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Review Article

Hypertension in Children

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Abstract

Prevalence of hypertension (HT) in children is increasing. Part of the reason is the rise in the population of children with obesity and part is better screening for HT though far from ideal. Neonatal and infantile HT remains relatively poorly described in terms of epidemiology, normative data, and available antihypertensive medications. The 2017 American Academy of Pediatrics guidelines on the management of HT in children have used data from children with normal body mass index thereby lowering the cutoffs for definition of HT compared to earlier. HT is now staged as elevated, Stage 1 and Stage 2, making earlier terminologies obsolete. Elevated blood pressure (BP) is important as studies show that an elevated BP as a child increases risk of developing HT as an adult as well as metabolic syndrome. Ambulatory BP monitoring in pediatrics is increasingly being used in various situations though so far there is no normative data for children <120 cm in height. Investigations into the cause of HT may be limited when the patient is over 6 years of age and is overweight or obese or has family history of HT and the physical examination is normal. The two major causes of secondary HT in pediatrics are renal/reno-vascular and endocrine. Lifestyle modification plays a major role in therapy. It includes weight reduction/control by increasing physical activity, nutritious, and low-fat diet and reducing salt intake. The first-line medications for oral therapy are angiotensin converting enzyme inhibitors, angiotensin receptor blockers, thiazide diuretics, and calcium channel blockers. Lifelong follow-up is essential for care of the pediatric patient with HT.

Key words: Blood pressure, hypertension, management, pediatrics

Introduction

Hypertension (HT) in children is an important cause of morbidity in childhood.[1] It is a precursor to HT and atherosclerosis related diseases in adulthood. Its prevalence is estimated to be 3.5% in the pediatric population. It is key to choose an appropriate cuff size and be meticulous while obtaining blood pressure (BP) in children. Unlike adult population, in the absence of obesity and family history, HT in young children is more likely to be secondary to renal or endocrine causes. The initial laboratory evaluation of children is tailored with that in mind. Additional investigations are performed as demanded by unique historical and clinical features of the child. Lifestyle modification plays a major role in control of pediatric HT associated with obesity. Initiating pharmacotherapy has to be a well thought out decision as the child may need lifelong medication. The range of medicines available to treat pediatric HT is limited.

Definition of HT

HT in pediatrics is diagnosed when abnormal BP reading (as defined below) is obtained at three separate visits using an appropriate BP cuff and manual auscultatory method. The cutoffs for children are defined by outliers from data collected from children with normal weights. This is unlike the definition of adult HT. Abnormal BP measurements are categorized into three stages: Elevated, Stage 1, and Stage 2. Each level has a particular management strategy. The software application MDCalc (downloadable app) has a BP tool developed in partnership with the American Academy of Pediatrics for use in children aged 1–17 years. It classifies the entered BP value into normal/ elevated/Stage 1 or Stage 2 HT based on age, sex, and height. The practice guidelines issued by the American Academy of Pediatrics in 2017[1] also have an easy reference table for office practice. This tabulates the screening BP values

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requiring further evaluation in boys and girls from age 1 to 13 years.

Age 0–12 months

This is a challenging subset for definition of HT for a myriad of reasons, especially in neonates. There is gestational age specific normative data available for neonates inclusive of premature babies and infants.[2,3]

Age 1 year–13 years

- Normal BP – Both systolic blood pressure (SBP) and diastolic blood pressure (DBP) <90th percentile.
- Elevated BP – SBP and/or DBP is between 90 and 95th percentile, or 120/80 mmHg to 95th percentile.
- A BP reading above 95th percentile defines Stage 1 and Stage 2 HT. It is Stage 1, if it is up to 12 mmHg over the 95th centile. It is Stage 2, if it is more than 12 mmHg over the 95th centile:
- Stage 1 hypertension – SBP and/or DBP ≥95th percentile to <95th percentile + 12 mmHg, or 130/80–139/89 mmHg.
- Stage 2 hypertension – SBP and/or DBP ≥95th percentile + 12 mmHg, or ≥140/90 mmHg (whichever is lower).

