REFRACTORY HYPERTENSION
A PROVIDER PERSPECTIVE

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Refractory Hypertension A Provider Perspective

ANCC Accredited NCPD Hours: 2.3 hrs

Target Audience: RN/APRN

Need Assessment

Among patients with refractory hypertension, blood pressure (BP) remains uncontrolled in spite of maximal medical therapy. Diagnosis of this condition happens at outpatient department itself from the history of disease, physical examination and analysis of drug compliance. While the exact prevalence of resistant hypertension is unknown, clinical trials suggest that it is not rare, involving perhaps 20% to 30% of the population. Efficacy assessments and much additional knowledge is needed to better identify and treat patients with resistant hypertension.

Objectives

- Describe the mechanism of refractory hypertension
- Recognise the various risk factors for refractory hypertension.
- Discuss the pathophysiology of refractory hypertension.
- Explain drug related refractory hypertension
- Analyse the various clinical considerations in the management of refractory hypertension.
- Identify the pharmacological and dietary therapy in the management of refractory hypertension.
- Enumerate the advanced evaluation methods of refractory hypertension.
- Enlist the indications for specialist referral in refractory hypertension.

Goals

The goal of this article is to explore the emerging data pertaining to the novel phenotype of antihypertensive treatment in refractory hypertension in terms of definition, prevalence, patient characteristics, risk factors, comorbidities, and possible underling etiologies.

Introduction

The term refractory hypertension has been applied with reference to an extreme subgroup of patients failing antihypertensive treatment in four separate scientific publications. Already, during the short duration between these four publications, the definition of refractory hypertension has evolved. While in all cases the term was applied in an attempt to identify patients failing maximum antihypertensive therapy, in the first iteration of the term, refractory hypertension was defined as hypertension uncontrolled with use of five or more antihypertensive agents from different classes that were otherwise unspecified. Based on published studies demonstrating the superiority of chlorthalidone over hydrochlorothiazide (HCTZ) and a large body literature strongly confirming the preferential benefit of spironolactone for treatment of refractory hypertension, with the most recent application of the term, the definition of refractory hypertension required absence of blood pressure control when treated with five or more antihypertensive agents, including specifically, use of a long-acting thiazide diuretic such as chlorthalidone and a mineralocorticoid receptor antagonist (MRA), such as spironolactone. As such, the most recent working definition of the term has become more specific in requiring, in addition to a combined total of five or more antihypertensive classes of agents, failure of an intensive antidiuretic combination as such chlorthalidone and spironolactone. [1, Rank 1]

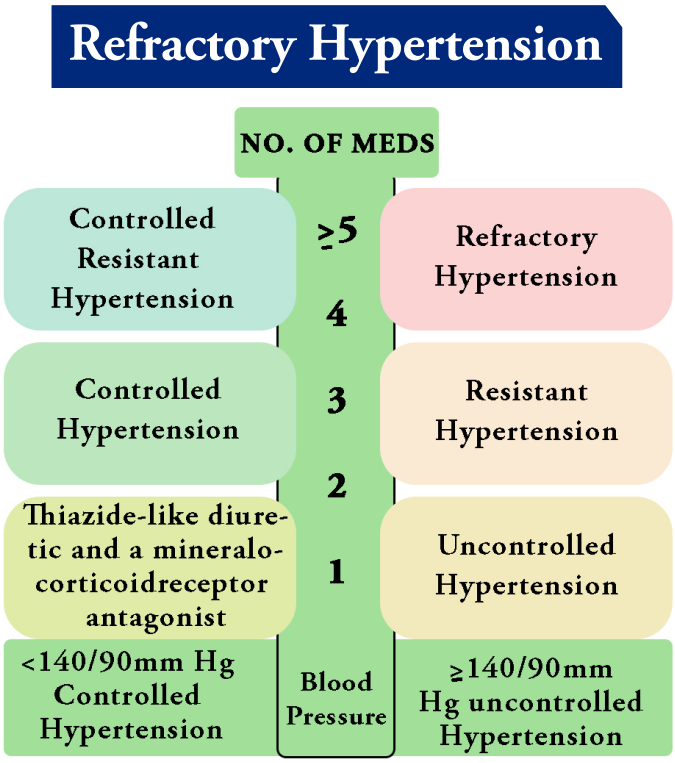

Figure 1: Refractory Hypertension

Resistant hypertension (RHTN) is defined as uncontrolled blood pressure despite the use of ≥3 antihypertensive agents of different classes, including a diuretic, usually thiazide-like, a long-acting calcium channel blocker, and a blocker of the renin- angiotensin system, either an ACE (angiotensin-converting enzyme) inhibitor or an ARB (angiotensin receptor blocker), at maximal or maximally tolerated doses. Antihypertensive medication

nonadherence and the white coat effect, defined as elevated blood pressure when measured in clinic but controlled when measured outside of clinic, must be excluded to make the diagnosis.

Assessment

Among currently published studies on refractory hypertension, the estimated prevalence rates have ranged from approximately 5 to 30% of patients with refractory hypertension. In the initial study of refractory hypertension, a retrospective analysis of over 300 patients referred for refractory hypertension, approximately 10% of the patients with adequate follow-up never achieved blood pressure control in spite of us of five or more antihypertensive agents. Later, when the same group of investigators published a prospective analysis of over 700 patients referred for refractory hypertension, only 29 or approximately 4% were identified as having refractory hypertension. There was an important distinction between studies in how refractory hypertension was defined. In the earlier, retrospective analysis, refractory hypertension was based only on needing five or more antihypertensive medications, without specifying classes of agents used. In the later, prospective analysis, refractory hypertension was defined more stringently, that

> **"Refractory hypertension is defined as uncontrolled blood pressure despite use of ≥ 5 antihypertensive agents of different classes, including a long acting thiazide-like diuretic and a mineralo-corticoid receptor antagonist, at maximal or maximally tolerated doses."**

is, patients had to be failing regimens incorporating five or more agents, including, chlorthalidone and spironolactone. That requirement of obligatory use of an intensive diuretic regimen likely facilitated better control rates, resulting in less cases of treatment failure.

Research on refractory hypertension was also based solely on the number of medications, i.e., five or more. In a cross-sectional analysis of 116 patients with refractory hypertension, 31% were uncontrolled on five more medications. All of the refractory patients were receiving a diuretic and most were receiving spironolactone (76%). [2, Rank 3]

The remaining study of refractory hypertension published so far was a cross-sectional evaluation of participants in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, a large (n=30239), community-based cohort

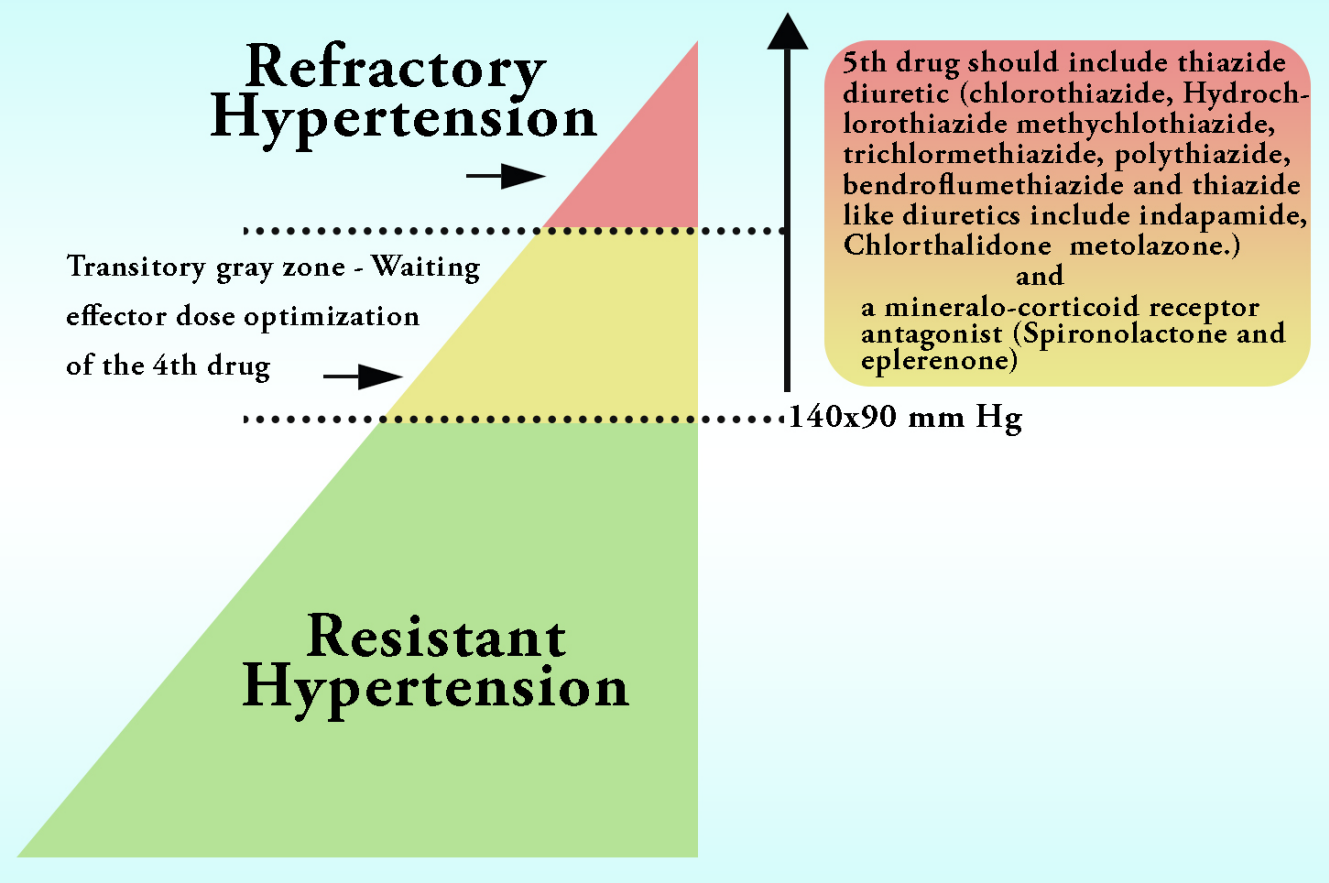

Figure 2: Resistant and Refractory Hypertension

study. In this analysis, refractory hypertension was defined as uncontrolled hypertension office blood pressure despite use of 5 or more different classes of agents. Diuretic use, including specifically chlorthalidone and spironolactone, was not required as part of the definition. The prevalence of refractory hypertension was 3.6% of patients with refractory hypertension (uncontrolled with three or more medications or controlled on four or more medications) and 0.5% of all hypertensive participants. While all of the REGARDS participants identified as having refractory hypertension were receiving a diuretic (either Hydrochlorothiazide- HCTZ or furosemide), none were receiving chlorthalidone or spironolactone. [2, Rank 2]

The currently published studies of refractory hypertension have so far indicated a wide, estimated prevalence from as low as 5% to as high as 30% of patients originally referred for refractory hypertension. The wide discrepancy is no doubt related to important differences in the analyzed cohorts and to how refractory hypertension was defined. Requiring use of chlorthalidone and spironolactone before considering a patient to be failing antihypertensive treatment, clearly substantially

reduces the occurrence of refractory hypertension. [3, Rank 4]

Mechanism of Refractory Hypertension

Findings from published studies provide evidence that refractory hypertension may be less volume dependent than resistant hypertension. This is suggested by its definition in that patients with refractory hypertension are identified only after failing intensive diuretic treatment, including the combination of chlorthalidone and spironolactone. Further, indirect indices of volume status suggest similar or even reduced fluid retention in patients with refractory versus controlled resistant hypertension. For example, in a prospective analysis of patients with refractory hypertension, prior to the standardization of the diuretic regimen with use of chlorthalidone and spironolactone, it was found that plasma renin activity, brain natriuretic peptide levels, and 24 hour urine aldosterone excretion were similar in the two groups, while dietary sodium ingestion (as indexed by 24 hour urinary sodium excretion) was significantly lower in the patients with refractory hypertension. In addition, thoracic fluid content measured by thoracic impedance was not different in the two groups. These findings are important in terms of excluding excess fluid retention, aldosterone production, and dietary sodium intake of greater magnitude as causes of antihypertensive treatment failure than that seen in the general population of patients with resistant hypertension. [8, Rank 2]

