Diagnosis, Epidemiology, and Management of Hypertension in Children

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abstract

National guidelines for the diagnosis and management of hypertension in children have been available for nearly 40 years. Unfortunately, knowledge and recognition of the problem by clinicians remain poor. Prevalence estimates are highly variable because of differing standards, populations, and blood pressure (BP) measurement techniques. Estimates in the United States range from 0.3% to 4.5%. Risk factors for primary hypertension include overweight and obesity, male sex, older age, high sodium intake, and African American or Latino ancestry. Data relating hypertension in childhood to later cardiovascular events is currently lacking. It is known that BP in childhood is highly predictive of BP in adulthood. Compelling data about target organ damage is available, including the association of hypertension with left ventricular hypertrophy, carotid-intima media thickness, and microalbuminuria. Guidelines from both the United States and Europe include detailed recommendations for diagnosis and management. Diagnostic standards are based on clinic readings, ambulatory BP monitoring is useful in confirming diagnosis of hypertension and identifying white-coat hypertension, masked hypertension, and secondary hypertension, as well as monitoring response to therapy. Research priorities include the need for reliable prevalence estimates based on diverse populations and data about the long-term impact of childhood hypertension on cardiovascular morbidity and mortality. Priorities to improve clinical practice include more education among clinicians about diagnosis and management, clinical decision support to aid in diagnosis, and routine use of ambulatory BP monitoring to aid in diagnosis and to monitor response to treatment.

Among adults, hypertension has been recognized as an important risk factor for cardiovascular disease for well over 50 years.[1] For every 20 mm Hg increase in systolic blood pressure (BP) or 10 mm Hg increase in diastolic BP, mortality from heart disease and stroke in adults doubles.[2] The first report on pediatric hypertension by the National Heart, Lung, and Blood Institute (NHLBI), published in 1977, declared that, "Detection and management of hypertension in children and the precursors of hypertension in adults are the next major frontier.[3]" The report also recommended annual BP measurement in all children ≥3 years. Unfortunately, nearly 40 years later, the diagnosis of hypertension is missed in the majority of cases, and familiarity with pediatric hypertension among clinicians is extremely poor.[4–6] Barriers to optimal recognition include not only poor knowledge, but also a failure to

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synthesize multiple BP readings over time, which is required to make a diagnosis.[4,6]

In 2013, the US Preventive Services Task Force (USPSTF) decided that "the current evidence is insufficient to assess the balance of benefits and harms of screening for primary hypertension in asymptomatic children and adolescents to prevent subsequent cardiovascular disease in childhood or adulthood."[7] This conclusion has been controversial and can be challenged on several grounds, including based on evidence accepted by the USPSTF. The USPSTF acknowledges that childhood BP does, to a significant degree, predict adult BP. It also acknowledges that hypertensive children are at especially high risk for progression of metabolic disorders, including insulin resistance and lipid disturbances. The USPSTF acknowledges that there is some evidence that drugs or lifestyle changes, alone or in combination, are effective in reducing BP. It found no evidence of harm in screening for hypertension in children. In contrast to these findings, which provide support for screening, the USPSTF found no evidence that routine BP measurement in childhood accurately identifies individuals at risk for adult cardiovascular disease. As will be discussed, evidence identifying a potential relationship between childhood hypertension and adult cardiovascular events is emerging. Finally, the USPSTF rejected identifying secondary hypertension as a rationale for screening because secondary hypertension was considered rare. As will be discussed, there is evidence that secondary hypertension is much more common than once thought. Notwithstanding the USPSTF's conclusion about the lack of conclusive evidence of benefit, and consistent with current guideline recommendations, this paper assumes that screening for hypertension is worthwhile and that childhood hypertension is an important and impactful condition.

TABLE 1 BP Criteria for Diagnosis of Hypertension[10]

	Normal	Prehypertension	Stage I Hypertension	Stage II Hypertension
Age 3–11 y	<90th percentile	90th–<95th percentile	95th–99th percentile + 5 mm Hg	>99th percentile + 5 mm Hg
Age 12–17 y	<90th percentile	90th–<95th percentile or > 120/80 mm Hg	95th-99th percentile + 5 mm Hg	>99th percentile + 5 mm Hg

BP criteria are based on an average of measurements taken on 3 occasions.

