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EDUCATIONAL REVIEW

Neonatal hypertension: an educational review

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Abstract

Hypertension is encountered in up to 3% of neonates and occurs more frequently in neonates requiring hospitalization in the neonatal intensive care unit (NICU) than in neonates in newborn nurseries or outpatient clinics. Former NICU neonates are at higher risk of hypertension secondary to invasive procedures and disease-related comorbidities. Accurate measurement of blood pressure (BP) remains challenging, but new standardized methods result in less measurement error. Multiple factors contribute to the rapidly changing BP of a neonate: gestational age, postmenstrual age (PMA), birth weight, and maternal factors are the most significant contributors. Given the natural evolution of BP as neonates mature, a percentile cutoff of 95% for PMA has been the most common definition used; however, this is not based on outcome data. Common causes of neonatal hypertension are congenital and acquired renal disease, history of umbilical arterial catheter placement, and bronchopulmonary dysplasia. The treatment of neonatal hypertension has mostly been off-label, but as evidence accumulates, the safety of medical management has increased. The prognosis of neonatal hypertension remains largely unknown and thankfully most often resolves unless secondary to renovascular disease, but further research is needed. This review discusses important factors related to neonatal hypertension including BP measurement, determinants of BP, and management of neonatal hypertension.

Keywords Hypertension · Blood pressure · Neonatal · Newborn · Premature · Oscillometric · NICU

Abbreviations

AKI	Acute kidney injury
AWAKEN	Assessment of Worldwide Acute Kidney Injury Epidemiology in Neonates
BP	Blood pressure
BPD	Bronchopulmonary dysplasia
IV	Intravenous
MRI	Magnetic resonance imaging
NICU	Neonatal intensive care unit
PMA	Postmenstrual age
SGA	Small for gestational age
UAC	Umbilical arterial catheter

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Introduction

Neonatal care in the past predominantly focused on survival without neurological morbidity, but more recently, other morbidities have become evident with advances in neonatal care and technology [1]. The importance of the in utero environment, neonatal exposures to nephrotoxic medications, poor growth, and other risk factors may have long-term implications on cardiovascular and renal health. One important risk factor for long-term cardiovascular or renal disease may be hypertension in the neonatal period. Neonatal hypertension knowledge has benefited significantly with many recent studies contributing normal blood pressure (BP) values in a variety of clinical situations [2–8]. Although the risks of long-term morbidities of neonatal hypertension remain unknown, the long-term cardiovascular and renal risks of preterm birth and neonatal intensive care unit (NICU) hospitalizations are coming into focus, and the risk is not negligible [9–11]. This article focuses on the identification, determinants, management, and treatment of hypertension in neonatal patients, particularly those hospitalized in the NICU. Given the risks associated with adult hypertension—accounting for 47% of all ischemic heart disease events around the world [12]—this is an important disease that needs to be recognized and addressed prior to NICU discharge.

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Blood pressure measurement

Measurement of BP in newborn infants, particularly preterm infants, remains a challenge despite advances in devices for non-invasive measurement. The gold standard for BP measurement remains to be the invasive intra-arterial measurement [13]. In hospitalized newborns, this is most commonly done in a NICU and measured with an umbilical artery catheter. The vast majority of umbilical arterial catheters are not placed to monitor for hypertension, but instead to monitor for hypotension and for frequent blood analyses. Other commonly used sites for invasive BP monitoring in neonates are the peripheral radial artery or the posterior tibial artery which have been shown to correlate with central arterial BPs in infants of varying gestational ages, weights, and postmenstrual age (PMA) [14]. Invasive BP monitoring in small preterm infants can still present challenges to obtain accurate readings. Immediately after placement of an umbilical arterial catheter, the artery is prone to spasm and transducer positioning in an isolette can significantly alter readings if not placed at heart level [15]. Despite these challenges, invasive measurement is frequently used in the first week of age in unstable preterm newborns, but less often in stable preterm infants, given the risk of line-associated bloodstream infections and thrombosis potentially resulting in later-onset hypertension.

