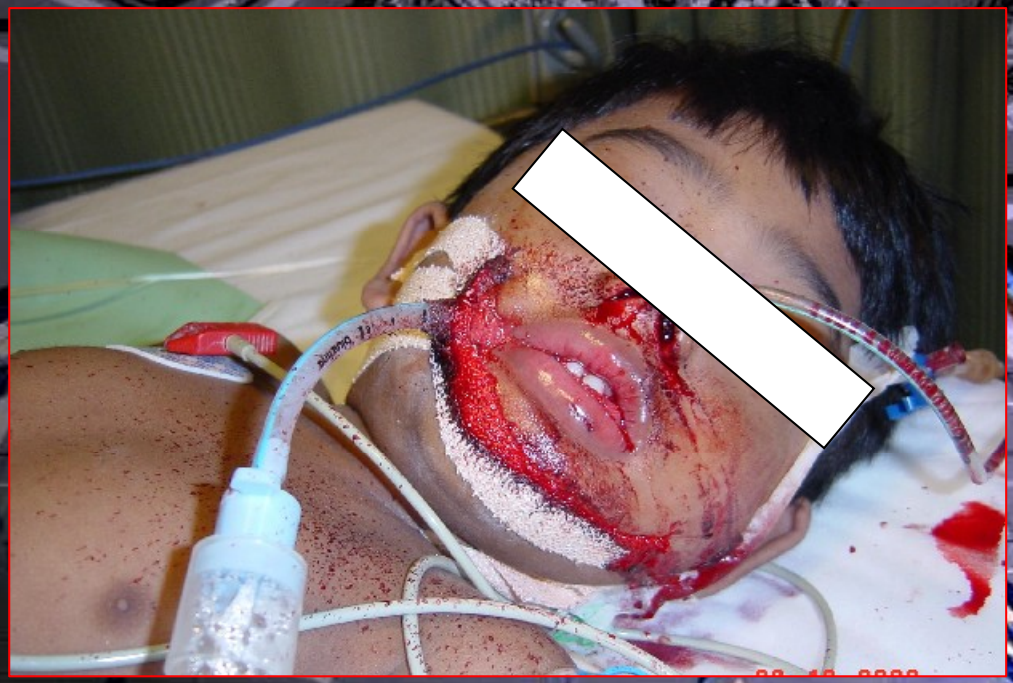
Dengue hemorrhagic fever and shock syndromes



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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

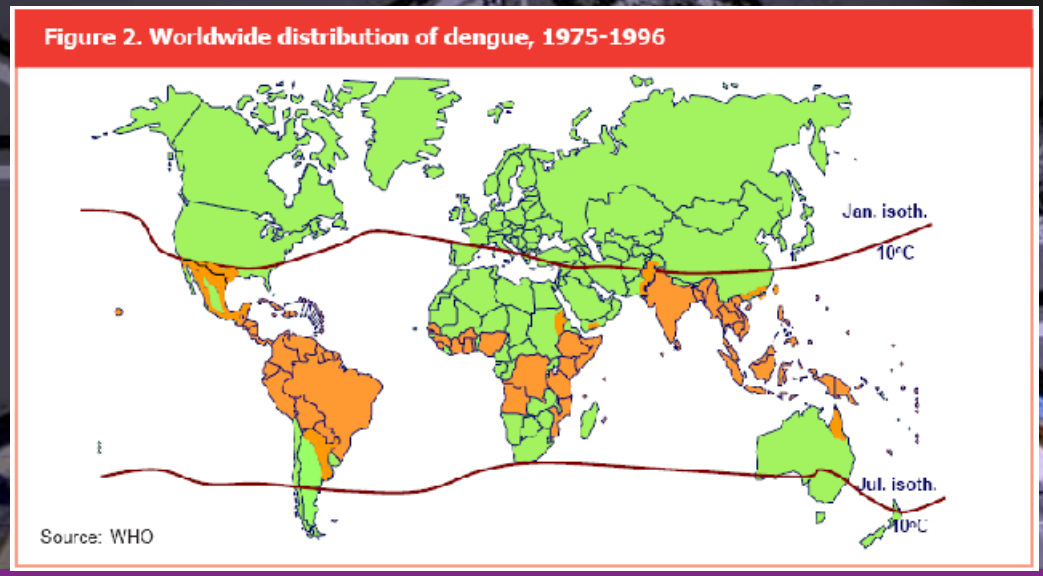
Dengue viral syndromes

- 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

Transmission: *the vector*

- *Aedes aegypti*
- bite during the daytime.
- 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

Halstead SB. Immunological parameters of togavirus disease. Biology, structure, replication. NY: Academic Press, 1980: 107-73.

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 immunesystem 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
Proceedings of the American Philosophical Society, Vol. 104, No. 6 ,1960

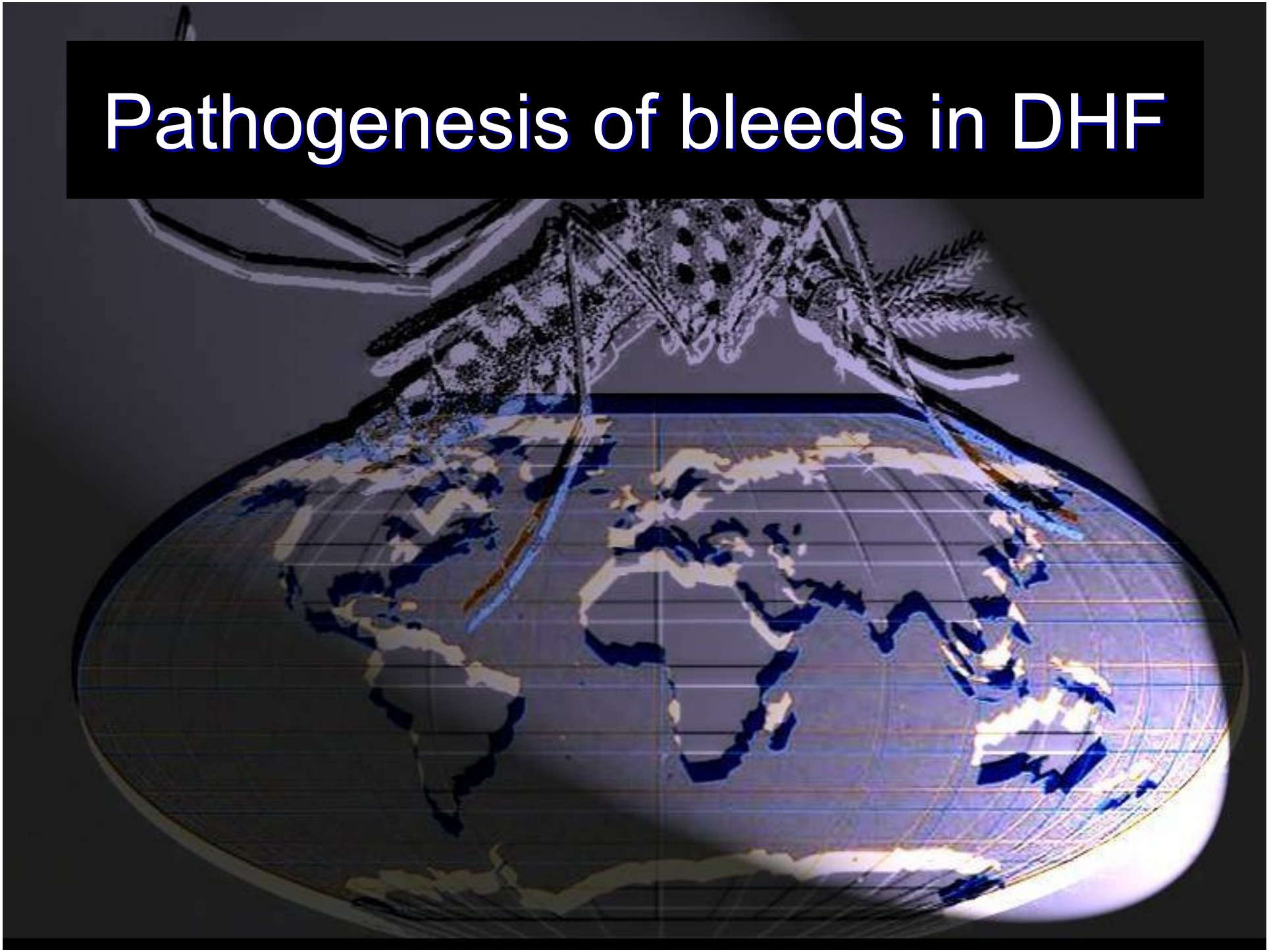
Release of inflammatory mediators

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:**

•Wills BA et al. Coagulation abnormalities in DHF: Serial investigations in 167 Vietnamese children with DSS. *CID 2002; 35: 277-85.*

•Srichaikul .Platelet function during the acute phase of dengue hemorrhagic fever. *Southeast Asian J Trop Med Public Health* 1989; **20**

Hemorrhage in DSS is multi-factorial

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

Wills BA et al. Coagulation abnormalities in DHF: Serial investigations in 167 Vietnamese children with DSS. CID 2002; 35: 277-85.

Factors that predispose to severe manifestations *(shock, hemorrhage)*

serotype 2

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.

