MANAGEMENT OF CIRCULATORY FAILURE

BACKGROUND AND DEFINITION

- There is no consensus on the definition of circulatory failure or shock in newborns; it can be defined as global tissue hypoxia secondary to an imbalance between systemic oxygen delivery (oxygenation and/or perfusion) and systemic oxygen demand. Its pathology is multifactorial and influenced by internal factors such as poor myocardial contractility and external factors like respiratory failure, PDA, anaemia, sepsis, asphyxia. Treatment for this condition lacks empirical evidence

ASSESSMENT

Bedside Clinical Parameters:

- *Body temperature*
  - A skin shin gap > 2°C can be associated with poor microcirculation as in significant dehydration or sepsis
- *Blood Pressure*
  - Blood Pressure (BP) = Cardiac Output (CO) x Systemic Vascular Resistance (SVR); Cardiac Output (CO) = Stroke Volume (SV) x Heart Rate (HR); Stroke volume depends on preload, contractility and afterload.
  - The gold standard measurement of blood pressure is performed via an invasive arterial catheter; alternatives include non-invasive oscillometric methods such as cuff blood pressure measurements. They have a good correlation with the invasive arterial methods. However, this is dependent on the accurate selection of an appropriate blood pressure cuff size and precise application.
- *Heart Rate*
  - A heart rate **>160 beats per minute** in a can be a **sign of hypovolaemia**.
  - Low specificity for predicting cardiovascular compromise.
- *Capillary Refill Time*
  - The vasomotor tone of surface capillaries in premature and low birth weight infants is not established. Capillary refill time is also dependent on the ambient temperature making it less reliable in situations such as total body cooling in HIE in term babies.
  - Evidence as to whether capillary refill time is reliable in assessing end organ perfusion is therefore conflicting. The sensitivity and specificity of a capillary refill time **>3 seconds** being **predictive of low SVC flow** (biomarker associated with intracranial haemorrhage) is 78% and 63% respectively when **combined with a mean BP of <30mmHg**. .

Invasive Blood pressure thresholds at 3rd percentile according to gestational age (GA)			
GA (weeks)	Systolic (mmHg)	Diastolic (mmHg)	Mean (mmHg)
24	32	15	26
25	34	16	26
26	36	17	27
27	38	17	27
28	40	18	28
29	42	19	28
30	43	20	29
31	45	20	30
32	46	21	30
33	47	22	30
34	48	23	31
35	49	24	32
36	50	25	32

- *Urine Output*
    - An association between low output SVC flow and low urine output in preterm infants has been found, but interpretation is difficult as in the first 24 hours in very premature infants urine output is already very low.
    - Reduction in urine output is often a **late sign** of poor perfusion.

Biochemical Parameters:

- *Lactate*
    - Levels **>4mmol/L in the first 48 hours** and **>3mmol/L thereafter** can indicate significant **tissue hypoxia** in infants at birth, but up to 4.4mmol/L in the first 24-48 hours can be normal.
    - When capillary refill time is **>3 seconds and lactate >4mmol/L** there is a 97% probability of finding **low SVC flow**.
- *Base Excess*
    - A base excess at birth of **-7.3mmol/L** has a sensitivity and specificity of 100% and 71% respectively for **death or cerebral injury**.
    - It correlates well to lactate levels in preterm infants.

Technological parameters including functional echocardiography:

- *Base Excess Oxygen Extraction Rate and Central Venous Saturation*
    - Tissue oxygenation can be estimated by looking at the **oxygen extraction rate (OER=SaO2 - ScvO2)/SaO2; normal=approx. 0.25).** For this we have to know what the **oxygen delivery (DO2= CO x (Hb x SaO2 x PaO2))** and **demand** (**VO2= CO x Hb x (SaO2 - SvO2))** is. This can be estimated with the knowledge of **cardiac output (CO), arterial saturation (SaO2) and central venous saturation (ScvO2 [surrogate for SvO2); normal=approx.65-75%).**
    - A **high OER** indicates a disturbed balance between DO2 and VO2, which could be caused by an increased VO2 and/or by a decreased DO2. The **tissue oxygenation is poor** when there is a **combination of low CO, low ScvO2, high OER and lactate.** There are four fundamental causes for a drop in ScvO2: a drop in CO, a low Hb, low SaO2, increased oxygen consumption without increase in oxygen delivery.

