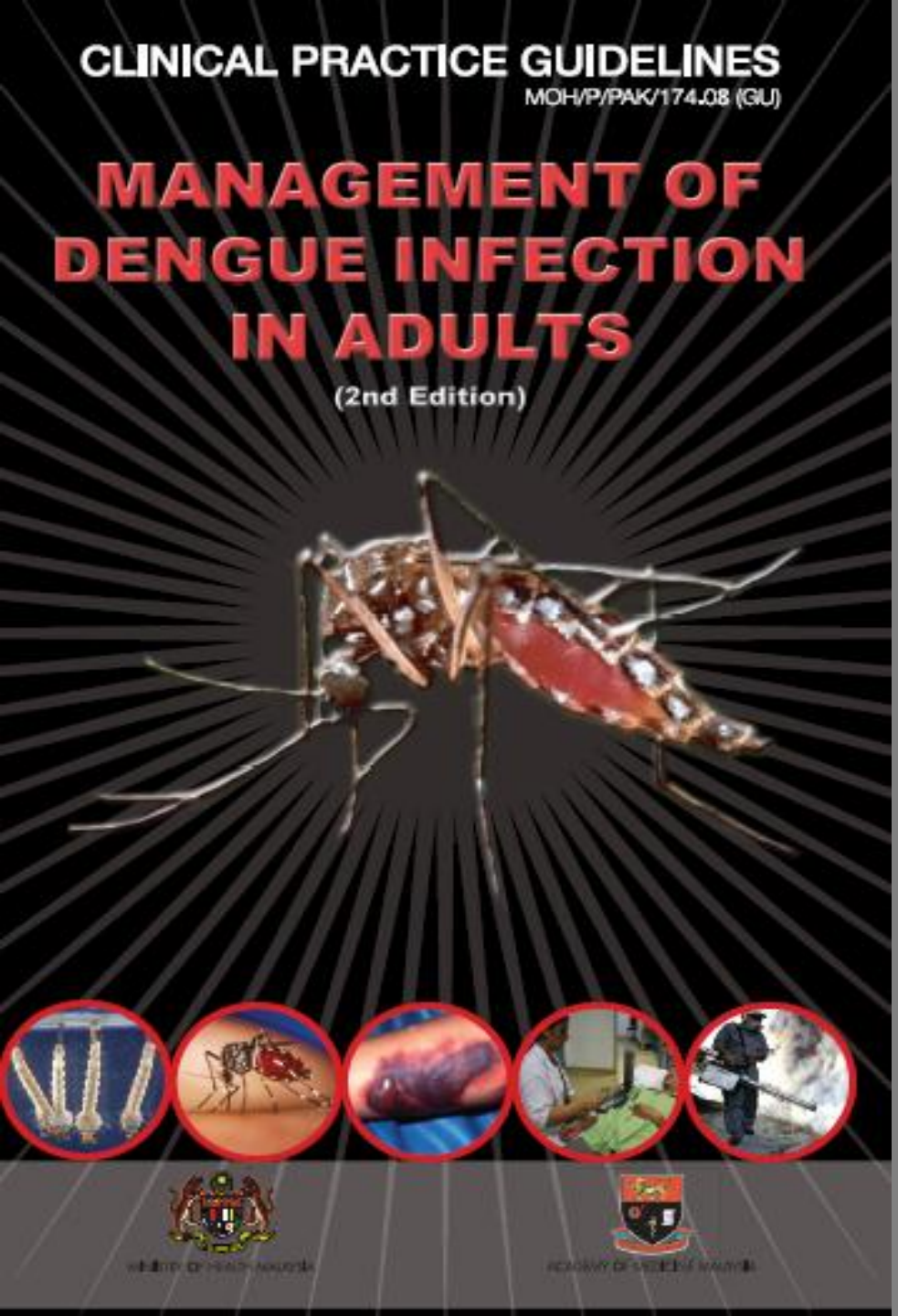
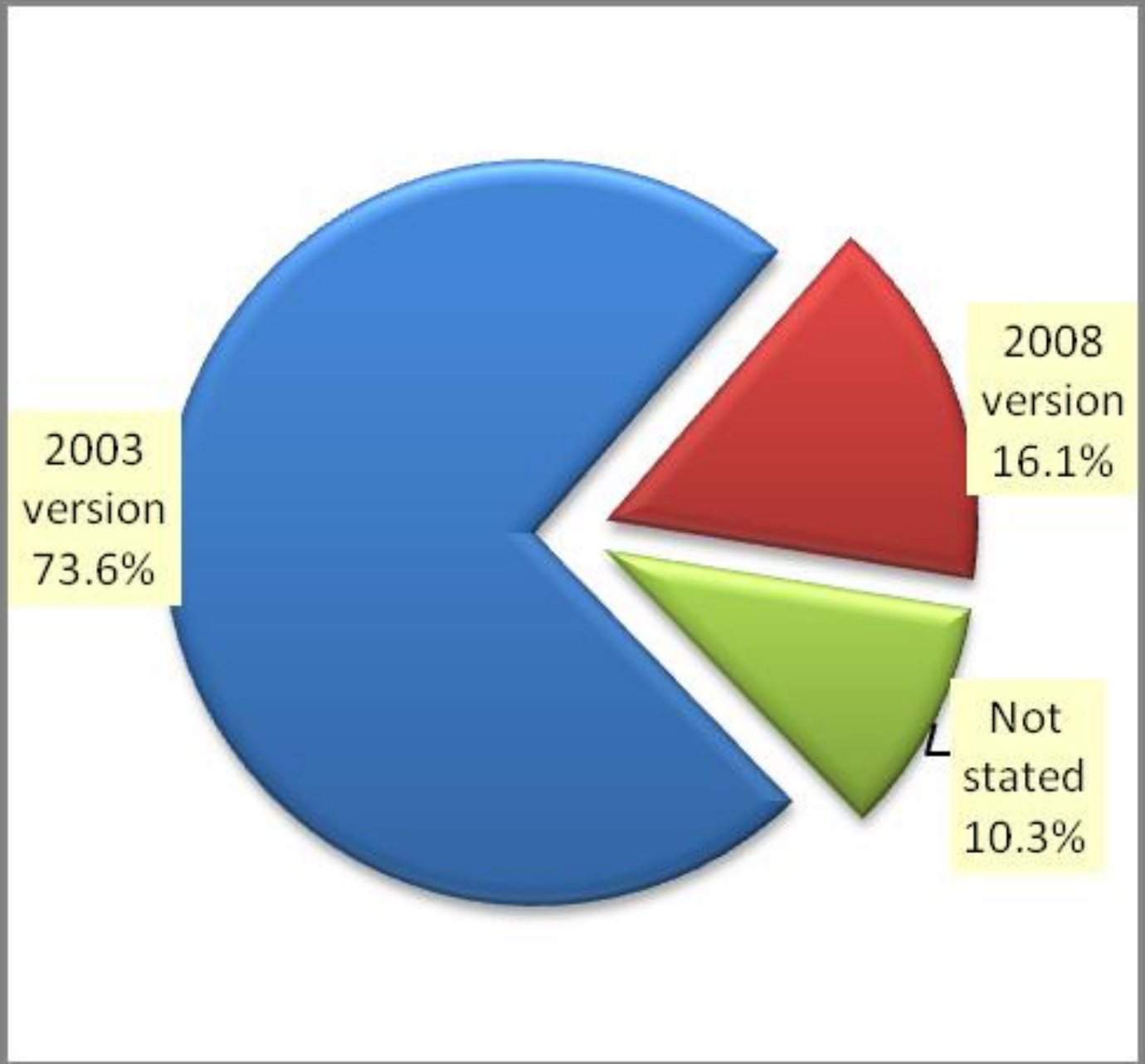
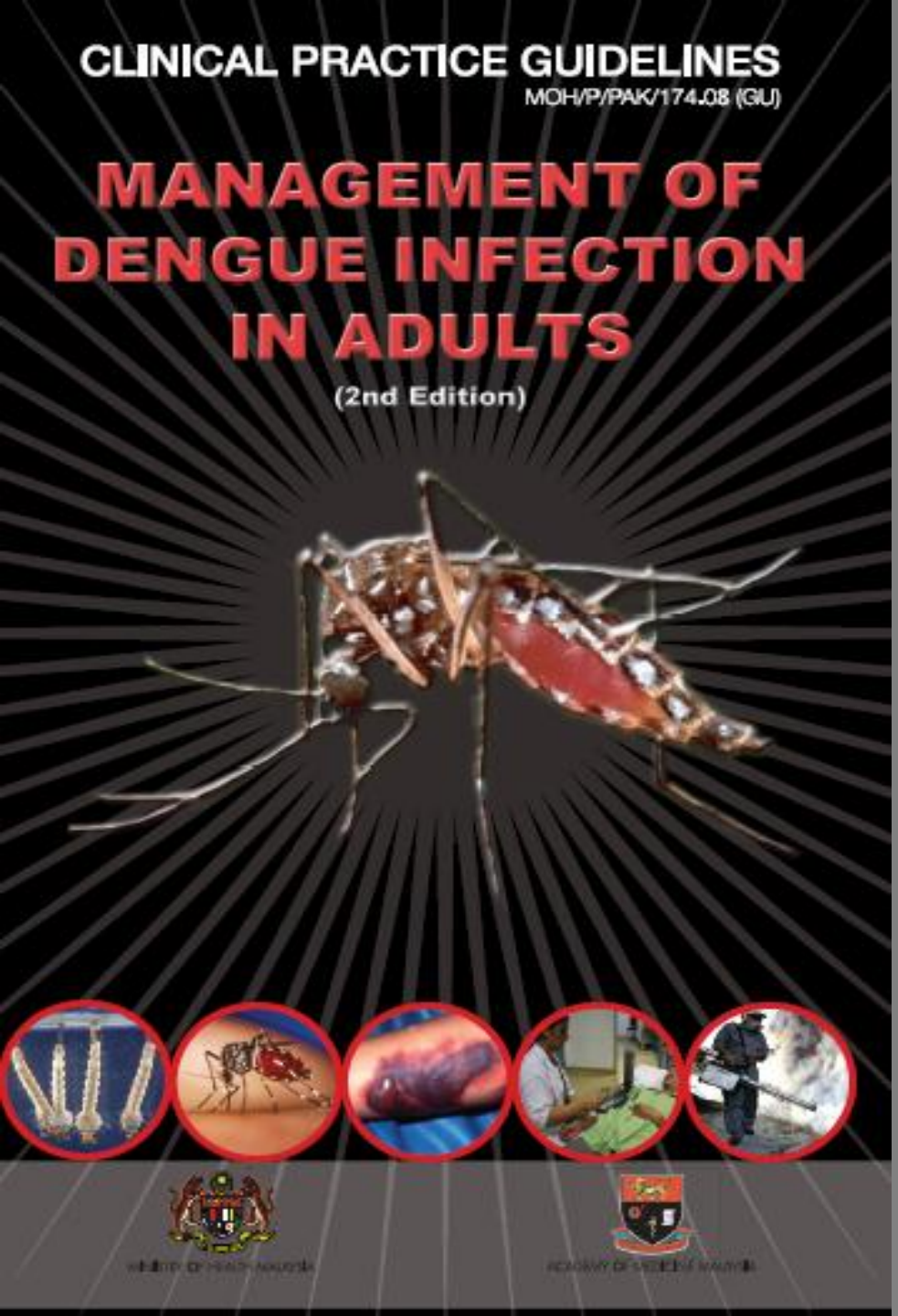


