TECHNICAL REPORT

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# Diagnosis, Evaluation, and Management of High Blood Pressure in Children and Adolescents

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## abstract

Systemic hypertension is a major cause of morbidity and mortality in adulthood. High blood pressure (HBP) and repeated measures of HBP, hypertension (HTN), begin in youth. Knowledge of how best to diagnose, manage, and treat systemic HTN in children and adolescents is important for primary and subspecialty care providers.

**OBJECTIVES:** To provide a technical summary of the methodology used to generate the 2017 "Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents," an update to the 2004 "Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents."

**DATA SOURCES:** Medline, Cochrane Central Register of Controlled Trials, and Excerpta Medica Database references published between January 2003 and July 2015 followed by an additional search between August 2015 and July 2016.

**STUDY SELECTION:** English-language observational studies and randomized trials.

**METHODS:** Key action statements (KASs) and additional recommendations regarding the diagnosis, management, and treatment of HBP in youth were the product of a detailed systematic review of the literature. A content outline establishing the breadth and depth was followed by the generation of 4 patient, intervention, comparison, outcome, time questions. Key questions addressed: (1) diagnosis of systemic HTN, (2) recommended work-up of systemic HTN, (3) optimal blood pressure (BP) goals, and (4) impact of high BP on indirect markers of cardiovascular disease in youth. Once selected, references were subjected to a 2-person review of the abstract and title followed by a separate 2-person full-text review. Full citation information,

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population data, findings, benefits and harms of the findings, as well as other key reference information were archived. Selected primary references were then used for KAS generation. Level of evidence (LOE) scoring was assigned for each reference and then in aggregate. Appropriate language was used to generate each KAS based on the LOE and the balance of benefit versus harm of the findings. Topics that could not be researched via the stated approach were (1) definition of HTN in youth, and (2) definition of left ventricular hypertrophy. KASs related to these stated topics were generated via expert opinion.

**RESULTS:** Nearly 15 000 references were identified during an initial literature search. After a deduplication process, 14 382 references were available for title and abstract review, and 1379 underwent full text review. One hundred twenty-four experimental and observational studies published between 2003 and 2016 were selected as primary references for KAS generation, followed by an additional 269 primary references selected between August 2015 and July 2016. The LOE for the majority of references was C. In total, 30 KASs and 27 additional recommendations were generated; 12 were related to the diagnosis of HTN, 13 were related to management and additional diagnostic testing, 3 to treatment goals, and 2 to treatment options. Finally, special additions to the clinical practice guideline included creation of new BP tables based on BP values obtained solely from children with normal weight, creation of a simplified table to enhance screening and recognition of abnormal BP, and a revision of the criteria for diagnosing left ventricular hypertrophy.

**CONCLUSIONS:** An extensive and detailed systematic approach was used to generate evidence-based guidelines for the diagnosis, management, and treatment of youth with systemic HTN.

## INTRODUCTION

The 2017 "Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents" serves as an update to the 2004 "Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents" (Fourth Report).[1] The Fourth Report was sponsored by the National Heart, Lung, and Blood Institute (NHLBI), whereas the 2017 Clinical Practice Guideline (CPG) is sponsored by the American Academy of Pediatrics (AAP) and has been endorsed by the American College of Cardiology and by the American Heart Association. The authors of the Fourth Report relied primarily on summary statements created by a panel of expert clinicians who carefully evaluated the existing published literature. However, since the publication of the Fourth Report, there has been a notable increase in the number of peer-reviewed primary references, review articles, and systematic reviews (SRs) related to high blood pressure (HBP) and systemic hypertension (HTN) in youth. Hence, the CPG was developed not only by including experts but also by using a reproducible, systematic search and reference archival process, detailed study design evaluation, and evidence strength determination. In developing the 30 key action statements (KASs) of the 2017 CPG, the subcommittee members assessed the individual and aggregate evidence quality and incorporated the balance of benefits and harms of the findings before assigning a recommendation strength.[2]

Systemic HTN is 1 of 7 markers of poor cardiovascular health, according to the American Heart Association.[3] The presence of systemic HTN in childhood and adolescence is 1 of the key risk factors predictive of HTN and cardiovascular disease (CVD) in adults.[4–6] Systemic hypertension in youth has been associated with increased left ventricular mass (LVM), greater carotid intima-media thickness (cIMT),[5] stiffer arteries,[7] reduced endothelial function,[8] and renal[9] as well as neurocognitive impairments.[10] HBP in children has been shown to track into adulthood,[11,12] and HTN in adulthood is a leading cause of morbidity and mortality.[13–15] For these reasons,

appropriate diagnostic, management, and treatment strategies should be used in children. However, the diagnosis of HTN can be challenging and is often missed.[16,17]

Estimates of the prevalence of elevated blood pressure (BP) and HTN in children are largely based on analyses of weighted samples from the NHANES.[18] Analyses of more recent NHANES (1999–2012) data, as well as other cross-sectional and prospective study data, suggest a strong association between obesity and HBP in youth,[19,20] such that the prevalence of childhood HTN is higher among children with overweight and obese status.[21] Children and adolescents with specific chronic diseases, such as chronic kidney disease (CKD), also have an increased prevalence of elevated BP and HTN. According to the Chronic Kidney Disease (CKD) in Children study, 37% of youth with CKD had elevated systolic blood pressure (SBP) or diastolic blood pressure (DBP) (>90th percentile), and 14% are hypertensive (based on repeated BP assessment), with either a SBP and/or DBP greater than or equal to the 95th percentile.[22–24]

## Stated Objective of the AAP Regarding the Preparation of Updated "Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents"

On February 6, 2014, members of the AAP Sections on Nephrology, Nutrition, and Cardiology and Cardiac Surgery made a formal request to the Executive Committee of the AAP to sponsor a new pediatric HTN CPG focused on the evaluation and management of HBP in children and adolescents. Arguments made to support the generation of an updated guideline included the following:

1. recognition of the need for an update to the Fourth Report to reflect the breadth of new evidence related to HBP in children and adolescents; and

2. greater clarity for primary care providers regarding the utility of BP assessment and management of HTN in the pediatric population.

