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REVIEW

Hypertension in infancy: diagnosis, management and outcome

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Abstract Advances in the ability to identify, evaluate, and care for infants with hypertension, coupled with advances in the practice of Neonatology, have led to an increased awareness of hypertension in modern neonatal intensive care units. This review will present updated data on blood pressure values in neonates, with a focus on the changes that occur over the first days and weeks of life in both term and preterm infants. Optimal blood pressure measurement techniques as well as the differential diagnosis of hypertension in the neonate and older infants will be discussed. Recommendations for the optimal immediate and long-term evaluation and treatment, including potential treatment parameters, will be presented. We will also review additional information on outcome that has become available over the past decade.

Keywords Blood pressure · Neonate · Infant · Prematurity · ACE inhibitor · Calcium channel blocker · Hypertension · Kidney disease

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Introduction

Recent advances in the ability to identify, evaluate, and care for infants with hypertension, coupled with advances in the practice of Neonatology, have led to an increased awareness of hypertension in infants since its first description in the 1970s [1–3]. While information on normal blood pressure (BP) in both premature and term infants has increased, defining hypertension and determining treatment criteria in infancy remain controversial. This paper will review available information on normative values and present suggested cut-points for diagnosis and treatment. We will also address the differential diagnosis of hypertension in the neonate, the pathophysiology and heritable aspects of the disease as well as the optimal immediate and long-term evaluation and treatment. Finally, the additional information on outcome that has become available over the past decade will be summarized.

Incidence

Most reports indicate that the incidence of hypertension in neonates is quite low, ranging from 0.2 to 3% [1, 2, 4–6]. It is so unusual in otherwise healthy term infants that routine BP determination is not advocated for this group [7]. For preterm and otherwise high-risk newborns admitted to modern neonate intensive care units (NICUs), however, the picture can be quite different. In a review of over 3000 infants admitted to a Chicago NICU, the overall incidence of hypertension was found to be 0.81% [6]. Hypertension was considerably more common in infants with bronchopulmonary dysplasia, patent ductus arteriosus, and intraventricular hemorrhage or in those with indwelling umbilical arterial catheters, with up to 9% developing

hypertension. In an Australian study of approximately 2500 infants followed for more than 4 years, the prevalence of hypertension was 1.3% [8]. Antenatal steroids, maternal hypertension, umbilical arterial catheter placement, postnatal acute renal failure, and chronic lung disease were among the most common concurrent conditions in babies with elevated BP [8].

Hypertension may also be detected long after discharge from the NICU. In a retrospective review of over 650 infants seen in follow-up after discharge from a tertiary level NICU, Friedman and Hustead found an incidence of hypertension (defined as a systolic BP of >113 mmHg on three consecutive visits over a 6-week period) of 2.6% [9]. Hypertension in this study was detected at a mean age of approximately 2 months post-term when corrected for prematurity. Although the differences were not significant, infants in this study who developed hypertension tended to have lower initial Apgar scores and slightly longer NICU stays than infants who remained normotensive, indicating a somewhat greater likelihood of developing hypertension in sicker babies, a finding similar to that of Singh et al. [6]. Unfortunately, this study has not been replicated, so the current prevalence of hypertension in high-risk infants remains unclear. However, these data do support routine BP monitoring following NICU discharge, as advocated in the Fourth Report [10].

Blood pressure measurement in infancy

The gold standard technique for BP measurement in neonates remains direct measurement by intra-arterial analysis of the pulse pressure wave form. While the brachial or radial artery may over-estimate the aortic pressure by up to 10 mmHg in older children due to systolic pressure amplification [11], there is a good correlation between umbilical artery and peripheral artery catheter BPs in neonates [12]. In addition to accurately measuring BPs, such catheters are also crucial in careful management of hypertension, particularly in infants with severe BP elevation. Indirect methods of measuring the BP, such as palpation and auscultation, are not practical in neonates, especially in the NICU setting, and ultrasonic Doppler assessment has largely been replaced by oscillometric devices [13].

The automated oscillometric method detects the pressure oscillations within the artery, determines the mean arterial pressure, and then uses an algorithm which is specific to each manufacturer to establish the systolic and diastolic BP. Studies have shown a good correlation between oscillometric and umbilical or radial artery BP in neonates and young children [14, 15]. Oscillometric devices are easy to use and provide the ability to follow BP trends over time. They are especially useful for infants who require BP monitoring after discharge from the NICU [16]. However, not all oscillometric devices are equal. A few studies have compared different oscillometric BP monitors to direct arterial measurements in neonates and have shown that the accuracy varied depending on the size of the infant [17], with a higher likelihood of oscillometric methods to over-read BP compared to direct measurement [18]. Users of these devices must also be aware that the first reading by the oscillometric machine after it has been turned on is less accurate as the cuff inflates to a high pre-set value and deflates in larger intervals than in subsequent readings. We would recommend that users become familiar with the specific oscillometric device being used within their own clinical setting so that they are aware of the strengths and limitations of their BP monitors.

The state of the infant at the time of the BP reading is important to record for interpretation of the measurement. Early observations noted that BP can vary based on the level of activity of the neonate from sleeping to awake or crying, feeding, or even being held head up [19]. The most consistent change is an increase in BP by as much as 20 mmHg when an infant is feeding, although even sucking on a pacifier/soother can increase the pressure by up to 10 mmHg. The reliability of repeat BP measurements on infants also decreases when infants are in a non-calm state [20]. As in older children, use of the proper cuff size is important and has been determined in neonates to be a cuff width to arm circumference ratio in the range of 0.45–0.55 [14, 21].

In order to standardize BP assessment in infants, a protocol has been suggested by Nwankwo and colleagues (Table 1). They studied the use of the standard protocol on newborns<2500 g when clinically stable and found that the first BP reading was higher than the others and that supine BPs were slightly higher than prone readings [22]. BP readings obtained during routine nursing care were significantly higher and had a wider variability than those obtained following the protocol. Except for the difficulty of

Table 1 Standardized protocol for blood pressure measurement in neonates [22]

•Measured by oscillometric device
•1.5 h after a feed or medical intervention
•Infant lying prone or supine
•Appropriately sized BP cuff
•Right upper arm
•After cuff placement, infant is left undisturbed for 15 min
•Infant asleep or in quiet awake state
•3 successive BP readings at 2-min intervals

BP, Blood pressure

having to wait for 1.5 h after a feed or medical intervention to take a BP reading, the protocol is quite reasonable and could easily become the nursing standard in NICUs, especially when accurate BP values are needed to guide clinical decision-making.

