@ BasuNephro

Kidney in Malaria and Dengue

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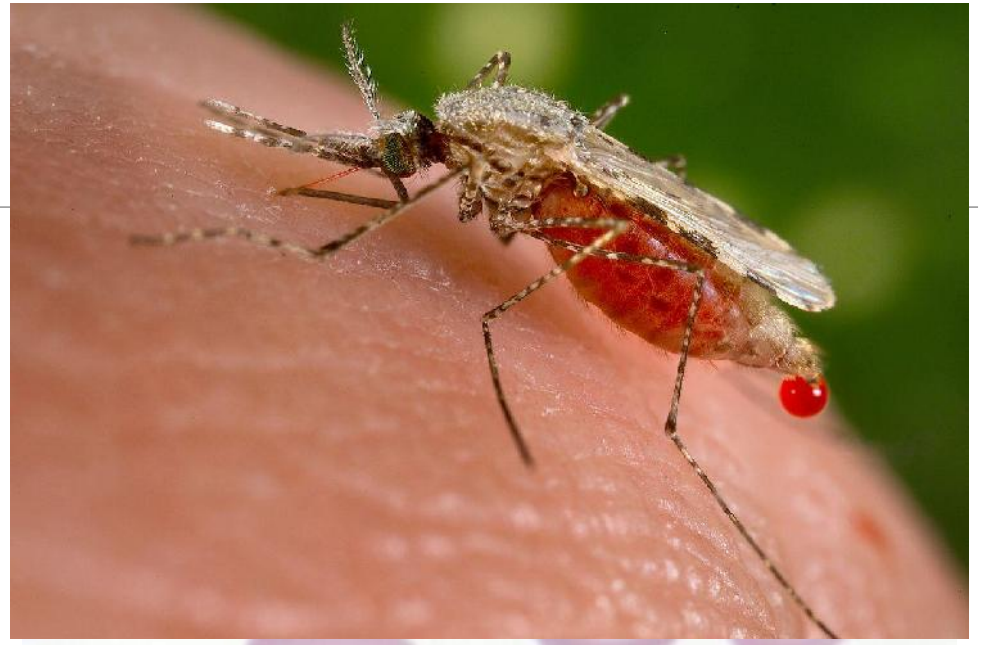
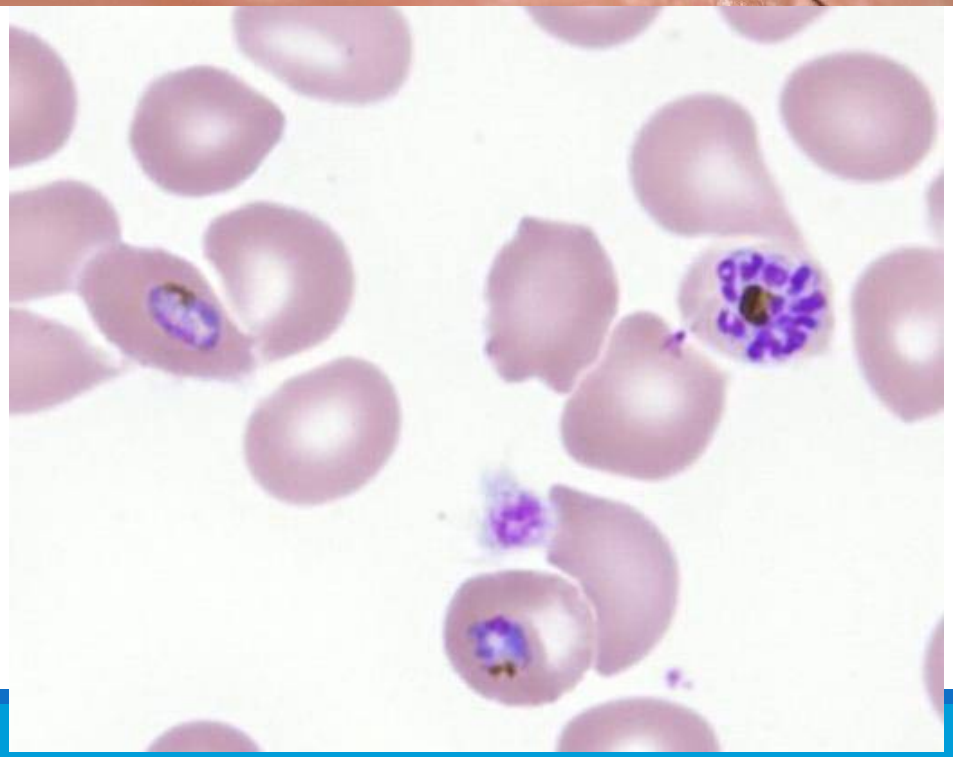
Distinguished Educator, The Transplantation Society
International Society of Nephrology - ISN Education Social Media Professional
APSN CME committee Member

What is Malaria?

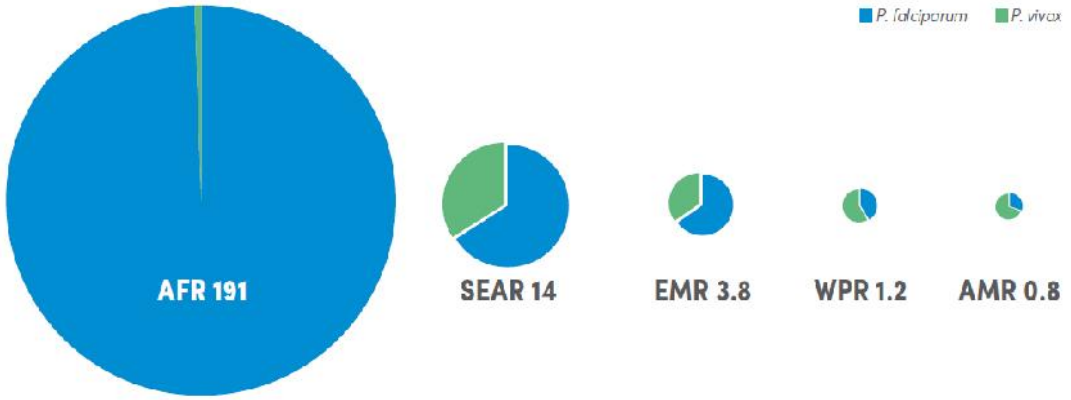
- Mal-aria – Bad Air
- Parasitic Disease - Plasmodium species
  - Plasmodium Falciparum p Africa, India, SE Asia, S America
  - Plasmodium vivax – Africa, India, SE Asia. S America
  - Plasmodium Malariae - Africa
  - Plasmodium Ovale – Africa, India
  - Plasmodium Knowlesi – SE Asia – Zoonotic Malaria from Macaque monkey reservoir hosts
- Vector Borne - Female Anopheles Mosquito vector
- Parasites circulate in blood – RBCs
- Febrile illness, Haemolysis, Jaundice, Acute kidney Injury, Cerebral malaria, Death





https://imagebank.hematology.org/image/3620/plasmodium-falciparum-infection--3?type=upload

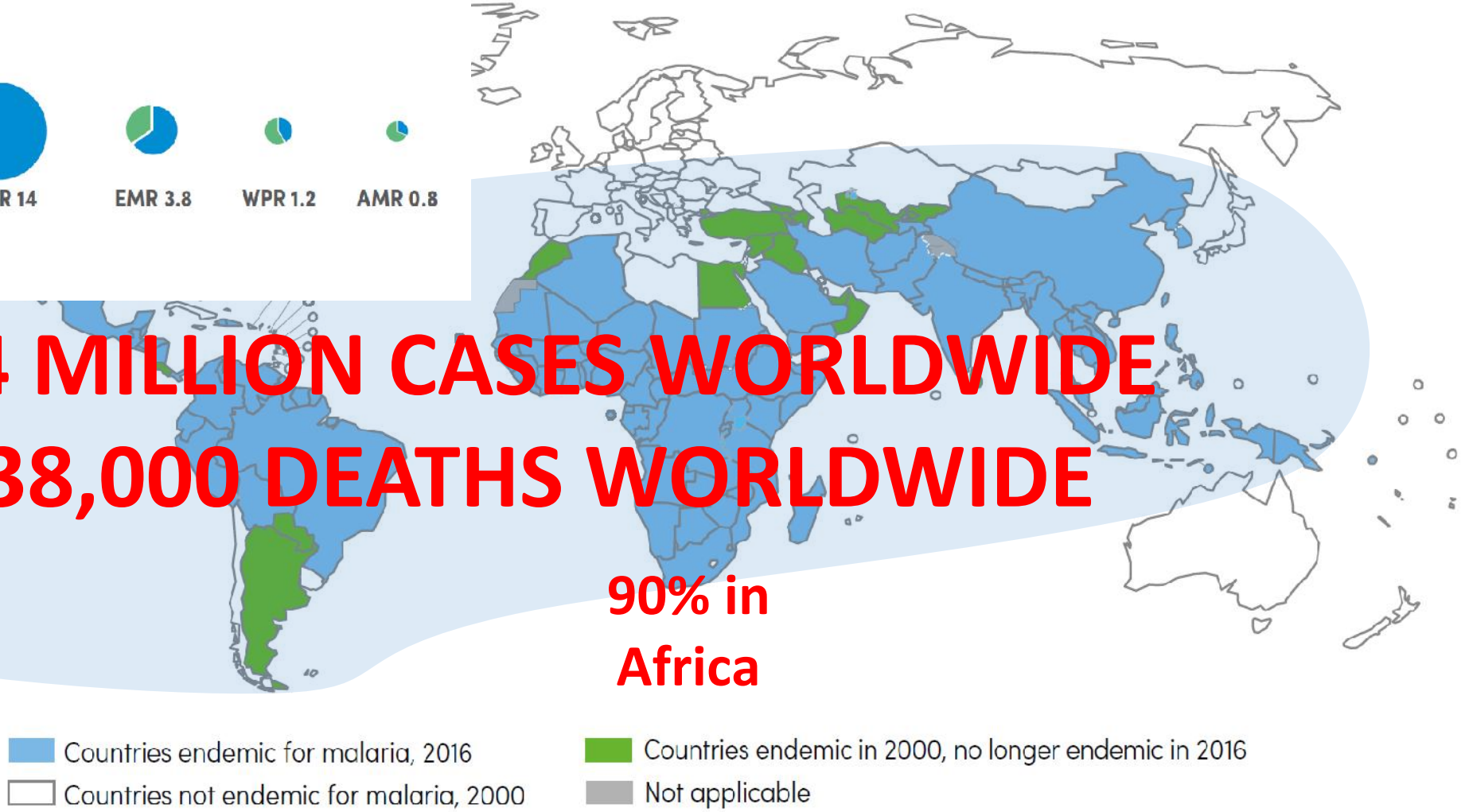
Is Malaria important?
Endemic Tropical Fever



214 MILLION CASES WORLDWIDE

438,000 DEATHS WORLDWIDE

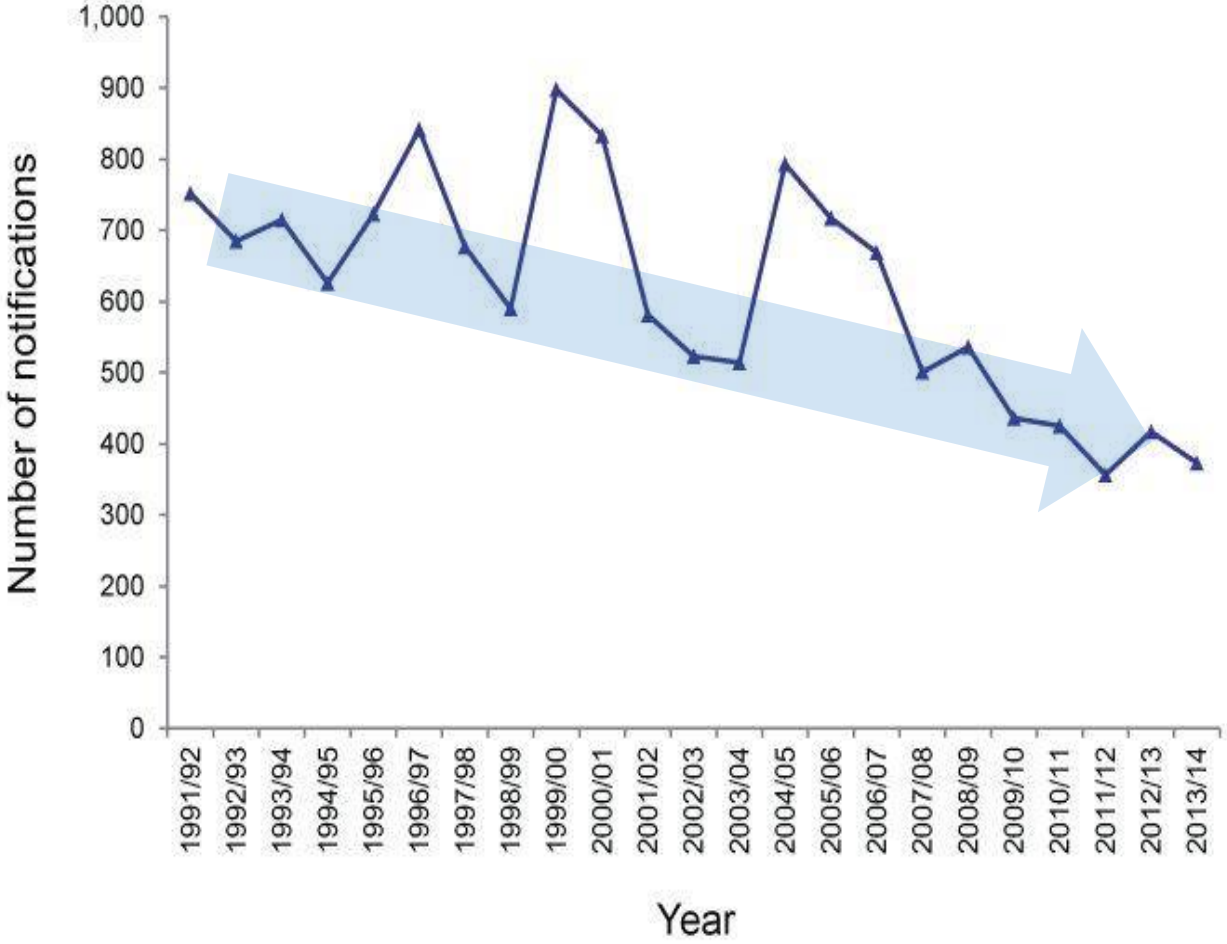
90% in Africa

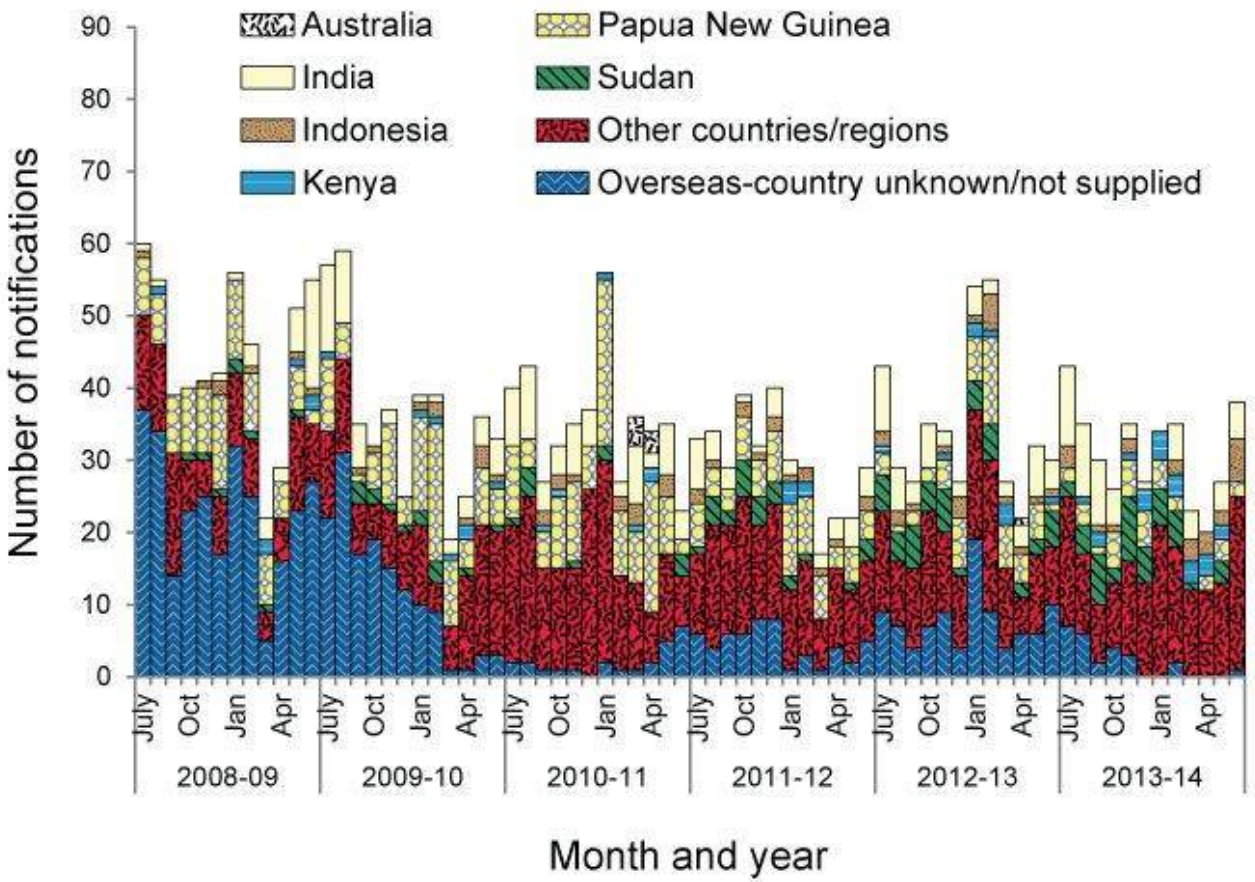


http://www.who.int/gho/malaria/en/

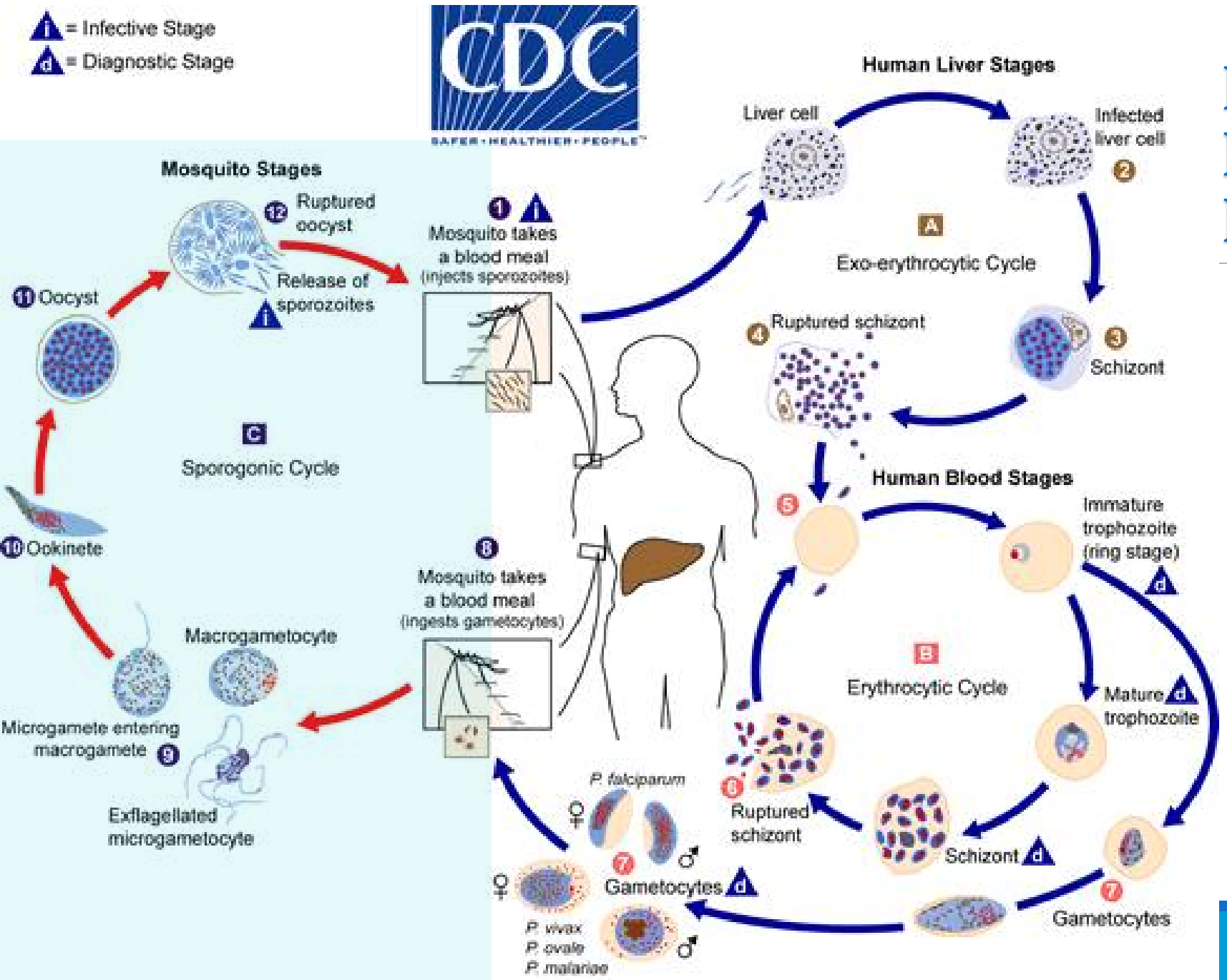
Is Malaria important in Aus / NZ?
Notifications of Malaria, Australia, 1991–2014

P. vivax - travel to Asia or Pacific nations
P. falciparum -Middle East, Africa and Papua New Guinea.
P. Knowlesi - None





http://www.health.gov.au/internet/main/publishing.nsf/content/cda-cdi4003n.htm



How does the Malarial Parasite work?

