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POSITION STATEMENT

Diagnosis and treatment of lung disease associated with alpha one-antitrypsin deficiency: A position statement from the Thoracic Society of Australia and New Zealand*

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ABSTRACT

AATD is a common inherited disorder associated with an increased risk of developing pulmonary emphysema and liver disease. Many people with AATD-associated pulmonary emphysema remain undiagnosed and therefore without access to care and counselling specific to the disease. AAT augmentation therapy is available and consists of i.v. infusions of exogenous AAT protein harvested from pooled blood products. Its clinical efficacy has been the subject of some debate and the use of AAT augmentation therapy was recently permitted by regulators in Australia and New Zealand, although treatment is not presently subsidized by the government in either country. The purpose of this position statement is to review the evidence for diagnosis and treatment of AATD-related lung disease with reference to the Australian and New Zealand population. The clinical efficacy and adverse events of AAT augmentation therapy were evaluated by a systematic review, and the GRADE process was employed to move from evidence to recommendation. Other sections address the wide range of issues to be considered in the care of the individual with AATD-related lung disease: when and how to test for AATD, changing diagnostic techniques, monitoring of progression, disease in heterozygous AATD and pharmacological and non-pharmacological therapy including surgical options for severe disease. Consideration is also given to broader issues in AATD that respiratory healthcare staff may encounter: genetic counselling, patient support groups, monitoring for liver disease and the need to establish national registries for people with AATD in Australia and New Zealand.

Key words: alpha1-antitrypsin deficiency, augmentation therapy, chronic obstructive pulmonary disease, emphysema.

INTRODUCTION

Alpha1-antitrypsin (AAT) deficiency (AATD) is an inherited disease that causes the production of defective AAT and low circulating blood levels of functioning

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AAT. This results, most commonly, in an increased susceptibility to pulmonary emphysema and liver cirrhosis. Rarer associations are necrotizing panniculitis and granulomatosis with polyangiitis while glomerulonephritis, inflammatory bowel disease and vascular aneurysm are possible associations.[1–3]

AAT is a member of the serpin superfamily of proteins, it is synthesized in the liver and acts as an irreversible proteinase inhibitor to protect tissues from the actions of inflammatory proteins, particularly neutrophil elastase. Protein synthesis is coded by two codominant alleles and, while many alleles have been detected within the human population, the most common are PiM (normal), PiS and PiZ, and pairings of these account for >99% of genotypes. Circulating AAT concentrations below 1.1 g/L usually define individuals with at least one deficiency allele and levels are reduced below 0.5 g/L in the most common AATD genotype, PiZZ.[4]

In Australia and New Zealand, the best information available suggests that the gene frequency for the PiZ allele is 13 and 22 per 1000, respectively.[5] This equates to similar predicted numbers of the severe form of PiZZ AATD as in North America of 1 in 2500 to 1 in 5000.[6] The frequency of the PiZ allele is reduced in most Asian populations and may be increased in Māori compared to New Zealand Europeans.[7] The less severely deficient PiS allele frequency is estimated to be 44 and 39 per 1000 in Australia and New Zealand, respectively.[8]

It is estimated that there are in excess of 30 000 individuals across Australia and New Zealand with AATD.[9,10] Many remain undiagnosed either because of a lack of clinical manifestation of their deficiency or through being unrecognized by their treating physicians. It has been reported, based upon allelic frequencies, that less than 10% of AATD individuals are diagnosed, while 1% of all patients with chronic obstructive pulmonary disease (COPD) have AATD.[11–15]

Understanding of the natural history of AATD is incomplete but the role of cigarette smoking is crucial.[16,17] There is some evidence that, while never-smoking individuals with AATD have an increased risk of developing COPD, they have a similar survival time to the general population.[17–19] Smoking individuals with AATD develop COPD 10–20 years earlier than smokers with normal AAT levels and they have a median survival time approximately 15 years less than their non-smoking AATD counterparts.[18,20]

Elements of care for the pulmonary manifestations of AATD for consideration by the clinician include usual care of COPD, surgical options and AAT augmentation therapy (regular infusion of AAT to increase an individual's blood levels above a threshold proposed to protect against lung disease). AAT augmentation therapy has been available in the United States and elsewhere for many years.[21] Its clinical efficacy has been the subject of some debate[22] and the use of AAT augmentation therapy was recently permitted by regulators in Australia and New Zealand, although treatment is not presently subsidized by the government in either country.

