Pharmacologic Treatment of Childhood Hypertension

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Abstract

Hypertension has traditionally been regarded as a rare occurrence in childhood and adolescence; however, there is compelling evidence to suggest that elevated blood pressure is increasingly common in this population. As a result, care providers are increasingly expected to appropriately evaluate and treat hypertensive pediatric patients. This chapter provides an overview of antihypertensive drug therapy in children, including indications for treatment and approaches to optimizing BP control. A detailed review of available antihypertensive agents is provided with an emphasis on pediatric-specific data with respect to dosing, efficacy, and safety.

Keywords

Pharmacotherapy • Clinical trials • Diuretics • Vasodilators • Calcium channel blockers • ACE inhibitors • Angiotensin receptor blockers • Beta-adrenergic blockers

Introduction

Historically, hypertension was thought to be exceedingly rare in young children and uncommon in adolescents. As recently as the early 1970s, there was ongoing debate regarding the clinical utility of routine blood pressure (BP) screening in the general pediatric population [1, 2]. In addition, there was no widely accepted definition of what constituted a hypertensive BP reading in children. Established standards for normal BP in infants and children of varying ages existed [3, 4]; however, in practice, BP values exceeding 130–140/85–90 were arbitrarily considered to be the upper limits of normal in all children. Results from the first Health and Nutrition Examination Survey (1971–1974) suggested that pediatric hypertension was far more common than previously thought [5]. Although they reported a prevalence rate of only 0.8 % in 12–17-year-olds, the definition used for

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hypertension was systolic BP > 160 mmHg or diastolic BP > 95 mmHg. When a less restrictive definition was applied (systolic BP > 140 or diastolic BP > 90), the prevalence rate in the same age group increased to 5.6 % [5]. Around this time, pharmacologic treatment of childhood hypertension was generally restricted to those with an established underlying cause and/or symptomatic disease. Given the rarity with which antihypertensive drugs were used in children, it is not surprising that young patients were largely ignored in early studies evaluating the safety and efficacy of these agents.

Over the last four decades, childhood BP has been studied more rigorously, resulting in clearer definitions of pediatric BP values and consensus recommendations pertaining to appropriate BP measurement and monitoring. This has resulted in a broader understanding of the prevalence of childhood hypertension as well as the implications of hypertension for short-term and long-term overall health. In addition, indications for the initiation of drug therapy have been further clarified.

Since the National Heart, Lung, and Blood Institute (NHLBI) commissioned the First Task Force on Blood Pressure Control in Children in 1977, normative BP values have been adopted as the standard for assessment of BP in children [6]. Hypertension has been defined as BP consistently above the 95th percentile for age, gender, and height. Normative BP values have been refined over time, with the most recent update presented in the National High Blood Pressure Education Program's (NHBPEP) Fourth Report published in 2004 [7]. Table 36.1 provides the classification schema for BP in childhood from the Fourth Task Force Report.

The widespread adoption of these definitions has facilitated increased uniformity in the classification of pediatric BP. As a result, the scope of disease burden has come into sharper focus. Screening studies dating back to the late 1970s and 1980s estimated that less than 2 % of children were persistently hypertensive [8, 9]. These studies also demonstrated the necessity of repeated BP measurement in order to make an accurate diagnosis of hypertension, as there is a clear trend of regression toward the mean in those with initially elevated readings, as well as significant lability of BP values, even in children with secondary forms of hypertension. Disturbingly, several recent studies suggest that the percentage of children and adolescents with hypertensive BP readings has doubled in the last two decades, with 3–5 % now affected [10–12]. In addition, there has been a concomitant rise in the prevalence of prehypertension, with 10–15 % of youths now affected [11, 12], as well as an increase in absolute systolic and diastolic BP values of 1.4 mmHg and 3.3 mmHg, respectively [13]. This upward trend in BP has generally been attributed to the ongoing childhood obesity epidemic.

Table 36.1 Classification of blood pressure in children

Blood pressure classification	Blood pressure percentiles
Normal	SBP and DBP < 90th percentile
Prehypertension	SBP or DBP 90–95th percentile or BP > 120/80 mmHg even if <90th percentile
Stage 1 hypertension	SBP or DBP ≥ 95–99th percentile + 5 mmHg
Stage 2 hypertension	SBP or DBP > 99th percentile + 5 mmHg

BP blood pressure, *DBP* diastolic blood pressure, *SBP* systolic blood pressure

With these data in mind, it is reasonable to assert that childhood hypertension can no longer be considered a rare entity. Pediatric providers are confronted with patients with elevated BP with increasing regularity. Unfortunately, there is evidence that primary care pediatricians remain uncomfortable with the evaluation and treatment of children with elevated BP [14, 15]. With respect to pharmacologic therapy, this is understandable given the underrepresentation of pediatric patients in drug trials and the attendant lack of clear dosing guidelines for the pediatric population historically. Important legislative initiatives over the last 15 years, including the Food and Drug Administration Modernization (FDAMA) Act of 1997 and Best Pharmaceuticals for Children Act of 2002, have stimulated a marked increase in pediatric trials of antihypertensive agents. As a result, there is now a growing

list of antihypertensive medications approved by the FDA for pediatric use. Similar efforts in Europe, specifically the Regulation of Medicinal Products for Paediatric Use, promise to further promote the rigorous study of antihypertensive medications in children [16]. Therefore, pediatric providers should feel emboldened by the increasing body of evidence-based data with respect to dosing, efficacy, and safety of antihypertensive drugs in children. It should, however, be noted that data pertaining to long-term outcomes of those receiving antihypertensive drug therapy, including effects on target-organ damage and cardiovascular morbidity, remain limited.

