RESISTENT HYPERTENSION

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Resistant Hypertension

- **Blood pressure remaining above goal in spite of concurrent use of 3 antihypertensive agents of different classes.**

- **Ideally, 1 of the 3 agents should be a diuretic & all agents should be prescribed at optimal dose amounts.**

Rationale

- **Identify high-risk patients**
- **Identify patients with reversible causes**
  - **Benefits from diagnostic tools**
  - **Therapeutic interventions**

Definition Highlights

- **Use of diuretic recommended but not required before diagnosing resistant hypertension.**

- **Doses should be optimal but not necessarily maximal before diagnosing resistant hypertension.**

- **Controlled resistant hypertension: high blood pressure controlled but with use of 4 of more agents should be considered resistant.**

Prevalence

- **Prevalence is unknown, but observational and clinical trials suggest it is a common clinical problem.**
- **In a recent analysis of National Health and Nutrition Examination Survey (NHANES) participants being treated for hypertension, only 53% were controlled to <140/90 mm Hg. [1]**
- **Of NHANES participants with CKD, only 37% were controlled to <130/80 mm Hg[2] and only 25% of diabetic participants were controlled to <130/85 mm Hg.[1]**
- **In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) after approximately 5 years of follow-up, 27% of participants were on 3 or more medications.[3]**

[1]Hajjar I, Kotchen TA. JAMA 2003; [2]Peralta CA et al. Hypertension 2005; [3]Cushman WC et al. Clin Hypertens.

Pseudo-resistant Hypertension

- The cuff pressure is inappropriately high compared with intra-arterial pressure because of extensive atheromatous and/or medial hyperplasia in the arterial tree

- The condition increases with age and diagnosis requires a high index of suspicion

Clinical clues suggestive of pseudo-hypertension

- Marked hypertension in the absence of target organ damage.
- Antihypertensive therapy produces symptoms consistent with hypotension in the absence of successful reduction of BP.
- Radiological evidence of pipe stem calcification in the brachial arteries.
- Brachial artery pressure higher than lower extremity pressure.
- Severe and isolated systolic hypertension.
- Positive Osler's maneuver
  - Inflating the BP cuff above the systolic BP: the maneuver is considered positive if a hard cord-like radial artery can still be palpated.

Patient Characteristics Associated with Resistant Hypertension

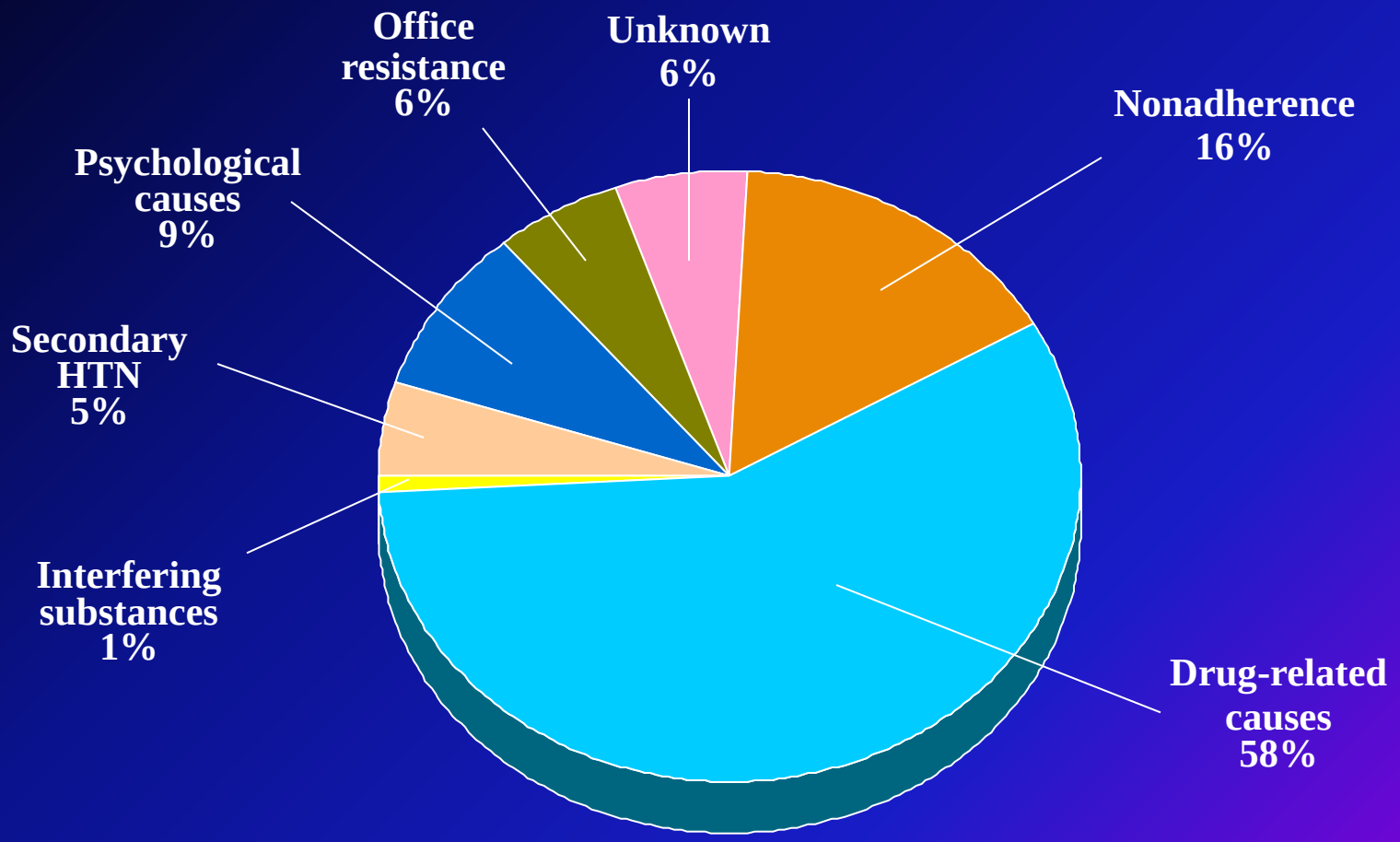
- High baseline blood pressure
- Older age
- Obesity
- Excessive dietary salt ingestion
- Chronic kidney disease
- Diabetes

