Hypotension in Neonates

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Education Gaps

1. Clinicians should understand the indications for treatment of hypotension in neonates.
2. Clinicians need to choose the right antihypotensive therapy based on the patient's clinical presentation.

Objectives

After completing this article, readers should be able to:

1. Understand the pathophysiology of hypotension in preterm neonates.
2. Define hypotension and understand the role of transition from fetal to perinatal circulation in causing blood pressure changes in neonates.
3. Describe the indications for treatment of hypotension in neonates.
4. Understand the mechanism of action of various inotropic agents and the indications for the use of different agents based on clinical presentation.

Abstract

Hypotension is frequently encountered in preterm infants. However, there is no standard definition for hypotension and the therapies for treating hypotension in neonates vary greatly, based on individual preferences. This article focuses on the pathophysiology of hypotension in preterm neonates, the role of the transition from fetal to perinatal circulation on neonatal blood pressure, the mechanisms of action of agents used in the treatment of hypotension, and the specific indications for the use of such agents.

INTRODUCTION

Neonatologists frequently diagnose and treat hypotension in preterm infants. The incidence of hypotension in this age group varies greatly among institutions because of differences in practice and lack of standardized norms. (1) In newborns, blood pressure (BP) varies with gestational age, postmenstrual age, and birthweight. BP increases after birth, with greater rates of increase seen in preterm infants than in term infants. Recent studies have shown that there is significant variability within the extremely low-birthweight (ELBW) population both in measurements and responses to therapies for hypotension. (2)

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DEFINITION OF HYPOTENSION

There is no standard definition of hypotension in neonates. In clinical trials and in practice, hypotension is defined as any value that falls below the 5th or 10th percentile for gestational and postnatal age. The most accepted definition of physiologic hypotension is the point at which cerebrovascular autoregulation is lost, leading to cerebral function compromise and tissue ischemia. (3) Unfortunately, there is no readily available clinical method of determining this point.

Whereas in adults and children, normative data for systolic, diastolic, and mean blood pressure (MBP) are available, in neonates "MBP" is used most often to define hypotension. Empirically, the gestational age in weeks has been used to define the lower limits of MBP during the first day after birth. However, this is unreliable and the BP should be evaluated in the context of the clinical condition. The BP rises significantly during the first 72 hours after birth, irrespective of gestational age, and all preterm infants should have an MBP greater than 30 mm Hg by this time. (4)

MEASUREMENT OF BLOOD PRESSURE IN NEONATES

The "gold standard" for determining BP in the critically ill neonate is a direct reading from an indwelling arterial line, and should be used whenever arterial access is available. MBP is considered most reflective of the systemic perfusion pressure because the systolic and diastolic values are thought to be affected by the small bubbles that may get introduced in the system. Other noninvasive methods of monitoring include the use of Doppler or oscillometric techniques, but their inability to provide continuous monitoring is a major drawback. (5) Table 1 lists the MBP in neonates of different gestational ages during the first 72 hours after birth. (6)

TRANSITION FROM FETAL TO PERINATAL CIRCULATION

Figure 1 illustrates the circulation of blood in the fetus. The oxygenated blood is carried by the umbilical vein from the placenta, through the liver via the ductus venosus, and into the inferior vena cava. From the inferior vena cava, it enters the right atrium, where most of it is shunted via the patent foramen ovale (PFO) to the left heart and then through the aorta to oxygenate the fetal body, aided by low systemic vascular resistance (SVR). The blood that does not cross the PFO continues to the right ventricle, through the pulmonary artery via the patent ductus arteriosus (PDA) into the aorta, and out to the systemic circulation. Pulmonary vascular resistance (PVR) is high during fetal life, making it difficult for blood to flow into the lungs, so it is easily shunted across the PDA. Only about 10% to 12% of blood travels to the fetal lungs. The presence of low SVR, high PVR, PDA, and PFO ensures that the most oxygenated blood from the mother is directed to the heart and brain of the fetus. After circulating through the fetal body, the blood then travels back to the placenta via the umbilical arteries. (7) At birth, the clamping of the cord results in removal of low-resistance placental circulation and increase in SVR. When the infant takes its first breath, lung expansion causes a reduction in PVR, increase in pulmonary blood flow, and fall in pulmonary artery pressure. Functional closure of the PFO occurs due to increased pressure in the left atrium compared to the right atrium. In addition, the PDA closes due to increased arterial oxygen saturation. (8)

