National Association of
Neonatal Nurse Practitioners
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The Management of Hypotension in the Very-Low-Birth-Weight Infant

Guideline for Practice

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American Academy of Pediatrics
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Contents

Abstract
This guideline, released in 2011, focuses on the clinical management of systemic hypotension in the very-low-birth-weight (VLBW) infant during the first 3 days of postnatal life.

Focus
Clinical management of systemic hypotension in the VLBW infant during the first week of postnatal life is one of the significant challenges that clinicians face. This guideline focuses on the clinical management of hypotension primarily during the first 3 postnatal days following a diagnosis of hypotension as established by generally accepted criteria for that diagnosis (see "Definitions").

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Objective

To provide an evidence-based clinical guideline for the management of systemic hypotension in VLBW infants during the first 3 days of postnatal life

Users and Setting

Neonatologists, neonatal nurse practitioners (NNPs), and nurses in neonatal intensive care units (NICUs)

Target Population

Premature infants born at 1,500 grams or less and less than 3 postnatal days old

Evidence Collection Methods

Evidence was collected via searches of three electronic databases—Medline, Neonatal Cochrane Collaboration, and Cumulative Index to Nursing and Allied Health Literature (CINAHL)—from 2000 to 2010. Search words included *hypotension, blood pressure, systemic blood flow, premature infant,* and *very low birth weight infant.*

Recommendations and Grading Criteria

The following grading system was employed to rate the quality and strength of the evidence to support the practice recommendations:

Rating System for the Hierarchy of Evidence

Level I: Evidence from a systematic review or meta-analysis of all relevant randomized controlled trials (RCTs) or evidence-based clinical practice guidelines based on systematic reviews of RCTs
Level II: Evidence obtained from at least one well-designed RCT
Level III: Evidence obtained from well-designed controlled trials without randomization
Level IV: Evidence from well-designed case-control and cohort studies
Level V: Evidence from systematic reviews of descriptive and qualitative studies
Level VI: Evidence from a single descriptive or qualitative study
Level VII: Evidence from the opinion of authorities or reports of expert committees

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Method for Synthesizing Evidence

Evidence tables and decision analysis using levels of evidence were used to construct the guideline. The opinions of experts were used when firm evidence documented by research was not available.

Prerelease Review

External reviewers and neonatal cardiovascular experts were asked to review the evidence with attention to clarity prior to the guideline's release.

Definitions

The following definitions were used in formulating the guideline:

Hypotension—Experts believe that three different levels of functional alteration in the VLBW infant can be used to refine the definition of *hypotension*: a loss of vital organ blood flow autoregulation, a loss of function, and a loss of tissue integrity (ischemic threshold).[1] However, many unanswered questions remain regarding the determination of the specific blood pressure values that indicate pathology in VLBW infants within each level. In addition, it is unclear how to determine the specific blood pressure parameters that affect morbidity, mortality, and long-term outcome in the VLBW infant.[1]

In general neonatal practice the two most common parameters used to define hypotension during the immediate transitional period are a blood pressure that falls below a mean arterial pressure (MAP) of 30 mm Hg or a MAP with a number lower than the infant's gestational age in weeks. These values will be used to define hypotension during the first 3 days of postnatal life because evidence exists that beyond this period, more than 90% of VLBW infants with gestational ages of 23–26 weeks will have a MAP greater than 30.[2] In addition, beyond this period the pathophysiology of hypotension is less likely to be affected by ductal and foramen ovale shunting, and this fact should be considered when one is treating hypotension beyond postnatal day 3. However, these definitions are primarily based on principles of developmental cardiovascular physiology and thus represent a rather simplistic and, at present, mostly non-evidence-based interpretation of what actually constitutes hypotension with clinically relevant consequences in the human neonate.

Very-low-birth-weight (VLBW) infant—a premature infant weighing less than 1,500 grams at birth.

Low systemic blood flow (LSBF)—the condition existing when a decreased amount of blood reaches systemic end organs, resulting in decreased oxygen delivery to the organs and the development of shock.

Recommendations and Rationale

The topic of hypotension and its treatment in the VLBW infant is complex. Our understanding of what constitutes hypotension in this population and our ability to effectively monitor hemodynamic changes at the level of tissue perfusion and organ blood flow remains limited. Although it is true that we can "normalize" blood pressure, it has become evident that blood pressure is only one of many components that determine overall tissue perfusion and thus oxygen delivery in VLBW infants.[1] Although neonatal care is often aimed at avoiding hypotension, it may be that caregivers need to be more concerned instead with preventing the consequences of shock.

