

### INTRODUCTION AND EPIDEMIOLOGY

Treating high blood pressure is a common challenge faced in primary care practice. Hypertension is a significant risk factor for coronary artery disease, stroke, heart failure, and renal failure. About 33% urban Indian adults – or approximately 60 million people and 25% rural Indian adults – or approximately 90 million people are hypertensive. Only 38% percent of urban Indians are being treated for their HTN, whereas only 25% of rural Indians suffering from HTN are under treatment. Only one fifth of urban Indians and one-tenth of rural Indians suffering from hypertension have their BP under control. Even in the United States, less than 25 percent of patients with hypertension have their blood pressure under control. The major causes of uncontrolled hypertension are inadequate therapy, inappropriate therapy, patient noncompliance, and lack of patient education. Other major causes of unresponsiveness to antihypertensive therapy include “white coat” hypertension, pseudo-hypertension, obesity, volume overload, excess alcohol intake and sleep apnea, and unfavorable interactions with prescription and other drugs. In many patients, these factors must be dealt with before blood pressure can be controlled.

### DEFINITIONS AND MANAGEMENT GOALS

Hypertension is defined as persons 18 years of age and above with a systolic blood pressure of 140 mm Hg or more or a diastolic reading of 90 mm Hg or more, or those taking antihypertensive medications. Between 90-95% of cases are essential hypertension in which there is no identifiable cause. A considerable number of patients fail to reach target blood pressure ranges despite lifestyle advice and standard medical therapy.

The blood pressure goal in uncomplicated patients is 140/90 mm Hg which could be relaxed to 150/90 mm Hg in patients greater than 60 years of age. A more appropriate treatment target in patients with end-organ damage is 130/80 mm Hg.

Resistant hypertension (HTN) is defined as a blood pressure (BP) value  $>140/90$  mm Hg or  $>130 / 80$  mm Hg in patients with diabetes or renal disease despite adherence to a medical regimen that includes at least 3 anti-hypertensive medications, one of which is a diuretic. Difficult-to-treat HTN is somewhat less well defined. It includes patients who do not meet the strict criteria of resistant HTN, but nonetheless their BP is not controlled despite aggressive intervention that may not necessarily include diuretic therapy.

### DIAGNOSIS

Blood pressure should be measured after a patient has been seated quietly for five minutes in a non-stressful environment, with his or her arm supported at heart level and with the use of a properly calibrated and sized cuff. If the cuff is too narrow or too short, readings may be erroneously high (typically by 5 to 15 mm Hg in the case of systolic pressure). The patient should be asked whether he or she has smoked a cigarette within the previous 15 to 30 minutes, since smoking can cause a transient elevation in systolic blood pressure of 5 to 20 mm Hg. Avoidance of coffee is also recommended, although the increase in systolic blood pressure after one cup of caffeinated coffee is usually only 1 to 2 mm Hg.

The diagnosis is based on the findings of at least two or three elevated blood-pressure measurements. However, if the blood pressure is above 160/100 mm Hg, additional readings are not required for diagnosis.

Some patients with difficult-to-treat hypertension have a normal blood pressure at home. This phenomenon has been attributed to “white-coat” hypertension in the physician’s office. Repeated home measurements or 24-hour ambulatory monitoring may differentiate this type of hypertension from truly resistant hypertension. White coat hypertension should be suspected in patients who remain resistant to therapy in the absence of target organ damage (retinopathy, nephropathy, left ventricular hypertrophy), who manifest symptoms of over medications (orthostatic symptoms, persistent fatigue) and/or who report home blood pressure values significantly lower than values measured in the office. Because white coat hypertension is so common, all patients with hypertension should be encouraged to obtain home blood pressure values.

Pseudo-hypertension is a falsely elevated blood pressure obtained by indirect cuff measurement secondary to loss of arterial compliance (sclerotic arteries in the elderly), requiring increased cuff pressure in order to compress the underlying artery. Pseudo-hypertension should be suspected in elderly patients whose blood pressures remain elevated despite therapy, who have little or no evidence of target organ damage or who manifest symptoms of over medications. The condition is suggested if the radial pulse remains palpable despite occlusion of the brachial artery by the cuff (the Osler maneuver), although this sign is not specific. The presence of this condition can be confirmed by intra-arterial blood-pressure measurement.

