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Review

# Neonatal hypertension: focus on diagnosis and therapy

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## Abstract

This study aimed to analyze and summarize the recent literature on the diagnosis and management approach of arterial hypertension in the newborn infant. Neonatal hypertension is a rare condition, with its incidence ranging from 0.2% to 3%. It is affected by several factors, with gestational age, post-conceptual age and birthweight having the strongest impact. Hypertension in the neonatal population is almost always secondary. The two major causes of neonatal hypertension are renovascular and renal parenchymal diseases, which account for 25% to 50% of all cases of hypertension in the Neonatal Intensive Care Unit (NICU). Usually, the symptoms are nonspecific, and hypertension is disclosed on routine monitoring of the newborn vital signs. Clinical history, physical examination, prior laboratory data, and prenatal scans are frequently enough to establish the underlying cause of hypertension. The majority of treatment protocols are based on case reports and experts experience and opinion, due to the lack of clinical trials evaluating the efficacy and safety of antihypertensive drugs in the neonatal population. However, most classes of antihypertensive drugs have been used in this age group, such as direct vasodilators, angiotensin-converting enzyme (ACE) inhibitors, beta-adrenergic blockers, calcium channel blockers, and diuretics. Thirty-two percent to 51% of hypertensive neonates are exposed to more than one antihypertensive drug, and the median duration of exposure is 10 days. Vasodilators are the most commonly used class of antihypertensive used in the NICU, being hydralazine the most frequent of all.

## Keywords

Newborn, hypertension, blood pressure, diagnosis, therapy, Neonatal Intensive Care Unit.

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## Introduction

Hypertension during the neonatal period was first described in the 1970s [1, 2]. At the time, no attention was paid to this condition due to the lack of knowledge about hypertension in this age group and the absence of methods, both invasive and non-invasive, to evaluate it [3]. Nowadays, there is still no consensus about the strict definition of hypertension in the neonate because normative data on blood pressure in this age group is scant [1]. An infant is considered to have hypertension if the systolic or diastolic blood pressure is above the 95$^{th}$ percentile, or above 2 standard deviations from the blood pressure baseline, for infants of the same gestational and postnatal age and similar size [3-8]. This study aimed to evaluate the recent literature on diagnosis and management approach of arterial hypertension in the newborn infant.

## Methods

A search was conducted at PubMed using the query (blood pressure OR hypertension) AND (neonatal OR infant OR neonate OR newborn) AND diagnosis AND (treatment OR management OR clinical approach OR therapy OR therapeutic). Studies published from 2007 onwards were included. Studies that were not written in English or Portuguese or not directly related to the subject were excluded. We included 19 studies in English and 1 study in Portuguese, being 14 review papers, 5 experimental papers, and 1 clinical case.

## Definition and risk factors

Neonatal hypertension is a rare condition, with its incidence ranging from 0.2% to 3% [7, 9] and so it is not recommended to routinely screen all newborns for high blood pressure [6, 10, 11]. It is more common in premature infants, who represent around 75% of all hypertensive neonates in the Neonatal Intensive Care Unit (NICU) [7, 12]. It may be affected by several maternal and neonatal factors [13]. Among the maternal factors, hypertension, pre-eclampsia, diabetes and drug consumption seem to positively affect the neonate blood pressure [1, 13]. The neonatal factors with the strongest impact are gestational age, post-conceptual age, and birthweight [13]. However, there is some controversy around this last factor; since Kent et al. did not find any difference in blood pressure regarding birthweight [14]. Genetic factors, namely cytochrome P450 (CYP2D6) genotype, may also be involved in the development of neonatal hypertension [15]. Neonatal drugs and neonatal diseases can also influence neonatal blood pressure [3]. Several studies show an increase in the systolic and diastolic blood pressure during the neonatal period, regardless of gestational age and birthweight, being the increase rate higher in the first 5 to 7 days and then more gradual [13]. When compared to full-term infants, preterm infants show a faster rise in their blood pressure [1, 11, 13]. Dionne et al., based on the limited published data until 2010, developed a table of normative values for blood pressure in the neonatal period (**Tab. 1**) [11].

