

HIGHLIGHTS OF THE 2016 EUROPEAN SOCIETY OF HYPERTENSION GUIDELINES FOR THE MANAGEMENT OF HIGH BLOOD PRESSURE IN CHILDREN AND ADOLESCENTSEmpar LURBE^{1,2}, Elke WÜHL³, Stella STABOULI⁴, Asle HIRTH⁵, Mieczyslaw LITWIN⁶, Denes PALL⁷, Tomas SEEMAN⁸

on behalf of the Working Group of the 2016 European Society of Hypertension Guidelines for the Management of High Blood Pressure in Children and Adolescents

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Increasing prevalence of hypertension (HTN) in children and adolescents has become a significant public health issue driving a considerable amount of research. The European Society of Hypertension (ESH) acknowledged the importance of diagnosis, management and treatment of high blood pressure (BP) in this age group and promoted the publication of the ESH Guidelines in Children and Adolescents in 2009⁽¹⁾ and an update in 2016⁽²⁾.

Aspects included in the newsletter highlight advances in the definition of HTN in 16 years or older, isolated systolic HTN which is the most frequent type of HTN in youth, the importance of out of office measurement, clinical evaluation and organ damage assessment and treatment strategies.

Definition and classification of hypertension

Office blood pressure. Diagnostic criteria for elevated BP in children are based on the concept that BP in children increases with age and body size, making it impossible to utilize a single BP level to define HTN, as done in adults. In the auscultatory method, Korotkoff sounds are used to assess systolic BP (K1) and diastolic BP (K5) while deflating the cuff.

Hypertension in children is defined as systolic BP and/or diastolic BP persistently ≥ 95 th percentile for sex, age and height measured on at least three separate occasions. Children with average systolic BP and/or diastolic BP ≥ 90 th, but < 95 th are classified as having high-normal BP. Furthermore, Stage 1 HTN is defined as between the 95th percentile and 99th percentile and stage 2 as > 99 th percentile plus 5 mmHg⁽²⁾. Reference values were the same as in 2009 Guidelines⁽¹⁾.

The definitions have been revised for older adolescents and a consensus is given that for boys and girls aged 16 or older, the definition of HTN should no longer be based on the 95th percentile but on the absolute cut-off used for adults, which defines high-normal (130-139/85-89 mmHg) and HTN ($\geq 140/90$ mmHg)⁽³⁾. Isolated systolic HTN is defined as systolic BP ≥ 95 th percentile specific for sex, age and height, with diastolic BP < 90 th percentile, in 16 years and older systolic BP ≥ 140 mmHg and diastolic BP < 90 mmHg⁽²⁾ (Figure 1).

The main issue about how to measure BP in children is whether to use the auscultatory or the oscillometric method. If an oscillometric method is applied, the monitor should have passed the validation procedure recommended by the ESH International Protocol⁽⁴⁾. Continuously updated information on monitor validation for children is found at www.dableducational.org. Values obtained with oscillometric equipment are considerably higher than the auscultatory ones. Therefore, if HTN is detected by the oscillometric method, it must be confirmed by the auscultatory one⁽²⁾.

24-hour ambulatory blood pressure. Ambulatory BP measurement is now increasingly recognized as providing extremely useful information for the diagnosis and management of HTN and has contributed significantly to our understanding of HTN by "unmasking" BP phenomena that were not readily apparent using office BP. Values obtained using 24-hour ambulatory blood pressure monitoring (ABPM) have some better relationship with the presence of organ damage and a higher reproducibility than those obtained using office BP⁽⁵⁾.

The clinical interpretation of 24-hour ABPM depends on the use of normal BP ranges as reference values. These have now been obtained

from different European populations⁽⁶⁾. The consensus of the Guidelines is that the 95th percentile can be used as a threshold for HTN in children and adolescents as long as the values are inferior to the accepted criteria for adults (24-hour 130/80 mmHg; daytime 135/85 mmHg, nighttime 120/70 mmHg)⁽²⁾. Recommendations for the use of 24-hour ABPM include measurements made with the purpose of diagnosis, evaluation during treatment as well as in clinical trials and other conditions, in which the presence of orthostatism or rapid and episodic elevation of BP are difficult to detect in the office. Especially in children, 24-hour ABPM should be recommended before starting antihypertensive treatment, in order to avoid treating with drugs children with "white-coat" HTN⁽²⁾.

