BMJ Best Practice

Primary aldosteronism

Straight to the point of care

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Summary

Primary aldosteronism (PA) is the most common specifically treatable and potentially curable form of hypertension. It accounts for at least 5% of hypertensive patients, with most patients being normokalaemic.

Approximately 30% have unilateral forms correctable by unilateral laparoscopic adrenalectomy, and 70% have bilateral forms in which hypertension responds well to aldosterone antagonist medicines.

Optimal detection involves screening all hypertensive patients using the plasma aldosterone/renin ratio, after controlling for factors (including medicines) that may confound results.

In patients with repeatedly elevated aldosterone/renin ratios, definitive confirmation or exclusion of diagnosis is required.

Subtype differentiation for optimal treatment involves genetic testing for familial forms where suspected. If genetic testing is not performed or negative, adrenal CT and adrenal venous sampling should be performed to differentiate unilateral from bilateral forms.

Definition

In PA, aldosterone production exceeds the body's requirements and is relatively autonomous with regard to its normal chronic regulator, the renin-angiotensin II system.[1] [2] This results in excessive sodium reabsorption via amiloride-sensitive epithelial sodium channels within the distal nephron, leading to hypertension and suppression of renin-angiotensin II. Urinary loss of potassium and hydrogen ions, exchanged for sodium at the distal nephron, may result in hypokalaemia and metabolic alkalosis if severe and prolonged.[1] [2]

THEORY

Epidemiology

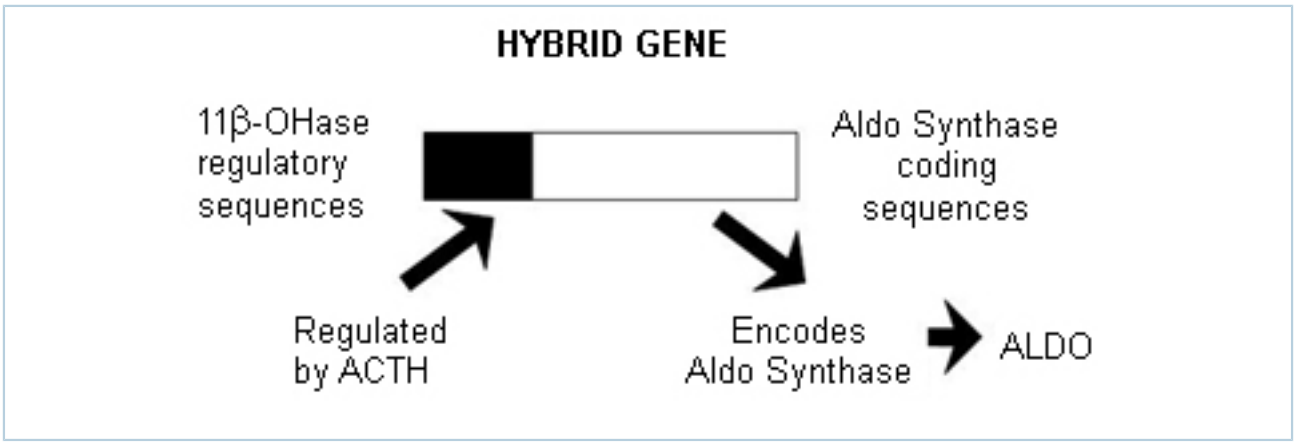
For many years, primary aldosteronism (PA) was considered a rare (<1%) cause of hypertension and not worth investigating as a potential cause unless hypokalaemia was present.[28] However, since 1992, evidence has accumulated that PA is much more common than was previously thought, and that most patients are normokalaemic.[28] [29] [30][31] Prevalence estimates vary considerably due to heterogeneity in source and type of data and non-standardised confirmation tests.[32] In one UK study of patients with newly diagnosed hypertension in the primary care setting, the prevalence of confirmed PA was 2.6%.[33] One study of people with established hypertension in Italy had a prevalence of PA of 5.9%, with the prevalence varying with the severity of hypertension (3.9% in stage 1 hypertension; 11.8% in stage 3 hypertension).[34]

At one Australian centre, adoption of a policy in 1991 to screen for PA by measuring the plasma aldosterone/renin ratio in all patients referred with hypertension, and not just those with hypokalaemia, led to a 10-fold increase in detection rate.[27] This was associated with a 4-fold increase in the rate of removal of aldosterone-producing adenomas.[27] The series of patients with PA at this centre is increasing at a rate of 50 to 90 patients per year. Only 22% of patients diagnosed since 1992 were hypokalaemic. The centre reported an incidence of confirmed PA of 8.5% among 199 consecutive hypertensive normokalaemic referred patients, and of 12% among 52 antihypertensive drug trial volunteers.[35] [36]

Since these initially reported findings, numerous other groups (spanning 6 continents and including the Mayo Clinic) similarly reported PA to be a much more common cause of hypertension than was previously suspected, with prevalence rates ranging from 3% to 32%, depending on the selectivity of hypertensive patients studied and the diagnostic criteria employed.[29] [30] [31][37] [38] [39] [40][41] [42] In all of these series, <50% of patients diagnosed with PA were hypokalaemic.

Aetiology

The aetiology of most forms of primary aldosteronism (PA) is unknown. The occurrence of PA within families is in keeping with a genetic basis for at least some forms of this condition.[10] [41] [43] One dominantly inherited and glucocorticoid-remediable variety of PA is familial hyperaldosteronism type I (FH-I). First described in 1966, FH-I is caused by a hybrid gene, which is composed of 11-beta-hydroxylase gene (CYP11B1) sequences at its 5' end and aldosterone synthase gene (CYP11B2) sequences at its 3' end.[44] [45]



Hybrid CYP11B1/CYP11B2 gene responsible for ACTH-regulated aldosterone overproduction in FH-I

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In 1991, a second familial variety of PA, familial hyperaldosteronism type II (FH-II), was described that was neither glucocorticoid-remediable nor associated with the hybrid gene.[12] [46] Although the term 'FH-II' was originally used to describe familial forms of PA other than FH-I, this term has been reassigned to familial PA caused by germline mutations within CLCN2 after the largest of the originally described families (and several other probands with PA) was found to have a mutation in that gene.[17] Characteristic clinical features of FH-II include early onset (<20 years of age) hypertension, a relatively mild form of PA in which hypertension is usually readily controlled with medications that block aldosterone action, minimal if any morphological abnormalities of the adrenal on imaging studies, and lack of responsiveness of aldosterone to upright posture.

A family with early and severe PA, markedly elevated levels of 'hybrid steroids' (18-hydroxy- and 18-oxocortisol), and marked zona fasciculata hyperplasia, first reported in 2008, and designated as having familial hyperaldosteronism type III (FH-III), was reported to have a germ-line mutation within KCNJ5 (encodes a potassium channel).[14] [15][47] Germ-line KCNJ5 mutations appear to be a rare cause of bilateral PA and are associated with an early onset (<18 years of age) but with variable severity (from mild to very florid PA) that is dependent on the type of mutation inherited.[16]

Germ-line mutations in CACNA1H (encodes a voltage-gated calcium channel) have also been identified in a small number of individuals with onset of PA before 10 years of age.[48] In some of these individuals, the mutation was inherited from a parent, giving rise to the term 'familial hyperaldosteronism type IV' to describe PA resulting from germ-line CACNA1H mutations. Germ-line mutations in CACNA1D (also encodes a voltage-gated calcium channel) were also found in two individuals with early onset PA (but as yet no known affected relatives) who suffered from seizures and other neurological disorders.[49]

Families with PA of uncertain genetic aetiology have been reported to be at least 5 times more common than FH-I.[23] Both aldosterone-producing adenoma and bilateral adrenal hyperplasia (BAH) are represented, often within the same family.[13] [22] These patients are clinically, biochemically, and morphologically indistinguishable from those with apparently sporadic PA, and responsible mutations may therefore underlie the development of PA in other patients who lack a family history of this condition.[4] [13] [22] [23]

Somatic mutations in KCNJ5 were identified in 8 of 22 large, apparently sporadic aldosterone-producing adenomas.[47] Other groups have reported somatic KCNJ5 mutations to be present in 30% to 40% of aldosterone-producing adenomas removed from white patients and in >60% removed from patients from Japan and China.[50] [51] [52] Somatic mutations have since been identified in ATP1A1 (encodes the α-subunit of Na+/K+ ATPase), ATP2B3 (a Ca2+ ATPase calcium channel), and CACNA1D (encodes a voltage-gated calcium channel) in much smaller proportions (5%, 2%, and 11% respectively) of APAs.[49] [53][54]

Studies involving immunohistochemical techniques have revealed the presence of abnormal foci of CYP11B2-expressing cells, termed aldosterone-producing cell clusters (APCCs), within adrenal cortices, which become more numerous with advancing age.[55] Concurrently, zona glomerulosa, typically continuous in childhood and early adulthood, becomes increasingly disrupted and relatively suppressed in terms of CYP11B2 expression. These observations support a potential pathophysiological mechanism (APCC formation) underlying the apparent gradual development of autonomous aldosterone production with ageing (as evidenced by rising ARR), and which may predispose to the development of frank PA, due either to bilateral adrenal hyperplasia (BAH) or to aldosterone-producing adenoma (APA) (or both).

Pathophysiology

In all forms of PA, aldosterone production is excessive to the body's requirements and relatively autonomous with regard to its normal chronic regulator, the renin-angiotensin II system.[56] This results in excessive sodium re-absorption through amiloride-sensitive epithelial sodium channels within the distal nephron, leading to hypertension and suppression of renin-angiotensin II. Urinary loss of potassium and hydrogen ions, exchanged for sodium at the distal nephron, may result in hypokalaemia and metabolic alkalosis if severe and prolonged enough. The exact causes of excessive, autonomous aldosterone production in aldosterone-producing adenoma and bilateral adrenal hyperplasia are unknown, but genetic factors related to adrenal cortical cellular growth regulation and/or steroid biosynthesis are likely to be involved. Abnormal foci of CYP11B2-expressing cells, termed APCCs, have been detected within adrenal cortices and become more numerous with advancing age.[55] Concurrently, renin becomes progressively suppressed, whereas aldosterone does not but becomes less responsive to salt, suggesting that aldosterone production by these APCCs may be constitutive and not responsive to renin. The clinical significance of these APCCs is uncertain, and includes the possibilities that they represent a pathological basis for BAH, precursors of APAs, or a new form of PA altogether.[57]

In FH-I, the causative hybrid gene encodes a hybrid enzyme of unique structure that synthesises aldosterone but, unlike CYP11B2, is regulated by adrenocorticotrophic hormone (ACTH) and not by angiotensin II.[45] Aldosterone production in FH-I is therefore regulated by ACTH rather than by angiotensin II, and can be suppressed and managed by administering small doses of glucocorticoids such as dexamethasone.[44]

Mutations in KCNJ5 (which encodes an inwardly-rectifying potassium channel) lead to reduced potassium/sodium channel selectivity and sodium influx, predisposing to cell membrane depolarisation, increased calcium influx, increased expression of genes promoting aldosterone synthesis, and increased aldosterone production by adrenocortical cells.[16] [47] Mutations in ATP1A1, ATP2B3, CACNA1H, and CACNA1D also appear to share increased calcium influx as a common pathophysiological mechanism for increased and autonomous production of aldosterone.[49] [53][54] Mutations in CLCN2 predispose to cell membrane depolarisation and possibly also to increased calcium influx.[17] How these effects lead to adrenal cell proliferation and tumour development remains uncertain.

Although morbidity in PA mainly results from hypertension, experimental, and clinical evidence strongly suggests that aldosterone excess can bring about adverse cardiovascular sequelae (including remodelling and fibrosis) independently of its hypertensive effects.[58] [59] In animal studies, both aldosterone excess and a high salt intake appear to be necessary for induction of cardiac fibrosis,[58] and coronary vasculitis has been observed to be an early manifestation.[60] These effects were preventable by the administration of mineralocorticoid receptor antagonists.[58] [60] The doses of aldosterone used in experimental studies have been very large, and the results of these studies may, therefore, have limited applicability to clinical situations. Nevertheless, several groups have convincingly demonstrated abnormalities in cardiovascular morphology or function in patients with PA that appear to be out of proportion to the elevation in BP.[59] [61] [62] [63] [64] These have included:

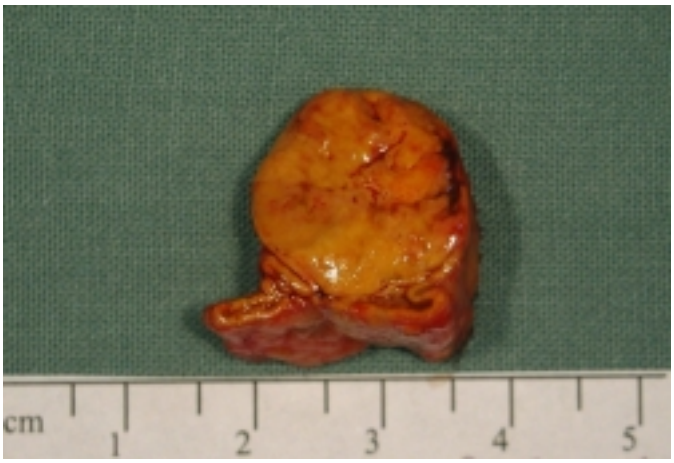
- Increased left ventricular mass index and reduced diastolic function, both of which markedly improved following specific treatment of PA[59] [61]
- Reduced myocardial perfusion at rest and during exercise[62] [63]
- Increased myocardial backscatter (an echo marker of myocardial fibrosis)[64]
- Increased proteinuria (as evidence of renal glomerular damage)[65]
- A greater incidence of cardiovascular events, which was reversed following specific surgical or medical treatment.[66] [67]

Evidence of left ventricular remodelling was also reported in individuals with genetically proven FH-I who had biochemical evidence of aldosterone excess but had not yet developed hypertension.[68]

Classification

Pathological classification[3] [4] [5]

- Aldosterone-producing adenoma (APA): a benign adrenocortical tumour of at least 10 mm in diameter autonomously producing aldosterone.



Aldosterone-producing adenoma

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APAs may be further sub-classified according to whether they are angiotensin-unresponsive (as in the classic Conn's tumour) or angiotensin-responsive, in which responsiveness is defined as a rise in plasma aldosterone by at least 50% over basal during 2 or 3 hours of upright posture following overnight recumbency or during an infusion of angiotensin II.

