Pediatric Hypertension: A Review for the Primary Care Provider

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Introduction

Hypertension affects nearly 50 million Americans and is associated with several diseases including atherosclerosis, coronary disease, diabetes mellitus, and end-stage renal disease (ESRD).[1] Age-specific mortality is 30 times higher in children with ESRD than in children without it.[2] Because hypertension contributes to ESRD, it is of great importance to identify and treat children with hypertension. Due to the significant effects of hypertension on several organs, adults in the United States are routinely screened for hypertension. The American Academy of Pediatrics recommends that this screening should be extended to the pediatric population in the United States, with annual blood pressure (BP) screening beginning with the child's third birthday. However, despite these recommendations, in a study of 4 emergency departments, Silverman and colleagues reported that a significant percentage of pediatric patients did not have their BP checked.[3] Although pediatric hypertension is rarely an emergency, it has been shown that childhood BP is the best predictor of adult BP.[4] Pediatric hypertension is more common than is often perceived, with a prevalence rate of systolic hypertension in school-aged children of 1% to 5.8%.[5-8] A positive family history of hypertension is an important risk factor for pediatric hypertension, because the incidence of hypertension in children of such families can be as high as 10%. Combined with the fact that children with HTN may have evidence of end-organ damage,[9] it becomes of utmost importance to screen children early for hypertension. In this article, we review the literature on pediatric hypertension for more effective management in the care of children with hypertension.

What is Hypertension?

Pediatric BP norms, more so than adult norms, vary across age, gender, and height. A task force was established in 1987 to report on BP values in children and adolescents. The Task Force, last updated in 1996, assigned values to percentiles by gender, age, and height. These percentile values have since been used to characterize hypertension in children and adolescents.[10] Normal BP is defined as repeated measurements below the 90th percentile. Patients are considered borderline hypertensive if repeated measurements are between the 90th and 95th percentiles. Systolic or diastolic readings greater than the 95th percentile are considered significant hypertension while those over the 99th percentile are considered severe hypertension.[1]

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While these data are the best currently available, Norwood points out that these task force–assigned values may not accurately reflect the norms or the risks for children outside the United States, or for those who have medical illnesses.[1] Sorof and Portman also find several weaknesses with these definitions as set forth by the task force.[11] They note that these definitions are statistical instead of functional as they are arbitrarily chosen as 2 SDs above the mean, and do not correlate with end-organ damage. These investigators also state that the task force values are based on casual BP measurements, which are limited by the fact that BP is a dynamic variable and changes from minute to minute. This, along with the phenomenon of white coat hypertension, can lead to an overdiagnosis of hypertension. Sorof and Portman recommend using ambulatory blood pressure monitoring (ABPM) to bypass the limitations of casual BP measurements.[11] They also suggest using BP load as opposed to mean BP values wherein BP load is defined as the percentage of BP readings for a given period that exceeds the 95th percentile of normal for the individual patient.[11]

How to Measure Blood Pressure Accurately?

A standardized method to measure BP was described by the task force. Accurate measurement of BP starts with choosing the correct sized cuff. The cuff should have a bladder width of about 40% of the arm circumference halfway between the olecranon and acromion. The patient should be in a seated position having rested for 3 to 5 minutes with the cubital fossa supported at the level of the heart. The average of at least 2 measurements should be used to determine the BP value. While the onset of Korotkoff sounds is used for determination of systolic BP, there is controversy as to which sound defines the diastolic BP. The disappearance of Korotkoff sounds (the fifth Korotkoff sound) has been designated by the American Heart Association as the standard for diastolic BP. In some pediatric patients, Korotkoff sounds can be auscultated to 0 mm Hg, in which case it excludes the possibility of diastolic hypertension.[10] Measuring BP by the auscultatory method may be particularly difficult in infants and therefore Doppler ultrasound has been used to measure BP in this population.

