Session 4: Identification and Assessment of Patients with Secondary Hypertension

Learning Objectives

1. Understand the indications for investigation of secondary causes of hypertension.
2. Utilize evidence-based approaches to evaluate and initiate treatment in patients at risk for secondary hypertension.
Session 4

Identification and Assessment of Patients with Secondary Hypertension

Faculty

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University of Pennsylvania School of Medicine
Associate Chief and Fellowship Training Program Director,
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Associate Dean for Graduate Medical Education
Philadelphia, Pennsylvania

Dr. Jeffrey Berns is currently professor of medicine and pediatrics at the University of Pennsylvania School of Medicine, associate chief and fellowship training program director of the University of Pennsylvania’s Renal-Electrolyte and Hypertension Division, and associate dean for graduate medical education. He received his MD and completed residency training in internal medicine at Case Western Reserve University School of Medicine in Cleveland, Ohio, then completed his fellowship in nephrology at Yale University. After spending 12 years in private practice he joined the faculty of the University of Pennsylvania School of Medicine. His clinical and research interests are in the areas of chronic kidney disease, glomerular diseases, renal pharmacology, and critical care nephrology. He has received many teaching awards and is actively involved in efforts to evaluate and improve training in nephrology. He has been deputy editor of NephSAP, serves on the ASN Training Program Director Executive Committee, and is vice-chair for clinical practice guidelines for NKF’s KDOQI program.

Faculty Financial Disclosure Statement
The presenting faculty reports the following:

Dr. Berns receives a consulting fee from Amgen and DSMB compensation from Affymax, and serves as an advisor for Litholink.
## AAFP Evidence-Based Recommendations: Course 2

<table>
<thead>
<tr>
<th>Practice Recommendation</th>
<th>In dialysis and nondialysis patients with CKD receiving ESA therapy, the Hb target should not be greater than 13.0 g/dL.</th>
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<tbody>
<tr>
<td>Strength of Evidence</td>
<td>Moderately strong evidence</td>
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<td>Date</td>
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<table>
<thead>
<tr>
<th>Practice Recommendation</th>
<th>Patients with nondiabetic kidney disease and spot urine total protein to creatinine ratio ≥ 200 mg/g, with or without hypertension, should be treated with an ACE inhibitor or ARB.</th>
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<tbody>
<tr>
<td>Strength of Evidence</td>
<td>There is strong evidence that the practice improves health outcomes (A)</td>
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<td>Date</td>
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Identification and Assessment of Patients with Secondary Hypertension

Jeffrey S. Berns, MD, FACP

Disclosures

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Learning Objectives

- Recognize the indications for investigation of secondary causes of hypertension, and perform an appropriate and evidence-based diagnostic work-up.
- Utilize evidence-based approaches to evaluate and manage patients at risk for secondary hypertension.

Secondary Hypertension Outline

- Pre-test
  - Primary aldosteronism
  - Renal artery stenosis
  - Resistant hypertension
  - Conclusions
  - Post-test

Pre-Activity Audience Response Questions

Primary aldosteronism should be considered as a cause of secondary hypertension in a patient that doesn’t respond to blood pressure medications and exhibits the following:

1. Hyperkalemia
2. Hypokalemia
3. Metabolic acidosis
4. None of the above
Surgery is most likely to provide a definitive cure for hypertension due to:
1. Aldosterone-producing adrenal adenoma
2. Idiopathic hyperaldosteronism
3. Pheochromocytoma
4. Atherosclerotic renal artery stenosis

Which of the following is/are TRUE regarding ACEi/ARB therapy compared to other drug therapies for treatment of renal artery stenosis (RAS)?
1. Lowers risk of progressing to ESRD
2. Lowers risk of acute kidney injury
3. Lowers risk of hyperkalemia
4. All of the above

What is the most common reason for resistant hypertension?
1. Secondary hypertension
2. Obesity
3. Use of NSAIDs
4. Patient nonadherence to hypertension therapy
5. "White coat" hypertension

CPAP for obstructive sleep apnea effectively treats secondary hypertension.
1. True
2. False