The request proposed a modification to the screening process and safeguards against both under- and overdiagnosis of HTN. New normative BP tables based on BP values obtained in children with normal BMI were proposed.[25] Furthermore, given increasing evidence to support the use of ambulatory blood pressure monitoring (ABPM) for more accurately assessing BP, it was proposed that the revision expand on the indications for ABPM.[26] The new CPG was intended to specifically incorporate methods for screening and diagnosing target organ damage (TOD), to include data from the pediatric antihypertensive clinical trials published since 2004, and to provide additional information regarding screening for secondary causes of HTN.

In spring 2014, the AAP Executive Committee authorized the formation of the Screening and Management of High Blood Pressure in Children Clinical Practice Guideline Subcommittee of the Council on Quality Improvement and Patient Safety (henceforth, "the subcommittee").

## Composition of the Subcommittee Members and Meetings

The subcommittee comprised individuals with expertise in the field of systemic HTN in youth, including representatives from a variety of relevant AAP committees. The subcommittee was cochaired by a pediatric nephrologist, Joseph Flynn, MD, MS, FAAP, and a general pediatrician, David Kaelber, MD, PhD, MPH, FAAP. Carissa Baker-Smith, MD, MPH, MS, FAAP, FAHA, a pediatric cardiologist, served as epidemiologist and methodologist for the CPG. She created the original content outline, drafted the patient, intervention, comparison, outcome,

and treatment/time (PICOT) questions, organized the literature search, structured the article review and selection process, assisted with archiving all selected references, drafted the evidence table (ET) and the technical report (TR). Kymika Okechukwu, MPA, was the AAP staff representative for the project. Susan K. Flinn, MA, was the professional medical editor, who drafted and edited the text of the CPG and assisted with editing the TR. Two librarians, knowledgeable in the process of SR, Kimberly Yang and Emilie Ludeman, assisted the epidemiologist in identifying search terms and conducting the literature search for reference selection in Medline, Cochrane Central Register of Controlled Trials (CENTRAL), and Excerpta Medica dataBASE (Embase).

All subcommittee members played an active role in the process of title and abstract review, article retrieval and storage in Mendeley,[27] reference review, KAS generation, ET generation, and editing of the CPG document sections. All conflicts of interests were disclosed at the beginning of the process and updated throughout the process. Reported conflicts of interest can be found at the end of this TR.

The subcommittee met face-to-face in June 2015 and March 2016. Conference calls occurred every 2 to 4 weeks, along with frequent and regular e-mail correspondence. These meetings, calls, and e-mails were used to assess the evidence and to draft the CPG content. Given the broad range of representation and expertise, potential biases were managed through group discussion and review of the data throughout the process.

## Definitions

- Children and adolescents: youth 1 to <18 years of age

- Infants: youth 1 to 12 months of age

- Neonates: youth 0 to 1 month of age
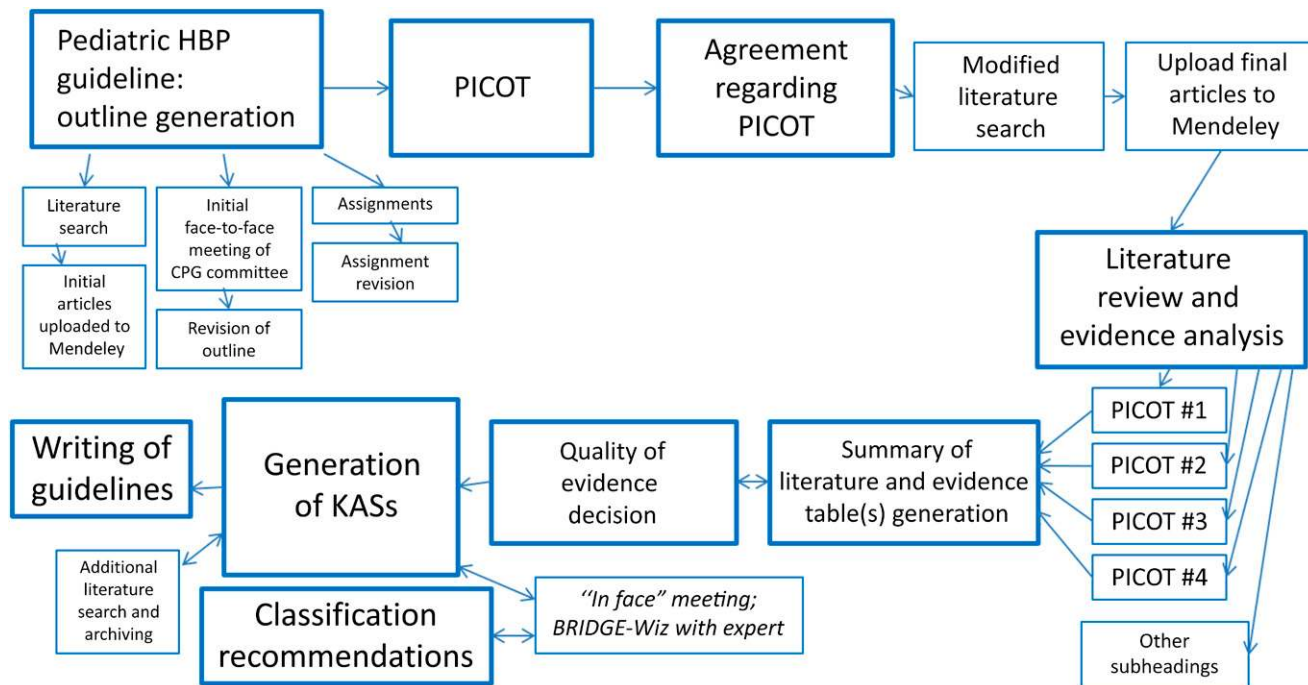
**FIGURE 1**
Process flow map used for creation of the 2017 "Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents."