In our discussion of the management of hypotension in the VLBW infant, it is critical that we include an understanding of the infant's presenting diagnosis, the intricacies

of the transition from fetal to transitional circulation, the importance of ductal and foramen ovale shunting during the first days of postnatal life, factors affecting cerebral hemodynamics such as pH and carbon dioxide tension in the first postnatal days, systemic vasodilation and vasoconstriction, levels of systemic blood flow (cardiac output), and the interaction between systemic and cerebral hemodynamics. For example, systemic blood flow in some VLBW infants during the first 6–12 hours of postnatal life, assessed by superior vena cava (SVC) blood flow, is low, and blood pressure values may not identify this problem.[3] The decrease in systemic blood flow that occurs during this period is thought to be related to the decreased ability of the immature myocardium to pump against the suddenly increased systemic vascular resistance that occurs following cord clamping and removal of the low-resistance placenta.[4] LSBF will improve as transition progresses and as the systemic blood flow (i.e., SVC flow) normalizes in VLBW infants by 36 hours of postnatal life.[5,6]

However, use of the measurement of SVC blood flow as a measure of systemic blood flow in VLBW infants has limitations, as does the measurement of another factor that is often used in neonatology, measurement of left ventricular output. The limitations related to use of this parameter are due to left-to-right ductal shunting that occurs during the first few postnatal days. Right ventricular output as measured by echocardiography during the first 24 hours of life is felt to be a relatively more accurate measure of systemic blood flow at that time because it is less affected by ductal flow than is left ventricular output at that time (this is true as long as left-to-right foramen ovale shunting, which affects the accuracy of right ventricular output, does not occur). In fact, low right ventricular output measured at less than 48 hours of life in VLBW infants has been correlated with low-amplitude-integrated electroencephalographic (EEG) activity in these infants, and low mean blood pressure has been correlated with low EEG continuity.[7] In premature infants low cerebral blood flow has been associated with discontinuous EEG activity, which has then been associated with poor long-term outcome.[7]

Other methods for assessing organ blood flow in the VLBW infant are currently being investigated. One method is the use of near-infrared spectroscopy (NIRS).[1] This method may help determine the blood flow to vital organs such as the brain by measuring certain oxygen-dependent compounds that selectively absorb NIR light during passage through the brain. These compounds can then be measured and oxygenation indices calculated. Cerebral blood flow is then measured using the Fick principle and the assumption of certain constants.[1] This technique holds promise, but many obstacles must be overcome before its validity is established for widespread use in this area. Understanding the complexities of measuring blood pressure in VLBW infants and determining what an improvement in overall systemic blood flow and tissue perfusion means to patients' outcomes have important implications for the treatment of hypotension in this population.

In discussions of hypotension and the VLBW infant, the parameter that has traditionally been thought to be critical in determining impact on patient outcome is the association between a history of hypotension and evidence of subsequent brain injury.[8,9] Some studies have shown that no correlation between cerebral blood flow and MAP exists. This finding suggests the presence of intact cerebral blood-flow autoregulation in these neonates; yet blood pressure alone may not be a primary determinant for clinically meaningful outcome measures.[10] Additional factors include the primarily indirect evidence that vital-organ assignment of the forebrain vasculature of the VLBW infant is incomplete at birth and that VLBW infants will respond to the stress of delivery with vasoconstriction of forebrain vessels (rather than vasodilation). Thus they may have low cerebral blood flow even when blood pressure is in the perceived normal range.[11] Indeed, it appears that steeply increased perfusion to the brain occurs between the day of delivery and the following day and that this increase is relatively independent of gestational age in preterm neonates up to 34 weeks' gestation.[12]

Despite all the unknowns associated with defining hypotension in VLBW infants and the growing knowledge of other methods to determine systemic blood flow, the measurement of blood pressure remains the primary measure used to indirectly evaluate satisfactory cardiac stability, blood flow, and tissue perfusion in the NICU, primarily because of the ease of monitoring this parameter.[13] As mentioned, some clinicians consider VLBW infants with a MAP of less than 30 mm Hg to require treatment for hypotension, while others regard infants with a MAP less than the infant's gestational age in weeks as in need of such treatment. However, the studies describing these approaches have most often arbitrarily used these numbers as treatment thresholds. Evidence that treating MAPs by either of these methods makes "any difference in anything other than the baby's blood pressure" is insufficient, and evidence that treatment affects other factors such as neurodevelopmental outcome is also lacking.[14] Nonetheless, lack of evidence of a positive or negative association between treatment and blood pressure outcome does not mean that there is evidence of *no* association. Therefore, this guideline will not address the question of whether to treat or not treat any specific blood pressure in VLBW infants. Instead, it will consider the best evidence available for treating hypotension in VLBW infants during the first 3 days of postnatal life, when treatment is thought to be indicated by those caring for the infant.

