Evaluation and Management of Resistant Hypertension: 2015

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DISCLOSURE OF FINANCIAL RELATIONSHIPS

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LEARNING OBJECTIVES

After participating in this educational activity, clinicians should be better able to:

• Understand the definition of resistant hypertension

• Discuss the clinical workup of resistant hypertension including the importance of 24-hr ABPM

• Recognize the importance of lifestyle modification and the evidence for the use of chlorthalidone vs. HCTZ, and mineralocorticoid receptor antagonism (spironolactone) to improve BP control in those with resistant hypertension

Issues in the Diagnosis and Management of Resistant Hypertension:

• Sam is a 58 y.o man with a 20 yr history of hypertension who is new to your practice. With a BMI of 32.2 kg/m², he has no history of ASCVD, diabetes, or other vascular disease. He has been treated with antihypertensive drugs for the past 10+ years including a combination diuretic/ACE inhibitor which had to be stopped due to a cough. He states his BP has never been well controlled and his physicians have always been concerned over this issue. When seen by you, he is on losartan/Hctz 100/25 and amlodipine 10 mg. His BP today in your office is 144/94.

• His physical exam is unremarkable including his eye ground exam.

• He has normal renal function, a potassium of 4.2, and his EKG reveals a NSR and voltage suggestive of LVH.
Resistant Hypertension: Tricks of the Trade for Controlling Blood Pressure

Questions to discuss:

- Does Sam have resistant hypertension?

- How important is “pseudo-resistant” vs. true resistant hypertension?

- How important is it to control resistant hypertension?
Resistant Hypertension

- JNC 7 definition
  - BP that remains above 140/90 in patients adhering to an adequate and appropriate triple-drug regimen (including a diuretic), with all drugs prescribed at near-maximum or maximum recommended doses.
- AHA Scientific Statement definition adds to the above definition
  - Uncontrolled BP despite use of 3 medications
  - BP controlled but requiring at least 4 medications—"controlled resistant hypertension"


Questions to discuss:

▪ Does Sam have resistant hypertension? - Yes
Prevalence of Resistant Hypertension

- True prevalence of resistant hypertension is not known\(^1\)
- Depending on locale, studies estimate the prevalence around
  - 10-30% in general practice
  - ≥ 50% in nephrology referral clinics\(^2\)
- NHANES (2003-2008) estimated prevalence of resistant hypertension
  - 8.9% (1 in 11) of US adults with hypertension
  - 12.8% (1 in 8) of all antihypertensive drug-treated US adults with hypertension\(^3\)
  - More recent 2005-2008 estimates show the prevalence of resistant hypertension continues to increase\(^4\)


Questions to discuss:

- **How important is “pseudo-resistant” or “apparent” resistant hypertension vs. true resistant hypertension?**
Resistant Hypertension: Tricks of the Trade for Controlling Blood Pressure

Resistant Hypertension

Pseudo-resistance
- Improper BP measurement
- White coat effect-consider 24-hr ABPM
- Poor Medication Adherence

Resistant Hypertension

True Resistant HTN

BP Measurement in the Office in Established Patient

1. Preferably taken before the patient ever sees the clinician caring for the patient

2. - 5 minutes of rest
   - no conversation
   - seated comfortably with feet on the floor, back supported
   - arm at heart level
   - no tobacco or caffeine for 30 minutes before BP taken

3. Two to Three seated readings (averaged)

4. An upright reading (taken after 1 minute of standing)

Resistant Hypertension: Tricks of the Trade for Controlling Blood Pressure

**Uncontrolled Blood Pressure**

**Apparent Resistant HTN**

**Pseudo-resistance**
- Improper BP measurement
- White coat effect—consider 24-hr ABPM
- Poor Medication Strategy or Adherence

**Resistant Hypertension**

**True Resistant HTN**


1/3 of “Resistant Hypertension” Is Actually White-Coat Hypertension by ABPM

*Spanish APBM Registry of 8295 Patients*

**12.20%**

**62.50%**

**37.50%**

de la Sierra, A. *Hypertension* 2011; 57:898-902
Resistant Hypertension: Tricks of the Trade for Controlling Blood Pressure

Uncontrolled Blood Pressure

Apparent Resistant HTN

Pseudo-resistance
- Improper BP measurement
- White coat effect—consider 24-hr ABPM
- Poor Medication Strategy or Adherence