PATHOPHYSIOLOGY OF HYPOTENSION IN PRETERM NEONATES

BP is affected by several factors, including the structure and function of the myocardium as a pump, the elasticity of

TABLE 1. **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)*

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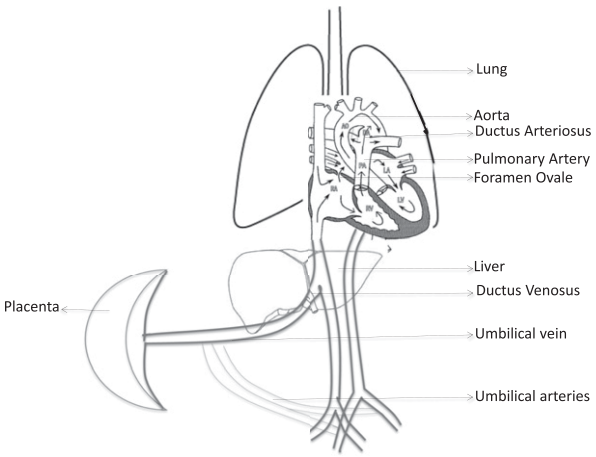

Figure 1. Fetal circulation.

blood vessels, blood volume, and blood viscosity. The autonomic nervous system plays an important role in maintaining adequate organ perfusion. The hemodynamic changes during the process of transition from intrauterine to extrauterine life also affect the BP in preterm neonates. (9) The major factors contributing to hypotension are discussed herein (summarized in Table 2).

1. Preterm myocardium. The immature heart is less capable of increasing cardiac output in response to an increase in preload than the mature heart, due to less contractile force and less compliance. (10) The neonatal cardiac myocyte is smaller and less organized than the mature myocyte, containing fewer myofibrils and mitochondria. In addition, it has less intracellular calcium and is dependent on trans-sarcolemmal calcium flux for myocardial contraction. (11)

TABLE 2. **Factors Contributing To Hypotension In Preterm Neonates**

1	Immature myocardium → decreased contractility
2	Transition from fetal to perinatal circulation → increased SVR
3	PDA → left-to-right shunt → steal syndrome
4	Perinatal hypoxia/asphyxia → neuroendocrine changes causing increased SVR
5	PPV → decreased venous return
6	Sepsis and inflammation → inflammatory mediators causing peripheral vasodilation and increased vascular permeability
7	Relative adrenal insufficiency → insufficient cortisol during stress/illness

PDA=patent ductus arteriosus; PPV=positive pressure ventilation; SVR=systemic vascular resistance.

