Hypertension in Children and Adolescents

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Education Gap

Hypertension in children and adolescents is often underdiagnosed. Blood pressure should be assessed at every medical encounter in children aged 3 years and older, as well as high-risk children younger than 3 years. Pharmacologic therapy is safe and effective for controlling blood pressure and preventing end-organ changes in this population.

Objectives

After completing this article, readers should be able to:

1. Recognize and properly classify hypertension in children and adolescents.
2. Develop a differential diagnosis and diagnostic approach for evaluation of hypertension, based on signs and symptoms.
3. Initiate a discussion with patients and their families on the nonpharmacologic management of hypertension.
4. Discuss the classes of antihypertensive medications used in children and adolescents.

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ABBREVIATIONS

ABPM	ambulatory blood pressure monitoring
ACE	angiotensin-converting enzyme
ADE	adverse drug event
ARB	angiotensin receptor blocker
CCB	calcium channel blocker
CT	computed tomographic
LV	left ventricular
MR	magnetic resonance

CASE STUDY

Danielle is a 16-year-old who presents to your office for a routine health maintenance visit. She has generally been feeling well, except for occasional headaches. They do not localize to a specific location, and they occur weekly and resolve spontaneously. They are not associated with any other neurological symptoms. Her past medical history is unremarkable. She is not taking any medications. Her family history is remarkable for hypertension in both the maternal and paternal grandparents. The review of systems has yielded otherwise negative findings.

The physical examination showed a height at the 25th percentile and a weight in the 75th percentile. Initial blood pressure obtained by using an automated oscillometric device was 154/82 mm Hg. At examination, she was well appearing and in no distress. Her physical examination findings were normal, except for a dark, velvety discoloration on her neck. A manual auscultatory blood pressure obtained at the end of the physical examination with the appropriately sized cuff and with the patient sitting was 134/78 mm Hg.

INTRODUCTION

Most data indicate that average pediatric blood pressure levels, as well as the prevalence of hypertension in the United States and the Western world, have increased markedly over the past several decades. (1) Although variable, studies suggest that the prevalence of hypertension in the United States now ranges from 5% to 20%. Lifestyle factors, including physical inactivity, increased caloric intake, high salt intake, and subsequent obesity, are thought to be primarily responsible. (1) In addition, hypertension in children is often underdiagnosed. (2) However, there is controversy related to the utility of screening for increased blood pressures in asymptomatic children and adolescents, as the US Preventive Services Task Force determined that there is insufficient evidence "to assess the balance of benefits and harms" of screening for hypertension to prevent cardiovascular disease in this population. (3) A recent review of hypertension in the journal *Pediatrics* refutes this conclusion and highlights the importance of screening. (4) Specifically, studies show that end-organ changes such as left ventricular (LV) hypertrophy and vascular remodeling seen in adult patients with hypertension, which portend increased future cardiovascular risk, are also noted in children and adolescents. (5) For this reason, it is imperative that primary care clinicians properly recognize, evaluate, and treat children and adolescents with hypertension.

DEFINITION OF HYPERTENSION

The "Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents" (hereafter the "Fourth Report") defines systolic and diastolic blood pressure levels according to the 50th, 90th, 95th, and 99th percentiles on the basis of the patient's age, height percentiles, and sex. (6) Blood pressures can be classified on the basis of both systolic and diastolic percentiles (Table 1). Blood pressure measurements below the 90th percentile are normal. If either the systolic or diastolic blood pressure is above the 90th percentile, prehypertension or hypertension is present. Prehypertension is defined as a blood pressure at or above the 90th percentile but less than the 95th percentile. In addition, if the blood pressure exceeds 120/80 mm Hg in an adolescent and is less than the 95th percentile, the blood pressure is consistent with prehypertension. Hypertension is present when measurements are at or above the 95th percentile. Specifically, stage 1 hypertension is classified as a blood pressure between the 95th to 99th percentile plus 5 mm Hg, and stage 2 hypertension is classified as a blood pressure above the 99th percentile plus 5 mm Hg. Because of the dependence of blood pressure on age and height in the pediatric patient, the complexity of the tables used to define pediatric hypertension has been cited as one of the reasons for the poor recognition of pediatric hypertension. (2) Use of the electronic medical record to highlight abnormal values may improve recognition of increased blood pressures in this population.

BLOOD PRESSURE MEASUREMENT

The "Fourth Report" suggests that all children over 3 years of age seen in the medical setting should have their blood pressure measured during office visits. (6) In addition, select patients younger than 3 years who have specific medical conditions should also have their blood pressure measured (Figure). Accurate assessment of blood pressure is challenging in children because readings vary substantially, depending on patient cooperation, cuff size, patient positioning, and type of blood pressure device used. Although oscillometric devices are convenient, use of a manual cuff with auscultation is the recommended method for measuring blood pressure for several reasons, except in special circumstances, such as in the intensive care setting, owing to the need for frequent monitoring. First, normative data contained within the "Fourth Report" were obtained by using auscultatory measurements. Second, oscillometric devices may be less accurate, owing to the need for frequent calibration. Finally, oscillometric devices are used to measure mean arterial pressure by assessing the magnitude of oscillations caused by changes in blood flow through the blood vessel. Systolic and diastolic blood pressures are then calculated by using proprietary software that is not subject to independent validation. Although the "Fourth Report" suggests that the mean of several measurements obtained with an oscillometric device can be used for comparison with the blood pressure tables, any blood pressure reading above the 90th percentile obtained with an oscillometric device must be repeated by using auscultation. Finally, correct assessment of blood pressure in children is also dependent on the selection of a cuff that is appropriate for the size of the child's arm. The recommended dimensions for blood pressure cuffs are presented in Table 2.

