Yorkshire and Humber Neonatal ODN (South) Clinical Guideline

Title: Hypotension

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Review date:

This clinical guideline has been developed to ensure appropriate evidence based standards of care throughout the Yorkshire & Humber Neonatal ODN (South). The appropriate use and interpretation of this guideline in providing clinical care remains the responsibility of the individual clinician. If there is any doubt discuss with a senior colleague.

Best practice recommendations represent widely used evidence-based practice and high quality standards that all Neonatal Units across the Network should implement. Subsequent suggested recommendations may be put into practice in local units. However, alternative appropriate local guidelines may also exist.

A. Summary page(s)

1. Aim of guideline

This guideline aims to provide a framework for the treatment of clinically significant hypotension and/or hypoperfusion in the neonatal period.

2. Summary flow chart or quick reference guide
(PRINTABLE as Appendix 1)

The below check-prompt box appears repeatedly throughout the guideline to support frequent reassessment, reconsideration of cause and to confirm that something is not being missed:

****C-THEME****

Cardiac: Large PDA, Congenital heart disease
Thoracic: Pneumothorax, high mean airway pressure
Hypovolaemia: Internal/external haemorrhage, losses e.g. NEC
Equipment: Pumps delivering, lines intact/in place, no leaks
Monitoring: Lines zeroed, adequate trace, exclude hyperthermia
Electrolyte abnormalities: K^+ Ca^{2+} PO_4^{3-} Mg^{2+}

Confirm the baby is hypotensive and has features of hypoperfusion

If visible or strongly suspected BLOOD LOSS – give blood

↓ **Inform Neonatal registrar/Tier 2 practitioner**

Initial trial of fluid resuscitation → give 10mL/kg normal saline

(or **red cells** in the case of haemorrhage) over 15-30 minutes

↓ **Continue monitoring and reassess within 20-30 minutes**

If still hypotensive ***and hypovolaemic*** (e.g. severe sepsis, NEC) consider a further 10ml/kg fluid resuscitation. This is rarely the case.

(In the case of visible or suspected **haemorrhage** → 10ml/kg red cells)

↓ **Continue monitoring and reassess within 20-30 minutes**

If not in place, attempt Central Venous Access promptly

If not in place, reconsider need for Invasive Arterial Monitoring

↓

If still hypotensive, reassess – are we **missing something**

C-THEME**

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Electrolyte abnormalities: K^+ Ca^{2+} PO_4^{3-} Mg^{2+}

↓

Start **DOPAmine** at 5 to 10 micrograms/kg/min
If known problematic PDA, or PPHN, or only peripheral IV access consider DOBUTamine 1st line

Increase 5 micrograms/kg/min every 15-30 min (Max: 20 micrograms/kg/min)
Once >10 micrograms/kg/min consider commencing 2nd inotrope

Commence 2nd inotrope if 1st >10microgram/kg/min ↓ **Inform Experienced Neonatal practitioner/Consultant**

If still hypotensive, confirm – are we **missing something**

↓

Trigger for transfer - DConsider discussion & referral for tertiary care

↓

Start **DOBUTamine** at 5 to 10 micrograms/kg/min
If already on DOBUTamine >15micrograms/kg/min commence DOPAmine

Increase 5 micrograms/kg/min every 15-30 min (Max: 20 micrograms/kg/min

↓

If still hypotensive → Echocardiogram (if at all possible)
If poor contractility and not already; commence DOBUTamine

Consider further investigations and urgent tertiary referral

↓ **Seek further Tertiary Neonatal Advice**

Further therapy options are at the discretion of the attending neonatal consultant

At all times consider possible causes of hypotension: C-THEME**

Speed of interventions and escalation may vary dependent upon the condition and response of the infant. Always consider referral for tertiary intensive care, especially once more than 1 inotrope commenced and/or if >20ml/kg volume replacement is considered necessary.

B. Full guideline

1. Background

Hypotension is a common neonatal problem; more than half ELBW infants will have at least one significant hypotensive episode[1].

Hypotension is associated with adverse outcomes including increased mortality, intraventricular haemorrhage, adverse neurodevelopmental outcomes and increased incidence of hearing loss[1–4]. Despite this there is no clear evidence that treating isolated hypotension in the first 24 hours of life improves outcome and there is some suggestion treatment may actually worsen outcome[5,6].

There is no universal definition of 'normal' blood pressure for neonates, nor an agreed threshold for hypotension. A frequently used definition of hypotension is that of a mean blood pressure below the gestational age in weeks[7]. An alternative is a value below the 5th or 10th centile for a birth weight and gestational age reference range, but these are drawn from small numbers of babies, primarily before widespread use of antenatal steroids. Blood pressure is a poor proxy for more important systemic blood flow[8,9].

Some evidence supports combined clinical parameters as a useful adjunct to assessment e.g. prolonged CRT and elevated lactate, which will be detailed later in this guideline.

