Kidney in Malaria and Dengue

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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 – 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

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

P. falciparum
- Endothelium activation;
- Erythrocytes adhesion;
- Mononuclear cells adhesion;
- Edema;
- Cognitive impairment.

P. vivax

P. knowlesi

P. malariae

P. ovale
- Endothelium activation;
- Erythrocytes adhesion;
- Mononuclear cells;
- TNF-α and sP-selectin;
- Immune complex deposition;
- Renal failure.

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

Pro-inflammatory cytokines
- Fever
- Pro-inflammatory cytokines

Sepsis (spleen)
- Uptake of infected or altered RBCs resulting in macrophage activation and cytokine production

Anemia (bloodstream)
- Adhesion and rupture of infected and altered RBCs

Impaired erythropoiesis (bone marrow)

Renal impairment and metabolic acidosis
- Increased glycolysis and lactic acid accumulation
- Hypoxia
- Hyperventilation

Cerebral malaria

Placental malaria

Acute respiratory distress

Low levels of RBCs

http://dx.doi.org/10.5772/65348
## Kidney Involvement in Malaria

<table>
<thead>
<tr>
<th>Species</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Plasmodium Falciparum</em></td>
<td>• AKI (Severe), Black water Fever</td>
</tr>
<tr>
<td><em>Plasmodium Vivax</em></td>
<td>• AKI (mild)</td>
</tr>
<tr>
<td><em>Plasmodium Malariae</em></td>
<td>• Glomerulonephritis</td>
</tr>
<tr>
<td><em>Plasmodium Ovale</em></td>
<td>• AKI (similar to vivax)</td>
</tr>
<tr>
<td><em>Plasmodium Knowlesi</em></td>
<td>• AKI (as part of MODS)</td>
</tr>
</tbody>
</table>
How does this happen?
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

- Inadequate reticulocyte response to anemia
- Reduced response to EPO
- Direct effect of parasite products: Hz, GPI
- Indirect effect of cytokines or other mediators: TNFα, IL-10, IL-12
- Indirect effect of HNE

**Key**
- Epo: Erythropoietin receptor
- Ig: Immunoglobulin
- RBC: Red blood cell
- iRBC: Infected red blood cell
- iRBC Ring: Ring-stage infected red blood cell
- Schizont: Schizont-stage infected red blood cell
- Progenitors

**Diagram**
- Clearance of uninfected RBC
- Clearance of uninfected RBC via complement-activated immune complexes and loss of deformability
- Activation of MØ
- Indirect effect of cytokines or other mediators: TNFα, IL-10, IL-12
- Extramedullary haematopoiesis
- Increased EPO
- Loss of RBC
Haemorheological Factors
Cytoadherence of infected RBCs and Sequestration

- Cytoadherence to endothelial cells
- Platelet-mediated clumping
- Infected erythrocyte at ring stage
- Infected erythrocyte at pigmented-trophozoite stage
- Rosetting

Obstruction | Adhesion | Anti-sequestration
---|---|---

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

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 α and proinflammatory cytokines, + decreased IL10
- Vasoconstriction, inflammation, capillary leak, hypovolemia
- Renal Hypoperfusion, Direct renal tubular toxicity

AKI – renal injury
Important mechanistic contributors to AKI

- Haemolysis
- Jaundice
- Microcirculatory obstruction
- Intravascular coagulation
- Rhabdomyolysis
- 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

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

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

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# Falciparum Malarial AKI

<table>
<thead>
<tr>
<th>AKI associated with MODS</th>
<th>Isolated AKI</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Most common</td>
<td>• Rare</td>
</tr>
<tr>
<td>• Present at the time of diagnosis</td>
<td>• Presents when acute complications of malaria have subsided</td>
</tr>
<tr>
<td>• Associated high parasitemia, anemia, acidosis, jaundice, hypoglycaemia, coma</td>
<td>• Oliguria is observed in 70–76% of the patients and may persist for 3–10 days</td>
</tr>
<tr>
<td>• Poor Prognosis</td>
<td>• Better prognosis</td>
</tr>
</tbody>
</table>

AKI in falciparum Malaria

RRT in 1/3\(^{rd}\) Mortality in upto 1/3\(^{rd}\)

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.
Glomerular Lesions in Falciparum Malaria

Pathology

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

IF: deposition of finely granular immunoglobulin M and C₃ along the capillary walls and in the mesangium, occasional detection of malarial antigens along the glomerular endothelium as well as the medullary capillaries.