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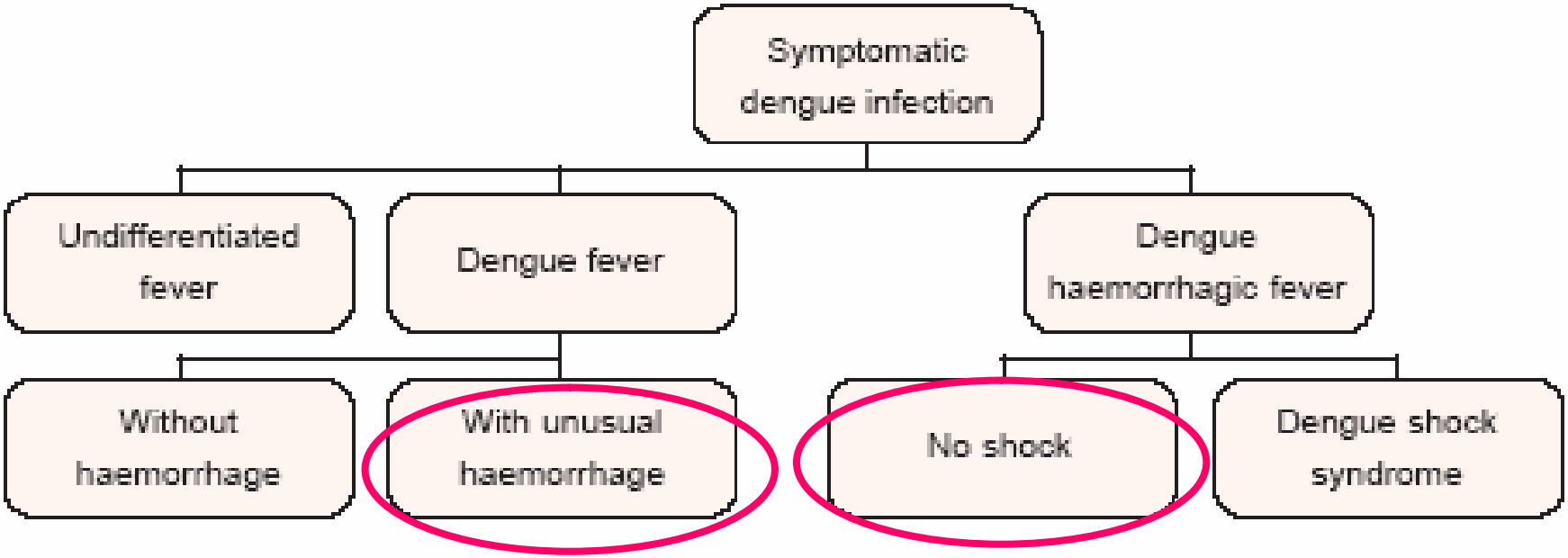
THE WHO CLASSIFICATION AND CASE DEFINITIONS

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



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/mm^3 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.)

Severity grading of dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS)

4 grades of severity

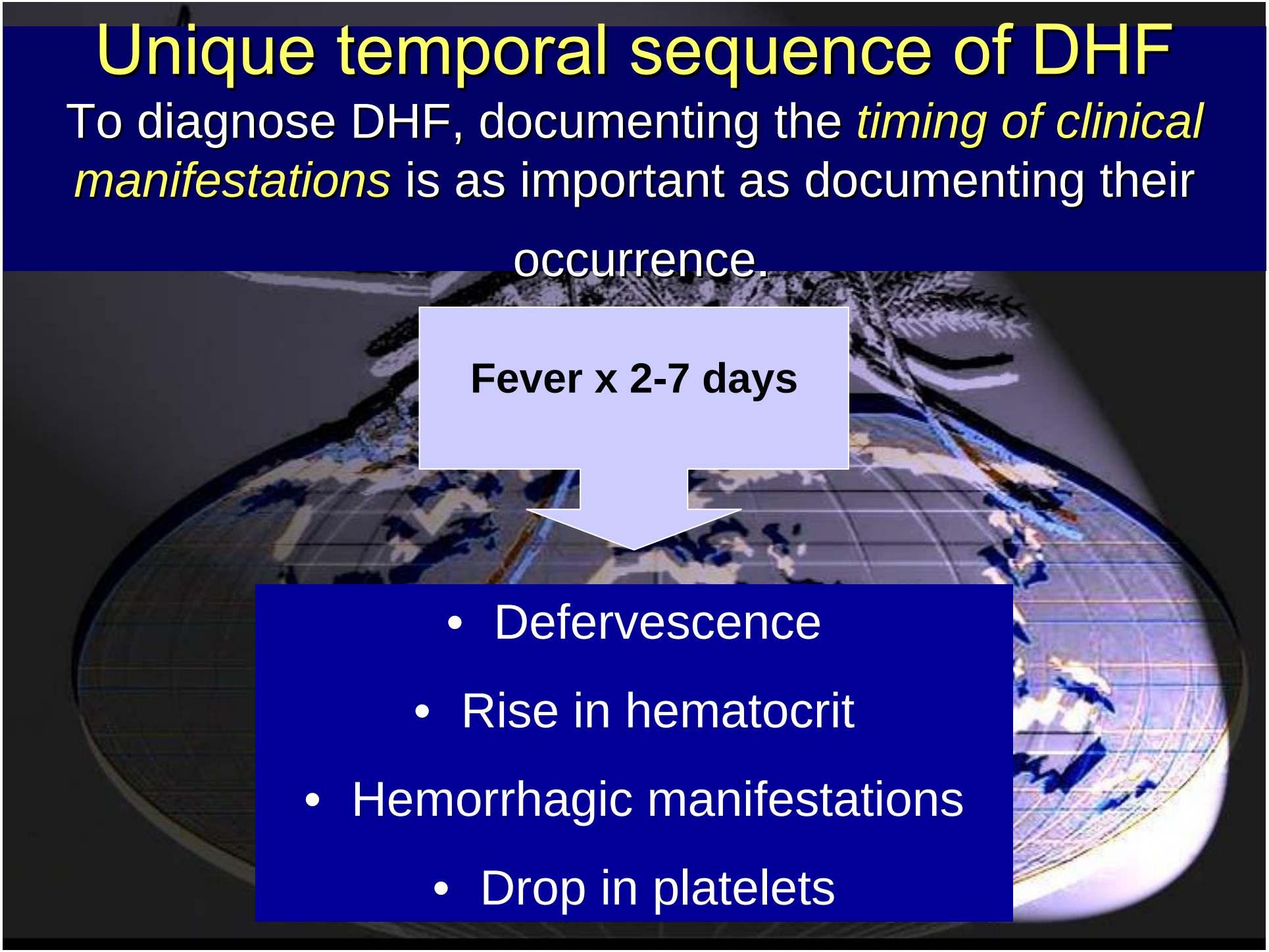
- **Grade 1**

- **Grade 2**

- ***Grade 3 (DSS)***
  - **Signs of shock, BP normal or reduced**
- ***Grade 4 (DSS)***
  - **Profound shock (undetectable pulse and BP)**

Unique temporal sequence of DHF

To diagnose DHF, documenting the *timing of clinical manifestations* is as important as documenting their occurrence.



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

Danger signs requiring urgent hospitalization

Emphasis on signs

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

Simoes et al. DHF study group. Evaluation of signs and symptoms for the clinical diagnosis of dengue hemorrhagic fever. Unpublished data. IMCI, WHO 2005

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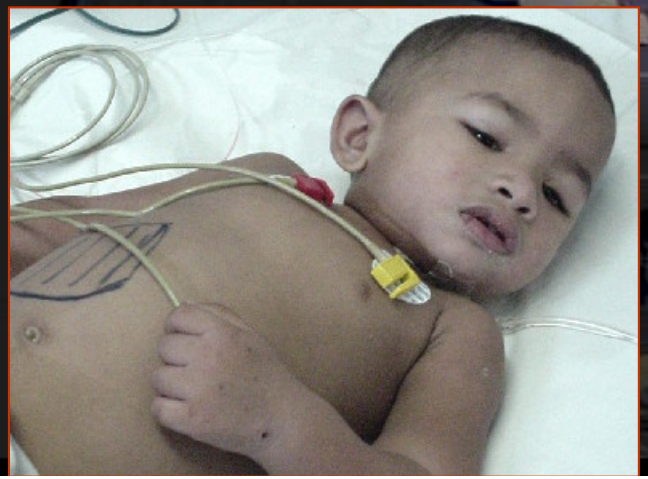
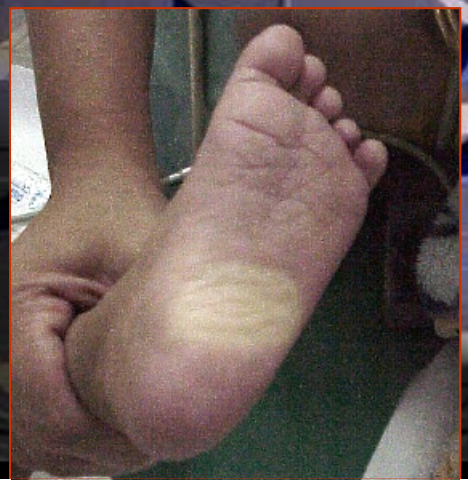
Pitfalls in the recognition & management of Dengue shock

