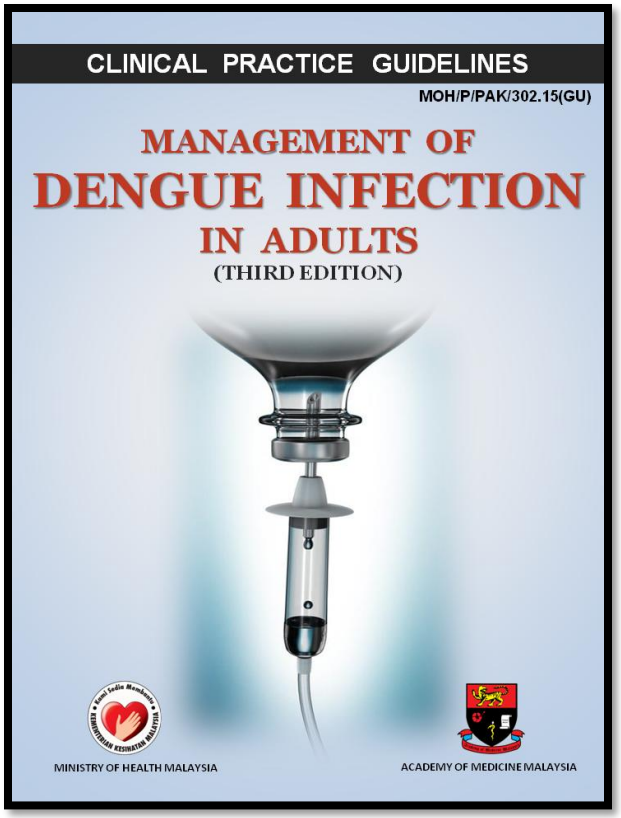


Critical Care of Dengue Patients

Objectives

- **Indications** for Intensive Care **referrals**- organ system
- **Respiratory** support
- **Haemodynamic** support -
- a) Haemodynamic monitoring-echo/usg
- b)Haemodynamic support- vasopressors/ ionotropes

- Algorithm C (new in this CPG)
- Metabolic acidosis/ lactic acidosis
- Guide on safety and risk of invasive procedures

- Management of severe dengue in the intensive care unit (ICU) follows the general principles of a critically ill patient

- Indications for intensive care referral can be categorised into organ systems

Respiratory	
1.	Acute respiratory distress with the following clinical signs: - RR >30/min - Dyspnoea - Use of accessory muscles - Agitation, confusion
2.	High levels of supplemental oxygen (O2 concentration ≥50% to maintain oxygen saturation >90%)
3.	Risk of respiratory compromise with large volume resuscitation e.g. congestive heart failure, chronic kidney disease
4.	Massive haemoptysis
5.	Potential need for non-invasive/invasive ventilation

Cardiovascular	
1.	Haemodynamic instability due to hypovolaemia, haemorrhage, myocarditis or other cause
2.	Complex cardiac dysrhythmias requiring close monitoring/intervention
3.	Underlying cardiac disease with risk of cardiorespiratory compromise e.g. unstable ischaemic heart disease, fixed cardiac output states

Neurologic	
1.	Seizures
2.	CNS depression
Gastrointestinal	
1.	Acute gastrointestinal bleeding with hypotension, continuous bleeding
2.	Severe acute hepatitis
Haematologic	
1.	Severe coagulopathy
2.	Significant bleeding
Renal	
1.	Acute kidney injury
2.	Acute rhabdomyolysis with renal insufficiency

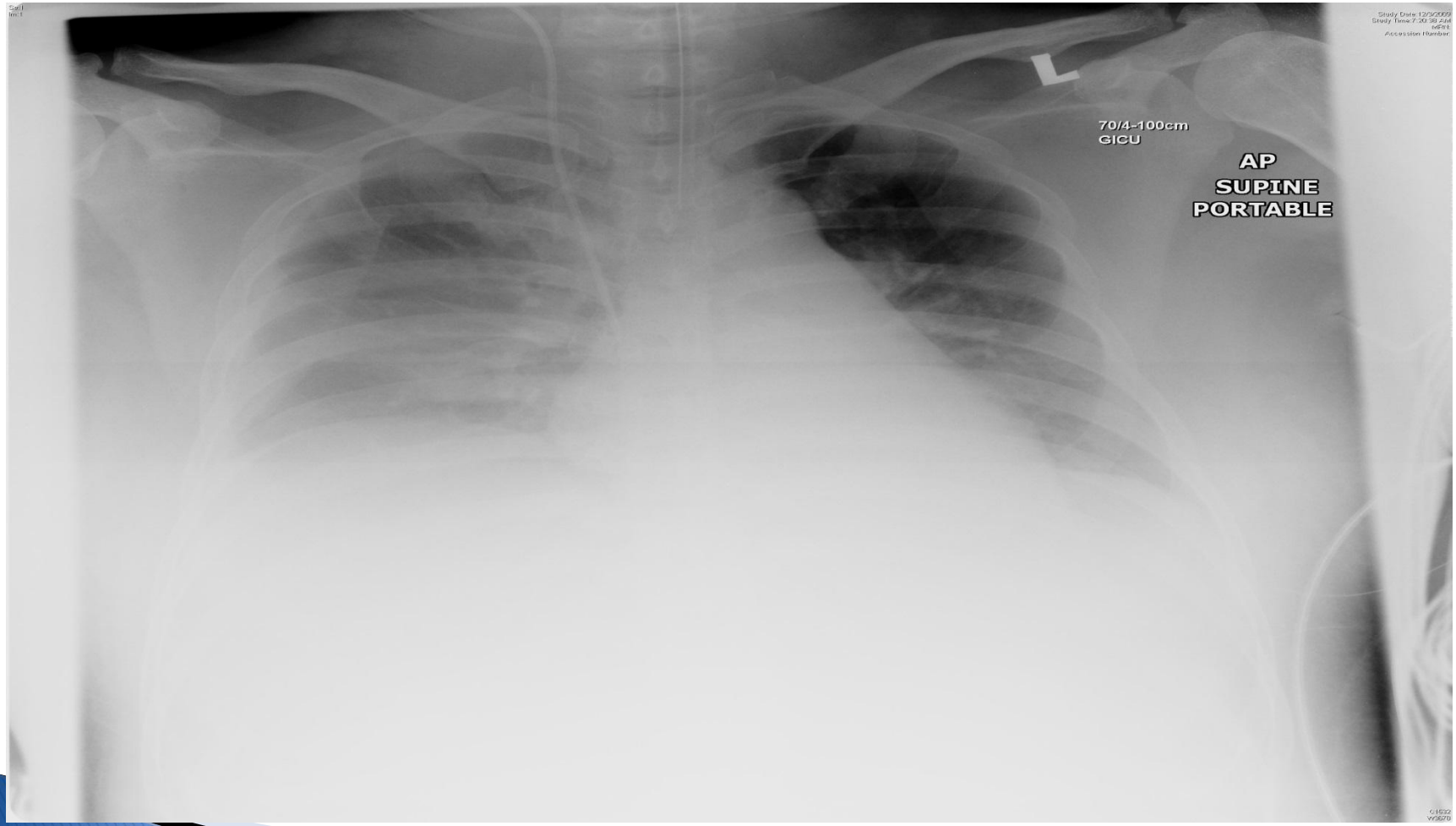
Respiratory support

- The **main objectives** of respiratory support are to:
  - support pulmonary gas exchange based on alveolar ventilation and arterial oxygenation.
  - reduce the metabolic cost of breathing by unloading the ventilatory muscles.

- **Indications for mechanical ventilation** in severe dengue:
  - persistent shock
  - acute respiratory failure secondary to massive pleural effusion ± ascites, fluid overload
  - severe metabolic acidosis
  - airway protection