Resistant Hypertension

True Resistant HTN


Resistant hypertension? Assessment of adherence by toxicological urine analysis


375 Patients Referred for Uncontrolled HTN on 3 Drugs

Maximized Doses
Excluded White Coat

108 Uncontrolled

15 with Secondary HTN
17 Controlled on 4 Drugs

76 Uncontrolled

40 Non-Adherent (30% taking no meds and 85% <half)

36 True Resistant HTN (3.5% of all 375 referred patients)

Questions to discuss:

- How important is “pseudo-resistant” hypertension? Very important accounting for up to 50% of those who appear to be resistant

Uncontrolled Blood Pressure

- Improper BP measurement
- White coat effect
- Poor adherence

True Resistant Hypertension

Questions to discuss:

- Do we believe there is a benefit to controlling resistant hypertension?

Consequences of Resistant Hypertension

- The degree to which CV risk is reduced with treatment is unknown, however the benefits of successful treatment are likely substantial

- In fact, two recent studies found resistant hypertension was associated with a 2.2-fold increased risk for CV morbidity and a 50% higher risk for CV events

- Furthermore, the recent ALLHAT post-hoc sub-study found significant increases in CHD, stroke, all cause mortality and HF in the 1/3 within the ALLHAT study who had resistant hypertension

Questions to discuss:

- Do we believe there is a benefit to controlling resistant hypertension? - Yes

Causes of True Resistant Hypertension

Identifiable (Secondary-Reversible) Causes of Hypertension

- Drug-Induced or Other Causes
- Volume Overload-high sodium intake, CKD, inadequate diuretic therapy
- Aldosterone Excess

Associated Conditions

- Obesity
- Excess alcohol intake
- Sleep apnea

Clinical Inertia

Resistant Hypertension: Tricks of the Trade for Controlling Blood Pressure

**Screening Tests for 2\(^{\circ}\) HTN**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Test</th>
</tr>
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<tbody>
<tr>
<td>↓, ↑ thyroid</td>
<td>TSH, free T4</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>plasma metanephrines</td>
</tr>
<tr>
<td>1(^{\circ}) aldosteronism</td>
<td>↓ or nl K(^{+}), ↑ plasma aldo (&gt;15) with Aldo/PRA &gt;20-30</td>
</tr>
<tr>
<td>Cushing’s disease</td>
<td>Overnight dex supp</td>
</tr>
<tr>
<td>Hyperparathyroid</td>
<td>Ca(^{++}), Alb, Cl/P, IPTh</td>
</tr>
<tr>
<td>Renal artery stenosis</td>
<td>Duplex Ultrasound, MRA</td>
</tr>
<tr>
<td>Sleep apnea</td>
<td>Hx(^{*}), polysomnography</td>
</tr>
</tbody>
</table>

\(^{*}\)Positive Epworth Sleepiness Score

**Drug-Induced (Medications) that Can Interfere with BP Control**

- NSAIDs/COX-2 inhibitors
- Oral contraceptives (estrogen predominant)
- Sympathomimetic agents (decongestants, diet pills, cocaine)
- Stimulants (amphetamines, methylphenidate)
- Alcohol
- Anti-depressants (TCAs and SNRIs)
- Cyclosporine
- Erythropoietin
- Natural licorice
- Herbal compounds (ephedra or ma huang)

Calhoun et al. AHA Scientific Statement: *Hypertension* 2008;51:1403-1419
Resistant Hypertension: Tricks of the Trade for Controlling Blood Pressure

**Causes of True Resistant Hypertension**

Identifiable (Secondary) Causes of Hypertension
- Drug-Induced or Other Causes
- Volume Overload-High Sodium Intake
  - CKD
- Inadequate Diuretic Therapy

Aldosterone Excess

Associated Conditions
- Obesity
- Excess alcohol intake
- Sleep apnea
- Clinical Inertia


**Resistant Hypertension: High/Low Dietary Salt Cross-Over Evaluation**

<table>
<thead>
<tr>
<th>Low Na 50 mmol/d</th>
<th>6 patients low-salt diet 1 week</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Na 250 mmol/d</td>
<td>6 patients high-salt diet 1 week</td>
</tr>
</tbody>
</table>

