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2016 EUROPEAN SOCIETY OF HYPERTENSION (ESH) GUIDELINES FOR THE MANAGEMENT OF HIGH BLOOD PRESSURE IN CHILDREN AND ADOLESCENTS

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Abstract:	Increasing prevalence of hypertension in children and adolescents has become a significant public health issue driving a considerable amount of research. Aspects

	discussed in this document include advances in the definition of hypertension in 16 year or older, clinical significance of isolated systolic hypertension in youth, the importance of out of office and central blood pressure measurement, new risk factors for hypertension, methods to assess vascular phenotypes, clustering of cardiovascular risk factors, and treatment strategies among others. The recommendations of the present document synthesize a considerable amount of scientific data and clinical experience, and represent the best clinical wisdom upon which physicians, nurses and families should base their decisions. In addition, because they call attention to the burden of hypertension in children and adolescents, and its contribution to the current epidemic of cardiovascular disease, these guidelines should encourage public policy makers to develop a global effort to improve identification and treatment of high blood pressure among children and adolescents.

Abbreviation	
ABPM	ambulatory BP measurement
ACE	angiotensin converting enzyme
ACEi	angiotensin converting enzyme inhibitor
ACTH	adeenocorticotropic hormone
ARB	angiotensin receptor blocker
BP	blood pressure
cIMT	carotid intima-media thickness
CKD	chronic kidney disease
CoA	coarctation of aorta
CPAP	continuous positive airway pressure
cPP	central pulse pressure
CS	Cushing syndrome
cSPB	central or aortic systolic blood pressure
CT	computed tomography
CV	cardiovascular
DBP	diastolic blood pressure
DIH	drug-induced hypertension
DM1	type 1 diabetes
DM2	type 2 diabetes
EM	ethnic minorities
ENaC	epithelial sodium channel
ESC	European Society of Cardiology
ESCAPE	Effect of Strict Blood Pressure Control and ACE Inhibitionon Progression of Chronic Renal Failure in Pediatric Patients
ESH	European Society of Hypertension
ESRD	end stage renal disease
EU	European Union
FH1,2,3	familial hyperaldosteronism type 1,2,3
GFR	glomerular filtration rate
HTN	hypertension
HTNR	hypertensive retinopathy
ISH	isolated systolic hypertension
LDL-C	low density lipoprotein cholesterol
LV	left ventricle
LVH	left ventricular hypertrophy
LVM	left ventricular mass
LVMI	left ventricular mass index
MR	mineralocorticoid receptor
MRI	magnetic resonance image
OSA	obstructive sleep apnea
PRES	posterior reversible encephalopathy syndrome
PUMA	Paediatric Use Marketing Authorisation
PWV	pulse wave velocity
RAS	renin-angiotensin system
SBP	systolic blood pressure
SNPs	single nucleotide polymorphisim
SPRINT	Systolic Blood Pressure Intervention Trial
TOD	target organ damage
UAE	Urinary albumin excretion
VEGF	vascular endothelial growth factor

CONDENSED ABSTRACT

The Scientific Council and the Working Group on Hypertension in Children and Adolescents of the ESH acknowledged the importance of diagnosis, management and treatment of high BP in this age group and recognised the need for an update of the 2009 guidelines because over the seven years elapsed from their publication a large body of new knowledge had been acquired, making, modifications and expansion of the previous recommendations necessary.

It is hoped the new knowledge summarised in these Guidelines will lead to increased efforts towards prevention and management of HTN in the pediatric age, thus also helping relieving the burden of cardiovascular disease in adults.

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Prof. Alberto Zanchetti
Editor-in-Chief
Journal of Hypertension

Valencia, 8th June 2016

Dear Prof. Zanchetti,

For the consideration of the Editorial Board of Journal of Hypertension*,* please find enclosed the proposal for a *Consensus Document "*2016 EUROPEAN SOCIETY OF HYPERTENSION (ESH) GUIDELINES FOR THE MANAGEMENT OF HIGH BLOOD PRESSURE IN CHILDREN AND ADOLESCENTS*".*

All authors have read and approved the submission of the manuscript; the manuscript has not been published and is not being considered for publication elsewhere, in whole or in part, in any language, except as an abstract.

Sincerely yours,

Empar Lurbe, MD, PhD, FAHA

2016 EUROPEAN SOCIETY OF HYPERTENSION (ESH) GUIDELINES FOR THE MANAGEMENT OF HIGH BLOOD PRESSURE IN CHILDREN AND ADOLESCENTS

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Abbreviation	
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GFR	glomerular filtration rate
HTN	hypertension
HTNR	hypertensive retinopathy
ISH	isolated systolic hypertension
LDL-C	low density lipoprotein cholesterol
LV	left ventricle
LVH	left ventricular hypertrophy
LVM	left ventricular mass
LVMI	left ventricular mass index
MR	mineralocorticoid receptor
MRI	magnetic resonance image
OSA	obstructive sleep apnea
PRES	posterior reversible encephalopathy syndrome
PUMA	Paediatric Use Marketing Authorisation
PWV	pulse wave velocity
RAS	renin-angiotensin system
SBP	systolic blood pressure
SNPs	single nucleotide polymorphisim
SPRINT	Systolic Blood Pressure Intervention Trial
TOD	target organ damage
UAE	Urinary albumin excretion
VEGF	vascular endothelial growth factor

1. INTRODUCTION AND PURPOSE

1.1 Purpose

The European Society of Hypertension (ESH) Guidelines on High Blood Pressure in Children and Adolescents published in 2009 (1) were undertaken because of growing evidence that mild blood pressure (BP) elevations are much more common among children and adolescents than previously thought; and BP abnormalities in youth frequently translate into adult hypertension (HTN), what is known as the tracking phenomenon.

The Scientific Council and the Working Group on Hypertension in Children and Adolescents of the ESH (ESH) acknowledged the importance of diagnosis, management and treatment of high BP in this age group and recognised the need for an update of the 2009 guidelines because over the seven years elapsed from their publication a large body of new knowledge had been acquired, making, modifications and expansion of the previous recommendations necessary.

It is hoped the new knowledge summarised in these Guidelines will lead to increased efforts towards prevention and management of HTN in the pediatric age, thus also helping relieving the burden of cardiovascular (CV) disease in adults.

1.2 What is new?

Increasing prevalence of HTN in children and adolescents has become a significant public health issue driving a considerable amount of research. Aspects discussed in this document include advances in the definition of HTN in 16 year or older, clinical significance of isolated systolic hypertension (ISH) in youth, the importance of out of office and central BP measurement, new risk factors for HTN, methods to assess vascular phenotypes, clustering of CV risk factors, and treatment strategies among others.

1.3 How the document has been prepared

The European members in charge of the 2016 guidelines were appointed by the ESH Council, on the basis of their recognized interest and experience in the area. Each member was assigned a specific writing task according to their expertise, and each contribution was

reviewed by all the co-authors. The text was finalized over approximately 12 months, during which the members corresponded intensively. It can thus be confidently stated that the recommendations issued by the 2016 ESH guidelines largely reflect the state of the art on HTN, as viewed by pediatricians and hypertension experts in Europe.

The document has 14 sections which contain 19 Tables, 4 Figures and 6 Boxes who summarize the most relevant recommendations providing an easy access to the readers. Data upon which recommendations are based are referenced at the end of the document.

1.4. How to detect hypertension in children: pros and cons of screening

The early recognition of BP abnormalities is crucial if there are to be early interventions that may reduce CV morbidity and mortality later in life. Current guidelines clearly state that a child should not be diagnosed with HTN until he or she has shown evidence of sustained BP elevation (1). Several prominent medical organizations, including the National High Blood Pressure Education Program, the American Academy of Pediatrics and the American Heart Association recommend routine measurement of BP in children and adolescents. However, these recommendations are not deeply grounded and controversy has been raised about benefits and costs of routine screening (2,3). In 2013, the US Preventive Services Task Force concluded that the "current evidence is insufficient to assess the balance of benefits and harms of screening for primary hypertension in asymptomatic children and adolescents to prevent subsequent CV disease in childhood or adulthood" (2). The pros and cons of screening have been widely debated, recently (4-6). The group responsible for these guidelines has considered that lack of evidence does not necessarily justify inaction; that opportunistic BP screening in children is associated with minimal cost and time inputs, and does not include invasive and expensive tests. It may also lead to further actions improving health outcomes (3). Therefore, the consensus of the present Guidelines is that BP should be measured in children starting from age 3 years. Once BP is measured, children considered normotensive should be re-evaluated every two years, whereas those with high-normal BP and no organ damage should be seen again after one year. This recommendation was already given in the 2009

Guidelines here reconfirmed. Also reconfirmed is the advice that, once a diagnosis of HTN has been established, children should be referred to units with expertise in managing this condition in the pediatric age.

2. DEFINITION AND CLASSIFICATION OF HYPERTENSION

2.1 Classification of hypertension

On the contrary to what happens for adults, the definition of HTN in children is arbitrary, and is based on the normal distribution of BP in healthy children and not on the CV morbidity and mortality associated with a certain level of BP. 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 hypertension, as done in adults. Because of the persisting lack of European reference values that incorporate age, sex and height, throughout the entire pediatric age range, we confirm the decision of the 2009 ESH Guidelines (1), to use the normative data on auscultatory clinic measurements provided by the US Task Force (7), providing BP percentiles for each sex, ages from 1-17 years and for seven height percentile categories.

As in the previous guidelines, hypertension in children is defined as systolic BP (SBP) and/or diastolic BP (DBP) persistently ≥95th percentile for sex, age and height measured on at least three separate occasions, as outlined in the Figure 2.1.1. Children with average SBP and/or DBP ≥90th, but <95th are classified as having high-normal BP. In the present document, the definitions have been revised for older adolescents. Considering the 95th percentile for age, sex and height as the definition of HTN, a 16 year old boy in the 95th percentile for height would be defined as hypertensive by an office SBP of 137-140 mmHg, while a 16 year old girl in the same height percentile by an office SBP of only 132 mmHg. One-two years later, no longer seen by a pediatrician, the girl will now be diagnosed as normotensive or high normal by the family physician on the basis of adult guidelines. Even greater differences in diagnosis will occur in adolescents shorter than the 95th height percentile. Due to these differences in diagnosis, a consensus in the present Guidelines 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 (≥140/90 mmHg) (Fig. 2.1.1 and Table 2.1.1).

In addition, HTN is further classified as grade 1 (95th percentile to the 99th percentile plus 5 mmHg) and grade 2 (>99th percentile plus 5 mmHg). In the case of subjects 16 years or older hypertension should be graded as for adults. Tables 2.1.2 and 2.1.3 report the BP percentiles for boys and girls, aged 1-15 years, adapted from the Fourth Report of the US Task Force (7).

2.2 Systolic versus diastolic

Elasticity of the great vessels is particularly relevant in youth, and causes SBP to be considerably higher in upper limb arteries than in the ascending aorta, increasing the presence of so-called ISH. This condition in youth is defined as SBP ≥95th percentile specific for sex, age and height, with DBP <90th percentile (8). In 16 years and older SBP ≥140 mmHg and DBP <90 mmHg, see Table 2.1.1. The clinical significance of ISH in youth is still debated, as discussed in section 1.4.5.

2.3 Risk of hypertension in adult life

Previous studies have demonstrated that elevated BP in childhood is the strongest predictor of HTN in the adult and the increment of risk of HTN in adult life results from adolescents in the highest BP percentiles (9-12). Increments in SBP of 15 mmHg or 30 mmHg above 90 mmHg in 15-year olds, represent probabilities of having HTN at 35 years of 0.18 and 0.33 respectively for boys. These probabilities are lower for girls, 0.04 and 0.08, respectively, with 4.25 more risk for boys than for girls (13). In a longitudinal study, BP at adolescence, even in the low-normotensive range linearly predicted progression to HTN in young adulthood (11). This progression was shown to be sex-dependent, and was 3- to 4-times higher among men than women in all BP categories.

Blood pressure values in adolescence can also be predictors of CV risk other than HTN. After 17 years of follow-up, BP values in young individuals show a significant association with cardiometabolic risk (14), and may also predict coronary artery disease in adult life (15). Likewise, BP values at adolescence are independent predictors of End Stage Renal Disease (ESRD) in middle-aged men (16).

2.4 Relative cardiovascular and renal risk

Hypertension impacts on the heart, kidney, central nervous system and vessels producing early functional or structural changes that can be detected by using appropriate assessment methods. Among children and adolescents with primary HTN, 30-40% had a left ventricular mass index (LVMi) above the 95th percentile and 10-15% of them had severe left ventricular hypertrophy (LVH) defined as LVMi above 51g/height$^{2.7}$ (17- 19). Renal damage is rarely observed in essential hypertensive children, but these subjects have greater albuminuria and excrete more N-acetyl glicosamine than their normotensive counterparts. The severity of albuminuria correlates with LVH (20,21). On the other hand antihypertensive treatment when successful in reducing BP, also leads to regression of LVH, decrease in carotid intima-media thickness (cIMT) and normalization of microalbuminuria (22-24). Likewise, in children with chronic kidney disease (CKD) proteinuria correlates with BP, and strict BP control leads to a decrease in proteinuria and a slowing of the progression of CKD (25). Therefore, assessment of early organ damage, as a measurement of the clinical consequences of increased BP, is essential for HTN management in youth (see section 4.7).

Monitoring organ damage in children and adolescents with elevated BP is even more important as the CV/renal sequelae of childhood-onset HTN may not become clinically relevant before adulthood. Prospective studies have shown that elevated BP in adolescence is associated with both subclinical dysfunction of the left ventricle in the fifth decade of life and increased arterial stiffness (26-29). Similarly, young adults with greater pulse wave velocity (PWV) had steeper increases of BP and visceral obesity from the age of 13 years (30).

3. EPIDEMIOLOGY

3.1 Prevalence

Because the definition of HTN in children is based on BP values greater that the 95th percentile in normal healthy individuals, the prevalence of HTN should be around 5%. This rarely happens, however, probably because the normative values used are limited to the USA and may not exactly apply to other part of the world, or because the normative data are more than twenty years old and the current epidemics of overweight and obesity may have changed the matter. Furthermore, despite the number of studies that have been performed, the prevalence of pediatric HTN worldwide is difficult to establish also because of the regional differences in the definition, the distribution of reference BP data, and the methods of BP measurement. Central-European studies showed the prevalence of HTN in adolescents to be 2.2% in Switzerland, 2.5% in Hungary and 4.9% in Poland (31-33). Data from Southern Europe identified higher prevalence; adolescent HTN was estimated as 9% in Turkey, 12% in Greece and 13% in Portugal (34-36). After the age of 10, primary HTN is the predominant form (37) and in the majority of the adolescent hypertensives, 81% were ISH (31). For European prevalence see Table 3.1.1.

The obesity epidemic in children and adolescents makes it plausible that prevalence rates of HTN are increasing over time (38). HTN was found in 1.4% of normal weight, 7.1% of overweight and 25% of obese adolescents (39). The relative risk of HTN for overweight subjects is 3.26 (CI: 2.5-4.2) (40) and based on a multiple regression model - besides gender - BMI is the strongest determining factor of adolescent blood pressure (32). A recent study reported the prevalence of HTN in overweight or obese 6-18 year old subjects, to range between 27 and 47%, according to different reference values (41).

3.2 Incidence

Reports on incidence of HTN in childhood are mainly concerned with progression from high-normal BP to HTN among adolescents and on the incidence of HTN in children from groups at risk of CV disease, such as masked HTN, type 2 diabetes mellitus (DM2), obesity or repaired

aortic coarctation (CoA). In a general population of adolescents, 10-19 years, the rate of progression from normotension to HTN was 0.4/100 subjects/year, and among those who had high-normal BP it was 1.1/100 subjects/year (42). In another study on normotensive children with a mean follow-up of 35 months, the incidence of sustained HTN was 0.6/100 subjects/year (43). In the same study, masked hypertensive subjects had an incidence of sustained HTN of 7/100 subjects/year, the risk being higher in boys than in girls (43). The incidence in adolescents with T2D was estimated as 4/100 subjects/year (44). Obese children aged 3 to 11 had a two-fold increased risk of developing HTN than normal weight children, while those with severe obesity had a more than four-fold increased risk (45). After successful repair of CoA, the incidence rate was found to be 1.3/100 subjects/year (46).