SEVERE DENGUE REVISITING

Dr Mahiran Mustafa
Chairman of CPG Development Committee

Awareness of CPG By Doctors





MANAGEMENT OF DENGUE INFECTION IN ADULTS (REVISED 2ND EDITION)

Dr Mahiran Mustafa
Chairman of CPG Development Committee

DENGUE

GUIDELINES FOR DIAGNOSIS, TREATMENT, PREVENTION AND CONTROL

New edition

2009

TDR For research on diseases of poverty
UNICEF • UNDP • World Bank • WHO

World Health Organization

CPG- INTRODUCTION

Current Problems:

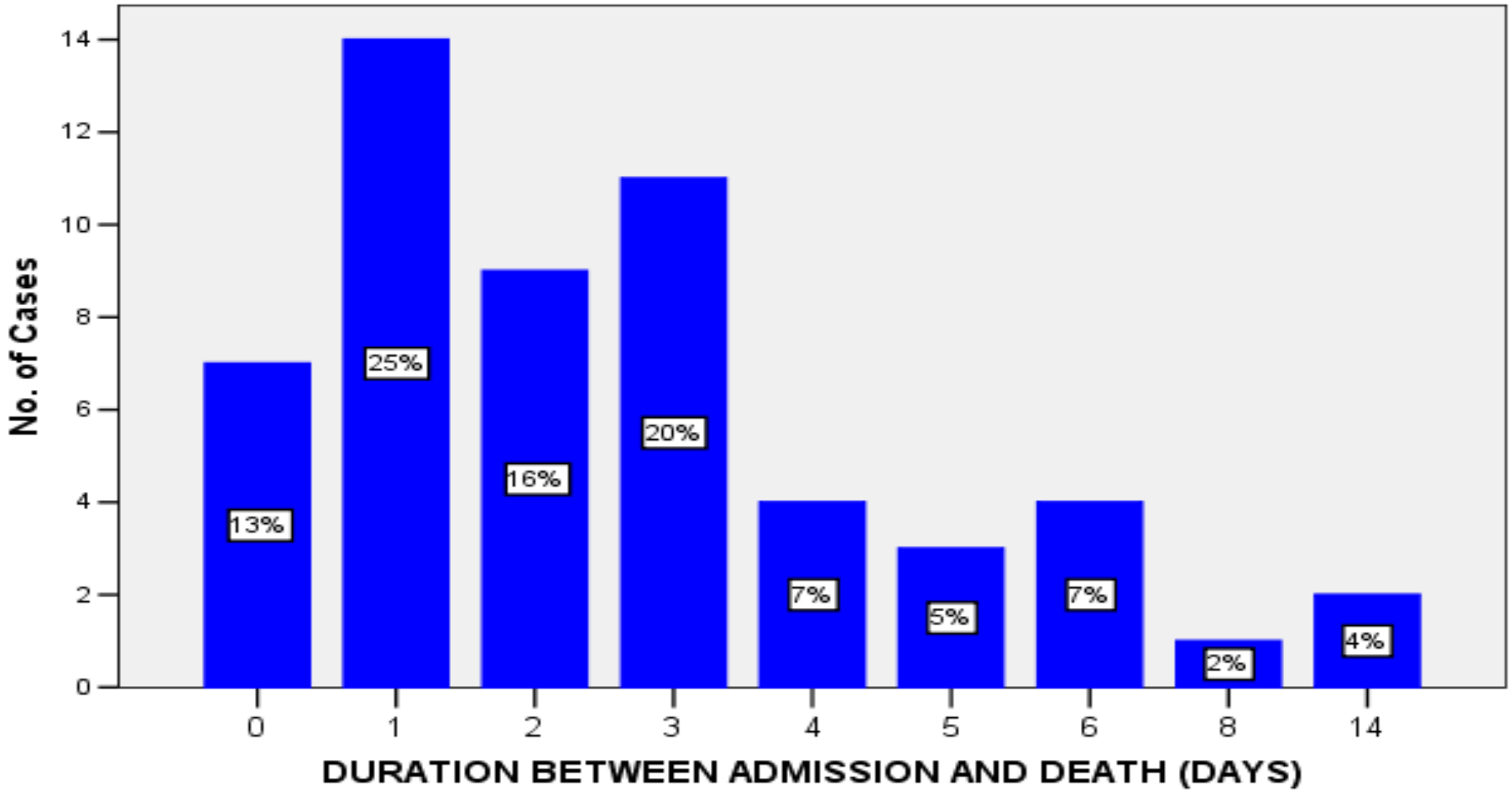
- Failure or delay in diagnosis
- Over emphasis on thrombocytopenia
- Lack of emphasis on warning signs and HCT value
- Poor clinical monitoring for in-patients
- Under-estimation of severity of disease and unable to recognize shock
- Inappropriate fluid therapy
- Inappropriate use of blood and blood products

AUDIT FINDINGS OF DENGUE MORTALITY CASES ANALYSIS 2009

- 53% of the death cases were preventable

- Contributing factors for dengue mortality
  - 47% late in seeking treatment (patients who died presented at the hospital at very late phase of their illness)
  - 35% patients management was not optimized
  - 40% multi organ failure
  - 20% others – uncontrolled DM/ HPT, Fits, Hepatitis

TIME INTERVAL OF ADMISSION TO DEATH



Doctors' Knowledge

- Use 10 Qs
- We have arbitarily decided to use 80% as the overall cut off indicating satisfactory knowledge.
- 17 (21.8%) of house officers
- 47 (30.9%) of medical officers
- 23 (71.9%) of specialists

Symptoms and Signs	Documentation of Symptoms and Signs			P value
	OPD	ED	Ward	
Fever	204 (99.5%)	214 (97.7%)	311 (100%)	0.01
Duration of fever / illness	201 (98.1%)	214 (97.7%)	311 (100%)	0.03
Vomiting/not tolerating orally	107 (52.2%)	152 (69.4%)	293 (94.2%)	0.00
Bleeding manifestation	121 (51.0%)	137 (62.6%)	276 (88.75%)	0.00
Abdominal pain	52 (25.4%)	95 (43.4%)	250 (80.39%)	0.00
Change of mental state	56 (27.3%)	75 (34.3%)	110 (35.37%)	0.14
Temperature	184 (89.8%)	207 (94.5%)	295 (94.86%)	0.05
Pulse Rate	113 (55.1%)	209 (95.4%)	300 (96.46%)	0.00
Blood Pressure	158 (77.1%)	211 (96.3%)	302 (97.11%)	0.00
Pulse Pressure	72 (35.1%)	92 (42.0%)	118 (37.94%)	0.39
GCS/Conscious Level	53 (25.9%)	139 (63.5%)	282 (90.68%)	0.00
Respiratory Rate	47 (22.9%)	118 (53.9%)	161 (51.77%)	0.00
Hydration Status	79 (38.5%)	100 (45.7%)	254 (81.67%)	0.15
Bleeding Manifestation	99 (48.3%)	78 (35.6%)	187 (60.13%)	0.01
Abdominal Examination	83 (40.5%)	151 (68.9%)	301 (96.78%)	0.00
Correct Diagnosis	134 (65.4%)	147 (67.1%)	241 (77.5%)	0.004
Satisfactory	**34 (16.6%)**	**32 (14.6%)**	**150 (48.2%)**	

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ISSUES- INCORRECT DIAGNOSIS

- Only 65.4% -77.5% was correct
  - -poor history taking
  - -poor clinical examinations

Male 56y, BWt 70 kg
Day 2

- Came to bring 2 sons to OPD with history of fever -3 days (2nd visit) FBC done - normal
- He also c/o Feeling unwell for 2 days
- Myalgia
- Afebrile T 37^{o}C, BP 126/70mmHg, PR 105/min

- Assessment: ??

