Secondary Hypertension Evaluation: Who, When, and How

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Disclosures

- None

Objectives

- Identify patients with risk factors for secondary hypertension.
- Evaluate patients for common causes of secondary hypertension.
- Appropriately manage patients with secondary hypertension.
- Recognize when specialist referral is needed for further evaluation and management of these patients.

Hypertension and Secondary Hypertension

- It is estimated that in the United States, nearly half of all adults (48% or 116 million) have hypertension.
- Approximately 10-20% of hypertension is attributable to secondary hypertension.
- It is important to recognize these patients as many types of secondary hypertension have targeted treatment or even cure.
- All patients with hypertension should undergo a review of their history, medications and supplements, and a thorough physical exam as well as targeted testing for end organ damage.
- It is not necessary or cost effective to perform extensive work-up for secondary causes on all patients with hypertension.

Patient 1

A 28 year old man presents to your clinic to establish care. He has no known health issues and takes no medications on a regular basis. He feels well and does not have any concerns with his own health.

He lives with his wife and 4 year old daughter and works as a financial planner. He has never smoked or used illegal drugs and has 4-6 alcoholic beverages per week.

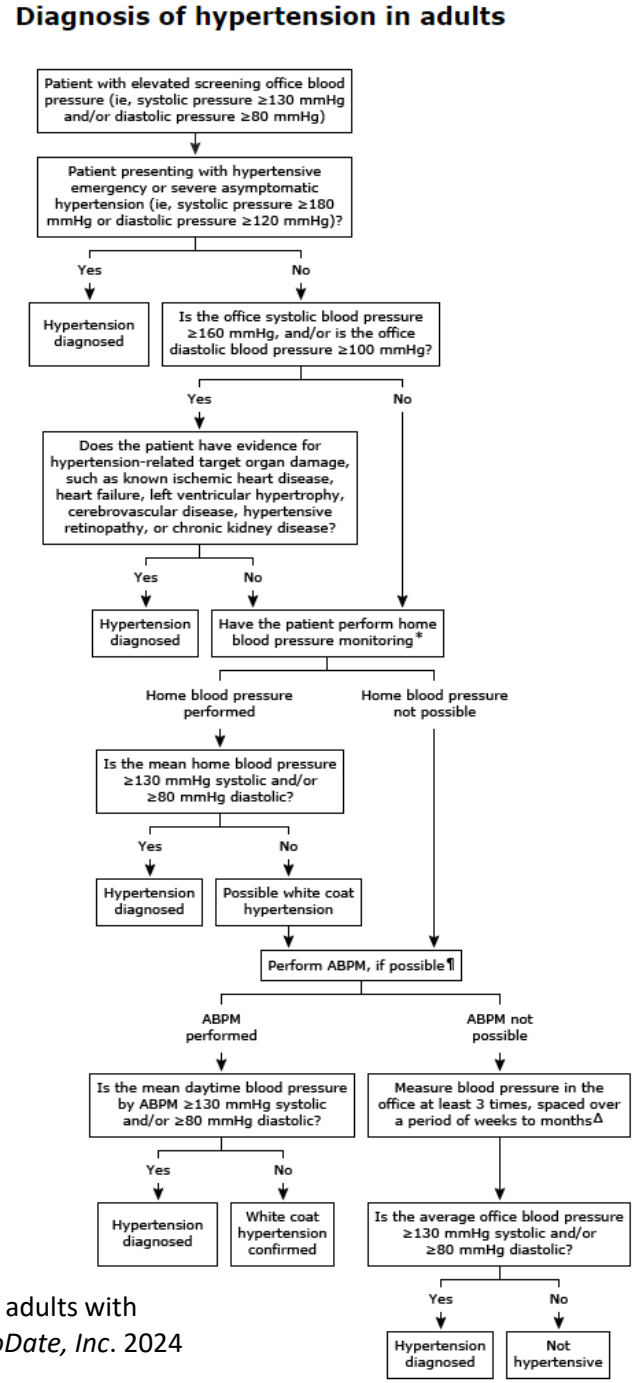
He has a family history of hypertension in his father, diagnosed around the age of 55. He does not have any family history of kidney disease, autoimmune disease, or early onset heart disease or stroke.

Vitals signs:

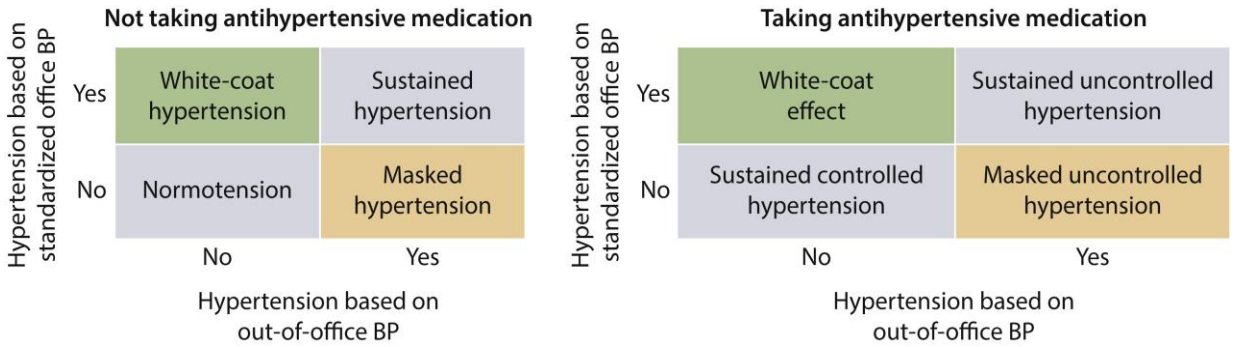
BP 155/92 (confirmed with serial blood pressure measurements), Pulse 74, Temp 36.4, O2 sat 94% on RA, Pain 0/10

Height: 72’, Weight 198 lbs, BMI 26.9

His exam is unremarkable



Initial evaluation of adults with hypertension. *UpToDate, Inc*. 2024



Kidney International 2021 99S1-S87 DOI: (10.1016/j.kint.2020.11.003)

The patient returns for a follow up visit 3 weeks after his initial visit. His in office blood pressure is improved to 133/83. He has been monitoring his blood pressures at home and brings you the following chart:

Date	AM	PM	Notes
2/3	143/78	135/82	
2/4	144/75	152/74	
2/5	141/79	147/85	Didn't sleep well
2/6	139/86	140/72	
2/7	129/80	135/68	
2/8	144/87	128/76	
2/9	145/73	144/81	Had extra coffee

What do you do next?

