

HYPOTENSION

Supporting information

This guideline has been prepared with reference to the following:

National Association of Neonatal Nurse Practitioners. The management of hypotension in the very-low-birth-weight infant: guideline for practice. 2011. Illinois. NANNP

What is the best method of measuring blood pressure in a neonate?

A 2020 systematic review found that studies investigating measurement location identified the upper arm as the most accurate and least variable location for oscillometric BP measurement (Dionne, 2020). Analysis of studies using Bland-Altman methods for comparison of intra-arterial to oscillometric BP measurement show that the 2 methods correlate best for mean arterial pressure, whereas systolic BP by the oscillometric method tends to overestimate intra-arterial systolic BP. Compared with intra-arterial methods, systolic BP, diastolic BP, and mean arterial pressure by oscillometric methods are less accurate and precise, especially in neonates with a mean arterial pressure <30 mm Hg.

Direct transducer readings through an umbilical line are commonly used in sick or very low birth weight neonates (Cordero, 2002), and are “widely accepted as the optimum method” (Dasgupta, 2003).

A combination of oscillometric and Doppler methods has been reported as providing better accuracy than each method on its own in a study in 174 term neonates (Nascimento, 2002). The use of an algorithm (SuperSTAT(R)) enabled non-invasive blood pressure measurement to comply with ANSI/AAMI accuracy standards (+/- 5 mm Hg, SD <= 8 mm Hg) and to be comparable to invasive methods (Nelson, 2002). It is important that measurements are taken when the infant is in “a restful state” (not necessarily asleep) (Nwankwo, 1997).

Dionne JM, Bremner SA, Baygani SK et al. Method of Blood Pressure Measurement in Neonates and Infants: A Systematic Review and Analysis. *J Pediatr.* 2020;221:23-31

Cordero L, Timan CJ, Waters HH, et al. Mean arterial pressures during the first 24 hours of life in < or = 600-gram birth weight infants. *J Perinatol* 2002;22:348-53
<http://www.nature.com/jp/journal/v22/n5/full/7210736a.html>

Dasgupta SJ, Gill AB. Hypotension in the very low birthweight infant: the old, the new, and the uncertain. *Arch Dis Child Fetal Neonatal Ed* 2003;88:F450-F454
<http://fn.bmj.com/content/88/6/F450.long>

Nascimento MC, Xavier CC, Goulart EM. Arterial blood pressure of term newborns during the first week of life. *Braz J Med Biol Res* 2002;35:905-11
http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0100-879X2002000800007&lng=en&nrm=iso&tlng=en

Nelson RM, Stebor AD, Groh CM, et al. Determination of accuracy in neonates for non-invasive blood pressure device using an improved algorithm. *Blood Press Monit* 2002;7:123-9

Nwankwo MU, Lorenz JM, Gardiner JC. A standard protocol for blood pressure measurement in the newborn. *Pediatrics* 1997;99:E10
<http://pediatrics.aappublications.org/content/99/6/e10.long>

Evidence Level: I

What is a normal blood pressure for a neonate, at term and preterm?

According to a 2017 literature review, “In the premature neonate, there is no consensus regarding normal blood pressure (BP)” (St Peter, 2017). “Hypotension affects close to half of all ELBW infants, yet an agreement on its definition is still lacking” (Fanaroff, 2006). A systematic review (Dempsey, 2007) failed to find evidence for a definitive threshold BP that was predictive of poor outcome. In low birthweight or preterm infants, the range of “normal” values is dependent on age in terms of weeks’ gestation and birthweight (Hegyí 1996; Hegyí 1994). New Zealand guidelines (Knight, 2000) suggest that, for VLBW infants, “a good rule of thumb is to aim for the baby’s gestational age as the desired minimum mean blood pressure”.

A postal questionnaire sent to all 120 neonatal ICUs in Canada (Dempsey, 2006), which had a 79% return rate (95 replies), found that 25.8% relied on blood pressure values as the sole criteria for

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intervention. A blood pressure less than gestational age in weeks was the most common trigger for treatment.

“Premature neonates stabilize their BP after 14 days of life, and at this time they have a BP similar to that of term infants” (Kent, 2009).

