Chapter

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Therapeutic Challenge of Resistant Hypertension — Indian Perspective

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The challenges to lower blood pressure to goal level in some patients may be formidable. One has to investigate the causes responsible for such difficult to treat hypertension and employ three or more antihypertensive drugs besides addressing the root causes of resistant hypertension. The incidence of resistant hypertension will increase in India with increase in incidence of hypertension per se. The incidence of hypertension (HT) has increased in India in the past five decades, more so in the urban areas[1].

It is apprehended that the Indian prevalence of HT will soon catch up the USA figure[1, 2]. Many of these Indian hypertensives will not achieve goal level of BP lowering and will come under category of resistant HT. (RH) This article will address the challenges of RH.

Table 1: Incidence of hypertension in India

– Overall incidence over last 50 yrs has risen
– Urban Indians > Rural Indians
– Indian incidence will rise to USA-level soon
– In some of them BP will not be controlled by 3 drugs

Ref: Gupta R. Proceeding of 4th National Conference on Hypertension. Hypertension Society of India 1996;14-23.

Out of 7211 patients attending Arya Clinic and Brahmadeo Free Clinic during the period 1st January 2005 to 31st March 2006, there were 580 persons (384 males and 196 females) with hypertension. The age ranged between 18 to 86 years. Out of these 580 patients, the goal BP could not be achieved in 178 (31.7%) out of which 96 were males and 82 were females, between age range of 18-68 years. Thus, a small survey from a very small sample showed that, 31.7% of hypertensives were unable to achieve goal BP.

Table 2: Incidence of HT

(Data from author's office practice 1st Jan 05 - 31st March 06)

No.	Male	Female	Age (Yrs)
580	384	196	18-86

Table 3: Incidence of resistant HT

(Data from author's office practice 1st Jan 05 - 31st March 06)

No.	Male	Female	%
178	96	82	31%

A review of findings of landmark trials of hypertension gives us an idea of the challenge of resistant hypertension. ALLAHAT Trial (2002)[3] followed 33000 patients over 55 years of age with hypertension for 5 years while on chlorthalidone, amlopidine and lisinopril and other antihypertensive drugs (AHDs). 34% of these subjects did not achieve goal BP at or below 140/90 mmHg, even though 27% of them were receiving three or more drugs. Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE TRIAL 2003)[4] showed that 33% of out of 16,600 patients put on Verapamil ER + Atenolol + Thiazides did not achieve goal BP.

In Losartan Intervention For End-Point reduction in Hypertension study (LIFE STUDY _ 2002)[5], 51-59% subjects did not achieve goal BP, in spite of Losartan and Atenolol.

It is well recognized that hypertension (HT) is now a major health problem in India[1]. There is paucity of large authentic, epidemiological studies regarding prevalence of hypertension in India. Over the years the WHO cut off point of BP ≥ 160/95mmHg to label a

person as hypertensive (1959) has been modified to ≥140/90 and this vitiates any assessment of trends of hypertension prevalence over the past four decades and a half (45 years)[1]. Nevertheless, the meta-analysis of studies from various parts of India has demonstrated that between 1990-2000, the prevalence of hypertension rose from 11.66% to 26.78% in males and from 13.67% to 27.65% in females in urban population[1]. In rural areas the prevalence from 1991 to 1999 ranged between 1%, 57% to 4.85% in men and between 3.6 to 5.8% in females[1]. There appears to be a steady increase in the prevalence of hypertension over the last 50 years in India and is likely to be similar to that in USA[1,2]. Evidence from clinical practice and from the literature suggest that approximately half of most common chronic disorders are undetected, that half of those detected are not treated, and that half of those treated are not controlled: 'rule of halves'[6]. This 'rule of halves' also holds good for hypertension[6].

