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Leonard G. Feld and Howard Corey  
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# Hypertension in Childhood

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Author Disclosure  
Drs Feld and Corey  
did not disclose any  
financial relationships  
relevant to this  
article. The authors  
discuss all drugs used  
for hypertension,  
although all drugs do  
not have pediatric  
labeling and safety  
information.

**Objectives** After completing this article, readers should be able to:

1. Describe the practical approach to confirming the diagnosis of hypertension.
2. Delineate the differential diagnosis and diagnostic approach for a child who has significant hypertension.
3. Discuss the role of the pediatrician in advising the parents and child/adolescent on the nonpharmacologic approach to treating hypertension.
4. List the primary classes of antihypertensive medications to treat hypertension in childhood.

## Case Study

*David is a 10-year-old boy who complains of frequent headaches. He generally is healthy, but he is overweight and has an anxiety disorder. There is a strong family history of hypertension. On physical examination, the seated blood pressure (BP) using a child-size cuff and an automated noninvasive blood pressure monitor is 140/85 mm Hg. Suspecting hypertension as the cause of the headache, his physician refers David to a pediatric nephrologist for additional investigation.*

*On the initial physical examination, the seated BP reading using an adult-size cuff and a manual aneroid manometer is 135/80 mm Hg. A second reading, taken 15 minutes later, is 122/72 mm Hg. His body mass index (BMI) exceeds the 95th percentile for age. The remainder of the physical examination findings are unremarkable.*

*Subsequently, a 24-hour ambulatory blood pressure monitor (ABPM) reveals that 35% of the daytime readings exceed the 95th percentile for age, sex, and height, confirming the diagnosis of hypertension. Echocardiography reveals mild left ventricular hypertrophy (LVH), but otherwise shows normal results, as do blood chemistries, urinalysis, plasma renin activity, catecholamine measurement, and renal ultrasonography. However, the plasma uric acid concentration is mildly elevated at 6.6 mg/dL (0.39 mmol/L).*

## Introduction

In the 3 decades since the first *Report of the Task Force on Blood Pressure Control in Children*, the guidelines for pediatric hypertension have been clarified, diagnostic evaluation has been refined, and therapeutic options have been expanded. Increasing evidence shows that the presence of hypertension in childhood and adolescence is not benign. There appears to be a good correlation among BMI, hypertension, LVH, and early coronary artery disease in the adolescent. In fact, children whose essential hypertension is untreated may have vascular injury (LVH and increased intima-media thickness of the carotid and femoral arteries) at the time of diagnosis. Because nearly one of every six Americans has or develops hypertension, pediatricians can play an important role in reducing the associated long-term cardiovascular morbidity and mortality through the early identification, evaluation, and treatment of this common disorder.

## Diagnostic Evaluation

The *Fourth Report by the National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents* provides guidelines for the diagnostic

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**Table 1. Recommended Dimensions for Blood Pressure Cuff Bladders**

Age Range	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

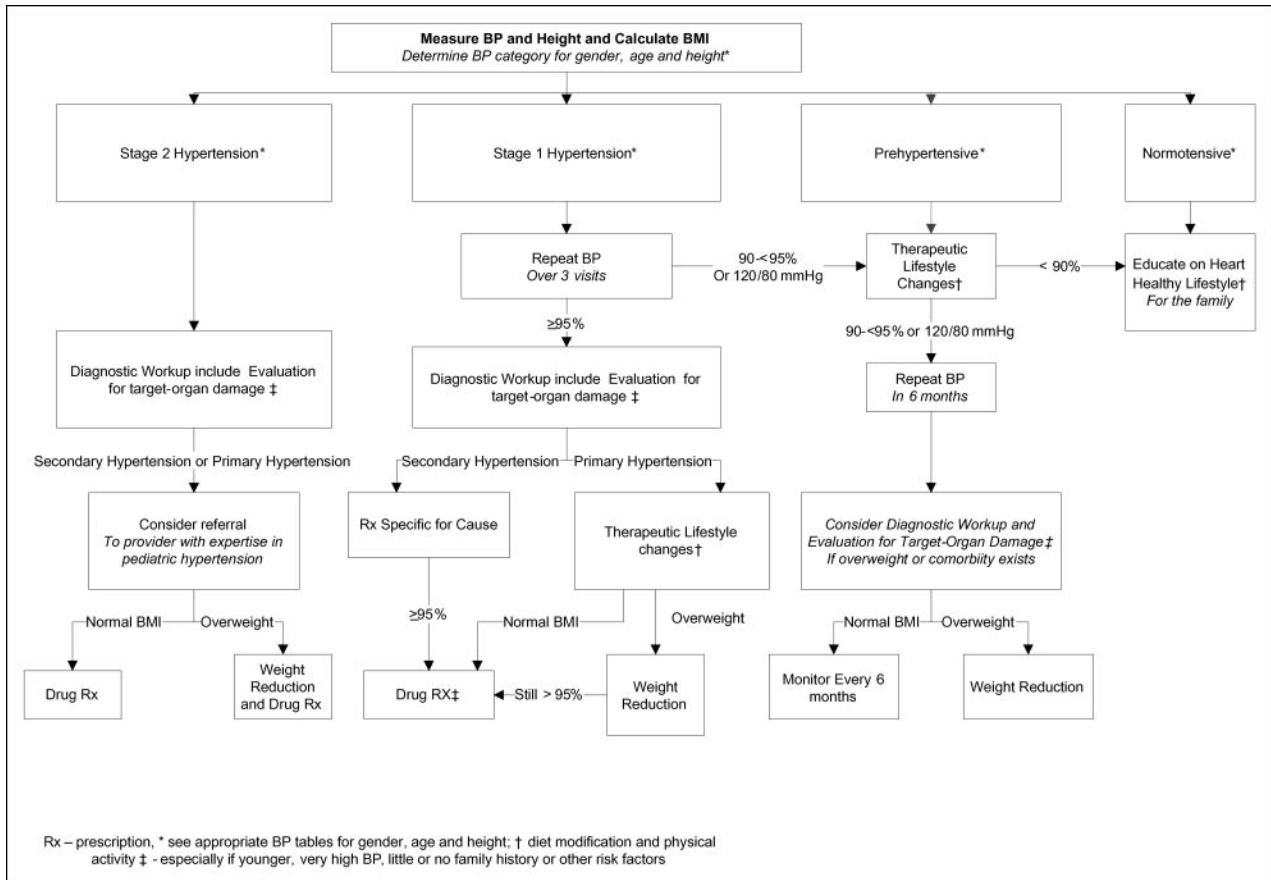
\*Calculated so that the bladder can encircle even the largest arm by at least 80%.

evaluation of the nearly 5% of children who have sustained hypertension. (1) These recommendations can be broken down into a four-step process using the mnemonic COST\*:

1. *Confirm* the diagnosis of hypertension.
2. *Organize* a diagnostic approach.
3. Determine the *Severity* of the hypertension.
4. *Treat* the hypertension effectively. \*Severe hypertension or hypertensive emergencies with significant symptoms of headache, epistaxis, diplopia, seizures, encephalopathy, hemiplegia, lethargy, or somnolence require hospitalization, a more aggressive evaluation, and intravenous antihypertensive therapy.

### Confirm the Diagnosis of Hypertension

Accurate measurement of the BP may be difficult in children because the readings vary significantly with cuff size, patient positioning, clinical setting, equipment used (mercury sphygmomanometer versus oscillometric methods), and training of the observer. Dimensions for appropriate cuff size are presented in Table 1. Hyperten-



**Figure 1. Algorithm for treatment of hypertension.** BP=blood pressure, BMI=body mass index. Reproduced with permission from The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents. *Pediatrics*. 2004;114:555–576.