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

Dempsey EM, Barrington KJ. Diagnostic criteria and therapeutic interventions for the hypotensive very low birth weight infant. *J Perinatol* 2006;26:677-81

Fanaroff AA, Fanaroff JM. Short- and long-term consequences of hypotension in ELBW infants. *Semin Perinatol* 2006;30:151-5

Hegy T, Carbone MT, Anwar M, et al. Blood pressure ranges in premature infants. I. The first hours of life. *J Pediatr* 1994;124:627-33

Hegy T, Anwar M, Carbone MT, et al. Blood pressure ranges in premature infants. II. The first week of life. *Pediatrics* 1996;97:336-42

Kent AL, Meskell S, Falk MC, et al. Normative blood pressure data in non-ventilated premature neonates from 28-36 weeks gestation. *Pediatr Nephrol* 2009;24:141-6

Knight D. Newborn Services Clinical Guidelines: Hypotension. 2012. Auckland District Health Board.

<http://www.adhb.govt.nz/newborn/Guidelines/Cardiac/Hypotension.htm>

St Peter D, Gandy C, Hoffman SB. Hypotension and Adverse Outcomes in Prematurity: Comparing Definitions. *Neonatology*. 2017;111:228-233

Evidence Level: V

What is the role of clinical assessment (e.g. skin turgor, urine output) in deciding whether or not to treat at a specific blood pressure reading?

No evidence can be identified with which to answer this question. There is general agreement that “decisions to treat hypotension should be based on the general condition of the infant, not on the mean arterial blood pressure alone” (Dasgupta, 2003), but no detail is given. Urine output is considered to be an unreliable indicator of hypotension (Dasgupta, 2003).

Dasgupta SJ, Gill AB. Hypotension in the very low birthweight infant: the old, the new, and the uncertain. *Arch Dis Child Fetal Neonatal Ed* 2003;88:F450-F454

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1763241/pdf/v088p0F450.pdf>

Evidence Level: V

Should IV fluid be used as a first line for the treatment of hypotension? If so, what type and how much?

Although hypovolaemia is a relatively uncommon cause of hypotension in the sick preterm infant, moderate fluid replacement is a reasonable precaution and so usually the first line treatment (Dasgupta, 2002). Two RCTs, in 63 (So, 1997) and 41 infants (Oca, 2003) respectively, have demonstrated that saline 0.9% is as effective as 5% albumin for treating neonatal hypotension. Isotonic saline has the further advantages of being cheap, of carrying no infection risk, and of causing less fluid retention in the first 48 hours (So, 1997). A recommended amount to use is 10-20 ml/kg over 30 minutes (Dasgupta, 2002).

Dasgupta SJ, Gill AB. Hypotension in the very low birthweight infant: the old, the new, and the uncertain. *Arch Dis Child Fetal Neonatal Ed* 2003;88:F450-F454

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1763241/pdf/v088p0F450.pdf>

Oca MJ, Nelson M, Donn SM. Randomized trial of normal saline versus 5% albumin for the treatment of neonatal hypotension. *J Perinatol* 2003;23:473-6

So KW, Fok TF, Ng PC, et al. Randomised controlled trial of colloid or crystalloid in hypotensive preterm infants. *Arch Dis Child Fetal Neonatal Ed* 1997;76:F43-F46

<http://fn.bmj.com/content/76/1/F43.long>

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Evidence Level: II

Should dopamine remain the first line drug treatment?

A Cochrane review of 5 RCTs (Subhedar, 2003) concluded that dopamine was more successful than dobutamine for short-term treatment of hypotension, with fewer infants having treatment failure (RD – 0.23; 95% CI –0.34 to –0.13). There was, however, no difference in mortality and no data on long term benefit or safety.