In spite of our increasing knowledge about the genes which influence pathophysiology of hypertension and influence response to pharmacological antihypertensive agents[7,8] not all hypertensives achieve their desired goal of blood pressure reduction. The Chennai Urban Population Study (CUPS)[9] also has shown that rules of halves is still valid in the Urban South Indian population and it may safely be assumed that the same more or less holds good in other parts of India. In CUPS it was shown that of 279 individuals with hypertension only 104 (37%) were already diagnosed cases of hypertension. Of the 104 known hypertensives only 52 subjects (50%) were under any kind of antihypertensive therapy and of these 52, only 21 (40%) had BP under control[9]. Many of the 21 patients in CUPS might have been given the label of resistant hypertension. We know that altered gene expression in fetus due to maternal malnutrition also "programmes" hypertension, and human genome project has identified candidate genes in human hypertension[8]. But we have yet to utilize this knowledge in treating patients of resistant hypertension. It is being predicted that we can find out salt sensitive patients by identifying which hypertensives have genetically reduced level of ANP (Atrial Natriuretic Protein)[8]. Still the problem of resistant HT is very much there.

According to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC-7 Report)[10] even in an advanced and developed country like USA, approximately 30% of adults are still unaware of their hypertension, more than 40% of individual with hypertension are not on treatment and 2/3rd of hypertensive patients are not being controlled to BP level less than 140/90. The situation in our country can be well imagined. A significant proportion of patients in the treated but not well-controlled group are patients of what is known as resistant hypertension. This article will address the challenge of resistant hypertension.

Definition of Resistant Hypertension[10,11]

Resistant hypertension is defined as the failure to achieve goal BP in a patient who is adhering to full dosage of an appropriate three drug-regimen that includes a diuretic[10, 11]. The goal BP is ≤ 140/90 mmHg (according to JNC-7 report). For hypertensives with diabetes mellitus or renal disease, the goal BP is ≤ 130/80 mmHg (according to JNC-7 report)[10].

British Hypertension Society guidelines (BHS) (1999)[12] however, had set slightly lower level of BP lowering goal of ≤ 140/85 mmHg in non-diabetic subjects, and ≤ 140/80 mmHg in diabetic hypertensives. BHS guidelines 2004[35] revised the goal level of BP reduction to ≤ 130/80 mmHg for diabetics and for patients of chronic renal disease. The Indian Guidelines for Management of Hypertension[13] has kept BP below 130/85 mmHg in young, middle aged or diabetic subjects and BP below 140/90 mmHg in elderly subjects as goal level of blood pressure reduction.

All these guidelines, however, accept that despite best practice these levels will be difficult to achieve in some hypertensive people[14].

It is this subset of hypertensives that poses a challenge to treating clinicians. The present review is intended to discuss methods to identify the causes of resistant hypertension and measures to treat such patients.

Causes of Resistant Hypertension

The causes of poor BP control are numerous[7,8] (Please see Table 4). The most likely causes are volume overload either due to excess sodium intake or inadequate diuretic, intolerance to medications, noncompliance and secondary hypertension[10,11,14]. Elderly patients and diabetics, on multiple drugs for other co-morbid conditions and who are uninformed about goal of therapy are more likely to be ones who's BP becomes resistant. Noncompliance, non adherence and non-affordability of costly AHD are important causes of resistant hypertension in India. In the pathogenesis of hypertension, the environmental factor that has received the greatest attention is salt intake. But studies have shown that only 60% of hypertensives are particularly

responsive to the restriction of sodium intake. Hence salt restriction will not work in the rest 40% hypertensive population[15]. This factor has to be kept in mind while deciding whether further curtailment of salt intake is necessary to reduce the BP. All the same, effect of salt restriction is important as 50% of salt sensitive hypertensives are found to have recognizable causes of hypertension like primary aldosteronism, bilateral renal artery stenosis, renal parenchymal disease and low-renin essential hypertension[15].

While probing the dietary history one has to assess whether the intake of calcium from dairy sources and potassium, from green vegetables is optimal. Epidemiological studies have shown that essential hypertension is more common in people whose diets are deficient in calcium and potassium. The time old conception about influence of excess sodium intake in causing high BP was tested in experimental studies[16]. It was found that genetically salt sensitive rats such as Dahl S and spontaneously hypertensive rats show clear hypertensive responses to a high salt diet. Neural mechanism play an essential role in salt-induced hypertension and recent studies indicate that centrally induced sympathetic hyperactivity actually causes the

Table 4: Causes of resistant hypertension (By different authors)[10,11,34]