The diagnosis of hypertension requires confirmation of increased readings at three or more separate office visits, and the appropriate timing of those visits is listed in Table 1, on the basis of the staging of the blood pressures (Table 1). The term "white-coat hypertension" is applied to patients who demonstrate normal blood pressure readings outside the medical setting but have office-based blood pressures

TABLE 1. **Classification of Hypertension in Children**

CLASSIFICATION	SBP OR DBP PERCENTILE	FOLLOW-UP
Prehypertension	90th to <95th percentile or, if BP exceeds 120/80 mm Hg, to <95th percentile	Recheck in 6 mo and consider school or home BP monitoring
Stage 1 hypertension	95th to 99th percentile plus 5 mm Hg	Evaluate within 1 mo
Stage 2 hypertension	>99th percentile plus 5 mm Hg	Evaluate within 1 wk or immediately if symptomatic
White-coat hypertension	BP >95th percentile in the medical setting but normal outside the medical setting	Consider ABPM, as well as school or home BP monitoring
Masked hypertension	BP <95th percentile in the medical setting but >95th outside the medical setting	Consider ABPM in high-risk populations (ie, chronic kidney disease and diabetes)

ABPM=ambulatory blood pressure monitoring, BP=blood pressure, DBP=diastolic blood pressure, SBP=systolic blood pressure.
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consistently above the 95th percentile (Table 1). This conditioned response to the medical setting may be confirmed by following blood pressures at school or at home.

CAUSES AND DIFFERENTIAL DIAGNOSIS OF HYPERTENSION

The causes of hypertension based on age are listed in Table 3. In general, the more severe the increase in blood pressure and the younger the patient, the more likely a secondary cause will be identified. Regardless of age, most identifiable causes of hypertension in children are due to renal parenchymal disease, including renal scarring secondary to pyelonephritis or reflux nephropathy and chronic glomerulonephritis. Chronic glomerulonephritides often associated with hypertension include focal-segmental glomerulosclerosis, membranoproliferative glomerulonephritis, and immunoglobulin A nephropathy. Other renal diseases associated with hypertension include polycystic kidney disease and obstructive uropathy. Renovascular disease is the second most common cause of identifiable hypertension. The most common of these is fibromuscular dysplasia, involving the medial layer of the renal artery. Other syndromes associated with renovascular disease include neurofibromatosis and Williams syndrome. Renal tumors such as Wilms tumor can also lead to extrinsic compression of the renal artery and development of renovascular hypertension. Endocrine causes are rare in the pediatric population but are usually treatable. Therefore, hyperthyroidism, hyperparathyroidism, Cushing syndrome, and other adrenal pathologic processes should be considered when evaluating these patients. Pheochromocytomas are rare in all age groups and account for less than 1% of identifiable causes in children. Iatrogenic hypertension is also an important consideration, particularly in the adolescent population. A number of medications are associated with clinically significant increases in blood pressure, including oral contraceptive pills, sympathomimetic agents, and glucocorticoids. A more complete list of medications and illicit substances associated with hypertension can be found in the review by Messerli and Frohlich. (7)

Hypertension in the neonatal period deserves special consideration. Similar to older children, in neonates, renovascular and renal parenchymal diseases are important causes of hypertension. In addition to renal artery stenosis, renovascular causes specific to the neonatal period include

Children <3 Years Old Who Should Have Their Blood Pressure Assessed

History of prematurity or very low birth weight
Congenital heart disease
Known renal or urologic malformations
Solid-organ transplant
Malignancy or bone marrow transplant
Treatment with medications known to raise blood pressure
Systemic illnesses associated with increased blood pressure (ie, tuberous sclerosis)

Figure. Indications for assessing blood pressure in children younger than 3 years. Adapted with permission from National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics.* 2004;114:555–576.

TABLE 2. **Suggested Dimensions for Blood Pressure Cuffs in Children**

AGE	WIDTH, cm	LENGTH, cm	MAXIMUM ARM CIRCUMFERENCE, cm
Newborn	4	8	10
Infant	6	12	15
Child	9	18	22
Small Adult	10	24	26
Adult	13	30	34
Large Adult	16	38	44

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the development of arterial thrombi associated with placement of umbilical artery catheters. Depending on the study, the rates of thrombus formation after umbilical artery catheter placement range from 25% to 80%. Hypertension in these patients is thought to develop as a result of embolization of thrombi to the renal vasculature, leading to infarction and increased renin secretion. A second cause of renovascular hypertension specific to the neonatal period is renal vein thrombosis, which typically appears with hypertension, gross hematuria, and thrombocytopenia at presentation. Infants with diabetic mothers are at higher risk for development of renal vein thrombosis. Coarctation of the aorta is also an important cause of vascular hypertension early in life, accounting for 30% of hypertension in the first year of life. Congenital renal parenchymal diseases are the next most common group of causes in the neonatal period—specifically, autosomal recessive polycystic kidney disease and renal obstruction. Hypertension associated with bronchopulmonary dysplasia is an important consideration in the premature infant. Interestingly, in a study of 65 infants discharged from the neonatal intensive care unit, the prevalence of hypertension in infants with bronchopulmonary dysplasia was 43%, compared to 4.5% of infants without bronchopulmonary dysplasia. Although the etiologic origins are unclear, hypoxemia has been cited as a possible cause. Finally, iatrogenic causes are another category of hypertension diagnoses that include substances such as dexamethasone, caffeine, and other adrenergic agents.

Finally, the increasing prevalence of increased body weight and obesity has been associated with an increase in the prevalence of primary or essential hypertension in children and adolescents. Dietary and lifestyle factors such as increased body mass index, carbohydrate intake, and sedentary behavior have all been associated with the development of primary hypertension in children. More importantly, primary hypertension remains a diagnosis of exclusion in children and, as discussed earlier, children do need to be evaluated for secondary causes as discussed herein.