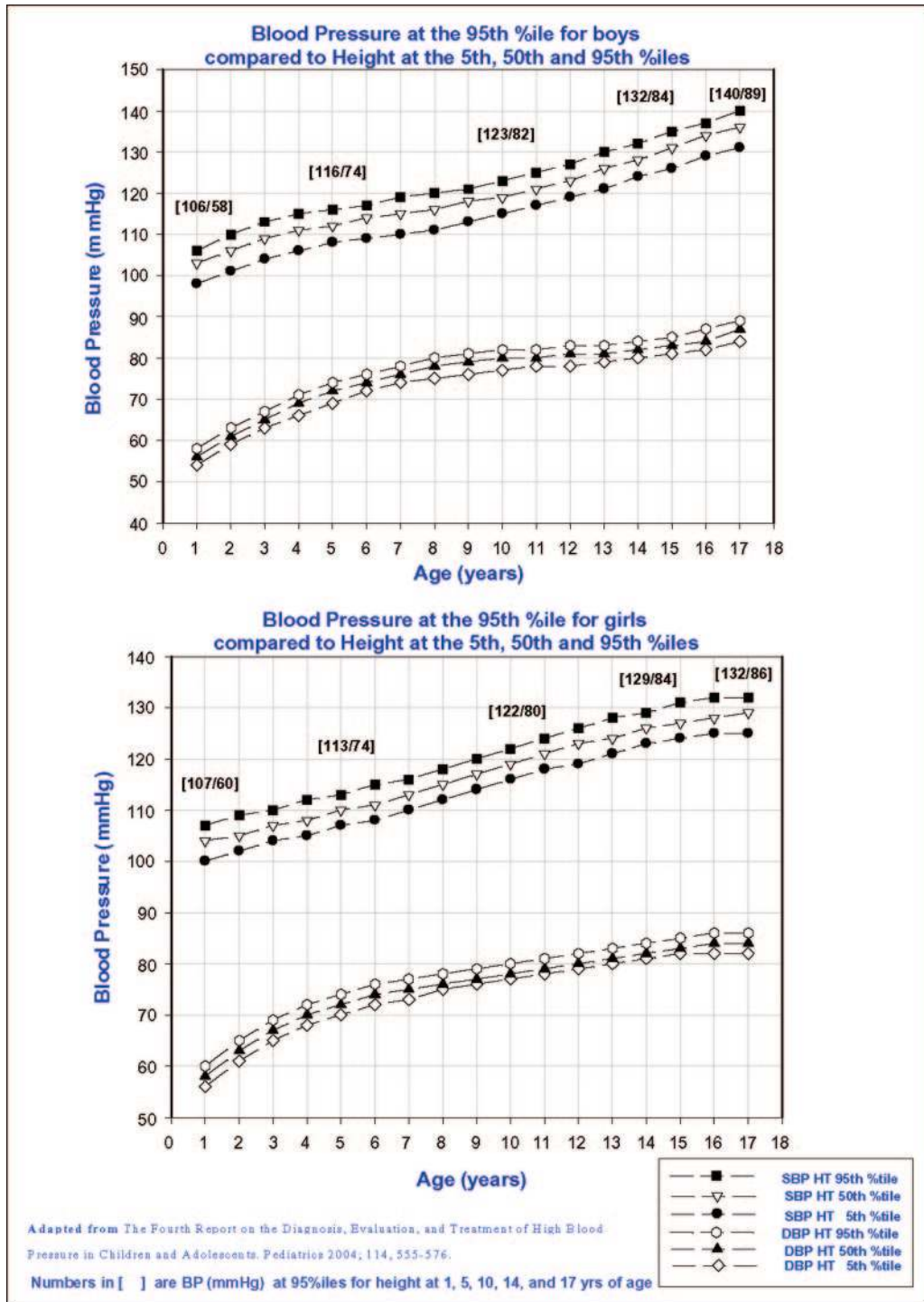


Figure 2. Blood pressure at the 95th percentile for boys and girls at height percentiles. Adapted from The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents. *Pediatrics*. 2004;114:555–576.

sion may be suspected when the BP reading is high for the height, age, and sex of the child.

The diagnosis of hypertension is confirmed when a

high reading is obtained at three or more separate office visits about 1 week apart (Figs. 1 and 2). If BP readings are normal outside of the office, the patient may have

Table 2. Grades of Hypertension in Children

Grade of Hypertension	Definition	Appropriate Next Step
"White-coat" hypertension	BP levels >95th percentile in a physician's office or clinic, but normotensive outside a clinical setting	Readings may be obtained at home with appropriate family training or with the assistance of a school nurse or with the use of ambulatory BP monitoring.
Prehypertension	Average SBP or DBP levels that are $\geq 90$ th percentile but <95th percentile; as with adults, adolescents who have BP levels $\geq 120/80$ mm Hg should be considered prehypertensive	Additional readings may be obtained at home with appropriate family training or with the assistance of a school nurse.
Stage I hypertension	Average SBP or DBP that is $\geq 95$ th percentile	A diagnostic evaluation in a nonurgent, phased approach may be organized.
Stage II hypertension	Average SBP or DBP that is >5 mm Hg higher than the 95th percentile	A diagnostic evaluation over a short period of time in conjunction with pharmacologic treatment may be organized.
Hypertensive urgency and emergency	Average SBP or DBP that is >5 mm Hg higher than the 95th percentile, along with clinical signs or symptoms	Patient hospitalized and treated to lower the BP.

BP=blood pressure, SBP=systolic blood pressure, DBP=diastolic blood pressure. Modified from The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents. *Pediatrics*. 2004;114:555–576.

"white-coat" hypertension. This form of stress-induced hypertension may be validated by BP monitoring at school, in the home, or in all locations with the use of an ABPM.

Some patients have borderline readings (systolic or diastolic readings between the 90th and 95th percentile), a state termed prehypertension. It is important to follow such patients over time and to implement lifestyle modifications such as weight reduction and increased physical activity. For those who have persistent elevations, the approach should be tailored to the magnitude of the elevation and the nature of concurrent signs or symptoms (Table 2). The use of an ABPM may aid in the diagnosis of hypertension by limiting inter- and intra-observer variability. Recent investigations provide normative reference values for ABPMs in children. (2)