A. Do nothing, follow up in 3 months

B. Start an antihypertensive

C. Begin evaluation for secondary causes of hypertension

D. Refer to nephrology

E. Perform blood chemistry, lipid profile, urinalysis, albumin:creatinine ratio, and EKG

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The initial laboratory evaluation of your patient returns:

Test	Result	RR
WBC	7.2	4.30-11.30 k/uL
Hgb	15.4	14.8-17.8 g/dL
Hct	46.2	44.2-53.0%
Platelets	234	159-439 k/uL

Urinalysis – Yellow, clear, SG 1.011, negative RBCs, WBCS, LE, protein, ketones, glucose

Urine protein to creatinine ratio -75 mg/g

EKG – normal

Lipid panel – Cholesterol 187 mg/dl, 90 mg/dl, Triglycerides 123 mg/dl, HDL 45 mg/dl

Test	Result	RR
Na	139	136-144 mmol/L
K	3.3	3.3-5.0 mmol/L
Cl	106	102-110 mmol/L
CO2	25	20-26 mmol/L
BUN	15	8-24 mg/dL
Creatinine	0.91	0.72-1.25 mg/dL
eGFR	118	ml/min/1.73 m^2
Glucose	95	64-128 mg/dL
Calcium	9.8	8.4-10.5 mg/dL
Albumin	3.8	3.5-5.0 g/dL
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Which patients should be evaluated for secondary hypertension?

- Age of onset before puberty
- Age under 30 (without obesity, family history of hypertension, or other risk factor)
- Hypertension associated with electrolyte or acid base disturbances
- Malignant hypertension (presence of end organ damage)
- Acute change or increased lability of blood pressure
- Severe or resistant hypertension (presence of hypertension despite adequate doses of at least 3 anti-hypertensives including a diuretic)
- Signs or symptoms of diseases associated with secondary hypertension

What are the common causes of secondary hypertension?

- Primary hyperaldosteronism
- Chronic kidney disease (polycystic kidney disease)
- Obstructive sleep apnea
- Renovascular disease (renal artery stenosis and fibromuscular dysplasia)
- Medications/substances

Which medications can cause secondary hypertension?

- Oral contraceptives
- Anabolic steroids/testosterone
- NSAIDs
- Chemotherapeutic agents (eg, tyrosine kinase inhibitors/VEGF blockade)
- Stimulants (eg, cocaine, methylphenidate)
- Calcineurin inhibitors (eg, cyclosporine)
- Antidepressants (eg, venlafaxine)
- Licorice, chewing tobacco, posaconazole

What are less common causes of secondary hypertension?

- Pheochromocytoma
- Cushing's syndrome
- Coarctation of the aorta
- Hyperthyroidism
- Hyperparathyroidism
- Other rare disorders (monogenic hypertension syndromes) – Liddle syndrome, Gordon syndrome, Syndrome of Apparent Mineralocorticoid Excess

What is the initial work-up for secondary hypertension?

- Sleep study if high suspicion (excessive daytime sleepiness and at least two of the following: habitual loud snoring; witnessed apnea, gasping, or choking; or diagnosed hypertension)
- Bedtime salivary cortisol (two measurements), 24-hour urinary free cortisol (UFC) excretion (two measurements), or the overnight 1 mg dexamethasone suppression test
- Metanephrines (urine recommended, plasma easier)
- TSH
- PTH if hypercalcemic
- **8 am** aldosterone-renin activity ratio
  - If high aldo, low renin – evaluate for primary hyperaldo
  - If high aldo, high renin – evaluate for RAS, aortic coarctation
  - If low aldo, low renin and no other cause identified, consider genetic hypertension syndromes

You start your patient on amlodipine 5 mg daily and refer him patient to nephrology and but decide to begin work-up for secondary hypertension while awaiting his appointment.

Test	Result	RR
TSH	1.74	0.27-4.20 mU/L
Aldosterone	32	4.0 - 31.0 ng/dL
Renin activity	0.2	0.5-4.0 ng/mL/hr
Aldosterone:renin activity level	160	< 25
Plasma metanephrines	0.21	0.00-0.49 nmol/L
Overnight salivary cortisol x2	0.056	11 p.m. to midnight: <0.1 ug/dL
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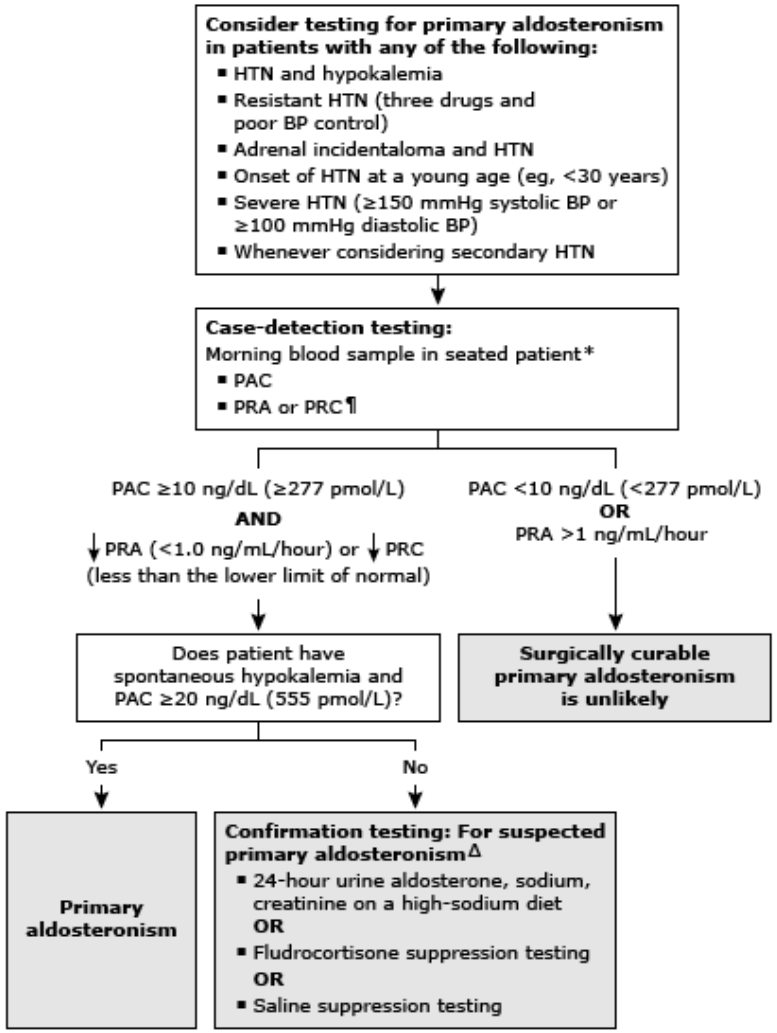
Primary Hyperaldosteronism