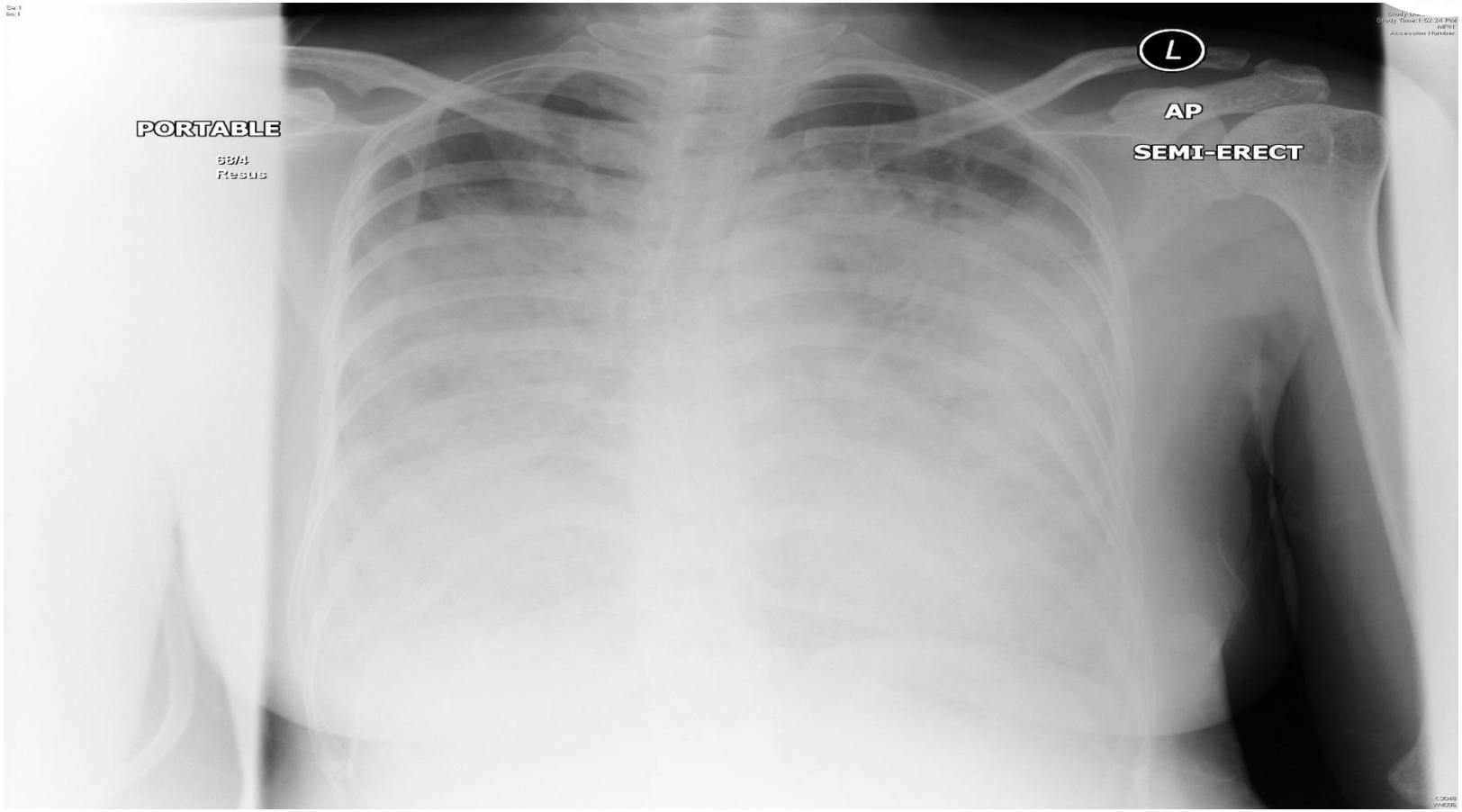
- Patients who are alert, cooperative and haemodynamically stable with or without mild metabolic acidosis may benefit from non-invasive ventilation.

BILATERAL PLEURAL EFFUSION



CPG Management of Dengue Infection in Adults (3rd Edition)

ARDS OR HEART FAILURE



Intubation/ventilation

- Intubation and ventilation in patients with severe dengue are not without risks.
- Initiation of positive pressure ventilation will further decrease the cardiac output by reducing venous return.
- Care must be taken to avoid trauma to the airway during intubation, which may cause bleeding
- In patients with pleural effusion and ascites, haemodynamics will be further compromised when higher airway pressure is applied to achieve adequate ventilation and oxygenation.

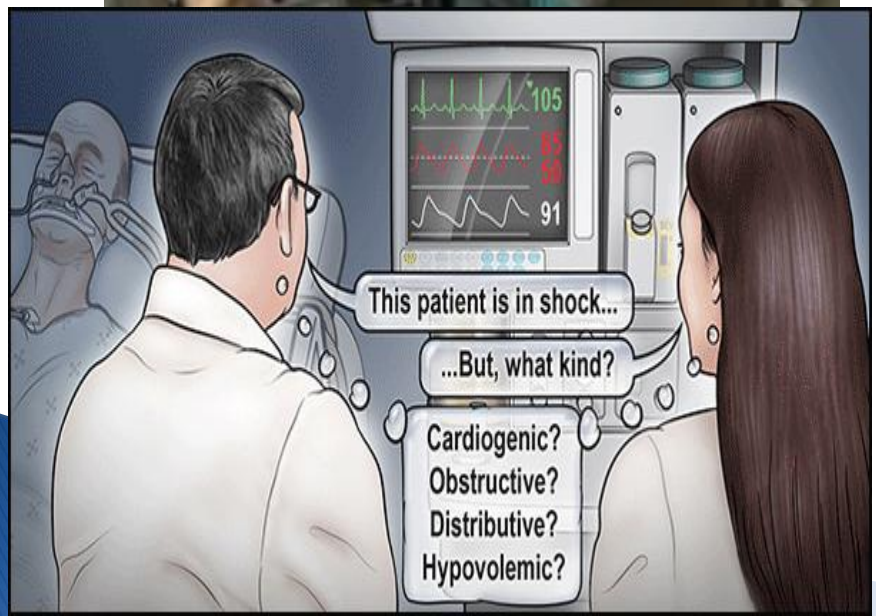
- In patients with metabolic acidosis, respiratory support should be considered despite preservation of relatively normal arterial blood pH.

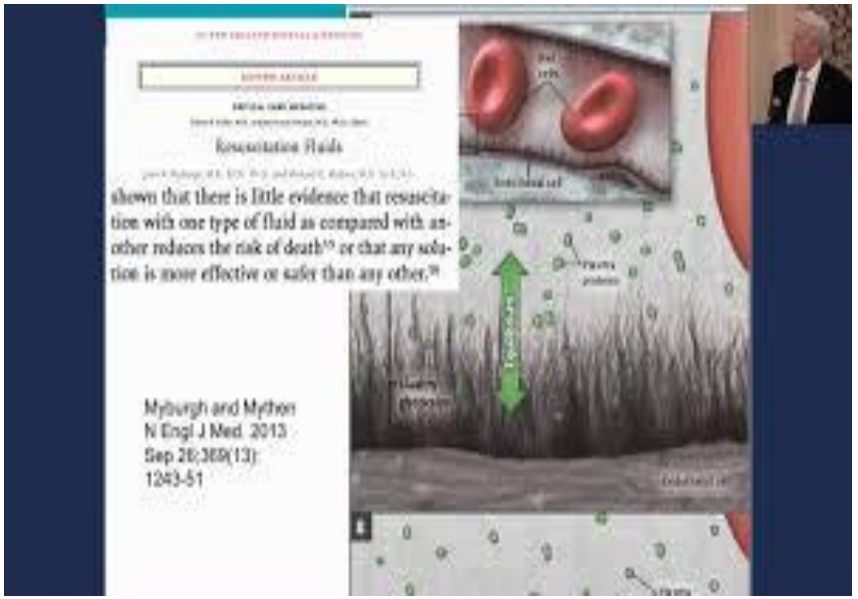
- When the actual PaCO2 is higher than the expected to compensate for the acidosis, consider intubation and mechanical ventilation.

Formula to calculate expected P_aCO_2 =

1.5 (Actual [HCO_3] mmol/L) + 8 ($\pm$ 2 mmHg)

Is shock in dengue all about fluids?



