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# The Demystification of Secondary Hypertension: Diagnostic Strategies and Treatment Algorithms

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**Keywords** Secondary hypertension · Endocrine hypertension · Drug-induced hypertension · Renovascular hypertension · Renal artery stenosis · Obstructive sleep apnea · Primary aldosteronism · Mineralocorticoid · Cushing's syndrome · Pheochromocytoma

**Abbreviations** *ACEi* Angiotensin-converting enzyme inhibitor · *ACTH* Adrenocorticotropic hormone · *AME* Apparent mineralocorticoid excess · *ARB* Angiotensin receptor blocker · *ARR* Aldosterone-to-renin ratio · *AVS* Adrenal vein sampling · *CAH* Congenital adrenal hyperplasia · *CCB* Calcium channel blocker · *CKD* Chronic kidney disease · *CPAP* Continuous positive airway pressure · *DST* Overnight dexamethasone suppression testing · *ENaC* Epithelial sodium channels · *FH* Familial hyperaldosteronism · *FMD* Fibromuscular dysplasia · *GRA* Glucocorticoid-remediable hypertension · *MAO* Monoamine oxidase · *MRA* Mineralocorticoid receptor antagonist · *NSAIDs* Nonsteroidal anti-inflammatory drugs · *OSA* Obstructive sleep apnea · *PA* Primary aldosteronism · *PAC* Plasma aldosterone concentration · *PRA* Plasma renin activity · *RAAS* Renin-angiotensin-aldosterone system · *PSV* Peak systolic velocities · *RAR* Renal-to-aortic ratio · *RAS* Renal artery stenosis · *VEGF* Vascular endothelial growth factor

## Abstract

*Purpose of review* Hypertension is one of the most common conditions encountered in the primary care setting, affecting 32–46% of people. While essential or primary hypertension is the most common form of the disease, secondary hypertension is quite prevalent, occurring in 10–20% of patients with hypertension. Accurately diagnosing secondary hypertension is a challenging and often time-consuming process that requires considerable expertise and effort. However, once the secondary etiology is identified, the patient benefits profoundly from a

potentially curative treatment that may lead to significant improvements in quality of life, morbidity, and mortality.
*Recent findings* Common causes of secondary hypertension include medication-induced hypertension, renal parenchymal disease, renovascular hypertension, obstructive sleep apnea, and primary aldosteronism. Other rarer forms include mineralocorticoid-driven hypertension or its mimics, as well as hypercortisolism and pheochromocytoma. Although complex, standard protocols have emerged for investigation, diagnosis, and treatment of these conditions.
*Summary* The current review aims to elucidate the many causes of secondary hypertension and describe their respective prevalence, clinical presentation, screening, diagnosis, treatment, and follow-up. By demystifying secondary hypertension, it is hoped that this disease will be more easily identified and treated so that the associated cardiovascular morbidity and end-organ damage may be mitigated.

## Introduction

Hypertension is one of the most common conditions encountered in the primary care setting, affecting 32–46% of people in the USA. It is the most common risk factor for cardiovascular death and, after cigarette smoking, is the leading preventable cause of death [1••].

While essential (primary) hypertension is the most common form, approximately 10–20% of patients have secondary hypertension with prevalence estimates varying depending on which criteria for secondary hypertension are used. Additionally, secondary and primary hypertension may coexist, especially in the elderly, further increasing the disparity between prevalence assessments.

The treatment of secondary hypertension is uniquely appealing to providers of many disciplines, as providing the appropriate therapy can be curative and profoundly alter cardiovascular outcomes and quality of life. However, despite the potential benefits of early diagnosis and subsequent treatment to both the patient and provider, many cases of secondary hypertension are undiagnosed. This reflects not a lack of provider interest but rather the complex and eclectic nature of the myriad of causes of secondary hypertension. Unfortunately, widespread testing of all hypertensive patients is not cost-effective and frequently leads to false-positive results. As such, the selective screening of patients both at high risk for or with signs and symptoms suggestive of secondary hypertension is necessary [1••, 2].

The classic presentations that trigger screening for secondary hypertension include resistant or refractory hypertension (≥ 3 or 5 antihypertensives, respectively, including a diuretic, with blood pressure ≥ 130/80 mmHg), drug-induced hypertension, abrupt onset or worsening of hypertension, malignant hypertension, hypertension onset in the young or elderly, spontaneous hypokalemia, and adrenal incidentaloma (Fig. 1) [1••]. While some presentations may point to a specific cause of secondary hypertension (e.g., spontaneous hypokalemia caused by primary aldosteronism), more often the underlying pathology cannot be readily discerned without broad testing for the more common causes of secondary hypertension.

This review will focus on the primary causes of secondary hypertension in adults, their presentation, screening and diagnosis, and treatment (Fig. 2). While many factors are associated with hypertension, including obesity, high sodium intake, poor potassium intake, and lack of physical fitness [1••], these all exacerbate primary hypertension and will not be discussed further. This review will also not discuss blood pressure targets, which have been thoroughly considered elsewhere [1••].

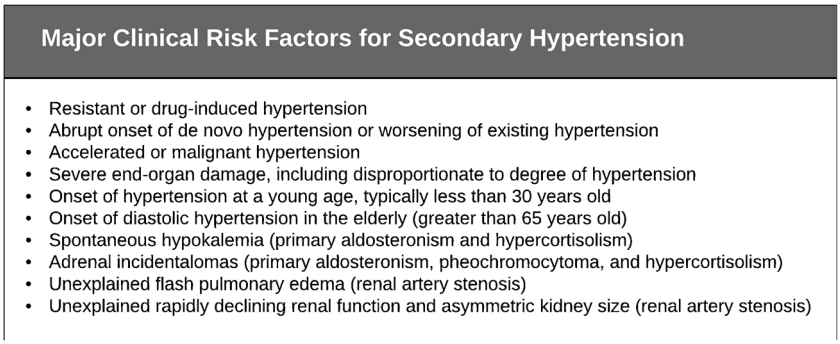


**Fig. 1.** Risk factors for secondary hypertension.

## Medications, drugs, and chemical agents

Drug-induced hypertension, one of the most common causes of secondary hypertension, is frequently overlooked and often remediable. Thus, a complete record of all medications should be obtained, including vitamins, supplements, herbals, illicit drugs, and other chemical ingestions. These chemicals may trigger elevations in blood pressure and often lead to resistant hypertension via a variety of mechanisms, including volume retention, sympathetic or renin-angiotensin-aldosterone activation, or other causes. (For a comprehensive list, see Table 1.)

Glucocorticoids cause volume retention and, as a result, induce or worsen hypertension in a dose-dependent fashion. Similarly, volume retention is induced by licorice ingestion, ketoconazole, oral contraceptives, androgen therapy, and nonsteroidal anti-inflammatory drugs (NSAIDs) [3•]. In addition to their volume expanding effect, NSAIDs raise blood pressure by increasing systemic vascular tone and interfere with common antihypertensives, including diuretics, beta-blockers, and angiotensin-converting enzyme inhibitors (ACEi), via a reduction in prostaglandin synthesis. Patients receiving NSAIDs appear to respond best to dihydropyridine calcium channel blockers (CCBs) [4, 5].

Decongestants commonly activate the sympathetic nervous system, as do methylphenidate, amphetamines, monoamine oxidase (MAO) inhibitors and other psychiatric and antidepressant drugs, ephedra alkaloids (a common herbal product), and cocaine. Erythropoiesis-stimulating agents, commonly used in kidney disease and oncology, can worsen hypertension as well [3•].

