HYPERTENSION

Emory University Internal Medicine Board Review
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Jeanie Park, MD MS
Assistant Professor
Emory University

Outline

• Primary hypertension
• Resistant Hypertension
• Hypertensive Urgency and Emergency

Case 1

49 year-old Caucasian male with no significant past medical history presents for routine annual physical exam. His blood pressure is noted to be 145/95 mm Hg. What is the most appropriate next step?

A. Start hydrochlorothiazide 25mg daily
B. Initiate lifestyle modifications, home blood pressure monitoring and follow-up in 4-6 weeks
C. Start amlodipine 5 mg and lisinopril 10 mg daily.
D. Obtain sleep study to rule out sleep apnea.

Lifestyle Modifications

1. Dietary salt restriction
2. Weight loss
3. DASH diet (fruits, vegetables and low-fat dairy, high in potassium and fiber, low in saturated fat and cholesterol)
4. Exercise
5. Limit alcohol intake (one drink/day in women, 2 drinks/day in men)

Case 1 (cont)

The patient returns to the office. His home blood pressure measurements average 139/88 mm Hg. His office blood pressure reading is 144/93 mm Hg.

Does the patient have hypertension based on his home BP readings? ________

What is this patient’s goal blood pressure? ________

Disclosures

None
BP Treatment Goals per JNC-8

<table>
<thead>
<tr>
<th>Age</th>
<th>Comorbidities</th>
<th>Goal mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 60 years</td>
<td>General population</td>
<td>&lt; 150/90</td>
</tr>
<tr>
<td>&lt;60 years</td>
<td>General population</td>
<td>&lt;140/90</td>
</tr>
<tr>
<td>Any age (≥18 years)</td>
<td>Chronic Kidney Disease</td>
<td>&lt;140/90</td>
</tr>
<tr>
<td>Any age (≥18 years)</td>
<td>Diabetes</td>
<td>&lt;140/90</td>
</tr>
</tbody>
</table>

BP Treatment Goals per Indication

- Diabetes: <140/90 (JNC 8)
- Chronic Kidney Disease: <140/90 (JNC 8)
- Chronic Kidney Disease with Proteinuria: <130/80 (MDRD, KDIGO)
- SPRINT (patients at high cardiovascular risk but without diabetes): SBP 120-125 mmHg
  - 1 or more risk factors: age≥75, cardiovascular disease, peripheral arterial disease, elevated coronary artery calcification score, LVH, ankle-brachial index <0.9, eGFR 20-59 mL/min/1.73m², 10-year Framingham Risk Score ≥15%  
- Excluded: diabetes, symptomatic heart failure, history of stroke, proteinuria, nursing home residents

Case 1 (cont)

All of the following can be considered as initial monotherapy in this 45 year-old Caucasian patient with uncomplicated hypertension, EXCEPT:

A. Thiazide diuretic  
B. Long-acting dihydropyridine calcium channel blocker  
C. Angiotensin-converting enzyme (ACE) inhibitor  
D. Angiotensin II receptor blocker (ARBs)  
E. Beta blocker

Initial antihypertensive treatment per JNC-8

- General nonblack population (including those with diabetes)  
  a. Thiazide diuretic  
  b. CCB  
  c. ACEI  
  d. ARB  
- General black population (including those with diabetes)  
  a. Thiazide diuretic  
  b. CCB  
- CKD (regardless of race or diabetes status)  
  a. ACEI or ARB

Case 1 (cont)

If instead, this patient is a 49 year-old African American male with diabetes, which of the following medication(s) should be considered for initial therapy: ___________

If instead, this patient is a 49 year-old African American male with diabetes and chronic kidney disease, the following medication(s) should be considered for initial or add-on therapy:  _________________

A. Amlodipine 5 mg daily  
B. Chlorthalidone 12.5 mg daily  
C. Metoprolol 25mg twice daily  
D. Lisinopril 20mg daily  
E. Losartan 50 mg daily

Case 1 (cont)

The patient is initiated on HCTZ 25mg daily. One month later, his clinic BP is noted to be 155/95 mm Hg. Lisinopril 20mg daily is added. One month later, his clinic BP is 150/100 mm Hg. The patient states he is feeling dizzy at home. All of the following are indications for 24-hour ambulatory blood pressure monitoring, EXCEPT:

A. Suspected white coat hypertension  
B. Suspected masked hypertension  
C. Hypertension resistant to increasing medications  
D. Suspected obstructive sleep apnea  
E. Suspected episodic hypertension (e.g. pheochromocytoma)  
F. Autonomic dysfunction
White Coat Hypertension
- Office readings that average more than 140/90 mm Hg, while reliable out-of-office readings average <140/90 mm Hg;
- Suspected when clinic BP is consistently elevated, but there is no evidence of end-organ damage.
- Cardiovascular risk is well below that of patient with sustained hypertension, and slightly higher than patient with persistent normotension

Masked Hypertension
- Normotensive by clinic office readings, but hypertensive outside the office
- Suspected when there is evidence of end-organ damage (particularly left ventricular hypertrophy), but consistently normal clinic blood pressure readings.

