Management of high blood pressure in children and adolescents: recommendations of the European Society of Hypertension

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Hypertension in children and adolescents has gained ground in cardiovascular medicine, thanks to the progress made in several areas of pathophysiological and clinical research. These guidelines represent a consensus among specialists involved in the detection and control of high blood pressure in children and adolescents. The guidelines synthesize a considerable amount of scientific data and clinical experience and represent best clinical wisdom upon which physicians, nurses and families should base their decisions. 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. *J Hypertens* 27:1719–1742 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Abbreviations: AAP, american Academy of Pediatrics; ABPM, ambulatory blood pressure measurement; ACE, angiotensin-converting enzyme; ACEI, angiotensin-converting enzyme inhibitor; alloTHF, allotetrahydrocortisol; ARB, angiotensin receptor blocker; b.i.d., twice daily; BP, blood pressure; CKD, chronic kidney disease; CO_2, CO_2 angiography; CT, computed tomography; CTA, CT angiography; DSA, digital subtraction angiography; EMEA, European Medicines Agency; ER, extended release; ESC, European Society of Cardiology; ESCAPE, Effect of Strict Blood Pressure Control and ACE Inhibition on Progression of Chronic Renal Failure in Pediatric Patients; ESH, The European Society of Hypertension; EU, European Union; FDA, Food and Drug Administration; GFR, glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; IGT, impaired glucose tolerance; IMT, intima-media thickening; LDL-C, low-density lipoprotein cholesterol; LVH, left ventricular hypertrophy; LVM, left ventricular mass; MRA, MR angiography; ONTARGET, Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial; OSA, obstructive sleep apnea; PRA, plasma renin activity; PUMA, Paediatric Use Marketing Authorization; q.d., once daily; SDB, sleep-disordered breathing; t.i.d., three times daily; TH18oxoF, 18-oxo-tetrahydrocortisol; THAD, tetrahydroaldosterone; THE, tetrahydrocortisone; THF, tetrahydrocortisol; UAE, Urinary albumin excretion

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Introduction and purpose

The European Society of Hypertension (ESH) and European Society of Cardiology (ESC) guidelines on the management of arterial hypertension, first published in 2003 [1] and subsequently updated in 2007 [2], regrettably did not contain any section devoted to hypertension in childhood and adolescence. This was not due to lack of awareness of the importance of this problem. Indeed, there is growing evidence that children and adolescents with mild blood pressure (BP) elevations are much more common than it was thought in the past. Longitudinal studies have now made it clear that BP abnormalities in those age ranges do not infrequently translate into adult hypertension, thereby emphasizing the importance of the tracking phenomenon not just epidemiologically but also clinically. Furthermore, hypertension in children and adolescents has gained ground in cardiovascular medicine, thanks to the progress made in several areas of pathophysiological and clinical research. For example, it has been possible to look at BP values of children and adolescents not just in the artificial environment of the physician's office but in the more meaningful context of

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daily life conditions. It has also become possible to look at the presence of subclinical organ damage through measures and markers much more sensitive than those available years ago, with the opportunity of detecting incipient modifications of organ function and structure previously impossible to discover, thus gaining a more precise assessment of the clinical significance of the existing BP abnormalities. It has lastly been possible to relate adult hypertension and organ damage to several abnormalities of the younger age, for example overweight and tachycardia, thus adding to the rationale of extending at least some of the cardiovascular prevention strategies previously derived for adults to pre-adult individuals.

However, there are at least two reasons justifying omission of children's hypertension in previous guidelines. The first is that clinical cares of children and adolescent, on one side, and of adults, on the other side, are entrusted to different sets of physician, and therefore a task force charged to formulate recommendations for high BP in children should have been opened to the fundamental contributions of experts in this area, what has been done for the preparation of the present document specifically related to pediatric hypertension.

The second, but not minor, reason is the different nature of data and arguments on which recommendations for high BP in adults and, respectively, children are based. In adults, most of the recommendations of guidelines can be on evidence provided by observational and interventional trials, although admittedly some are only based on wisdom or experts' opinion [2,3]. For instance, the definition of hypertension in adults is founded on observational data in more than 1 million people showing a continuous relation between increasing SBP and DBP values with cardiovascular events such as stroke and myocardial infarction [4]; arbitrary cutoffs subdividing normotension from hypertension, and different grades of hypertension are indicated (although with various weights of evidence) by the results of intervention trials; and, finally, intervention trials on more than 250 000 patients provide comparative information on the effects of BP lowering *per se* and with different agents.

Nothing of the like is available in children and adolescents. The remoteness of incident cardiovascular events from BP values many years beforehand makes the relationship of BP values with events hardly feasible. Large intervention studies are lacking and, therefore, cannot provide hints about cutoffs for evidence-based recommendations about initiation of treatment and goal BP values, or the preferential use of one or other classes of drugs in various conditions. Many of the classifications and recommendations in children are based on statistical considerations, and result from assumptions rather than the results of experiments or from extrapolations from evidence obtained in adults. Despite the fact that guidelines on pediatric hypertension is only based on wisdom, it would be unethical to neglect giving due attention to this medically and socially important problem. Accompanying recommendations with the awareness that a lot of information is still missing may help devising observational and interventional studies filling some of the existing gaps of knowledge. This is not the least aim of the present guidelines, and a special section at the end of this document is devoted to the planning of future studies.

Definition and classification of hypertension

The incorporation of BP measurement into routine pediatric healthcare and the publication of norms for BP in children [5–7] has not only enabled detection of significant asymptomatic hypertension secondary to a previously undetected disorder, but it has also confirmed that mild elevations in BP during childhood are more common than was previously recognized, particularly in adolescents.

The roots of hypertension in adulthood extend back to childhood. Indeed, childhood BP has been shown to track into adulthood. That is to say, children with elevated BP are more likely to become hypertensive adults [8–12], an observation emphasizing the importance of BP control in children and adolescents. Importantly, both the use of repeated measurements (aiming at the reduction of measurement error) in the identification of those children with elevated BP [8], as well as the assessment of comorbidities (in particular, obesity) and family history of cardiovascular disease [12], critically improve accuracy of the prediction of hypertension later in life [13].

As mentioned in the introduction, one limit to the attempt to create recommendations is that there are no prospective studies with sufficiently long follow-up to directly link childhood BP levels to the occurrence of cardiovascular disease or mortality. Therefore, surrogate markers of hypertensive end-organ damage (heart, blood vessels and kidney) have been used instead, although the body of available data is substantially smaller than in adults [14,15]. Left ventricular hypertrophy (LVH) [16,17], thickening and stiffening of large arteries [18–22] and urinary albumin excretion (UAE) [23] are among the most valuable markers.

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.

Extensive pediatric normative data on auscultatory clinic measurements have been provided for the United States, based on more than 70 000 children [24]. BP percentiles have been calculated for each sex, age group and for seven height percentile categories (www.pediatrics.org/

cgi/content/full/114/2/S2/555). Height percentiles are based on the growth charts of the Center for Disease Control and Prevention (www.cdc.gov/growthcharts). In Europe, reference values were obtained in 1991 by pooling data from 28 043 individuals using the auscultatory method [25], but unfortunately, tables do not include age, sex and height together. However, normative values have been calculated for Italy in 1999 from auscultatory data in 11 519 school children aged 5–17 years and reported for age, sex and height [26]. Two more recent studies [27,28] provide normative data for the oscillometric method with the Dinamap model 8100, the accuracy of which has known limitations. Oscillometric data with a validated equipment have quite recently been reported from the Nord-Trondelag Health Study II [29], but these are limited to adolescents (age 13–18 years); furthermore, 95th percentile values are rather high even after exclusion of overweight and obese individuals. Validated oscillometric data have also become available from a large cohort of Hong Kong Chinese schoolchildren [30], but these can hardly be extrapolated to the European population.

In conclusion, because of the large amount of data available, the Task Force for Blood Pressure in Children [24] is still the study of reference. It should be considered, however, that the data of the US Task Force do not refer to a European population and that at all ages they are several mmHg lower than those measured by the same auscultatory method in the Italian normative study [26] and about 10 mmHg lower than the oscillometric data of the Norwegian study [29]. Further problems concerning the use of oscillometric devices versus the auscultatory method are discussed in the section entitled 'Office and clinic blood pressure'.

According to the criteria of the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents [24], criteria shared by this report, normal BP in children is defined as SBP and DBP less than 90th percentile for age, sex and height, whereas hypertension is defined as SBP and/or DBP persistently 95th percentile or more, measured on at least three separate occasions with the auscultatory method. Children with average SBP or DBP 90th percentile or more but less than 95th percentile are classified as having high-normal BP. Adolescents with BP 120/80 mmHg or more even if less than 90th percentile are also considered as having high-normal BP (Table 1). Tables 2 and 3 report the BP percentiles for boys and girls aged 1–18 years, as provided by the Fourth Report [24].

Additionally, the Fourth Report provides criteria for staging the severity of hypertension in children and adolescents, which can then be used clinically to guide evaluation and management. Stage 1 hypertension is defined as BPs from the 95th percentile to the 99th percentile plus 5 mmHg. Stage 2 hypertension denotes any BP above the 99th percentile plus 5 mmHg. Children or adolescents with stage 2 hypertension should be evaluated and treated more quickly and/or intensively than those with a lower degree of BP elevation.

