Secondary Hypertension: Diagnosis and Management

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Objectives

• Identify when secondary hypertension should be considered
• Devise a rational strategy for assessing the possible causes of secondary hypertension
• Discuss the management of secondary causes of hypertension
Secondary hypertension

- 1 in 3 adults has HTN, most of which is “essential”
- “Secondary” = underlying, potentially correctable cause
- Obviously not the vast majority of hypertension
Pathophysiologic mechanisms

Genetic

Environmental

Angiotensinogen, GRA, AME, Liddle syndrome

Stress

Sex

CNS

Sympathetic activation

Cardiac output

Cardiac

Sodium retention

Renal

Obesity, micronutrients, alcohol

Gastrointestinal

Endocrine

Insulin, aldosterone

Age

Smooth-muscle cells

Arteriole

Endothelium

Endothelin, nitric oxide


Annals of Internal Medicine
New patient evaluation - 3 goals

1) Identify comorbidities / other risk factors
2) Assess for target organ damage
3) Exclude secondary causes

* Predicated on accuracy of BP measurements
Evaluation - history

• Flushing, paroxysmal
  – Pheochromocytoma

• Cold or heat intolerance
  – Thyroid dysfunction

• Snoring /apneic episodes
  – Obstructive sleep apnea
Medications, supplements, illicits

Drugs that elevate BP
• Estrogen (OCPs)
• NSAIDs
• Many antidepressants
• Corticosteroids
• Decongestants
• Diet pills

Herbals and illicits
• Ephedra
• Ginseng
• Ma Huang
• Amphetamines
• Cocaine

Evaluation - exam

• Arm-leg discrepancy or ↓ femoral pulses
  – Coarctation of the aorta

• Renal bruit
  – Renal artery stenosis

• “Buffalo hump” or moon facies
  – Cushing syndrome
Evaluation - labs

• Hypokalemia (unprovoked)
  – Aldosteronism

• Elevated hematocrit
  – Polycythemia

• Azotemia or proteinuria
  – Renal disease

• Rise (>30%) in creatinine after ACEI or ARB
  – Renal artery stenosis
New patient evaluation

• Most of the time
  – No suggestion of secondary cause
### Secondary hypertension differential – one approach

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Secondary hypertension prevalence

- Varies by age group
  - 5% to 10% of adults
  - 85% of children

- Another approach
  - Epidemiology / pretest probability
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<td>Renal failure</td>
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Early onset hypertension

- Up to 85% of pre-adolescent children with hypertension have secondary cause
  - Most commonly renal parenchymal disease (GN, congenital, reflux nephropathy)
  - May not present until adolescent/young adult

- Consider adding urine culture and renal ultrasonography as part of routine evaluation of children with hypertension

Early onset hypertension

- Up to 41% of children with hypertension have left ventricular hypertrophy (Confirm HTN with ambulatory BP monitoring)
- If not done as part of initial evaluation, consider echocardiogram
- Not only assesses for LVH but also coarctation of the aorta


Coarctation of the aorta

• 2\textsuperscript{nd} most common cause of HTN in children
• 2-5 times more common in boys
• May present in neonate as heart failure, but more typically diagnosed around age 5 with onset of HTN or a cardiac murmur
• Discrepancy between bilateral brachial or brachial and femoral BPs suggests diagnosis
• Classic “three” sign or rib notching on CXR
Coarctation of the aorta

- Echo for children
- MRI more for adults
Coarctation of the aorta
Late onset hypertension

- Older patient with new onset hypertension consider renal artery stenosis due to atherosclerotic disease
- Value of detecting is debatable since medical management (i.e., BP lowering) may be as good as revascularization

Resistant hypertension

• ~12% of patients with hypertension
• After ruling out measurement error and white coat effect (with out-of-office monitoring), consider secondary causes again, especially
  – Aldosteronism
  – Obstructive sleep apnea
  – Renal artery stenosis

Aldosteronism

1. Angiotensinogen
   - Renin
2. Angiotensin I
   - Converting enzyme
3. Angiotensin II
   - Stimulation of aldosterone secretion
5. Aldosterone
   - Increased water and sodium retention
   - Increased preload
6. Increased preload
7. Increased afterload
8. Constriction of vascular smooth muscle
Aldosterone → Na+ retaining

- Can be aldo-producing adenoma or bilateral idiopathic hyper-aldo
- Hypokalemia only occurs in ~30%
- ~10%-20% of patients with resistant hypertension
- 25% have normal aldo levels
- Best initial test is aldo/renin ratio