Age more than 13 years

- Static cutoff numbers (no percentile charts) are similar to adult cutoff values for HT:
- Normal BP – BP <120/80 mmHg.
- Elevated BP – SBP 120–129 with a DBP <80 mmHg.
- Stage 1 hypertension – BP between 130/80 and 139/89 mmHg.
- Stage 2 hypertension – BP ≥140/90 mmHg.

The group of "elevated BP" is important as there is progression to persistent HT in adulthood in almost a third of affected children.[4,5]

The above definition is followed in the United States. The European union uses adult guidelines for children aged 16 years and older, instead of 13 years.[6]

Masked HT is defined as HT at home but not in the office. White coat HT is defined as HT in the office but not at home.

Measurement Protocol

Two measurements to be taken at each visit, after the child is calm and quiet and seated, with at least 2–3 min gap between measurements. The child should have the right arm supported, and at the heart level. The diaphragm of the stethoscope should be kept on the brachial pulse.

An appropriately sized cuff is selected. The selected cuff's bladder length should encircle the bare arm 80–100% and the width of the bladder should be at least 40% of the mid-arm circumference.

The manual auscultatory method with an aneroid sphygmomanometer is preferred; normative data used for defining HT is based on manual auscultation. The cuff is inflated 30–40 mmHg above the level of disappearance of sounds. It should then be slowly deflated till Korotkoff sounds reappear (SBP) and then disappear (DBP).

The automated oscillometric devices are easier to use but have been shown to have higher readings. Hence, manual measurements are always preferable. A hypertensive reading obtained by the oscillometric device has to be rechecked by the manual method.

A lower limb BP should also be recorded in the initial evaluation. The normal lower limb BP is 10–20 mmHg higher than the upper limb.

Screening for HT

Diagnosis of HT in pediatrics is missed because there are lack of symptoms or inability to convey symptoms. Hence, screening for HT is essential. In the absence of any risk factor, BP measurement should be taken annually starting from age 3 years. In the presence of any risk factor, BP measurement should be taken at every clinic visit irrespective of age.

Risk Factors for Developing HT

Premature birth has been linked to HT in children, including abnormal circadian BP pattern. Relevant family history, childhood obesity, dyslipidemia, hyperglycemia, high salt intake, low potassium intake, and obstructive sleep apnea (OSA) are risk factors in children.[7,8] There is a four-fold increase in HT if the body mass index (BMI) is >99% percentile and a 2 fold increase in HT if BMI is >95% percentile.[9] The prevalence of HT in children with OSA is 3–14%.

Ambulatory BP Monitoring in Pediatrics

There are limited data of ambulatory BP monitoring (ABPM) in pediatrics.[10,11] ABPM is monitored by oscillometric method and has separate cutoffs for definition of HT. Normative data for ABPM in pediatric age groups is available.[8] There is no reference for children <120 cm tall. In addition, in most parts of the third world, availability of ABPM apparatus is a challenge.

Possible indications of ABPM in pediatrics include:

1. White coat HT
2. Masked HT (prevalent in obese children)
3. Persistent HT in the Elevated range
4. Stage 1 or 2 HT with a high suspicion of secondary HT not detected with routine tests
5. Chronic kidney disease
6. Long-term follow-up of patients post-correction of coarctation of the aorta
7. Dysautonomic syndromes
8. BP response to medical therapy.

Etiology of HT

HT could be primary HT or secondary to identified causes. It is essential to differentiate the two using historical, clinical, and

laboratory parameters. Diagnosing secondary HT permits better control or potential resolution of the HT.

Primary HT used to be considered a diagnosis of exclusion. However, numerous studies have demonstrated that in hypertensive children aged more than 6 years of age, coexistent over-weight status/obesity, family history of HT, and absence of any physical findings consistent with secondary HT or end organ damage may suggest that secondary HT is very less likely. Accordingly, the American Academy of Pediatrics 2017 clinical practice guideline for screening and management of HT in children and adolescents[1] states that extensive work up is not required in such instances.