Exoerythrocytic Cycle in Liver

- Sporozoites →Schizont→ Merozoites

Erythrocytic Cycle in RBCs

- Asexual reproduction
  - Red cell to red cell transmission of trophozoites through schizont
- Sexual Reproduction
  - Gametocytes in RBC --> picked up by mosquito – Multiply in mosquito

***P. vivax* & *P. ovale* invade young RBCs**
***P. malariae* infects aging RBCs.**
***P. Jalciparum* invade RBCs of all ages,**

P.S. *P. vivax* and *P. ovale* a dormant stage [hypnozoites] can persist in the liver and cause relapses by invading the bloodstream weeks, or even years later.

What does it do to us?

CLINICAL FEATURES

- Cyclical Febrile illness
  - Chill→Fever→Crisis – sweating
  - Periodicity
- Constitutional manifestations - headache, malaise, and muscle and joint aches
- The spleen may be enlarged, particularly with relapsing disease.

ORGAN INVOLVEMENT

- Haemolysis
- Cerebral malaria
- AKI – Black water fever
- NC Pulmonary Oedema / ARDS
- Hepatitis
- GI system – vomiting, diarrhea, ascites
- Sepsis syndrome / MODS
- Adrenal h'ge - shock

WHO criteria for severe malaria

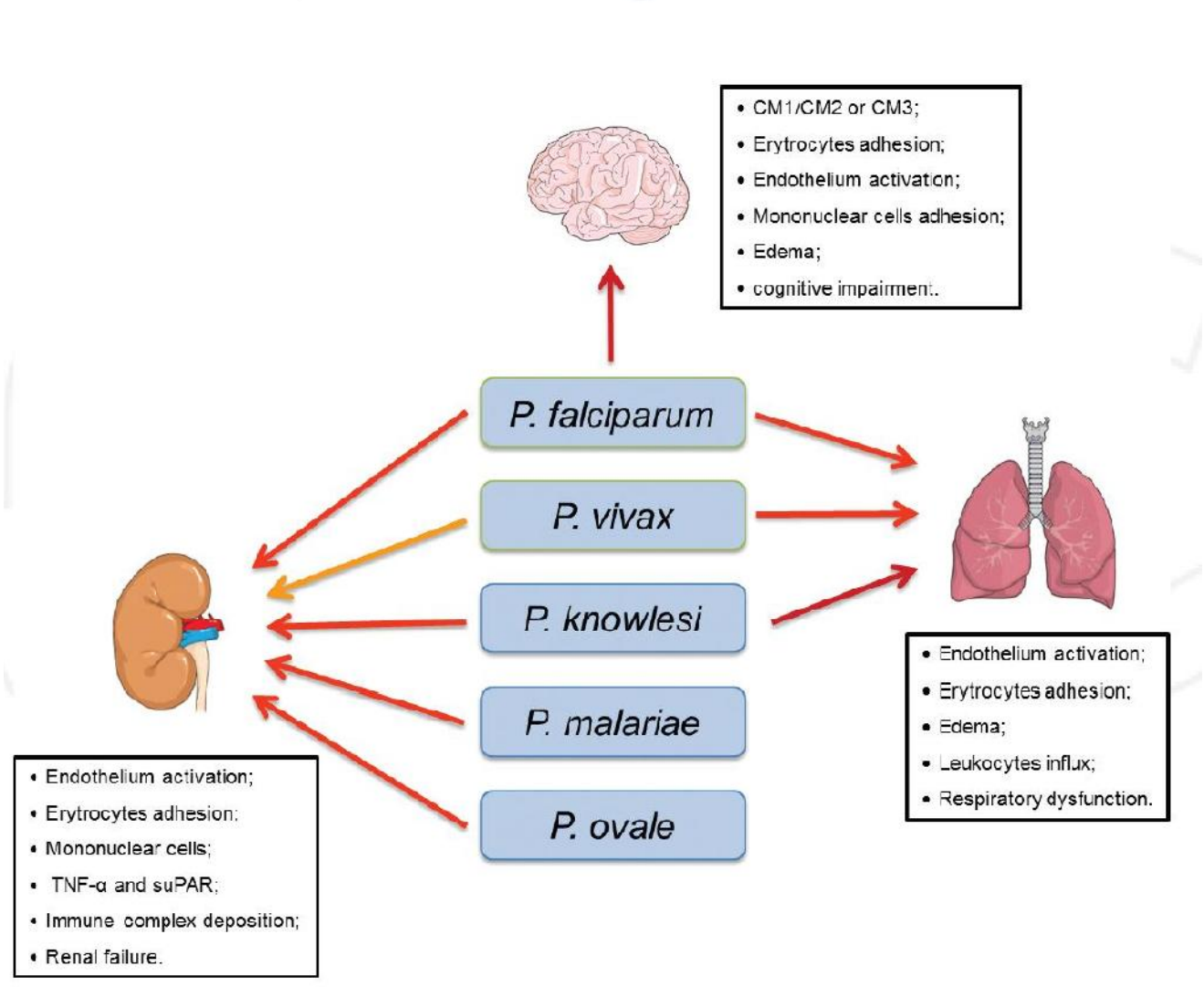
One or more of:

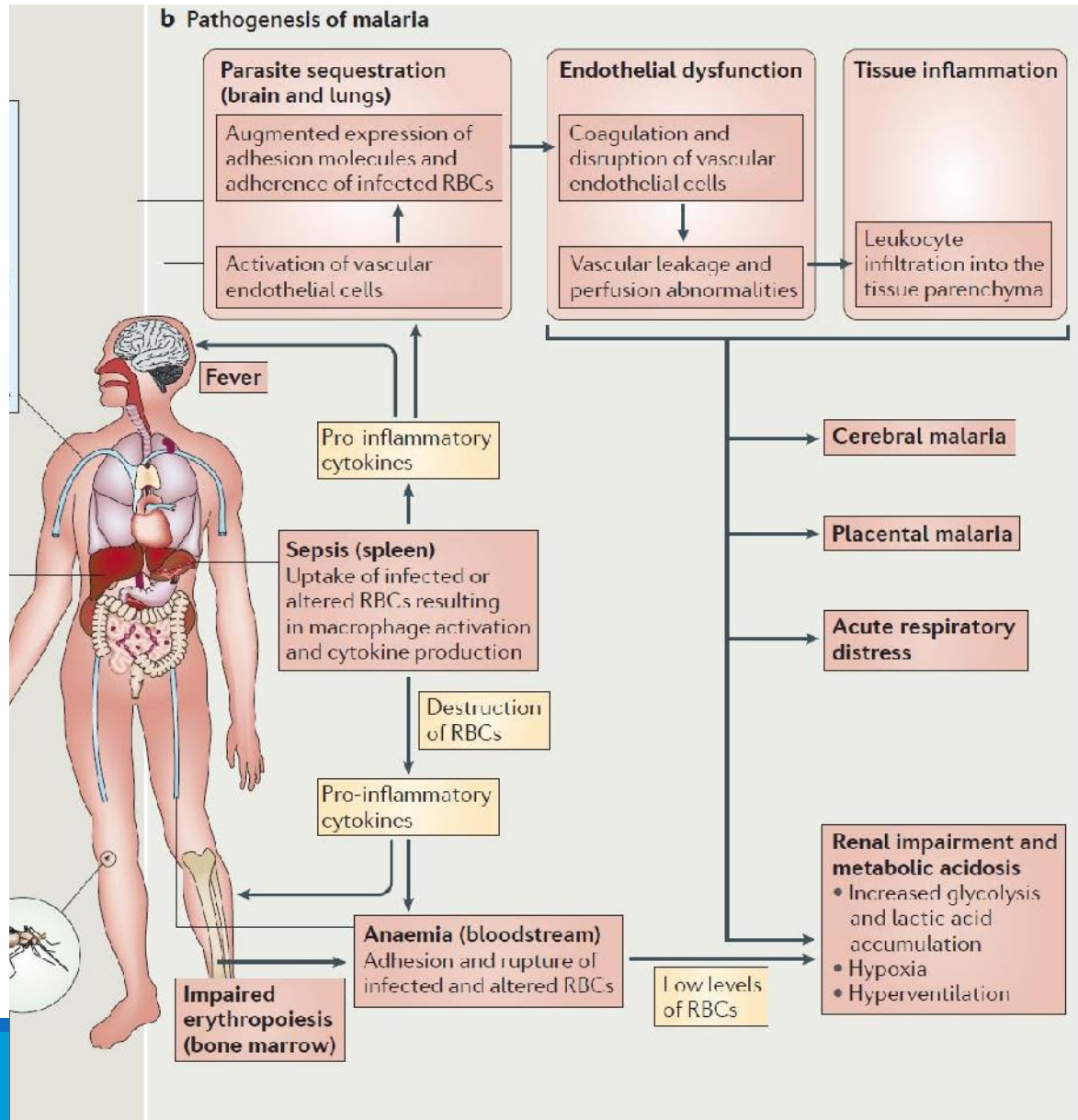
- cerebral malaria (CM)
- respiratory distress (RD)
- severe normocytic anaemia
- renal failure
- hyperparasitaemia
- pulmonary oedema
- hypoglycaemia
- circulatory collapse
- spontaneous bleeding/DIC
- repeated generalized convulsions
- acidosis
- malarial haemoglobinuria

Other manifestations include:

- impaired consciousness, but rousable
- prostration, severe weakness
- jaundice
- hyperpyrexia

Major Organ Involvement of Malaria



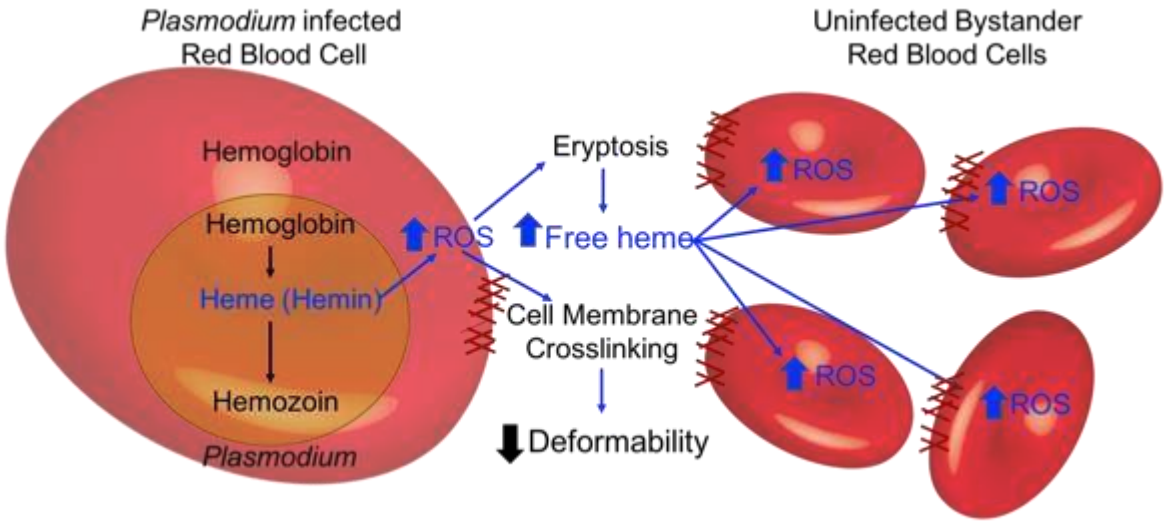


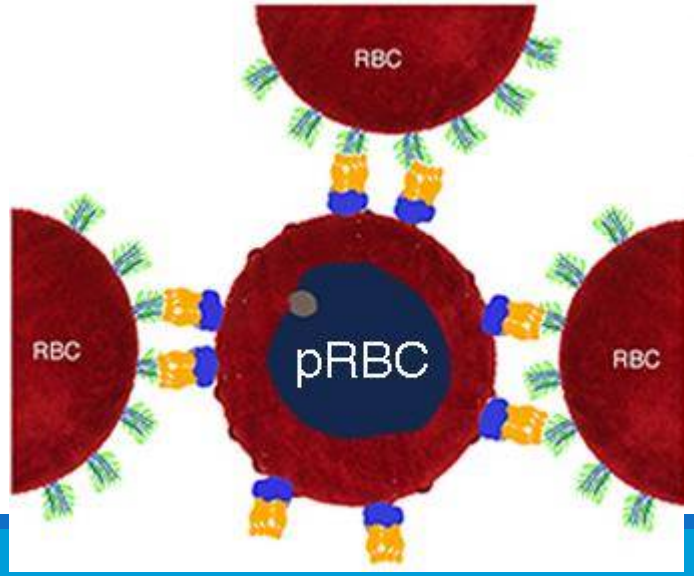
http://dx.doi.org/10.5772/65348

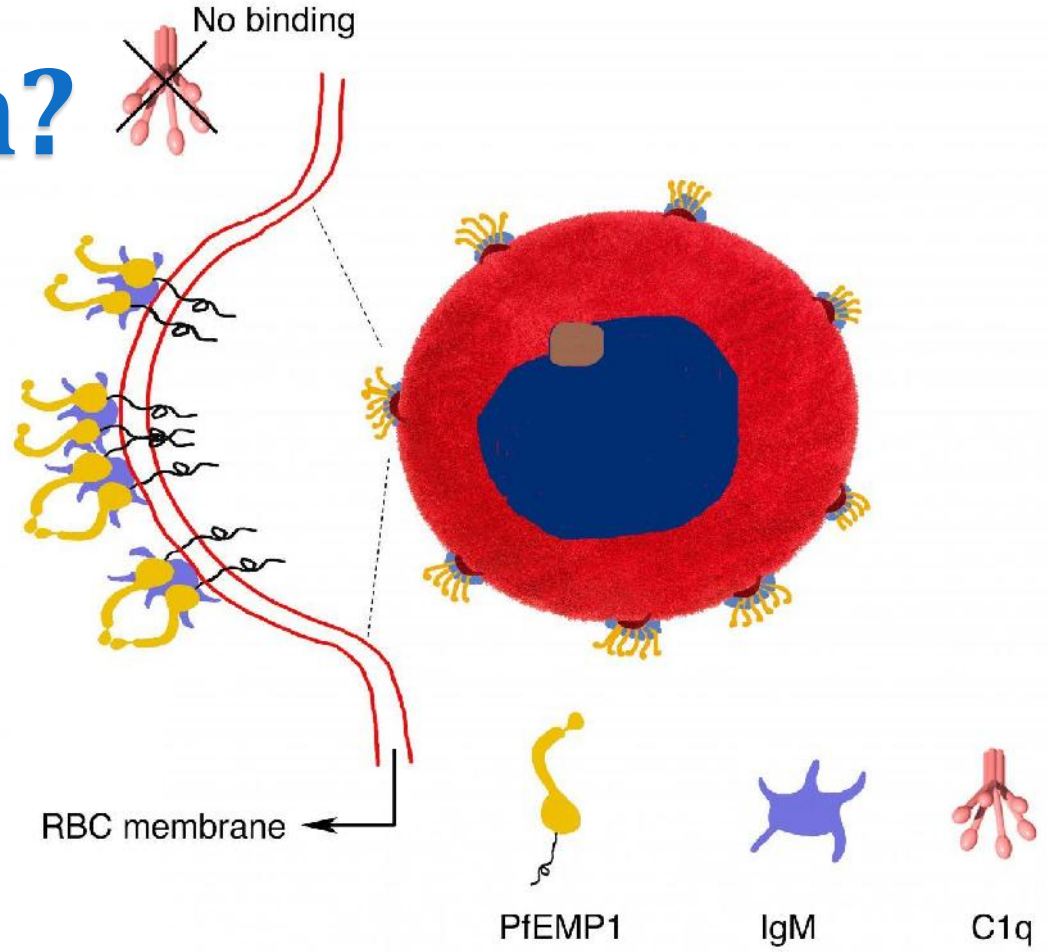
Kidney Involvement in Malaria

Plasmodium Falciparum	• AKI (Severe), Black water Fever
Plasmodium Vivax	• AKI (mild)
Plasmodium Malariae	• Glomerulonephritis
Plasmodium Ovale	• AKI (similar to vivax)
Plasmodium Knowlesi	• AKI (as part of MODS)

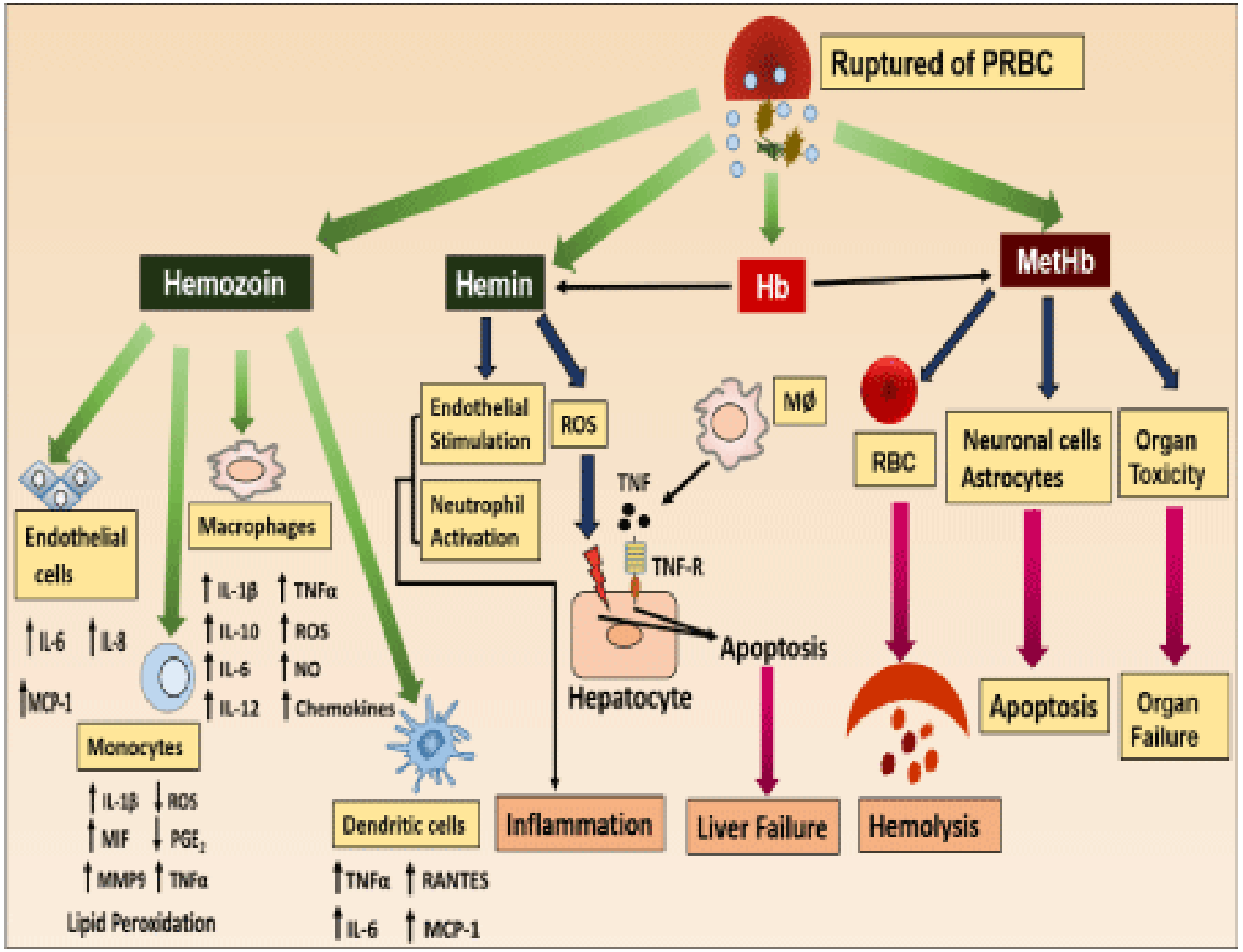
How does this happen?







