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Consensus Document Title:
Hypertension in children and adolescents: A consensus document from ESC Council on Hypertension, European Association of Preventive Cardiology, European Association of Cardiovascular Imaging, Association of Cardiovascular Nursing & Allied Professions, ESC Council for Cardiology Practice and Association for European Paediatric and Congenital Cardiology

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Graphical Abstract
Yes, I can explain the Graphical Abstract in the consensus document. The Graphical Abstract provides a visual summary of the suggested diagnostic algorithm, clinical work-up, and management of arterial hypertension in children and adolescents.

The Graphical Abstract is divided into three main sections: diagnosis, evaluation, and management. The diagnosis section includes the initial screening with office blood pressure measurement, followed by the confirmation of hypertension with ambulatory blood pressure monitoring (ABPM) or home blood pressure monitoring (HBPM). The evaluation section includes the assessment of hypertension-mediated target organ damage, evaluation of possible vascular, renal, and hormonal causes, and assessment of concomitant risk factors. The management section includes lifestyle modifications, pharmacological treatment, and follow-up.

The Graphical Abstract also highlights the importance of an individualized approach to the diagnosis and management of hypertension in children and adolescents, taking into account the patient's age, sex, height, and comorbidities. The use of validated blood pressure measurement devices and the need for specialized centers with expertise in the diagnosis and treatment of hypertension in pediatric age are also emphasized.

Overall, the Graphical Abstract provides a clear and concise visual summary of the suggested diagnostic algorithm, clinical work-up, and management of arterial hypertension in children and adolescents, emphasizing the importance of an individualized approach and specialized care.

Abstract about the Consensus Guidelines

Definition and management of arterial hypertension in children and adolescents are uncertain, due to different positions of current guidelines. The European Society of Cardiology task-force, constituted by Associations and Councils with interest in arterial hypertension, has reviewed current literature and evidence, to produce a Consensus Document focused on aspects of hypertension in the age range of 6–16 years, including definition, methods of measurement of blood pressure, clinical evaluation, assessment of hypertension-mediated target organ damage, evaluation of possible vascular, renal and hormonal causes, assessment and management of concomitant risk factors with

specific attention for obesity, and anti-hypertensive strategies, especially focused on life-style modifications. The Consensus Panel also suggests aspects that should be studied with high priority, including generation of multi ethnic sex, age and height specific European normative tables, implementation of randomized clinical trials on different diagnostic and therapeutic aspects, and long-term cohort studies implementation of the contents of the present Consensus to link with adult cardiovascular risk. Finally, suggestions for the successful document are also given

Gudielines Keywords: High blood pressure, Organ damage, Cardiovascular prevention, Obesity, Left ventricular mass, Antihypertensive therapy, Lifestyle changes

Introduction

Identification of arterial hypertension (HTN) is challenging in children and adolescents, as standards and definitions are complex during body growth, and outcome cardiovascular (CV) studies cannot be designed. Therefore, a statistical definition of childhood/adolescence HTN is necessary(1).

Three current guidelines propose different definitions(2),(3),(4). Table 1 summarizes recent criteria for definition, compared with the 4th Report from the National High Blood Pressure Education Programme (NHBPEP),(5) which has been a standard reference,because of the adoption of normative tables, based on age, sex, and height, renewed by the American Academy of Paediatrics (AAP)(2).

In addition to the differences in HTN definition (Table 1), the 2017 AAP guidelines excluded youths with overweight/obesity (OW/OB) from normative tables.

Due to these different indications, European Society of Cardiology together with the affiliated (ESC) Associations and Councils, Association for European Paediatric and Congenital Cardiology, produce this document to try to reconcile these different views, also suggesting measures to be undertaken in the near future to better clarify discordant points.

Table 1:

Table 1 in the consensus document provides a summary of the different guidelines and their definitions of arterial hypertension in children and adolescents. The table includes the year of release, the method used, and the cut-off points for each guideline.

The National High Blood Pressure Education Program (NHBPEP) released its 4th report in 2004, which has been a standard reference for hypertension in children and adolescents. The NHBPEP uses age-sex-height nomograms and defines hypertension as blood pressure measurements at or above the 95th percentile for age, sex, and height, or at or above 140/90 mmHg for individuals aged 18 years or older.

The European Society of Hypertension (ESH) released its guidelines in 2016, which also use age-sex-height nomograms. The ESH defines hypertension as blood pressure measurements at or above the 95th percentile for age, sex, and height for individuals under 16 years of age, or at or above 140/90 mmHg for individuals aged 16 years or older.

The American Academy of Pediatrics (AAP) released its guidelines in 2017, which use new age-sex-height nomograms only in normal weight individuals. The AAP defines hypertension as blood pressure measurements at or above the 95th percentile for age, sex, and height for individuals under 13 years of age, or at or above 130/80 mmHg for individuals aged 13 years or older.

The Hypertension Canada Guideline Committee (HCGC) released its guidelines in 2020, which also use new age-sex-height nomograms only in normal weight individuals. The HCGC defines hypertension as blood pressure measurements at or above the 95th percentile for age, sex, and height.

Overall, the different guidelines have different definitions and cut-off points for hypertension in children and adolescents, which can make it challenging to evaluate the prevalence of hypertension on a global scale.

Chapter 1: Definition and classification

Compared to 2017 US paediatric guidelines which recommended US adult cut-points (≥ 130/80 mm Hg) for adolescents starting at age 13,(2,6) the 2016 European Society of Hypertension (ESH) guidelines recommended European adult cut-points for adolescents starting at age 16 (≥140/ 90 mmHg),(3,7) a choice which is more consistent with the physiological body growth(8). Adopting the NHBPEP's normative tables,(5) however, ESH guidelines did not exclude OW/OB [body mass index (BMI) ≥85th percentile], which could influence the range of normal blood pressure (BP) values and classify as normotensive youngsters who are identified as hypertensive by the AAP nomogram(9,10). Moreover, consistent with the rising evidence of the link of OW/OB with both higher BP and hypertension-mediated organ damage (HMOD) also in children and adolescents,(11,12) the AAP guidelines recommend HTN thresholds defined after excluding OW/OB individuals. Adoption of AAP normative reference tables leads to an overall increase in the prevalence of HTN,(9,10) and to increased sensitivity in detecting organ damage, in particular left ventricular hypertrophy (LVH). This increased sensitivity is achieved, however, at the possible cost of decreased specificity(13,14). A recent position paper endorsed by the Italian Society of HTN and the Italian Society of Paediatrics expressed an opinion in favour of maintaining the NHBPEP nomograms(1).