Home blood pressure. Home BP correlates closely with daytime ambulatory BP values and has superior reproducibility to office BP. Some preliminary evidence exist that home BP in children correlates with organ damage better than office BP. Methodological aspects and recommendations for use of home BP are BP monitoring for 6-7 days, with duplicate morning and evening measurements, as most available studies in children used a schedule of at least 6 day-monitoring. A 3-day monitoring was found to be the minimum reliable schedule against 6 day-readings⁽²⁾. One school-based study provided the only normalcy data for home BP in children and adolescents⁽⁷⁾ and the criteria to define HTN based on home BP is being higher than or equal to 95th percentile for sex and height, as long as the values are inferior to the criteria accepted for adults (average 135/85 mmHg)⁽²⁾.

To obtain robust reference values for office, home and ambulatory BP based on a European pediatric population, further work for urgent increase in knowledge is required.

Office and ambulatory discrepancies: The case of white-coat and masked hypertension. White-coat HTN is defined as elevated BP in office, yet normal being elsewhere. The reported frequency of white-coat HTN varies from 1% to 44%⁽⁸⁾. At present, no long-term follow-up data are available for children with white-coat HTN at initial assessment, in order to know the reproducibility and the real impact of this condition.

The inverse phenomenon, masked HTN, defined as normal BP in the office but elevated BP outside the office, occurs in approximately 10% of children and adolescents⁽⁹⁻¹⁰⁾. In 40% of children, the abnormal elevation of the daytime ambulatory BP persisted over a minimum of 6 months⁽¹⁰⁾. Masked HTN has been linked with progression to HTN in youth, with the risk being higher in boys than in girls⁽¹¹⁾. Masked HTN warrants follow-up, and if it persists, left ventricular mass should be assessed.

Isolated systolic hypertension

This issue is closely related to the understanding of the clinical value of central SBP in the assessment of adolescents with isolated systolic hypertension, because in a number of cases the elevation of brachial systolic BP is not accompanied by a central BP elevation. Central SBP may be especially relevant in asymptomatic children incidentally found to have isolated peripheral systolic HTN in the absence of target organ damage.

Clinical evaluation and organ damage assessment

All children identified as having HTN should have their height and weight measured and classified by percentiles. Other than the findings of HTN

itself and obesity, physical examination in children with HTN is frequently entirely normal. Nevertheless, a careful examination is mandatory to identify features of disorders that may be the cause of secondary HTN as well as identifying evidence of early organ damage.

Assessment of left ventricular mass remains a cornerstone when looking for organ damage in sustained pediatric HTN. Children and adolescents with HTN may have left ventricular hypertrophy even in early stages of disease⁽²⁾ and delaying the assessment may misclassify them with regard to their cardiovascular risk. The ESH Guidelines promote the concept that search and detection of early organ damage may identify hypertensive children and adolescents at high risk who may need more intensive management treatment both through lifestyle modification and pharmacological treatment^(2,12).

Therapeutic management of hypertension

The decision to initiate antihypertensive treatment should not be taken on BP levels alone but should consider the risk for cardiovascular (CV) and renal events. The presence or absence of organ damage, and other risk factors for CV morbidity and mortality such as family history of CV diseases, hyperlipidemia, renal diseases or diabetes establish the CV risk. In children with remediable secondary HTN, specific treatment of the underlying disease (renal, endocrine, CV) must be initiated immediately after detection. However, in those with primary HTN, antihypertensive therapy should first target the risk factors for BP elevation (i.e. overweight/obesity, increased salt intake, low physical activity).

Lifestyle changes (non-pharmacological therapy) should be initiated in youths with high-normal BP also. It should be continued even after starting pharmacological therapy, as it can improve the overall CV risk profile in hypertensive children.

Pharmacological therapy should be started in all children with symptomatic HTN, hypertensive mediated organ damage, secondary HTN or type 1 Diabetes Mellitus (DM) or type 2 DM, as well as in those who are unresponsive to non-pharmacological therapy⁽¹³⁾, i.e. those who have persistent HTN despite non-pharmacological therapy for about 1 year. It may be considered individually in children with high-normal BP if organ damage is already present⁽²⁾.