Akhouri, Reetesh Raj et al.
Cell Reports , Volume 14 , Issue 4 , 723 - 736

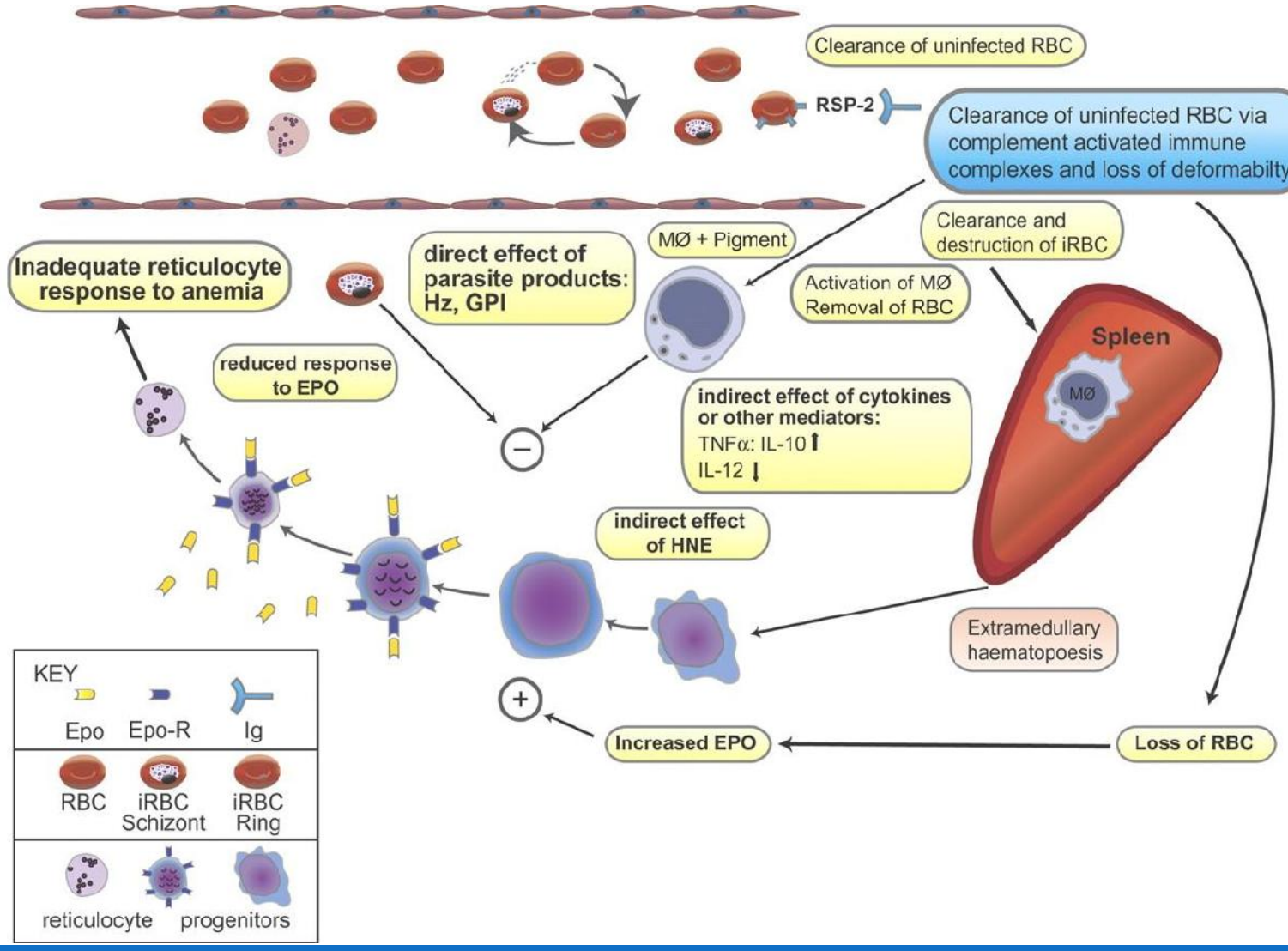


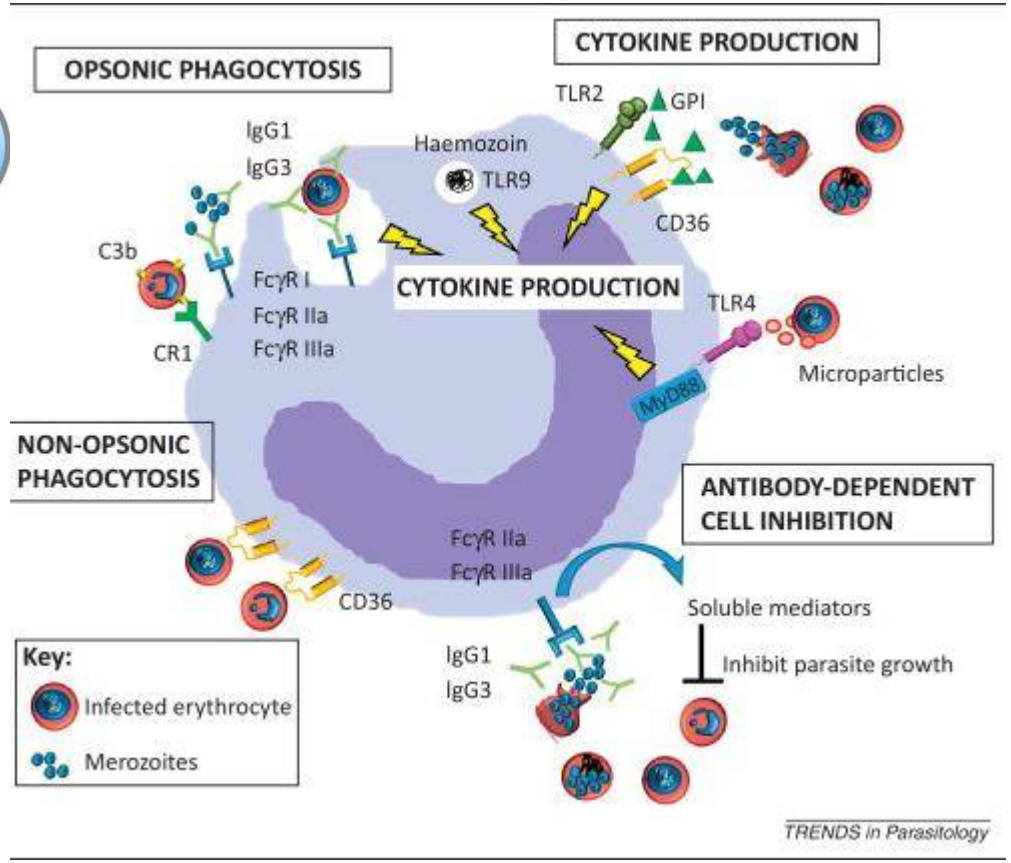
How does this happen?

Paroxysms of fever

- Rupture of Red cells to release merozoites infection proceeds in accordance to life cycle of the parasite
- Haemolysis
- Release of inflammatory mediators in response

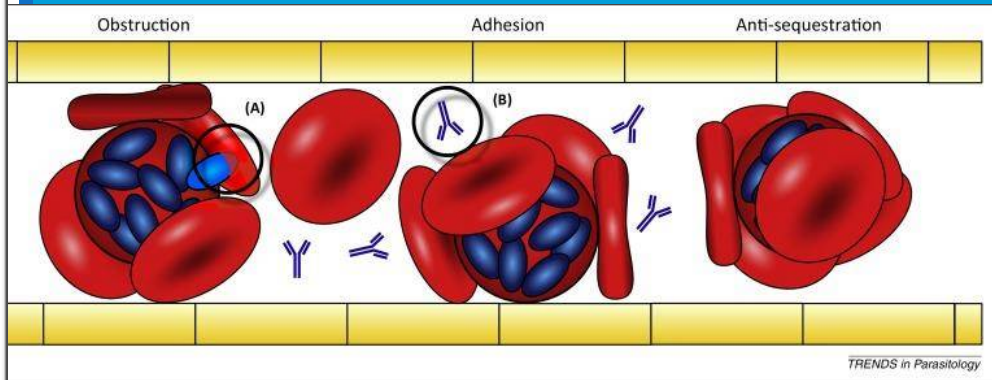
Haemolysis, Anemia and Macrophage activation in Malaria



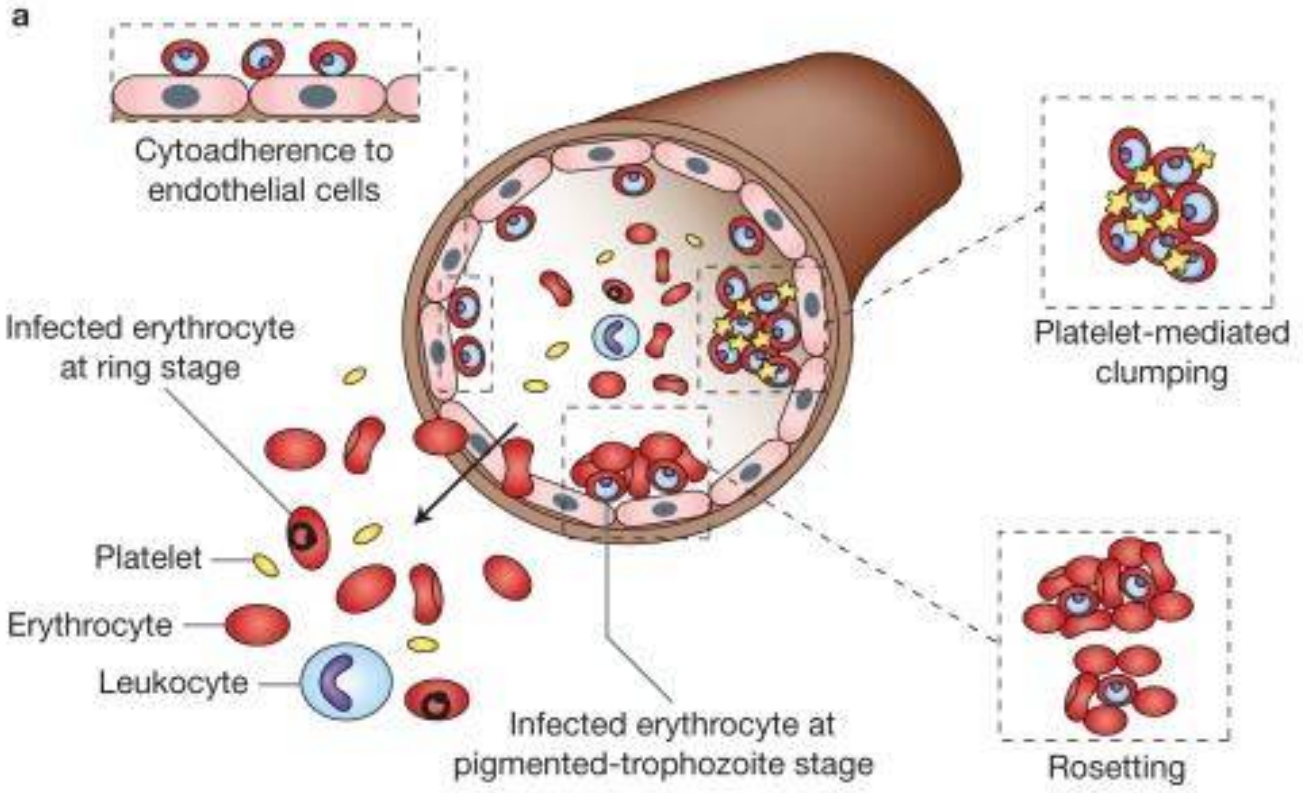


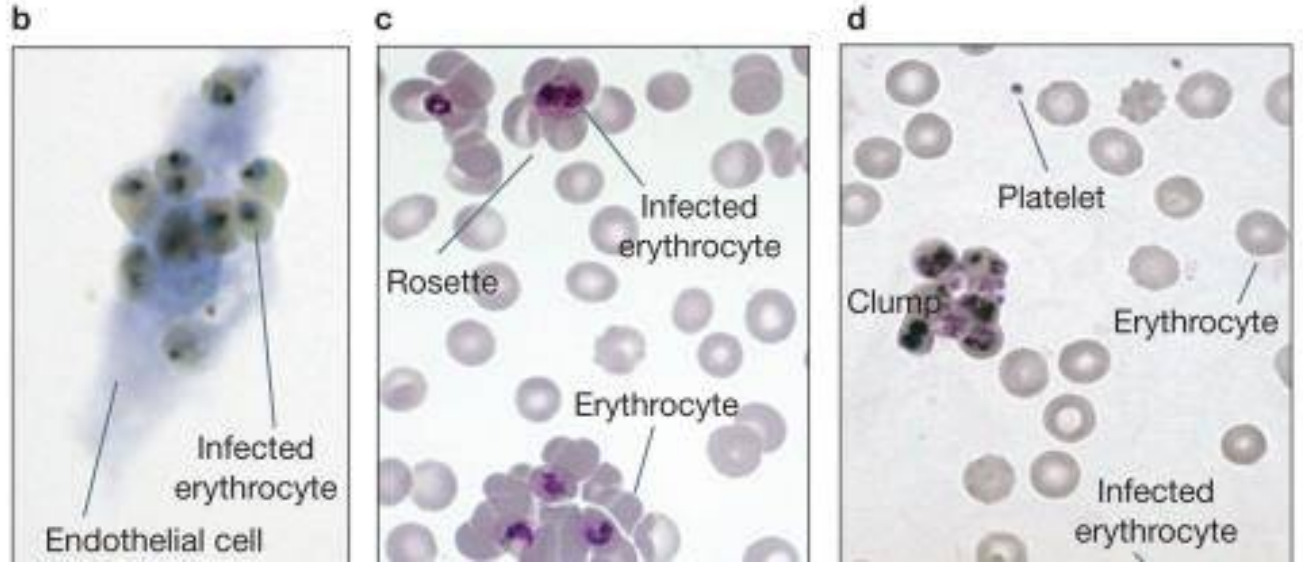
Haemo-rheological Factors

Cytoadherence of infected RBCs and Sequestration



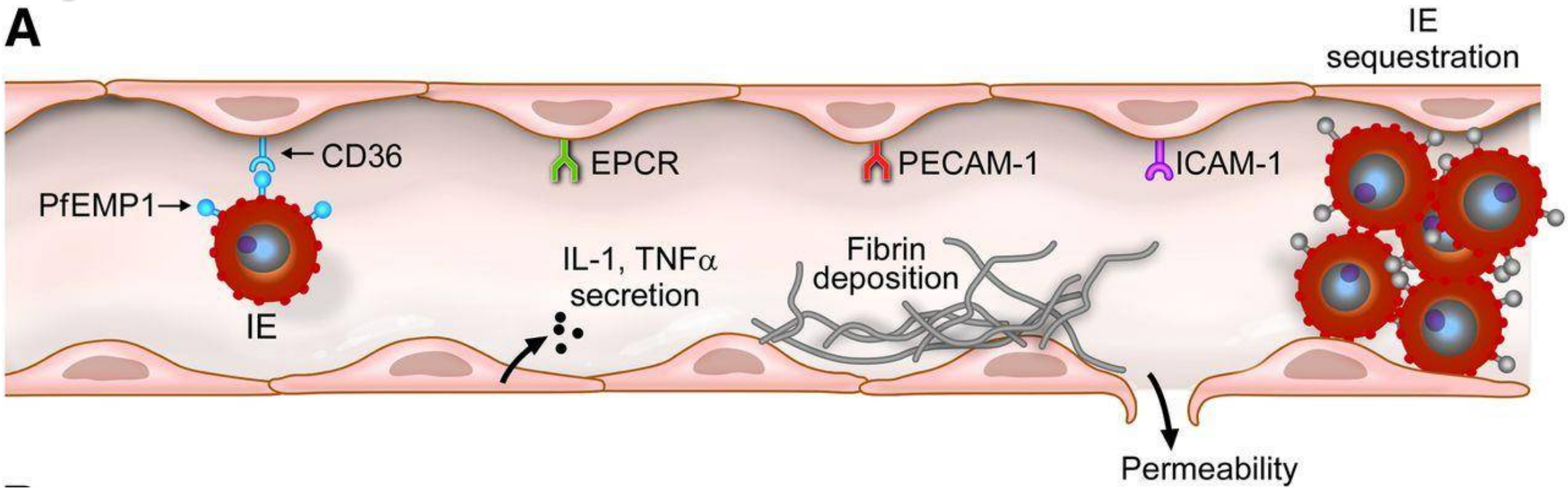
- Microcirculatory obstruction
- Local hypoxia
- Ischemia induced substrate depletion
- Lactic Acidosis, Hypoperfusion, organ Injury