TABLE 3. **Common Causes of Pediatric Hypertension**

AGE GROUP	ETIOLOGIC ORIGIN
Neonates	Renal artery or venous thrombosis Renal artery stenosis Congenital renal abnormalities Coarctation of the aorta Bronchopulmonary dysplasia Iatrogenic origin
30 d to 1 y	Renal artery stenosis Renal parenchymal disease Coarctation of the aorta Iatrogenic origin
1–6 y	Renal parenchymal disease Renal artery stenosis Coarctation of the aorta Endocrinopathies Iatrogenic origin
6–12 y	Renal parenchymal disease Renovascular disease Primary hypertension Coarctation of the aorta Endocrinopathies Iatrogenic origin
12–18 y	Primary hypertension Iatrogenic origin Renal parenchymal disease Endocrinopathies Renal artery stenosis

CLINICAL FEATURES

The "Fourth Report" emphasizes that the evaluation of hypertension should begin with a history and physical examination, since the information gathered during the history and physical examination directs the laboratory evaluation. Symptoms noted during the medical history may be related to the cause of hypertension or directly related to increased blood pressure. In terms of symptoms of hypertension, children often present with nonspecific symptoms, including sleep disturbance, daytime fatigue, inattention at school, headache, and shortness of breath. Signs and symptoms noted during the history and physical examination that may suggest a secondary cause are summarized in Table 4. Briefly, hematuria, edema, polyuria, and nocturia all point to a renal parenchymal disorder. Weight loss, tremors, and excessive sweating may suggest endocrinopathy. Past medical history of prematurity, congenital heart disease, or recurrent urinary tract infections should also be red flags. A careful and complete family history should include a history of essential hypertension, renal disease, endocrine tumors, premature cardiovascular disease, and sudden death.

TABLE 4. **Pertinent Findings on History, Physical Examination, and Relevant Studies in Pediatric Patients with Hypertension**

ETIOLOGIC ORIGIN	HISTORY	PHYSICAL EXAMINATION FINDING	STUDIES
Renal parenchymal disease	Swelling Gross hematuria Urinary tract infections Polyuria Nocturia History of oligohydramnios Failure to thrive Muscle weakness Family history of renal disease	Edema Short stature Palpable mass Pallor	Complete blood cell count Serum creatinine level Blood urea nitrogen level Electrolyte levels Urinalysis Renal ultrasonography Consider genetic testing for monogenetic forms of hypertension
Renovascular disease	Neonatal history of an umbilical artery catheter	Carotid or abdominal bruit Abdominal mass Café-au-lait spots Adenoma sebaceum Ash leaf spots Neurofibromas	Renal ultrasonography with Doppler Serum renin level Serum aldosterone level CT angiography, MR angiography Angiography
Endocrinopathies	Weight loss Flushing Tremor Heat intolerance Muscle weakness	Acne Moon facies Striae Tachycardia Goiter Hirsutism Virilization	Free thyroxine, thyrotropin Serum renin level Serum aldosterone level Cortisol level Corticotropin Adrenal imaging Plasma and urine steroids
Primary hypertension	Smoking Family history of cardiovascular disease Sedentary behavior Weight gain Daytime fatigue Snoring	Increased body mass index Acanthosis nigricans	Hemoglobin A_{1c} Fasting lipids Polysomnography
Iatrogenic origin	Prior medical history Decongestants Stimulants Immunosuppressants Contraceptive pills		Drug screen
Cardiac origin	History of congenital cardiac disease Shortness of breath	Decreased pulses in lower extremity Leg blood pressure 10 mm Hg lower than arm blood pressure	Echocardiogram

CT=computed tomographic, MR=magnetic resonance.

The physical examination findings in most children with hypertension will be normal. Four extremity blood pressures should be assessed in all patients to evaluate the presence of coarctation of the aorta. Skin examination can demonstrate evidence of systemic disease, including systemic lupus erythematosus, neurofibromatosis, or tuberous sclerosis. Detection of an abdominal mass may suggest hydronephrosis, Wilms tumor, or polycystic kidney disease. An abdominal bruit provides evidence of renovascular disease. A more complete list of physical examination findings associated with hypertension is shown in Table 4.

EVALUATION

The "Fourth Report" recommends that the evaluation of all patients with persistent blood pressure above the 95th percentile should include a complete blood count, urinalysis, serum blood urea nitrogen level, serum creatinine level, electrolyte levels, urine culture, and renal ultrasonography, because renal disorders are common causes of secondary hypertension. (6) Because of the association between hypertension and other cardiovascular comorbidities, including diabetes mellitus and hyperlidipemia, all hypertensive patients, as well as obese patients with prehypertension, should undergo a fasting lipid panel and fasting glucose testing. (6)

Other biochemical and radiologic studies are indicated if the cause of hypertension remains unclear. Plasma renin levels can be used to assess monogenetic forms of hypertension, including Liddle syndrome, glucocorticoid-remediable aldosteronism, and apparent mineralocorticoid excess, in which salt retention and volume expansion often lead to suppression of serum renin levels. Hypokalemia and metabolic alkalosis are also encountered as a result of secondary hyperaldosteronism. To further delineate the type of monogenetic hypertension, urinary steroid profiles or genetic testing can be used in select patients. A high plasma renin level is a specific but not sensitive measure of renovascular disease because 20% of patients with renovascular disease will have a normal renin level. It is also important that plasma renin levels are interpreted on the basis of appropriate age-specific reference ranges and daily sodium intake.

