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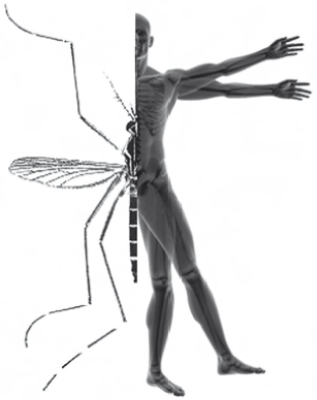
Dengue beyond Plasma Leakage

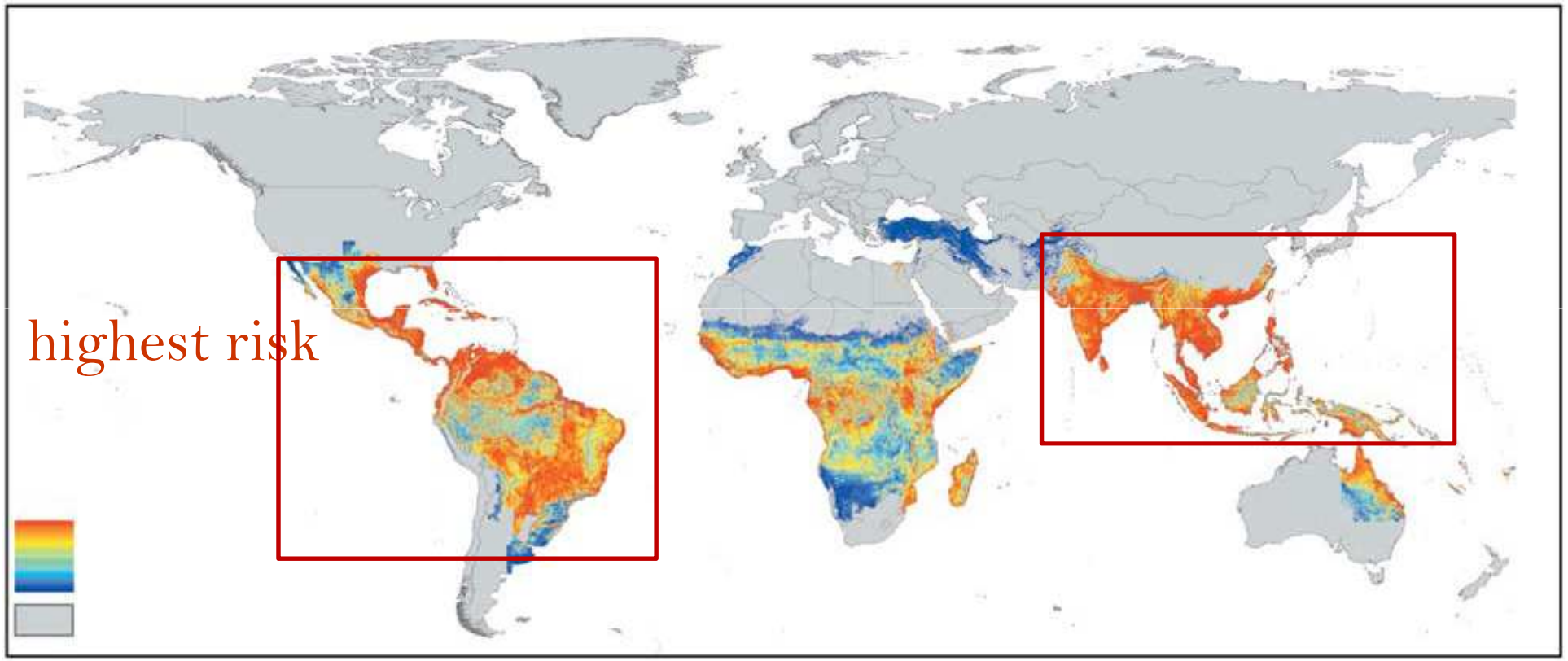


Sharifah Faridah Syed Omar

Associate Professor and Consultant in Infectious Diseases

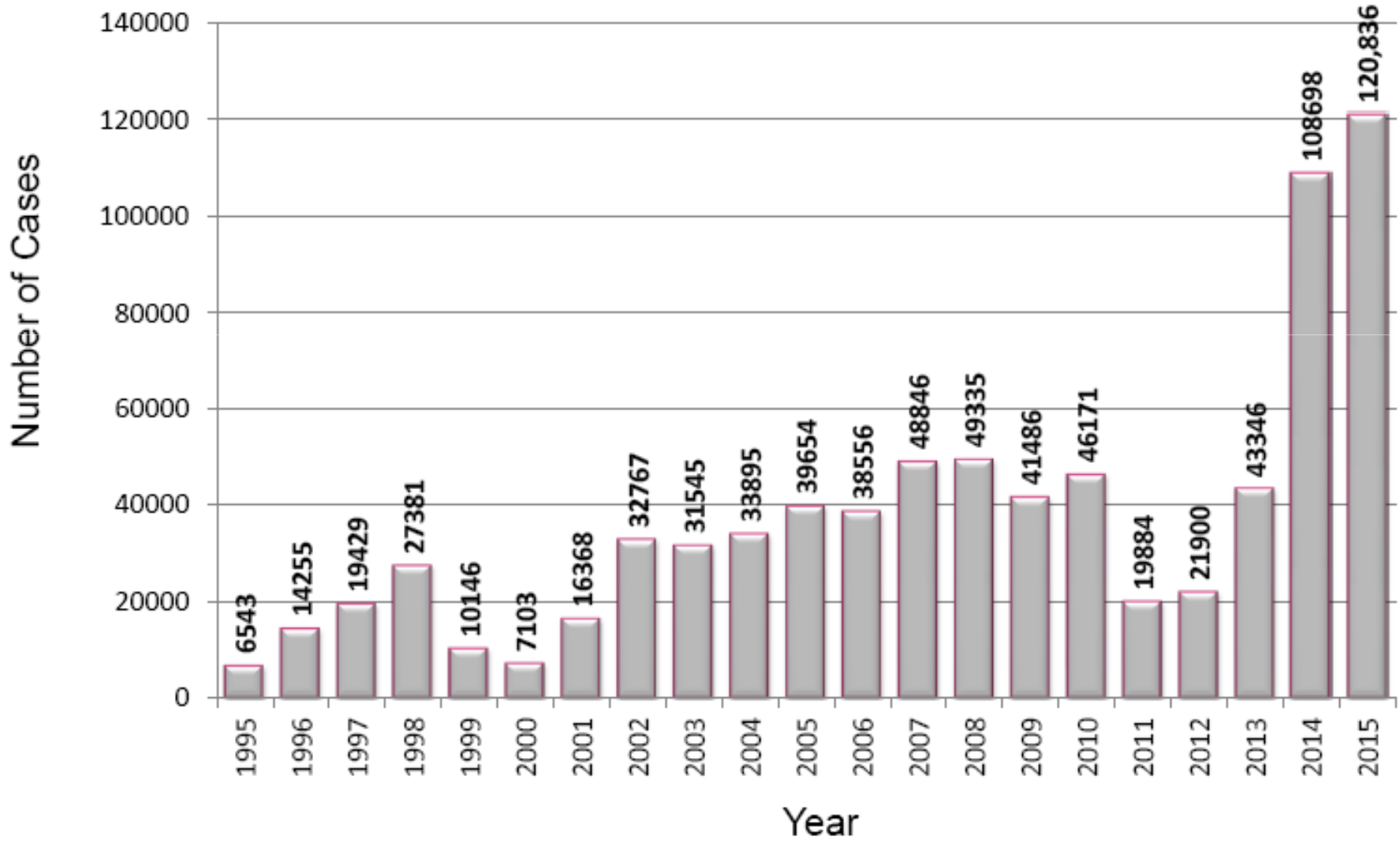
University Malaya

Global Dengue Risk

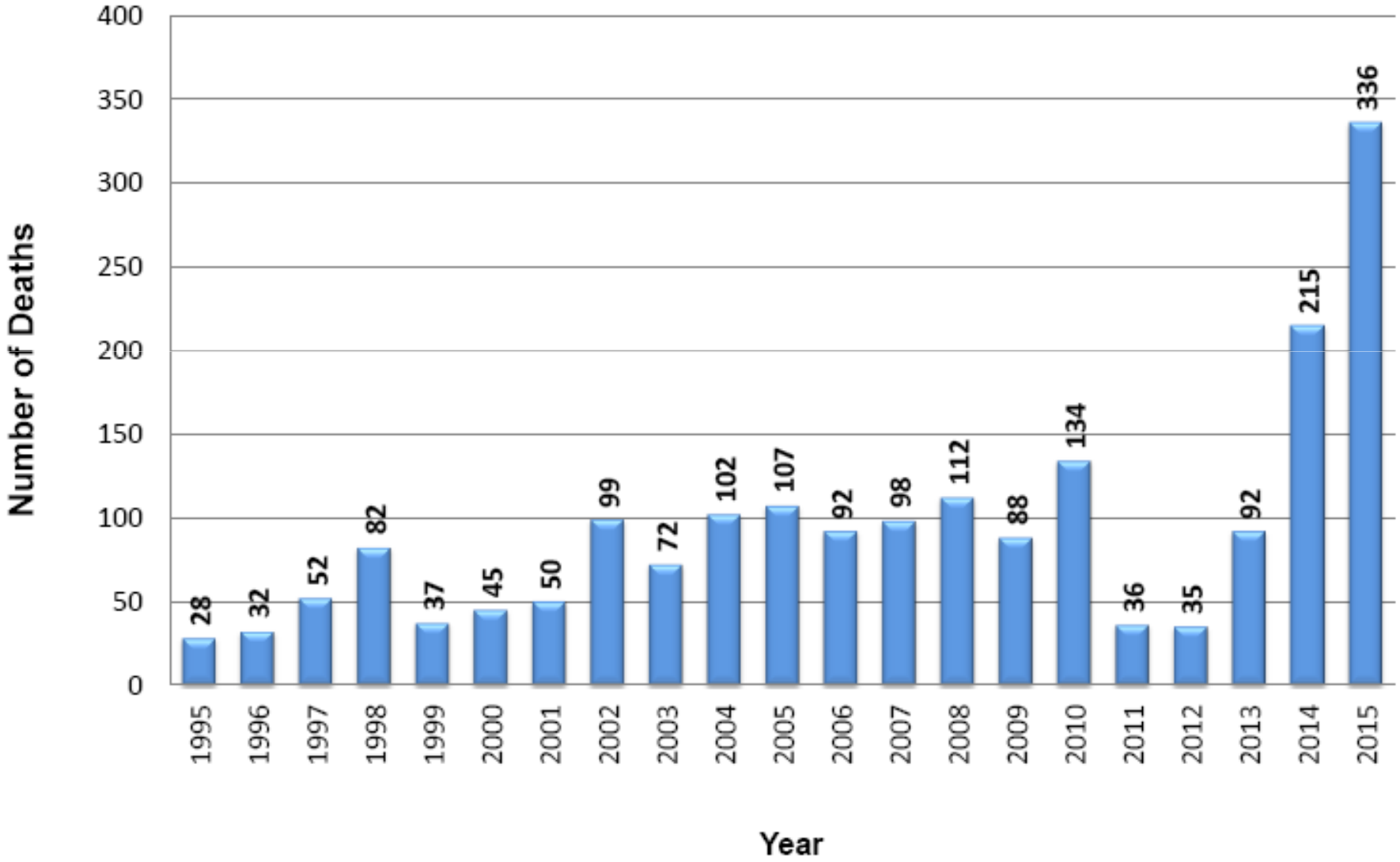


Simmons CP, et al. Dengue. N Engl J Med 2012;366:1423-32