Aird WC et al Blood 2014 123:163-167

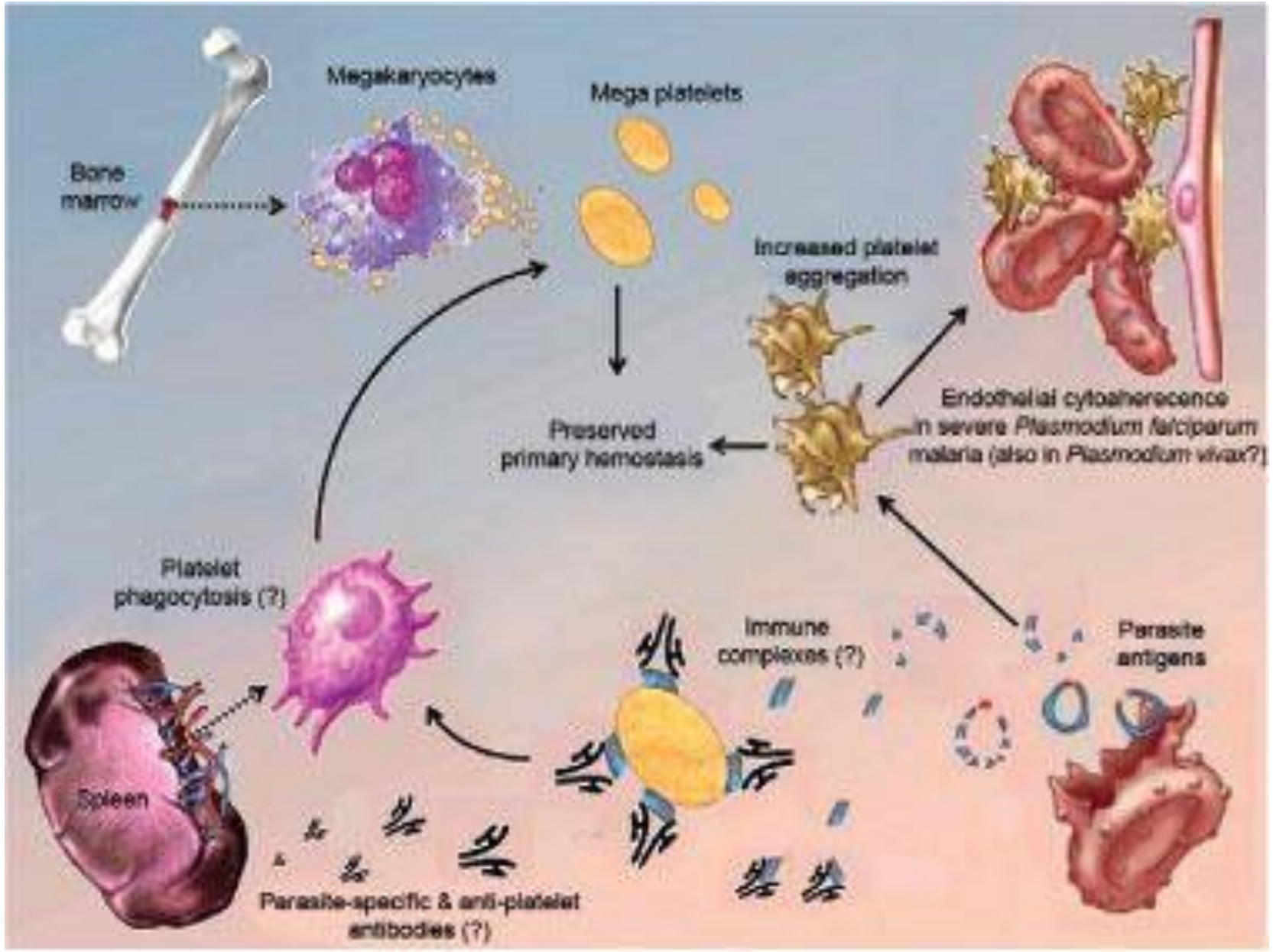
Cytoadherence to Inflammation



The parasite shown on the left is clonally expressing a PfEMP1 variant on the IE surface that binds CD36 on ECs. In addition to CD36, ECs may also express EPCR, PECAM-1, and ICAM-1. IE binding to these receptors is encoded by specific PfEMP1 domain cassettes (DCs): DC8 and DC13 bind EPCR, DC5 binds PECAM-1, and DC4 binds ICAM-1. Parasites expressing a PfEMP1 variant containing more than one DC presumably bind more than one receptor on individual ECs. Activation of the endothelium by developing parasites and downstream events such as secretion of proinflammatory cytokines, deposition of fibrin, and loss of barrier integrity, result in microvascular inflammation, obstruction, and perivascular leakage.

Thrombo-cytopenia

- Increased Platelet aggregation
- Endothelial cytoadherence
- Immune mediated platelet activation
- Mega – platelet – immune complex coating and Platelet phagocytosis
- Splenomegaly



Major mechanisms associated to malaria-triggered thrombocytopenia and the possible relationship with severe disease.

Immunologic Factors

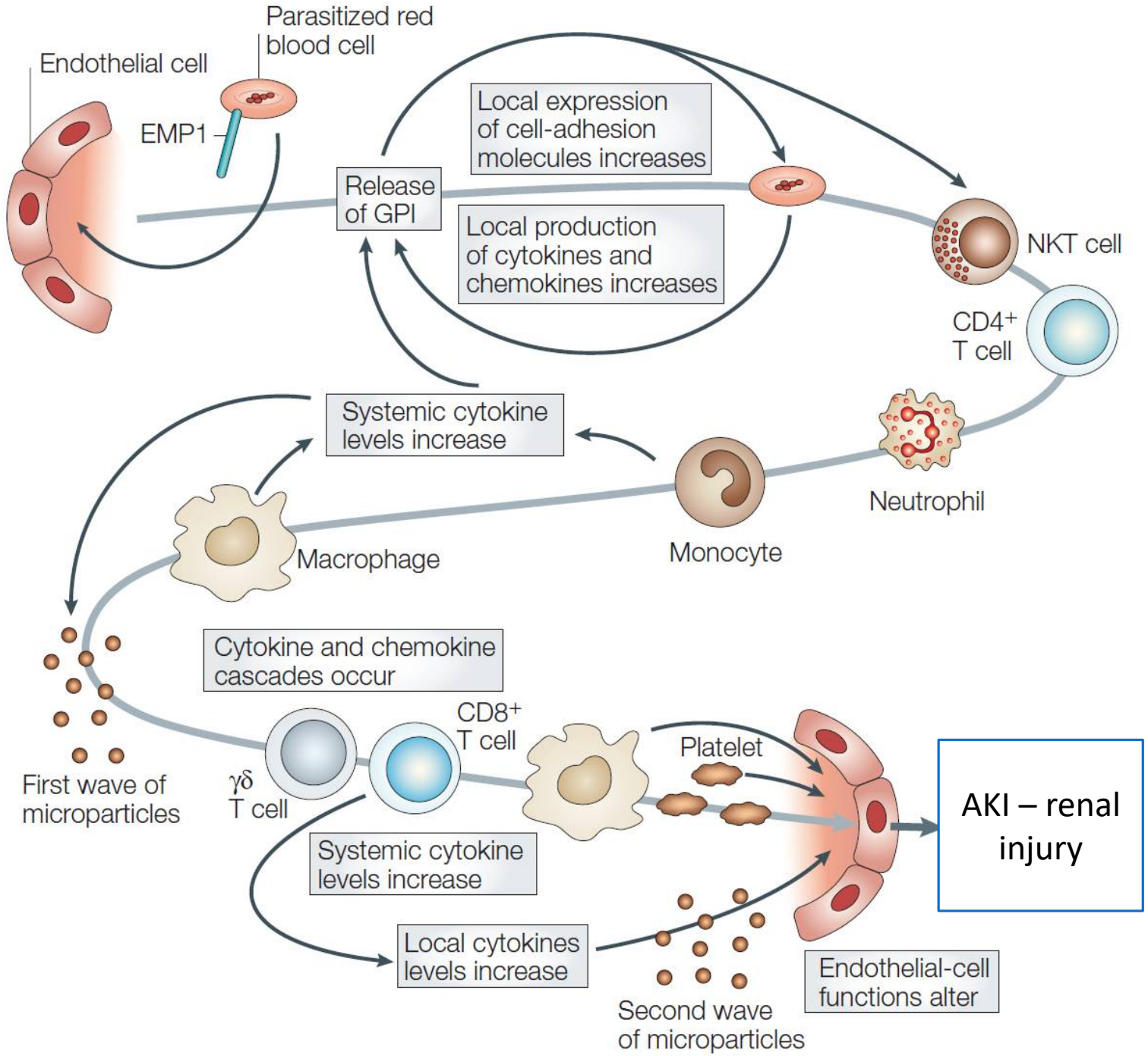
Glycophosphatidyl inositol moieties released from infected RBCs interact with NKT Cells, monocytes

Increased release of TNF a and proinflammatory cytokines, + decreased IL10

Vasoconstriction, inflammation, capillary leak, hypovolemia

Renal Hypoperfusion,

Direct renal tubular toxicity



Important mechanistic contributors to AKI

- Haemolysis
- Jaundice
- Micro-circulatory obstruction
- Intravascular coagulation
- Rhabdo-myolysis
- Non-cardiogenic Pulmonary Oedema
- Hypoxia
- Lactic acidosis

Acute Kidney Injury in Malaria

Among Tropical febrile illnesses at CMC Vellore, South India

Table 2. Diagnosis of tropical acute febrile illness and the incidence of acute kidney injury, dialysis therapy and mortality by RIFLE criteria

Diagnosis	Total *n* (%)	Total AKI	Risk	Injury	Failure	Dialysis	Mortality
Scrub typhus *n* (%)	188 (51.2)	80 (42.6)	38 (20.2)	21 (11.2)	21 (11.2)	11 (5.9)	25 (13.3)
Falciparum malaria *n* (%)	38 (10.4)	24 (63.2)	7 (18.4)	3 (7.9)	14 (36.8)	9 (23.7)	5 (13.2)
Enteric fever *n* (%)	32 (8.7)	2 (6.3)	0	1 (3.1)	1 (3.1)	0	0
Dengue *n* (%)	28 (7.6)	10 (35.7)	4 (14.3)	1 (3.6)	5 (17.9)	2 (7.1)	7 (25)
Mixed malaria *n* (%)	24 (6.5)	13 (54.2)	6 (25.0)	2 (8.3)	5 (20.8)	4 (16.7)	1 (4.2)
Leptospirosis *n* (%)	12 (3.3)	6 (50.0)	3 (25.0)	1 (8.3)	2 (16.7)	0	0
Spotted fever *n* (%)	7 (1.9)	2 (28.6)	1 (14.3)	0	1 (14.3)	1 (14.3)	1 (14.3)
Vivax malaria *n* (%)	6 (1.6)	2 (33.3)	2 (33.3)	0	0	0	0
Hantaan virus infection *n* (%)	1 (0.3)	1 (100.0)	0	0	1 (100.0)	0	0
Undifferentiated *n* (%)	31 (8.4)	11 (35.5)	3 (9.7)	6 (19.4)	2 (6.5)	2 (6.5)	6 (19.4)
Total *n* (%)	367	151 (41.1)	64 (17.4)	34 (9.3)	53 (14.4)	29 (7.9)	45 (12.3)

Basu G et al Nephrol Dial Transplant. 2011 Feb;26(2):524-31

Malaria - AKI

AKI incidence varies: 15-65%

Varies with age and immunity and endemicity

- Patients, especially children from **Endemic area have less AKI** (5-15%)
- **Nonimmune adults** from areas of low transmission and older children are susceptible to develop acute kidney injury
- Those with **imported malaria / travel associated malaria** have higher incidence of AKI (30-65%)

AKI occurs with 30% of Cerebral Malaria

Dialysis requirement in 25-40% of the AKI

Case Fatality rate : 13% - 40%

AKI is a risk factor for mortality

Risk factors associated with the development of AKI in malaria
Older adults and children
Late referral
Short acute illness
High parasitemia
Oliguria
Hypotension
Severe anemia
Significant jaundice
Severe diarrhea
Multisystem involvement, cerebral malaria
Hepatitis
Acute respiratory distress
Opportunistic pulmonary viral or bacterial infections

Basu G et al. Nephrol Dial Transplant. 2011 Feb;26(2):524-31
Doolan DL et al Clin Microbiol Rev. 2009;22(January (1)):13–36. 24.
Weber MW et al. Trop Med Parasitol. 1991;42(June (2)):115–118. 25.
Waller D et al. Clin Infect Dis. 1995;21(3):577–587.
Zewdu W. Ethiop Med J. 1994;32(April (2)):79–87. 27.
Panda SK, et al. Indian J Nephrol. 2003;13(April (2)):55. 28.
Satpathy DSK et al. Indian J Pediatr. 2004;71(February (2)):133–135. 29.
Kute VB et al. Emerg Infect Dis. 2012;18(May (5)):842–845.

Falciparum Malarial AKI

AKI associated with MODS

- Most common
- Present at the time of diagnosis
- Associated high parasitemia, anemia, acidosis, jaundice, hypoglycaemia, coma
- Poor Prognosis

Isolated AKI

- Rare
- Presents when acute complications of malaria have subsided
- Oliguria is observed in 70– 76% of the patients and may persist for 3–10 days
- Better prognosis

AKI in falciparum Malaria

RRT in 1/3rd

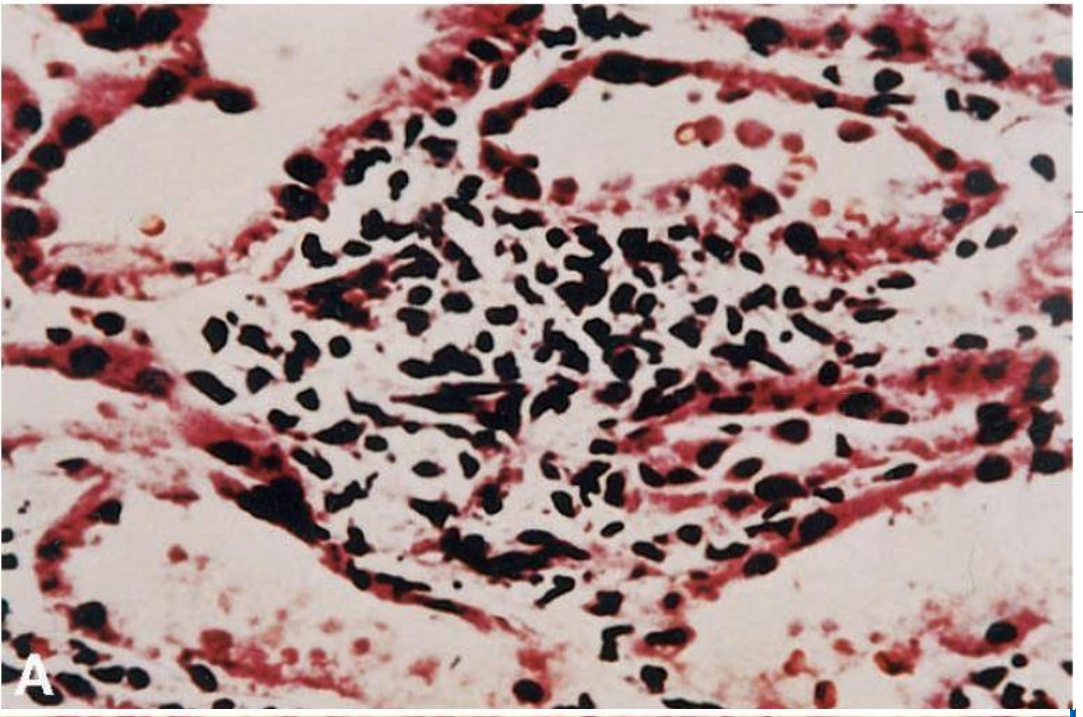
Mortality in upto 1/3rd

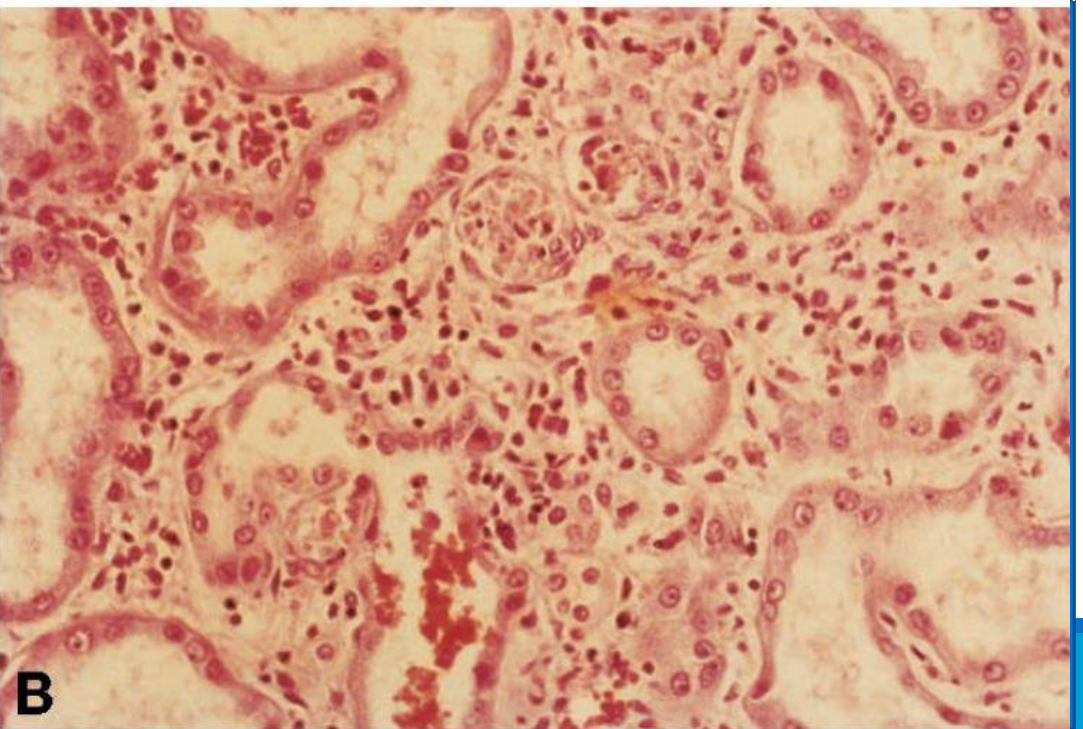
Mishra SK, Das BS. Malaria and acute kidney injury. Semin Nephrol. 2008;28(July (4)):395–408.

Renal Involvement in Malaria

- Black Water Fever – oliguric ***AKI with haemoglobinuria*** / Dark- acid hematin in urine
  - Subnephrotic proteinuria and Haematuria can be seen in 20-50% cases
  - Proteinuria and Haematuria are self limiting in most cases
  - Nephrotic proteinuria is very rare
- ***Acute glomerulonephritis*** is also very rare
- Acute phase illness could potentially have hypocomplementemia – C3 and C4
- Hypertension is very unusual manifestation
- Prolonged Oligo anuric AKI – could be due to ***Cortical Necrosis*** secondary to DIC

Renal lesions associated with Malarial AKI





- Acute tubular necrosis (note the remarkable epithelial disruption, red cells in the tubular lumen, and interstitial oedema and cellular infiltration).
- Hemoglobin in tubular epithelium with hemolysis
- Acute interstitial nephritis.