37-year-old woman with recent diagnosis of hypertension
- She was told BP was “a bit high” in the past but has never been treated
  - Reports that she tries to avoid salty foods; exercises (walks) 2-3 times per week
  - (+) Family history of hypertension
  - BP 160/85 mmHg; BMI 25
  - Remainder of exam normal; no edema
  - Labs: K 3.7 mmol/L, remainder within normal ranges
Case 1

What do you do first?
1. Start thiazide diuretic
2. Start an angiotensin receptor blocker (ARB)
3. Advise on lifestyle and dietary modification
4. Obtain renin and aldosterone levels

Case 1

She is started on HCTZ 12.5 mg daily
- One month later, she calls complaining of weakness, cramps in hands
- BP 160/82 mmHg
- Potassium 2.8 mmol/L; TCO₂ 28 mmol/L

When Should Secondary Hypertension Be Considered?
- Under age 30 years
- BP remains above goal in spite of concurrent use of 3 antihypertensive agents of different classes
- Hypertensive urgency or emergency
  - Usually due to medication noncompliance
- BP ≥160/100 mmHg after the age of 55 years
- Severe target organ damage
- Recurrent pulmonary edema
- Hypokalemia, elevated creatinine, proteinuria
- Specific findings on history or physical exam

Hypertension in Adults is a Global Epidemic
- Estimated prevalence
  - Worldwide: 20% (50% over age 50)
  - Europe: 44%
  - China: 14%
  - United States: 27%
- CKD patients: 60% - 100%
- Resistant hypertension (observed in clinical trials): 20% - 30%
- Secondary hypertension accounts for 5% - 10% of all hypertension cases

JNC-7 Hypertension Classification

<table>
<thead>
<tr>
<th>BP Classification</th>
<th>SBP mmHg</th>
<th>DBP mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;120</td>
<td>and &lt;80</td>
</tr>
<tr>
<td>Prehypertension</td>
<td>120-139</td>
<td>or 80-89</td>
</tr>
<tr>
<td>Stage 1 Hypertension</td>
<td>140-159</td>
<td>or 90-99</td>
</tr>
<tr>
<td>Stage 2 Hypertension</td>
<td>≥ 160</td>
<td>or ≥ 100</td>
</tr>
</tbody>
</table>

Causes of Secondary Hypertension

- Abnormal renal function
  - Chronic kidney disease
  - Bladder outlet obstruction
- Abnormal renal perfusion
  - Renovascular hypertension
  - Aortic coarctation
- Hormonal disturbance
  - Primary aldosteronism
  - Hypo- or hyperthyroidism
  - Pheochromocytoma
  - Cushing’s disease
  - Hyperparathyroidism
- Other
  - Obstructive Sleep Apnea
  - Drug/diet-induced
**Hypertension and Hypokalemia**

- Primary hypertension and high sodium intake
- Primary hyperaldosteronism
- Renal artery stenosis
  - Fibromuscular dysplasia (FMD)
  - Atherosclerotic RAS
- Liddle syndrome
- Cushing syndrome
- Syndrome of apparent mineralocorticoid excess (AME)
- Pseudohyperaldosteronism
- Renin-secreting tumor
- Natural licorice ingestion

**Primary Aldosteronism**

- Prevalence: Estimated 5%-13% of hypertensive patients
  - Depends on referral patterns, severity of BP, etc.
- Mechanism: Excessive secretion of aldosterone due to adenoma or bilateral adrenal cortical hyperplasia
- Presentation: Hypokalemia, metabolic alkalosis, drug-resistant hypertension

**Primary Aldosteronism: Who to Screen?**

- Hypertension with
  - Unprovoked hypokalemia
  - Hypokalemia provoked by diuretic
- Severe hypertension BP > 160/100 mmHg
- Resistant hypertension
- Hypertension at young age (< 20 years)
- Known adrenal mass
- Family history of primary hyperaldosteronism
- Whenever secondary hypertension is a concern

**Primary Aldosteronism**

- ~1/3 Aldosterone-producing adenoma
- ~2/3 Idiopathic hyperaldosteronism
  - Older
  - More mild hypertension
  - More likely to be normokalemic
- Other rarer forms
  - Unilateral hyperplasia, adrenocortical carcinoma

**PAPY Study**

- Hypokalemia: more likely to have adenoma
- More severe hypertension: more likely to have aldosterone excess

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PAPY Study


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Primary Aldosteronism Diagnosis

**Aldosterone Renin Ratio (ARR)**

Even within physiologic range, higher aldosterone levels associated with higher BP and hypertension.

