



Management of pediatric hypertension

Hypertension is one of the major contributors to cardiovascular, renal and CNS morbidity and mortality. Although it is more prevalent in adults, hypertension and its sequelae are being seen with increasing frequency in pediatrics recently. The majority of children have hypertension secondary to renovascular and renal parenchymal disease, and it appears that the increased incidence is primarily related to the epidemic of obesity, which is a known risk factor for the development of the condition. After the diagnosis of hypertension is established, a thorough evaluation for secondary causes should be conducted according to existing guidelines. Nonpharmacologic interventions should be discussed in any child, even though the diagnosis of hypertension may not be confirmed, but if risk factors are identified. Those interventions should be even more encouraged if the diagnosis of hypertension or prehypertension is confirmed. Nonpharmacologic intervention focuses on salt restriction, diet modification, exercise and physical activity, as well as improved sleep habits. Initiation of medical therapy is guided by the degree of blood pressure elevation, presence of symptoms and existing risk factors. A wide variety of oral medications and intravenous therapies are available for use in children with mild, moderate or severe blood pressure elevations. This article reviews the diagnosis and evaluation of hypertension in children, and provides an update on the pharmacologic and nonpharmacologic treatment options for hypertension, including hypertensive urgency and emergency.

KEYWORDS: antihypertensive agents, children, exercise, hypertension, therapy

Hypertension and its long-term effects on the cardiovascular and cerebrovascular system has become a major concern for providers involved in the care of children. Recent data support an increase in the prevalence of hypertension in the pediatric population [1,2]. Public education and standardized guidelines for the evaluation of hypertension have led to increased awareness of the possible long-term health risks associated with high blood pressure. Despite increased recognition, the optimal management remains uncertain, as outcome data reflecting the true long-term systemic effects of hypertension in children are limited. Strategies to control hypertension are divided into conservative intervention and treatment with medications with the goal to achieve normotension. The focus of current research is to minimize long-term cardiovascular effects of hypertension and reduce associated morbidity and mortality. A recently published guideline by the National High Blood Pressure Program, the *'Fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents'*, provides a framework for the approach to hypertension in children [3].

Incidence & prevalence of hypertension in children

The exact incidence of hypertension in children is unknown. Nevertheless, with childhood obesity having become an epidemic, and given the well-documented association of obesity with elevated blood pressure [4], the incidence appears to be steadily increasing.

The prevalence of persistently elevated blood pressure readings in children between the ages of 4 and 15 years is estimated to be 1.5–2% and rising [5]. Several studies have shown significant variation in the prevalence of hypertension depending on age and ethnicity [2,6,7]. This increase can at least in part be explained by the epidemic of childhood obesity, which has become a major focus of concern within and outside of the USA [8–10]. More than 33% of children in the USA are at risk for being overweight, more than 17% are truly overweight. These numbers have been steadily increasing since the late 1990s [11]. On the other hand, some authors find unconvincing evidence of an increased incidence of obesity related to hypertension rather than other possible factors [12]. Those include birth weight as outlined by Barker's hypothesis, tendency to a

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sedentary lifestyle and dietary factors. Kidney disease is the main etiologic factor for hypertension in children. The reported prevalence of hypertension in children with chronic kidney disease is much higher compared with primary hypertension. A review of almost 4000 children with chronic renal failure enrolled in the North American Pediatric Renal Trials and Collaborative Studies estimated the prevalence of hypertension to be as high as 50% [13].

Etiology of hypertension

The etiology of hypertension is quite different in children when compared with adults. One important risk factor, if not the most important one, for the development of hypertension is having a positive family history. The incidence of hypertension in children who are members of hypertensive families has been estimated to be as high as 10% [14]. Whereas primary or essential hypertension is the most common diagnosis in adults, secondary causes of hypertension are far more common in children. Leading causes in the first decade of life are renal parenchymal disease, followed by renovascular disease and heart disease, especially coarctation of the aorta. In the second decade of life, the three most common causes of hypertension are renal disease, essential hypertension and obesity [5].

Renal parenchymal hypertension in children can develop due to a large number of underlying causes, including acute and chronic glomerulonephritis, vasculitis, hemolytic uremic syndrome, reflux nephropathy or obstructive uropathy, as well as hereditary diseases such as polycystic kidney disease [15]. Renovascular disease, diagnosed in 5–10% of children with hypertension, is commonly secondary to thrombotic or embolic events of the renal artery or vein, especially in the neonatal age group, or due to external compression of the blood vessels.