The authors of this guideline strongly support collecting clinical data that use clinically relevant outcome measures to support evidence of hypotension in VLBW infants and then, according to appropriately established blood pressure values, treating hypotensive infants using this information.

A number of therapeutic interventions can improve hypotension in VLBW infants. Common treatments currently include volume expansion and vasopressor-inotropes, lusitropes, and corticosteroids. It is important to note that all these treatments have potential adverse effects (see the section "Potential Harms and Benefits"). The following recommendations and rationales include the best evidence (including evidence from clinical experts in the field when there is not sufficient evidence) currently available in the management of hypotension in the VLBW infant during the first week of postnatal life.

Practice Recommendation	Level of Evidence	Reference(s)
1. Hypotension in VLBW infants should be treated on the basis of the etiology of the hypotension whenever an etiology is known. **Rationale**: It is generally agreed by experts that adequate treatment of blood pressure requires identification of the primary factor leading to the hypotension.	VII	15, 16, 17
2. In general, the early use of volume expansion with normal saline, fresh frozen plasma, albumin, plasma substitute, or blood in VLBW infants with hypotension is not recommended. **Rationale**: Evidence that VLBW infants with hypotension benefit from volume expansion is insufficent, as is evidence to determine what type of volume expansion should be used in VLBW infants.[18,19] The majority of VLBW infants who are hypotensive are not hypovolemic and have normal circulating blood volume.[15,16]	I VII	18, 19 15, 16
3. In VLBW infants with evidence of placenta previa, abruption, blood loss from the umbilical cord, fetal anemia, or evidence of fetal-maternal transfusion, the administration of a volume expander such as normal saline, ringers lactate, or O Rh-negative blood may be used as an initial dose of 10 ml/kg given over 5–10 minutes. This dose may be repeated.[20] Albumin is not generally recommended for use as a volume expander in VLBW infants. **Rationale**: In VLBW infants with evidence of blood loss, the effective circulating blood volume may be decreased, which can result in hypotension. Volume expansion will restore normal intravascular volume, increase preload, and thus increase cardiac output in a hypovolemic baby.[20,21,22] Use of albumin is not generally recommended because of the increased risk of infection (it is a blood product); also, the cost of isotonic saline is approximately one-fifth the cost of 4.5% human albumin.[23]	VII	20, 21, 22, 23
4. Dopamine, carefully titrated to the optimum hemodynamic response, should be considered prior to dobutamine for treatment of hypotension alone in VLBW infants when the cause of hypotension is unknown. **Rationale**: Dopamine is more effective than dobutamine for treating hypotension in premature infants. Dopamine does not appear to affect the incidence of severe periventricular hemorrhage, periventricular leukomalacia, or tachycardia. *Cautious stepwise increases* in dopamine in hypotensive VLBW infants are not associated with an abnormal neurologic picture, combined adverse outcomes (death, cerebral palsy, or profound neurodevelopmental delay), or developmental delay.	I III	24 25, 26
5. In VLBW infants with hypotension and LSBF during the *first postnatal day* caused by the immature myocardium's inability to pump against the sudden increased peripheral resistance that occurs with the removal of the placenta (myocardial dysfunction is caused by the VLBW infant's decrease in cardiac output when faced with an increase in peripheral resistance) and vasoconstriction of the immature forebrain vasculature, dobutamine may be considered the initial treatment choice in improving blood pressure. If blood pressure decreases after beginning dobutamine, low-dose dopamine can be added to the treatment regimen. **Rationale**: Dobutamine has a direct positive inotropic effect and has a variable degree of peripheral vasodilatory response. Thus, in situations where the VLBW infant's cardiac output has been compromised by the sudden increased peripheral resistance caused by removal of the low resistance placenta, as happens after birth, experts believe that *cautious stepwise increases* in dobutamine may increase cardiac output by promoting systemic vasodilation and improving LSBF. However, *no evidence* that dobutamine promotes vasodilation in the 1-day-old VLBW infant exists. Use of dopamine, primarily at high doses, in these patients may further increase vasoconstriction and decrease systemic blood flow and thus decrease cardiac output.[28]	I VII	27 28

(continued)