Plasma aldosterone concentration/plasma renin activity (ARR) ≥ 20
- Test with normal serum K
- Avoid β-blockers and aldosterone receptor antagonists and ACE/ARB and aliskerin
- Sensitivity ~ 75-85%; specificity ~ 75%


**Sodium Loading Test:**

- Intravenous saline loading
  - 2 liters normal saline over 4 hours
  - Measure plasma aldosterone levels
- Oral sodium chloride loading
  - 12 g/d NaCl for 4 days
  - Measure 24-hr urine aldosterone and sodium

Primary Aldosteronism Diagnosis

**Adrenal Vein Sampling (AVS)**

Necessary to establish the diagnosis
- Among pts with elevated ARR or (+) saline loading test
  - AVS bilateral abnormality with unilateral CT/MRI: 14.6%
    - At risk for inappropriate adrenalectomy
  - AVS unilateral with bilateral or normal CT/MRI: 19.1%
    - At risk for inappropriate avoidance of adrenalectomy
  - Overall AVS-CT/MRI discordance: 37.8%


Primary Aldosteronism

**Treatment**

- Aldosterone-producing adenoma
  - Surgery normalizes K, improves BP
  - Laparoscopic approach recommended
  - Normalizes BP in 30%-60%
- Idiopathic hyperaldosteronism
  - Spironolactone or eplerenone


Primary Aldosteronism

**Summary**

- Patients with Hypertension at increased risk for PA
- Use ARR to screen for cases
- Conduct confirmatory testing
- (Adrenal CT)
- Salty Net Diet
- Spironolactone
- Bilateral
- AVS
- MR antagonist
- Unilateral aldosterone ARR


Other (Rare) Causes of Hypertension and Hypokalemia

- Liddle’s syndrome
  - Activating mutation(s) in epithelial Na channel (ENaC) of the collecting duct
  - Impaired regulatory mechanism leads to increased # of ENaC channels and Na reabsorption
  - Severe salt sensitive hypertension, marked hypokalemia, low renin and low aldosterone
- Syndrome of apparent mineralocorticoid excess (AME)
  - Mutation in 11β hydroxysteroid dehydrogenase 2 (11βHSD2)
  - Severe salt-dependent hypertension with hypokalemia, low plasma renin, low plasma aldosterone level, usually in childhood, can present in adulthood
Other (Rare) Causes of Hypertension and Hypokalemia cont'd

Licorice ingestion
- Contains glycyrrhizic acid; inhibits 11-beta-hydroxysteroid dehydrogenase allowing cortisol to exert an aldosterone-like effect
  - Cortisol is not metabolized to cortisone
  - Only in natural licorice; some chewing tobaccos
- Hypertension, hypokalemia, low renin and low aldosterone

Glucocorticoid remediable hypertension
- Chimeric gene encodes protein with aldosterone synthase activity ectopically expressed in adrenal fasciculata under control of ACTH
- Constitutive aldosterone secretion, volume expansion and hypertension
- Early-onset hypertension with low renin and high aldosterone

Conclusions
- Primary hypertension is a lot more common than primary aldosteronism
- Patients with primary hypertension on diuretics, especially with high sodium intake, will have mild hypokalemia even in absence of aldosteronism
- Primary aldosteronism is not rare; it can be treated so screening is appropriate in selected patients
  - Other forms of secondary hypertension with hypokalemia are less common or rare

Secondary Hypertension
Outline
- Pre-test
- Primary aldosteronism
- Renal artery stenosis
- Resistant hypertension
- Conclusions
- Post-test

Case 2
- 64-year-old Caucasian man
  - Long-standing well-controlled hypertension
    - Usual BP 125/75 mmHg
    - About 6 months ago at routine visit BP found to be higher than usual
    - Patient reports no change in compliance, diet, exercise
  - PMH: MI → PTCA/stent for CAD 3 years ago
  - Smoked 1 ppd for 40+ years, stopped 3 years ago