One somewhat separate and surprisingly common entity to consider is the so-called 'white-coat' hypertension, which in the pediatric age group is seen primarily in older children [16]. These individuals often have significantly elevated blood pressure readings when seen in the doctor's office, but have absolutely normal readings when checked casually. Its incidence has been reported to be between 45 and 62%, depending upon the normative data used. [16]

Diagnosis of hypertension

The fourth report on the diagnosis, evaluation and treatment of high blood pressure in children and adolescents published in 2004 revised the

guidelines for the correct diagnosis of hypertension in children and adolescents [3]. Children 3 years of age and older should have their blood pressure measured at least yearly [17]. Under certain circumstances, including past admission to the neonatal intensive care unit, prematurity, congenital heart disease and known renal or urologic disease, blood pressures should be measured even earlier in life. Blood pressure normal values for children have been established according to age, gender and height. Hypertension is defined as average systolic and/or diastolic readings above the 95th percentile adjusted for the child's gender, age and height. Blood pressure elevation has to be confirmed on three independent occasions, given the known blood pressure variability between readings in children. Blood pressure readings between the 90th and 95th percentile is considered as prehypertension. Under certain circumstances, blood pressure readings greater than or equal to 120/80 mmHg can fall below the 90th percentile. Under these circumstances, the child should be considered prehypertensive. The relationship between high blood pressure and risk of cardiovascular events and other end-organ damage is continuous and independent of other risk factors. In adults, increments of 10 mmHg in diastolic blood pressure or 20 mmHg in systolic blood pressure doubles the risk of cardiovascular events at a blood pressure range of 115/75 to 185/115 mmHg. [18]

The national high blood pressure education program working group included the 99th percentile for blood pressure normal values, and proposed a staging of hypertension [3]:

- Stage 1: Blood pressure between the 95th percentile and the 99th percentile plus 5 mmHg
- Stage 2: Blood pressure greater than the 99th percentile plus 5 mmHg

The difference between blood pressures in the 95th and the 99th percentile is usually small, and given possible variability in measurement, the 5 mmHg addition was introduced to allow differentiation between mild and more severe hypertension.

Reliable and correct blood pressure measurement is essential in making the correct diagnosis, especially in younger children who are quite often uncooperative. Several factors are to be considered when attempting a blood pressure reading in children, including a quiet, comforting environment, appropriate cuff size and positioning, accurately calibrated

and maintained equipment, and a short resting phase before the measurement is taken [19]. In infants, blood pressure readings should be obtained in the recumbent position, whereas the sitting position (with arm at heart level) is preferred in older children. The legs should not be crossed, as it can increase the blood pressure readings. [20]. The appropriate sized cuff should have an inflatable bladder, the width of which should cover approximately 40% of the child's arm circumference at the midpoint of the arm between acromion to the olecranon, whereas the length should cover 80–100% of the arm circumference [21].

Evaluation of hypertension

Confirmed hypertension in the pediatric population requires a thorough evaluation. In the majority of children, the rule is 'the higher the blood pressure and the younger the child, the more likely the secondary causes of hypertension'. A relationship between body mass index and hypertension has been documented in the past by several well-designed studies [22,23]. The recommended evaluation recognizes presence and absence of overweight and obesity. All children with hypertension should have a careful review of their medical history carried out, including neonatal phase, family history, sleep habits and assessment of risk factors including diet and substance abuse. Particularly in teenagers, interviewing the patient alone might need to be considered. A complete review of systems, focusing not only on hypertension-related symptoms, but also underlying illnesses leading to hypertension, should be performed [24].

A thorough physical exam is mandatory. This should include an assessment of femoral and pedal pulses, auscultation for a possible abdominal bruit, palpation of the kidneys and fundoscopic exam.

Four extremity blood pressure measurements should always be carried out as the readings might be helpful in the evaluation of coarctation of the aorta. Bloodwork for a complete blood count, renal function and electrolytes, fasting lipid panel and glucose should be sent. Fasting blood tests should also be considered in obese children with borderline hypertension, and in the presence of a positive family history or chronic renal disease. Renal ultrasound, routine urinalysis and urine culture should be obtained. Additional studies are recommended, depending on the degree of hypertension, age of the child and presence or absence of risk factors. Most of those additional tests are usually ordered under specialist care once the child is referred.

Ambulatory blood pressure monitoring (ABPM) is a valuable tool used commonly in specialty clinical practice, as it allows for better assessment of the degree of hypertension, urgency of intervention and response to therapy. Multiple blood pressures are taken by machine, usually over a 24-h period. In a recent American Heart Association scientific statement, recommendations are made for standard assessment of ABPM in children, giving the indications, methodology, calculations and interpretation [25]. Some experts in the field of pediatric hypertension recommend the use of ABPM early, given the known shortcomings in reliability of the casual blood pressure check in the office setting [26].

