Hypertension throughout a woman’s life cycle

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- Research Grants
  - NHLBI
  - NIDDK
- Clinical Trials Adjudication Committee
  - Merck and Company

Prevalence among Americans by Age and Sex: NHANES data


Even if you make it to age 65 without HTN, you’ll likely develop it


CLINICAL PEARL # 1

Hypertension in early childhood almost always has a secondary cause.
Adolescence (12 to 18 years)

- ~10 to 15% due to secondary causes
- Most common causes:
  - Renal parenchymal disease
  - Endocrine disorders
  - Essential hypertension
  - Metabolic Syndrome

Adapted from Pediatrics August 1, 2004 vol. 114 no. Supplement 2 555-576

CLINICAL PEARL # 2

The Metabolic Syndrome is becoming more common in adolescents and may lead to hypertension

Acceptable antihypertensives in children and adolescents

- Adrenergic blockers (e.g. labetolol, atenolol, metoprolol)
- Calcium channel blockers (e.g. amlodipine)
- Vasodilators (e.g. Hydralazine, minoxidil)
- ACEI / ARB
- Diuretics
- Central alpha blocker (clonidine)
- Peripheral alpha blockers (doxazosin)

Adapted from Pediatrics August 1, 2004 vol. 114 no. Supplement 2 555-576

Hypertension in adults

- Stage 1 Hypertension: Clinic BP ≥ 140/90 mmHg
- Stage 2 Hypertension: Clinic BP ≥ 160/100 mmHg
- Severe Hypertension: Clinic systolic BP ≥ 180 mmHg OR Clinic diastolic BP ≥ 110 mmHg

- Daytime average ABPM or HBPM ≥ 135/85 mmHg

ABPM = ambulatory BP measurement
HBPM = home BP measurement

Young adulthood (19 to 39 years)

- 5% of cases due to secondary causes
- Most common causes:
  - Essential Hypertension
  - Thyroid dysfunction
  - Fibromuscular dysplasia
  - Renal parenchymal disease

Adapted from Am Fam Physician 2010 Dec 15;82(12):1471-1478

Epidemiology: Fibromuscular Dysplasia

Fibromuscular Dysplasia is an idiopathic, segmental, non-inflammatory, non-atherosclerotic disease of arterial musculature.

- Prevalence
  - 4/1000 for symptomatic renovascular
  - 1-2% of hypertensive patients
- Usually diagnosed in young adults
  - 3rd to 4th decade (women in their 20s and 30s)
- Significant female predominance
  - 4:1 female: male ratio
Radiographic evaluation

- Classic “string of beads” appearance
- Less commonly can also present with single aneurysmal dilation or tubular narrowing
- Angiography gold standard for diagnosis but CTA and MRA now commonly performed


Management of Fibromuscular Dysplasia

<table>
<thead>
<tr>
<th>No HTN</th>
<th>HTN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serial Renal U/S for monitoring kidney size</td>
<td>Consider percutaneous balloon angioplasty (high success rate)</td>
</tr>
<tr>
<td>Follow BP, creatinine.</td>
<td>Repeat duplex renal U/S shortly after to assess for adequate treatment of stenosis.</td>
</tr>
<tr>
<td>Consider angioplasty if renal impairment or loss of renal volume</td>
<td>Medical management of residual HTN</td>
</tr>
</tbody>
</table>


CLINICAL PEARL # 3

Fibromuscular Dysplasia is a treatable cause of hypertension which is seen in young women

Hypertension in young women

- Hypertension occurs in 1 to 6% of young women.
  - Diastolic HTN is more common than Systolic
- All antihypertensives appear to be equally efficacious
- ACE-I /ARBs are contraindicated in pregnancy
  - ~ 50 % of pregnancies are unintended
- ACOG Guidelines on the Use of Contraceptives:
  - Oral contraceptives (including newer agents) may increase BP by as much as 8 / 6 mm Hg.
  - In women < 35 years of age with well-controlled HTN, a trial of combination OCPs is reasonable
  - Progestin-only contraceptives an option

