Pharmacologic Management of Pediatric Hypertension

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Abstract:

Hypertension in children is common, and the prevalence of primary hypertension is increasing with the obesity epidemic and changing dietary choices. Careful measurement of blood pressure is important to correctly diagnose hypertension, as many factors can lead to inaccurate blood pressure measurement. Hypertension is diagnosed based on comparison of age, sex, and height-based norms with the average systolic and diastolic blood pressures on three separate occasions.

In the absence of hypertensive target organ damage (TOD), stage I hypertension is managed first by diet and exercise, with the addition of drug therapy if this fails. First-line treatment of stage I hypertension with TOD and stage II hypertension includes both lifestyle changes and medications. First-line agents include angiotensin-converting enzyme (ACE) inhibitors, thiazide diuretics, and calcium-channel blockers. Hypertensive emergency with end-organ effects requires immediate modest blood pressure reduction to alleviate symptoms. This is usually accomplished with IV medications. Long-term reduction in blood pressure to normal levels is accomplished gradually.

Specific medication choice for outpatient hypertension management is determined by the underlying cause of hypertension and the comparative adverse effect profiles, along with practical considerations such as cost and frequency of dosing. Antihypertensive medication is initiated at a starting dose and can be gradually increased to effect. If ineffective at the recommended maximum dose, an additional medication with a complementary mechanism of action can be added.

Key Points:

Elevated blood pressure is an increasingly common, but still under-recognized, problem in children.

First line management of ambulatory hypertension is generally centered on lifestyle change, but end-organ damage or significant hypertension may require immediate pharmacologic intervention.

ACE inhibitors, thiazide diuretics, and calcium-channel blockers may all be considered reasonable first-line choices for children requiring drug treatment of hypertension.

1. Disease Background

1.1 Epidemiology and Definitions

Normal blood pressure in children is defined as SBP and DBP that are <90th percentile for age, gender, and height [1]. Prehypertension is defined as an average SBP or DBP levels on one occasion that are <95th percentile but ≥ either 90th percentile or 120/80 mmHg, whichever is lower [1]. Hypertension in children is defined as an average systolic blood pressure (SBP) and/or diastolic blood pressure (DBP) greater than or equal to the 95th percentile for sex, age, and height – accurately measured on three separate occasions [1]. Hypertension is classified as stage I if the average SBP or DBP is between the 95th percentile and the 99th percentile + 5 mmHg, and stage II hypertension if the average of either SBP or DBP exceeds the 99th percentile + 5 mmHg.

Epidemiological studies indicate that pediatric hypertension is becoming more common. Historically, prevalence rates were thought to be around 1%, but data from the National Health and Nutrition Examination Survey (NHANES) from 1998-2012 indicate that 1.6-3.1% of children aged 8-17 have hypertension, and up to 15% of adolescents have prehypertension or hypertension [2]. A screening study of 5,102 children aged 10-19 years in the Houston public schools demonstrated that 4.5% of children had hypertension, and 11% with BMI greater than or equal to the 95th percentile had hypertension [3]. A repeat study in the Houston schools of 6,790 adolescents aged 11-17 showed that 81.1% of children had normal BP, 15.7% had prehypertension, and 3.2% had hypertension [4]. The increase in the prevalence of hypertension is due in large part to the increased prevalence of obesity among children and adolescents [5]. With this change has come a shift in the most common etiology of hypertension: 50-90% of patients diagnosed with pediatric hypertension at referral centers have primary (essential) hypertension [6]. The association of hypertension with obesity is observed as early as five years of age, and is common in patients greater than ten years of age [7, 8]. The increased quantity of sodium and high fructose corn syrup (HFCS) in the typical diet of US children over the past 20-40 years is also thought to have contributed to the rise in childhood hypertension [9, 10].

Though primary hypertension is increasingly the cause of high blood pressure in children, secondary hypertension remains more common in children than it is in adults, and is the predominant cause of hypertension in children less than 6 years of age [11]. The diagnostic evaluation for hypertension should be guided by history, physical examination, and patient characteristics. The specific laboratory and imaging workup of confirmed hypertension is reviewed in detail in “The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents” [1].

White coat hypertension (WCH) is an especially common cause of elevated blood pressure measurements, accounting for up to 46% of patients referred for evaluation of hypertension [12]. Patients with WCH have elevated blood pressures in a medical setting, but outside this environment their blood pressures are normal [1]. In adults, there is evidence that WCH is a non-benign condition with high risk of progression to true hypertension; it is unknown whether this holds true for children with WCH [13, 14]. While current guidelines do not recommend a diagnostic workup for children with WCH, this condition may represent an intermediate state between normal blood pressure and hypertension [1, 15]. Thus, patients with WCH may benefit from modification of unhealthy lifestyle habits and monitoring for worsening hypertension.

Masked hypertension can be considered to be the inverse of white coat hypertension, with normal in-office blood pressures but elevated average blood pressures on home monitoring or 24-hour ambulatory blood pressure monitoring (ABPM). Populations at high risk of masked hypertension should be routinely screened with ABPM or home BP monitoring in order to correctly identify and respond to this entity. Some examples of at-risk populations include kidney transplant recipients, pediatric dialysis patients, and children with chronic kidney disease (CKD) or sickle cell disease. In at-risk populations, the prevalence of masked hypertension has ranged from 10-22%, and masked hypertension is associated with left ventricular hypertrophy in these patients [16]. Further study is needed to determine which additional groups of children may benefit from screening for masked hypertension.