The purpose of this position statement is to provide information to clinicians on the investigation and treatment of AATD and it does not represent a guideline. It is divided into four sections covering (i) diagnosis, (ii) AAT augmentation therapy, (iii) surgical options and (iv) other pharmacological and non-pharmacological care of COPD written in a question-and-answer format. This position statement is endorsed by the Thoracic Society of Australia and New Zealand (TSANZ) and will be disseminated through publication in *Respirology*. The clinical relevance of this document will be reviewed at 5 years from publication.

METHODS

To create the position statement, J.D. was appointed to chair a working group of 14 members selected for their expertise in the diagnosis and treatment of AATD and COPD. The working group comprised eight respiratory physicians, a respiratory nurse, a respiratory scientist, a hepatologist, a cardiothoracic surgeon, a pharmacoepidemiologist and one patient representative, and there was representation from across Australia and New Zealand. Two patient representatives were added after the initial draft of the manuscript for participation in the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) panel. The panel worked with a methodologist, A.E.H., who is a physiotherapist. The methodologist prepared evidence summaries for the AAT augmentation section and participated in discussions but did not vote on recommendations. The majority of the working group did not have a conflict of interest and the working group did not receive any commercial sponsorship. In initial meetings, we developed and agreed principles for managing conflicts of interest (Appendix S1 in Supplementary Information),[23,24] we defined the scope of the position statement and we assigned sections to writing groups. Each writing group undertook a comprehensive literature review for their section. The sections were collated into a manuscript and all members of the working group and two additional patient representatives then had the opportunity to contribute to and review the entire document.

Because we anticipated there would be a variety of views on AAT augmentation therapy, both within the working group and the wider Australian/New Zealand respiratory community, we completed a systematic review of the relevant literature for this section and used the GRADE process to move from evidence to recommendation.[25] The risk of bias was assessed using the Cochrane Risk of Bias tool for randomized trials.[26] The methodologist created evidence profiles for each outcome of interest, which categorized the certainty of evidence as high, moderate, low or very low. The panellists reviewed the evidence tables (Appendix S2 in Supplementary Information) and provided feedback. We used the GRADE framework to move from evidence to recommendation.[25] This included assessments regarding the balance between desirable and undesirable consequences, patient values and preferences, costs, feasibility and acceptability of AAT augmentation therapy. The panel met by teleconference to discuss the evidence profiles and formulate a

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recommendation. Voting on this recommendation was conducted anonymously online.

DIAGNOSIS OF AATD

Who should be tested for AATD?

What are the characteristics of patients most likely to have AATD?

Patients with AATD most often present with dyspnoea and to a lesser extent cough and wheeze.[13,27] Lung disease in AATD is characteristically premature (<45 years), pan-lobular emphysema with lower zone predominance; however, upper zone predominance of emphysema and bronchiectasis and partially reversible airflow obstruction are also well recognized.[3,27,28] The World Health Organization (WHO) recommendations, which are supported by the European and North American guidelines for AATD management, are that all adults with chronic airflow obstruction or assumed diagnosis of adult-onset asthma be screened for AATD, although local and international asthma guidelines do not make a similar recommendation.[1,12,29–33] We suggest that AATD testing should be considered in patients with asthma when clinically relevant, particularly in patients with persistent airflow limitation, emphysema disproportionate to the smoking history or in the presence of liver or skin disease.

