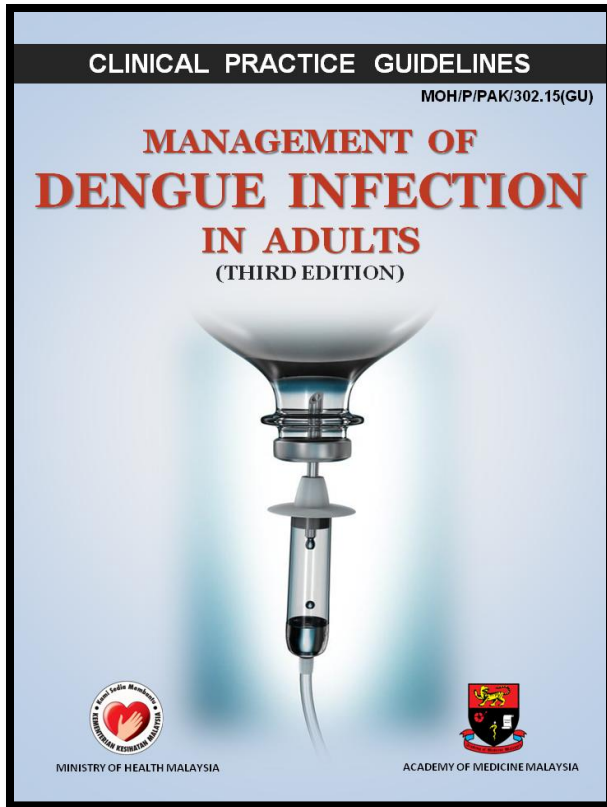




Management of Bleeding Complications in Dengue Infection



LEARNING OBJECTIVES

- ▶ Coagulation abnormalities in dengue
- ▶ Risk factors for bleeding
- ▶ Recognising bleeding early
- ▶ Role of blood and blood products



Haemostatic Changes in Dengue

1. Vasculopathy/ Endothelial activation
 - Hess's test is an early sign
 - Plasma leakage
2. Thrombocytopenia
3. Coagulation abnormalities

Thrombocytopenia?

- ▶ Platelet count begins to fall towards the end of febrile stage
 - Lowest during leakage phase
- ▶ Bone marrow suppression
 - Minor role, early in the disease
- ▶ Immune complex-mediated platelet destruction of platelets



Coagulation Abnormalities

Prolonged APTT: 54.6%

Prolonged PT: 33.3%

Variable but no significant reduction in coagulation factors II, V, VII, VIII, IX, XII and X

These do not mean that patient has DIC!



Coagulation Abnormalities

- ▶ In general, only mild and improves after fluid replacement or cease spontaneously after recovery of illness
- ▶ However prolonged shock can lead to acidosis and DIC resulting in occult or overt bleeding and end-organ damage

