Pediatric Hypertension
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Disclosures

Objectives
• Define hypertension in children and review screening guidelines
• Identify long term health risks associated with hypertension
• Review causes of primary and secondary pediatric hypertension
• Review non-pharmacologic and pharmacologic management strategies to reduce blood pressure in children
• Discuss when to refer to a specialist

Abbreviations
• AH = Antihypertensive
• ARF = Acute renal failure
• CKD = Chronic kidney disease
• CVD = Cardiovascular disease
• DBP = Diastolic blood pressure
• HTN = Hypertension
• SBP = Systolic blood pressure
• cIMT = carotid intimal medial thickness
• LVM = left ventricular mass
• LVH = left ventricular hypertrophy

• Showed an upward shift of the entire distribution of childhood BP by 1.4 mm Hg for SBP and 3.3 mm Hg for DBP
• Prevalence of HTN in children also increased and is currently ~2-5%
• There were higher rates of HTN seen in non-Hispanic blacks and Mexican Americans
• Adjustment of the data for BMI suggested some of the increase was likely related to obesity
• Longitudinal evaluation has also confirmed higher BMI increased the incidence of pre HTN converting to HTN

Why do these trends matter? The Bad
• High BP is one of several risk factors of CVD identified in adults & it is has been shown to track from childhood to adulthood
• Full implementation of HTN guidelines in adults could result in ~56,000 fewer CV events and 13,000 fewer deaths annually
• Atherosclerotic changes are seen in childhood and can be accelerated by obesity, hypertension, & other risk factors
• Children with severe secondary HTN (e.g. CKD) have increased risk of stroke, hypertensive encephalopathy, congestive heart failure, and death

What is Cardiovascular disease (CVD)
• Atherosclerosis is an inflammatory process that causes plaque made of fat, cholesterol, calcium, and other substances to build up in arteries
• Progressive atherosclerosis in various arterial systems of the body can lead to obstruction and/or rupture

Cardiovascular disease
• Coronary heart disease (CHD) → myocardial infarction (MI), angina pectoris, heart failure, and coronary death
• Cerebrovascular disease → stroke and transient ischemic attack
• Peripheral artery disease → intermittent claudication
• Aortic atherosclerosis → thoracic or abdominal aortic aneurysm

Established risk factors for CVD in adults
• High blood pressure
• Family history
• Age
• Gender
• Nutrition/diet
• Physical Inactivity
• Smoking
• Blood lipid levels
• Overweight/obesity
• Diabetes
• Metabolic syndrome
• Perinatal factors
• Inflammatory markers

• Bogalusa, LA Heart Study
  CV risk factors (lipids, BP, BMI, smoking) were measured as part of a comprehensive school-based epidemiological study of a biracial community
  • Autopsy studies were done on those who died of non-CVD related causes (accidental deaths)
  • Arterial plaque and lesions were examined
  • Strong correlations were seen between the presence & intensity of risk factors & extent of severity of atherosclerosis
  • Obesity, HTN, & high cholesterol in children → tracked to adulthood
  • SBP from childhood to adulthood was a significant predictor of adult left ventricular mass (LVM)

Cardiovascular Risk in Young Finns Study
• Large prospective CV risk study in Europe with follow-up from childhood to adulthood
• Study variables: serum lipoproteins, BP, obesity indices, insulin, glucose, lifestyle, family risk, socioeconomic, and psychological variables
• Childhood HTN was related to higher adult pulse-wave velocity which indicates increased arterial stiffness

International Childhood Cardiovascular Cohort (i3C) Consortium
• Pooled data of several large long-standing cohort studies
• Most looked at similar lifestyle and biological risk factors including BP, lipids, and adiposity measures
• Over 40,000 children were examined, with ~10,000 contributing data as kids and adults
• Higher BP measurements as young as 12 years of age predicted increased adult cIMT

The Good news
• CVD events are rare in the pediatric population
• We know that treatment of HTN in adults decreases CVD risk*
• We also know that intense management of HTN in children with CKD slows progression of disease**