Patient Characteristics Associated with Resistant Hypertension

- Left ventricular hypertrophy
- African American race
- Female gender
- Residence in Southeastern United States

Cause of Resistance

Cause of resistance found in 133/141 – 94% (83/91 – 91%) cases



Primary cause of resistant hypertension

Garg JP, et al. Am J Hypertens 2003;16:925-930

Lifestyle Factors Contributing to Resistant Hypertension

- Obesity or overweight
- High salt diet
- Physical inactivity
- Ingestion of low-fiber, high-fat diet
- Heavy alcohol ingestion

Causes of Resistance to Hypertension Treatment

- Poor adherence with prescribed medications
- Inaccurate blood pressure measurement
- White coat hypertension

Evaluation of Resistant Hypertension

- Confirm appropriate treatment
- Identify causes
  - Secondary?
- Document target organ damage

Substances that Can Interfere with Blood Pressure Control

- **Non-Narcotic Analgesics**
  - **Non-steroidal anti-inflammatory agents including aspirin**
  - **Selective COX-2 inhibitors**

- **Sympathomimetic agents**
  - **decongestants**
  - **diet pills**
  - **cocaine**

- **Stimulants**
  - **-methylphenidate**
  - **-dexmethylphenidate,**
  - **-dextroamphetamine**
  - **- amphetamine, methamphetamine**
  - **-modafinil**

Substances that Can Interfere with Blood Pressure Control

- Alcohol
- Oral contraceptives
- Cyclosporine
- Erythropoietin
- Natural licorice
- Herbal compounds
  - -ephedra
  - - ma huang

Secondary Causes of Resistant Hypertension

Common

- Obstructive sleep apnea
- Renal parenchymal disease
- Primary aldosteronism
- Renal artery stenosis

Primary Aldosteronism

- A much more common cause of hypertension than had been demonstrated historically
- Prevalence of primary hyperaldosteronism was found to be 6.1% (13% among patients with severe hypertension (180/110 mm Hg). Series with 600 patients
- Serum potassium levels were rarely low in patients confirmed to have primary aldosteronism, suggesting that hypokalemia is a late manifestation
- Primary aldosteronism is common in patients with resistant hypertension with a prevalence of approximately 20%-30%.

Calhoun et al, Hypertension 2008

Secondary Causes of Resistant Hypertension

Uncommon

- Pheochromocytoma
- Cushing's disease
- Hyperparathyroidism
- Aortic coarctation
- Intracranial tumor

Pharmacological Treatment of Resistant Hypertension

- Withdrawal of interfering medications e.g. NSAID (replace with acetaminophen?)
- Diuretic therapy (lack or under use)
- Combination therapy
- Mineralcorticoid receptor antagonists
- Dosing schedule

Calhoun et al, Hypertension 2008

Combination Therapy (JNC – VII)

- ACE inhibitors and calcium channel blockers (CCBs).
- ACE inhibitors and diuretics
- ARBs and diuretics.
- Beta blockers and diuretics.
- Centrally acting drug and diuretic.
- Diuretic and diuretic: e.g. amiloride and hydrochlorothiazide.