Stimulated by the observation of higher clinic heart rates in the earlier retrospective analysis of patients with refractory hypertension, the study was designed to prospectively explore other indices of sympathetic tone. Patients with refractory hypertension were found to have higher resting heart rates compared to patients with controlled resistant hypertension both in the clinic and by ambulatory monitoring. The difference was most pronounced at night, with night time ambulatory heart rates of 72.7 ± 9.0 vs. 65.6 ± 9.0 beats/min in patients with refractory vs. controlled resistant hypertension, respectively. Further evidence of increased sympathetic tone included increased 24 hour urinary excretion of normetanephrines, increased vascular resistance as indexed by pulse wave analysis and velocity, and reduced heart rate variability. If heightened sympathetic tone is confirmed by prospective assessments of these parameters in larger cohorts or by direct measurement of sympathetic outflow, the finding would suggest an important mechanistic distinction between

refractory compared to resistant hypertension, that is, refractory hypertension may be more neurogenic in etiology whereas resistant hypertension tends to be more volume dependent. Further, this observation may have important therapeutic implications in that control of refractory hypertension may require application of effective sympatholytic strategies either with pharmacologic agents or device-based approaches as opposed to continued intensification of diuretic therapy. [8, Rank 3]

Risk Factors and Comorbidities

Important similarities and differences in risk factors have been identified in persons with refractory hypertension compared to the larger population of patients with refractory hypertension. Refractory hypertension is more common among patients of African ancestry compared to those of European descent. In addition, patients with essential hypertension tend to be younger but of similar weight compared to the larger cohort of patients with refractory hypertension, indicating that increasing age and higher BMI are not risk factors for having refractory hypertension compared to refractory hypertension. There is evidence of gender differences between refractory versus refractory hypertension cohorts. While not observed in the retrospective or cross-sectional analyses, the prospective study of refractory hypertension that utilized the most rigorous definition of the phenotype, i.e., requiring failure of 5 or more drug regimen including chlorthalidone and spironolactone, refractory hypertension was more common in women, such that African American women were the race-gender subgroup most affected. [5, Rank 4]

While it seems intuitive that patients with refractory hypertension, given their history of severe blood pressure elevation, should have more comorbidity, particularly cardiovascular disease, than patients with refractory hypertension, the published literature has not consistently supported this conclusion. In the cross-sectional analysis of the REGARDS cohort, refractory hypertension was more commonly associated with chronic kidney disease. (i.e., albuminuria) and diabetes than was refractory hypertension, and patients with refractory patients were more likely to have a history of stroke or heart disease compared to all hypertensive individuals. In the retrospective analysis of patients at a Hypertension Clinic, patients with refractory, compared to controlled refractory hypertension, were more likely to have a history of prior stroke or congestive heart failure (CHF), but not diabetes or chronic kidney disease.

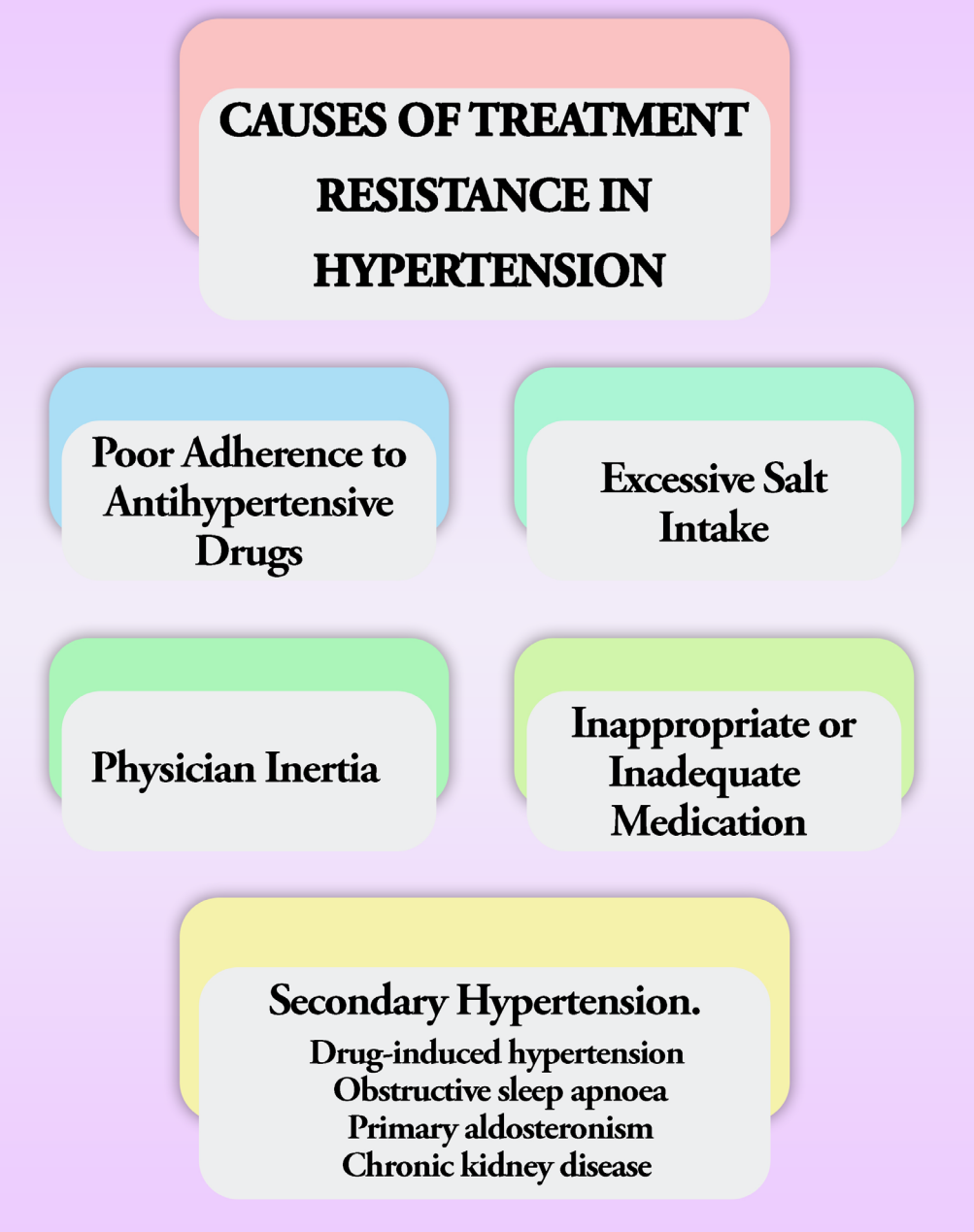

Figure 3: Aetiology of Refractory Hypertension

Similarly, in the prospective assessment done by the same investigators, diabetes chronic kidney disease, and prior stroke were not more common in refractory patients compared to those with controlled refractory hypertension, but refractory patients were more likely to have been in comorbidities between patients with refractory versus controlled refractory hypertension except that refractory patients were more likely to have left ventricular hypertrophy (LVH) based on echocardiography. [6, Rank 3]

The lack of consistency in the reported associations between refractory hypertension and various comorbidities is likely attributable, at least in part, to differences in study design, especially in how refractory

hypertension was defined. For example, both the retrospective and prospective studies carried out in the Hypertension Clinic and the cross-sectional analysis done at the Refractory hypertension Clinic at the University of Campinas specifically excluded patients with Stage 4 and 5 chronic kidney disease, thereby precluding identification of any association between refractory hypertension and advanced chronic kidney disease. [7, Rank 4]

The finding of heightened sympathetic tone in patients with refractory hypertension is potentially critical in identifying an important mechanistic cause of antihypertensive treatment failure. However, the findings to date are not definitive and have not been consistently observed across studies. For example, higher heart rates were not observed in the cross-sectional analyses of participants in the study nor in the cross-sectional analysis of patients with refractory hypertension in their university-based clinic. Further, increases in sympathetic tone may represent a secondary phenomenon rather than an underlying cause of refractory hypertension. Possible secondary causes of increased heart rates and sympathetic tone in patients with refractory hypertension include more severe CKD, underlying CHF, over diuresis, obstructive sleep apnea, and/or greater use of vasodilators, all of which are known to promote increased sympathetic output. Design of future studies to further explore this proposed phenotype should take these competing possibilities into consideration. [8, Rank 2]

Role of blood pressure measuring technique

Poor BP measuring technique is a common underlying cause for falsely diagnosed RHTN and refractory hypertension. Studies have shown that poor BP measuring technique accounts for a high prevalence of falsely diagnosed RHTN or refractory hypertension. Studies recently determined the prevalence of falsely diagnosed uncontrolled RHTN due to poor BP measuring technique. In this retrospective analysis of 130 patients referred to a hypertension clinic, routinely measured clinic triage BP readings were then compared to BP measurements obtained by physician examiners using an automated, unattended BP device. The investigators found that 33% patients had been falsely diagnosed as having uncontrolled RHTN as compared to the routine BP assessments. [9, Rank 3]

Medication non-adherence

Medication non-adherence may be the most common cause of apparent RHTN. In an evaluation of patients with

RHTN referred for renal denervation (RDN), it was reported that 53% of patients were partially non-adherent and 30% were not taking any of the prescribed antihypertensive medications. In this study, levels of antihypertensive agents or their metabolites were measured in the urine. Similarly, researchers found non-adherence among a cohort of patients with RHTN to be 47%, also having directly measured medication levels or its metabolites. [9, Rank 4]

Combined causes of pseudo-resistant hypertension

Researchers estimated the prevalence of combined causes of pseudo-resistant hypertension, such as white coat effect, medication non-adherence, or use of suboptimal treatment dosages in the same cohort of 140 primary care patients. Of these, 22% were controlled on 24-hr ambulatory BP monitoring, 29% were uncontrolled and non-adherent, leaving only 49% adherent to their medications and having uncontrolled hypertension by 24-hr ambulatory BP monitoring. In this study, prescribed antihypertensive medications and doses were documented, all study participants underwent 24-hr ambulatory BP monitoring, and medication adherence was determined with use of electronic monitoring. Overall, one-half of the RHTN were attributed to white coat effect and poor medication adherence, and all of the remaining patients with RHTN were on apparently suboptimal drug combinations and/or dosages. [9, Rank 5]

Studies reported that among the 172 432 hypertensive patients, 35.9% had uncontrolled hypertension. Of these, almost all were undertreated, 21% received less than maximal dosages of prescribed medications, 9% were not receiving a diuretic, 48% had been dispensed less than 3 antihypertensive agents, and 20% had been dispensed none of the prescribed agents. After exclusion of these patients, only 2.2% of the patients with uncontrolled hypertension met the criteria for RHTN. These findings suggest that uncontrolled BP in treated patients is much more likely attributable to the combination of undertreatment and poor medication adherence. [10, Rank 3]

Similar findings of undertreatment were documented by researchers who analyzed trends in antihypertensive medication use among US patients with RHTN over a 6-year period. Using a large, national claims database, which contains medical and prescription claims data that is representative of patients covered by employer-based insurance programs, the authors found that among patients with RHTN, the use of

chlorthalidone and spironolactone, remained extremely low. In this study of 18 to 65 years old patients with ≥6 months of continuous enrollment, a hypertension diagnosis, and ≥1 episode of overlapping use of ≥4 antihypertensive drugs were included. Patients with heart failure were excluded. [10, Rank 4]

The investigators found that despite the recognized preferential use of chlorthalidone over hydrochlorothiazide, chlorthalidone use had increased only by 2.6% between 2008 and 2014 in patients with RHTN. Overall, by the end of 2014, 92.9% of patients were still receiving hydrochlorothiazide versus the 6.4% receiving chlorthalidone. Furthermore, despite the clearly established benefit of spironolactone for treatment of RHTN, only ≈10% of patients were prescribed spironolactone. In a separate study, it was further demonstrated the effectiveness of optimized pharmacological therapy for treatment of RHTN. After excluding non-adherent individuals, patients with RHTN were randomized to RDN or to adjustment and intensification of pharmacological therapy guided by measurement of impedance cardiography to estimate volume status. In this small study, 9 patients were randomized to titration of drug therapy and 10 patients randomized to RDN, the authors demonstrated that guided medication adjustment and intensification was superior to RDN as indicated by reduction in systolic and diastolic BP and changes in 24-hr ambulatory BP levels at 6-month follow-up evaluations. [10, Rank 5]

These findings further support the contention that apparent RHTN is often attributable to poor medication adherence and/or undertreatment. It highlights the need for better education of practitioners on how to optimize antihypertensive regimens, including specifically, use of a long-acting thiazide-like diuretic and an MRA. [10, Rank 3]

Pathophysiology

Resistant hypertension does not represent a single pathologic entity. Some individuals initially classified as resistant instead may have pseudo-resistant hypertension, a distinction arising from limitations in BP measurement and management. Resistant individuals who have increased office BPs as a result of white-coat hypertension, improperly measured BPs, or medication non-adherence are reclassified as having pseudo-resistant hypertension. This difference is useful not only in identifying pathology, but also in predicting outcomes. Patients with true resistant BP have an increased risk of cardiovascular events

including stroke, myocardial infarction, and end-stage renal disease.