What is blood pressure (BP)?
• The balance between cardiac output (CO) and systemic vascular resistance (SVR); a rise in either variable without a compensatory decrease in the other will lead to increased BP
• CO regulators: baroreceptors, extracellular volume, effective circulating volume (atrial natriuretic hormones, mineralocorticoids, angiotensin), sympathetic nervous system
• SVR regulators: Pressors (angiotensin II, calcium (intracellular), catecholamines, sympathetic nervous system, vasopressin. Depressors—atrial natriuretic hormones, endothelial relaxing factors, kinins, prostaglandin E₂, prostaglandin I₂

Changes in electrolytes also affect BP:
• Sodium: Retention increases extracellular volume → changes in GFR and tubular reabsorption of Na → increased excretion
• Calcium: Increased intracellular levels → increased contractility; stimulates release of renin, synthesis of Epi, & SNS activity
• Potassium: Increased levels suppress renin release, inducing natriuresis and lowering BP

BP in children & adolescent
• Considered normal when SBP and DBP values are < the 90th percentile for age, sex, and height
• BP increases with age & height and is usually higher in males
• BP also increases with higher BMI, but this is likely pathologic and not reflected in percentiles
• Ethnic differences in BP are minimal after accounting for differences in body size*

What is hypertension (HTN)?
• Stage 1: BP is > the 95th percentile, but ≤ to the 99th percentile + 5 mm Hg
• Stage 2: BP is > the 99th percentile + 5 mm Hg

What is prehypertension (pre HTN)?
• SBP and/or DBP between the 90th to 95th percentile on 3 or more measurements or BP ≥ 120/80 mmHg in any adolescent
• Previously termed ‘high normal’
• Higher risk of progressing to sustained HTN

Screening for HTN
• Annual assessment in children 3 years and older*
• BP should be obtained via auscultation (right arm is preferred)**
• Cuff size should fit child’s upper arm with a bladder width-to-length ratio of at least 1:2
• Measure at well child and sick visits

Screening for HTN before 3 years of age
• Prematurity, VLBW, NICU stay
• Congenital heart disease (repaired or non-repaired)
• Recurrent UTI, hematuria, or proteinuria
• Known renal disease or urologic issues
• Family history of congenital renal disease
• Solid organ transplant
• Malignancy or BMT
• Use of meds that raise BP
• Systemic illnesses associated with HTN (e.g. neurofibromatosis)
• Evidence of elevated intracranial pressure

Screening for HTN
• A sphygmomanometer device is recommended (mercury or other)
• Automated oscillometric devices are not recommended for routine use, but are helpful in infants where auscultation is difficult
• High BP values via oscillometric devices must be followed-up by a sphygmomanometer device

Screening Pitfalls
• Incorrect cuff size can overestimate BP (too small) or underestimate (too large); it’s better to have a cuff that is too big, than too small
• BP in the clinic setting doesn’t account for day to night variations, white coat effect, etc. and can limit accurate assessment of HTN which is key in preventing end-organ damage, such as increased left ventricular mass
• For this reason, ambulatory blood pressure monitoring (ABPM) is increasingly used as it can more precisely detail changes in BP throughout daily activities

Usefulness of ABPMs
• Differentiate white coat HTN
• Identify masked HTN when there is clinical suspicion or persistent pre HTN
• Assess BP patterns in high-risk patients
• Assess for abnormal circadian variation in BP such as blunted dipping or isolated sleep HTN*
• Assess the severity and persistence of BP elevation in patients at high risk for hypertensive target-organ damage
• Evaluate for drug-resistance/effectiveness of AH drug therapy
• Confirm BP control in treated patients, especially those with secondary HTN
• Identify drug-related hypotension in symptomatic individuals

ABPM
• ABPM values differ substantially from normal BP measurements & expanded normative data is needed; reference values provided by the German Working Group on Pediatric HTN are currently considered the best available data for pediatric ABPM
• ABPM determinants: age, birth weight, ethnicity (may be due to differences in body size, psychosocial stress), gender (males > females), and stimulants (including ADHD meds)
• Oscillometric and auscultatory monitors are available for use in pediatric ABPM, but most centers use oscillometric devices