Lung disease is seen in the severely deficient patients, most commonly PiZZ, but also rarer alleles, either homozygous or heterozygous with another severely deficient allele such as PiMmalton or Pi Null variants.[3,13,27,34] Lung disease in AATD, although common in never-smokers, is much more common, occurs earlier, is more severe and progresses more rapidly in smokers. A summary of the progression of emphysema in AATD reported that in PiZZ siblings of index cases, emphysema occurred in 90% of smokers and 65% of non-smokers.[3,34] Annual loss of forced expiratory volume in 1 s (FEV_1) in AATD is 23–316 mL with the greater losses associated with smoking, male gender, age between 30 and 44, FEV_1 between 35% and 79% predicted, reduced AAT levels and airway responsiveness.[3,35] This highly variable decline in FEV_1 has been shown to exceed that consistent with normal ageing in 76% and 42% of those with and without established COPD, respectively.[36] PiMZ heterozygotes have an increased risk of obstructive lung disease in smokers but not in non-smokers.[37,38] PiSZ heterozygotes likely have an increased risk of emphysema in smokers but the data from studies are not conclusive.[12,39,40] PiMS and PiSS phenotypes are not at increased disease risk.[39,41,42]

Lung function in AATD is often characterized by earlier reduction in gas transfer and FEV_1 often declines later in disease progression.[11,27] However, similar to other lung manifestations there is wide variability between individuals.[14,35,36,43,44] A recent study in the United Kingdom reported a decline in gas transfer greater than 1% predicted per year in 50% of AATD patients with normal spirometry, whereas only 25% had a decline in FEV_1 greater than 1% predicted per year, suggesting better sensitivity of gas transfer for detecting progression in early disease. The difference in the two measures was less in patients who already had COPD.[36] Lung volumes help further characterize the physiological impact of hyperinflation and gas trapping.[6]

Computed tomography (CT) lung scans help define the pattern and extent of disease in AATD even in those with normal lung function.[6,45] CT lung densitometry is currently a valuable research tool in quantitating emphysema in AATD studies but its role in patient management remains unclear.[6,12,46]

What are the reasons for testing for AATD?

Identification of patients with or at risk of lung disease (severely deficient patients, PiMZ and PiSZ heterozygotes) associated with AATD prompts genetic counselling (see section *AAT augmentation therapy*) and advice regarding additional risk factors such as smoking and occupational exposures.[3,6,11,12,15] Identification of individuals for consideration of specific treatment, should it become available, or clinical trials for specific treatment of AATD, is important.[3,6,12,15] Furthermore, identification of at-risk phenotypes for liver disease (e.g. PiZ and PiMmalton) leads to recommendations regarding reduction of exposure to hepatotoxins, relevant vaccinations and monitoring of progression of disease and development of complications, especially hepatocellular carcinoma.[3,6,12,15] Identification of AATD in necrotizing panniculitis and granulomatosis with polyangiitis allows better understanding of the pathogenesis of their disease and may lead to specific therapies and/or involvement in clinical trials. Understanding disease progression and disease associations is enhanced by monitoring those with known AATD and AAT variation.

Has screening for AATD in patients at risk shown to improve clinical outcomes?

There are limited data on the clinical benefit due to screening of relatives of index cases or targeted screening of potential AATD patients. The diagnosis of AATD in patients with obstructive lung disease allows consideration of specific treatment or clinical trials of specific treatment (see section *Diagnosis of AATD*). Screening for liver disease helps to identify patients at higher risk of developing liver complications who may benefit from closer surveillance.[47,48] Data from neonatal screening studies suggest that awareness of the deficiency reduces smoking behaviour in patients with identified AATD; however, screening increases parental stress and can have a negative impact on parent–child relationships.[49,50]

Summary

- **Clinical and physiological presentation of AATD is variable.**
- **Testing for AATD should be considered in all patients with chronic airflow obstruction.**
- **Testing for AATD should be considered in asthma patients with persistent airflow limitation, emphysema disproportionate to the smoking history or in the presence of liver or skin disease.**

- **Baseline tests in AATD-related lung disease should include spirometry, lung volumes, gas transfer and CT chest scan.**
- **Identification of AATD patients allows interventions to reduce risk of disease, consider genetic counselling, monitor disease progression and associations and offer specific treatments.**
- **Demonstrably improved clinical outcomes from screening for AATD are limited.**

How do we make the diagnosis of AATD?

What are the available tests?