Practice Recommendation	Level of Evidence	Reference(s)
6. If hypotension in the VLBW infant is related to evidence of infection, dopamine should be considered as the first-line treatment. If dopamine is not effective, treatment with epinephrine should be considered. **Rationale**: Hypotension related to infection is primarily caused by systemic vasodilation. Only in the late phase of sepsis is hypotension related to myocardial dysfunction. Therefore, hypotension in VLBW infants with probable infection should be treated with a vasopressor or intropic agent such as dopamine or epinephrine that will promote vasoconstriction as well as myocardial function.	VII	28, 29, 30
7. Epinephrine can be as effective as dopamine in increasing blood pressure in hypotensive VLBW infants, but knowledge about epinephrine's effect on systemic blood flow is limited. **Rationale**: Low-dose epinephrine has strong beta- and somewhat weaker alpha-adrenergic effects and produces an increase in cardiac output and blood pressure. *Cautious stepwise increases* in epinephrine in hypotensive VLBW infants are not associated with an abnormal neurologic picture, combined adverse outcomes (death, cerebral palsy, or profound neurodevelopmental delay), or developmental delay.	II	25, 28, 31, 32, 33
8. The use of hydrocortisone is as effective as dopamine in improving hypotension in VLBW infants, but data on the long-term safety of corticosteroids for this use are insufficient. Thus, its use should be reserved for infants with refractory hypotension. Hydrocortisone should *not* be used concurrently with indomethacin. When one is considering the use of hydrocortisone for treatment, it may be useful to obtain a baseline serum cortisol level; this may identify infants with low levels who will benefit from hydrocortisone treatment. **Rationale**: Hydrocortisone has been shown to improve hypotension, increase tissue perfusion, and prevent ischemic tissue injury. However, hydrocortisone's neurodevelopmental effects and long-term effects are unclear. Nor is it clear whether longer-term clinical outcomes are improved with the use of hydrocortisone. Low baseline serum cortisol levels may identify infants who will benefit from hydrocortisone treatment; one study demonstrated that infants with serum cortisol levels below the median who were treated with hydrocortisone had increased survival without bronchopulmonary dysplasia when compared to those who did not receive hydrocortisone.	I II V VI VII	34 35, 36, 37, 38 39 40 41, 42
9. A single dose of dexamethasone may increase blood pressure in hypotensive VLBW infants, but dexamethasone cannot be recommended because of its documented negative effect on neurodevelopmental outcomes if given during the first postnatal days. **Rationale**: Several studies using both long and short courses of dexamethasone with relatively high doses have demonstrated significant effects on central nervous system development. Because of these findings and the lack of information on the safety of a short-course, lower-dose dexamethasone for treatment of hypotension, it cannot be recommended for use at this time.	I II VII	34 43, 44, 45, 46 15
10. At present, no evidence supports the use of milrinone for the treatment of hypotension in VLBW infants. **Rationale**: A double-blinded randomized controlled trial comparing the effectiveness of milrinone versus placebo on LSBF in VLBW infants demonstrated that milrinone did not prevent LSBF in these infants. No adverse effects were demonstrated with milrinone.	II	47
11. Research to recommend the use of dopamine (or other vasopressor-inotropes) for the treatment of hypotension related to a patent ductus arteriosus (PDA) in VLBW infants is scant. **Rationale**: Only one observational prospective study has been conducted that suggested that dopamine increased pulmonary vascular resistance in VLBW infants with hypotension and PDA and thus increased blood pressure and systemic blood flow (SVC flow) by decreasing the left-to-right shunt.	VI VII	48 49

Patients' Preferences

Not applicable

Potential Benefits and Harms

The primary goal of treating hypotension in VLBW infants is to maintain systemic blood flow, preserving end-organ perfusion and thus oxygen delivery to the tissues. The clinical emphasis is generally placed specifically on preserving cerebral blood flow and oxygen delivery.[15] Studies have correlated hypotension with LSBF, decreased cerebral blood flow, increased incidence of brain injury, and increased adverse neurodevelopmental outcome.[8,50,51,52] Intestinal injury due to decreased organ perfusion has also been a concern.

However, evidence exists that maintaining normal blood pressure may be only a part of the picture for the VLBW infant and that assessment of systemic blood flow requires more than measuring systemic blood pressure. The interaction among blood pressure, systemic blood flow, systemic vascular resistance, and blood flow regulation in vital and nonvital organs during transition to extrauterine life in the VLBW neonate is complex. Multiple factors—SVC flow, pulmonary blood flow, peripheral and pulmonary resistances, ductal flow, right ventricular output, immaturity of the myocardium, vital organ assignment, disease pathology, and tissue oxygen and carbon dioxide levels—are important to an understanding of the hemodynamics that affect VLBW infants and their well-being.[3,11,15] However, most of these parameters cannot be continually monitored at the patient's bedside in easily measured absolute numbers. Monitoring LSBF is considered to be important for successfully managing the cardiovascular system in the VLBW infant,[3] but one must keep in mind the limitations of the available technologies and remain cognizant of the more complex picture when addressing these issues.

