Secondary Hypertension: Diagnostic Approach and Management

Andrew Bland, MD, FACP, FAAP

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Secondary Hypertension: Diagnostic Approach and Management

Learning Objectives

By the end of this handout, students will be able to:

1. **Identify clinical features** that suggest secondary hypertension and determine when to pursue testing
2. **Understand the pathophysiology** of primary aldosteronism, renovascular disease, pheochromocytoma, Cushing syndrome, and other secondary causes
3. **Apply diagnostic algorithms** for each major cause, including screening tests and confirmatory studies
4. **Interpret tests appropriately:** Aldosterone-renin ratio, renin measurements, imaging, suppression testing
5. **Manage refractory hypertension** and identify candidates for intervention (revascularization, adrenalectomy, etc.)
6. **Recognize syndromic presentations** and order appropriate testing in context

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I. Overview: When to Suspect Secondary Hypertension

Epidemiology

- **Essential (primary) hypertension:** 90–95% of hypertension cases
- **Secondary hypertension:** 5–10% overall; up to 30% in resistant/refractory cases
- **Most common secondary causes:** CKD, primary aldosteronism, renovascular disease, pheochromocytoma, Cushing syndrome

Clinical Clues Suggesting Secondary Hypertension

Finding	Consider
Age <30 or >50 with sudden HTN onset	Renovascular disease, pheochromocytoma, Cushing syndrome

Finding	Consider
Resistant HTN (uncontrolled on ≥3 agents)	Primary aldosteronism, pheochromocytoma, Cushing, OSA, CKD
Acute HTN crisis with symptoms	Pheochromocytoma, Cushing, renovascular disease, preeclampsia
Hypokalemia (unprovoked or on diuretics)	Primary aldosteronism, Cushing, hypomagnesemia
Flash pulmonary edema	Renovascular disease (bilateral or in single kidney)
Abdominal bruit on exam	Renovascular disease (fibromuscular dysplasia or atherosclerotic)
Family history of early HTN or strokes	Renovascular disease, genetic forms (rarely: monogenic HTN)
Palpitations, headaches, sweating spells	Pheochromocytoma, hyperthyroidism
Proximal weakness, moon facies, striae	Cushing syndrome
Sleep apnea symptoms (snoring, daytime somnolence)	OSA-related HTN
Medication-induced	NSAIDs, oral contraceptives, decongestants, anesthetics

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II. Primary Aldosteronism (Hyperaldosteronism)

Definition & Epidemiology

Primary aldosteronism (PA) is **autonomous aldosterone secretion** from the adrenal cortex **independent of the renin-angiotensin system**.

- **Prevalence:** 5–15% of hypertensive patients; up to 20% of resistant HTN
- **Most common secondary cause of hypertension** in developed countries
- **Often overlooked:** Many patients remain undiagnosed for years

Pathophysiology

Normal physiology (renin-angiotensin-aldosterone axis): 1. Low renal perfusion or hypovolemia ☐ juxtaglomerular cells ☐ ☐ renin release 2. Renin ☐ angiotensinogen ☐ angiotensin I (inactive) 3. ACE ☐ angiotensin II (active) 4. Angiotensin II ☐ aldosterone secretion from zona glomerulosa 5. Aldosterone ☐ Na+ reabsorption (ENaC channels), K+ excretion 6. ☐ Intravascular volume ☐ BP ☐ ☐ feedback suppression of renin (negative feedback)

In primary aldosteronism: - Aldosterone secretion becomes **autonomous** (not suppressed by normal renin feedback) - Renin is **suppressed** (from volume expansion caused by excessive aldosterone-driven Na+ reabsorption) - **Characterized by:** ☐ Aldosterone + ☐ Renin (reverse of normal) - **Classic presentation:** HTN + hypokalemia + metabolic alkalosis

Forms of Primary Aldosteronism

1. Aldosterone-Producing Adenoma (APA) — "Conn's Syndrome" (35–40%) - **Single adenoma** (unilateral), usually small (<2 cm) - Autonomously secretes aldosterone (ACTH-independent) - **Presentation:** Often younger patients (30–50s), more severe HTN - **Prognosis:** Surgically curable (adrenalectomy normalizes BP in 30–60%) - Genetic basis in ~40%: **KCNJ5 mutations** (potassium channel), CYP11B2 mutations, CACNA1D

2. Bilateral Idiopathic Adrenal Hyperplasia (IHA) — "Idiopathic Hyperaldosteronism" (60–65%) - **Bilateral adrenal tissue** hyperplasia (diffuse or nodular) - No identifiable adenoma on imaging - **Presentation:** Often older, less severe HTN than APA - **Prognosis:** Not surgically curable; requires medical management (MRA: spironolactone, eplerenone) - Genetic basis unclear; possibly polygenic or acquired (chronic ACTH stimulation)

3. Familial Hyperaldosteronism Type I (FH-I) — Glucocorticoid-Remediable Aldosteronism (GRA) — RARE (1%) - **Genetic chimera:** CYP11β1/CYP11β2 gene fusion □ aldosterone regulated by ACTH (not renin) - **Autosomal dominant inheritance** - **Presentation:** Very early-onset HTN (teens–20s), hypokalemia, metabolic alkalosis - **Unique finding:** Aldosterone secretion **suppressed by dexamethasone** (ACTH-suppressed) - **Molecular test:** Genetic analysis for chimeric gene or long-range PCR - **Treatment:** Low-dose glucocorticoid (dexamethasone) or amiloride (K+-sparing diuretic)

