Dengue hemorrhagic fever and shock syndromes

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Outline: management of DHF/DSS

1. Brief overview: Epidemiology, Virology and transmission

3. Clinical syndromes
4. Pitfalls in diagnosis and treatment
5. Fluid management 1: what fluid, how much?
6. Titrating endpoints of fluid therapy:
7. Complications in sick patients
8. Can we decrease the burden of disease and improve outcome?
9. Conclusion
Factors Responsible for the dramatic resurgence and emergence of epidemic DHF
Resurgence closely associated with demographic and societal changes over the past 50 years.

Unprecedented global population growth and the associated unplanned and uncontrolled urbanization, especially in tropical developing countries. This has created ideal conditions for increased transmission

- **Lack of effective mosquito control** in areas where dengue is endemic

- **Increased air travel**, which provides the ideal mechanism for the transport of dengue worldwide.

*DUANE J. GUBLER. Dengue and Dengue Hemorrhagic Fever, July 1998*
Global Significance Of The Problem

Dengue viral syndromes

- Leading cause of death and disability amongst children in the tropics
- Most important vector borne disease after malaria
- Classified by WHO as “newly emerging/re-emerging arthropod borne viral disease of global importance”

Gibbons, BMJ 2001
WHO 2001
A newly emerging/re-emerging arthropod borne viral disease of global importance

- Prior to 1970, only 9 countries had a dengue epidemic
- Now, epidemic in >100 countries
- 2/5th of world’s population are at risk of getting dengue
- 50 million cases each year, with 500,000 requiring hospitalization

Halstead SB, Curr Opin Inf Dis 2002
Dengue: *Virology and Transmission*

- Dengue is caused by infection with one of **four dengue virus serotypes**, i.e. DEN 1-4.
- Infection with one serotype provides life-long immunity against the same serotype, but not against the others.
- Most infections are **asymptomatic** but a **small proportion** can progress to **severe disease**.
- **Severe DHF/DSS** is more prevalent in secondary infection with different serotype of dengue virus.
- **Infants** can manifest with **severe disease** with **1st infection**.
Aedes aegypti is the principal mosquito vector of dengue. Adult mosquitoes shelter indoors and bite during the daytime. They are adapted to breed around human dwellings.
Pathogenesis

• DHF/DSS pathogenesis is a complex, multifactorial process involving co-circulation of various dengue virus serotypes and the interplay of host and viral factors.

  risk of severe disease is increased at least 15-fold during secondary infections.

Differences in virulence of viral genotypes

Halstead SB. Dengue virus infection, shock, and hemorrhage: a pathogenic cascade. Reviews of Infectious Disease 1989; 11 (suppl 4) S830-39.
Pathogenesis…. (2)

Complex interplay of host and viral factors that results in immune potentiation with secondary infections → severe forms of DHF

1. Antibody dependent enhancement (ADE)
2. T-cell activation and destruction
3. Release of inflammatory cytokines and coagulation cascades

antibody enhancement (ADE),

During secondary infection:

Pre-existing antibodies
Instead of neutralizing
Protect the virus from destruction
Then enhance its uptake

unchecked virus replication
vasoactive mediators

*The non-neutralizing antibodies thus impart a “double blow”*
Pathogenesis ....(4) (contd)

The T-cell: A *major contributor to severe dengue manifestations*

- Profound T-cell activation and programmed T-cell death
- Original antigenic sin in the T-cell responses may suppress viral elimination

End result: *with second infection*

- Higher viral loads and
- Shortened incubation times
- Increased immunopathogenicity and severity of infections
Original antigenic sin of the T cell response

• The propensity of the body’s immune system to preferentially utilize immunological memory based on a previous infection when a second slightly different serotype is encountered.

• This leaves the immune system "trapped" by the first response and unable to mount potentially more effective responses during subsequent infections.

It is named by analogy to the theological concept of original sin.