The immunosuppressing calcineurin inhibitors (cyclosporine and tacrolimus) commonly increase blood pressure via activation of the renin-angiotensin-aldosterone system (RAAS) and an increase in sympathetic nerve activity [6, 7]. Due to their propensity to increase renal sodium reabsorption [7, 8], treatment with thiazide diuretics is an attractive option in hypertensive patients on such drugs [8, 9].

Many other common medications and chemical agents raise blood pressure, although the mechanism is often incompletely understood. Commonly implicated agents include tobacco, alcohol, lead, highly active antiretroviral therapy for HIV, scopolamine, metoclopramide, prochlorperazine, carbamazepine, lithium, and anti-vascular endothelial growth factor (VEGF) medications and many other chemotherapeutic agents [3•]. Regular use of acetaminophen has

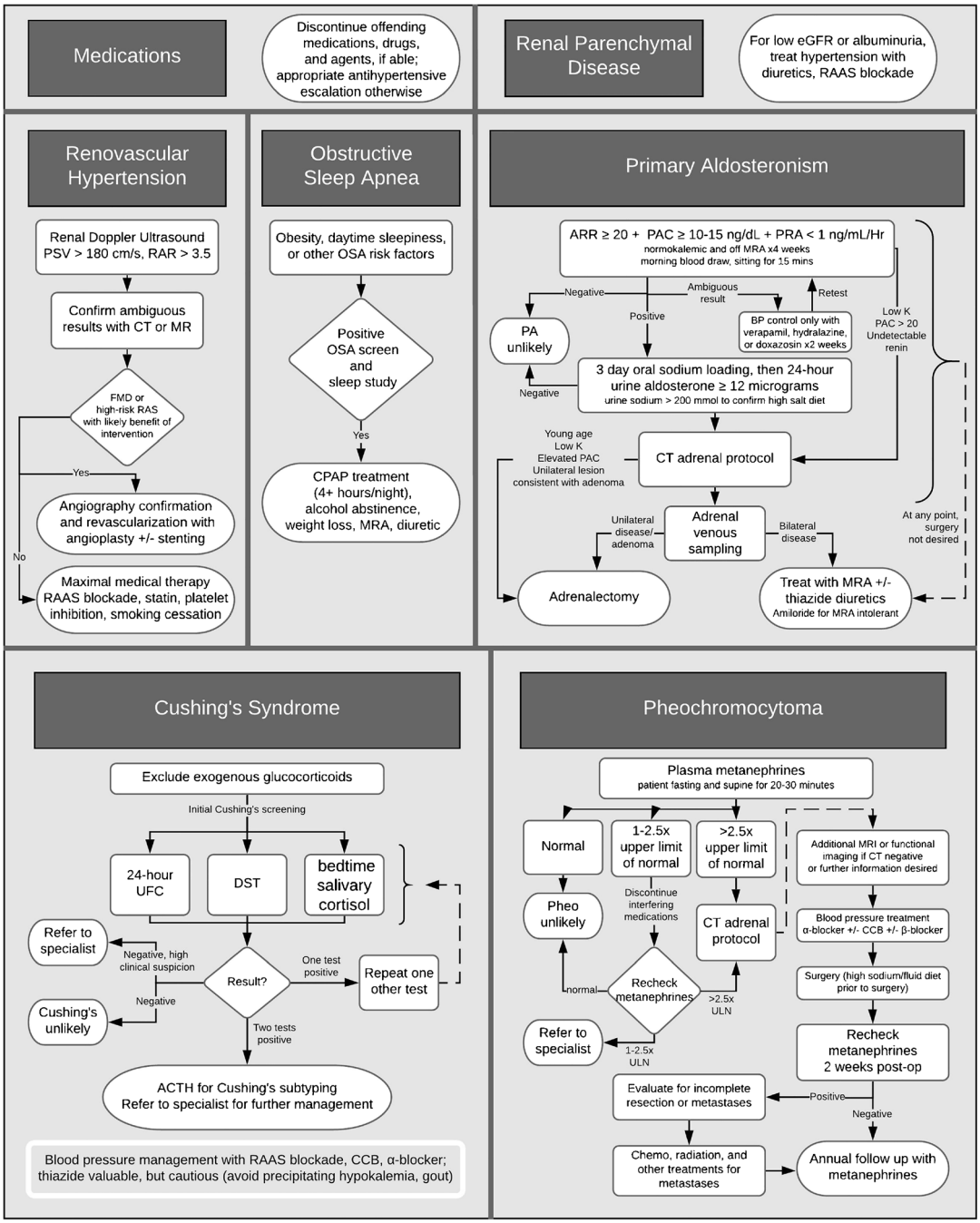


**Fig. 2.** The most common conditions associated with secondary hypertension, with their diagnostic workup and treatment. High-risk RAS with likely benefit includes resistant hypertension, failing maximal medical therapy; severe hypertension with acute coronary syndrome; recurrent congestive heart failure or flash pulmonary edema; and ischemic nephropathy with rapidly declining renal function. Risk factors for OSA include male gender, obesity, craniofacial and upper airway abnormalities, and active cigarette smoker. *ARR* aldosterone-to-renin ratio, *CCB* calcium channel blocker, *CPAP* continuous positive airway pressure, *DST* overnight dexamethasone suppression testing, *FMD* fibromuscular dysplasia, *MRA* mineralocorticoid receptor blocker, *OSA* obstructive sleep apnea, *PAC* plasma aldosterone concentration, *PRA* plasma renin activity, *PSV* peak systolic velocities, *RAAS* renin-angiotensin-aldosterone system, *RAR* renal-to-aortic ratio, *RAS* renal artery stenosis, *UFC* urinary free cortisol, *ULN* upper limit of normal

**Table 1. Common medications (alphabetized) implicated in exacerbating or causing hypertension**

| |
|---|
| Acetaminophen |
| Alcohol |
| Alizapride |
| **Alkylating agents** (cyclophosphamide, ifosfamide) |
| Amphotericin B |
| **Androgens** |
| Buspirone |
| Carbamazepine |
| Carbenoxolone |
| Clozapine |
| Cocaine |
| Danazol |
| **Erythropoiesis-stimulating agents** |
| Estrogen/Progesterone |
| Fluoxetine |
| Glucocorticoid |
| **Highly active antiretroviral therapy (HAART)** |
| **Immunosuppressive agents** (cyclosporine, tacrolimus, mycophenolate mofetil) |
| Ketoconazole |
| Lead |
| Licorice |
| Lithium |
| Metoclopramide |
| **Monoamine oxidase inhibitors** |
| **Nonsteroidal anti-inflammatory drugs (NSAIDs)** |
| Paclitaxel |
| Phenylephrine |
| Posaconazole |
| Prochlorperazine |
| Pseudoephedrine |
| Scopolamine |
| Selegiline |
| **Tricyclic antidepressants** |
| **Vascular endothelial growth factor (VEGF) inhibitors** (axitinib, bevacizumab, ponatinib, pazopanib, regorafenib, sorafenib, sunitinib) |
| Venlafaxine |
| Yohimbine hydrochloride |

Drug classes are bolded

recently been associated with increased risk of hypertension, which may be due to cyclooxygenase inhibition, indirect activation of cannabinoid receptors [3•], or increases in aldosterone secretion [10].

While caffeine can significantly increase blood pressure, it appears that when obtained through coffee consumption, the risk of worsening hypertension is small, although it may transiently raise blood pressure [11, 12].