- More common than historically thought – up to 12.7% in primary care practice and 29.8% in referral centers (Kayser et al. 2016)
- Classic triad – hypertension, hypokalemia, metabolic alkalosis
- But presentation is variable - Hypokalemia is only present in 9-37% of patients
  - Hypokalemia and normotension
  - Normokalemia and hypertension

Case-detection testing for diagnosis of primary aldosteronism



HTN: hypertension; BP: blood pressure; PAC: plasma aldosterone concentration; PRA: plasma renin activity; PRC: plasma renin concentration.

* Patient out of bed for at least two hours and seated for at least 5 to 15 minutes before sample is drawn.

¶ Direct PRC can be measured instead of PRA. However, UpToDate authors prefer PRA. Refer to UpToDate topic on diagnosis of primary aldosteronism for interpretation of PRC cutoffs and normal values.

Δ Oral sodium loading over three days is one confirmation test that many experts use. An alternative is the saline infusion test. Details of both are reviewed in the UpToDate topic on diagnosis of primary aldosteronism.

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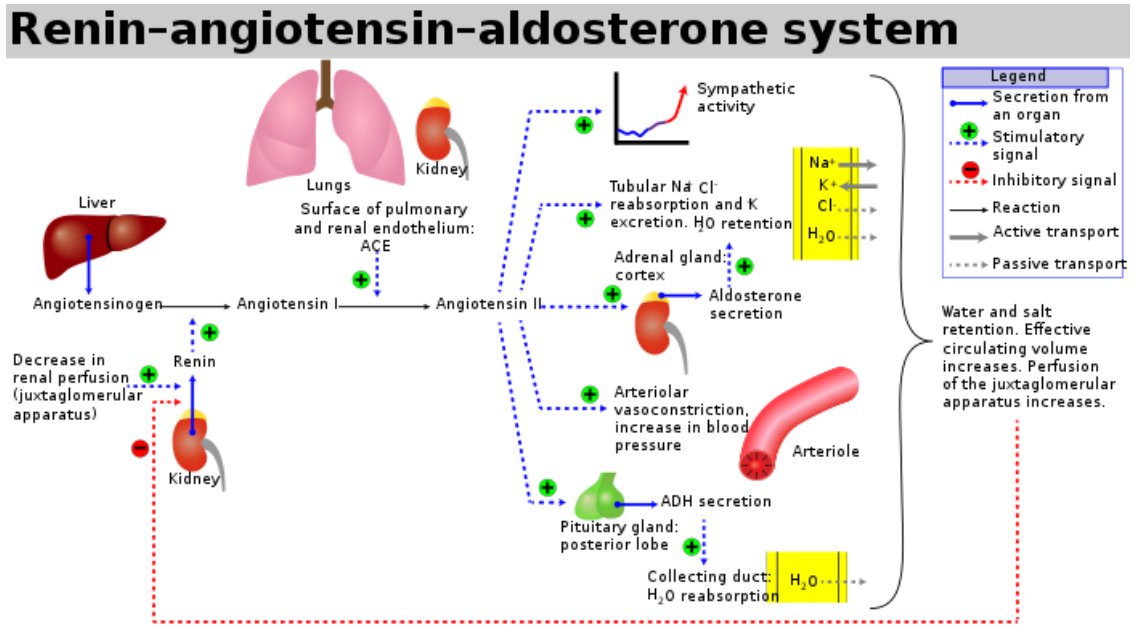
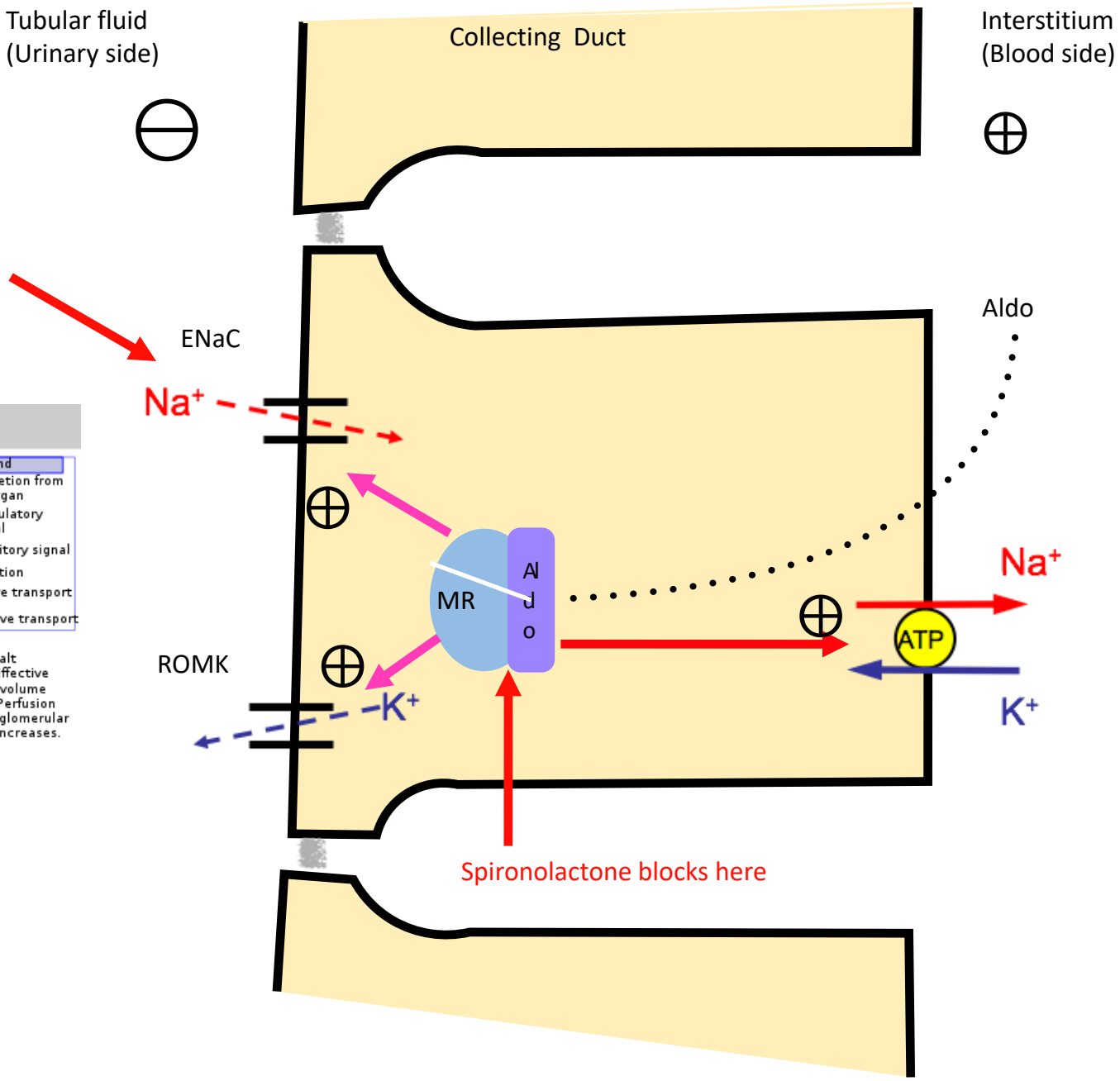
Diagnosis of primary hyperaldosteronism. *UpToDate, Inc*. 2024.



