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TOPIC HIGHLIGHT

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# Pediatric hypertension: An update on a burning problem

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## Abstract

A large number of adults worldwide suffer from essential hypertension, and because blood pressures (BPs) tend to remain within the same percentiles throughout life, it has been postulated that hypertensive pressures can be tracked from childhood to adulthood. Thus, children with higher BPs are more likely to become hypertensive adults. These "pre-hypertensive" subjects can be identified by measuring arterial BP at a young age, and compared with age, gender and height-specific references. The majority of studies report that 1 to 5% of children and adolescents are hypertensive, defined as a BP > 95th percentile, with higher prevalence rates reported for some isolated geographic areas. However, the actual prevalence of hypertension in children and adolescents remains to be fully elucidated. In addition to these young "pre-hypertensive" subjects, there are also children and adolescents with a normal-high BP (90th-95th percentile). Early intervention may help prevent the development of essential hypertension as they age. An initial attempt should be made to lower their BP by non-pharmacologic measures, such as weight reduction, aerobic physical exercise, and lowered sodium intake. A pharmacological treatment is usually needed should these measures fail to lower BP. The majority of antihypertensive drugs are not formulated for pediatric patients, and have thus not been investigated in great detail. The purpose of this review is to provide an update concerning juvenile hypertension, and highlight recent developments in epidemiology, diagnostic methods, and relevant therapies.



**Key words:** Children; Hypertension; Blood pressure; Epidemiology; Diagnosis; Therapy

**Core tip:** It is generally presumed by cardiologists that arterial hypertension is a disease that typically develops only in adult life. However, a number of studies testify that this pathologic process can begin early in childhood, as evidenced by occasional increases in blood pressure (BP) or abnormal BP responses to physical or psychological stress. This review provides a detailed analysis concerning the epidemiology, diagnostic methods, and therapies for pediatric hypertension.

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## INTRODUCTION

Although secondary arterial hypertension (HTN) was thought to be more frequent than essential arterial HTN in children, recent reports indicate that essential HTN is the most frequently manifested form of the disease during both childhood and adolescence[1]. Pediatric HTN is now commonly known worldwide to be an early risk factor for cardiovascular morbidity and mortality. The essential HTN subsequently detected in adults may have already been manifested at an early age, observed as occasional raises in blood pressure (BP) or abnormal BP response to physical or psychological stress. Similar to other types of chronic illness, the hypertensive process likely develops several decades prior to the onset of clinical signs and symptoms[2,3]. As BP levels are typically retained throughout life, children with higher BPs are more likely to become hypertensive adults[4].

Extensive normative data on BP in children have long been available both in the United States and Europe. Pediatric BP nomograms were developed by the Task Force on BP Control in Children, commissioned by the National Heart, Lung, and Blood Institute of the National Institutes of Health, by using results obtained from 83000 children and adolescents of both genders. The percentile curves were first published in 1987 and described age-specific distributions of systolic and diastolic BPs for an age range between 5 and 17 years, with corrections for height and weight[5]. The third report from the Task Force, published in 1996, provided additional details regarding the diagnosis and treatment of HTN in infants and children[6]. In 2004, the fourth report added further information and adapted the data to growth charts previously developed from the Centers for Disease Control and Prevention[7]. In an update to the HTN guidelines published by the European Society of Cardiology in 2009, a new chapter was devoted to HTN in children, with an approach similar to the American version[8].

In accordance with the recommendations of the Task Force, BP is considered normal when the systolic and/or diastolic values are less than the 90$^{th}$ percentile for the child's age, sex, and height. BP is considered high for systolic and/or diastolic values > 95$^{th}$ percentile. For BPs between the 90$^{th}$ and 95$^{th}$ percentile, a new category (pre-HTN) has been introduced, defined as a BP ⩾ 120/80 mmHg. In cases where systolic and diastolic pressures are discrepant with respect to classification, the child's condition should be categorized using the higher value[7].

BP usually depends on the balance between cardiac output and vascular resistance. BP increases following a rise in either of these variables without a compensatory decrease from the other[9]. Factors affecting cardiac output include the following: baroreceptors, extracellular volume, effective circulating volumes of atrial natriuretic hormones, mineralocorticoids, and angiotensin, as well as contributions from the sympathetic nervous system[10]. Factors influencing vascular resistance include pressors, such as angiotensin Ⅱ, calcium (intracellular), catecholamines, vasopressin and the sympathetic nervous system, as well as depressors, such as atrial natriuretic hormones, endothelial relaxing factors, kinines, prostaglandin $E_2$ and prostaglandin $I_2$[10].