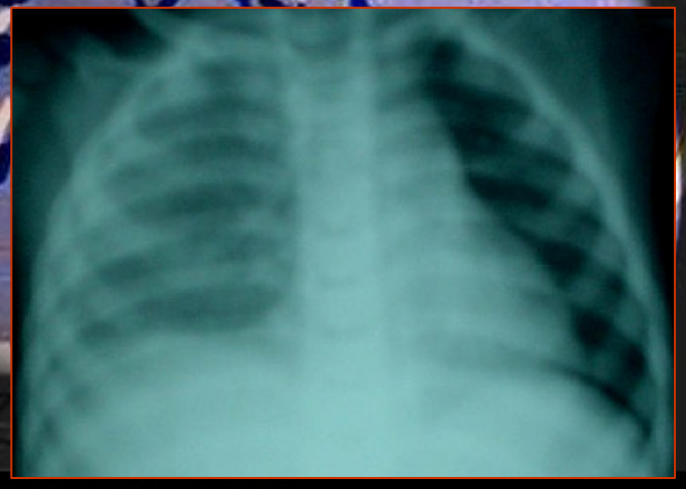
- *Delayed diagnosis:*
  - Failure to recognize temporal sequence of DHF

- *Hypovolemic shock (with a difference)*
  - No measurable losses
  - Features of dehydration absent

  (edema, large liver, lung crackles may suggest over-hydration)

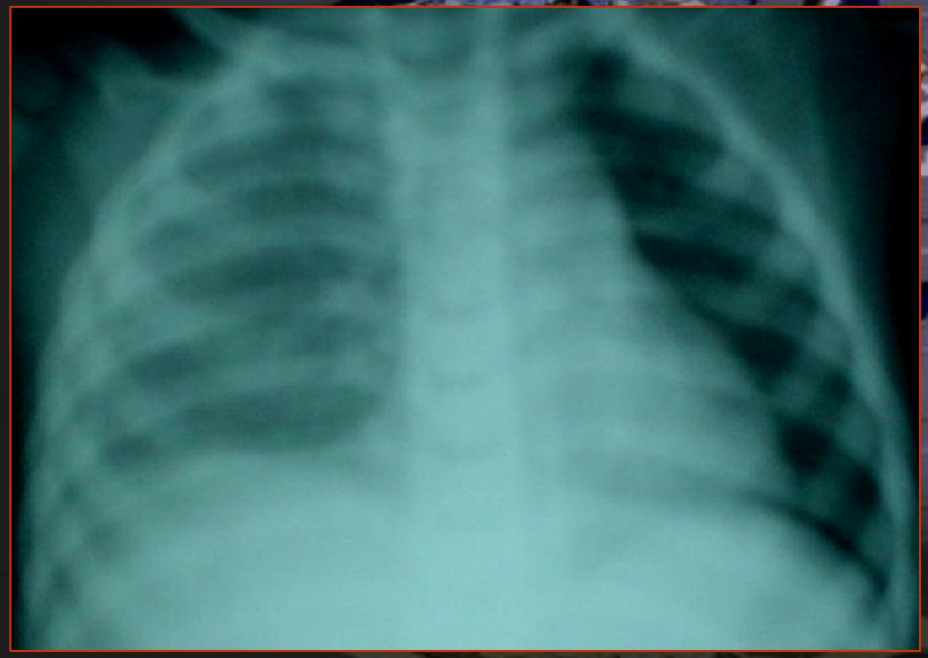




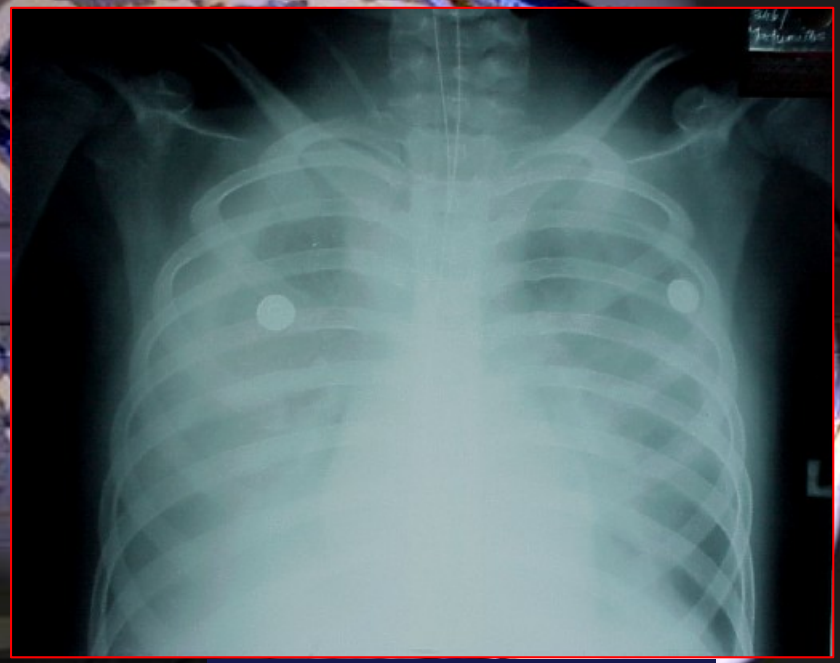


Pitfalls in recognition and management (cont'd)

- 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

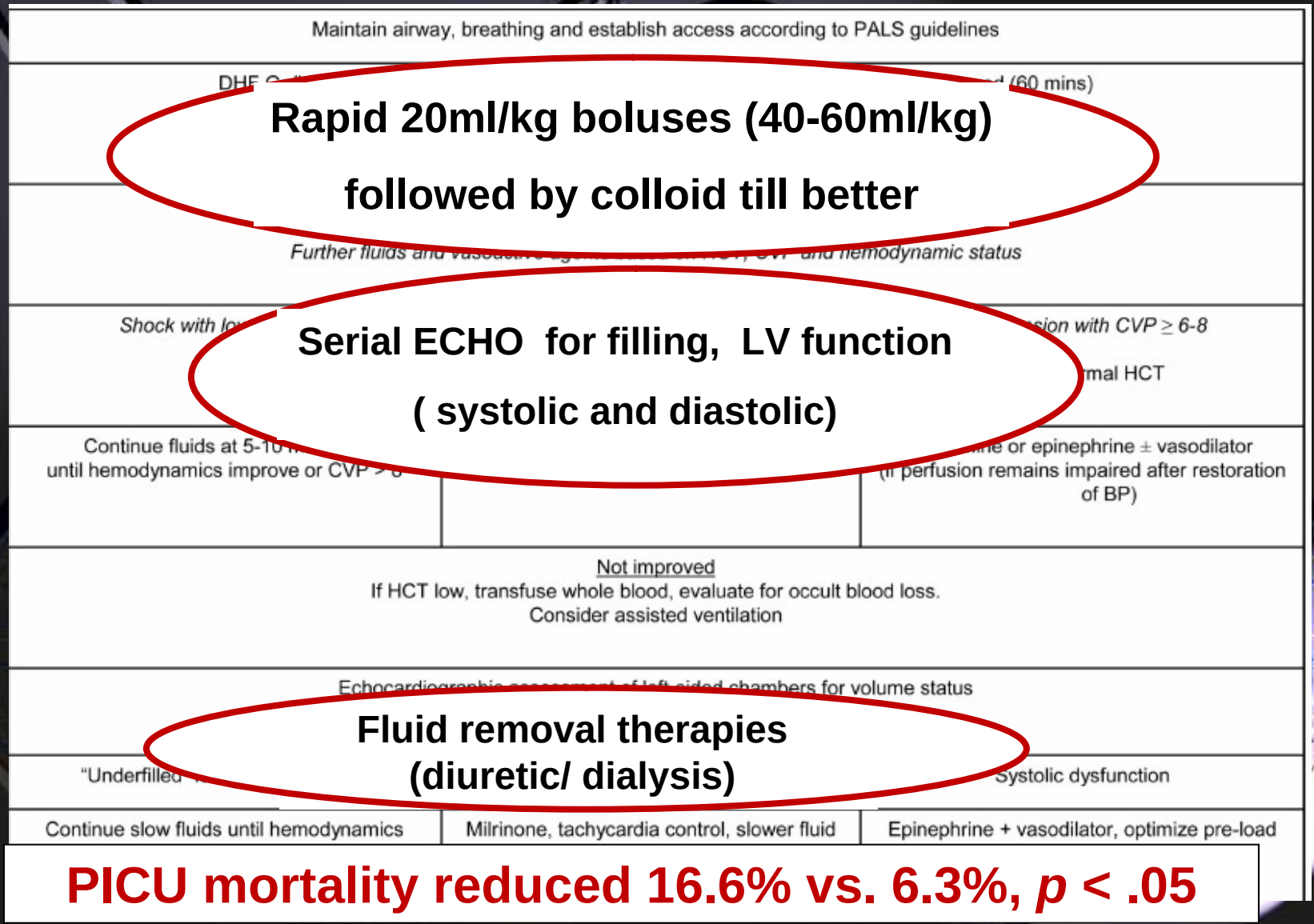
•Typhus

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*

Suchitra Ranjit, MBBS; Niranjan Kissoon, MBBS; Indira Jayakumar, MBBS

Pediatr Crit Care Med 2005 Vol. 6, No. 4

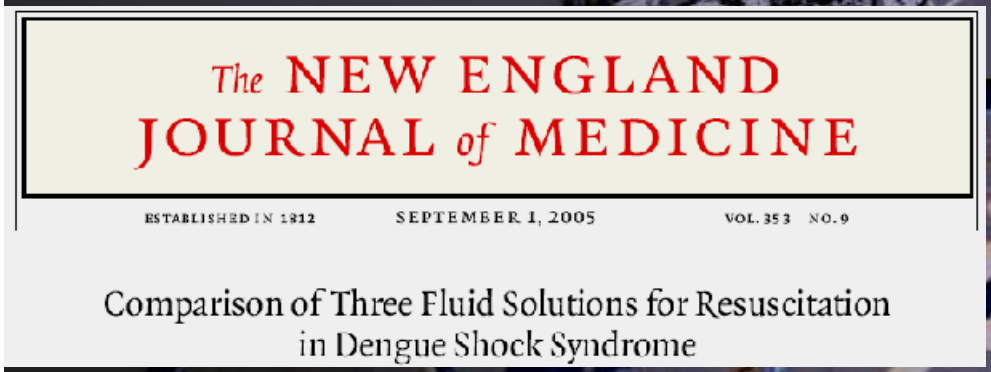


PICU mortality reduced 16.6% vs. 6.3%, $p < .05$

Can the ACCM/PALS Guidelines be applied for severe Dengue Shock Syndrome?

improved outcomes *45/ 86*

patients needed therapies to remove fluid



Bridget Wills et al

Mortality 0.2% !!