Am Fam Physician. 2007 Apr 15;75(8):1252-1258

Middle Adulthood (40 to 64 years)

- 8 to 12 % due to secondary causes
- Most common causes:
  - Essential hypertension
  - Aldosteronism
  - Thyroid dysfunction
  - Obstructive sleep apnea
  - Cushing syndrome
  - Pheochromocytoma

Am Fam Physician. 2010 Dec 15;82(12):1471-1478

Causes of Secondary Hypertension

<table>
<thead>
<tr>
<th>Medical Conditions</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic kidney disease</td>
<td>NSAIDS</td>
</tr>
<tr>
<td>Primary hyperaldosteronism</td>
<td>Oral contraceptives</td>
</tr>
<tr>
<td>Renovascular disease</td>
<td>Adrenal steroids</td>
</tr>
<tr>
<td>Chronic steroid therapy</td>
<td>Sympathomimetans</td>
</tr>
<tr>
<td>Cushing’s syndrome</td>
<td>Cyclosporine or tacrolimus</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>Erythropoetin</td>
</tr>
<tr>
<td>Aortic coartation</td>
<td>Ephedra, mu huang, bitter orange</td>
</tr>
<tr>
<td>Thyroid or parathyroid disease</td>
<td>Cocaine or amphetamines</td>
</tr>
<tr>
<td>Sleep apnea</td>
<td>Alcohol</td>
</tr>
</tbody>
</table>

Chobanian AV et al. JAMA 2003;289:2560-2572
Prevalence of Secondary Causes of Hypertension

<table>
<thead>
<tr>
<th>COMMON</th>
<th>RARE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep Apnea (Very Common)</td>
<td>Pheochromocytoma (&lt;0.5%)</td>
</tr>
<tr>
<td>Renal Disease (1-8%)</td>
<td>Coarctation of Aorta (&lt;1%)</td>
</tr>
<tr>
<td>Hyperaldosteronism (1.5-15%)</td>
<td>Cushing’s Syndrome (0.5%)</td>
</tr>
<tr>
<td>Renal Artery Stenosis (3-4%)</td>
<td>Acromegaly</td>
</tr>
</tbody>
</table>

Obstructive Sleep Apnea

- **EEG arousals**
  - Fragmented sleep
  - Increased sympathetic activity

- **Apnea/Hypopnea**
  - Hypoxia
  - Hypercapnia

- **Resumption of breathing**
  - Labile blood pressure

- In resistant hypertension 96% of men and 65% of women have OSA
- Sympathetic over activation is cause
- Reduction of blood pressure (BP) and heart rate (HR) after 6 months of CPAP treatment

Sympathetic Activity in Sleep Apnea

Blood Pressure in OSA

Effect of CPAP on Blood Pressure

Changes in blood pressure with effective (blue bars) vs subtherapeutic (orange bars) nCPAP.

Becker et al. 2003
CLINICAL PEARL # 4
Obstructive Sleep Apnea is a Common Cause of Resistant Hypertension

- Most cases are caused by bilateral adrenal hyperplasia
- Hypertension refractory to treatment with 3 or more drugs
- Spontaneous hypokalemia (<3.5 mmol/L).
- Profound diuretic-induced hypokalemia (<3.0 mmol/L).
- Low normal potassium levels, even in the presence of drugs that should raise potassium
  - K+ supplements
  - ACE inhibitors

Spironolactone

<table>
<thead>
<tr>
<th>BP response (mm Hg)</th>
<th>Systolic BP</th>
<th>Diastolic BP</th>
</tr>
</thead>
<tbody>
<tr>
<td>6wk</td>
<td>-21</td>
<td>-10</td>
</tr>
<tr>
<td>3mo</td>
<td>-23</td>
<td>-10</td>
</tr>
<tr>
<td>6mo</td>
<td>-25</td>
<td>-12</td>
</tr>
</tbody>
</table>

CAUTION: Extreme caution when creatinine > 2.5, K > 5.0


CLAES TO PRESENCE OF HYPERALDOSTERONISM

Primary Aldosteronism is more common than previously thought and is a cause of many cases of resistant hypertension

