East of England Neonatal ODN
(Hosted by Cambridge University Hospitals)

Clinical Guideline: Management of Hypotension in the Neonate

Author: David Hopkins, Consultant Peterborough City Hospital

2017 Consulting Author: Katharine McDevitt, Consultant Peterborough City Hospital

For use in: Eastern Neonatal Units
Guidance specific to the care of neonatal patients

Used by: Medical Staff

Key Words: Blood pressure, hypotension, prematurity, dopamine, dobutamine, adrenaline, hydrocortisone

Date of Ratification: December 2021

Review due: December 2024

Registration No: NEO-ODN-2021-6

Approved by:

Neonatal Clinical Oversight Group	
Clinical Lead Mark Dyke	**Matthew James**

Audit Standards:

1. All infants meeting the BAPM intensive care category, should have an admission blood pressure (BP) recorded.
2. Infants being treated for hypotension should have 15 minutely recordings of BP if not invasively monitored.
3. Infants should not receive a bolus of saline unless there is documented evidence to support a clinical suspicion of hypovolaemia.

1. Introduction:

Neonatal hypotension is usually the result of abnormal peripheral vasoregulation or myocardial dysfunction. Rarely is it due to hypovolaemia.

The definition of hypotension in neonates varies, the threshold for intervention and benefits of intervention are not well established to this day[1,2,22]. Hypotension has been associated with an increased likelihood of adverse outcomes[3].

2. Definition of Hypotension:

Blood pressure (BP) is used as a marker of systemic perfusion however BP correlates only weakly with cardiac output.

2.1 Preterm neonates

Various definitions of hypotension are used in preterm infants including:

- a mean arterial blood pressure (MAP) below the 10th centile for gestation/birth weight and postnatal age[4] (see Appendices 1 and 2)
- a MAP below an infant's gestation age in weeks.

More recently severe hypotension in preterm neonates has been defined in some studies as a mean arterial pressure of 5mmHG or more below gestational age (minMAP≤GA-5). There is some evidence of greater benefit of intervention in this group[22].

Tolerating isolated hypotension in a stable preterm neonate with no signs suggestive of poor perfusion is increasingly becoming commonplace[1].

2.2 Term neonates

Hypotension in term neonates is less common and occurs due to a wider range of reasons than in preterm infants. Hypotension in term neonates is less well studied than in preterm neonates. Isolated hypotension is uncommon in term neonates thus permissive hypotension in term babies is not a common consideration.

2.3 First 48-72 hours of life (transition period)

Values below the third percentile of mean blood pressure in the first 72 hours approximate the gestational age in weeks for an averagely sized infant[5]. In the presence of a large patent ductus arteriosus (PDA), the mean blood pressure

may be reduced significantly, in which case the systolic blood pressure may be a more accurate marker of the baby's cardiovascular stability.

2.4 After the first 48-72 hours of life (post transition period)

Values for gestational age are as below (see also Appendices 1[4] and 2[6]).

Corrected Gestational Age (wks)	Systolic Blood Pressure (mmHg)	Mean Blood Pressure (mmHg)
23-26	35-45	30
27-32	40-55	35
33-36	45-55	40
37-42	55-65	45

3. Measurement of Blood Pressure

Oscillometric cuff measurement may overestimate blood pressure in hypotensive preterm newborns[7,8] therefore if unwell or intervention is being considered insertion of an arterial line should be considered being wary of the associated and significant risks of their use[9,10,11].

An appropriately sized cuff should be used with the infant supine, when the infant is settled and with the arm at the level of the right atrium.

Transduced intra-arterial blood pressure monitoring systems need to be interpreted with care:

- Damping can occur due to the small diameter catheter, partial occlusion by the vessel wall or the presence of air bubbles[12]
- Use of a pedal artery may cause systolic pressure to appear higher than when measured by a central catheter[13]
- The position of the transducer should be level with the heart
- The arterial line should be re-zeroed before acting on a hypotensive reading

4. Risk Factors for Hypotension

- Prematurity
- Positive pressure ventilation (particularly with high mean airway pressures and HFOV)
- Large Patent Ductus Arteriosus – ductal steal can reduce MAP and coronary artery blood flow
- Lack of antenatal steroids prior to delivery
- Sepsis
- Haemorrhage – eg APH, cord prolapse, twin to twin transfusion syndrome, large intracranial haemorrhage, large pulmonary haemorrhage
- Congenital cardiac disease
- Adrenal insufficiency

