Neonatal Hypertension

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Education Gaps

1. Recognition of hypertension in the neonate is challenging due to changing blood pressure values with age and size and lack of outcomes-based normative data.
2. Although recommendations exist on when to initiate antihypertensive therapy, data regarding whether treatment of mild hypertension affects cardiovascular and other outcomes need to be determined.
3. There is a lack of data and knowledge regarding the use of antihypertensive medications in preterm and term newborn infants, including dosing, short-term adverse reactions, and longer-term sequelae.

Abstract

In the past few decades, as neonatal intensive care technology has advanced, so has identification and awareness of hypertension in this population. As in older children, the definition of normal blood pressure and accordingly, hypertension, remains a statistical definition rather than based on outcomes. Although the overall incidence of hypertension in neonatal nurseries is low, certain groups of neonates are at higher risk and should be monitored more closely. This article reviews the parameters defining normal and elevated blood pressures in neonates using current available data, etiology and risk factors, approach to investigation, and management of neonatal hypertension.

Objectives After completing this article, readers should be able to:

1. Identify infants at risk for developing hypertension.
2. Better recognize and diagnose hypertension in neonates.
3. Understand the evaluation of hypertension in the NICU.
4. Begin antihypertensive therapy when necessary, choosing the appropriate agent.
5. Understand the importance of proactively alleviating known risk factors, when possible, in at-risk neonates.

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ABBREVIATIONS

BP	blood pressure
CAKUT	congenital anomalies of the kidney and urinary tract
SD	standard deviation

INTRODUCTION

Hypertension is seen in fewer than 3% of infants in the NICU. (1)(2)(3) The incidence rises in high-risk neonates with umbilical arterial catheters, bronchopulmonary dysplasia, intraventricular hemorrhage, acute and/or chronic renal failure, and congenital anomalies of the kidneys and urinary tract. Data regarding normal and elevated blood pressure (BP) based on statistical models have become available, thus facilitating the identification of infants with BPs higher than expected compared with their peers of the same sex, size, and postconceptual age. When identified, appropriate evaluation should be instituted to determine the etiology of hypertension; in turn, this can be used to inform appropriate management, and when indicated, pharmacotherapy. When choosing antihypertensives, one must consider the effects of medications on the developing and growing human body. It remains unclear when to initiate antihypertensive therapy because data pertaining to outcomes of untreated versus treated hypertension are lacking. Most neonates require antihypertensives for only a short period, with only a small minority requiring long-term therapy. (3)

MEASURING BP IN NEONATES

To discriminate between normal BP and hypertension using data from clinical studies, it is important to standardize the method by which BP is measured in young infants. Although invasive arterial BP monitoring remains the gold standard, noninvasive methods using oscillometric devices are commonly used in most modern NICUs; most recent studies now use this method, making data more clinically relevant and usable for bedside clinicians. Direct arterial BP measurement via umbilical or peripheral arterial catheters is the most reliable method in critically ill neonates.

Noninvasive BP monitoring using conventional sphygmomanometry is not recommended in newborns because Korotkoff sounds are unreliable in this age group. (4) Another noninvasive method of BP measurement is the ultrasonic Doppler. This method tends to underestimate systolic BP compared with simultaneous oscillometric measurements, is cumbersome, and is rarely used in clinical practice. (5)

Oscillometric devices measure the mean arterial pressure, then project a systolic and diastolic BP value based on an algorithm. (6) BP monitors from different manufacturers use varied algorithms for oscillometric detection and have variable accuracy, which can lead to discrepant BP values. (7) Although BP measurements using oscillometric devices are generally considered comparable with invasive intra-arterial measurements, (8) in ill neonates, these measurements may not be ideal. This is because oscillometric devices have been shown to overestimate the systolic and diastolic BP compared with BP values obtained from invasive methods in the cohort of sick neonates, hence direct arterial BP monitoring is preferable in this particular population. (9) On the other hand, in small for gestational age infants, another study demonstrated that oscillometric devices underestimated systolic BP. (10)

A standardized method for noninvasive BP measurement in infants using an oscillometric device is depicted in Table 1, based on the study by Nwankwo et al. (11) This procedure minimizes factors that may artificially increase BP, such as feeding (may increase BP by 20 mm Hg), crying, head being tilted or kept up, sucking on a pacifier, etc. (5) Conversely, sleeping infants have systolic BP that is 5 mm Hg lower than in infants who are awake. (4)