The Hypertension Canada Guideline Committee (HCGC) (4) endorsed the new AAP tables, but the attempt to provide a simpler method based on fixed cut points also in children, in alternative to BP percentiles, resulted in increasing confusion. Simplification should involve the classification system and, especially, the clinical procedure to confirm diagnosis of HTN.

Overall, evaluation of prevalence of HTN in this range of age is made very difficult on a global scale, due to the variety of different definitions.

Box 1 in the consensus document highlights the need for the development of new European ambulatory blood pressure monitoring (ABPM) nomograms for age, sex, and height in a larger multi-ethnic, normal-weight population. The current normative values used for ABPM were derived from a homogeneous population of Caucasian German children, last updated in 2002. The development of new ABPM nomograms is considered critically important to improve the accuracy of ABPM interpretation and diagnosis of hypertension in children and adolescents.

The box also emphasizes the importance of an age-stratified approach to classify ABPM values in children and adolescents. The cutoff values and classification of ABPM values are still under debate, and the Consensus Panel recommends the use of European age-sex-height nomograms for ABPM interpretation.

In addition, the box highlights the importance of performing ABPM in secondary or tertiary centers with specific skills in the diagnosis and treatment of hypertension in pediatric age to minimize the risk of misdiagnosing hypertension. The box also recommends an approach to ABPM data interpretation based on the definition of hypertensive phenotypes identified using both office blood pressure and ABPM values.

BP measurement
At the present, all current guidelines suggest repeated office measurements (details can be found in Chapter 2), to confirm clinical observations of the first visit. The three guidelines recommend at least three different office visits, a challenging protocol that may cause dropout, and therefore, rarely adopted in the real world. Even one single BP assessment done by a doctor, or a nurse, can help identifying children with high BP, though diagnosis of HTN should always be confirmed by a second visit(15).

The Consensus Panel agrees that once HTN is detected, just a second visit is needed to confirm HTN, as already previously recommended(16,17). Advice should be given to favour home BP measurements (HBPMs), recommending automated devices validated for children (Refer Chapter 2), as recommended by all paediatric guidelines and adult European guidelines.

Since the commonly suggested ambulatory BP monitoring (ABPM) the uses a Caucasian German paediatric reference database, Consensus Panel strongly supports the generation of a broad multi-ethnic European reference population for ABPM in children and adolescents, to optimize the use of this important diagnostic tool (Refer Box 1).

Definition of HTN
HTN should be defined according to the modified AAP tables (2) up to age 16, but, clearly, Europe needs specific normative standards to be as accurate as

possible (Refer Box 1). For adolescents 16 year old or older, the suggested office values of ≥ 130/85 mmHg are adequate cut points to align older youths to the adult cut-off for high-normal values(7).

The Consensus Panel agrees that the value of ≥ 130/85 mmHg be sufficient to diagnose HTN. According to AAP nomograms, rarely, systolic BP exceeding normal adult cut-point is found between 13 and 16 years, especially in particularly tall boys, but this phenomenon can be explained with the peripheral amplification of the pulsatile wave that is greatest in this range of age (up to 20 mmHg and more)(18). More research is needed on effect of peripheral pulse wave amplification in this range of age.

The Consensus Panel agrees that echocardiography can be an important add-on to confirmed diagnosis, when it is likely to influence decision making (Refer Chapters 3 and 4). Table 2 summarizes the points of agreement of the Consensus Panel.

Table 2 in the consensus document provides a summary of the different methods used to measure blood pressure in children and adolescents. The table includes the method, the advantages, the disadvantages, and the recommended use for each method.

The methods listed in the table include office blood pressure measurement, ambulatory blood pressure monitoring (ABPM), home blood pressure monitoring (HBPM), and central blood pressure measurement.

Office blood pressure measurement is the most commonly used method and is recommended for initial screening. However, it has several disadvantages, including the white coat effect, observer bias, and lack of standardization.

ABPM is a non-invasive method that measures blood pressure over a 24-hour period and is recommended for the diagnosis of hypertension and for the evaluation of blood pressure variability. ABPM has several advantages, including the ability to detect masked hypertension and the absence of observer bias. However, it is more expensive and less available than office blood pressure measurement.

HBPM is a self-measurement method that is recommended for the diagnosis and management of hypertension. HBPM has several advantages, including the ability to detect white coat hypertension and the convenience of home measurement. However, it requires patient compliance and may be affected by measurement errors.

Central blood pressure measurement is a non-invasive method that measures blood pressure in the central arteries and is recommended for the evaluation of arterial stiffness and the prediction of cardiovascular events. However, it is more expensive and less available than other methods and requires specialized equipment and expertise.

Overall, the table provides a useful summary of the different methods used to measure blood pressure in children and adolescents, their advantages and disadvantages, and their recommended use.

Chapter 2: how to measure BP in children and adolescents
BP can be recorded by office BP (OBP) measurement, ABPM, and HBPM(19). However, while OBP nomograms created from large reference populations are available, albeit with limitations,(2),(3),(5) the reference values for ABPM and HBPM are generated from single studies. Whatever measurement is adopted, a pivotal issue is cuff dimension, because too small cuffs overestimate and too large cuffs underestimate BP values. The width of the optimally sized cuff should be approximately 40% of the circumference of the arm at its midpoint between acromion and olecranon, and the cuff bladder length should cover 80 to 100% of the circumference of the arm (2) (Figure 1).