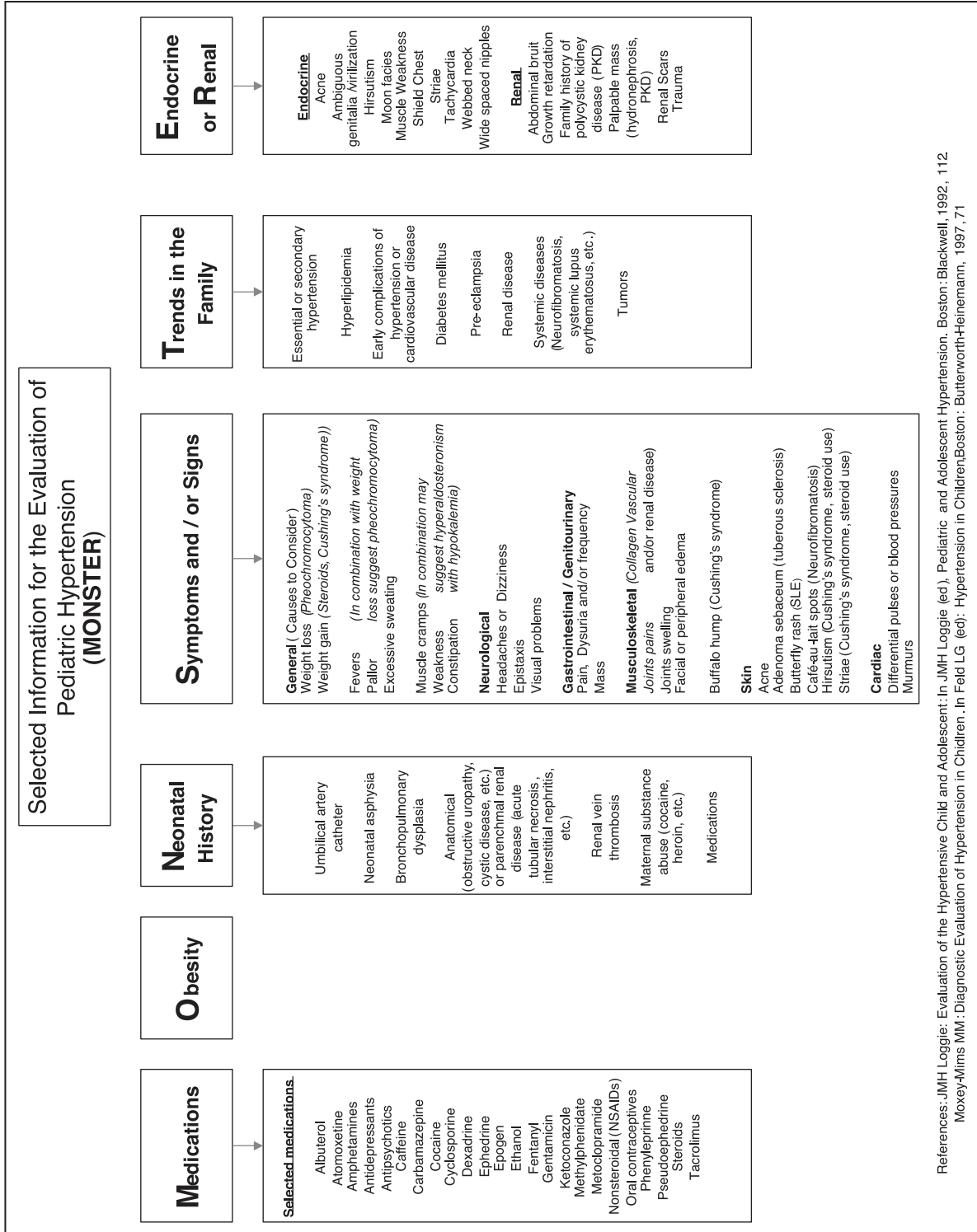
### Organize a Diagnostic Approach

A simple sequence or mnemonic to start the diagnostic process is MONSTER: Medications, Obesity, Neonatal history, Symptoms or Signs, Trends in the family, Endocrine or Renal (Fig. 3). Some medications prescribed for other conditions may cause hypertension, such as amphetamines, corticosteroids, contraceptives, and cyclosporine, as might many over-the-counter medications

(ie, allergy or cold medication) and licorice (glycyrrhizic acid).

During the evaluation, obesity and obstructive sleep apnea syndrome (OSAS) need to be considered. In the United States, more than 9 million children or youth older than 6 years of age are obese, (3) defined as having a BMI  $\geq 95$ th percentile according to the age- and sex-specific Centers for Disease Control and Prevention BMI charts. Compared with nonobese children, those who are obese are approximately three to five times more likely to have hypertension. Additional consequences of obesity include glucose intolerance, insulin resistance, type 2 diabetes mellitus, dyslipidemia, hepatic steatosis, cholelithiasis, sleep apnea, and orthopedic problems.

OSAS affects 1% to 3% of the preschool population. Patients who have OSAS diagnosed by polysomnography have significantly higher diastolic BPs during both wakefulness and sleep. (4) The degree of the hypertension appears to correlate with the severity of obstructive sleep apnea and the BMI. Although the mechanism for hypertension is unknown, it probably is similar to that described in adults: sympathetic nervous system activation due to arousal, hypoxemia, and possibly to changes in cardiac output caused by intrathoracic pressure swings.



References: JMH Loggie: Evaluation of the Hypertensive Child and Adolescent: In JMH Loggie (ed), Pediatric and Adolescent Hypertension. Boston: Blackwell, 1992, 112  
Moxey-Mims MM: Diagnostic Evaluation of Hypertension in Children. In Feld LG (ed): Hypertension in Children. Boston: Butterworth-Heinemann, 1997, 71

Figure 3. Selected information for evaluation of hypertension (MONSTER). Data from Loggie JMH. Evaluation of the hypertensive child and adolescent. In: Pediatric and Adolescent Hypertension. Boston, Mass: Blackwell; 1992:112 and Moxey-Mims MM. Diagnostic evaluation of hypertension in children. In: Feld LG, ed. Hypertension in Children. Boston, Mass: Butterworth-Heinemann; 1997:71.



The neonatal history or selected findings can provide important information regarding possible complications during or in the early postnatal course, such as asphyxia, use of an umbilical artery catheter, occurrence of a renal vein thrombosis, maternal substance abuse, disparities between upper extremity and lower extremity pulses or blood pressures, abdominal bruits, abnormal urinalysis findings (hematuria, proteinuria), abdominal masses (hydronephrosis/obstructive uropathy), and bronchopulmonary dysplasia.

Although essential hypertension is becoming more prevalent in children, a secondary cause should be sought, especially in the preadolescent. The evaluation is guided by history and physical examination findings to identify symptoms or signs of hypertension that may direct specific evaluation and avoid unnecessary and invasive testing (Figs. 3 and 4). The data gathered through history and physical examination allow the clinician to select the most appropriate laboratory investigations in the next phase of evaluation.

Biochemical and imaging studies are used to address three primary organ systems: endocrine, renal, and cardiovascular. Although high plasma renin activity or direct renin measurements suggest renal vascular disease, a low value may be even more significant because it implies endocrine or genetic causes of hypertension. Low renin concentrations are present in the following disorders: steroidogenic enzyme defects (steroid 11-beta-hydroxylase deficiency, steroid 11-alpha-hydroxylase deficiency/17, 20-lyase deficiency), hyperaldosteronism (primary aldosteronism, adrenocortical hyperplasia, idiopathic primary aldosteronism, glucocorticoid-remediable aldosteronism), apparent mineralocorticoid excess, and nonsteroidal defects (Liddle syndrome, pseudohypoaldosteronism II or Gordon syndrome). (5)(6) In these disorders, overactivity of the epithelial sodium channel (ENaC), either as a primary or secondary effect, leads to salt retention, volume expansion, and hypertension. Although these specific disorders are uncommon, polymorphisms of the ENaC may be common and have been implicated in promoting essential hypertension. (7) In these entities, specific therapy with amiloride, glucocorticoids, or spironolactone may normalize the BP.

Because renal disorders are among the most common causes of secondary hypertension in children, many studies are used to investigate the possibility of renal parenchymal or vascular disease. For example, a complete blood count may detect anemia of chronic renal disease, urinalysis provides an index of both glomerular (protein, blood) and tubular function (pH, specific gravity, glucose), and the plasma blood urea nitrogen (BUN) and

creatinine values assess the glomerular filtration rate ( $\text{mL}/\text{min}/1.73 \text{ m}^2$ ), calculated as  $\text{length in cm} \times \text{K}/\text{plasma creatinine concentration}$  (K is the coefficient of 0.45 for <1 to 12 months of age; 0.55 for 2 to 13 years of age, and 0.7 for 14 to 18 years of age via the Schwartz Formula). In addition, renal ultrasonography with Doppler provides information about size, location, echogenicity, and vascular flow of the kidney. Small renal scars can cause hypertension.

Cardiovascular disorders, such as coarctation of the aorta and the mid-aortic syndrome, are important and often overlooked causes of hypertension in children. Investigations such as the measurement of serum lipids and echocardiography provide essential information about key cardiovascular risk factors to guide therapeutic intervention. For example, cardiac hypertrophy is a major indication for hypertensive therapy, even for patients who have only borderline high BP readings.

Two recent studies have provided additional information on the predictive role of serum uric acid concentration in the development of hypertension. In the Bogalusa Heart Study, a high plasma uric acid concentration was associated with high BP readings in childhood that may persist into adulthood. (8) Feig and Johnson, in a study of 125 children, observed a strong relationship between serum uric acid concentrations and essential hypertension. (9) Interestingly, a serum uric acid value higher than 5.5 mg/dL (0.33 mmol/L) was found in 89% of children who had primary hypertension but only in about 30% of those who had secondary forms of hypertension. None of the controls or patients who had white-coat hypertension had elevated values. The possible mechanisms for the relationship between hyperuricemia and hypertension remain unclear.