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

The 2 types of pediatric shock probably distinct and early differentiation between them may be important

ORIGINAL ARTICLE

Pediatric Emergency Care®

Early Differentiation Between Dengue and Septic Shock by Comparison of Admission Hemodynamic, Clinical, and Laboratory Variables

Volume 23, Number 6, June 2007

Suchitra Ranjit, MD, Niranjan Kissoon, MD,† Deepika Gandhi, MD,* Anjul Dayal, MD,* Rajeshwari N, MD,* and Shrishu R. Kamath, MD**

- Fluid required for shock reversal in DSS significantly less
- Predominant vasoconstrictory state

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

Ranjit S et al.PEC 2007: 23, 6, Early Differentiation Between DSS and SS

Dengue shock vs septic shock: *Twins or distant cousins? (contd…)*

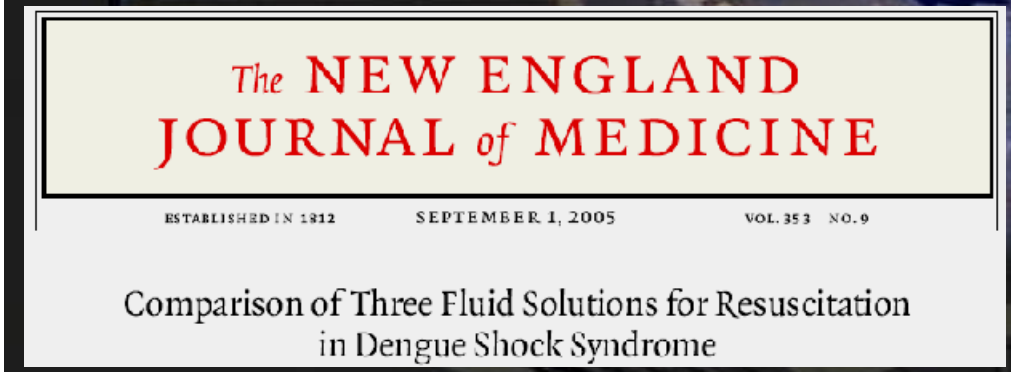
Patients with Dengue Shock Syndrome

- 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***

Tassniyom et al: Failure of high-dose methylprednisolone in established DSS. A placebo-controlled, double-blind study. *Pediatrics* 1993; 92:111–115

Research in dengue: *Vietnam leading the way*

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



Wills BA et al. Coagulation abnormalities in DHF: Serial investigations in 167 Vietnamese children with DSS. *CID 2002; 35: 277-85.*

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

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

Shock + HCT< 35

Packed RBC 10 ml/kg

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

Titrating fluid therapy in DSS

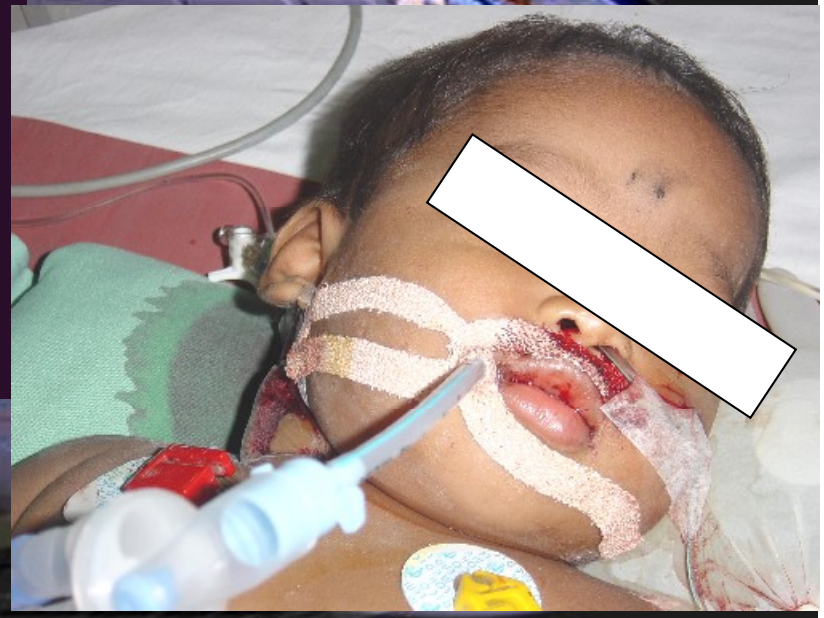
Objective end-points

- Improved perfusion and blood pressure with widening/normalization of pulse pressure
- Steady fall in hematocrit = 20% *(if not bleeding)*
- Adequate urine output *(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



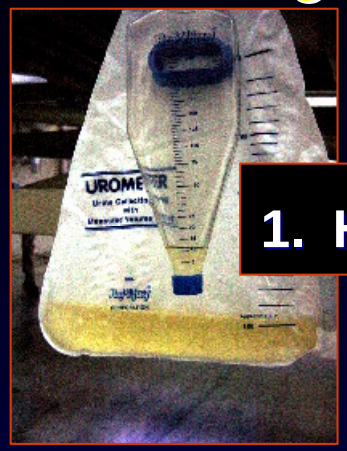
Low tech CVP equivalent 1 : *The urinary catheter*