Thomas Francis. On the Doctrine of Original Antigenic Sin
Release of inflammatory mediators

*Of cascades and perfect storms*…

ultimately cause an increase in vascular permeability and coagulopathy

Halstead SB. Dengue virus infection, shock, and hemorrhage: a pathogenic cascade. Reviews of Infectious Disease 1989; 11 (suppl 4) S830-39.
Pathogenesis of bleeds in DHF
Hemorrhage in DSS is multi-factorial

- Vasculopathy:

- Thrombocytopenia:

- Platelet dysfunction:

- Coagulopathy:


• Srichaikul. Platelet function during the acute phase of dengue hemorrhagic fever. Southeast Asian J Trop Med Public Health 1989; 20
Patients with severe dengue have coagulation abnormalities but these are not severe enough to cause major bleeding.

Risk for major DIC and uncontrollable bleeds:

**Profound shock**

Factors that predispose to severe manifestations (shock, hemorrhage)

- Infection with dengue virus serotype 2
- Age less than 11 years
- Good nutritional status

Thisyakorn U, Nimmannitya S. Nutritional status of children with dengue hemorrhagic fever. *Clin Infect Dis*
Risk factors for mortality

- duration of hypovolemic shock
- late presentation
- Early identification and prompt correction of shock will improve outcomes

Lucy Chai See Lum, Personal communication to IMCI, WHO, Kuala Lumpur, Malaysia
Deen JL. Late presentation and increased mortality in children with DHF. Tropical Doctor 2000; 30:227-8.
2. Clinical syndromes

3. Hemocrit in Indian children

4. Pitfalls in diagnosis and treatment

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6. Fluid management 2: how much fluid?

7. Titrating fluid therapy: CVP, urinary catheter and serial hematocrit

8. Complications in sick patients
The pathological hallmark that sets apart DHF is the presence of increased vascular permeability.
Clinical Case Definition for Dengue hemorrhagic fever (DHF) *(WHO 1999)*

**4 Necessary Criteria:**

- Fever, or recent history of acute fever
- Hemorrhagic manifestations
- Low platelet count (100,000/mm³ or less)
- Objective evidence of "leaky capillaries:"
  - *elevated hematocrit* (20% or more over average for age, sex and population)
  - *low albumin*
  - signs of plasma leakage such as pleural effusion, ascites, and hypoproteinemia
  - a *drop in the hematocrit* following volume-replacement (= 20% of baseline.)
4 grades of severity

- **Grade 1**
  - Fever and nonspecific constitutional symptoms
  - Positive tourniquet test (only hemorrhagic manifestation)

- **Grade 2**
  - Grade 1 manifestations + spontaneous bleeding

- **Grade 3 (DSS)**
  - Signs of shock, BP normal or reduced

- **Grade 4 (DSS)**
  - Profound shock (undetectable pulse and BP)
To diagnose DHF, documenting the *timing of clinical manifestations* is as important as documenting their occurrence.

- Fever x 2-7 days
- Defervescence
- Rise in hematocrit
- Hemorrhagic manifestations
- Drop in platelets
Laboratory Diagnosis of DHF

The diagnosis of dengue is based on clinical criteria and may be confirmed by:

- **Virus isolation** using culture or polymerase chain reaction (early febrile stage)

- **Serological studies** a fourfold or more increase in the hemagglutination inhibition (HAI) test between acute and convalescent sera

- **Enzyme-linked immunosorbent assay (ELISA)** test for dengue-specific IgM/ IgG
<table>
<thead>
<tr>
<th>Danger signs requiring urgent hospitalization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emphasis on signs that occur early enough and can be recognised by health workers in first-level referral centres.</td>
</tr>
</tbody>
</table>

- **Abrupt change from fever to hypothermia**
- **Shock:**
- **Lethargy:**
- **Bleeding:**
- **Severe abdominal pain** and vomiting

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Pitfalls in the recognition & management of Dengue shock