### CHANGES IN THE DEFINITION OF HYPERTENSION IN YOUTH

According to the Fourth Report and its predecessors, the diagnosis of HTN in youth is purely a statistical determination based on the distribution of BP values obtained in youth. Unfortunately, BPs used for developing BP percentiles in the Fourth Report were obtained from children with both normal and unhealthy weight, skewing the mean. In addition, it was also appreciated that at approximately 13 years of age, the 90th percentile for BP is ~120/80 mm Hg. Previously, it was possible for youth, entering adult care at 18 years of age, to have a "normal" pediatric BP, but, unchanged, an "abnormal" adult BP categorization. As a result, the definition of HTN was revised in the 2017 CPG to reflect statistical definitions for HTN in children younger than 13 years and to use adult cutoff values for youth 13 years of age and older.

### FORMULATION AND ARTICULATION OF THE QUESTIONS ADDRESSED BY THE CPG SUBCOMMITTEE

The process of creating the CPG involved ensuring that key topics related to HTN in youth were addressed, ensuring that the literature search was complete and unbiased in identifying the most relevant references, ensuring that data were extracted and analyzed correctly, and that the selected references were summarized fully and accurately. The subcommittee also sought to ensure that the process of KAS generation was transparent and based on the available evidence and that the language used to describe a particular KAS corresponded to the recommendation strength, level of evidence (LOE), and benefits versus harms of the published findings.[28] A process flow map of the steps taken to generate the CPG can be found in Fig 1.

### Content Outline

The epidemiologist created a general topic outline. The original content outline included 16 main topics and a total of 100 subtopics that determined the breadth of topics to be addressed in the updated CPG. Agreement regarding outline content was obtained from all subcommittee members. Some of the originally selected topics were ultimately excluded because of lack of sufficient evidence, and other topics were combined to generate a more concise CPG.

### SR Process

The SR was conducted in accordance with the Preferred Reporting Items for Systemic Reviews and Meta-Analysis guidelines.[29] The epidemiologist carefully drafted 4 PICOT questions to guide the literature search. These questions addressed how the diagnosis of systemic HTN should be made in

infants, children, and adolescents; the recommended clinical and laboratory-based approach for identification of potential causes of systemic HTN (eg, evaluation for secondary causes); the target BP to be achieved with treatment; and the impact of BP severity on indirect markers of CVD in youth. Outcome measures, inclusion and exclusion criteria, and comparison groups were predetermined before the initiation of the literature search. The primary literature search was conducted by Emilie Ludeman and Kimberly Yang.

A line-by-line description of the search strategy is presented in Supplemental Appendix A, including the dates of the primary search for each PICOT. At the time of KAS generation, between August 2015 and July 2016, subcommittee members conducted additional searches. The epidemiologist was not directly involved in these additional literature searches but requested that search criteria, date, and time of each search be stored. All selected citations, including those identified during the initial and subsequent searches, were entered into 4 separate spreadsheets by PICOT (eg, PICOT 1, PICOT 2, PICOT 3, PICOT 4). Originally identified references, selected on the basis of the SR, were numbered. Added references, selected between August 2015 and July 2016, were labeled not with a number but as "added." All selected references, either chosen on the basis of title and abstract review or later chosen on the basis of separate searches conducted by subcommittee members during the KAS generation phase, were downloaded as a PDF from the Internet and then uploaded into Mendeley, a commercially available reference management software, used for reference storage and deduplication. Mendeley served as the subcommittee's central reference repository for easy access to selected articles during the article review and appraisal process.[27]

An ET was created for storage of data from references selected for inclusion in the CPG. The following information was entered for each reference in the ET: PICOT number, citation number in the CPG, original search reference number (identification number within the PICOT 1–4 spreadsheet), author(s), relevant KAS number, relevant CPG section number, year of publication, journal of publication, full citation, LOE assignment for the individual reference, type of study (eg, observational, randomized controlled trial [RCT], etc), primary population, reported sample size, subpopulations of interest, method of BP assessment (eg, manual, oscillometric, ABPM), intervention (if applicable), quality of BP measurements (at least 3 measurements made during a single visit), study findings, identified benefits of the study findings, potential harms related to the study findings, benefit versus harm analysis, and potential limitations of the study.

## PICOT Questions Generation

Once the CPG subcommittee members agreed on the topics to be covered, 4 PICOT questions were created (see below). Nearly 80% of the topics included in the outline were amenable to a PICOT search strategy and included in the PICOT formatted search (see Supplemental Tables 1 through 4 for outline topics addressed by the 4 PICOT questions); 20% were not. Topics that were not amenable to the PICOT search format included the following: strategies for prevention, challenges in the implementation of pediatric hypertension guidelines, economic impact of BP management, patient perspective, parental perspective, evidence gaps, and proposed future directions. Definition of HTN in neonates (0–1 month), infants (1–12 months of age), children (1–13 years of age), adolescents (13–18 years of age), and the definition of left ventricular

hypertrophy (LVH) were also not searched via a PICOT format (see Supplemental Table 5). These topics were individually researched, and expert opinion was used to create statements relevant to these topics.

