Clinical Management of Dengue

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Clinical Director Communicable Disease Centre
Director Institute of Infectious Disease and Epidemiology
Tan Tock Seng Hospital

SIIDC 2017 Singapore
Communicable Disease Centre

Centralised outbreak management centre

Communicable Disease Centre
No of Beds: 211
Built in 1907

Communicable Disease Centre 1
80 Isolation Rooms
In the middle of SARS

Communicable Disease Centre 2
Self-contained
No of Beds: 94
Near end of SARS
Interim enhancement of isolation facilities
1907 Smallpox, plaque
1938 Typhoid
1945-46 Polio outbreak
1957 Asian Flu
1958 Polio
1959 Smallpox

1961 Diphtheria
1963 Cholera
1964 Typhoid
1999 Nipah Outbreak

2000s
2003 SARS
2005 Worst dengue epidemic
2008 Chikungunya
2009 H1N1
2013 Worst dengue epidemic
2016 Zika
2012 Formed IIDE

H7N9
EBOLA
MERS CoV

1907 Isolation camp
1920 Middleton Hospital
1985 Merged with TTSH
1992 Dept ID formed

National Centre for Infectious Diseases (NCID)
Dengue in Singapore

Despite vector control, low breeding index, Singapore faces successive waves of dengue epidemic.

Predominantly adult dengue and increasingly more senior adults.

Increasing recognition of atypical dengue.
2.5 billion people -40% of world population – are at risk of dengue

100 million dengue virus infections worldwide every year

Half a million with severe dengue
“Atypical” presentations

Switzerland, 2008) agreed that “dengue is one disease entity with different clinical presentations and often with unpredictable clinical evolution and outcome.”

Expect the unexpected
“Atypical” presentations
Dengue epidemic

Are admission and iv fluid necessary?
Dengue management

Enhance care at community

Febrile phase

Admission criteria

Secondary Care Hospitalization

• Adequate trained staff
• Lab support
• Adequate consumables

Critical phase

Hospitalisation

Fluid management

Primary Care

• Early recognition / suspicion of dengue
• POCT / rapid combined Ag/Abs
• Daily monitoring
• Early recognition of warning signs

Tertiary Care ICU

Specialized dengue care unit

Final Outcome

Recovery

WHO 2009
Emphasis on early diagnosis and identify early predictors to effectively manage the entire course of dengue illness.

Early diagnosis

Early predictors
Day 8 illness, afebrile
Simple **cheap** clinical and or laboratory tools are needed to better diagnose dengue and able to diagnose dengue early.

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**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)
**Dengue diagnostics** - Use the right tool at the right time

<table>
<thead>
<tr>
<th>Clinical sample</th>
<th>Diagnostic method</th>
<th>Methodology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute serum (1–5 days of fever) and necropsy tissues</td>
<td>Viral isolation</td>
<td>Mosquito or mosquito cell culture inoculation</td>
</tr>
<tr>
<td></td>
<td>Nucleic acid detection</td>
<td>RT-PCR and real time RT-PCR</td>
</tr>
<tr>
<td></td>
<td>Antigen detection</td>
<td>NS1 Ag rapid tests</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NS1 Ag ELISA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Immuno-histochemistry</td>
</tr>
</tbody>
</table>

**Virus detection and its components**

**Serological response**

<table>
<thead>
<tr>
<th>Paired sera (acute serum from 1–5 days and second serum 15–21 days after)</th>
<th>IgM or IgG seroconversion</th>
<th>ELISA</th>
<th>Neutralization Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum after day 5 of fever</td>
<td>IgM detection (recent infection)</td>
<td>ELISA</td>
<td>Rapid tests</td>
</tr>
<tr>
<td></td>
<td>IgG detection</td>
<td>IgG ELISA</td>
<td>HIA</td>
</tr>
</tbody>
</table>

IgG = immunoglobulin G; IgM = immunoglobulin M

**WHO 2012**
Dengue diagnosis in 20 minutes

- 246 patients at TTSH
- Over 8 months
NS1 only Sen 82%, Spec 98%     NS1/IgM,IgG Sen 94%, Spec 92%
Either WHO 1997 or 2009 is sensitive (>90%) but not specific (20-26%)
Just 30 mins to check if you have dengue

The CDC hopes to get clinics here to start using a new dengue test kit which can produce results in 20 to 30 minutes, with just three drops of blood. — ST PHOTO: ANDREA ONG

Straits Time 22nd Nov 2012

Reaching out to community
More asking for dengue tests at clinics

By KASH CHEONG

AS DENGUE numbers continue to climb in Singapore, more patients at some private clinics are asking for blood tests to diagnose the disease.