Changes in electrolyte blood concentrations (particularly changes in sodium, calcium, and potassium levels), may also affect vascular resistance. Under normal conditions, extracellular volume is maintained by the excretion of sodium in amounts equal to those ingested. Retention of sodium results in an increase in extracellular volume, and an elevation of BP. Sodium balance is restored by renal changes in both the glomerular filtration rate and the tubular reabsorption of sodium, resulting in natriuretic excretion of excess sodium. Elevated calcium concentrations can increase vascular smooth cell contractility, and stimulate the release of renin, synthesis of epinephrine, and enhance sympathetic nervous system activity and increasing BP. Reduced potassium intake can also increase BP by stimulating the production and release of renin and reducing natriuresis. The renin-angiotensin system and the hypothalamus-hypophysis-adrenal gland axis are suspected to be involved in the elevation of BP as well[11,12]. This complexity demonstrates the difficulty in identifying the mechanism that accounts for HTN, and explains why treatment is often designed to affect regulatory factors rather than the cause of the disease. For example, BP can be elevated as a result of increased sodium renal reabsorption, insulin resistance, leptin resistance, vascular resistance, and sympathetic tone caused by hyperinsulinemia.

## EPIDEMIOLOGY

The prevalence of HTN in the pediatric population was examined as early as 1963[13], though the precise rates are not known. The majority of studies report rates ranging from 1% to 5%, although prevalence as high as 10% has been reported for some isolated geographic areas[14-19]. However, regression to the mean from repeated measurements included from more recent studies has placed the prevalence of HTN at less than 5%[19]. The discrepancy in reported values is likely due, in part, to the arbitrary definition of HTN and the BP measurement method[20]. The frequent use of non-specific population BP nomograms may exaggerate the prevalence of HTN in children and adolescents in some specific geographic areas. In fact, genetic and environmental differences can influence HTN incidence between regions. Although reference standards established in the US have been adopted worldwide, many local percentile curves are still being used, especially in northern Europe[14,16,20,21], and clinicians from every ethnic group or geographic area in the world should produce their own national BP nomograms relating to age, gender, and height.

A review by Chiolero *et al*[13] examined the HTN prevalence rates reported in large-scale school-based studies (> 2000 children) from all over the world published between 1980 and 2006. Most studies determined HTN from a single BP measurement, with a prevalence of isolated systolic HTN at 7.2%-19.4%. However, in the only study where three different BP measurements were used, the overall prevalence of HTN was 4.5%. While some authorities recommend only one recording, others advocate taking the average of two or three pressures, which more accurately reflects the overall BP of the individual patient[22]. According to the United States Task Force, elevated pressures must be confirmed on repeated visits before characterizing a child as having HTN, with at least three different measurements strongly recommended[7,14]. The prevalence of pediatric HTN can also be influenced by the method of measurement, as oscillometric devices vary by manufacturer and require validation and calibration, and auscultation is subject to operator-dependent biases such as rounding errors (digit preference), expectation bias, and operator skill[23].

Recent reports on the prevalence of normal-high BP or pre-HTN (between 90th and 95th percentile) in younger individuals is concerning, as it is associated with an intermediate degree of organ damage[24]. In three different recent surveys performed in the United States, the prevalence of normal-high BP ranged from 3.4% to 31.4% in large cohorts of children and adolescents, which was largely influenced by age and weight[25-27]. In a study on high school students by McNiece *et al*[28], the prevalence of combined pre-HTN and HTN was over 30% in obese boys and 23%-30% in obese girls, depending on ethnicity. A three-year longitudinal screening of BP in Italy found that pediatric pre-HTN and HTN are equally prevalent[29,30].

## DIAGNOSTIC TOOLS

Two non-invasive methods, auscultatory and oscillometric, are typically used to diagnose HTN in children and adults. When the auscultatory method is used, pediatric systolic BP is defined on the basis of the first Korotkoff sound, while the diastolic BP usually corresponds to the fifth Korotkoff sound[31]. However, a meta-analysis from the Bogalusa Heart Study indicated that the fourth Korotkoff sound is a more reliable measure of diastolic BP and a better predictor of adult HTN than the fifth[32]. Moreover, a comparison of these methods for BP measurement in the San Antonio Triethnic Children's BP Study indicated that systolic and diastolic pressure readings were 10 and 5 mmHg higher, respectively, with an oscillometric compared to an auscultatory device[33]. Thus, caution must be used when diagnosing HTN with an automated device.

