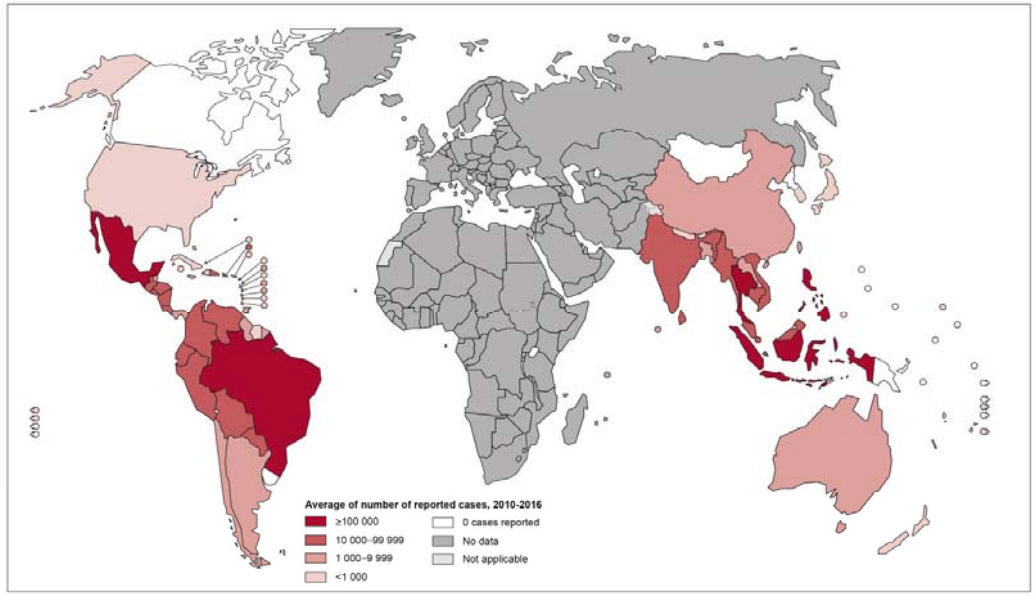
UNIVERSITAS
GADJAH MADA

Organ Dysfunctions in Dengue Infection

Ida Safitri Laksono
Department of Child Health[1]
Master Program of Tropical Medicine[2]
Universitas Gadjah Mada, Indonesia

Epidemiology

Distribution of dengue, worldwide, 2016



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Data Source: World Health Organization
Map Production: Control of Neglected Tropical Diseases (NTD)
World Health Organization

World Health Organization

An estimated 500 000 people with severe dengue infection require hospitalization annually, with 2.5% case fatality each year

WHO 2018. Dengue and severe dengue.

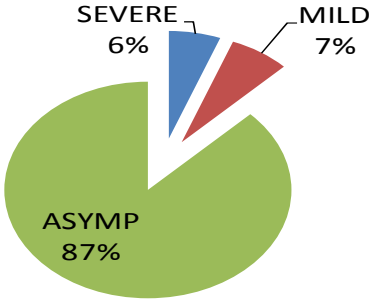
Epidemiology

A global decline in case fatality (28%) have been recorded between 2010-2016 due to improvement in case management. Early detection and access to proper medical care lowers fatality rates below 1%

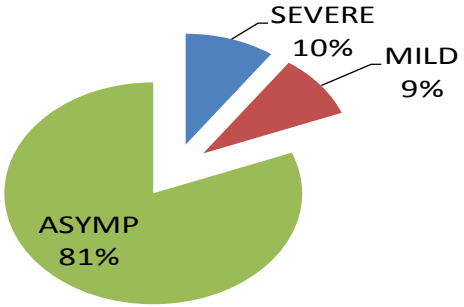
Severe dengue is a leading cause of serious illness and death among children in some Asian and Latin American countries.

WHO 2018. Dengue and severe dengue.
Kalayanarooj S, Nimmannitya S. Clinical and laboratory presentations of dengue patients with different serotypes. Dengue Bull. 2000;24:53–9.