Evaluation of the patient with difficult-to-control

**Table 1: Checklist for difficult-to-treat hypertension**

Step 1	Exclude pseudo-resistance by 24-h ABPM or home (or self) BP measurements
Step 2	Recheck for secondary causes (in particular renoparenchymal disease, renal artery stenosis, hyperaldosteronism)
Step 3	Maximize lifestyle changes (e.g., salt restriction, weight reduction, physical activity)
Step 4	Evaluate patient's adherence
Step 5	Optimize pharmacologic therapy
Step 6	Consider renal denervation

hypertension should include an assessment of adherence to the prescribed management plan, including recommended lifestyle modifications (Table 1). Explaining to the patient that combination of the dietary modifications and low sodium intake can be as effective as a single antihypertensive medication may help motivate patients.

Patients often do not persist in taking their antihypertensive medications. A once-daily regimen can improve adherence to antihypertensive treatment, as well as prescription of fixed-dose combination pills, because most patients require more than one class of antihypertensive medication. Asking about and addressing side effects may also improve adherence by enhancing patient's understanding of treatment. Above all, the physician and the patient must be convinced that treating to reach a goal blood pressure level of less than 140/90 mm Hg is worthwhile.

A very common reason for failure to reach blood pressure goal is suboptimal therapy. Physicians may prescribe inadequate doses of antihypertensives or have resistance to add additional agents. Greater blood pressure reduction is achieved by combining lower doses of drugs from different antihypertensive classes rather than increasing the dose of a single medication. Importantly, one of the drug classes should be a diuretic. The lower dose combination strategy is also more likely to minimize side effects.

## PATIENT FACTORS

### Obesity

Obese patients do not respond as well as leaner patients to antihypertensive medication. Thus, weight reduction is a particularly important adjunct to drug therapy in obese patients with difficult to treat hypertension. Progressively higher doses of antihypertensive drugs are required to control blood pressure as the body mass index increases. However, even lean patients with hypertension, glucose intolerance and hyperinsulinemia may require higher drug dosages, suggesting that obesity, a sedentary lifestyle, glucose intolerance and insulinemia, all of which are related to insulin resistance, may cause refractory hypertension.

## Alcohol abuse and other interfering exogenous substances

Excess alcohol intake raises blood pressure in both treated and untreated patients with hypertension, and blood pressure either returns to normal or becomes easier to control when alcohol intake ceases. Alcohol abuse is also a frequent cause of non-compliance with medications. Other potentially interfering agents that should be considered in patients with difficult-to-control hypertension include cocaine, amphetamines, anabolic steroids, oral contraceptives, cyclosporine, antidepressants, herbal supplements (e.g.; ginseng) and nonsteroidal anti-inflammatory drugs (NSAIDs). NSAIDs including cyclooxygenase-2 inhibitors not only raise blood pressure, but can interfere with the mechanism of nearly every antihypertensive drug class.

## Sleep Apnea

Sleep apnea affects 2 to 4 percent of middle-aged adults, most of whom are unaware they have this disorder. Associations between sleep apnea and both diurnal hypertension and morbidity and mortality due to cardiovascular and cerebrovascular causes have been reported. The association between sleep apnea and diurnal hypertension is independent of obesity, age and sex, and appears to be related to stimulation of the sympathetic nervous system by repetitive upper-airway closure. A sleep study is indicated in patients with resistant hypertension and other signs and symptoms of sleep apnea, including obesity, large neck size (size 17 inches or greater in men and size 16 inches or greater in women), excessive loud snoring, interrupted sleep, daytime somnolence, polycythemia and carbon dioxide retention.

## Volume overload

Whether related to excess sodium intake or inadequate/inappropriate diuretic treatment, is the most common cause of resistant hypertension in patients who adhere to therapy. All patients with hypertension should be counseled to avoid foods high in sodium and to increase their consumption of fruits, vegetables and low-fat dairy products. These foods contain micronutrients that reduce the pressor effects of concomitant sodium intake. In patients with hypertension and normal renal function, thiazide diuretics are more effective than loop diuretics in lowering blood pressure. However a switch to a loop diuretic may be warranted in patients with renal dysfunction (glomerular filtration rate less than 30 mL per minute; serum creatinine approximately 3 to 4 mg per dL).

## CONCLUSION

Using planned systematic approach achieving BP goals with appropriate combination therapy in most patients is possible. In addition to an appropriate antihypertensive treatment regimen, it is important to be aware of poor adherence and to monitor patients for the use of substances that interfere with antihypertensive therapy. Patients with white-coat hypertension can be recognized using ABPM. Patients with secondary hypertension due to conditions such as renal artery stenosis or renal

642 parenchymal disease, can be identified with appropriate screening. In patients with difficult-to-treat hypertension, the regimen may be intensified but careful monitoring is mandatory.

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