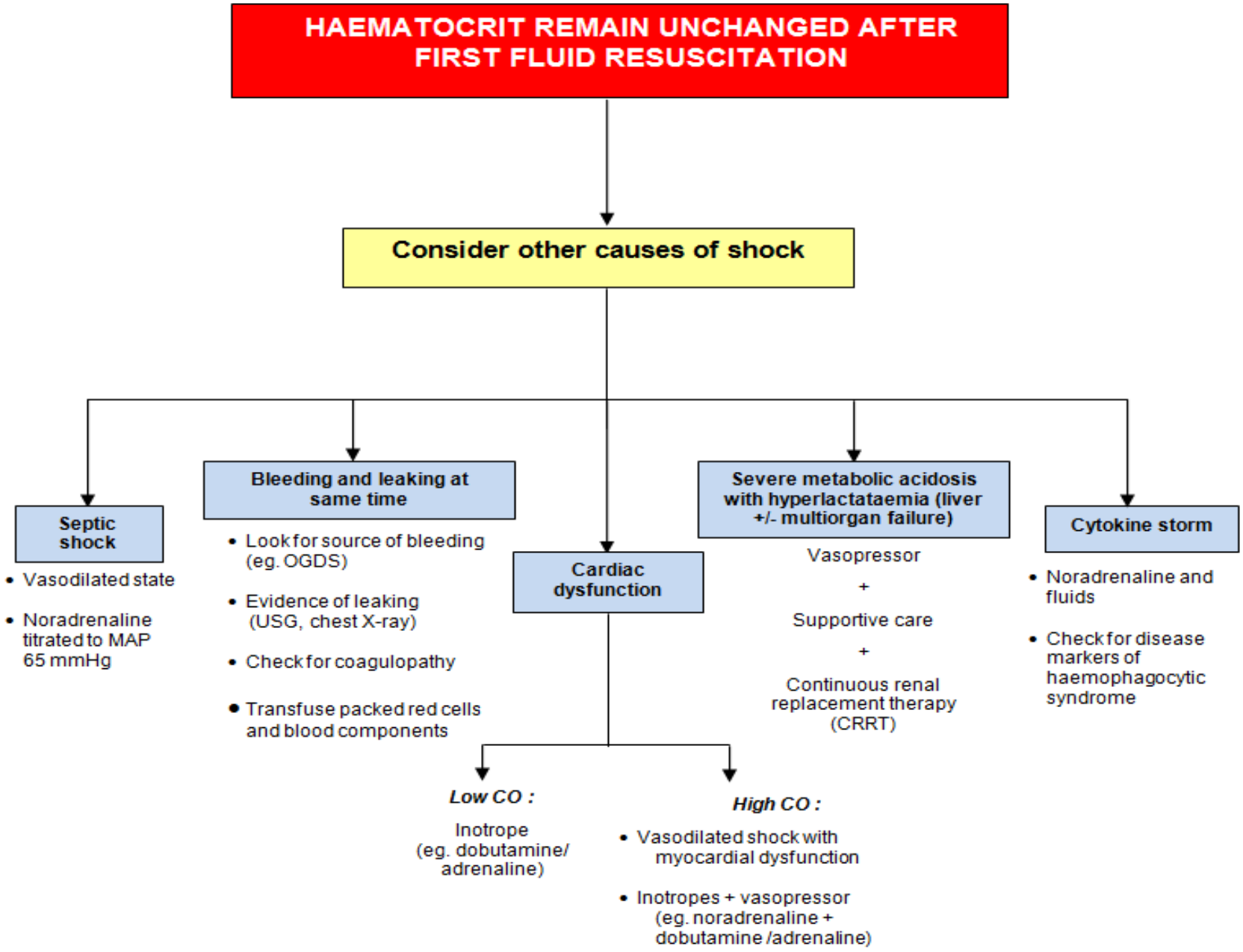


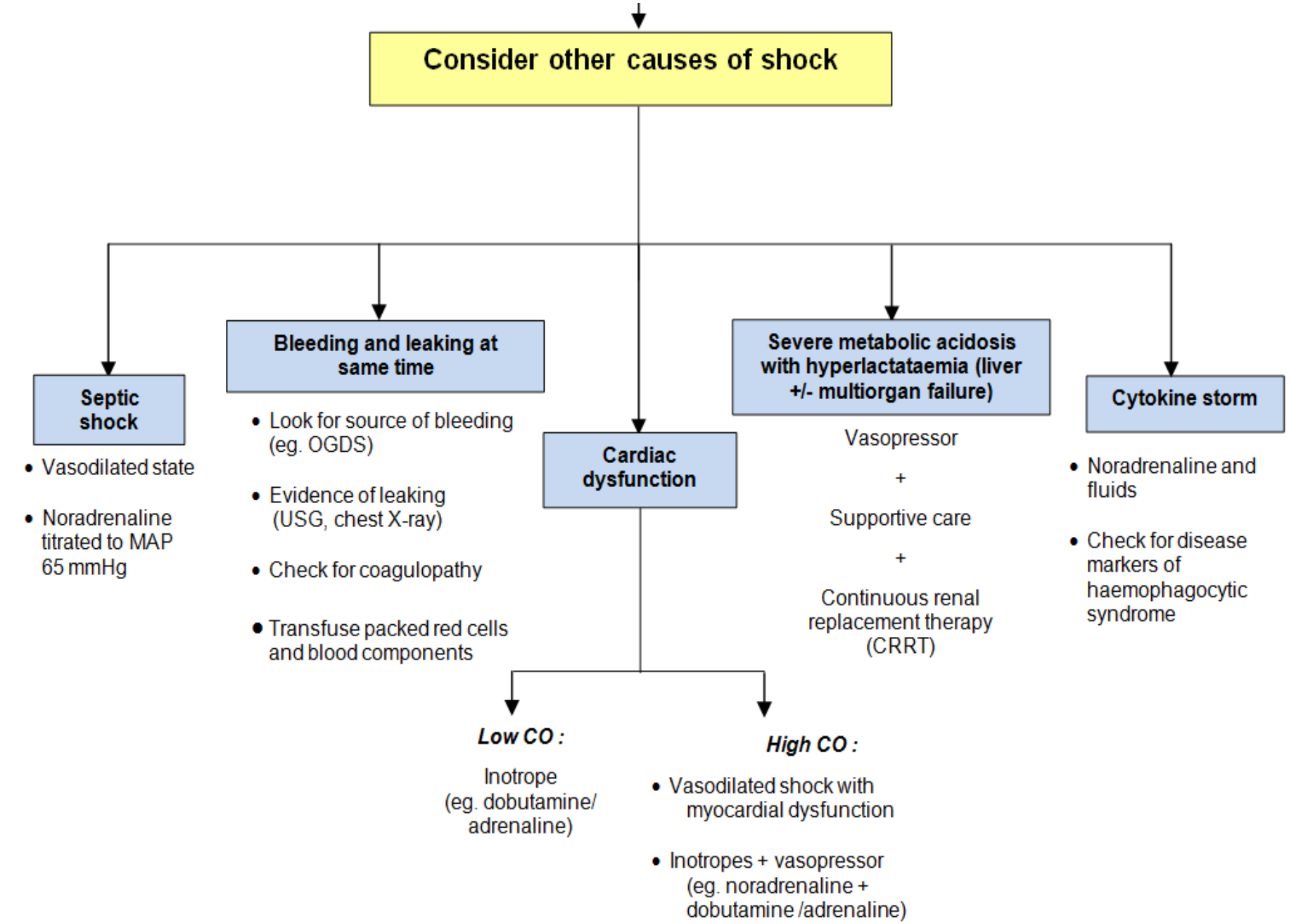
- Fluid resuscitation is crucial and is mainstay of treatment of shock and should be initiated early as per guidelines in the section on fluid management.

- However if a patient is in persistant shock other causes need to be considered.

- This is outlined in treatment **Algorithm C.**

ALGORITHM C - FLUID MANAGEMENT IN DECOMPENSATED SHOCK (WITH PRESENCE OF BLEEDING & LEAKING OR OTHER CAUSES OF SHOCK)




Consider other causes of shock
Septic shock
• Vasodilated state
• Noradrenaline titrated to MAP 65 mmHg
Bleeding and leaking at same time
• Look for source of bleeding (eg. OGDS)
• Evidence of leaking (USG, chest X-ray)
• Check for coagulopathy
• Transfuse packed red cells and blood components
Cardiac dysfunction
Low CO :
Inotrope (eg. dobutamine/ adrenaline)
High CO :
• Vasodilated shock with myocardial dysfunction
• Inotropes + vasopressor (eg. noradrenaline + dobutamine /adrenaline)
Severe metabolic acidosis with hyperlactataemia (liver +/- multiorgan failure)
Vasopressor
+
Supportive care
+
Continuous renal replacement therapy (CRRT)
Cytokine storm
• Noradrenaline and fluids
• Check for disease markers of haemophagocytic syndrome

CARDIAC DYSFUNCTION

1. Haemodynamic instability due to myocarditis and myocardial dysfunction

2. Complex cardiac dysrhythmias requiring close monitoring/ intervention

3. Underlying cardiac disease with risk of cardiorespiratory compromise e.g. unstable ischaemic heart disease, fixed cardiac output states, CCF

Published in final edited form as:
Crit Care Med. 2012 February ; 40(2): 477–483. doi:10.1097/CCM.0b013e318232d966.

Cardiac function in Vietnamese patients with different dengue severity grades

Sophie Yacoub, MRCP, MSc, DTM&H[1], **Anna Griffiths, BSc**[2], **Tran Thi Hong Chau, MD**[3], **Cameron P Simmons, PhD**[4], **Bridget Wills, MD, FRCPCH**[4], **Tran Tinh Hien, MD, PhD**[4], **Michael Henein, PhD, FRCP**[5], and **Jeremy Farrar, PhD, FRCP**[4]

Possible mechanisms include regional vulnerability to coronary hypoperfusion, “cytokine storm “as per severe sepsis, direct myocardial inflammation and altered calcium homeostasis.

The indirect and direct cardiac effects of dengue may differ from that of septic shock but the management implications are similar

Measurements and Main Results—Patients with severe dengue had worse cardiac function compared to dengue, in the form of left ventricular (LV) systolic dysfunction with increased Left myocardial performance index (LMPI) (0.58 (0.26-0.80) vs. 0.38 (0.22-0.70), P=0.006). Septal myocardial systolic velocities (S′) were reduced, (6.4 (4.8-10) vs. 8.1 (6-13) cm/s, P=0.01) as well as right ventricular (RV) systolic (11.4 (7.5-17) vs. 13.5 (10-17) cm/s, P=0.016), and diastolic (E′) velocities (13 (8-23) vs. 17 (12-25) cm/s, P=0.0026). In the severe group, these parameters improved from hospital admission to discharge; septal S′ to 8.8 (7-11) cm/s (P=0.002), RV S′ to 15.0 (11.8-23) cm/s, (P=0.003) and diastolic velocity E′ to 21 (11-25) cm/s (P=0.002). Patients with cardiac impairment were more likely to have significant pleural effusions.