Summary of Key Points
1. Hypertension diagnosis should be based on an average of two or more properly measured readings at each of two or more office visits after an initial screen.
   - JNC 7 definitions (2003)
   - Normal BP <120/80mm Hg
   - Prehypertension: SBP 120-139 mm Hg, DBP 80-89 mm Hg
   - Stage 1: SBP 140-159 mm Hg, DBP 90-99 mm Hg
   - Stage 2: SBP ≥ 160 mm Hg, DBP ≥ 100 mm Hg. Consider starting two agents at a time if BP ≥ 160/100 mm Hg
   - Based on ambulatory or home readings (ESH/ESC 2013 Guidelines)
   - 24 hour average ≥ 130/80 mm Hg
   - Daytime (awake) average ≥ 135/85 mm Hg
   - Nighttime (asleep) average ≥ 120/70 mm Hg

2. Goal BP <140/90 mm Hg in patients younger than 60, and all diabetics, and CKD patients regardless of age. Goal BP < 150/90 patients >60 years

3. Initial antihypertensive treatments in: A) general nonblack population: thiazide diuretic, CCB, ACEI, ARB; B) general black population: thiazide diuretic, CCB; C) CKD: ACEI, ARB

Case 2
55 year-old African American female is referred to you for further management of hypertension. The patient is currently on the following antihypertensive medications: Metoprolol 25 mg twice per day, amlodipine 5 mg daily, and lisinopril 40 mg daily. Her office blood pressure is 160/100 mm Hg. Does this patient have resistant hypertension? 

Resistant Hypertension
Defined as blood pressure that remains above goal despite the use of three antihypertensive agents of different classes, including a diuretic, each at optimal doses. (JNC 7)

Case 3
55 year-old Caucasian male with hyperlipidemia and hypertension presents for further management. He was diagnosed with hypertension 5 years earlier at age 50 years. He denies a history stroke or coronary disease, but does state that he had an echocardiogram done last year that showed an "enlarged heart." He doesn’t exercise and does not follow a low sodium diet. He takes ibuprofen 400-800 mg 3 times per week for chronic headaches. He denies chest pain, shortness of breath, or voiding symptoms.
Case 3 (cont)

Meds: Amlodipine 10mg daily, HCTZ 25mg daily, labetalol 300 mg BID, simvastatin 40 mg daily, Levothyroxine 100 mcg daily, Nasal decongestant containing pseudoephedrine daily as needed

PMHx: HTN, hyperlipidemia, hypothyroidism


Physical exam: BP 162/95, HR 72, BMI 39
Trace lower extremity edema

Approach to the patient with resistant hypertension

- Rule out pseudoresistant hypertension
  - Adherence, BP measurement technique, suboptimal therapy

- Careful history for Associated Factors
  - Drugs (NSAIDs, decongestants), illicit drugs, excessive alcohol use, obesity

- Labs: serum electrolytes, glucose, creatinine, urinalysis

- Evaluation for sleep apnea if indicated

- Workup for Identifiable Causes as warranted

Identifiable Causes of Resistant Hypertension

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Diagnostic Test</th>
</tr>
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<tbody>
<tr>
<td>Chronic Kidney Disease</td>
<td>Estimated GFR</td>
</tr>
<tr>
<td>Obstructive Sleep Apnea</td>
<td>Sleep study with O2 saturations</td>
</tr>
<tr>
<td>Primary hyperaldosteronism and other mineralocorticoid excess states</td>
<td>Plasma aldosterone to renin ratio, or 24-hour urinary aldosterone level</td>
</tr>
<tr>
<td>Renovascular hypertension (Renal artery stenosis or fibromuscular dysplasia)</td>
<td>Doppler flow study or magnetic resonance angiography</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>Plasma metanephrines/normetanephrines or 24-hour urinary metanephrines/normetanephrines</td>
</tr>
<tr>
<td>Coarctation of the Aorta</td>
<td>CT angiography</td>
</tr>
<tr>
<td>Cushing’s syndrome and other glucocorticoid excess states</td>
<td>Dexamethasone suppression test</td>
</tr>
</tbody>
</table>

