

Update on Dengue Management

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BD
Physicians



Bangladesh Society
of Infectious &
Tropical Diseases

Scan to watch
the video:

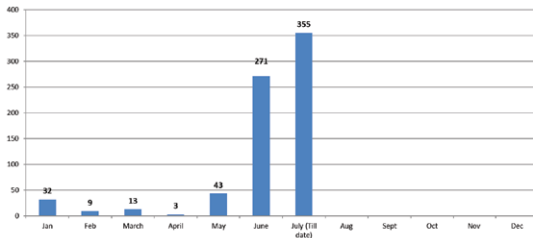
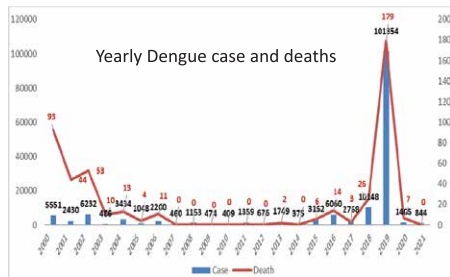




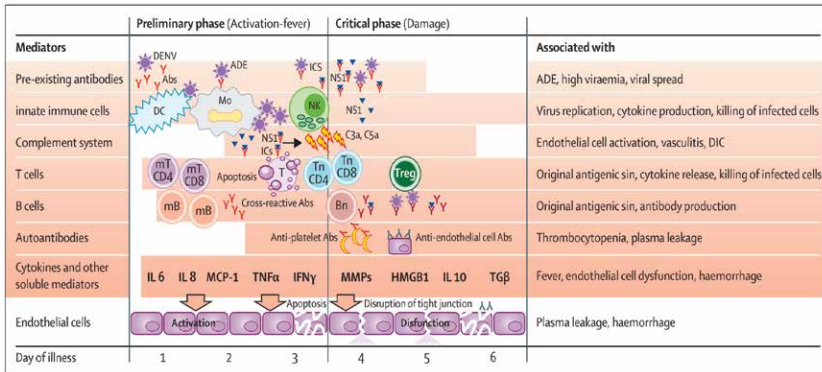
“Dengue is one disease entity with different clinical presentations and often with unpredictable clinical evolution and outcome”

Monthly dengue cases:

| Month | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 |
|--------------|------------|-------------|-------------|-------------|--------------|---------------|-------------|
| January | 15 | 0 | 13 | 92 | 26 | 38 | 199 |
| February | 7 | 0 | 3 | 58 | 7 | 18 | 45 |
| March | 2 | 2 | 17 | 36 | 19 | 17 | 27 |
| April | 0 | 6 | 38 | 73 | 29 | 58 | 25 |
| May | 8 | 10 | 70 | 134 | 52 | 193 | 10 |
| June | 9 | 28 | 254 | 267 | 295 | 1884 | 20 |
| July | 82 | 171 | 926 | 286 | 946 | 16253 | 23 |
| August | 80 | 765 | 1451 | 346 | 1796 | 52636 | 68 |
| September | 76 | 965 | 1544 | 430 | 3087 | 16856 | 47 |
| October | 63 | 869 | 1077 | 512 | 2406 | 8143 | 164 |
| November | 22 | 271 | 522 | 409 | 1192 | 4011 | 546 |
| December | 11 | 75 | 145 | 126 | 293 | 1247 | 231 |
| Total | 375 | 3162 | 6060 | 2769 | 10148 | 101354 | 1405 |



Pathogenesis of dengue virus infection according to phase of illness

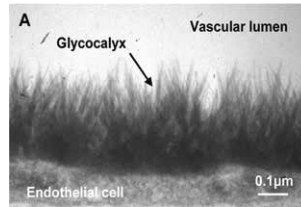
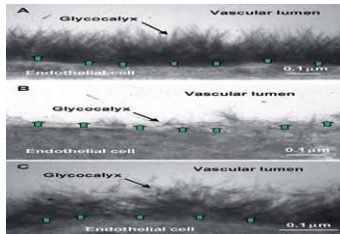
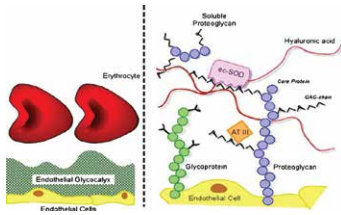


Lancet 2015;385:453-65

Pathophysiology of Thrombocytopenia

- Reduced production from bone marrow suppression
 - Direct viral bone marrow suppression
- Increased destruction
 - Platelet consumption during coagulopathy process
 - Activation of fibrinolytic system
 - Activation of complement system
 - Activation of inflammatory cytokines and other soluble mediators
 - Transient autoimmunity with cross-reactive antibodies

Pathophysiology of Plasma Leakage



Plasma Leakage

- Adult dengue at D4-5 (critical phase) is associated with increased risk of DHF
- Endothelial glycocalyx breakdown is higher in DHF compared to DF
- Increased serum hyaluronic acid was associated with vascular leak and thrombocytopenia in adult dengue

Clinical Case Classification by severity

Dengue case classification by severity

Dengue \pm warning signs

Severe dengue



Criteria for dengue \pm 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
- Leucopenia
- 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 >2cm
- *Laboratory:* Increase in HCT concurrent with rapid decrease in platelet count

* Requiring strict observation and medical intervention

Criteria for severe dengue

1. Severe plasma leakage

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

2. Severe bleeding

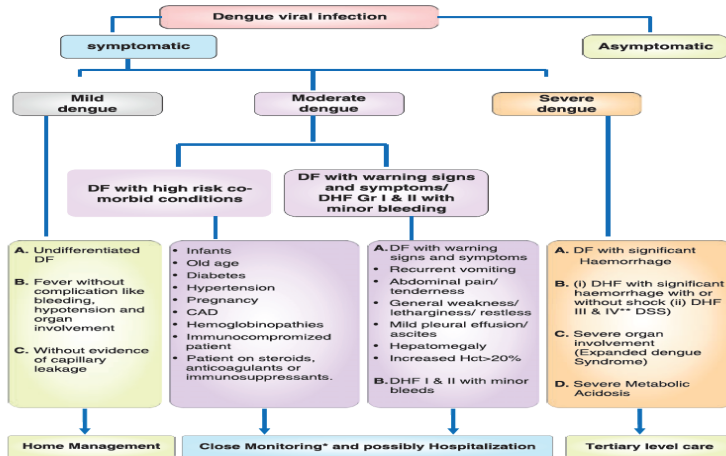
as evaluated by clinician

3. Severe organ involvement

- Liver: AST or ALT \geq 1000
- CNS: Impaired consciousness
- Heart and other organs

www.WHO.SEARO

Warning sign, Risk factors, Level of care



National guideline on dengue management, india, 2017

Dengue Syndrome- Clinical features

Dengue Fever (Infection)

- Headache
- Retro-orbital pain
- Myalgia
- Arthralgia/ bone pain (break-bone fever)
- Rash
- Hemorrhagic Manifestations
- Leukopenia (WBC < 5,000 cells/ mm³)
- Platelet count ≤ 150,000 cells/mm³
- Rising HCT 5-10%

Diagnosis :

**Tourniquet test positive + WBC ≤ 5,000 cells/cu.mm
(positive predictive value = 83%)**



Cao Xt al(2002);Trop Med Int Hlth2002;7(2):125-32

DHF and DSS

Dengue Hemorrhagic Fever

Clinical

- High, continuous fever 2-7 days
- Hemorrhagic manifestations: tourniquet test positive, petechiae, epistaxis, hematemesis, etc...
- (Liver enlargement)
- (Shock)

Laboratory

- Evidence of plasma leakage; rising Hct $\geq 20\%$, pleural effusion, ascites, hypoalbuminemia (serum albumin < 3.5 gm% or < 4 gm% in obese patients), UTZ
- Platelet count $\leq 100,000$ cells/mm³.