- Volume overload (Inadequate diuretic, excess salt intake, obliguric kidney disease)
- Pseudoresistance
  - White coat hypertension or office elevations
  - Pseudohypertension in the elderly
- Drug related causes:
  - Non-adherence, inadequate doses
  - Inappropriate combination (Tricyclic anti depressants plus MAO inhibitors; food with high tyramine content e.g. red wine and cheese plus MAO inhibitors; propranalol plus clonidine.
  - Drugs having potential to raise BP
    a. Sympathomimetics in nasal decongestants, appetite suppressants ergotamine, sandostatin, metoclopramide.
    b. Caffeine, chronic cocaine abuse and other street drugs.
    c. Herbal drugs e.g. ginseng; ephedra, ma haung, bitter orange
    d. Oral contraceptives
    e. Adrenal steroids, anabolic steroids, bromocriptine
    f. Non-steroidal anti-inflammatory drugs (including cyclo-oxygenase-2 selective inhibitors)
    g. Carbenoxolone sodium, licorice (as may be found in chewing tobacco)
    h. Erythropoietin, cyclosporin, tacrolimus, sibutramine.
    i. Ephedrine, MDMA (ecstasy) methyl phenidate, modafinil, phenyl propanalamine, clozapine, disulfuram, indinavir
- Heavy metal poisoning; lead, mercury, thallium and arsenic.
- Insecticides; Parathion
- Insect bites; spider, scorpion
- Diagnostic Agents; Thyrotrophrin Releasing Hormone, Pentagastrim, Indigo carmine.
- Associated conditions
  - Smoking
  - Excess Sodium intake
  - Obesity
  - Sleep apnea
  - Excess alcohol intake (>1ounce/day)
  - Panic attacks
  - Arteritis, Raynands' phenomenon (both are due to intense vasoconstriction).
  - Insulin-resistance, hyper insulinemia (metabolic syndrome)
- Secondary hypertension (Identifiable causes of HT)
  - Obstructive uropathy, chronic kidney disease, polycystic kidneys, renovascular hypertension
  - Coarctation of aorta
  - Cushing's syndrome, chronic corticosteroid therapy
  - Pheochromocytoma, primary hyper-aldosteronism
  - Hypertension associated with pregnancy
  - Hyperthyroidism, hypothyroidism, acromegaly, hypercalcemia.
- Lack of Patient education.
- Elderly patients; uninformed about goal of therapy, non affordability due to high cost of drugs
- Stoppage of drugs once BP-goal-level is achieved.
- It is important to remember that all NSAID including Cox-2 inhibitors interfere with action of all groups of antihypertensive drugs except calcium channel blockers.

hypertension. It has been predicted that genetic studies even in human beings would, in future, identify persons with genetically reduced level of atrial natriuretic protein, who will be salt sensitive. Then it will be easier to emphasize on such genetically salt sensitive individuals the importance of restriction of salt[16].

Table 5: Causes of resistant HT (author's series)

1. Non-compliance, non-adherence	51
2. Inadequate doses of AHD	48
3. Volume overload:	
Salt intake	47
Inadequate diuretic	46
4. Pseudo resistance:	
White-coat HT	19
Pseudohypertension in elderlies	18

NB: Many patients had more than one cause

Yakovlevitch and Black (1991)[17] in a series of 91 patients with resistant hypertension found that the causes were sub-optional drug regimen (mainly inadequate diuretic dosage) in 43%, intolerance to medication in 22%, non compliance in 10% and secondary hypertension in 11%[17].

Blood pressure of patients who, by nature and temperament, are averse to taking drugs[15] and of diabetics tend to be more resistant[18]. Lack of compliance is an universal problem but is more so in India where the clinicians in hospital and office practice are over burdened and cannot or do not find time for educating patients about virtues of continued and prolonged treatment and about dangers of uncontrolled hypertension e.g. stroke, coronary artery disease, renal failure, ocular complication and peripheral vascular disease. Improper BP measurement; can lead to a false perception that patients' BP is not under control[10, 11]. In elderly persons whose brachial arteries are heavily calcified or arteriosclerotic and cannot be fully compressed, the BP may falsely be found to be high[10,11]. This is known as pseudo hypertension. BP may be recorded higher in clinics than the home BP measurement. This is termed as white coat hypertension and is best detected by ambulatory BP measurement.

