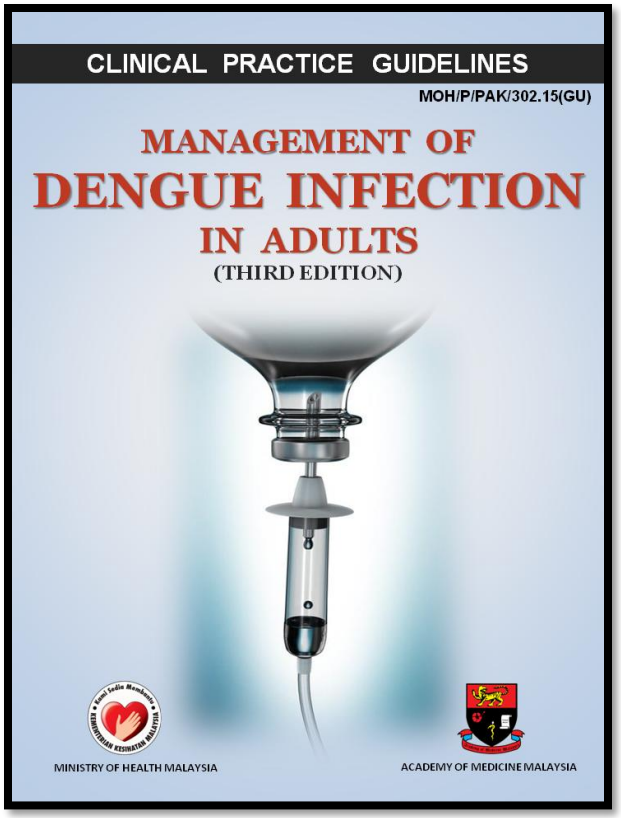


Clinical Manifestation and Pathophysiology

Learning objectives

1. Spectrum of dengue infection
2. Dengue classification
3. Pathogenesis
    i. Plasma leakage in severe dengue
    ii. Organ complication in dengue
4. Clinical course of dengue

"Dengue is one disease entity with **different clinical presentations** and often with **unpredictable clinical evolution and outcome**"

Expert consensus groups in Latin America (Havana, Cuba, 2007), (Kuala Lumpur, Malaysia, 2007), WHO headquarters in Geneva, Switzerland, 2008

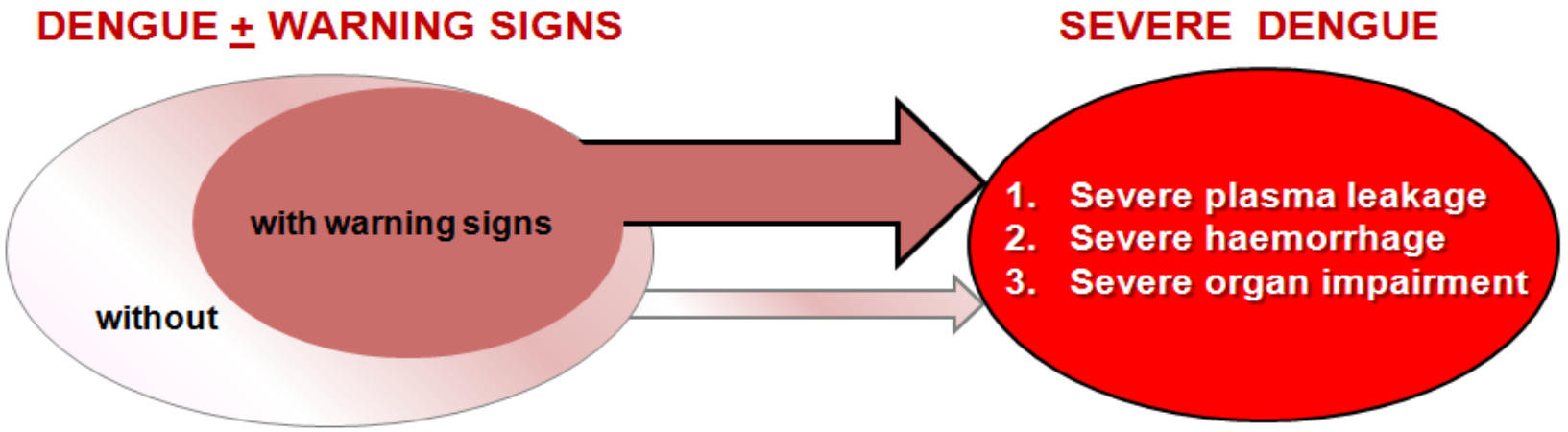
Spectrum of dengue infection

- Incubation period : 4-7 days (range 3-14)

- Asymptomatic → undifferentiated mild febrile illness → severe disease

- Symptomatic dengue infection :
  - systemic and dynamic disease
  - clinical, haematological and serological profiles changing from day to day

Dengue Classification



CRITERIA FOR DENGUE ± WARNING SIGNS

Probable dengue
- Live in/travel to dengue endemic/ hotspot/outbreak area.
- Fever and 2 of the following criteria:
- Nausea, vomiting
- Rash
- Aches and pains
- Leucopaenia
- Any warning sign

Laboratory-confirmed dengue
(important when no sign of plasma leakage)