A step-wise approach to diagnosing secondary HT is essential.

Age-wise Distribution of Causes of Secondary HT

Neonates

1. Lower gestational age and low-birth weight
2. Administration of antenatal steroid or post natal use
3. NICU related factors: Fluid overload conditions, periprocedural pain, suctioning, prolonged TPN, and ECMO
4. Umbilical artery catheter related thrombus (renal artery flow is disturbed)
5. Bronchopulmonary disease
6. Coarctation of the aorta
7. Congenital Adrenal Hyperplasia
8. Hyperthyroidism
9. Renal diseases
   a. Renal vein thrombosis
   b. Renal artery stenosis: Fibromuscular dysplasia, neurofibromatosis, William syndrome, and congenital Rubella infection
   c. Polycystic kidney disease
   d. Obstructive uropathy
   e. Wilms tumor, neuroblastoma.

Children and Adolescents

The prevalence studies have shown that adolescents are more likely to have primary (essential) HT. The other most common reasons would renal or endocrine causes. On the other hand, in the age group <12 years, the most likely cause of HT would be renal and endocrine, followed by primary HT.

These are the various causes of secondary HT.

1. Renal Disease: About half of the cases of secondary HT may be renal in origin.[12,13] HT is a common feature of chronic renal failure, end-stage renal disease, and post-renal transplant status. Chronic kidney disease has a 37% prevalence of HT.
   a. Renal parenchymal disease: Glomerulonephritis, acute tubular necrosis, hemolytic-uremic syndrome, polycystic kidney disease, recurrent urinary tract infections, and obstructive uropathy.
   b. Renal vascular disease: This cause is identified in 5–10% of children and adolescents with HT and affected patients present frequently with Stage II HT. Fibromuscular dysplasia, aorto-arteritis (Takayasu arteritis), neurofibromatosis, William syndrome, congenital Rubella infection, extrinsic compression on the renal vessels by a mass, and renal venous thrombosis due to a prothrombotic state are common causes.
2. Coarctation of the aorta.
3. Endocrine disturbances: Pheochromocytomas, congenital adrenal hyperplasia, Cushing disease, hyperthyroidism, hypothyroidism (diastolic HT), diabetes (type I and II), and primary hyperaldosteronism.
4. OSA.
5. Exogenous medications: Steroids, caffeine, over-the-counter medications for cold (ephedrine, and pseudoephedrine), medications for attention deficit hyperactivity disorder, tacrolimus, cocaine, oral contraceptive pills, and recreational drugs.
6. Central causes of HT: Space occupying lesions, and disturbances of the vasomotor center.

Evaluation of HT in Children and Adolescents

A stepwise approach to evaluation is critical for satisfactory management of HT [Table 1].

Management of HT

Elevated BP reading: Advise lifestyle changes. Repeat measurement in 6 months. If still in elevated BP range, then consider ambulatory BP monitoring.

Stage 1 Hypertension: Lifestyle changes if applicable. Repeat measurement in 1–2 weeks as appropriate. Consider diagnostic workup.

Stage 2 Hypertension: If the patient is symptomatic or if the BP is elevated by more than 30 mmHg above the 90th percentile, referral should be made to emergency care dept. If the patient is asymptomatic, the BP is repeated in 1 week and then work up and treatment initiated. Symptoms of HT include headache, visual disturbances, seizures and focal neurological deficits, and symptoms of underlying disease in cases of secondary HT laboratory investigations of children and adolescents with Stage 2 HT [Table 2].