2. Maladaptive transition from intrauterine to extrauterine circulation. At birth, the lower pressure umbilical circulation is eliminated, resulting in increased SVR. Due to the structure of the preterm myocardium, it may not be able to overcome this increased resistance, leading to low systemic blood flow. Hence, neonates born at less than 30 weeks' gestation commonly have low systemic blood flow, (12) which contributes to low BP. BP is the product of peripheral resistance and the blood flow through the vessel. (13)
3. Patent ductus arteriosus. In term infants, the ductus arteriosus normally closes within 12 to 15 hours of birth. However, the closure of the ductus is delayed in preterm infants due to the elevated PVR associated with lung disease, decreased sensitivity of ductal tissue to oxygen, and increased circulating prostaglandin E2. A large ductus causes decreased systemic flow due to left-to-right shunt. Because the ductus is open during both systole and diastole, there is a "steal syndrome" that leads to decreased diastolic blood flow to organs such as the kidney and intestines. (14)
4. Perinatal hypoxia/asphyxia. During uterine contractions, oxygen delivery decreases intermittently, leading to neuroendocrine changes such as increased production and release of catecholamines, renin, angiotensin, and vasopressin. These contribute to the postnatal increase in SVR and decrease in systemic blood flow. If the neonate sustains a hypoxic insult due to perinatal asphyxia, myocardial dysfunction ensues and may contribute to hypotension. (7)
5. Positive pressure ventilation. Preterm infants frequently require positive pressure ventilation for respiratory support, which contributes to decreased systemic blood flow by increasing the intrathoracic pressure and decreasing the venous return. (13)
6. Sepsis and inflammatory response. Sepsis, necrotizing enterocolitis, and chorioamnionitis are causes of hypotension in both preterm and term infants. These conditions are associated with release of inflammatory mediators like interleukin 1 and tumor necrosis factor, which lead to peripheral vasodilation and increased vascular permeability. This causes hypovolemia and hypotension. (15)
7. Relative adrenal insufficiency. Relative adrenal insufficiency is defined as an inability to produce sufficient cortisol in response to stress or illness and can contribute to hypotension in premature infants. Preterm neonates are at risk for relative adrenal insufficiency due to immaturity of the adrenal gland. They have limited 3β-hydroxysteroid dehydrogenase, which is required for the synthesis of cortisol. Moreover, the fetal

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hypothalamic-pituitary axis is suppressed due to the maternal cortisol transmitted through the placenta. (16)

ADVERSE EFFECTS OF HYPOTENSION IN NEONATES

Many studies show an association between hypotension and poor neurodevelopmental outcomes in neonates. (17)(18) Although this does not prove causation, low BP does lead to impaired cerebral blood flow (CBF), particularly in preterm neonates who have immature cerebral autoregulation, and is a common rationale for treating hypotension in neonates. (19)

Arteries constrict in response to an increase in transmural pressure and dilate in response to a decrease in pressure, resulting in almost constant blood flow with a range of arterial blood pressures. This ability to autoregulate is immature in preterm neonates and occurs only over a narrow range of BP (shown as the plateau between 2 ends of pressure passivity in Fig 2). Hence, preterm neonates are particularly susceptible to ischemia with low BP and hemorrhage with high BP. (20) The MBP at which cerebral autoregulation is lost in preterm infants is not known, but is estimated to be as high as 28 to 30 mm Hg, even in ELBW infants. (3) In animal models, the ischemic BP threshold is reached when the corresponding CBF is approximately 50% of the resting CBF. (20)

Laughon et al (1) conducted a prospective study to determine the factors associated with treatment of hypotension in extremely low gestational age newborns during the first week after birth. Treatment of hypotension was associated with lower gestational age, male gender, low birthweight, and higher score for neonatal acute physiology-II values. The decision to intervene was associated more strongly with institutional practices than with the infant's clinical attributes.

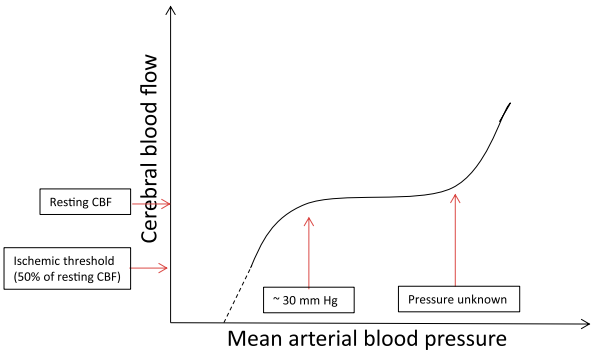

Figure 2. Relationship between cerebral blood flow and mean blood pressure in cerebral circulation. The autoregulatory plateau is the flat portion on the curve. The upper threshold is unknown, but lower threshold is estimated to be about 30 mm Hg. Adapted from Batton B, Li L, Newman NS, et al; Eunice Kennedy Shriver National Institute of Child Health & Human Development Neonatal Research Network. Use of antihypotensive therapies in extremely preterm infants. *Pediatrics*. 2013;131(6):e1865–e1873. (21)