The purpose of this review is to address 4 broad and important questions: (1) How is hypertension in children defined and diagnosed? (2) What is the epidemiology, including prevalence, risk factors, and etiology of hypertension in children? (3) What is the rationale for identification and treatment of hypertension? (4) What is the latest evidence for pharmacotherapy of hypertension in children? In addition, based on available original papers and established guidelines, this review includes a description of important knowledge gaps and research priorities and recommendations for practice.

DEFINITION AND DIAGNOSIS OF PEDIATRIC HYPERTENSION

Hypertension in adults is defined as persistent systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg. The 140/90 mm Hg standard is supported by outcomes data and therefore serves as a useful criterion standard.[8] Outcomes data, such as cardiovascular morbidity and mortality, are not available for children. Master et al[9] first suggested in 1950 using population-based normative data to define hypertension in adults. Because BP is approximately normally distributed, they recommended a threshold of systolic and diastolic BP that is 2 SDs above the mean, or roughly the 95th percentile. This is the approach used with children (summarized in Table 1) whereby normal, prehypertension, stage I hypertension, and stage II hypertension are defined according to normative percentiles of BP averaged over 3 occasions.[9] These percentiles are in turn adjusted for children's age, sex, and height percentiles, which are variables known to influence BP. Whichever of systolic or diastolic BP percentile is higher defines the BP category. The underlying normative data in the fourth report of the NHLBI's National High Blood Pressure Education Program Working Group on Children and Adolescents comes from the 1999–2000 National Health and Nutrition Examination Survey (NHANES) and other large epidemiologic studies.[10]

Use of Ambulatory BP Monitoring

Although diagnostic standards are based on separate, office-based readings, both the NHLBI and European guidelines state that ambulatory BP monitoring (ABPM) may be useful in confirming the diagnosis of hypertension, monitoring treatment, and evaluating for secondary causes.[11,12] ABPM is usually carried out over a 24-hour period, with BP readings taken with a portable device attached to the arm, at 15- to 30-minute intervals during waking times and every 20 to 60 minutes during sleep.[13] Both systolic BP and diastolic BP normally decline at night. The American Heart Association has proposed standards for abnormal ABPM values based on mean ambulatory systolic BP >95th percentile, combined with systolic load of 25% to 50% (the percent of systolic measurements >95th percentile over the entire

24-hour period using standard NHLBI percentiles).[12] These criteria, as later pointed out by Flynn and Urbina,[14] are imperfect because they do not, for example, consider ambulatory diastolic BP, which may be abnormal in the absence of abnormal systolic BP. Population-based ABPM values are different than clinic-based measurements. Normative ABPM values are available, but have been derived from white German children only, rather than form more diverse populations.[12] Nevertheless, as a diagnostic tool, ABPM has a distinct advantage over clinic based values for several reasons.[13] Most importantly, it identifies the phenomenon of white coat hypertension (WCH), in which clinic values are elevated and ABPM is normal.[15] WCH is very common, with a prevalence of 30% to 40% among children with high clinic BP readings.[16,17] WCH is more common among younger children and obese children. It is also more common among children with mildly elevated BP readings, including those with prehypertension. Although, there is some evidence that WCH is not benign,[18] ABPM is useful in reducing overdiagnosis of hypertension. ABPM is also extremely useful in identifying secondary hypertension. Daytime diastolic BP load >25% plus nocturnal systolic load >50% have been shown to have 92% specificity for predicting secondary hypertension.[19] In addition, evidence is emerging that ABPM is more useful than clinic BP in predicting target organ damage.[20,21] Other uses of ABPM include the detection of masked hypertension (normal clinic pressures but abnormal ABPM) and monitoring BP in conditions, such as diabetes, where tight control is needed.[13]

EPIDEMIOLOGY AND ETIOLOGY

Prevalence

Prevalence estimates have been surprisingly variable. Din-Dzietham et al[22] applied the percentile criteria from Table 1 to survey data from 1963 to 2002. The prevalence of high BP was estimated to be 37.2% in 1963 to 1970, but only 2.7% in 1988 to 1994. The huge difference is likely because of different measurement techniques. In early surveys, for example, recorded BP was based on a single initial reading, rather than repeated measurements. Other studies from the United States published between 2001 and 2008 report an overall prevalence of 0.8% to 4.5%.[4,23–26] Studies from other countries frequently report much higher rates owing at least partly to different populations and standards. Zhang and Wang,[27] for example, report a prevalence in China of "high BP status" (based on a single measurement) among boys and girls of normal weight ages 7 to 17 years of 17.00% and 14.13%, respectively. By contrast, one notable retrospective cohort study by Lo et al[28] based on review of electronic health records (EHRs) of ~200 000 diverse children in California, Minnesota, and Colorado reported a prevalence of hypertension (based on NHLBI criteria) of just 0.3%. All children were insured, and the index BP measurement for each child was taken at a well-child visit. Of note, the overall prevalence of obesity (14.3%) was significantly lower than national estimates.