Hourly output measurement

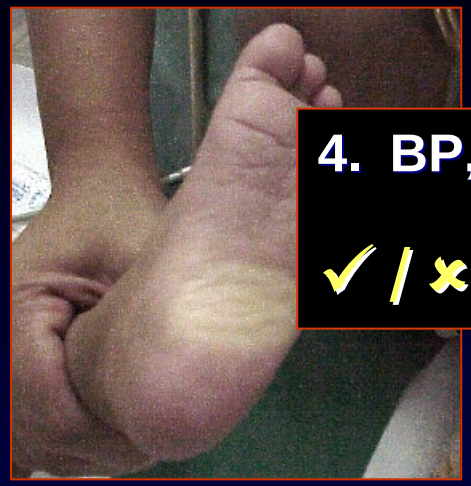
Renal blood flow

Perfusion status

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

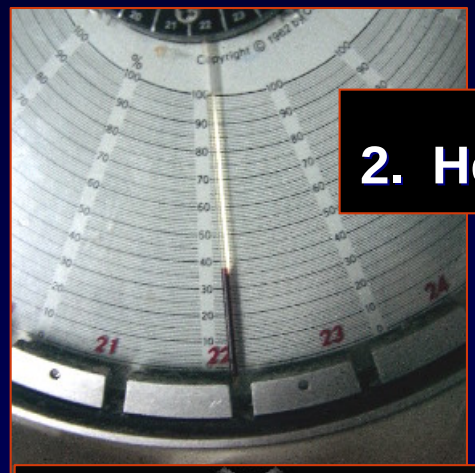


1. Hourly urine ✓ ✓

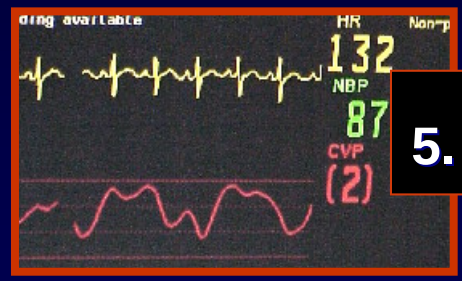


4. BP, clinical exam

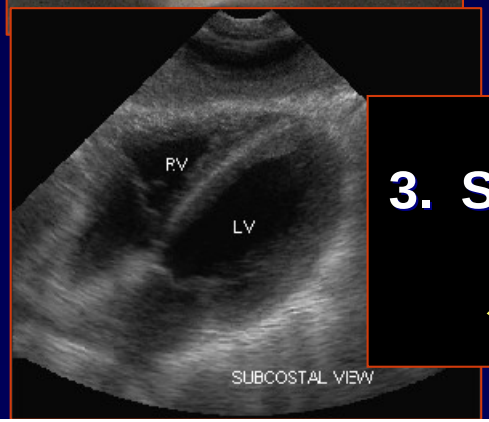
✓ / ✗



2. Hematocrit ✓ ✓ ✗

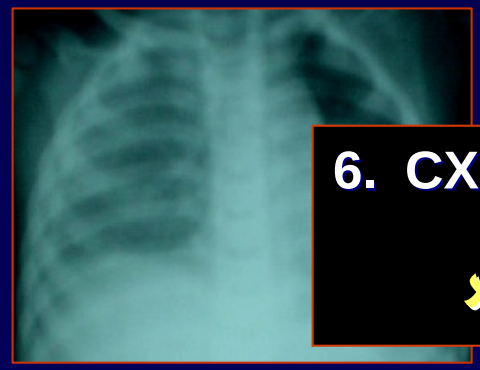


5. CVP ✗ /✓



3. Serial ECHO

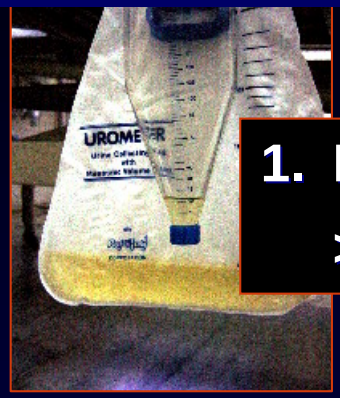
✓ ✓ ✗



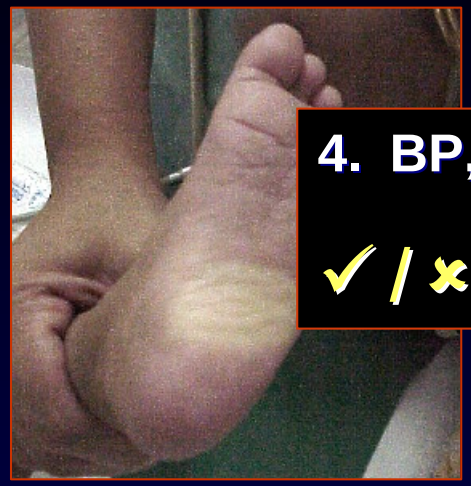
6. CXR, resp exam

✗ ✗ / ✓

Also important to monitor for fluid over load

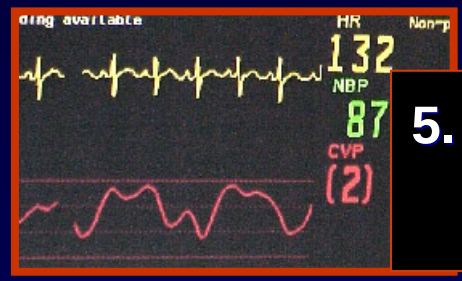


1. Hourly urine
   > 3ml/kg/hr ✓ ✓

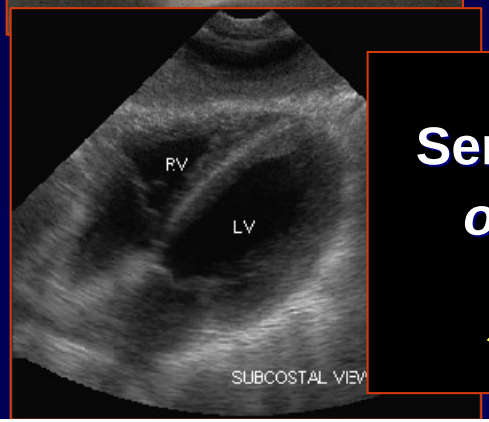


4. BP, clinical exam
   ✓ / ✗

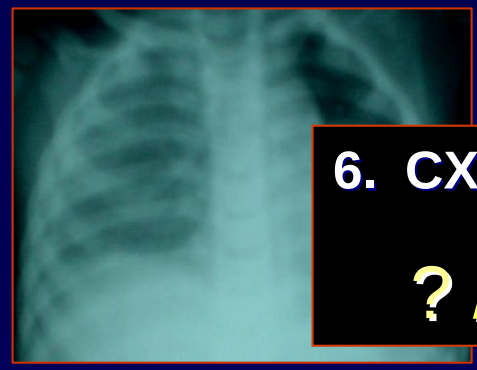
2. Hematocrit fall
   > 20% ✓ ✓ ✗



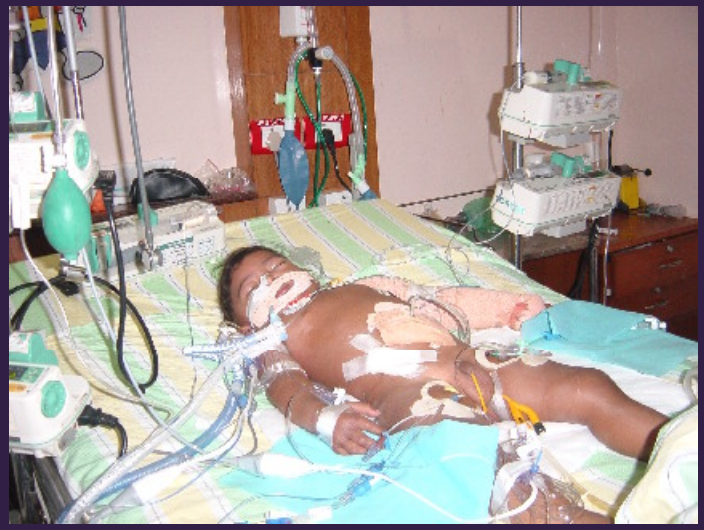
5. CVP high
   ? / ✗ / ✓

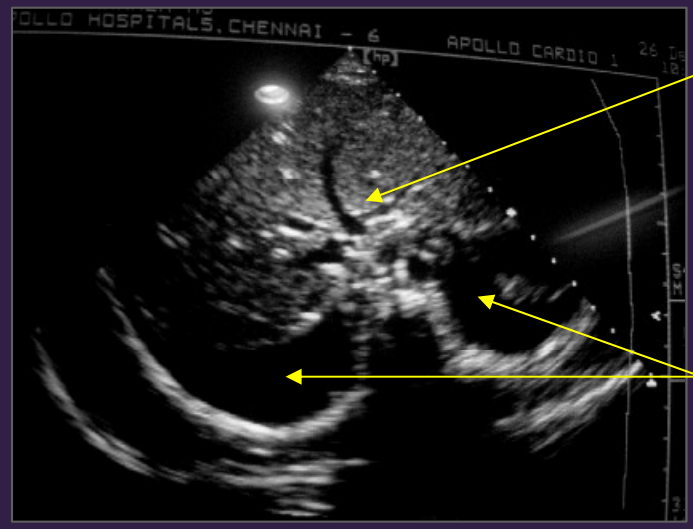


Serial ECHO:
overfilled
✓ ✓ ✗



6. CXR, resp exam
   ? / ✗ ✗ / ✓



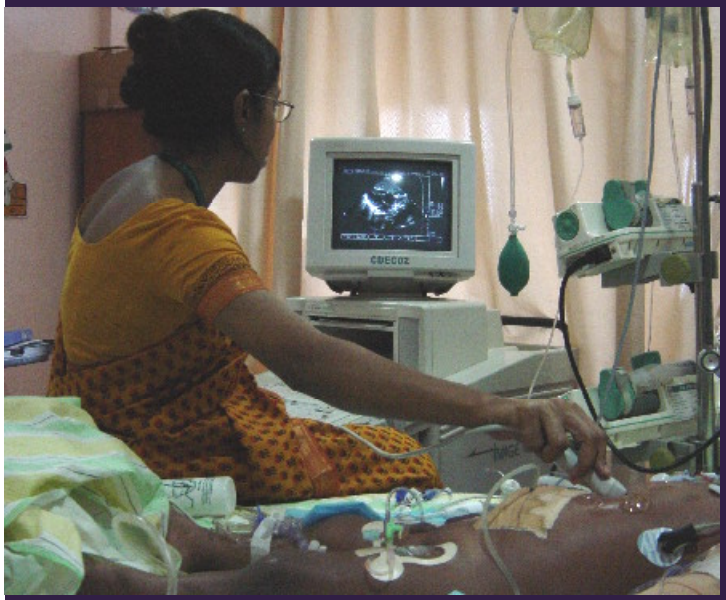


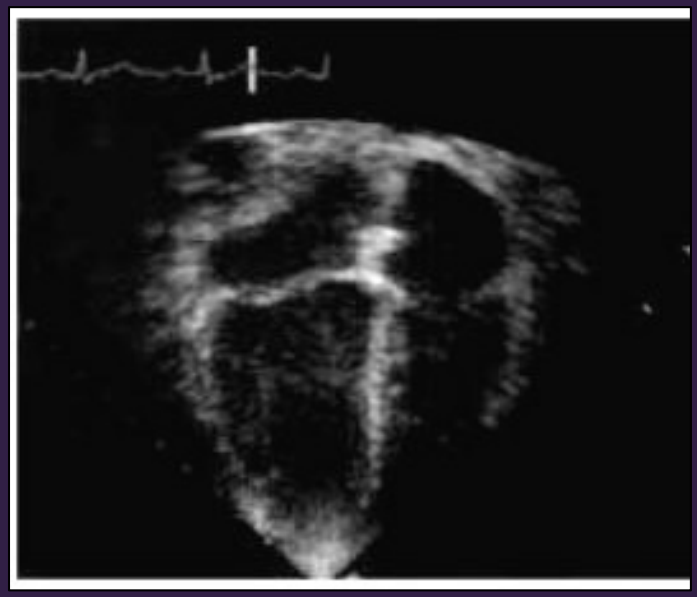
Hepatic veins, IVC

Bilateral pleural effusion

Serial bedside ECHO:

Helps to titrate fluid & inotrope infusions





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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.