Additional information may be obtained by a urine drug screen or polysomnography based on the initial review of systems.

There is no consensus on the best modality for renal vascular imaging, except that the gold standard is digital subtraction or conventional angiography with differential renal vein renin sampling. Other imaging modalities have limitations and may fail to detect intrarenal vascular lesions. Magnetic resonance angiography, computed tomographic angiography (CTA), isotope or renal nuclear medicine scanning, and renal ultrasonography with color Doppler may provide normal results in the face of significant segmental renal arterial disease. Despite the radiation and use of intravenous contrast, CTA may be considered in a nonemergent situation in lieu of other radiologic testing such as renal ultrasonography and renal nuclear

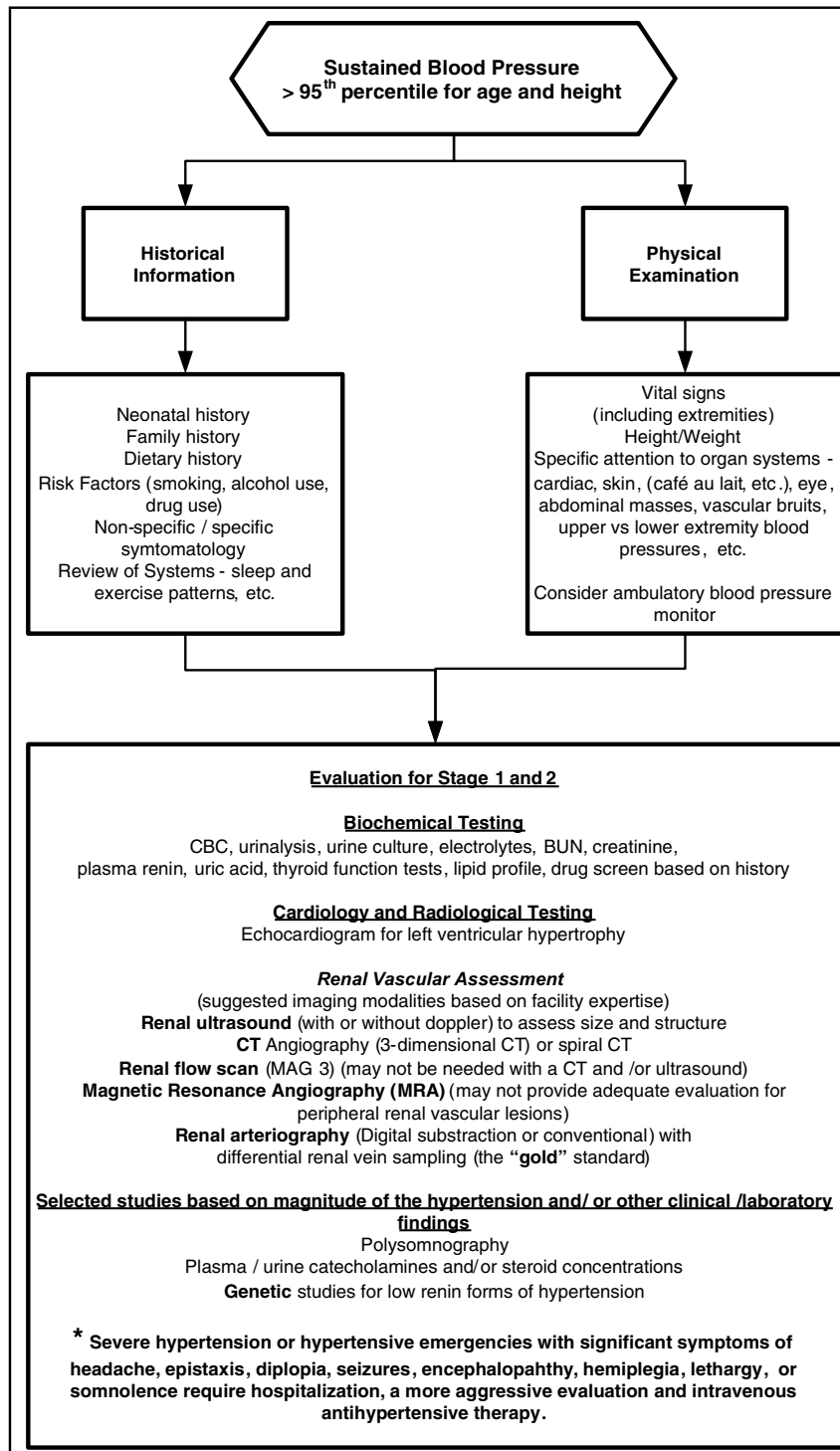


Figure 4. Suggested evaluation of hypertension in children. Modified with permission from Moxey-Mims MM. Diagnostic evaluation of hypertension in children. In: Feld LG, ed. *Hypertension in Children*. Boston, Mass: Butterworth-Heinemann; 1997:74 and The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents. *Pediatrics*. 2004;114:555-576.



Table 3. Public Health Considerations

Environment	Suggestions
Healthy Marketplace/Media	Promote healthy foods and beverages with nutrition product packaging; limit or prohibit direct marketing to children (selected foods, tobacco, and alcohol)
Schools/Communities/Built Environment	Subsidize or extend school meal funding for children at risk of obesity, limit fast food in schools, and prohibit soft drinks and vending machines in schools Encourage and build environments for increased physical activity and provide physical activity report cards
Home	Encourage family dinners and limit fast foods and non-nutritious snacks; limit television and handheld and computer gaming; promote physical behaviors, with parents serving as role models for stopping smoking and limiting alcohol consumption.

From Institute of Medicine. *Preventing Childhood Obesity: Health in Balance*. Washington, DC: National Academics Press; 2005.

scans to exclude renal vascular disease. (10) The therapeutic interventions for renal artery stenosis include angioplasty, use of stenting, or surgical revascularization with a graft to bypass the lesion.

In cases of suspected pheochromocytoma, 24-hour urinary measurement of catecholamines (fractionated metanephrine, epinephrine, norepinephrine) or plasma catecholamines is appropriate. For functional localization of the neural crest tissue, nuclear imaging with I<sup>123</sup> or I<sup>132</sup> metaiodobenzylguanidine (MIBG scan) is performed.

Other causes of hypertension include anemia (systolic hypertension), hyperthyroidism (systolic hypertension), Williams syndrome (elfin facies), Turner syndrome (webbed neck, wide spaced nipples), Cushing syndrome, neurofibromatosis, and lower extremity traction.

### Determine the Severity of the Hypertension

The combination of the magnitude of the BP elevation and presence of LVH on echocardiography are proof of sustained hypertension. The finding of LVH suggests risk for future cardiovascular disease, which underscores the importance of recognizing and treating BP elevation in children and adolescents. (11)

### Treat the Hypertension Effectively

#### Nonpharmacologic Therapy

Lifestyle modifications or environmental changes must be implemented or at least attempted. The Institute of Medicine's approach to prevention of childhood obesity addresses nonpharmacologic interventions for hypertension, including reducing sodium intake (no added salt diet, ~2 to 3 g/d or 88 to 132 mEq/d), increasing activity, stopping smoking, reducing alcohol intake, and

intervening in other public health areas (Table 3). (3) Three easy steps to reduce salt intake include limiting grocery purchases of salt-added foods, limiting meals from fast-food restaurants/take-outs, and not adding salt to cooking. A referral to a dietitian may improve compliance through education and follow-up re-evaluations.