- Surgical intervention
- Hypoxic ischaemic encephalopathy (HIE)
- Persistent Pulmonary Hypertension of the Newborn (PPHN)
- Drugs – e.g. morphine infusions, maternal labetalol treatment

5. Complications of Hypotension[4,15,16]

- Intraventricular haemorrhage
- Periventricular leukomalacia
- Long term neurological impairment
- End-organ dysfunction

6. Diagnosis

6.1 Clinical Assessment

Signs and symptoms of inadequate tissue perfusion may include:

- Urine output <1ml/kg/hr
- Central capillary refill >3 seconds (a poor indicator alone but useful if associated with other features)
- Base deficit >5
- Lactate >2mmol/L
- Pallor
- Tachycardia
- Cold extremities
- Weak pulses (femoral palpation best in hypotensive infants[14])
- Apnoea and bradycardia
- Low blood pressure for gestational age

6.2 Monitoring

Infants with hypotension should ideally be monitored closely:

- Continuous monitoring of mean arterial pressure (if arterial access available)
- Cuff BP set to 15minute readings which are recorded (if arterial access not available)
- Continuous heart rate and saturation monitoring
- Central capillary refill time
- Urine output
- Core-peripheral temperature gap (>2^{o}C is abnormal)
- Regular blood gas/lactate monitoring

6.3 Echocardiography

Echocardiography (if expertise is available) may detect the presence of:

- PDA which may be contributing to hypotension
- Pulmonary hypertension (PPHN)
- Poor cardiac contractility
- Congenital cardiac disease

6.4 Consider contributing causes and intervention

- Blood loss/hypovolaemia

- Pneumothorax
- Sepsis
- PDA[18]
- High mean airway pressure compromising venous return to the heart
- Adrenocortical insufficiency[19,20]

7. Management of Hypotension:

Not intervening in babies with isolated hypotension and no signs of cardiovascular compromise remains reasonable. Intervention should be considered particularly in infants with clinical evidence of poor perfusion associated with hypotension or those with isolated severe hypotension (minMAP≤GA-5)[22].

Evidence of benefit is conflicting. Studies have shown that anti-hypotensive therapy in the extremely preterm neonate is independently associated with increased risk of death and neurodevelopmental impairment/developmental delay when controlling for risk factors known to affect those outcomes[21]. Other studies have shown benefit of treating isolated hypotension[22].

7.1 Inotropes[28,29,30,31,32]

Dopamine at lower doses (2-4 microgram/kg/mins) increases myocardial contractility and renal blood flow. At higher doses (10-20 microgram/kg/min) it increases vascular resistance. Dopamine is more effective than Dobutamine in the short term at raising the blood pressure in preterm infants, but this may not correlate with improving organ perfusion.

Dobutamine is a direct-acting inotropic agent which stimulates the ß-receptors of the heart and blood vessels causing increased cardiac output, vasodilation and reduced vascular resistance.

Adrenaline at low doses causes systemic and pulmonary vasodilation with an increase in the heart rate, stroke volume and contractility. Low doses of Adrenaline have been shown to be as effective as low/moderate doses of dopamine[33,34].

Note: High doses of both Adrenaline (≥ 500-600ng/kg/min) and Dopamine (≥ 15mcg/kg/min) can cause intense systemic vasoconstriction.

Drug	Category	Mode of Action	Haemodynamic effect	Dose
Dobutamine	Inotrope	Beta adrenergic agonist	Enhanced myocardial	**IVI 5-20 micro-grams/kg/minute**

			contractility and output	
Dopamine	Inotrope/ vasopressor	Alpha and beta adrenergic agonist	Peripheral vasoconstriction Enhanced myocardial contractility and output	**IVI 5-20 micro-grams/kg/minute**
Adrenaline	Inotrope/ vasopressor	Alpha and beta adrenergic agonist	Enhanced myocardial contractility and output; peripheral vasoconstriction	**IVI 100nanograms/kg/minute – 1.5micrograms/kg/minute**
Norepinephrine	Vasopressor	Alpha(and beta) adrenergic agonist	Peripheral vasoconstriction	**IVI 20-100nanograms/kg/minute Maximum 1microgram/kg/minute**
Milrinone	Lusitrope	Increases cAMP	Increase myocardial contractility Decreases vascular tone in systemic and pulmonary arteries.	**Loading dose IV 50-75 micro-grams/kg over 30-60 minutes then IVI 30-45 micrograms/kg/hour**

