CLINICAL REVIEW

Resistant Hypertension

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Resistant hypertension (RH) is defined as blood pressure above a goal despite adherence to at least 3 optimally dosed antihypertensive medications of different classes, one of which is a diuretic. Evaluation of possible RH begins with an assessment of adherence to medications. The white-coat effect should be ruled out by out-of-office blood pressure monitoring. Obesity, heavy alcohol intake, and interfering substances all contribute to RH. Dietary sodium restriction is an important part of management. RH may be secondary to problems such as renal disease, obstructive sleep apnea, or aldosteronism, and testing for these conditions should be considered. Adequate diuretic treatment is a key part of therapy. Chlorthalidone is more effective than hydrochlorothiazide in reducing blood pressure because it is more potent and lasts longer. In addition, it may reduce cardiovascular events to a greater extent than hydrochlorothiazide. When glomerular filtration rate is <30 mL/min, a loop diuretic usually is needed. The addition of spironolactone, with careful attention to potassium levels, is an evidence-based strategy for the treatment of RH. Other strategies include use of a vasodilating β-blocker, adding a long-acting nondihydropyridine calcium channel blocker, or adding clonidine. When blood pressure is not coming under control despite 4 or 5 agents, referral to a hypertension specialist may be warranted. (J Am Board Fam Med 2012;25:487–495.)

Keywords: **Hypertension, Review**

Resistant hypertension is defined as blood pressure (BP) above goal (usually 140/90 mm Hg) despite adherence to a combination of at least 3 optimally dosed antihypertensive medications of different classes, one of which ideally is a diuretic.[1] What constitutes an "optimal dose" of medication is presumably at least a moderate dose but not necessarily a maximum dose. Patients requiring ≥4 antihypertensive medications (even if controlled) are classified as having resistant hypertension. Based on trials during which participants were aggressively titrated to reach target BP, the prevalence of resistant hypertension has been estimated to be 20% to 30%.[1] More recently, an analysis of US National Health and Nutrition Examination Survey data suggests that among hypertensive adults treated with medications, approximately 13% have resistant hypertension.[2] A recent study of resistant hypertension in Spain found a similar rate of 12%.[3] Although this prevalence is lower than initially thought, it is nonetheless quite high and likely will get worse. The goal of this narrative review is to discuss the evaluation and management of patients with resistant hypertension. Note that most recommendations are Strength of Recommendation Taxonomy (SORT) grade C because of blood pressure being a disease-oriented outcome.

This article was externally peer reviewed.
Submitted 20 September 2011; revised 28 November 2011; accepted 5 December 2011.
From the Department of Family Medicine, University of North Carolina at Chapel Hill School of Medicine, Chapel Hill.
Funding: none.
Conflict of interest: The author has served on the Medical Advisory Board to SunTech Medical, the maker of a model of ambulatory blood pressure monitors.
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Assess Adherence to Therapy

Evaluation of the patient with suspected resistant hypertension should begin with an assessment of adherence to the prescribed management plan. In practice, it can be difficult to ascertain whether a patient truly is adherent to an optimally dosed 3-drug regimen and therefore qualify as having resistant hypertension. Instructing patients to bring all their medicines to an appointment affords the opportunity to reconcile medication lists and re-

view how they take their medications. Nonjudgmental approaches to asking about adherence may provide the most accurate answers.[4] A possible approach is to say something like, "Many patients will occasionally miss a dose—or even a few doses—of their medication(s). How often is missing medications a problem for you?" Side effects also may contribute to poor adherence to medication schedules. Asking about and addressing side effects may enhance patients' understanding and adherence.

