Playing the Oldies but the Goodies to Manage Patients with Treatment Resistant Hypertension

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Definition
• Uncontrolled: blood pressure (BP) above goal and 3 or more treatment options, preferably a diuretic is included
• Controlled: BP at goal with 4 or more medications

The Who and The Why

At-Risk Groups
• Increasing age
• Obesity
• Left ventricular hypertrophy
• Chronic kidney disease (CKD)
• Diabetes
• African American
• Female

Pathophysiology
• Normal cardiac output with:
  – ↑ systemic vascular resistance
  – ↑ plasma volume
• Degree of plasma aldosterone levels elevation and renin suppression

Learning Objective
• Discuss the place in therapy of spironolactone, hydralazine, clonidine and alpha-antagonists in the management of treatment resistant hypertension.
• Given a patient with treatment resistant hypertension, develop a pharmacological treatment regimen.

Before you add another track...

Conduct a Thorough Assessment
• Pseudoresistance
  – Adherence to medications
  – “White coat” phenomena
  – Drug-induced causes
• Obstructive sleep apnea
• Primary aldosteronism
• Renal artery stenosis
• Others: Cushing’s syndrome, pheochromocytoma, aortic coarctation

The Top Hits!

JAMA 2014;311:507-20
http://blogs.luc.edu/hubbub/featured/trending-vinyl-records-are-cool-again/

Hypertension 2005-2008

Hypertension 2001;51:1403-19; J Am Soc Hypertension 2014;5:473-57

Hypertension 2008;51:1403-19; J Am Soc Hypertension 2014;5:473-57
Is a mineralocorticoid receptor antagonist the answer?

Aldosterone

- Renal
  - Na+/K+ retention
  - K+ excretion
  - Extracellular volume
  - Microalbuminuria

- Cardiac
  - Vascular damage
  - Remodeling
  - Hypertrophy
  - Arrhythmias

- Vasculature
  - Arterial stiffness
  - Vasoconstriction
  - Endothelial dysfunction

- Spironolactone as add-on therapy associated with significant BP reductions in several placebo-controlled trials

PATHWAY-2 Trial

- Spironolactone vs. bisoprolol, doxazosin and placebo (n=322)
- 230 received all four treatments; each "cycle" was 12 weeks
- Notable exclusion criteria:
  - Type 1 diabetes
  - Estimated Glomerular Filtration Rate (eGFR) < 45 ml/min
  - Recent cardiovascular event
  - Active cancer therapy
- Spironolactone associated with improved BP reduction compared to other therapies/placebo

Take home point: spironolactone 25-50 mg/day as 4th agent for BP treatment in general population

Mineralocorticoid receptor antagonist: safety

- Hyperkalemia risk increased:
  - Diabetes
  - Renal disease
  - Advanced age
  - Concurrent non-steroidal anti-inflammatory agent use
- Start at lower dose when renal disease present
- Use in hemodialysis, Stage 3 or 4 CKD not well established

Monitoring is KEY!!!

What else should we put on the B side?

- Direct renin inhibitor
- Mecamylamine
- Methyldopa
- Loop diuretic
- Minoxidil
- Beta-blocker
- Hydralazine
- Clonidine
- Alpha-antagonist

Second line options?

Aliskerin (Tekturna®)
- Should not be used in patients with diabetes or CKD receiving an angiotensin converting enzyme inhibitor/ angiotensin receptor blocker

Mecamylamine (Vecamyl®)
- Not for use in those with significant atherosclerosis
- Side effects heightened in those with renal disease
- Cumbersome regimen
- Sodium restriction not recommended

Methyldopa
- Adverse effect profile
- Typically reserved for use during pregnancy

Second line options?

Loop diuretic
- Maybe necessary in those with advanced renal disease instead of a thiazide
- For volume overload

Minoxidil
- Reflex tachycardia and other adverse effects
- Concomitant diuretic therapy (and often beta-blocker) required

Beta-blocker
- Not as effective, as first line therapy, in reducing BP and clinical outcomes compared to other agents
- For use in those with compelling indications
  - Heart failure
  - Coronary disease
  - Arrhythmias

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PATHWAY-2 Trial

Drugs 2015;75:473–85

Mineralocorticoid receptor antagonist: safety


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Second line options?

Tekturna® (aliskerin); Novartis, East Hanover, NJ 2015; Vecamyl® (mecamylamine); Turing Pharmaceuticals, New York, NY 2015; Methyldopa, Mylan Pharmaceuticals, Morgantown, WV 2015.

Atrium Medical Corporation, Biologics Division and Atrium Medical Corporation, Atrium Center for Innovation. East Hanover, NJ 2015.
Second line options?

**Hydralazine**
- Twice daily
- Adverse effect profile

**Clonidine**
- Side effect profile limits use in the elderly
- Transdermal patch available

**Alpha-antagonists**
- Male patient with benign prostatic hypertension
- Orthostatic hypotension risk


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Non-Pharmacological Strategies

**Renal denervation**
- Initial trials encouraging
- SYMPLECTY-HTN-3: large, prospective, randomized, controlled trial did not show benefit
- PRAGUE-15: BP control similar to spironolactone; both in addition to standard medications


**Others**
- Ultrasonic sound technology
- Carotid baroreflex activation therapy

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Which medication should be added next?

- 74 y/o obese woman
- Systolic BP above 160 mmHg x 3 months; HR 60 BPM
- PMH:
  - Diabetes
  - Hypertension
  - Hypothyroidism
- Labs within normal limits; CrCl - 65 ml/min
- BP medications:
  - chlorothalidone 25 mg/d
  - lisinopril 40 mg/d
  - felodipine 10 mg/day
- Secondary causes ruled out

CrCl = creatinine clearance

Which medication should be added next?

- A. clonidine
- B. doxazosin
- C. hydralazine
- D. spironolactone

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Treatment algorithm

* minoxidil and methyldopa last line; aliskiren increased side effects in combination with other RAAS inhibitors if diabetes/CKD, avoid mecamylamine

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More tracks on the way...

- Prevalence of Resistant Hypertension with Directed Observed Therapy (DOT)
  - DOT x 1 month followed by 24 hour ambulatory care BP monitoring
  - No adjustments in medication therapy
- Safety and Efficacy Study of LHW090 in Resistant Hypertension Patients
- Resistant Hypertension Optimal Treatment (ReHOT) Study
  - Traditional backbone 3 medication regimen
  - Spironolactone vs. clonidine x 3 months
- TRIUMPH Study
  - Exercise training, sodium and calorie reduction, and weight management compared to physician advice and standard education

*https://clinicaltrials.gov/ct2/show/NCT01530204
https://clinicaltrials.gov/ct2/show/NCT01261805
Clin Cardiol 2014;37:1–6, Am J Kid 2015;170:986-94*
Including the smash hit "Don't forget about spironolactone"

http://www.foreveroldies.com/classic2.htm