Physical activity should be encouraged to reduce obesity, improve BP, and prevent children from becoming handicapped or stigmatized. Before encouraging a child to participate in sports, the following questions should be asked: Is there a history of exercise-associated syncope; light-headedness; chest pain; dyspnea; or family history of sudden death, dysrhythmias, or hypertrophic cardiomyopathy? (12)

In general, BP responds to different types of activity in different ways. During brisk dynamic exercise (swimming, running, cycling), peripheral vascular resistance decreases, resulting in an increase in systolic BP, a moderate rise in mean arterial pressure, and a fall in the diastolic value. In static exercise, large intramuscular forces develop with a limited change in muscle length. In contrast to dynamic exercise, static or isometric exercise (weight or strength training) causes significant increases in systolic, mean, and diastolic BP with no change in total peripheral resistance. The magnitude of the increase in BP during static exercise can exceed values for dynamic exercise significantly. Most physical activities and sports have both static and dynamic components, and a few basic rules can guide exercise: (12)(13)

- Decisions to restrict participation should be based on the cardiovascular demands of the activity and the demands of the practice, training, or preparation for that activity.

Table 4. Guidelines, Principles, and Response to Therapy

Suggested Guidelines to Improve Compliance of Therapy<sup>1</sup>

- Be aware of inadequate intake of medications
- Provide written instructions and blood pressure guidelines (high and low) for when to call the physician
- Make patient/family aware that the goal is the normalization of blood pressure
- Maintain phone contact with patient/family
- Implement home/school blood pressure monitoring
- Use nonpharmacologic therapy in combination with antihypertensive therapy
- Communicate and monitor adverse effects
- Provide feedback and validation of success
- Obtain laboratory studies on a reasonable schedule
- Contact patients who do not return for follow-up

Suggested Principles of Therapy<sup>2</sup>

- Consider starting with one drug and maximizing dose before adding a second agent to achieve normalization or near-normalization of blood pressure (this may improve compliance, but the approach needs to be individualized)
- Provide written instructions with clear blood pressure limits (high and low) when to call the physician
- Be considerate of patient and family routines (daily dosing if possible)
- Select agent(s) that have the lowest adverse effect profile

Possible Causes of Inadequate Response to Therapy<sup>3</sup>

- Errors with the equipment or measuring technique
- Noncompliance with therapy
- Progression of underlying disease
- Unacceptable adverse effects
- Selection of drug inappropriate for the suspected cause of hypertension
- Drug interactions (eg, steroids, cyclosporine, caffeine, sympathomimetics)
- Drug metabolism
- Rapid inactivation (eg, rapid acetylator with hydralazine)
- Slow bioactivation of prodrug (eg, angiotensin receptor blockers)

<sup>1</sup>Adapted with permission from Kaplan NM. Systemic hypertension: an overview of the problem. *Semin Nephrol.* 2005;25:191.

<sup>2</sup>Adapted from Choi KL, Bakris GL. Hypertension treatment guidelines: practical implications. *Semin Nephrol.* 2005;25:198.

<sup>3</sup>Adapted with permission from Blowey DL. Approach to the pharmacologic treatment of pediatric hypertension. In: Portman RJ, Sorof JM, Ingelfinger JR, eds. *Pediatric Hypertension.* Totowa, NJ: Humana Press; 2004:429.

• Children and adolescents who have significant essential or severe hypertension should avoid weight/power lifting, body building, and strength training. Those who have secondary causes of hypertension or severe essential hypertension should avoid strenuous static exercise and restrict competitive sports to those of low intensity (low dynamic/low static demands) such as bowling, golf, cricket, curling, or riflery, until an evaluation is performed and target organ damage is excluded.

• Exercise restriction should be based on the possibility that an abrupt increase in BP may place the child or adolescent at a higher risk of a catastrophic event, exacerbate the BP effect on end-organ damage significantly, or contribute to sustained BP elevation.

### Pharmacologic Therapies

The goal of therapy is the normalization or near-normalization of BP based on age, sex, and height, using a drug regimen that causes minimal adverse effects. It

also is important to appreciate the guidelines for and principles of drug therapy as well as the causes of inadequate response to therapy in treating children who have hypertension (Table 4). The physician experienced in managing hypertension can employ numerous approaches to improve adherence to therapeutic regimens, but it is equally important to appreciate reasons that lead to a poor response to therapy, such as drug interactions, unacceptable adverse effects, and inaccuracies in the BP measurements.

The approach to antihypertensive therapy is based on whether the patient has primary (essential) or secondary (identifiable cause) hypertension (Table 5). Many antihypertensive drugs are available for children, although clinical trials are limited, and most recommendations are based on extrapolation from adult dosage recommendations or clinical experience. Because the drug compendium is extensive, only practitioners experienced with their use should prescribe these medications. In our

Table 5. Antihypertensive Drugs for Outpatient Management of Hypertension in Children 1 to 17 Years of Age\*

Class	Drug	Dose (Interval)	Common Adverse Effects/Special Considerations of Each Class
Angiotensin Converting Enzyme Inhibitor (ACEi)	Captopril <sup>S</sup>	Initial: 0.3 to 0.5 mg/kg per dose (tid) Maximum: 6 mg/kg per day	All ACEis are contraindicated in pregnancy Periodically measure serum creatinine and potassium concentrations Cough and angioedema are less common with new ACEis Some agents can be made into a suspension United States Food and Drug Administration (FDA) approval is limited to children $\geq 6$ yrs of age and creatinine clearances $\geq 30$ mL/min per 1.73m <sup>2</sup> Consider for renoprotective effect for renal disease with proteinuria and diabetes mellitus
	Enalapril <sup>S</sup>	Initial: 0.08 mg/kg per day up to 5 mg/d (once daily–bid) Maximum: 0.6 mg/kg per day up to 40 mg/d	
	Benazepril	Initial: 0.2 mg/kg per day up to 10 mg/d Maximum: 0.6 mg/kg per day up to 40 mg/d	
	Lisinopril	Initial: 0.07 mg/kg per d up to 5 mg/d Maximum: 0.6 mg/kg per d up to 40 mg/d	
	Fosinopril	Children >50 kg: Initial: 5 to 10 mg/d Maximum: 40 mg/d	
	Quinapril	Initial: 5 to 10 mg/d Maximum: 80 mg/d	
Angiotensin Receptor Blocker (ARB)	Irbesartan	6 to 12 y: 75 to 150 mg/d (once daily) $\geq 13$ y: 150 to 300 mg/d	All ARBs are contraindicated in pregnancy Periodically measure serum creatinine and potassium concentrations Losartan can be made into a suspension FDA approval is limited to children $\geq 6$ y of age and creatinine clearances $\geq 30$ mL/min per 1.73m <sup>2</sup>
	Losartan	Initial: 0.7 mg/kg per day up to 50 mg/d (once daily) Maximum: 1.4 mg/kg per day up to 100 mg/d	
Calcium Channel Blocker	Amlodipine <sup>S</sup>	Children 6 to 17 y: 2.5 to 5 mg once daily Initial: 2.5 mg/d Maximum: 10 mg/d Initial: 0.15 to 0.2 mg/kg per day (tid–qid) Maximum: 0.8 mg/kg per day up to 20 mg/d Initial: 0.25 to 0.5 mg/kg per day (once daily–bid) Maximum: 3 mg/kg per day up to 120 mg/d	Amlodipine and isradipine can be compounded into stable extemporaneous suspensions Felodipine and extended–release nifedipine tablets must be swallowed whole May cause tachycardia and edema
	Felodipine		
	Isradipine <sup>S</sup>		
Extended–release nifedipine			
Alpha and Beta Blocker	Labetalol <sup>S</sup>	Initial: 1 to 3 mg/kg per d (bid) Maximum: 10 to 12 mg/kg per day up to 1,200 mg/d	Asthma and overt heart failure are contraindications Heart rate is dose–limiting May impair athletic performance Should not be used in those who have insulin–dependent diabetes
Beta Blocker	Atenolol <sup>S</sup>	Initial: 0.5 to 1 mg/kg per day (once daily–bid) Maximum: 2 mg/kg per day up to 100 mg/d	Noncardioselective agents (propranolol) are contraindicated in those who have asthma and heart failure Heart rate is dose–limiting May impair athletic performance Should not be used in those who have diabetes mellitus
	Metoprolol <sup>S</sup>	Initial: 1 to 2 mg/kg per day (bid) Maximum: 6 mg/kg per day up to 200 mg/d	
	Propranolol <sup>S</sup>	Initial: 1 to 2 mg/kg per day (bid–tid) Maximum: 4 mg/kg per day up to 640 mg/d	