Note: *Patients who have definite evidence of plasma leakage, hemorrhagic manifestations and thrombocytopenia might not be present as the exception.*



Two hallmarks of (DHF/DSS) are
plasma leakage & abnormal Hemostasis

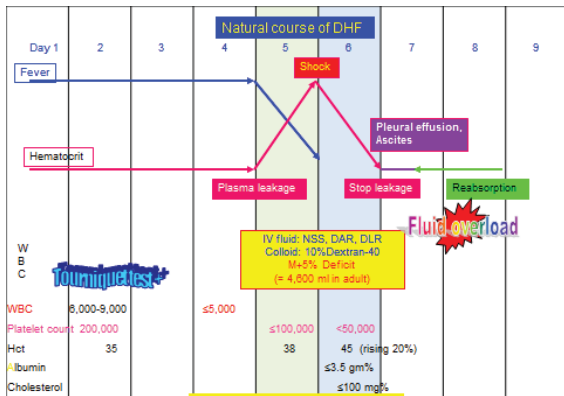
Deen JL et al. Lancet. 2006;368:170-3

DSS(compensated and Decompensated)

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

National guideline for clinical management of Dengue syndrome-2018,DGHS,GOB

Natural course, Phases of Dengue syndrome



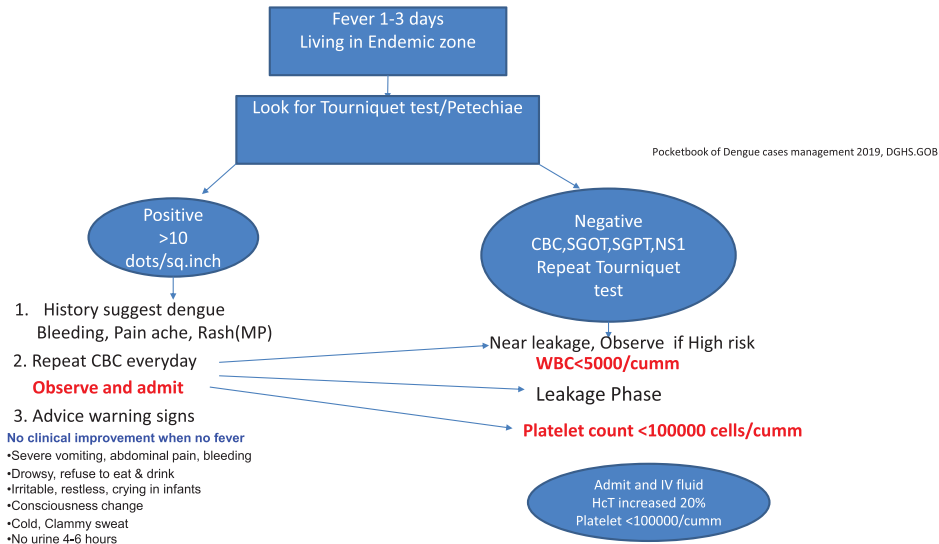
1. Febrile phase 2 – 7 days with mean duration of 4 days
2. Critical/Leakage phase 24 –48 hours – The best simple indicator available is Platelet $\leq 100,000$ cells/mm³
3. Convalescence phase 3 –5 days – Aware that reabsorption of extravasated plasma occurs about 36 hours after shock and 60 hours after Platelet $< 100,000$ cells/mm³

Signs of recovery include:

A – Appetite, B – Bradycardia,

C – Convalescence rash or Itching, D – Diuresis

OPD consultation and triage



Indications for Admission

- Very weak, poor appetite or severe dehydration
- **Presence of warning signs**
- Significant bleeding (especially in female patient, there may be significant PV bleeding or excessive menstrual bleeding)
- $WBC \leq 5,000$ Cells/mm³ in high risks group (infants, Elderly, Pregnancy, prolonged shock, significant bleeding, underlying diseases, neurological manifestations)
- Platelet count $\leq 100,000$ cells/mm³ and presence of weakness, poor appetite, persistent vomiting
- Rising Hct 10-20%
- No clinical improvement and weakness when no fever
- Shock or impending shock
 - No fever but rapid pulse (in infant without crying)
 - Capillary refill > 2 seconds
 - Cold, clammy extremities, skin mottling
 - Irritable, restless, confusion,
 - Pulse pressure ≤ 20 mmHg
 - Fainting, postural hypotension
- Less urine in 4-6 hours
- **Extreme family anxiety**

Dengue Chart

Monitoring Chart for Dengue Patients

Instructions - Do CBC daily/bd and PCV 6 hly. Monitor other parameters 3-4 hly and when leaking detected monitoring every hour.

| | | |
|------|---------|-------------|
| Case | = Refer | = Walk in |
| OPD | = Shock | = Non shock |
| IPD | = Shock | = Non shock |

Indications to call for immediate advice

- Pulse rate > 120/min with fever or >100/min without fever.
- Pulse Pressure < 20 mmHg or less (in supine position)
- Postural drop of SBP >20mmHg.
- Significant bleeding (Haematemesis, Melena, Bleeding PV etc.)
- UOP < 0.5ml /kg/hr
- CRFT < 2 sec

| Date | Time | BP | Temp | PR | RR | PP | RR | HCT (%) | Clinical/ Lab/ Treatment | Nursing Care/ Signs | INTAKE | | | | OUTPUT | | | |
|----------------------|------|-----------------------|------|---------------|----|--|----|---------|--------------------------|---------------------|----------------------|-----------|------|-------|--------------|--------------|-------|--|
| | | | | | | | | | | | Blood/ rate & Amount | IV Amount | Oral | Total | Urine/ Stool | Vomit /Bleed | Total | |
| | | | | | | | | | | | | | | | | | | |
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| | | | | | | | | | | | | | | | | | | |
| CBC Day of Admission | | BW= kgs. Height = cms | | Date of Fever | | Day of Illness | | | | | | | | | | | | |
| Hct = WBC = | | IBW = kgs. | | TT | | | | | | | | | | | | | | |
| PH = Lym = | | Maintenance fluid = | | Liver | | | | | | | | | | | | | | |
| PMN = | | M + 5% Deficit = | | Bleeding | | | | | | | | | | | | | | |
| | | | | Epistaxis | | | | | | | | | | | | | | |
| | | | | Abdomen | | | | | | | | | | | | | | |
| Name | | Age HN | | AN | | Pulse: F = Full M= Moderate W= Weak N = Not Palpable | | | | | | | | | | | | |
| Ward | | Attending Physician | | | | | | | | | | | | | | | | |

- **Clinical:** - consciousness, appetite, bleeding, abdominal pain, vomiting
- **Vital signs:**
 - T every 4-6 hours
 - BP, PR, RR every 2-3 hours in non-shock and every 1 hour in shock cases
- **Hematocrit (Hct)** : every 4-6 hours, more frequent if suspected bleeding
- **Urine output** : every 8 hours in uncomplicated case, keep urine output 0.5-1 ml/kg/hr. Keep urine 0.5 ml/kg/hr in infants, obese patients and pregnant women

Pocketbook of Dengue cases management 2019, DGH5.GOB

Srilankan national guideline of Dengue 2016

Fluid Requirement:

The fluid requirement, **both oral and intravenous, in critical phase (48 hours)** is calculated as **M+5% (maintenance + 5% deficit)**.

5% deficit is calculated as 50 ml/kg up to 50kg.

Calculations for normal maintenance of intravenous fluid Infusion:

Normal maintenance fluid per hour can be calculated on the basis of the following formula* (equivalent to Holliday- Segar formula):

- 4 ml/kg/hr for first 10 kg body weight
- + 2 ml/kg/hr for next 10 kg body weight
- + 1 ml/kg/hr for subsequent kg body weight

For example, in a child weighing 20 kg,
The deficit of 5% is $50 \text{ ml/kg} \times 20 = 1000 \text{ ml}$. The maintenance is 1440 ml for one day. Hence, the total of M + 5% is 2440 ml. *This volume is to be administered over 48 hours in nonshock patients.*

Rate of IV fluid, Ideal body wt for obese

RATE IV FLUID : COMPARE ADULT AND CHILDREN

| | Child (ml/kg/hr) | Adult (ml/hr) |
|--------------------|---------------------|------------------|
| M/2 | 1.5 | 40 |
| Maintenance (M) | 3 | 80 |
| M +5%D | 5 | 100-120 |
| M +7%D | 7 | 150 |
| M + 10%D | 10 | 300 - 500 |