- Aldosterone-producing nodule (APN): a benign adrenocortical lesion of less than 10 mm in diameter autonomously producing aldosterone.
- Aldosterone-producing adrenocortical carcinoma (APACC): a malignant adrenocortical tumour autonomously producing aldosterone.
- Other unilateral forms: one adrenal excessively and autonomously producing aldosterone, but with no discrete tumour identified on pathological examination. Instead, the adrenal is shown to contain either one or multiple aldosterone-producing micronodules (APM or MAPM) that stain positive for CYP11B2 by immunohistochemistry but are not distinguishable from the surrounding cortex by haematoxylin-eosin staining. More rarely, aldosterone-producing diffuse hyperplasia (APDH) shows a broad continuous region of hyperplastic, CYP11B2-positive zona glomerulosa cells.
- Bilateral forms: both adrenals affected by diffuse and/or nodular hyperplasia and excessively and autonomously producing aldosterone; includes both non-glucocorticoid-remediable (idiopathic) and glucocorticoid-remediable forms. Rarely, bilateral hyperplasia is macronodular with autonomous secretion of cortisol more often than of aldosterone.

Functional (treatment-oriented) classification[6] [7] [8] [9] [10]

- Unilateral PA:

- Includes APA, APN, APACC, and unilateral (or primary) adrenal hyperplasia.
- Bilateral PA:
  - Non-glucocorticoid-remediable: includes bilateral (idiopathic) adrenal hyperplasia which is rarely macronodular (non-familial, familial hyperaldosteronism type II, and familial hyperaldosteronism type III) and bilateral APA.
  - Glucocorticoid-remediable (familial hyperaldosteronism type I).

Familial classification[4] [10][11] [12] [13] [14] [15] [16] [17]

- Familial hyperaldosteronism type I (FH-I; glucocorticoid-remediable; associated with hybrid gene).
- Familial hyperaldosteronism type II (FH-II; non-glucocorticoid-remediable; associated with germ-line mutations of CLCN2).
- Familial hyperaldosteronism type III (FH-III; non-glucocorticoid-remediable; associated with germ-line mutations of KCNJ5).
- Familial hyperaldosteronism type IV (FH-IV; non-glucocorticoid-remediable; associated with germ-line mutations of CACNA1H).
- Apparently non-familial PA (without known affected relatives).

Case history

Case history #1

A 54-year-old man presents with a 10-year history of hypertension that has been difficult to control with antihypertensive medicines. His symptoms include frequent headaches, nocturia (3-4 times per night), and lethargy. He has no other medical conditions or past medical history. Apart from a blood pressure (BP) of 160/96 mmHg, findings on physical examination are unremarkable. Plasma electrolytes are normal.

Case history #2

A 28-year-old woman presents with a 2-year history of hypertension, associated with nocturia (4-5 times per night), polyuria, palpitations, limb paraesthesias, lethargy, and generalised muscle weakness. There is no other past medical history. Physical examination is unremarkable apart from a BP of 160/100 mmHg, global hyporeflexia, and weak muscles. Plasma potassium is 2.2 mmol/L (2.2 mEq/L), bicarbonate is 34 mmol/L (34 mEq/L), and serum creatinine is normal.

Other presentations

Hypertension in primary aldosteronism (PA) may be mild or severe and is rarely malignant.[18] BP levels vary widely among patients with either aldosterone-producing adenoma or bilateral adrenal hyperplasia, and cannot be used to distinguish these subtypes.[19] In familial hyperaldosteronism type I (FH-I), hypertension is often delayed, especially in females, but can be of early onset and severe enough to cause early death, usually from haemorrhagic stroke.[20] [21] Family screening in FH-I and families with PA of uncertain genetic aetiology has revealed highly diverse phenotypes with some patients normotensive, consistent with PA evolving through a pre-clinical phase.[4] [13] [21] [22] [23] [24] [25]

Less than one quarter of patients diagnosed with PA and less than half of those with aldosterone-producing adenoma are hypokalaemic.[26] [27] In these patients, PA is indistinguishable from essential hypertension unless renin and aldosterone are measured. When hypokalaemia does occur, it may be associated with nocturia, polyuria, muscle weakness, cramps, paraesthesias, and/or palpitations. Nocturia is frequent even in the absence of hypokalaemia. Other common symptoms among either normokalaemic or hyperaemic patients include headaches, lethargy, mood alterations (including irritability, anxiety, or depression), and impaired mental concentration. During pregnancy, hypertension and symptoms may improve. This is thought to be due to the anti-mineralocorticoid effects of high circulating levels of placental progesterone, which antagonise aldosterone action at the mineralocorticoid receptor.

Approach

The diagnosis of primary aldosteronism (PA) should be considered in all patients with hypertension, regardless of severity and plasma potassium level. When present, symptoms suggestive of hypokalaemia (such as muscle weakness, paraesthesias, muscle cramps, nocturia, polyuria, and palpitations) are highly suggestive of PA. However, these symptoms are usually absent, as most patients are normokalaemic.[31] Other symptoms or signs that may be present are usually non-specific and non-contributory to diagnosis. These may include lethargy, difficulty concentrating, and mood disturbances such as irritability, anxiety, and depression.

A critical component of the diagnostic work-up is careful discussion with the patient. Each phase of the diagnostic process should be explained in detail to the patient before a decision is made whether to proceed with it.

Screening

Because only a minority (approximately 20%) of patients with PA are hypokalaemic, measurement of plasma potassium lacks sensitivity as a screening test. However, when hypokalaemia is present (especially when not provoked by the use of diuretics), it serves as a valuable clue towards the presence of this condition.

The aldosterone/renin ratio is the most reliable available screening test, being more specific than renin measurement (levels of which are almost always suppressed) and more sensitive than plasma potassium or aldosterone measurement.[10] [28] [41][70] The ratio becomes elevated before aldosterone or plasma potassium leave their normal ranges.[6] [71] [72] However, false positives and negatives are possible.[10] [28][73]

- Dietary salt restriction, concomitant malignant or renovascular hypertension, pregnancy (in which high levels of progesterone antagonise aldosterone action at the mineralocorticoid receptor), and treatment with diuretics (including spironolactone), dihydropyridine calcium channel antagonists, angiotensin-converting enzyme (ACE) inhibitors, or angiotensin receptor antagonists can all lead to false-negative ratios by stimulation of renin secretion.[6] [71] [72][74] [75] [76][77] [78]
- Because potassium is a powerful chronic regulator of aldosterone secretion, hypokalaemia may also be associated with false-negative ratios.[73]
- Beta-blockers, alpha-methyldopa, clonidine, and non-steroidal anti-inflammatory drugs (NSAIDs) can suppress renin levels and produce false-positives.[6] [10] [41][71] [74] [79]
- False-positives can occur in premenopausal women during the luteal phase of the menstrual cycle, and also in women receiving oestrogen-containing contraceptive agents or hormone replacement therapy, but only when renin is measured as direct active renin concentration and not as plasma renin activity.[80] [81] [82]
- False-positives may also be seen in patients with impaired renal function (renin production is reduced, whereas any associated hyperkalaemia tends to elevate aldosterone), in advancing age (during which production of renin falls more quickly than that of aldosterone), and in familial hyperkalaemic hypertension, also known as pseudohypoaldosteronism type II or Gordon syndrome.[10] [72] [83]
- Treatment with antidepressants of the selective serotonin reuptake inhibitor (SSRI) class lowers the aldosterone/renin ratio, but whether they can cause false-negatives in patients with PA remains uncertain.[84]

Diuretics should be discontinued for at least 6 weeks and other interfering medicines for at least 2 (and preferably 4) weeks before measuring the ratio, substituting other medicines that have a lesser effect on results, such as verapamil slow-release (plus or minus hydralazine), prazosin, and moxonidine, in order to maintain hypertension control.[71] [72] [85] In cases where a potentially interfering medicine cannot be withdrawn, useful information can still be obtained by taking into account its known effects when interpreting the ratio result. For example, an elevated ratio in patients receiving a diuretic, ACE inhibitor, angiotensin receptor blocker, or dihydropyridine calcium blocker would make PA very likely, whereas a normal ratio in the presence of beta-blocker treatment would make the diagnosis very unlikely.

Hypokalaemia should be corrected and the patient should be encouraged to follow a liberal salt diet before ratio measurement. Because of the effects of posture and time of day, sensitivity of the ratio is maximised by collecting blood mid-morning from seated patients who have been upright (sitting, standing, or walking) for 2 to 4 hours.[71] [72]

The ratio should be regarded as a screening test only, and should be measured more than once (serially if conditions of sampling, including medicines, are being altered) before deciding whether to go on to a suppression test to definitively confirm or exclude the diagnosis.

Confirmation of diagnosis

Confirmatory testing is required before the diagnosis of PA can be definitively confirmed or excluded.[10] [41] An oral sodium loading test or saline infusion test is recommended.[28] [70]

The oral sodium loading test can be performed at home, but not in the presence of severe hypertension, hypokalaemia, kidney impairment, or cardiac arrhythmia.[86] Patients ingest >200 mmol/day sodium (approximately 6 g/day) for 3 days.[28] Urinary aldosterone (along with urinary sodium) is measured in a 24-hour urine collection beginning at 8 a.m. on the morning of day 3 to the morning of day 4.[28] [86] Patients should receive adequate slow-release potassium chloride supplementation to maintain plasma potassium in the normal range.

Saline infusion testing is performed in the hospital setting.[86] Two litres of saline is administered intravenously over 4 hours, starting at 8 to 9:30 a.m.[28] Blood samples for renin and aldosterone are drawn at time zero, and at the end of the 4-hour infusion. Patients should be seated during the 30-minute period before saline infusion, and during the entirety of the infusion.[87]

Subtype differentiation

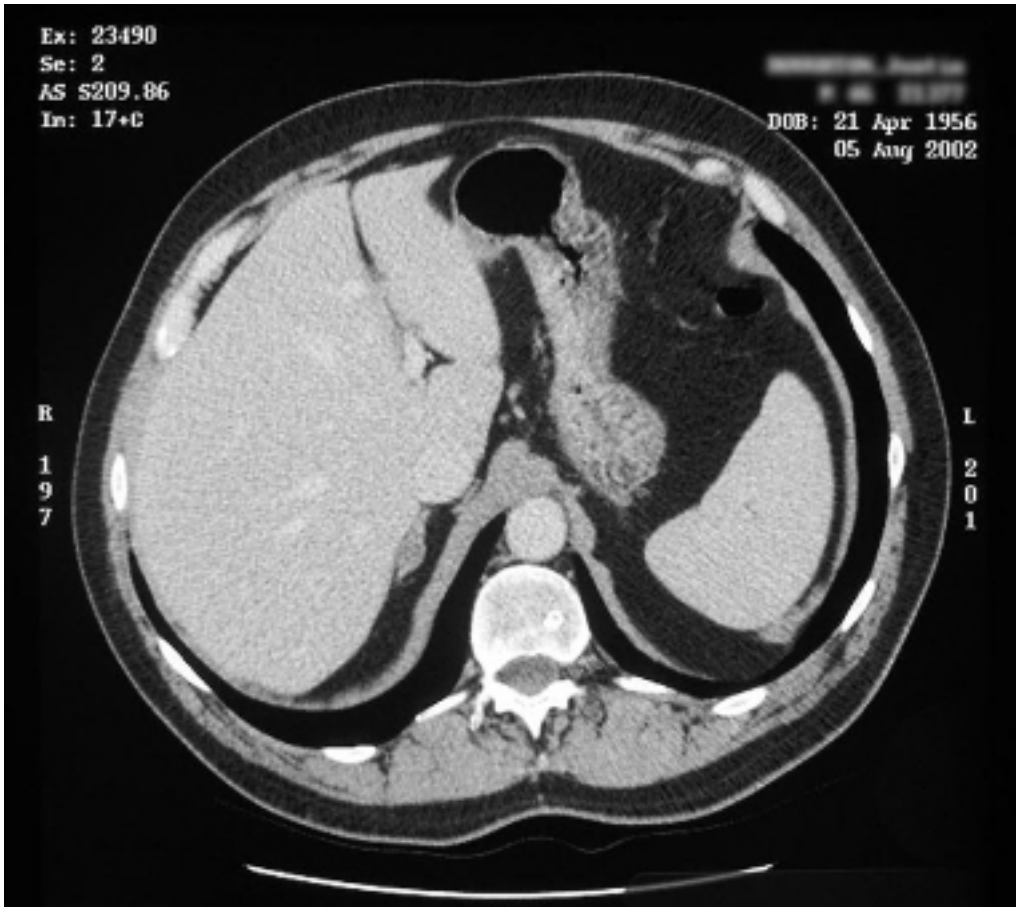
If the confirmatory test is positive, further investigations are directed towards determining the subtype of PA (unilateral aldosteronism, mainly caused by aldosterone-producing adenoma; or bilateral adrenal hyperplasia), as the treatment of first choice for each subtype differs.[28] Familial hyperaldosteronism type I (FH-I) is rare, but important to diagnose as hypertension is readily controlled by treatment with glucocorticoids.[11]

- If FH-I is suspected (for example, on the basis of early onset of PA or a family history of early onset hypertension, PA, or stroke), genetic testing of peripheral blood for the hybrid gene should be performed before going on to other tests aimed at subtype differentiation, as a positive genetic test will make them superfluous. Because presence of the hybrid gene is diagnostic for FH-I, testing for it has virtually supplanted the tedious and less reliable biochemical methods of diagnosing this subtype (e.g., demonstration of marked, persistent suppression of plasma aldosterone during several days of dexamethasone administration).[88] [89] [90] The great majority of patients with

PA, however, will test negative for the hybrid gene, leaving the more difficult task of separating the unilateral tumourous forms from varieties of bilateral adrenal hyperplasia (BAH). In patients with early onset PA who test negative for the hybrid gene, consideration should be given for genetic testing for mutations in CLCN2, KCNJ5, and CACNA1H for diagnosis of FH-II, FH-III, and FH-IV respectively.[41]

- Adrenal CT scanning is recommended in all patients to confirm subtype and exclude adrenocortical carcinoma.[10] [28] [41] It is usually able to detect aldosterone-producing carcinomas because of their relatively large size (usually >3 cm) but frequently misses aldosterone-producing adenomas (which have an average size of approximately 1 cm).[9] CT may be misleading, as it cannot distinguish aldosterone-producing adenomas from non-functioning nodules.[6] [27] [71] [91] [92] Similar limitations apply to adrenal MRI.[93]
- Responsiveness of plasma aldosterone (defined as a rise of at least 50% over basal) during 2 or 3 hours of upright posture following overnight recumbency or during angiotensin II infusion was once considered specific for BAH among patients with PA.[94] [95] However, similar findings are also observed in the angiotensin II-responsive variety of aldosterone-producing adenoma, which accounts for over 50% of aldosterone-producing adenomas in some series.[4] [96] [97] Examination of the aldosterone response to posture in patients with PA is nevertheless worthwhile, as its absence narrows the diagnosis to angiotensin II-unresponsive aldosterone-producing adenoma or FH-I in most cases. Hybrid steroid levels (18-hydroxy- and 18-oxo-cortisol) are elevated in FH-I and angiotensin II-unresponsive aldosterone-producing adenoma, and are useful evidence suggesting one or the other of these two conditions. However, they are not widely available, and because they are normal in both BAH and angiotensin II-responsive aldosterone-producing adenoma, they do not distinguish unilateral from bilateral PA.[89] [96] [97]