DEFINITION AND DIAGNOSIS OF HYPERTENSION

The generally accepted definition of hypertension in newborns is derived from older children in whom systolic and/or diastolic BP values persistently greater than or equal to the 95th percentile for height, age, and sex constitutes hypertension. A newborn is diagnosed with hypertension if the systolic and/or diastolic BP readings on 3 separate occasions are at or above the 95th percentile for postconceptual age. (12)(13) If BP elevation is more severe, that is,

TABLE 1. Standardized Method for Blood Pressure (BP) Measurement in Newborns (11)

Infant position: Prone or supine
Device type: Oscillometric devices
Cuff size: Appropriate for neonates—cuff width to arm circumference ratio 0.45–0.70
Cuff location: Right upper arm
Timing:
- Infant should be asleep, or if awake, should be quiet
- Ensure that the infant is not disturbed for at least 15 min after the cuff is placed
- Feed or medical intervention should have been at least 1.5 hours before the BP measurement
Number of BP readings: At least 3 readings, 2 minutes apart

TABLE 2. **Neonatal Blood Pressures and Potential Treatment Parameters**

POSTCONCEPTUAL AGE	50th PERCENTILE	95th PERCENTILE	99th PERCENTILE
44 weeks			
SBP	88	105	110
DBP	50	68	73
MAP	**63**	**80**	**85**
42 weeks			
SBP	85	98	102
DBP	50	65	70
MAP	**62**	**76**	**81**
40 weeks			
SBP	80	95	100
DBP	50	65	70
MAP	**60**	**75**	**80**
38 weeks			
SBP	77	92	97
DBP	50	65	70
MAP	**59**	**74**	**79**
36 weeks			
SBP	72	87	92
DBP	50	65	70
MAP	**57**	**72**	**77**
34 weeks			
SBP	70	85	90
DBP	40	55	60
MAP	**50**	**65**	**70**
32 weeks			
SBP	68	83	88
DBP	40	55	60
MAP	**49**	**64**	**69**
30 weeks			
SBP	65	80	85
DBP	40	55	60
MAP	**48**	**63**	**68**
28 weeks			
SBP	60	75	80
DBP	38	50	54
MAP	**45**	**58**	**63**

Continued

TABLE 2. (Continued)

POSTCONCEPTUAL AGE	50th PERCENTILE	95th PERCENTILE	99th PERCENTILE
26 weeks			
SBP	55	72	77
DBP	30	50	56
MAP	**38**	**57**	**63**

This table provides estimated values for blood pressures after 2 weeks of age in infants of 26 to 44 weeks' postconceptual age. The 95th and 99th percentile values are intended to serve as a reference to identify infants with persistent hypertension who may require treatment. Data are based on several studies using both Doppler and oscillometric blood pressure measurements. DBP=diastolic blood pressure; MAP=mean arterial blood pressure; SBP=systolic blood pressure.

values are above the 99th percentile for postconceptual age, it should certainly warrant further investigation.

NORMAL BP IN PRETERM AND TERM INFANTS

There are no comprehensive data defining normal BP values in preterm and term neonates. Several studies have been performed to determine the norms, but almost all have major drawbacks or used different methods of BP measurement, which limit our ability to compare data between studies. For preterm infants, the most commonly used BP normative value table is presented in Table 2, which was developed by pooling and extrapolating data from 7 studies, of which 4 used oscillometric methods and the remainder used Doppler methods for measuring BP. (14)

For term infants up to age 12 months, the commonly used reference for BP data is derived from the Report of the Second Task Force on Blood Pressure Control in Children (1987), which pooled data from various studies to establish these norms. In all these studies, the BPs were measured using a Doppler instrument, which may not be transferable to oscillometric measurements commonly used today. (13) These data are shown in Table 3A for boys and Table 3B for girls.

We pooled data from 3 newer and 1 older study for term infants and compiled the data presented in Table 4. All 4 studies used oscillometric devices for BP measurement. (15)(16)(17)(18) An older study by Tan (18) using the oscillometric method was reported differently for the awake and asleep states. Only awake values are presented in this table. Asleep values were minimally lower. Values were reported

TABLE 3A. **BP Values Measured with Doppler in Term Boys Less Than 1 Year of Age (13)**

AGE IN MONTHS	0	1	2	3	4	5	6	7	8	9	10	11	12
SBP	72	84	90	90	90	90	90	90	90	90	90	90	90
50th percentile													
DBP	56	53	50	50	52	53	54	54	55	56	57	57	57
SBP	87	101	106	106	106	106	106	106	106	106	106	106	106
90th percentile													
DBP	68	65	63	63	63	65	66	67	68	68	69	69	69
SBP	91	103	110	110	110	110	110	110	110	110	110	110	110
95th percentile													
DBP	72	68	66	66	66	70	71	72	72	72	73	73	74

BP=blood pressure; DBP=diastolic blood pressure; SBP=systolic blood pressure.