Estimated Ideal Body Weight for Overweight or Obese Adults

| Height (cm) | Estimated, IBW (kg) for adult males | Estimated IBW (kg) for adult females |
|-------------|--|---|
| 150 | 50 | 45.5 |
| 160 | 57 | 52 |
| 170 | 66 | 61.5 |
| 180 | 75 | 70 |

National guideline for clinical management of Dengue syndrome-2018,DGHS,GOB

Calculation of Fluids in Obese or Overweight Patients'

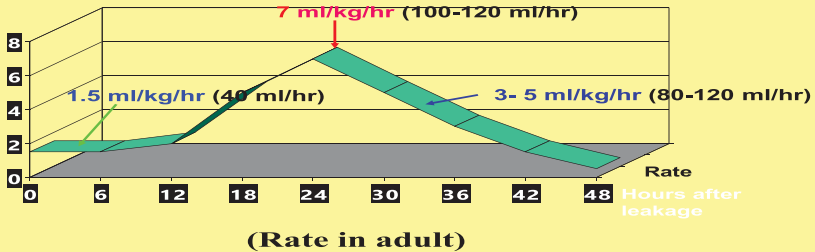
| Estimated body weight, or IBW (kg) | Normal maintenance fluid [ml/hour] based on Holliday-Segar formula | Fluid regimen based on 2-3 ml/kg/hour (ml/hour) | Regimen based on 1.5-2ml/hour (ml/hour) |
|------------------------------------|--|---|---|
| 5 | 10 | 10-15 | |
| 10 | 20 | 20-30 | |
| 15 | 30 | 30-45 | |
| 20 | 60 | 40-60 | |
| 25 | 65 | 50-75 | |
| 30 | 70 | 60-90 | |
| 35 | 75 | 70-105 | |
| 40 | 80 | 80-120 | |
| 50 | 90 | 100-150 | |
| 60 | 100 | | 90-120 |
| 70 | 110 | | 105-140 |
| 80 | 120 | | 120-150 |

| Ideal wt (kg) | Maintenance (ml) | M+5% deficit (ml) | Ideal body wt (kg) | Maintenance (ml) | M+5% deficit (ml) |
|---------------|------------------|-------------------|--------------------|------------------|-------------------|
| 5 | 500 | 750 | 35 | 1800 | 3550 |
| 10 | 1000 | 1500 | 40 | 1900 | 3900 |
| 15 | 1250 | 2000 | 45 | 2000 | 4250 |
| 20 | 1500 | 2500 | 50 | 2100 | 4600 |
| 25 | 1600 | 2850 | 55 | 2200 | 4950 |
| 30 | 1700 | 3200 | 60 | 2300 | 5300 |

WHO guideline, SEARO, 2014

Flow diagram for non-shock case

Rate of IV Fluid in Patients Category B DHF 1&2



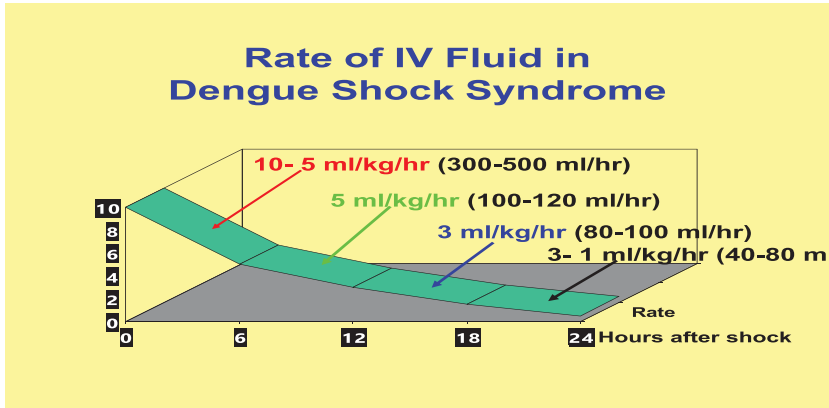
National guideline for clinical management of
Dengue syndrome-2018,DGHS,GOB

ABCS

| ABREVIATION | LABORATORY INVESTIGATIONS | NOTES |
|-----------------|-----------------------------------|--|
| A. Acidosis | Blood gas (Capacity or venous) | Indicate prolonged shock. Organ involvement should also look for; Liver function and BUN., Creatinine. |
| B. Bleeding | Hematocrit | If dropped compared to the previous value or not rising, cross match for rapid blood transfusion. |
| C. Calcium | Electrolyte, Ca ⁺⁺ | Hypocalcemia is found in almost all cases of DHF but asymptomatic. Ca supplement in more severe/ complicated cases is indicated. The dosage is 1 ml/kg dilute to 2 times IV push slowly, maximum dose 10 ml of Ca gluconate. |
| S- Blood sugar. | Serum sugar (Dextrostix) | Most severe DHF cases have poor appetite together with vomiting. Those with impaired liver function may have hypoglycemia. Some cases may have hyperglycemia. |

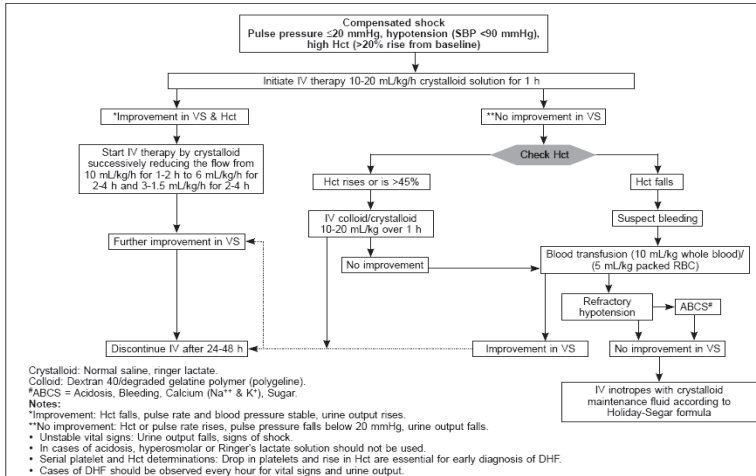
National guideline for clinical management of Dengue syndrome-2018,DGHS,GOB

Diagram of IV fluid rate in DSS (compensated shock)

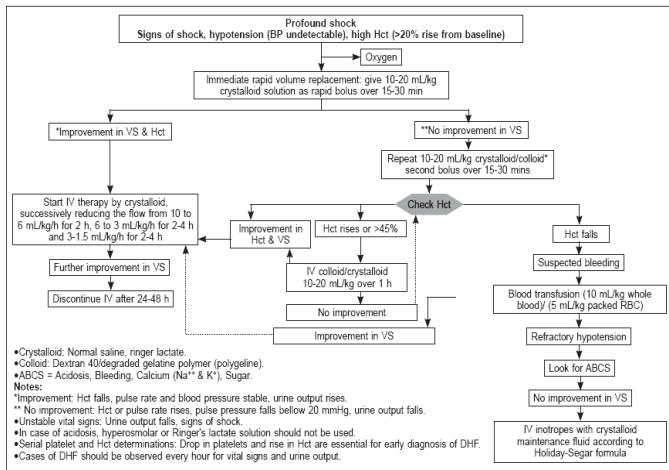


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IV FLUID THERAPY for Compensated Shock



Flow diagram for profound shock (decompensated shock)