For the above reasons, adrenal venous sampling (AVS) is the only dependable way to differentiate bilateral from unilateral PA.[28] [71] [92] [98] [99] Some centres therefore recommend this procedure in all patients with PA (other than those with FH-I).[100] Some guidelines suggest that AVS may be bypassed in patients aged <35 years with unilateral adenoma before proceeding to unilateral adrenalectomy.[10] [28] [41][101]



CT showing lesion in right adrenal gland in patient with right aldosterone-producing adenoma

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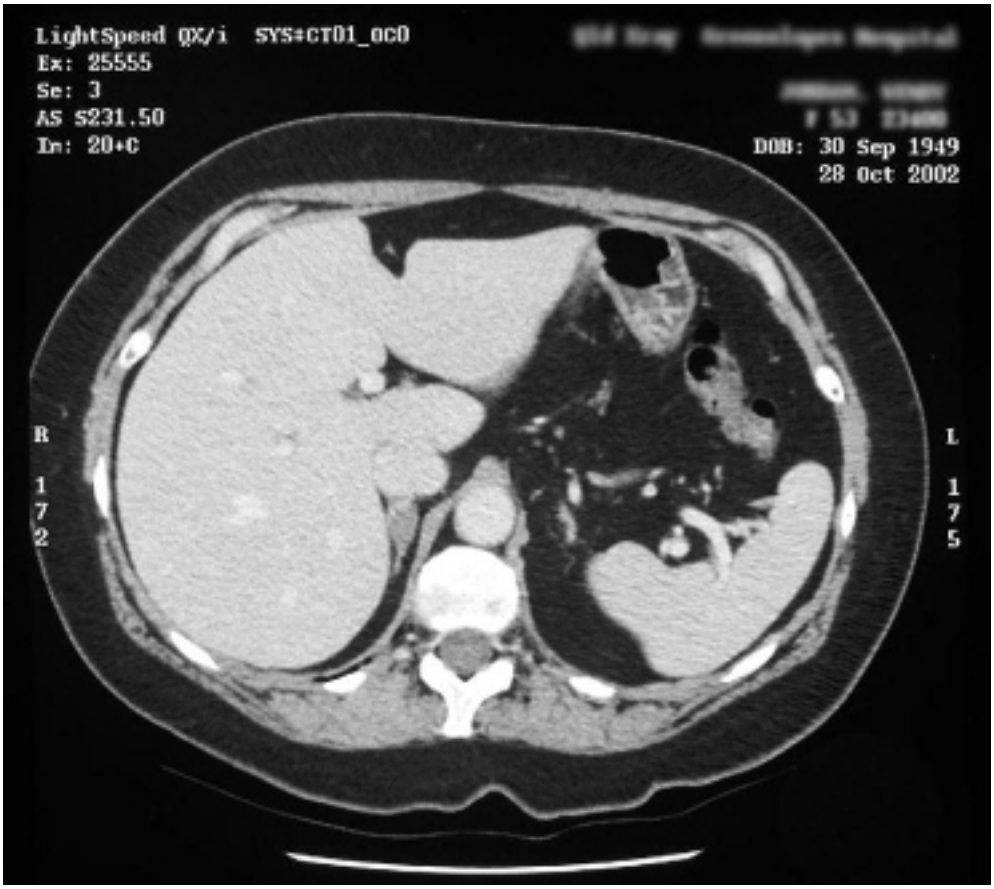

Computed tomography (CT) showing lesion in right adrenal gland in patient with bilateral adrenal hyperplasia

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- Nuclear imaging using positron emission tomography-computed tomography (PET-CT) with labelled metomidate as a ligand of CYP11B1 and CYP11B2 has been proposed to be a viable alternative to AVS, or as an adjunct to AVS in difficult cases.[102] [103] In this protocol dexamethasone pre-treatment is used to suppress adrenocorticotropic hormone and CYP11B1 expression. The short half-life and lack of specificity for CYP11B2 of the currently used isotope limits the widespread application and reliability of this technique, however, work is ongoing to find alternatives.

DIAGNOSIS

History and exam

Key diagnostic factors

hypertension (common)

- Any degree of severity and duration. A family history of hypertension was once thought to make a treatable cause less likely, but now, because of familial hyperaldosteronism type II, it makes PA more likely.
- May be of early onset in familial hyperaldosteronism types I, II, III, and IV.[16] [17][20] [21] [47] [48] [105]

presence of risk factors (uncommon)

- Risk factors include: family history of primary aldosteronism and family history of early onset (e.g., <40 years) hypertension and/or stroke.

Other diagnostic factors

age 20 to 70 years (common)

- Most commonly occurs in adults aged 20 to 70 years, but occasionally diagnosed in children (familial hyperaldosteronism types I, II, III, and IV but rarely other forms) and older adults.[7] [104]

nocturia, polyuria (common)

- Whether or not hypokalaemic.[7]

lethargy (common)

- Whether or not hypokalaemic.

mood disturbance (irritability, anxiety, depression) (common)

- Whether or not hypokalaemic.

difficulty concentrating (common)

- Whether or not hypokalaemic.

paraesthesias, muscle cramps (uncommon)

- If hypokalaemic.[56]

muscle weakness (uncommon)

- If hypokalaemic.[56]

palpitations (uncommon)

- If hypokalaemic.[56]

Risk factors

Strong

family history of PA

- There are at least 4 familial forms of primary aldosteronism (PA). An autosomal dominant pattern of inheritance is seen in familial hyperaldosteronism type I (FH-I), familial hyperaldosteronism type II (FH-II), familial hyperaldosteronism type III (FH-III), and familial hyperaldosteronism type IV (FH-IV).[4] [13] [22] [47] [48]
- FH-I, FH-II, FH-III, and FH-IV all appear to be rare (<1% of PA cases), but FH-I is currently the most commonly reported amongst these entities. The percentage of cases of familial hyperaldosteronism for which the underlying genetic basis has yet to be elucidated is around 6%, but the precise prevalence for each causative mutation will remain uncertain until these are identified, permitting genetic detection of affected individuals.[69]

- The fact that patients with familial hyperaldosteronism of indeterminate genetic origin are clinically indistinguishable from those with apparently sporadic PA (which accounts for 5% to 10% of referred hypertensive patients) raises the possibility that mutations underlying PA in these families may account for a substantial proportion of PA cases in general.[4] [13] [22]

family history of early onset of hypertension and/or stroke

- In familial hyperaldosteronism type I (FH-I), II (FH-II), III (FH-III), and IV (FH-IV), hypertension can be of early onset (e.g., <40 years of age) and in FH-I FH-III may be severe enough to cause early stroke (usually of the haemorrhagic variety).[17] [20] [21][47] [48]
- However, the prevalence of FH-I to IV among patients presenting in this way, and among their relatives, is unknown.

Investigations

1st test to order

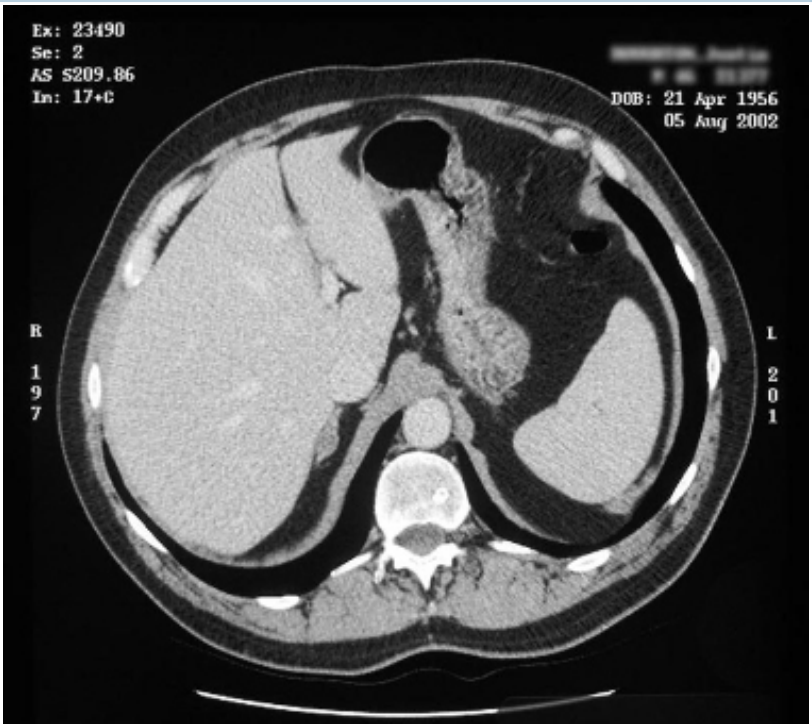
Test	Result
plasma potassium • Plasma potassium is low in approximately 20% of patients with primary aldosteronism.[31] • Precautions must be taken to avoid false elevations of potassium that mask hypokalaemia. The following are recommended:[72] • Avoiding fist clenching and releasing the tourniquet after venipuncture has been achieved. • Waiting for at least 10 seconds before gently withdrawing blood. • Using a syringe and needle rather than a Vacutainer, so that blood can be withdrawn in a slow and careful manner, and then gently discharged down the side of the opened sample tube. • Measuring potassium in plasma rather than serum. • Separating the plasma from the cells within 30 minutes of collection.	**normal or low**
aldosterone/renin ratio • This is the most reliable available screening test.[10] [28] [41][70] • A grey zone exists in ratios between 20 and 35. Some regard a ratio of >20 in combination with a plasma aldosterone concentration of >15 nanograms/dL as a positive screen.[39] This approach, however, will miss some patients with primary aldosteronism (more than one third in one series), including those with aldosterone-producing adenoma (one-fifth) who have lower plasma aldosterone levels.[27] • Diuretics should be ceased for at least 6 weeks and other interfering medicines for at least 2 (and preferably 4) weeks before measuring the ratio, substituting other medicines that have a lesser effect on results, such as verapamil slow-release (plus or minus hydralazine), prazosin, and moxonidine, in order to maintain hypertension control.[6] [71] [72] [85] • Hypokalaemia should be corrected and the patient should be encouraged to follow a liberal salt diet before ratio measurement. • Because of the effects of posture and time of day, sensitivity of the ratio is maximised by collecting blood mid-morning from seated patients who have been upright (sitting, standing, or walking) for 2 to 4 hours.[6] [71] [72] • The ratio should be regarded as a screening test only, and should be measured more than once (serially if conditions of sampling, including medicines, are being altered) before deciding whether to go on to a suppression test to definitively confirm or exclude the diagnosis. • Renin can be measured in terms of its enzymatic activity (plasma renin activity, PRA) or its mass (direct active renin concentration, DAR). PRA gives a better reflection of angiotensin II levels, and is less likely to give misleading results in the face of changes in substrate (angiotensinogen) concentrations (e.g., due to the menstrual cycle or due to treatment with female hormones for contraceptive or postmenopausal hormone replacement purposes).[80] [81] [106] • Automated immunometric assays for measuring DAR have been widely adopted as they are faster and more convenient than PRA. However, considerable work is required to validate and improve these	**ratio is alternatively >70 for aldosterone in picomol/L and direct active renin concentration in mU/L; ratio >20 for plasma aldosterone in nanograms/100 mL (or nanogram/dL) and plasma renin activity in nanograms/mL/hour**

Test	Result
methods to an acceptable standard. In the meantime, PRA remains the preferred approach.	

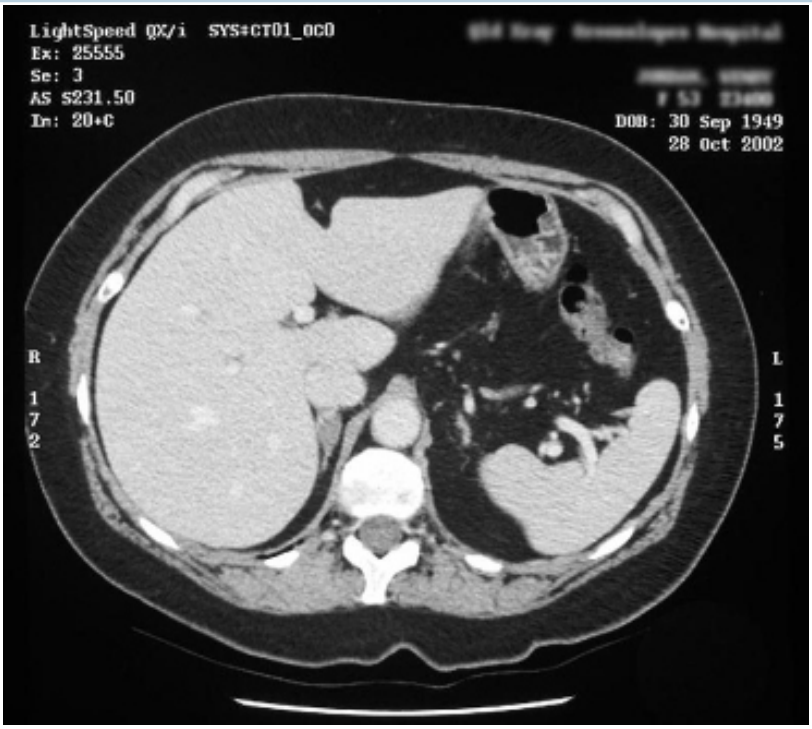
Other tests to consider

Test	Result
oral salt loading test • Patients ingest >200 mmol/day sodium (approximately 6 g/day) for 3 days.[28] Urinary aldosterone (along with urinary sodium) is measured in a 24-hour urine collection beginning at 8 a.m. on the morning of day 3 to the morning of day 4.[28] [86] • Patients should receive adequate slow-release potassium chloride supplementation to maintain plasma potassium in the normal range. • Test may be performed at home, but not in the presence of severe hypertension, hypokalaemia, kidney impairment, or cardiac arrhythmia.[86] There are potential problems related to completeness of urine collection and accuracy and interpretation of urinary aldosterone measurements.[107]	**24-hour urinary aldosterone level >12 micrograms/day makes primary aldosteronism highly likely**
saline infusion testing • Performed in the hospital setting.[86] Two litres of saline is administered intravenously over 4 hours, starting at 8 to 9:30 a.m.[28] • Blood samples for renin and aldosterone (and cortisol and plasma potassium) are drawn at time zero, and at the end of the 4-hour infusion. • Patients should be seated during the 30-minute period before saline infusion, and during the entirety of the infusion.[87] •	**post-infusion plasma aldosterone of >170 pmol/L (>6 ng/dL) confirms primary aldosteronism (provided plasma cortisol concentration is lower than the value obtained basally)**
genetic testing • The genetic defect in familial hyperaldosteronism type I (FH-I) is a 'hybrid gene'.[88] Testing was initially performed in specialised genetic laboratories using a Southern blot.[45] A more rapid long-PCR-based approach is now more widely available.[88] • In patients with early onset primary aldosteronism who test negative for the hybrid gene, consideration should be given for genetic testing for mutations in KCNJ5, CACNA1H, and CLCN2.	**positive for hybrid gene in patients with FH-I**
adrenal CT • Detects almost all aldosterone-producing adrenocortical carcinomas (because of their usual large size), but misses approximately 50% of aldosterone-producing adenomas, and can be misleading by demonstrating non-functioning nodules either in the gland contralateral to one containing an aldosterone-producing adenoma or in a patient with bilateral adrenal hyperplasia.[6] [71] [108] • Important for detecting adrenal lesions that warrant consideration for removal based on their size alone (and hence their malignant potential; e.g., those of at least 2.5 cm). • Useful for localising adrenal veins, which facilitates successful cannulation during subsequent adrenal venous sampling.[6] [98]	**detection of adrenal mass lesion**