Seminars in Nephrology,
Vol 28, No 4, July 2008, pp 395-408

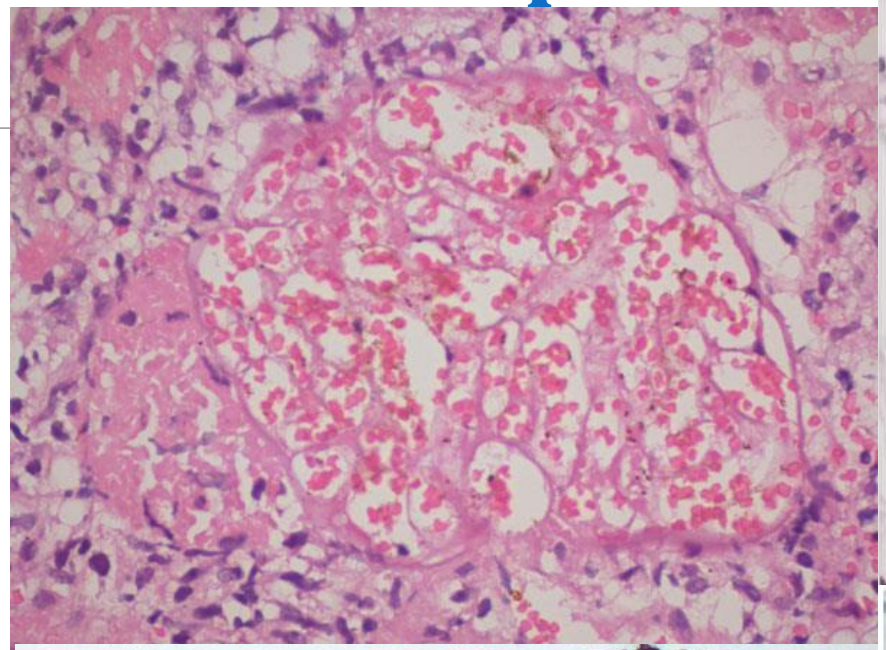
Glomerular Lesions in Falciparum Malaria

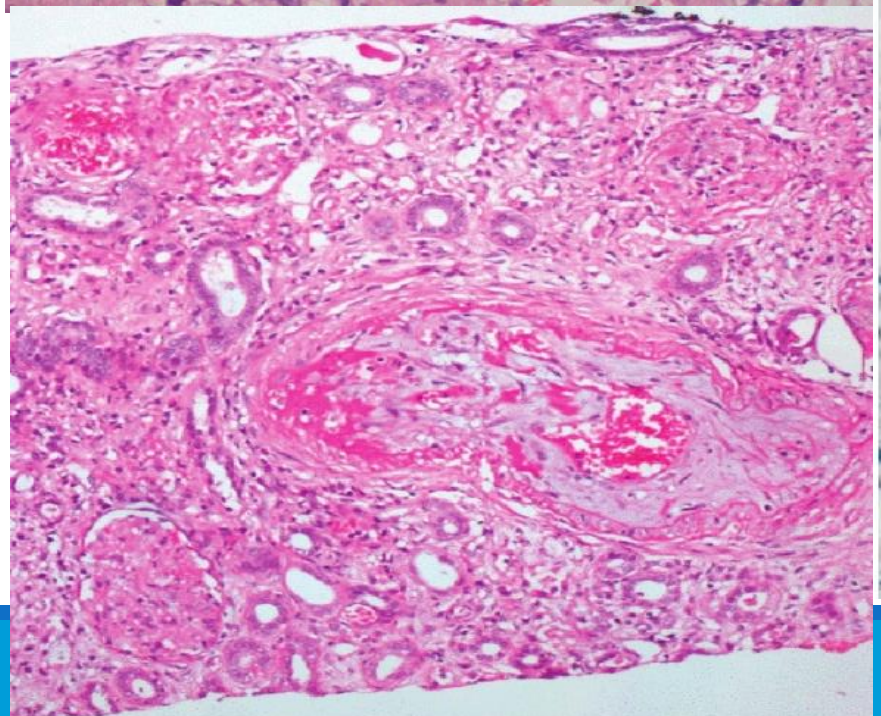
Pathology

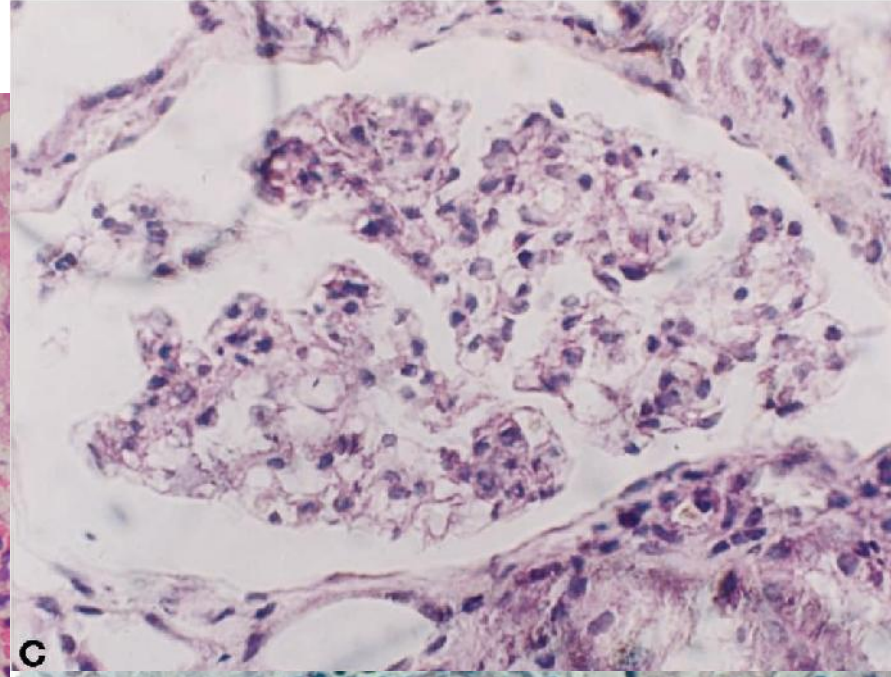
LM: mild mononuclear cell infiltration; prominent mesangial proliferation; increased mesangial matrix; normal, bloodless, or erythrocyte-containing glomerular capillaries[7,23]

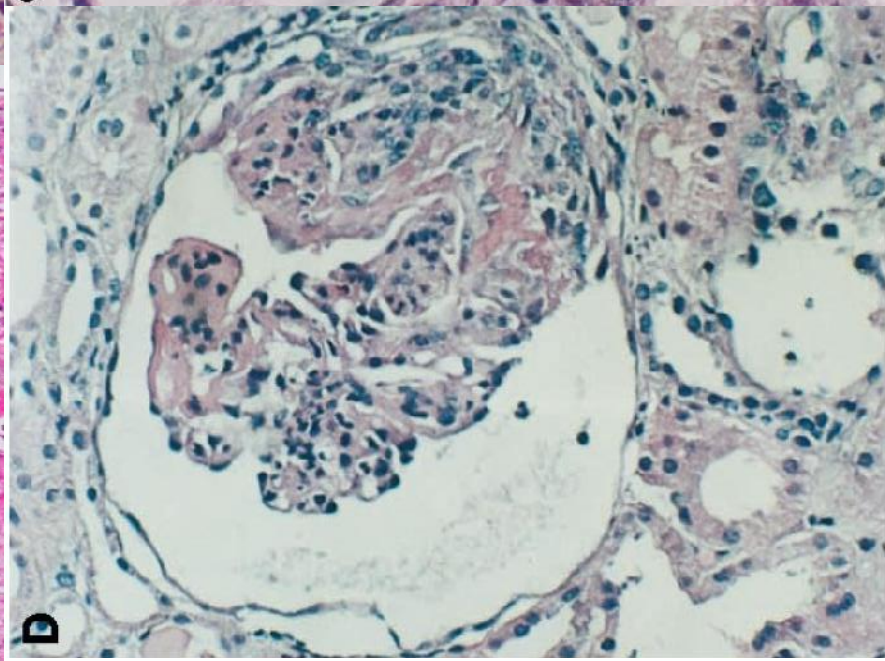
IF: deposition of finely granular immunoglobulin M and C_3 along the capillary walls and in the mesangium, occasional detection of malarial antigens along the glomerular endothelium as well as the medullary capillaries[22]

EM: subendothelial, mesangial, and paramesangial electron-dense deposits along with granular, fibrillar, and amorphous material[23]









Patel M et al Indian J Nephrol 2013;23:74-5
Kute VB et al. Emerg Infect Dis. 2012;18(5):842-845.

Electrolyte abnormalities in Malaria

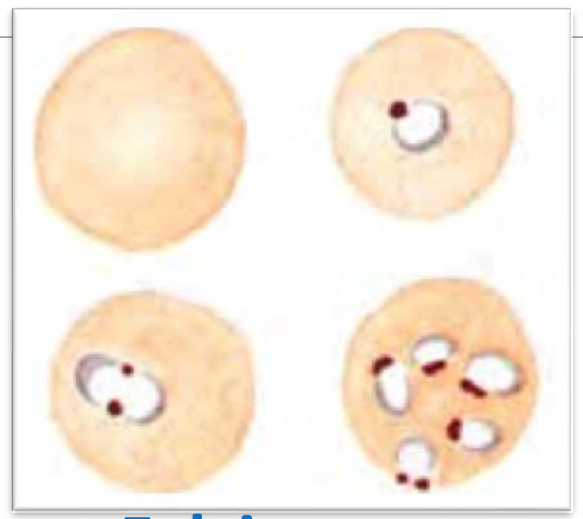
Electrolyte abnormality	Mechanism
Hyponatremia	Trapping of sodium inside the cells due to decreased functioning of the Na-K-ATPase pump (internal dilution) Increased antidiuretic hormone (ADH) secretion (not an important mechanism) Resetting of the osmoreceptor
Hypernatremia	Occurs in cerebral malaria Blunted thirst mechanism and decreased access to water
Hypokalemia	Hyperventilation and respiratory alkalosis Decreased intake and increased losses
Hyperkalemia	Occurs with acute kidney injury and hemolysis
Hypocalcemia	Intracellular calcium shift Low serum albumin level
Hypophosphatemia	Shift of phosphate into the cells due to respiratory alkalosis Hypoparathyroidism
Lactic acidosis	Tissue hypoxia and anaerobic glycolysis

Eiam Ong et al *Seminars* in *Nephrology,* Vol 23, No 1 (January), 2003: pp 21-33

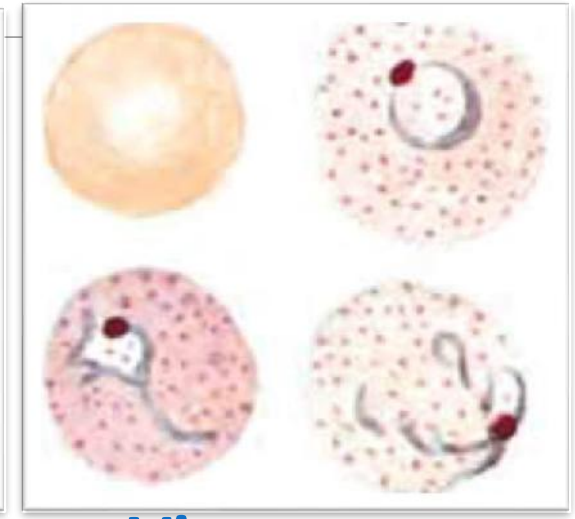
Diagnosis

- Confirmation + Parasitemia (% of infected red cells in smear)
  - Peripheral Blood Thick / Thin smear - direct visualization of the parasite in Giemsa stain
  - Fluorescence staining with acridine-orange enhances the diagnostic accuracy of peripheral blood examination.
- Rapid Diagnostic tests based on detection of
  - histidine-rich protein 2 (HRP2) antigen or
  - plasmodium-falciparum-specific lactate dehydrogenase (PfLDH).
- DNA probes
- Serology is of limited diagnostic value, particularly in endemic areas.

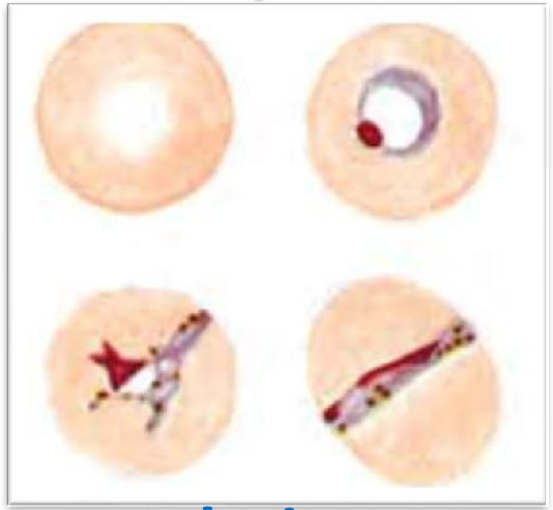
Plasmodiae in Giemsa Stain Blood Smear



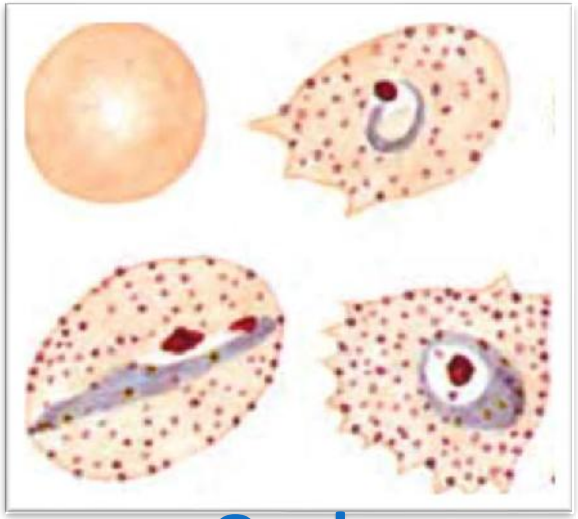
Falciparum



Vivax



Malariae



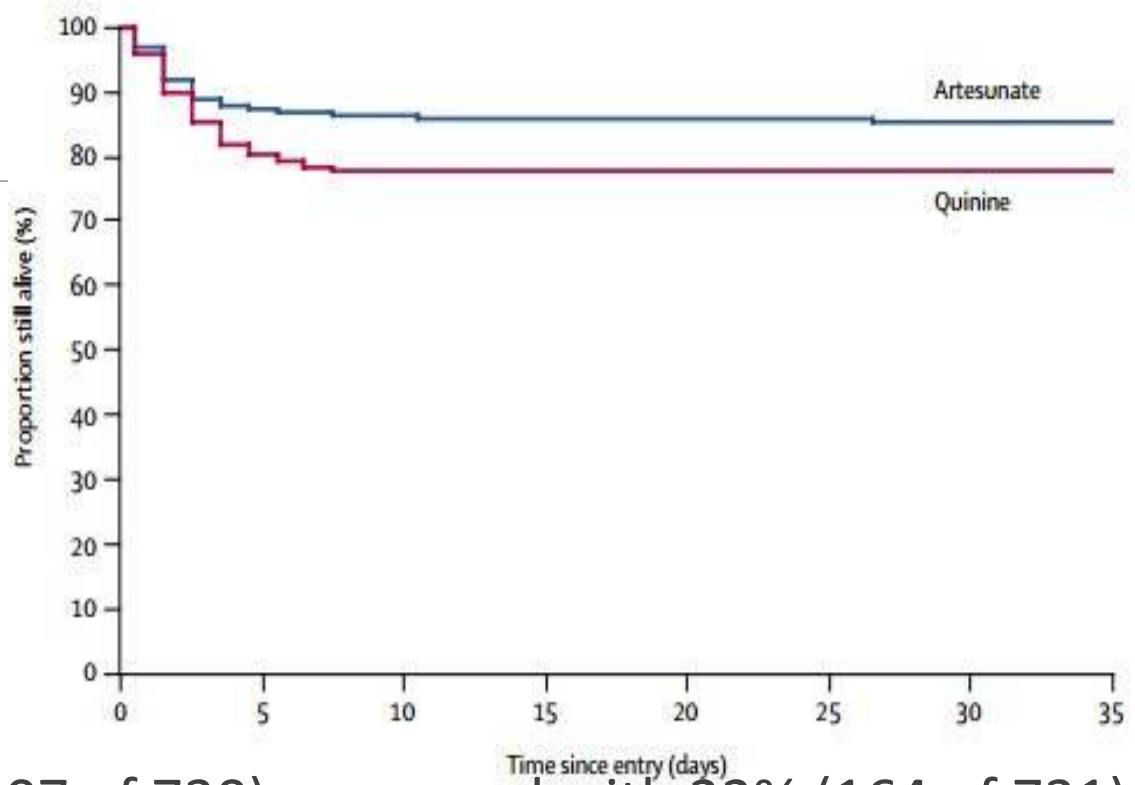
Ovale

Management – Antimalarial Drug – SEAQUAMAT Trial

- Large multicentre, open-label, randomised controlled trial
- parenteral artesunate (Inj AS) and parenteral quinine (Inj Q)
- 1461 patients with severe *P. falciparum* over the age of two.
- 2003-05 in Bangladesh, Myanmar (Burma), India, and Indonesia.

AS (730 assigned) vs Q (731 assigned).

(202 were children)



Conclusions of the study:

- Mortality in artesunate recipients was 15% (107 of 730) compared with 22% (164 of 731) in quinine recipients
- An absolute reduction of 34.7% in mortality for patients treated with Inj AS
- Treatment with artesunate was well tolerated, whereas quinine was associated with hypoglycaemia
- Inj AS should become the treatment of choice for severe *P. falciparum* malaria cases in adults.

Dondorp A, Nosten F, Stepniewska K, Day N, White N. South East Asian Quinine Artesunate Malaria Trial (SEAQUAMAT) group.Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial. Lancet. 2005; 366(September (9487)):717–725.

Antimalarial Rx

World Health Organization : IV or IM Artesunate for the initial 24 h / until oral medication is tolerated.

Rx should be completed with 3 days of artemisinin-based combination therapy.

Dosing and adverse effects of artesunate and quinine.

Drug	Artesunate	Quinine
Dosage	Larger children and adults: 2.4 mg/kg at 0, 12, and 24 h and then once daily Children weighing less than 20 kg: 3 mg/kg/dose	20 mg/kg loading dose followed by 10 mg/kg 8th hourly
Follow on therapy	Artemether/lumefantrine should be given twice a day for a total of 6 doses. The first 2 doses should be spaced 8 h apart	10 mg/kg thrice daily orally
Adverse effects	Well tolerated Post-artemisinin delayed hemolysis	Hypotension Hypoglycemia QTc prolongation and cardiac arrhythmias Cinchonism – tinnitus, disturbed vision, and nausea
Renal dose modification	Not required	If no improvement occurs by 48 h then the dose should be reduced to 10 mg/kg given 12th hourly; dose adjustment is not necessary if the patient is receiving hemodialysis or hemofiltration

Exchange Transfusion

Rapid Reduction of Parasitaemia with removal of Infected RBCs and replacement with uninfected RBCs – by venesection and Transfusion

- Manual vs Automated Eryhtrocytapheresis

Removal and replacement of infected red cells is logical Rx option in Malaria

- Previously recommended for used with
  - Parasitaemia >10% with organ involvement – cerebral / AKI or
  - Parasitaemia >30%

Reserved for the sickest of the malaria patients

Independent assessment of data including meta analysis, reveal ***no major survival advantage of using exchange trasnfusiin*** versus not using the same.

In 2013 CDC was unable to demonstrate a survival benefit of the ET.

CDC no longer recommends exchange transfusion as an adjunct for the treatment of severe malaria.

https://www.cdc.gov/malaria/diagnosis_treatment/treatment.html

Fluid Resuscitation in Malaria

Volume status assessment important in Malaria – No specific tools – Careful clinical monitoring is important.