Sphygmomanometers
All current guidelines refer to the same database obtained from measurements made with mercury sphygmomanometers (Refer Chapter 1), which have been recently discontinued because of concerns about mercury toxicity. This has opened the way to automated electronic sphygmomanometers, mostly based on oscillometric technique. However, only a limited number of automated oscillometric devices have been validated for the paediatric age, and their cost is not negligible(20). Since oscillometric devices do not measure but rather estimate BP, their accuracy might be considered uncertain. However, a recent meta-analysis has confirmed their strong measurement validity, when compared with mercury sphygmomanometers, supporting their appropriateness also for use in children and adolescents, in clinical and epidemiological studies(21).

The Consensus Panel agrees that generation of global BP paediatric reference nomograms obtained by oscillometric devices is a high priority for future studies (Refer Box 1), though few regional BP standards have already been proposed(22),(23). Only validated oscillometric devices should be used in children. To confirm diagnosis of HTN, oscillometric BP values should be confirmed with auscultatory method, using calibrated (every 6 months) aneroid sphygmomanometers (2),(3).

Office blood pressure
OBP should be measured with the subject sitting quietly for a few minutes, with the arm resting on a support at heart level (2). In the case of auscultatory methods, systolic BP corresponds to the appearance of the tone (1st Korotkoff’s) and diastolic BP to the disappearance of the tones (5th Korotkoff’s).

Figure 1 in the consensus document illustrates the correct method for measuring blood pressure in children and adolescents. The figure shows a child sitting with their back supported and their feet flat on the floor. The arm should be supported at heart level, and the cuff should be placed around th

e upper arm. The figure also shows the correct placement of the stethoscope on the brachial artery to listen for the Korotkoff sounds.

The figure also includes a note that only validated electronic devices shou ld be used for blood pressure measurement in children and adolescents. The figure provides a link to a website (https:// stridebp.org/bp-monitors/37-p dfs/734-home?format=pdf&tmpl= component&box=children.) where validated elec tronic devices can be found.

Overall, Figure 1 provides a visual guide for healthcare professionals on t he correct method for measuring blood pressure in children and adolescents, emphasizing the importance of proper positioning, cuff placement, and use o f validated devices.

In office, BP should be measured three times, 1–2 min apart (2)(3)(7) (avera ging the last two, discarding the first). At initial visit, BP should be als o taken in both arms and one leg in the supine position to rule- out aortic coarctation (CoA, Refer Chapter 4). For diagnosis of HTN, confirmation is re quired in a second outpatient visit after some time, the interval depending on the concern about the level of BP.

The Consensus Panel agrees that automated unattended oscillo- metric BP mea surements in children and adolescents should not be used for diagnosis, bec ause no studies are available in children and adolescents to demonstrate be tter diagnostic value than conventional OBP.

Ambulatory blood pressure monitoring Consistent with recommendations in adu lt individuals, in children and adolescents, available guidelines acknowled ge the importance of 24 h ABPM. However, due to the paucity of reference va lues for interpretation in this range of age,(24) clinical interpretation o f ABPM values is at present limited. The scarce compliance of children with ABPM measurements, especially during night, makes interpretation of 24 h an d, more specifically, of nocturnal BP difficult. It seems reasonable that chi ldren/adolescents HTN guidelines recommend an approach to ABPM data interpr etation which is based on definition of hypertensive phenotypes identified us ing both OBP and ABPM values (25). Because the normative values that are us ed were derived from a homogeneous population of Caucasian German children, last updated in 2002(24), an effort to create new European ABPM nomograms f or age, sex and height, in a larger multi-ethnic, normal weight population, is critically important (Refer Box 1).

As suggested by AAP(2), ESH (3), and AHA (26) guidelines, ABPM can be usefu l in selected cases (suspected white coat, secondary HTN, diabetes, monitor ing of antihypertensive therapy and clinical trials), and should be perform ed in secondary or tertiary centres, with specific skills in the diagnosis a nd treatment of HTN in paediatric age, to minimize the risk of misdiagnosin g HTN.

An age stratified approach has been suggested in children and adolescents to classify APBM values. However, ABPM cutoff values and age thresholds at whi ch adult cutoffs should be applied differ between the United States and Eur ope (3), (27).

The Consensus Panel agrees that the 95th percentile of ABPM values can be u sed as a threshold for HTN diagnosis in children and adolescents, as long a s the values are inferior to the accepted criteria for adults(3)(7). It is important to take into consideration that ABPM values are often higher than the corresponding office values in children and adolescents, a difference th at is function of age (28) According to available European reference values of ABPM for children (24), based on the 95th percentile, ABPM values might be even higher than ABPM HTN thresholds for adults (28),(29). To avoid this apparent paradox, due to the higher peripheral amplification of pressure wav e in this range of age,(30),(31) as well as to the greater physical activit y especially during day-time,(28) application of adult ABPM norms has been suggested for paediatric age (29),(32).

The Consensus Panel agrees on the following points for ABPM:

- Daytime measurements should be scheduled every 20 min and night measureme nts every 30 min.

- It is important to explain the reason for the exam to the young patient t o minimize anxiety and maximize cooperation.

- The ABPM measurements should always be interpreted on the background of O BP evaluation.26

Home blood pressure monitoring Also for HBPM, reference nomograms are deriv ed from a single population in which only one HBPM device, validated in chi ldren, was used (23). There are limited data on the association between HBP M and HMOD in children and adolescents, and, as observed for ABPM, the rela tion between HBPM and OBP varies with children’s age (33). Additional diffic ulties for use of HBPM in children and adolescents include limited research on clinical application, lack of data on nocturnal BP and current uncertain ty on its diagnostic role (34).

The Consensus Panel agrees that European age-sex-height nomograms should be generated (Refer Box 1 details).