Test	Result



Computed tomography (CT) showing lesion in right adrenal gland in patient with right aldosterone-producing adenoma
From the personal collection of Dr Michael Stowasser; used with permission



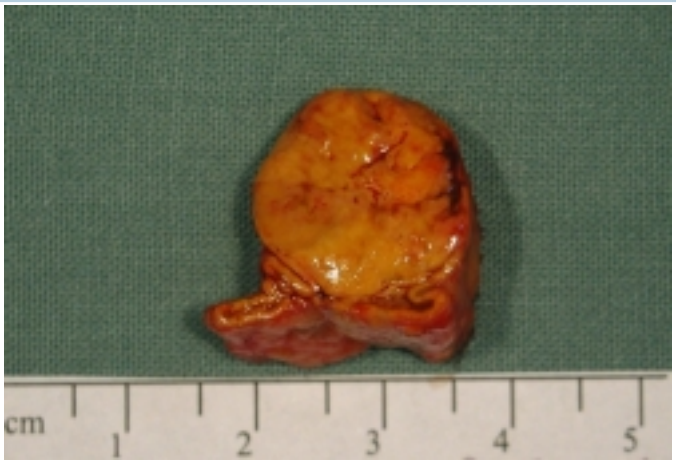
Computed tomography (CT) showing lesion in right adrenal gland in patient with bilateral adrenal hyperplasia
From the personal collection of Dr Michael Stowasser; used with permission

Test	Result
adrenal venous sampling • Adrenal venous sampling (AVS) by an experienced radiologist is recommended when surgical treatment is feasible and desired by the patient to differentiate unilateral from bilateral adrenal disease.[28] [70] Some guidelines suggest that AVS may be bypassed in patients aged <35 years with unilateral adenoma before proceeding to unilateral adrenalectomy.[10] [28][41] • To avoid effects of posture and diurnal variation on steroid levels, sampling should be performed in the morning after overnight recumbency. Stress should be avoided and any venous cannulation should be delayed until the start of the procedure. • An adrenal vein to peripheral vein or low IVC cortisol gradient of at least 3.0 (at least 5.0 if adrenocorticotropic hormone stimulation is used) indicates successful cannulation. Calculation of the aldosterone/cortisol ratio for each adrenal and peripheral (or IVC) venous sample corrects for differences in dilution of adrenal with non-adrenal venous blood and is essential for interpretation. • If the aldosterone/cortisol ratio on one side is significantly higher (>2 times higher) than the simultaneous peripheral venous ratio, with a ratio no higher than peripheral on the other side, the study is considered to show lateralisation, indicating that unilateral adrenalectomy should cure or significantly improve the hypertension. • Aldosterone levels (uncorrected for cortisol) measured on the side of the suppressed, normal gland are always higher than peripheral due to effects of adrenocorticotropic hormone and potassium, and can thereby give the mistaken impression of bilateral adrenal autonomous aldosterone production.[6] [71] [98] [109] • In the uncommon circumstance that a patient with primary aldosteronism is also suspected of having autonomous adrenal cortisol overproduction based on overnight dexamethasone suppression testing, consideration should be given to using metadrenaline (rather than cortisol) to gauge success of adrenal venous cannulation and to correct aldosterone levels for differences in dilution of adrenal venous blood.[110]	**aldosterone production lateralises to one adrenal in unilateral forms (e.g., aldosterone-producing adenoma (APA) or carcinoma, unilateral adrenal hyperplasia); production is bilateral in bilateral forms (usually bilateral adrenal hyperplasia but also bilateral APAs)**

	Left CV	PV	Right CV	PV
Aldosterone (ng%)	968	21.3	1496	21.4
Cortisol (µg%)	183	16.6	1120	16.5
A/C ratio	5.3	1.3	1.3	1.3

Adrenal/peripheral cortisol gradients exceed 3.0 on both sides, confirming adequate sampling of both adrenal veins. Adrenal venous aldosterone/cortisol ratios are significantly higher than peripheral on the left but not the right side, consistent with lateralization of aldosterone production to the left.

Adrenal venous sampling results from patient with left aldosterone-producing adenoma
From the personal collection of Dr Michael Stowasser; used with permission

Test	Result
adrenal MRI • As with CT, can miss smaller aldosterone-producing adenomas and can be misleading by demonstrating non-functioning nodules either in the gland contralateral to one containing an aldosterone-producing adenoma or in a patient with bilateral adrenal hyperplasia.[93] [108]  *Aldosterone-producing adenoma* *From the personal collection of Dr Michael Stowasser; used with permission*	**detection of adrenal mass lesion**
posture stimulation testing • Plasma aldosterone measured at 7 a.m. or 8 a.m. following overnight recumbency and again at 10 a.m. after 2 to 3 hours of upright posture (sitting, standing, or walking).[94] [96] [97]	**plasma aldosterone responsive (rises by at least 50% over basal) in angiotensin II-responsive aldosterone-producing adenoma and in most cases of bilateral adrenal hyperplasia (BAH); unresponsive in angiotensin II-unresponsive aldosterone-producing adenoma, in familial hyperaldosteronism type I, and in some cases of BAH**
angiotensin II infusion testing • Plasma aldosterone is measured basally and 60 minutes after commencement of an intravenous infusion of angiotensin II, given at a rate of 2 nanograms/kg/minute in the early morning following overnight recumbency.[95] [96] [97]	**plasma aldosterone responsive (rises by at least 50% over basal) in angiotensin II-responsive aldosterone-producing adenoma and in most cases of bilateral adrenal hyperplasia (BAH); unresponsive in angiotensin II-unresponsive aldosterone-producing adenoma, in familial hyperaldosteronism type**

Test	Result
	l, and in some cases of BAH
24-hour urinary hybrid steroids (18-hydroxy- and 18-oxo-cortisol) • Measured in specialised laboratories only.[96] [97] [111]	**elevated in angiotensin II-unresponsive aldosterone-producing adenoma and familial hyperaldosteronism type I; normal in bilateral adrenal hyperplasia and in most cases of angiotensin II-responsive aldosterone-producing adenoma**
dexamethasone suppression testing • Measure serum cortisol and adrenocorticotropic hormone (ACTH) at 8 a.m. to 9 a.m. Repeat serum cortisol at 8 a.m. to 9 a.m. the following day after administering dexamethasone at 11 p.m.	**failure of serum cortisol to suppress to <2 micrograms/100 mL, accompanied by a low basal (pre-dexamethasone) ACTH, suggests concomitant autonomous adrenal overproduction of cortisol**

Emerging tests

Test	Result
^{11}C-Metomidate PET/CT • Nuclear imaging using PET-CT with labelled metomidate as a ligand of CYP11B1 and CYP11B2 has been proposed to be a viable alternative to adrenal vein sampling, or as an adjunct to AVS in difficult cases.[102] [103]	**detection of unilateral isotope uptake in patients with aldosterone-producing adenoma**

Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
Essential hypertension (HTN)	• No differentiating signs or symptoms.	• Aldosterone/renin ratio will be normal if performed off interfering medicines. May be elevated if patient receiving medicines (such as beta-blockers) that cause false positives, in which case test should be repeated after such medicines are withdrawn for at least 2 (and preferably 4) weeks. • A normal ratio in a patient receiving medications that can cause false positives makes primary aldosteronism (PA) highly unlikely. • In a minority of cases of PA, there is unprovoked hypokalaemia.
Thiazide-induced hypokalaemia in patient with essential HTN	• History of use of thiazides.	• Aldosterone/renin ratio will be normal after correcting hypokalaemia and withdrawing thiazide for at least 6 weeks.[72]
Renal artery stenosis	• Known renal artery stenosis, history of arterial disease elsewhere, or risk factors for atherosclerosis (e.g., smoking, diabetes mellitus, and hyperlipidaemia).	• Aldosterone/renin ratio will be normal or low.[72] [83] • Imaging studies will demonstrate renal artery stenosis.
Liddle syndrome	• Family history of Liddle syndrome. • Usually presents in childhood.	• Although patients are usually hypokalaemic and have suppressed renin levels, aldosterone levels are also low and the ratio usually is normal.[72] [112]
Syndrome of apparent mineralocorticoid excess	• Family history of this syndrome. Hereditary form usually presents in childhood. • History of excessive consumption of liquorice, which can lead to an acquired form.	• Although patients are usually hypokalaemic and have suppressed renin levels, aldosterone levels are also low and the ratio usually is normal. Urinary free cortisol/cortisone ratio is elevated.[72] [112]

Condition	Differentiating signs / symptoms	Differentiating tests
Hypertensive forms of congenital adrenal hyperplasia	• Family history of congenital adrenal hyperplasia due to 11beta-hydroxylase or 17alpha-hydroxylase deficiency. • Usually presents in childhood. • History of either virilisation (in the case of 11beta-hydroxylase deficiency) or feminisation (in the case of 17alpha-hydroxylase deficiency).	• Although patients are usually hypokalaemic and have suppressed renin levels, aldosterone levels are also low and the aldosterone/renin ratio usually is normal. • In 11beta-hydroxylase deficiency, plasma cortisol and corticosterone are low, whereas basal or adrenocorticotropic hormone-stimulated levels of deoxycorticosterone and 11-deoxycortisol are elevated. • In 17alpha-hydroxylase deficiency, plasma levels of 17alpha-hydroxyprogesterone, 11-deoxycortisol, and cortisol are reduced, whereas gonadotrophins (LH and FSH) are increased.[72] [112]
Primary glucocorticoid resistance	• Family history of this syndrome (but can be acquired). • May be associated with androgenisation.	• Although patients are usually hypokalaemic and have suppressed renin levels, aldosterone levels are also low and the aldosterone/renin ratio usually is normal. • Associated with increased adrenocorticotropic hormone and cortisol levels, and resistance of cortisol to adrenal suppression by dexamethasone, in the absence of clinical stigmata of Cushing syndrome.[72] [112]
Ectopic adrenocorticotropic hormone syndrome	• Clinical findings of underlying tumour. • Clinical findings due to raised cortisol levels (Cushing syndrome) including ecchymoses, muscle weakness, and diabetes mellitus.	• Although patients are usually hypokalaemic and have suppressed renin levels, aldosterone levels are also low and the aldosterone/renin ratio usually is normal. • Evidence of underlying tumour on imaging studies. • Cortisol and adrenocorticotropic hormone levels elevated and non-suppressible with high-dose dexamethasone.[72] [112]

Condition	Differentiating signs / symptoms	Differentiating tests
Activating mutations of the mineralocorticoid receptor	• Family history of this syndrome. • Exacerbation of HTN and development of hypokalaemia during pregnancy.	• Although patients are usually hypokalaemic and have suppressed renin levels, aldosterone levels are also low and the aldosterone/renin ratio usually is normal.[72] [112]
Familial hyperkalaemic hypertension (pseudohypoaldosteronism type II, Gordon syndrome)	• Family history of this syndrome but can be due to de novo mutations.	• Although renin levels are usually suppressed and aldosterone/renin ratio is often elevated, plasma potassium levels are elevated.[72] [112]

Screening

Screening for PA in people with hypertension

primary aldosteronism (PA) is the most common specifically treatable and potentially curable form of hypertension. It accounts for at least 5% of hypertensive patients, with most patients being normokalaemic. Optimal detection involves screening all hypertensive patients using the plasma aldosterone/renin ratio, after controlling for factors (including medicines) that may confound results. See Diagnostic approach .

Familial hyperaldosteronism type I (FH-I)

Screening should be offered to relatives (whether hypertensive or normotensive) of patients found to have FH-I because:[22] [89]

- FH-I progresses through an asymptomatic (including normotensive) phase
- The implications of missing the diagnosis of this condition (which can lead to severe, resistant hypertension and early death from hypertensive stroke) are considerable.

This is most effectively accomplished by genetic testing of peripheral blood DNA for the presence of the causative hybrid gene.[22] [89] Being a dominantly inherited condition, family screening can lead to the detection of large numbers of affected individuals who would then be candidates for close clinical monitoring and more timely commencement of highly effective, specific medical treatment.[22] [89]

Familial hyperaldosteronism type II (FH-II)

Screening should be offered to hypertensive relatives of patients with FH-II, and especially to those known to have developed hypertension before the age of 18 years. This can be accomplished by direct sequencing of peripheral blood DNA for the presence of the CLCN2 mutation found to be present in the proband. Early detection facilitates early institution of effective, specific treatment with medicines that antagonise aldosterone action.[17] [113]

Familial hyperaldosteronism type III (FH-III)

Screening should be offered to hypertensive relatives of patients with FH-III, and especially to those known to have developed hypertension before the age of 18 years. This can be accomplished by direct sequencing of peripheral blood DNA for the presence of the KCNJ5 mutation found to be present in the proband. Early detection facilitates early institution of effective, specific treatment (either aldosterone antagonist medicines, or, for those with severe forms, bilateral adrenalectomy).[16] [47]

Familial hyperaldosteronism type IV (FH-IV)

Screening should be offered to hypertensive relatives of patients with FH-IV, and especially to those known to have developed hypertension before the age of 18 years. This can be accomplished by direct sequencing of peripheral blood DNA for the presence of the CACNA1H mutation found to be present in the proband. Early detection facilitates early institution of effective, specific treatment (either aldosterone antagonist medicines, or, for selected patients severe refractory disease, bilateral adrenalectomy).[37]

Familial hyperaldosteronism of unknown genetic aetiology

Screening should be offered to hypertensive relatives of patients with familial PA of unknown genetic aetiology because PA in more than one member of a family is not uncommon. As no genetic test is available, this is best done by aldosterone/renin ratio testing, performed according to the guidelines described in detail in the Diagnostic Approach section, and, if negative, repeated at least once after a gap of at least a year, or if plasma potassium falls or hypertension develops.