Blood pressure can be monitored with both invasive and non-invasive methods. The invasive method, which uses an intra-arterial transducer to monitor blood pressure, is considered to be the gold standard method [3, 11] and the most commonly used vessels are the umbilical artery, the posterior tibial artery and the radial artery [3]. However, arterial catheterization-related complications, such as thrombus formation, hemorrhage or infection may arise [5], and the technique itself can be difficult to perform, especially in low birth weight infants [16]. Therefore, it is reserved for critically ill neonates [9, 12]. The most common method used to evaluate and monitor blood pressure is the non-invasive oscillometric device [3, 16]. The time of reading should be one hour and a half after

**Table 1.** Estimated blood pressure levels at 95$^{th}$ and 99$^{th}$ percentile in neonates with 2 weeks of age.

| | Postconceptional age in weeks | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **26** | **28** | **30** | **32** | **34** | **36** | **38** | **40** | **42** | **44** |
| **95$^{th}$ percentile (systolic/diastolic)** | 72/50 | 75/50 | 80/55 | 83/55 | 85/55 | 87/65 | 92/65 | 95/65 | 98/65 | 105/68 |
| **99$^{th}$ percentile (systolic/diastolic)** | 77/56 | 80/54 | 85/60 | 88/60 | 90/60 | 92/70 | 97/70 | 100/70 | 102/70 | 110/73 |

Adapted from Dionne et al., 2012 [11].

the newborn last feeding or medical intervention and an appropriate sized cuff must be placed on the right upper arm with the infant lying in a prone or supine position [16]. The cuff length must be at least 80% of the length of the neonate upper limb and the cuff width of at least 60% of the circumference of the upper arm [7]. The neonate should be left undisturbed for at least 15 minutes or until the neonate is asleep or in a quiet state [16], since crying, feeding, pain, and agitation rise blood pressure [3]. Three successive blood pressure readings must be taken, 2 minutes apart from each other [16].

## Etiology

Hypertension in the neonatal population is almost always secondary [12, 17]. The prevalence of idiopathic hypertension, when no cause can be identified, ranges from 5% to 57% [18], and it is usually an exclusion diagnosis [8]. There are several causes for hypertension, and the two main categories are renovascular and renal parenchymal diseases [6, 7, 11, 12], responsible for 25% to 50% of hypertension in the NICU [2].

Sahu et al. showed that the major risk factors for hypertension in preterm infants differ from the ones for hypertension in full-term infants [18]. Bronchopulmonary dysplasia and iatrogenic factors are the main risk factors for hypertension in preterm infants, while for full-term infants the main risk factors are cardiac and other systemic diseases [18].

### *Renovascular diseases*

Umbilical artery catheter-associated thromboembolism is the primary cause of renovascular hypertension and hypertension in general in this age group [6, 7, 9]. During the catheterization of the umbilical artery, the vascular endothelium might be disrupted, leading to a thrombus formation. Subsequently, the thrombus might embolize to the aorta and/or renal arterial supply [3, 9, 11]. Consequently, the decreased perfusion of the kidney induces secondary activation of the renin-angiotensin-aldosterone system with subsequent water and sodium retention [4] and blood vessels constriction, increasing systemic vascular resistance [2-4]. The longer the duration of the catheterization, the higher is the risk of developing hypertension [3, 7, 9, 11]. Hence, it is recommended to remove the catheter from the umbilical artery within 5 to 7 days [3]. The comparison of the catheter placement, "high" versus "low," showed that, even though its high placement was associated with fewer ischemic events, like ischemic enterocolitis, there is no difference regarding the incidence of hypertension [1].

Another cause of renovascular hypertension is renal venous thrombosis, which usually occurs in the clinical setting of a high-risk prothrombotic disorder, such as Factor V Leiden mutation [3], associated with polycythemia [5] or as a consequence of perinatal hypoxia [3-5]. It typically presents at least with one of the following three cardinal signs: macroscopic hematuria, thrombocytopenia, and a palpable renal mass; and resulting hypertension may be severe [3, 19]. Renal artery stenosis due to fibromuscular dysplasia is another cause of renovascular hypertension. Despite having healthy main renal arteries on the angiography, these infants have significant branch vessel disease, responsible for hypertension [3]. Idiopathic arterial calcification, renal artery stenosis secondary to congenital rubella infection and mechanical compression of one or both of renal arteries by abdominal masses, tumors or hydronephrotic kidneys, account for the remaining causes of renovascular hypertension [3].

### *Renal parenchymal diseases*

The other main category of diseases causing neonatal hypertension is a parenchymal renal disease, which comprises both congenital structural malformations and acquired parenchymal disease [11]. Regarding congenital renal conditions, both autosomal dominant and autosomal recessive polycystic kidney disease can present with hypertension and nephromegaly [5, 11]. In the most severe cases, severe hypertension may lead to congestive heart failure [5, 11]. Unilateral multicystic dysplastic kidneys have also been associated with hypertension in the neonatal period, although the underlying mechanism is not understood, since the kidneys are usually thought to be non-functioning [11]. Renal obstruction, as a result of congenital ureteropelvic junction obstruction, and ureteral obstruction, due to compression by intra-abdominal masses, may be accompanied by hypertension. Although the mechanism behind them is unclear, it can result from activation of the renin-angiotensin-aldosterone system [11] or impingement on the

renal vessels [5]. Unilateral renal hypoplasia, although uncommon, is another cause of hypertension in this age group [6]. Acquired renal parenchymal causes are less common than congenital abnormalities [6] and comprise conditions such as severe acute tubular necrosis and cortical necrosis, generally as a consequence of severe asphyxia [5]. These conditions, along with interstitial nephritis, induce hypertension due to volume overload or hyperreninemia [4, 6].