Class	Drug	Dose (Interval)	Common Adverse Effects/Special Considerations of Each Class
Central Alpha Blocker	Clonidine	Children $\geq 12$ y: Initial: 0.2 mg/d (bid) Maximum: 2.4 mg/d	May cause dry mouth or sedation Transdermal preparation is available Sudden cessation of therapy can lead to severe rebound hypertension
Vasodilator	Hydralazine <sup>§</sup>	Initial: 0.75 mg/kg per day (qid) Maximum: 7.5 mg/kg per day up to 200 mg/d	Tachycardia and fluid retention are common Contraindicated with pericardial effusion, supraventricular tachycardia, and tachydysrhythmias Hydralazine can cause lupus-like syndrome
	Minoxidil <sup>§</sup>	Children <12 y: Initial: 0.2 mg/kg per day (once daily-tid) Maximum: 50 mg/day Children $\geq 12$ y: Initial: 5 mg/kg per day (once daily-tid) Maximum: 100 mg/day	Prolonged use of minoxidil can cause hypertrichosis Minoxidil usually is reserved for patients who have hypertension that is resistant to multiple drugs
Diuretics	Hydrochlorothiazide	Initial: 1 mg/kg per day (once daily) Maximum: 3 mg/kg per day up to 50 mg/day	All patients taking diuretics should have electrolytes monitored after initiation of therapy and periodically Potassium-sparing diuretics (spironolactone, triamterene) may cause severe hyperkalemia, especially in conjunction with ACEi or ARB Furosemide is useful adjunctive therapy for patients who have renal disease Some agents may be useful in low renin forms of hypertension
	Furosemide	Initial: 0.5 to 2 mg/kg per day (once daily-bid) Maximum: 6 mg/kg per day	
	Spirolactone <sup>§</sup>	Initial: 1 mg/kg per day (once daily-bid) Maximum: 3.3 mg/kg per day up to 100 mg/d	
	Triamterene	Initial: 1 to 2 mg/kg per day (bid) Maximum: 3 to 4 mg/kg per day up to 300 mg/d	

Modified from The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents. *Pediatrics*. 2004;114:555-576.  
\*Check pediatric labeling and safety information on all agents. Also, see <http://www.fda.gov/oc/opt/default.htm> for complete United States Food and Drug Administration labeling and levels of evidence for dosing recommendations. Comments apply to all members of each drug class except where otherwise stated. The table does not include all available drugs in each category. Some drugs require adjustment for renal disease or specific glomerular filtration rates. These medications should be used by physicians experienced in the treatment/management of children who have hypertension.  
<sup>§</sup>Extemporaneous formulations (liquid) may be prepared by a pharmacy.

opinion, the preferable adverse effect and compliance profiles support the use of angiotensin-converting enzyme inhibitors (ACEis), angiotensin receptor blockers (ARBs), and calcium channel blockers (CCBs) as first-line therapy. Although beta blockers (propranolol, atenolol), an alpha and beta blocker (labetalol), direct vasodilators (hydralazine, minoxidil), and central alpha agonists (clonidine) have been used in pediatrics, they should not be considered first-line medications except under specific circumstances (ie, clonidine patch to improve compliance in adolescents).

#### ANGIOTENSIN-CONVERTING ENZYME INHIBITORS.

ACEis block the conversion of angiotensin I to angiotensin II and inhibit kininase II, an important participant in the kinin/kallikrein system, resulting in increased circulating concentrations of vasodilatory bradykinins. The

predominant antihypertensive effect is the inhibition of angiotensin II production. There is a renal protective effect in addition to the antihypertensive effects of ACEis that adds to their value as first-line antihypertensive medications. (14)

Captopril and enalapril were the first ACEis used in children. Pediatric dosing and adverse effect profiles are well described for these drugs (Table 5). Captopril and enalapril can be used in neonates and young children, employing formulations that improve the ability to titrate doses. For older patients maintained on stable doses, the use of daily dosing intervals is preferred over more frequent doses of the shorter half-life formulations.

The adverse effects of ACEis in children do not differ from those in adults. Renal impairment, hyperkalemia, neutropenia, anemia, dry cough, and angioedema have

been reported in children. (14) The use of an ACEi is contraindicated in patients who have bilateral renal artery stenosis, hyperkalemia, or pregnancy. If renal impairment occurs with ACEi therapy, it generally is reversible with discontinuation of the drug. Hyperkalemia may be related to medication-induced renal failure but may occur in patients who have relatively normal renal function because of aldosterone inhibition. We suggest measuring BUN, creatinine, and electrolytes within 1 week after starting an ACEi, with any dosage changes, and every 3 to 6 months for the patient receiving therapy. Hematologic complications are rare and are reversible when the drug is discontinued.

In contrast to adults, the dry, nonproductive cough (not dose-related) is a rare complication in children and adolescents. The mechanism causing the cough may be related to kininase inhibition resulting in increased bradykinin production. If a cough occurs, it improves with discontinuation of the ACEi. It is important to ask about the cough because parents and patients may attribute coughing to asthma or upper respiratory tract infection or they may take the medication less frequently than recommended to avoid symptoms.

ACEis are contraindicated in pregnancy. Maternal use of such drugs during pregnancy can result in fetal hypotension, anuria, renal tubular dysplasia, and death. Infants who have only first-trimester exposure to ACEis have an increased risk of major congenital malformations (ie, cardiac). (15)

**ANGIOTENSIN RECEPTOR BLOCKERS.** ARBs directly block the action of angiotensin II on their cell membrane receptors. Although there are fewer adverse effects (eg, dry cough), the laboratory monitoring, contraindications in pregnancy, and risk of renal impairment are similar to the ACEis. The use of ARBs in combination with ACEis has increased recently for patients who have chronic renal failure as a renoprotective regimen to reduce proteinuria and delay progression of renal disease. Based on extensive experience, ACEis and ARBs are the drugs of choice for patients who have diabetes mellitus and chronic glomerular disease.

**CALCIUM CHANNEL BLOCKERS.** CCBs act as direct vasodilators by inhibiting calcium transport into vascular smooth muscle and other contractile cells, thereby limiting contractility and vasoconstriction. (14) The major class of CCBs used in pediatrics for hypertension is the dihydropyridines (nifedipine, nicardipine, isradipine, felodipine, amlodipine) because of the relative selec-

tivity for arteriolar smooth muscle. The nondihydropyridines (phenylalkylamines, benzothiazepines), such as verapamil and diltiazem, have more effects on cardiac conduction and contractility than do the dihydropyridines.

Pediatric experience with CCBs demonstrates safety and efficacy with an acceptable adverse effect profile. They are used as first-line therapy and have particular usefulness in those patients for whom ACEis are contraindicated and in children who have renal disease in whom ACEis/ARBs alone are inadequate to control the hypertension. As the dose of CCBs approaches the maximal range, the incidence of adverse effects, particularly peripheral edema, increases significantly. Due to their formulations, nicardipine (intravenous) and isradipine (can be compounded into stable suspensions) are used in the emergency and intensive care settings. Rapid, safe, and effective reductions in BP have been achieved with continuous infusions, providing an alternative to nitropruside or intravenous labetalol.

Some controversy continues to surround the use of nifedipine (sublingual or immediate-release dosage forms) to treat hypertensive emergencies in children due to the reported cerebrovascular and cardiovascular adverse events associated with aggressive treatment of increased BP by the use of sublingual nifedipine in adults. The most commonly observed adverse effects of CCBs are peripheral edema, dizziness, nausea, headache, flushing, weakness, and transient postural hypotension. (14) These effects are uncommon with sustained-release preparations and rarely necessitate discontinuing the drug.