- IM Voltaran/
- Paracetamol

Male 56y, BWt 70 kg
Day 5

- Brought to ED at District Hospital:
- He had fainting episode while having bath and became drowsy.
- Wife said that patient had fever for 4 days
- Sons fully recovered
- Myalgia No fits
- Afebrile T 37^{o}C, BP 81/70mmHg, PR 125/min
- No neck stiffness, unconcious, RR 34/min
- Ventilated

- Assessment: Encephalitis

Male 56y, BWt 70 kg
Day 5

- Given Fluid resuscitation 1 L and Transferred to General Hospital:
- BP 90/75mmHg HR 110/min Ventilated
- PH 7.06 HCO3 5mmol/l TWC 15.6, HCT 57, Platelet 23000
- He developed Acute Renal Failure, Liver Failure and Sepsis

- **Died on D6: DSS with Multiorgan Failure & Sepsis**

- Dengue Ig M positive Blood C&S Neg Lepto Ab Neg

Male 47y, BWt 70 kg
Day 5

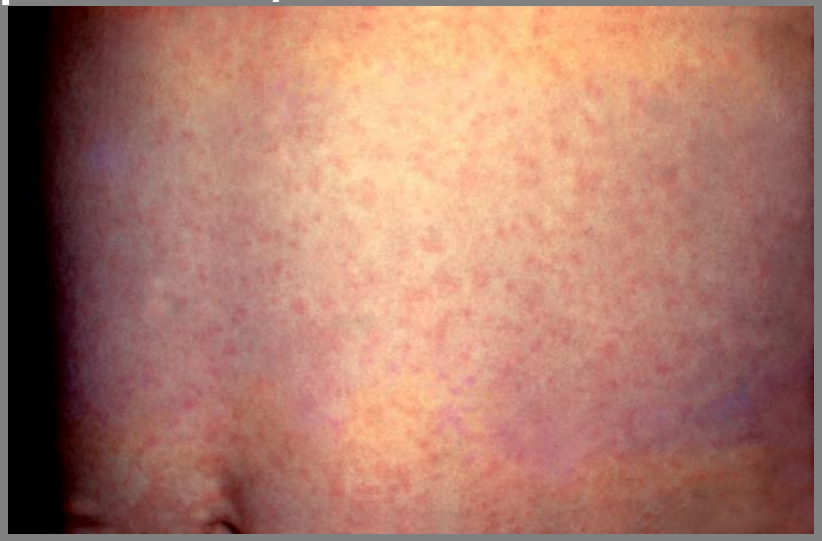
- Fever for 5 days
- Rash, vomiting, abdominal pain for 2 days
- Fogging nearby
- Lethargic, febrile
- T 38^{o}C, BP 86/52 mmHg, PR 120/min
- Cool peripheries
- Respiratory : clear
- Abdomen epigastric tenderness, liver 2 cm palpable

- Hb 12.7g/dl Hct 40%
- Platelets 111,000

Male 47y, BWt 20 kg
Management

- ***Diagnosis: Fever with gastritis***

- IVD 1x NS – BP picked up to 100/80mmHG
- Ranitidine
- IM voltaran
- Paracetamol
- Discharge

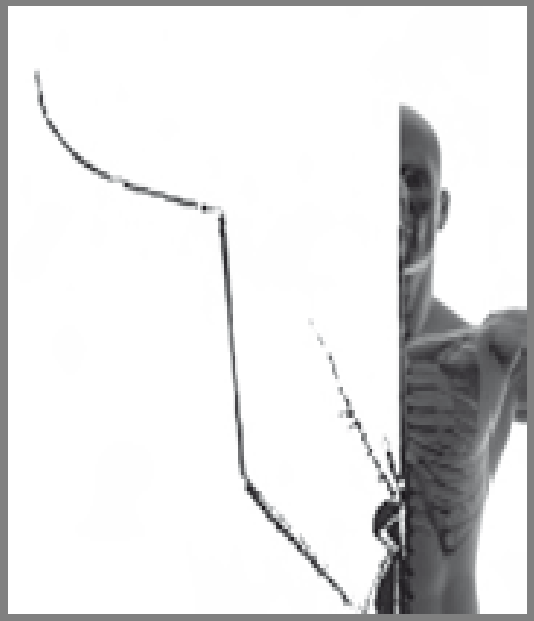


WHO 09: Probable dengue

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



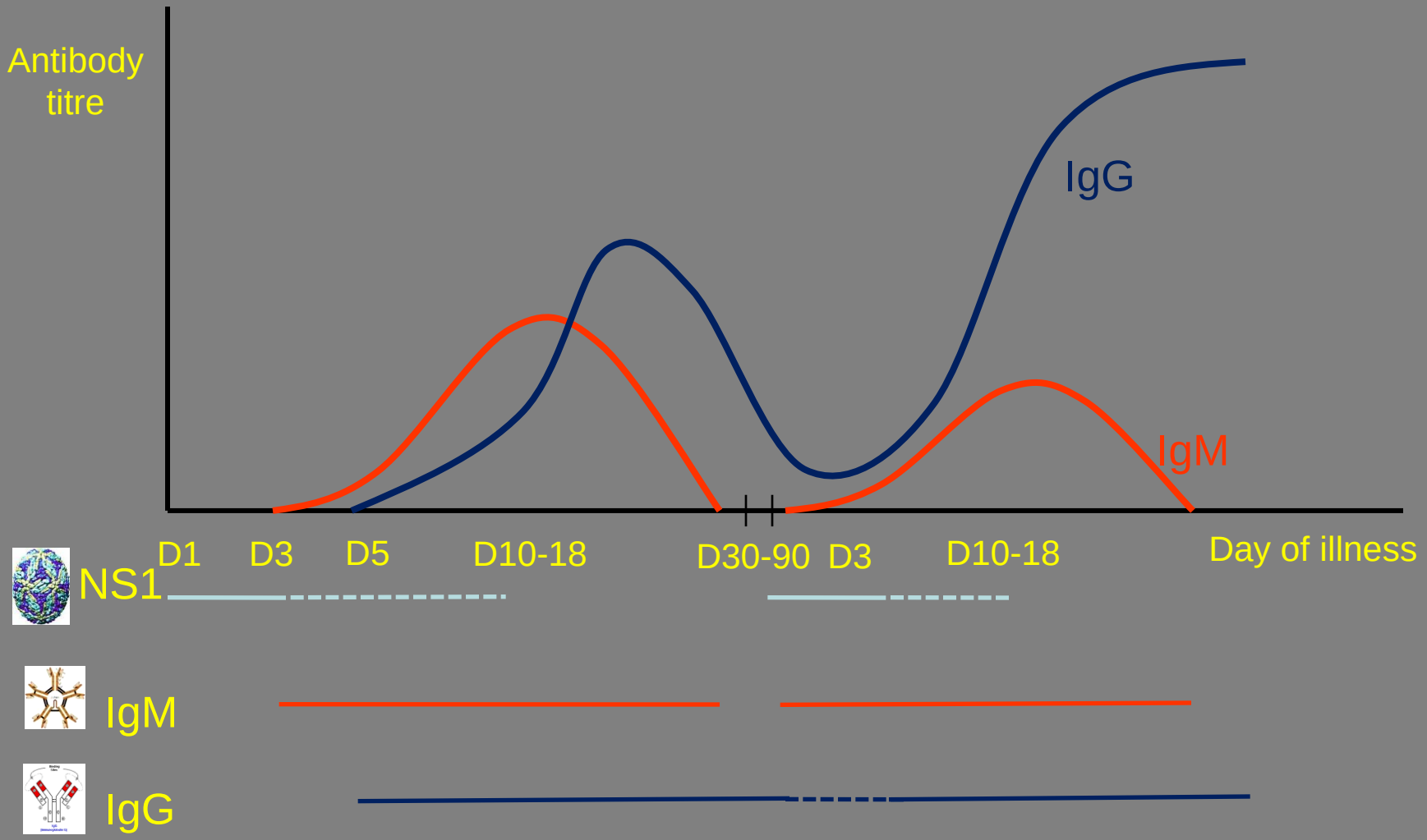
WARNING SIGNS

- ✓Vomiting
- ✓Abdominal pain
- Restlessness or altered mental state
- Mucosal Bleed
- Sudden change of temperature to subnormal
- Raising HCT with rapid drop in platelet

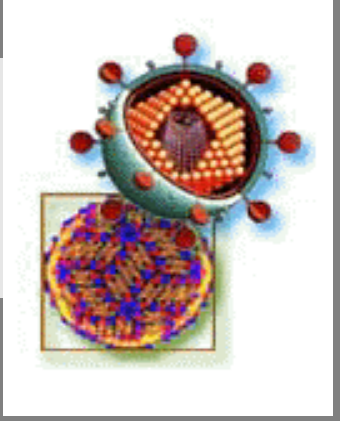
Is it Dengue, is it not?