*Pulmonary diseases*

Pulmonary conditions may also lead to hypertension in the newborn infant [3, 11]. Bronchopulmonary dysplasia is the most common non-renal cause of hypertension in this age group [3, 7] and it was first described in the mid-1980s [3, 11]. The cause of hypertension in this condition is still not clear, but increased production of renin, catecholamine [2, 3, 18] and antidiuretic hormone, pulmonary hypertension, steroid use, hypercapnia [18] or chronic hypoxia might be involved [3, 11]. The development of hypertension seems to be related to the severity of pulmonary disease [3, 11]. The other pulmonary conditions that can lead to hypertension are pneumothorax and congenital neuroblastoma of the lungs [3].

*Cardiovascular diseases*

Aortic coarctation is the most common cardiovascular cause of high blood pressure during the neonatal period [2, 11]. It is easily diagnosed by measuring blood pressure on the neonate four limbs [1, 3, 11]. However, its management is not that straightforward, since hypertension may persist or reappear after early surgical repair [11]. Abdominal aortic atresia has also been associated with hypertension [5], as well as patent ductus arteriosus [18]. Hypertension related to this last condition may be from pulmonary congestion and hypoxemia, renal hypoperfusion, drug-related nephrotoxicity or thromboembolism [18]. Besides that, after patent ductus closure, cardiac output increases, leading to a transient rise in the neonate blood pressure [18].

*Endocrinologic disorders*

Some endocrinologic disorders, such as congenital adrenal hyperplasia with 11-β-hydroxylase or 17-α-hydroxylase deficiency, primary hyperaldosteronism, and hyperthyroidism, may also lead to the development of hypertension in the newborn infant [5, 11].

Detailed information about endocrinologic pathologies is beyond the scope of this review.

*Drugs and nutrition*

Several drugs given to infants, like theophylline, caffeine, bronchodilators, vasopressors, phenylephrine ophthalmic drops, prolonged use of pancuronium or vitamin D toxicity, may also increase the neonate blood pressure [3, 5, 11]. This type of hypertension, induced by the use of specific drugs, usually resolves when the drug is withdrawn, or its dose adjusted [11]. Perinatal corticosteroids, like dexamethasone, administered for fetal lung maturation in preterm infants, have been linked to epigenetic programming of hypertension [2, 4, 11]. However, some studies don't find that association [4, 18]. Nevertheless, its usage is recommended due to its positive impact of the preterm infant survival [11]. Certain substances consumed during pregnancy may lead to hypertension in the neonate [11]. It is the case of cocaine and heroin, which can have some negative impact on the developing kidney [7, 11]. This drug-related hypertension may also be a sign of withdrawal [5].

High blood pressure in the neonate can also be secondary to total parenteral nutrition, due to salt and water overload, or hypercalcemia [3, 11], caused either by excessive calcium intake or indirectly by vitamin A or D intoxication [6].

*Neoplastic conditions*

Tumors which present in the neonatal period, like neuroblastoma, Wilms tumor, and mesoblastic nephroma, are another cause of high blood pressure in this age group. They can induce hypertension either by compression of the renal vessels or ureters or by the production of vasoactive substances such as catecholamines [3, 11]. Catecholamines are mostly associated with pheochromocytoma or neuroblastoma [5].

*Neurologic conditions*

Neurologic disorders should also be considered as causes of episodic hypertension. Among them are seizures, intracranial hypertension and pain [2, 11].

Neurologic diseases that lead to these conditions are beyond the scope of this paper.

Other etiologies of hypertension in the newborn infant are listed in **Tab. 2**.

## Clinical presentation

Hypertension during the neonatal period is typically found on routine monitoring of vital signs [3, 5, 11], especially in the most acutely ill infants [6], since its clinical presentation is usually either silent or its symptoms are non-specific, like apnea, increased tone, tachypnea, tachycardia, cyanosis, mottling, lethargy, vomiting, irritability, abdominal distension, feeding intolerance, failure to thrive [3, 5, 11, 12]. In more severe cases of high blood pressure, life-threatening complications may develop, such as congestive heart failure, cardiogenic shock, seizures, renal dysfunction or hypertensive retinopathy [3, 11]. In some instances, the neonate may present with cardiogenic shock and hypotension, being hypertension revealed only when the myocardial function is improved [12].