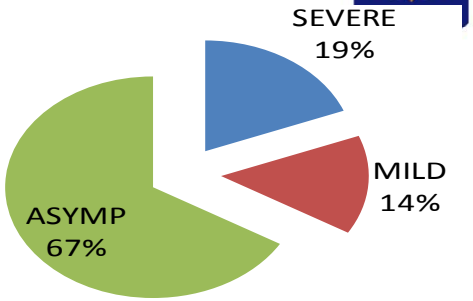
OUTCOME OF DENV INFECTION



Bangkok, Thailand 80-81: DENV-1 and 2
Burke et al. ,Am J Trop Med Hyg 1988



Vietnam 04: DENV-2

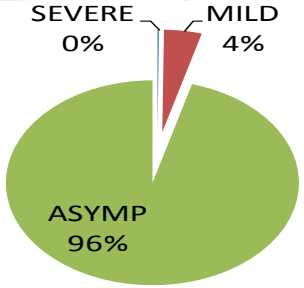


Vietnam 07: DENV-1

Trans R Soc Trop Med Hyg, 2010

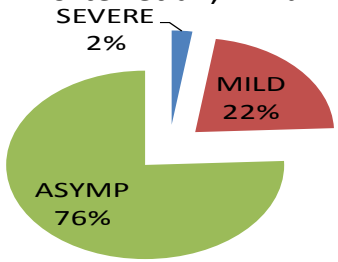
Singapore 04: DENV-1

Yew et al., Ann Acad Med Singapore 2009



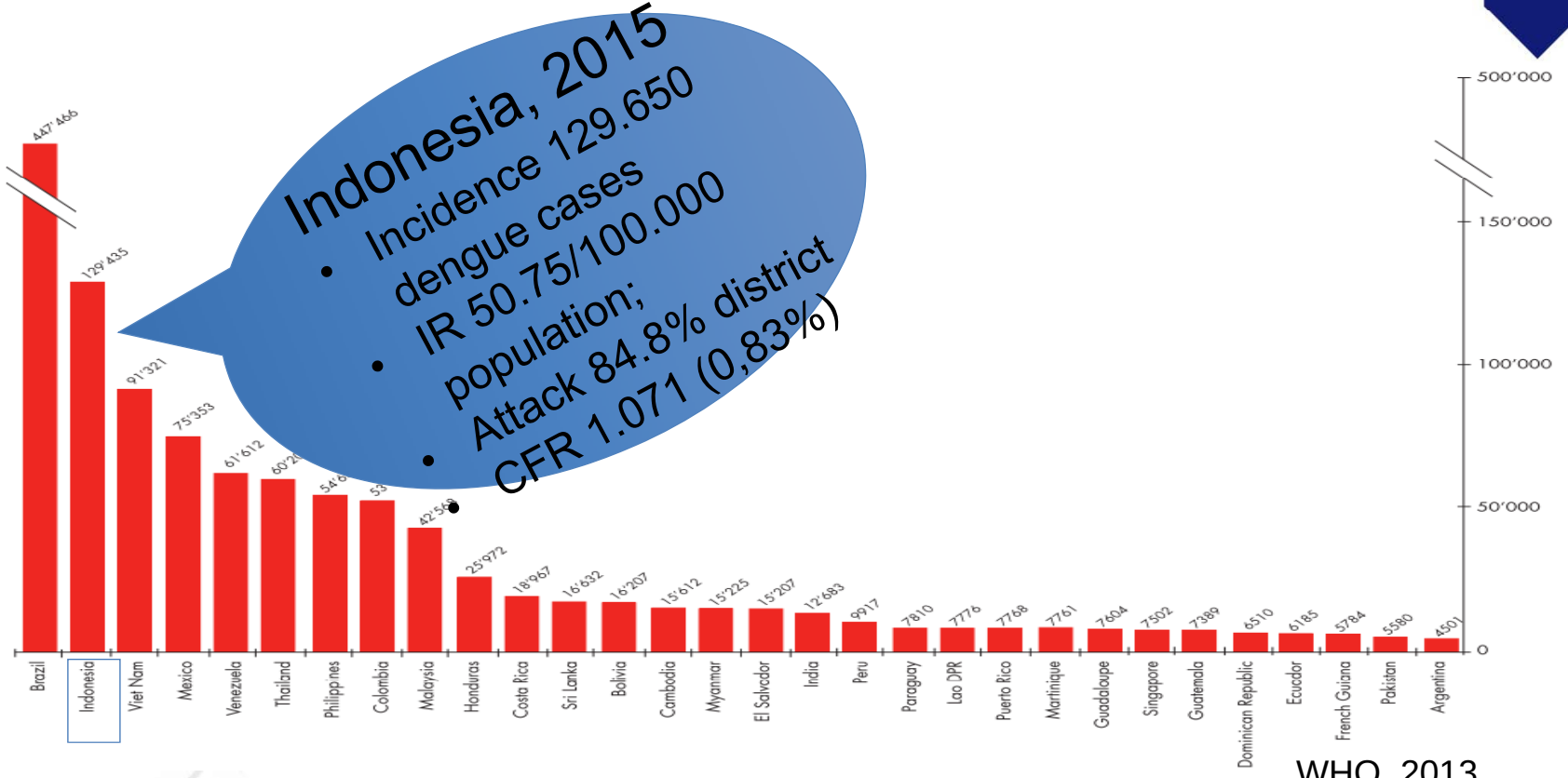
West Java, Indonesia 00-02: DENV-2

Porter et al., Am J Trop Med Hyg, 2005



ANAVAJ SAKUNTABHAI M.D., D.PHIL.
INSTITUT PASTEUR
PRESENTED AT THE 3RD ASIAN DENGUE SUMMIT,
KUALA LUMPUR, MALAYSIA MAY 7, 2018

Global Incidence of Dengue Infection



WHO, 2013

Diagnosis classification according to existing guidelines

1997	2009	2011
Guideline for treatment of DF and DHF in small hospitals – WHO Searo 1999	**Dengue – Guidelines for diagnosis, treatment, prevention and control – WHO TDR 2009**	**Comprehensive guideline for prevention and control of Dengue and DHF – WHO Searo 2011**
Dengue fever	Dengue without warning signs	Dengue fever
DHF grade I	Dengue with warning signs	DHF grade I
DHF grade II		DHF grade II
DHF grade III	**Severe dengue** : shock, resp distress →severe plasma leakage, severe hemorrhage and severe organ involvement	DHF grade III
DHF grade IV		DHF grade IV
		* **Expanded dengue syndrome → isolated organopathy**

- Severe dengue: every dengue case that has one or more of the following manifestations (Pang et al, 2016, Martinez and Capo, 2018)