4. Familial Hyperaldosteronism Type II & III (FH-II, FH-III) — VERY RARE - Genetic basis unclear or identified (CLCN2 for FH-II) - Autosomal dominant - Present with APA-like or IHA-like features

Diagnostic Algorithm for Primary Aldosteronism

Step 1: Screening (Case Detection) Indications for screening: - Resistant hypertension (≥3 agents) - Hypertension + hypokalemia (spontaneous or diuretic-induced) - HTN + adrenal incidentaloma - Hypertension + family history of early stroke/HTN - All newly diagnosed HTN patients (PA is common; some advocate universal screening)

Screening test: Aldosterone-Renin Ratio (ARR)

Measurement	Unit	Interpretation
Plasma renin activity (PRA)	ng/mL/hour	Suppressed in PA
Plasma aldosterone concentration (PAC)	ng/dL	Elevated in PA
ARR = PAC / PRA	(ng/dL) / (ng/mL/h)	ARR >20–30 suggests PA (threshold varies by lab)

Conditions for accurate ARR: - **OFF diuretics for 4–6 weeks** (if possible; diuretics raise renin, lower ARR sensitivity) - **OFF ACE-I/ARB for 2+ weeks** (raise renin, lower ARR) - **OFF β-blockers for 1–2 weeks** (can suppress renin) - **Avoid NSAIDs, licorice, phenylephrine** (affect renin/aldosterone) - **Patient sitting upright for 5 min** before blood draw (standing raises renin) - **Morning blood draw** (aldosterone and renin follow circadian rhythm) - **Normokalemia** (if hypokalemic, correct first; hypokalemia suppresses aldosterone)

ARR interpretation: - **ARR >20–30:** Suggests PA (exact cutoff varies by lab; check your institution's reference range) - **ARR <10:** PA unlikely - **ARR 10–20:** Borderline; repeat or consider confirmatory testing

Step 2: Confirmatory Testing If ARR elevated, confirm with suppression/stimulation tests:

A. Saline Suppression Test (Gold Standard)

- **Protocol:** IV normal saline 0.9%, 500 mL/hour × 4 hours (total 2 L)
- **Measure:** PAC at baseline and end of infusion; PRA optional
- **Interpretation:**
  - **PAC remains >5 ng/dL after saline:** Confirms PA (aldosterone not suppressed by volume expansion)
  - **PAC <4 ng/dL after saline:** PA excluded
  - **PAC 4–5 ng/dL:** Borderline (repeat or use other test)

B. Oral Sodium Suppression Test

- **Protocol:** High-sodium diet (200+ mEq Na/day) × 3 days; measure 24-h urine sodium and plasma aldosterone on day 3
- **Interpretation:**
  - **PAC >5 ng/dL + 24-h urine Na >200 mEq:** Confirms PA
  - More physiologic than IV saline but slower, patient-dependent

C. Captopril Challenge Test

- **Protocol:** Baseline PAC/PRA, then captopril 25 mg PO; repeat labs 60 min later
- **Interpretation:**
  - **Lack of PRA increase (remains <1 ng/mL/h) + PAC remains elevated:** Suggests PA
  - Less specific than saline suppression; mostly historical

Step 3: Subtype Differentiation (APA vs. IHA) After confirming PA, distinguish APA (surgically curable) from IHA (medical management) with:

A. Imaging (CT or MRI of adrenals) - **Look for:** Unilateral nodule/adenoma vs. bilateral hyperplasia - **APA:** Usually single nodule, <1.5 cm, may not be visible if very small - **IHA:** Bilateral diffuse or micronodular hyperplasia, or apparently normal - **Caveat:** ~30% of PA from adenoma are NOT visible on imaging; aldosterone/renin ratio and clinical context guide subtyping

B. Adrenal Venous Sampling (AVS) — GOLD STANDARD for lateralization

Indication: If CT suggests unilateral adenoma (to confirm), or if subtype unclear and surgery being considered.

Protocol: - Bilateral adrenal vein catheterization - Draw blood from each adrenal vein + IVC for PAC and cortisol - Measure **aldosterone-to-cortisol ratio** in each adrenal vein

Interpretation (Selectivity Criteria): - **Selectivity Index = (Adrenal Aldosterone / Adrenal Cortisol) / (IVC Aldosterone / IVC Cortisol)** - Selectivity Index >2 (or >4 with ACTH stimulation) = adequate sampling - **Lateralization:** Aldosterone ratio (high-to-low adrenal side) >4 (or >3 with ACTH stim) = unilateral secretion (APA) - **No lateralization:** Bilateral secretion (IHA)

C. Genetic Testing - If FH-I suspected (very early onset, family history, dexamethasone-suppressible): Test for CYP11β1/CYP11β2 chimera - KCNJ5, CYP11B2, CACNA1D mutations for APA (research/specialized centers)

Management of Primary Aldosteronism

Medical Management (First-line or for IHA) Mineralocorticoid Receptor Antagonists (MRAs):

Agent	Dose Range	Mechanism	Notes
Spironolactone	12.5–50 mg daily	Non-selective MRA (also androgen antagonist)	Gynecomastia, sexual dysfunction common; long onset (weeks)
Eplerenone	50–100 mg daily	Selective for MR; fewer endocrine side effects	Better tolerance; more expensive; less potent than spironolactone
Finerenone	10–20 mg daily	Non-steroidal MRA (newer)	Renal and CV protective effects; emerging data

Expected BP reduction: 10–20 mmHg with MRA monotherapy; often combined with other agents.