Normative values

Defining normal BP in newborn infants is complex. Just as BP in older children has been demonstrated to increase with increasing age and body size [10], studies in both term and preterm infants have demonstrated that BP in neonates increases with both gestational and postconceptional age as well as with birth weight [23–31]. The rate that BPs change over time also differs from neonates (newborn infants <28 days old) to older infants and may be affected by prematurity and size for gestational age. All of these factors need to be taken into account when reviewing the literature on published normal values as well as in clinical practice.

Day 1 of life

Useful data on early BP was published in 1995 by The Philadelphia Neonatal Blood Pressure Study Group led by Zubrow and associates [29]. In this study, serial BPs were measured on all infants admitted to several NICUs over a period of 3 months. The oscillometric method was used, and the measurements were made prior to feeding, when the infant was quiet. Based on data collected on 329 infants on day 1 of life, these researchers were able to define the mean plus upper and lower 95% confidence limits for BP; their data clearly demonstrate increases in BP with increasing gestational age and birth weight

More recent studies have attempted to refine the patient selection when analyzing newborn BPs as both preterm and term infants can vary quite significantly in health. Pejovic et al. [24] limited their analysis to hemodynamically stable premature and term infants admitted to the NICU in Belgrade. BPs were taken by the oscillometric method, after a feed, while the infants were asleep or quietly awake. More than 70% of the 373 infants studied had a very low birth weight and were ≤32 weeks gestational age. This study also showed that BPs on day 1 of life correlated with gestational age and birth weight (Fig. 1). Healthy term infants do not seem to demonstrate this same pattern. A study of more than 400 term infants admitted to a post-natal ward in Australia showed no difference in BP on day 1 of life based on birth weight, length, or gestational age [25]. There seems to be physiologic differences in premature infants with respect to BPs that are not unexpected but which do emphasize the importance of establishing appropriate normative values for the populations at risk.

First month of life

Several studies have demonstrated that BPs in premature newborns increase more rapidly over the first week or two of life followed by a slowing of the rate of increase. The previously mentioned Philadelphia study categorized over 600 infants in the NICU into gestational age groups and showed a similar rate of BP increase over the first 5 days of life, regardless of gestational age [29]. Systolic BPs increased from 2.2 to 2.7 mmHg/day and diastolic from 1.6 to 2.0 mmHg/day over the first 5 days. The rate of increase then slowed to about 0.25 mmHg/day for systolic and 0.15 mmHg/day for diastolic BPs over the following 90 days. The more recent study by Pejovic and colleagues on stable NICU infants showed a similar pattern, with BPs in each gestational age category of premature infants increasing at a faster rate over the first week of life followed by subsequent slowing [24]. In these infants, the researchers determined that the rate of rise was more rapid in the preterm than full-term infants (Fig. 2). Another study of stable premature infants by Kent and colleagues suggested that the more rapid rise in BP occurs over the first 2–3 weeks in infants born at 28–31 weeks gestation but only over the first week in infants born at>32 weeks gestational age [26].

Many neonatal physiologic maturational processes seem to be related to developmental stage or gestational age and, therefore, using post-conceptional age, defined as gestational age at birth plus days of life, would seem to be an appropriate method for defining BP standards. Although possibly confounded by the inclusion of infants during their rapid increase in BP phase, data from the Philadelphia study referenced earlier [29] demonstrated a significant correlation between BP and postconceptional age. Illustrated in Fig. 3 are the regression lines between postconceptional age and systolic and diastolic BP, along with the upper and lower 95th confidence limits for systolic and diastolic BP for each week of postconceptional age.

In term infants, there also seems to be a difference in BP pattern between small and appropriate for gestational age infants. In the Australian study of healthy term infants [25], the BPs were higher on day 2 of life compared to day 1 but not thereafter, although the number of infant BP measurements on subsequent days decreased. A study from Spain of 149 term infants showed the lowest birth weight infants (small for gestational age) had the lowest BP at birth but subsequently the fastest rate of rise so that by 1 month of age, all term infants had similar BPs [27].

There are many complexities to the changing patterns of BPs in the newborn period, and consideration of gestational age at birth, postnatal and postconceptional age, and

