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The hypertensive neonate

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ABSTRACT

Hypertension in neonates is increasingly recognized because of improvements in neonatal intensive care that have led to improved survival of premature infants. Although normative data on neonatal blood pressure remain limited, several factors appear to be important in determining blood pressure levels in neonates, especially gestational age, birth weight and maternal factors. Incidence is around 1% in most studies and identification depends on careful blood pressure measurement. Common causes of neonatal hypertension include umbilical catheter associated thrombosis, renal parenchymal disease, and chronic lung disease, and can usually be identified with careful diagnostic evaluation. Given limited data on long-term outcomes and use of antihypertensive medications in these infants, clinical expertise may need to be relied upon to decide the best approach to treatment. This review will discuss these concepts and identify evidence gaps that should be addressed.

1. Introduction

Advances in neonatal care have led to survival of increasing numbers of premature infants, many of whom will develop complications of prematurity such as chronic lung disease, acute kidney injury and hypertension. While hypertension in neonates has been known as a clinical entity since the late 1970s[1,2], recognition, evaluation and management of hypertensive neonates remain challenging for many clinicians. Reasons for this include a lack of robust normative data on neonatal blood pressure (BP) values, exclusion of neonates from clinical trials of antihypertensive medications [3], and the relatively low frequency of hypertension in this age group. Despite these issues, it is important to develop an understanding of basic principles surrounding identification, evaluation and management of these infants. This review will address key aspects of this clinical entity, hopefully in a manner that will be useful to the practicing clinician, and will also identify important gaps in knowledge that require further research. Hypertension outside of the immediate neonatal period has been reviewed elsewhere [4,5] and will not be addressed here.

2. Defining neonatal hypertension

2.1. Physiologic changes in neonatal blood pressure

Defining hypertension during the newborn period is difficult, as there are subtle complexities to changes in BP patterns in newborns. Blood pressure values change rapidly over the first days and weeks of life, especially in those born prematurely. Pejovic et al. found that in infants born <28 weeks' gestational age, the mean arterial pressure (MAP) increases by 26% in the first week and >50% over the first month of life [6]. Even in term infants, BP increased by >20% over the first month of life. For most term infants, BP increases significantly from the first to second day of life but less so on subsequent days [7]. In premature infants, BP on day one of life is primarily determined by the gestational age at birth and birth weight. Both Pejovic et al. [6] and Zubrow et al. [8] have shown a linear correlation of blood pressure on day one of life with birth weight and gestational age, with the most premature and lowest weight neonates having the lowest blood pressures at birth. While other factors may play a minor role, gestational age and birth weight are consistently the strongest determinants of neonatal blood pressure on day one of life.

In premature infants, blood pressure rapidly changes over the first weeks of life. Pejovic et al. determined that all premature infants experience a rapid increase in blood pressure over the first week of life with the most rapid rate of increase in the most premature infants [6]. Kent et al. determined that the phase of most rapid increase in blood pressure occurred over the first 2–3 weeks of life in infants born <32 weeks' gestation and only over the first week of life in infants born at 32–36 weeks' gestation [9]. They noted that the blood pressure following the phase of rapid increase is similar to term infants at birth. Lurbe et al. found that term infants born small for gestational age also had a lower BP at birth compared to those born appropriate for

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gestational age but then had a rapid increase in their BP over the first month of life to reach values similar to other neonates [10]. These various patterns of BP changes over the first weeks of life have been discussed in greater detail elsewhere [4].

After the initial rapid rise in BP, premature infants settle into a phase of slower, and steadily increasing BP by postmenstrual age. Zubrow and the Philadelphia Neonatal Blood Pressure Study Group found that after 5 days of life, neonates increase their systolic BP by about 1 mmHg every 4 days whether born prematurely or at term [8]. These authors generated graphs of BP by post-conceptional (now termed post-menstrual) age (Fig. 1) although unfortunately MAP was not included. More recently, we were able to combine BP data from the literature into a reference table of infant BP values after 2 weeks' postnatal age by current post-menstrual age [11]. The table provides the 50th, 95th, and 99th percentile values for systolic, mean, and diastolic BP for infants 26–44 weeks' postmenstrual age [Table 1]. Unfortunately, most BP studies in neonates have relatively small patient numbers, heterogeneous populations, and inconsistent measurement methodology, resulting in relatively weak normative BP data. A large multi-center prospective study of neonatal BP is urgently needed to establish more robust normative data.