## Diagnostic evaluation

Diagnosis of neonatal hypertension and its etiology is crucial to institute the proper treatment and prevent further complications [4].

The infant should go through a complete evaluation to expose the underlying cause of hypertension since it is rarely idiopathic [3]. This evaluation, as in any other situations, includes a complete clinical history and physical examination, followed by complementary diagnostic exams [9].

The investigation starts with a perinatal history, which can disclose important diagnostic clues, such as prenatal exposures (maternal abuse of illicit substances, as cocaine and heroin, or maternal diabetes), procedures the newborn infant has undergone, like umbilical artery or venous catheterization, drugs that have been administered to the neonate and affect blood pressure or cause renal toxicity (e.g. aminoglycosides) [1, 3, 5, 6, 11] and postnatal complications, such as meconium aspiration, hypotension [9] and asphyxia [5]. Prenatal scans should also be reviewed since they can show renal structural and vascular abnormalities, abdominal masses and malformations [3].

On physical examination, the clinician should ensure that the proper blood pressure measurement technique is being performed to assure correct readings [3, 5, 11]. Both femoral pulses must be checked, and blood pressure measurement should

**Table 2.** Neonatal hypertension etiologies.

| | | |
|---|---|---|
| **Renovascular disease** | | Thromboembolism |
| | | Renal artery stenosis |
| | | Renal artery thrombosis |
| | | Renal vein thrombosis |
| | | Renal artery compression |
| | | Idiopathic arterial calcification |
| **Renal parenchymal disease** | **Congenital** | Polycystic kidney disease |
| | | Multicystic-dysplastic kidney |
| | | Ureteropelvic junction obstruction |
| | | Unilateral renal hypoplasia |
| | | Renal tubular dysgenesis |
| | | Congenital nephrotic syndrome |
| | | Tuberous sclerosis |
| | **Acquired** | Acute tubular necrosis |
| | | Cortical necrosis |
| | | Interstitial nephritis |
| | | Hemolytic-uremic syndrome |
| | | Obstruction (abdominal/ pelvis masses, stones) |
| **Pulmonary** | | Bronchopulmonary dysplasia |
| | | Pneumothorax |
| | | Congenital neuroblastoma of lungs |
| **Cardiac** | | Aortic coarctation |
| | | Abdominal aortic atresia |
| | | Patent ductus arteriosus |
| **Endocrine** | | Congenital adrenal hyperplasia |
| | | Hyperaldosteronism |
| | | Hyperthyroidism |
| | | Pseudohypoaldosteronism type II |
| **Neoplasia** | | Wilms tumor |
| | | Neuroblastoma |
| | | Pheochromocytoma |
| | | Mesoblastic nephroma |
| **Neurologic** | | Pain |
| | | Intracranial pressure |
| | | Seizures |
| | | Subdural hematoma |
| | | Familial dysautonomia |
| **Drugs** | **Neonate** | Inotropic agents, caffeine, theophilline, dexamethasone, pancuronium, phenylephrine, vitamin D intoxication |
| | **Mother** | Heroin, cocaine |
| **Miscellaneous** | | Total parenteral nutrition |
| | | Closure of abdominal wall defect |
| | | Hypercalcemia |
| | | Birth asphyxia |
| | | Extracorporeal membrane oxygenation (ECMO) |
| | | Adrenal hemorrhage |
| | | Fluid overload |

Adapted from Dionne et al., 2012 [11].

be obtained in all four extremities of the neonate at least once to screen for coarctation of the aorta [1, 3, 6, 11]. Differential pressure between the lower and upper extremities suggests aortic coarctation [5]. Assessment of the general appearance of the infant, paying particular attention to dysmorphic features that may suggest a diagnosis like congenital adrenal hyperplasia, Turner, Noonan or William's syndrome (syndromes that cause high blood pressure), is a very important step [3, 6, 11]. A cardiac, pulmonary, abdominal and genitourinary examination should be performed [3, 5, 11]. On cardiac examination, the physician should look for murmur, mottling, tachycardia, cyanosis and suggestive signs of heart failure [3]. Tachycardia and flushing are suggestive of secreting tumor-like neuroblastoma [5], and the murmur is indicative of coarctation of the aorta [9]. The abdominal examination must determine the presence of an abdominal mass, which may indicate renal vein thrombosis, cystic kidney disease, polycystic kidney disease or ureteropelvic junction obstruction [3, 11], or any epigastric bruit, that might be a sign of renal artery stenosis [6, 11]. Genitourinary assessment should be performed to rule out any anomalies or virilization signs, that might be present in case of congenital adrenal hyperplasia [3], associated with hyperpigmentation [5].

