Pediatr Nephrol (2000) 14:332–341

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Neonatal hypertension: diagnosis and management

Received: 20 April 1999 / Revised: 2 August 1999 / Accepted: 13 August 1999

Abstract Hypertension in the term or preterm neonate may be seen in up to 2% of all infants cared for in the modern neonatal intensive care unit. Although the definition of hypertension in this age group has not been completely standardized, recent studies have provided new normative data that may be used to facilitate identification of such infants. Common causes of hypertension in neonates include thromboembolic events related to umbilical catheterization, congenital problems such as aortic coarctation, structural renal malformations and renovascular disease, as well as acquired renal disease and certain medications. A careful history and physical examination will usually identify the probable cause in most cases without the need for extensive laboratory or radiologic testing. Therapy of neonatal hypertension should be tailored to the severity of the blood pressure elevation, and to the underlying cause of hypertension as appropriate. A wide range of therapeutic agents are now available for management of neonatal hypertension in both the acute and chronic settings. In most cases hypertension will resolve, but some infants may require prolonged treatment.

Key words Hypertension · Neonates · Premature infants · Antihypertensive therapy

Introduction

Hypertension as a clinical problem in newborn infants was first recognized in the 1970s [1]. However, recent advances in our ability to identify, evaluate and care for hypertensive infants, coupled with advances in the practice of neonatology in general, have lead to an increased awareness of hypertension in modern neonatal intensive care units (NICUs). Since most hypertension in infants is related to renovascular or renal parenchymal disease [2, 3], the evaluation and management of neonatal hypertension frequently requires the expertise of a pediatric nephrologist. This review will focus on the differential diagnosis of hypertension in the neonate, the optimal diagnostic evaluation, and both acute and chronic antihypertensive therapy.

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Definition and incidence of neonatal hypertension

Defining what is considered a normal blood pressure in newborn infants is a complex task. Just as blood pressure in older children has been demonstrated to increase with increasing age and body size [4], studies in both term and preterm infants have demonstrated that blood pressure in neonates increases with both gestational and postconceptual age, as well as with birth weight [5–11]. Extremely useful data in this regard has recently been published by Zubrow et al. [9], who prospectively obtained serial blood pressure measurements from 695 infants admitted to several NICUs in a large metropolitan area over a period of 3 months. From these data, they were able to define the mean plus upper and lower 95% confidence limits for blood pressure for the infants studied; their data clearly demonstrated increases in blood pressure with increasing gestational age, birth weight and postconceptual age (Figs. 1–3). Based on these data, we would consider an infant's blood pressure to be elevated if it fell above the upper limit of the 95% confidence interval for infants of similar gestational or postconceptual age and size.

For older infants found to be hypertensive following discharge from the NICU [12], the percentile curves generated by the Second Task Force (Fig. 4) [13] appear to be the most useful. Based on serial blood pressure measurements obtained from nearly 13,000 infants, these curves allow blood pressure to be characterized as nor-

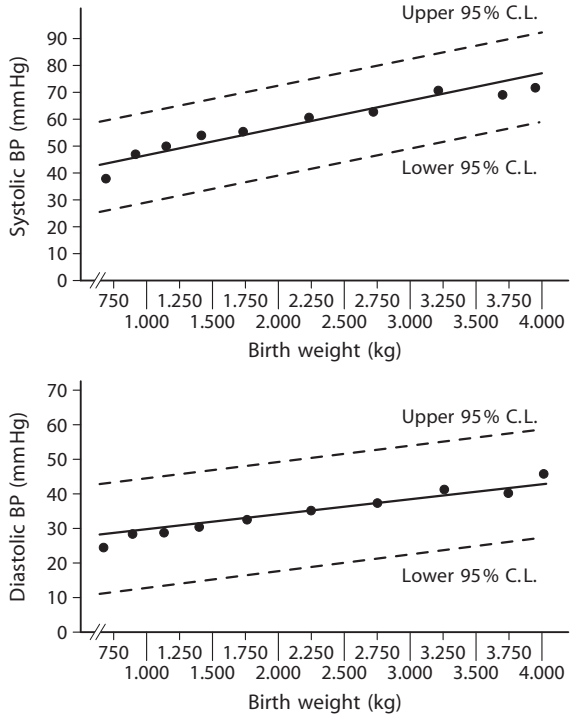

Fig. 1 Linear regression of mean systolic and diastolic blood pressures by birth weight on day 1 of life, with 95% confidence limits (*upper* and *lower dashed lines*). Reproduced from Zubrow et al. [9], with permission from the copyright holders, Stockton Press, a division of Nature America