3.3 Family aggregation and Genetics

There is extensive evidence from family studies that BP is moderately heritable with 15-40% of office SBP and 15-30% of office DBP explained by variation in genetic factors (47). Ambulatory BP appears more heritable with 69% and 51% for the ambulatory night-time systolic and DBP, respectively (48). A recent analysis of BP heritability in families of the Gubbio population followed-up for 25 years shows that also the SBP/DBP variation with aging has a genetic component (33-43% for SBP, 24-25% for DBP), with a much smaller component (4-17%) due to shared environment (49). These findings suggest that BP is a complex, polygenic trait with no single gene exerting a predominant effect on the trait. However, we are also aware of several rare syndromes with classic Mendelian inheritance, which present with very high or low BP early in life (50). The discovery of genes responsible for these monogenic syndromes has highlighted the importance of the kidneys and the adrenal glands in BP regulation as well as indicating efficacious treatments driven by the understanding of molecular pathophysiology of each of these rare syndromes. Furthermore, family screening is now available in national reference laboratories. In summary, HTN is a polygenic trait with the rare syndromes representing the extreme end of the BP distribution (51).

3.4. Ethnic minorities

Childhood BP, particularly ambulatory BP measurement (ABPM), remains seriously understudied in "ethnic minorities" (EM), meaning descendants of non-'Europeans', generally South Asian, sub-Saharan African or African-Caribbean by origin in Europe, as well as among refugee children (52). Despite the lack of direct evidence, the latter are likely to have higher or potentially much higher BP values. Without evidence, the standard guidelines have to apply to EM children, with safeguards for generational time since (parental) migration. Ethnic minority children may well have been born smaller, possibly from more frequent hypertensive/pre-eclamptic pregnancies, so at greater CV risk themselves.

4. DIAGNOSTIC EVALUATION

4.1 Blood pressure measurement

Office BP measurement has provided the basis for the present knowledge of the potential risk associated with HTN and has guided patient management for many years. Although office BP should be used as a reference, BP values obtained out-of-office may improve the evaluation in untreated and treated subjects. Additionally, in the last years, the assessment of central BP has been introduced.

4.1.1 Office blood pressure

The main issue about how to measure BP in children is whether to use the auscultatory or the oscillometric method. In the auscultatory method, Korotkoff sounds are used to assess SBP (K1) and DBP (K5) while deflating the cuff (1). Oscillometric devices measure mean BP directly from the point of maximum oscillation; neither SBP nor DBP are measured directly, but are calculated using an algorithm based on a putative relationship between the oscillations. If an oscillometric method is applied, the monitor should have passed the validation procedure recommended by the British Hypertension Society (53), the American Association for the Advancement of Medical Instrumentation (54) or the ESH International Protocol (55). Few oscillometric devices for office, home or ambulatory BP monitoring have been successfully validated using an established protocol in children. Continuously updated information on monitor validation for children is found at www.dableducational.org. It should be noted, however, that available reference values for defining BP categories (See tables 2.1.2 and 2.1.3) have been obtained by the auscultatory method. 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. After the recommendations of the 2009 ESH Guidelines, recent studies have been conducted to develop reference values using oscillometric devices (56-58). Unfortunately the heterogeneity of the studies does not allow pooling of the information. The specific recommendations for office BP measurement in children and adolescents are shown in Box 1.

4.1.2 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. Blood pressure measurement in the more meaningful context of daily real-life conditions, not just in the artificial environment of the physician's office and clinic, has allowed much more in-depth investigation of BP. Values obtained using 24-hour ABPM have some better relationship with the presence of organ damage and a higher reproducibility than those obtained using office BP (59).

Average daytime and night-time BP can be calculated on the basis of the reported times of getting up and going to bed, or using fixed time periods (daytime from 8am to 10 pm, night-time from midnight to 6 am), in which the rising and retiring periods—which differ from individual to individual —are eliminated. For recommended methodology, the reader is referred to the Guidelines of Ambulatory BP measurement of the ESH (60).

A positive correlation exists between ambulatory and office BP for both systolic and DBP in normotensive children, even though ambulatory BP values are generally higher than their office BP counterparts. The higher ambulatory BP in normotensive children is reversed when monitoring hypertensives (61), a behaviour similar to that observed in the adult population, in which the difference between office and ambulatory BP gradually diminishes the lower is office BP, until for SBP values of about 120 mmHg also in adults ambulatory becomes higher than office BP (61.62). While the higher ambulatory than office BP in normotensive children has been attributed, at least in part, to physical activity, additional reasons may reside in the different method of measuring BP (61), the algorithm used to calculate systolic and DBP from the maximal amplitude (63), and the phenomenon of regression to the mean (61).

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 (Tables 4.1.2.1, 4.1.2.2, 4.1.2.3 and 4.1.2.4) but were not obtained in parallel with the office BP values available, since they come from different populations, countries and years. Based on the

arguments discussed in section 2.1 on Classification of Hypertension, the consensus of the present 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, nightime 125/75 mmHg).

The night-to-day BP ratio represents circadian variability due to the physiological nocturnal BP fall. Blood pressure normally decreases during the night—defined as 'dipping'. Although the degree of night-time dipping has a normal distribution in a population setting, it is generally agreed that the finding of a nocturnal BP fall of >10% of daytime values (night-day BP ratio <0.9) can be accepted as an arbitrary cut-off to define subjects as 'dippers', although one should bear in mind that the reproducibility of the dipping pattern is limited. Possible reasons for absence of dipping are sleep disturbance, obstructive sleep apnoea, obesity, high salt intake in salt-sensitive subjects, orthostatic hypotension, autonomic dysfunction, CKD and diabetes, both type 1 and type 2.

Recommendations for the use of 24-hour ABPM are given in Box 2. They 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.

4.1.3 Home blood pressure

Feasibility of home BP monitoring in children and adolescents has been reported in different ethnic populations (64-66) Home BP correlates closely with daytime ambulatory BP values and has superior reproducibility to office BP, similar to that of ABPM (67). Home BP is lower than daytime ambulatory BP in children and adolescents (65, 68-70). Some preliminary evidence exists that home BP in children correlates with target organ damage (TOD) better than office BP (71), and that it may also better reflect the effect of risk factors on BP, such as family history or obesity (66, 72-73). Two research groups reported good performance of home BP to

diagnose white-coat HTN, but a low sensitivity and positive predictive value to predict masked HTN compared to ABPM (68,74). Methodological aspects and recommendations for use of home BP are shown in Box 3. Home BP monitoring for 6-7 days, with duplicate morning and evening measurements is recommended, 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 (75).

One school-based study provided the only normalcy data for home BP in children and adolescents (Table 4.1.3.1) (64). The criteria to define HTN based on home BP is BP 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). Several issues about the clinical application of the method, including validated devices, remain under-investigated.

4.1.4 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, perhaps as a result of the criteria used to establish the diagnosis, ranging from 1% to 44% (76). 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. Hence, it remains to be clarified whether white-coat HTN is an innocuous phenomenon or a prelude to future sustained HTN.

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 (74, 77-80). The persistence and clinical significance of the phenomenon has shown that in 40% of children, the abnormal elevation of the daytime ambulatory BP persisted over a minimum of 6 months (79). Masked HTN has been linked with progression to HTN in youth, with the risk being higher in boys than in girls (43). Masked HTN warrants follow-up, and if it persists, left ventricular mass (LVM) should be assessed.

4.1.5 Central blood pressure

Mean and DBP are nearly constant throughout the arterial tree, but SBP varies, with peripheral higher than central or aortic (cSBP) (81). Compared with adults, this phenomenon differs significantly in children, whose SBP amplification is substantial, a mean ~20 mmHg, almost twice as in adults (82). If cSBP relates more closely than peripheral SBP to TOD, including LVH, as some claim in adults (83), it may be very useful clinically to estimate its values in children, but its benefit and independence from peripheral BP remains unknown. The recent publication of percentiles for cBP in children and adolescents, specific for sex and age or height, has the potential for widespread clinical use and may provide additional information about vascular phenotype (84), if the method is correctly validated in children. Although a range of devices are now available to estimate cBP using different noninvasive techniques in adults, but we need further data on agreement between these various devices.

The potential value of cSBP and central pulse pressure (cPP) in the assessment of adolescents with ISH, is a controversial issue. cBP may be especially relevant in asymptomatic children incidentally found to have isolated peripheral systolic HTN without TOD. In children and young adults at high risk of future adverse CV outcomes (e.g. with essential HTN or CKD), research is needed on what factors determine systolic amplification as well as interventions that have differential impact on central rather than peripheral systolic pressure. Because of their high correlation, cBP will only offer incremental value over peripheral BP if cBP identifies TOD better.

4.1.6 Blood pressure during exercise

The BP response during physical exercise has been suggested for that diagnostic assessment of BP in children. Longitudinal studies have shown that SBP or the calculated heart rate and SBP product during exercise are positively associated with future resting BP, even independent of resting SBP and other CV risk factors (85,86). An exaggerated BP response to treadmill exercise has been observed in children with white-coat HTN (87). Likewise, an exaggerated SBP during exercise has also been reported in children at risk for early damage in vascular structure and functioning (88-90). In order to establish the clinical usefulness of BP response to exercise

testing in children and adolescents with HTN, a larger body of data is needed. Even though reference values for SBP during exercise are now available, they are restricted to the age range 12-16 years (91). The ESH Guidelines in adults suggest performing 24-hour ABPM in subjects with a hypertensive response during the treadmill test searching for the possible presence of masked HTN (92). Even though evidence in youth is lacking, this recommendation can be applied in adolescents.

4.2. Family and clinical history

Family and clinical history should precede further diagnostic evaluation of HTN in children and adolescents to allow a targeted individualized approach and avoid inappropriate, expensive and invasive tests. Family history of HTN or CV disease may identify children and adolescents with essential HTN, but history of hereditary diseases associated with secondary forms of HTN should also be relevant (1,37). Parental history of HTN has been associated with masked HTN, early TOD, changes in central and peripheral hemodynamics, and can guide further evaluation (79,93-95). A complete clinical history assessment may include information summaraised in Table 4.2.1.

4.3. Birth weight

The importance of intrauterine and early life events in development of cardiometabolic disease in adult life has been underlined (96-100). The time immediately before and after birth may be a sensitive period in which multiple interactions between hemodynamic and metabolic parameters foreshadow the clustering of cardiometabolic risk factors later in life (101,102). A critical window of opportunity to modify programming may exist during pregnancy and throughout the first years of life when strategies aiming to reduce risk can be implemented. This is an expanding area for promising further investigation.

4.4. Physical examination

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 end-organ damage. See Table 4.4.1.

4.5. Laboratory investigation

Routine laboratory tests and imaging studies must be performed in all children with HTN. Other additional tests are necessary in specific conditions. See Table 4.5.1.

4.6. Genetic analysis

Genetic analysis merits a specific comment even if it has not yet been demonstrated to have a clear role to play in the routine assessment of children with HTN.

The human genome project in 2001 led the way to large-scale genomic studies in populations. The current list of known variants contributing to genetic architecture of BP and HTN includes more than 25 rare mutations and 53 single nucleotide polymorphisms (SNPs) as recently reviewed (51). It is now possible to use whole genome DNA sequencing or exome sequencing to diagnose rare monogenic syndromes although more traditional single gene PCR-based tests are also used successfully.

Monogenic causes of HTN are rare, but they should be detected during the pediatric age, for successful treatment and avoidance of the HTN associated morbidity and mortality. The monogenic HTN syndromes are good examples of perfect pharmacogenetic, where the knowledge of the functional genetic mutation allows for targeted therapy. All presently known monogenic causes of HTN are characterized by abnormal sodium transport in the kidney, volume expansion and low renin. Among them, Liddle's syndrome, glucocorticoid-remediable aldosteronism, apparent mineralocorticoid excess, Gordon's syndrome, mineralocorticoid receptor hypersensitivity syndrome and hypertensive forms of congenital adrenal hyperplasia have been identified (1). Monogenic diseases should be suspected in children with low renin

HTN and a family history of early-onset severe HTN, death from cerebral vascular accidents and heart failure or refractory HTN. Hypokalemia is a common feature of the majority of low renin HTN stated with the exception of Gordon's syndrome.

4.7. Searching for target organ damage

Once HTN is confirmed, organ damage evaluation should be assessed due to the importance of subclinical organ damage as an intermediate stage in the continuum of vascular disease. Subsequently, evaluation of organ damage is also useful as an intermediate endpoint for monitoring treatment. A summary of the criteria to define HTN-induced organ damage can be found in Table 4.7.1.

4.7.1. Heart

Assessment of LVM and geometry remain a cornerstone when looking for end-organ damage in sustained pediatric HTN (17,103). Following the Joint European Association of Echocardiography and American Society of Echocardiography (104), LVM should be calculated using the cube formula (105) and indexed (LVMI) by height$^{2.7}$ (106). Traditionally left ventricular hypertrophy (LVH) has been defined as LVMI or relative wall thickness (RWT) ≥ 95th percentile by age and gender (107,108). A recent paper by Chinali and Co-workers suggest to use a simplified approach for the identification of LVH in infants, children and adolescents with a single partition value across the whole age range (109). Using LVM/[height]$^{2.16}$ a single partition value of 45 g/m$^{2.16}$ and validated against a cohort of 130 healthy subjects, no false positives for LVH were found.

The ratio of Doppler transmitral flow (E) and tissue Doppler derived early diastolic velocity (E´), reflecting diastolic function, independently predicts primary cardiac events in hypertensive adults (110). Reference values of E/E´ are poorly defined in children and adolescents. Nevertheless, if technically available, it is recommended to include it in the longitudinal follow-up of individual patients and it most certainly should be included in future echocardiographic study protocols of hypertensive children and adolescents. A 12-lead ECG adds little to early

detection of cardiac end-organ damage (LVH) due to its overall poor reliability in children (111,112).

4.7.2. Blood vessels

Improved imaging methods (high definition ultrasound and echotracking) have enhanced 'reference' values for cIMT and arterial distensibility in healthy children aged 3-18 years (113,114). Carotid intima media thickness and distensibility, associated with age, anthropometry and BP are elevated in at-risk children with familial hypercholesterolaemia (115,116), overweight (117,118), HTN (119,120), and type 1 diabetes (121).

Arterial stiffening measured by PWV predicts CV events and mortality in adults (122). Reference values for PWV are now available from three studies that have been performed in childhood (84,123,124). Overall, current data suggest childhood BP only variably predicts increased PWV (125-127). Emerging data suggest that functional changes in large vessels are the earliest detectable findings in children, for example in those with familial hypercholestrolaemia and CKD (128,129).

Routine assessment of arterial stiffness and central BP parameters are not currently recommended and they should be maintained as a research area until further information is available.

4.7.3. Kidney

High BP itself may affect kidney function by inducing albuminuria (albumin/creatinine quotient >30mg/g creatinine or >3mg/mmol creatinine) or even proteinuria (>300mg/g creatinine or >30mg/mmol creatinine or 200 mg/m²/day) (130). Hematuria, proteinuria and edema formation indicate glomerular damage, but also failure to thrive, polyuria and polydipsia are symptoms of renal disease.

Full blood count, plasma sodium, potassium and calcium, urea, creatinine, uric acid and urinalysis (hematuria, proteinuria, leukocyturia) plus quantitative measurement of albuminuria and proteinuria should be performed in all children with HTN (1,7). Reduced glomerular

filtration rate (GFR in ml/min per 1.73m²) should be estimated according to Schwartz formula and permanently (>3 months) reduced estimated GFR indicates renal damage.

Renal imaging by renal ultrasound is required in every child with HTN to exclude Wilms tumor, neuroblastoma and renal cystic diseases or dysplasia. Reduced renal perfusion by renal artery stenosis or by mid aortic stenosis increases BP and can be detected by renal Doppler ultrasound, magnetic resonance tomography or direct renal angiography, the gold standard (131).

4.7.4. Fundoscopy

Data on incidence, findings and prognosis of hypertensive retinopathy (HTNR) in children are scarce (132). American children with essential HTN had HTNR based on arteriolar narrowing in fundus photographs and fluorescein angiography in 51% of 97 children (133). This was not the case when HTNR was examined by an ophthalmologist and assessed by dilated ophthalmoscopy; only 3/35 (8.6%) had mild HTNR (134). In a British sample, 7/39 children (18%) had HTNR, 6 with severe disease (hemorrhages, exudates, disc edema), some with permanent visual reduction (135). Fundoscopy should likely be limited to children with symptoms, encephalopathy or malignant HTN.

4.7.5. Brain

Sustained and severe high BP may affect the brain by various symptoms and signs (cerebral seizures, stroke, visual impairment and retinal vascular changes) (136). Then, neurologic clinical evaluation and diagnostic procedures, e.g. electroencephalography, ultrasonography during infant age, and by cranial computed tomography (CT), to exclude intracranial haemorrhage, need to be performed. Severe acute HTN causes a hypertensive emergency with specific symptoms (headache, visual impairment, dizziness, impaired consciousness, seizures or neurological deficits, e.g. facial nerve paresis). In these cases Magnetic Resonance Image (MRI) is required, which is able to identify small silent brain infarcts, microbleeds, white matter lesions and posterior reversible encephalopathy syndrome (PRES) (137).

