SYMPTOM TO DIAGNOSIS
An Evidence-Based Guide

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I have a patient with hypertension. How do I determine the cause?

**CHIEF COMPLAINT**

**PATIENT 1**

Mr. U is a 48-year-old man with a BP of 165/90.

What is the differential diagnosis of hypertension? How would you frame the differential?

**CONSTRUCTING A DIFFERENTIAL DIAGNOSIS**

First, what is normal BP, and when is a patient hypertensive? The most recent Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High BP (JNC 7) classifies BP as follows, based on the mean of 2 seated BP measurements on each of 2 or more office visits:

1. Normal: systolic BP < 120 and diastolic BP < 80.
2. Prehypertension: systolic BP 120–139 or diastolic BP 80–89.
4. Stage 2 hypertension: systolic BP ≥ 160 or diastolic BP ≥ 100.

Hypertension is either primary (essential) or secondary (resulting from a specific identifiable cause). Causes of secondary hypertension can be organized using an organ/system framework:

A. Primary (essential) hypertension
B. Secondary hypertension
   1. Endocrine
   a. Primary aldosteronism
   b. Pheochromocytoma
   c. Thyroid disease
   d. Hyperparathyroidism
   e. Cushing’s syndrome
2. Renal
   a. Chronic kidney disease
   b. Acute renal failure
3. Vascular
   a. Renovascular disease
   b. Coarctation of the aorta
4. Pulmonary: sleep apnea
5. Drug induced or related
   a. Chronic steroid therapy
   b. Nonselective nonsteroidal anti-inflammatory agents
   c. COX-2 inhibitors
   d. Cocaine
   e. Alcohol
   f. Sympathomimetics (decongestants, anorectics)
   g. Oral contraceptives
   h. Cyclosporine and tacrolimus
   i. Erythropoetin

Mr. U’s BP is high. He has wanted to avoid taking medication and has been trying to watch his diet and lose weight. Both of his parents and several of his siblings have hypertension. His medical history is notable only for smoking 1 pack/day for 30 years; he does not use alcohol and takes no medications.
At this point, what is the leading hypothesis, and what are the active alternatives? What other tests should be ordered?

ORGANIZING THE DIFFERENTIAL DIAGNOSIS

Ninety-five to 99% of patients with hypertension have essential hypertension. Coexistent diabetes and a family history of hypertension both increase the pretest probability of essential hypertension. Patients between the ages of 20 and 50 have about twice the risk of developing hypertension if they have 1 first-degree relative with hypertension; the relative risk is 3–4 if 2 first-degree relatives have hypertension. Secondary causes are quite rare in unselected populations; estimated prevalences are 0.18–4.4% for renovascular hypertension, 0.04–0.2% for pheochromocytoma, 0.01–0.4% for primary hyperaldosteronism, and 0.3% for Cushing’s syndrome (Table 26–1). More common conditions that can contribute to or cause hypertension include either hyper- or hypothyroidism, renal insufficiency, excessive alcohol use, sleep apnea, and use of drugs listed previously.

Mr. U’s review of symptoms (ROS) is negative for chest pain, shortness of breath, claudication, headache, dizziness, palpitations, weight change, constipation, daytime sleepiness, and snoring. On physical exam, BP is 165/90 in both arms; pulse, 84; RR, 16. He weighs 220 pounds, with a body mass index (BMI) of 30. Fundoscopic exam shows some arteriolar narrowing with no hemorrhages or exudates. Jugular venous pressure is normal. Lungs are clear, and

Table 26–1. Diagnostic Hypotheses for Mr. U

<table>
<thead>
<tr>
<th>Diagnostic Hypotheses</th>
<th>Clinical Clues</th>
<th>Important Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Leading hypothesis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Essential hypertension</td>
<td>Family history, obesity, coexistent diabetes</td>
<td></td>
</tr>
<tr>
<td><strong>Active alternatives: most common</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>Often none, sometimes edema, malaise</td>
<td>Serum creatinine</td>
</tr>
<tr>
<td>Sleep apnea</td>
<td>Obesity (&gt;120% ideal body weight), neck circumference &gt; 17 in, frequent snoring, daytime sleepiness, witnessed apnea</td>
<td>Polysomnogram</td>
</tr>
<tr>
<td>Thyroid disease</td>
<td>Hyperthyroidism: weight loss, loose stools, palpitations, sweating;</td>
<td>TSH</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Alcohol history, CAGE</td>
<td></td>
</tr>
<tr>
<td>Drug/medication use</td>
<td>Hypothyroidism: weight gain, constipation, fatigue, Alcohol history</td>
<td>Medication/drug history</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Other hypotheses</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal artery stenosis</td>
<td>Abrupt onset or accelerated HTN, azotemia after use of ACE inhibitor, HTN refractory to ≥3 meds, abdominal or flank bruit, other vascular disease (coronary, carotid, or peripheral), smoking, severe retinopathy</td>
<td>MRA with gadolinium, CT angiography</td>
</tr>
<tr>
<td>Hyperaldosteronism</td>
<td>Resistant hypertension, hypokalemia</td>
<td>Aldosterone–renin ratio</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>Labile BP/paroxysmal HTN, headache, sweating, orthostasis, tachycardia</td>
<td>Plasma metanephrine</td>
</tr>
</tbody>
</table>

TSH, thyroid-stimulating hormone; HTN, hypertension; ACE, angiotensin-converting enzyme; MRA, magnetic resonance angiography; CT, computed tomography.
CHAPTER 26

Cardiac exam shows an S₄ but no S₃ or murmurs. There are no abdominal bruits; carotid, radial, femoral, posterior tibialis, and dorsalis pedis pulses are normal. There is no peripheral edema. Neurologic exam is normal.

