Frequently Asked Questions relating to Screening for Primary Aldosteronism

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What are the clinical features of primary aldosteronism?

Elevated blood pressure may be the only clinical feature.

Other potential features may relate to:

- hypertension (eg. headaches)
- aldosterone-mediated sodium retention (oedema, polyuria, nocturia)
- hypokalaemia (muscle weakness, cramping)
- end-organ damage (heart failure, atrial fibrillation, stroke, renal impairment).

What are different causes of primary aldosteronism?

The most common causes of PA are bilateral adrenal hyperplasia and aldosterone-producing adrenal adenoma.

Unilateral disease is curable by laparoscopic adrenalectomy.

Bilateral disease can be managed by targeted medical therapy in the form of mineralocorticoid receptor (MR) antagonists, such as spironolactone or eplerenone, which block the effects of aldosterone.

Why is it important to diagnose primary aldosteronism and offer targeted treatment?

Targeted treatment of patients with primary aldosteronism by adrenalectomy or spironolactone/eplerenone can improve blood pressure control (with fewer medications) and reduce aldosterone-mediated cardiovascular risk (eg. reverse left ventricular hypertrophy, reduce proteinuria, reduce mortality). Patients' quality of life can also be improved.

Who should be screened for primary aldosteronism?

According to the Endocrine Society guidelines for testing, people who fulfil the following criteria should be tested for primary aldosteronism:

- Sustained blood pressure (BP) above 150/100 mmHg on each of three measurements obtained on different days, or
- Hypertension (BP > 140/90 mmHg) resistant to three conventional antihypertensive drugs (including a diuretic), or
- Controlled BP (<140/90) on four or more antihypertensive drugs, or

- Hypertension and spontaneous or diuretic-induced hypokalaemia, or
- Hypertension and adrenal incidentaloma, or
- Hypertension and obstructive sleep apnoea, or
- Hypertension and a family history of early onset hypertension or stroke at a young age (<40 years), or
- All hypertensive first-degree relatives of a patient with primary aldosteronism

It would be easiest to test for primary aldosteronism in patients with hypertension before they are started on anti-hypertensive medications to avoid interference with test results.

How to screen for primary aldosteronism?

The screening blood test to order is: aldosterone, renin and aldosterone to renin ratio (ARR). Renal function and electrolytes (UEC) should be checked at the same time.

The test is best done around two hours after getting up in the morning.

The test does not require fasting though a fasting sample is still valid.

Serum potassium should be corrected if it is low, because hypokalaemia can cause a false negative ARR result.

- Use slow release potassium chloride to top up potassium
- May require 4 – 12 tablets per day if serum potassium < 3.0 nmol/L
- Recheck the potassium a week later to ensure it has normalised (aim for > 4.0 nmol/L) and if it has not, increase the dose.

In most laboratories, ARR >70 is considered a positive screening test (where both aldosterone [pmol/L] and renin [mU/L] are measured by chemiluminescent assays). However, the threshold can vary between laboratories. Use your local threshold.

How to screen for primary aldosteronism in patients who are taking antihypertensive medications already?

The most commonly used anti-hypertensives can affect either aldosterone or renin concentration, and therefore cause false negative or false positive results.

For patients on treatment, the ideal approach to accurate screening involves:

1) Stop all interfering medication (Box 1), if safe to do so;

2) Replace them with medications that have minimal effect on aldosterone and renin concentration (Box 2), if needed to maintain BP < 140/90 during the investigative period.

This is not always practical, so stopping certain medications should be prioritised over others (Box 1,reference: https://www1.racgp.org.au/ajgp/2020/march/screening-for-primary-aldosteronism).

The approach outlined here recognises the importance of avoiding inaccurate testing but also acknowledges that sometimes it is just too difficult to completely optimise medications.