Table 36.2 Indications for initiation of pharmacologic therapy in hypertensive children

Clinical indication	Blood pressure goal[a]
Persistent hypertension despite therapeutic lifestyle changes	<95th percentile
Hypertension with associated end-organ damage	<90th percentile
Hypertension in the setting of chronic kidney disease	<90th percentile
Hypertension in the setting of diabetes mellitus (types 1 or 2)	<90th percentile
Secondary hypertension	<90th percentile
Symptomatic primary hypertension	<95th percentile

[a]based on casual/office blood pressure measurement

General Approach to the Hypertensive Child

The Fourth Report of the NHBPEP provided clinicians with updated recommendations for BP screening in the pediatric population as well as guidelines for the diagnosis, evaluation, and treatment of hypertension. Revised tables were provided that include the 50th, 90th, 95th, and 99th percentiles by gender, age, and height percentiles. Based on these guidelines, annual BP screening is presently recommended in all children >3 years of age; routine BP measurement in children <3 years is limited to those with increased risk of hypertension [7].

If BP elevations are noted on screening, confirmation using appropriate equipment and measurement technique is critical. Given the high prevalence of reactive ("white coat") hypertension in children [17–19], ambulatory BP monitoring (ABPM) is increasingly utilized to confirm elevated office readings (see Chap. 11). In those with confirmed hypertension, a detailed evaluation is recommended to distinguish between primary and secondary hypertension, to assess for additional cardiovascular risk and to assess for target end-organ damage (as detailed in Chaps. 29 and 32). In all patients, appropriate counseling regarding therapeutic lifestyle changes is indicated. Recommendations in this regard generally involve family-based interventions to modify the diet, increase physical activity, and facilitate weight loss (see Chap. 35). In childhood, drug therapy for hypertension is typically reserved for patients with definite indications, as outlined in Table 36.2.

In the adult population, death from ischemic heart disease and stroke increases progressively and linearly from systolic blood and diastolic BPs of 115 mmHg and 75 mmHg, respectively [20]. Efforts to increase awareness of the risks associated with hypertension and optimize therapy in adults have resulted in favorable trends in morbidity and mortality attributed to hypertension [21]. Cardiovascular events are rare in children and, therefore, are not practical end points in the study of antihypertensive therapies. Although subclinical end-organ damage (left ventricular hypertrophy, increased carotid artery intimal-medial thickness; discussed in detail in Chap. 29) [22–24] has been increasingly recognized in hypertensive children, there are few studies looking at the impact of therapy on progression and/or regression. Given the paucity of outcome-based studies in the pediatric population, goals for antihypertensive therapy in children have not been well established and are largely inferred from adult studies. As recommended in the NHBPEP Fourth Task Force Report, in uncomplicated primary hypertension, the goal should be reduction of BP to less than the 95th percentile. In the setting of concurrent disease or target end-organ damage, BP should be lowered to less than the 90th percentile [7]. Recent recommendations by the European Society of Hypertension

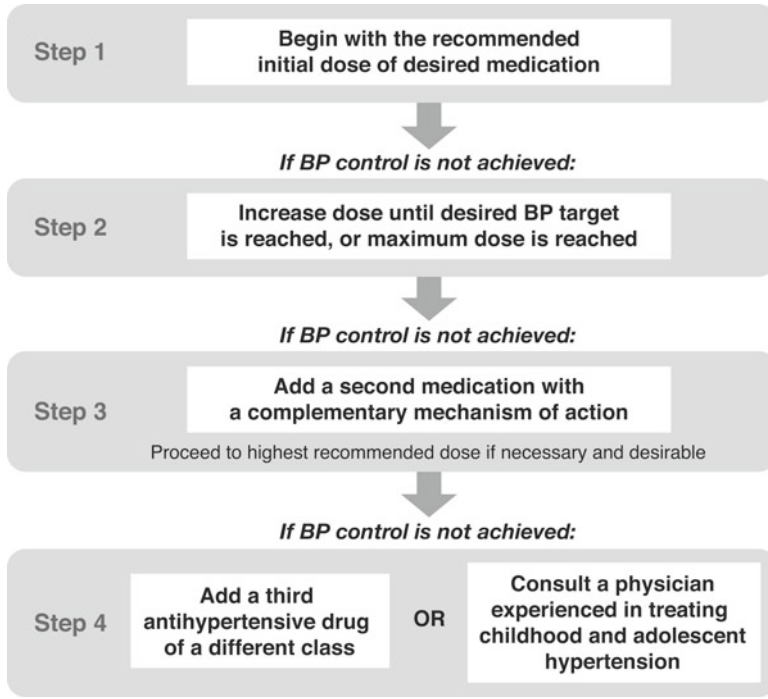

Fig. 36.1 Stepped-care approach to prescribing antihypertensive medications in children and adolescents

advocate for more rigorous BP control, with target BPs below the 90th percentile in uncomplicated hypertensive children, below the 75th percentile in children with CKD, and below the 50th percentile in children with concomitant CKD and proteinuria [16]. These goals were derived based on evidence that more aggressive BP control may be particularly beneficial in slowing renal functional decline in children with chronic kidney disease [25]. One comment about these recommendations is that they are based on ABPM targets; how they relate to the usual approach to treatment using office BP values remains unclear at this time.

