Hypertension in Children and Adolescents

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The interest in arterial hypertension on the part of pediatricians has traditionally been rather limited, one reason being that involvement of target organs was recognized only recently in children and adolescents. This situation has changed over the last 10 – 20 years. The incorporation of blood pressure measurements in routine pediatric examination and the expansion of accurate blood pressure monitoring equipment have facilitated the detection and evaluation of childhood hypertension. The concept that primary (essential) hypertension in adults has its root in childhood has enforced the idea of early prevention by regular blood pressure screening [35]. In addition, the increasing survival of pediatric patients with chronic disorders associated with hypertension such as aortic coarctation or end-stage renal disease (ESRD) has engaged an increasing number of pediatricians, especially pediatric nephrologists. Finally, new antihypertensive drugs available for children have improved the management of hypertensive children. The growing interest in this topic is documented by a number of recent meetings and an expanding bibliography on juvenile hypertension [11, 49, 74, 84, 91a, 94, 100, 108, 120, 128].

Measurement of Blood Pressure in Children

Reliable techniques for blood pressure measurement are an important precondition for handling hypertensive children. Several factors have been identified to explain variations of blood pressure in the same child at different times. Some of these are intrinsic (e.g. circadian rhythms), while others are exogenous (e.g. induced by exercise). Taking simple precautions may reduce variations in blood pressure readings in children. Although the technique of blood pressure measurement today is fairly standardized in this age group, it is often difficult in clinical practice to follow proposed guidelines. The following guidelines, based mainly on European experience [94, 96, 109], deviate in some points from American guidelines [15].

Blood pressure measurements in children require a great amount of patience, especially in infants and toddlers. After the child is sufficiently relaxed, a resting time of at least 5 minutes should be observed before measurement. Although in most epidemiological studies children were examined in sitting position, in clinical practice the supine position might be preferred for measurements in young, restless children.

The two conventional non invasive techniques to determine casual (random) blood pressure in children are sphygmomanometry and oscillometry. Both require a cuff bladder that must be adapted to the size of the child [47]. If the cuff is too large, inappropriately low readings are obtained and vice versa. As a rule, the largest cuff that can comfortably be applied should be used, and its inflatable part should cover about $^{2}/_{3}$ of the upper arm's circumference. Usually a bladder width of 8 cm

is suitable for small children and a width of 12 – 14 cm (adult size) is required for older children and adolescents. Unfortunately, the commercially available cuffs for pediatric use are heterogeneous among different manufacturers [5].

In older children, *sphygmomanometry* is the method of choice. Auscultation of the first Korotkoff sounds corresponds to the systolic blood pressure, and disappearance of the sounds to diastolic blood pressure [84, 96]. If the value at the fifth phase is close to zero, although it rarely occurs, the measurement should be repeated. If this gives a similar value, phase 4 should be used [96]. In practice the difference between the figures obtained by accepting the two different phases is minimal.

Oscillometric methods by applying automatic devices (e.g. Dinamap) have become popular mainly in infants and small children because pulse detection by auscultation, as used in sphygmomanometry, is often troublesome [89]. Systolic and diastolic blood pressure is calculated by the device as a function of the mean arterial presssure, which is the point of maximal oscillation. Although oscillometric devices reduce observer bias, only a few instruments have been validated in children [61]. Measurements obtained by conventional sphygmomanometry and oscillometry should not be used interchangeably. At present, only limited normative blood pressure data are available in children. Therefore, further studies are needed before auscultatory methods can be eliminated [21]. The pediatric experience with other novel techniques to determine blood pressure noninvasively is still limited in children [130].

Noninvasive, repetitive blood pressure measurements over 24 hours, through the use of automated monitors, have also been successfully applied in children during normal physical activity [8, 15, 75]. *Ambulatory blood pressure monitoring* (ABPM) proved to be feasible and reliable, even in small children [40]. In many centers, it has become a standard procedure to follow children and adolescents with suspected or proven hypertension. Various types of automatic devices have been applied. Most pediatric experience is based on oscillometric monitors (e.g. SpaceLabs 90207). The main advantage of ABPM compared to casual blood pressure recordings is a reliable assessment of the circadian variations of blood pressure that appear to have prognostic significance, especially in patients with renal disorders [131]. ABPM also seems to be a sensitive tool to differentiate the determinants of primary hypertension and to detect early incipient hypertension in renal disorders [73]. The optimal method to evaluate rhythmicity of ABPM data is still debated.

Normal Blood Pressure Standards

In normal children there is a consistent increase of systolic and diastolic casual blood pressure with age, height, and weight [63]. Therefore, expression of blood pressure data in pediatric populations must be based on percentiles related to these variables. Full-term newborns have a mean systolic blood pressure of only 70 mmHg, which rapidly rises in the first months of life. In premature infants the rise of blood pressure levels is more rapid than in term infants [41]. The rapid rise of blood pressure during infancy and puberty (especially in males) seems to be related to increased growth and hormonal changes.

Combined material from many epidemiological studies performed in the US [84, 103] and Europe [31] provides representative

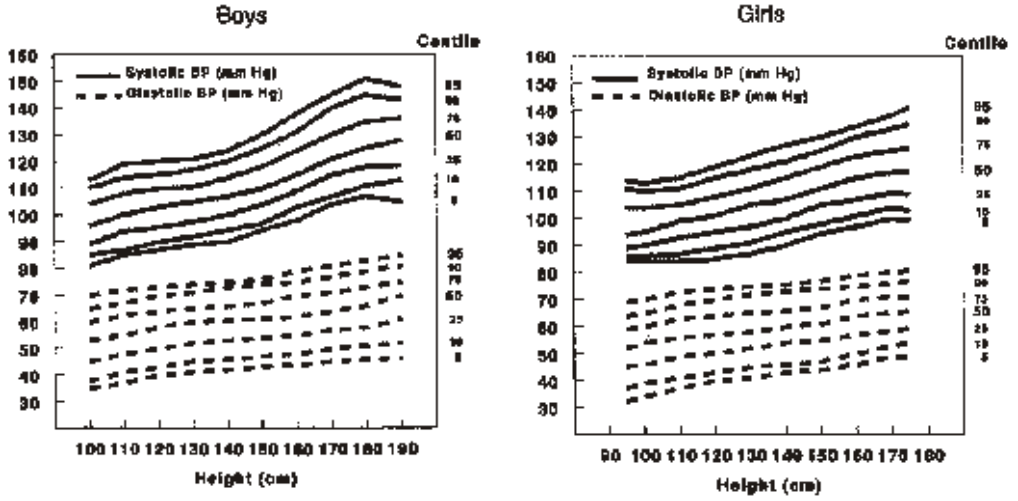

Figure 1. Height-specific percentiles of systolic and diastolic blood pressure in boys and girls. Adapted from de Man et al., J Hypertens 9: 112, 1991 [31]. Used with permission.

Table 1. 95th percentile of systolic/diastolic blood pressure (in mmHg) in North American boys and girls aged 3 – 16 years according to height percentile (extracted from [84]).

AGE (years)	BOYS 5th	BOYS 50th (median)	BOYS 95th	GIRLS 5th	GIRLS 50th (median)	GIRLS 95th
3	104/63	109/65	113/67	104/65	107/66	110/68
6	109/72	114/74	117/76	108/71	111/73	114/75
10	114/77	119/80	123/82	116/77	119/78	122/80
13	121/79	126/82	130/84	121/80	125/82	128/84
16	129/83	134/85	138/87	125/83	128/84	132/86

sex-related reference charts for casual blood pressure measured by sphygmomanometry in normal children and adolescents, although these are mainly based on cross-sectional studies.

For estimating a child's physiological blood pressure, body height appears to be a better indicator than age or weight [135]. Consequently, tall children are allowed relatively higher normal blood pressure values when related to height rather than to age. The European centile charts have related blood pressure to both age and height [31] (Figure 1). Recently pooled American data give the 90th and 95th percentiles of systolic and diastolic blood pressure by percentile of height [84] (Table 1).