The Consensus Panel agrees that HBPM should be recorded as recommended for adults in the ESC/ESH guidelines (7). HBPM would be most useful when diagno sis is uncertain, especially when reliable reference values will be availab le. HBPM can be very useful to monitor effects of therapy.

When using HBPM, parents should be instructed on how the measurements must be performed.

Chapter 3: clinical evaluation and assessment of hypertension-mediated ta rget organ damage

Clinical evaluation When HTN is suspected, careful history and physical exa mination are needed. Table 3 presents the key historical points to collect as recommended by paediatric and adult European guidelines (3),(7).

The Consensus Panel agrees that BMI and waist circumference (WC) should be measured according to consolidated methods.35,36 Since no validated paediat ric European tables on WC are available, based on age and sex, the Panel ag rees that WC should be normalized for height (waist-to-height ratio) with a suggested cut-off value of 0.50.37

Routine laboratory tests should be always requested (Table 4, row Blood che mistry), with additional tests to exclude secondary causes, when clinical s uspicion exists (Refer Chapter 4).

Based on recent evidence, the Consensus Panel agrees that electrocardiogram (ECG) can be useful also in this range of age, if properly interpreted.38

Assessment of hypertension-mediated organ damage

Assessment of HMOD has been recommended in paediatric guidelines. The Conse nsus Panel agrees that three main areas should be explored, kidney, CV syst em, and brain.

Kidney function should be evaluated independently of known chronic kidney d isease (CKD) to:

Box 2 in the consensus document provides information on the equations used to estimate glomerular filtration rate (GFR) in children and adolescents wi th hypertension. The box suggests two equations for GFR estimation: one bas ed on serum creatinine and the other based on serum cystatin. The equation for GFR estimation based on serum creatinine is as follows: GFR = K x heigh t (cm) / creatinine (µmol/L), where K is a constant value of 32.5 for all i ndividuals and 36.5 for boys aged 13 years or older. This equation is recom mended for use in children and adolescents with hypertension to identify an d stage preclinical kidney disease and monitor the impact of hypertension a nd/or therapy on kidney function. The equation for GFR estimation based on serum cystatin is as follows: GFR = 70.69 x (cysC^-0.931). This equation is also recommended for use in children and adolescents with hypertension to e stimate GFR. The box also emphasizes the importance of using the enzymatic method rather than the colorimetric method to measure serum creatinine for GFR estimation. Additionally, the box suggests that microalbuminuria should be measured as a marker of hypertension-mediated target organ damage and th at annual GFR monitoring is appropriate for individuals with eGFR < 90 ml/m in/1.73 m^2 and/or microalbuminuria. Overall, Box 2 provides important info rmation on the equations and methods used to estimate GFR in children and a

dolescents with hypertension, which is crucial for the early identification and management of kidney disease in this population.

(a) identify and stage preclinical kidney disease and (b) monitor the impac t of HTN and/or therapy on kidney function.

Enzymatic method should be used rather than colorimetric, to measure serum creatinine for estimation of glomerular filtration rate (eGFR); cystatin may be also used.

Microalbuminuria should be measured as a marker of HMOD (3),(4). Even consi dering that data are limited (39), values >30 mg/g creatinine on a spot uri ne specimen should be considered abnormal.

Table 3 in the consensus document provides information on the anamnestic in formation that should be collected during the clinical evaluation of childr en and adolescents with hypertension. The table lists five categories of in formation that should be considered during the evaluation, including: 1. Fa mily history of hypertension(namely pregnancy hypertension), cardiovascular disease (CVD), familial hypercholesterolemia 2. Birth weight and gestationa l age 3. Environmental factors, such as smoking habit, salt intake, alcohol consumption, drug/substance intake 4. Physical exercise/leisure time 5. Pos sible symptoms, such as headache, epistaxis, vertigo, visual impairment, st rokes, low school performance, attention defects, dyspnea, chest pain, palp itations, and syncope. The table emphasizes the importance of a comprehensi ve evaluation that takes into account both genetic and environmental factor s that may contribute to the development of hypertension in children and ad olescents. It also highlights the need to consider possible symptoms that m ay be associated with hypertension-mediated target organ damage. Overall, T able 3 provides a useful guide for clinicians to collect important anamnest ic information during the clinical evaluation of children and adolescents w ith hypertension, which can help inform the diagnosis and management of the condition.

Table 4 in the consensus document provides information on the clinical and laboratory differences between primary and secondary hypertension in childr en and adolescents.
As per the table 4 in the consensus guidelines, primary hypertension typica lly emerges in children and adolescents. It is often associated with a posi tive family history, though symptoms are generally absent. Clinical signs i nclude the absence of murmurs and normal femoral pulses. Excess weight is f requently observed, and blood chemistry usually reveals normal levels of po tassium (K+), serum creatinine, and glomerular filtration rate. Micro/macro hematuria is typically absent, and thyroid-stimulating hormone remains norm al, with hyperuricemia being a common occurrence.
Contrastingly, secondary hypertension manifests at different ages:

- In infants, it might be linked to aortic coarctation.

- Young children may experience secondary hypertension due to renal disease, congenital adrenal hyperplasia, thyrotoxicosis, or iatrogenic causes.
- Adolescents may encounter secondary forms like renovascular hypertension, pheochromocytoma, primary hyperaldosteronism, thyrotoxicosis, or iatrogenic reasons.

Secondary hypertension is often devoid of a positive family history, and symptoms may be present, correlating with the severity of the condition. Clinical signs can include cardiac and/or abdominal murmurs and weak or absent femoral pulses. Excess weight is rarely present in secondary hypertension cases. Blood chemistry may reveal abnormal potassium levels, high creatinine, and a low glomerular filtration rate. Possible blood cell casts in urine sediment and elevated thyroid-stimulating hormone in the presence of obesity may also be observed. Hyperuricemia is more frequent in secondary hypertension cases but infrequent in primary hypertension.
This comprehensive overview highlights the nuanced clinical differences between primary and secondary hypertension in pediatric patients.