WHO guideline, SEARO,2014

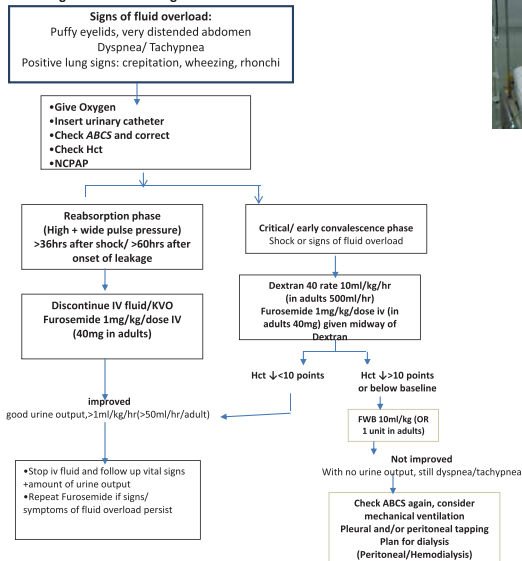
Assessment in shock case-7 things

| Parameters | Stable Condition | Compensated Shock | Hypotensive Shock |
|-----------------------|---|--|--|
| Sensorium | Clear and lucid | Clear and lucid (shock can be missed if you do not touch the patient) | Change of mental status (restless and combative) |
| Capillary refill time | Brisk (<2 sec) | Prolonged (>2sec) | Very prolonged, mottled skin |
| Extremities | Warm and pink | Cool peripheries | Cold and clammy |
| Peripheral pulse | Good volume | Weak and thready | Feeble or absent |
| Heart rate | Normal for age | Tachycardia | Severe tachycardia with bradycardia in the late shock. |
| Blood pressure | Normal for age Normal pulse pressure for age | Normal systolic pressure but rising diastolic pressure. Narrowing pulse pressure. Postural hypotension | Narrowed pulse pressure (<20 mmHg) Hypotension (see definition below) Unrecordable BP Metabolic Acidosis, |
| Respiratory rate | Normal for age | Tachypnea | Hyperpnea, Kussmaul breathing |

WHO guideline, SEARO, 2014



Flow diagram for the Management of Fluid Overload

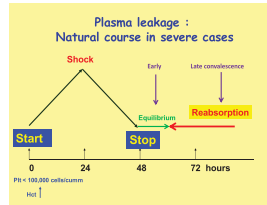


Siripen Kalayanaraj et al. 2014. Clinical practice guideline of DF/DHF management of economic community

Pocketbook of Dengue cases management
 2019, DGHS.GOB

Colloid(Dextran/Plasmasol) + furosemide (in the middle or after 10-15 mins)

- Shock
- During critical period
- Not in reabsorption phase



- Furosemide depletes intravascular volume, (not deplete ascites or pleural effusion)
- Colloid(Dextran/Plasmasol) holds intravascular volume or draws back ascites and pleural effusion

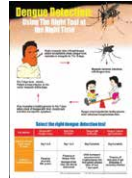
Siripen Kalayanarroj et al. 2014.Clinical practice guideline of DF/DHF management of economic community

Indications for using Colloid [(10% Dextran-40 in NSS)/Plasmasol/Human albumin]

- Signs of fluid overload
- Dyspnea, tachypnea, puffy eyelids, tense/distended abdomen
- Positive lung signs: crepitation, rhonchi, wheezing
- Persistent high Hct, 25 - 30% hemoconcentration for > 4-8 hours.

How to give Colloid (Dextran – 40)

- Always give in a bolus dose.
 - 10 ml/kg/hr in children at a time
 - 500 ml/hr in adults at a time
 - Dextran will bring down PCV by 10 points, but not below baseline PCV
- Hct before and immediately after
 - If Hct drops > 10 points, indicates significant bleeding
 - If Hct drops below baseline, indicates bleeding
- Maximum dose.
 - 30 ml/kg/24 hrs or 60 ml/kg/48 hours of leakage in children.
 - 1500 ml/24 hrs or 3,000 ml/48 hours of leakage in adult
 - Aware of sticky urine
 - With this recommended dose, there are no kidney complications or involvement.



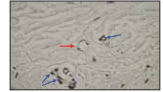
Siripen Kalayanarroj et al. 2014. Clinical practice guideline of DF/DHF management of economic community

Indication of Blood transfusion (FWB,PRC)



- Overt bleeding (more than 10% or 6-8ml/kg)
- Significant drop of HCT < 40 (< 45 for males) after fluid resuscitation
- Hypotensive shock + low/normal HCT
- Persistent or worsening metabolic acidosis
- Refractory shock after fluid 40-60 ml/kg

Recovery signs and Discharge criteria



Stable pulse, blood pressure and breathing rate.

Normal temperature.

No evidence of external or internal bleeding.

Return of appetite.

No vomiting, no abdominal pain.

Good urinary output.

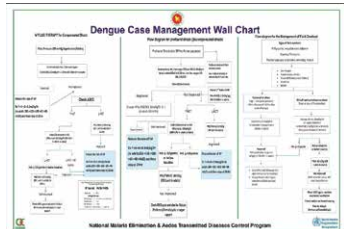
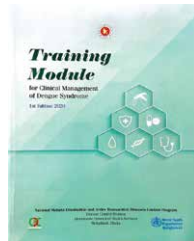
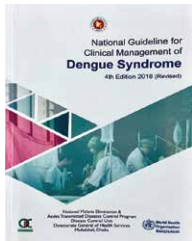
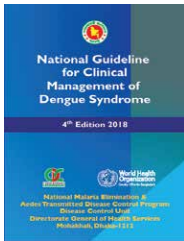
Stable haematocrit at baseline level.

Convalescent confluent petechiae rash or itching, especially on the extremities.



- **Absence of fever for at least 24 hours without the use of anti-fever therapy.**
- **Return of appetite.**
- **Visible clinical improvement.**
- **Satisfactory urine output.**
- **A minimum of 2–3 days have elapsed after recovery from shock.**
- **No respiratory distress from pleural effusion and no ascites.**
- **Platelet count of more than 50 000/mm³.**

National guideline for clinical management of Dengue syndrome-2018,DGHS,GOB





Clinico-epidemiologic characteristics of the 2019 dengue outbreak in Bangladesh

Mohammad Jahid Hasan^{1,2*}, Tamanna Tabassum³, Mohiuddin Sharif⁴, Mohammad Abdullah Saeed Khan⁵, Akhli Roy Bipasha⁶, Ariful Basher⁷, Mohammad Rafiqul Islam⁸, Mohammad Robed Amin⁹, and David Gezal¹⁰

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ORIGINAL PAPER

NIHR | National Institute
for Health Research

PROSPERO
International prospective register of systematic reviews

Epidemiological characteristics of dengue in Bangladesh: A systematic review
Mohammed Jahid Hasan, Moonmoon Akter, Noor-E Ambia, Md. Abdullah Saeed Khan, Mohammad Robed Amin

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Article

Detection of Anti-Nucleocapsid Antibody in COVID-19 Patients in Bangladesh Is not Correlated with Previous Dengue Infection

Simon D. Lytton^{1,*}, Mahmuda Yeasmin², Ashish Kumar Ghosh³, Md. Rakibul Hassan Bulbul⁴, Md. Maruf Ahmed Molla⁵, Martha Herr⁶, Helmut Duchmann⁷, Md. Mohiuddin Sharif⁸, Tasnim Nafisa⁹, Md. Robed Amin¹⁰, Nur Hosen², Md. Tanvir Rahman¹¹, Sunaiya Islam¹², Alimul Islam⁴ and Abul Khair Mohammad Shamsuzzaman²

J MEDICINE 202; 13 : 160-164

Dengue: A Practical Experience of Medical Professionals in Hospital

QUAZI TARIKUL ISLAM¹, ARIFUL BASHAR², ROBED AMIN³

Research Article

Dengue Situation in Bangladesh: An Epidemiological Shift in terms of Morbidity and Mortality

Pulak Mutsuddy¹, Sayya Tahmina Ibtosa, Abul Khair Mohammad Shamsuzzaman, S. M. Golam Kaiser, and Md Nasir Ahmed Khan

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DENGUE FEVER, EXPANDED DENGUE SYNDROME AND DENGUE SHOCK SYNDROME: CLINICAL PROFILE, MANAGEMENT AND OUTCOME OF PATIENTS AT A TERTIARY HOSPITAL, DHAKA, BANGLADESH

ROZANA ROUF¹, RAHMAN RAHMAN², PRATIK DEWAN³, MIRZA NAZIM UDDIN⁴, JAHANGIR ALAM⁵, KAZI ALI HANNAF⁶, MD. ABU BAKAR⁷, MD. NORIED AMIN⁸, ANOVAR HOSSAIN⁹

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Accepted: 12 June 2020



Investigation of the efficacy and safety of eltrombopag to correct thrombocytopenia in moderate to severe dengue patients - a phase II randomized controlled clinical trial

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Original Article

Chinese Medical Journal

Clinical study on paradigm shift of dengue syndrome in Bangladesh

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Vol. 8(1), pp. 8-17, February 2020
DOI: 10.30918/IJMMMS.81.20.013
ISSN: 2354-211X
Review