Table 1 Definition and classification of hypertension in children and adolescents

Class	SBP and/or DBP percentile
Normal	<90th
High-normal	≥90th to <95th ≥120/80 even if below 90th percentile in adolescents
Stage 1 hypertension	95th percentile to the 99th percentile plus 5 mmHg
Stage 2 hypertension	>99th percentile plus 5 mmHg

Modified from Task Force on High Blood Pressure in Children and Adolescents [24]. The term prehypertension has been changed to 'high-normal' according to the ESH/ESC guidelines 2007 [1].

Diagnostic evaluation

Blood pressure measurement

The diagnosis of hypertension should be based on multiple office BP measurements, taken on separate occasions over a period. Although office BP should be used as reference, BP values obtained out of office may improve the evaluation in untreated and treated individuals.

Office or clinic blood pressure

Office BP measurement has provided the basis for the present knowledge of the potential risk associated with hypertension [31] and has guided patient management for many years. There are certain issues in the measurement of BP that apply to both children and adults, and they have been discussed in the ESH/ESC Guidelines [1].

In children and adolescents, one aspect to be taken into consideration is whether to use auscultatory or oscillometric methods. Korotkoff sounds-based measurement has been the most frequently used to assess SBP (K1) and DBP (K4 or K5). Although initially K4 was officially accepted as the measure of DBP for children under 13 years of age, today K5 is recommended [24]. Oscillometric devices, which calculate BP from pressure oscillations detected in the arm cuff, have been introduced more recently. This method determines mean BP directly from the point of maximum oscillation. Neither SBP nor DBP is measured directly, but is calculated using an algorithm based on a putative relationship between the oscillations. Then, in cases in which the oscillation is shorter than usual, as is common in children, the potential for erroneous measurement increases [32]. If an oscillometric method is applied, the monitor should have passed the validation procedure recommended by the British Hypertension Society [33], the American Association for the Advancement of Medical Instrumentation [34] or the European Society of Hypertension International Protocol [35]. Few oscillometric devices for office, home or ambulatory BP monitoring have been

Table 2 Blood pressure for boys by age and height percentiles

		Systolic (mmHg) percentile of height							Diastolic (mmHg) percentile of height						
Age (years)	BP percentile	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 [24].

successfully validated using an established protocol. The continuously updated data available on monitor validation for children is found at www.dableducational.org. It should, however, be noticed that available reference values for defining BP classes (such as those of Tables 2 and 3) have been obtained by the auscultatory method, and that values obtained with oscillometric equipments are considerably higher [29,36,37]. Therefore, if hypertension is detected by the oscillometric methods, it must be confirmed by the auscultatory method. The recent banning of mercury devices in the European Community will undoubtedly favor the development of oscillometric devices, but it is also true that the auscultatory method can continue to be used with manometers other than the mercury one. It would be convenient, however, to start assembling reference BP data using oscillometric devices.

The specific recommendations for office BP measurement in children and adolescents are shown in Box 1 [24,38,39].

Ambulatory blood pressure

Ambulatory BP measurement (ABPM) is now increasingly recognized as being indispensable to the diagnosis

Table 3 Blood pressure for girls by age and height percentiles

		Systolic (mmHg) percentile of height							Diastolic (mmHg) percentile of height						
Age (years)	BP percentile	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 [24].

and management of hypertension [40,41], and it has contributed significantly to our understanding of hypertension by 'unmasking' BP phenomena that were not readily apparent using office BP. These have included the dipping and nondipping patterns of nocturnal BP [42], white coat [43] and masked hypertension [44].

The clinical use of 24-h ABPM depends on the use of normal BP ranges as reference values. Preliminary reference values have been obtained in some European populations [45,46]. Although the relatively small number of individuals limits the normative usefulness of the data, the information represents an important starting point for the future development of stronger normative data (Tables 4 and 5).

Recommendations for the use of 24-h ABPM are given in Box 2. Use of ABPM in clinical trials may play an even more important role in children than it does in adults [47] because of the smaller number of children who have hypertension.

Home blood pressure

Concerning home BP measurements, evidence in children and adolescents is limited. In children, home BP has

Box 1. Specific recommendations for office BP measurement in children and adolescents

- The recommended method is auscultatory
- Use K1 for systolic BP and K5 for diastolic BP
- If the oscillometric method is used, the monitor needs to be validated
- If hypertension is detected by the oscillometric method, it needs to be confirmed using the auscultatory method
- Use the appropriate cuff size according to arm width (40% of the arm circumference) and length (4×8 cm, 6×12 cm, 9×18 cm, 10×24 cm, to cover 80–100% of the individual's arm circumference).
- Children above 3 years of age who are seen in a medical setting should have their BP measured.
- In younger children, BP should be measured under special circumstances that increase the risk for hypertension: under neonatal conditions requiring intensive care, congenital heart disease, renal disease, treatment with drugs known to raise BP and evidence of elevated intracranial pressure.

superior reproducibility than office BP has and is similar to that for ABPM [48]. One study suggests that home monitoring for 3 days, with duplicate morning and evening measurements, is the minimum schedule required, though 6–7 days of monitoring is recommended [49]. Home BP in children is lower than daytime ambulatory BP, probably due to a high level of physical activity during the day [50–52]. It is likely that home BP has a slightly better correlation than does casual BP with ABPM for daytime BP, although not for night-time BP [53]. One school-based study in 778 children and adolescents has provided an initial approach to normalcy data for home BP (Table 6) [51].

White-coat (or isolated office) and masked (or isolated ambulatory) hypertensions

In adults, ambulatory and, less frequently, home BP monitorings are also used to define those patients whose BP values are in the hypertensive range in the office but not out-of-office (white-coat) or, vice versa, are in the normotensive range in the office but not out-of-office (masked) [54]. Definition of these conditions is more difficult in children and adolescents, however, because of the above-mentioned uncertainties in reference values of office and, particularly, ambulatory and home BP. Furthermore, although in adults, ambulatory and home BP values and their cutoffs for definition of hypertension are normally lower than those measured in the office, in children and adolescents, daytime ambulatory BP and often home BP are reported to be no lower and perhaps slightly higher than office BP (compare Tables 2 and 3 with Tables 4–6). This may be due to a marked level of physical activity in children or, alternatively, to the paucity and, consequently, the imprecision of the available reference values.

It is no surprise, therefore, that the reported prevalence of white-coat hypertension in various studies on children and adolescents has ranged from 1 to 44% [55–57]. Only two studies have investigated masked hypertension [56,57] and report it in approximately 10% of cases. In children as in adults, both white-coat [55,56] and masked hypertensions [57] have been found to be associated with higher left ventricular mass (LVM) than confirmed in normotensive individuals.

Diagnosis and evaluation

Several steps should be followed, from screening to confirmation, to rule out secondary causes of hypertension, if indicated. The proposed diagnostic algorithm is found in Fig. 1. Once hypertension is confirmed, organ damage evaluation should include heart, great vessels, kidney, central nervous system and retina if possible, due

Table 4 Systolic and diastolic ambulatory blood pressure (systolic/diastolic) values for clinical use

	Boys						Girls					
	Day			Night			Day			Night		
Age (years)	75th	90th	95th	75th	90th	95th	75th	90th	95th	75th	90th	95th
5	116/76	120/79	123/81	99/59	103/62	106/65	114/77	118/80	121/82	100/61	105/66	108/69
6	116/76	121/79	124/81	100/59	105/63	108/66	115/77	120/80	122/82	101/61	106/65	110/68
7	117/76	122/80	125/82	101/60	106/64	110/67	116/77	121/80	123/82	102/60	107/65	111/67
8	117/76	122/80	125/82	102/60	108/64	111/67	117/76	122/80	124/82	103/60	108/64	112/67
9	118/76	123/80	126/82	103/60	109/64	112/67	118/76	122/80	125/82	103/59	109/64	112/67
10	119/76	124/80	127/82	104/60	110/64	113/67	119/76	123/79	126/81	104/59	110/64	113/67
11	121/76	126/80	129/82	105/60	111/64	115/67	120/76	124/79	127/81	105/59	110/63	114/66
12	123/76	128/80	132/82	107/60	113/64	116/67	121/76	125/80	128/82	105/59	110/63	114/66
13	126/76	131/80	135/82	109/60	115/64	119/67	122/77	126/80	129/82	106/59	111/63	114/66
14	129/77	134/80	138/82	112/61	118/64	121/67	123/77	127/80	130/82	106/59	111/63	114/65
15	132/77	137/81	141/83	114/61	120/64	123/66	124/77	128/80	130/82	107/59	111/63	114/65
16	135/78	140/81	144/84	117/61	123/64	126/66	124/77	129/80	131/82	107/59	111/63	114/65

The values are in mmHg. Data from [46].

