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Review / Derleme

New guidelines for the diagnosis, evaluation, and treatment of pediatric hypertension

Güncel kılavuzlar eşliğinde çocukluk çağı hipertansiyonu

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The known about this topic

The prevalance of childhood hypertension is increasing. New guidelines for the diagnosis, management and treatment of hypertension are required.

Contribution of the study

AAP and ESH has updated pediatric hypertension guidelines and new recommendations was done. A new percentile table with non obese and overweight children was established. The importance of ABPM in the diagnosis of hypertension was increased. Primary investigations for the evaluation of primary hypertension was limited. Left ventricular hypertrophy criteria was updated.

Abstract

Childhood hypertension has become a significant public health problem due to increased prevalence in recent decades. High blood pressure causes increased mortality and morbidity in childhood, precedes adult hypertension, and causes increased cardiovascular events in adulthood. These concerns have led to an update of guidelines about childhood hypertension by the European Society of Hypertension in 2016 and the American Academy of Hypertension in 2017. This review highlights the important developments in these guidelines and recent literature about childhood hypertension in terms of diagnosis, prevalence, risk factors, diagnostic tools, prevention and management.

Keywords: Blood pressure, guideline, hypertension, pediatric, puberty

Öz

Çocuk ve ergenlerde son yıllarda sıklığı artan hipertansiyon önemli bir halk sağlığı sorunu haline gelmiştir. Çocukluk dönemindeki yüksek kan basıncı sadece çocukluk döneminde morbidite ve mortalite artışına değil aynı zamanda erişkin dönemdeki hipertansiyon ve artmış kardiyovasküler olaylara da yol açmaktadır. Bu kaygılar ile 2016 yılında European Society of Hypertension ve 2017 yılında American Academy of Pediatrics çocukluk çağı hipertansiyon kılavuzlarını güncellemiştir. Bu derlemede bu iki kılavuz ve güncel dizinler ışığında çocuklarda hipertansiyon tanımı, sıklığı, risk etmenleri, tanı yöntemleri, tedavi şeması ve önlemek için yapılması gereken adımlardan söz edilecektir.

Anahtar sözcükler: Çocuk, ergen, hipertansiyon, kan basıncı, kılavuz

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Introduction

In recent years, the prevalence of hypertension has increased with the increase in the prevalence of overweight and obesity and change in eating habits in children and adolescents (1–4). When adult data are examined, it can be observed that the frequency of hypertension, which is the most important risk factor and cause of mortality for cardiac diseases, reaches up to 40% after the age of 25 years (4). The origins of hypertension in adulthood extend to childhood ages, and the frequency of increased blood pressure (BP) in adolescence progresses to hypertension by 7% yearly (5, 6). In the light of these data, new studies related to childhood hypertension have been conducted, and hypertension guidelines have been updated in view of the information obtained (1, 2).

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There are mainly two guidelines for childhood hypertension. The first is the European Society of Hypertension (ESH) guideline, which was constituted and published by the ESH in 2009 and updated in 2016 (1, 7). The other is the American Academy of Pediatrics (AAP) guideline, which was updated in 2017 (3, 8). The AAP guideline includes 30 key recommendations and 27 consensus opinions (Appendix 1). Both guidelines created great reactions and were discussed in the scientific community. This article will discuss the approach to childhood hypertension in company with the current literature including mainly these two guidelines.

1. Frequency and risk factors

It has been predicted that the prevalence of hypertension in childhood is 3.5%, and the prevalence of increased blood pressure (a blood pressure between the 90–94 percentiles or a blood pressure between 120/80 mm Hg and 130/80 mm Hg in adolescents) is between 2.2% and 3.5% (2). There is a limited number of studies related to the epidemiology of childhood hypertension in Turkey (9, 10). In these studies, the prevalence of hypertension in children aged between 6 and 15 years was found to range between 8.5% and 15%.

The frequency of hypertension increases in some conditions including obesity, sleep apnea syndrome, chronic renal disease, and prematurity (2, 11, 12). According to data of the World Health Organization (WHO), there were 42 million obese or overweight children aged under 5 years worldwide in 2013 (12, 13). According to Turkish data, the prevalence of obesity increased from 0.6% in the period of 1990–1995 to 7.3% between 2011 and 2015 (14). The prevalence of hypertension is 4–14% in overweight children and 11–23% in obese children (11, 12). Excessive salt intake by diet is also an important risk factor especially for obese and overweight children (15, 16). In addition, co-existence of hypertension and obesity increases cardiovascular risk factors (for example, dyslipidemia, disrupted glucose tolerance) (17).