AATD is diagnosed by a combination of serum AAT levels, AAT phenotyping and/or AAT genotyping (most commonly by polymerase chain reaction or PCR) and/or AAT gene sequencing. More than 150 AAT variants have been described.[51] Most have been identified by isoelectric focusing (IEF) and many further characterized by gene sequencing.[3,6,11,12,15]

AAT levels. AAT levels are usually measured on serum by nephelometry.[1,3,12] Normal levels of AAT vary depending on the test used. For nephelometry, a level below 1.1 g/L usually defines patients with at least one deficiency allele.[4,14] As AAT is an acute phase reactant, borderline levels or levels which do not concur with clinical impression should lead phenotypic or genotypic analysis.[11] AAT and C-reactive protein (CRP) levels are measured concurrently: this may identify patients with an inflammatory state potentially affecting AAT levels.[3,12]

Severely deficient phenotypes, most commonly PiZZ but also Pinullnull, Znull and some rarer variants, usually have levels of AAT below 0.5 g/L.[4] Intermediate deficiency phenotypes (PiMS, PiSS, PiMZ and PiSZ in order of decreasing levels with overlap) have levels of AAT between 0.5 and 1.4 g/L. PiMS individuals can have levels within the normal range and some with the PiSZ phenotype have levels below 0.5 g/L. The sensitivity and specificity of AAT levels in determining AAT-deficient alleles depends on the cut-off value for defining deficiency. A level below 1.1 g/L will capture most carriers of the most common deficiency alleles, S and Z, as opposed to PiMM individuals (sensitivity: 73.4%, specificity: 88.5%).[4,12] Some AAT types are dysfunctional (e.g. Z and F) so AAT levels do not truly reflect the protective capacity of the protein.[3,13]

AAT phenotyping. AAT phenotype is determined by IEF. The variants of AAT denoted A–Z migrate differently in the IEF gel at pH 4–5. The Z protein, which folds incorrectly and forms aggregates, moves most slowly whilst F, for example, moves quickly. The most common M variants migrate in the middle of the gel. Some rarer M variants are difficult to distinguish from the common variants on IEF, and the null alleles produce no AAT protein in the serum, so that as with AAT levels if IEF-defined AAT phenotype does not seem to coincide with AAT levels then genotyping or gene sequencing is needed to define the variant.[1,3,13]

AAT genotyping. AAT genotyping is usually done by PCR. It can only test for those variants for which PCR primers are available.[52,53] There are now methods available to test multiple alleles covering more than 99% of patients with abnormal alleles.[54] These tests can be undertaken on buccal swabs or dried blood spots. It is expected that these methods will become available in Australia. When available, this approach would become the preferred second test after AAT levels (as opposed to IEF).[3,6,12]

AAT gene sequencing. Gene sequencing has become more practical with newer techniques but remains highly specialized and is generally used only to characterize rare variants in situations where, after AAT levels, AAT phenotype and possibly genotype, a high index of suspicion of a deficiency variant remains. This would most commonly be with a null variant.[6,12]

What is the sequence of tests?

The first screening test should be AAT levels (and CRP) followed by IEF or genotyping (if available) if there is concern for deficiency.[1,3,4,11,12] Gene sequencing might be undertaken if there is still a suspicion of deficiency variant. It has been suggested that if a PiMM phenotype has AAT levels less than 0.9 g/L or a PiMZ or PiMS phenotype has levels less than 0.7 g/L, then gene sequencing should be undertaken to search for rare deficiency alleles. The vast majority of variants will be captured by this approach with the exception of very rare gene deletions and intron mutations.[4,11,12]

Summary

- **AAT levels can determine who should have further testing with a high degree of sensitivity and specificity and should be measured with CRP.**
- **AAT phenotyping by IEF or genotyping by PCR should be undertaken when AAT variation is suspected after clinical assessment and testing of AAT levels.**
- **IEF for AAT will be surpassed by AAT genotyping as this technology becomes more readily available.**
- **AAT gene sequencing may be used for selected patients with suspected rare AAT alleles not detected by IEF or genotyping.**

AAT AUGMENTATION THERAPY

In patients with AATD, does augmentation therapy improve outcomes compared to usual care?