PTCA = Percutaneous transluminal coronary angioplasty

Back to Case 1
- ARR 38 ng/dL per ng/mL per hr
- Plasma aldosterone 32 ng/dL
- Plasma renin activity 0.84 ng/mL per hr
- CT showed left adrenal mass
- AVS confirmed localization of left adrenal
- Laparoscopic adrenalectomy performed
  - 3 months later: BP 130/75 mmHg on low dose diuretic; normal potassium

Case 2

<table>
<thead>
<tr>
<th>6 mo ago</th>
<th>4 mo ago</th>
<th>2 mo ago</th>
<th>Now</th>
</tr>
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<tbody>
<tr>
<td>BP (mmHg)</td>
<td>148/90</td>
<td>152/92</td>
<td>155/90</td>
</tr>
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</table>

Medication

<table>
<thead>
<tr>
<th>HCTZ dosing</th>
<th>Amlopidine dosing</th>
<th>Carvedilol dosing</th>
<th>Losartan dosing</th>
<th>Creatinine (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NEW</td>
<td></td>
<td></td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.1</td>
</tr>
</tbody>
</table>
Case 2

What would you do next?
1. Add ACE inhibitor
2. Change HCTZ to loop diuretic
3. Renal ultrasound with duplex Doppler
4. Renal arteriogram
5. Magnetic resonance angiography (MRA) of renal arteries

Clinical Features Suggestive of Atherosclerotic Renovascular Disease (RVD)

- Hypertension onset >55 yrs
  - Often abrupt onset
  - Often with unexplained creatinine increase and/or progressive renal insufficiency
- History of smoking
- Whites > Blacks
- Established, treated hypertension suddenly becomes worse and more difficult to control
- Malignant hypertension
- Evidence of diffuse atherosclerotic cardiovascular disease
- Abdominal or renal artery bruit

Clinical Features Suggestive of Atherosclerotic RVD continued

- Increase in serum creatinine with use of ACE inhibitors/ARBs or with significant lowering of blood pressure by any agent
  - Typically noted after 3-7 days
  - Most common with bilateral RAS or RAS in solitary functioning kidney
- “Flash” pulmonary edema with severe hypertension
- Renal size asymmetry
- Nonfunctioning kidney by renal nuclear imaging

Unilateral Renal Artery Stenosis

- Diagnostic Tests
  - Plasma renin activity elevated
  - Enhanced lateralization of diagnostic tests
  - Glomerular filtration rate (GFR) in stenotic kidney may fall
- Diagnostic Tests
  - Imaging tests for anatomic diagnosis
- Effect of blockade of RAS
  - Reduced arterial pressure
  - Enhanced renal perfusion
- Angiographic stenosis

RAS vs Essential Hypertension: Clinical Characteristics are Similar

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Essential HTN (%)</th>
<th>Renovascular HTN (%)</th>
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<tr>
<td>Duration of hypertension &lt;1 year</td>
<td>12</td>
<td>24</td>
</tr>
<tr>
<td>Age at onset after 50 years</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td>Family history of hypertension</td>
<td>71</td>
<td>46</td>
</tr>
<tr>
<td>Grade 3 or 4 funduscopic changes</td>
<td>7</td>
<td>15</td>
</tr>
<tr>
<td>Abdominal bruit</td>
<td>9</td>
<td>46</td>
</tr>
<tr>
<td>Blood urea nitrogen &gt;20mg/100mL</td>
<td>8</td>
<td>15</td>
</tr>
<tr>
<td>Serum K&lt;3.4mEq/L</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>32</td>
<td>46</td>
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</table>

Renal Artery Duplex Sonography
American College of Radiology Practice Guideline

- Moderate to high suspicion of renovascular hypertension
- Follow-up post renal artery stents or renal artery surgical reconstruction
- Suspected abdominal bruit
- Suspected vascular abnormality
- Acute renal failure when there is a suspected vascular cause
- Renal artery blood flow in patients with aortic dissection/other aortic abnormalities that may compromise blood flow to the kidneys
- Discrepant renal size in a patient with hypertension
- Renal insufficiency in patients with a high likelihood of renal vascular disease

