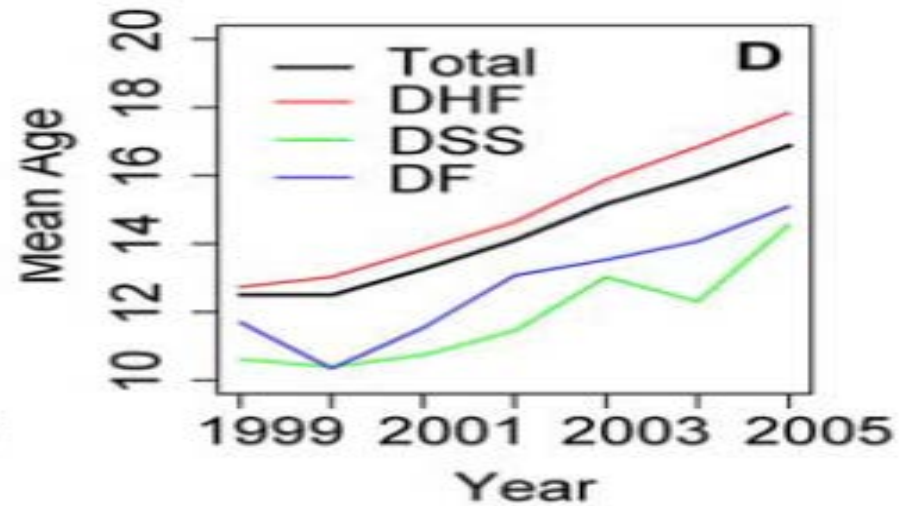# Evidence-Based Management of Adult Dengue and Its Complications
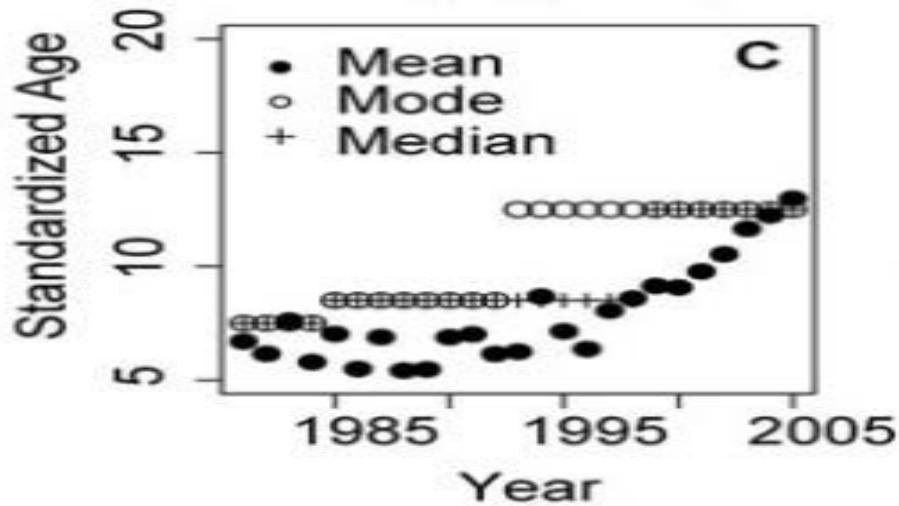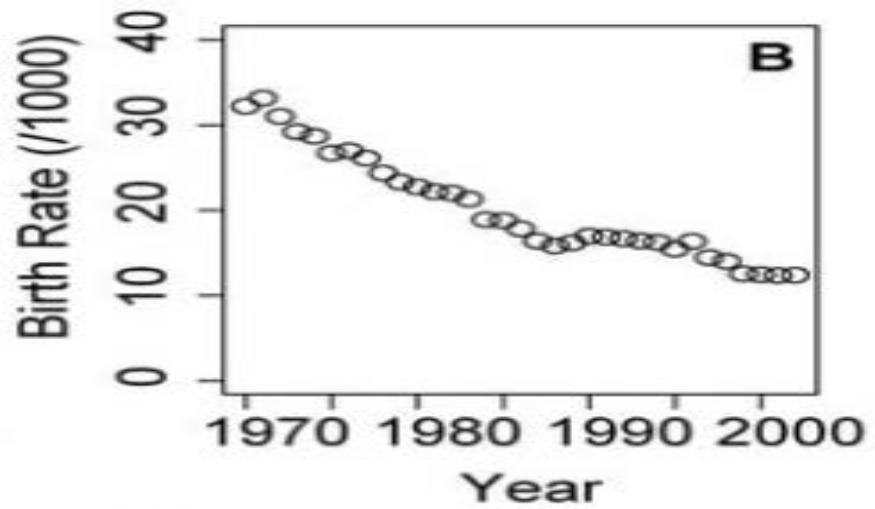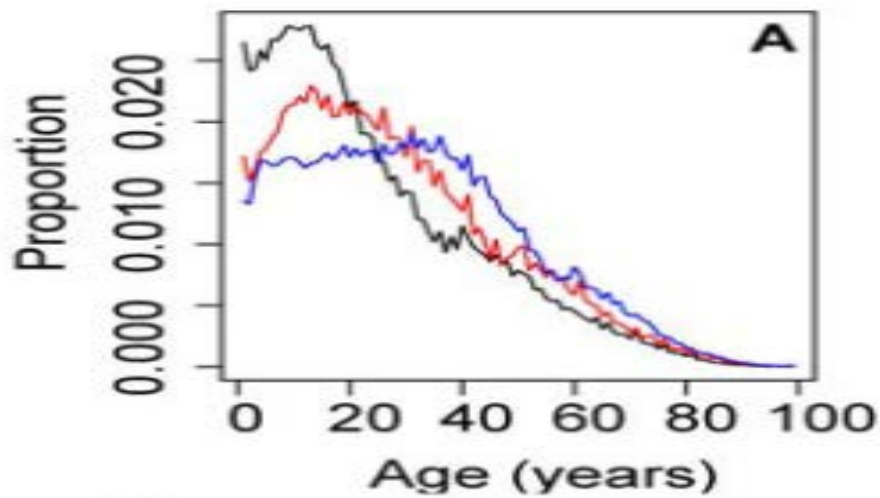
Prof. Terapong Tantawichien,M.D.
President of Infectious Disease
     Association of Thailand
Head of Division of Infectious Diseases
     Department of Medicine
     Chulalongkorn University
Assistant Director of Queen Saovabha
     Memorial Institute, Thai Red Cross

Demographic changes in Thailand and changes in the age distribution of dengue illness. (A) Age structure of the Thai population 1980 (black), 1990 (red), and 2000 (blue). (C) Mean, median, and modal age of age standardized dengue incidence data in Thailand 1981–2005. Cummings D; Pols Medicine 2009

Confirmed adult dengue deaths in Singapore: 5-year multi-center retrospective study.

28 adult dengue deaths, median age was 59 yrs and co-morbidities 75%.

From illness onset, patients presented for admission at a median of 4 days and death occurred at a median of 12 days.

Hematocrit change >20% with platelet count < 20,000/cumm was associated with the shortest interval to death at a median of 3 days.

Deaths were due to shock and organ failure.

Acute renal impairment occurred in 71.4%, impaired consciousness 57.1% and severe hepatitis 53.6%.

Fatal Dengue Hemorrhagic Fever in Adults: Emphasizing the Evolutionary Pre-fatal Clinical and Laboratory Manifestations

Of 309 adults with DHF, 10 fatal patients and 299 survivors (controls) were retrospectively analyzed.

Regarding causes of fatality, massive gastrointestinal (GI) bleeding was found in 4 patients, dengue shock syndrome (DSS) alone in 2; DSS/subarachnoid hemorrhage, Klebsiella pneumoniae meningitis/bacteremia, ventilator associated pneumonia, and massive GI bleeding/Enterococcus faecalis bacteremia each in one.

Fatal patients were found to have significantly higher frequencies of early altered consciousness (<24 h after hospitalization), hypothermia, GI bleeding/massive GI bleeding, DSS, concurrent bacteremia, pulmonary edema, renal/hepatic failure, and subarachnoid hemorrhage.

Table 2 Travel related dengue and dengue hemorrhagic fever.

Setting[(Ref)]	Number of travelers	Hospitalization (%)	DHF/DSS (%)	Complicated dengue (%)[a]
Geosentinel international case registry[32]	522	24	2.3	NR
TropNet Europe case registry[51]	250	24	2.0	1.2
European travelers[43]	219	23	0.9	11
Austrian travelers[40]	93	68	7.3	11.8
Japanese travelers[44]	62	100[b]	3.2	20
Spanish travelers[52]	61	100[b]	0	8.2
Dutch travelers[53]	46	24	4.8	8.7
British travelers[54]	16	100[b]	18.9	NR

NR – not reported.

[a] Complications other than DHF: such as bleeding phenomena without criteria for DHF, ocular damage, encephalopathy, etc. (definitions vary between publications).

[b] Hospital based series.

Severe Dengue Virus Infection in Travelers: Risk Factors and Laboratory Indicators

219 Imported dengue infection.
Serological analysis revealed a secondary response in 17%.
(associated with both spontaneous bleeding and severe dengue)

Spontaneous bleeding was observed in 17 (8%) patients
Was associated with
Increased SGOT/SGPT and lower platelet counts.