4.8. Biomarkers

Biomarkers could be considered as tools to stratify the risk of patients at an individual level and/or to serve as surrogate endpoints of CV events (138).

A biomarker should be tested against stringent criteria including a proof of concept, prospective validation, incremental value, clinical utility, clinical outcomes, cost-effectiveness and reference values (139). Biomarkers which fulfill most of the above criteria currently are not available today.

The most likely scenario is that the emerging disruptive technologies such as genomics, proteomics and metabolomics would change the way we use biomarkers. Instead of a search for one perfect biomarker, we would rely on hundreds or even thousands of molecular markers considered jointly to pave the way for the development of precision medicine (140).

5. COMORBIDITIES

5.1. Obesity and Metabolic Syndrome

Childhood obesity is the most common nutritional problem in developed and developing countries and its prevalence in children has doubled since the mid-1980s (141-143) reaching pandemic proportions and increasing not only in prevalence but also in severity. According to the WHO, 42 million children under the age of 5 were overweight or obese worldwide in 2013 (144). The increasing tendency for obesity to appear during childhood and to track into adult life, as well as the firmly established relationships between obesity, DM2 and HTN in adults, means that obese children appear to be at particularly high risk of becoming diabetic and hypertensive as they age (145,146).

Identifying children most at risk for the development of future hypertensive disease is as important as assessing BP's association with other cardiometabolic risk factors. A process of clustering may occur when high BP acts together with one or more cardiometabolic risk factors, hyperinsulinemia and lipid abnormalities, producing TOD and cardiometabolic disease (6). Although the clustering in adults has been labelled as 'the metabolic syndrome', a consensus definition has been difficult to reach also for the pediatric population. Several definitions of metabolic syndrome have been proposed using not only different parameters but also different cut-offs. Moreover, as insulin resistance, the major driver of metabolic syndrome, is influenced by pubertal stage, it is questionable to use definitions that do not take into account pubertal status in pediatric age. As a consequence a widely variable prevalence of between 6% and 39% has been reported. High normal BP and HTN are frequently associated with one or more cardiometabolic risk factors (147). Therefore, lifestyle changes, particularly weight loss and increased physical exercise, are recommended for all individuals. For antihypertensive treatment see section 9.4 for specific recommendations.

5.2. Diabetes Mellitus

In young people, both type 1 diabetes (DM1) and DM2 are increasing in prevalence. The correct diagnosis of DM1 and DM2, and monogenic DM is important because it helps to guide

therapy, however distinguishing between DM1 and DM2 in children can be difficult since autoantibodies and ketoacidosis may be present in patients with features of DM2 (including obesity and acanthosis nigricans) (148). Compared with antibody negative, antibody positive DM2 are less overweight, have lower BP, better lipid profile, and are more likely to be males (149). Youth-onset DM2 occurs at a much greater prevalence in those of non-White European descent (Africans, native North Americans, Hispanics, Asians, and Pacific islanders) and in Japan, Hong Kong and Taiwan where > 60% of youth-onset diabetes is DM2. In contrast to the USA and Europe where nearly all youths with DM2 are overweight/obese, in Asia they are often normal weight (149).

The prevalence of elevated BP is generally higher in youths with DM2 than DM1 (16-36% vs 4-16%) and reduced nocturnal dipping may also be identified. Higher BP levels predispose to the development of microalbuminuria, nephropathy, HTNR, and carotid thickening and significant comorbidities may already be present at the time of DM2 diagnosis (150,151). The determinants of BP levels in children with diabetes include poor diet, adiposity, diabetes–related autonomic imbalance, and poor glucose control (152).

The Search for Diabetes in Youth Study described the prevalence of elevated BP, awareness, treatment, and control in 3691 children with DM1 and 410 with DM2 who attended a visit from 2001 to 2010 (150). Compared with youths with DM1, those with DM2 were older and more likely female, had an older age at diagnosis, were more likely to be obese (26.5 vs 11.1%) and belong to EM (19-76% vs 2.9%). Likewise, they had significantly higher SBP and DBP, lower Hb A1C, and higher prevalence of microalbuminuria, despite their shorter duration of DM. The percentage of youths receiving BP-lowering medication was very low and children with DM2 were more likely to receive such treatment. Recent data confirm that HTN is under-diagnosed in youths with DM 1 <13 yr of age (153). As a whole, awareness, screening, diagnosis, and treatment of elevated BP in youths with DM are not yet satisfactory.

5.3. Chronic kidney disease and renal insufficiency

In contrast to adults, where CKD is mainly considered as TOD as a consequence of primary HTN, pediatric HTN occurs mostly (in at least 85% of cases) secondarily to an underlying renoparenchymal or renovascular disease. The prevalence of HTN in pediatric CKD ranges from 20 to 80% depending on the degree of renal dysfunction (154-157). However, even children with CKD stage 2 (i.e. GFR 60 to 90 ml/min/1.73 m2) may present with elevated BP (158).

Even though HTN may not be the primary cause of renal disease, BP affects the rate of renal failure progression. In adults, HTN is an independent risk factor for CKD progression (159-161) and also in a large prospective study of children with CKD SBP greater than 120 mmHg has been associated with a faster decline of GFR (162).

Chronic kidney disease may additionally affect the physiological diurnal variation of BP. The integrity of the nocturnal fall of BP ('dipping') plays a significant role in renal failure progression, in addition to and independent of the absolute BP level. Non-dipping is a well-known and common characteristic of renal HTN and an independent CV risk factor (163), and is associated with faster progression of renal failure in adult CKD patients (164,165).

6. EVIDENCE FOR THERAPEUTIC MANAGEMENT OF HYPERTENSION

6.1. General overview

Numerous randomized clinical trials in hypertensive adults have provided evidence that antihypertensive treatment reduces the risk of death and major CV events such as stroke, myocardial infarction, heart failure and renal failure and improves life expectancy (166-170). Major CV events are extremely uncommon in childhood, and their rarity has so far prevented the running of event-based randomized therapeutic trials. Despite this, clinical experience shows that reduction of high BP in life-threatening conditions, such as acute heart failure, hypertensive encephalopathy and malignant HTN, improves survival and reduces sequelae in children. Because of the rarity of events, most of the limited evidence available so far is based on the use of organ damage markers including LVH, urinary albumin excretion, CKD progression and increased intima media thickness as endpoints.

6.2. Randomized trials based on intermediate end-points

6.2.1. Heart

Antihypertensive treatment results in improved cardiac function and LVH regression, which in turn reduces the risk of major CV events in adults (171-173). In children, information on the effects of antihypertensive treatment on cardiac end-organ damage is mostly limited to uncontrolled studies in heterogeneous populations with primary and secondary HTN. Nonetheless, there is pediatric evidence that effective antihypertensive treatment induces regression of LVH, ameliorates cardiac geometry and function (22, 23,174-176). In children with CKD receiving angiotensin converting enzyme inhibitors (ACEi), improved BP control resulted in LVH regression and improved systolic function within 12 months of treatment. Lowering BP to the low-normal range, however, resulted in a slightly more marked improvement in myocardial function but not in LVMi (175).

6.2.2. Renal function and disease

The effects of BP lowering treatment on renal function and disease in adults, especially in those with chronic renal disease, are still an area of dispute. A recent meta-analysis (177) has concluded for no significant effect on renal failure, but single studies have yielded discordant results, which may depend on the different nature of renal disease (e.g., diabetic or nondiabetic), presence or absence of proteinuria, and the type of BP-lowering agents (renin-angiotensin system inhibitors vs other classes). In children, however, the pediatric ESCAPE Trial (Effect of Strict Blood Pressure Control and ACE Inhibition on Progression of Chronic Renal Failure in Pediatric Patients) demonstrated that superior long-term nephroprotection is achieved by targeting for a low-normal 24-hour mean arterial pressure as compared to a high-normal BP target (25). The partially discrepant findings from experience with adults may be explained by methodological and population differences. Patient age, ethnicity, underlying renal diseases, pharmacological treatment protocols, duration of follow-up and dropout rates varied markedly between the studies. Furthermore, the use of ambulatory BP monitoring in the pediatric ESCAPE trial may have allowed more accurate monitoring of the achieved BP than achieved in the adult trials, where only casual BP readings were obtained.

Nevertheless, in all adult studies, patients with proteinuria seemed to benefit from intensified BP control, while there was no significant effect in patients without proteinuria. Furthermore, a recent meta-analysis including almost 80,000 patients from 21 randomized clinical trials demonstrated that the drug-induced reduction of albuminuria is predictive of subsequent nephroprotection (178).

7. THERAPEUTIC APPROACH

7.1. When to initiate antihypertensive treatment

The decision to initiate antihypertensive treatment should not be taken on BP levels alone, but should consider the total risk for CV and renal events. The presence or absence of TOD, and other risk factors for CV morbidity and mortality such as family history of CV diseases, hyperlipidemia, renal diseases or diabetes establish the global 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) in the same way as described in section 8.1. of "Lifestyle changes". 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. The decision about when to initiate pharmacological therapy cannot be supported by mortality/morbidity trial evidence, which is lacking because in children eventual outcomes are expected after a long time incompatible with the duration of a controlled trial. Consequently, the suggestions indicated in the decision-making tree of Figure 7.1.1 are formulated in analogy with what has been demonstrated in adults, and are largely based on wisdom.
Pharmacological therapy should be started in all children with symptomatic HTN, hypertensive TOD, secondary HTN or DM1 or DM2, as well as in those who are unresponsive to non-pharmacological therapy (179), 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 hypertensive TOD is already present (180,181)

7.2. Goal of treatment

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 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.

7.2.1. Blood pressure target in the general hypertensive pediatric population

In the absence of prospective long-term studies on the impact of different BP levels on intermediate or major CV and renal end-points in children, the 95th percentile is considered as 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, but it is probably wiser and safer to aim at a BP below the 90th percentile provided this goal can be attained by well tolerated treatment (see Table 7.2.1).

7.2.2. Home and 24-hour ambulatory blood pressure target

Ambulatory BP monitoring is regarded to substantially add to the diagnosis and monitoring of HTN, particularly because it can detect both white-coat and masked hypertensives. In children with renal HTN a substantially less variable BP response to antihypertensive treatment was observed when using ABPM as compared to office BP monitoring only (182), supporting the use of ABPM to monitor attainment and maintenance of BP targets. As ABPM cannot be performed very frequently, office and home BP monitoring should be utilized routinely. It appears appropriate to aim for the same target percentiles for all three modalities of BP assessment (7, 56, 64, 183). Blood pressure goal in hypertensive children (for office, home and ABPMs) are shown in Table 7.2.1.

7.2.3. Blood pressure target in diabetic and renal disease

The current European (92) and US guidelines (184) recommend a target BP below 140/90 mmHg in adults with CKD due to insufficient published evidence for an additional benefit of an even lower target concerning mortality or CV or cerebrovascular morbidity. However, the National Institute of Health recently carried out the Systolic Blood Pressure Intervention Trial (SPRINT), a randomized controlled trial comparing SBP targets of 140 and 120 mm Hg

respectively in 9,300 hypertensive adults aged 50 years and older (185). Results of this trial would not seem generalizable to children and adolescents because the SPRINT was on older adults at high risk for CV events what seems far removed from a pediatric setting (186).

For children with CKD, the prospective randomized ESCAPE trial has provided evidence that strict BP control aiming for a 24-h BP target below the 50th percentile leads to improved long-term renal survival (25). On average 1.9 antihypertensive drugs (including the ACE inhibitor ramipril provided at a fixed dose) were required to achieve the lower BP target. A post-hoc analysis indicates similar renal outcomes occurred with any 24-h BP below the 75th percentile, whereas 5-year renal survival increasingly deteriorated when achieved BP remained above this cutoff level (25,187).

Proteinuria is an important modifier of the renoprotective efficacy of intensified BP control. The renal survival benefit of intensified BP control appears limited to children with - even mild - proteinuria (188,189). Hence, at the current state of knowledge it appears appropriate to target BP to the 75th percentile in children with non-proteinuric CKD and to below the 50th percentile in children with proteinuria of any degree with close monitoring of creatinine.

Although overt diabetic nephropathy is rarely observed in children with diabetes, these patients are considered at increased long-term risk for HTN and renal damage (190,191). Subtle alterations such as slight increases of SBP and/or a blunted circadian BP variation are commonly found by ABPM early in the course of the disease (191,192) when office BP is still normal. Impaired nocturnal dipping often precedes microalbuminuria, the earliest marker of diabetic nephropathy (191). Although pediatric evidence regarding the efficacy of preventive antihypertensive and antiproteinuric treatment strategies in juvenile diabetes is still lacking, ample experience with adult diabetes reinforces the recommendation of aiming at a strict BP control in children with diabetes.

8. TREATMENT STRATEGIES

8.1. Lifestyle changes

Considerable advances have been made in recent years in identifying conditions often associated with and considered responsible for high BP in children and adolescents. More limited evidence has been accumulated on the results of corrective interventions. In overweight and obese children it has been demonstrated that lifestyle interventions incorporating a dietary component along with exercise or behavioural therapy can lead to improvements in both weight and cardiometabolic factors, including BP (193). In overweight adolescents weight reduction is associated with a decrease in office BP (194,195) and is the primary therapy for obesity-related HTN (1). After one year of lifestyle intervention, changes in obesity measures were closely related to changes in 24-h, daytime and night-time BP (196). Children with insufficient physical activity are about 3 times more likely to have elevated BP (1) and regular physical activity has CV benefits. Meta-analysis concluded that short-term physical activity leads to a small but not significant decrease in BP (197). However, regular physical activity results in a significant reduction of BP, not only when measured in the office, but also when monitored for 24-h BP. After 3 months of exercise training the effects on BP were 7-12 mmHg for SBP and 2-7 mmHg for DBP (198). Higher levels of physical activity were associated with lower BP and results suggested that the volume of activity might be more important than the intensity (199). The recommendations for physical activity (200) are included in Box 4. Although children less than 5 years old benefit from being active, more research is needed to determine what dose of physical activity provides the greatest health benefits.

Prospective studies have shown the effects of diet on lifetime BP (201). Consumption of >1 servings of dairy products/day and >2 servings of fruits and vegetables/day throughout adolescence has shown to lead to about a 35% lower risk of elevated BP (202). Likewise, saturated fat–reduced diet since infancy decreases BP (203). Higher sugar sweetened beverage consumption is associated with higher SBP in adolescents (204). High salt intake in children and adolescents is positively correlated with high SBP and an elevated risk of HTN (205) and a meta-analysis has shown that a 3g/day reduction of salt intake leads to a decrease in SBP and

DBP of 1.2/1.3 mmHg (206). Starting in newborns, a 15 year follow-up study has suggested a predictive role of the effect of salt intake in early life on BP (207). Excessive salt intake seems to be not only linked with BP elevation but also with other CV risk factors since salt produces a reduction in vascular nitric oxide bioavailability that limits endothelium-dependent dilation (208).

Environmental exposure to tobacco is an important risk factor contributing to the development and severity of CV disease. The heart and vascular system are highly vulnerable to tobacco smoking. Discouraging maternal smoking and maintaining a strictly smoke-free environment are of great importance due to the accumulating evidence on the importance of fetal and early life factors in determining CV risk (209). In adolescents, promotion of smoke-free rules at home may help prevent the uptake of cigarettes. While in active smokers, cessation of smoking is mandatory in order to improve CV risk due to the acute pressor effect that may raise daytime ambulatory BP (92). In box 4 the life style recommendations and goals are summarized.

8.2. Pharmacological Therapy

8.2.1. Therapeutic orphans and Regulatory Issues

There is a general paucity of high quality efficacy and safety data for the large majority of drugs used to treat HTN in children. As a consequence of this, dosing and assumptions about the therapeutic risk/benefit-ratio of many drugs is based on data derived from studies in hypertensive adults. Attempts have been made to improve this inequity through legislation on both sides of the Atlantic. The 1997 US Food and Drug Administration Modernization Act contained a provision granting a 6 month patent protection to industry if pediatric studies were conducted for new drugs. The subsequent Best Pharmaceuticals for Children Act, Pediatric Research Equity Act and FDA Amendments Act of 2007 have led to further initiatives, including the online public posting of internal FDA pharmacology and efficacy reviews and mechanisms to promote studies of drugs with expired patents. In Europe, the Regulation of Medicinal Products for Pediatric Use (EU Regulation 1901/2006/EC) similarly provided a six-

month extension of market exclusivity for new drugs where approved pediatric studies were conducted. For drugs no longer under patent protection, the Paediatric Use Marketing Authorisation (PUMA; Art. 40, EU Regulation) provides ten years of market protection as a reward for performing appropriate studies as part of an agreed Paediatric Investigation Plan. These legislative changes have resulted in a substantial growth in the number of studies of antihypertensive (and other) agents being conducted in children and a commensurate increase in the number achieving a pediatric licence. However, these studies have principally been restricted to newer antihypertensive agents; to date no older drug has received licensing as a result of PUMA (EMA).