Non-invasive measurement of BP in neonates is now done universally by oscillometric devices [16], and a discussion of previous techniques can be found in a review by Weindling [17]. Measurement with an oscillometric device is based on the principle that pulsatile blood flow through a vessel will produce oscillation of the arterial wall which can be transmitted to a BP cuff [18]. The actual measurement using this technique is the mean arterial pressure, and the systolic and diastolic pressures are calculated. This technique has been shown to correlate with intra-arterial measurements previously, but recently, several nuances have been identified [8, 19]. In small for gestational age (SGA) infants, this method can underestimate systolic BP, and in sick neonates, it can overestimate both systolic and diastolic BPs [3, 4]. In addition, different brands of oscillometric BP monitors have given different results when measuring the same infants [20]. Specifically with regard to hypertension, one study showed that mean BP values are overestimated regardless of the brand used [21]. Despite these drawbacks, this method remains the simplest and most accurate way to get frequent and non-invasive BP measurements.

The specific method of obtaining non-invasive oscillometric BP readings in sick neonates in the NICU importantly is standardized in most units. Multiple different methodologies have been recommended based on the state of the infant and the knowledge that sleep versus the awake state can significantly change values [22]. Nwankwo et al. recommended only obtaining neonatal BPs in either the sleep or quiet resting alert state to get an accurate measurement. Recently, Dionne et al. have also found that the first reading with an oscillometric machine is less accurate than subsequent readings [13]. Given all these factors, Nwankwo et al. and, more recently, Mistry and Gupta developed the following recommendations: use the right upper arm, use an appropriate sized cuff (cuff width-to-arm circumference ratio of 0.45–0.7, most often a size of 2–4 cm), obtain measurement during quiet awake or sleep after the cuff has been on undisturbed for 15 min (if possible, obtain measurement 1.5 h after last feed or medical intervention), and finally, obtain three measurements, and if the first is elevated, take the average of the second two measurements [22, 23]. If high blood pressures are reported but have not been obtained using this methodology, repeat BP measurements should be measured using this protocol.

Determinants of normal blood pressure

When evaluating an infant's BP in the NICU, it is critical to know the gestational age of the infant at birth. In one of the largest neonatal BP studies, systolic and diastolic BP measurements were made in 608 newborns admitted to 14 different NICUs [24]. In this study, they found that gestational age and BP correlated strongly on the first day of age. However, methodology in this study constituted systolic measurements only with Doppler ultrasound. More recently, Kent et al. analyzed a group of stable preterm neonates between 28 and 36 weeks of gestation and produced normograms for BP at different gestations [25]. In a non-invasive BP measurement study, Pejovic et al. found that gestational age was a significant predictor of BP through the first 30 days of age [26]. In the extremely preterm population, Batton et al. found similar trends—arterial BP was lower in the lower gestational ages—but noted that each gestational age had wide variation [5].

With regard to age, one of the largest determinants of preterm neonatal BP is the PMA of the infant. Several studies have demonstrated a rise in the first 3–7 days of age in both systolic and diastolic BPs; thus, this is considered normal [24–26]. Kent et al. showed that BP increased throughout the first few weeks of life such that preterm neonates at 3 weeks of age had equivalent BPs to term neonate equivalents [25]. In the healthy term neonatal population, the increase in BP occurs more rapidly, primarily during days 1 and 2 [27]. Following the first week of age, BP then slowly rises over the first year of age, and a good summary of normal BPs by PMA was published by Dionne et al. (Table 1) [13].

