MMed and DCH Lectures

Dengue in children

September 27 2021

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Aims of today's session

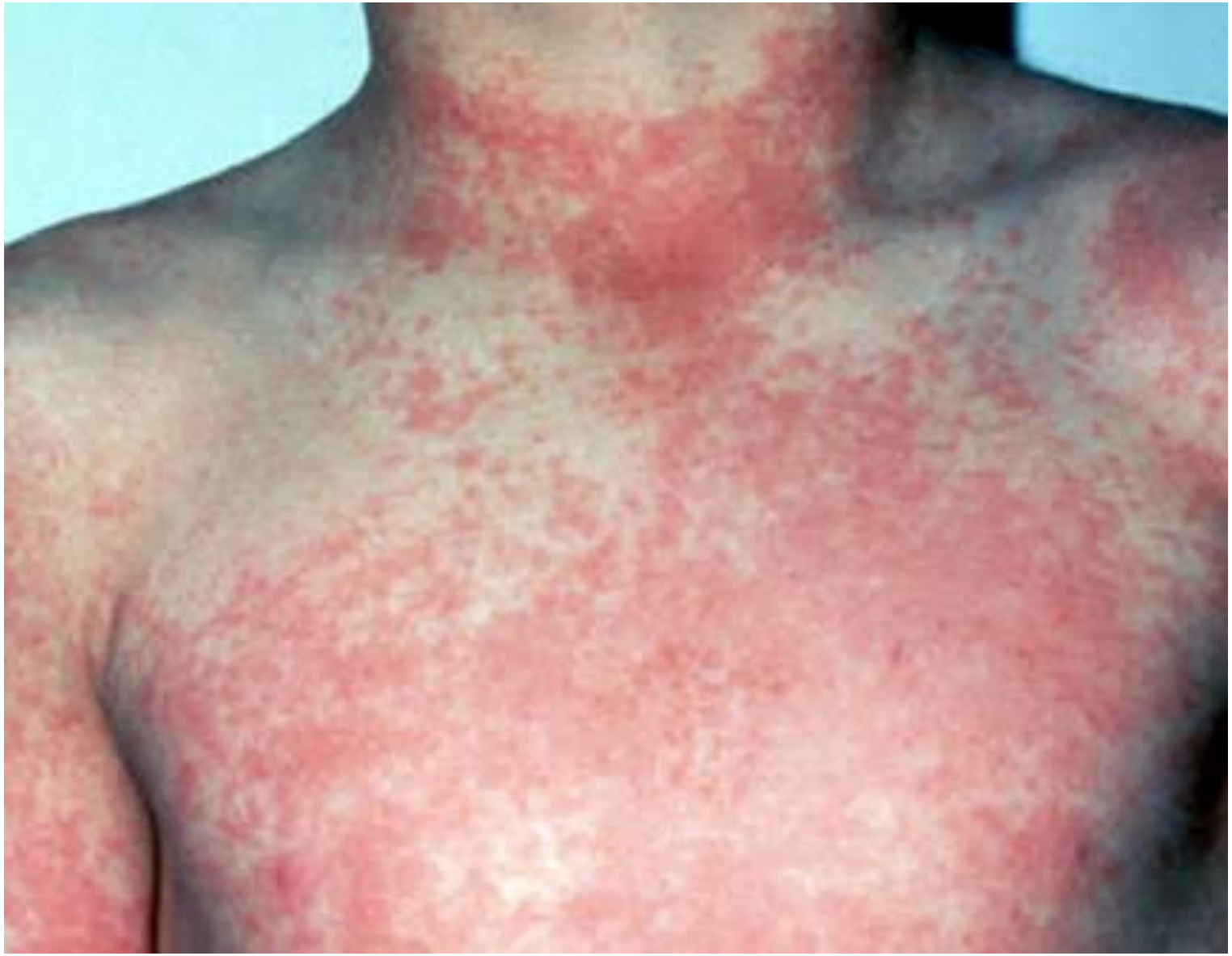
- Learn about dengue
- Understand the immunopathology, including "antibody-dependent enhancement"
- Understand why there is vascular permeability
- Know the clinical signs and differential diagnosis
- Understand the fluid management and supportive care of dengue of different severity