The prevalence of hypertension is 4–16% in children and adolescents with type 1 diabetes and 12–31% in children and adolescents with type 2 diabetes; these prevalences are higher compared with the general population (2, 8, 18, 19). Individuals with type 2 diabetes carry a high risk in terms of end-organ damage because type 2 diabetes is associated with obesity. In sleep apnea syndrome, which is another risk factor, the prevalence of increased blood pressure ranges between 3.6% and 14% (2, 20). Hypertension is found in 6.1% of children with neurofibromatosis-1, and this prevalence is higher compared with the general population (21). Fifty percent of children and adolescents who have chronic renal disease are hypertensive, and hypertension is not under control in 20–70% of these patients. The frequency ranges between 48% and 70% in adolescents who have end-stage renal disease (2, 22, 23).

2. Definitions

According to both AAP and ESH guidelines, a blood pressure (BP) value below the 90th percentile by age, sex, and height is considered as normal blood pressure (BP) (1, 2). Hypertension is defined as a systolic and/or diastolic blood pressure measured clinically at or above the 95th percentile. The adult hypertension guideline (American Heart Association and American College of Cardiology) (24) is recommended to be used for individuals aged 13 years and older by the AAP guideline and for individuals aged 16 years and above by the ESH guideline (1, 2).

a) New blood pressure values (1–18 years)

In the 2017 AAP guideline, a new BP percentile table was established with children who had normal weight (BMI <85th p). In the previous guideline from 2014, an important portion of the children who were included in the percentile table (21%) consisted of overweight and obese children (8). Therefore, the new BP values are below the 2004 values (2, 8).

In the new percentile tables, normal values for systolic blood pressure (SBP) and diastolic blood pressure (DBP) were given by age, sex, height, and weight percentiles, and the height values were added to the table as centimeters and inches (2).

The AAP guideline established a simplified blood pressure table that could be used conveniently by primary care physicians (https://doi.org/10.1542/peds.2017-1904). For these data, the 5th percentile height and 90th percentile age and sex values were used. According to this table, it was recommended that children who were found to have increased BP should be evaluated using the extended percentile table established for diagnosis, or the value of 120/80 mm Hg should be used for children aged 13 years and above (2).

b) Diagnosis of hypertension in children aged between 0 and 1 year

The values established by Dionne et al. (25) are recommended to be used for newborns, and the values established by the Task Force (26) in 1987 are recommended to be used for infants (2).

3. Blood pressure measurement

Measurement frequency

Yearly BP measurements are recommended for all children aged three years and older. However, BP measure-

ments are recommended at each follow-up visit in the presence of obesity, renal disease, diabetes, aortic coarctation or in conditions that predispose to hypertension including use of drugs that increase blood pressure (1, 2).

In children aged below three years, BP should be measured in presence of congenital heart disease, recurrent urinary tract infection, urological malformation, solid organ transplantation, blood marrow transplantation, malignancy, neurofibromatosis, tuberosclerosis or sickle cell anemia. BP should also be measured below the age of three years in low-birth-weight and preterm (<32nd GW) babies and in babies who need umbilical catheters (2).

Points to take into consideration during measurement

Before measurement of blood pressure, the child should be made to sit in a comfortable position for 3–5 minutes. The measurement should be performed in the right arm and at the level of the heart. The height of the cuff's expanding part should cover 80–100% of the arm circumference and its width should cover at least 40% of the arm circumference. The cuff's lower end should be placed 2–3 cm above the antecubital fossa and the stethoscope should be placed on the brachial artery.

The first BP measurement may be performed using an oscillometric device validated for children or by auscultation (mercurial or air sphygmomanometer). If the first BP is found to be increased, at least two more measurements should be performed, and the measurements should be confirmed by auscultation. Subsequently, the three measurements should be averaged and classified. Measurement at the forearm or wrist is not recommended (2). The classification by blood pressure values and approach to patients are shown in Table 1 (2, 27).