1.2. Pathophysiology

1.2.1 Primary Hypertension

Primary hypertension has a polygenic inheritance pattern, though family history does play a prominent role. High sodium intake, high fructose corn syrup intake, and increased sympathetic tone have been connected to the development of primary hypertension in obese patients.[9, 10] Obesity itself adds to the systemic load against which the heart pumps due to the additional vasculature needed to supply extra body mass. In obese adolescents, blood pressure falls by an average of 1-2 mmHg per pound of weight lost and rises by an average of 1.5 mmHg per 1,000 mg additional daily sodium intake [9, 17].

Uric acid is frequently elevated in patients with primary hypertension, and reduction of uric acid levels in hypertensive and prehypertensive adolescents may reduce blood pressure [18, 19]. However, these were small, proof-of-concept studies, and this finding has not been replicated on a large scale. Animal studies show that elevated uric acid levels cause hypertension through reduction in endothelial nitric oxide and stimulation of renin, with

prolonged exposure resulting in sodium-sensitive hypertension due to endothelial dysfunction which does not respond to reduction of uric acid levels [18, 20].

1.2.2 Secondary Hypertension

A full discussion of the pathophysiology of secondary hypertension is beyond the scope of this review. In the monogenic hypertension states, single gene defects lead to inappropriate renal sodium retention (via any one of multiple pathways), leading to volume retention and intravascular volume overload [21]. In disorders which activate the renin-angiotensin-aldosterone axis, such as renovascular hypertension and hypertension mediated by renal parenchymal disease, peripheral vasoconstriction due to angiotensin II is added to the effect of sodium retention due to increased aldosterone production. Other major mechanisms of secondary hypertension include catecholamine excess due to tumors such as pheochromocytoma or neuroblastoma, and iatrogenic causes including medications (see table 1). If a patient is found to have a secondary hypertensive state, the specific etiology of the hypertension determines the subsequent choice of treatment, including first- and second-line drug classes and/or non-pharmacologic treatments as indicated.

1.3 Clinical Presentation and Diagnosis

Hypertension can present with nonspecific symptoms (e.g. headache, fatigue), but commonly remains asymptomatic until the blood pressure reaches very high levels, at which point severe headache, blurry vision, fatigue, or confusion may develop [22]. It is therefore recommended that blood pressure be checked routinely at each well-child visit for patients ≥ 3 years of age, with screening for patients <3 years of age only if they have specific risk factors for hypertension. Blood pressure should be compared to age, gender, and height specific norms so that an elevated blood pressure is not overlooked [1]. The diagnosis of prehypertension can be made on the basis of the average of blood pressure measurements on a single occasion, while diagnosis of hypertension requires measurements on three separate occasions [1].

The accuracy of blood pressure measurement is essential to making a correct diagnosis. Casual blood pressures measured by auscultation have low inter-operator reliability. Mercury-containing sphygmomanometers are preferred for accuracy, though environmental and occupational safety concerns limit their use. Aneroid sphygmomanometers are an acceptable alternative, but they need to be calibrated frequently, which is often not done in clinical practice. It is recommended that blood pressure measurements be obtained in a controlled environment, after five minutes of rest, with the patient seated and with the arm supported at heart level [1]. Single measures of blood pressure in the

clinic can be affected by many variables, including terminal digit preference by the clinician, improper cuff size, incorrect patient position, and the white coat effect. Repeat blood pressure measurements increase precision and reproducibility of results, and taking at least three measurements per clinic visit is recommended [1, 23, 24]. Oscillometric blood pressure devices measure the point of greatest oscillation in the arterial wall, which is the mean arterial pressure. From this value, systolic and diastolic blood pressures are calculated using proprietary algorithms. Different device manufacturers use different algorithms to calculate the SBP and DBP, and even within manufacturers, different algorithms may be used from device to device. Some are known to overestimate SBP by as much as 10 mmHg, while others may underestimate SBP [25, 26]. It is recommended that any blood pressure which exceeds the 90th percentile for age, gender, and height using an oscillometric device be confirmed by auscultation [1].

Twenty-four-hour ambulatory blood pressure monitoring (ABPM) is fast becoming the gold standard for determination of hypertension in both children and adults, and seems to correlate better with outcomes [27]. However, it is primarily restricted to subspecialty use in pediatrics.

2. Disease management

2.1 Disease management overview

The long-term effects of childhood hypertension are largely unknown, as has been detailed in the recent United States Preventative Services Task Force (USPSTF) report, which highlights the need for more evidence to fully understand the relationship between childhood hypertension and cardiovascular disease [27, 28]. The development of target organ damage, including carotid intima-media thickening, left ventricular hypertrophy, hypertensive nephropathy, and retinopathy are all well-established consequences of childhood hypertension. A recent study of 1.3 million children with military insurance found that 8% of children diagnosed with hypertension had hypertensive target organ damage on echocardiography [29]. In addition, longitudinal studies have shown that childhood hypertension frequently persists into adulthood, and that childhood hypertension is the strongest predictor of adult hypertension [30]. The best evidence for rates of persistence of hypertension comes from the i3C cohort, a subgroup analysis of 1,602 children with elevated blood pressure from four prospective studies: the Bogalusa Heart Study, the Cardiovascular Risk in Young Finns Study, the Muscatine Study, and the CDAH study. Analysis showed that 60% (969/1602) of children with elevated blood pressure had continued blood pressure elevation as adults, and that improvement in blood pressure tracked most closely with decrease in BMI [31].