Usually, the probable cause of hypertension is suggested by the infant's clinical history, physical examination and prior laboratory data [6, 11]. Hence, few additional complementary exams are needed [6, 11]. The first line exams include: assessment of renal function (serum creatinine and blood urea nitrogen); urine examination for hematuria, leukocytosis, renal cast, urine culture, urine protein/creatinine ratio, urine albumin/creatinine ratio for renal parenchymal disease or urinary tract infection; serum electrolytes (hypokalemia in case of congenital adrenal hyperplasia, hyperkalemia in case of pseudohypoaldosteronism type II, hypercalcemia); complete blood count (thrombocytopenia in case of renal vein thrombosis and anaemia in case of renal dysfunction [3, 11, 12]) and arterial blood gas analysis [3, 7, 11]. A Doppler ultrasound imaging test of the genitourinary tract is a non-invasive economical exam that should be performed in all hypertensive neonates, since it can disclose correctable causes of hypertension, such as renal venous thrombosis and aortic and renal arterial thrombi, anatomical renal abnormalities, congenital renal diseases [5, 11, 12] and abdominal masses, and also allows adrenal evaluation [3]. A chest X-ray is useful to evaluate cardiomegaly in infants with congestive heart failure or murmur on cardiac auscultation [3, 5, 6, 11]. In cases of suspected intraventricular hemorrhage, which may be either a cause or a consequence of high blood pressure, a cranial ultrasound can be performed [3].

The first line exams might suggest etiologies that need further investigation [3]. If an endocrinal cause is suspected, thyroxine levels (for hyperthyroidism), serum cortisol (for Cushing's syndrome), serum aldosterone, urinary 17-hydroxysteroids and 17-ketosteroids (for congenital adrenal hyperplasia) and urinary metanephrines and vanillyl mandelic acid (VMA) (for pheochromocytoma and congenital neuroblastoma) levels should be obtained [3, 5, 11]. If hypertension is thought to be of a renal cause, subsequent studies may be needed, as voiding cystourethrogram, if a urinary tract malformation is suspected, radionuclide scintigraphy, for abnormal perfusion detection, or dimercaptosuccinic acid (DMSA) scan if suspicious of arterial infarction [3]. However, due to the newborn's immature renal function, the role of nuclear scanning in detecting abnormalities of perfusion is limited [1, 5] and this study is often deferred [9]. The gold standard method to diagnose hypertension of renovascular cause is magnetic resonance angiography [3]. Percutaneous femoral renal arteriography is the most accurate procedure to diagnose renal artery stenosis since the intrarenal vascular branch disease responsible for hypertension in infants with fibromuscular dysplasia cannot be detected by computed tomography or magnetic resonance angiography [8, 11]. However, in these cases, the infant's size is a limiting factor to the performance of the arteriography, which may be postponed until the neonate grows to the appropriate size for the angiography to be safely performed [11].

Meanwhile, hypertension should be managed medically [11]. Determination of plasma renin activity has been recommended, since it is typically increased in renovascular disease and decreased in primary hyperaldosteronism [3, 11]. However, plasma renin activity normal values for infants are not consensual, especially for preterm ones, and data available shows that plasma renin activity is higher in infancy [5, 6, 8, 11]. Additional exams that can be performed include: computerized tomography, to evaluate abdominal masses;

I-131-metaiodobenzyl-guanidine scanning, to detect pheochromocytoma [3, 7]; echocardiogram, useful to evaluate both causes and consequences of hypertension, like coarctation of the aorta and target organ damage and dysfunction, respectively [9, 12]; renal biopsy (rarely needed), for intrinsic renal pathology [3]; and evaluation for thrombophilia in cases of renal thrombosis [9].

A simplified diagram regarding diagnostic approach can be found in **Fig. 1**.

## Therapy

Hypertension during the neonatal period can lead to short-term adverse effects on several organs [3], including hypertensive retinopathy, encephalopathy, left ventricular hypertrophy and cardiomyopathy [18]. Long-term effects of high blood pressure in this age group are not well studied [14], but they may also lead to adverse outcomes in the future [3]. Except in severely hypertensive infants with visible end-organ manifestations, there is no consensus about when to start treating hypertension, and most of the antihypertensive drugs are not approved for use in the neonatal population [1, 3, 12]. The majority of the treatment protocols are based on case reports and experts experience and opinion [1-3, 9, 10, 20]. However, sustained blood pressure levels equal to or greater than the 99$^{th}$ percentile are likely to have unmeasurable cardiac, renal and central nervous system effects [1, 2, 9]. Thus, treatment of hypertension is usually instituted when blood pressure levels reach the 95$^{th}$ percentile [2, 7]. However, before starting antihypertensive drug therapy, reversible causes of hypertension should be addressed [3, 6, 9, 11]. Among them are: iatrogenic causes, such as volume overload, managed with fluid restriction and diuretics if needed [3, 5]; inotropic agents, which should be adjusted; hypercalcemia; pain, treated with analgesia; umbilical artery catheter, which must be removed; endocrine disorders, counterbalanced with appropriate hormonal therapy [3, 9]; or hypoxemia (in infants with bronchopulmonary dysplasia) [6, 11].