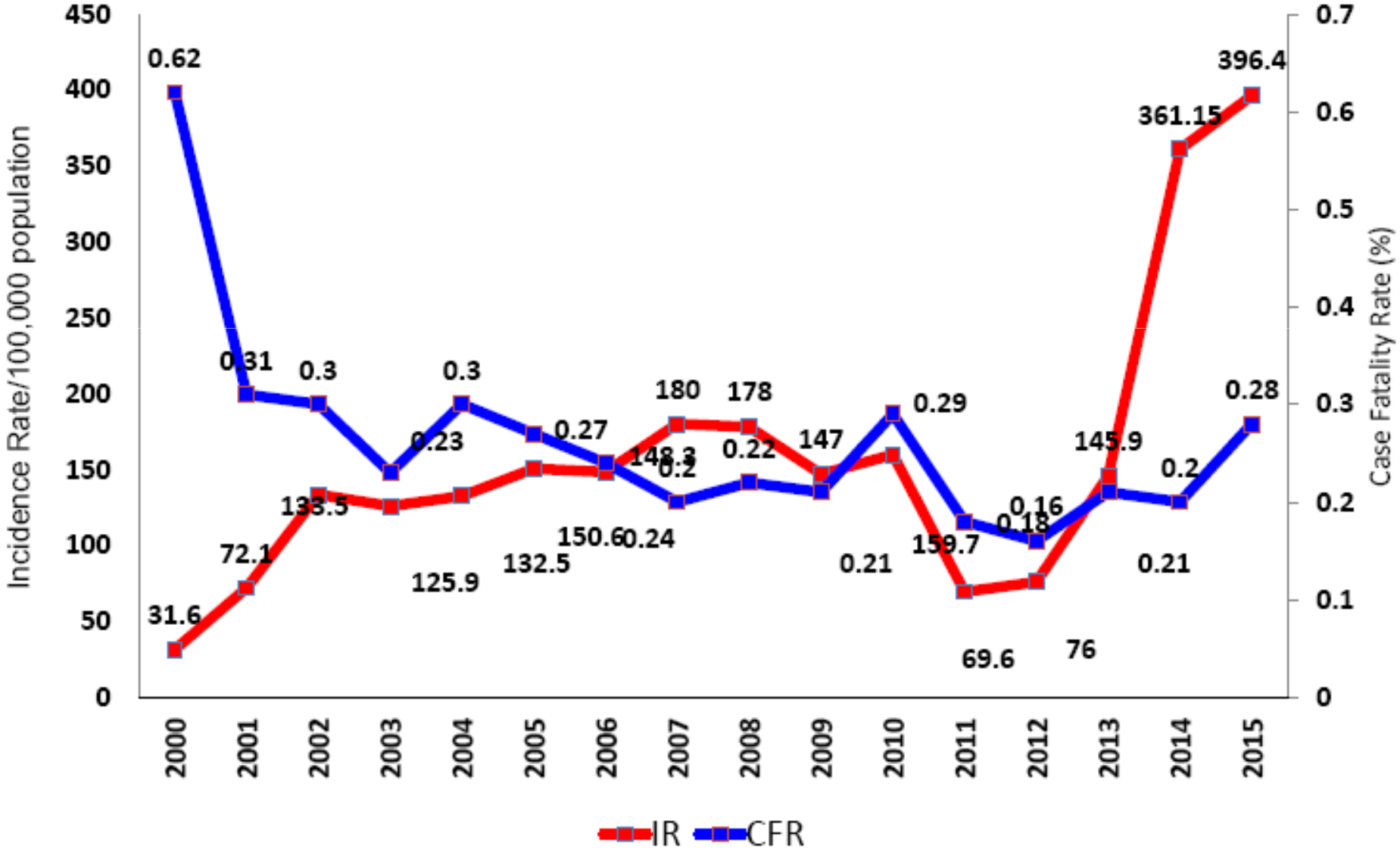
MALAYSIA
DENGUE CASES 1995 – 2015



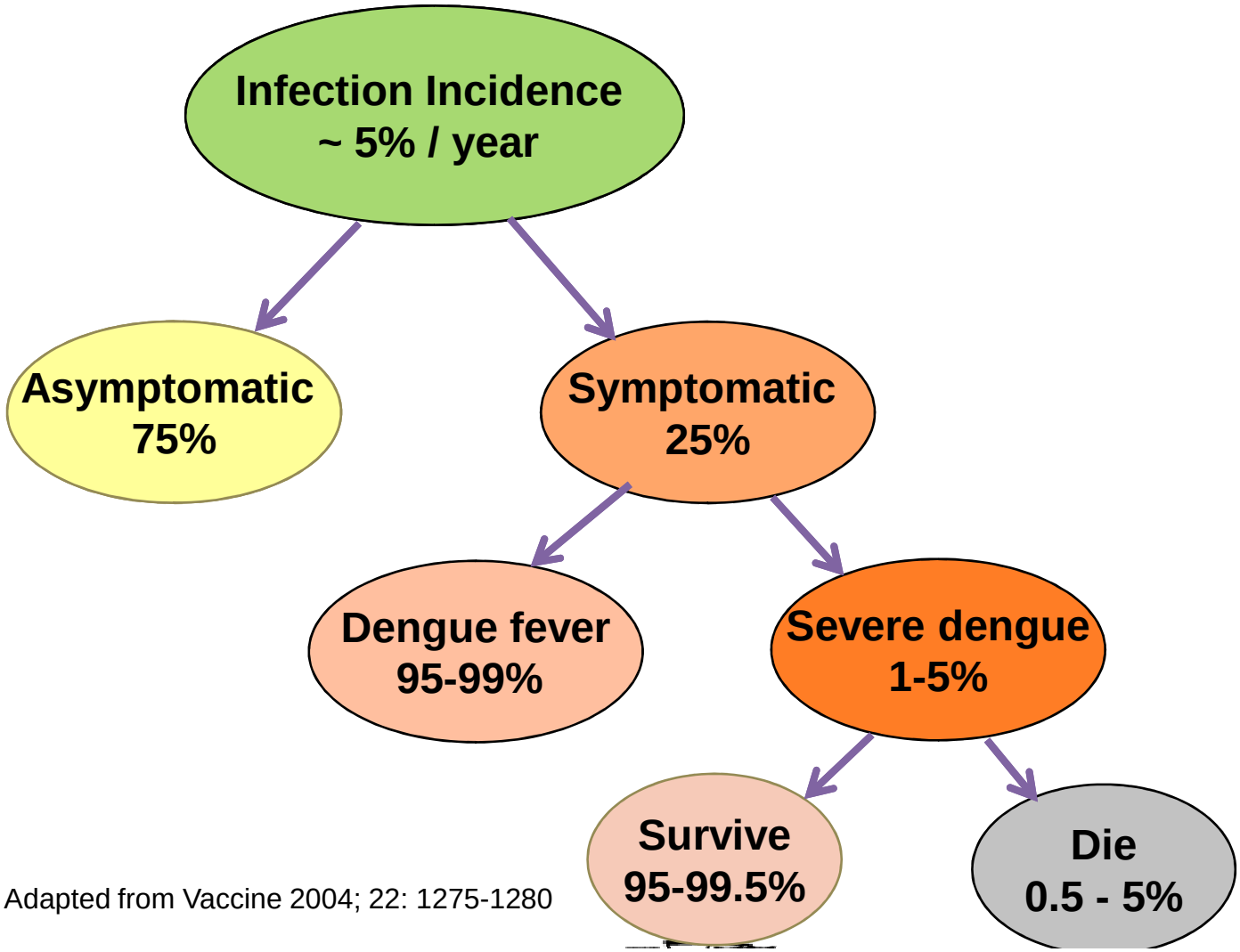
MALAYSIA
DENGUE DEATHS 1997 – 2015



MALAYSIA
DENGUE INCIDENCE RATE & CASE FATALITY RATE
FOR YEAR 2000-2015



Natural History of DENV Infections



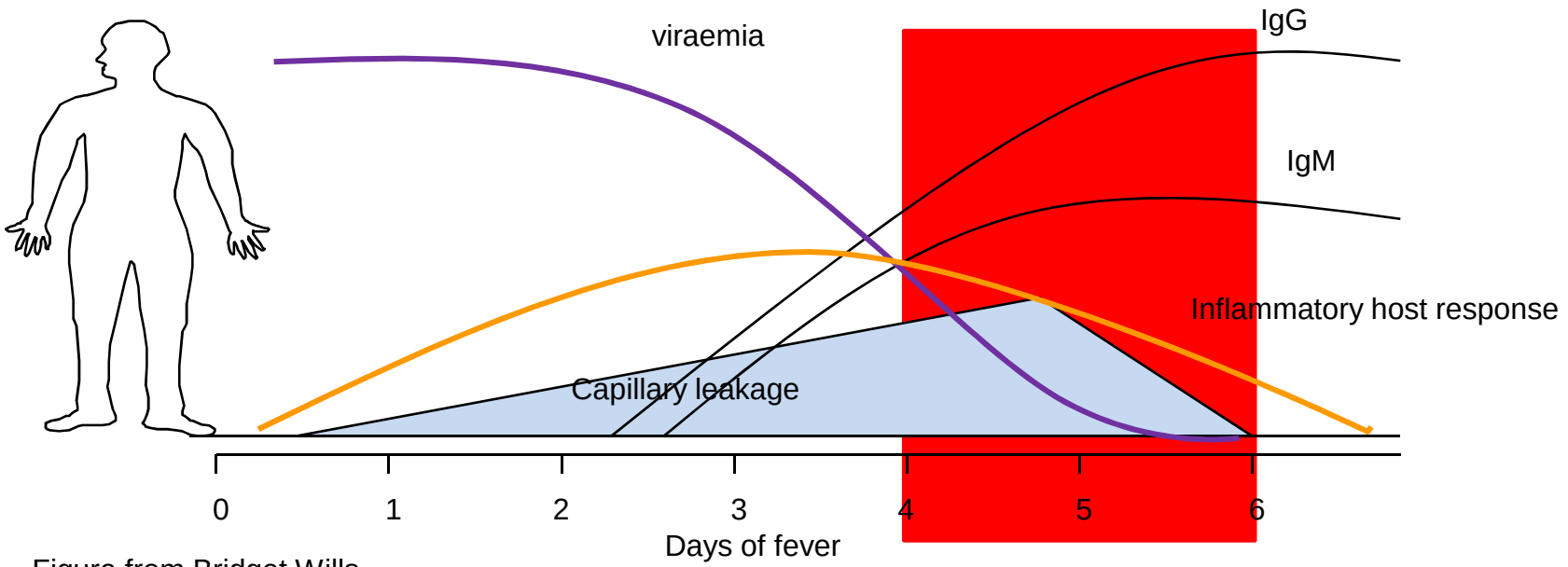
Adapted from Vaccine 2004; 22: 1275-1280

Slide from WHO dengue training module