Representative reference data for ABPM have only recently become available in children and adolescents [51, 97, 98]. A multicenter study from Germany provided height-related centile charts for daytime, nighttime,

Table 2. Oscillometric mean ambulatory blood pressure values in healthy children: summary for clinical use. Used with permission.

Height in cm (n)	Percentile for 24-hour period		Daytime percentile*		Nighttime percentile	
	50th	95th	50th	95th	50th	95th
Boys						
120 (33)	105/65	113/72	112/73	123/85	95/55	104/63
130 (62)	105/65	117/75	113/73	125/85	96/55	107/65
140 (102)	107/65	121/77	114/73	127/85	97/55	110/67
150 (108)	109/66	124/78	115/73	129/85	99/56	113/67
160 (115)	112/66	126/78	118/73	132/85	102/56	116/67
170 (83)	115/67	128/77	121/73	135/85	104/56	119/67
180 (69)	120/67	130/77	124/73	137/85	107/56	122/67
Girls						
120 (40)	103/65	113/73	111/72	120/84	96/55	107/66
130 (58)	105/66	117/75	112/72	124/84	97/55	109/66
140 (70)	108/66	120/76	114/72	127/84	98/55	111/66
150 (111)	110/66	122/76	115/73	129/84	99/55	112/66
160 (156)	111/66	124/76	116/73	131/84	100/55	113/66
170 (109)	112/66	124/76	118/74	131/84	101/55	113/66
180 (25)	113/66	124/76	120/74	131/84	103/55	114/66

* = Daytime 8 a.m. to 8 p.m., Midnight to 6 a.m. [123].

and 24-hour blood pressure obtained from more than 1100 boys and girls [123]. Compared to standards for casual blood pressure [31, 84] systolic daytime ABPM values increased only moderately with height; diastolic blood pressure remained almost the same, independent of height (Table 2, Figure 2). For systolic blood pressure the 95th centile of daytime values obtained by ABPM was higher than casual blood pressure in small children, but lower in tall European children. Diastolic ABPM values at daytime exceeded casual blood pressure by > 10 mmHg in the smallest height groups. The reasons for the variable results are not yet clear. Systolic and diastolic blood pressures recorded at night (from midnight to 6 a.m.) are 13 6% and 23 9% lower than blood pressure measured from 8 a.m. to 8 p.m., respectively [123]. For easier evaluation, these ABPM data may be expressed as SD scores after correction of their skewed distribution using a new statistical tool [140].

Definition and Prevalence of Hypertension

Many epidemiological studies in normal children tried to define a pathological blood pressure range, which is still debated [15]. Systolic and diastolic values below the 95th centile are considered as normal. Childhood hypertension is defined as (casual) systolic and/or diastolic blood pressure greater than or equal to the 95th centile, if confirmed by two further examinations [84, 96]. Blood pressure readings tend to decrease with repeated measurements in the same child, because children accommodate to the measure-

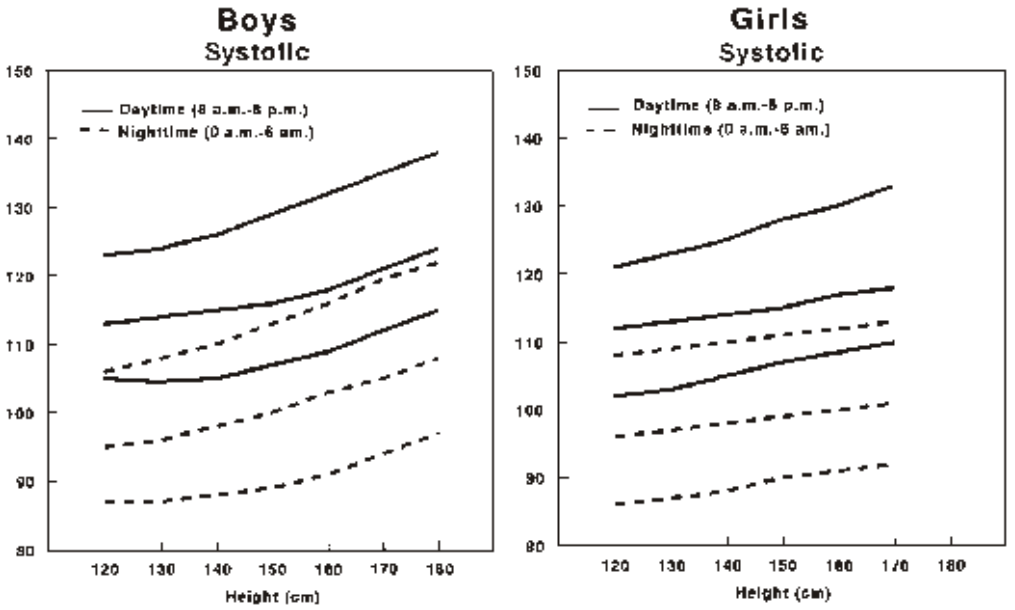

Figure 2a. Daytime and nighttime systolic blood pressure means related to height in boys and in girls for the 10th, 50th and 95th percentiles. Adapted from [123] p 180. Used with permission.

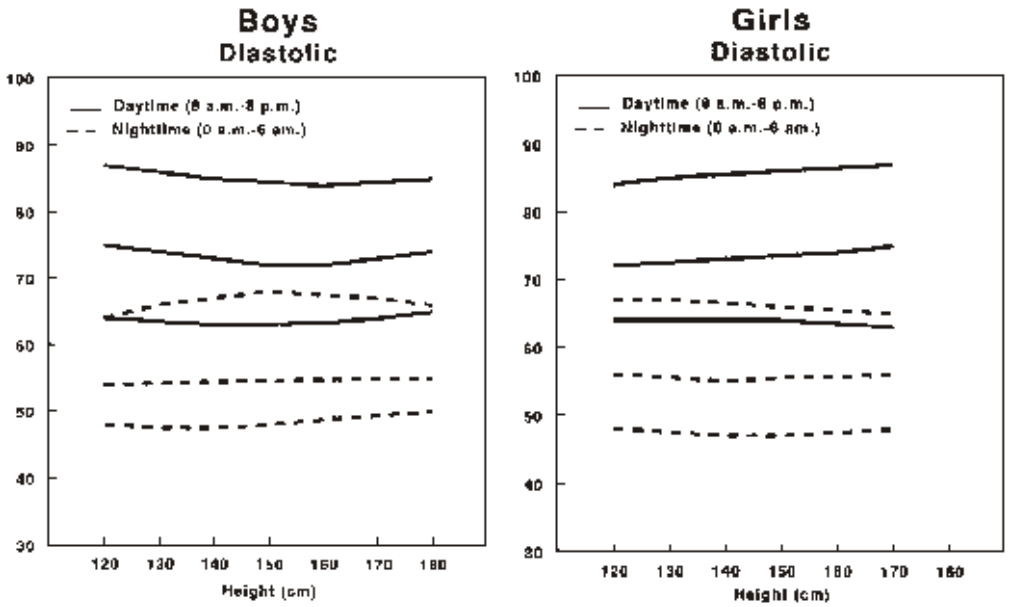

Figure 2b. Daytime and nighttime diastolic blood pressure means related to height in boys and in girls for the 10th, 50th and 95th percentiles. Adapted from [123] p 181. Used with permission.

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ment procedure and also because of the statistical phenomenon of regression towards the mean [120]. Therefore, only about 1% of the childhood population appears to have significant persistent hypertension, i.e. a blood pressure level above which medical evaluation and intervention are recommended. French researchers have defined established hypertension as a systolic and/or diastolic blood pressure 10 – 30 mmHg above the height- and sex-related 97.5th centile, if verified on three occasions. Values > 30 mmHg above the 97.5th percentile would correspond to immediately threatening hypertension [4]. For older adolescents an upper normal limit of 140/90 mmHg is usually accepted as normal. It is expected that in the future the application of ABPM and prolonged follow-up studies will allow a better distinction between normal blood pressure and clinically relevant hypertension.

