1. What is Resistant Hypertension and what are potential causes?
2. What are some common misconceptions regarding resistant hypertension?
3. What role do aldosterone antagonists play in resistant hypertension?
4. How to initiate, monitor and titrate an AA in a multi-drug regimen
5. Adverse events and how to manage them
6. African Americans vs. Caucasian – efficacy standpoint?
7. How to diagnosis Primary Aldosteronism (PA)
   a. Is it necessary to diagnose Primary Aldosteronism?
8. Should you dose AA's high or low?
9. Do thiazides cause PA?
10. Is hyperkalemia a significant problem?
11. In resistant hypertension, What role do OTHER antihypertensives play?
12. What OTHER agents alter aldosterone concentration?
13. Can spironolactone be used with angiotensin blocking agents safely?
14. Why is there hesitation in utilizing spironolactone?
15. When to use eplerenone?
16. Is amiloride or triamterene efficacious for resistant hypertension?

**Drug Class Members**
- Spironolactone
- Eplerenone
- Amiloride
- Triamterene

**Uses:** Both FDA and Non-FDA approved
- Acne vulgaris, Ascites, Edema, Bronchopulmonary dysplasia, Heart failure, Hirsutism, Hyperaldosteronism, Hypokalemia, Low-renin associated essential hypertension, Postmyocardial infarcton, Polycystic ovary syndrome, Premenstrual syndrome, Pulmonary edema

**Aldosterone Antagonists (AAs)**

**Focus on Treating Resistant Hypertension**

**Highlights: The Quick-Read Information**

1. Which of these 4 medications is NOT FDA-approved for Hypertension?
   a. [Spironolactone]; b. [Eplerenone]; c. [Amiloride]; d. [Triamterene]
2. How common is white-coat hypertension in patients?
   a. 5-15%; b. 20-30%; c. 50-60%; d. 80-90%
3. Which of these 4 agents is contraindicated in CrCl < 50ml/min?
   a. [Spironolactone]; b. [Eplerenone]; c. [Amiloride]; d. [Triamterene]
4. At what dose of spironolactone does potential breast tenderness and/or gynecomastia become more prevalent?
   a. 12.5 mg; b. 25 mg; c. 50 mg; d. All doses
5. Which of the 4 drugs is contraindicated with CYP3A4 inhibitors?
   a. [Spironolactone]; b. [Eplerenone]; c. [Amiloride]; d. [Triamterene]
6. True or False, It is safe and efficacious to use Aldosterone Antagonists with Angiotensin Blockers
   a. True; b. False

**Aldosterone** is a hormone with potent mineralcorticoid actions. Due to its effect on the Na+/K+ gradient, aldosterone has a profound effect on potassium. It has a possible role in the pathogenesis of vascular damage. There is evidence that there is a blood pressure-independent effect related to aldosterone on left ventricular structure, increasing collagen disposition and fibrosis and on the development of systolic and diastolic dysfunction.

**Primary Aldosteronism (PA)** is diagnosed if the plasma renin activity (PRA) is suppressed (< 1.0 ng/ml/h) and the 24-h urinary aldosterone excretion is high (> 12 µg/24h) during dietary sodium ingestion (> 200 mEq/24h). Patients with elevated aldosterone levels have greater cardiovascular risk and end-organ damage than matched subjects with essential hypertension. They are also more likely to develop resistant hypertension than other hypertensive individuals.

**Aldosterone-to-Renin Ratio (ARR)** is a marker of aldosterone activity has been correlated to arterial stiffness, a major cardiovascular risk.