Patients may have difficulty adhering to antihypertensive medications because of financial reasons, or they may not understand the medication regimen because of health literacy, cultural, or language barriers. Therefore, it is important to keep the medication regimen as simple as possible. A once-daily regimen improves patients' adherence to antihypertensive medications.[5] Fixed-dose combination pills, many of which are available as generics, also may improve adherence.[6]

Rule Out Measurement Error and the White-Coat Effect

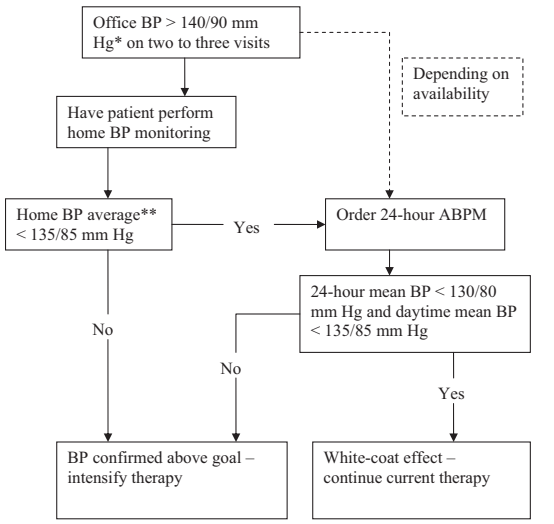
Attention to proper technique when measuring BP is important to assure readings that are as accurate as possible. Confirm that BP has been measured accurately using an appropriately sized cuff, with the patient correctly positioned and not talking after at least a 5-minute rest.[7,8] A cuff that is too small will lead to overestimation of BP. Measurement in obese patients, who may have large arms, may be particularly challenging. Use of a thigh cuff or measurement at the forearm, while not ideal, may be necessary.[7]

Some patients seem to have resistant hypertension based on their office BP measurements but actually have controlled BP when assessed by out-of-office measurements—the so-called "white-coat" effect. In a study of 611 patients with office BP >140 mm Hg systolic or >90 mm Hg diastolic, nearly 40% of those taking 1 or 2 medications and almost 30% of those taking 3 medications had controlled BP on ambulatory BP monitoring.[9] In another recent study of more than 8200 patients with resistant hypertension in Spain, 38% of the resistant hypertension was attributed to the white-coat effect based on 24-hour ambulatory BP monitoring.[3] This white-coat effect may lead to unnecessary increases in dose or number of antihypertensive medications that could result in hypotension or other side effects.

Automated office BP measurements using devices that take several BPs automatically at preprogrammed intervals without an observer present may be useful to mitigate the white-coat effect.[10] Otherwise, given the high prevalence of the white-coat effect among patients suspected of having resistant hypertension based on office measurements, out-of-office BP measurements should be used to clarify status (Figure 1) (SORT C). Ambulatory BP monitoring (over 24 hours) is the ideal strategy but is not always available (or covered by insurance for this indication). An alternative to ambulatory BP monitoring is home (or self) BP monitoring.[11] Patients should choose a home BP monitor model that has been validated independently. A list of such devices is available at www.dableducational.org.

Before relying on home BP measurements, it is important to ensure that the patient has the appropriate size cuff and to check the patient's monitor

Figure 1. Ruling out the white-coat effect in patients with suspected resistant hypertension. The systematic use of out-of-office blood pressure (BP) measurements should be employed to rule out the white-coat effect. If readily available, it is reasonable to proceed directly to ambulatory BP monitoring. Otherwise, home BP monitoring can be used as an initial strategy. If the home BP monitoring confirms that BP is indeed above goal, no further testing is needed. If home BP monitoring suggests the white-coat effect, it is recommended to proceed to ambulatory BP monitoring to confirm (SORT C). *Target BP may be lower in patients with diabetes or chronic kidney disease. **Refer to Table 1. ABPM, ambulatory blood pressure monitoring. (Adapted from Refs. 11 and 52.)



against a validated clinical device. One method is to take a BP measurement with the clinical device, then take another measurement 1 minute later on the same arm using the home monitor. This might be repeated once or twice. Readings within a range of approximately 5 to 10 mm Hg (systolic and diastolic) probably are acceptable, depending on the level of accuracy needed for the particular patient and circumstance.[12] Patients also should be instructed on how to perform home BP measurements and be observed to make sure they perform them correctly. Last, a systematic approach to collecting the measurements should be used. A suggested protocol for home BP monitoring is shown in Table 1.[13] If home BP monitoring is used and readings suggest the white-coat effect, 24-hour ambulatory BP monitoring, if available, should be considered for confirmation. In a patient with otherwise uncomplicated hypertension, if the 24-hour average BP is <130/80 mm Hg (or a daytime average <135/85 mm Hg), the patient can continue current therapy. If the 24-hour average BP is ≥130/80 mm Hg (or the daytime average is ≥135/85 mm Hg), therapy should be intensified.