Introduction

AAT augmentation therapy is currently the only specific therapy available for AATD. Augmentation therapy, so

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called because it augments the circulatory concentrations of AAT serum levels above a proposed protective threshold,[55,56] consists of intravenous (i.v.) therapy with exogenous AAT protein that is harvested from pooled blood products.[57] AAT augmentation therapy was first approved by the United States Food and Drug Administration in 1987 for emphysema associated with severe AATD.[21] Several AAT augmentation therapy preparations are available, all of which have to be administered intravenously, usually on a weekly basis.[57]

In Australia, AAT augmentation therapy was first approved by the Therapeutic Goods Administration in November 2016; however, it is not subsidized by the Australian Government. There are currently two AAT preparations, which are listed on the Australian Register of Therapeutic Goods and thus can be lawfully supplied in Australia: Prolastin-C alpha 1-proteinase inhibitor (Grifols Australia Pty Ltd, Melbourne, Australia) and Zemaira alpha 1-proteinase inhibitor (CSL Behring Australia Pty Ltd, Melbourne, Australia). Medsafe, the New Zealand Medicines and Medical Devices Safety Authority, registered Glassia alpha 1-proteinase inhibitor (Shire New Zealand Ltd, Auckland, New Zealand) in November 2017.

AAT augmentation therapy has been approved by several national drug administration and safety authorities based on its effect to raise AAT levels,[58] without evidence of the effectiveness of treatment based on clinically important outcomes such as quality of life or mortality or validated surrogate markers.[59]

A number of systematic reviews have been conducted on the topic of treatment for AATD,[60–62] including a 2016 Cochrane review, which included three randomized controlled trials (RCT).[63] The most recent international statement on the diagnosis and treatment of AATD was published by the European Respiratory Society (ERS) in 2017[12] —the first international statement since publication of the joint statement on AATD by the American Thoracic Society (ATS) and the ERS in 2003.[1] The Canadian Thoracic Society published clinical practice guidelines on targeted testing for AATD and augmentation therapy in 2012.[64] We conducted a systematic review aiming to determine whether AAT augmentation therapy improves health outcomes when compared to usual care in patients with AATD.

Methods

We reviewed all studies included in the most recently published systematic review on AAT augmentation therapy published in May 2017, which included studies published up until April 2015.[65] We updated the literature search using the following electronic bibliographic databases: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R); Embase; Cochrane Central Register of Controlled Trials; and Cochrane Database of Systematic Reviews. The literature search was conducted with the help of an experienced research librarian. Databases were searched from January 2015 to 12 July 2018 (we searched from January, rather than April, 2015 to ensure that no relevant papers were missed). Details of the search strategy can be found in Appendix S3 (Supplementary Information).

RCT and observational studies with a comparator group published in any language that reported on the effectiveness of AAT augmentation therapy in adults aged 18 years or older with AATD, with or without formal diagnosis of COPD, and with any smoking status (current, ex-smoker and never-smoker), were eligible for inclusion. Outcomes of interest were mortality, exacerbations/lung infections, quality of life, healthcare use (emergency department visits and hospitalizations), lung function measurements and lung density measured by CT. We excluded studies that measured biochemical outcomes only (e.g. plasma or serum AAT level) and studies with no parallel comparison group (e.g. studies that assessed the same cohort before and after an intervention).

All titles and abstracts and the full texts of all articles identified on the basis of title and abstract were assessed by at least two independent reviewers. Data were extracted using a standardized form for characteristics (author, study design, inclusion and exclusion criteria, patient characteristics, interventions, comparisons and outcomes). Outcome categories were grouped and analysed without quantitative pooling. We then used the GRADE process to move from evidence to recommendation as described above.[25]

Results

The literature search identified 420 unique citations, of which 43 were included for full-text review and 8 studies met the inclusion and exclusion criteria (Appendix S4 in Supplementary Information). Appendix S5 (Supplementary Information) gives an overview of the included studies. Three studies were RCT,[60–62] one study was an open-label extension of an RCT[46] and four studies were retrospective cohort studies.[66–69] The evidence profiles for each outcome can be found in Appendix S2 (Supplementary Information).