The degree to which birth weight affects BP does not have a correlation nearly as strong as PMA. In term infants, one large neonatal BP study with 473 infants found that with each additional 0.5 kg rise in birth weight, there was a 3.61-mm rise in systolic BP [28]. In contrast, Kent et al. found no correlation or difference with birth weight and BP. An interesting subgroup of infants in whom BP may actually be inversely

Table 1 Normative BP based on PMA [13]

PMA (weeks)	Blood pressure	Systolic, mean, and diastolic blood pressure for infants after 2 weeks of life by PMA		
		50th percentile	95th percentile	99th percentile
44	SBP	88	105	110
	MAP	63	80	85
	DBP	50	68	73
42	SBP	85	98	102
	MAP	62	76	81
	DBP	50	65	70
40	SBP	80	95	100
	MAP	60	75	80
	DBP	50	65	70
38	SBP	77	92	97
	MAP	59	74	79
	DBP	50	65	70
36	SBP	72	87	92
	MAP	57	72	77
	DBP	50	65	70
34	SBP	70	85	90
	MAP	50	65	70
	DBP	40	55	60
32	SBP	68	83	88
	MAP	49	64	69
	DBP	40	55	60
30	SBP	65	80	85
	MAP	48	63	68
	DBP	40	55	60
28	SBP	60	75	80
	MAP	45	58	63
	DBP	38	50	54
26	SBP	55	72	77
	MAP	38	57	63
	DBP	30	50	56

Adapted from [13] and used with permission

PMA postmenstrual age, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *MAP* mean arterial pressure

correlated with birth weight is those born SGA. Specifically in the preterm population, in the first week of life, infants born SGA had an inverse relationship with BP while the appropriate for gestational age infants had a positive correlation [29].

Although often not the first thought when evaluating BP of a neonate, several maternal factors should be considered as contributing to neonatal BP. Both maternal age and maternal BP have been shown to affect neonatal BP—but the data is conflicting in both situations with further information needed to show causality [7]. Medications given to mothers prior to birth can result in changes in neonatal BP. Antenatal corticosteroids result in increased neonatal BP in the first 48 h after birth [30] and also increase the risk of developing neonatal hypertension [31]. Magnesium sulfate given to mothers for tocolysis, pregnancy-induced hypertension, preeclampsia, and neonatal neuroprotection has not been shown to result in hypotension in neonates, and these infants are actually less likely to have hypotension in the first week of life [32–34]. With regard to antihypertensives given to mothers, there is little research on the effect in the early postnatal period and further research is required [7].

Neonatal hypertension: definition, incidence, presentation, and etiology

With so many determinants of neonatal BP, a simple uniform definition is not feasible. For each neonate, the gestational age, PMA, and birth weight need to be considered when defining hypertension. The most commonly used definition for neonatal hypertension is systolic or diastolic BPs greater than the 95th percentile for PMA [13]. For infants in the first few days of age, Zubrow et al. provide normal and > 95th percentile values for BP based on the three most important determinants of BP: PMA, birth weight, and gestational age [24]. For each of these three factors, Zubrow et al. found that both systolic and diastolic BPs increased with advancing gestational age at birth, advancing PMA, and increased birth weight. For infants greater than 2 weeks of age, a recent publication by Dionne et al. combined literature to develop norms for BP based on PMA (Table 1) [13].

For infants who have been discharged from the NICU but remain less than 1 year of age, there has been a lack of published data over the past 30 years. Most recently used measurements came from the Second Task Force data from 1987, but these BP measurements were determined using a Doppler instrument that is not commonly used today [35]. Recently, Mistry and Gupta pooled data from four studies that used oscillometric devices to come up with percentiles for term infants up to 1 year of age [23, 26, 27, 36, 37]. In this table for infants 1 month of age, they report 50th percentile for BP values of 77/50 and 95th percentile BP values of 87/58. For older infants 6 months of age, 50th percentile BP values are reported as 102/63 and 95th percentile BP values as 120/75. Given that most NICUs now use oscillometric devices, the most accurate values to use would be the pooled oscillometric data from Mistry and Gupta, which is more likely to reflect current practice compared to the Second Task Force data from 1987.