Consider Associated Comorbidities

Certain comorbidities or patient factors are associated with resistant hypertension. Older patients are more likely to have hypertension that is resistant to treatment.[14] However, older age itself is not a reason to withhold antihypertensive therapy from those whose BP is not controlled, and even patients 80 years and older who are treated with antihypertensives have a reduction in morbidity and mortality.[15] Many of these individuals will have isolated systolic hypertension. In older patients with coronary artery disease, the theoretical risk of excessive lowering of diastolic BP, leading to compromised myocardial perfusion, may limit the reductions in systolic BP that can be achieved comfortably. However, in this population, it seems safe to reduce BP to a diastolic measurement of 70 mm Hg.[16]

In some older patients, atherosclerosis may be so severe that it interferes with accurate BP measurement. When measuring BP using an upper-arm cuff, occlusion of the brachial artery should cause disappearance of the ipsilateral radial pulse. If the radial pulse remains palpable despite such occlusion (the Osler maneuver), "pseudohypertension" should be suspected. Clinical clues pointing to the possibility of pseudohypertension in an elderly patient include the development of dizziness or weakness temporally related to antihypertensive medications and the absence of significant target organ damage despite a very high clinic BP measurement.

Obesity is common in patients with hypertension and can make hypertension more resistant to treatment because of increased sodium and fluid retention.[14] Therefore, higher doses of antihypertensive medications often are needed. Weight loss must be emphasized not only as an important part of improving overall health but also as an important part of hypertension management (SORT C). For every kilogram of weight loss, systolic BP is reduced by approximately 1 to 2 mm Hg.[17]

Chronic kidney disease (CKD) is also common in patients with resistant hypertension.[14] CKD may result from hypertension and, like obesity, makes hypertension more resistant to treatment because of increases in sodium and fluid retention. An emphasis on dietary sodium restriction, therefore, particularly is warranted in such patients, and a diuretic is almost always required for optimal BP control (see Volume Overload). Blockade of the renin-angiotensin-aldosterone system with either an angiotensin converting enzyme (ACE) inhibitor or angiotensin-II receptor blocker (ARB) (with monitoring of serum potassium levels and glomerular filtration rate) also should be part of the hypertension management of the patient with CKD.[18]

Reconsider Secondary Causes

Once hypertension is confirmed as resistant, secondary causes of hypertension should be reconsidered (Table 2) (SORT C). Although possible secondary causes of hypertension often are considered during initial evaluation of a patient with newly diag-

Table 1. Suggested Home Blood Pressure Measurement Protocol

Have the patient perform measurements for a minimum of 5 consecutive days
On each day, 3 morning and 3 evening measurements should be performed approximately 1 minute apart without removing the cuff
Have patient record dates and times of all measurements
When calculating the average, discard the first 2 days' measurements and the first measurement of each triplicate set of measurements
Average the remaining measurements

Information from Ref. 13.

Table 2. Secondary Causes of Hypertension

More common
Aldosteronism
Obstructive sleep apnea
Renal artery stenosis
Renal parenchymal disease (can be cause or consequence)
Less common
Carcinoid syndrome
Coarctation of aorta
Cushing's Disease
Hyperparathyroidism
Pheochromocytoma
Polycythemia

Adapted from Refs. 1, 18, and 52.

nosed hypertension, patients with resistant hypertension comprise a subpopulation in which these causes will be more common. Even in these patients, however, rare causes of secondary hypertension such as pheochromocytoma are still rare. Primary aldosteronism (PA), obstructive sleep apnea (OSA), and renal artery stenosis are the most common secondary causes to reconsider.