The strongest support for the Guytonian theory of the pathophysiology of hypertension is its survival through more than 40 years of experimentation and discovery in the field of hypertension. Based on computer models, Guyton and Coleman concluded that the kidney's regulation of sodium excretion made up the critical pathway that determines the chronic level of intra-arterial pressure. The high gain of the renal function curve is posited in the long run to override any extra renal mechanisms of BP control. Under this theory, a rightward shifted renal function curve would be observed in all forms of hypertension.

Apparent versus True

The term apparent as opposed to true refractory hypertension has been used by investigators to refer to patients with refractory hypertension based on the number of prescribed medications, without accounting for common causes of pseudoresistance, i.e., inaccurate blood pressure measurements, non-adherence, under-treatment, or white coat effects. Such causes of pseudoresistance are common such that up to 50% of patients with apparent refractory hypertension may not be truly resistant to treatment.

Estimates of the prevalence of the different causes of pseudoresistance have been largely done considering one factor at a time in different cohorts. Analysis of the Spanish Ambulatory Blood Pressure Monitoring Registry estimated that the prevalence of white coat refractory hypertension, that is, uncontrolled office but controlled ambulatory blood pressure levels, to be 37.5% of participants otherwise fulfilling the criteria for having refractory hypertension. A cross-sectional evaluation of almost 500 patients with refractory hypertension who had undergone ambulatory blood pressure monitoring, reported very similar results, with 37.0% of patients having white coat refractory hypertension. [4, Rank 4]

Poor adherence to antihypertensive drug treatment is a common cause of pseudo-resistance among patients with apparent refractory hypertension. Researchers evaluated patients referred to a university-based nephrology clinic for refractory hypertension. After exclusion of secondary causes of hypertension and white coat refractory hypertension, adherence was quantified by testing for prescribed antihypertensive medications or their metabolites by liquid chromatography-mass spectrometry analy

sis of urine samples. Of the 76 patients assessed, 53% were identified as being non-adherent: 30% were taking none of their prescribed medications, with the remainder being only partially adherealnt. In a prospective assessment of 339 patients undergoing evaluation for refractory hypertension while either hospitalized or as an outpatient, researchers determined adherence by measuring serum antihypertensive medication concentrations by liquid chromatography-mass spectrometry. Overall 47% of patients were considered non-adherent, with roughly half taking none of their medications. [4, Rank 2]

Most studies have quantified single causes of pseudo-resistance in their respective cohorts. In contrast, a study simultaneously determined the prevalence of poor adherence, white coat refractory hypertension, and under-treatment as causes of pseudo-refractory hypertension in the same cohort. This study was a retrospective analysis of primary care patients with refractory hypertension who were participants in a study of determinants of blood pressure control that included electronic pill monitoring and ambulatory blood pressure measurement. Of the 69 patients analysed, 22% had white coat refractory hypertension and 29% were non-adherent with their medications based on taking <80% of the prescribed doses. Accordingly, only half of the patients could be classified as having true refractory hypertension based on being adequately adherent with their prescribed medications and having elevated ambulatory blood pressure levels. Further, none of these patients were optimally treated in that only a small number of them were receiving a maximum recommended dose of an angiotensin converting enzyme inhibitor, angiotensin receptor blocker, or calcium channel blocker, and none were receiving chlorthalidone or spironolactone. Combined, these studies clearly demonstrate that pseudo-refractory hypertension represents a large proportion of patients with apparent refractory hypertension, since more than 50% of patients in these cohorts were not adequately compliant with their prescribed medications, had white coat refractory hypertension, or were undertreated. [5, Rank 5]

The pathophysiology of resistant hypertension also involves a rightward shift of the renal function curve. Resistance to standard pharmacologic therapies - calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, thiazide diuretics, β-blockers, α-blockers, central acting agents, and peripheral vasodilators characterizes secondary forms of hypertension.

Vascular biology assumes a pivotal role in the initiation and perpetuation of

hypertension and cardiovascular TOD (Target-organ damage). Oxidative stress (ROS and RNS), inflammation (increased expression of redox-sensitive pro-inflammatory genes, cellular adhesion molecules and recruitment migration and infiltration of circulating cells) and autoimmune vascular dysfunction (T cells and B cells) are the primary pathophysiologic and functional mechanisms that induce vascular disease. All three of these are closely inter-related and leads to vascular smooth muscle and cardiac dysfunction, hypertension, vascular disease, atherosclerosis and cardiovascular disease. Hypertension is not a disease but is the correct and chronically dysregulated response with an exaggerated outcome of the infinite insults to the blood vessel with subsequent environmental-genetic expression patterns and downstream disturbances in which the vascular system is the innocent bystander. This becomes a maladaptive vascular response that was initially intended to provide vascular defense to the endothelial insults. Hypertension is a vasculo-pathy characterized by disturbance of endothelium derived factors, structural remodeling, vascular inflammation, increased arterial stiffness, reduced distensibility and loss of elasticity. These insults are biomechanical (BP, pulse pressure, blood flow, oscillatory flow, turbulence, augmentation, pulse wave velocity and reflected waves) and bio-humoral or biochemical which includes all the non-mechanical causes such as metabolic, endocrine, nutritional, toxic, infectious and other etiologies. In addition to the very well established connections for endocrine and nutritional causes of hypertension, toxins and infections also increase BP. Various toxins such as polychlorinated biphenyls, mercury, lead, cadmium, arsenic and iron also increase BP and cardiovascular disease. Numerous microbial organisms have been implicated in hypertension and congestive heart disease. All of these insults lead to impaired micro-vascular structure and function which manifests clinically as hypertension. The level of BP may not give an accurate indication of the micro-vascular involvement and impairment in hypertension. Hypertensive patients have abnormal microvasculature in the form of inward eutrophic remodeling of the small resistance arteries leading to impaired vasodilatory capacity, increased vascular resistance, increased media to lumen ratio, decreased maximal organ perfusion and reduced flow reserve, especially in the heart with decreased coronary flow reserve. Significant functional than structural microvascular impairment occurs even before the BP begins to rise in normotensive offspring of hypertensive parents evidenced by

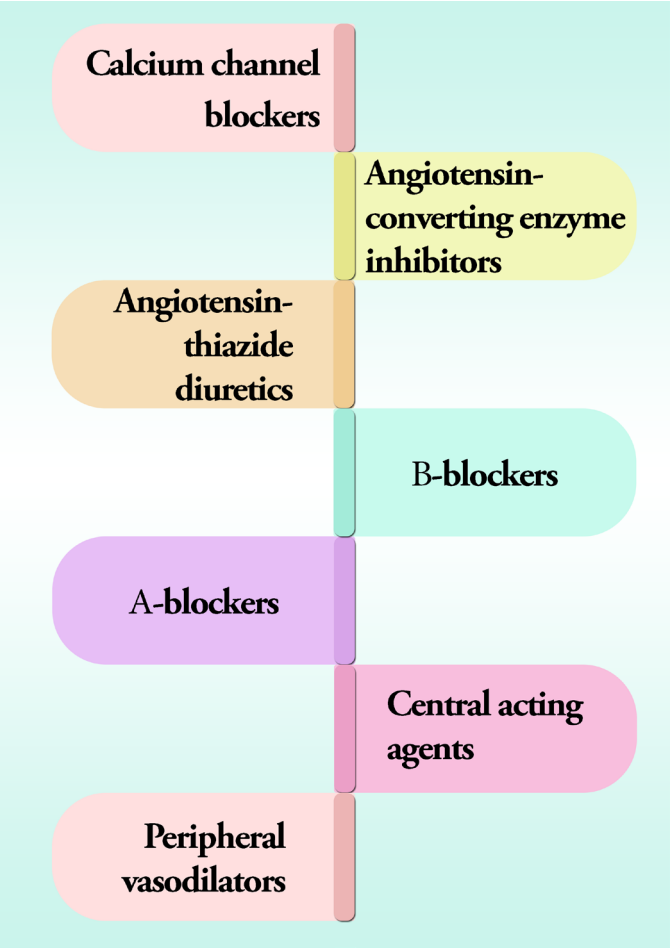

Figure 4: Standard Drug therapy for Hypertension

disturbance of endothelium derived factors, impaired vasodilation, forearm vascular resistance, diastolic dysfunction, increased left ventricular mass index, increased septal and posterior wall thickness and left ventricular hypertrophy. Thus, the cellular processes underlying the vascular perturbations constitute a vascular phenotype of hypertension that may be determined by early life programming and imprinting which is compounded by vascular aging. [11, Rank 3]

Pathophysiological changes in Hypertension

Oxidative Stress

Oxidative stress, with an imbalance between ROS and RNS (Reactive oxygen species and reactive nitrogen species) and the anti-oxidant defense mechanisms, contributes to the etiology of hypertension in humans. Radical oxygen species and reactive nitrogen species are generated by multiple cellular sources, including nicotinamide adenine dinucleotide phosphate hydrase (NADPH) oxidase, mitochondria, xanthine oxidase, uncoupled endothelium-derived nitric oxide (NO) synthase (U-eNOS), cyclo-oxygenase and lipo-oxygenase. Superoxide anion is the predominant ROS species produced by these tissues, which neutralizes NO and also leads to downstream production of other ROS. Hypertensive patients have impaired endogenous and exogenous anti-oxidant defense mechanisms, an increased plasma oxidative stress and an exaggerated oxidative stress response to various stimuli. Hypertensive subjects also have lower plasma ferric reducing ability of plasma, lower vitamin C levels and increased plasma 8-isoprostanes, which correlate with both systolic and diastolic BP.