Measurement of ambulatory blood pressure

Twenty-four–hour ambulatory blood pressure measurement (ABPM) consists of night-day blood pressure measurements performed with 20–30–minute intervals. The place and importance of ABPM in the diagnosis and follow-up of hypertension, was increased in the new AAP guideline. Evaluation with ABPM is recommended for patients who are found to be hypertensive at the time of diagnosis or for children who have had increased blood pressure for one year or longer. It is again strongly recommended for high-risk groups including patients with obesity, diabetes, prematurity, chronic renal disease, sleep apnea syndrome, and solid organ transplantation.

Normal pediatric ABPM values should be used when evaluating the data. These values are different from normal blood pressure values and reference values are present only for 120 cm and above (28). In the evaluation of ambulatory blood pressure measurement, SBP and DBP values below the 95th percentile and SBP and DBP load below 25%, indicate normal blood pressure.

Ambulatory blood pressure measurement can be performed to diagnose masked hypertension or white coat hypertension. In white coat hypertension, clinical measurements are at or above the 95th percentile, but ABPM values are in the normal range. Its association with end-organ damage could not be shown in childhood. Masked hypertension encompasses conditions in which clinical measurements are normal, but ABPM measurements are found to be increased. The prevalence is predicted as 5.8%. Masked hypertension leads to end-organ damage and may accompany obesity, chronic renal disease, and repaired aortic coarctation.

4. Causes

Primary hypertension

In the United States, primary hypertension is the most common cause of hypertension observed in children and adolescents (2). Its general characteristics are as follows: it is observed in older children (≥6 years), familial history is positive (mother/father and or grandmother/grandfather), and it is associated with overweight/obesity.

Primary and secondary hypertension cannot be predicted according to blood pressure values, but it is thought that increased DBP indicates secondary hypertension in particular, and increased SBP indicates primary hypertension. According to the AAP guideline, detailed investigation is not necessary if the child is aged 6 years or above and overweight or obese, familial history is positive, and a physical examination and history do not suggest secondary hypertension (2).

Secondary hypertension

Secondary hypertension is observed more commonly in childhood compared with adulthood. Therefore, all children diagnosed as having hypertension should be evaluated in terms of secondary causes. Renal diseases and renovascular diseases are the most common causes of hypertension. Renal diseases constitute 34–79% of secondary causes and renovascular diseases constitute 12–13%. Secondary hypertension in particular should be considered in children aged below 6 years, and in cases of severe hypertension accompanied by end-organ damage. Endocrine causes are involved in the etiology of hypertension with a rate of 0.05–6%. They are rarer compared with other causes, but the diagnosis is important because hypertension can regress with treatment of the etiology (2). The causes of secondary hypertension are shown in Table 2.

Table 1. New blood pressure classification and recommendations (2)

Classification	<13 years	<13 years	Recommendations
Normal blood pressure	<90th percentile	<120/80 mm Hg	If normal or repeated measurements are normal, it is recommended that it should be measured at the well child follow-up visit one year later
Increased blood pressure	Between ≥90th percentile and <95th percentile or between 120/80 mm Hg and <95th percentile (whichever is lower)	Between 120/80 and 129/80 mm Hg	**1st step:** Lifestyle modifications (healthy diet, sleep and physical activity) should be recommended. The patient should be asked to attend a follow-up visit six months later. If necessary, the patient may be referred to the unit related to nutrition and/or body weight. **2nd step:** If increased blood pressure still persists in the end of follow-up visits performed with 6 month intervals at the first year after presentation, ABPM and diagnostic tests should be performed, and the child should be referred to pediatric nephrology.
Stage 1 hypertension	Between ≥95th percentile and <95th percentile+12 mm Hg or between 130/80 and 139/89 mm Hg (whichever is lower)	Between 130/80 and 139/89 mm Hg	**1st step:** If blood pressure is found at a level of stage 1 hypertension and is asymptomatic, the patient is asked to attend follow-up visits with 1–2 week intervals. **2nd step:** blood pressure is measured in the right arm, left arm and single leg (right or left). Recommendations related to nutrition and body weight control are given. **3rd step:** If still increased after three follow-up visits, ABPM and investigations should be performed. The child should be referred to pediatric nephrology or pediatric cardiology.
Stage 2 hypertension	≥95th p+12 mm Hg or ≥140/90 mm Hg	≥140/90 mm Hg	**1st step:** If blood pressure measurement indicates stage 2 hypertension and the patient is asymptomatic, blood pressure is measured in the right arm, left arm and single leg. Lifestyle recommendations are given. **2nd step:** If still increased in one week, the patient is referred to relevant center. ABPM is recommended. *If the patient is symptomatic or if the blood pressure value is in the 95th percentile+30 mm Hg or above 180/120 mm Hg, however, the patient is referred to emergency department