Case 4

52 year-old African American male with hypertension presents for evaluation. His medications include: Amlodipine 10mg daily, Clonidine 0.2mg TID, Lisinopril 40mg daily, Hydralazine 100 mg TID. He denies headaches, chest pain, shortness of breath, anxiety, or dizziness. His office blood pressure is 162/100. His laboratory values include:

<table>
<thead>
<tr>
<th>EKG: LVH</th>
<th>UA: Trace protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>143</td>
<td>105</td>
</tr>
<tr>
<td>3.0</td>
<td>18</td>
</tr>
<tr>
<td>1.6</td>
<td>103</td>
</tr>
<tr>
<td>6.7</td>
<td>38</td>
</tr>
<tr>
<td>190</td>
<td>K</td>
</tr>
</tbody>
</table>

What is the most appropriate next step?

A. 24 hour urinary metanephrines and normetanephrines
B. Plasma aldosterone concentration and plasma renin activity
C. Dexamethasone suppression test
D. MRA of the renal arteries
E. Sleep study

Case 4 (Cont)

The following values for plasma aldosterone concentration and plasma renin activity are obtained.

Plasma Aldosterone Concentration: 19 ng/dL
Plasma Renin Activity: 0.5 ng/mL/hr
PAC/PRA: 38

What is the most appropriate next step?

A. Adrenal MRI
B. Adrenal CT scan
C. Adrenal vein sampling
D. Salt suppression test
E. Adrenalectomy
F. Initiate spironolactone 50mg twice per day
Primary Aldosteronism

- Suspected in patient with resistant or difficult-to-control hypertension and unexplained hypokalemia
- Screening test is to check plasma aldosterone concentration (PAC) and plasma renin activity (PRA). PAC is usually >15 ng/dL, PRA is suppressed and <1 ng/mL/hr, and PAC:PRA ratio is >20.
- Patient with a positive screening test should undergo a confirmatory salt suppression test.
  - Oral sodium loading: 5000 mg sodium diet or tabs daily for 3 days. Repeat 24 h urine. 24h urine sodium >200 meq for adequate loading, and urine aldosterone excretion of>12 mcg is consistent with primary aldosteronism
  - Saline infusion test: 2 L of IV NS are given over 4 hours. PAC should fall to <5ng/dL in normal subjects, but remain >10 ng/dL in patients with primary aldosteronism.

Case 4 (cont)

The patient underwent a saline suppression test. PAC after 2 liters of NS infusion was 13 ng/dL. The patient is diagnosed with primary aldosteronism. Subsequently, an adrenal CT shows a left adrenal adenoma of 0.5 cm. The most appropriate next step is:

A. Adrenal MRI
B. Left adrenalectomy
C. Adrenal vein sampling
D. Initiate spironolactone 50 mg twice daily

Primary Aldosteronism (cont)

- If patient has a positive salt suppression test (i.e. PAC does not suppress with salt load), then patient has primary aldosteronism and should undergo an adrenal CT scan
- If the CT scan shows > 1 cm adenoma on one adrenal gland, the contralateral adrenal gland is normal, and the patient is younger than 35 years, may proceed directly to adrenalectomy. Otherwise, obtain adrenal vein sampling.
- If adrenal vein sampling shows localization to one side (i.e. the PAC:cortisol ratio in the affected adrenal gland is at least 4 x higher than normal gland), then patient has unilateral aldosterone excess and should undergo adrenalectomy. If it is less than 3 x higher, then patient has bilateral hyperplasia and should be treated with spironolactone or eplerenone.

Fibromuscular Dysplasia

Case: 33 yo female with newly diagnosed hypertension presents with headaches. On exam she has bilateral carotid bruits. She has the following findings on angiography.

