Choosing the Path of Least Resistance: Managing Resistant Hypertension

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No significant financial relationships with commercial entities were disclosed by any of the speakers.
Objectives

◆ Define resistant hypertension
◆ Identify causes of resistant hypertension
◆ Discuss treatment strategies for the management of resistant hypertension
◆ Describe the role of pharmacists in resistant hypertension management
Competition!

- Work in groups of 2-3 or individually
- Complete the fill-in-the-blank worksheet
- The answers will be revealed during the presentation
- Add up your correct answers with the corresponding points for each question
- We will compare total scores at the end and determine the winner!
## Resources

<table>
<thead>
<tr>
<th>American College of Cardiology/ American Heart Association Task Force</th>
</tr>
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</table>

<table>
<thead>
<tr>
<th>American Heart Association</th>
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</thead>
<tbody>
<tr>
<td>2018 Resistant Hypertension: Detection, Evaluation, and Management</td>
</tr>
</tbody>
</table>

### Clinical Guidelines

### Scientific Statement
Hypertension (HTN) Guidelines

Review of the Clinical Practice Guidelines
### Categories

<table>
<thead>
<tr>
<th>Category</th>
<th>Systolic</th>
<th>Diastolic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>and</td>
<td></td>
</tr>
<tr>
<td>Elevated</td>
<td>and</td>
<td></td>
</tr>
<tr>
<td>Hypertension Stage 1</td>
<td>or</td>
<td></td>
</tr>
<tr>
<td>Hypertension Stage 2</td>
<td>or</td>
<td></td>
</tr>
</tbody>
</table>

If reading falls within two categories, the higher category should apply. Based on an average of \( \geq 2 \) readings obtained on \( \geq 2 \) occasions.

## BP Goal

<table>
<thead>
<tr>
<th>Population</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults with confirmed hypertension and known CVD or 10-year ASCVD event risk of 10%</td>
<td></td>
</tr>
<tr>
<td>Adults with confirmed hypertension, without additional markers of increased CVD risk</td>
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</tr>
</tbody>
</table>

Stage 2 hypertension and >20/10 mmHg above BP target: Consider initiation of therapy with 2 antihypertensive agents of different classes.
### Nonpharmacological Interventions

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>A</td>
<td>Weight loss in adults who are overweight or obese</td>
</tr>
<tr>
<td>I</td>
<td>A</td>
<td>A heart-healthy diet, such as the DASH (Dietary Approaches to Stop Hypertension) diet, that facilitates achieving a desirable weight</td>
</tr>
<tr>
<td>I</td>
<td>A</td>
<td>Sodium reduction</td>
</tr>
<tr>
<td>I</td>
<td>A</td>
<td>Potassium supplementation (preferably in dietary modification) unless contraindicated</td>
</tr>
<tr>
<td>I</td>
<td>A</td>
<td>Increased physical activity with a structured exercise</td>
</tr>
<tr>
<td>I</td>
<td>A</td>
<td>Limit alcohol (male=2 drinks, females=1 drink)</td>
</tr>
</tbody>
</table>

COR=Class of Recommendation, LOE= Level of Evidence

Initial Therapy Recommendations

- Thiazide Diuretics
- Calcium channel blockers
- ACE Inhibitors
- ARBs

Resistant Hypertension (RH) Overview

Definition and Background
Definitions

- Patients not at their goal BP despite concurrent use of 3 or more antihypertensive drug classes, commonly including a long-acting CCB, ACEi or ARB, and a diuretic at maximum or maximally tolerated daily doses.

- Patient at BP goal on 4 or more antihypertensive medications.
Demographics

Higher prevalence in:
- African Americans
- Older age
- Male sex

Comorbidities

- More common in RH than non-RH:
  - Obesity
  - Left ventricular hypertrophy
  - Albuminuria
  - Diabetes mellitus (DM)
  - Chronic kidney disease (CKD)
  - Higher Framingham 10-year risk score
  - Obstructive sleep apnea (OSA)

Assessment of RH

Patient Evaluation
Assessment of RH

- Confirm Resistance
- Exclude Pseudoresistance
- Access for Secondary RH
- Access for Target Organ Damage

Assessment of RH

- Confirm adherence to medications (pill counts, interview, refill history, etc.)
- Confirm accurate BP measurement
- Exclude White Coat Syndrome
  - 24 hour ambulatory care cuff (if available)
  - At-home BP monitor

Assessment of RH

Exclude Pseudoresistance

![Graph showing estimated prevalence (%) for medication non-adherence, white coat effect, under-treatment, and inaccurate BP measurement.](image-url)
Assessment of RH