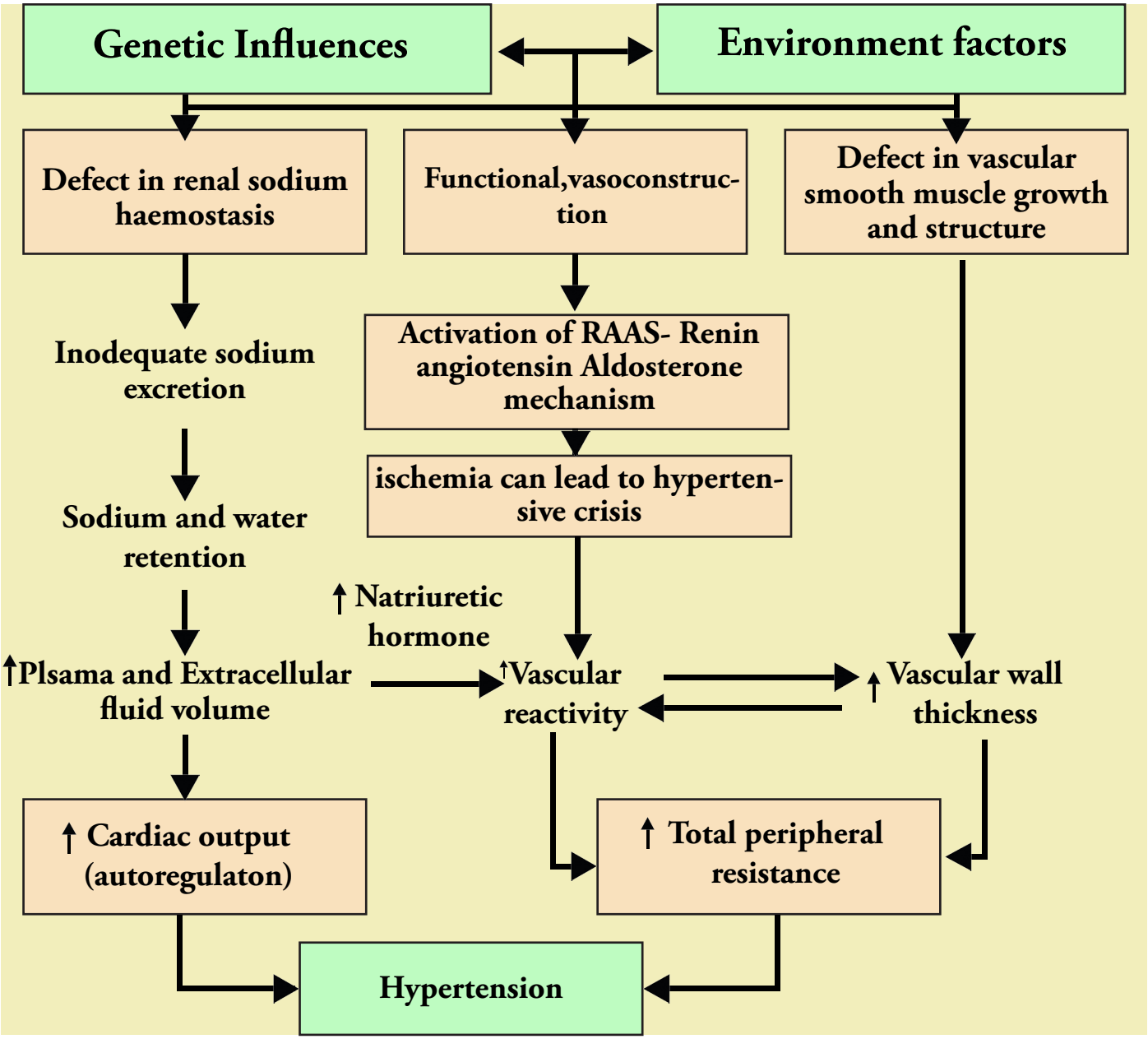

Figure 5: Pathophysiology of Hypertension

Various single-nucleotide polymorphisms (SNP's) in genes that codify for anti-oxidant enzymes are directly related to hypertension. These include NADPH oxidase, xanthine oxidase, superoxide dismutase 3 (SOD 3), catalase, glutathione peroxidase 1 (GPx 1) and thioredoxin. Antioxidant deficiency and excess free radical production have been implicated in human hypertension in numerous epidemiologic, observational and interventional studies. Radical oxygen species directly damage endothelial cells, degrade NO, influence eicosanoid metabolism, oxidize LDL, lipids, proteins, carbohydrates, DNA and organic molecules, increase catecholamines, damage the genetic machinery, influence gene expression and transcription factors. The

increased oxidative stress, inflammation and autoimmune vascular dysfunction in human hypertension results from a combination of increased generation of ROS and RNS, an exacerbated response to ROS and RNS and a decreased antioxidant reserve. Increased oxidative stress in the rostral ventrolateral medulla (RVLM) enhances glutamatergic excitatory inputs and attenuates GABA-ergic inhibitory inputs to the RVLM which contributes to increased sympathetic nervous system (SNS) activity from the paraventricular nucleus. Activation of the AT1R in the RVLM increases NADPH oxidase and increases oxidative stress and superoxide anion, increases SNS outflow causing an imbalance of SNS/ PNS activity with elevation of BP, increased heart rate and alterations in heart rate variability and heart rate recovery time, which can be blocked by AT1R blockers. [12, Rank 5]

Inflammation

The link between inflammation and hypertension has been suggested in both cross-sectional and longitudinal studies. Increases in high sensitivity C-reactive protein (HS-CRP) as well as other inflammatory cytokines such as interleukin-1B, (IL-1B), IL-6, tumour necrosis alpha (TNF-α) and chronic leukocytosis occur in hypertension and hypertensive- related TOD, such as increased carotid IMT. HS-CRP predicts future cardiovascular events. Elevated HS-CRP is both a risk marker and risk factor for hypertension and cardiovascular disease. Increases in HS-CRP of over 3 μg/ mL may increase BP in just a few days that are directly proportional to the increase in HS-CRP. Nitric oxide and e-NOS are inhibited by HS-CRP. The AT2R, which normally counterbalances AT1R, is down-regulated by HS-CRP. Angiotensin II (A-II) up regulates many of the cytokines, especially IL-6, CAMs and chemokines by activating nuclear factor Kappa B (NF-κB) leading to vasoconstriction. These events, along with the increases in oxidative stress and endothelin-1, elevate blood pressure. [15, Rank 4]

Autoimmune dysfunction

Innate and adaptive immune responses are linked to hypertension and hypertension-induced CVD through at least three mechanisms: cytokine production, central nervous system stimulation and renal damage. This includes salt sensitive hypertension with increased renal inflammation as a result of T cell imbalance, dysregulation of CD4+ and CD8+ lymphocytes and chronic leukocytosis with increased neutrophils and reduced lymphocytes. Leukocytosis, especially increased neutrophils and decreased lymphocyte count increase BP in

Blacks by 6/2 mmHg in the highest vs the lowest tertile. Macrophages and various T-cell subtypes regulate BP, invade the arterial wall, activate Toll-like receptors and induce autoimmune vascular damage. Angiotensin II activates immune cells (T cells, macrophages and dendritic cells) and promotes cell infiltration into target organs CD4+ T lymphocytes express AT1R and PPAR gamma receptors, and release TNF-α, interferon and interleukins within the vascular wall when activated. IL-17 produced by T cells may play a pivotal role in the genesis of hypertension caused by Angiotensin II. Hypertensive patients have significantly higher Toll-like receptor 4 mRNA in monocytes compared to normal. Intensive reduction in BP to systolic BP (SBP) less than 130 mm Hg vs SBP to only 140 mmHg lowers the Toll-like receptors 4 more. A-II activates the Toll-like receptors expression leading to inflammation and activation of the innate immune system. When Toll-like receptors 4 is activated there is downstream macrophage activation, migration, increase metalloproteinase 9, vascular remodelling, collagen accumulation in the artery, left ventricular hypertrophy and cardiac fibrosis. The autonomic nervous system is critical in either increasing/ decreasing immune function or inflammation.Efferent cholinergic anti-inflammatory pathways via the vagal nerve innervate the spleen, nicotine acetylcholine receptor subunits and cytokine producing immune cells to influence vasoconstriction and blood pressure. Local Central nervous system inflammation or ischemia may mediate vascular inflammation and hypertension. [16, Rank 4]

Aldosterone is associated with increased adaptive immunity and autoimmune responses with CD4+ T cell activation and Th 17 polarization with increased IL 17, TGF-β and TNF-α which modulate over 30 inflammatory genes. Increased serum aldosterone is an independent risk factor for cardiovascular disease and coronary heart disease through non-hemodynamic effects as well as through increased blood pressure. Blockade of mineralocorticoid receptors in the heart, brain, blood vessels and immune cells reduces cardiovascular risk even with the persistence of hypertension. [15, Rank 5]

Prognosis

An increasing number of longitudinal and prospective studies clearly demonstrate that patients with refractory hypertension have an increased risk of cardiovascular and renal complications and all-cause mortality compared to patients with more easily

controlled hypertension. For example, investigators evaluated the risk of incident stroke and coronary heart disease (CHD) and all-cause mortality among 2043 participants with refractory hypertension relative to 12279 REGARDS participants with controlled hypertension being treated <4 antihypertensive medication classes or uncontrolled hypertension treated with 1 or 2 antihypertensive medication classes. Refractory hypertension was stratified into two subgroups, including participants with controlled hypertension on ≥ 4 antihypertensive medication classes (i.e., controlled refractory hypertension) and uncontrolled hypertension on ≥3 antihypertensive medication classes (i.e., uncontrolled refractory hypertension). During a median follow-up of 5.9 years and after multivariable adjustment, the risk of incident stroke was increased by 25% (hazard ratio, 1.25; 95% confidence interval, 0.94-1.65 compared to participants without refractory hypertension. During a median follow-up of 4.4 years, incident coronary heart disease was increased by 69% (1.69; 1.27-2.24) and all-cause mortality by 29% (1.29; 1.14-1.46) during a median follow-up of 6.0 years. Compared with controlled refractory hypertension, uncontrolled refractory hypertension was associated with increased risk of coronary heart disease (2.33; 1.21-4.48), but not stroke or mortality. Having refractory hypertension that was controlled did not increase risk of stroke, coronary heart disease or mortality compared to participants without refractory hypertension. [7, Rank 2]

In an analysis of the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial, investigators determined the risk of incident stroke, coronary heart disease, peripheral artery disease (PAD), end-stage renal disease (ESRD), and all-cause mortality in participants with controlled or uncontrolled refractory hypertension (n=1870) versus participants without refractory hypertension (n=12814) defined as controlled blood on ≤3 antihypertensive medications. The average follow up was 4.9 years. Incidence of all outcomes as well as all-cause mortality was increased in participants with refractory hypertension. Increased risk was highest for development of ESRD (95%), CHF (88%), and stroke (57%). Risk of incident CHD and PAD was increased by 44% and 23%, respectively. All-cause mortality was increased by 30% compared to participants without refractory hypertension. Interestingly, the crude incidence rates for CHD, CHF, PAD and ESRD were each higher among participants with controlled refractory hypertension compared to participants

without refractory hypertension, suggesting a residual risk for incident cardiovascular and renal disease even after blood is controlled but with use of 4 or more medications. These two studies, as well as other prospective studies, clearly indicate that refractory hypertension that requires 4 or more medications substantially increases risk of cardiovascular and renal complications and as well as death compared to hypertension that is controlled with use of 3 or less medications. [7, Rank 3]

Drug-Related Refractive Hypertension

Several classes of pharmacologic agents can increase Blood Pressure and contribute to the drug induced Refractive Hypertension.

Nonsteroidal anti-inflammatory agents (NSAIDs) increase BP by reducing the production of prostaglandins E2 and I2, leading to reduced vasodilation and sodium excretion. With their widespread use, NSAIDs are considered one of the most common offending agents affecting BP control. The results of meta-analyses have indicated that the average increase in mean arterial pressure is highly variable, with a range of reports from 2 to 5 mm Hg. Several studies found no effect of NSAIDs on BP in patients who were using diuretics.

