Evaluation and treatment of resistant hypertension

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ABSTRACT

Resistant hypertension is defined as blood pressure that remains uncontrolled in spite of use of three or more antihypertensive medications in effective doses, usually including a diuretic. Stricter goals, higher obesity rates, increase in life expectance, and increased use of exogenous substances are related to an increasing prevalence of resistant hypertension. The evaluation of patients with resistant hypertension is focused on identifying contributing and secondary causes of hypertension, such as hyperaldosteronism, obstructive sleep apnea, renal parenchymal disease, renal artery stenosis, and pheochromocytoma. Hyperaldosteronism is now recognized as the most common cause of resistant hypertension and all patients with resistant hypertension should be screened with a plasma aldosterone/renin ratio even if the serum potassium level is normal. Treatment includes removal of contributing factors, appropriate treatment of secondary causes, and use of effective multi-drug regimens. Recent studies indicate that the addition of spironolactone to standard treatment regimens induces significant BP reduction in patients with resistant hypertension.

KEY WORDS

Blood pressure, hypertension, resistant hypertension, secondary hypertension, hyperaldosteronism.

INTRODUCTION

Resistant hypertension is defined as blood pressure (BP) that remains above goal in spite of use of three antihypertensive medications in effective doses, usually including a diuretic[1]. Patients who are intolerant of diuretics and have uncontrolled BP with regimens of 3 drugs from different classes should also be considered to have resistant hypertension. The goal BP is less than 140/90 mmHg in general population and less than 130/80 mmHg in patients with diabetes and chronic kidney disease (CKD) (glomerular filtration rate $<$ 60 mL/min/1.73 m^2; serum creatinine $>$ 1.5 mg/dL in men or $>$ 1.3 mg/dL in women; albuminuria $>$ 300 mg/24hr or $>$ 200 mg/g creatinine)[1]. Patients with controlled BP on 4 or more medications are considered to have resistant hypertension.

In spite of improvements in the diagnosis and treatment of hypertension, the control rate remains low. In the National Health and Nutrition Examination Survey III (NHANES III) only 31% of patients with hypertension had controlled BP levels[2]. The true prevalence of uncontrolled hypertension in community practice is unknown, but in clinical studies, it varies between 18% and 50%. In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) 34.4% of subjects remained uncontrolled and 27.3% of patients were on three or more medications after 5 years of follow-up[3]. In The International Verapamil-Trandolapril Study (INVEST) 51% of patients were on three or more antihypertensive drugs after 24 months[4].

Demographic factors that predispose to the development of resistant hypertension include severe hypertension, older age, obesity, and little physical activity. Other factors include greater emphasis on controlling systolic hypertension, increased use of exogenous substances, and newer stricter treatment goals. There are a variety of causes of uncontrolled hypertension (Table 1) including secondary forms of hypertension (Table 2).

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Table 1. Causes related to uncontrolled blood pressure

Pseudoresistance
Sub-optimal treatment
Adherence
White-coat effects
Contributing factors
Obesity
Dietary salt
Exogenous substance

Table 2. Secondary causes of hypertension

Hyperaldosteronism
Obstructive sleep apnea
Renal parenchymal disease
Renal artery stenosis
Pheochromocytoma
Central nervous system tumors
Coarctation of the aorta
Thyroid diseases

PSEUDORESISTANCE

Pseudoresistance is the appearance of lack of BP control caused by inappropriate drug choice/doses, inaccurate measurement of BP, nonadherence to prescribed therapy, and/or white-coat effect.

Suboptimal treatment

Suboptimal medical treatment is an important contributing factor to lack of blood pressure control. In retrospective analysis of 141 patients with high office BP on regimens consisting of 3 or more medications who had been referred to hypertension specialty clinic, 53% achieved the treatment goal after treatment optimization that included most often addition of or change in diuretic therapy[5]. Suboptimal treatment is related to provider's failure to increase the dose or the number of antihypertensive medications, particularly the failure to add a diuretic or failure to change the diuretic according renal function (i.e., failure to use a loop diuretic in patients with chronic kidney disease).

Nonadherence

Poor adherence to prescribed medications is a common cause of uncontrolled hypertension. Non-compliance to treatment was related to uncontrolled BP in 50% of patients with hypertension referred to a hypertension specialty clinic[6]. Cost of treatment, poor doctor and patient rapport, multiple pills, inconvenient dosing, and adverse effects from prescribed agents are important causes of poor adherence. Determining the degree of adherence is dependent of upon patient self-report and is facilitated by good provider-patient rapport.

