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Treatment resistant hypertension (TRH) is defined by office blood pressure (BP) uncontrolled on ≥ 3 or controlled on ≥ 4 antihypertensive medications, preferably at optimal doses and including a diuretic. Apparent (a)TRH is used when optimal therapy, adherence, and measurement artifacts are unknown. Among treated hypertensives, $\sim 30\%$ of uncontrolled and 10% of controlled individuals have aTRH, with a higher prevalence in Blacks than other race-ethnicity groups. In $\geq 50\%$ of aTRH patients, BP measurement artifacts ('office' TRH), suboptimal regimens, or suboptimal adherence are present, ie, pseudo-resistance. While patients with 'office' TRH have fewer cardiovascular events than those with 'true' TRH, no evidence confirms that patients with suboptimal regimens or adherence are spared. Averaging several office BPs obtained with an automated monitor can reduce 'office' TRH. Home or ambulatory BP monitoring can identify office resistance. Prescribing ≥ 3 different antihypertensive medication classes, eg, thiazide-type diuretic, renin-angiotensin blocker and calcium antagonist at $\geq 50\%$ of maximum recommended doses reasonably defines optimal therapy. Intensifying diuretic therapy, eg, adding an aldosterone antagonist, is effective for many TRH patients who are volume expanded. Clinical information, hemodynamic and renin-guided therapeutics can inform other treatment options. Attention to adverse effects, medication costs, and pill burden can improve adherence and control. Patients with aTRH and suspected secondary hypertension should be evaluated. Interfering substances or medications should be discontinued. These approaches will identify or correct the problem in $\sim 80\%$ of aTRH patients. Referral to a hypertension specialist and newer therapeutic approaches are options for TRH patients who cannot take or do not respond to optimal therapy. *Ethn Dis.* 2015;25(4):495-498; doi:10.18865/ed.25.4.495

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INTRODUCTION

Treatment resistant hypertension (TRH) has been defined as BP above goal on ≥ 3 or controlled to goal on ≥ 4 BP medications prescribed at optimal doses and preferably including a diuretic.¹⁻⁴ The term, apparent treatment resistant hypertension (aTRH), is frequently used since measurement artifacts, suboptimal treatment regimens, ie, contributors to pseudoresistance, are often unknown.¹ Prevalent aTRH nearly doubled from 1988–1994 to 2007–2010 as percentages of adults with controlled hypertension rose from 27% to 52%. This increase in the prevalence of treatment resulted in an overall increase in the prevalence of aTRH, along with a rise in predisposing factors, eg, increasing age, obesity, diabetes, and kidney disease.

Apparent TRH impacts $\sim 30\%$ of treated uncontrolled and 10% of treated controlled adults in the

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United States or ~ 8 million individuals; aTRH is more prevalent in adults of African descent in the United States than other race/ethnicity groups.² Given the high prevalence of aTRH and unfavorable prognosis,³ it is important for primary care clinicians to identify and manage most of these individuals since referring all for specialty care is impractical. This review and Table 1 summarizes an effective approach that can be implemented in primary care for evaluating and managing aTRH.

MEASUREMENT ARTIFACTS COMMON IN UNCONTROLLED ATRH

Ambulatory BP monitoring identifies 'office' TRH in 30%–50% of aTRH patients. 'Office' TRH has a better prognosis than true TRH.^{2,3} Using an accurate, automated office BP monitor to obtain a series of readings with the patient alone in the examination room minimizes the office effect.⁴ Ambulatory BP monitoring (ABPM) is useful for identifying 'office' TRH and provides additional information of prognostic importance, eg, nocturnal BP.⁵ However, ABPM is not readily available in many primary care settings in the United States. Non-hypertensive home BP in the setting of 'office' TRH also identifies a subset of patients at lower risk for clinical cardiovascular events.⁶

Table 1. A 7-step plan for evaluation and management of treatment resistant hypertension²

1. *Confirm treatment resistance.* Office BP $\geq 140/90$ on ≥ 3 BP medications at optimal doses and preferably including a diuretic
2. *Exclude Pseudoresistance.* Is the patient adherent with an optimal treatment regimen? Is out-of-office BP elevated?
3. *Identify and address contributing lifestyle factors,* eg, obesity, physical inactivity, excess alcohol, and high salt intake
4. *Discontinue or reduce interfering substances,* eg, NSAIDs, sympathomimetics, oral contraceptives, erythropoietin, ephedra (non-prescription weight loss)
5. *Screen for secondary causes of hypertension,* eg, obstructive sleep apnea, primary aldosteronism, chronic kidney disease, renal artery stenosis, pheochromocytoma
6. *Continue to optimize pharmacologic treatment.* Enhance diuretic therapy (see text); consider α_1 and β_1 adrenoceptor blockade in patient with an otherwise optimal regimen (avoid combining β -blockade and non-dihydropyridine CCB)
7. *Refer to a Hypertension Specialist* for definitive evaluation and treatment of known or suspected secondary cause(s) of hypertension or if BP remains uncontrolled after 6 months

SUBOPTIMAL TREATMENT REGIMENS

In our experience, ~50% of patients with uncontrolled aTRH are not prescribed an optimal regimen defined as three different BP medications including a diuretic at $\geq 50\%$ of the maxim recommended doses, eg, 25 mg of hydrochlorothiazide, 20 mg of lisinopril, and 5 mg amlodipine.³ While some patients may not tolerate optimal therapy, clinicians have many opportunities to improve BP control by optimizing therapy in aTRH.