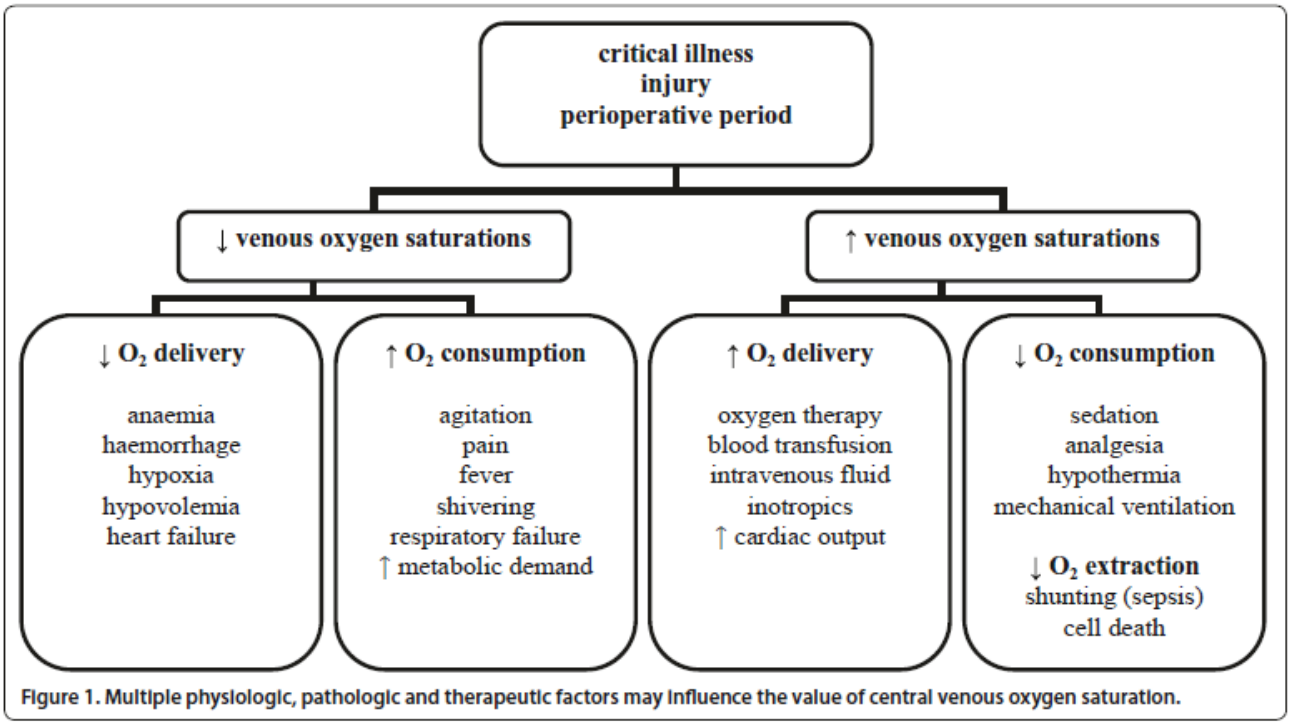


Figure 1. Multiple physiologic, pathologic and therapeutic factors may influence the value of central venous oxygen saturation.

- *CVP*
  - Can be used in sick patient as a guide for volume status - normal level 0-6mmHg; beware of high values due to right sided cardiac failure
- *Near-Infrared Spectroscopy (NIRS)*
  - There is good correlation between SVC and cardiac output.
  - For detailed information on what to measure and how to use the information obtained with NIRS **please see separate guidance on Near-Infrared Spectroscopy.**
- *Functional Echochardiography (fnECHO)*
  - Functional echocardiography (fnECHO) is a useful objective method for assessing the systemic and pulmonary blood flow and myocardial performance in different clinical circumstances such as PPHN, PDA, arterial hypotension, acute hypovolaemia or sepsis. It can be used to add information about the haemodynamic status and provide guidance in the choice of inotropic support and treatment options in different clinical scenarios.
  - For detailed information on what to measure and how to use the information obtained with echocardiography **please see separate guidance (Functional Echocardiography).**
- *aEEG*
  - aEEG (and Cerebral Fractional Oxygen Extraction) becomes abnormal at MBP <23mmHg in very low birthweight infants suggesting that cerebral perfusion might be compromised.