Fluid Resuscitation – carefully undertaken

Fine balance between
- Pulmonary Oedema
- Hypovolemia

Cardiac output often preserved well – fluid resuscitation could potentially precipitate APO

Liberal fluid resuscitation even guided by PiCCO in ICU setting has only resulted in increased mortality (PRISM trial and VHS study)

Fluid resuscitation did not reduce
- AKI
- Metabolic (Lactic) acidosis
- Deaths

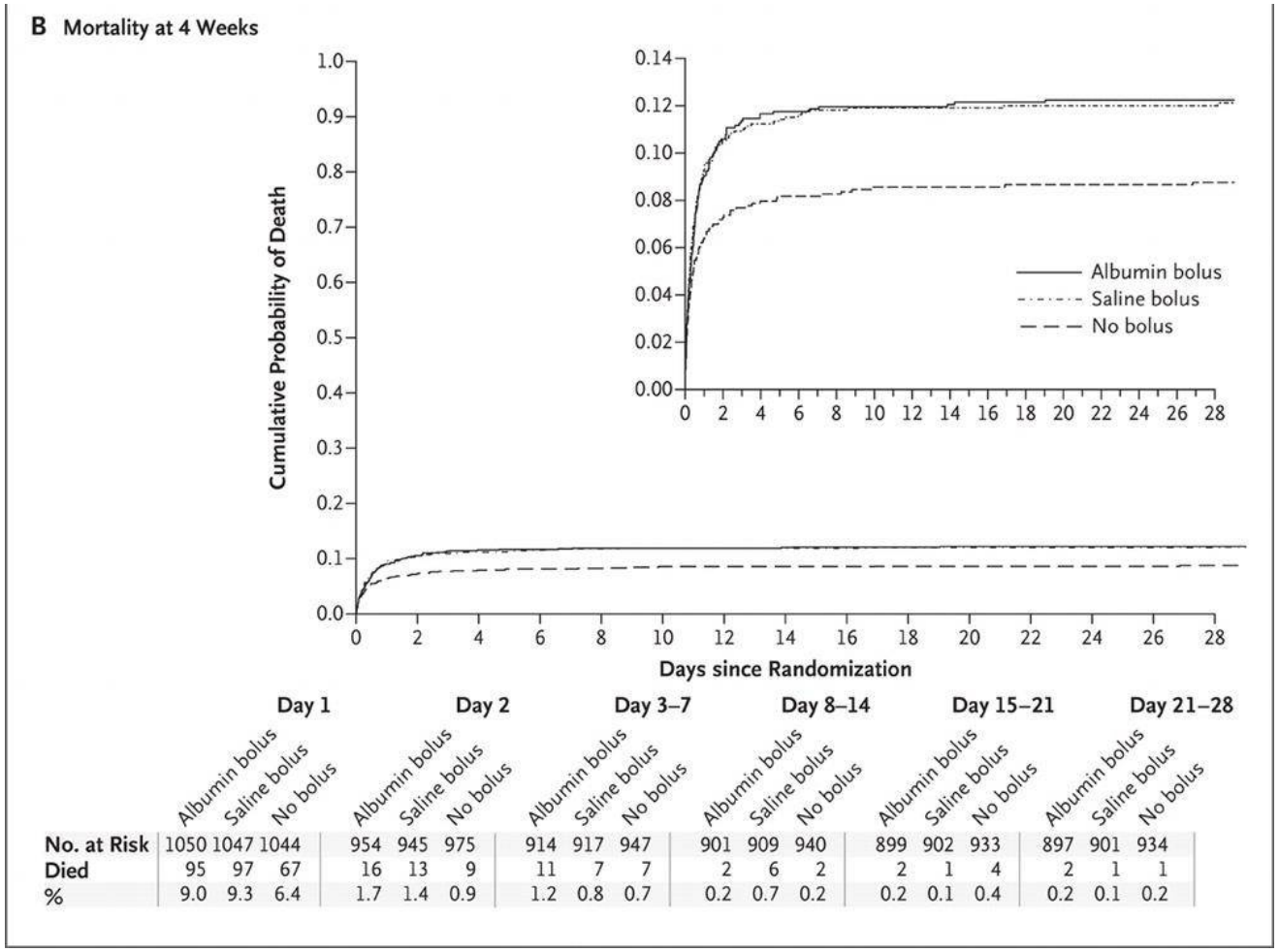
These complications are less related to hypovolemia but more related to RBC sequestration.
there may only be little advantage in infusing fluid beyond a maintenance rate of 1–2 ml/kg/h.

Little advantage in infusing fluid beyond a maintenance rate of 1–2 ml/kg/h.

Blood Transfusions if Hb <70g/L

Hanson JP et al . Crit Care Med. 2013;41(April (4)):972–981.
Phu NH et al. PLoS ONE. 2011;6(October (10)):e25523.
Hanson J, et al. Crit Care. 2014;18:642.

Fluid Resuscitation



	Day 1			Day 2			Day 3–7			Day 8–14			Day 15–21			Day 21–28		
	Albumin bolus	Saline bolus	No bolus	Albumin bolus	Saline bolus	No bolus	Albumin bolus	Saline bolus	No bolus	Albumin bolus	Saline bolus	No bolus	Albumin bolus	Saline bolus	No bolus	Albumin bolus	Saline bolus	No bolus
No. at Risk	1050	1047	1044	954	945	975	914	917	947	901	909	940	899	902	933	897	901	934
Died	95	97	67	16	13	9	11	7	7	2	6	2	2	1	4	2	1	1
%	9.0	9.3	6.4	1.7	1.4	0.9	1.2	0.8	0.7	0.2	0.7	0.2	0.2	0.1	0.4	0.2	0.1	0.2

FEAST trial – Unexpected results of a trial of Fluid resuscitation in young children with Sepsis in Subsaharan Africa - 3141 patients

20ml/Kg of NS vs 20ml/Kg of Albumin vs no Bolus

Increased mortality in bolus groups vs no bolus group

57% of them had Malaria

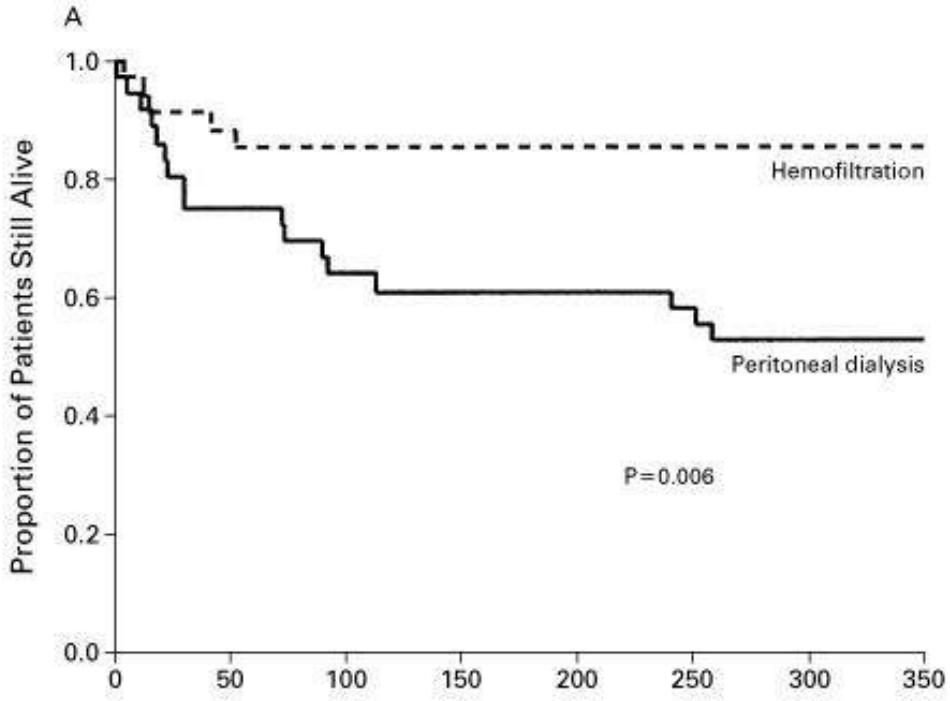
The increased mortality observed resulted from cardiovascular collapse and not due to pulmonary oedema but due to refractory shock and arrhythmia

WHO: For management of severe malaria crystalloid or colloid boluses are contraindicated.

Maitland K, Kiguli S, Opoka RO, et al. Mortality after fluid bolus in African children with severe infection. N Engl J Med. 2011 [Internet]. Available from: http://www. nejm.org/doi/full/10.1056/NEJMoa1101549. [cited 06.04.16]. 76. Myburgh J, Finfer S. Causes of death after fluid bolus resuscitation: new insights from FEAST. BMC Med. 2013;11(March):67.

Renal Replacement Therapy

- Aki in malaria is often Hypercatabolic!!
- Prompt initiation of renal replacement therapy reduces mortality
- There is no consensus on the best modality of renal replacement in malaria.
  - Acute PD for AKI IN Malaria - concern that it is ? Inadequate
    - Poor clearance due to microcirculatory obstruction
  - Intermittent HD
    - possibility of hemodynamic worsening.
  - CRRT increasingly used.



A study done in Vietnam compared mortality in Acute PD vs Haemofiltration

- 47% in PD vs 15% in HF.
- The rates of resolution of acidosis and decline in serum creatinine were also two times higher in the hemofiltration group.

Phu et al. N Engl J Med 2002;347:895-902

Quartan Malarial Nephropathy

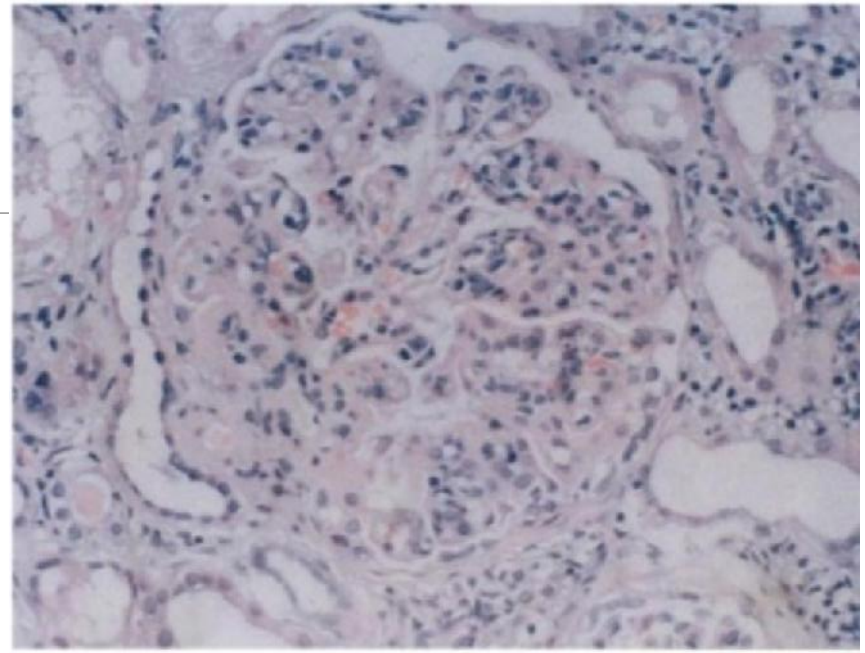
P.Malariae – Subsaharan Africa and SE Asia

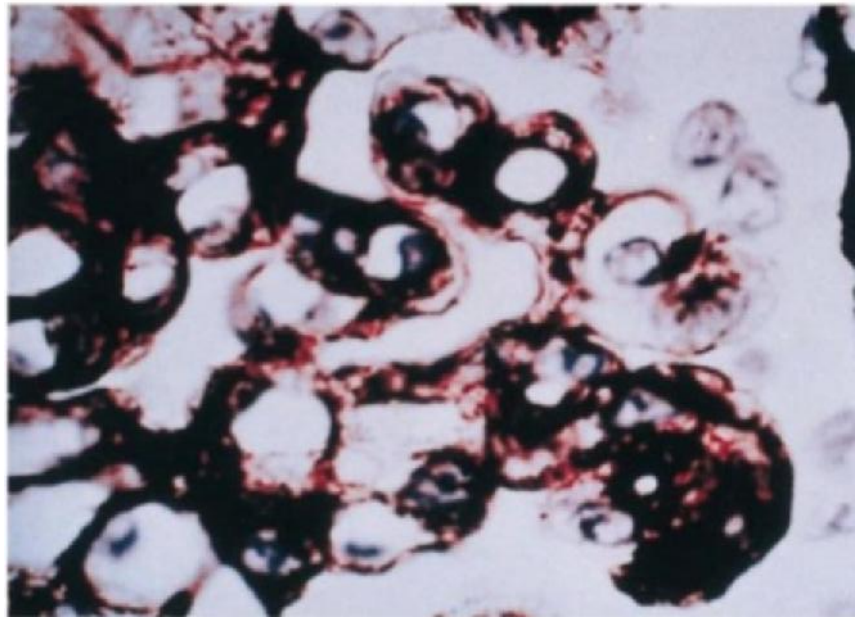
Acute transient nephritis

- Occurs 2-3 wks after infection
- Resolves in 6-12 weeks
- Mild to moderate proteinuria
- Precipietated by exertion
- Normal renal function
- IgM deposition in IF with proliferative GN – mesangial / MPGN
- Spontaneous resolution

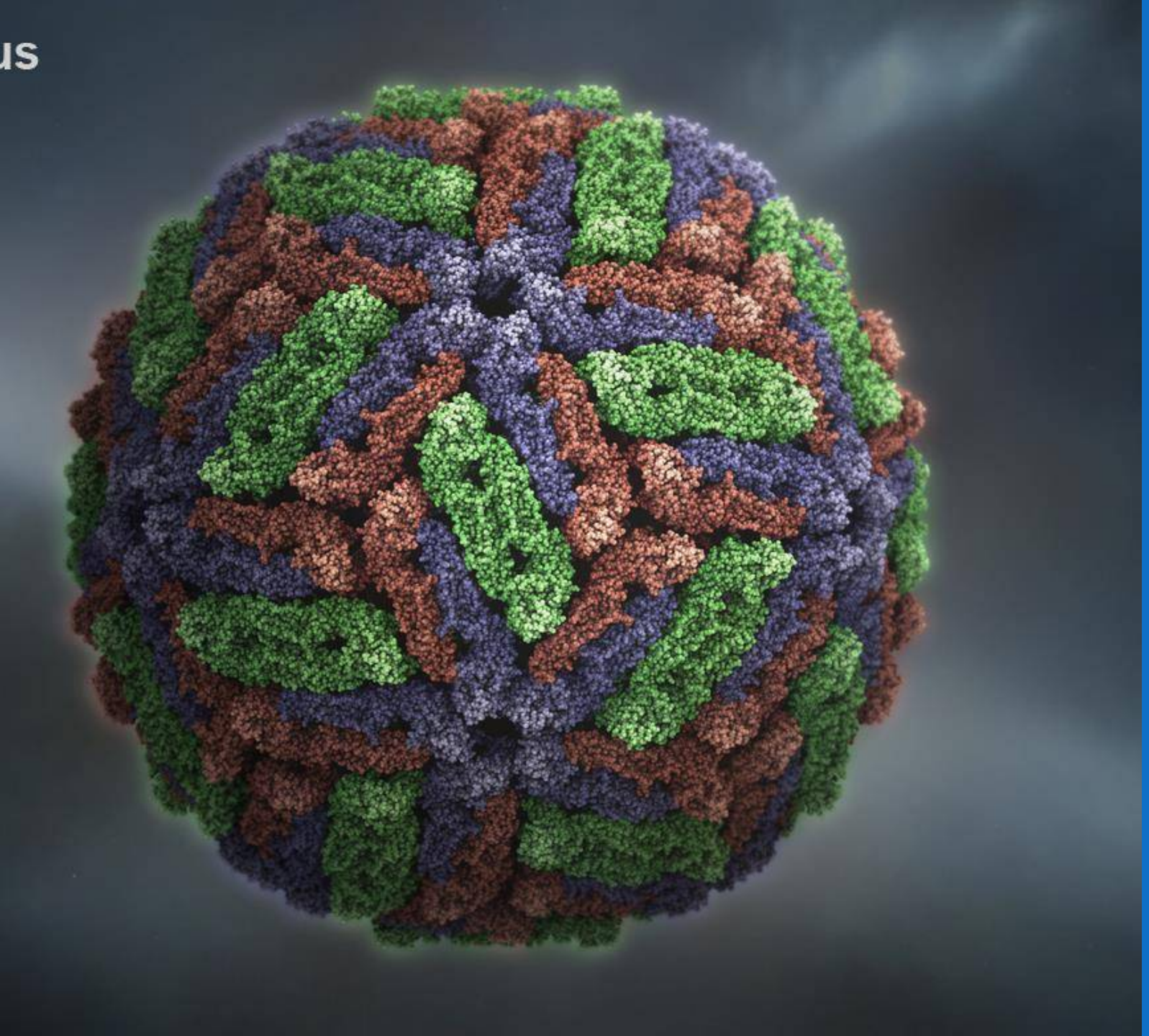
Chronic malarial nephropathy

- Severe and more persistent involvement of kidney
- Children 5 -7 years are at risk
- Anasarca – Nephrotic syndrome
- Hepatospelnomegaly
- Hypertension in later stage
- No Haematuria usually
- MPGN / DPGN with granular IgG in mes/CW deposits
- Poor response to stroids / IMS
- ESRD in 3-5 years





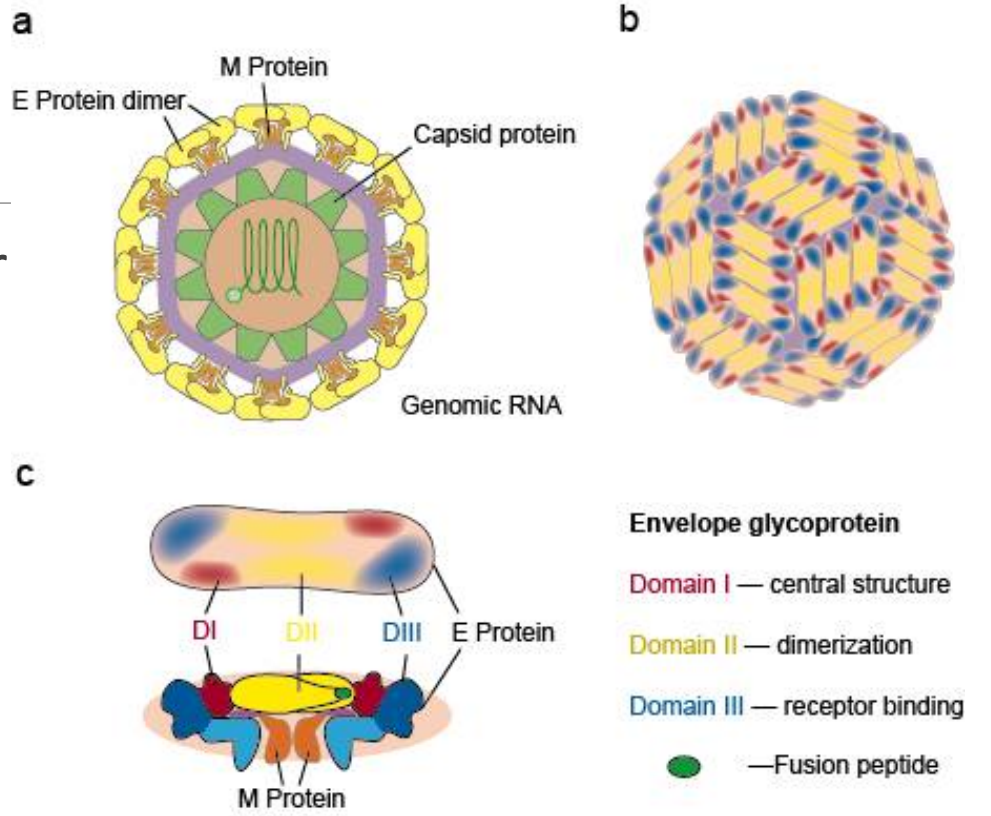
ENDRICKSE et al Kidney International, Vol. 16 (1979), pp. 64-74
Eiam Ong et al *Seminars* in *Nephrology,* Vol 23, No 1 (January), 2003: pp 21-33

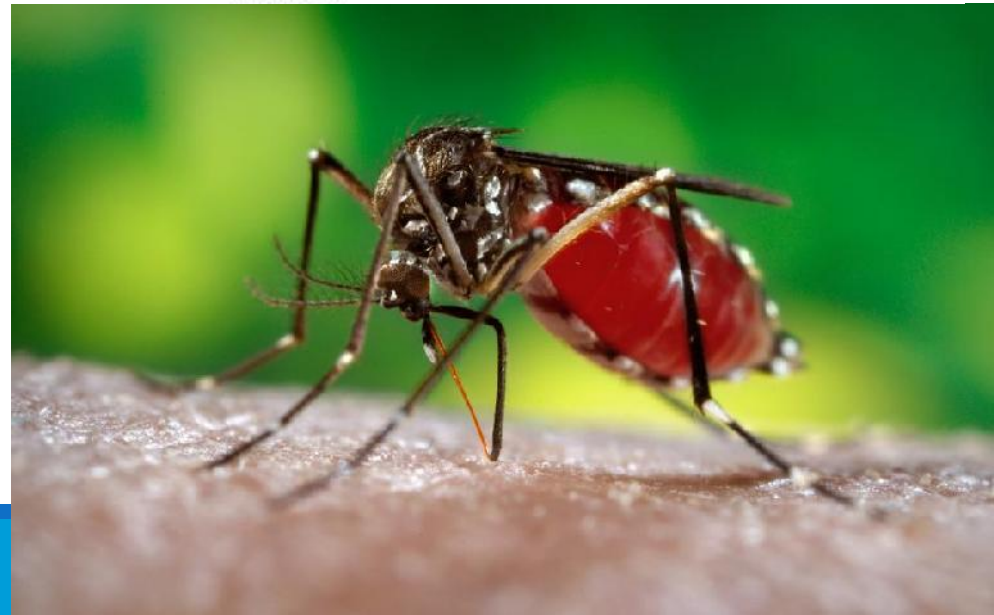


Dengue and the Kidney

Dengue

- Dengue Is a Mosquito-Borne viral haemorrhagic fever
- Dengue virus is a RNA flavivirus
- Worldwide incidence
- 4 serotypes of the dengue virus (DEN-1 to DEN-4), a RNA flavivirus.
  - They are closely related antigenically,
  - Infection with one serotype produces
    - lifelong immunity to that serotype,
    - Immunity to other serotypes lasts only a few months
- Female Aedes Aegypti mosquito vector
  - Urban water swamps
  - Day biting mosquito





Modis Y et al. Nature, 2004, 427(6972): 313-319.

