Research Gaps in Primary Pediatric Hypertension

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Hypertension affects >40% of the US population and is a major contributor to cardiovascular-related morbidity and mortality. Although less common among children and adolescents, hypertension affects 1% to 5% of all youth. The 2017 Clinical Practice Guideline for the Diagnosis and Management of High Blood Pressure in Children and Adolescents provided updates and strategies regarding the diagnosis and management of hypertension in youth. Despite this important information, many gaps in knowledge remain, such as the etiology, prevalence, and trends of hypertension; the utility and practicality of ambulatory blood pressure monitoring; practical goals for lifestyle modification that are generalizable; the long-term end-organ impacts of hypertension in youth; and the long-term safety and efficacy of antihypertensive therapy in youth. The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, in collaboration with the National Heart, Lung, and Blood Institute and the US Food and Drug Administration, sponsored a workshop of experts to discuss the current state of childhood primary hypertension. We highlight the results of that workshop and aim to (1) provide an overview of current practices related to the diagnosis, management, and treatment of primary pediatric hypertension; (2) identify related research gaps; and (3) propose ways to address existing research gaps.

Hypertension afflicts between 1% and 5% of all children and adolescents in the United States.[1] Rates of elevated blood pressure (BP) in children may be underestimated on the basis of current practices and guidelines because of the increasing prevalence of obesity in young people. Hypertension in youth is a condition that has been associated with target-organ changes, such as impaired cognition,[2] left ventricular hypertrophy (LVH),[3] and subclinical markers of cardiovascular disease (CVD), for example, increased carotid intima thickness.[4] Observational studies in youth have demonstrated an association between BP values >90th percentile and alterations in cardiac and vascular structure.[5–7]

It is also known that BP in childhood tracks into adulthood,[8] at which point it becomes a major contributor to the development of heart failure, stroke, and myocardial infarction. Longitudinal data linking hypertension in youth to myocardial infarction, stroke, and other hard CVD outcomes in adulthood are limited.[9] Although no randomized trials have been conducted to determine if screening for and treating hypertension in children can delay the onset, or reduce the incidence, of adverse cardiovascular outcomes in adulthood, longitudinal studies have demonstrated

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TABLE 1 BP Categories and Staging in Children and Adolescents

	Children and Adolescents 1–<13 y of Age	Adolescents ≥13 y of Age
Normal BP	<90th percentile and <120/80 mm Hg	<120/<80 mm Hg
Elevated BP	≥90th to 95th percentile or 120/80 mm Hg to <95th percentile (whichever is lower)	120/<80–129/<80 mm Hg
Stage 1 hypertension	≥95th percentile or 130/80–139/89 mm Hg (whichever is lower)	130/80–139/89 mm Hg
Stage 2 hypertension	≥95th percentile and 12 mm Hg or ≥140/90 mm Hg (whichever is lower)	≥140/90 mm Hg

Adapted from Flynn JT, Falkner BE. New clinical practice guideline for the management of high blood pressure in children and adolescents. Hypertension. 2017;70(4):683–686.

that harmful BP trajectories begin as early as age 7.[10]

The Best Pharmaceuticals for Children Act (BPCA) program sponsored a meeting on September 25, 2017, to address the topic of primary hypertension in youth, with particular focus on the current gaps in knowledge related to the identification and treatment of the disease. The BPCA is mandated by legislation that requires the National Institutes of Health, in consultation with the US Food and Drug Administration (FDA) and experts in pediatric research, to identify and prioritize drugs and therapeutic areas with existing knowledge gaps and promote and sponsor evidence-based data related to medications used to treat childhood illnesses.

The impetus for the 2017 workshop was a BPCA-cofunded retrospective review of medication use in pediatric primary care practices in various diseases, including hypertension, using the resources of the Pediatric Research in the Office Setting network. The results of this study covering a cohort of 389 079 patients were published in *Pediatrics* in December 2016.[11] Within this population, 12 138 satisfied the Fourth Report[12] criteria for a diagnosis of hypertension on the basis of BP readings, but only 2813 received a diagnostic code (eg, *International Classification of Diseases, Ninth Revision*) for hypertension. Of those diagnosed with hypertension, only 158 (5.6%) were treated with antihypertensive medication. It is unclear how many were referred to lifestyle intervention (eg, sleep, healthy diet, reduced sedentary behavior, and increased physical activity). This study, along with others, underscores the possibility of missed opportunities to diagnose and treat hypertension in youth.[13]

This article reviews current practices in the diagnosis and management of primary pediatric hypertension and addresses how the medical and research communities can begin to fill research gaps.