ABPM is a method that has gained popularity in recent years. It allows the BP to be measured several times within a defined period and reflects the dynamic nature of BP. ABPM also allows BP measurement in the patient's normal surroundings, which helps to eliminate white coat hypertension.[11,12] ABPM is helpful in the diagnosis of borderline hypertension and it is well tolerated and easily reproducible. It has also proven to be useful in determining altered circadian rhythms, which may be a clue to modified vascular reactivity.[7,13]

What Are the Causes of Hypertension in Children?

There are many causes of hypertension in children and include essential hypertension, white coat hypertension, renal disease, cardiac disease, and endocrine diseases (Table 1). A secondary cause is more likely to be found in young children with severe hypertension.[13] The age of the child and the pattern of elevation can provide clues to the cause of hypertension. Genetic and environmental factors may also play a role in hypertension in children.

Although rare in a child, essential hypertension is the leading cause of hypertension among adolescents. Furthermore, an elevated systolic or diastolic blood pressure is also observed in 80% of obese adolescents.[3] The major determinant for BP in children is body size as well as physical fitness.[10] Sorof and colleagues found that early primary hypertension might be represented by isolated systolic hypertension in children.[11] These investigators also suggested that the association between obesity and hypertension is modulated by sympathetic nervous system hyperactivity. They note that the antecedents of essential hypertension are manifested in children, with progression along a clinical spectrum from a mild baseline hyperkinetic state, to enhanced cardiovascular reactivity to stress, to persistent isolated systolic hypertension.[5] Other factors that play a role in essential hypertension include vascular smooth muscle reactivity, the interaction of the kidney and the renin-angiotensin system, cardiac index, and hormonal factors.[14] A family history of hypertension is often seen in a pediatric patient with essential hypertension. Candidate genes for hypertension have recently been identified.[15] Children found to have blood pressure values in the higher percentiles often go on to develop hypertension in adulthood. Children of Asian descent have been reported to have higher systolic and diastolic blood pressures than whites and Hispanics.[16] African-American adults

Table 1

CAUSES OF HYPERTENSION IN CHILDREN

Age	Renal	Cardiac	Other
<1 yr	Renal artery thrombosis Renal artery stenosis Renal venous thrombosis Congenital renal abnormalities Renal parenchymal disease Acute renal failure Obstructive uropathy	Coarctation of the aorta Patent ductus arteriosus Aortic thrombosis	Drug-related Endocrine Pain Fluid overload Bronchopulmonary dysplasia Increased intracranial pressure
Child	Renovascular disease Renal parenchymal disease Renal failure (acute/chronic) Glomerular disease Hemolytic uremic syndrome Chronic pyelonephritis	Coarctation of the aorta Anemia Patent ductus arteriosus Arteriovenus fistula	Essential Endocrine Drug-related Pain Metabolic
Adolescent	Renal parenchymal disease Renovascular disease Glomerular disease Renal failure (acute/chronic)	Coarctation of the aorta Anemia Patent ductus arteriosus Arteriovenus fistula	Essential Endocrine Drug-related Metabolic Pain

have an incidence of hypertension that is twice that of whites, suggesting that race and ethnicity may also be important factors in the cause of hypertension.[1] Differences in body size and sexual maturation could explain the higher incidence of essential hypertension in certain races.[17] In addition, as compared to white children, African-American children showed an increased pressor reactivity to mental and physical stress, decreased dopamine beta-hydroxylase levels, decreased renin levels, reduced heart rates, increased peripheral resistance, increased insulin levels, decreased blood glucose levels, as well as decreased potassium excretion.[18,19] However, in a cohort of over 19,000, 10- to 15-year-old children screened in Minneapolis, Minnesota, no difference was found in blood pressure between African Americans and whites. Interestingly, girls in this population had significantly more hypertension than boys (2.7% vs. 1.3%).[8]

White coat HTN is defined as a transient increase in BP into the hypertensive range that occurs in the presence of a medical professional. Sorof and Portman suggest using ABPM to differentiate white coat hypertension from other causes, because it allows measurements in the patient's normal surroundings. Using the task force definition of hypertension, they found a white coat hypertension prevalence of 53%.[11]