TABLE 3B. **BP Values Measured with Doppler in Term Girls Less Than 1 Year of Age (13)**

AGE IN MONTHS	0	1	2	3	4	5	6	7	8	9	10	11	12
SBP	66	83	87	88	90	90	90	90	90	90	90	90	90
50th percentile													
DBP	55	53	52	52	53	53	53	53	54	54	54	54	54
SBP	76	98	101	104	105	106	106	106	106	106	106	105	105
90th percentile													
DBP	68	65	64	64	65	65	66	66	66	67	67	67	67
SBP	91	103	105	106	107	110	110	110	110	110	110	110	110
95th percentile													
DBP	72	68	67	67	68	70	70	72	72	72	72	72	72

BP=blood pressure; DBP=diastolic blood pressure; SBP=systolic blood pressure.

as mean ± standard deviation (SD). Mean was assumed as the 50th percentile, 2 SDs as the 95th percentile, and 3 SDs as the 99.7th percentile. (18) Similar assumptions about mean and SDs were made by Pejovic et al using oscillometric measurements. (17)

EPIDEMIOLOGY

Although the American Academy of Pediatrics does not recommend routine BP evaluation in healthy term neonates, (19) BP measurements are important in infants admitted to the NICU, because they are at a higher risk for hypertension. (12) Hypertension has been reported to have a variable but low incidence in newborns. The incidence is reported to be around 0.2% in healthy term newborns and up to 3% in the infants in NICUs. (1)(20)(21)(22) The exact prevalence of hypertension in premature infants is not known but a study from Houston reported that 1.4% preterm compared with 1% term infants required antihypertensive therapy during NICU stay. (23)

ETIOLOGY

Over the years, several factors have been identified as being either risks or direct etiologic factors for hypertension in newborns. Table 5 lists the various risk factors and causes of hypertension in neonates.

Renal parenchymal and vascular anomalies account for the majority. (12)(20)(22) Umbilical arterial catheter–related thromboemboli are known to be associated with neonatal hypertension (1)(24)(25) with longer duration related to more thrombus formation. (26) Vascular endothelial disruption during umbilical artery catheter placement leads to thrombus formation (27) in the renal vasculature, which increases renin and aldosterone production due to decreased renal perfusion. (2)(28) Thus, the length of the arterial catheter may not be as important as catheter placement per se. Renin and aldosterone also increase salt and water retention, further exacerbating the hypertension. It is important to note that thrombus formation may not always be evident on radiologic studies.

Renal vein thrombosis may present with hypertension. The classic triad of gross hematuria, thrombocytopenia, and palpable flank (renal) mass occurs in only 13% of patients at presentation. (29) Thus, presence of any of these signs in high-risk patients, for example, infants of diabetic mothers or those with factor V Leiden mutation, should prompt investigation for this complication.

Congenital anomalies of the kidney and urinary tract (CAKUT) have also been associated with hypertension in infants, for example, autosomal recessive and less commonly, autosomal dominant polycystic kidney disease, multicystic dysplastic kidney, ureteropelvic junction obstruction, and urethral obstruction. Autosomal recessive polycystic kidney disease usually presents with severe hypertension in the first year after birth, requiring multiple agents to manage. Acquired renal parenchymal abnormalities, eg, interstitial nephritis and cortical necrosis, can also lead to hypertension, but not as frequently as CAKUT. (27)

The commonest association with nonrenal hypertension in infants is chronic lung disease and bronchopulmonary dysplasia. Hypertension is reported to have a high incidence of 13% to 43% in neonates with bronchopulmonary

TABLE 4. **Pooled Mean BP Values for Normal Term Infants Less Than 1 Year Old as Measured with Oscillometric Devices from Various Studies (15)(16)(18)**

	RANGE	50th PERCENTILE	90th PERCENTILE	95th PERCENTILE	99.7th PERCENTILE
Day 1					
SBP	46-94	66		81	89
DBP	24-57	43		54	74
MAP	31-63	50		62	71
Day 2					
SBP	46-91	68	78	84	93
DBP	27–58	43	49	57	67
MAP	37–68	52	58	66	76
Day 3					
SBP	51-93	71		88	99
DBP	26-61	45		59	68
MAP	36-70	55		71	82
Day 4					
SBP	60-88	72		89	97
DBP	34-57	47		62	73
MAP	41-65	56		71	81
Day 5					
SBP		74		91	99
DBP		48		64	73
MAP		58		75	84
Day 6					
SBP		73		89	97
DBP		47		63	64
MAP		58		74	83
Day 7					
SBP		71		81	86
DBP		46		56	61
MAP		54		64	66
Day 30					
SBP		77		87	87
DBP		50		58	62
MAP		59		67	71

