Alpha-1 Antitrypsin: guidelines for requesting

Version:	1.0
Ratified by:	Clinical Biochemistry Senior Staff Meeting
Date ratified:	24/05/2018
Name of originator/author:	Mr C Rowe
Director responsible for implementation:	Dr Edmund Lamb
Date issued:	13/06/2018
Review date:	27/07/2022
Target audience:	Healthcare professionals in primary and secondary care

Version control schedule

version	date	author	status	comment
1.0	27/07/2020	Mr C Rowe	Active	Reviewed by K Shah 27/07/2020 No changes required

Contents

1. Policy summary

This policy gives guidance on requesting alpha-1 antitrypsin (A1AT) measurement for the investigation of lung and liver disease where A1AT deficiency is suspected.

2. Introduction

Alpha-1 antitrypsin is a glycoprotein synthesised in the liver, with a molecular weight of 54 kDa. It is the predominant protein found in the α1-globulin fraction on serum protein electrophoresis, accounting for more than 90% of plasma tryptic inhibitory activity. Its major role in vivo is the inhibition of neutrophil elastase, a serine protease enzyme secreted by neutrophils and macrophages during inflammation, responsible for degradation of bacteria and host tissue. Markedly reduced A1AT concentrations are associated with tissue damage in the liver and lungs. Normal serum concentrations for wild type individuals are between 1.1 g/L – 2.1 g/L. Lower values are observed in the first twelve months of life and in the elderly. Increased concentrations are seen during pregnancy, in individuals taking exogenous oestrogens and in patients with an ongoing inflammatory response.

Alpha-1 antitrypsin deficiency is a rare genetic condition that can cause pulmonary emphysema, chronic obstructive pulmonary disease, acute neonatal hepatitis, neonatal cholestasis and progressive juvenile cirrhosis, chronic liver disease and panniculitis, a serious skin condition. A1AT deficiency is a potentially life-threatening condition affecting approximately 1:2,500 people in the European Union with severe deficiency (<0.6 g/L) occurring in the United Kingdom with an incidence of approximately 1: 2,000. Reduced capacity to inhibit elastase is seen in the 'deficiency' phenotypes such as PI ZZ and PI SZ, as well as the non-functional alleles such as Mduarte. The reduction in plasma tryptic inhibitory activity and failure to effectively inhibit elastase and macrophage lysosomal enzymes increases tissue damage during the active inflammation process. Smoking contributes to the severity of lung disease in deficient individuals.

A1AT deficiency related emphysema is said to account for 6% of all cases of emphysema in Western Europe and up to 20% of all cases of neonatal cholestasis (when congenital abnormalities of the biliary tract have been excluded). Patients with A1AT deficiency related emphysema are likely to have a poor quality of life (with some patients requiring a lung transplant), and an increased risk of early mortality. However, if the condition is diagnosed early and is appropriately managed, individuals have the possibility to lead a normal life.

3. Purpose and scope

This policy outlines the biochemical abnormalities that support a request for quantitative A1AT measurement. It is intended for use by healthcare professionals across both primary and secondary care.

4. Definitions

A1AT: Alpha-1 antitrypsin
PI: Protease inhibitor

5. Duties

All staff involved in the requesting of A1AT, whether clinical or laboratory must adhere to this policy.

6. Investigating suspected alpha-1 antitrypsin deficiency

6.1 Limitations of A1AT quantitative measurement

A1AT is a slow rising acute phase reactant. The plasma concentration of patients with the normal MM A1AT phenotype can rise two or three fold within days of trauma, acute infection or tissue necrosis. Persistent elevations in serum concentrations are seen in patients with chronic infections and malignant disease. Therefore a serum A1AT concentration within the stated reference range does not exclude A1AT deficiency. Ideally samples for quantitative analysis for the investigation of A1AT deficiency should be taken in the absence of, or after recovery from infection/inflammation.