Is the clinical information sufficient to make a diagnosis? If not, what other information do you need?

Leading Hypothesis: Essential Hypertension

Textbook Presentation

Essential hypertension generally presents as the gradual onset of elevated BP, most often in middle-aged people with positive family histories. Coexisting diabetes or obesity is common but not universal.

Disease Highlights

A. Patients who are normotensive at age 55 have a 90% lifetime risk of developing hypertension (HTN).
B. Across the BP range of 115/75 to 185/115, each increment of 20 mm Hg systolic BP or 10 mm Hg diastolic BP doubles the risk of cardiovascular disease.

Evidence-Based Diagnosis

The evaluation of patients with hypertension focuses primarily on assessing other cardiovascular risk factors and assessing the presence or absence of target organ damage (TOD). Extensive testing for secondary causes is generally not done unless the patient has specific symptoms strongly suggestive of a specific secondary cause or if BP control cannot be achieved. Therefore, there are 3 objectives of testing in patients with hypertension:

A. Objective 1: Assess presence or absence of TOD (Table 26–2).
B. Objective 2: Assess presence or absence of other cardiovascular risk factors.
   1. Smoking
   2. Obesity (BMI > 30)
   3. Physical inactivity
   4. Dyslipidemia
   5. Diabetes
   6. Microalbuminuria or estimated glomerular filtration rate (GFR) < 60 mL/min
   7. Age (> 55 for men, > 65 for women)
   8. Family history of premature cardiovascular disease (men < 55, women < 65)
C. Objective 3: Identify secondary hypertension.
   1. In the absence of any of the clinical clues listed previously, it is unlikely that the patient has renal artery stenosis, hyperaldosteronism, or pheochromocytoma.
   2. Testing should focus on screening for more common causes or contributors to hypertension, such as renal or thyroid disease, that are easily diagnosed with simple blood tests.

Table 26–2. Assessing Target Organ Damage in Patients With Hypertension

<table>
<thead>
<tr>
<th>Target Organ</th>
<th>Clinical Manifestations</th>
<th>Important Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>Left ventricular hypertrophy</td>
<td>Physical exam, ECG, echo in selected patients</td>
</tr>
<tr>
<td></td>
<td>Coronary artery disease (angina, myocardial infarction)</td>
<td>History, ECG, stress test in selected patients</td>
</tr>
<tr>
<td></td>
<td>Congestive heart failure</td>
<td>History, physical exam, echo</td>
</tr>
<tr>
<td>Brain</td>
<td>Stroke, transient ischemic attack</td>
<td>History, physical exam</td>
</tr>
<tr>
<td>Kidneys</td>
<td>Proteinuria, renal insufficiency</td>
<td>Urinalysis, serum creatinine</td>
</tr>
<tr>
<td>Eyes</td>
<td>Retinopathy</td>
<td>Fundoscopic or ophthalmologic exam</td>
</tr>
<tr>
<td>Peripheral vasculature</td>
<td>Peripheral vascular disease</td>
<td>History and physical exam, ABIs in selected patients</td>
</tr>
</tbody>
</table>

ECG, electrocardiogram; ABI, ankle brachial index.
MAKING A DIAGNOSIS

Mr. U’s initial test results are as follows:
- ECG: left ventricular hypertrophy (LVH) by voltage, otherwise normal
- TSH: 1.0
- Urine albumin–creatinine ratio: normal
- Na: 145; K: 4.2; Cl: 100; BUN: 11; creatinine: 0.5
- Fasting glucose: 90
- Fasting lipid panel: total cholesterol, 240; HDL, 40; triglycerides, 100; LDL, 180

Have you crossed a diagnostic threshold for the leading hypothesis, essential hypertension? Have you ruled out the active alternatives? Do other tests need to be done to exclude the alternative diagnoses?

Based on Mr. U’s history, physical exam, and initial lab results, it is not necessary to do any further testing for secondary causes of hypertension. He does have other modifiable cardiovascular risk factors (smoking, obesity, and hypercholesterolemia), and some evidence for TOD (early retinopathy and LVH).

CASE RESOLUTION

Mr. U is counseled regarding smoking cessation and referred to a nutritionist for guidance regarding diet and exercise programs. He is started on hydrochlorothiazide, 12.5 mg daily, for his hypertension and atorvastatin, 10 mg daily, for his hypercholesterolemia (see Table 26–3 for treatment guidelines). One month later, his BP is 145/85. He has not yet started to exercise and has not quit smoking. You again counsel him regarding the importance of these lifestyle modifications and the possibility of avoiding a second medication if he exercises and loses weight. Six months later, after changing his diet and faithfully exercising 3 times a week, he has lost 5 pounds, and his BP is 137/85; he continues to smoke.

Treatment of Essential Hypertension

A. Treatment goals
   1. Reduce BP.
      a. Target of < 130/80 if patient also has diabetes or renal disease

Table 26–3. Guidelines for Treatment of Hypercholesterolemia

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL Goal (mg/dL)</th>
<th>Initiate Lifestyle Changes at LDL of</th>
<th>Consider Drug Therapy at LDL Level of</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD or CHD risk equivalent (10-year risk &gt; 20%)</td>
<td>&lt; 100&lt;sup&gt;a&lt;/sup&gt;</td>
<td>≥ 100&lt;sup&gt;b&lt;/sup&gt;</td>
<td>≥ 130&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>2+ risk factors (10 year risk 10–20%)</td>
<td>&lt; 130</td>
<td>≥ 130</td>
<td>≥ 130</td>
</tr>
<tr>
<td>2+ risk factors (10 year risk &lt; 10%)</td>
<td>&lt;130</td>
<td>≥ 130</td>
<td>≥ 160</td>
</tr>
<tr>
<td>0–1 risk factors</td>
<td>&lt; 160</td>
<td>≥ 160</td>
<td>≥ 190 (drug optional at LDL 160–189)</td>
</tr>
</tbody>
</table>