Conclusions—Patients with severe dengue have evidence of systolic and diastolic cardiac impairment, with septal and right ventricular wall being predominantly affected.

- Measurement of ejection fraction is quite tricky to interpret as it is sensitive to changes in preload and afterload.
- So for a more detailed study, cardiac indices that are independent of preload are necessary by myocardial Tissue Doppler Imaging .
- The least severe dengue infections had transient evidence of systolic and diastolic dysfunction with possible segmental wall abnormalities of the septum and right ventricular wall and more severe had more frequently of these abnormalities detected
- The more RV involvement the more the pleural effusion
- SEEMED TO REQUIRE MORE FLUID AND LONGER ICU STAY

Myocardial depression in dengue hemorrhagic fever: Prevalence and clinical description*

Apichai Khongphatthanayothin, MD; Pornthep Lertsapcharoen, MD; Pentip Supachokchaiwattana, MD; Vidhawas La-orkhun, MD; Aree Khumtonvong, MD; Charoon Boonlarptaveechoke, MD; Chitsanu Pancharoen, MD

Objectives: To determine the prevalence of myocardial depression and its effect on the clinical severity in patients with dengue hemorrhagic fever.

Design: Clinical study.

Setting: King Chulalongkorn Memorial Hospital, Bangkok, Thailand.

Patients: Ninety-one children (age 10.5 ± 2.9 yrs, male/female = 52/39) with serologically or polymerase chain reaction-proven dengue virus infection.

Interventions: Left ventricular ejection fraction (EF) was measured. The proportions of patients with EF <50% were identified in patients with dengue fever (DF, n = 30), dengue hemorrhagic fever without shock (DHF, n = 36), and dengue shock syndrome (DSS, n = 25). Comparisons of clinical findings were made among DSS patients with depressed ventricular function (EF <50%), fair ventricular function (EF ≥50% and <60%), and good ventricular function (EF ≥60%). Serum troponin T was analyzed in nine patients.

Measurements and Main Results: EF during toxic stage was significantly lower in patients with DSS than DHF, and lower in DHF than DF ($p = .05$) with rapid recovery within 24–48 hrs. EF <50% was found in 6.7%, 13.8%, and 36% of patients with DF, DHF, and DSS during the toxic stage, respectively ($p = .01$). DSS patients with poor ventricular function had significantly more tachycardia and hepatomegaly. While end-diastolic volumes were similarly reduced, patients with lower EF tended to have lower cardiac output, required more aggressive intravenous fluid resuscitation, developed larger pleural effusion, and had higher incidence of respiratory embarrassment. No patient had elevated troponin T level.

Conclusions: Transient myocardial depression is not uncommon in patients with DSS. Cardiac dysfunction in children with DSS may contribute to the clinical severity and the degree of fluid overload in these patients. (Pediatr Crit Care Med 2007; 8:524–529)

KEY WORDS: dengue; dengue hemorrhagic fever; dengue shock syndrome; cardiac function; pleural effusion; fluid overload

EF<50 %, seen in 6.7%, 13.8% and 36% of pts with DF, DHF AND DSS , its transient

Intensive Care Med (2003) 29:570–574
DOI 10.1007/s00134-003-1671-9

ORIGINAL

Apichat Khongphatthanayothin
Monnipa Suesaowalak
Sunthorn Muangmingsook
Parvapan Bhattarakosol
Chitsanu Pancharoen

Hemodynamic profiles of patients with dengue hemorrhagic fever during toxic stage: an echocardiographic study

Decreased preload is accompanied by decreased left ventricular performance, and possibly a subnormal heart rate response in some patients.

Recommendation in CPG

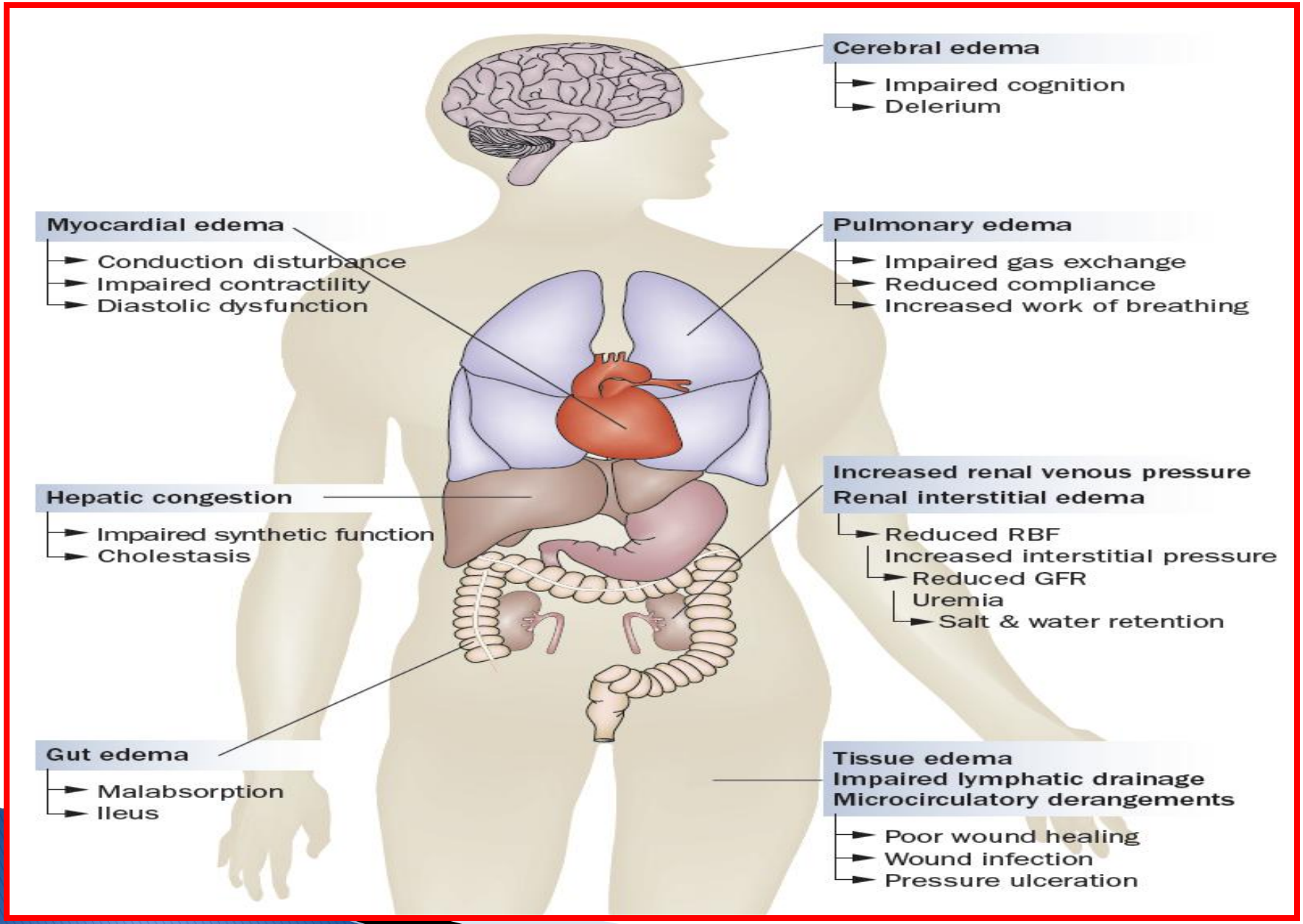
Recommendation 8

- Echocardiography is indicated in refractory shock despite adequate fluid resuscitation and in suspected myocardial dysfunction in dengue infection.
- Adequate fluid resuscitation should be ensured before myocardial dysfunction can be diagnosed in dengue infection.