A prospective multicenter study by the National Institute of Child Health and Human Development neonatal research network examined the relations between 15 definitions of low BP, antihypotensive therapy, and in-hospital outcomes and did not find any benefit of treating low BP in this population. (21) It has been suggested that intervention must be done with caution, and that hypotension should be treated only when it is prolonged or associated with metabolic acidosis, hypoxia, hypocapnia, hypercapnia, or conditions associated with impaired cerebral autoregulation. (19)

TREATMENT OF HYPOTENSION

In 2011, the National Association of Neonatal Nurse Practitioners (NANN) developed a guideline for the management of systemic hypotension in very low-birthweight (VLBW) infants during the first 3 postnatal days, which was endorsed by the American Academy of Pediatrics. (22) The essence of these guidelines is discussed in the following section. The treatment of hypotension should be directed to address the underlying pathology. In most instances, the clinical presentation of the infant provides clues to the etiology of hypotension. (23) Modalities for treatment of hypotension include volume replacement and vasopressor and inotropic support, and should be used based on the overall clinical picture rather than a number. Frequent evaluation of vital signs, perfusion, urine output, chemistry, and neurologic status are used to monitor and guide therapy. There is also recent interest in the use of targeted/functional echocardiography (TnECHO) to assist in diagnosing and monitoring these infants. (4) It is being used to identify the underlying pathophysiology of the cardiovascular compromise and assist neonatologists in making a decision about the type of cardiovascular support to use and monitor the response to treatment. However, its use involves learning the skills to perform and interpret TnECHO, which may need 6 to 12 months of training. (19)

1. Volume expanders are frequently used for treatment of hypotension, though there is no evidence to support their benefit in preterm infants. (24) In addition, indiscriminate use of volume has been associated with pulmonary, cardiovascular, gastrointestinal, and central nervous system morbidity and mortality. Cautious administration of 10 to 20 mL/kg of volume can be useful in situations in which fetal blood loss and hypovolemia are contributing to hypotension. If there is a history of hemorrhage or severe anemia, packed red blood cells should be used. (25) Otherwise, isotonic crystalloid solutions, such as normal saline, are preferred over colloid.

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(26) If sustained normalization of BP is not achieved with a single bolus, inotropic support should be initiated. (25)

2. Dopamine is the inotropic medication most commonly used to control low BP. (4) It exerts its effects by dose-dependent stimulation of the α and β adrenergic and dopaminergic receptors. In adults and children, dopamine at low doses (2–4 μg/kg per minute) dilates the renal and splanchnic vessels by its action on the vascular dopaminergic receptors. At moderate doses (5–10 μg/kg per minute), it predominantly increases cardiac contractility and heart rate by stimulating the cardiac β_1, β_2, and α_1 adrenergic and the dopaminergic receptors. At high doses (≥10–20 μg/kg per minute), dopamine increases peripheral vascular resistance by stimulating vascular α_1 receptors. However, pharmacodynamic data on dose-related effects of dopamine in the neonate are limited. Moreover, dopamine exerts most of its inotropic effects by releasing stored norepinephrine from the terminal nerve endings, a limitation in the preterm neonate because of the depletion of myocardial norepinephrine stores within 8 to 12 hours. (27) Despite these disadvantages, dopamine is recommended as a first-line pharmacologic treatment for hypotension in most situations and should be carefully titrated to achieve an adequate hemodynamic response.
3. Dobutamine is a synthetic, relatively cardioselective inotrope that acts on the α- and β-adrenergic receptors and exerts direct inotropic but limited chronotropic effect. (25) It increases cardiac contractility by its action on the β_1 receptor and increases cardiac output by increasing stroke volume in a dose-dependent manner. It has minimal effect on the systemic BP and afterload, because the α_1-mediated vasoconstriction is almost cancelled by the β_2-mediated vasodilation. (28) Dobutamine is the preferred drug for treating hypotension in neonates with myocardial dysfunction due to perinatal asphyxia, because a decrease in myocardial contractility is the primary cause of cardiovascular compromise in this population. (27)