In treatment of hypertension, the Fourth Report [1] states that goal blood pressure should be below the 95th percentile for children who have primary hypertension without end-organ damage, and below the 90th percentile for children who are at high risk for cardiovascular morbidity and mortality (children with chronic kidney disease [CKD], diabetes mellitus, or a renal transplant) [1]. The 2009 European Society of Hypertension pediatric guidelines recommend goal blood pressures below the 90th percentile for children with uncomplicated primary hypertension, below the 75th percentile for diabetic or CKD patients without proteinuria, and below the 50th percentile in diabetic or CKD patients with proteinuria [27].

Hypertension in children is frequently under-recognized and undertreated. The Chronic Kidney Disease in Children study showed that even in children with CKD, who have a 37% prevalence of hypertension, 39% of patients with confirmed hypertension were not receiving antihypertensive drugs [32]. A study of 1.3 million children with military health insurance found that only 34% of children diagnosed with hypertension underwent echocardiography, and only 38.9% of children diagnosed with hypertension received an antihypertensive medication [29]. Blood pressures should be monitored regularly in follow-up to determine if the intervention is resulting in reduction of blood pressures to goal levels. If target organ damage is identified, it should also be monitored periodically for progression or regression.

2.2 Non-pharmacologic treatment

Dietary modification, such as the Dietary Approaches to Stop Hypertension (DASH) diet, weight loss, and regular aerobic exercise are the cornerstones of therapy for primary hypertension, and can be helpful in many other forms of hypertension as well [33]. These so-called therapeutic lifestyle changes (TLC) should be applied as monotherapy when either prehypertension or uncomplicated stage I hypertension is diagnosed. TLC should be prescribed together with anti-hypertensive medications when blood pressure is stage II or greater, or for stage I hypertension if compelling indications for pharmacologic treatment are present. Such indications include diabetes mellitus, pre-existing CKD, or evident hypertensive target organ damage. Hypertensive target organ damage seen in children can include retinopathy, carotid intima-media thickening, left ventricular hypertrophy, or hypertensive nephropathy.

3. Outpatient pharmacologic therapy for hypertension (see table 2 for specific agents and dose ranges)

3.1 Overview of pediatric drug treatment of hypertension

Many antihypertensive medications have not been formally studied in children, which has led to the widespread use of antihypertensive agents without FDA-approved pediatric labeling. A recent study showed that 7% of drugs used

in children were neither labeled for pediatric use nor considered recommended for use in children, and 29% of drugs used in children under 6 years of age were not indicated for use in that age group [34]. In addition to a lack of labeling, many drugs lack evidence for their efficacy in children. A recent Cochrane review identified 21 trials of antihypertensive drugs in pediatrics, of which only 5 compared the antihypertensive with placebo [35]. This review highlights the lack of evidence for the efficacy of many commonly used antihypertensive medications in children. While the 1997 Food and Drug Administration Modernization Act (FDAMA) resulted in increased pediatric trials of many newer medications, there are currently no incentives for industry-sponsored trials of older medications in children. Thus, the discussion of many of the medications below is off-label and is based on adult data, clinical experience, and expert opinion [1]. The discussions of the drug classes below are not intended as a comprehensive reference; readers are directed to package labeling and reliable electronic resources for a complete listing of warnings and contraindications.

3.2 Calcium Channel Blockers

3.2.1 Mechanism of action

Calcium channel blockers inhibit calcium channels within smooth muscle cells in the vasculature, resulting in decreased vasoconstriction and thus decreased peripheral vascular resistance.

3.2.2 Indications and contraindications

This class of medications has relatively few absolute contraindications, and is among the first-line agents for the treatment of hypertension. The adverse effects of calcium channel blockers are generally minor and include peripheral edema and headache. These are due to the peripheral vasodilation caused by these agents [35, 36]. If a primary care physician is uncertain how to proceed with hypertension workup, but needs to start therapy (e.g. due to stage II or symptomatic hypertension) while a subspecialist referral is pending, calcium-channel blockers are a reasonable first choice, as their use generally does not interfere with subsequent evaluation of the renin-angiotensin-aldosterone axis or measurement of metanephrines and/or catecholamines if indicated. Hypotension is unlikely with use of standard starting doses. Caution should be exercised when prescribing extended-release nifedipine by computerized order entry, as immediate-release and extended-release nifedipine preparations may be easily confused in a computer order system.