Diagnosis of Causes of Resistant Hypertension

History

a. **Diet:** Patients should be inquired about the amount of common salt in their diet. Many Indian patients have the habit of adding extra salt over and above that used during cooking and to them low salt intake means simply cutting down on that added salt. Pickles form an usual component in meals in many Indian homes and these are heavily salted. This information must be elicited.

Table 6: Diseases causing resistant HT(author's series)

Diabetic nephropathy	42
Non-diabetic kidney disease	34
Obesity	28
Anxiety induced HT	15
Eclampsia	10
Sleep apnoea	05
SLE	03
Renal artery stenosis	02
Porphyria	01
Coarctation of aorta	01

Thorough history about diet will also give us information about causes of obesity, which again is a contributory factor in lack of BP control. It is known that established obesity or being overweight are associated with hypertension. Heightened sympathetic nervous system activity, hyperinsulinemia, insulin resistance and hyperleptinemia or a combination of these contribute to obesity-related hypertension[19]. Weight loss program should be an essential component of treatment of resistant hypertension[19].

b. **Method of BP measurement:** Patients should be asked about how their BP is being recorded and this will give us a clue to falsely raised BP if standard cuff is being used to measure BP in obese patients. Thorough and meticulous history will assess whether BP measurement is being taken according to standards set by Indian guideline for management of hypertension[13]. The Indian guidelines clearly state that patient should rest for at least five minutes and refrain from smoking or drinking tea or coffee for at least 30 minutes before BP measurement. BP should be measured in supine, sitting and standing posture, specially in elderly subjects to detect postural hypotension. The BP should be measured in both arms and higher of the two readings should be recognized as the true BP of the patients.

c. **Compliance:** One should assess the compliance of the patients. With revolution of information technology in India many educated hypertensive patients get information from internet about the drugs which have been prescribed by their treating

doctors. They are scared of the possibilities of side effects like hypokalemia, dyslipidemia, rise of their blood sugar and uric acid levels and impotence, hyponatremia, hypocalcemia, neutropenia, thrombocytopenia and pancreatitis[20], and tinnitus and deafness specially by large doses of loop diuretics and reversible acute myopia due to indapamide. Due to apprehensions either such persons stop the drugs or reduce doses drastically. Lack of compliance is an universal phenomenon[10-12], but it is more so in Indian perspective. There have been interesting studies[21,22] on non-compliance by patients of hypertension. It can now be shown objectively whether the resistant hypertension is due to poor compliance and poor persistence with prescribed antihypertensive drug regimen or due to drug-non-responsiveness[21]. It has been accepted that about 50% of the patients of resistant hypertension are poor compliers, whose response to simple regimens usually proves satisfactory once their compliance with prescribed regimens is corrected. To quote, Urquhart, "Electronic means for compiling ambulatory patients' drug dosing histories have now made it both technically and economically feasible to distinguish clearly between non-compliers and non-responders which, clinical judgment cannot do, because it is no better at making this crucial distinction than a coin-toss. With the advent of reliable, economical measurement of patient compliance with prescribed drug dosing regimens, we can probably eliminate most of the compliance problems[21]. Another problem of whether low dose thiazide diuretics and β-blockers should be prescribed as first drugs to improve compliance and persistence with therapy has been addressed by Spence, et al[22]. They found that in a Canadian family practice teaching unit, at least 50.8 to 66.7% of patients with hypertension had associated conditions that, according to consensus guidelines are contraindications to β-blocker and diuretics. There is substantial evidence that patients who are taking drugs with less adverse effects, such as angiotensin antagonists [ACE-inhibitors and angiotensin-receptor blockers (ARB)] are more likely to be persistent with therapy, and that persistence with therapy is associated with reduced cost. Hence in treating resistant hypertension substitution of β-blocker and diuretics by newer drugs like ACE-inhibitors, ARBs, calcium channel blockers may yield the desired results, and should no longer be taboo. The problem of non-compliance and non-adherence to therapy are also linked to adverse effects of drugs. To quote Düsing[23], "Side effects may induce variable compliance and non-persistence by yet another mechanism. Therapy turbulence, i.e., any change in medication, necessitated by adverse effects of earlier therapy is also associated with non-persistence. Therefore side effects may directly or indirectly (via inducing therapy turbulence) underlie variable compliance and non-persistence[23]. This fact should not be lost sight of while assessing cause of resistant hypertension.