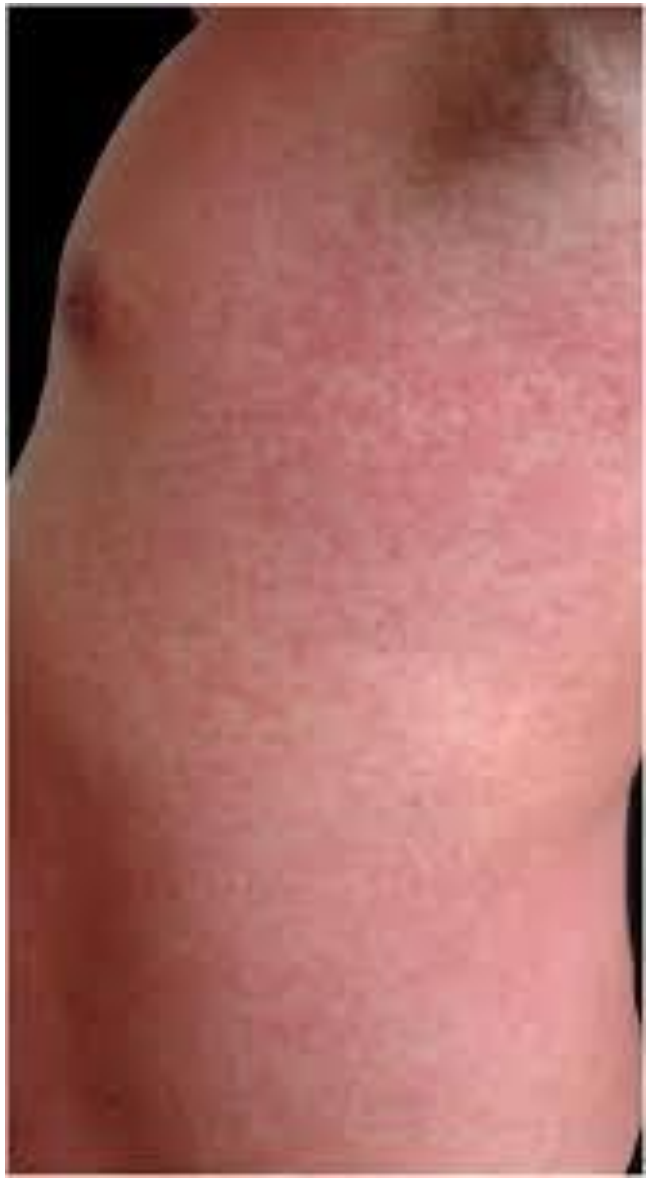
Classification

1. Dengue fever
2. Dengue with warning signs
3. Severe dengue – dengue haemorrhagic fever, shock syndrome

Dengue fever

- Incubation period 4-10 days
- 2-7 days of high fever, headaches, pain behind eyes, muscle aches and pains, nausea, vomiting, rash
- Rash – erythematous, looks like any other viral rash, conjunctival injection
- To distinguish from influenza – dengue has no respiratory symptoms



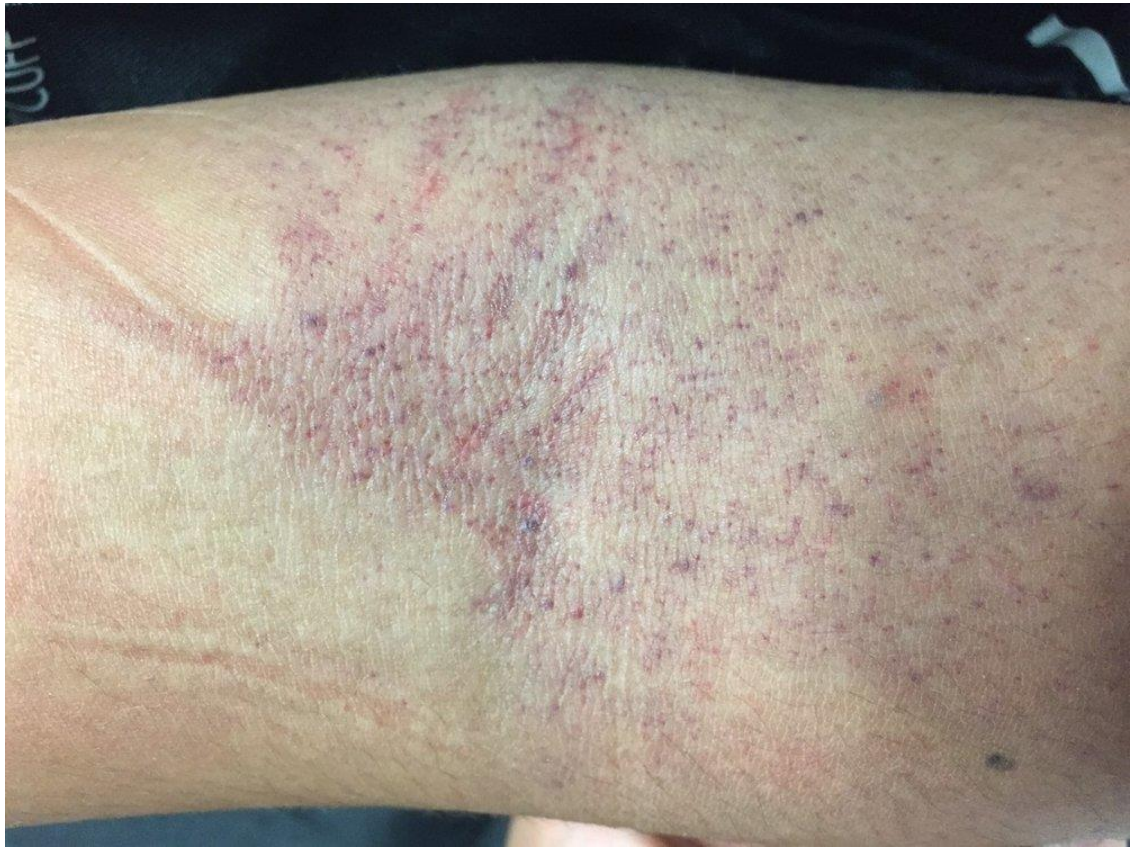


Severe dengue / Dengue haemorrhagic fever

- Warning signs 3-7 days after onset of symptoms:
  - Sudden weakness, severe abdominal pain, persistent vomiting, rapid breathing, bleeding gums, fatigue, restlessness, blood in vomit
- Capillary leak, oedema (lung, pleural effusions, ascites), respiratory distress, mucosal bleeding, organ failure
- Hct ↑, Platelets ↓, AST and ALT ↑, albumin ↓
- Narrow pulse pressure, e.g. 90/70, then sudden hypotension
- Gastrointestinal haemorrhage – ischaemia, usually only in shock

