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# 23 Resistant hypertension

**Dr. Prabhakar** K MD(Gen Med), FIAMS, AFISC, MNAMS [1],
**Dr. Balamurali K** [2]
1, Professor of Medicine, Sri Devaraj Urs Medical college , Sri Devaraj Academy of Higher Education and Research, Kolar, Karnataka.
Hon Professor of IMA-CGP.
2, Resident of Pharmacology, Sri Devaraj Urs Medical college , Sri Devaraj Academy of Higher Education and Research, Kolar.

## Introduction

Hypertension doubles the risk of cardiovascular diseases, including coronary heart disease, congestive heart failure , ischemic and hemorrhagic stroke, renal failure, and peripheral arterial disease. It is seen that approximately 80-95% of hypertensive patients are diagnosed as having 'essential' hypertension also called as primary or idiopathic hypertension . In the remaining 5-20% of hypertensive patients, there can be underlying causes leading to 'secondary hypertension' that can be identified. The basic approach to a treat a hypertensive patient involves lifestyle interventions followed by pharmacological therapy which includes thiazide diuretics, angiotensin converting enzyme blockers, angiotensin receptor blockers, aldosterone antagonist, beta blockers, alpha adrenergic blockers, sympatholytics, Caclium channel blockers and direct vasodilators. The selection of antihypertensive agents should be individualized after taking into account the severity of hypertension, comorbid conditions and other practical considerations. Sometimes a combination of drugs can be used rather than monotherapy in the treatment of hypertension. Although these antihypertensive agents reduce the risk of cardiovascular and renal disease some segment of hypertensive population continue to remain hypertensive despite the use of a combination of these drugs and are resistant to pharmacological treatment.

**Definition**: Resistant hypertension can be defined as the persistence of usual blood pressure above 140/90 mm Hg despite treatment with full doses of three or more different classes of medication including a diuretic in full combination and full dose[1]. Blood pressure which is under control but requires more than or equal to 4 drugs to do so is also considered resistant to treatment.

Resistant hypertension remains as one of the most common cause for referral to a hypertension specialist.Though the prevalence of resistant hypertension is difficult to estimate it is seen that in around 30-50% of hypertensive patients, blood pressure is not reduced to the target level of below 140/90

## Causes of Resistant hypertension

In practice, the problem of resistant hypertension usually falls into one of the four categories :

1. Pseudoresistance
2. Inadequate medical regimen
3. Non-adherence or ingestion of pressor substances
4. Secondary hypertension
5. Some of the rare genetic causes for resistant hypertension are mutations of the â and ã subunits of the epithelial sodium channel (ENaC).[2] Mutations of these subunits can cause Liddle's syndrome, a rare monogenic form of patients with resistant hypertension.

The other cause is the presence of a particular CYP3A5 allele (CYP3A5*1) which has been associated in African-American patients with higher systolic blood pressure levels in normotensive participants and hypertension more resistant to treatment. The CYP3A5 enzyme (11_-hydroxysteroid dehydrogenase type 2) plays an important role in the

metabolism of cortisol and corticosterone, particularly in the kidney.

* The other causes are lifestyle factors like obesity, high salt intake and heavy consumption of alcohol e" 30 drinks per week have been associated with hypertension which is resistant to treatment.

* Pseudoresistance : It refers to the 'white coat' aggravation, i.e 'white coat' effect superimposed on chronic hypertension that is well controlled with medications outside the physician's office. It also includes the hypertensive population who have high blood pressures in office ( high office blood pressure) and lower blood pressure once back home. When a patient's mean daytime ambulatory blood pressure is below 135/85 mmHg it can indicate a favorable prognosis and adequate therapy. Sometimes in older patients with severe sclerotic arteries it might be difficult to measure their blood pressure, especially when radial pulse remains palpable despite occlusion of the brachial artery by the cuff (Osler maneuver ), in such cases the actual blood pressure can be measured by direct intraarterial measurement. White coat hypertension can be excluded by a 24 hour ambulatory monitoring of the blood pressure and home based blood pressure monitoring.