MANAGEMENT IMPLICATIONS

- Make sure preload is optimised before concluding the poor contractility is due to myocardial dysfunction
- Ionotropes (dobutamine/adrenaline)
- Judicious fluids (cut down)/ stop
- Non invasive ventilation
- Non invasive hemodynamic monitoring

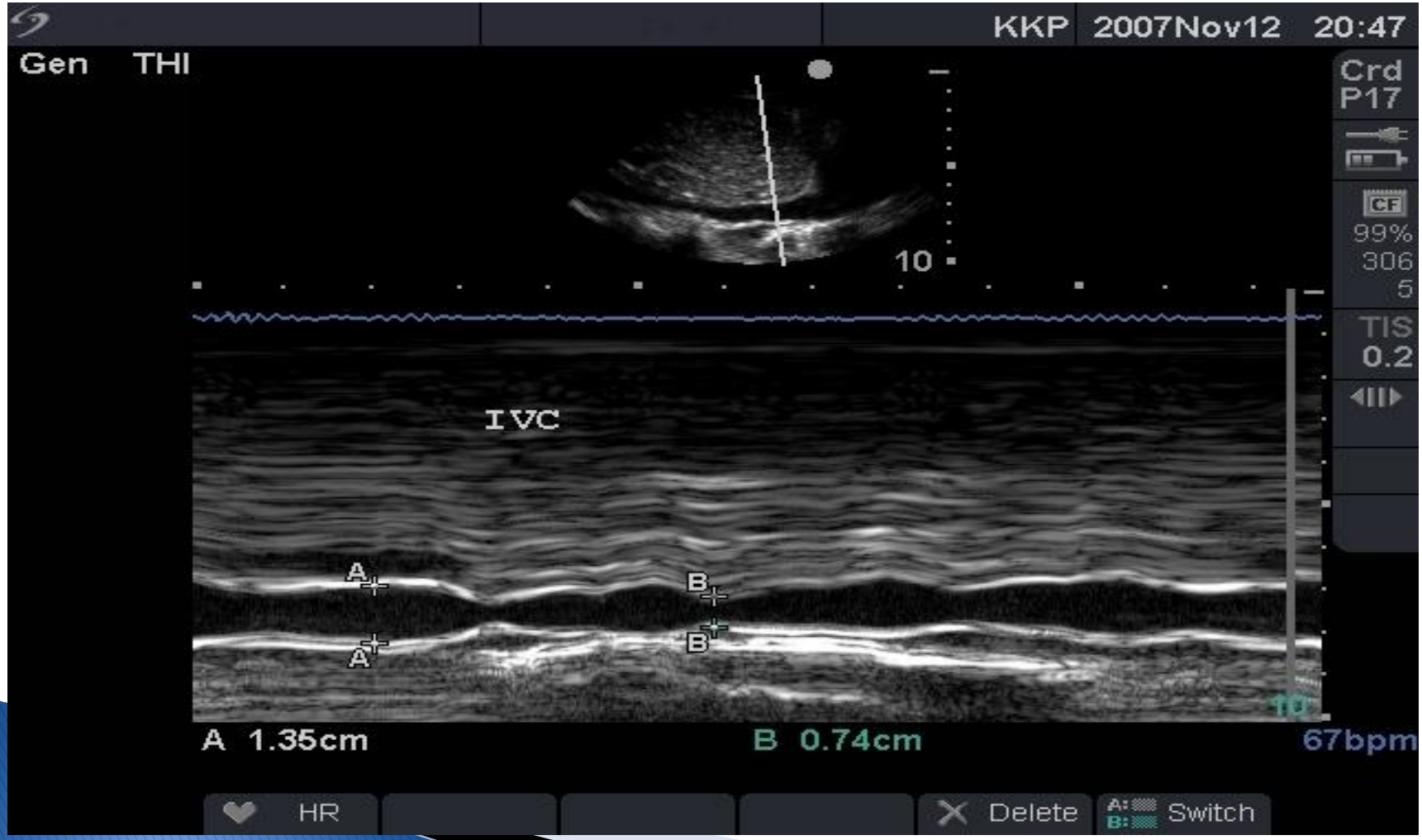
Fluid overload and organ dysfunction

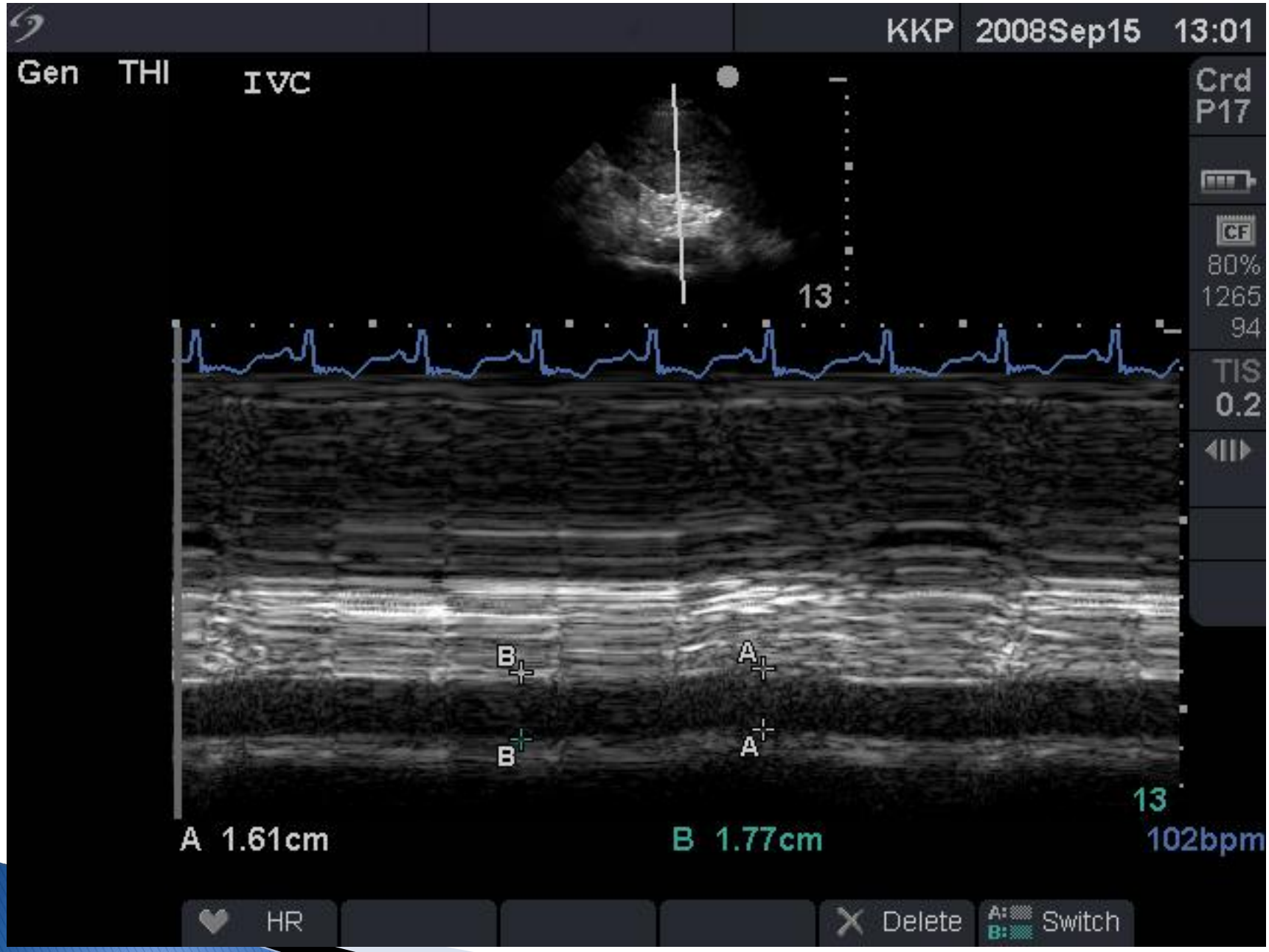


NON INVASIVE MONITORING– to assess fluid responsiveness

- Echocardiography
- Ultrasonography
  - to assess leakage
  - respiratory variation of IVC diameter in spontaneous breathing patient
  - respiratory variation of IVC in mechanical ventilated patient
- Passive leg raise test
- USCOM (Ultrasound Cardiac Output Monitoring)

IVC diameter showing respiratory variation




KKP 2008Sep15 13:01
Gen THI
IVC
Crd P17
CF
80%
1265
94
TIS 0.2
13
B
A
B
A
13
A 1.61cm
B 1.77cm
102bpm
HR
Delete
A:
B:
Switch

C. Imaging parameters (recommended but not mandatory)

✓ Improvement of IVC collapsibility index (spontaneous breathing patient)

$$\frac{\text{IVC expiratory diameter} - \text{IVC inspiratory diameter}}{\text{IVC expiratory diameter}} \times 100 = \text{Caval index (\%)}$$

*Caval index close to 100% is indicative of almost complete collapse, therefore volume depletion and 0% suggests minimal collapse i.e. likely volume overload.
>40% collapse will be fluid responsive.[72]

Adapted : Goldflam K, Saul T and Lewiss R. Focus on: inferior vena cava ultrasound. ACEP News 6. 2011. pp 24-25. (available at : http://www.acep.org/Content.aspx?id=80791)

CAUTION : IVC assessment should be performed by trained personnel and not to be interpreted in isolation.

