PRIMARY HYPERALDOSTERONISM – GUIDELINES FOR INVESTIGATION

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Version Control Schedule

Version	Date	Author	Status	Comment
1.0	20/07/10	Ruth Lapworth	Archived	
2.0	20/07/13	Ruth Lapworth	Archived	
3.0	14/10/14	E Kearney/E Hanon	Archived	New format and revised document. Produced in conjunction with clinical teams
4.0	18/8/2016	E Kearney		Reference to Renal Unit Saline Infusion Protocol
5.0	5/06/2018	E Kearney		Correction of sample type
6.0	26/07/2018	E Kearney		Clarity for inpatients and sample stability
7.0	8/8/2019	E Kearney		Clarification on inappropriate kaliuria
8.0	8/1/2020	E Kearney		Permitted drugs in the screening phase

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1 Policy Summary

This policy gives guidance to clinicians when investigating suspected primary hyperaldosteronism.

2 Introduction

Primary hyperaldosteronism (PA) is characterised by an inappropriately increased aldosterone concentration compared to the plasma renin activity. Previously PA was thought to always be associated with hypokalaemia and an uncommon cause of hypertension, occurring in less than 1% of the hypertensive population. It is now apparent that PA is more common (around 5% of hypertensive patients) and can occur with normokalaemia.

PA may be caused by:

- Continuous aldosterone secretion by an unilateral adrenal adenoma (Conn's syndrome)
- Idiopathic hyperaldosteronism associated with bilateral zona glomerulosa hyperplasia
- Unilateral primary adrenal hyperplasia
- Glucocorticoid-suppressible aldosteronism (inherited condition)
- Aldosterone-producing adrenocortical carcinoma

It is currently recommended that case detection of PA be undertaken in patient groups with a relatively high prevalence of the disorder rather than screening all patients with hypertension. Groups with a high prevalence of PA:

- Resistant hypertension, generally defined as systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg, despite treatment with ≥3 anti-hypertensive medications including a thiazide diuretic at optimal/best tolerated doses
- Hypertensive patients with spontaneous or diuretic-induced hypokalaemia
- Hypertension with abnormal adrenal imaging
- Family history of early-onset hypertension or cerebrovascular incident at a young age (< 40 years)

3 Purpose and Scope

This policy outlines the procedure to investigate suspected primary hyperaldosteronism.

4 Definitions

Renin is a proteolytic enzyme secreted by the juxtaglomerular apparatus in the kidney in response to decreased afferent arteriolar pressure. This enzyme catalyses the conversion of angiotensinogen to angiotensin I, which is in turn converted to angiotensin II in the lungs by angiotensin-converting enzyme (ACE). Renin may be measured as activity. In East Kent renin activity is reported in pmol/mL/h.

Angiotensin II stimulates arteriolar vasoconstriction to increase blood pressure, anti-diuretic hormone (ADH) secretion to increase water absorption by the kidney and aldosterone secretion to stimulate sodium reabsorption and potassium excretion.

Aldosterone is a steroid hormone produced by the adrenal gland that stimulates renal sodium reabsorption in exchange for potassium and hydrogen ions and expands the extracellular fluid volume. Aldosterone concentration is expressed in pmol/L.

Primary hyperaldosteronism (PA) is an endocrine cause of hypertension characterised by and inappropriately elevated aldosterone concentration compared to the plasma renin activity.

5 Duties

All staff involved in the investigation of patients with suspected primary hyperaldosteronism, whether clinical or laboratory, must adhere to this policy.

6 Primary hyperaldosteronism – guidelines for investigation

6.1 Patient preparation

The renin-aldosterone axis is primarily regulated by renal blood flow, therefore:

- Subjects under investigation should ideally not be taking any drugs that interfere with fluid balance or potassium (Table 1). If these drugs cannot be withdrawn, please refer to section 6.2.2 Table 3 for interpretation of the results. Patients should not consume products derived from liquorice root e.g. confectionary liquorice, chewing tobacco and pastis.
- In Acclerated Phase Hypertension (APH) ARR should not be measured in the acute phase as both Aldosterone and Renin will most likely both be increased. These patients should ideally have ARR measured after at least 2 to 4 weeks with well controlled BP.

- Potassium depletion inhibits aldosterone production and may give artefactually low results. Attempt to correct any hypokalaemia prior to investigation. Slow K two tablets tds will provide 48 mmol K^+ per day; Sando K two tablets tds will provide 72 mmol K^+ per day.

- Encourage patients to liberalise rather than restrict sodium intake. Use Slow Sodium two tabs tds (= 60 mmol/day) if urinary sodium known to be <120 mmol/day.

- Sample should be taken in the morning, ideally around 09:00 to coincide with the diurnal peak of aldosterone.