A meta-analysis (Sassano-Higgins, 2011) found that “dopamine increases mean arterial blood pressure (12 studies; N=163; $r=0.88$, 95% CI=0.76 to 0.94) and systolic blood pressure (8 studies; N=142; $r=0.81$, 95% CI=0.42 to 0.94). For the increase in blood pressure, dopamine administration was associated with a significantly greater overall efficacy than dobutamine (seven studies; N=251; $r=0.26$; 95% CI=0.20 to 0.32), colloid (two studies; N=67; $r=0.60$; 95% CI=0.41 to 0.74) and hydrocortisone (one study; N=28; $r=0.40$; 95% CI=0.034 to 0.67). CBF increased following dopamine administration (five studies; N=75; $r=0.36$; 95% CI=-0.059 to 0.67) and the increase in CBF was greater in hypotensive than normotensive preterm infants (eight studies; N=153; $r=0.16$; 95% CI=-0.0080 to 0.32). There were no statistically significant differences in adverse neurological outcome between dopamine and dobutamine (three studies; N=118; $r=-0.13$; 95% CI=-0.31 to 0.059), epinephrine (two studies; N=46; $r=0.06$; 95% CI=-0.23 to 0.34), colloid (two studies; N=80; $r=0.0070$; 95% CI=-0.218 to 0.23) or hydrocortisone administration (one study; N=40; $r=-0.10$; 95% CI=-0.40 to 0.22).

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;31:647-55

Subhedar NV, Shaw NJ. Dopamine versus dobutamine for hypotensive preterm infants. *Cochrane Database of Systematic Reviews* 2003, Issue 3. Art. No.: CD001242

<http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001242/full>

Evidence Level: I

What is the role of dobutamine?

Dobutamine is generally used as a second line drug, in patients unresponsive to dopamine (Dasgupta, 2003). A range of doses from 5-20 mcg/kg/min has been used, and there is no clear evidence as to which of these is “correct” (Subhedar, 2003). New Zealand guidelines (Knight, 2000) suggest starting at the lower dose and increasing incrementally to the higher, after the dopamine dose has been increased to 10-20 mcg/kg/min without response.

Dasgupta SJ, Gill AB. Hypotension in the very low birthweight infant: the old, the new, and the uncertain. *Arch Dis Child Fetal Neonatal Ed* 2003;88:F450-F454

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1763241/pdf/v088p0F450.pdf>

Knight D. Newborn Services Clinical Guidelines: Hypotension. 2012. Auckland District Health Board.

<http://www.adhb.govt.nz/newborn/Guidelines/Cardiac/Hypotension.htm>

Subhedar NV, Shaw NJ. Dopamine versus dobutamine for hypotensive preterm infants. *Cochrane Database of Systematic Reviews* 2003, Issue 3. Art. No.: CD001242

<http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001242/full>

Evidence Level: II

What is the role of adrenaline (epinephrine)?

A Cochrane review (Paradis, 2004) identified only one on-going randomised study comparing adrenaline (epinephrine) with dopamine and this indicated that both agents significantly increased heart rate and mean BP, with no statistically significant effect on left or right ventricular outputs. No other outcomes were reported. The review concluded that there was insufficient data to make any recommendations, and called for larger trials to be carried out.

A retrospective “chart review” in 31 very low birthweight infants not responding to dopamine (Heckmann, 2002) found that the mean arterial blood pressure ($=7$ (-1 to 13) mmHg, $p=0.000001$) and the heart rate ($+10$ (-10 to 42) bpm, $p=0.000036$) increased significantly in all cases in response to a continuous infusion of adrenaline (epinephrine) in doses of 0.05-2.6 mcg/kg(-1)/min within the first 24

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hours. No decrease in urine output was recorded. An increase in metabolic acidosis was noted as a potential adverse effect.

Heckmann M, Trotter A, Pohlandt F, et al. Epinephrine treatment of hypotension in very low birthweight infants. *Acta Paediatr* 2002;91:566-70

Paradis M, Osborn DA. Adrenaline for prevention of morbidity and mortality in preterm infants with cardiovascular compromise. *The Cochrane Database of Systematic Reviews* 2004, Issue 1. Art. No.: CD003958
<http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003958.pub2/full>

Evidence Level: I

What is the role of steroids?

A randomised comparison between dopamine and hydrocortisone in 40 very low birthweight infants (Bourchier, 1997) found the two treatments broadly equivalent in efficacy.

A retrospective review of 21 preterm infants given hydrocortisone as rescue therapy (Seri, 2001) noted a rapid increase in blood pressure (from 29.3 +/- 4.1 to 34.1 +/- 5.2 after 2 hours, rising to 41.8 +/- 6.6 mmHg after 6 hours).

Steroids may also have a role in the prevention of hypotension in preterm infants with low cortisol levels (Subhedar, 2003).