Widely varying estimates of the prevalence of hypertension based on different populations, different standards, and using different techniques are not useful to clinicians who need a reliable estimate of how frequently they are likely to encounter the problem. Kit et al[29] provide an estimate based on analysis of NHANES data from 2011 to 2012, which included a diverse sample of 1665 white, black, Hispanic, and Asian American children ages 8 to 17 years. Three successive readings were taken 30 seconds apart and averaged. This is somewhat different than the NHLBI recommendation for diagnosis of hypertension, in which BP is to be averaged over 3 separate occasions. Therefore, the outcomes included "high BP" (≥95th percentile) and "borderline high BP" (90–95th percentile) rather than hypertension and prehypertension. The prevalence of high BP varied from 1.1% among white to 2.4% among Hispanic children. It is unknown how closely the estimates of high BP would match the prevalence of actual hypertension in the community. Nevertheless, hypertension is unlikely to be a rare problem. There are an estimated 74 million Americans <18 years old.[30] Even a 1% prevalence in this population translates to 740 000 hypertensive children.

Risk Factors

Several risk factors have been associated with pediatric hypertension across many studies from many different settings, among which overweight and obesity are the most consistently documented. The prevalence of hypertension is much higher among overweight and obese children with estimates of 4% to 14% and 11% to 23% respectively.[23,31–33] Curiously, based on recent NHANES data analyzed by Kit et al,[29] the prevalence of hypertension was higher among overweight and normal-weight children than obese children. When either high or borderline high BP was considered as an outcome, however, prevalence estimates by Kit et al[29] were consistent with other reports in which overweight and obesity was associated with higher BP. Rosner et al[34] report an increase in the prevalence of high BP (single reading) from the NHANES between 1988 and 1994 and between 1999 and 2008 from 15.8% to 19.2% among boys and from 8.2% to 12.6% among girls. This increase was largely explained by an increase in the prevalence of obesity. In addition, abdominal

TABLE 2 Causes of Secondary Hypertension in a Tertiary Pediatric Hypertension Clinic

Causes	Total No. (%)	Age at Diagnosis, y, Median (Range)	Male Sex No. (%)
Autoimmune	3(1)	10.5 (9–17)	2 (67)
Cardiac	4(3)	4.5 (1–11)	3 (75)
Endocrine	9 (6)	12 (6–17)	2 (22)
Gastrointestinal	2(1)	9.5 (0.17–0.75)	2 (100)
Hematologic	1(1)	8	1 (100)
Medications	21 (13)	13 (0.08–18)	16 (76)
Neurologic	19 (12)	10 (0.25–18)	14 (74)
Renal	53 (34)	10 (0.08–19)	33 (62)
Respiratory	32 (20)	1 (0.01–17)	20 (63)
Sleep-disordered breathing	12 (8)	14 (4–17)	10 (83)
Total	156		

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obesity, measured as increased waist circumference, has been shown in a number of studies to be associated with hypertension, independent of BMI.[35] Additional risk factors for hypertension include dietary salt intake (especially among overweight and obese children), male sex, older age (adolescents vs preadolescents), and ethnicity.[28,36] Kit et al[29] report a prevalence of high or borderline high BP among Hispanic and non-Hispanic black children of 11.5% and 15.3% respectively, compared with 9.4% among white children. Some reports have also shown a higher prevalence among Asian American than white children.[28]