Table 5 Systolic and diastolic ambulatory blood pressure (systolic/diastolic) values for clinical use

	Boys						Girls					
	Day			Night			Day			Night		
Height (cm)	75th	90th	95th	75th	90th	95th	75th	90th	95th	75th	90th	95th
120	116/77	122/80	125/82	99/58	103/61	106/63	114/77	118/80	120/82	99/60	103/63	106/65
125	117/76	122/80	125/82	100/58	105/61	108/63	115/77	119/80	121/82	100/60	104/63	107/66
130	117/76	122/80	126/82	101/59	106/62	110/64	116/76	120/80	122/82	101/59	106/63	108/66
135	117/76	123/80	126/82	102/59	108/63	111/65	116/76	120/80	123/82	102/59	107/63	109/66
140	118/76	123/80	126/82	104/60	109/63	113/65	117/76	121/80	124/82	103/59	108/63	110/66
145	119/76	124/79	127/81	105/60	111/64	114/66	118/76	123/80	125/82	103/59	109/63	112/66
150	120/76	125/79	128/81	106/60	112/64	116/66	119/76	124/80	127/82	104/59	110/63	113/66
155	122/76	127/79	130/81	107/60	113/64	117/66	121/76	125/80	128/82	106/59	111/63	114/66
160	124/76	129/79	133/81	108/60	114/64	118/66	122/76	126/80	129/82	106/59	111/63	114/66
165	126/76	132/80	135/82	110/60	116/64	119/66	123/77	127/80	130/82	107/59	112/63	114/66
170	128/77	134/80	138/82	112/61	117/64	121/66	124/77	128/80	131/82	108/61	112/67	115/71
175	130/77	136/81	140/83	113/61	119/64	122/66	125/78	129/81	131/82	109/59	113/63	115/66
180	132/77	138/81	142/83	115/61	120/64	124/66	N/A	N/A	N/A	N/A	N/A	N/A
185	134/78	140/81	144/84	116/61	122/64	125/66	N/A	N/A	N/A	N/A	N/A	N/A

The values are in mmHg. N/A, not available. Data from [46].

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-induced protection. Boxes 3–5 contain the most relevant aspects of the family and clinical history, examination, laboratory and other investigations recommended at the time of evaluation of hypertension in children and adolescents [58–62].

Evaluation of target organ damage

Heart LVH remains to date the most thoroughly documented form of end-organ damage caused by hypertension in children and adolescents. LVH is known to be an independent risk factor for cardiovascular events in adults, although no such evidence is available from prospective studies in children, it appears prudent to identify LVH in children at any early time, as this may facilitate primary prevention of cardiovascular disease. Echocardiography is a tool sensitive enough to assess LVM in children. LVM is calculated using the Devereux equation [63] and should be standardized to height ($m^{2.7}$) to minimize the effect of changes in body size during childhood [64]. If LVH is

Table 6 Systolic and diastolic home blood pressure values for clinical use (systolic/diastolic)

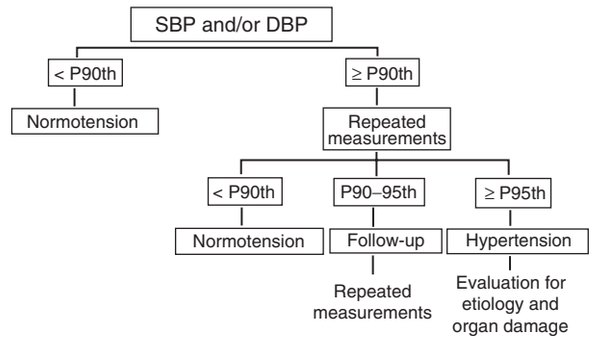
	Boys			Girls		
Height (cm)	*N*	50th	95th[a]	*N*	50th	95th[a]
120–129	23	105/64	119/76	36	101/64	119/74
130–139	51	108/64	121/77	51	103/64	120/76
140–149	39	110/65	125/77	61	105/65	122/77
150–159	41	112/65	126/78	71	108/66	123/77
160–169	45	115/65	128/78	148	110/66	124/78
170–179	91	117/66	132/78	46	112/66	125/79
180–189	57	121/67	134/79	7	114/67	128/80

Data from [51]. [a]Proposed thresholds for home hypertension.

Box 2. Recommendations for 24-h ambulatory BP monitoring

During the process of diagnosis
Confirm hypertension before starting antihypertensive drug treatment
Type 1 diabetes
Chronic kidney disease
Renal, liver or heart transplant
During antihypertensive drug treatment
Evaluation of refractory hypertension
Assessment of BP control in children with organ damage
Symptoms of hypotension
Clinical trials
Other clinical conditions
Autonomic dysfunction
Suspicion of catecholamine-secreting tumours

Fig. 1



Diagnostic algorithm of hypertension. P, percentile.

Box 3. Clinical data to record

FAMILY HISTORY
Hypertension
Cardiovascular and cerebrovascular disease
Diabetes mellitus
Dyslipidemia
Obesity
Hereditary renal disease (Policystic kidney disease)
Hereditary endocrine disease (pheochromocytoma, glucocorticoid-remediable aldosteronism, multiple endocrine neoplasia type 2, von Hippel–Lindau)
Syndromes associated with hypertension (neurofibromatosis)
CLINICAL HISTORY
Perinatal history
Birth weight, gestational age, oligohydramnios, anoxia, umbilical artery catheterization
Previous history
Hypertension
Urinary tract infection, renal or urological disease
Cardiac, endocrine (including diabetes) or neurological disease
Growth retardation
Symptoms suggestive of secondary hypertension
Dysuria, thirst/polyuria, nocturia, hematuria
Edema, weight loss, failure to thrive
Palpitations, sweating, fever, pallor, flushing
Cold extremities, intermittent claudication
Virilization, primary amenorrhea and male pseudohermaphroditism
Symptoms suggestive of target organ damage
Headache, epistaxis, vertigo, visual impairment
Facial palsy, fits, strokes
Dyspnea
Sleep history
Snoring, apnea, daytime somnolence
Risk factor history
Physical exercise, dietary habits
Smoking, alcohol
Drug intake
Anti-hypertensives
Steroids, cyclosporine, tacrolimus or other
Tricyclic anti-depressants, atypical antipsycotics, decongestants
Oral contraceptives, illegal drugs
Pregnancy

Box 4. Physical examination: data to record

Height, weight, body mass index
External features of syndromes/conditions associated with hypertension
Neurofibromatosis, Klippel–Trenaunay–Weber, Feuerstein–Mims, von Hippel–Lindau, multiple endocrine neoplasia, pseudoxanthoma elasticum, Turner, William, Marfan, Cushing, hyperthyroidism, lupus, vasculitis, congenital adrenal hyperplasia
Cardiovascular examination
Pulse and BP measurement in both arms and legs
Bruits/murmurs – heart, abdomen, flanks, back, neck, head
Signs of left ventricular hypertrophy or cardiac failure
Abdomen
Masses – Wilms, neuroblastoma, pheochromocytoma, autosomal dominant and recessive polycystic kidney disease, multicystic kidney displasia, obstructive uropathy
Hepatosplenomegaly – autosomal recessive polycystic kidney disease
Neurological examination
Fundoscopy for hypertensive changes and retinal amartoma (von Hippel–Lindau)
Evidence of VIII nerve palsy
Other neurological defects including stroke

defined when LVM $g/m^{2.7}$ is 95th percentile or more (the same cutoff percentile used for defining hypertension) a value of 38.6 $g/m^{2.7}$ has been reported [65]. However, the cutoff value used in adults (51 $g/m^{2.7}$) corresponds to the 97.5th percentile. Furthermore, reference data have been calculated from relatively small cohorts, prospective data are missing, and the few available studies have used different criteria. Therefore, it is no surprise if LVH prevalences ranging from 14 to 42% have been reported [66–68].

Blood vessels The first morphological changes of the arterial wall, thickening of the intima-media complex, can be identified by high-resolution ultrasound. Investigators have used intima-media thickening (IMT) to study children at high risk for development of atherosclerosis later in life. Children with familial hypercholesterolemia have higher IMT than age-matched healthy children [69]. Overweight and obesity are associated with increased IMT in children with or without essential hypertension [70,71]. Jourdan *et al.* [72] proposed normative values for carotid and femoral IMT and large vessel distensibility in the cross-sectional study of 247 healthy adolescents. They found that 38.8% of hypertensive children had a carotid IMT greater than 2 SDs above normal [66].

Increased arterial stiffness has also been reported to be more common in hypertensive children than in normotensive ones [15], but a large body of data for establishing normal ranges of arterial distensibility, or its inverse arterial stiffness in children is desirable before safer conclusions can be reached.

Kidney Diagnosis of hypertension-related renal damage is based on a reduced renal function or an elevated UAE.

Box 5. Laboratory investigations

Routine tests that have to be performed in all hypertensive children
Full blood count
Plasma sodium, potassium and calcium, urea, creatinine
Fasting plasma glucose
Serum lipids (cholesterol, LDL cholesterol, HDL cholesterol)
Fasting serum triglycerides
Urinalysis plus quantitative measurement of microalbuminuria and proteinuria
Renal ultrasound
Chest Xray, ECG and 2-D echocardiography
Recommended additional screening tests
Plasma renin activity, plasma aldosterone concentration
Urine and plasma catecholamines or metanephrines
Tc99 dimercaptosuccínic acid scan
Urinary free cortisol
More sophisticated tests that should await results of above screening
Color Doppler ultrasonography
Captopril primed isotope studies
Renal vein renin measurements
Renal angiography
I123 metaiodobenzylguanidine scanning
Computed tomography/ Magnetic resonance imaging
Urine steroid analyses and more complex endocrine investigations
Molecular genetic studies (Apparent mineralocorticoid excess, Liddle's syndrome, etc)
Test to be used in specific clinical conditions are included in Box 9

Renal insufficiency is classified according to the glomerular filtration rate (GFR) calculated by the Schwartz formula, which is based on age, body height and serum creatinine, in which GFR (ml/min per $1.73\,m^2$) = $K \times$ (body height in cm/serum creatinine in mg/dl). K is an age-dependent coefficient (preterm neonates 0.33; term neonates 0.45; children 2–12 years 0.55; girls 13–18 years; 0.55; boys 13–18 years; 0.70). Permanently reduced estimated GFR indicates renal damage. Although a temporary increase in serum creatinine (up to 20%) may occur when antihypertensive therapy is initiated or potentiated, mainly with the use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), this should not be taken as a sign of progressive renal deterioration.