- ***Early febrile phase***
- Full Blood Count
- Dengue IgM is negative
- Viral isolation/PCR will be positive
- ? Neighbourhood dengue

Time Course of Development of Immune Response to Dengue



Antigen Detection



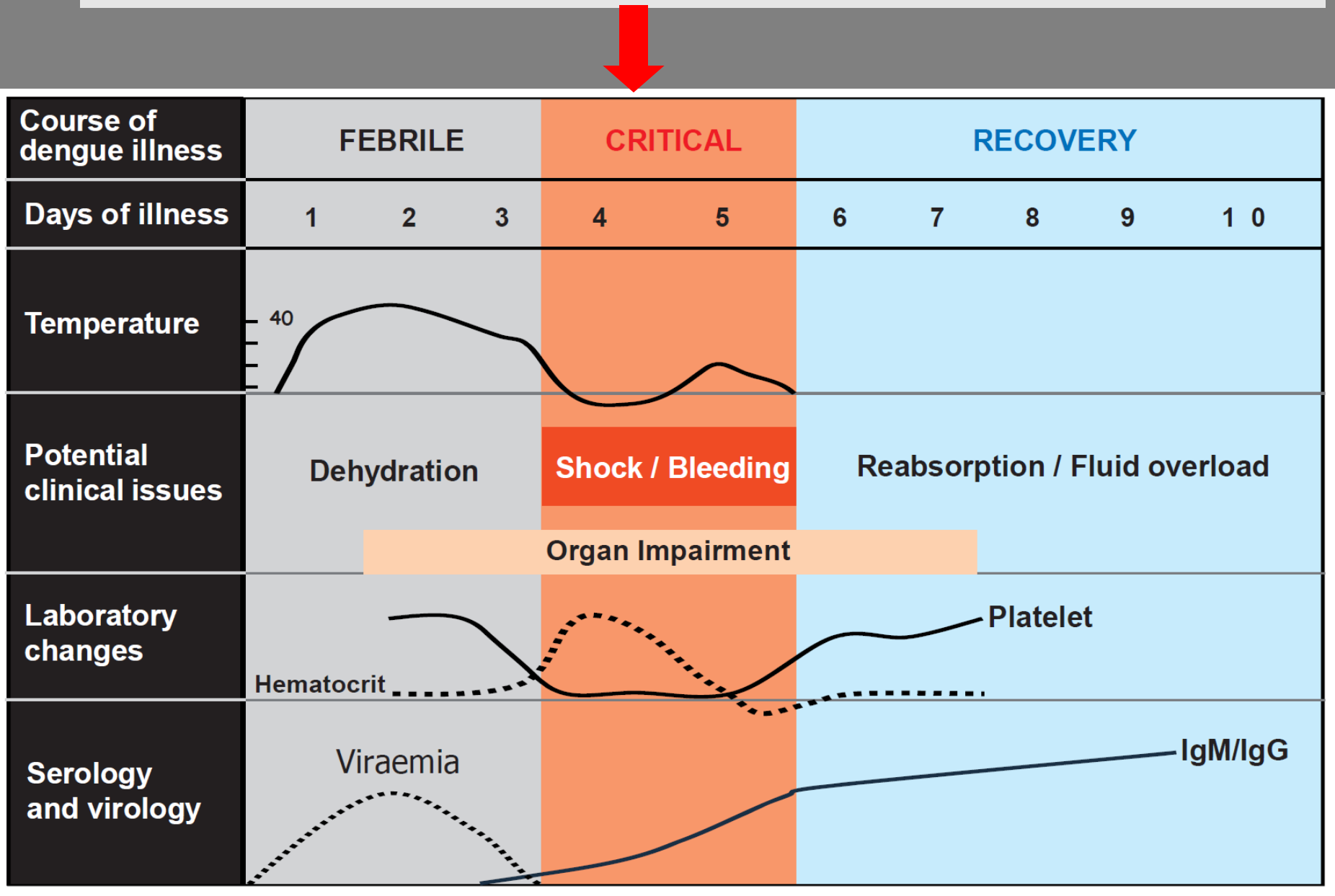
NS1 Antigen Assays

- ELISA and Rapid Test
- Higher detection rate in the 1st 6 days of infection and in primary dengue infection (75-93%)
- Detection rate is lower in secondary infection(60-70%)

- Test Duration ELISA 3 to 3.5 hours
  Rapid test 15 minutes

- Cost ELISA ~RM26
  Rapid test ~RM 35

Clinical course of DHF



Diagnosis, assessment of disease phase and severity

Step III. Management

1 Disease notification

2 Management decisions. Depending on the clinical manifestations and other circumstances,

– be sent home (Group A);

– be referred for in-hospital management (Group B);

– require emergency treatment and urgent referral (Group C).

Diagnosis, assessment of disease phase and severity

Step III. Management

- If admission is indicated (refer to admission criteria) :
- Stabilise the patient at primary care before transfer (refer to intravenous fluid regime)
- Communicate with the receiving hospital/ Emergency & Trauma Department before transfer

Pitfalls of Diagnosis

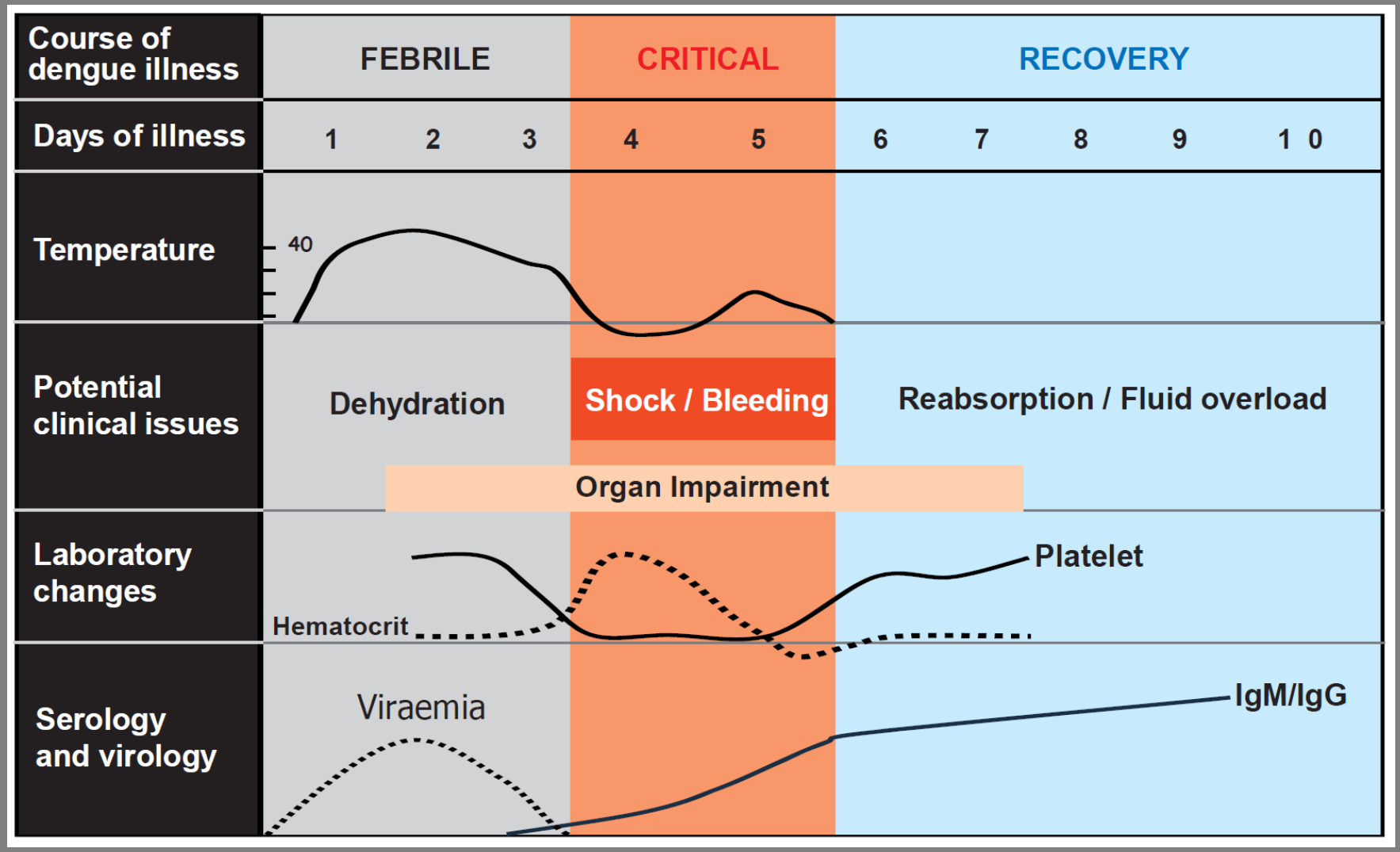
- Failure to classify dengue disease correctly Severe Dengue
- Impact of failure to classify dengue disease correctly
  - Inappropriate management
  - Underestimate the severity
  - May increase morbidity and mortality.