Warning signs*
- Abdominal pain or tenderness
- Persistent vomiting (≥3 times per day)
- Persistent diarrhoea (≥3 times per day)
- Clinical fluid accumulation
- Mucosal bleed
- Lethargy, confusion, restlessness
- Tender liver
- Laboratory: increase in HCT concurrent with rapid decrease in platelet count

*(requiring strict observation & medical intervention)

CRITERIA FOR SEVERE DENGUE

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

Severe bleeding
As evaluated by clinician

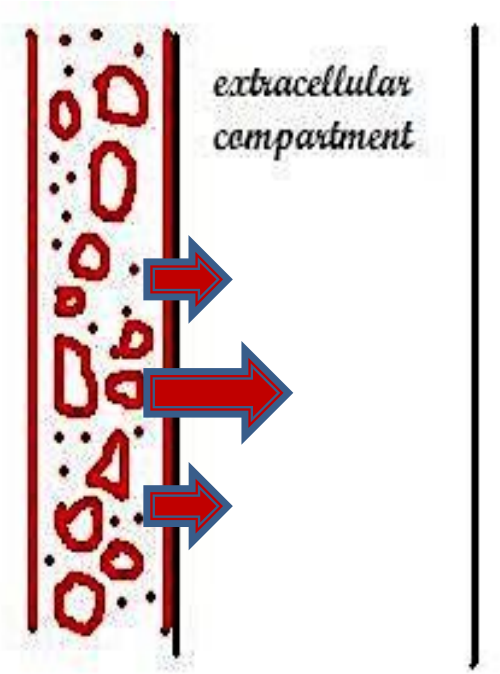
Severe organ involvement
Liver : AST or ALT ≥ 1000
CNS : Impaired consciousness
Heart and other organs

Pathogenesis of plasma leakage in severe dengue – 1

- Infection with a virulent dengue virus
- Presence of antibodies that enhance dengue virus infection (ADE) – in secondary dengue
- Intense immune activation

Pathogenesis of plasma leakage in severe dengue - 2

- Rapidly elevated cytokines (TNF-a, IL-2, IL-6, IL-8, IL-10, IL-12, and IFN-g)
- Malfunction of vascular endothelial cells
- Plasma leakage from intra to extravascular space



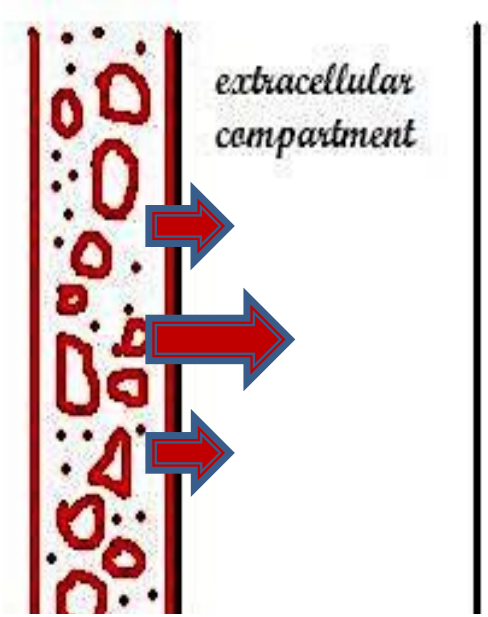
Pathogenesis of plasma leakage in severe dengue - 3

- Cytokine Storm
- Self limited & ends after 48 hours
- Severe dengue
  - ✓ subversion of protective pathways by both viral and host factors
  - ✓ altered host responses
  - ✓ excessive inflammation

Pathogenesis of plasma leakage in severe dengue - 4

- In severe dengue, the loss of plasma is critical
- Patient becomes hypovolaemic
- Signs of circulatory compromise
- Progress to shock, organ failure, death