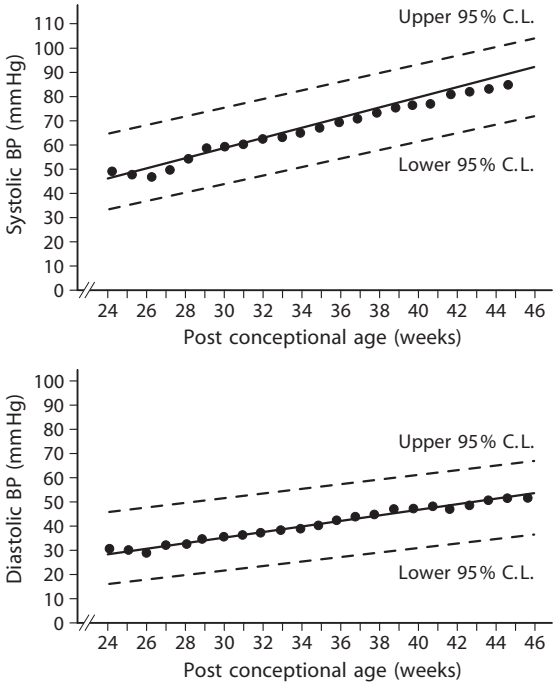

Fig. 3 Linear regression of mean systolic and diastolic blood pressures by postconceptual age in weeks, with 95% confidence limits (*upper* and *lower dashed lines*). Reproduced from Zubrow et al. [9], with permission from the copyright holders, Stockton Press, a division of Nature America

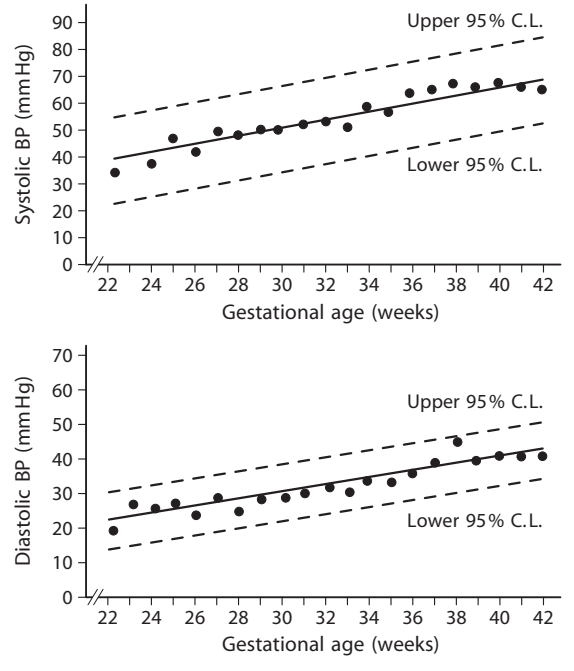

Fig. 2 Linear regression of mean systolic and diastolic blood pressures by gestational age on day 1 of life, with 95% confidence limits (*upper* and *lower dashed lines*). Reproduced from Zubrow et al. [9], with permission from the copyright holders, Stockton Press, a division of Nature America

mal or elevated not only by age and gender, but also by size, albeit to a somewhat limited extent. Hypertension in this age group would be defined as blood pressure elevation above the 95th percentile for infants of similar age, size and gender.

Although the upper limit of normal blood pressure has been defined as the 95th percentile, the actual incidence of hypertension in neonates is quite low, ranging from 0.2% to 3% in most reports [1, 2, 14–16]. It is so unusual in otherwise healthy term infants that routine blood pressure determination is not advocated for this group [17]. For premature and otherwise high-risk newborns admitted to modern NICUs, however, the picture can be quite different. In a review of over 3,000 infants admitted to a Chicago NICU, the overall incidence of hypertension was found to be 0.81% [16]. Hypertension was considerably more common in infants with bronchopulmonary dysplasia, patent ductus arteriosus, intraventricular hemorrhage or that had indwelling umbilical arterial catheters. In this latter group, approximately 9% of the infants studied developed hypertension.