Continued

TABLE 4. (Continued)

	RANGE	50th PERCENTILE	90th PERCENTILE	95th PERCENTILE	99.7th PERCENTILE
6 months					
SBP	72–131	102	116	120	
DBP	34–81	63	73	75	
MAP	48–99	75	84	87	
12 months					
SBP	75–130	101	114	118	
DBP	41–84	64	75	78	
MAP	55–94	75	85	89	

BP=blood pressure; DBP=diastolic blood pressure; MAP=mean arterial blood pressure; SBP=systolic blood pressure.

dysplasia. (30)(31) Although the exact mechanism is unknown, it is thought to be related to increased systemic arterial stiffness. (32) As expected, corticosteroid treatment for such patients has been shown to contribute to transient hypertension. (33)

Medication-induced hypertension, when present, is usually transient and is generally expected to resolve when the inciting medication is discontinued. (27) Idiopathic hypertension has been reported to have a variable incidence of 5% to 57% in various studies. (1)(12)(23)

TABLE 5. Etiology and Risk Factors for Neonatal Hypertension

Maternal factors: Maternal hypertension, antenatal steroid exposure, maternal BMI >30, maternal diabetes, abnormal uteroplacental perfusion
Prematurity
Low birthweight
Perinatal hypoxia
Renal disease
Renal vascular, eg, renal artery thrombosis (due to umbilical artery catheter placement) or renal vein thrombosis, fibromuscular dysplasia, renal artery stenosis, compression of one or both renal arteries externally (eg, by tumors)
Renal parenchymal, eg, polycystic kidney disease, acute tubular or cortical necrosis, acute kidney injury
Cardiac disease, eg, PDA, coarctation of thoracic aorta
Medications: Steroids, indomethacin, vasopressors, bronchodilators
Parenteral nutrition: Excess volume, sodium overload, hypercalcemia
ECMO
Bronchopulmonary dysplasia
Endocrine disorders, eg, congenital adrenal hyperplasia, hyperaldosteronism, hyperthyroidism
Neoplastic disorders, eg, neuroblastoma, Wilms tumor
Intraventricular hemorrhage
Cytochrome P450 (CYP2D6) CC genotype in preterm infants
Pain
Hemolytic uremic syndrome
Idiopathic

BMI=body mass index; ECMO=extracorporeal membrane oxygenation; PDA=patent ductus arteriosus.

CLINICAL FEATURES OF HYPERTENSION IN NEONATES

In most cases, hypertension in neonates is detected as a result of routine continuous monitoring in the NICU. Because the incidence of hypertension is so low in normal term infants, hypertension in this cohort is incidentally discovered when the infant presents to a tertiary care center for various symptoms and receives an evaluation of vital signs, including BP measurement. Most patients do not exhibit the usual symptoms of hypertension that older children do, and symptoms and signs are often difficult to differentiate from those of concurrent medical conditions, such as cardiorespiratory failure, feeding difficulties, irritability, and gastrointestinal symptoms.

INVESTIGATION AND DIAGNOSTIC EVALUATION

A general approach to evaluation of a hypertensive neonate is outlined in the Figure. Once recognized, a diagnostic evaluation should be undertaken to determine the etiology of hypertension (Table 6). Renal parenchymal or renovascular causes account for the vast majority of cases in which an etiology is identified; therefore, it is important that this system be included in the initial evaluation in all infants. (1) As the sensitivity and detail obtained by prenatal ultrasonography improve, many CAKUT are prenatally diagnosed. These infants are at higher risk of developing hypertension and should be monitored in the NICU and following discharge.

A thorough history and physical examination should assist in determining the etiology of the hypertension (Table 5), and once hypertension is detected, historical information may need to be reviewed. Attention should be focused on the cardiovascular, abdominal, and genitourinary systems during a targeted physical examination. Usually, dysmorphic features suggestive of genetic disorders or syndromes would have been apparent by the time hypertension manifests. Infants must be evaluated for coarctation of the aorta (cardiac murmurs, 4-extremity BPs, femoral pulses, brachiofemoral delay), and renal