Dopamine versus dobutamine. There is a long-standing controversy on the effectiveness and safety of using dopamine versus dobutamine to treat hypotension in preterm infants. Dopamine has been preferred by many neonatologists because of its safety profile, effect of increasing renal and splanchnic blood flow at low doses, and ability to increase BP due to its potent inotropic and chronotropic effects at high doses. On the other hand, dobutamine has limited vasomotor activity and increases BP mainly through its inotropic effect. (29) Although dobutamine increases stroke volume and heart rate, the resulting increase in cardiac output does not always result in increase of BP. (30) However, unlike dopamine, the effects of dobutamine are not dependent on the release of endogenous catecholamines. (31)

According to a Cochrane meta-analysis, dopamine is more effective than dobutamine for the short-term treatment of hypotension in premature infants. Dopamine does not appear to affect the incidence of severe periventricular hemorrhage, periventricular leukomalacia, or tachycardia. (32) Dopamine is recommended as the first-line agent when hypotension is caused by vasodilation whereby an increase in afterload is required to raise BP and restore organ perfusion, (23) as seen in clinical sepsis.

Dobutamine is a better choice in situations of compromised cardiac output such as may occur immediately after birth. This is because of the sudden increase in SVR that occurs with removal of low-resistance placental circulation or when there is myocardial dysfunction due to perinatal asphyxia. In these patients, restoring myocardial contractility and lowering SVR will result in restoration of tissue and organ perfusion. (30) With hypotension due to shock, the myocardial dysfunction, impaired SVR, and relative or absolute hypovolemia are best treated with combination therapy of dobutamine and dopamine. (30)

4. Epinephrine, an endogenous catecholamine, is released by the adrenal gland in response to stressful stimulation. It has a potent nonselective α−agonist action and causes activation of both β_1- and β_2-adrenergic receptors. (28) Thus, it increases BP and systemic blood flow by increasing SVR and cardiac output. In clinical practice, epinephrine administered at low dosages (0.01–0.1 μg/kg per minute) stimulates β receptors, resulting in enhanced myocardial contractility and peripheral vasodilatation. At higher doses (>0.1 μg/kg per minute), additional stimulation of α receptors causes peripheral vasoconstriction and increased SVR. (33) Data on the use of epinephrine in preterm infants are limited. Valverde et al conducted a randomized controlled trial (RCT) to compare the effectiveness of low/moderate-dose dopamine and epinephrine for cardiovascular support in preterm infants with hypotension in the first few days after birth. (34) They concluded that low-dose epinephrine is as effective as low/moderate-dose dopamine in increasing systemic BP in low-birthweight infants and has a greater chronotropic effect. However, epinephrine causes disturbances in the carbohydrate and lactate metabolism by stimulating β_2 receptors in the liver and skeletal muscle, thus increasing the risk of hyperglycemia and increased lactate. (34) Hence, most neonatologists use epinephrine only in patients unresponsive to high-dose dopamine. Due to its effect on vascular tone and myocardial contractility, it presents an effective

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choice for treatment of low SVR with or without impaired myocardial contractility, such as septic shock or certain cases of perinatal asphyxia. (27)

Norepinephrine (another endogenous catecholamine), released predominantly from sympathetic nerve terminals, is a potent nonselective α agonist with some effect at the β_1 receptor and is the first line of treatment for adult and pediatric vasodilatory shock. It is rarely used in neonatal practice because of the limited studies on its use and concerns about its safety in this population. (28)