Hypertension may also be detected well after discharge from the NICU. In a retrospective review of over 650 infants seen in follow-up after discharge from a teaching hospital NICU, Friedman and Hustead [12] found an incidence of hypertension (defined as a systolic blood pressure of greater than 113 mmHg on three consecutive visits over 6 weeks) of 2.6%. Hypertension in this study was detected at a mean age of approximately

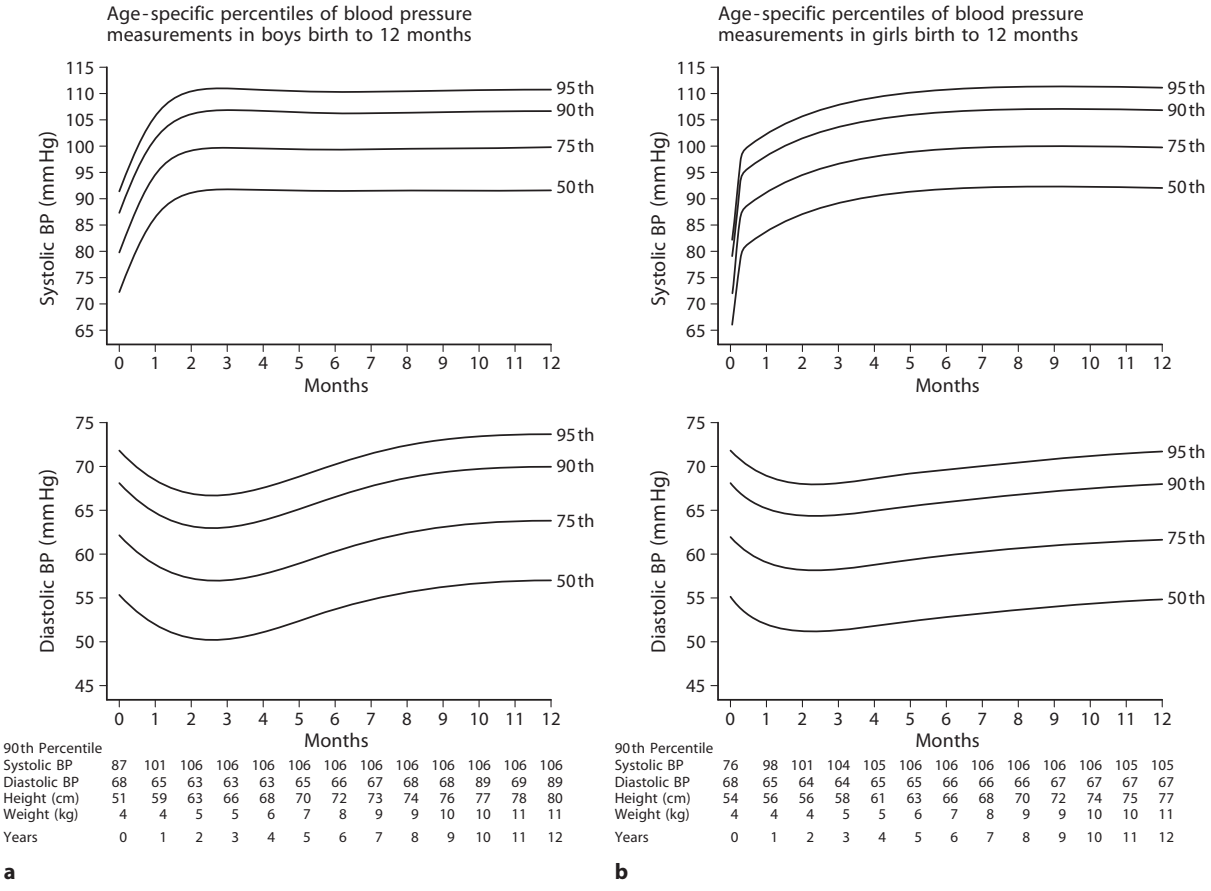

Fig. 4 Age-specific percentiles for blood pressure in boys (**a**) and girls (**b**) from birth to 12 months of age. Reproduced with permission from [13]

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. [16]. Even with the increasing rates of survival of premature infants, however, hypertension remains a relatively infrequent clinical problem that is primarily confined to the NICU.