Pathophysiology of Severe Dengue

- Epidemiologic studies found severe dengue more common during secondary heterologous infections and among infants

- Timing of severe manifestations at height of inflammatory host response suggest immune driven phenomenon



.Figure from Bridget Wills

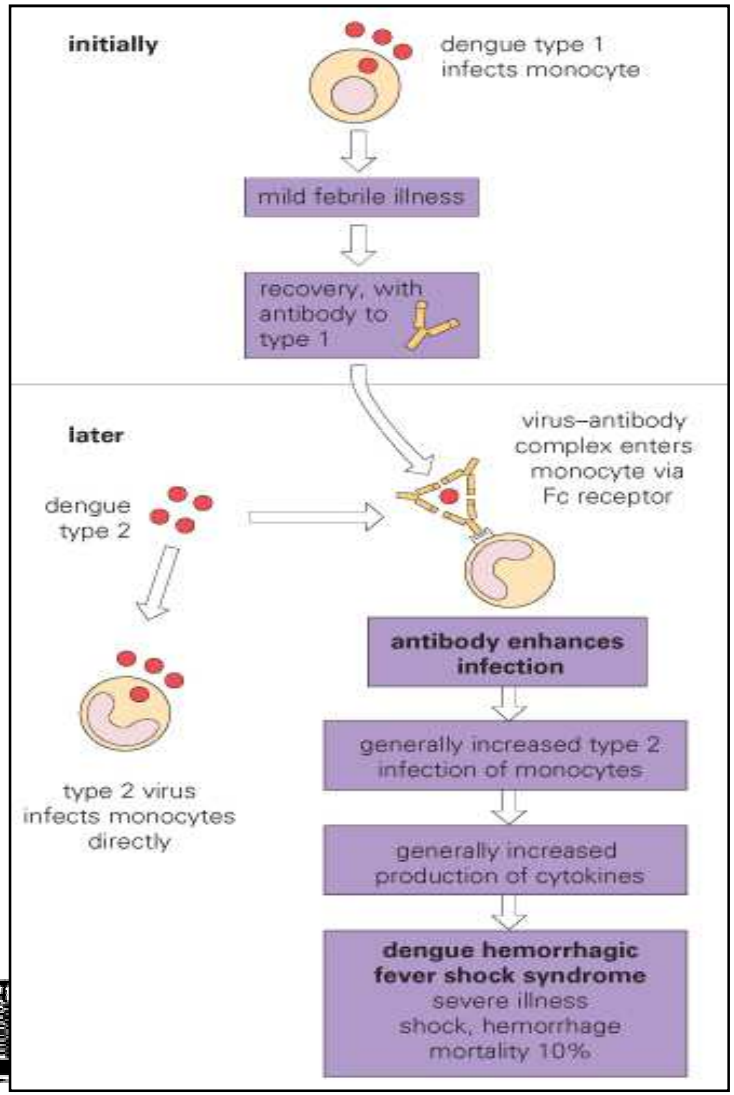
Slide from WHO dengue training module

WHY DO SOME PEOPLE GET DHF?

