

Key Summary/Highlights

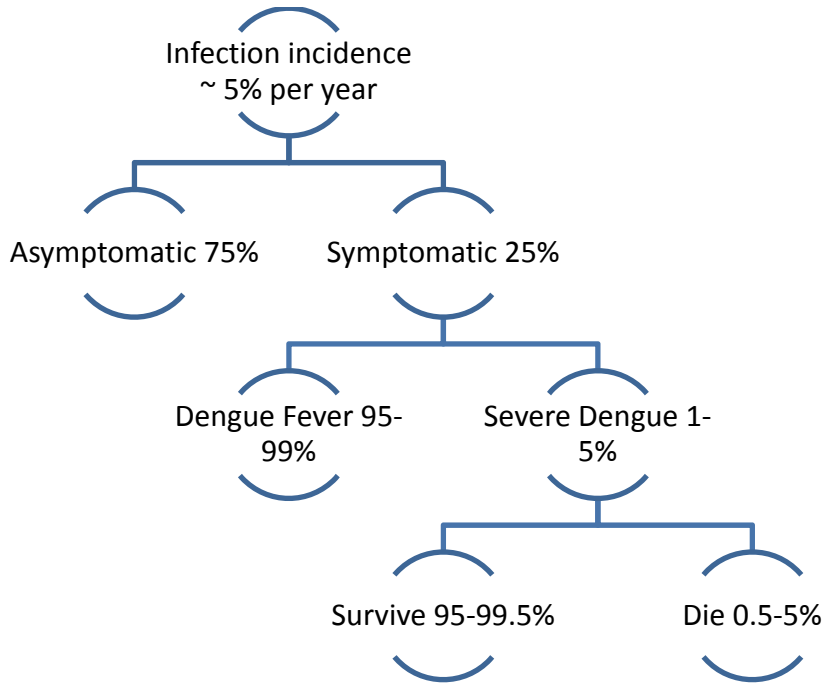
Saturday Teach-in: Haematology – Difficult Dengue 13 September 2014 Malaysia Academy of Medicine KL

Topic 1: Dengue control – From prevention to case registration by Dr B. Venugopalan (drbvenu@moh.gov.my)