Etiology

Hypertension can be categorized as primary or secondary. Primary hypertension does not have a clearly identifiable etiology, but rather is related to genetics and lifestyle. Hypertension associated with obesity is usually categorized as primary. Secondary hypertension, by contrast, is caused by a specific disease entity or other factor, including a wide range of renal diseases, pulmonary diseases, and medications.[37] Accurate identification of secondary hypertension is extremely important because many causes are reversible. Secondary hypertension has long been thought to be more common in younger children than in older children and adolescents.[13,38] Actual data to support this perception, however, is scarce. Gupta-Malhotra et al[39] recently described the etiology of hypertension among 423 children from a pediatric hypertension clinic. Patients were referred immediately for management from primary care or other settings after detection of elevated BP rather than after management in those settings had been unsuccessful. A total of 275 children were diagnosed with hypertension. A total of 156 (57%) had an identifiable secondary cause; 119 (43%) had primary hypertension. Interestingly, 51% of teenagers had a secondary cause. The breakdown of causes is shown in Table 2. Despite the unavoidable bias in studying a referral-based rather than secondary community-based population, the study represents the most recent and comprehensive data about the prevalence and etiology of secondary hypertension and challenges conventional thinking in 2 ways. Firstly, as a proportion of all pediatric hypertension, secondary hypertension is much more common than was once thought, especially among adolescents, an observation consistent with a study by Flynn et al.[40] Secondly, renal causes have long been thought to be the most common group of secondary causes, a belief supported by the study from Gupta-Malhotra et al.[39] Pulmonary causes, such as bronchopulmonary dysplasia, which have received little attention in previous papers,[24,25] however, were also very common, especially in children <5 years old.

RATIONALE FOR IDENTIFICATION AND TREATMENT

Pediatric Hypertension and Intermediate Outcomes

The USPSTF found no randomized trials of the impact of screening for hypertension on future outcomes.[7] In addition, no cohort studies have yet linked pediatric hypertension to adult cardiovascular events. In the absence of hard cardiovascular outcomes, the importance of hypertension until now has been extrapolated on the basis of a number of intermediate outcomes, which, among adults, are unequivocally associated with cardiovascular events. Although this is not ideal, the data on intermediate outcomes is compelling.

The International Childhood Cardiovascular Cohort (I3c) Consortium was initiated in 2002 and consists of 7 large cohorts in the United States, Finland, and Australia, brought together to link childhood cardiovascular risk factors to adults disease.[41] Twelve-thousand cohort members have had measurements of risk factors in both childhood and adulthood. The majority are now in their twenties and thirties. Through publications from the I3c Consortium and a number of related studies, it is clear that pediatric hypertension is predictive of adult BP and has a significant impact on the heart and blood vessels. Key evidence is summarized below:

1. A number of longitudinal studies have shown significant tracking of childhood BP into adulthood. In a systematic review, Chen and Wang[42] identified 60 cohort studies that tracked BP into adulthood. The mean BP tracking correlation coefficient was 0.38

for systolic pressure and 0.28 for diastolic pressure. The strength of tracking increased with baseline age. Essentially, childhood BP, whether normal or high, is strongly predictive of adult BP, reinforcing the importance of early recognition.

2. Left ventricular hypertrophy (LVH), which is strongly associated with hypertension in adults, is an established, independent risk factor for cardiovascular events. A number of reports have identified a strong relationship between LVH and hypertension in children.[43–46] Prevalence estimates vary widely because of slightly differing standards for left ventricular mass (LVM). Roughly 8% to 41% of hypertensive children have LVM >95th percentile, adjusted for age, sex, and height, and roughly 10% to 15.5% of children have values >51 g/m^2, a level known to be associated with significant cardiovascular morbidity and mortality in adults.[47]

3. Early or structural atherosclerosis can be detected using ultrasound carotid intima-media thickness (cIMT). Among adults, elevated cIMT is associated with cardiovascular events and stroke.[48] In a systematic review of 67 observational pediatric studies, Lamotte et al[49] reviewed the association of risk factors in children with increased cIMT. Obesity, insulin-dependent diabetes, dyslipidemia, chronic renal failure, and hypertension were all significantly associated with increased cIMT in the majority of studies. More recently, a study from the I3C Consortium revealed that among 4210 participants, elevated BP that persisted from childhood into adulthood was associated with increased cIMT. By contrast, cIMT was not elevated among individuals with elevated BP in childhood that resolved by adulthood.[50] The impact of hypertension is not limited to major vessels. Mitchell et al[51] have shown that hypertension is associated with retinal arteriolar narrowing in children.

4. Microalbuminuria is a powerful predictor of both renal insufficiency and cardiovascular morbidity and mortality in adults.[52] The prevalence of microalbuminuria among children diagnosed with hypertension is estimated to be 20%. Microalbuminuria is more common among children with stage 2 hypertension than with stage 1 hypertension, and among hypertensive children with LVH.[53,54]

Forthcoming Evidence From the I3c Consortium

The I3C Consortium has recently received funding for a study to measure cardiovascular events among all 7 cohorts beginning in 2015, comprising >40 000 children (T. Dwyer, MBBS, MD, MPH, personal communication, 2015). The study, to be completed in 2018, will provide extremely valuable information, including an estimate of the long-term risk, if any, conferred by pediatric hypertension, including cardiovascular events, and potential validation of current BP standards in relation to cardiovascular events.

