related ARDS except **avoiding permissive hypercapnia** (may exacerbate raised ICP)

Cerebral malaria

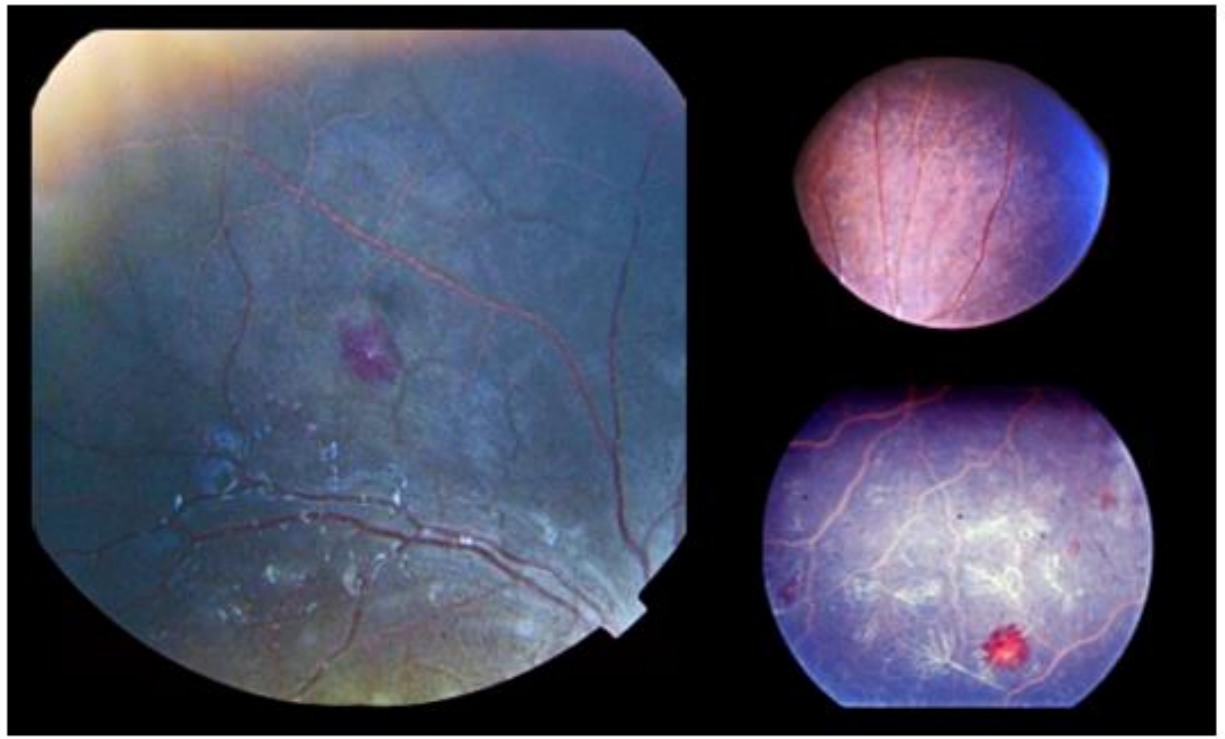
- Decreased consciousness
- Seizures
- Cerebral oedema / ↑ ICP (but not predict depth of coma / survival)

Cerebral malaria

- **Rule out hypoglycemia and other potential causes**
- Pathognomonic retinopathy changes in some
- Meningism or photophobia suggestive of alternative pathology
- Brain imaging
- Lumbar puncture +/- empirical CNS infection cover in selected cases
  - LP maybe contraindicated (thrombocytopenia; raised ICP)
  - CSF analysis usually normal or slightly ↑ protein / cell count

- Vessel changes (less red)
- White centred haemorrhage
- Whitening in areas of retina

Vessel changes in optic fundi



Vessel changes in the optic fundi of patients with cerebral malaria. Vessels that are normally red in color become orange or yellow because they contain parasitized red cells. The parasite consumes some of the hemoglobin in solution, so those red cells become less red. In the image on the left, all three features of malarial retinopathy are present (white-centered hemorrhages, vessel changes, and whitening in areas of the retina).