Primary Hypertension

Early studies were chiefly centered on severe cases of childhood hypertension that usually are secondary to defined organ disorders. The concept was advanced that primary (essential) hypertension originates in childhood [14]. Although early mild essential hypertension poses little immediate risk to children, the findings of left ventricular hypertrophy (LVH) and hemodynamic changes are consistent with an adverse effect before adulthood [26]. Many epidemiological studies have demonstrated that the *initial* blood pressure of an individual child is the most powerful predictor of primary hypertension [129]. However, the tendency of blood pressure to "track", i.e., to remain within a given age-related centile over a longer period of time, is less marked in normal children than in adults. Tracking correlations of childhood (above 1 year of age) with adult levels of systolic and diastolic blood pressure range from 0.21 to 0.39 and from 0.11 to 0.50, respectively [65]. Therefore, a confident prediction of future blood pressure cannot be made for individual subjects, especially those in early childhood. Serial measurements over years might better identify children at risk for primary hypertension [10, 44], especially with respect to ethnic differences of blood pressure changes [30].

Except for age and body size, a number of other *determinants* of blood pressure have been identified in children that may influence the expression of primary hypertension: heart rate, gender, race, biological maturation (puberty), social class, genetic factors, nutrition, and some other exogenous factors [15, 129].

Genetic factors seem to play a major role in the determination of blood pressure levels during childhood [56, 114, 115]. Experimental investigations and numerous family, twin, and adoption studies have supported this concept. Family aggregation of blood pressure was especially convincing in a Minneapolis study which showed that pressure values of children were persistently higher in the presence of a family history of hypertension [83]. In addition, molecular genetic studies have supported the idea that primary hypertension has a hereditary background. Monogenic forms of hereditary hypertension apparently are rare (see Chapter I-20 by Luft F.C.: Essential Hypertension). Studies using markers adjacent to the renin locus and the angiotensin-converting enzyme (ACE) locus failed to find significant associations between blood pressure in siblings with primary hypertension, but possibly a link exists between the angiotensinogen gene locus and hypertension. Genetically determined mechanisms related to blood pressure control include erythrocyte membrane transport, kallikrein excretion, and the combined occurrence of hyper-

tension, hyperlipidemia, and insulin resistance (metabolic syndrome). Although recognition of the genetic determinants of blood pressure may help identify high-risk children, it is not yet a suitable tool for prevention of hypertension [44].

Among *nutritional factors* determining blood pressure levels, the impact of *salt intake* is still controversial in man [15, 118]. Various population studies have shown a relationship between salt intake and prevalence of essential hypertension. In populations with extremely low sodium intake from birth on (e.g. New Guinea), blood pressure does not rise with age and primary hypertension is virtually absent, as demonstrated by the International Cooperative Intersalt Study. Reduced exposure to salt during infancy in Western societies leads to an attenuated increase of blood pressure in the first 6 months of life. However, low salt intake in the first months of life has no influence on blood pressure levels at 8 years of age [56]. It appears possible, but has not been proven by epidemiological studies, that maintenance of low salt intake in older infants and children would result in a lower proportion of adults with primary hypertension [44]. Clinical trials with dietary salt restriction have so far been controversial in children and adolescents [15].

High potassium intake appears to protect against the development of hypertension in laboratory animals, while contradictory results have been reported from interventional studies in humans [70]. In a long-term observation of children aged 15 – 17 years extending over seven years, the slope of blood pressure increase was inversely related to the urinary excretion of potassium [39]. However, other epidemiological studies were not conclusive in attributing any role to potassium for blood pressure regulation in childhood [118, 122].

The same is true regarding *calcium intake*, although a recent investigation has demonstrated a small lowering effect on blood pressure by increased dietary calcium in preschool children [45].

The influence of *dietary fat intake* on blood pressure is controversial. Low fat intake and high ratios of polyunsaturated to saturated (P/S) fatty acids have been associated with low blood pressure in humans. However, an intervention study in healthy teenagers failed to confirm an effect of increasing nutritional P/S ratios on blood pressure [44].

Increased body fat (obesity) is one of the most important predictors of high blood pressure, especially when it involves the central compared to the peripheral compartment. Children with relatively high body size have elevated blood pressure levels compared to their slender peers. The Bogalusa Study showed a 5 – 7 kg increase in body weight in a cohort of normal children aged 7 – 9 years who were followed from 1973 – 1981 compared to a second cohort examined from 1984 – 1992 [42]. This relative increase in weight was associated with adverse changes in serum lipid and lipoprotein levels and with an increased final systolic blood pressure. It seems, therefore, that the secular trend toward obesity induces an exaggerated cardiovascular risk for adolescents. Factors contributing to the secular trend for relative obesity seem to be a more sedentary lifestyle and higher availability of food.

An influence of *maternal nutrition* on childhood blood pressure and later cardiovascular risk has been suspected because a correlation was found between the latter and maternal stature, birth weight, and placental weight. However, the absence of consistent relationships between social factors and blood pressure in the offspring provides little support for the hypothesis that maternal diet has an important influence on cardiovascular risk factors in childhood [138]. The fetal influences on adult blood pressure require further investigation [66].

Physical activity has long been claimed to reduce blood pressure. It is unclear if it acts only by reducing body weight. Studies in healthy preschool children do not confirm the favorable influence of physical activity in adults [60]. There is no doubt, however, that high physical activity in childhood predicts later activity in adult life with consequent benefits on cardiovascular morbidity.

Among *exogenous factors* related to hypertension, the role of alcohol consumption and smoking has not been clarified in adolescence. A British study found that the onset of smoking by age 10 or later was related to *low* diastolic blood pressure at age 10 [22].

Secondary Hypertension

The spectrum of secondary hypertension in children and adolescents comprises a large number of renal, cardiovascular, endocrine, central nervous system (CNS), and iatrogenic diseases [49, 128]. Up to the age of adolescence, secondary forms of hypertension prevail, while most adolescents present with mild essential hypertension.

Acute transient forms of secondary hypertension may be distinguished from chronic persistent forms. In both forms renal disorders predominate.

Transient Hypertension

Renal Disorders

Acute postinfectious glomerulonephritis (GN) is associated with initial hypertension in about half of pediatric patients [16]. Our own experience in 150 children with this disorder showed a prevalence of hypertension of 59% at onset with a rapid improvement within 1 to 2 weeks, resulting in a frequency of only 2% after 6 years of observation [110]. Hypertension is usually mild in idiopathic nephrotic syndrome responding to steroid treatment and associated with minimal glomerular lesions [62]. Transient hypertension is also frequently observed in other acute glomerular disorders, such as Henoch-Schönlein nephritis [139] and hemolytic-uremic syndrome (HUS). In vascular forms of microangiopathy associated with HUS, affecting mainly the medium-sized renal arteries, hypertension is more severe and more often persists compared to glomerular microangiopathy [50]. Various other disorders leading to acute renal failure (ARF) in infancy and childhood are accompanied by a transient rise in blood pressure, depending on the degree of renal dysfunction.

Nonrenal Disorders

Transient hypertension was described in children with increased intracranial pressure [59], convulsions, and other acute conditions of the central and peripheral nervous system [49]. Its pathogenesis is still poorly understood. Another unexplained type of juvenile hypertension was described after skeletal leg traction [52].

Chronic Persistent Hypertension

The prevalence of persistent secondary hypertension in children was estimated to be about 0.1% [68]. Table 3 lists the most frequent causes. In general, the younger the child and the higher the blood pressure, the

Table 3. Causes of persistent hypertension in children and adolescents.