LDL, low-density lipoprotein; CHD, congestive heart disease.
Ten-year risk calculated using Framingham model (see http://hin.nhlbi.nih.gov/atp/iii/calculator.asp). CHD risk equivalents = other vascular disease (cerebrovascular, peripheral vascular, abdominal aortic aneurysm), diabetes, Framingham risk > 20%. Risk factors = smoking, hypertension (BP ≥ 140/90 or on antihypertensive therapy), high-density lipoprotein (HDL) < 40 (if HDL > 60, decrease risk factor count by 1), family history of premature coronary artery disease (male first-degree relative < 55 years, female first-degree relative < 65 years), age (men ≥ 45 years, women ≥ 55 years)
<sup>a</sup>Some experts recommend an LDL goal of 70 for high-risk patients.
<sup>b</sup>Many experts recommend statin therapy for all patients in this category.
Adapted, with permission, from Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults. JAMA 2001;285:2485.
b. Target of < 140/90 for everyone else


B. Nonpharmacologic approaches to treating hypertension (see Tables 26–4 and 26–5)
1. Two to 6 months a reasonable length of time for a trial of lifestyle modification
2. Should be discussed with all patients, even if medication also necessary

C. Overview of pharmacologic treatment of hypertension
1. In general, can divide patients into those who have other diseases that would guide choice of therapy (called "compelling indications" by JNC 7) and those without such compelling indications
a. No compelling indications
   (1) Start with thiazide diuretic in most patients.
   (2) Add angiotensin-converting enzyme inhibitor, beta blocker, angiotensin receptor blocker (ARB), or calcium channel blocker if goal not reached in 1–2 months.
   (3) Optimize dose of second drug until BP goal reached.
   (4) Add third drug from a different class if goal not reached on combination of thiazide diuretic and maximal tolerated dose of second drug; do not combine beta blockers and verapamil because of excessive blockage of atrioventricular (AV) node.

b. Compelling indications
   (1) Heart failure
      (a) Left ventricular (LV) dysfunction without symptoms: use ACE inhibitors and selective beta blockers (carvedilol, metoprolol)
      (b) With symptoms: use loop diuretics, ACE inhibitors, beta blockers, spironolactone.
   (2) Ischemic heart disease
      (a) Stable angina: use beta blockers.
      (b) Acute coronary syndromes: use beta blockers and ACE inhibitors.
      (c) Post-MI: use beta blockers, ACE inhibitors.
   (3) Diabetes
      (a) Most patients will need at least 2 drugs to achieve BP goal < 130/80.
      (b) Use thiazide diuretic and ACE inhibitor or ARB initially
      (c) Can combine ACE inhibitor and ARB, or add beta blocker or calcium blocker in patients who need a third drug
   (4) Chronic kidney disease
      (a) Use ACE inhibitor or ARB.
      (b) If creatinine > 2.5, use loop diuretic instead of thiazide
   (5) Cerebrovascular disease
      (a) Use combination of thiazide and ACE inhibitor.
      (b) Beware of rapid reduction of BP in patients with acute stroke.

**Table 26–4. Nonpharmacologic Approaches to Managing Hypertension**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Approximate Reduction in Systolic BP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight reduction</td>
<td>5–20 mm Hg/10 kg weight loss</td>
</tr>
<tr>
<td>DASH diet (see Table 26–5)</td>
<td>8–14 mm Hg</td>
</tr>
<tr>
<td>Reduced sodium diet (&lt; 2.4 g sodium/day)</td>
<td>2–8 mm Hg</td>
</tr>
<tr>
<td>Aerobic exercise, 30 min/day several days/week</td>
<td>4–9 mm Hg</td>
</tr>
<tr>
<td>Limitation of alcohol consumption to ≤ 2 drinks/day for men, ≤ 1 drink/day for women</td>
<td>2–4 mm Hg</td>
</tr>
</tbody>
</table>

**Table 26–5. DASH Diet**

<table>
<thead>
<tr>
<th>Food group</th>
<th>No. servings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grains/grain products</td>
<td>7–8/day</td>
</tr>
<tr>
<td>Vegetables</td>
<td>4–5/day</td>
</tr>
<tr>
<td>Fruits</td>
<td>4–5/day</td>
</tr>
<tr>
<td>Low fat dairy products</td>
<td>2–3/day</td>
</tr>
<tr>
<td>Meats, poultry, fish</td>
<td>2–3/day</td>
</tr>
<tr>
<td>Fats, oils</td>
<td>2–3/day</td>
</tr>
<tr>
<td>Sweets</td>
<td>5/week</td>
</tr>
<tr>
<td>Nuts, seeds, dried beans</td>
<td>4–5/week</td>
</tr>
</tbody>
</table>

2. Should also consider cost and dosing frequency: low-cost once-a-day drugs increase compliance.

3. If goal not reached on optimal doses of 3 drugs, consider noncompliance with therapy, excess sodium intake, excess alcohol intake, volume overload from kidney disease, use of medications/drugs that contribute to hypertension, and/or secondary hypertension.

CHIEF COMPLAINT

PATIENT 2

Mrs. X is a 66-year-old woman with a long history of hypertension treated with a thiazide diuretic, ACE inhibitor, and beta blocker. Her BP has generally been in the 140–145/85–95 range over the last several years. At her last visit 1 year ago, she weighed 160 pounds and her BP was 140/90. Today she weighs 170 pounds (BMI, 29), and her BP is 180/100. She feels fine, with no headache, chest pain, shortness of breath, or edema. Other than her antihypertensive medications, she takes only Pravachol. Her medical history is notable for smoking 1 pack/day for 40 years, peripheral vascular disease manifested by stable claudication on walking 6 blocks, and chronic renal insufficiency, with a serum creatinine of 1.7. Physical exam is notable for clear lungs, an S4 without an S3 or murmurs, carotid and femoral bruits, and absent posterior tibial (PT) and dorsalis pedis (DP) pulses. Abdominal exam is normal, without bruits. There is no peripheral edema.