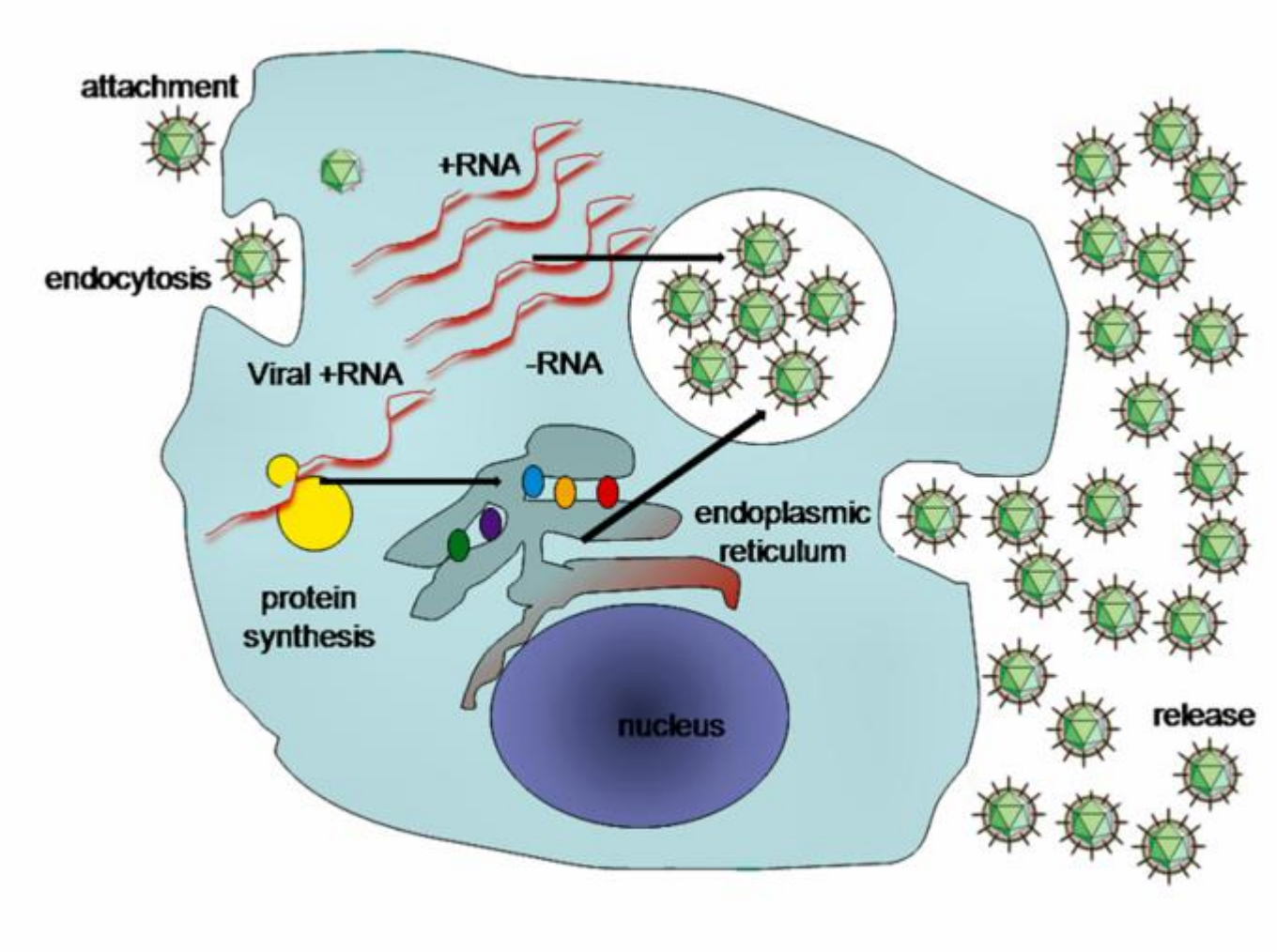
Dengue haemorrhagic fever

- Tourniquet test – inflate BP cuff between systolic and diastolic, leave for 5 minutes: >20 petechial spots = capillary fragility (+/= thrombocytopenia)
- *Non-specific*



Virus infections: the basics

- Viruses only replicate if they are intracellular
- They use host machinery (organelles)
- The ease with which a virus can enter a cell influences the amount of virus replication.