23 (11%) travelers had severe clinical manifestations:
   Internal hemorrhage
   Plasma leakage
   Shock
   Severe thrombocytopenia
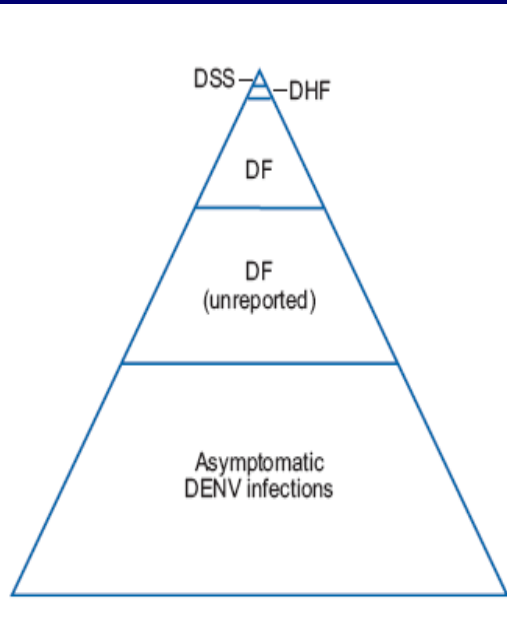
Expert consensus groups in Latin America (Havana, Cuba, 2007), South-East Asia
(Kuala Lumpur, Malaysia, 2007), and at WHO headquarters in Geneva, Switzerland in 2008 agreed that:
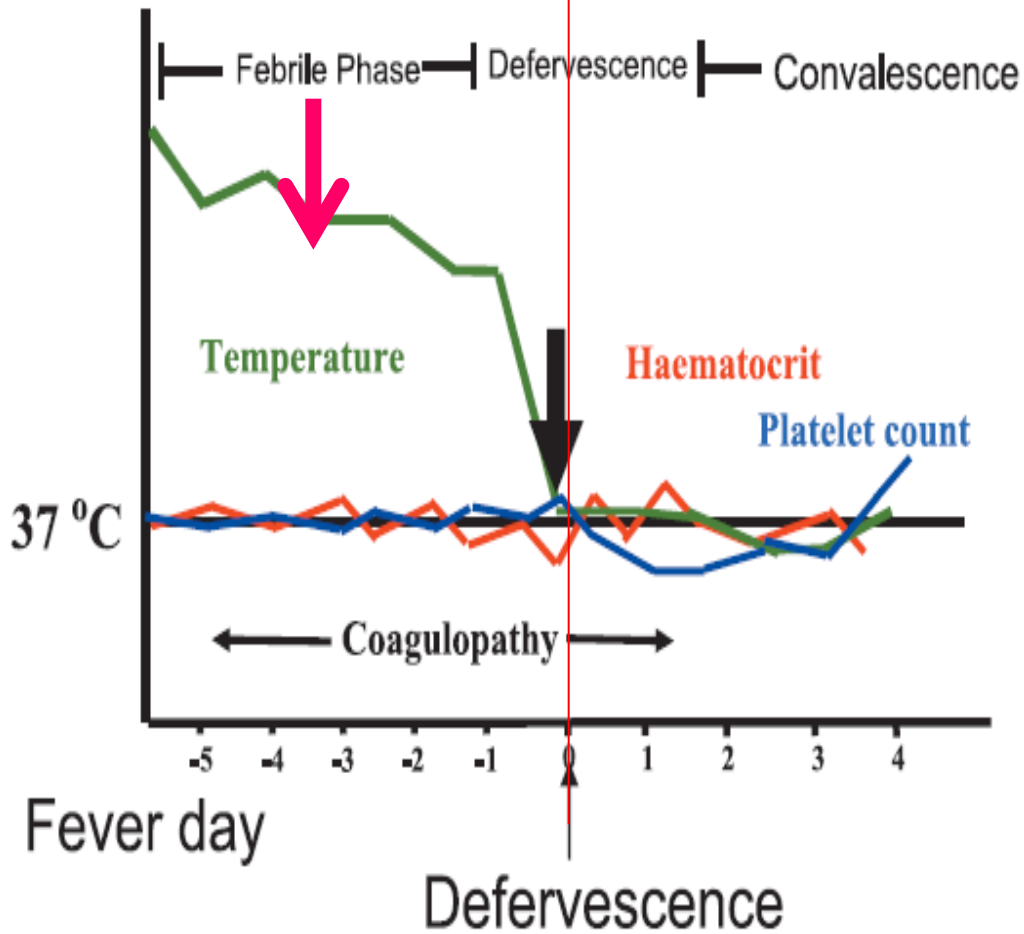
"Dengue is one disease entity with different clinical presentations and often with unpredictable clinical evolution and outcome";

Who Guideline 2009

Table 1: The World Health Organization (WHO) case definitions of dengue fever and dengue haemorrhagic fever.

Dengue fever (DF)	Dengue haemorrhagic fever (DHF)
Probable DF is an acute febrile illness with *two or more* of the following:	DHF case definition (all 4 components must be met)
– Headache	1) Fever or history of fever, lasting 2–7 days, occasionally biphasic.
– Myalgia	2) Haemorrhagic tendencies.
– Arthralgia	3) Thrombocytopenia (100,000 cells per mm^3 or less)
– Retro-orbital pain	4) Evidence of plasma leakage manifested by at least one of the
– Rash	following:
– Haemorrhagic manifestations	– a rise in the haematocrit equal or greater than 20% above average for age,
– Leukopenia;	sex and population
and	– a drop in the haematocrit following volume-replacement treatment equal to or
Supportive serology or occurrence at the same	greater than 20% of baseline
location and time as other confirmed cases of dengue.	– signs of plasma leakage such as pleural effusion, ascites, and hypoproteinaemia.
Confirmed DF is a case confirmed by laboratory criteria	Defintion of dengue shock syndrome (DSS): DHF cases with documented narrow
(serology, viral isolation, viral genome detection).	pulse pressure (< 20 mmHg), hypotension or other signs of shock.

Anon Srikiatkhachorn ; **Thromb Haemost 2009**

Warning signs
Dengue/severe dengue

Warning signs
Dengue/severe dengue
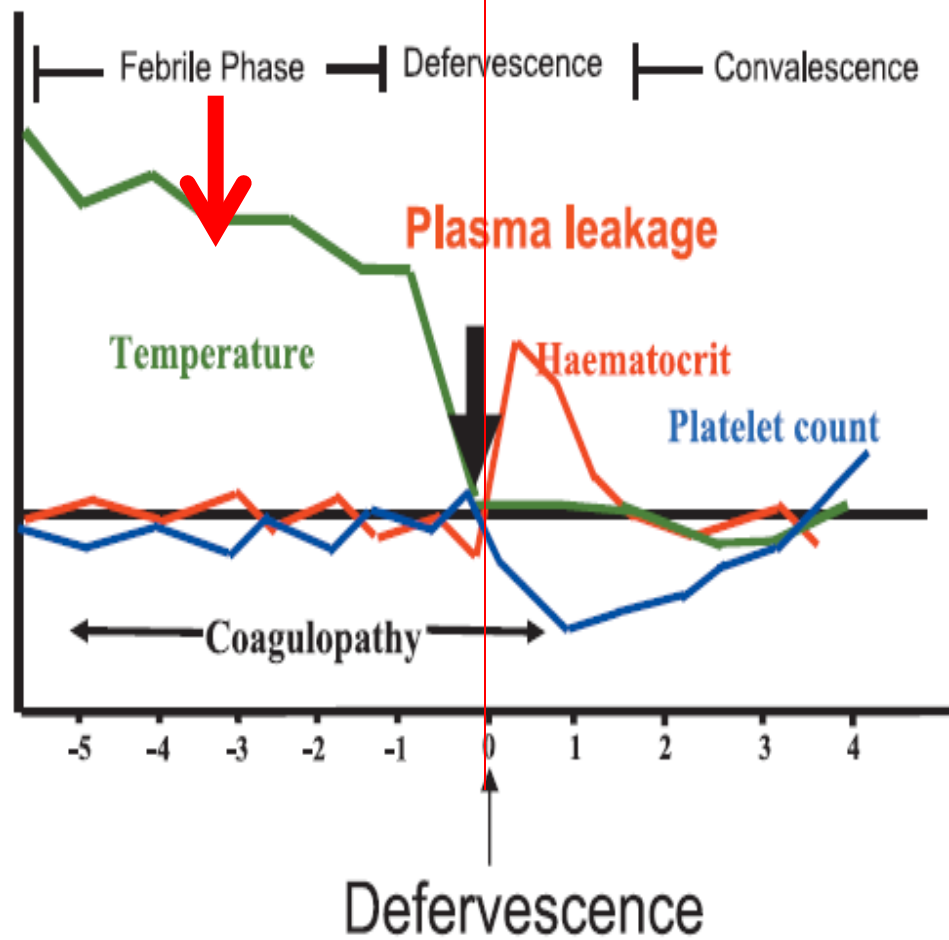
Severe dengue should be considered if the patient is from an area of dengue risk presenting with fever of 2–7 days plus any of the followings

• **There is evidence of plasma leakage, such as:**
  – **high or progressively rising haematocrit;**
  – **pleural effusions or ascites;**
  – **circulatory compromise or shock (tachycardia, cold and clammy extremities, capillary refill time greater than three seconds, weak or undetectable pulse, narrow pulse pressure or, in late shock, unrecordable blood pressure).**

• **There is significant bleeding.**
• **There is an altered level of consciousness (lethargy or restlessness, coma, convulsions).**
• **There is severe gastrointestinal involvement (persistent vomiting, increasing or intense abdominal pain, jaundice).**
• **There is severe organ impairment (acute liver failure, acute renal failure, encephalopathy or encephalitis, or other unusual manifestations, cardiomyopathy) or other unusual manifestations.**

Who Guideline 2009

Management of Adult Dengue

Concern dengue infection in our practice:
> Early diagnosis

Severe bleeding:
> Severe thrombocytopenia, coagulopathy

Hemodynamic abnormality:
> Leakage syndrome- DHF, DSS in adults
>> Rate and volume of IV replacement in DHF/DSS
>> Avoid inadequate volume / volume overload

Elevated liver enzymes:
> Unnecessary drugs, viral hepatitis………

Unusual manifestations in a few cases:
> Renal failure, hepatic failure, encephalopathy
> bacteremia, co-infections………..

Guideline for outpatient/inpatient management of dengue infections in adults (Figures 2 and 3)

Figure 2. Guideline for management of dengue infections in adults

Presumptive dengue infection[1]

Fever $\leq$ 3 days[2]

Fever 4 - 10 days[2]

Tourniquet test should be performed

+/- CBC (or blood smear)

The following laboratory tests should be performed:
- CBC (or blood smear)
- Tourniquet test [not recommend if platelet count < 80,000 cell/mm^3 (< 80x10^9/L) or spontaneous petechiae]
- Consideration of blood tests for AST, ALT in cases of severe vomiting, hepatomegaly or pregnancy

Not presumptive diagnosis: Consider to work up as other causes of acute febrile illness

Early diagnosis of dengue infection[2]

Consider NS1 or PCR for confirmation of dengue infection[3]