Drugs that may Worsen or Cause HTN
- Hormonal therapies
  - Estrogen, Oral contraceptives
- Herbal therapies
  - Ephedra, ginseng, ma huang
- NSAIDS / Cox -2 inhibitors
  - ibuprofen, naproxen, celecoxib
- Psychiatric
  - Buspirone, carbamazepine, Clozaril, fluoxetine
- Steroids
  - Methylprednisolone (Depo-Medrol), prednisone
- Sympathomimetic
  - Decongestants, diet pills

Older adulthood (65 to 80 years)

- ~17% due to secondary causes
- Most common causes:
  - Essential Hypertension
  - Atherosclerotic renal artery stenosis
  - Renal failure
  - Hypothyroidism

Am Fam Physician. 2010 Dec 15;82(12):1471-1478
2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults: Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8)

9 Recommendations

**Recommendation # 1**

1. In patients aged ≥60 years, initiate pharmacologic treatment in systolic BP ≥150mmHg or diastolic BP ≥90mmHg and treat to a goal systolic BP <150mmHg and goal diastolic BP <90mmHg.

(Strong Recommendation – Grade A)

In other words:

Ease up on Hypertension Treatment in Older Adults (60 years of age or older)

Aim for <150/90

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3,845 patients ≥80 years with HTN and STANDING SBP ≥ 160 mmHg

Randomized to a diuretic/ACE inhibitor combo (Indapamide SR ± perindopril) or placebo and followed for 2 years. TARGET BP was 150/80

**All stroke (30% reduction)**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Indapamide SR ± perindopril</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Mortality (21% reduction)</td>
<td>Placebo</td>
<td>Indapamide SR ± perindopril</td>
</tr>
<tr>
<td>Fatal Stroke (39% reduction)</td>
<td>Placebo</td>
<td>Indapamide SR ± perindopril</td>
</tr>
</tbody>
</table>
CLINICAL PEARL # 6
Loosen BP goals in older adults to 150/90 mm Hg

CLINICAL PEARL # 7
Always measure BP in the standing as well as the sitting position in the very elderly as orthostatic hypotension is very common

How did they decide that patients 60 and older should get the higher goal?

- The JNC 8 authors had a very strict definition of the evidence they would use
- The authors state that there is evidence (albeit low quality) that setting a goal SBP of LOWER than 140 mm Hg in this age group provides NO additional benefit
- The RCTs that led to this recommendation include HYVET, Syst-Eur, SHEP, JATOS, VALISH, and CARDIO-SIS

Blood Pressure Distribution in the Population According to Age

Very elderly (> 80 years)

- Many cases complicated by secondary causes
  - Atherosclerotic RAS
  - Renal failure
  - Hypothyroidism
- Diastolic BP DECREASES with age, therefore Pulse pressure WIDENS
- HTN contributes to HFpEF
- Orthostatic HYPOtension common

(JAMA. Published online December 18, 2013. doi:10.1001/jama.2013.284427)

Adapted from: Third National Health and Nutrition Examination Survey, Hypertension 1995;25:305-13

CLINICAL PEARL # 8
Try not to lower the diastolic blood pressure below 55-60 mm Hg as coronary perfusion may be compromised if DBP gets too low.

Heart Failure with Preserved Ejection Fraction (HFpEF)
- About half of all HF cases
- Mortality similar to HFrEF
- Much more common in older patients
- Much more common in women
- Hypertension is a primary etiologic factor

Hormonal Transition Times are a Vulnerable Time for Development of Hypertension
- Puberty
- Pregnancy
- Menopause

Puberty
- A transient insulin resistant state occurs during puberty and is part of normal human development.
- Insulin resistance increases immediately at the beginning of puberty, peaks mid-puberty, and then declines to prepubertal levels by early adulthood.
  - Girls are more IR than boys during puberty
- Insulin resistance contributes to development of prehypertension and hypertension during puberty
- Pubertal hypertension confers a 10 X higher risk of adult hypertension
- Maintaining a healthy weight, diet and exercise limit hypertension in puberty

Pregnancy

Owan et al. NEJM 2006;355:251.