Seated Blood Pressure/ABPM

- 12 patients
- 3.4 BP meds
- Office BP = 146/84 mm Hg
- Wash-out 2 weeks
- Low Na 50 mmol/d
- High Na 250 mmol/d

24-hr Urine for Na, K, Aldo
- BNP, PRA
- PWV, AIx

Pimenta, E et al. *Hypertension* 54: 475-481, 2009
Resistant Hypertension: Tricks of the Trade for Controlling Blood Pressure

Large Reduction in Systolic and Diastolic BP with Dietary Na Restriction

Initial Medications For The Management of Hypertension


Pimenta, E et al. Hypertension 54: 475-481, 2009
Which “Thiazide”?

- **Thiazide**
  - Hydrochlorothiazide
  - Chlorthiazide
  - bendroflumethiazide
- **Thiazide-like**
  - Chlorthalidone
  - Metolazone
  - Indapamide

Switching Hctz to Chlorthalidone at Same Dose Now Controls Those with Resistant Hypertension

Resistant Hypertension: Tricks of the Trade for Controlling Blood Pressure

### Study Design

(Chlorthalidone vs Hctz as Add-On)

**Phase 3, multicenter, double-blind randomized study**

- **Screening, washout, placebo run-in**
- **AZL 40 mg**
- **AZL–CLD**
  - 40 mg + 12.5 mg
  - 40 mg + 25 mg
- **AZL + HCTZ**
  - 40 mg + 12.5 mg
  - 40 mg + 25 mg

**Monotherapy**

Day -1
Randomization, baseline ABPM

Week 2
Week 6
Week 10
Final ABPM

**Follow-up**

- Forced addition of CLD or HCTZ
- Optional titration

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### Primary Efficacy Endpoint

Change in Trough Sitting Clinic SBP (mm Hg) at 6 and 10 weeks

**Week 6**

- **AZL–CLD**
  - 164.7±9.1
  - -35.1a

- **AZL + HCTZ**
  - 164.4±9.9
  - -29.5

**Week 10**

- **AZL–CLD**
  - 164.7±9.1
  - -37.8a

- **AZL + HCTZ**
  - 164.4±9.9
  - -32.8

(N=303)
(N=306)

*a P<0.001

Diuretic Use: Practical Considerations

Chlorthalidone
• Dosing 12.5-25 mg daily

• Metabolic complications slightly worse, especially hypokalemia, but greatly lessened when used with RAS blocker

• May be given with spironolactone (but watch out for hyponatremia)

Diuretic Use: Practical Considerations

Spironolactone
• Dosing 12.5–25 mg daily

• Hyperkalemia uncommon if good renal function

• CKD; the use of an ACEI, ARB, or Renin inhibitor, and/or NSAIDs all increase the risk of hyperkalemia

• Generally well tolerated up to 25 mg

• Breast tenderness/gynecomastia dose dependent, was more common in the dig era
Diuretic Use: Practical Considerations
Loop diuretics (LD)

- Venodilators; Lower BP but are not “antihypertensive”.
- Not preferred until your forced to use them; i.e. GFR < 30-35 mL/min/1.73m²
- Combine LD with BB when using minoxidil (not used often anymore) or hydralazine
- Long acting agent (torsemide) preferred but use LD at least twice-3X daily if using furosemide to avoid distal paradoxical sodium reclamation

Prevalence of Idiopathic Hyperaldosteronism in Subjects With Resistant Hypertension

PA = primary aldosteronism.
BP Response with Spironolactone 25-50 mg as 4th Drug: ASCOT Results

<table>
<thead>
<tr>
<th></th>
<th>Pre</th>
<th>Post</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP</td>
<td>156.9</td>
<td>135.1</td>
</tr>
<tr>
<td>DBP</td>
<td>85.3</td>
<td>75.8</td>
</tr>
</tbody>
</table>

△ SBP = -21.9
△ DBP = -9.5
N=1411
6% discontinuation rate due to adverse effects


Causes of True Resistant Hypertension

Identifiable (Secondary) Causes of Hypertension
Drug-Induced or Other Causes
Volume Overload-high sodium intake, CKD, inadequate diuretic therapy
Aldosterone Excess