2.2. Other influences on neonatal blood pressure

In addition to these expected physiologic changes, multiple other factors can affect BP in infants. Genetic factors likely also play a role in determining BP, although limited studies have been reported to date. One study identified cytochrome P450 (CYP2D6) CC genotype as being associated with higher BPs in preterm infants during hospitalization and at neonatal follow-up [12]. Maternal factors, including medications, underlying illnesses, and adequacy of nutrition during pregnancy, can also influence a neonate's BP [13]. Higher infant BPs have correlated

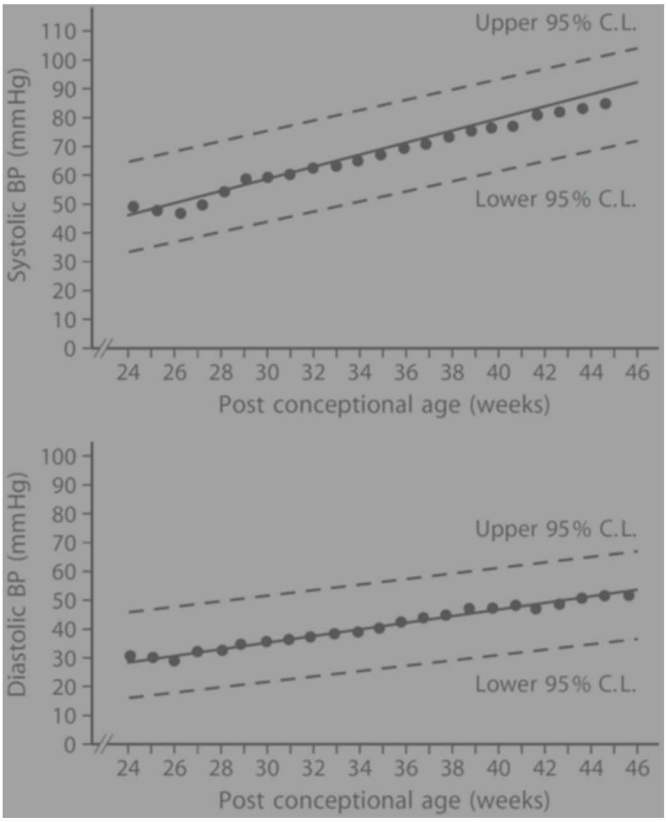

Fig. 1. Linear regression of systolic and diastolic blood pressure post-conceptual (post-menstrual) age with 95% confidence limits (upper and lower solid lines). Reprinted with permission from Zubrow et al. [8].

Table 1
Neonatal blood pressure percentiles[a].

Postmenstrual 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	75	90	95
DBP	45	60	65
MAP	55	70	75
36 Weeks			
SBP	70	85	90
DBP	40	55	60
MAP	50	65	70
34 Weeks			
SBP	68	83	88
DBP	40	55	60
MAP	48	62	69
32 Weeks			
SBP	65	80	85
DBP	40	55	60
MAP	48	65	68
30 Weeks			
SBP	60	75	80
DBP	38	50	54
MAP	45	58	63
28 Weeks			
SBP	55	72	77
DBP	30	50	56
MAP	38	57	63
26 Weeks			
SBP	50	70	76
DBP	30	48	53
MAP	38	55	61

[a] Adapted from Dionne and colleagues [15].

with maternal body mass index >30 kg/m^2 and low socioeconomic status in Nigerian infants [14] and in an Australian study to premature infants born to mothers with diabetes or neonates with abnormal uteroplacental perfusion by placental pathology [15]. There is some suggestion in the literature that chorioamnionitis and HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome may be related to lower infant BPs and even symptomatic hypotension [16,17]. On the other hand, a recent study showed that in neonates exposed to early-onset pre-eclampsia, BPs started to rise on DOL 2 compared to infants not exposed to pre-eclampsia, and remained higher over the first 4 weeks of life [18]. In summary, it is increasingly clear that many antenatal and postnatal processes combine to influence BP values in the newborn period.

2.3. Criteria for hypertension

There is considerable variation in neonatal BP, both within the same infant over time, and between infants based on the aforementioned factors. Given this, plus the lack of robust reference BP values for neonates, there is a lack of clarity on what criteria to use for defining hypertension in neonates. The 2017 American Academy of Pediatrics Clinical Practice Guideline on Childhood Hypertension [5] recommends use of the tables created by Dionne et al., which provide derived systolic and diastolic BP percentiles based on post-menstrual age (Table 1), as the best available reference data. Infants with BP values persistently above the 95th percentile should be closely monitored, and those with

BP values over the 99th percentile should be investigated and potentially treated depending on the clinical situation.

3. Incidence of neonatal hypertension

The incidence of neonatal hypertension can vary depending upon infant factors as well as their neonatal course. In a study of 2500 Australian infants admitted to a NICU over 4 years, there was a 1.3% incidence of hypertension [19]. Hypertensive neonates in this study commonly had coexisting risk factors for hypertension, including antenatal steroid exposure, maternal hypertension, umbilical artery catheter (UAC) placement, acute kidney injury, and chronic lung disease. An identical prevalence of hypertension was seen in a more recent case series that included over 4000 infants [20]. Similar to the Australian series, these investigators found that perinatal risk factors including maternal hypertension, antenatal steroid administration, and maternal substance use were associated with hypertension. One large, multicenter study that used administrative data from a consortium of pediatric hospitals reported an incidence of 1% in infants admitted to an NICU [21]. In this study, hypertension was associated with greater illness severity, extracorporeal membrane oxygenation (ECMO) therapy, and kidney disease (either acquired or congenital).