Approach

Treatment decisions should not only take into account the results of adrenal venous sampling (AVS) and other diagnostic procedures, but should also be tailored to the particular characteristics and wishes of the individual patient.[6] [7] [10][28] Surgical treatment may therefore be inappropriate for some patients who lateralise on AVS, for example due to comorbidities, and, conversely, may be a reasonable option in rare patients with bilateral disease who do not, for example, tolerate medical treatment.

Careful discussion with the patient (and family, if appropriate) is a critical component of treatment. All management options and their possible outcomes should be fully explored and explained before a treatment is chosen.

Surgical treatment of PA

Approximately 30% of patients with primary aldosteronism (PA) who undergo AVS demonstrate clear lateralisation, with definite aldosterone production by one adrenal and contralateral suppression of the other.[6] [7] These patients are candidates for unilateral adrenalectomy, which results in cure of hypertension in 50% to 60%, and significant improvement in the remainder.[70][114] [115] [116] Less than 20% of patients require equivalent or increased medicine doses after surgery.[101] In order to obtain optimal results from surgery, an essential prerequisite is to have performed suppression testing and successful AVS, that is, all appropriate criteria have been met. Importantly, cure or improvement is universally seen regardless of whether patients are hypokalaemic or normokalaemic preoperatively.[105] Laparoscopic surgery enables a faster recovery and fewer complications than the open approach.[117] These may include haemorrhage, wound infection, wound hernia, and DVT/pulmonary embolism, but incidence rates are low.[117]

Surgery almost invariably results in correction of hypokalaemia if present preoperatively, and patients consistently report a marked improvement in quality of life.[114] [115] [116]

Almost always, the entire adrenal is removed even when an apparent adenoma is seen on CT scanning or on visualisation of the gland. This is because AVS as currently performed indicates only which adrenal is at fault, and cannot establish whether the visualised nodule is actually an aldosterone-producing adenoma. For example, it could be a non-secreting nodule that happens to be situated in the same gland as a smaller, non-visualised, hyper-functioning one. A possible exception can be made in the patient who presents with a recurrence of PA associated with a definite nodule on CT in the remaining adrenal some years after unilateral adrenalectomy for aldosterone-producing adenoma. In this situation, an option is to remove the nodule and preserve the residual adrenal tissue, provided it appears morphologically normal and the blood supply can be preserved.[118] This may avoid the need for replacement steroid therapy, but the patient should be warned that steroid cover may be required for any future operation or emergency, especially if the remnant is small. This approach also carries the risk of permitting a further recurrence of PA.

Immediately before surgery, potassium supplementation should be withdrawn, aldosterone antagonists discontinued, and other antihypertensive therapy reduced, if appropriate.

Particularly in patients with lateralising PA whose hypertension has been severe and/or long-standing and has caused significant hypertensive heart disease, preoperative treatment with an aldosterone antagonist over a period of several months will usually improve cardiovascular function and general condition by optimising hypertension control, repleting body potassium stores and antagonising other adverse effects

of aldosterone excess, which will reduce operative risk.[6] [7] Furthermore, the perioperative period and the postoperative recovery are smoother, with postoperative hypoaldosteronism (with hyperkalaemia) due to continuing renin suppression being avoided. It could be argued that this approach would benefit all patients coming to unilateral adrenalectomy for PA.

In the uncommon circumstance that a patient with unilateral PA is suspected of having concomitant autonomous adrenal overproduction of cortisol, the need for steroid cover peri-operatively and for a variable period following surgery should be anticipated.

In patients with bilateral forms of PA, rarely it may be appropriate to consider and carefully discuss with the patient the option of unilateral adrenalectomy. For example, both spironolactone and, less commonly, amiloride have sometimes been tolerated poorly even at low doses, or the dose of spironolactone required to control hypertension has produced adverse effects such as painful gynaecomastia in males, and mastalgia and menstrual disturbance in females. The appropriate action in this situation is to remove the gland that has the higher aldosterone/cortisol ratio on AVS, or if both are equally affected, the larger gland, which greatly reduces the dosage of aldosterone-blocking drug required for control.

If bilateral adrenal hyperplasia is disclosed by AVS but one adrenal contains a mass 2.5 cm or larger (some centres use higher cutoffs of 3.0 cm or even 4.0 cm), the surgical option should also be considered and discussed because of the risk of developing a malignancy.[6]

For rare patients with marked, bilateral adrenal hyperplasia and severe, bilateral PA (including those with severe forms of FH-III), bilateral adrenalectomy (often in 2 stages, to gauge the effect of unilateral adrenalectomy first) may be required to control hypertension and biochemical manifestations of PA.[16] [47]

Successful removal of an aldosterone-producing adenoma during pregnancy has been rarely reported.[119] Although case reports suggest the optimal time for surgery is during the middle trimester, it is clearly preferable when possible to postpone surgery in patients found to have an aldosterone-producing adenoma during pregnancy until after delivery. This, however, raises the question of possible adverse effects of aldosterone-blocking drugs on the fetus. Fortunately, most or all of the adverse effects of aldosterone excess on the mother can disappear during pregnancy, only to reappear postnatally.[77] This is thought to be due to very high placentally derived progesterone levels blocking aldosterone action.

Postoperative treatment

Perioperative and postoperative fluids should be given as normal saline 1 litre every 12 hours or 8 hours. All potassium replacement is withheld during the operation and in the first 24 hours postoperatively. Potassium-sparing diuretics (such as spironolactone, eplerenone, and amiloride) should be withheld peri-operatively. Other antihypertensives can generally be withheld while the situation is assessed and only reintroduced if required. Sometimes, especially in young females, no further antihypertensives are required after surgery, but more usually a gradual withdrawal of antihypertensive medications is possible over the ensuing 3 to 12 months.[6]

Due to chronic suppression of renin-aldosterone and hence of aldosterone production by the contralateral adrenal, there is a significant risk of hyperkalaemia once the overproducing adrenal has been removed. Hypokalaemia observed in the immediate postoperative period is mainly due to the cessation of potassium supplements and/or aldosterone antagonists immediately preoperatively, plus the perioperative and postoperative administration of normal saline or other potassium-free fluids intravenously. However, this is often transient and is improved or corrected once the patient starts eating. Plasma potassium levels

should therefore be monitored at least twice daily for the first 2 days following unilateral adrenalectomy for aldosterone-producing adenoma, and at least daily thereafter for another 3 days. Patients who have been treated for several months preoperatively with aldosterone antagonist agents such as spironolactone or amiloride usually demonstrate a smoother perioperative course, with BP levels that are easier to control and a lower likelihood of developing either hypokalaemia or hyperkalaemia once medicines are withdrawn postoperatively.

Postoperative testing (at 1-3 months) may be considered to assess for persisting autonomous aldosterone production by the remaining adrenal. In one centre, all patients lateralising preoperatively on AVS showed either biochemical cure of PA (70%) or significant improvement (30%) on postoperative fludrocortisone suppression testing.[105] [115] Patients with residual hypertension and remaining unsuppressible aldosterone production demonstrate excellent responses to small doses of amiloride or spironolactone.

Twenty percent of patients diagnosed with unilateral PA preoperatively show evidence of ongoing PA after surgery. If residual hypertension is due to aldosterone excess, it may respond well to aldosterone antagonist medication, but, because aldosterone levels have been reduced by surgery, caution is required. As BP may continue to fall for months after surgery, especially in males, commencement of this or non-specific medication is often deferred for several weeks after surgery.

Medical treatment of PA

Treatment with drugs that block aldosterone action is indicated in patients:[28] [70]

- with PA who do not lateralise aldosterone production to one side;
- who lateralise but prefer medical to surgical treatment, or
- who are not candidates for surgery.

Spironolactone has a steroidal structure and competitively inhibits aldosterone at its receptor. Amiloride acts directly on the epithelial sodium channel where aldosterone exerts its effects.

Treatment with aldosterone antagonists usually brings about a relatively slow-onset marked improvement in hypertension control and corrects hypokalaemia easily and swiftly in all but the severest cases of PA.[27] [105] [120] [121] Potassium supplements should therefore be ceased or serially reduced based on plasma potassium measurements when these drugs are commenced. There is also evidence that spironolactone is able to ameliorate non-BP-dependent adverse cardiovascular and renal effects of aldosterone excess.[58] [61] [122] [123] [124] Whether similar benefits are associated with amiloride treatment remains uncertain.

The BP responses to medical treatment, however, are generally not as complete as those in lateralising patients who undergo unilateral adrenalectomy, and improvements in quality of life are significant, but less striking.[105]

In most patients, only modest doses of spironolactone or amiloride are required for optimal therapeutic effect.[6] [7] Occasionally, with florid cases, spironolactone at higher doses may be necessary, but dose-dependent adverse effects are then much more likely. Even at lower doses, adverse pro-oestrogen effects by blocking androgen receptors (e.g., gynaecomastia and reduced libido, menstrual irregularities, and aggravation of breast fibrocystic change) occur in approximately 10% of patients taking spironolactone.[105] [121] Side-effects from amiloride are rare. Eplerenone, a more selective aldosterone antagonist, appears to be relatively free of these adverse effects and has been shown to be effective as an antihypertensive agent in essential hypertension and to reduce morbidity and mortality in patients with heart failure post-MI.[125] [126] While one study has shown eplerenone to be at least as effective

in controlling hypertension as spironolactone in patients with PA, another has reported a lesser degree of efficacy.[127] [128] At present, recognised indications for use in different countries vary and in some countries it is not approved for government-subsidised use in PA. Its use is then relatively expensive, and in Australia many patients decline to use it on a long-term basis. This will presumably change when its patent expires. It has been suggested that eplerenone be given to all hypertensive patients as an alternative to screening for PA.[129] [130] However, this opinion is not based on experience treating PA patients, and should not be seriously considered.

Eplerenone can be used in patients in whom spironolactone is poorly tolerated and where amiloride is unable to achieve sufficient aldosterone blockade. As there can be causes other than aldosterone excess contributing to failure of complete response of blood pressure to aldosterone blockade, an indicator of adequacy of blockade is required. Provided that there are no medicines in use that influence the aldosterone-renin ratio, and that the assays are sound, the normality of the ratio, which depends on renin becoming unsuppressed, is the best guide to whether or not adequate blockade of aldosterone is being achieved.

Since over-treatment with these anti-aldosterone agents can cause volume contraction with pre-renal failure, elevated creatinine levels, and life-threatening hyperkalaemia, their use should always be accompanied by regular close monitoring of potassium levels. Aldosterone antagonists must be used with great caution in patients with any reduction in renal glomerular function, because of the increased potential for hyperkalaemia. In such patients, concurrent administration of a potassium-wasting diuretic in low dosage can be helpful to avoid hyperkalaemia, but potassium and creatinine levels should still be carefully monitored.

Amiloride, spironolactone, and eplerenone have a slow onset of antihypertensive action. Patience is therefore essential. Reduction in blood pressure after their commencement or increase in dose may not be apparent for 2 weeks. It takes much longer, even months, before their full effect is seen. If necessary, other antihypertensive agents with more rapid onset of action could be employed during this period, and then later reduced or withdrawn.

Treatment for familial hyperaldosteronism type I

In familial hyperaldosteronism type I (FH-I), hypertension is readily controlled by giving glucocorticoids in low doses.[131] [132] The hybrid gene that causes excessive aldosterone production is regulated tightly by adrenocorticotrophic hormone (ACTH). By suppressing ACTH and hybrid gene expression, glucocorticoids rapidly and effectively ameliorate hypertension.[13] [22][44] [45][131]

Complete suppression of ACTH-regulated aldosterone production is not usually necessary and raises the risk of Cushingoid adverse effects.[132] A reasonable approach is to use the lowest dose of glucocorticoid treatment required to maintain normotension (as assessed by clinic, home, and ambulatory BP monitoring) and by periodic (e.g., yearly) echocardiographic assessments of left ventricular mass index and diastolic function. Patients on long-term glucocorticoids should be monitored for the development of glucocorticoid-induced osteoporosis by dual energy-ray absorptiometry (DXA) performed every 1 to 2 years (and in children for slowing of height advancement). Because of the known adverse effects of aldosterone which are independent of BP, it remains uncertain whether avoidance of left ventricular hypertrophy, impaired diastolic function, and proteinuria during treatment with glucocorticoids is sufficient to guarantee optimal treatment of FH-I in comparison with aldosterone blockade.

Spironolactone, eplerenone, and amiloride are alternative treatments to glucocorticoids. Amiloride may be the preferred option when treating affected children, because it avoids the potential impairment of growth

associated with the use of glucocorticoids, and the potential adverse effects resulting from blockade of sex steroid receptors by spironolactone. A similar argument could be raised for using eplerenone in children with FH-I, but data on its safety and efficacy in this situation are lacking.

For pregnant patients, low-dose glucocorticoids have been used successfully to control hypertension. Prednisolone and hydrocortisone are thought to be preferable to dexamethasone, as the latter is incompletely metabolised by placental 11beta-hydroxysteroid dehydrogenase and is readily transferred to the fetus. Alternatives to glucocorticoids are any of the recognised pregnancy-safe antihypertensives.

Family screening by genetic testing should always be undertaken to identify affected relatives as early as possible in their lives in order to avoid unnecessary morbidity.[13] [20]

Treatment for other types of familial hyperaldosteronism

To date, no targeted treatment is available for patients with FH-II, FH-III, or FH-IV; however, some therapeutic possibilities are emerging.[133]Treatment for FH-II and FH-IV follows similar guidelines to that for apparently sporadic bilateral PA.[37] [134]

In families with FH-III, some KCNJ5 mutations cause severe, bilateral PA requiring, bilateral adrenalectomy may be required to control hypertension and other manifestations.[14] [37] [134] For patients with mutations causing milder disease, treatment with medicines which antagonise aldosterone action (spironolactone, eplerenone, or amiloride) following similar guidelines to that for apparently sporadic bilateral PA, may be sufficient.

Treatment algorithm overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Ongoing (summary)			
unilateral PA			
	surgical candidates	**1st**	**unilateral laparoscopic adrenalectomy**
		adjunct	**preoperative aldosterone antagonists**
		adjunct	**postoperative aldosterone antagonists**
	non-surgical candidates	**1st**	**aldosterone antagonists**
bilateral PA (excluding familial hyperaldosteronism type I)			
	no adrenal lesion ≥2.5 cm	**1st**	**aldosterone antagonists**
		2nd	**laparoscopic adrenalectomy**
		plus	**pre- and postoperative aldosterone antagonists**
	adrenal lesion ≥2.5 cm	**1st**	**unilateral laparoscopic adrenalectomy**
		plus	**pre- and postoperative aldosterone antagonists**
familial hyperaldosteronism type I			
	adults	**1st**	**glucocorticoids**
		2nd	**aldosterone antagonists**
	children (pre- and peri-pubertal)	**1st**	**amiloride**
		2nd	**eplerenone**

Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Ongoing

unilateral PA

surgical candidates

1st **unilateral laparoscopic adrenalectomy**

» Unilateral adrenalectomy in carefully selected patients after a full work-up provides a high chance of biochemical cure of primary aldosteronism (PA; 70% cured and 100% improved), including cure of hypokalaemia in all patients in whom it was present preoperatively.[105] [114] [115] [116] Hypertension is cured in 50% to 60% of fully worked-up patients, and improved in all remaining patients.[114] [115] [116] Less than 20% of patients require equivalent or increased medicine doses after surgery.[101]

» Almost always, the entire adrenal is removed - even when an apparent adenoma is seen on CT scanning or on visualisation of the gland.