**Resistant Hypertension** is described as elevated blood pressure in spite treatment with 3 different antihypertensive agents.
<table>
<thead>
<tr>
<th></th>
<th>Available Doses</th>
<th>Combo Formulations</th>
<th>FDA Indications</th>
<th>Off-Label Uses</th>
<th>Kinetics</th>
<th>IHA Tier Info</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Spironolactone (Aldactone)</strong></td>
<td>25, 50 &amp; 100mg</td>
<td>Spironolactone/HCTZ (Aldactazide) 25mg/25mg</td>
<td>Ascites, Edema, Hyperaldosteronism, Hyperaldosteronism Diagnosis, Hypertension, Hypokalemia, Pulmonary Edema</td>
<td>Acne Vulgaris, Bronchopulmonary Dysplasia, Heart Failure, Hirsutism, Polycystic Ovary Syndrome, Premenstrual Syndrome</td>
<td>-Highly absorbed, more so with food -1st pass elimination &amp; enterohepatic recirculation -Metabolized via hepatic pathways by active metabolites -Half life 1.3-2 hrs -Half life of active metabolite 10-35 hrs</td>
<td>1st</td>
</tr>
<tr>
<td><strong>Eplerenone (Inspra)</strong></td>
<td>25 and 50mg</td>
<td>n/a</td>
<td>Heart Failure, Hypertension, Post myocardial Infarction</td>
<td>Low-renin associated essential hypertension</td>
<td>-Good oral bioavailability, not affected by food -Metabolized by CYP3A4 enzyme but does not significantly inhibit or induce the CYP450 system or affect p-glycoprotein -Half life is 4-6 hrs</td>
<td>1st</td>
</tr>
<tr>
<td><strong>Amiloride (Midamor)</strong></td>
<td>5mg</td>
<td>Amiloride/HCTZ (Moduretic) 5mg/50mg</td>
<td>Edema, Heart Failure, Hypertension, Hypokalemia</td>
<td>Ascites</td>
<td>-Absorbed 50% by oral administration and then can be decreased by 50% when taken with food -40% protein bound -Not metabolized by the liver -Half life is 6-9 hrs</td>
<td>1st</td>
</tr>
<tr>
<td><strong>Triamterene (Dyrenium)</strong></td>
<td>50 and 100mg</td>
<td>Triamterene/ HCTZ (Dyazide &amp; Maxzide) 37.5mg/25mg &amp; 75mg/50mg</td>
<td>Ascites, Edema, Hyperaldosteronism, Hypokalemia</td>
<td>Hypertension, Premenstrual Syndrome</td>
<td>-Rapidly but incompletely absorbed with intermediate bioavailability -67% bound to plasma proteins -Half life is 1-2 hrs -Metabolite half life is ~3 hrs</td>
<td>1st</td>
</tr>
</tbody>
</table>
Points of Interest

Mechanism of Action

- **Spironolactone/Eplerenone** – inhibits the effects of aldosterone in the distal tubule. The diuretic effect is only exhibited in the presence of aldosterone. Sodium, chloride and water excretion is enhanced, whereas excretion of potassium, ammonium and phosphate is reduced. By competitively inhibiting dihydrotestosterone, these agents block androgen receptors. At high doses, they also interfere with steroid synthesis in the adrenal glands and the gonads. Carbonic anhydrase activity is not inhibited with these medications.

- **Amiloride/Triamterene** – inhibits the sodium-potassium ion exchange in the distal renal tubule. Inhibiting sodium transport mechanisms allows these drugs to directly interfere with sodium reabsorption. The electrical-potential difference across the membrane acts to block the passive distal tubular secretion of potassium. The potassium-sparing effects of these agents are derived from this action. There is an increase in urinary excretion of sodium, bicarbonate, calcium and water leading to slight diuresis. However, unlike spironolactone or eplerenone, these agents are not aldosterone antagonists. Carbonic anhydrase activity is not inhibited with these medications.

Adverse Effects

- Hyperkalemia leading to arrhythmias
- Impotence, Libido decrease, Polyuria, Bladder spasm
- Gynecomastia
  - Spironolactone & Eplerenone specifically
- Menstrual irregularities, Postmenopausal bleeding, Breast tenderness, Hirsutism, Deepened voice, Amenorrhea, Infertility
  - Spironolactone & Eplerenone specifically
- Anorexia, Nausea/Vomiting, Cramping, Diarrhea, Gastritis, Abdominal pain, Gastric bleeding, Ulceration, Jaundice
- Headache, Lethargy, Drowsiness, Ataxia, Weakness, Mental confusion, Xerostomia
- Azotemia, Renal dysfunction, Renal failure

These medications manage a variety of different disorders. The following is a review of the disease states by the drug that is proven beneficial in that situation.