Such tests cost at least $400 at private clinics. The Straits Times spoke to, but those with fever seem to want to play it safe. “This, despite doctors saying dengue blood tests are accurate only if a fever persists for a few days.

At the Healthcare clinic in Tampines Street 71, about four in 10 patients with fever have been asking for these tests to find out if they have the disease, resident doctor Philip Koh said. This is in contrast to last year, when Dr Koh saw virtually no such requests.

“Patients used to be taken aback when we asked them to do blood tests; now, they are receptive and some have even been asking for it,” he said. “More are concerned because our clinic is in a major dengue hot spot.”

At Eden Family Clinic in Jurong West Street 41, two in 10 patients with a persistent fever have asked to be tested for dengue, said Dr Elias Tam.

Singapore is in the grip of what could be its worst dengue epidemic, with 9,683 cases diagnosed so far this year. From Sunday till 3pm yesterday, there were 397 new cases of dengue. ST PHOTO: JOHNS WONG

ST 13th June 2013
5th ASEAN Dengue Day Seminar - 2015

13 Jun 2015: Attended by over 140 general practitioners, physicians, researchers, nurses, pharmacists, and other healthcare professionals

Engaging Primary Care
Field Evaluation and Impact on Clinical Management of a Rapid Diagnostic Kit That Detects Dengue NS1, IgM and IgG

Anne-Claire Andries¹, Veesna Duong¹, Chantha Ngan², Sivuth Ong¹, Rekol Huy², Kim Kim Sroïn³, Vantha Te⁶, Bunthin Y¹, Patrich Lorn Try⁷, Philippe Buchy¹*

Table 2. Concordance of the NS1 test between hospitals' laboratories and IPC.

<table>
<thead>
<tr>
<th></th>
<th>IPC</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Negative</td>
<td>Positive</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>Hospitals</td>
<td>Negative</td>
<td>98</td>
<td>2</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>1</td>
<td>56</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>99</td>
<td>58</td>
<td>157</td>
</tr>
</tbody>
</table>

*K 0.96, 98.1% agreement

Table 3. Concordance of the IgM/IgG tests between hospitals' laboratories and IPC.

<table>
<thead>
<tr>
<th></th>
<th>IPC</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Negative</td>
<td>IgM positive</td>
<td>IgG positive</td>
<td>IgM and IgG positive</td>
<td>Total</td>
</tr>
<tr>
<td>Hospitals</td>
<td>Negative</td>
<td>45</td>
<td>2</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>IgM positive</td>
<td>0</td>
<td>10</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>IgG positive</td>
<td>0</td>
<td>0</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>IgM and IgG positive</td>
<td>3</td>
<td>3</td>
<td>7</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>48</td>
<td>15</td>
<td>29</td>
<td>65</td>
</tr>
</tbody>
</table>

*K 0.55, 68.8% agreement

June – Oct 2011
2 hospitals + reference lab
162 enrolled, 157 analysed
85 confirmed, 41 probable
(32DF, 84DHF, 8DSS)
31 negative
Table 4. Performances of the kit against confirmed and probable dengue cases in hospitals and IPC.

<table>
<thead>
<tr>
<th>Test kit</th>
<th>Place</th>
<th>Sensitivity % [CI95%]</th>
<th>p-value*</th>
<th>Specificity % [CI95%]</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>SD Dengue Duo NS1</td>
<td>Hospitals</td>
<td>44.4 (56/126) [35.6–53.6]</td>
<td>1</td>
<td>96.8 (30/31) [83.3–99.9]</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>IPC</td>
<td>45.2 (57/126) [36.4–54.3]</td>
<td></td>
<td>96.8 (30/31) [83.3–99.9]</td>
<td></td>
</tr>
<tr>
<td>SD Dengue Duo NS1/IgM/IgG</td>
<td>Hospitals</td>
<td>85.7 (108/126) [78.4–91.3]</td>
<td>0.003</td>
<td>83.9 (26/31) [66.3–94.5]</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>IPC</td>
<td>94.4 (119/126) [88.9–97.7]</td>
<td></td>
<td>90.0 (27/30) [73.5–97.9]</td>
<td></td>
</tr>
</tbody>
</table>

*Mc Nemar test.