Hypertension can also be diagnosed long after the neonate has been discharged from the NICU. The classic study is that of Friedman and Hustead, who retrospectively studied 650 infants seen in a follow-up clinic after discharge from a tertiary NICU, and found an incidence of hypertension of 2.6% [22]. These infants, in whom hypertension was defined as a systolic BP higher than 113 mmHg on three consecutive visits over 6 weeks, were diagnosed with hypertension at a mean age of approximately 2 months' corrected gestational age (approximately 48 weeks' postmenstrual age), and were more likely to have a more complex and longer NICU course with lower initial Apgar scores and longer NICU stays. More recently, Shah et al. reported similar findings from a single center outpatient hypertension clinic, with 13 of 36 hypertensive infants diagnosed following discharge from the NICU [23]. These data provide support for the AAP recommendation that BP should be routinely monitored in children <3 years of age who were cared for in the NICU [5].

4. Differential diagnosis of neonatal hypertension

There are many potential causes of hypertension in neonates (Table 2), with the most frequent being catheter-associated thromboembolism, renal parenchymal disease, and chronic lung disease. However, it is also quite common that no underlying cause can be identified – a recent multicenter case series reported that no specific cause was found in approximately 50% of hypertensive neonates [24].

Thrombus formation associated with umbilical artery catheter (UAC) placement is the most common renovascular abnormality associated with hypertension in neonates. First described in the 1970s [25], this association has been repeatedly confirmed [26]. Hypertension appears to develop in infants with UACs even without demonstration of actual thrombi in renal arteries. Therefore, it is thought that catheter-related hypertension results from disruption of the vascular endothelium at the time of line placement, leading to formation of small clots that may embolize into the renal parenchyma. Reported rates of thrombus formation in many studies are typically around 25% [27]. While longer duration of catheter placement has been associated with an increased risk of thrombus formation [28], the location of the line does not appear to matter – in a systematic review, hypertension occurred at equal frequency with either "high" or "low" UAC positioning [29].

Other renovascular abnormalities that may also lead to neonatal hypertension include renal vein thrombosis, fibromuscular dysplasia, arterial calcification and compression of the renal arteries by tumors. Renal vein thrombosis usually presents with the classic triad of flank mass, gross hematuria, and hypertension [30]. Renal vein thrombosis

Table 2
Potential causes of neonatal hypertension\.

- Renovascular
  - Thromboembolism
  - Renal artery stenosis
  - Mid-aortic syndrome
  - Renal venous/arterial thrombosis
  - Renal artery compression
  - Idiopathic arterial calcification
  - Congenital rubella syndrome
- Renal Parenchymal Disease
  - Congenital
    - Polycystic kidney (ARPKD, ADPKD)
    - Multicystic-dysplastic kidney disease
    - Severe renal dysplasia
    - Ureteropelvic junction obstruction
    - Unilateral renal hypoplasia
    - Congenital nephrotic syndrome
    - ACE inhibitor fetopathy
  - Acquired
    - Acute kidney injury
    - Cortical necrosis
    - Interstitial nephritis
    - Hemolytic-uremic syndrome
    - Obstruction (stones, tumors)
- Pulmonary
  - Bronchopulmonary dysplasia
  - Pneumothorax
- Cardiac
  - Aortic coarctation
- Endocrine
  - Congenital adrenal hyperplasia
  - Hyperaldosteronism
  - Hyperthyroidism
  - Pseudohypoaldosteronism type II
  - Glucocorticoid remediable aldosteronism
- Medications/Intoxications
  - Infant
    - Dexamethasone
    - Adrenergic agents
    - Vitamin D intoxication
    - Theophylline
    - Caffeine
    - Pancuronium
    - Phenylephrine
  - Maternal
    - Cocaine
    - Heroin
    - Antenatal steroids
- Neoplasia
  - Wilms tumor
  - Mesoblastic nephroma
  - Neuroblastoma
  - Pheochromocytoma
  - Chorioangioma
- Neurologic
  - Pain
  - Intracranial hypertension
  - Seizures
  - Familial dysautonomia
  - Subdural hematoma
- Other causes
  - Volume overload
  - Abdominal wall defect closure
  - Adrenal hemorrhage
  - Hypercalcemia
  - Traction
  - Birth asphyxia
  - ECMO

Abbreviations usedin table: ACE, angiotensin converting enzyme; ADPKD, autosomal dominant polycystic kidney disease; ARPKD, autosomal recessive polycystic kidney disease; ECMO, extracorporeal membrane oxygenation.

may be associated with risk factors including perinatal asphyxia, dehydration, and maternal diabetes mellitus. The hypertension may be quite severe in these cases and frequently persists beyond the neonatal period, often related to retained atrophic kidneys [30,31]. Fibromuscular dysplasia (FMD) and resultant renal arterial stenosis is an important cause of renovascular hypertension in the neonate, as many infants with FMD will have normal appearing main renal arteries but significant branch vessel disease [32]. In addition, in FMD renal arterial stenosis may also be accompanied by other vascular abnormalities, including the so-called mid-aortic syndrome [32,33].