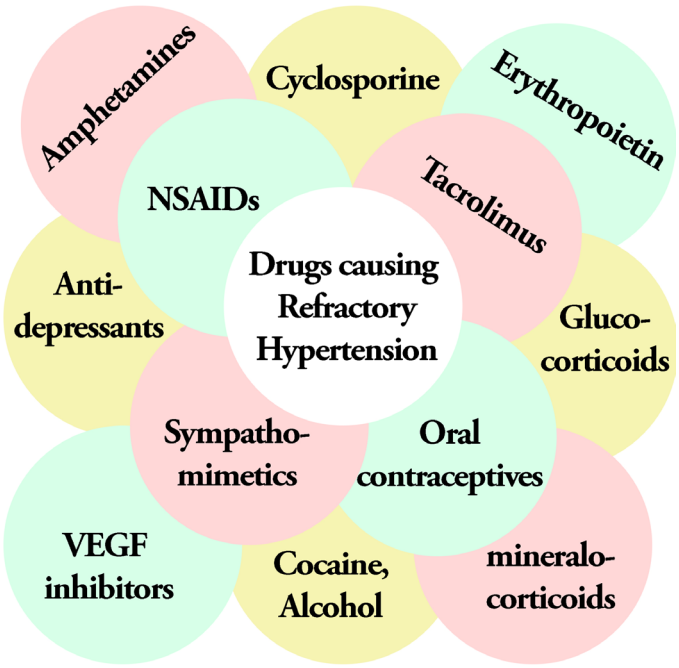

Figure 6 : Drugs and Other Substances Exacerbate Elevated BP

The BP effect appears to be dose-dependent, involving the inhibition of COX-2 in the kidneys, with a reduction in sodium excretion and an increase in intravascular volume. In contrast, low-dose aspirin does not have COX-2–inhibiting or BP-increasing effects.

Oral contraceptives raise BP and induce hypertension by increasing angiotensin biosynthesis. A study in hypertensive women reported that women taking oral contraceptives had more severe hypertension and poorer BP control rates than women using other contraceptive methods. The type of oral contraceptives is important, with combined oral contraceptives (progestin and estradiol) associated with BP elevations at greater rates than lower-dose

estradiol-only and progestin-only oral contraceptives. Postmenopausal hormone replacement therapy uses much lower estrogen doses than oral contraceptives, combined with progestin for women with an intact uterus. Estrogen replacement therapy and hormone replacement therapy appear to have a neutral effect on BP, as illustrated by the following observations from 2 large randomized trials.

Sympathetic amines increase BP by activation of the sympathetic nervous system. The association of sympathomimetic amines with dose-related increases in BP has been well established. Although sympathomimetic-induced hypertension may not be clinically significant in healthy patients, these BP levels can be concerning in individuals with comorbid conditions. Sympathomimetic amines include amphetamines and similar compounds such as pseudoephedrine and ephedrine. Historically, these compounds were contained in some over-the-counter cough and cold preparations and appetite suppressants, with several, most notably phenylpropanolamine, taken off the current market.

Recombinant human erythropoietin can increase BP by complex mechanisms in a dose-dependent fashion. Long-term use of erythropoietin promotes vascular smooth muscle cell growth, vascular remodeling, and medial hypertrophy; with maintained elevated BP. Erythropoietin-induced hypertension can be controlled with antihypertensive medications, often with a single agent.

> **"Cyclosporine and tacrolimus increase BP by inducing systemic and renal vasoconstriction and sodium retention. Hypertension is reported in the majority of patients undergoing renal, hepatic, or heart transplantation treated with cyclosporine."**

In patients being treated for malignancies, antineoplastic drugs that target the VEGF (vascular endothelial growth factor) pathway have emerged as inducers of hypertension. Tachycardia and BP elevation are common clinical manifestations of cocaine use. BP elevation is caused by increased central sympathetic outflow and blockade of neuronal norepinephrine reuptake. Amphetamines increase norepinephrine production, augmenting sympathetic nervous system activation. The complications of amphetamines are comparable to those of cocaine and include hypertension and tachycardia.

Monoamine oxidase inhibitors may lead to severely elevated BP in individuals

who consume foods containing tyramine. Tranylcypromine is the most likely of the agents to raise BP compared with moclobemide and brofaromine. Tricyclic antidepressants have been found to increase BP in patients with panic disorders.

Clinical Considerations of Refractory Hypertension for a health care provider

Treatment

Many of the natural compounds in food, certain nutraceutical supplements, vitamins, antioxidants or minerals function in a similar fashion to a specific class of antihypertensive drugs. Although the potency of these natural compounds may be less than the antihypertensive drug, when used in combination with other nutrients and nutraceutical supplements, the antihypertensive effect is additive or synergistic. [13, Rank 3]

Reducing blood volume not only reduces central venous pressure, but even more importantly, reduces cardiac output by the Frank-Starling mechanism due to the reduction in ventricular preload. An added benefit of these drugs is that they reduce systemic vascular resistance with long-term use.

> **"Arterial pressure can be reduced by decreasing cardiac output, systemic vascular resistance, or central venous pressure. An effective and inexpensive way of reducing venous pressure and cardiac output is by using drugs that reduce blood volume. Diuretics act on the kidney to enhance sodium and water excretion."**

Many antihypertensive drugs have their primary action on systemic vascular resistance. Some of these drugs produce vasodilation by interfering with sympathetic adrenergic vascular tone (sympatholytics) or by blocking the formation of angiotensin II or its vascular receptors. Other drugs are direct arterial dilators, and some are mixed arterial and venous dilators. Although less commonly used because of a high incidence of side effects, there are drugs that act on regions in the brain that control sympathetic autonomic outflow. By reducing sympathetic efferent activity, centrally acting drugs decrease arterial pressure by decreasing systemic vascular resistance and cardiac output. Some antihypertensive drugs, most notably beta-blockers, depress heart rate and contractility by blocking the influence of sympathetic nerves on the heart. Calcium-channel blockers also reduce cardiac

ANTIHYPERTENSIVE DRUGS	
Diuretics	• Thiazide diuretics • Loop diuretics • Potassium-sparing diuretics
Vasodilators	• Alpha-adrenoceptor antagonists (alpha-blockers) • Angiotensin converting enzyme inhibitors (ACE inhibitors) • Angiotensin receptor blockers (arbs) • Calcium-channel blockers • Direct acting arterial dilators • Ganglionic blockers • Nitrodilators • Potassium-channel openers • Renin inhibitors
Cardioinhibitory drugs	• Beta-blockers • Calcium-channel blockers
Centrally acting sympatholytics	• Clonidine • Guanabenz • Guanfacine • A-methyldopa

Table 1: Medical Management of Hypertension

output by decreasing heart rate and contractility.

Combining food and nutrients with medications

Several of the strategic combinations of nutra-ceutical supplements together or with anti-hypertensive drugs, have been shown to lower BP more than the medication alone. Many anti-hypertensive drugs may cause nutrient depletions that can actually interfere with their anti-hypertensive action or cause other metabolic adverse effects manifest through the lab or with clinical symptoms. Diuretics decrease potassium, magnesium, phosphorous, sodium, chloride, folate, vitamin B6, zinc, iodine and coenzyme Q10; increase homo-cysteine, calcium and creatinine; and elevate serum glucose by inducing insulin resistance. [16, Rank 5]

Vascular biology such as endothelial and VSMD plays a primary role in the initiation and perpetuation of hypertension, cardiovascular disease and Target Organ Damage. Nutrient-gene interactions and epigenetics are a predominant factor in promoting beneficial or detrimental effects in cardiovascular health and hypertension. Food and nutrients can prevent, control and treat hypertension through numerous vascular biology mechanisms. Oxidative stress, inflammation and autoimmune dysfunction initiate and propagate hypertension and cardiovascular disease. A clinical approach which incorporates diet, foods, nutrients, exercise, weight reduction, smoking cessation, alcohol and caffeine restriction, and other lifestyle strategies can be systematically and successfully incorporated into clinical practice. [12, Rank 4]

Dietary Approaches to Stop Hypertension

The Dietary Approaches to Stop Hypertension (DASH) I and II diets conclusively demonstrated significant reductions in BP in borderline and stageI hypertensive patients. Studies were conducted to evaluate how the DASH diet increases plasma renin activity (PRA) and serum aldosterone levels in response to the BP reductions. The mean increase in plasma renin activity was 37 ng/ mL per day. There was an associated of response with the G46A polymorphism of beta 2 adrenergic receptor. The A allele of G46A had a greater BP reduction and blunted PRA and aldosterone. The arachidonic acid (AA) genotype had the best response and the GG genotype had no response. Adding an angiotensin receptor blockers, ACE inhibitors or Dietary Reference Intake improved BP response to the DASH diet in the GG group due to blockade of the increase in plasma renin activity. A low sodium DASH diet decreases oxidative stress (urine F2-isoprostanes), improves vascular function (augmentation index) and lowers BP in salt sensitive subjects. In addition, plasma nitrite increased and pulse wave velocity decreased at week two on the DASH diet. [14, Rank 3]

Sodium (Na+) reduction

The average sodium intake in the US is 5000 mg/d with some areas of the country consuming 15000-20000 mg/d. However, the minimal requirement for sodium is probably about 500 mg/ d. Epidemiologic, observational and controlled clinical trials demonstrate that an increased sodium intake is associated with higher BP as well as increased risk for cardio vascular disease, Cerebro vascular accident, left ventricular hypertrophy, coronary heart disease, myocardial infarction, renal insufficiency, proteinuria and over activity of the sympathetic nervous system. A reduction in sodium intake in hypertensive patients, especially the salt sensitive patients, will significantly lower BP by 4-6/ 2-3 mmHg that is proportional to the degree of sodium restriction and may prevent or delay hypertension in high risk patients and reduce future CV events. [9, Rank 5]

Salt sensitivity (≥ 10% increase in MAP with salt loading) occurs in about 51% of hypertensive patients and is a key factor in determining the cardiovascular, cerebrovascular, renal and BP responses to dietary salt intake. Cardiovascular events are more common in the salt sensitive patients than in salt resistant ones, independent of BP. The risk is independent of

BP for cerebro vascular accident with a relative risk of 1.04 to 1.25 from the lowest to the highest quartile. In addition, patients will convert to a non-dipping blood pressure pattern with increases in nocturnal blood pressure as the sodium intake increases.

Increased sodium intake has a direct adverse effect on endothelial cells. Sodium promotes cutaneous lymphangiogenesis, increases endothelial cell stiffness, reduces size, surface area, volume, cytoskeleton, deformability and pliability, reduces eNOS and NO production, increases asymmetric dimethyl arginine (ADMA), oxidative stress and TGF-β. All of these abnormal vascular responses are increased in the presence of aldosterone. These changes occur independent of BP and may be partially counteract by dietary potassium. The sodium intake per day in hypertensive patients should be between 1500 to 2000 mg. Sodium restriction improves BP reduction in those on patients that are on pharmacologic treatment and the decrease in BP is additive with restriction of refined carbohydrates. Reducing dietary sodium intake may reduce damage to the brain, heart, kidney and vasculature through mechanisms dependent on the small BP reduction as well as those independent of the decreased BP. [8, Rank 4]

Potassium

The average U.S. dietary intake of potassium (K+) is 45 mmol/ d with potassium to sodium (K+/Na+) ratio of less than 1:2. The recommended intake of K+ is 4700 mg/d (120 mmol) with a K+/Na+ ratio of about 4-5 to 1. Numerous epidemiologic, observational and clinical trials have demonstrated a significant reduction in BP with increased dietary K+ intake in both normotensive and hypertensive patients. The average BP reduction with a K+ supplementation of 60 to 120 mmol/d is 4.4/2.5 mmHg in hypertensive patients but may be as much as 8/4.1 mmHg with 120 mmol/d (4700 mg). In hypertensive patients, the linear dose-response relationship is 1.0 mmHg reduction in SBP and 0.52 mmHg reduction in diastolic BP per 0.6 g/d increase in dietary potassium intake that is independent of baseline dietary potassium ingestion. High potassium intake reduces the incidence of cardiovascular (CHD, MI) and CVA independent of the BP reduction. There are also reductions in CHF, LVH, diabetes mellitus and cardiac arrhythmias. If the serum potassium is less than 4.0 meq/ dL, there is an increased risk of cardiovascular disease mortality, ventricular tachycardia, ventricular fibrillation and CHF. Red blood cell potassium is a better indication of total body stores and

cardiovascular disease risk than is serum potassium. [14, Rank 5]

Magnesium

A high dietary intake of magnesium of at least 500-1000 mg/d reduces BP in most of the reported epidemiologic, observational and clinical trials, but the results are less consistent than those seen with Na+ and K+. In most epidemiologic studies, there is an inverse relationship between dietary magnesium intake and BP. A study of 60 essential hypertensive subjects given magnesium supplements showed a significant reduction in BP over an eight week period documented by 24 h ambulatory BP, home and office blood BP. The maximum reduction in clinical trials has been 5.6/2.8 mmHg but some studies have shown no change in BP. The combination of high potassium and low sodium intake with increased magnesium intake had additive anti-hypertensive effects. Magnesium also increases the effectiveness of all anti-hypertensive drug classes. [13, Rank 3]

Zinc

Low serum zinc levels in observational studies correlate with hypertension as well as CHD, type II DM, hyperlipidemia, elevated lipoprotein a [Lp(a)], increased 2 h postprandial plasma insulin levels and insulin resistance. Zinc is transported into cardiac and vascular muscle and other tissues by metallothionein. [7, Rank 4]

> **"An increased sodium intake has a direct positive correlation with BP and the risk of cerebro-vascular disease and Coronary Heart Disease."**

Protein

Observational and epidemiologic studies demonstrate a consistent association between a high protein intake and a reduction in BP and incident BP. The protein source is an important factor in the BP effect; animal protein being less effective than non-animal or plant protein, especially almonds. In the Inter-Salt Study of over 10000 subjects, those with a dietary protein intake 30% above the mean had a lower BP by 3.0/2.5 mmHg compared to those that were 30% below the mean (81 vs 44 g/d). However, lean or wild animal protein with less saturated fat and more essential omega-3 fatty acids may reduce BP, lipids and CHD risk.