Pathophysiology of plasma leakage in severe dengue



Increase in vascular permeability

↓

Leakage of plasma to extravascular compartment

↓

Haemoconcentration and hypovolaemic shock
Generalized vasoconstriction

↓

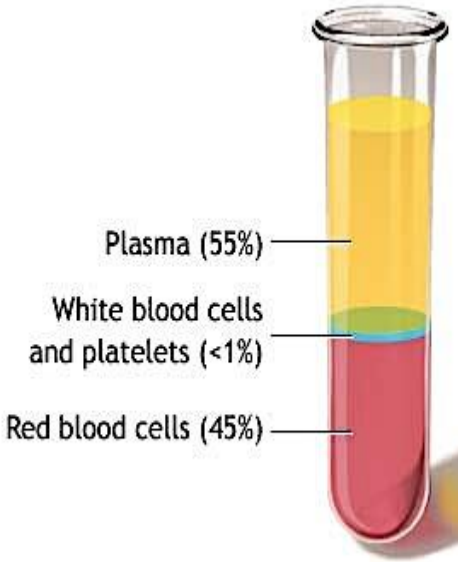
Inadequate tissue perfusion

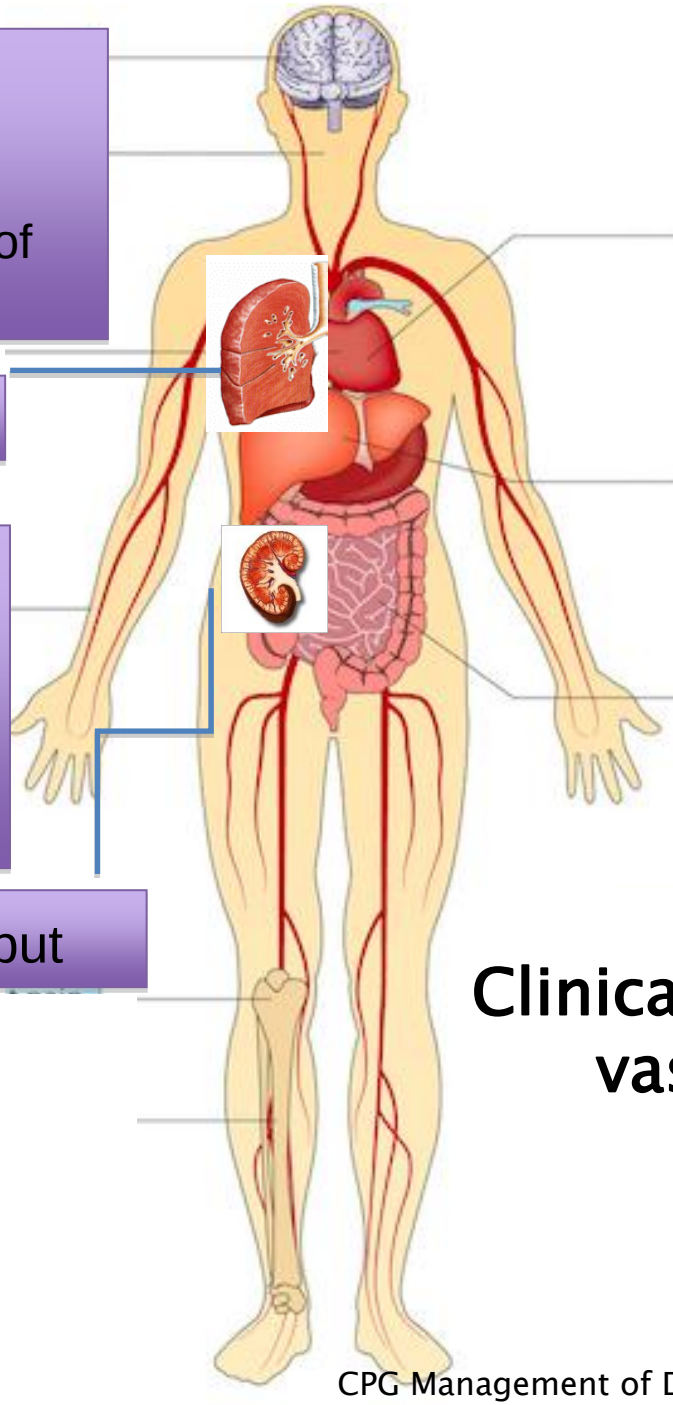
↓

Anaerobic glycolysis & lactic acidosis

↓

Depress myocardium & further hypotension





- Lethargy
- Restlessness
- Apprehension
- Reduced level of consciousness

tachypnoea

- Coolness
- Pallor
- Delayed capillary refill time
- Poor pulse volume

↓↓ urine output

- ↑dBP
- narrowing of pulse pressure

- Vomiting
- Abdominal pain
- Tender enlarged liver

Clinical manifestation of vasoconstriction

A continuum from normal circulation to compensated and decompensated shock

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

Pathogenesis of organ dysfunction in severe dengue

- **Encephalitis**
  - direct viral infection of central nervous system (CNS), autoimmune reaction, metabolic and hemorrhagic disturbances
- **Carditis**
  - regional vulnerability to coronary hypoperfusion, cytokine storm, direct myocardial inflammation and altered calcium homeostasis
- **Haemophagocytic syndrome (HPS)**
  - extreme immune activation leading to cytokine storm with increased IL-2, TNF-a, IL-6, IL-8, interferon g generated by uncontrolled activation of histiocytes and T-cells

Diagnosis

Acute febrile illness + 2 of :-

- headache
- retro-orbital pain
- myalgia
- arthralgia
- rash
- haemorrhagic manifestations
- leucopenia