* Inadequate medical regimen : As volume expansion seems the

most frequent pathogenic finding in these patients. [3] An appropriate diuretic to decrease volume overload remains a cornerstone of therapy. [4] Absence of diuretic ,inappropriate use of diuretic in patients with normal renal functions , infrequent dosing with a short acting loop diuretic ( eg : once a day furosemide) or a low dose thiazide in a patient with impaired renal function are the common cause for apparent drug resistance. Studies suggest that changes in diuretic therapy (adding a diuretic, increasing the dose, or changing the diuretic class based on kidney function) will help 60% of these patients achieve BP goals[5] Effective doses of Thiazide diuretics is 12.5 mg/day provided kidney function is normal and can be increased up to 50 mg for additional BP reduction .Of note, there are differences between

thiazide and thiazide-type diuretics. [5] A recent trial comparing hydrochlorothiazide 50 mg and chlorthalidone 25 mg daily demonstrated that the latter provided greater ambulatory BP reduction, with the largest difference occurring overnight. Additionally, a small study of patients with resistant hypertension demonstrated that switching from the same dose of hydrochlorothiazide to chlorthalidone resulted in an additional 8 mm Hg drop in systolic BP and increased the number of subjects at goal. [5] The most crucial part of diuretic therapy is to know when kidney function has deteriorated, so that one may select the proper class of diuretic. For thiazides, this deterioration is generally thought to have occurred when the estimated glomerular filtration rate (eGFR) falls to 50 ml/min/ 1.73m$^2$, chlorthalidone can still be effective to an eGFR of 40 ml/min/1.73 m$^2$ if hypoalbuminemia or hyperkalemia is not present. For patients with eGFR -40 ml/min/1.73 m$^2$, a loop diuretic should be used.[5] Furosemide or bumetanide must be given twice daily, and possibly thrice daily in some cases, as they have short durations of action of3 to 6 h. Thus, once-daily use is associated with intermittent natriuresis and consequent reactive sodium retention mediated by increases in the Renin angiotensin system.[5] The loop diuretic torsemide has a longer duration of action and may be given once or twice daily.

* Nonadherence or ingestion of pressor substances : Several classes of pharmacological agents can produce transient or persistent rise in BP. Nonsteroidal anti-inflammatory drugs (NSAIDs) are a common cause of worsening BP control. They increase BP by an average of 5 mm Hg, in part because of inhibition of renal prostaglandin production decreases in renal blood flow, followed by sodium and fluid retention. They also interfere with BP-lowering of all antihypertensive drug classes except calcium antagonists.[6] The effect of NSAIDs on BP is more pronounced in patients with reduced kidney function. Selective cyclo-oxygenase-2 inhibitors have effects similar to those of NSAIDs on BP control. Sympathomimetic agents (nasal decongestants, anorectic pills, cocaine,alcohol, amphetamine-like stimulants), oral contraceptives, glucocorticoids,

anabolic steroids, erythropoietin, and cyclosporine are also commonly used agents that can interfere with BP control. Black licorice, included in some oral tobacco products, and herbal supplements (e.g., ma huang and ginseng), also raise BP.[7] The effect of these agents varies; most people manifest little or no effect, but certain persons may experience severe BP elevations. Lastly, illicit drugs can be a major unappreciated cause of resistant hypertension. Agents such as steroids and cocaine are common causes of resistant hypertension.

* Secondary hypertension : common identifiable causes are :

1. Renal arterial disease: More than 90% of renal artery stenoses are atherosclerotic in origin. The likelihood of atherosclerotic renal artery stenosis is increased in older patients, in smokers, in patients with known atherosclerotic disease, especially peripheral arterial disease, and in patients with unexplained renal insufficiency. Bilateral renal artery stenoses should be suspected in patients with a history of "flash" or episodic pulmonary edema, especially when echocardiography indicates preserved systolic heart function. Less than 10% of renal lesions are fibromuscular in etiology developing most commonly in women, less than 50 years of age. Duplex ultrasound, magnetic resonance angiography (MRA), renal scintigraphy, and computed tomography (CT) angiography have good test characteristics in published studies and MRA is highly sensitive for stenosis.

2. primary aldosteronism : Primary aldosteronism is common in patients with resistant hypertension with a prevalence of approximately 20% Generalized activation of the renin-angiotensin-aldosterone system has been described with obesity, while other studies suggest that adipocytes may release secretagogues that stimulate aldosterone release independent of angiotensin-II. In addition, preliminary results relate aldosterone excess to sleep apnea in patients with resistant hypertension. Although cause-and-effect has not been confirmed, these studies suggest that the increased occurrence of primary aldosteronism may be linked to the increasing incidence of obesity.