The Consensus Panel agrees that two equations for GFR estimation should be adopted (Refer Box 2 and references (40),(41)). When eGFR is <90 ml/min/1.73 m^2, and/or microalbuminuria is present, annual controls are appropriate.

Depending on the clinical conditions and progression, and possible changes in clinical presentation, echocardiograms may be repeated, especially to evaluate changes in LVM in response to treatment.

Heart and blood vessels
All paediatric guidelines suggest echocardiography at the time of confirmed HTN, though with different indications and objectives.

The Consensus Panel agrees that echocardiography should be undertaken when the results can impact on decision making.

Current guidelines do not recommend routine carotid ultrasound, even when other CV risk factors are present. The Association for European Paediatric Cardiology provided important methodological suggestions, but no cut points for any parameter.46

The Consensus Panel agrees that there is no evidence that carotid ultrasound provides further refinement of cardiometabolic risk in this age range.

Allometric normalization of left ventricular mass (LVM) for height should be used. Commonly, indexation in metres raised to the power 2.7 is proposed, with the adoption of either adult prognostically validated cut-points,5 or specific partitions for children and adolescents.3,12 An age-specific exponent has been proposed, which eliminate residual regression of LVM index with age and height.42,43 The Consensus Panel is aware that this remains a controversial issue, and, possibly, more than one single approach should be adopted.

The Consensus Panel agrees that the proposed cut-point of ≥45 g/m^2 (16) is the most reasonable partition value for identification of LVH by echocardiography in this age-range.43 Alternatively, LVH may be also defined by 95th percentile of height2,7-normalized LVM for age and sex, a method that revealed excellent sensitivity.12,44 Because also relative wall thickness (RWT) correlates with age, the Consensus Panel agrees that RWT be age-adjusted (RWTa) and that RWT_a≥ 0.38 be diagnostic for concentric left ventricular geometry.45 There is no evidence that more advanced ultrasound techniques are clinically useful.

Brain
HTN in childhood and adolescence is a risk factor of cognitive impairment earlier in life.47 HTN in youths is also associated with lower performance in neurocognitive testing.48

The Consensus Panel agrees that further research is needed in this area and that indications for neuropsychiatric exam in hypertensive children and adolescents are uncertain, although it might be considered whenever it may influence the clinical management.

Chapter 4: secondary hypertension

Secondary causes of HTN are more common in children than adults. However, due to increasing prevalence of obesity-related primary HTN, the proportion of secondary paediatric HTN has been decreasing from 85 to 9%49 and is mostly seen in tertiary paediatric HTN clinics.50

The common causes of secondary HTN in children and adolescents are renal (parenchymal and/or vascular), cardiac (CoA) or endocrine (primary hyperaldosteronism, congenital adrenal hyperplasia, pheochromocytoma, and hyperthyroidism).

In the general population, prevalence of renal fibromuscular dysplasia is 400 cases per 100,000, accounting for about 10% of all renovascular HTN, with female predominance and usual clinical presentation between 15 and 50 years.51,52 Unfortunately, no specific data are available for the 6- to 16-year-old age group.53

CoA presents in 25–44 individuals per 100,000 children, representing approximately 5–8% of congenital heart disease.54,55 CoA is mostly diagnosed and treated during infancy or early childhood. Among hypertensive children older than 6 years, CoA has been re- ported in five cases per 1,000 idividuals.56 Following treatment, HTN might persist or return later in life, with or without evidence of re- lapsed CoA.

Only 1% of adrenal tumour are diagnosed in children,57 and ,3% of pheochromocytomas is found under 16 years.58 Primary aldosteronism likely represents an under-recognized cause of secondary HTN in the paediatric age group.59 I

t is estimated that as many as 4% HTN cases in this range of age exhibits a ldosterone/renin ratio levels .10.59

Despite some differences about prevalence and suggested diagnostic pathways , all major current guidelines agree on the importance of promptly identify ing and treating secondary causes of HTN in paediatric age.(2–4),(7) Table 4 gives indications on when a focused clinical assessment of secondary caus es of HTN is appropriate. Particular attention should be paid to age of det ection, as secondary HTN is more frequent ,12 years.(60)

The Consensus Panel agrees that the first approach for the differential diag nosis between primary and secondary HTN should include the following steps:

1. Detailed family history.
2. Physical examination including three-extremity BP measurements and asses sment of brachial and femoral pulses, to screen for CoA.
3. Laboratory test including assessment of:
(a) renal function (estimate of GFR—Refer Chapter 3); (b) serum electrolyte s; (c) urinalysis for proteinuria, micro-haematuria and urine sediment;
(d) Aldosterone/renin ratio, considering that interpretation might be diffic ult, because values vary with gender, age, effects of possible ongoing phar macological and treatment;61
(e) Thyroid Stimulating Hormone and free thyroid hormones.

In case of abnormal lab tests or Stage 2/severe HTN that does not respond t o non-pharmacologic lifestyle interventions, the Consensus Panel agrees tha t further diagnostic investigations may be conveniently undertaken, includi ng the following:

1. Renal ultrasound to check for structural kidney disease.
2. Echocardiogram.
3. Nuclear magnetic resonance or computed tomography of the adrenal glands.
4. Twenty-four-hour urinary or blood metanephrines and normetanephrines.
5. Renal digital subtraction angiography for detection of renal artery sten osis.

Chapter 5: treatment of hypertension

The most recent guidelines agree that management of HTN begins with non-pha rmacological interventions.2–4 Lifestyle changes are re- commended as the i nitial action, an important strategy to delay drug treatment, or complement BP lowering effect of antihypertensive treatment.

HTN in children should be primarily managed by improving their adhesion to a healthy lifestyle, as shown in Table 5.