Chuasumrit A. et al. The use of recombinant activated factor VII for controlling life-threatening bleeding in Dengue Shock Syndrome . Blood Coagul Fibrinolysis. 2004 Jun;15

De Castro DA et al. Am J Trop Med Hyg. 2007 Apr;76

Outline: *management of DHF/DSS*

1. Overview and epidemiology
2. Clinical syndromes
3. Hemocrit in Indian children
4. Pitfalls in diagnosis and treament
5. Fluid management 1: what fluid?
6. Fluid management 2: how much fluid?
7. Titrating fluid therapy: objective endpoints
8. Complications in sick patients
9. Conclusion

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

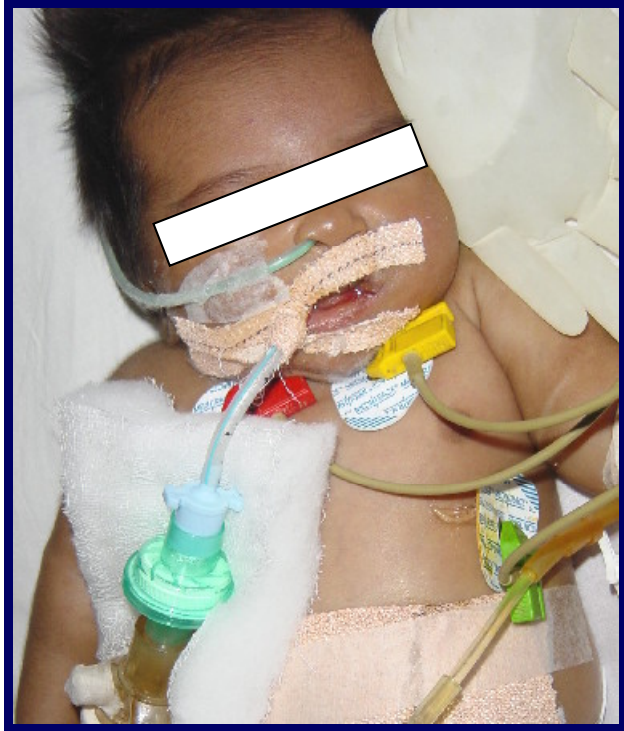
Srichaikul T, Nimmanitya S. Hematology in dengue and dengue haemorrhagic fever. Baillieres Best Pract Res Clin Haematol 2000

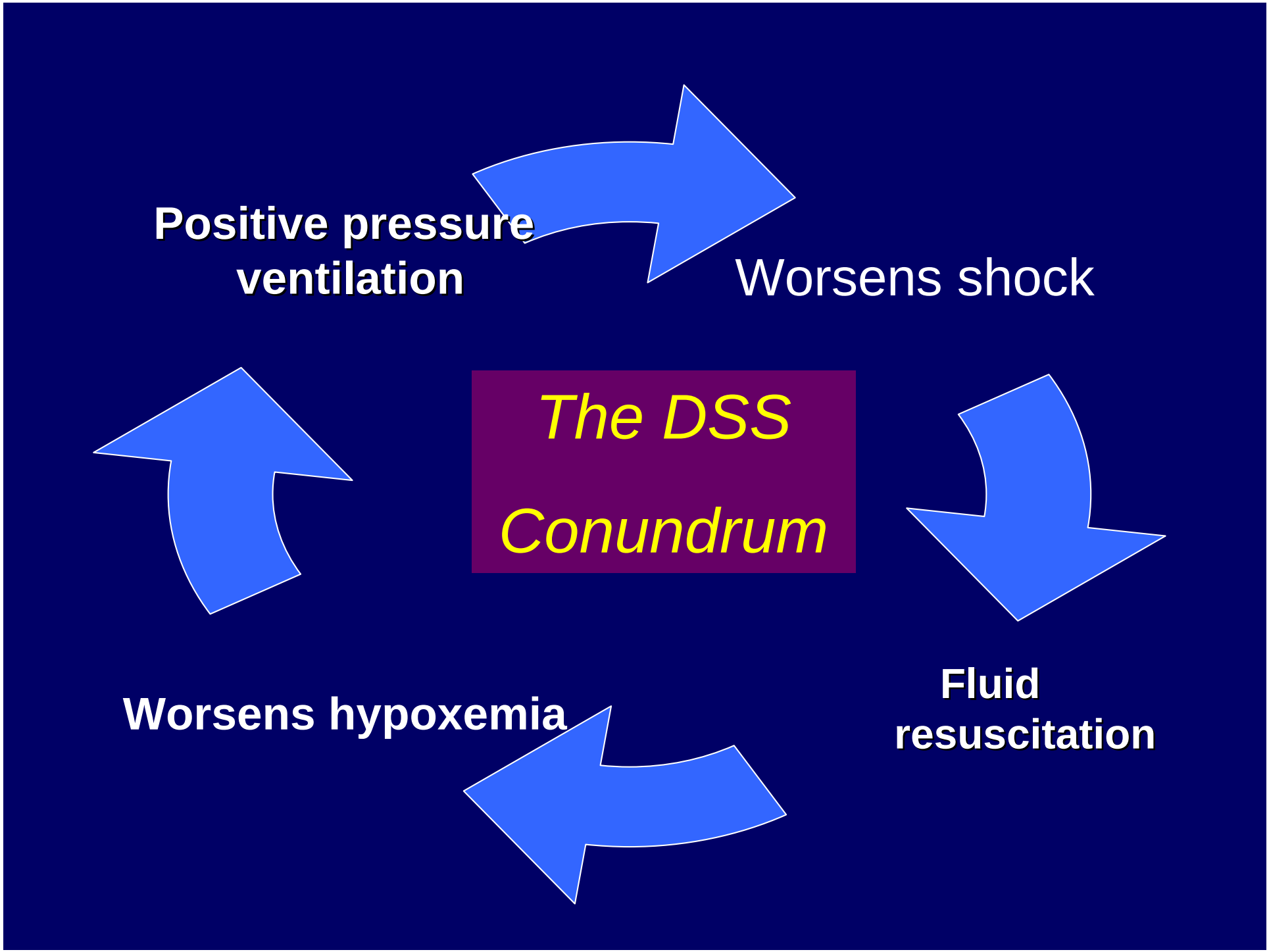
DSS complications: **Fluid overload**

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

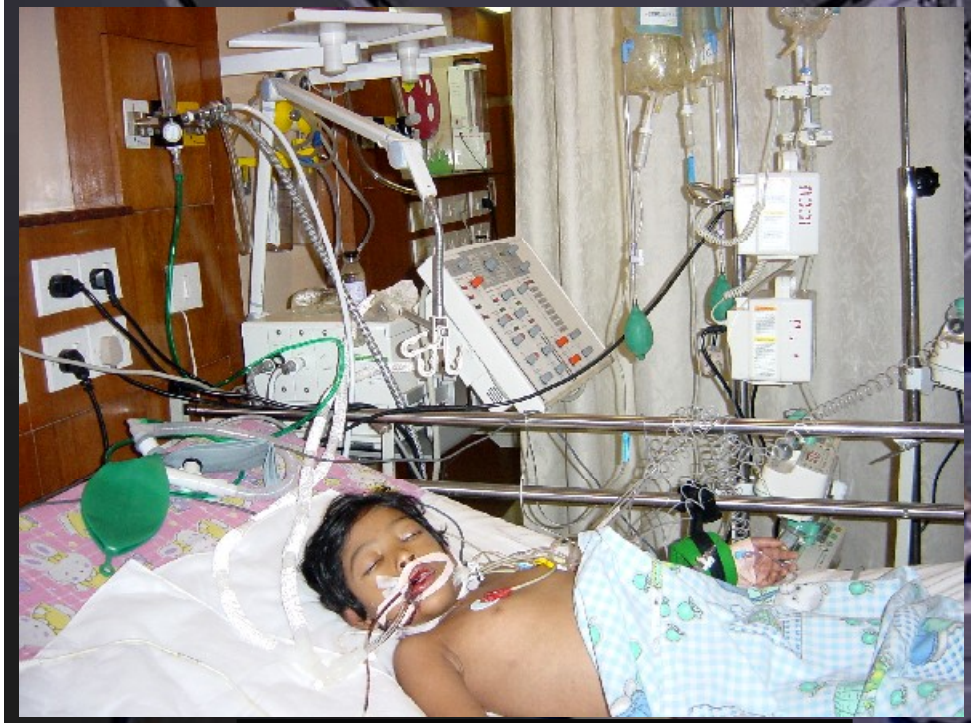
- **Fluid overload** is as **important cause of mortality as uncorrected shock**