3.2.3 Relevant within class differences

Amlodipine is dosed once daily; full effect is commonly not seen until the after steady state is reached, often after 5-6 days of therapy, due to its long half-life of 36-45 hours [36]. A multicenter pharmacokinetics study showed that weight-adjusted clearances and volume of distribution were significantly greater in younger children, suggesting a need for higher amlodipine mg/kg/day doses in children less than 6 years of age [37]. Nifedipine is a short-acting calcium channel blocker which is available in an extended release formulation; dosing recommendations are available for children 6 years of age and older. The short-acting form, however, should be used with some caution as it has the potential to cause overly rapid drops in blood pressure [36]. Nifedipine's extended release formulation is available in tablet form only, but is sometimes preferable to amlodipine as it reaches steady state faster than amlodipine due to nifedipine's short half-life of 2-4 hours [36]. Felodipine is only available as an extended-release formulation for which the dosage form must be swallowed whole, limiting utility in younger children. Isradipine must be dosed 3-4 times daily and there is less experience with its use in children. Non-dihydropyridines, such as verapamil and diltiazem, have a negative inotropic effect and are therefore more commonly used for angina and rate control of atrial fibrillation than for hypertension [36]. Additionally, there are little data or experience available on the use of non-dihydropyridines for hypertension in children.

3.3 ACE inhibitors

3.3.1 Mechanism of action

ACE inhibitors prevent the conversion of angiotensin I to angiotensin II by blocking the effects of angiotensin converting enzyme. Angiotensin II causes direct systemic vasoconstriction and sodium retention in the renal tubules, both by direct action in the proximal tubule and by stimulation of aldosterone production in the adrenal cortex. Angiotensin converting enzymes also catalyze the breakdown of bradykinin, and buildup of this vasoactive substance in patients taking ACE inhibitors is thought to contribute to their beneficial effects on cardiac remodeling. By reducing intraglomerular pressures, ACE inhibition extends nephron lifespan and decreases proteinuria in patients with albuminuria due to CKD or diabetes mellitus.

3.3.2 Indications and contraindications

ACE-inhibitors are teratogenic and should not be used by pregnant women or females who are at risk of becoming pregnant [38]. They can precipitate acute kidney injury (AKI) in patients with bilateral renal artery stenosis, or for patients with a solitary kidney who have renal artery stenosis. They are known to cause hyperkalemia through their inhibition of aldosterone production, and can also decrease glomerular filtration rate (GFR), though this decrease is

usually mild and acceptable in patients with normal baseline renal function. They should be avoided in the setting of acute kidney injury as they can decrease GFR and prolong recovery.

ACE inhibitors are generally well-tolerated, and the common adult side-effect of chronic cough was seen in less than 3% of a pediatric population treated with enalapril [39]. Given the beneficial effects on cardiac function and remodeling, these drugs are considered the drug of choice for patients with diminished cardiac function or left ventricular hypertrophy. Preliminary data indicate improvement in lipid profile and insulin resistance in obese children with metabolic syndrome receiving ACE inhibitors [40]. Their renal protective effects make them the drug of choice for patients with CKD or diabetes mellitus, and they are a good first-line drug for patients who lack the contraindications above. In addition to their antihypertensive effect, ACE inhibitors are often used as adjunctive agents for proteinuria control in children with nephrotic syndrome or other proteinuric renal disease states.

3.3.3 Relevant within class differences

Of the ACE inhibitors, captopril is the oldest and best-studied in children, and is useful when quick up-titration of drug dose is desired [27]. However, its three times daily dosing is inconvenient for patients and families, so once-daily agents such as lisinopril and enalapril are often used instead, though they have been studied less than captopril in children. Lisinopril has been studied in a double-blind placebo-controlled pediatric study and generally costs less than newer ACE inhibitors [41]. Enalapril has also been studied in children and is currently the only commercially-available solution, though at this time the commercial solution may be more costly than compounded lisinopril, for example. There is little evidence to suggest that newer, more expensive ACE-inhibitors are superior to the older, generic choices.

3.4 Angiotensin Receptor Blockers (ARBs)

3.4.1 Mechanism of action

ARBs block the angiotensin II receptor competitively, blocking vasoconstriction and thus decreasing systemic vascular resistance.

3.4.2 Indications and contraindications

As with ACE-inhibitors, ARBs are teratogenic, but ARB exposure in pregnancy may be more harmful than that of ACE inhibitors [38]. Use in patients with bilateral renal artery stenosis can precipitate acute kidney injury, or for patients with a solitary kidney who have renal artery stenosis. They should be avoided in patients with acute kidney injury. Adverse effects reported in trials for patients less than 6 years of age have led to some safety concerns [42,

43], though they are used with some regularity in this age group. ARBs do not inhibit the breakdown of kinins and therefore cause cough less frequently than ACE inhibitors. Although outcome studies in diabetic patients with proteinuria are lacking, the similar mechanism of action to ACE inhibitors suggests that ARBs may be the next best choice for patients who cannot tolerate ACE inhibitors but otherwise have an indication for an ACE inhibitor [1].

3.4.3 Relevant within class differences

Although ARBs have widely varying half-lives, all are dosed once-daily. Consideration to the improved bioavailability of valsartan when administered as a compounded suspension should be given when switching between dosage forms. As of the time of this writing, losartan is available as a generic formulation, and may therefore be less expensive than other ARBs. If blood pressure control is not sustained for a full 24 hours for patients taking losartan, a split dose administered twice daily may be considered. As an aside, this strategy can be employed for other once daily antihypertensives as well, though the practitioner should keep in mind that there is a significant decrease in adherence to twice daily vs. once daily medication regimens.

