Secondary Hypertension
The Primary Care Perspective

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What Is Hypertension

• For Children/Adolescents:
  – Average SBP/DBP ≥ 95th percentile for age, gender, and height.
  – “Prehypertension” is ≥ 90th percentile
  – 3 separate readings on 3 separate visits.
  – Incidence appears to be increasing over time.

What is Hypertension (JNC 7)

<table>
<thead>
<tr>
<th>Classification of Blood Pressure (BP)</th>
<th>SBP (mm Hg)</th>
<th>DBP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;120</td>
<td>&lt;80</td>
</tr>
<tr>
<td>Prehypertension</td>
<td>120-139</td>
<td>80-89</td>
</tr>
<tr>
<td>Hypertension, Stage 1</td>
<td>140-159</td>
<td>90-99</td>
</tr>
<tr>
<td>Hypertension, Stage 2</td>
<td>≥160</td>
<td>≥100</td>
</tr>
</tbody>
</table>

Blood Pressure Measurement Techniques

- office: Two readings, 5 minutes apart, sitting in chair. Continuous stethoscope on sternal border area.
- Ambulatory BP monitoring: Indicated for evaluation of “white coat hypertension.” Ambition of 24-hour percent decrease may indicate white coat CVD, etc.
- Patient self-check: Provides information on response to therapy. May help improve adherence to therapy and is useful for evaluating “white coat hypertension.”

What is Essential/Primary Hypertension

• HTN with no identifiable cause
• Often develops gradually over years
• Much of HTN still falls in this category - up to 85% in many reports.
• Likely a complex interaction between multiple risk factors/causes in many cases.
## What is Secondary Hypertension?

- Meets Criteria for HTN
- Results from an identifiable, potentially correctable cause
- Accounts for significant number of Resistant HTN cases
- Estimated to account for 5-15% of cases of HTN
- Prevalence of hypertension in adults between 20-30% (50-70 million people). Conservatively, probably 3-5 million people in U.S. affected.

## Unclear Association with HTN

- Caffeine
  - May cause short spike in BP
  - No sustained effect noted
  - May be more significant in older/overweight
- Stress/Anxiety/Type A
  - Clearly causes short-term increases
  - Unclear if sustained stress can truly cause HTN

## Associations with Hypertension

- Family History – first degree relatives
- Race – more common in African Americans
- Physical Inactivity
- Dyslipidemia
- Obesity
- Vitamin D deficiency

## When to Suspect Secondary HTN

- Early age of onset
  - Young adult without family history or risk factors
  - Onset prior to puberty
- Severe or resistant HTN
  - Remember – fewer than 50% of patients well controlled on a single medication
- Acute onset or change in control when previously stable
- Malignant/End-organ changes
- Abnormal exam findings (e.g. abdominal bruit)
Evaluation for type of HTN

• Confirm Diagnosis

• History

• Physical Exam

• Diagnostic Testing (Blood Tests, Urine, ECG, Imaging)

History

• Birth History
  – More premature babies reaching adulthood
  – Use of Umbilical artery catheters may post some risk
  – Aware of any prolonged hospital stay when born

• Childhood History
  – Recurrent UTI’s, urinary reflux
  – Traumas/Infections - PSGN

Confirms elevated blood pressures

• In office
  – Proper Cuff/Technique

• Outside of office
  – Useful to identify “White Coat” hypertension
    • May account for 20-30% of HTN by some estimates
  – Ambulatory BP monitor
  – Home BP monitor
    • Discuss optimal conditions for measurement
    • Discuss proper equipment
    • Correlates well with Ambulatory Monitors

History

• Family history
  – HTN, Endocrine disorders, early heart disease, strokes, kidney failure, blindness, sleep apnea, etc.

• Current known medical conditions
• Pregnancy status
• Compliance with medications
### Social History

- **Diet**
  - Salt Intake
    - No one ‘adds’ salt
    - Ask about fast food or processed foods
  - Licorice – excessive ingestion
- **Tobacco Use**
- **Alcohol Consumption**
- **Illicit drugs**
  - Cocaine, amphetamines, ecstasy (MDMA)
- **Toxic/Environmental Exposures**
  - Lead
  - Arsenic

### Medications - Prescription

- **Antidepressants**
- **Anti-inflammatories, including Cox-2**
- **Hormones**
  - Contraception
  - Testosterone Supplement
- **Glucocorticoids**
- **Stimulant medications (ADHD, etc)**
- **Migraine medications**
- **Transplant Medications (cyclosporine/tacrolimus)**
- **Weight Loss medications**
- **Erythropoietin**