As mentioned previously, Flynn recommends using ABPM as part of the initial evaluation of hypertension.[20] He suggests that casual blood pressure monitoring may not be the most accurate means of measuring BP and that the pattern of hypertension may help with the diagnosis of the cause. Compared to patients with essential hypertension, patients with secondary hypertension demonstrated increased diastolic BP load during the day and at night, and also demonstrate significantly increased systolic BP load at night. He also found that if the daytime diastolic BP load was greater than 25% and the nighttime systolic BP load was greater than 50%, the patients were more likely to have a secondary cause for their hypertension. Children with secondary causes were also found to have significantly lower nocturnal BP dips.[20]

Renal causes of hypertension are common and include many diseases. The most common cause in preadolescents is acute and

chronic renal parenchymal disease.[1] Volume retention and vasoconstrictor release are the underlying mechanisms for BP elevation.[6] Reflux nephropathy is frequently missed as a cause of secondary hypertension, whereas congenital anomalies and glomerulonephritides are usually discovered during the initial evaluation.[1] Renovascular disease is also a common cause of hypertension in pediatrics. Eight percent to 10% of children with severe hypertension have renal artery stenosis resulting from fibromuscular dysplasia. The mechanism for increased BP in renovascular disease is activation of the renin-angiotensin system.[6] Another renin-mediated hypertension occurs in unilateral ureteral stenosis, which is not uncommon in severe hypertension where no urinary or serum evidence of renal disease is found.[1,6] The renal parenchymal scarring seen with recurrent urinary tract infections can often be silent until late childhood when 10% of affected patients develop significant, or even malignant, hypertension. The common use of umbilical artery catheters in the neonatal intensive care unit makes renal artery thrombi a potential cause in this setting especially in the case of severe hypertension.[1]

Approximately one third of hypertension in infants is due to coarctation of the aorta.[1] In this condition, the plasma renin level is inappropriately high for the increased extracellular fluid volume and the baroreceptors are not sensitive to an elevated pulse pressure. Another factor is the increased resistance at the stenotic site. Increased diastolic filling, myocardial stretch, contraction force, and stroke volume occur in arteriovenous fistula, leading to a wide pulse pressure systolic hypertension.[6]

Endocrine abnormalities can also cause hypertension. An increase in glucocorticoids, whether by increased endogenous production or exogenous administration, causes volume expansion and fluid volume shifts due to the glucocorticoid-induced enhanced sensitivity of vasopressor agents.[21] Volume expansion occurs with excess mineralocorticoids due to their enhancing effect on sodium reabsorption and potassium excretion in the distal renal tubule.[6] Catecholamine-mediated hypertension occurs due to alpha and beta-adrenergic peripheral arteriolar constriction, as well as salt and water retention resulting from decreased glomerular filtration rate, and increased sodium retention.[22] Pheochromocytoma is a rare but important cause of pediatric hypertension. Hypertension found with this tumor is usually sustained as opposed to intermittent.[1] The elevated levels of circulating catecholamines and activation of the sympathetic nervous system that occur with pheochromocytoma lead to an increased total peripheral resistance, which is the cause of the sustained hypertension.[23] Elevated insulin levels cause increased renal tubular reabsorption of sodium thereby affecting blood pressure regulation. Other effects of increased insulin levels include increased sympathetic nervous system activity and increased uptake of sodium and calcium by vascular endothelial cells.[24]

How Do You Evaluate a Child with Hypertension?