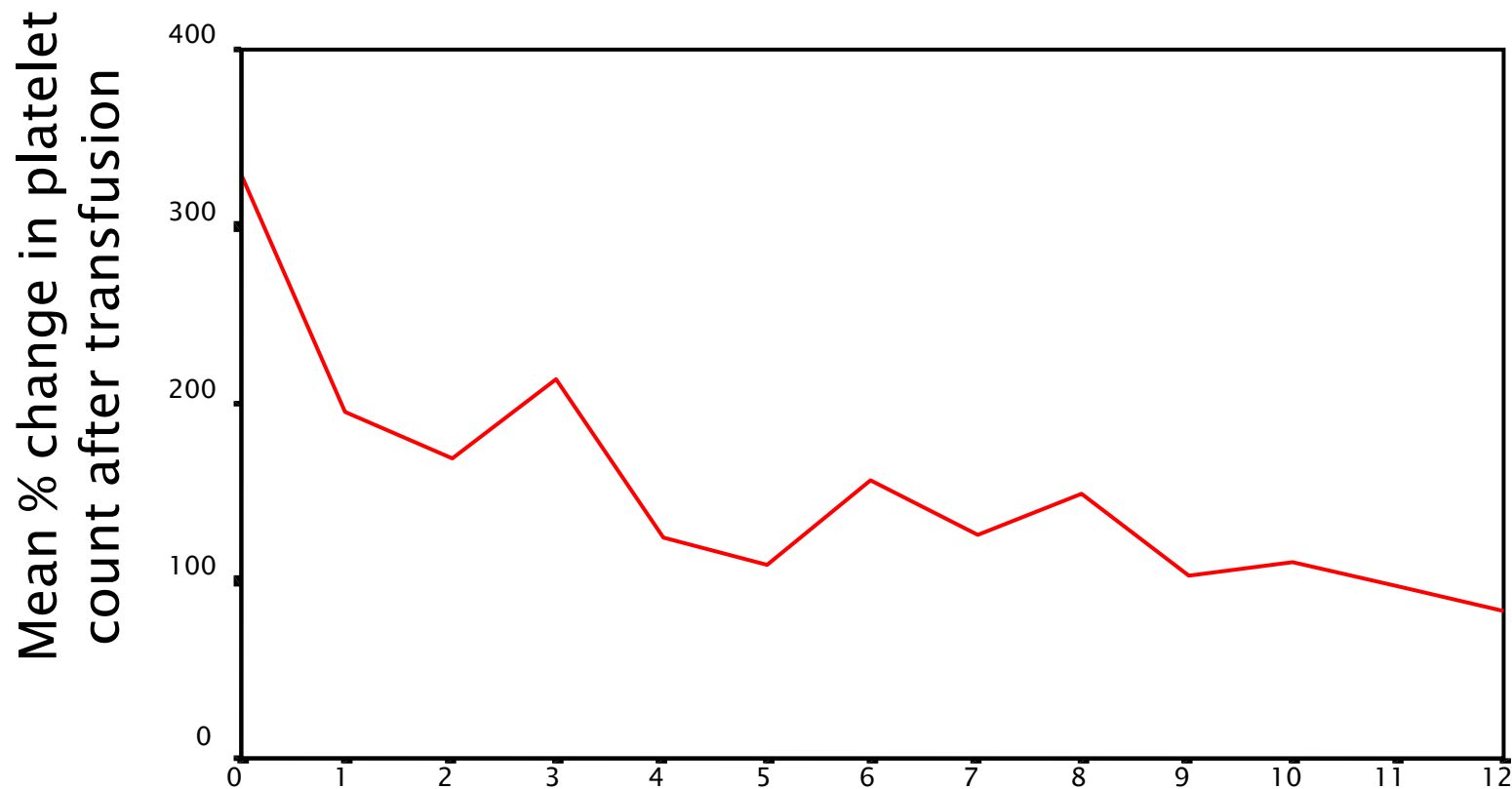


Prophylactic platelet transfusion



Clinical parameter*	Treatment groups#		
	Received bld prod (n=60)	Did not receive bld prod (n=46)	P value
Duration of shock (hours)	4.0	4.0	0.918
% increase in hematocrit	53.0	42.0	0.239
Lowest platelet count (x 10 ⁹ /L)	20.5	22.0	0.127
Highest PTR	1.2	1.1	0.207
Highest PTT (sec)	77.7	71.3	0.347
FFP transfused (ml/kg)	20.0	0	0.000
Total platelets transfused (units/kg)	0.2	0	0.000
→ Total fluid balance (ml/kg)	121.0	107.0	0.045
Days of thrombocytopenia	5.0	4.0	0.395
→ Days of hospitalization	7.0	5.0	0.000
^Incidence (%)of bleeding	60.0	43.5	0.136
→ Incidence (%)of pulmonary edema	30.0	6.5	0.006

Behaviour of transfused platelets in DSS



Prophylactic platelet transfusion

- ▶ 256 adult dengue patients – 2004
 - Platelet count $< 20,000$, no prior clinical bleeding (petechiae excluded)
- ▶ 188 were given platelets
- ▶ No difference in incidence of bleeding
- ▶ No effect of platelet transfusion on mean platelet count after 24 h

No correlation between PLT count and bleeding

Platelet count ($\times 10^3$ platelets/ml)	Clinical bleeding
> 150	6%
100–149	12%
80–99	11%
50–79	10%
20–49	11%
10–19	13%
< 10	0%
$p = 0.22$, by test for trend	

Lye DC et al., 2009

Prophylactic platelet transfusion

Parameter	P0 <10,000	P0 11,000–20,000	P0 21,000–30,000	P value
Number of cases				0.972
Treatment group	21	14	5	
Control group	22	16	6	
Bleeding, yes				
Number of cases	15	18	6	0.090
WHO grade of bleeding, n				
Grade 1	7	6	2	0.707
Grade 2	8	12	4	
Response to platelet transfusion				
Responders	06 (29)	09 (64)	04 (80)	0.035
Non-responders	15 (71)	05 (36)	01 (20)	
Progression to WHO grade 3 or higher bleeding				
Number of cases	0	0	1	0.035
Adverse events,				
Transfusion reactions	2	0	0	0.774
Death	1	0	0	
P0 = Baseline platelet count.				