Imaging for Suspected RAS
Non-Invasive Tests

- Doppler Duplex Ultrasound
  - Operator and patient dependent
  - Local sensitivity and specificity usually not known
- CT and MR Angiography
  - Sensitivity ~ 80%; probably higher for atherosclerotic RAS
  - Specificity ~ 90-95%
  - Preferred non-invasive imaging study
  - Requires contrast in all (CT) or most (MR) patients
- IV Digital Subtraction Angiography
  - Large contrast load; rarely done anymore
- Captopril Renography
  - Not recommended

Atherosclerotic Narrowing of Proximal Renal Artery

Imaging for Suspected RAS
Invasive Tests

- Renal Arteriography (MRA)
  - The “gold standard”
  - Can combine with trans-stenosis pressure measurements
  - Stenosis not generally considered to be hemodynamic significant if < 70% narrowing
- Carbon Dioxide (CO₂) Angiography
  - In patients unable to get contrast

Natural History of Renovascular Disease

Hypertension
- BP may increase, become more difficult to control
- BP stable (i.e., does not progressively increase) in many patients
  *Kidney function stable in most patients
  - < 10% progress to ESRD
  *High CV mortality due to concomitant atherosclerotic coronary, cerebrovascular, and peripheral vascular disease
  *“Flash” pulmonary edema

Cardiovascular Disease and RAS

Incidences in Medicare patients with and without known atherosclerotic renovascular disease

Treatment Options for Atherosclerotic Renovascular Disease

- Transluminal angioplasty with or without stent placement
- Medical Therapy
- Surgery

Angioplasty for Renal Artery Stenosis

- Early studies suggested 20-30% hypertension “cure” and up to 75% “improvement” in angioplasty-treated RAS
- But....
  - Uncontrolled studies in highly selected pts
  - BP data often inadequate
  - Variable definitions of improvement
- Current BP meds makes angioplasty for purposes of BP control less necessary


‘True” Ostial vs. Origin Disease

Renal Artery Stenosis

Medical Therapy

- Statins
- Aspirin
- Management of DM and CKD
- Cohort studies suggest renin-angiotensin aldosterone system (RAAS) blockade is associated with better cardiovascular and mortality outcomes
  - Higher incidence of acute kidney injury and hyperkalemia
  - Lower risk of ESRD

Use of ACEi or ARB in Renovascular Disease - A Cohort Study

<table>
<thead>
<tr>
<th>Outcome</th>
<th>n (rate for outcome)</th>
<th>Adjusted HR (95% CI)</th>
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<tbody>
<tr>
<td>Primary</td>
<td>285(10.0)</td>
<td>0.70</td>
</tr>
<tr>
<td>Death</td>
<td>203(6.8)</td>
<td>0.56</td>
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<tr>
<td>Stroke</td>
<td>47(1.6)</td>
<td>0.86</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>78(2.7)</td>
<td>1.07</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>118(4.0)</td>
<td>0.69</td>
</tr>
<tr>
<td>Acute Renal Failure</td>
<td>35(1.2)</td>
<td>1.87</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>24(0.8)</td>
<td>1.07</td>
</tr>
<tr>
<td>Long-term dialysis</td>
<td>45(1.5)</td>
<td>0.62</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>50(1.9)</td>
<td>1.38</td>
</tr>
</tbody>
</table>

* Rates expressed as number of events per 100 patient-years at risk

Primary outcome: Death, MI, stroke


Surgical Revascularization

- No recent high quality comparisons of surgery vs. angioplasty
- Most comparisons show no benefit of surgery on mortality, dialysis-free survival, or BP control
- Complications of surgery > angioplasty
- May be a role in highly selected patients only
  - Should only be performed by surgeons with expertise in this area
Angioplasty in RAS

Role for angioplasty alone still unclear
• No long-term follow up
• No assessment of RAS restenosis
• Most would not intervene if stenosis is < 70%
  – In trial of such patients BP did not differ after
    angioplasty w/o stent compared to medical therapy
• Most favor doing stent if going to intervene at all
  – Stenting of ostial RAS reduced re-stenosis but no
    difference in BP control or kidney function


Angioplasty With or Without Stent
The ASTRAL Trial

• Multicenter RCT of 806 patients with RAS
• Inclusion Criteria
  – Substantial RAS in at least one renal artery
    suitable for endovascular revascularization
  – Referring MD uncertain if angioplasty would
    be beneficial
• Angioplasty with or without stents
• Medical treatment both group – local practice
• Primary Outcome – Change in renal function
  based on mean slope 1/Cr vs time


