Neonatal Hypertension

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Hypertension was initially recognized clinically in neonates in the 1970s, but recent technological advances in the NICU have led to heightened awareness and increased diagnostic frequency. Neonatal hypertension is defined as systolic blood pressure (BP) of at least the 95th percentile for gestational age, birthweight, and sex on 3 separate occasions. The incidence of neonatal hypertension in the NICU ranges from 0.2% to 3% and most commonly affects term and preterm infants in the intensive care setting.

Abnormally elevated BP, especially severe (defined by systolic BP >99th percentile) in critically ill or premature infants can result in vascular injury, left ventricular hypertrophy, encephalopathy, and hypertensive retinopathy. In addition to complications from end organ damage, certain forms of neonatal hypertension are linked to hypertension beyond infancy, making it imperative to swiftly diagnose and aggressively manage severe or persistent hypertension.

As with older children and adults, there are multiple causes of neonatal hypertension (Table 1), with the most common being renal parenchymal and renovascular abnormalities. A well-established renovascular etiology is umbilical arterial catheter-associated hypertension, both with and without demonstrable thromboembolic events. Umbilical catheter placement is thought to disrupt vascular endothelium, resulting in decreased perfusion and increased renin and aldosterone production. Chronic lung disease or bronchopulmonary dysplasia (BPD) is the most common nonrenal cause of hypertension in premature infants, with an incidence ranging from 13% to 43% in neonates with BPD, especially in those severely affected. In fact, among very low birthweight infants, those with BPD are twice as likely to develop hypertension as those without BPD. In other clinical scenarios, other diagnoses associated with hypertension should be considered: patent ductus arteriosus, intraventricular hemorrhage, endocrine abnormalities, neoplasia, and medication adverse effects.

The clinical presentation of hypertension in neonates is quite variable, with nonspecific signs and symptoms such as irritability, poor feeding, lethargy, tachypnea, cyanosis, seizures, apnea, and poor perfusion, or more life-threatening events such as congestive heart failure and cardiogenic shock. For term neonates, routine evaluation of BP is not recommended by the American Academy of Pediatrics (AAP), and because most of this group will be asymptomatic, hypertension may be diagnosed incidentally during vital sign monitoring.

Given the variation in clinical presentation, it is important to determine BP accurately in tertiary settings. The gold standard for reliable measurement of BP, especially in critically ill neonates, remains invasive arterial BP monitoring through an indwelling radial or umbilical catheter. However, in the absence of other indications for catheter insertion, noninvasive BP monitoring has become the clinical mainstay for diagnosis. Ultrasonic Doppler was routinely used in previous studies of hypertension but can underestimate systolic BP. Sphygmomanometry is not recommended because Korotkoff sounds are often barely

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Systemic Hypertension in Very Low Birth Weight Infants with Bronchopulmonary Dysplasia: Incidence and Risk Factors. Alagappan A, Malloy H. *Am J Perinatol.* 1998;15(1):3–8

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TABLE 1. **Causes of Neonatal Hypertension**

Renovascular	Medications
Thromboembolism (umbilical arterial catheter)	Caffeine
Renal vein thrombosis	Corticosteroids
Renal artery stenosis (fibromuscular dysplasia)	Indomethacin
Renal parenchymal	Vasopressors
Congenital structural abnormality	Bronchodilators
Polycystic kidney disease	Neoplasia
Multicystic dysplastic kidney	Wilms tumor
Acute tubular necrosis	Pheochromocytoma
Acute cortical necrosis	Neuroblastoma
Hemolytic uremic syndrome	Neurologic
Obstruction (ureteropelvic junction, stones)	Intraventricular hemorrhage
Cardiovascular	Pain
Coarctation of the aorta	Seizures
Interrupted aortic arch	Drug withdrawal
Patent ductus arteriosus	Maternal risk factors
Pulmonary	Antenatal steroids
Chronic lung disease	Drugs (cocaine, heroin)
Pneumothorax	Miscellaneous
Endocrine	Total parenteral nutrition (hypercalcemia, fluid or sodium overload)
Congenital adrenal hyperplasia	Perinatal asphyxia
Hyperaldosteronism	Extracorporeal membrane oxygenation
Hyperthyroidism	Adrenal hemorrhage