When antihypertensive drug therapy is necessary, a stepped-care approach (see Fig. 36.1) to the initiation and escalation of drug dosing is typically recommended [7, 26]. After a first-line agent is selected, it should be started at the lowest recommended dose range with ongoing BP monitoring to determine effect. If the BP remains above the desired range, the dose is gradually increased until adequate BP control is achieved or until the maximum recommended dose is reached, at which time a medication from a different class should be added. All patients require monitoring for medication-related side effects, which may be dose limiting and require addition of a second agent earlier or replacement of the first agent altogether.

Given the lack of pediatric data on the optimal first-line agent, selection of an initial antihypertensive agent is largely dependent on the judgment of the individual provider. Although specific drugs may be preferential in particular clinical settings based on putative benefits or predicted response (see below, Directed Therapy), considerable variation exists in the choice of a first agent, particularly in the setting of primary hypertension. A survey of pediatric nephrologists revealed that 47 % used angiotensin-converting enzyme (ACE) inhibitors, 37 % calcium channel blockers (CCBs), 15.3 % diuretics, and 6.6 % beta-adrenergic blockers as first-line therapies in primary hypertension [27]. Studies comparing the efficacy of the different classes of antihypertensive medications in children are lacking. The vast majority of studies evaluating the

BP-lowering effect of the various antihypertensive classes in children have demonstrated a significant absolute reduction in BP as a result of treatment [28], with ACE inhibitors, angiotensin II receptor antagonists (ARBs), and CCBs demonstrating similar antihypertensive efficacy [29]. In addition to assessing putative benefit and likelihood of response to a particular agent, it is also important to consider potential adverse effects prior to initiating therapy. For example, noncardioselective beta-adrenergic blockers are generally avoided in those with reactive airway disease due to an increased risk of bronchospasm [30] and ACE inhibitors/ARBs are absolutely contraindicated in pregnancy due to the potential for fetopathy [31].

The following sections provide a review of classes of antihypertensive agents, emphasizing those with existing pediatric efficacy and safety data. For each class, a brief summary of the mechanism of action is provided. Table 36.3 provides dosing guidelines for medications commonly used in hypertensive children.

Angiotensin-Converting Enzyme Inhibitors

ACE inhibitors have a number of modulatory effects on the renin-angiotensin-aldosterone system (RAAS) that result in a reduction in BP. Foremost, ACE inhibitors downregulate the conversion of angiotensin I to angiotensin II, a potent vasoconstrictor that also stimulates the secretion of aldosterone from the adrenal cortex. In addition, ACE inhibitors prevent the metabolism of bradykinin, an endogenous vasodilator and stimulator of natriuresis through direct renal tubular effects [32].

Relative to other antihypertensive classes, ACE inhibitors have the largest body of evidence supporting their use in pediatric patients [33]. The large majority of these agents have been systematically studied in FDAMA-related industry-sponsored trials. As a result, there are robust pediatric specific data related to dosing, efficacy, and safety.

Captopril, the first orally available ACE inhibitor, was developed in 1975 and received FDA approval for the treatment of adult hypertension in 1981 [34, 35] In 1979, Oberfield et al. [36] described the use of captopril in the successful treatment of a child with malignant hypertension refractory to therapy with other oral antihypertensive agents. Since that time, a number of small, uncontrolled, and largely descriptive studies have recapitulated the utility of captopril in hypertensive children over a broad range of age groups and helped elucidate complications associated with therapy, including hypotension, hyperkalemia, diminished glomerular filtration rate (GFR), and leukopenia [37–41]. Although captopril does not have a pediatric specific indication, owing largely to its patent expiration prior to passage of the FDAMA, established dosing guidelines exist [7] and it continues to be a valuable agent in the treatment of selected children with elevated BP. Information is available for the preparation of a stable extemporaneous solution. Disadvantages of captopril include it's short duration of action, necessitating three times daily dosing.

Well-designed pediatric-specific trials have been conducted for most of the longer-acting ACE inhibitors, resulting in published safety and efficacy data. Enalapril, lisinopril, and fosinopril have been studied using similar double-blind, placebo-controlled, dose-response designs. In patients aged 6–16 years, enalapril and lisinopril were both found to reduce BP in a dose-dependent manner that was maintained across all study subgroups (age, gender, race, and ethnicity) [42, 43]. Minimum effective doses were similar for enalapril and lisinopril (0.08 mg/kg/day and 0.07 mg/kg/day, respectively). Few adverse events were reported during either trial; however, the short duration of each (4 weeks) precluded robust conclusions with respect to safety and tolerability. As a result of these trials, FDA-approved labeling for enalapril and lisinopril includes clear dosing guidelines as well as instructions for preparation of an extemporaneous suspension [44].

The fosinopril trial demonstrated substantial reduction of systolic and diastolic BP in low (0.1 mg/kg/day)-, medium (0.3 mg/kg/day)-, and high (0.6 mg/kg/day)-dose groups; however, no dose-response relationship was observed [45].