If an endocrinopathy is suspected, performing thyroid studies and obtaining serum aldosterone and plasma steroid levels are indicated. In cases of a pheochromocytoma, 24-hour urine measurement of fractionated metanephrines, epinephrine, and norepinephrine, as well as plasma catecholamines, is suggested. In fact, plasma free metanephrine tests have a high sensitivity of 99% for detection of catecholamine-secreting tumors. However, because of low specificity, these tests can lead to a high rate of false-positive findings. Therefore, these tests should only be used if the primary investigation did not yield a cause.

In recent studies, an association has been detected between increases in serum uric acid levels and primary hypertension. Although the pathologic mechanism has not been elucidated, an increased serum uric acid level may be useful for identification of patients with primary hypertension. Urine drug screening and polysomnography are also useful in targeted populations on the basis of information obtained during the history.

In terms of imaging, intra-arterial digital subtraction angiography and renal vein renin measurements are the standard of reference for evaluation of the renal vasculature. However, these techniques are invasive and require technical skill not available at all centers. Other imaging techniques have limitations, and no consensus is available on alternative approaches to angiography. Renal ultrasonography with Doppler, magnetic resonance (MR) angiography, radionuclide renal scans, and computed tomographic (CT) angiography have been used as screening tests for renovascular disease but may not demonstrate stenoses in the segmental renal arteries.

Another important tool for evaluation of increased blood pressure in children and adolescents is ambulatory blood pressure monitoring (ABPM). (8) ABPM involves placement of a portable blood pressure device that is worn by a patient for 24 hours. Interpretation generally requires a minimum of 1 reading per hour, with at least 40 readings obtained over the 24-hour period. This technique allows for determination of mean blood pressure over 24 hours, during waking hours, and while asleep. It also allows the clinician to determine the amount of time blood pressures exceed normal limits, termed *blood pressure load*. Normative values for interpretation of ABPM are available. (8) This technique is especially helpful in assessing patients with white-coat hypertension, as well as assessing the response to antihypertensive therapy. It is also recognized that high-risk populations, including patients with diabetes and chronic kidney disease, may have normal office-based blood pressures but demonstrate clinically significant increases outside of the office. Termed *masked hypertension,* these increases are associated with development of end-organ damage.

Finally, evaluation of hypertension also includes assessment of end-organ changes. LV hypertrophy is a well-recognized complication of hypertension in children and adults. LV hypertrophy is also associated with increased risk of cardiovascular morbidity and mortality in adult patients with hypertension. Therefore, the use of echocardiography to assess LV mass is the primary assessment tool for end-organ changes in children. The presence of LV hypertrophy is an indication for initiation of antihypertensive therapy in patients with borderline blood pressures or for intensification of antihypertensive therapy in patients currently undergoing therapy. If LV hypertrophy is present, echocardiograms should be performed every 6 months to assess progression. Other tools used for assessment of end-organ changes, including carotid intimal-medial thickness and pulse wave velocity, are currently not recommended for routine clinical use but may be used in the future assessment of end-organ changes. Retinal vascular narrowing has also been associated with hypertension and may portend increased cardiovascular risk. Proper examination requires referral to an experienced ophthalmologist. Hypertensive retinopathy is graded from I to IV. There is no specific treatment, but grades I and II are generally reversible in children when the blood pressure is lowered.

MANAGEMENT OF HYPERTENSION

Nonpharmacologic Therapy

Healthy lifestyle changes are the primary treatment tool for initial management of prehypertension and hypertension. Dietary modifications, enhancing physical activity, minimizing sedentary behavior, and smoking cessation should be addressed with all patients. Dietary modifications are often more successful when using a team approach, which includes a dietitian. Recommendations include reducing sodium intake to 2 to 3 g per day, reducing cholesterol intake, and reducing intake of sweetened drinks. By using a family-based approach, patients should be instructed to limit portion sizes and eliminate skipping meals. Although sodium restriction is difficult in children, families should be advised to avoid processed foods, refrain from adding additional salt to foods, and follow and account for the sodium content on food labels. A meta-analysis involving 966 children showed that control of dietary sodium intake was associated with reductions in both systolic and diastolic blood pressure. (9)

Physical activity in these patients should also be encouraged. A meta-analysis involving children and adolescents demonstrated a 1% reduction in systolic blood pressure and a 3% reduction in diastolic blood pressure with exercise. (10) Current recommendations suggest 60 minutes of daily physical activity, with a reduction in sedentary behavior to 2 hours daily. Both resistance training and aerobic activity are recommended for the treatment of hypertension in youth. However, there is concern that blood pressure changes that occur during exercise can cause harm. In dynamic exercise, an increase in systolic blood pressure and an associated increase in mean arterial pressure are noted. In contrast, diastolic blood pressure and total peripheral resistance decrease. During static exercise, such as weight lifting, systolic blood pressure, diastolic blood pressure, and mean arterial pressure increase substantially, whereas total peripheral resistance remains unchanged. The increase in diastolic blood pressure is particularly concerning, although some evidence suggests minimal risk with static exercise. For this reason, pediatric athletes with stage 2 hypertension should be temporarily restricted from participating in sports until the blood pressure is controlled. (11) A history of exercise-associated chest pain or trouble breathing, as well as a family history of sudden death, may warrant additional investigation before an exercise regimen is initiated. (11)

Pharmacologic Therapy

Timing of the initiation of pharmacologic therapy is based on several factors. Pharmacologic therapy should be started immediately in patients with confirmed hypertension and evidence of end-organ damage, diabetes, chronic kidney disease, clinically significant symptoms, and secondary hypertension. (6) In patients with persistent hypertension despite implementation of nonpharmacologic therapy, initiation of pharmacologic therapy depends on the severity of the blood pressure increases. In patients with asymptomatic stage 2 hypertension, pharmacologic therapy should be initiated early, in the hopes of preventing the development of end-organ changes.

