Secondary Hypertension
The Primary Care Perspective

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What Is Hypertension (JNC 7)

<table>
<thead>
<tr>
<th>Classification of Blood Pressure (BP)*</th>
<th>SBP mmHg</th>
<th>DBP mmHg</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>&gt;80-89</td>
</tr>
<tr>
<td>Hypertension, Stage 1</td>
<td>140-159</td>
<td>&gt;90-99</td>
</tr>
<tr>
<td>Hypertension, Stage 2</td>
<td>≥160</td>
<td>≥100</td>
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</table>

**Blood Pressure Measurement Techniques**

<table>
<thead>
<tr>
<th>Method</th>
<th>Notes</th>
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<tbody>
<tr>
<td>In-office</td>
<td>Two readings, 5 minutes apart, sitting in chair. Confirm elevated reading in contralateral arm.</td>
</tr>
<tr>
<td>Ambulatory BP monitoring</td>
<td>Indicated for evaluation of “white coat hypertension.” Absence of 10-20 percent BP decrease during sleep may indicate increased CVD risk.</td>
</tr>
<tr>
<td>Patient self-check</td>
<td>Provides information on response to therapy. May help improve adherence to therapy and is useful for evaluating “white coat hypertension.”</td>
</tr>
</tbody>
</table>
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 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.

Associations with Hypertension

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

### 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)

Confirm 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

<table>
<thead>
<tr>
<th>• Birth History</th>
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<tbody>
<tr>
<td>– More premature babies reaching adulthood</td>
</tr>
<tr>
<td>– Use of Umbilical artery catheters may post some risk</td>
</tr>
<tr>
<td>– Aware of any prolonged hospital stay when born</td>
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<table>
<thead>
<tr>
<th>• Childhood History</th>
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</thead>
<tbody>
<tr>
<td>– Recurrent UTI’s, urinary reflux</td>
</tr>
<tr>
<td>– Traumas/Infections - PSGN</td>
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<table>
<thead>
<tr>
<th>• Family history</th>
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<tbody>
<tr>
<td>– HTN, Endocrine disorders, early heart disease, strokes, kidney failure, blindness, sleep apnea, etc.</td>
</tr>
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| • 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 - 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
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

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

- Abdominal
  - Nausea
  - Vomiting
  - Abdominal Pain
  - Fullness/swelling of abdomen
- Musculoskeletal
  - Muscle Weakness
  - Leg Cramps
- Neurologic
  - TIA symptoms
- Vascular
  - Cold Feet
  - Claudication
- Skin changes
  - Striae
  - Pigmentation
  - Excessive dryness, hair loss

Physical Exam

- General
  - 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
- HEENT:
  - Acromegaly, Moon facies, Hirsuitism
  - Eyes – Papilledema, AV Nicking, Hemorrhages, Exudates
  - Obstructed Nasal Passages
  - Tonsillar/Uvular enlargement
  - Nasal Congestion, suggestion of Adenoid Hypertrophy
  - Crowded Mouth
  - Overbite/Retrognathia/Micrognathia
## Physical Exam

- **Neck**
  - Goiter
  - Neck size $\geq 17$ inches in men ($\geq 16$ inches in women) associated with OSA

- **Cardiovascular Exam**
  - Murmurs
  - PMI displacement
  - RV heave
  - Radial/femoral delay
  - Tachycardia

- **Abdominal Exam**
  - Bruit
  - Mass (PCKD, Wilms tumor, neuroblastoma)
  - Bladder enlargement (obstructive lesion with hydronephrosis).

## Physical Exam

- **Musculoskeletal**
  - Joint swelling
  - Muscle weakness

- **Skin**
  - Striae
  - Acne
  - Malar rash
  - Flushing/Pallor/Sweating
  - Petechiae/Purpura
Lab/Test Evaluation

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

Obesity
Lifestyle Changes

<table>
<thead>
<tr>
<th>Lifestyle Modification Recommendations</th>
<th>Avg. SBP Reduction Range¹</th>
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<tbody>
<tr>
<td>Weight reduction</td>
<td>5-20 mmHg/10 kg</td>
</tr>
<tr>
<td>DASH eating plan</td>
<td>8-14 mmHg</td>
</tr>
<tr>
<td>Dietary sodium reduction</td>
<td>2-4 mmHg</td>
</tr>
<tr>
<td>Aerobic physical activity</td>
<td>4.5 mmHg</td>
</tr>
<tr>
<td>Moderation of alcohol consumption</td>
<td>2-4 mmHg</td>
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¹ A drink is 12 oz or 360 ml (alcohol is 0.6 oz or less; 5 oz wine, 15 oz beer).
² Effects are dose and time dependent.

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.

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.
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
### 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.

## 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.
Primary Aldosteronism

- 17-23% of RH cases
- Only 9-37% have hypokalemia
- Several Subtypes

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.

Adrenal Histology

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

### 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](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

- 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.
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.

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.

## Treatment of Pheochromocytoma

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

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

### Cushing’s Syndrome: Clinical

- Central obesity, hypertension, glucose intolerance
- Moon face
- Abdominal striae
- Menstrual irregularity
<table>
<thead>
<tr>
<th>Cushing’s Syndrome</th>
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<tbody>
<tr>
<td>• Overstimulation of the mineralocorticoid receptor by cortisol.</td>
</tr>
<tr>
<td>• 70+% of Cushing’s patients have HTN.</td>
</tr>
<tr>
<td>• Sleep apnea and insulin resistance also contribute to high BP.</td>
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<tr>
<td>• 24hr urine cortisol is 3 times upper limit of normal.</td>
</tr>
<tr>
<td>• Urine and late night salivary cortisol should be checked twice.</td>
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</table>
## 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.

## 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.
### Hyperthyroidism

- Results in increase in heart rate, cardiac contractility, and stroke volume.
- Systolic HTN is common.
- Salt sensitive.
- Use B blocker if tolerated.

### Coarctation of the Aorta

- Congenital or acquired (Takayasu arteritis)
- More common in males
- 30-40% have a bicuspid aortic valve
- 10% have an intracranial aneurysm
Coarctation of the Aorta

- HTN in the upper extremities and diminished femoral pulses (brachial – femoral delay).
- Measure brachial and popliteal BP.
- Headache, cold feet, pain in legs with exercise.
- Cardiomegaly and LV strain on EKG.
- Diagnosis made by Echo with doppler.

Coarctation Management

- Adults should have CT or MRA of thoracic aorta and intracranial vessels.
- Angioplasty/Stent is preferred at some centers.
- Surgery – resection +/- bypass graft.
Renal Denervation

Targeting Renal Nerves

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

Vessel
Lumen

Media

Adventitia
Renal Nerves

Data on file. Medtronic, Inc.
Images provided courtesy of Medtronic
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.

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)
<table>
<thead>
<tr>
<th>Symplicity HTN 3 Referrals</th>
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</thead>
<tbody>
<tr>
<td>• Phone: 614-292-5315 – Denise Fadorsen</td>
</tr>
<tr>
<td>• EPIC: Ambulatory Referral Nephrology or Cardiology for Resistant Hypertension</td>
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</tbody>
</table>