8.2.2. Choice of antihypertensive drugs

8.2.2.1. Monotherapy

When prescribing antihypertensive therapy for adults, decisions regarding the choice of agent can be based upon evidence from clinical trials in a large numbers of subjects, many of these having compared one class of agent with another (210). While an increased emphasis on conducting drug trials in children and adolescents over the past 15 years has yielded important advances, there remains a general lack of high quality long-term outcome data to guide choice of drug therapy for pediatricians managing HTN. It is important to understand that what works for adults does not necessarily work for children and adolescents.

Those trials that have been conducted have mainly investigated the BP reducing effects of single agents in isolation, with very few comparing drugs of the same or different class to assess relative efficacy or safety. One exception is a study comparing valsartan with enalapril, which showed similar efficacy and adverse event rates for these two agents (211). Follow-up studies are generally limited in duration and little is known about the long term effects of antihypertensive agents on many outcomes, including growth and cognitive development. A recent Cochrane review identified a total of 21 randomised controlled trials of at least two weeks duration comparing antihypertensive agents as either monotherapy or combination therapy with either placebo or another medication, or comparing different doses of the same

medication in a total of 3454 children with HTN (212). Outcomes were limited to BP with no study investigating efficacy of preventing target end organ damage. The most data are available for candesartan, which has demonstrated low-quality evidence of a modest lowering effect on BP. No evidence could be found of a consistent dose response relationship for escalating doses of angiotensin receptor blockers (ARBs), calcium channel blockers and angiotensin converting enzyme (ACE) inhibitors. Side effects were generally minor, including headaches, dizziness and upper respiratory infections.

Until such time that high quality clinical trial data are available to compare one class of antihypertensive drug with another, several different agents may potentially be first-line agents. These include the five classes for which evidence of CV event reduction is available in adults (213), ACE-inhibitors, ARBs, 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 commence 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. Once-daily administration of medicines is also widely recognised to improve adherence (214).

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; and a diuretic most appropriate in the child with corticosteroid-induced HTN. Alternatively, there may be compelling reasons to avoid

certain agents, for instance beta-blockers in the hypertensive child with asthma or diabetes, and ACE inhibitors or ARBs in female teenagers at high risk of pregnancy. Diuretics and beta-blockers should generally be avoided in competitive athletes; these may impair performance through decreased intravascular volume and decreased cardiac output respectively and are also listed among doping substances (215).

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; in adults these agents appear to reduce the incidence of new-onset diabetes and may increase insulin sensitivity (216). Where these are not tolerated, calcium channel blockers are a reasonable alternative. Given their known effects on glucose metabolism and insulin resistance it is sensible to avoid the use of beta-blockers without vasodilatory capacity and thiazide diuretics (217). In children with HTN not related to obesity there are no substantial data upon which to make a recommendation to support the use of any one agent over another.

Once the appropriate agent has been selected, the child should commence on the lowest recommended dose (see Table 8.2.1 and 8.2.2) (1,218). 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. These are drug-specific and some require routine monitoring, e.g. the assessment of kidney function and potassium balance in children receiving ACE inhibitors and ARBs. Drug-related side effects may be dose limiting, resulting in the early addition of a second agent or complete replacement of the initial agent.

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. Presenting features and appropriate therapies are shown in Table 8.2.3 (adapted from 215).

8.2.2.2. Combination therapy

Where the use of the maximum recommended or tolerated 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 2013 Guidelines (92) (Figure 8.2.1). It is logical to combine agents from different drug classes and preferably those with complementary modes of action, e.g. an ACE inhibitor with a diuretic or a vasodilator with a diuretic or a beta-blocker. Following the review of adult data from the ONTARGET (219), ALTITUDE (220) and VA NEPHRON-D (221) studies, the European Medicines Agency have formally recommended that no two drugs which act separately on the renin-angiotensin system should be used in combination because of risks of hyperkalaemia, impaired kidney function and hypotension (www.ema.europa.eu). Dual therapy with ACE inhibitors, ARBs and direct renin inhibitors should therefore be avoided, although it may be cautiously used in patients with heavy proteinuria under strict renal function and potassium levels monitoring. Few data exist on the use of fixed-dose combination agents in children and these are rarely used, though may have a place in the treatment of adolescents with the aim of improving medication adherence (222).

9. THERAPEUTIC APPROACHES IN SPECIAL CONDITIONS

9.1. Diabetes mellitus

Consensus-based guidelines have recommended, mostly on the basis of expert opinion, that measures to prevent persistent microalbuminuria, such as optimal blood glucose control, participation in physical activity, a low-protein diet, smoking cessation, and BP control, should be promoted (152). Blood pressure treatment includes defining the BP goal, how achievement of this goal will be checked, and which class of antihypertensive drug will be more appropriate.

The BP goal for diabetic patients is a relevant and controversial issue in children as well as in adults. In the latter no clear evidence is available that the BP should be lower in diabetic than in nondiabetic hypertensives (92). In children longitudinal studies with CV or renal events are absent. Because of some evidence that youths with DM1 or DM2 develop early atherosclerotic lesions before the age of 30 (218), the American Heart Association suggests the BP goal be lower than the 90th percentile for age, sex and height (152). A post-hoc analysis of a trial on DM1 suggests that a lower BP target may be beneficial in reducing urinary albumin excretion (UAE) and the risk to develop proteinuria (223). The goals recommended by the present panel are indicated in Table 7.2.1: the opinion of the panel is that a goal below the 90th percentile (or below 130/80 mmHg at age 16 and above) may be achieved in both children and adolescent, provided treatment is well tolerated.

At the time to select the antihypertensive drugs two key issues should be considered, the most relevant is to achieve the BP goal over the 24 hours and the necessity to reduce salt-intake due to the sodium-dependent component of HTN in diabetes (224). An additional benefit of starting with drugs blocking the renin angiotensin system (either ACE inhibitor or ARB), is promised by their ability to reduce urinary albumin excretion and delay the onset of nephropathy, although the advantage in long-term protection has not been established (225).

9.2. Heart failure

Unlike in the adult, HTN is not a common cause of heart failure in children and adolescents. However, children and adolescents with end stage renal failure, diabetes, congenital heart disease or Kawasaki disease are at increased risk of early CV events and heart failure and the management of HTN in these patients needs special attention (226). First-line therapy includes salt restriction and agents that target the renin-angiotensin-aldosterone-system combined with beta-blockers in low doses if necessary to achieve BP control. Addition of diuretics is recommended in patients with volume overload (175,176). Occasionally one may see patients with critical CoA presenting with heart failure and upper limb HTN. Surgical or catheter intervention to relieve the obstruction is the first treatment of choice. However, HTN may persist in some patients despite successful repair (see chapter 11.8)

Treatment of a hypertensive crisis causing acute heart failure includes the use of intravenous vasodilatory agents (nicardipine), with nitroprusside limited to situations where other agents fail, or to brief periods of time (227) (see secion 9.6 and Table 9.6.1).

9.3. Non-diabetic renal disease

In section 7.2 'Goal of treatment', the current evidence is summarized suggesting that HTN in children with CKD, especially if accompanied by proteinuria, requires more intense management in order to reduce proteinuria and prevent progressive deterioration of renal function. Although non-pharmacological options should be considered, drug treatment remains the mainstay of antihypertensive management in all stages of CKD. The different classes of antihypertensive agents are comparable with respect to their BP-lowering efficacy in children with CKD (228,229), but most of the available clinical evidence has been obtained with drugs blocking the renin-angiotensin system (RAS) (25,228,230). They have a powerful, dose-dependent antiproteinuric action in pediatric nephropathies (231). RAS inhibitors in general have a favourable side effect profile; however, a few fatalities have been documented in infants with acute intravascular volume depletion while receiving angiotensin receptor blockers (231,232). It is recommended to use RAS blocking agents as first choice with

appropriate risk counselling in all proteinuric patients with CKD. In hypertensive infants with non-proteinuric CKD, calcium channel blockers may be considered as first-line therapy for safety considerations.

In three-quarters of hypertensive children with CKD stage 2-4, BP control can be achieved by antihypertensive monotherapy, but at least 50% of children require more than one drug to achieve a sufficiently low BP target. If multiple drug therapy is required, diuretics and calcium channel blockers are the most suitable addition to a RAS blocker . Whereas the combined administration of ACE inhibitors, ARBs and the renin inhibitor aliskiren exert additional antiproteinuric effects in adults and children (233,234), it is recommended not to use such combination therapies because of increased rates of serious adverse events such as acute kidney injury and hyperkalemia observed in large randomized trials of high-risk adult patients (219-221).

9.4. Metabolic syndrome

Despite the difficulties in defining metabolic syndrome in children and adolescents (see section 5.2.), the construct of clustering of cardiometabolic risk factors are useful in the clinical setting. The key issue is to reduce the highly prevalent overweight and obesity, a complex task to maintain overtime. All effort should be done to educate young people as early as possible to a healthy lifestyle. A combination of physical exercise plus dietary intervention is commonly required. Several complementary actions, such as family- and school-based interventions and benefiting from internet-delivered intervention, are crucial to achieve success (235).

Information about the use of drugs to reduce obesity and/or increase insulin sensitivity is scarce, but the CV serious side effects of sibutramine (236) and the gastrointestinal side effect of orlistat do not recommend their use. The use of metformin for abdominal obesity seems to be effective in the short-term but information about the efficacy overtime is lacking (237).

Besides intervention for obesity, the rest of the cardiometabolic risk factors should be treated, aiming not to increase weight or insulin resistance. For HTN, thiazide diuretics and classic beta-blockers are not recommended, while drugs that block the renin-angiotensin system are

preferable (92,238). If beta-blockers are a compelling indication, those with vasodilating capacity should be used. A controversial issue is the role of hyperuricemia in the risk of developing HTN and CV risk, but today not significant evidence exists to give grounded recommendations.

9.5. Resistant hypertension

Hypertension may be termed resistant to treatment, or refractory, when a therapeutic plan that has included attention to lifestyle measures and the prescription of at least three drugs in adequate doses (one diuretic) has failed to lower systolic and DBP sufficiently (92). This condition implies very high CV and renal risk and requires prompt intervention. In children and adolescents, once white coat and adherence to treatment has been checked, there is always a secondary cause of HTN. Even though there are no systematic studies reporting secondary causes of resistant HTN, primary glomerulopathies, renal insufficiency, vascular diseases and neurological tumours are the most frequent diseases. In these cases it is not difficult to diagnose with simple analytical or image technique procedures. If this is not the case, genetic causes of HTN should be ruled out.

Among the genetic causes the most common are the sodium-dependent ones, although some others should be taken into account such as autosomal dominant brachydactyly with HTN associated with increased activation of pressure centres in brain stem and increased peripheral vascular resistance.

9.6. Hypertensive emergencies

A hypertensive emergency is a life-threatening condition associated with severe HTN. Although there is no absolute level of BP to define severe HTN some authors suggest to use a cut-off of 20% above the stage 2 HTN limit, which corresponds with an SBP of 178 mmHg in a 17 year old boy (239). This should be differentiated from a hypertensive urgency that is defined as severe HTN without acute target organ dysfunction.

Life-threatening conditions include organ dysfunction, mainly neurological, renal or cardiac. The most common symptoms of a hypertensive crisis are headache, dizziness, nausea/vomiting, seizures, confusions, visual symptoms and facial nerve palsy (240). Acute encephalopathy syndromes can also be produced with no extreme BP elevations when the HTN appears as a sudden onset, since the autoregulation of cerebral flow is not able to control the rapid BP increment.

The etiology of HTN causing a hypertensive crisis is mostly secondary (renal, endocrine, or cardiac). The evaluation of a child with a hypertensive emergency should include fundoscopic exam (hemorrhages, exudates, papilledema) and neurologic clinical evaluation and CT (to exclude hemorrhage) or MRI (for edema of white matter in the parieto-occipital regions, named PRES) in case of symptoms of hypertensive encephalopathy.

Children with hypertensive emergencies should be treated in an intensive care unit to ensure monitoring and support of the vital organs including neurologic status. The treatment strategy must be directed towards the immediate reduction of BP to reduce the hypertensive damage to the target organs, but not at a rate that would be likely to cause hypoperfusion of vital organs by an excessively rapid reduction of BP (mainly cerebral hypoperfusion with neurological sequelae or renal hypoperfusion with acute kidney injury).

There is no experimental evidence upon which recommendations on the optimal rate of BP reduction in hypertensive emergencies could be based. From clinical experience, BP should be lowered by no more than 25% of the planned BP reduction over the first 6-8 hours, followed by a further gradual reduction over the next 24-48 hours (227,241-244). Faster normalisation of severe HTN must be strictly avoided as it can cause more harm than severe HTN itself. Then, careful neurological and CV assessment should be undertaken throughout the initial treatment.

Children with a hypertensive emergency should always be treated with intravenous drugs. Continuous infusion is safer than bolus in regard to complication (unexpected hypotension with vital organ hypoperfusion and irreversible neurological damage such as visual loss). Sodium nitroprusside and labetalol are the most commonly used drugs for hypertensive

emergencies in children. However, some drugs are no longer available in some countries. Hypertensive urgencies can be treated by oral drugs. Table 9.6.1 indicates drugs and doses used for pediatric hypertensive crises.

9.7. Malignant hypertension

Malignant HTN was classically defined by the presence of an acute increase of BP values, with or without previous HTN, and a funduscopy stage III or IV. Today it is considered an acute elevation of BP associated with impairment of at least three different target organs or even the presence of microangiopathic haemolytic anaemia. The prevalence of malignant HTN has clearly fallen with the advent of anti-hypertensive medication. Early recognition and management of malignant HTN are fundamental to any improvement in prognosis, although parenteral drug administration is not necessary (245).

10. TREATMENT OF ASSOCIATED RISK FACTORS

10.1. Lipid lowering agents

The 2011 National Heart, Lung, and Blood Institute Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents (218) recommend to consider statin therapy for children >10 years with LDL-C levels of ≥190 mg/dL (< 4.9 mmol/L) without other risk factors, or ≥160 mg/dL (<4.1 mmol/L) if additional risk factors are present and in those with LDL-C levels >130 mg/dL (>3.4 mmol/L) after 6 months of lifestyle changes. In contrast, the 2013 American College of Cardiology and American Heart Association Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults recommends medication for individuals younger than 40 years only if their LDL-C level is at least 190 mg/dL (4.9 mmol/L) (246). Children <10 years should not be treated with a lipid lowering medication unless they have a severe primary familial hyperlipidemia or high-risk conditions. Given the conflicting lipid treatment guidelines for youth and current uncertain state of knowledge on long-term safety of statin therapy (247,248), the panel recommend to initially address modifiable risk factors such as diet, exercise, weight and abstinence from tobacco, and institute a lipid-lowering therapy only after careful evaluation of potential benefits, harms, and patient preferences. In children on statins, monitoring of hepatic enzymes and clinical assessment for muscle toxicity are strongly recommended. Fish oil should be used to reduce triglyceride levels.

10.2. Glycaemic control

Lifestyle changes should be initiated at the time of diagnosis of DM2 as well as in children with hyperglycaemia and elevated risk of DM2. Nutritional advice must focus on eliminating sugar-containing soft drinks, increasing fruit and vegetable intake, reducing processed, pre-packaged food and controlling portions. Youths should be encouraged to engage in moderate-to-vigorous exercise for at least 60 min daily. Initial pharmacologic treatment for children with DM2 should include metformin and insulin, alone or in combination, depending on symptoms, severity of hyperglycemia, and presence or absence of ketosis/ketoacidosis (225). The TODAY

Study compared the efficacy of three treatment regimens to achieve durable glycemic control in 699 children and adolescents with recent-onset DM2 (249). Results showed that metformin alone is effective in maintaining durable glycemic control in only half of children, and the addition of rosiglitazone, but not intensive lifestyle intervention, is superior to metformin alone. These findings suggest that most children require a combination treatment or insulin therapy within a few years after diagnosis and that more effective lifestyle regimens for children must be identified. Several clinical trials of newer oral hypoglycemic agents are underway in DM2 youth, but recruitment is slow and results are not expected for many years.