## Renal parenchymal disease

Chronic kidney disease (CKD) is one of the most common causes of secondary hypertension with an overall prevalence of approximately 15%. Even more notably, CKD reliably causes secondary hypertension in close to 85% of patients. Black patients and those with more severe kidney disease have an even higher prevalence of hypertension [13, 14]. The relationship between CKD and hypertension is bidirectional, with each disease impacting and potentially worsening the other. Renal parenchymal disease may be identified by an increase in serum creatinine, the presence of albuminuria (or proteinuria), or renal ultrasound imaging suggestive of kidney disease.

The pathophysiology of hypertension in CKD is multifactorial and includes activation of the RAAS [15] and sympathetic system hyperactivity, causing efferent vasoconstriction, increase in glomerular pressure [16], impairment in sodium excretion, and increased arterial stiffness with decreased nitric oxide release [17]. Patients with advanced CKD often receive erythropoiesis-stimulating agents for anemia and have concomitant hyperparathyroidism, both of which can worsen hypertension.

The treatment of hypertension in CKD is critical in delaying the progression of renal parenchymal damage, as well as lowering overall cardiovascular risk. Most CKD patients will require a diuretic, generally a thiazide type such as the effective and long-acting chlorthalidone. In more advanced stages of CKD, a switch to a loop diuretic may be warranted for more potent natriuresis, although many patients benefit from a multi-target diuretic strategy, including a thiazide and loop. RAAS blockade is a mainstay of treatment, particularly in patients with proteinuria, and a drop of up to 30% in glomerular filtration rate at treatment initiation should be tolerated. CCBs appear to be particularly helpful for Black patients generally, often dosed in combination with RAAS blockade (ACEi or angiotensin receptor antagonist [ARB]) [18]. As patients with CKD tend to have relatively elevated nighttime blood pressure, chronotherapy (i.e., administering some antihypertensives at night) is a reasonable strategy for improved 24-hour blood pressure control [18, 19•].

Patients with acute kidney injury related to glomerulonephritis usually have volume-mediated hypertension and require diuretics, whereas hypertension in acute vascular-mediated processes such as vasculitis or scleroderma renal crisis is caused by RAAS upregulation. These latter scenarios are best treated with RAAS blockade.

## Renovascular hypertension and renal artery stenosis

Renovascular disease is one of the most common causes of secondary hypertension and is most commonly attributable (85% of cases) to atherosclerotic renal artery stenosis (RAS). Advanced age, smoking, dyslipidemia, diabetes mellitus, and pre-existing hypertension are risk factors for atherosclerotic disease. Other causes of renovascular hypertension include fibromuscular dysplasia (FMD), arterial occlusion from embolic disease (iatrogenic following endovascular aortic stents and grafts), aortic dissection, and vascular inflammatory diseases such as Takayasu arteritis, vasculitis, and scleroderma [20].

In response to the decreased renal perfusion due to the stenotic renal artery, the juxtaglomerular apparatus increases the secretion of renin, leading to elevated levels

of angiotensin II and aldosterone. The latter two substances cause hypertension via vasoconstriction and sodium retention [21]. In unilateral RAS, the contralateral normal kidney responds to increases systemic pressure by decreasing renin and enhancing sodium excretion, a process known as pressure natriuresis. In bilateral RAS or stenosis of a solitary kidney, decreased renal perfusion leads to excess renin and sodium retention. Renin tends to decrease in many patients because of intrinsic renal disease, however, and levels may therefore vary.

Rapid changes in blood pressure in patients younger than 30 or greater than 50, or accelerated hypertension in those already treated for hypertension, are clues for diagnosing renovascular hypertension. Worsening renal failure with treatment of hypertension and congestive heart failure with flash pulmonary edema also suggest significant RAS [1••].

Patients with RAS may have signs of peripheral artery disease in other areas such as asymmetric blood pressures, carotid or abdominal bruits, and retinal changes consistent with hypertension. Renal function may be normal or diminished and may already show signs of CKD. Renin and the aldosterone-to-renin ratio may be elevated. Renin sampling from the renal vein of the stenotic kidney is elevated, although this is not done in routine practice.

Renal ultrasound with Doppler of the renal arteries is the initial imaging technique to diagnose RAS, and with experienced sonographers, the measurement of the peak systolic velocities (PSV) has 85% sensitivity and 92% specificity [22]. Significant stenosis of greater than 60% can be characterized with a PSV of > 180 cm/s (normal is < 180 cm/s) and a renal-to-aortic ratio (RAR; ratio of PSV of prerenal aortic velocities to the renal artery velocities) of > 3.5 (normal is < 3.5) [23, 24] (see Fig. 2).

CT and MR angiographies effectively establish the presence of renal artery stenosis with a sensitivity and specificity above 90% and are often useful when intervention is for procedural planning. However, these studies are occasionally limited by the risk of contrast administration in high-risk patients. (The risk for contrast-induced nephropathy with iodinated contrast or nephrogenic systemic fibrosis with gadolinium are both low, but rise with estimated glomerular filtration rates of less than 30 mL/min/1.73 $m^2$, and thus caution should be taken in patients with chronic kidney disease stages 4 and 5, end-stage renal disease, or acute kidney injury. Consultation with a nephrologist may be helpful in these circumstances.)

Conventional intra-arterial angiography remains the gold standard in identifying and intervening on renal artery stenosis. A greater than 70% diameter stenosis is considered severe or significant. However, when more moderate 50–70% stenosis is present, translesional gradients should be obtained. A translesional gradient of ≥ 20 mmHg systolic or ≥ 10 mmHg mean, or a fractional flow reserve (FFR) ≤ 0.8, is all considered hemodynamically significant [25•, 26]. For patients at high risk of contrast nephropathy, $CO_2$ angiography may be an option.

The three major clinical studies to determine the efficacy of intervention on RAS lesions – STAR [27], ASTRAL [28], and CORAL [29] – failed to show significant benefits for intervention in blood pressure control, renal recovery, or death. Thus, most patients who are asymptomatic or well-controlled on medical therapy should not undergo invasive revascularization and should instead receive maximal medical therapy, which includes RAAS blockade, cholesterol reduction (high-intensity statin), antiplatelet therapy, glucose control, and smoking cessation [29]. These studies included many patients with

moderate stenosis and did not enroll the highest risk patients who may be most likely to benefit from revascularization, including [1••, 20, 25•, 26]:

- Resistant or refractory hypertension, failing maximal medical therapy
- Severe hypertension with acute coronary syndrome
- Recurrent congestive heart failure or flash pulmonary edema
- Ischemic nephropathy with rapidly declining renal function

Other clinical situations, in which prospective data may be lacking, should be carefully considered, weighing the risks and benefits of the intervention as compared to medical management [20, 26].

FMD, which affects children of both genders and adult women, is amenable to interventional therapies and is typically treated percutaneously using both conventional angiography, FFR, and intra-arterial imaging (intravascular ultrasound or optical coherence tomography). Stent placement is generally not indicated unless a flow limiting dissection is noted. Occasionally, surgery is required when large renal aneurysms are present. While balloon angioplasty for FMD is quite effective, repeat angioplasty is needed in 11–23% of patients [30].

## Obstructive sleep apnea

Sleep disturbances in general, and obstructive sleep apnea (OSA) in particular, are associated with hypertension [31]. While OSA and hypertension share similar risk factors, even after adjusting for confounders, a link exists between OSA and the development or worsening of hypertension [32, 33]. Approximately one third of all hypertensive patients have OSA [33–35]. The link is even stronger in patients with resistant (60–80% have OSA) and refractory hypertension (almost all patients have OSA) [33, 35, 36].