ORGANIZING THE DIFFERENTIAL DIAGNOSIS

Although Mrs. X's BP was previously near the treatment goal of < 140/90, her BP is now clearly uncontrolled on her usual 3 medications. Although there are patients with essential hypertension who need maximal doses of 4 or even 5 drugs to achieve control, secondary causes of hypertension must be considered in patients who need so much medication. There are several “adverse lifestyle changes” alone could explain the significant increase in her BP. One would not expect such a marked increase in her BP with a 10-pound weight gain. Therefore, it is necessary to strongly consider secondary causes of hypertension. She does have preexisting renal insufficiency, which could have progressed and caused her BP to increase. Notably, she has several risk factors for renal artery stenosis (RAS); according to a clinical predication model (details discussed later), her pretest probability of RAS is at least 20%. The last consideration would be hyperaldosteronism, which manifests as resistant hypertension, and often hypokalemia. She has no symptoms to suggest pheochromocytoma (Table 26–6).

She reports that she takes all of her medications every day and never adds salt to her food. She does not drink alcohol and is afraid to use over-the-counter medications. Her walking is limited because of her claudication, but she does walk a few blocks every day. Initial laboratory tests include the following: Na, 140; K, 2.9; Cl, 100; HCO3, 26; BUN, 35; creatinine, 1.8.

Is the clinical information sufficient to make a diagnosis? If not, what other information do you need?

Leading Hypothesis: Atherosclerotic Renal Artery Stenosis

Textbook Presentation

Patients generally present either with very abrupt hypertension, with hypertension that worsens by > 15% over 6 months, or with hypertension refractory to treatment with 3 drugs. The classic patient with atherosclerotic renal artery stenosis has other vascular disease (cerebrovascular disease, coronary artery disease, peripheral vascular disease) or risk factors such as smoking or diabetes.

Disease Highlights

A. Must distinguish renovascular disease from renovascular hypertension

1. Renovascular disease means significant stenosis of 1 or both renal arteries.
### Evidence-Based Diagnosis

**A. Clinical characteristics**

1. Abdominal bruits, moderate to severe retinopathy, peripheral vascular disease often present

2. Predictive value of abdominal bruits
   - **a.** Should listen over all 4 abdominal quadrants and also spine and flanks between T12 and L2
   - **b.** Should be systolic and diastolic
   - **c.** Prevalence of 6.5–31% in a healthy population; prevalence of 28% in patients with hypertension
   - **d.** Prevalence of 78–87% in patients with proven renal artery stenosis
   - **e.** Sensitivity 39–63%, specificity 90–99%

3. Family history of hypertension often absent

4. Hypokalemia often seen as a result of stimulation of aldosterone release; metabolic alkalosis also often seen

5. A clinical predication model has been developed (Table 26–7); it should not be considered totally

### Table 26–6. Diagnostic Hypotheses for Mrs. X

<table>
<thead>
<tr>
<th>Diagnostic Hypotheses</th>
<th>Clinical Clues</th>
<th>Important Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Leading hypothesis</strong></td>
<td>Abrupt onset or accelerated HTN, azotemia after use of ACE inhibitor, HTN refractory to ≥ 3 meds, abdominal or flank bruit, other vascular disease (coronary, carotid, or peripheral), smoking, severe retinopathy</td>
<td>MRA with gadolinium, CT angiography</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Active alternatives: most common</strong></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Worsening renal function</td>
<td>None; sometimes edema, malaise</td>
<td>Serum creatinine</td>
</tr>
<tr>
<td>Adverse lifestyle changes (weight gain, high-sodium diet, excess alcohol intake, reduction in exercise, noncompliance with medications)</td>
<td>History</td>
<td>History</td>
</tr>
<tr>
<td>Use of other medications, especially NSAIDs, decongestants</td>
<td>History</td>
<td>History</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Other hypotheses:</strong></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperaldosteronism</td>
<td>Resistant hypertension, hypokalemia</td>
<td>Aldosterone–renin ratio</td>
</tr>
</tbody>
</table>

HTN, hypertension; MRA, magnetic resonance angiography; ACE, angiotensin-converting enzyme; CT, computed tomography; NSAID, nonsteroidal anti-inflammatory drug.
accurate but does give an estimate of pretest probability.

6. Response to ACE inhibition

a. Some patients with bilateral renal artery stenosis (or unilateral stenosis in patients with only 1 functioning kidney) develop a reversible increase in serum creatinine when put on ACE inhibitors.

b. One study reported, in a population of high-risk patients, a 20% increase in creatinine had 100% sensitivity and 70% specificity for the diagnosis of RAS (defined as > 50% bilateral stenosis).

B. Imaging studies

1. Renal arteriography is the gold standard; can also be therapeutic through performance of angioplasty or placement of stent.