### Medications - OTC

- **NSAIDS, Aspirin**
- **Cough/Cold Medications**
  - Pseudoephedrine, phenylephrine, dextromethorphan
- **Herbals**
  - Ginseng
  - St. John’s Wort
  - Ephedra, ma huang
- **Energy Drinks**
  - Often contain caffeine or herbal ingredients

### Review of Systems

- **General**
  - Weight Changes
  - Fatigue/Weakness
  - Sleep Quality
  - Diaphoresis
  - Flushing/Pallor
- **HEENT**
  - Headaches
  - Dizziness
  - Blurred Vision
  - Snoring
  - Nasal Congestion
  - Nosebleeds
- **Cardiovascular**
  - Chest Pain
  - Palpitations
  - Paroxysmal Nocturnal Dyspnea
- **Respiratory**
  - Shortness of breath/Dyspnea on Exertion
  - Gasping during sleep/Choking
### Review of Systems

<table>
<thead>
<tr>
<th>System</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal</td>
<td>Nausea, Vomiting, Abdominal Pain, Fullness/swelling of abdomen</td>
</tr>
<tr>
<td>Neurologic</td>
<td>TIA symptoms</td>
</tr>
<tr>
<td>Vascular</td>
<td>Cold Feet, Claudication</td>
</tr>
<tr>
<td>Skin changes</td>
<td>Striae, Pigmentation, Excessive dryness, hair loss</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Muscle Weakness, Leg Cramps</td>
</tr>
</tbody>
</table>

### Physical Exam

<table>
<thead>
<tr>
<th>Component</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neck</td>
<td>Goiter, Neck size &gt;/= 17 inches in men (&gt;/= 16 inches in women) associated with OSA</td>
</tr>
<tr>
<td>Cardiovascular Exam</td>
<td>Murmurs, PMI displacement, RV heave, Radial/femoral delay, Tachycardia</td>
</tr>
<tr>
<td>Abdominal Exam</td>
<td>Bruit, Mass (PCKD, Wilms tumor, neuroblastoma), Bladder enlargement (obstructive lesion with hydronephrosis)</td>
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### Physical Exam

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<tr>
<td>General</td>
<td>Height/Weight/BMI/Percentiles, In children, poor growth may be sign of chronic disease such as renal insufficiency, hypothyroidism, etc, Obesity – typical vs central/cushingoid</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Joint swelling, Muscle weakness</td>
</tr>
<tr>
<td>Skin</td>
<td>Striae, Acne, Malar rash, Flushing/Pallor/Sweating, Petechiae/Purpura</td>
</tr>
</tbody>
</table>
Lab/Test Evaluation

- Blood
  - Glucose, H/H, lipid panel, potassium, creatinine, calcium, TSH
- Urine
  - Urinalysis, consider urine albumin/creatinine ratio
  - Urine HCG
- ECG

Lifestyle Changes

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Amount</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily sodium intake</td>
<td>2,300 mg or less (1 tsp of salt per day)</td>
<td>For people with hypertension.</td>
</tr>
<tr>
<td>Regular physical activity</td>
<td>30 minutes per day, at least 5 days per week</td>
<td>For overall health.</td>
</tr>
<tr>
<td>Moderate alcohol consumption</td>
<td>1 drink per day for women, 2 drinks per day for men</td>
<td>Depending on sex and weight.</td>
</tr>
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Obesity

- True prevalence of sleep apnea difficult to determine. Estimated that 4-9% of people are symptomatic with sleep apnea, and another 10% may meet criteria but be relatively asymptomatic.
- In one study of resistant HTN, 83% had unsuspected sleep apnea.

Obstructive Sleep Apnea

- Obstructive Sleep Apnea
- True prevalence of sleep apnea difficult to determine. Estimated that 4-9% of people are symptomatic with sleep apnea, and another 10% may meet criteria but be relatively asymptomatic.
- In one study of resistant HTN, 83% had unsuspected sleep apnea.
**Obstructive Sleep Apnea**

- Intermittent hypoxemia and/or increased upper airway resistance cause increased sympathetic nervous system activity.

**Referral**

- Because many / most of the other causes of secondary and resistant hypertension directly or indirectly involve the kidneys, referral to Nephrologist common for uncontrolled/resistant/secondary HTN

**Treatment: CPAP for OSA**

- Mixed results, but some studies show 9-14 mmHg decrease in SBP and 7-9 mmHg decrease in DBP.
- Largest benefit in severe OSA and in patients also on BP medications.

**Secondary Hypertension**

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Disclosure

- I am the Site Co-PI for Symplicity HTN – 3, a clinical trial of renal denervation to treat resistant hypertension sponsored by Medtronic Ardian LLC, Mountain View, CA.