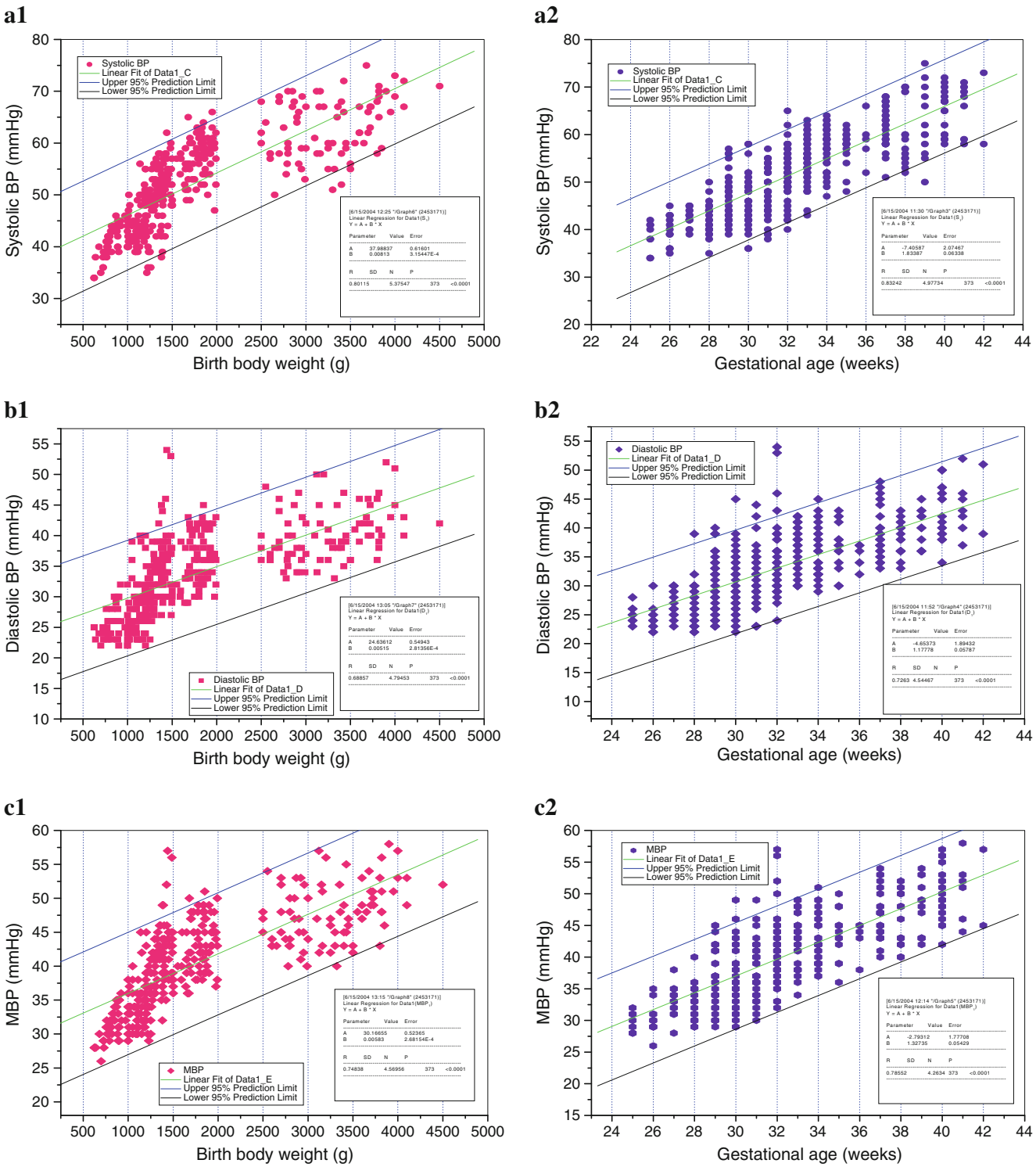

Fig. 1 Linear regression of systolic (**a**), diastolic (**b**) and mean (*M*) (**c**) blood pressures (*BPs*) by birth weight (**1**) and gestational age (**2**) on day 1 of life, with 95% confidence limits. Reproduced from Pejovic et al. [24] with permission from Springer Science + Business Media

appropriateness of size for gestational age are all contributory factors. Taking these factors into account, we have derived a reference table of estimated BP values after 2 weeks of age in infants from 26 to 44 weeks postconceptional age from the limited published data in neonates [23–29] that may be useful clinically (Table 2). The 95th and 99th percentile values are intended to serve as a reference to identify infants with persistent hypertension that may require treatment (see below). The mean arterial pressure (MAP) provides a quick assessment of the perfusion pressure and helps guard against

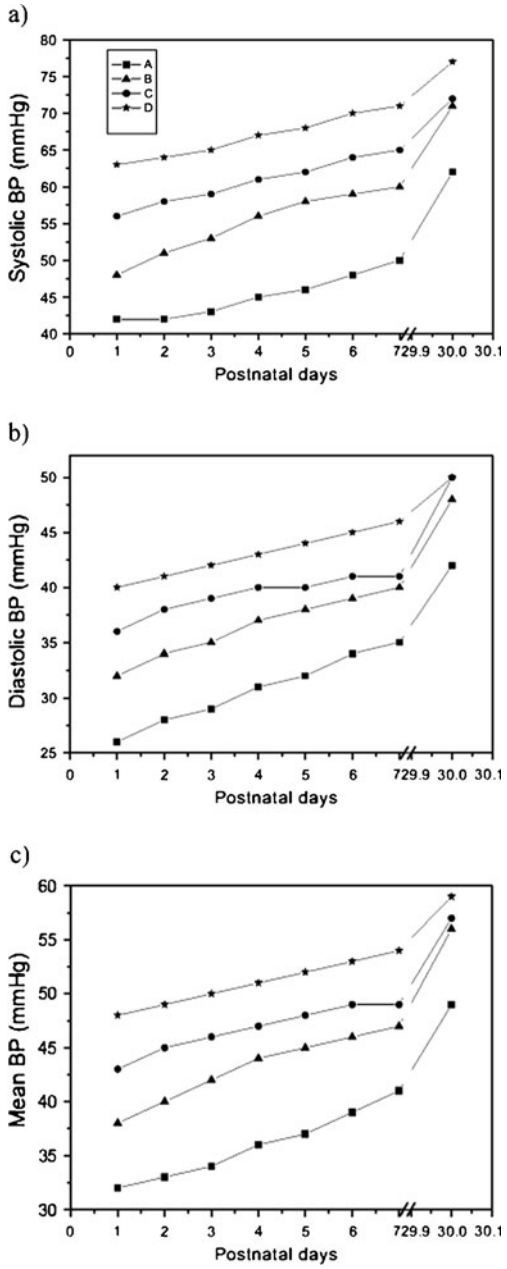

Fig. 2 Increase in systolic (**a**), diastolic (**b**), and mean (**c**) BP during the first month of life in infants classified by estimated gestational age: *A*≤28 weeks, *B* 29–32 weeks, *C* 33–36 weeks, *D*≥37 weeks. Reproduced from Pejovic et al. [24] with permission from Springer Science + Business Media

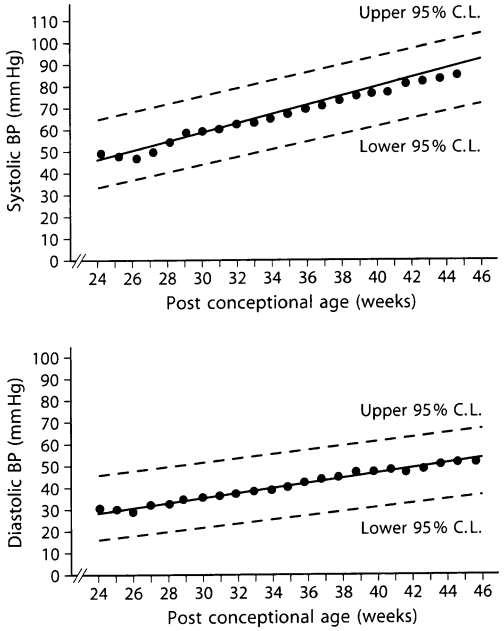

Fig. 3 Linear regression of mean systolic (upper panel) and diastolic (lower panel) BPs by postconceptional age in weeks, with 95% confidence limits (*C.L.*, *upper and lower dashed lines*). Reproduced from Zubrow et al. [29] with permission from the Nature Publishing Group

treating isolated systolic hypertension in infants with labile BPs. It should be noted that this table is based upon our best synthesis of available data and is not the result of a prospective clinical study, which is truly needed.