EVALUATION AND TREATMENT

Detailed recommendations for evaluation and treatment of hypertension in children have been proposed by the NHLBI and the European Society of Hypertension.[10,11] The goals of evaluation are threefold: to identify target-organ damage, to identify additional cardiovascular risks, and to identify secondary hypertension when suspected. Nonpharmacological lifestyle-based approaches are recommended as the first line treatment. These include standard, widely accepted recommendations to reduce obesity and cardiovascular risk in general, such as limiting dietary cholesterol to <300mg/day, limiting saturated fat intake to ≤10% of total daily caloric intake, and encouraging moderate to vigorous physical activity every day. How best to successfully implement these recommendations in practice to maximize uptake by patients and the impact of these recommendations on BP are unknown.

Given the lack of long-term outcomes data, all guideline recommendations were based on consensus only. Rather than reviewing these established recommendations in detail, 4 scenarios that represent common situations of hypertension together with the recommended NHLBI evaluation and treatment recommendations can be found as abbreviated, evolving case studies in Table 3. As a number of different first-line medications can be used according to the guidelines, the medications listed in the case studies were selected to reflect a range of possible choices, rather than correct or recommended agents. Significant differences between NHLBI and European recommendations have been noted.

Since the US Food and Drug Administration Modernization Act of 1997, a number of medications have been shown to be effective in lowering BP in children in short-term trials and are approved for use. A comprehensive list with additional details can be found in the NHLBI Guidelines and in Table 4.[10] Although recommendations for a specific first-line agent or class of agents are not available, angiotensin-converting enzyme inhibitors and calcium channel blockers were preferred in a survey of 185 pediatric nephrologists.[55] This section on pharmacotherapy is informed by 4 sources: (1) a comprehensive Cochrane collaboration systematic

TABLE 3 Case Scenarios of Hypertension and Corresponding Guidelines-Based Evaluation and Management Recommendations

Scenario	Case Study[a]	Recommended Evaluation	Outcomes of Initial Evaluation	BP Goal	Initial Treatment (Step 1)	Outcomes of Initial Treatment	Next Level Treatment (Step 2)	Outcomes of Step 2 Treatment	Next-Level Treatment (Step 3) and Outcome
Stage 1 hypertension with no TOD	13-y-old obese boy with 3 BP readings averaging 97th percentile; ABPM, mean, 98%; systolic load, 40%.	Basic workup: Medical/family/sleep hx, physical exam, CBC, renal panel, U/A, renal U/S, Echocardiogram, fasting lipids, glucose.	Unremarkable history and physical exam except for obesity. Lipid profile reveals elevated triglycerides. Other tests are negative.	<95th percentile (<90th percentile according to European guidelines)	Lifestyle changes (discourage sugar-sweetened beverage, saturated and trans fats, encourage high dietary fiber consumption, physical activity, appropriate portions, etc)[b] for up to 6 mo, with monitoring at 3 or 6 mo	BP remains at 97th percentile; ABPM, mean, 97th percentile; systolic load, 30%. No change in BMI percentile.	Continued lifestyle changes. Enalapril, starting at 5 mg/d, titrating up to 20 mg/d	BP <95th percentile; normal ABPM. No change in BMI percentile.	N/A
Stage 1 HTN with TOD	15-y-old girl, obese, with 3 BP readings averaging 99th percentile; ABPM, mean, 99th percentile; systolic load, 50%	Basic workup	History and physical exam unremarkable. Has impaired fasting glucose and dyslipidemia with elevated TG and low HDL. LVM of 52 g/m^2 (above adult threshold). Other tests negative.	<90th percentile	Lifestyle changes plus candesartan starting at 8 mg a day, titrating up to 16 mg/day. Monitor BP every 3–6 mo.	No improvement in BP after 6 mo	Aggressive encouragement of weight loss. Increase candesartan to maximum of 32 mg/d.	BP <90th percentile; normal ABPM; LVM 38 g/m^2. Modest weight loss of 8 lbs.	N/A
Stage 2 HTN	11-y-old boy, modestly overweight with 3 BP readings taken over 2 wk, all slightly >99th percentile. ABPM, mean, 99th percentile; systolic load, 40%.	Basic workup plus extended workup or referral to pediatric hypertension expert.[c]	Basic and extended workup negative, except for strong family history of hypertension.	<95th percentile; (<90th percentile according to European guidelines which are based on same population data)	Lifestyle changes plus amlodipine starting at 2.5mg a day. Monitor BP every 3–6 mo.	BP improved but remains between 95 and 99th percentiles; ABPM, mean, 96th percentile; systolic load, 30%. No change in BMI percentile.	Amlodipine titrated up to maximum of 10mg daily. Monitor every 3–6 mo.	BP improved further on maximum dose but still slightly above 95th percentile; ABPM, no improvement. No change in BMI percentile.	Add hydrochlorothiazide 12.5 mg/d. Normal BP and ABPM. No change in BMI percentile.