Resistant Hypertension (RH)

- BP above goal in spite of concurrent use of 3 antihypertensive agents of different classes.
- One should be a diuretic.
- All should be at optimal doses.
- Includes patients who are controlled on 4 or more meds.
- Goal – 140/90 or 130/80 if DM or CKD.

Secondary HTN

- 12.7% of patients over age 50 referred to a HTN clinic had a secondary cause.
- Causes
  - Renal artery stenosis (35% of those with a secondary cause)
  - Primary Aldosteronism (17-23% of RH cases), GRA
  - Renal parenchymal disease
  - OSA
  - Pheochromocytoma
  - Cushing’s disease
  - Thyroid disease
  - Coarctation of Aorta

Renal Artery Stenosis

- Randomized trials have not shown benefit in terms of renal function or BP with intervention as compared to medical therapy.
- >90% are atherosclerotic (older age, smokers, known PAD).
- <10% are FMD, commonly women under age 50.
## Renal Artery Stenosis

- MRA is highly sensitive, but may suggest that a minimal lesion is moderate or severe.

- Value of renal artery doppler or CT angiogram depends on institutional expertise.

- ACEI or ARB use is advised with RAS, but do not tolerate >30% rise in Cr.

## Primary Aldosteronism

- 17-23% of RH cases

- Only 9-37% have hypokalemia

- Several Subtypes

## Treatment of Renal Artery Stenosis

- Angioplasty almost always improves/cures HTN if FMD.

- Angioplasty/stenting not superior to medical therapy if atherosclerotic.

- Consider angioplasty/stenting of atherosclerotic RAS if drugs not effective or recurrent flash pulmonary edema.

## Subtypes of PA

- Aldosterone Producing Adenoma (Conn 1954)

- Unilateral or Bilateral Adrenal Hyperplasia

- Glucocorticoid Remediable Aldosteronism

- Aldo producing adrenal carcinoma

- Aldo producing ovarian or renal tumor
Evaluation - Primary Aldosteronism

- Aldo/renin ratio is elevated (>25) and aldo level >15 ng/dl.
- ARR is an effective screening test if spironolactone, eplerenone, amiloride, triamterene are not in use.

Evaluation of Primary Aldosteronism

- Adrenal CT is recommended.
- Carcinomas are usually >4cm.
- Adenoma may be < 1cm and not visualized.
- If surgery is an option, adrenal vein sampling is necessary.

Treatment of AP adenoma

- Laparoscopic adrenalectomy
- After surgery 40-65% will have persistent essential HTN

Treatment of PA with Bilateral Hyperplasia

- Mineralocorticoid antagonist
  - Spironolactone (Aldactone) 25-400mg daily
  - Also progesterone agonist and androgen antagonist
  - Breast tenderness, irregular menses, impotence
  - $16-35.00 a month
  - Eplerenone (Inspra) 25-100mg daily
  - Selective for MC receptor
  - $100.00 a month
  - Should be used BID
Glucocorticoid Remediable Aldosteronism

- Ectopic expression of aldosterone synthase in the adrenal zona fasciculata.
- Cells of the zona fasciculata produce both cortisol and aldosterone.
- Increased levels of 18-OH cortisol.
- Exogenous glucocorticoid suppresses activity of the zona fasciculata.

Glucocorticoid-Remediable Aldosteronism

- Familial, autosomal dominant.
- FH of primary aldosteronism or stroke before age 40.
- Onset of HTN before age 21.
- Dx by genetic testing.
- Treatment is prednisone 2.5 to 5mg QHS.

Adrenal Histology

Image from http://en.wikipedia.org/wiki/Adrenal_gland

Glucocorticoid-Remediable Aldosteronism Genetic Testing

- International Registry for Glucocorticoid-Remediable Aldosteronism
- Phone: 1-800-722-5520, ext. 25011
- Internet: http://www.brighamandwomens.org/Departments_and_Services/medicine/services/endocrine/Services/gra/default.aspx
**Renal Parenchymal Disease**
- Less than 15% of CKD patients in Nephrology clinics had BP <130/80 despite an average of 3 different medications.
- Sodium and fluid retention lead to treatment resistance.
- Failure to use diuretics, inadequate dose of diuretic, and use of thiazides with low GFR are common problems.

**Pheochromocytoma**
- In autopsy studies 75% were not clinically suspected.
- Episodic headaches, palpitations, sweating has diagnostic specificity of 90%.
- Plasma free metanephrines – 91% sensitive and 99% specific.

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**Pheochromocytoma**
- 0.1% to 0.6% of HTN.
- 10% of pheochromocytomas are malignant.
- Increased BP variability which is a risk factor for CV morbidity/mortality.
- Paroxysmal HTN may be due to this or an intracranial tumor.
- Average 3 years from symptoms to Dx.