Despite the lack of clinical trials evaluating the efficacy and safety of antihypertensive drugs in the neonatal population [1, 2, 11], most classes of antihypertensive drugs have been used in this age group [12], such as direct vasodilators, angiotensin-converting enzyme (ACE) inhibitors, beta-adrenergic blockers, calcium channel blockers [5, 11] and diuretics [2, 5]. Thirty-two percent to 51% of hypertensive neonates are exposed to more than one antihypertensive drug [2, 10, 12], and the median duration of exposure is 10 days [9, 10]. Vasodilators are the most commonly used class of antihypertensive used in the NICU, being hydralazine the most frequent of all [9, 12].

### *Clinical approach to neonatal hypertension*

The approach to neonatal hypertension should be tailored to the severity of blood pressure elevation [5], and the antihypertensive agent used should depend on the clinical condition of the neonate [9].

Cases of blood pressure above the 99$^{th}$ percentile with or without systemic symptoms are considered to be severe hypertension cases, and they are a neonatal emergency [3, 11], requiring prompt management [9]. The adequate treatment is a continuous intravenous infusion of a short-acting antihypertensive agent, since it allows a fast increase or decrease in the infusion's rate to achieve the desired blood pressure level [3, 11, 12, 17]. Monitoring of blood pressure levels must be performed, either directly via an indwelling arterial catheter (the preferred method), or, more frequently, with oscillometric device readings every 5 to 15 minutes, to allow titration of the drug's dose [3, 11, 12]. Caution should be taken to avoid a too quickly decrease in the blood pressure level, which might lead to cerebral ischemia and hemorrhage. The risk is particularly high in premature infants because of their periventricular circulation immaturity [11, 12]. The goal is to decrease blood pressure to a level lower than the 95$^{th}$ percentile [12]. Twenty-five percent to 30% of the planned reduction should occur over the first 6 to 8 hours [12, 17], the next third over the following 24 to 36 hours, and the last third over the next 48 to 72 hours [12]. Infusions of nicardipine seem to be particularly useful in infants with severe acute hypertension [3, 7, 11, 12]. It reduces peripheral resistance and does not have a negative inotropic effect [17]. In the case of significant reflex tachycardia and flushing as side effects [17], labetalol infusions must be added [7]. Other antihypertensive agents that have been safely used are esmolol and nitroprusside [11, 17]. Nitroprusside is useful in hypertension-induced congestive cardiac failure, since it reduces both pre- and after-load [17]. If intravenous infusion medications are not readily available, short-acting intravenous or oral antihypertensive drugs constitute an alternative [12].

Intravenous intermittent administration of antihypertensive agents is associated with fluctuations