**ABPM**
• Mild sleep disturbances can occur
• Contraindications to ABPM include severe clotting disorders, rhythm disturbances, latex allergy
• ABPM should be applied to the nondominant arm to avoid interference with school work, unless there is h/o arterial surgery, such as repair of coarctation of the aorta or creation of an arteriovenous fistula
• Serious adverse events have not been reported in children, but arm vein thrombosis has been reported in adults

**ABPM**
• ABPM and clinic BP should be measured and compared after application; adjustments or calibration should be made if there is a > 5 mm Hg difference
• The arm should be kept still during readings and the family should maintain a diary of sleep and wake times, activities that can influence BP (e.g. stressful situations, exercise, or medication administration), and any symptoms of dizziness*
• An adequate ABPM monitoring period has at least 1 or 2 valid readings per hour over 24 hours (including during sleep); ideally readings should occur q 15-20 min (slightly decreased during sleep)

**ABPM**
• Mean SBP/DBP are calculated for the 24-hours and awake and sleep periods are identified
• BP load, the proportion of readings above the 95th percentile* and dipping, the drop in mean from daytime to nighttime levels, are calculated
• Values that fall outside range for SBP (60-220), DBP (35-120), HR (40-180), and pulse pressure (40-120) are discarded
• The standard parameters of mean SBP/DBP, BP load, and dipping are compared against normative values to determine normal or elevated BP

**Evaluation HTN**
• The goals of evaluation are to identify the etiology of HTN (primary vs. secondary), identify other CVD risk factors, and detect end-organ damage
• The basic work-up includes a detailed history and physical exam, labs, and imaging

**History**
• Family: Essential HTN, Atherosclerosis, Stroke, Renal disease (polycystic kidney, familial nephritis)
• Medical: NICU stay (possible UAC), BPD; Frequent UTIs, obstructive uropathies, kidney trauma, surgery, or radiation; History of coarctation repair; Weakness or muscle cramps
• Meds: corticosteroids, amphetamines, anti-asthmatics, cold meds, contraceptives, nephrotoxic abx, cyclosporine, cocaine

**Physical Exam**
• Delayed growth → renal disease
• Bounding peripheral pulses $\rightarrow$ patent ductus arteriosus, aortic regurgitation
• Weak or absent femoral pulses, BP gradients (UE > LE) $\rightarrow$ coarctation
• Abdominal bruits $\rightarrow$ renovascular disease
• Tenderness over the kidney $\rightarrow$ renal infection

**Labs**
• Electrolytes, BUN/Creatinine: renal function, abnormalities in glucose, K-homeostasis, or monogenic disorders
• Fasting glucose, lipids: DM, dyslipidemia (especially if obese, fam hx, or CKD)
• UA, urine culture: renal function & end-organ damage
• CBC: Anemia of chronic disease, e.g. vasculitis, CKD, or polycythemia

**Imaging**
• Echocardiogram to assess for end-organ damage $\rightarrow$ increased left ventricular mass is an indication to initiate or intensify AH therapy
• Subclinical end-organ damage (increased LVM and cIMT) is seen in 1/3 of children with HTN; proven predictors of adult CVD risk
• A prospective study of 86 adolescents w/ primary HTN showed regression of end-organ damage after 12 months of lifestyle modifications and treatment with AH agents
• Renal ultrasound to determine presence of both kidneys, congenital anomalies, or disparate renal size

**Diet and exercise recommendations**

**Dietary recommendations to lower BP:**
• Obesity in relation to primary HTN makes weight management a large part of your treatment plan; an 8-10% reduction in BMI can reduce BP by 8-16 mm Hg
• DASH style diet of fruits, vegetables, fish, poultry, beans, whole grains, and low-fat/fat-free dairy products
• Limit salt intake through low-salt (potassium-rich) foods
• Encourage regular aerobic exercise
• Counsel avoidance of smoking, excessive alcohol consumption, and oral contraceptives*

**Physical activity recommendations**
• At least 60 min daily; Moderate: walking briskly, jogging; Vigorous (3x/week): running, tennis, soccer
• Limit sedentary activities to < 2 hours daily; Video games; Computer time; TV watching