BP: Blood pressure; ABPM: Ambulatory blood pressure measurement

5. Diagnostic approach

History

Detailed history including perinatal history, previous treatments, current medications, nutritional history, history of physical activity, psychosocial history and familial history, should be obtained (Table 3). Complications experienced by the mother during pregnancy, gestational age, birth weight, and history of hospitalization in the neonatal intensive care unit, if present, and especially history of intervention (including umbilical catheter) should be interrogated.

Nutritional habits should be interrogated in detail in patients who are investigated because of hypertension. It is known that increased salt intake leads to childhood hypertension and to an increase in left ventricular mass index. Increased fat intake is associated with adiposity

Table 2. Causes of secondary hypertension and assistive diagnostic tests (1, 2)

Chronic renal failure	Erythrocyte, protein, erythrocyte cylinders in urinalysis
	Serum potassium and creatinine
	Renal USG
Renovascular hypertension	Renin
	Renal Doppler USG
	MR/CT angiography
Aortic coarctation	ECHO
Pheochromocytoma	Catecholamine or metanephrine in 24-hour urine and in plasma
	MRI
	MIBG
Hyperthyroidism	TSH, fT3, fT4
Cushing syndrome	Plasma cortisol, ACTH
	Free cortisol in 24-hour urine
Congenital adrenal hyperplasia	Plasma deoxycorticosterone and corticosterone, 18-hydroxycorticosterone, 18-hydroxy deoxycorticosterone and 11 deoxycortisole
Monogenic hypertension	Plasma renin, serum electrolytes, Familial history
(Familial hyperaldosteronism type 1 or glucocorticoid remediable aldosteronism, pseudohypoaldosteronism type 2 (Gordon syndrome), overt mineralocorticoid excess, familial glucocorticoid resistance, mineralocorticoid receptor activating mutation and congenital adrenal hyperplasia)	(Plasma renin level is suppressed and sodium absorption in the distal tubule is increased. Serum potassium anomalies, metabolic acid-base disorders and abnormal plasma aldosterone concentrations may accompany)
Drugs	Oral contraceptives, glucocorticoids, NSAIDs
	Sympathomimetics, antiinflammatory drugs, erythropoietin, cyclosporine, tacrolimus, cocaine, metabolic steroids, pseudoephedrine
Heavy metals	History, plasma level
(e.g. lead, cadmium, mercury, phthalates)	(exposure to mercury is especially associated with acute severe hypertension)

USG: Ultrasonography; ECHO: Echocardiography; MIBG: i123 metaiodobenzylguanidine; ACTH: Adrenocorticotropic hormone; TSH: Thyroid- stimulating hormone; ft3: free triiodothyronine; fT4: free thyroxine; NSAID: Non-steroid anti-inflammatory drug

and central obesity. Consumption of take-home foods and packaged foods should be interrogated. Information about intake of vegetable-fruit and milk products and patients' physical activity states should be obtained.

Physical examination

Weight, height, body mass index (BMI) and percentiles should be evaluated in all children. In children who have a diagnosis of hypertension, BP should be measured in the right arm, left arm, and single leg. The blood pressure is normally 10–20 mm Hg higher in the leg measurements compared with arm measurements. If the contrary is found, evaluation in terms of aortic coarctation should be made (1, 2). With detailed physical examinations, both secondary causes of hypertension can be diagnosed, and findings related to end-organ damage can be identified (Table 4).