**Spironolactone**

- Acne Vulgaris (non-FDA)
  - MOA – anti-androgenic effects
  - Clinical response is dose dependent with 150-200mg seeing best response

- Ascites
  - MOA – diuretic effect
  - Recommended to reduce other diuretics by ½ when adding spironolactone
  - Dose by the urinary Na+/K+ ratio
    - Ratio > 1: 100-150mg daily
    - Ratio < 1: 200-300mg daily

- Bronchopulmonary Dysplasia in children (non-FDA)
  - MOA – reduction in airway resistance, increase in airway conductance and pulmonary compliance
  - Studied in infants in combination with chlorthalidone
  - Conflicting results – older studies show improvement with spironolactone but more recent studies show no improvement with thiazide + spironolactone vs thiazide alone.¹
  - Combination therapy is mostly still used

- Edema (d/t nephrotic syndrome, CHF or hepatic disease)
  - MOA – diuretic effect
- Used monotherapy or in combination with other diuretics that act more proximally in the renal tubule
  - Heart Failure (non-FDA)
    - For severe (Class IV) heart failure; shown to improve survival and reduce hospitalizations in addition to ACEI + loop +/- digoxin therapy
  - Hirsutism in females (non-FDA)
    - MOA – anti-androgenic effects
  - Hyperaldosteronism
    - MOA – diuretic effect is enhanced in presence of aldosterone; also acts as androgen receptor blocker
    - Dose 100-400mg while awaiting surgery
    - If surgery is not an option, use lowest dose responsive
  - Hyperaldosteronism Diagnosis
    - Short test – administer 400mg x 4 days
      - If plasma K+ concentration rises initially during therapy but then decreases, when drug is discontinued then primary aldosteronism may be inferred
    - Long test – administer 400mg x 3-4 weeks
      - If plasma K+ rises to within normal limits and hypertension is corrected this is presumptive evidence for primary hyperaldosteronism
  - Hypertension
    - MOA – diuretic effect; also inhibits aldosterone’s effect on arteriole smooth muscle
    - Treat at least two weeks to see maximum effect
  - Hypokalemia
    - Use when oral potassium supplements or other potassium-sparing regimens are inappropriate
    - MOA – potassium sparing diuretic – increasing exertion of sodium, chloride and water while reducing elimination of potassium, ammonium and phosphate.
  - Polycystic Ovary Syndrome (non-FDA)
    - MOA – anti-androgenic effects
  - Premenstrual Symptoms (non-FDA)
    - Treats bloating and weight gain
    - MOA – diuretic effect
    - Should be limited to patients who PMS weight gain is > 1.4kg
  - Pulmonary Edema
    - MOA – diuretic effect

**Eplerenone**

- Hypertension
  - MOA – antagonizes epithelial and nonepithelial aldosterone effects within the kidney, blood vessels and heart; also increases urinary secretion of plasma renin, serum aldosterone and sodium.
  - Antihypertensive effects seen after two weeks of treatment with maximum blood pressure reduction occurring after four weeks of therapy.
  - > 100mg/daily has not been seen to achieve any additional benefit, only increased risk of hyperkalemia.
- Heart Failure in stable Post-myocardial Infarction patients with Left Ventricular Dysfunction (< 40%)
  - EPHESUS trial showed a reduction in all-cause mortality with the addition of eplerenone (mean dose 43mg/day) to other therapy 3-14 days post-MI.
    - Other therapy included ACEI or ARBs, diuretics, beta-blockers and coronary reperfusion therapy

**Amiloride**

- Ascites (non-FDA)
  - MOA – diuretic effect
  - Used alone or in combination with furosemide
- Heart Failure (Peripheral Edema)
  - MOA – diuretic effect
  - Not to be used as monotherapy
- Hypertension
  - MOA – reduces cardiac output as well as plasma and extracellular fluid volume
  - As adjunctive therapy to loop or thiazide diuretics, has been shown to provide some benefit
- Hypokalemia
  - MOA – Blocks the passive distal tubular secretion of potassium
  - Useful in patients who cannot tolerate or were unresponsive to potassium supplements

**Tiamterene**
- Ascites
  - MOA – diuretic effect
- Edema
  - MOA – diuretic effect
- Hyperaldosteronism
  - Has been shown to be efficacious in reducing blood pressure in hyperaldosteronism patients in combination with 25mg of HCTZ
- Hypertension (non-FDA)
  - MOA – diuretic effect
  - Very weak antihypertensive
- Hypokalemia
  - MOA – potassium sparing, distal tubule diuretic
  - Used in patients who cannot tolerate or who were unresponsive to oral potassium supplements
- Premenstrual Syndrome (PMS) (non-FDA)
  - MOA – diuretic effect
  - Should be limited to patients who experience PMS weight gain > 1.4kg