2. Duplex ultrasonogram

a. Sensitivity 90–95%, specificity 60–90%; LR+ = 2.4–9; LR− = 0.11–0.17

b. Test characteristics not as good with less experienced technicians, obese patients

3. Captopril renogram

a. Diuretics and ACE inhibitors held for 48 h

b. Renal blood flow measured before and after captopril using nuclear medicine techniques

c. Not reliable if serum creatinine > 2.0

d. Sensitivity 83%, specificity 93%; LR+ = 11.8; LR− = 0.18

4. Magnetic resonance angiography (MRA) with gadolinium

a. Sensitivity 88–95%; specificity 94%; LR+ = 14.7–15.8; LR− = 0.03–0.05

b. Test of choice

5. CT angiography

a. Sensitivity/specificity similar to MRA with gadolinium but nephrotoxic contrast required

C. Blood tests

1. Plasma renin level

a. Sensitivity 57%, specificity 66%

b. LR+ = 1.7, LR− = 0.65

2. Captopril augmented plasma renin level

a. Diuretics and ACE inhibitors held for 2 weeks; renin measured before and 30 min after captopril dose

b. A positive test is plasma renin > 21 ng/mL/h, an absolute increase of at least 10 ng/mL/h, or an increase of 150%

c. 96% sensitivity, 55% specificity; LR+ = 2.1, LR− = 0.07

(1) The peak creatinine occurs somewhere between 4 days and 2 months.

(2) Creatinine returns to baseline within 1 week of stopping the ACE inhibitor.

---

**Table 26–7. Clinical Predication Rule for Estimating Pretest Probability of Renal Artery Stenosis**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Points (No History of Smoking)</th>
<th>Points (Former or Current Smoker)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>20 0 3</td>
<td>30 1 4</td>
</tr>
<tr>
<td>40</td>
<td>2 2</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>3 5</td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>4 5</td>
<td></td>
</tr>
<tr>
<td>70</td>
<td>5 6</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>2 2</td>
<td></td>
</tr>
<tr>
<td>Sign/symptoms of vascular disease</td>
<td>1 1</td>
<td></td>
</tr>
<tr>
<td>Onset of hypertension within 2 years</td>
<td>1 1</td>
<td></td>
</tr>
<tr>
<td>BMI &lt; 25</td>
<td>2 2</td>
<td></td>
</tr>
<tr>
<td>Presence of abdominal bruit</td>
<td>3 3</td>
<td></td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>0.4 0 0</td>
<td>0.7 1 1</td>
</tr>
<tr>
<td>0.9</td>
<td>2 2</td>
<td></td>
</tr>
<tr>
<td>1.1</td>
<td>3 3</td>
<td></td>
</tr>
<tr>
<td>1.7</td>
<td>6 6</td>
<td></td>
</tr>
<tr>
<td>2.3</td>
<td>9 9</td>
<td></td>
</tr>
<tr>
<td>Lipid-lowering therapy</td>
<td>1 1</td>
<td></td>
</tr>
</tbody>
</table>

Score of 9 = pretest probability of 10%; score of 10 = pretest probability 15–20%; score of 12 = pretest probability > 30%.

MAKING A DIAGNOSIS

Mrs. X suffers from claustrophobia and does not want to have an MRI scan. Consequently, you order a duplex ultrasonogram to evaluate her renal arteries. The report reads “technically difficult study; no evidence for renal artery stenosis.”

Have you crossed a diagnostic threshold for the leading hypothesis, renovascular hypertension? Have you ruled out the active alternatives? Do other tests need to be done to exclude the alternative diagnoses?

Worsening renal insufficiency and “adverse lifestyle changes” have been ruled out by the history and unchanged serum creatinine. Primary aldosteronism needs to be considered in patients with resistant hypertension and hypokalemia.

Alternative Diagnosis: Primary Hyperaldosteronism

Textbook Presentation
Primary hyperaldosteronism is usually diagnosed when a patient with hypertension has unexplained hypokalemia.

Disease Highlights
A. Results from a unilateral aldosterone-producing adenoma in 30–60% of cases (Conn’s syndrome)
B. Results from idiopathic adrenal hyperplasia in most other patients
C. True prevalence unknown but could be as high as 12% in selected populations of patients with resistant hypertension
D. Pathophysiology
   1. High aldosterone levels lead to salt and water retention and potassium wasting.
   2. Because aldosterone is being produced autonomously, it is not suppressed by volume expansion, as it is normally.
   3. Volume expansion suppresses plasma renin levels.
E. About 30% of patients with primary hyperaldosteronism are eukalemic.

Evidence-Based Diagnosis
A. Should consider in patients with hypertension and hypokalemia or with resistant hypertension regardless of potassium level
B. Diagnosis potentially complicated; may be best done in consultation with an endocrinologist
C. The aldosterone–renin ratio (ARR) most commonly used screening test
   1. Hypokalemia must be corrected before testing.
   2. Patients should eat a liberal salt diet before testing (would normally suppress aldosterone).
   3. Ideally, patients are off all medication, because many medications affect renin levels; in practice, this often cannot be done.
      a. Calcium channel blocker, alpha blockers, and beta blockers probably do not affect result.
      b. Spironolactone must be stopped.
      c. ACE inhibitor can falsely elevate renin levels.
   4. Measure plasma aldosterone (ng/dL) and plasma renin (ng/mL/h) simultaneously in the morning after the patient has been ambulatory for 2 h.
   5. Mean ARR 4–10 in patients with essential hypertension; mean of 30–50 in patients with primary hyperaldosteronism
   6. Studies of test characteristics of ARR are poorly done; reported sensitivities range from 44–98%; specificities 66–99%.
   7. See algorithm in Figure 26–1 for suggested approach.

Treatment
A. Surgery for adenomas
B. Otherwise, treat with the aldosterone antagonist, spironolactone.