Table 36.3 Medications for the treatment of hypertension in children

Class	Drug	Starting dose	Interval	Maximum dose[a]
ARAs	Eplerenone	25 mg/day	QD–BID	100 mg/day
	Sprinolactone[b]	1 mg/kg/day	QD–BID	3.3 mg/kg/day up to 100 mg/day
ARBs	Candesartan[b]	1–6 years: 0.2 mg/kg/day	QD	1–6 years: 0.4 mg/kg/day
		6–17 years: <50 kg 4–8 mg QD		6–17 years: <50 kg 32 mg daily
		>50 kg 8–16 mg QD		>50 kg: 32 mg daily
	Losartan[b]	0.7 mg/kg/day (up to 50 mg QD)	QD	1.4 mg/kg/day (max 100 mg QD)
	Olmesartan[b]	20–35 kg: 10 mg QD	QD	20–35 kg: 20 mg QD
		>35 kg: 20 mg QD		>35 kg: 40 mg QD
	Valsartan[b]	<6 years: 5–10 mg/day	QD	<6 years: 80 mg QD
		6–17 years: 1.3 mg/kg/day (up to 40 mg QD)		6–17 years: 2.7 mg/kg/day (up to 160 mg QD)
ACE inhibitors	Benazepril[b]	0.2 mg/kg/day (up to 10 mg/day)	QD	0.6 mg/kg/day (up to 40 mg/day)
	Captopril[b]	0.3–0.5 mg/kg/dose	BID–ID	0.6 mg/kg/day (up to 450 mg/day)
	Enalapril[b]	0.08 mg/kg/day	QD–BID	0.6 mg/kg/day (up to 40 mg/day)
	Fosinopril	0.1 mg/kg/day (up to 10 mg/day)	QD	0.6 mg/kg/day (up to 40 mg/day)
	Lisinopril[b]	0.07 mg/kg/day (up to 5 mg/day)	QD	0.6 mg/kg/day (up to 40 mg/day)
	Quinapril	5–10 mg/day	QD	80 mg/day
α- and β-adrenergic antagonists	Carvedilol[b]	0.1 mg/kg/dose (up to 6.25 mg BID)	BID	0.5 mg/kg/dose up to 25 mg BID
	Labetalol[b]	2–3 mg/kg/day	BID	10–12 mg/kg/day (up to 1.2 g/day)
β-adrenergic antagonists	Atenolol[b]	0.5–1 mg/kg/day	QD	2 mg/kg/day up to 100 mg day
	Bisoprolol/HCTZ	2.5/6.25 mg daily	QD	10/6.25 mg daily
	Metoprolol	1–2 mg/kg/day	BID	6 mg/kg/day (up to 200 mg/day)
	Propranolol[c]	1 mg/kg/day	BID–QD	8 mg/kg/day (up to 640 mg/day)
CCBs	Amlodipine[b]	0.06 mg/kg/day	QD	0.3 mg/kg/day (up to 10 mg/day)
	Felodipine	2.5 mg/day	QD	10 mg/day
	Isradipine[b]	0.05–0.15 mg/kg/dose	TID–QD	0.8 mg/kg/day up to 20 mg/day
	Extended release nifedipine	0.25–0.5 mg/kg/day	QD–BID	3 mg/kg/day (up to 120 mg/day)
Central a-agonist	Clonidine[b]	5–20 mcg/kg/day	QD–BID	25 mcg/kg/day (up to 0.9 mg/day)
Diuretics	Amiloride	5–10 mg/day	QD	20 mg/day
	Chlorthalidone	0.3 mg/kg/day	QD	2 mg/kg/day (up to 50 mg/day)
	Furosemide[c]	0.5–2 mg/kg/dose	QD–BID	6 mg/kg/day
	HCTZ	0.5–1 mg/kg/day	QD	3 mg/kg/day (up to 50 mg/day)
Vasodilators	Hydralazine	0.25 mg/kg/dose	TID–QD	7.5 mg/kg/day (up to 200 mg/day)
	Minoxidil	0.1–0.2 mg/kg/day	BID–TID	1 mg/kg/day (up to 50 mg/day)

ACE angiotensin-converting enzyme, *ARA* aldosterone receptor antagonist, *ARB* angiotensin II receptor blocker, *CCB* calcium channel blocker, *HCTZ* hydrochlorothiazide

[a]The maximum recommended adult dose should not be exceeded

[b]Information on preparation of a stable extemporaneous suspension is available for these agents

[c]Available as a FDA-approved commercially supplied oral solution

During the randomized placebo withdrawal phase, a significant increase in systolic BP was observed in the placebo arm, though the absolute difference between the two groups was only 3.7 mmHg. The study included a 52-week open-label extension, during which BP reduction was maintained long term on fosinopril with favorable safety and tolerability profiles. Unfortunately, fosinopril was administered only in the tablet form during the study. As a result, the FDA-approved label information only includes dosing recommendations for children weighing >50 kg, as an appropriate dose strength is not available for those weighing <50 kg [44]. Of note, post hoc analysis of the fosinopril trial results demonstrated reduced efficacy in black children compared to non-black children, a finding similar to studies of ACE inhibitors in adults [46, 47].

There are limited published data regarding the efficacy and safety of benazepril, quinapril, and ramipril. FDA analyses of the benazepril and ramipril trials are, however, available online. Benazepril was granted pediatric exclusivity after pharmacokinetic (PK) and dose-response studies were submitted to the FDA [48]. Dose-response analysis demonstrated positive slopes for both systolic and diastolic BP, though it did not reach statistical significance [48]. The placebo group exhibited a significant withdrawal effect, with increases in mean systolic (5.18 mmHg) and diastolic (5.16 mmHg) BP greater than the mean changes in the overall benazepril group. PK studies also found an extemporaneously compounded suspension to be bioequivalent to the tablet formulation. Thus, FDA-approved labeling for benazepril includes pediatric-specific dosing recommendations as well as instructions for preparation of the suspension. Results from the ramipril trial were disappointing. Specifically, prospective analyses of BP showed no significant effects [48]. The authors speculated that this was related to the trial design and the extremely long-acting effects of ramipril compared to other ACE inhibitors (R Portman, personal communication). The only pediatric data published regarding quinapril are from a small PK study in 24 patients aged 2.5 months to 6 years. Effect of therapy on BP was not reported and dosing guidelines for children are not available.