7.2 Volume expansion

Volume expansion should be given only if there is significant clinical suspicion of hypovolaemia, increased capillary leak or blood loss. Giving fluid boluses can be counterproductive if there is an already poorly functioning myocardium or a PDA. Early use of Dopamine is more successful than colloid in increasing the blood pressure[23].

As of yet there is insufficient evidence to determine whether infants with cardiovascular compromise benefit from volume expansion[24] and extensive use is associated with significant untoward effects especially in preterm infants[25].

10mls/kg of 0.9% sodium chloride should be given over 20-30 minutes if volume is chosen to treat hypotension[26,27]. Blood or Fresh Frozen Plasma should only be considered instead of sodium chloride if the baby is actively bleeding, thought to have lost significant blood volume or has deranged coagulation.

7.3 Corticosteroids

Adrenocortical insufficiency is becoming increasingly recognised as a cause of hypotension in preterm infants[35,36,37]. Adrenal corticoid insufficiency typically presents as severe refractory hypotension in preterm infants.

Hydrocortisone has been used successfully for treating refractory hypotension in preterm infants leading to stabilisation of blood pressure within 6-8 hours and to successful weaning from inotropes within 72 hours[38]. It is reasonable to consider use of hydrocortisone in infants who are still hypotensive despite treatment with dual inotropes.

Babies at highest risk are those:

- Under 30 weeks
- Under 14 days of age
- Concurrent perinatal stress (RDS, mechanical ventilation, surgery)

Blood cortisol levels can be useful in babies with refractory hypotension, if taken before giving hydrocortisone, and for assessing response to therapy. An unstimulated cortisol level <200nmol/L is suggestive of a degree of adrenal insufficiency. Whilst it is useful to have the cortisol level, the decision to start hydrocortisone should not depend on the result which may take hours.

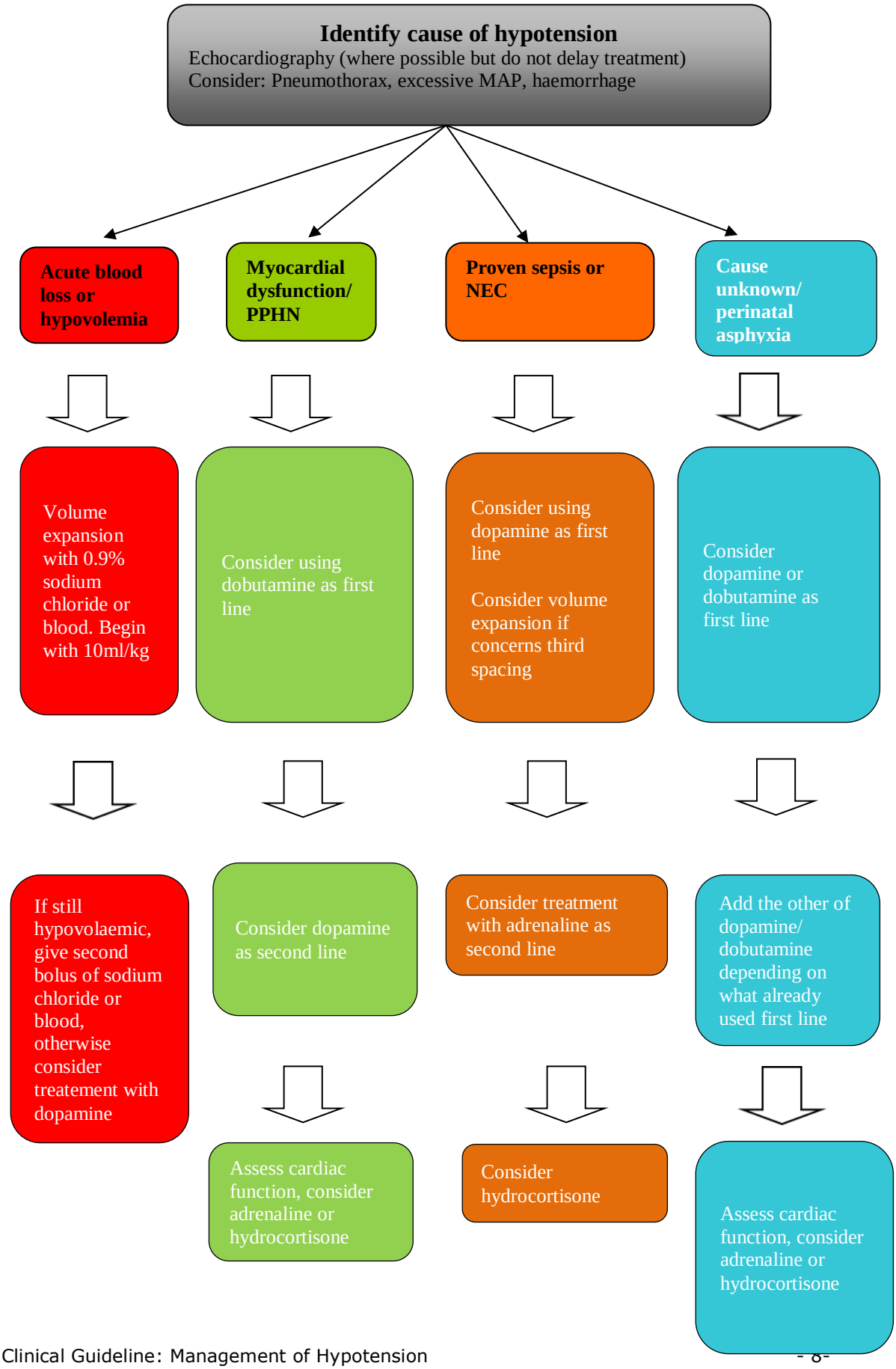
An initial dose of Hydrocortisone 2.5mg/kg can be repeated at 4 hours if required, followed by 2.5mg/kg every 6 hours for 48hrs or until BP recovers. Then reduce treatment over at least 48hrs[39].