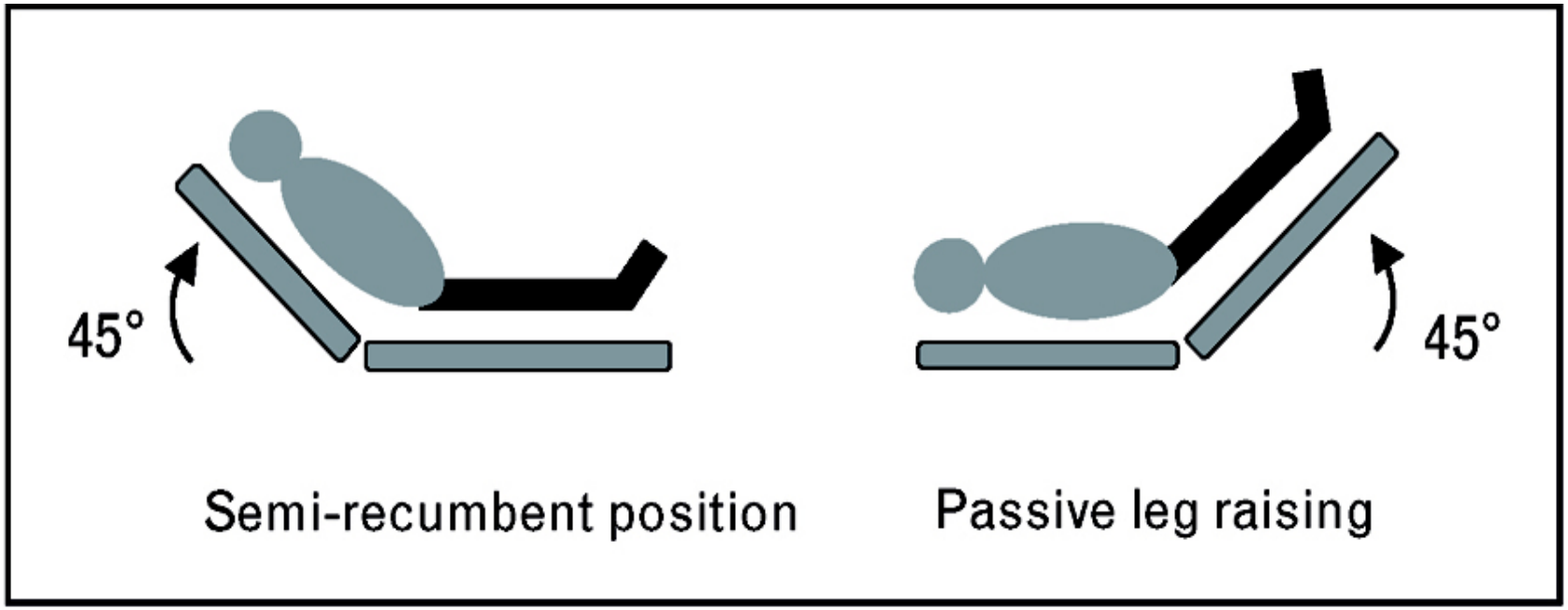
- Inferior vena cava collapsibility index (IVCCI) is a suggested method to gauge fluid status however this has only been validated in controlled mode of ventilation, sedated patient with no spontaneous breathing in sinus rhythm and normal intrabdominal pressures (Charron C).

- Thus its limitations need to be considered in awake spontaneously breathing patients with right heart impairment.

- An (IVCCI) more than 50% in spontaneously breathing patients is suggestive of fluid responsiveness.

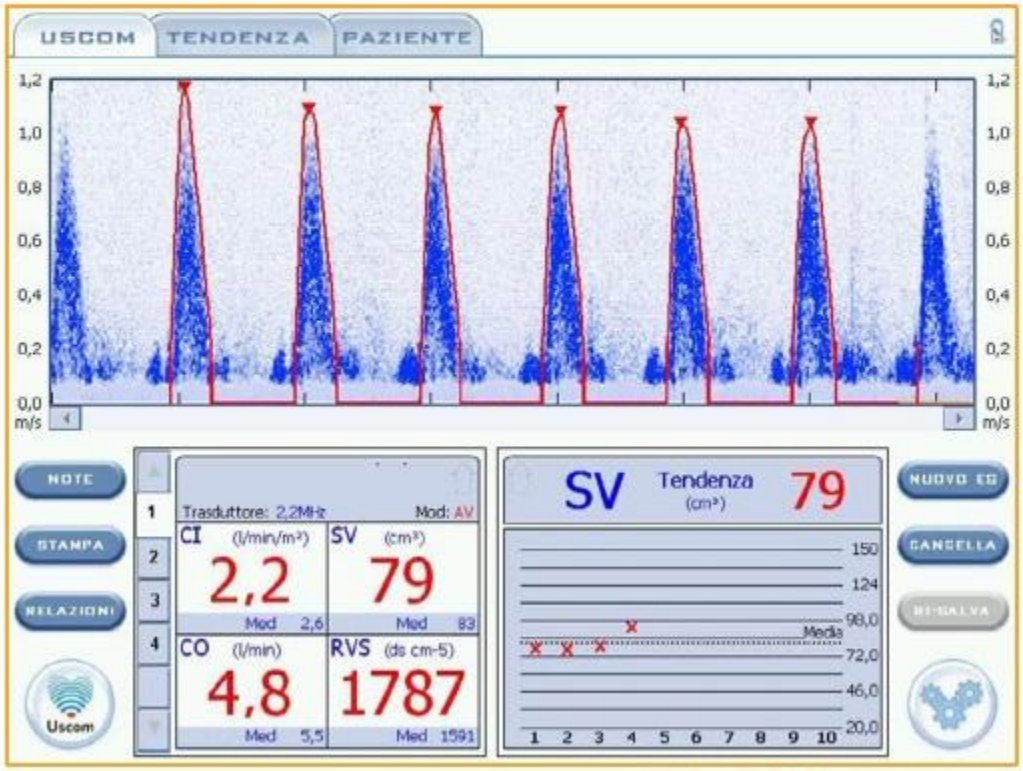
- In spontaneously breathing patients fluid responsiveness can be assessed also by Passive Leg Raise test

PASSIVE LEG RAISING TEST



The passive leg-raising test consists of measuring the hemodynamic effects of a leg elevation up to 45°. A simple way to perform the postural maneuver is to transfer the patient from the semi-recumbent posture to the passive leg-raising position by using the automatic motion of the bed.