Laboratory tests

The objective of laboratory tests is to investigate underlying secondary causes. Simple screening tests should be performed primarily. If history, physical examination, and initial tests cause suspicion, specific tests should be performed (Table 2 and 5). Genetic analysis should be performed in terms of monogenic hypertension if plasma renin activity is suppressed or the aldosterone/renin ratio is increased (>10, aldosterone ng/dL, renin ng/mL), if there is a family member who was diagnosed as having hypertension at early age or if hypokalemia accompanies. As there are insufficient data related to microalbuminuria and blood uric acid levels, routine use of these tests is not recommended (2).

Imaging for renovascular disease

Doppler renal ultrasonography (USG) may be used with

Table 3. Symptoms and findings that should be noted in the history in patients presenting with hypertension (1, 2)

1. History characteristics
   - a. Evaluation of risk factors
     - Diabetes mellitus
     - Obesity
     - Physical activity
     - Eating habits (consumption of salt and take-home foods)
     - Alcohol
     - Sleep history (snoring, apnea)
   - b. Perinatal history
     - Birth weight and gestational age
     - Oligohydramniosis
     - Hypoxia, asphyxia
     - Umbilical artery catheterization
     - Renal artery/vein thrombosis
   - c. Present morbidities
     - Urinary tract infection/renal/urologic diseases
     - Systemic diseases (systemic lupus erythematosus)
     - Cardiac
     - Endocrine
     - Neurologic
     - Growth retardation
   - d. History of drug use
     - Anti-hypertensive drugs
     - Steroid, cyclosporine, tacrolimus
     - Tricyclic antidepressants, decongestants
     - Contraceptive pills
   - e. Familial history
     - Hypertension
     - Cardiovascular and cerebrovascular disease
     - Diabetes mellitus
     - Dyslipidemia
     - Obesity
     - Congenital renal/endocrine diseases (polycystic kidney, Alport syndrome, adrenal tumors, MEN type 2, monogenic hypertension)
     - Syndromes accompanied by hypertension (neurofibromatosis)
   - f. Diagnosis and management of hypertension
     - Age at the time of diagnosis
     - Previous blood pressure measurements
     - Drugs used currently and previously
     - Treatment compliance and adverse effect profile
2. Symptoms
   - a. Symptoms that suggest secondary hypertension
     - Dysuria, thirst/ polyuria, nocturia, hematuria
     - Edema, weight loss, inability to gain weight
     - Palpitations, sweating, fever, paleness, flushing
     - Cold extremities, claudication
     - Virilization, primary amenorrhea and male pseudohermaphrodism
   - b. Symptoms suggesting organ damage
     - Headache, epistaxis, dizziness, visual disturbance
     - Facial paralysis, stroke, seizure

the objective of screening children aged 8 years and older with normal weight who are considered to have renal artery stenosis (RAS). Patient compliance, radiologist's experience, the child's age and BMI should be considered. In the diagnosis of RAS, conventional arteriography is the gold standard. Magnetic resonance (MR) or computed tomography (CT) are acceptable noninvasive imaging methods. Although CT angiography has diagnostic advantages compared with MR angiography, the increased exposure to radiation should be considered. Nuclear renography should not be used in children due its low sensitivity and specificity (2).

Investigations directed to end-organ damage

Echocardiography: It is important to evaluate the presence of left ventricular hypertrophy (LVH). Left ventricular hypertrophy is associated with the disease course in adulthood. The AAP recommends that cardiac imaging should include left ventricular ejection fraction, mass, and wall thickness. Cardiac imaging should be performed at the beginning of treatment. In severe acute-onset hypertension, left ventricular ejection fraction may be reduced to a level that may lead to congestive heart failure.

End-organ damage should be checked at 6–12–month intervals. If end-organ damage is not present at the first presentation, yearly checking is sufficient (2).

Fundoscopic examination: Fundoscopic examinations are recommended in acute severe hypertension (encephalopathy or malign hypertension). Hypertensive retinopathy findings (hemorrhage, exudate, disc edema) have been found in approximately 18% of children with severe hypertension (29).