Lung density measured by CT. Lung density on CT as a marker of emphysema progression was assessed in three RCT.[60–62] Two RCT did not find a significant difference in the change of lung density between the group treated with AAT augmentation and placebo, but both were underpowered.[61,62] A larger trial by Chapman *et al*. found a significant difference in the annual rate of lung density loss between the AAT augmentation group and the placebo group when lung density was measured at total lung capacity (TLC), but not when it was measured at functional residual capacity (FRC) or when FRC and TLC were combined.[60] A pooled estimate of the effectiveness of AAT augmentation therapy on lung density measured by CT in the three RCT was obtained in a Cochrane review, which showed significantly less deterioration in the AAT augmentation treatment group compared with the placebo group over the 2–3 years of follow-up (pooled mean difference of change in lung density: 0.86 g/L/year (95% CI: 0.31–1.42, $P = 0.002$)).[63]

Lung function. Lung function parameters were the most commonly measured outcomes in the reviewed studies. There was no significant difference in overall change in FEV_1 between the AAT augmentation and control groups in three RCT[60–62] and two retrospective cohort studies.[66,69] One retrospective cohort study found that the annual decline in FEV_1 in the AAT augmentation group was significantly lower than in the untreated group ($P = 0.02$).[68] Change in the diffusion capacity of the lung for carbon monoxide (DL_{CO}) and change in the transfer coefficient of the lung for carbon monoxide (K_{CO}) were measured in three[60–62] and two studies,[61,62] respectively, and showed no significant differences between groups.

Exacerbations/lung infections/hospitalizations. Two RCT assessed the impact of AAT augmentation therapy on exacerbations.[60,62] There was no significant difference between the AAT augmentation group and the control group in the frequency or duration of exacerbations.

Quality of life. Two RCT measured changes in quality of life using the St George's Respiratory Questionnaire (SGRQ) and did not find any significant differences between the AAT augmentation therapy group and the control group.[60,62]

Functional capacity. There was no significant difference between AAT augmentation therapy group and control group in functional capacity change, measured as change in an incremental shuttle walk test in an RCT[60] and as change in 6-min walking distance (6MWD) in an observational study.[67]

Mortality. None of the reviewed studies were powered to evaluate mortality as an outcome. Of the studies that reported deaths,[60,62,66,69] one showed a significantly higher risk of mortality in the control group.[66]

Adverse events of AAT augmentation therapy. In the three studies that reported adverse events (two RCT[60,62] and one open-label extension study following an RCT[46]), adverse events were frequently reported in the treatment as well as in the control group with no significant difference between groups.

Recommendation

- **Augmentation therapy could be considered in non-smoking patients with AATD (conditional recommendation and low-quality evidence).**

Panel vote: eight in favour, five against and four abstain.

Justification. The panel expressed a wide variety of views regarding whether AAT augmentation therapy should be offered, and we could not reach consensus on this recommendation. We have made a conditional recommendation because, while clinical trials do not currently provide conclusive evidence of benefit, weaknesses in this body of evidence mean that a benefit cannot be excluded, and some panel members noted their own experience of improvement in patient well-being, which they attributed to AAT augmentation therapy. There are no important side effects (based on the available evidence), although the burden of weekly i.v. infusion and costs of treatment should be considered. AAT augmentation therapy can be considered on a case-by-case basis using shared decision-making. We acknowledge the resignation and withdrawal of authorship of one panel member on the basis that a strong recommendation in favour of AAT augmentation therapy should have been made. We also acknowledge that some panel members felt that any potential benefits of AAT augmentation therapy were outweighed by its substantial costs.

Subgroup considerations. People with AATD-related COPD who continue to smoke should not be eligible for augmentation therapy as the constituents of cigarette smoke will likely make this therapy less effective and all RCT have excluded current smokers.

Implementation. Consideration should be given to establishing specialist centres to oversee delivery of this treatment.

Monitoring and evaluation. Given the uncertainty around long-term outcomes that cannot be adequately measured in the timeframes of clinical trials, the panel strongly recommends that an Australian/New Zealand registry is established. The registry should monitor smoking status, lung function, exercise capacity and health-related quality of life in patients with AATD-related COPD. The registry should be independent and should regularly report to government.

Research priorities. Further research is necessary to establish the effect of AAT augmentation therapy on mortality, as well as long-term effects on health-related quality of life, exercise capacity and lung function. Further research is also required to establish the relationship between change in rate of decline of lung density measured by CT and mortality, health-related quality of life, exercise capacity and lung function.