### PICOT 1

How should systemic HTN (primary HTN, renovascular HTN) be diagnosed in neonates, infants, and children (0–18 years of age)? How should white coat hypertension (WCH) and masked hypertension (MH) be diagnosed in children and adolescents? What is the optimal approach to diagnosing HTN in children and adolescents?

### PICOT 2

What is the recommended workup for evaluating children and adolescents with suspected or confirmed systemic HTN? How do we best identify the underlying etiologies of secondary HTN in children and adolescents, including renal-, endocrine-, environment-, medication-, and obesity-related causes? When should providers suspect a monogenic form of systemic HTN among children and adolescents?

### PICOT 3

What is the optimal goal SBP and/ or DBP for children and adolescents? What nonpharmacologic and pharmacologic therapies are available for the treatment of HTN in children and adolescents?

### PICOT 4

In children and adolescents 1 to 18 years of age, how does the presence and the severity of systemic HTN influence indirect markers of CVD and vascular dysfunction (eg, flow-mediated dilation [FMD], cIMT), and how does HTN in children impact long-term risk of HTN into adulthood? Among children and adolescents with systemic HTN, how does the presence and the

**FIGURE 2**
Integrating evidence quality appraisal with anticipated benefits versus harms[27]: individual references were graded, benefits versus harms of the findings were assessed, and the aggregate evidence quality was used to generate a strong, moderate, or weak recommendation.

severity of systemic HTN influence comorbidities such as dyslipidemia, obstructive sleep apnea syndrome (OSAS), and cognition?

## Search Strategy

The epidemiologist and 2 librarians created a list of appropriate search terms and strategies (see Appendix A). Search terms included keywords and database-specific terminology (eg, medical subject headings terms, Emtree). The primary literature review for all PICOT questions was limited to studies published between 2003 and 2015. PubMed, CENTRAL, and Embase database searches were conducted on September 1, 2015, for PICOT 1; September 2, 2015, for PICOT 2; September 15–16, 2015, for PICOT 3; and September 17, 2015 for PICOT 4.

Inclusion criteria (see Supplemental Table 6) included the following:

- neonates, infants, children, and adolescents;

- male and female sex;

- all races and/or ethnicities;

- RCTs and observational studies (eg, cross-sectional, retrospective cohort, and prospective cohort); and

- case series for rare conditions for which large population studies were unavailable.

Exclusion criteria included the following:

- abstract only;

- adult-only population (especially when relevant pediatric studies were available);

- duplicate studies (in some cases, the same data were presented in another reference, and submitted to a different journal);

- primary population was non-United States (unless there were an insufficient number of US studies to address the key question);

- non–English language studies;

- letters;

- commentaries; and

- references related to topics that were not included in the CPG.

The citation information and any reasons for study exclusion were recorded by the methodologist. Review articles, meta-analyses, and most SRs were included for background. Adult studies were excluded from KAS generation but may have been included for background or table content. Studies that took place outside of the United States were included only when US data regarding the topics were not available or were limited.

## Evidence Review and Selection

### Analysis of Available Evidence, Assignment of LOE, Assignment of Grade Strength

AAP policy stipulates that the evidence in support of each KAS be prospectively identified, appraised, and summarized and that an explicit link between the LOE and grade of recommendation be defined. A summary of the available grades is described in Fig 2.[28]

### Strong Recommendation

A strong recommendation is the highest level of recommendation, reserved for recommendations supported by evidence with grade A or B that demonstrates a preponderance of benefit over harm. Interventions based on level X evidence might also be categorized as "strong" on the basis of their risk-benefit profile. A strong recommendation in favor of a particular action is made when the anticipated benefits of the recommended intervention clearly exceed the harms (as a strong recommendation against an action is made when the anticipated harms clearly exceed the benefits) and the quality of the supporting

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evidence is excellent. In some clearly identified circumstances, strong recommendations are made when high-quality evidence is impossible to obtain and the anticipated benefits strongly outweigh the harms. The implication for clinicians is that they should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.

### Moderate Recommendation

A moderate recommendation is made when the anticipated benefit exceeds the harms but the methodology used to generate the evidence is not sound. Moderately recommended KASs are to be supported by grade B or grade C evidence. Level X evidence may also be used to support a moderate recommendation depending on risk-benefit considerations. A recommendation in favor of a particular action is made when the anticipated benefit exceeds the harm but the quality of evidence is not as strong. In some clearly identified circumstances, moderate recommendations are made when high-quality evidence is impossible to obtain but the anticipated benefits outweigh the harms. The implication for clinicians is that they should be prudent when following a moderate recommendation but should remain alert to new information and sensitive to patient preferences.

### Weak Recommendation and No Recommendation

When published evidence is lacking, and/or when the limited evidence available demonstrates an equivocal risk-benefit profile, no recommended key action is offered. No recommendation indicates that there is a lack of pertinent published evidence and that the anticipated balance of benefits and harms is presently unclear. The implication for clinicians is that they should be alert to new published evidence that clarify the balance of benefit versus harm. The classification of

recommendations for the 2017 CPG is depicted in Fig 2.