Although some antihypertensives are US Food and Drug Administration approved for children, data on pharmacologic treatment in children and in adolescents are limited. Similar to adults, the initial drug choice should target the underlying etiologic origins of the patient's hypertension when possible. For example, in a patient with fluid overload, a diuretic would be the ideal choice. In other scenarios, choosing an agent that has established pediatric labeling or indications is best. The trend in the treatment of hypertension in children has been the use of angiotensin-converting enzyme (ACE) inhibitors, long-acting calcium channel blockers (CCBs), and angiotensin receptor blockers (ARBs). The goal of therapy is lowering the blood pressure to the 90th percentile for age, height, and sex, with minimal side effects. Only physicians experienced with monitoring these medications should prescribe them. The specific classes of antihypertensive agents are discussed herein (Table 5).

ACE Inhibitors

ACE inhibitors block the conversion of angiotensin I to angiotensin II and the degradation of the vasodilatory molecule bradykinin through the blockade of the kinin-kallikrein system. In addition to lowering blood pressure, ACE inhibitors have also been found to demonstrate cardio- and renoprotective properties. ACE inhibitors have been shown to slow progression of chronic kidney disease in diabetic patients, with or without hypertension. ACE inhibitors are also considered first-line agents in patients with congestive heart failure and LV dysfunction because ACE inhibitors promote cardiac remodeling and have anti-inflammatory

TABLE 5. **Pharmacologic Agents for Pediatric Hypertension**

CLASS	AGENT	DOSE
Angiotensin-converting enzyme inhibitor	Captopril	Initial: 0.3–0.5 mg/kg per dose (tid to qid) Maximum: 6 mg/kg per day
	Enalapril	Initial: 0.08 mg/kg per day (qd to bid) Maximum: 0.6 mg/kg per day to 40 mg/day
	Lisinopril (>6 y of age)	Initial: 0.07 mg/kg per day (qd) Maximum: 0.6 mg/kg per day to 40 mg/day
Angiotensin receptor blocker	Irbesartan	6–12 y, 75–150 mg/day
	Losartan	Initial: 0.7 mg/kg per day Maximum: 1.4 mg/kg per day to 100 mg/day
Calcium channel blocker	Amlodipine	Children 6–17 y, 2.5–5.0 mg once daily
	Felodipine	Initial: 2.5 mg/day Maximum: 10 mg/day
	Isradipine	Initial: 0.15–0.20 mg/kg per day (tid to qid) Maximum: 0.8 mg/kg per day up to 20 mg/day
	Nifedipine XR	Initial: 0.25 to 0.5 mg/kg per day (qd to bid) Maximum: 3 mg/kg per day up to 120 mg/day
β-Blocker	Atenolol	Initial: 0.5 to 1 mg/kg per dose (qd to bid) Maximum: 2 mg/kg per day up to 100 mg/day
	Metoprolol	Initial: 1–2 mg/kg per day (bid) Maximum: 6 mg/kg per day to 200 mg/day
	Propranolol	Initial: 1–2 mg/kg per day (bid to tid) Maximum: 4 mg/kg per day to 640 mg/day
	Labetalol	Initial: 1–3 mg/kg per day (bid) Maximum: 10–12 mg/kg per day up to 1,200 mg/day
Diuretic	Hydrochlorothiazide	Initial: 1 mg/kg per day (qd) Maximum: 3 mg/kg per day up to 50 mg
	Furosemide	Initial: 0.5–2.0 mg/kg per day (qd to bid) Maximum: 6 mg/kg per day
	Amiloride	Initial: 0.4–0.6 mg/kg per day (qd) Maximum: 20 mg/day
	Spironolactone	Initial: 1 mg/kg per day (qd to bid) Maximum: 3.3 mg/kg per day up to 100 mg/day
	Triamterene	Initial: 1–2 mg/kg per day (bid) Maximum: 3–4 mg/kg per day to 300 mg/day
Central α-blocker	Clonidine	Children >12 y Initial: 0.2 mg/day (bid) Maximum: 2.4 mg/day
Vasodilator	Hydralazine	Initial: 0.75 mg/kg per day (qid) Maximum: 7.5 mg/kg per day up to 200 mg/day
	Minoxidil	Children <12 y Initial: 0.2 mg/kg per day (qd to tid) Maximum: 50 mg/day Children >12 y Initial: 5 mg/kg per day (qd to tid) Maximum: 100 mg/day

bid=twice daily, qd=once daily, qid=four times daily, tid=three times daily.

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properties. These medications are generally well tolerated, and the pharmacodynamic properties in children and adolescents seem to be similar to those in adults.

One of the more common adverse drug events (ADEs) associated with ACE inhibitors is a dry cough, which was noted in less than 3% of patients in a pediatric trial of enalapril. Hyperkalemia, neutropenia, thrombocytopenia, angioedema, and decreased renal function have been reported in children and adolescents. Renal impairment is secondary to dilation of the efferent arteriole and a decrease in glomerular pressure. Although reversible after discontinuation of the medication, renal impairment is usually associated with volume depletion or concomitant use of vasoactive medications, such as nonsteroidal anti-inflammatory agents. Laboratory studies, including a complete blood cell count, electrolyte levels, serum creatinine level, and blood urea nitrogen level, should be monitored shortly after initiation of an ACE inhibitor or after changes in dosage. In patients undergoing stable therapy, performing laboratory monitoring every 3 to 6 months is appropriate. The use of ACE inhibitors is contraindicated in a patient with bilateral renal artery stenosis, hyperkalemia, and pregnancy. ACE inhibitors should be avoided in all trimesters of pregnancy because of the risk of cardiac defects, as well as renal defects that lead to oligohydramnios and pulmonary hypoplasia.