As with any definition that has not been standardized, determining incidence can be challenging. For neonatal hypertension, the overall incidence has been estimated to be between 0.2 and 3.0% [38–41]. This incidence is completely dependent on the population of interest: in healthy term newborns, it is closer to 0.2%, and for ex-critically ill preterm newborns, it is likely

between 1 and 3%. In the recent Assessment of Worldwide Acute Kidney Injury Epidemiology in Neonates (AWAKEN) study, the incidence of documented neonatal hypertension was 2%; however, importantly, it was possible that a further 3.7% was undiagnosed with BP measurements above the 95th percentile [42].

The presentation of a neonate with hypertension is most frequently an asymptomatic neonate with several recent routine BP checks that have been elevated. In rare circumstances where BP has not been routinely monitored, neonates may present with heart failure, feeding intolerance, or failure to thrive. In this situation, the initial vital sign evaluation should reveal the cause of symptoms as a very elevated BP prompting a thorough evaluation.

There are a multitude of causes of neonatal hypertension (Table 2) [13] that differ significantly from the most common causes of childhood or adult hypertension. In neonates, historically, the leading cause of hypertension has been renal abnormalities [6, 31, 39, 41, 43]. However, recently, Jenkins et al. found in a multicenter study that nearly 50% of neonatal hypertension lacks an explanation [2]. In children with renal causes, the abnormality is either a congenital problem or acquired disease. With respect to congenital disorders, both autosomal recessive and autosomal dominant polycystic kidney diseases are causes of neonatal hypertension, while multicystic dysplastic kidneys are an unusual cause of hypertension in the neonatal time period. An increasingly recognized acquired kidney problem in the NICU, acute kidney injury (AKI), is associated with elevated BP. The AWAKEN study has shown a significant association with AKI and neonatal hypertension [44]. The exact timing and persistence of hypertension after AKI is unclear and requires further investigation.

A well-established link between chronic lung disease of prematurity or bronchopulmonary dysplasia (BPD) and neonatal hypertension has been documented in many studies [2, 45–47]. This may be related to an element of pulmonary hypertension requiring elevated systemic BP to maintain pulmonary blood supply. However, this is not always the case and the mechanism of this association has not yet been determined, with the incidence of hypertension increasing as the severity of chronic lung disease increases [45]. In addition to the unknown effect of BPD on BP, patients with BPD often have exposure to steroids including dexamethasone, prednisolone, and hydrocortisone which are known to cause hypertension [48]. Diuretic use for BPD with resultant nephrocalcinosis is also a possible cause for neonatal hypertension and requires further research.

A unique cause of neonatal hypertension is vascular-associated umbilical arterial catheter (UAC) thrombosis that is not encountered in older populations. Several studies have shown that thrombi are common in patients with UACs and can result in partially or completely occlusive thrombi in the aorta that can then embolize into the renal parenchyma [49, 50]. Other vascular causes outside of catheter-associated embolism, like coarctation, renal vein thrombosis, and renal artery stenosis, can also be causes of neonatal hypertension.

Table 2 Causes of neonatal hypertension

Renovascular
Thromboembolism
Renal artery stenosis
Mid-aortic coarctation
Renal venous thrombosis
Compression of renal artery
Congenital rubella syndrome
Renal parenchymal disease
Congenital
Polycystic kidney disease
Multicystic-dysplastic kidney disease
Tuberous sclerosis
Ureteropelvic junction obstruction
Congenital nephrotic syndrome
Renal tubular dysgenesis
Acquired
Acute tubular necrosis
Cortical necrosis
Interstitial nephritis
Hemolytic-uremic syndrome
Obstruction (stone, tumors)
Pulmonary
Bronchopulmonary dysplasia
Pneumothorax
Cardiac
Thoracic aortic coarctation
Endocrine
Congenital adrenal hyperplasia
Hyperaldosteronism
Hyperthyroidism
Pseudohypoaldosteronism type II
Medications/intoxications
Infant
Dexamethasone
Adrenergic agents
Vitamin D intoxication
Theophylline
Caffeine
Pancuronium
Maternal
Cocaine
Heroin
Neoplasia
Wilms tumor
Mesoblastic nephroma
Neuroblastoma
Pheochromocytoma
Neurologic
Pain
Intracranial hypertension
Seizures
Familial dysautonomia
Subdural hematoma
Miscellaneous
Total parenteral nutrition
Closure of abdominal wall defect
Adrenal hemorrhage
Hypercalcemia
Traction
Extracorporeal membrane oxygenation
Birth asphyxia
Nephrocalcinosis