### Evidence Selection Process

A 3-step process was used to select references for review. The first step included the selection of references from 3 databases (eg, Medline, CENTRAL, Embase). References were deduplicated. Next, by using preestablished written criteria for article selection for each PICOT, references were selected on the basis of title and abstract review. When the 2 reviewers disagreed, the epidemiologist provided the deciding vote on whether to include a particular reference. A third and final step involved full reference review.

A final search of articles published between August 2015 and July 2016 was completed at the time of KAS generation to identify any additional relevant references. Subcommittee teams also had the option of incorporating additional background references into the text preceding each KAS. Additional references were selected on the basis of expert opinion and familiarity with the literature. Background references selected for inclusion in the final document were also achieved in the ET.

### Generation of KASs

KASs were actionable statements, drafted on the basis of the assembled evidence, intended to guide clinical practice. Writing teams consisting of 2 or more subcommittee members were established to generate KASs for each selected topic. The clinical expertise of subcommittee members was used during the KAS generation phase. Subcommittee members with expertise in the topic were selected to either review the references relevant to a particular topic or serve as primary author(s) of the KAS relevant to their clinical expertise. In other cases, authors for the KAS were selected on the basis of previous involvement in article selection for

the particular topic. In addition to the creation of KAS writing teams, expert work groups were established to address (1) the revision of the HTN definition (members were Flynn, Kaelber, Giddings, Falkner, and Urbina) and (2) defining LVH (members were Giddings, Urbina, De Ferranti, and Baker-Smith).[30]

### Building Recommendations in a Developer's Guideline Editor

The language used for each KAS was specifically chosen to reflect the strength of recommendation by using Building Recommendations in a Developer's Guideline Editor (BRIDGE-Wiz),[31] an interactive clinical software application that has been adopted by the AAP to aid CPG authors. This application leads guideline writing teams through a series of questions intended to create clear, transparent, and actionable KASs. BRIDGE-Wiz incorporates LOE and benefit-harm assessment into a final determination of each recommendation strength. BRIDGE-Wiz provides safeguard against creating vague and/or underspecified recommendations. This software was used to generate KASs during an in-person meeting held at the AAP headquarters on March 21, 2016. BRIDGE-Wiz was also used to help generate the text for KASs generated after the March 21, 2016, meeting.

### Generation of Recommended KAS

After considering the available LOE and recommendation grades, the subcommittee formulated 30 KASs.[32] Each KAS included the following:

- an aggregate evidence quality score;
- a list of the potential benefit(s) of the proposed KAS;
- a description of the risks, harms, and costs of the proposed KAS;
- a benefit-harm assessment;
- a description of any intentional vagueness;

- a description of the role of patient preference;
- any exclusions;
- an assessment of the strength of the recommendation; and
- key references used to generate the specific KAS.

## RESULTS

### Summary of Findings by PICOT

*PICOT 1*

How should systemic HTN (primary HTN, renovascular HTN) be diagnosed in neonates, infants, and children (0–18 years of age)? How should WCH and MH be diagnosed in children and adolescents? What is the optimal approach to diagnosing HTN in children and adolescents?

A comparison between central aortic or brachial artery BP and cuff BP was beyond the scope of this CPG but has been described in a recent SR.[33] Criteria for the diagnosis of systemic HTN in neonates and infants has not been prospectively studied, at least since 2003. Only review articles were identified to suggest appropriate BP cutoffs for neonates born at 26 to 44 weeks' gestation.[34,35] The gold standard method for BP assessment in the neonate is intra-arterial analysis; the estimated prevalence of HTN in the neonate is approximately 0.2% to 3% but is higher in those with bronchopulmonary dysplasia, persistent ductus arteriosus, intraventricular hemorrhage, or an indwelling umbilical artery catheter (eg, up to 9% develop HTN). BP patterns may vary depending on developmental stage and gestational age at birth. According to the available literature, it may be best to use gestational age at birth and days of life when determining appropriateness of BP.[35]

At the present time, specific BP levels in youth have not yet been linked to cardiovascular outcomes in adulthood. Current normative values for BP are based on auscultatory BP measurements for normal-weight children. Unchanged from the Fourth Report, defining abnormal BP in youth 1 to <13 years of age continues to rely on a statistical definition.[25,36] The methods involved in determining statistical BP cutoff values have been peer reviewed and published.[25] For youth 13 years of age and above, adult BP cutoff values were adopted.[36]

Regarding the methods used for diagnosis of systemic HTN in children 3 to <18 years of age, initial BPs in children may be assessed via use of an approved oscillometric device, an aneroid sphygmomanometer or mercury sphygmomanometer (HgS).[36,37] Proper technique is essential for proper BP assessment.[38,39] When possible, manual BP assessments are preferred over oscillometric assessments, given data suggesting that oscillometric BP assessments routinely overestimate BP.[40]

Repeated measurement of BP remains an important step in determining whether a child truly has HBP.[41–43] Existing evidence would suggest that not all providers, practices, and/or patients adhere to recommendations for follow-up BP assessment within the recommended time frame.[41] The BPs obtained when vital signs are initially assessed do not necessarily reflect the true BP.[38] By more recent estimates, 90.0% (*n* = 1569) of children undergoing repeated measure of BP within a single visit did not experience a change in BP. However, 6.2% (*n* = 107) experienced a decrease in BP category and 2.9% (*n* = 49) experienced an increase in BP category.[42] A single BP measurement may lead to a misclassification of BP category and inappropriate action. Repeated BP measurement remains a requirement for diagnosing HTN.