1. Renal

Diseases of the renal parenchyma
- Glomerulonephritis: primary or secondary to systemic disorders (e.g. collagen diseases, Henoch-Schönlein purpura)
- Reflux nephropathy (renal scars)
- Obstructive uropathy (hydronephrosis)
- Hemolytic-uremic syndrome
- Polycystic kidney disease
- Chronic tubulointerstitial nephropathies (pyelonephritis, nephrophthisis etc.)
- Renal dysplasia

Renovascular
- Stenosis of renal artery and its branches (frequently combined with extrarenal vascular lesions)
  Primary: fibromuscular dysplasia, unknown histology
  Secondary: neurofibromatosis, thrombosis, aneurysm, arteriovenous fistula, aorto-arteritis, hilar compression, irradiation, post-trauma
  Syndromes of Williams-Beuren, Alagille, Ehler-Danlos, Klippel-Trenaunay, Marfan, Rett, Rothmund, pseudoxanthoma elasticum, tuberous sclerosis, calcifying arteriopathy
  Vasculitis: periarteritis, Kawasaki disease
- Renal vein thrombosis

Renal failure
- acute
- chronic

Other renal disorders
- Tumors (Wilms tumor, nephroblastoma, hemangiopericytoma)
- Toxic nephropathies
- Metabolic disorders (e.g. diabetes, hyperoxaluria)
- Post-renal biopsy, post-surgery

2. Cardiovascular
Coarctation
Patent ductus arteriosus
Arteriovenous fistula
Aortoarteritis (Takayasu disease)

Table 3. Part 2

3. Endocrine
- Pheochromocytoma
- Neuroblastoma, ganglioneuroma
- Adrenocortical disorders (see Table 5)
- Hyperthyroidism
- Hyperparathyroidism
- Turner syndrome
- Polycystic ovary syndrome

4. Neurologic
- Increased intracranial pressure (tumor, meningitis, trauma)
- Guillain-Barré syndrome
- Polymyelitis
- Dysautonomia (Riley syndrome)
- Psychic stress (anxiety)

5. Drug-related
- Corticosteroids, DOCA
- Erythropoietin
- Heavy metals
- Amphetamine
- Sympathomimetic drugs (nose drops, cold preparations)
- Tricyclic antidepressants
- Use of birth control pills
- Cyclosporine

6. Miscellaneous
- Bronchopulmonary dysplasia (in newborns)
- Intermittent porphyria
- Hypercalcemia
- Burns
- Cyclic vomiting with dehydration-related to leg traction (stretching of femoral nerve)

7. Primary (essential)

more likely a secondary cause of hypertension is present. In different series of children and adolescents reported with secondary persistent hypertension, disorders of the kidney predominate with 86% on the average, but distribution of different nephropathies varies considerably (Table 4).

Three groups of persistent renal hypertension may be distinguished: renal parenchymal

Table 4. Causes of persistent secondary hypertension in 1575 children and adolescents compiled from eight published studies [3, 6, 16, 31a, 43, 74, 133, 141].

Renal parenchymal disease	75.2%	(68 – 89)
Glomerulonephritis	28.1%	(13 – 50)
Pyelonephritic scars (with or without reflux)	23.0%	(10 – 33)
Obstructive uropathy (hydronephrosis)	10.0%	(0 – 18)
Hemolytic-uremic syndrome	5.0%	(0 – 16)
Polycystic kidneys	4.0%	(0 – 10)
Chronic tubulointerstitial nephropathies	1.0%	(0 – 6)
Other renoparenchymal disorders and renal tumors	4.0%	(0 – 10)
Renovascular disorders	10.6%	(0 – 20)
Coarctation	6.5%	(0 – 39)
Endocrine disorders	4.1%	(0 – 12)
Other disorders	3.5%	(0 – 8.5)
All persistent forms of secondary hypertension	(n = 1575)	100%

Most series include to a varying extent patients with preterminal renal failure and also some children on renal replacement therapy [43, 133]. The data are expressed as mean proportion of all children with persistent secondary hypertension (in parenthesis minimum and maximum proportion of patients reported from individual centers). The number of patients with primary hypertension reported from the same centers was 396, i.e. 20% (10 – 45%) of all forms of hypertension.

disorders, diseases of the renal vessels, and chronic renal insufficiency including transplantation. Various pathomechanisms have been proposed to explain transient and persistent renal hypertension, e.g. sodium and water retention (mainly in acute GN), vasoconstrictor mechanisms including the renin-angiotensin and sympathetic nervous system leading to renal ischemia as in HUS, and intravascular volume depletion resulting in the release of vasoactive hormones as in idiopathic nephrotic syndrome.

Renal Parenchymal Disease

Chronic GN, usually associated with the steroid-resistant idiopathic nephrotic syndrome, is responsible for about 30% of all cases of persistent renal hypertension if patients progressing to renal failure are included [16, 107]. Among the various histologic types, focal segmental glomerulosclerosis (FSGS), membranoproliferative glomerulonephritis (MPGN), and crescentic glomerulonephritis (CGN) most frequently lead to increased blood pressure. A high prevalence of hypertension is also observed in secondary glomerulopathies, e.g. in systemic lupus erythematosus (SLE).

A high proportion of pediatric patients with persistent hypertension is associated with chronic pyelonephritis, usually associated with *reflux nephropathy* and scars. After a follow-up of > 10 years, about 10% of patients with vesicoureteral reflux became hypertensive [117]. As shown by recent ABPM studies, blood pressure rises at an early stage of the disease [64, 90], but hypertension usually becomes manifest only in late childhood or adolescence in the presence of severe bilateral nephropathy and after reflux and urinary

tract infection (UTI) have already resolved (see Chapter I-13 by Arant B.S.: Reflux Nephropathy). The pathoanatomical and radiologic picture of scarring in reflux nephropathy associated with severe hypertension was described earlier as Ask-Upmark kidney [55] or as segmental hypoplasia [104]. It is characterized by segmental shrinking of renal parenchyma containing small, hyalinized glomeruli, dilated tubules, thickened and tortuous arterioles, and interstitial fibrosis. Usually, histologic examination does not determine whether these changes correspond to a congenital lesion or whether they are a result of scar formation from reflux or UTI in early life. The associated hypertension seems to be due to local renin secretion, although peripheral renin activity is often normal [57]. Genetic factors interfere in the pathogenesis of hypertension in reflux nephropathy.

Hypertension is also a feature of other forms of *urinary tract malformations*, especially in obstructive uropathy (e.g. ureteral stenosis). However, it appears that with earlier and improved diagnosis and treatment of these lesions in young children, the associated hypertension has become less frequent in recent years.

Polycystic kidneys (PKD) in children often present with an early increase of blood pressure before renal insufficiency occurs. Hypertension requiring drug therapy is found in 60 – 70% of patients with the autosomal recessive form of PKD (formerly called infantile type) and often becomes manifest already after the first year of life [143]. Interestingly, hypertension sometimes improves spontaneously. The autosomal dominant form of PKD (formerly called adult type) has a similar prevalence as the recessive form in childhood, but hypertension and renal insufficiency are less frequent. However, the application of ABPM reveals that blood pressure is increased in one-third of patients at a mean age of 12 years in the absence of clinical symptoms or a reduced glomerular filtration rate (GFR) [116]. To allow an early intervention, regular blood pressure monitoring is therefore recommended in these subjects.

Renovascular Hypertension

Renovascular hypertension is defined as hypertension resulting from lesions that impair blood flow to a part, or all, of one or both kidneys [18, 32, 54]. It represents about 10% of patients (20% of infants) referred to pediatric centers for persistent hypertension, and it more commonly affects young children (Table 4). Renovascular hypertension deserves special attention in childhood, because, except for aortic coarctation, it constitutes the most important cause of persistent hypertension amenable to surgical correction [126]. Considerable advances have been made in recent years regarding diagnosis and treatment of renovascular hypertension in childhood (discussed later).