Primary Aldosteronism

PA is now recognized as one of the most common causes of resistant hypertension. In patients referred to hypertension specialty clinics, as many as 20% demonstrate PA.[19–21] The diagnosis may have been overlooked during the initial evaluation when the patient was first diagnosed with hypertension because many of these patients actually have normal potassium levels. In one study of 1616 patients with resistant hypertension, 182 (11%) had PA. Among that 11%, however, only 83 (46%) had hypokalemia.[22] Therefore, testing for PA should be considered in patients with resistant hypertension. The best initial test is a morning plasma aldosterone-to-renin ratio. A ratio below 20 (when plasma aldosterone is reported in ng/dL and plasma renin activity is in ng/mL/hr) effectively rules out PA. A ratio of ≥20 with a serum aldosterone >15 ng/dL suggests PA, but the diagnosis must be confirmed by a salt suppression test.[23] In the study just mentioned, half of the patients with a high ratio did not have PA. The optimal diagnostic strategy for distinguishing adrenal adenoma from bilateral adrenal hyperplasia is controversial. Therefore, if a patient screens positive for PA, referral to an endocrinologist or hypertension specialist for confirmatory testing and evaluation should be considered.

Obstructive Sleep Apnea

Among patients with hypertension that is difficult to control, OSA is very common. In obese patients and those who report a history of snoring, witnessed apnea, or excessive daytime sleepiness, OSA should be suspected. The gold standard for diagnosis is a polysomnography (a sleep study), but clinical assessment tools such as the Epworth Sleepiness Scale or the Sleep Apnea Clinical Score coupled with nighttime pulse oximetry may be sufficient for the diagnosis of moderate to severe OSA, particularly if cost and availability are limiting factors.[24,25] In some patients, however, resistant hypertension may be the only sign. In one study of patients with resistant hypertension, 83% were diagnosed with unsuspected OSA on the basis of polysomnogram results.[26] Therefore, a polysomnogram should be considered in patients with resistant hypertension. In those found to have OSA, treatment with continuous positive airway pressure may help improve BP control.[27]

Renal Artery Stenosis

In younger adults, particularly women, renal artery stenosis caused by fibromuscular dysplasia is one of the most common causes of secondary hypertension. The finding of an audible, high-pitched, holosystolic renal artery bruit would raise suspicion and warrant imaging. Either magnetic resonance imaging (MRI) with gadolinium or computed tomography angiography can be used to visualize stenosis. Depending on availability, MRI might be preferable because it does not use radiation and can determine the physiologic degree of stenosis. MRI also can be used for individuals with poor renal function. If MRI and computed tomography angiography are contraindicated or not available, renal Doppler can be used, which provides useful information regarding blood flow, but its accuracy is hampered by body habitus and operator skill.[28]

Although identifying renal artery stenosis caused by fibromuscular dysplasia is important, identifying renal artery stenosis caused by atherosclerosis (usually in older adults) is less critical because evidence does not show a benefit of revascularization over medical management (ie, blood pressure control, statin, antiplatelet agents).[29]

Address Volume Overload and Interfering Substances

Volume Overload

An expansion in extracellular volume, which can be either relative or absolute, frequently contributes to resistant hypertension. Volume overload may be related to a high-sodium diet, CKD (leading to sodium retention), or both. Volume overload may not manifest as peripheral edema detectable on physical examination, yet it should be considered in the patient with persistently elevated BP despite multiple medications, even when one of the medications is a low-dose thiazide diuretic.

Patients with resistant hypertension may be more sensitive to sodium than the general hypertensive population. In one study in which patients with resistant hypertension were randomized to low-salt versus high-salt diets, mean office BP was reduced 23/9 mm Hg more in the low-salt diet group.[30] Patients with resistant hypertension should be encouraged to reduce their dietary sodium intake as much as possible (SORT C). A nutrition consultation may be worthwhile to help patients learn how to reduce the sodium content of their meals adequately.