Despite the fact that neonatal BPs have been measured for decades, we are still in the early phase of identifying the normal patterns of infant BP, and there are still many physiologic changes that need further investigation before definitive reference data can be generated.

First year

For older infants, the percentile curves reported by the Second Task Force of the National High Blood Pressure Education Program (NHBPEP) Working Group (Fig. 4) [32] remain the most widely available reference values. These curves allow BP to be characterized as normal or elevated not only by age and gender, but also by size, albeit to a somewhat limited extent. Unfortunately, these BP values were determined by a single measurement using Doppler ultrasonic method, on awake infants, which reduced the number of diastolic BP readings by more than half. Comparison with the more recently published values for 1-year-olds in the Fourth Report from the NHBPEP [10] reveals significant differences that further call into question the validity of the 1987 curves.

A more recent study was completed on 406 healthy term infants with BPs measured by the oscillometric method on day 2 of life, and then at 6 and 12 months of age [28]. The readings were all completed by one research nurse, with the infants asleep or resting, and the average of three measurements was used for analysis. The BP values increased significantly from day 2 of life to 6 months of age but not between 6 and 12 months of age, and they are slightly higher than the Task Force values (Fig. 5). The lack of data on BP values between newborn and 6 months of age makes this study less user friendly than the Task Force curves, although the values are more consistent with those measured with the method of BP assessment currently in use in most NICUs and pediatric clinics.

Table 2 Estimated BP values after 2 weeks of age in infants from 26 to 44 weeks postconceptional age[a]

Postconceptional 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**	**71**
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	**48**	**62**	**69**
30 Weeks			
SBP	65	80	85
DBP	40	55	60
MAP	**48**	**65**	**68**
28 Weeks			
SBP	60	75	80
DBP	38	50	54
MAP	**45**	**58**	**63**
26 Weeks			
SBP	55	72	77
DBP	30	50	56
MAP	**38**	**57**	**63**

SBP, Systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure

[a] Derived from data presented in references [23–29]

Etiology

There are many potential causes of hypertension in neonates (Table 3), with the two largest categories being renovascular and other renal parenchymal diseases [1–6, 8, 9]. Umbilical artery catheter-associated thromboembolism affecting either the aorta and/or the renal arteries was first demonstrated by Neal et al. in the early 1970s [33]. Aortography performed at the time of umbilical artery catheter removal demonstrated thrombus formation in 18 of 19 infants, as well as several instances of clot fragmentation and embolization. Thrombosis was also seen at autopsy in seven of 12 additional infants who had died, for an overall incidence of 25 of 31 infants, or approximately 81% of infants studied.

Following that report, the association between umbilical arterial catheter-associated thrombi and the development of neonatal hypertension was confirmed by several other investigators [34–39]. Hypertension was demonstrated in infants who had undergone umbilical arterial catheterization even when thrombi were unable to be demonstrated in the renal arteries. Rates of thrombus formation have generally been much lower than those reported by Neal et al. [33], typically in the range of 25% [34, 40, 41].

Although there have been several studies that have examined the duration of line placement and line position as factors involved in thrombus formation, these data have not been conclusive. Longer duration of umbilical catheter placement has been associated with higher rates of thrombus formation [42]. A recent Cochrane review comparing “low” versus “high” umbilical artery catheters determined that the “high” catheter placement was associated with fewer ischemic events, such as necrotizing enterocolitis,

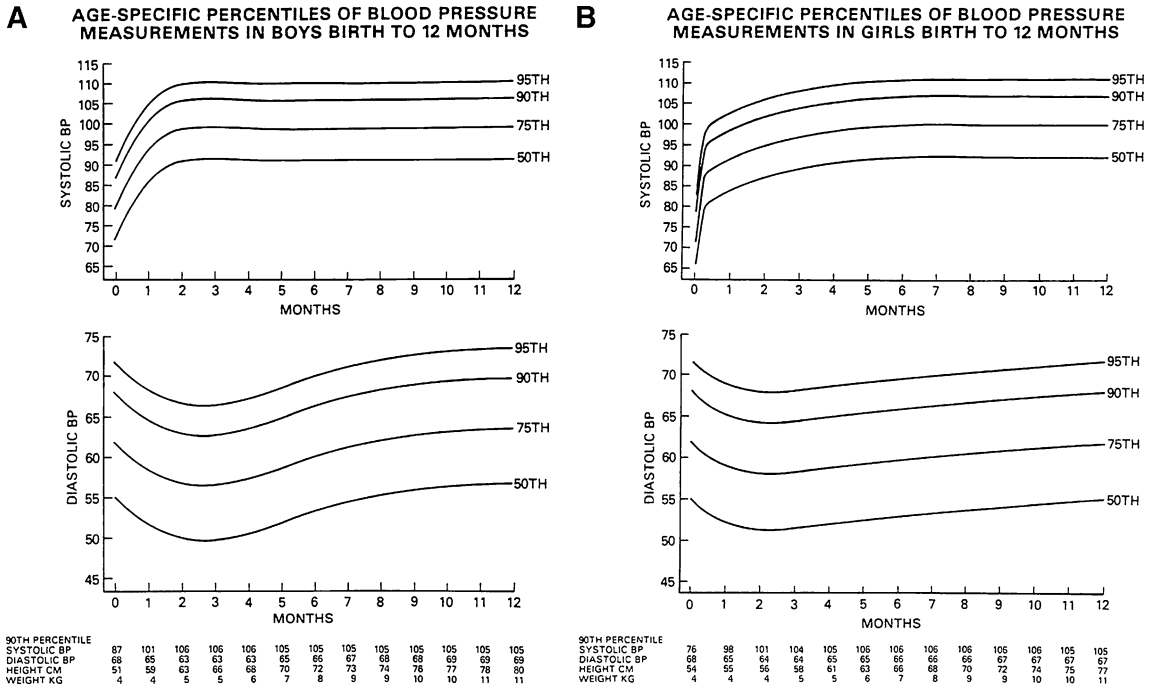

Fig. 4 Age-specific percentiles for blood pressure in boys (**a**) and girls (**b**) from birth to 12 months of age. Reprinted from the Task Force on Blood Pressure Control in Children [32]

but that hypertension occurred at equal frequency with either position [43]. Thus, it is assumed that catheter-related hypertension is related to thrombus formation at the time of line placement because of disruption of the vascular endothelium of the umbilical artery, particularly in preterm infants.