Additional agents: - **ACE-I or ARB:** Adds 5–10 mmHg reduction; protects kidney; often combined with MRA - **Dihydropyridine calcium channel blocker (amlodipine, nifedipine):** Synergistic with MRA - **Thiazide diuretic:** Can be used cautiously with MRA (monitor K+) - **Amiloride or triamterene:** K+-sparing diuretics; alternative if MRA not tolerated; less effective than MRA

Monitoring on MRA: - **Potassium levels:** Check baseline, 1–2 weeks after initiation, then periodically (risk of hyperkalemia) - **Creatinine/eGFR:** Baseline, then periodically (MRA can worsen renal function if not carefully dosed) - **Aldosterone-renin ratio:** May normalize with suppressed aldosterone

Surgical Management (For APA) Indications: - **Confirmed APA (adenoma)** with: - Young age (<50, ideally) - Good surgical candidate (no major comorbidities) - Desire to normalize BP (avoid lifelong MRA) - Successful AVS lateralization

Procedure: Laparoscopic adrenalectomy (minimally invasive)

Expected outcomes: - **60–70% of patients achieve BP normalization** (off all antihypertensive meds) - **20–30% achieve partial BP improvement** (reduced medications) - Cure best if younger, shorter duration of HTN, smaller adenoma

Preparation: - **Alpha-blockade first:** Start phentolamine or doxazosin before surgery to prevent intraoperative hypertensive crisis - **Continue MRA** until surgery (maintains K+ balance)

Complications: - Acute adrenal insufficiency if bilateral adrenals damaged (rare with unilateral adrenalectomy) - Recurrent HTN if incomplete tumor resection or if IHA (not APA) wrongly operated on

Special Case: FH-I (GRA)

- **Medical management:** Low-dose dexamethasone (0.5 mg nightly) suppresses ACTH, normalizes aldosterone, controls BP
- **Alternative:** Amiloride 5–10 mg daily (K+-sparing diuretic)
- **No surgical benefit** (ACTH-driven, not tumor)

III. Renovascular Hypertension

Definition & Epidemiology

Hypertension caused by **renal artery stenosis (RAS)** leading to activation of the renin-angiotensin system.

- **Prevalence:** 1–2% of general hypertensive population; 10–15% of resistant HTN; up to 25% in acute coronary syndrome
- **Hemodynamically significant RAS (>60% stenosis):** In ~20% of patients found to have any RAS on imaging

Types of Renal Artery Stenosis

1. Atherosclerotic RAS (ARAS) — 90% of cases - Fibrous plaque in renal artery (usually proximal 1/3) - Associated atherosclerosis elsewhere (CAD, cerebrovascular disease, peripheral arterial disease) - **Demographics:** Older patients (>50), smoking history, dyslipidemia, male predominance - **Natural history:** Progressive stenosis in many; ~25% develop total occlusion over 5 years if untreated - **Risk:** Atheroemboli during intervention (angiography, angioplasty)

2. Fibromuscular Dysplasia (FMD) — 10% of cases - **Medial fibroplasia (85%):** "String of pearls" appearance, multiple segmental stenoses - **Intimal fibroplasia (5%):** Young patients, rapid progression - **Adventitial fibroplasia (5%):** Rare; affects outer arterial layers - **Demographics:** Young to middle-aged women (F:M = 5:1), no atherosclerosis risk factors - **Natural history:** May be stable over years; rarely progresses to total occlusion - **Associated conditions:** Connective tissue disorders (Ehlers-Danlos, Marfan), fibromuscular dysplasia in other vascular beds - **Better intervention outcomes** than atherosclerotic RAS (balloon angioplasty often curative; PCI/stent less often needed)

Pathophysiology of Renovascular HTN

Mechanism (Goldblatt two-kidney, one-clip model): 1. Renal artery stenosis ☐ ☐ renal perfusion pressure 2. Juxtaglomerular cells sense ☐ perfusion ☐ ☐ renin release 3. Renin ☐ angiotensin II (via ACE) 4. Angiotensin II effects: - **Systemic:** Vasoconstriction, sympathetic activation ☐ ☐ BP - **Renal:** Efferent arteriole vasoconstriction ☐ maintains GFR in stenotic kidney

(initially) 5. **Untreated:** Progressive renal fibrosis; non-stenotic kidney may develop secondary HTN-related glomerulosclerosis

Clinical consequence: "Flash" pulmonary edema can occur in bilateral RAS or RAS to solitary kidney (from sudden pressure drop across stenosis causing renal ischemia).