Common Errors at Outpatient & A&E Department

- Failure to recognise dengue shock in an afebrile patient.
- How to overcome this:

  In the afebrile patient, always have an index of suspicion for
  - Nausea, vomiting, abdominal pain
  - Manifestations of compensated and decompensated shock
  - Changing haematocrit (rather than platelet count)

Clinical course of DHF



CLINICAL ISSUES IN DIFFERENT PHASES OF DENGUE ILLNESS

Critical	- Plasma leakage occurs as patient progresses to late febrile phase or as temperature begins to defervescence (T < 38.0 °C). - Clinical deterioration occurs during this phase due to plasma leakage. - Plasma leakage results in haemoconcentration and hypovolemia/ shock. - Excessive plasma leakage due, in part, to intravenous fluid therapy may cause respiratory distress. - Bleeding can be precipitated by prolonged shock and shock can be perpetuated by bleeding. - May mimic acute abdomen of other causes. - May be confused with septic shock or other forms of shock.

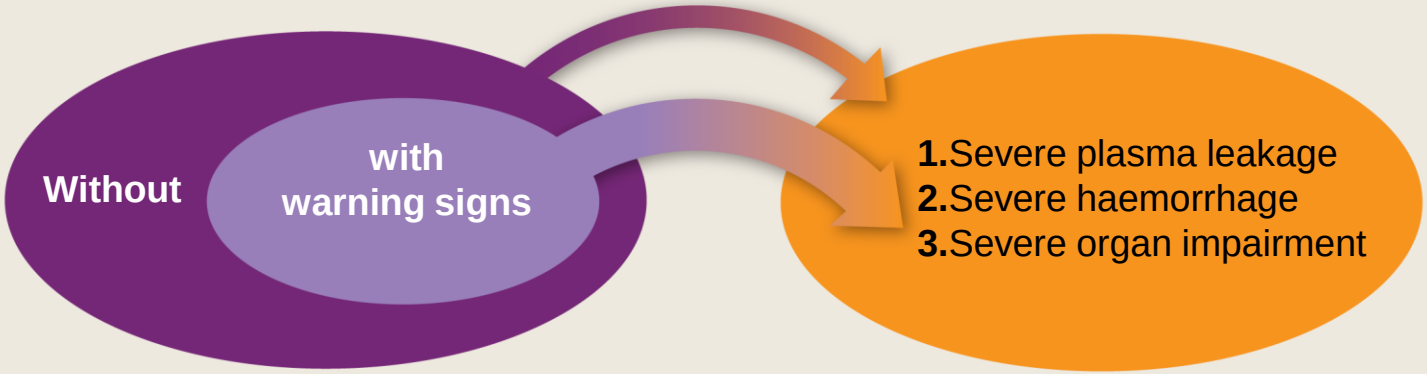
Warning Signs

Malaysia	WHO 09
• Vomiting • Abdominal pain • Restlessness or altered mental state • Mucosal Bleed • Sudden change of temperature to subnormal • Raising HCT with rapid drop in platelet • Liver enlargement	• Abdominal pain or tenderness • Persistent vomiting • Clinical fluid accumulation • Mucosal bleed • Lethargy, restlessness • Liver enlargment >2 cm • Laboratory: increase in HCTconcurrent with rapid decrease in platelet count

Dengue case classification by severity

Dengue ± warning signs

Severe dengue



Criteria for dengue ± warning signs

Criteria for severe dengue

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
- Leucopenia
- 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 enlargement >2cm
- *Laboratory:* Increase in HCT concurrent with rapid decrease in platelet count

** Requiring strict observation and medical intervention*

1. Severe plasma leakage
leading to:
- Shock (DSS)
- Fluid accumulation with respiratory distress

2. Severe bleeding
as evaluated by clinician

3. Severe organ involvement
- Liver: AST or ALT>=1000
- CNS: Impaired consciousness
- Heart and other organs

SEVERE MANIFESTATIONS

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

Normal Circulation	Compensated shock	Decompensated / Hypotensive shock
Clear consciousness	Clear consciousness – shock can be missed if you do not touch the patient	Change of mental state – restless, combative or lethargy
Brisk capillary refill time (<2 sec)	Prolonged capillary refill time (>2 sec)	Mottled skin, very prolonged capillary refill time
Warm and pink extremities	Cool extremities	Cold, clammy extremities
Good volume peripheral pulses	Weak & thready peripheral pulses	Feeble or absent peripheral pulses
Normal heart rate for age	Tachycardia	Severe tachycardia with bradycardia in late shock
Normal blood pressure for age	Normal systolic pressure with raised diastolic pressure Postural hypotension	Hypotension/unrecordable BP
Normal pulse pressure for age	Narrowing pulse pressure	Narrowed pulse pressure (<20 mmHg)
Normal respiratory rate for age	Tachypnoea	Metabolic acidosis/ hyperpnoea/ Kussmaul's breathing
Normal urine output	Reduced urine output	Oliguria or anuria

Complications

- Inadequate perfusion of the tissue leads to increased anaerobic glycolysis and resultant lactic acidosis
- Shock that leads to DIC and bleeding

Parameter for monitoring	Frequency of monitoring		
	Febrile phase	Critical phase	Recovery phase
Clinical Parameters			
General well being **Appetite/ oral intake** **Warning signs** **Symptoms of bleeding** **Neurological/ mental state**	Daily or more frequently towards late febrile phase	At least twice a day and more frequently as indicated	Daily or more frequently as indicated
Haemodynamic status • *Pink/ cyanosis* • *Extremities (cold/warm)* • *Capillary refill time* • *Pulse volume* • *PR* • *BP* • *Pulse pressure* **Respiratory status** • *RR* • *SpO_2*	4-6 hourly depending on clinical status	2-4 hourly depending on clinical status **In shock** Every 15-30 minutes till stable then 1-2 hourly	4-6 hourly
Signs of bleeding, abdominal tenderness, ascites and pleural effusion	Daily or more frequently towards late febrile phase	At least twice a day and more frequently as indicated	Daily or more frequently as indicated
Urine output	4 hourly	2-4 hourly **In shock** Hourly	4-6 hourly

Parameter for monitoring	Frequency of monitoring		
	Febrile phase	Critical phase	Recovery phase
Clinical Parameters			
FBC + HCT	Daily or more frequently if indicated	4-12 hourly depending on clinical status **In shock** Repeated before and after each attempt of fluid resuscitation and as indicated	Daily
BUSE/ Creatinine **LFT** **RBS** **Coagulation profile** **HCO_3 / TCO_2 / Lactate**	As indicated	At least daily or more frequently as indicated **In shock** Crucial to monitor acid-base balance/ ABG closely	As indicated

Adapted from [2, *Level 9*; 65, *Level 9*]

NAME _____ RN _____ I/C _____

DATE	/ /	/ /	/ /	/ /	/ /
TIME					
TEMPERATURE °C 40					
39					
38					
37					
36					
BLOOD PRESSURE ↑ 190					
180					
170					
160					
150					
140					
130					
120					
110					
100					
PULSE RATE ● 90					
80					
70					
60					
50					
40					
RR					
SpO2					
Dstix					
CRT					
Pulse volume					
Peripheries					
Vomiting					
Abd pain					
Bleeding					
Staff's Initial					

