Diagnosis of hypertension in children and adolescents: 2019 update

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Abstract

High blood pressure during childhood and adolescence has evolved as a significant health issue with regard to population cardiovascular health. Guidelines on the diagnosis and management of high BP in children and adolescents aim to offer evidence-based guidance to the primary care physician with regard to screening, diagnosis, evaluation and treatment of high BP in routine clinical practice. In the era of updated guidelines the primary care physician has to familiarize with new definitions, normative data, BP measurement techniques, and treatment algorithms. In addition, controversies between guidelines may add further difficulty in implementation of recommendations into routine clinical practice and may result in disproportional management of BP levels among pediatric populations. The aims of this review is to discuss practical points for the screening, diagnosis, laboratory investigation of high BP in children and adolescents based on the 2016 European Society Hypertension and the 2017 American Academy of Pediatrics guidelines, and to evaluate rational approaches based at large on the similarities between the guidelines.

Key words: Blood pressure; Hypertension; Children; Adolescents; Screening; Diagnosis; Treatment

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Introduction

Hypertension in childhood and adolescence represents a risk for future adult hypertension and adverse cardiovascular or renal outcomes. Large cohort studies have shown that the presence of high blood pressure (BP) at any instance from childhood to adulthood is associated with subclinical arterial damage and underline the significance of early and continuous prevention [1]. The awareness of disease is increasing, but yet a significant proportion of children and adolescents with high BP are under-diagnosed or undertreated [2,3].

Pediatric high BP prevalence estimates show that about 3.5% of children and adolescents have hypertension and another 10-11% elevated (high normal) BP [4]. In the American continent, 74 million children under the age of 18 are hypertensive [5]. The wide range of the prevalence estimates has been also showed through several studies in Central-European countries. The prevalence of hypertension in adolescents was 2.2% in Switzerland, 2.5% in Hungary, and 4.9% in Poland. In Southern Europe higher prevalence was identified; adolescent hypertension was estimated at 9% in Turkey, 12% in Greece, 13% in Portugal[6], whereas in Italy 4% of schoolchildren had high BP (both hypertension and high normal BP) [7].

Published guidelines on the diagnosis and management of high BP in children and adolescents offer evidence-based or consensus guidance to the primary care physician with regard to screening, diagnosis, evaluation and treatment of high BP in pediatric clinical practice. The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Working Group on Children and Adolescents and the European Society Hypertension (ESH) guidelines in 2009 provided similar recommendations on normative data, definition and management of high BP in children and adolescents [8,9]. The agreement between guidelines had increased the early recognition of disease and significant body of evidence was published, evolving at the same time gaps of knowledge and need for further research. In 2016 the ESH updated the guidelines expanding previous recommendations [6]. Similarly, the United States (US) guidelines were updated by the American Acad-

emy of Pediatrics (AAP) in 2017 including overall significant changes in the diagnosis of hypertension [10]. In the era of these two updated guidelines the primary care physician is challenged to familiarize with new definitions, normative data, measurement techniques, and treatment algorithms. In addition, controversies in diagnosis between guidelines may add further difficulty in implementing into routine clinical practice, and possibly disproportional management of BP levels among pediatric populations.

The aim of this review is to discuss practical points on screening, diagnosis, and laboratory investigation of high BP in children and adolescents based on the latest American (AAP 2017) and European (ESH 2016) guidelines. We also assessed the evidence behind different recommendations. Finally, we evaluated rational approaches based at large on the similarities between the guidelines.

Diagnosis of Hypertension

The lack of validated BP thresholds in children and adolescents against outcomes has emerged the need of using statistically defined normative data, as well as a dependency on extrapolations from the adult thresholds. Age, sex, and height are all considered major determinants of BP in childhood, and the 95th percentile (pc) of the BP levels distribution has been suggested by the published guidelines to define hypertension [6,10]. Thus, the use of normative BP tables is requisite for the evaluation of hypertension in children. However, while a single BP level is used to define hypertension in adults irrespective of sex, race, and ethnicity, the ideal normative tables for children and adolescents have been contested on the basis of racial and ethnic differences [11]. In many countries regional normative data have been produced presenting significant differences among each other and with the largest available normative BP database by the Blood Pressure in Children and Adolescents by the National High Blood Pressure Education Program (NHBPEP), which has been included in the Fourth Report and in the ESH 2009 and 2016 guidelines.