Also now available is aliskiren, a direct renin inhibitor. Its side effect profile is similar to that of ACE inhibitors and ARBs. Pediatric phamacokinetic and safety data have been published, but pediatric experience with this medication is limited [44]. It is only available in tablet form.

3.5 Diuretics

3.5.1 Mechanism of action

Diuretics decrease left ventricular filling pressure through volume reduction. Long-term use results in decreased systemic vascular resistance through unclear mechanisms.

3.5.2 Indications and contraindications

Thiazide diuretics are a reasonable first-line choice for the treatment of hypertension in children, though some advocate avoiding them in obese patients as they are known to alter glucose metabolism in adults, particularly when combined with beta-blockers [27]. Both loop and thiazide diuretics can cause electrolyte disturbances, including hypokalemia, so routine electrolyte monitoring is recommended with their use. They can also cause volume depletion, so they may not be a good choice for athletes, who are at risk of volume depletion with training and exercise. Similarly, they are relatively contraindicated in very young or developmentally delayed children who lack independent access to fluids or the ability to respond to increased thirst by increasing fluid intake.

3.5.3 Relevant within class differences

Hydrochlorothiazide is widely available as a tablet or compounded suspension. Chlorothiazide has previously been produced as a commercially available solution, though recent drug shortages have impacted its availability. Chlorthalidone is thiazide-like and has a longer half-life, but is available as a tablet only. All three decrease calcium excretion in the urine. Most thiazide and thiazide-like diuretics do not work well in the setting of GFR less than 30 ml/min/1.73 m^2 due to decreased delivery of the diuretic to the distal tubule, though metolazone does retain its activity at lower GFRs.

Loop diuretics such as furosemide are rarely used for treatment of hypertension alone. Although they are more effective diuretics than thiazides and thiazide-like agents, they are less effective as antihypertensive medications. Furosemide can cause ototoxicity, especially when given at high doses and in patients with decreased renal function.

Potassium-sparing diuretics, such as spironolactone and amiloride, are infrequently used in the treatment of hypertension except in cases of monogenic hypertension, such as Liddle syndrome or apparent mineralocorticoid excess (AME), in which setting they are considered first-line agents. Spironolactone may also be employed as add-on therapy in the treatment of resistant hypertension. In contrast to the other diuretics, hyperkalemia is a risk with these medications.

3.6 Beta-Blockers

3.6.1 Mechanism of action

Beta-adrenergic antagonists block the action of endogenous catecholamines and norepinephrine at their sites of action on vascular smooth muscle, myocardium, kidneys, bronchi, and other locations. Their activity in the kidneys results in decreased renin secretion. They decrease systemic vascular resistance by decreasing vascular tone, and decrease cardiac output by decreasing heart rate and cardiac contractility.

3.6.2 Indications and contraindications

The overall side effect profile of beta-blockers in children is considered more significant than that of other antihypertensives: they are therefore indicated as second or third line drugs for the treatment of pediatric hypertension, unless they are specifically indicated for another reason (e.g. migraine prophylaxis, hypertensive cardiomyopathy, etc.). Beta blockers are relatively contraindicated in athletes, as they can decrease maximum sports performance and endurance.[1] They are also contraindicated in patients with moderate to severe asthma or chronic lung disease, as beta-2 receptor antagonism can precipitate bronchospasm [1]. They should be avoided in insulin-dependent diabetics, as beta blockade may mask the symptoms of hypoglycemia [1]. Bradycardia is a dose-limiting

adverse effect. Abrupt cessation of beta-blockers should be avoided, as rebound hypertension and tachycardia can result. This is due to increased sympathetic tone as a result of upregulation of β-adrenoreceptors during chronic treatment [45].

3.6.3 Relevant within class differences

Cardioselective beta-blockers such as metoprolol and atenolol have a greater affinity for the beta-1 than the beta-2 receptor, and thus have less effect on bronchial smooth muscle. At higher doses, however, this selectivity is lost. Though metoprolol is available as a compounded suspension, it should be noted that this is an immediate-release/short-acting drug form; only the extended-release metoprolol preparation has been tested in pediatric clinical trials [46]. Bisoprolol/HCTZ has been studied in a placebo-controlled trial; it produced a significant reduction of diastolic but not systolic blood pressure in children [35, 47]. Labetalol is a combination alpha and beta blocker, and is available in IV or enteral form. Propranolol is commercially available as an oral solution. Carvedilol has only been studied in children for heart failure.

3.7 Direct Vasodilators

3.7.1 Mechanism of action

This class causes vasodilation of arterioles through direct action on vascular smooth muscle.

3.7.2 Indications and contraindications

As a class, direct vasodilators are indicated as a second or third line agent due to their side effect profile. Direct vasodilators cause sodium and water retention and result in increased cardiac preload, which may precipitate heart failure in patients with poor ventricular compliance. Minoxidil is effective in lowering blood pressure in children and adolescents, but the adverse effect of hypertrichosis limits its use to patients with hypertension resistant to other agents [1]. Due to rapid onset of action, hydralazine is frequently used as an as-needed medication for acute rises in blood pressure. However, it is infrequently useful for chronic management of hypertension, as it requires 3-4x per day dosing and patients are often noted to escape its effect over time. Other adverse effects common to both medications include flushing, headache, tachycardia, fluid retention, and palpitations [1].