Renal parenchymal causes of hypertension may be congenital such as renal dysplasia or autosomal recessive polycystic kidney disease, associated with a urologic abnormality such as posterior urethra valve, or acquired such as acute kidney injury [34] or cortical necrosis. Both autosomal dominant and autosomal recessive polycystic kidney disease (PKD) may present with hypertension; autosomal recessive PKD more commonly leads to hypertension early in life, sometimes in the first months of life [35]. Hypertension may be seen in infants with kidney dysplasia and hydronephrosis as well. Less frequently, hypertension has also been reported in infants with unilateral multicystic dysplastic kidneys (MCDK), possibly secondary to excess renin production [36]. Obstructive uropathy, such as ureteropelvic junction obstruction, may be accompanied by hypertension, which often normalizes after surgical correction, but persistent hypertension has occasionally been reported [37].

Hypertension in neonates with chronic lung disease/bronchopulmonary dysplasia (BPD) was first described by Abman and colleagues [38], who found that hypertension affected 43% of infants with BPD 43%, versus 4.5% of infants without BPD. Over half of the hypertensive

infants with BPD were not diagnosed until after NICU discharge, again highlighting the importance of monitoring BP following NICU discharge [5]. Multiple studies have subsequently confirmed that hypertension occurs more frequently in infants with BPD compared to comparable infants without BPD, and it appears to be more common with increasing severity of pulmonary disease [24,39]. Factors such as hypoxemia and increased BPD severity appear to be associated with the development of hypertension. Recently, alterations in aortic wall thickness and vasomotor functioning have been demonstrated in infants with BPD, suggesting another potential mechanism for development of hypertension in this population [40]. The high incidence of hypertension in neonates with chronic lung disease reinforces that such infants are clearly at increased risk of hypertension and need close monitoring of BPs, both during their NICU stay and after hospital discharge.

As illustrated in Table 2, hypertension may also be seen in disorders of several other organ systems, either as the presenting sign or accompanying other signs. Examples include coarctation of the aorta, endocrinopathies, and neurologic disorders. Tumors, including neuroblastoma, Wilms tumor, and many others, can cause hypertension either from production of vasoactive substances such as catecholamines [41] or from direct compression of renal vessels and/or ureters. Infants undergoing abdominal wall closure (e.g., gastroschisis or other abdominal wall surgical procedures) commonly have hypertension, with one-third to one-half of neonates demonstrating hypertension following the procedure. This is thought to result from increased intraabdominal pressure and resultant changes in renal blood flow as well as increased catecholamine secretion. A recent single institution case-series of infants with giant omphaloceles undergoing repair found that almost 80% of patients had hypertension that largely resolved prior to discharge [42]. An important association is hypertension in neonates receiving ECMO, which has been reported to occur in up to half of neonates requiring ECMO [43]. This form of hypertension appears to be multifactorial and may be secondary to fluid overload, impaired water and renal sodium handling, and does not appear to be related to alterations in renin activity [44].

Not to be overlooked in the NICU is hypertension related to various medications. Dexamethasone [45], theophylline, phenylephrine ophthalmic drops [46], and pancuronium have all been implicated as causes of hypertension in neonates. Medication-induced hypertension is often dose-dependent and resolves with dose-reduction or withdrawal of the offending agent. Substance use during pregnancy, most notably cocaine [47] and heroin, has been reported to cause hypertension. Additionally, in infants of drug-addicted mothers, withdrawal from sedative or analgesic agents may be associated with hypertension. Hypertension from salt and water overload may be seen in neonates receiving parenteral nutrition, or from hypercalcemia either from excessive calcium intake or from vitamin A or D intoxication. Medications may also result in hypertension by causing acute kidney injury. Given the many problems surrounding the detection of AKI in neonates, hypertension may be the first indication of kidney injury and may lead to retrospective identification of AKI. Finally, although not a medication *per se*, exposure to phthalates in the NICU has recently been associated with the development of hypertension, with the proposed mechanism being activation of the mineralocorticoid receptor via inhibition of 11-beta-hydroxysteroid dehydrogenase 2 [48].

5. Clinical presentation of neonatal hypertension

Many neonates with hypertension are asymptomatic and will be discovered on routine, repeated measurement of vital signs. Alternatively, there may be non-specific signs such as irritability, poor feeding, vomiting, or restlessness. In either case, it can be challenging to identify infants with true hypertension meriting further evaluation and treatment. Even in cases where signs are present, the magnitude of hypertension may not correlate with the presence or severity of signs.

However, there are important severe presentations of neonatal hypertension that occur rarely, including cardiogenic shock and congestive heart failure, that can be life threatening [49,50]. There may also be variable neurologic signs such as lethargy, tremors, seizures, apnea, and hemiparesis that may be difficult to distinguish from intracranial pathology. Thus, it is important to have a high index of suspicion and pay careful attention to vital signs, as correction of hypertension may be life-saving.