Assir MJK et al., 2013

Life-threatening complications of blood/ blood products



- ▶ Bacterial contamination
- ▶ TRALI: Transfusion-related acute lung injury
- ▶ TTI: Transfusion-transmitted infections
- ▶ Wrong blood





No role for prophylactic transfusion of platelets or FFP

- ▶ Do not produce sustained changes in the coagulation status and platelet count in patients with DHF/DSS
- ▶ Do not change or reduce the bleeding outcome in DHF
- ▶ Inappropriate transfusion of blood products increases the risk of pulmonary oedema and respiratory embarrassment



Risk factors for severe bleeding in Dengue





Thrombocytopenia and coagulation abnormalities do not reliably predict bleeding in dengue infection

Chaudhary R 2006; Mairahu AT 2003; Krishnamurti C 2001;



Risk factors for hemorrhage in severe dengue

Clinical /laboratory parameter	Group 1 (significant hemorrhage) (n=22)	Group 2 (no/mild hemorrhage) (n=92)	P value
Age (mean) (years)	6.1 $\pm$ 4.0	5.9 $\pm$ 3.5	0.8
Male : Female ratio	1:1	1:0.9	0.9
Platelet count (x 10⁹/L)	72 $\pm$ 54	71 $\pm$ 50	0.9
Lowest platelet count	23 $\pm$ 18	28 $\pm$ 21	0.4
Serum sodium (mmol/L)	127 $\pm$ 6	130 $\pm$ 6	0.49

Risk factors for hemorrhage in severe dengue

Clinical/Laboratory features	Odd ratio	95% CI	b	P value
Encephalopathy	0.01	0.00-41.89	-4.40	0.289
Mottling	0.08	0.00-15.50	-2.50	0.350
Hypotension	2.28	0.18-28.19	0.08	0.521
Duration of shock	2.11	1.13-3.92	0.75	0.019
HCT at admission	0.72	0.55-0.95	-0.33	0.020
Liver failure	1.8x10 ⁴	0.50-6.80x10 ⁸	9.83	0.067
Renal failure at adm	1.44	0.10-249.90	0.37	0.889
Prothrombin time ratio	0.10	0.00-46.89	-2.30	0.454
Abnormal glycemia	2.71	0.22-33.68	1.00	0.437
Partial thromboplastin time	1.03	0.98-1.07	0.03	0.262



Results

- ▶ Bleeding is not related to degree of thrombocytopenia
- ▶ Bleeding is related to the duration of shock due to plasma leakage

Risk factors for major bleeding

- ▶ have prolonged/refractory shock;
- ▶ have hypotensive shock and renal or liver failure and/or severe and persistent metabolic acidosis;
- ▶ are given non-steroidal anti-inflammatory agents;
- ▶ have pre-existing peptic ulcer disease;
- ▶ are on anticoagulant therapy;
- ▶ have any form of trauma, including intramuscular injection



Recognising bleeding early in dengue





Bleeding in dengue

- ▶ Bleeding from the gums or per vagina, epistaxis and petechiae are common but will usually cease spontaneously and are **often not significant**.
- ▶ Bleeding is considered significant when it results in haemodynamic instability.

Suspect significant occult bleeding in the following situations



- ▶ HCT not as high as expected for the degree of shock to be explained by plasma leakage alone.
- ▶ A drop in haematocrit without clinical improvement despite adequate fluid replacement (40–60 ml/kg).
- ▶ Severe metabolic acidosis and end-organ dysfunction despite adequate fluid replacement.