<table>
<thead>
<tr>
<th>PPV % [CI95%]</th>
<th>p-value**</th>
<th>NPV % [CI95%]</th>
<th>p-value**</th>
</tr>
</thead>
<tbody>
<tr>
<td>98.2 (56/57)</td>
<td>1</td>
<td>30.0 (30/100)</td>
<td>1</td>
</tr>
<tr>
<td>[90.6–100]</td>
<td></td>
<td>[21.2–40]</td>
<td></td>
</tr>
<tr>
<td>98.3 (57/58)</td>
<td></td>
<td>30.3 (30/99)</td>
<td></td>
</tr>
<tr>
<td>[90.8–100]</td>
<td></td>
<td>[20.6–39.3]</td>
<td></td>
</tr>
<tr>
<td>95.6 (108/113)</td>
<td>0.49</td>
<td>59.1 (26/44)</td>
<td>0.09</td>
</tr>
<tr>
<td>[90.0–98.5]</td>
<td></td>
<td>[43.2–73.7]</td>
<td></td>
</tr>
<tr>
<td>97.5 (119/122)</td>
<td></td>
<td>77.1 (27/35)</td>
<td></td>
</tr>
<tr>
<td>[93.0–99.5]</td>
<td></td>
<td>[59.9–89.6]</td>
<td></td>
</tr>
</tbody>
</table>

Dengue duo NS1/IgM/IgG
Hospital labs: 85.7% Sn, 83.9% Sp, PPV 95.6%, NPV 59.1%
Reference lab: 94.4% Sn, 90% Sp, PPV 97.5%, NPV 77.1%
Figure 1.4 Suggested dengue case classification and levels of severity

**DENGUE ± WARNING SIGNS**
- with warning signs
- without

**SEVERE DENGUE**
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

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

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

**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 >= 1,000
- CNS: Impaired consciousness
- Heart and other organs

*requiring strict observation and medical intervention*
Utilities and Limitations of the World Health Organization 2009 Warning Signs for Adult Dengue Severity

Tun-Linn Thein1,3, Victor C. Gan1,3, David C. Lye1,2, Chee-Fu Yung1, Yee-Sin Leo1,2

Table 3. Performance of warning signs (WS) for predicting dengue hemorrhagic fever (DHF) (n = 1507).

<table>
<thead>
<tr>
<th>Warning signs</th>
<th>Sn</th>
<th>Sp</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individual WS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain or tenderness</td>
<td>0.29</td>
<td>0.73</td>
<td>0.17</td>
<td>0.85</td>
</tr>
<tr>
<td>Persistent vomiting</td>
<td>0.06</td>
<td>0.93</td>
<td>0.16</td>
<td>0.82</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>0.01</td>
<td>0.99</td>
<td>0.20</td>
<td>0.81</td>
</tr>
<tr>
<td>Hematocrit rise and rapid platelet count drop</td>
<td>0.09</td>
<td>0.92</td>
<td>0.17</td>
<td>0.83</td>
</tr>
<tr>
<td>Clinical fluid accumulation</td>
<td>0.02</td>
<td>0.98</td>
<td>0.18</td>
<td>0.83</td>
</tr>
<tr>
<td>Mucosal bleeding</td>
<td>0.42</td>
<td>0.88</td>
<td>0.31</td>
<td>0.93</td>
</tr>
<tr>
<td>Lethargy</td>
<td>0.33</td>
<td>0.55</td>
<td>0.28</td>
<td>0.61</td>
</tr>
<tr>
<td>WS count*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any number of seven WS</td>
<td>0.87</td>
<td>0.18</td>
<td>0.30</td>
<td>0.77</td>
</tr>
<tr>
<td>Any number of six WS (without lethargy)</td>
<td>0.81</td>
<td>0.57</td>
<td>0.19</td>
<td>0.96</td>
</tr>
<tr>
<td>One WS</td>
<td>0.64</td>
<td>0.70</td>
<td>0.18</td>
<td>0.95</td>
</tr>
<tr>
<td>Two WS</td>
<td>0.44</td>
<td>0.89</td>
<td>0.25</td>
<td>0.95</td>
</tr>
<tr>
<td>Three WS</td>
<td>0.21</td>
<td>0.96</td>
<td>0.27</td>
<td>0.95</td>
</tr>
<tr>
<td>Four WS</td>
<td>0.04</td>
<td>0.98</td>
<td>0.14</td>
<td>0.94</td>
</tr>
</tbody>
</table>