Passive Leg Raise
to test for fluid response



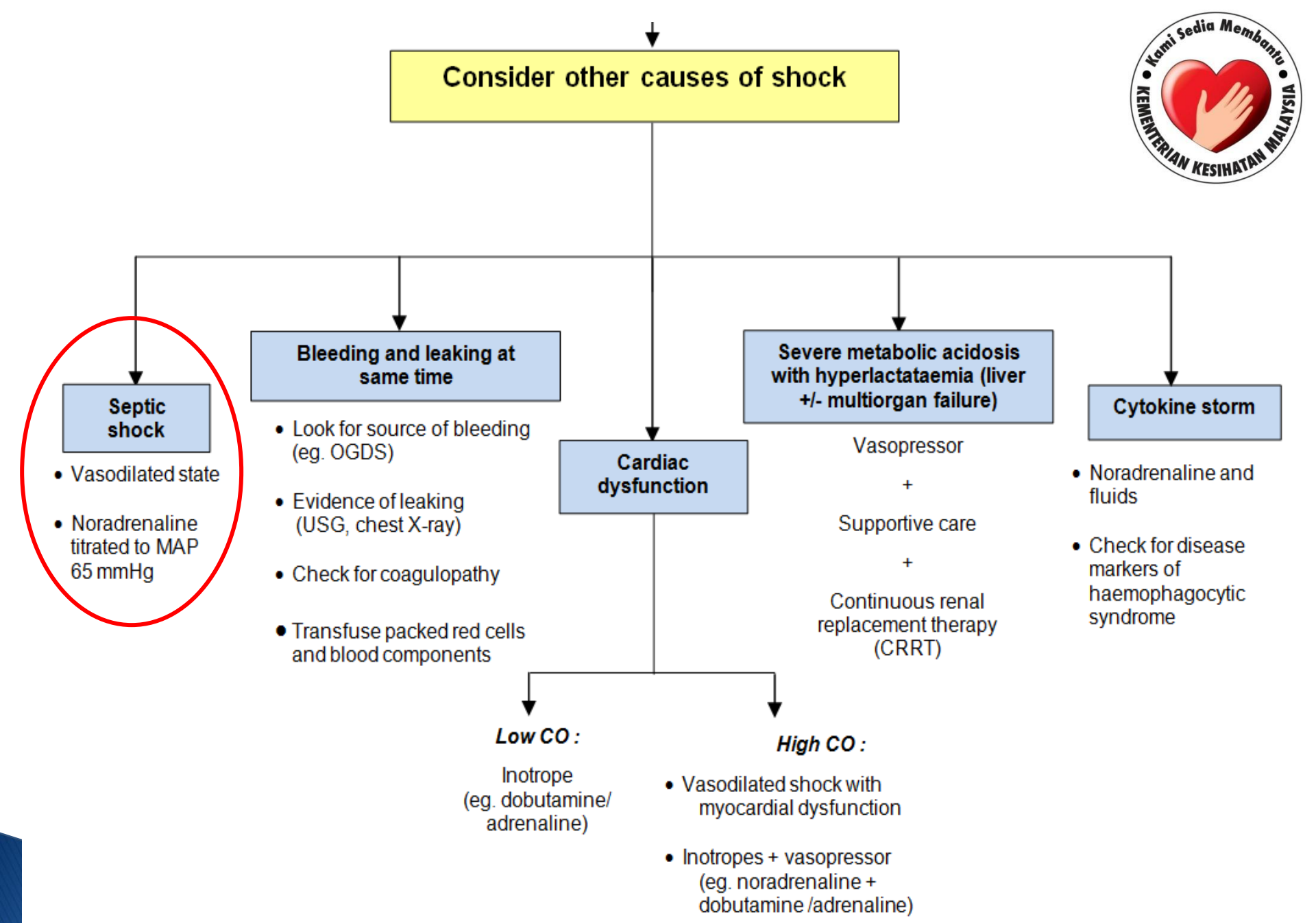
The Measure of Life

Passive leg raise to assess fluid responsiveness in spontaneously breathing patient

- Passive leg raising (PLR) is a simple reversible maneuver that mimics rapid fluid loading and increases cardiac preload.
- The effects of this endogenous volume expansion on stroke volume enable the testing of fluid responsiveness with accuracy in spontaneously breathing patients.
- However, this maneuver requires the determination of stroke volume with a fast-response device, because the hemodynamic changes may be transient.

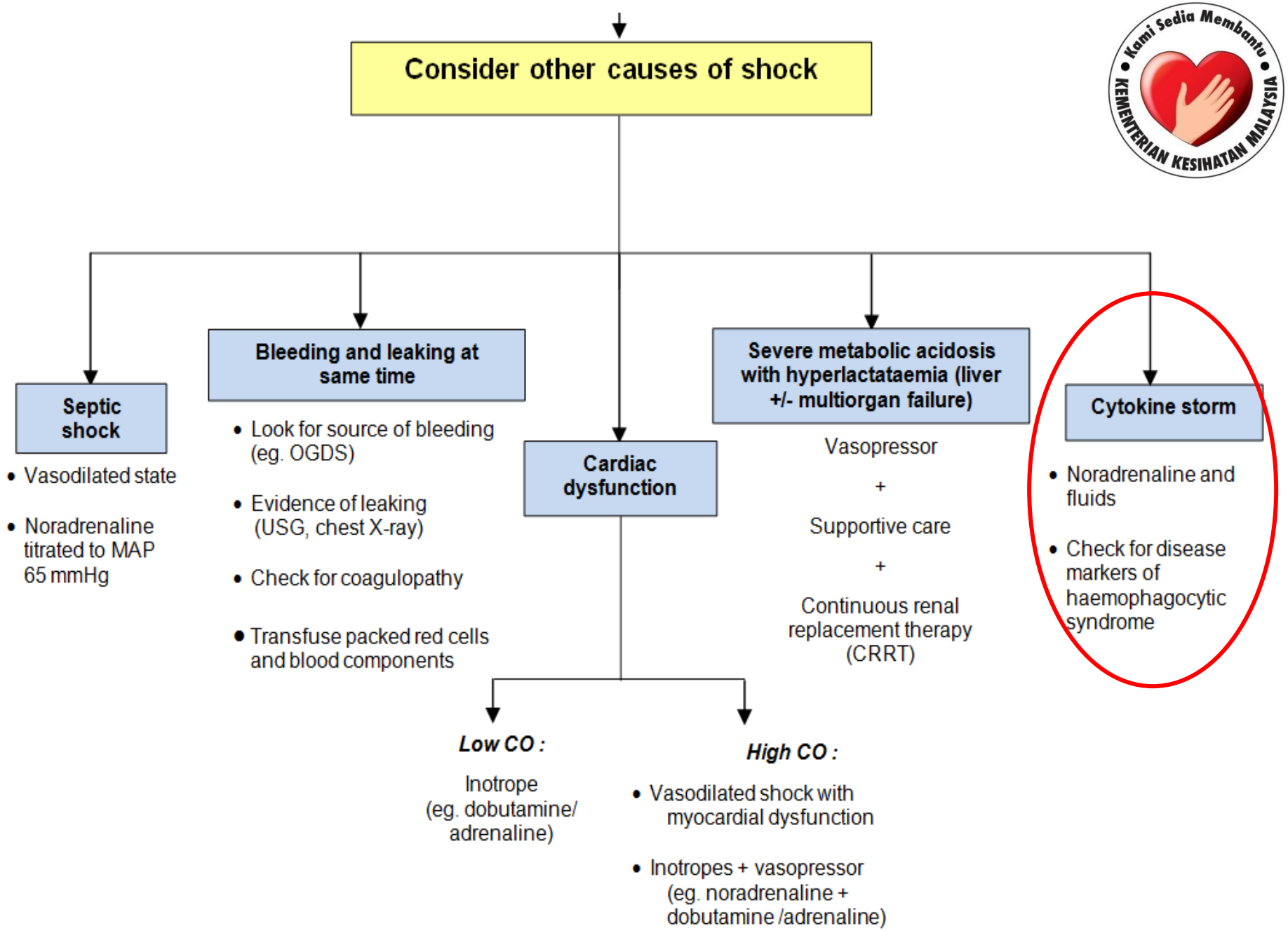
- **TECHNIQUE**
- sit patient at 45 degrees head up semi-recumbent position
- lower patient's upper body to horizontal and passively raise legs at 45 degrees up
- maximal effect occurs at 30-90 seconds
- assess for a 10% increase in stroke volume (cardiac output monitor) or using a surrogate such as pulse pressure (using an arterial line)

- **PERFORMANCE CHARACTERISTICS**
- 9% increase in stroke volume has 86% sensitivity and 90% specificity
- 10% increase in pulse pressure has 79% sensitivity and 85% specificity


Consider other causes of shock
Septic shock
• Vasodilated state
• Noradrenaline titrated to MAP 65 mmHg
Bleeding and leaking at same time
• Look for source of bleeding (eg. OGDS)
• Evidence of leaking (USG, chest X-ray)
• Check for coagulopathy
• Transfuse packed red cells and blood components
Cardiac dysfunction
Low CO :
Inotrope (eg. dobutamine/ adrenaline)
High CO :
• Vasodilated shock with myocardial dysfunction
• Inotropes + vasopressor (eg. noradrenaline + dobutamine /adrenaline)
Severe metabolic acidosis with hyperlactataemia (liver +/- multiorgan failure)
Vasopressor
+
Supportive care
+
Continuous renal replacement therapy (CRRT)
Cytokine storm
• Noradrenaline and fluids
• Check for disease markers of haemophagocytic syndrome

Shock in Dengue is it all about fluids?

- Sepsis and dengue
- Eg leptospirosis and dengue, gram negative sepsis and dengue, appendicitis and dengue, nosocomial infection and sepsis
- Which case treat as per the current sepsis protocol, early vasopressor rather than just fluids and antibiotics/source control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DHF/DSS and cytokine storm

Department of Research Policy and Cooperation, World Health Organization, Geneva, Switzerland
2Institute of Health and Community Medicine, Universiti Malaysia Sarawak, Kuching, Malaysia
3Department of Virology, PAHO/WHO Collaborating Center for the Study of Dengue and its Vectors, Instituto de Medicina Tropical Pedro Kouri, Havana, Cuba
Correspondence: Dr T Pang, Department of Research Policy and Cooperation, World Health Organization, Ave Appia 20, Geneva 1211, Switzerland. E-mail: pangt@who.int
Received 19 September 2006; Accepted 26 September 2006; Published online 28 November 2006.

REVIEW

Of cascades and perfect storms: the immunopathogenesis of dengue haemorrhagic fever-dengue shock syndrome (DHF/DSS)

Tikki Pang[1], Mary Jane Cardosa[2] and Maria G Guzman[3]

- Following reinfection with a dengue virus of different serotype, severe disease is linked to high levels of antibody-enhanced viral replication early in illness which is followed by a cascade of memory T-cell activation and a 'storm' of inflammatory cytokines and other chemical mediators.

- These compounds are released mainly from T cells, monocytes/macrophages and endothelial cells, and ultimately cause an increase in vascular permeability.

Shock in Dengue is it all about fluids?