5. Vasopressin, also known as *arginine vasopressin*, is an antidiuretic hormone that is formed in the hypothalamus and secreted from the posterior pituitary gland. Its exogenous form is used in the treatment of catecholamine-resistant hypotension in vasodilatory shock. (35) The vascular effects of vasopressin occur by stimulation of the G protein–coupled V_{1a} and V_2 receptors in the cardiovascular system. The V_{1a} and V_2 receptors induce vasoconstriction and vasodilation by activation of the inositol trisphosphate and cyclic adenosine monophosphate (cAMP) pathways, respectively. The potent vasoconstrictive effects of vasopressin dominate when it is used as an infusion. (36) No large RCT has evaluated the use of arginine vasopressin in the neonatal population. A recent RCT compared vasopressin to dopamine as initial therapy in ELBW infants who had hypotension during the first 24 hours after birth. (37) They did not find any differences between the 2 treatment groups with regard to their primary efficacy outcomes (ie, percent responders and time to adequate MBP). However, the infants receiving vasopressin had lower mean partial pressure of carbon dioxide, received fewer doses of surfactant, and did not have tachycardia during study drug administration compared with the infants in the dopamine group. The authors attributed the respiratory benefits and absence of tachycardia to the pulmonary vasodilatory effects and lack of cardiac effects of vasopressin.
6. Milrinone is a selective phosphodiesterase III inhibitor and exerts its cardiovascular effects by increasing cAMP, independent of β-adrenergic receptors. By increasing the concentration of cAMP, milrinone enhances myocardial contractility without raising myocardial oxygen consumption or increasing afterload, and decreases vascular tone in the systemic and pulmonary vascular beds. (38) Because of its unique profile of cardiovascular actions, milrinone is increasingly being used in the NICU to treat low cardiac output after corrective surgery for congenital heart defects, in near-term and term neonates with persistent pulmonary hypertension of the neonate, as an adjunct to inhaled nitric oxide, and for low BP in extremely preterm infants. (39) A large retrospective study of 1,446 infants evaluated the safety of milrinone use in this population and reported thrombocytopenia and hypotension requiring pressors as its most common adverse effects. (39) Hence, milrinone should be used with caution in hypotensive patients, particularly because the half-life of milrinone is 4 hours and is likely to be prolonged in the setting of prematurity and organ dysfunction. (40) An RCT comparing early prophylactic milrinone (loading dose 0.75 μg/kg per minute for 3 hours followed by maintenance dose of 0.2 μg/kg per minute until 18 hours after birth) with placebo in the prevention of low systemic blood flow in high-risk preterm infants failed to demonstrate any benefit. (41) Hence it is only used in the aforementioned situations for the management of hypotension.
7. Hydrocortisone. Cortisol concentrations are inversely related to gestational age and particularly low in infants receiving inotropic support. (42) Figure 3 shows the negative feedback loop regulating the secretion of cortisol. During critical illness, downregulation of the adrenergic receptors leads to a gradual desensitization of the cardiovascular system to the effects of catecholamines, resulting in the need for escalating pressor support. In addition, relative or absolute adrenal insufficiency may contribute to pressor resistance. (25)(43)

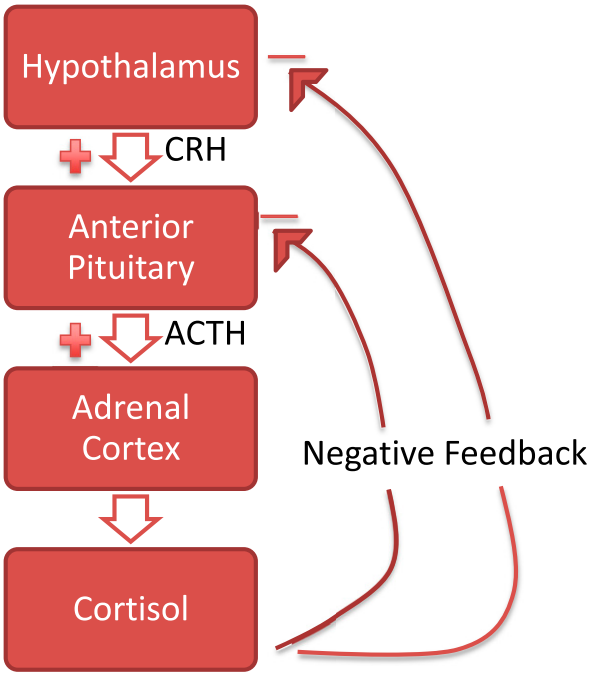

Figure 3. Negative feedback loop regulating cortisol production. ACTH=adrenocorticotropic hormone; CRH=corticotropin-releasing hormone.

