Yorkshire and Humber Neonatal ODN Clinical Guideline

Title: Management of Cardiovascular Instability in the Neonate (Hypotension)

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This clinical guideline has been developed to ensure appropriate evidence-based standards of care throughout the Yorkshire and Humber Neonatal ODN. 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.

Guideline

This is a guideline for the suggested management of neonates with cardiovascular instability. An isolated finding of hypotension in a newborn may be acceptable. Hypotension in conjunction with other signs of cardiovascular compromise however is abnormal and requires investigation and management. It is therefore imperative that prompt clinical examination accompanies the finding of hypotension, to aid decision making for ongoing management.

This does not cover PPHN, there is a separate guideline for that.

If at any point you are unsure how to manage the patient, you should get help. This may be from the consultant on call.

Management pathway

The flow chart below summarises common neonatal conditions that can cause hypotension and cardiovascular insufficiency. It highlights the pathophysiology behind them, and therefore suggested management plans including choice of vasoactive drugs. Further information is below and in the appendices. Please note, there is little 'quality' evidence in neonates regarding vasoactive drugs. Treatment for hypotension does not improve neurodevelopmental outcomes.

History
APH, no DCC, abruption
Chorioamnionitis
Prematurity
HIE
PPHN
Large PDA
Sepsis/NEC
Fluid/blood loss

Clinical Assessment
CRT
Peripheral pulses
Lactate
Metabolic acidosis
Oligurea
Tachycardia (>160)

Targeted ECHO (If available)
Filling
Ventricular function
Rule out congenital heart disease

Check equipment: is the BP reading accurate?

Hypotension

Systolic BP < 3rd Centile

Decreased LV stroke volume
Decreased contractility
Increased afterload

Possible causes
Transitional circulation (high SVR)
Mechanical ventilation (decreased venous return)
Early sepsis (cold shock) normal diastolic
PPHN (separate guideline)
Cardiogenic shock: asphyxia or myocardial disease
Early pneumothorax or pericardial effusion

Treatment options
Treat the cause e.g sepsis, pneumophorax, ventilation etc
Fluid (improve filling)
Dobutamine (improve contractility)
Adrenaline
Milrinone (d/w NICU or Embrace)

Diastolic BP < 3rd centile

Decreased systemic vascular resistance
Hypovolemia
Significant PDA*

Possible causes
Significant PDA*
Hypovolemia
Severe pulmonary haemorrhage
Warm shock eg sepsis, NEC
Donor in twin to twin transfusion

Treatment options
Volume replacement
Blood if blood loss
Dopamine (vascular tone)
Hydrocortisone (if severe)
Noradrenaline (if severe)
(Vasopressin under specialist guidance)

Systolic and Diastolic BP < 3rd

Advanced disease
Adrenal insufficiency
LV failure

Possible causes
Worsening cardiogenic shock
Severe pneumothorax or cardiac tamponade
PPHN (worsening)
Severe sepsis
Severe hypovolemia
Significant PDA with heart failure*

Treatment options
Fluid
Dopamine or Dobutamine
Adrenaline (if not already on)
Hydrocortisone
ECHO (if possible)

Other management
Drain pneumothorax/ tamponade
Review ventilation requirements if high MAP
Review for over-sedation
Review for adequate management of sepsis

BP 3rd Centiles

Corrected gestation	Systolic	Diastolic	Mean
22	30	13	25
23	32	14	25
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

CO = HR x SV
BP = CO x SVR

**symptomatic PDA management may require specialist guidance*

Adapted from Hypotension coursework by Dr Afif El-Khuffash, May 2018

Clinical Triggers & Assessment

Hypotension can be an acceptable finding in neonates, and *treating hypotension alone is strongly advised against*. A finding of hypotension should lead to a thorough assessment of the baby, before empirically starting any treatments. The assessment should both look for a cause of hypotension and for signs of poor tissue perfusion. N.B. low blood pressure readings could be due to equipment error - make sure arterial lines have been zeroed and the sensor is at the level of the heart. For non-invasive readings check the BP cuff is the correct size (see appendices below).