d. **Adequacy of antihypertensive drugs:** It should be assessed whether the dosage and frequency of antihypertensive medication are appropriate. It is important to find out whether a diuretic has been incorporated in the drug regimen, as this may be the clue to cause of resistant hypertension.

e. **Hypertension inducing drugs:** Detailed history about the concomitant use of medications that are known to push up BP e.g. contraceptive pills, non-steroidal anti-inflammatories including Cox-2 inhibitors, corticosteroids, licorice (carbenoxolone), erythropoietin, cyclosporin, tacrolimus or anti-obesity drugs like sibutramine should be elicited. In younger patients it is important to ask about use of illicit drugs like cocaine, amphetamines etc. It goes without saying that history of excess alcohol consumption and smoking should be elicited. Probing questions may yield information about use of herbal drugs like ginseng and ephedra. Inappropriate combination of drugs like concomitant use of tricycle antidepressive and an MAO-inhibitors causes steep rise of BP which will only come down if one of these drugs is stopped.

f. **Sleep apnea:** History of snoring, at night and daytime drowsiness specially in obese patients will give a clue to sleep apnea as the cause of resistant hypertension.

g. **Urinary symptoms:** One should elicit history of hematuria, nocturia, polyuria, dysuria, hesitancy and

Table 7: Drugs causing resistant HT (authors series)
(Not disclosed by patients unless asked)

NSAID (including Cox-2 inhibitors)	30
Corticosteroids	28
Erythropoietin	10
Contraceptive Pills	05
Cyclosporin	01
Sibutramine	01
Combination of MAO-inh+Tricyclics	01

urgency to exclude renal causes and obstructive uropathy, as the real etiology of resistant hypertension.

h. **Intractable pain:** Chronic pain hampers control of HTN.

i. **Psychogenic conditions:** One should assess whether patient is having history suggestive of anxiety-induced hyperventilation and panic attacks.

j. **White coat hypertension:** If the patients complains that his or her home BP is in normal range, this should not be ignored as the high BP recorded in clinic may be due to white-coat-hypertension.

k. **Hyperaldosteronism:** History of tetany, episodic muscular weakness without edema, may give a clue to primary aldosteronism as the underlying cause of resistant hypertension.

l. **Smoking and excessive consumption of alcohol:** History of excessive smoking and indulgence in alcohol should be elicited. These lead to ineffectiveness of antihypertensive drugs.

Clinical Examination

Correct BP recording, measurement of waist circumference and palpation of peripheral pulses for atherosclerosis are important steps to know the cause of uncontrolled BP. Palpation for femoral pulses, renal lump and auscultation over abdomen for renal artery bruit will exclude coarctation of aorta, renal hypertension and renovascular hypertension respectively which all may be underlying causes of resistant hypertension. Clinical features of Cushing's syndrome, hypothyroidism and thyrotoxicosis should be looked for. Ophthalmoscopy will detect malignant or accelerated hypertension as cause of resistant hypertension.

Table 8: Personality related resistant HT (authors series)

VIP syndrome	12
Daily BP check-up: Daily change of dose of AHD	
Smoking	08
Excess of alcohol	04
Aversion to drugs	03

Laboratory Investigations, Radiology and Imaging

Urinalysis for sugar, albumin, red cells, pus cells, casts etc to exclude diabetes mellitus and renal lesion is important. Biochemical evaluation for sugar, urea, creatinine, potassium, serum cortisol, urinary free cortisol and Free T_3, Free T_4, TSH will detect causes of secondary hypertension like diabetes mellitus, renal hypertension, primary aldosteronism, Cushing's syndrome and thyroid dysfunction as causes of resistant hypertension respectively.

Presence of porphobilinogen in urine will lead to appropriate investigations for acute intermittent porphyria as this may be cause of resistant hypertension. Tests for antinuclear factor and anti-double-stranded-DNA may be done to confirm systemic lupus erythematosus (SLE) as a cause of resistant hypertension, if actinic dermatitis, butterfly erythema, arthralgia and arthritis, lymphadenopathy, hepatosplenomegaly, raised blood urea and creatinine point to a possibility of SLE.