11. SCREENING AND TREATMENT OF SECONDARY FORMS OF HYPERTENSION

11.1. General strategy to when and how to look for secondary hypertension in children and adolescents

Secondary HTN is generally accepted to be much more common in children and adolescents than in the adult population, with some studies reporting prevalence as high as 75-85% in younger children (250-252). More recent reports, however, have highlighted the increasing prevalence of primary HTN, which is strongly linked to childhood obesity, particularly in the adolescent population.

Secondary HTN should be suspected in the younger patient in whom there is a very high BP or secondary complications (hypertensive encephalopathy, cranial nerve palsy, heart failure etc.) or HTN is difficult to treat. A good general rule to follow is that the likelihood of identifying a secondary cause of HTN is inversely related to the age of the child and directly related to the degree of BP elevation (253).

The clinical history should identify potential indicators to a secondary cause for HTN, including previous urine infection, gross haematuria or oedema, episodes of acute kidney injury, umbilical artery catheterisation, vascular events, snoring and sleep problems suggestive of obstructive sleep apnoea and any strong family history of HTN at a young age. Examination should seek to identify clinical signs suggestive of systemic disorders associated with HTN (refer to Table 4.4.1). In general, young children, children with very high or complicated HTN, and those with the aforementioned clinical symptoms and signs should be investigated more extensively than the older child with seemingly mild HTN.

11.2. Renal parenchymal disease

Since the most common form of secondary HTN in children and adolescents are diseases of the renal parenchyma, screening to detect an underlying cause of HTN should start with specific tests to detect renal abnormalities. This includes urine analysis (hematuria, proteinuria) and blood tests (creatinine, urea, uric acid, electrolytes) as well as renal function tests (1). For the diagnosis of chronic glomerular diseases renal biopsy is often necessary to clarify the form of

glomerulonephritis and the degree of glomerular damage, and a special kind of involvement, e.g. focal segmental glomerulosclerosis. Ultrasonography is able to detect autosomal-dominant and autosomal-recessive forms of polycystic kidney diseases, renal dysplasia or reflux nephropathy. Reflux nephropathy (pyelonephritic scarring) results from vesicoureteric reflux combined with urinary-tract infection in early life, and requires a micturition cystourethrography. Additional techniques of renal imaging (e.g. scintigraphy CT, MRI) are seldom needed. In cases of suspected genetic disease (e.g. Alport syndrome, congenital nephrotic syndrome) genetic testing is required. For treatment approach see section 9.3.

11.3. Renovascular hypertension

Diseases of the renal vessels resulting from lesions that cause significant impairment of blood flow to kidneys are far rarer than diseases of the renal parenchyma. The most single cause of renovascular HTN in children is fibromuscular dysplasia (254). Stenosis of the renal artery is not often associated with neurofibromatosis, but it should be excluded. Also other syndromes, e.g. Klippel–Trenaunay, Turner and Alagille syndrome have to be considered (255).
Plasma renin activity is often recommended to detect renovascular HTN, but it is not sensitive or specific and has a role to detect low renin HTN, mainly monogenic forms of HTN. Imaging procedures by abdominal ultrasound including colour-aided and Doppler sonography of the renal artery shows increased systolic and particularly diastolic flow velocity in the renal arteries. MRI angiography is more sensitive and specific to demonstrate abdominal or renal artery stenosis; this is the diagnostic procedure of choice. However, its sensitivity and specificity is lower than the gold standard procedure, i.e. renal angiography.
Renal artery revascularization is often able to control HTN in fibromuscular dysplasia (256). When angioplasty is not effective, surgical procedures should be chosen as the next therapeutic approach (257).

11.4. Phaeochromocytoma

Pediatric pheochromocytomas and extra-adrenal catecholamine-producing tumours are more frequently familial, bilateral, multifocal and malignant. Half of these tumours are associated with a mutation of one of the 12 known susceptibility genes. These tumours are often identified during presymptomatic screening in children with genetic syndromes such as multiple endocrine neoplasia type 2, von Hippel-Lindau disease, type 1 neurofibromatosis and the paraganglioma syndromes (258,259). Plasma and/or urine metanephrine measurement and MR imaging are recommended as first-line diagnostic approach. Surgical resection, with appropriate perioperative management of catecholamine-related symptoms, is the treatment of choice. In the case of metastatic disease, surgical removal of metastases and I-131-MIBG radiotherapy can be performed (258,259).

11.5. Primary aldosteronism

Primary aldosteronism is characterized by HTN with low plasma renin and elevated aldosterone and often associated with hypokalemia. An early-onset primary aldosteronism suggests inherited causes. Three familial aldosteronisms have been described: FH-1 (glucocorticoid-remediable aldosteronism caused by mutations affecting aldosterone synthase), FH-2 (with unknown molecular basis), and FH-3 (two distinct syndromes with or without adrenal hyperplasia resulting from different mutations in genes coding for ion channels) (260). FH-1 is associated with high morbidity and mortality at an early age and should be treated in children with eplerenone to avoid glucocorticoid effects on growth or antiandrogenic effects of spironolactone. Children with FH-3 and bilateral adrenal hyperplasia present with severe HTN refractory to treatment and need bilateral adrenalectomy. FH-2 is clinically and biochemically indistinguishable from sporadic forms (260).

11.6. Cushing's syndrome

In children >7 years of age the most frequent cause of endogenous Cushing syndrome (CS) is an ACTH-secreting pituitary microadenoma (75%), whereas adrenocortical tumours (70%

malignant) are more common in younger children. Micronodular adrenal hyperplasia can also occur as part of genetic disorders such as the McCune–Albright syndrome and the primary pigmented bilateral adrenocortical nodular disease (261). This latter may be associated with Carney complex (multiple endocrine tumors, lentigines and myxomas). The most common presenting features are weight gain and growth retardation. Hypertension is present in about half of children with CS. High SBP levels persist one year after surgery in 5.5-21% of children (262,263).

11.7. Obstructive sleep apnea

Prevalence of sleep-apnea syndrome in children is around 2-3% in the general population (264), although among obese adolescents the prevalence varies between 13% and 66% (265-268). Dayyat et al. (269) described two types of obstructive sleep apnea (OSA) in children. While Type I is characterized by amigdalar hypertrophy, mild overweight, hyperactivity, and with recurrent infections, Type II is present in obese subjects with diurnal hypersomnia, HTN and metabolic disturbances. Nocturnal pulsioxymetry can identify children and adolescents at high risk of OSA. During monitoring, three or more desaturations per hour have up to 97% predictive value in children without any other health problem. However, if the test is normal, this does not exclude the presence of OSA, as the test has a 47% negative predictive value. Several studies have linked OSA and the alterations in the glucose metabolism with insulin resistance, besides the BP elevation. The mechanisms that link obesity, OSA and insulin resistance are controversial. Some authors defend the hypothesis that the sleep fragmentation and the nocturnal hypoxia are responsible for insulin resistance (270), increment of cortisol, overdrive of the sympathetic nervous system (271) and the increment in insulin (272). Others consider that the primary alteration is obesity and insulin resistance, resulting in a respiratory disorder during sleep, facilitating the collapse of the upper airway through inflammatory mediators and a reduction in the neural drive of the dilatory muscle of the airway (273). Hypertension treatment in these adolescents should be based on treating obesity. In the most severe forms resistant to losing weight, continuous positive airway pressure (CPAP) should be

used.

11.8. Coarctation of aorta

Coarctation of the aorta (CoA) accounts for 5%-7% of all congenital heart disease with an incidence of approximately 3 cases per 10000 births (274). Patients with less severe CoA may not be diagnosed until later in childhood when a murmur is heard or HTN noted. In addition, residual or late-onset HTN is a well-known complication in successfully repaired CoA. The chronic burden of HTN in CoA patients is likely significantly higher than in other at-risk populations due to the early onset of the illness (275). This population needs to be treated as at particularly high risk, and HTN should be aggressively sought and treated. Before considering antihypertensive agents a re-coarctation must be ruled out. In children aged 7-16 years the prevalence of restenosis is suggested to be as high as 21% (276) and masked HTN is common, then ABPM should be performed regularly from the age of seven (80). Exercise HTN may also be present despite the lack of early or long-term residual or recurrent obstruction. The clinical significance of abnormal BP response to exercise is somewhat controversial (277). It has been suggested that it is a predictor of chronic HTN (278,279).

Before considering antihypertensive agents a re-coarctation must be ruled out. Beta-blockers, calcium channel blockers and drugs affecting the renin-angiotensin-aldosterone system efficiently lower BP (280,281).

11.9. Drug-induced hypertension

Drug-induced hypertension (DIH) is defined as HTN caused by the unintended effect of a drug, or from a drug's antagonizing effects on antihypertensive treatment (282). The two major mechanisms of DIH are sodium retention and sympathomimetic effect (Table 11.9.1). Treatment of DIH is by withdrawal of the drug causing DIH and sometimes short term antihypertensive treatment may be needed. When therapy with a therapeutic agent causing DIH cannot be stopped, chronic antihypertensive treatment should be started. DIH may present as resistant HTN or exacerbation of HTN in a child already treated with

antihypertensive drugs, or de novo in a previously normotensive child (282,283). The distinct cause of DIH is the use of illicit pyschostimulants which exert sympathoexcitatory effect. Oral-contraceptive drugs should be considered in adolescent girls and should be removed when HTN is detected; BP can be increased even after two months of withdrawal. The recent introduction in cancer treatment of anti-angiogenic drugs has become a relevant cause of DIH. Inhibitors of angiogenesis produce reduced activity of vascular endothelial growth factor (VEGF) pathway via tyrosin kinase.

Treatment of DIH is based on expert opinions and case series. The most frequent DIH, mechanism and recommended treatment are in Table 11.9.1.

11.10. Monogenic causes of hypertension

Monogenic diseases should be suspected in children with low renin HTN and a family history of early-onset severe HTN, death from cerebral vascular accidents and heart failure or refractory HTN. A trend to hypokaliemia is a common feature of the majority of the low renin hypertensive states, with the exception of Gordon's syndrome.

Most forms of monogenic HTN are sodium-dependent secondary to mineralocorticoid effect caused by mineralocorticoids, cortisol, mineralocorticoid-independent sodium reabsorption by epithelial sodium channel (ENaC), activated mineralocorticoid receptor or deoxycorticosterone (282,283). Figure 11.10.1 outlines a rational approach to each of the most frequent monogenic causes. Following the clinical suspicion, a specific test should be performed.

Treatment of monogenic HTN is directed against main pathophysiological disturbances and confirmed by results of case series. Treatment of sodium-dependent, low-renin monogenic HTN is based on low-sodium diet and blockade of pathological mechanisms of sodium reabsorption. Treatment of pseudohypoaldosteronism type II is based on thiazides. Treatment of Liddle syndrome and of activating mutation of MR treatment is directed against ENaC and based on amiloride or triamterene. In apparent mineralocorticoid excess (defective metabolism of cortisol to cortison) treatment is based on dexamethasone, blockers of ENaC

and MR. Congenital adrenal hyperplasia associated with HTN, i.e. deficiency of 11β or of 17α hydroxylase, is treated with dexamethasone and blockers of MR. Treatment of choice in familial hyperaldosteronism type I is dexamethasone and in familial hyperaldosteronism type II are blockers of MR. In autosomal dominant brachydactyly with HTN multidrug regimen based on beta-blockers devoided of sympathomimetic action, alpha-blockers and calcium channel blockers are suggested (284). (Figure 11.10.1).

12. FOLLOW-UP

Depending on the underlying cause of HTN, periodic, probably life-long follow-up is advisable in the majority of children. Regular home BP monitoring can greatly facilitate the management of HTN for better assessing of BP control. In children with CKD or diabetes, regular ABPM measurements at 6-12-month intervals are recommended to rule out selective nocturnal HTN. In patients with LVH or inadequately controlled BP, cardiac assessment should be repeated at least every six months. Fundoscopy should be performed at least annually in patients with hypertensive HTNR. Patients with well-controlled HTN and no target organ pathology should be monitored at larger intervals, e.g. every 12 to 24 months, to rule out de novo TOD.

In some patients, in whom treatment is accompanied by an effective BP control for an extended period, it may be possible to reduce the number and dose of drugs. This may be particularly the case if BP control is accompanied by healthy lifestyle changes, such as weight loss, exercise habits and a low-fat and low-salt diet, which remove environmental pressor influences. Reduction of medications should be made gradually and the patient should frequently be checked because of the risk of reappearance of HTN.

13. IMPLEMENTATION OF GUIDELINES AND WHERE TO INTERVENE – Community settings and stakeholders

Synergistic actions at various levels (learned societies and international expert committees, general practitioners, pediatricians, nurses and other healthcare providers, schools, parents, and policy makers) should be successfully implemented In order to limit, and even reduce, the burden of HTN in children and adolescents. The role of learned societies, particularly 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.

In parallel, a concerted public action is needed to both improve identification and treatment of high BP among children and adolescents, and to encourage lifestyle factors, namely healthy nutrition, low salt intake, non smoking, alcohol avoidance, and exercise activity, as preventive and curative measures. 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. Indeed, a comprehensive preventive program in each European country involving all the above actors, as well as families and school teachers, is a prerequisite to promoting management implementation in practice and improving child and adolescent health.

A converging action is the only means to closing the gap between experts' recommendations and undiagnosed HTN in children and adolescents, undetected TOD, and poor BP control.

The writing committee is well aware of the fact that issuing these guidelines does not imply implementation. These guidelines represent a consensus among specialists involved in the detection and control of high BP in children and adolescents. Scientific evidence derived from trials is not available in children, and therefore these guidelines are likely to be modified in forthcoming years depending on new evidence to be acquired. The recommendations of the present document synthesize a considerable amount of scientific data and clinical experience, and represent the best clinical wisdom upon which physicians, nurses and families should base their decisions. In addition, because they call attention to the burden of HTN in children and adolescents, and its contribution to the current epidemic of CV disease, these guidelines

should encourage public policy makers to develop a global effort to improve identification and treatment of high BP among children and adolescents.

14. FUTURE RESEARCH

Several times, these guidelines have acknowledged and lamented the lack of solid, trial based evidence for recommendations on diagnosis and management of pediatric HTN. Areas requiring urgent increase in knowledge have been listed in Box 6. A commitment to finding answers to the outlined issues should guide concerted actions over the next several years in Europe.

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LEGEND OF FIGURES

FIGURE 2.1.1. Flow-chart for the diagnosis of hypertension based on Percentile distribution of age, sex and height. *(< 16 y) and on defined threshold (≥16y)*

P, percentile.

Figure 7.1.1. When to initiate antihypertensive treatment.

One or more of the conditions listed in the box are required for the start of antihypertensive drugs. Persistent hypertension, despite nonpharmacological measures, requires initiation of antihypertensive drug treatment.

Figure 8.2.1. Recommendation for combination of antihypertensive drugs (From ref 92).

Green/continuous: preferred. Green/dashed: useful (with some limitations). Black/dashed: possible but less well tested. Red/continuous: not recommended

Only dihydropyridines to be combined with β-blockers. Thiazides + β-blockers increase risk of new onset Diabetes Mellitus. (ACE) Angiotensine converting enzyme + Angiotensine-receptor blockers combination discouraged

Figure 11.10.1. Mendelian causes of hypertension. Metabolite profile and recommended treatment.

Diagnostic algorithm in low plasma renin activity hypertension and genetic testing. Ratio of urinary THF+alloTHF/THE, normal less than 1.3, apparent mineralcorticoid excess 5-10 fold higher. (THE) tetrahydrocortisone; (THF) tetrahydrocortisonl (alloTHF) allotetrahydrocortisol; (R) renin; (PRA) Plasma renin activity. (Aldo) aldosterone. (GFR) Glomerular filtration rate. (ACTH) Adrenocorticotropic hormone; (AD) Autosomal dominant) (AR) Autosomal recesive. (GRA) Glucocorticoide remediable aldosteronism. Shaded área corresponds to the recommended treatment.