  1. Shock or respiratory distress due to severe plasma leakage.
  2. Severe bleeding (e.g. hematemesis, melena, ample metrorrhagia, and central nervous system bleeding).
  3. **Severe organ involvement, such as major liver (AST or ALT >1000 IU), central nervous system, heart or kidney impairment**.

Pang J, Leo YS, Lye DC. Critical care for dengue in adult patients: An overview of current knowledge and future challenges. Curr Opin Crit Care. 2016;22(5):485–90.
Martinez E, Capó V. Dengue Associated Multiple Organ Failure. Austin Crit Care J. 2018;5(1):1–3.

Complication among children with severe dengue infection (102)

Complications	*n* (%)
Encephalopathy	7 (2.7)
Hepatitis	29 (11.1)
Intracranial hemorrhage	2 (0.8)
Fulminant hepatic failure	2 (0.8)
Acute kidney injury	6 (2.3)
Myocarditis	5 (1.9)
Pericardial effusion	3 (1.1)
Pneumonia	31 (11.9)
Pulmonary hemorrhage	4 (1.5)
Acute respiratory distress syndrome	4 (1.5)
Hemophagocytic syndrome	2 (0.8)
Refractory shock	6 (2.3)
Myositis	3 (1.1)
Disseminated intravascular coagulopathy	4 (1.5)
Co-infections	19 (7.2)

Data as number (%)

Of 500,000 people with severe dengue infection require hospitalization annually, 90% of them are children <5 years of age

Pothapregada S, Kamalakannan B, Thulasingham M, Sampath S. Clinically Profiling Pediatric Patients with Dengue. J Glob Infect Dis. 2016;8(3):115–20.