Other renovascular problems may also lead to neonatal hypertension. Renal venous thrombosis classically presents with the triad of gross hematuria, thrombocytopenia, and palpable renal mass in the clinical setting of high-risk

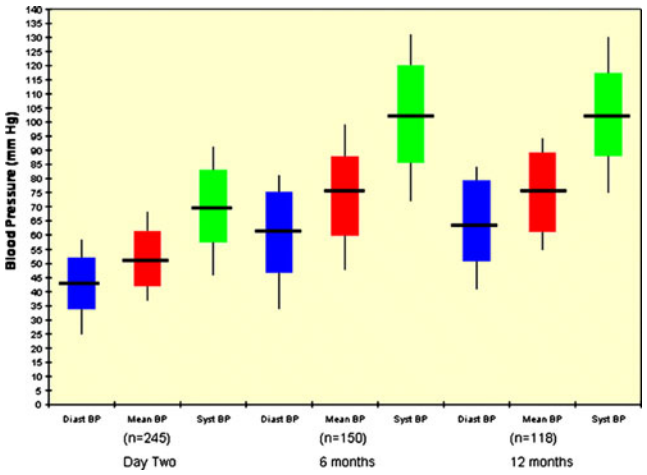

Fig. 5 Diastolic (*blue*), mean (*red*) and systolic (*green*) BP measurements at 2 days, 6 months, and 12 months of age. The *boxes* indicate the 5th to 95th percentiles. Reproduced from Kent et al. [28] with permission from Springer Science + Business Media

prothrombotic disorders, including infant of a diabetic mother or Factor V Leiden mutation [44–49]. Hypertension may be quite severe in such cases and may persist beyond the neonatal period [45, 48]. Fibromuscular dysplasia leading to renal artery stenosis is another potential cause of renovascular hypertension in infancy. Many of these infants may have main renal arteries that appear fairly normal on angiography but demonstrate significant branch vessel disease that can cause severe hypertension [50]. In addition, renal artery stenosis may also be accompanied by mid-aortic coarctation and cerebral vascular stenoses [51, 52]. Other blood vessel abnormalities may also lead to hypertension in the neonate, including idiopathic arterial calcification [53, 54] and renal artery stenosis secondary to congenital rubella infection [55]. Finally, mechanical compression of one or both renal arteries by tumors, hydronephrotic kidneys, or other abdominal masses may also lead to hypertension.

The next largest group of infants with hypertension comprises those with congenital renal parenchymal abnormalities. It is well known that both autosomal dominant and autosomal recessive polycystic kidney disease (PKD) may present in the newborn period with severe nephromegaly and hypertension [56–58]. With recessive PKD, for example, the majority of affected infants will be discovered to be hypertensive during the first year of life [56]. The most severely affected infants with PKD are at risk for development of congestive heart failure due to severe, malignant hypertension. Although much less common than

Table 3 Causes of neonatal hypertension

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

in PKD, hypertension has also been reported in infants with unilateral multicystic dysplastic kidneys [4, 59–61]. This is somewhat paradoxical as such kidneys are usually thought to be non-functioning.

Renal obstruction may be accompanied by hypertension, even in the absence of renal artery compression. This has been seen, for example, in infants with congenital ureteropelvic-junction obstruction [4, 9, 62] and has been reported to persist following correction of the obstruction [63]. The importance of congenital urologic malformations as a cause of neonatal hypertension was recently highlighted in a referral series from Brazil [62], in which 13 of 15 hypertensive infants had urologic causes. Median age at the diagnosis of hypertension was 20 days (range 5–70 days), emphasizing the need for regular BP measurement in infants with urologic malformations in order to detect hypertension. Ureteral obstruction by other intra-abdominal masses may also be accompanied by hypertension. The mechanism of hypertension in such instances is unclear, although activation of the renin–angiotensin system has been implicated [64, 65]. Finally, unilateral renal hypoplasia may also present with hypertension [66], although this is uncommon.

Hypertension due to acquired renal parenchymal disease is less common than that due to congenital renal abnormalities. However, severe acute tubular necrosis, interstitial nephritis, or cortical necrosis may be accompanied by significant hypertension, usually on the basis of volume overload or hyperreninemia. Hemolytic uremic syndrome, which has been described in both term and preterm infants [67], is usually also accompanied by hypertension. Such hypertension may be quite difficult to control, requiring multiple agents.

Hypertension as a consequence of bronchopulmonary dysplasia (BPD) was first described in the mid-1980s by Abman and colleagues [68]. In a study of 65 infants discharged from a NICU, the incidence of hypertension in infants with BPD was 43% versus that of 4.5% in infants without BPD. Investigators were unable to identify a clear cause of the hypertension, but postulated that hypoxemia might be involved. Over half of the infants with BPD who developed hypertension did not manifest it until after discharge from the NICU, highlighting the need for the measurement of BP in NICU "graduates," whether or not they have lung disease [9, 10, 69].

The findings of Abman et al. [68] have only been reproduced once, in 1998 by Alagappan et al. [70], who found that hypertension was twice as common in very low birth weight (VLBW) infants with BPD than in all VLBW infants, with VLBW defined as infants<30 weeks' gestation and<1500 g at birth. The development of hypertension appeared to be correlated with the severity of pulmonary disease as all of the hypertensive infants required supplemental oxygen and aminophylline. In infants with severe BPD, the development of hypertension has been shown to correlate with a greater need for diuretics and bronchodilators [69, 71]. Moreover, those that show concurrent nephrocalcinosis are significantly more likely to develop late-onset hypertension [72]. These observations reinforce the impression that infants with severe BPD are clearly at increased risk and need close monitoring for the development of hypertension [73]. This is especially true in infants who

require ongoing treatment with theophylline preparations and/or corticosteroids.

An important factor to be considered in the context of the VLBW infant is the growing evidence that nephrogenesis is impaired in preterm and small-for-gestational-age infants [74, 75]. As a consequence, low birth weight infants have low nephron mass which makes them more vulnerable to the development of hypertension, cardiovascular, and renal disease later in life [76, 77]. This further emphasizes the need for routine screening for hypertension as well as proteinuria in the low birth weight preterm infant after discharge from the NICU [78, 79]

Hypertension may also be seen in disorders of several other organ systems. Aortic coarctation is readily detectable in the newborn period and has been reported in numerous case series of neonatal hypertension [2, 4, 6, 9]. Hypertension may persist or reappear in these patients even after early surgical repair of the coarctation [80]. Repair early in infancy seems to have led to improved long-term outcomes [81], although the recurrence of stenosis and hypertension in childhood remain significant problems that merit close follow-up with ambulatory BP monitoring [80, 81]. Endocrinologic disorders that can produce hypertension in infancy include congenital adrenal hyperplasia with 11-β-hydroxylase or 17-α-hydroxylase deficiency [82–85]. Other heritable forms of hypertension, including primary hyperaldosteronism [86, 87] and hyperthyroidism [88], albeit rare, are also important diseases that should be considered in the setting of normal renin hypertension.