- Antibody-dependent enhancement theory

- Depends on virus:
  - serotype (DEN-2)
  - virulence

- Depends on host:
  - age (<15 yrs)
  - immune status
  - genetic factors
  - 2ary infection



Slide from WHO dengue training module

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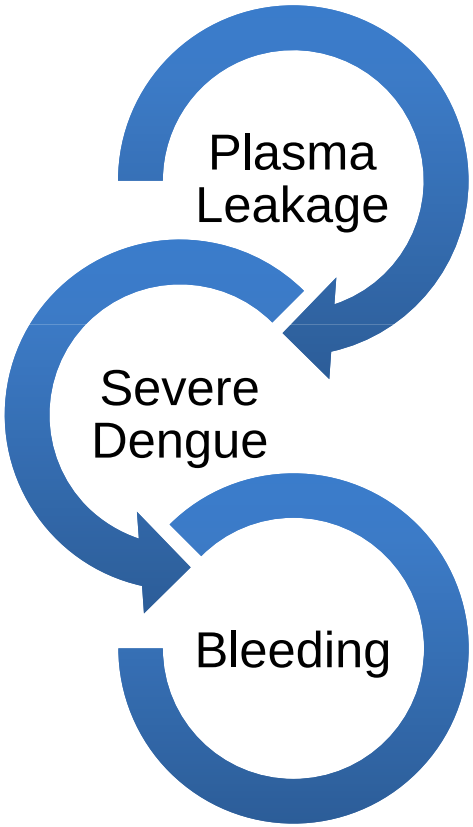
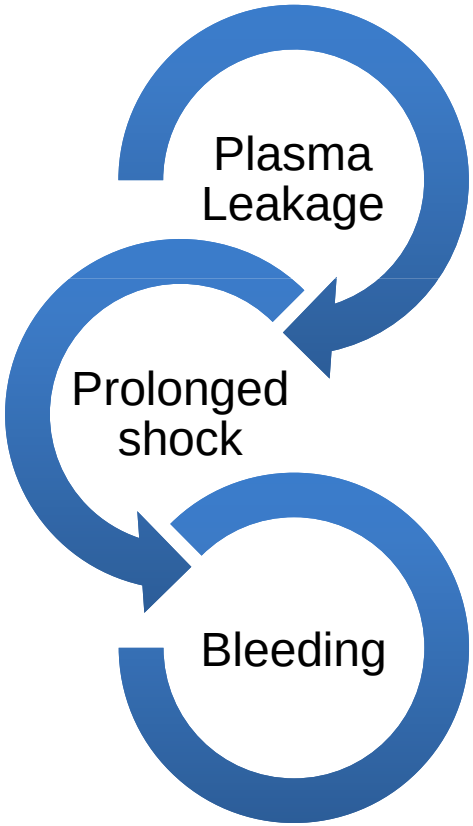
DENGUE, BLEEDING AND PLATELET TRANSFUSION

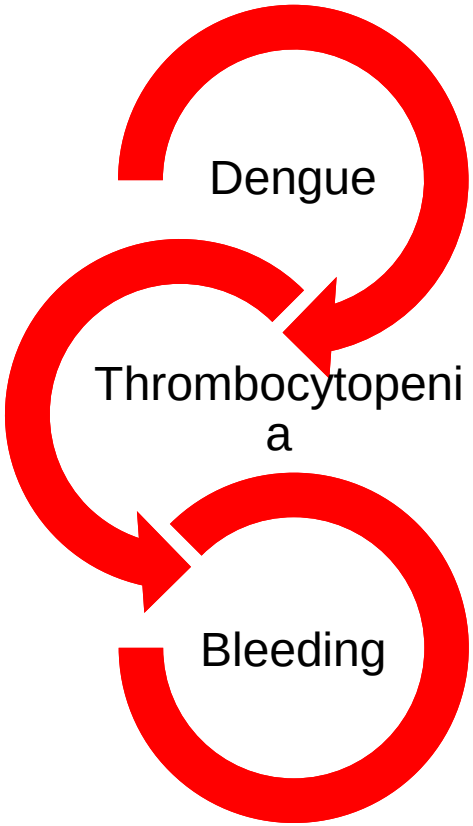
ASMEIT 2017

Bleeding in Dengue



Bleeding in Dengue





Prophylaxis platelet transfusion

WHY DO PATIENTS WITH DENGUE BLEED?

Endothelial activation

Markers of activation:
⇧thrombomodulin
⇧tissue factor
⇧VWF

→

Markers often seen in severe dengue.
⇧May promote microvascular thrombosis and EOD

Thrombocytopenia and Coagulation activation

Do not reliably predict bleeding indengue

Risk factors for bleeding?

Risk factors for hemorrhage in severe dengue infections

Lucy Chai See Lum, MBBS, MRCP, EDIC, Adrian Yu Teik Goh, MBBS, MMed, MRCP, Patrick Wai Keong Chan, MBBS, MMed, MRCP, Abdel-Latif Mohd El-Amin, MBBS, MPH, MPH (Epid), and Sai Kit Lam, MSc, PhD, FRCPath, FRCP, FASc

The purpose of this study was to identify the early indicators of hemorrhage in severe dengue infections in 114 patients; 24 patients had severe hemorrhage and 92 had no hemorrhage. The platelet counts were not predictive of bleeding. The duration of shock (OR, 2.11; 95% CI, 1.13 to 3.92; $P = .019$) and low-normal hematocrit at the time of shock (OR, 0.72; 95% CI, 0.55 to 0.95; $P = .020$) were risk factors of severe hemorrhage. (J Pediatr 2002;140:629-31)

Patients at risk of major bleeding WHO 2009

- prolonged/refractory shock
- hypotensive shock and renal or liver failure and/or severe and persistent metabolic acidosis
- given NSAIDs
- have pre-existing PUD
- on anticoagulant therapy
- have any form of trauma, including IM injection
- haemolytic conditions-at risk of acute haemolysis with haemoglobinuria

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Prophylaxis platelet transfusion

Lack of Efficacy of Prophylactic Platelet Transfusion for Severe Thrombocytopenia in Adults with Acute Uncomplicated Dengue Infection

David C. Lye,[1] Vernon J. Lee,[2,3] Yan Sun,[4] and Yee Sin Leo[1]

Departments of [1]Infectious Disease and [2]Clinical Epidemiology, Tan Tock Seng Hospital, [3]Biodefence Center, Ministry of Defence, and [4]Clinical Project Management and Planning, National Healthcare Group, Singapore

Thrombocytopenia in dengue infection raises concerns about bleeding risk. Of 256 patients with dengue infection who developed thrombocytopenia (platelet count, $<20 \times 10^3$ platelets/μL) without prior bleeding, 188 were given platelet transfusion. Subsequent bleeding, platelet increment, and platelet recovery were similar between patients given transfusion and patients not given transfusion. Prophylactic platelet transfusion was ineffective in preventing bleeding in adult patients with dengue infection.

Clinical Infectious Diseases 2009; 48:1262–5

Transfusion Medicine and Hemotherapy

Original Article

Transfus Med Hemother 2013;40:362–368
DOI: 10.1159/000354837

Received: May 31, 2012
Accepted: December 13, 2012
Published online: September 11, 2013

Effectiveness of Platelet Transfusion in Dengue Fever: A Randomized Controlled Trial

Muhammad Zaman Khan Assir[a] Umair Kamran[a] Hafiz Ijaz Ahmad[b] Sadia Bashir[a]
Hassan Mansoor[a] Saad Bin Anees[a] Javed Akram[c]

Summary

Background: Scientific data regarding effects of platelet transfusion on platelet count in dengue-related thrombocytopenia is scanty. **Methods**: A single center, randomized non-blinded trial was conducted on adult patients with dengue fever and platelet counts less than 30,000/μl. Patients were randomized to treatment and control group. Treatment group received single donor platelets. Patients with post-transfusion platelet increment (PPI) ≥10,000/μl and/or corrected count increment (CCI) ≥5,000/μl 1 h post-transfusion were considered responders. Primary outcome was platelet count increments at 24 and 72 h. **Results**: 87 patients were enrolled,

ments at 24 and 72 h. **Results**: 87 patients were enrolled, and 43 (48.2%) received platelet transfusion. Mean PPI and CCI at 1 h post-transfusion in the treatment group were 18,800/µl and 7,000/µl respectively. 22 (53.6%) patients in the treatment group were non-responders. Mean platelet increments at 24 and 72 h were higher in the treatment group as compared to the control group. Responders showed significantly higher increments when compared to non-responders and the control group at 24 h ($p = 0.004$ and $p < 0.001$, respectively) and 72 h ($p = 0.001$ and $p < 0.001$, respectively). Significant differences were found between non-responders and the control group at 24 h ($p < 0.001$), but not at 72 h ($p = 0.104$). Patients with lower baseline platelet count were more likely to be non-responders. Platelet transfusion neither prevented development of severe bleeding nor shortened time to cessation of bleeding. Three severe transfusion reactions and two deaths occurred in treatment group. **Conclusion**: In this trial, almost half the patients showed no response to a high-dose platelet transfusion. Platelet transfusion did not prevent development of severe bleeding or shorten time to cessation of bleeding and was associated with significant side effects. Therefore, platelet transfusion should not be routinely done in the management of dengue fever.