The most frequent underlying abnormality is *renal artery stenosis* by fibromuscular dysplasia (70%). This affects primarily the media of the arterial wall leading to localized or extended narrowing of renal vessels that may be interrupted by aneurysmal sections. The disease is bilateral in about 70% of cases and may involve the main renal artery, peripheral branches, or both [32]. In a study in 54 patients with renovascular disease, main renal arteries were involved exclusively in 24% and intrarenal vessels exclusively in 44% [29].

The pathogenesis of fibromuscular dysplasia is unknown, but familial occurrence has been described, especially when associated with intimal hypoplasia and with autosomal-dominant *neurofibromatosis*. This condition seems to be the most prevalent ge-

netic disorder associated with renovascular disease [58]. In one series it was found in 15% of renovascular disease in children [18], but the true incidence is probably higher [91]. The gene involved (NF1) was localized to chromosome 17, and several mutations are known.

Renal artery stenosis has been associated with other inherited disorders or syndromes (Table 3). Some of these are combined with anomalies of extrarenal arteries, e.g. aorta, hepatic, or intracranial vessels [13, 29]. The combination with coarctation is known as middle aortic syndrome [127]. Renovascular hypertension is also induced by systemic vasculitis, unspecific aortoarteritis (Takayasu disease) [77], and other conditions listed in Table 3. Following renal artery thrombosis, it is mainly observed in newborns [2].

Chronic Renal Failure and Post-transplantation

Children and adolescents with chronic renal failure (CRF) and ESRD and after renal transplantation represent a growing group of patients suffering from hypertension [104a, 106, 113, 125]. In many pediatric series reporting on renal hypertension (Table 4), they are not clearly differentiated from patients with normal renal function. It is thereby often difficult to determine whether the hypertension is a consequence of the underlying renal disease or the result of renal insufficiency.

Frequency and severity of hypertension depend on the degree of renal failure, the nature of the primary renal disease, and the concomitant treatment. In an earlier study we found that blood pressure starts to rise at lower serum creatinine levels and is more severe in glomerular disorders, reflux nephropathy with renal scars, and polycystic disease than in renal hypoplasia or urinary tract malformations [107]. Practically all children and adolescents become hypertensive when their renal conditions approach end-stage.

In *chronic dialysis patients*, it is difficult to define hypertension precisely because of treatment-related fluctuations of blood pressure and possible changes of the day-night rhythm. In the first weeks or months after start of dialysis, blood pressure usually decreases, allowing a rapid reduction of antihypertensive medication [106], but in many dialyzed children and adolescents hypertension persists. According to EDTA data, 55% of dialyzed children in Europe received antihypertensive drugs with no difference between hemodialysis (HD) and peritoneal dialysis (PD) patients. Nevertheless, about one-third of all children had pressure levels > 10 mmHg above the 95th centile [76]. Determination of blood pressure by casual recordings fails to give consistent results in dialyzed children. The application of ABPM allows a more accurate measurement of interdialytic pressure. Using this technique, we found that hypertension is more prevalent in children and adolescents treated by PD than in those on HD (70% vs. 33%), while the day-night rhythm is conserved with both forms of treatment [71].

The two main *pathomechanisms* of hypertension in predialysis patients as well as those who have started dialysis are salt and water retention and stimulation of the renin-angiotensin system by renal ischemia and arterial damage. The first mechanism prevails in most oliguric dialysis patients when volume balance cannot be maintained, e.g. by reduced compliance with fluid restriction, which is a frequent problem, especially in adolescents. However, daytime blood pressure is not correlated with weight gain, suggesting that factors other than volume overload are involved in the hypertension of dialysis patients. In some patients (mainly with primary glomerular disorders), high renin secretion

from contracted native kidneys induces severe persistent hypertension. In such children, attempts to remove salt and water may paradoxically increase blood pressure in response to hypovolemia. A third pathogenetic factor of hypertension in dialysis patients is a stimulation of the sympathetic nerve activity [88]. It is notable that children exhibit a 2- to 4-fold increase in plasma noradrenaline and adrenaline during a HD or hemofiltration (HF) session [95].

After *renal transplantation*, hypertension seems to be more frequent in pediatric than in adult patients [17]. An American multicenter study found that 70% of young graft recipients require antihypertensive medication at 1 month and 59% at 2 years after grafting [9]. Similar findings were reported from Europe [76]. However, ABPM confirmed hypertension or normotension in only two-thirds of transplanted children and adolescents [72]. This and further studies also showed that the physiological nocturnal dip of blood pressure was attenuated in 30% of grafted pediatric patients, mainly in association with renal artery stenosis or chronic rejection and independent of GFR.

The pathomechanisms of post-transplantation hypertension are multiple [17, 24]. In the early phase, volume expansion, acute rejection crises, and treatment with high-dose glucocorticoids are the most important factors. Renal artery stenosis was reported in up to 20% of hypertensive grafted children [17] and seems to be caused mainly by vascular damage at the time of harvesting and by small vessel calibers in kidneys from young donors [53]. High renin release from native kidneys is less frequent. In later stages after transplantation, chronic rejection is the predominant etiology of hypertension. In addition, some studies found that immunosuppression by calcineurin inhibitors contributes to post-transplantation hypertension in children.

Endocrine Hypertension

Endocrine forms account only for 4% of secondary hypertension in children (Table 4). They present an important group because they are often amenable to surgery.

Pheochromocytoma in children is usually characterized by persistent hypertension and a high prevalence of extrarenal localization and multiple tumors [27]. The diagnosis is established by increased urinary excretion and plasma levels of catecholamines and their metabolites. We refer to Chapter I-23 (Sekkarie M.S.: Secondary Nonrenal Hypertension). To localize the tumor, ultrasonography and abdominal computed tomography (CT) are useful, if the tumor is large enough. Arteriography and venous catecholamine sampling (after adequate sympathetic blockade) are the most helpful techniques for localization. Metaiodobenzylguanidine (MIBG) scanning may yield false negative results.

Different *adrenocortical disorders* (usually inherited) are known to produce hypertension [49] (Table 5). They are generally characterized by renin suppression and hypokalemia. The hypertensive forms of congenital adrenal hyperplasia are associated with increased production of mineralocorticoids. Blood pressure is readily reduced by cortisol replacement [101]. Dexamethasone-suppressible hyperaldosteronism is an important differential diagnosis against the very rare Conn syndrome; low plasma renin activity (PRA) is an important marker [142]. In Cushing syndrome, an exceptional condition in children, cortisol production is increased by a tumor or hyperplasia. In the latter case, hypercortisolism is the result of stimulated ACTH secretion. Much more frequently, corticosteroid excess is due to high-dose administration of glucocorticoids.

Apparent mineralocorticoid excess and Liddle syndrome [134] are different forms of

Table 5. Adrenocortical forms of hypertension in children.

Disorder	Defect	Treatment
Congenital adrenal hyperplasia (adrenogenital syndrome)	11 -hydroxylase deficiency (deoxycorticosterone) or 17 -hydroxylase deficiency (17 deoxysteroids)	cortisol
Conn syndrome = primary hyperaldosteronism (tumor or hyperplasia)	aldosterone secretion	surgery, spironolactone
Dexamethasone-suppressible hyperaldosteronism (glucocorticoid remediable)	abnorma aldosterone synthesis, aldosterone excretion after ACTH	prednisone
Cushing syndrome (tumor or hyperplasia)	cortisol in Cushing's disease by ACTH	surgery, OPDDD
Apparent mineralocorticoid excess	11 -OH steroid dehydrogenase deficiency t/2 of cortisol serum aldosterone	dexamethasone, spironolactone, amiloride
Liddle syndrome	distal tubular sodium transport aldosterone	triamterene, KCl
Gordon syndrome (type II pseudoaldosteronism)	proximal tubular sodium transport	thiazides

(= increased production)

pseudohyperaldosteronism with autosomal dominant inheritance; clinically they are indistinguishable. Gordon syndrome is characterized by increased serum potassium levels, in contrast to the adrenocortical disorders associated with hypertension mentioned previously.