White-coat effect

White-coat effect is defined by an elevated clinic BP and significantly lower out-of-clinic BP. White coat hypertension appears to be as common among patients with resistant hypertension as in general hypertensive patients. A large study evaluated 286 patients with uncontrolled clinic BP in spite of use 3 or more antihypertensive agents[7]. After 24-hr ambulatory BP monitoring, 56.3% of patients were found to have true resistant hypertension, that is high clinic and ambulatory BP levels, with the remaining patients having white-coat resistance, that is high office BP levels, but normal ambulatory levels.

White-coat effect should be suspected in patients with symptoms of hypotension, such as dizziness and weakness, and in patients with high office BP but not evidence of target organ damage. White-coat effect can be assessed by 24-hr ambulatory or by home BP monitoring.

CONTRIBUTING FACTORS

Obesity

Obesity is common in patients with resistant hypertension. In the Framingham population, persons with a body mass index (BMI) $\geq$ 30 kg/m^2 had a 50% higher probability of uncontrolled BP control than patients with a BMI $<$ 25 kg/m^2.[8] A cross sectional study of 45,125 subjects evaluated antihypertensive treatment in relation to obesity. Patients with BMI $\geq$ 40 kg/m^2 had 5,3 and 3,2 higher risk of needing 4 or 3 antihypertensive medications, respectively, compared to normal weight subjects[9]. Increased sodium and fluid retention, sympathetic activation, and stimulation of the renin-angiotensin-aldosterone system appear to contribute to hypertension in obese subjects[10].

Dietary salt

Dietary salt reduction has not been specifically evaluated in patients with resistant hypertension, but is an important lifestyle intervention to reduce BP. Modest salt reduction can decrease systolic by 5-8 mmHg and diastolic BP by 1-3 mmHg[11]. Certain patient groups such as the elderly, African Americans, and patients with CKD tend to be more salt-sensitive and such that dietary salt restriction can result in large reductions in blood pressure.

Exogenous substances

Exogenous substances most commonly related to resistant hypertension are listed in Table 3. A history of use of these agents should be queried in all patients with resistant hypertension. Withdrawal of these agents can promote better BP control or in some cases even normalize BP in patients with resistant hypertension.

Table 3. Most often exogenous substances that can contribute to resistant hypertension

Nonsteroidal anti-inflammatory
Oral contraceptives
Alcohol
Corticosteroids
Anabolic steroids
Sympathomimetic agents (nasal decongestants, diet pills)
Caffeine
Chemotherapeutic agents
Antidepressants

Nonsteroidal anti-inflammatory (NSAID) drugs, including selective COX-2 inhibitors, are a common cause of uncontrolled BP and renal impairment. Elderly, diabetic patients, and or patients with CKD are more susceptible to these adverse effects. A meta-analysis suggested that nonsteroidal anti-inflammatory agents elevate mean BP by 5.0 mmHg[12]. NSAIDs also worsen BP control by antagonize the effect of most classes of antihypertensive medications. Indomethacin, naproxen, and piroxicam in particular have been associated with significant increases in BP in hypertensive patients[13]. Among selective COX-2, rofecoxib is more likely to raise BP than celecoxib in both normotensive and hypertensive subjects[14]. One mechanism by which NSAIDs increase BP is through volume retention. Inhibition of vasodilating prostaglandins in the kidney is thought to impair natriuresis resulting in fluid retention.

Oral contraceptives tend to induce mild hypertension in young women, but the effect can be severe in some patients. The Nurses' Health Study prospective followed 68,297 premenopausal women without hypertension. Oral contraceptive users had 80% increased risk of developing hypertension compared with non-users[15]. Oral contraceptive use is also associated with uncontrolled BP. A cross-sectional study evaluated the association between oral contraceptives and BP control in 171 hypertensive women. Oral contraceptive users had poorer BP control and tended to have more severe hypertension than users of other contraceptive methods or non-users[16]. Oral contraceptives with estrogen and progestin are more often associated with BP increases than progestin-only oral contraceptives. The combination of estrogen and progestin has been associated with increases in plasma renin activity and aldosterone excretion. Those hormonal and BP effects tend to normalize with discontinuation of the oral contraceptive.

