

## American Society of Hypertension Self-Assessment Guide

### Treatment: special conditions

#### Resistant hypertension

Henry R. Black, MD, MACP, FASH



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One of the most common reasons that physicians and other health care providers refer a patient to a hypertension specialist is because that patient's blood pressure (BP) is not at goal. The term that has become most commonly used now to classify and define these patients is "resistant hypertension," but some still refer to these patients as having refractory hypertension.

A resistant hypertensive patient as defined by the Seventh Joint National Committee on the Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7), is one whose properly measured BP in the office is above goal on three or more appropriately chosen antihypertensive agents administered at appropriate doses, that the patient is taking. One of these agents must be a diuretic.

There are several elements to this definition that bear emphasis:

- (a) Properly measured—before classifying a patient as having resistant hypertension, the clinician must be sure that the office BP is measured properly. Some specialists are now using measurements from out-of-office techniques (ambulatory BP monitoring or home monitoring) before classifying a patient as a resistant hypertensive. If home or ambulatory BP is used, then the accuracy of the instrument and the technique that the patient uses should also be validated. Similar attention to the accuracy of an office-based measurement is equally important. Since this is often difficult or impossible to do, most specialists do not use out-of-office BP to classify a patient as having

resistant hypertension. It is likely that out-of-office measurements will shortly become more widely accepted as an alternative definition.

- (b) Goal blood pressure. Current US guidelines (so-called JNC 8) define the treatment goal for office systolic BP to be <140 mm Hg and a diastolic BP of <90 mm Hg for individuals <60 years of age, and <150 mm Hg for systolic BP and a diastolic BP of <90 mm Hg for those ≥60 years of age. This change in the goal for treatment is not universally accepted, even from five of the 16 members of the so-called JNC 8 Committee. In patients with diabetes mellitus (DM), or chronic kidney disease, the revised goal is ≤140 mm Hg for systolic BP and of <90 mm Hg for diastolic BP. Treatment goals for patients with coronary artery disease or/heart failure are currently under review by several guideline committees and were not addressed in so-called JNC 8. The BP level that constitutes treatment resistance is not as well characterized for out-of-office readings as they are for office BP. Most experts feel that a patient with an average 24-hour systolic BP of ≥135 mm Hg and/or a diastolic BP of ≥85 mm Hg on an appropriate regimen, would be considered resistant.

#### Three or More Appropriately Chosen Antihypertensive Agents at Appropriate Doses

Before a patient should be considered to be a resistant hypertensive, the drugs used must be appropriate and in appropriate doses. For most patients, a combination of a blocker of the renin/angiotensin/aldosterone system, a calcium channel blocker, and a diuretic appropriate to the level of renal function (a thiazide or thiazide-like diuretic for those with normal or minimally abnormal renal function [an estimated glomerular filtration rate (eGFR) of ≥45–50 mL/min/1.73 m<sup>2</sup>]), and a loop active agent for those

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\*Corresponding author: Henry R. Black, MD, MACP, FASH, Adjunct Professor of Medicine, NYU Langone School of Medicine New York, NY. Tel.: +1-212-924-0054; fax: +1-212-924-0054.

E-mail: [hrbmd63@gmail.com](mailto:hrbmd63@gmail.com)

**Table 1**

## Etiology of resistant hypertension

## Etiology

- White coat hypertension, incorrectly measured BP, and pseudohypertension
- Hypertension with an identifiable cause (so-called secondary hypertension)
  - Acromegaly
  - Anxiety
  - Autonomic dysfunction
  - Baroreflex failure
  - Carcinoid tumors
  - Central nervous system tumors
  - Coarctation of the aorta
  - Glucocorticoid excess
  - Hypercalcemia
  - Mineralocorticoid excess
  - Pheochromocytoma
  - Porphyria
  - Renal parenchymal disease
  - Renal vascular disorders
  - Thyroid disease, both hypo- and hyperthyroidism
- Elevated blood pressure due to incorrect choice of antihypertensive agents
  - Inadequate dose(s) of one or more agents
  - Incorrect diuretic for the degree of renal insufficiency
  - Use of two or more antihypertensives with same or similar mechanism of action
- Interfering substances
  - Amphetamines
  - Anabolic steroids
  - Anti-inflammatory agents
  - Appetite suppressants
  - Caffeine
  - Cocaine
  - Corticosteroids
  - Cyclooxygenase-2 inhibitors
  - Cyclosporine
  - Erythropoietin
  - Ephedra (ma huang)
  - Ethanol
  - Ginseng
  - Guarana
  - Licorice (natural licorice, herbal remedies, and chewing tobacco)
  - Monoamine oxidase inhibitors
  - Neosynephrine
  - Nicotine
  - Oral contraceptives
  - Phenylephrine
  - Phenylpropanolamine
  - Pseudoephedrine
  - Sibutramine
  - Sodium chloride
  - Sympathomimetics
  - Tacrolimus
  - Venlafaxine
  - Yohimbine

**Table 1 (continued)**

- Biological factors
  - Obesity
  - Obstructive sleep apnea
- Psychological factors
- Non-adherence to prescribed regimen

Adapted from: Gonzales-Santos L, Elliott WJ, Setaro JF, Black HR. Resistant Hypertension. A Companion to Braunwald's Heart Disease. 2nd Edition. HR Black and WJ Elliott, eds. Philadelphia: Saunders Elsevier; 2013. pp. 378–84.

with a lower eGFR, must be part of the regimen. If less than fully tolerated doses of these agents are used or even if more than three drugs at suboptimal doses are prescribed, it does not mean the patient is resistant to therapy. Adjustments must be made to the regimen to get the patient to fully tolerated doses before classifying him/her as resistant. If the regimen includes drugs with similar mechanisms of action (for example, an angiotensin-converting enzyme inhibitor and an angiotensin receptor blocker), then these should not be considered to be two separate drugs. Some authorities feel that anyone on four or more antihypertensives who is not at goal also should be considered as having treatment-resistant hypertension, but this definition is not widely accepted as yet, and we must ascertain that the patient is taking what is prescribed. Non-adherence to an appropriate regimen can make a patient appear to be a resistant hypertensive, and so adherence should be ascertained before classifying a patient as resistant. In our experience, non-adherence was not a common reason for resistance for a patient referred to a hypertension specialist.