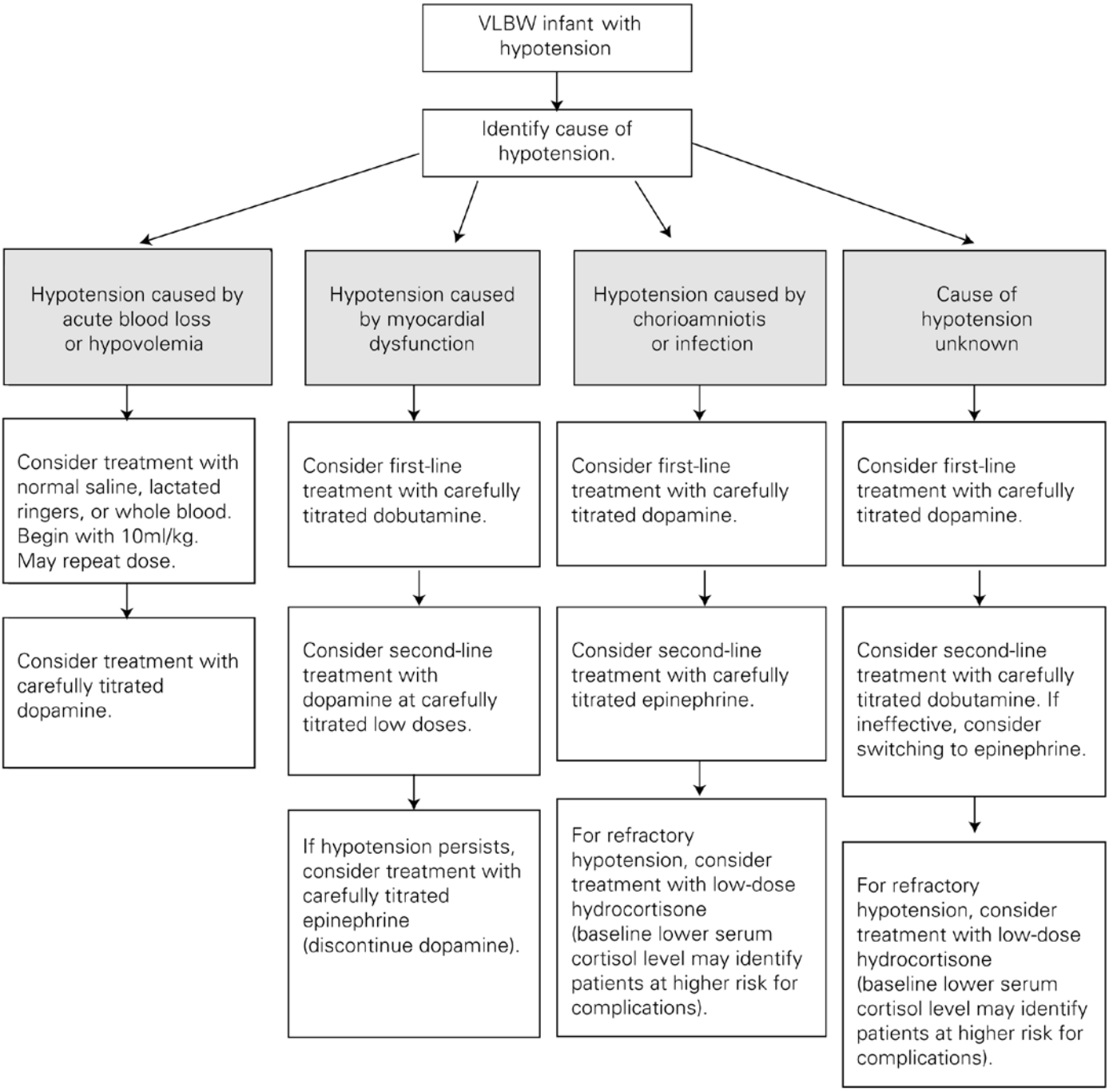
We must be sure that we are not doing more harm than good. In fact, we have no convincing evidence that treating hypotension in VLBW infants decreases mortality and neurologic morbidity,[18] and findings from one study (albeit a study with limitations) imply that treatment may be associated with development of intraventricular hemorrhage.[53] Recent retrospective studies have also suggested that "treated hypotension" is associated with adverse outcomes. The results of one study suggested that treated hypotension was associated with morbidity and hearing loss in VLBW infants.[54] Another retrospective study demonstrated that treated hypotension in VLBW infants was associated with adverse outcomes.[55] Although these retrospective findings are cautionary for treatment of hypotension and demonstrate the need for well-executed prospective studies that examine permissive hypotension and its consequences in this population, it is entirely unclear from these studies whether treatment has anything to do with the documented association. Indeed, it is possible that treatment of hypotension identifies a more vulnerable patient population or that treatment was initiated too late in the course of the clinical presentation or was ineffective, resulting in cerebral hypoperfusion and long-term neurodevelopmental disability.