Adapted with permission from Flynn JT. Neonatal hypertension: diagnosis and management. Pediatr Nephrol. *2000;14(4):332–341.*

audible and thus unreliable in neonates. Currently in the NICU, noninvasive BP monitoring is often performed using automated oscillometric devices, where pulsatile blood flow sends oscillations to the arterial wall, which are then transmitted to the cuff. The mean arterial pressure measured is then converted through an algorithm to provide projected systolic and diastolic BP values. Although the readings vary slightly from an indwelling catheter, the BP trends are reliable and easily accessed at the bedside. Oscillometric devices are accurate only when used with a proper cuff size; a cuff that is too small gives falsely high BP readings. Of note, BP measurement should be standardized to create uniform results by selection of an appropriate cuff size, measurement in the right upper arm, placement of the infant in the supine position, minimizing infant activity, and timing at least 1.5 hours after feeding or medical intervention.

Once hypertension is evident, the first step in determining its cause is to take a detailed history, with particular focus on exposure to both antenatal (eg, family history, antenatal corticosteroid use) and perinatal (eg, umbilical catheter placement) risk factors. Likewise, a thorough physical examination focused on dysmorphic features, cardiovascular, abdominal, and genitourinary systems can point the clinician

TABLE 2. **Neonatal Blood Pressure Values After 2 Weeks of Age**

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

Continued

TABLE 2. (Continued)

POSTCONCEPTUAL AGE	50TH PERCENTILE	95TH PERCENTILE	99TH PERCENTILE
DBP	38	50	54
MAP	45	58	63
26 wk			
SBP	55	72	77
DBP	30	50	56
MAP	38	57	63

All values are given in mm Hg. DBP=diastolic blood pressure, MAP=mean arterial pressure, SBP=systolic blood pressure.
Reprinted with permission from Dionne JM, Abitbol CL, Flynn JT. Hypertension in infancy: diagnosis, management, and outcome. Pediatr Nephrol. *2012;27(1):17–32.*

toward a diagnosis. Auscultation for abdominal bruits or a flank mass may suggest renal artery stenosis or ureteropelvic junction obstruction, respectively, whereas coarctation of the aorta may enter in the differential diagnosis after auscultation for murmurs, comparison of brachial and femoral pulses, and measurement of 4 extremity BPs as well as preductal and postductal oxygen saturations.

In most instances of neonatal hypertension, laboratory evaluation is needed to assess renal function (eg, urinalysis and serum electrolytes, including calcium, blood urea nitrogen, and creatinine), as well as renal and bladder ultrasonography with Doppler flow, a quick noninvasive procedure. Other laboratory values, such as serum thyroxine, cortisol, aldosterone, urinary 17-hydroxy-steroids, 17-ketosteroids, urine vanillylmandelic acid, and urine homovanillic acid, can be measured based on clinical suspicion and pertinent history. If a renovascular cause is suspected, computed tomographic angiography is beneficial to evaluate the aorta and renal arteries. However, an angiogram is invasive and technically challenging in the neonate. Furthermore, magnetic resonance angiography data in children are still controversial and cannot be generally applied to the neonatal population. If a cardiac etiology seems likely, an echocardiogram is useful not only for evaluation of coarctation but also for identifying complications of long-standing hypertension, including cardiomyopathy, and/or left ventricular hypertrophy, dilation, or dysfunction.

No definitive normal BP values have been determined for term and preterm neonates because of discrepancies in BP measurement techniques, different definitions of BP used, and variations in neonatal clinical status when measurements were taken. However, for neonates 26 to 44 weeks' postconceptual age, useful normative data have been established based on gestational age, birthweight, and sex (Table 2).

Management of hypertension should be tailored to each infant's clinical status, in consultation with a pediatric nephrologist and cardiologist, as necessary. First, any iatrogenic cause (eg, corticosteroids, fluid, or salt overload) should be corrected and any underlying cause (eg, cardiac or endocrine) should be treated. The paucity of evidence on treating neonatal hypertension makes controversial the choice, timing, and even benefit of antihypertensive agents. However, it is generally agreed that severe hypertension greater than the 99th percentile for gestational age, postconceptual age, and birthweight should be treated with an intravenous infusion to reduce the risk of potential end organ damage. In severe hypertension, BP should be continuously monitored through an intra-arterial catheter or frequent cuff readings, and care should be taken to avoid rapidly reducing BP to prevent cerebral ischemia and hemorrhage. Oral therapy should be considered in patients with less severe hypertension. Commonly used antihypertensive agents include vasodilators, calcium channel blockers, diuretics, and α- and β-adrenergic antagonists (Table 3). Diuretics may be helpful in controlling BP and improving pulmonary function in infants with chronic lung disease. Other classes of agents that can be used are central α-agonists and β-blockers. Of note, angiotensin-converting enzyme inhibitors should be avoided in neonates because they may impair nephron development and cause acute kidney injury and/or hyperkalemia. β-Blockers are not