Aldo/renin ratio

- Plasma aldosterone (ng/dl) and renin activity (mg/ml/hr)
- Ideally in morning at least 2 hours after waking and in upright position
- Aldo/renin ratio >20 and aldol>15
  - LR+4.6  LR-0.27
- Aldo/renin ratio >30 and aldol>15
  - LR+28  LR-0.16
Aldo/renin testing protocol

- Liberalize (rather than restrict) sodium intake
- Withdraw for 48 hrs
  - Spironolactone, eplerenone, amiloride, triamterene
  - K+-wasting diuretics
  - (Licorice)
- Ideally off ACEI/ARBs, BBs also

OK to use:
- Verapamil SR
- Hydralazine
- Alpha-blockers

- Note renal failure can lead to false positive
+ Aldo/renin ratio

- Refer to endocrine for a salt suppression test to confirm
- Treatment if adenoma may be resection
- If hyperplasia, mineralocorticoid antagonist
Obstructive sleep apnea

- Consider sleep study in patients with resistant hypertension
- Epworth Sleepiness Scale or Sleep Apnea Clinical Score coupled with nighttime pulse oximetry when sleep study not available
- Treatment with CPAP reduces BP

Obstructive sleep apnea

• Cause or contributor
• Surges in BP at night
• Sympathetic nervous system overactivity & alterations in vascular function and structure caused by oxidant stress and inflammation
• BP can remain elevated during the daytime, even when breathing is normal
Renal artery stenosis

• Atherosclerotic – older patient, questionable value of detecting
• Fibromuscular dysplasia – young patients, especially women
  – Revascularization curative in 20 to 85%; improved BP in nearly all
  – MRI with gadolinium or CTA

Renal artery stenosis

- MRI vs CTA vs renal Doppler
  - MRI and CTA equally accurate
  - MRI does not use radiation and can be used in pts with poor renal function (esp if no contrast, although with ↓ sens & spec)
  - If both contraindicated, renal Doppler (although affected by body habitus and operator skill)
  - Radiology at UNC → clinician’s preference
# Summary of Test Characteristics

<table>
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<tr>
<th>Diagnosis under consideration</th>
<th>Test</th>
<th>LR+</th>
<th>LR-</th>
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<tr>
<td>Coarctation</td>
<td>Echo</td>
<td>47</td>
<td>0.06</td>
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<tr>
<td>Cushing</td>
<td>24-hr urinary free cortisol</td>
<td>10.6</td>
<td>0.16</td>
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<td>Late-night salivary cortisol</td>
<td>8.8</td>
<td>0.07</td>
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<td>Low-dose dex suppression</td>
<td>11.6</td>
<td>0.09</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>24-hr urinary total metanephrines</td>
<td>8.0</td>
<td>0.13</td>
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<tr>
<td></td>
<td>Plasma free metanephrines</td>
<td>5.5</td>
<td>0.01</td>
</tr>
<tr>
<td>Renal artery stenosis</td>
<td>Captopril renal scan</td>
<td>1.4</td>
<td>0.76</td>
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<tr>
<td></td>
<td>CTA</td>
<td>13.4</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>MRI with contrast</td>
<td>13.9</td>
<td>0.03</td>
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<tr>
<td>Renal parenchymal disease</td>
<td>Renal ultrasound</td>
<td>2.9</td>
<td>0.3</td>
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History, exam, routine lab testing

Clinical clues at initial evaluation
- Testing based on clinical clues
  - Renal ultrasound

No clinical clues, but concern for secondary hypertension remains
- Child
  - Renin-aldosterone levels
- Young adult*
  - Renal artery MRI or CTA
- Middle-aged*
  - Renin-aldosterone levels

*TSH should also be considered if not done at initial evaluation
Evaluation for Secondary Hypertension (cont)

- **Child**
  - Renal ultrasound
  - Echocardiography*

- **Young adult**
  - Renal artery MRI or CTA
  - Sleep study

- **Middle-aged**
  - Renin-aldo levels
  - 24-hour urinary cortisol
  - 24-hour urinary metanephrines

*If not done at initial evaluation
Take away message

• Consider secondary hypertension
  All newly diagnosed patients, especially early or late onset
  …and consider it again in those with Resistant hypertension

• In absence of clinical clues, evaluate using an age-based differential