Key Points
- More common in young females
- Most commonly involves renal arteries (70%) and internal carotid arteries
- "String of beads" pattern on angiography
- Treatment via percutaneous transluminal angioplasty

Approach to patient with hypokalemia and hypertension

<table>
<thead>
<tr>
<th>Renin</th>
<th>Aldosterone</th>
<th>State</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>High</td>
<td>Primary Hyperaldosteronism</td>
</tr>
<tr>
<td>High</td>
<td>High</td>
<td>Renovascular disease (Renal artery stenosis, fibromuscular dysplasia)</td>
</tr>
<tr>
<td>Low</td>
<td>Low</td>
<td>Liddle’s syndrome or Apparent Mineralocorticoid Excess (licorice)</td>
</tr>
</tbody>
</table>

Renal Atherosclerotic Disease

Case: 78 year-old male with coronary artery disease, peripheral artery disease, hypertension and Stage III chronic kidney disease. He was started on an ACEI and his serum Cr increased from 1.7 to 2.7. He has presented 3 times in the last 6 months with hypertensive emergency and flash pulmonary edema.

Key Points
- Suspect in patient with diffuse atherosclerosis, recurrent flash pulmonary edema, >30% reduction in eGFR after ACE/ARB
- ACE/ARB are effective in the treatment of unilateral and bilateral RAS
- Studies have failed to show advantage of revascularization over medical therapy
- May consider revascularization in patients with progressive unexplained renal failure, recurrent flash pulmonary edema, intolerance or failure of optimal medical therapy

NEJM 361;20 (November 12, 2009)
Case 5

42 year-old white female presents with muscle cramps. She is noted to be hypertensive with BP of 154/95. She recently went to Europe and bought licorice which she has been snacking on daily for the past several weeks.

Labs:
K: 2.9 mEq/L
HCO3: 31 mEq/L
Plasma renin activity: 0.8 ng/dL
Plasma aldosterone: 3 ng/dL

The most likely diagnosis is:
A. Acquired apparent mineralocorticoid excess
B. Primary aldosteronism
C. Renal artery stenosis
D. Glucocorticoid remediable hyperaldosteronism

Apparent Mineralocorticoid Excess (AME)

- Cortisol binds the MR with the same affinity as aldosterone. However, cortisol is converted by 11βHSD2 to cortisone which does not bind the MR.
- AME occurs when there is a genetic defect in 11βHSD2, or chronic ingestion licorice which contains glycyrrhetinic acid which inhibits 11βHSD2.
- Presents with hypertension, hypokalemia, metabolic alkalosis, low renin, and low aldosterone levels.

Case 6

43 year-old Caucasian female presents with headaches and sweating for the past 3 months. She has frontal headaches that occur daily, and generalized sweating, even when the weather is cold. She also feels anxious and has palpitations. Her family has commented that she often looks pale. Her seated blood pressure in the office is 166/100 mm Hg, with heart rate of 70 bpm. Her standing blood pressure is 148/85 mm Hg, with a heart rate of 90 bpm. The most appropriate next step is:
A. Plasma aldosterone and renin
B. Adrenal MRI
C. 24 hour urine vanillymandelic acid (VMA)
D. Clonidine Suppression Test
E. 24-hour urine normetanephrines/metanephrines

Pheochromocytoma

- Catecholamine-secreting tumors that arise from chromaffin cells of the adrenal medulla and the sympathetic ganglia
- Classic triad: headache, sweating, tachycardia
- Familial syndromes: multiple endocrine neoplasia type 2 (MEN 2), neurofibromatosis 1 (NF1), von Hippel-Lindau (VHL) disease
- 10% are malignant. 10 % are extraadrenal.
- Screening test is 24-hour urine fractionated metanephrines and catecholamines (96% sens, 98% spec) or plasma fractionated metanephrines (96-100% sens, 89% spec)
- Obtain abdominal CT or MRI if biochemical test is positive
- MIBG scan can be done if abdominal imaging is negative, and an extra adrenal paraganglioma is suspected.
- Pre-operative management with alpha-adrenergic blocker (phenoxybenzamine) followed by cautious addition of a beta-blocker
Case 7

67 year-old African American female with hypertension presents to the ED with headache and dizziness. She had run out of her antihypertensive medications two days prior. Her BP is 210/120 mm Hg. Her exam reveals S4, and trace edema but otherwise unremarkable. CXR shows cardiomegaly and EKG is consistent with LHV. Her labs reveal serum Cr of 2.0 mg/dL and UA shows 15-20 RBCs/hpf. Three months ago, her Cr was 1.3 mg/dL.