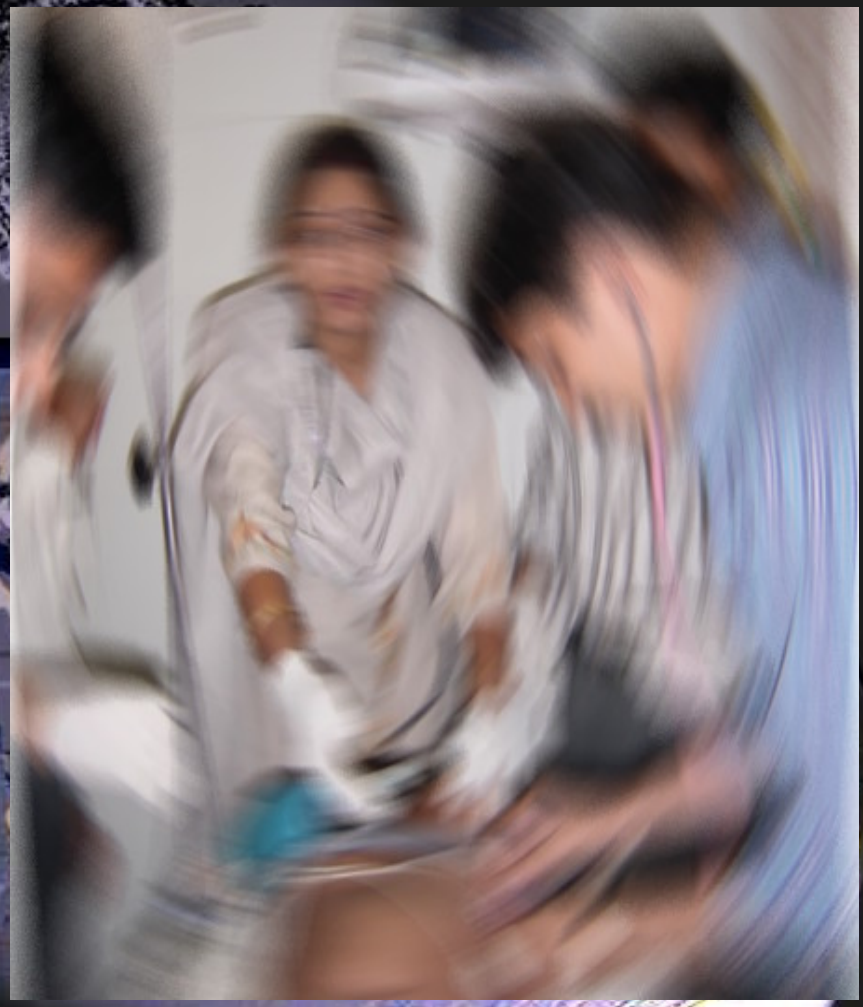
no specific therapy,

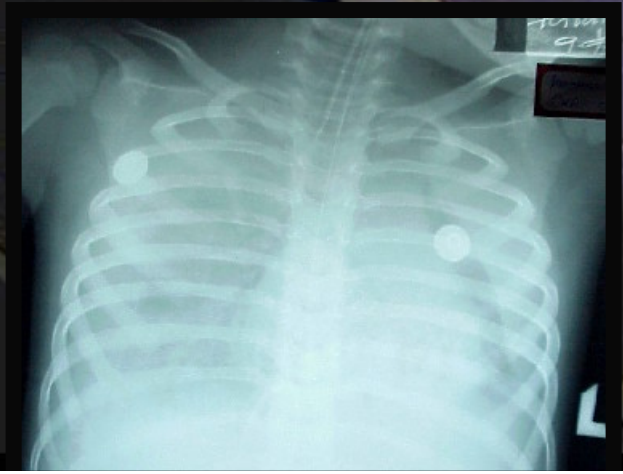



Positive pressure ventilation
Worsens shock
The DSS Conundrum
Fluid resuscitation
Worsens hypoxemia

Shock, DIC and ARDS: *Not a happy triad*







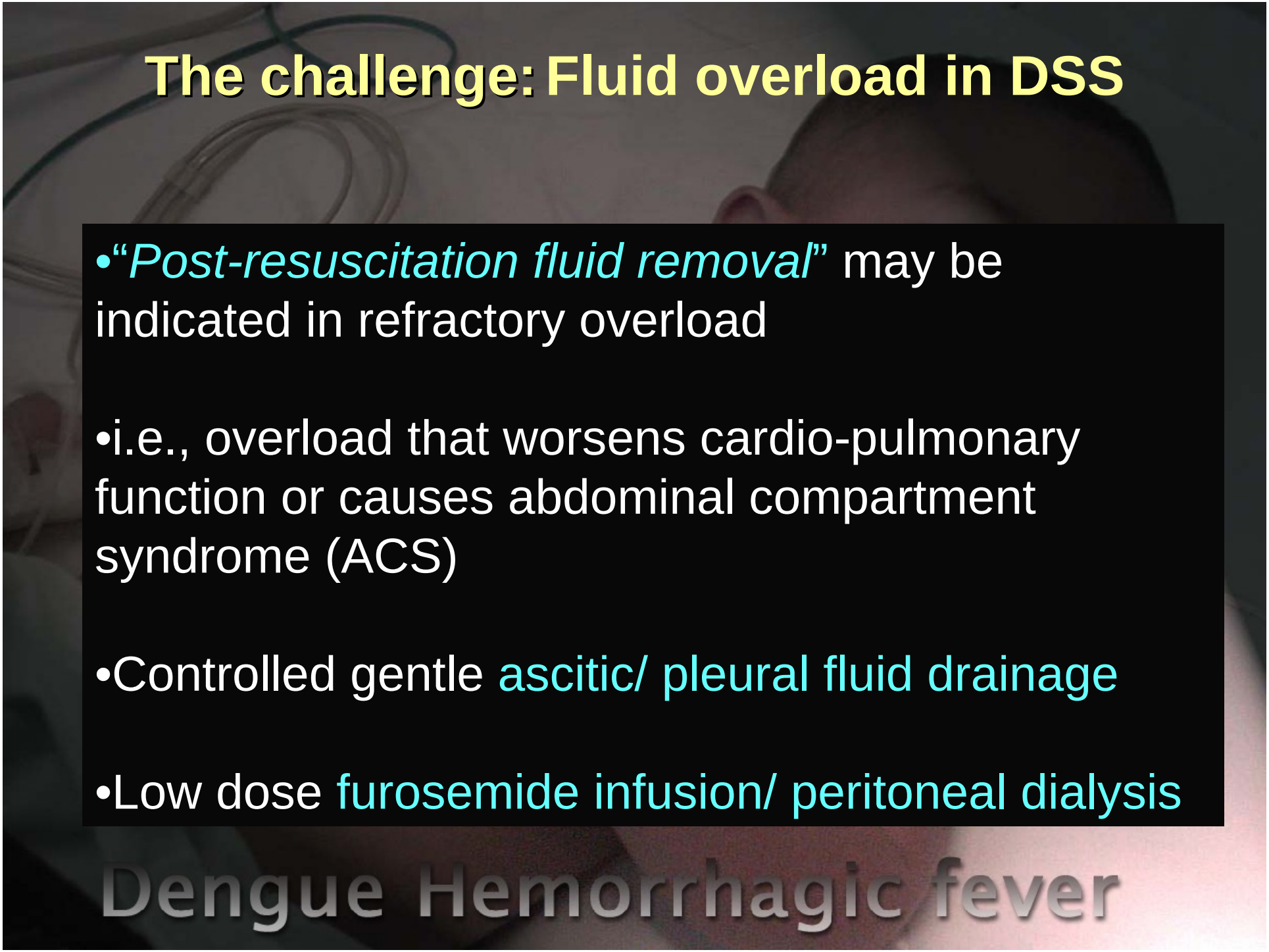
The challenge: Fluid overload in DSS

- "*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?

How?

Why?

Dengue H

Ranjit S, Kissoon N, Jayakumar I
Ped Crit Care Med 2005; 6(4): 412-419

Peritoneal dialysis

Who

How

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

Ranjit S, Kissoon N et al.Ped Crit Care Med 2005; 6(4): 412-419

Refractory shock

Single most important cause is late presentation

Diastolic dysfunction

- *Catecholamines main culprit*

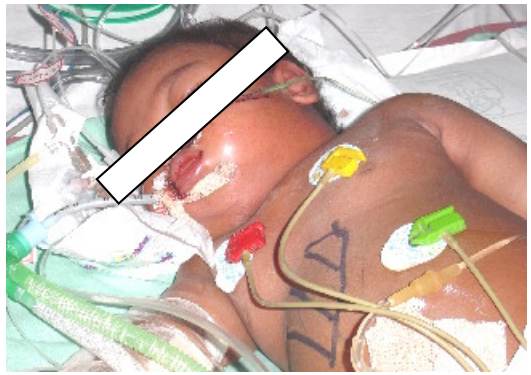
Management

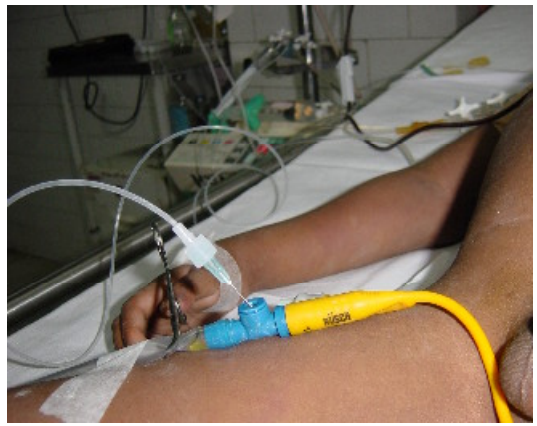
Ranjit S, Kissoon N, Jayakumar I
Ped Crit Care Med 2005; 6(4): 412-419

DSS complications: *Abdominal compartment syndrome*

ACS defined as abdominal distention with

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





Abdominal compartment syndrome in children. Pediatr Crit Care Med. 2001 Jan;2(1):51

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9. Prevention and public health

REAPPRAISAL OF THE WHO CLASSIFICATION

WHO classification may be inappropriate for the following reasons: …

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.