Heavy alcohol ingestion increases the risk of uncontrolled hypertension. In a cross sectional analysis, men with excessive alcohol intake ($\geq$ 4 glasses per day) had 50% higher probability of poor BP control than patients with more moderate alcohol ingestion[17]. Alcohol cessation promotes BP reduction and improves adherence to treatment. A prospective study evaluated the effect of 1 month of abstinence on 24-hr BP in heavy drinkers[18]. A reduction of 7.2 mmHg for 24-hr systolic BP and 6.6 mmHg for 24-hr diastolic was observed. The percentage of subjects considered to be hypertensive also decreased from 42% to 12%. In patients with resistant hypertension, alcohol consumption should be limited to $\leq$ 2 drinks per day.

Exogenous substances that contribute to hypertension should be avoided in patients with high BP and should be discontinued if possible in patients with uncontrolled BP. In subjects in whom these substances cannot be avoided, increased doses and/or numbers of antihypertensive medications may be required.

SECONDARY HYPERTENSION

The prevalence of secondary hypertension is greater in patients with resistant hypertension than in the general hypertensive population. The most common secondary causes of resistant hypertension are hyperaldosteronism, CKD, renal artery stenosis and obstructive sleep apnea (OSA) (Table 2). The prevalence of secondary hypertension increases with age, mainly due to increases in the incidence of renal artery stenosis, CKD, and OSA.

Hyperaldosteronism

Hyperaldosteronism is now recognized as the most common cause of secondary hypertension and a common contributor[19-25]. An extensive evaluation of 600 patients with hypertension revealed that the prevalence of primary aldosteronism (PA) increased with increasing severity of the hypertension. Using the JNC VI (Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High BP) criteria in untreated patients, the prevalence of hyperaldosteronism was 2% in patients with Stage 1 hypertension, 8% in patients with Stage 2 hypertension, and 13% in patients with Stage 3 hypertension[19].

The prevalence of PA is particularly high in patients with resistant hypertension[26-29]. In a prospective evaluation of patients referred to a specialty hypertension clinic for resistant hypertension, defined as uncontrolled hypertension in spite of use of three or more medications, 18 of 88 (prevalence of 20%) patients had PA based on suppressed renin activity and high 24-hr urinary aldosterone excretion during a high salt diet[26].

It is likely that the diagnosis of PA is being made more frequently, at least in part, because it has been recently recognized that the large majority of of patients with PA have normal potassium levels such that hypokalemia is no longer used as a criterion for screening. Also, the recently observed

high prevalence rates of PA is likely related to broader screening of hypertensive populations allowed by use of the plasma aldosterone/renin activity ratio. In addition, description of recent associations between aldosterone excess, obesity, and OSA suggest a possible link between increasing aldosterone levels and worsening rates of obesity[30,31].

All patients with resistant hypertension should be evaluated for hyperaldosteronism, even those with normal potassium levels. PA manifests as high aldosterone levels in the setting of suppressed renin activity. As opposed to assessing plasma aldosterone concentration (PAC) levels or plasma renin activity (PRA) independently, measurement of the PAC/PRA ratio (ARR) has been shown to have sufficient sensitivity to serve as an effective screening test for PA. Although the exact test characteristics of the ARR have varied widely between studies, its negative predictive value has been generally good such that a low ARR ($<$ 20 when PAC is measured in ng/dL and PRA is measured in ng/mL/min) reliably excludes PA. The specificity of ARR is less consistent such that a high ratio ($>$ 20-30) is suggestive but not diagnostic of PA. Accordingly, a high ARR is suspicious for PA, but the diagnosis must be confirmed.

Assessment of 24-hr urinary excretion of aldosterone is a reasonable approach to confirm primary aldosteronism. We will firstly obtain the 24-hr urine collection for aldosterone and sodium during while the patient is ingesting his or her normal diet. (Measuring aldosterone and sodium from the same urine collection requires use of a non-salt preservative such as acetic acid). If the aldosterone is high ($>$ 12-14 μg/24-hr) and the sodium is high ($>$ 200 meq/24-hr), indicative of chronic high salt intake, we have found that is not necessary to do additional salt loading to confirm PA (Figure 1). If the aldosterone is high but the sodium $<$ 200 meq/24-hr in the first collection, we will repeat the collection after salt supplementation for 3 days sufficient to increase the sodium $>$ 200 meq/24-hr.