Causes of hypertension in neonates

As in older infants and children, the causes of hypertension in neonates are numerous (Table 1), with the two largest categories being renovascular and other renal parenchymal diseases [1–3, 12, 14–16]. More specifically, umbilical artery catheter-associated thromboembolism affecting either the aorta and/or the renal arteries probably accounts for the majority of cases of hypertension seen in the typical NICU. A clear association between use of umbilical arterial catheters and development of arterial thrombi was first demonstrated in the early 1970s by Neal et al. [18]. They performed aortography at the time of umbilical artery removal in a group of 19 infants, demonstrating thrombus formation in 18 of the 19 infants, as well as several instances of clot fragmentation and embolization. Thrombosis was also seen at autopsy in 7 of 12 infants who had died, for an overall incidence of 25 out of 31 infants, or approximately 81% of infants studied.

Following the report of Neal et al., the association between umbilical arterial catheter-associated thrombi and the development of neonatal hypertension was confirmed by several other investigators [19–24]. Hypertension was demonstrated in infants who had undergone umbilical arterial catheterization even when thrombi could not be demonstrated in the renal arteries. Rates of thrombus formation have generally been much lower than in the report of Neal et al., typically in the range of 25% [19, 25, 26]. Although there have been several studies that have examined duration of line placement and line position ("low" vs "high") as factors involved in thrombus formation, these data have not been conclusive [25–27]. Thus, the assumption has been made that the cause of hypertension in such cases is related to thrombus formation at the time of line placement, probably related to disruption of the vascular endothelium of the umbilical artery. Such thrombi may then embolize to the kidneys, causing areas of infarction and increased renin release. A similar phenomenon has been reported in infants with dilatation of the ductus arteriosus [28].

Table 1 Causes of neonatal hypertension (*ECMO* extracorporeal membrane oxygenation, *HTN* 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
Renal parenchymal disease	Phenylephrine
Congenital	Maternal
Polycystic kidney disease	Cocaine
Multicystic-dysplastic kidney disease	Heroin
Tuberous sclerosis	Neoplasia
Ureteropelvic junction obstruction	Wilms tumor
Unilateral renal hypoplasia	Mesoblastic nephroma
Congenital nephrotic syndrome	Neuroblastoma
Acquired	Neurologic
Acute tubular necrosis	Pain
Cortical necrosis	Intracranial hypertension
Interstitial nephritis	Seizures
Hemolytic-uremic syndrome	Familial dysautonomia
Obstruction (stones, tumors)	Subdural hematoma
Pulmonary	Miscellaneous
Bronchopulmonary dysplasia	Total parenteral nutrition
Pneumothorax	Closure of abdominal wall defect
Cardiac	Adrenal hemorrhage
Thoracic aortic coarctation	Hypercalcemia
Endocrine	Traction
Congenital adrenal hyperplasia	ECMO
Hyperaldosteronism	Birth asphyxia
Hyperthyroidism	Essential HTN?
Pseudohypoaldosteronism type II	

Other renovascular problems may also lead to neonatal hypertension. Renal venous thrombosis classically presents with the triad of hypertension, gross hematuria, and an abdominal mass. Hypertension may be quite severe in such cases and may persist beyond the neonatal period [13, 29, 30]. Fibromuscular dysplasia leading to renal arterial stenosis is another important cause of renovascular hypertension in the neonate. 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 [31]. In addition, renal arterial stenosis may also be accompanied by mid-aortic coarctation and cerebral vascular stenoses [31]. Other vascular abnormalities may also lead to hypertension in the neonate, including idiopathic arterial calcification [32, 33] and renal artery stenosis secondary to congenital rubella infection [34]. 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 are neonates who have 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 [35, 36]. With recessive PKD for example, the majority of affected infants will be discovered to be hypertensive during the 1st year of life [35]. 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 in PKD, hypertension has also been reported in infants with unilateral multicystic dysplastic kidneys [14, 37–39]. This is somewhat paradoxical, as such kidneys are usually thought to be non-functional.