3.7.3 Relevant within class differences

Hydralazine and minoxidil differ in their adverse drug effect profiles and frequency of dosing as noted above. Each can be compounded into an oral suspension. One common recipe for compounded hydralazine is only stable for 7

days, limiting its usefulness in the outpatient setting, though a compounded hydralazine recipe with ≥ 30 day stability is available [48].

3.8 Alpha blockers

3.8.1 Mechanism of action

Peripheral alpha-adrenergic antagonists block the action of endogenous catecholamines and metanephrines on the peripheral vasculature, causing peripheral vasodilation and decreased venous return.

3.8.2 Indications and contraindications

These medications are generally reserved for resistant hypertension due to their significant side effect profile, including first dose syncope, anticholinergic effects, headache, fluid retention, palpitations, drowsiness, weakness, and priapism. In adult studies, alpha-adrenergic antagonists increased heart-failure and cardiovascular events when used to lower blood pressure [49].

3.8.3 Relevant within class differences

Doxazosin is dosed once daily due to its longer half-life. Prazosin capsules can be opened and the contents mixed in food to be given to younger patients. None of the alpha-adrenergic antagonists are available as an oral suspension.

3.9 Central alpha agonists

3.9.1 Mechanism of action

Central alpha agonists decrease central sympathetic outflow by stimulating alpha-2 adrenergic receptors in the central nervous system (CNS).

3.9.2 Indications and contraindications

Central alpha agonists are well-known to cause rebound hypertension with abrupt cessation of the drug, and cause significant drowsiness, which often abates somewhat after several weeks. These and other adverse drug effects limit them to use in resistant hypertension, but they can be of particular use in cases of hypertension related to increased CNS sympathetic tone, such as in patients with brain injury and autonomic storming or abnormal central nervous systems. Additionally, clonidine can be very useful for patients who cannot tolerate enteral intake when given as a transdermal continuous-release patch. This class is also often used to treat aggressive behavior in patients with attention deficit hyperactivity disorder (ADHD) [1].

3.9.3 Relevant within class differences

Enteral clonidine must be dosed frequently due to its short half-life, but it is also available as a transdermal continuous-release patch, which needs to be changed weekly [1]. The patch cannot be divided or cut due to its formulation. Extended-release guanfacine is becoming more widely used as an adjunctive agent for treatment of ADHD. Caution should be taken with the rapid cessation of either agent, as rebound hypertension can be seen with abrupt discontinuation.

4. Management of Hypertensive Urgency/Emergency in Pediatrics

Hypertensive urgency is defined as severe hypertension without signs of acute end-organ damage, whereas hypertensive emergency is severe hypertension with signs of acute end-organ damage, such as encephalopathy, seizures, heart failure, or blindness/severe visual disturbance [27]. Severe hypertension has no specific definition; in general, blood pressures need be greater than the cutoff for stage II hypertension to be considered severe. Further determination depends on signs, symptoms, and clinical judgement. The rapidity of blood pressure rise, degree of rise over baseline, and presence or absence of symptoms are of greater importance than absolute blood pressure values. The patient should be evaluated for contraindications to acute reduction of blood pressure, such as intracranial mass or injury, and for underlying causes which require a specific treatment approach. More complete references are available to guide the practitioner in the evaluation and management of hypertensive urgency and emergency [1, 27, 50].

Once severe blood pressure elevation has been reliably confirmed and contraindications to blood pressure reduction have been rapidly ruled out, blood pressure should be promptly reduced by no more than 25% in the first 6-8 hours, with further slow reduction thereafter.

Consultation with a specialist in pediatric hypertension is advisable to guide therapy. One approach is to administer an IV hydralazine dose of 0.2 mg/kg (up to a usual adult dose of 10 – 20 mg), followed by a nicardipine drip starting at 0.5-1 mCg/kg/min and titrated to achieve a 25% reduction in blood pressure up to a maximum of 4-5 mCg/kg/min [50]. Some concern has recently been raised as to the reliability and safety of IV hydralazine based on a single center retrospective study [51]. Nitroprusside infusion or labetalol bolus followed by labetalol infusion are alternative strategies (table 3). Caution and close monitoring should be employed with labetalol infusion, as its long half-life can lead to greater than anticipated antihypertensive effects with prolonged infusions or with rapid upward titration.

Rapid reduction of blood pressure beyond 25% risks ischemic stroke and other tissue ischemia due to accommodation of cerebral and peripheral vasculature to elevated blood pressures. Blood pressures while on continuous antihypertensive drip medications should be monitored frequently, either by continuous intra-arterial blood pressure measurement or by cuff measurement at least every 15 minutes. Once blood pressure has been stabilized on an antihypertensive medication drip, a longer-acting medication can be started orally and the drip can be tapered as oral medications take effect.

Hypertensive urgency is defined as severe hypertension without acute end-organ effects; it warrants urgent evaluation and treatment as the risk for acute end-organ effects in this setting is high. Evaluation for underlying cause is central in guiding therapy. Oral agents such as hydralazine, clonidine, isradipine, nicardipine, and minoxidil can be used to lower blood pressure acutely, despite less rapid onset as compared to IV medications. If oral intake is not tolerated, blood pressure can be reduced using IV agents (e.g. hydralazine, labetalol). As noted above, care should be taken to avoid rapidly lowering blood pressure when it is suspected that blood pressure elevation has been longstanding [50].