The electronic health record (EHR) may also be helpful in diagnosing HTN among youth. Challenges associated with use of a complex table may lead to lack of recognition.[44] However, the EHR may be a useful tool for improved recognition of abnormal BP.[45,46] Finally, ABPM is a reliable, although less accessible, method for distinguishing WCH and MH from systemic hypertension.[47] Limitations of ABPM include a lack of reference data for children <120 cm in height and BP cutoff values that differ from those used to define abnormal in-office BP. Use of ABPM is currently recommended for confirmation of diagnosis and measurements obtained via ABPM may be more reproducible than those obtained via office or home BP.[36,48]

*PICOT 2*

What is the recommended workup for evaluating children and adolescents with suspected or confirmed systemic HTN? How do we best identify the underlying etiologies of secondary HTN in children and adolescents, including renal-, endocrine-, environment-, medication-, and obesity-related causes? When should providers suspect a monogenic form of systemic HTN among children and adolescents?

The evaluation of children and adolescents with suspected HTN consists of confirmation of the diagnosis. Potential secondary causes of systemic HTN can be found in Table 14 of the CPG.[36] Additional diagnostic studies may be required.[36] It has been suggested that primary HTN accounts for most cases of HTN among children older than 6 years and among 90% of children older than 15 years.[49–51] Patients with secondary HTN tend to be younger and are more likely to have abnormal serum creatinine, renal ultrasonography, and echocardiography findings.[50] Youth with secondary causes of HTN may be at greater risk for

hypertensive emergency and require more immediate management and intervention.[52]

## PICOT 3

What is the optimal goal SBP and/or DBP for children and adolescents? What nonpharmacologic and pharmacologic therapies are available for the treatment of HBP in children and adolescents?

The optimal goal SBP and DBP for children and adolescents remain unknown. However, data from a recent survey study indicate that compared with normotension, elevated BP can be associated with the development of TOD in adults.[53] Additionally, more recent cross-sectional data demonstrate an association between elevated BP (>90th percentile) and TOD in youth.[7] Thus, the CPG recommends a target BP of <90th percentile, even for children and adolescents with primary HTN.

Nonpharmacologic treatment options include diets low in sodium (eg, Dietary Approaches to Stop Hypertension [DASH] diet) and fat and diets rich in low-fat dairy,[54] fresh fruits, vegetables, and legumes.[55] Pharmacologic treatment options include angiotensin-converting enzyme inhibitors (ACEi), long-acting calcium channel blockers (CCB), angiotensin receptor blockers (ARB), and thiazide diuretics. A detailed SR in which the roughly 21 antihypertensive trials conducted in 3454 hypertensive children with follow-up between 3 and 24 weeks are summarized has been published and has been referenced in the CPG.[56] α agonists and β-blockers are not routinely recommended for the initial treatment of hypertension in youth.

The PICOT 3 search was focused on identifying references that addressed the question of BP management, both nonpharmacologic and pharmacologic, in children and adolescents. It is well known that lifestyle modifications can have a significant and positive impact on BP management.[57] Furthermore, since the enactment of the 1997 Food and Drug Administration Modernization Act and passage of the Best Drugs for Children Act,[58] the path for assessing the pharmacokinetics, dose-effect, and safety of antihypertensive therapy in children has been cleared. The goals of PICOT 3 and its associated KASs were to both identify effective therapies (eg, lifestyle, noninvasive therapies, and antihypertensive therapies) and to evaluate response to therapy.

## PICOT 4

In children and adolescents 1 to <18 years of age, how does the presence and the severity of systemic HTN influence indirect markers of CVD and vascular dysfunction (eg, FMD, cIMT), and how does HTN in children impact long-term risk of HTN into adulthood? Among children and adolescents with systemic HTN, what is the relationship between severity of systemic HTN comorbid conditions such as dyslipidemia, OSAS, and impaired cognition?

The question of hypertension's impact on long-term cardiovascular health in children has been debated. Indirect measures of CVD risk include cIMT, FMD, and LVH. PICOT 4 sought to address the question of hypertension's impact on these and other indirect markers of CVD risk. In particular, the subcommittee evaluated whether a change in BP was associated with a change in FMD, cIMT, and/or LVH. This PICOT also addressed other potential comorbidities associated with HTN, including obesity, diabetes mellitus, dyslipidemia, OSAS, metabolic syndrome, cognitive impairment, and proteinuria.

On the basis of cumulative data from 4 large prospective cohort studies, the Cardiovascular Risk in Young Finns Study, Childhood Determinants of Adult Health Study, the Bogalusa Heart Study, and the Muscatine Study, the strength of association between the presence of childhood risk factors for premature CVD and the presence of cIMT is dependent on age of onset of elevation in SBP in 6- to 18-year-olds, whereas elevations in DBP were not associated with abnormal cIMT.[5]

### General Results From Full Search

A total of 14 763 references were selected after the initial PICOT search. After deduplication, 14 382 references were available for title and abstract review. The 2-person abstract and title review resulted in a total of 1379 references for full text review. A total of 124 references were selected for KAS generation (see Supplemental Table 7). An additional 269 primary references were selected for inclusion during the expanded search.

### Primary Literature Search, PICOT 1

The primary questions used to conduct the literature search for PICOT 1 were as follows: How should HTN in children and adolescents be diagnosed and what is the optimal approach to diagnosing HTN in children and adolescents?

Of the 304 selected references, 266 were excluded (see Supplemental Table 8). An additional 58 references were selected during KAS generation (see Supplemental Table 9). Of the total 48 primary references used for KAS generation, there were 2 LOE A references, 19 LOE B references, 16 LOE C references, and 4 were SRs, and 7 were background references. Ten KASs were generated related to PICOT 1.