Renin-angiotensin system. *Wikipedia.* 2024.



Plasma renin activity vs. plasma renin concentration

- In many cases, both results are accurate and can be used interchangeably or as a composite
- For women on combined contraceptives or hormone replacement therapy, renin is suppressed in part due to increased activity of renin substrates (angiotensinogen) so measuring plasma renin concentration can lead to false positive screening

Which medications can affect screening for primary hyperaldosteronism?

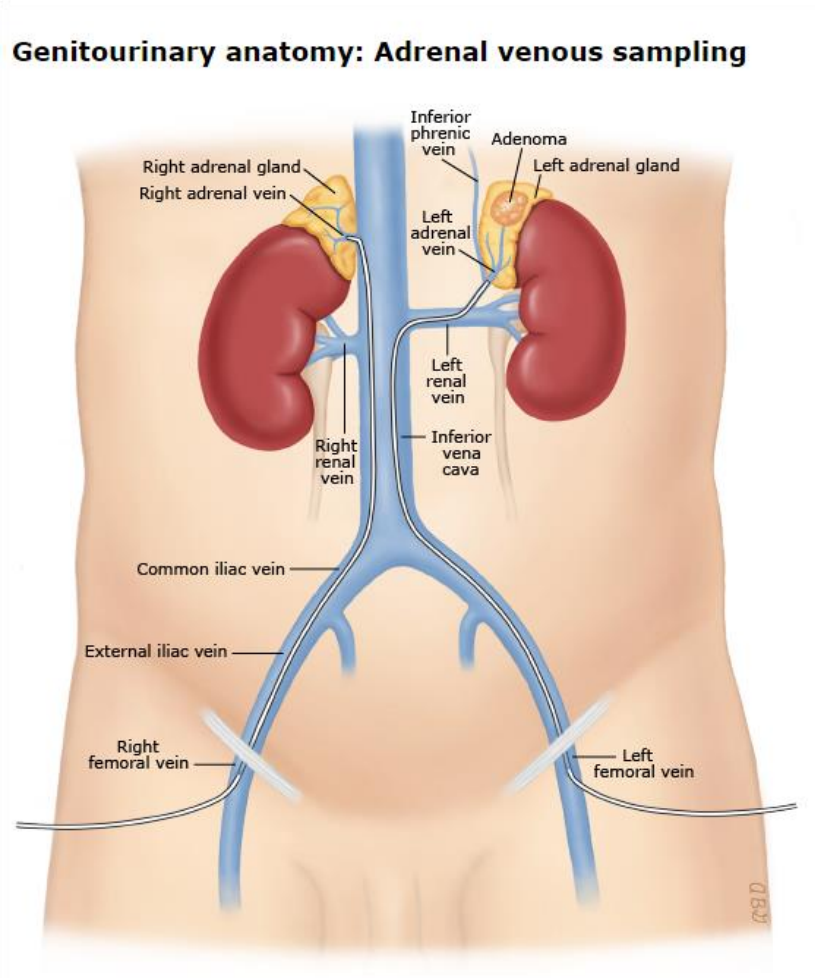
- Mineralocorticoid receptor antagonists (spironolactone, eplerenone, finerenone) can lead to false negative testing if they induce enough sodium loss to lead to decreased plasma volume and stimulation of RAAS.
  - Spironolactone must be held 4-6 weeks prior to reassessment
- ACE inhibitors and ARBs can lead to increase in plasma renin activity and plasma renin concentration, potentially leading to false negative test results. They are not commonly held prior to testing.
- Amiloride can have variable effects on aldosterone.