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Evaluation, management, and follow-up

Once the diagnosis of hypertension has been confirmed in a neonate, the initial evaluation is focused on the most common causes. A physical examination focusing on cardiovascular, abdominal, and genitourinary systems should be performed that could yield an immediate cause or specific diagnosis [16, 23]. BPs should be checked in all four limbs and pulses palpated to assess for the possibility of aortic coarctation. Certain dysmorphic features may necessitate genetics consultation to evaluate for an underlying genetic disorder that may be associated with hypertension, such as Turner syndrome and Williams syndrome. Physical examination should also focus on the other vital signs, paying particularly close attention to any irregular respiratory rate or bradycardia which may be indicative of increased intracranial hypertension. Pediatric nephrology consultation is warranted following the diagnosis of hypertension in a NICU patient. The pediatric nephrologist can help guide the evaluation, titrate medications, and provide long-term follow-up for the patient once discharged. While awaiting consultation, the history of the neonate should be reviewed for prenatal exposures, prenatal imaging, and perinatal events. Documentation of umbilical artery and venous catheters should be determined, as this is common in critically ill neonates and a frequent cause of neonatal hypertension.

The first step in the work-up should be Doppler ultrasound to evaluate the kidneys, adrenal glands, urologic system, and renal arteries and veins (Table 3). This would detect both congenital and acquired abnormalities that are the most frequent causes of neonatal hypertension [41]. A serum creatinine should be obtained to evaluate renal function along with electrolytes, urea, and calcium. Sodium values should be carefully assessed and, if low in association with hypertension, could lead the clinician to evaluate a diagnosis of renovascular hypertension. A urinalysis should be evaluated as this may point to underlying kidney disorders that are not detectable via ultrasonography. An echocardiogram should be standard in neonates to rule out aortic coarctation as the cause and to verify normal cardiac function. Unfortunately, not all neonatal echocardiograms can detect coarctations that are outside of the typical aortic arch: a dedicated chest and or abdominal ultrasound may be needed to rule this out.

Further testing may be necessary if the above first-line tests do not point to an obvious cause of hypertension. This includes other imaging techniques, such as a head ultrasound to rule out intracranial hemorrhage or mass. More specific advanced renal evaluation may be indicated dependent on consultant recommendations. Specific imaging may be necessary, including micturating cystourethrogram, nuclear medicine scans, or magnetic resonance imaging (MRI) depending on institution protocols. Further laboratory testing of plasma, renin activity and aldosterone levels are beneficial for a potential diagnosis. Evaluation of thyroid and cortisol levels can rule out easily treatable causes of hypertension.

Treatment of neonatal hypertension should consist of treating the underlying cause, but treatment aimed at reducing the BP needs to be considered carefully in conjunction with an expert pediatric nephrologist with experience in this population. The literature on treatment of neonatal hypertension is small, given the low incidence of neonatal hypertension, and primarily consists of small studies [51–54]. Expert opinion for the treatment of hypertension in children > 1 year was recently updated but, unfortunately, does not translate well to the treatment of neonates [55]. The authors of this guideline comment on the definition of hypertension in children less than 1 year of age but do not propose any strict definitions. Given the lack of clear guidelines, we suggest the definitions and treatment recommendations proposed in Table 4. The initiation of treatment should be guided by the pediatric nephrologist in conjunction with the neonatologist, and options for treatment are wide ranging and listed in Table 5. Treatments based on these recommendations focus on three main factors: BP percentile for PMA, clinical status, and evidence of end-organ damage. The recent update to the fourth report on BP management in children recommends treatment of BP to below the 90th percentile, given the risk of end-organ damage with persistently