Vector borne viral diseases: An emerging threat and their control strategies in Bangladesh perspectives

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Accepted 10 February, 2020

J MEDICINE 2019; 12: 19-23

Knowledge Attitude and Practice of Dengue Syndrome Management on the Basis of National Guideline by the Physicians of Dhaka City

Mohammad Rafiqul Islam¹, Sarmistha Bhowmik², Mohammad Robed Amin³, Md. Ridwanur Rahman⁴

J MEDICINE 2019; 12: 100-108

Clinical Profile and Outcome of Patients with Dengue Syndrome In Hospital Care

HANUF MOHAMMAD¹, DEVIDEKA NATH SARKAR², KIROBED AHON³, A BISHAK⁴, T AHMED⁵

Randomized trials

- Three randomized, blinded studies have compared crystalloids to colloids in the treatment of shock in dengue infection
- All conducted in Vietnam in pediatric population



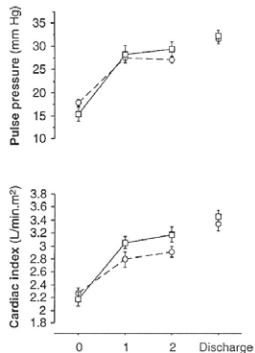
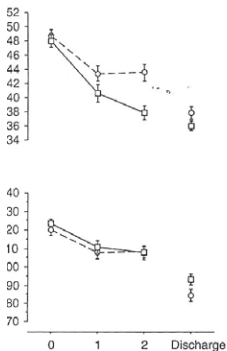
crystalloid or colloid?

Randomized trials

- **Trial 1:**
- 50 children
- Randomized to:
 - –Crystalloid (25): 0.9% NS (12 pts), Ringer's lactate (13 pts)
 - –Colloid (25): Dextran 70 (12 pts), Gelafundin (13 pts)
- 500 mls of study fluid administered at 20 mL/kg for first hour then 10 mL/kg for subsequent hour
- Further infusion was given on open basis after resuscitation



Colloid restored cardiac index, blood pressure and normalized hematocrit more rapidly than crystalloid



Trial 2:

Acute Management of Dengue Shock Syndrome: A Randomized Double-Blind Comparison of 4 Intravenous Fluid Regimens in the First Hour

222 children

• Randomized to:

– Crystalloid (111): 0.9% NS (56 pts), Ringer's lactate (55 pts)

– Colloid (111): Dextran 70 (55 pts), Gelatin (56 pts)

• 500 mls of study fluid administered at 20 mL/kg for first hour then 10 mL/kg for subsequent hour

• Further infusion of Ringer's lactate was given on open basis after



Ngo Thi Nhan,¹ Cao Xuan Thanh Phuong,^{1a} Rachel Kneen,^{2,3} Bridget Wills,^{2,3} Nguyen Van My,¹
Nguyen Thi Que Phuong,¹ Chu Van Thien,¹ Nguyen Thi Thuy Nga,¹ Julie A. Simpson,^{2,3} Tom Solomon,^{2,3}
Nicholas J. White,^{2,3} and Jeremy Farrar^{2,3}

¹Dong Nai Paediatric Hospital, Bien Hoa, Dong Nai Province, ²Wellcome Trust Clinical Research Unit, Centre for Tropical Diseases, Ho Chi Minh City, Vietnam; and ³Centre for Tropical Medicine, Nuffield Department of Medicine, University of Oxford, Oxford, United Kingdom

Clinical Infectious Diseases 2001;32:204–13

Trial 2:

Primary and secondary end points

Primary end point:

- Pulse pressure recovery time (PPRT) = time from start of fluid therapy until pulse pressure >30mmHg
- Difference in median PPRT between the 4 groups was small but reached significance
- Lactate Ringer's group had longest recovery time (11/55 children, 20% had PPRT>1h)

Secondary end point:

- Dextran 70 group had maximum reduction in hematocrit at 1 hour
- Dextran 70 required the least support with rescue fluids after the first hour

•PPRT recovery time >1h was significant

for pulse pressure <10 vs >10

•Ringer's lactate (Group C) had PPRT

recovery time >1h significantly more than

gelatin (Group B)

Trial 3

**The NEW ENGLAND
JOURNAL of MEDICINE**

ESTABLISHED IN 1812

SEPTEMBER 1, 2005

VOL. 353 NO. 9

**Comparison of Three Fluid Solutions for Resuscitation
in Dengue Shock Syndrome**

Bridget A. Wills, M.R.C.P., Nguyen M. Dung, M.D., Ha T. Loan, M.D., Dong T.H. Tam, M.D., Tran T.N. Thuy, M.D.,
Le T.T. Minh, M.D., Tran V. Diet, M.D., Nguyen T. Hao, M.D., Nguyen V. Chau, M.D., Kasia Stepniowska, Ph.D.,
Nicholas J. White, F.R.C.P., and Jeremy J. Farrar, F.R.C.P.

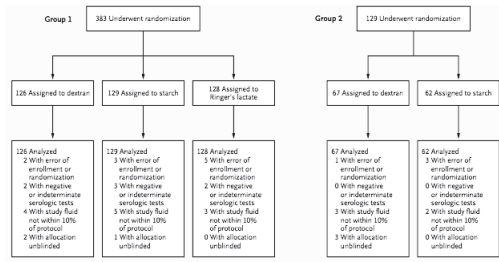
Primary outcome:

- requirement for supplemental intervention with rescue colloid at any time after the infusion of the study fluid.

Secondary outcome:

- time taken to achieve initial cardiovascular stability;
- time taken to achieve sustained cardiovascular stability;
- the volumes of rescue colloid and total parenteral fluid required,
- the pattern of change in the hematocrit, and
- the number of days in the hospital

Randomization



Group 1= moderate shock (pulse pressure > 10mmHg and <=20mmHg)

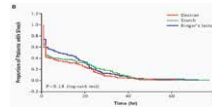
Group 2= severe shock (pulse pressure <= 10mmHg)

Group 1 compared dextran, starch and Ringer's lactate

Group 2 compared dextran and starch only



Outcome



- **No difference in number of patients requiring rescue colloid, volume of rescue colloid or length of hospital stay between groups**
- **Hematocrit reduction was significantly greater in dextran (25%) and starch (22%) compared to Ringer's lactate (9%)**
- **Children receiving Ringer's lactate took longer to achieve initial cardiovascular stability than patients receiving colloids. However, not sufficiently compromised to warrant rescue colloids**
- **Time to final cardiovascular stability was not different between crystalloid and colloids**
- **Risk of allergic type reactions higher with colloids, otherwise fluid overload and bleeding were not significantly different**

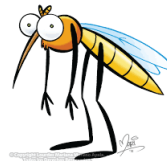
In dengue shock syndrome have you used corticosteroids before?

Zhang F, Kramer CV

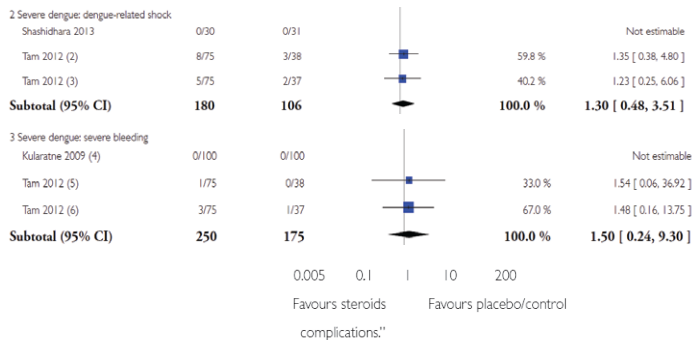


**THE COCHRANE
COLLABORATION®**

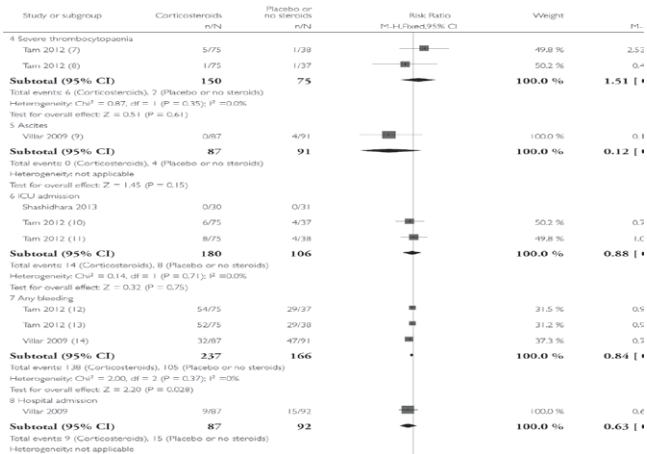
A 2014 Cochrane meta-analysis examined **8 studies with 948 patients** for corticosteroid use compared to placebo in dengue