The current United States Task Force recommendation for choosing an appropriate size cuff for measuring BP is a bladder width equal to 40% of the upper arm circumference (UAC). However, most physicians use the older two-thirds or three-fourths upper arm length (UAL) recommendations to choose a cuff, and significant differences have been highlighted between the methods. Specifically, systolic BP measured using the 40% UAC criterion reflects a directly measured radial arterial pressure and significantly overestimates the diastolic pressure. Using available cuffs for indirect measurements by two-thirds and three-quarters UAL criteria significantly underestimates systolic as well as diastolic BPs when compared with radial intra-arterial BP[34]. Therefore, recommendations for BP cuff selection should be reviewed. Moreover, labeling of BP cuffs for infant, pediatric, small adult, adult, and large adult patients is misleading, and such designations should be eliminated. Cuff sizes should be standardized, indicate bladder size, and be uniformly color-coded for convenience[35].

Twenty-four-hour ambulatory BP monitoring (ABPM) can more precisely characterize changes in BP during daily activities, and is superior to clinical BP monitoring in predicting cardiovascular morbidity and mortality in adults[36,37]. As children and adolescents tend to be more emotional with consequent BP raises that can indicate HTN, ABPM may differentiate those with "white coat" HTN from those with chronic HTN. As a result, ABPM is gaining acceptance as a useful modality for the evaluation of BP levels in research and clinical settings[38,39], and may help overcome some of the challenges clinicians face when attempting to categorize a young patient's BP levels[40]. ABPM is recommended for the standard assessment of pediatric patients for confirming the diagnosis of HTN (*e.g.*, exclusion of "white coat" HTN), evaluating for the presence of masked HTN, assessing BP variability, determining dipping status in patients at high risk for larger organ damage (*e.g.*, those suffering from sleep apnea), assessing the severity and persistence of HTN, and evaluating BP levels in chronic pediatric diseases associated with HTN. In addition, ABPM can be used to evaluate the effectiveness of drug therapy, monitor for drug-resistant HTN, and determine whether symptoms are a result of drug-related hypotension.

## PEDIATRIC BP MONITORING

For monitoring BP in children, a suitable ABPM device should be selected, such as devices with appropriate cuff sizes that have been validated according to the standards set by the Association for Advancement in Medical Innovation or the British Heart Society. Moreover, individuals with specific training in the application and interpretation of ABPM data in pediatric patients should obtain the readings using a standard approach. Monitors should be applied to the non-dominant arm unless contraindicated (*e.g.*, the presence of an arteriovenous fistula). After application, results should be compared with resting BP measured in the clinic using the same technique as used by the ambulatory device (auscultatory or oscillometric). Calibration between methods should be considered adequate when there is agreement within 5 mmHg between the average of three clinic and three ambulatory BP measurements. Cuff placement and proper device function should be verified for values falling outside this range. Wide disagreement between resting and ambulatory device measurements of diastolic BP may occur with the use of auscultatory ABPM devices that lack pediatric settings to adjust for the larger fourth and fifth Korotkoff sound differences often seen in younger children. If this occurs, an oscillometric device may be preferred, or interpretation may be restricted only to the values for systolic BP.

Patients or their guardians should be instructed to record their antihypertensive medication intake, and activity, sleep, and wake times in a diary. As a sufficient number of valid BP recordings are needed to provide interpretable data, devices should be programmed to record BP every 20 to 30 min during waking hours and every 30 to 60 min during sleep hours. ABPM recordings should be edited for outlying values and data should be visually inspected for gross inconsistencies, such as BPs and heart rates that fall considerably outside the ranges normal for the patient's age, such as a systolic BP 60 to 220 mmHg, diastolic BP 35 to 120 mmHg, heart rate 40 to 180 beats per minute, or pulse pressure 40 to 120 mmHg. As a general rule, the above stated limits should be programmed into the ABPM software to minimize subjective editing of ABPM data. Standard calculations should be reported (mean ambulatory systolic and diastolic BP during the 24 h, daytime, and nighttime periods). Dipping (percent day-night difference) should be determined for systolic and diastolic pressures: (mean daytime BP-mean nighttime BP)/mean daytime BP × 100. ABPM levels should be interpreted using appropriate pediatric normative data, such as gender- and height-specific data obtained from large pediatric populations using similar techniques. A diagnosis of HTN is indicated by significant abnormalities in ambulatory BP levels and loads occurring during the daytime, nighttime, or the entire 24-h period[41,42].

## THERAPY

An initial attempt should be made to lower BP by means of non-pharmacologic procedures, in spite of scientific evidence underlining the limited efficacy of this type of approach. There is a strong association between BP values and body weight, and weight loss in children is correlated with lowered BPs[43-48]. Therefore, the primary objective should be to achieve and maintain a normal body weight. Regular exercise and a reduction in sedentary activities (such as watching TV or playing videogames) will result in enhanced weight loss and improved BP values[49]. In addition, the intake of sugary drinks and calorie-rich foods should be limited and fresh fruits and vegetables encouraged, to ensure a satisfying and healthy diet. The help of a dietician specializing in the treatment of children and adolescents may be particularly useful in motivating self-control[50-52].