Predicting DHF

NPV 0.96 in the absence of any WS

> 3 WS specific but not sensitive
Utility of warning signs in guiding admission and predicting severe disease in adult dengue

Mucosal bleeding the most common WS

NPV for severe disease in the absence of any WS was 100%

Table 4 Performance of individual warning signs in predicting DHF and SD in outpatients

<table>
<thead>
<tr>
<th>Warning sign</th>
<th>DHF I–IV (N = 70)</th>
<th>DHF II–IV (N = 43)</th>
<th>SD (N = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sn</td>
<td>Sp</td>
<td>PPV</td>
</tr>
<tr>
<td>Abdominal pain (N = 88)</td>
<td>31</td>
<td>78</td>
<td>25</td>
</tr>
<tr>
<td>Persistent vomiting (N = 16)</td>
<td>7</td>
<td>96</td>
<td>31</td>
</tr>
<tr>
<td>Clinical fluid accumulation (N = 1)</td>
<td>1</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Mucosal bleeding (N = 154)</td>
<td>61</td>
<td>64</td>
<td>28</td>
</tr>
<tr>
<td>Hepatomegaly (&gt; 2 cm) (N = 2)</td>
<td>1</td>
<td>100</td>
<td>50</td>
</tr>
<tr>
<td>↑ in hematocrit; rapid ↓ of platelet (N = 10)</td>
<td>14</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Any warning sign (N = 203)</td>
<td>79</td>
<td>52</td>
<td>27</td>
</tr>
<tr>
<td>Two warning signs (N = 61)</td>
<td>33</td>
<td>88</td>
<td>38</td>
</tr>
<tr>
<td>Three warning signs (N = 7)</td>
<td>6</td>
<td>99</td>
<td>57</td>
</tr>
</tbody>
</table>

Leo et al. BMC Infectious Diseases 2013, 13:498
Majority had WS 1 day prior to onset of severe illness
Considerable within-patient variation

Higher UACR values in dengue cases

Peak UACR values for dengue cases observed around day 5
Predictive Value of Proteinuria in Adult Dengue Severity

Farhad F. Vasanwala¹,²,³, Tun-Linn Thein²,³, Yee-Sin Leo²,³,⁴, Victor C. Gan², Ying Hao², Linda K. Lee², David C. Lye²,³

PADS prospective study
168 dengue cases
34 DHF
Predictive Value of Proteinuria in Adult Dengue Severity

Farhad F. Vasanwala¹,², Tun-Linn Thein²,³, Yee-Sin Leo²,³,⁴, Victor C. Gan², Ying Hao², Linda K. Lee², David C. Lye²,³
Figure 1.4 Suggested dengue case classification and levels of severity

**DENGUE ± WARNING SIGNS**

- **Probable dengue**
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  - Fever and 2 of the following criteria:
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    - 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 enlargement >2 cm
- Laboratory: increase in HCT concurrent with rapid decrease in platelet count

**CRITERIA FOR SEVERE DENGUE**

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

* (Requiring strict observation and medical intervention)
Dengue Fever
Dengue Hemorrhagic fever
Dengue Shock Syndrome
Case definition for dengue haemorrhagic fever

The following must all be present:

- Fever, or history of acute fever, lasting 2–7 days, occasionally biphasic.
- Haemorrhagic tendencies, evidenced by at least one of the following:
  - a positive tourniquet test
  - petechiae, ecchymoses or purpura
  - bleeding from the mucosa, gastrointestinal tract, injection sites or other locations
  - haematemesis or melaena.
- Thrombocytopenia (100,000 cells per mm$^3$ or less).
- Evidence of plasma leakage due to increased vascular permeability, manifested by at least one of the following:
  - a rise in the haematocrit equal to or greater than 20% above average for age, sex and population;
  - a drop in the haematocrit following volume-replacement treatment equal to or greater than 20% of baseline;
  - signs of plasma leakage such as pleural effusion, ascites and hypo-proteinaemia.
Capillary permeability, age and DHF

Figure 3. $K_f$ data obtained from 89 healthy Vietnamese volunteers aged 5 to 77 years.