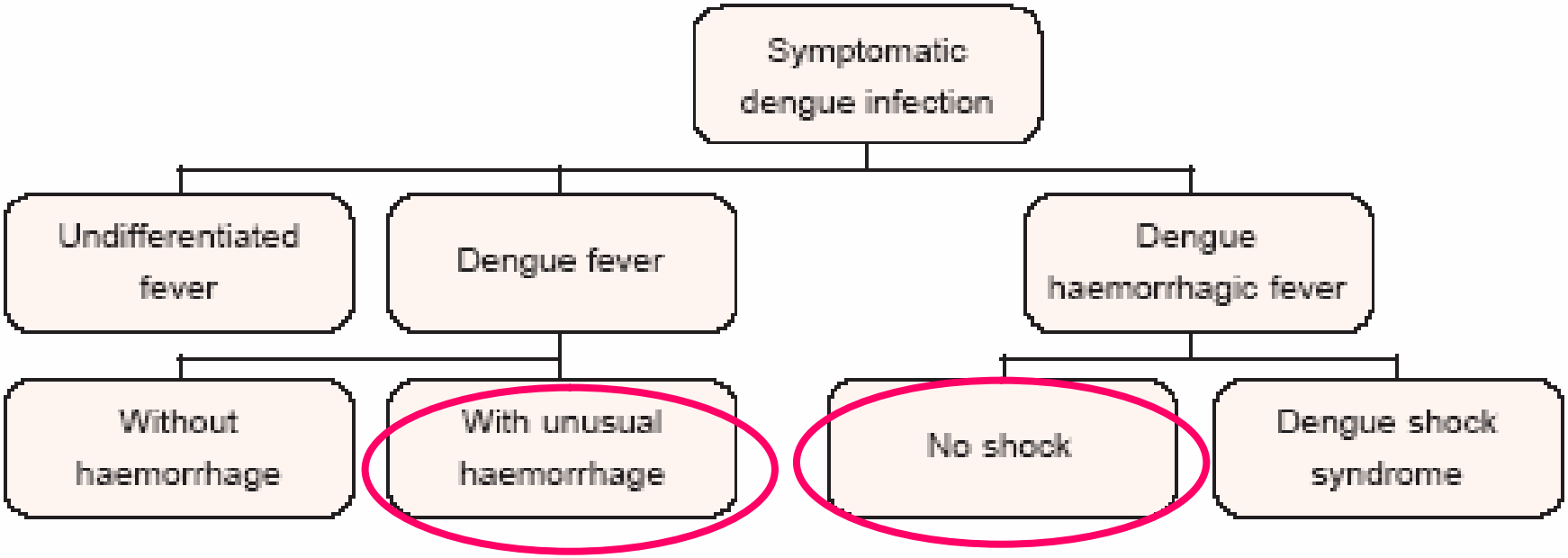
- Haemorrhage may or may not be present in severe dengue and conversely may occur in children with otherwise uncomplicated dengue.

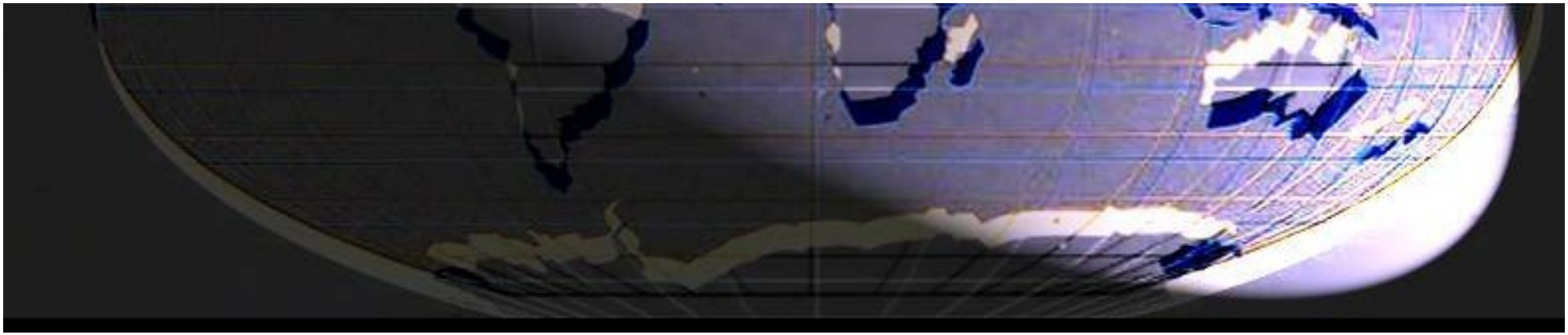
- When life-threatening haemorrhage does occur in severe dengue, it is almost invariably a late manifestation and associated with profound or prolonged shock

Phuong C. Clinical Diagnosis and assessment of severity of confirmed dengue infections in Vietnamese Children: Is the World Health Organization Classification system helpful? American Journal of Tropical Medicine and Hygiene 2004; 70: 172-9.

THE WHO CLASSIFICATION AND CASE DEFINITIONS

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



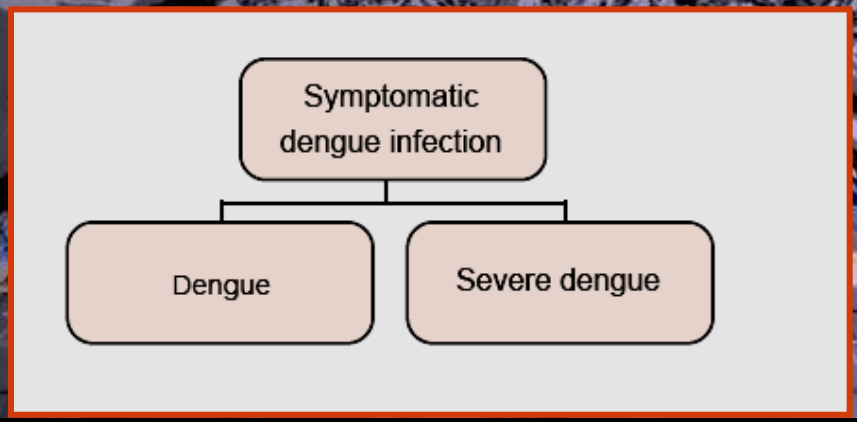


REAPPRAISAL OF THE WHO CLASSIFICATION

It may probably be better to use the terms

Dengue and severe dengue

as shown below, with no emphasis on bleeding or on a specific platelet count cut-off

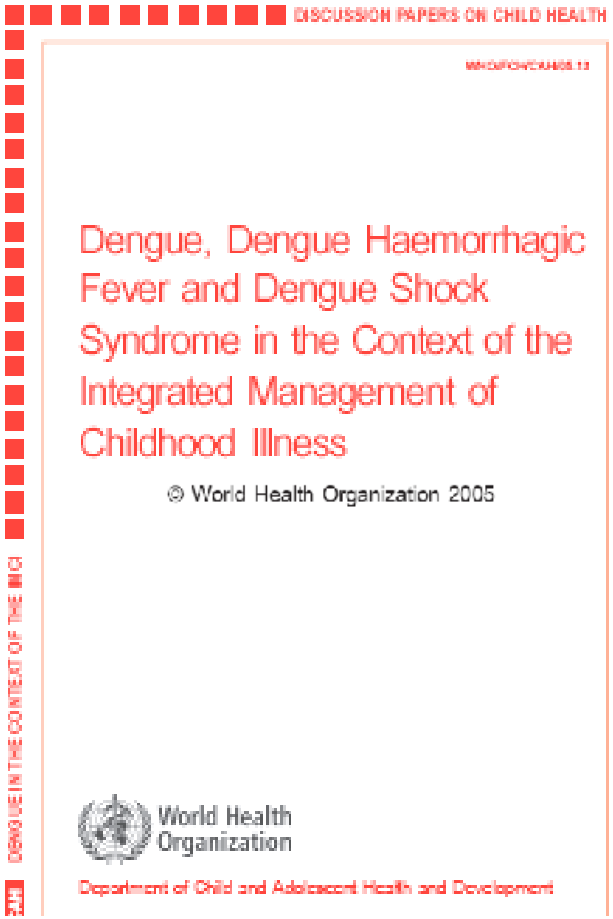


In this simplified classification system, vascular permeability resulting in plasma leakage would be the hallmark of severe dengue.

.

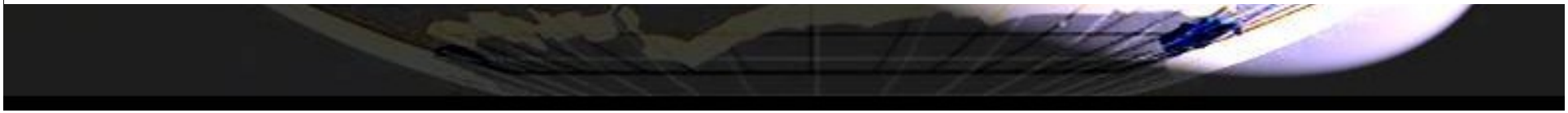
Danger signs of severe dengue would include

- Circulatory compromise
- Altered sensorium (unconscious, lethargic, combative),
- Abnormal bleeds
- Unusual manifestations (hepatic damage, cardiomyopathy, encephalopathy)



Prediction of Severe Disease

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


PDVI
Pediatric DENGUE
VACCINE INITIATIVE
PDVI Mission:
To accelerate the development and introduction of affordable dengue vaccine(s) for children in endemic countries.
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