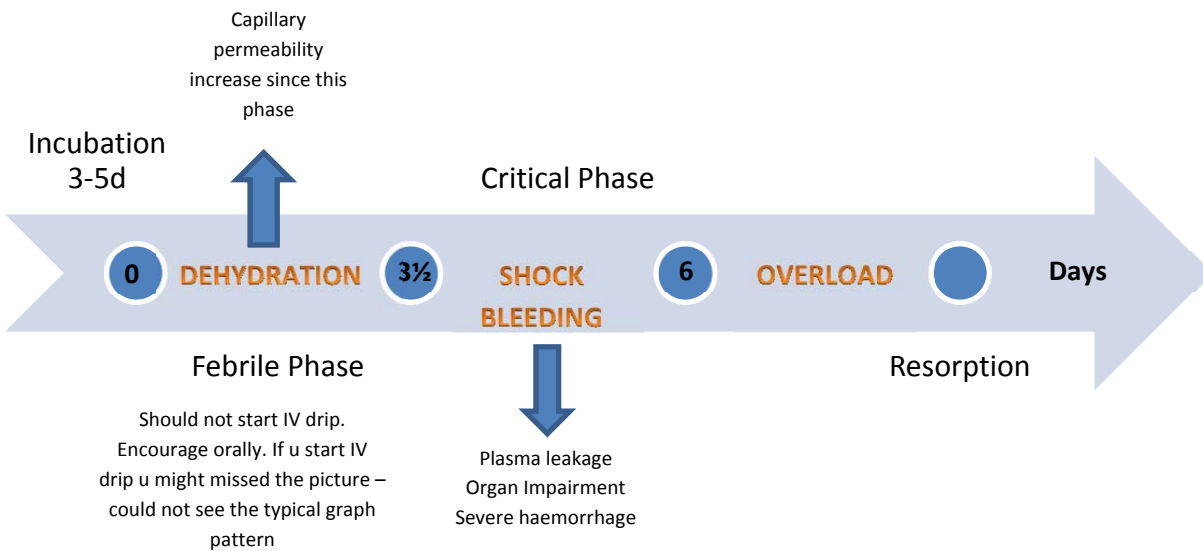
- Aedes mosquitos – as urban terrorist – survive and breed only require 5cc of clear water, eggs able to withstand drying for 6 months (transovarian transmission can up to 5 generations)
- Vector control measures
 - Source reduction** - remove potential breeder- most important
 - Thermal fogging – only kill “infected and adult” mosquito only
 - ULC fogging
 - Larviciding
- Educate your patient – fogging is NOT MAGIC BULLETS
- Notification is a responsibility of Medical officer – with accurate biodata/address/workplace/contact number (DETAILS SHOULD NOT COPY FROM IC)
- Dengue control challenge in Selangor
 - Population density
 - Community mobility
 - Cleanliness at home and workplace
 - Environmental cleanliness
 - Cleanliness at common user area
 - University students
 - Foreigners 20%
- Outbreak control – 90% of outbreak able to control within 14 days
- Why still high incidence? – dengue prevention weak
- Prevention vs outbreak control:
 - Primary responsibility of premise/site owners/responsible agencies
 - Require 24/7 commitment
- Paradigm shift
 - Outbreak control → prevention of 1st case
 - Mosquito focus → cleanliness focus
- Dengue diagnosis
 - Back to basis – history, examination, immediate access to FBC results
 - GP without FBC should refer out – not to manage without assess daily
 - Assess clinically and documentation!!
 - Now all GP clinics in Selangor will be supplied with rapid kit for Dengue FOC from JKN
 - The use of diagnostic kit:
 - IgM/IgG ELISA – require 2 days
 - primary dengue infection – IgM raised from day 4 up to 3 months of illness
 - secondary dengue infection – IgM can be undetected at beginning of illness but IgG tends to raise first
 - RT PCR only use for death to confirm ?dengue-caused death
- Dengue case registration
 - All notified cases don't mean are registered!!
 - Only lab confirmation cases (NS-1 or IgM/IgG positive) need to register
- June 15 as Dengue Day