Captopril has been used extensively in neonates and is effective for both short-term and long-term blood pressure control. However, its short half-life limits its use because multiple daily doses are required. Enalapril is associated with fewer ADEs than captopril and is available in extemporaneous formulations for small children. Lisinopril and ramipril have been found to be safe and effective in children and adolescents.

Angiotensin Receptor Blockers

ARBs block the binding of angiotensin II to type 1 angiotensin II receptors. Blockade of the angiotensin II receptor by ARBs does not interfere with the kinin-kallikrein system, so adverse effects such as dry cough are not observed. However, the risk of renal impairment and contraindications in pregnancy discussed earlier are similar, so periodic laboratory monitoring is required.

Losartan has been shown to lower blood pressure in children younger than 18 years, with minimal adverse events. Irbesartan safety and effectiveness have been studied in children 6 to 16 years of age.

Calcium Channel Blockers

CCBs lower blood pressure by blocking the influx of calcium into smooth muscle, resulting in arteriole dilatation and lowered peripheral resistance. There are two primary classes of CCB with the dihydropyridines (nifedipine, isradipine, and amlodipine) being used most commonly in pediatrics. The nondihydropyridines (verapamil and diltiazem) are rarely used because of both vascular and cardiac effects. CCBs are particularly useful in patients in whom use of an ACE inhibitor or ARB is contraindicated. Because of reports of sudden death, CCB agents should be avoided in infants.

The most commonly prescribed CCB for pediatric hypertension is amlodipine. Dosage modification is not required in patients with altered renal function. ADEs are infrequent, are dose related, and include peripheral edema, flushing, headache, gingival hyperplasia, and orthostatic hypotension. Short-acting CCBs, including isradipine and nifedipine, are often used in the setting of hypertensive urgency for rapid lowering of blood pressure. However, the use of sublingual nifedipine is controversial because it is associated with cerebrovascular and cardiovascular events in adults.

β-Blockers

β-blockers decrease blood pressure through several different mechanisms, including inhibition of renin secretion, reduction of peripheral resistance, lowering of cardiac output, and decreasing plasma volume. β-blockers are classified as cardioselective antagonists, which have a higher affinity for $\beta 1$ receptors in the heart, or nonselective antagonists, which act on $\beta 1$ receptors, as well as $\beta 2$ receptors in the bronchial tree. In addition, agents in this class have substantial differences in pharmacologic properties, including lipid solubility, intrinsic sympathomimetic activity, and anti-α-adrenergic antagonism.

β-blockers should be avoided in specific populations. Because of decreased cardiac output and fatigue, β-blockers should be avoided in athletes. β-blockers are also contraindicated in patients with asthma because of potential bronchospasm. In diabetic patients, these agents may mask the symptoms of hypoglycemia, including tachycardia and palpitations. Other ADEs include orthostatic hypotension, fatigue, depression, altered lipid profiles, impotence, and hyperkalemia.

Propranolol is the most widely used β-blocker in children and adolescents, but it is associated with side effects that may affect compliance, as discussed earlier. Atenolol and metoprolol have been studied in adolescents. Labetalol is a β-blocker that also possesses α-blocking activity that does not appear to have the negative effects on lipid profiles and exercise seen with other agents. However, it is not approved by the Food and Drug Administration for use in children.

Diuretics

Diuretics are the first-line treatment for primary hypertension in adults. These agents lower blood pressure by decreasing plasma volume and lowering peripheral resistance. In pediatric patients, diuretics are generally no longer considered first-line therapy because of the availability of newer classes of medications, such as ACE inhibitors and ARBs, but also because of side effects. Diuretics work synergistically with agents such as ACE inhibitors and ARBs, so they are useful in multiple drug regimens. ADEs associated with these medications include metabolic derangements, such as hyperlipidemia and altered glucose metabolism, electrolyte disturbances (hypokalemia, hypomagnesemia), and dehydration.

The classification of diuretics is based on their site of action. Thiazide diuretics inhibit the Na^+-Cl^- cotransporter in the early distal convoluted tubule. The medication must be within the lumen of the renal tubule to exert its effects. Therefore, these agents are generally ineffective in patients with a glomerular filtration rate below 30 mL/min per 1.73 m^2. Loop diuretics act in the ascending loop of Henle and are more potent than thiazide diuretics. The potassium-sparing diuretics (amiloride, triamterene, and spironolactone) are useful in patients who require diuretic therapy, but use is limited by hypokalemia. Amiloride and triamterene are also effective in low-renin forms of hypertension, discussed earlier.

Central α-Agonists

Clonidine is a centrally acting α_2-agonist that stimulates α_2-receptors to lower peripheral resistance and heart rate. This agent is often limited by its ADEs, including dry mouth, sedation, fatigue, and severe rebound hypertension after rapid discontinuation. The use of transdermal clonidine may increase compliance in some patients, since patches are changed weekly.

Vasodilators

The primary agents in this class include hydralazine and minoxidil, which act directly on vascular smooth muscle to reduce vascular wall tension and peripheral vascular resistance. Both agents are effective in the acute setting. However, their side effect profile limits their use in the management of long-term hypertension. Common ADEs include headache, tachycardia, flushing, fluid retention, and palpitations. Hydralazine is associated with a lupus-like syndrome, and minoxidil causes hypertrichosis, which often affects compliance.

LONG-TERM MONITORING

Children with prehypertension should be seen in the medical setting every 6 months to monitor and reinforce the importance of nonpharmacologic therapy. Patients with stage 1 hypertension should be evaluated every 3 to 4 months, once appropriate blood pressure control has been achieved. Initially, patients with stage 2 hypertension should be seen every 2 to 3 weeks, but once the blood pressure stabilizes, every 3 to 4 months will be sufficient. If blood pressure has been controlled for an extended period of time (ie, 12 months), it is not unreasonable to attempt to wean the patient off of antihypertensive therapy. However, close monitoring of blood pressure during this time is necessary. ABPM may assist the clinician in determining if a trial period with the patient not taking antihypertensive therapy is reasonable.