Suspect significant occult bleeding in the following situations



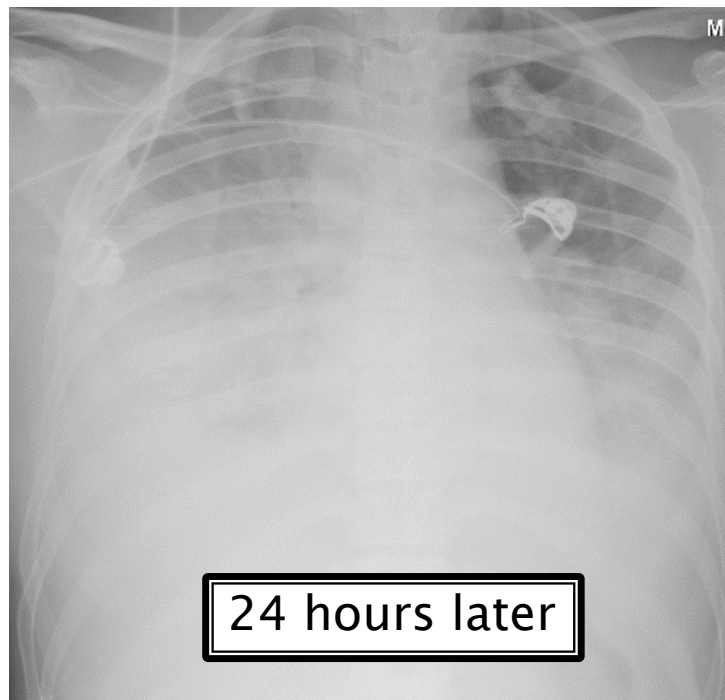
- ▶ HCT not as high as expected for the degree of shock to be explained by plasma leakage alone.
- ▶ A drop in haematocrit without clinical improvement despite adequate fluid replacement (40–60 ml/kg).
- ▶ Severe metabolic acidosis and end-organ dysfunction despite adequate fluid replacement.

HCT not high for the degree of shock

- ▶ 32 yr old lady
- ▶ Arrives in ED 10.47 PM
- ▶ Fever 4 days, vomiting, gum bleeding
- ▶ Colour – Pink
- ▶ CRT – 3 secs
- ▶ Temp – cold peripheries
- ▶ Volume – low
- ▶ Rate – 82/min
- ▶ BP 77/40
- ▶ HCT 42.5
- ▶ PLt count – 50,000
- ▶ Same morning, in KK
- ▶ Afebrile, BP 90/70, PR 100/min
- ▶ HCT 43, PLt – 99,000

Delay in recognising bleeding

- ▶ Patient is managed with repeated boluses of crystalloids and colloids.
- ▶ Blood transfusion given only 4 hours later



Fluid overload

Causes of fluid overload

- ▶ **excessive and/or too rapid** intravenous fluids
- ▶ inappropriate use of large volumes of intravenous fluids in patients with **unrecognized severe bleeding**
- ▶ **inappropriate transfusion** of fresh-frozen plasma, platelet concentrates and cryoprecipitates;
- ▶ **continuation of intravenous fluids** after plasma leakage has resolved
- ▶ **co-morbid conditions** such as congenital or ischaemic heart disease, chronic lung and renal diseases.

Suspect significant occult bleeding in the following situations



- ▶ HCT not as high as expected for the degree of shock to be explained by plasma leakage alone.
- ▶ A drop in haematocrit without clinical improvement despite adequate fluid replacement (40–60 ml/kg).
- ▶ Severe metabolic acidosis and end-organ dysfunction despite adequate fluid replacement.

Appropriate vs inappropriate drop in HCT

23 year old female

Nausea, vomiting, abdominal pain, postural giddiness

Day 4 menses – but bleeding not excessive

- ▶ Colour – Pink
- CRT – 2 secs
- Temp – cold peripheries
- Volume – weak
- Rate – 100/min
- ▶ BP 90/50