Mandatory Drug withdrawal	
Drug	**Time to remove interference**
β-blockers	2 weeks
NSAID's	2 weeks
Spironolactone, eplerenone, amiloride (& triamterene)	6 weeks
Drugs which are ideally withdrawn. ARR can still be measured as an initial screen. Interpret in line with section 6.2.2	
ACE inhibitors & Angiotensin receptor blockers.	2 weeks
Calcium channel blockers	2 weeks
Diuretics	2 weeks
Oestradiol	6 weeks

Table 1: Interfering drugs and period of withdrawl (washout) before sampling

6.2 Screening for primary hyperaldosteronism

Screening for PA relies on measurement of the plasma aldosterone:renin ratio in a blood sample collected after the patient has been seated for at least 5-15 mins. This ratio is preferable to measurement of either analyte alone and is the screening test of choice in patient groups with a high prevalence of PA.

6.2.1 Biochemical Testing

The demonstration of inappropriate kaluria is a key feature of PA. However, this is only possible when a patient has hypokalaemia.We recommend sending serum, plasma and urine samples as describe in Table 2. Request form should ideally state blood pressure and current medications. Ideally a 24 hour urine potassium result will be available to aid interpretation.

Sample type	Biochemical tests
Serum	Creatinine, sodium, potassium, bicarbonate, chloride
Plasma	Aldosterone:renin ratio
Urine (24h)	Potassium, sodium, chloride

Table 2: Biochemical tests to request when investigating primary hyperaldosteronism

A 10 mL (2 tubes) EDTA blood sample is collected for measurement of aldosterone and plasma renin activity and calculation of the ratio.

INPATIENT - A sample may be collected midmorning after patients have been up (standing, sitting, walking) for two hours. They can then be bled after 5-15 mins seated.
If required and agreed by the Duty Biochemist a sample may be collected at 08:00 following overnight recumbence, and at 12:00.

OUTPATIENT - Alternatively a sample may be collected after patients have been up (standing, sitting, walking) for two hours. They can then be bled after 5-15 mins seated.

The blood must be transported immediately to the local laboratory at room temperature. After centrifugation the resultant plasma should be divided between two plastic tubes and frozen within one hour of venepuncture. Samples up to 4 hours are acceptable. For this reason patients, other than inpatients, must be bled in the Outpatient Department at either K&C, QEQMH or WHH.

6.2.2 Result Interpretation

Patients with PA have been reported to have serum sodium concentrations in the upper half of the reference range accompanied by hypokalaemia (<3.5 mmol/L) and alkalosis. Urine potassium excretion is usually inappropriate for the degree of hypokalaemia.

In patients with PA the aldosterone concentration and renin activity change in the opposite direction (aldosterone ↑, renin activity ↓). Calculation of the aldosterone:renin ratio in a random sample maximises any alterations in these analytes and reduces the effects of drug therapy, posture, day to day and diurnal variations.

An aldosterone:renin ratio greater than 1000 requires further investigation and a value greater than 2000 suggests PA as the cause of the hypertension. The diagnosis is unlikely in a patient with a ratio less than 800. These reference ranges only apply in hypertensive patients.

However the ratio may be falsely elevated in patients with renal failure, in those on β blocker or diuretic therapy and after potassium administration. Conversely, ACE inhibitors and calcium channel blockers tend to lower the ratio which may give false negative results.

If interfering drugs cannot be stopped: when the aldosterone:renin ratio is used as a first line test, results can be interpreted in relation with the known effects on the drugs on renin and aldosterone (Table 3). If not possible, antihypertensive drugs may be continued for an initial screening sample with the exception of spironolactone, eplerenone, amiloride (& triamterene) and oestrogen (stop for at least 4 weeks), β-blockers and NSAIDs (stop for at least 1 week).

6.3 Diagnostic confirmation

Patients with abnormal aldosterone and renin results should be referred to an endocrinologist or other specialist with expertise in investigation and management of suspected secondary hypertension.

Further investigations may include “aldosterone suppression tests”, adrenal imaging and adrenal venous sampling.

Aldosterone suppression tests are:

- oral sodium loading
- saline infusion[9]
- fludrocortisone suppression
- captopril challenge

6.4 Subtype classification

Further investigations such as computed tomography or magnetic resonance image scanning and adrenal venous sampling should be undertaken only at referral centres to distinguish between aldosterone-producing adrenal adenoma and adrenal hyperplasia. In unilateral disease, hypokalaemia resolves and the hypertension improves and/or is cured after gland ablation; while in bilateral adrenal hyperplasia and glucocorticoid-suppressible aldosteronism medical therapy is the treatment of choice.

The aldosterone concentration at 12:00 may be helpful. Failure of aldosterone concentration to increase from an elevated basal value (08:00) suggests an adenoma or glucocorticoid-suppressible hyperaldosteronism rather than bilateral adrenal hyperplasia as the cause of PA.