TABLE 3 Continued

Scenario	Case Study[a]	Recommended Evaluation	Outcomes of Initial Evaluation	BP Goal	Initial Treatment (Step 1)	Outcomes of Initial Treatment	Next Level Treatment (Step 2)	Outcomes of Step 2 Treatment	Next-Level Treatment (Step 3) and Outcome
Secondary HTN	9-y-old girl, modestly overweight with 3 BP readings averaging 95th percentile; ABPM, mean, 95th percentile; systolic load, 60%; diastolic load 25%.	Basic and extended workup, through pediatric hypertension expert.	Bilateral renal artery stenosis; diagnosed with fibromuscular dysplasia.	<90th percentile	Revascularization through surgery and modest weight loss through lifestyle changes.	BP eventually decreased to 80th percentile; ABPM, mean 75%, systolic load, 20%; diastolic load, 5%.	N/A	N/A	N/A

CBC, complete blood count; HDL, high density lipoprotein cholesterol; HTN, hypertension; hx, history; N/A, not applicable; TG, triglycerides; TOD, target organ damage; U/A, urinalysis; U/S, ultrasound.

[a] Percentiles refer to whichever is higher of the systolic or diastolic BP.

[b] These are described in more detail in the NHLBI Guidelines

[c] Extended workup according to both NHLBI and European Guidelines includes plasma renin (low rennin suggests mineralocorticoid-related disease), renovascular imaging, plasma and urine steroid levels, plasma and urine catecholamines.

review of 21 clinical trials published in 2014 on pharmacological interventions for hypertensive children (up to date as of October 2013)[56]; (2) a search of PubMed for the years 2013 to 2016 using the search terms hypertension AND medication limited to children and clinical trials; (3) a search of the clinical trials database, ClinicalTrials.gov, using the dates 2013 to 2016 and limited to trials with results; (4) a separate PubMed search for studies published anytime using any design describing impact of treatment on target organ damage using various combinations of search terms, such as hypertension AND left ventricular hypertrophy AND treatment, etc. Three types of outcomes were sought: the short-term impact of medications on BP; short-term adverse effects of medications; and impact of medications on established target organ damage.

The PubMed search did not reveal any new hypertension treatment trials for the 2013–2016 period. The search of ClinicalTrials.gov revealed 4 relevant trials updated since 2013: a pharmacokinetic and safety study of azilsartan medoxomil[57]; a safety and efficacy study of the renin inhibitor aliskiren[58]; an open-label randomized trial of 3 different dosage regimens of losartan[59]; and a randomized study of losartan compared with losartan/hydrochlorothiazide, which terminated early without allocation to treatment due to limited availability of enrollment sites.[60] Rather than a review of each individual study from the 4 sources, what follows are general conclusions with an example or summary of supporting evidence. All antihypertensive medication trials were of short duration ranging from 3 to 24 weeks. The quality of trials was highly variable.

Several classes of medication and many agents commonly used in adults have been shown to lower BP