Cardiovascular Causes of Hypertension

Coarctation of the aorta is usually detected in infancy and is the most common cardiovascular form of hypertension. Characteristic findings are decreased blood pressure in the lower compared with the upper extremities, higher blood pressure in the right compared to the left arm, and a systolic ejection murmur over the back. The pathophysiology of hypertension in coarctation involves hormonal, renal, and mechanical factors. The diagnosis is usually made by echocardiography.

Other Forms of Hypertension in Childhood

A variety of lesions of the central and peripheral nervous system are associated with hypertension (Table 3). The pathomechanisms

are not well defined [49]. Sometimes systemic disorders or abnormalities that secondarily involve the central nervous system (CNS) induce hypertension (e.g. hypercalcemia). In adolescent females, hypertension may occur during pregnancy, is often associated with preeclampsia, and causes increased maternal and fetal morbidity and mortality. Care should be taken to avoid certain antihypertensive agents such as ACE inhibitors during pregnancy because of their toxic action on the fetus.

Among the drugs and environmental substances known to cause hypertension, glucocorticoids, sympathomimetic compounds, and tricyclic antidepressants are most important during the pediatric age. Their hypertensive action may be enforced by renal dysfunction.

Clinical Manifestations

In general, hypertensive children present less frequently with clinical symptoms and signs than do hypertensive adults. The clinical manifestations are age dependent. In infants common features are congestive heart failure (CHF), respiratory distress, cyanosis, feeding problems, vomiting, irritability, and convulsions [46, 68]. In older children hypertension is often silent and detected mainly on routine examination. Symptoms and signs are rarely found unless blood pressure is particularly high. They include headache, dizziness, nausea, abdominal pain, polydipsia, fatigue, cardiac failure, epistaxis, weight loss, and growth retardation. Many symptoms appear to be more the result of the underlying disease than of hypertension itself. Physical examination may reveal damage to target organs, notably the heart (functional and structural abnormalities, e.g. LVH) [112], kidney (proteinuria, hematuria), the CNS [111], and the retina. Sometimes it provides a clue for the etiology of hypertension, as in aortic coarctation (see above), or in the presence of abdominal masses (polycystic kidneys, renal or adrenal tumor), or of characteristic features of malformation syndromes associated with hypertension (Table 3).

Diagnostic Approach

The early recognition of hypertension in childhood requires regular measurements of blood pressure, even in asymptomatic children [96]. Once the diagnosis of persistent hypertension is clearly established, a careful history and thorough physical examination are required [31a]. The use of checklists and algorithms for the evaluation of hypertension is recommended [128]. The family history should include an inquiry on cardiovascular disorders, diabetes mellitus (DM), familial nephropathies, and some systemic disorders known to be associated with hypertension (e.g. phacomatoses). The patient's history should not only relate to actual symptoms of hypertension but also investigate back to the newborn period (asphyxia, umbilical catheter?). The use of potentially hypertensinogenic drugs (especially steroids, amphetamines, sodium-containing drugs, contraceptive pills) and substance abuse (smoking etc.) should be recorded. A dietary history (sodium, fat) may be contributory. Rapid weight gain or loss should be noted and its cause investigated. Further questions should be directed to systemic disorders and possible abdominal trauma.

Diagnostic studies need to be guided by the severity and persistence of hypertension. If blood pressure is > 10 mmHg above the 95th centile, the screening procedure outlined in Table 6 is recommended, independent of age

Table 6. Primary investigations proposed in children and adolescents with moderate and severe hypertension.

- Urine analysis: cells, protein, culture, vanillylmandelic acid
- Blood count
- Serum: creatinine, urea, electrolytes, plasma renin activity
- Abdominal ultrasound, including Doppler sonography
- ^{99m}Tc-DMSA or MAG^3 scintigraphy of kidneys
- Chest X-ray
- Electrocardiography
- Echocardiography
- Fundoscopy

adapted from [96]

and of the presence of clinical symptoms. If any investigation reveals an abnormality or if hypertension is severe, further studies are indicated that should focus on the organ involved (Table 7).

If a *renal etiology* is suspected, kidney function and imaging studies are required that are designed to differentiate renal parenchymal disease from renovascular disease. Ultrasonography and radionucleotide scintigraphy should be supplemented by color-aided Doppler flow studies to delineate the intrarenal vasculature [19]. Further imaging aids are urography, voiding cystourethrography, CT, magnetic resonance imaging (MRI), intraarterial (digital subtraction) angiography, and some more sophisticated meth-

Table 7. Supplementary investigations in hypertensive children and adolescents.

In case of suspected *renal* etiology:
- Glomerular filtration rate
- Intravenous urography
- Voiding cystourethrography
- ^{123}I-hippuran scintigraphy of kidneys under basic conditions and after captopril administration
- Renal angiography or digital subtraction angiography
- Renin sampling from renal veins and vena cava
- Computed tomography (CT) scan
- Renal biopsy

In case of suspected *endocrine* etiology:
- Plasma catecholamines, <u>if high</u>:
  - ^{123}I-meta-iodobenzylguanidine (MIGB) scan
  - vena cava sampling of catecholamines
  - urinary catecholamines
- Plasma aldosterone, <u>if high:</u>
  - urine mineralocorticoids
  - dexamethasone suppression test
  - adrenal scintigraphy

  <u>if low:</u>
  - urine mineralocorticoids
  - other plasma mineralocorticoids
  - cortisol response to ACTH or dexamethasone

In case of suspected *cardiovascular* etiology:
- Echocardiography
- Angiography or digital subtraction angiography
- Cardiac catheterization

adapted from [96]

ods [32]. As a screening for renovascular hypertension, the hypotensive response to oral captopril may be a suitable test [25], while the predictive value of the response of peripheral blood renin to captopril seems to be low in children [38]. Captopril (0.5 – 1.0 mg/kg) has also been used to unmask renal artery stenosis by increased radioisotope uptake, with a sensitivity of 80% in children [80].

Split renin sampling from renal veins is helpful for localization and evaluation of vascular lesions but is meaningful only in absence of antihypertensive therapy [32]. Preferably, angiography and split vein renal renin sampling are performed as a combined procedure, at least in young children, to avoid repeated general anesthesia. If nephrectomy is considered, an attempt should be made to determine the contribution of the affected kidney to total renal function by split renal clearance studies.

Prevention of Primary Hypertension

The preventive effects of early recognition and treatment of secondary hypertension in childhood appear to be limited because of the small proportion of patients involved. However, the prevention of *primary* hypertension in childhood has become a large-scale issue in public health.

Two strategies have been proposed for preventing primary hypertension in childhood [44]. The *population approach* attempts to modify the risks among all individuals of a population to achieve a moderate lowering of mean blood pressure by reducing cardiovascular morbidity. Within the population approach of prevention, an educational (active) and an environmental (passive) approach can be distinguished. The first is usually based on health education in schools by health professionals, mass media, and government programs and is practiced mainly in the US. At present, it seems to be the most promising strategy. It should involve family members and focus on physical activity and eating habits, prevention of obesity and smoking, and avoiding high salt intake. The environmental (passive) approach for preventing future cardiovascular disease does not require active steps on the part of the individual child. The efficacy of this method has mainly been proven by modifying the nutritional salt intake.

In contrast to the population approach, the *high-risk approach* concerns selected children with borderline hypertension who do not have a blood pressure high enough to require immediate treatment but may be destined to develop essential hypertension in adult life, especially in the presence of a positive family history or of an increased left-ventricular mass. Nonpharmacologic interventions proposed include weight reduction and increased physical activity. Some difficulties may be encountered when such an approach is followed strictly [44]. First, the precise identification of a high-risk child is difficult because the prediction of adult blood pressure from childhood values is not accurate with present methodology that applies rare casual blood pressure recordings. In future the use of ABPM or of reliable genetic markers of primary hypertension might improve the prediction. Secondly, the efficacy of early intervention strategies to reduce the risk of early cardiovascular disease in high-risk children has, in fact, not been clearly demonstrated, although it is expected that an intervention starting in childhood is more efficient than if delayed until adulthood. Finally, the cost effectiveness of a high-risk approach has been questioned. It should be comparable to screening programs for other disorders and

also to the population approach for preventing hypertension. Furthermore, wrong labeling of a child as being at a high cardiovascular risk could induce deleterious somatic and psychological effects. Therefore, the long-term benefits of intervention programs in high-risk children are considered to be modest [44].