In adults, an increase in UAE is a marker of hypertension-induced renal damage. Proteinuria is a marker of glomerular damage in primary and secondary glomerulopathies. It can increase as a consequence of elevated BP, so it is an indication for BP-lowering interventions. Even small amounts of UAE are correlated with progression of nephropathy and to a higher cardiovascular risk. An increased rate of urinary albumin or protein excretion indicates a deranged glomerular filtration barrier. Microalbuminuria (20–300 μg/g creatinine, 2–30 mg/mmol creatinine, 30–300 mg/day, 20–200 μg/min) has been shown to predict the development of diabetic nephropathy, whereas the presence of overt proteinuria (>300 mg/day) indicates the existence of established renal parenchymal damage. The role of microalbuminuria assessment in pediatric essential hypertension, however, has yet to be fully established except for the observation that LVH and microalbuminuria are often associated in children with essential hypertension [73].

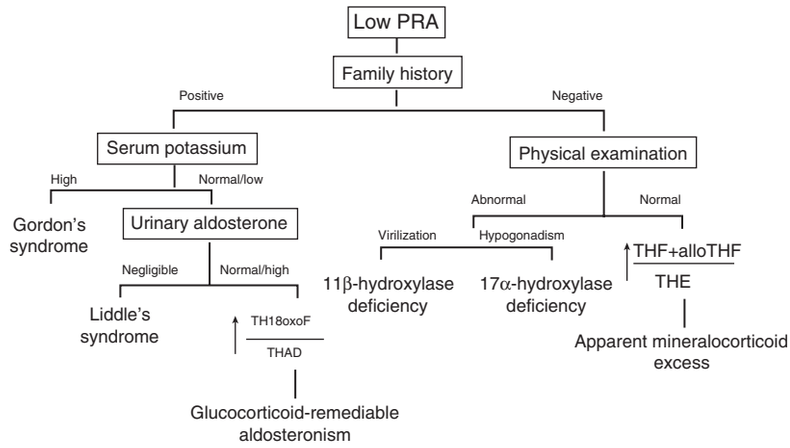
Brain Cerebral seizures, stroke, visual impairment and retinal vascular changes are complications associated with severe hypertension in children and even in infants. Nowadays, these complications seldom occur in infants and children due to early diagnosis and efficient antihypertensive treatment. Diagnostic procedures, other than a neurologic and ophthalmologic clinical evaluation, include electroencephalography and in emergency cases, cranial computed tomography (CT), to exclude intracranial hemorrhage. MRI techniques have replaced the routine CT scan, in the rare cases when small silent brain infarcts, microbleeds and white matter lesions have to be identified.

Fundoscopy Vascular injuries to small arteries (narrowing of arterioles) may occur early in the development of hypertension. Few studies of retinal abnormalities have been conducted in children with hypertension so far. In a study of 97 children and adolescents with essential hypertension, Daniels *et al.* [74] found that 51% displayed retinal abnormalities, as detected from direct ophthalmoscopy. Recently Mitchell *et al.* [75] showed that even in young children aged 6–8 years, each 10 mmHg increase in SBP was associated with 1.43–2.08 μm narrowing of retinal arterioles detected from quantitative analysis of digital retinal photographs. The routine application of fundoscopy should be restricted to assessing the presence of hypertensive encephalopathy or malignant hypertension.

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 hypertension. Monogenic causes of hypertension are rare, but they should be detected during the pediatric age, for successful treatment and avoidance of the hypertension-associated morbidity and mortality [76,77]. All presently known monogenic causes of hypertension are characterized by abnormal sodium transport in the kidney, volume

Fig. 2



Diagnostic algorithm in low plasma renin activity hypertension and genetic testing. Ratio of urinary TH18oxoF/THAD normal from 0 to 0.4, glucorticoid remediable aldosteronism more than 1. Ratio of urinary THF + alloTHF/THE, normal less than 1.3, apparent mineralocorticoid excess 5–10-fold higher. alloTHF, allotetrahydrocortisol; PRA, plasma renin activity; TH18oxoF, 18-oxo-tetrathydrocortisol; THAD, tetrahydroaldosterone; THE, tetrahydrocortisone; THF, tetrahydrocortisol.

expansion and low renin. Among them, Liddle's syndrome [78], glucocorticoid-remediable aldosteronism [79], apparent mineralocorticoid excess [77], Gordon's syndrome [80], mineralocorticoid receptor hypersensitivity syndrome [81] and hypertensive forms of congenital adrenal hyperplasia [82] have been identified. Monogenic diseases should be suspected in children with low renin hypertension and a family history of early-onset severe hypertension, death from cerebral vascular accidents and heart failure or refractory hypertension. Hypokalemia is a common feature of the majority of low renin hypertension stated with the exception of Gordon's syndrome. Figure 2 outlines a rational approach for performing a genetic test.

Preventive measures

Correlates of high blood pressure

As most cases of high-normal BP and hypertension in childhood are now known not to be cases of secondary hypertension to be detected and specifically treated, efforts should be made to understand conditions associated in order to return BP within the normal range or to avoid high-normal BP in youth developing into full hypertension in adulthood.

Considerable advances have been made in recent years in identifying conditions often associated with and considered responsible for high BP in children and adolescents, whereas more limited evidence has been accumulated on the results of corrective interventions.

Overweight is probably the most important of the conditions associated with elevated BP in childhood [83] and accounts for more than half the risk for developing hypertension [84–87]. Fatter children are known to be more likely to remain fat, and adiposity is the most powerful risk factor for higher BP. Unfortunately, from 1970 to 1990, the prevalence of overweight in US children and adolescents increased from 5 to 11% [88], and a similar trend was observed in British children [89]. A recent survey of school-aged (6–11 years) children in Milan, Italy, has reported a prevalence of overweight ranging from 17.0 to 38.6% according to the different definitions used [90]. In addition to body mass index, waist circumference (abdominal obesity) has been shown to play a role [91]. Birth size and postnatal growth have also been recently implicated in the development of high BP and adult cardiovascular disease [92–97]. Finally, dietary habits early in life, and particularly high salt intake, have been implicated as factors favoring higher BP values [98,99].

Life style measures

Data about BP reduction from randomized intervention trials for reducing weight are limited. Lifestyle trials are currently under way in many settings [100,101], but until these are finished, evidence-based recommendations are limited. Most, however, are obvious and common sense. From reviews, it appears that '40 min of moderate to vigorous aerobic-based physical activity 3–5 days/week is required to improve vascular function and reduce BP in obese children' [83].

Thus, any intervention that not only reduces energy intake but also increases physical activity in these children is likely to be helpful in keeping BP lower. In general, such interventions should be global policy in schools and as 'advice' to parents, not just advice directed

Box 6. Life-style recommendations to reduce high BP values

GOALS
BMI < 85th percentile: Maintain BMI to prevent overweight
BMI 85–95th percentile: Weight maintenance (younger children) or gradual weight loss in adolescents to reduce BMI to <85th percentile
BMI > 95th percentile: Gradual weight loss (1–2 kg/month) to achieve value <85th percentile
GENERAL RECOMMENDATIONS
Moderate to vigorous physical aerobic activity 40 min, 3–5 days/week and avoid more than 2 h daily of sedentary activities
Avoid intake of excess sugar, excess soft drinks, saturated fat and salt and recommend fruits, vegetables and grain products
Implement the behavioural changes (physical activity and diet) tailored to individual and family characteristics
Involve the parents/family as partners in the behavioural change process
Provide educational support and materials
Establish realistic goals
Develop a health-promoting reward system
Competitive sports participation should be limited only in the presence of uncontrolled stage 2 hypertension

at individual children. Group activities, a whole new ethos of outdoor lifestyle promotion, wherever and whenever possible, as part of school curricula, and regular vigorous activity sessions for boys and girls are regarded as essential components in helping children and parents (re-)learn that these are the foundation of what we currently know of how to keep BPs low through childhood and adolescence. Specific dietary measures, again, are only partially evidence based, but guidelines are available [100–102]. These include proposals for salt reduction and increased potassium at young ages [103–105]. As above, dietary trials are underway [100,101,104]. Recommendations are outlined in Box 6.

The accumulating evidence on the importance of fetal and early life factors in determining cardiovascular risk should call attention to a very early onset of preventive measures, such as discouraging maternal smoking and encouraging breast feeding for 6–9 months [106]. Sodium restriction in bottle feeds may also be important, as shown in the Dutch trial followed to age 15 years for effects on BP [98].