Signs of poor perfusion (These assessments individually can trigger an overall assessment):

- Decreased urine output
- Metabolic acidosis/high lactate/high negative base excess
- Prolonged capillary refill time
- Tachycardia
- Pale/floppy/listless
- Other nursing concerns

If there are additional concerns about poor tissue perfusion alongside hypotension you should initiate hypotension management (as well as treating the underlying cause). Invasive arterial blood pressure monitoring is highly advised: cuff readings can be inaccurate. Invasive blood pressure monitoring allows for accurate readings and assessment of response to treatments.

Causes of hypotension/Cardiovascular instability

1. Pathology

- Low pre-load (sepsis, NEC, blood loss eg large IVH, APH, fetomaternal haemorrhage, cord tear, subgaleal haemorrhage)
- Impaired contractility (extreme prematurity, HIE)
- Low systemic vascular resistance (sepsis, NEC)
- Critical congenital heart disease

2. Other causes of cardiovascular instability

- High mean airway pressure (eg HFOV)
- Pneumothorax
- Pericardial tamponade
- Electrolyte abnormalities (K^{+}, Ca^{2+}, $PO4^{3-}$, Mg^{2+})
- Temperature control issues
- Drug reactions eg anaphylaxis, or over-sedation (eg with morphine or midazolam)
- Inadequate source control of infection eg abscesses and collections
- Equipment errors: check pumps are working and check lines for any leaks to ensure all infusions are correctly running and reaching the patient
- Monitoring issues (lines zeroed, trace - is this a true low blood pressure?)

Normal Blood Pressure values

There is limited evidence for 'normal' blood pressures in neonates. For the purpose of this guideline it has been agreed to accept a 'normal' mean blood pressure for a baby as greater than the 3rd centile (see flowchart). There is no evidence based consensus for the blood pressure values in babies who are more than a few days old. There is a steep rise in blood pressure in the first 72 hours of life, so it would be appropriate to increase blood pressure thresholds for babies after this time. There are further blood pressure charts in Appendix 2 which may help in these circumstances, please note from the papers that they were taken, the minimum values are the 5th centile. Additionally babies who are particularly growth restricted may benefit from 'weight-based' blood pressure values, which are also shown in appendix 2.

*Please note that the blood pressure values for babies born at 22 and 23 weeks gestation have been estimated from a graph plotted from the blood pressures observed in other gestational ages.

Mean arterial blood pressure is:

(Systolic blood pressure + 2x Diastolic blood pressure)/3

Therefore, in pre-term infants who may have a significant PDA and therefore a low diastolic blood pressure, their overall mean blood pressure may be low, but their systolic blood pressure and systemic perfusion may be totally adequate and not require treatment. Additionally, pre-term infants are not able to auto regulate their cerebral blood flow well. Low blood pressure and swings in blood pressure in preterm infants is associated with IVH and brain injury. However treating hypotension in these infants has not been shown to improve neurodevelopmental outcomes.

Fluid

Hypovolemia is an uncommon cause of cardiovascular instability in neonates. Certain conditions eg NEC or sepsis may trigger a SIRS response, causing blood vessels to leak fluid in to the extravascular compartment. Fluid loss can be 'hidden' eg in to the bowel with NEC. There may be a large bleed eg acute severe IVH or subgaleal haemorrhage, and therefore blood replacement is preferable (may need to be O negative).

Judicious use of fluid is advised and if needed then should be given over 30 minutes especially in preterm infants.

Re- assessment and escalation

Babies with cardiovascular instability require regular clinical review and reassessment as they may need escalation of treatment. Observations should be performed every 15 minutes. It is preferential to have inotropes in 20 ml syringes rather than 50 ml syringes as this leads to less errors with consistent drug delivery. Inotropes run at very low volumes and most pumps will run infusions at a rate as low as 0.1ml/hr. For some cardiovascular drugs the 'starting' dose may be lower than the pump can run at, in which case you should start at the lowest possible dose that the pump will run at.