Angiotensin Receptor Blockers

ARBs, like ACE inhibitors, produce a BP-lowering effect through modulation of the RAAS. Specifically, ARBs act by inhibiting the activation of the AT_1 receptor by angiotensin II [49]. Therefore, the actions of angiotensin II on the AT_1 receptor, as described previously, are downregulated by ARBs, leading to increased effects on the AT_2 receptor. ARBs do not, however, affect the bradykinin system.

As one of the newest antihypertensive drug classes, virtually all ARBs were still on patent when the FDAMA was enacted. As a result, industry-sponsored trials have provided a wealth of reliable data regarding dosing, efficacy, and safety of these agents in children and adolescents. Thus far, pediatric exclusivity has been granted for losartan, candesartan, olmesartan, and valsartan [44], with additional agents of this class still under study in the pediatric age group.

The losartan trial evaluated the effect of once-daily dosing of this agent on hypertensive children 6–16 years of age [50]. After 3 weeks of therapy, significant dose-dependent reductions of diastolic and systolic BP were demonstrated. During the randomized placebo washout phase, BP increased after discontinuation of losartan in moderate-dose (0.75 mg/kg) and high-dose (1.44 mg/kg) groups though no difference was noted in the low-dose (0.07 mg/kg) group, suggesting a similar response to placebo. Based on these results, 0.75 mg/kg/day has been recommended as an effective starting dose. Losartan was well tolerated across all dosing ranges, although the brief study duration (5 weeks) precluded robust conclusions regarding safety. A suspension formulation was studied and instructions for preparation are provided in the FDA-approved labeling information along with pediatric-specific dosing guidelines. A trial of losartan in hypertensive children aged 6 months to 6 years is ongoing, but no longer recruiting participants [51].

Candesartan has been studied in pediatric patients ranging in age from 1 to 17 years [52, 53]. In older children (6–17 years), no dose-response relationship was demonstrated across

low-, moderate-, and high-dose treatment groups; however, systolic BP was noted to be significantly reduced in all treatment groups when compared to placebo [52]. There was no apparent difference in BP response based on age, sex, or Tanner stage, though the reduction in BP did appear to be attenuated in blacks compared to non-blacks. Response appeared to be sustained over a 52-week open-label extension phase with safety and tolerability profiles comparable to adults. In younger children (1–6 years), dose-dependent decreases in systolic and diastolic BP were observed that appeared to be independent of age, sex, or race [53]. No placebo-controlled washout phase was included, though a 52-week extension phase did suggest that the antihypertensive effect of candesartan was sustained with good tolerability and safety profiles. A pre-planned regression analysis combined the efficacy results from both candesartan trials and demonstrated that reductions in systolic BP and diastolic BP were monotonic and dose related for the 1–17 age range as a whole [53]. FDA-approved labeling includes dosing recommendations for children 1–17 years as well as instructions for the preparation of a stable oral solution [44].

Similar to candesartan, valsartan trials have been completed in hypertensive children ranging in age from 1 to 16 years. In older children (6–16 years), valsartan therapy resulted in dose-dependent reductions in systolic and diastolic BP that were independent of weight, age, sex, and race [42]. During the placebo withdrawal phase, the increase in BP was significantly higher in the pooled placebo group compared to the pooled valsartan group. During the 52-week open-label phase, valsartan was well tolerated with only two serious adverse events that were thought to be drug related. In younger children (1–5 years), valsartan treatment significantly lowered systolic and diastolic BP in low-, medium-, and high-dose groups; however, no dose-response relationship was demonstrated. The BP-lowering effect was further confirmed by reversal of effect in those assigned to placebo during the withdrawal. As with the older cohort of children, a favorable safety and tolerability profile was seen during the 52-week open-label extension phase. Additionally, effects on development were assessed, although in a limited fashion, and showed no adverse effects of valsartan. Dosing ranges for 6–16-year-olds now appear on the FDA-approved labeling as do instructions for preparation of suspension; however, use is not recommended in children less than 6 years of age due to safety concerns [54].

Irbesartan and olmesartan have both been studied in pediatric patients as well. The olmesartan trial in 6–16-year-old children demonstrated a dose-response effect, though only two dosing regimens were evaluated [55]. This study included a separate cohort of black children. Although BP-lowering efficacy was observed in patients of all ethnic backgrounds, the predominantly non-black patient cohort achieved greater BP reductions than the black patient cohort. FDA-approved labeling for olmesartan includes dosing guidelines for children 6–16 years as well as instructions for solution preparation. Early studies of irbesartan suggested efficacy in hypertensive children, particularly those with chronic kidney disease [56, 57]. However, a later study did not find a significant effect on systolic BP at doses ranging from 0.5 to 4.5 mg/kg [38].

Aldosterone Receptor Antagonists

Aldosterone receptor antagonists (ARAs) exert their BP-lowering effects by competitively blocking mineralocorticoid receptor sites in the distal renal tubule, increasing sodium chloride and water excretion while conserving potassium and hydrogen. In addition, they may block the effect of aldosterone on arteriolar smooth muscle as well.