Severe dengue disease is characterized by circulatory damages, associated in **most cases with hepatic dysfunctions**

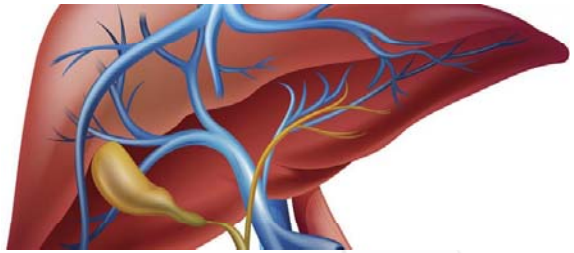
These injuries may be a direct consequence of the virus presence and/or resulted by an exacerbation of the immune response after infection.

Pathologic feature:

- all showed severe parenchyma and circulatory alterations
- all showed hemorrhage and edema

Póvoa TF, Alves AMB, Oliveira CAB, Nuovo GJ, Chagas VLA, Paes M V. The pathology of severe dengue in multiple organs of human fatal cases: Histopathology, ultrastructure and virus replication. PLoS One. 2014;9(4)

Liver



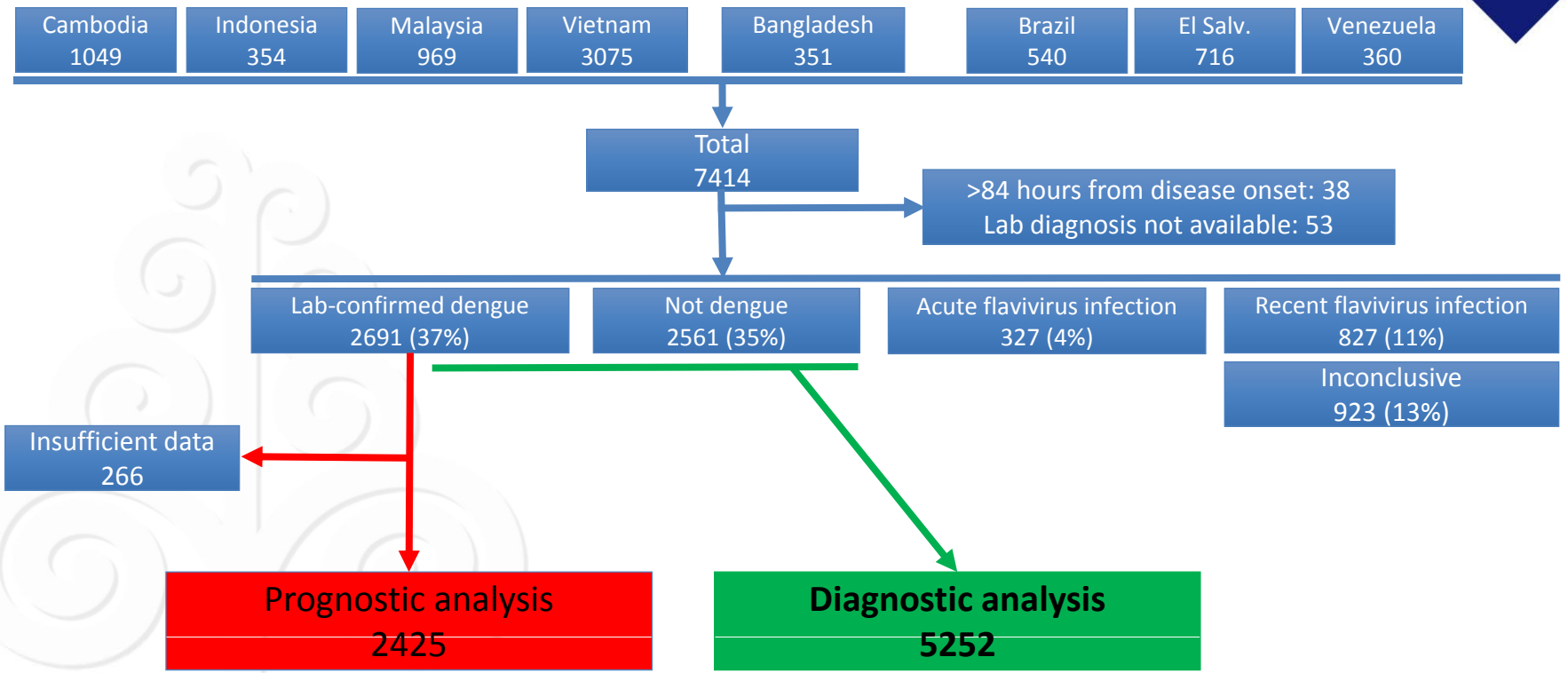
Most important gastrointestinal manifestation