Babies may need multiple vasoactive drugs. As a general rule additional treatment may be required when on:

- Dopamine or Dobutamine at 15 micrograms/kg/minute
- Adrenaline or noradrenaline at 0.2 micrograms/kg/minute

If you have concerns you should escalate these to the senior clinician/consultant on call.

Network Formulary

https://www.networks.nhs.uk/groups/yorkshire-humber-neonatal-odn/documents/folders/11/

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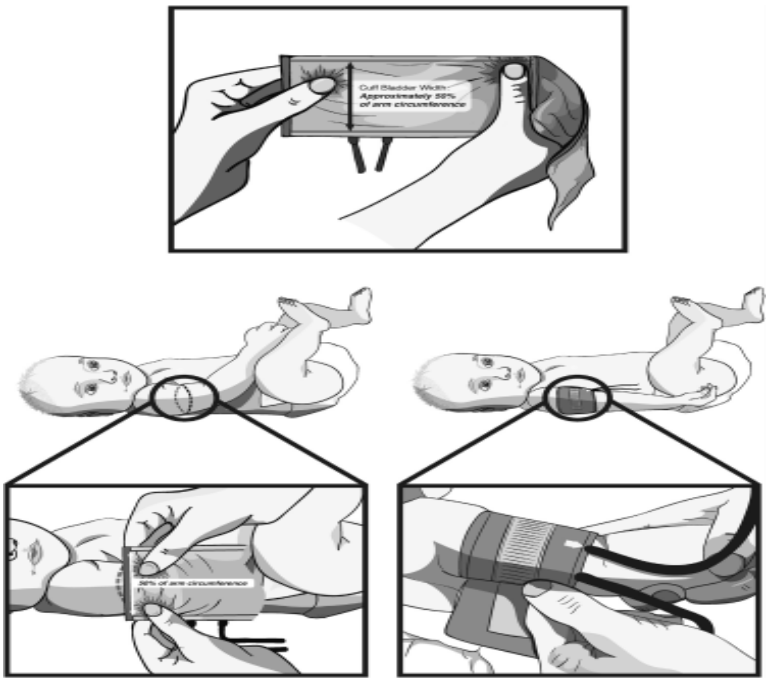
Appendices

Appendix 1: Measuring Blood Pressure

The Gold standard is intra-arterial monitoring. However, Cuff BP is mostly used. There is a degree of inaccuracy with cuff blood pressures. Readings are most accurate in the right arm. It is vital that the cuff is fitted adequately. The width of the cuff should be half of the arm circumference. See below:



Adapted from Method of Blood Pressure Measurement in Neonates and Infants: A Systematic Review and Analysis, Dionne JM et al, The Journal of Pediatrics, Vol 221, June 2020, p23 – 31

Appendix 2: Further Blood Pressure Charts

Table 2. Normal blood pressure values in newborns by adjusted gestational week

Gestational week	Systolic			Diastolic			Mean (Calculated)		
	Maximum	Median	Minimum	Maximum	Median	Minimum	Maximum	Median	Minimum
24	68	49	33	46	29	14	53	36	20
25	69	51	36	47	30	15	54	37	22
26	70	52	38	48	31	17	55	38	24
27	71	54	40	49	32	18	56	39	25
28	72	55	41	50	33	19	57	40	26
29	73	56	42	51	34	20	58	41	27
30	78	59	43	52	35	21	60	43	28
31	78	61	46	53	36	22	61	44	30
32	80	62	48	54	37	23	63	45	31
33	81	63	50	55	38	24	64	46	33
34	83	66	51	56	39	25	65	48	34
35	84	69	52	57	40	26	66	50	35
36	87	71	55	58	41	27	68	51	36
37	89	72	57	59	42	28	69	52	38
38	90	75	59	60	43	29	70	54	39
39	91	78	60	60	44	30	70	55	40
40	92	80	61	61	44	30	71	56	40
41	93	81	62	62	46	31	72	58	41
42	95	82	63	63	47	32	74	59	42
43	97	83	65	64	48	33	75	60	44
44	98	86	66	65	49	34	76	61	45
45	100	88	69	66	50	35	77	63	46
46	102	89	71	66	51	36	78	64	48