Figure

Figure 2.1.1

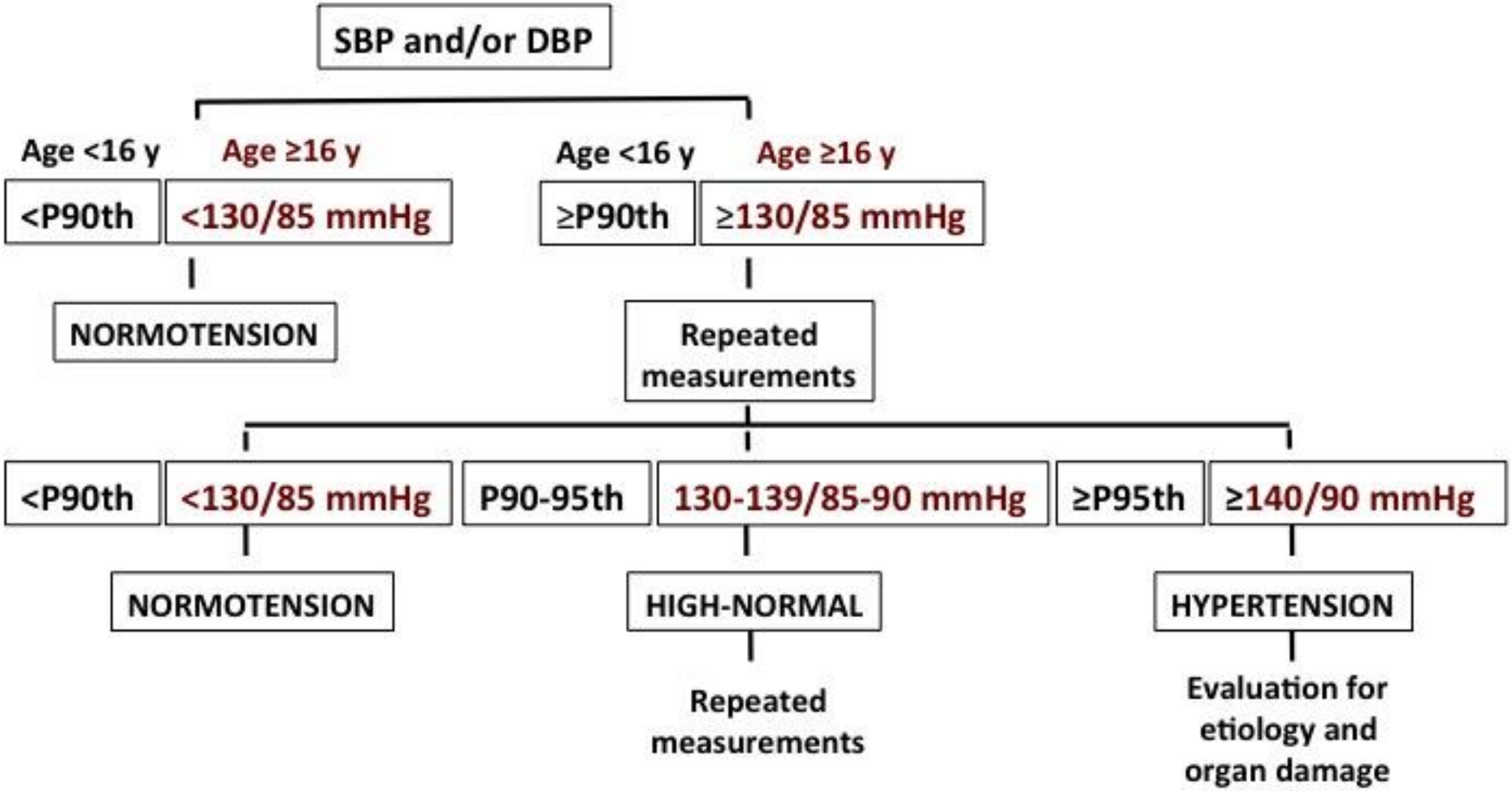


Figure 7.1.1.

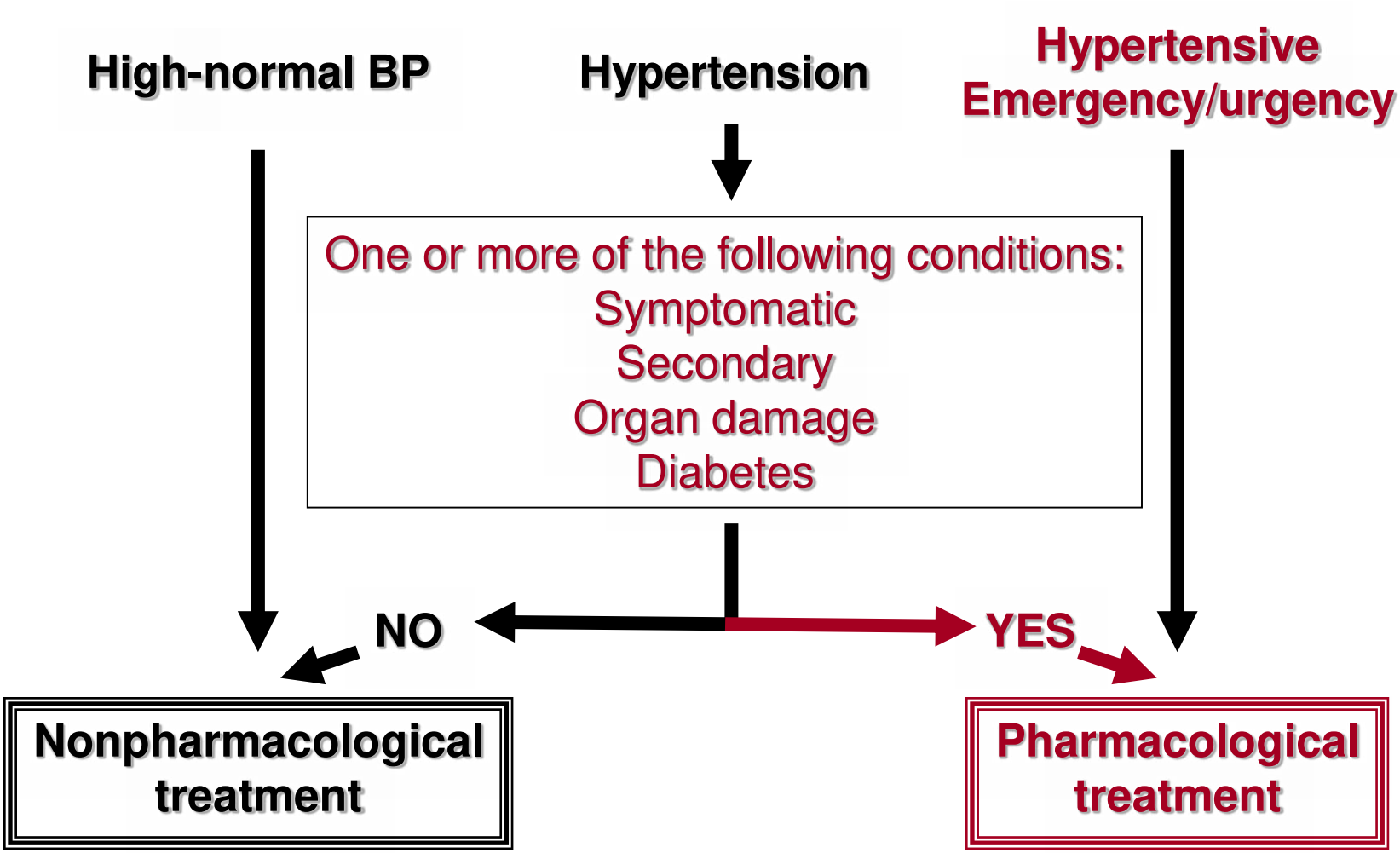

High-normal BP
Hypertension
Hypertensive Emergency/urgency
One or more of the following conditions:
Symptomatic
Secondary
Organ damage
Diabetes
NO
YES
Nonpharmacological treatment
Pharmacological treatment

Figure 8.2.1.

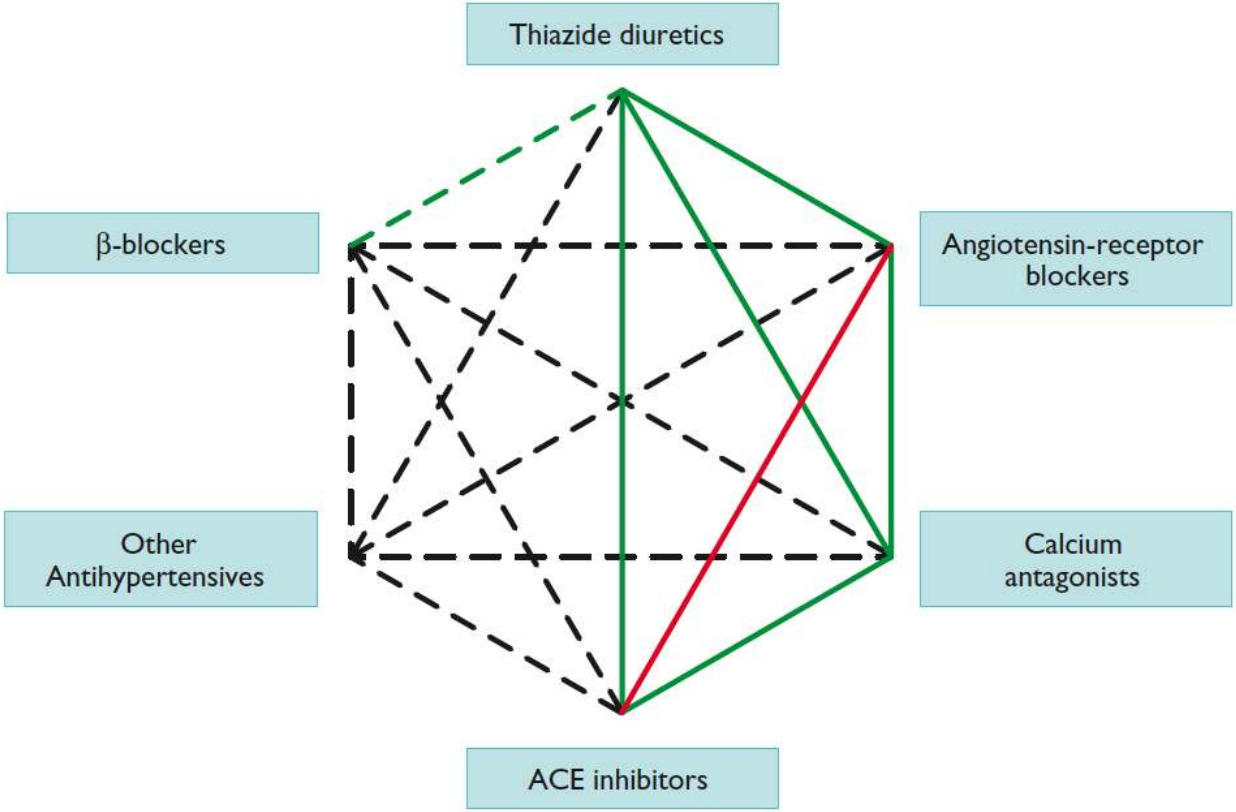
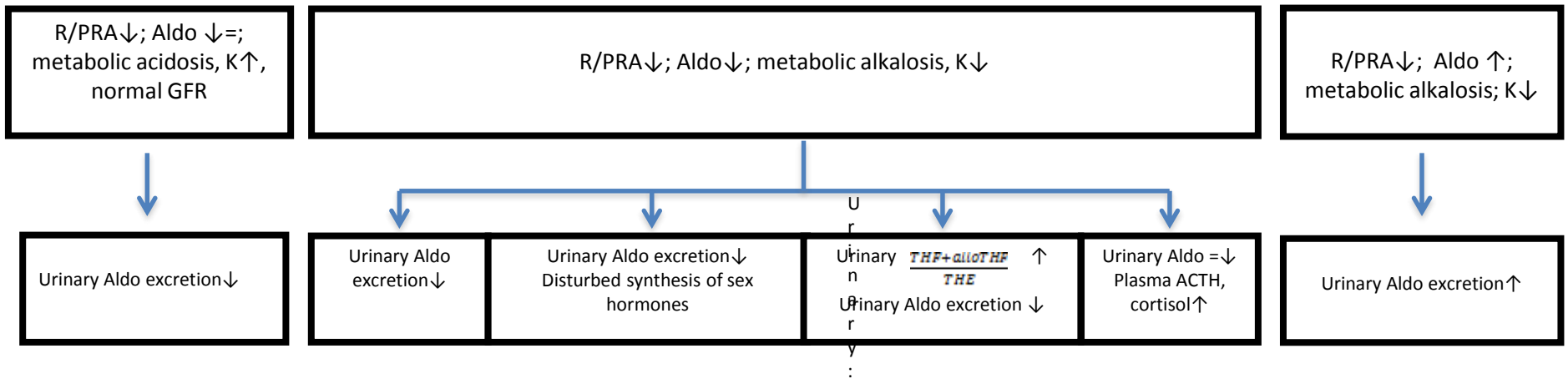

Thiazide diuretics
β-blockers
Angiotensin-receptor blockers
Other Antihypertensives
Calcium antagonists
ACE inhibitors

Figure 11.10.1.



Pseudohypoaldosteronism type II (Gordon syndrome) (AD)

Liddle s. (AD)

Activating mutation of MR receptor (AD)

Congenital adrenal hyperplasia: -11β hydroxylase deficiency (AR)

-17α hydroxylase (AR)

Apparent mineralocorticoid excess AME (AR)

Generalized glucocorticoid resistance (AD)

Familial hyperaldosteronism type 1 (glucocorticoid remediable aldosteronism - GRA) (AD)

Treatment: dexamethasone

Familial hyperaldosteronism type II

Treatment: thiazides

Treatment: amiloride triamteren

Treatment: dexamethasone

Treatment: dexamethasone triamterene, amiloride spironolactone eplerenone

Treatment: dexamethasone spironolactone eplerenone

Treatment: spironolactone eplerenone

Table

Table 2.1.1. Classification of hypertension in children and adolescents

	0-15 year	16 year and older
Category	**SBP and/or DBP Percentile**	**SBP and/or DBP values**
Normal	<90th	<130/85 mmHg
High-Normal	≥90th to <95th percentile	130-139/85-89 mmHg
Hypertension	≥95th percentile	≥140/90 mmHg
Stage 1 Hypertension	95th percentile to the 99th percentile plus 5 mmHg	140-159/90-99 mmHg
Stage 2 Hypertension	>99th percentile plus 5 mmHg	160-179/100-109 mmHg
Isolated Systolic Hypertension	SBP ≥95th percentile and DBP<90th percentile	≥140/<90 mmHg

Table 2.1.2 Blood pressure for boys by age and height percentiles

Age (years)	BP percentile	Systolic (mmHg) percentile of height							Diastolic (mmHg) percentile of height						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	90th	94	95	97	99	100	102	103	49	50	51	52	53	53	54
	95th	98	99	101	103	104	106	106	54	54	55	56	57	58	58
	99th	105	106	108	110	112	113	114	61	62	63	64	65	66	66
2	90th	97	99	100	102	104	105	106	54	55	56	57	58	58	59
	95th	101	102	104	106	108	109	110	59	59	60	61	62	63	63
	99th	109	110	111	113	115	117	117	66	67	68	69	70	71	71
3	90th	100	101	103	105	107	108	109	59	59	60	61	62	63	63
	95th	104	105	107	109	110	112	113	63	63	64	65	66	67	67
	99th	111	112	114	116	118	119	120	71	71	72	73	74	75	75
4	90th	102	103	105	107	109	110	111	62	63	64	65	66	66	67
	95th	106	107	109	111	112	114	115	66	67	68	69	70	71	71
	99th	113	114	116	118	120	121	122	74	75	76	77	78	78	79
5	90th	104	105	106	108	110	111	112	65	66	67	68	69	69	70
	95th	108	109	110	112	114	115	116	69	70	71	72	73	74	74
	99th	115	116	118	120	121	123	123	77	78	79	80	81	81	82
6	90th	105	106	108	110	111	113	113	68	68	69	70	71	72	72
	95th	109	110	112	114	115	117	117	72	72	73	74	75	76	76
	99th	116	117	119	121	123	124	125	80	80	81	82	83	84	84
7	90th	106	107	109	111	113	114	115	70	70	71	72	73	74	74
	95th	110	111	113	115	117	118	119	74	74	75	76	77	78	78
	99th	117	118	120	122	124	125	126	82	82	83	84	85	86	86
8	90th	107	109	110	112	114	115	116	71	72	72	73	74	75	76
	95th	111	112	114	116	118	119	120	75	76	77	78	79	79	80
	99th	119	120	122	123	125	127	127	83	84	85	86	87	87	88
9	90th	109	110	112	114	115	117	118	72	73	74	75	76	76	77
	95th	113	114	116	118	119	121	121	76	77	78	79	80	81	81
	99th	120	121	123	125	127	128	129	84	85	86	87	88	88	89
10	90th	111	112	114	115	117	119	119	73	73	74	75	76	77	78
	95th	115	116	117	119	121	122	123	77	78	79	80	81	81	82
	99th	122	123	125	127	128	130	130	85	86	86	88	88	89	90
11	90th	113	114	115	117	119	120	121	74	74	75	76	77	78	78
	95th	117	118	119	121	123	124	125	78	78	79	80	81	82	82
	99th	124	125	127	129	130	132	132	86	86	87	88	89	90	90
12	90th	115	116	118	120	121	123	123	74	75	75	76	77	78	79
	95th	119	120	122	123	125	127	127	78	79	80	81	82	82	83
	99th	126	127	129	131	133	134	135	86	87	88	89	90	90	91
13	90th	117	118	120	122	124	125	126	75	75	76	77	78	79	79
	95th	121	122	124	126	128	129	130	79	79	80	81	82	83	83
	99th	128	130	131	133	135	136	137	87	87	88	89	90	91	91
14	90th	120	121	123	125	126	128	128	75	76	77	78	79	79	80

	95th	124	125	127	128	130	132	132	80	80	81	82	83	84	84
	99th	131	132	134	136	138	139	140	87	88	89	90	91	92	92
15	90th	122	124	125	127	129	130	131	76	77	78	79	80	80	81
	95th	126	127	129	131	133	134	135	81	81	82	83	84	85	85
	99th	134	135	136	138	140	142	142	88	89	90	91	92	93	93
16	90th	125	126	128	130	131	133	134	78	78	79	80	81	82	82
	95th	129	130	132	134	135	137	137	82	83	83	84	85	86	87
	99th	136	137	139	141	143	144	145	90	90	91	92	93	94	94
17	90th	127	128	130	132	134	135	136	80	80	81	82	83	84	84
	95th	131	132	134	136	138	139	140	84	85	86	87	87	88	89
	99th	139	140	141	143	145	146	147	92	93	93	94	95	96	97

BP, blood pressure. Modified from Task Force on High Blood Pressure in Children and Adolescents (7)

Shaded area corresponds to reference values of boys 16 years or older in which the reference values for adults are recommended.