EM: subendothelial, mesangial, and paramesangial electron-dense deposits along with granular, fibrillar, and amorphous material.
# Electrolyte abnormalities in Malaria

<table>
<thead>
<tr>
<th>Electrolyte abnormality</th>
<th>Mechanism</th>
</tr>
</thead>
</table>
| 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 |
**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.**
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.
**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 artemesunate and quinine.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Artesunate</th>
<th>Quinine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosage</strong></td>
<td>Larger children and adults: 2.4 mg/kg at 0, 12, and 24 h and then once daily</td>
<td>20 mg/kg loading dose followed by 10 mg/kg 8th hourly</td>
</tr>
<tr>
<td></td>
<td>Children weighing less than 20 kg: 3 mg/kg/dose</td>
<td></td>
</tr>
<tr>
<td><strong>Follow on therapy</strong></td>
<td>Artemether/lumefantrine should be given twice a day for a total of 6 doses.</td>
<td>10 mg/kg thrice daily orally</td>
</tr>
<tr>
<td></td>
<td>The first 2 doses should be spaced 8 h apart</td>
<td></td>
</tr>
<tr>
<td><strong>Adverse effects</strong></td>
<td>Well tolerated</td>
<td>Hypotension</td>
</tr>
<tr>
<td></td>
<td>Post-artemisnin delayed hemolysis</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>QTc prolongation and cardiac arrhythmias</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cinchonism – tinnitus, disturbed vision, and nausea</td>
</tr>
<tr>
<td><strong>Renal dose modification</strong></td>
<td>Not required</td>
<td>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</td>
</tr>
</tbody>
</table>
Exchange Transfusion

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

- Manual vs Automated Erythrocytapheresis

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

- Previously recommended for use 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 transfusion 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
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.
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.

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
- Precipitated 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
- Hepatospnedomegaly
- Hypertension in later stage
- No Haematuria usually
- MPGN / DPGN with granular IgG in mes/CW deposits
- Poor response to steroids / IMS
- ESRD in 3-5 years

ENDRICKSE et al Kidney International, Vol. 16 (1979), pp. 64-74
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

Dengue Prevalence

100 Million cases every year

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

Fever, Headache, retroauricular pain, Myalgia, arthralgia, Rash. Lecuopenia, Thrombocytopenia

Sec. Infection - High fever for 2-7 days, Hemorrhagic manifestations Thrombocytopenia, Capillary leak syndrome

Dengue Shock syndrome

DHF features with Severe plasma leakage and Shock syndrome. High mortality 40%

Table 2. World Health Organization Definition of Dengue Infection

<table>
<thead>
<tr>
<th>Dengue fever</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute febrile illness with 2 or more of the following:</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Retro-orbital pain</td>
</tr>
<tr>
<td>Myalgia</td>
</tr>
<tr>
<td>Rash</td>
</tr>
<tr>
<td>Hemorrhagic manifestations</td>
</tr>
<tr>
<td>Leukopenia</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Dengue hemorrhagic fever</th>
</tr>
</thead>
<tbody>
<tr>
<td>All of the following must be present:</td>
</tr>
<tr>
<td>Fever, lasting 2 to 7 days, occasionally biphasic</td>
</tr>
<tr>
<td>Hemorrhagic manifestations with at least one of the following:</td>
</tr>
<tr>
<td>Positive tourniquet test,</td>
</tr>
<tr>
<td>Petechiae, ecchymoses, or purpura</td>
</tr>
<tr>
<td>Bleeding from mucosa, gastrointestinal tract, injection sites, or other locations</td>
</tr>
<tr>
<td>Hematemesis or melena</td>
</tr>
<tr>
<td>Thrombocytopenia (≤100,000/mm³)</td>
</tr>
<tr>
<td>Evidence of plasma leakage manifested by at least one of the following:</td>
</tr>
<tr>
<td>Increase in the hematocrit level ‘20% for age, sex, and population</td>
</tr>
<tr>
<td>Decrease in the hematocrit after volume replacement ≥20% of baseline</td>
</tr>
<tr>
<td>Signs of plasma leakage such as pleural effusion, ascites, and hypoproteinemia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dengue shock syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Criteria for DHF associated with:</td>
</tr>
<tr>
<td>Tachycardia</td>
</tr>
<tr>
<td>Pulse pressure &lt;20 mm Hg</td>
</tr>
<tr>
<td>Hypotension for age</td>
</tr>
<tr>
<td>Cold skin and restlessness</td>
</tr>
</tbody>
</table>

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

Data from World Health Organization.
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

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

## Dengue - AKI

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

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

References:

Garcia JH et al. Transplant 2006; 82: 850–851
Acharya S et al. Ann Indian Acad Neurol 2010; 13: 221–222
Hommel D et al. Nephron 1999; 83: 183
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

Garcia JH et al. Transplant 2006; 82: 850–851
Acharya S et al Ann Indian Acad Neurol 2010; 13: 221–222
Hommel D et al. Nephron 1999; 83: 183
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

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 Resuscitation in Dengue – aggressive in view of capillary leak phenomena
- Prevent Malaria and Dengue – Save lives and Kidneys