Figure 4. Hypothetical pattern of microvascular permeability with time for uninfected adults, uninfected children, and children with dengue hemorrhagic fever (DHF) with and without hemodynamic shock.
Increasing DHF with younger patients; 0.3 in 1997 to 0.07 in 2000
Pediatric Dengue
Severe plasma leakage

Adult dengue
Pleural effusion
Typically right side
Fever and hypotension

39, Female designer, history of Thalassemia, Prolapsed intervertebral disc,

No recent travel for the past 2 weeks before illness onset

Consulted GP twice (D1 and D3 illness-> referred to ED)

1st ED presentation at D3 Illness 14:00: T 39.6 C, lowest BP recorded 86/50, HR 91/min
1.5 L NS given, advised admission but patient requested AMA (personal commitment) BP 94/58, HR 90/min upon ED discharge

2nd ED presentation D3 illness 21:26: returned for admission, BP 78/58, HR 99/min, total 2 L IV NS given, IV dopamine 5 → 10 mcg/kg/min
ECG: D3 4:20 PM

Rate 79: Age not entered, assumed to be 50 years old for purpose of ECG interpretation
HR 759: Sinus rhythm. Normal P axis, V-rate 50-99
PR 170: Low voltage extremity leads. All extremity leads <0.5mV
QRS 89
QT 408
QTcB 448
QTcF 447
---AXIS---
P 74
QRS 10
T 50

12 Lead: Standard Placement

Unconfirmed Diagnosis
ECG D4 1:35 PM

Rate: 65 Hz

Age not entered, assumed to be 50 years old for purpose of ECG interpretation

Sinus rhythm

Normal P axis, V-rate 50-99

PR: 277 ms

Sinus pause

Long R-R interval, normal QRS

QRS: 92 ms

Prolonged PR interval

Pr >210, V-rate 50-99

Qp: 448

Low voltage, extremity leads

All extremity leads <0.4mV

QPC: 459 ms

Nonspecific T abnormalities, lateral leads

T <0.10mV, I AVL V5 V6

AXIS

P: 93

QRS: 76

T: 55

I2 Lead Standard Placement

Unconfirmed Diagnosis
ECG D5  8:30 AM

Rate  54  Age not entered, assumed to be 50 years old for purpose of ECG interpretation
FR  135  Unknown rhythm, irregular rate  V-rate 46-64, variation>10%
QRS  99  Low voltage, extremity leads <0.5mV
QTc  478

ABNORMAL ECG -

12 Lead; Standard Placement

Unconfirmed Diagnosis
Rate 92: Age not entered, assumed to be 50 years old for purpose of ECG interpretation

Sinus rhythm

PR 104: Short PR interval

QRS 88: Low voltage, extremity leads <0.5 mv

QT 413: Abnormal T, consider ischemia, anterolateral I & aVL V2-V6

QTc 511: Prolonged QT interval

--AXIS--

P 56
QRS 22
T 254

12 Lead: Standard Placement

Unconfirmed Diagnosis
Proposed viral and immune mechanisms in the cardiac manifestations of dengue

**Figure 2** Proposed viral and immune mechanisms involved in the cardiac and vascular manifestations of dengue. DENV is taken up into macrophages with the resulting T-cell activation and release of vasoactive and proinflammatory cytokines implicated in the capillary leak and possibly also in myocardial impairment. The interaction between the NS1 and the glycoalyx layer of the vascular endothelium is thought to increase capillary permeability. The resulting plasma leakage can contribute to the cardiac dysfunction in the form of reduced preload, altered coronary microcirculation, and myocardial interstitial oedema. Altered intracellular calcium homeostasis has also been demonstrated in dengue infected myotubes. Abbreviations: DENV, dengue virus; NS1, nonstructural protein 1.