Next steps

- Adrenal CT (can be done without contrast if there is a contraindication) to determine the sub-type of hyperaldosteronism
  - Adrenal carcinoma (suspect with unilateral mass > 4 cm)
  - Bilateral adrenal hyperplasia
  - Unilateral macroadenoma (> 1 cm but < 4 cm)
- For patients under the age of 35 with unequivocal hyperaldosteronism and a unilateral mass, surgery can be pursued
- For patients over 35, the next step is adrenal vein sampling (due to high prevalence of adrenal adenomas)

Adrenal vein sampling

- Aldosterone and cortisol concentrations are measured in the blood from all three sites (right adrenal vein, left adrenal vein, and IVC). All of the blood samples should be assayed at 1:1, 1:10, and 1:50 dilutions



Diagnosis of primary hyperaldosteronism. *UpToDate, Inc.* 2024

Adrenal vein sampling

- Can be done with or without continuous cosyntropin infusion
- Cortisol-corrected aldosterone ratio from high to low side of > 4:1 indicates unilateral aldosterone production

Results from AVS in a 31y/o female with a history of hypertension and hypokalemia who was found to have PA by ARR (237). CT (not shown) showed normal appearing bilateral adrenal glands. Samples were taken with continuous cosyntropin infusion at 50 µg/hr. Left sided sampling was done in the common phrenic adrenal trunk. Ratios between the adrenal vein cortisol and IVC cortisol, the SI, are used to determine sampling adequacy. In this case SI on the right is 38.1 (914/24) and 6.6 (159/24) on the left, the latter number lower because of dilution from the inferior phrenic vein. The lateralization index is 20 (7.2/.35) with a CSI of 0.16 (.35/2.2). The patient underwent left adrenalectomy with hypertension and biochemical cure

	Aldosterone (ng/dl)	Cortisol (µg/dl)	A/C ratio
Right Adrenal Vein	319	914	0.35
Left Adrenal Vein	1144	159	7.2
Inferior Vena Cava	52	24	2.2

Quencer K. Adrenal vein sampling: technique and protocol. *CVIR Endovasc*. 2021

Treatment of Primary Hyperaldosteronism

- Adrenalectomy for unilateral disease
  - Cure of hypertension in 35-60% of patients
  - Success depends on age, degree of hypertension, and biochemical profile
- Mineralocorticoid Receptor Blockers
  - Start low but don’t be afraid to up-titrate – max dose spironolactone 400 mg/day
- Potassium sparing diuretics
- Patients will likely need additional antihypertensive medications

Patient 2

A 65 year old woman presents for an annual follow up visit. Her chronic medical issues are hypertension and hyperlipidemia. Both have been present for 10 years and has historically been well-controlled with amlodipine 5 mg daily and atorvastatin 20mg daily respectively. Today she reports that her home blood pressures have been high for the past 3 months, now averaging 160/90. Prior to this, her home blood pressure was averaging 128/76. She has not started any new medications. The only supplement she takes is an OTC vitamin D. She feels well.

Upon reviewing her history, you note that she has a 25 pack year smoking history but quit 10 years ago when she was diagnosed with hypertension.

Vitals signs:

BP 161/92 (confirmed with serial blood pressure measurements), Pulse 81, Temp 36.6, O2 sat 96% on RA, Pain 0/10

Height: 5’4”, Weight 168 lbs, BMI 28.8

Physical exam is unremarkable.

You obtain routine blood and urine tests.

Patient 2:

Test	Result	RR
WBC	7.2	4.30-11.30 k/uL
Hgb	14.2	12.6-15.9 g/dL
Hct	42.6	36-49%
Platelets	310	159-439 k/uL

Urinalysis – Yellow, clear, SG 1.009, negative RBCs, WBCS, LE, protein, ketones, glucose

Urine albumin to creatinine ratio:
78 mg/g

Test	Result	RR
Na	141	136-144 mmol/L
K	3.2	3.3-5.0 mmol/L
Cl	104	102-110 mmol/L
CO2	23	20-26 mmol/L
BUN	10	8-24 mg/dL
Creatinine	0.74	0.72-1.25 mg/dL
eGFR	90	ml/min/1.73 m^2
Glucose	112	64-128 mg/dL
Calcium	9.2	8.4-10.5 mg/dL
Albumin	4.0	3.5-5.0 g/dL
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What do you do next?

A. Start lisinopril 10 mg daily
B. Start spironolactone 25 mg daily
C. Perform work-up for secondary hypertension
D. Follow up in clinic in 2-4 weeks
E. Continue current management

What do you do next?

A. **Start lisinopril 10 mg daily**
B. Start spironolactone 25 mg daily
C. **Perform work-up for secondary hypertension**
D. **Follow up in clinic in 2-4 weeks**
E. Continue current management

Patient 2

Your patient returns for a follow up visit 2 weeks after starting lisinopril. Her blood pressure is improved and home blood pressures are now averaging 120/76. Repeat labs show:

Test	Result	RR
Na	140	136-144 mmol/L
K	4.5 (3.2)	3.3-5.0 mmol/L
Cl	109	102-110 mmol/L
CO2	21	20-26 mmol/L
BUN	25 (10)	8-24 mg/dL
Creatinine	1.62 (0.74)	0.72-1.25 mg/dL
eGFR	35 (90)	ml/min/1.73 m^2

What do you do next?

A. Stop lisinopril
B. Repeat labs in 1 week
C. Screen for renovascular hypertension
D. Refer to nephrology
E. Continue current management

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B. **Repeat labs in 1 week**
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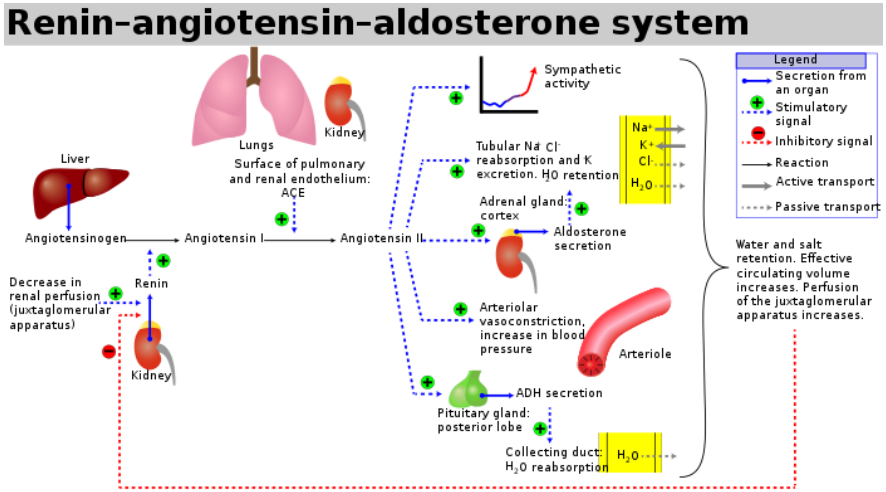
Renovascular hypertension

- Hypertension resulting from hormonal response to decreased renal blood flow
- The causes can vary
  - Renal artery stenosis (unilateral or bilateral)
  - Fibromuscular dysplasia (FMD)
  - Arteritidies – antiphospholipid antibody syndrome, Takayasu's, polyarteritis nodosa
  - Extrinsic compression
  - Dissection or infarction
  - Radiation fibrosis
  - Obstruction from aortic graft



Who should be screened for renovascular hypertension?