Prevention

At risk groups:

- ➔ VLBW infants; Increased risk **without:**
  - Antenatal steroids
  - Delayed cord clamping
- ➔ HIE
- ➔ Congenital Heart Disease
- ➔ Sepsis
- ➔ NEC

Identification of those most at risk of hypotension can support prevention and early identification of evolving problems. Delayed cord clamping has been shown to result in less hypotension and fewer vasoactive treatments[10–12].

2. Clinical assessment & equipment

Clinically significant hypotension

Defined as: Blood pressure inadequate to meet tissue oxygenation demand; clearly difficult to measure. There is no international consensus on diagnosis of shock in the newborn[13]. The majority of neonatal units in the UK use a gestational age equivalent blood pressure threshold to define hypotension in the 1st 72 hours of life[14].

In a well baby, i.e. passing urine, good perfusion, easy to ventilate, not acidotic, normal lactate, not septic; taking acceptable mean blood pressure around the gestational age is appropriate[5,14,15]. In the first 48-72 hours of life Table 1 offers estimates of acceptable mean arterial blood pressures (MABP), though from small numbers of infants[16]. Beyond 72 hours most preterm infants maintain MABP above 30mmHg[1718].

Birth Weight (grams)	10th centile for MABP (mmHg)
500-750	26
750-1000	28
1000-1250	29
1250-1500	30
2000-2999	32
3000-3999	36
4000	42

Table 1: 10th centile mean arterial blood pressures (MABP) according to birth weight, in the first 72 hours of life

If blood pressure **is lower than these criteria**, it may warrant treatment, but we should always evaluate clinical evidence of hypoperfusion. There remains minimal evidence as to whether treatment improves (or worsens) outcomes[17,19].

There is no validated scoring system for neonatal perfusion, it remains subjective. Serial examinations and assessments are key; although single capillary refill time (CRT), lactate or other measures are poorly predictive of hypoperfusion, trends over serial assessments have higher predictive value[17,20]. There will be a time lag in any rise or fall in serum lactate which should be factored in to assessment. Where clinical assessment of **perfusion, serum lactate and UOP are normal**, the infant is highly unlikely to require treatment at that time.

Clinical Assessment

This is challenging in the presence of hypothermia – bear this in mind and make attempts to warm the baby to an appropriate degree. Assessment should include the following features - a comprehensive combined approach is most likely to select those babies in need of treatment:

Feature	**Indicative of hypoperfusion**
General observation	Pallor, peripherally cold / ”shut down”
Central (femoral) pulses	Presence, tachycardia, low volume
Toe - core temperature gap	>2°C
Central Capillary refill time	Delayed ≥4s *or rising trend*
Acid base balance	Raised lactate >4 *or rising trend*
Urine output (UOP)	<1ml/kg/hr *or falling trend*
Saturation & oxygenation	Rising oxygen requirement / oxygenation index
Cardiac function	Echocardiographic evidence of poor contractility or low SVC flow

In a critically sick baby with **sepsis or persistent pulmonary hypertension** (PPHN) blood pressure required for effective tissue oxygenation may be significantly higher than common arbitrary thresholds for treatment. Table 2 describes average (invasive) MABP and the upper confidence limits, again based upon birthweight. In critically sick infants, term or preterm, we should **aim for the average MABP**, potentially higher under experienced tertiary guidance[16,18,21].

Birth Weight (grams)	**Average (MABP) mmHg**	**95% upper confidence limit (mmHg)**
500-750	35	44
750-1000	38	47
1000-1250	39	48
1250-1500	40	49
2000-2999	41	50
3000-3999	47	55
4000	52	62

Table 2: Average mean arterial blood pressures (MABP) according to birth weight, in the first 72 hours of life and upper confidence limits of these values

Physiology

Both hypotension, **and its treatment** independent of MABP values, are associated with worse outcomes than normotension; a real diagnostic and therapeutic challenge[1,5,13]. Many preterm babies are hypotensive by commonly used definitions and more than half will have significant episodes of hypotension during their neonatal admission[19,22].

Early hypotension is often secondary to low systemic vascular resistance associated with abnormal vasoregulation e.g. large PDA. Low cardiac output may also relate to myocardial dysfunction, but **rarely due to hypovolaemia**. Key to optimising outcomes, but difficult to clinically evaluate is delivery of oxygenated blood to the tissues (Tissue oxygen delivery; DO_2).

$$DO_2 = [(1.39 \times Hb \times SaO_2) + (0.03 \times PaO_2)] \times \text{Cardiac Output}$$

Blood pressure depends upon cardiac output (CO) and stroke volume (SV), with CO in turn dependent on heart rate, preload, afterload and contractility. The MABP therefore reflects vasoconstriction/dilatation, relative filling of the vasculature and blood flow generated by relative myocardial function. Tissue oxygen delivery will be impaired by significant vasoconstriction and can be improved by vasodilatation, particularly where myocardial function is poor e.g. post hypoxia ischaemia. Reduced circulating Hb also reduces tissue oxygen delivery but circulating volume alone has little relationship with systolic BP[23].