Pulse Volume - G - Good / W - Weak

Peripheries - W - Warm / C - Cold

RR																												
SpO2																												
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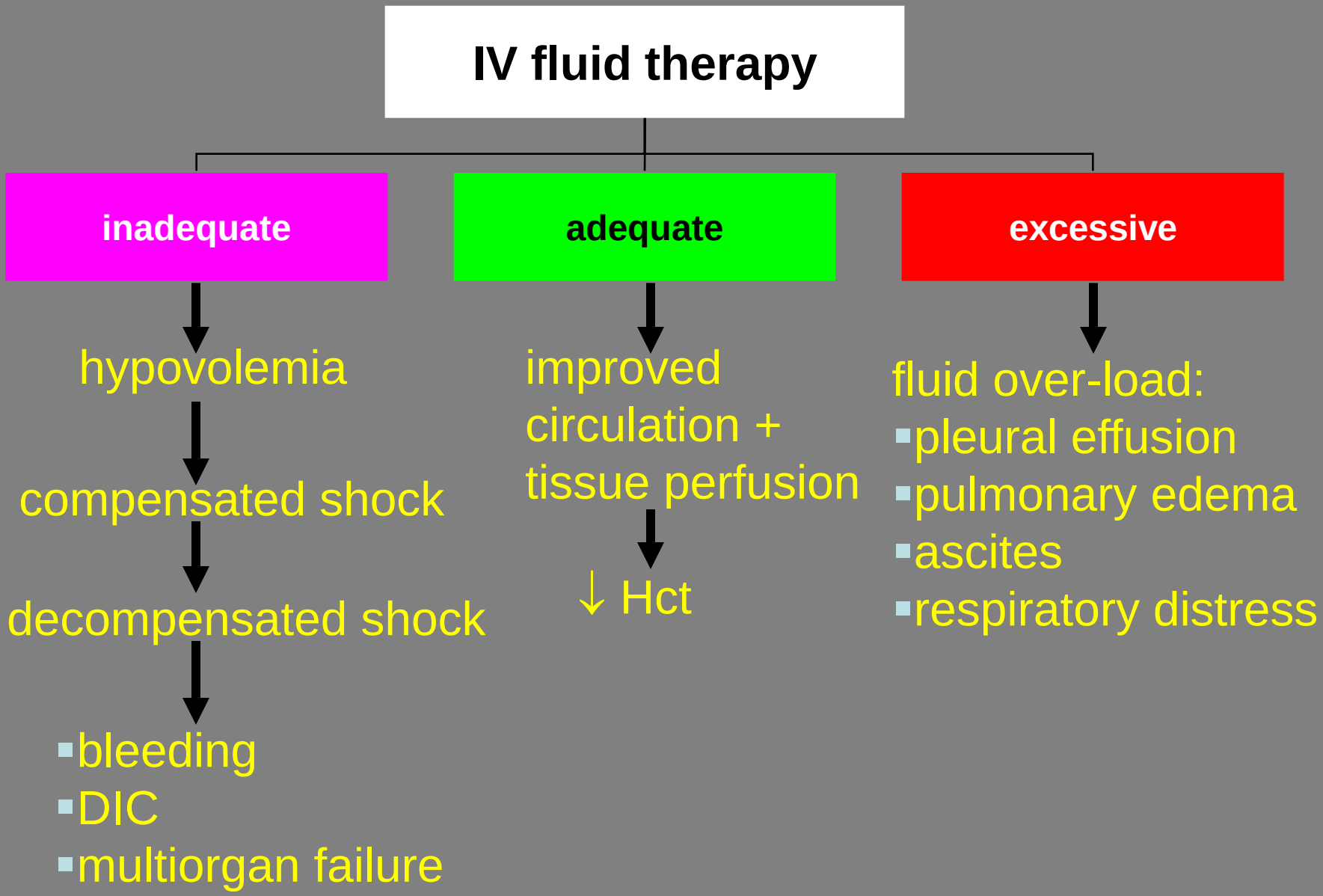
IV fluid therapy



Fluid Guidelines

Fluid Therapy: Dengue without warning signs & Non Shock

Recommendation

- Encourage adequate oral fluid intake**. (Grade C)**
- IV fluid is indicated in patients who are vomiting or unable to tolerate oral fluids. **(Grade C)**
- IV fluid is also indicated in patients with increasing HCT (indicating on-going plasma leakage) despite increased oral intake. (**Grade C)**
- Crystalloid is the fluid of choice for non shock patients**. (Grade C)**

Fluid management - maintenance

- **Calculations for normal maintenance of intravenous fluid infusion per hour:**

  (Equivalent to Halliday-Segar formula)

4 mL/kg/h for first 10kg body weight
+ 2 mL/kg/h for next 10kg body weight
+ 1 mL/kg/h for subsequent kg body weight

*For overweight/obese patients calculate normal maintenance fluid based on ideal body weight

Ideal bodyweight can be estimated based on the following formula

Female: 45.5 kg + 0.91(height -152.4) cm

Male: 50.0 kg + 0.91(height -152.4) cm

Maintenance fluid regimen

Adults

- *Choice of fluids*
  NS ± KCl

- *Volume of fluids*
  4mL/kg/h for first 10kg
  + 2mL/kg/h for next 10kg
  + 1mL/kg/h for subsequent

Eg: 50 kg patient
(40+20+30 = 90ml/hr
For 24 hours :
90 x 24 = 2160ml/24 hour

OR

5Okg x 1.5ml x 24 hours
= 1800ml

Fluid management - general rules

- Frequent adjustment of maintenance fluid regime,
- 1.2-1.5 X Maintenance in critical phase,
- If > 1X Maintenance required, regime need to be reviewed 4-6 Hly.
- Rising HCT- increase infusion rate
- DSS – fluid resuscitation algorithm
- Stop fluid therapy once after critical phase and patient is stable (post defevercence).

FLUID MANAGEMENT
Dengue with warning signs

- All patients with warning signs should be considered for monitoring in hospitals
- Start with 5–7 ml/kg/hour for 1–2 hours, then reduce to 3–5 ml/kg/hr for 2–4 hours, and then reduce to 2–3 ml/kg/hr or less according to the clinical response.

Dengue Shock Syndrome – DSS

- Medical emergency
- Early and prompt management lead to better outcome,
- Should be nursed in HDU or ICU
- Fluid resuscitation should be prompt,
- Following initial resuscitation there maybe recurrent episodes of shock because capillary leakage can continue for 24-48 hours

DSS – Fluid resuscitation

- **2 IV lines (largest branula possible)**
- 1st line: for replacement/bolus
- 2nd line: for blood taking OR blood transfusion

What treatments are effective for the management of shock in severe dengue?

- 3 studies have been conducted comparing crystalloids to colloids in the treatment of DSS
  - ***The first study*** in 1999 of 50 subjects ages 5-15 compared 4 IV regimens (Ringer's lactate, normal saline, 3% gelatin and dextran 70)

Results showed no difference in the duration of shock (p=.36) or the number of episodes of shock (p=.46)

Dung, N. M., et al. Clin Infect Dis, 1999. 29(4): p. 787-94.

What treatments are effective for the management of shock in severe dengue?

- ***2nd study*** in 2001 of 230, ages 1-15 years also compared 4 IV fluid regimens (Ringer's lactate, normal saline, 3% gelatin and dextran 70).
- WHO definition of shock in DHF III (DSS) as a pulse pressure=20 mmHg and a more"severe" group pulse pressure of =10 mmHg.

- **They found a small but significant difference in the median pulse pressure recovery times between the four groups favouring colloids (p=.03)**
- **For 51 of 230 presented with pulse pressure =10 mmHg (p=.01)**

Ngo, N. T., et al., Acute management of dengue shock syndrome: a randomized double-blind comparison of 4 intravenous fluid regimens in the first hour. Clin Infect Dis, 2001. 32(2): p. 204-12.

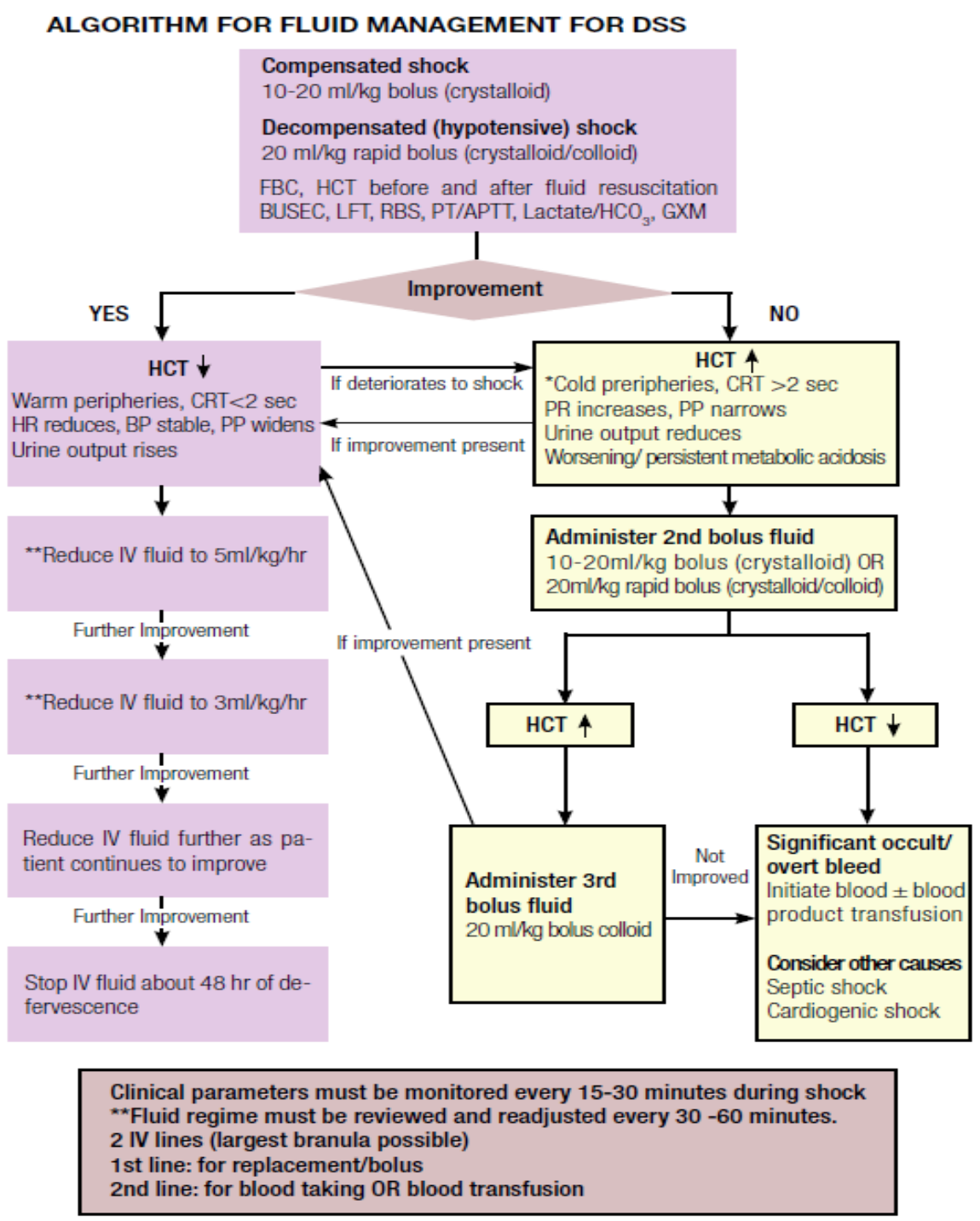
What treatments are effective for the management of shock in severe dengue?