Topic 2: Clinical course and principle of management of Dengue – Prof Lucy

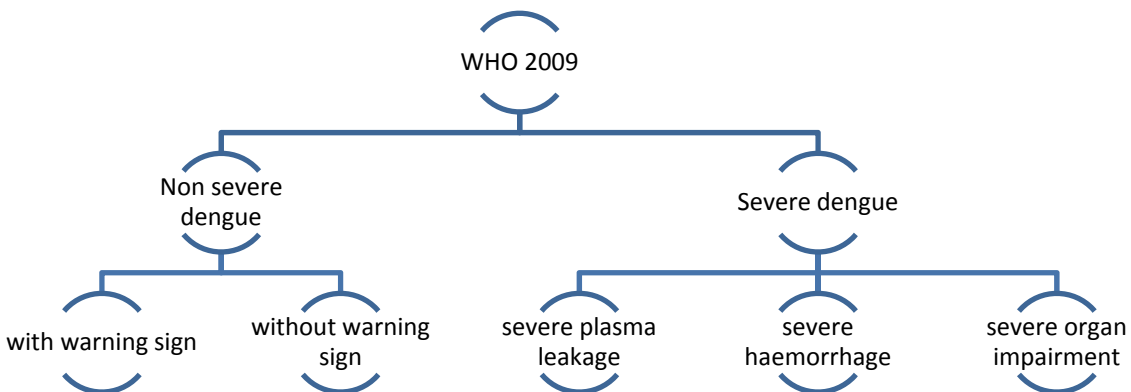
Natural history of DENV infection



- Dengue is a systemic and dynamic disease NOT a PLATELET COUNT DISEASE

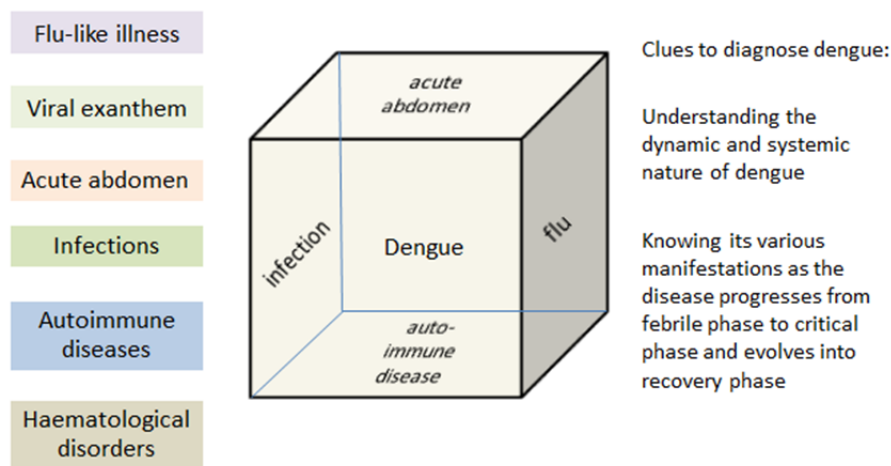


- Classify dengue according to severity



- 1st 1-2 days of vomiting IS NOT WARNING SIGN – is due to viraemia – manage with oral hydration
- Warning signs developed after 72hrs of illness (pitfall)
 - Abdominal pain/tenderness – liver congestion/ascites? surgical acute abdomen? Is it due to overload?
 - Persistent vomiting – more than 3 times per day, unable to tolerate oral fluid
 - Mucosal bleeding
 - Lethargic/ restlessness – confine in bed, loss interest in food and TV, too weak to walk to toilet
 - Liver enlargement >2cm
 - Clinical fluid accumulation
 - Rapid increasing HCT and dropping of Plt – maybe masked by fluid therapy
- Not all patients will experience Critical Phase – some patients without significant increase in vascular permeability – after fever subsides, appetite and general condition improves, they may have leukopenia and mild to moderate thrombocytopenia
- Criteria
 - Severe plasma leakage – shock DSS, fluid accumulation with respiratory distress
 - Severe bleeding – causing haemodynamically instability and may require blood transfusion
 - Severe organ impairment – AST/ALT > 1000, impaired cardiac function and consciousness

Dengue mimics many clinical syndromes



Conditions that mimic the febrile phase of dengue Conditions that mimic the critical phase of dengue

Viral infections	Influenza, measles, rubella <u>Chikungunya</u> , West Nile virus <u>Enterovirus</u> Other viral haemorrhagic fever Infectious mononucleosis Acute HIV seroconversion illness	Acute abdomen	Acute appendicitis Acute cholecystitis Perforated viscus Diabetic ketoacidosis
Bacterial infections	Leptospirosis Typhoid Rickettsia infections (typhus, scrub typhus, etc.)	Acidotic breathing/ respiratory distress	Diabetic ketoacidosis Lactic acidosis Renal failure Acute respiratory distress syndrome (ARDS)
Parasitic infections	Malaria	Infections	Sepsis, septic shock Acute gastroenteritis <u>Leptospirosis</u> , typhoid, typhus, malaria Viral hepatitis Acute HIV seroconversion illness
Febrile illness with a rash	Measles, rubella Infectious mononucleosis, <u>enterovirus</u> <u>Chikungunya</u> , West Nile virus, Scarlet fever, meningococcal infection <u>Leptospirosis</u> , typhoid Rickettsia infections (typhus, scrub typhus, etc.) Syphilis, acute HIV seroconversion illness Autoimmune diseases (e.g. SLE) Adverse drug reaction	Autoimmune diseases	Systemic lupus erythematosus <u>Idiopathic thrombocytopenic purpura</u> <u>Thrombotic thrombocytopenic purpura</u> Systemic vasculitis
Diarrhoeal diseases	Rotavirus Salmonellosis Other enteric infections	Malignancies	Acute leukaemia Lymphoma Other malignancies
		Others	Liver cirrhosis with portal hypertension Adverse drug reaction