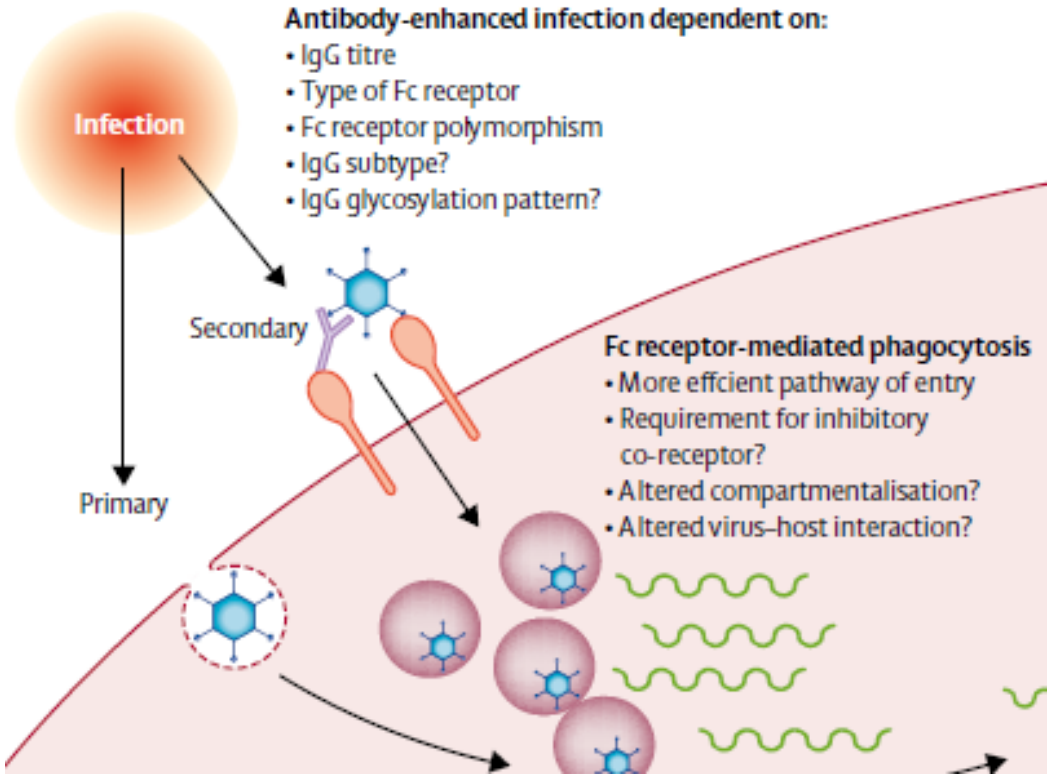


Antibodies produced in dengue infection

- Dengue neutralizing antibodies – protective (usually)
- Dengue cross-reactive *non-neutralizing* antibodies - enhancing

1. Antibody-dependent enhancement

- Primary infection: normal virus replication
- Secondary infection (in presence of antibodies).
  - Virus-IgG complex binds to Fc receptor on macrophages, monocytes
  - **100-fold increase in virus production**
  - Enhanced disease severity



2. T-cell activation and memory T-cells

- Secondary infection
  - Enhanced pro-inflammatory response (↑ interleukin-6 and other cytokines)
  - Diminished antiviral immune response (↓interferon)
  - Increased complement activation

3. Dengue vascular permeability syndrome

- Late in the febrile period of dengue – sudden vascular permeability syndrome, massive capillary leak
  - → oedema, ↓albumin, hypovolaemia, ↑ Hct, pleural effusions, ascites
- The cause – **a dengue virus protein toxin: NS1**
  - NS1 (non-structural protein 1) produced when cells are infected by *any* of the 4 dengue viruses.
  - NS1 interacts with receptors on monocytes, macrophages and endothelial cells → cytokines (e.g. IL-6)
  - NS1 stimulates enzymes which directly break down endothelial barriers.

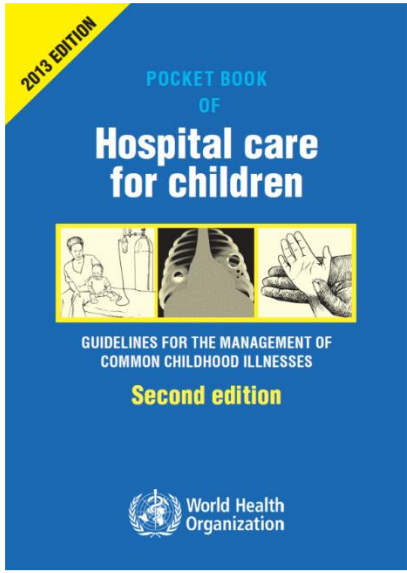
Who is at risk?

- Children (and adults) who become infected with a second dengue serotype after an initial ‘primary’ dengue infection with a different serotype (peak 3-5 years)

- Infants with primary dengue infections whose mothers have some DV immunity
  - Peak 7 months (2 months after neutralising antibodies have degraded below a protective level, but *non-neutralising* antibodies may still lead to enhanced virus replication)

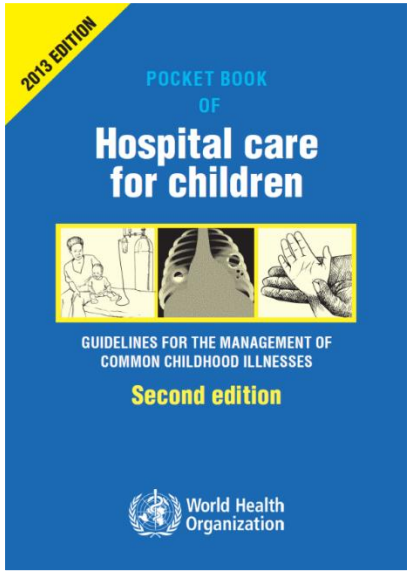
- Secondary infections: 40 x risk of DHF than primary infections