An echocardiogram is recommended when initiating antihypertensives. Left ventricular hypertrophy (LVH) is diagnosed if indexed LV mass is >115 g for boys and 95 g for girls. An ECG has low sensitivity to diagnose LVH. However, it gives information on pulse rate and electrolyte disturbances. Ambulatory BP monitoring may be performed as part of work up. Subtle clues in favor of secondary HT such as elevated diastolic pressure readings in daytime and elevated systolic BP readings at night time may be picked up on ABPM. Some units advocate plasma renin activity as part of initial laboratory work up. This would diagnose renal causes

Table 1: Evaluation of a child with hypertension

Component	Details	Remarks
History	Birth/Antenatal history	Maternal history of HT, low birth weight, other factors (see neonatal HT section)
	Family history	HT, early (<55 years age) onset ischemic heart disease, familial hyperlipidemia, sudden cardiac death, hereditary renal, or endocrine syndromes
	Family Structure	Nuclear/joint/both parents working. May determine ease of following dietary or activity advice given
Diet	Intake of high sodium, high fat, caffeine	
Physical activity level	Exercise/field sports/cycling/skating, etc.	
Screen time	Time spent on mobile phone/laptop/tablet/television	Inversely proportional to physical activity level. Hence, important to crosscheck.
Sleep	Less sleep, snoring, day time sleepiness	Obstructive sleep apnea
Physical exam	Weight/Height/BMI	Obesity, endocrine/renal causes
	Dysmorphology	Endocrine causes
	Peripheral/periorbital edema	Renal causes
	Enlarged thyroid	
	Skin lesions: Acne, acanthosis nigricans, xanthelasmas, xanthomas, café au lait spots	Obesity, hyperlipidemia, Cushing syndrome, neurofibromatosis
	Pulse volume and rate	Coarctation, arteritis, hyperthyroidism
	Apical heave, murmur	End organ affect left ventricular hypertrophy
	Abdominal bruit/mass	Arteritis, renal-suprarenal mass
	Joints	Arthritis in certain autoimmune causes of glomerulonephritis
	Ambiguous genitalia	Congenital adrenal hyperplasia

HT: Hypertension, BMI: Body mass index

Table 2: Laboratory investigations of children and adolescents with Stage 2 hypertension

Test	Details	Remarks
Blood	Complete blood count, serum sodium, potassium, chloride levels; serum blood urea nitrogen, serum creatinine, estimated eGFR; lipid profile	In obese patients: Serum fasting blood sugar, HbA1c, serum ALT, serum AST
Urine	Routine and microscopic	
Imaging	Renal ultrasound with Doppler	The Doppler component is more reliable in non-obese children and children above 8 years of age. The alternative to renal Doppler is CT angiography or MR angiography
	CT angiogram or MR angiography	Complete visualization of the aorta and branches including renal vessels. Additional information in mass lesions. Radiation dose should be minimized in CT
	Echocardiogram	When considering antihypertensives

eGFR: Estimated glomerular filtration rate, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, CT: Computed tomography, MR: Magnetic resonance, MR

of HT and also help choose antihypertensives. A high plasma renin level prompts usage of an angiotensin converting enzyme (ACE) inhibitor as drug of first choice.[14] Additional testing is determined by index of suspicion for secondary cause of HT.

Treatment of HT

Asymptomatic HT: The goal of therapy is to obtain BP readings that are <90th percentile for age[1]. For children with end-stage renal failure, the goal should be to obtain readings at 50th percentile for age.

Lifestyle Modifications

This includes activity and dietary changes and reduction in stress.[1,15] The entire family has to adapt to the change for success. Encourage outside activity/sports involving moderate physical exertion for 40–60 min at least 3–5 times

in a week, reduction in screen time and age appropriate sleep time.[16]

Diet

In general, the DASH diet (dietary approach to stop HT) can be applied to children.[17] Such a diet is high in minimally processed food, whole grains, lentils, vegetables and fruits, low fat milk and milk products, and fish and lean red meat. There should reduction in refined sugar containing products and salt. Salt reduction implies no table salt and avoiding salty snacks and processed foods. Sodium intake should be <2.3 g (1 teaspoon of salt) per day.[18] A high potassium diet has also been advocated.[19] Avoid caffeinated drinks. Weight control/reduction with a dietician consultation should be availed as appropriate. There is a fall in BP by an estimated 2–4 mmHg for every kg weight reduction in obese adolescents.[20]