**Delayed diagnosis:**
- Failure to recognize temporal sequence of DHF

**Hypovolemic shock (with a difference)**
- No measurable losses
- Features of dehydration absent
  - (edema, large liver, lung crackles may suggest over-hydration)
Smooth slide from fluid responsive shock to fluid overload

At admission

12 hrs later
Many infections can result in fever, shock and bleeding amongst children in the tropics

- Dengue
- Malaria
- Bacterial septic shock
- Leptospirosis
- Typhus

Can the ACCM/PALS Guidelines be applied for severe Dengue Shock Syndrome?
Aggressive management of dengue shock syndrome may decrease mortality rate: A suggested protocol*

**Maintain airway, breathing and establish access according to PALS guidelines**

- **DHE** (20ml/kg) boluses (40-60ml/kg) followed by colloid till better

- **Serial ECHO** for filling, LV function (systolic and diastolic)

- **Fluid removal therapies** (diuretic/dialysis)
  - Underfilled
  - Systolic dysfunction
  - "Underfilled"

**PICU mortality reduced 16.6% vs. 6.3%, p < .05**
Can the ACCM/PALS Guidelines be applied for severe Dengue Shock Syndrome?

*improved outcomes* 45/86

patients needed therapies to remove fluid

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**Fluids in Dengue shock**

- 25ml/kg over 2 hours (Gr III)
- Ringers Lactate as good as colloid for moderate shock
- Colloid may be preferred in severe shock

**Mortality 0.2% !!**

**The 2 types of pediatric shock probably distinct and early differentiation between them may be important**
• Fluid required for shock reversal in DSS significantly less

• Predominant vasoconstrictory state
<table>
<thead>
<tr>
<th></th>
<th>Septic shock N=16</th>
<th>Dengue shock N=16</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of SIRS</td>
<td>15</td>
<td>9</td>
<td>0.04</td>
</tr>
<tr>
<td>HR &gt; 95th centile for age</td>
<td>25</td>
<td>4</td>
<td>0.01</td>
</tr>
<tr>
<td>Temperature (&lt;36.8 C or &gt;38.58C)</td>
<td>12</td>
<td>0</td>
<td>0.00</td>
</tr>
<tr>
<td>Pulse pressure mm Hg</td>
<td>42.7 ± 8.2</td>
<td>24.7 ± 7.7</td>
<td>0.00</td>
</tr>
<tr>
<td>Extremity hypoperfusion</td>
<td>9</td>
<td>16</td>
<td>0.009</td>
</tr>
<tr>
<td>Initial fluid resuscitation volume (mL/kg)</td>
<td>57.5ml/kg (40–70)</td>
<td>28.5ml/kg (20–47.5)</td>
<td>0.03</td>
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<tr>
<td>Vasopressor ± inotrope use</td>
<td>11</td>
<td>3</td>
<td>0.003</td>
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<tr>
<td>Steroids</td>
<td>6</td>
<td>0</td>
<td>0.007</td>
</tr>
<tr>
<td>Mortality</td>
<td>2</td>
<td>1</td>
<td>NS</td>
</tr>
</tbody>
</table>

Ranjit S et al. PEC 2007: 23, 6, Early Differentiation Between DSS and SS
Dengue shock vs septic shock: *Twins or distant cousins?* (contd…)

Patients with Dengue Shock Syndrome

- Usually *apyrexial* at onset of shock
- *Relative bradycardia* for degree of shock
- Cytokine mediated ↑vascular permeability, but other features of "SIRS" may not be not prominent
- Shock with predominant vasoconstriction (vs vasodilatory/vasoconstrictory septic shock)

*No role for steroids*

The clinical studies from Drs Bridget Wills and Jeremy Farrar group in Children’s Hospital, Ho Chi Minh City, Vietnam have clarified many issues in the treatment of DHF, more good quality studies ongoing.