MANAGEMENT

Prevention:

- *Cord Milking or Delayed Cord Clamping*
  - Lead to less transfusions
  - Better SVC flow
  - Less intraventricular haemorrhages
  - Negligible side-effects
- *Permissive Hypotension (**ALL CRITERIA**)*
  - Mean BP in mmHg lower than gestational age in weeks
  - Capillary refill time <4 seconds
  - Lactate <5 mmol/L
  - Base excess <-7 mmol/L
  - Core-shin temperature gap of $<2^0C$
  - Urine output >1ml/kg/hour

Treatment:

- *Volume Replacement*
  - There is no simple objective method to assess fluid-responsiveness. However, goal directed therapies indicate that aggressive fluid resuscitation is beneficial in scenarios of acute large volume loss and fluid re-distribution to third spaces.
  - Current evidence suggests that neither colloids nor crystalloids are superior in terms of successfully treating hypotension, mortality or long-term morbidity except for albumin.
  - Aliquots of 10-20ml/kg boluses of 0.9% saline are effective and safe for raising blood pressure and cardiac output.
  - Where circulatory failure is associated with blood loss it is recommended that packed red cell transfusion of 15-20ml/kg be given and fresh frozen plasma is useful in conditions where hypotension is associated with deranged clotting.
- *Inotropic Therapy*
  - Dopamine:
    - Dopamine is an agonist of multiple receptors including α, β, and dopaminergic receptors (in the newborn predominantly affects peripheral and pulmonary vasculature by α adrenergic effect).
    - 25% of infused dopamine is converted into norepinephrine which may contribute to its cardiovascular effects. Dopaminergic effect on kidneys in newborns is not proven.

- Dopamine is more successful than dobutamine at raising a neonate's blood pressure. There is no difference with regards to short and long term morbidity or mortality.
- Caution when using in PPHN due to possible increase PVR

- Dobutamine:
  - Dobutamine has predominantly β1 and β2 adrenergic activity and (-) enantiomer has α1 adrenergic effects. In the peripheral vasculature α1 and β2 adrenergic activity negate each other. In the heart the activitiy is predominantly β1 adrenergic at low doses. There is minimal impact on the SVR and afterload.
  - It has been shown to moderately increase blood pressure and right ventricular output as well as significantly increase superior vena cava and left ventricular output in response to infusions of 10–20mcg/kg/min.
  - It decreases systemic and pulmonary vascular resistance and increase renal and gut perfusion, so may have a role in neonatal surgical pathology.
- Adrenaline:
  - Adrenaline is believed to act in a similar manner to dopamine in the preterm population; potent non-selective α agonist and also activates both β1 and β2 receptors; activates both β1 and β2 receptors at low doses 0.02-0.3mcg/kg/min and α1 and β1 receptors at high doses 0.3-1.5mcg/kg/min.
  - It increases SV, CO, SVR
  - One trial found adrenaline to be as good a dopamine in increasing a neonate's blood pressure. Adrenaline is more likely to cause issues with hyperglycaemia, myocardial oxygen use, raised lactate levels and arrhythmias.
- Noradrenaline:
  - Norepinephrine is a potent non-selective α agonist with some effect at the β1 receptor.
  - It is released from peripheral nerve endings, it is a potent vasoconstrictor that will also increase myocardial contractility.
  - It has not been studied systematically in the neonatal population. However it is a first line therapy in adult and paediatric vasodilatative shock and has shown less adverse events than Dopamine in the management of adult shock (higher risk of arrhythmias).
- Milrinone:
  - Milrinone is a selective phosphodiesterase-3 (PDE-3) inhibitor that increases intracellular $3^{o}5^{o}$ cyclic adenosine-mono-phosphate (cAMP). Augmentation of

intracellular cAMP leads to positive inotropy, lusitropy, reduction in PVR and reduction in systemic afterload.

- Used predominantly in the maintenance of cardiac output post cardiac surgery and in PPHN; caution when using in PPHN babies with low BP (consider combination with adrenaline or noradrenaline).