**Physical activity benefits**
• Lower body fat and BMI
• Lower SBP/DBP
• Improved fitness measures
• Improved lipid profiles
• Increased activity can increase the amount of lipoprotein lipase activity in skeletal muscle $\rightarrow$ fatty acids & TG are used for energy instead of fat

**Competitive Sports**
• Competitive sports participation is not limited in those with pre HTN or those with stage 1 HTN and no evidence of end-organ injury; BP should be checked 1-2 weeks after starting competitive sports
• Children with stage 2 HTN and no evidence of end-organ injury should be restricted from high-static sports (IIIA to IIIC)
• Children with stage 2 HTN, once treated and documented to be normotensive, can resume sports with ongoing monitoring of BP

When to treat w/ antihypertensive agents
• Symptomatic HTN
• Stage 2 HTN
• Stage 1 HTN that persists despite 4-6 months of lifestyle modifications
• Stage 1 or 2 HTN with evidence of end organ damage
• Stage 1 HTN in presence of other significant risk factors, e.g. diabetes type 1 and 2, dyslipidemia, or family hx of early CVD complications

Antihypertensive (AH) agents
• Recent era placebo-controlled trials examining the use of AH agents in children have shown good tolerance, effective reduction of BP in children, and few treatment-related adverse effects
• Most new studies have primarily focused on new AH agents including ACE inhibitors, ARBs, calcium channel blockers, and a small number of others
• Adverse effects of most AH agents are similar to those seen in adults; headache and dizziness are most common
• The risk of hypotension in those receiving standard doses is small, but still of concern

Choosing an AH agent
• There is little evidence to guide the initial AH agent for treatment of pediatric HTN; initial therapy is usually with ACE inhibitors, beta blockers, or calcium channel blockers
• Children who have not reached puberty have a higher chance of secondary HTN; calcium channel blockers are preferred rather than ACEi or ARB initially 2/2 concerns of undiagnosed renal artery stenosis
• ARBs are difficult to prescribe sometimes due to insurance limitations

AH agents
• Most agents have comparable BP lowering effects, but other factors to consider one over another include:
  o Formulation & availability
  o Associated diagnoses, especially associated kidney disease
  o Ethnicity: Black children do not respond as well to ACE inhibitors as white children*
• Upward dose titration is recommended for children who fail to achieve the target BP after a period of observation and adjustments should occur q 2 weeks
• First-line drug therapy should be chosen for max efficacy with min side effects; start at lowest known effective dose
• Choose long-acting AH agents to increase compliance (once daily dosing)

Therapeutic goals
• Reduction in BP below the 95th percentile for age and height; aim for 90th percentile in those with diabetes or CKD
• Doses should be titrated frequently for effect, about every 2-4 weeks; adding a 2nd drug to achieve desired BP may be necessary if the highest recommended level is reached or there are side effects.
• Consider discontinuing AH agents in those with well-controlled BP for about a year, successful implementation of lifestyle changes (e.g. reduction in BMI), and resolved target organ damage (e.g. no LVH).

Drugs for outpatient management of HTN
• Angiotensin-converting enzyme (ACE) inhibitors
• Angiotensin II receptor antagonists (ARBs)
• β-blockers
• Calcium channel blockers
• Central α-antagonists
• Diuretics
• Vasodilators

ACE inhibitors
• Captopril, Enalapril, Lisinopril, Benazepril, and Fosinopril
• Act by blocking the angiotensin converting enzyme \( \rightarrow \) inhibits production of angiotensin II
• Well-tolerated, but hypotension can occur, especially w/ volume depletion
• Lipid and glucose metabolism not effected like w/ high doses of diuretics, beta blockers
• Use cautiously in those reduced GFR, e.g. renal artery stenosis
• Side effects related to reduced angiotensin II formation: hypotension, ARF, hyperkalemia; related to increased kinins: cough, angioedema, and anaphylaxis
• Stop if hyperkalemia cannot be controlled or serum creatinine rises more than 30 percent above baseline
• Contraindicated in pregnancy, associated with 2\textsuperscript{nd}/3\textsuperscript{rd} trimester fetopathy