- Deciding IV Fluid Administration

- Step 1: History taking

- Important history in dengue patient

- Date of fever onset
 - Symptoms and severity
 - 3 golden questions:
 - How much fluid intake – quality and quantity
 - How much urine output – freq, volume, time of most recent voiding
 - What activities can the patient do during febrile illness
 - Other fluid loss – vomiting, diarrhea
 - Presence of warning sign

- Step 2: Clinical examination

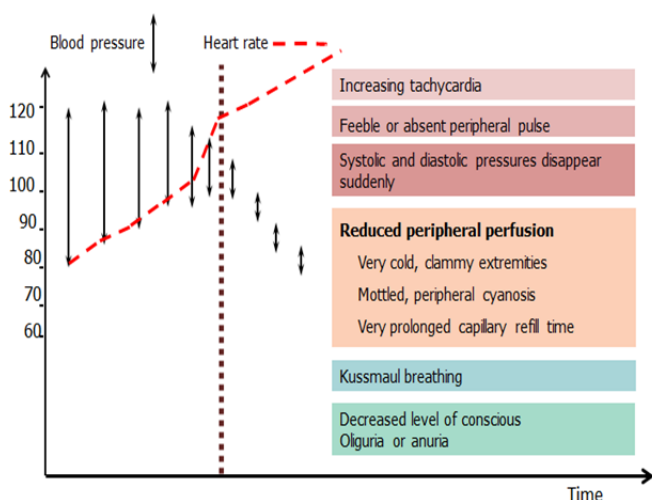
- 5 in 1 maneuver (magic touch) – 30 seconds to recognize shock

- Capillary refilling time
 - Colour
 - Temperature
 - Volume (Pulse)
 - Rate (Pulse)

- General assessment

- Mental status
 - Hydration status
 - Haemodynamic status – 9 clinical parameters (by checking CCTVR already cover 5/9!!)
 - Peripheral perfusion – ¹CRT, ²colour, ³temperature, ⁴pulse volume
 - Cardiac output – ⁵HR, ⁶BP, Pulse pressure
 - Organ perfusion – ⁷consciousness, ⁸urine output
 - Respiratory compensation for tissue hypoxia – ⁹respiratory rate
 - Clinical evidence of warning signs
 - Others – rash, tourniquet sign, acidotic breathing

Hemodynamic Changes in Hypotensive Shock



Parameters	Stable Circulation	Compensated shock	Hypotensive shock
Conscious level	Clear and lucid	Clear and lucid	Restless, combative → Reduced brain perfusion
Capillary refill time	Brisk (<2 sec)	Prolonged (>2 sec)	Very prolonged, mottled skin → Reduced peripheral perfusion
Extremities	Warm and pink	Cool peripheries	Cold, clammy → Reduced peripheral perfusion
Peripheral pulse volume	Good volume	Weak & thready	Feeble or absent → Reduced peripheral perfusion
Heart rate (HR)	Normal HR for age	Tachycardia for age	Severe tachycardia or bradycardia in late shock → Reduced cardiac output
Blood pressure (BP)	Normal BP for age	Normal systolic pressure, rising diastolic pressure	Hypotension Unrecordable BP → Reduced cardiac output
Pulse pressure (PP)	Normal PP for age	Narrowing PP Postural hypotension	Narrowed pulse pressure (≤20 mmHg) → Reduced cardiac output
Respiratory rate (RR)	Normal RR for age	"Quiet" tachypnea	Kussmaul breathing → Severe tissue acidosis
Urine output	Normal	Reducing trend	Oliguria or anuria → No kidney perfusion

- Hypotension definition:

- Adult: SBP < 90 or MAP < 70, dropping SBP >40 in hypertensive patient
 - Child (up to 10 yo): SBP < 70 + (Age x2)

- Always look at the big pictures before zooming in (consider all clinical features not in isolation)