7.4 Flow chart for management

The following flow chart is adapted from the Luton and Dunstable guideline[40]. There may be differences in the choice of dopamine or dobutamine as first line where the cause of hypotension is unknown depending on unit experience and preference.

The most recent Cochrane review of dopamine vs. dobutamine[32] would suggest using dopamine as first line therapy based on the fact that it is more likely to result in an increase in blood pressure and if this fails the addition of dobutamine may be considered. The evidence that dopamine is more effective only extends as far as the short-term effect on blood pressure and there is an argument that dobutamine may be more likely to increase systemic blood flow.

If there is a significant PDA present or if there is echo evidence of cardiac dysfunction the use of dobutamine before dopamine may be more logical[32].


Identify cause of hypotension
Echocardiography (where possible but do not delay treatment)
Consider: Pneumothorax, excessive MAP, haemorrhage
Acute blood loss or hypovolemia
Myocardial dysfunction/ PPHN
Proven sepsis or NEC
Cause unknown/ perinatal asphyxia
Volume expansion with 0.9% sodium chloride or blood. Begin with 10ml/kg
Consider using dobutamine as first line
Consider using dopamine as first line
Consider volume expansion if concerns third spacing
Consider dopamine or dobutamine as first line
If still hypovolaemic, give second bolus of sodium chloride or blood, otherwise consider treatement with dopamine
Consider dopamine as second line
Consider treatment with adrenaline as second line
Add the other of dopamine/ dobutamine depending on what already used first line
Assess cardiac function, consider adrenaline or hydrocortisone
Consider hydrocortisone
Assess cardiac function, consider adrenaline or hydrocortisone

Appendix 1[1]