OSA appears to cause endothelial dysfunction and increases sympathetic tone and renal sympathetic nerve stimulation, with the latter leading to increased renin secretion and sodium retention [33]. Patients with OSA, especially those with obesity and the metabolic syndrome, have relatively elevated aldosterone levels [32, 37–39], which correlate with the severity of OSA [38, 39].

Treatment of OSA with nighttime continuous positive airway pressure (CPAP) has been disappointing for improving blood pressure [40] or reducing cardiovascular events [40–42]. This may be due to the heterogeneous nature of the disease [43]. Indeed, some investigators argue that, in particular, high-risk subgroups may benefit from nighttime CPAP [44]. More recent studies have found that patients who use CPAP for more than 4 hours per night may have a reduced risk of major adverse cardiac events [45] and better 24-hour blood pressure control [46]. In general, patients with moderate-to-severe OSA and resistant hypertension have been found to have some improvement in blood pressure when adherent with CPAP treatment, although the magnitude of benefit is mixed and generally mild (e.g., decreases in systolic or diastolic blood pressure of less than 5 mmHg) [46–51]. Post hoc analysis of the SYMPLICITY trial and preliminary, open-label trials of renal denervation for patients with OSA have shown improvement in blood pressure compared with no intervention, but randomized, prospective trials are lacking [52, 53].

In addition to encouraging CPAP use, hypertension in patients with OSA may be most effectively addressed by correcting other comorbid and lifestyle

factors. Dietary modification, with a reduction in salt intake and alcohol consumption; increased physical activity; and weight loss (for obese patients) all can facilitate blood pressure control [1••, 33], especially when combined with effective CPAP treatment [54, 55]. Small trials of mineralocorticoid receptor antagonists (MRAs) have shown improvement in sleep apnea indicators [56–58] as well as blood pressure control [57, 58], which may be attributable to the association between OSA and hyperaldosteronism [59]. Many patients with OSA have a positive sodium balance, and intensive treatment with diuretics (thiazides in combination with a MRA) can improve blood pressure control and OSA [32, 56–58, 60] (see Fig. 2). Similar to CKD patients, those with OSA benefit from chronotherapy [19•].

# Primary aldosteronism

Primary aldosteronism (PA), also known as Conn's syndrome [61], is a group of disorders defined by an inappropriately elevated plasma aldosterone for a given sodium status, with relatively autonomous production. Hypertension invariably ensues due to unopposed mineralocorticoid activity leading to sodium reabsorption from upregulation of epithelial sodium channels (ENaC) in the principal cells of the renal cortical collecting tubules. The major causes of PA are idiopathic hyperaldosteronism (including bilateral, and occasionally unilateral, adrenal hyperplasia) and adrenal adenoma. A subtype of PA, familial hyperaldosteronism, has a clear genetic basis [62].

Historically, the prevalence of PA was thought to be quite low. However, more recent work has confirmed that 5–10% of all hypertensive patients and up to 20% of patients with resistant hypertension have PA [1••, 63–65]. Comprising half to two thirds of cases, idiopathic hyperaldosteronism (typically bilateral adrenal hyperplasia) predominates, while adrenal adenomas and, more rarely, unilateral adrenal hyperplasia are found in one third to one half of cases [1••, 65]. Aldosterone-producing carcinomas have been described but are exceedingly rare. Hypokalemia, a supposed classic finding in PA, is actually uncommon, occurring in only a substantial minority of patients [65, 66••, 67]. Normal serum potassium levels have a low negative predictive value and are thus unhelpful in ruling out PA.

## Screening and diagnosis (see Fig. 2 and Table 2)

Screening for PA is typically performed with a morning blood draw after the patient is out of bed for about 2 hours and sitting for about 15 minutes. The checking of plasma aldosterone-to-renin ratio (ARR) – a simultaneous plasma aldosterone concentration (PAC) and plasma renin activity (PRA) – should be performed in normokalemic patients who have been off aldosterone antagonists for at least 4 weeks [66••]. While many antihypertensives can alter test results, they tend not to cause too much concern. In the case of ambiguous results, all agents should be withheld for 2 weeks except in patients with severe hypertension who might be harmed by treatment cessation. In such patients, the preferred antihypertensives include verapamil, hydralazine, and doxazosin (see Table 3 for causes of false-positive and false-negative ARR results).

**Table 2.** Renin and aldosterone findings, diagnosis, and treatment of low renin hypertension

| | Renin | Aldosterone | Screening | Confirmation | Treatment |
|---|---|---|---|---|---|
| Primary aldosteronism | ↓ | ↑ | Elevated ARR; elevated urinary aldosterone following salt loading | CT adrenal protocol; adrenal vein sampling | Medical (MRA) or surgical (adrenalectomy) |
| Cushing's syndrome (endogenous) | ↓/↔ | ↓/↔ | Mildly elevated deoxycorticosterone; elevated 24-hour urine free cortisol; low-dose dexamethasone suppression testing; bed-time salivary cortisol test | Two positive screening tests; further evaluation to identify cause | Surgery (pituitary or adrenal) +/- medical suppressive therapy; for hypertension, RAAS blockade +/- MRA +/- CCB |
| 11β-hydroxylase deficiency (congenital adrenal hyperplasia) | ↓ | ↓ | Elevated deoxycorticosterone, 11-deoxycortisol, androstenedione, and dehydroepiandrostenedione sulfate | Genetic testing | Exogenous glucocorticoid |
| 17α-hydroxylase deficiency (congenital adrenal hyperplasia) | ↓ | ↓ | Elevated deoxycorticosterone and 11-deoxycortisol; decreased androstenedione, and dehydroepiandrostenedione sulfate | Genetic testing | Exogenous glucocorticoid |
| Deoxycorticosterone tumor | ↓ | ↓ | Elevated deoxycorticosterone level, and adrenal tumor on CT imaging | Histology of tumor | Surgical removal of tumor |
| Chrousos Syndrome (primary glucocorticoid resistance) | | | Increased serum cortisol and 24-hour urinary free cortisol without clinical hypercortisolism | Dexamethasone suppression and genetic testing | Dexamethasone |
| Apparent mineralocorticoid excess | ↓ | ↓ | Increased 24-hour urinary free cortisol and elevated urinary cortisol to cortisone ratio | Genetic testing in hereditary cases | MRA and occasional dexamethasone; removal of offending drug |
| Geller syndrome (mineralocorticoid receptor-activating mutation) | ↓ | ↓ | | Genetic testing | Amiloride |
| Gordon syndrome (pseudohypoaldosteronism type II) | ↓ | ↓/↔ | | Genetic testing | Low sodium diet; thiazide diuretic |
| Liddle syndrome (pseudohyperaldosteronism) | ↓ | ↓ | | Genetic testing | Amiloride |

*ARR* aldosterone-to-renin ratio, *CCB* calcium channel blocker, *MRA* mineralocorticoid receptor blocker, *RAAS* renin-angiotensin-aldosterone