The AAP 2017 guideline has introduced modified NHBPEP normative tables and definitions for hypertension staging, which resulted in 2-3 mmHg

lower BP values to define each hypertension stage according to age, sex and height category compared to the Fourth Report and the ESH 2016 guidelines [10]. The new AAP 2017 BP normative tables included only normal weight children based on the rationale that obesity is a well-recognized, significant risk factor for hypertension and thus, overweight and obese children could not be included in the reference population sample used for normative tables [11,12]. This new lower levels fitted well with the lower BP limit suggested by the 2017 AHA/ACC high BP clinical practice guideline to define hypertension in adults. However, the quest of an ideal reference population for pediatric normative data may not end by removing overweight and obese children. Blood pressure trends do not always parallel those of obesity [13-15]. In the NHANES studies the increase in obesity from 1988-1994 to 1999-2000 could explain only 29% and 12% of the increase in systolic and diastolic BP levels, respectively [16]. Moreover, during the last decade decreasing trends in BP have been reported in the US adolescent population even in the overweight and obese groups [13,14]. Genetic and environmental factors, diet and physical activity, may also determine BP levels in childhood and adolescence [17]. A multiethnic reference population without risk factors remains a challenge for those involved in hypertension management in children and adolescents.

The adult single BP threshold has been suggested by both the AAP 2017 and the ESH 2016 guidelines to define hypertension in adolescents [18,19]. Based on the adult recommended BP threshold, and following the controversy between the adult guidelines, the age of this change is different between the two guidelines. The age at which adolescents could be managed as adults is not based in strong scientific evidence, longitudinal, observational, or interventional studies. Adult BP thresholds are similar with the pediatric BP normative data in tall children, but may underestimate BP elevation in short children. Sexual maturation may differ among adolescents of the same age, and girls have lower BPs resulting in lower BP levels according to the corresponding 95th BP pc [6,10]. Whether considering shorter and female adolescents as normotensives, would be as-

sociated with worse cardiovascular outcomes, will be a target for future prospective studies. Adolescence is a critical window for primary prevention in the young population. The results of meta-analysis on BP tracking during childhood and adolescence have shown that BP during adolescence presents the highest correlation with adult BP [20]. A single prospective study from the US showed a linear association between BP at 17 years of age and BP at adulthood with an interaction by body mass index and sex, stressing the significance of early multiple cardiovascular risk reduction interventions [21]. Of note in the latter study, neither the adult, nor the pediatric BP thresholds could safely predict outcome, providing evidence for the use of adult definition by the ESH 2016 guideline at late adolescence.

Screening

The first step to diagnose hypertension is to establish a BP screening strategy. The US Preventive Services Task Force has recently challenged the cost-effectiveness of BP screening in children and adolescents [2,22]. However, the available evidence is not reassuring and in the face of a future epidemic of cardiovascular events, the majority of scientific societies argued in favor of universal BP screening in children and adolescents. Both the AAP 2017 and ESH 2016 guidelines recommend routine BP screening in all children and adolescents starting at the age of 3 years, or earlier, if the child has a high-risk condition for hypertension. Screening is suggested at the office, well-child care visits setting. The recommendation on screening has remained unchanged from previous AAP and ESH guidelines, but several reports have shown under-diagnosis of hypertension in part due to failure of properly classifying BP levels, possibly because of complexity of normative BP data, which included 476 BP thresholds according to age, sex, and height [2,3,23]. Simplified methods of screening could facilitate the primary care physicians and increase adherence to guidelines [23]. This was the concept in both guidelines for the adolescent population, which is seen both by pediatrician but also by family physicians. Endorsing the adult BP threshold at office screening would also facilitate the transition of adolescents in adult care [6,10].