LVRS AND LUNG TRANSPLANTATION

In some patients with AATD-related emphysema, disease progresses to an advanced stage where surgical options for management should be considered. For lung transplantation, the International Society for Heart and Lung Transplantation (ISHLT) guidelines for the selection of lung transplant candidates with COPD recommend referral for lung transplant assessment when the FEV_1 is <25% predicted, with listing for lung transplantation recommended when the FEV_1 is <20% predicted or when there have been three or more severe exacerbations during the preceding year, or one severe exacerbation with acute hypercapnic respiratory failure independent of the measured FEV_1.[70] In this

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section of the position statement, we review the evidence for the efficacy of lung transplantation and lung volume reduction therapies in the management of patients with AATD-related emphysema.

In patients with AATD, does lung volume reduction therapy improve outcomes compared to usual care?

A 2016 Cochrane review on lung volume reduction surgery (LVRS) in patients with emphysema concluded that LVRS leads to a decrease in long-term mortality.[71] Note should be made that the patients were highly selected and the results were heavily influenced by data from a single study (National Emphysema Treatment Trial, NETT)[72] of which only 1.3% of patients had AATD. High rates of post-operative complications, especially persistent air leak and pneumonia, were noted.

There are several published case series of LVRS in patients with AATD; however, the total number of published cases is less than 100.[73–78] Overall, these case series suggest some improvement in lung function and symptoms at 12 months; however, the magnitude of benefit appears less than for those with conventional smoking-related emphysema. Cassina *et al.* suggest that the differences in emphysema pathology and anatomy in AATD could explain the difference in results.[73]

There is good evidence to support endobronchial lung volume reduction with the use of endobronchial valves in highly selected patients with cigarette smoking-related emphysema. A 2017 Cochrane review noted short-term (up to 1 year) improvements in lung function and disease status with high rates of adverse events especially pneumothorax.[79] It is important to note that patients with AATD were excluded from these trials. Two case series describing the use of endobronchial lung volume reduction in AATD with a total of 21 patients have been published.[80,81] Short-term improvements in lung function and symptoms were described.

Lung volume reduction by conventional surgery or by endobronchial techniques for the management of AATD remains controversial with very small case numbers, very low representation in NETT and no representation in endobronchial controlled trials. Reported cases are highly selected and reports of positive outcomes may be subject to reporting and other biases. Definitive recommendations cannot be made until long-term data from RCT are available.

Summary

- **Lung volume reduction therapy (outside of clinical trials) is not advised for AATD due to a lack of evidence supporting its use.**

In patients with AATD, does lung transplantation improve outcomes compared to usual care?

Lung transplantation provides a viable treatment option for selected patients with end-stage lung disease. Until June 2017, almost 65 000 adult lung transplant procedures had been reported to the ISHLT Registry, with the number increasing year-on-year. Now 4500 are reported each year globally.[82] Until 2017, the most common indication for lung transplantation was COPD unrelated to AATD, accounting for approximately 30% of procedures.[83] However, there have been an increasing number of transplants performed for idiopathic pulmonary fibrosis (IPF) over the past decade, so that from 2017 IPF became the most common indication for lung transplantation worldwide.[82] The proportion of transplants performed for patients with AATD-related emphysema has fallen from 15% 25 years ago to under 5% over the past decade. However, the absolute number of transplants performed has remained relatively static.[83] Another important trend over the past two decades has been the dramatic increase in the proportion of patients receiving bilateral, rather than single, lung transplants, particularly for obstructive lung diseases. In 2016, 94% of patients transplanted for AATD-related emphysema received a bilateral procedure,[82] with these patients experiencing superior survival.[82] Despite this growing activity, there have been no controlled studies performed to determine the effectiveness of lung transplantation for any indication, let alone for AATD-related emphysema. However, multiple cohort studies describing outcomes in individuals with severe AATD-related emphysema who enrolled in national registries have been published.