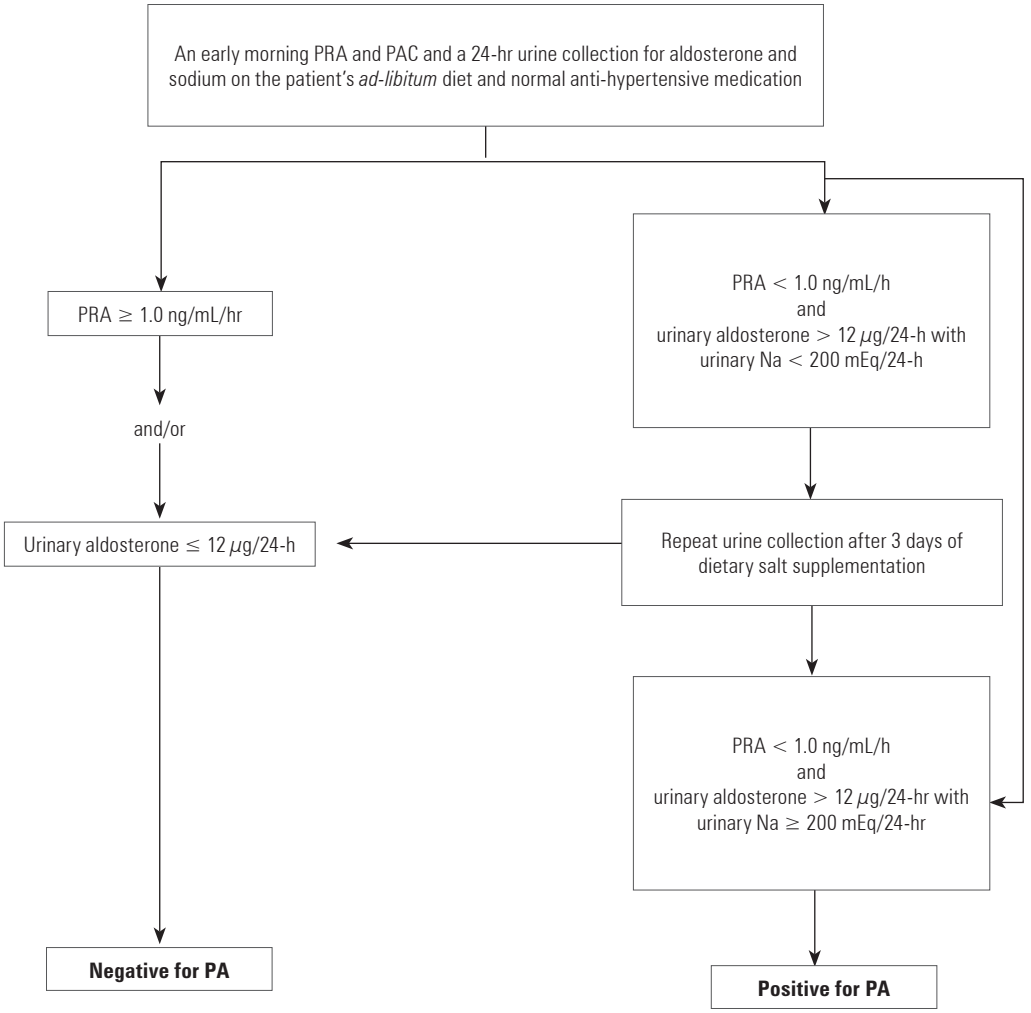

Figure 1. Flow chart for the diagnostic evaluation for primary aldosteronism (PA). PRA indicates plasma renin activity; PAC, plasma aldosterone concentration; Na, sodium. Adapted from Nishizaka *et al*. Am J Hypertens 2005;18:805-12.

Obstructive Sleep Apnea

OSA is a common finding in patients with resistant hypertension. OSA is strongly related to high BP and predicts development of hypertension in normotensive subjects[32,33]. A cross sectional study analyzed overnight polysomnographic evaluations in 41 patients with resistant hypertension. OSA, defined as an apnea-hypopnea index of $\geq$ 10 events/hour, was present in 83% of patients. The prevalence and severity of OSA was significantly higher in male compared to female patients with resistant hypertension[34].