In summary, any treatment option should be carefully examined with these considerations in mind. When any vasoactive agent is used, careful titration of the drug is critical; only cautious stepwise increases should be made. In addition, clinicians need not wait more than approximately 3–5 minutes between the dose changes while titrating the drug, as long as drug delivery with correct line priming is ensured and the infusion pump has been appropriately set up.[1,26]

It is imperative that one consider all parameters rather than just blood pressure before deciding on specific interventions for treating hypotension in VLBW infants. This guideline is based on the best evidence available through both neonatal research and consultation of experts on the subject. It suggests a conservative treatment approach that is logical, safe, and physiologically based. The insufficient fund of knowledge on transitional cardiovascular physiology in general and pathophysiology in particular makes establishment of strict guidelines on the treatment of hypotension in VLBW neonates impossible. This is also the reason that clinical studies addressing this question have been unable to provide the appropriate information and levels of evidence to guide management of neonatal hypotension in clinical practice.[11] What becomes clear when presenting the evidence is how much more we need to know.

Algorithm

Algorithm for Treatment of Hypotension in the VLBW Infant During the First 3 Days of Postnatal Life



Implementation Considerations

Management of hypotension in the VLBW infant is a complex issue that demands continued scrutiny and well-developed research. A key issue in implementing these guidelines is the reliable and accurate understanding of what constitutes hypotension in VLBW infants. Despite a large body of research on the topic, there is still no standard definition of hypotension in VLBW infants (especially those with birth weights less than 1,000 grams).[56,57] In addition, the standard definitions that are routinely used are supported by a paucity of published literature.[54] The authors and reviewers of this guideline recognize the importance of substantiating our clinical treatment through research and ensuring that the treatments used in VLBW infants are safe and are associated with positive long-term outcomes. We strongly advocate that further research be carried out to establish clearer parameters of hypotension in VLBW infants, but we recognize that the definitions of hypotension used by different clinicians will significantly affect how the recommendations in this guideline are interpreted. We strongly encourage those who are considering treatment of hypotension to use other indirect clinical signs of decreased organ perfusion as adjuncts to assessing systemic blood flow in the attempt to define the need for blood pressure treatment in VLBW infants. These clinical signs include changes in urine output, evidence of metabolic acidosis with increased serum lactate levels, and possibly increased heart rate and capillary refill time.[58]

Outcome Review Criteria

It is difficult to conduct an outcome review on this topic without further research on the management of hypotension in VLBW neonates. Decreased mortality and improved neurodevelopmental outcomes in VLBW infants who have been treated for hypotension following this guideline are the criteria by which it should ultimately be measured. Further evaluation of research within the update timeframe of the guideline will allow this judgment to be made.

Update Plan

This guideline will be updated every 5 years. It will expire in 2016 and will be updated in 2016.