- Unexplained creatinine elevation and/or acute and persistent elevation in serum creatinine of at least 50% after administration of ACE inhibitor, ARB, or renin inhibitor
- Moderate to severe hypertension in a patient with diffuse atherosclerosis, a unilateral small kidney, or asymmetry in kidney size of more than 1.5 cm that cannot be explained by another reason
- Moderate to severe hypertension in patients with recurrent episodes of flash pulmonary edema
- Onset of hypertension with blood pressure >160/100 mmHg after age 55 years
- Systolic or diastolic abdominal bruit (specific but not very sensitive)

Screening for renovascular hypertension

- Non-invasive testing
  - Duplex Doppler ultrasonography
    - Resistive indices can also assist with prognosis
  - Computed tomographic angiography
  - Magnetic resonance angiography
- Renal arteriography (gold standard)
  - May be necessary in patients with FMD if mild disease
- Renin activity or aldosterone:renin ratio
- Captopril renogram
- Renal vein renin measurements

Treatment of renovascular hypertension

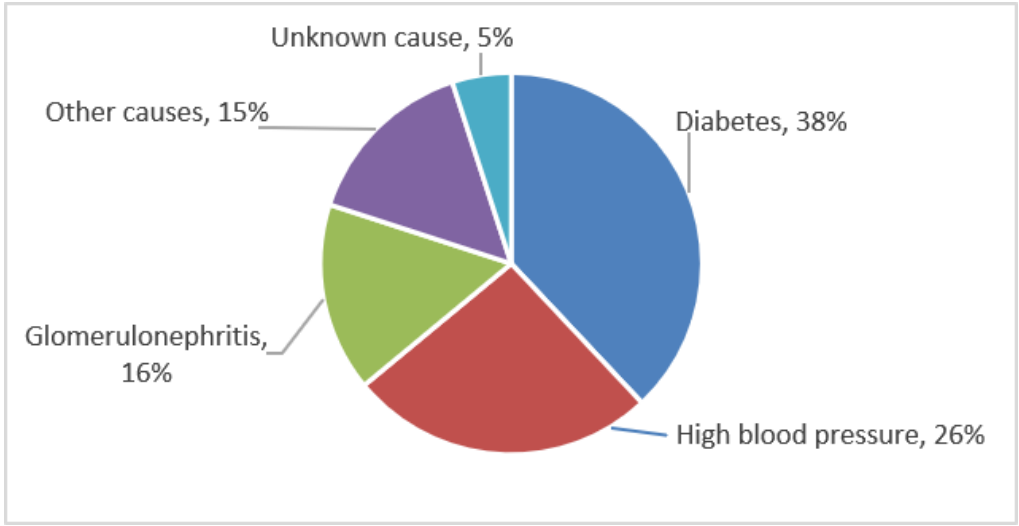
- Medical management – ACE-I or ARB are the treatment of choice if tolerated
  - ASA, statin for RAS
- Revascularization
  - Unilateral RAS
    - Short duration of hypertension
    - Failure of medical therapy/intolerance to medical therapy
    - Recurrent flash pulmonary edema or heart failure
  - Bilateral RAS/Single functional kidney
    - Meeting criteria above
    - Unexplained worsening renal function

Obstructive sleep apnea

- 50% of patients with OSA have hypertension
- OSA is detected in up to 85% of patients with **resistant hypertension** referred for sleep study
- Consider referral for patients with obesity, snoring, daytime sleepiness
- Unfortunately, use of CPAP seems to have only a modest effect on blood pressure (average lowering 2-3 mmHg systolic) – statistically but probably not clinically significant

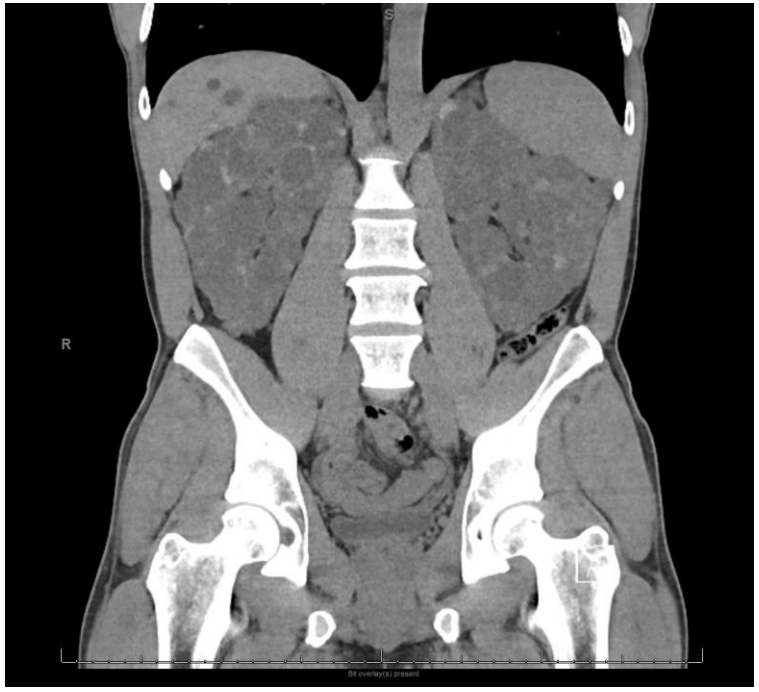
Kidney disease and hypertension

- Hypertension can occur with both acute glomerular disease and chronic kidney disease.
- Hypertension is the second most common cause of end stage renal disease in the US.
- Approximately 80-85% of patients with chronic kidney disease have hypertension with prevalence increasing as eGFR declines.