Clinical Presentation

Classic features: - HTN with **atherosclerotic risk factors** (smoking, old age, dyslipidemia) - **Abdominal or flank bruit** on exam - **Hypomagnesemia** (can accompany renovascular disease; unknown mechanism) - **Acute kidney injury** after starting ACE-I/ARB (paradoxically)

"Flash pulmonary edema": - Acute dyspnea, orthopnea, crackles on lung exam - Often without significant systemic HTN at moment - **Mechanism:** Renal ischemia ☐ ☐ renin ☐ angiotensin II-driven efferent arteriole vasoconstriction ☐ acute ☐ GFR ☐ fluid retention ☐ pulmonary edema - **Classic scenario:** Elderly patient with atherosclerotic RAS, often bilateral or in single kidney

Diagnostic Approach

Step 1: Screening Indications for RAS workup: - Resistant HTN (≥3 agents) + age >55 - Sudden HTN onset (any age) - HTN + flash pulmonary edema - HTN + abdominal bruit - Acute kidney injury after starting ACE-I/ARB - Unexplained progressive renal insufficiency - Peripheral arterial disease (high prevalence of concurrent RAS) - Young woman with HTN (FMD)

Step 2: Imaging Modalities

Modality	Sensitivity/Specificity	Pros	Cons	Radiation
Doppler ultrasound	85/92% (operator-dependent)	Non-invasive, no contrast, cheap	Difficult in obesity, aortic disease	None
CT angiography (CTA)	94/90%	Excellent spatial resolution, fast	Iodinated contrast (nephrotoxicity risk), radiation	Yes
MR angiography (MRA)	90/95%	Excellent for vessel anatomy, no radiation	Gadolinium (NSF risk in eGFR <30), expensive	No

Modality	Sensitivity/Specificity	Pros	Cons	Radiation
Captopril renography	85/85%	Functional (renin-mediated), no contrast	Slow (requires time), mostly historical	Yes
Renal artery angiography	Gold standard	Direct visualization, ability to intervene	Invasive, contrast nephropathy risk, atheroemboli	Yes

Clinical approach: - **First-line:** CTA or MRA (excellent sensitivity/specificity, good for treatment planning) - **If eGFR <30:** MRA preferred (gadolinium caution <30) or Doppler ultrasound - **If contrast allergy:** MRA or Doppler - **If imaging shows stenosis:** Angiography reserved for when intervention planned

Step 3: Functional Testing (Captopril Renography) — Mostly Historical

- **Protocol:** Baseline and post-captopril nuclear renography
- **Interpretation:** ACE-I causes ☐ efferent arteriole vasoconstriction ☐ ☐ GFR in stenotic kidney ☐ asymmetric perfusion pattern
- **Largely replaced by newer imaging** but can provide functional correlation if needed

Management of Renovascular Hypertension

Medical Management (First-line for most) ACE-I or ARB: - **Mechanism:** Block angiotensin II effects (both systemic and efferent vasoconstriction) - **Effect:** Normalize BP in many patients (partial angiotensin II-dependent HTN) - **Caution:** In **bilateral RAS or RAS to single kidney**, ACE-I/ARB can precipitate **acute kidney injury** (loss of efferent vasoconstriction-maintained GFR) - Monitor creatinine closely; expect small rise initially - If Cr rises >30% from baseline, reassess (may need intervention or discontinuation)

Additional agents: - **Calcium channel blockers** (dihydropyridines like amlodipine) - **Thiazide diuretics** - **Beta-blockers** (for CAD if present)

Medical management alone is appropriate if: - HTN controlled on ≤2 agents - Stable renal function - No evidence of recurrent fluid overload/flash pulmonary edema - Patient preference to avoid intervention

Percutaneous Transluminal Angioplasty (PTA) and Stenting PTA (balloon angioplasty): - Superior results in **fibromuscular dysplasia** (~90% success, durable) - Less durable in atherosclerotic RAS (restenosis 30–40% at 1 year)

Stenting (preferred for ARAS): - Better patency rates than PTA alone in atherosclerotic disease - But **evidence for superiority over medical management alone is limited** - ASTRAL trial

(2009): Stent + medical vs. medical alone showed NO difference in renal function decline or BP control in most patients - Exception: Flash pulmonary edema, recurrent fluid overload (stenting may help) - **Complications:** Atheroemboli (blue toe syndrome), access site complications, in-stent restenosis, contrast nephropathy

Indications for intervention (PTA or stenting): - **Definite:** Recurrent flash pulmonary edema, rapidly declining renal function attributable to RAS - **Probable:** HTN refractory to medical therapy + hemodynamically significant stenosis + good LVEF - **Consider:** Young patient with FMD (better durability with PTA) - **Avoid:** Asymptomatic stenosis with stable HTN and renal function (medical therapy sufficient)

Surgical Revascularization (Rare)

- Indications: Failed PTA, complex anatomy, need for concurrent surgery
- Options: Aortorenal bypass, endarterectomy
- Morbidity higher than PTA; reserved for select cases

Special Scenario: Flash Pulmonary Edema from Bilateral RAS

Pathophysiology: - Bilateral stenoses or single-kidney RAS ☐ renal ischemia in both kidneys - ☐ Renin-angiotensin activation ☐ systemic and renal vasoconstriction - Acute oliguria ☐ rapid volume accumulation ☐ pulmonary edema despite HTN sometimes not severe