Box 1. How to prioritise medication changes prior to screening for PA
Group 1: Should be replaced for accurate screening, unless absolutely required • All loop diuretics (e.g. frusemide) • All thiazide diuretics (e.g. hydrochlorothiazide, indapamide) • All MR antagonists (e.g. spironolactone, eplerenone)
Group 2: Replace wherever possible • All ACE inhibitors (eg. perindopril, ramipril) • All ARB (e.g. Olmesartan, telmisartan) • All dihydropyridine calcium channel blockers (e.g. amlodipine)
Group 3: Replace only after addressing the above: • Selective and non-selective beta-blockers (e.g. atenolol)

Interfering medications should be ceased and replaced with sustained release verapamil, prazosin, moxonidine, and/or hydralazine (Box 2). These new medications can be started the same day that the other anti-hypertensives are ceased with caution advised when changing from a beta blocker to verapamil so as to include a period of weaning before switching medication. The new medication regime should be continued for six weeks prior to screening.

Our experience suggests that if the patient has no significant end-organ damage then the process of switching medications is usually straightforward. Patients who have existing nephropathy or ischaemic heart disease can still be screened in a primary care setting, but more frequent blood pressure and adverse effect monitoring will be required. In patients with heart failure and a current LVEF of less than 50%, ACE-I and ARB should not be withdrawn.

Box 2. Medications which do not affect screening and how to use them		
Medication	**Dose**	**Practice Points**
Sustained release verapamil	180 mg PO daily, up to 240 mg PO daily	Must be sustained release. Higher doses produce adverse effects. If not at target, add another agent. Common adverse effects include constipation and bradycardia. Infrequently, it can cause or worsen AV blockade and heart failure.
Moxonidine	200 microg once nocte, can increase to 400 microg nocte after 2 weeks	Only eligible on PBS as a second antihypertensive. Contraindicated in heart failure, bradycardia, AV block and CrCl <30mL/min. Common adverse effects include dry mouth, somnolence, dizziness, and weakness.
Prazosin	0.5mg PO BD, increase up to 5mg PO TDS	Up-titrate slowly to avoid postural hypotension. Avoid if symptomatic cataract requiring surgery. Common adverse effects include dizziness, palpitations, dry mouth, and blurred vision. Infrequently tachycardia, urinary incontinence and fainting may occur.
Hydralazine (Alphapress)	12.5mg PO BD, can increase up to 50mg PO TDS[14].	Common adverse effects include flushing, headache, palpitations, oedema and dizziness while infrequently angina and a lupus-like syndrome can occur.

What are other medications which can interfere with the ARR?

The combined oral contraceptive pill (COCP) can cause a false positive ARR result (when renin concentration is measured; does not affect plasma renin activity). Reliable contraception must be advised if the COCP is stopped for the investigation of PA.

The Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) guidelines state that the COCP is not recommended for use in the setting of hypertension, so it is reasonable to stop the COCP and re-evaluate BP.

Can the screening test result be interpreted in patients who are taking interfering medications?

For patients who are too elderly or frail, or have strong indications for their existing antihypertensive therapy, their ARR can be measured without switching medications.

The results will need to be carefully interpreted according to the anticipated effect of the interfering medication.

For example, if a patient has a low or low normal renin concentration despite taking an ACE-I or ARB, which generally increase renin, then one should be highly suspicious of underlying PA.

Specialist advice may be sought in this setting, including whether it is better to forego additional investigations and instead opt for a trial of spironolactone based on an abnormal or suspicious ARR

What to do after a positive screening test?

After a positive screening test, it is advisable to:

1. Keep the patient on the non-interfering medications.

2. Maintain a normal serum potassium (aim > 4 nmol/L), using slow-release potassium supplements.

3. Explain to the patient that increased aldosterone may be the cause of their hypertension and further testing (seated saline suppression test) is required. Patient-friendly information can be found on the Primary Aldosteronism page of Hormones Australia website, as well as the Primary Aldosteronism Foundation website (US-based consumer advocacy group).

4. Refer the patient to an Endocrine Hypertension Service or specialists with an interest in endocrine hypertension.

If specialist services are not easily available, empiric treatment with spironolactone, starting at 25mg per day, is a reasonable next step with the aim of normalising BP, serum potassium and renin concentration.