The mechanisms by which OSA leads to hypertension are not completely elucidated. Demonstration of sympathetic activation in patients with OSA suggests that intermittent hypoxemia may increase BP through adrenergic activation[35]. Continuous positive airway pressure (CPAP) treatment is the gold standard for management of OSA. CPAP likely improves BP control, but the reports have not been consistent. In a randomized study of effective or sub-therapeutic nasal CPAP, mean arterial BP decreased by 9.9 mmHg in the effective treatment group. Similarly decreases were seen in diastolic and systolic BP, and in ambulatory nighttime and daytime values[36]. CPAP also significantly reduced BP in 11 patients with resistant hypertension both after the first night and after 2 months after CPAP treatment[37]. However, in contrast, a 6 week prospective study reported no significant difference in BP after 6 weeks of treatment in patients that received optimal or sham CPAP[38].

Chronic Kidney Disease

CKD is a common cause of resistant hypertension and as well as a consequence of poor BP control. For example, in ALLHAT, 70.9% of patients with a serum creatinine $\geq$ 1.5 mg/dL needed 2 or more antihypertensive medications and 40.1% were on three or more medicines at 5 years follow-up compared to 62.0% and 26.6%, respectively, in patients with serum creatinine $<$ 1.5 mg/dL[3]. Fluid retention, excessive activation of the renin-angiotensin system, and use of certain medications as erythropoietin that increase BP contribute to treatment resistance in patients with impaired renal function[39].

All patients with resistance hypertension should be evaluated with calculation of the estimated glomerular filtration rate by Modification of Diet in Renal Disease (MDRD) or Cockcroft-Gault equations[40]. Serum creatinine is an unreliable marker of CKD, particularly in elderly patients. Dietary salt restriction plays an important role controlling BP in patients with CKD in order to minimize volume expansion. Loop diuretics may be necessary to effectively reduce volume and facilitate BP control. Angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB) are not contraindicated in patients with mild to severe CKD and, in fact, should be preferentially prescribed, as the blockade of the renin-angiotensin system in these patients has been shown to reduce cardiovascular risk, improve BP control, reduce proteinuria, and slow progression to end stage renal disease[41].

Renal Artery Stenosis

Renovascular disease is a common finding in hypertensive patients with multiple risk factors and extra-renal atherosclerotic disease, particularly among patients with resistant hypertension. For example, unilateral or bilateral artery stenosis $\geq$ 70% was diagnosed in 22% of patients undergoing cardiac catheterization for suspected coronary artery disease in a veterans hospital, but in only 3.5% of patients in a general hospital[42,43].

Fibromuscular dyplasia causes 10% of renal artery stenosis and occurs most commonly in women younger than 50 years of age. Hypertension is cured or improved in 93% of 27 patients with renal artery fibromuscular dysplasia treated with balloon angioplasty[44]. Restenosis occurs in 20% of patients after one year.

The remaining 90% of renal artery lesions are atherosclerotic and the prevalence increases with age[45]. Patients with known atherosclerotic disease, declining renal function, or a history of flash pulmonary edema have an increased likelihood of atherosclerotic renal disease. However, the choice treatment for atherosclerotic renal lesions is controversial due to lack of strong evidence demonstrating superiority of medical treatment versus angioplasty with stenting either in regards to BP control or progression to advanced renal failure[46]. Screening for and angioplasty of renal artery stenosis seems to be an appropriate in patients with resistant hypertension as they have generally failed medical treatment. Angioplasty should include stenting as enhanced benefit has been observed[47].

Pheocromocytoma

The prevalence of pheocromocytoma in the general hypertensive population is 0.1-0.6%[48,49], but timely diagnosis and treatment is essential as severe and difficult-to-control hypertension often occur. Headache, palpitations, and diaphoresis are the most common findings, but the clinical presentation of pheocromocytoma is widely variable[50]. Pheocromocytoma is associated with increased BP variability due to the fluctuations in the levels of norepinephrine secreted by the tumor[51].

Screening should be done in all patients with hypertension and symptoms of pheochromocytoma. Also, pheocromocytomas should be removed from pregnant women with hypertension before 20 weeks of gestation or when symptoms and hypertension are paroxysmal because of significant risk of maternal and fetal morbidity and mortality[52]. Measurement of plasma free metanephrines is the best screening test for pheocromocytoma having both a high sensitivity and specificity[50].