Management: - **ACE-I/ARB caution:** May worsen hyperkalemia and reduce GFR (but often needed for systemic BP control) - **Diuretics:** Aggressive; loop diuretics often required - **Intervention (PTA ± stent):** Often necessary to restore renal perfusion, reduce renin-angiotensin drive - **Renal replacement therapy:** If acute kidney injury severe

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IV. Pheochromocytoma and Paraganglioma

Definition & Epidemiology

Pheochromocytoma is a **neuroendocrine tumor** arising from chromaffin cells of the adrenal medulla, secreting **catecholamines (epinephrine, norepinephrine)** causing episodic HTN, tachycardia, and headaches.

- **Prevalence:** 0.1–0.5% of hypertensive patients; 5–15% if HTN is paroxysmal/resistant
- **Incidence:** 1–4 per million per year
- **Age of onset:** Typically 30–50 years
- **Rule of 10s (older data, now outdated):**
  - 10% bilateral (adrenal medulla)
  - 10% extra-adrenal (paraganglioma)
  - 10% malignant
  - 10% familial
  - **Modern data:** ~30–40% have germline mutations; ~10% bilateral; ~5% malignant

Genetic Syndromes Associated with Pheochromocytoma

Syndrome	Gene	Tumor Risk	Associated Features
Multiple Endocrine Neoplasia 2 (MEN2)	RET	50%	Medullary thyroid cancer, primary hyperparathyroidism
Neurofibromatosis Type 1 (NF1)	NF1	1–5%	Café-au-lait spots, optic nerve glioma, scoliosis
Familial Paraganglioma Syndromes	SDHx (B, C, D, E)	Variable	Extra-adrenal tumors, malignancy risk
Von Hippel-Lindau (VHL)	VHL	10–20%	Hemangioblastomas, RCC, pancreatic cysts

Recommendation: Screen family members if pheochromocytoma diagnosed, especially if <40 years old or familial syndrome suspected.

Pathophysiology

Catecholamine excess effects:

Mechanism	Effect	Manifestation
α1-adrenergic (vasoconstriction)	Systemic vasoconstriction	HTN, particularly systolic; tachycardia
α2-adrenergic	Presynaptic inhibition	Often blunted in pheochromocytoma (less relevant)
β1-adrenergic (cardiac)	☐ HR, contractility, renin	Tachycardia, palpitations, tremor
β2-adrenergic (vasodilation)	Peripheral vasodilation, metabolic effects	Hyperglycemia, hypokalemia (with sympathetic stimulation shift)

Result of episodic catecholamine surge: - Sudden **severe HTN** (SBP 160–200+) - **Intense headache** (migraine-like) - **Profuse diaphoresis** (sweating) - **Palpitations and tachycardia** - **Tremor, anxiety, sense of impending doom** - **Episodes last 15 min – 1 hour**, then resolve spontaneously

Clinical Presentation

Classic triad: 1. **Episodic headache** 2. **Diaphoresis (sweating)** 3. **Palpitations**

Additional findings: - **HTN:** Often sustained with episodic spikes; some patients normotensive between episodes - **Anxiety, panic attacks:** Can mimic panic disorder - **Pallor alternating with flushing** - **Orthostatic hypotension:** Between episodes (catecholamine depletion) - **Weight loss:** From hypermetabolic state - **Hyperglycemia:** From catecholamine-mediated insulin suppression

Red flags for pheochromocytoma: - Young age + resistant HTN - Episodic symptoms with normal BP between episodes - Family history of pheochromocytoma or genetic syndrome - Adrenal incidentaloma + HTN symptoms

Diagnostic Approach

Step 1: Biochemical Screening First-line test: 24-hour urine catecholamines or metanephrines

Test	Interpretation	Advantages
24-h urine free catecholamines	Epinephrine + norepinephrine	Most specific but less sensitive
24-h urine metanephrines	O-methylated catecholamine metabolites	Most sensitive (95%); preferred initial test
Plasma free metanephrines	Measured in supine position	Very sensitive; may be more convenient than 24-h urine

Diagnostic criteria: - **Urine metanephrines >2x upper limit of normal:** Suggestive of pheochromocytoma (sensitivity ~97%) - **Normal urine metanephrines:** Pheochromocytoma unlikely (but not ruled out if testing done during asymptomatic phase)

Conditions affecting test validity: - **Foods:** Caffeine, chocolate, bananas, citrus (contain catecholamines/tyramine) — avoid 48 hours before test - **Medications:** Decongestants (phenylephrine), tricyclic antidepressants, some antibiotics — hold 2 weeks if possible - **Stress:** Physical or emotional stress can elevate catecholamines; retest if elevated and low suspicion

Repeat testing: - If borderline elevation and low clinical suspicion, repeat in 1–2 weeks - If markedly elevated (>4x ULN), pheochromocytoma very likely

Step 2: Imaging Once biochemistry confirmed, localize tumor:

A. CT Abdomen/Pelvis - First-line localization - Sensitivity ~95% for adrenal masses >1 cm - Look for **bilateral adrenal masses** (MEN2, NF1) - Look for **extra-adrenal tumors** (paragangliomas, typically along aorta or at organ junctions)