The decision to begin pharmacological therapy is recommended in the presenc e of signs and/or symptoms attributable to HTN, HMOD, stage 2 HTN, concomit ant comorbidities (Refer Chapter 7), and when there is unresponsiveness to

lifestyle modifications.2,3 Recommended first-line of antihypertensive agents includes angio- tensin converting enzyme inhibitors (ACEi), angiotensin rec eptor blockers (ARB), dihydropyridine calcium channel blockers (CCB) and di uretics, considering that children and adolescents of African an- cestry ex hibit reduced antihypertensive response to ACEi/ARB monotherapy.62 Beta-adr energic blockers are not recommended, except in specific conditions, due to potential side-effects. A stepped-care approach is strongly and unanimously suggested (Figure 2).2–4

Lifestyle modifications
The Consensus Panel agrees with the lifestyle suggestion of current guideli nes,2,3 as displayed in Table 5, from 2016 ESH guidelines.3

Drug selection
Most antihypertensive agents currently approved for paediatric use are limi ted to children 6 years of age or older. Legislative efforts, in- cluding n ew paediatric drug regulations in Europe,63 have facilitated ongoing attent ion to this area. Choice of initial medication is often unclear, some exper ts use a pathophysiologic approach, but in gen- eral the choice of agent is left up to the individual prescriber.2,3,64

The Consensus Panel agrees that, due to the heterogeneous nature of childho od HTN, drug choice should be based on the following:

1. Presumed underlying pathophysiology.
2. Presence of concurrent disorders.
3. Availability of appropriate med formulations.

Pharmacologic treatment should be limited to agents licensed for use in chi ldren. Figure 2 displays a stepped-care approach on which Consensus Panel m embers agree.

The benefits and likelihood of response are important in choosing a specific medication. However, it is equally crucial consider potential adverse effec ts prior the initiation of selected antihypertensive therapy.

Resistant HTN requires a careful search for adherence and/or screening for secondary HTN. Acute severe HTN requires urgent intervention and exclusion of hypertensive emergency.65,66

Similar to adult suggestions,67 the Consensus Panel agrees that HTN emergen cy requires admission in Paediatric Intensive Care Unit and should be treat ed with intravenous drugs with appropriate doses, giving priority to labeta lol, nicardipine, and sodium doses, nitroprusside.

Table 5 in the document summarizes lifestyle modifications recommended for managing hypertension in children and adolescents from reference [2]. These modifications are based on the 2016 European Society of Hypertension guidel ines and include the following:

General Recommendations:
1. Physical activity and tailored diet: Encouraging regular physical activity and promoting a balanced, healthy diet tailored to the individual's needs.
2. Encourage parents/family participation: Involving parents and family members in supporting and promoting healthy lifestyle changes.
3. Encourage smoke-free environment: Creating an environment free from tobacco smoke to promote overall health.
4. Provide educational support and materials: Offering educational resources and support to help individuals and families understand and implement healthy lifestyle changes.
5. Establish realistic goals: Setting achievable and realistic health and wellness goals to work towards.
6. Develop a health-promoting reward system: Implementing a system to reward and reinforce positive health behaviors and achievements.

BMI:
1. If needed, graduate weight-loss program: Implementing a gradual weight-loss program if an individual's body mass index (BMI) indicates the need for weight management.

Physical Activity:
1. At least 60 minutes of activity per day, at least moderate: Encouraging at least 60 minutes of moderate to vigorous physical activity daily, such as jogging, cycling, or swimming.
2. More activity = more good health: Emphasizing the positive impact of increased physical activity on overall health.
3. Aerobic mostly, but with resistance components (3 times/week): Promoting aerobic activities with some resistance training components at least three times per week.
4. No more than 2 hours of sedentary behavior per day: Limiting sedentary behaviors, such as screen time, to no more than 2 hours per day.
5. If stage 2 hypertension, avoid competitive sports: Considering the avoidance of competitive sports in cases of stage 2 hypertension.

Diet:
1. Avoid free sugar (≤5% of total calories), soft-sweetened drinks, saturated fat: Encouraging the avoidance of free sugars, soft-sweetened drinks, and saturated fats in the diet.
2. Prefer fruits, vegetables, and grain products (ideally, ≥4–5 servings/day): Promoting the consumption of fruits, vegetables, and whole grain products as part of a healthy diet.
3. Limit sodium intake (≤2300 mg/daily): Advising to limit daily sodium intake to 2300 mg or less.

These recommendations aim to promote a healthy lifestyle, including regular physical activity and a balanced diet, to help manage hypertension and improve overall health in children and adolescents.

Goal of treatment

There is an ongoing debate on BP targets in children and adolescents. Guide lines propose different BP goals and targets,2–4 in line with the BP thresh olds for HTN diagnosis (Refer Chapter 1). The ESH and AAP guidelines also s uggest more strict BP goals in case of CKD, mainly in the presence of prote inuria, using ABPM-based criteria.68 The Consensus Panel agrees that in chi ldren with primary HTN without organ damage, achievement of BP values ,95th percentile is acceptable, aligning with the cut-off for diagnosis of HTN. I n the presence of HMOD or secondary HTN, the Consensus Panel agrees that BP threshold ,90th percentile is preferable. Children with CKD, without protei nuria, should be targeted to a 24-hour ABPM ,75th percentile, while for CKD with proteinuria, the target should be 24-hour ABPM ,50th percentile.3,69,7 0 Consistent with the adult guidelines criteria,7 and recommendations from 2016 ESH guidelines,3 in adolescents aged 16 years or older, the first obje ctive should be lowering OBP to ,130/85 mmHg in all patients, with the goal of achieving a target OBP of 120/75 mmHg in patients with HMOD and/or CKD, pending careful follow-up of GFR and electrolytes.

The Consensus Panel promotes HBPM as a useful strategy to fol- low response to antihypertensive treatment. Repeated ABPM is mandatory to optimize treat ment in youth with CKD69 using devices certified for paediatric use (Refer C hapter 2).

Figure 2 provide Stepped Care Approach for Arterial Hypertension in Childre n and Adolescents

In this visual guide, we navigate through a stepped care approach designed to manage arterial hypertension in young individuals. The process involves a sequence of steps, each crucial for tailoring the treatment plan to the s pecific needs of the patient.