**What is Resistant Hypertension?**
- Resistant hypertension is defined as an elevated blood pressure in spite of treatment with 3 different antihypertensive treatments.
- This condition is a common clinical problem and is increasingly so with age and increasing weight.
- Secondary causes for resistant hypertension include
  - **Hyperaldosteronism**
  - **Obstructive Sleep Apnea**
  - Renal parenchymal disease
  - Renal artery stenosis
  - Endocrine Issues:
    - Cushing’s disease
    - Pheochromocytoma
    - Hyperparathyroidism
    - Thyrotoxicosis and myxedema
    - Acromegaly
  - Ureteral or bladder outlet obstruction
  - Aortic coarctation
- Exogenous substances that contribute to the development of resistant hypertension and blunt the benefit of many antihypertensive classes
  - Dietary salt
  - Nonnarcotic analgesics
    - NSAIDs
    - Acetaminophen
  - Sympathomimetic agents (decongestants, diet pills, cocaine, caffeine)
  - Stimulants
  - Alcohol
  - Oral contraceptives
  - Cyclosporine
  - Erythropoietin
  - Licorice
• Causes for poorly controlled hypertension – [Not Resistant Hypertension]
  o Nonadherence
  o Ineffective antihypertensive regimen
    ▪ Underuse of diuretic therapy
      • Recommended use of long-acting is the most effective
      • In renal insufficiency, long-acting loop diuretics are more efficient \( \rightarrow \) bumetanide or torsemide
    ▪ In most trials, the most effective antihypertensive regimen was shown as
      • ACE-I or ARB, CCB + Thiazide diuretic

\[\text{In three major studies, ALLHAT, CONVINCE, and LIFE, approximately 30-50\% of subjects remained above target blood pressure even with intensive antihypertensive therapies including three or more agents.}\]

⇒ With these results, it seems as though a large portion of the hypertensive population may see benefits with the addition of an aldosterone antagonist to their multidrug regimen.

How to Assess Resistant Hypertension

• A complete evaluation should be done including
  o Serum electrolytes
  o Simultaneous early morning plasma aldosterone and renin levels (i.e. ARR ratio)
  o 24 hour urine for sodium, creatinine, aldosterone and protein

• Evaluation of out-of-clinic blood pressure levels is recommended to identify white-coat hypertension which is present in 20-30\% of patients

• Patients with sleep apnea should be referred for polysomnographic
  o Improvement of sleep apnea can improve BP control

• Ensure proper lifestyle modifications are being met (can lower BP by 5-10mmHg)
  o High fiber, low fat (DASH) diet
  o Dietary salt restriction (<100mEq sodium/day; ~6g of salt)
  o Weight loss if obese or overweight
  o Regular exercise to all patients

The Original Hypothesis

It is thought that after observing such a high prevalence of primary aldosteronism with resistant hypertension, the blocking of aldosterone would provide significant antihypertensive benefit in this population. The decrease in blood pressure by the addition of an aldosterone antagonist should be predicted by urinary aldosterone excretion as well as the aldosterone-to-renin ratio. In conclusion, it is expected that patients with higher aldosterone levels would receive the maximum benefit with the most significant reduction in blood pressure.
What is the function of an Aldosterone Antagonist in Resistant Hypertension?

- Hyperaldosteronism has been found in 15-30% of the resistant hypertensive population.
- With this discovery, various studies have shown the addition of an aldosterone antagonist to be efficacious in reducing blood pressure in patients with a multidrug antihypertensive regimen.
- This confirms that conventional antihypertensive treatments such as angiotension-converting enzyme inhibitors and angiotensin receptor blockers are not sufficient at blocking circulating aldosterone.

What Aldosterone Antagonists have been Studied in Resistant Hypertension?

- Evidence is abundant for the use of spironolactone in treatment of resistant hypertension in a multidrug regimen.
- However the newest aldosterone antagonist, eplerenone, has not yet been investigated in patients with resistant hypertension. The theory is that with a similar mechanism of action as spironolactone and a better adverse
event profile, the effect of eplerenone in patients with resistant hypertension would be beneficial as well. Future studies will give us a definite answer.

- **Amiloride** which is a potassium sparing diuretic has indirect aldosterone antagonist effects by antagonizing the epithelial sodium channels in the distal collecting duct of the kidney that are up-regulated by aldosterone. Trials have shown positive outcomes in reducing blood pressure, after addition of amiloride to two-drug combination therapies including diuretics and calcium channel blockers in African American subjects. In regards to treating hyperaldosteronism, amiloride has shown to be inferior to spironolactone monotherapy in studies. However, there have been no specific studies of amiloride in resistant hypertension patients.