6. Diagnostic evaluation

6.1. Blood pressure measurement

Correct identification of neonatal hypertension requires careful, accurate BP measurement [51]. For many years, the gold standard for BP measurement in neonates has been direct intra-arterial measurement, with similar BP values detected by either umbilical or peripheral artery catheters [52]. However, in clinical practice indirect measurement of BP with oscillometric devices is more common and practical. Oscillometric devices are easy to use, and allow frequent monitoring/repeated measurements over time. There is usually reasonable correlation between invasive monitoring and oscillometric assessment; however, accuracy may vary depending on the size of the infant, with oscillometric devices more likely to over-read BP in smaller neonates [53]. Auscultation is difficult in neonates but, as in older children [5], should be considered to confirm elevated BP readings obtained with oscillometric devices, particularly in the NICU graduate or asymptomatic infant with observed elevated BPs.

The accuracy of BP measurement in neonates can be affected by many factors. BP measurements will be most accurate in a quiet, resting infant and can be elevated by a variety of activities such as crying, feeding, or even non-nutritive sucking (Fig. 2) [54,55]. Consistent measurement technique is essential to obtain accurate BP values [50]. Standardized protocols for measurement of BP are available [56,57] and help to ensure that accurate BP values are obtained to guide clinical decision making. Common elements of these standardized protocols include proper infant positioning, measurement technique (including appropriate cuff size), and timing of measurement (Table 3). Issues related to neonatal BP measurement have recently been comprehensively reviewed by the International Neonatal Consortium [51].

6.2. Diagnostic evaluation

Identification of neonatal hypertension begins with a careful history and physical examination. A focused history should be obtained, starting with the prenatal history, including maternal medication use, details of the delivery, including whether there was perinatal asphyxia, then moving to further details of the neonate's clinical course, including presence of concurrent medical conditions associated with hypertension, current and past medications, and any procedures the neonate has undergone (e.g., UAC placement).

Physical examination may indicate the underlying cause of the hypertension or may detect pathologic effects of hypertension or end-organ dysfunction from hypertension, such as neurologic abnormalities or congestive heart failure. BP readings should be obtained in all four extremities to rule out coarctation of the aorta or an aortic thrombus occluding the thoracic or abdominal aorta. It should be mentioned that since upper and lower extremity BPs can be similar in neonates, an echocardiogram is required to confirm the diagnosis of coarctation [58]. The infant's general appearance should be assessed for dysmorphic features, which may suggest an underlying genetic syndrome that includes hypertension as a clinical manifestation. Careful cardiac and abdominal examinations should be performed, as abdominal distention or a flank mass may be indicative of urinary obstruction, polycystic kidney disease, or abdominal tumors.

Laboratory testing should be focused on assessing kidney function and determining whether kidney disease is present. Further diagnostic

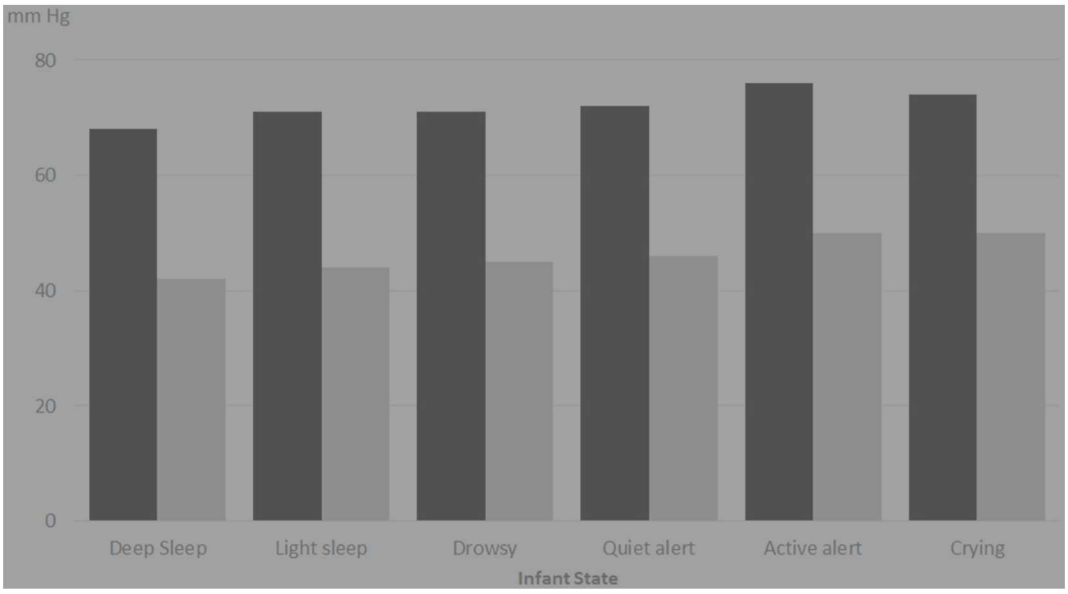

Fig. 2. Effect of infant state on blood pressure (black bars, systolic BP; grey bars, diastolic BP). Data adapted from Satoh et al. [54].