Treatment of Resistant Hypertension

Non-Pharmacologic Recommendations

- Weight loss
- Regular exercise (at least 30 min most days of the week)
- Low dietary salt ingestion (<100 mEq sodium/24-hr)
- Moderate alcohol ingestion (no more than 2 drinks per day for most men and 1 drink per day for women or lighter weight persons)
- Ingestion of low-fat, high-fiber diet
- Treat obstructive sleep apnea if present

Lifestyle Modifications

Modification	Approximate SBP Reduction (range)
Weight Reduction	5-10 mmHg/10kg
Adopt DASH eating plan	8-14 mmHg
Dietary sodium reduction	2-8 mmHg
Physical activity	4-9 mmHg
Moderation of alcohol consumption	2–4 mmHg

Treatment of Resistant Hypertension

Pharmacologic Recommendations

- Withdrawal or down titration of interfering substances as possible
- Use of a long-acting thiazide diuretic, preferably chlorthalidone
- Combine agents with different mechanisms of action
- Recommended triple regimen of
  - -ACE inhibitor or ARB
  - - Calcium channel blocker
  - -Thiazide diuretic

Treatment of Resistant Hypertension

- Consider addition of mineralocorticoid receptor antagonist
- Use of loop diuretic may be necessary in patients with CKD (creatinine clearance <30 mL/min)

Referral to a Specialist

- **If a specific secondary cause of hypertension is suspected in a patient with resistant hypertension, referral to the appropriate specialist is recommended as needed.**

- **In the absence of suspected secondary causes of hypertension, referral to a hypertension specialist is recommended if the blood pressure remains elevated in spite of 6 months of treatment.**

Controlled Resistant Hypertension

- **Such patients are at increased risk of reversible and/or secondary causes of hypertension.**

- **Consider adjustment of the treatment regimen to maintain blood pressure control but with use of fewer medications and/or with use of a regimen that minimizes adverse effects.**

Resistant Hypertension: Diagnostic and Treatment Recommendations

Confirm Treatment Resistance

- Office blood pressure >140/90 or 130/80 mm Hg in patients with diabetes or chronic kidney disease

and

- Patient prescribed 3 or more antihypertensive medications at optimal doses, including if possible a diuretic

or

- Office blood pressure at goal but patient requiring 4 or more antihypertensive medications

Exclude Pseudoresistance

- Is patient adherent with prescribed regimen?
- Obtain home, work, or ambulatory blood pressure readings to exclude white coat effect

Identify and Reverse Contributing Lifestyle Factors

- Obesity
- Physical inactivity
- Excessive alcohol ingestion
- High salt, low-fiber diet

Screen for Secondary Causes of Hypertension

- Obstructive sleep apnea (snoring, witnessed apnea, excessive daytime sleepiness)
- Primary aldosteronism (elevated aldosterone/renin ratio)
- Chronic kidney disease (creatinine clearance <30 mL/min)
- Renal artery stenosis (young female, known atherosclerotic disease, worsening renal function)
- Pheochromocytoma (episodic hypertension, palpitations, diaphoresis, headache)
- Cushing's disease (moon facies, central obesity, abdominal striae, inter-scapular fat deposition)
- Aortic coarctation (differential in brachial or femoral pulses, systolic bruit)

Pharmacologic Treatment

- Maximize diuretic therapy, including possible addition of mineralocorticoid receptor antagonist
- Combine agents with different mechanisms of action
- Use of loop diuretics in patients with chronic kidney disease and/or patients receiving potent vasodilators (e.g., minoxidil)

Refer to Specialist

- Refer to appropriate specialist for known or suspected secondary cause(s) of hypertension
- Refer to hypertension specialist if blood pressure remains uncontrolled after 6 months of treatment

Take Home Messages -1

- Resistant hypertension affects approximately 10% of the hypertensive patient population. It should be differentiated from white-coat hypertension and pseudo-resistant hypertension.
- Non-compliance to anti-hypertensive therapy remains the most common cause of resistant hypertension
- Primary hyperaldosteronism is not as uncommon as previously thought,
- Low-renin resistant hypertension responds to aldosterone blockade when other drugs are apparently inadequately effective
- Normal blood levels of potassium in resistant hypertension do not exclude the possible presence of hyperaldosteronism

Take Home Messages -2

- Ambulatory BP monitoring provides information about the level and variability of BP
- Patients with white-coat hypertension do not necessarily exhibit any signs of anxiety and the increased BP is often not associated with tachycardia
- It remains controversial whether it is necessary to start antihypertensive medications in patients with white-coat hypertension
- white coat hypertension may not be an entirely harmless phenomenon.