**Table 3. Causes of false-positive and false-negative results in primary aldosterone screening with aldosterone-to-renin ratio**

| | Plasma aldosterone concentration (PAC) | Plasma renin activity (PRA) | Aldosterone-to-renin ratio (ARR) |
|---|---|---|---|
| False-positive result | | | |
| β-blockers | ↓ | ↓↓ | ↑ |
| Central α2-agonists (e.g., clonidine) | ↓ | ↓↓ | ↑ |
| NSAIDs | ↓ | ↓↓ | ↑ |
| Hyperkalemia | ↑ | ↓/↔ | ↑ |
| Older age | ↓ | ↓↓ | ↑ |
| Chronic kidney disease | ↔ | ↓ | ↑ |
| Sodium loading | ↓ | ↓↓ | ↑ |
| False-negative result | | | |
| $K^+$ wasting diuretics | ↑/↔ | ↑↑ | ↓ |
| $K^+$ sparing diuretics, including MRAs | ↑ | ↑↑ | ↓ |
| ACEi | ↓ | ↑↑ | ↓ |
| ARB | ↓ | ↑↑ | ↓ |
| Dihydropyridine CCB | ↓/↔ | ↑ | ↓ |
| SSRI antidepressants | ↑ | ↑↑ | ↓ |
| Hypokalemia | ↓ | ↑/↔ | ↓ |
| Pregnancy | ↑ | ↑↑ | ↓ |
| Sodium restriction | ↑ | ↑↑ | ↓ |
| Equivocal result | | | |
| α1-blockers | ↔ | ↔ | ↔ |

*ACEi* angiotensin-converting enzyme inhibitors, *ARB* angiotensin receptor antagonist, *CCB* calcium channel blocker, *MRA* mineralocorticoid receptor blocker, *NSAIDs* nonsteroidal anti-inflammatory drugs, *SSRI* selective serotonin reuptake inhibitor

An ARR ≥ 20 in the setting of a PAC ≥ 15 ng/dL and PRA < 1 ng/mL/hour (or a plasma renin concentration below the limit of detection) is suggestive of PA, although the most commonly used ARR cutoff is 30 [1••, 66••]. Whether the PAC must be greater than or equal to 15 is controversial, as some studies have found PA with PAC in the 9–15 range, although the predominant etiology at such levels is bilateral adrenal hyperplasia [63, 66••].

While confirmatory testing is typically recommended, the triad of spontaneous hypokalemia, undetectable PRA, and PAC > 20 ng/dL obviates the need for additional testing [66••]. In general, increasing ARR values correspond to increasing specificity and a lower false-positive rate, with some arguing that confirmatory testing may be obviated in some circumstances (e.g., specificity approaches 100% with ARR > 50) [68].

At least four major confirmatory tests have been described – oral sodium loading, saline infusion, fludrocortisone suppression, and captopril challenge. Diagnostic superiority has not been established [66••, 69, 70], and thus in practice, ease of use is often a consideration. Most practically, oral sodium loading for 3 days (sodium 5000 mg or 218 mEq, or about 12.8 g sodium chloride, which can be taken as tablets) can be performed, followed by 24-hour urine collection (from day 3 to 4) for aldosterone, sodium (with greater than 200 mmol to confirm a high salt diet), and creatinine (to confirm adequate collection). Finding of urine aldosterone ≥ 12 micrograms (33 nmol) per 24 hours is confirmatory. Blood pressure and serum potassium should be monitored closely, as sodium loading can worsen hypertension and precipitate hypokalemia.

For centers able to accommodate intravenous saline infusion testing, the protocol requires a 2-L intravenous saline infusion over 4 hours, with a PAC level > 10 ng/dL confirming the diagnosis. Levels between 5 and 10 are indeterminate – although several studies have found 7 or 8 to be a reasonable cutoff [70, 71] – and are sometimes seen in adrenal hyperplasia [66••, 72].

Following positive screening and confirmatory testing, a CT scan with an adrenal protocol should be performed to rule out carcinoma and assist in operative management [66••]. Typical findings include adrenal adenoma and bilateral hyperplasia, although imaging may be normal in the latter. Small nodules may occasionally be erroneously interpreted as adenomas when they represent hyperplasia and vice versa [66••]. CT is preferred over MRI, unless the patient is unable to undergo the former.

## Treatment and outcomes

Regardless of confirmatory testing, if the patient wishes not to proceed or is not a candidate for additional testing or invasive procedures, treatment can be initiated with a MRA – either spironolactone or eplerenone. Spironolactone is commonly the initial agent of choice, with a starting dose of 25 mg per day. Thereafter, spironolactone may be titrated from 25 mg up to as high as 400 mg per day in either single or split doses. Such high doses are usually not required, and most patients require 100 mg per day or less (in either single or split doses). The major complication of spironolactone is the development of gynecomastia, which is dose-related and occurs in up to half of patients at doses greater than 150 mg per day, and erectile dysfunction. Eplerenone, a more selective MRA without antiandrogen and progesterone agonist effects, has a much lower incidence of gynecomastia. Its potency for mineralocorticoid receptor blockade is about 50% of spironolactone, so higher doses are frequently needed, and it may be cost prohibitive for some patients. The starting dose is 25 mg twice daily. MRAs should be titrated to a serum potassium in the upper normal range, and additional antihypertensives (especially thiazide diuretics) can be used as adjuncts for blood pressure control [66••]. Amiloride, an ENaC blocker, can be used to effectively block mineralocorticoid-induced renal sodium reabsorption in patients intolerant to therapeutic doses of MRAs (although like MRAs, amiloride can cause hyperkalemia so should be dosed carefully).

The standard treatment for patients with bilateral disease is with a MRA, whereas for patients with unilateral disease (most commonly adrenal adenoma), the guideline recommended treatment is adrenalectomy [1••, 66••]. Prior to undergoing adrenalectomy, adrenal vein sampling (AVS) should be

undertaken, and this has been shown to have more favorable outcomes than diagnosis via adrenal CT (or MR) alone in preoperative testing, as misdiagnoses are common with the latter [73–75]. Attempts to obviate AVS were undertaken in a recent randomized trial, which found no difference in 1-year outcomes between patients following a CT-only treatment pathway and those undergoing AVS [76], but this study was heavily criticized for having an unrepresentative population, a poor primary outcome, and insufficient follow-up blood pressure management [77]. Adrenalectomy, typically performed laparoscopically, is quite safe, with an overall complication rate of approximately 5–10% (mostly mild complications) and a mortality well under 1% [78–80].

No prospective, randomized controlled trials have been conducted to prove superiority of any one treatment approach. Most studies have found no difference between surgical and medical approaches for outcomes such as cerebrovascular and cardiovascular disease, left ventricular hypertrophy, or severity of hypertension [79, 81]. Medically treated PA patients may have a higher risk of atrial fibrillation than those treated surgically [82], although not all studies have found this [79], and some recent retrospective studies suggest that the incidence of chronic kidney disease and end-stage renal disease may be higher in MRA treated patients [83, 84]. Patients with PA have been shown to have a worse quality of life and more depression and anxiety than age-matched controls, and this is most notable in women. These symptoms largely improve with treatment, although surgically corrected PA tends to have better outcomes than treatment with MRA [79, 85–87].

Patients treated surgically tend to require fewer antihypertensives (an average of 1.5 versus 2.8 for medical management) [81]. Following adrenalectomy, approximately one third are cured and require no further treatment for hypertension, one third to one half improve significantly (lower blood pressure and/or fewer medications), and about 30–40% experience no clinical benefit [88–90]. A variety of risk factors are associated with failure to achieve cure with surgery. These include older age, male gender, a longer duration of hypertension, a higher number of preoperative antihypertensives, and evidence of target organ damage [91, 92].

Ultimately the choice of medical versus surgical treatment must be tailored to patient-specific wishes, taking into consideration associated risks, benefits, and other modifying circumstances.