Treatment

General Management

Hypertensive children and their parents need advice concerning diet and lifestyle. With mild hypertension, nonpharmacological forms of therapy will often be sufficient. The effect of a low-sodium diet or potassium supplementation on adolescent blood pressure is controversial [122]. Restriction of sodium intake may be reasonable, especially in salt-sensitive patients (e.g. those with renal failure) in order to spare antihypertensive drugs. Practical problems in reducing sodium intake should be handled in cooperation with a dietitian.

Weight loss is indicated in all obese children and adolescents with hypertension. It not only reduces blood pressure, but also salt sensitivity [99]. Regular exercise of the dynamic (aerobic) type seems to be appropriate unless hypertension is severe.

Pharmacotherapy

Long-Term Treatment

In view of the high morbidity and mortality, severe, sustained hypertension in children should generally be treated by antihypertensive drugs. Some authors believe that antihypertensive drugs are also indicated if blood pressure is only slightly above the 95th percentile. The individual decision to start pharmacotherapy should depend on the persistence and etiology of hypertension (early treatment in renal failure), the presence of other risk factors for cardiovascular disease (e.g. family history, hypercholesterolemia), and the concomitant involvement of target organs (e.g. LVH). In any case, nonpharmacologic forms of therapy should be considered before any pharmacotherapy is started. The goal of any pharmacotherapy is not only to achieve normotension, but also to improve the function of target organs and specifically to induce a regression of LVH.

Experience with antihypertensive drug therapy is limited in children and adolescents compared to adults [34, 48, 69, 91a, 119]. Study designs for testing antihypertensive medications in children have only recently been proposed [23]. In clinical practice, many drugs have been empirically found to be safe and effective in childhood although formal therapeutic trials in this age group are rare. The use of percentile charts of normal blood pressure is helpful for the management of hypertensive children.

Practical Approach to Oral Antihypertensive Treatment

Long-term therapy with antihypertensive agents generally follows a “stepped care” pattern, starting with a low dose of a given drug that is increased up to a tolerated maximum level and subsequently adding further drugs in a similar fashion until normotensive blood pressure levels are attained. Because a full effect is to be expected with most agents only after several days or weeks, a rapid change of the dose schedule must be avoided. With the introduction of more potent antihypertensive drugs with relatively few side effects, it is

Table 8. Dosage and side effects of oral antihypertensive drugs.

	Initial	Maximum dose in mg/kg/day	Interval (hours)	Side effects possible	Application in Renal Failure
Diuretics:					
Hydrochlorothiazide	0.5	2	12	Hypokalemia	–
Chlorthalidone	0.5	2	2 – 4	Hypokalemia	–
Furosemide	1	5	8 – 12	Hypokalemia	+
Spironolactone	1	5	8 – 12	Hyperkalemia	–
Triamterene	2	3			–
-andrenergic blockers:					
Atenolol	1	3	24	Bradycardia,	+
Metoprolol	1	4	12	hypoglycemia,	–
Propranolol	1	5	8 – 12	bronchospasm etc.	(+)
-blocker:					
Prazosin	0.02	0.5	8 – 12	Orthostatism	+
- and -blocker:					
Labetalol	1.5	10	12	Myopathy	(+)
Calcium antagonists:					
Nifedipine (sustained release preparation)	0.5	3	8 – 12	Flushing, tachycardia, peripheral edema, gingival hyperplasia	+
Vasodilators:					
Hydralazine	1	5	8 – 12	Flushing, palpitations, headache, fluid retention, lupus-like rash	+
Minoxidil	0.1	0.5	12	Hypertrichosis, edema	+
$_2$-agonist:					
Clonidine	0.005	0.03	8 – 12	Sedation	+
Converting enzyme inhibitors:					
Captopril	0.5	3	8 – 12	Leukopenia	(+)
In newborn babies	0.1	0.5	8 – 12	Rash, cough, loss of taste	
Enalapril	0.1	0.5	12 – 24	Decreased GFR, hyperkalemia	(+)

now often possible to control hypertension with monotherapy as in adult patients. However, as a rule a multiple drug regimen using low doses is preferable to a high-dose monotherapy accompanied by side effects. The initial drugs should be chosen individually on the basis of the actual blood pressure level, the pathophysiology of the underlying disorder, the side effects to be expected, and the personal experience of the treating physician.

The most frequently recommended classes of antihypertensive agents suggested for monotherapy are -adrenergic receptor blocking agents, calcium channel blockers, and ACE inhibitors. As a dual pharmacotherapy, the supplementation of a -blocking agent with a diuretic agent or a calcium antagonist has been successful in children.

Table 8 lists drugs used for oral antihypertensive treatment in children and adolescents,

initial and maximum doses recommended, and the most important side effects. A short description of the individual drug classes follows. For further pediatric information, the reader is referred to reviews on the subject [1, 34, 69, 91a, 119].

Supervision of antihypertensive treatment should include regular (initially daily) home measurements with documentation of blood pressure after adequate technical information of the patient or his parents and frequent medical follow-up visits, especially if therapy has been changed. With longer treatments, drug dosage needs to be adapted to body size and corresponding blood pressure norms. Noncompliance is an important problem, especially in adolescents, and is related to the use of multiple drugs and frequency of dosing.

Diuretics

The antihypertensive response to diuretics depends on their diuretic action, resulting in decreased extracellular volume, associated with a reduction in peripheral vascular resistance (PVR). Hydrochlorothiazide has been used most widely in children [81]. Its application should be restricted to patients with a GFR > 50 mL/min/1.73 m^2. The most important side effect is hypokalemia, which requires potassium supplementation. In some cases chlorthalidone may be preferable because of its prolonged action.

The loop diuretics are capable of inducing a brisk diuresis of greater size than other agents induce and are therefore indicated in patients with significant fluid retention. Furosemide given intravenously (IV) or orally (PO) is effective even in advanced renal failure, but its renal clearance is smaller in children than in adults [67]. It has successfully been applied in hypertensive children with acute GN. It is also useful as an adjunct to other antihypertensive drugs in patients with acute or chronic renal failure, especially if sodium restriction is difficult to obtain by dietary measures alone. Side effects are volume depletion, hypokalemia, and ototoxicity, which is often related to high blood levels during high-dose IV application. Furosemide-induced hypercalciuria may lead to nephrocalcinosis, especially in pre-term infants.

Potassium-sparing diuretics such as spironolactone and amiloride may occasionally be given to prevent hypokalemia. They also have a place in the management of adrenocortical forms of hypertension (Table 5).

-adrenergic Receptor Blocking Drugs (-Blockers)

The action of -blockers is complex and includes competitive inhibition of catecholamines on -receptor-mediated effects in heart, kidney, and the central nervous system. Cardiac output falls, the activity of the renin-angiotensin system is reduced, and the peripheral release of noradrenaline is impaired. Propranolol as a short-acting drug has been replaced in many pediatric centers by more cardioselective agents with a prolonged half-life ($t_{1/2}$), like atenolol, metoprolol, or acebutolol. Side effects are relatively infrequent in children. Resting bradycardia is rarely severe enough to withdraw the drug. Peripheral vasoconstriction may lead to Raynaud-like symptoms. In obstructive lung disease, -blockers may exacerbate asthmatic attacks, even when cardioselective agents are applied. In young fasting children, severe attacks of hypoglycemia have been described.

-adrenergic Receptor Blocking Agents (-Blockers)

The long-acting agent phenoxybenzamine and the short-acting phentolamine have a

place in the management of pheochromocytoma [27]. Prazosin and doxazosin, which have a high selectivity for $_1$-adrenoreceptors, may be applied in other forms of hypertension and are often combined with a blocker. Side effects are relatively mild.