Courtesy of Susan Lewallen and Nicholas Beare.

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Cerebral malaria

- Intubate for airway protection as indicated
- Anticonvulsants e.g. benzodiazepine for clinical seizure
- No role for prophylactic anti-convulsants/ routine EEG monitoring

Cerebral malaria

- Dexamethasone and mannitol maybe harmful
- Warrell DA et al NEJM 1982
  - 100 patients, 74 adults
  - Dexamethasone 0.5mg/kg IV once then 10mg q6h x 7 more doses
  - Prolonged duration of coma, ↑pneumonia and GI bleeding
- Mohanty S et al CID 2011
  - 61 adult patients with CT confirmed cerebral oedema
  - Mannitol 1.5g/kg IV once then 0.5g/kg q8h up to 72 hours
  - Prolonged duration of coma

Acute kidney injury

- WHO criteria different from more commonly used criteria
- 23 to > 50% in series of imported malaria
- Pathogenesis likely multifactorial
  - Microvascular obstruction
  - Free plasma haemoglobin
  - Cytokine
  - Immune complex

Acute kidney injury

- Fluid resuscitation unlikely helpful
- Treatment is supportive
  - Electrolyte and acid base correction
  - Renal replacement therapy as indicated
- Acetaminophen maybe renoprotective (Plewes K et al CID 2018)
  - Antagonizing oxidative effects of plasma free haemoglobin
  - Acetaminophen 1g q6h for 72 hours
- Prognosis usually good

Hypoglycemia

- < 2.2mmol/L
- 1-20% in series of imported malaria case
- Impaired host gluconeogenesis; parasite glucose consumption
- Threshold to intervene = 3 mmol/L
- Dextrose bolus (100ml D20/ 40ml D50) and maintenance
- **Frequent monitoring** especially pregnant patients

Haematological

- Anaemia
  - Haemolysis; removal by spleen; dyserythropoiesis
  - No good quality evidence to guide transfusion target
  - Haemoglobin threshold of 7g/dL

Haematological

- Thrombocytopenia
  - Common
  - ↑ consumption; sequestration in spleen
  - No good quality evidence to guide transfusion target
- Disseminated intravascular coagulation
  - Uncommon (5-10%)
  - Treated conventionally

Exchange transfusion

- Rationale
  - Rapid removal of infected RBC
  - ↓ antigen load, parasite derived toxins, toxic mediator from host
  - Replace rigid unparasitized RBC by more deformable cells
  - Anecdotal reports and case series claimed benefit
- Manual procedure / automated erythrocytapheresis
- Potential harm and difficulties
  - Significant blood volume involved (0.5 - 1 blood volume)
  - Intensive nursing care

Exchange transfusion

- WHO – No consensus on indications, benefits, dangers, practical details; **Not possible** to make **any recommendations**
- CDC – **Not recommended**
  - Tan KR et al CID 2013
    - Clinical outcomes not different despite rapid parasitaemia clearance
    - Even less substantiated when artemisinin is available

Concomitant infection

- Invasive concomitant bacterial infection infrequent in adults
  - Nguyen et al CID 2020
    - 845 Vietnamese adults with severe falciparum malaria
    - 1.1% blood culture positive
    - 5.2% for parasitaemia > 20% ; 0.7% for parasitaemia < 20%
- **Beware of features atypical for severe malaria (hypotension, rash..)**
- Empirical antibiotic choice should take places of travel and possibility of resistant organisms into account

Adjunctive treatment

- Many agents studied
- **None proved effective, some may even cause harm**
  - Heparin, desferroxamine, anti-TNF antibody, cyclosporine A, hyperimmune serum, *N*-acetylcysteine etc.

Take home messages

- Severe malaria is a medical emergency
- Prompt recognition in anyone at risk
- Prompt administration of IV artesunate
- ICU management largely supportive
- Unique pathophysiology, usual sepsis management not fully apply
- Restrictive fluid management strategy
- Beware of concomitant infection when clinical picture does not fit