When prescribing antihypertensive treatment, therapy can include the five classes for which evidence of CV event reduction is available in adults⁽³⁾, drugs blocking the renin angiotensin system (either ACE inhibitor or ARB), beta-blockers, calcium channel blockers and diuretics. Clinicians who care for children and young adults with HTN need to be familiar with at least one drug from each class of agent. Given the substantial efforts that have been made to perform pediatric-specific studies confirming (at least short term) efficacy and safety in children, it seems sensible to initiate therapy with those agents which have a license for use in children. It is logical to choose an agent which can be administered once-daily because of the benefits that this provides in terms of simplicity of administration, allowing tablet-taking to be incorporated into the patient's daily routine (e.g. bedtime, tooth brushing etc.) and avoiding having to take drugs during school hours. Drug choice should be targeted to the child's underlying pathophysiology and presence of concurrent disorders.

Primary HTN is a growing problem in the pediatric age group, intrinsically linked to the increased global incidence of obesity. There is some evidence to suggest the use of ACE inhibitors and ARBs as first line agents in the obesity-linked primary HTN population. Where these are not tolerated, calcium channel blockers are a reasonable alternative.

Once the appropriate agent has been selected, the child should commence on the lowest recommended dose. This dose should be up-

titrated until the BP falls within the target range or until the maximum recommended dose is reached, at the same time carefully monitoring for the development of side-effects.

When the use of the maximum recommended dose of any single agent does not successfully achieve target BP, then the use of combination therapy is recommended. There is no evidence in the current pediatric literature to support the use of one particular combination over another, though some guidance based on adult data is provided in the ESH/ESC 2018 Guidelines⁽³⁾.

Drug choice should be targeted to the child's underlying pathophysiology and presence of concurrent disorders. For instance, in a child with HTN associated with DM and microalbuminuria, or with CKD and proteinuria, an ACE inhibitor or ARB is the most appropriate first line agent because of their antiproteinuric effect. Similarly, a beta-blocker or calcium channel blocker is the most appropriate agent in the child with HTN and migraine or where HTN has persisted after coarctation repair.

Monogenic forms of HTN are rare disorders, occurring as a result of single gene mutations and characteristically associated with low renin levels with alterations in acid base and potassium levels. Their recognition is important because patients are readily treated by a specific antihypertensive agent which targets the defective tubular function⁽²⁾.

Treatment goals. Blood pressure control in hypertensive patients has two major treatment objectives: the prevention of CV events and renal damage (or deterioration of renal function in patients with already existing chronic kidney disease (CKD)). However, the evidence for a specific BP goal in children is scarce and there is uncertainty as to the relative roles of BP targets and drug specific effects on CV and renal outcomes. In the absence of prospective long-term studies on the impact of different BP levels on intermediate or major cardiovascular and renal endpoints, the 95th percentile is considered as a cut-off for defining HTN in children and adolescents. This provides a rationale for targeting children and adolescents with essential HTN to a BP below the 95th percentiles for age, sex, and height, although aiming at a BP below the 90th percentile is probably safer, provided that this goal can be attained by a well-tolerated treatment. In individuals aged 16 years or older the adult cut-off values for office BP, that is, less than 140/90mmHg, are recommended as a target by ESH, but values of less than 130/80mmHg are not excluded⁽³⁾.

In patients with CKD, a BP less than 75th percentile is recommended as a target in children with nonproteinuric CKD whereas a BP less than 50th percentile in those with proteinuric chronic kidney disease. There is no evidence that a low BP goal improves renal survival in nonproteinuric CKD patients^(12,14). Target values apply to office, home, and 24-h ambulatory BP based on the prospective randomized ESCAPE trial⁽¹⁵⁾, which has provided evidence that a strategy that pursues reduction in these pressures, improves long-term renal survival.

Implementation of guidelines

Synergistic actions at various levels should be successfully implemented in order to limit, and even reduce, the burden of HTN in children and adolescents. The working group on HTN in Children and Adolescents and the ESH are working on a concerted action that will provide evidence according to whether new strategies would improve BP control without substantially increasing the cost, workload, and side effects of treatment. Only an aggressive public policy initiative will lead healthcare providers, insurers and other payers to increase the reimbursement of costs associated with the investigation and long-term treatment of high BP in children and adolescents. The role of the ESH is crucial not only for spreading the guidelines all over European countries, but also for obtaining the acceptance by national hypertension societies and leagues.

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