Microalbuminuria: Microalbuminuria may be observed in conditions such as chronic renal failure, obesity, insulin resistance, dyslipidemia, and intense physical activity in children. However, there are insufficient data related to the place of microalbuminuria in childhood hypertension

Table 4. Physical examination signs to be noted in patients evaluated because of hypertension

General examination: edema, cushingoid appearance, growth retardation
Anthropometric measurements: body weight, height, BMI
Abdominal examination
Mass (e.g. Wilms tumor, neuroblastoma, pheochromocytoma, polycystic kidney disease)
Hepatosplenomegaly (autosomal recessive polycystic kidney disease)
Cardiovascular examination
Pulse and BP measurement in both arms and in one leg
Murmurs: heart, abdomen, neck, back
Left ventricular hypertrophy or findings of heart failure
Characteristics related to syndromes/conditions where hypertension is observed
Neurocutaneous diseases
Genetic (Turner syndrome, Williams syndrome, Marfan syndrome)
Endocrine (Cushing syndrome, hyperthyroidism, congenital adrenal hyperplasia)
Rheumatic (SLE, vasculitis)
Neurological examination
Fundoscopic examination
Facial paralysis
Other (stroke)

BMI: Body mass index; BP: Blood pressure; SLE: Systemic lupus erythematosus

Table 5. Laboratory evaluation in patients evaluated because of hypertension according to the American Academy of Pediatrics guideline (2)

All patients	Obese patients	Optional tests
Urinalysis	Hemoglobin A1C	Fasting serum glucose (for screening DM)
Biochemical panel including electrolytes, BUN and creatinine	AST, ALT	TSH (if hyperthyroisidm is suspected)
Lipid profile (fasting or postprandial, HDL and total cholesterol)	Fasting lipid panel (dyslipidemia screening)	Drug screening
Renal USG		Sleep study (If history of snoring, daytime drawsiness or apnea is present)
		Hemogram (if growth retardation and disrupted urinalysis is found)

BUN: Blood urea nitrogen; HDL: High-density lipoprotein; USG: Ultrasonography; DM: Diabetes mellitus

and its use as a cardiovascular risk indicator in the long term. Therefore, microalbumin measurements are not routinely recommended in children and adolescents with primary hypertension (2).

Vascular evaluation: Measurement of carotid intima-media thickness and pulse wave velocity (PWV) using ultrasonography is used in adults. However, vascular evaluation is not recommended in children because there are insufficient data to support routine use (2).

6. Treatment

Target blood pressure values

The objective in treatment is to prevent end-organ damage and to reduce the risk of hypertension and cardiovascular disease in adulthood. The target blood pressure is <130/80 mm Hg or a SBP and DBP values below the 90th percentile (whichever is lower). The mean arterial pressure should be kept below the 50th percentile in patients with chronic renal disease (2).

Lifestyle modification

Both the AAP and ESH recommend lifestyle modifications for controlling BP (1, 2). In particular, restriction of salt intake and increased consumption of olive oil are important in the control of blood pressure. The "Dietary Approach to Stop Hypertension" (DASH)-type diet recommends consumption of high levels of fruit, vegetables, low-fat milk products, whole grain products, chicken, fish, hazelnuts, and lean meat (30).

Walking for 30–60 minutes 3–5 times weekly should be recommended as an activity to help to reduce blood pressure (1, 2, 31). A combination of diet and activity provides better outcomes.

Pharmacologic treatment-when?

Pharmacologic treatment may be initiated if the patient is hypertensive despite lifestyle modifications, symptomatic hypertension is present, stage 2 hypertension is present in the absence of modifiable risk factors (such as obesity), end-organ damage such as LVH is present, and chronic renal disease or diabetes is present at any stage of hypertension.

Treatment should be initiated with a single drug and at the lowest dose. After treatment is initiated, blood pressure should be measured at 2–4–week intervals. The dose should be increased if the blood pressure does not reach the targeted value. Adverse effects should also be considered for dose increments. If hypertension is controlled, evaluation with 4–6–week intervals is sufficient.

A second drug is added if hypertension cannot be controlled with a single drug. The second agent to choose is diuretics because antihypertensive drugs cause water and salt retention. In this period, lifestyle modifications should definitely be continued. Consumption of healthy foods including mainly vegetables and fruit, reduced salt consumption, and exercise should be emphasized.

After the targeted blood pressure is reached, follow-up evaluation is performed with 3–4–month intervals. Home measurements may be used for follow-up. Ambulatory blood pressure measurements may be used in risky conditions including chronic renal disease. At each follow-up visit, it should be interrogated as to how the treatment is being used and if the patient adheres to the recommendations, and laboratory tests should be examined, if necessary (1, 2).