- Similar to amiloride, **Triamterene** was studied in hyperaldosteronism and not resistant hypertension. It did show positive results in reduction of blood pressure in combination of a thiazide diuretic.

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**Literature Highlight:** Nishizaka M. The Role of Aldosterone Antagonists in the Management of Resistant Hypertension. Current Hypertension Reports. 2005. 7;343-347. (6)

With the realization of how common hyperaldosteronism was in the resistant hypertensive population, Nishizaka et al. designed a trial with the hypothesis that aldosterone antagonists would provide substantial benefits to at least the participants that had high aldosterone concentrations. 

**Results:** After adding 12.5-50 mg of spironolactone to patients on a mean of four antihypertensives, including in almost all a diuretic, an ACEI or ARB and a CCB, a large reduction in blood pressure was seen. At a mean dose of 30 mg daily, systolic BP was reduced by 25 +/- 20 and DBP was reduced by 12 +/- 12mmHg. Spironolactone was reported safe and well tolerated as an additive therapy.

**Conclusion:** Contrary to their original thought, the reduction in blood pressure was seen in patients regardless of their plasma aldosterone or plasma renin levels. Although they did not push the dose, the authors believe there may be a dose-related response in patients with PA and that they may see extended benefit at doses as high as 200 mg.

⇒ Such high doses of spironolactone have been tested in diagnosed PA patients and have proven safe and efficacious. However, the risk of adverse events greatly increases above 50 mg daily.

How to Initiate an Aldosterone Antagonist onto a Multidrug Regimen

<table>
<thead>
<tr>
<th></th>
<th>Initial*</th>
<th>MDD</th>
<th>CrCl&lt;50ml/min</th>
<th>CrCl&lt;10ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spironolactone</td>
<td>25mg</td>
<td>400mg</td>
<td>Extend interval</td>
<td>Avoid</td>
</tr>
<tr>
<td>Eplerenone</td>
<td>50mg</td>
<td>100mg</td>
<td>Cx</td>
<td>Cx</td>
</tr>
<tr>
<td>Amiloride</td>
<td>2.5mg</td>
<td>20mg</td>
<td>Decrease by 50%</td>
<td>Cx</td>
</tr>
</tbody>
</table>

*See below for special populations’ initial doses

**Spironolactone**
- If patient has chronic kidney disease and/or the patient is elderly, begin 12.5mg once daily

**Eplerenone**
- Contraindicated with CYP3A4 inhibitors
- Initiate at 25mg daily in diabetics

**Amiloride**
- Although manufacturer recommends a maximum of 20mg/day, doses up to 40mg/day has been used in treating PA
- 40mg has been shown in trials to be the plateau of the diuretic effect

**All Aldosterone Antagonists**
- Discontinue or reduce the dose of potassium supplements with close monitoring for hyporenin hyperkalemia
- Advise the patient against the use of salt substitutes or herbal preparations that contain potassium
Monitoring
- 4 weeks after initiation, monitoring of potassium and renal function are necessary
  - In high-risk patients, this monitoring may be done as soon as 1 week after beginning an aldosterone antagonist

Titration
- Based on blood pressure response, dose titration can be done at 4-6 week intervals.
- An increase in serum potassium to a level > 5.5 mEq/l requires cessation of aldosterone antagonist therapy.
  - May consider restarting at a lower dose once potassium level returns to normal range
- An increase in potassium levels up to 5-5.5mEq/l can be managed by a decrease in dose

Adverse Events
- **Breast tenderness** with or without enlargement (gynecomastia)
  - Most commonly occurring in men, but seen in women as well
  - Dose dependent → Rare at doses 12.5-25mg/daily; steep increase at 50mg or more daily
  - ADE mostly seen during titration
  - D/C spironolactone until breast tenderness resolves, then restart at a lower dose
- Sexual dysfunction
  - Mostly erectile dysfunction in men
- Hyperkalemia – rare
- GI upset – noted with amiloride

Is there a difference in efficacy in Caucasian vs. African American patients?
- Although this has been an issue with other antihypertensive agents, trials have NOT shown any significant difference between Caucasian and African American populations in regards to blood pressure lowering through the use of aldosterone antagonists.