The AAP 2017 guideline further intended in increasing screening and diagnosis of high BP focusing in simplifying screening even in younger children. A simplified BP table with single BP values by age, resulting in 13 sets of thresholds for each sex, has been incorporated in the AAP 2017 guideline [10]. This table includes the 90th BP pc and 5th height pc for each age and sex category and has been modified according to the new lower normative BP thresholds from the simple table initially proposed by Kaebler et al., based on the NHBPEP data [24]. However, the table needs to extensively validate for its performance in different pediatric populations. Simplified methods to screen for BP in children and adolescents gained a lot of interest in the literature in the recent years. Ma et al. compared 11 proposed simplified BP screening methods and found the best performance in those that included height to identify children and adolescents with high BP [25]. Simple, user-friendly, web-based applications may also facilitate screening, but again validation of any model is crucial, before using it in routine pediatric clinical practice .

Increased BP variability in childhood and adolescence and the significance of the hypertension diagnosis arise the need of multiple BP measurements over time to avoid over- or under-diagnosis of hypertension [26]. While screening may rely on a single visit measurement, there is consensus among guidelines that diagnosis should be based on BP measurements at least in 3 separate occasions.

BP measurement

BP measurement methodology is critical for diagnosis and proper BP classification. Office BP remains the basis for hypertension screening and diagnosis. The AAP 2017 guideline recommends that trained health care professionals should make the diagnosis of pediatric hypertension in the office setting. A large part of the AAP 2017 guideline is dedicated to BP measurement techniques in the office, including a link for a video demonstration, in order to ascertain the use of proper methodology in the pediatric primary care. The ESH 2016 guideline also includes step-by-step recommendations for office BP technique. Oscillometric devices are acceptable by both guidelines for initial BP assessment [6,10]. However, the use of normative tables, in which BP has been measured by auscultation, is the rationale to perform the subsequent confirmatory BP measurements by auscultation in case of high BP levels. Oscillometric devices may be easier to use and are operator independent, but only few devices have been successfully gone through international validation protocols [27].

Out of office BP measurements are considered to further add on the BP phenotype, and to result in more accurate hypertension or normotension diagnosis [28]. Moreover, out of office BP measurements seem to have higher predictive value for hypertensive target organ compared to office BP [29]. The role of out of office BP measurements especially ambulatory BP monitoring (ABPM) has been reinforced by both the AAP 2017 and the ESH 2016 guidelines. Despite limitations in terms of expertise, normative tables, and monitor validation, there is a consensus that diagnosis of hypertension should be confirmed by ABPM to avoid treatment of white-coat hypertension. Moreover, children and adolescents with suspected masked hypertension, or with high-risk conditions should undergo ABPM to establish abnormal BP phenotype diagnosis. These recommendations may not apply to primary care physicians and support further evaluation of hypertensive children and adolescents by pediatric hypertension specialists. The accessibility to specialty centers and cost of this approach could be a drawback in terms of equal care in all pediatric patients. Yet, the prevalence of disease in youth, indicating lower number of patients eligible for ABPM compared to adults, and the expected profit, either on cardiovascular outcomes, or in case of out of office normotension by avoiding unnecessary treatment, or extensive investigation, seem to overcome the limitations [30,31]. Finally, ABPM use during pediatric hypertension treatment is based on strong evidence. The ESCAPE trial offers unique randomized longitudinal prospective data on the beneficial effect of BP control guided by ABPM with end point the progression of kidney disease [32].

Out of office BP measurements may also include home BP monitoring. The evidence for home BP

measurement is relatively limited in children and adolescents, but is suggested by the ESH 2016 guideline to be routinely used as adjunct to ABPM and office BP measurements after the diagnosis of hypertension in a child or an adolescent [6]. The AAP 2017 guideline also suggests the complimentary use of home BP after diagnosis for pharmacological treatment dose titration, assessment of BP control, and timing of repeating ABPM [10]. The ESH 2016 guidelines provide tables on the indications of both ABPM and home BP, as well as available normative data and practical recommendations with regard to methodology of home BP. Finally, a similar approach to office BP for the use of adult thresholds in adolescents ≥ 16 years old is also recommend for out of office BP monitoring [6].