+

lab diagnosis

Probable dengue

Confirmed dengue

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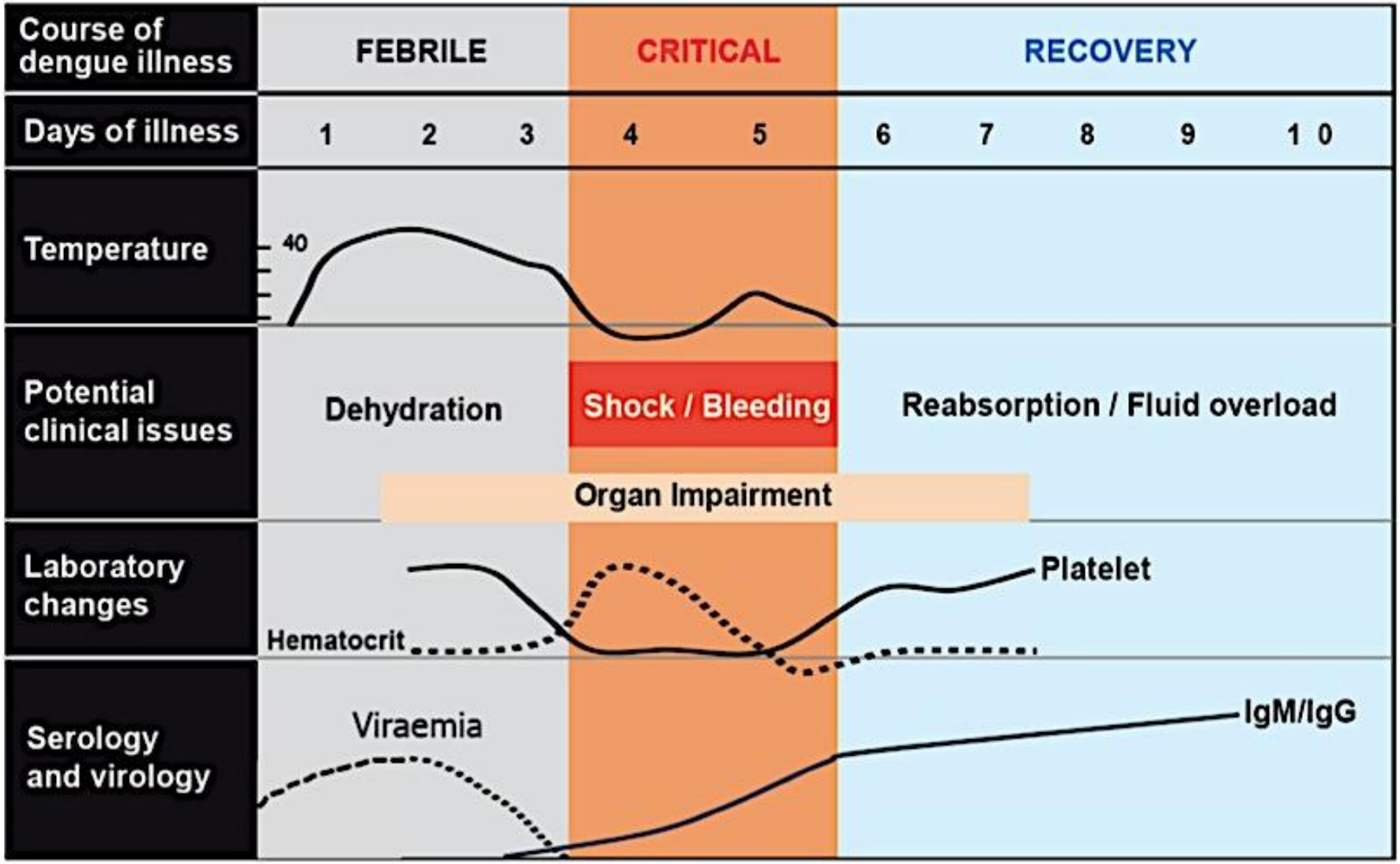
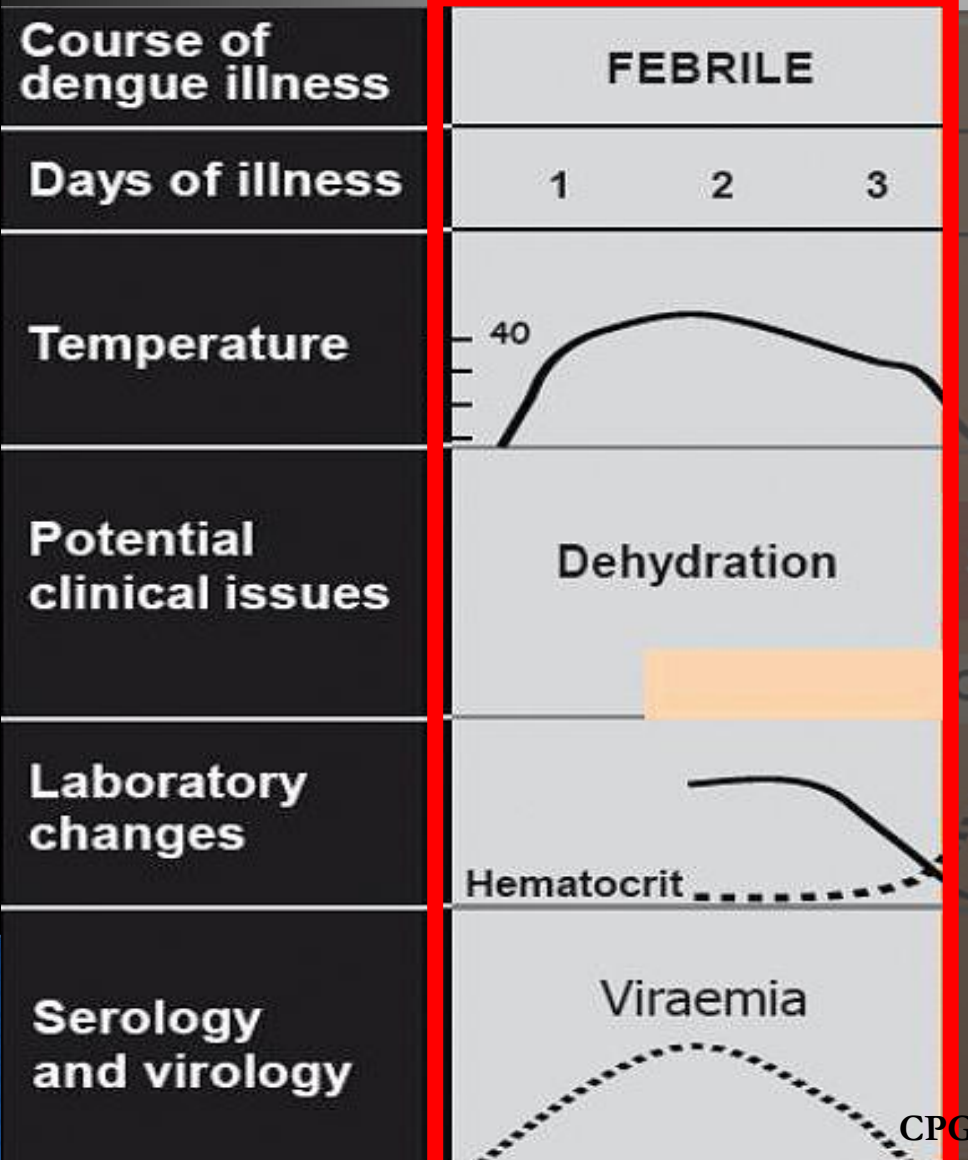
Clinical course of dengue infection



