

Secondary Hypertension The Primary Care Perspective

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What is Hypertension

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

What Is Hypertension (JNC 7)

| CLASSIFICATION OF BLOOD PRESSURE (BP) ^a | | |
|----------------------------------------------------|------------|---------------|
| CATEGORY | SBP mmHg | DBP mmHg |
| Normal | <120 | and <80 |
| Prehypertension | 120-139 | or 80-89 |
| Hypertension, Stage 1 | 140-159 | or 90-99 |
| Hypertension, Stage 2 | \geq 160 | or \geq 100 |

| BLOOD PRESSURE MEASUREMENT TECHNIQUES | |
|---------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|
| METHOD | NOTES |
| In-office | Two readings, 5 minutes apart, sitting in chair. Confirm elevated reading in contralateral arm. |
| Ambulatory BP monitoring | Indicated for evaluation of “white coat hypertension.” Absence of 10-20 percent BP decrease during sleep may indicate increased CVD risk. |
| 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

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

- 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

- **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

- **Neck**
 - Goiter
 - Neck size ≥ 17 inches in men (≥ 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

- **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, Hirsutism
 - 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

- **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**

Lifestyle Changes

| MODIFICATION | RECOMMENDATION | Avg. SBP Reduction Range [†] |
|-----------------------------------|---------------------------------------------------------------------------------------------------------------------|---------------------------------------|
| Weight reduction | Maintain normal body weight (body mass index 18.5-24.9) | 5-20 mmHg/10 kg |
| DASH eating plan | Adopt a diet rich in fruits, vegetables, and lowfat dairy products with reduced content of saturated and total fat. | 8-14 mmHg |
| Dietary sodium reduction | Reduce dietary sodium intake to ≤ 100 mmol per day (2.4 g sodium or 6 g sodium chloride). | 2-8 mmHg |
| Aerobic physical activity | Regular aerobic physical activity (e.g., brisk walking) at least 30 minutes per day, most days of the week. | 4-9 mmHg |
| Moderation of alcohol consumption | Men: limit to ≤ 2 drinks* per day. Women and lighter weight persons: limit to ≤ 1 drink* per day. | 2-4 mmHg |

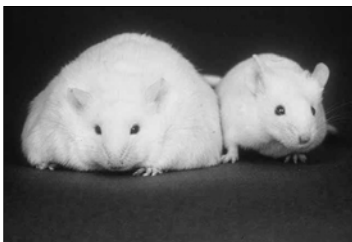
[†] 1 drink = 12 oz of 5% alc/vol ethanol (eg, 12 oz beer, 5 oz wine, 1.5 oz 80-proof whiskey).

* Effects are dose and site dependent.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
National Heart, Lung, and Blood Institute
National High Blood Pressure Education Program

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Obesity

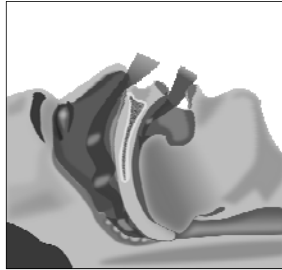


Obstructive Sleep Apnea

- 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.

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

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.

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 aldosterone level >15 ng/dl.
- ARR is an effective screening test if spironolactone, eplerenone, amiloride, triamterene are not in use.

Treatment of AP adenoma

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

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 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

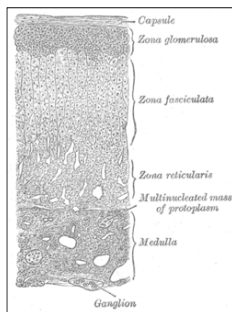


Image from http://en.wikipedia.org/wiki/Adrenal_gland

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.

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.**

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.**

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

- 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 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 Management

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

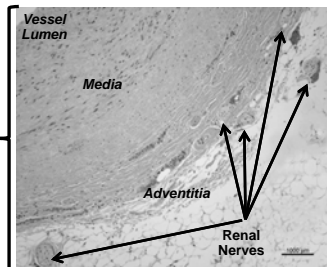
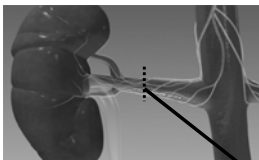
Renal Denervation

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



Data on file. Medtronic, Inc.

Images provided courtesy of Medtronic

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 Referrals

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

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)