Labetalol has both selective $_1$- and non-selective -adrenergic blocking activity and is used both PO and IV in children [20], mainly to treat hypertensive emergencies.

Calcium Channel Blockers

Calcium channel blockers inhibit the inward flux of calcium through voltage-dependent slow channels in cell membranes, resulting in vasodilatation. Pediatric experience was reported on verapamil [105], nifedipine [87, 93], nitrendipine [137], nicardipine, felodipine [132], and amlodipine [102]. For treatment of moderate forms of persistent hypertension, the long-acting preparations of nifedipine and nicardipine (given twice daily) are widely applied as monotherapy in pediatric patients. These agents are also useful in post-transplant hypertension, because they counteract the cyclosporin A-induced increase of blood pressure mediated by afferent arteriolar constriction. Side effects of calcium channel blockers (Table 8) are rare with sustained-release preparations and are usually limited to a short period after initial drug administration.

Other Vasodilating Agents

These consist of a pharmacologically heterogeneous group of agents that act on vascular smooth muscles to reduce PVR.

Hydralazine is still in use in some pediatric centers, although it is less effective than newer compounds and has many side effects. It should therefore be prescribed only in small dosages combined with a -blocking agent or diuretic.

Minoxidil is a strong vasodilator with similar side effects and with the additional danger of hypertrichosis 2 – 3 weeks after onset of treatment. It is therefore advocated only in hypertensive states resistant to other drugs.

Clonidine acts centrally as an $_2$-receptor agonist and may be given by the oral or percutaneous route. Although it frequently provokes sedation and a dry mouth it has proven useful in the treatment of sudden blood pressure elevation in chronic hypertension.

Angiotensin-converting Enzyme (ACE) Inhibitors

The introduction of ACE inhibitors has greatly facilitated the management of children with severe hypertension in recent years. ACE inhibitors interfere with the enzymatic conversion of angiotensin I to the active angiotensin II, a major vasoconstrictor and stimulus for aldosterone production. They are effective especially in patients with high plasma renin activity (PRA).

Captopril given orally decreases blood pressure within 15 – 30 min and reaches peak blood levels in 1 – 2 hours. It has a $t_{1/2}$ of only 2 hours in children [121], but its pharmacodynamic $t_{1/2}$ is considerably longer, which allows a dosage 2 – 3 times daily. Captopril, which has been extensively studied in children and adolescents [82], is particularly useful in newborns and infants in whom its potency is greater compared to older children [86]. Captopril treatment in this age group should therefore be started with only 0.01 mg/kg/dose, while in older children the recommended starting dose is 0.2 mg/kg, which can be increased up to 0.5 – 1 mg/kg/dose given 2 – 3 times daily.

Table 9. Antihypertensive drugs for hypertensive emergencies in children.

Drug	Dose
Nifedipine	0.3 – 1.0 mg/kg PO
Nicardipine	0.5 – 3.0 g/kg/min by IV infusion
Diazoxide	2 – 6 mg/kg rapidly IV
Labetalol	1 – 3 mg/kg IV
Clonidine	0.002 – 0.006 g/kg slowly IV or 10 g/kg/4 h by IV infusion
Hydralazine	0.2 – 0.8 mg/kg IV
Minoxidil	0.1 – 0.2 mg/kg PO
Sodium nitroprusside	0.5 – 10 g/kg min IV infusion (titration from lowest dose upwards every 20 min)
Urapidil	initial 1 – 4 mg/kg/h, reducing to 0.5 – 2 mg/kg/h by IV infusion

PO = oral, IV = intravenous

Enalapril and ramipril have a delayed action starting 1 – 2 hours and continuing for 18 – 48 hours after administration [79]. Therefore, these drugs are now preferred for long-term use in children [136] and are used also to reduce proteinuria [92, 124, 140a].

ACE inhibitors and their metabolites are excreted by the kidney, which requires a dose reduction in renal failure. The various side effects described previously with the use of captopril have become less frequent with reduced dosage and the introduction of long-acting preparations. Persistent cough still remains a problem in about 1% of patients. In the case of hypovolemia, ARF with hyperkalemia and renal artery thrombosis may develop due to the vasodilating action of ACE inhibitors on the efferent glomerular arterioles. Therefore, care has to be taken to avoid states of dehydration (e.g. by the use of diuretics). Before the start of any treatment with ACE inhibitors, renal artery stenosis should be excluded. Serum creatinine and potassium should be monitored frequently during treatment.

Clinical experience with the use of angiotensin receptor inhibitors (e.g. losartan, irbesartan) is still limited in children [36], and therefore these agents cannot yet be generally recommended.

Hypertensive Emergencies

Hypertensive emergencies are defined as a sudden increase of blood pressure (usually > 180/120 mmHg in older children) and are not regularly associated with clinical symptoms such as cardiac failure, headache, encephalopathy, facial palsy, or eye ground changes. Immediate intervention, even in asymptomatic cases, is important to avoid damage of target organs, especially the CNS [111]. It is debated if blood pressure should immediately be reduced to normal levels, because this might decrease brain perfusion [28].

Table 9 lists the recommended doses of antihypertensive drugs applied PO or IV to children with hypertensive emergencies. Oral nifedipine has become the drug of first choice in all pediatric age groups because it is effective, safe, and easy to administer [37, 93]. It is rapidly absorbed and reaches its maximum action after about 1 hour. In emergencies, the drug should be removed from the capsule either by having older children bite through the

capsule or by withdrawing its content and applying it by a syringe [119]. Sublingual administration, as formerly recommended, is not needed. If the response is insufficient, the initial dose may be repeated and possibly doubled. Recently, nifedipine has also been administered as an IV infusion (e.g. 5 mg/1.73 m^2 nifedipine given over 4 – 8 hours). The preparation is light sensitive. Frequent side effects of calcium antagonists are tachycardia and flushing of the skin.

As alternatives, IV boluses of diazoxide and labetalol [20] are recommended; however, they have more side effects. They are preferably given as continuous infusion [69, 119]. Clonidine has the advantage of also being applicable by the transcutaneous route.

In severe symptomatic cases of hypertension and in case of resistance to other drugs, sodium nitroprusside given as IV infusion is the drug of choice. However, it should be applied only under permanent monitoring of blood pressure, because this may rapidly drop to dangerous hypotensive levels. Side effects like vomiting and neurological symptoms are due to toxic metabolic products that accumulate, especially in children with renal insufficiency. As an alternative, infusions of urapidil have recently been recommended. Hypertensive crises due to sodium and water retention (e.g. in acute GN) are best treated by IV furosemide (2 – 5 mg/kg).

Surgical Treatment

Only a few relatively rare hypertensive conditions are amenable to a surgical treatment, including revascularization procedures. They include aortic coarctation, chromaffin and adrenocortical tumors, and different renal conditions. Surgical repair or balloon angioplasty of coarctation is frequently followed by an insufficient drop of blood pressure and may require additional drug therapy.

Unilateral nephrectomy is indicated in the case of a nonfunctioning kidney, that is, if the structure and function of the contralateral kidney are more or less intact as in the case of hydronephrosis or of a renal tumor. Recent studies have stressed the value of unilateral nephrectomy in various forms of renal hypertension [7]. After nephrectomy, it often takes weeks or months until the blood pressure normalizes, and pharmacotherapy must be continued in the meantime. Polar resection is sometimes indicated in presence of segmental renal scars.

Percutaneous transluminal angioplasty has become the first-choice treatment in short, isolated stenosis of the main renal artery and may be successful even in small children [85]. Long-term medical treatment over years is a suitable alternative in infants until they have reached an adequate size for surgery [12]. In bilateral and complicated cases of renal artery stenosis, other surgical techniques, including autotransplantation, have also been successful in children [33, 78, 126].

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