Clinical presentation:

- acute hepatitis with elevated liver enzyme values (AST being more significantly elevated than ALT)
- Jaundice
- altered mental status
- seizures
- severe hypoglycemia
- Acute liver failure (Manoj et al. 2014 and Kumarasena et al. 2010)

Kalayanarooj S, Nimmannitya S. Clinical and laboratory presentations of dengue patients with different serotypes. Dengue Bull. 2000;24:53–9.
Kaushik A, Pineda C, Kest H. Diagnosis and management of dengue fever in children. Pediatr Rev. 2010;31(4):e28-35.

IDAMS STUDY (2012 -2016)



Insufficient data = No information during DOI 4-7, OR <3 visits during DOI 4-7 with no summary

Indonesia site → Yogyakarta

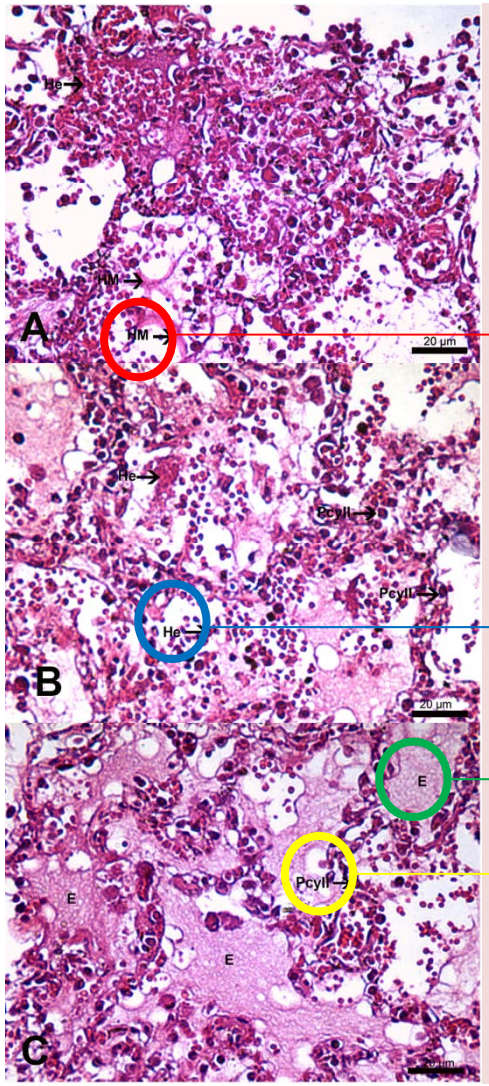
- > 5 yo patients presenting to outpatient clinics of PHC with fever < 72hrs, without focal infection
- 354 enrolled → 40.1% confirmed dengue (DF and DHF)
- **Prevalence of liver dysfunction : 42.79%**
- Significance increased of liver enzyme during fever defervescence
- No one with renal dysfunction/ AKI

Laboratory result of hepatic involvement

Studies	Patients	Raised AST	Raised ALT	Hypoalbuminemia	Raised bilirubin
Itha et al[26]	45	96%	96%	76%	30%
Wong et al[24]	127	90.6%	71.7%	16.5%	13.4%
Saha et al[21]	1226	52% (5 times normal was criteria)	50%	12.9%	16.9%
Kuo et al[3]	270	93.3%	82.2%	-	7.2%
Souza et al[4]	1585	63.4%	45%	-	-

- Pathologic feature:
  - microsteatosis or macrosteatosis
  - focal areas of necrosis with mononuclear infiltrates
  - cell death (probably apoptotic process)
  - virus antigens in hepatocytes, Kupffer cells and endothelium