Evaluation for secondary hypertension

The greater prevalence of secondary hypertension in the pediatric age range is well known to physicians caring for children with hypertension. The indications for further evaluation of hypertensive children and adolescents for underlying disorders and proper diagnostic evaluation is a key issue in the pediatric guidelines. The indications are similar in the ESH 2016 and AAP 2017 guidelines for younger children. ESH 2016 also considers that children and adolescents with stage 2 hypertension are in higher risk for an underlying pathology [6]. In the AAP 2017 guideline it is recommended that obese children, older than 6 years old, having positive family history of hypertension, and no signs of underlying cause would not require extensive evaluation for secondary causes [10]. It is also commented that diastolic hypertension, rather than severity of BP elevation, is more predictive of secondary hypertension, based on the results of limited observational studies [33,34]. Even so, evidence on obesity epidemic in children at all stages of CKD is provided by US and European pediatric patients' registries, and may suggest to maintain some index of suspicion for secondary hypertension in overweight/obese asymptomatic children, as initial Chronic Kidney Disease Stages (CKD) presentation could only include high BP values [35-37].

History and clinical examination is recommended to guide patient specific diagnostic evaluation beyond initial laboratory tests that should be offered to all children according to ESH 2016 guideline (**Figure 1**). A targeted, cost saving approach with regard to initial laboratory test for evaluation of secondary causes of hypertension has been suggested by the AAP 2017 guideline. Renal ultrasound for children older than 6 years is reserved only for those with abnormal creatinine levels, or urine analysis [10]. However, neither creatinine, nor urine analysis are sensitive markers of underlying renal pathology in early CKD. Renal scars, cysts, small size or dysplastic kidneys, solitary kidney may underlie the pathogenesis of secondary hypertension without any laboratory sign of abnormal kidney function [38,39]. Moreover, in older children renal ultrasound may give clues for the presence of renovascular hypertension [40]. Although renal ultrasound is subjective to operator experience and skills, its role on the detection of asymptomatic underlying kidney pathology is vital for early detection and appropriate clinical decision-making. Once CKD is diagnosed preventive measures may start to slow the progression of disease and strict BP control has been established by strong evidence [32].

Hypertensive target organ damage

In the absence of hard outcomes in childhood and adolescents it has been generally accept that intermediate markers, including left ventricular hypertrophy, arterial stiffness, carotid intima media thickness, and albuminuria or proteinuria, may be used to estimate the presence of subclinical cardiovascular or renal damage attributed to hypertension. In the new AAP 2017 guideline evaluation for left ventricular hypertrophy (LVH) is delayed until consideration of pharmacological treatment arguing the subjective nature of the echocardiography and high cost of the test. The AAP 2017 guideline suggests targeting clinical decisions on BP levels, rather than treating an increased left ventricular mass [10]. However, in the BP targets section it is reported that LVH may appear at BP levels between the 90th and 95th pc, and that BP reduction below the 90th pc can reverse LVH. Further keeping a controversy in the same guideline repeated echocardiography is recommended after
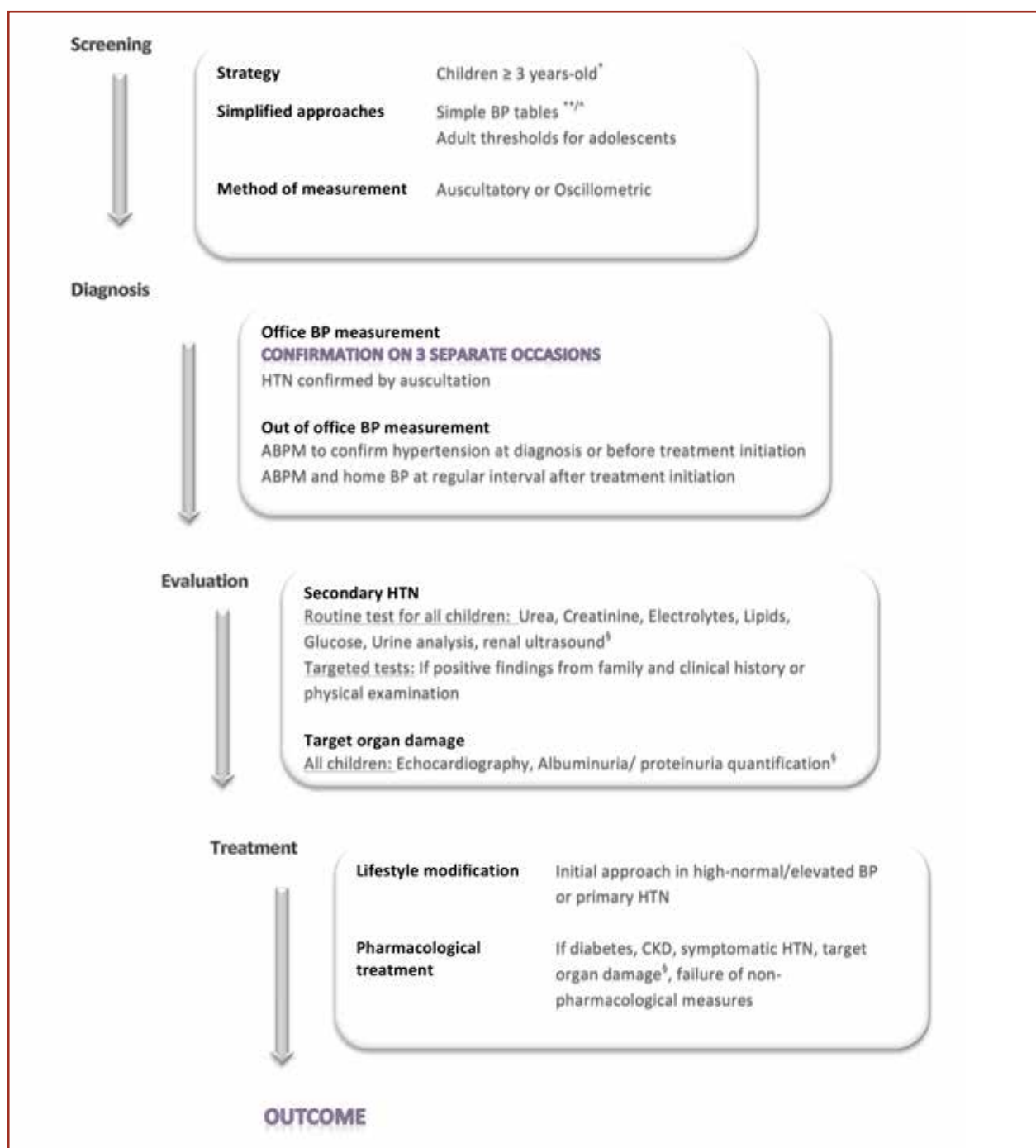
Figure 1. *A rationale approach for the diagnosis and management of high BP in children and adolescents in the era of ESH 2016 and AAP 2017 guidelines*