Maintaining cerebral blood flow (CBF) and oxygenation is a priority concern. CBF varies widely with pCO_2 fluctuation and Hb concentration; it is particularly important to avoid low pCO_2 when systemic blood flow is compromised. **Hypotension and hypocarbia is a worrying combination**.

Monitoring

Invasive monitoring of BP is the most accurate modality; non-invasive cuff measurements (NIBP) may overestimate particularly in the first 24 hours of life[21,24,25]. There is however good correlation between invasively measured and NIBP in the **majority** of infants, independent of gestational age or weight[25].

In normotensive but sick, or newly admitted infants NIBP should be checked and documented hourly as a minimum. In hypotensive infants or those receiving vasoactive treatments, NIBP monitoring should be escalated to at least every 15 minutes.

Estimation of BP cuff size by quick visual impression is inaccurate[26]. Four sizes of cuff are commonly available (Table 3).

Cuff number (Size)	Appropriate limb size
1	3-6 cm
2	4-8 cm

3	6-11 cm
4	7-17 cm

Table 3: Blood Pressure cuff sizes (1-4) and corresponding limb **(always preferably upper)** sizes at which they most closely estimate invasive or "true" blood pressure readings.

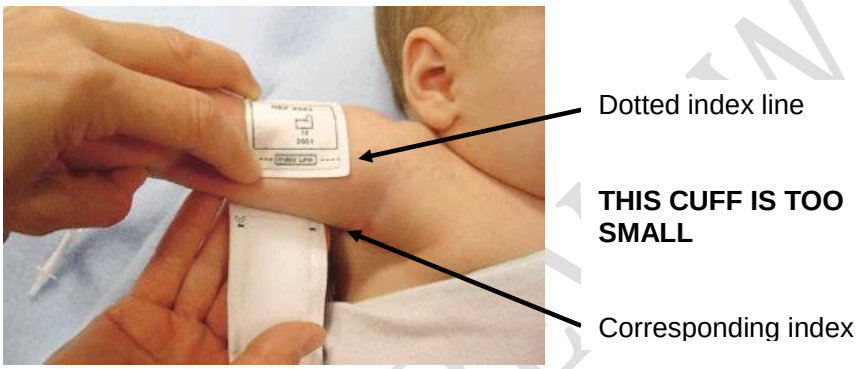

Image 1: Sizing BP cuffs for non-invasive monitoring. The cuff shown is *too small* as the index points will not overlap when wrapped around (Source: GE Healthcare Technologies)

Cuffs have **visible index lines** to illustrate appropriate sizing (Image 1). The dotted index line applied over the limb first should fall within (overlap) the index markings on the opposing part of the cuff. The cuff shown in Image 1 is too small and more likely to overestimate the MABP.

**** Confirmation & Trouble shooting ****

To confirm an invasive BP reading is accurate:

- Check the scale on the patient monitor is appropriate and/or "optimized" automatically for the waveform
- The trace is of sufficient quality and not "damped" with an infeasibly small difference between systolic and diastolic
- The transducer has been calibrated and positioned correctly. The transducer should be **zeroed in its resting position – aligned with the mid axillary line at the level of the heart.**

We are all human - Ensure that more than 1 person has **independently** checked fluids and lines to the baby:

- The syringe pump is working, and volumes match expectations
- All clamps on lines are open as intended
- Correct hourly amounts of fluids/infusions are reaching the baby
- Lines appear intact, and no leaks can be identified

Diagnosis: C-THEME

Continuing through the C-THEME check-prompt will help to establish what may be causing or contributing to the hypotension:

C-THEME**

Cardiac: Large PDA, Congenital heart disease
Thoracic: Pneumothorax, high mean airway pressure
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In extreme preterm infants causes may include a large PDA, pulmonary haemorrhage or IVH, though vascular dysregulation is the most likely cause. In any newly born infant **is there a history of significant APH we were not aware of? If bleeding or blood loss – give blood.**

High intrathoracic pressure from a large pneumothorax should **always** be excluded and effects of high mean airway pressure secondary to ventilation considered. Hypovolaemia is rare - external haemorrhage may be obvious, but severe sepsis or NEC leading to relative hypovolaemia can be challenging to detect. Significant vasodilatation (brisk CRT, flushed appearance) may occur with gram negative sepsis. Double check the temperature - iatrogenic hyperthermia may lead to significant tachycardia and hypotension in a previously stable baby.

If a specific underlying, or likely contributory cause is identified, this should be addressed promptly – seek tertiary neonatal advice at any stage.

3. Treatment

Is treatment required?

There should be a thorough assessment of the baby's clinical haemodynamic status (see clinical assessment table earlier) leading to the decision to treat, documented at the earliest convenience. Initial fluid resuscitation of 10ml/kg normal saline (or **packed red cells in the presence of blood loss**/anaemia) is reasonable - over 15 to 30 minutes depending on severity of hypoperfusion.

Ensure the neonatal registrar/Tier 2 practitioner is informed of the baby's status if not already aware.

Consider - **Do you have or will you need central venous access?**
Do you have or will you need invasive arterial monitoring?