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Hydrocortisone exerts its cardiovascular action by the following mechanisms:

- Upregulation of cardiovascular adrenergic receptors, which can result in vasoconstriction, increased cardiac output, and increased BP. (44)
- Upregulation of angiotensin II receptors and their second messenger systems, which play important roles in BP regulation. (44)(45)
- Inhibition of the expression of inducible nitric oxide synthase and vasodilatory prostaglandin action. (44)(45)
- Inhibition of catecholamine metabolism and the release of vasoactive factors. (46)
- Increase in the intracellular calcium concentration leading to enhanced myocardial and vascular responsiveness to catecholamines. (46)

In addition, in the critically ill preterm and term neonate with relative adrenal insufficiency, low-dose hydrocortisone administration also serves as hormone replacement therapy. (45) A Cochrane review of corticosteroid use for treating hypotension in preterm infants did not find sufficient evidence to support its use in primary treatment of hypotension. However, the authors suggest using corticosteroids (hydrocortisone and dexamethasone) to treat preterm infants with refractory hypotension receiving inotropes. (47) The recommended starting dose of hydrocortisone is 15 mg/m^2 or 1 to 2 mg/kg every 6 to 12 hours intravenously. (48) The dosing interval is 6 to 8 hours for infants of more than 35 weeks of gestation and 8 to 12 hours for infants of less than 35 weeks of gestation. (48) The treatment is deemed to be effective if BP and urine output improve and the need for inotropic support decreases. With this improvement, a reduction in the dose to 0.5 mg/kg per dose is recommended. If the duration of treatment is 3 days or less, hydrocortisone may be discontinued without tapering because the hypothalamic-pituitary-adrenal axis is not suppressed. (46)(48)

Although corticosteroids seem to be safe in the short term, their long-term safety and effect on neurodevelopmental outcome is unclear. (22)(47) The NANN practice guideline suggests that hydrocortisone should not be used with indomethacin. When considering the use of hydrocortisone for treatment, a baseline cortisol level will help to identify infants with low levels who will benefit from hydrocortisone treatment. (22)

8. Dexamethasone. We have discussed the role of cortisol deficiency in hypotension in preterm infants and the benefit of using corticosteroids in treating refractory hypertension in this population. A retrospective database review showed that low-dose dexamethasone rapidly increases BP and decreases pressor requirements in VLBW neonates with volume and pressor-resistant hypotension. (49) Another double-blinded placebo-controlled study showed that a single dose of 0.25 mg dexamethasone improved severe hypotension in preterm infants unresponsive to volume expansion and dopamine infusion within 12 hours of administration. (50) However, several studies have demonstrated significant negative neurodevelopmental outcomes with the use of dexamethasone. (51)(52) Because little information is available about the safety of short courses of low-dose dexamethasone, its use in the treatment of hypotension is not routinely recommended.

CONCLUSION

A thorough understanding of the pathophysiology of cardiovascular compromise is essential to appropriately manage and treat hypotension in neonates. Unfortunately, recommendations for the clinical use of medications to treat hypotension are extrapolated from studies of diverse designs in addition to limited RCTs. Careful titration of the selected medication with close hemodynamic monitoring is essential for effectively treating the hypotension while minimizing the potential adverse effects of these medications.

American Board of Pediatrics Neonatal—Perinatal Content Specification

- Know the pathophysiology of a term or preterm infant with a condition affecting the systemic blood pressure, such as hypotension.
- Formulate a differential diagnosis for an infant with systemic hypotension.
- Know the mechanism of action of commonly used adrenergic vasopressor and/or inotropic drugs (eg, dopamine, dobutamine, epinephrine).
- Know the therapeutic indications for, and toxicity of, commonly used adrenergic drugs.
- Know the mechanisms of action, therapeutic indications for, and toxicity of chronotropic drugs.
- Know the mechanisms of action, therapeutic indications for, and toxicity of inotropic drugs.