Associated Conditions- assoc w Increased SNS and MRA
- Obesity - excess volume and SNS overactivity
- Excess intermittent alcohol intake-SNS overactivity
- Sleep apnea - CPAP reduces BP but does not cure HTN

Clinical Inertia

Resistant Hypertension: Tricks of the Trade for Controlling Blood Pressure

Sleep Apnea Patient

The Effect of CPAP on Resistant Hypertension is Modest, At Best*
HIPARCO Randomized Clinical Trial

Methods:
- Spanish Study in 194 patients with resistant htn and OSA (AHI >15)
- CPAP vs no CPAP
- Primary Endpoint = Change in 24 hour mean BP as measured by ABPM

Mean Change in BP with CPAP modest
- Diastolic BP – 3.2 mm Hg
- Systolic BP – 3.1 mm Hg
- Greater prevalence of dipping (35.9% vs 21.6%)

* But important for concomitant conditions linked with sleep apnea including stroke, MI, HF, Atrial fib, CKD

Martinez-Garcia et al.JAMA 2013; 310: 2407
Resistant Hypertension: Tricks of the Trade for Controlling Blood Pressure

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**Clinical Inertia**
Suboptimal antihypertensive drug combinations


**What Is Clinical Inertia?**

The failure of healthcare providers to initiate or intensify therapy when indicated
Resistant Hypertension: Tricks of the Trade for Controlling Blood Pressure

Uncontrolled Hypertension in NHANES, 2005-2008

- 52% Untreated
- 34% Taking <3 meds
- 14% Clinical Inertia
- 2% Apparent Treatment Resistant


The Effect of Therapeutic Inertia

- 62 practices in N.C., S.C., Ga. Part of the Hypertension Initiative
- N=7,253 hypertensive patients that had ≥4 visits and ≥1 elevated BP
- Therapeutic inertia = SBP ≥140 mm Hg and/or DBP ≥90 mm Hg with no change in antihypertensive therapy
- Occurred in 86.9% of visits

- With TI
  - BP (mm Hg): SBP 139.6, DBP 125.8
  - BP Control Rate (% Patients): 77.9

- Without TI
  - BP (mm Hg): SBP 125.8, DBP 73.4
  - BP Control Rate (% Patients): 45.1

Okonofua EC et al. Hypertension 2006;47:1-7
Resistant Hypertension: Tricks of the Trade for Controlling Blood Pressure

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Volume Overload—high sodium intake, CKD, inadequate diuretic therapy

Aldosterone Excess

Associated Conditions

- Obesity
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Clinical Inertia


**Bedtime Dosing of One BP Medication in Resistant Hypertension**

Best for RAS Blocker or CCB


Hermida AM J HTN 2010, 23: 432

Hermida et al. *Chronobiol Intern*. 2010; 27: 1629
Resistant Hypertension: Tricks of the Trade for Controlling Blood Pressure

**Device-Based Therapy for Resistant Hypertension - Not Ready for Prime Time Not FDA Approved**

- **Baroreflex Activation Therapy** - back to the drawing board
- **Renal Denervation Therapy** - re-evaluating the data

We will have to wait to see if either of these devices meet with Future FDA approval

**Final Points:**

- In the future we may define resistant hypertension as an elevated BP in patients fully adherent to maximally tolerated doses of multiple-drug regimens, including a long-acting thiazide diuretic (chlorthalidone preferred) and a mineralocorticoid receptor antagonist (MRA), like spironolactone, while on a low-salt diet. In addition, as part of their workup, patients should have a 24-hr ABPM placed in the morning after personally administering their medications to confirm true resistant and not white-coat resistant hypertension. Preferring once-a-day medications, where possible, should improve adherence even if one or more antihypertensive medications is taken at bedtime.
Resistant Hypertension: Tricks of the Trade for Controlling Blood Pressure

Summary

- Resistant hypertension is a medical problem that is increasing in prevalence and of clinical concern.
- Mechanisms are multiple, but aldosterone excess and high dietary salt ingestion contributing to persistent intravascular fluid retention w/o clinical edema appears to be an important contributing factor.
- Treatment is predicated upon lifestyle changes, combining agents from different classes at effective doses, with effective use of diuretics, including Mineralocorticoid Antagonists (MRA’s).
- Future approval of device therapy in the US to treat resistant hypertension remains uncertain but is currently being evaluated for further study.

Thank you