Table 3 Investigations for neonatal hypertension

	Initial testing	Secondary testing
Radiology/scans	Doppler renal ultrasound	VCUG
	Echocardiogram	Head ultrasound
		Nuclear medicine scan
		MRI
Blood work	Serum creatinine and BUN	Plasma renin and aldosterone
	Serum electrolytes (including calcium)	Serum thyroid and cortisol levels
	CBC and platelet count	
Urine	Urine analysis	Urinary VMA/HMA
	Urine albumin/creatinine ratio	

CBC complete blood count, *BUN* Blood urea and nitrogen, *VCUG* voiding cystourethrogram, *MRI* magnetic resonance imaging, *VMA* vanillylmandelic acid, *HMA* homovanillic acid

Table 4 Definitions and treatment recommendations for neonatal hypertension

Stage	BP percentile for PMA	Clinical status	End-organ involvement[a]	Treatment	Type of Tx
Normal	< 95th percentile	–	–	No	–
Mild hypertension	95th–99th percentile	Healthy	No	No, observe	–
		Hospitalized or CKD	No	Consider treatment	Oral or IV
Moderate hypertension	95th–99th percentile	Healthy	Yes	Treat	Oral
		Hospitalized or CKD	Yes	Treat	Oral or IV
Severe hypertension	> 99th percentile	Healthy	No	Treat	Oral
		Healthy, hospitalized, or CKD	Yes	Treat	IV
Hypertensive emergency hypertension	SBP > 120 or DBP > 90 (term) or DPB > 80 (preterm)	Healthy, hospitalized, or CKD	–	Treat	IV infusion

[a] End-organ involvement: left ventricular hypertrophy, altered mental status, and acute kidney injury

BP blood pressure, *PMA* postmenstrual age, *CKD* chronic kidney disease, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *Tx* treatment, *IV* intravenous

elevated BP. While there is no evidence as to what levels should be considered for neonatal hypertension treatment, this goal seems reasonable, given pediatric and adult experience at minimizing end-organ damage [59].

Prior to initiating treatment, a few specific situations should be considered. In the patient with intracranial hypertension, this should be treated prior to reducing the BP. If the etiology of hypertension is not yet confirmed, obtaining aldosterone and renin levels before starting therapy that could alter these levels is important diagnostic information. In the patient with only intermittently severely elevated BPs, two diagnoses are most likely: a moving clot and pheochromocytoma. To determine these diagnoses, repeat detailed renovascular imaging and urine amines (homovanillic acid and vanillylmandelic acid) should be considered.

The decision to treat with intravenous (IV) or oral medications depends on the clinical situation and the severity of the hypertension. In an infant with sustained very high BP in an intensive care unit with continuous monitoring, a continuous infusion may be the best option. This allows for a slow decrease in BP so as to not induce cerebral hypoxemia or bleeding [59]. It should be noted that for infants with myocardial dysfunction secondary to severe hypertension, often more than one medication is necessary to reach a sufficiently low BP for the heart to function appropriately. For infants with intermittent hypertension and IV access or the inability to tolerate oral medications, a short-acting IV medication may be best to more quickly see a response and determine the amount of medication needed to properly treat the BP. When utilizing angiotensin-converting enzyme inhibitors in preterm infants, there is a risk of sudden prolonged hypotension resulting in ischemia and seizures [60]. If these medications are utilized, a pediatric nephrologist should be directing treatment and the starting dose should be lower than that for term infants [56]. Once dosing is determined, a plan can be made to transition to enteral treatment as appropriate. For outpatient management of neonatal hypertension, starting at a low dose so as not to induce hypotension is important. The particular choice of antihypertensive depends on the patient and institutional practices.