Nonpharmacologic management

After the diagnosis of hypertension is confirmed and secondary, treatable causes (especially renal–parenchymal and renovascular disease) are excluded, nonpharmacological management options need to be considered depending on the presence or absence of obesity and the degree of hypertension. Therapeutic lifestyle changes are recommended for both stages of hypertension and children with prehypertension. Successful nonpharmacologic management depends on several important factors that need to be considered. The treating provider will need to comprehensively assess if the family understands the scope of the problem and the potential long-term health risk for the child. Understanding hypertension as a major health concern will in part determine if the family is ready for lifestyle changes. It is also important to realize that even though the focus of concern is on the child, the entire family will have to make those changes and adjust to the needs of the child. Depending on the family structure and motivation, the conservative management can be very time-consuming and exhausting for families and providers. In our experience, we favor a structured team approach at each visit, and frequent focused follow-up appointments with a clear goal for each visit.

■ Weight loss & exercise

The relationship between obesity and hypertension has been well documented. Recently, new light has been shed on the pathophysiology of obesity-related hypertension [27]. It appears that increased levels of insulin and insulin-mediated stimulation of the sympathetic nervous system may lead to sodium and water retention and expansion of the extracellular fluid volume. Weight loss, if sustained, has been shown to have a pronounced effect on blood pressure

control and other risk factors associated with cardiovascular disease in children between 6 and 14 years of age [28]. In obese adolescents, a weight loss of 5% has been shown to reduce the blood pressure significantly, and the blood pressure may actually normalize well before ideal body weight is achieved [29]. However, one of the major concerns in clinical practice is our inability to successfully manage weight loss in obese children. Most obese pre-adolescent children, and greater than 70% of obese adolescents, will grow up to become obese adults [30].

■ Dietary modifications

A healthy diet is recommended for all children, regardless of the presence or absence of hypertension. The effects of dietary sodium restriction on blood pressure have been extensively studied in the past. It appears that a subset of hypertensive patients are sodium sensitive, and could benefit from dietary sodium restriction. In children, sodium restriction has overall shown to only minimally reduce the blood pressure [31,32]. Sacks *et al.* have reported a reduction of dietary sodium to be associated with a clear reduction in systolic blood pressure when combined with a diet rich in fruits, vegetables and low-fat dairy [33]. Also, urinary sodium excretion as a measure of intake has been shown to be a determinant of blood pressure curves in African-American children [34]. Two recently published studies by He *et al.* [35,36] not only provided further support of the significance of dietary sodium and the effects on blood pressure, but also demonstrated evidence of a link between dietary salt intake and consumption of sugar-containing sodas. This could be of importance, as a reduction in dietary salt could have an effect on the incidence of obesity and related cardiovascular disease. In a recent randomized, controlled trial of diet, exercise and weight loss (DEW-IT) it was shown that in subjects receiving single hypertensive agent treatment, a comprehensive lifestyle intervention can substantially lower blood pressure and improve control [37]. Several dietary factors other than salt have been discussed as being potentially important in blood pressure control. These include dietary micronutrients such as potassium, calcium and magnesium; macronutrients such as polyunsaturated fatty acids and fiber; breast milk and formula. In a study by Couch *et al.*, it is shown that a Dietary Approaches to Stop Hypertension (DASH)-type diet – rich in fruit, vegetables and low in dairy products, fats and salt – is more effective

in reducing systolic blood pressure than a routine diet [38]. Certainly, additional studies on larger patient populations are needed.

■ Sleep

Obstructive sleep apnea is a known risk factor for hypertension in adults, but, to date, little is known about that relationship in children. Obesity is associated with the development of obstructive sleep apnea and hypertension, but not all obese children develop hypertension. A recent study by Raede *et al.* proposed the presence of hypopnea in obese children as a possible important link between obesity and hypertension [39]. A recent meta-analysis by Zintzaras *et al.* showed no clear association between elevated blood pressure readings and sleep-disordered breathing in children [40]. Nevertheless, as the authors point out, there are few studies, with only small numbers of cases on the topic, and larger, standardized studies will be necessary to further assess the issue.

Pharmacologic therapy

Indications for pharmacologic therapy of childhood hypertension include symptomatic hypertension, persistent blood pressure elevation despite nonpharmacologic interventions and during evaluations of stage 2 hypertension to avoid any complications. The recommended goal of pharmacologic therapy is to lower the blood pressure below the 95th percentile for the child's gender, age and height, unless concurrent conditions exist in which case the goal blood pressure should be below the 90th percentile [3]. Despite those guidelines, the lack of documentation of benefit from pharmacologic intervention leaves a degree of uncertainty among providers as to when to recommend initiation and from families when to agree to medication therapy [41]. Interestingly, the results of a questionnaire of North American pediatric nephrologists, a group of specialty providers commonly involved in the care of hypertensive children, has shown that the majority is aiming for blood pressure reduction below the 90th percentile or even lower [42]. When deciding on medication therapy in hypertensive children, several factors need to be carefully considered, as treatment in children is quite different compared with adults. Formulation of the drug, frequency of administration and side-effect spectrum all significantly influence compliance of the patient. The overall goal is to achieve optimal blood pressure control with as little medication as possible and the least amount of expected side

effects. Therefore, single-agent therapy is often preferred with the goal to titrate the dose to a maximum before considering switching to a different agent if therapy is unsuccessful, or to add a second agent if the response remains suboptimal. Once the decision to treat is made, the provider has a variety of medications available to choose from. As outlined below, several categories of medications are available for the treatment of the hypertensive child. A wide variety of agents can be found in some of those categories, which can sometimes be confusing for the provider. In the authors' experience, it is advisable to be very familiar and comfortable with the indications, side effects, pharmacokinetics and pharmacodynamics of one or two agents in each group, rather than having limited knowledge about a larger number.