Kidney disease and hypertension

- Serum creatinine, urinalysis, and urine protein should be included in the initial evaluation of patients with hypertension.
- For patients with family history of kidney disease (especially polycystic kidney disease) or history of urologic events, consider kidney imaging.

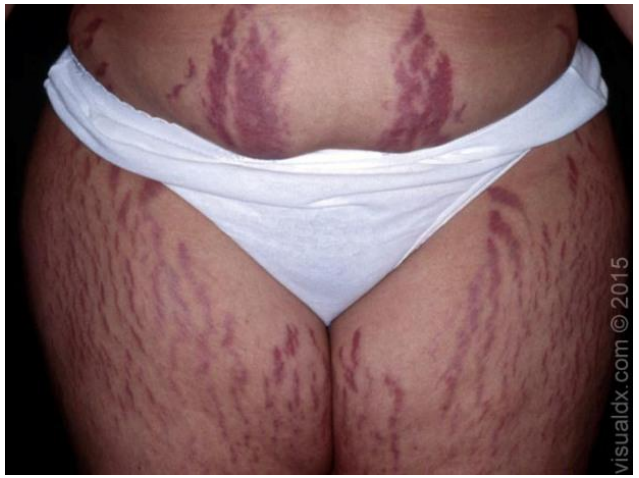


Kidney disease and hypertension

- Goal blood pressure < 130/80 or
- < 120/80 by standard office measurement (KDIGO guidelines 2021)
- Standard guidance regarding exercise and dietary sodium restriction
- ACE-I or ARB for proteinuric kidney disease (diabetic or non-diabetic)
- Otherwise, can start with ACE-I/ARB, thiazide, or dihydropyridine calcium channel blocker

Cushings syndrome

- Hypercortisolemia that occurs as a result of excess pituitary ACTH production, ectopic ACTH production by a non-pituitary tumor, or constitutive cortisol production as a result of adrenal adenoma or carcinoma, or bilateral adrenal hyperplasia
- Common associated symptoms include proximal muscle weakness, facial plethora, striae on abdomen, bruising, supraclavicular fat pads, body fat redistribution



Cushings syndrome

- Hypertension occurs as a result of activation of the mineralocorticoid receptor by excess cortisol
- Cortisol is normally converted to cortisone by 11 beta-hydroxysteroid dehydrogenase 2 but increased production overwhelms the enzyme's capacity for conversion.
- This can present similarly to hyperaldosteronism with hypertension, hypokalemia, and metabolic alkalosis but aldosterone and renin will be suppressed.

Cushings syndrome

- Diagnosis
  - 24 hour urinary cortisol
    - Caution with CKD
  - Bedtime salivary cortisol
    - Caution in shift workers
  - Dexamethasone suppression test – 1 mg vs. 2 mg
    - Not accurate in pregnancy
- Random or timed cortisol and ACTH tests are not adequate screening
- After initial diagnosis, need to distinguish ACTH dependent vs. independent processes

Cushings syndrome

- Management
  - Cushing disease
    - Resection when possible
    - Medical therapy – cabergoline, pasireotide, mifepristone
    - Chemotherapy or radiation
  - Ectopic ACTH
    - Resection when possible
    - Bilateral adrenalectomy
    - Medical therapy – ketoconazole, metyrapone, or etomidate
  - Primary adrenal disease
    - Adrenalectomy for unilateral disease
    - Bilateral adrenalectomy vs. medical management for bilateral hyperplasia

Pheochromocytoma

- Tumor secreting catecholamine that arises from the adrenal medulla. Tumors arising from the sympathetic ganglia are paragangliomas.
- Rare cause of secondary hypertension (less than 0.2% of hypertensive patients)
- Presentation varies
  - Classic triad – episodic headaches, sweating, tachycardia
  - Paroxysmal hypertension in about ½ of patients
  - Provoked paroxysmal hypertension
- Can be associated with syndromes such as MEN2, NF1, or von Hippel-Lindau

Pheochromocytoma

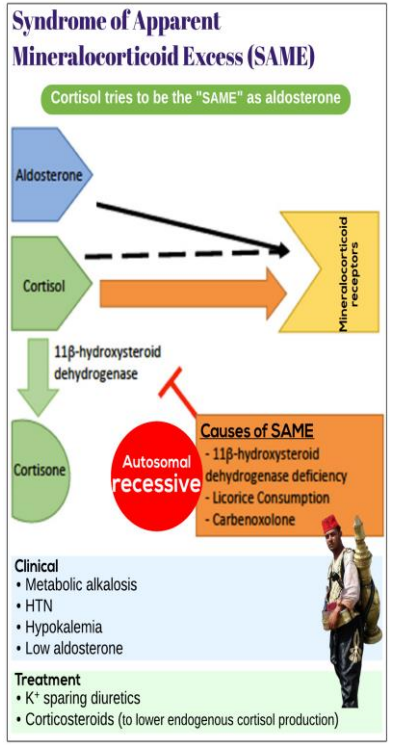
- Initial testing
  - 24 hour urinary metanephrines
  - Plasma metanephrines drawn supine with indwelling catheter (false positive if not done correctly)
- Imaging
  - CT or MRI of abdomen and pelvis
  - Can consider advanced imaging if high suspicion and negative CT or MRI – 68-Ga DOTATE PET, FDG-PET, iobenguane I-123
- Not recommended – AVS or biopsy

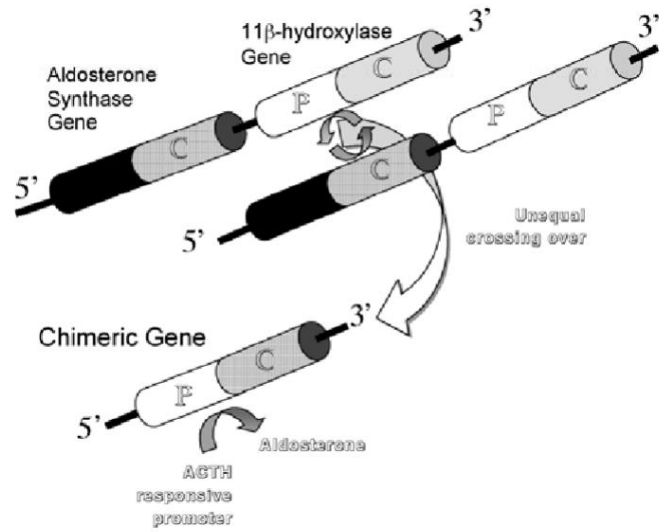
Pheochromocytoma

- Management
  - Pre-operative alpha blockade – phenoxybenzamine
  - High sodium diet
  - Beta blockade
  - Adrenalectomy/tumor removal