**24 hr Urine Studies for Pheochromocytoma**
- 100% sensitive and 94% specific
- Diagnostic findings:
  - Norepinephrine > 170 mcg
  - Epinephrine > 35 mcg
  - Dopamine > 700 mcg
  - Normetanephrine > 900 mcg
  - Metanephrine > 400 mcg
### Treatment of Pheochromocytoma

- Control BP and prevent intraoperative hypertensive crisis.
- Alpha blocker > 14 days before surgery.
- After 3 days of alpha blockade, 5g Na diet and volume expansion to prevent orthostasis and catecholamine induced volume contraction.

### Surgery for Pheochromocytoma

- Laparoscopic adrenalectomy is possible in 90%
- 16% recur
- Annual biochemical screening indicated

### Treatment of Pheochromocytoma

- Start beta blocker 3 days before surgery.
- If beta blocker is used first, unopposed alpha receptor stimulation can increase BP.

### Cushing’s Syndrome: Clinical

- Central obesity, hypertension, glucose intolerance
- Moon face
- Abdominal striae
- Menstrual irregularity
### Cushing’s Syndrome

- Overstimulation of the mineralocorticoid receptor by cortisol.
- 70+% of Cushing's patients have HTN.
- Sleep apnea and insulin resistance also contribute to high BP.

### Cushing’s Syndrome - Treatment

- MC receptor antagonist like spironolactone or eplerenone works best.
- Excision of an ACTH producing pituitary tumor or cortisol producing adrenal tumor lowers BP.

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### Cushing’s Syndrome

- 24hr urine cortisol is 3 times upper limit of normal.
- Urine and late night salivary cortisol should be checked twice.

### Hypothyroidism

- Found in 3.6% of referred HTN patients.
- There is decreased release of endothelial derived relaxation factor which increases peripheral vascular resistance.
- Sodium restriction, diuretics, CCB are treatment of choice.
<table>
<thead>
<tr>
<th><strong>Hyperthyroidism</strong></th>
<th><strong>Coarctation of the Aorta</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Results in increase in heart rate, cardiac contractility, and stroke volume.</td>
<td>• HTN in the upper extremities and diminished femoral pulses (brachial –femoral delay).</td>
</tr>
<tr>
<td>• Systolic HTN is common.</td>
<td>• Measure brachial and popliteal BP.</td>
</tr>
<tr>
<td>• Salt sensitive.</td>
<td>• Headache, cold feet, pain in legs with exercise.</td>
</tr>
<tr>
<td>• Use B blocker if tolerated.</td>
<td>• Cardiomegaly and LV strain on EKG.</td>
</tr>
<tr>
<td></td>
<td>• Diagnosis made by Echo with doppler.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Coarctation of the Aorta</strong></th>
<th><strong>Coarctation Management</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Congenital or acquired (Takayasu arteritis)</td>
<td>• Adults should have CT or MRA of thoracic aorta and intracranial vessels.</td>
</tr>
<tr>
<td>• More common in males</td>
<td>• Angioplasty/Stent is preferred at some centers.</td>
</tr>
<tr>
<td>• 30-40% have a bicuspid aortic valve</td>
<td>• Surgery – resection +/- bypass graft.</td>
</tr>
<tr>
<td>• 10% have an intracranial aneurysm</td>
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</tr>
</tbody>
</table>
Renal Denervation

- Renal sympathetic nerves contribute to elevated SNS activity and HTN.
- Denervation reduces sympathetic control of renal function and removing renal afferent contribution to BP elevation.

Targeting Renal Nerves

- Nerves arise from T10-L2
- The nerves arborize around the artery and primarily lie within the adventitia

Renal Denervation

- Limited to investigational use.
- Catheter based delivery of low level RF energy through the wall of the renal artery to denervate the kidney.
### Symplicity HTN -2

- RCT of 106 patients
- At 6 months mean decrease in BP 32/12 mmHg.
- At 12 months mean decrease in BP 28/10.
- 3% complication rate: renal artery dissection, femoral artery hematoma, pseudoaneurysm.

### Symplicity HTN 3

- Bilateral Renal Denervation in Patients with Uncontrolled Hypertension.
- Prospective, single blind, randomized, controlled.
- Primary Endpoint is blood pressure.
- All patients have renal angiogram, randomized 2:1 to denervation vs. sham.
- Inclusion Criteria
  - Age 18-80
  - SBP > 160mmHg
  - GFR>45 ml/min
  - Full doses of 3 meds including diuretic (25mg HCTZ, 80mg furosemide)

### Symplicity HTN 3 Referrals

- Phone: 614-292-5315 – Denise Fadorsen
- EPIC: Ambulatory Referral Nephrology or Cardiology for Resistant Hypertension