In cases of secondary hypertension, therapy should be directed toward the underlying etiology of the hypertension whenever possible.

In recent years, the number of trials of antihypertensives in children has increased significantly secondary to the US FDA Modernization Act (1997) [101], and change in the Federal 2002 Best Pharmaceuticals for Children Act. Nevertheless, it is important to be aware that still very few antihypertensives have received US FDA approval for all pediatric age groups. A summary of commonly used antihypertensives in children can be found in TABLE 1.

■ Angiotensin-converting enzyme inhibitors

Several angiotensin-converting enzyme (ACE) inhibitors have been studied in the pediatric population and are routinely used. ACE inhibitors competitively block the conversion from angiotensin I to angiotensin II, an octapeptide with vasoconstrictive properties resulting in a decrease in blood pressure. They are usually well tolerated with a limited side-effect spectrum. For the clinician, major adverse events include hyperkalemia, azotemia (especially in the setting of pre-existing abnormal renal function), cough and angioedema, among several others. Captopril has been studied extensively in the pediatric population [43,44]. Enalapril is one of the first antihypertensive medications, in use since the 1980s, but only received US FDA approval for pediatric labeling in 2001. Wells *et al.* have shown its safety and efficacy in clinical trials in children [45,46]. Lisinopril, a newer ACE inhibitor with a longer half-life and duration compared with enalapril, has also been studied in children, and US FDA-approved pediatric labeling information is available [47].

■ Angiotensin receptor blockers

Angiotensin receptor blockers (ARBs) are a relatively new class of agents available for use in the treatment of hypertension in children. Available ARBs include irbesartan, losartan and valsartan. ARBs block the effects of angiotensin II on one of its receptors, AT₁. Binding of angiotensin II to AT₁ induces vasoconstriction, activation of the sympathetic nervous system and sodium plus water retention. ARBs counteract high blood pressure by preventing those effects. Very few pediatric studies involving ARBs are available. Sakarcin *et al.* reported the safe use of irbesartan in children and adolescents with a mean reduction in blood pressure by 16 mmHg for systolic and 10 mmHg for diastolic values at treatment day 28 [48]. In a recent trial by Benjamin *et al.*, no significant efficacy was demonstrated in reduction of both systolic and diastolic blood pressure using irbesartan, but the limitation in the trial was the fact that higher than adult doses were not tried [49]. In addition, pediatric liquid formulations were not used. A recently published double-blinded, randomized, multicenter study, the first one to use an antihypertensive agent in children less than 6 years of age, showed that valsartan safely and effectively lowered both the systolic and diastolic blood pressure [50].

■ Calcium-channel blockers

Several calcium-channel blockers have been used for treatment of hypertension in children. These include nifedipine, isradipine and felodipine. US FDA-approved pediatric labeling information is available for amlodipine. Calcium-channel blockers, initially used in clinical practice for the treatment of angina, lower blood pressure by decreasing cellular calcium uptake and release from intracellular calcium stores; this in turn leads to dilatation of peripheral arterioles and decrease in peripheral vascular resistance. The side-effect spectrum of calcium-channel blockers is overall minimal. Nifedipine is known to cause gingival hyperplasia; amlodipine was reported in conjunction with peripheral edema. One of the best-studied drugs in children is probably amlodipine, a member of the dihydropyridine class, which was shown in several studies to be effective with an acceptable side effect spectrum [51,52]. A significant number of children achieve acceptable blood pressure control with monotherapy and once-daily dosing, but it appears that younger children require higher doses per kilogram of body weight [53].

Table 1. Commonly used oral antihypertensive medications in children.