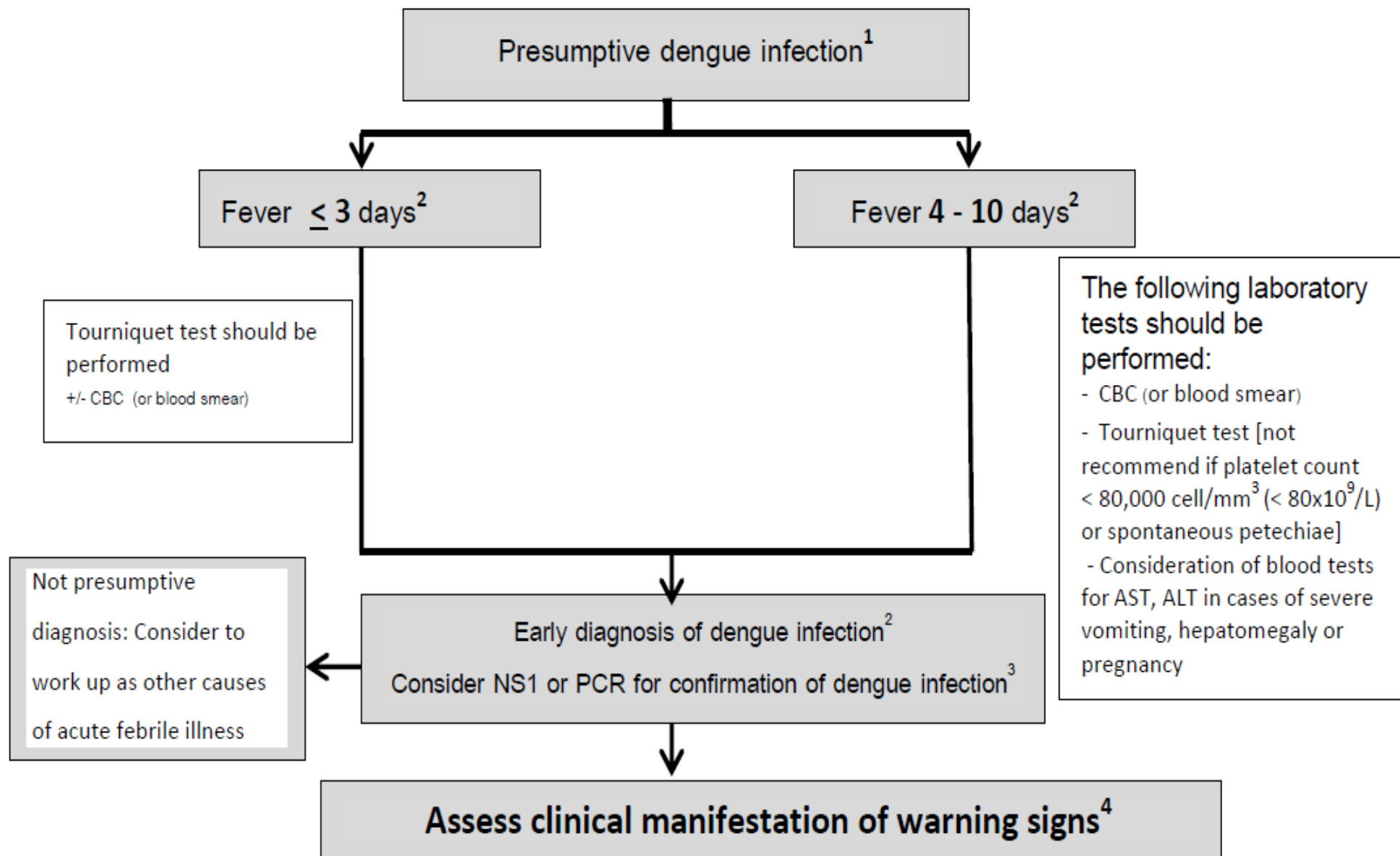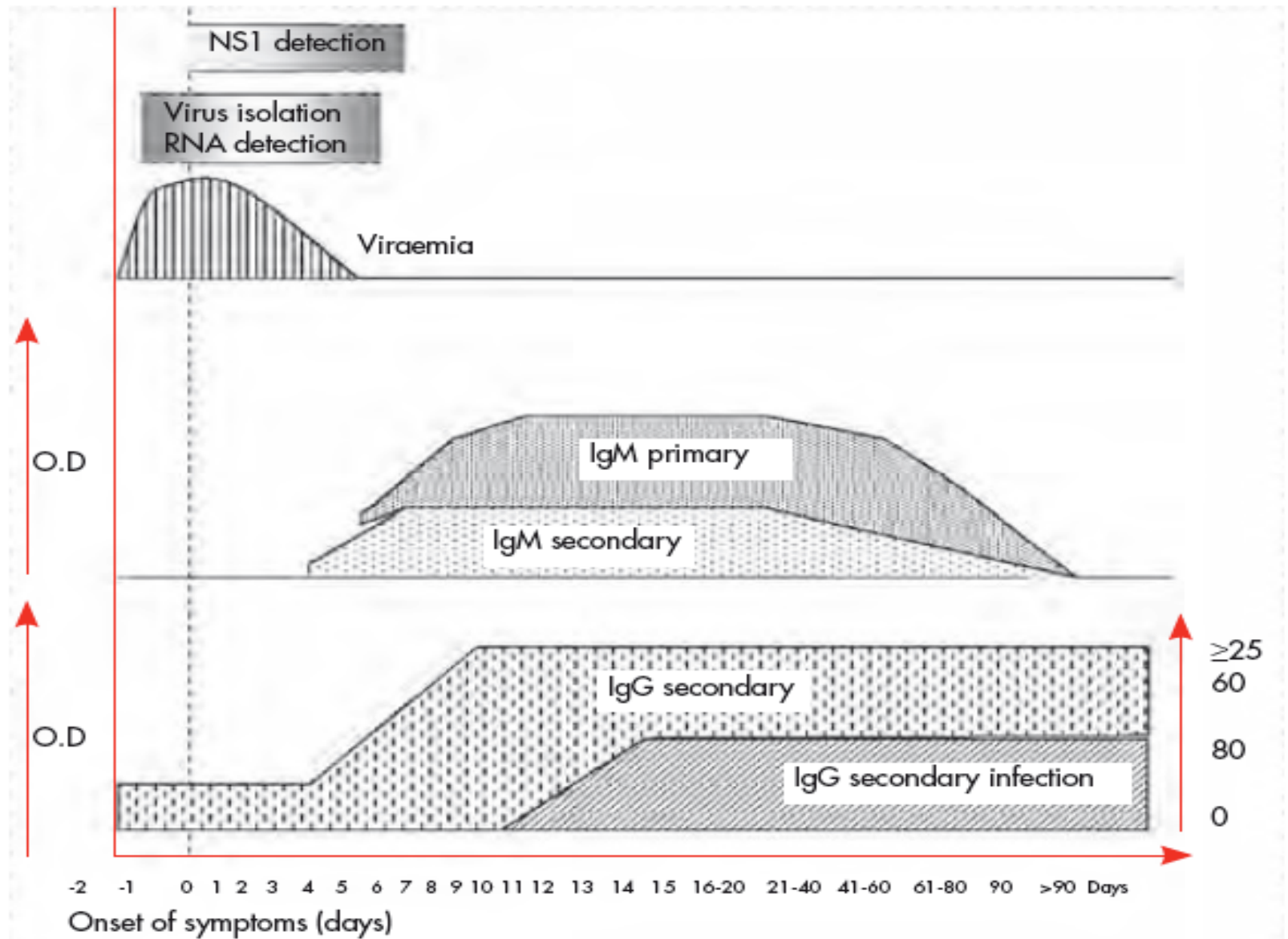**Assess clinical manifestation of warning signs[4]**

Figure 4.1 Approximate time-line of primary and secondary dengue virus infections and the diagnostic methods that can be used to detect infection

NS1 detection

Virus isolation
RNA detection

Viraemia

O.D

IgM primary

IgM secondary

O.D

IgG secondary

≥25
60

IgG secondary infection

80

0

-2 -1 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16-20 21-40 41-60 61-80 90 >90 Days

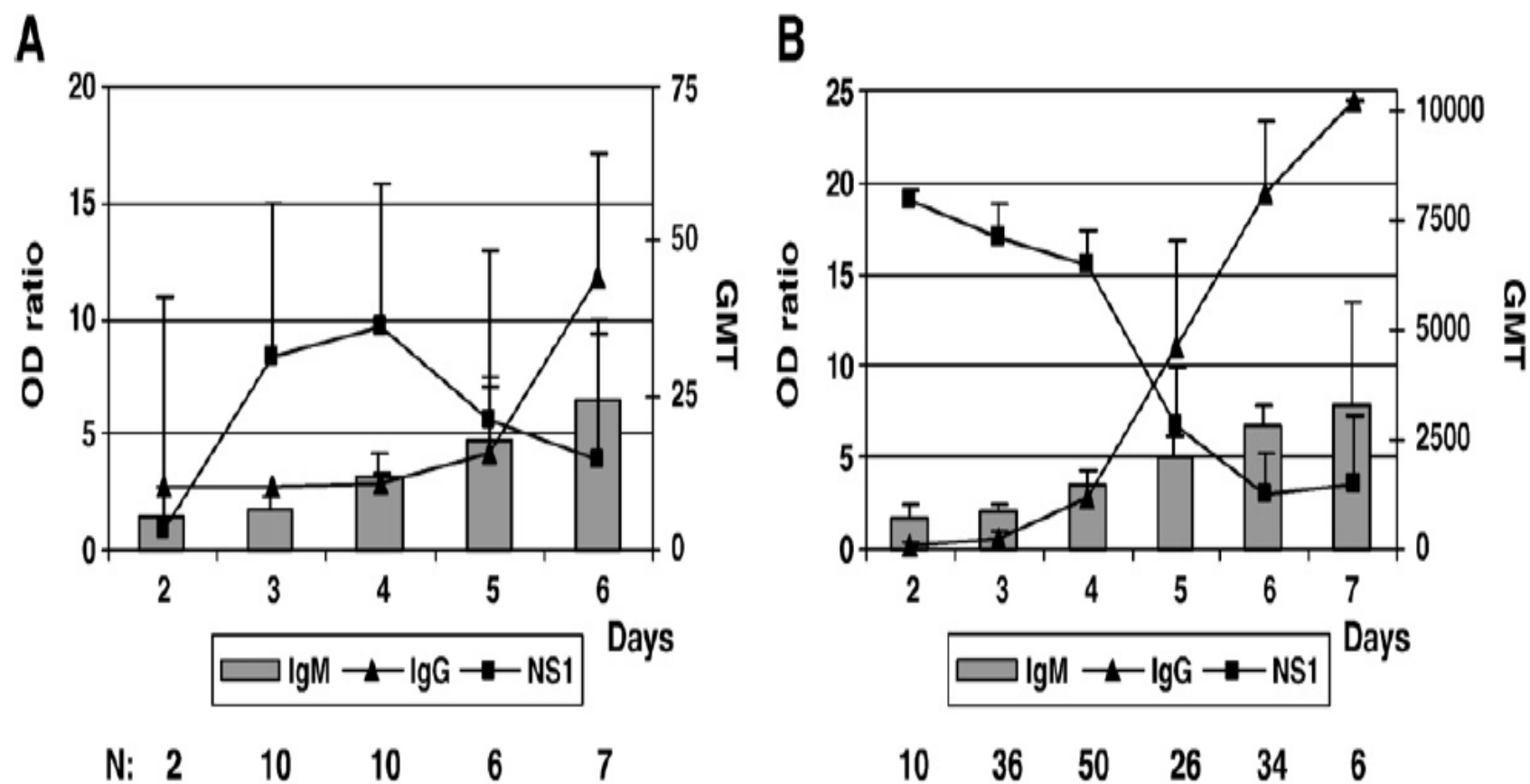Onset of symptoms (days)

WHO Guideline 2009

Fig. 1. Kinetics of NS1 protein and antidengue IgM and IgG antibodies in serum samples from primary (A) and secondary (B) cases. The principal axis y shows the NS1 and IgM OD mean ratio and 95% CIs. The GMT of the IgG antibodies and 95% CI are shown in secondary axis y. N = number serum samples collected each day.