B. MRI Abdomen/Pelvis - Alternative if CT contraindicated or inconclusive - Excellent soft-tissue contrast - Similar sensitivity to CT

C. I-123 Metaiodobenzylguanidine (MIBG) Scintigraphy - Functional imaging; uptake by catecholamine storage vesicles - **Indications:** Extra-adrenal tumor suspected, metastatic disease suspected, familial syndrome - Better sensitivity for paragangliomas and metastases than CT/MRI

D. Positron Emission Tomography (PET) — F-18 FDOPA or F-18 FDG - Research/specialized centers - Useful for localizing occult tumors, assessing malignancy

E. Whole-body imaging with MIBG or PET if malignancy risk (SDH mutations, extra-adrenal location, large size, high plasma metanephrines)

Management

Alpha-Blockade (Essential Before Any Intervention) **Why:** Pheochromocytoma release of catecholamines can cause **hypertensive crisis** if unopposed (α-effects cause vasoconstriction). Must block α-effects first, then add β-blockade if tachycardia develops.

Alpha-blockers:

Agent	Dose	Onset	Notes
Phentolamine	5 mg IV (emergency only)	Immediate	For acute hypertensive crisis; short duration
Phenoxybenzamine	10–20 mg PO BID–TID (up to 60+ mg)	Days	Non-selective α-antagonist; most durable; long half-life
Doxazosin	1–8 mg daily	Days	Selective α1-antagonist; shorter acting; less ideal
Prazosin	1–5 mg TID	Days	Selective α1; similar to doxazosin

Target: - Titrate to **normalization of BP** (goal <140/90) - Also achieves **volume expansion** (catecholamine-induced hypovolemia corrected) - Continue for ≥7–10 days before surgery to allow volume equilibration

Beta-Blockade (After Alpha-Blockade) **When to add:** If tachycardia develops after alpha-blockade or ongoing palpitations

Agents: - **Propranolol** 10–40 mg TID (non-selective β-antagonist) - **Labetalol** 100–400 mg TID (combined α and β; can be used alone but less ideal)

Critical point: NEVER start β-blockade without α-blockade first (unopposed α-effects ☐ hypertensive crisis, stroke, MI)

Surgical Management (Adrenalectomy or Tumor Resection) **Timing:** After ≥1 week of adequate alpha-blockade (ideally 2–3 weeks)

Surgical approach: - **Adrenalectomy** (laparoscopic or open) for adrenal pheochromocytoma - **Resection of paraganglioma** for extra-adrenal tumor - Monitor for **intraoperative catecholamine surge** (can be life-threatening; anesthesist vigilance essential)

Success rate: Cures 95%+ of nonmalignant pheochromocytomas; BP often normalizes.

Medical Management (If Surgery Not Possible or Malignant)

- **Long-acting α-blocker:** Phenoxybenzamine (as above) or doxazosin
- **Additional agents:** Calcium channel blocker (nifedipine) for HTN control
- **Chemotherapy:** For malignant pheochromocytoma (SDCT: streptozotocin + doxorubicin + cisplatin)
- **I-131 MIBG:** Radionuclide therapy for metastatic disease (limited utility)

V. Cushing Syndrome

Definition & Epidemiology

Hypertension from **excessive glucocorticoid exposure**, either endogenous (pituitary adenoma, adrenal tumor) or exogenous (medication).

- **Prevalence of endogenous Cushing:** 1–2 per million (rare)
- **HTN prevalence in Cushing:** 60–80%
- **Exogenous Cushing (from steroids):** Most common form of iatrogenic Cushing; much more common

Pathophysiology

Glucocorticoid effects on HTN: 1. **Increased angiotensinogen production** ☐ renin-angiotensin activation 2. **Enhanced vascular responsiveness to catecholamines** (permissive effect) 3. **Salt retention** (via mineralocorticoid receptor activation; cortisol has ~1% activity at MR despite selective receptor; high cortisol overcomes selectivity) 4. **Impaired vasodilation** (suppression of NO production) 5. **Sympathetic nervous system activation**

Result: Hypertension in 60–80% of Cushing patients.

Clinical Presentation (Endogenous Cushing)

Classic features ("central obesity"): - **Proximal muscle weakness** (quadriceps, deltoid atrophy) - **Central weight gain** (dorsocervical fat pad/"buffalo hump," supraclavicular fullness, truncal obesity with relatively thin extremities) - **Moon facies** (facial plethora, roundness) - **Purple striae** (depressed, violaceous stretch marks, typically >1 cm wide) - **Easy bruising** (collagen weakness) - **Skin atrophy** (paper-thin, transparent) - **Hirsutism and acne** (androgen excess from ACTH) - **Hypokalemic metabolic alkalosis** (salt retention, K+ wasting) - **Hypertension** (present in 60–80%)

Psychiatric features: - Depression, mood lability, anxiety, psychosis

Other manifestations: - Osteoporosis, pathologic fractures - Immunosuppression (recurrent infections) - Hyperglycemia, diabetes - Hypogonadism

Diagnostic Approach (Endogenous Cushing)