In recent years, there has been an increased understanding of the role of aldosterone on overall cardiovascular health in adults. Beyond the traditional sodium-retaining effect of aldosterone, it is now clear that the hormone may activate receptors in multiple other organs including the heart, brain, and blood vessels ultimately leading to inflammation and fibrosis [58]. This knowledge, in combination with emerging adult

data showing a decrease in mortality in patients with severe heart failure treated with aldosterone blockade [59, 60], has sparked renewed interest in this drug class.

Currently, there are two available ARAs, spironolactone and eplerenone. Spironolactone has been available for decades; however, published data regarding efficacy and safety in the treatment of pediatric hypertension remains limited. A recent observational study reported acceptable safety and tolerability profiles in children receiving spironolactone, largely as part of multidrug diuretic regimens in the setting of heart disease or chronic lung disease [61]. No BP data were reported and adverse events were limited to dyskalemia. Problematic progesterone-like and antiandrogenic adverse effects can be seen in adults due to nonspecific binding to steroid receptors, including gynecomastia, erectile dysfunction, and decreased libido in men and menstrual abnormalities in women [62, 63]. Although instructions for preparation of an extemporaneous suspension are available for spironolactone, only unlabeled pre-FDAMA dosing guidelines exist for the treatment of hypertensive children.

Eplerenone is a newer, selective ARA with fewer endocrinologic side effects than spironolactone. In a recent trial, the antihypertensive effect of eplerenone was evaluated in pediatric patients 4–17 years of age [64]. Reductions in both systolic and diastolic BP were achieved on therapy; however, this reached significance only in the high-dose group. No dose-response effect was demonstrated. There were few adverse events reported during the trial, though the brief duration of the study precluded assessment of tolerability with chronic use.

Beta-Adrenergic Antagonists

The β-adrenergic antagonists are a large class of medications with heterogeneous pharmacologic properties. They act by blocking stimulation of β1- and β2-adrenoreceptors of the nervous system, resulting in decreased BP by a number of mechanisms, including a reduction in cardiac output, a diminution of renin release, a decrease in central nervous system sympathetic outflow, and a presynaptic blockade that inhibits catecholamine release [65]. All currently available agents antagonize cardiac β1-receptors competitively, but vary in the degree of β2-receptor blockade in extra cardiac tissues. In addition, there are other β-adrenergic antagonists that have vasodilating properties either through concomitant alpha blockade or through the generation and release of nitric oxide. With this in mind, it is not surprising that there is considerable within-class variability with respect to tolerability and side effect profiles [66].

Most β-adrenergic antagonists no longer had patent protection when the FDAMA was enacted. Hence, few drugs in this class have been studied rigorously in hypertensive children and evidence-based data with respect to efficacy and safety in this population are lacking. Two notable exceptions are metoprolol and bisoprolol, the latter of which was studied in a combination preparation with hydrochlorothiazide (HCTZ). Using an extended release formulation, the pediatric metoprolol trial demonstrated a significant reduction in systolic BP in those treated at moderate (1 mg/kg) and high (2 mg/kg) doses and a significant reduction in diastolic BP at high dose [67]. In addition, the placebo-corrected change in diastolic BP exhibited a statistically significant dose-response relationship. A 52-week open-label extension revealed a favorable tolerability and safety profile. In the bisoprolol/HCTZ study, treatment groups did exhibit significant reductions in systolic and diastolic BP [68]. However, there was a large placebo effect and the percentage of children who achieved BP less than the 90th percentile was not significantly different in the bisoprolol/HCTZ group compared to the placebo group. Of note, the bisoprolol/HCTZ group had fewer overall adverse events and fewer serious adverse events than subjects treated with placebo.

Propranolol was the first β-adrenergic antagonist available in the United States and, historically, is the most extensively used in children and adolescents [69]. However, the availability of controlled clinical trials of this agent in children is lacking. There are published reports describing

the use of propranolol in children, though these involve a limited number of subjects making it difficult to draw conclusions with respect to efficacy and safety [70–72]. It should be noted that propranolol is available in a commercially available oral solution.

Vasodilatory β-adrenergic antagonists have recently garnered much attention as potential alternatives to traditional beta-blockers in the management of hypertension in the adult population. Carvedilol and labetalol cause vasodilation through α1-receptor blockade and nebivolol induces endothelium-dependent vasodilation by stimulating nitric oxide activity [73]. Whereas conventional β-adrenergic antagonists tend to raise peripheral vascular resistance (PVR) and reduce cardiac output (CO), these reduce PVR while maintaining or improving CO. At this point, none of these agents have been specifically studied for hypertension in the pediatric population.

Calcium Channel Blockers

Calcium channel blockers (CCBs) are a pharmacologically heterogeneous class of drugs that have a long history of use in the treatment of both adult and childhood hypertension. CCBs antagonize the L-type voltage-dependent slow channel of the cellular membrane of myocardial and vascular smooth muscle, ultimately resulting in decreased contraction and a reduction of BP through dilation of the peripheral arteries [69].

CCBs are divided into two classes: the tertiary amines and the dihydropyridines. The tertiary amines, diltiazem and verapamil, are used primarily as antiarrhythmic agents because of their effect on AV nodal conduction, although both are effective antihypertensive agents as well. Neither diltiazem nor verapamil has been specifically studied in hypertensive children. Dihydropyridine CCBs commonly used in pediatric hypertension include nifedipine, isradipine, felodipine, and amlodipine.