Table 3
Techniques for proper blood pressure measurement.

Infant should be prone or supine, resting comfortably
Measure blood pressure ≥1.5 h after a medical procedure or feeding
Use appropriately sized blood pressure cuff and measure in right upper arm[a]
Obtain several blood pressure measurements in succession using an oscillometric device

[a] Calf values are equivalent to values obtained in the upper arm until about 6 months of age.

testing should be guided by the initial evaluation and screening test results and should be individualized for each infant (Table 4). Plasma renin activity (PRA) measurement deserves special mention, as it can be quite high in neonates, especially those born prematurely [59]; however, it may also be suppressed, especially in neonates with pulmonary disease [24] making interpretation difficult. Given these concerns, measurement of PRA should usually be deferred unless other laboratory abnormalities (e.g., hypokalemia, alkalosis) suggest a possible monogenic form of hypertension [60].

Most hypertensive neonates will require one or more imaging studies to determine the cause of their hypertension. Renal ultrasound with Doppler evaluation should be the initial imaging modality of choice. It can identify kidney masses, urinary tract obstruction, or cystic disease, with Doppler flow studies most useful in evaluation for potential arterial or venous thrombosis. Radionuclide imaging has been used to assess for kidney perfusion abnormalities secondary to thromboembolism [61]. However, in our experience the utility of nuclear imaging is limited in the neonatal time period because of immature kidney function. Other studies, including echocardiograms and voiding cystourethrograms, should be performed as clinically indicated.

Extreme BP elevation should prompt the clinician to consider vascular imaging to evaluate for renal artery stenosis (RAS) or mid-aortic syndrome. In neonates, most authorities would agree that neither computed tomographic nor magnetic resonance angiography has sufficient resolution to accurately detect most cases of renovascular disease. Arteriography offers the most accurate method of diagnosing RAS, particularly given the high incidence of branch vessel disease seen in neonates [62]. However, although successful angioplasty of RAS in a neonate has been reported [63], many centers may lack both the equipment and expertise to perform this procedure safely in newborns, so it may be necessary to control the hypertension medically until the infant is large enough for an arteriogram to be safely performed for both definitive diagnosis and endovascular treatment.

Table 4
Diagnostic evaluation of hypertension in neonates[a].

Routine/screening studies	Additional studies (if indicated)
Urinalysis (+/− culture)	Thyroid studies
CBC & platelet count	Urine VMA/HVA
Electrolytes	Plasma Renin Activity
BUN, Creatinine	Aldosterone
Calcium	Cortisol
Chest x-ray	Echocardiogram
Renal Ultrasound with Doppler	Abdominal/pelvic ultrasound
	VCUG
	Arteriogram
	Renal angiography
	Nuclear scan (DTPA/Mag-3)

[a] Abbreviations used in table: BUN, blood urea nitrogen; CBC, complete blood count; DTPA, diethylene triamine pentaacetic acid; HVA, homovanillic acid; Mag-3, Mercaptoacetylitriglycerine VMA, vanillylmandelic acid.

7. Treatment of neonatal hypertension

While data on the treatment of hypertension in neonates is limited, the approach to management can be adapted from that used in older children, except that non-pharmacologic therapy likely has little or no role. The first step should be to determine if there is an easily correctable cause of hypertension. These might include excessive inotrope administration, dexamethasone or other medications, hypercalcemia, or volume overload. Other specific approaches may also be warranted, such as treatment of pain, correction of hypoxemia in infants with BPD, and hormonal replacement in those with endocrine disorders.

Clinical criteria for initiating antihypertensive medications are not well defined, so except in severe hypertension with end-organ manifestations (e.g., heart failure or seizures), this can be a difficult decision. No data exist on the adverse effects of chronic hypertension in infancy, and few antihypertensive medications have ever been studied in neonates. Available case series and other studies do indicate that a wide variety of antihypertensive medications has been prescribed to hypertensive neonates [20,21,64]. Finally, as noted earlier, determining what BP threshold at which to consider drug treatment can be difficult because of the lack of robust normative data. Therefore, clinical expertise should be used to guide decision-making.

In neonates with sustained moderate blood pressure elevation felt to warrant therapy, oral antihypertensives (Table 5) may be used. A good initial choice is the calcium channel blocker isradipine [65,66]. While amlodipine may also be used, it has a slower onset of action, and its prolonged duration of effect may be less useful in the acute setting [67]. Both isradipine and amlodipine can be extemporaneously compounded into a 1 mg/mL solution, allowing for administration of the small doses required in neonates (amlodipine is also now available commercially in suspension form). Hydralazine and minoxidil, which are direct vasodilators, may also be useful. Beta adrenergic blockers may need to be avoided in chronic therapy of neonatal hypertension if there is significant coexisting chronic lung disease. With respect to diuretics, they are rarely useful as first-line agents, but may be appropriate if a second agent is required. Two recent case series have demonstrated that spironolactone can be effective in selected cases of neonatal hypertension thought to be related to phthalate exposure [24,48]. Finally, in infants with BPD, diuretics may not only control hypertension but can improve the pulmonary status [24,68].