Factor	Effect on aldosterone concentration	Effect on renin activity	Effect on ARR
Medications			
β-adrenergic blockers	↓	↓↓	↑ (FP)
Central α-2 agonists (e.g. clonidine, α-methyldopa)	↓	↓↓	↑ (FP)
NSAIDs	↓	↓↓	↑ (FP)
K^+ wasting diuretics	→ ↑	↑↑	↓ (FN)
K^+ sparing diuretics	↑	↑↑	↓ (FN)
ACE inhibitors	↓	↑↑	↓ (FN)
ARBs	↓	↑↑	↓ (FN)
Ca^{2+} blockers (DHPs)	→ ↑	↑	↓ (FN)
Renin inhibitors	↓	↓	↑ (FP)
Potassium status			
Hypokalaemia	↓	→ ↑	↓ (FN)
Potassium loading	↑	→↓	↑ (FP)
Dietary sodium			
Sodium restricted	↑	↑↑	↓ (FN)
Sodium loaded	↓	↓↓	↑ (FP)
Advancing age	↓	↓↓	↑ (FP)
Other conditions			
Renal impairment	→	↓	↑ (FP)
PHA-2	→	↓	↑ (FP)
Pregnancy	↑	↑↑	↓ (FN)
APH	↑	↑↑	↓ (FN)
Accelerated Phase HT	↑	↑↑	↓ (FN)

Table 3: Factors affecting aldosterone concentration and renin activity
From The Endocrine Society's Clinical Guidelines (2008)

7 Key Stakeholders, Consultation, Approval and Ratification Process

East Kent Hospitals University NHS Foundation Trust is the key stakeholder for this policy.

Consultation has been through e-mail communication between clinical biochemistry staff, Trust consultant Endocrinologists (Dr Flynn and Dr Williams) and Trust consultant Nephrologist (Dr Doulton), Dr S Barnes and Mr M Scanlon from Imperial College Hospitals Trust. Copies of correspondence are held on the "T" network drive. Twdata on 'Ekhuft-tw-01'/Pathology/Clinical Biochemistry/Communications with Users/Guidelines/Hyperaldosteronism

8 Review and Revision Arrangements

Three years from implementation date, by author.

9 Dissemination and Implementation

SharePoint, by proactive implementation through the Divisions by appropriate clinical leads and by proactive dissemination to primary care partners.

10 Document Control including Archiving Arrangements

Archive of this document will be through QPulse.

11 Monitoring Compliance

Within the Trust, compliance with this policy must rest with the requesting Divisions with vetting of requests in Clinical Biochemistry. Compliance will also be subject to occasional audit within Clinical Biochemistry.

12 References

1. Westerdahl C, Bergenfelz A, Isaksson A, Nerbrand C & Valdemarsson S. Primary aldosteronism among newly diagnosed and untreated hypertensive patients in a Swedish prmary care area. Scand J Prim Health Care 2011; **29**:57-62

2. The Endocrine Society's Clinical Guidelines. Case detection, diagnosis, and treatment of patients with primary aldosteronism. JCEM 2008; **93**:3266-3281.

3. Stowasser M, Taylor PJ, Pimenta E, Al-Asaly Ahmed AH, Gordon RD. Laboratory investigation of primary aldosteronism. Clin Biochem Rev. 2010;**31**:39-56

4. McKenna TJ, Sequiera SJ, Heffernan A,Chambers J& Cunningham S. Diagnosis under random conditions of all disorders of the renin:Aldosterone axis, including primary hyperaldosteronism. J Clin Endo Metab. 1991; **73**:952-7

5. SAS Handbook for Hormones and Generic Enzymes. Specialised assay services for the hospital laboratory Ed. M J Wheeler. SAS Hormone Publications 2000.

6. Nadan S, Lip G YH and Beevers D G. Primary Hyperaldosteronism. Ann Clin Biochem 2003;**40**:439-452

7. Young W F. Primary aldosterone:renaissance of a syndrome. Clinical Endocrinology 2007;**66**:607-18

8. Funder J N et al. Case detection, diagnosis and treatment of patients with primary hyperaldosteronism: and endocrine society clinical practice guideline. J Clin Endocrinol Metab 2008:**93**:3266-81

9. EKHUFT Department of Renal Medicine: Saline Suppression Test

13 Associated Documentation

Not applicable

Appendix A - Equality Impact Assessment

Equality and Human Rights Impact Analysis (EHRIA)

Part One – Screening Tool

Name of the policy, strategy, function or methodology:	Primary hyperaldosteronism – guidelines for investigation

Details of person completing the EHRIA	
Name	Dr Elodie Hanon
Job Title	Senior clinical scientist
Department/Specialty	Laboratory medicine/clinical biochemistry
Telephone Number	x86165

1. Identify the policy, strategy, function or methodology aims

What are the main aims, purpose and outcomes of the policy, strategy, function or methodology?
To ensure appropriate investigation of patients with potential primary hyperaldosteronism across the health service in East Kent.
Does it relate to our role as a service provider and/or an employer?
Service provider.