INADEQUATE ADHERENCE

Inadequate adherence or failing to take $\geq 75\%$ of prescribed medication, impacts ~10%–60% of aTRH.^{2,3} Direct questions on medication adherence often elicit inaccurate information. Open invitations to share concerns about costs, side effects or other barriers can be useful. Any admission of non-adherence is often associated with taking $<75\%$ of prescribed medication. Concerned fam-

ily members may have insight on patient adherence and barriers.

Medication possession ratio (MPR), ie, the days the patient possesses the medication during a given time period, eg, 6–12 months, is a reasonable proxy for adherence.⁷ A conversation with the pharmacist and examining pill bottles to assess the number of prescription refills relative to the dates of the initial prescription and visit are useful, albeit imperfect assessment of MPR. Reducing out-of-pocket costs and prescribing single-pill combinations, can improve adherence and control. Addressing side effects and, engaging uncontrolled aTRH patients in BP self-monitoring are proven strategies for improving adherence and control.^{2,8}

Adherence to a healthy lifestyle is also important in uncontrolled and TRH. The benefits of sodium restriction⁹ and avoiding excess alcohol and drugs, such as amphetamines and cocaine, are important.² Most obese patients will have a fall in BP with weight loss.² The Dietary Approaches to Stop Hypertension (DASH) eating plan lowers BP without weight loss.¹⁰

SECONDARY HYPERTENSION

Once common contributors to pseudoresistant hypertension are determined to be unlikely explanations for aTRH, further evaluation is important. Suspected secondary causes of hypertension can be assessed in most office settings.² Patients with resistant hypertension are often obese and volume expanded, which contribute to sleep apnea.¹¹ Better control of volume, eg, adding spironolactone, can improve BP and sleep apnea.¹²

Primary aldosteronism is the most common secondary hypertension,² but not all patients are hypokalemic. Plasma renin activity is suppressed together with excess aldosterone production.¹³ While an aldosterone/renin ratio >20 – $30:1$ is a screening test for primary aldosteronism, patients with low-renin hypertension can satisfy ratio criteria without having aldosterone excess. Marked hypokalemia can reduce aldosterone production and should be corrected prior to evaluation. Preferably, patients are not on medications impacting the renin-angiotensin-aldosterone axis for several weeks prior to the assessment for pri-

primary aldosteronism. Practically, a disproportionate share of treated patients with TRH has suppressed plasma renin activity on treatment, although patients should not be taking aldosterone antagonists or epithelial sodium channel antagonists, eg, amiloride, when assessing primary aldosteronism. If low plasma renin occurs with excess aldosterone in a 24-hour urine sample, the diagnosis is confirmed by failure to suppress aldosterone with saline infusion or a high-salt diet. The majority of patients with primary aldosteronism have bilateral adrenal hyperplasia, rather than aldosterone-producing adenoma. If a unilateral adrenal lesion is identified, confirmation of excess aldosterone from that gland is important prior to surgery as incidental, inactive adrenal lesions are relatively common. Patients with aldosterone-producing adenoma and bilateral adrenal hyperplasia often respond to aldosterone antagonists with other agents, eg, thiazide diuretics and calcium antagonists.

INTERFERING SUBSTANCES AND MEDICATIONS

Various over-the-counter and prescribed medications can raise BP.² When possible, these agents should be discontinued.

ADDITIONS AND CHANGES TO THE PHARMACOLOGICAL REGIMEN

Adding a low-dose aldosterone antagonist, eg, 12.5–50 mg spironolactone lowers BP in many TRH

patients.^{2,14} If patients are not ideal candidates for spironolactone, eg, baseline serum K^+ >4.5 or eGFR <50 mL/1.7m²/min, then changing from hydrochlorothiazide (HCTZ) to chlorthalidone can lower BP. Chlorthalidone is more likely than HCTZ to be effective with eGFR 30–44 (Stage 3B chronic kidney disease). Patients with eGFR <30 mL/1.7m²/min, may require a loop diuretic, eg, torsemide to improve volume control and lower BP. Patients with eGFR <15 may require dialysis for volume and BP control.

In patients with progesterone and anti-androgenic effects of spironolactone, eplerenone is an aldosterone antagonist without sex-steroid effects. Amiloride, which blocks epithelial sodium channels, is also effective, especially at higher doses of 10–40 mg daily, as aldosterone raises BP in part by increasing the number and activity of these channels. Monitoring for hyperkalemia is important with both aldosterone antagonists and epithelial sodium channel antagonists.

For patients with neurogenic hypertension, alpha and/or beta-receptor blockade or central sympatholytics, eg, guanfacine, can lower BP. Hemodynamic-, and renin-guided therapy can identify effective medications.¹⁵ With renin-guided therapy, evidence suggests that low-renin patients have a better BP response to diuretics and aldosterone, α_1 -adrenoceptor, and calcium antagonists. Conversely, high-renin patients can have more robust BP responses to angiotensin converting enzyme inhibitors or angiotensin receptor, β -adrenoceptor, and renin blockers.

CONCLUSION

In summary, aTRH is a common condition. With a pragmatic approach, clinicians can identify and address pseudo-resistance, screen for secondary hypertension, and initiate changes to lifestyle and pharmacotherapy to improve BP control. It is likely that $\geq 80\%$ of aTRH patients can be successfully managed in primary care. For complex cases of secondary hypertension and truly refractory hypertension, referral to a hypertension specialist for further management and consideration of device-based therapies is a cogent option.

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