Key Steps for Proper BP Measurements

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1</td>
<td>Properly prepare the patient</td>
</tr>
<tr>
<td>Step 2</td>
<td>Use proper technique for BP measurements</td>
</tr>
<tr>
<td>Step 3</td>
<td>Take the proper measurements needed for diagnosis and treatment of elevated</td>
</tr>
<tr>
<td></td>
<td>BP/hypertension</td>
</tr>
<tr>
<td>Step 4</td>
<td>Properly document accurate BP readings</td>
</tr>
<tr>
<td>Step 5</td>
<td>Average the readings</td>
</tr>
<tr>
<td>Step 6</td>
<td>Provide BP readings to patient</td>
</tr>
</tbody>
</table>

Exclude Pseudoresistance

### Exclude Pseudoresistance

<table>
<thead>
<tr>
<th>Step 1: Properly prepare the patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Have the patient relax, sitting in a chair (feet on floor, back supported) for &gt;5 min.</td>
</tr>
<tr>
<td>2. The patient should avoid caffeine, exercise, and smoking for at least 30 min before measurement.</td>
</tr>
<tr>
<td>3. Ensure patient has emptied his/her bladder.</td>
</tr>
<tr>
<td>4. Neither the patient nor the observer should talk during the rest period or during the measurement.</td>
</tr>
<tr>
<td>5. Remove all clothing covering the location of cuff placement.</td>
</tr>
<tr>
<td>6. Measurements made while the patient is sitting or lying on an examining table do not fulfill these criteria.</td>
</tr>
</tbody>
</table>
Step 2: Use proper technique for BP measurements

1. Use a BP measurement device that has been validated, and ensure that the device is calibrated periodically.
2. Support the patient’s arm (e.g., resting on a desk).
3. Position the middle of the cuff on the patient’s upper arm at the level of the right atrium (the midpoint of the sternum).
4. Use the correct cuff size, such that the bladder encircles 80% of the arm, and note if a larger- or smaller-than-normal cuff size is used (Table 9).
5. Either the stethoscope diaphragm or bell may be used for auscultatory readings.

Assessment of RH

1. Confirm Resistance
2. Exclude Pseudoresistance
3. Access for Secondary RH
4. Access for Target Organ Damage
Access for Secondary RH

- Medications
- Conditions
Assessment of RH

Access for Secondary RH

Medications

- NSAIDs
- Oral Contraceptives
- Antidepressants
- Glucocorticoids, mineralocorticoids
- Amphetamines
- Sympathomimetics
- Erythropoietin
- Cyclosporine, Tacrolimus
- Cocaine
- Alcohol

Assessment of RH

Access for Secondary RH

- Primary aldosteronism
- Renal parenchymal disease
- Renal artery stenosis
- Cushing syndrome
- Hypo/hyperthyroidism
- Hyperparathyroidism
- CKD (eGFR <60 ml/min/1.73m²)
- Renal artery steonosis
- OSA
- Drug or alcohol induced

Assessment of RH

1. Access for Target Organ Damage
2. Access for Secondary RH
3. Exclude Pseudoresistance
4. Confirm Resistance
Assessment of RH

- Ocular
- Cardiac
- Renal
- Peripheral Artery Disease
Management of RH
Treatment Strategies and Recommendations
Management of RH

Step 1
Exclude other causes + Lifestyle interventions + Optimize 3-drug regimen

BP not at target

Step 2
Substitute optimally dosed thiazide-like diuretic (chlorthalidone) for the prior diuretic

BP not at target

Step 3
Add a mineralocorticoid receptor antagonist (MRA) such as spironolactone or eplerenone

BP not at target

Note: Thiazide-like diuretics maintain efficacy down to eGFRs of 30 ml/min/1.73m²

Management of RH

**Step 4**
Add a beta-blocker or alpha/beta blocker if heart rate ≥ 70 bpm
- If contraindicated, consider central acting alpha-2 agonist (clonidine patch or guanficine HS)
- If not tolerated, consider once-daily diltiazem

**Step 5**
Add hydralazine 25 mg three times daily and titrate*

**Step 6**
Switch hydralazine to minoxidil 2.5 mg BID to TID and titrate**

*Requires concomitant use of a beta-blocker and diuretic
**Requires concomitant use of a beta-blocker and loop diuretic

**NOTE: Steps 4-6 are based on expert opinion and should be individualized**

BP not at target

BP not at target

BP not at target

HTN specialist and/or experimental studies

PATHWAY-2 Trial

- Double-blind, crossover trial in 335 patients with RH (confirmed with ambulatory BP monitoring) randomized to spironolactone, bisoprolol, doxazosin, or placebo for 12 weeks