Fig. 5. Algorithm for fluid management of compensated shock: in adults

Compensated shock
(Systolic pressure maintained + signs of reduced perfusion)

- Start isotonic crystalloid
  5-10 ml/kg/hr for 1 hour

- **IMPROVEMENT***
  - IV crystalloid, reduce gradually
    5-7 ml/kg/hr for 1–2 hours
    3–5 ml/kg/hr for 2–4 hours
    2–3 ml/kg/hr for 2–4 hours

- As clinical improvement is noted, reduced fluids accordingly

- Further boluses may be needed for the next 24–48 hours

- **IMPROVEMENT***
  - Reduce IV crystalloids
    7-10 ml/kg/hr for 1–2 hours

- **IMPROVEMENT***
  - Crystalloid (2nd bolus) or colloid**
    10-20 ml/kg/hr for 1 hour

- Check HCT
  - HCT↑ or High

- Severe overt bleed
  - Yes
  - Urgent blood transfusion
  - HCT↓

- No
  - Colloid 10-20 ml/kg/hr
  - Evaluate to consider blood transfusion if no clinical improvement

- Stop IV fluids at 48 hours

---

***Reassess the patient’s clinical condition, vital signs, pulse volume, capillary refill time and temperature of extremities.

**Colloid is preferable if the patient has already received previous boluses of crystalloid

- IV: intravenous, HCT: haematocrit, ↑: increased, ↓: decreased.
Bleeding in dengue fever
Older adults with dengue have more atypical presentations, more organ involvement, more pre-existing comorbidities, higher mortality, require higher index of suspicion to diagnose, closer monitoring and careful management.
Dengue (DHF) in the elderly

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

**Table 1**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Elderly (≥ 65 years)</th>
<th>Non-elderly (19-64 years)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years; mean ± SD)</td>
<td>70.2 ± 4.7</td>
<td>48.8 ± 11.9</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Male/female (%)</td>
<td>31 (47)/35 (53)</td>
<td>108 (44.8)/133 (55.2)</td>
<td>0.781</td>
</tr>
<tr>
<td>Underlying disease/condition† (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>19 (28.8)</td>
<td>43 (17.8)</td>
<td>0.058</td>
</tr>
<tr>
<td>Hypertension</td>
<td>35 (53)</td>
<td>57 (23.7)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>16 (24.2)</td>
<td>8 (3.3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>COPD</td>
<td>15 (22.7)</td>
<td>6 (2.5)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Chronic renal disease</td>
<td>10 (15.2)</td>
<td>4 (1.7)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Corticosteroid use</td>
<td>17 (25.8)</td>
<td>4 (1.7)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Malignancy</td>
<td>4 (6)</td>
<td>4 (1.7)</td>
<td>0.068</td>
</tr>
<tr>
<td>Heart disease</td>
<td>2‡ (3)</td>
<td>38 (1.2)</td>
<td>0.293</td>
</tr>
<tr>
<td>DSS (%)</td>
<td>7 (10.6)</td>
<td>11 (4.6)</td>
<td>0.077</td>
</tr>
<tr>
<td>Length of fever (day; mean ± SD)</td>
<td>4.4 ± 2.5</td>
<td>4.5 ± 1.9</td>
<td>0.454</td>
</tr>
<tr>
<td>Acute renal failure (%)</td>
<td>8 (12.1)</td>
<td>4 (1.7)</td>
<td>0.001</td>
</tr>
<tr>
<td>Rhabdomyolysis, n/N (%)</td>
<td>3/7 (42.9)</td>
<td>0/4 (0)</td>
<td>0.236</td>
</tr>
<tr>
<td>Concurrent bacteremia, n/N (%)</td>
<td>4/23 (17.4)</td>
<td>2/59 (3.4)</td>
<td>0.049</td>
</tr>
<tr>
<td>Receiving antibiotic therapy (%)</td>
<td>19 (28.8)</td>
<td>42 (17.4)</td>
<td>0.054</td>
</tr>
<tr>
<td>Pleural effusion (bilateral or unilateral), n/N (%)</td>
<td>26/46 (56.5)</td>
<td>60/173 (34.7)</td>
<td>0.010</td>
</tr>
<tr>
<td>Gallbladder edema, n/N (%)</td>
<td>16/31 (51.6)</td>
<td>73/131 (42.2)</td>
<td>0.693</td>
</tr>
<tr>
<td>Ascites, n/N (%)</td>
<td>10/31 (32.3)</td>
<td>54/131 (41.2)</td>
<td>0.418</td>
</tr>
<tr>
<td>Length of hospital stay (day; mean ± SD)</td>
<td>7.9 ± 4.9</td>
<td>6.3 ± 2.9</td>
<td>0.049</td>
</tr>
<tr>
<td>Fatality (%)</td>
<td>5 (7.6)</td>
<td>2 (0.8)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Co-morbidity, ARF, Pleural effusion, fatality
# Prophylactic Platelets in Dengue: Survey Responses Highlight Lack of an Evidence Base