The use of angiotensin-converting enzyme inhibitors (ACEI) or other antihypertensive agents affecting the renin-angiotensin-aldosterone system (RAAS) in neonates has been controversial, mostly because there is concern that these agents may impair completion of kidney development. Captopril is actually one of the only antihypertensive agents that has been studied in neonates. It was demonstrated to lower BP effectively, but may cause an exaggerated fall in BP, especially in premature infants [69,70]. Other reported complications of ACEI treatment in neonates include hyperkalemia and AKI [71,72]. These are all related to the known activation of the RAAS in neonates, which is necessary for nephron development [73,74]. While a recent systematic review [3] provides reassuring data on the safety of ACEI in children overall, we usually avoid prescribing ACEI until infants have reached a corrected post-menstrual age of 44 weeks.

7.1. Acute severe hypertension in neonates

For treatment of acute severe hypertension in neonates, defined as hypertension with evidence of end-organ dysfunction, continuous infusions of intravenous antihypertensive agents (Table 5) are indicated [75]. Continuous infusions have several advantages, most importantly the ability to titrate the infusion based on response until the desired BP is reached. As with all patients with severe hypertension, care should be taken to avoid rapid reduction of BP, which may result in cerebral ischemia or hemorrhage. This complication may be more likely to occur in premature infants because of immaturity of the periventricular circulation [76]. In the setting of severe hypertension, oral agents should be avoided given their variable duration of effect, onset of action, and unpredictable response. Several case series suggest that the intravenous calcium channel blocker nicardipine may be particularly useful in infants with acute severe hypertension [77,78]. Other intravenous antihypertensives that have been reported effective in neonates include sodium nitroprusside, esmolol, and labetalol [79–81]. Whenever intravenous infusions are used, the neonate's BP should be monitored continuously, preferably via an indwelling arterial catheter, alternatively using an automated device to obtain repeated cuff readings, so that the infusion can be titrated to the desired BP reduction.

Intermittently administered intravenous agents may also have a role in the treatment of some hypertensive neonates, particularly in those with mild-to-moderate hypertension who cannot tolerate oral medications because of necrotizing enterocolitis or other gastrointestinal processes Bolus doses of hydralazine and labetalol (Table 5) in particular have been widely used in infants, and appear to be well tolerated.

Table 5
Recommended doses for selected antihypertensive medications for neonatal hypertension.

Class	Drug	Route	Dose	Interval	Comments
ACE Inhibitors[a]	Captopril	Oral	<3 m: 0.01–0.5 mg/kg/dose Max 2 mg/kg/day >3 m: 0.15–0.3 mg/kg/dose Max 6 mg/kg/day	TID	First dose may cause rapid drop in BP, especially if receiving diuretics Monitor serum creatinine and K+ Intravenous enalaprilat NOT recommended – see text Limited experience with Lisinopril in infants
	Enalapril[b]	Oral	0.08–0.6 mg/kg/day	QD-BID	
	Lisinopril[b]	Oral	0.07–0.6 mg/kg/day	QD	
α and β antagonists	Labetalol	Oral	0.5–1.0 mg/kg/dose Max 10 mg/kg/day	BID-TID	Heart failure, BPD relative contraindications
		IV	0.20–1.0 mg/kg/dose 0.25–3.0 mg/kg/hr	Q4-6hr Infusion	
	Carvedilol	Oral	0.1 mg/kg/dose up to 0.5 mg/kg/dose	BID	May be useful in heart failure
β - antagonists	Esmolol	IV	100-500 mcg/kg/min	Infusion	Very short-acting–continuous infusion necessary.
	Propranolol[b]	Oral	0.5–1.0 mg/kg/dose Max 8–10 mg/kg/day	TID	Monitor heart rate; potentially avoid in BPD
Calcium channel blockers	Amlodipine	Oral	0.05–0.3 mg/kg/dose Max 0.6 mg/kg/day	QD - BID	All may cause reflex tachycardia
	Isradipine	Oral	0.05–0.15 mg/kg/dose Max 0.8 mg/kg/day	QID	
	Nicardipine	IV	1-4 mcg/kg/min	Infusion	
Central α-agonist	Clonidine	Oral	5-10 mcg/kg/day Max 25 mcg/kg/day	TID	May cause mild sedation
Diuretics	Chlorothiazide[b]	Oral	5–15 mg/kg/dose	BID	Monitor electrolytes
	Hydrochlorothiazide	Oral	1–3 mg/kg/dose	QD	May be useful in BPD
	Spironolactone	Oral	0.5–1.5 mg/kg/dose	BID	
Direct Vasodilators	Hydralazine	Oral	0.25–1.0 mg/kg/dose Max 7.5 mg/kg/day	TID - QID	Tachycardia and fluid retention are common side effects
		IV	0.15–0.6 mg/kg/dose	Q4hr	IV administration can cause unpredictable drops in BP
	Minoxidil	Oral	0.1–0.2 mg/kg/dose	BID - TID	Tachycardia and fluid retention common side effects; prolonged use causes hypertrichosis
	Sodium Nitroprusside	IV	0.5–10 mcg/kg/min	Infusion	Thiocyanate toxicity can occur with prolonged (>72 h) use or in kidney disease