	Hours postnatal age								
	3	12	24	36	48	60	72	84	96
500	35/23	36/24	37/25	38/26	39/28	41/29	42/30	43/31	44/33
600	35/24	36/25	37/26	39/27	40/28	41/29	42/31	44/32	45/33
700	36/24	37/25	38/26	39/28	42/29	42/30	43/31	44/32	45/34
800	36/25	37/26	39/27	40/28	41/29	42/31	44/32	45/33	46/34
900	37/25	38/26	39/27	40/29	42/30	43/31	44/32	45/34	47/35
1000	38/26	39/27	40/28	41/29	42/31	43/32	45/33	46/34	47/35
1100	38/27	39/27	40/29	42/30	43/31	44/32	45/34	46/35	48/36
1200	39/27	40/28	41/29	42/30	43/32	45/33	46/34	47/35	48/37
1300	39/28	40/29	41/30	43/31	44/32	45/33	46/35	48/36	49/37
1400	40/28	41/29	42/30	43/32	44/33	46/34	47/35	48/36	49/38
1500	40/29	42/30	43/31	44/32	45/33	46/35	48/36	49/37	50/38

Fig. 2. Table of mean MBP and 10th percentiles by birthweight and postnatal age. The first figure is the mean MBP at the given weight and postnatal age and the second figure is the tenth percentile.

Reprinted from Early Human Development, 19, Watkins AMC, West CR, Cooke RWI, Blood pressure and cerebral haemorrhage and ischaemia in very low birthweight infants, Pge.106, Copyright (1989), with permission for Elsevier.[1]

Appendix 2[4]

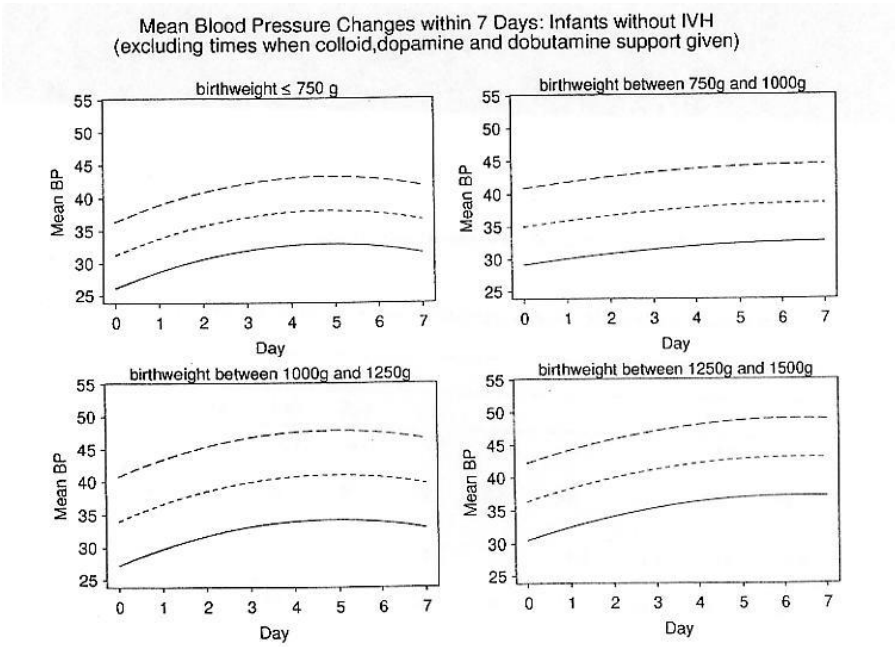


Fig. 1. Mean blood pressure reference ranges for infants in the four birthweight groups during the first seven days of life. Inclusion and exclusion criteria are given in the text. Centiles displayed are 10th, 50th and 90th.

[1] Left hand column indicates weight in grams and mean blood pressure measured in mmHg

Reprinted from Early Human Development, 56, Cunningham S, Symon AG, Elton RA et al, Intra-arterial blood pressure reference ranges, death and morbidity in very low birthweight infants during the first seven days of life, Page 157, copyright (1999), with permission from Elsevier.[2]

References

1. Dempsey EM, Barrington KJ. Treating hypotension in the preterm infant: when and with what: a critical and systematic review. J Perinatol 2007;27:469–78. doi:10.1038/sj.jp.7211774

2. Dempsey EM, Barrington KJ, Marlow N On behalf of the HIP consortium, *et al* Hypotension in Preterm Infants (HIP) randomised trial *Archives of Disease in Childhood - Fetal and Neonatal Edition* 2021;**106:**398-403.