Urological survey including ultrasound for kidney, bladder, residual urine and prostate to exclude obstructive uropathy is essential to detect remediable cause of uncontrolled HT.

Ultrasound and doppler flowmetry and MR angiography will be helpful in detecting renal artery stenosis and should be later confirmed by captopril renal scintigraphy and digital subtraction angiography.

Management of Resistant Hypertension

1. *Reiteration of low salt intake*: Patients should be advised to add only 1 to 1½ teaspoonfull of common salt (which comes to about 4-6 gm sodium chloride) in 24 hrs to unsalted food after cooking, it is important, though it will reduce BP in only salt-sensitive persons.
2. *Advice about stoppage of pickles*, papads, namkins, mathrees, potato chips, smoking and stoppage or moderation of alcohol (to 2 ounces of whisky, 10 ounces of wine or 24 ounces of beer per day) and stoppage of chewing of tobacco containing licorice is important.
3. *Dosage of diuretics* and other hypotensive drugs should be escalated to their recommended maximum. In patients of chronic renal impairment thiazide diuretics should be replaced by loop diuretics like frusemide or torsemide[10]. Patients, in whom diuretics or β-blocker are contraindicated, and are still being used should be put on newer drugs[22].
4. *Drugs which escalate BP* as mentioned earlier should be stopped. If stoppage is not possible, then dose of antihypertensive drug should be increased or more drugs from other groups added.
5. *Sleep apnea* should be diagnosed with help of sleep laboratory, if facilities exist. It should be treated with

use of C-PAP (Continuous Positive Airway Pressure) and antiobesity measures should also be instituted.

6. *Anxiolytics* may be added to treat anxiety-induced hyperventilation and panic attacks.
7. *Identifiable causes* should be treated appropriately. If bilateral renal artery stenosis is detected, then ACE-inhibitor or angiotensin receptor blocker should be stopped, and angioplasty with or without stenting should be employed. Trans-aortic renal endarterectomy or renal artery bypass may be taken recourse to, if angioplasty fails[24].
8. Stoppage of cocaine and other street drug-abuse.

Surgical treatment or extracorporeal shockwave lithotripsy for renal calculi should be carried out. If hydronephrosis due to PUJ obstruction is there it should be treated surgically. Obstructive uropathy should undergo urological intervention.

Cushing's syndrome and thyroid dysfunction should be treated. Coarctation of aorta should have balloon angioplasty or surgical resection of coarctated site.

Addressing Increased CVD-risk in Resistant Hypertension

The resistant hypertensive patients have been exposed to high level of BP for long. The risk of cardiovascular disease (CVD) beginning at 115/75 mmHg doubles with each increment of 20/10 mmHg[10]. The patients of resistant hypertension are at many times higher risk of CVD. Therefore this CVD risk should be addressed at the same time as reduction of BP to goal level. Besides lifestyle modification and three or four antihypertension drugs, there is need of statin and aspirin in such patients, more so if the patient is a diabetic and elderly[22-24].

Role of Aspirin in Resistant Hypertension[25-27,35]

Aspirin 75 mgm OD should be started in elderly (50 year and above) or/and hypertensive patients with diabetes mellitus after their BP has been brought down to goal level (130/80 in diabetics and patients of renal disease and 140/90 in others) if their 10 years coronary artery disease risk (CAD-risk) is $\geq$ 15% and/or ten year cardiovascular disease (CVD) risk is more than 20%[35], if serum cholesterol is $\geq$ 5 mmol/L and if target organ damage (TOD) or clinical cardiovascular disease (CCD) exist. The incidence of CAD and ischemic stroke is definitely reduced.

Role of Statins in Resistant Hypertension[25-27, 35]

Statins have been proved to reduce the incidence of coronary events, stroke and all cause mortality and are safe simple and well tolerated, in hypertensives more so in elderlies and/or diabetic. Statins are indicated in resistant hypertensives with diabetes mellitus up to the age of 75 years if serum cholesterol is $\geq$ 5 mmol/L and 10 years CAD risk is $\geq$ 30% and/or 10 year risk of (CVD) is more than 20%[35] specially if the patient has angina of effort or has history of or is suffering from myocardial infarction. Statins lower blood pressure also and they correct dyslipidemia that may be found in patients of resistant hypertension.