Figure 1.4 Suggested dengue case classification and levels of severity

DENGUE ± WARNING SIGNS　　　　　　　　**SEVERE DENGUE**

with warning signs

without
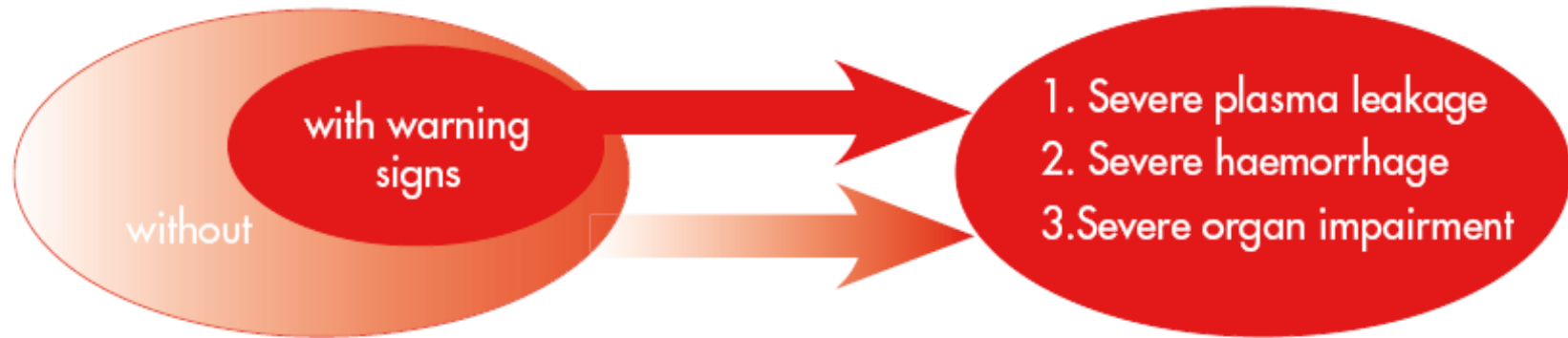
1. Severe plasma leakage
2. Severe haemorrhage
3. Severe organ impairment

CRITERIA FOR DENGUE ± WARNING SIGNS

Probable dengue

live in /travel to dengue endemic area.
Fever and 2 of the following criteria:

- Nausea, vomiting
- Rash
- Aches and pains
- Tourniquet test positive
- Leukopenia
- Any warning sign

Laboratory-confirmed dengue

(important when no sign of plasma leakage)

Warning signs*

- Abdominal pain or tenderness
- Persistent vomiting
- Clinical fluid accumulation
- Mucosal bleed
- Lethargy, restlessness
- Liver enlargment >2 cm
- Laboratory: increase in HCT concurrent with rapid decrease in platelet count

*(requiring strict observation and medical intervention)

CRITERIA FOR SEVERE DENGUE

Severe plasma leakage

leading to:

- Shock (DSS)
- Fluid accumulation with respiratory distress

Severe bleeding

as evaluated by clinician

Severe organ involvement

- Liver: AST or ALT >=1000
- CNS: Impaired consciousness
- Heart and other organs

Who Guideline 2009

Dengue Case Management

Assessment

Presumptive Diagnosis:
Live in / travel to endemic area plus
Fever and two of the following:
• Anorexia and nausea
• Rash
• Aches and pains
• Warning signs
• Leucopenia
• Tourniquet test positive

Lab.confirmed dengue
(important when no sign of plasma leakage)

Warning signs:
• Abdominal pain or tenderness
• Persistent vomiting
• Clinical fluid accumulation
• Mucosal bleed
• Lethargy; restlessness
• Liver enlargement >2cm
• Laboratory: Increase in HCT concurrent with rapid decrease of platelet count
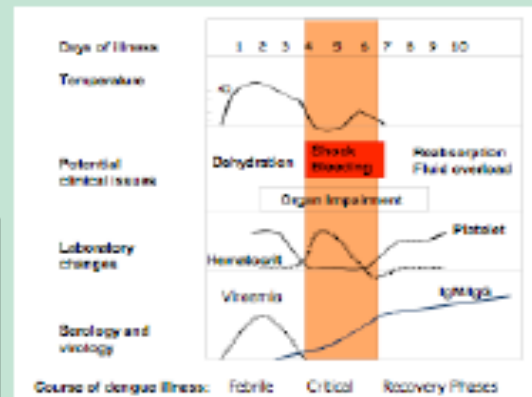
Classification

negative

positive

Co-existing conditions
Social circumstances → positive

negative

| Dengue without warning signs | Dengue with warning signs | Severe Dengue |

| Group A | Group B | Group C |
| May be sent home | Referred for in-hospital care | Require emergency treatment |

RCPT guideline- Thailand
Indications for hospitalization (one of the followings):

- - Signs/symptoms that physicians considers make the admission of the patient necessary **(eg. intractable nausea/vomiting, serious illness etc.)**
  - **Significant bleeding** eg. gastrointestinal bleeding etc.
  - Dengue shock syndrome (DSS)
  - **Hematocrit > 50 %**
  - **Platelet $\leq$ 20,000/ mm3 ($\leq$ 20x10^9/L)**
  - **AST or ALT > 500 IU/mL**
  - Acute renal failure, hepatic failure, heart failure, alteration of consciousness, severe hypoxemia
  - **Pregnant woman**
  - **Morbid obesity**
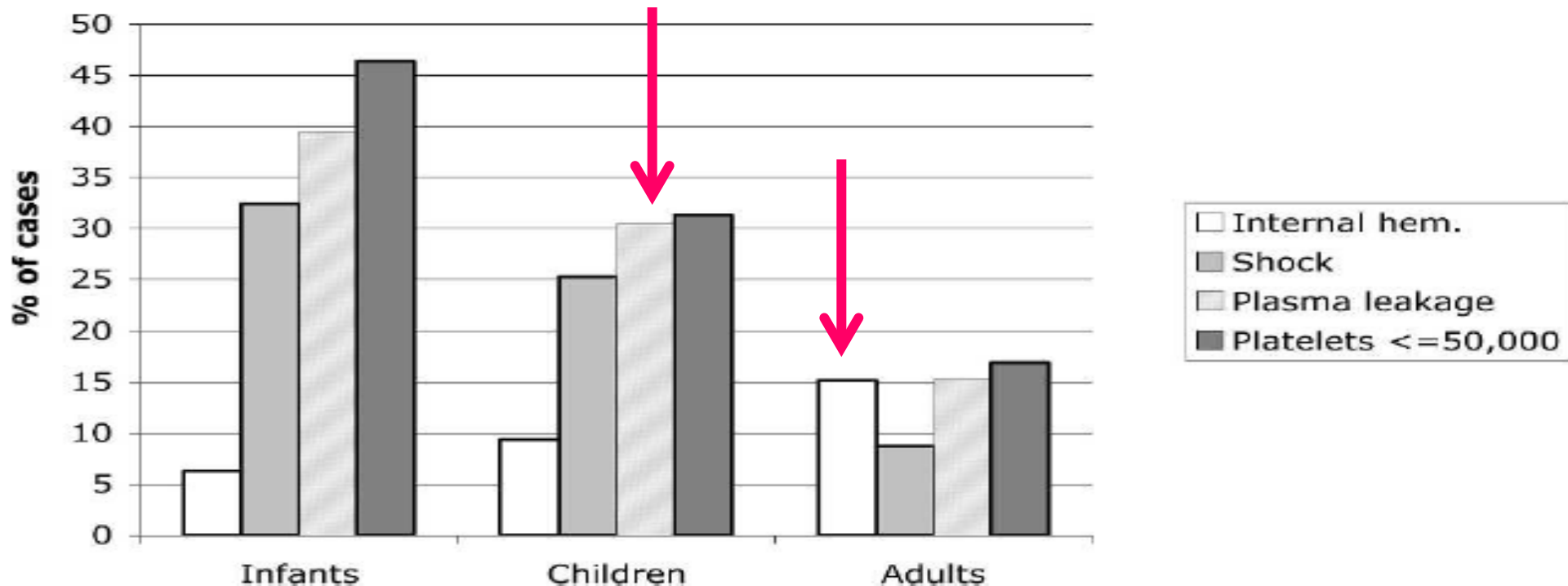 - Patients could not follow up as out-patient setting

FIGURE 2. Prevalence of severe clinical manifestations of dengue in infants, children, and adults. The percentage of cases in each age group presenting with internal hemorrhage, shock, signs of plasma leakage (hemoconcentration, pleural effusion, and/or ascites), and/or marked thrombocytopenia (platelet count $\leq$ 50,000/mm^3) was plotted, as indicated. Infants, < 1 year old; children, 1–14 years old; adults, > 14 years old.

DIFFERENCES IN DENGUE SEVERITY IN INFANTS, CHILDREN, AND ADULTS IN A 3-YEAR HOSPITAL-BASED STUDY IN NICARAGUA
                    SAMANTHA NADIA HAMMOND: Am J Trop Med Hyg 2005

If major bleeding occurs it is usually from the gastrointestinal tract, and/or vagina in adult females.
Internal bleeding may not become apparent for many hours until the first black stool is passed.

Patients at risk of major bleeding are those who:
   – **have prolonged/refractory shock;**
   – **have hypotensive shock and renal or liver failure and/or severe**
       and persistent metabolic acidosis;
   – **are given non-steroidal anti-inflammatory agents;**
   – **have pre-existing peptic ulcer disease;**
   – **are on anticoagulant therapy;**
   – have any form of trauma, including intramuscular injection.

Patients with haemolytic conditions are at risk of acute haemolysis with haemoglobinuria and will require blood transfusion.

Gastroduodenoscopic findings in 26 Dengue patients

Findings	No. of cases	%
DU	11	**42.3**
GU + superficial gastritis	3	11.5
DU + superficial gastritis	3	11.5
GU + DU + superficial gastritis	3	11.5
GU or DU or hemorrhagic gastritis or erosion	6	23

Tsai CJ; Am J Gastroenterology 1991

TABLE 1
Endoscopic findings and rates of incidence in the 97 patients with upper gastrointestinal bleeding*

Endoscopic findings	No. of cases (incidence, %)	Overall incidence, %
HG	24 (24.7)	HG = 67.0
HG + GU	23 (23.7)	
HG + DU	10 (10.3)	
HG + DU + GU	5 (5.2)	
HG + EU	2 (2.1)	
HG + GU + EU	1 (1.0)	
GU	21 (21.6)	GU = 57.7
GU + HG	23 (23.7)	
GU + DU	6 (6.2)	
GU + DU + HG	5 (5.2)	
GU + EU + HG	1 (1.0)	
DU	5 (5.2)	DU = 26.8
DU + HG	10 (10.3)	
DU + GU	6 (6.2)	
DU + GU + HG	5 (5.2)	
EU + HG	2 (2.1)	EU = 3.1
EU + GU + HG	1 (1.0)	

* HG = hemorrhagic and/or erosive gastritis; GU = gastric ulcer; DU = duodenal ulcer; EU = esophageal ulcer.

Patients having PU with recent hemorrhage require more transfusions with PRBCs and FFP for management of UGI bleeding than do those without recent hemorrhage.

PU with recent hemorrhage is encountered during an endoscopic procedure, endoscopic injection therapy is not an effective adjuvan treatment of hemostasis in dengue patients with UGI bleeding.

Chiu YC, Am J Trop Med 2005

Severe bleeding can be recognized by:

    – persistent and/or severe overt bleeding in the presence of unstable haemodynamic status, regardless of the haematocrit level;

    – **a decrease in haematocrit after fluid resuscitation** together with unstable haemodynamic status;

    – refractory shock that fails to respond to consecutive fluid resuscitation of 40-60 ml/kg;

    – **hypotensive shock with low/normal haematocrit** before fluid resuscitation;

    – persistent or worsening metabolic acidosis <u>+ </u>a well-maintained systolic blood pressure, especially in those with severe abdominal tenderness and distension.