Febrile phase - 1



Clinical presentation

- Sudden high grade fever
- Last 2-7 days
- Facial flushing, skin erythema, generalised body ache, myalgia, arthralgia, headache
- Sore throat, injected pharynx, conjunctival injection +/-
- Anorexia,nausea, vomiting
- Mild haemorrhagic manifestations
- Progressive ↓ in WBC

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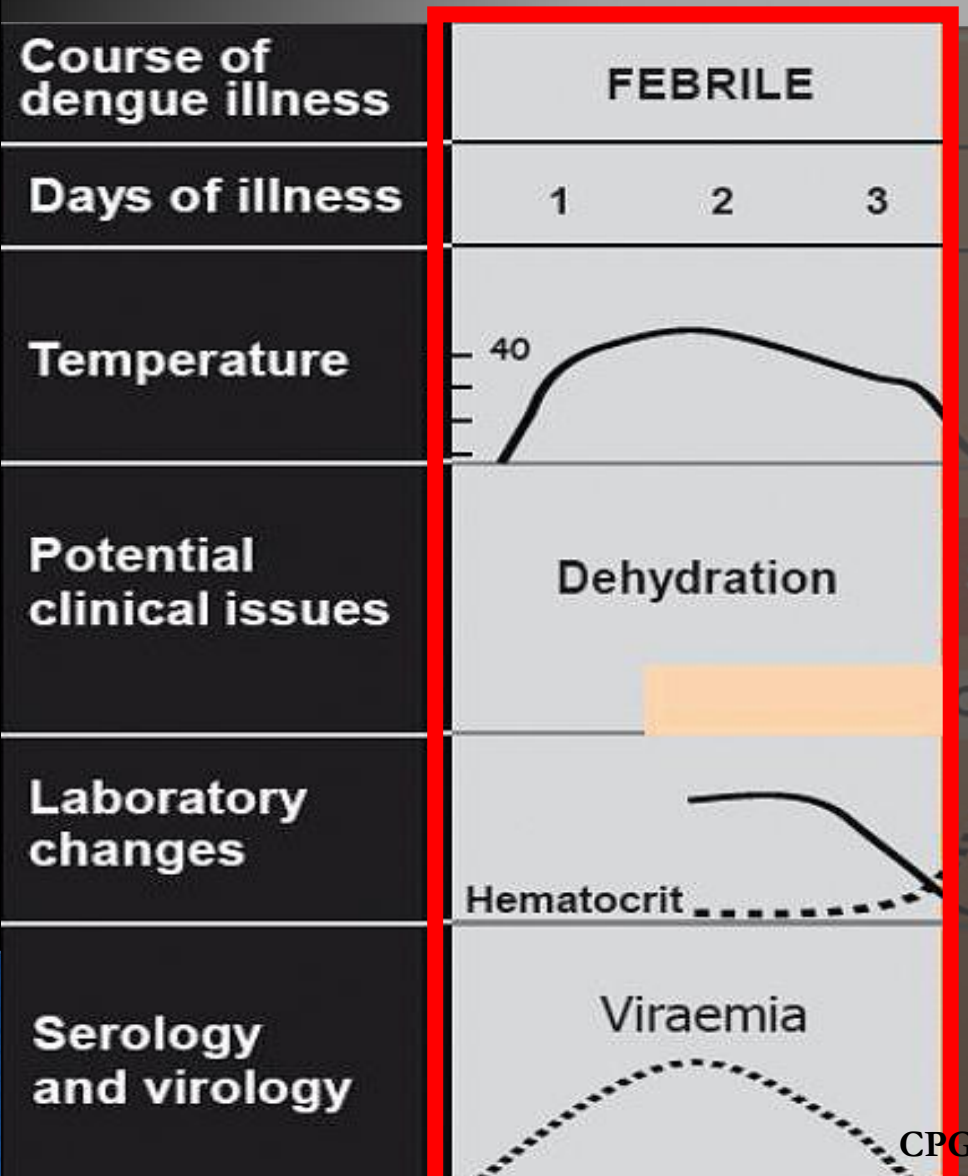
Febrile phase - 2