6.2 A1AT quantitative analysis

A1AT quantitative analysis should only be requested/will only be processed if at least one of the following criteria is met:

- Adults with emphysema or asthma
- Individuals with chronic obstructive pulmonary disease
- Individuals with bronchiectasis
- Individuals with unexplained liver disease, this includes neonates, children and adults

- Asymptomatic individuals with persistent obstruction on pulmonary function tests with identifiable risk factors – cigarette smoking, occupational exposure
- Adults with necrotising panniculitis
- Family members of an individual with A1AT deficiency

- **Where a reduced alpha-1 globulin fraction is observed on serum protein electrophoresis, A1AT quantitative analysis will be added to the sample and processed providing the clinical details fit with the above criteria.**

A1AT quantitative analysis should **NOT** be requested/will **NOT** be processed in:

- Individuals with liver disease where the aetiology is clear (e.g. alcoholic liver disease, alcoholic hepatitis, viral hepatitis)

6.3 A1AT phenotyping requesting

The A1AT gene is located on chromosome 14. Polymorphisms in the gene give rise to protein products with differing mobility on isoelectric focussing. Thus PI (protease inhibitor) alleles are designated by alphabetic symbols corresponding their phenotype; their isoelectric point relative to the most common allele PI*M.

PI MM is the commonest phenotype in all populations and racial groups. PI*S and PI*Z alleles are more common in the Caucasian population. Only alleles which give rise to functional deficiency are of clinical relevance. The deficiency alleles include: S, P, W, Z, Mmalton, Mduarte, and null. Patients who are homozygous for one of these alleles, or who are heterozygous for any two, will usually have A1AT concentrations <0.6 g/L. Individuals who are heterozygous for one of these deficiency alleles with other “normal” alleles in the PI system will typically show A1AT concentrations between approx. 0.6 g/L – 1.4 g/L although this can be higher when there is a background acute phase response. Subjects with non-functional alleles e.g. Mduarte may have normal A1AT concentrations. Asymptomatic individuals who are found to be heterozygous for one deficiency allele are at relatively low risk of developing symptoms, although smoking may be a contributory factor in the development of emphysema in PI MZ heterozygotes.

- **Samples with an A1AT concentration ≤1.0 g/L will be referred for A1AT phenotyping to identify the presence of alleles known to be associated with more severe disease.**

A1AT phenotyping is indicated for:

- Family studies resulting from the identification of a subject with a severe deficiency state. These requests are usually under the guidance of Clinical Genetics.
- Spouses and prospective spouses of individuals found to be heterozygous for deficiency alleles, especially if there is a family history of A1AT deficiency associated disease on either side
- First degree relatives and spouses of an identified A1AT deficient patient
- All children with liver disease irrespective of their A1AT concentration.

7. Key Stakeholders, Consultation, Approval and Ratification Process

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

This document has been prepared in consultation with Dr Jo Sheldon, consultant immunologist at St George's Hospital, London. Consultation has been through e-mail communication between clinical biochemistry staff and medical consultants. CCG leads were also circulated with a draft of this policy and given the opportunity to comment. Email correspondence is stored on the shared drive.

8. Review and Revision arrangements

Three years from implementation date, by author.

9. Dissemination and Implementation

The guidance will be hosted on the Health Professionals/Pathology area of TrustNet, and will be proactively implemented 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 via Q-Pulse.

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. Alpha-1 in the European Union Expert recommendations. Recommendations of the Alpha-1 Expert group Initiated and chaired by Members of the European Parliament.
2. Protein Reference Units Handbook of Clinical Immunochemistry. Ninth Edition (2007). ISBN: 0-948722-15-0.

Appendix A - Equality Impact Assessment

Equality and Human Rights Impact Analysis (EHRIA)

Part One – Screening Tool

Name of the policy, strategy, function or methodology:	Alpha-1 Antitrypsin: guidelines for requesting

Details of person completing the EHRIA	
Name	Mr Ceri Rowe
Job Title	Senior Clinical Scientist
Department/Specialty	Pathology/Clinical Biochemistry
Telephone Number	723 6165

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 suspected Alpha 1 antitrypsin deficiency 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 Ceri Rowe, Senior Clinical Scientist

Signed …… Date: ……

Approval and sign-off	Name
Head of Department/Director	Mr Edward Kearney, 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:	Alpha-1 Antitrypsin: guidelines for requesting		
Version Number:	1.0		
Approval Date:		**Dissemination lead:**	Mr Ceri Rowe
Previous document already being used?	No		
If yes, in what format (paper / electronic) and where (e.g. Directorate / Trust wide)?	n/a		
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	Trustnet	electronic	
Primary care	Trustnet	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:**