Medical Therapy vs. Stent for RAS
STAR Trial Results

• Multicenter RCT of 140 patients with RAS
• Inclusion Criteria
  – Ostial RAS > 50%
    • Nearly 20% of enrolled patients had RAS < 50% and
      did not have intervention
  – BP controlled < 140/90 mmHg
  – eGFR 80-15 ml/min/1.73m²
• Angioplasty with stent vs. medical treatment alone
  – Both groups got medical therapy
• Primary Outcome – 20% or greater decrease in estimated
  creatinine clearance
• Stent placement + medical therapy not superior to medical
  therapy alone and associated with major complications


Treatment for Renovascular Hypertension
Summary

• Available studies of medical vs. surgery vs.
  angioplasty with/without stent not definitive
  – CORAL Study results awaited soon…..
• No clinical or radiologic features accurately
  predict which patients might benefit from
  revascularization
• Revascularization can be considered for
  – RAS > 70% with severe, poorly controlled
    hypertension and/or declining kidney function or
    “flash” pulmonary edema despite optimal medical
    therapy
• In addition to aggressive BP treatment patients need
  management of other atherosclerotic disease
  – Statins
  – Aspirin
  – ACEi/ARB
• Do not revascularize for
  – Chronic (controlled) hypertension
  – Preservation of renal function if stable in patients with
    unilateral RAS and contralateral renal artery is normal
    – RAS < 70%
• Revascularization can be associated with major
  complications

Back to Case 2

Underwent angioplasty with stent of right renal artery ostial stenosis
  – No procedural complication
• BP improved (142/78 mmHg), renal function improved (creatinine 1.4 mg/dL)
• Maintained on statin, aspirin, carvedilol, losartan, HCTZ

Secondary Hypertension
Outline
  • Pre-test
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  • Resistant hypertension
  • Conclusions
  • Post-test

Angioplasty and Stent Placement
Correction of atherosclerotic narrowing of proximal right renal artery

Case 3
• 47-year-old African-American man
  – Hypertension since age 25 years
  – Obese
  • Gained 25 pounds in last 10 years
  • Sedentary occupation
  • Little exercise
  – Microalbuminuria
  – No other significant PMHx
  – FH (+) for hypertension, DM, CKD/ESRD
  – Medications: Chlorthalidone 25 mg daily, amlodipine 10 mg daily, metoprolol 50 mg BID, ramipril 5 mg BID, clonidine 0.2 mg BID

Case 3
• BP 162/92 mmHg; BMI 33 kg/m²
• Remainder of exam is normal

What would you do next?
1. Serum aldosterone, plasma renin activity
2. Add another BP medication
3. Sleep study
4. MRI of renal arteries
5. No studies or medication changes

Does He Have “Resistant Hypertension”?

JNC-7:
Blood pressure ≥ 140/90 mmHg (130/80 mmHg in patients with diabetes or CKD) despite adherence to treatment with full doses of at least three antihypertensive medications, including a diuretic
Resistant Hypertension

Causes of Resistant Hypertension

- Measurement artifacts
- Medication adherence
- Lifestyle issues; diet
- Drug-related adherence
- Obstructive sleep apnea
- Inadequate dosing
- Secondary hypertension
- Drug interactions
- Suboptimal combinations
- Interfering or exogenous substances


Measurement Artifacts: Proper Technique

- Upper arm measurements on bare arm
- Proper cuff size
- 5 minutes of rest for first measurement; wait at least one minute for second measurement
- Arm supported with cuff at heart level
- Back supported, legs uncrossed, feet on floor
- No talking

Multiple Antihypertensive Agents Are Needed to Achieve Target BP

<table>
<thead>
<tr>
<th>Trial</th>
<th>Target BP (mmHg)</th>
<th>Mean # Antihypertensive Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKPDS</td>
<td>DBP &lt;85</td>
<td>1</td>
</tr>
<tr>
<td>ABCD</td>
<td>DBP &lt;75</td>
<td>2</td>
</tr>
<tr>
<td>MDRD</td>
<td>MAP &lt;92</td>
<td>3</td>
</tr>
<tr>
<td>HOT</td>
<td>DBP &lt;80</td>
<td>4</td>
</tr>
<tr>
<td>IDNT</td>
<td>SBP &lt;135/DBP &lt;85</td>
<td>*In addition to study drug</td>
</tr>
<tr>
<td>AASK</td>
<td>MAP &lt;92</td>
<td>*</td>
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</tbody>
</table>