» Laparoscopic adrenalectomy is associated with shorter hospital stays and fewer complications.[117]

» Immediately before surgery, potassium supplementation should be withdrawn, aldosterone antagonists discontinued, and other antihypertensive therapy reduced, if appropriate.

» Postoperative intravenous fluids should be given as normal saline without potassium chloride. A generous sodium diet should be recommended to avoid the hyperkalaemia due to chronic contralateral adrenal gland suppression.[6] In rare instances, temporary fludrocortisone therapy may be required.

» Successful removal of an aldosterone-producing adenoma during pregnancy has been rarely reported.[119] Although case reports suggest the optimal time for surgery is during the middle trimester, it is clearly preferable when possible to postpone surgery in patients found to have an aldosterone-producing adenoma during pregnancy until after delivery.

adjunct **preoperative aldosterone antagonists**

Treatment recommended for SOME patients in selected patient group

Ongoing

Primary options

» spironolactone: 12.5 to 50 mg orally once daily or in 2 divided doses, higher doses have been reported, maximum 200 mg/day

Secondary options

» amiloride: 2.5 to 15 mg orally once daily or in 2 divided doses, higher doses have been reported, maximum 40 mg/day

OR

» eplerenone: 25 to 100 mg orally once daily or in 2 divided doses, maximum 100 mg/day

» For surgical candidates with severe hypertension and left ventricular hypertrophy (LVH) pre-surgery, spironolactone is the drug of first choice, with amiloride or eplerenone (in countries where available as a subsidised treatment for primary aldosteronism) reserved mainly for those who develop sex-steroid-related adverse effects.

» Over-treatment can cause volume contraction with pre-renal failure, raising creatinine levels and causing life-threatening hyperkalaemia.

» In patients with reduced renal glomerular function, concurrent administration of a low-dose potassium-wasting diuretic can be helpful to avoid hyperkalaemia, but potassium and creatinine levels should still be carefully monitored.[6]

» Hyperkalaemia is more likely in patients who have renal dysfunction or are taking other potassium-retaining agents such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin-II receptor antagonists, or non-steroidal anti-inflammatory drugs (NSAIDs).

» Spironolactone can be associated with sex-steroid-related adverse effects, including gynaecomastia and loss of libido, menstrual irregularities, and aggravation of breast fibrocystic change.[121] The incidence is dose-related. At 12.5 to 50 mg daily, the incidence of gynaecomastia is approximately 10% to 15%.[105] [122]

adjunct **postoperative aldosterone antagonists**

Treatment recommended for SOME patients in selected patient group

Ongoing

non-surgical candidates — **1st** — **aldosterone antagonists**

Primary options

» amiloride: 2.5 to 10 mg orally once daily or in 2 divided doses

OR

» spironolactone: 12.5 to 25 mg orally once daily or in 2 divided doses

OR

» eplerenone: 25 to 50 mg orally once daily or in 2 divided doses

» Twenty percent of patients diagnosed with unilateral primary aldosteronism (PA) preoperatively show evidence of ongoing PA after surgery. If residual hypertension is due to aldosterone excess, it may respond well to aldosterone antagonist medication, but, as aldosterone levels have been reduced by surgery, caution is required.

» Eplerenone (in countries where available as a subsidised treatment for PA) is another option for patients in whom spironolactone is poorly tolerated and where amiloride is unable to achieve sufficient aldosterone blockade. Normality of the ratio, which depends on renin becoming unsuppressed, is the best guide to whether or not adequate blockade of aldosterone is being achieved.

» The lowest recommended dose should usually be used at introduction.

» Over-treatment can cause volume contraction with pre-renal failure, raising creatinine levels and causing life-threatening hyperkalaemia.

» In patients with reduced renal glomerular function, concurrent administration of a potassium-wasting diuretic in low dosage can be helpful to avoid hyperkalaemia, but potassium and creatinine levels should still be carefully monitored.[6]

» Hyperkalaemia is more likely in patients who have renal dysfunction or are taking other potassium-retaining agents such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin-II receptor antagonists, or non-steroidal anti-inflammatory drugs (NSAIDs).

Ongoing

Primary options

» amiloride: 2.5 to 15 mg orally once daily or in 2 divided doses, higher doses have been reported, maximum 40 mg/day

OR

» spironolactone: 12.5 to 50 mg orally once daily or in 2 divided doses, higher doses have been reported, maximum 200 mg/day

OR

» eplerenone: 25 to 100 mg orally once daily or in 2 divided doses, maximum 100 mg/day

» Indicated in patients with unilateral primary aldosteronism (PA) who prefer medical treatment or are unfit for surgery.[28][70]

» Because of its less potent aldosterone antagonist action and its much lower propensity to induce adverse effects, amiloride may be the drug of first choice in many patients, particularly those with milder degrees of hypertension, biochemical disturbance, and target organ effects (e.g., echocardiographically demonstrated LVH).

» Side-effects from amiloride are rare. Spironolactone can be associated with sex-steroid-related adverse effects, including gynaecomastia and loss of libido, menstrual irregularities, and aggravation of breast fibrocystic change.[121] The incidence is dose-related. At 12.5 to 50 mg daily, the incidence of gynaecomastia is approximately 10% to 15%.[105] [122]

» Amiloride and spironolactone can also be used in combination to minimise the dose of spironolactone and the risk of sex-steroid-related adverse effects.

» Eplerenone (in countries where available as a subsidised treatment for PA) is another option for patients in whom spironolactone is poorly tolerated and where amiloride is unable to achieve sufficient aldosterone blockade. Normality of the ratio, which depends on renin becoming unsuppressed, is the best guide to whether or not adequate blockade of aldosterone is being achieved.

» Over-treatment can cause volume contraction with pre-renal failure, rising creatinine levels,

Ongoing

and life-threatening hyperkalaemia. In patients with reduced renal glomerular function, concurrent administration of a potassium-wasting diuretic in low dosage can be helpful to avoid hyperkalaemia, but potassium and creatinine levels should still be carefully monitored.[6]

» Hyperkalaemia is more likely in patients who have renal dysfunction or are taking other potassium-retaining agents such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin-II receptor antagonists, or non-steroidal anti-inflammatory drugs (NSAIDs).

» Amiloride, spironolactone, and eplerenone have a slow onset of antihypertensive action. Benefit may not be apparent for 2 weeks, even months. If necessary, other antihypertensive agents with more rapid onset of action could be employed during this period, and then later reduced or withdrawn.

bilateral PA (excluding familial hyperaldosteronism type I)

no adrenal lesion ≥2.5 cm — **1st** — **aldosterone antagonists**

Primary options

» amiloride: 2.5 to 15 mg orally once daily or in 2 divided doses, higher doses have been reported, maximum 40 mg/day

OR

» spironolactone: 12.5 to 50 mg orally once daily or in 2 divided doses, higher doses have been reported, maximum 200 mg/day

OR

» eplerenone: 25 to 100 mg orally once daily or in 2 divided doses, maximum 100 mg/day

» Lesions ≥2.5 cm should be considered for removal based on their malignant potential. Some centres use higher cutoffs of 3.0 cm or even 4.0 cm, but this increases the risk of missing a malignant lesion. CT should be repeated in 3 to 6 months and then annually to recognise growth which would suggest malignancy.

» Because of its less potent aldosterone antagonist action and its much lower propensity to induce adverse effects, amiloride may be the drug of first choice in many patients,

Ongoing

particularly those with milder degrees of hypertension, biochemical disturbance, and target organ effects (e.g., echocardiographically demonstrated LVH).

» Side-effects from amiloride are rare. Spironolactone can be associated with sex-steroid-related adverse effects, including gynaecomastia and loss of libido, menstrual irregularities, and aggravation of breast fibrocystic change.[121] The incidence is dose-related. At 12.5 to 50 mg daily, the incidence of gynaecomastia is approximately 10% to 15%.[105] [122]

» Amiloride and spironolactone can also be used in combination to minimise the dose of spironolactone and the risk of sex-steroid-related adverse effects.

» Eplerenone (in countries where available as a subsidised treatment for primary aldosteronism [PA]) is another option for patients in whom spironolactone is poorly tolerated and where amiloride is unable to achieve sufficient aldosterone blockade. Normality of the ratio, which depends on renin becoming unsuppressed, is the best guide to whether or not adequate blockade of aldosterone is being achieved.

» Over-treatment can cause volume contraction with pre-renal failure, raising creatinine levels and causing life-threatening hyperkalaemia. In patients with reduced renal glomerular function, concurrent administration of a potassium-wasting diuretic in low dosage can be helpful to avoid hyperkalaemia, but potassium and creatinine levels should still be carefully monitored.[6]

» Hyperkalaemia is more likely in patients who have renal dysfunction or are taking other potassium-retaining agents such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin-II receptor antagonists, or non-steroidal anti-inflammatory drugs (NSAIDs).

» Amiloride, spironolactone, and eplerenone have a slow onset of antihypertensive action. Benefit may not be apparent for two weeks, even months. If necessary, other antihypertensive agents with more rapid onset of action could be employed during this period, and then later reduced or withdrawn.

2nd **laparoscopic adrenalectomy**

» It is sometimes appropriate to consider the option of unilateral adrenalectomy in patients

Ongoing

with bilateral forms of primary aldosteronism (PA) because both spironolactone and amiloride have been tolerated poorly even at low doses, or the dose of spironolactone required to control hypertension has produced adverse effects.

» For rare patients with marked, bilateral adrenal hyperplasia and severe, bilateral PA (including those with severe forms of familial hyperaldosteronism type III), bilateral adrenalectomy (often in 2 stages, to gauge the effect of unilateral adrenalectomy first) may be required to control hypertension and biochemical manifestations of PA.[16] [47]

» The aim of adrenalectomy is to reduce the mass of adrenal tissue that is excessively and autonomously producing aldosterone, and thereby bring about improvements in BP levels and marked reductions in the doses of aldosterone antagonist medicines required to control hypertension. BP responses under these circumstances are much less predictable than in patients with unilateral PA.

» Laparoscopic adrenalectomy is associated with shorter hospital stays and fewer complications.[117]

» Immediately before surgery, potassium supplementation should be withdrawn, aldosterone antagonists temporarily discontinued, and other antihypertensive therapy reduced, if appropriate.

» Postoperative intravenous fluids should be given as normal saline without potassium chloride. A generous sodium diet should be recommended to avoid the hyperkalaemia due to chronic contralateral adrenal gland suppression.[6] In rare instances, temporary fludrocortisone therapy may be required. Plasma potassium levels should be monitored at least twice daily for the first 2 days.

» Successful removal of an aldosterone-producing adenoma during pregnancy has been rarely reported.[119] Although case reports suggest that the optimal time for surgery is during the middle trimester, it is clearly preferable to postpone surgery in patients with PA during pregnancy until after delivery where possible.

plus **pre- and postoperative aldosterone antagonists**

Treatment recommended for ALL patients in selected patient group

MANAGEMENT

Ongoing

Primary options

» amiloride: 2.5 to 15 mg orally once daily or in 2 divided doses, higher doses have been reported, maximum 40 mg/day

OR

» spironolactone: 12.5 to 50 mg orally once daily or in 2 divided doses, higher doses have been reported, maximum 200 mg/day

OR

» eplerenone: 25 to 100 mg orally once daily or in 2 divided doses, maximum 100 mg/day

» It is highly desirable that hypertension and hypokalaemia be controlled preoperatively. This usually involves treatment with an aldosterone antagonist. If not tolerated, other antihypertensive agents can be used.

» Recommencement of aldosterone antagonist medicine postoperatively can usually be deferred for several weeks. The lowest recommended dose should be used initially, and electrolyte and renal function carefully monitored.

» Over-treatment can cause volume contraction with pre-renal failure, raising creatinine levels and causing life-threatening hyperkalaemia. In patients with reduced renal glomerular function, concurrent administration of a potassium-wasting diuretic in low dosage can be helpful to avoid hyperkalaemia.[6]

» Hyperkalaemia is more likely in patients who have renal dysfunction or are taking other potassium-retaining agents such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin-II receptor antagonists, or non-steroidal anti-inflammatory drugs (NSAIDs).

» Spironolactone can be associated with sex-steroid-related adverse effects, including gynaecomastia and loss of libido, menstrual irregularities, and aggravation of breast fibrocystic change.[121] The incidence is dose-related. At 12.5 to 50 mg daily, the incidence of gynaecomastia is approximately 10% to 15%.[105] [122]

» Eplerenone (in countries where available as a subsidised treatment for primary aldosteronism) is another option for patients in whom spironolactone is poorly tolerated

Ongoing

and where amiloride is unable to achieve sufficient aldosterone blockade. Normality of the ratio, which depends on renin becoming unsuppressed, is the best guide to whether or not adequate blockade of aldosterone is being achieved.

adrenal lesion ≥2.5 cm — **1st** — **unilateral laparoscopic adrenalectomy**

» Lesions of this size should be considered for removal based on their malignant potential. Some centres use higher cutoffs of 3.0 cm or even 4.0 cm, but this increases the risk of missing a malignant lesion.

» Laparoscopic adrenalectomy is associated with shorter hospital stays and fewer complications.[117] Open adrenalectomy may be required, however, in the case of very large lesions.

» Immediately before surgery, potassium supplementation should be withdrawn, aldosterone antagonists discontinued, and other antihypertensive therapy reduced, if appropriate.

» Postoperative intravenous fluids should be given as normal saline without potassium chloride. A generous sodium diet should be recommended to avoid the hyperkalaemia due to chronic contralateral adrenal gland suppression.[6] In rare instances, temporary fludrocortisone therapy may be required.