Step 1: Screening for Cushing (Confirm HTN from Cushing) Cushing should be suspected if: - HTN + suggestive clinical features (proximal weakness, striae, easy bruising, facial plethora) - Resistant HTN + metabolic abnormalities (hypokalemia, hyperglycemia)

Screening tests:

Test	Method	Interpretation
24-h urinary free cortisol (UFC)	Urine collection	UFC >4x ULN highly suggestive; sensitivity ~95%
Late-night salivary cortisol	Saliva at 11 PM	Should be <1.8 ng/dL; elevated in Cushing
Low-dose dexamethasone suppression test	Dexamethasone 1 mg at 11 PM, measure 8 AM cortisol	Normal <1.8 ng/dL; cortisol remains elevated in Cushing
Morning plasma ACTH	Blood draw 8–9 AM	ACTH <5 pIU/mL suggests adrenal cause; high ACTH suggests pituitary or ectopic

If screening positive (elevated UFC or suppressed cortisol on dex):

Step 2: Source Localization Measure morning ACTH:

If ACTH-dependent Cushing (ACTH >10 pIU/mL): - Could be pituitary adenoma or ectopic ACTH secretion - **High-dose dexamethasone suppression test:** Dexamethasone 8 mg, measure cortisol - **Cortisol suppresses >50%:** Pituitary adenoma (Cushing's disease) - **Cortisol does NOT suppress:** Ectopic ACTH (carcinoid, small cell lung cancer, pheochromocytoma) - **Pituitary MRI:** Look for adenoma; ectopic imaging if imaging unrevealing

If ACTH-independent (ACTH <5 pIU/mL): - Autonomous adrenal secretion - **Adrenal imaging (CT/MRI):** Look for adenoma or carcinoma - **Adrenal biopsy** if imaging shows bilateral disease

Management of Cushing Syndrome-Related Hypertension

Endogenous Cushing (Surgical)

- **Pituitary adenoma:** Transsphenoidal pituitary surgery
- **Adrenal tumor:** Adrenalectomy
- **Ectopic ACTH:** Resection of ectopic tumor (if possible)
- **Expected outcome:** HTN often improves/resolves after cure of Cushing

Exogenous Cushing (Steroid-Induced)

- **Taper/discontinue steroids** if possible
- **If steroids necessary:** Use lowest effective dose; consider alternate-day dosing
- **Additional antihypertensives:** Often needed while on chronic steroids
- **Monitor potassium** (salt-retaining effect of glucocorticoids)

Medical Management (Temporary, if Surgery Delayed)

- **Metyrapone:** 11β-hydroxylase inhibitor; blocks final step of cortisol synthesis
  - Dose: 500–1000 mg QID; titrate to normalize cortisol

  - Monitors: 24-h UFC, clinical response
- **Ketoconazole:** Inhibits P450 enzymes; blocks multiple steps of steroid synthesis
  - Dose: 200–400 mg TID
  - Risk of hepatotoxicity; monitor LFTs
- **Mitotane:** Adrenolytic agent; used for adrenocortical carcinoma
  - Toxic; requires monitoring; causes adrenal insufficiency
- **Etomidate:** IV agent for acute, severe Cushing; rapid cortisol suppression
  - Used only in ICU setting

VI. Other Secondary Causes of Hypertension

Thyroid Disease

Hyperthyroidism: - ☐ Sympathetic sensitivity to catecholamines - ☐ Cardiac output, ☐ HR - Widened pulse pressure - **Management:** Treat thyroid; beta-blockers for symptom control

Hypothyroidism: - Usually ☐ diastolic BP (decreased CO, increased SVR) - **Management:** Thyroid hormone replacement

Hyperparathyroidism

- PTH ☐ ☐ serum calcium
- Hypercalcemia ☐ vascular smooth muscle contraction, volume expansion
- **Prevalence of HTN in hyperparathyroidism:** 30–50%
- **Management:** Parathyroidectomy if indicated for hypercalcemia

Obstructive Sleep Apnea (OSA)

- Most common **secondary cause of resistant HTN**
- Hypoxia-induced sympathetic activation
- Multiple arousals ☐ blood pressure surges nightly
- **Management:** CPAP (positive airway pressure) therapy; effective BP reduction

Oral Contraceptives and Estrogen Therapy

- Angiotensinogen ☐, renin-substrate ☐ ☐ renin-angiotensin activation
- **HTN incidence:** 3–5% of users
- **Risk factors:** Age >35, smoking, prior HTN
- **Management:** Switch to progestin-only or non-hormonal contraception; lower estrogen doses

NSAIDs and Decongestants

- **NSAIDs:** Inhibit renal prostaglandin synthesis ☐ fluid retention, HTN
- **Sympathomimetics (phenylephrine, pseudoephedrine):** Direct vasoconstriction
- **Management:** Discontinue or use alternative

Coarctation of the Aorta

- Narrowing of descending aorta (usually left of ductus arteriosus)
- Upper body HTN, lower body hypotension
- **Clinical clue: Rib notching** on chest X-ray (erosions from intercostal arteries)
- **Diagnosis:** CTA, MRA, echo
- **Management:** Surgical repair or percutaneous stenting