- Step 3: Investigation:
 - Who should get an FBC test?
 - All patients with fever >3 days***
 - All patients with warning sign
 - All patients in shock
 - *** if resources available, all febrile patients should get a baseline FBC at first visit
 - If limited resources, FBC for febrile patient with poor oral intake and urine output
 - When to refer?
 - Rising hct or high hct
 - Leukopenia and/or thrombocytopenia
 - Presence of warning sign/in shock
 - Poor oral intake/not passing urine
 - Dengue diagnostic kit
 - For confirmation – NS1/IgM/IgG
 - Other investigation
 - Biochemical test – RP/LFT/RBS
- Step 4: Diagnosis, phase of illness, and severity
 - Who should be given IV fluid?
 - Those who are not able to drink enough to pee enough – only give for short duration
 - In shock/cannot take orally
 - When to start IV drip?
 - Febrile phase (subclinical plasma leakage) – limit IV fluid – only oral; early IV fluid can lead to overload
 - Critical phase – IV fluid for 24-48 hrs; when pt presented in shock – IV therapy <48hrs, because already 24hrs of shock over
 - Recovery – stop IV fluids
 - Type of fluid
 - NS/Ringer lactate – to be given alternately (avoid hyperchloremic metabolic acidosis)
 - NS contains Na/Cl 154 mEq/L
 - Ringer lactate – Na 130 mEq/L + Cl 109 mEq/L + K 4mEq/L + Ca 3 mEq/L
 - Hartmann – Na 131 mEq/L + Cl 111 mEq/L + K 5mEq/L + Ca 2 mEq/L
 - Colloid- in shock 30-50ml/kg/day
 - If no clinical improvement with reduced Hct – think of Occult bleeding – prepare transfuse blood
 - Should not use – dextrose solution, hypotonic solution, albumin/FFP
 - When to stop fluids? – stepwise reduction until stop
 - Definite stop:
 - Hypertension with good pulse volume
 - Breathing – rhonchi/crepitation
 - After 48 hrs
- Haemodynamic state should be PRINCIPAL driver of IV fluid therapy. Haematocrit level should only a guide NOT the other way around!!!
- How to recognize severe bleeding: unstable haemodynamic status + any one of the following:-
 - Persistent and/or severe overt bleeding, regardless of Hct level
 - Decreased Hct after fluid resuscitation especially colloid
 - Hypotensive shock with low/normal Hct before fluid resuscitation
 - Refractory shock
 - Persistent metabolic acidosis

- How not to miss the point when IVF should be reduced
 - Quantify oral and IVF last few hours
 - Quantify urine output
 - Evaluate what happened after IVF administration
 - CCTVR
 - How does the patient feel? – better or worse
 - Is he breathing slower/faster
 - Is abdominal pain less or more severe
 - How much was urine passed
- Summary of IVF therapy in dengue
 - IVF therapy should be managed like drug therapy
 - No ideal IV solution, a combination may avoid complication of using exclusively one type of fluid
 - Dynamic situation means frequent assessment and adjustment according to patient response or lack of response
 - Not according to perceived protocol
- To reduce dengue death
 - Knowledge – dengue case management and of internal medicine
 - Attitude – know our own limitation, seek help early
 - Practice – basic medicine – history, physical examination and careful non invasive monitoring and charting of serial responses, lab parameters vs “high tech” modern medicine

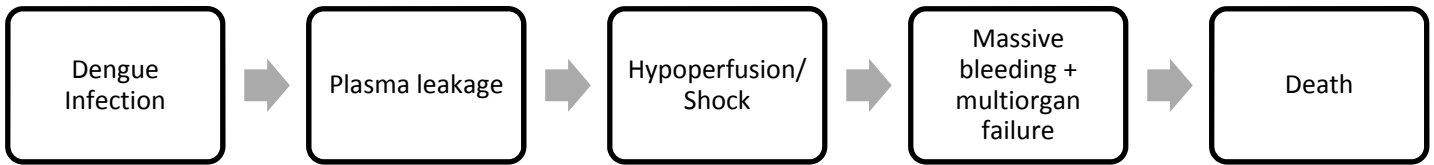
Topic: Dengue with Bleeding by Dr Bahariah Khalid