### Primary Literature Search, PICOT 2

The primary questions used to conduct the literature search for PICOT 2 were as follows: What is the recommended workup for hypertension in neonates, infants, children, and adolescents? How do we best identify the underlying

etiologies of secondary hypertension in the pediatric population?

The literature search for PICOT 2 was focused on the diagnostic approach for identifying renal, renovascular, cardiac, endocrine (including pheochromocytoma), medication-related, and genetic causes of HTN. A total of 1567 references were selected on the basis of initial search terms (see Supplemental Table 7). After the deduplication process, a total of 1565 references were selected. Abstract and title review led to the exclusion of 196 references after full reference review. See Supplemental Table 10 for the excluded PICOT 2 references.

Of a total of 225 references selected, 86 references (see Supplemental Table 11), 9 were selected for KAS generation. Seventy-two additional references that were added during the search conducted between August 2015 and July 2016 were also used to generate KASs related to PICOT 2.

Of the selected references used to generate PICOT 2–related KASs, 4 were LOE B and 24 were LOE C. Eight background references were selected at the discretion of the KAS authors.

### Primary Literature Search, PICOT 3

The primary questions used to conduct the literature search for PICOT 3 were as follows: What is the optimal goal SBP and/or DBP for children and adolescents? What nonpharmacologic and pharmacologic therapies are available for the treatment of HBP in children?

A total of 6958 references were selected on the basis of initial search terms (see Supplemental Table 7). A minimum therapeutic follow-up period of 3 months was required for inclusion of a study. After a deduplication process conducted in Mendeley, a total of 6710 references were selected. Abstract and title

review led to the selection of 631 references for full reference review and data extraction. A total of 59 references were initially selected for inclusion in KAS generation. Some of the references were excluded because the topics covered were beyond the scope of the CPG (eg, RCTs of the use of dark chocolate, cocoa, beetroot juice, dietary fiber, dietary protein, diet rich in fish, or garlic to treat hypertension in children),[59–66] (see Supplemental Table 12 for the excluded PICOT 3 references), and other references were excluded because they pertained to a particular subset of children with hypertension (eg, pharmacologic management of hypertension in children with CKD).[67,68] There were many trials in which combination therapy in the adult population was addressed. Such topics were not explored in the CPG,[69–74] and such references were ultimately excluded. Some references considered to be duplicates (eg, reports of the pediatric candesartan trial) were excluded.[75,76] In total, 587 references were excluded (see Supplemental Table 12).

After the updated search and KAS generation, 45 additional references were selected for inclusion for a total of 60 references (see Supplemental Table 13). The majority of selected references were cross-sectional studies. A total of 60 primary references were used to generate KASs for PICOT 3: 10 were LOE A, 11 were LOE B, 31 were LOE C, and none were LOE D/EO. In addition, 5 background references and 3 SRs were selected for inclusion and KAS generation.

### Primary Literature Search, PICOT 4

The primary question used to conduct the literature search for PICOT 4 was as follows: In children and adolescents 0 to 18 years of age, how does the presence and the severity of systemic hypertension influence indirect markers of CVD

and vascular dysfunction (eg, FMD, cIMT), and how does hypertension in children impact long-term risk of hypertension into adulthood?

A total of 3857 references were selected after a deduplication process was conducted in Mendeley. Abstract and title review led to the selection of 3744 references for full review and data extraction. In total, 219 references were selected for full review (see Supplemental Table 7), and 196 were excluded for the following reasons: 1 abstract only, 10 non-English language and/or non-US population, 110 adult-only population, and 98 for other reasons (eg, review article, duplicate reference, etc; see Supplemental Table 14).

After the updated search, a total of 23 references were selected for inclusion in PICOT 4. The majority of selected references were cross-sectional studies or retrospective cohort studies.

## SPECIAL ADDITIONS TO THE CPG

### Creation of New BP Tables

The subcommittee engaged Bernard Rosner, PhD, the statistician previously consulted by the NHLBI on past pediatric BP guidelines, to generate new normative BP tables on the basis of values obtained only in children with normal BMI. The goal was to eliminate the effects of obesity on the normative values, which was a criticism of the normative BP tables published in the Fourth Report. Methods used to generate these tables have previously been published.[25]

Data included in this updated analysis were already presented in the National High Blood Pressure Education Program NHLBI database and consisted of 11 pediatric BP studies conducted between 1976 and 2000.[77–86] For the new normative BP table, only subjects with BMI <85th percentile based on Centers for

Disease Control and Prevention age- and sex-specific BMI growth charts were used. Separate sex-specific analyses were performed for SBP and DBP. Of note, the heights used in the new tables are those for children of x years, 6 months, and therefore may differ from height values found in standard growth charts.

To remove study effects, a restricted cubic spline linear regression model was run of BP on study age, height $z$ score, and weight $z$ score, represented as 10 dummy variables. Height and height $z$ scores corresponding to height at age x years+ 6 months and not the CDC height percentiles, were used. The study effects from the regression model were used to compute "adjusted BP" (eg, BP_adj), which was the BP that would be obtained if a subject came from an average study. A second restricted cubic spline regression was then run of the adjusted BP on age, height, and age × height, with knots at the fifth, 27.5th, 50th, 75th, and 95th percentiles and residuals that were assumed to be normally distributed.