Table 2.1.3. Blood pressure for girls by age and height percentiles

Age (years)	BP percentile	Systolic (mmHg) percentile of height							Diastolic (mmHg) percentile of height						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	90th	97	97	98	100	101	102	103	52	53	53	54	55	55	56
	95th	100	101	102	104	105	106	107	56	57	57	58	59	59	60
	99th	108	108	109	111	112	113	114	64	64	65	65	66	67	67
2	90th	98	99	100	101	103	104	105	57	58	58	59	60	61	61
	95th	102	103	104	105	107	108	109	61	62	62	63	64	65	65
	99th	109	110	111	112	114	115	116	69	69	70	70	71	72	72
3	90th	100	100	102	103	104	106	106	61	62	62	63	64	64	65
	95th	104	104	105	107	108	109	110	65	66	66	67	68	68	69
	99th	111	111	113	114	115	116	117	73	73	74	74	75	76	76
4	90th	101	102	103	104	106	107	108	64	64	65	66	67	67	68
	95th	105	106	107	108	110	111	112	68	68	69	70	71	71	72
	99th	112	113	114	115	117	118	119	76	76	76	77	78	79	79
5	90th	103	103	105	106	107	109	109	66	67	67	68	69	69	70
	95th	107	107	108	110	111	112	113	70	71	71	72	73	73	74
	99th	114	114	116	117	118	120	120	78	78	79	79	80	81	81
6	90th	104	105	106	108	109	110	111	68	68	69	70	70	71	72
	95th	108	109	110	111	113	114	115	72	72	73	74	74	75	76
	99th	115	116	117	119	120	121	122	80	80	80	81	82	83	83
7	90th	106	107	108	109	111	112	113	69	70	70	71	72	72	73
	95th	110	111	112	113	115	116	116	73	74	74	75	76	76	77
	99th	117	118	119	120	122	123	124	81	81	82	82	83	84	84
8	90th	108	109	110	111	113	114	114	71	71	71	72	73	74	74
	95th	112	112	114	115	116	118	118	75	75	75	76	77	78	78
	99th	119	120	121	122	123	125	125	82	82	83	83	84	85	86
9	90th	110	110	112	113	114	116	116	72	72	72	73	74	75	75
	95th	114	114	115	117	118	119	120	76	76	76	77	78	79	79
	99th	121	121	123	124	125	127	127	83	83	84	84	85	86	87
10	90th	112	112	114	115	116	118	118	73	73	73	74	75	76	76
	95th	116	116	117	119	120	121	122	77	77	77	78	79	80	80
	99th	123	123	125	126	127	129	129	84	84	85	86	86	87	88
11	90th	114	114	116	117	118	119	120	74	74	74	75	76	77	77
	95th	118	118	119	121	122	123	124	78	78	78	79	80	81	81
	99th	125	125	126	128	129	130	131	85	85	86	87	87	88	89
12	90th	116	116	117	119	120	121	122	75	75	75	76	77	78	78
	95th	119	120	121	123	124	125	126	79	79	79	80	81	82	82
	99th	127	127	128	130	131	132	133	86	86	87	88	88	89	90
13	90th	117	118	119	121	122	123	124	76	76	76	77	78	79	79
	95th	121	122	123	124	126	127	128	80	80	80	81	82	83	83
	99th	128	129	130	132	133	134	135	87	87	88	89	89	90	91
14	90th	119	120	121	122	124	125	125	77	77	77	78	79	80	80

	95th	123	123	125	126	127	129	129	81	81	81	82	83	84	84
	99th	130	131	132	133	135	136	136	88	88	89	90	90	91	92
15	90th	120	121	122	123	125	126	127	78	78	78	79	80	81	81
	95th	124	125	126	127	129	130	131	82	82	82	83	84	85	85
	99th	131	132	133	134	136	137	138	89	89	90	91	91	92	93
16	90th	121	122	123	124	126	127	128	78	78	79	80	81	81	82
	95th	125	126	127	128	130	131	132	82	82	83	84	85	85	86
	99th	132	133	134	135	137	138	139	90	90	90	91	92	93	93
17	90th	122	122	123	125	126	127	128	78	79	79	80	81	81	82
	95th	125	126	127	129	130	131	132	82	83	83	84	85	85	86
	99th	133	133	134	136	137	138	139	90	90	91	91	92	93	93

BP, blood pressure. Modified from Task Force on High Blood Pressure in Children and Adolescents (7)

Shaded area corresponds to reference values of boys 16 years or older in which the reference values for adults are recommended.

Table 3.1.1. European studies of hypertension prevalence in children and adolescents

Study	Subjects, n	Origin	Age range and/or mean age (yrs)	Methods	Readings, n	Prevalence
Chiolero et al. (31)	5207	Region of Switzerland	12.3	Oscillometric	3 visits to confirm high BP	2.2%
Katona et al. (32)	10,194	Debrecen, Hungary	15-18, 16.6	Oscillometric	3 visits to confirm high BP	2.5%
Ostrowska-Nawarycz et al. (33)	25,309	Tódź, Poland	7-18	Auscultatory method	Separate visits to confirm high BP	4.9%
Akgun et al. (34)	1963	Van, Turkey	7-16	N/A	Single visit	9%
Maldonado et al. (36)	5381	Portugal	4-18, 12.5	Oscillometric	Single visit	13%
Flechtner-Mors et al. (41)	57,915 (overweight or obese)	188 centers from Germany, Austria, and Switzerland	6-18	Oscillometric or auscultatory method	Median BP of 6 weeks	22%

Table 4.1.2.1. Systolic and diastolic ambulatory blood pressure (systolic/diastolic) values for age (Boys)

Boys												
Age	**24-hr**				**Day**				**Night**			
(yr)	**50th**	**75th**	**90th**	**95th**	**50th**	**75th**	**90th**	**95th**	**50th**	**75th**	**90th**	**95th**
5	105/65	109/69	113/72	116/74	111/72	116/76	120/79	123/81	95/55	99/59	103/62	106/65
6	106/66	110/69	115/73	118/75	112/72	116/76	121/79	124/81	96/55	100/59	105/63	108/66
7	106/66	111/70	116/73	119/75	112/73	117/76	122/80	125/82	96/56	101/60	106/64	110/67
8	107/66	112/70	117/73	120/75	112/73	117/76	122/80	125/82	97/56	102/60	108/64	111/67
9	108/67	113/70	118/73	121/75	113/72	118/76	123/80	126/82	97/56	103/60	109/64	112/67
10	109/67	114/70	119/73	123/75	113/72	119/76	124/80	127/82	98/56	104/60	110/64	113/67
11	110/67	116/71	121/74	12576	115/72	121/76	126/80	129/82	99/56	105/60	111/64	115/67

12	113/67	118/71	124/74	127/76	117/72	123/76	128/80	132/82	101/56	107/60	113/64	116/67
13	115/67	121/71	126/74	130/76	120/72	126/76	131/80	135/82	103/56	109/60	115/64	119/67
14	118/68	124/71	129/75	133/77	122/73	129/77	134/80	138/82	106/57	112/61	118/64	121/67
15	121/68	127/72	132/75	136/77	125/73	132/77	137/81	141/83	108/57	114/61	120/64	123/66
16	123/69	129/72	135/76	138/78	128/74	135/78	140/81	144/84	111/57	117/61	123/64	126/66

The values are in mmHg. Data from (183)

Table 4.1.2.2. Systolic and diastolic ambulatory blood pressure (systolic/diastolic) values for age (Girls)

Girls												
Age	**24-hr**				**Day**				**Night**			
(yr)	**50th**	**75th**	**90th**	**95th**	**50th**	**75th**	**90th**	**95th**	**50th**	**75th**	**90th**	**95th**
5	103/66	108/69	112/72	115/74	108/73	114/77	118/80	121/82	95/56	100/61	105/66	108/69
6	104/66	109/69	114/72	116/74	110/73	115/77	120/80	122/82	96/56	101/61	106/65	110/68
7	105/66	110/69	115/72	118/74	111/72	116/77	121/80	123/82	96/56	102/60	107/65	111/67
8	107/66	112/69	116/72	119/74	112/72	117/76	122/80	124/82	97/55	103/60	108/64	112/67
9	108/66	113/70	117/73	120/74	112/72	118/76	122/80	125/82	98/55	103/59	109/64	112/67
10	109/66	114/70	118/73	121/75	113/72	119/76	123/79	126/81	98/55	104/59	110/64	113/67
11	110/66	115/70	119/73	122/75	114/72	120/76	124/79	127/81	99/54	105/59	110/63	114/66

12	111/67	116/70	120/74	123/76	115/72	121/76	125/80	128/82	100/54	105/59	110/63	114/66
13	112/67	117/71	121/74	124/76	116/72	122/77	126/80	129/82	101/54	106/59	111/63	114/66
14	113/67	118/71	122/74	125/76	118/73	123/77	127/80	130/82	101/55	106/59	111/63	114/65
15	114/68	118/71	123/75	125/77	119/73	124/77	128/80	130/82	102/55	107/59	111/63	114/65
16	115/68	119/71	123/75	126/77	120/74	124/77	129/80	131/82	103/55	107/59	111/63	114/65

The values are in mmHg. Data from (183)

Table 4.12.3. Systolic and diastolic ambulatory blood pressure (systolic/diastolic) values for height (Boys)

	Boys											
Height	**24-hr**				**Day**				**Night**			
(cm)	**50th**	**75th**	**90th**	**95th**	**50th**	**75th**	**90th**	**95th**	**50th**	**75th**	**90th**	**95th**
120	105/66	109/70	114/74	117/77	111/72	116/77	122/80	125/82	94/54	99/58	103/61	106/63
125	105/66	110/70	115/74	118/77	111/72	117/76	122/80	125/82	95/55	100/58	105/61	108/63
130	106/66	111/70	116/74	119/77	112/72	117/76	122/80	126/82	96/55	101/59	106/62	110/64
135	107/66	112/70	117/74	120/77	112/72	117/76	123/80	126/82	97/56	102/59	108/63	111/65
140	108/67	113/71	118/75	121/77	113/72	118/76	123/80	126/82	98/56	104/60	109/63	113/65

145	110/67	115/71	120/75	123/77	114/72	119/76	124/79	127/81	99/56	105/60	111/64	114/66
150	111/67	116/71	121/75	124/77	115/72	120/76	125/79	128/81	100/56	106/60	112/64	116/66
155	113/67	118/71	123/75	126/77	117/72	122/76	127/79	130/81	101/56	107/60	113/64	117/66
160	114/67	120/71	124/75	127/77	119/72	124/76	129/79	133/81	103/56	108/60	114/64	118/66
165	116/68	121/71	126/75	129/78	121/72	126/76	132/80	135/82	104/57	110/60	116/64	119/66
170	118/68	123/72	128/75	131/78	123/73	128/77	134/80	138/82	106/57	112/61	117/64	121/66
175	120/68	125/72	130/75	133/78	124/73	130/77	136/81	140/83	107/57	113/61	119/64	122/66
180	122/68	127/72	131/76	134/78	126/73	132/77	138/81	142/83	109/57	115/61	120/64	124/66
185	123/68	128/72	133/76	136/78	128/73	134/78	140/81	144/84	110/57	116/61	122/64	125/66

The values are in mmHg. Data from (183)

Table 4.1.2.4. Systolic and diastolic ambulatory blood pressure (systolic/diastolic) values for height (Girls)

Girls												
Height	**24-hr**				**Day**				**Night**			
(cm)	**50th**	**75th**	**90th**	**95th**	**50th**	**75th**	**90th**	**95th**	**50th**	**75th**	**90th**	**95th**
120	104/66	108/69	112/71	114/72	110/73	114/77	118/80	120/82	95/55	99/60	103/63	106/65
125	105/66	109/69	113/71	116/73	111/73	115/77	119/80	121/82	96/55	100/60	104/63	107/66
130	106/66	110/69	114/72	117/73	111/72	116/76	120/80	122/82	96/55	101/59	106/63	108/66
135	107/66	111/70	115/72	118/74	112/72	116/76	120/80	123/82	97/55	102/59	107/63	109/66
140	108/66	112/70	116/73	119/75	112/72	117/76	121/80	124/82	98/55	103/59	108/63	110/66
145	109/66	113/70	117/73	120/75	113/72	118/76	123/80	125/82	98/54	103/59	109/63	112/66

150	110/67	115/70	119/74	121/76	114/72	119/76	124/80	127/82	99/54	104/59	110/63	113/66
155	111/67	116/71	120/74	123/76	116/72	121/76	125/80	128/82	100/54	106/59	111/63	114/66
160	112/67	117/71	121/74	123/76	117/72	122/76	126/80	129/82	101/55	106/59	111/63	114/66
165	114/67	118/71	122/74	124/76	118/73	123/77	127/80	130/82	102/55	107/59	112/63	114/66
170	115/68	119/71	123/74	125/76	120/74	124/77	128/80	131/82	103/55	108/61	112/67	115/71
175	116/69	120/72	124/75	126/76	121/75	125/78	129/81	131/82	105/55	109/59	113/63	115/66

The values are in mmHg. Data from (183)

4.1.3.1.Systolic and diastolic home blood pressure values (systolic/diastolic)

	Percentiles for boys (n=347)		Percentiles for girls (n=420)	
Height (cm)	50th	95th	50th	95th
120 – 129	105/64	119/76	101/64	119/74
130 – 139	108/64	121/77	103/64	120/76
140 – 149	110/65	125/77	105/65	122/77
150 – 159	112/65	126/78	108/66	123/77
160 – 169	115/65	128/78	110/66	124/78
170 – 179	117/66	132/78	112/66	125/79
180 – 189	121/67	134/79	114/67	128/80

The values are in mmHg. Data from (64)

Table 4.2.1. Family and clinical history

Family History

- Hypertension
- Diabetes
- Dyslipidemia
- Cardiovascular disease
- Hereditary renal disease (Polycystic kidney disease, Alport syndrome)
- Hereditary endocrine disease (Adrenal tumors, glucocorticoid-remediable aldosteronism, multiple endocrine neoplasia type 2, monogenic syndromes of hypertension)
- Syndromes associated with hypertension (Neurofibromatosis)

Clinical History

1. History or symptoms of secondary hypertension

    a) Perinatal history: oligohydramnios, anoxia, umbilical artery catheterization, renal artery/vein thrombosis

    b) Underlying or concurrent diseases:

    - Renal or urologic disease, trauma, recurrent urinary tract infections, edema, weight loss, failure to thrive, thirst/polyuria, nocturia, hematuria
    - Cardiac, endocrine, or neurological disease, cold extremities, intermittent claudication, palpitations, sweating, fever, pallor, flushing, muscle weakness, crumbs, virilization, primary amenorrhea, male pseudo- hermaphroditism, skin abnormalities
    - Systemic disease (lupus erythematosus)

    c) Drug/substance intake: steroids, calcineurin inhibitors, tricyclic anti-depressants, decongestants, oral contraceptives, amphetamines, cocaine

2. History or symptoms of target organ damage

- Headache, epistaxis, vertigo, visual impairment, facial palsy, seizures, strokes, low school performance, dyspnea, chest pain, palpitations, syncope