LUNG



Hyaline membran formation

Hemorrhage

Edema

Hypertrophy of type II pneumocytes

- Mononuclear inflammatory infiltrate
- Hyperplasia of alveolar macrophages
- Hyaline membrane : in diabetes and obesity, probably due to DSS

- Virus antigens in alveolar macrophages, type II pneumocytes, and endothelium

Rodrigues RS, Brum ALG, Paes MV, Póvoa TF, Basilio-de-Oliveira CA, Marchiori E, et al. Lung in dengue: Computed tomography findings. PLoS One. 2014;9(5).

Causes of acute respiratory distress and failure:

- severe metabolic acidosis from severe shock
- fluid overload – large pleural effusions and ascites
- acute pulmonary oedema
- acute respiratory distress syndrome (ARDS)

Lung manifestation in 100 seropositive adult dengue patients

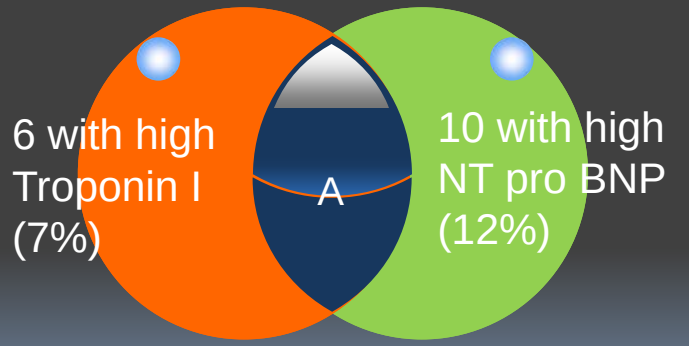
	Dengue fever (%)	Dengue hemorrhagic fever (%)	Dengue shock syndrome (%)
Adult respiratory distress syndrome	0	19.4	53.3
Pulmonary hemorrhage	0	21.4	6.6
Unilateral pneumonitis	0	0	0
Bilateral pneumonitis	0	9.5	6.6
Pleural effusion	0	7.14	0
More than one presentation	0	38.1	33.3

Mohamed NA, El-Raoof EA, Ibraheem HA. Respiratory manifestations of dengue fever in Taiz-Yemen. Egypt J Chest Dis Tuberc. 2013;62(2):319–23.

Heart

Miranda et al 2013

Study over 81 dengue subjects



A
4 with high level of both markers

4 patients had acute heart failures

3 patients had chest pain

3 patients had shock and hypotension

Miranda CH, Borges MDC, Matsuno AK, Vilar FC, Gali LG, Volpe GJ, et al. Evaluation of cardiac involvement during dengue viral infection. Clin Infect Dis. 2013;57(6):812–9

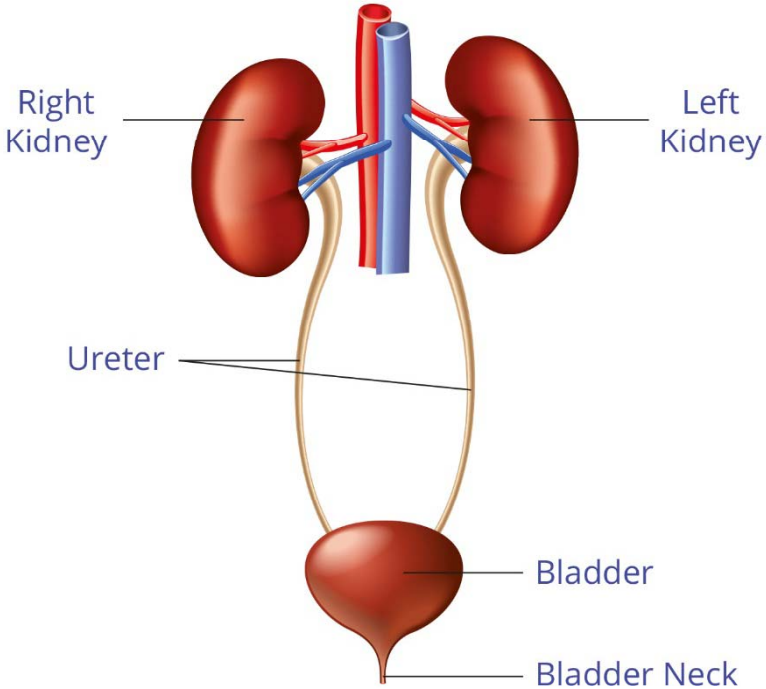
- All patients with elevated biomarker showed:
  - more intense inflammatory activity confirmed by a higher leukocyte count and C-reactive protein levels.
  - lower viral load, suggesting no association between viral load and cardiac injury.
- Pathologic feature:

Myocarditis with cardiac fibers degradation

Virus antigens in
- myocardial fibers
- perinuclear region,
- monocytes/macrophages
- endothelium

Póvoa TF, Alves AMB, Oliveira CAB, Nuovo GJ, Chagas VLA, Paes M V. The pathology of severe dengue in multiple organs of human fatal cases: Histopathology, ultrastructure and virus replication. PLoS One. 2014;9(4)

Kidney



Renal involvement:

- Elevation of serum creatinine level
- **Acute kidney injury**
- Acute tubular necrosis
- Hemolytic uremic syndrome
- Proteinuria
- Glomerulopathy
- Nephrotic syndrome

Mallhi TH, Khan AH, Adnan AS, Sarriff A, Khan YH, Jummaat F. Incidence, characteristics and risk factors of acute kidney injury among dengue patients: A retrospective analysis. PLoS One. 2015;10(9):1–16.

Acute Kidney Injury (AKI)

Incidence : 14.2% among dengue patients aged ≥ 12 yo

Significant morbidity, mortality, longer hospital stay and poor renal outcomes

Etiopathogenesis

- direct action by the virus
- hemodynamic instability
- rhabdomyolysis
- hemolysis
- acute glomerular injury

Rare complication but poor prognosis....!

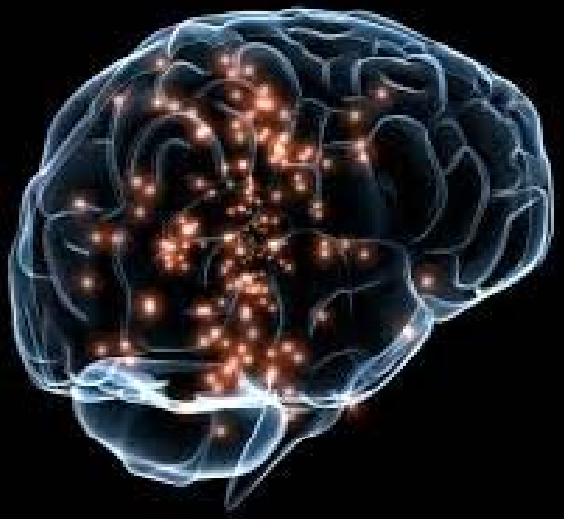
Picollo Oliveira JF, Burdmann EA. Dengue-associated acute kidney injury. Clin Kidney J. 2015;8(6):681–5.

- Prospective cohort study
- Objective : predict renal involvement in dengue mortality
- DSS patients 1mo- 18 yo hospitalized in Dr Sardjito Hospital
- August 2015- March2017

- **Kidney involvement as AKI was prognostic factor of mortality in children with dengue shock syndrome (*adjusted* RR 11.93 CI 95% 1.76-80.71; p=0.011)**
- **Kidney involvement occured in dengue infection, from mild spectrum to severe**

Budyarini et al, unpublished data

Nervous System



In Indonesia, 70% of fatal dengue infections (n=30) presented with one or more neurological signs, and 7% were admitted for viral encephalitis, which was listed as the cause of death

- Central nervous system (CNS) disease is attributed to various factors, including direct viral invasion of the CNS, liver failure, electrolyte disturbances, and cerebral edema (AAP, 2010).
- Manifestation of encephalopathy were the same for all four serotypes but....

