Next steps when BP won’t come down

A poor response to therapy should trigger a search for a secondary cause of hypertension. Use this review as your guide.

Hypertension, the most common chronic condition encountered in the ambulatory setting, affects about 30% of US adults, less than a third of whom achieve adequate control. In many cases, poor adherence to the treatment regimen is to blame. In about 5% to 10% of patients with hypertension, however, the lack of response may be an indication of a secondary cause—and the need to search for an underlying, and possibly curable, condition.

Features suggestive of secondary hypertension include an early age of onset (<30 years); a poor response to an appropriate 3-drug regimen, at least one of which is a diuretic; and renal insufficiency. The text and **TABLE** that follow detail causes of secondary hypertension, appropriate diagnostic tests, and treatment.

What to include in the workup

Whether you’re doing an initial evaluation of a patient with high blood pressure (BP) or examining a patient with resistant hypertension, the history should focus on the duration of hypertension, previous BP levels, and comorbid conditions. It is also important to take a targeted family history, inquiring about hypertension as well as genetic disorders that increase the likelihood of secondary hypertension.

**Inherited diseases** associated with secondary hypertension include polycystic kidney disease, multiple endocrine neoplasia type 2 (MEN2), and von Hippel-Lindau syndrome. All are inherited in an autosomal dominant pattern. Patients with von Hippel-Lindau syndrome may present with multiple tumors, which can develop in the eyes, brain, adrenal glands, pancreas, liver, spinal cord, kidneys, or other parts of the body. Pheochromocytoma is a manifestation of both MEN2 and von Hippel-Lindau syndrome, and some specialists recommend that everyone with a family history of either condition undergo screening for pheochromocytoma.
BP measurement is key

The physical examination should start with a calculation of body mass index, as well as a careful measurement of BP. The patient should be seated quietly in a chair for ≥5 minutes, with both feet on the floor and the arm being tested supported at heart level.

Unfortunately, reliability on the office BP measurement can be a confounding factor in the diagnosis of hypertension. “White coat hypertension”—in which BP is persistently elevated in the office and persistently normal in nonclinical settings—should be considered in patients who have high BP but no other signs or symptoms, and ambulatory monitoring used to rule out hypertension.15,16

Physicians also need to consider the opposite effect: Masked hypertension, characterized by normal office readings and elevated ambulatory readings, is more serious, of course, with patients at higher risk for end organ damage from unrecognized hypertension.17,18 Asking patients who self-monitor what type of BP readings they’re getting can be helpful in identifying masked hypertension. Ambulatory monitoring may be used to identify this condition, as well.

Other components in the physical workup include a fundoscopic exam; assessment of the thorax for murmurs and the abdomen for enlarged kidneys, masses, and abnormal aortic pulsation; auscultation for abdominal and carotid bruits; palpation of the thyroid gland; and palpation of the lower extremities for edema and pulses.

Include these tests in the workup

Routine tests for a patient with hypertension include:

- electrocardiogram
- blood glucose and hematocrit
- serum potassium, creatinine, and fasting lipid profiles
- urinalysis with measurement of microalbumin.

Microalbuminuria, a sensitive marker of early renal disease, is defined as a urinary albumin excretion between 30 and 300 mg/d.19 The albumin-creatinine ratio (30-300 mcg/mg), measured in spot urine specimens, is a more convenient way to detect it.20

Suspicous findings prompt further testing.

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) recommends specific testing—much of it detailed below—if any aspect of the initial evaluation raises suspicion of a secondary cause or the patient has hypertension that’s of sudden onset or hard to control.21 (According to the National Heart, Lung, and Blood Institute, JNC 8 is due for release later this year.)

Kidney disease may be a consequence or a cause

The overall prevalence of hypertension in patients with renal disease is 60%,22 but varies according to the type of nephropathy. Eighty-seven percent of patients with diabetic nephropathy also have hypertension, and hypertension and diabetes are the 2 most common causes of end-stage renal disease.23,24

A combination of 2 or more drugs is usually needed to achieve the target BP of <130/80 mm Hg in patients with diabetes.21 ACE inhibitors and angiotensin receptor blockers have been found to slow the progression of diabetic nephropathy.25-27

Is renal artery stenosis to blame?

Renal artery stenosis is the most common form of secondary hypertension that’s reversible, affecting about 0.2% to 3.1% of hypertensive patients.5,6,26 The condition leads to renal ischemia, thereby stimulating the renin-angiotensin-aldosterone axis and causing secondary hyperaldosteronism.