Figure abbreviations: HTN: hypertension, CKD: chronic kidney disease

* In children < 3 years old if high risk conditions exist including neonatal conditions requiring intensive care, congenital heart disease, renal disease, solid organ or bone marrow transplantation treatment with drugs known to raise blood pressure, systemic diseases associates with hypertension, and evidence of elevated intracranial pressure

** Need to be validated in different populations

^ Based on the AAP 2017 guideline

§ Based on the ESH 2016 guideline

treatment initiation at regular intervals, including those without LVH at initial echocardiographic assessment, if having stage 2, secondary or resistant hypertension. The frequency of repeated echocardiography during treatment is similar to that recommended by the ESH 2016, while the main difference between guidelines is that ESH 2016 maintain the recommendation to evaluate for hypertensive target organ damage at diagnosis of hypertension. Assessment of subclinical cardiovascular damage could guide clinical decisions from diagnosis with regard to intensity of non-pharmacological treatment, time to wait for initiation of pharmacological treatment, and choice of drug.

Hypertensive renal damage, although rare in children and adolescents with primary hypertension, may accompany cardiac damage [41,42]. Moreover, obesity has been shown as major risk factor for CKD, and coexistence with hypertension in childhood and adolescence may enhance the course of disease [43,44]. Obesity causes renal vasodilation and glomerular hyperfiltration to compensate for the obesity increased sodium sensitivity, which along with increased BP and metabolic abnormalities may lead to glomerular injury and a vicious cycle between hypertension and renal injury. The clinical utility of routine testing for albuminuria in all patients has been recognized by the ESH 2016, but not by the AAP 2017 guideline. Evaluation for proteinuria in the CKD patient with hypertension is recommended by both guidelines for clinical decision-making. With regard to arterial damage, there is an agreement among guidelines concerning the recommendation for non-routine assessment of arterial damage due to insufficient pediatric evidence.