Pharmacologic treatment-which drugs?

There are limited data related to antihypertensives used in childhood, and their adverse effects and long-term cardiovascular outcomes. The AAP recommends angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), long-acting calcium channel blockers or thiazide diuretics as initial treatment (2). Beta-blocker drugs should not be used as first-line therapy in children in terms of safety. Angiotensin converting enzyme inhibitors and ARBs are contraindicated during pregnancy because they can lead to congenital malformation and mortality in the fetus. It is recommended that they should not be used in adolescents and in patients of child-bearing potential.

In patients in whom chronic renal disease, proteinuria or diabetes is involved in the etiology of hypertension, an ARB or ACE inhibitor is recommended as the first-line therapy if there is no contraindication. Other therapies (α-blocker, β-blocker, combination of both, potassium-sparing diuretics and vasodilators) may be preferred in patients who do not respond to two or more drugs. The pharmacologic agents that are used most commonly in the treatment of hypertension and their doses are shown in Table 6 (1, 2).

Treatment-resistant hypertension

Treatment-resistant hypertension is defined as persistence of hypertension despite intake of three or more antihypertensive drugs at the highest doses (2, 32). One should be sure that treatment is received at the recommended doses. Renovascular hypertension should be considered primarily in the differential diagnosis. Renal Doppler USG, MR or CT angiography may be planned according to the clinical status. Renin-aldosterone values and serum electrolytes may give information in terms of monogenic hypertension. Ambulatory blood pressure measurements may be used to confirm the diagnosis.

Treatment consists of salt restriction, avoidance of substances that may increase blood pressure, and if present, investigation and elimination of the cause of secondary hypertension that could not be diagnosed previously.

In pharmacologic treatment, extended release drugs should be preferred and the highest dose that will not lead to adverse effects should be used. All drugs should be used as instructed, and one of these drugs should be a diuretic (2, 30). Clinical studies have shown that the addition of aldosterone receptor blockers (such as spironolactone) is helpful in the treatment of undiagnosed hyperaldosteronism and in the elimination of excess volume in adults. There are insufficient data related to this issue in children, and it is recommended that precautions similar to those taken in adults should be taken (2).

Table 6. Antihypertensive drugs and doses (1)

Drug class	Drug	Initial dose	Maximum dose	Daily intervals	Contraindications
ACE inhibitors	Captopril	0.3–0.5 mg/kg/dose	6 mg/kg	2–3 doses	Pregnancy, hyperkalemia, single kidney or renal artery stenosis, renal artery stenosis in both kidneys
	Enalapril	0.08–0.6 mg/kg		Single dose	
	Ramipril	1.5–6mg		Single dose	
ARBs	Losartan	0.7 mg/kg–50 mg	1.4 mg–100 mg	Single-two doses	
Calcium channel blockers	Amlodipine	0.06–0.3 mg/kg	5–10 mg	Single dose	Congestive heart failure
	Nifedipine (extended release form)	0.25–0.5 mg/kg	3 mg/kg –120 mg	Single-two doses	
Diuretic	Amiloride	0.4–0.6 mg/kg	20 mg	Single dose	Sports people, diabetes mellitus
	Furosemide	0.5–2 mg/kg	6 mg/kg	Single-two doses	
	Spironolactone	1 mg/kg	3.3 mg/kg–100 mg	Single-two doses	
	Hydrochlorothiazide	0.5–1 mg/kg	3 mg/kg/day	Single-two doses	
Beta blocker	Atenolol	0.5–1 mg/kg	2 mg/kg–100 mg	Single-two doses	Asthma
	Propranolol	1 mg/kg	4 mg/kg–640 mg	2–3 doses	
Central alpha-blocker	Clonidine	0.2 mg/kg	2.4 mg	2 doses	
Peripheral alpha-blocker	Doxazosin	1 mg	4 mg	Single dose	
	Prazosin	0.05–0.1 mg/kg	0.5 mg/kg	3 doses	
Vasodilator	Hydralazine	0.75 mg/kg	7.5 mg/kg–200 mg	4 doses	
	Minoxidil	0.2 mg/kg	50–100 mg	Single-3 doses	