Evidence for therapeutic management

Cardiovascular endpoints such as myocardial infarction, stroke, renal insufficiency or heart failure are extremely uncommon in childhood, and their rarity has so far prevented 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 hypertension, 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 and increased UAE as study endpoints.

Trials based on intermediate endpoints

Heart

Pediatric research about the effects of antihypertensive treatment on cardiac end-organ damage are limited to small, uncontrolled studies in heterogeneous populations with primary and secondary hypertension. Some data, nevertheless, suggest that effective antihypertensive treatment may ameliorate cardiac geometry in children. Regression of LVH was reported in three children with essential hypertension receiving enalapril, in 19 children with primary and secondary hypertension treated with ramipril for 6 months, and in 65 children with chronic kidney disease (CKD) stage 2–4 receiving ramipril for up to 2 years [107–109]. All published studies in children refer to ACE inhibitors, and comparative data with other classes of antihypertensive agents are available.

Renal function and disease

Data in adults have shown that, among antihypertensive agents, blockers of the renin–angiotensin system are particularly effective in reducing proteinuria and CKD progression (see section entitled 'Pharmacological therapy'). This evidence has prompted a large pediatric intervention study; the Effect of Strict Blood Pressure Control and ACE Inhibition on Progression of Chronic Renal Failure in Pediatric Patients (ESCAPE) trial, which has shown efficient BP and proteinuria reduction for the ACE inhibitor ramipril in 352 children with CKD [110]. Still, a gradual rebound of proteinuria despite persistently good BP control was observed on extended treatment, questioning the long-term nephroprotective advantage of ACE inhibition in children [111].

When to initiate antihypertensive treatment

As in adults, also in children, the decision to initiate antihypertensive treatment should not be taken on BP levels alone, but should also consider the presence or absence of target organ damage, other risk factors or diseases such as obesity, renal diseases or diabetes. In children with proven secondary hypertension, specific treatment of the underlying disease must be initiated immediately after detection. In children with primary hypertension, antihypertensive therapy should first target the risk factors for BP elevation (i.e. overweight, increased salt intake, low physical activity) in the same

Box 7. Therapeutic management of hypertension

EVIDENCE FOR THERAPEUTIC MANAGEMENT
Reduce mortality and sequelea in life-threatening conditions
Reduce left ventricular hypertrophy
Reduce urinary albumin excretion
Reduce rate of progression to end-stage renal disease
WHEN TO INITIATE ANTIHYPERTENSIVE TREATMENT
Non-pharmacological therapy should be initiated in all children with high normal BP or hypertension
Non-pharmacological therapy should be continued after starting pharmacological therapy
Pharmacological therapy should be initiated when patients have symptomatic hypertension, hypertensive target organ damage, secondary hypertension or diabetes mellitus type 1 or 2 at the time of presentation
WHAT THE BP TARGETS ARE
In general
BP below the 90th age–sex and height specific percentile
Chronic kidney disease
BP below the 75th percentile in children without proteinuria, and below the 50th percentile in cases of proteinuria

way as described in the section entitled 'Preventive measures'.

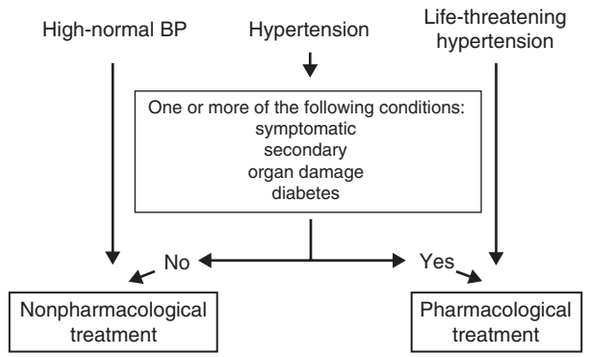
Nonpharmacological therapy should be continued even after starting pharmacological therapy, as it can improve the overall cardiovascular risk profile in hypertensive children. Pharmacological therapy should be started as stated in Box 7. Unfortunately, the decision about when to initiate pharmacological therapy cannot be supported by trial evidence, which is totally missing. Consequently, the suggestions indicated in the decision-making tree of Fig. 3 are formulated in analogies with what has been shown in adults, and are based on wisdom. Particularly in small children, closer attention should be paid to the benefit-to-risk ratio of prolonged drug administration.

Goal of treatment

Blood pressure target in the general hypertensive population

In adults, the recommendation of reducing BP to below 140/90 mmHg is sufficiently evidence based [2,3]. In the absence of prospective long-term studies linking children BP levels to cardiovascular outcomes, pediatric BP targets are commonly defined in relation to the distribution of BP in the normal population. The 95th percentile is commonly used as a cutoff for defining hypertension in children and adolescents. This provides a rationale for targeting children and adolescents with essential hypertension to a BP below the 95th age, sex and height specific percentiles, but it is probably wiser and safer to aim at a BP below the 90th percentile.

Fig. 3



When to initiate antihypertensive treatment. One or more of the conditions listed in the box need to the start of antihypertensive drugs. Persistent hypertension, despite nonpharmacological measures, needs to start antihypertensive drug treatment.

Blood pressure target in renal and diabetic disease

Current guidelines recommend reducing casual BP in adults with hypertension and additional diseases such as diabetes, cardiovascular and renal disease to below 130/80 mmHg with a BP target below 120/75 mmHg suggested in proteinuric adults [1]. It has recently been recognized, however, that recommendations in favor of these very low targets may deserve additional evidence [3].

In children with CKD, there is preliminary evidence from the prospective randomized ESCAPE trial that strict BP control aiming for a 24-h target below the 50th percentile of mean arterial pressure by the addition of other antihypertensive agents to ACEI therapy results in a better 5-year renal survival, despite a return of proteinuria toward pretreatment values [112]. Peer-reviewed publication of the results of this important trial is required for more precise recommendations. Nonetheless, some further preliminary information can be reported from still unpublished analyses of ESCAPE by courtesy of the authors. Analysis by achieved BP levels shows similar renal outcomes with any 24-h BP below the 75th percentile, contrasting with significantly reduced 5-year renal survival in patients exceeding this cutoff level. A poorer renal survival is associated with an attained 24-h BP above the 90th percentile. Proteinuria appears to be an important modifier of the renoprotective efficacy of intensified BP control. Despite the dissociation in time of the renoprotective and antiproteinuric effects, an improved renal survival is associated with targeting BP to lower levels only in children with even mild baseline proteinuria, whereas no benefit of more intense

BP lowering is found in children with nonproteinuric disease. Apart from the renoprotective effect, unpublished data from the ESCAPE trial suggest that intensified BP control, adding to ramipril other antihypertensive drugs, may be associated with regression of the LVH previously reported in these children at baseline [113].

Although overt diabetic nephropathy is rarely observed in children with diabetes, these patients are considered to be at increased long-term risk for hypertension and renal damage [114,115]. 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 [115,116] when casual BP is still normal. Impaired nocturnal dipping often precedes microalbuminuria, the earliest marker of diabetic nephropathy [115]. Although pediatric evidence of the efficacy of preventive antihypertensive and antiproteinuric treatment strategies in juvenile diabetes is still lacking, evidence established in adults reinforces the recommendation of aiming at a strict control in children with diabetes.

Home and ambulatory blood pressure targets

Ambulatory BP monitoring is regarded as the gold standard for the diagnosis and monitoring of hypertension, and detecting both white-coat and masked hypertensions. In children, data of the ESCAPE study show a less variable BP response to antihypertensive treatment with ABPM as compared with office BP measurement [117]. Therefore, it seems wise to recommend the use of ABPM to monitor attainment and maintenance of BP targets in children with renal disease. As ABPM cannot be done frequently, both office and home BP monitorings should be utilized as supplementary information. BP values obtained by home monitoring correlate more closely than do office BP values to ABPM-derived mean daytime BP and should be considered superior information.

Therapeutic strategies

Lifestyle changes

These have been reported in the section entitled 'Preventive measures', but it should be reiterated here that lifestyle measures should not only precede but also accompany pharmacological treatment.

Pharmacological therapy

Therapeutic orphans

Until recently, no antihypertensive drug was licensed for use in children and adolescents. The US effort (Best Pharmaceuticals for Children Act, Pediatric Research Equity Act) has stimulated European authorities to realize that children also have the right to be treated with drugs that have been studied in and authorized for children. The goal of the Regulation of Medicinal Products for Pediatric Use (EU Regulation 1901/2006/EC) [118] is to increase the availability of medicines authorized for children, as well as to improve the information on the use of medicinal products in the pediatric population defined in the above EU regulation as aged 0–18 years. Cardiovascular drugs in particular are not licensed for use in children and the inventory list for pediatric needs (Assessment of pediatric needs – Cardiovascular products, EMEA 436949/2006) – contains all antihypertensive agents that need to be studied in this age group. Pharmaceutical companies will receive an incentive of a 6-month prolongation of market exclusivity for adequately performed pediatric studies. Furthermore, studies on the pediatric population with drugs that are off-patent will get a new exclusivity according to the Paediatric Use Marketing Authorization (Art. 40, EU regulation). With this procedure, ACEIs, beta-blockers, calcium channel blockers, dihydralazine, prazosin and diuretics can be licensed for infants, children and adolescents.