In younger patients, especially women between 15 and 50 years of age, fibromuscular disease is the most common cause of renovascular hypertension.29,30 In older patients, atherosclerosis (which accounts for 90% of renovascular hypertension) is more likely.29,30

The choice of initial imaging tests includes duplex renal ultrasonography, magnetic resonance angiography (MRA), and spiral computed tomographic angiography. Contrast angiography is the gold standard, but it carries a risk of contrast-induced nephropathy. Duplex ultrasonography and MRA do not use iodinated contrast media,
Secondary hypertension: What you’ll see, what to test for

<table>
<thead>
<tr>
<th>Secondary cause*</th>
<th>Signs and symptoms</th>
<th>Screening tests</th>
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<tr>
<td>Renal disease</td>
<td>Depends on underlying cause (eg, diabetes, polycystic kidney disease, glomerulonephritis)</td>
<td>Serum creatinine, urinalysis, renal ultrasound</td>
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<tr>
<td>Renal artery stenosis</td>
<td>Abdominal or flank bruits</td>
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<td>Pheochromocytoma</td>
<td>Paroxysms of palpitations, diaphoresis, headaches</td>
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<td>Cushing’s syndrome</td>
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<td>Obesity, daytime somnolence, nighttime snoring</td>
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<tr>
<td>Coarctation of the aorta‡</td>
<td>Murmur of anterior and posterior thorax; claudication and weak femoral pulses</td>
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CT, computed tomography; MRA, magnetic resonance angiography; OSA, obstructive sleep apnea; PA/PRA, plasma aldosterone-plasma renin activity.

*Secondary hypertension may also be drug-induced, related to pregnancy (hypertension complicates up to 15% of pregnancies), or associated with inherited syndromes.

†Highly prevalent in obese patients.

‡Higher prevalence in childhood hypertension; rarely diagnosed in adulthood.

and are safe for patients with chronic kidney disease.8

**Treatment.** Percutaneous transluminal renal artery angioplasty is a treatment option for patients with renal artery stenosis. Angioplasty achieves higher cure rates for patients with fibromuscular dysplasia than for those with atherosclerotic renal artery stenosis.31 Most patients referred for renal artery revascularization have atherosclerosis. Because they’re generally older individuals with comorbidities, the benefits of stent revascularization for this group is controversial. Such patients require antihypertensive therapy with drugs that block the renin-angiotensin system.32

**Endocrine disorders must be ruled out**

Primary hyperaldosteronism is thought to be present in 0.3% to 1.4% of patients with hypertension.5,6 The prevalence varies widely from one source to another, however, and may be as high as 5% to 20% among patients with resistant hypertension.33,34

Hyperaldosteronism is related to either an aldosterone-secreting adrenal adenoma (in about 40% of cases) or bilateral adrenal hyperplasia (in the remaining 60%), and leads to increased sodium reabsorption and, typically, to a loss of potassium.35

Renin-secreting tumor, which usually arises from the juxtaglomerular cells of the kidney, is a rare cause of hyperaldosteronism. Extrarenal renin-secreting tumors have also been reported.36

**What should raise your suspicion.** Suspect hyperaldosteronism in patients who have both hypertension and hypokalemia, but keep in mind that not all patients with hyperaldosteronism have low serum potassium.37 Further laboratory evaluation should include a simultaneous measurement of plasma aldosterone (PA) and plasma renin activity (PRA). Patients with hyperaldosteronism will have elevated PA and suppressed PRA.

**Testing considerations.** It is important to ensure that the PA/PRA test is performed

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**INSTANT POLL**

Do you screen patients with resistant hypertension for genetic disease?

- Yes, I routinely take a detailed family history.
- No, hypertension is rarely related to an inherited disorder.
- Only if there are other signs of genetic disease.
- Other (Please specify) ________

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in the morning, with the patient in an upright position. He or she should be on a high sodium diet in preparation for the test, consuming 2 to 3 grams of sodium per meal for ≥2 days.

In patients with a positive PA/PRA ratio (≥20), a 24-hour urinary aldosterone excretion test should be performed. A finding >12 to 14 mcg, along with a PRA <1.0 ng/mL per hour, confirms the diagnosis of primary hyperaldosteronism. Computed tomography or magnetic resonance imaging of the adrenal glands will distinguish between aldosterone-producing adenoma and bilateral adrenal hyperplasia.

Treatment. Laparoscopic adrenalectomy is the accepted surgical treatment of primary hyperaldosteronism. Patients with bilateral disease due to idiopathic hyperaldosteronism are not candidates for surgery and should be treated medically, with potassium-sparing diuretics such as spironolactone.

Cushing’s syndrome is marked by rapid weight gain
High BP may be a manifestation of Cushing’s syndrome, which affects 0.1% to 0.5% of patients with hypertension. Other signs and symptoms of Cushing’s syndrome include fatigue, weakness, hirsutism, amenorrhea, moon facies, dorsal hump, purple striae, truncal obesity, and hypokalemia. Rapid weight gain is the most common manifestation, and typically the one for which patients seek medical attention.

The most widely used screening test for Cushing’s syndrome is a 24-hour urine collection measuring urinary-free cortisol. Normal urinary cortisol excretion is 20 to 100 mcg/dL in 24 hours; most patients with Cushing’s syndrome produce >250 mcg/dL in that time frame.