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PLOS | NEGLECTED TROPICAL DISEASES

RESEARCH ARTICLE

Potential Harm of Prophylactic Platelet Transfusion in Adult Dengue Patients

Tau-Hong Lee[1]*, Joshua G. X. Wong[1], Yee-Sin Leo[1,2], Tun-Linn Thein[1], Ee-Ling Ng[1], Linda K. Lee[1], David C. Lye[1,2]

March 2016

ASMEIT 2017

Method

We conducted a retrospective non-randomised observational study of dengue patients with platelet count < 20,000/mm^3 without bleeding (except petechiae) admitted to Tan Tock Seng Hospital from January 2005 to December 2008. Baseline characteristics and clinical outcomes were compared between the non-transfused vs. transfused groups. Outcomes studied were clinical bleeding, platelet increment, hospital length of stay, intensive care unit admission and death.

Results

Of the 788 patients included, 486 received prophylactic platelet transfusion. There was no significant difference in the presence of clinical bleeding in the two groups (18.2% in non-transfused group vs. 23.5% in transfused group; P = 0.08). Patients in the transfused group took a median of 1 day longer than the non-transfused group to increase their platelet count to 50,000/mm^3 or more (3 days vs. 2 days, P <0.0001). The median duration of hospital stay in the non-transfused group was 5 days vs. 6 days in the transfused group (P< 0.0001). There was no significant difference in the proportion requiring ICU admission (non-transfused 0.66% vs. transfused 1.23%, P = 0.44) and death (non-transfused 0% vs. trans-fused 0.2%, P = 0.43).

Conclusion

Platelet transfusion in absence of bleeding in adult dengue with platelet count <20,000/mm^3 did not reduce bleeding or expedite platelet recovery. There was potential harm by slowing recovery of platelet count to >50,000/mm^3 and increasing length of hospitalization.

Prophylactic platelet transfusion plus supportive care versus supportive care alone in adults with dengue and thrombocytopenia: a multicentre, open-label, randomised, superiority trial

David C Lye, Sophia Archuleta, Sharifah F Syed-Omar, Jenny G Low, Helen M Oh, Yuan Wei, Dale Fisher, Sasheela S L Ponnampalavanar, Limin Wijaya, Linda K Lee, Eng-Eong Ooi, Adeeba Kamarulzaman, Lucy C Lum, Paul A Tambyah, Yee-Sin Leo

Lancet March 2017

Methods We did an open-label, randomised, superiority trial in five hospitals in Singapore and Malaysia. We recruited patients aged at least 21 years who had laboratory-confirmed dengue (confirmed or probable) and thrombocytopenia (≤20 000 platelets per µL), without persistent mild bleeding or any severe bleeding. Patients were assigned (1:1), with randomly permuted block sizes of four or six and stratified by centre, to receive prophylactic platelet transfusion in addition to supportive care (transfusion group) or supportive care alone (control group). In the transfusion group, 4 units of pooled platelets were given each day when platelet count was 20 000 per µL or lower; supportive care consisted of bed rest, fluid therapy, and fever and pain medications. The primary endpoint was clinical bleeding (excluding petechiae) by study day 7 or hospital discharge (whichever was earlier), analysed by intention to treat. Safety outcomes were analysed according to the actual treatment received. This study was registered with ClinicalTrials.gov, number NCT01030211, and is completed.

Findings Between April 29, 2010, and Dec 9, 2014, we randomly assigned 372 patients to the transfusion group (n=188) or the control group (n=184). The intention-to-treat analysis included 187 patients in the transfusion group (one patient was withdrawn immediately) and 182 in the control group (one was withdrawn immediately and one did not have confirmed or probable dengue). Clinical bleeding by day 7 or hospital discharge occurred in 40 (21%) patients in the transfusion group and 48 (26%) patients in the control group (risk difference −4·98% [95% CI −15·08 to 5·34]; relative risk 0·81 [95% CI 0·56 to 1·17]; p=0·16). 13 adverse events occurred in the transfusion group and two occurred in the control group (5·81% [−4·42 to 16·01]; 6·26 [1·43 to 27·34]; p=0·0064). Adverse events that were possibly, probably, or definitely related to transfusion included three cases of urticaria, one maculopapular rash, one pruritus, and one chest pain, as well as one case each of anaphylaxis, transfusion-related acute lung injury, and fluid overload that resulted in serious adverse events. No death was reported.

Interpretation In adult patients with dengue and thrombocytopenia, prophylactic platelet transfusion was not superior to supportive care in preventing bleeding, and might be associated with adverse events.

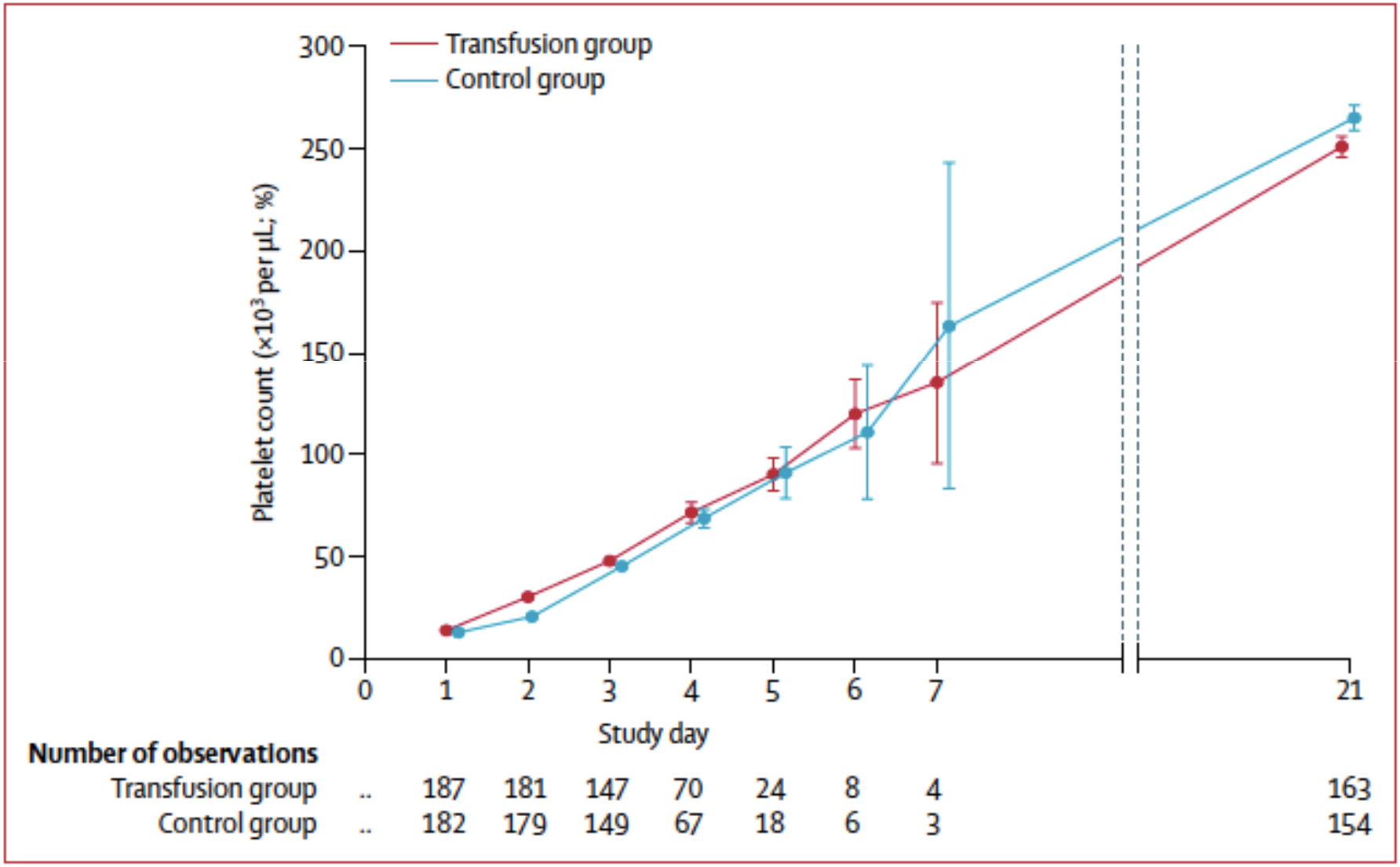
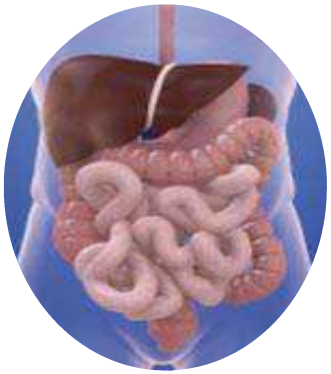
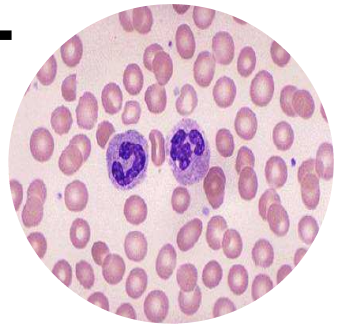