Dengue shock vs septic shock: *putting it all together*

**Approach is similar yet different:**

*Emphasis on early filling but at slower controlled rates*

- Educate 1º caregivers to diagnose, initiate fluid early and refer
- *Gr III shock:* 20ml/kg crystalloid over 30-60 mins
- *Severe/Gr IV DSS:* 20ml/kg colloid over 30 mins, repeat as indicated
- Volume should be just sufficient to maintain effective circulation during the period leakage
- With improvement, fluid rates should be gradually decreased discontinued after 24 to 48 hours

*Fluid overload as important a cause of death as intractable shock*
Management of DHF Grade III and IV (DSS)

NS (Gr III), / Hetastarch (Gr IV) 10-20 ml /kg boluses x 1-2
Correct glucose, calcium, acidosis, HCT, insert urine catheter

Cardiopulmonary assessment, HCT

Improvement

NS 10 ml/kg /hr
Gradually ↓ fluid rate
10 → 7 → 5 → 3 ml / kg

No improvement

Shock + HCT < 35
HCT, ECHO , check for occult hge

Shock + high HCT >38
Starch 10 ml/kg/hr
2 - 3 boluses

Improvement: ↓ fluid

No improvement
CVP, Echo, HCT

Improvement: ↓ fluid

CVP Low:
Fluids/blood, ventilation, echo

CVP high:
Inotropes, ventilation, echo
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7. Fluid management 2: Flow chart
8. Complications in sick patients
Objective end-points

- Improved perfusion and blood pressure with widening/normalization of pulse pressure
- Steady fall in hematocrit = 20% \textit{(if not bleeding)}
- Adequate urine output \textit{(aim for low normal)}
- Demonstration of IVC and chamber filling on ECHO
Role of CVP

- **Aim of measurement**: determine intravascular volume status

- *Useful if low in the presence of shock*

- May be ‘falsely’ high due to large pleural and ascitic collections

- Insertion may be **hazardous** in the bleeding shocking patient

- Other surrogates of filling more relevant
Low tech CVP equivalent 1: *The urinary catheter*

Hourly output measurement

Renal blood flow

Perfusion status
Titrating fluid therapy in DSS: **Objective end-points**

1. Hourly urine ✓ ✓
2. Hematocrit ✓ ✓ ✗
3. Serial ECHO ✓ ✓ ✗
4. BP, clinical exam ✓ / ✗
5. CVP ✗ / ✓
6. CXR, resp exam ✗ ✗ / ✓
Titrating fluid therapy in DSS:

1. Hourly urine > 3ml/kg/hr ✓ ✓
2. Hematocrit fall > 20% ✓ ✓ x
3. Serial ECHO: overfilled ✓ ✓ x
4. BP, clinical exam ✓ / x
5. CVP high ? / x / ✓
6. CXR, resp exam ? / x x / ✓

Also important to monitor for fluid over load.
Serial bedside ECHO:

*Helps to titrate fluid & inotrope infusions*
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6. Indications for blood products
7. Fluid management 2: how much fluid?
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Indications for platelet transfusion /FFP

**Indications for platelets**

- Active significant bleeds
- >50,000 mm$^3$ for invasive procedures
- <20,000 mm$^3$ in the acute phase

**FFP/ cryoprecipitate**

- Significant bleeds
- DIC
Therapies that have also been tried in uncontrollable bleeding...

The role of recombinant activated factor VII life-threatening bleeding in Dengue Shock Syndrome

rFVIIa appears to be a useful adjunctive treatment to blood component transfusion for controlling active bleeding in children with DHF especially when platelet concentrate is not readily available.


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Complications can occur in any organ/system
DIC with life threatening hemorrhage

Triad of severe shock, acidosis and DIC

Need for multiple blood products:
Risk of fluid overload

DSS complications: Fluid overload

Water, water everywhere, but not enough in the right place….