**BETA-ADRENERGIC ANTAGONISTS (BETA BLOCKERS).** These drugs are among the first and most widely used antihypertensive medications in children. Several mechanisms for their antihypertensive effect have been proposed, including decreased cardiac output, decreased peripheral vascular resistance, inhibition of renin secretion, decreased circulating plasma volume, and inhibition of central nervous system (CNS) sympathetic activity. (14) The relative importance of each of these mechanisms is unclear and may depend on which particular drug from the class is being used.

Several characteristics distinguish one beta blocker from another, including cardioselectivity, intrinsic sympathomimetic activity, alpha-adrenergic antagonism, and relative hydrophilic and lipophilic characteristics. Use of the prototype beta blocker propranolol is limited by its lack of selectivity for cardiovascular beta<sub>1</sub> receptors. Because of effects on peripheral beta<sub>2</sub> receptors, manifested



as bronchoconstriction, impaired glucose tolerance, and altered lipid profiles, drugs that have relative cardioselectivity were created.

Intrinsic sympathomimetic activity is characteristic of some, but not all, drugs in the class. This characteristic may be of benefit for several reasons, including reduced impairment of left ventricular function, reduced compromise of peripheral vasculature, and minimized effects on lipid profiles.

Labetalol and carvedilol (not approved by the United States Food and Drug Administration in children and used primarily for congestive heart failure) essentially have beta-blocking effects and peripheral alpha-adrenergic antagonism. This vasodilatory effect on peripheral vasculature provides synergistic antihypertensive efficacy.

Many patients treated with beta blockers experience significant CNS effects; newer formulations have been developed to limit CNS absorption through alterations in hydrophilicity and lipophilicity. Each of these characteristics—cardioselectivity, intrinsic sympathomimetic activity, alpha-adrenergic antagonism, and hydrophilicity/lipophilicity—can be individualized when selecting a beta blocker for a particular patient.

Most pediatric experience with beta blockers involves the use of propranolol, but the unacceptable adverse effects, as well as the availability of equally efficacious and better-tolerated alternatives, have limited its use as a first-line treatment for pediatric hypertension. Other beta blockers used in pediatrics include atenolol (cardioselective, no intrinsic sympathomimetic activity), labetalol (not cardioselective, no intrinsic sympathomimetic activity, significant alpha antagonism), and metoprolol (cardioselective, no intrinsic sympathomimetic activity). Review of the pediatric literature shows minimal new research on the use of beta blockers in pediatric hypertension.

No direct comparisons of beta blockers with diuretics or with CCBs or ACEis as first-line pediatric antihypertensives have been published. Clinical practice and experience, rather than direct comparison, seems to have relegated beta blockers to a second or third choice for treating essential hypertension. However, these agents may be particularly useful when combined with vasodilators that produce reflex tachycardia or in patients for whom ACEis or CCBs are contraindicated.

The most common adverse effects of beta blockers include cardiovascular changes (bradycardia, syncope, fluid retention), CNS effects (lightheadedness, ataxia, dizziness, sleepiness, irritability, hearing and visual disturbances, vivid dreams/nightmares, weakness, fatigue,

depression), gastrointestinal changes (nausea, diarrhea, cramping, constipation), hematologic effects (transient eosinophilia, idiosyncratic cytopenia), and impotence. (14) Beta blockers are contraindicated in patients who have asthma, Raynaud phenomenon, cystic fibrosis, bronchopulmonary dysplasia, uncompensated congestive heart failure, hyperactive airway disease, bradycardia or heart block, or cardiogenic shock (14) as well as in athletes (may affect performance and prevent potassium reentry into the cells on strenuous exercise).

**CENTRAL ALPHA AGONIST OR SYMPATHOLYTIC AGENT (CLONIDINE).** The mechanism of action of the central sympatholytic (CA) agents is based on modulation of CNS centers for cardiovascular control. Clonidine acts as an agonist of CNS alpha-adrenoceptors (primarily alpha-2). (14) The initial dose may be associated with a transient increase in blood pressure, suggesting that clonidine also stimulates peripheral (vasoconstrictive) alpha receptors in addition to its primary mechanism of CA activity.

To increase compliance, especially in adolescents, the use of a transdermal clonidine preparation can be considered. A steady-state concentration is achieved in about 2 to 3 days, and patches are changed weekly. (14) The possible benefits of this formulation are stable serum concentrations, fewer adverse effects, and reduction in the incidence of rebound hypertension when the medication is discontinued. Skin reactions (allergic, irritation) are observed in up to 20% of patients. Although clonidine may be considered second-tier treatment for symptoms of attention-deficit/hyperactivity disorder, its effect is less than that of stimulants and is associated with many adverse effects, including sedation, dry mouth, fatigue, hallucinations/nightmares, and rebound hypertension on abrupt discontinuation.

**VASODILATORS.** The typical use of vasodilators is treatment of hypertensive emergencies. Hydralazine acts primarily to dilate the arteriolar resistance vessels, with a less pronounced effect on the venous capacitance vessels. (14) In the acute setting, hydralazine is an effective antihypertensive, although its long-term effectiveness has been limited by the body's compensatory responses to its actions (increased cardiac output, fluid retention), by development of tolerance, and by adverse effects. Minoxidil use as an antihypertensive medication is limited to refractory cases. In these cases, concurrent therapy with other medications (eg, diuretics) often is necessary. The common pediatric adverse effects of vasodilators include headache, palpitations, tachycardia, flushing, fluid



Table 6. Selected Combinations of Drug Products\*

Combination	Some Available Preparations
<b>ACEi plus CCB</b>	
Benazepril/Amlodipine	10 mg/2.5 mg; 10 mg/5 mg; 20 mg/5 mg
<b>ACEi plus Diuretic</b>	
Benazepril/Hydrochlorothiazide	5 mg/6.25 mg; 10 mg/12.5 mg; 20 mg/12.5 mg
Captopril/Hydrochlorothiazide	25 mg/15 mg; 25 mg/25 mg
Enalapril/Hydrochlorothiazide	5 mg/12.5 mg; 10 mg/25 mg
Lisinopril/Hydrochlorothiazide	10 mg/12.5 mg; 20 mg/12.5 mg
<b>ARB plus Diuretic</b>	
Losartan/Hydrochlorothiazide	50 mg/12.5 mg; 100 mg/12.5 mg
Irbesartan/Hydrochlorothiazide	150 mg/12.5 mg; 300 mg/12.5 mg

ACEi=angiotensin-converting enzyme inhibitor, CCB=calcium channel blocker, ARB=angiotensin receptor blocker  
 \* Check pediatric labeling and safety information on all agents. These drug combinations do not have specific pediatric testing or indications but are recommended on the basis of clinical experience primarily in adolescents and young adults. See <http://www.fda.gov/oc/opt/default.htm> for complete FDA labeling and levels of evidence for dosing recommendations.

and sodium retention, and lupus-like syndrome (hydralazine). Minoxidil has caused pericardial effusion, congestive heart failure, and hypertrichosis (leads to poor compliance). Pediatric contraindications to the use of minoxidil include congestive heart failure and the presence or suspicion of pheochromocytoma. (14)

**DIURETICS.** Diuretics are safe, effective, first-line therapy for hypertension. Thiazide diuretics are the preferred choice to treat essential hypertension in adults. In children, there is no consensus on the best or preferred medications due to the lack of data. Clinicians are guided by their own experience, except in cases where there are clear advantages or contraindications to other classes of drugs. With the development of alternatives to diuretics such as ACEis, ARBs, and CCBs, some practitioners have limited the use of diuretics as first-line medications. Such decreased use may relate to their adverse effects. In some situations, diuretics can be synergistic with other agents, such as ACEis and ARBs, and are included in combination products (Table 6).