Failure to reach BP goal in trials: 5-10%
Many of these patients with CKD and/or DM

Nonadherence to Hypertension Medication

- Up to 40% of newly diagnosed hypertensive patients will discontinue their antihypertensive medications during the first year
- Only 40% of the remaining patients continue their therapy over the next decade

Adherence to Medications Influenced by Dosing Schedule

<table>
<thead>
<tr>
<th>Prescribed Dosing Frequency</th>
<th>Percent Compliance (%)</th>
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</thead>
<tbody>
<tr>
<td>QD</td>
<td>80</td>
</tr>
<tr>
<td>BID</td>
<td>70</td>
</tr>
<tr>
<td>TID</td>
<td>60</td>
</tr>
<tr>
<td>QID</td>
<td>50</td>
</tr>
</tbody>
</table>
Improving Patient Adherence to Hypertension Therapy

- Patient education
- Increase frequency of visits
- Prescribe a drug regimen least likely to cause adverse effects
- Choose the least costly regimen likely to be effective
- Prescribe QD or BID regimen
- Use fixed-dose combinations
- Acknowledge progress toward goal
- Inquire about compliance obstacles
- Self-measurements of BP

Lifestyle Modifications

<table>
<thead>
<tr>
<th>Modification</th>
<th>Approximate SBP Reduction (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight Reduction</td>
<td>5-10 mmHg/10kg</td>
</tr>
<tr>
<td>Adopt DASH eating plan</td>
<td>8-14 mmHg</td>
</tr>
<tr>
<td>Dietary sodium reduction</td>
<td>2-8 mmHg</td>
</tr>
<tr>
<td>Physical activity</td>
<td>4-9 mmHg</td>
</tr>
<tr>
<td>Moderation of alcohol consumption</td>
<td>2-4 mmHg</td>
</tr>
</tbody>
</table>

DASH = Dietary Approaches to Stop Hypertension

Drugs That Can Interfere with BP Control

- NSAIDs
- Sympathomimetic drugs:
  - Phenylephrine
  - Cocaine
  - Amphetamines
- Cancer chemotherapy:
  - Angiogenesis inhibitors
- Cyclosporine, tacrolimus, steroids
- Buspirone
- Antidepressants:
  - Venlafaxine
  - Tricyclics
- Metoclopramide
- Oral contraceptives
- Erythropoietin

Diet and Supplements That Can Interfere with BP Control

- Alcohol: >1 drink/day for women
  >2 drinks/day for men
- Dietary salt: > 5 grams daily
- Caffeine
- Black licorice
- Herbs:
  - Ginseng
  - Ginger
  - Yohimbine
  - Ephedra

Diuretic Maximization

- Chlorthalidone is approximately 2x as potent as HCTZ
  - 25 mg chlorthalidone = 50 mg HCTZ
  - Longer acting
  - More hypokalemia
- Loop diuretics
  - Use twice daily in most patients, especially with eGFR < 30 mL/min/1.73m²
- Combinations
  - Loop + thiazide
  - Thiazide + K-sparing
  - Loop + K-sparing
  - Loop + thiazide + K-sparing

Aldosterone Blockade in Resistant Hypertension

Low-dose aldosterone antagonist added to diuretic + ACEi or ARB in subjects with resistant HTN +/- primary aldosteronism

Causes of Secondary Hypertension

- Abnormal renal function
- Abnormal renal perfusion
- Hormonal disturbance
- Other
  - Chronic kidney disease
  - Bladder outlet obstruction
  - Renovascular hypertension
  - Aortic coarctation
  - Primary aldosteronism
  - Hypo- or hyperthyroidism
  - Pheochromocytoma
  - Cushing's disease
  - Hyperparathyroidism
  - Obstructive Sleep Apnea
  - Drug/diet-induced