3. obstructive sleep apnea : Untreated obstructive sleep apnea is strongly associated with hypertension and in normotensive persons predicts development of hypertension.[8] Sleep apnea is particularly common in patients with resistant hypertension. The mechanisms by which sleep apnea contributes to the development of hypertension have not been fully elucidated. A well-described effect is that the intermittent hypoxemia, and/or increased upper airway resistance associated with sleep apnea, induces a sustained increase in sympathetic nervous system (SNS) activity. Increases in SNS output would be expected to raise blood pressure through increases in cardiac output and peripheral resistance as well as by increased fluid retention.

4. Less common forms of secondary hypertension include pheochromocytoma, Cushing's syndrome, hyperparathyroidism and hypoparathyroidism, aortic coarctation, and intracranial tumors.

* Some of the points may require special mention in the general physical examination of the resistant cases of hypertension, they are

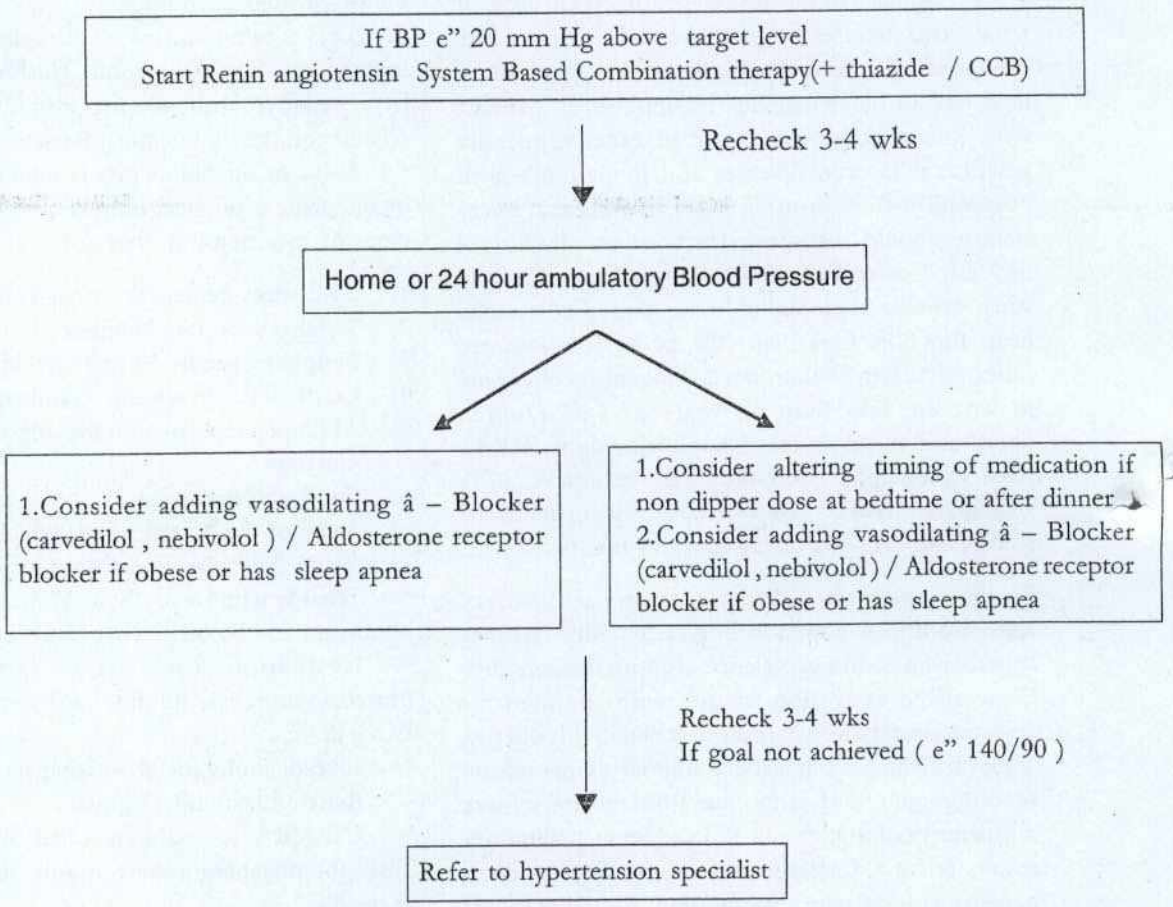
1. BP measurement (contralateral, all arms)
2. Weight, waist circumference
3. Peripheral pulses, bruits, thyroid examination
4. Cardiovascular system examination
5. Abdomen examination for masses, bruit, aortic pulsation
6. Fundus examination