Care of any seriously ill child



- Triage
- Emergency treatment
- History and examination
- Laboratory investigations, if required
- Main diagnosis and other diagnoses
- Treatment
- Supportive care
- Monitoring
- Discharge planning
- Follow-up

Triage

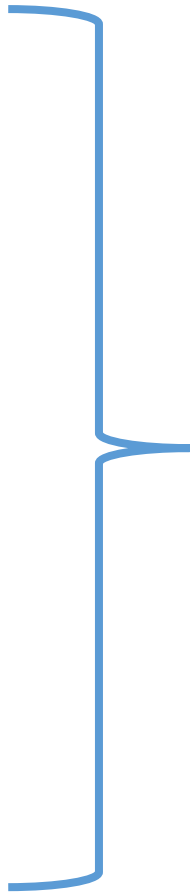


- Brief history of the presenting problem
- Take temperature and weight

A. Listen for stridor or obstructed breathing
B. Look for cyanosis and for signs of respiratory distress (chest indrawing, tracheal tug), check SpO_2
C. Feel the skin temperature of the hands and feet, feel the pulse for volume (narrow pulse pressure), check capillary refill time
D. Assess for lethargy and level of interaction.

Check for dengue warning signs

- Any Emergency signs
- Abdominal pain (hepatomegaly)
- Persistent vomiting
- Oedema
- Respiratory distress
- Petechiae / bruising / bleeding
- Lethargy
- Oliguria
- Hct ↑, platelets ↓