<table>
<thead>
<tr>
<th></th>
<th>Blood pressure (mm Hg)</th>
<th>Change from baseline (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spironolactone</td>
<td>134.9 (134.0 to 135.9)</td>
<td>-12.8 (-13.8 to -11.8)</td>
</tr>
<tr>
<td>Doxazosin</td>
<td>139.0 (138.0 to 140.0)</td>
<td>-8.7 (-9.7 to -7.7)</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>139.4 (138.4 to 140.4)</td>
<td>-8.3 (-9.3 to -7.3)</td>
</tr>
<tr>
<td>Placebo</td>
<td>143.6 (142.6 to 144.6)</td>
<td>-4.1 (-5.1 to -3.1)</td>
</tr>
</tbody>
</table>

**Mean differences**

- Spironolactone vs placebo: 8.70 (-9.72 to -7.69), p<0.0001
- Spironolactone vs mean bisoprolol and doxazosin: -4.26 (-5.13 to -3.38), p<0.0001
- Spironolactone vs doxazosin: -4.03 (-5.04 to -3.02), p<0.0001
- Spironolactone vs bisoprolol: -4.48 (-5.50 to -3.46), p<0.0001

Management of RH

Other options:

- Alpha-1 blockers (doxazosin, prazosin, terazosin)
  - (-) Potential orthostatic hypotension
  - (+) Additional benefits in benign prostatic hyperplasia
Management of RH

PATHWAY-2 Trial

- Spironolactone was the most effective add-on drug for the treatment of resistant hypertension

- 6 of 285 patients receiving spironolactone experienced hyperkalemia (serum potassium >6.0 mmol/L)

A meta-analysis of add-on use of spironolactone in patients with resistant hypertension

- 4 Prospective randomized trials (n=869)
- Reduction in BP was greater with spironolactone than placebo
  - SBP 16.7 mm Hg (95% CI, 5.8 to 27.5; P<0.01)
  - DBP 6.1 mm Hg (95% CI, 2.9 to 9.3; P<0.001)
- Serious adverse effects or withdrawal higher with spironolactone than placebo
  - Odds Ratio 2.11 (95% CI, 0.98 to 4.53; P=0.05)

Management of RH

Specific Clinical Issues Associated With Treatment Resistance

<table>
<thead>
<tr>
<th>Issue Associated With Treatment Resistance</th>
<th>Management Consideration(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume control, edema resolution</td>
<td>Thiazide→chlorothalidone→loop diuretic</td>
</tr>
<tr>
<td>Heart rate control inadequate</td>
<td>β-Blocker, α,β-blocker, verapamil, diltiazem</td>
</tr>
<tr>
<td>Renin and aldosterone levels low</td>
<td>Low-salt diet, avoid nighttime shift work, amiloride</td>
</tr>
<tr>
<td>Renin low, aldosterone normal to high normal</td>
<td>Mineralocorticoid receptor antagonist</td>
</tr>
<tr>
<td>Would split dosing of medications improve control?</td>
<td>Evaluate BP pattern according to home and ambulatory BP monitoring</td>
</tr>
</tbody>
</table>
## Specific Clinical Issues Associated With Treatment Resistance

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<th>Management Consideration(s)</th>
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<tr>
<td>Medication adherence questionable</td>
<td>Initiate indirect or direct methods to detect nonadherence; if nonadherence is documented (partial or complete), discuss frankly, nonjudgmentally with patient and family</td>
</tr>
<tr>
<td>Pattern of BP response to medications outside clinician visit times unknown</td>
<td>Identify meal effects on BP, duration of medication effect, relationship of BP to side effects using out-of-office BP monitoring</td>
</tr>
<tr>
<td>Sleep disordered breathing; significant anxiety associated with highly variable hypertension</td>
<td>Initiate nondrug strategies concurrently with or separately from antihypertensive drug therapy</td>
</tr>
</tbody>
</table>
Pharmacists Role

Opportunities for the Pharmacist
Pharmacist's Role

- Medication counseling
- Assess patients for RH (Accurate BP, secondary causes, etc.)
- Adherence assessment and intervention (simplify regimen, encourage adherence aids, etc.)
- Therapy adjustments per guidelines and evidence
- Treatment monitoring and follow-up
- Engage in patient-provider decision making
Competition!

- Total up your score!
- WINNER IS......
Resistance HTN patients are more likely to suffer the combined outcomes of death, myocardial infarction, heart failure, stroke, or CKD

By understanding available clinical evidence and guidelines, pharmacists can engage in disease state management to improve CV outcomes
Thank you!

Any questions?

Email: Troy.Lewis@Wilkes.edu