Diagnostic challenges

- Recognizing dengue
- Sx non-specific
- Mimic many other diseases & infections
- High index of suspicion
- Co-infection may present
- Present of organ complications may cause misleading of diagnosis i.e encephalitis

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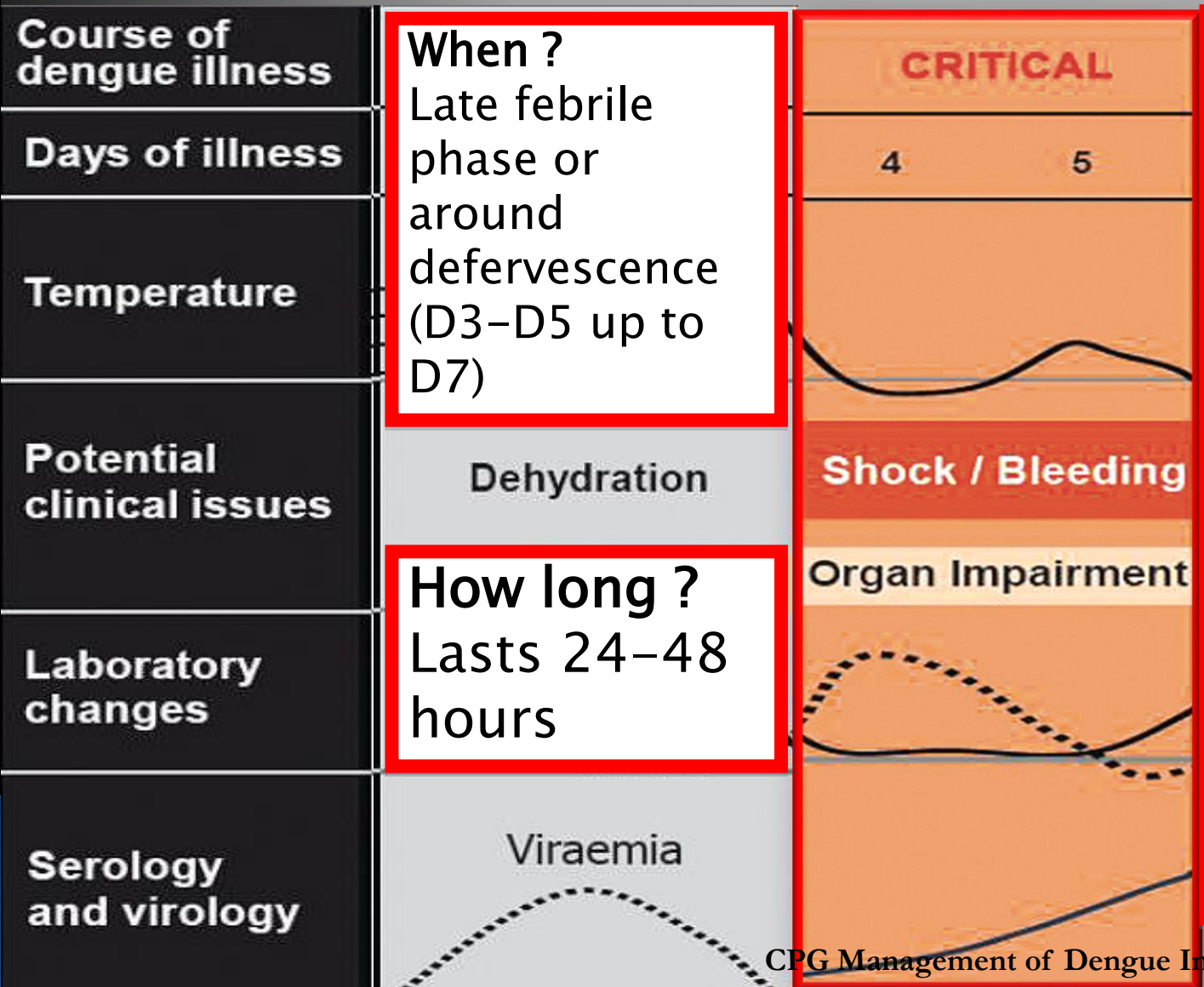
Critical phase – 1



Hallmark

Clinical :

Varying degree of circulatory disturbances

Lab :

- ↓Plt & ↑ HCT usually detectable before subsidence of fever & onset of shock
- HCT correlates well with plasma vol loss and disease severity
- ↑ AST > ALT

Critical phase – 2

During this phase if,

- **Minimal or no plasma leakage occurs**
  - Patient feels better as the temperature subsides
  - **Dengue fever without warning signs**

- **Critical volume of plasma leakage occurs**
  - Varying degrees of circulatory disturbances occur depending on the degree of plasma leakage
  - **Dengue fever with warning signs/Dengue shock syndrome**

Critical phase – 3

Shock– occurs when a critical volume of plasma is lost through leakage

- Often preceded by **warning signs**

- **Any abdominal pain/tenderness**
- **Persistent vomiting (≥3 times over 24 hours)**
- **Persistent diarrhoea (≥3 times over 24 hours)**
- **Third space fluid accumulation (such as ascites, pleural and pericardial effusion)**
- **Spontaneous bleeding tendency**
- **Lethargy/restlessness/confusion**
- **Tender liver**
- **Raised HCT with rapid drop in platelet:**
  - **HCT male ≤60 years - 46**
  - **HCT male >60 years - 42**
  - **HCT female (all age groups) - 40**

*median value of normal HCT in Malaysian population[33,level II-2.]