Intra-uterine and post-natal nutritional and environmental exposures constitute another important category of potential etiologies of infant hypertension. Perinatal treatment with corticosteroids, including dexamethasone, is linked to "epigenetic" phenomena that may result in the programming of hypertension and cardiovascular disease throughout life [77, 89–91]. Importantly, the use of single-dose prenatal dexamethasone for fetal lung maturation to modify the course of respiratory distress syndrome in preterm infants continues to be recommended given its positive impact on infant survival, and despite its known potential long-term adverse cardiovascular effects.

Other medications given to infants for treatment of chronic lung or other systemic diseases, including corticosteroids [92, 93], bronchodilators, and vasopressors, have clearly been shown to elevate the BP. In addition, high doses of adrenergic agents, prolonged use of pancuronium, or the administration of phenylephrine ophthalmic drops may raise the BP [94]. Such hypertension typically resolves when the offending agent is discontinued or its dose reduced. Substances ingested during pregnancy may also lead to significant problems with hypertension in the neonate. In particular, maternal cocaine or heroin use may have a number of undesirable and prolonged effects on the developing kidney that may lead to hypertension [95, 96]. For infants receiving prolonged total parenteral nutrition, hypertension may result from salt and water overload or from hypercalcemia caused either directly by excessive calcium intake or indirectly by vitamin A or D intoxication [97].

Tumors, including neuroblastoma, Wilms tumor, and mesoblastic nephroma, may all present in the neonatal period and may produce hypertension, either because of compression of the renal vessels or ureters or because of the production of vasoactive substances, such as catecholamines [98–101]. Neurologic problems, such as seizures, intracranial hypertension, and pain, constitute fairly common causes of episodic hypertension in older children and infants and should be considered in neonates as well [102]. In the modern NICU, postoperative pain must not be overlooked as a cause of hypertension [103]. Provision of adequate analgesia may constitute the only required "antihypertensive" in such infants.

There are numerous other miscellaneous causes of hypertension in neonates, the most common of which are listed in Table 2. Of these, hypertension associated with extracorporeal membrane oxygenation (ECMO) deserves comment. This may be seen in up to 50% of infants requiring ECMO [104] and may result in serious complications, including intracranial hemorrhage [105]. Despite extensive investigation, the exact pathogenesis of this form of hypertension remains poorly understood. Fluid overload, altered handling of sodium and water, and derangements in atrial baroceptor function have all been proposed as causative factors [104, 105]. There is clearly a need for further investigation of ECMO-related hypertension given the ongoing use of this life-saving procedure.

Clinical presentation and diagnostic approach

Typically, elevated BP will be detected on routine monitoring of vital signs, particularly in critically ill infants. However, other classic presentations of neonatal hypertension have been described. Congestive heart failure and cardiogenic shock represent life-threatening consequences of hypertension that may resolve with appropriate BP reduction [106]. Renal dysfunction and hypertensive retinopathy have also been described in severely hypertensive neonates [5]. In the less acutely ill infant, feeding difficulties, unexplained tachypnea, apnea, lethargy, irritability, or seizures may constitute symptoms of unsuspected hypertension. In older infants who have been discharged from the nursery, unexplained irritability or failure to thrive may be the only manifestations of hypertension.

Diagnostic evaluation

Diagnosing the etiology of hypertension is a fairly straightforward task in most hypertensive neonates. A relatively focused history should be obtained, paying attention to determining whether there were any pertinent prenatal exposures, as well as to the details of the infant's clinical course and any concurrent conditions. The procedures that the infant has undergone (e.g., umbilical catheter placement) should be reviewed, and the current medication list should be scrutinized for substances that can elevate BP.

The physical examination, likewise, should be focused on obtaining pertinent information to assist in narrowing the differential diagnosis. BP readings should be obtained in all four extremities at least once in order to rule out coarctation of the aorta. The proper BP measurement technique should be followed to ensure accurate readings (see preceding section). The general appearance of the infant should be assessed, with particular attention paid to the presence of any dysmorphic features that may indicate an obvious diagnosis, such as congenital adrenal hyperplasia. A careful cardiac and abdominal examination should be performed. The presence of a flank mass or of an epigastric bruit may point the clinician towards a diagnosis of either ureteropelvic junction obstruction or renal artery stenosis, respectively.

In most instances, few additional laboratory data need to be obtained, as the correct diagnosis is usually suggested by the history and physical examination, and there is typically ample prior laboratory data available for review. It is important to assess renal function and to examine a specimen of the urine in order to ascertain the presence of renal parenchymal disease. A quantitative measurement of the urine protein, creatinine, and microalbumin can provide evidence of renal parenchymal injury and serve as a baseline for future assessments. A chest X-ray may be useful as an adjunctive test in infants with congestive heart failure, or in those with a murmur on physical examination. Other diagnostic studies, such as the determination of cortisol, aldosterone, or thyroxine levels, should be obtained when there is a pertinent history (Table 4).

The determination of plasma renin activity has traditionally been recommended in the assessment of neonates with hypertension, although little data are available on what constitutes normal values for infants, particularly for those who are preterm. The data that are available indicate that plasma renin concentrations and/or activity are typically quite high in infancy, particularly in premature infants, with a direct correlation to gestational age [107–109]. Although renal artery stenosis and thromboembolism are typically considered high renin states, peripheral plasma renin activity may not be elevated in such infants despite the presence of significant underlying pathology. Conversely, plasma renin may be falsely elevated by medications that are commonly used in the NICU, such as the methylxanthines, caffeine, and aminophylline [110]. In consideration of these limitations, the assessment of plasma renin activity in the initial evaluation of hypertension in infants may be deferred. An exception to this would be infants with electrolyte abnormalities, such as hypokalemia, that suggest a potential genetic disorder in tubular sodium handling [85].