Dengue Prevalence

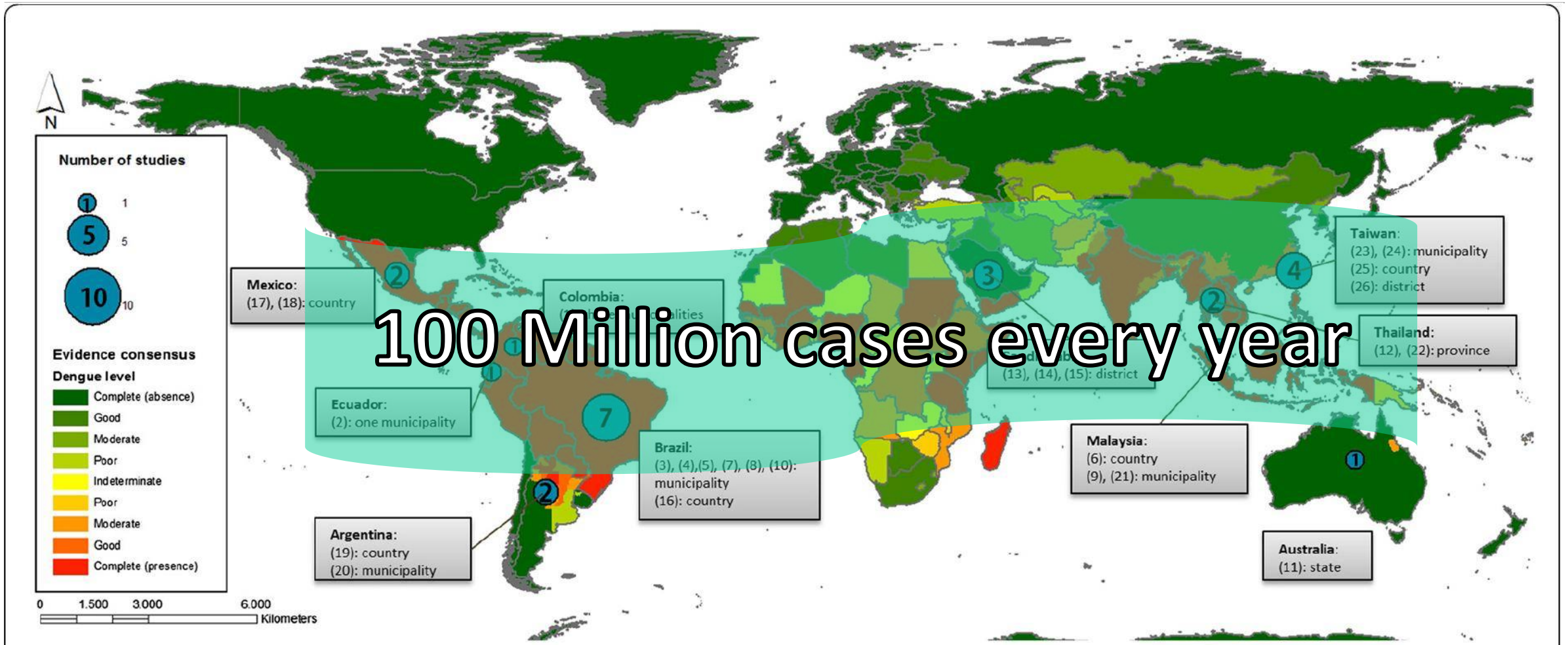


Figure 2 World map of dengue evidence consensus (adapted from Brady et al. [8]) with number of publications reviewed in respective countries. Geographic scale (municipality, district, state/province, country) of studies is given in grey boxes.

Clinical Features

Mosquito bite

Viremic Phase

Dengue fever	Dengue hemorrhagic fever	Dengue Shock syndrome
Fever, Headache, retorauricular pain, Myalgia, arthralgia, Rash. Lecuopoenia, Thrombocyotpneia	Sec. Infection - High fever fo 2-7 days, Hemorhhagic manifestaitions Thrombocytopenia, Capillary leak syndrome	DHF features with Severe plasma leakage and Shock syndrome. High mortality 40%

Table 2. World Health Organization Definition of Dengue Infection

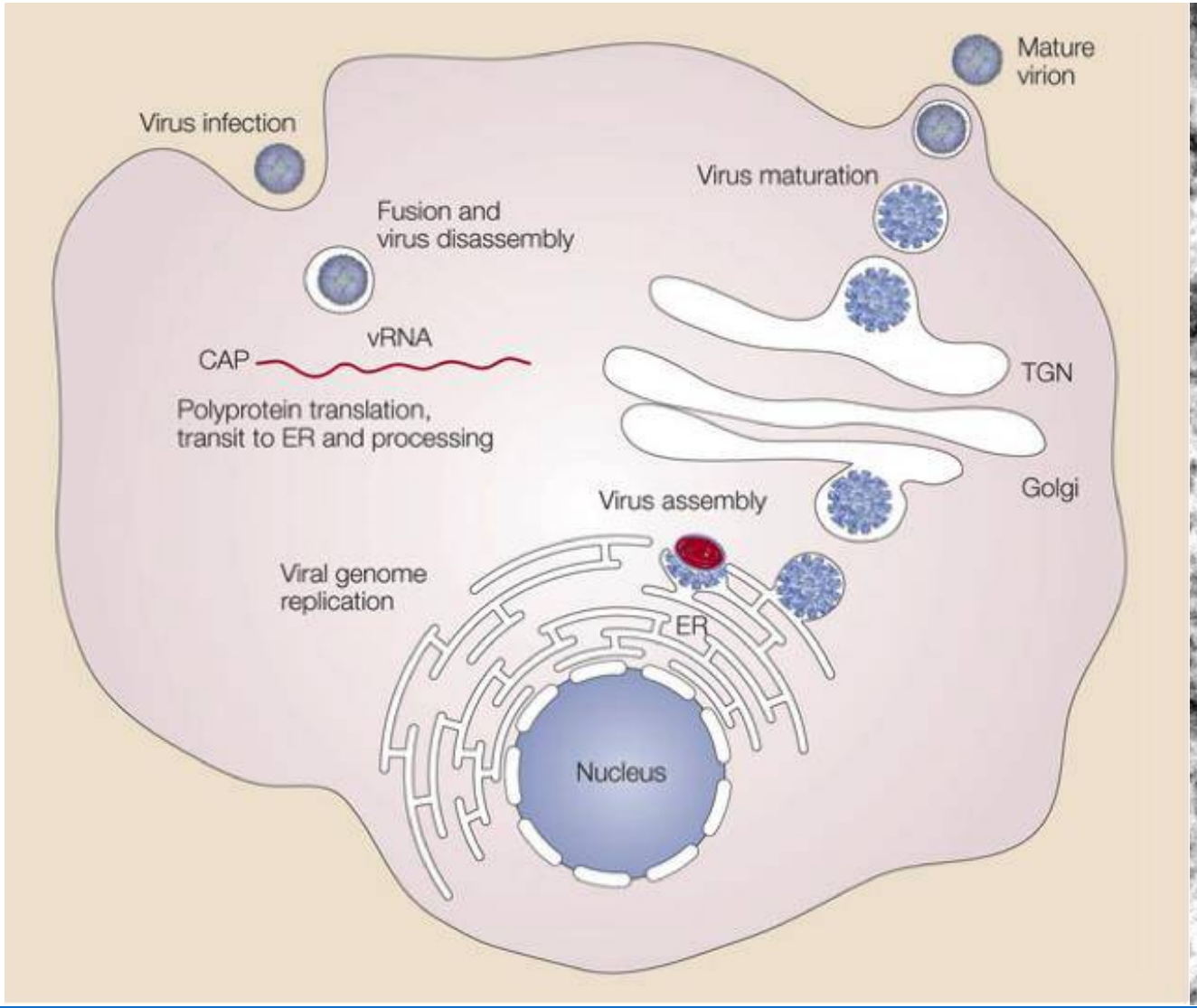
Dengue fever
- Acute febrile illness with 2 or more of the following:
  - Headache
  - Retro-orbital pain
  - Myalgia
  - Rash
  - Hemorrhagic manifestations
  - Leukopenia

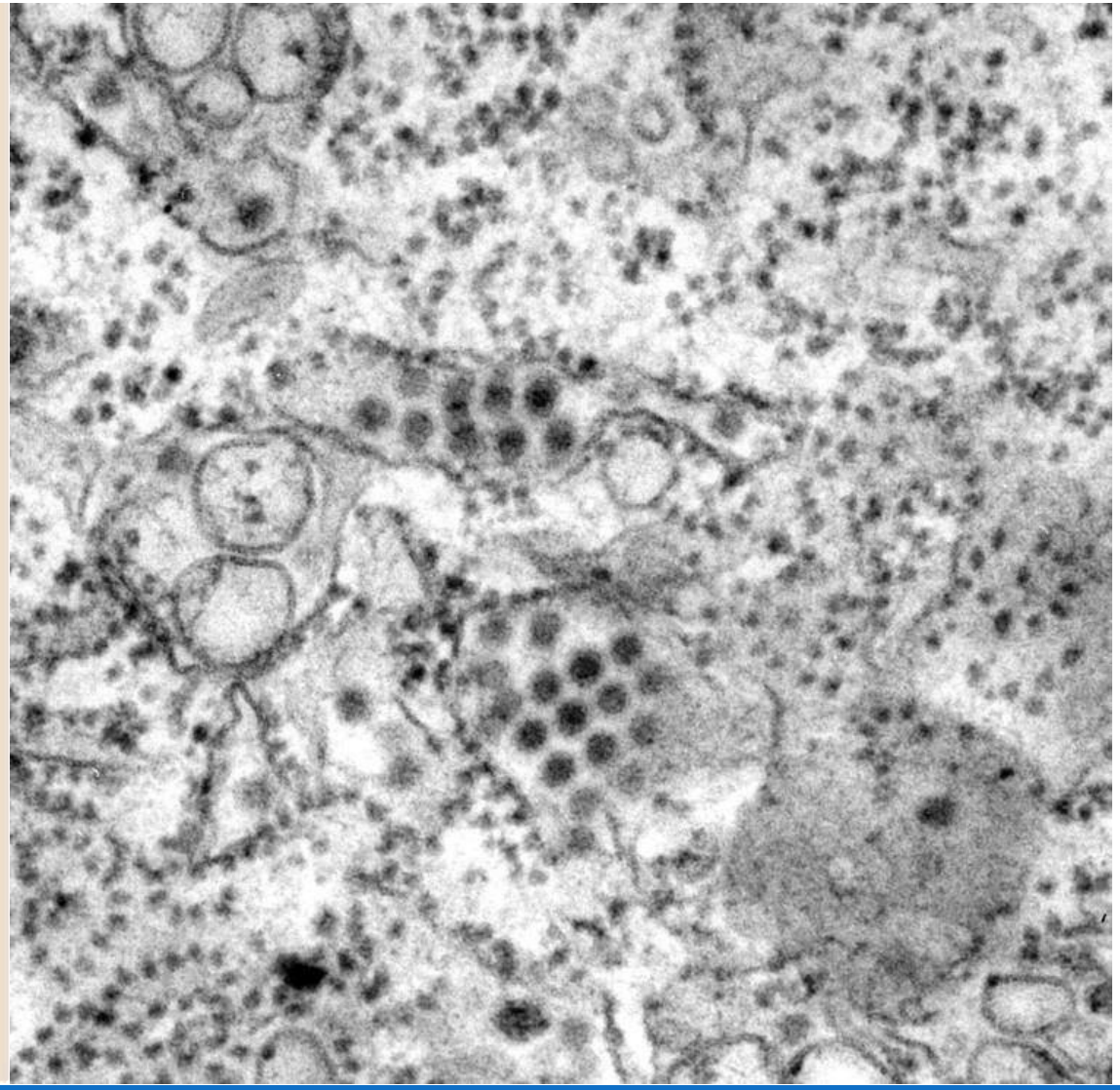
Dengue hemorrhagic fever
- All of the following must be present:
  - Fever, lasting 2 to 7 days, occasionally biphasic
  - Hemorrhagic manifestations with at least one of the following:
    - Positive tourniquet test,
    - Petechiae, ecchymoses, or purpura
    - Bleeding from mucosa, gastrointestinal tract, injection sites, or other locations
    - Hematemesis or melena
  - Thrombocytopenia (≤100,000/mm^3)
  - Evidence of plasma leakage manifested by at least one of the following:
    - Increase in the hematocrit level ’20% for age, sex, and population
    - Decrease in the hematocrit after volume replacement ≥20% of baseline
    - Signs of plasma leakage such as pleural effusion, ascites, and hypoproteinemia

Dengue shock syndrome
- Criteria for DHF associated with:
- Tachycardia
- Pulse pressure <20 mm Hg
- Hypotension for age
- Cold skin and restlessness

Laboratory criteria confirmation
- At least one of the following:
- Isolation of the dengue virus from serum or autopsy samples
- ≥4-fold change in IgG or IgM antibody specific to dengue virus
- Detection of dengue virus in tissue, serum, or cerebrospinal fluid by immunohistochemistry, immunofluorescence, or enzyme-linked immunosorbent assay

Data from World Health Organization.[55]





http://theconversation.com/modifying-mosquitoes-to-stop-transmission-of-dengue-fever-42287