References

1. McClean CW, Cayabyab RG, Noori S, Seri I. Cerebral circulation and hypotension in the premature infant: diagnosis and treatment. In: Perlman JM, Polin RA, editors. Neonatology questions and controversies: neurology. Philadelphia: Saunders/Elsevier; 2008. p. 3-26.
2. Nuntnarumit P, Yang W, Bada-Ellzey HS. Blood pressure measurements in the newborn. Clin Perinatol. 1999;26:981-6.
3. Kluckow M, Evans N. Low systemic blood flow in the preterm infant. Semin Neonatol. 2001;6:75-84.
4. Evans, N. Assessment and support of the preterm circulation. Early Hum Dev. 2006;82:803-10.
5. Kluckow M, Evans N. Low superior vena cava flow and intraventricular hemorrhage in preterm infants. Arch Dis Child Fetal Neonatal Ed. 2000;82:F188-94.
6. Kluckow M, Evans N. Superior vena cava flow in newborn infants: a novel marker of systemic blood flow. Arch Dis Child Fetal Neonatal Ed. 2000;82:F182-7.
7. West C, Groves AM, Williams CE, Harding JE, Skineer JR, Kuschel CA, et al. Early low cardiac output is associated with compromised electroencephalographic activity in very preterm infants. Pediatr Res. 2006;610-5.
8. Miall-Allen VM, de Vries LS, Whitelow AG. Mean arterial blood pressure and neonatal cerebral lesions. Arch Dis Child. 1987;62:1068-9.
9. Watkins AM, West CR, Cooke RW. Blood pressure and cerebral hemorrhage and ischaemia in very low birthweight infants. Early Hum Dev. 1989;19:103-10.
10. Tyszczuk L, Meek J, Elwell C, Wyatt JS. Cerebral blood flow is independent of mean arterial blood pressure in preterm infants undergoing intensive care. Pediatrics. 1998;102:337-41.
11. Noori S, Stavroudis TA, Seri I. Systemic and cerebral hemodynamics during the transitional period after birth. Clin Perinatol. 2009;36:723-36.
12. Kehrer M, Blumenstock G, Ehehalt S, Goelz R, Poets C, Schoning M. Development of cerebral blood flow volume in preterm neonates during the first two weeks of life. Pediatr Res. 2005;58:927-30.
13. Short BL, Van Meurs K, Evans JR, Cardiology Group. Summary proceedings from the cardiology group on cardiovascular instability in preterm infants. Pediatrics. 2006;117:S34-9.
14. Evans N. Support of the preterm circulation: keynote address to the fifth evidence versus experience conference. 2008 Jun; Chicago. J Perinatol. 2009;29:S50-7.
15. Seri, I, Evans J. Controversies in the diagnosis and management of hypotension in the newborn infant. Curr Opin Pediatr. 2001;13:116-23.
16. Seri I. Circulatory support of the sick preterm infant. Semin Neonatol. 2001;6:85-95.
17. Fanaroff JM, Fanaroff AA. Blood pressure disorders in the neonate: hypotension and hypertension. Semin Fetal Neonatal Med., 2006;11:174-81.
18. Osborn DA, Evans NJ. Early volume expansion for prevention of morbidity and mortality in very preterm infants. Cochrane Database Syst Rev. 2004;2:CD002055.
19. Osborn DA, Evans NJ. Early volume expansion versus inotrope for prevention of morbidity and mortality in very preterm infants. Cochrane Database Syst Rev. 2001;2:CD002056.
20. American Academy of Pediatrics and American Heart Association. Textbook of neonatal resuscitation. 5th ed. Elk Grove Village (IL): The Academy and the Association; 2006.
21. Evans N. Which inotrope for which baby? Arch Dis Child Fetal Neonatal Ed. 2006;91:F213-20.
22. Kluckow M, Seri I. Clinical presentations of neonatal shock: the VLBW infant during the first postnatal day. In: Kleinman CS, Seri I, editors. Neonatology questions and controversies: hemodynamics and cardiology. Philadelphia: Saunders/Elsevier; 2008. p. 178-94.
23. 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:F450-4.
24. Subhedar NV, Shaw NJ. Dopamine versus dobutamine for hypotensive preterm infants. Cochrane Database Syst Rev. 2003;2:CD001242.
25. Pellicer A, Bravo MC, Madero R, Salas S, Quero J, Cabañas, F. Early systemic hypotension and vasopressor support in low birth weight infants: impact on neurodevelopment. Pediatrics. 2009;123:1369-76.
26. Seri I, Rudas G, Bors Z, Kanyicska B, Tulassay T. Effects of low-dose dopamine infusion on cardiovascular and renal functions, cerebral blood flow, and plasma catecholamine levels in sick preterm neonates. Pediatr Res. 1993;34:742-9.
27. Osborn DA, Paradisis M, Evans N. The effect of inotropes on morbidity and mortality in preterm infants with low systemic or organ blood flow. Cochrane Database Syst Rev. 2007;1:CD005090.
28. Seri I. Management of hypotension and low systemic blood flow in the very low birth weight neonate during the first postnatal week. J Perinatol. 2006;26:S8-13.
29. Yanowitz TD, Jordan, JA, Gilmour CH, Towbin R, Bowen A, Roberts JM, et al. Hemodynamic disturbances in premature infants born after chorioamnionitis: association with cord blood cytokine concentrations. Pediatr Res. 2002;51:310-6.
30. Yanowitz TD, Baker RW, Roberts JM, Brozanski BS. Low blood pressure among very-low-birth-weight infants with fetal vessel inflammation. J Perinatol. 2004;24:299-304.
31. Valverde E, Pellicer A, Madero R, Elorza D, Quero J, Cabañas F. Dopamine versus epinephrine for cardiovascular support in low birth weight infants: analysis of systemic effects and neonatal clinical outcomes. Pediatrics. 2006;117:e1213-22.
32. Pellicer A, Valverde E, Elorza MD, Madero R, Gaya F, Quero J, et al. Cardiovascular support for low birth weight infants and cerebral hemodynamics: a randomized, blinded, clinical trial. Pediatrics. 2005;115:1501-12.
33. Barrington KJ, Finer NN, Chan WK. A blind, randomized comparison of the circulatory effects of dopamine and epinephrine infusions in the newborn piglet during normoxia and hypoxia. Crit Care Med. 1995;23:740-8.
34. Subhedar NV, Duffy K, Ibrahim H. Corticosteroids for treating hypotension in preterm infants. Cochrane Database Syst Rev. 2007;1:CD003662.
35. Efird MM, Heerens AT, Gordon, PV, Bose CL, Young DA. A randomized-controlled trial of prophylactic hydrocortisone supplementation for the prevention of hypotension in extremely low birth weight infants. J Perinatol. 2005;25:119-24.
36. Ng PC, Lee CH, Bnur FL, Chan IH, Lee AW, Wong E, et al. A double-blinded, randomized, controlled study of a "stress dose" of hydrocortisone for rescue treatment of refractory hypotension in preterm infants. Pediatrics. 2006;117:367-75.
37. Watterberg KL, Gerdes JS, Cole CH, Aucott SW, Thilo EH, Mammel MC, et al. Prophylaxis of early adrenal insufficiency to prevent bronchopulmonary dysplasia: a multicenter trial. Pediatrics. 2004;114:1649-57.