• Fluid overload is as important a cause of mortality as uncorrected shock

no specific therapy,
Positive pressure ventilation

Worsens shock

The DSS Conundrum

Worsens hypoxemia

Fluid resuscitation
Shock, DIC and ARDS: Not a happy triad
The challenge: Fluid overload in DSS

• “Post-resuscitation fluid removal” may be indicated in refractory overload

• i.e., overload that worsens cardio-pulmonary function or causes abdominal compartment syndrome (ACS)

• Controlled gentle ascitic/pleural fluid drainage

• Low dose furosemide infusion/ peritoneal dialysis
Furosemide infusion

When?

- After establishing normovolemia

How?

- 1-2mg/kg/day as a continuous infusion, max 5mg/kg/d
- Aim for urine output of 2-5ml/kg/hr

Why?

- Results in a kinder, gentler, steady diuresis, less fluctuations in intravascular volume

Ranjit S, Kissoon N, Jayakumar I
Peritoneal dialysis

Who

- Preferred method in hemodynamically unstable patients
- Normovolemia established
- Compartment syndrome failed furosemide

How

- Initial passive drainage itself may improve perfusion, urine
- Alternate isotonic and hypertonic cycles
- Aim for removal of 2–5 ml/kg/hr

Most useful for tense large volume collections that compromise cardio-resp status

Refractory shock

Single most important cause is late presentation
Diastolic dysfunction

- Stiff edematous myocardium
- Early pulmonary edema with rapid fluid challenges
- Catecholamines main culprit
- CVP may be high despite hypovolemia
- Tachycardia worsens shock
- Systolic function normal

Management

- Lusitropic agents (milrinone) useful
- Discontinue catecholamines

Ranjit S, Kissoon N, Jayakumar I
DSS complications: *Abdominal compartment syndrome*

ACS defined as abdominal distention with

- oliguria or anuria
- respiratory decompensation
- hypotension or shock
- metabolic acidosis

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8. Future directions
9. Prevention and public health
5. The term “DHF” puts undue emphasis on haemorrhage:

- The hallmark of severe dengue (and the manifestation that should be watched for) is not haemorrhage but vascular permeability leading to shock.

- Haemorrhage may or may not be present in severe dengue and conversely may occur in children with otherwise uncomplicated dengue.

- When life-threatening haemorrhage does occur in severe dengue, it is almost invariably a late manifestation and associated with profound or prolonged shock.

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THE WHO CLASSIFICATION AND CASE DEFINITIONS

The WHO guidelines propose the following classification for symptomatic dengue infection (68):

- Symptomatic dengue infection
  - Undifferentiated fever
  - Dengue fever
    - Without haemorrhage
    - With unusual haemorrhage
  - Dengue haemorrhagic fever
    - No shock
    - Dengue shock syndrome
In this simplified classification system, vascular permeability resulting in plasma leakage would be the hallmark of severe dengue.

**Danger signs of severe dengue would include**
- Circulatory compromise
- Altered sensorium (unconscious, lethargic, combative),
- Abnormal bleeds
- Unusual manifestations (hepatic damage, cardiomyopathy, encephalopathy)
Prediction of Severe Disease

Unfortunately, difficult to predict which patient with dengue will progress to severe disease.

If the early determinants of disease severity were understood in detail, more effective and less costly case management might be devised.
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Prevention and public health

- Aim is to maintain a low incidence of dengue through an integrated mosquito control programme

- Source reduction, health education and law enforcement

- A very high degree of elimination of the vector in dengue-prone areas needs to be achieved and sustained in order to control transmission
The Pediatric Dengue Vaccine Initiative (PDVI) is embarked on a quest to accelerate the development, evaluation, and introduction of vaccines that will help control one of the world's most important and rapidly spreading tropical infectious diseases.
Conclusion

✓ Sick children with DHF/DSS are amongst the most challenging patients encountered by pediatric acute care givers in the tropics.

✓ Dengue Shock syndrome is likely a different entity from bacterial septic shock; fluid resuscitation rates and volumes are different (less).

✓ Earlier detection and supportive treatment can prevent complications and improve outcome.