Renal obstruction may be accompanied by hypertension, even in the absence of renal arterial compression. This has been seen for example in infants with congenital ureteropelvic-junction obstruction [12, 14, 16], and sometimes may persist following surgical correction of the obstruction [40]. Ureteral obstruction by other intra-abdominal masses may also be accompanied by hypertension. The mechanism of hypertension in such instances is unclear, although the renin-angiotensin system has been implicated [41, 42]. Finally, unilateral renal hypoplasia may also present with hypertension [43], 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 [14, 16], usually on the basis of volume overload or hyperreninemia. Hemolytic uremic syndrome, which has been described in both term and preterm infants, is usually also accompanied by hypertension. Such hypertension may be quite difficult to control, requiring multiple agents [44].

Hypertension as a consequence of bronchopulmonary dysplasia (BPD) was first described in the mid-1980s by Abman et al. [45]. In a study of 65 infants discharged from an NICU, the instance of hypertension in infants with BPD was 43%, versus an incidence of 4.5% in infants without BPD. Investigators were unable to identify a clear cause of hypertension, but postulated that hypoxemia might be involved. Over half of the infants with BPD who developed hypertension did not manifest it until discharged from the NICU, highlighting the need for measurement of blood pressure in NICU "graduates," whether or not they have lung disease [12].

The findings of Abman et al. have been reproduced by other investigators, most recently in 1998 by Alagappan and Malloy [46], who found that hypertension was twice as common in very low birth weight infants with BPD compared to the incidence in all very low birth weight infants. Development of hypertension appeared to be correlated with the severity of pulmonary disease, as all of the hypertensive infants required supplemental oxygen and aminophylline. A greater need for diuretics and bronchodilators has also been shown to correlate with the development of hypertension in infants with severe BPD [47]. These observations reinforce the impression that infants with severe BPD are clearly at increased risk and need close monitor-

ing for the development of hypertension. This is especially true in infants who require ongoing treatment with theophylline preparations and/or corticosteroids.

Hypertension may also be seen in disorders of several other organ systems. Coarctation of the thoracic aorta is easily detected in the newborn period, and has been reported in numerous case series of neonatal hypertension [2, 3, 12, 14, 16]. Hypertension may persist in these infants even after surgical repair of the coarctation. Repair early in infancy seems to lead to an improved long-term outcome compared to delayed repair [48]. Endocrinologic disorders, particularly congenital adrenal hyperplasia [49, 50], hyperaldosteronism [51] and hyperthyroidism [52] constitute easily recognizable clinical entities that are accompanied by hypertension.

Iatrogenic causes of hypertension constitute another important category of diagnoses. Medications given to infants for treatment of pulmonary disease such as dexamethasone and aminophylline have clearly been shown to elevate blood pressure [53, 54]. In addition, high doses of adrenergic agents, prolonged use of pancuronium, or administration of phenylephrine ophthalmic drops [55] may raise blood pressure. Such hypertension typically resolves when the offending agent is discontinued or its dose reduced. For infants receiving prolonged parenteral nutrition (TPN), 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.

Substances ingested during pregnancy may also lead to significant problems with hypertension in the neonate. In particular, maternal cocaine use may have a number of undesirable effects on the developing kidney that may lead to hypertension [56]. Hypertension has also been reported to occur in infants of drug-addicted mothers withdrawing from heroin.

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 production of vasoactive substances such as catecholamines [12, 57–60]. Neurologic problems such as seizures, intracranial hypertension and pain constitute fairly common causes of episodic hypertension. In the modern NICU, postoperative pain must not be overlooked as a cause of hypertension. 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 1. Of these, hypertension associated with extracorporeal membrane oxygenation (ECMO) deserves comment. This may be seen in up to 50% of infants requiring ECMO [61], and may result in serious complications, including intracranial hemorrhage [62]. 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 [61, 62]. Given the widespread use of ECMO both in neonates and in older children, this problem is ripe for further investigation.

Clinical presentation and diagnostic approach

In many infants, hypertension will be discovered on routine monitoring of vital signs, particularly in the most acutely 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 blood pressure reduction [63]. 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.

No matter what the presentation, it is crucial that blood pressure is being measured accurately so that hypertension will be correctly identified. Fortunately, in most acutely ill neonates, blood pressure is usually monitored directly via an indwelling arterial catheter either in the radial or umbilical artery. This method provides the most accurate blood pressure readings, and is clearly preferable to other methods [64]. In addition to accurately measuring blood pressures, such catheters are also crucial in careful management of hypertension, particularly in infants with extremely severe blood pressure elevation.