VII. Clinical Pearls

1. **ARR >20–30 is screening positive** for primary aldosteronism; confirm with suppression test before pursuing imaging/AVS.
2. **Renovascular HTN can present with flash pulmonary edema** without severe systemic hypertension; think of this diagnosis in elderly patients with acute pulmonary edema and renal disease.
3. **ACE-I/ARB can worsen renal function in bilateral RAS or single-kidney RAS**; monitor Cr carefully when initiating, but don't reflexively discontinue if small rise.
4. **Pheochromocytoma: ALWAYS alpha-block before beta-block** to avoid unopposed α-adrenergic crisis.
5. **Pheochromocytoma can mimic panic disorder**; high clinical suspicion (episodic symptoms) warrants biochemical testing even in psychiatric patients.
6. **Cushing syndrome can present with "resistant HTN"** but should have clinical clues (proximal weakness, striae, easy bruising); screen with 24-h UFC.
7. **OSA is the most common secondary cause of resistant HTN** in modern practice; ask all resistant HTN patients about snoring, witnessed apneas, daytime somnolence.
8. **Young women with hypertension should be screened for fibromuscular dysplasia** (RAS) if HTN is severe or medication-resistant; FMD has excellent outcomes with PTA.
9. **FH-I (GRA) is dexamethasone-suppressible** — a unique form where low-dose dexamethasone, not MRA, is the treatment.
10. **All patients with adrenal pheochromocytoma should be screened for familial syndrome** (RET, NF1, VHL, SDH) if <40 years or family history present; affects counseling and follow-up.

VIII. Practice Questions

Question 1: A 45-year-old man with resistant hypertension (on amlodipine, lisinopril, and spironolactone) has labs: K 3.1 mEq/L (normal), Na 140 mEq/L, eGFR 82, BP 160/100 in office. ARR on diuretics is 32 (nl <10). What is the next step?

A) Increase spironolactone dose immediately
B) Confirm ARR by repeating OFF diuretics; if elevated, proceed to confirmatory testing

C) Order adrenal CT for adenoma
D) Start eplerenone in addition to spironolactone

Correct Answer: B Explanation: ARR is falsely elevated while on diuretics (diuretics raise renin, lower aldosterone ratio interpretation). The ARR should be rechecked OFF diuretics (ideally hold ≥4–6 weeks) to accurately assess. Only if off-diuretic ARR is elevated should confirmatory testing (saline suppression) proceed. Jumping to imaging without confirming PA would be premature.

Question 2: A 68-year-old man with COPD, smoking history, and resistant hypertension presents with acute pulmonary edema. He is on lisinopril and amlodipine. Creatinine rose from 1.2 to 1.8 mg/dL over 3 months. Abdominal exam reveals a faint bruit. CXR shows pulmonary edema with normal heart size. What is the MOST likely diagnosis?

A) Acute heart failure from hypertensive cardiomyopathy
B) Acute coronary syndrome causing cardiogenic shock
C) Bilateral renal artery stenosis causing "flash" pulmonary edema from renal ischemia
D) Acute interstitial pneumonia

Correct Answer: C Explanation: The **classic triad** is: resistant HTN + acute pulmonary edema (often without marked systemic HTN at moment) + **progressive renal insufficiency** + **abdominal bruit** (RAS) = **flash pulmonary edema from bilateral RAS**. The mechanism is renal ischemia ☐ renin-angiotensin activation ☐ systemic HTN + renal vasoconstriction ☐ oliguria ☐ volume overload ☐ pulmonary edema. Creatinine worsening with ACE-I supports this (loss of efferent vasoconstriction). Need imaging (CTA/MRA) and consideration of intervention.

Question 3: A 35-year-old woman presents with episodic severe headaches (bilateral, throbbing), profuse diaphoresis, and palpitations lasting 20–30 minutes, then resolving completely. BP in clinic today 148/92 but during episode "very high" per patient. Two 24-hour urine catecholamine collections show normal epinephrine and norepinephrine. 24-hour urine metanephrines are elevated at 1.8x ULN (reference <0.9 μmol/day). What should you do?

A) Reassure patient; pheochromocytoma ruled out because catecholamines normal
B) Repeat 24-h urine metanephrines; pheochromocytoma remains in differential if again elevated
C) Start phentolamine for symptomatic management; if symptoms improve, diagnose pheochromocytoma
D) Order adrenal imaging now; proceed to CT/MRI

Correct Answer: B Explanation: **Urine metanephrines are more sensitive than urine catecholamines** for pheochromocytoma detection (95% vs. 80–85% sensitivity). The elevated metanephrines warrant **repeat testing** to confirm. If repeat is again elevated (especially >2x ULN), imaging is justified. If repeat is normal and clinical suspicion remains high, testing during an episode or extended monitoring might help. Phentolamine acutely for symptom management is reasonable, but alpha-blockade is permanent therapy, not diagnostic.

IX. References

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End of Handout

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Clinical Resources

- Clinical Review: Hypertension Management Patient Bp Monitoring Guide — Comprehensive clinical review with PubMed references
- Clinical Review: Renovascular Hypertension Review — Comprehensive clinical review with PubMed references
- Clinical Review: Hypertension Management Report — Comprehensive clinical review with PubMed references