## Uncommon forms of primary aldosteronism

Glucocorticoid-remediable hypertension (GRA), or familial hyperaldosteronism (FH) type I, accounts for less than 1% of all PA cases. A genetic defect, which is inherited in an autosomal dominant pattern, leads to aldosterone production under the control of adrenocorticotropic hormone (ACTH).

GRA typically presents in childhood, and patients are at increased risk for hemorrhagic strokes and intracranial aneurysms. Diagnosis is through genetic testing (sequencing of CYP11B1/CYP11B2 chimeric gene), and treatment is through ACTH suppression with exogenous steroids (dexamethasone) at night and a MRA if needed for blood pressure control [62].

Two other extremely rare forms of FH exist, both of which are inherited in an autosomal dominant fashion. FH type II leads to PA not suppressible by steroids and often include active adrenal adenomas. FH type III acts similarly, except that adrenal hyperplasia rather than adenomas form [62].

# Rare forms of low renin hypertension (see Table 2)

## Cushing's syndrome and hypercortisolism (ACTH dependent and independent)

Cushing's syndrome is a heterogeneous group of diseases defined by chronic exposure to excess glucocorticoids – either endogenous or exogenous – leading to signs and symptoms that include weight and adiposity increase with supraclavicular fat pads, facial plethora, glucose intolerance, hypertension, proximal muscle weakness, skin thinning and easy bruising, acne, OSA, and increased irritability. Unlike patients with typical obesity and metabolic syndrome, patients with Cushing's syndrome often develop these symptoms simultaneously, progress and worsen over time, and present in otherwise unusual patient ages [93, 94•, 95]. While patients have an increased risk of cardiovascular and cerebrovascular complications and mortality, long-term outcomes are excellent following successful treatment [96, 97], underscoring the importance of accurate diagnosis and treatment.

The primary causes of Cushing's syndrome are exogenous or iatrogenic. Endogenous Cushing's syndrome, somewhat rarer, is ACTH- and pituitary-dependent in 70% of cases and primarily affects women ages 25–45. Other endogenous forms of Cushing's disease are adrenal adenoma or carcinoma, more commonly seen in childhood and age 50–60s (15–20% of endogenous disease), and ectopic ACTH, which is associated with small-cell lung cancer in half of cases (10–15% of endogenous disease) [93, 94•, 95].

As the exogenous form of hypercortisolism is far more common than the endogenous form (latter has incidence of less than one per 1 million people per year) [94•], a thorough medication history focused on exogenous steroid use in any form – parenteral, injectable, inhaled, and topical – should be ascertained. Screening for exogenous glucocorticoids can be performed by finding of low levels of ACTH, dehydroepiandrosterone sulfate, and cortisol alongside a positive synthetic glucocorticoid screen.

Once exogenous forms are excluded, testing for endogenous Cushing's includes measurement of baseline cortisol levels in addition to evaluating the suppressive or stimulatory response of the hypothalamic-pituitary-adrenal axis. Three primary first-line tests exist, and two should be positive: 24-hour urinary free cortisol, overnight dexamethasone suppression testing (DST), and bedtime or late-night salivary cortisol test [93, 95] (see Fig. 2). Serum cortisol levels or ACTH alone are not recommended for screening [96]. In all forms of hypercortisolism, renin and aldosterone are typically low or normal.

The first test recommended is 24-hour urinary free cortisol, although patients with advanced CKD may have a false-negative result. (Patients at high risk of Cushing's with an initial negative urine test should have this repeated.) Alternatively, DST involves taking 1 mg of dexamethasone at 11:00 PM, followed by next morning (8:00 AM) serum cortisol testing. A cortisol level of < 50 nmol/L (1.8 μg/dL) excludes Cushing's syndrome. This latter test is a good first screening for adrenal incidentalomas, but should be avoided in patients on estrogen or anti-epileptics. The late-night salivary test involves soaking absorbent cotton for 2–3 minutes at 11:00 PM and refrigerating it overnight until it is brought to a laboratory the next day. It should not be performed on patients

with altered sleep habits (e.g., shift workers), immediately following cigarette smoking or eating or following vigorous exercise [93, 95]. Following an initial positive test, a second screening test should be performed, and if positive, then Cushing's syndrome is likely and morning ACTH levels can help narrow the etiology. These patients should be referred to endocrinology for additional Cushing's subtyping and treatment planning, as identifying the source and managing therapy is complex [97].

The mainstay of therapy for Cushing's has traditionally been surgical removal of the tumor (either pituitary or adrenal). Occasionally repeat surgery for complete resection or radiation therapy is necessary, particularly for pituitary tumors. Pharmacotherapy plays a role in the pre-operative period, post-operative period as adjuvant treatment, and for patients with contraindications to surgery. Medical agents used to treat Cushing's target ACTH suppression (somatostatin analogs or dopamine agonists), steroidogenesis inhibition (ketoconazole, metyrapone, mitotane, etomidate), and glucocorticoid receptor antagonism (mifepristone). Generally, successful treatment of hypercortisolism reverses but may not fully normalize some features of Cushing's, including quality of life, bone mineral density, and hypertension [96].

The cause of hypertension in hypercortisolism is multifaceted and complex and includes upregulated RAAS, increased mineralocorticoid activity due to saturation of 11β-hydroxysteroid dehydrogenase type 2 (enzyme responsible for cortisol to inactive cortisone conversion in the kidney), and a hyperactive sympathetic nervous system [98]. Up to 85% of patients with endogenous disease have hypertension, compared to only 20% of patients with the exogenous form. The risk and severity of hypertension is not directly correlated with cortisol levels but increases with the duration of disease [98].

Treatment for cortisol-induced hypertension begins with RAAS blockade, followed by MRA if the patient has persistent hypokalemia (otherwise, CCBs can be used). If the patient remains hypertensive, alpha-blockers can be used. Thiazide diuretics and beta-blockers may be appropriate but should be used cautiously given the propensity of the former to worsen hypokalemia, gout, and diabetes, and the latter toward dysglycemia [98]. In general, successful treatment of hypercortisolism improves and sometimes cures hypertension, although only about 50% of treated patients come off antihypertensives entirely. Long-term exposure to higher levels of cortisol increases the risk of persistent hypertension [97, 98].

## Congenital adrenal hyperplasia

A rare group of autosomal recessive disorders, congenital adrenal hyperplasia (CAH) is caused by a defect in adrenal steroid synthesis, leading to deficient cortisol. This leads to increases in ACTH and subsequently elevations in cortisol precursors. The most common cause of CAH is 21-hydroxylase deficiency, which does not cause hypertension. Deficiencies of 11β-hydroxylase and 17α-hydroxylase lead to hypertension due to mineralocorticoid excess from deoxycorticosterone. While mostly diagnosed in childhood, partial defects may have a later presentation or diagnosis [94•].

Patients with 11β-hydroxylase or 17α-hydroxylase deficiency have elevated deoxycorticosterone and 11-deoxycortisol, leading to hypertension, hypokalemia, and low levels of aldosterone and renin. Both are very rare, although 11β-

hydroxylase (prevalence 1 in 100,000) is the more common of the two disorders (prevalence of 17α-hydroxylase is 1 in 1,000,000) [94•]. The main difference in presentation is related to sex steroids and their gender-related effects. Treatment for both includes exogenous glucocorticoid supplementation to suppress endogenous steroidogenesis [62].