- Rathakrisnan A 2012 – Cytokine expression profile of dengue patient at different phases of illness
 - Increased Hct → ↓ prostaglandin secretion → increase risk of GI bleeding
- In secondary infection, peak of IgM not as high as in primary infection – due to antibody dependent enhancement (IL 6 and IL 8) → cytokine storm
- Overt/assumption of bleeding
 - Understanding haemostasis
 - Immediate bleeding
 - Defect in primary haemostasis – low platelet
 - Vascular abnormality – capillary leak, procedures
 - Delayed bleeding
 - Defect in secondary haemostasis
 - Bleeding history is important!
 - Understand the possible causes for deranged coagulation profiles
 - Investigate the cause of a significant bleeding history and prolonged clotting time
 - Managing coagulopathy
- Parameters to indicate risk of bleeding in general
 - Age > 85
 - Active gastroduodenal ulcers
 - Bleeding in 3 months before admission
 - CVL insertion
 - Current cancer
 - Hepatic failure INR >1.5
 - ICU/CCU admission
 - Male sex

- Platelet < 50
- Rheumatic disease
- Severe renal failure
- WHO bleeding grade
 - Grade 0 – none
 - Grade 1 – petechiae, ecchymoses, occult blood in body secretion, and mild vaginal spotting
 - Grade 2 – evidence of gross haemorrhage not requiring red cell transfusion over routine transfusion needs e.g. epistaxis, haematemesis, haematuria
 - Grade 3 – haemorrhage requiring transfusion of 1 or more unit red cell/day
 - Grade 4 – life threatening haemorrhage – defined as massive bleeding causing haemodynamic compromise or bleeding into a vital organ eg intracranial, pericardial or pulmonary haemorrhage
- Prophylaxis platelet transfusion necessary? – unresolved issue
- Platelet transfusion
 - At least 7.1×10^9 platelet are consumed daily in endothelial support function
 - Usually need when WHO bleeding grade 2 or more
 - Grade 3 or 4 usually associated with other factors not low platelets alone
 - Uraemia, drugs, ulcers, bleeding tumours
 - 2 types of platelets
 - Random blood donor – collected from whole blood, expected increment per unit $5-7 \times 10^9$, should contain $> 55 (80) \times 10^9$ platelet per bag in approximately 50ml of plasma – disadvantage: exposure to many donor viral and bacterial transmission, many donor allosensitisation
 - Single donor apheresis – collected from apheresis by automated instrumentation, expected increment per unit – $30-50 \times 10^9$, should contain $> 300 \times 10^9$ platelet per bag in approximately 250ml of plasma – advantage: single donor exposure, disadvantage = expensive RM 300, more volume (equivalent to 4-6 random donor)
 - Response: Measure platelet count from 10 min to 3 hrs after transfusion
- FFP = stored at -30°C , frozen within 8 hrs, 1 unit 150-300ml will increase each clotting factor activity by 2-3%
 - Should not use for
 - increase blood volume or albumin concentration
 - coagulopathy that can be corrected by Vit K administration
 - normalizing abnormal coagulation screen result in the absence of bleeding
 - 12-15ml/kg would increase fibrinogen level by 1g/L
- Whole blood – equivalent to 1FFP + 1 PC + 1 unit RDP
- Massive transfusion leads to DIVC
 - What is massive transfusion?
 - Transfuse $\frac{1}{2}$ body volume in 24 hrs
 - 10 units or more
- Transfusion in sepsis dilemmas - Surviving sepsis guideline 2013
 - red blood cell transfusion only when Hb decrease to <7 to target haemoglobin concentration in adult 7-9g/dL, (grade 1B)
 - not using erythropoietin as a specific treatment of anaemia associated with severe sepsis (grade 1B)
 - FFP not be used to correct lab clotting abnormalities in the absence of bleeding or planned procedure (grade 2D),
 - in severe sepsis, administer prophylactic platelet when counts are $< 10\ 000$ in the absent of apparent bleeding; if has significant risk transfuse if $< 20\ 000$; higher platelet counts ($>50\ 000$) are advised for active bleeding, surgery or invasive procedures (grade 2D)
- CONCLUSION: avoid hypothermia, haemodilution/overload, acidosis and prolonged unsolved bleeding at all times as it affects the poor function of the coagulation factors