It is well recognized that the complications of hypertension noted in adults are also present in children. Pediatric patients demonstrate alterations in both cardiac and vascular structure at the time of diagnosis. Moreover, these patients have subtle changes in renal function and cerebrovascular reactivity. Hypertension is also associated with poor school performance and learning disabilities. Therefore, prompt recognition and treatment of hypertension in the pediatric population is imperative. Because the prevalence of hypertension is increasing, awareness by pediatricians is essential to improving outcomes in this patient population by recognizing, evaluating, and treating patients with this disorder.

HYPERTENSIVE EMERGENCIES

There is no absolute level of blood pressure that constitutes a hypertensive crisis in childhood or adolescence, but similar to adult values, blood pressures above the cutoff for stage 2 hypertension are typical. Other labels for hypertensive emergencies include hypertensive crisis or hypertensive urgency. Severe hypertension with the presence of life-threatening symptoms or end-organ injury defines a hypertensive emergency, whereas hypertensive urgency is characterized by a similar increase in blood pressure but no evidence of acute target organ injury and less marked symptoms. In contrast to adults, in whom hypertensive emergencies are thought to be secondary to uncontrolled primary hypertension, acute hypertension in children is generally considered secondary to a disorder of the kidney, heart, or endocrine system (Table 6).

One of the primary mechanisms to prevent hypertensive organ injury in response to hypertension is autoregulation. Of these, autoregulation of the cerebral blood flow is the most widely examined. Constant cerebral blood flow is achieved primarily by small arteries and arterioles, which either dilate or constrict under the influence of multiple stimuli, including blood pressure. When blood pressure exceeds the upper limits of the autoregulatory range, the compensatory response of vasoconstriction is not sufficient, and blood flow increases with mean arterial pressure. This leads to endothelial dysfunction and vessel wall edema, which causes central nervous system, renal, and cardiac complications.

Children may present with severe symptoms, or they may be asymptomatic. After confirming that blood pressure has been measured properly, the initial history should focus on symptoms and signs of target-organ damage, as well as possible etiologic origins. Central nervous system findings include retinopathy, encephalopathy, and seizure activity. Additional central nervous system symptoms include hemiplegia and facial palsy. Tachypnea, pulmonary edema, and a new heart murmur are suggestive of congestive heart failure, a common presentation of acute hypertension in infants. Additional signs that may suggest renal disease include peripheral edema, gross hematuria, or change in urine output. An abdominal bruit may suggest renovascular hypertension. Hyperthyroidism is associated with exophthalmos, tremors, and/or hair loss. An abdominal mass can suggest Wilms tumor, neuroblastoma, hydronephrosis, or polycystic kidney disease. Skin lesions such as café-au-lait spots, axillary freckling, or ash leaf spots may suggest neurofibromatosis or tuberous sclerosis. Diminished blood pressure in the lower extremities and decreased, delayed, or absent femoral pulse suggest coarctation of the aorta.

All children should undergo urinalysis to evaluate the presence of hematuria and proteinuria as evidence of glomerular disease. Electrolyte, blood urea nitrogen, and creatinine levels should be obtained to assess renal function. A complete blood cell count can be performed to evaluate chronic illness or evidence of microangiopathic hemolytic anemia. A pregnancy test in adolescent girls should be performed because pre-eclampsia may be present with severe hypertension. A chest radiograph might demonstrate vascular congestion and an enlarged cardiac silhouette. An echocardiogram is useful to assess the presence of LV hypertrophy and/or coarctation, but waiting for the test to be performed should not delay therapy. It is important to conduct a toxicology screening in select patient populations on the basis of the history and physical examination findings. Renal ultrasonography should be performed to evaluate the presence of renal anomalies and renovascular disease. If renovascular disease is suspected, as discussed earlier, CT angiography or MR angiography should be performed after the blood pressure stabilizes. If signs of encephalopathy are present, a CT study of the head should be performed to evaluate the presence of possible intracranial hemorrhage, stroke, cerebral edema, or mass. Additional studies, such as MR imaging of the brain, can be performed while the patient stabilizes. MR imaging will also demonstrate edema of the white matter in the parieto-occipital regions, as seen in posterior reversible leukoencephalopathy. Additional studies may be required, based on the history and physical examination findings.

The patient with a hypertensive emergency should be placed in the intensive care unit for frequent blood pressure measurements and close monitoring of neurological status. Preferably, continuous intra-arterial monitoring should be used for hypertensive emergencies. Frequent automated oscillometric or manual auscultatory readings may be adequate for hypertensive urgencies in some cases. The "Fourth Report" recommends lowering blood pressure by less than 25% in the first 8 hours after presentation, then gradually normalizing blood pressure over the next 26 to 48 hours to prevent complications. Continuous intravenous antihypertensive agents that have been used for treatment include nicardipine, labetalol, and sodium nitroprusside. Intermittent agents that may be helpful include clonidine, hydralazine, isradipine, or enalaprilat (active metabolite of enalapril).