The legislation changes in the United States (Food and Drug Administration Modernization Act, 1997, Best Pharmaceuticals for Children Act, 2002) [119] have led to the study and approval of new antihypertensive medications for use in children and adolescents. The recent Regulation of Medicinal Products for Paediatric Use (EU Regulation 1901/2006/EC) in Europe will lead to further approval of antihypertensive agents for children and even infants. Several antihypertensive drugs are commercially available in liquid form or can be extemporaneously compounded for flexible dosing and ease of administration. Recent clinical trials have expanded the number of drugs that have pediatric dosing information based on dose finding studies. For new drugs and lower administration ages, more information will be provided in the near future. One negative consequence of the new regulation is that for older compounds with expired patent protection, reliable pediatric data obtained from controlled studies (dose finding and efficacy) are lacking. Probably, the Paediatric Use Marketing Authorization (PUMA) will help resolve this problem, at least in part. For the time being, the present recommendations are based on few industry-sponsored studies, and mostly on single-center case series, collective clinical experience, expert opinion and extrapolation from data obtained in adults.

Monotherapy

It is reasonable that in children, treatment should be started with a single drug administered at a low dose in order to avoid rapid fall in BP. If BP does not decrease sufficiently after a few weeks, usually 4–8, an increase to the full dose should be initiated. When BP does not respond adequately or significant side effects occur, the switching to another antihypertensive drug of a different class is recommended. This procedure allows finding the patient's best individual response to the drug in terms of efficacy and tolerability. As the response rate is often not sufficient in single-drug treatment, particularly in moderate or severe hypertension, combination therapy is often necessary.

Like in adults, choice of antihypertensive agents can include ACEIs, angiotensin receptor antagonists (ARBs), calcium antagonists, beta-blockers and diuretics. A few placebo-controlled studies are available, but almost no head-to-head study directly comparing the efficacy and safety of different antihypertensive drugs in children or adolescents. A recent review [120] of 27 pediatric studies reports comparable BP reductions with ACEIs (10.7/8.1 mmHg), ARBs (10.5/6.9 mmHg) and calcium antagonists (9.3/7.2 mmHg).

Beta-adrenergic blockers

Propranolol has been included in treatment recommendations for pediatric hypertension for many years, but it has only been studied specifically as an antihypertensive agent in few trials on very few children [121,122]. Most of the information about the safety and efficacy of this drug comes from studies of nonhypertensive children with cardiac disease or portal hypertension [123]. The situation is similar for atenolol and metoprolol [124]. The only study specifically directed to hypertension is a recent 52-week trial [125] on 140 children (aged 6–11 years) reporting that an extended-release preparation of metoprolol produced significant reductions in SBP and DBP at 1.0 and 2.0 mg/kg when compared with placebo. The drug was well tolerated, and only 5% of participants had to drop out due to adverse events.

Calcium antagonists

The efficacy and safety data for diltiazem, verapamil, nifedipine, felodipine and isradipine [126] are limited. There have been, however, several trials for amlodipine [120], which is extensively used in the treatment of hypertension in children [127]. Amlodipine decreased SBP compared with placebo in a large multicenter trial [128] that included 268 children aged from 6 to 16 years. A significant dose–response relationship was established with doses from 0.06 to 0.34 mg/kg per day. A pharmacokinetic study [129] indicated that amlodipine pharmacokinetic parameters for children younger than 6 years with low body weight were significantly different than were those for older/larger individuals. This suggests the need for higher doses (on a mg/kg basis) when treating young children with amlodipine.

Angiotensin-converting enzyme inhibitors

The oldest ACEI, captopril, has been extensively studied in children. Its efficacy and safety appear to be well established, but the drug has a short duration of action. As it must be administered two or three times a day, it has been replaced by the longer-acting ACEIs [130]. Some of these have been studied recently in children [120]. Placebo-controlled efficacy results are available for enalapril [131], fosinopril [132] and lisinopril [133], whereas pharmacokinetic studies have been carried out for enalapril [134], lisinopril [135] and quinapril [136]. The enalapril [131] and lisinopril [133] trials have established minimum effective doses of 0.08 mg/kg per day, but doses of 0.6 mg/kg per day were well tolerated. These drugs were studied in an extemporaneous suspension formulation. The fosinopril study [132] failed to establish a dose–response effect on BP reduction. The authors suggested that probably all the doses used were too high (0.1, 0.3 and 0.6 mg/kg per day; the maximum dose permitted was 40 mg/day). Fosinopril [132], however, did produce greater SBP reduction than did placebo, and the drug was well tolerated. The study included a 52-week open-label extension that provided more information about safety and tolerability than did other trials. Ramipril has been studied mostly in children with chronic renal disease. At a dose of 6 mg/m^2 daily, it reliably reduced 24-h mean BP, especially in severely hypertensive or proteinuric children [110]. Ramipril at a lower dose of 2.5 mg/m^2 per day reduced BP and proteinuria also in children with primary hypertension and renal hypertension with chronic renal failure [137].

Angiotensin receptor blockers

Data on the effects of ARBs in hypertensive children have accumulated recently [120]. Short-term treatment with losartan in children with estimated GFRs 30 ml/min per 1.73 m^2 or more produced significant dose-dependent reductions in DBP [138]. The effective starting dose was 0.75 mg/kg per day, but doses as high as 1.44 mg/kg per day were well tolerated. For irbesartan, a small pharmacokinetic study indicated that doses of 75–150 mg/day were effective in children with hypertension [139]. Another small trial [140] in hypertensive children with proteinuria showed that irbesartan at doses from 3.8 to 5.9 mg/kg per day significantly reduced BP and proteinuria. Data for candesartan come from a small study conducted in 17 children 1–6 years old. Candesartan [141] was used at a once-a-day dose of 0.16–0.47 mg/kg body weight. BP significantly decreased, and the effect on BP was similar in individuals with or without overt proteinuria, which also decreased in a similar way. Recently, valsartan has effectively lowered SBP and DBP compared with placebo in children 1–5 years old [142].

Other antihypertensive agents

No pediatric studies have been conducted for diuretics, except for a very small old study on chlorthalidone [122], direct vasodilators, centrally acting agents, or alpha-1 receptor antagonists, despite their having a long history of clinical use in the pharmacological management of hypertension in children [143]. Pediatric experience has been reported with hydrochlorothiazide and chlorthalidone. The latter has a longer half-life, and the dose interval is 24 or 48 h. Very high doses of thiazides affect BP only marginally, but may be associated with increased incidence and severity of side effects.

Therefore, the selection of the drug used to initiate the lowering of BP depends on extrapolations from

Table 7 Recommended initial doses for selected antihypertensive agents for the management of hypertension in children and adolescents

Class	Drug	Dose	Interval
Diuretics	Amiloride	0.4–0.6 mg/kg per day	q.d.
	Chlorthalidone	0.3 mg/kg per day	q.d.
	Furosemide	0.5–2.0 mg/kg per dose	q.d.–b.i.d.
	Hydrochlorothiazide	0.5–1 mg/kg per day	q.d.
	Spironolactone	1 mg/kg per day	q.d.–b.i.d.
Beta-adrenergic blockers	Atenolol	0.5–1 mg/kg per day	q.d.–b.i.d.
	Metoprolol	0.5–1.0 mg/kg per day	q.d. (ER)
	Propanolol	1 mg/kg per day	b.i.d.–t.i.d.
Calcium channel blockers	Amlodipine	0.06–0.3 mg/kg per day	q.d.
	Felodipine[a]	2.5 mg per day	q.d.
	Nifedipine	0.25–0.5 mg/kg per day	q.d.–b.i.d. (ER)
Angiotensin-converting enzyme inhibitors	Captopril	0.3–0.5 mg/kg per dose	b.i.d.–t.i.d.
	Enalapril	0.08–0.6 mg/kg per day	q.d.
	Fosinopril	0.1–0.6 mg/kg per day	q.d.
	Lisinopril	0.08–0.6 mg/kg per day	q.d.
	Ramipril[a]	2.5–6 mg per day	q.d.
Angiotensin-receptor blockers	Candesartan	0.16–0.5 mg/kg per day	q.d.
	Irbesartan[a]	75–150 mg per day	q.d.
	Losartan	0.75–1.44 mg/kg per day	q.d.
	Valsartan	2 mg/kg per day	q.d.

q.d., once daily; b.i.d., twice daily; t.i.d., three times daily; ER, extended release. The maximum recommended adult dose should never be exceeded. [a] No dose referenced to weight is available.

pathophysiological aspects and clinical experience. As many of children and adolescents requiring antihypertensive drug therapy have some degree of renal disease, the most widely used drugs are agents inhibiting the renin–angiotensin system, mainly ACEIs, or ARBs if intolerance to ACEIs exists. Loop diuretics such as furosemide are essential in children with advanced chronic renal failure or with heart failure. The recommended doses for antihypertensive drugs in children are shown in Table 7, and the specific recommendations and contraindications are shown in Table 8.