3. Faust K, Härtel C, Preuß M for the Neocirculation project and the German Neonatal Network (GNN), et al. Short-term outcome of very-low-birthweight infants with arterial hypotension in the first 24 h of life. Archives of Disease in Childhood - Fetal and Neonatal Edition 2015;100:F388-F392

4. Watkins AM, West CR, Cooke RW. (1989) Blood pressure and cerebral haemorrhage and ischaemia in VLBW infants. *Early Human Development.* May;19(2):103-10 [III]

5. Nuntnarumit P, Yang W, Bada-Ellzey HS. (1999) Blood pressure measurements in the newborn. *Clinics in Perinatology*. December; 26(4):981-96. [IV]

6. Cunningham S, Symon AG, Elton RA, Zhu C, McIntosh N. (1999) Intra-arterial blood pressure reference ranges, death and morbidity in very low birthweight infants during the first seven days of life. *Early Human Development*. 56:151-165. [III]

7. Diprose GK, Evans DH, Archer LN, Levene MI. (1986) Dinamap fails to detect hypotension in very low birthweight infants. *Archives of Disease in Childhood.*August;61(8):771-3. [III]

8. Wareham JA, Haugh LD, Yeager SB, Horbar JD. (1987) Prediction of arterial *blood pressure in the premature neonate using the oscillometric method. American Journal of Disease in Childhood.* October;141(10):1108-10. [III]

9. Gevers M, van Genderingen HR, Lafeber HN, Hack WW. (1996) Accuracy of oscillometric blood pressure measurement in critically ill neonates with reference to the arterial pressure wave shape. *Intensive Care Medicine.* March; 22(3):242-8. [IIa]

10. Danniveg I, Dale HC, Liestol K, Lindenmann R. (2005) Blood pressure in the neonate: three non-invasive oscillometric pressure monitors compared with

[2] Blood pressure measured in mmHg

invasively measured blood pressure. *Acta Paediatrica.* February;94(2):191-6.[Ia]

11. Sonesson SE, Broberger U. (1987) Arterial blood pressure in the very low birthweight neonate. *Acta Paediatrica Scandinavia.* March;76(2):338-41. [III]

12. Moniaci V, Kraus M. (1997) Determining the relationship between invasive and non-invasive blood pressure values. *Neonatal Network.* February;16(1):51-6.[IIb]

13. Park MK, Rotham JL, German VF. (1983) Systolic pressure amplification in pedal arteries in children. *Critical Care Medicine.* April;11(4):286-289. [IIb]

14. Ng PC. Adrenocortical insufficiency and refractory hypotension in preterm infants. *Archives of Disease in Childhood - Fetal and Neonatal Edition* 2016;101:F571-F576.

15. Miall-Allen VM, De Vries LS, Whitelaw AGL. (1987) Mean arterial blood pressure and neonatal cerebral lesions. *Archives of Disease in Childhood.* October; 62(10):1068-9. [III]

16. Bada HS, Korones SB, Perry EH et al. (1990) Mean arterial blood pressure changes in premature infants and those at risk for intraventricular haemorrhage. *Journal of Pediatrics*. October; 117(4):607-14. [III]

17. Sarti A, Savron F, Ronfani L, Pelizzo G, Barbi E. (2006) Comparison of three sites to check the pulse and count the heart rate in hypotensive infants. *Paediatric Anaesthesia.* April; 16(4):394-8. [III]

18. Evans N, Moorcraft J. (1992) Effect of patency of the ductus arteriosus on blood pressure in very preterm infant. *Archives of Disease in Childhood.* October; 67(10 Spec No): 1169-73. [III]

19. Helbock HJ, Insoft RM, Conte FA. (1993) Glucocorticoid-responsive hypotension in extremely low birth weight newborns. *Pediatrics.* November; 92(5):715-7. [III]

20. Korte C, Styne D, Merritt AT, Mayes D, Wertz A, Helbock HJ.(1996) Adrenocorticoid function in the very low birth weight infant: Improved testing sensitivity and association with neonatal outcome. *Journal of Pediatrics*. February; 128(2):257-263. [Ib]

21. Batton B, Li L, Newman NS for the Eunice Kennedy Shriver National Institute of Child Health & Human Development Neonatal Research Network*, et al.* Early blood pressure, antihypotensive therapy and outcomes at 18–22 months' corrected age in extremely preterm infants

Archives of Disease in Childhood - Fetal and Neonatal Edition 2016;**101:**F201-F206.