5. Conclusions

Hypertension in children is common, and the prevalence of primary hypertension is increasing with the obesity epidemic and changing dietary choices. Careful measurement of blood pressure and comparison with age, gender, and height-based norms is important to correctly diagnose hypertension. White coat hypertension, prehypertension, and uncomplicated stage I hypertension should initially be treated non-pharmacologically with weight reduction, increased physical activity, and dietary modification including decreased sodium and high-fructose corn syrup consumption – so called “therapeutic lifestyle changes.”

When pharmacological treatment is indicated, the choice of drug and drug class is determined by the underlying cause of hypertension and the comparative side-effect profiles of the medications. When choosing a drug within a particular class, practical issues such as frequency of drug dosing (daily dosing preferred), availability at local pharmacies, insurance formulary agents, and/or availabilities of low-cost generics should also be considered as they have important effects on adherence. Antihypertensive medication should be initiated at a starting dose and gradually increased to effect. If ineffective at maximum dosing, an additional medication with a complementary mechanism of action can be added [52].

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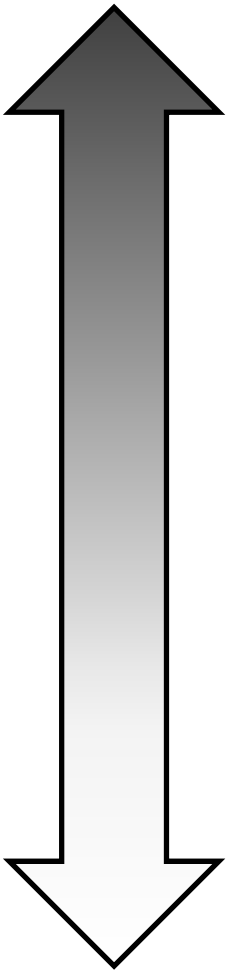
Table 1. Causes of Hypertension

More important in younger patients



Idiopathic hypertension of prematurity
Renal artery or venous thrombosis
Congenital anomalies of the kidney and urinary tract (CAKUT)
Coarctation of the aorta
Congenital adrenal hyperplasia (11β- hydroxylase deficiency)
Medication effect
Pain
Pyelonephritis/renal scarring
Acute urinary tract obstruction
Chronic kidney disease
Glomerulonephritis
Acute kidney injury
Renal artery stenosis
Licorice intoxication
Monogenic hypertension (Liddle syndrome, AME, GRA, etc.)
Hyperthyroidism
Hypercalcemia
Paraneoplastic effects (pheochromocytoma, neuroblastoma)
Increased central nervous system sympathetic outflow
Increased intracranial pressure
Substance abuse
Primary hypertension

More important in adolescents

Note: Relatively more common causes of hypertension are listed in bold.

Table 2. Selected antihypertensive drugs for management of outpatient hypertension in patients 1-17 years of age [1, 53-58].