Step 1: Lifestyle Modifications: Initiate the management journey with lifes tyle changes, including dietary adjustments, increased physical activity, a nd weight management. The goal is to reduce blood pressure through non-phar macological means.

Critical Point - No Effect: Evaluate the effectiveness of lifestyle modific ations. If there is insufficient reduction in blood pressure, it's time to reassess the treatment plan and explore alternative strategies.

Step 2: Pharmacological Therapy: Progress to pharmacological interventions if lifestyle modifications alone are not effective. This may involve medica tions like ACE inhibitors, angiotensin receptor blockers, calcium channel b lockers, or diuretics.

Critical Point - Side Effect: Monitor for potential side effects of medicat ions. If side effects arise, the figure emphasizes the importance of adjust ing or changing the medication to maintain effective blood pressure control while minimizing adverse effects.

Step 3: Combination Therapy: If blood pressure is not adequately controlled with a single medication, advance to combination therapy. This step utilize s two or more medications with different mechanisms of action to achieve be tter blood pressure control.

Critical Point - Stage 2 Secondary Hypertension: Address a stage dedicated to the diagnosis and management of stage 2 hypertension in children and adolescents. This involves specific criteria for defining stage 2 hypertension and corresponding treatment considerations.
Critical Point - Change Drug: Modify pharmacological therapy based on the individual's response to treatment. This step involves considerations for changing the type or dosage of medication to optimize blood pressure control while minimizing side effects.
Step 4: Referral to Specialist Care: If blood pressure remains uncontrolled or underlying medical conditions contribute to hypertension, consider referral to specialist care. This step may involve consultation with pediatric cardiologists, nephrologists, or other specialists for a more specialized approach.
In summary, this figure serves as a dynamic flowchart, guiding healthcare professionals through the stepped care approach. It integrates critical points for evaluation at each step, ensuring a flexible and individualized strategy based on the patient's response and unique circumstances. This visual aid enhances the understanding of the comprehensive management of arterial hypertension in children and adolescents. If you have specific questions or need further clarification, feel free to ask.

Consensus Panel suggestions for filling gap in knowledge
The Consensus Panel agrees that data about treatment of HTN in youth are limited and the lack of studies hampers evidence-based management.
Unmet needs and procedures to advance in knowledge are suggested in Box 3.
The results of much needed research will help ensure that the young receive safe, effective, and age-appropriate antihypertensive drugs.

Box 3 Suggested actions for treatment are follows:
Need of clinical trials to be implemented on specific benefits and disadvantages of BP lowering agents, to establish adequate doses and combinations.
Strong need of clinical trials on 24-hour ABPM, to facilitate assessment of efficacy of antihypertensive strategies and their impact on BP variability.
Need of long-term large cohort studies to link with adult CV risk.
Need of specific studies to implementing e- and m-Health.

Chapter 6: assessment and management of concomitant risk factors

Cardiometabolic risk factors (CMRFs) often coexist with primary HTN also in children and adolescents,3,71 with a common denominator represented by unhealthy lifestyle behaviours, insulin resistance, hyperuricaemia72,73 and low-grade inflammation. Thus, early recognition and management of concomitant CMRF in hypertensive children and adolescents is important to prevent CV disease later during adulthood.

There is no unified definition of CMRF across the most recent guide-lines.2–4 Concomitant CMRFs (dyslipidaemia, diabetes, even OB) are sometimes indicated as ‘comorbidities’ and listed together with sur- rounding conditions, suc

h as CKD or obstructive sleep apnoea, which might be rather causes of secon dary HTN (Refer Chapter 4).

The Consensus Panel agrees that in children and adolescents a clear-cut dis tinction should be made between co-morbidity factors that might have causat ive effect (Refer Chapter 4) and CMRF that often coexist with HTN and are m ostly modifiable by lifestyle changes (Table 6).

OB is the most important CMRF to consider in childhood, due to the high pre valence early in the life, the high odds of clustering with other CMRF and the high rate of persistence in adults.74 Clear-cut OW and OB children (Tab le 6)75,76 exhibit 5.0% and 15.3% prevalence of HTN, respectively compared to 1.9% in normal-weight children.11 Table 6 also lists recognized definitio n of all CMRF. Childhood OB and HTN are 'insidious siblings', gradually bec oming a serious health hazard with an increasing global prevalence associat ed with unhealthy, sedentary lifestyle among children.77-79 Since both OB a nd HTN are independently associated with increased LV mass, OB status shoul d be considered when deciding for therapy based on the presence of cardiac HMOD.80,81

Table 6 offers a comprehensive summary of modifiable cardio-metabolic risk factors and their associated thresholds for defining risk in children and a dolescents. The first risk factor, overweight and obesity, is assessed thro ugh Body Mass Index (BMI) measurements falling at or above the 85th and 95t h percentiles of national reference tables, as well as with consideration o f WHO age-specific normative tables and the International Obesity Task Forc e Reference.
Moving on to dyslipidemia, various lipid parameters are considered. Elevate d total cholesterol levels equal to or exceeding 200 mg/dL, LDL-C (Low-Dens ity Lipoprotein Cholesterol) at or above 130 mg/dL, non-HDL (Non-High-Densi ty Lipoprotein Cholesterol) surpassing 145 mg/dL, HDL (High-Density Lipopro tein Cholesterol) below 40 mg/dL, and triglyceride levels meeting or exceed ing 100 mg/dL for individuals under 9 years and 130 mg/dL for those aged 10 years and older, are indicative of heightened risk.
The third risk factor, hyperglycemia, is gauged through Fasting Blood Gluco se (FBG) readings equal to or greater than 100 mg/dL and HbA1c (Glycated He moglobin) levels reaching or surpassing 5.7% (39 mmol/mol).
Finally, physical inactivity is identified by less than 60 minutes per day of moderate/vigorous physical activity and an excess of 2 hours per day of sedentary behavior.
Abbreviations utilized in the table include BMI (Body Mass Index), FBG (Fas ting Blood Glucose), HbA1c (Glycated Hemoglobin), and TG (Triglycerides). T hese defined thresholds serve as critical indicators for the identification and assessment of modifiable risk factors related to cardiovascular and met abolic health in the pediatric and adolescent population. Vigilant monitori ng and management of these factors are paramount for promoting healthy life style behaviors and mitigating the long-term risk of cardiovascular disease

and metabolic disorders in this age group. Should further clarification or specific inquiries arise, feel free to seek additional information.