Angiotensin-receptor blockers
• Losartan, Irbesartan*
• Acts by displacing angiotensin II AT1 receptor \( \rightarrow \) antagonizing all effects \( \rightarrow \) leads to a decrease in peripheral resistance
• Typically well-tolerated with similar side effects to ACE inhibitors (hyperkalemia, azotemia)
• Lower rates of cough & angioedema than ACEi, but higher rates of hypotension
• Contraindicated in pregnancy & any condition that reduces renal blood flow, e.g. chronic kidney disease
• Acute volume depletion is a concern: A 2 year old receiving an ARB died due to volume depletion from acute gastroenteritis

β-blockers
• Atenolol, Bisoprolol, Metoprolol, Propranolol
• Acts by selectively inhibiting beta\textsubscript{1}-adrenergic receptors; competitively blocking beta\textsubscript{1}-receptors
• May be helpful in patients with migraines
• Available in combination with HCTZ for dual therapy
• Side effects: Bradycardia—heart rate is dose limiting; may impair athletic performance; hypoglycemia—should not be used in insulin-dependent diabetics
• Can cause increased bronchial obstruction and airway reactivity; non-cardioselective agents (propranolol) should not be used in those with asthma

**Calcium channel blockers**

• Amlodipine
  • Acts directly on vascular smooth muscle to produce peripheral arterial vasodilation reducing peripheral vascular resistance and BP
  • Minimum dose formulation is tricky in younger children & can lead to a larger daily dose \( \rightarrow \) increased side effects
  • Side effects: Headache, dizziness or lightheadedness, flushing, and peripheral edema
  • Monitor liver enzymes

**Central \( \alpha \)-antagonists**

• Clonidine
  • Acts by stimulating alpha\( _2 \)-adrenoceptors in the brain stem \( \rightarrow \) inhibitory neuron activation results in reduced sympathetic outflow from the CNS \( \rightarrow \) decreased peripheral resistance, renal vascular resistance, HR, and BP
  • Side effects: CNS depression, bradycardia, dry-mouth
  • Half-life elimination is prolonged in those with severe renal dx
  • Abrupt discontinuation causes rapid increase in BP and symptoms of sympathetic over-activity

**Diuretics**

• HCTZ, Furosemide, Spironolactone, Triamterene, Amiloride
  • Consider as initial therapy in post-pubertal adolescents with primary HTN because of established efficacy and low cost
  • Useful as add-on therapy in those treated with other drug classes, especially ACEi & beta-blockers
  • Side effects: K-sparing diuretics can cause severe hyperkalemia; especially with ACEi or ARB
  • Furosemide is labeled only for treatment of edema, but can be helpful in those with resistant HTN, especially w/ renal dx

**Vasodilators**

• Hydralazine, Minoxidil
  • Action by direct vasodilation of arterioles (with little effect on veins) \( \rightarrow \) SVR
  • Can have stimulation of hair growth 2/2 vasodilation, increased cutaneous blood flow, hair follicle stimulation
  • Max therapy with other AH agents should be used before Minoxidil
  • Side effects: Reflex tachycardia, fluid retention, lupus-like syndrome, peripheral neuritis

**When to refer to a specialist**

• Stage 2 or symptomatic HTN
• Multiple associated risk factors
• Unsuccessful treatment via lifestyle modifications (4-6 months)
• Evidence of end-organ damage, e.g. LVH
• Comorbid conditions:
  • Diabetes
  • Hyperlipidemia
- CKD
- Congenital heart disease
- Collagen vascular disease
- Childhood cancer survivors

Case presentations

Take home messages

- All children should be screened at least annually starting at 3 years of age (or sooner with special conditions)
- Ambulatory blood pressure monitoring can assist in the accurate diagnosis of HTN
- Secondary causes of HTN are more common in younger children
- Diet and lifestyle modifications are an important part of every treatment plan
- There are several AH agents that have been studied and proven safe and effective in children