Nifedipine is available in a short-acting and extended release formulation, neither of which has been rigorously studied in children. The published literature regarding the use of nifedipine in hypertensive pediatric patients is largely restricted to the use of the short-acting agent in the setting of hypertensive urgencies [74–77]. More recently, the use of this agent has been avoided for acutely elevated BP as it has been associated with a precipitous drop in BP and an increased risk for myocardial infarction, stroke, and death in the adult population [78]. Pediatric data suggest that short-acting nifedipine may be used safely with judicious dosing in otherwise healthy children [79, 80]; however, many recommend abandoning its use in children given the availability of safer alternatives [81, 82]. There is a paucity of published reports describing the use of nifedipine for the treatment of chronic hypertension in children. One study compared the efficacy and tolerability of extended release nifedipine and amlodipine in a small cohort of pediatric renal transplant recipients [83]. The two drugs were noted to have comparable efficacy, though nifedipine appeared to be associated with more side effects, particularly gingival hyperplasia. Based on published reviews, it seems safe to assume that extended release nifedipine is commonly used in children for the management of chronic hypertension [84]. One factor limiting the use of extended release nifedipine is the necessity to swallow a pill, which may not be feasible in younger children.

As with nifedipine, efficacy and safety data for isradipine in childhood hypertension are limited. A number of single-center case series have been published detailing isradipine use in children [85–87]. Most of the children included in these studies were hospitalized with new onset secondary hypertension. In this population, isradipine effectively lowered systolic and diastolic blood pressure with a low rate of adverse events. Most children required dosing three to four times daily, which may limit the use of isradipine for long-term therapy. Acutely, isradipine appears to be a safe and effective medication for reduction of severe hypertension and its use has been advocated over nifedipine in children [88]. A stable extemporaneous solution can be compounded that allows for appropriate dosing in infants and young children.

Felodipine use in childhood hypertension has been more rigorously studied than either nifedipine or isradipine. A highly variable kinetic profile

similar to that seen in young adults was noted in a small number of pediatric transplant patients who underwent pharmacokinetic testing [89]. In a single-center crossover study, once-daily dosing of felodipine was found to be more effective than extended release nifedipine in children with hypertensive renal disease as assessed by ambulatory BP monitoring [90]. In addition, compliance was significantly better in those treated with felodipine. In the industry-sponsored clinical trial, felodipine 5 mg resulted in significantly improved diastolic BP values over placebo; however, no dose-response relationship was observed and no significant difference in BP values was noted at lower or higher doses [91].

Considerably more data are available regarding the use of amlodipine in childhood hypertension than the other CCBs. In single-center pediatric studies, amlodipine consistently demonstrated efficacy in reducing BP in patients with both primary and secondary hypertension [92–96]. Amlodipine was reported to provide sustained BP control on stable dosing with favorable safety and tolerability over a mean follow-up duration of 20 months [97]. Population pharmacokinetic studies demonstrated clearance and distribution characteristics in older children that were similar to adults. Plasma concentrations were similar whether amlodipine was dosed once or twice daily, suggesting that once-daily regimens were likely sufficient in children [98]. In the industry-sponsored clinical trial, amlodipine produced significantly greater BP reductions than placebo with a dose-response effect on systolic and diastolic BP at doses greater than 0.06 mg/kg/day [99]. In addition, an extemporaneous suspension has been studied that has been shown to be stable for 3 months with bioequivalence that is not different from the tablet [100, 101]. Instructions for formulation of the suspension are available on the FDA-approved labeling.

Diuretics

Diuretics exert their effect by promoting urine production through a reduction in renal tubular sodium reabsorption. There are a number of agents available that act on different sites of the nephron, with variable degrees of potency. While diuretics are commonly used in adults, often as first-line agents, their use is more limited in children. No controlled clinical trials examining diuretic use in pediatric hypertension have been conducted. Dosing guidelines exist for many diuretics with several available in suspension form; however, the clinical indication is for the treatment of edema not hypertension.

Direct Vasodilators

Vasodilators, such as minoxidil and hydralazine, reduce BP by relaxing arterial smooth wall with a resultant decrease in peripheral vascular resistance. Several single-center case series have been published describing the use of minoxidil in children suggesting efficacy in the treatment of severe childhood hypertension [102–104]. No controlled clinical trials in children have been performed and long-term safety data is lacking. Minoxidil use in children has generally been reserved for those with severe refractory hypertension due to the high incidence of hypertrichosis in those with long-term exposure. There is notably little data with respect to efficacy and safety of hydralazine in childhood hypertension.

Other Antihypertensive Agents

No pediatric trials have been conducted for alpha-blockers or central acting agents, so little is known about the efficacy or safety of these agents in children. Alpha-blockers play an important role in treatment of some disorders, such as pheochromocytoma; though they have limited utility in pediatrics given their poor tolerability profile. Clonidine, the most widely used central acting agent, inhibits central sympathetic outflow resulting in decreased peripheral vascular resistance. Small studies suggest that clonidine may be an effective agent for the treatment of childhood hypertension [105]; however, there

is a poor side effect profile and risk for rebound hypertension when the medication is discontinued suddenly.