» Successful removal of an aldosterone-producing adenoma during pregnancy has been rarely reported.[119] Although case reports suggest that the optimal time for surgery is during the middle trimester, it is clearly preferable to postpone surgery in patients with primary aldosteronism (PA) during pregnancy until after delivery where possible.

plus — **pre- and postoperative aldosterone antagonists**

Treatment recommended for ALL patients in selected patient group

Primary options

» amiloride: 2.5 to 15 mg orally once daily or in 2 divided doses, higher doses have been reported, maximum 40 mg/day

OR

MANAGEMENT

Ongoing

» spironolactone: 12.5 to 50 mg orally once daily or in 2 divided doses, higher doses have been reported, maximum 200 mg/day

OR

» eplerenone: 25 to 100 mg orally once daily or in 2 divided doses, maximum 100 mg/day

» Where possible, hypertension and hypokalaemia should be controlled preoperatively, ideally with an aldosterone antagonist.

» Postoperatively, residual hypertension usually responds well to recommencement of aldosterone antagonist medicine. This is usually deferred for several weeks. The lowest recommended dose should be used initially.

» Over-treatment can cause volume contraction with pre-renal failure, rising creatinine levels, and life-threatening hyperkalaemia. In patients with reduced renal glomerular function, concurrent administration of a potassium-wasting diuretic in low dosage can be helpful to avoid hyperkalaemia.[6]

» Hyperkalaemia is more likely in patients who have renal dysfunction or are taking other potassium-retaining agents such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin-II receptor antagonists, or non-steroidal anti-inflammatory drugs (NSAIDs).

» Spironolactone can be associated with sex-steroid-related adverse effects, including gynaecomastia and loss of libido, menstrual irregularities, and aggravation of breast fibrocystic change.[121] The incidence is dose-related. At 12.5 to 50 mg daily, the incidence of gynaecomastia is approximately 10% to 15%.[105] [122]

» Eplerenone (in countries where available as a subsidised treatment for primary aldosteronism) is another option for patients in whom spironolactone is poorly tolerated and where amiloride is unable to achieve sufficient aldosterone blockade. Normality of the ratio, which depends on renin becoming unsuppressed, is the best guide to whether or not adequate blockade of aldosterone is being achieved.

familial hyperaldosteronism type I

Ongoing

adults — **1st** — **glucocorticoids**

Primary options

» dexamethasone: 0.125 to 0.5 mg orally once daily

OR

» prednisolone: 2.5 to 5 mg orally once daily

» Glucocorticoids rapidly and effectively ameliorate hypertension.[13][22][44] [45][131]

» The risk of Cushingoid adverse effects is minimal because the required doses are low.[132] However, patients should still be monitored for clinical development of Cushingoid features. Periodic dual energy-ray absorptiometry (DXA) bone scanning should be performed to monitor the development of osteoporosis.

» Treatment should be avoided in children because of the potential to impair growth.

» For pregnant patients, low-dose glucocorticoids have been used successfully to control hypertension. Prednisolone and hydrocortisone are thought to be preferable to dexamethasone. Alternatives to glucocorticoids are any of the recognised pregnancy-safe antihypertensives.

2nd — **aldosterone antagonists**

Primary options

» amiloride: 2.5 to 15 mg orally once daily or in 2 divided doses, higher doses have been reported, maximum 40 mg/day

OR

» spironolactone: 12.5 to 50 mg orally once daily or in 2 divided doses, higher doses have been reported, maximum 200 mg/day

OR

» eplerenone: 25 to 100 mg orally once daily or in 2 divided doses, maximum 100 mg/day

» Aldosterone antagonists are an alternative way to control hypertension in patients with familial hyperaldosteronism type I (FH-I).

Ongoing

» They may be used in patients who wish to avoid or have been unable to tolerate glucocorticoid treatment, or in whom such treatment is otherwise contraindicated.

» Because of its less potent aldosterone antagonist action and its much lower propensity to induce adverse effects, amiloride may be the drug of first choice in many patients, particularly those with milder degrees of hypertension, biochemical disturbance, and target organ effects (e.g., echocardiographically demonstrated LVH). Amiloride and spironolactone can also be used in combination to minimise the dose of spironolactone and the risk of sex-steroid-related adverse effects.

» Eplerenone (in countries where available as a subsidised treatment for primary aldosteronism) is another option for patients in whom spironolactone is poorly tolerated and where amiloride is unable to achieve sufficient aldosterone blockade. Normality of the ratio, which depends on renin becoming unsuppressed, is the best guide to whether or not adequate blockade of aldosterone is being achieved.

» Over-treatment can cause volume contraction with pre-renal failure, rising creatinine levels, and life-threatening hyperkalaemia. In patients with reduced renal glomerular function, concurrent administration of a potassium-wasting diuretic in low dosage can be helpful to avoid hyperkalaemia.[6]

» Hyperkalaemia is more likely in patients who have renal dysfunction or are taking other potassium-retaining agents such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin-II receptor antagonists, or non-steroidal anti-inflammatory drugs (NSAIDs).

» Spironolactone can be associated with sex-steroid-related adverse effects, including gynaecomastia and loss of libido, menstrual irregularities, and aggravation of breast fibrocystic change.[121] The incidence is dose-related. At 12.5 to 50 mg daily, the incidence of gynaecomastia is approximately 10% to 15%.[105] [122]

children (pre- and peri-pubertal) — **1st** — **amiloride**

Primary options

» amiloride: 2.5 to 7.5 mg orally once daily or in 2 divided doses

Ongoing

» Although glucocorticoids are highly effective in controlling hypertension and hypokalaemia (where present) in familial hyperaldosteronism type I (FH-I), they may impair growth in children and their use should therefore be avoided in that patient group.

» Amiloride is a potassium-sparing diuretic and effective against hypertension and hypokalaemia in patients with primary aldosteronism of all forms, including FH-I.[121] Although spironolactone is more effective in this respect than amiloride, its propensity to induce sex-steroid-related adverse effects and, in particular, to interfere with sexual development, renders its use in children undesirable.

» Over-treatment with amiloride can cause volume contraction with pre-renal failure, rising creatinine levels, and life-threatening hyperkalaemia. In patients with reduced renal glomerular function, concurrent administration of a potassium-wasting diuretic in low dosage can be helpful to avoid hyperkalaemia.[6]

» Hyperkalaemia is more likely in patients who have renal dysfunction or are taking other potassium-retaining agents such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin-II receptor antagonists, or non-steroidal anti-inflammatory drugs (NSAIDs).

2nd **eplerenone**

Primary options

» eplerenone: consult specialist for guidance on dose

» Eplerenone is a mineralocorticoid receptor antagonist that appears to be more selective for the receptor than spironolactone, and is, therefore, less likely to produce sex-steroid-related adverse effects such as gynaecomastia and loss of libido, menstrual irregularities, and aggravation of breast fibrocystic change.[135] It may also be less likely to interfere with sexual development in children. Hence, it may be particularly suited for adult patients who have demonstrated intolerance to spironolactone because of sex-steroid-related adverse effects, or in children with primary aldosteronism (PA; including those with familial hyperaldosteronism type I).

» Eplerenone is already available and being used in clinical practice. However, indications for its use in different countries vary, and in some countries it is not approved for government-

Ongoing

subsidised use in PA. Furthermore, data regarding its safety and efficacy in children with PA are lacking. Hence, it should remain a second-line option in this clinical context.

Emerging

Aldosterone synthase inhibitors

Several of these agents are being assessed in phase II studies and hold some promise as alternative treatment approaches for PA.[136] [137] Further data are required to confirm their efficacy and safety in this situation. Remaining challenges include lack of specificity for aldosterone synthase (with evidence, for example, of reduced cortisol synthesising capacity) and inferior treatment effect when compared to mineralocorticoid receptor antagonism.[138] [139]

Targeted therapy for specific mutations

Studies on the use of macrolides as treatment for individuals with mutations in the KCNJ5 gene are in progress.[140] [141] [142] For patients with CACNA1D or CACNA1H mutations, selective calcium-channel blockade may be possible.[49] [57][133] [143]

Primary prevention

There are no known methods of primary prevention of primary aldosteronism. However, early detection (e.g., through screening of kin for familial hyperaldosteronism types I-IV) can facilitate early intervention such as dietary salt restriction, which may have the potential to delay or even prevent onset of hypertension in affected individuals, or at least permit more timely intervention when required.

Secondary prevention

Patients with primary aldosteronism (PA) have a higher risk of cardiovascular adverse events, atrial fibrillation, and chronic kidney disease than patients with essential hypertension.[28] [66] Therefore, early diagnosis and initiation of specific treatment is essential to reduce the risk of complications. In addition to blood pressure control, suppressed renin levels are also associated with worse cardiovascular outcomes.[136] There is evidence that spironolactone is able to ameliorate non-BP-dependent adverse cardiovascular and renal effects of aldosterone excess.[58] [61] [122] [123] [124] Lifestyle modifications (including maintenance of a healthy weight, regular exercise, avoidance of alcohol excess, dietary salt restriction, and smoking cessation) should be initiated in all patients. Dietary salt restriction may also reduce the dose of aldosterone blocking drug required. Patients should be screened for diabetes or dyslipidaemia with fasting blood sugar and lipid levels. The prevalence of diabetes in people with PA is approximately 20%; around double the prevalence in the general population or matched hypertensive controls.[145] [146]

Patient discussions

As with all forms of hypertension, patients should be given instructions on:

- Lifestyle modification (including maintenance of a healthy weight, regular exercise, avoidance of alcohol excess, dietary salt restriction, and smoking cessation). Dietary salt restriction may reduce the dose of aldosterone blocking drug required.
- Self-monitoring of BP is usually appropriate.
- Importance of medication compliance.

FOLLOW UP

Monitoring

Monitoring

Patients who have undergone unilateral adrenalectomy for unilateral primary aldosteronism (PA)

- BP, plasma electrolytes, and aldosterone and renin levels should be monitored every 6 to 12 months for clinical and biochemical evidence of recurrence (if cured postoperatively) or worsening (if improved but not cured) of PA. Patients should have an adrenal CT scan performed at 1 year postoperatively, and at 1- to 3-year intervals thereafter. This is because it has become apparent from careful postoperative follow-up of patients that some have a natural history of the disease in which the remaining adrenal slowly increases in size and becomes nodular, and which may turn out to be in a different class genetically. Occasionally, a new adenoma that may or may not be secreting aldosterone requires removal on size criteria alone (e.g., ≥2.5 cm, although some centres use higher cutoffs of 3.0 cm or even 4.0 cm), with preservation of an apparently normal limb of the adrenal if possible.

Patients receiving aldosterone medications

- Electrolytes and renal function should be monitored regularly (e.g., every 3 to 6 months), watching for development of hyperkalaemia (more likely in patients who have renal dysfunction or are taking other potassium-retaining agents such as angiotensin-converting enzyme [ACE] inhibitors, angiotensin-II receptor antagonists, or non-steroidal anti-inflammatory drugs [NSAIDs]), hyponatraemia, and uraemia. Renin levels can be used to guide doses of treatment, provided that the method is sound and results are not confounded by the use of other medicines. In all patients with PA treated medically, CT of the adrenals should be performed annually at first and, if no nodular growth is seen, every 3 to 4 years, indefinitely.

Patients with familial hyperaldosteronism type I (FH-I)

- Hypertension is readily controlled by administering glucocorticoids in low doses. Control can be assessed by clinic, home, and ambulatory BP monitoring, and by periodic (e.g., yearly) echocardiographic assessments of left ventricular mass index and diastolic function. Patients should also be monitored for the development of glucocorticoid-induced osteoporosis by dual-energy x-ray absorptiometry (DXA) performed every 2 to 3 years.

FOLLOW UP

Complications

Complications	Timeframe	Likelihood
perioperative complications (e.g., bleeding, infection, wound hernia, cardiovascular events)	**short term**	**low**
Laparoscopic adrenalectomy is generally associated with a low rate of perioperative complications. The laparoscopic approach has allowed for a shorter recovery than open adrenalectomy.[117]		
stroke	**long term**	**medium**
Can occur due to hypertension-accelerated cerebrovascular disease and ischaemic or haemorrhagic cerebral events. The prevalence appears to be higher than in patients with essential hypertension.[66] This is thought to be related to non-blood pressure-dependent adverse cardiovascular effects of aldosterone excess causing remodelling of the heart and blood vessels. For uncertain reasons, the risk of haemorrhagic stroke is particularly high in patients with familial hyperaldosteronism type I.[22]		
myocardial infarction	**long term**	**medium**
Can occur due to hypertension accelerating coronary disease and causing left ventricular hypertrophy. The prevalence appears to be higher than in patients with essential hypertension.[66] This is thought to be related to non-blood pressure-dependent adverse cardiovascular effects of aldosterone excess causing remodelling of the heart and blood vessels.		
heart failure	**long term**	**medium**
Can occur due to hypertension accelerating coronary disease and causing left ventricular hypertrophy. Non-blood pressure-dependent adverse cardiovascular effects of aldosterone excess causing remodelling of the heart and blood vessels also probably contribute.[123]		
atrial fibrillation	**long term**	**medium**
Can occur due to hypertension causing left ventricular hypertrophy, and, in some cases, hypokalaemia. The prevalence appears to be higher than in patients with essential hypertension.[66] This is thought to be related to non-blood pressure-dependent adverse cardiovascular effects of aldosterone excess causing remodelling of the heart and blood vessels.		
impaired renal function	**long term**	**medium**
Can occur due to hypertension accelerating renal injury, and contributed to by aldosterone excess causing renal hyperfiltration.[144]		

Complications	Timeframe	Likelihood
aldosterone antagonist- or mineralocorticoid receptor antagonist-induced hyperkalaemia	**variable**	**medium**
Because they are potassium-sparing, spironolactone, amiloride, and eplerenone can all cause hyperkalaemia.[6] [121] The risk is higher in patients with renal dysfunction, older people, diabetic patients, and patients receiving other agents known to raise plasma potassium levels.		

Prognosis

Patients undergoing unilateral adrenalectomy for unilateral PA

This procedure leads to cure of hypertension in 50% to 60% of carefully selected patients and improvement in all of the remainder.[27] [105] [114] [115] [116] BP typically normalises or shows maximum improvement in 1 to 6 months after unilateral adrenalectomy, but can continue to fall for up to 1 to 2 years in some patients.[6] Primary aldosteronism (PA) is biochemically cured in 70% of fully worked-up patients, and improved in all remaining patients.[27] [105] [115] Less than 20% of patients require equivalent or increased medicine doses after surgery.[101] There is a consistent improvement in quality of life. Cohort studies have shown marked improvements in cardiovascular parameters (including left ventricular mass on echo).[61] [124]

Recurrence of PA in those apparently cured after 12 months is uncommon. In patients with persistent (albeit improved) PA, hypertension may respond well to small doses of aldosterone antagonist medicines, but caution is required as the levels of aldosterone have probably been substantially reduced.[6]

Patients undergoing treatment with aldosterone antagonist medicines

Hypertension is improved and control achieved in the majority.[27] [105] [121] Hypokalaemia, when present, is almost always corrected.