How to Diagnosis Primary Aldosteronism (PA)
- During a high dietary sodium ingestion > 200mEq/24h
  - Suppressed renin level < 1.0ng/ml/h
  - High 24-hour urinary excretion of aldosterone >12-15µg/24h
  - ARR ≥ 25ngdL⁻¹/ng/mL⁻¹

ARR ≥ 25 ng dL⁻¹ / ng mL⁻¹ h⁻¹ and plasma aldosterone ≥ 12 ng/dL
n=157

This flow chart shows the clinical parameters used to identify patients with Primary Aldosteronism. After this is done, a series of diagnostic tests are completed to determine the source of the hyperaldosteronism. Some of these techniques are invasive but may cure patients’ hypertensive disease for the rest of their lives.

However, other times the result returns with pharmacotherapy as the only option for management.

The controversy today is whether or not these invasive procedures are necessary before treating hyperaldosteronism.

Taken from Sartori M, et al. Aldosterone and Refractory Hypertension. AJH. Apr 2006;19:4 (8)
Is it Necessary to Diagnosis PA?

- As stated in the original hypothesis, it was thought that patients with diagnosed PA would respond to the addition of an aldosterone antagonist with significant reduction in their blood pressure.
- After various investigations it was discovered that patients with diagnosed PA OR patients with only resistant hypertension by itself were seeing benefits with the addition of an aldosterone antagonist to their regimen.
- Reduction in blood pressure was found to be similar in both populations, with or without PA, and the degree of blood pressure reduction was not correlated to baseline renin activity, plasma aldosterone concentration or 24-hour urinary aldosterone excretion.
- From this discovery in various trials, the thought is that excess mineralcorticoids may be producing a much larger effect on resistant hypertension than what appears from the diagnosed ~20%.
- Whether or not all patients need to be tested for PA prior to being treated with an aldosterone antagonist is controversial at this point.
  - Assessing for PA can be expensive as well as invasive putting some patients at involving adrenal vein sampling and adrenalectomy.
  - Also, most patients with PA have idiopathic aldosteronism in which surgery is not warranted and pharmacotherapy is the only option.
  - On the other hand, failure to properly diagnose with PA that is secondary to an aldosterone-producing tumor will cause a patient to endure lifelong pharmacotherapy when an adrenalectomy may have more effectively treated or even cured their PA and hypertension.
  - Lastly, dosing of aldosterone antagonists has only been studied in its highest of ranges amongst those who have been diagnosed with PA. Safety and benefit is unclear at large doses in patients without PA.
- Since there is benefit seen with addition of an aldosterone antagonist to a multidrug regimen in resistant hypertension regardless of diagnosed PA, potassium concentration (as explained in article summary below) may be the future indicator for adjunct therapy of an AA.


This investigation correlated BP response of 50mg spironolactone to baseline ARR in a population of longstanding hypertensive patients who were uncontrolled on 3+ agents as well as a group of patients who were treatment naïve.

**Results:** There was a highly significant correlation between BP reduction and ARR log in patients that were never before treated for hypertension. However for patients that had previously been on antihypertensive therapy, spironolactone demonstrated no relationship between BP decrease and ARR despite large reductions in blood pressure. There was a greater response in patients with a potassium concentration < 4mmol/L opposed to those whose potassium levels were ≥ 4mmol/L.

**Conclusion:** Although spironolactone proved beneficial in both groups, ARR as well as low renin activity only predicts outcomes in treatment naïve individuals.

⇒ This may be due to the affect that other antihypertensive agents have on the ARR.

Aldosterone-Producing Adenoma

- As described in the flow chart above, patients whose levels are indicative of PA will have a CT or MRI performed.
- If a nodular lesion is found, adrenal vein sampling is warranted which is a difficult and invasive procedure.
- Sampling of the adrenal venous and infrarenal inferior vena cava blood is done for measurement of plasma aldosterone and cortisol.
- An aldosterone-producing adenoma is diagnosed when the adrenal venous aldosterone-to-cortisol ratio is at least twice that of the vena cava sample on the side of the nodule but not higher than the vena cava sample of the opposite side.
- In this situation surgical therapy is appropriate.
Difference in Low Dose vs. High Dose Spironolactone

- Initially it was thought that patients with diagnosed PA would require higher doses of aldosterone antagonists in order to see a benefit in blood pressure lowering.
- Trials have been completed and it has been shown safe and efficacious to use up to 400mg/day of spironolactone in patients with diagnosed PA.\(^{10}\)
- However, as stated earlier, with the increase in dose, the likelihood of adverse effects significantly increase.
- At least one study has been done using low-dose spironolactone, initiating at 12.5-25mg, in patients with or without PA but whom all had resistant hypertension. The result showed that even a low-dose of spironolactone can have a substantial additive effect on a combination antihypertensive regimen in patients with or without PA.