Genetic Hypertension Syndromes

Name	Defect	Inheritance	Renin	Aldo	Treatment	Buzzwords/Key Concepts
Liddle	eNAC	AD, GOF	Low	Low	Amiloride	High HCO3
Geller's	MR	AD, GOF	Low	Low	Amiloride	Pregnancy No spironolactone
Gordon's (Familial Hyperkalemic HTN, Pseudohypoaldo 2)	WNK4 WNK1 (Cullin-4, Kelch-3)	AR, LOF AR, GOF (mutants impair WNK degradation)	Low	Low	Thiazide	Hyperkalemia/metabolic acidosis
Apparent Mineralocorticoid Excess	11-beta HSD2	AR	Low	Low	Spiro, K, Amil, Dex	Hypercalciuria, nephrocalcinosis. Urine cortisol>>> cortisone. Licorice, chewing tob, posaconazole
Glucorticoid remediable aldosteronism, Familial Hyperaldo I	Aldo synthase driven by 11-beta hydroxylase promoter	AD	Low	High	Glucocorticoids (pred) at bedtime	FH of CVA < 40, intracranial aneurysm





Chimeric gene duplication in glucocorticoidremediable aldosteronism. P= promoter sequence. C= coding sequence.

McMahon. Glucocorticoid-Remediable Aldosteronism. 2004

Which patients should see a nephrologist?

- Resistant hypertension
- Suspected or proven secondary hypertension (+/- due to OSA)
- Hypertension with electrolyte abnormalities
- Hypertension with underlying renal disease – acute or chronic
  - Hypertension can be the initial presenting symptom in patients with polycystic kidney disease and often precedes impairment in kidney function

My Approach to Secondary Hypertension Evaluation

1. Perform thorough history and physical exam with particular attention to medications and supplements as well as PE findings.
2. Perform CBC, RFP, UA, and UPCR plus EKG at least once in all patients with hypertension.
3. Targeted secondary work-up if clear signs or symptoms present.
4. Refer patients for sleep study if suspicion for OSA.

My Approach to Evaluation of Secondary Hypertension

4. If hypokalemia present/strong suspicion for primary hyperaldosteronism, first perform 8 AM Aldosterone:renin activity ratio.
    a. If suggestive of hyperaldosterism, follow algorithm.
    b. If low aldosterone and low renin, perform additional hormonal work-up including screening for Cushings, pheochromocytoma, and hyperthyroidism.
    c. If high aldosterone/high renin evaluate for renovascular hypertension.
5. Consider genetic testing for young patients and/or electrolyte abnormalities without other explanation.

Patient 3

An 18 year old man presents for evaluation for hypertension. His blood pressure was noted to be elevated at 149/84 at a recent visit with his primary care provider. He feels well and takes no medications or supplements. He does not do any dedicated exercise. He does not smoke, drink, or use drugs. He has been monitoring his blood pressure at home since his PCP visit and readings are ranging 130-140s/80s-90s.

Vital signs: BP 147/88, Pulse 85, Temp 36.8, O2sat 98%, Ht 71” Weight 160 lbs, BMI 22.5 kg/m^2

Exam is normal.

Patient 3:

Test	Result	RR
WBC	5.55	4.30-11.30 k/uL
Hgb	16.0	12.6-15.9 g/dL
Hct	42.6	36-49%
Platelets	213	159-439 k/uL

Urinalysis – Yellow, clear, SG 1.029, negative RBCs, WBCS, LE, protein, ketones, glucose

Urine albumin to creatinine ratio:
20 mg/g

Test	Result	RR
Na	140	136-144 mmol/L
K	3.9	3.3-5.0 mmol/L
Cl	109	102-110 mmol/L
CO2	25	20-26 mmol/L
BUN	16	8-24 mg/dL
Creatinine	0.79	0.72-1.25 mg/dL
eGFR	132	ml/min/1.73 m^2
Glucose	106	64-128 mg/dL
Calcium	9.3	8.4-10.5 mg/dL
Albumin	4.4	3.5-5.0 g/dL
Phos	4.3	2.2-4.5 mg/dL

Additional work-up shows:

Test	Result	RR
TSH	2.32	0.27-4.20 mU/L
Aldosterone	5.9	4.0 - 31.0 ng/dL
Renin activity	3.2	0.5-4.0 ng/mL/hr
Aldosterone:renin activity level	1.5	< 25
Plasma metanephrines	0.31	0.00-0.49 nmol/L
Overnight salivary cortisol x2	0.032	11 p.m. to midnight: <0.1 ug/dL
	0.041	

Retroperitoneal US: Normal renal size and echogenicity. No hydronephrosis.

Genetic testing: negative for disease causing mutations

Sometimes, it’s just essential hypertension.

References

Ahmed AH, Gordon RD, Taylor PH, Ward G, Pimenta A, & Stowasser M. Effect of contraceptives on aldosterone/renin ratio may vary according to the components of contraceptive, renin assay method, and possibly route of administration. *J Clin Endocrinol Metab.* 2011;96(6):1797.

Ahmed AH et al. Effect of combined hormonal replacement therapy on the aldosterone/renin ratio in postmenopausal women. *J Clin Endocrinol Metab*. 2017;102(7):2329.

Kayser et al. Study heterogeneity and estimation of prevalence of primary aldosteronism: a systematic review and meta-regression analysis. *J Clin Endocrinol Metab*. 2016;101(7):2826.

Logan AG et al. High prevalence of unrecognized sleep apnea in drug-resistant hypertension. *J Hypertens*. 2001;19(12):2271.

Quencer K. Adrenal vein sampling: technique and protocol, a systematic review. *CVIR Endovasc*. 2021;4:38.

Tomson CVR et al. Management of blood pressure in patients with chronic kidney disease not receiving dialysis: synopsis of the 2021 KDIGO clinical practice guideline. *Clinical Guidelines*. 2021