Hemorrhagic Dengue with Spontaneous Splenic Rupture: Case Report and Review

Dengue fever is an endemic mosquito-borne viral disease of the tropical and subtropical regions of the world that is transmitted by the bite of *Aedes aegypti* mosquitoes. All four dengue serotypes cause a variety of clinical manifestations such as sudden onset of fever with chills, headache, retro-orbital pain, general malaise, myalgias, arthralgias, cutaneous erythema, early neutropenia with lymphocytosis, thrombocytopenia, and mild elevation of liver enzymes.

A more-severe clinical form of the disease is the dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS), which is characterized by hemoconcentration (hematocrit increased >20%), thrombocytopenia (platelet count, <100,000/mm^3), vascular collapse, abdominal pain, and hemorrhagic manifestations. Other manifestations of the disease include circulatory failure, respiratory distress, pleural effusion, and encephalopathy. Laboratory test results reveal severe thrombocytopenia, hemoconcentration, and signs of consumption coagulopathy (e.g., hypofibrinogenemia and prolonged partial thromboplastin
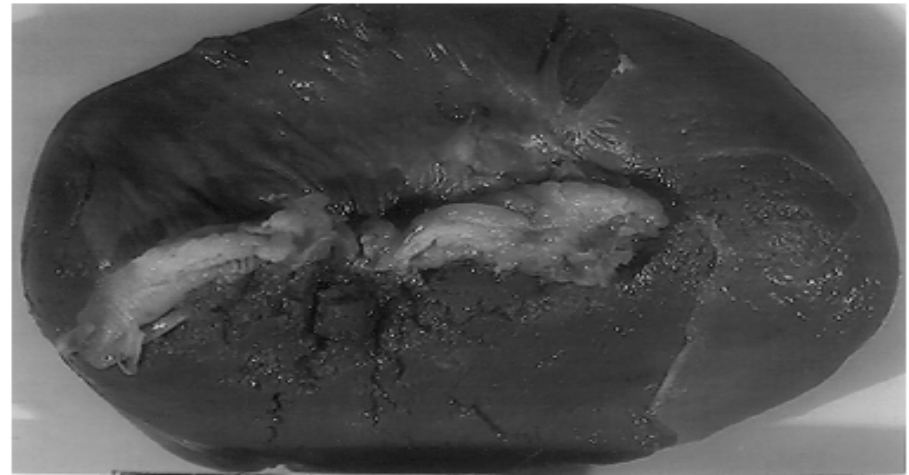

Figure 1. Spleen of a 23-year-old female who had hemorrhagic dengue with spontaneous splenic rupture. The spleen weighed 100 g and measured 10.5 × 7.5 × 4.5 cm. The serosal surface was a brilliant reddish-brown and had areas of rupture measuring up to 0.4 cm. Cut sections were friable and hemorrhagic.

A FATAL CASE OF SPONTANEOUS RUPTURE OF THE SPLEEN DUE TO DENGUE VIRUS INFECTION: CASE REPORT AND REVIEW. Southeast Asian J Trop Med Hyg 2008 Apatcha Pungjitprapai, Terapong Tantawichien.

Lack of efficacy of prophylactic platelet transfusion for severe thrombocytopenia in adults with acute uncomplicated dengue infection.

Lyn DC; Clin Infect Dis 2009

Thrombocytopenia in dengue infection raises concerns about bleeding risk. Of 256 patients with dengue infection who developed **thrombocytopenia (platelet count, < 20 x 10^3 platelets/microL)** 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.**

-Cardiovascular

- Shock: Plasma leakage in DHF/DSS

Volume overload/ pulmonary edema

Decreased EF, diastolic volume, ST-T change

Co-morbidity- CHF, coronary heart disease

- Cardiac arrhythmia

Sinus bradycardia

APC, PVC, 1st degree AV block,

2nd degree AV block Mobitz type 1

Apichai K; Intensive Care Med 2003
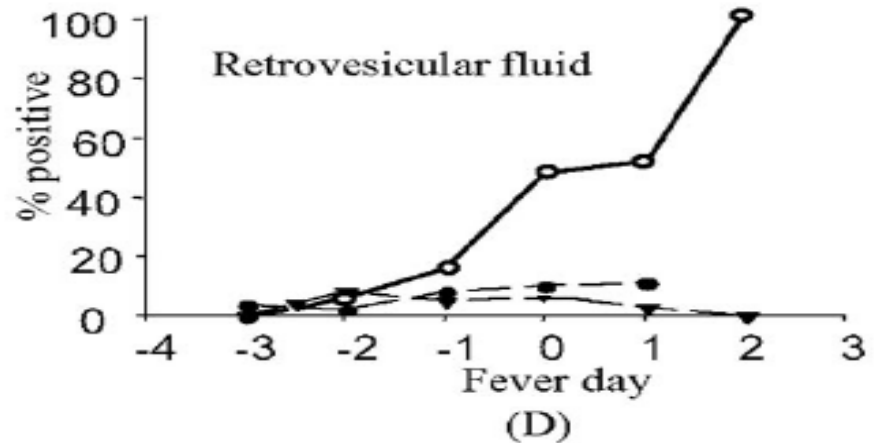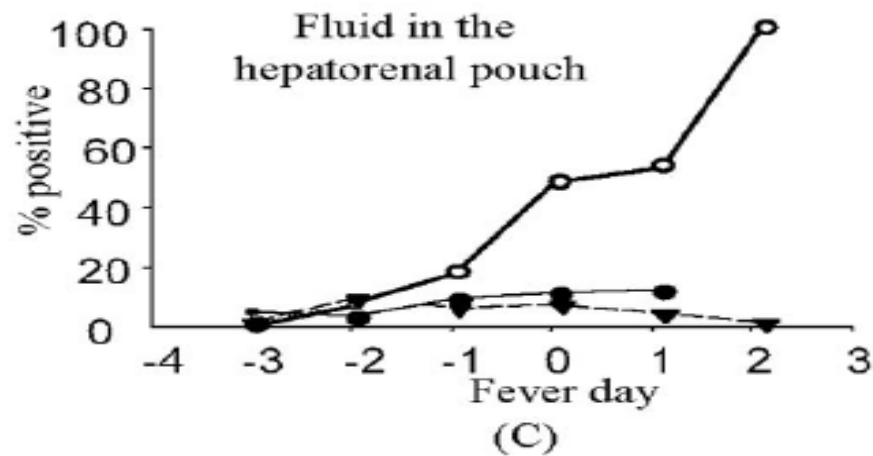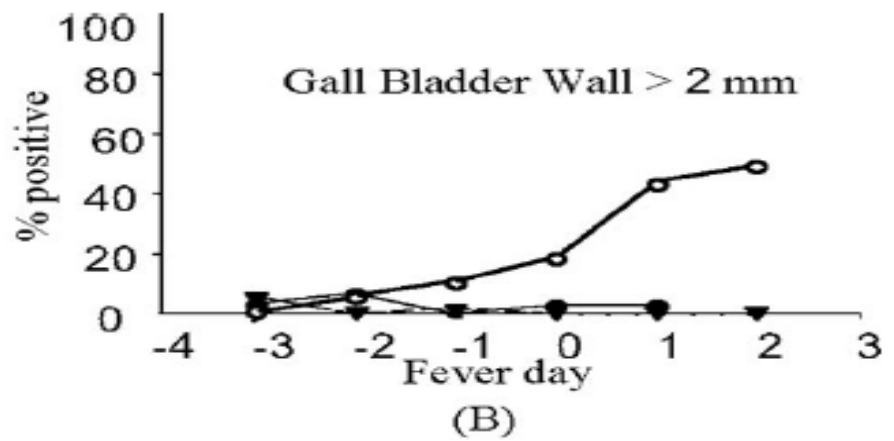V. LA-ORKHUN; Annals of Tropical Paediatrics (2011) 31, 123–128
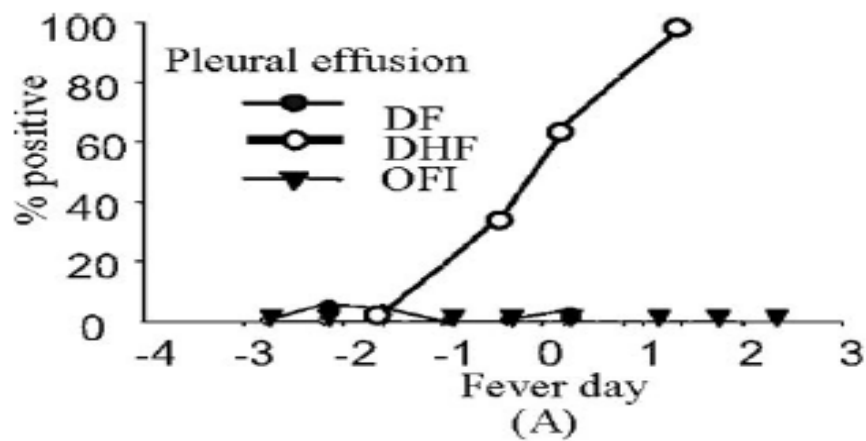
FIGURE 3. Percentages of patients with various ultrasound findings indicative of plasma leakage during the course of illness: (A) pleural effusion, (B) gallbladder wall thickness over 2 mm, (C) fluid in the hepatorenal pouch, (D) retrovesicular fluid. Empty circle: DHF, filled circle: DF, filled triangle: OFI.