## Deoxycorticosterone-producing tumor

Deoxycorticosterone-producing tumors are a very rare form of adrenal tumor. These patients typically present with relatively rapid onset of hypertension, with suppressed aldosterone level, an elevated deoxycorticosterone level, and adrenal tumor on CT imaging. Surgical treatment, typically an adrenalectomy, is often curative [94•, 99].

## Chrousos syndrome (primary glucocorticoid resistance)

Patients with Chrousos syndrome have a genetic defect in the human glucocorticoid receptor leading to partial insensitivity to glucocorticoids. This leads to ACTH overproduction, adrenal hyperplasia, and increased cortisol, deoxycorticosterone, and corticosterone secretion. While the clinical presentation is quite varied, these patients typically present with hypertension. Screening is performed finding increased 24-hour urinary free cortisol, up to 50-fold higher than the upper reference limit, without clinical hypercortisolism. Serum cortisol is also markedly elevated. Diagnosis is confirmed with dexamethasone suppression and genetic testing (sequencing of the NR3C1 gene). The mainstay of treatment is dexamethasone to suppress ACTH secretion [100].

## Apparent mineralocorticoid excess

Cortisol typically undergoes enzymatic conversion to inactive cortisone in the kidney. The defect in 11β-hydroxysteroid dehydrogenase type 2 lead to excess cortisol, which acts as a mineralocorticoid leading to hypertension, hypokalemia, metabolic alkalosis, low renin and aldosterone, and normal plasma cortisol levels. The two primary causes of apparent mineralocorticoid excess (AME) are hereditary (extremely rare) and inhibition of enzyme activity [101]. Exogenous inhibition is classically associated with glycyrrhizic acid (licorice root) [102], but other items including grapefruit [103], posaconazole [104], and an herb called mumijo [105] have been implicated. AME is diagnosed with 24-hour urine collection demonstrating a high ratio of cortisol to cortisone, often increased tenfold above normal [94•], and genetic testing can confirm the defect in hereditary cases.

Severe cases of AME typically present in infancy. Milder forms of the disease can present later as does the acquired form. Long-standing disease can lead to cardiovascular disease, nephrocalcinosis, and renal cysts [62]. Treatment is with MRA, potassium supplementation, and, when applicable, removal of the offending agent [101]. Treatment with dexamethasone to suppress endogenous corticosteroid production has been described [62].

## Geller syndrome (mineralocorticoid receptor-activating mutation)

While perhaps the most well-known mineralocorticoid receptor mutation is a loss of function leading to autosomal dominant pseudohypoaldosteronism type I with salt wasting hypotension, a rare gain-of-function mutation has been

described – thus far in only one family – leading to a constitutively active mineralocorticoid receptor. These patients have suppressed renin and aldosterone levels and severe hypertension. Interestingly, common MRAs, including spironolactone and progesterone, activate the mutated receptor, worsening hypertension. In the latter case, pregnancy can significantly exacerbate this disease [106]. As spironolactone is contraindicated, amiloride is the preferred treatment in this scenario.

### Gordon syndrome (pseudohypoaldosteronism type II)

Gordon's syndrome, also known as pseudohypoaldosteronism type II or familial hyperkalemic hypertension, is caused by a gain-of-function mutation and a subsequent increase in the thiazide-sensitive NaCl cotransporter in the distal renal tubule. The increase in sodium reabsorption leads to hyperkalemia, metabolic acidosis, low renin, and low-normal aldosterone. Mutations in at least four different genes have been implicated, with varying modes of inheritance. Treatment is with a low-salt diet and thiazide diuretics [107].

### Liddle syndrome (pseudohyperaldosteronism)

Presenting similar to PA – hypertension and hypokalemia – but with low levels of renin and aldosterone, Liddle syndrome or pseudohyperaldosteronism is an autosomal dominant mutation leading to constitutive activation of the ENaC in the distal portion of the renal tubule. It is extremely rare, having been described in fewer than 100 families. Diagnosis includes ruling out other causes of hypertension with low renin and aldosterone, with genetic testing available. Treatment involves blocking the affected channel with amiloride or triamterene [107].

## Other rare forms of secondary hypertension

### Thyroid disease

Both hyper- and hypothyroid disorders can lead to hypertension, although the exact prevalence of thyroid-associated hypertension is unknown. Hyperthyroidism causes tachycardia, increased cardiac output, decreased systemic vascular resistance, and increased systolic blood pressure. Hypothyrodisim may lead to diastolic hypertension via increase in systemic vascular resistance and volume expansion [94•].

Screening involves checking thyroid-stimulating hormone and free thyroxine. Positive cases require definitive treatment of thyroid disease. Beta-blockers are the interim mainstay of treatment for hypertension and tachycardia in hyperthyroidism [94•].

### Hyperparathyroidism

Hyperparathyroidism appears to be associated with hypertension [94•] and blood pressure variability [108], largely due to hypercalcemia, although the effect is mild [109]. Patients with hypercalcemia should be screened for hyperparathyroidism and referred to an endocrinologist for definitive management. Correction of the underlying disorder has mixed effect on blood pressure control, and many patients remain hypertensive [94•].

### Acromegaly

Excess growth hormone from a pituitary tumor leads to acromegaly. Hypertension is common in these patients and is associated with sodium retention and volume expansion. Treatment in these cases is focused on managing the underlying disease with growth hormone reduction. Diuretics are helpful in managing the hypertension otherwise [94•].

### Coarctation of the aorta

While mostly diagnosed in childhood, coarctation of the aorta can present later with less severe, post-ductal lesions. The classic presentation is hypertension in the right upper extremity with diminished or absent femoral pulses. The diagnosis is made by suprasternal notch echocardiography, with MRI or CT confirmation. Treatment is procedural (percutaneous catheter intervention versus surgical repair), and hypertension can be managed with RAAS blockade or beta-blocker both prior to and post-surgery. Treatment even of normotensive patients with ramipril has been shown to decrease proinflammatory cytokine expression [110], and while candesartan was more effective and better tolerated than atenolol, metoprolol was found to be more effective than candesartan [111].

One third of patients have persistent hypertension following coarctation repair, with the risk rising with older age at time of repair [112] and reaching 75% after age 15 [113]. All patients require long-term follow-up, as up to 68% of patients develop chronic hypertension (mostly systolic), which has been attributed to vascular pathology, impaired baroreceptor sensitivity, and permanent hemodynamic changes [111, 114].

Atypical disease, caused by Takayasu arteritis, is treated with corticosteroids or anti-TNF agents.

### Renin-producing tumor

Reninoma, or renal juxtaglomerular cell apparatus tumor, is a rare, typically benign, neoplasm leading to secondary hyperaldosteronism from unopposed renin overproduction. It typically presents in the second or third decade of life (although it has been described in the elderly), and while the primary manifestation is hypertension and occasionally hypokalemia, headaches are commonly reported. Renal imaging typically identifies a renal mass, although the tumor is rarely present in other locations. Surgery (partial nephrectomy) is curative and is preferred over medical therapy which is often insufficient [115], and cases of successful radiofrequency ablation have been described [116].

## Pheochromocytoma

Pheochromocytomas are rare tumors and an uncommon cause of hypertension. While pheochromocytomas comprise approximately 0.2% of unselected hypertensive patients, autopsy studies suggest that many pheochromocytomas go undiagnosed [117]. Recent increases in the use of advanced diagnostic are increasing the detection of pheochromocytomas, especially clinically quiescent ones [118]. Approximately 5% of adrenal incidentalomas are pheochromocytomas [117, 119•].