TABLE 6. **Causes of Hypertensive Emergencies Based on Age**

AGE	CAUSE
Infant	Coarctation of the aorta Renal parenchymal disease Renovascular causes
Young child	Renal parenchymal disease Renovascular causes Endocrine causes (eg, thyrotoxicosis) Coarctation of the aorta
School age	Renal parenchymal disease (eg, hemolytic uremic syndrome, Henoch-Schönlein purpura, acute poststreptococcal glomerulonephritis) Renovascular causes Endocrine causes Coarctation of the aorta
Adolescent	Renal parenchymal disease Renovascular causes Endocrine causes Medication and recreational substances

Summary

- On the basis of strong research evidence, numerous studies have demonstrated that the prevalence of hypertension in the pediatric population is increasing, in part related to worsening obesity. (1)
- On the basis of expert opinion, current consensus defines pediatric hypertension on the basis of a mean systolic or diastolic blood pressure measurement by using an appropriately sized cuff equal to or above the 95th percentile, based on the child's age, sex, and height percentile. (6)
- On the basis of expert opinion and current consensus opinion, children 3 years of age and older should have their blood pressure obtained during every health care encounter. (6)
- On the basis of limited research evidence, on confirmation of hypertension, all children should be evaluated to rule out secondary causes of hypertension, with the extent of the evaluation determined by the age of the child and the degree of blood pressure increase. (6)
- On the basis of limited research evidence, athletes with blood pressure consistent with stage 2 hypertension should be withheld from sports participation until the blood pressure is controlled. (11)

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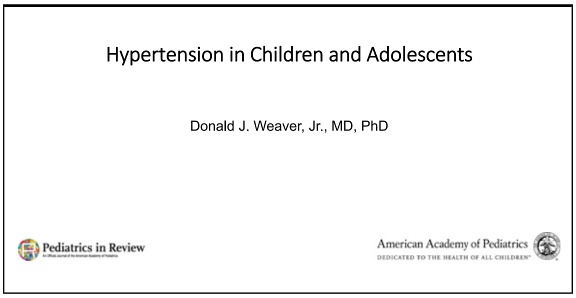

References and Suggested Readings for this article are at http://pedsinreview.aappublications.org/content/38/8/369.

Parent Resources from the AAP at HealthyChildren.org

* High Blood Pressure in Children - https://www.healthychildren.org/English/health-issues/conditions/heart/Pages/High-Blood-Pressure-in-Children.aspx

For a comprehensive library of AAP parent handouts, please go to the *Pediatric Patient Education* site at http://patiented.aap.org.

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1. A 2-year-old boy is seen for the first time at your clinic for a health supervision visit. His family recently moved to town. He was born at 27 weeks' gestation with a birth weight of 1.1 kg. His neonatal course was complicated by neonatal hypoglycemia and apnea of prematurity, for which he required mechanical ventilation in the neonatal intensive care unit. He was discharged from the neonatal intensive care unit at 10 weeks of age with an apnea and bradycardia monitor, which was discontinued 4 weeks after discharge. He has had several hospitalizations for bronchiolitis over the past year. He is currently undergoing occupational and physical therapy for moderate motor delays. At physical examination today, his weight, height, and head circumference are at the 25th percentile, age corrected for prematurity. The rest of his physical examination findings are unremarkable, except for mild motor delay. In addition to this information, which of the following data are the most appropriate to obtain today as part of this patient's health maintenance visit?
   - A. Apnea-monitoring results.
   - B. Blood pressure.
   - C. Glucose level.
   - D. Magnetic resonance (MR) images of the brain.
   - E. Preschool evaluations.
2. A 12-year-old girl is seen for a health supervision visit. Her height and weight are at the 50th percentile, and she has been healthy, without any clinically significant chronic medical conditions. She is an honors student, and she plays sports. Her blood pressure today with an oscillometric device is 136/74 mm Hg, placing her in the category of prehypertension (between the 90th and the 95th percentiles). Which of the following is the most appropriate next step in the care of this patient?
   - A. Ambulatory blood pressure measurement.
   - B. Blood pressure assessment with a manual cuff.
   - C. Echocardiography.
   - D. Hospitalization for full evaluation of hypertension.
   - E. Follow-up visit in 6 months to recheck blood pressure.
3. A 4-year-old girl was found to have a blood pressure of 130/80 mm Hg in 3 separate measurements. Her height is at the 50th percentile for age, and her weight is at the 25th percentile for age. In addition to confirming that the blood pressure was obtained by using a correctly sized cuff, which of the following is the immediate next best step in the evaluation of this patient?
   - A. Blood glucose measurement.
   - B. Computed tomography (CT) of the abdomen.
   - C. Four extremity blood pressures.
   - D. MR imaging of the kidneys.
   - E. Radiography of the chest.
4. You are seeing a 15-year-old boy who has a history of diabetes since 6 years of age. He is being seen today for intermittent headaches. His height is at the 25th percentile, and his weight is at the 50th percentile. His urinalysis findings in the office are normal. His hemoglobin A_{1c} level is mildly increased. His vital signs are in the normal range today. His vision screening result is normal. In addition to recommending that the patient keep a headache diary, which of the following is the most appropriate next step in the evaluation of this patient's chronic intermittent headaches?
   - A. Ambulatory blood pressure monitoring.
   - B. Echocardiography.
   - C. CT of the abdomen.
   - D. Four extremity blood pressures.
   - E. MR imaging of the kidneys.

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5. A 17-year-old boy is seen for a sports preparticipation clearance physical examination. Review of his vital signs shows a blood pressure over the 99th percentile for his height and age. The blood pressure was confirmed by using a manual, appropriately sized cuff, with similar blood pressure readings on 3 separate occasions. He denies intake of any sports supplements, and he is taking no medications. Among the following, which is the most appropriate next step in the care of this patient?

   A. Ambulatory blood pressure measurement.
   B. Hospitalization for full evaluation of hypertension.
   C. Follow-up visit in 6 months to recheck blood pressure.
   D. Referral for consultation with a dietitian.
   E. Restriction from participating in his weight-lifting class at school.

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Hypertension in Children and Adolescents

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