2. Assess the likely impact on human rights and equality

Use this table to check if the policy, strategy, function or methodology:

- could have a negative impact on human rights or on any of the equality groups, or
- could have a positive impact on human rights, contribute to promoting equality, equal opportunities or improve relations.

It is not necessary to complete each box, nor to mark whether it is positive or negative, although you can do this if you find it helpful.

	Protected Characteristic								
	Race	**Sex**	**Disability**	**Sexual Orientation**	**Religion or belief**	**Age**	**Gender reassignment**	**Marriage & Civil Partnership**	**Pregnancy & Maternity**
Could this policy, procedure, project or service affect this group differently from others? **YES/NO**									
Could this policy, procedure, project or service promote equal opportunities for this group? **YES/NO**									
Right to life *e.g. decisions about life-saving treatment, deaths through negligence in hospital*									
Right not to be tortured or treated in an inhuman or degrading way *e.g. dignity in care, abuse or neglect of older people or people with learning disabilities.*									
Right to respect for private and family life e.g. *respecting lgb relationships, confidentiality*									
Right to freedom of thought, conscience and religion *e.g. respect for cultural and religious requirements*									
Right to freedom of expression *e.g. access to appropriate communication aids*									
Right to freedom of assembly and association *e.g., right to representation, to socialise in care settings*									
Right to education *e.g. access to basic knowledge of hygiene and sanitation*									
Right to liberty e.g. informal detention of patients who do not have capacity									

3. How does it impact on people's human rights and equality?

Using the table above, explain anticipated impacts. If a full EHRIA is recommended, you can summarise the impacts - it is not necessary to set these out in detail,

Could people's human rights be impacted negatively? Could the policy, strategy, function or methodology result in inequality or discrimination?
No.
Could this policy, strategy, function or methodology result in positive impacts on people's human rights or equality? Could it present opportunities to promote equality?
No

4. Recommendations

Is a full EHRIA recommended? If not, give reasons
No. The policy has equal impact.

5. Publication of EHRIA

Give details of where Screening Tool or the full EHRIA will be published and when this will take place
With document.

Details of person completing the EHRIA	
Name	Mr E Kearney

Signed …… Date: ……

Approval and sign-off	Name
Head of Department/Director	Dr S Stock, Head of Service Clinical Biochemistry

Signed …… Date: ……

	Name
Trust Board approval and sign-off	not applicable

Signed …… Date: ……

Appendix B – Author's Checklist of compliance with the Policy for the Development and Management of Organisation Wide Policies and Other Procedural Documents

POLICY:

To be completed and attached to any policy when submitted to the appropriate committee for consideration and approval.

	Requirement:	Compliant Yes/No/ Unsure	Comments
1.	**Style and format**	Yes	
2.	**An explanation of any terms used in documents developed**	Yes	
3.	**Consultation process**	Yes	
4.	**Ratification process**	Yes	
5.	**Review arrangements**	Yes	
6.	**Control of documents, including archiving arrangements**	Yes	
7.	**Associated documents**	n/a	
8.	**Supporting references**	Yes	
9.	**Relevant NHSLA criterion specific requirements**	n/a	
10.	**Any other requirements of external bodies**	n/a	
11.	**The process for monitoring compliance with NHSLA and any other external and/or internal requirements**	n/a	

Appendix C – Plan for Dissemination of Policies

To be completed and attached to any policy when submitted to the appropriate committee for consideration and approval.

Acknowledgement: University Hospitals of Leicester NHS Trust (Amended)

Title of document:	Primary hyperaldosteronism – guidelines for investigation		
Version Number:	8		
Approval Date:		**Dissemination lead:**	Elodie Hanon
Previous document already being used?	yes		
If yes, in what format (paper / electronic) and where (e.g. Directorate / Trust wide)?	Electronic on Trust websiote and QPulse		
Proposed instructions regarding previous document:	n/a		

To be disseminated to:	**How will it be disseminated, who will do it and when?**	**Format (i.e. paper or electronic)**	**Comments:**
Trust clinical staff	Trust website	electronic	
Primary care	Trust website	electronic	
Clinical Biochemistry staff	Q Pulse	electronic	

Author's Dissemination Record - to be used once document is approved – to be kept with the master document

Date document forwarded to be put on the Trust's central register / in SharePoint:		**Date document put on Directorate register (if appropriate) / on Directorate webpage (if applicable)**	

Disseminated to: (either directly or via meetings, etc.)	**By Whom?**	**Format (i.e. paper or electronic)**	**Date Disseminated:**