Once hypercortisolism is established, determination of the cause is the next step. A serum adrenocorticotropic hormone (ACTH) level is needed to localize it. Normal (9-52 pg/mL) or elevated ACTH indicates a pituitary or ectopic source, while low levels of ACTH are an indication of an adrenal source.

Treatment. Surgical resection of the tumor is often curative. For pituitary tumors, transsphenoidal resection is the standard of care. For adrenal adenomas, unilateral adrenalectomy is the best option.

Pheochromocytomas:
Most are adrenal, sporadic, and benign
Pheochromocytomas—neuroendocrine, catecholamine-secreting tumors that develop from the adrenal medulla—are another cause of secondary hypertension. Catecholamines include norepinephrine and epinephrine and, rarely, dopamine secreted either intermittently or continuously. The prevalence of pheochromocytoma is 0.1% to 0.3% among patients with hypertension. A “rule of 10” (90:10 ratio) is often applied to pheochromocytomas because of the following:

- 90% of pheochromocytomas are located in the adrenal glands; the remaining 10% are extra-adrenal and can occur anywhere along the sympathetic chain
- 90% are sporadic; 10% are familial
- 90% are benign; 10% are malignant
- 90% are found in adults; 10% affect children.

Signs and symptoms of pheochromocytomas include palpitations, headache, dyspnea, diaphoresis, and flushing, as well as paroxysmal hypertension. Measurement of 24-hour urinary catecholamines and their metabolites has been the screening test of choice, but recent evidence suggests that measurement of plasma metanephrine and normetanephrine is a far more sensitive screen.

Treatment. Surgical resection is the treatment of choice. Alpha blockade is started 7 to 10 days preoperatively; a beta-blocker is added only after an adequate alpha blockade has been established, as unopposed alpha stimulation could precipitate a hypertensive crisis. Laparoscopic adrenalectomy is routinely performed for small (<5 cm) pheochromocytomas.

Don’t forget these (relatively) common secondary causes
Obstructive sleep apnea (OSA) is one of the most common conditions associated with resistant hypertension. Signs and symptoms...
include snoring, daytime somnolence, and obesity (body mass index ≥30 kg/m²).

OSA involves upper airway collapse during inspiration, causing intermittent hypoxemia with resultant sympathetic nervous system activation. The underlying mechanism of OSA-induced hypertension is strongly related to sympathetic activation.

Overnight polysomnography is required for diagnosis.

Continuous positive airway pressure is the treatment of choice for patients unable to lose weight.

Pregnancy-induced hypertension is the most common medical problem encountered in pregnancy. It occurs in up to 15% of pregnancies, either during the pregnancy itself or postpartum. Postpartum hypertension may be related to preexisting chronic hypertension or to the persistence of gestational hypertension or preeclampsia, which usually occurs after 20 weeks’ gestation and is characterized by the presence of hypertension and proteinuria.

Methyldopa and labetalol are commonly used treatments for hypertension during pregnancy.

Drug-induced hypertension. Several drugs can cause or exacerbate hypertension, rendering it resistant to therapy. A careful review of the patient’s medication regimen is essential. Generally, drug-induced hypertension falls into 2 broad categories based on mechanism of action: volume overload and sympathetic activity.

Corticosteroids can elevate BP in a dose-dependent manner, as a result of volume overload. Glycyrrhizic acid, the main ingredient in licorice, produces a state of excess mineralocorticoid, with a similar effect. Estrogen-containing oral contraceptives can cause an increased synthesis of angiotensin in the liver, resulting in greater aldosterone secretion and volume overload.

Drugs that stimulate sympathetic activity include cocaine, ephedrine, amphetamine, phenylephrine, phenylpropanolamine, caffeine, and alcohol. Nonsteroidal anti-inflammatory drugs may interfere with the action of ACE inhibitors and cause renal vasoconstriction, leading to sodium and water retention and hypertension.

Discontinuation of the medication in question is preferable. In many cases, an agent that does not affect BP can be found to replace it.

If the patient is a child
Hypertension is uncommon in young people. However, coarctation of the aorta, a congenital narrowing associated with secondary hypertension, is typically diagnosed in childhood. In rare cases, the condition remains undetected well into adulthood. Clinical signs include weak femoral pulses, visible pulsations in the neck, a systolic murmur of the anterior and posterior thorax, and elevated BP in the upper extremities with low BP in the lower extremities.

Thus, once hypertension is confirmed in a young patient, BP should be measured in both arms and legs. Delayed or absent femoral pulses and a difference in systolic BP of ≥20 mm Hg between the arms and legs provide evidence of aortic coarctation. In adults, stenting is the initial treatment for this condition because of the morbidity associated with surgery. Stenting is an option for children with this condition, as well.

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