Sodium intake should also be limited. Many studies have reported that a reduced-sodium diet decreases BP values in children by 1-3 mmHg[53-58]. A randomized trial demonstrated that adolescent BPs were significantly reduced by limiting sodium intake in early childhood[59]. Current recommendations for sodium intake are 1.2 g/d for children between the ages of 4 and 8 years, and 1.5 g/d for older children[60], which are lower than the amount of sodium present in a typical daily diet. Thus, a reduction in salt intake together with a reduced-calorie diet may enhance the effects achieved by weight loss alone[7]. Other lifestyle changes, such as improving the quality of sleep or quitting smoking, can also help to lower BP[61,62].

Pharmacologic treatment is indicated for HTN that persists despite these lifestyle changes, as well as for secondary HTN, HTN associated with organ dysfunction, and HTN in diabetic patients (type 1 and type 2), according to United States guidelines[7]. In addition, children or adolescents with dyslipidemia, although not included in the therapeutic indications, may also benefit from administration of a low-dose antihypertensive therapy[63,64]. The main therapeutic aim is to reduce BP to below the 95$^{th}$ percentile, or below the 90$^{th}$ percentile if other cardiovascular risk factors are present. The number of antihypertensive drugs specifically indicated for use in children has risen considerably in recent years, including beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers, calcium channel blockers, and diuretics. Trials using these drugs in children have been directed almost exclusively at assessing their efficacy in lowering BP, and show these drugs to be safe and well-tolerated with satisfactory short-term BP reduction[7]. Several classes of drugs are particularly indicated for use in hypertensive subjects with specific concomitant diseases. As an example, ACE inhibitors and angiotensin-receptor blockers are recommended for hypertensive diabetics or those with microalbuminuria, as well as in patients with chronic renal failure and proteinuria, whereas beta-blockers and calcium channel blockers are indicated for use in patients affected by migraine and headache. The lowest dose of antihypertensive drug should be used and gradually increased until the desired BP values are achieved. If peak doses are reached without any appreciable benefit, or the young patient manifests adverse effects, it may be advisable to implement a combined therapy with a second drug that enhances the efficacy of the first[7]. Particular care should be taken in monitoring children for organ dysfunction and potential adverse effects, as well as in assessing the efficacy of treatment. For example, children undergoing treatment with ACE inhibitors and/or diuretics should be carefully monitored for electrolytic balance. Combination pharmacotherapy in children has not been well studied, and is not recommended as an initial treatment. Multi-drug combinations, such as bisoprolol and hydrochlorothiazide, should only be prescribed in particularly unresponsive and severe cases[65]. A "step-down" therapy may be implemented in patients achieving satisfactory BP values over a lengthy period, such as a gradual tapering of treatment in overweight/obese children who have lost a significant amount of weight. In some cases, treatment may be withdrawn, though patients should undergo long-term follow-up to monitor for relapse[7,66].

Pharmacologic treatment is inherently more difficult in children than it is in adults. Unlike children, adults are able to learn to live with their condition, maintain treatment compliance, and are mindful of the consequences of untreated HTN[67]. The majority of drugs available for the treatment of HTN do not have pediatric formulations, and often assume a distasteful flavor when divided or pulverized, though thiazide diuretics (hydrochlorothiazide and chlorthalidone), calcium channel blockers (lercanidipine), and angiotensin receptor antagonists (candesartan) do not have any flavor and can therefore easily be administered to small children[65,68]. Drugs that are prescribed for hypertensive children should have minimal side and prolonged therapeutic effects, though slow-release formulations should be avoided as they are poorly absorbed by children and lose their prolonged effect once the tablets are split. Adverse side effects are most frequent with diuretics, followed by beta-blockers, calcium antagonists, ACE-inhibitors and fast angiotensin receptor blockers[65,68]. Moreover, similar to other classes of compounds, antihypertensive drugs have different pharmacokinetics in children, particularly in very young children; therefore, drug dosage should be adjusted[65,68].

## CONCLUSION

Cardiovascular diseases such as HTN develop slowly and their pathogenesis often begins in childhood. A routine use of specific and carefully constructed BP tables will allow pediatric clinicians and cardiologists to identify pathophysiologic conditions in their patients that may only clinically manifest after several decades. The diagnosis and treatment of pediatric high BP and HTN should therefore be considered as a preventative measure, rather than simply the tracking of an early predisposition to a fatal destiny in adulthood.

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