22. Durrmeyer X, Marchand-Martin L, Porcher R, Gascoin G, Roze JC, Storme L, Favrais G, Ancel PY, Cambonie G; Hemodynamic EPIPAGE 2 Study Group. Abstention or intervention for isolated hypotension in the first 3 days of life in extremely preterm infants: association with short-term outcomes in the EPIPAGE 2 cohort study. Arch Dis Child Fetal Neonatal Ed. 2017 Nov;102(6):490-496. doi: 10.1136/archdischild-2016-312104. Epub 2017 Mar 16. PMID: 28302697.

23. Dasgupta SJ, Gill AB. (2003) Hypotension in the very low birthweight infant: the old, the new and the uncertain. *Archives of Disease in Childhood Fetal & Neonatal Ed.* 88; F450-454. [IV]

24. Osborn DA, Evans N. (2004) Early volume expansion for prevention of morbidity and mortality in very preterm infants. *Cochrane Database of Systematic Reviews.* (2):CD002055. [Ia]

25. Seri I, Evans J. (2001) Controversies in the diagnosis and management of hypotension in the newborn infant. *Current Opinion in Pediatrics.* April; 13(2):116-23. [IV]

26. BAPM (1999) *Guidelines for good practice in the management of neonatal respiratory distress syndrome.* [IV]

27. Oca MJ, Nelson M, Donn SM. (2003) Randomized trial of normal saline versus 5% albumin for the treatment of neonatal hypotension. *Journal of Perinatology.* September; 23(6):473-6. [Ia]

28. Seri I, Rudas G, Bors Z, Kanyicska B, Tulassay T. (1993) Effects of low-dose dopamine infusion on cardiovascular and renal functions, cerebral blood flow and plasma catecholamine levels in the sick preterm infant. *Pediatric Research.* December;34(6):742-9. [III]

29. Roze JC, Tohier C, Maingueneau C, Lefevre M, Mouzard A. (1993) Response to dobutamine and dopamine in the hypotensive very preterm infant. *Archives of Disease in Childhood.* July; 69(1 Spec No):59-63. [Ia]

30. Seri I. (1995) Cardiovascular, renal, and endocrine actions of dopamine in neonates and children. *Journal of Pediatrics.* March; 126(3):333-44.

31. Klarr JM, Faix RG, Pryce CJ, Bhatt Mehta V. (1994) Randomised, blind trial of dopamine versus dobutamine for treatment of hypotension in preterm infants with respiratory distress syndrome. *Journal of Pediatrics.* July; 125(1):117-22. [Ia]

32. Subhedar NV, Shaw NJ. (2003) Dopamine versus dobutamine for hypotensivie preterm infants. *Cochrane Database of Systematic Reviews.*

(3):CD001242. [Ia]

33. Heckmann M, Trotter A, Pohlandt F, Lindner W. (*2002*) Epinephrine treatment of hypotension in very low birth weight infants. *Acta Paediatrica.* 91(5):566-70. [III]

34. Valverde E, Pellicer A, Madero R, Elorza D, Quero J, Cabanas F. (2006) Dopamine versus epinephrine for cardiovascular support in low birth weight infants: analysis of systematic effects and neonatal clinical outcomes. *Pediatrics.* June; 117(6) e1213-22. [Ib]

35. Watterberg KL. (2002) Adrenal insufficiency and cardiac dysfunction in the preterm infant. *Pediatric Research.* April; 51(4):422-424. [IV]

36. Scott SM, Watterberg KL. (1995) Effect of gestational age, postnatal age and illness on plasma cortisol concentrations in premature infants. *Pediatric Research.* January; 37(1):112-6. [III]

37. Ng PC, Lam CW, Fok TF, Lee CH, Ma KC, Chan IH, Wong E. (2001) Refractory hypotension in preterm infants with adrenocortical insufficiency. *Archives of Disease in Childhood Fetal Neonatal Ed*. March; 84(2):F122-4. [III]

38. Seri I, Tan R, Evans J. (2001) Cardiovascular effects of hydrocortisone in preterm infants with pressor resistant hypotension. *Pediatrics.* May;107(5):1070-74. [III]

39. British National Formulary March 2017.

40. Pahuja A, Chetcuti Gando C, Somisetty S, Egyepong J: Guideline for the management of Neonatal Hypotension; Luton and Dunstable Hospital, January 2015.