FLUID RESUSCITATION

10ml/kg volume may suffice to "normalise" MABP with no further intervention. RARELY 20ml/kg volume may be given. Normal saline is fluid of choice - there is no evidence supporting routine use of colloid in neonates[15,27,28].

Many contributors to neonatal hypotension can be worsened by additional circulating volume. **There is no evidence that further fluid volumes are of benefit;** some data support worse outcomes including chronic lung disease, symptomatic arterial ducts and death[1,27,28].
Bolus volumes >20 mL/kg are reserved either for acute life threatening haemorrhage (**Packed Red Cells in 5-10ml/kg aliquots**) or at discretion of the neonatal consultant on call.

In the presence of coagulopathy or extensive bruising **Fresh Frozen Plasma 10ml/kg** may be appropriate 1st line.

The baby should be reassessed within 20-30 minutes of each intervention and this should be documented at earliest convenience. If still hypotensive after 10ml/kg resuscitation, with evidence of hypoperfusion, an experienced Neonatal Practitioner/Consultant should be informed.

If central venous access is not present, attempt long line insertion **ONCE** 10ml/kg volume resuscitation has been given and/or peripheral dobutamine has been commenced (see DOBUTamine below). Make every attempt to keep the baby warm.

If still hypotensive, are we missing something (See **C-THEME** prompt list).

a) 1st line vasopressors

Start DOPAmine at 5-10 micrograms/kg/min (depending on the degree of hypotension). Remember to purge the lines/giving sets as close to the baby as possible to ensure delivery in a timely fashion. If not invasively monitored, cuff BP monitoring should be set to 5 minute cycle, preferably on an upper limb, with a well-fitting cuff.

ACCESS

** If central access has not been established the risk of an extravasation injury from DOPAmine is high. **DOBUTamine conversely acts as a vasodilator so may be started peripherally** if essential and is 1st line in this instance**

If the most experienced team members available have been unable to secure adequate vascular access, in extremis after discussion with the tertiary neonatal consultant it *may* be feasible to give DOBUTamine via the UAC (umbilical arterial catheter).

Increase the first vasopressor by 5 micrograms/kg/min every 15-30 minutes (maximum 20 micrograms/kg/min). Observe the rate of rise of the blood pressure AND changes in other clinical parameters rather than MABP alone. Avoid rapid changes or swings in blood pressure as a priority. Unless a bespoke weaning plan has been determined, once MABP has been maintained **3-5 mmHg above the 10th centile** for that birth weight or gestation threshold for at least 30 minutes, wean the infusion rate by between 1 and 5 micrograms/kg/min depending on the current dose and response.

DOBUTamine may be 1st choice for term infants with/suspected to have PPHN, or in the case of sepsis with "cold shock" (shut down, weak pulses, cold peripheries).

Comment [CS1]: I think a sentence about contacting tertiary centre for advice should go in here

b) Commencing 2nd line vasopressors

Consider starting DOBUTamine 2nd line if DOPAmine has not effectively treated the hypotension at 10micrograms/kg/min AND you are confident the infusion has reached the baby. If still hypotensive, confirm – are we missing something (See **C-THEME** prompt list).

Consider discussion with the Tertiary Neonatal Consultant if this has not already taken place.

When starting DOBUTamine, commence 5-10micrograms/kg/min (depending on the degree of hypotension). Remember to purge the lines/giving sets as close to the baby as possible to ensure delivery in a timely fashion. If not invasively monitored, cuff BP monitoring should be set to 5 minute cycle, preferably on an upper limb, with a well-fitting cuff.

Increase by 5micrograms/kg/min every 15-30minutes (maximum 20 micrograms/kg/min). Observe the rate of rise of the blood pressure and changes in other clinical parameters rather than MABP alone. Avoid rapid changes or swings in blood pressure as a priority. Unless a bespoke weaning plan has been determined, once MABP has been maintained **3-5 mmHg above the 10th centile** for that birth weight or gestation threshold for at least 30 minutes, wean support by reducing infusion rate by between 1 and 5 micrograms/kg/min depending on the current dose and response.

DOPAMINE AND DOBUTAMINE

Both drugs result in widely varying plasma levels between individuals for any given dose[29,30]. Dopamine, a noradrenaline precursor, is generally more effective than dobutamine for short term treatment of neonatal hypotension[31]. This is mediated via vasoconstriction with some positive inotropic and chronotropic effects at intermediate doses of 5-10micrograms/kg/min.

Doses >10 micrograms/kg/min increase vasoconstriction – BOTH systemic vascular resistance and pulmonary vascular resistance increase which may be detrimental in some babies e.g. PPHN. In most infants **Dopamine as a single vasopressor >10micrograms/kg/min is likely to reduce cardiac output** and not improve oxygen delivery[16].

Dobutamine is a synthetic catecholamine increasing cardiac output, vasodilation and reducing systemic vascular resistance. If myocardial contractility is poor e.g. Hypoxic Ischaemic infants, dobutamine may be 1st line and may improve systemic blood flow and tissue oxygenation, but with **little measurable change in blood pressure**. Regular clinical reassessment may reveal improved UOP, CRT or reduction in lactate.