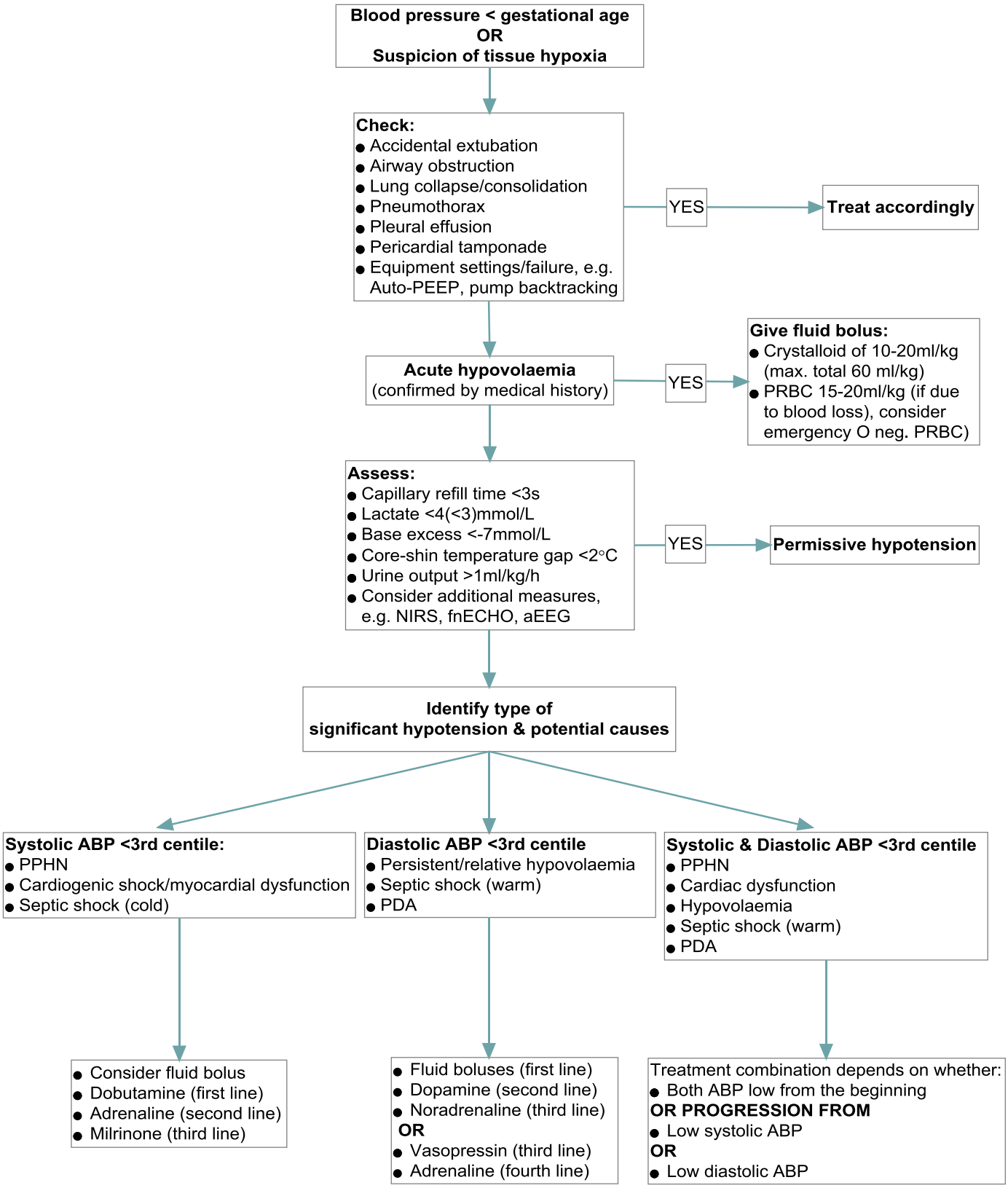
- Vasopressin:
  - Vasopressin is an endogenous neuropeptide which is secreted from the posterior pituitary gland; it increases reabsorption of water (V2 receptors in the collecting duct of the kidney - may cause low Na), vasoconstriction (V1 receptors located in vascular smooth muscle), reduction in heart rate (V1 receptors located in central nervous system), increases adrenal cortisol secretion in presence of ACTH.
  - In severe shock vasopressin has shown to be depleted and the rationale for its use is to increase these depleted levels and promote vasoconstriction (avoid using together with Noradrenaline, if possible).
- Pentoxifylline:

  Pentoxifylline, a xanthine derivative, is a phosphodiesterase inhibitor that suppresses TNF-production by adenyl cyclase activation and increased cellular cyclic adenosine 3',5'-monophosphate concentration. Inhibition of TNF-production negates this response and thereby may improve outcome. It also has vasodilative effects and beneficial effects on endothelial cell function, coagulation and immune system.
- Hydrocortisone:
  - Corticosteroids up-regulate cardiovascular α receptors and addresses a preterm neonate's relative adrenocortical insufficiency. It up-regulates and potentiates receptor pathways for both α agonists and angiotensin II, induces the final enzyme in the conversion of stored norepinephrine to epinephrine, increases circulating catecholamine and inhibits local production of vasodilators such as inducible nitric oxide synthase and prostacyclin.
  - Has primarily been used in vasopressor resistant shock and has been shown to increase systemic blood pressure in preterm infants with refractory hypotension within 2–6h without compromising cardiac function, systemic or end-organ blood flow.
  - Helps improve capillary leak syndrome.
  - Concerns about effect on long term development appear to be unfounded, but has been associated with spontaneous intestinal perforation (especially when combined with NSAID).

Drug	Dose Range (IV)	SV and CO	SVR	PVR
Dopamine	1–20 mcg/kg/min	⇑ + HR	⇑⇑*	⇑⇑⇑
Noradrenaline	0.01–1 mcg/kg/min	⇑ - no effect	⇑⇑⇑	⇓
Vasopressin	0.00003-0.002 units/kg/min	⇓	⇑⇑⇑	⇓
Dobutamine	1–20 mcg/kg/min	⇑⇑	⇓*	⇓ - no effect
Adrenaline	0.01-0.1 mcg/kg/min. 0.1-1 mcg/kg/min	⇑⇑⇑ ⇑⇑	⇓⇓ ⇑⇑⇑	unknown ⇑⇑
Milrinone	0.35-0.75 mcg/kg/min	⇑⇑	⇓⇓	⇓⇓
Pentoxifylline	5mg/kg/h for 6h from 3-6 days	no effect	⇓	
Hydrocortisone	2 mg/kg single dose + 1mg/kg TDS	no effect	⇑	

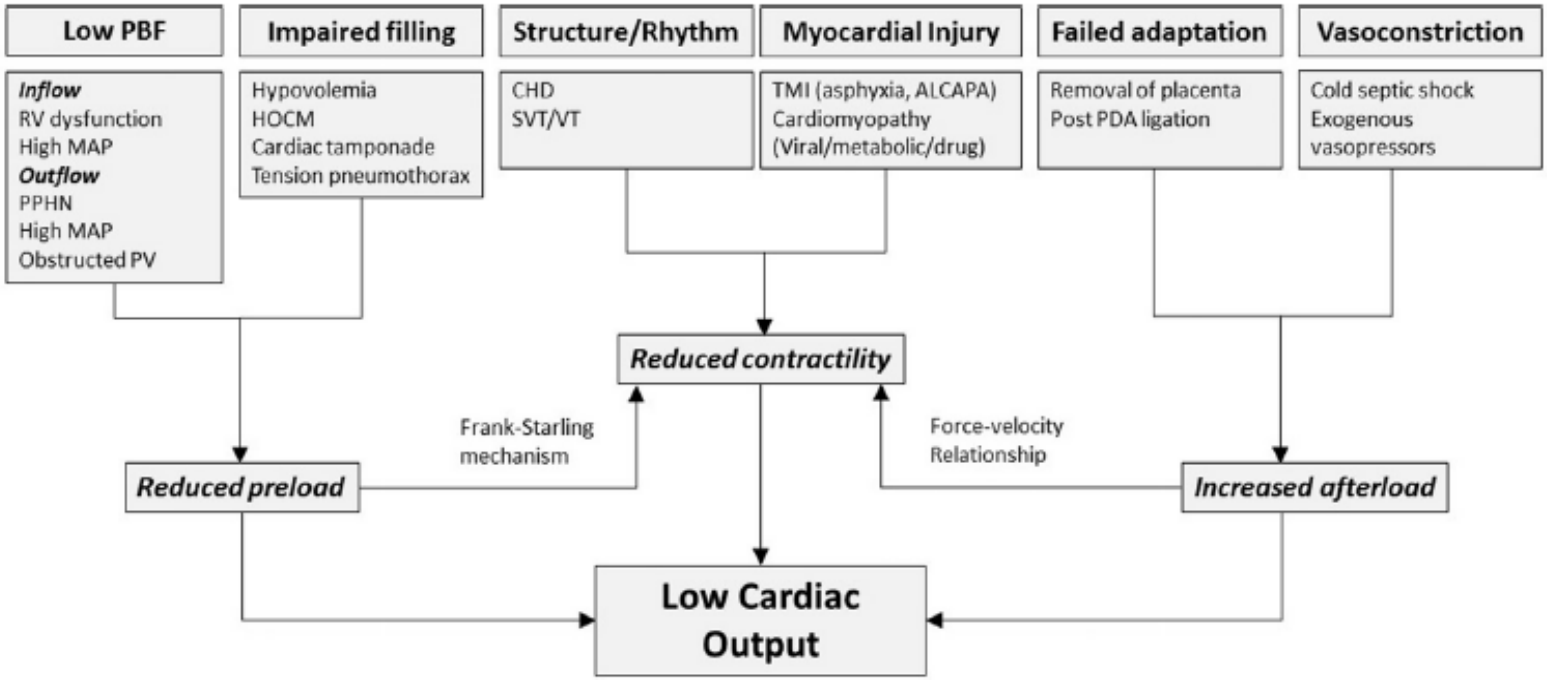
SVR=Systemic Vascular Resistance; PVR= Pulmonary Vascular Resistance; SV=Stroke Volume; CO= Cardiac Output;