7. Hypertensive emergencies

Life-threatening conditions related to hypertension constitute hypertensive emergencies, which should be considered in the presence of a blood pressure value at the 95th percentile+30 mm Hg. Accompanying end-organ damage is mostly related to the nervous system (headache, nausea/vomiting, seizure, confusion, visual symptoms, and facial nerve paralysis), heart (LVH, congestive heart failure, cardiomyopathy) or kidney (acute renal injury, proteinuria) (33). Acute cerebral symptoms mostly develop suddenly and are observed in conditions where there is insufficient time for autoregulation in cerebral blood flow. Mostly, there is an underlying secondary cause (renal, endocrine or cardiac). It is recommended that patients should be followed up in the intensive care unit, fundoscopic examinations (hemorrhage, exudate or papilledema) and detailed neurologic examinations should be performed, and evaluations in terms of posterior reversible encephalopathy (PRES) should be performed using cranial CT or MRI (1).

There are limited data related to acute severe hypertension in children and adolescents. Most data are based on adult studies. Oral treatment should be considered if the patient can use oral medication and life-threatening complications are absent. Intravenous agents should be considered if oral intake is not possible and the patient's clinical status is not stable or severe complications are present (such as congestive heart failure). The planned reduction in blood pressure should be calculated and 25% of this target should be achieved in the first 8 hours; the remainder should be achieved in 12–24 hours. In the short-term, the 95th percentile values should be targeted (1, 2, 33).

8. Hypertension and sports

Children should be encouraged to actively participate in sports and to increase physical activity. Permission for participation can be given after blood pressure is controlled with appropriate antihypertensive drugs if the patient wishes to participate in competitive sports and if LVH is present. If the patient is going to participate in static sports (e.g. weight lifting, boxing), blood pressure should be controlled in advance even if end-organ damage is absent (2).

9. Prevention of hypertension

It is known that hypertension in childhood and adolescence persists in adulthood. Children who carry risk epidemiologically should be determined. In particular, the presence of family members with a diagnosis of hypertension, overweight and obesity, high-sodium diets, consumption of unhealthy foods, reduced consumption of vegetables and fruit, inactive lifestyle, and other risk fac-

tors should be considered. Even if familial history cannot be modified, it is possible to increase physical activity and initiate a DASH-type diet (e.g. rich in vegetables and fruit, foods containing whole grain and low-fat meat and milk products, diet poor in saturated fat and sugar) (1, 2). Walking for 60 minutes daily is important in controlling blood pressure. Sleep hours should be regulated and avoidance of smoking should be supported. Daily salt intake should be restricted to less than 3 g (2). These preventive strategies should constitute the primary step in fighting childhood and adolescence hypertension.

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Appendix 1. Significant updates in hypertension guidelines

1. New percentile tables for normal blood pressure have been established with individuals with normal body weight.
2. A screening table appropriate for use by primary care physicians has been established.
3. For individuals aged 13 years and above, the American Heart Association and American College of Cardiology guideline normal values have been recommended.
4. Blood pressure classification has been updated, and specific recommendations have been made by classification.
5. The place of ambulatory blood pressure measurement in the diagnosis and treatment of hypertension, has been expanded.
6. Detailed assessment for secondary causes is not recommended, if the child is aged six years and above, accompanying obesity/overweight and familial history of hypertension are present, and physical examination and history suggesting secondary causes are absent.
7. Electrocardiography is not recommended for the evaluation of left ventricular hypertrophy.
8. Echocardiography is recommended for the evaluation of target organ damage.
9. In children aged eight years and above, renal doppler ultrasonography to be performed by an experienced radiologist, is recommended, if renal artery stenosis is considered. Diuretic renal scintigraphy is not recommended in children.
10. The target blood pressure is <90th percentile of the systolic and diastolic blood pressure or below 120/80 mmHg.
11. Life-style modifications including healthy diet, limitation of salt intake and exercise, should be recommended to all children.
12. If hypertension persists despite life-style modifications, pharmacologic treatment is recommended
    - in presence of target organ damage such as left ventricular hypertrophy
    - in presence of symptomatic hypertension or stage 2 hypertension in the absence of modifiable factors (such as obesity).
13. First-line therapy should include a single drug at the minimum dose. Angiotensin converting enzyme inhibitors, ARBs, calcium channel blockers or diuretics may be used.