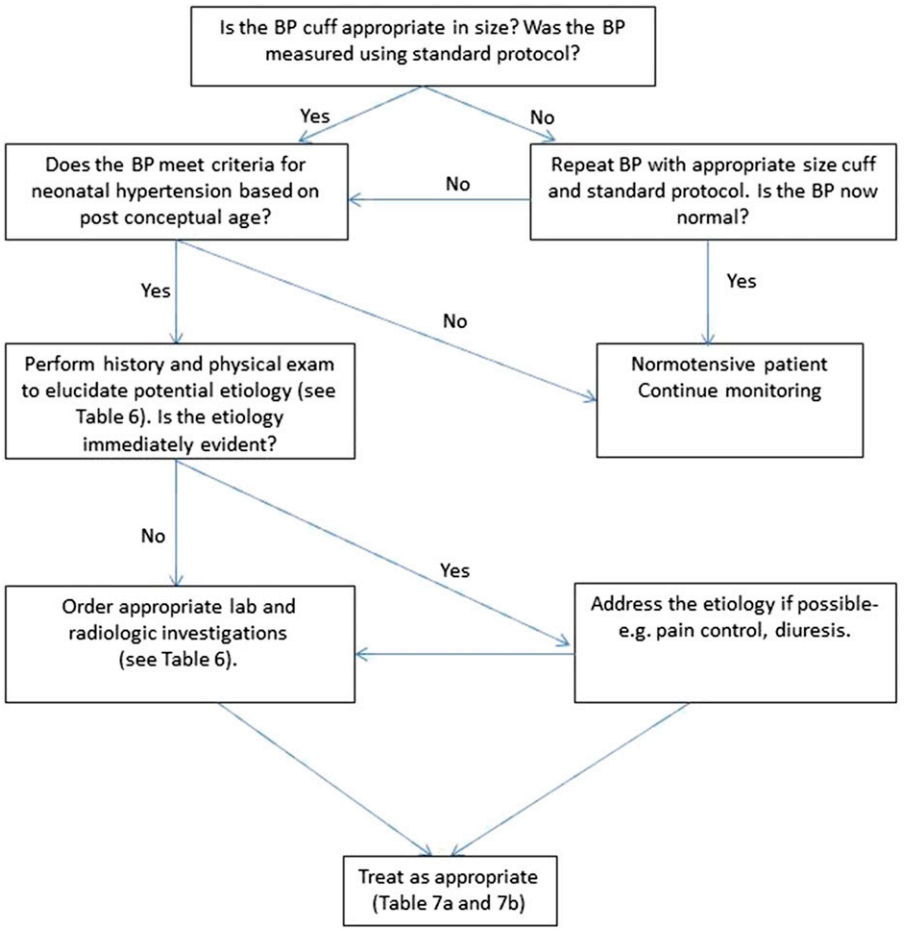

Figure. Approach to the hypertensive neonate.

TABLE 6. **Diagnostic Evaluation of Infants with Hypertension**

History[a]	1. Maternal a. Steroids, cocaine, heroin b. Hypertension, diabetes mellitus, obesity 2. Prenatal oligo- or polyhydramnios 3. Renal anomalies on prenatal ultrasounds 4. Postnatal medications administered to the infants: Steroids, adrenergic agonists, indomethacin, caffeine 5. History of umbilical catheterization
Targeted physical examination[a]	1. Volume status and weight trends 2. Dysmorphic features suggestive of a syndrome or genetic abnormality, eg, external ear abnormalities and/or preauricular pit(s) in BOR syndrome 3. Cardiovascular a. 4-extremity BP b. Murmurs c. Femoral and radial/brachial pulses 4. Genitourinary and renal a. Abdominal masses (renomegaly) b. Abdominal wall anomalies c. Bruits d. Genitalia (congenital adrenal hyperplasia)
Laboratory investigations	1. Urinalysis[a] 2. Electrolytes, calcium, BUN, creatinine[a] 3. Additional investigations guided by clinical suspicion a. Thyroid studies b. Plasma renin activity and aldosterone c. Cortisol level d. 11-deoxycortisol and 11-deoxycorticosterone e. Plasma and urine catecholamines, metanephrines and normetanephrines
Radiologic studies	1. Aortic and renal ultrasound with Doppler[a] 2. VCUG 3. CT angiogram to evaluate aorta and renal arteries 4. Nuclear medicine studies a. DMSA or MAG3 scans b. Captopril renal scan 5. Cranial imaging with ultrasound or MRI
Cardiology	1. Echocardiogram

BOR=branchio-otorenal; BP=blood pressure; BUN=blood urea nitrogen; CT=computed tomography; DMSA=dimercaptosuccinic acid; MAG3=mercaptoacetyltriglycine; MRI=magnetic resonance imaging; VCUG=voiding cystourethrography.
[a]First-line investigations in all patients.

parenchymal and renovascular abnormalities like abdominal masses and bruits.