A Cochrane systematic review (Subhedar, 2007) concluded that in view of the scanty evidence for benefit and lack of long-term safety data, dexamethasone could not be recommended for routine use in preterm hypotension.

A retrospective observational study in 117 infants (Baker, 2008) found that treatment with hydrocortisone increased the mean arterial pressure at 2, 6, 12 and 24 h after initiation, decreased the total inotrope dose at 6, 12 and 24 h and was associated with resolution of oliguria.

A meta-analysis of 12 studies (Higgins, 2010) confirmed that hydrocortisone increases blood pressure (seven studies; N=144; r=0.71, 95%CI=0.18 to 0.92) and decreases the requirement for vasopressors (five studies; N=93; r=0.74, 95%CI=0.0084 to 0.96), but without demonstrating clear clinical benefit.

A Cochrane systematic review of 4 studies in a total of 123 babies (Ibrahim, 2011) found that, in one study, persistent hypotension was more common in hydrocortisone treated infants as compared to those who received dopamine as primary treatment for hypotension (RR 8.2, 95% CI 0.47 to 142.6; RD 0.19, 95% CI 0.01 to 0.37). In two studies comparing steroid versus placebo, persistent hypotension (defined as a continuing need for inotrope infusion) was less common in steroid treated infants as compared to controls who received placebo for refractory hypotension (RR 0.35, 95% CI 0.19 to 0.65; RD -0.47, 95% CI - 0.68 to - 0.26; NNT = 2.1, 95% CI 1.47, 3.8). There were no statistically significant effects on any other short or long-term outcome. The authors concluded that: "With long term benefit or safety data lacking, steroids cannot be recommended routinely for the treatment of hypotension in preterm infants."

Baker CF, Barks JD, Engmann C, et al. Hydrocortisone administration for the treatment of refractory hypotension in critically ill newborns. *J Perinatol* 2008;28:412-9

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:F174-F178
<http://fn.bmj.com/content/76/3/F174.long>

Higgins S, Friedlich P, Seri I. Hydrocortisone for hypotension and vasopressor dependence in preterm neonates: a meta-analysis. *J Perinatol* 2010;30:373-8

Ibrahim H, Sinha IP, Subhedar NV. Corticosteroids for treating hypotension in preterm infants. *Cochrane Database of Systematic Reviews* 2011, Issue 12. Art. No.: CD003662
<http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003662.pub4/full>

Seri I, Tan R, Evans J. Cardiovascular effects of hydrocortisone in preterm infants with pressor-resistant hypotension. *Pediatrics* 2001;107:1070-4

Subhedar NV. Treatment of hypotension in newborns. *Semin Neonatol* 2003;8:413-23

Evidence Level: I

What are the best parameters for assessing hypovolaemia in the neonate?

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Hypovolaemia is uncommon and also difficult to diagnose in the sick preterm infant, due to the unreliability of indicators such as urine output and capillary refill time (Dasgupta, 2003). In view of the danger of excessive volume expansion (Ewer, 2003), it has been suggested (Evans, 2003) that echocardiography should be used to define systemic blood flow.

Dasgupta SJ, Gill AB. Hypotension in the very low birthweight infant: the old, the new, and the uncertain. Arch Dis Child Fetal Neonatal Ed 2003;88:F450-F454

Evans N. Volume expansion during neonatal intensive care: do we know what we are doing? Semin Neonatol 2003;8:315-23

Ewer AK, Tyler W, Francis A, et al. Excessive volume expansion and neonatal death in preterm infants born at 27-28 weeks gestation. Paediatr Perinat Epidemiol 2003;17:180-6

Evidence Level: V

Does neonatal hypotension increase the risk of developmental delay?

A prospective cohort study in 945 infants (Logan, 2011) found that, after adjustment for potential confounders, no indicators of hypotension were associated with either a Bayley Mental Development Index (MDI) score or a Psychomotor Development Index (PDI) score of <70 at 24 months of age.

Logan JW, O'Shea TM, Allred EN, et al. Early postnatal hypotension and developmental delay at 24 months of age among extremely low gestational age newborns. Arch Dis Child Fetal Neonat Ed 2011;96:F321-8

Evidence Level: III

Last amended December 2021
Last reviewed December 2021