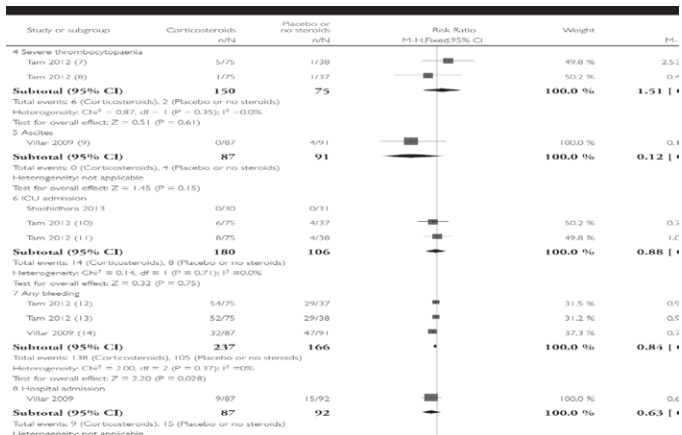
No significant effect on severe dengue manifestations (shock or severe bleeding)



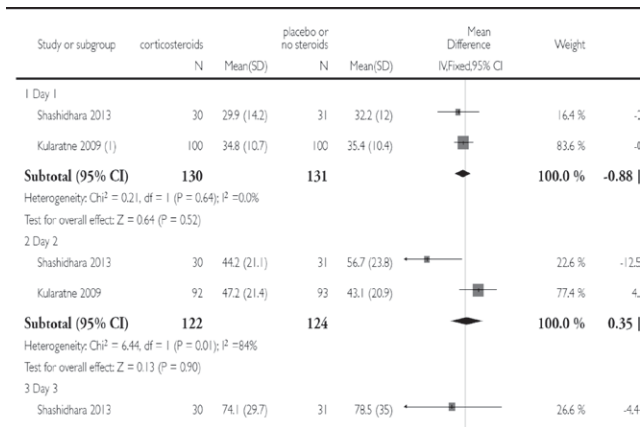
No significant effect on thrombocytopenia or bleeding



No significant effect on ICU or hospital admission



No significant effect on platelet count recovery



No significant effect on haematocrit change

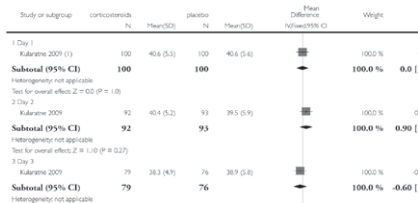


Analysis 2.3. Comparison 2 Steroids versus placebo/no steroids in patients with dengue at an early stage
Outcome 3 Haematocrit on days one to four.

Review: Corticosteroids for dengue infection

Comparison: 2 Steroids versus placebo/no steroids in patients with dengue at an early stage

Outcome: 3 Haematocrit on days one to four



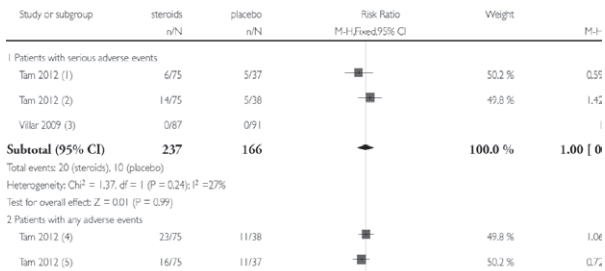
No significant increase in SAE/AEs

Analysis 2.5. Comparison 2 Steroids versus placebo/no steroids in patients with dengue at an early stage Outcome 5 Adverse events in dengue at an early stage.

Review: Corticosteroids for dengue infection

Comparison: 2 Steroids versus placebo/no steroids in patients with dengue at an early stage

Outcome: 5 Adverse events in dengue at an early stage



Corticosteroids in DSS(2010)

A 2010 Cochrane meta-analysis examined 4 studies with 284 patients for corticosteroid use compared to placebo in DSS



Analysis 1.1. Comparison 1 Corticosteroids versus no corticosteroids or placebo, Outcome 1 Death.

Review: Corticosteroids for treating dengue shock syndrome

Comparison: 1 Corticosteroids versus no corticosteroids or placebo

Outcome: 1 Death

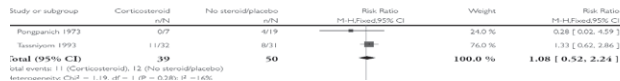


Analysis 1.2. Comparison 1 Corticosteroids versus no corticosteroids or placebo, Outcome 2 Blood transfusion.

Review: Corticosteroids for treating dengue shock syndrome

Comparison: 1 Corticosteroids versus no corticosteroids or placebo

Outcome: 2 Blood transfusion



Efficacy of low dose dexamethasone in severe thrombocytopenia caused by dengue fever: a placebo controlled study

S A M Kularatne,¹ C Walathara,¹ S I Mahindawansa,¹ S Wijesinghe,¹ M M K Pathirage,¹

Postgrad Med J 2009;**85**:525–529.

Table 1 Distribution of baseline data between the two groups

| Characteristics | Dexamethasone | Placebo | p Value |
|-------------------------------------|---------------|-------------|---------|
| Gender, number (%) | | | |
| Male | 71 (51) | 67 (49) | 0.54* |
| Female | 29 (47) | 33 (53) | |
| Mean age (SD) (years) | 32.4 (13.3) | 33.6 (14.3) | 0.56† |
| Mean (SD) days illness at enrolment | 4.7 (1.5) | 4.7 (1.6) | |
| Mean (SD) haemoglobin (g/dl) | 13.6 (2.0) | 13.3 (2.1) | 0.37† |
| Total no in a group | 100 | 100 | |

* χ^2 test; † t test.

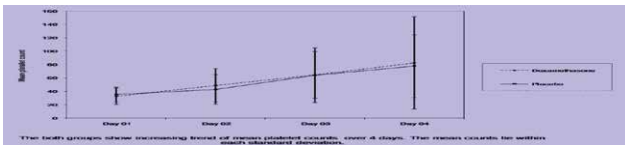


Table 2 Mean (SD) parameters (secondary outcomes) of the two groups

| Sign/outcome | Day 1 | p Value | Day 2 | p Value | Day 3 | p Value | Day 4 | p Value |
|---|------------|---------|------------|---------|------------|---------|------------|---------|
| Haematocrit | | | | | | | | |
| Dexamethasone | 40.6 (5.5) | 0.95 | 40.4 (5.2) | 0.25 | 38.8 (4.9) | 0.82 | 39.2 (4.5) | 0.08 |
| n | 97 | | 87 | | 75 | | 36 | |
| Placebo | 40.6 (5.6) | | 39.5 (5.9) | | 38.9 (5.8) | | 37.2 (5.5) | |
| n | 99 | | 94 | | 73 | | 46 | |
| WBC ($\times 10^9/l$) | | | | | | | | |
| Dexamethasone | 4.8 (2.4) | 0.02 | 5.9 (2.6) | 0.87 | 6.6 (3.0) | 0.49 | 7.01 (2.8) | 0.75 |
| n | 80 | | 54 | | 45 | | 24 | |
| Placebo | 5.7 (2.9) | | 5.9 (3.3) | | 7.1 (3.3) | | 7.3 (3.6) | |
| n | 87 | | 63 | | 44 | | 26 | |

n, number of patients; p value calculated with Student's t test.
WBC, white blood cells.

In summary

Senaka Rajapakse et al .Corticosteroids in the treatment of dengue shock syndrome.