- Cytokine storm implications?
- Will have more capillary leakage –needing more fluids
- Some vasodilated due to inflammatory mediators (iNOs, TNF)
- Vasopressors can reduce amount of fluids given

CPG – Haemodynamic support

- The role of inotropic and vasopressor agents in dengue shock has not been investigated in clinical trials.
- Vasopressors may be able to maintain the blood pressure but do not improve tissue perfusion if the intravascular volume has not been restored.
- The use of inotropic and vasopressor agents should be limited to the following clinical situations (Refer **Algorithm C**):

CPG- hemodynamic support

- As a **temporary measure to prevent life-threatening hypotension** while aggressive fluid resuscitation is being carried out or during induction for intubation.

- **Cardiogenic shock**
- In the case of cardiac dysfunction, it is appropriate to use inotropic agents such as dobutamine or adrenaline in combination with a vasopressor.

- **Concomitant septic shock**
- Noradrenaline is preferred to other vasopressors as first-line therapy.

Shock in dengue is it all about fluids?- Liver failure

- Liver failure-Judicious fluids and pressors/ionotrope with hemodynamic monitoring to guide shock management

- mostly need Vasopressor as they have vasodilated shock and if lactates cause severe acidosis and myocardial depression (will also need ionotropes)

- A grade 3 or 4 encephalopathy is often an indication for intubation and ventilation in order to protect airway
- Complications of liver disease, such as intraabdominal hypertension (IAH) secondary to bowel oedema, ascites, pleural effusion, acute lung injury and ARDS all compromise ventilation
- levels of positive end expiratory pressure (PEEP) should be avoided if possible because they may increase hepatic congestion and ICP

Management of liver failure key points

- Simple neuromeasures (Cerebral Resuscitation) implemented
- Elevate head to 30 degrees to improve cerebral perfusion pressure (CPP)
- The patient should be appropriately sedated to prevent stimuli from rising intracranial pressure
- (ICP)
- Avoid of hypotension maintain MAP 80-90mmhg
- . This may require use vasopressors as generally a vasodilated state
- Prevent hypoxaemia , hyperthermia

Management of liver failure key points

- Target PaCO2 (35-40)mmhg
- Tight glycaemic control sugars targetted 6-10mmo/l
- Mannitol (0.5g/kg) is used to treat intracranial hypertension associated with cerebral oedema in non dengue situation
- However, mannitol is associated with marked reductions in blood pressure through decreases in vascular resistance (SVR) and a poorly understood acute vasodilatory effect systemically
- Boluses of **hyperpertonic saline** can be utilised with similar benefits, without the haemodynamic side effects
- Doses of 1-2mls/kg of 3% saline bw given and monitor levels not to increase sodium by > 1 mmol/2 hrs
- . Target serum sodium 145-155mmol/l and serum osmolality 305-325mosm/l

IV NAC for acute liver failure in severe dengue

- Regime is controversial
- Suggested regime
  - 100 mg/kg/day as infusion for 5 days
  - 150 mg/kg in 200 ml D5% over 1 hour followed by 12.5mg/kg/hour in 500 ml D5% for 4 hours and then 6.25 mg/kg/hour in 1000ml D5% for 72 hours

Management of liver failure key points

- Renal replacement therapy (RRT) should be provided early in the course of AKI complicating ALF
- As prevent worsening acidosis and fluid overload.
- Continuousvenovenous haemodialysis (CVVHD) is
- preferred over intermittent haemodialysis (IHD) due to the associated haemodynamic instability of the IHD

Lactates in dengue

- **compensated metabolic acidosis** is an early sign of shock due to leakage or bleeding in a patient who is normotensive

- Lactic acidosis due to tissue hypoxia and hypoperfusion is the most common cause of metabolic acidosis in dengue shock.

- A lactate level of <2 mmol/L in a critically ill patient generally implies that the patient has adequate tissue perfusion, although higher levels are not necessarily the result of tissue hypoxia.

- Monitoring of blood lactate levels is commonly carried out in patients with severe dengue, frequency depends on severity

- Delay in lactate clearance or persistent lactate elevation is associated with poor outcome.

- Persistent lactic acidosis contributes to myocardial depression, arrhythmias, vasodilatation, increase in respiratory muscle workload, reduced oxygen delivery, decreased ATP production and multi-organ failure

Lactate clearance

- A likely more useful parameter for guiding therapy is **lactate clearance**.
- Lactate clearance is calculated as below:

$$\frac{\text{lactate initial} - \text{lactate subsequent}}{\text{initial lactate}} \times 100$$

- A 20% clearance in 2 hours improves survival.

Other causes of acidosis

- Correction of shock and adequate fluid replacement will correct the metabolic acidosis.

- If metabolic acidosis remains uncorrected by this strategy, one should suspect severe bleeding, liver failure, acute kidney injury, sepsis, cardiac dysfunction, drugs (e.g. beta2 agonists, metformin) and hyperchloremic metabolic acidosis.

Hyperchloremic metabolic acidosis

- Hyperchloraemia, caused by the administration of large volumes of 0.9% sodium chloride solution (chloride concentration of 154 mmol/L)

- may cause metabolic acidosis with normal lactate levels and presents as a normal anion gap metabolic acidosis.

- If serum chloride levels increase, change the fluid to balanced solution such as sterofundin or ringers lactateHartmann's. This improves chloride related acidosis.

- Sodium bicarbonate for metabolic acidosis caused by tissue hypoxia is not recommended for pH $\geq$7.10.

- Bicarbonate therapy is associated with sodium and fluid overload, an increase in lactate and pCO2 and a decrease in serum ionized calcium.

Guide on Safety and Risk of Invasive Procedures

- **Central venous catheter (CVC) insertion**

- In any condition that requires fluid resuscitation, rapid and large volume of fluids can be infused via a large bore peripheral venous catheter.

- A well sited proximal peripheral venous catheter is sufficient if it is expected that vasopressor is required for only short duration (1-2 hours).

- The commonly available CVCs are long and multi-lumens with relatively smaller individual lumen.

- The need for CVC arise:
- inadequate peripheral venous access patient requires an infusion of vasopressor for prolonged period.
- Apart from the above indications, CVC should not be inserted solely for monitoring of CVP.
- CVP is not reliable to predict left ventricular filling volume or to predict hemodynamic response to fluid challenge.
- Thus, CVP should not be used to guide fluid management in dengue.

- A subclavian approach should be avoided in these patients as the subclavian artery and vein is not accessible to direct compression.
- The use of real time USG is recommended for CVC insertion if it is available and there is expertise.
- Routine prophylactic transfusion of platelets and FFP in severe thrombocytopenia prior to insertion of CVC should not be done as there is no clear evidence to support this practice.
- If platelet is to be transfused, a CVC should be done within 4 hours following transfusion for maximum effect.
- The most recent recommendation by American Association of Blood Banks suggested transfusion as low as 20,000 prior to CVC insertion.

Diuretics in severe Dengue with ARDS (deresuscitation)

RESEARCH BRIEF

Furosemide Infusion in Children with Dengue Fever and Hypoxemia

KR BHARATH KUMAR REDDY, GV BASAVARAJA AND SHIVANANDA

From Department of Pediatric Intensive Care, Indira Gandhi Institute of Child Health, Bangalore, Karnataka, India. Correspondence to: Dr KR Bharath Kumar Reddy, Indira Gandhi Institute of Child Health, South Health Complex, Dharmaram Post, Bangalore 560 029, Karnataka, India. bharathreddykr@yahoo.co.in

Objectives: To study the role of furosemide infusion in the management of Acute respiratory distress syndrome (ARDS) associated with dengue fever.

Methods: Children between the ages of 1 month to 18 years, who fulfilled the WHO clinical criteria for dengue infection and American European Consensus Criteria criteria for ARDS with Dengue IgM positivity, were evaluated. Patients were studied as group D (receiving diuretic therapy alone) and group B (both ventilation and diuretics), and compared to a historical control group V (ventilation alone). Furosemide infusion was administered at 0.05-0.1 mg/kg/hour for 48 hours, maintaining a urine output of 2-4 mL/kg/hour.

Results: There was a significant difference in survival in the three groups. Significant difference was noted between pre- and post-intervention arterial blood gases with respect to PCO_2 (P=0.02), pO_2 (P=0.003), PaO_2/FaO_2 ratio (P<0.001) and alveolar-arteriolar oxygen gradient (P=0.002).

Conclusion: Diuretic infusion improves outcome in dengue with ARDS.

Keywords: *ARDS, Dengue, Diuretics, Outcome.*

RECOMMENDATIONS

Recommendation 10

- Non-invasive ventilation may be beneficial in dengue patients who are alert, cooperative and haemodynamically stable with or without mild metabolic acidosis.
- Caution should be exercised during intubation as sedatives and mechanical ventilation may worsen haemodynamic instability in dengue patients.
- Intravenous fluid therapy is the mainstay of treatment in decompensated dengue shock syndrome (DSS), however inotrope and vasopressors may be used as a temporary measure.
- In DSS:
  - central venous pressure should not be used to guide fluid therapy
  - subclavian vein cannulation should be avoided
  - real time ultrasonography is recommended for central venous cannulation if it is available and there is expertise

- Thank you for you attention