CMRF need to be targeted alongside treatment of high BP. CMRF are associate d with premature atherosclerosis, often referred to as early vascular aging , and are tied with unhealthy lifestyle, insulin resistance and low-grade i nflammation.

The Consensus Panel agrees on the following points:

1. There is a research gap on how to score 'CV risk' in children and adoles cents.

2. Given the young age, doubts remain about the utility of diag- nosing met abolic syndrome (MetS) as a CV predictor in children and adolescents,82 des pite some evidence of association with HMOD.83 Insulin resistance, lipid pr ofile and BP levels show fluctuations during puberty, and might influence the strength of associations between CMRF and outcome in adults.78 Longitudinal studies could not demonstrate superiority of MetS over BMI or OB in the pre diction of subclinical atherosclerosis, type 2 diabetes or MetS in adulthoo d.79

3. OB during childhood and adolescence tends to persist in adults84 and rep resents a strong predictor of adult CV risk fac- tors and adverse outcomes. 85

Childhood physical inactivity is a critical link among obesity, HTN, in inflammation, insulin resistance and late atherosclerosis adulthood.86

The Consensus Panel strongly agrees that the most important step in managem ent of CMRF is lifestyle modifications, as indicated by current guidelines a nd recent position from AHA2,3,71 (Refer Table 5). Physical activity interv entions alone or in combination with diet are effective in reducing risk of childhood OB.87

General institutional intervention should be promoted with respect to socio economic and environmental factors,88,89 especially those that promote life space mobility and access to healthy food markets89,90

The Consensus Panel agrees that if a good control of CMRF is not achieved b y lifestyle modifications, additional pharmaceutical therapy may be consider ed, namely in selected cases with high CV risk profile.3,71

In children aged 10 years or older, high LDL-cholesterol may be treated wit h statins and/or additional cholesterol absorption inhibitors, if well tole rated. High triglycerides may justify treatment with fenofibrates, after con sideration of their side effects, or supplementation of omega-3 fatty acids . Metformin is recommended in overt type 2 diabetes. When multiple CMRFs co exist, a multidisciplinary approach is needed.

It is impossible to study adverse CV end points in children and adolescents , which necessitates considering the association between CMRF and markers o f preclinical CV disease as surrogate end points (e.g. left ventricular geo metry).91

The Consensus Panel agrees that future research will have to determine whet her combination of CMRFs with HMOD in childhood and adolescence can be used to address early therapeutical strategies.

Chapter 7: implementation of suggestions in the real world

The standard recommendations for HTN screening in childhood and adolescence are often neglected92,93 and efforts at different implementation in clinica l levels are required for successful practice.94

The Consensus Panel noted that publication of guidelines and evidence-based indications do not necessarily imply adherence to them in day-to-day clinic al practice. The engagement of major stake- holders such as scientific socie ties, associations, and public health agencies, are critical to promote imp lementation of suggestions given in this document, to improve detection and treatment of HTN in younger people.

International scientific societies International scientific societies should:

- Inform national professional societies, both in the clinical [e.g. genera l practitioners (GPs), paediatricians, cardiolo- gists, paediatric nurses] and those in preventive arenas (e.g. school nurses, adolescent health profe ssionals) about guidelines and other expert evidence-based documents to imp rove the detection and treatment of HTN in children and adolescents.

- Stimulate national societies to inform and instruct their members.

- Organize surveys for GPs, cardiologists and paediatricians at the interna tional level to evaluate the adherence to guidance in daily practice.

National societies National societies should:

- Develop national strategies to implement guidance in clinical practice a nd prevention programmes.

- Inform and instruct the members on why, when and how to cor- rectly measu re BP in children and adolescents, and what to do when HTN is diagnosed. Th is task can be accomplished in courses, national congresses, society journa ls and other media.

- Partner with public health agencies to design strategies to engage and in form general public.

- Integrate key performance indicators on HTN management in children and a dolescents, in quality of care monitoring and benchmarking.

Public health agencies Public health agencies should:

- Ensure that prevention and management of HTN in children and adolescents are given greater prominence in the public health agenda.

- Make aware and inform the general public on risks of HTN in children and adolescents, using lay-press, social media, or inte- gration in large-scale public health campaigns.

- Establish information campaigns regarding the impact of lifestyle changes on BP, such as high levels of physical activity, healthy nu- trition, low s alt intake, low free-sugar intake, and non-smoking.
(4) Guarantee protected time for children on TV and social media without an y promotion of junk food or potentially deleterious lifestyle habits.

Conclusions

This document highlights the discordant positions of the main cur- rent gui delines for HTN in children and adolescents and identifies the limited infor mation available for clinical daily practice. The Panel of this consensus d ocument tried to reconcile different positions and highlighted needed actio ns to reduce our knowledge gap. Among the main measures that need to be und ertaken, the Panel strongly suggest:

1. to implement the development of appropriate multiethnic European normati ve tables for OBP, ABPM and HBPM, through the organization of longitudinal registries, with the prospective to link with adult CV risk and

2. to develop randomized clinical trials, using surrogate end- points to do cument specific benefits and disadvantages of BP lowering agents and behaviou ral lifestyle strategies.

The Consensus Panel strongly encourages the implementation of international world-wide initiative to generate normative tables for children and adolesc ents from all continents, to have general rules on identification of arteria l HTN in this range of age.

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