Dopamine and dobutamine can both suppress TSH, T4 and prolactin levels[30].

If still hypotensive consider whether significant inotrope induced tachycardia (HR >200) could be impairing cardiac filling, reducing stroke volume. **Perform an echocardiogram** if at all possible/not already performed.

If still hypotensive, confirm – are we missing something and **DOUBLE CHECK lines and pumps before escalating treatment.** Discuss with the Tertiary Neonatal Consultant if this has not already taken place.

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c) **<u>Further treatment steps are at the discretion of the on call neonatal consultant</u>**

Hydrocortisone may be added for inotrope refractory hypotension[32–34]. Whether or not the baby has recently, or is, receiving ibuprofen may determine this. The baby should be reassessed within 30 minutes of each intervention and this should be documented at the earliest convenience. If the Consultant recommends hydrocortisone:

- Start at 2.5 mg/kg IV as initial dose
- If feasible send pre-treatment cortisol level (Lithium-Heparin sample)
- Regular doses of 2.5 mg/kg 6-8 hourly can be prescribed dependent upon severity of condition and hypotension as per the Neonatal Formulary

HYDROCORTISONE

Evidence supports use of steroids to acutely raise blood pressure in premature neonates with inotrope refractory hypotension, and in improving weaning from inotrope treatments[2,6,32–34]. **Concurrent use of Hydrocortisone with ibuprofen should be avoided** due to concerns for intestinal perforation.

Therapeutic effect is likely a combination of inhibiting catecholamine enzyme metabolism leading to higher plasma levels, and inhibition of prostacyclins limiting pathological vasodilation in septic states. The mechanism is primarily upregulation of gene expression **occurring over HOURS** rather than minutes. There are few short term effects of this brief treatment regime but hyperglycaemia is more common than among untreated infants. There is no data as to whether steroids or vasoactive infusions should be weaned first.

If still hypotensive, confirm – are we are **missing something**:

C-THEME**

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Management In extremis

Where significant hypotension has not responded to **both** DOPAmine and DOBUTamine at doses equal to/higher than 15micrograms/kg/min, and where hydrocortisone is either contraindicated or has been commenced, an adrenaline infusion, or rarely other drug treatments, may be indicated.

Among extremely preterm infants, particularly less than 26 weeks gestation, these further "4th line" measures and treatments are extremely unlikely to

improve the outcome, but may be offered at the discretion of the tertiary neonatal consultant.

Start Adrenaline at **0.05 – 0.1micrograms/kg/min**.

Observe the rate of rise of the blood pressure and changes in other clinical parameters rather than the blood pressure number alone. Increase by 0.05micrograms/kg/min every 15-20 minutes cautiously. There is data to support a **maximum therapeutic dose of 0.5micrograms/kg/min** with an excess in side effects without therapeutic gain beyond that dose[35] [6,13].

Aim to steadily reduce DOPAmine to 5 micrograms/kg/min as the excess delivery of catecholamine precursors is unlikely to be of benefit and may cause excess side effects. Titrate DOBUTamine as low a dose as tolerated, referencing your target blood pressure and clinical parameters. Wean adrenaline by reducing infusion rate by between 0.05 to 0.1 micrograms/kg/min, depending on the blood pressure's response.

ADRENALINE

This is a potent inotrope and chronotrope: in low doses promotes vasodilatation, in high doses is a potent vasoconstrictor. It may improve cerebral blood flow compared to dopamine in neonates, though significant and problematic rise in lactate and blood glucose may occur with escalating adrenaline dose[2–4,15]. No beneficial effects have been demonstrated in neonates at doses in excess of 0.25micrograms/kg/min and excess adverse effects reported frequently at higher doses.

4. Medications not in routine use locally:

NORADRENALINE

This is a potently vasoconstricting catecholamine with minimal inotropic effect. It is rarely used, we have little experience in its titration and effects. It may be useful in profoundly vasodilated states e.g. Gram negative Sepsis, and has a positive effect on coronary blood flow secondary to increased diastolic BP. There is currently no evidence of either benefit or harm in neonates.

When recommended doses are of the order of 0.1 – 0.5 micrograms/kg/**min**.

MILRINONE

This phosphodiesterase III inhibitor is used widely in adults though far less so in neonatal practice. It is a positive inotrope, improving contractility, and vasodilates both peripheral and pulmonary vasculature, reducing afterload. Small amounts of data available show no general benefit in treating systemic hypotension in neonates[36,37]. In a study specifically referencing neonates with severe PPHN there is a more suggestive trend shown towards improved blood pressure[38,39] [32]. Its use would be a consultant only decision.