  DEN-2 and DEN-3 are most frequently reported as the cause of severe neurological disease

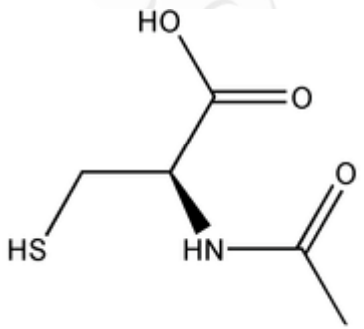
Kaushik A, Pineda C, Kest H. Diagnosis and management of dengue fever in children. Pediatr Rev. 2010;31(4):e28-35.
Kalayanarooj S, Nimmannitya S. Clinical and laboratory presentations of dengue patients with different serotypes. Dengue Bull. 2000;24:53–9.

- Clinical manifestation
  - Dengue encephalopathy
  - DENV encephalitis
  - Immune-mediated syndromes (acute disseminated encephalomyelitis [ADEM], myelitis, neuritis brachialis, and GBS, among others)
  - Dengue-associated stroke
  - Neuro-ophthalmic complications

García-Rivera EJ, Rigau-Pérez JG. Encephalitis and dengue. Lancet. 2002;360(9328):261.
Carod-Artal F. Neurological manifestations of dengue viral infection. 2014;2014(5):95–104.

How to manage organ dysfunction ?

- Main principle: supportive treatment
- **Acute liver failure:**



N-AcetylCysteine

N-Acetyl cysteine (NAC): restore hepatocellular glutathione stores, free radical scavenger, improves antioxidant defense.

Kumarasena, et al. : 5 of 8 patients treated with NAC recovered from hepatic encephalopathy while 3 died.

Kumarasena RS, Mananjala SS, Sivaraman K, et al. Intravenous N-acetylcysteine in dengue-associated acute liver failure. Hepatol Int 2010; 4:533-534

Picollo Oliveira JF, Burdmann EA. Dengue-associated acute kidney injury. Clin Kidney J. 2015;8(6):681–5.

- **Acute kidney injury**

– Fluid adequacy, shock management, renal replacement therapy

- **Pulmonary oedema and ARDS**

– Goals of therapy : optimize oxygenation and ventilation and stabilize the haemodynamic situation.

– Indications for mechanical ventilation:

  - patients who have shock and are restless, combative or confused
  - respiratory failure from acute pulmonary oedema/ARDS ± shock
  - patients who fail to respond to non-invasive ventilation.

Dengue encephalopathy	Correction of metabolic causes such as liver dysfunction, hyponatremia, metabolic acidosis, or hypokalemia
DENV encephalitis	Adequate hydration, nutrition, maintenance of airway, and monitoring of consciousness level
Dengue stroke	Treat as stroke
Guilain Barre Syndrome	Treat as Guilain Barre Syndrome
Dengue immune-mediated neurological complications	Steroids (intravenous methylprednisolone pulses, oral prednisolone) (safety and efficacy not established yet)
Myalgia and transitory muscle dysfunction	Hydration, resting, and analgesic drugs
Severe neurological complications including myelitis	Rehabilittation

Carod-Artal F. Neurological manifestations of dengue viral infection. 2014;2014(5):95–104.

Outcome

AKI was found to be an independent predictor [OR (95% CI): 1.3 (0.84–2.01), P = 0.044] of longer hospitalization

Dengue patients with three or more organ failures on ICU admission were reported to have a 67% mortality rate

ICU nonsurvivors were significantly associated with nonhematological organ failure → respiratory, cardiovascular, and neurological complications

Mallhi TH, Khan AH, Adnan AS, Sarriff A, Khan YH, Jummaat F. Incidence, characteristics and risk factors of acute kidney injury among dengue patients: A retrospective analysis. PLoS One. 2015;10(9):1–16.
Pang J, Leo YS, Lye DC. Critical care for dengue in adult patients: An overview of current knowledge and future challenges. Curr Opin Crit Care. 2016;22(5):485–90.

Summary

- ✓ Organ dysfunction in dengue can manifest from mild to severe organ impairment even with serious and fatal outcome
- ✓ Organ dysfunction can occur in both DF and DHF
- ✓ Proper supportive treatment is essential in dealing with organ dysfunction in dengue

Thank You