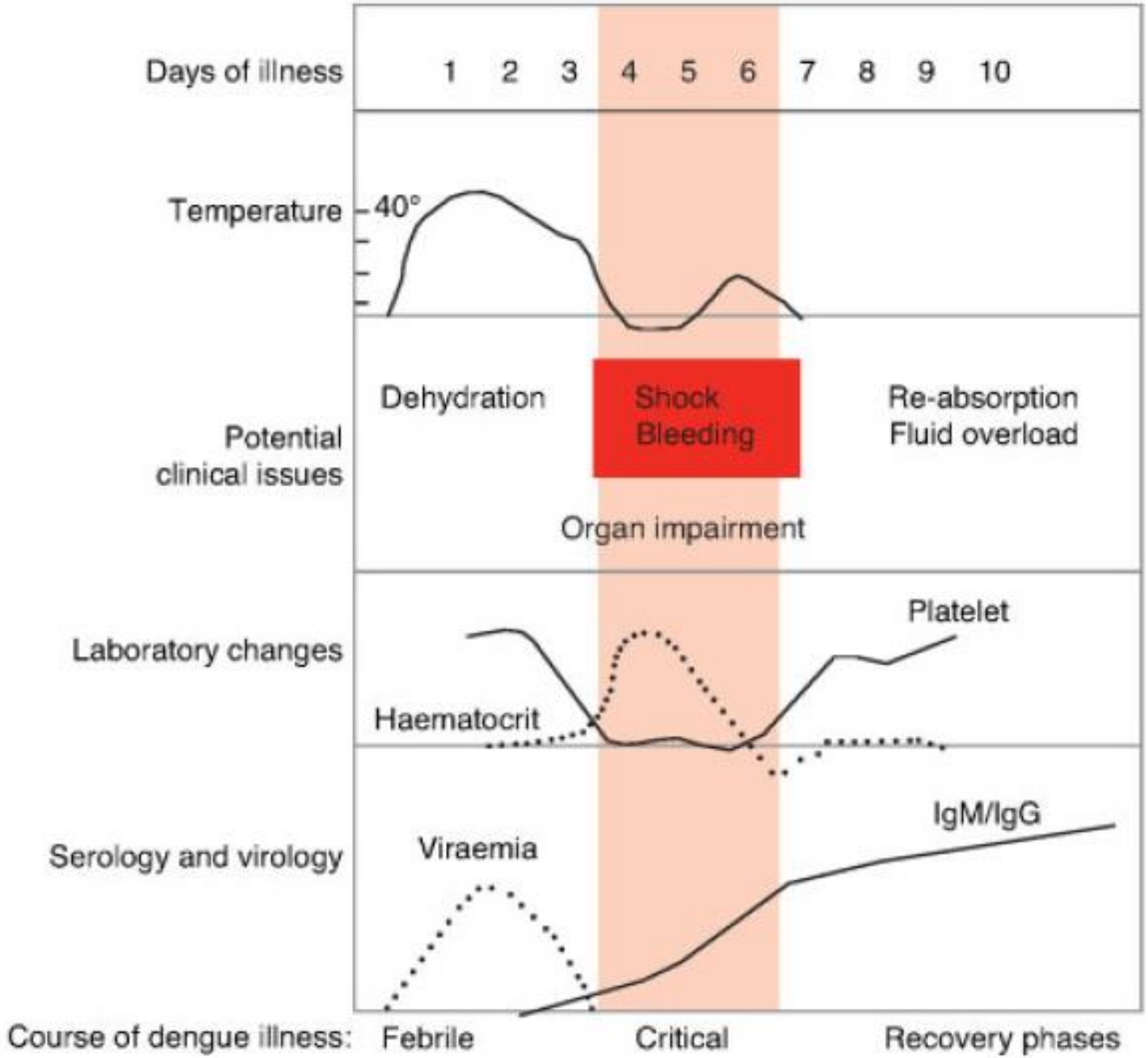
Admit to hospital

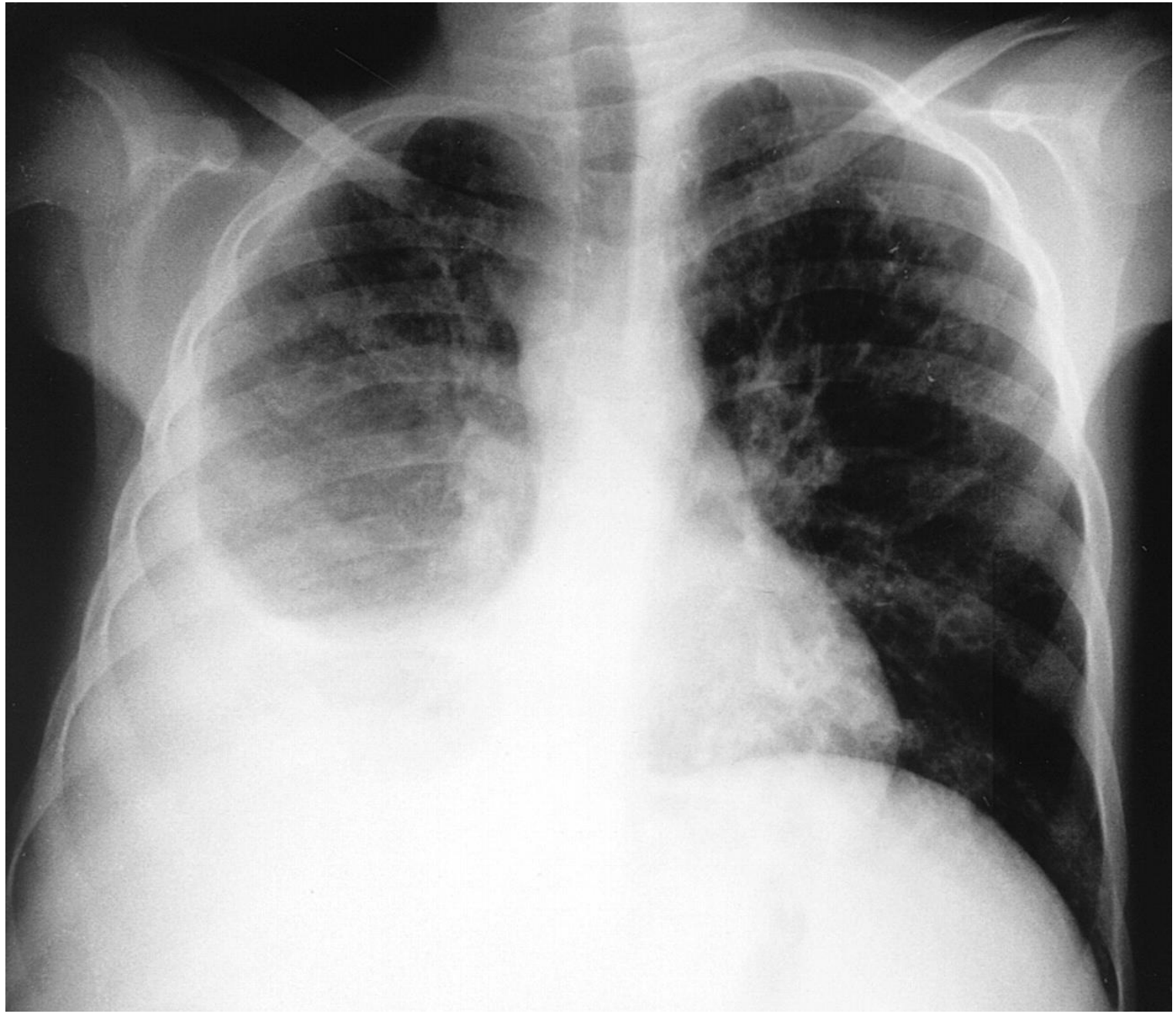
Differential diagnosis

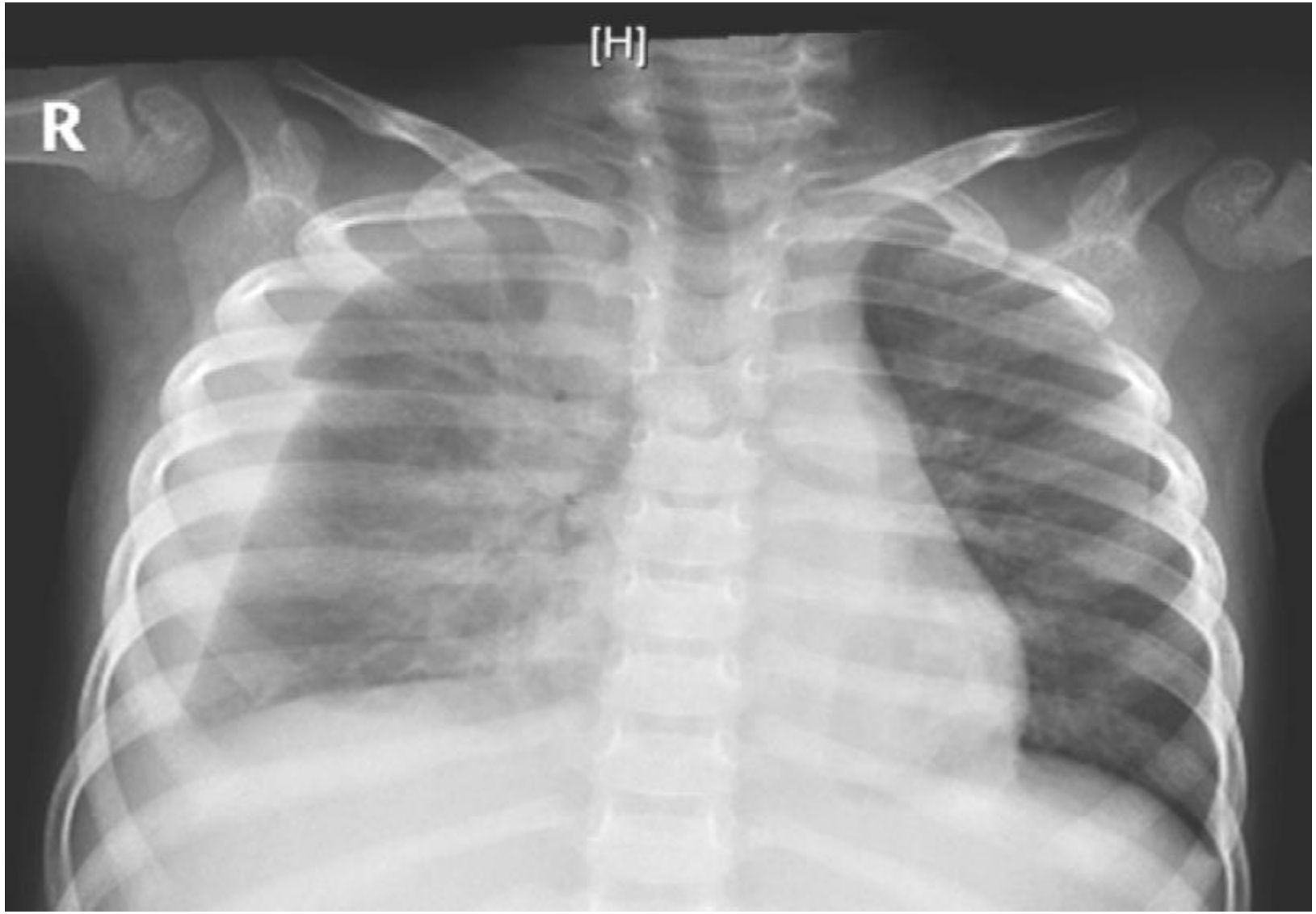
- Febrile stage
  - Malaria
  - Measles, rubella
  - Enterovirus, adenovirus, influenza
  - Bacterial sepsis
  - Typhoid
  - Other arboviral infections (Chikungunya)
  - COVID-19

Investigations

- Dengue virus PCR
- Viral antigen NSI
- Dengue IgM – nonspecific, and late
- FBE: High Hct, leukopenia, thrombocytopenia
- Hypoalbuminaemia
- Metabolic acidosis
- Chest x-ray: pleural effusion


Days of illness
1 2 3 4 5 6 7 8 9 10
Temperature
40°
Potential clinical issues
Dehydration
Shock Bleeding
Re-absorption Fluid overload
Organ impairment
Laboratory changes
Platelet
Haematocrit
Serology and virology
Viraemia
IgM/IgG
Course of dengue illness:
Febrile
Critical
Recovery phases

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Treatment

- Dengue fever
  - Analgesia – paracetamol, do not give aspirin or ibuprofen (increased bleeding risk)
  - Review daily until fever resolves, assess for warning signs of severe dengue
- Severe dengue
  - Supportive care – analgesia, fluids, respiratory, circulation support
  - Monitor for complications – shock, bleeding, pleural effusions, pulmonary congestion, kidney and liver dysfunction