Pheochromocytomas are tumors of adrenal chromaffin cells that produce catecholamines (adrenaline [epinephrine], noradrenaline [norepinephrine], or dopamine) and require treatment given their associated morbidity and risk of malignancy. Most patients are diagnosed in the fourth to fifth decades of life, without a gender predominance [117].

While most pheochromocytomas are benign, 10–15% of pheochromocytomas and 20–50% of paragangliomas are malignant [120]. Most pheochromocytomas are intra-adrenal in location. However, a very small minority are extra-adrenal (paragangliomas). The latter are typically confined to the abdominal or pelvic cavity, although rarely they extend to other more distant sites.

Familial pheochromocytoma is well described as part of multiple endocrine neoplasia, neurofibromatosis type 1, and Von-Hippel Lindau syndrome, and many other genetic disorders have been implicated. As up to one third of patients will have germline mutations [119•], some centers now routinely screen all patients with pheochromocytoma for genetic mutations [117], and US and European society guidelines recommend consideration for genetic testing [119•, 121].

The classic presentation of pheochromocytoma is headache, sweating, and tachycardia, and others refer to the 5 "Ps": paroxysmal hypertension, pounding headache, perspiration, palpitations, and pallor. These former presentations are relatively rare [118], with the actual presentation quite variable, and overlapping with many other disorders [120]. Hypertension, occasionally paroxysmal, is invariably noted in up to 90% of patients. [118, 122, 123]. Hypotension is more rarely noted [117], especially with epinephrine-predominant disease [120]. Other presentations of catecholamine excess include weight loss, fatigue, anxiety, and hyperglycemia [117], as well as cardiac complications, including cardiomyopathy and heart failure, myocardial infarction, arrhythmias, and aneurysms [120, 124].

Many medications can precipitate a pheochromocytoma crisis, which may be life-threatening, and include: dopamine antagonists, beta-blockers, sympathomimetics, opioid analgesics, norepinephrine reuptake inhibitors, tricyclic antidepressants, MAO inhibitors, corticosteroids, and neuromuscular blocking agents [119•].

## Screening and diagnosis (see Fig. 2)

The initial evaluation of pheochromocytoma involves measuring the catecholamine metabolites, known as metanephrines, either plasma free metanephrines or 24-hour urinary fractionated metanephrines. These two tests have roughly equal sensitivity, although the former has better specificity. Notably, plasma metanephrines should ideally be drawn with the patient fasting and in the supine position (for 20–30 minutes), as sitting may lead to false-positive results, and a liquid chromatography method is preferred over immunoassay due to the poor sensitivity of the latter [119•, 125, 126]. Antihypertensives do not appear to impact the performance characteristics of the screening tests and do not need to be withheld [127]. Patients with advanced chronic kidney disease and end-stage renal failure pose a diagnostic challenge, as they have higher baseline metanephrine levels – often overlapping with pheochromocytoma patients – with a 25–85% false-positive screening rate [128, 129].

Due to the relatively low prevalence of pheochromocytoma, a positive initial test is likely a false-positive result, and indeed mildly elevated metanephrine levels most often represent normal physiologic variation or acute stress, laboratory error, or medication interference [130]. Commonly implicated medications include acetaminophen, mesalamine, sulfasalazine, tricyclic antidepressants, MAO inhibitors, levodopa, sympathomimetics, and some alpha-blockers [119•]. The most common diagnosis following a false-positive test result is essential hypertension, and thus most hypertensive patients do not require testing [130]. Screening should only be performed in the presence of significant clinical suspicion. Some examples include resistant, paroxysmal, or young-onset hypertension; hyperadrenergic spells; family history of pheochromocytoma; incidental mass; paradoxical response to beta-blockers or severe hypertension following a procedure; and the like [117].

Results greater than 2.5–3 times the upper limit of normal are highly suggestive of pheochromocytoma and should lead to imaging evaluation without additional screening [119•, 130]. Patients with abnormal results not reaching that threshold should be retested in the supine position after stopping all offending medications. Persistent ambiguity poses a diagnostic challenge and is best handled by experienced specialists.

CT imaging of the abdomen and pelvis with contrast (adrenal protocol) is preferred over MRI for patients with positive screening tests for initial imaging. For skull base and neck paraganglioma, MRI is preferred. In positive cases, follow-up functional imaging for metastatic disease and treatment planning includes 123I-metaiodobenzylguanidine (MIBG) scintigraphy and/or 18F-fluorodeoxyglucose positron emission tomography/CT scanning, with the modality choice dependent on extent of disease and planned treatment [119•, 120].

## Treatment and outcomes

Treatment of pheochromocytoma is surgical (typically adrenalectomy for most tumors, which are intra-adrenal), and pre-operative management includes blood pressure control with alpha-blockers for 7–14 days prior, with many centers preferring phenoxybenzamine due to its nonselective, irreversible, and long-lasting action [131]. Dihydropyridine CCBs (amlodipine and nifedipine) can be used for additional blood pressure control as needed, and beta-blockers can be used as adjunct – but not alone – to address tachycardia. During this time, a high-sodium and fluid diet should be encouraged to prevent post-operative hypotension [117, 119•]. Peri- and intra-operative hemodynamic management is complex and is best managed by an experienced interdisciplinary team of surgeons, anesthesiologists, and endocrinologists [117].

Hypertension typically resolves following surgery, but for some patients, it may take 4–8 weeks to recover. About 2 weeks after surgery, patients should have metanephrine levels rechecked; persistent elevation indicates incomplete resection or occult metastases [117]. Surgical resection appears to ameliorate cardiac damage, with regression of left ventricular mass index and carotid intima-media thickness [132]. Lifelong follow-up with annual biochemical testing is recommended [119•].

While most patients have an indolent course with favorable long-term survival, 10–15% have a more aggressive course, with survival fewer than 5

years. Risk factors for poor outcome include male sex, older age, dopamine hypersecretion, metastases at time of initial diagnosis, and larger primary tumor size, and not undergoing surgical resection of primary tumor [133]. Approximately 10% of pheochromocytomas are malignant (and up to 35% mediastinal and abdominal paragangliomas, but only 4% of head and neck paragangliomas) [117]. For patients with metastatic disease or unresectable lesions, there is no standard chemotherapy or radiation regimen, and this should be addressed at experienced centers. Some common therapies include 131MIBG, external beam radiation, combination chemotherapy (cyclophosphamide, vincristine, dacarbazine), and, more recently, targeted therapy with tyrosine kinase inhibitors [15, 120].

Given the overall complexity of the workup, diagnosis, treatment, and follow-up of patients with suspected or confirmed pheochromocytomas, management by an experienced multidisciplinary group is preferred and improves diagnostic accuracy, clinical pathways, and overall processes of care [131, 134]. Underscoring the importance of a collaborative approach, misdiagnosis (both under and over) is common and can lead to errors, including unnecessary adrenalectomies [135].

## Conclusion

Although most patients with hypertension have the primary form, a substantial minority of patients have a discreet secondary type. The two forms may also coexist, and some patients remain hypertensive even following successful treatment of their secondary cause. Identifying patients who would benefit from screening and correctly diagnosing them is crucial. Targeted treatments, which are often curative, can provide significant long-term cardiovascular benefits and improvements in quality of life.

## Compliance with Ethical Standards

**Conflict of Interest**
Jamie S. Hirsch and Susana Hong each declare no potential \conflicts of interest.

**Human and Animal Rights and Informed Consent**
This article does not contain any studies with human or animal subjects performed by any of the authors.

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