*=with increasing dose


Blood pressure < gestational age
OR
Suspicion of tissue hypoxia
Check:
Accidental extubation
Airway obstruction
Lung collapse/consolidation
Pneumothorax
Pleural effusion
Pericardial tamponade
Equipment settings/failure, e.g. Auto-PEEP, pump backtracking
YES
Treat accordingly
Acute hypovolaemia
(confirmed by medical history)
YES
Give fluid bolus:
Crystalloid of 10-20ml/kg (max. total 60 ml/kg)
PRBC 15-20ml/kg (if due to blood loss), consider emergency O neg. PRBC)
Assess:
Capillary refill time <3s
Lactate <4(<3)mmol/L
Base excess <-7mmol/L
Core-shin temperature gap <2°C
Urine output >1ml/kg/h
Consider additional measures, e.g. NIRS, fnECHO, aEEG
YES
Permissive hypotension
Identify type of
significant hypotension & potential causes
Systolic ABP <3rd centile:
PPHN
Cardiogenic shock/myocardial dysfunction
Septic shock (cold)
Diastolic ABP <3rd centile
Persistent/relative hypovolaemia
Septic shock (warm)
PDA
Systolic & Diastolic ABP <3rd centile
PPHN
Cardiac dysfunction
Hypovolaemia
Septic shock (warm)
PDA
Consider fluid bolus
Dobutamine (first line)
Adrenaline (second line)
Milrinone (third line)
Fluid boluses (first line)
Dopamine (second line)
Noradrenaline (third line)
OR
Vasopressin (third line)
Adrenaline (fourth line)
Treatment combination depends on whether:
Both ABP low from the beginning
OR PROGRESSION FROM
Low systolic ABP
OR
Low diastolic ABP