When rarely recommended doses are of the order 30-60 micrograms/kg/**hour (**equivalent to 0.5 – 1 microgram/kg/**min)**

VASOPRESSIN AND ITS ANALOGUES

The neuropeptide hormone vasopressin (ADH) and its analogues have been used to treat refractory hypotension in neonates though meta-analysis suggests insufficient evidence for routine practice[40,41]. It may rarely be useful in profound sepsis such as refractory gram negative septic shock. Significant side effects include marked hyponatraemia which should be anticipated.

When rarely recommended doses are of the order of 0.01 – 0.04 units/kg/**hour**.

5. Suggested Audit Points

At risk infants should have appropriate blood pressure monitoring: continuous intra-arterial monitoring, or hourly non-invasive blood pressures with an appropriately sized cuff.

All infants receiving treatment for hypotension should have a documented clinical assessment of their compromised haemodynamic status leading to treatment.

All infants receiving vasoactive treatments should have evidence of frequent reassessments during that time.

6. Practice recommendations/grades of evidence:

A Use of Dopamine likely to be more effective than volume resuscitation in increasing blood pressure

A Hydrocortisone as an effective option in increasing neonatal blood pressure

B Invasive blood pressure likely to be most accurate method of monitoring neonatal blood pressure

B Fluid resuscitation up to 10ml/kg followed by Dopamine as the first line inotrope as standard therapies

C Target blood pressure should be based upon gestational age in weeks, or an appropriate reference table in the first 48-72 hours

C Blood pressure should not be used as the only marker of systemic perfusion and basis for cardiovascular therapies

7. References

1. Fanaroff JM, Wilson-Costello DE, Newman NS, Montpetite MM, Fanaroff A a. Treated hypotension is associated with neonatal morbidity and hearing loss in extremely low birth weight infants. *Pediatrics*. 2006;117(4):1131-1135. doi:10.1542/peds.2005-1230.
2. Pellicer A, Valverde E, Dolores Elorza M, et al. Cardiovascular Support for Low Birth Weight Infants and Cerebral Hemodynamics: A Randomized, Blinded, Clinical Trial. doi:10.1542/peds.2004-1396.
3. Diagnosis and management of hypotension in neonates REVIEW.
4. Goldstein RF, Thompson RJ, Oehler JM, Brazy JE. Influence of acidosis, hypoxemia, and hypotension on neurodevelopmental outcome in very low birth weight infants. *Pediatrics*. 1995;95(2):238-243. http://www.ncbi.nlm.nih.gov/pubmed/7530835.
5. Batton B, Li L, Newman NS, et al. Use of antihypotensive therapies in extremely preterm infants. *Pediatrics*. 2013;131(6):e1865-73. doi:10.1542/peds.2012-2779.
6. Batton B, Li L, Newman NS, et al. Early blood pressure, antihypotensive therapy and outcomes at 18-22 months' corrected age in extremely preterm infants. *Arch Dis Child Fetal Neonatal Ed*. 2016;101(3):F201-F206. doi:10.1136/archdischild-2015-308899.
7. Dempsey EM, Barrington KJ. Diagnostic criteria and therapeutic interventions for the hypotensive very low birth weight infant. *J Perinatol*. 2006;26(August):677-681. doi:10.1038/sj.jp.7211579.
8. Dempsey EM, Al Hazzani F, Barrington KJ. Permissive hypotension in the extremely low birthweight infant with signs of good perfusion. *Arch Dis Child Fetal Neonatal Ed*. 2009;94(4). doi:10.1136/adc.2007.124263.
9. Cayabyab R, McLean CW, Seri I. Definition of hypotension and assessment of hemodynamics in the preterm neonate. *J Perinatol*. 2009;29:S58-S62. doi:10.1038/jp.2009.29.
10. Rabe H, Reynolds G, Diaz-Rossello J. A systematic review and meta-analysis of a brief delay in clamping the umbilical cord of preterm infants. *Neonatology*. 2008;93(2):138-144. doi:10.1159/000108764.
11. Rabe H, Diaz-Rossello JL, Duley L, Dowswell T. Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes. In: *Cochrane Database of Systematic Reviews*. ; 2012. doi:10.1002/14651858.CD003248.pub3.
12. McDonald SJ, Middleton P, Dowswell T, Morris PS. Cochrane in context: Effect of timing of umbilical cord clamping in term infants on maternal and neonatal outcomes. *Evidence-Based Child Heal A Cochrane Rev J*. 2014;9(2):398-400. doi:10.1002/ebch.1965.
13. Laughon M, Bose C, Allred E, et al. Factors associated with treatment for hypotension in extremely low gestational age newborns during the first postnatal week. *Pediatrics*. 2007;119(2):273-280. doi:10.1542/peds.2006-1138.
14. Bhojani S, Banerjee J, Rahman MM. Management of neonatal hypotension - a national questionnaire survey. *Infant*. 2010;6(5):152-154.
15. Seri I, Evans J. Controversies in the diagnosis and management of hypotension in the newborn infant. *Curr Opin Pediatr*. 2001;13(2):116-123. doi:10.1097/00008480-200104000-00005.
16. Watkins AM, West CR, Cooke RW. Blood pressure and cerebral haemorrhage and ischaemia in very low birthweight infants. *Early Hum Dev*. 1989;19(2):103-110. http://www.ncbi.nlm.nih.gov/pubmed/2737101.
17. Farrugia R, Rojas H, Rabe H. Diagnosis and management of hypotension in neonates. *Future Cardiol*. 2013;9(5):669-679. doi:10.2217/fca.13.59.
18. Cunningham S, Symon AG, Elton RA, Zhu C, McIntosh N. Intra-arterial blood pressure reference ranges, death and morbidity in very low birthweight infants during the first seven days of life. *Early Hum Dev*. 1999;56(2-3):151-165. doi:10.1016/S0378-3782(99)00038-9.
19. Batton B, Li L, Newman NS, et al. Early blood pressure, anti-hypotensive therapy and outcomes at 18 to 22 month corrected age in extremely preterm infants.
20. Moran M, Miletin J, Pichova K, Dempsey EM. Cerebral tissue oxygenation index and superior vena cava blood flow in the very low birth weight infant. *Acta Paediatr*. 2009;98(1):43-46. doi:10.1111/j.1651-2227.2008.01006.x.
21. Gevers M, Van Genderingen HR, Lafeber HN, Hack WWM. Accuracy of oscillometric blood pressure measurement in critically ill neonates with reference to the arterial pressure wave shape. *Intensive Care Med*. 1996;22(3):242-248. doi:10.1007/BF01712244.
22. Saigal S, Streiner D, Boyle M, Pinelli J, Paneth N. Transition of Extremely Low-Birth-