3. Risk factors

- Diabetes mellitus
- Dyslipidemia
- Obesity, growth patterns

- Physical exercise, dietary habits
- Smoking, alcohol
- Birth weight, gestational age
- Snoring, sleep apnea history

4. Hypertension onset and management

- Age at presentation
- Previous BP measurements
- Past and current treatment
- Compliance-adverse effects

Table 4.4.1. Physical examination

Organ system / finding	Causative factor for hypertension	Sequelae of hypertension
General	Poor growth, pallor; CKD Oedema Obesity Cushingoid features Features of Turner, William, Marfan, Klippel-Trenaunay-Weber, Feuerstein-Mims, von Hippel-Lindau, multiple endocrine neoplasia syndromes	
Skin	Rash; SLE, vasculitis Neurofibromas, axillary freckling Acanthosis nigricans Pseudoxanthoma elasticum Congenital adrenal hyperplasia	
Eye	Cataract; corticosteroids Haemangioblastoma; von Hippel-Lindau Proptosis; hyperthyroidism	Hypertensive retinopathy
Abdomen	Mass; Wilms tumour, neuroblastoma, phaeochromocytoma, recessive or dominant polycystic kidney disease, multicystic dysplastic kidney, obstructive uropathy, acute renal venous thrombosis Hepatosplenomegaly; recessive polycystic kidney disease	
Neurological		Cranial nerve palsy (particularly IIIrd and VIth cranial nerves) Hemiparesis / other evidence of stroke
Cardiovascular	Cardiac murmur (coarctation, aortic stenosis) Bruit over flanks (renal artery), abdomen, back, neck, head Weak femoral pulses, interscapular bruit (coarctation, mid-aortic syndrome) Tachycardia (phaeochromocytoma)	Left ventricular enlargement Left ventricular failure
Genitalia	Virilisation (congenital adrenal hyperplasia)	

CKD (Chronic kidney disease); (SLE) Systemic lupus erythematosus

Table 4.5.1. Laboratory investigation and imaging studies

Laboratory tests	Comments
Routine laboratory tests to be performed in all children with hypertension	
Plasma creatinine, urea, electrolytes, uric acid	
Fasting plasma glucose	
Plasma cholesterol (total, HDL, LDL) and triglycerides	
Urinalysis and culture	Microscopy for red cell casts indicative of glomerular disease; white cell casts indicative of interstitial disease
Quantification of albuminuria (albumin:creatinine ratio) proteinuria (protein:creatinine ratio)	
Echocardiography	
Renal ultrasonography	
Additional laboratory tests in specific circumstances	
Plasma renin activity (PRA) and aldosterone	Renovascular hypertension (high PRA), primary hyperaldosteronism (PRA is very low in mineralocorticoid-related diseases and there may be associated hypokalaemia)
Urine and plasma catecholamines or metanephrines	Pheocromocytoma, extra-adrenal chatecolamine producing tumours
Urinary free cortisol	Cushing syndrome
Urinary steroid profiles and more complex endocrine investigations	
Plasma cortisol, ACTH, 24h urinary free cortisol	
Molecular genetic studies e.g. apparent mineralocorticoid excess*, Liddle syndrome*, glucocorticoid-remediable aldosteronism*, hypertensive forms of congenital adrenal hyperplasia (11β-hydroxylase deficiency, 17α-hydroxylase deficiency, neurofibromatosis, von Hippel-Lindau , multiple endocrine neoplasia syndromes	*Monogenic causes of hypertension (suspect where low renin hypertension and family history of early onset severe hypertension / death from cerebrovascular events and refractory hypertension)
Thyroid function tests: FT4, TSH	Thyrotoxicosis
Plasma deoxycorticosterone and corticosterone, 18-hydroxycorticosterone, 18-hydroxy deoxycorticosterone, 11 deoxycortisol	Congenital adrenal hyperplasia
Drug levels	Identify drugs that may cause hypertension e.g. amphetamines, ecstasy

(PRA) Plasma renin activity; (HDL) high density lipoprotein; (LDL) low density lipoprotein; (ACTH) adrenocorticotropic hormone; (FT4) thyroxine; (TSH) Thyroid-stimulating hormone

4.7.1. Criteria to define hypertension-induced organ damage

Left ventricular hypertrophy

Left ventricular hypertrophy should be defined as LVMI or relative wall thickness (RWT) ≥ 95th percentile by age and gender (107,108,109).

Carotid intima thickness

cIMT ≥ 95th percentile by age and gender (113,114)

Pulse wave velocity

PWV ≥ 95th percentile by age and gender (84,123,124)

Kidney

Albuminuria (as measured by urinary albumin/creatinine quotient >30mg/g creatinine or >3mg/mmol creatinine) or even proteinuria (as measured by urinary albumin/creatinine quotient (>300mg/g creatinine or >30mg/mmol creatinine) or by 24 h urinary protein excretion (>200 mg/m²/day) (1)

(LVMI) left ventricular mass index; (RWT) relative wall thickness; (cIMT) carotid intima media thickness; (PWV) Pulse wave velocity

Table 7.2.1. Blood pressure goal in hypertensive children (for office, home and 24-hour ambulatory blood pressure measurements).

General hypertensive population[a]	
Blood pressure goal	< 95th pct is recommended < 90th pct should be considered
Diabetes type 1 and type 2[b]	
Blood pressure goal	< 90th pct is recommended < 75th pct is recommended in children with non-proteinuric CKD < 50th pct is recommended in children with proteinuric CKD
Children with CKD[c]	
Blood pressure goal	< 75th pct is recommended in children with non-proteinuric CKD < 50th pct is recommended in children with proteinuric CKD

[a] In subjects aged 16 year or older, the adult cut-off values for office BP are used, 140/90 mmHg;

[b] In subjects aged 16 year or older, the adult cut-off values for office BP are used, 130/80 mmHg or 125/75 mmHg with proteinuric CKD;

[c] In subjects aged 16 year or older, the adult cut-off values for office BP are used, 130/80 mmHg or 125/75 mmHg with proteinuric CKD

(CKD) Chronic kidney disease

Table 8.2.1. Antihypertensive medications for use in children and young adults

Class of drug	Drug	Recommended starting dose (per day)	Maximal dose (per day)	Dosing interval
Diuretics	Amiloride	0.4-0.6mg/kg	20mg	Daily
	Chlortalidone	0.3mg/kg	2mg/kg up to 50mg	Daily
	Furosemide	0.5-2mg/kg	6mg/kg	Daily – Twice daily
	Hydrochlorothiazide	0.5-1mg/kg	3mg/kg/day	Daily
	Spironolactone	1mg/kg	3.3mg/kg up to 100mg	Daily – Twice daily
	Eplerenone	25mg	100mg	Daily – Twice daily
	Triamterene	1-2mg/kg	3-4mg/kg up to 300mg	Twice daily
Beta blockers	Atenolol	0.5-1mg/kg	2mg/kg up to 100mg	Daily – Twice daily
	Metoprolol	0.5-1mg/kg	2mg/kg	Daily – Twice daily
	Propranolol	1mg/kg	4mg/kg up to 640mg	Twice-Three times daily
Calcium channel blockers	Amlodipine	0.06-0.3mg/kg	5-10mg	Daily
	Felodipine	2.5mg	10mg	Daily
	Nifedipine (extended release form)	0.25-0.5mg/kg	3mg/kg up to 120mg	Daily – Twice daily
ACE inhibitors	Benazepril	0.2mg/kg up to 10mg	0.6mg/kg up to 40mg	Daily
	Captopril	0.3-0.5mg/kg PER DOSE	6mg/kg	Twice – Three times daily
	Enalapril	0.08-0.6mg/kg		Daily
	Fosinopril	0.1-0.6mg/kg	40mg	Daily
	Lisinopril	0.08-0.6mg/kg	0.6mg/kg up to 40mg	Daily
	Ramipril	1.5-6mg/		Daily
ARBs	Candesartan	0.16-0.5mg/kg		Daily
	Irbesartan	75-150mg	300mg	Daily
	Losartan	0.7mg/kg up to 50mg	1.4mg/kg up to 100mg	Daily– Twice daily
	Valsartan	0.4mg/kg	40-80mg	Daily
Alpha and beta blocker	Labetolol	1-3mg/kg	10-12mg/kg up to 1200mg	Twice daily
Central alpha-agonist	Clonidine	0.2mg/kg	2.4mg	Twice daily
Peripheral alpha-blockers	Doxazosin	1mg	4mg	Daily
	Prazosin	0.05-0.1mg/kg	0.5mg/kg	Three times daily
Vasodilators	Hydralazine	0.75mg/kg	7.5mg/kg up to 200mg	Four times daily
	Minoxidil	0.2mg/kg	50-100mg/day	Daily to three times daily

Table 8.2.2. Clinical conditions for which specific antihypertensive drug classes are recommended or contraindicated

Antihypertensive class	Recommended	Contraindicated
Diuretics potassium-sparing	Hyperaldosteronism	Chronic renal failure (*) Competitive athletes
Thiazide and thiazide-like diuretics	Chronic renal failure Corticosteroid-induced HTN	Competitive athletes Diabetes
Diuretics Loop-acting	Congestive heart failure	
Beta-adrenergic blockers	Coarctation of aorta Congestive heart failure Migraine	Bronchial asthma (*) Diabetes Competitive athletes Psoriasis
Calcium channel blockers	Posttransplantation Migraine Coarctation of aorta	Congestive heart failure
Angiotensin-converting enzyme inhibitors	Chronic kidney disease Diabetes mellitus Microalbuminuria Congestive heart failure Obesity-linked primary HTN	Bilateral renal artery stenosis (*) Renal artery stenosis in solitary kidney (*) Hyperkalemia (*) Pregnancy (*) Females of child-bearing potential should use reliable contraception
Angiotensin-receptor blockers	Chronic kidney disease Diabetes mellitus Microalbuminuria Congestive heart failure Obesity-linked primary HTN	Bilateral renal artery stenosis (*) Renal artery stenosis in solitary kidney (*) Hyperkalemia (*) Pregnancy (*)
Intravenous vasodilators	Life-threatening conditions	

(*) absolute contraindication

Table 8.2.3. Presenting features and appropriate therapies for monogenic hypertension

Disorder	Inheritance	Gene	Presentation	Potassium	Renin	Aldosterone	Treatment
Apparent mineralocorticoid excess	AR	*HSD11b2*	All ages	Low/N	Low	Low	Spironolactone, eplerenone, amiloride
Glucocorticoid remediable aldosteronism	AD	*CYP11B2/ CYP11B1*	Infant / Child	Low/N	Low	Low/N	Amiloride, triamterene, dexamethasone
Congenital adrenal hyperplasia	AR	*CYP21A2* *CYP11B1*	Infant	Low/N	Low	Low	Spironolactone, eplerenone dexamethasone
Liddle syndrome	AD	*SCNN1B, SCNN1G*	Child/Adult	Low/N	Low	Low	Amiloride. triamterene
Gordon syndrome	AD	*KLHL3, CUL3, WNK1, WNK4*	Adult/Child	High/N	Low	High/N	Thiazide

AR, autosomal recessive; *AD,* autosomal dominant

HSD11b2, 11b hydroxysteroid dehydrogenase type 2 enzyme (11beta-HSD2) gene

CYP11B1, Steroid 11β-hydroxylase deficiency (11β-OHD) gene

CYP11B2, Aldosterone synthase gene

*CYP21A*2, Steroid 20β-hydroxylase deficiency (11β-OHD) gene

SCNN1G and SCNN1B, Subunits of ENaC genes

KLHL3, Kelch-like 3 gene

CUL3, Cullin3 gene

WNK1 or 4, With-no-lysine kinase 1 and 4

Table 9.6.1. Antihypertensive drugs for hypertensive emergencies and urgencies

Drug	Class	Route	Dose	Onset of action	Comment
Sodium nitroprusside	Direct vasodilator	Intravenous infusion	0.5-8 µg/kg per min	Within seconds	May cause thiocyanate toxicity, inactivated by light
Nitroglycerine	Direct vasodilator	Intravenous infusion	0.1-2 µg/kg per min	1-2 minutes	May cause methemoglobinemiia vasodilating effect primarily on the venous side – efficient in heart failure, limited efficacy in children
Labetalol	Alpha and beta blocker	Intravenous infusion	0.25-3 mg/kg per hour	5-10 min.	Contraindication in asthma, heart failure, may cause bradycardia
Nicardipine	Calcium channel blocker	Intravenous infusion	1-3 µg/kg per min	Within minutes	Reflex tachycardia
Clonidine	Central alpha-agonist	Intravenous bolus	2-6 µg/kg per dosis	10 min.	Dry mouth, sedation, rebound hypertension
Esmolol	Beta-blocker	Intravenous infusion	100-500 µg/kg/min	within seconds	Contraindication in asthma, may cause bradycardia
Enalaprilat	ACEI	Intravenous bolus	0.005-0.01 mg/kg per dosis	15 min.	Contraindication in suspected bilateral renal artery stenosis
Furosemide	Loop diuretic	Intravenous bolus	0.5-5 mg/kg per dosis	within minutes	Hypokalemia. Useful in volume hypertension
Urapidil	Peripheral alpha blocker and centra agonist of 5-HT_{1A} receptors	Intravenous infusion	initial dose: 0.5-4.0 mg/kg per hour maintenance dose: 0.2-2.0 mg/kg per hour	1-5 minutes	May cause sedation, palpitation, nausea
Nifedipine	Calcium channel blocker	Orally	0.25 mg/kg per dosis	20-30 min.	May cause unpredictable hypotension, reflex tachycardia
Isradipine	Calcium channel blocker (L-type)	Orally	0.05-0.1 mg/kg per dosis	1 hour	higher doses may cause BP drop of >25%
Captopril	ACEI	Orally	0.1-0.2 mg/kg per dosis	10-20 min.	Contraindication in suspected bilateral renal artery stenosis
Minoxidil	Direct vasodilator	Orally	0.1-0.2 mg/kg per dosis	5-10 min.	Fluid retention

Table 11.9.1. Drug-induced hypertension

Drug/substance	Mechanism of action	Treatment
Glicocorticoids	Sodium retention, RAAS activation, sympathetic system activation	Decrease dose if possible, diuretics, ACEi/ARB, DCCB
Cyclosporine	Arteriolar constriction, sodium retention	DCCB, ACEi/ARB; switch to tacrolimus
Tacrolimus	Less potent hypertensive effect than Cyclosporine	DCCB
Liquorice	Mineralocorticoid effect caused by inhibition of 11beta dehydrogenase isoform 2	Avoid; mineralocortiocid receptor antagonists
Non-steroidal antinflammatory drugs; cyclloxigenase 2 inhibitors	Sodium retention (indomethacin is most potent)	Sodium restriction, diuretics, DCCB
Antidepressants and antipsychotics (velafaxine, desvenlafaxine, tricyclic antidepressants, clozapine)	Inhibition of serotonin and norepinephrine reuptake	
Monoamine oxidase inhibitors	Sympathomimetic effect	Avoidance of tyramine-rich foods; chlorpromazine
Oral contraceptives containing estrogens and progesterone	Mineralocorticoid effect , increased synheosis of angiotensinogen	Diuretics, ACEi/ARB
Androgens	Mechanism not know. Probable mineralocorticoid effect.	Diuretics, ACEi/ARB, DCCB
Phenylephrine hydrochloride (used as upper respiratory tract decongestant and as opthalmic drops in neonates/infants)	Sympathomimetic effect	Beta and alpha-adrenolytics
Pseudoephedrine hydrochloride	Sympathomimetic effect	Alpha-adrenolytics
Ketamine hydrochloride	Sympathomimetic effect	alpha-adrenolytics, DCCB; propohol attenuates sympathomimetic effect
Methylphenidate, amphetamine	Sympathomimetic effects	Not known – beta and alpha-adrenolytics proposed
Anti-VEGF pathway drugs	Increase of peripheral vascular resistance	DCCB, ACEi/ARB
Erythropoetin/erythtropoesis stimulating agents	Increase of peripheral vascular resistance	DCCB, lower hemoglobin target
Caffeine	Sympathomimethic effects	Beta-adrenolytics
Cocaine, amphetamine, modafenil	Sympathomimetic effect	Benzodiazepines; avoid beta-adrenolytics
Ephedra alkaloids, synephrine, octopamine	Sympathomimetic effect	Avoid

(ACEi) Angiotensine converting enzyme inhibitors; (ARB) Angiotensine II receptor blocker; (DCCB) dihydropyridine calcium channel blockers; VEGF vascular endothelial growth factor; RAAS, renin-angiotensin-aldosterone system

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