The highest and lowest values indicate 95% confidence interval

Zubrow AB, Hulman S, Kushner H, Falkner B. Determinants of blood pressure in infants admitted to neonatal intensive care units: a prospective multicenter study. J Perinatol. 1995

Blood Pressure by gestational age at birth

Blood Pressure by weight

Weight for 300 and 400grams calculated from plotting the other values

Weight (grams)	Mean Blood Pressure (5th centile)
300	15
400	16
500	20
600	21
700	22
800	23
900	24
1000	26
1100	27
1200	28
1300	29
1400	30
1500	31

Adapted from:
Lee J, Rajadurai VS, Tan KW. Blood pressure standards for very low birthweight infants during the first day of life. Archives of Disease in Childhood-Fetal and Neonatal Edition. 1999 Nov 1;81(3):F168-70.

Blood pressure by corrected gestational age (10th centile)

Mean Blood Pressure (mm Hg) in Neonates With Gestational Ages 23 Weeks To Term*

	POSTNATAL AGE (HOURS)						
GESTATIONAL AGE (WEEKS)	0	12	24	36	48	60	72
23–26	24	25	26	27	28	29	30
27–32	30	31	32	33	34	35	36
33–36	36	37	38	39	40	41	42
‡37	43	44	45	46	47	48	49

*Blood pressures are recorded during the first 72 hours after birth. Results are adapted from Nuntnarumit P, Yang W, Bada-Ellzey HS. Blood pressure measurements in the newborn. Clin Perinatol. 1999;26(4):981–996. (6)

Taken from 'Hypotension in Neonates' guideline, Ashford and St Peter's Hospitals, Dr Ranjith Kulappura.

Appendix 3: Vasoactive Drugs and method of action

1. Dopamine

Agonist of alpha, beta and dopaminergic receptors[2]. Is a pre-cursor of noradrenaline[3]. Increases cardiac output and systemic vascular resistance[2]. Variable effects on the neonate[2]. Animal models suggest at lower doses (5-10 mcg/k/min) there is more of an increase in myocardial contractility whereas at higher doses (>10 mcg/kg/min) there is more systemic vasoconstriction[2,4]. With more vasopressor effect you risk affecting end organ perfusion[4]. There is no evidence that renal blood flow is increased at low doses[2]. Pulmonary vascular resistance is increased more than the systemic resistance[2].

At high doses there is a risk of arrhythmia[2]. There is also an associated reduction in TSH, prolactin and growth hormone levels[3]. Dopamine may have negative effects of the cerebrovascular auto-regulation in very preterm infants, and neurodevelopmental outcomes at 3 years may be worse in neonates treated with dopamine rather than dobutamine[4].

Dose 5-20 mcg/kg/min.

2. Adrenaline

Non-selective alpha and beta receptor agonist[2]. Increases stroke volume, cardiac output and systemic vascular resistance, potentially more than dopamine[2]. Increases pulmonary vascular resistance in proportion with systemic vascular resistance (unlike dopamine)[2]. Low doses (0.02-0.1mcg/kg/min) increase contractility and heart rate with modest vasodilatation in systemic and pulmonary circulations [3,4]. Increases cerebral blood flow by increasing systemic BP[2]. High dose (>0.5 mcg/kg/min) causes excessive vasoconstriction, and disorganised energy use [3,4].

Adrenaline use increases lactate and glucose levels, and can cause a significant tachycardia [2,3,4]. Longterm use of adrenaline may result in myocardial ischemia due to adrenaline mediated coronary vessel vasoconstriction[2].

Dose 0.02-1 mcg/kg/min.