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1. An infant is born at 27 weeks' gestational age to a mother with chorioamnionitis. He is admitted to the NICU and is administered nasal continuous positive airway pressure. The blood pressure is measured via umbilical arterial catheter. Which of the following correctly describes how preterm infants' blood pressure may be influenced by various risk factors and treatments?
    A. Placing the infant on increased positive pressure ventilation via intubation and mechanical ventilation will increase the blood pressure by decreasing pulmonary vascular resistance.
    B. Chorioamnionitis is associated with higher blood pressure in the neonate due to release of mediators such as tumor necrosis factor, which leads to increased catecholamine release.
    C. The preterm infant may have relatively low systemic blood flow due to the structure of the preterm myocardium, which may be less able to overcome the increased systemic vascular resistance that occurs after birth.
    D. In preterm infants, there is increased sensitivity of the ductus arteriosus tissue to oxygen, which leads to abnormal early constriction, leading to dysregulation of the transition to neonatal circulation.
    E. Increased oxygen delivery during and after birth leads to decreased vasopression release and decreases the systemic vascular resistance and increases systemic blood flow.
2. The 27-week gestational age infant has hypotension during the first day in the NICU. Which of the following statements about the potential impact of hypotension and risks involved with treatment for hypotension in preterm infants is correct?
    A. Although treatment is often given for preterm hypotension, no studies have shown any association between hypotension and long-term adverse outcomes.
    B. Preterm infants are particularly susceptible to keeping a constant blood flow through arterial circulation regardless of transmural pressure changes, and therefore, it is difficult to interpret the impact of arterial blood pressure measurements.
    C. Preterm infants are more susceptible to ischemia with low blood pressure and hemorrhage with high blood pressure.
    D. Due to lower limits of what is considered normal blood pressure according to gestational age, treatment for hypotension is more commonly required for higher gestational age preterm infants.
    E. Female infants are more likely to require treatment for hypotension compared with male infants of equal gestational age.
3. Due to the diagnosis of hypotension, the infant is given normal saline followed by the initiation of dopamine infusion. Which of the following statements concerning these treatments in preterm infants with hypotension is correct?
    A. Normal saline is the preferred treatment for hypotension for volume expansion, even when there is severe anemia or fetal blood loss.
    B. Normal saline infusion of at least 30 to 50 mL/kg should be administered before considering the initiation of inotropic medications such as dopamine.
    C. Dopamine selectively stimulates only the dopaminergic receptors at higher doses (≥10 to 20 μg/kg per minute).
    D. Dopamine is particularly efficacious in preterm infants due to a relatively large amount of stored norepinephrine in nerve endings right after birth.
    E. At moderate doses of 5 to 10 μg/kg per minute, dopamine predominantly increases cardiac contractility and heart rate by stimulating the cardiac β_1, β_2, and α_1 adrenergic and dopaminergic receptors.

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4. The infant has persistent hypotension after treatment with dopamine. The team is considering the use of other cardiovascular medications. Which statement on other treatments for hypotension in the NICU is correct?
    A. According to a Cochrane meta-analysis, dobutamine is a more effective treatment for hypotension in preterm infants compared to dopamine.
    B. Epinephrine has a nonselective α-agonist action, causes activation of both β1- and β2-adrenergic receptors, and increases blood pressure and systemic blood flow by increasing both systemic vascular resistance and cardiac output.
    C. At low doses, epinephrine will stimulate only α-agonist receptors, leading to peripheral vasoconstriction.
    D. At high doses, epinephrine stimulates α receptors in the pancreas, increasing the risk of hypoglycemia in preterm infants.
    E. Arginine vasopressin used in very preterm infants is associated with higher partial pressure of carbon dioxide and increased tachycardia compared with dopamine.
5. You are considering corticosteroid administration for a patient who remains hypotensive. Which of the following is correct regarding corticosteroids and preterm infants?
    A. Hydrocortisone downregulates angiotensin II receptors, leading to increased vascular resistance.
    B. Hydrocortisone inhibits the expression of inducible nitric oxide synthase and vasodilatory prostaglandin action.
    C. Dexamethasone is preferred over hydrocortisone in extremely preterm infants due to a safer profile regarding long-term neurodevelopmental outcomes.
    D. Both dexamethasone and hydrocortisone are associated with increased catecholamine metabolism.
    E. Cortisol concentrations tend to be increased in preterm infants who are receiving inotropic support.

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