A cubic spline was used because it is considered to be more flexible than a single ordinary polynomial regression over the entire age and/or height $z$ score. The cubic spline is a concatenation of separate cubic polynomials with smooth intersections at the knots. The restricted cubic spline model assumes normal residuals, which implies that the effects of age and height are the same for all quantiles of BP. To relax this assumption, quantile regression methods were used. With quantile regression, mean BP was modeled by using restricted cubic spline. However, a separate set of regression coefficients was obtained for each quantile (s = 0.01, 0.05, 0.10, 0.25, 0.50, 0.75, 0.90, 0.95, and 0.99). The quantile regression approach, using separate restricted cubic splines for each quantile, offers the most flexibility in terms of

both specification of the regression function for a specific quantile and allowance for separate regression equations for different quantiles.

Complete tables for the 90th percentile are available in Table 4 of Rosner et al,[87] along with the regression equations used to generate each of the quantiles(s) in the restricted cubic spline in addition to a macro that ran 99 quantile regressions for s = 0.01, 0.99 (0.01) and estimated the closest quantile that agrees with a child's given BP, age, sex, and height. These percentiles, both in tabular form for assessment of BP of individual children and in a SAS macro for assessment of BP percentiles in batch mode for larger numbers of children, are available online.[88]

Information regarding how to incorporate 2017 CPG BP definitions into the EHR can be found in Supplemental Appendix B.[87]

### Simplified BP Table

The CPG also includes a new, simplified table for initial BP screening based on the 90th percentile BP for age and sex for children at the fifth percentile for height. This gives the BP values in the simplified table a negative predictive value of more than 99%.[89] The simplified table was designed for use only as a screening tool to identify children and adolescents who need further BP evaluation.

It is not intended that one will use the simplified table to diagnose elevated BP or hypertension but rather to determine when a BP measurement should be repeated. To diagnose elevated BP or hypertension, it is important to use the actual BP values in the complete BP tables because these may be as much as 9 mm Hg higher than those in the simplified table, depending on the child's age and length or height. A typical use case for this simplified table is for nursing staff to quickly identify BP

that may need further evaluation either by the nurse himself or herself or by the clinician. For adolescents ≥13 years of age, a threshold of 120/80 mm Hg was used in the simplified table regardless of sex to align with adult guidelines for detection of elevated BP.[90]

### New Definition of LVH

Echocardiography is used to assess the presence of left ventricular target organ injury related to hypertension in children.[1] The basis for this assessment is (1) the relationship of LVM to BP,[91] (2) the independent and strong relationship of LVH to adverse CVD outcomes in adults,[92–94] and (3) the fact that a significant percentage of children and adolescents with hypertension demonstrate a degree of LVH associated with adverse outcomes in adults.[95–97]

The left ventricle (LV) structure in the CPG is stratified into 4 groups on the basis of LVM (normal or hypertrophied) and relative LV wall thickness (normal or increased). The 4 stratified groups proposed for LVM include (1) normal geometry with normal LVM and normal relative wall thickness (RWT), (2) concentric geometry with normal LVM and increased RWT, (3) eccentric LVH with increased LVM and normal RWT, and (4) concentric LVH with both increased LVM and increased RWT[98,99] (see Supplemental Table 15).

Because the heart increases in size in relation to body size, indexing LVM is required.[100]

For the 2017 CPG, the following definitions for LV target organ injury were chosen regarding hypertrophy, RWT, and ejection fraction (EF). These definitions are based on published guidelines from the American Society of Echocardiography and associations of thresholds for indexed LVM with adverse outcomes in adults[92,93,98,100]:

- LVH is defined as left ventricular mass, indexed >51 g/m$^{2.7}$ or LVM >115 g/body surface area (BSA) for boys and LVM >95 g/BSA for girls. (Note that the values for LVH are well above the 95th percentile for distributions of LVM in children and adolescents.[98] The clinical significance of values between the 95th percentile of a population-based distribution and these thresholds is uncertain.[101])
- An LV RWT >0.42 indicates concentric geometry. LV wall thickness >1.4 cm is abnormal.[102]
- Decreased LV EF is a value <53%.

## CONCLUSIONS

The 2017 "Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children in Adolescents" is a comprehensive, evidence-based guideline intended for use by primary and subspecialty care providers. In this TR, we review the methodology used to generate the guideline. A systematic approach was used to generate evidence-based guidelines for the diagnosis, management, and treatment of youth with HBP.

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**ABBREVIATIONS**

AAP: American Academy of Pediatrics
ABPM: ambulatory blood pressure monitoring
ACEi: angiotensin-converting enzyme inhibitor
BP: blood pressure
BRIDGE-Wiz: Building Recommendations in a Developer's Guideline Editor
BSA: body surface area
CENTRAL: Cochrane Central Register of Controlled Trials
cIMT: carotid intima-media thickness

CKD: chronic kidney disease
CPG: Clinical Practice Guideline
CVD: cardiovascular disease
DASH: Dietary Approaches to Stop Hypertension
DBP: diastolic blood pressure
EF: ejection fraction
EHR: electronic health record
Embase: Excerpta Medica dataBASE
ET: evidence table
FMD: flow-mediated dilation
HBP: high blood pressure
HgS: mercury sphygmomanometer
KAS: key action statement
LOE: level of evidence
LV: left ventricle

LVH: left ventricular hypertrophy
LVM: left ventricular mass
MH: masked hypertension
NHLBI: National Heart, Lung, and Blood Institute
OSAS: obstructive sleep apnea syndrome
PICOT: patient, intervention, comparison, outcome, and treatment/time
RCT: randomized controlled trial
RWT: relative wall thickness
SBP: systolic blood pressure
SR: systematic review
TOD: target organ damage
TR: technical report
WCH: white coat hypertension

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