Table 4 Diagnostic testing in neonatal hypertension

Generally useful diagnostic tests	Diagnostic tests useful in selected infants
Urinalysis (± culture)	Thyroid studies
Quantitative Upr/cr; Ualb/cr	Urine VMA/HVA
CBC & platelet count	Plasma renin activity
Electrolytes	Aldosterone
BUN, creatinine	Cortisol
Calcium	Echocardiogram
Chest X-ray	Abdominal/pelvic ultrasound
Renal ultrasound with Doppler	VCUG
	Aortography
	Renal angiography
	Nuclear scan (DTPA/Mag-3)

CBC, Complete blood count; BUN, blood urea nitrogen; Upr/cr, urine protein:creatinine ratio; Ualb/cr, urine albumin:creatinine ratio; VMA/HVA, vanillylmandelic acid/homovanillic acid; DTPA, diethylene triamine pentaacetic acid

The role of imaging in the evaluation of hypertensive neonates has been reviewed extensively elsewhere [111], so only a few comments will be made here. Doppler ultrasound imaging of the genitourinary tract is a relatively inexpensive, noninvasive, and quick study that should be obtained in all hypertensive infants. An accurate renal ultrasound can help uncover potentially correctable causes of hypertension, such as renal venous thrombosis, may detect aortic and/or renal arterial thrombi, and can identify anatomic renal abnormalities or other congenital renal diseases.

For infants with extremely severe BP elevation, angiography may be necessary. In our experience, a formal arteriogram utilizing the traditional femoral approach offers the most accurate method of diagnosing renal artery stenosis, particularly given the high incidence of intrarenal branch vessel disease in children with fibromuscular dysplasia. Although theoretically possible in infants, size is obviously a limiting factor. Computed tomography or magnetic resonance angiography will not detect branch stenosis in neonates and should not be ordered. Given these considerations, it may be necessary to defer angiography, managing the hypertension medi-

cally until the baby is large enough for an arteriogram to be performed safely.

Although nuclear scanning has been shown in some studies to demonstrate abnormalities of renal perfusion caused by thromboembolic phenomenon [37, 111], in our practice it has had little role in the assessment of infants with hypertension, primarily due to the difficulties in obtaining accurate, interpretable results in this age group. Other studies, including echocardiograms and voiding cystourethrograms, should be obtained as indicated. Echocardiography may be especially important in detecting left ventricular hypertrophy, the presence or absence of which will clearly influence management decisions.

Therapy

The first step in treatment should be correction of any iatrogenic causes of hypertension, such as excessive or unnecessary inotrope administration, hypercalcemia, volume overload, or pain. Hypoxemia should be treated in infants with BPD, and appropriate hormone replacement should be initiated in those with endocrine disorders.

After that, a decision will need to be made as to whether antihypertensive medications are indicated. We recommend that drug therapy be considered when the neonate's BP is consistently at the 99th percentile (Table 2) or greater (for older infants, Task Force recommendations should be followed). An important caveat in the decision to initiate pharmacologic treatment of hypertension is that few if any antihypertensive medications have ever been studied in neonates. The few published case series that include information on treatment reveal that a wide variety of agents are employed by clinicians, including direct vasodilators, diuretics, angiotensin-converting enzyme (ACE) inhibitors, beta-adrenergic blockers, and calcium channel blockers [5, 8, 9, 62, 107]. Clearly, appropriately conducted randomized trials are sorely needed in order to generate efficacy and safety data. Given the absence of such data, the recommendations in the following paragraphs are by necessity based upon expert opinion and not on evidence. Finally, we believe that the initiation of treatment must be based on the experience and discretion of the clinician at the bedside.

In infants with acute severe hypertension, usually well above the 99th percentile (see Table 2), with systemic symptoms, continuous intravenous infusions of antihypertensive agents should be utilized [112]. The wide fluctuations in BP frequently seen when intermittently administered agents are utilized make them inappropriate for treatment of severe hypertension. The advantage of intravenous infusions are numerous, the most important of which is the ability to quickly increase or decrease the rate of infusion to achieve the desired level of BP control. As in patients of any age with malignant hypertension, care should be taken to avoid too rapid a reduction in BP [112, 113] in order to avoid cerebral ischemia and hemorrhage, a problem that premature infants, in particular, are already at increased risk due to the immaturity of their periventricular circulation. Here again, continuous infusions of intravenous antihypertensives offer a distinct advantage.

Unfortunately, limited data are available regarding the use of these agents in neonates, so in many cases the choice of agent will depend on the individual clinician's experience. Our experience [114] and that of others [115] suggest that infusions of the calcium channel blocker nicardipine may be particularly useful in infants with acute severe hypertension. Other drugs that have been successfully used in neonates include esmolol [116], labetalol [117], and nitroprusside [118]. Oral agents in general are probably not appropriate given their variable onset and duration of effect and unpredictable antihypertensive response [112]. Whatever agent is used, the BP should be monitored continuously via an indwelling arterial catheter, or else by frequently repeated (every 10–15 min) cuff readings with an oscillometric device so that the dose can be titrated to achieve the desired degree of BP control.

For some infants, intermittently administered intravenous agents do have a role in therapy. Hydralazine and labetalol in particular may be useful in infants with mild-to-moderate hypertension that are not yet candidates for oral therapy because of gastrointestinal dysfunction. Enalaprilat, an intravenous ACE inhibitor, has also been used in the treatment of neonatal renovascular hypertension [119, 120]. However, in our experience, this agent should be used with great caution: even doses at the lower end of published ranges may lead to significant, prolonged hypotension and oliguric acute renal failure. It should also be noted that all available doses for enalaprilat are based on the previously mentioned, uncontrolled case series. For these reasons, we do not recommend its use in hypertensive neonates.