All infants with hypertension should have a urinalysis, and measurement of electrolytes, blood urea nitrogen, creatinine, and calcium, and radiologic examination should include aortic, renal, and bladder ultrasonography with Doppler. These studies will identify almost all infants with CAKUT. Further investigation should be guided by clinical suspicion.

Echocardiography may be helpful in evaluating for coarctation of the aorta. Longstanding and more severe hypertension may lead to hypertensive cardiomyopathy, which may manifest as left ventricular hypertrophy, dilation, and/or dysfunction. When present, end-organ dysfunction should prompt a more thorough investigation for a cause, and the management to achieve normal BP should be more aggressive.

MANAGEMENT

Treatment of hypertension should be individualized depending on the severity and etiology. We recommend working in conjunction with consultant pediatric nephrologists and/or cardiologists, as deemed appropriate, to manage

TABLE 7A. **Selected Antihypertensive Agents for Intravenous Use (34)**

CLASS OF DRUG	DRUG	USUAL DOSE	NOTES AND PRECAUTIONS
Vasodilators	Hydralazine	0.1–0.5 mg/kg/dose IV every 6–8 hours Max 2 mg/kg/dose	May cause tachycardia and edema
	Sodium nitroprusside	Start 0.2 μg/kg/min infusion	Renal failure, prolonged use >72 hours and/or doses >2 μg/kg/min lead to thiocyanate and cyanide toxicity
		Max 10 μg/kg/min	Do not use max dose for more than 10 min
Calcium channel blockers	Nicardipine	0.5-2 μg/kg/min infusion	May cause tachycardia and edema
β-adrenergic blockers	Esmolol	Term neonates 0–7 days old:	Extravasation of esmolol can cause skin necrosis
		50 μg/kg/minute infusion; titrate dose by 25 to 50 μg/kg/min every 20 min	May lead to hyperkalemia, especially in presence of renal failure. Monitor serum potassium
		Term neonates 8 to 28 days: Initial 75 μg/kg/minute; titrate dose by 50 μg/kg/minute every 20 min	Use with caution in bronchospastic disease
		Max 500 μg/kg/min	Follow closely for bradycardia
	Propranolol	Initial: 0.01 mg/kg/dose every 6–8 hours Max 0.15 mg/kg/dose every 6–8 hours	
α- and β-adrenergic blockers	Labetalol	0.1-1 mg/kg/dose IV every 4–6 hours or 0.25–3 mg/kg/hour infusion	Use with caution in patients with congestive heart failure and bronchospastic disease
ACE-inhibitors	Enalaprilat	5-10 μg/kg/dose every 8–24 hours	Use with caution in patients with hyponatremia, hypovolemia, severe congestive heart failure, decreased renal function, or in those receiving diuretics Avoid use in preterm infants Do not use in neonates with GFR <30 mL/min/1.73 m^2 Monitor serum sodium, potassium and creatinine

Use is considered off-label. ACE=angiotensin-converting enzyme; GFR=glomerular filtration rate; IV=intravenous.

infants with hypertension. The timing of antihypertensive therapy is controversial and data regarding the benefit of treatment of milder hypertension are lacking. The natural history of hypertension when it presents in neonates is unique compared with older children. Most infants require treatment for only short periods, rarely more than 6 months. In a large study by Blowey et al, (3) with over 700 NICU infants with hypertension, the median exposure to antihypertensive therapy was 10 days. Thus, the benefits of treatment of mild hypertension that is usually transient, is unclear.

Most experts agree that severe hypertension, greater than the 99th percentile for postconceptual age and/or sex and/or size, should be managed with pharmaceutical agents. Long-standing persistent hypertension in neonates can lead to sequelae such as left ventricular hypertrophy, encephalopathy, and retinopathy. (3) No agents have been studied in neonates and very few in older children, so most clinicians use these agents off label.

In general, severe and/or symptomatic hypertension should be treated with intravenous agents. Milder hypertension can be treated with oral medications. The most commonly used agents are vasodilators like hydralazine, angiotensin-converting enzyme inhibitors, and calcium channel blockers (Table 7A and Table 7B). Other classes of agents that can be used include α- and β-adrenergic antagonists, diuretics, and central α-agonists (Table 7A and Table 7B). Angiotensin-converting enzyme inhibitors should be avoided in preterm infants, those with acute renal failure, and those with hyperkalemia.