Weight. *Jama*. 2006;295(6):667-675.
23. Bauer K, Linderkamp O, Versmold HT. Systolic blood pressure and blood volume in preterm infants. *Arch Dis Child*. 1993;69(5 Spec No):521-522. doi:10.1136/adc.69.5_Spec_No.521.
24. Nuntnarumit P, Yang W, Bada-Ellzey HS. Blood pressure measurements in the newborn. *Clin Perinatol*. 1999;26(4):981-96, x.
25. Meyer S, Sander J, Gräber S, Gottschling S, Gortner L. Agreement of invasive versus non-invasive blood pressure in preterm neonates is not dependent on birth weight or gestational age. *J Paediatr Child Health*. 2010;46(5):249-254. doi:10.1111/j.1440-1754.2009.01679.x.
26. Devinck A, Keukelier H, De Savoye I, Desmet L, Smets K. Neonatal blood pressure monitoring: Visual assessment is an unreliable method for selecting cuff sizes. *Acta Paediatr Int J Paediatr*. 2013;102(10):961-964. doi:10.1111/apa.12328.
27. Greenough A, Cheeseman P, Kavvadia V, Dimitriou G, Morton M. Colloid infusion in the perinatal period and abnormal neurodevelopmental outcome in very low birth weight infants. *Eur J Pediatr*. 2002;161(6):319-323. doi:10.1007/s00431-002-0950-8.
28. Osborn DA, Evans NJ. Early volume expansion versus inotrope for prevention of morbidity and mortality in very preterm infants. In: *Cochrane Database of Systematic Reviews*. ; 2001. doi:10.1002/14651858.CD002056.
29. Subhedar N V, Shaw NJ. Dopamine versus dobutamine for hypotensive preterm infants. In: *Cochrane Database of Systematic Reviews*. ; 2003. doi:10.1002/14651858.CD001242.
30. Filippi L, Pezzati M, Poggi C, Rossi S, Cecchi A, Santoro C. Dopamine versus dobutamine in very low birthweight infants: Endocrine effects. *Arch Dis Child Fetal Neonatal Ed*. 2007;92(5). doi:10.1136/adc.2006.098566.
31. Sassano-Higgins S, Friedlich P, Seri I. A meta-analysis of dopamine use in hypotensive preterm infants: Blood pressure and cerebral hemodynamics. *J Perinatol*. 2011;31(10):647-655. doi:10.1038/jp.2011.2.
32. Seri I. Hydrocortisone is effective in treatment of vasopressor-resistant hypotension in very low birth weight neonates. *J Pediatr*. 2006;149(3):422-423. doi:10.1016/j.jpeds.2006.06.012.
33. Hochwald O, Palegra G, Osiovich H. Adding hydrocortisone as 1st line of inotropic treatment for hypotension in very low birth weight infants. *Indian J Pediatr*. 2014;81(8):808-810. doi:10.1007/s12098-013-1151-3.
34. Bourchier D, Weston PJ. Randomised trial of dopamine compared with hydrocortisone for the treatment of hypotensive very low birthweight infants. *Arch Dis Child Fetal Neonatal Ed*. 1997;76(3):F174-8. doi:10.1136/fn.76.3.F174.
35. Fanaroff JM, Fanaroff AA. Blood pressure disorders in the neonate: Hypotension and hypertension. In: *Neonatology: A Practical Approach to Neonatal Diseases*. ; 2012:585-592. doi:10.1007/978-88-470-1405-3_78.
36. Paradisis M, Evans N, Kluckow M, Osborn D, McLachlan AJ. Pilot study of milrinone for low systemic blood flow in very preterm infants. *J Pediatr*. 2006;148(3):306-313. doi:10.1016/j.jpeds.2005.11.030.
37. Paradisis M, Evans N, Kluckow M, Osborn D. Randomized trial of milrinone versus placebo for prevention of low systemic blood flow in very preterm infants. *J Pediatr*. 2009;154(2):189-195. doi:10.1016/j.jpeds.2008.07.059.
38. McNamara PJ, Laique F, Muang-In S, Whyte HE. Milrinone improves oxygenation in neonates with severe persistent pulmonary hypertension of the newborn. *J Crit Care*. 2006;21(2):217-222. doi:10.1016/j.jcrc.2006.01.001.
39. Chang AC, Atz AM, Wernovsky G, Burke RP, Wessel DL. Milrinone: Systemic and pulmonary hemodynamic effects in neonates after cardiac surgery. *Crit Care Med*. 1995;23(11):1907-1914. doi:10.1097/00003246-199511000-00018.
40. Biban P, Gaffuri M. Vasopressin and terlipressin in neonates and children with refractory septic shock. *Curr Drug Metab*. 2013;14:186-192. doi:10.2174/138920013804870655.
41. Leone M, Martin C. Role of terlipressin in the treatment of infants and neonates with catecholamine-resistant septic shock. *Best Pract Res Clin Anaesthesiol*. 2008;22(2):323-333. doi:10.1016/j.bpa.2008.02.008.