A continuum from normal circulation to compensated and decompensated shock

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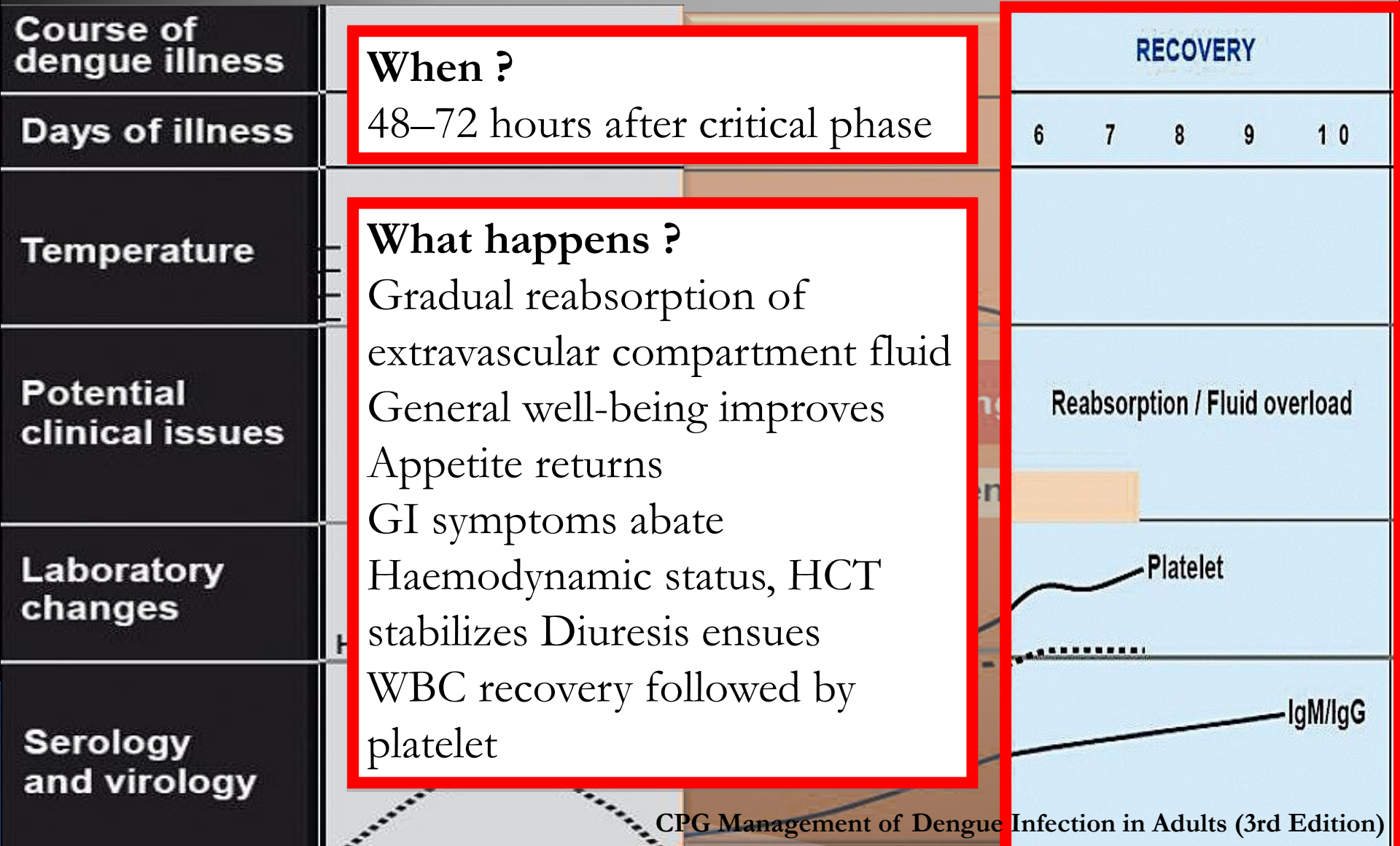
Recovery phase – 1



When ?

48–72 hours after critical phase

What happens ?