<table>
<thead>
<tr>
<th>Literature Highlight: Nishizaka et al. Efficacy of Low-Dose Spironolactone in Subjects with Resistant Hypertension, AJH. 2003;16;925-930(^{(11)})</th>
</tr>
</thead>
</table>
| Previous studies have established the efficacy of high dosed spironolactone in PA and, to a lesser extent, in resistant hypertension. This study is investigating the value of low dose spironolactone in combination with a diuretic and an ACE-inhibitor or an ARB in resistant hypertension with or without PA.

**Results:** An initial addition of 12.5-25mg of spironolactone was added to the multidrug regimen. If necessary, the spironolactone dose was increased to 50mg/day. Even at these low-doses, a significant reduction in blood pressure was seen in patients with and without primary aldosteronism (mean decrease of 25 +/- 20mmHg SBP and 12+/− 12mmHg DBP x 6 months of treatment). The BP reduction was similar in both groups.

**Conclusion:** Low-dose spironolactone is effective in reducing blood pressure in patients with resistant hypertension whether or not diagnosed with PA. There was no difference in efficacy of spironolactone found in regards to race either.

⇒ Starting low on the dose of spironolactone during initiation seems to be the right approach to reduce ADEs.

Possible Thiazide Effect on Hyperaldosteronism

- Secondary hyperaldosteronism may be provoked by longstanding thiazide diuretic therapy
- Thiazides as well as loop diuretics increase the release of renin and plasma levels of angiotensin that in turn stimulates the release of aldosterone.
- Multiple studies have also examined the effect thiazides have on potassium depletion, which correlates with the release of aldosterone.\(^9,12\)
- These investigations have concluded that the effects of potassium depletion may even cancel out the cardiovascular protective benefits thiazides held.

How Spironolactone is Different

- Its diuretic effect is only exhibited in the presence of aldosterone unlike amiloride or triamterene.
- Doses as low as 25mg/day have an inhibitory effect on cardiovascular reactivity to both adrenergic and the renin-angiotensin system
- One study referred to spironolactone as more “durable” than ACE-inhibitors in the fact that the withdrawal from inhibition of the RAAS that occurs after long-term ACE inhibitor therapy does not occur with spironolactone treatment.\(^{12}\)

Hyperkalemia

- Patients presenting with PA were commonly seen to have hypokalemia (< 3.5mmol/L). However, this is not seen as frequently anymore.
- Patients are more often seen with normal potassium levels or concentrations < 4mmol/L.
- Many studies have also seen better response to spironolactone in patients with potassium levels < 4mmol/L opposed to those whose concentrations were 4 ≥ mmol/L.
It is not known if this is indicative of higher prevalence of hyperaldosteronism or a higher renin:aldosterone ratio. By selecting patients based on potassium concentrations, this may reduce the risk of hyperkalemic events. Another way of doing this is by keeping a thiazide diuretic on hypertensive patients’ regimens, which will also decrease the amount of hypokalemia adverse events.

What Role Do Other Antihypertensives Play in Combination with Aldosterone Antagonists?  
- Difficult to predict synergistic or antagonistic effects of multiple agents used simultaneously
- Trials did show that other antihypertensives played a larger role on altering plasma renin levels and a smaller role on changing plasma aldosterone levels.
- Atenolol changed the ARR more so than any other antihypertensive.

Other Drugs That Alter Aldosterone Secretion
- Heparin and Low-molecular weight heparin
  - Suppress aldosterone secretion – use as an antihypertensive does not seem likely
- Dopamine agonists
  - Suppress aldosterone release
- Dopamine antagonists
  - Stimulate aldosterone release from adrenal glands
- 5-HT₄ receptor agonist – Cisapride (recently been withdrawn from market)
  - Increases plasma aldosterone

<table>
<thead>
<tr>
<th>Drug</th>
<th>Renin</th>
<th>Aldosterone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atenolol</td>
<td>Decrease</td>
<td>Decrease</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>Increase</td>
<td>Decrease</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>Increase</td>
<td>Decrease</td>
</tr>
<tr>
<td>Irbesartan</td>
<td>Increase</td>
<td>Decrease</td>
</tr>
</tbody>
</table>