REVIEW OF CURRENT PRACTICE: WHAT IS AVAILABLE? WHAT IS BEING DONE?

Efforts to standardize definitions and practice guidelines for the diagnosis and treatment of hypertension in youth began in 1977.[14] During the past several decades, pediatric hypertension guidelines have undergone 5 iterations, with the most recent being the 2017 Clinical Practice Guidelines sponsored by the American Academy of Pediatrics.[15,16] Previous iterations have been sponsored by the National Heart, Lung, and Blood Institute.[17]

Definitions of Hypertension in Youth

Hypertension in youth is currently defined as repeated systolic or diastolic BP >95th percentile for youth ages 1 to 12 and BP >130/80 mm Hg (hypertension) for youth ages 13 years and older (Table 1). In the past, the definition of BP in youth was based on statistical norms and data that included BP measurements from youth with normal weight to those with obesity.[12] However, the medical community has recognized that (1) the use of data from youth with overweight or obesity has likely led to BP cutoff values that are too high, creating the potential for under-recognition of youth with abnormal BP who are also at risk for CVD; (2) incongruencies between the definitions of high blood pressure (HBP) in youth and adults complicate the transition from a pediatric to an adult provider; and (3) given the high reported prevalence of white coat hypertension (BP that is elevated in, but normal out of, the office) among youth, ambulatory blood pressure monitoring (ABPM) may be more appropriate. The 2017 Clinical Practice Guidelines addressed these issues by revising the definition of hypertension and recommending the use of ABPM to confirm a diagnosis of hypertension.

Prevalence of Disease

Two large studies of the prevalence of hypertension in youth were conducted in Texas and Switzerland.[18,19] Thrice-repeated BP measurements, using a validated oscillometric device, revealed an estimated prevalence of 2.2% and 3.2%, respectively (using Fourth Report definitions), with a higher estimated prevalence among children with BMI >85th percentile. Furthermore, data of nearly 15 000 youth from 1 clinical center in urban Ohio suggest that the prevalence may be closer to 4%.[13]

Risk factors for the development of primary pediatric hypertension have not been clearly defined. Children with obesity are at increased risk for hypertension, which is consistent with the known pathophysiological relationship between excess adiposity and elevated BP.[20–22] However, studies have not consistently

TABLE 2 Current FDA-Approved Oral Antihypertensive Drugs for Use in Pediatric Patients

Proprietary Name	Active Ingredient	Dosage Form	Pediatric Approval	Approved Ages
Vasotec	Enalapril maleate	Oral tablets	2002	1 mo–16 y
Prinivil	Lisinopril	Oral tablets	2003	6–16 y
Zestril	Lisinopril	Oral tablets	2003	6–16 y
Monopril	Fosinopril sodium	Oral tablets	2003	6–16 y
Lotensin	Benazepril hydrochloride	Oral tablets	2004	6–16 y
Toprol XL	Metoprolol succinate	Emergency department oral tablets	2007	≥6 y
Norvasc	Amlodipine besylate	Oral tablets	2004	6–17 y
Cozaar	Losartan potassium	Oral tablets	2004	6–16 y
Atacand	Candesartan cilexetil	Oral tablets	2009	1–<17 y
Diovan	Valsartan	Oral tablets	2007	6–16 y
Benicar	Olmesartan medoxomil	Oral tablets	2010	6–16 y
Tekturna	Aliskiren	Oral pellets	2017	6–16 y

demonstrated an increased prevalence of childhood hypertension coincident with the increased prevalence of childhood obesity and overweight, indicating that multiple factors may contribute to the development of hypertension.[23]

Other pediatric subpopulations at risk for hypertension include children with chronic kidney disease.[24] Diagnosis of hypertension in such children is based on ABPM data, which rely on a different set of BP values.[25] Additional factors associated with HBP in youth include higher dietary sodium intake, premature birth, family history, high adiposity, and increased waist circumference.[26]