Once dietary sodium is addressed, an initial pharmacologic step in managing patients with resistant hypertension is to increase the dose of the diuretic or change to a more potent diuretic. Chlorthalidone was the thiazide-like diuretic used in several of the large clinical trials with patient-oriented outcomes.[31,32] It is longer acting and provides greater BP reduction than equivalent doses of hydrochlorothiazide.[33,34] In addition, compared with hydrochlorothiazide, it reduces the progression to left ventricular hypertrophy and cardiovascular events to a greater degree.[35,36] Therefore, changing from hydrochlorothiazide to chlorthalidone, if applicable, is often a good initial step (SORT B). It is important to remember that low-dose thiazide diuretics only are effective when renal function is adequate. In patients with a serum creatinine value >1.8 mg/dL or a glomerular filtration rate <30 mL/min, a loop diuretic should be used.[1] The short-acting loop diuretics (furosemide and bumetanide) need to be given 2 to 3 times per day. Torsemide is a longer-acting loop diuretic.

Interfering Substances

Many exogenous substances can interfere with BP control by directly raising BP, interfering with the mechanisms of antihypertensive drugs, or both. Nonsteroidal anti-inflammatory drugs (NSAIDs), for example, not only raise BP but can interfere with the mechanism of nearly every class of antihypertensive drug. Because NSAIDs are available over the counter, it can be difficult to gauge the degree to which they may play a role in the patient with resistant hypertension. The use of NSAIDs should be discouraged or limited to the extent possible. Other agents that should be considered but that are less commonly involved in resistant hypertension include oral contraceptives, some antidepressants (eg, bupropion, venlafaxine); appetite suppressants; sympathomimetics (eg, amphetamines, cocaine, pseudoephedrine); and herbal supplements (eg, ginseng) (Table 3). Eliminating or reducing a possible interfering agent may help patients gain control of BP.

Heavy alcohol intake also will make BP much more difficult to control. Compliance with advice to reduce alcohol intake is less than 30% at 3 years, and many hypertensive patients do not even recall getting advice to limit their alcohol intake.[37,38] Therefore, anyone drinking in excess of acceptable amounts (no more than 2 drinks [1 oz ethanol] per day for men or 1 drink [0.5 oz ethanol] per day for women) should be advised (or re-advised) to reduce their intake (SORT C).

Intensify Therapy

Management of hypertension includes lifestyle modifications as well as antihypertensive medica-

Table 3. Some Substances That May Interfere with Blood Pressure Control

Acetaminophen
Alcohol
Certain antidepressants (eg, bupropion, tricyclic antidepressants, selective serotonin reuptake inhibitors, venlafaxine, monoamine oxidase inhibitors)
Corticosteroids
Cyclosporine
Dietary and herbal supplements (eg, ginseng, ephedra, ma huang, bitter orange)
Erythropoietin
Licorice (including some types of chewing tobacco)
Nonsteroidal anti-inflammatory drugs (including cyclooxygenase-2 inhibitors)
Oral contraceptives
Sympathomimetics (eg, cocaine, amphetamines, diet pills, decongestants)
Tacrolimus

Adapted from Refs. 1, 18, and 52.

tions, and both can be suboptimal. For patients with resistant hypertension, lifestyle modifications should be re-emphasized. Patients may not realize that the Dietary Approaches to Stop Hypertension eating plan combined with low sodium intake can be as effective in lowering BP as a single antihypertensive medication.[39] The importance of weight loss (for overweight patients) should be reiterated.

An important principle of antihypertensive therapy is that greater BP reduction is achieved by combining drugs from different classes rather than by maximally increasing the dose of a single medication.[40] As mentioned earlier, in almost all cases, one of the drug classes should be a diuretic. Other medication classes among the first 3 or 4 agents usually would include an ACE inhibitor or ARB (note that ACE inhibitors and ARBs should not be used together[41]), a long-acting dihydropyridine calcium channel blocker (CCB) (eg, amlodipine), and possibly a β-blocker (eg, metoprolol).

The aldosterone antagonist spironolactone is an evidence-based treatment option for patients with resistant hypertension (SORT C). Spironolactone can reduce systolic BP by as much as approximately 20 mm Hg in patients with hypertension that is resistant to ≥3 drugs.[42,43] When using spironolactone, careful attention must be paid to potassium levels, especially in patients who also are taking an ACE inhibitor or ARB. Spironolactone can cause gynecomastia in men. Eplerenone is an alternative aldosterone antagonist that does not cause gynecomastia. Amiloride is another alternative agent that functions as an indirect aldosterone antagonist.[44] These drugs are contraindicated in patients with severe renal impairment.