However, improvements aren't as dramatic as after unilateral adrenalectomy for lateralising lesions. In cohort studies, the mean number of antihypertensive medicines required did not fall as markedly, and there was less impressive improvement in echocardiographically derived left ventricular mass.[27] [61]

Patients with FH-I undergoing treatment with glucocorticoid medicines

Hypertension in familial hyperaldosteronism type I (FH-I) is frequently of early onset and may be severe enough to cause early death, usually from haemorrhagic stroke, unless specifically treated.[20] [21] However, treatment with glucocorticoids, given in low doses that do not cause Cushingoid adverse effects, is usually highly effective at controlling hypertension (and thereby preventing stroke), with supplementary antihypertensives only occasionally required.[131]

Diagnostic guidelines

Europe

Subtype diagnosis, treatment, complications and outcomes of primary aldosteronism and future direction of research (https://pubmed.ncbi.nlm.nih.gov/32890265)

Published by: Working Group on Endocrine Hypertension of the European Society of Hypertension **Last published:** 2020

Genetics, prevalence, screening and confirmation of primary aldosteronism (https://pubmed.ncbi.nlm.nih.gov/32890264)

Published by: Working Group on Endocrine Hypertension of the European Society of Hypertension **Last published:** 2020

North America

NCCN clinical practice guidelines in oncology: neuroendocrine and adrenal tumors (https://www.nccn.org/guidelines/category_1)

Published by: National Comprehensive Cancer Network **Last published:** 2025

The management of primary aldosteronism: case detection, diagnosis, and treatment (https://www.endocrine.org/clinical-practice-guidelines)

Published by: Endocrine Society **Last published:** 2016

Treatment guidelines

Europe

The 2020 Italian Society of Arterial Hypertension (SIIA) practical guidelines for the management of primary aldosteronism (https://pubmed.ncbi.nlm.nih.gov/33447758)

Published by: Italian Society of Arterial Hypertension (SIIA) **Last published:** 2020

North America

NCCN clinical practice guidelines in oncology: neuroendocrine and adrenal tumors (https://www.nccn.org/guidelines/category_1)

Published by: National Comprehensive Cancer Network **Last published:** 2025

The management of primary aldosteronism: case detection, diagnosis, and treatment (https://www.endocrine.org/clinical-practice-guidelines)

Published by: Endocrine Society **Last published:** 2016

Asia

Japan Endocrine Society clinical practice guideline for the diagnosis and management of primary aldosteronism 2021 (https://square.umin.ac.jp/endocrine/english/JES-guidelines.html)

Published by: The Japan Endocrine Society **Last published:** 2021

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Images

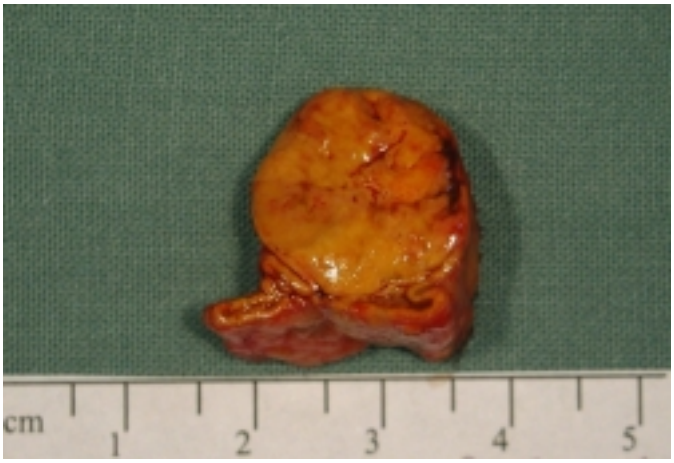

Figure 1: Aldosterone-producing adenoma

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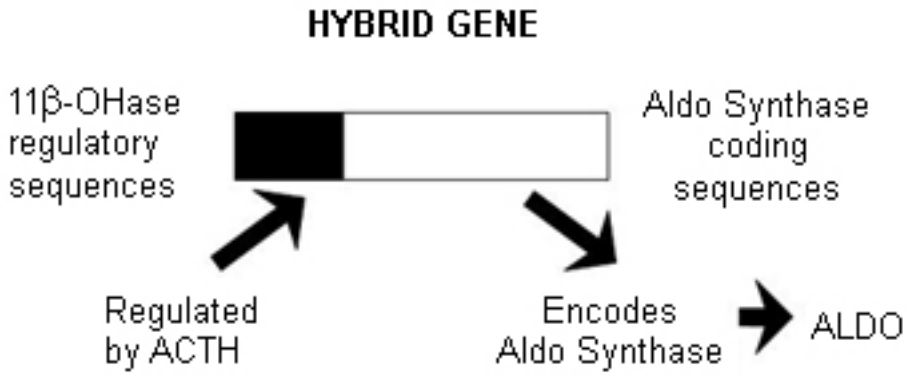

Figure 2: Hybrid CYP11B1/CYP11B2 gene responsible for ACTH-regulated aldosterone overproduction in FH-I

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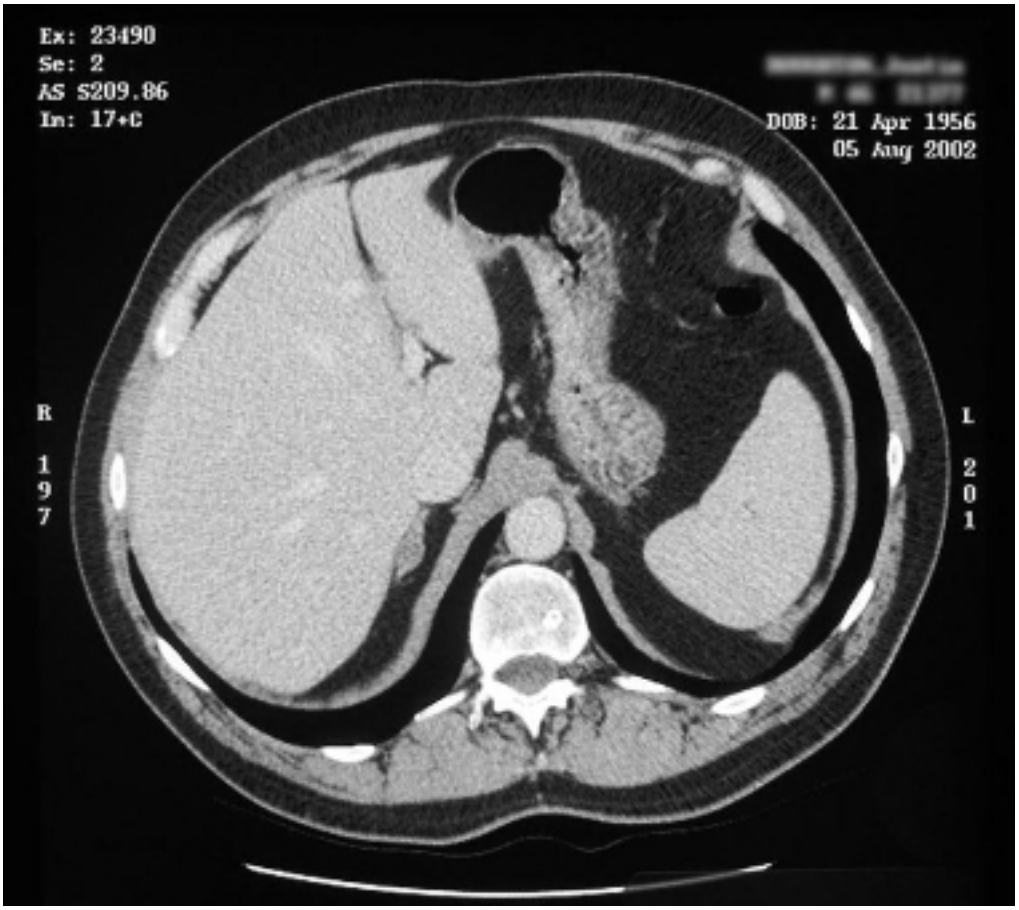

Figure 3: CT showing lesion in right adrenal gland in patient with right aldosterone-producing adenoma

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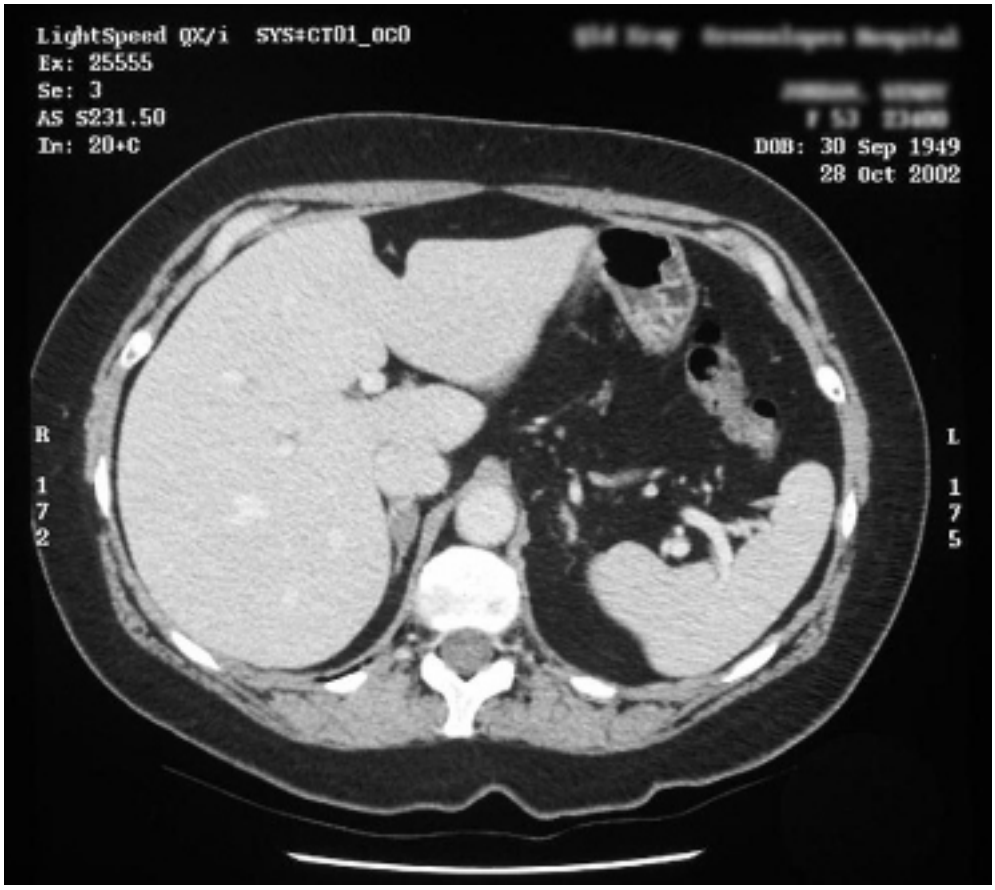

Figure 4: Computed tomography (CT) showing lesion in right adrenal gland in patient with bilateral adrenal hyperplasia

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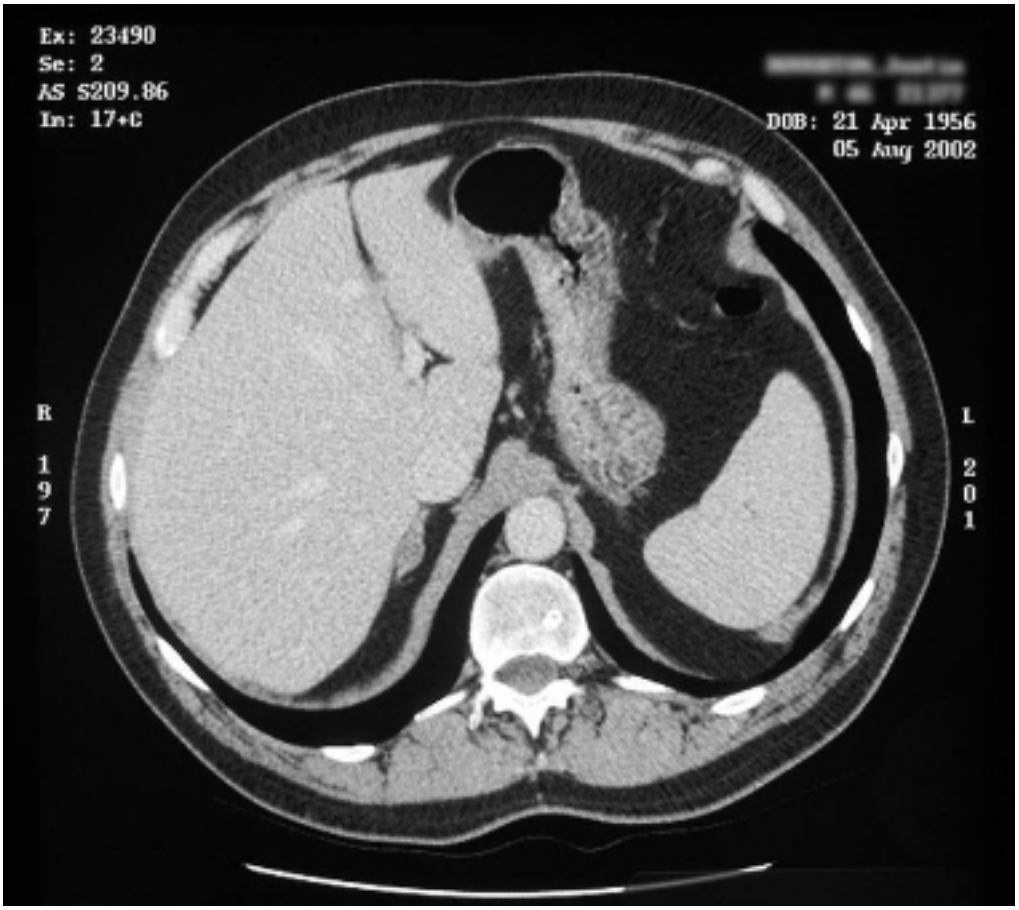

Figure 5: Computed tomography (CT) showing lesion in right adrenal gland in patient with right aldosterone-producing adenoma

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	Left CV	PV	Right CV	PV
Aldosterone (ng%)	968	21.3	1496	21.4
Cortisol (µg%)	183	16.6	1120	16.5
A/C ratio	5.3	1.3	1.3	1.3

Adrenal/peripheral cortisol gradients exceed 3.0 on both sides, confirming adequate sampling of both adrenal veins. Adrenal venous aldosterone/cortisol ratios are significantly higher than peripheral on the left but not the right side, consistent with lateralization of aldosterone production to the left.

Figure 6: Adrenal venous sampling results from patient with left aldosterone-producing adenoma

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This approach is in line with the guidance of the International Bureau of Weights and Measures Service.

Figure 1 – BMJ Best Practice Numeral Style

5-digit numerals: 10,000

4-digit numerals: 1000

numerals < 1: 0.25

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