Oral antihypertensive agents (Table 5) are best reserved for infants with less severe hypertension or infants whose acute hypertension has been controlled with intravenous infusions and are ready to be transitioned to chronic therapy. We typically start with the calcium channel blocker isradipine [121, 122] as it can be compounded into a stable 1 mg/mL suspension [123], facilitating dosing in small infants. Amlodipine may also be used, but its slow onset of action and prolonged duration of effect may be problematic in the acute setting. Orally administered "sublingual' nifedipine should be avoided for several reasons, including the lack of an appropriate oral formulation and unpredictable magnitude of antihypertensive effect [124]. Other vasodilators which may be used include hydralazine and minoxidil. Beta blockers may need to be avoided in chronic

Table 5 Recommended doses for selected antihypertensive agents for treatment of hypertensive infants

Class	Drug	Route	Dose	Interval	Comments
ACE Inhibitors	Captopril	Oral	<3 months: 0.01-0.5 mg/kg/dose, max 2 mg/kg/day; >3 months: 0.15–3 mg/kg/dose, max 6 mg/kg/day	TID	(1) First dose may cause rapid drop in BP, especially if receiving diuretics. (2) Monitor serum creatinine and K^+. (3) Intravenous enalaprilat NOT recommended (see text). (4) Only captopril & enalapril are FDA approved in infancy
	Enalapril	Oral	0.08–0.6 mg/kg/day	QD–BID	
	Lisinopril	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/h	Q4-6 h 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	Ultra short-acting-constant infusion necessary
	Propranolol	Oral	0.5–1.0 mg/kg/dose, max 8-10 mg/kg/day	TID	Monitor heart rate; avoid in BPD
Calcium channel blockers	Amlodipine	Oral	0.05–0.3 mg/kg/dose, max 0.6 mg/kg/day	QD	All may cause mild 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	Oral	5–15 mg/kg/dose	BID	Monitor electrolytes
	Hydrochlorothiazide	Oral	1–3 mg/kg/dose	QD	
	Spironoclatone	Oral	0.5–1.5 mg/kg/dose		
Vasodilators	Hydralazine	Oral	0.25–1.0 mg/kg/dose, max 7.5 mg/kg/day	TID–QID	Tachycardia and fliud retention are common side effects
		IV	0.15-0.6 mg/kg/dose	Q4h	
	Minoxidil	Oral	0.1–0.2 mg/kg/dose	BID–TID	Tachycardia and fluid retention common side effects; prolonged use causes hypertrichosis; Pericardial effusion may occur
	Sodium nitroprusside	IV	0.5–10 mcg/kg/min	Infusion	Thiocyanate toxicity can occur with prolonged (>72 h) use or in renal failure

BID, Twice daily; BPD, broncopulmonary dysplasia; IV, intravenous; QD, once daily; QID, four times daily; TID, three times daily; BPD, bronchopulmonary dysplasia

therapy of neonatal hypertension, particularly in infants with chronic lung disease. In such infants, diuretics may have a beneficial effect not only in controlling BP but also in improving pulmonary function [125]. On the other hand, it should be noted that propranolol is available commercially as a suspension, which makes it convenient to use when beta blockade is not contra-indicated.

The use of ACE inhibitors (ACEIs) in neonates is controversial. Captopril is one of the only antihypertensive agents that has actually been shown to be effective in infants [126], but it is well-known to cause an exaggerated fall in BP in premature infants [127]. This effect is related to the activation of the renin–angiotensin system in neonates mentioned previously, which in turn is a reflection of the importance of the renin–angiotensin system in nephron development [128]. Although few data exist on this topic, the concern over use of ACEIs in infants is that they may impair the final stages of renal maturation. Based on this concern, we typically avoid use of captopril (and other ACEIs) until the preterm infant has reached a corrected post-conceptual age of 44 weeks.

Surgery is indicated for treatment of neonatal hypertension in a limited set of circumstances [129, 130]. In particular, hypertension caused by ureteral obstruction or aortic coarctation [81] is best approached surgically. For infants with renal artery stenosis, it may be necessary to manage the infant medically until he/she has grown sufficiently to undergo definitive repair of the vascular abnormalities [49, 131]. The outcome of such surgical procedures can be quite good if performed at centers that have built up a large experience [50, 132]. However, unilateral nephrectomy may be needed in rare cases. Infants

with hypertension secondary to Wilms tumor or neuroblastoma will require surgical tumor removal, possibly following chemotherapy. A case has also been made by some authors for removal of multicystic–dysplastic kidneys because of the risk of development of hypertension [61], although this approach is controversial. Infants with malignant hypertension secondary to recessive PKD may require bilateral nephrectomy. Fortunately, such severely affected infants are quite rare.

Outcome

For most hypertensive infants, the long-term prognosis should be good, depending of course on the underlying etiology of the hypertension. Although better data are needed, for infants with hypertension related to an umbilical artery catheter, available information and personal experience suggest that in such babies, the hypertension will usually resolve over time [133, 134]. These infants may require increases in their antihypertensive medications over the first several months following discharge from the nursery as they undergo rapid growth. Following this, it is usually possible to wean their antihypertensives by making no further dose increases as the infant continues to grow. Home BP monitoring by the parents is a crucially important component of this process. It is our standard of care to arrange for home BP equipment, usually an oscillometric device, for all infants discharged from the NICU on antihypertensive medications.

Some forms of neonatal hypertension may persist beyond infancy. In particular, PKD and other forms of renal parenchymal disease may continue to cause hypertension throughout childhood [56–58, 135]. Infants with renal venous thrombosis may also remain hypertensive [45], and some of these children will ultimately benefit from removal of the affected kidney [44, 45, 49]. Persistent or late hypertension may also be seen in children who have undergone repair of renal artery stenosis or thoracic aortic coarctation [80]. The reappearance of hypertension in these situations should prompt a search for re-stenosis by the appropriate imaging studies.

What are sorely needed at this point are true long-term outcome studies of infants with neonatal hypertension. Glomerulogenesis is incomplete in preterm infants [75], so it is possible that many hypertensive infants will not have developed the full complement of glomeruli normally seen in term infants. Reduced nephron mass is hypothesized to be a risk factor for the development of hypertension in adulthood [136, 137]. Thus, it may be possible that hypertensive neonates (and possibly also normotensive premature neonates) are at increased risk compared to term infants for the development of hypertension in late adolescence or early adulthood [138]. Since we are now entering the era in which the first significantly premature NICU "graduates" are reaching their second and third decades of life, it is not only possible but imperative that appropriate studies can be conducted to address this question.

Conclusions

Although there are many areas in which better data are needed, particularly with respect to pathophysiology and antihypertensive medication use, much has been learned about neonatal hypertension over the past several decades. Normal BP in neonates depends on a variety of factors, including gestational age, post-natal age, and birth weight. Hypertension is more often seen in infants with concurrent conditions, such as BPD, or in those that have undergone umbilical arterial catheterization. A careful diagnostic evaluation should lead to determination of the underlying cause of hypertension in most infants. Treatment decisions should be tailored to the severity of the hypertension, and may include intravenous and/or oral therapy. Most infants will resolve their hypertension over time, although a small number may have persistent BP elevation throughout childhood.

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