Topic: Haemophagocytosis in Dengue (Reactive Haemophagocytic syndrome): Do we need to think of it soon or later? Dr Tan Lian Huat

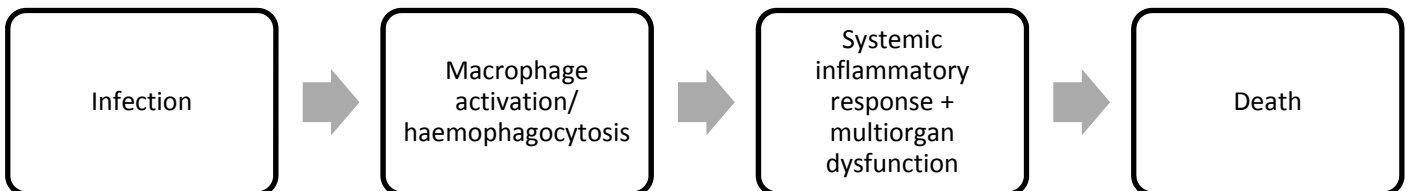
Conventional understanding of severe dengue – DHF/DSS



Severe dengue – How many of you observed the following?

1. Persistent fever and cytopenia
 - Beyond plasma leakage phase
2. Severe transaminitis/hepatitis
 - In the absence of shock
 - Continues to worsen beyond plasma leakage phase
3. Multi organ failure
 - In the absence of shock/plasma leakage
4. Progressive drop in haemoglobin
 - In the absence of bleeding/haemolysis
5. Unexplained progressive metabolic acidosis
 - Despite good perfusion

Haemophagocytic syndrome (HS)/ macrophage activation syndrome (MAS): a final common pathway of a cytokine storm – Szyper-Kravitz M. *Isr Med Assoc J* 2009; 11(10); 633-4



Haemophagocytic Lymphohistiocytosis(HLH) Syndrome Pathophysiology

- In HLH, there is an inherited or acquired defect of NK and CTL cells, so they are unable to cope effectively with the infectious agent or antigen
- This results in accumulation of activated T lymphocytes and activated histiocytes with increasingly high level of cytokines (cytokine storms)
 - Key cytokines found at extremely high levels in plasma of patients with HLH include interferon gamma, tumor necrosis factor alpha, interleukins IL-6, IL-8, IL-10, IL-12, IL-18 and soluble IL-2 receptor (CD25)

Clinical findings

More common

- Prolonged fever – increase IL-1, TNF alpha, IL-16
- Hepatosplenomegaly – organ infiltration by activated immune cells
- Neurologic – organ infiltration by activated immune cells, seizures, CN palsy, LP in more than half of the patients with slightly elevated cell count and or moderately increased protein, Imaging can include diffuse abnormalities, focal lesion and parenchymal calcification

Less common

- Lymphadenopathy, rash, jaundice

Characteristic Laboratory Values

- Cytopenia
 - Suppression by TNF alpha and INF gamma and consumption by haemophagocytosis
 - Anaemia and thrombocytopenia are common
- Elevated ferritin
 - Passive release due to cell damage
 - Increased secretion by macrophage and or release during erythrophagocytosis
 - Increased ferritin gene expression by cytokines TNF alpha
 - Decreased clearing due to lower glycosylation
 - For ferritin >500 in diagnosis of HLH – sensitivity 82% specificity 42%
 - For ferritin >10,000 in diagnosis of HLH – sensitivity 90% specificity 96%
- Transaminitis
- Elevated LDH
- Elevated TG
 - Increased level of TNF alpha suppress activity of lipoprotein lipase
- Depressed fibrinogen
 - Increased levels of plasminogen activators secreted by activated macrophage
- Hyponatremia
- Impaired NK cell activity
- Elevated soluble IL2 receptor (sCD25)