CASE RESOLUTION
Because Mrs. X is somewhat overweight, and the duplex ultrasonogram was technically difficult, the normal study does not rule out renovascular hypertension. Options at this point included performing an imaging study with a better sensitivity, such as MRA, and testing for the alternative diagnosis of primary hyperaldosteronism. Considering her risk factors, renovascular hypertension is much more likely
Patient with hypertension and hypokalemia (not diuretic induced), or resistant hypertension

Measure ARR

- ↑ Renin
- ↑ Aldo
- ARR ≈ 10
  - Consider other diagnoses:
    - Renovascular HTN
    - Diuretic use
    - Renin-secreting tumor
    - Malignant HTN
    - Coarctation

- ↓ Renin
  - ↑ Aldo (> 15 ng/dL)
  - ARR > 20
  - Possible primary hyperaldosteronism
    - Confirm lack of suppression of aldosterone (replete K, oral salt loading for 3 days, measurement of 24-h urine aldosterone, Na, K)
    - Urine Na ≥ 200 mEq and urine aldosterone ≥ 14 µg/24 h = primary hyperaldosteronism
    - CT or MRI scan to look for adenoma or hyperplasia

- ↓ Renin
  - ↓ Aldo
  - Consider CAH, Cushing’s

ARR, aldosterone–renin ratio; HTN, hypertension; CAH, congenital adrenal hyperplasia

Figure 26-1. Algorithm for diagnosing primary aldosteronism. (Adapted, with permission, from Young et al. Trends in Endocrinology and Metabolism. 1994;5:97–106.)

Treatment of Atherosclerotic Renovascular Hypertension

A. Not clear which patients benefit from revascularization
B. Asymmetric renal blood flow on nuclear studies and ultrasonographic renal resistance index might identify responders.
C. Cure of hypertension is unusual, but number of medications necessary to achieve control often reduced
D. Revascularization might preserve renal function.
E. Risk factor management (eg, cholesterol, smoking, diabetes mellitus) important
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CHIEF COMPLAINT

Mr. J is a 45-year-old man with a 10-year history of hypertension. When you last saw him 1 year ago, his BP was 160/95. He ran out of his medications 6 months ago and was unable to obtain refills because of financial problems. Today he has stopped by to see your nurse for new prescriptions. Because he complains of a headache, she checks his BP and then runs to find you because it is 220/120.

At this point, what is the leading hypothesis, and what are the active alternatives? What other tests should be ordered?

ORGANIZING THE DIFFERENTIAL DIAGNOSIS

Mr. J’s BP clearly needs to be lowered, and the primary question is how quickly this needs to be accomplished. In other words, is this a hypertensive emergency or hypertensive urgency? The definitions are not totally standardized, but most experts define hypertensive emergency as a situation in which it is necessary to immediately lower BP (not necessarily to normal ranges) to prevent or limit TOD. The common associated clinical syndromes include malignant hypertension (retinopathy and acute nephrosclerosis), hypertensive encephalopathy, pulmonary edema, myocardial ischemia, intracranial hemorrhage, aortic dissection, and preeclampsia–eclampsia. In hypertensive urgencies, it is desirable to lower the BP within a few hours. Examples include patients with “upper levels” of stage 3 hypertension (stage 3 is defined as > 180/110) and severe perioperative hypertension (Table 26–8).

To some extent, the degree of the acute TOD in patients with very elevated BP depends on the time course of the BP elevation. For example, normotensive women who develop acute hypertension from eclampsia can have significant TOD at pressures of 160/100, whereas patients with chronic hypertension can be asymptomatic at much higher pressures. So, despite his very elevated BP, it is quite likely that Mr. J falls into the “hypertensive urgency” rather than the “hypertensive emergency” category. Nevertheless, hypertensive emergency is always the “can’t miss” diagnosis in such patients.

Table 26–8. Diagnostic Hypotheses for Mr. J

<table>
<thead>
<tr>
<th>Diagnostic Hypotheses</th>
<th>Clinical Clues</th>
<th>Important Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leading hypothesis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertensive urgency</td>
<td>Absence of hypertensive emergency syndromes</td>
<td></td>
</tr>
<tr>
<td>Active alternative: can’t miss</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertensive emergencies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction/ischemia</td>
<td>Chest pain</td>
<td>ECG, cardiac enzymes</td>
</tr>
<tr>
<td>Aortic dissection</td>
<td>Chest, back pain, diastolic murmur</td>
<td>CXR, TEE, chest CT</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>Dypsnea, rales</td>
<td>CXR</td>
</tr>
<tr>
<td>Hypertensive encephalopathy</td>
<td>Headache, nausea/vomiting, delirium, seizures, coma, papilledema</td>
<td>MRI</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>Headache, nausea/vomiting, coma, focal neurologic symptoms</td>
<td>Head CT</td>
</tr>
<tr>
<td>Malignant hypertension</td>
<td>Papilledema, retinal hemorrhages/exudates; renal insufficiency</td>
<td>Serum creatinine, urinalysis</td>
</tr>
</tbody>
</table>
ings of confusion, vomiting, or focal weakness or numbness. He generally appears well and is clearly happy to have a new job with insurance. Physical exam confirms BP of 220/120, pulse of 84, and RR of 16. It is difficult to see his disks on fundoscopic exam, but you do not think there is papilledema. Lungs are clear, jugular venous pressure (JVP) is not elevated, there is an S4 and a 2/6 systolic ejection murmur without an S3, abdomen is nontender, there is no peripheral edema, and neurologic exam is normal.

Is the clinical information sufficient to make a diagnosis? If not, what other information do you need?

Leading Hypothesis: Hypertensive Urgency

Textbook Presentation
A patient with chronic hypertension presents with extremely high BP; by definition, patients have no symptoms or signs of acute TOD.

Evidence-Based Diagnosis
A. Must rule out acute TOD through history, physical, and selected lab tests
B. All patients must have a serum creatinine and urinalysis.
C. Patients with symptoms suggestive of myocardial ischemia or pulmonary edema should have an ECG, chest x-ray film (CXR), and cardiac enzymes.
D. Patients with neurologic signs or symptoms need a head CT scan.