Infection and Drug Resistance 2014;7 137–143
10 studies with 1103 patients

S M Rathnasiri Bandara et al. Management of Dengue and Post Dengue Complication Syndrome: A Review. ACTA SCIENTIFIC

MICROBIOLOGY (ISSN: 2581-3226) Volume 2 Issue 4 April 2019
Highlights steroid protocol-hypothetical

S. M. Rathnasiri Bandara a, H. M. M. T. B. Herath. Effectiveness of corticosteroid in the treatment of dengue e A.systemic review. Heliyon 4 (2018) e00816.doi: 10.1016/j.heliyon.2018. E00816. This review includes thirteen studies enrolling 1293 children and adult participants

- There is currently no high-quality evidence supporting the beneficial effects of corticosteroids for treatment of shock, prevention of serious complications, or increasing platelet counts.
- Non-randomized trials of corticosteroids given as rescue medication for severe shock have shown possible benefit.
- The evidence base is small, and good-quality trials are lacking.
- The need for well-designed and adequately powered randomized controlled trials of corticosteroids for the treatment of dengue shock.

Planned RCT in Bangladesh: 2019-Onwards

A phase III double blind Randomized controlled trial of Methylprednisolone vs crystalloid (Normal Saline) in patient with decompensated dengue shock syndrome with or without expanded dengue syndrome in Bangladesh.

- **The controversy on the effects of corticosteroids in dengue arises from the lack of good-quality trials and the overemphasis of poor-quality evidence from early studies.**
- **There is a definite need for an adequately powered and carefully designed randomized controlled trial of high-dose corticosteroids in the treatment of patients with severe dengue shock syndrome**
- **Justification for such a trial is supported by the fact that no major adverse effects have been demonstrated with the administration of corticosteroids in dengue**



Intravenous Immunoglobulins?

- Efran D Mannaio et al. Lack of efficacy of high dose intravenous immunoglobulin treatment for severe thrombocytopenia in pt with secondary dengue infection. Am J Trop Med 77(6)2007.1135-138
- No difference in platelet recovery between IVIG (closed circle) and no IVIG (open circle)



Prophylactic Platelet Transfusion?

Risk factors for hemorrhage in severe dengue infections

Lucy Chai See Lum, MBBS, MRCP, EDIC, Adrian Yu Teik Gob, MBBS, MMed, MRCP,
Patrick Wai Keong Chan, MBBS, MMed, MRCP, Abdel-Latif Mohd El-Amin, MBBS, MPH, MPH (Epid),
and Sai Kit Lam, MSc, PhD, FRCPath, FRCP, FASc Journal of paediatrics may 2002



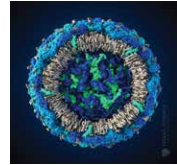
Table 1. Clinical and laboratory data (univariate analysis) and outcome of severe hemorrhage in DSS

| Clinical/laboratory data | Group 1 (significant hemorrhage) n = 22 ^a | Group 2 (no/mild hemorrhage) n = 92 ^a | P value |
|--|--|--|---------|
| Age (y) ^b | 7.0 (0.3–12.0) | 6.0 (0.2–11.7) | .801 |
| Hypotension (%) | 68.1 | 37.8 | .010 |
| Mottling (%) | 45.0 | 22.0 | .027 |
| Encephalopathy (%) | 65.3 | 28.3 | .002 |
| Liver failure (%) | 63.6 | 22.0 | .000 |
| Abnormal glycaemia (%) | 61.9 | 17.4 | .000 |
| Duration of shock (h) ^b | 12.0 (2.0–24.0) | 4.0 (0–10.2) | .000 |
| Platelet count at admission ($\times 10^9/L$) ^b | 60.5 (7.0–219.0) | 61.0 (11.5–187.9) | .902 |
| Hematocrit at admission (%) ^b | 39.5 (14.0–64.0) | 45.0 (31.3–60.0) | .032 |
| Lowest platelet count ^b | 17.0 (7.0–90.0) | 22.0 (5.3–99.5) | .227 |
| Prothrombin time ratio ^b | 2.16 (1.0–4.0) | 1.19 (1.0–2.4) | .000 |
| Partial thromboplastin time (s) ^b | 120.0 (48.5–200.0) | 72.2 (36.8–182.8) | .001 |
| Serum creatinine (μmol/L) at admission ^b | 198.0 (44.0–938.0) | 74.0 (24.5–637.7) | .022 |

^aData shown are median (2.5–97.5 percentile).

^bNumber of deaths was 6 of 22 for group 1; none for group 2 ($P = .001$).

Prophylactic Platelet Transfusion?



- Retrospective cohort study
- 1973 patients admitted to a single hospital in Singapore fulfilled WHO criteria for dengue fever and who had positive diagnostic laboratory tests
- 1666 patients had platelet nadir of $>20 \times 10^9/L$ (including 51 who had bleeding and/ or received platelet transfusion) were excluded
- 256 patients with platelet $< 20 \times 10^9/L$ without any major bleeding were studied

No significant trend between platelet count and incidence of clinical bleeding

Of 256 patients with platelets $<20 \times 10^9/L$, prophylactic platelet transfusion was given to 188 patients

•No significant difference in bleeding, platelet recovery, hospital length of stay between the two groups

RESEARCH ARTICLE

Potential Harm of Prophylactic Platelet Transfusion in Adult Dengue Patients

Tau-Hong Lee^{1*}, Joshua G. X. Wong¹, Yee-Sin Leo^{1,2}, Tun-Linn Thein¹, Ee-Ling Ng¹, Linda K. Lee¹, David C. Lye^{1,2}

Retrospective non-randomised observational study

- Dengue patients with platelet count < 20,000/mm³ without bleeding (except petechiae) from January 2005 to December 2008
- 788 patients included, 486 received prophylactic platelet transfusion

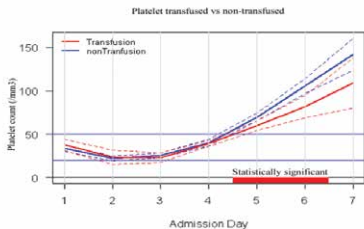


Fig 1. Platelet trend between treatment groups. Patients receiving platelet transfusion took significantly longer time to recover to platelet count of more than 50,000/mm³.

Table 2. Clinical outcomes of cohort.

| Variable | Non-transfused (n = 302) | Transfused (n = 486) | P |
|--|--------------------------|----------------------|--------|
| Clinical outcome ^a | | | |
| Volume of platelet given (mL) | NA | 256 (100–416) | NA |
| Volume of fluid received (mL) per day | 1020 (300–2076) | 1020 (300–2028) | <0.01 |
| Resected blood transfusion | 1 | 5 | 0.41 |
| Time to clinical bleeding, days | 1 (0–3) | 1 (0–3) | 0.77 |
| Platelet increment nadir day × 10 ³ platelets/mm ³ | 5 (4–33) | 8 (4–3) | <0.001 |
| Time to platelet count > 50 × 10 ³ platelets/mm ³ days | 2 (0–4) | 3 (0–6) | <0.001 |
| Clinical bleeding without petechiae | 55 (18.2%) | 156 (32.5%) | 0.06 |
| Internal bleeding | 4 (1.3%) | 17 (3.4%) | 0.07 |
| External bleeding | 26.8 (8.9%) | 85 (17.2%) | 0.001 |
| Median length of hospital stay, days | 1 (0–7) | 6 (0–6) | <0.001 |
| Urea failure | 0 | 2 | 0.03 |
| Renal failure | 0 | 1 | 1 |
| ICU admission | 2 (0.6%) | 1 (0.2%) | 0.44 |
| Death | 1 (0%) | 1 (0.2%) | 0.40 |

* sign as 1st–95th percentile

Prophylactic platelet transfusion plus supportive care versus supportive care alone in adults with dengue and thrombocytopenia: a multicentre, open-label, randomised, superiority trial

Lancet. 2017 Apr 22;389(10079):1611-1618

David C Lye, Sophia Archuleta, Sharifah F Syed Omar, Jimmy G Looi, Helen M Oti, Yuan Wu, Dale Fisher, Seshoela S L Ponnampalanasar, Limin Wijaya, Linda K Lee, Eng Eng Ooi, Adebola Karamo-Adesan, Lucy C Lum, Paul A Tambiyah, Yee Sin Lee

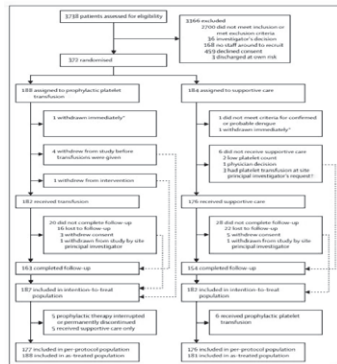


Figure 1. Trial profile.
*These patients did not receive any treatment and did not have any available haemostatic or outcome data, and were therefore excluded from the intention-to-treat analysis. (Because of egipstatin (n=2) and haemoferrin (n=3).