The natural history of neonatal hypertension has yet to be fully elucidated, but there have been a few studies looking at the length of hypertensive treatment that is needed. In a large study by Blowey et al., they found that the median exposure to antihypertensive treatment in NICU infants was 10 days [43]. In another study, 41% of patients diagnosed with hypertension in the NICU were discharged home on antihypertensive medications and, by the age of 6 months, only 3 of the 20 patients remained on antihypertensive treatment [31]. In a specific subset of patients with hypertension associated with BPD, these infants have hypertension that almost universally resolves by 2 years of age, often by 8 months [46]. There are a few specific diagnoses in which one would expect chronic therapy is needed, and these are autosomal recessive polycystic kidney disease and neonates with a history of renal vein thrombosis [61, 62]. Unfortunately, there are no data evaluating the long-term renal and cardiovascular outcomes of neonates with either short-term hypertension or hypertension requiring long-term treatment. This is an area that deserves future study and evaluation.

Neonatal hypertension, while uncommon, is an important potential sequela of NICU graduates. Standardization of measurement is important and should be an important component of education for both medical and nursing staff in neonatal units. Once recognized, history and examination should form the first part of the process for determining the cause, followed by appropriate investigations. Determining treatment should be a combined decision between neonatologists and pediatric nephrologists, with ongoing follow-up throughout childhood. While those with obvious renal anomalies require ongoing management and follow-up, it is unclear for those with no obvious cause for

Table 5 Common medications for the treatment of hypertension [13, 56–58]

Drug	Class	Route	Dose	Interval	Comments
IV infusion agents					
Esmolol*	Beta blocker	IV infusion	Start at 50 mcg/kg/min and increase by 25–50 mcg/kg/min every 5 min until desired BP. Max dose up to 1 mg/kg/min in term neonates	Continuous infusion	- Very short-acting; constant infusion is necessary - May be useful for management of acute HTN after repair of aortic coarctation - May cause hypotension at high doses - Can cause phlebitis
Hydralazine**		IV infusion	Infusion of 0.2 mcg/kg/min Max dose of 2 mg/kg/day	Continuous infusion	May increase heart rate. Always start with a lower dose and increase the dose depending upon the response. Exerts effect by directly relaxing vascular smooth muscle tone and lowering peripheral vascular resistance
Nicardipine***	Calcium channel blocker	IV infusion	0.5 to 4 mcg/kg/min	Continuous infusion	May cause mild reflex tachycardia
Nitroprusside***	Vasodilator	IV infusion	0.25 to 0.5 mcg/kg/min Usual maintenance dose is 2 mcg/kg/min	Continuous infusion	Thiocyanate toxicity can occur with prolonged (> 72 h) use or in renal failure. - Monitor renal and liver fxn daily
Intermittent IV agents					
Labetalol*	Beta and alpha blocker	IV bolus	0.2 to 1 mg/kg/dose Max 10 mg/kg/day	2 or 3 times daily	Acute decompensated heart failure and bronchopulmonary dysplasia relative contraindications
Hydralazine***		IV bolus	0.1 to 0.5 mg/kg/dose Max 8 mg/kg/day If used orally, double IV dose	3 to 4 times per day	- Tachycardia and fluid retention are common side effects - Diarrhea, emesis, and temporary agranulocytosis
Oral agents					
Labetalol*	Beta and alpha blocker	Oral	0.5 to 1.5 mg/kg/dose Max 10 mg/kg/day	2 times daily	Acute decompensated heart failure and bronchopulmonary dysplasia relative contraindications
Propranolol***	Beta Blocker	Oral	0.25 to 1 mg/kg/dose Max 8 to 10 mg/kg/day	3 to 4 times per day	- Monitor heart rate - Avoid in bronchopulmonary dysplasia
Isradipine**	Calcium channel blocker	Oral	0.05 to 0.15 mg/kg/dose Max 0.8 mg/kg/day	4 times per day	May cause mild reflex tachycardia
Amlodipine**	Calcium channel blocker	Oral	0.1–0.4 mg/kg	Daily	Adverse effects may include hypotension, feed intolerance and alteration of liver function tests, flushing, peripheral edema, and palpitations. Caution when used in combination with other antihypertensives. Caution when used with other medications metabolized via CYP3A4 (e.g., erythromycin, antifungals)
Captopril***	ACE inhibitor	Oral	< 3 months: 0.01 to 0.05 mg/kg/dose initially Max 2 mg kg/day	3 to 4 times per day	- First dose may cause rapid drop in BP, especially if receiving diuretics. - In infants already receiving a diuretic, start at the lowest recommended dose.