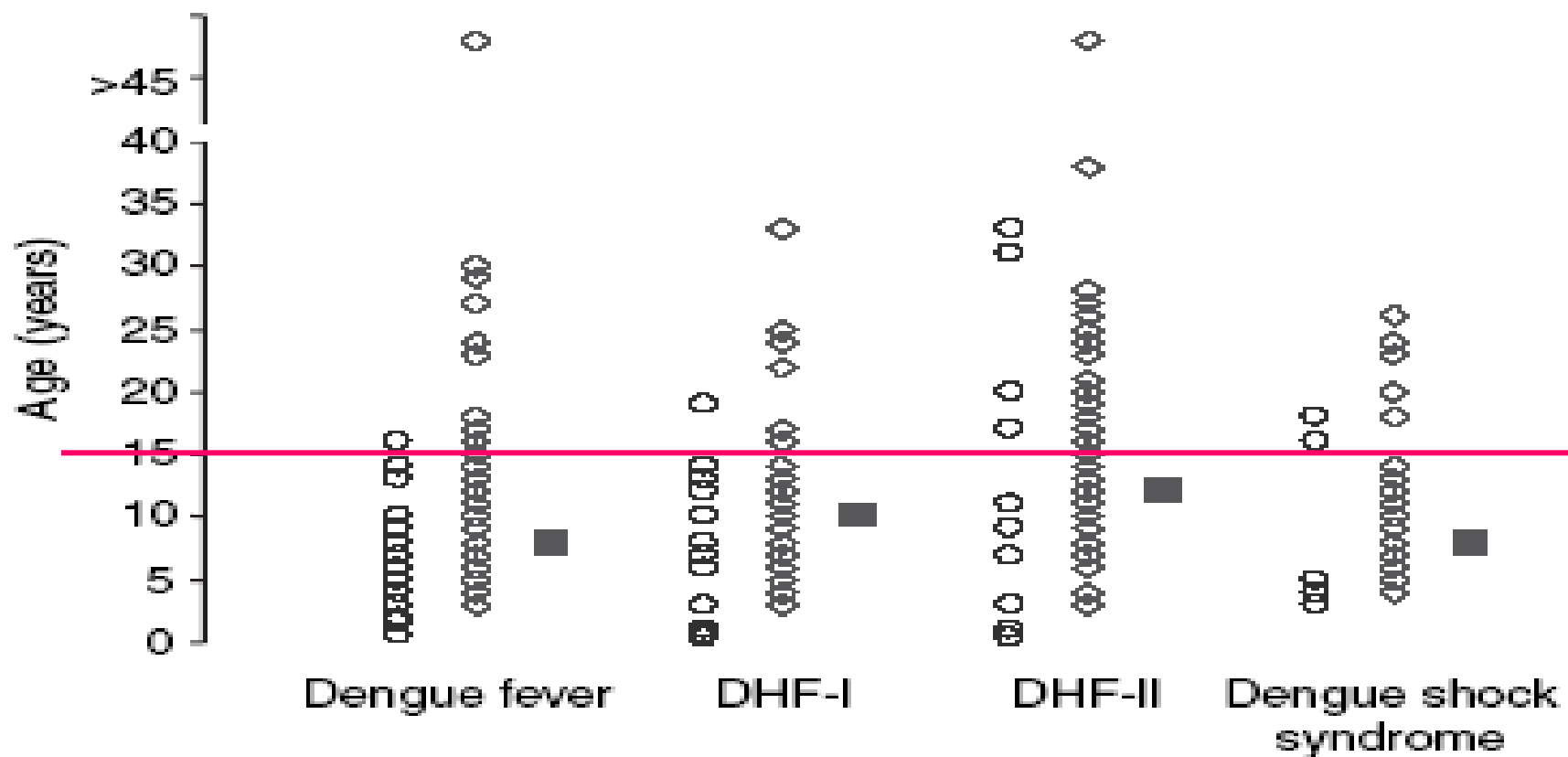**Figure 1** Age distribution of patients with primary (○) and secondary (◇) dengue infection classified according to disease severity. DHF = dengue haemorrhagic fever. The average was calculated as median (■).
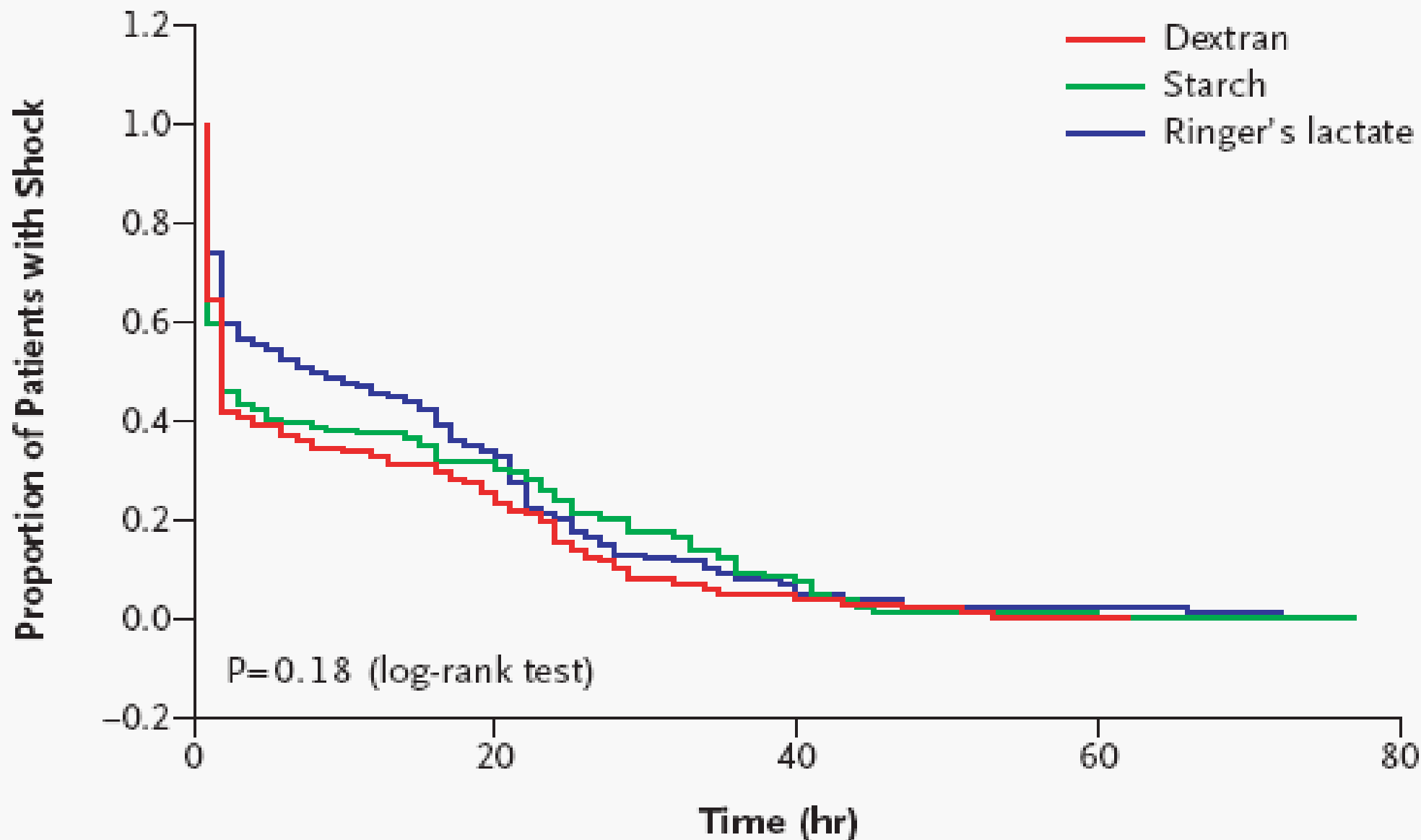
Figure 2. Kaplan–Meier Curves for Time from Study Entry to Initial (Panel A) and Sustained (Panel B) Cardiovascular Stability among Children in Group 1, According to the Resuscitation Fluid Received.

Stage II of dengue hemorrhage fever (plasma leakage syndrome)			
Normal blood pressure and pulse pressure >20 mmHg	**Hypotension and/or pulse pressure ≤20 mmHg**	**Shock**	**Persistent shock despite adequate crystalloid replacement**
<u>Methods</u> IV 5%D saline, NSS for patients without shock, (intravenous fluid replacement only in patients with vomiting, or cannot tolerate oral diet or ORS), with rate of 40-80 ml/hr and adjust according to vital signs, Hct, urine output, urine sp.gr. If patients turn to critical phase, the rate of fluid replacement should be adjusted as indicated by vital signs, Hct, urine output.	<u>Methods</u> IV isotonic crystalloid e.g. 0.9% saline or RLS 5-7 ml/kg/hr for 1-2 hr ● If clinical setting and parameters are improved, decrease the rate to 3-5 ml/Kg/hr for 2-4 hr, and then 2-3 ml/Kg/hr until stable vital signs. ● If clinical setting and parameters are worsened or not improved, increase the rate to 7-10 ml/Kg/hr for 1-2 hr and re-evaluate within 2-4 hr. If not improved, patients should be treated as "shock."	<u>Methods</u> IV isotonic crystalloid e.g. 0.9% saline or RLS 10-20 ml/kg/hr (500-1000 ml) for 1-2 hr ● If clinical setting and parameters are improved, decrease the rate to 5-7 ml/Kg/hr for 1-2 hr and then gradually decrease the rate. ● If clinical setting and parameters are worsened or not improved, change solution to colloid. e.g. 5% albumin, dextran, or FFP 10 ml/kg/hr for 1 hr. If not improved, patients should be treated as "persistent shock despite adequate crystalloid replacement."	<u>Methods</u> Evaluate for other co-morbidities. e.g. severe bleeding, metabolic acidosis, severe sepsis, pneumothorax Start vasopressors e.g. norepinephrine 0.1-0.2 mcg/kg/min. Adjust dosage every 10-15 min (max dose 1-2 mcg/kg/min), and decrease dosage when clinical setting and parameter are improved. <u>Note</u> Patients with shock should have their vital signs and parameters closely monitored until resolution of shock.

Causes of fluid overload are:

- excessive and/or too rapid intravenous fluids;
- incorrect use of hypotonic rather than isotonic crystalloid solutions;
- inappropriate use of large volumes of intravenous fluids in patients with unrecognized severe bleeding;
- inappropriate transfusion of fresh-frozen plasma, platelet concentrates and cryoprecipitates;
- continuation of intravenous fluids after plasma leakage has resolved (24–48 hours from defervescence);
- co-morbid conditions such as congenital or ischaemic heart disease, chronic lung and renal diseases.

WHO Guideline 2009

GI Manifestations in dengue

- **Nausea/ vomiting**
- **Diarrhea**
- **GI bleeding**
- **Liver complication:**

    Abnormal transaminase (increased AST and ALT)

    Viral factor (DEN3,DEN4)

    Prolonged shock , ischemic hepatitis

    Reye's syndrome

    Drug-induced liver injury

    Co-infection: Viral hepatitis A, B,C,E

    Pre-existing liver diseases
- **Ascites, acute appendicitis**

Liver function test in DF/DHF patients

	Kuo CH*	Kalaganaroaj S**		Tantawichien T.	
	DF n=230	DF n=20	DHF n=21	DF n=38	DHF n=30
Age:Mean±SD	41±12	3.7±1	4.3±1.2	28.6±13.2	23.4+7.6
AST : Mean±SD	220±341	64±46	124±166	258±436	399±554
Range	17-3210			17-2128	15-2580
ALT : Mean±SD	146±178	35±18	51±59	184±255	261+321
Range	8-1177			19-1171	3-1382
Bilirubin :					
Abnormal/range	7.2%0.2-35			0%	1 case (5)
Akaline phasphatase					
Abnormal/range	16%320-536			all<1.5	all<1.5