- The third study in 2005 of 512 Vietnamese children ages 2-15 years compared 3 intravenous fluid regimens (Ringer's lactate, dextran 70 and 6% starch).

- **Results: no difference in either severity group in the**
  - **i. Requirement for colloid subsequent to the initial episode of shock (p=.38)**
  - **ii. Volumes of rescue colloid (p=.16)**
  - **iii. Total parenteral fluid administered (p=.17)**
  - **iv. Number of days in the hospital (p=.81)**

Wills, B.A., et al., Comparison of three fluid solutions for resuscitation in dengue shock syndrome. N Engl J Med, 2005

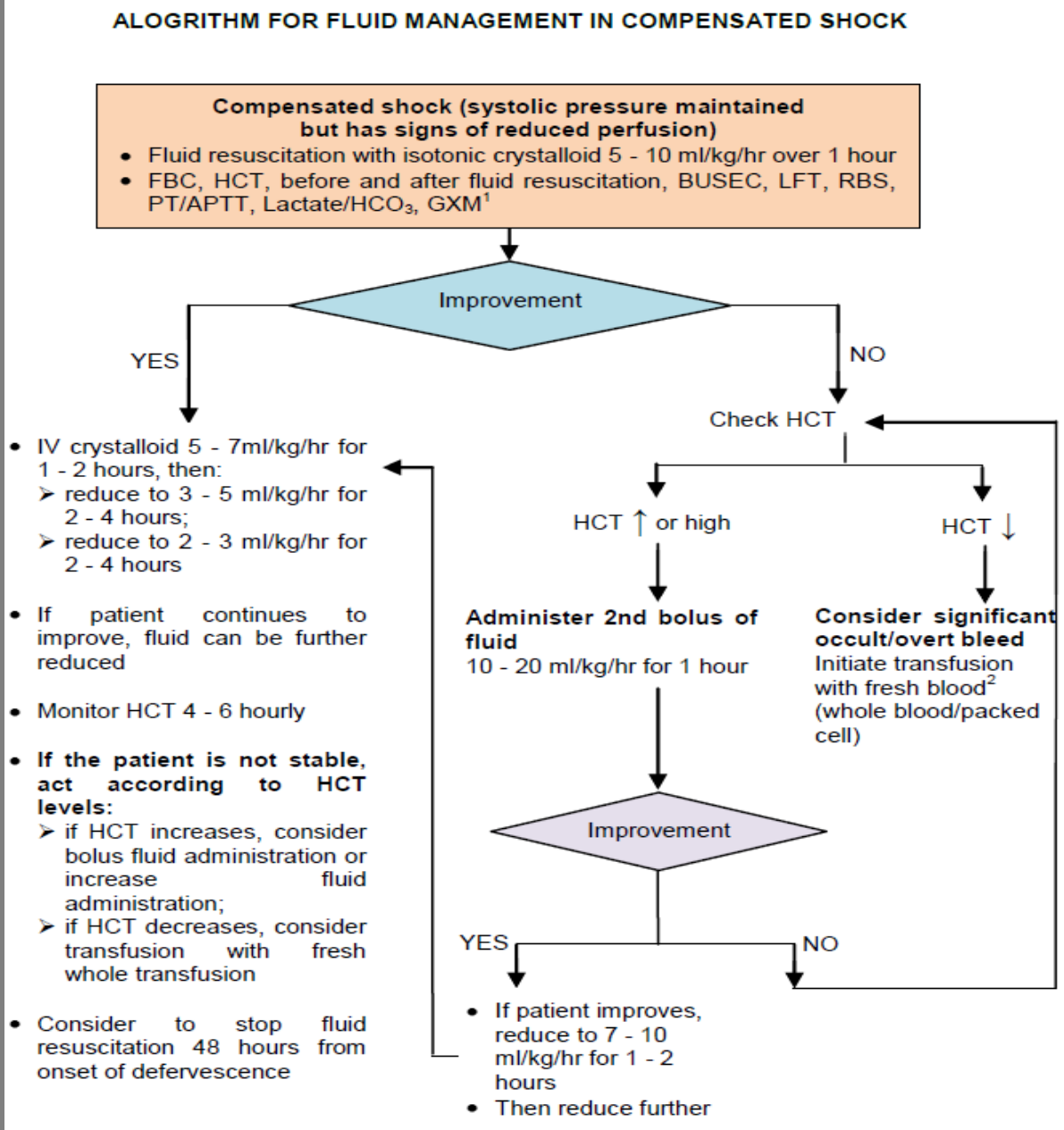
OLD FLUID MANAGEMENT IN DSS



NEW FLUID MANAGEMENT IN DSS

For GXM

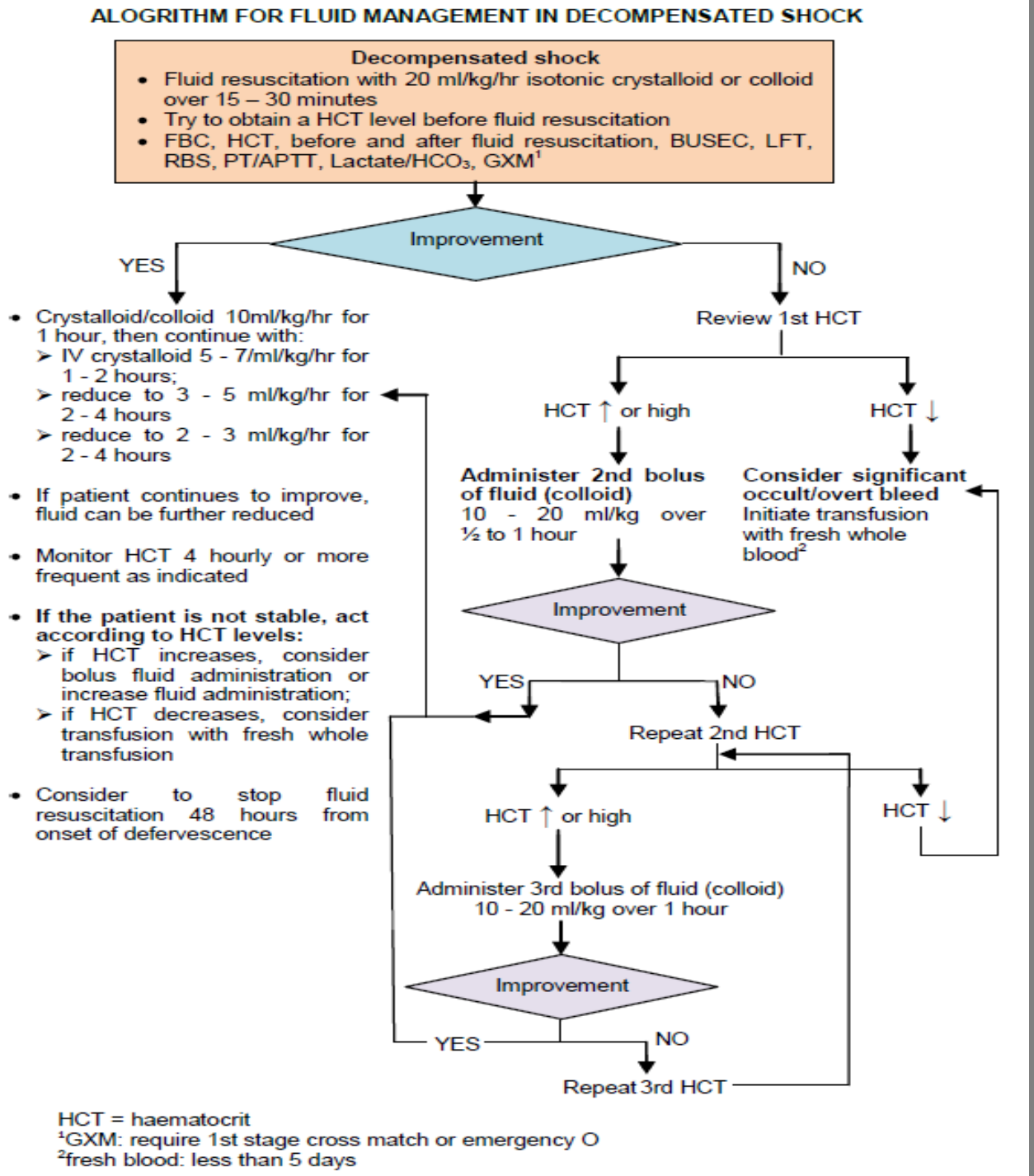
Use 1st stage cross match or emergency O.