Diuretics exert their action on the kidney by inhibiting absorption of solute, resulting in decreased reabsorption of water and enhanced urine flow. (14) The classification of diuretics is based on the mechanism of their inhibition of solute reabsorption. Due to the potential adverse effect of hypokalemia, serum potassium concentrations should be monitored regularly. Common adverse effects include fluid and electrolyte disturbances (hypokalemia, volume depletion/hypotension, hypomagnesemia, hypercalcemia); metabolic disturbances (decreased glucose tolerance, hyperlipidemia, hyperuri-

cemia); gastrointestinal effects (anorexia, gastric irritation, nausea/vomiting, cramping, diarrhea, intrahepatic cholestatic jaundice, pancreatitis); and ototoxicity in patients receiving furosemide, particularly when combined with other ototoxic medications. (14)

Potassium-sparing diuretics (spironolactone, triamterene, amiloride) are used primarily when diuretics are needed, but there is concern about hypokalemia. The diuretic effect of spironolactone results from its action as a competitive antagonist of aldosterone. It is efficacious in children who have increased plasma aldosterone concentrations because of

conditions such as hyperaldosteronism, congestive heart failure, or hepatic disease. (14) Amiloride and triamterene have utility in low renin forms of hypertension. As noted, diuretics generally are used as adjunctive therapy with other drugs to improve blood pressure control.

### Continuation of Case Study

*The obese child who had hypertension underwent an extensive evaluation without discovery of a secondary cause of his hypertension, aided by the use of the appropriate cuff size and ABPM. His elevated serum uric acid concentration was strongly predictive of essential hypertension. Due to the LVH and the magnitude of the hypertension, he was a candidate for concomitant nonpharmacologic and pharmacologic therapy to reduce his risk factors for coronary artery disease. He was referred to a nutritionist to assist in nonpharmacologic treatment (dietary modifications of calories, lipids, and sodium). Initial pharmacologic therapy was hydrochlorothiazide (12.5 mg/day with monitoring of his electrolytes). Over the next 12 months under close follow-up, his hypertension was controlled. Because of significant weight loss, his diuretics were discontinued, and his blood pressure was normal at the 50th percentile for age and height. Subsequent echocardiography demonstrated normal left ventricular wall thickness.*

### Conclusion

The evaluation and treatment of hypertension in childhood has continued to evolve over the past 4 decades. The genetic verification of selected forms of hypertension, newer imaging modalities, and improved antihypertensive drugs have provided a more focused approach to

pediatric hypertension. Despite these advances, the basic requirements for detecting and evaluating the hypertensive youth remain a thorough history and physical examination.

## References

1. The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents. *Pediatrics*. 2004;114:555–576
2. Wuhl E, Witte K, Soergel M, Mehls O, Schaefer F. German Working Group on Pediatric Hypertension. Distribution of 24-h ambulatory blood pressure in children: normalized reference values and role of body dimensions. *J Hypertens*. 2002;20:1995–2007
3. Institute of Medicine. *Preventing Childhood Obesity: Health in Balance*. Washington, DC: National Academics Press; 2005
4. Marcus CI, Greene MG, Carroll JL. Blood pressure in children with obstructive sleep apnea. *Am J Respir Crit Care Med*. 1998;157:1098–1103
5. New MI, Crawford C, Virdis R. Low renin hypertension in childhood. In: Lifshitz F, ed. *Pediatric Endocrinology*. 3rd ed. New York, NY: Marcel Dekker;1995:775–789
6. Ingelfinger JR. Monogenic and polygenic genetic contributions to hypertension. In: Portman RJ, Sorof JM, Ingelfinger JR, eds. *Pediatric Hypertension*. Totowa, NJ: Humana Press; 2004: 225–240
7. Hannila-Handelberg T, Kontula K, Tikkanen I, et al. Common variants of the beta and gamma subunits of the epithelial sodium channel and their relation to plasma renin and aldosterone levels in essential hypertension. *BMC Med Genet*. 2005;20:6:4
8. Alper AB Jr, Chen W, Yau L, Srinivasan SR, Berenson GS, Hamm LL. Childhood uric acid predicts adult blood pressure: the Bogalusa Heart Study. *Hypertension*. 2005;45:34–38
9. Feig DI, Johnson RJ. Hyperuricemia in childhood primary hypertension. *Hypertension*. 2003;42:247–252
10. Vade A, Agrawal R, Lim-Dunham J, Hartoin D. Utility of computed tomographic renal angiogram in the management of childhood hypertension. *Pediatr Nephrol*. 2002;17:741–747
11. Daniels SR, Loggie J, Khoury P, Kimball TR. Left ventricular geometry and severe left ventricular hypertrophy in children and adolescents with essential hypertension. *Circulation*. 1998;97: 1907–1991
12. American Academy of Pediatrics. Committee on Sports Medicine and Fitness. Medical conditions affecting sports participation. *Pediatrics*. 2001;107:1205–1209
13. Maron BJ, Mitchell JH. 26<sup>th</sup> Bethesda Conference: recommendations for determining eligibility for competition in athletes with cardiovascular abnormalities. *J Am Coll Cardiol*. 1994;24: 845–889
14. Feld LG, Waz WR. Pharmacologic therapy of hypertension. In: Feld LG, ed. *Hypertension in Children*. Boston, Mass: Butterworth-Heinemann; 1997:133–178
15. Cooper WO, Hernandez-Diaz S, Arbogast PG. Major congenital malformations after first-trimester exposure to ACE inhibitors. *N Engl J Med*. 2006;354:2443–2451

## PIR Quiz

Quiz also available online at [www.pedsinreview.org](http://www.pedsinreview.org).

1. A 9-year-old boy is seen for a check-up before participating in summer camp that involves swimming and basketball. Findings on his physical examination are normal except for a blood pressure of 123/84 mm Hg measured by an appropriate-size cuff. The 95th percentile value for blood pressure for boys who are at the 75th percentile for his height is 119/80. Of the following, the *most* appropriate next step is to:
  - A. Allow swimming but not basketball at camp.
  - B. Initiate angiotensin-converting enzyme inhibitor therapy.
  - C. Obtain a complete blood count and serum electrolyte, creatinine, and blood urea nitrogen measurements.
  - D. Reassure the family that no additional action is needed.
  - E. Schedule two subsequent visits to measure blood pressure.
2. A 15-year-old girl presents with tiredness and decreased effort tolerance for 3 months. Her academic performance has declined over the last year. She frequently falls asleep at school. She has a history of loud snoring during sleep that has become worse over the last year. Her height is at the 50th percentile and her weight and body mass index are above the 95th percentile. Her blood pressure is 135/90 mm Hg. No other abnormalities are noted. Which of the following is *most* helpful in determining the long-standing nature of her hypertension?
  - A. Echocardiography.
  - B. Electrocardiography.
  - C. Funduscopy.
  - D. Serum creatinine measurement.
  - E. Serum lipid profile.
3. A 9-year-old girl has just been started on captopril therapy for management of hypertension resulting from renal scars. Which of the following is a serious potential adverse effect of captopril (and other angiotensin-converting enzyme inhibitors)?
  - A. Hypercalcemia.
  - B. Hyperkalemia.
  - C. Hypermagnesemia.
  - D. Hyponatremia.
  - E. Hyperuricemia.
4. Hypertension is confirmed in an 11-year-old girl after ambulatory blood pressure monitoring. She has no complaints and feels fine. Her height and weight are at the 50th percentile, and her physical examination results are normal. Her blood pressure is 125/83 mm Hg. The 95th percentile value for blood pressure is 121/79 mm Hg. Laboratory evaluation shows normal urinalysis and complete blood count as well as normal blood urea nitrogen and creatinine values. Of the following, the *most* appropriate next step is to:
  - A. Determine 24-hour urine catecholamine values.
  - B. Initiate captopril therapy and re-examine the girl in 1 week.
  - C. Initiate hydrochlorothiazide therapy and re-examine the girl in 1 week.
  - D. Perform renal ultrasonography.
  - E. Reassure the parents and re-examine the girl in 1 week.

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