HAEMATOLOGY	15/05/2015 01:51	15/05/2015 08:00	15/05/2015 10:31	15/05/2015 15:00	15/05/2015 19:16	15/05/2015 22:43	16/05/2015 06:00
GENERAL HAEMATOLOGY							
RBC	5.70	H 6.07	H 5.94	H 6.05	H 6.31	H 6.42	H 6.71
Hemoglobin	14.7	16.0	15.6	15.7	H 16.7	H 17.0	H 17.4
HCT	42	46	45	45	H 48	H 49	H 50
MCV	L 74	L 76	L 76	L 75	L 76	L 76	L 75
MCH	L 25.8	L 26.4	L 26.3	L 26.0	L 26.5	L 26.5	L 25.9
MCHC	34.9	34.6	34.5	34.8	35.0	34.8	34.6
RDW	14.0	14.3	14.1	14.2	14.2	14.1	14.0
WBC	L 2.2	L 2.2	L 2.6	L 2.8	L 3.6	5.0	4.3
Platelets	* C 17	* C 7	* C 13	* C 7	L 22	* C 15	* C 5
Neutrophils%	73	69	73	70	72	H 76	67
Neutrophils#	L 1.61	L 1.52	L 1.90	L 1.96	2.59	3.57	2.88
Lymphocytes%	20	23	20	21	21	L 17	22
Lymphocytes#	L 0.44	L 0.51	L 0.52	L 0.59	L 0.76	L 0.80	L 0.95
Monocytes%	6	8	7	9	7	7	10
Monocytes #	L 0.13	L 0.18	L 0.18	0.25	0.25	0.33	0.43
Eosinophils%	1	L 0	L 0	L 0	L 0	L 0	L 0
Eosinophils#	L 0.02	L 0.00	L 0.00	L 0.00	L 0.00	L 0.00	L 0.00
Basophils%	0	0	0	0	0	0	1
Basophils#	0.00	0.00	0.00	0.00	0.00	0.00	0.04
Atypical Lymph%							
Atypical Lymph#							

60ml/hour Normal saline IV drip

Inappropriate drop in HCT

After 10cc/kg/hr – 700cc – colloid

HCT 50 to 39

Lactate decreased 3.4 to 2.9

After another 500cc colloid over 1 hour

Still has abdominal pain

Nausea but no vomiting

- ▶ Colour – Pink
- CRT – < 2 secs
- Temp – cold peripheries
- Volume – low volume but improved
- Rate – 100/min
- ▶ BP 100/60
- ▶ HCT 39 to 37 (baseline HCT42)
- ▶ Lactate 2.9 to 3.6

colloids

Packed cell

HAEMATOLOGY	16/05/2015 06:00	16/05/2015 10:28	16/05/2015 16:53	16/05/2015 21:06	17/05/2015 00:00
GENERAL HAEMATOL					
RBC	H 6.71	5.17	H 5.85	5.54	5.10
Hemoglobin	H 17.4	13.3	15.7	14.8	13.5
HCT	H 50	39	45	42	39
MCV	L 75	L 75	L 77	L 76	L 77
MCH	L 25.9	L 25.7	L 26.8	L 26.7	L 26.5
MCHC	34.6	34.2	34.9	35.0	34.6
RDW	14.0	14.1	14.6	14.5	14.5
WBC	4.3	4.3	4.5	4.6	4.1
Platelets	* C 5	* C 3	* C 7	* C 4	* C 9

Lactate



Fresh Blood Needed?

- ▶ Recently published studies done in critically ill patients and patients undergoing cardiac surgery have **not shown** any difference in clinical outcomes and lactate recovery when transfused with **shorter-term storage packed cells (7–10 days)** compared to **longer-term storage packed cells (21–28 days)**.

Transfusion of blood in patients with significant bleeding

CPG:

- ▶ Transfuse blood (5–10ml/kg of packed red cells) and observe the clinical response.
- ▶ Consider repeating the blood transfusion if there is further blood loss or no appropriate rise in HCT after blood transfusion.
- ▶ No significant difference in terms of clinical outcomes and lactate recovery when transfused with shorter-term storage packed cells compared to longer-term storage packed cells.

Management of Upper GI Bleeding

- ▶ The common reasons of GIT haemorrhage in dengue are haemorrhagic (and/or erosive) gastritis, peptic ulcer and oesophageal ulcer
- ▶ Medical treatment
 - fluid therapy,
 - transfusion of fresh blood and blood products and
 - administration of proton pump inhibitor
- ▶ If persistent bleeding,
 - Endoscopy is indicated

Endoscopic therapy

- ▶ High risk for re bleeding or ongoing bleeding
 - active arterial bleeding,
 - nonbleeding visible vessels,
 - nonbleeding adherent clots or
 - persistent oozing
- ▶ Endoscopic injection therapy is not recommended in dengue infection with gastrointestinal haemorrhage

Chiu Yc et al., Am J Trop Med Hyg. 2005;73(2):441–4

TAKE HOME MESSAGE

- ▶ No role for prophylactic transfusion of platelets or FFP
- ▶ Early detection of bleeding is essential
 - High index of suspicion in high risk situations
- ▶ Packed red cells transfusion is required for significant bleeding
- ▶ No difference in terms of age of the blood in storage
- ▶ Persistent or significant upper GI bleeding – do endoscopy

THANK YOU