Combination therapy

In children with renal disease, monotherapy is often not sufficient to achieve adequate BP control. Therefore, early combination therapy is required. Early dose combination of antihypertensive agents is more efficient and has a lower rate of adverse drug reaction compared with that of high-dose monotherapy. Antihypertensive drugs of different classes have complementary effects, resulting in a higher degree of BP reduction and a lower rate of adverse drug reaction. The best choices of antihypertensive drug combinations are those recommended in the ESH/ESC 2007 Guidelines [2]. Fixed-dose combinations of two drugs are rarely used in children, as individual-based contributions are preferred, but fixed combinations may have a place in treating adolescents to improve compliance [144].

Therapeutic approaches under special conditions

Associated diseases

Hypertension requires specific therapeutic approaches in several situations not only out of the necessity to reach

Table 8 Clinical conditions for which specific antihypertensive drug classes are recommended or contraindicated

Antihypertensive class	Recommended	Contraindicated
Diuretics	Hyperaldosteronisms	Chronic renal failure
Potassium-sparing		
Diuretics	Chronic renal failure	
Loop-acting	Congestive heart failure	
Beta-adrenergic blockers	Coarctation of aorta	Bronchial asthma
	Congestive heart failure	
Calcium channel blockers	Posttransplantation	Congestive heart failure
Angiotensin-converting enzyme inhibitors	Chronic kidney disease	Bilateral renal artery stenosis
	Diabetes mellitus	Renal artery stenosis in solitary kidney
	Congestive heart failure	Hyperkalemia
		Pregnancy
		Females of child-bearing potential should use reliable contraception
Angiotensin-receptor blockers	Chronic kidney disease	Bilateral renal artery stenosis
	Diabetes mellitus	Renal artery stenosis in solitary kidney
	Congestive heart failure	Hyperkalemia
		Pregnancy
		Females of child-bearing potential should use reliable contraception
Intravenous vasodilators	Life-threatening conditions	

lower goals than are usually recommended, but also because of the presence of characteristic mechanisms that can benefit from particular antihypertensive agents. CKD, diabetes mellitus and metabolic syndrome, heart failure and sleep apnea are among the most common.

Chronic kidney disease

In the section entitled 'Goal of treatment', we have summarized recent preliminary evidence from the ESCAPE trial, suggesting that hypertension in children with CKD, especially if accompanied by proteinuria, requires more intensive management in order to reduce proteinuria and prevent progressive deterioration of renal function. Although nonpharmacological options should be considered, pharmacological 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 [120,145], but most of the available clinical evidence has been obtained with drugs blocking the renin–angiotensin system, [110,120,146]. They have a powerful antiproteinuric action in pediatric nephropathies and display a favorable safety profile. Furthermore, the only study so far comparing the effects of an ARB, irbesartan, and a calcium antagonist, amlodipine, in children with proteinuric nondiabetic CKD has shown a significant reduction of proteinuria only with ARB treatment, despite similar effects of the two randomized treatments on BP [140].

At this time, therefore, it appears reasonable to recommend agents blocking the renin–angiotensin system as first choice in proteinuric, and also in nonproteinuric patients with CKD.

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 options. ARBs in combination with ACEIs have been suggested to have additional antiproteinuric and renoprotective effects [147], and a very small short-term study has also been done in children [148]. However, the negative results recently reported in the high-risk adult patients of ONTARGET [149] for the combination of the blockers of the renin–angiotensin system call for caution in the use of this combination at all ages. Clearly, more evidence is required.

Diabetic nephropathy

Diabetic nephropathy, albeit uncommon in this age group, requires a similar approach to other CKD. Extrapolating from findings on adults, it appears appropriate to consider the microalbuminuric stage as a signal to begin BP lowering in order to reduce the risk of progression to the proteinuric stage. In this case, nocturnal BP control can play a key role. ABPM is useful in order to assess the BP goal. In the absence of hypertension or microalbuminuria, treatment with ACEIs or ARBs can be considered if circadian BP variability is persistently blunted [115].

Diabetes mellitus and metabolic syndrome

In type 2 diabetes or insulin resistance, the underlying mechanisms of metabolic syndrome [150], treatment of high BP should be based on lifestyle changes, diet and physical exercise, which allows for weight reduction and improves muscular blood flow. If recourse to drugs is decided, the preferred drugs should be those that might induce reduction of insulin resistance and subsequent changes in the lipid profile and in glucose levels. Therefore, ACEIs, ARBs or calcium antagonists are preferable over diuretics and beta-blockers if no compelling contraindications are present. If a combination of drugs is required, low-dose diuretics can be used, but a combination of thiazide diuretics and beta-blockers should better be avoided [151].

Heart failure

Hypertension is a major risk factor for the development of heart failure. As in adults, the treatment of heart failure in children includes diuretics, beta-blockers and drugs blocking the renin–angiotensin system [152]. No outcome trials have been done in children, but evidence from many studies in adult heart failure suggests that ACEIs (and alternatively ARBs) together with beta-blockers may not only reduce symptoms but increase survival in children with heart failure [153]. Diuretics (loop and aldosterone antagonists) are indicated in children with heart failure and fluid overload. Diuretics should not be administered alone, but in combination with drugs blocking the renin–angiotensin and cardiac sympathetic system, although all drugs should be administered in slowly increasing doses. In case of acute heart failure from a hypertensive emergency, intravenous loop diuretics and vasodilatory drugs are preferred.

Sleep apnea syndrome

The sleep apnea syndrome is frequently associated with hypertension, particularly among overweight children. During the last few years, the potential relationship between childhood sleep-disordered breathing (SDB)/obstructive sleep apnea (OSA) and cardiovascular diseases in children has been underlined. The evidence linking moderate to severe SDB in childhood and elevated risk of hypertension is controversial. A meta-analysis of studies investigating the relation between high apnea–hypopnea index and hypertension in children reported, an increased risk of hypertension [odds ratio of 2.93; 95% confidence interval (CI) = 1.18–7.29] [154], whereas a more recent one failed to find a statistically significant association (random-effect odds ratio of 1.87; 95% CI = 0.73–4.80) [155]. The impact of overweight and obesity on both hypertension and SDB can be a confounding factor. For the time being, it appears wise to

address treatment to reducing overweight. In extreme cases with severe OSA, positive pressure breathing equipment or surgery might become necessary [156].

Hypertensive emergencies

A hypertensive crisis (emergency or urgency) is a life-threatening condition associated with severe hypertension. Hypertensive emergency is defined as severe hypertension complicated with acute target organ dysfunction (mainly neurological, renal or cardiac). Hypertensive urgency is defined as severe hypertension without acute target organ dysfunction. Children with hypertensive emergencies should be treated in an intensive care unit to ensure monitoring and support of the vital organs.

The treatment strategy must be directed toward the immediate reduction of BP to reduce the hypertensive damage to the target organs, but not at a rate likely to cause hypoperfusion of vital organs by an excessively rapid reduction of BP (mainly cerebral hypoperfusion with neurological sequelae). Then, careful neurological and cardiovascular assessment should be undertaken throughout the initial treatment. 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 25–30% over the first 6–8 h, followed by a further gradual reduction over the next 24–48 h [157,158]. Faster normalization of severe hypertension must be strictly avoided, as it may cause more harm than severe hypertension itself. Children with a hypertensive emergency should always be treated with intravenous drugs. Continuous infusion is safer than is bolus injection with regard to complications (unexpected hypotension with vital organ hypoperfusion). Sodium nitroprusside and labetalol are the most commonly used drugs for hypertensive emergencies in children. Hypertensive urgencies can be treated with orally administered drugs. Table 9 indicates drugs and doses used for pediatric hypertensive crises.

Resistant hypertension

Resistant hypertension is defined as hypertension in which a therapeutic plan including lifestyle measures and prescription of at least three drugs, including a diuretic in adequate doses, has failed to lower SBP and DBP to goal. Resistant hypertension in children and adolescents, once verified with ABPM and having excluded the conditions outlined in Box 8, almost invariably indicates presence of secondary hypertension. Consequently, a judicious workup should be performed, as outlined in the section entitled 'Screening of secondary forms of hypertension'.

Treatment of associated risk factors

Lipid-lowering agents

The new guidelines of the American Academy of Pediatrics (AAP) recommend measuring lipoproteins starting at age 2 in overweight or hypertensive or diabetic children or in those with a family history of dyslipidemia or early coronary artery disease [159]. If lipid values are within age-specific and gender-specific normal ranges, children should be retested in 3–5 years. For those out of normal ranges, initial treatment should be focused on recommending a diet low in cholesterol (<200 mg/day) and saturated fat (<7% of calories) supplemented with plant sterols and dietary fibers (child's age + 5 g/day up to 20 g at 15 years of age) [160]. Increased physical activity may be useful for modifying HDL-C and triglycerides. According to the AAP, statins should be considered for children 8 years and older if any of the following conditions exists: LDL-C remains 190 mg/dl (4.94 mmol/l) or more; LDL-C remains 160 mg/dl (4.16 mmol/l) or more and there is a family history of early coronary artery disease or the presence of other risk factors as obesity, hypertension and smoking; LDL-C remains 130 mg/dl (3.38 mmol/l) or more in children with diabetes mellitus. The Food and Drug Administration (FDA) and European Medicines Agency (EMEA) have approved the use of pravastatin for children with familial hypercholesterolemia who are 8 years and older. It should be noted, however, that AAP recommendations are controversial:

Table 9 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
Labetalol	Alpha and beta blockers	Intravenous infusion	0.25–3 mg/kg per h	5–10 min	Contraindication in asthma, heart failure, may cause bradycardia
Nicardipine	Calcium antagonist	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 per min	Within seconds	Contraindication in asthma, may cause bradycardia
Enalaprilat	ACEI	Intravenous bolus	0.05–0.1 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
Nifedipine	Calcium antagonist	Orally	0.25 mg/kg per dosis	20–30 min	May cause unpredictable hypotension, reflex tachycardia
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

ACEI, angiotensin-converting enzyme inhibitor.