[a] Abbreviations used in table: ACE, angiotensin converting enzyme; BID, twice daily; BPD, bronchopulmonary dysplasia; IV, intravenous; QD, once daily; QID, four times daily; TID, three times daily.
[b] Commercially marketed suspension available.

7.2. The role of surgery

In selected hypertensive neonates, a surgical approach may be appropriate. Surgery is obviously indicated for neonates with hypertension related to aortic coarctation or kidney obstruction [82]. For neonates with RAS, medical management of hypertension will often be necessary until the infant has grown enough to safely undergo endovascular repair [83]. Rarely, unilateral nephrectomy may be necessary in infants with RAS if BP control cannot be achieved medically [84]. Nephrectomy has also been reported in neonates with MCDK and severe hypertension [85]. In neonates with hypertension associated with a malignancy such as neuroblasotoma, surgical tumor removal or debulking may be indicated, possibly following chemotherapy.

8. Outcomes

Long term outcomes of neonatal hypertension are generally thought to be good, although few studies are available. Outcomes are largely dependent upon the underlying cause of hypertension, especially hypertension related to PKD or other congenital kidney conditions. Neonates with renal vessel thrombosis may continue to be hypertensive, and in some cases this hypertension merits unilateral nephrectomy for BP control [86]. A significantly increased risk of chronic kidney disease and hypertension was found in a recent cohort study that followed neonates with renal venous thrombosis for a median of 15 years [87], mandating long-term follow-up of such patients well beyond the neonatal period. Aortic coarctation-even successfully repaired in infancy-recurs in a large percentage of patients [88], so these children also require long-term follow up.

Most causes of neonatal hypertension are related to probable thromboembolism or are idiopathic, and available information suggests that hypertension in these neonates will resolve over time [19,24]. These infants may initial require increases in their antihypertensive medication over the first several months of life as they demonstrate catch-up growth. However, after that initial period, it may be possible to wean the medication either by decreasing the dose or by making no further dose increases as the infant grows. One single center study demonstrated that most hypertensive neonates will be off medication by 6 months of age [19], but a more recent, multi-center study showed that some infants required treatment for up to 2 years after discharge from the NICU [89].

Long term monitoring of infants with neonatal hypertension is essential. Home BP monitoring should be used for any infant receiving antihypertensive medication to not only monitor and adjust medication doses between office visits, but also as a safety measure. Setting up such services can be challenging, but we strongly feel that this should be considered the standard of care. In our experience, use of an oscillometric device is the best option for home monitoring. Other aspects of long-term monitoring may include serial assessment of kidney function, urine testing for microalbuminuria, and repeat kidney ultrasounds to follow kidney growth.

9. Conclusions

Neonatal BP is determined by several well established factors, including birth weight, gestational age, and post-menstrual age. Other perinatal factors and maternal health conditions such as pre-eclampsia also play important roles. Hypertension is more frequently observed in neonates with concurrent conditions such as bronchopulmonary dysplasia/chronic lung disease, underlying kidney disease, or in those who have undergone UAC placement. The diagnosis of neonatal hypertension depends on accurate BP measurement, which can make identification of hypertension challenging. Once hypertension is identified, a careful diagnostic evaluation should lead to a specific or suspected etiology in most neonates. Treatment should be determined by severity of the hypertension; when pharmacotherapy is indicated, it may include intravenous and/or oral agents. Most infants will resolve their hypertension over time, although a small number may have persistent BP elevation. Despite the increased knowledge over the past several decades, there remain many areas in which better data are needed, particularly with respect to normative BP data, diagnostic thresholds, and the use of antihypertensive medications.

Practice points

- Accurate identification of abnormal blood pressure in neonates requires comparison with blood pressure values obtained in neonates of similar post-menstrual age.
- Common causes of hypertension in neonates include thromboembolism, chronic lung disease and congenital kidney diseases.
- Evaluation of a neonate with suspected hypertension begins with careful blood pressure measurement, and then proceeds through history, physical examination, laboratory testing and selected imaging.
- Available data indicate that hypertensive neonates will resolve their hypertension over the first 6–24 months of life.
- Long-term follow-up is warranted to detect recurrence of hypertension, especially in hypertensive neonates with conditions known to result in recurrence of hypertension later in life.

Research directions

- Development of robust normative blood pressure data for premature and term neonates.
- Further study into the efficacy and safety of antihypertensive medications in neonates.

Declaration of competing interest

Joseph Flynn reports receiving royalties from Up to Date and Springer.

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