Class of agents	Agent	Starting dose	Precautions	Selected adverse effects
Calcium-channel blockers	Amlodipine	0.05–0.6 mg/kg/day or 5–10 mg daily in children age 6–17 years Children <13 years of age need twice as much as children >13 years of age	CHF, severe aortic stenosis, hepatic dysfunction	Peripheral edema, angioedema Jaundice, muscle cramps Arthralgia
	Nifedipine (extended release)	0.25–0.5 mg/kg/day or divided b.i.d. Maximum 3 mg/kg/day up to 120 mg/day	CHF, severe aortic stenosis	Similar to amlodipine
	Isradipine	0.05–0.2 mg/kg/dose t.i.d. to q.i.d. Usual dose: 0.3–0.4 mg/kg t.i.d. Maximum 0.8 mg/kg/day up to 20 mg/day	CHF, hepatic dysfunction	Edema, palpitations, flushing, urinary frequency, abdominal discomfort
	ACE inhibitors	Enalapril Maximum 0.1 mg/kg daily or divided b.i.d. Maximum 0.6 mg/kg/day up to 40 mg/day	All ACE inhibitors and ARBs: Renal impairment, hyponatremia, hypovolemia Pregnancy: risk for fetopathy	All ACE inhibitors and ARBs: angioedema, azotemia, hyperkalemia and muscle cramps
ARBs	Lisinopril	0.07 mg/kg/day in children 6 years and above Maximum 0.6 mg/kg/day up to 40 mg/day		
	Benazepril	0.2 mg/kg/day with maximum of 10 mg/day Maximum 0.6 mg/kg/day up to 40 mg/day		
	Captopril	0.3–0.5 mg/kg/dose three-times per day 6 mg/kg/day up to 450 mg/day		
	Losartan	0.7 mg/kg/day (maximum initial dose 50 mg) Maximum 1.4 mg/kg/day up to 100 mg/day		
β-blockers	Irbesartan	6–12 years: 75–150 mg/day >13 years: 150–300 mg/day		
	Atenolol	0.5–1 mg/kg/day Maximum dose of 6 mg/kg/day up to 200 mg/day	CHF, renal dysfunction, asthma, diabetes, hyperthyroidism	All β-blockers: bradycardia, AV block, edema, fatigue, constipation, nausea, bronchospasm
	Metoprolol	1–2 mg/kg/day o.d. to b.i.d. (nonsustained released) Maximum daily dose of 100 mg	Hepatic dysfunction, peripheral vascular disease	
	Propranolol	0.5–1 mg/kg/day divided b.i.d. to q.i.d. Maximum 16 mg/kg/day up to 640 mg/day	Diabetes mellitus, peripheral vascular disease, renal and hepatic dysfunction	

Data taken from [3,41,74].
ACE: Angiotensin-converting enzyme; ARB: Angiotensin-receptor blockers; b.i.d.: Twice a day; CHF: Congestive heart failure; o.d.: Once daily; q.i.d.: Four times a day; SLE: Systemic lupus erythematosus; t.i.d.: Three-times a day.

Table 1. Commonly used oral antihypertensive medications in children.

Class of agents	Agent	Starting dose	Precautions	Selected adverse effects
Diuretics	Furosemide	1–2 mg/kg/day o.d. or b.i.d. Maximum upto 6 mg/kg/day	Hepatic cirrhosis	Urticaria, photosensitivity, hypokalemia, hyponatremia, hypocholeremic alkalosis, pre-renal azotemia, nephrocalcinosis, ototoxicity
	Hydrochlorothiazide	1 mg/kg/day o.d. Maximum dose 50 mg/day	Renal and liver disease Gout, diabetes mellitus and SLE	Photosensitivity Hypokalemia, hypocholeremic metabolic, alkalosis, hepatitis, polyuria
Others	Spirolactone	1 mg/kg/day o.d. to q.i.d. Maximum daily dose up to 100 mg/day	Dehydration, hyponatremia Hepatic dysfunction	Hyperkalemia, hyperchloremic metabolic Acidosis Agranulocytosis, muscle weakness
	Triamterene	1–2 mg/kg o.d. or b.i.d. Maximum daily dose up to 300 mg/day	Impaired hepatic or renal function Diabetes mellitus, nephrolithiasis	Hyperkalemia, hyponatremia Metabolic acidosis Photosensitivity Abnormal liver function tests
Others	Clonidine	5–10 µg/kg/day divided b.i.d. to t.i.d.	Renal impairment, cardio- or cerebro-vascular disease, monitor for signs of depression	Rebound hypertension after discontinuation, insomnia, anxiety, depression, sodium and water retention
	Hydralazine	0.75–1 mg/kg/day divided q.i.d. Maximum up to 7.5 mg/kg/day up to 200 mg/day		

Data taken from [3,41,74].
ACE: Angiotensin-converting enzyme; ARB: Angiotensin-receptor blockers; b.i.d.: Twice a day; CHF: Congestive heart failure; o.d.: Once daily; q.i.d.: Four times a day; SLE: Systemic lupus erythematosus; t.i.d.: Three-times a day.

■ Direct vasodilators

Hydralazine and minoxidil are both direct primary arteriolar vasodilators decreasing peripheral vascular resistance and blood pressure. US FDA-approved pediatric labeling information is available for both drugs. Minoxidil has been known for several decades to be an effective antihypertensive agent for children [54,55]. Both medications are usually reserved for either severe hypertension or insufficient blood pressure control, despite use of multiple medications [56]. Hypertrichosis is a cosmetic side effect seen uniformly in all patients treated with minoxidil, and it is important to discuss this with the family before therapy is initiated. Concomitant therapy with a diuretic is necessary in almost all patients due to fluid retention as a consequence of the profound vasodilatory effect.