The most appropriate management:
A. Clonidine 0.2 mg PO
B. Resume home BP medications
C. Admit to the ICU and start IV nicardipine drip
D. Sublingual Nifedipine
E. Renal protocol CT

Hypertensive Urgency and Emergency

- Hypertensive Urgency is defined as severe hypertension (>180/120) without evidence of end-organ damage
- Hypertensive Emergency is defined as severe hypertension with evidence of end-organ damage (encephalopathy, intracerebral hemorrhage, acute MI or unstable angina, pulmonary edema, acute kidney injury, dissecting aortic aneurysm).
- Hypertensive emergency should be admitted to the ICU for continuous monitoring and treated with IV agents (nicardipine, labetalol, nitroprusside)
- Goal in hypertensive emergency is to reduce MAP by ≤ 25% within 1 hour, then to 160/100-119 mm Hg within the next 2-6 hours. If this is tolerated, then further reduction to goal BP over the next 24-48 hours. Exceptions include aortic dissection (more rapid lowering) and acute stroke (less rapid or no lowering)
- Hypertensive urgency can be treated with oral agents – reinstitution of drugs if adherence is the issue, or adjustment in the medication regimen.

References

- Case detection, diagnosis, and treatment of patients with primary aldosteronism: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2006;91(9):3296
- 2013 ESC/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens. 2013;31(7):1281
- 2014 Evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA. 2014;311(5):507

Answers

Slide 4: B. The diagnosis of hypertension requires at least two or more properly measured readings at each of two or more office visits after an initial screening. All patients with elevated blood pressure readings should institute recommended lifestyle modifications as listed on Slide 5.

Answers

Slide 6:
The patient returns to the office. His home blood pressure measurements average 139/88 mm Hg. His office blood pressure reading is 144/93 mm Hg.

Does the patient have hypertension based on his home BP readings? _____NO_____

Diagnosis of hypertension based on home BP measurements requires an average of >135/85 mm Hg.

What is this patient’s goal blood pressure? ____<140/90_____
Answers
Slide 9. E. Per JNC-8 guidelines, first-line initial treatments for the general nonblack population include thiazide diuretics, calcium channel blockers, ACE inhibitors, and angiotensin receptor blockers. Beta blockers are no longer considered first-line agents.

Answers
Slide 10. If instead, this patient is a 49 year-old African American male with diabetes, which of the following medication(s) should be considered for initial therapy: __A, B________

First-line agents for the general black population are thiazide diuretics and calcium channel blockers.

If instead, this patient is a 49 year-old African American male with diabetes and chronic kidney disease, the following medication(s) should be considered for initial or add-on therapy: ______D,E___________

ACE inhibitors and ARBs should be considered for initial or add-on treatment in patients with CKD.

Answers
Slide 12. D.
The other suspected diagnoses are indications for 24 hour ambulatory blood pressure monitoring. Patients with suspected sleep apnea should be referred for a sleep study.

Answers
Slide 15. 55 year-old African American female is referred to you for further management of hypertension. The patient is currently on the following antihypertensive medications: Metoprolol 25 mg twice per day, amlodipine 5 mg daily, and lisinopril 40 mg daily. Her office blood pressure is 160/100 mm Hg. Does this patient have resistant hypertension? _____NO_____

According to JNC-7, resistant hypertension is defined as blood pressure that remains above goal despite the use of three antihypertensive agents of different classes, including a diuretic, each at optimal doses. This patient is not on optimal doses, and not on a diuretic.

Answers
Slide 20. C.
All of the other factors are associated with difficult to treat hypertension.

Answers
Slide 23. B. This patient has resistant hypertension, hypokalemia, metabolic alkalosis, and chronic kidney disease, suspicious for primary hyperaldosteronism. The screening test is a plasma renin activity and plasma aldosterone levels.
Slide 24. D. After a positive screening test, patients with suspected primary hyperaldosteronism should undergo a confirmatory salt suppression test as described in Slide 25.

Slide 26. C. To determine if the left adrenal adenoma is a functional adenoma, adrenal vein sampling should be performed. Details are provided on Slide 27.

Slide 31. A. This patient has hypertension, hypokalemia, metabolic alkalosis, and suppressed renin and aldosterone levels. This presentation is consistent with the syndrome of apparent mineralocorticoid excess due to licorice ingestion. Pathogenesis of this condition is explained on Slide 32.

Slide 34. E. This patient has hypertension, orthostatic hypotension, headaches, sweating, anxiety, palpitations, and pallor. These symptoms and findings are suspicious for pheochromocytoma. The screening test is a 24 hour urine for metanephrines or plasma metanephrines. See Slides 35-36.

Slide 37. C. This patient has hypertensive emergency because she has severe hypertension with evidence of end-organ damage (acute kidney injury with microscopic hematuria). She should be managed with IV medications and continuously monitored in the ICU.