<table>
<thead>
<tr>
<th>Clinical case</th>
<th>Asia  (n = 134)</th>
<th>Africa (n = 39)</th>
<th>S. America &amp; Caribbean (n = 130)</th>
<th>UK  (n = 3)</th>
<th>Total  (n = 306)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylactic platelet transfusion threshold:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50×10^9/L</td>
<td>8 (6)</td>
<td>23 (59)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>31 (10.1)</td>
</tr>
<tr>
<td>&lt;40×10^9/L</td>
<td>1 (0.7)</td>
<td>7 (17.9)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>8 (2.6)</td>
</tr>
<tr>
<td>&lt;30×10^9/L</td>
<td>1 (0.7)</td>
<td>7 (17.9)</td>
<td>2 (1.5)</td>
<td>0 (0)</td>
<td>10 (3.3)</td>
</tr>
<tr>
<td>&lt;20×10^9/L</td>
<td>12 (9)</td>
<td>1 (2.6)</td>
<td>2 (1.5)</td>
<td>2 (66.7)</td>
<td>17 (5.6)</td>
</tr>
<tr>
<td>&lt;10×10^9/L</td>
<td>33 (24.6)</td>
<td>0 (0)</td>
<td>12 (9.2)</td>
<td>1 (33.3)</td>
<td>46 (15)</td>
</tr>
<tr>
<td>Not in absence of bleeding</td>
<td>75 (56)</td>
<td>1 (2.6)</td>
<td>39 (30)</td>
<td>0 (0)</td>
<td>190 (62.1)</td>
</tr>
</tbody>
</table>
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 Ponnampalam, Limin Wijaya, Linda K Lee, Eng-Eong Ooi, Adeeba Kamarulzaman, Lucy C Lum, Paul A Tambyah, Yee-Sin Leo

<table>
<thead>
<tr>
<th></th>
<th>Transfusion group (n=188)</th>
<th>Control group (n=181)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>7 (4%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>5 (3%)</td>
<td>0</td>
</tr>
<tr>
<td>Severe</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Effect on study Intervention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>9 (5%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Temporarily Interrupted</td>
<td>1 (1%)</td>
<td>0</td>
</tr>
<tr>
<td>Permanently discontinued</td>
<td>3 (2%)</td>
<td>0</td>
</tr>
<tr>
<td>Relation to study Intervention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unrelated</td>
<td>4 (2%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Possibly related</td>
<td>3 (2%)</td>
<td>0</td>
</tr>
<tr>
<td>Probably related</td>
<td>4 (2%)</td>
<td>0</td>
</tr>
<tr>
<td>Definitely related</td>
<td>2 (1%)</td>
<td>0</td>
</tr>
<tr>
<td>Recovered</td>
<td>13 (7%)</td>
<td>2 (1%)</td>
</tr>
</tbody>
</table>

Table 3: Adverse events
No dengue mortality – a necessary stretch goal

- Asymptomatic
- Mildly symptomatic
- Dengue Fever
- Dengue with warning signs
- Severe
- Death
NCID – functionally go-live in April 2018

Building ready in 2018-2019

Welcome to NCID
Singapore

CHI
9-storey educational and training building

NCID
14-storey clinical building
330 beds

4 basements with
850 car park lots
Food and retail outlets

NATIONAL CENTRE FOR INFECTIOUS DISEASES
DESIGNING FOR THE FUTURE

INSTITUTE OF INFECTIOUS DISEASES AND EPIDEMIOLOGY