Reversible and treatable factors contributing to hypertension should be appropriately addressed. For example, steroids should be reduced and discontinued when able, and fluid overload should be managed. Surgical or

TABLE 7B. **Selected Antihypertensive Agents for Oral Use (34)**

CLASS OF DRUG	DRUG	USUAL DOSE	NOTES AND PRECAUTIONS
Calcium channel blockers	Amlodipine	0.1–0.5 mg/kg/day PO given once daily	May cause tachycardia and edema. Younger children <6 years have greater weight-based clearance and volume of distribution
ACE-inhibitors	Captopril	Term neonates 0–7 days old: Initiate 0.01 mg/kg/dose PO every 8–12 hours	Use with caution in patients with hyponatremia, hypovolemia, severe congestive heart failure, decreased renal function, or in those receiving diuretics
		Term neonates >7 days: Initial: 0.05–0.1 mg/kg/dose PO every 8–24 hours	Avoid use in preterm infants
		Max 0.5 mg/kg/dose PO every 6–24 hours	Do not use in neonates with GFR <30 mL/min/1.73 m^2
	Enalapril	0.04 to 0.1 mg/kg/day PO every 12–24 hours	Monitor serum sodium, potassium and creatinine.
		Max 0.27 mg/kg/day in neonates, 0.58 mg/kg/day in infants.	
	Lisinopril	0.07 to 0.1 mg/kg/dose PO once daily	
		Max 0.5 mg/kg/day PO	
β-adrenergic blockers	Propranolol	0.25 mg/kg/dose PO every 6–8 hours	May lead to hyperkalemia, esp. in presence of renal failure. Monitor serum potassium.
		Max 5 mg/kg/day PO	Use with caution in bronchospastic disease.
			Follow closely for bradycardia.
α- and β-adrenergic blockers	Labetalol	1–3 mg/kg/day PO every 12 hours Max 10–12 mg/kg/day	Use with caution in patients with congestive heart failure and bronchospastic disease.
Diuretics	Chlorothiazide	20–40 mg/kg/day PO every 12 hours	Monitor for hypercalcemia, hypokalemia, hypochloremic alkalosis, hyponatremia, and hypomagnesemia.
	Spironolactone	1–3 mg/kg/day PO every 12–24 hours	Caution in renal failure Monitor for hyperkalemia
Central α agonist	Clonidine	3–10 μg/kg/day PO every 8–12 hours	May cause CNS depression and bradycardia
		Max 25 μg/kg/day PO	Avoid abrupt discontinuation, which may cause severe rebound hypertension
Vasodilators	Hydralazine	0.25–1 mg/kg/dose PO every 6–8 hours Max 7.5 mg/kg/day PO	May cause tachycardia and edema
	Minoxidil	0.1–0.2 mg/kg PO once daily	Very potent vasodilator usually reserved for severe refractory hypertension
		Max 1 mg/kg/day PO every 12–24 hours	May cause fluid retention, pericardial effusion and tachycardia

Use is considered off-label. CNS=central nervous system; PO=oral route.

interventional radiologic management may be required for renal artery stenosis.

Decisions regarding the need for umbilical arterial catheters, and use of potential nephrotoxins, especially aminoglycosides and nonsteroidal anti-inflammatory agents like indomethacin, should be carefully considered in NICU infants, weighing the risks and benefits. Preterm infants and those who are small for gestational age are already predisposed to chronic kidney disease and hypertension due, in part, to reduced nephron endowment. Nephronogenesis continues postnatally in preterm infants until 36 weeks' estimated gestational age, and injury to developing

nephrons secondary to any insult, whether hypoxia, hypotension, and/or nephrotoxin exposure, leads to more significant and chronic sequelae.

CONCLUSION

Hypertension in normal neonates is rare; however, certain groups of infants are at higher risk and should be monitored. Most data regarding normal BP in neonates are old and based on Doppler measurements, which cannot be used to interpret data obtained with oscillometric devices commonly used in NICUs and community pediatrician offices today. Furthermore, the diagnosis of hypertension is a statistical one rather than outcomes based, and thus the degree of BP elevation requiring treatment has not been clearly delineated. Severe and long-standing hypertension can lead to end-organ damage and should be appropriately managed.

When possible, use of potential nephrotoxins and umbilical arterial catheters should be avoided in infants at higher risk for hypertension, such as those with underlying known CAKUT, preterm and small-for-gestational age infants, as risk of hypertension increases even further. Most infants with hypertension will have no identifiable cause, and in those in whom a cause is recognized, renal parenchymal and renovascular causes are the most common.