Hypertension

- Most common medical complication of pregnancy
- 6 to 8% of gestations in the US.
- Third leading cause of maternal mortality
- In 2000, the National High Blood Pressure Education Program defined 4 categories of hypertension in pregnancy:
  - Chronic hypertension
  - Pregnancy Induced (gestational) hypertension
  - Preeclampsia
  - Preeclampsia superimposed on chronic hypertension

Treatment of Chronic Hypertension

- Methyldopa, labetalol, and nifedipine most common oral agents.
- AVOID: ACEI and ARBs, atenolol, thiazide diuretics
- Women in active labor with uncontrolled severe chronic hypertension require treatment with intravenous labetalol or hydralazine.

ORAL TREATMENT OF HYPERTENSION IN PREGNANCY

<table>
<thead>
<tr>
<th>AGENT</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methyldopa</td>
<td>Preferred based on long term studies of child development and uteroplacental blood flow</td>
</tr>
<tr>
<td>Beta Blockers</td>
<td>Reports of IUGR, particularly for atenolol at conception or in the first trimester; generally safe</td>
</tr>
<tr>
<td>Labetalol</td>
<td>Increasingly preferred for efficacy and few side effects</td>
</tr>
<tr>
<td>Clonidine</td>
<td>Limited data</td>
</tr>
<tr>
<td>Calcium Channel Blockers</td>
<td>Limited data</td>
</tr>
<tr>
<td>Diuretics</td>
<td>Most experience with nifedipine and isradipine</td>
</tr>
<tr>
<td>ACE Inhibitors</td>
<td>Contraindicated, reports of fetal toxicity and death</td>
</tr>
<tr>
<td>ARBs</td>
<td>Contraindicated, reports of fetal toxicity and death</td>
</tr>
</tbody>
</table>

Pregnancy: a stress test for the cardiovascular system

- Pregnancy transiently throws a woman into a metabolic syndrome – like state.
- Women who are already predisposed to MetSyn develop gestational hypertension or diabetes
- Pregnancy induced risk factors often re-emerge later in life
- Mortality from cardiovascular disease in later life is increased

Pregnancy Induced Hypertension

- HTN that occurs as a consequence of pregnancy
- Usually mild and later in pregnancy
- Often DOES NOT always require drug treatment
- No renal or other systemic involvement
- Resolves 12 wks postpartum
- May become preeclampsia

Preeclampsia

- New onset HTN after 20 weeks of gestation with additional manifestations
  - Proteinuria > 300 mg/24hr
  - Oliguria or Serum-plasma creatinine ratio > 0.09
  - Headaches with hyperreflexia, eclampsia, clonus or visual disturbances
  - ↑ LFTsThrombocytopenia, ↑ LDH, hemolysis, DIC
- Usually resolves within 48 hrs of delivery
- More common in Blacks, twin gestations, those with a family history of preeclampsia, very young mothers, older mothers, primigravidas
Pregnancy – a Stress Test for Life

- Preeclampsia with preterm delivery
  - 8 x ↑ risk death CVD
  - 5 x ↑ risk stroke
- Preeclampsia with full term delivery
  - 3 x ↑ risk death CVD
- Gestational diabetes
  - 20-60% will develop type 2 DM within 5-16 years

Treating Hypertension During Lactation

- Breastfeeding encouraged.
- Little information on excretion of agents in breast milk or long-term effects on exposed infants.
- No short-term adverse effects reported with methyldopa or hydralazine.
- Beta-blockers: propanolol & labetalol recommended.
- No data on calcium antagonists.
- Diuretics may reduce milk volume/suppress lactation.
- ACEI and ARB should be avoided.

Menopause

Factors contributing to hypertension in postmenopausal women.

- Most women will develop hypertension
- The prevalence of hypertension rises more steeply in women than men after middle age.
- Diastolic hypertension is more prevalent among younger patients, but for those older than 50, systolic hypertension is more prevalent.
- Treatment of hypertension reduces stroke, MI, heart failure, and death. Lifestyle changes can significantly decrease BP
- Hormonal transitions are high risk times for development of HTN