A hypertensive emergency is defined by the presence of clinical symptoms, not by the degree of BP elevation.

MAKING A DIAGNOSIS
Mr. J’s serum creatinine is 1.4, unchanged from 1 year ago. His urinalysis is normal. Mr. J wants to know if he can have a couple of acetaminophen tablets for his headache, get his prescriptions, and leave; he has to pick up his son at school.

Have you crossed a diagnostic threshold for the leading hypothesis, hypertensive urgency? Have you ruled out the active alternatives? Do other tests need to be done to exclude the alternative diagnoses?

Alternative Diagnosis: Hypertensive Emergencies
Acute coronary syndromes, aortic dissection, pulmonary edema, and subarachnoid hemorrhage are discussed in other chapters. This section focuses on hypertensive encephalopathy.

Textbook Presentation
Patients present with the acute or subacute development of lethargy, confusion, headache, and visual disturbances, sometimes followed by seizures (focal or generalized) and coma. The syndrome can occur with or without proteinuria and retinopathy.

Disease Highlights
A. Cerebral blood flow is autoregulated within specific limits.
   1. In normotensive people, cerebral blood flow is unchanged between mean arterial pressures (MAP) of 60–120: mean arterial pressure = [(2 × diastolic) + systolic]/3
      a. Cerebral vasoconstriction limits hyperperfusion up to a MAP of 180.
      b. Above a MAP of 180, autoregulation is overwhelmed.
   2. In hypertensive patients, cerebral blood flow can be maintained at MAPs of up to 200.
      a. Thought to be due to arteriolar thickening
      b. Such patients also need higher MAPs to maintain adequate cerebral blood flow (ie, abrupt lowering of the BP to a MAP of < 100–110 can potentially lead to cerebral ischemia).
B. Failure of autoregulation leads to cerebral vasodilation and cerebral edema.

Evidence-Based Diagnosis
A. Hypertensive encephalopathy is primarily a clinical diagnosis.
   B. Head CT should be done to exclude intracranial hemorrhage (intracerebral or subarachnoid bleeding) and acute ischemic stroke.
   C. MRI findings include posterior leukoencephalopathy (white matter edema).
      1. Predominantly affects white matter of the parieto-occipital regions
      2. Occasionally found in the brain stem or other regions of the brain
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3. Usually symmetric but not always
4. Can sometimes see on CT
5. Posterior leukoencephalopathy also seen with eclampsia and use of some immunosuppressive agents and cytotoxic drugs
6. Reversible with treatment of hypertension or removal of inciting agent

Treatment
A. Treating hypertension in the setting of hypertensive encephalopathy
1. All patients should be admitted to the hospital; many will need to be treated in the ICU with IV medications.
2. Little or no evidence to guide choice of specific drugs or rate of BP lowering in hypertensive encephalopathy
3. Guidelines recommend lowering the MAP by not more than 25% in the first 2 h and achieving a BP of 160/100 (MAP = 120) within 6 h.
4. Agents commonly used include labetalol and enalapril, both of which are thought to maintain cerebral blood flow (Table 26–9).
5. Some authors strongly recommend ACE inhibitors and beta blockers, because patients generally have high renin levels.

Table 26–9. Treatment of Hypertensive Emergencies

<table>
<thead>
<tr>
<th>Target Organ Involved</th>
<th>Suggested Approach</th>
<th>Example of IV Medication</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic dissection</td>
<td>Beta blocker or alpha/beta blocker; vasodilator such as nitroprusside only after beta blockade</td>
<td>Labetalol: alpha/beta blocker Nitroprusside: vasodilator</td>
<td>Heart block, nausea/vomiting, bronchospasm cyanide toxicity, hypotension, nausea/vomiting</td>
</tr>
<tr>
<td>Hypertensive encephalopathy</td>
<td>Alpha/beta blocker or ACE inhibitor; avoid clonidine</td>
<td>Enalaprilat: ACE inhibitor</td>
<td>Hypotension, renal failure</td>
</tr>
<tr>
<td>Cerebral infarction or hemorrhage</td>
<td>Avoid centrally acting agents; avoid rapid decrease in BP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial ischemia/infarction</td>
<td>Beta blocker, nitroglycerin</td>
<td>Nitroglycerin: venodilator</td>
<td>Headache, vomiting</td>
</tr>
<tr>
<td>Acute pulmonary edema</td>
<td>Diuretics, ACE inhibitor</td>
<td>Furosemide: diuretic</td>
<td>Hypokalemia, dehydration, hypotension</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>Diuretics with caution, calcium blockers</td>
<td>Nicardipine: calcium channel blocker</td>
<td>Reflex tachycardia, flushing, hypotension</td>
</tr>
<tr>
<td>Eclampsia</td>
<td>Hydralazine, labetalol, calcium blockers; avoid nitroprusside</td>
<td>Hydralazine: arterial vasodilator</td>
<td>Hypotension, reflex tachycardia</td>
</tr>
</tbody>
</table>
agent such as labetalol to maintain a systolic BP between 140 and 160, carefully monitoring for signs of cerebral hypoperfusion.

b. In patients with subarachnoid hemorrhage, use labetalol if the diastolic BP is > 130; avoid vasodilators such as nitroprusside or nitroglycerin because they increase intracranial pressure.

c. One study found that oral nimodipine (a dihydropyridine calcium channel blocker) improved outcomes when started within 4 days of a subarachnoid hemorrhage.

CASE RESOLUTION

Mr. J has no signs or symptoms of stroke, intracranial hemorrhage, pulmonary edema, myocardial ischemia, or aortic dissection. He has a headache, but he does not have other symptoms, such as lethargy or confusion, to suggest hypertensive encephalopathy. Although his fundi were not optimally visualized, it is unlikely that he has malignant hypertension considering his stable renal function and normal urinalysis. There is no need to perform any further testing at this point.