The criteria to define target organ damage differ between ESH 2016 and AAP 2017 guidelines. Although an observational studies showed associations of LVH with the Fourth Report staging scheme there is no study on the relation with future cardiovascular events [45]. The lack of validated target organ damage thresholds in children and adolescents against outcomes was the main argument of the AAP 2017 guideline for not using statistical definitions, despite accepting statistical BP thresholds in children. Finally, the criteria to define different organ damage indices based on age and sex pc suggested by the ESH 2016 guideline offer the only available recommendation for the entire pediatric age range [6].

Conclusions, practical points and considerations

In a tailor made for adults cardiovascular medicine many recommendations are based on evidence extrapolated from adults. The extent, at which translation of adult cardiovascular medicine is safe for the young, challenges the wisdom of the writing committees in the current and future guidelines. For example the results of SPRINT study with the unattended office BP measurements that had a huge impact in the 2017 AHA/ACC and consequently in the AAP guidelines, is uncertain whether could be translated in the young pediatric population [46].

Diagnosis of HTN should be based on accurate diagnosis avoiding misclassify children and adolescents, neither as normotensives, nor as hypertensives with consequences on future health or insurance. In many practical aspects common recommendations among guidelines offer appropriate guidance for health practitioners caring for children and adolescents (Figure 1). On the other hand controversy issues may be barriers to the best care of children and adolescents with high BP. Among other controversy issues, the most fundamental one is concerning definitions and normative values. From a practical point of view children and adolescents should be managed using recommendations on pediatric normative data in line with the endorsed adult ones in their country in order to ensure a uniform classification and transition to adult care. Diagnostic evaluation of a child using laboratory tests and ultrasounds may differ among countries. Availability or cost of a test and insurance aspects could modify the implementation of the recommendations and may result in endorsing either the US or the European guidelines. Finally, any approach should be based in the best available evidence taking into account the paucity of long-term data in the young and with the perspective of longevity at the best cardiovascular health. ◇

Conflict of interest

There is no conflict of interest.

Περίληψη

Διάγνωση της αρτηριακής υπέρτασης στα παιδιά και τους εφήβους 2019

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Η υψηλή αρτηριακή πίεση στην παιδική και την εφηβική ηλικία προκαλεί σημαντική ανησυχία για τη δημόσια υγεία σε σχέση με την καρδιαγγειακή υγεία στο γενικό πληθυσμό. Κατευθυντήριες οδηγίες για τη διάγνωση και αντιμετώπιση της υψηλής αρτηριακή πίεσης στα παιδιά και τους εφήβους παρέχουν τεκμηριωμένη καθοδήγηση στον ιατρό πρωτοβάθμιας υγείας για την ανίχνευση, τη διάγνωση και τη θεραπεία της αρτηριακής υπέρτασης στην καθημερινή κλινική πράξη. Με τη δημοσίευση νεότερων κατευθυντήριων οδηγιών ο ιατρός πρέπει να εξοικειωθεί με νέους ορισμούς, φυσιολογικές τιμές, νεότερες μεθόδους μέτρησης αρτηριακής πίεσης και αλγόριθμους διάγνωσης. Οι διαφορές μεταξύ των κατευθυντήριων οδηγιών προσθέτουν επιπλέον δυσκολίες στην εφαρμογή των οδηγιών στην καθημερινή κλινική πράξη. Ο στόχος αυτής της ανασκόπησης είναι να συζητηθούν οι κλινικές προσεγγίσεις για τον έλεγχο, τη διάγνωση και τον εργαστηριακό έλεγχο της υψηλής αρτηριακής πίεσης στα παιδιά και τους εφήβους με βάση τις κατευθυντήριες οδηγίες της Ευρωπαϊκής Εταιρείας Υπέρτασης το 2016 και τις οδηγίες της Αμερικάνικης Παιδιατρικής Ακαδημίας το 2017 αναζητώντας τις ομοιότητες και τις διαφορές μεταξύ των ανωτέρω οδηγιών.

Λέξεις ευρετηρίου: Αρτηριακή πίεση, Υπέρταση, Παιδιά, Έφηβοι, Προληπτικός έλεγχος, Διάγνωση, Θεραπεία

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