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TREATMENT OF RESISTANT HYPERTENSION

Treatment of the patient with resistant hypertension includes removal of contributing factors, appropriate treatment of secondary causes, and use of effective multi-drug regimens. Non-pharmacologic therapies, such as weight loss, exercise, dietary salt restriction, and moderation of alcohol intake should be encouraged in all patients. Interfering substances should be withdrawn or down-titrated as possible and OSA should be treated.

Factors related to poor adherence must be assessed. Discussion of medication costs, adverse effects, number of pills, consequences of poorly controlled hypertension, and treatment goals can improve the patient adherence. A multidisciplinary treatment approach including nurses, pharmacists, nutritionists, psychologists, and fitness trainers is expensive but can improve treatment results[53].

Pharmacologic treatment

Inappropriate and ineffective antihypertensive treatment regimens remain a common cause of pseudoresistance. A triple regimen of an ACE or ARB, calcium channel blocker, and a thiazide diuretic is generally very effective and well tolerated. Patients with resistant hypertension generally have occult volume retention and effective diuretic therapy is essential for BP control[5,54]. Long-acting thiazide diuretics in low doses are effective in most patients with resistant hypertension. Loop diuretics are preferable in patients with CKD (creatinine clearance $<$ 30 mL/min). Furosemide is relatively short-acting and should be prescribed at least twice daily. With use of all diuretics, serum potassium levels must be monitored to avoid hypokalemia.

Recent studies have reported that aldosterone antagonists provide significant additional BP reduction in patients with resistant hypertension (Figure 2)[55-58]. One study from our group described the effect of low-dose (12.5 to 25 mg/day) of spironolactone in patients with uncontrolled BP on an average of 4 medications, including an ACE inhibitor or ARB, and a diuretic[57]. The reduction after 6 months follow-up was 25 mmHg in systolic and 12 mmHg in diastolic BP. There was a similar BP reduction in patients with and without PA and overall the BP reduction was not predicted by the baseline PAC or PRA or by 24-hr urinary aldosterone. The benefit also was similar in African American and white subjects. Data from Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT) also demonstrated a significant BP lowering effect of spironolactone as fourth-line therapy. Systolic and diastolic BP was reduced by 21.9 and 9.5 mmHg, respectively, with spironolactone treatment in 1,411 participants[58].

Spironolactone was well tolerated is these studies with breast tenderness occurring in about 10% of male subjects.

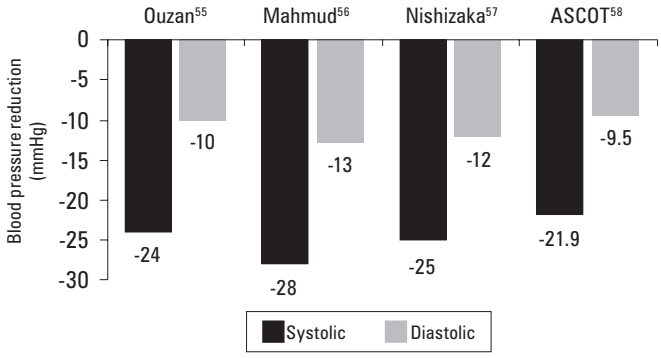

Figure 2. Effect of aldosterone in patients with resistant hypertension.

Hyperkalemia, with or without acute renal insufficiency, is uncommon even in the setting of concomitant ACE inhibitor or ARB use, but it can occur, necessitating close biochemical monitoring. Older age, CKD, diabetes, and concomitant NSAID use increase risk of hyperkalemia. Potassium supplementation or salt substitutes that contain potassium should be discontinued or reduced when beginning treatment with spironolactone.

Eplerenone, is a selective mineralocorticoid receptor antagonist causing less of the sex-related adverse effects (breast tenderness, gynecomastia, sexual dysfunction, and menstrual irregularities) than spironolactone[59]. However, the efficacy of eplerenone has not been evaluated in patients with resistant hypertension, and so its use in this setting should be reserved for patients who are intolerant of spironolactone. Use of spironolactone or eplerenone requires monitoring of serum potassium and creatinine levels.

CONCLUSION

Resistant hypertension defined as uncontrolled BP in spite of use of at least 3 antihypertensive medications is an increasingly common problem. Factors associated with resistant hypertension include older age, obesity, high dietary salt intake, CKD, and OSA. Secondary causes of hypertension are common in patients with resistant hypertension with hyperaldosteronism likely being the most common. Spironolactone can be an effective therapeutic option for the treatment of resistant hypertension even in the absence of demonstrable aldosterone excess.

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