■ β -blockers

β -adrenergic blockers were one of the first widely used agents for the management of childhood hypertension. There are several mechanisms proposed for their antihypertensive effects, such as decreased inotropy and chronotropy, decreased sympathetic tone to reduce peripheral resistance and partial blockade of renin release [57]. Amongst commonly used agents are propranolol (noncardioselective β -blocker), atenolol/metoprolol (cardioselective β -blockers) and labetalol (α - and β -blocker) [5]. Some β -blockers like bisoprolol are used in conjunction with hydrochlorothiazide to potentiate the antihypertensive effect. One of the very few randomized, double-blinded and placebo-controlled trials of this drug combination did not show any difference in reduction in blood pressure between treatment and placebo groups, and the absolute reduction in systolic and diastolic blood pressure was less than seen in adults [58]. β -blockers are contraindicated in patients with asthma and diabetes; they are known to reduce exercise performance and can potentiate depressive symptoms. The common side effects of β -blockers include bradycardia, syncope, light-headedness, dizziness, somnolence, nightmares and others, but these are seen more often with noncardioselective β -blockers. In view of their limited efficacy and narrow therapeutic:toxicity ratio, β -blockers are not considered as first-line antihypertensive agents [59,60]. They can be used in conjunction with other drugs or under special clinical circumstances, including hypertensive urgency and emergency where labetalol, a nonselective α - and β -blocker is very useful as a titratable drug [61]. In a Cochrane database systematic

review, β -blockers were not found to be superior to calcium-channel blockers and renin-angiotensin inhibitors; evidence also did not support them as first-line medications for treatment of hypertension [59,60].

■ Diuretics

Treatment with diuretics has shown to improve blood pressure by reducing plasma volume and peripheral vascular resistance [5]. In general, diuretics have stood the test of time in management of childhood hypertension. Despite the increasing use of calcium-channel blockers, ACE inhibitors and ARBs, diuretics are clinically valuable drugs, mostly in conjunction with the aforementioned agents to augment their effects and to improve blood pressure control. Thiazide diuretics are commonly used in clinical practice and have been well-studied in the adult population. As they need to be secreted into the tubular lumen to inhibit sodium-chloride reabsorption distally by competing for chloride sites on the sodium-chloride cotransporter, the effectiveness depends on the glomerular filtration rate. Loop diuretics, just like thiazides, work on the tubule from the lumen side, competing for the chloride binding sites of the sodium-potassium-two-chloride cotransporter in the thick ascending loop of Henle. Loop diuretics are rarely used as first-line agents, but can be valuable in children with chronic kidney disease or as an adjunct therapy, especially to counteract fluid retention in hypertensive children treated with agents inducing vasodilatation [62]. A third group of diuretics are potassium-sparing agents, such as spironolactone, which either directly blocks the epithelial sodium channel in the distal tubule and collecting ducts (amiloride, triamterene) or by competitive inhibition of the aldosterone receptor (spironolactone). As mentioned above, compliance is a very important factor to be considered when treating a child for hypertension. Diuretics, especially loop diuretics, increase urine output making frequent bathroom breaks necessary; this effect can significantly interfere with the social life of older children [57]. As diuretics, depending on the group, can have a profound effect on serum electrolyte balance and urine electrolyte excretion, interval monitoring of serum electrolytes is recommended.

■ Others

Clonidine, a central α_2 -receptor agonist, is an antihypertensive agent available for the treatment of hypertension in children, and the US FDA has approved pediatric dosing of this drug. Effects of

the drug are mediated through diminished sympathetic outflow decreasing vasomotor tone and heart rate. Unfortunately, the side-effect profile is considerable, so that its use as a first-line agent is limited. Caution needs to be exerted, as abrupt discontinuation of the medication can result in significant rebound hypertension. Peripheral α -receptor antagonists include doxazosin, prazosin and terazosin. Even though dose recommendations based on expert opinion exist, US FDA-approved pediatric labeling information is not available for any of these drugs.

■ Therapy with combination drugs

Several studies of combination drugs have been performed in the adult population, but very little data is available in children. Sorof *et al.* reported significant blood pressure reduction of systolic and diastolic blood pressures in a combination of β -blockers and thiazide diuretics compared with placebo. They also observed a large placebo effect in the control group, and failure to achieve target blood pressure control put the usefulness as a first-line agent into question [58]. To our knowledge, there is no reported data on combination therapy with antihypertensives and lipid-lowering agents in children.