Once a pediatric patient has been determined to have hypertension, it is important to distinguish between primary and secondary types. Which patients should be evaluated and how far those evaluations should be taken are questions that are not easy to answer. Before any evaluation begins, it is essential to document that hypertension is indeed present. The evaluation and treatment of a patient erroneously diagnosed with persistent hypertension may be unnecessary and very costly. A study performed by Flynn suggests that ABPM should be used as part of the initial evaluation of hypertension in children.[20] After confirming that the child is indeed hypertensive, the first step in the evaluation is to perform a thorough personal and family history. The history should focus on symptoms attributable to hypertension such as headache, chest pain, flushing, rash, visual disturbances, weight change, and epistaxis.[6] A neonatal history, developmental pattern, history of present or past renal disorders, medication history, and symptoms related to endocrine disorders associated with hypertension should also be elicited. Physical examination should include growth parameters, and evaluation of peripheral pulses. One should look for features of genetic syndromes and for signs of endocrine disorders, hypertensive encephalopathy, retinopathy, pulmonary edema, congestive heart failure, and renal diseases.[13] Blood pressure measurements in all four limbs should be performed because decreased BP in the lower limbs may indicate coarctation of the aorta.[6] The extent of the evaluation is dependent on the child's age, severity of hypertension, presence of end-organ damage, and long-term risk factors.[1] Bartosh and Aronson state that the identification of secondary causes of hypertension is likely directly related to the de-

gree of blood pressure elevation and inversely related to the age of the child.[13] Patients with blood pressures between the 90th and 95th percentiles should be followed closely due to the high likelihood of the development of overt hypertension. If a patient is found to have persistent BP values above the 95th percentile, he/she must be evaluated further. Further evaluation is also warranted in the presence of risk factors such as history of umbilical lines, recurrent urinary tract infections, diabetes, other cardiovascular diseases, or a significant family history.[1] Routine laboratory tests are often required to evaluate for secondary causes of hypertension.

One of the most common causes of childhood hypertension is renovascular disease. Patients most likely to have renovascular disease are young children with severe hypertension. Renal disease screening includes urinalysis to check for hematuria and proteinuria. Renal anatomy can be evaluated with renal ultrasonography.[13] The development of renovascular hypertension is linked to the renin-angiotensin-aldosterone system.[25] An elevated plasma renin level can be used to confirm renovascular disease as the cause of the child's hypertension.[26] Renal angiography is the gold standard, but the difficulty in performing this test in young children has led to the use of other techniques such as the captopril challenge test, digital subtraction angiography, and magnetic resonance arteriography. Bartosh and Aronson recommend using renal arteriography when renovascular hypertension is highly suspected.[13] One advantage of renal arteriography is that it can be followed by balloon angioplasty, if required, during the same procedure. Pheochromocytoma should be ruled out before any invasive procedure is performed due to the possibility of a sympathetic storm. The screening for this rare tumor includes a urinary catecholamine measurement.[1]

Cardiac evaluation is performed to rule out end-organ damage and includes echocardiography to check for left ventricular hypertrophy. Standard electrocardiographs and chest radiographs are insensitive and have been surpassed by the more sensitive and quantifiable echocardiograph.[1] Children demonstrate retinal changes less frequently than adults, but an ophthalmic examination is nevertheless important in the evaluation of pediatric hypertension.[1] Endocrine causes need not be investigated in the initial evaluation of hypertension in children unless signs or symptoms of endocrine disease are present.[6]

The question of when to halt the evaluation and make the diagnosis of essential hypertension is difficult to answer and is at the discretion of the care provider. If the history, physical, or screening laboratory investigations suggest a secondary cause, a thorough evaluation of those causes must be undertaken. Further evaluation can usually be bypassed in an obese patient with a negative medical history, positive family history, normal laboratory results, and negative ultrasounds.[1]

Treatment

Anti-hypertensive agents form a large number of drugs tested by the pharmaceutical industry. The US Food and Drug Administration formed a "Pediatric Priority List" after Congress passed acts to help stimulate research of drugs for use in children. Interestingly, a large number of drugs on this "Pediatric Priority List" are anti-hypertensive medications,[27] further underscoring the importance of hypertension in the pediatric population (Table 2).