Drug Therapy

The preferred medications for pediatric HT are ACE inhibitors, angiotensin receptor blockers, thiazide diuretics, and calcium channel blockers.[21] Beta blockers are not preferred as first line as their side effect profile is not favorable. See Table 3 for common oral antihypertensive medications used in pediatrics. Calcium channel blockers can be safely started on children while they undergo investigations for secondary HT as these do not interfere with the renin-angiotensin axis. Thiazide diuretics are less effective in children with glomerular filtration rate <30 ml/min/1.7 m^2.

Patients should be seen monthly for titrating drugs. A second or a third drug is rarely required. Second or third line antihypertensives include beta blockers, arterial vasodilators, alpha blockers, and central alpha agonists. See Table 4 for second and third line drugs. Despite all measures, if the child is persistently hypertensive while on three antihypertensives (resistant HT), a trial of spironolactone may be made. Certain disease states benefit from a particular class of antihypertensives. For example, ACE inhibitors are preferred in children with chronic kidney disease with proteinuria. There are data on the efficacy of ramipril in such children, aged 1.9–19 years.[22] Clonidine is helpful in HT due to brain injury and autonomic disorders. Labetalol is useful in pheochromocytoma induced HT, after phenoxybenzamine or prazosin is used.

Contraindications and Common Side effects of Oral Antihypertensives

ACE inhibitors

They are contraindicated in females at risk of becoming pregnant and patients with bilateral renal artery stenosis. Important side

Table 3: First line oral anti-hypertensives for pediatric hypertension

Drug	Dose range (initiating to maximum)	Doses per day	Remarks
Enalapril	0.05–0.3 mg/kg/dose	Twice	>Age 1 month (max dose range: 5 mg–40 mg/day)
Lisinopril	0.07–0.6 mg/kg/dose	Once	Age >6 years (max dose range: 5 mg–40 mg/day)
Ramipril	1.6–6 mg/m^2/dose	Once	Max dose in adults: 2.5 mg–20 mg/day. Has been used in children above 18 months of age
Candesartan	0.01–0.2 mg/kg/dose	Twice	Age 1–5 years (max dose range: 8 mg–32 mg/day)
	4–16 mg/dose	Twice	Age >6 years (max dose range: 8–32 mg/day)
	8–16 mg/dose	Twice	Age >6 years and weight >50 kg (max dose range (8–32 mg/day)
Olmesartan	10–20 mg/dose	Once	Age >6 years, weight <35kg
	20–40 mg/dose	Once	Age >6 years, weight >35 kg
Losartan	0.7–1.4 mg/kg/dose	Once	Age >6 years (max dose range: 50–100 mg/day)
Valsartan	0.4–3.4 mg/kg/dose	Once	Age 1–5 years and weight >8kg: Max dose: 40 mg (<18 kg) to 80 mg (>18 kg)/day
	1.3–2.7 mg/kg/dose	Once	Age: >6 years Max dose range: 40–160 mg/day
Hydrochlorothiazide	0.5–1 mg/kg/dose	Twice	Max dose range: 25–75 mg/day
Chlorothiazide	5–10 mg/kg/dose	Twice	Max dose for age <2 years: 375 mg/day Max dose for 2–12 years: 1000 mg/day Max dose for >12 years: 2000 mg/day
Amlodipine	0.1–0.6 mg/kg/dose	Once	Age 1–5 years. (max dose 5 mg/day)
	2.5–10 mg/dose	Once	Age >6 years. (max dose 10 mg/day)
Nifedipine (extended release)	0.1–1.5 mg/kg/dose	Twice	Max dose: 60 mg twice a day

effect is hyperkalemia and acute renal failure especially in infants. Chronic cough is not as frequent as in adults.