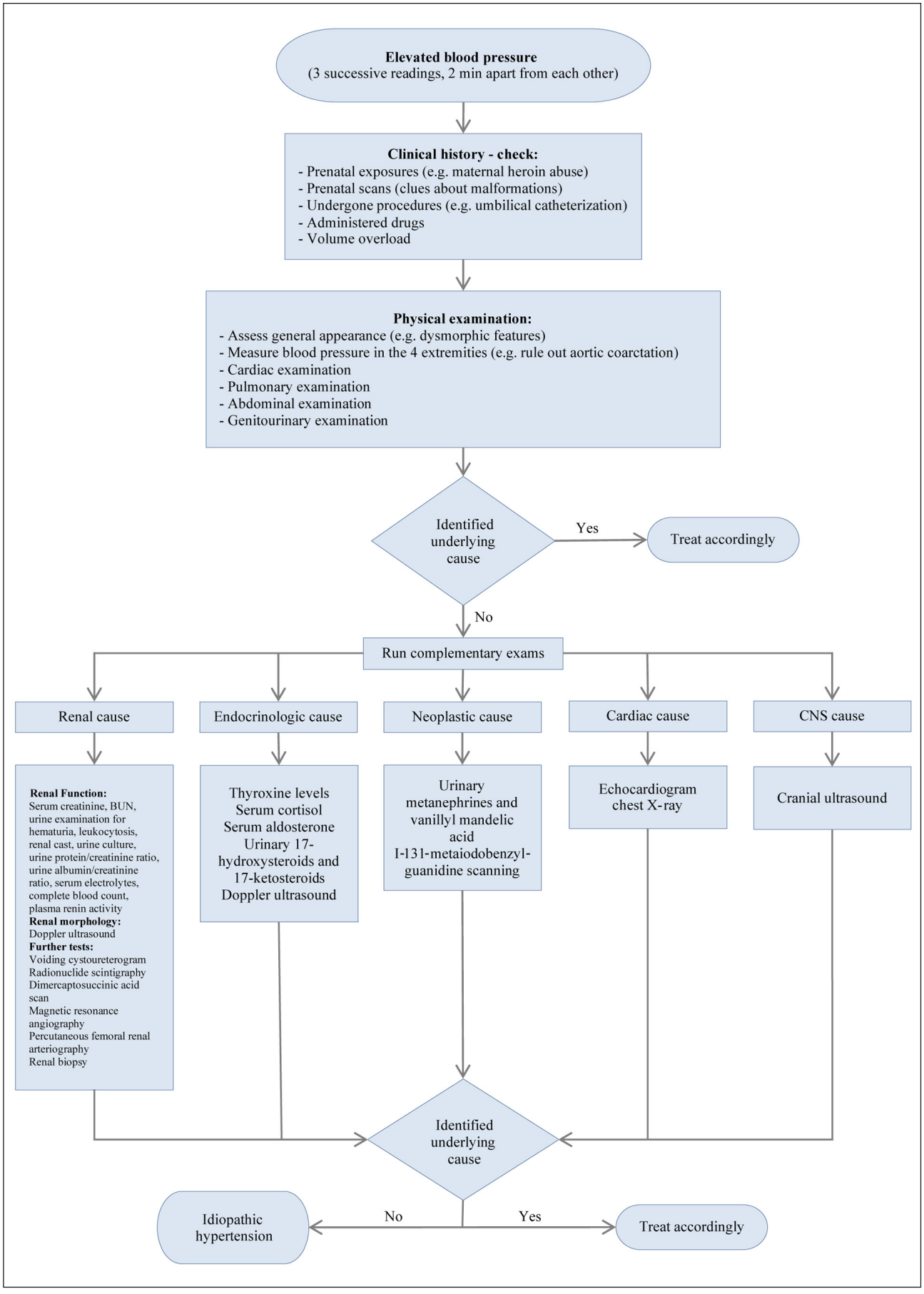


**Figure 1.** Diagnostic evaluation.
Adapted from: Hipertensão Arterial Neonatal, 2014 [8].

of blood pressure; thus, it is not the preferred choice to manage severe hypertension [11]. However, it is useful in mild to moderate hypertension when the neonate is not a candidate for oral therapy due to gastrointestinal dysfunction [7, 11]. Hydralazine and labetol are useful in this situation [7, 11].

Oral antihypertensive drugs are preferred in infants with less severe hypertension or in those who have their severe acute hypertension controlled with intravenous infusion and are ready to start chronic therapy [1, 6, 7, 11].

Special attention must be paid whenever antihypertensive drugs are combined, since their side effects might be intensified.

In cases of moderate hypertension (blood pressure between the 95$^{th}$ percentile and 99$^{th}$ percentile without any end-organ dysfunction), diuretics are the first line therapy, but propranolol and hydralazine also constitute therapeutic options [3].

Neonates with mild hypertension should be under close observation and regular monitoring of blood pressure [3]. In case of need for an antihypertensive drug, thiazide diuretics must be chosen over loop diuretics [3, 7].

Details regarding the drugs used to manage hypertension in the newborn infant are listed in **Tab. 3**.

## Surgical treatment

Surgical management is the chosen approach in less than 10% of the cases of infants with hypertension [12]. Surgical procedures may be