Clinical criteria for diagnostic of Haemophagocytic syndrome

- A. Molecular diagnosis (ie gene mutation known to cause HLH)
- B. Signs and symptoms (5 out of following criteria)
 - a. Fever
 - b. Splenomegaly
 - c. No evidence of malignancy
 - d. Cytopenia (2 Or 3 haematopoietic lineage on complete blood count)
 - i. Haemoglobin < 9
 - ii. Platelet < 100
 - iii. Neutrophil < 1.0×10^9
 - e. Hypertriglyceridemia and or hypofibrinogenemia
 - i. Fasting TG at least 3 mmol/L
 - ii. Fibrinogen at least 1.5g/L
 - f. Haemophagocytosis in bone marrow or spleen or lymph nodes
 - g. Low or absent NK cell activities
 - h. Ferritin at least 500 µg/L
 - i. Soluble CD25 at least 2400 U/ml

Recognition of dengue associated HS

- Fever + persistent cytopenia/pancytopenia
- Rapid decline in red cell counts without evidence of intravascular haemolysis or massive bleeding
- Atypical skin changes
- Persistent/high swinging fever + hepato/splenomegaly + cytopenia + hepatitis
- Fever + cytopenia + hepato/splenomegaly + multiorgan dysfunction/failure

Haemophagocytosis in Dengue: comprehensive report of six cases – Tan LH, Lum LCS, Syed Omar SF, Kan FK, J Clin Virol 2012, Sep; 55(1):79-82

Proposed HLH Diagnostic criteria, 2009

1. Molecular diagnosis of HLH or X-linked lymphoproliferative syndrome
2. Or at least 3 of 4
 - a. Fever
 - b. Splenomegaly
 - c. Cytopenia (minimum 2 cell lines reduced)
 - d. Hepatitis
3. And at least 1 of 4
 - a. Haemophagocytosis
 - b. Increase ferritin
 - c. Increase SCD25
 - d. Absence or very decreased NK function
4. Other results supportive of HLH
 - a. hyperTG
 - b. hypofibrinogenemia
 - c. hyponatremia

Treatment

- HLH-94/2004 protocol – FHL, HS associated with hereditary immunodeficiency, EBV associated HS
- Other infection associated HS – specific guidelines DO NOT exist
- In dengue associated HS
 - Haemophagocytosis is a transient disease process in majority of the patient
 - NOT ALL DENGUE associated HS needs immunochemotherapy
 - Steroid ± immunoglobulin may be enough for most cases if indicated

Transient haemophagocytosis in dengue immunopathogenesis – Lei HY et al – immunopathogenesis of dengue haemorrhagic fever, American Journal of Infectious Disease 4 (1): 1-9, 2008

It's important to note the transient but potentially catastrophic nature

Treatment approach should take into account this transient nature

Moving forward

- Dengue associated HS is an under recognised severe complication of dengue
- We really need to think of it soon and NOT later to enable timely intervention
 - That can potentially change the course of severe dengue and can reduce morbidity and mortality
- Persistent fever, cytopenia in association with multiorgan dysfunction, particularly drastic increase in transaminases should prompt clinical suspicion of HS

Topic: Results of Phase III Dengue Vaccine Efficacy Study in Asia

YFV17D-based Chimeric Dengue Vaccine

Yellow Fever Virus + DENV-1 DENV-2 DENV-3 DENV-4 = Recombinant DENV-1,-2,-3 and -4

- CYD14 was a randomized, observer blind, placebo-controlled, multicenter Phase III trial
- Patients (n=10275) from 10 highest dengue-endemic countries were recruited in this study, including 5 ASEAN countries – Thailand, Philippines, Malaysia, Vietnam, and Indonesia.
- Vaccine was given to the infants. (RANDOMISED 2:1 – vaccine: placebo) So far no significant adverse effect (observed for 6 yrs), no trial to adult yet
- Primary endpoint – vaccine efficacy against virologically confirmed dengue