A blood pressure reduction below the 95th percentile and a decrease in the long-term effects of persistent hypertension are the goals of hypertension treatment in pediatrics. Treatment of hypertension includes non-pharmacologic and pharmacologic methods.[27] Controversy surrounds when to start a child on pharmacologic treatment, but most physicians choose to begin treatment without medication unless severe hypertension or end-organ damage is present.[1] Pharmacologic treatment is usually reserved for patients with blood pressure values above the 99th percentile. The major non-pharmacologic treatment is weight reduction along with salt restriction, exercise, and smoking cessation. A regimen of dynamic exercise and organized sports should be recommended for all hypertensive patients unless they have severe hypertension. In the case of severe hypertension, exercise should be discouraged only until adequate control of the child's hypertension is achieved.[1] Significant reductions in BP have been observed in obese adolescents with weight loss, and the BP reduction is even greater when the weight loss is combined with regular physical exercise.[28] It is also recommended that pediatric patients with hypertension avoid oral contraceptives, decongestants, cocaine, cigarettes, steroids, and licorice.[29] Non-pharmacologic treatment should be the initial therapy in children with BP above the 90th percentile but less than 99th percentile, in children with risk factors for hypertension.[10] In the case of non-compli-

Table 2

PHARMACOLOGIC TREATMENT OF HYPERTENSION IN CHILDREN

	Drug	Brand Name	Initial Dose	Maximum Dose	Side Effects
Diuretics	Furosemide	Lasix Delone Diaqua Furocot Lo-Aqua	1–2 mg/kg/dose-PO 1 mg/kg/dose-IV	6 mg/kg/dose Q 6 hrs-PO 6 mg/kg/dose Q 6–12 hrs IV	Hypokalemia Hypercalciuria Dehydration Hyperuricemia Hyperglycemia
	Bumetanide Hydrochlorothiazide	Bumex/Burinex Esidrix Aquazide-H Diaqua Ezide	0.015–0.1 mg/kg/dose Q 6–26 hrs PO/IV/IM 1 mg/kg/day	10 mg per day 2 mg/kg/day	Same as Furosemide Hypokalemia Hyperlipidemia Dehydration Hyperuricemia, Hyperglycemia
	Metolazone	Mykrox Zaroxolyn	0.1 mg/kg/d	3 mg/kg/d	Same as hydrochlorothiazide
	Spironolactone	Aldactone Spirono	1.5 mg/kg/day	3.5 mg/kg/day	Hyperkalemia
ACEI	Captopril	Capoten	1.5 mg/kg/day	6 mg/kd/day	Rash, Neutropenia, Hyperkalemia, Cough
	Enalapril	Vasotec	0.08 mg/kg/day (up to 5 mg)	40 mg/d (this dose not studied in children)	Same as Captopril
	Lisinopril	Prinivil Zestril	2.5 mg/d	20 mg/d	Same as Captopril
Calcium channel blockers	Nifedipine	Adalat Procardia Nifedical	0.25 mg/kg/d	3 mg/kg/d	Tachycardia Flushing Headache, Hypotension
	Amlodipine	Norvasc	0.1 mg/kg/d	20 mg/d	Same as Nifedipine
	Isradipine	DynaCirc			Same as Nifedipine
Beta-blockers	Propanolol	Betachron Inderal Pronol	1 mg/kg/day	8 mg/kg/day	Bradycardia Bronchospasm Nightmares, Fatigue
	Atenolol	Tenormin Senormin	1 mg/kg/dose QD	2 mg/kg/dose	Same as Propanolol
	Labetalol	Normodyne Trandate	4 mg/day	40 mg/day	Alopecia Dizziness Headaches

ance with non-pharmacologic treatment or treatment failure, medications should be initiated. Most children with secondary hypertension will need pharmacologic treatment, and therapy should be aimed at the cause of the hypertension.[27] Several medications can be used in the treatment of pediatric hypertension, which include diuretics, angiotensin-converting enzyme inhibitors (ACEI), calcium channel blockers (CCB), and beta-blockers.[13]