TABLE 4 Antihypertensive Medications With Pediatric Experience

Class	Drug	Initial Dose	Maximal Dose	Dosing Interval	Evidence for Effectiveness	FDA Approved
Angiotensin-converting enzyme inhibitor (ACE)	Benazepril	0.2 mg/kg/day up to 10 mg/day	0.6 mg/kg/day up to 40 mg/day	qd	Randomized controlled trial	Yes
Angiotensin-converting enzyme inhibitor (ACE)	Captopril	0.3–0.5 mg/kg/dose (>12 mo)	6 mg/kg/day	tid	Randomized controlled trial, Case series	No
Angiotensin-converting enzyme inhibitor (ACE)	Fosinopril	Children >50 kg: 5–10 mg/day	40 mg/day	qd	Randomized controlled trial	Yes
Angiotensin-converting enzyme inhibitor (ACE)	Lisinopril	0.07 mg/kg/day up to 5 mg/day	0.6 mg/kg/day up to 40 mg/day	qd	Randomized controlled trial	Yes
Angiotensin-converting enzyme inhibitor (ACE)	Quinapril	5–10 mg/day	80 mg/day	qd	Randomized controlled trial, Expert opinion	No
Angiotensin-receptor blocker (ARB)	Irbesartan	6–12 y: 75–150 mg/day; ≥13 y: 150–300 mg/day	300 mg/day	qd	Case series	Yes
Angiotensin-receptor blocker (ARB)	Losartan	0.7 mg/kg/day up to 50 mg/day	1.4 mg/kg/day up to 100 mg/day	qd-bid	Randomized controlled trial	Yes
Angiotensin-receptor blocker (ARB)	Valsartan	5–10 mg/day 0.4 mg/kg/day	40–80 mg/day 3.4 mg/kg/day	qd	Randomized controlled trial	No
α- and β-antagonist	Labetalol	1–3 mg/kg/day	10–12 mg/kg/day up to 1200 mg/day	bid	Case series, Expert opinion	No
β-antagonist	Atenolol	0.5–1 mg/kg/day	2 mg/kg/day up to 100 mg/day	qd-bid	Case series	No
β-antagonist	Bisoprolol/HCTZ	2.5–6.25 mg/day	10/6.25 mg/day	qd	Randomized controlled trial	No
β-antagonist	Metoprolol	Children >6 y: 1 mg/kg/day (12.5–50 mg/day)	2 mg/kg/day up to 200 mg/day	bid	Case series	Yes
β-antagonist	Propranolol	1-2 mg/kg/day	4 mg/kg/day up to 640 mg/day	bid-tid	Randomized controlled trial, Expert opinion	Yes
Calcium channel blocker	Amlodipine	Children 6-17 y: 2.5 mg/day	5 mg/day	qd	Randomized controlled trial	Yes
Calcium channel blocker	Felodipine	2.5 mg/day	10 mg/day	qd	Randomized controlled trial, Expert opinion	No
Calcium channel blocker	Isradipine	0.15-0.2 mg/kg/day	0.8 mg/kg/day up to 20 mg/day	tid-qid	Case series, Expert opinion	No
Calcium channel blocker	Extended-release nifedipine	0.25-0.5 mg/kg/day	3 mg/kg/day up to 120 mg/day	qd-bid	Case series, Expert opinion	No
Central α-agonist	Clonidine	Children ≥12 y: 0.2 mg/day	2.4 mg/day	bid	Expert opinion	Yes
Diuretic	HCTZ	1 mg/kg/day	3 mg/kg/day up to 50 mg/day	qd	Expert opinion	Yes
Diuretic	Chlorthalidone	0.3 mg/kg/day	2 mg/kg/day up to 50 mg/day	qd	Expert opinion	No
Diuretic	Furosemide	0.5-2.0 mg/kg/ dose	6 mg/kg/day	qd-bid	Expert opinion	No
Diuretic	Spironolactone	1 mg/kg/day	3.3 mg/kg/day up to 100 mg/day	qd-bid	Expert opinion	No
Diuretic	Triamterene	1-2 mg/kg/day	3-4 mg/kg/day up to 300 mg/day	bid	Expert opinion	No
Diuretic	Amiloride	0.4-0.625 mg/kg/day	20 mg/day	qd	Expert opinion	No
Peripheral α-antagonist	Doxazosin	1 mg/day	4 mg/day	qd	Expert opinion	No
Peripheral α-antagonist	Prazosin	0.05-0.1 mg/kg/ day	0.5 mg/kg/day	tid	Expert opinion	No
Peripheral α-antagonist	Terazosin	1 mg/day	20 mg/day	qd	Expert opinion	No
Vasodilator	Hydralazine	0.75 mg/kg/day	7.5 mg/kg/day up to 200 mg/day	qid	Expert opinion	Yes

TABLE 4 Continued

Class	Drug	Initial Dose	Maximal Dose	Dosing Interval	Evidence for Effectiveness	FDA Approved
Vasodilator	Minoxidil	Children <12 y: 0.2 mg/kg/day; children ≥ 12 y: 5 mg/day	Children <12 y: 50 mg/day; children >12 y: 100 mg/day	qd-tid	Case series, expert opinion	Yes

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in children. Among the most effective is candesartan, which compared with placebo lowered systolic BP by 6.50 mm Hg (95% confidence interval [CI], −9.44 to −3.56) and diastolic BP by 5.50 mm Hg (95% CI, −9.62, to −0.138).[61] Other medications shown to be effective in the short-term in lowering BP include telmisartan, metoprolol, losartan, and the investigational rennin inhibitor, aliskiren.