TABLE 3. **Selected Antihypertensive Agents**[a]

CLASS OF DRUG	IV DRUG AND DOSE	PO DRUG AND DOSE
α– and β-adrenergic blockers	Labetalol, 0.2–1 mg/kg per dose IV Q4-6h or 0.25–3 mg/kg per hour IV infusion	Labetalol, 0.5–1 mg/kg per dose PO Q12h (maximum 10 mg/kg per day) Carvedilol, 0.1-0.5 mg/kg per dose PO Q12h
Calcium channel blockers	Nicardipine, 0.5–2 μg/kg per minute IV infusion	Amlodipine, start at 0.05 mg/kg per dose PO daily (maximum 0.6 mg/kg per day) Isradipine, start 0.05–0.1 mg/kg per dose PO Q8–12h (maximum 0.6 mg/kg per day or 10 mg per day)
Diuretics		Chlorothiazide, 10–20 mg/kg per dose PO Q12h Hydrochlorothiazide, 1–2 mg/kg per dose PO Q12h Spironolactone, 1–3 mg/kg per day PO daily or divided Q12h
Vasodilators	Hydralazine, 0.1–0.5 mg/kg per dose IV Q6-8h (maximum 2 mg/kg per dose) Sodium nitroprusside, start 0.3 μg/kg per minute IV infusion (maximum 10 μg/kg per minute)	Hydralazine, 0.25–1 mg/kg per dose PO Q6-8h (maximum 7.5 mg/kg per day) Minoxidil, 0.1–0.2 mg/kg per dose PO daily

IV=intravenous, PO=orally, Q4–6/6–8/8–12/12h=every 4 to 6/6 to 8/8 to 12/12 hours.
[a]*Dosing is based on NeoFax (http://neofax.micromedexsolutions.com/neofax/neofax.php) and Lexicomp (http://online.lexi.com).*

recommended for emergency hypertension or with chronic lung disease.

Neonatal hypertension, although rare, is increasingly screened for and diagnosed during routine monitoring of vital signs in the NICU. Normative data values for BP based on gestational age, birthweight, and postconceptual age, despite the inconsistent techniques used to derive them, are the best available standard. Although there is no clear consensus for initiation and dosing of antihypertensive drugs, therapy should be targeted to treat severe hypertension, tailored to the underlying cause, and formulated to avoid potential adverse outcomes from both the underlying condition and the treatment chosen.

COMMENT: BP is, of course, routinely monitored in an intensive care setting so that the issue of screening in the absence of symptoms does not usually apply to premature infants. For well-appearing neonates born at term, the most recent AAP guidelines (*Pediatrics*. 2017;140[3]:e20171904) do not recommend routine screening, which should begin annually only at 3 years of age. Children with specific risk factors, including obesity, renal disease, a history of coarctation of the aorta, diabetes, or use of a medication that raises BP, should have their pressures checked at every medical encounter, again beginning at age 3 years.

Identifying elevated BP in neonates is critical because, unlike the situation with older children and especially adults, primary hypertension without an identifiable underlying cause is not a consideration—significant renal, cardiac, pulmonary, or endocrine disease is. Furthermore, epidemiologic evidence continues to mount that hypertension in childhood substantially raises the likelihood of hypertension in adulthood, with all its attendant risks.

– Henry M. Adam, MD
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ANSWER KEY FOR JUNE 2020 PEDIATRICS IN REVIEW

Pediatric Rhabdomyolysis: 1. B; 2. D; 3. C; 4. E; 5. C.
Clarifying Misleading Lumps and Sinuses in the Newborn: 1. D; 2. E; 3. C; 4. C; 5. D.
Uticaria, Angioedema, and Anaphylaxis: 1. C; 2. C; 3. C; 4. A; 5. C.

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