Fluid management

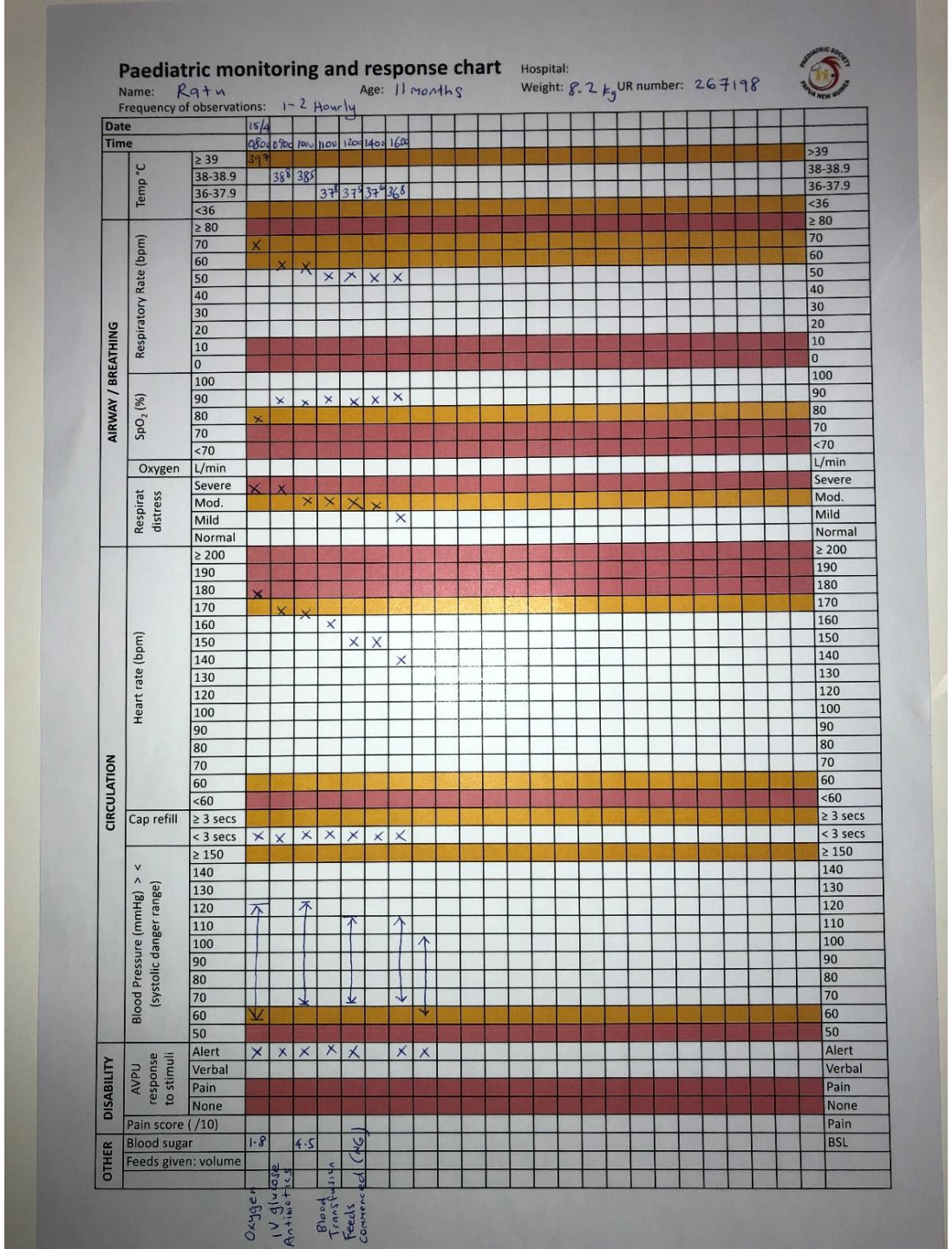
- Fever – encourage oral fluids
- Severe dengue
  - Plasma leak into extravascular compartment
  - Intravascular volume depletion
  - Cold limbs, pulse pressure <20, rapid weak pulse
  - Coagulopathy
  - Replace fluid deficit IV
- Convalescent phase
  - Excess extravascular fluid is reabsorbed into the intravascular space
  - Patient is fluid overloaded, reduce fluid to avoid pulmonary oedema

Dengue shock

- Isotonic crystalloid: IV fluid should be kept to the minimum required to maintain cardiovascular stability until capillary permeability is normal
- Assess pulse pressure:
  - Normal pulse pressure = no shock
  - <20 mmHg = shock
    - 10-20 ml/kg over 1 hour
    - Reassess circulation (hands and feet, pulse pressure)
- Give whole blood first if severe bleeding and shock
- Platelet transfusion if
  - <50,000 and severe bleeding, or
  - <5000 with any bleeding

Age	Systolic blood pressure	Diastolic blood pressure	Pulse pressure
Birth and neonate	60-85	45-55	25-35
Infant (1-12 mo)	80-100	55-65	35-45
Pre-school (1-5 y)	95-107	60-71	35-45
School-age (6-9 y)	95-110	60-73	35-50
Preadolescent (10-11 y)	100-119	65-76	35-50
Adolescent (12-15 y)	110-124	70-79	40-50

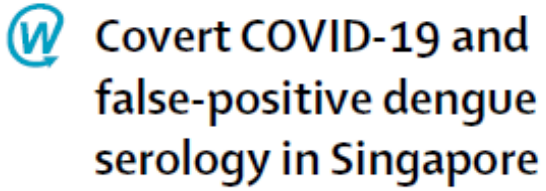
- Monitor closely in a HDU area



Convalescent / recovery phase

- Oxygen or CPAP may be needed for respiratory support
  - Wet lungs
  - Non-compliant lungs
  - Effusions
- When shock resolves the child is still oedematous with effusions
- Give diuretics if shock has resolved (normal pulse pressure, warm hands, capillary refill <3 seconds) if excess to remove fluid from lungs

Dengue and Covid-19



- Cross reactivity of dengue IgM and IgG, initially positive, but later COVID-19 PCR positive and dengue serology negative

New ways of controlling dengue

- Embryonic introduction of bacterium Wolbachia into *A. aegypti* populations.
- Wolbachia-infected *A. aegypti* are partially resistant to dengue virus infection.