Diuretics, available in several forms such as thiazide, thiazide-

like, loop, and potassium-sparing, are most effective in patients with renal disease. They decrease blood volume and peripheral vascular resistance, and thereby reduce systemic blood pressure.[6] Loop diuretics have their action on the Na-K-Cl co-transporter in the ascending loop of Henle and are useful in patients with less than 50% of their renal function remaining.[1,6] They are less effective in hypoalbuminemia, which is usually associated with nephrotic syndrome or liver disease, because the drugs are bound to protein. Hypokalemic alkalosis, hypercalciuria, nephrocalcinosis, and ototoxicity are potential side effects of loop diuretics. Thiazides prevent sodium transport in the distal tubule by blocking the Na-Cl transporter and provide a less vigorous and more sustained diuresis than loop diuretics. Side effects of thiazides consist of hyponatremia, hypokalemic alkalosis, glucose intolerance, and adverse lipid profile changes.[1] Potassium-sparing diuretics are useful when hyperaldosteronism is present.[6] They prevent the effects of aldosterone and therefore block the reabsorption of sodium in the collecting duct. They provide a weak diuresis but prevent the loss of potassium.[1]

Angiotensin-converting enzyme inhibitors are effective in reducing BP and carry the added advantage of positive effects on cardiac function, peripheral vasculature, and renal function.[30] They prevent the formation of angiotensin II and its potent vasoconstricting effects.[6] These agents also allow an increase in vasodilatory kinins by blocking the action of kininase II. ACEI are most useful in renin-mediated hypertension such as that caused by reflux nephropathy, chronic glomerulonephritis, and renovascular disease. This class of drugs should not be used in the presence of bilateral renal artery stenosis and should be used with great caution in patients with moderate renal failure as hyperkalemia and acute renal failure may result.[1,31] It is also known to be teratogenic, resulting in fetal anuria, calvarial defects, renal development failure, and fetal death[1,10] and should therefore, be avoided in sexually active adolescent females.

Calcium channel blockers inhibit vasoconstriction by reducing calcium movement into vascular smooth muscle. The dihydropyridine class of CCB is the most widely used, because it is the most selective for arteriolar smooth muscle.[1] CCBs are metabolized by the liver and so can be used in the event of renal failure. Headache, gastrointestinal upset, tachycardia, tremor, peripheral edema, and flushing are potential side effects, but are relatively uncommon.[6] The ability of CCBs to reduce afferent arteriolar constriction makes them useful following renal transplant.[32] Due to their few side effects and good safety and efficacy profiles, these drugs are useful in hypertensive emergencies and chronic hypertensive therapy.[1]

Beta-blockers have an extensive list of side effects including bradycardia, syncope, cardiac failure, central nervous system depression, bronchoconstriction, hypoglycemia, and altered serum lipid profile. By blocking beta-receptors, this class of drugs decreases cardiac output along with peripheral vascular resistance.[1] Short-acting beta-blockers are particularly effective in neonatal hypertension. Labetalol has more potent beta-blocking than alpha-blocking effects and is useful in pediatric hypertensive emergencies.[6]

Surgery has a role in some forms of hypertension. In the case of renal artery stenosis, balloon angioplasty or operative bypass may be necessary. This may help to preserve the function of the affected kidney while correcting hypertension. Partial or complete nephrectomy may be needed if segmental renal infarct, unilateral renal hypoplasia, or chronic obstruction is present. Pheochromocytoma is also an indication for surgery. However, medications should be used to block the tumor before surgery is performed.[1]

Conclusions

Pediatric hypertension is a serious disease that should be neither overlooked nor ignored. Guidelines for defining pediatric hypertension were set forth by the task force and last updated in 1996. As in adults, BP in children, especially in those with a family history of hypertension or in those with known risk factors for hypertension, should be measured routinely and accurately. A child with elevated BP must be evaluated for persistent hypertension. Such evaluations can be complex and expensive and should be individualized to the specific patient. Once a cause for the hypertension is found, appropriate treatment should be instituted immediately. By recognizing the signs of this disease in its early stages, hypertension can be effectively managed in children by their primary care providers.

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