RESISTANT HYPERTENSION

RAKSHAK SARDA
IOWA HEART CENTER

DISCLOSURE

- None.

DEFINITION AND CLINICAL SIGNIFICANCE

- **Criteria:** BP >130/80 mmHg on 3+ medications (including a diuretic).
- **Controlled Resistance:** BP at goal but requiring 4+ medications.
- **Epidemiology:** Affects 10–15% of hypertensive patients.
- **Prognosis:** Significantly higher risk for Stroke, MI, and Renal Failure.

ELIMINATING "PSEUDO-RESISTANCE"

- **The "White Coat" Effect:** Elevates office readings by 20+ mmHg.
- Confirm via ABPM or Home Monitoring.

- **Technique Errors:** Improper cuff size (especially "cuff hypertension" in obesity).

- **The Adherence Gap:** Up to 40% of patients are non-adherent.

SECONDARY CAUSES & TARGETED SCREENING

Condition	Primary Screening Test
Primary Aldosteronism: 20% of RH	Plasma Aldosterone / Renin Ratio (PAC/PRA)
Sleep Apnea (OSA)	STOP-BANG Questionnaire / Overnight Pulse Ox
Renal Artery Stenosis	Renal Artery Duplex Ultrasound or CT Angio
CKD	Comprehensive Metabolic Panel
Pheochromocytoma	Plasma metanephrine

DEEP DIVE

PRIMARY ALDOSTERONISM

WHO AND WHEN TO SCREEN

- **Prevalence:** Up to 20% in Resistant HTN populations.

- **High-Risk Indicators:**
- BP >150/100 mmHg on three separate measurements.
- Hypokalemia (spontaneous or diuretic-induced).
- Adrenal incidentaloma.
- Family history of early-onset HTN or stroke.

- **Goal:** Identify "Surgical" vs. "Medical" candidates early.

THE SCREENING PROCESS (PAC/PRA)

- **The Test:** Plasma Aldosterone Concentration (PAC) and Plasma Renin Activity (PRA).

- **The "Positive" Result:**
- PAC/PRA Ratio >30.
- PAC must be elevated (usually >15 ng/dL).
- Renin must be suppressed (PRA <1.0 ng/mL).

- **Confounders:** Beta-blockers (false +), ACEi/ARBs (false -).

- **Preparation:** Correct hypokalemia before testing to avoid false negatives.

CONFIRMATORY TESTING & SUBTYPE LOCALIZATION

- **Confirmation:** Oral Salt Loading or Saline Infusion Test (failure to suppress Aldosterone).
- **Imaging:** Adrenal CT (thin-cut) to look for masses.
- **Gold Standard: Adrenal Vein Sampling (AVS)**.
- Essential if surgery is considered.
- Distinguishes Unilateral Adenoma (Surgical) from Bilateral Hyperplasia (Medical).
- **Treatment:** Adrenalectomy (unilateral) vs. MRA therapy (bilateral).

PREPARING FOR THE PAC/PRA TEST

- **Correct Hypokalemia First:** Low potassium can falsely suppress aldosterone levels.
- **The "Washout" Goal:** Minimize interference with the Renin-Angiotensin-Aldosterone Axis.
- **High-Interference Drugs (Stop for 4 weeks):**
- Spironolactone, Eplerenone, Amiloride (MRAs and K-sparing diuretics).
- **Moderate-Interference Drugs (Stop for 2 weeks):**
- Beta-blockers, Clonidine, NSAIDs (can lower Renin).
- ACE inhibitors, ARBs, and Diuretics (can raise Renin).
- **"Safe" Meds to Continue:** Verapamil (Slow-release), Hydralazine, Doxazosin/Prazosin.

LIFESTYLE & SUBSTANCE TRIGGERS

- **Dietary Sodium:** Target <2,300mg (ideally <1,500mg) per day.
- **The NSAID Factor:** Ibuprofen/Naproxen blunt antihypertensive efficacy.
- **Alcohol:** Dose-dependent relationship with BP elevation.
- **Sympathomimetics:** Decongestants, stimulants, and herbal supplements.

SUBSTANCE AUDIT

- NSAIDs: Switch to Acetaminophen.
- Sodium: Advise <2 grams total daily.
- Alcohol: Limit to 1 drink/day for women, 2 drinks/day for men.
- Recreational drugs cessation

PHARMACOLOGIC OPTIMIZATION

- **Maximize Diuretics: Switch HCTZ to Chlorthalidone or Indapamide.**

- **The 4th Line Agent: Spironolactone (Mineralocorticoid Receptor Antagonist).**
- **Amiloride (if Spironolactone is not tolerated) or Eplerenone 50 mg (if gynecomastia occurs).**
- ***Check K+ and Creatinine at 1-2,4, and 12 weeks.***

- **Beta-Blockers: Prioritize vasodilating types (Carvedilol/Nebivolol).**

- **Vasodilators: Hydralazine or Minoxidil for refractory cases.**

- **Volume Status: If GFR <30 mL/min, switch to Loop Diuretic**
  (Torsemide preferred over Furosemide for better bioavailability).

OTHER DRUGS

- Centrally Acting Alpha-2 Agonists
- Common Drugs: Clonidine (Catapres), Methyldopa (Aldomet), Guanfacine.

- Methyldopa: The gold standard for hypertension in pregnancy.
- Clonidine: Often used as a "rescue" medication for hypertensive urgencies or in patients who have failed multiple other therapies. Significant sedation and dry mouth.
- Abruptly quitting clonidine can cause a "rebound" spike in blood pressure that can lead to a stroke.