Antihypertensive medications in children are generally safe and well tolerated in the short-term. Adverse effects in short-term trials were relatively minor and included headache and dizziness.

Antihypertensive medications have been shown to reverse progression of target organ damage. Metteuci et al[62] have demonstrated regression of LVH and improved systolic function among 84 hypertensive children with chronic kidney disease with treatment with ramipril. The positive effect of ramipril on LVH has also been documented by Seeman et al[63] in a smaller study of 21 children with primary or renal hypertension. Furthermore, a combination of enalapril and hydrochlorothiazide has been shown to reverse microalbuminuria and LVH among hypertensive children.[64] A recent 12-week clinical trial of losartan has demonstrated a substantial 35.80% (95% CI, 27.55% to 43.11%) decrease in urinary protein/creatinine ratio among hypertensive children ages 6 to 17 years with proteinuria.[58] Litwin et al[65] have shown improvement in cIMT in hypertensive children when BP was controlled with either enalapril or losartan.

RECOMMENDATIONS TO IMPROVE CLINICAL PRACTICE

Given its low rate of recognition, more awareness of pediatric hypertension is needed among clinicians. Continuing education and national implementation of quality measures related to diagnosis could be helpful. The National Quality Forum adopted a BP screening measure in 2009.[66] Accurate diagnosis of hypertension, however, requires integration of multiple BP readings with complex age, sex, and height-percentile adjusted BP standards. Clinical decision support, which provides this integration, could be helpful in improving rates of diagnosis.[67] Even simple, real-time alerts within EHRs coupled with provider education have been shown to increase awareness of elevated BP values.[68]

In addition to improving recognition based on clinic BP values, ABPM should be used in all children with clinic BP values in the prehypertensive and hypertensive ranges to confirm diagnoses and identify WCH, and to help identify secondary hypertension. ABPM should also be used in children with normal clinic values but with elevated values in other settings (eg, school and home) to identify masked hypertension. Finally, ABPM should be used periodically in all children to monitor response to therapy.

A wide variety of medications is approved for use in children and has been shown to be effective in lowering BP and to be safe in the short-term. Until more evidence emerges about their long-term impact, no first-line class of agents can be recommended. Rather, the choice of initial agent should be based on availability, clinician familiarity, and patient preferences.

SUMMARY OF CURRENT STATE OF THE FIELD AND GAPS IN KNOWLEDGE

Despite the recognition of its importance 4 decades ago, pediatric hypertension remains underdiagnosed. Many questions are unanswered. What is known is that, based on current NHLBI standards, hypertension is a relatively common

problem that is associated with target organ damage. BP in childhood is predictive of BP in adulthood. Risk factors for primary hypertension include overweight and obesity, male sex, older age, race/ethnicity, and dietary salt intake. Medications are effective in controlling BP and reversing progression of target organ damage.

Research in pediatric hypertension should address 2 important priorities, described below:

1. An accurate population-level estimate of the prevalence of hypertension is needed, with better estimates of the prevalence among specific subpopulations, (eg, racial minorities). Prevalence estimates from large, representative national samples are difficult to obtain. The study by Lo et al[47] represents an important direction in obtaining such estimates. Large clinical data research networks, which are now forming and make use of data collected from the EHRs of thousands or hundreds of thousands of children, may be useful in this regard.[69] BP values collected as part of routine clinical care can be extracted and synthesized into prevalence estimates.
2. Measures of the degree of risk conferred by pediatric hypertension for adult cardiovascular outcomes, including morbidity and mortality, are needed. Fortunately, this evidence will be available through the i3C Consortium shortly. Although pediatric hypertension has an unquestionable short term-impact on target organs, emerging evidence from the i3C Consortium should answer the critical question about the long- term impact of pediatric hypertension and its overall importance to lifelong cardiovascular health.

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ABBREVIATIONS

ABPM: ambulatory blood pressure monitoring
BP: blood pressure
CI: confidence interval
cIMT: carotid intima-media thickness
EHR: electronic health record
I3c: International Childhood Cardiovascular Cohort
LVH: left ventricular hypertrophy
LVM: left ventricular mass
NHANES: National Health and Nutrition Examination Survey
NHLBI: National Heart, Lung, and Blood Institute
USPSTF: US Preventive Services Task Force
WCH: white coat hypertension

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