Obstructive Sleep Apnea (OSA) and Hypertension

- OSA: >10 apneic and hypopneic episodes per sleep hour
- About 10% of adults 30-60 years of age
- About 50% of patients with "primary hypertension" have OSA, and vice versa
- OSA prevalence/severity directly correlates with hypertension prevalence/severity in OSA patients
- Successful treatment of OSA is associated with a significant reduction in BP

Obstructive Sleep Apnea and Hypertension
Potential Mechanisms

- Hypertension
- Endothelial dysfunction
- Impaired baroreflex
- 1 Renal function
- Hyperleptinemia
- Systemic inflammation
- Oxidative stress
- Insulin resistance
- 1 Sympathetic activity
- Obstructive Sleep Apnea (OSA)

Ten-Year Risk of Developing Obesity-Related Hypertension in the US

- 77690 female nurses and 46060 male health professionals
- Adjusted for age, smoking status, and race

Effect of CPAP on Blood Pressure in Obstructive Sleep Apnea

- BP goal of <140/90 mmHg supported by CV outcome trials
- Large RCTs have not demonstrated benefit of lower BP goal (<130/80 mmHg or 125/75 mmHg) in preserving kidney function or further reducing CV events (ie, MDRD and AASK trials)
- May provide benefit in patients with CKD and proteinuria
- Appropriate use of diuretics is essential
- Home BP monitoring should be encouraged

CKD and Hypertensive Nephrosclerosis
Blood Pressure Goals

- BP goal of <140/90 mmHg supported by CV outcome trials
- Large RCTs have not demonstrated benefit of lower BP goal (<130/80 mmHg or 125/75 mmHg) in preserving kidney function or further reducing CV events (ie, MDRD and AASK trials)
- May provide benefit in patients with CKD and proteinuria
- Appropriate use of diuretics is essential
- Home BP monitoring should be encouraged

Obstructive Sleep Apnea and Hypertension

Back to Case 3

- Treated with CPAP
- Diet and exercise routine with weight loss
- Restriction of dietary sodium
- HCTZ changed to chlorthalidone
- Off clonidine; other BP medications unchanged
- BP 136/78 mmHg

Causes of Secondary Hypertension That Must Not be Overlooked

- Pheochromocytoma—deadly if missed
  - Triad of HA, palpitations, sweating
  - Plasma-free metanephrine, 24-hr urine metanephrine, 24-hr urine vanillylmandelic acid (VMA)
  - Surgery offers the most definitive treatment
- Obstructive uropathy—reversible
- Less common familial and hereditary causes will require expert assistance to diagnose

Secondary Hypertension Outline

- Pre-test
- Primary aldosteronism
- Renal artery stenosis
- Resistant hypertension
- Conclusions
- Post-test

Secondary Hypertension Summary

- The obvious—most people don't have it!
- Look selectively, especially for more common causes
  - Primary aldosteronism
  - Renal artery stenosis—Atherosclerosis, Fibromuscular dysplasia
  - Obesity, sleep apnea
  - CKD
- Don't look if you are not going to do something about it

When to Evaluate for Secondary Hypertension Summary

- Atypical features: Age
- Worsening of previously controlled hypertension
- Stage 2 hypertension
- Sudden onset of hypertension
- Unexpected target end-organ damage
- Failure to achieve BP goals

Post-Activity Audience Response Questions
Primary aldosteronism should be considered as a cause of secondary hypertension in a patient that doesn’t respond to blood pressure medications and exhibits the following:

1. Hyperkalemia
2. Hypokalemia
3. Metabolic acidosis
4. None of the above

Surgery is most likely to provide a definitive cure for hypertension due to:

1. Aldosterone-producing adrenal adenoma
2. Idiopathic hyperaldosteronism
3. Pheochromocytoma
4. Atherosclerotic renal artery stenosis

Which of the following is/are TRUE regarding ACEi/ARB therapy compared to other drug therapies for treatment of renal artery stenosis (RAS)?

1. Lowers risk of progressing to ESRD
2. Lowers risk of acute kidney injury
3. Lowers risk of hyperkalemia
4. All of the above

What is the most common reason for resistant hypertension?

1. Secondary hypertension
2. Obesity
3. Use of NSAIDs
4. Patient nonadherence to hypertension therapy
5. “White coat” hypertension

CPAP for obstructive sleep apnea effectively treats secondary hypertension.

1. True
2. False