Mr. J’s previous regimen was hydrochlorothiazide, 25 mg; atenolol, 50 mg; and amlodipine, 10 mg. You instruct him to fill his prescriptions after he picks up his son at school, to take an atenolol tonight, and then to take all 3 medications in the morning. When he returns in 2 days, his BP is 160/100; 3 weeks later it is 145/90.

Treatment of Hypertensive Urgency

A. In selected situations, such as perioperative hypertension, it is necessary to reduce the patient's BP within a few hours.

1. The BP goal is 160/110 over several hours.

2. Can use short-acting oral medications such as captopril (6.25–25 mg), felodipine (5 mg), furosemide (20 mg), or clonidine (0.1 mg)

3. Although sublingual preparations exist, they can cause abrupt and somewhat unpredictable BP lowering.

NEVER use sublingual nifedipine to lower BP.

B. However, in stable outpatients with chronically elevated BP, there is NOT an urgent need to reduce the BP, and it is fine if it takes several days for the BP to be reduced.

1. In patients who have stopped their medications, it is sufficient just to restart them.

2. Can also just choose 2 agents, such as a diuretic and either beta blocker or ACE inhibitor, and start them

3. Whether or not such patients need to be observed depends on their reliability and comorbid conditions.

C. Too rapid reduction of BP can lead to hypotension and cerebral hypoperfusion.

Do not be in a hurry to normalize BP!

REVIEW OF OTHER IMPORTANT DISEASES

Pheochromocytoma

Textbook Presentation

The classic presentation is a patient with attacks of paroxysmal hypertension, headache, palpitations, and sweating occurring several times daily, weekly, or every few months. Patients generally have orthostatic hypotension on physical exam.

Diseases Highlights

A. Ninety-five percent of patients have headache, sweating, OR palpitations.

B. Ten percent of pheochromocytomas are malignant and tend to have a less typical presentation.

C. 10–15% are familial (multiple endocrine neoplasia type II, von Hippel-Lindau disease, neurofibromatosis); these are more often asymptomatic (and normotensive) than sporadic cases.

D. See Table 26–10 for distribution of symptoms, taken from a series of patients with pheochromocytoma, about half of whom presented with paroxysmal hypertension and about half of whom had persistent hypertension.

Evidence-Based Diagnosis

A. Pretest probability of 0.5% in hypertensive patients who have suggestive symptoms
B. Pretest probability of 4% in patients with incidentally discovered adrenal masses

C. Plasma metanephrine is the single best test to rule out pheochromocytoma (Table 26–11).
   1. If the plasma metanephrine is normal, pheochromocytoma is excluded.
   2. If the plasma metanephrine is > 2.5 times normal, pheochromocytoma is very likely, and CT or MRI should be done to look for an adrenal mass
      a. CT: sensitivity of 93–100% for detecting adrenal pheochromocytomas, 90% for extra-adrenal tumors; specificity 50–70%
      b. MRI: similar sensitivity for adrenal tumors
   3. If the plasma metanephrine is mildly elevated, the test should be repeated, along with plasma catecholamines.
      a. Some patients will also require clonidine or glucagon suppression testing.
      b. Should proceed to imaging once biochemical diagnosis confirmed

Treatment

A. Surgery is the definitive treatment.

B. Must give both alpha- and beta-blocking agents preoperatively
   1. The alpha blocker opposes catecholamine-induced vasoconstriction.
   2. The beta blocker opposes the reflex tachycardia that occurs with alpha blockade.
   3. Should be done in consultation with an endocrinologist because of the complexities of ensuring adequate alpha blockade

   Never give a patient with a pheochromocytoma a beta blocker without first giving an alpha blocker.

C. Twenty-seven to 38% of patients have residual hypertension.

D. Patients with familial pheochromocytoma often have multiple, bilateral tumors; the optimal approach to therapy is not clear.

Table 26–10. Signs and Symptoms in Pheochromocytoma

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Pheochromocytoma and Paroxysmal Hypertension</th>
<th>Pheochromocytoma and Persistent Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe headaches</td>
<td>92%</td>
<td>72%</td>
</tr>
<tr>
<td>Sweating</td>
<td>65%</td>
<td>69%</td>
</tr>
<tr>
<td>Palpitations and/or tachycardia</td>
<td>73%</td>
<td>51%</td>
</tr>
<tr>
<td>Anxiety/panic</td>
<td>60%</td>
<td>28%</td>
</tr>
<tr>
<td>Tremulousness</td>
<td>51%</td>
<td>28%</td>
</tr>
<tr>
<td>Chest or abdominal pain</td>
<td>48%</td>
<td>28%</td>
</tr>
<tr>
<td>Nausea ± vomiting</td>
<td>43%</td>
<td>26%</td>
</tr>
</tbody>
</table>

Table 26–11. Diagnostic Tests for Pheochromocytoma

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>LR+</th>
<th>LR−</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma metanephrine level</td>
<td>99%</td>
<td>89</td>
<td>9.00</td>
<td>0.010</td>
</tr>
<tr>
<td>Plasma catecholamine level</td>
<td>85%</td>
<td>80</td>
<td>4.25</td>
<td>0.188</td>
</tr>
<tr>
<td>24-h urine catecholamine</td>
<td>83%</td>
<td>88</td>
<td>6.92</td>
<td>0.190</td>
</tr>
<tr>
<td>24-h urine metanephrine</td>
<td>76%</td>
<td>94</td>
<td>12.7</td>
<td>0.260</td>
</tr>
<tr>
<td>24-h urine vanillymandelic acid level</td>
<td>63%</td>
<td>94</td>
<td>10.5</td>
<td>0.390</td>
</tr>
</tbody>
</table>