38. Peltoniemi O, Kari MA, Heinonen K, Saarela T, Nikolajev K, Andersson S, et al. Pretreatment cortisol values may predict responses to hydrocortisone administration for the prevention of bronchopulmonary dysplasia in high-risk infants. J Pediatr. 2005;146:632-7.

39. Higgins S, Friedlich P, Seri I. Hydrocortisone for hypotension and vasopressor dependence in preterm neonates: a meta analysis. J Perinatol. 2010;30:373-8. Epub 2009 Aug 20.

40. Noori S, Friedlich P, Wong P, Ebrahimi M, Siassi B, Seri I. Hemodynamic changes following low-dose hydrocortisone administration in vasopressor-treated neonates. Pediatrics. 2006;118:1456-66.

41. Seri I. Hydrocortisone and vasopressor-resistant shock in preterm neonates. Pediatrics. 2006;117:516-8.

42. Barrington KJ. Hypotension and shock in the preterm infant. Semin Fetal Neonatal Med. 2008;13:16-23.

43. Gaissmaier RE, Pohlandt F. Single dose dexamethasone treatment of hypotension in preterm infants. J Pediatr. 1999;134:701-5.

44. Stark AS, Carlo WA, Tyson JE, Papile L, Wright, LL, Shankaran S, et al. Adverse effects of early dexamethasone treatment in extremely-low-birth-weight infants. N Engl J Med. 2001;344:95-101.

45. Shinwell ES. Early postnatal dexamethasone treatment and increased incidence of cerebral palsy. Arch Dis Child. 2000;83:F177-81.

46. O'Shea TM, Kothadia JM, Klinepeter KL, Goldstein DJ, Jackson BG, Weaver RG, et al. Randomized placebo controlled trial of a 42-day long tapering course of dexamethasone to reduce the duration of ventilator dependency in very low birth weight infants: outcome of study participants at 1 year adjusted age. Pediatrics. 1999;104:15-21.

47. Pardisis 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;154:189-95.

48. Bouissou A, Rakza T, Klosowski S, Tourneux P, Vanderborght M, Storme L. Hypotension in preterm infants with significant patent ductus arteriosus: effects of dopamine. J Pediatr. 2008;153:790-4.

49. Seri I, Noori S. Diagnosis and treatment of neonatal hypotension outside the transitional period. Early Hum Dev. 2005;81:405-11.

50. Goldstein RF, Thompson RJ, Oehler JM, Brazy JE. Influence of acidosis, hypoxia and hypotension on neurodevelopmental outcome in very low birth weight babies. Pediatrics. 1995;95:238-43.

51. Osborn DA, Evans N, Kluckow M. Hemodynamic and antecedent risk factors of early and late periventricular/intraventricular hemorrhage in preterm babies. J Pediatr. 2003;112:33-9.

52. Hunt RW, Evans N, Rieger I, Kluckow M. Low superior vena cava flow and neurodevelopmental outcome at three years in very preterm babies. J Pediatr. 2004;145:588-92.

53. Synnes AR, Chien LY, Peliowski A, Baboolal R, Lee SK. Variations in intraventricular hemorrhage incidence rates among Canadian neonatal intensive care units. J Pediatr. 2001;138:525-31.

54. Fanaroff JM, Wilson-Costello DE, Newman NS, Montpetite MM, Fanaroff AA. Treated hypotension is associated with neonatal morbidity and hearing loss in extremely low birth weight infants. Pediatrics. 2006;117:1131-5.

55. Dempsey EM, 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:F241-4. Epub 2009 Jan 27.

56. Evans JR, Short BL, Meurs KV, Sachs HC. Cardiovascular support in preterm infants. Clin Ther. 2006;28:1366-84.

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

58. Engle WD. Definition of normal blood pressure range; the elusive target. In: Kleinman CS, Seri I, editors. Neonatology questions and controversies: hemodynamics and cardiology. Philadelphia: Saunders/Elsevier; 2008. p. 39-65.

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