*Kuo CH; Am J Trop Med Hyg 1992
**Kalayanarooj S; JID 1997
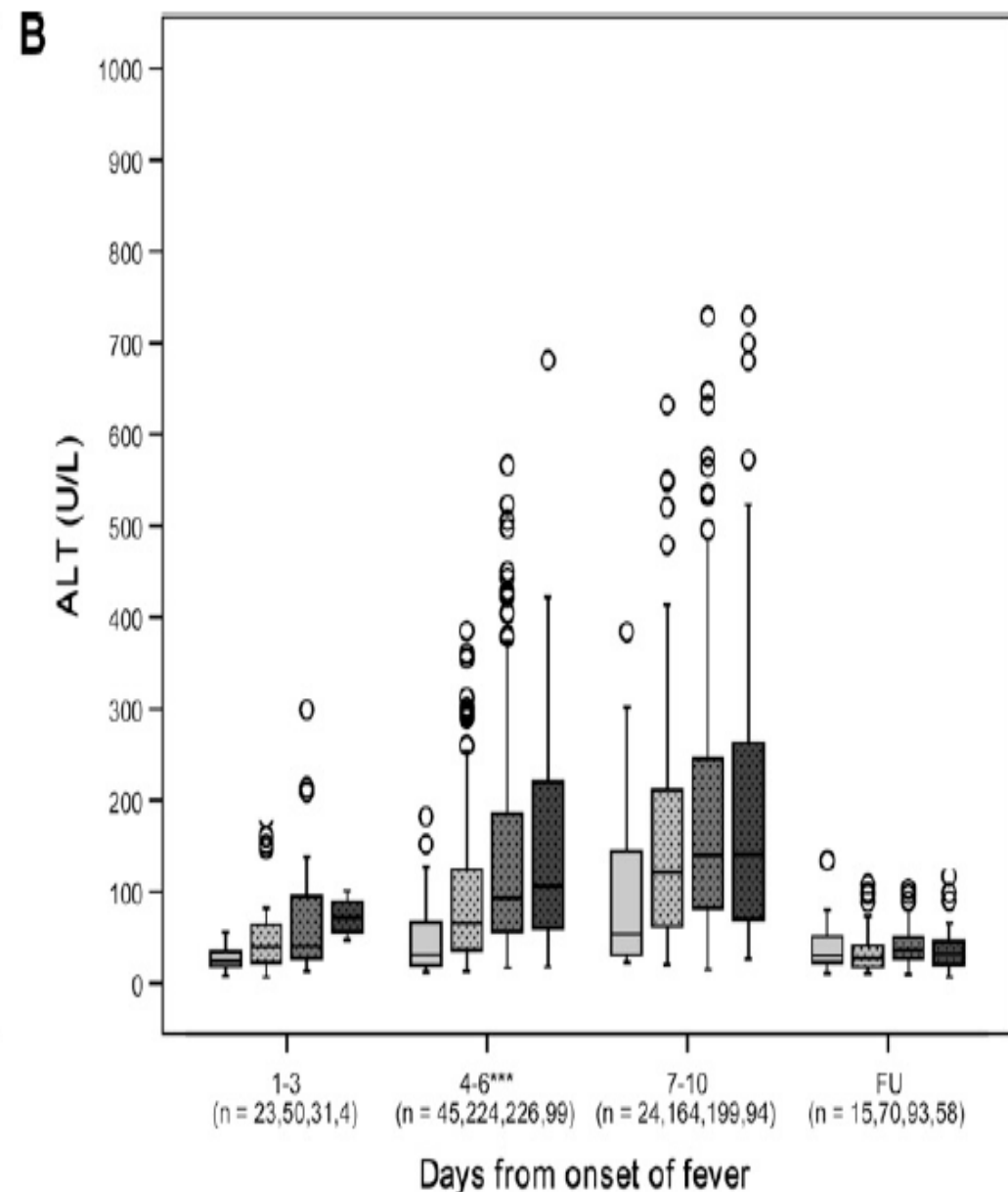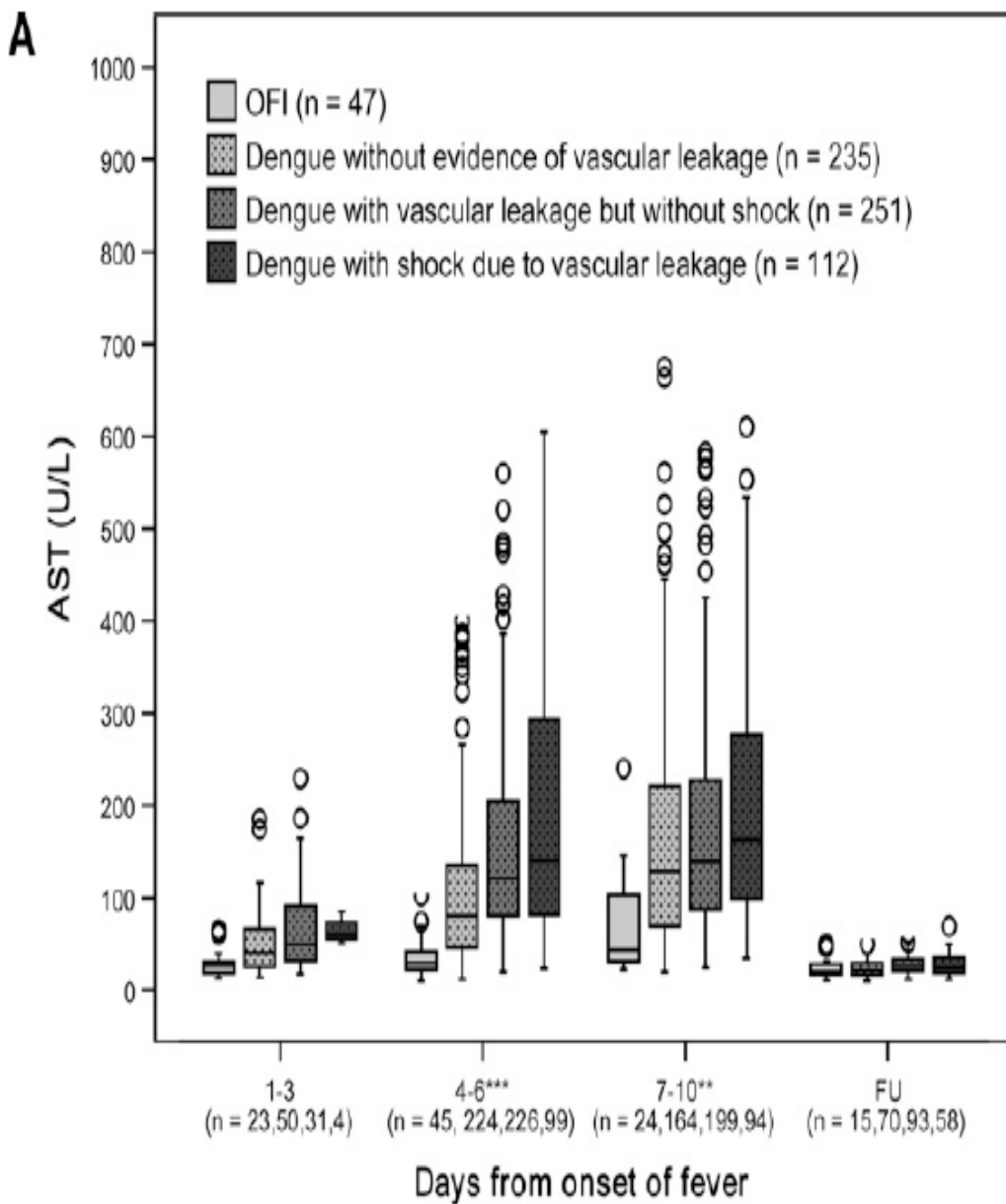
Liver Involvement Associated with Dengue Infection in Adults in Vietnam

Dinh The Trung,* Le Thi Thu Thao, Tran Tinh Hien, Nguyen The Hung, Nguyen Ngoc Vinh,
Pham Tran Dieu Hien, Nguyen Tran Chinh, Cameron Simmons, and Bridget Wills

TABLE 3

Effect of chronic hepatitis B virus co-infection on bleeding severity and transaminase levels in 618 adults with dengue*

Characteristic	Chronic HBV co-infection (n = 69)	No evidence for HBV infection (n = 549)	P†
Severe bleeding	7 (10)	44 (8)	0.55
Mucosal bleeding or any severe bleeding	46 (67)	312 (57)	0.12
AST in critical period‡	122 (28–548)	105 (30–483)	0.07
ALT in critical period‡	118 (29–520)	81 (22–385)	0.001
AST in convalescent period§	152 (58–443)	137 (41–563)	0.68
ALT in convalescent period§	144 (50–637)	135 (30–581)	0.21

*Values are no. (%) for categorical variables and median (90% range) for continuous variables. HBV = hepatitis B virus; AST = aspartate aminotransferase; ALT = alanine aminotransferase.
† Chi-square test or Fisher's exact test or Mann-Whitney test were used as appropriate.
‡ No. of patients with and without chronic HBV co-infection in critical period are 62 and 498, respectively.
§ No. of patients with and without chronic HBV co-infection in convalescent period are 56 and 417, respectively.

-**Increased levels of AST, ALT, G-GT have been observed in patients with episodes of bleeding**

Case Report

Fatal Fulminant Hepatic Failure in a Diabetic with Primary Dengue

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We report a 49-year-old diabetic with dengue hemorrhagic fever who developed fulminant hepatitis, severe coagulopathy, shock, and refractory metabolic acidosis and died on the eighth day of illness. This is the only second report of an adult with fatal fulminant hepatic failure due to dengue, and the first case arising from a primary dengue infection.
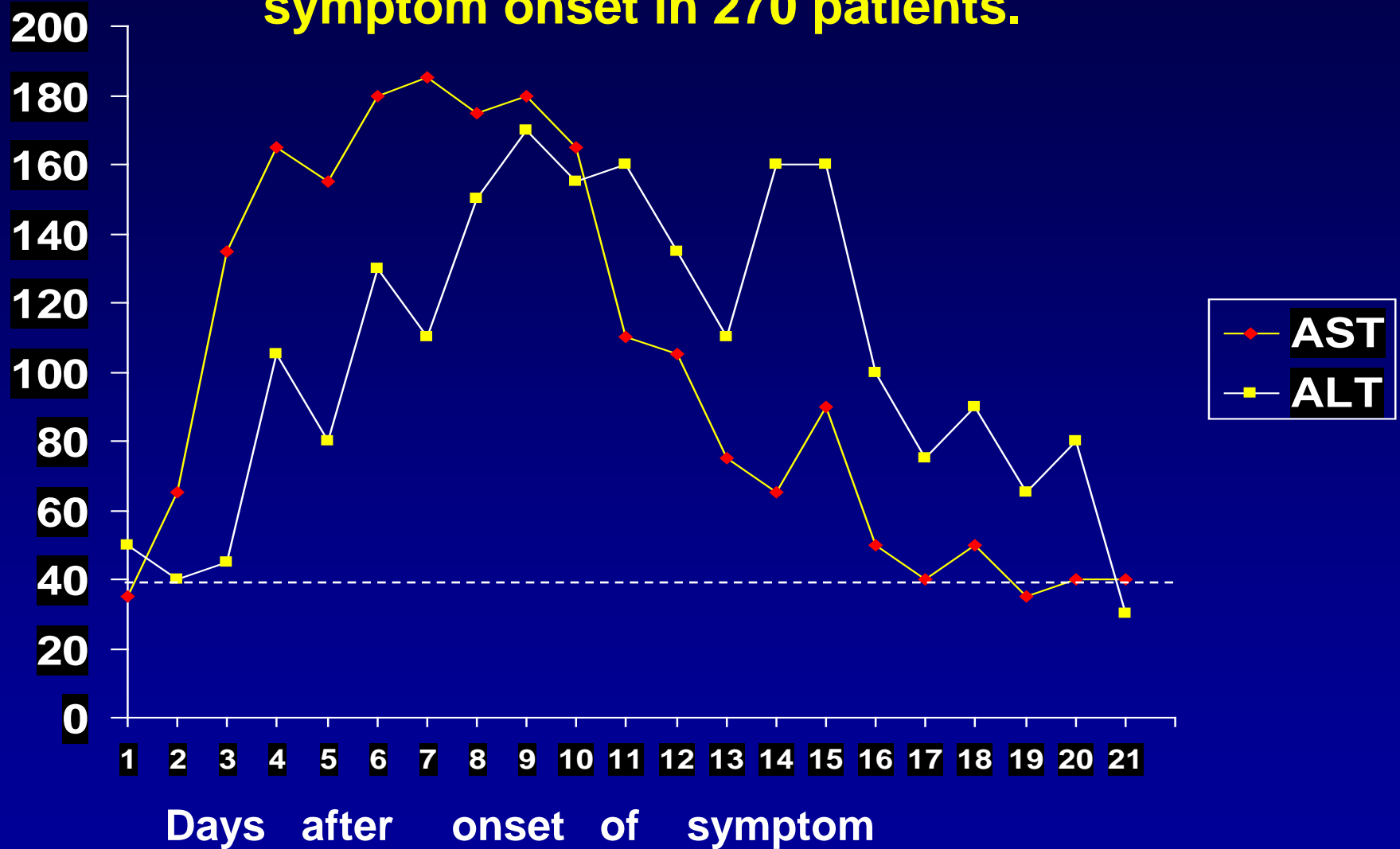
Recent suggestions for the treatment of dengue patients with acute liver failure