Angiotensin receptor blockers

They are more teratogenic than ACE inhibitors. Side effects are the same; cough is even less frequent.

Thiazide diuretics

They can cause hypokalemia and volume depletion. Prescribe with caution in athletes.

Calcium channel blockers

Peripheral edema and headache. Short acting Nifedipine should be avoided in office practice as it can cause precipitous drop in BP.

Beta blockers

They can reduce endurance in athletes. They are contraindicated in children with severe asthma or diabetes. Rebound HT and tachycardia are seen with abrupt withdrawal of beta blockers.

Alpha blocker (Prazosin)

Syncope with first dose; dry mouth, headache, and weakness.

Central alpha agonist (clonidine)

Drowsiness is a common side effect.

Emergency Treatment of HT

A patient presenting with symptoms/signs of HT, such as headache, delirium, seizures, visual disturbances, or heart failure will require admission to the intensive care unit. Alongside starting medications for control of HT, attempt must be made to thoroughly investigate for secondary HT. Specifically intracranial mass or injury has to be ruled out. Differentiating hypertensive encephalopathy from signs and symptoms of an intracranial mass or a hemorrhage or thromboembolism may require urgent neuroimaging. The target BP should be at the 95th percentile for age/sex/height of the child. The aim of BP control in a hypertensive emergency is to achieve 25% of the desired reduction over 8 h and the remaining over the next 12–24 h. Intravenous medications used in hypertensive emergencies are tabulated in Table 5. In general, a continuous infusion of nicardipine or labetalol is preferred.

Sports Participation

Physical exercise improves cardiac health in children.[23] Children with elevated or Stage 1 HT should not be restricted. Athletes with Stage 2 HT should be restricted from participating in high static activities such as weight lifting, boxing, and wrestling until BP control is achieved. Athletes should be evaluated for effects on the heart, kidneys, and retina before lifting restrictions.

Summary

Protocols for pediatric HT evaluation and management have evolved over the past some decades. The currently recommended protocols for defining and treating HT have simplified care to a large extent. To achieve control of HT, substantial emphasis should be on encouraging physical activity and low sodium, nutritious diet. Initiating drug therapy has to be a well thought out decision. The array of anti hypertensives available for use lags behind drugs available for adults with HT.

Table 4: Second line oral anti-hypertensives for pediatric hypertension

Drug	Dose range (initiating to maximum)	Doses per day	Remarks
Atenolol	0.25–1 mg/kg/dose	Twice	Max dose range: 50–100 mg/day
Metoprolol	0.5–3 mg/kg/dose	Twice	Max dose range: 100–200 mg/day
Metoprolol extended release	1–2 mg/kg/dose	Once	Max dose range: 50–200 mg/day
Propranolol	0.5–1.2 mg/kg/dose	Thrice	Max dose range: 80–640 mg/day
Labetalol	0.5–10 mg/kg/dose	Twice	Max dose range: 200–1000 mg/day
Prazosin	0.02–0.15 mg/kg/dose	Thrice	Max dose range: 2–20 mg/day
Clonidine	2.5–5 mcg/kg/dose	Twice	Max dose range:200–900 mcg/day

Table 5: Intravenous drugs for pediatric hypertensive emergencies

Drug	Dose	Remarks
Nicardipine infusion	0.5–4 mcg/kg/min	Reflex tachycardia is a side effect. Can be used even in infants.
Labetalol infusion	0.25–3 mg/kg/h	Bolus or infusion is contraindicated in asthma and frank heart failure.
Labetalol bolus	0.2–1 mg/kg/dose. Max 40 mg/dose	Can be repeated every 10 min.
Sodium nitroprusside	0.5–3 mcg/kg/min. max dose 10 mcg/kg/min	Avoid in chronic renal disease.
Hydralazine bolus	0.1–0.2 mg/kg/dose. Max 0.4 mg/kg/dose	Onset of action is slower. Can be repeated every 4 h. Can be given intramuscularly as well. Tachycardia is a side effect. Can be used in infants.

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