Appendix 1: Printable Quick Reference Algorithm
See also guideline text for special cases and refined guidance

Confirm the baby is hypotensive and has features of hypoperfusion

If visible or strongly suspected BLOOD LOSS – give blood

↓ **Inform Neonatal registrar/Tier 2 practitioner**

Initial trial of fluid resuscitation → give 10mL/kg normal saline

(or **red cells** in the case of haemorrhage) over 15-30 minutes

↓ **Continue monitoring and reassess within 20-30 minutes**

If still hypotensive ***and hypovolaemic*** (e.g. severe sepsis, NEC) consider a further 10ml/kg fluid resuscitation

(In the case of visible or suspected **haemorrhage** → 10ml/kg red cells)

↓ **Continue monitoring and reassess within 20-30 minutes**

If not in place, attempt Central Venous Access promptly

If not in place, reconsider need for Invasive Arterial Monitoring

↓

If still hypotensive, reassess – are we **missing something**

C-THEME**
Cardiac: Large PDA, Congenital heart disease
Thoracic: Pneumothorax, high mean airway pressure
Hypovolaemia: Internal/external haemorrhage, losses e.g. NEC
Equipment: Pumps delivering, lines intact/in place, no leaks
Monitoring: Lines zeroed, adequate trace, exclude hyperthermia
Electrolyte abnormalities: K^+ Ca^{2+} PO_4^{3-} Mg^{2+}

↓

Start **DOPAmine** at 5 to 10 micrograms/kg/min
If – known problematic PDA, or PPHN, or only peripheral IV access consider DOBUTamine 1st line

Increase 5 micrograms/kg/min every 15-30 min (Max: 20 micrograms/kg/min)
Once >10 micrograms/kg/min consider commencing 2nd inotrope

Commence 2nd inotrope if 1st >10microgram/kg/min ↓ **Inform Experienced Neonatal practitioner/Consultant**

If still hypotensive, confirm – are we **missing something**

↓

Trigger for transfer - Consider discussion & referral for tertiary care

↓

Start **DOBUTamine** at 5 to 10 micrograms/kg/min
If already on DOBUTamine >15micrograms/kg/min commence DOPAmine

Increase 5 micrograms/kg/min every 15-30 min (Max: 20 micrograms/kg/min

↓

If still hypotensive → Echocardiogram (if at all possible)
If poor contractility and not already; commence DOBUTamine

Consider further investigations and urgent tertiary referral

↓ **Seek Tertiary Neonatal Advice**

Further therapy options are at the discretion of the attending neonatal consultant

At all times consider possible causes of hypotension: C-THEME**

Speed of interventions and escalation may vary dependent upon the condition and response of the infant. Always consider referral for tertiary intensive care, especially once more than 1 inotrope commenced and/or if >20ml/kg volume replacement is considered necessary.

Appendix 2: Neonatal Blood Pressure Reference Ranges

MABP – Mean arterial Blood Pressure

Birth Weight	10th percentile for MABP (mmHg)	Average MABP (mmHg)
500-750 grams	26	35
750-1000 grams	28	38
1000-1250 grams	29	39
1250-1500 grams	30	40
2000-2999 grams	32	41
3000-3999 grams	36	47
4000 grams	42	52

Birth Weight	Average MABP (mmHg)	95% upper confidence limit (mmHg)
500-750 grams	35	44
750-1000 grams	38	47
1000-1250 grams	39	48
1250-1500 grams	40	49
2000-2999 grams	41	50
3000-3999 grams	47	55
4000 grams	52	62