Can Spironolactone Be Used with Angiotensin Blocking Agents Safely?  
- In multidrug regimens of resistant hypertensive patients it is very common to see patients on either an ACE-inhibitor or an angiotensin-receptor blocker.
- With this in mind, many trials tested patients that included either of these agents in their regimens and found that it was not only efficacious but also safe as well to treat patients simultaneously.  
- Potassium concentrations must be assessed on a regular basis due to the increased risk of hyperkalemia in combination use with angiotensin blockers and aldosterone antagonists. However, this combination did not show an increase in adverse event rate in completed trials.

Why is there Hesitation with Spironolactone Use?  
- Delay in Effect
  - 3-5 weeks between initiation and full therapeutic effect
- Adverse Events
  - Although most studies report this not being an issue in their investigation, they are dose dependent and reversible.
- Compared to Other Agents
  - Spironolactone may only block 2% of the daily renal absorption due to aldosterone, but cumulative sodium loss over 4 weeks can exceed a loop diuretic

⇒ With the effectiveness of aldosterone antagonists seen at low-doses, adverse effects can be minimized with proper initiation and dose titration. Hyperkalemia was a very rare event reported in trials and can be managed as stated in the Hyperkalemia section and frequent laboratory monitoring.
When to Use Eplerenone?

- Eplerenone is a selective aldosterone antagonist with low affinity for progesterone and androgen receptors.
- Because of this, eplerenone is much less likely to cause side effects seen with spironolactone such as breast tenderness, gynecomastia, sexual dysfunction and menstrual irregularities.
- It has been established as efficacious and safe in treating primary hypertension in both African Americans and Caucasian patients and also has been shown to provide additive benefits with an ACE-I or an ARB.15
- As seen with spironolactone, there has been predictive response to blood pressure based on the ARR.16
- Many of the investigators of these trials believe that eplerenone will work just as efficacious as spironolactone but the evidence is yet to come. Until then, it is suggested to use eplerenone in patients that cannot tolerate spironolactone.
- Eplerenone should be initiated at 50mg daily and titrated to a goal of 50mg twice daily. However, if the patient is a diabetic or has renal insufficiency, 25mg is an appropriate starting dose. Keep in mind, eplerenone is contraindicated at CrCl < 50ml/min.6
- Monitoring is the same as spironolactone – serum potassium and renal function.

Is Amiloride or Triamterene Efficacious?

- Amiloride can be used efficacious in combination with other antihypertensives for the treatment of primary aldosteronism.
- However, compared to spironolactone it is not as effective.
  - 400mg daily of spironolactone monotherapy can reduce arterial BP by approximately 20% whereas 40mg daily of amiloride monotherapy will only reduce BP by 10.4%.4
- Triameterene-thiazide combinations have been investigated in PA patients and have showed a significant reduction in blood pressure (averaging 168/101 → 130/84mmHg).
- However, most patients on this treatment did see a rise in serum potassium

Future of Treatment 4

- Research is underway for the development of drugs that can inhibit the action of aldosterone synthase, reducing the production of aldosterone.
- Aldosterone synthase is the key enzyme that has been shown to be over-produced in patients with hyperaldosteronism.
- The gene for aldosterone synthase, CYP11B2, has been identified in recent years.
  - Possible future treatment will include gene therapy to reduce the expression of or even inhibit the action of mRNA of CYP11B2 at the cellular level
  - Even normotensive individuals with aldosterone synthase polymorphisms will have the opportunity to partake in genetic testing that can identify predispositional inappropriate aldosterone secretion.
  - This will allow preventative measures to be taken as well as treating associated hypertension at a much earlier stage.
Wrong answer...try again or read on.

[Back to quick-read info and quiz question]

Answer Key:
1. D
2. B
3. B
4. C
5. B
6. True

Some Key references:
Individual product information sheets for each drug were also utilized. Links to each provided in first chart.

1. Aldosterone Inhibitors in Infants and Children: Use of Spironolactone in Chronic Lung Disease
3. Saha et al. Improvement in Blood Pressure with Inhibition of the Epithelial Sodium Channel in Blacks with Hypertension.
8. Sartori M. Aldosterone and Refractory Hypertension: A Prospective Cohort Study. AJH. 2006. 19;373-379.