Figure 3: **Mean daily platelet count**

Dengue is a systemic and dynamic disease.

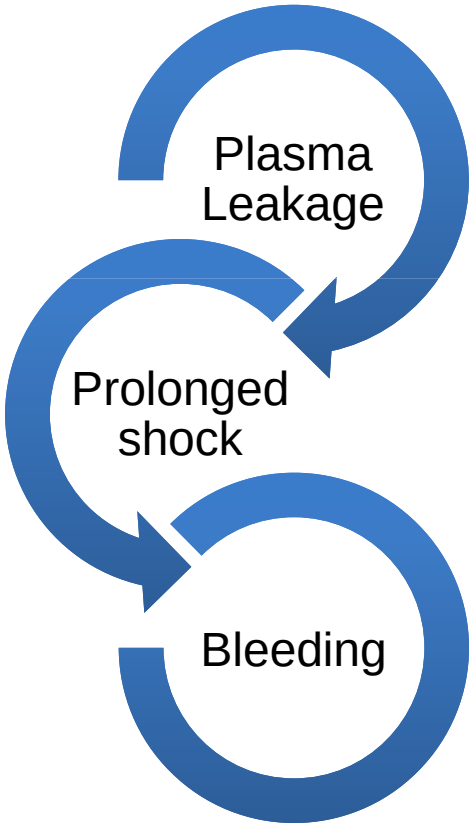


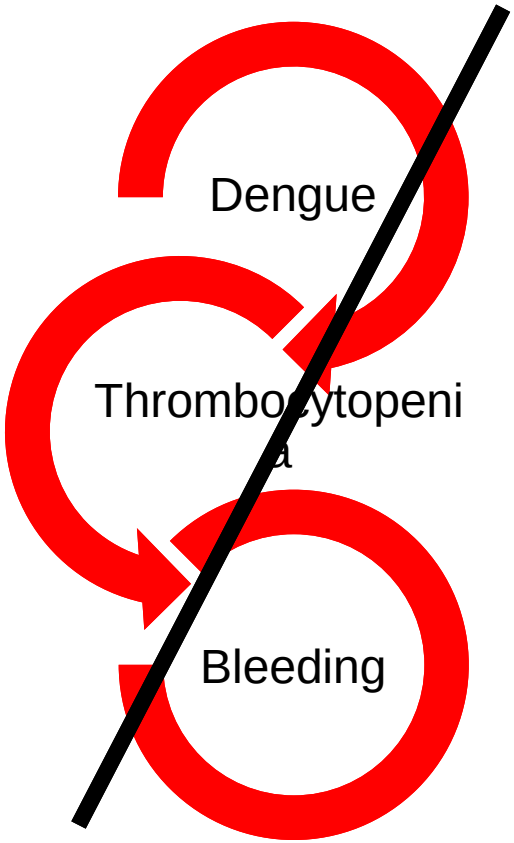
PLATELET COUNT

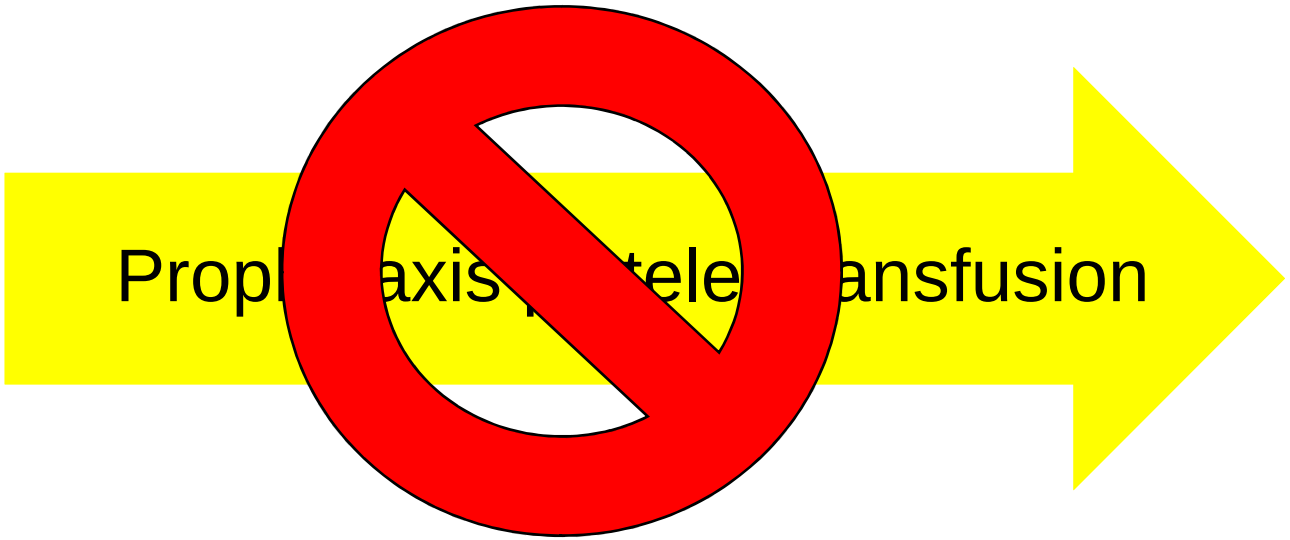


Dengue is NOT a PLATELET count disease

Bleeding in Dengue






Prop axis tele ansfusion

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HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH)/MACROPHAGE ACTIVATION SYNDROME (MAS) IN DENGUE

ASMEIT 2017

HLH

A rare hyperinflammatory disorder related to macrophage activation

Usually presents as prolonged fever and a sepsis-like syndrome

HLH and infection

- Secondary or reactive form associated with viral, bacterial, fungal, or parasitic infections; connective tissue disorders and malignancy
- Mimic infectious diseases such as overwhelming bacterial sepsis

HLH Pathophysiology

Defect of NK and CTL cells

Accumulation of activated T-lymphocytes and activated histiocytes

Increasingly high levels of cytokines (cytokine storm)

HLH/MAS:
a final common pathway of a cytokine storm

Infection

- ► Macrophage activation/haemophagocytosis
  - ► Systemic inflammatory response
    + Multi-organ dysfunction
      - ► Death