Soy protein lowers BP in hypertensive patients in most studies. Soy protein intake was significantly and inversely associated with both SBP and DBP in 45694

Chinese women consuming 25 g/d or more of soy protein over 3 years and the association increased with age. [7, Rank 2]

In addition to ACEI effects, protein intake may also alter catecholamine responses and induce a natriuretic effect. Low protein intake coupled with low omega 3 fatty acid intake may contribute to hypertension in animal models. The optimal protein intake, depending on level of activity, renal function, stress and other factors, is about 1.0 to 1.5 g/kg per day. [7, Rank 3]

Amino acids and related compounds

L-arginine:

L-arginine and endogenous methylarginines are the primary precursors for the production of nitric oxide, which has numerous beneficial cardiovascular effects, mediated through conversion of L-arginine to nitric oxide by eNOS (endothelial nitric oxide synthase). Patients with hypertension, hyperlipidemia, diabetes mellitus and atherosclerosis have increased levels of High Sensitivity C-Reactive Protein and inflammation, increased microalbumin, low levels of apelin (stimulates nitric oxide in the endothelium), increased levels of arginase (breaks down arginine) and elevated serum levels of ADMA, which inactivates NO (nitric oxide).

Under normal physiological conditions, intracellular arginine levels far exceed the Km [Michaelis Menton constant (MMC)] of endothelial nitric oxide synthase which is less than 5 μmol. However, endogenous NO formation is dependent on extracellular arginine concentration. The intracellular concentrations of L-arginine are 0.1-3.8 mmol/L in endothelial cells while the plasma concentration of arginine is 80-120 μmol/L which is about 20-25 times greater than the Michaelis Menton constant. Despite this, cellular NO formation depends on exogenous L-arginine and this is the arginine paradox. Renal arginine regulates BP and blocks the formation of endothelin, reduces renal sodium reabsorption and is a potent antioxidant. [15, Rank 4]

L-carnitine and acetyl -L-carnitine:

L-carnitine is a nitrogenous constituent of muscle primarily involved in the oxidation of fatty acids in mammals. Human studies on the effects of L-carnitine and acetyl-L-carnitine are limited, with minimal to no change in BP. In patients with MS, acetyl-L-carnitine at one gram bid over 8 wk, improved dysglycemia and reduced SBP by 7-9 mmHg, but diastolic BP was significantly decreased only in those with higher glucose. Low carnitine levels are associated with a nondipping BP pattern in Type 2 DM. Carnitine has antioxidant and anti-inflammatory effects and may be useful in the

treatment of essential hypertension, type II DM with hypertension, hyperlipidemia, cardiac arrhythmias, congestive heart failure and cardiac ischemic syndromes. Doses of 2-3 g twice per day are recommended. [16, Rank 3]

Taurine

Taurine is a sulfonic beta-amino acid that is considered a conditionally-essential amino acid, which is not utilized in protein synthesis, but is found free or in simple peptides with its highest concentration in the brain, retina and myocardium. In cardiomyocytes, it represents about 50% of the free amino acids and has a role of an osmoregulator, inotropic factor and anti-hypertensive agent.

Human studies have noted that essential hypertensive subjects have reduced urinary taurine as well as other sulfur amino acids. Taurine lowers BP, systemic vascular resistance and heart rate, decreases arrhythmias, congestive heart failure symptoms and sympathetic nervous system activity, increases urinary sodium and water excretion, increases atrial natriuretic factor, improves insulin resistance, increases nitric oxide and improves endothelial function. Taurine also decreases A-II, plasma renin activity, aldosterone, sympathetic nervous system activity, plasma norepinephrine, plasma and urinary epinephrine, lowers homocysteine, improves insulin sensitivity, kinins and acetyl choline responsiveness, decreases intracellular calcium and sodium, lowers response to beta receptors and has antioxidant, anti-atherosclerotic and anti-inflammatory activities, decreases intima-media thickness and arterial stiffness and may protect from risk of Coronary heart disease. A lower urinary taurine is associated with increased risk of hypertension and cardiovascular disease. [5, Rank 4]

> **"Genetic deficiencies of metallothionein with intramuscular zinc deficiencies may lead to increased oxidative stress, mitochondrial dysfunction, cardiomyocyte dysfunction and apoptosis with subsequent myocardial fibrosis, abnormal cardiac remodeling, heart disease, heart failure, or hypertension. Intracellular calcium increases oxidative stress which is reduced by zinc."**

Omega-3 fats

The omega-3 fatty acids found in cold water fish, fish oils, flax, flax seed, flax oil and nuts lower BP in observational, epidemiologic and in prospective clinical trials.

The findings are strengthened by a dose-related response in hypertension as well as a relationship to the specific concomitant diseases associated with hypertension.

The recommended daily dose is 3000 to 5000 mg/d of combined DHA (docosahexaenoic acid) and EPA (eicosapentaenoic acid) in a ratio of 3 parts EPA to 2 parts DHA and about 50% of this dose as GLA combined with gamma/ delta tocopherol at 100 mg per gram of DHA and EPA to get the omega 3 index to 8% or higher to reduce BP and provide optimal cardioprotection. Docosahexaenoic acid is more effective than eicosapentaenoic acid for reducing BP and should be given at 2 g/d if administered alone. [7, Rank 5]

Omega-9 fats

Olive oil is rich in the omega-9 docosahexaenoic acid) (MUFA) oleic acid, which has been associated with BP and lipid reduction in Mediterranean and other diets. Olive oil and docosahexaenoic acid) s have shown consistent reductions in BP in most clinical studies in humans. In one study, the SBP fell 8 mmHg ($P \leq 0.05$) and the DBP fell 6 mmHg ($P \leq 0.01$) in both clinic and 24 h ambulatory BP monitoring in the docosahexaenoic acid) treated subjects compared to the PUFA(Poly Unsaturated Fatty Acids) treated subjects. Extra virgin olive oil (EVOO) is also contains lipid-soluble phytonutrients such as polyphenols. Approximately 5 mg of phenols are found in 10 g of EVOO. About 4 tablespoons of Extra virgin olive oil is equal to 40 g of extra virgin olive oil which is the amount required to get significant reductions in BP. [20, Rank 5]

> **"The omega-3 Fatty Acids have a multitude of other cardiovascular consequences which modulates BP such as increases in endothelial nitric oxide synthase and nitric oxide, improvement in endothelial dysfunction (ED), reduction in plasma nor-epinephrine and increase in para sympathetic nervous system tone, suppression of ACE activity and improvement in insulin resistance."**

Fiber

The clinical trials with various types of fiber to reduce BP have been inconsistent. Soluble fiber, guar gum, guava, psyllium and oat bran may reduce BP and reduce the need for antihypertensive medications in hypertensive subjects, diabetic subjects and hypertensive-diabetic subjects. The average reduction in BP is about 7.5/5.5 mmHg on

40 to 50 g/d of a mixed fiber. There is improvement in insulin sensitivity, endothelial function, reduction in Sympathetic Nervous System activity and increase in renal sodium loss. [13, Rank 3]

Vitamin C

Vitamin C is a potent water-soluble electron-donor. At physiologic levels it is an antioxidant although at supra-physiologic doses such as those achieved withintravenous vitamin C it donates electrons to different enzymes which results in pro-oxidative effects. At physiologic doses vitamin C recycles vitamin E, improves ED and produces a diuresis. Dietary intake of vitamin C and plasma ascorbate concentration in humans is inversely correlated to SBP, DBP and heart rate.

An evaluation of published clinical trials indicate that vitamin C dosing at 250 mg twice daily will significantly lower SBP 5-7 mmHg and diastolic BP 2-4 mmHg over 8 wk. Vitamin C will induce a sodium water diuresis, improve arterial compliance, improve endothelial function, increase nitric oxide and PGI2, decrease adrenal steroid production, improve sympathovagal balance, increase RBC Na/K ATPase, increase SOD, improve aortic elasticity and compliance, improve flow mediated vasodilation, decrease pulse wave velocity and augmentation index, increase cyclic GMP, activate potassium channels, reduce cytosolic calcium and reduce serum aldehydes. [14, Rank 4]

Vitamin E

Most studies have not shown reductions in BP with most forms of tocopherols or tocotrienols. Patients with T2DM and controlled hypertension (130/76 mmHg) on prescription medications with an average BP of 136/76 mmHg were administered mixed tocopherols containing 60% gamma, 25% delta and 15% alpha tocopherols. The BP actually increased by 6.8/3.6 mmHg in the study patients ($P < 0.0001$) but was less compared to the increase with alpha tocopherol of 7/5.3 mmHg ($P < 0.0001$). This may be a reflection of drug interactions with tocopherols via cytochrome P 450 (3A4 and 4F2) and reduction in the serum levels of the pharmacologic treatments that were simultaneously being given. Gamma tocopherol may have natriuretic effects by inhibition of the 70pS potassium channel in the thick ascending limb of the loop of Henle and lower BP. Both alpha and gamma tocopherol improve insulin sensitivity and enhance adiponectin expression via PPAR gamma dependent processes, which have the potential to lower BP and serum glucose. If vitamin E has an antihypertensive

effect, it is probably small and may be limited to untreated hypertensive patients or those with known vascular disease or other concomitant problems such as diabetes or hyperlipidemia. [14, Rank 5]

Vitamin D

Vitamin D3 may have an independent and direct role in the regulation of BP and insulin metabolism. Vitamin D influences BP by its effects on calcium-phosphate metabolism, RAA system, immune system, control of endocrine glands and ED. If the Vitamin D level is below 30 ng/mL the circulating plasma renin activity levels are higher which increases angiotensin II, increases BP and blunts plasma renal blood flow. The lower the level of Vitamin D, the greater the risk of hypertension, with the lowest quartile of serum Vitamin D having a 52% incidence of hypertension and the highest quartile having a 20% incidence. Vitamin D3 markedly suppresses renin transcription by a VDR-mediated mechanism viathe JGA apparatus. Its role in electrolytes, volume and BP homeostasis indicates that Vitamin D3 is important in amelioration of hypertension. Vitamin D lower ADMA, suppresses pro-inflammatory cytokines such as TNF-α, increases nitric oxide, improves endothelial function and arterial elasticity, decreases vascular smooth muscle hypertrophy, regulates electrolytes and blood volume, increases insulin sensitivity, reduces free fatty acid concentration, regulates the expression of the natriuretic peptide receptor and lowers HS-CRP.