Newer Roles of Older AHD in Resistant Hypertension (RH)[28-30]

Some older AHDs are being used to treat resistant cases of hypertension

Hydralazine[28] has been found to be effective in RH of pre-eclampsia and in hypertensive emergencies.

Minoxidil[28, 29] has become the last resort for treatment of resistant and accelerated hypertension more so in patients of advanced renal disease. It is best used with β-blockers, verapamil or diltiazem and a diuretic to counteract the tachycardia and fluid retention. One has however to remember hypertrichosis and rarely idiosyncratic pericardial effusion in users of minoxidil as side effects.

Low dose aldosterone-antagonists:[30] About 20% of patients of resistant hypertension have been found to have hyper aldosteronism (AS). Small doses of spirinolactone 12.5 mg to 25 mgm have been recommended as add–on therapy to previous two or three drug-regimen in cases of resistant hypertension. Some patients without classical AS, and high urinary aldosterone but low plasma renin also respond to aldosterone antagonists like spirinolactone or triamterene[30].

Newer Horizons[31,32]

Newer weapons in our armamentorium have been put to trials like EPHESUS[31] (on *Eplerenone*) and OCTAVE[32] (on *Omapatrilat*).

Eplerenone[31]: This is a selective aldosterone receptor blocker which blocks androgen and progesterone receptors only minimally. Hence incidence of side effect of gynecomastia is negligible.

Omapatrilat[32]: This neutral endopeptidase inhibitor has superior antihypertensive effect then enalapril in patients of resistant hypertension.

Lercanidipin[33]: It is a vasoselective dihydropyridine 3rd generation calcium channel blocker. It blocks calcium–ion influx through calcium channels in the cell membrane. It is highly lipophilic and therefore has

slower but sustained action. This drug is now available in India and the author has found it useful in treating resistant hypertension.

However, there is need of meta-analysis of several long-term randomized placebo controlled trials before these drugs can achieve category 1(a) evidence-based medicine status.

The AB-CD Algorithm of BHS Guidelines-IV (2004)[35]

In this 'A' denotes Angiotension Receptor Blockers (ARBs) or ACE-inhibitors and 'B' stands for β-blockers, whereas 'C' stands for calcium channel blockers (CCBs) and 'D' denotes Diuretics. Blood pressure of patients with high serum renin level will respond to ACE-inhibitors, ARBs and β-blockers (A+B). Those with low serum renin level will not respond to these drugs; for them CCBs and diuretics (C+D) will be more effective.

The ABCD protocol is based on the evidence than younger patients below 55 years and the Caucasian race tend to have high serum level than people aged 55 years or older or the black population.

Hence, if we want to reduce the incidence of resistant hypertension, young Caucasians should be treated with ACE-inhibitors or ARBs and or β-blockers (A+B) and older white people or black people of any age should be managed by CCBs and diuretics (C+D).

When hypertension remains resistant, A+B+C+D or addition of an α-blocker or low dose spirinolactone may be effective.

However in patients with strong family history of type-2 diabetes, impaired glucose tolerance, and or other features of metabolic syndrome, caution should be exercised in using β-blockers and diuretics (B and D).

PRIMARY AND SECONDARY PREVENTION OF RESISTANT HYPERTENSION[35]

British Hypertension Society guideline for hypertension management 2004 (BHS-IV) has indicated certain points, which will reduce the burden of resistant hypertension by propagating changes in the diet and lifestyle of whole population. Increasing awareness of hypertension in general public and their education about the goal of BP reduction and persistence with treatment will go a long way to reduce the incidence of resistant hypertension. Lifestyle modifications and appropriate use of Statin and Aspirin are important steps to reduce the mortality and morbidity due to cardiovascular and cerebrovascular disease in patients of resistant hypertension.

In people with high risk of cardiovascular (CV) disease e.g. elderly patients with Diabetes Mellitus, CAD and those with target organ damage and multiple CV risks, the etiology of resistant hypertension should be sought and treated appropriately.

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