Other pharmacologic strategies for treating resistant hypertension (depending on what agents the patient already is taking) include a vasodilating β-blocker (eg, labetalol, carvedilol, nebivolol); a direct vasodilator (eg, hydralazine); or a centrally

Table 4. Approach to Management of the Patient with Resistant Hypertension

Assess adherence to therapy	• Ask about adherence to the treatment plan
	• Ensure adherence to medications is as simple as possible (eg, once daily dosing regimens, generics, fixed-dose combination pills)
Rule out measurement error and white coat effect	• Repeat office measurement of BP making sure cuff size is correct (too small a cuff will overestimate BP) and proper technique is followed
	• Consider out-of-office monitoring (Figure 1)
Consider associated comorbidities	• Address chronic kidney disease if present
	• Emphasize weight loss if patient is overweight
	• In older patients with coronary artery disease, a low diastolic BP may limit degree to which systolic BP can be reduced
Reconsider secondary causes	• Test for primary aldosteronism
	• Consider testing for obstructive sleep apnea
	• Consider rarer causes such as Cushing's syndrome, coarctation of the aorta, pheochromocytoma, and hyperparathyroidism
Address volume overload and interfering substances	• Emphasize reducing dietary sodium; consider consulting nutrition specialist to assist
	• Discontinue or reduce medications, supplements, and other agents (eg, alcohol) that interfere with BP control (Table 3)
Intensify therapy	• Options for intensifying pharmacologic therapy (assumes patient already on low-dose thiazide diuretic, an ACEI or ARB, a long-acting calcium channel blocker, and possibly a beta-blocker): - Increase dose of diuretic (or change HCTZ to chlorthalidone) or change to a loop diuretic for those with GFR <30 mL/min - If no contraindications, add spironolactone as first-choice (starting at 12.5 mg daily); eplerenone (starting at 25 mg daily), or amiloride (starting at 2.5 mg daily) are alternatives - Use a vasodilating β-blocker (eg, carvedilol) - Add a calcium channel blocker from the alternate class (eg, add a nondihydropyridine if already on a dihydropyridine) - Add clonidine or guanfacine
Consult hypertension specialist	For directory of hypertension specialists, see http://www.ash-us.org/HTN-Specialist/HTN-Specialists-Directory.aspx

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BP, blood pressure; GFR, glomerular filtration rate; HCTZ, hydrochlorothiazide.

acting agent such as clonidine (transdermal or oral) or guanfacine. In men with comorbid benign prostatic hyperplasia, an α-blocker (eg, terazosin) is a reasonable addition. Another strategy that may be particularly useful in patients with comorbid diabetes or CKD is adding a CCB of the alternate class (eg, adding a nondihydropyridine to a dihydropyridine).[45,46] Keep in mind that a nondihydropyridine CCB combined with a β-blocker may promote bradycardia, which can be worsened by clonidine. Consider referral to a hypertension specialist when a patient's BP is not controlled adequately despite 4 or 5 agents. A summary of evaluation and management of resistant hypertension is shown in Table 4.

Future Directions

In recent years there has been growing interest in nonpharmacologic interventions to treat resistant hypertension. Electrical stimulation of the carotid sinus baroreceptor has been shown to decrease BP. A few small studies have demonstrated that an implantable baroreflex stimulator is feasible and may be quite effective.[47–49] In one study, 45 patients with resistant hypertension and an average BP of 179/105 mm Hg had reductions in BP of 21/12 mm Hg at 3 months, and some had persistent effect at 2 years after implantation of the device.[48]

Catheter-based radio frequency renal denervation is another promising approach that currently is being studied.[50,51] Renal sympathetic activity contributes to hypertension in part through simulation of renin release, increased sodium reabsorption, and neurogenic mechanisms. Selective denervation of the renal nerves responsible for these effects has been shown to reduce BP. In the Symplicity HTN-2 Trial, resistant hypertension patients (with mean baseline BP of 178/96 mm Hg) randomized to catheter-based radio frequency denervation had a 6-month mean reduction of office BP that was 31/12 mm Hg greater than controls.[51] Further studies are in progress.

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