Table 5 (continued)

Drug	Class	Route	Dose	Interval	Comments
			> 3 months (0.15 to 0.3 mg/kg/ dose initially) Max 6 mg/kg/day		- Monitor serum creatinine and potassium. - ACE inhibitors should not be used in infants who are less than 44 weeks PMA
Clonidine***	Central alpha agonist	Oral	0.5 to 1 mcg/kg initially 5 to 10 mcg/kg/day max	Divided four to six times daily	May cause mild sedation
Hydrochlorothiazide*	Diuretic	Oral	1–4 mg/kg/day	Once daily or as two divided doses per day	Monitor electrolytes
Spironolactone*	Diuretic	Oral	0.5 to 1.5 mg/kg/dose	Twice per day	Monitor Electrolytes

Please see neonatal pharmacy recommendations for updated information on dosing, frequency, and side effects

BP blood pressure, *PMA* postmenstrual age, *HTN* hypertension, *mg* milligram, *mcg* microgram, *kg* kilogram, *min* minute, *h* hour, *IV* intravenous

*First-line medications: the authors acknowledge that there is currently minimal evidence on which are the most effective and safe medications to use in neonatal hypertension, but have provided suggestions for first-line choices based on the mode of action of the medication and adverse effect profiles

**Second-line medications: the authors acknowledge that there is currently minimal evidence on which are the most effective and safe medications to use in neonatal hypertension, but have provided suggestions for second-line choices based on the mode of action of the medication and adverse effect profiles

***Agents only to be used at the recommendation of a pediatric pharmacist or pediatric nephrologist with neonatal expertise

neonatal hypertension how long and what follow-up is required. Further research is required to determine whether these neonates are at risk of hypertension or renal disease later in life.

Key summary points

1. Determination of blood pressure in neonates is challenging; the gold standard remains intra-atrial measurement, but the most common method is oscillometric.
2. Neonatal blood pressure in the first week of age is determined by three major factors: gestational age, postmenstrual age, and birth weight.
3. Neonatal hypertension is defined as greater than the 95th percentile for postmenstrual age and is not based on long-term outcomes.
4. Neonatal hypertension is more frequently encountered in sick NICU patients and more often in preterm than term neonates.
5. Treatment of neonatal hypertension is not evidence-based and most often driven by local practices and requires further research.

Multiple-choice questions (answers are provided following the reference list)

1. What is the most common method of blood pressure measurement in neonates?

a) Doppler
b) Ultrasound
c) Intra-arterial
d) Oscillometric

2. The proper method to take a neonatal blood pressure is:

a) 1.5 hours after a feed
b) While asleep
c) 3 different times, two minutes apart
d) All of the above

3. Neonatal hypertension for a > 2-week-old neonate is defined as:

a) > 95th percentile for PMA
b) Systolic BP > 80
c) MAP > 60
d) > 90th percentile for birth weight

4. The most common cause of neonatal hypertension is:

a) Cardiovascular
b) Respiratory

c) Renal
d) Iatrogenic

5. Evaluation of neonatal hypertension should always include which of the following:

a) Renal ultrasound with Doppler
b) Plasma renin
c) Thyroid studies
d) Head ultrasound

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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Multiple-choice questions answers

1. d; 2. d; 3. a; 4. c; 5. a