Box 8. Causes of resistant hypertension

Secondary hypertension
Poor adherence to treatment
Weight gain
Continued intake of BP-raising drugs
Severe obstructive apnea syndrome
Persistence of volume overload:
  Inadequate diuretic therapy
  Progressive renal insufficiency
  High sodium intake

they are not evidence based and the long-term effects of statins on children are unknown. The use of ezetimibe is approved in the United States (but not in Europe) only for those rare children with familial homozygous hypercholesterolemia or with sitosterolemia. Bile-acid sequestrants are difficult to tolerate over the long term. Fibrates may be used in adolescents with triglycerides 500 mg/dl or more who are at increased risk of pancreatitis [159,160].

Glycemic control

Increasing prevalence of pediatric type 2 diabetes coincides with increasing obesity in children. Most obese children have insulin resistance (60%), 5% have impaired glucose tolerance (IGT), 1% impaired fasting glucose and 0.2% type 2 diabetes [161]. Reducing overweight and IGT may help prevent or delay the development of type 2 diabetes in high-risk youths. Behavioral modification (dietary changes and $\geq$60 min daily of physical activity), using techniques to motivate children and families [162], is effective at reducing insulin levels and reverting IGT to normal. Metformin is the only oral medication that has been adequately studied in children and approved by the FDA and some European agencies for use in children over 10 years of age with type 2 diabetes. In morbidly obese insulin-resistant children, metformin has been shown to have favorable effects on body composition, fasting insulin and fasting glucose [163]. A clinical trial to investigate whether aggressive pharmacological reduction in insulin resistance early in the course of type 2 diabetes is superior to lifestyle modification in adolescents is in progress [164].

Screening of secondary forms of hypertension

Usually, sustained hypertension in children and adolescents is classified as secondary when a specific cause can be found, which can often be corrected with specific intervention. The most common causes of hypertension can change during childhood. Essential hypertension is rarely seen in infants and young children, but its prevalence increases significantly in adolescence [4]. A good general rule to follow is that the likelihood of identifying a secondary cause of hypertension is inversely related to the age of the child and directly related to the degree of BP elevation [165]. Consequently, the evaluation of children with hypertension, especially young children and those with severe hypertension, should be comprehensive and aimed at identifying known causes of the disease.

The distribution of causes clearly varies with age. Renal parenchymal disorders [166] with renovascular disease and coarctation of the aorta account for 70% [167] to 90% [168] of all cases. These figures vary depending not only on age, but also on referral center and referral bias. In a number of cases, hypertension is related to the prescription of drugs with hypertensive potential. Other causes of sustained hypertension, tumors and central nervous and endocrine disorders, though infrequent, must be considered once the more common causes have been excluded. An emerging cause of secondary hypertension is a single gene mutation that produces large changes in BP [169].

Hypertension may be seen in up to 2% of all term or preterm infants in neonatal intensive care units. Although the definition of hypertension in this age group has not been completely standardized, useful data have been published [170] and may be used to facilitate diagnosis in these infants. As in older children, the causes of hypertension in neonates are numerous, with the two largest categories being renal (vascular and parenchymal) diseases. More specifically, umbilical artery catheter-associated thromboembolism affecting either the aorta and/or the renal arteries probably accounts for the majority of cases of hypertension seen in a typical neonatal intensive care unit [171]. A careful history and physical examination will usually identify the cause in most cases, without the need for extensive laboratory or radiological testing.

In very young children (<6 years), hypertension is most often the result of renal parenchymal diseases such as glomerulonephritis, renal scarring, polycystic kidney, renal artery stenosis and renal dysplasia. Cardiovascular disorders like coarctation of the aorta are less frequent causes of hypertension in this age group. Late in the first decade and throughout the second, essential hypertension is the most common cause of sustained hypertension, particularly in those children with mild asymptomatic disease [172].

Faced with a child with chronic hypertension of unknown cause, a diagnostic evaluation should take into account level of BP, age, sex, clinical findings and family history. A careful selection of the necessary test often shortens the diagnostic process (Box 9), but a detailed description of the selection process is beyond the scope of this guide [173,174].

Long-term follow-up

Depending on the underlying cause of hypertension, investigative procedures such as monitoring plasma electrolytes

Box 9. Diagnosis of secondary causes of hypertension

Chronic kidney disease	Protein, erythrocytes and erythrocyte casts in urine Serum creatinine concentration and potassium Abdominal ultrasound [$^{99}Tc^{m}$]dimercaptosuccinic acid static scanning
Renovascular hypertension	Plasma renin activity Abdominal ultrasound Doppler ultrasound Renal scintigraphy MRI angiography Angiography
Pheochromocytoma and paraganglioma	24-h urine and plasma chatecolamines or metanephrines Magnetic resonance image I123 metaiodobenzylguanidine
Primary aldosteronism	Plasma renin activity Plasma aldosterone
Cushing's syndrome	Plasma cortisol, ACTH 24-h urinary free cortisol
Coarctation of aorta	Rx chest Echocardiography Magnetic resonance image angiography Aortography
Mendelian	DNA testing
Drug-induced	Liquorice, oral contraceptives, glucocorticoids, non-steroidal anti-inflammatory drugs, sympathomimetics, erythropoietin, cyclosporine, tacrolimus, cocaine, metabolic steroids
Hyperthyroidism	TSH, FT3, FT4
Congenital adrenal hyperplasia	Plasma deoxycorticosterone and corticosterone, 18-hydroxycorticosterone, 18-hydroxy deoxycorticosterone, 11 deoxycortisol

and creatinine, GFR measurements at intervals, renal and renovascular imaging by ultrasound and isotopic studies, possibly repeat angiography [digital subtraction angiography (DSA), CO_2 angiography (CO_2), MR angiography (MRA) or CT angiography (CTA)] will need to be undertaken. For pheochromocytoma or paraganglioma, repeat catecholamine measurements or I123 MIGB scanning may be indicated. Cautious reduction of therapy after long-term BP control achieved may be indicated, even discontinuing therapy in some patients. Life-long follow-up, however, is indicated in the majority of children. Home monitoring of BP can greatly facilitate this management. In children with renal hypertension, regular ABPM measurements at 6–12-month intervals are indispensible to rule out selective nocturnal hypertension.

Future research

In several places, these guidelines have acknowledged, and lamented, the lack of solid, trial-based evidence for recommendations on diagnosis and management of pediatric hypertension. Areas requiring urgent gain of knowledge are listed in Box 10. A commitment to find answers to the outlined issues should guide concerted actions over the next several years in Europe.

Implementation of guidelines

In order to limit, and even reduce, the burden of hypertension in children and adolescents, and its complications, the present guidelines should be successfully implemented. This requires synergistic actions at various levels: learned societies and international expert committees, general practitioners, pediatricians, nurses and other healthcare providers, schools, parents and policy makers. A converging action is the only means to close the gap between experts' recommendations and undiagnosed hypertension in children and adolescents, undetected target organ damage and poor BP control. The role of learned societies, particularly the ESH, is crucial not only for spreading the guidelines all over European countries, but also for obtaining their acceptance by national hypertension societies and leagues.

In parallel, a concerted public action is needed both to improve identification and treatment of high BP among children and adolescents and to encourage lifestyle factors, namely healthy nutrition, low salt intake, nonsmoking, alcohol avoidance, and exercise activity, as preventive and curative measures. Only an aggressive public policy initiative will lead healthcare providers, insurers and other payers

Box 10. Future research

- Develop accurate non-mercury sphygmomanometer for auscultatory BP measurement and accurate devices for oscillometric BP measurement, and carefully compare values obtained with the two methods in infants, children and adolescents.
- Obtain robust reference values for office, home and ambulatory BP based on a European pediatric population.
- Increase knowledge in the use of out-of-office BP measurements.
- Collect information about early organ damage so as to refine risk stratification and use the information to set intermediate objectives during treatment.
- Conduct large, long term randomized therapeutic trials using onset of organ damage (such as onset of microalbuminuria and/or left ventricular hypertrophy) to obtain information about when to initiate antihypertensive drug treatment and about the BP goals to achieve.
- Conduct controlled studies with antihypertensive drugs in order to improve knowledge about specific benefits and disadvantages of BP lowering agents and establish adequate doses.

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 promote management implementation in practice and improve childhood and adolescent health.

The writing committee is well aware of the fact that issuing these guidelines does not imply implementation. However, these guidelines represent a consensus among all specialists involved in the detection and control of high BP in children and adolescents. Although for several aspects scientific evidence derived from trials is not available in children, and these guidelines are likely to be modified in forthcoming years depending on new evidence if the studies here recommended will be promptly initiated, the recommendations of the present document synthesize a considerable amount of scientific data and clinical experience, and represent 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 BP among children and adolescents.

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