Therapy should be targeted to etiology. Data pertaining to pharmacokinetics and pharmacodynamics of antihypertensive drugs in neonates require further study to optimize dosing guidance. When indicated, most neonates require antihypertensives only transiently, with longer-term therapy required by those with underlying renal or renovascular abnormalities. Longer-term outcomes data are required to guide the benefit of therapy in newborn infants.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Formulate a differential diagnosis for an infant with systemic hypertension in early infancy.
- Know the management of an infant with systemic hypertension, including adverse effects of management.
- Know the factors that regulate systemic blood pressure in term and preterm infants and know the normal range of pressures and pressure patterns.
- Know the clinical and diagnostic features of an infant with systemic hypertension, including laboratory and imaging studies.

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Parent Resources from the AAP at HealthyChildren.org

High Blood Pressure in Children: https://www.healthychildren.org/English/health-issues/conditions/heart/Pages/High-Blood-Pressure-in-Children.aspx

For a comprehensive library of AAP parent handouts, please go to the *Pediatric Patient Education* site at http://patiented.aap.org.

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1. A female infant born at 28 weeks' gestational age is in the NICU and receiving parenteral nutrition and nasal continuous positive airway pressure. She is receiving blood pressure measurement by both arterial catheter and oscillometric device. Which of the following statements regarding blood pressure measurement in patients such as this is correct?
    A. The oscillometric device will most likely have lower systolic and diastolic pressures compared with the arterial catheter.
    B. Direct arterial blood pressure measurement via arterial catheter is the most reliable method in critically ill neonates.
    C. Small-for–gestational age infants will usually have an overestimate of systolic blood pressure using an oscillometric device.
    D. Feeding or pacifier sucking will usually cause a decrease in the blood pressure.
    E. In contrast to adults and older children, sleeping infants will typically have systolic blood pressure higher than when awake.
2. A term infant with hypoxic-ischemic encephalopathy is in the NICU and is noted to have hypertension. As you evaluate the infant, the differential diagnosis includes renal vein thrombosis. Which of the following statements regarding this condition is correct?
    A. The classic triad of gross hematuria, thrombocytopenia, and palpable flank mass occurs in 95% of patients.
    B. Infants of diabetic mothers and those with factor V Leiden mutation have higher risk for this condition.
    C. The diagnosis is only possible if an umbilical arterial catheter has been placed.
    D. This is likely a result of volume overload that occurred during resuscitation.
    E. This condition is often associated with hemophilia or von Willebrand disease.
3. A male infant born at 27 weeks' gestational age is now 10 weeks old and remains in the NICU. He is receiving oral and gavage feedings and nasal cannula oxygen. He has had a complicated NICU course, with intraventricular hemorrhage and an episode of suspected necrotizing enterocolitis that was treated medically. Which of the following conditions has the most common nonrenal association with hypertension?
    A. Necrotizing enterocolitis.
    B. Retinopathy of prematurity.
    C. Intraventricular hemorrhage.
    D. Central line infection and sepsis.
    E. Bronchopulmonary dysplasia.
4. A 3-day-old term female infant presents to the NICU with poor feeding and is noted to have hypertension. On physical examination, there appear to be weak femoral pulses. You are planning a diagnostic investigation. Which of the following statements concerning evaluation of a neonate with hypertension is correct?
    A. The utility of laboratory tests in hypertension is questionable and blood tests should only be obtained if there is a specific abnormality suspected.
    B. If a prenatal ultrasound were to show normal kidneys, no further information would be obtained from a postnatal scan.
    C. An echocardiogram may be helpful to evaluate for coarctation of the aorta.
    D. The vast majority of cases of hypertension in neonates are related to sepsis.
    E. To prevent false-positive data, this patient should have blood pressure monitored at most once a day, and only while peacefully sleeping.
5. A female infant born at 25 weeks' gestational age is now 4 weeks old. The nurse reports that the infant has been hypertensive on the last 2 blood pressure measurements, and on further review, you note that the blood pressure has had an increasing trend over the past few days. A diagnostic evaluation is pursued and no clear etiology is found. Which of the following statements regarding treatment and prognosis is correct?

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A. In observational studies, it has been shown that preterm infants who receive antihypertensive medications in the initial NICU hospital course have a strong likelihood (>50%) of requiring lifelong antihypertensive therapy.
B. Angiotensin-converting enzyme inhibitors should be avoided in preterm infants, those with acute renal failure, and those with hyperkalemia.
C. α- and β-adrenergic agonists are the most effective antihypertensive drugs in preterm infants.
D. Nephrogenesis stops at approximately 24 weeks' gestational age, and therefore, subsequent postnatal therapies will have little clinical benefit in this population.
E. There is no indication or role for oral antihypertensive medications in the NICU.

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