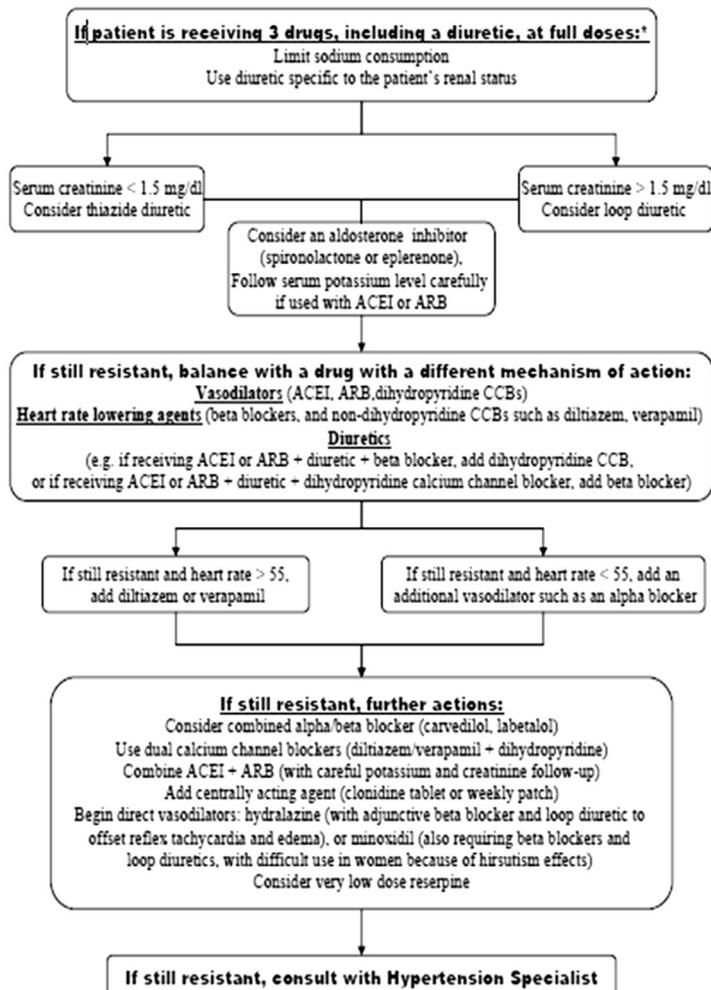
Resistant hypertension should be viewed as a syndrome with a multiplicity of possible etiologies. (See [Table 1](#))

### Treatment of the Resistant Hypertensive

The hypertension specialist must first take a careful and detailed medication and dietary history. Many patients use dietary supplements and other over-the-counter preparations that they don't consider to be "drugs" but that can raise BP. (See [Table 1](#)). A careful dietary history of exactly what the patient is ingesting with a special emphasis on sodium intake and alcohol consumption is crucial. Patients need to be educated as to how read and understand food labels and limit their sodium and saturated fat intake, especially if they eat many meals away from home as so many Americans do. Patients with lipid disorders and/or DM will need additional instructions. While alcohol in moderation (2–3 drinks per day for men and 1–2 for women) does not raise BP, a greater intake can elevate BP. The next step is to do a "directed" physical examination focusing on physical findings that might indicate an identifiable cause for elevation of BP or associated cardiovascular risk factors (ie, an abdominal bruit; an abdominal mass;

(continued)

## APPROACH TO OPTIMIZING DRUG THERAPY IN THE RESISTANT HYPERTENSION PATIENT



\*See JNC 7, Chobanian A et al. for full listing of maximal doses and available combinations  
CCB= calcium channel blocker, ACEI= angiotensin converting enzyme inhibitor,  
ARB= angiotensin receptor blocker

**Figure 1.** Approach to optimizing drug therapy in the resistant hypertension patient. ACEI, Angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; JNC-7, Joint National Committee 7th Report.

cutaneous signs of glucocorticoid excess, DM, or dyslipidemia) and basic laboratory studies looking for hypokalemia, renal insufficiency, dyslipidemias, DM). An evaluation for an identifiable cause (so-called secondary hypertension) is only appropriate if there are historical, clinical, or laboratory clues that an identifiable cause is likely to be present. The basic laboratory studies should also include an evaluation for end-organ damage and co-morbid conditions (urinalysis, urinary albumin/creatinine ratio, complete lipid panel, glycosylated hemoglobin, electrocardiogram, and perhaps a cardiac echo). A 24-hour measurement of protein excretion, Lp(a), lipid particle size, and number are not necessary for most resistant hypertensive patients.

The next step is to optimize the treatment regimen focusing on choosing three appropriate drugs in appropriate doses and proceed as indicated in Figure 1.

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