N-acetylcysteine (NAC)
Providing temporary liver support – Artificial liver support

Treeprasertsuk S; Southeast Asian J Trop Med Public Health 2015

Mean transaminase levels (U/l) in relation to days after symptom onset in 270 patients.

Days after onset of symptom

Kuo CH; Am J Trop Med Hyg 1992

Clinical Characteristics, Risk Factors, and Outcomes in Adults Experiencing DHF Complicated with Acute Renal Failure

TABLE 2
Demographics, clinical characteristics, and outcomes of the included DHF patients*

Variable	Patients with acute renal failure ($N = 10$)	Patients without acute renal failure ($N = 294$)	P
Age (years)			0.002
Mean ($\pm$SD)	65.3 ($\pm$12.9)	52.9 ($\pm$13.8)	
Median (range)	69.5 (33–78)	55 (19–88)	
Male (%)	10 (100)	127 (43.2)	< 0.001
Underlying disease† (%)			
Diabetes mellitus	1 (10)	60 (20.4)	0.693
Hypertension	6 (60)	85 (28.9)	0.071
Previous stroke	4 (40)	21 (7.1)	0.005
Chronic renal disease	2 (20)	9‡ (5.7)	0.046
Severity of DHF (%)			< 0.001
Non-shock DHF (Grade I and II)	2 (20)	284 (96.6)	
DSS (Grade III or IV)	8§ (80)	10 (3.4)	
Length of fever, median day (range)	6.5 (0–7)	4.5 (0–10)	0.105
Gastrointestinal bleeding (%)	8 (80)	45 (15.3)	< 0.001
Rhabdomyolysis¶ [n/N (%)]	2/2 (100)	1/9 (11.1)	0.055
Concurrent bacteremia [n/N (%)]	3/7 (42.8)	3/67 (4.5)	0.009
Gallbladder swelling [n/N (%)]	3/5 (60)	87/157 (55.4)	1.0
Ascites [n/N (%)]	1/5 (20)	63/157 (40.1)	0.649
Pleural effusion [n/N (%)]	7/10 (70)	79/208 (37.9)	0.053
Fatality (%)	6 (60)	0	< 0.001

Neurological manifestations in dengue virus infection

Headache, dizzeness, delirium, mental irritability
Encephalopathy, seizure, meningism,coma
Delay symptoms : paralysis, dementia,epilepsy, psychosis,
optic neuritis (post-infectious encephalopathy)

Central nervous system involvement in dengue
A study in fatal cases from a dengue endemic area

F.M.C. Arau´jo,Neurology 2012

46.3% encephalitis,34.1% meningoencephalitis, and 19.5% meningitis, giving a frequency of 48.8% of the 84 dengue-positive cases.

Proposed definitions for neurological features of dengue

Dengue diagnostic test /confirming acute dengue virus infection(WHO), AND one of the following clinical categories:

Dengue CNS involvement: one of the following:

impaired consciousness, neck stiffness, focal neurological signs, or seizure

Dengue encephalopathy: Dengue CNS involvement, AND

• Presence of one of the following dengue complications: hepatic failure, metabolic acidosis, severe hyponatraemia, prolonged shock, DIC, or brain haemorrhage, AND

• Normal CSF (in brain haemorrhage, blood in CSF is possible)

Dengue encephalitis: Dengue CNS involvement, AND

• Presence of dengue virus RNA, IgM, or NS1 antigen in CSF, AND

• CSF pleocytosis without other neuroinvasive pathogens

Immune-mediated dengue CNS involvement

Other or non-specified dengue CNS involvement

Dengue-associated neuromuscular complications: GBS, Rhabdomyolysis, Other or non-specified peripheral NMcomplications

Dengue-associated neuro-ophthalmic complications: Clinical symptom, AND

• Optic neuropathy, maculopathy, retinal vasculitis, retinal haemorrhages, exudative retinal detachment, cotton wool spots, or signs of foveolitis or anterior uveitis

CLINICAL CHARACTERISTICS AND RISK FACTORS FOR CONCURRENT BACTEREMIA IN ADULTS WITH DENGUE HEMORRHAGIC FEVER LEE IK; J Trop Med Hyg 2004

Concurrent bacteremia (dual infection=5.5%) in patients DHF/DSS

100patients with DHF/DSS (7 with a dual infection and 93with DHF/DSS alone [controls])

Patients with a dual infection were older, and tended to have prolonged fever, higher frequencies of acute renal failure,
GI bleeding, altered consciousness, unusual dengue manifestations, and DSS.

Acute renal failure (odds ratio [OR] 51.45,P=0.002,
and prolonged fever (> 5 days) (OR 26.07,p=0.017 were independent risk factors for dual infection.
Bacteremia : *Klebsiella pneumoniae, enterococci, Moraxella, Rosemonas*

Concurrent Dengue and Malaria in Cayenne Hospital, French Guiana

Bernard Carme, Severine Matheus, Gerd Donutil, Olivia Raulin, Mathieu Nacher, and Jacques Morvan

Dengue–malaria co-infection reports are scarce. Of 1,723 consecutive febrile patients in Cayenne Hospital, 238 had dengue (174 early dengue fever cases) and 393 had malaria (371 acute malaria); 17 had both. Diagnosis of 1 of these 2 infections should not rule out testing for the other infection.

Co-infection with Dengue Virus and Pandemic (H1N1) 2009 Virus

To the Editor: Dengue is a mosquito-borne viral infection caused by 4 related dengue viruses. Each of these viruses is capable of causing classic dengue fever or dengue hemorrhagic fever (DHF), but may also cause non-specific febrile illnesses. As a result, dengue is often difficult to diagnose clinically, especially because peak dengue season often coincides with that of other common febrile illnesses in tropical regions (*1*). Concurrent outbreaks of influenza and dengue have been reported (*2,3*); this circumstance often leads to delayed recognition of the presence of one or other disease in the community.

Maternal Dengue and Pregnancy Outcomes
A Systematic Review

Sawyer H. Pouliot, MPH,* Xu Xiong, MD, DrPH,† Emily Harville, PhD,‡
Valerie Paz-Soldan, PhD,§ Kay M. Tomashek, MD, MPH, DTM,¶
Gerard Breart, MD,** and Pierre Buekens, MD, PhD††,‡‡

The case reports examined showed high rates of cesarean deliveries (44.0%) and pre-eclampsia (12.0%) among women with dengue infection during pregnancy, while the case series showed elevated rates of preterm birth (16.1%) and cesarean delivery (20.4%).

One comparative study found an increase in low birth weight among infants born to women with dengue infections during pregnancy, compared with infants born to noninfected women.

Vertical transmission was described in 64.0% and 12.6% of women in case reports and case series (respectively), as well as in one comparative study. The authors conclude that there is a risk of vertical transmission, but whether maternal dengue infection is a significant risk factor for adverse pregnancy outcomes is inconclusive.

Clinical and Laboratory Characteristics and Risk Factors for Fatality in Elderly Patients with Dengue Hemorrhagic Fever

Ing-Kit Lee, Jien-Wei Liu,* and Kuender D. Yang

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DHF :
66 elderly (mean 70 yrs)
VS and 241 adults
(mean 48 yrs).

Elderly had more
CRF,COPD, HT, previous
stoke, steroid use

TABLE 2

Symptoms and signs of 307 adult patients with dengue hemorrhagic fever*

Symptom/sign	Elderly (≥ 65 years) [N = 66 (%)]	Non-elderly (19–64 years) [N = 241 (%)]	P
Fever	60 (90.9)	239 (99.2)	0.002
Abdominal pain	22 (33.3)	130 (53.9)	0.003
Bone pain	24 (36.4)	147 (61)	< 0.001
Retro-orbital pain	8 (12.1)	28 (11.6)	1.0
Headache	30 (45.4)	111 (46.1)	1.0
Arthragia	7 (10.6)	35 (14.5)	0.545
Cough	25 (37.8)	84 (34.9)	0.665
Myalgia	12 (18.2)	35 (14.5)	0.446
Rashes†	10 (15.2)	83 (34.4)	0.002
Dizziness	16 (24.2)	42 (17.4)	0.217
Nausea/vomiting	11 (16.7)	37 (15.4)	0.848
Diarrhea	7 (10.6)	39 (16.2)	0.332
Any hemorrhagic 5sign‡	56 (84.8)	216 (89.6)	0.279
Petechiae	35 (53)	158 (65.6)	0.084
Gastrointestinal bleeding	21 (32)	47 (19.5)	0.044
Gum bleeding	11 (17)	52 (21.6)	0.492
Hematuria	7 (10.6)	21 (8.7)	0.632
Hemaptysis	9 (13.6)	21 (8.7)	0.245
Subconjunctival hemorrhage	3 (4.5)	3 (1.2)	0.116
Epistaxis	1 (1.5)	6 (2.5)	1.0
Menorrhage	0	8 (3.3)	

Clinical and Laboratory Characteristics and Risk Factors for Fatality in Elderly Patients with Dengue Hemorrhagic Fever

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DHF : 66 elderly (mean 70 yrs) VS and 241 adults (mean 48 yrs).
Elderly had more CRF,COPD, HT, previous stoke, steroid use
Results :
Elderly individuals had significantly
- concurrent bacteremia (P=0.049),
- gastrointestinal bleeding (P=0.044),
- acute renal failure (P= 0.001),
- pleural effusion (P= 0.010);
- prolonged prothrombin time (P= 0.025);
- lower mean hemoglobin level (P < 0.001);

longer hospitalization (P=0.049); and a higher fatality rate (P=0.006).
Multivariate analysis showed that only DSS (odd ratio 77.33, P 0.001) was an independent risk factor for fatality in elderly patients.