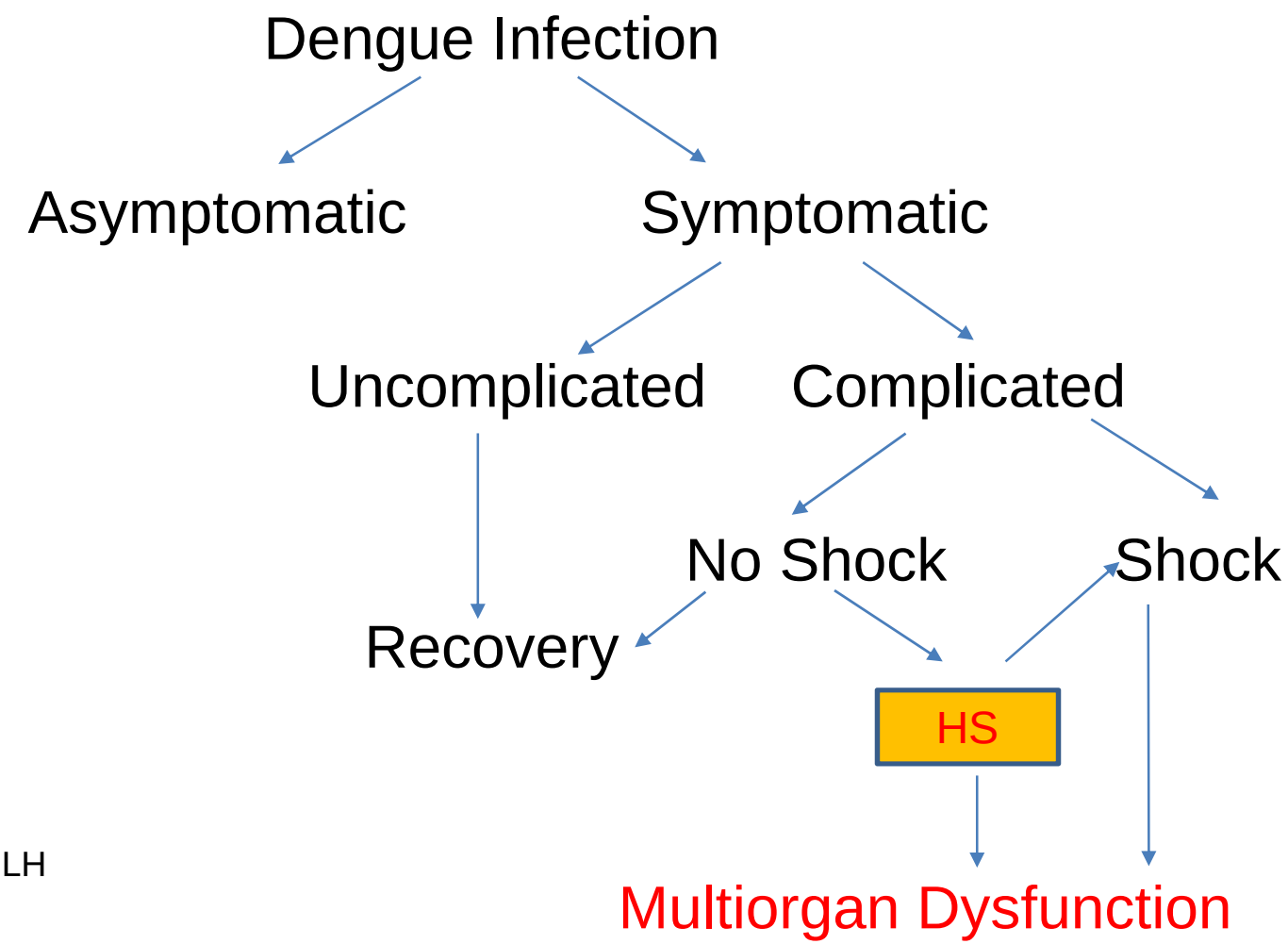

Diagram courtesy Dr Tan LH

Diagnostic criteria for HLH (>5 out of 8)

Criteria:
Fever
Splenomegaly
Cytopenia (2-3 cell lines affected) - Hb <9 mg/dL - Plt <100 x 10^9/L - Neutrophils <1.0 x 10^9/L
HyperTG and/or hypofibrinogenaemia - Fasting TG > 3mmol/L - Fibrinogen =< 1.5 g/L
Haemophagocytosis in BM or spleen or LN
No evidence of malignancy
Ferritin >= 500ug/L
Soluble CD25 (soluble IL-2 receptor) >=2400 IU/ml

Ferritin > 500
Sensitivity 82%, Specificity 42%
Ferritin > 10,000
Sensitivity 90%, Specificity 96%

Is it HLH?

Persistent fever and cytopenia

Severe transaminitis/hepatitis

Multi-organ failure

Progressive drop in haemoglobin

Unexplained progressive metabolic acidosis

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Evidence of HS in Dengue in the early days…

Nelson ER, Bierman HR, Chulajata R.

Hematologic phagocytosis in post mortem marrows of dengue hemorrhagic fever

Am J Med Sci 1966;252:68-74

HEMATOLOGIC PHAGOCYTOSIS IN POSTMORTEM BONE MARROWS OF DENGUE HEMORRHAGIC FEVER

(HEMATOLOGIC PHAGOCYTOSIS IN THAI HEMORRHAGIC FEVER)
(PEDIATRIC DENGUE)

By Ethel R. Nelson, M.D.
PATHOLOGIST, BANGKOK SANITARIUM & HOSPITAL, BANGKOK, THAILAND

Howard R. Bierman, M.D.
DIRECTOR, INSTITUTE FOR CANCER AND BLOOD RESEARCH, BEVERLY HILLS, CALIFORNIA
CLINICAL PROFESSOR OF MEDICINE, DEPARTMENT OF MEDICINE, LOMA LINDA UNIVERSITY, LOS ANGELES, CALIFORNIA

AND

Ruchee Chulajata, M.D.
PEDIATRICIAN, BANGKOK SANITARIUM AND HOSPITAL, BANGKOK, THAILAND

Phagocytic reticulum cells have been described in the spleen and lymph nodes of necropsied cases of Thai hemorrhagic fever due to dengue virus Types III to VII (Phamarapravati[9], Piyarata[9]). These are seen not infrequently (Fig. 1). Interestingly enough, erythrophagocytosis has also been described in other viral diseases. Histopathological examination at postmortem of the human liver and spleen (Iyer *et al.*[7]) and in monkeys (Webb and Chatterjea[10]) dying from experimentally induced Kyasanur Forest Disease in

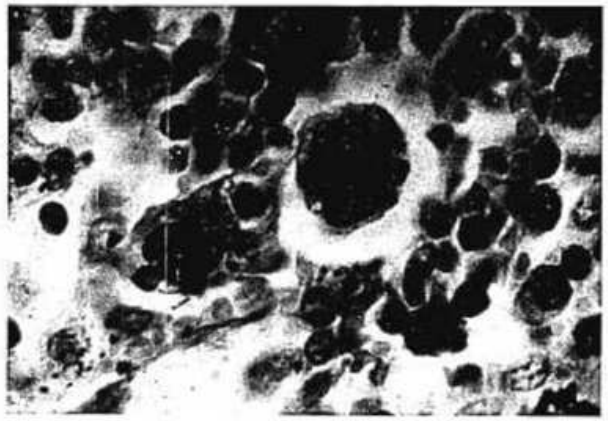

Fig. 1.—Phagocytic reticulum cell in the spleen in Thai hemorrhagic fever (× 1000).
(102/68)

Slide courtesy Dr Tan LH

Journal of Clinical Virology 55 (2012) 79–82

Contents lists available at SciVerse ScienceDirect

Journal of Clinical Virology

journal homepage: www.elsevier.com/locate/jcv

Case report

Hemophagocytosis in dengue: Comprehensive report of six cases

Lian Huat Tan[a,1], Lucy Chai See Lum[b,*], Sharifah Faridah Syed Omar[c,2], Foong Kee Kan[d,3]

Table 1
Summary of important clinical and laboratory features in P1–P6.

Patient	Age (years)	Dengue confirmatory tests	Plasma leakage	Shock	Persistent fever	Acute renal failure	CNS manifestations	Highest measured ferritin (mg/L) (day)	Bone marrow evidence[a]	Treatment for HPS
P1	16	IgM seroconversion	Yes	No	Yes	No	No	28,060 (D16)	Yes	No
P2	16	NS1Ag positive and IgM seroconversion	Yes	Yes	Yes	Yes	Yes	36,484 (D12)	Yes	Yes
P3	43	IgM and IgG positive D6	Yes	Yes	Yes	Yes	Yes	154,300 (D8)	ND	Yes
P4	20	NS1Ag positive and IgM seroconversion	Yes	No	Yes	No	No	55,640 (D7)	ND	No
P5	34	NS1Ag positive and IgM seroconversion	Yes	No	Yes	No	No	37,678 (D6)	ND	Yes
P6	36	NS1Ag positive, IgM and IgG positive D7	No	No	Yes	No	No	20,569 (D7)	Yes	Yes

CNS: central nervous system; HPS: hemophagocytic syndrome.
ND: not done.
[a] Bone marrow evidence of hemophagocytosis.