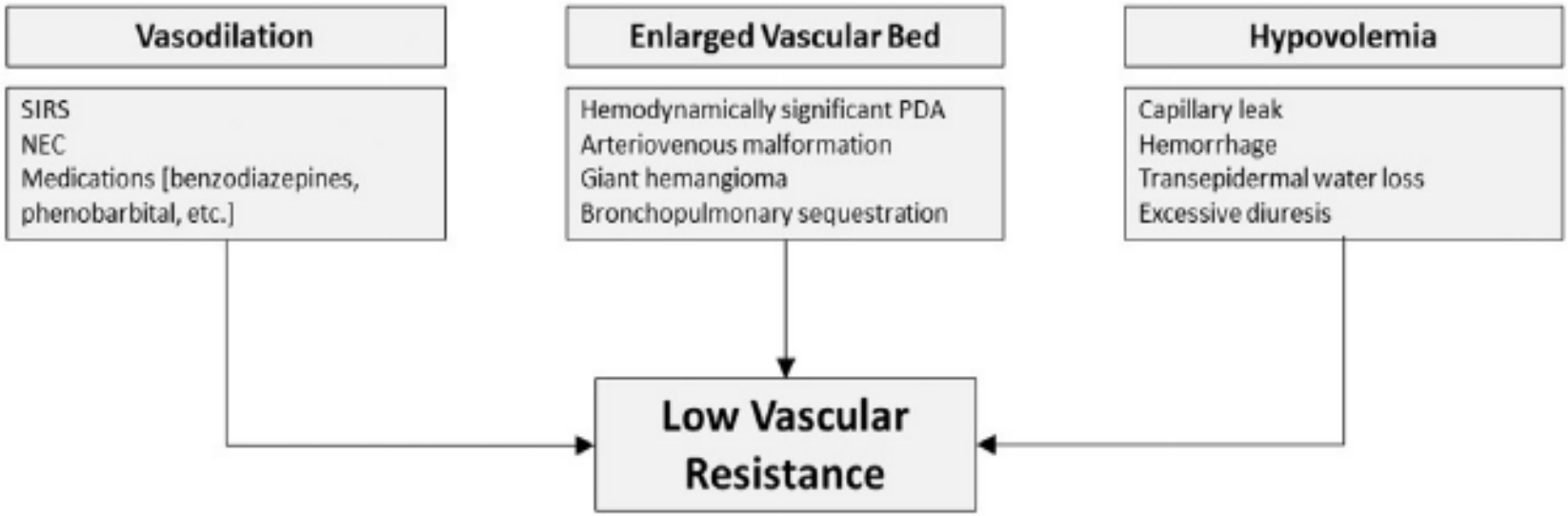
Specific Treatment Considerations:

- ***Systolic Hypotension (ABP <3rd centile), low Cardiac Output***

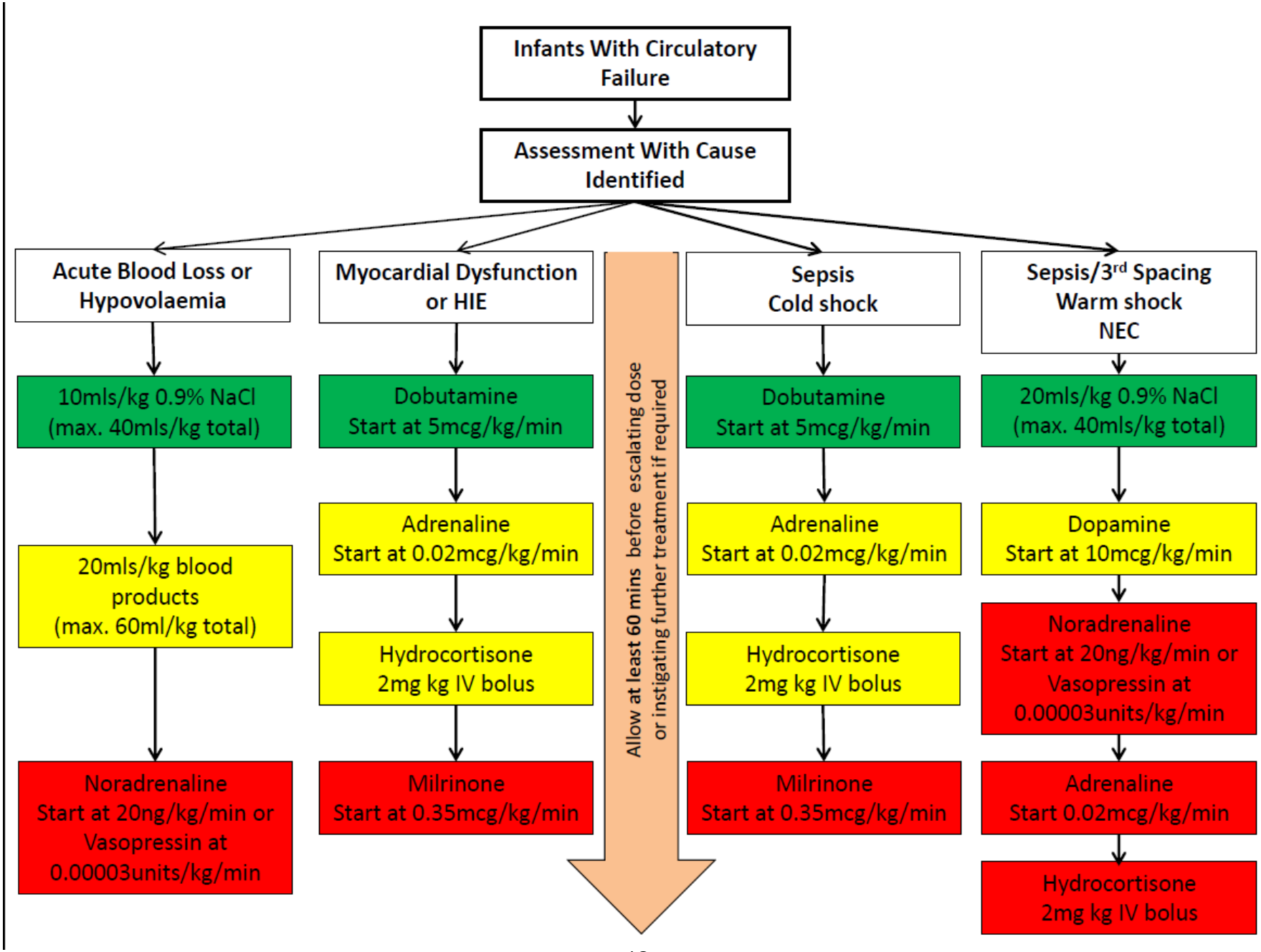


- Rule out non cardiovascular factors contributing to low LV filling (preload) such as pneumothorax, chest effusion, pneumopericard, pericardial effusion, high mean airway pressure.
- Check heart rate for arrhythmias and if possible cardiac function with fnECHO.
- Aim for ScvO2 >70% and SVC flow above 40ml/kg/min.
- Consider a fluid bolus 10-20ml/kg.
- **Start Dobutamine (first line), Adrenaline (second line), Milrinone (third line).**
- **Consider iNO, Prostaglandin, Tolazoline, Mg-Sulfate, Prostacyclin for PPHN**
- Beware that during hypothermia CO reduces by 60-70%

- ***Diastolic Hypotension (ABP <3rd centile), low Systemic Vascular Resistence***



  - Inotropic agents should be avoided in hypovolaemia as these neonates are typically hypercontractile and tachycardia may impair filling and worsen SBF.
  - Aim for ScvO2 >70% and SVC flow above 40ml/kg/min.
  - Treat acute hypovolaemia (absolute/relative) with liberal fluid replacement (total max. 60 ml/kg), either Normal Saline and/or Blood Products as indicated. **Avoid Albumin.**
  - **Give volume (first line), start Dopamine (second line), Noradrenaline or Vasopressin (third line), Adrenaline (fourth line), consider Phenylephrine.**
  - **Consider permissive hypercapnia, shorter IT< 0.35s, higher PEEP >4.5cmH2O, fluid restriction, dobutamine and NSAID in PDA.**
- Consider **Pentoxyfilline in NEC** on day 3-6.
- Consider adding **Hydrocortisone, if catecholamine resistant shock** is present (no response despite using two inotropic agents).


Infants With Circulatory Failure
Assessment With Cause Identified
Acute Blood Loss or Hypovolaemia
10mls/kg 0.9% NaCl (max. 40mls/kg total)
20mls/kg blood products (max. 60ml/kg total)
Noradrenaline Start at 20ng/kg/min or Vasopressin at 0.00003units/kg/min
Myocardial Dysfunction or HIE
Dobutamine Start at 5mcg/kg/min
Adrenaline Start at 0.02mcg/kg/min
Hydrocortisone 2mg kg IV bolus
Milrinone Start at 0.35mcg/kg/min
Allow at least 60 mins before escalating dose or instigating further treatment if required
Sepsis Cold shock
Dobutamine Start at 5mcg/kg/min
Adrenaline Start at 0.02mcg/kg/min
Hydrocortisone 2mg kg IV bolus
Milrinone Start at 0.35mcg/kg/min
Sepsis/3rd Spacing Warm shock NEC
20mls/kg 0.9% NaCl (max. 40mls/kg total)
Dopamine Start at 10mcg/kg/min
Noradrenaline Start at 20ng/kg/min or Vasopressin at 0.00003units/kg/min
Adrenaline Start 0.02mcg/kg/min
Hydrocortisone 2mg kg IV bolus