Automated, oscillometric devices are the most common alternative method of blood pressure measurement in most NICUs. Although readings obtained using such devices may differ slightly from intra-arterial blood pressure measurements [65], they are easy to use and provide the ability to follow blood pressure trends over time. They are especially useful for infants who require blood pressure monitoring after discharge from the NICU [66]. When using such devices, however, attention should be paid to using a properly sized cuff, and also to the extremity used. Most normative blood pressure data, not only in infants but also in older children, have been collected using blood pressures obtained in the right arm [13]. Since blood pressures obtained in the leg may be higher than those obtained in the arm [67, 68], the use of other extremities for routine blood pressure determination may complicate to some extent the evaluation of hypertension. Nursing staff should document the extremity used for blood pressure determinations and try to use the same extremity for subsequent determinations if possible. Finally, the infant's state of activity may also affect the accuracy of blood pressure readings. Increased activity, including oral feeding, increases blood pressure [5, 69]. It may, therefore, be important to obtain blood pressure readings while infants are sleeping to obtain the most accurate readings.

Table 2 Diagnostic testing in neonatal hypertension (*CBC* complete blood count, *VMA/HVA* vanillylmandelic acid/homovanillic acid, *VCUG* voiding cystourethrograms)

Generally useful	Useful in selected infants
Urinalysis (± culture)	Thyroid studies
CBC and platelet count	Urine VMA/HVA
Electrolytes	Aldosterone
BUN, creatinine	Cortisol
Calcium	Echocardiogram
Plasma renin	Abdominal/pelvic ultrasound
Chest X-ray	VCUG
Renal ultrasound with Doppler	Aortography
	Renal angiography
	Nuclear scan (DTPA/Mag-3)

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 particulars of the infant's nursery course and any concurrent conditions. The procedures that the infant has undergone (e.g., umbilical catheter placement) should be reviewed, and their current medication list should be scrutinized.

The physical examination, likewise, should be focused on obtaining pertinent information to assist in narrowing the differential diagnosis. Blood pressure readings should be obtained in all four extremities to rule out coarctation of the thoracic aorta. The general appearance of the infant should be assessed, with particular attention paid to the presence of dysmorphic features that may indicate an obvious diagnosis such as congenital adrenal hyperplasia. Careful cardiac and abdominal examination should be performed. The presence of a flank mass or of an epigastric bruit may point the clinician towards diagnosis of either ureteropelvic junction obstruction or renal arterial stenosis, respectively.

In most instances, few laboratory data are needed in the evaluation of neonatal hypertension, as the correct diagnosis is usually suggested by the history and physical examination. It is important to assess renal function, as well as to examine a specimen of the urine to ascertain the presence of renal parenchymal disease. 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 cortisol, aldosterone, or thyroxine levels, should be obtained when there is pertinent history (Table 2).

Determination of plasma renin activity is frequently performed in the assessment of neonates with hypertension [14], although there are few data on what constitutes normal values for infants, particularly for premature infants. The data that are available indicate that renin values are typically quite high in infancy, at least in term newborns [70, 71]. Although renal arterial stenosis and thromboembolic phenomenon are typically considered high renin forms of hypertension, a peripheral renin level 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 aminophylline [72]. Despite these difficulties, assessment of plasma renin activity may be helpful in the evaluation of some infants, especially when elevated, and is therefore usually included as part of the initial laboratory evaluation.

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 [29], may detect aortic and/or renal arterial thrombi [19, 24], and can identify anatomic renal abnormalities or other congenital renal diseases. For these reasons, ultrasound has largely replaced intravenous pyelography, which has little if any use in the routine assessment of neonatal hypertension.

For infants with extremely severe blood pressure elevation, angiography may be necessary. In our experience, a formal angiogram utilizing the traditional femoral venous approach offers the most accurate method of diagnosing renal arterial stenosis, particularly given the high incidence of intrarenal branch vessel disease in children with fibromuscular dysplasia [31]. In extremely small infants, it may be appropriate to defer angiography, managing the hypertension medically until the baby is large enough for an angiogram to be performed safely.

Although nuclear scanning has been shown in some studies to demonstrate abnormalities of renal perfusion caused by thromboembolic phenomenon [1, 15, 16, 23, 28], 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.