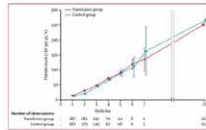


Figure 2. Mean daily platelet counts.
Data for egipstatin (n=2) and haemoferrin (n=3) are not included for display.

| | Transfusion group (n=1837) | Control group (n=1827) |
|----------------------------------|-------------------------------|---------------------------|
| Severity | | |
| Mild | 7 (0.4%) | 3 (0.2%) |
| Moderate | 3 (0.2%) | 0 |
| Severe | 2 (0.1%) | 0 (0.0%) |
| Effect on study intervention | | |
| None | 1674 (91%) | 2 (0.1%) |
| Temporarily discontinued | 2 (0.1%) | 0 |
| Permanently discontinued | 2 (0.1%) | 0 |
| Reasons to study discontinuation | | |
| Intervenor | 4 (0.2%) | 3 (0.2%) |
| Physician decision | 3 (0.2%) | 0 |
| Physically related | 6 (0.3%) | 0 |
| Difficultly related | 3 (0.2%) | 0 |
| Non-compliance | 1 (0.05%) | 2 (0.1%) |
| Other | 0 | 0 |

In adult patients with dengue and thrombocytopenia, prophylactic platelet transfusion was not superior to supportive care in preventing bleeding, and might be associated with adverse events.

Caricapapaya leaf extract

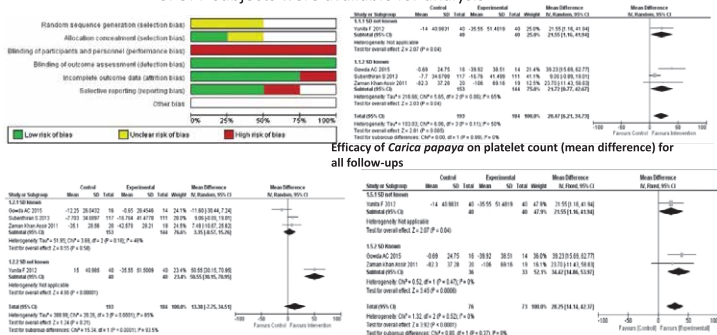
[Int J Appl Basic Med Res.](#) 2016 Oct-Dec; 6(4): 249–254. doi: [10.4103/2229-516X.192596](#) PMID: [PM25108100](#). PMID: [27857891](#)

Efficacy and safety of *Carica papaya* leaf extract in the dengue: A systematic review and meta-analysis

A systematic review and meta-analysis

[Jaykaran Charan](#), [Deepak Saxena](#),¹ [Jagdish Prasad Goyal](#),² and [Sandul Yasobant](#)¹

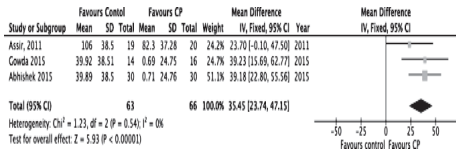
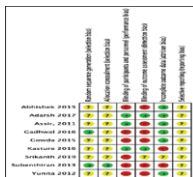
Total four trials enrolling 439 subjects were included in the analysis. Of 439 subjects, data of 377 subjects were available for analysis



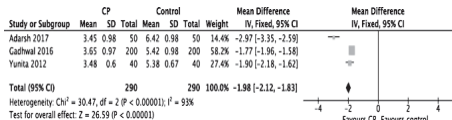
Carica papaya extract in dengue: a systematic review and metaanalysis. 2019.Rajapakse et al. BMC Complementary and Alternative Medicine 56 ()0129:https://doi.org/10.1186/s12906-019-2678-2

Senaka Rajapakse*, Nipun Lakshitha de Silva, Praveen Weeratunga, Chaturaka Rodrigo, Chathurani Sigeru and Sumadhya Deepika Fernando

Nine studies (India-6, Pakistan-1, Indonesia-1, Malaysia-1) met the inclusion criteria.



Forest plot of three studies comparing mean difference of platelet count between fifth and first day between two groups



Forest plot of three studies comparing period of hospitalization between two groups

C. papaya leaves extract improve the platelet count .The wider CI, the rise in platelet count may be very less and may not be clinically significant.

Summary of evidence

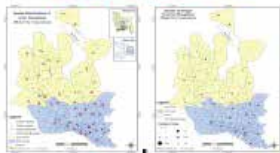
Table 1 Summary of evidence of benefit for available intervention in dengue infection

| Intervention | Conclusion |
|--------------------------------|---|
| Choice of intravenous fluid | RCTs show no benefit of colloids over crystalloids, ¹⁷⁻¹⁹ although a trend towards benefit is seen with colloids over crystalloids in severe cases |
| Rate of fluid infusion | No evidence available, regimens based on experience of centers treating large numbers of cases |
| Transfusion of blood products | Small RCT suggests that fresh frozen plasma may increase platelet counts ²¹ |
| Nasal CPAP | RCT shows benefit in terms of improvement of hypoxemia and reduction of the need for ventilation in patients with dengue and acute respiratory failure ³³ |
| Carbazochrome sodium sulfonate | RCT shows no evidence of benefit, but underpowered ³⁵ |
| Corticosteroids | Systematic review of RCTs shows no benefit, but available RCT evidence is from studies performed > 20 years ago; ^{25,26} case series provide limited evidence of possible benefit in severe dengue ²⁸ |
| Immunoglobulins | Single RCT shows no benefit for thrombocytopenia; ⁵⁴ no evidence available for other manifestations ⁵⁵ |

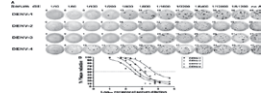
| | Do'S | Do Not |
|---|--|--|
| 1 | Administration of Paracetamol for high fever and myalgia. | Send patients with non-severe dengue home with no follow-up and inadequate instructions |
| 2 | Clinical assessment of the haemodynamic status before and after each fluid bolus | Administer of acetylsalicylic acid (aspirin) or ibuprofen |
| 3 | Give intravenous fluids for repeated vomiting or a high rapidly rising haematocrit | Avoid clinical assessment of patient with respect to fluid therapy |
| 4 | Use the Appropriate isotonic intravenous fluids for severe dengue in appropriate time and dose | Administer of intravenous fluids to any patient with mild dengue (those who can take by mouth) |
| 5 | Avoid intramuscular injections | Give intramuscular injections to dengue patients |
| 6 | Tight Glycemic control | avoid monitoring blood glucose |
| 7 | Give appropriate colloid, PRC or Fresh Whole blood if indicated | give excessive fluid, blood and blood products |



Prevention



Update on vaccine



- **Chimera vaccine (CYC-TDV)**

- Yellow fever & dengue
- Launched 2016
- Partial immunity

Risk of secondary infection

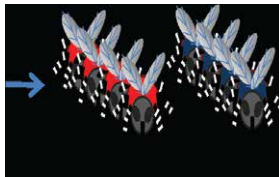
- Serostatus affects the efficacy and safety
- Seropositive case-75% efficacy(9-16 yrs)
- Seronegative case- Severe dengue and Hospitalization

- **Attenuated vaccine**

- 6-8 cycles in DKC (Dog kidney cells)



Wolbachia Aedes



Cytoplasmic incompatibility

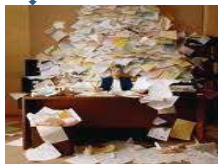
Carries Wolbachia



Maternally transmitted

Resistant to infection
Blocks dengue transmission

Clinical research





Changing World ? Changing Trend

Trust and Partnership

Epidemiology and the Spread of the Epidemic

The Genomic Revolution and Global Health

Open Access (of what?), Sharing (what?) Centres of Gravity

Notes: _____

Notes: _____

Notes: _____

Notes: _____