Screening for Hypertension

The National High Blood Pressure Education Program Working Group recommended in the Fourth Report that screening begin at age 3 for all children.[12] Youth at higher risk for hypertension, such as those with a history of prematurity, bronchopulmonary dysplasia, low birth weight, known kidney or heart disease (including coarctation of the aorta and patients with transplant), or obesity or diabetes, should be screened before age 3.[16] Additional data are needed for how and when to obtain BP measurements for screening purposes as well as additional evidence on the diagnostic accuracy of screening for primary hypertension.[1]

To improve screening for elevated BP in youth, the 2017 Clinical Practice Guidelines introduced simplified screening BP tables.[16] The BP values in these tables represent the 90th BP percentile and the fifth height percentile by age and sex with a maximum threshold value of 120/80 mm Hg. The 2017 Clinical Practice Guidelines recommend that measurements be repeated when initial BP values meet or exceed these cutoffs. The use of values from this table results in 100% sensitivity for people with subsequent hypertension. However, the specificity is lower, which necessitates subsequent BP measurements for confirmation.

Diagnosis of Hypertension

Hypertension is currently diagnosed in the clinic or office through repeated BP measurements during 3 separate well-child visits. Home BP and ABPM measurements may be used to confirm a diagnosis of hypertension or help determine if a child has white coat hypertension. ABPM measurements are also useful for diagnosing masked hypertension (BP that is normal in, but abnormal out of, the office). However, the availability and high cost (~$3000) of devices have limited the use of ABPM. If ABPM use becomes more frequent, the question remains whether it should replace in-office measurement to diagnose hypertension. Another question centers on whether the oscillometric nature of ABPM leads to overestimation of BP. The 2017 Clinical Practice Guidelines recommend that any elevated BP obtained via oscillometry in the primary care office be repeated via auscultation with an aneroid manometer. However, incorporating this recommendation into the busy general pediatric patient workflow warrants further investigation.

Clear recommendations on how best to diagnose hypertension in infants (<12 months old) are also lacking. Current data for BP diagnosis in infants vary by age: first day of life,[27] first 2 weeks of life,[28] and 2 weeks of life and beyond. It is currently recommended that providers refer to the Second Task Force Report from 1987 for BP norms for youth >2 weeks of age.[29] However, it remains to be determined how best to diagnose hypertension in infancy and how BP in infancy correlates with later BP trajectories and/or CVD-related risk, particularly in preterm, low birth weight infants and infants with congenital heart disease.

The 2017 Clinical Practice Guidelines provide clearer definitions and criteria for diagnosing hypertension in youth (Table 1), and data support the use of ABPM to confirm the diagnosis of hypertension. However, more research is needed on BP measurement from infancy through

TABLE 3 Pediatric Hypertension Research Gaps and Opportunities

Research Topic Area	Research Gap(s)	Research Opportunities
Epidemiology and/or observational studies	Underestimated prevalence of childhood hypertension	Conduct longitudinal studies to estimate the true prevalence and incidence of hypertension and masked hypertension across the life span in diverse populations, particularly those at high risk.
	Limited studies in children of all ages, but particularly in children <1 y of age, to determine if screening for hypertension in youth is effective in delaying the onset or reducing the incidence of adult CVD outcomes	Conduct long-term cohort studies and/or use existing data sets to elucidate the associations among childhood hypertension, adult hypertension, and surrogate measures of CVD and subclinical cardiovascular TOD in childhood and adulthood as well as adult clinical CVD.
	Unknown baseline factors that predict optimal BP-lowering response (ie, precision medicine)	
Measurement and/or equipment	Limited data on the accuracy and reliability of automated devices in children and adolescents, especially those with obesity	Conduct studies that examine home BP screening versus ABPM in the US population.
	Need for practical and sustainable approaches to implementation of the 2017 Clinical Practice Guidelines	Examine the reproducibility, cost, and use of standardized protocols to measure TOD noninvasively across the life span.
		Develop training modules for improving workflow in physician offices for the recognition, follow-up, and expansion of the referral base for patients with elevated BP; use existing tools such as AAP EQIPP modules as example platforms.
Clinical trials, including lifestyle interventions	Limited information for establishing generalizable goals for lifestyle interventions	Conduct comparative effectiveness studies of lifestyle interventions to achieve sustained reductions in BP and longer-term modification of adult hypertension and cardiovascular risk in children with primary hypertension.
		Conduct treatment trials and examine surrogate or subclinical cardiovascular outcomes, TOD, medication harms, measures of long-term compliance, and individual components of multifactorial interventions during adolescence or young adulthood.
		Conduct lifestyle and medication trials to determine the amount of wt loss required to achieve clinically meaningful reductions in BP (including treating excessive adiposity), particularly among youth with severe obesity.
		Examine the combined effects of the DASH diet and other dietary patterns with physical activity programs on BP and vascular health in children and adolescents, including how digital health tools and mobile technologies can enhance adherence.
Pharmacologic studies	Limited information in labeling regarding long-term antihypertensive use in children	Conduct short- and long-term studies that examine the comparative efficacy or effectiveness and the synergistic mechanism of different classes of antihypertensive medications in children with primary hypertension, diabetes (types 1 or 2), or chronic kidney disease; after repair of aortic coarctation; and in patients of different racial and ethnic backgrounds.
		Examine the short- and long-term safety of antihypertensive medications on children's growth, development, vascular reactivity, cognitive development, and cardiovascular morbidity.