OTHER DRUGS

- **Alpha-1 Blockers**
- **Common Drugs: Doxazosin (Cardura), Prazosin (Minipress), Terazosin.**
- **First-Dose Phenomenon.**

- **Peripheral Adrenergic Inhibitors : Reserpine**
- **It depletes the body's stores of norepinephrine**
- **Causes severe, deep depression and nasal congestion.**

THE FUTURE: DEVICE-BASED THERAPY

- **Renal Denervation (RDN):** Radiofrequency or Ultrasound nerve ablation.
- **Mechanism:** Reduces sympathetic outflow from the kidneys.
- **Baroreflex Activation:** Implantable carotid sinus stimulators.
- **Target:** Patients who remain uncontrolled despite maximal medical therapy.

FAQ

WITH THE RISE OF GLP-1 AGONISTS, HOW MUCH SHOULD WE FOCUS ON WEIGHT LOSS VS. ADDING A FOURTH OR FIFTH ANTIHYPERTENSIVE?

- Weight loss remains foundational. GLP-1s and dual GIP/GLP-1 agonists (like Tirzepatide) are changing the landscape of RH management because they address the visceral adiposity and insulin resistance that drive sympathetic overactivity.

- While we must control the BP immediately with meds, the 'exit strategy' for polypharmacy in obese patients is now increasingly centered on these metabolic therapies.

IN THE PATHWAY-2 TRIAL, SPIRONOLACTONE WAS THE CLEAR WINNER. BUT WHAT DO I DO IF THE PATIENT DEVELOPS HYPERKALEMIA OR GYNECOMASTIA?

- Hyperkalemia is the main limiting factor, especially in CKD patients. If potassium is the issue, we can look at potassium binders, patiromer (Veltassa) and sodium zirconium cyclosilicate (Lokelma), sodium polystyrene sulfonate (SPS, Kayexalate) to 'enable' MRA use, or switch to Amiloride.

- For men who develop gynecomastia, switching from Spironolactone to Eplerenone—which is more selective—usually resolves the issue, though it may require a higher dose to achieve the same BP effect.

HOW LONG SHOULD I WAIT BEFORE DECIDING A PATIENT HAS 'FAILED' MEDICAL THERAPY AND REFERRING THEM FOR RENAL DENERVATION (RDN)?

- Current consensus suggests at least 6 months of optimized medical therapy, including a diuretic and an MRA.

- However, RDN is also becoming a conversation for patients with 'medication intolerance.' If a patient is non-adherent because they cannot tolerate the side effects of 4+ pills, we might consider RDN earlier in the sequence rather than forcing a regimen that the patient simply won't take.

IS THERE STILL A ROLE FOR HYDRALAZINE, OR IS IT TOO OUTDATED FOR MODERN RH MANAGEMENT

- Hydralazine is effective but difficult to use correctly. It requires TID (three times a day) dosing due to its short half-life and often causes reflex tachycardia and fluid retention. It’s a 'last resort' drug.

- If you use it, ensure the patient is already on a Beta-blocker and a potent diuretic to counteract those side effects.
- In most cases, optimizing the MRA or adding a long-acting alpha-blocker like Doxazosin is preferred first.

WHY DO YOU EMPHASIZE CHLORTHALIDONE OVER HCTZ SO STRONGLY?

- Potency and duration. HCTZ is a 12-hour drug being used for a 24-hour problem.

- Chlorthalidone has a half-life of 40–60 hours and is significantly more potent per milligram. Most 'resistant' cases are simply cases where the diuretic wasn't strong enough to overcome the patient's sodium intake or the activation of the RAAS system overnight.

HOW OFTEN SHOULD WE BE SCREENING FOR PHEOCHROMOCYTOMA IN THE RH POPULATION?

- Routine screening for everyone isn't cost-effective, but the threshold should be low.
- If the patient has paroxysmal 'spells' (headache, palpitations, sweating) or if their BP is highly labile and resistant to standard blockers, a plasma metanephrine test is a simple and necessary step.
- It’s rare, but it’s a 'must-not-miss' diagnosis.

EVIDENCE-BASED FOUNDATION (MAJOR TRIALS)

- 1. The "Gold Standard" for 4th-Line Therapy
- PATHWAY-2 (2015): Proved Spironolactone is the most effective add-on drug for RH, superior to bisoprolol, doxazosin, or placebo.
- Relevance: Established the protocol of using Mineralocorticoid Receptor Antagonists (MRAs) to treat "concealed" volume expansion.

- 2. The Diuretic Debate
- ALLHAT (2002): Demonstrated the long-term CV benefits of Chlorthalidone, showing it was superior to lisinopril and amlodipine in preventing heart failure.
- DCP Trial (2022): Compared HCTZ vs. Chlorthalidone; while primary CV outcomes were similar in a general population, Chlorthalidone remains the preferred agent for true resistance due to its 24-hour potency.

EVIDENCE-BASED FOUNDATION (MAJOR TRIALS)

- 3. Renal Denervation (The "Comeback")
- RADIANCE-HTN TRIO (2021): Proved that ultrasound renal denervation significantly reduced BP in patients who were strictly adherent to a three-drug regimen.
- SPYRAL HTN-ON MED (2022): Demonstrated that radiofrequency denervation works as an "always-on" therapy alongside medication.

- 4. Obesity & Metabolic Drivers
- STEP Trials (2021–2023): While primarily weight-loss trials, Semaglutide (GLP-1) showed significant systolic BP reductions, highlighting a new pathway for treating RH in patients with obesity.

THANK YOU