Gradual reabsorption of extravascular compartment fluid

General well-being improves

Appetite returns

GI symptoms abate

Haemodynamic status, HCT stabilizes Diuresis ensues

WBC recovery followed by platelet

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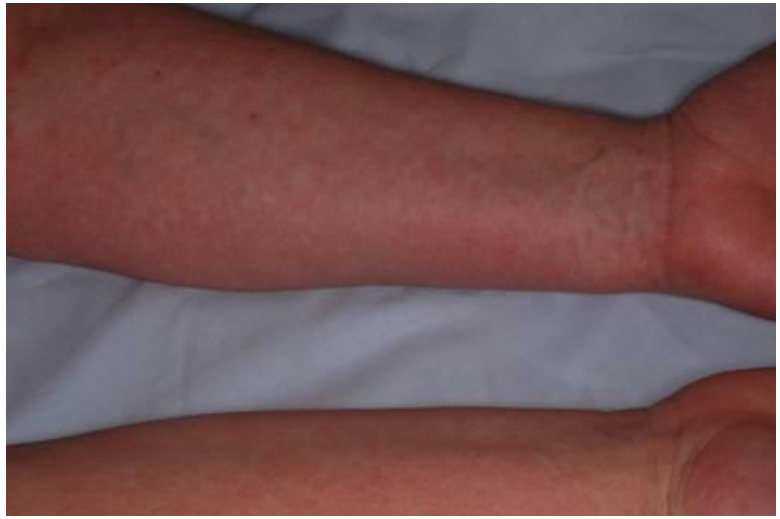
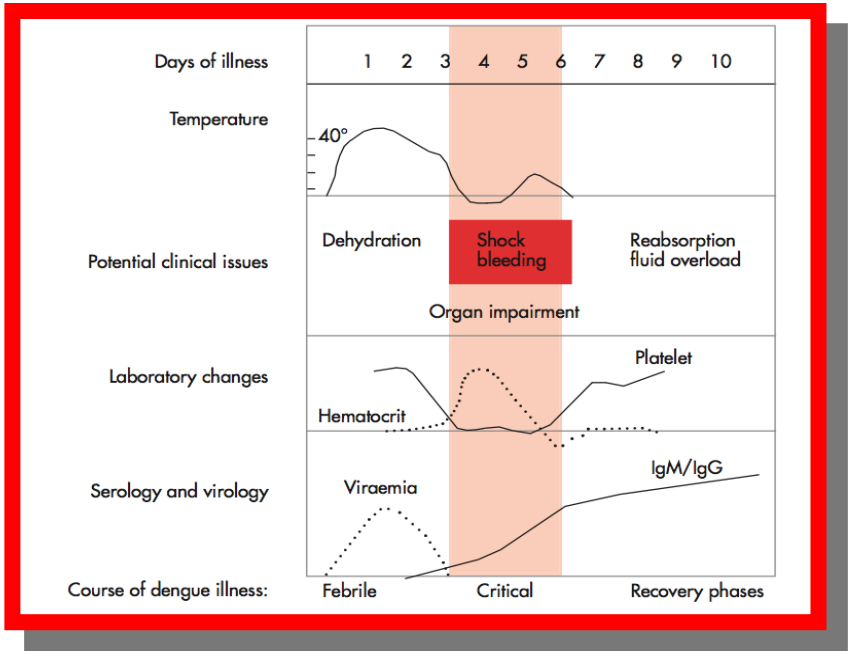
Recovery phase – 2

- Herman's rash– "isles of white in the sea of red"
- HCT stabilizes/lower due to the dilutional effect of reabsorbed fluid
- WBC ↑soon after defervescence while the recovery of platelet count is typically later than that of WBC.



Summary of clinical implications

1. **Febrile phase**
   - ✓ Diagnosis
   - ✓ Dehydration
   - ✓ Organ cx – eg encephalitis
2. **Critical phase**
   - ✓ Shock/Hemorrhage
   - ✓ organ cx
3. **Recovery phase**
   - ✓ hypervolemia



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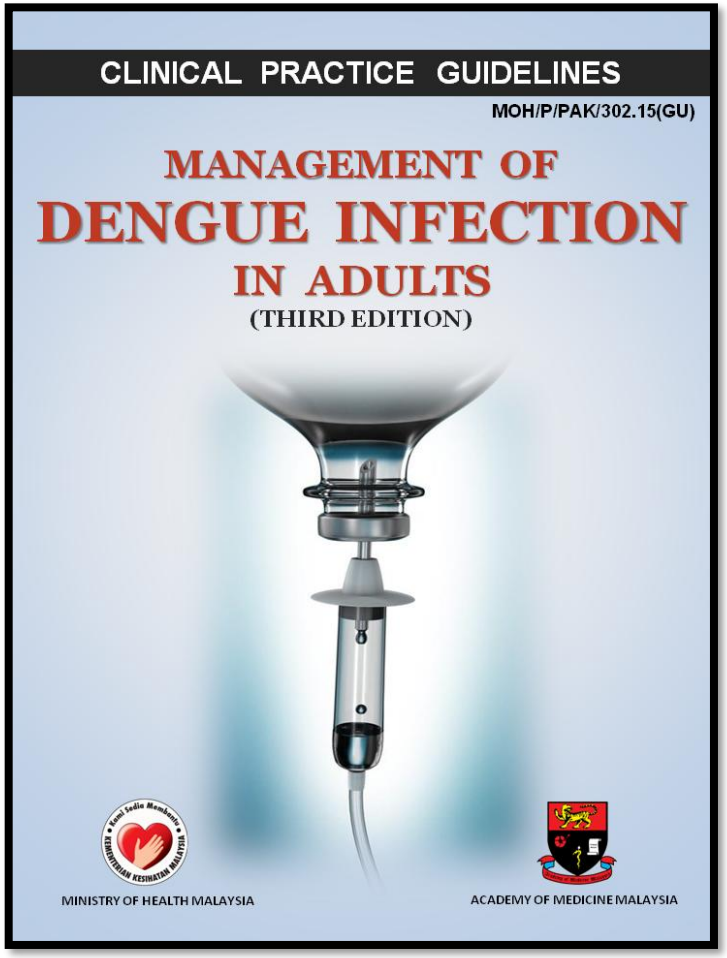
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