Therapy of neonatal hypertension

Today's clinician has available an ever-expanding list of agents that can be used for treatment of neonatal hypertension (Tables 3, 4). Prior to embarking on drug therapy, however, the infant's clinical status should be assessed and any easily correctable iatrogenic causes of hypertension addressed, such as infusions of inotropic agents, volume overload, or pain. Following this, an antihypertensive agent should be chosen that is most appropriate for the specific clinical situation. For the majority of acutely ill infants, particularly those with severe hypertension, it has been our experience that continuous intravenous infusions are the most appropriate approach. While intermittently administered agents also have a role in the management of hypertension, the wide fluctuations in blood pressure frequently seen when these agents are utilized make them inappropriate for treatment of severe hypertension. The advantage of intravenous infusions are numerous, most importantly including

Table 3 Intravenous agents for acute hypertension and hypertensive emergencies/urgencies (*ACE* angiotensin converting enzyme, *IV* intravenous, *BPD* bronchopulmonary dysplasia)

Drug	Class	Dose	Route	Comments
Diazoxide	Vasodilator (arteriolar)	2–5 mg/kg per dose	Rapid bolus injection	Slow injection ineffective; duration unpredictable; use with caution – may cause rapid hypotension
Enalaprilat	ACE inhibitor	15±5 μg/kg per dose Repeat Q 8–24 h	Injection over 5–10 min	May cause prolonged hypotension and acute renal insufficiency
Esmolol	β blocker	Drip: 100–300 μg/kg per min	IV infusion	Very short-acting – constant infusion necessary
Hydralazine	Vasodilator (arteriolar)	Bolus: 0.15–0.6 mg/kg per dose Drip: 0.75–5.0 μg/kg per min	IV bolus or infusion	Tachycardia frequent side-effect; must administer Q 4 h when given IV bolus
Labetalol	α & β blocker	0.20–1.0 mg/kg per dose 0.25–3.0 mg/kg per h	IV bolus or constant infusion	Heart failure, BPD relative contraindications
Nicardipine	Ca^{2+} channel blocker	1–3 μg/kg per min	Constant infusion	May cause reflex tachycardia
Sodium nitroprusside	Vasodilator (arteriolar & venous)	0.5–10 μg/kg per min	Constant infusion	Thiocyanate toxicity can occur with prolonged (>72 h) use or in renal failure

the ability quickly to increase or decrease the rate of infusion to achieve the desired level of blood pressure control. As in patients of any age with malignant hypertension, care should be taken to avoid too rapid a reduction in blood pressure [73, 74] to avoid cerebral ischemia and hemorrhage, a problem that premature infants in particular are already at increased risk for due to the immaturity of their periventricular circulation. Here again, continuous infusions of intravenous antihypertensives offer a distinct advantage.

Unfortunately, there are few data 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 [75] and that of others [76] suggests that infusions of the calcium channel blocker nicardipine may be particularly useful in this population. Other drugs that have been successfully used in neonates include esmolol [77], labetalol and nitroprusside [73]. Whatever agent is used, blood pressure should be monitored continuously via an indwelling arterial catheter, or else by frequently repeated (Q 10–15 min.) cuff readings so that the dose can be titrated to achieve the desired degree of blood pressure 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, the intravenous angiotensin converting enzyme inhibitor, has also been reported to be useful in the treatment of neonatal renovascular hypertension [78, 79]. 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.

Oral antihypertensive agents (Table 4) 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. Captopril in particular is a useful agent for many causes of neonatal hypertension and is our oral drug of choice for most infants seen in our unit. Care must be taken to avoid giving a dose that is too high to premature infants, as they may have an exaggerated fall in blood pressure following captopril administration [80]. For infants whose blood pressure is unable to be controlled by captopril alone, the addition of a diuretic frequently will result in the desired degree of blood pressure control. Beta blockers may need to be avoided in chronic therapy of neonatal hypertension, particularly in infants with chronic lung disease. In such infants, diuretics may have a beneficial effect not only in controlling blood pressure but also in improving pulmonary function [81]. Other drugs that we have found useful in some infants include hydralazine, minoxidil and the calcium channel blocker isradipine [82]. When a vasodilator is indicated, isradipine may be superior to the older agents hydralazine and minoxidil since it can be compounded into a stable suspension [83] that can be dosed with accuracy, even in tiny infants. We no longer use nifedipine in our unit because of the difficulty in administering small doses, and because of the rapid, profound, and short-lived drops in blood pressure that are typically produced by this agent.