HCT = haematocrit

[1]GXM: require 1st stage cross match or emergency O

[2]fresh blood: less than 5 days



- For GXM
- Use 1st stage cross match or emergency O.

After 1st bolus fluid – IMPROVED? YES

Clinical parameters must be monitored every 15-30 minutes during shock!

****Fluid regime must be reviewed and readjusted every 30 -60 minutes.**

Recurrent episodes of shock can occur after initial resuscitation (due to continuing plasma leakage) – for 2nd bolus fluid resuscitation

After fluid resuscitation – assessment for improvement

Clinical parameters

- Improvement of general well being/ mental state
- Warm peripheries
- Capillary refill time < 2sec
- BP stable
- Improving pulse pressure
- Less tachycardia
- Increase in urine output
- Less tachypnoea

Laboratory parameters

- Decrease in HCT
- Improvement in metabolic acidosis

Common pitfalls in fluid therapy

- Treating patient with unnecessary fluid bolus based on raised HCT as the sole parameter without considering other clinical parameters
- Excessive and prolong fixed fluid regime in stable patients
- Infrequent monitoring and adjustment of infusion rate.
- Continuation of intravenous fluid during the recovery phase

Pitfalls

- Inotropes should not be the first line treatment in DSS before adequate fluid replacement is instituted.
- Albumin + FFP should not be used as "plasma expanders", they are not plasma expanders and will leak as well.
- Frusemide should not be used in the plasma leakage phase as it may aggravate intravascular volume depletion.

Why patient develops significant bleeding?

- Significant bleeding is associated with prolonged and uncorrected shock from plasma leakage

- Significant bleeding can be prevented by prompt recognition and appropriate treatment of shock

Haemostatic changes in Dengue

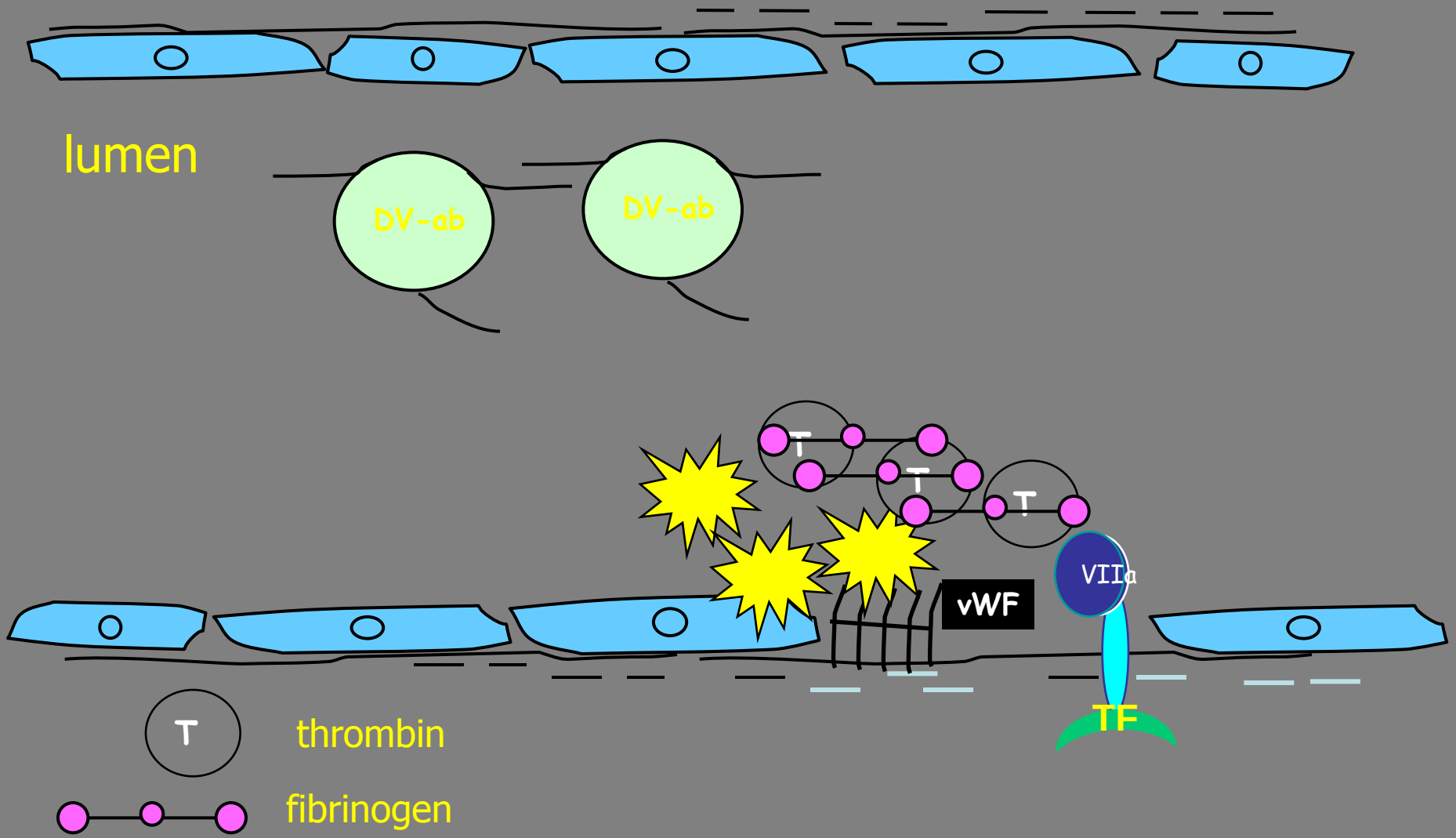
Vasculopathy

- Hess's test is an early sign
- Precedes increased vascular permeability and thrombocytopenia

Platelet abnormalities

Coagulation defects

Platelet Activation-Coagulation activation



Do we treat thrombocytopenia?

- No!
- The degree of thrombocytopenia is not predictive of bleeding
- Platelet transfusion in dengue:
  - May aggravate platelet aggregation and activation and may potentially be harmful
  - Does not alter clinical outcome
  - Potential risk of transfusion-transmitted infections (TTI) and adverse reactions

Do we treat prolonged PT/APTT?

- No!
- Prolonged PT/APTT is an expected finding in dengue

  Prolonged APTT: 54.6%

  Prolonged PT: 33.3%
- Prolonged PT/APTT in dengue ≠ DIC
- Transfusion of blood products does not change the clinical outcome

When to transfuse blood/blood components? (2)

- Evidence of significant bleeding (overt or occult):
  - Haemodynamic instability despite more than 60ml/kg of resuscitation fluids
  - HCT not as high as expected for the degree of shock to be explained totally by plasma leakage
  - A drop in HCT without clinical improvement, e.g., despite a drop of HCT from 48% to 43% , patient still haemodynamically unstable
  - Severe metabolic acidosis and end organ dysfunction

MANAGEMENT OF BLEEDING

Recommendations:

- Patients with mild bleeding (eg: gums or per vagina, epistaxis and petechiae) do not require blood transfusion. **(Grade C)**
- Blood transfusion (whole blood or packed cell <1 week) ± blood component is indicated in significant bleeding. **(Grade C)**
- There is no role for prophylactic transfusion with platelets and plasma in dengue. (**Grade C)**

Blood transfusion in patients with significant bleeding

- Transfuse 5 - 10 ml/kg of fresh-packed red cells or 10 - 20 ml/kg of fresh whole blood at an appropriate rate and observe the clinical response.
- Consider repeating the blood transfusion if there is further blood loss or no appropriate rise in HCT after blood transfusion.

Indications for referral to Intensive

- Recurrent or persistent shock
- Requirement of respiratory support (non-invasive and invasive ventilation)
- Significant bleeding
- Encephalopathy or encephalitis

CLINICAL ISSUES IN DIFFERENT PHASES OF DENGUE ILLNESS

Reabsorption	- Cessation of plasma leakage. - Reabsorption of fluid from extravascular compartment. - Haemodilution occurs following fluid reabsorption. - Hypervolaemia and pulmonary oedema if intravenous fluid therapy is continued.

DISCHARGE CRITERIA

- Afebrile for 48 hours
- Improved general condition
- Improved appetite
- Stable haematocrit
- Rising platelet count
- No dyspnoea or respiratory distress from pleural effusion or ascites
- Resolved bleeding episodes
- Resolution/recovery of organ dysfunction