The hypotensive effect of vitamin D was inversely related to the pre-treatment serum levels of 1,25(OH)2D3and additive to antihypertensive medications. Short-term supplementation with vitamin D3 and calcium is more effective in reducing SBP than calcium alone. The reduction in BP is related to the pre-treatment level of vitamin D3, the dose of vitamin D3 and serum level of vitamin D3, but BP is reduced only in hypertensive patients. Although vitamin D deficiency is associated with hypertension in observational studies, randomized clinical trials and their meta-analysis have yielded inconclusive results. In addition, vitamin D receptor gene polymorphisms may effect the risk of hypertension in men. A 25 hydroxyvitamin D level of 60 ng / mL is recommended. [8, Rank 3]

Vitamin B6 (pyridoxine)

Low serum vitamin B6 (pyridoxine) levels are associated with hypertension in humans. High dose vitamin B6 at 5 mg/kg per day for 4 wk significantly lowered BP by 14/10 mmHg. Pyridoxine (vitamin B6) is a cofactor in neurotransmitter and hormone

synthesis in the central nervous system (norepinephrine, epinephrine, serotonin, GABA and kynurenine), increases cysteine synthesis to neutralize aldehydes, enhances the production of glutathione, blocks calcium channels, improves insulin resistance, decreases central sympathetic tone and reduces end organ responsiveness to glucocorticoids and mineralocorticoids. Vitamin B6 is reduced with chronic diuretic therapy and heme pyrollactams. Vitamin B6 thus has similar action to central alpha agonists, diuretics and CCB's. The recommended dose is 200 mg/d orally. [3, Rank 3]

Flavonoids

Over 4000 naturally occurring flavonoids have been identified in such diverse substances as fruits, vegetables, red wine, tea, soy and licorice. Flavonoids (flavonols, flavones and isoflavones) are potent free radical scavengers that inhibit lipid peroxidation, prevent atherosclerosis, promote vascular relaxation and have antihypertensive properties. In addition, they reduce stroke and provide cardioprotective effects that reduce CHD morbidity and mortality. Resveratrol is a potent antioxidant and antihypertensive found in the skin of red grapes and in red wine. Resveratrol administration to humans reduces augmentation index, improves arterial compliance and lowers central arterial pressure when administered as 250 mL of either regular or dealcoholized red wine. [8, Rank 4]

Lycopene

Lycopene is a fat-soluble phytonutrient in the carotenoid family. Dietary sources include tomatoes, guava, pink grapefruit, watermelon, apricots and papaya in high concentrations. Lycopene produces a significant reduction in BP, serum lipids and oxidative stress markers. [16, Rank 5]

Pycnogenol

Pycnogenol, a bark extract from the French maritime pine, at doses of 200 mg/d resulted in a significant reduction in SBP from 139.9 mmHg to 132.7 mmHg ($P < 0.05$) in eleven patients with mild hypertension over eight weeks in a double-blind randomized placebo crossover trial. Diastolic BP fell from 93.8 mmHg to 92.0 mmHg. Pycnogenol acts as a natural ACEI, protects cell membranes from oxidative stress, increases NO and improves endothelial function, reduces serum thromboxane concentrations, decreases myelo-peroxidase activity, improves renal cortical blood flow, reduces urinary albumin excretion and decreases HS-CRP. Other studies have shown reductions in BP and a decreased

need for ACEI and CCB, reductions in endothelin-1, HgA1C, fasting glucose, LDL-C and myeloperoxidase. [17, Rank 5]

Garlic

Clinical trials utilizing the correct dose, type of garlic and well absorbed long acting preparations have shown consistent reductions in BP in hypertensive patients with an average reduction in BP of 8.4/7.3 mmHg. Not all garlic preparations are processed similarly and are not comparable in antihypertensive potency. In addition, cultivated garlic (allium sativum), wild uncultivated garlic or bear garlic (allium urisinum) as well as the effects of aged, fresh and long acting garlic preparations differ. Garlic is also effective in reducing BP in patients with uncontrolled hypertension already on anti-hypertensive medication. A garlic homogenate-based supplement was administered to 34 prehypertensive and stageI hypertensive patients at 300 mg/d over 12 wk with a reduction in BP of 6.6-7.5/4.6-5.2 mmHg. Aged garlic at doses of 240 to 960 mg/d given to 79 hypertensive subjects over 12 wk significantly lowered SBP 11.8 ± 5.4 mmHg in the high dose garlic group. A time released garlic may reduce BP better than the shorter acting garlic. A Cochrane Database review indicated a net reduction in BP of 10-12/6-9 mmHg in all clinical trials with garlic. In a double-blind parallel randomized placebo-controlled trial of 50 patients, 900 mg of aged garlic extract with 2.4 mg of S-allylcysteine was administered daily for 12 wk and reduced SBP 10.2 mmHg ($P = 0.03$) more than the control group. [13, Rank 5]

Approximately 10000 mcg of allicin (one of the active ingredients in garlic) per day, the amount contained in four cloves of garlic (5 g) is required to achieve a significant BP lowering effect. Garlic has ACE Inhibitors activity, calcium channel blocking activity, reduces catecholamine sensitivity, improves arterial compliance, increases bradykinin and nitric oxide and contains adenosine, magnesium, flavonoids, sulfur, allicin, phosphorous and ajoenes that reduce BP. [14, Rank 4]

Seaweed

Wakame seaweed is the most popular, edible seaweed. In humans, 3.3 g of dried Wakame for four wk significantly reduced both the SBP 14 ± 3 mmHg and the DBP 5 ± 2 mmHg ($P < 0.01$). In a study of 62 middle-aged, male subjects with mild hypertension given a potassium-loaded, ion-exchanging, sodium-adsorbing, potassium-releasing seaweed preparation, significant BP reductions occurred at four weeks on 12 and 24 g/d of the seaweed preparation ($P <$

0.01). The MAP fell 11.2 mmHg (P < 0.001) in the sodium-sensitive subjects and 5.7 mmHg (P < 0.05) in the sodium-insensitive subjects, which correlated with PRA.

Seaweed and sea vegetables contain most all of the seawater's 77I minerals and rare earth elements, fiber and alginate in a colloidal form. The primary effect of Wakame appears to be through its ACEI activity from at least four parent tetrapeptides and possibly their dipeptide and tripeptide metabolites, especially those containing the amino acid sequence Val-Tyr, Ile-Tyr, Phe-Tyr and Ile-Try in some combination. Its long-term use has demonstrated its safety. Other varieties of seaweed may reduce BP by reducing intestinal sodium absorption and increasing intestinal potassium absorption. [11, Rank 4]

Sesame

Sesame has been shown to reduce BP in a several small randomized, placebo controlled human studies over 30-60 d. In a group of 13 mild hypertensive subjects, 60 mg of sesamin for 4 wk lowered SBP 3.5 mmHg (P < 0.044) and DBP 1.9 mmHg (P < 0.045). Black sesame meal at 2.52 g/d over 4 wk in 15 subjects reduced SBP by 8.3 mmHg (P < 0.05) but there was a non-significant reduction in DBP of 4.2 mmHg. Sesame oil at 35 g/d significantly lowered

> **"Sesame lowers BP alone or in combination with nifedipine diuretics and beta blockers."**

central BP within 1 h and also maintained BP reduction chronically in 30 hypertensive subjects, reduced heart rate, reduced arterial stiffness, decreased augmentation index and pulse wave velocity, decreased HSCRP, improved NO, decreased endothelin-Iand improved antioxidant capacity.

In addition sesame lowers serum glucose, HgbA1C and LDL-C, increases HDL, reduces oxidative stress markers and increases glutathione, SOD, GPx, CAT, vitamins C, E and A. The active ingredients are natural ACEI's such as sesamin, sesamolin, sesaminol glucosides, furoufuran lignans which also suppressors of NF-κB. All of these effects lower inflammation and oxidative stress improve oxidative defense and reduce BP. [5, Rank 3]

Beverages: Tea, coffee, and cocoa

Green tea, black tea and extracts of active components in both have demonstrated reduction in BP in humans. In a double blind placebo controlled trial of 379 hypertensive subjects given green tea extract 370 mg/d for 3 mo, BP was reduced significantly at 4/4 mmHg with simultaneous decrease in HS CRP, TNF-α, glucose and

insulin levels. [6, Rank 1]

Dark chocolate (100 g) and cocoa with a high content of polyphenols (30 mg or more) have been shown to significantly reduce BP in humans. Cocoa may also improve insulin resistance and endothelial function.

Polyphenols, chlorogenic acids (CGAs), the ferulic acid metabolite of chlorogenic acids and di-hydro-caffeic acids decrease BP in a dose dependent manner, increase eNOS and improve endothelial function in humans. chlorogenic acids in green coffee been extract at doses of 140 mg/d significantly reduced SBP and DBP in 28 subjects in a placebo- controlled randomized clinical trial. A study of 122 male subjects demonstrated a dose response in Systolic BP and Diastolic BP with doses ofchlorogenic acids from 46 mg/d to 185 mg/d. The group that received the 185 mg dose had a significant reduction in BP of 5.6/3.9 mmHg ($P < 0.01$) over 28 d. Hydroxyhydroquinone is another component of coffee beans which reduces the efficacy of Chlorogenic acids in a dose-dependent manner which partially explains the conflicting results of coffee ingestion on BP. Furthermore, there is genetic variation in the enzyme responsible for the metabolism of caffeine modifies the association between coffee intake, amount of coffee ingested and the risk of hypertension, heart rate, MI, arterial stiffness, arterial wave reflections and urinary catecholamine levels. Fifty-nine percent of the population has theIF/IA allele of the CYP1A2 genotype which confers slow metabolism of caffeine. Heavy coffee drinkers who are slow metabolizers had a 3.00 HR for developing hypertension. In contrast, fast metabolizers with theIA/ IA allele have a 0.36 HR for incident hypertension. [7, Rank 2]

Additional compounds

Melatonin demonstrates significant anti-hypertensive effects in humans in a numerous double-blind randomized placebo controlled clinical trials at 3-5 mg/d. The average reduction in BP is 6/3 mmHg. Melatonin stimulates GABA(Gamma Amino Butyric Acid) receptors in the Central Nervous System and vascular melatonin receptors, inhibits plasma A II levels, improves endothelial function, increases NO, vasodilates, improves nocturnal dipping, lowers cortisol and is additive with ARBs. Beta blockers reduce melatonin secretion. [10, Rank 3]

Hesperidin significantly lowered DBP 3-4 mmHg ($P < 0.02$) and improved microvascular endothelial reactivity in 24 obese hypertensive male subjects in a randomized, controlled crossover study over 4 wk for each of three treatment groups

consuming 500 mL of orange juice, hesperidin or placebo. [8, Rank 2]

Pomegranate juice is rich in tannins and has numerous other properties that improve vascular health and reduces the Systolic BP by 5%-12%. A study of 51 healthy subjects given 330 mg/d of pomegranate juice had reduction in BP of 3.14/2.33 mmHg ($P < 0.001$). Pomegranate juice also suppresses the postprandial increase in SBP following a high-fat meal. Pomegranate juice reduces serum ACE activity by 36%, and has anti-atherogenic, antioxidant and anti-inflammatory effects. Pomegranate juice at 50 mL/d reduced carotid IMT by 30% over one year, increased PON 83%, decreased oxLDL by 59%-90%, decreased antibodies to oxLDL by 19%, increased total antioxidant status by 130 %, reduced TGF-β, increased catalase, SOD and GPx, increased eNOS and NO and improved endothelial function. Pomegranate juice works like an ACEI. [11, Rank 4]

Grape seed extract (GSE) was administered to subjects in nine randomized trials, meta-analysis of 390 subjects and demonstrated a significant reduction in SBP of 1.54 mmHg ($P < 0.02$). Significant reduction in BP of 11/8 mmHg ($P < 0.05$) were seen in another dose response study with 150 to 300 mg/d of GSE over 4 wk. GSE has high phenolic content which activates the PI3K/Akt signaling pathway that phosphorylates eNOS and increases NO. [14, Rank 5]

Coenzyme Q10 (Ubiquinone)

Coenzyme Q10 has consistent and significant antihypertensive effects in patients with essential hypertension.