Surgery is indicated for treatment of neonatal hypertension in a limited set of circumstances [84]. In particular, hypertension caused by ureteral obstruction or aortic coarctation [48] is best approached surgically. For infants with renal arterial stenosis, it may be necessary to manage the infant medically until it has grown suffi-

Table 4 Oral agents useful for hypertension in infants

Drug	Class	Dose	Interval	Comments
Captopril	ACE Inhibitor	<6 m: 0.01–0.5 mg/kg per dose Max 6 mg/kg per day	TID	Drug of choice for most neonatal HTN monitor serum creatinine and K^+
Clonidine	Central α agonist	0.05–0.1 mg per dose	BID–TID	Side effects include dry mouth & sedation; rebound hypertension with abrupt discontinuation
Hydralazine	Vasodilator (arteriolar)	0.25–1.0 mg/kg per dose Max 7.5 mg/kg per day	TID–QID	Suspension stable up to 1 week; tachycardia & fluid retention common side-effects; lupus-like syndrome may develop in slow acetylators
Isradipine	Ca^{2+} channel blocker	0.05–0.15 mg/kg per dose Max 0.8 mg/kg per day	QID	Suspension may be compounded; useful for both acute & chronic HTN
Amlodipine	Ca^{2+} channel blocker	0.1–0.3 mg/kg per dose Max 0.6 mg/kg per day	BID	Less likely to cause sudden hypotension than isradipine
Minoxidil	Vasodilator (arteriolar)	0.1–0.2 mg/kg per dose	BID–TID	Most potent oral vasodilator; excellent for refractory HTN
Propranolol	β – blocker	0.5–1.0 mg/kg per dose	TID	Maximal dose depends on heart rate; may go as high as 8–10 mg/kg per day if no bradycardia. Avoid in infants with BPD
Labetalol	α and β blocker	1.0 mg/kg per dose Max. 10 mg/kg per day	BID–TID	Monitor heart rate; avoid in infants with BPD
Spironolactone	Aldosterone antagonist	0.5–1.5 mg/kg per dose	BID	Potassium "sparing"; monitor electrolytes. Takes several days to see maximum effectiveness
Hydrochlorothiazide	Thiazide diuretic	1–3 mg/kg per dose	QID	Monitor electrolytes
Chlorothiazide	Thiazide diuretic	5–15 mg/kg per dose	BID	Monitor electrolytes

ciently to undergo definitive repair of the vascular abnormalities [85]. Outcome of such surgical procedures can become quite good if performed at centers with a large experience [86]. Infants with hypertension secondary to Wilms tumor or neuroblastoma will require surgical tumor removal [57, 58, 84], 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 [37–39], although this is controversial. Infants with malignant hypertension secondary to polycystic kidney disease may require bilateral nephrectomy. Fortunately, such severely affected infants are quite rare.

Outcome of neonatal hypertension

The long-term prognosis for infants with hypertension is in most cases quite good, depending of course on the underlying etiology of the infant's hypertension. For infants with hypertension related to an umbilical arterial catheter, the hypertension will usually resolve over time [87, 88]. These infants may require increases in their antihypertensive medications in 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 blood pressure monitoring by the parents is a crucially important component of this process. It is our standard of care to arrange for home blood pressure equipment, either a Doppler or 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 [35, 36, 89]. Infants with renal venous thrombosis may also remain hypertensive [30], and some of these children will ultimately benefit from removal of the affected kidney [29, 30]. Persistent or late hypertension may also be seen in children who have undergone repair of renal arterial stenosis [86] or thoracic aortic coarctation [48]. Reappearance of hypertension in these situations should prompt a search for restenosis by the appropriate imaging studies.

Conclusions

Blood pressure in neonates depends on a variety of factors, including gestational age, post-natal age and birth weight. Hypertension can be seen in a variety of situations in the modern NICU, and is especially common in infants who 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 blood pressure elevation throughout childhood.

Acknowledgements The author wishes to acknowledge Drs. David Kershaw and Martha Nelson for their thoughtful review of the manuscript, and Ruth Primas for her secretarial assistance.

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