A B S T R A C T

Hemophagocytic syndrome is a potentially fatal disorder. It is being increasingly reported but remained under-recognized in dengue. Most reported cases were in association with plasma leakage and shock but multi-organ impairment was also observed. We describe the time-lines of 6 cases of confirmed dengue with varying severities of hemophagocytosis. All had persistent fever, cytopenia and elevated transaminases with markedly elevated ferritin levels during and beyond the plasma leakage phase. Acute renal failure and central nervous system manifestation were observed in two patients. Morphological hemophagocytosis was demonstrated in three patients. All survivors showed clinical and biochemical resolution of hemophagocytosis indicating its transient nature. Persistence of fever and cytopenia together with multi-organ dysfunction, out of proportion to and beyond the plasma leakage phase should prompt clinicians to consider this phenomenon.

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Ab-Rahman *et al. SpringerPlus (2015) 4:665*
DOI 10.1186/s40064-015-1463-z

SpringerPlus
a SpringerOpen Journal

CASE STUDY **Open Access**

CrossMark

Dengue death with evidence of hemophagocytic syndrome and dengue virus infection in the bone marrow

Hasliana Azrah Ab-Rahman[1,2,3], Pooi-Fong Wong[3], Hafiz Rahim[4], Juraina Abd-Jamil[1], Kim-Kee Tan[1,2], Syuhaida Sulaiman[1,2], Chai-See Lum[4,5], Syarifah-Faridah Syed-Omar[4] and Sazaly AbuBakar[1,2*]

Abstract

Introduction: HPS is a potentially life-threatening histiocytic disorder that has been described in various viral infections including dengue. Its involvement in severe and fatal dengue is probably more common but is presently under recognized.

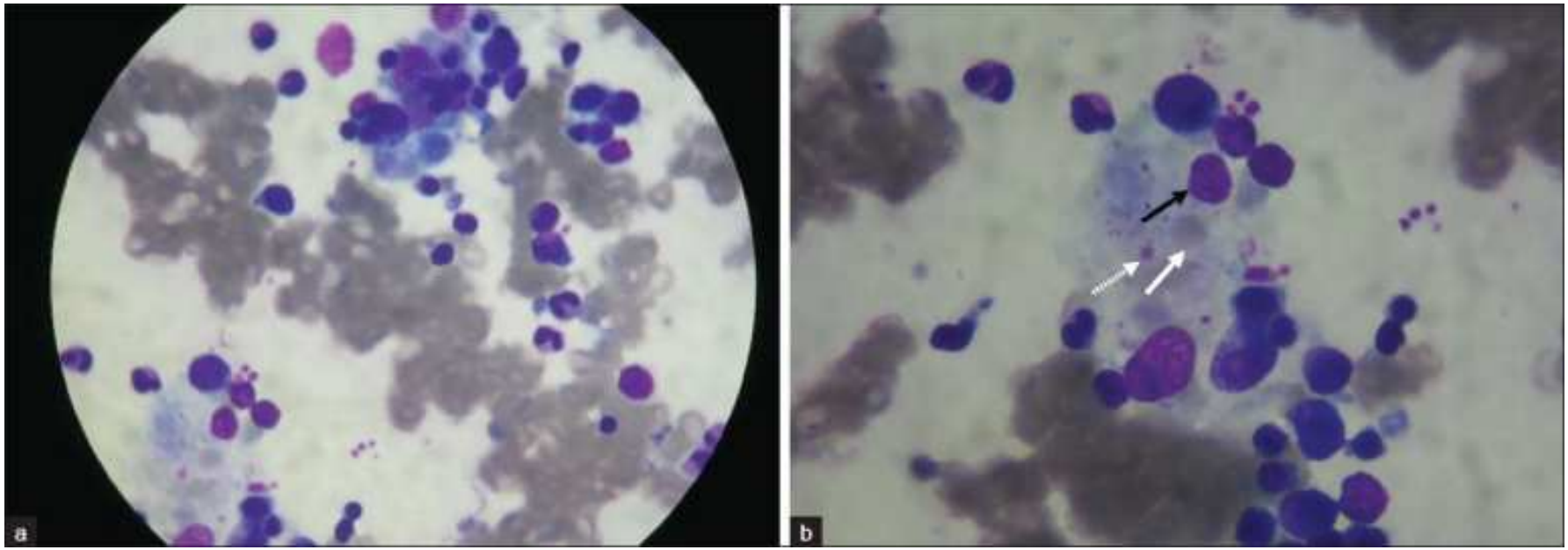
Case description: A 38-year-old female was admitted after 5 days of fever. She was deeply jaundiced, leukopenic and thrombocytopenic. Marked elevation of transaminases, hyperbilirubinemia and hypoalbuminemia were observed. She had deranged INR values and prolonged aPTT accompanied with hypofibrinogenemia. She also had splenomegaly. She was positive for dengue IgM. Five days later she became polyuric and CT brain image showed gross generalized cerebral edema. Her conditions deteriorated by day 9, became confused with GCS of 9/15. Her BMAT showed minimal histiocytes. Her serum ferritin level peaked at 13,670.00 µg/mL and her sCD163 and sCD25 values were markedly elevated at 4750.00 ng/mL and 4191.00 pg/mL, respectively. She succumbed to the disease on day 10 and examination of her tissues showed the presence of dengue virus genome in the bone marrow.

Discussion and evaluation: It is described here, a case of fatal dengue with clinical features of HPS. Though BMAT results did not show the presence of macrophage hemophagocytosis, other laboratory features were consistent with HPS especially marked elevation of ferritin, sCD163 and sCD25. Detection of dengue virus in the patient's bone marrow, fifteen days after the onset of fever was also consistent with the suggestion that the HPS is associated with dengue virus infection.

Conclusions: The findings highlight HPS as a possible complication leading to severe dengue and revealed persistent dengue virus infection of the bone marrow. Detection of HPS markers; ferritin, sCD163 and sCD25, therefore, should be considered for early recognition of HPS-associated dengue.

Sayantan Ray, et al. Hemophagocytic Syndrome in Classic Dengue Fever.

J Glob Infect Dis. 2011 Oct-Dec; 3(4): 399–401



The macrophage at the center of the image with engulfed red blood cells (white arrow), leukocytes (black arrow)

Thai adult dengue hemorrhagic fever during 2008-2010: seven cases presented with severe multiorgan failure and successfully treated with high dose of corticosteroids and intravenous immunoglobulin G.

Sorakkhunpipitkul L, Punyagupta S, Srichaikul T, Tribudddharat S. J Infect Dis Antimicrob Agents 2011;28(2):99-103

Table 3. Clinical features of 7 adult DHF with severe multiorgan failure.

No	Sex	Complication	Clinical Feature									Rx Start on Day			Out	Days of
	Age (yrs)	on Day	HPCS	Shock	ARDS	Cardiac	CNS	GI	RF	DIC	Bleeding	Dexa	MP	IV IgG	come	Hospitalization
1	F 22	D2	+	+	+	+	+	-	-	-	+	D2-6	D5	D3-7	S	7
2	F 43	D6	+	+	+	+	-	+	-	-	-	D4	D5-7	D8	S	9
3	F 45	D2	+	-	+	+	+	+	+	+	+	D6-8	-	D5-6	F	10
4	M 65	D3	+	-	-	-	+	+	+	+	-	D3-7	-	D7	F	7
5	M 40	D4	-	-	-	+	-	+	-	-	-	D4-7	-	D7	S	10
6	F 48	D6	-	+	-	-	-	+	-	-	+	D4-7	-	-	S	8
7	M 16	D6	-	-	-	-	-	+	-	+	+	D6	-	-	S	6

MP = methylprednisolone, RF= renal failure, S = survive, F = fatal

Should we give steroids?

A transient disease process in majority of patients

Steroids ± immunoglobulin may be enough for most cases if indicated

Shorter courses of steroids usually sufficed if indicated

Take Home Messages

- Plasma Leakage
  - Still the key driver to severe disease in dengue
- Severe dengue beyond plasma leakage
  - Bleeding- no role for prophylactic platelet transfusion
  - Organ damage- related to HLH?

THANK YOU