- Compared to normotensive patients, essential hypertensive patients have a higher incidence (6 fold) of coenzyme Q10 deficiency documented by serum levels
- Doses of 120 to 225 mg/d of coenzyme Q10, depending on the delivery method or the concomitant ingestion with a fatty meal, are necessary to achieve a therapeutic level of 3 ug/ mL.

This dose is usually 3-5 mg/ kg per day of coenzyme Q10. Oral dosing levels may become lower with nanoparticle and emulsion delivery systems intended to facilitate absorption. Other favorable effects on cardiovascular risk factors include improvement in the serum lipid profile and carbohydrate metabolism with reduced glucose and improved insulin sensitivity, reduced oxidative stress, reduced heart rate, improved myocardial left ventricular

> "Alpha lipoic acid (ALA) is known as thioctic acid and it is a prescription medication. It is a sulfur-containing compound with antioxidant activity both in water and lipid phases. Its use is well-established in the treatment of certain forms of liver disease and in the delay of onset of peripheral neuropathy in patients with diabetes."

function and oxygen delivery and decreased catecholamine levels. [3, Rank 4]

Alpha lipoic acid

Recent research has evaluated its potential role in the treatment of hypertension, especially as part of the MS. In a double-blind cross over study of 36 patients over 8 wk with coronary heart disease and hypertension, 200 mg of lipoic acid with 500 mg of acetyl-L-carnitine significantly reduced BP 7/3 mmHg and increased brachial artery diameter.

The QUALITY study of 40 patients with diabetes mellitus and stage-I hypertension showed significant improvements in BP, urinary albumin excretion, flow-mediated dilation and insulin sensitivity over 8 wk with a combination of Quinapril (40 mg/d) and lipoic acid (600 mg/d) that was greater-than either alone. Lipoic acid increases levels of glutathione, cysteine, vitamin C and vitamin E, inhibits NF-κB, reduces endothelin-1, tissue factor and VCAM-1, increases cAMP, downregulates CD4 immune expression on mononuclear cells, reduces oxidative stress,

inflammation, reduces atherosclerosis in animal models, decreases serum aldehydes and closes calcium channels which improves vasodilation, increases NO and nitrosothiols, improves endothelial function and lowers BP. Lipoic acid normalizes membrane calcium channels by providing sulfhydryl groups, decreasing cytosolic free calcium and lowers SVR. In addition, lipoic acid improves insulin sensitivity which lowers glucose and advanced glycosylation end products which improves BP control and lowers serum triglycerides. [6, Rank 3]

Evaluation of Secondary Causes

Further screening investigations for secondary causes are not compulsory. Additional tests should be chosen depending on the clinical circumstances of the patient as revealed by history and examination (as shown in Figure 8) finally, all patients with ongoing uncontrolled hypertension should be assessed routinely for any signs of end-organ compromise. This may include measures such as yearly fundoscopy, electrocardiogram and urine dipstick.

DISORDER	SUGGESTED INVESTIGATION
Primary hyperaldosteronism	Plasma aldosterone: renin ratio
Thyroid disorder	TFT
Pheochromocytoma	24 hour urine catecholamine level Plasma metanephrines
Cushings syndrome	Urinary cortisol
Obstructive sleep apnoea	Polysomnography
Renovascular disease	Renal artery duplex scan
Renal parenchymal disease	Renal ultrasound scan
Coarctation of the aorta	Cardiac ultrasound scan

Figure 7: Evaluation of Secondary causes in Refractory hypertension

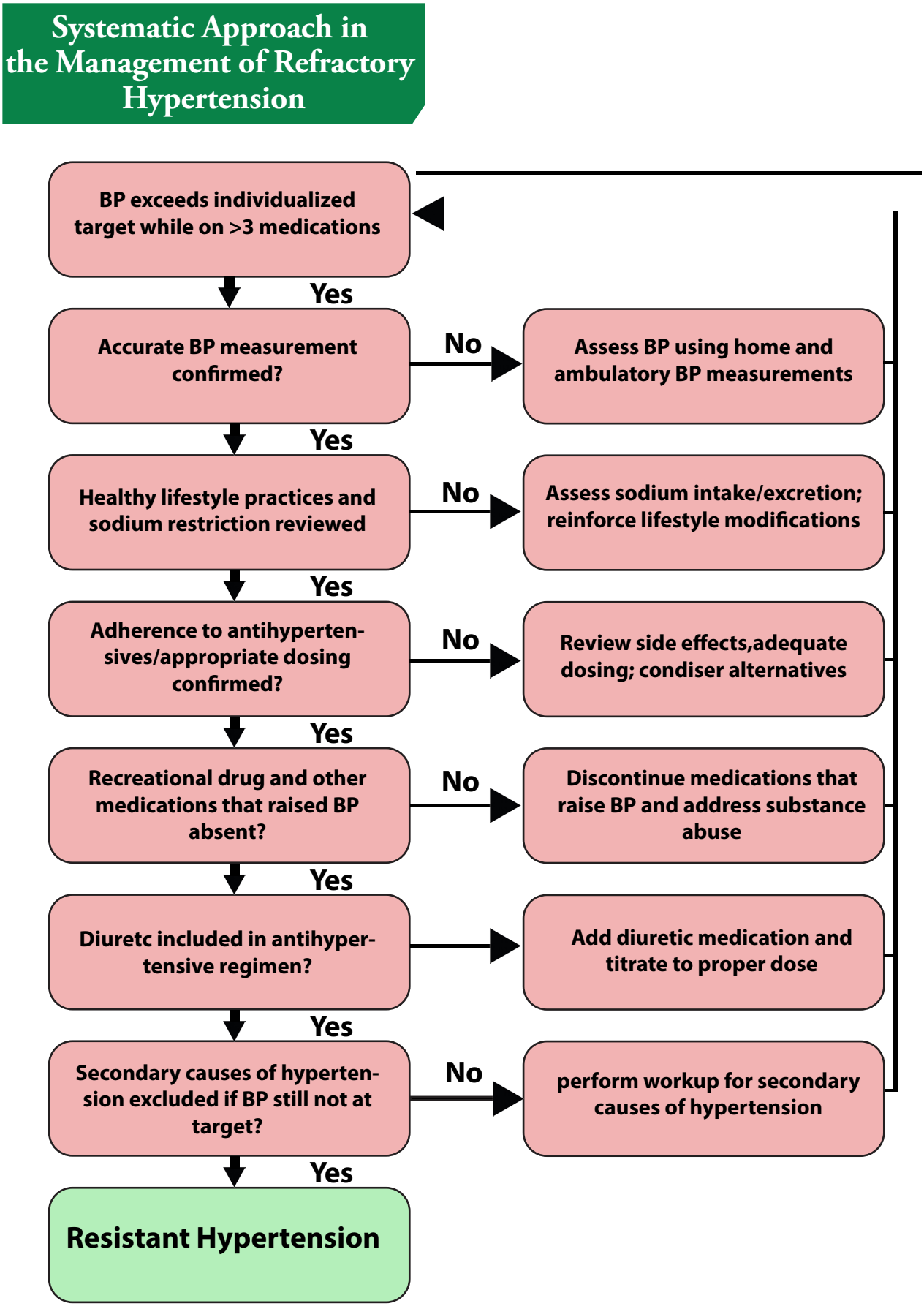

Figure 8: Systematic Approach in the Management of Refractory Hypertension

A systematic approach to evaluating the patient with suspected Refractory Hypertension is illustrated by Branko Braam and Sandra J. Taler et. al (as shown in Figure 7) [21]

First, the accuracy of BP measurements using optimal technique needs to be established. Common pitfalls include improper patient positioning, wrong cuff size, poor timing of measurements, and equipment-related error. Ambulatory BP monitoring (ABPM) is an important component of the evaluation.

The US Preventive Services Task Force recommends Ambulatory BP monitoring as the standard for confirmation of a hypertension diagnosis outside of the clinical setting. It is important to detect nondipping, defined as <10% nocturnal drop in BP, in assessing overall BP control and for prognostic significance. Thus, even in the setting of goal office measurements, it might be useful to pursue ABPM, such as when disproportionate target organ damage is present.

Specialist Referral

Difficult patients will require referral to a hypertension specialist. Indications for referral include patients with uncontrolled blood pressure despite receiving maximum tolerated doses of four medications, patients suffering end-organ damage as a consequence of their high blood pressure, or patients with a suspected secondary cause. All patients unresponsive to quadruple therapy should be revaluated for a secondary cause.

Conclusion

A novel phenotype of antihypertensive treatment failure is proposed based on the inability to control high blood pressure with use of 5 or more different classes of antihypertensive agents, including a long-acting thiazide-type diuretic, such as chlorthalidone, and a Mineralocorticoid receptor antagonists, such as spironolactone. Findings from a small number of recent studies suggest the phenotype is rare, with a prevalence of less than 5% of patients referred to hypertension centers for uncontrolled resistant hypertension. The degree to which pseudo-causes of treatment failure, such as poor adherence and white coat effects, contribute to the apparent prevalence the phenotype is unknown. [4, Rank 3]

Refractory hypertension is being proposed as a novel phenotype of antihypertensive treatment failure. While evolving, the definition of the phenotype has mostrecently been defined as the inability to

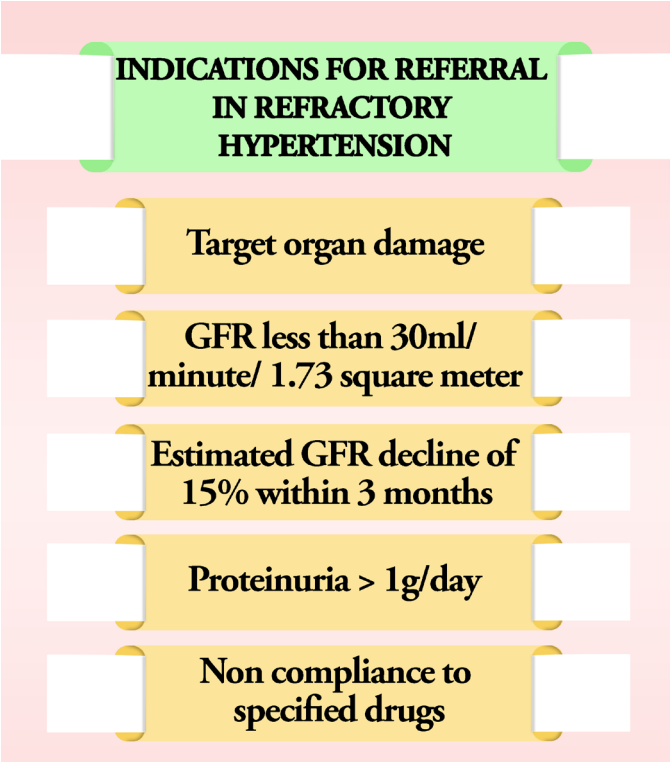

Figure 9: Indications for Referral

control blood pressure with use of five or more different antihypertensive classes, including a long-acting thiazide diuretic and a Mineralocorticoid receptor antagonists. Initial studies suggest that risk factors for the phenotype include obesity, CKD, being of African origin, and possibly, female gender. Patients with refractory hypertension, like the larger subgroup of patients with resistant hypertension, have evidence of more advanced target organ damage compared to patients whose blood pressure can be controlled, include higher rates of CKD, LVH, CHF, and prior stroke. Given its history of uncontrolled and often severe hypertension, having refractory hypertension likely portends a poor prognosis, but outcome studies specific for the phenotype are currently lacking. [12, Rank 5]

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