3. Dobutamine

Has alpha 1, beta 1 and beta 2 adrenergic activity[1]. Increases stroke volume, heart rate and contractility [2,3,4]. Increases stroke volume in a dose dependent fashion[2]. The peripheral effects of alpha 1 and beta 2 receptors vary and may 'cancel each other out' so that there is minimal effect on systemic BP and afterload[2]. Often however it causes moderate vasodilatation [3,4]. Compared to dopamine, dopamine causes a greater increase in mean BP, whereas dobutamine increases left and right ventricular output[4]. Probably improves SVC flow (surrogate marker of cerebral blood flow) in preterm infants with low blood pressure, when compared to those receiving dopamine and placebo[2,4].

Takes 10-60 minutes to see inotropic effects[2]. Shortly after starting the infusion tachycardia can be seen[2]. Tachycardia can potentially lead to increased myocardial oxygen consumption[3].

Dose 5-20 mcg/kg/min.

4. Milrinone

Selective phosphodiesterase 3 inhibitor (PDE- 3)[2]. Increases intracellular cAMP, which causes a decrease in intracellular calcium and therefore relaxation of smooth muscle[2]. PDE-3 receptors are present in systemic and pulmonary vasculature[2]. Has been shown to improve both right and left ventricular function in term neonates with various conditions[2]. For preterm infants there is evidence to support its use prophylactically in PDA ligation, and with PPHN[2]. Vasodilates the systemic and pulmonary vascular bed[2,3]. Positive inotropic and lusitropic properties[2]. Can reduce systemic blood pressure therefore use with caution in the setting of hypotension (may need an adjunct)[2].

Half-life is estimated in term infants to be 4 hours and likely longer in prematurity, organ dysfunction, HIE etc[2,3]. Clearance depends on renal function, gestation and postnatal age[3].

Often a loading dose of 50mcg/kg is given followed by continuous infusion[4]. Tachycardia and hypotension have been described as side effects therefore caution with babies who have a low blood pressure[4].

Dose 250-750 ng/kg/min.

5. Noradrenaline

Non-selective alpha agonist with some beta 1 activity[2]. Predominantly vascular and myocardial alpha 1 activity, mild to moderate beta 1 and minimal beta 2 activity[3]. Mainly peripheral vasoconstriction with some positive inotropy[2]. Vasodilatory effect on pulmonary vascular tone in babies with high pulmonary vascular tone [2,3]. In high doses excessive tachycardia can increase myocardial oxygen demand and worsen ventricular function[3].

Dose 0.02-1 mcg/kg/min.

6. Vasopressin

Main effects are on plasma osmolality, circulating blood volume and vascular tone[2]. Potent vasoconstriction via V1 receptors in smooth muscle[2,4]. V2 receptors cause vasodilatation on cerebral and renal arterioles and on the collecting duct in the kidneys increasing aquaporin channels increasing water reabsorption with some sodium[2,4]. V3 receptors in the CNS can reduce heart rate[2]. Vasopressin can have negative inotropic effects therefore use with caution in neonates with risk of impaired myocardial performance[2]. Weakly vasoconstrictive or even vasodilatory effect of pulmonary, coronary and cerebral circulation especially at low doses[2,3].

Some neonatal data supports its use in catecholamine resistant shock[2].

Short half-life of 5-15 minutes[4]. Effects last for 30-60 minutes[4]. One study comparing dopamine to vasopressin in very preterm neonates showed similar increases in BP but less tachycardia in the vasopressin group[4].

Can cause hyponatraemia, transient thrombocytopenia and hepatic necrosis[3].
Dose is 0.00001 to 0.002 unit/kg/min[3].