Pathogenesis of Dengue

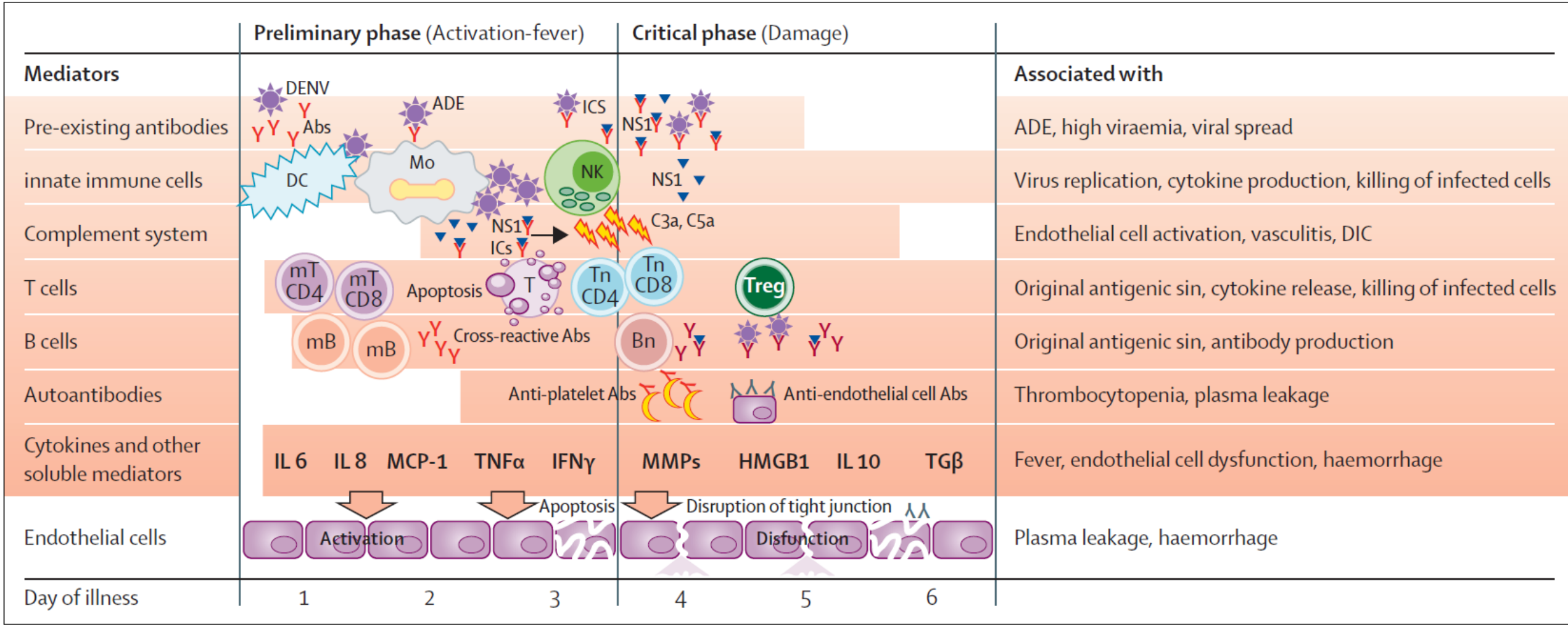


Figure 3: Pathogenesis of dengue virus infection according to phase of illness

Martina et al Clin. Microbiol. Rev. October 2009 vol. 22 no. 4 564-581

DIAGNOSIS

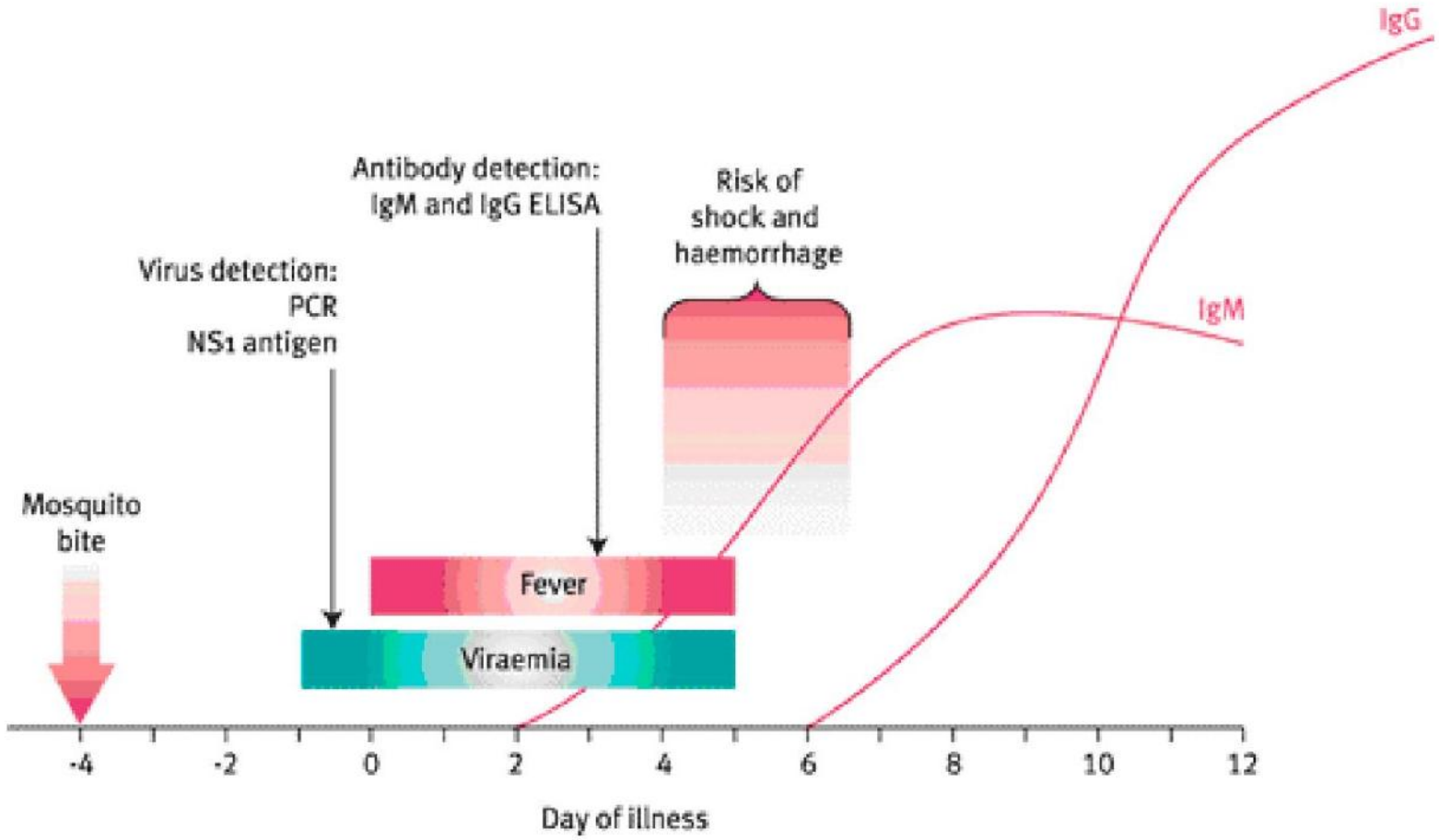
Serology – IgM dengue positivity / Rising titre

- IgM seen in 4-7 days of fever and subsides in 3 weeks
- IgG seen after 2 weeks and persists for years

Confirmation by Dengue Viral PCR in blood

- NS1 domain

Primary Dengue Infection – typical time course



https://www.health.qld.gov.au/__data/assets/pdf_file/0022/444433/dengue-mgt-plan.pdf

Dengue - AKI

Table 2 The prevalence of acute kidney injury induced by dengue virus infection

Author	Year of study	N	Age (years)	Country	DVI	AKI (%)
Vachvanichsanong et al. [42]	1987-2007	2,221	<15	Thailand	DF/DHF/DSS	0.2
Laoprasopwattana et al. [47]	1989-2007	2,893	<15	Thailand	DF/DHF/DSS	0.9
Mendez and Gonalez [48]	1992-2002	617	<13	Columbia	DHF	1.6
Khan et al. [37]	2004	91	6-94	Saudi Arabia	DHF	2.2
Lee et al. [22]	2002	304	> 18	Taiwan	DHF/DSS	3.3
Kuo et al. [49]	2002	273	48 ± 18	Taiwan	DF/DHF/DSS	5.5†
						27.1‡
Bunnag et al. [50]	2008-2009	50	Children	Thailand	DSS	10.0
Mehra et al. [51]	-	223	26.2 ± 18.2	India	DF/DHF	10.8
Khalil et al. [52]	2008-2010	532	15-85	Pakistan	DF/DHF/DSS	13.3
Basu et al. [53]	2007-2008	28	Adults	India	-	35.7

Dengue and Kidney

Acute Kidney Injury – well known but poorly studied complication

AKI was associated with a longer hospital stay and higher mortality in Dengue

Histological correlates include:

- Acute tubular necrosis,
- thrombotic microangiopathy and
- rarely acute glomerulopathy

AKI Mechanisms

- hemodynamic instability
- rhabdomyolysis
- haemolysis
- acute glomerular injury
- direct viral effect

Mohsin N et.al. Renal Fail 2009; 31: 736–739
Repizo LP et al. Rev Inst Med Trop Sao Paulo 2014; 56: 85–88
Wiersinga WJ et al. Clin Infect Dis 2006; 43: 800–801
Upadhaya BK et al. Saudi J Kidney Dis Transpl 2010; 21: 521–525

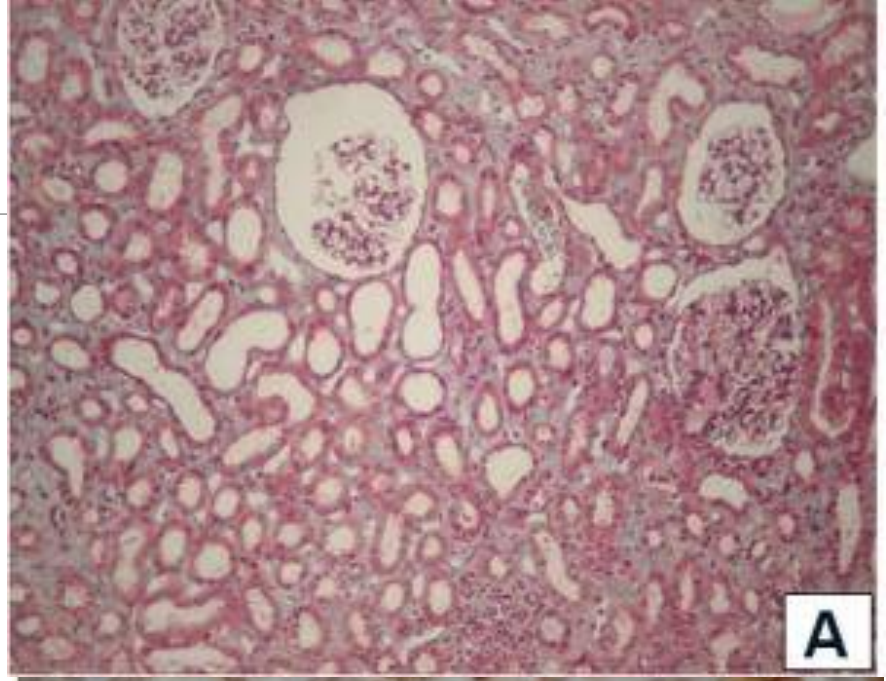
AKI - Pathogenesis

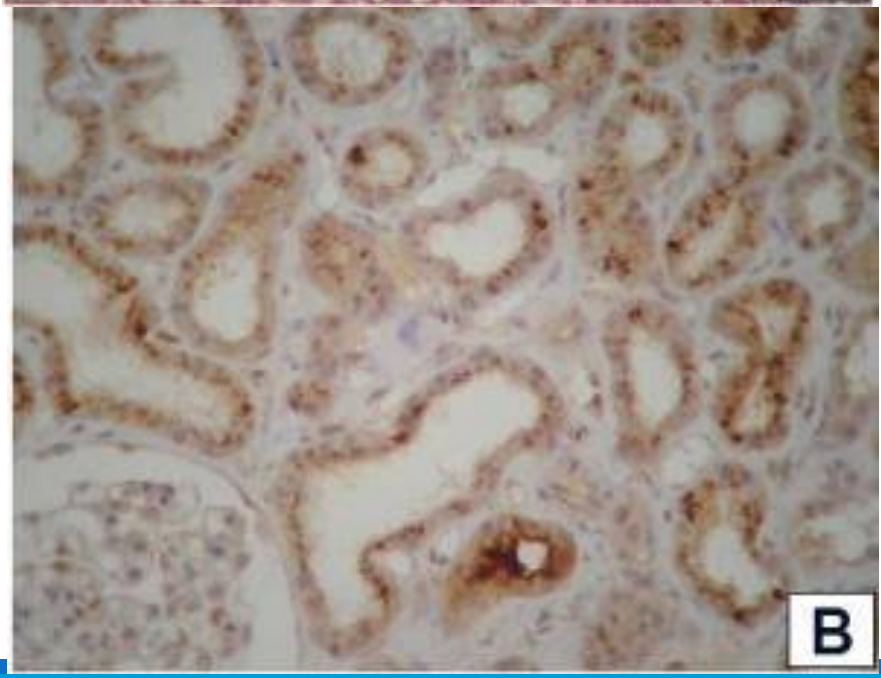
Hemodynamic Instability

- 80% of the cases have AKI associated with shock or hypotension and haemodynamic instability
- Correlated with severity of the illness

Rhabdomyolysis

- Compartment syndrome due to capillary leak, Cytokine or cellular myositis, Direct viral invasion, shock
- Myalgia, elevated CK, myoglobinuria, tubular myoglobin deposits in biopsy





Lima EQ et al. Nephrol Dial Transplant 2007; 22: 3322–3326
George R et al. Southeast Asian J Trop Med Public Health 1988; 19: 585–590
Radakovic-Fijan S et al. J Am Acad Dermatol2002; 46: 430–433
Gunasekera HH et al. Ceylon Med J 2000; 45: 181
Garcia JH et al. Transplant 2006; 82: 850–851
Bhagat M et al Paediatr Int Child Health 2012; 32: 161–163
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Davis JS et al. Clin Infect Dis 2004; 38: e109–e111
Hommel D et al. Nephron 1999; 83: 183
Mishra A et al. BMJ Case Rep 2015; 2015:bcr2014209074.
Wiwanitkit V. Saudi J Kidney Dis Transpl 2016;27:1280-2

AKI - Pathogenesis

Haemolysis / DIC / TMA

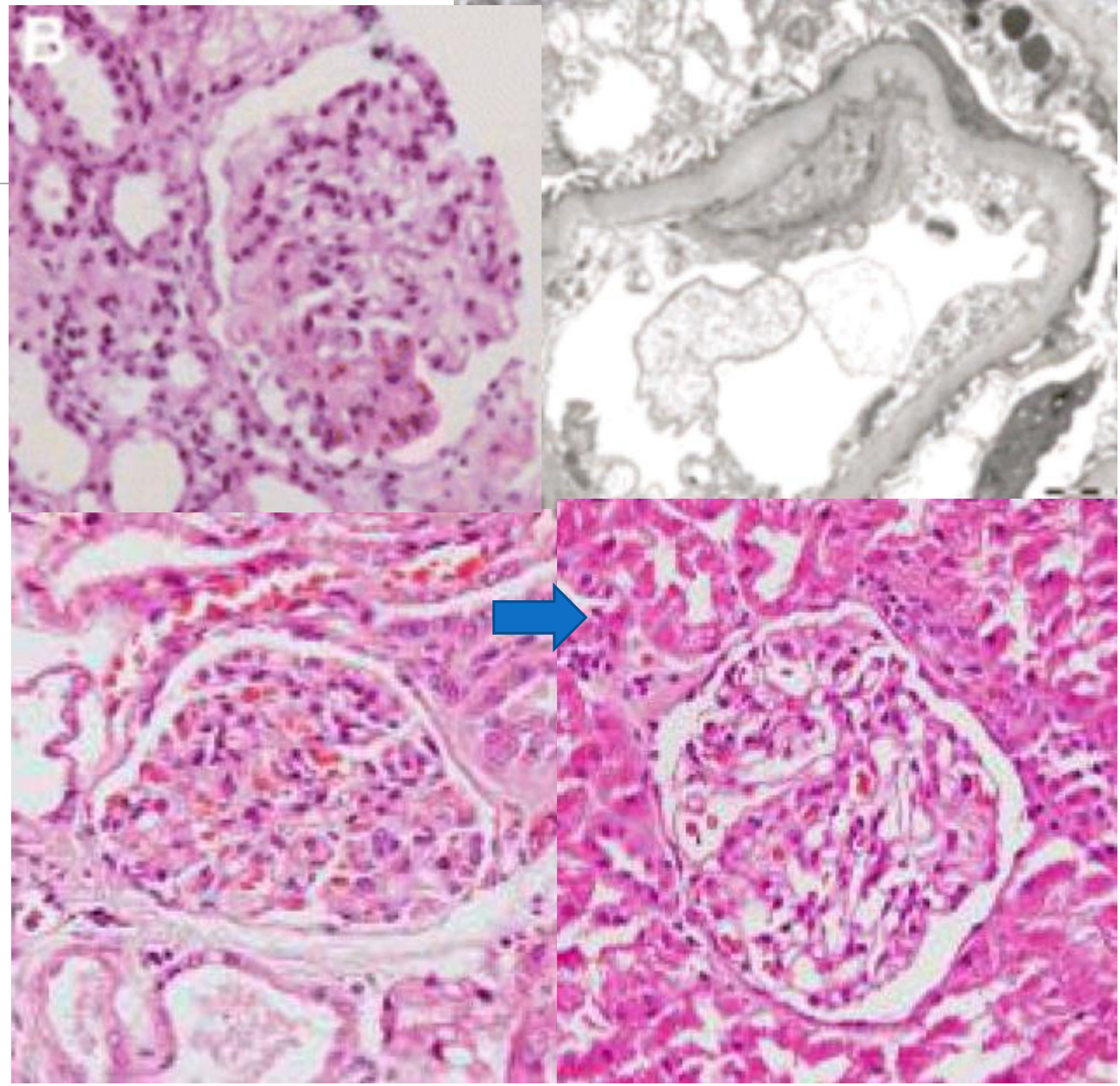
- DIC common - hemoglobinuria is possible cause for AKI
- Dengue related TMA also can cause AKI

Acute Glomerulopathy

- Proteinuria ? Capillary leak related – self limiting
- Mesangial proliferative GN with IgG, IgM and C3 deposits in the glomeruli
- IgA nephropathy - association

Direct Viral Effect

- Variable reports of Viral antigens on tubular epithelium and glomerular immune deposits, but no viral RNA in these cells
- Clinical Significance unknown



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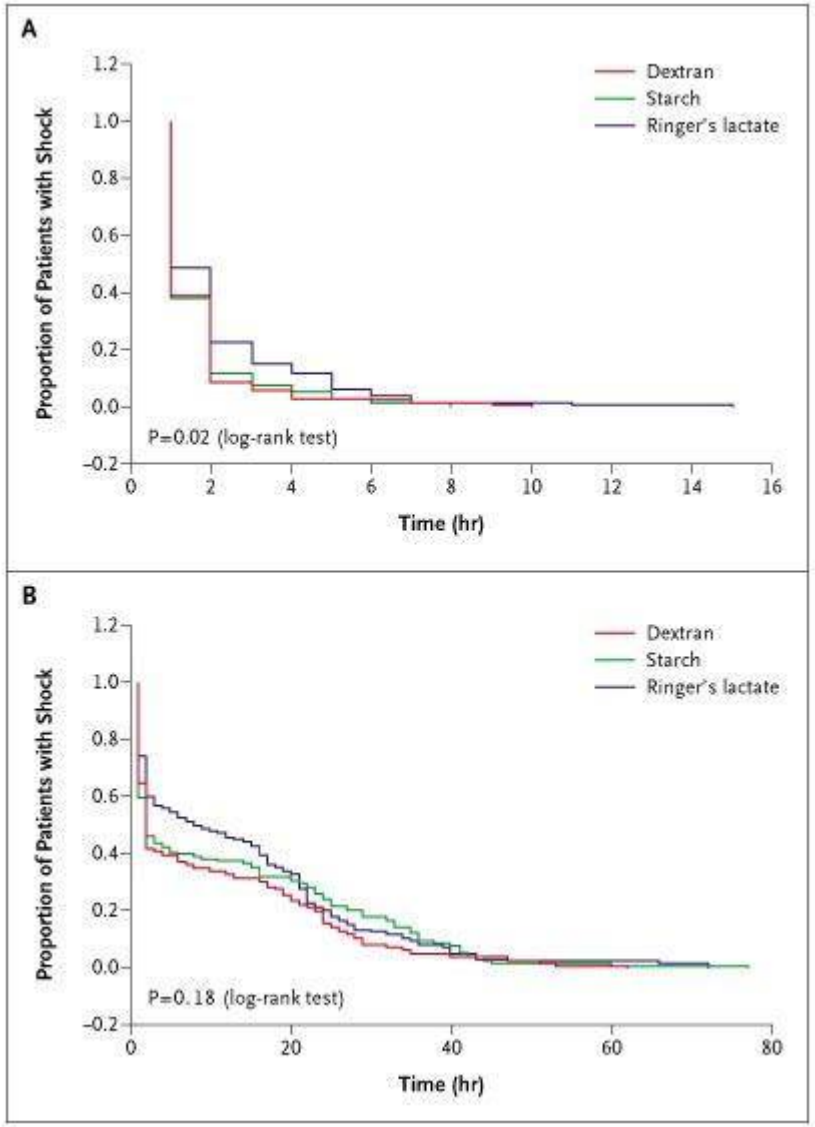
Management

- Early recognition of progressive and severe Dengue
- Supportive care
- Fluid resuscitation is of prime importance to prevent hemodynamic instability
  - RCT of 3 fluids strategies
    - Initial Resus with Ringer Lactate is beneficial
    - Increased SAE with Starch / Dextran – therefore not first line
- Appropriate critical care
- No antiviral drugs



Wills et al. N Engl J Med 2005; 353:877-889

Management

- The use of parenteral corticosteroids in cases of severe dengue is controversial
- Serum CK levels should be monitored
- support treatment should be timely and adequately performed
- Renal replacement therapy is currently indicated as conventionally used
- Aspirin should not be used because of the high risk of Reye’s syndrome and bleeding

Conclusions

- Malaria and Dengue affect MILLIONS IN TROPICAL BELT
- Both associated with significant risk of AKI and Mortality
- ATN predominant manifestation
- Renal Hypoperfusion and Inflammation are common causes
- Malarial AKI - Parasitized RBC mediated sequestration, haemolysis and hypoperfusion
- Dengue AKI - Hemodynamic instability and Rhabdomyolysis and TMA
- Fluid resuscitation in Malaria should be limited to maintenance and avoid boluses
- Fluid Resussication in Dengue – aggressive in view of capillary leak phenomena
- Prevent Malaria and Dengue – Save lives and Kidneys