Ø Some of the investigations which might help in identifying the cause of resistant hypertension are :

* renal function tests, thyroid function tests ,serum potassium and blood glucose levels .
* Evaluation for target organ damage (microalbuminuria, fundus, cardiac assessment by ECG, 2DE)
* Investigations for identifying secondary causes
- Renal ultrasound, Doppler
- CT, MRA, aortography (renal angiogram)

Tests for phaeochromocytoma or other conditions as needed

## Initiate treatment for hypertension




**Treatment**

As a first step in the treatment of resistant hypertension lifestyle modifications should be adopted .for patients with obesity weight loss should be advised and other measures like dietary salt restriction ideally to less than 100 mEq of sodium/ 24-hour, and moderation in consumption of alcohol and high fibre low fat diet should be advised . All interfering drugs should be withdrawn and judicious use of diuretic therapy should be made.

As there is a high prevalence of primary aldosteronism in patients with resistant hypertension studies have demonstrated that mineralocorticoid receptor antagonists like spironolactone provide significant antihypertensive benefit when added to existing multidrug regimens.

Amiloride can be added which is a potassium-sparing diuretic associated with BP reductions in patients with resistant hypertension. When physicians prescribe these agents, especially in combination with an ACE inhibitor or an ARB, they should monitor potassium levels closely .

If BP control is still not achieved with full doses of a 4-drug combination, use of other agents such as centrally acting alpha-agonists (methyldopa and clonidine) or vasodilators (hydralazine or minoxidil) is needed. These agents are very effective for lowering BP, but have poor tolerability and lack of positive outcome data.[9] All secondary causes of hypertension as mentioned before require due treatment.

It must be noted, however, that if therapy has progressed to adding a fourth agent, referral to a clinical hypertension specialist is warranted.[10] Recent trials have also shown that the combination of a renin inhibitor (aliskiren) with an Angiotensin Receptor Blocker produced an additional BP drop. Ongoing trials of endothelin-receptor antagonists (ERAs).[11] darusentan, a selective ERA seems to hold some answers to the treatment of resistant cases of hypertension .

## Conclusions

The phenomenon of resistant hypertension needs more detailed study,

Treatment also requires the recommendations to be based on pathophysiological principles and clinical experience. Effective management of resistant hypertension requires, first, a careful examination for and exclusion of factors associated with pseudo-resistance, and second, identification and, when possible, modification of factors related to true BP elevations.

## Case Scenarios :

1 . A 65 year old male come to the medical OPD for routine check up with complaints of ankle edema. On enquiring further it was found that he was taking T.Nicardia ( Nifedipine 40 mg ) since the last six months . On examination his blood pressure was 150/90, system examination was normal . What need to be done to control his hypertension.

1. Lifestyle modifications ( advise walking, diet ,salt restriction )
2. Increase the dose of Nifidipine to 80 mg
3. Add a diuretic ( thiazide – hydrochlorothiazide ) along with ARB ( losartan ) and Calcium channel blocker( amlodipine )

Answer : the first and the third options are right answers, in view of preexisting ankle edema increasing the dose of nifedipine would only further worsen the complaint the patient has, adding a diuretic along with ARB and CCB ( amlodipine) could help the control the hypertension to a greater extent.

2 a 40 year old male comes to the medical OPD with complaints of wheezing , he is a known case of asthma who had been taking alternate medicine for the last six months he is also a known case of hypertension on Propanalol 20mg daily for the last 6 months .On examination the patient had Cushingoid features and a BP of 150/100 what needs to be done for him

1 Stop all forms of alternative medicine ( could contain steroids)

2. Start the patient on diuretic along with calcium channel blockers

3. stop B- blockers ( propanolol)

4. all of the above .

Answer: All of the above options are correct, the steroids in alternate medicine could worsen his condition and lead to Cushing syndrome ,hence it needs to be discontinued . The patient is on monotherapy with a betablocker propanolol , which could worsen his asthma, hence it should be stopped. Addition of more than one drug consisting of a diuretic helps in the better control of resistant hypertension than monotherapy .

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