7. Hydrocortisone

Increases systemic blood pressure within 2-6 hours in preterm infants with refractory hypotension[2]. Causes alpha agonist receptor and angiotensin 2 receptor up-regulation[2]. Increases calcium availability in vascular smooth muscle and inhibits local production of vasodilators[2]. May increase adrenergic receptor expression[2]. Increases circulating catecholamines: induces the final enzyme in the conversion of stored noradrenaline to adrenaline in the adrenal glands and release in to circulation[2]. Relative adrenal insufficiency is well documented in patients with critical illness and neonates, especially those born preterm[2]. May also reduce capillary leak in sepsis[2]. Doesn't affect cardiac function, systemic or end organ blood flow[2].

Dose 2.5mg/kg 4-6 hourly.

Appendix 4: Evidence for vasoactive drugs in neonates

Intervention	Systematic review and meta-analyses	Clinical trials	Impact on practice
Volume expansion	• Osborn 2004 – Cochrane review. <32 weeks of gestation. Insufficient evidence to comment on whether volume expansion is beneficial for preterm infants with cardiovascular instability	• Kooi 2013 – observational study on preterm infants with signs of poor perfusion found no improvement of cerebral perfusion following a fluid bolus.	Insufficient evidence on efficacy No significant effects (negative or positive) on mortality or neurodisability
Dopamine	• Subhedar 2003 – Cochrane review: dopamine more effective than dobutamine in short term treatment of hypotension. Absence of data confirming long term benefits and safety • Sassano-Higgins 2011: dopamine more effective than dobutamine, colloid or hydrocortisone alone in increasing BP. Not associated with greater incidence of adverse effects	• Osborn 2007. <30w GA **dopamine versus dobutamine**. No difference detected in combined rates of death or disability • Dempsey 2014. The HIP study – terminated • Rios 2015. ELBW <24 hours of age. **Dopamine versus vasopressin**. Vasopressin is safe to use	Dopamine is more effective in increasing the blood pressure in preterm infants. No evidence that it is superior to other treatments in long term oucomes
Dobutamine	As above	• Bravo 2015. <31 weeks, first 96 ours of life. **Dobutamine versus placebo**. Dobutamine improved VC flow and short term clinical outcomes such as brain perfusion	Dobutamine superior to placebo in increasing SVC flow Compared to dopamine – as above
Hydrocortisone	• Ibrahim 2011 – Cochrane review. <37 weeks. Hydrocortisone was compared to placebo, volume expansion and dopamine. Hydrocortisone can be as effective as dopamine as a first line agent. Effective for refractory hypotension.	• Hochwald 2013. <30 weeks first 48 hours of life. **Hydrocortisone versus dopamine** – post volume (11 patients). No more adverse effects than dopamine	Hydrocortisone is effective in treatment of hypotension as first line or add-on therapy

Intervention	Systematic review and meta-analyses	Clinical trials	Impact on practice
Adrenaline	• Paradisis 2004. Insufficient evidence for the use in hypotensive preterm infants	• Pellicer 2005. <32 weeks first 24 hours of life. **Adrenaline versus dopamine**. The tow drugs are equally effective in increasing BP • In 2006 Valverde et al studied infants <32 weeks of gestation first 2 hours of life comparing **dopamine versus adrenaline**. Adrenaline is as effective as dopamine in raising BP. No differences were detected in medium term morbidity • Pellicer 2009. LBW <24 hours of life. **Adrenaline versus dopamine.** No significant differences in abnormal neurological status, developmental delay or combined outcome of death OR CP OR neurodevelopmental delay	Evidence just from RCTs Adrenaline can be as effective as dopamine with no significant differences in long term outcomes
Milrinone	▪ No SRs or MAs	• Paradisis 2009. <30w first 6 hours of life. Milrinone versus placebo for prophylaxis. No significant differences in prevention of low BP. Safe to use	Limited evidence
Vasopressin	• Shivanna 2013. No incomplete or ongoing trials identified	• Bidegain 2010. ELBW infants with refractory hypotension. Vasopressin increased BP. No evidence on long term effects or mortality • Rios 2015. Pilot study <30 weeks of gestation first 24 hours of life. Vasopressin is safe to use in these infants. No evidence on long term effects	Limited evidence showing effects in raising BP No evidence on long term effects