AAP, American Academy of Pediatrics; DASH, Dietary Approaches to Stop Hypertension; EQIPP, Education in Quality Improvement for Pediatric Practice.

age 10 years as well as longitudinal data on BP throughout childhood.

Treatment of Hypertension

The 2017 Clinical Practice Guidelines recommend that treatment of hypertension in youth begin with a nonpharmacologic intervention. Pharmacologic interventions are recommended when HBP is persistent, BP is insufficiently lowered with nonpharmacologic intervention (ie, lifestyle changes), or LVH is observed on echocardiography. Recommended options for pharmacologic therapy include angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, and thiazide diuretics. In general, short-term administration of these agents in children have not shown significant safety concerns; however, their long-term effects are unknown.[30–49]

The majority of antihypertensive agents currently FDA approved for pediatric use are limited to patients 6 years of age and older. In general, pediatric approval of these agents was based on demonstration of antihypertensive efficacy from

a single controlled safety and efficacy trial along with pharmacokinetic data to support the proposed pediatric dosing. In patients <6 years of age, only 2 drugs are approved for oral use, and none are approved for use in neonates (Table 2).

Assessment for Target Organ Injury

When pharmacologic treatment is considered, the 2017 Clinical Practice Guidelines recommend that youth undergo assessments for target organ damage (TOD). Measurements of left ventricular mass index to body size and relative wall thickness should be obtained to classify the ventricular mass and geometry. Longitudinal studies that evaluate the changes in left ventricular geometry over time, as well as their significance, are also needed.

GAPS IN RESEARCH

Thus far, the review of current practices has identified several areas where data remain limited and knowledge about the diagnosis and management of hypertension in youth is incomplete. Table 3 provides a list of research gaps and strategic approaches to addressing them.

CONCLUSIONS

Given the potential long-term cardiovascular consequences of elevated BP in youth,[10,50] the need to close the numerous knowledge gaps regarding primary pediatric hypertension is paramount. Many of these gaps can be closed through targeted research efforts. We already know that cardiac structural, functional, and vascular abnormalities are associated with hypertension in youth, with some evidence for vascular structural (eg, carotid intima thickness) changes seen in even prehypertensive patients.[5] Additional data on the level of BP associated with TOD in youth will emerge from ongoing studies, such as the Study of High Blood Pressure in Pediatrics: Adult Hypertension Onset in Youth.[51] However, given what we already know in adults (ie, LVH is an independent predictor of cardiovascular events in adults) and the potential impact of neurocognitive impairment related to high BP,[52] the medical and research communities must generate new data, as well as innovative use of existing data sets and cohorts, that focus on the impact of earlier treatment of high BP on improving outcomes in children and adolescents. Strategic collaborations among industry, academia, and government are key to moving this field forward.

The ultimate goal for improving the health of our children is "primordial prevention." As stated by Dr Stephen Daniels during the 2017 workshop, "Putting together the evidence from adults and children, it appears that we should be working together to prevent the development of hypertension at a young age and treating it once it occurs." As a medical community, we have some sense that the diagnosis and treatment of hypertension can improve cardiac structure and function as well as cognitive outcomes in the short-term. What we need as a medical community is more evidence about the long-term implications of identification and treatment.

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ABBREVIATIONS

ABPM: ambulatory blood pressure monitoring
BP: blood pressure
BPCA: Best Pharmaceuticals for Children Act
CVD: cardiovascular disease
FDA: Food and Drug Administration
HBP: high blood pressure
LVH: left ventricular hypertrophy
TOD: target organ damage

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