Hypertensive urgency & emergency

Severe hypertension in children, though rarely encountered in clinical practice, is considered a medical emergency and needs to be addressed without delay. Even though the terminology is not consistent throughout the literature, hypertensive emergency describes blood pressure elevation in either a symptomatic child, or evidence of end-organ injury requiring prompt reduction of the blood pressure into a safe range. Hypertensive urgency allows for a more gradual decrease in blood pressure. The etiology of the secondary hypertension is most commonly renal or endocrine disease. Agents used for the treatment usually have short half lives to allow easier titration, and are preferably administered by the intravenous route [63].

■ Pharmacologic therapy of hypertensive urgency & emergency

Several medications are available for the treatment of a child with severe hypertension. The goal of therapy is to reduce the blood pressure by approximately 25% to 'safe' levels within a short period of time, usually 8 h. Once this goal is achieved, the strategy is to normalize the blood pressure over the next 24–48 h. The rationale for this approach is to keep a balance in the

reduction of blood pressure to avoid end-organ injury from elevated blood pressure versus blood pressure reduction-induced organ hypoperfusion and ischemic injury. It has been described that prolonged elevation in blood pressure results in structural and functional changes in the vasculature, shifting autoregulation of blood pressure to a higher level than physiologic, so a sudden drop in blood pressure will reduce the perfusion pressure resulting in ischemic damage [64,65]. Admission to the Pediatric Intensive Care Unit in children with symptomatic and severe hypertension, especially in the presence of end-organ involvement, is almost mandatory [66]. Some hypertensive urgencies can be managed on an outpatient basis if close follow-up is guaranteed, and once the blood pressure is in a safe range. Nevertheless, in the author's experience, it is safer to proceed with in-patient admission, especially if treatment with intravenous antihypertensive medications is considered.

A summary of commonly used medications for the treatment of urgent and emergent hypertensive situations can be found in TABLE 2. As mentioned in a comprehensive review on the topic by Adelman *et al.*, it is important that the treating provider chooses medications he is comfortable and experienced with as no universally applicable algorithm exists [63]. Preferred intravenous medications in our pediatric intensive care unit include labetalol, sodium nitroprusside, nicardipine and hydralazine.

Bunchman *et al.* reported good response to labetalol, in the intravenous form a α_1 - and β -adrenergic blocker, regardless of the absence or presence of renal dysfunction [61].

Nicardipine is the first intravenously given dihydropyridine calcium-channel blocker. Available data, including two case series of significantly hypertensive children due to renal disease and other etiologies, showed effective control of the blood pressure [67,68].

A subset of patients with hypertensive urgency can be safely treated with oral medications, but this is definitely more the exception rather than standard. In our institution, the first-line agent for oral therapy is nifedipine, which is also a member of the dihydropyridine group with powerful vasodilatory effects. Good response to therapy has been documented including infants and children with renal disease [69,70].

Conclusion

The goal of therapy in children with hypertension is to decrease the blood-pressure readings to normal or borderline values, depending

Table 2. Medications used for treatment of hypertensive urgency and emergency.

	Route of administration	Starting dose	Precautions	Adverse effects
Nicardipine	Intravenous drip	Neonates: 0.5 µg/kg/min Children: 0.5–1 µg/kg/min	Liver dysfunction	Tachycardia
Nitroprusside	Intravenous	0.3–0.5 µg/kg/min, titrate to effect Usual dose 3 µg/kg/min Maximum dose 8–10 µg/kg/min	Severe renal impairment Hepatic failure Increased intracranial pressure	Hypotension Cyanide toxicity
Labetalol	Intravenous	0.2–1 mg/kg/dose maximum 20 mg/dose	Hyper-reactive airway disease Congestive heart failure Diabetes mellitus	Orthostatic hypotension Tingling on scalp/skin Bronchospasm
	Intravenous drip	0.4–1 mg/kg/h, maximum of 3 mg/kg/h	Liver dysfunction	
Hydralazine	Intravenous	0.1–0.2 mg/kg/dose every 4–6 h	SLE-like syndrome	
	Intramuscular		Severe renal disease Cerebrovascular disease	
Nifedipine	Oral	0.25–0.5 mg/kg/dose, maximum dose 10 mg/dose and 1–2 mg/kg/day	Congestive heart failure	Flushing
			Aortic stenosis	Dizziness

SLE: Systemic lupus erythematosus.

on several associated factors. It is well-documented in studies conducted in adults with hypertension that the risk of hypertension-related organ disease is diminished with better control of blood pressure. Unfortunately, the current recommendations for children are based on parameters obtained from a cross-section of healthy controls, and long-term data confirming a preventative effect on cardiovascular disease are few. Left-ventricular hypertrophy has commonly been used as a marker of end organ injury and new techniques are being developed [71]. It needs to be emphasized that the current recommendations are a work-in-progress, and that the guidelines will likely be refined as more long-term data become available. What is truly important is the fact that the approach to blood-pressure control in children has changed dramatically over the years, and that the awareness of hypertension as a potential health problem, especially when associated with obesity, has increased.