Class	Drug	Dose	Dosing Interval
Calcium-Channel Blocker	Amlodipine[a]	Initial: 0.05-0.1 mg/kg/day, up to 5 mg/day Maximum: 0.6 mg/kg/day, up to 10 mg/day	Daily
	Extended-release nifedipine[b]	Initial: 0.25-0.5 mg/kg/day, up to 60 mg/day Maximum: 3 mg/kg/day up to 120 mg/day	Daily-BID
	Other available drugs in this class include isradipine, felodipine, verapamil, and diltiazem.		
ACE Inhibitor	Captopril[a, c]	Initial: 0.9-1.5 mg/kg/day up to 40 mg/day[d] Maximum: 6 mg/kg/day	TID
	Enalapril[a]	Initial: 0.08 mg/kg/day, up to 5 mg/day Maximum: 0.6 mg/kg/day, up to 40 mg/day	Daily-BID
	Lisinopril[a]	Initial: 0.07 mg/kg/day, up to 5 mg/day Maximum: 0.6 mg/kg/day, up to 40 mg/day	Daily
	Other available drugs in this class include benazepril, fosinopril, and quinapril.		
Angiotensin-receptor blocker (ARB)	Losartan[b]	Children ≥ 6 years of age: Initial: 0.7 mg/kg/day, up to 50 mg/day Maximum: 1.4 mg/kg/day, up to 100 mg/day	Daily
	Valsartan[a]	**Children 1-5 years of age, weighing ≥ 8 kg:** Initial: 0.4 mg/kg/day Maximum: 3.4 mg/kg/day up to 40 mg/dose if <18 kg, up to 80 mg/dose if ≥18 kg. **Children 6-16 years of age:** Initial: 1.3 mg/kg/day up to 40 mg/day Maximum: 2.7 mg/kg/day up to 160 mg/day	Daily
	Other available drugs in this class include candesartan, irbesartan, and telmisartan.		
Thiazide Diuretics	Chlorthalidone[b]	Initial: 0.3 mg/kg/day up to 12.5 mg/day[d] Maximum: 2 mg/kg/day up to 50 mg/day	Daily
	Chlorothiazide[a]	Initial: 10-20 mg/kg/day Maximum: Age <2 years – 375 mg/day Age 2-12 years – 1000 mg/day Age >12 years – 2000 mg/day	BID
	Hydrochlorothiazide[a]	Initial: 1 mg/kg/day up to 25 mg/day[d] Maximum: 3 mg/kg/day up to 50 mg/day	Daily-BID
Potassium-Sparing Diuretic	Spironolactone[a]	Initial: 1 mg/kg/day up to 50 mg/day[d] Maximum: 3.3 mg/kg/day up to 100 mg/day	Daily-BID
	Other available drugs in this class include triamterene and amiloride.		
Beta-Blocker	Atenolol[a]	Initial: 0.5-1 mg/kg/day up to 50 mg/day Maximum: 2 mg/kg/day up to 100 mg/day	Daily-BID
	Metoprolol tartrate[a]	Initial: 1-2 mg/kg/day up to 100 mg/day[d] Maximum: 6 mg/kg/day up to 200 mg/day	BID
	Metoprolol succinate (extended release)	Age ≥ 6 years: Initial: 1 mg/kg/day up to 50 mg/day Maximum: 2 mg/kg/day up to 200 mg/day	Daily
	Propranolol[a]	Initial: 1-2 mg/kg/day up to 80 mg/day[d] Maximum: 4 mg/kg/day up to 640 mg/day	BID-TID
	Other available drugs in this class include bisoprolol/HCTZ		
Alpha and Beta-Blocker	Labetalol[a]	Initial: 1-3 mg/kg/day up to 200 mg/day[d] Maximum: 10-12 mg/kg/day up to 1200 mg/day	BID
Direct Vasodilator	Hydralazine[a]	Initial: 0.75-1 mg/kg/day up to 25 mg/day[d] Maximum: 7.5 mg/kg/day up to 200 mg/day	QID
	Minoxidil[a]	**Age <12 years:** Initial: 0.1-0.2 mg/kg/day up to 5 mg/day[d] Maximum: 50 mg/day **Age ≥ 12 years:** Initial: 5 **mg/day** Maximum: 100 mg/day	Daily
Peripheral alpha-blocker	Prazosin[b]	Initial: 0.05-0.1 mg/kg/day up to 2 mg/day[d] Maximum: 0.5 mg/kg/day up to 20 mg/day	TID
	Other available drugs in this class include doxazosin and terazosin		
Central alpha-agonist	Clonidine[a]	Initial: 5-10 **mCg**/kg/day up to 0.2 **mg/day**[d] Maximum: 0.9 **mg/day** [53]	Q8H-Q12H Patch: weekly

BID – twice daily, TID – three times daily. [a] Information on compounding a stable oral suspension available. [b] Not readily available in liquid form. [c] Infant/neonatal dose varies substantially from the child dose. [d] Maximum starting dose based on adult starting dose [56, 57]. The adult maximum dose should never be exceeded.

Table 3. Selected antihypertensive medications for treatment of severe hypertension in patients 1-17 years of age [1, 50, 59].

Class	Drug	Dose	Route	Comments
Calcium-Channel Blocker	Nicardipine	Infusion: 0.5-4 **mCg**/kg/min	IV infusion	May cause reflex tachycardia.
Alpha and Beta-Blocker	Labetalol	Bolus: 0.2-1 mg/kg/dose up to 40 mg/dose Infusion: 0.25-3 mg/kg/hr	IV bolus or infusion	Asthma and overt heart failure are relative contraindications.
Beta-Blocker	Esmolol	100-500 **mCg**/kg/min	IV infusion	May cause profound bradycardia.
Direct Vasodilator	Hydralazine	0.1-0.6 mg/kg/dose up to 20 mg/dose	IV, IM	Should be given every 4 hours when given as IV bolus.
	Sodium Nitroprusside	Initial: 0.3-0.5 **mCg**/kg/min Maximum: 10 **mCg**/kg/min	IV infusion	Monitor thiocyanate levels with prolonged use (>72 hours) or in renal failure; or co-administer with sodium thiosulfate.
ACE Inhibitor	Enaliprilat	5-10 **mCg**/kg/dose up to 1.25 mg/dose[b]	IV bolus	Less useful for severe hypertension with significant symptoms; may cause prolonged hypotension and AKI, especially in neonates
Oral agents – useful for patients with less significant symptoms				
Calcium-Channel Blocker	Isradipine[a]	0.05-0.1 mg/kg/dose up to 5 mg/dose	PO	Immediate release formulation usually given every 6-8 hours.
Direct Vasodilator	Hydralazine[a]	0.25 mg/kg/dose up to 25 mg/dose	PO	May be repeated every 4-6 hours if needed.
	Minoxidil[a]	0.1-0.2 mg/kg/dose	PO	Most potent oral vasodilator, long-acting.
Central Alpha Agonist	Clonidine[a,c]	0.05-0.1 **mg/dose**, may be repeated up to 0.8 mg total dose	PO	Side effects include dry mouth and drowsiness.

IV – intravenous, IM – intramuscular, PO – by mouth/orally. [a] Information on compounding a stable oral suspension available. [b] Dosing and safety in pediatrics is not well-established. [c] Dose referenced to weight is not available. See table 3 for oral clonidine dosing in non-urgent hypertension.