**Table 3.** Antihypertensive medications.

| Class | Drug | Route | Dose | Interval | Side effects |
|---|---|---|---|---|---|
| **Calcium channel blockers** | Nicardipine | IV | 0.5-4 mg/kg/min | Infusion | Hypotension; tachycardia, flushing. Caution in perinatal asphyxia |
| | Isradipine | Oral | 0.05-0.15 mg/kg/dose | Q 6-8h | Hypotension; tachycardia, edema. Caution with QTc prolongation |
| | Amlodipine | Oral | 0.05-0.30 mg/kg/dose | Once daily | Edema, tachycardia. Gingival hypertrophy |
| | Nifedipine | Oral | 0.1-0.25 mg/kg/dose | Q 4-6h | Hypotension; tachycardia. Neurologic injury |
| **Angiotensin-converting enzyme (ACE) inhibitors** | Captopril | Oral | 0.01-0.50 mg/kg/dose | 3 times daily | Fast drop in blood pressure levels; monitor serum creatinine and K+; angioedema, agranulocytosis; avoid until 44 weeks of post-conceptual age |
| | Enalapril | Oral | 0.08-0.60 mg/kg/dose | Once-twice daily | |
| **β-blockers** | Esmolol | IV | 125-1,000 mg/kg/min | Infusion | Caution in chronic lung disease, heart block and unstable heart failure |
| | Propanolol | Oral | 0.50-1 mg/kg/dose | 3 times daily | |
| **α- and β-blockers** | Labetelol | IV | 0.25-3 mg/kg/hour | Infusion | |
| **Vasodilators** | Hydralazine | Oral | 0.25-1.0 mg/kg/dose | 3 to 4 times daily | Tachycardia; fluid retention; diarrhea, emesis, agranulocytosis |
| | | IV | 0.15-0.60 mg/kg/dose | Q 4h | |
| | Minoxidil | Oral | 0.10-0.21 mg/kg/dose | 2 to 3 times daily | Tachycardia and fluid retention; hypertrichosis (if prolonged use), pericardial effusion |
| | Nitroprusside | IV | 0.25 mg/kg/min | Infusion | Hypotension; tachycardia; thiocyanate toxicity |
| **Diuretics** | Furosemide | Oral | 1-6 mg/kg/dose | 4 times daily | Hyponatremia; hypokalemia; ototoxicity; nephrocalcinosis |
| | Hydrochlorothiazide | Oral | 1-3 mg/kg/dose | Once daily | Hyponatremia; hypokalemia; alkalosis |
| | Amiloride | Oral | 0.4-0.625 mg/kg/dose | Once-twice daily | Hyperkalemia. Caution in renal failure |
| | Spironolactone | Oral | 0.50-1.50 mg/kg/dose | Twice daily | Hyperkalemia. Caution in renal failure |

Adapted from: Batisky, 2014 [9] and Dionne et al., 2012 [11].

performed in the following conditions: renal artery stenosis, renal vein thrombosis, polycystic kidney disease, Wilm's tumor, neuroblastoma, aortic coarctation or obstructive uropathy [3, 12]. In cases of renovascular disease, neonatal hypertension may need to be controlled medically before surgical intervention is performed to correct the lesion [9]. Rarely, severe refractory hypertension requires unilateral nephrectomy [9]. Renal arterial or venous thrombosis may end up needing a surgical intervention [9]. However, most cases can be managed with thrombolytic agents [9]. Autosomal recessive polycystic kidney disease may need bilateral nephrectomy to control malignant hypertension [9].

## Outcome

Long-term outcome data on hypertension in the neonatal population is lacking [1]. End-organ damage features are risk factors for poor prognosis [3] and neonatal hypertension prognosis depends on the underlying cause, early diagnosis, and appropriate management [3, 5]. Most of the cases will resolve over time [5]. A study showed that, out of the hypertensive neonates discharged from the NICU on antihypertensive drugs (around 40%), only 15% were on medical therapy after 3 to 6 months [9]. Some neonates might require long-term treatment [5, 9], namely infants with renal or renovascular diseases [9], and some of them will benefit from the removal of the affected kidney [6]. Infants who undergo renal artery stenosis and thoracic aortic coarctation repair may also show persistent or late hypertension [11]. In such cases, investigation for re-stenosis should be performed using the appropriate imaging tests [11].

## Conclusion

Neonatal hypertension is a rare condition, with its incidence ranging from 0.2% to 3% and it is more common in premature infants, who represent around 75% of all cases in the NICU. There are several causes for neonatal hypertension, and the two main categories are renovascular and renal parenchymal diseases, responsible for 25% to 50% of hypertension in the NICU. Decisions regarding therapeutic approach are not always easy to make either because of the lack of useful normative blood pressure data or because of the lack of information concerning the safety and efficacy of the available drugs. However, most classes of antihypertensive drugs have been used in this age group, such as direct vasodilators, ACE inhibitors, beta-adrenergic blockers, calcium channel blockers, and diuretics. Vasodilators are the most commonly used class of antihypertensive used in the NICU, being hydralazine the most frequent of all. Thirty-two percent to 51% of hypertensive neonates are exposed to more than one antihypertensive drug, and the median duration of exposure is 10 days.

Neonatal hypertension prognosis depends on the underlying cause, early diagnosis, and appropriate management. Although most of the cases will resolve over time, some neonates might require long-term treatment, namely infants with a renal or renovascular disease, and some of them benefit from the removal of the affected kidney.

In clinical practice, it is essential that each NICU has a specific hypertension management protocol to standardize the hypertension approach and allow benchmarking among NICUs.

## Declaration of interest

The Authors declare no conflicts of interest. There was no funding to perform this study.

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