Targeted Approach to Therapy

The decision to initiate antihypertensive medications in any child should not be taken lightly. Although there is a growing body of evidence with respect to the safety and tolerability of particular agents, follow-up studies are limited in duration and little is known regarding the impact of long-term pharmacologic therapy on growth and cognitive-development. In an effort to maximize benefit, a targeted approach to therapy should be employed. Given the higher prevalence of secondary hypertension in children, the pathophysiologic mechanism of BP escalation can often be identified. In some cases, this facilitates selection of a specific therapeutic agent. In patients with concomitant diseases such as diabetes, a particular drug may be particularly beneficial. A thorough review of this topic is beyond the scope of this chapter; however, the following section provides a brief discussion of some clinical situations where a specific antihypertensive agent may be particularly advantageous. Indications for directed therapy with corresponding medications are provided in Table 36.4.

Table 36.4 Indications for specific/directed drug therapy

Condition	Drug
Renal artery stenosis	ACE-I, ARB, diuretic, vasodilator
Diabetes (type 1 or type 2)	ACE-I, ARB
Coarctation of aorta	Beta-agonist
Renal parenchymal disease	ACE-I, ARB
Liddle syndrome	Amiloride
Glucocorticoid remediable aldosteronism	GC, eplerenone, spironolactone
Gordon syndrome	Thiazide diuretic
Pheochromocytoma	Sequential alpha- and beta-agonists
Posttransplant hypertension	CCB, ACE-I, ARB

Renovascular Hypertension

In the setting of renal artery stenosis, perfusion to a part or to the entire kidney is compromised, stimulating the release of renin and subsequent upregulation of the entire RAAS [106, 107]. In this setting, angiotensin blockade with ACE inhibitors or ARBs are obviously rational choices to treat blood pressure elevation. Unfortunately, such therapy carries a risk of acute kidney injury due to relaxation of the afferent arteriole and concomitant reduction in glomerular capillary hydrostatic pressure. For this reason, bilateral renal artery stenosis is considered an absolute contraindication to ACE inhibitor or ARB treatment. However, if disease is isolated to one side or to segmental renal arteries, these medications are generally safe and particularly effective. Gradual dose titration and judicious monitoring is mandated. Given the increased renin secretion, there is always sodium retention and volume overload in patients with renovascular hypertension; therefore, diuretics and vasodilators may also play important roles in therapy.

Chronic Kidney Disease

Hypertension is common in children with chronic kidney disease. Recent analysis of data from the ongoing Chronic Kidney Disease in Children cohort revealed a prevalence rate of 54 %. [108]. Uncontrolled hypertension, hyperfiltration, and proteinuria are known risk factors for accelerated renal decline in adult patients [109–111]. There is a preponderance of evidence that angiotensin blockade slows the progression of renal decline in adults, likely secondary to antihypertensive, antiproteinuric, and antifibrotic properties [112–114]. Relative to adult studies, there is a dearth of pediatric data regarding similar benefits in children. One notable exception is the ESCAPE trial, which reported that treatment with ramipril was effective in reducing systolic and diastolic BP in a cohort of pediatric patients with CKD [25]. All subjects in this study received ramipril at the highest antihypertensive dose approved in adults (10 mg/day) adapted for

body size (6 mg/m^2/day), some on combination with other antihypertensive agents to achieve desired BP control. Final analysis of this trial showed that intensive blood pressure control, defined as 24-h mean arterial pressure <50th percentile, led to significantly fewer patients reaching the primary end point, defined as 50 % reduction in GFR or progression to ESRD. Overall, there appears to be general agreement that ACE inhibitors and ARBs should be considered as first-line therapy for hypertensive therapy in children with CKD. Given the risk for depressed GFR and hyperkalemia in this population, judicious monitoring of electrolyte balance and renal function is mandated. The management of hypertension in chronic kidney disease is discussed in detail in Chap. 22.

Primary Hypertension

Primary hypertension is an increasing problem in childhood, largely the result of the ongoing obesity epidemic [10]. Some of these patients may be managed successfully with therapeutic lifestyle interventions; however, treatment with antihypertensive medications is often required. Generally speaking, choice of an agent in this setting is based on provider preference and experience rather than pathophysiologic underpinnings. In the adult population, evidence has emerged to suggest that a renin-guided approach in these patients may be beneficial. Laragh postulates that long-term BP control is sustained by two intervening forces: (1) the sodium volume (V) content and (2) plasma renin-angiotensin vasoconstrictor (R) activity [115, 116]. With this in mind, the plasma renin level may be used to determine the relative involvement of V and R factors in determining BP, making it possible to identify an appropriate intervention. Low-renin volume-dependent hypertension should be treated with an anti-V drug (diuretic, CCB, mineralocorticoid receptor antagonist) and high-renin vasoconstrictive hypertension should be treated with an anti-R drug (ACE inhibitor, ARB, β-adrenergic antagonist). Recent data suggest that such an approach is efficacious [117, 118]. Moreover, there is also evidence that selection of a "wrong" drug (an anti-V drug for R hypertension or an anti-R drug for V hypertension) can lead to a paradoxical rise in BP [119]. There is no body of evidence that such an approach is effective in pediatric patients and further studies in this age group are warranted.

Conclusion

The prevalence of pediatric hypertension is increasing and pediatricians are increasingly expected to provide appropriate therapeutic interventions. There is a growing body of pediatric-specific data with respect to efficacy and safety of pharmaceutical therapies; however, much is still to be learned about their impact on long-term outcomes, including growth, cognitive development, cardiovascular morbidity, and mortality. When medications are required, a rational approach to selecting an appropriate agent with respect to pathophysiology, potential benefit, and the likelihood for side effect is advocated.

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