Uncontrolled hypertension appears to carry a significant risk for long-term cardiovascular and cerebrovascular disease in children and adults. Even though there are few long-term data available, early and correct diagnosis of hypertension, completion of the recommended evaluation and initiation of nonpharmacologic and pharmacologic therapy is proposed to decrease long-term morbidity and mortality. Nonpharmacologic therapy is focused on changes to pursue a healthier lifestyle, including weight reduction in the presence of obesity, scheduled exercise and dietary adjustments including salt restriction. Depending on success

or failure of nonpharmacologic intervention, the degree of hypertension and associated risk factors for long-term morbidity and mortality, initiation of medical therapy needs to be considered. A multidisciplinary and family-centered approach is recommended, especially in cases obese of children, consultation with a behavior health specialist might be beneficial [72].

Future perspective

Preventable causes of hypertension have become a major health concern in children over the past two decades. Primary prevention of obesity and early recognition of children at risk for hypertension needs to continue to improve by increasing awareness through public education. Even though long-term data are few, it appears intuitive that promoting a healthy lifestyle and weight loss reduce the rates of hypertension in children and decrease long-term morbidity and mortality. Clinical trials to assess the success of provider-recommended conservative management strategies should be supported, and experiences shared to allow a more standardized approach. In addition to conservative interventions, including lifestyle and dietary changes, a wide variety of antihypertensive agents are available for the treatment and control of hypertension in children, but have not been studied to yield sufficient data to allow them to be approved. Unfortunately, the number of antihypertensive trials and approved medications are still few in children compared with adults, and trial failure rate is high [49]. Careful review of completed clinical trials to assess inclusion criteria and reasons for study termination might allow for an increase

in efficiency of study enrollment, and ultimately allow pediatric labeling of more antihypertensive drugs [73]. Also, the lack of long-term outcome data makes it difficult to assess how successful intervention and treatment truly are. Large, prospective, multicenter trials are necessary to increase our knowledge on therapy response, disease prevention as well as safety and efficacy of antihypertensive agents in children.

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Executive summary

Introduction

- Pediatric hypertension has become a major healthcare concern in the recent past.
- Standardized gender, height and age-related blood pressure norms, and improved measuring techniques, have led to an increase in detection of hypertension in children.

Incidence & prevalence of hypertension in children

- The exact incidence of hypertension in children is unknown, but the overall prevalence estimated to be 1.5–2%.
- The epidemic of childhood obesity is partially responsible for an increased incidence in hypertension.

Etiology of hypertension

- Kidney disease is the most common etiology of hypertension in children.
- Obesity and hypertension are closely linked, with the epidemic of childhood obesity being a major contributing factor for the increased incidence of childhood obesity.

Diagnosis of hypertension

- Hypertension in children is defined as three independent blood pressure readings for either the systolic and/or diastolic value above the 95th percentile corrected for gender, height and age.
- Blood pressures have to be taken in a resting child in a quiet environment with the appropriate cuff size.
- Ambulatory blood pressure monitoring can be a very useful tool to exclude white-coat hypertension and to monitor the therapeutic efficacy of antihypertensives.

Evaluation of hypertension

- After the diagnosis of hypertension is confirmed, a thorough evaluation for secondary causes is needed. In addition to a complete medical history and physical exam, this usually includes bloodwork for a complete blood count, renal function, electrolytes and fasting lipid profile. Urinalysis and culture should be sent. Renal ultrasound should be considered.

Nonpharmacologic management

- Lifestyle modification should be discussed in any child with documented hypertension or in the presence of significant risk factors.
- Weight loss, a healthy and balanced diet, scheduled exercise and optimized sleeping habits might be beneficial in controlling blood pressure and minimizing the risk for long-term hypertension-related complications.

Pharmacologic therapy

- Medical therapy is indicated for all children with stage 2 hypertension, symptomatic hypertension and for those with persistent hypertension despite nonpharmacologic interventions.
- Single-agent therapy is usually preferred with a goal to titrate the dose to a maximum prior to switching or adding a second agent.

Hypertensive urgency & emergency

- Children with symptomatic and severe hypertension should be monitored and treated on an in-patient basis.
- The preferred route of medication administration is intravenous.

Conclusion

- The goal of therapy is to reduce the elevated blood pressure to normal or near normal levels in order to diminish the likelihood of end organ damage.
- The choice of antihypertensives should be directed at the underlying pathophysiologic mechanism of hypertension, in conjunction with nonpharmacologic therapy aimed at pursuing a healthier lifestyle.
- A multidisciplinary family-centered approach is recommended specially in obese children, in whom a behavior health specialist might also be beneficial.

Future perspective

- Controlled studies are necessary to determine the long-term risk of cardiovascular disease in hypertensive children, and to assess the usefulness of current intervention strategies.

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