Quality of life

Only one study was identified that systematically investigated the impact of lung transplantation on quality of life in patients with AATD-related emphysema. Stone *et al.* studied 32 patients who were transplanted in the United Kingdom, matched with 48 patients who did not undergo lung transplantation selected from the UK Registry. In 14 patients for which quality of life data were available, lung transplantation was associated with marked improvements in the SGRQ scores across all domains, with the total score falling (improving) from 67.5 (51–77.8) to 7.5 (5–13.8, $P \leq 0.01$).[84] In the largest study addressing the benefit of lung transplantation on quality of life in patients with a variety of disease indications, the Toronto programme found that transplantation conferred a very large improvement in health-related quality of life across multiple instruments, with the SGRQ score falling by 46.5 (48.4–44.5) points. Improvements in quality of life were similar across diagnostic groups, although the number of patients with AATD-related emphysema was very small.[85] In a multicentre US study that included 131 lung transplant recipients, large improvements in the Medical Outcomes Study 36-Item Short-Form Health Survey, version 2 were seen in the first year after transplantation. This benefit was seen in all patient groups, including those with COPD; however, the number of patients with AATD-related emphysema was not described.[86] The Hannover group also described very substantial improvements in health-related quality of life for all solid organ transplant types, including 112 lung transplant recipients.[87]

Quality of life outcomes are not captured by the ISHLT Registry. However, despite the paucity of published studies, the magnitude and consistency of these benefits suggest that lung transplantation may improve health-related quality life for patients with AATD-related emphysema.

Survival

As there have been no randomized studies performed, we are reliant on evidence from cohort studies of patients who have undergone transplantation, matched as closely as possible with patients with similar disease severity who did not undergo transplantation. Several cohort studies have assessed transplant-free survival in patients with severe (generally PiZZ) AATD-related emphysema. In the largest US study, Stoller *et al*. studied 1129 National Heart, Lung, and Blood Institute Registry participants and found that 3-year mortality was 36.2% in those with an FEV_1 < 15% predicted at enrolment, 20% in those with FEV_1 15–19% predicted and 13.5% in those with an FEV_1 between 20 and 34% predicted. The 5-year mortality was 53%, 43% and 25%, respectively.[88] This large registry study hence provides reference measures for 3- and 5-year survival in patients with AATD-related emphysema without lung transplantation, therefore allowing an estimate of any survival benefit associated with lung transplantation.

In a large Swedish study, survival in 83 patients with PiZZ AATD who underwent transplantation was compared to that of 70 matched controls. The mean FEV_1 was 22% predicted in the transplant and 23% predicted in the control groups, respectively. Transplantation was associated with significantly better survival (median 11 vs 5 years, $P = 0.006$) even though the majority (75%) of patients received a single lung transplant.[89] As noted above, in the modern era, almost all patients receive bilateral lung transplants with these procedures associated with superior long-term survival.[90] In a Danish registry study which included all patients who commenced long-term oxygen therapy ($n = 21\,964$; $n = 234$ with AATD-related emphysema), 38% of the AATD patients were transplanted. There was a significant survival advantage (hazard ratio (HR) for death 0.66 (95% CI: 0.44–0.99); median survival 6.0 years with, and 3.3 years without, lung transplantation) for patients transplanted whilst receiving long-term oxygen therapy.[91] In a similar Swedish study, data for 14 644 patients with COPD (284, 1.9%, with AATD-related emphysema) who received supplementary oxygen therapy were available. Median survival in the AATD-related emphysema group was very similar to the Danish study at 7.2 years with and 3.5 years without transplantation.[92] Both these groups had a mean FEV_1 of 22% predicted. The 1-, 3- and 5-year survival rates without transplantation were 84%, 55% and 36%, respectively—all significantly lower than registry-reported post-transplant survival rates. In summary, these non-randomized studies appear to support a survival benefit of transplantation in patients with AATD-related emphysema with an FEV_1 <25% predicted and/or those prescribed supplementary oxygen therapy.

In contrast, in the UK registry study, 32 patients who received 28 bilateral and 4 single lung transplants experienced similar survival after transplantation (81.3% 90-day, 74.2% 1-year, 52.9% 5-year and 45.2% 10-year survival) compared to the non-transplanted group.[84] However, the non-transplanted group had slightly better lung function (26.3% vs 23.1%), and the early post-transplant survival described in this study is significantly worse than that reported in the International Thoracic Organ Transplant Registry,[90] especially for AATD where post-transplant survival is superior to all other diagnoses (including cigarette smoking-related emphysema) except cystic fibrosis.[83] The reported post-transplant survival is also significantly worse than that reported by Australian transplant programmes (90%, 74% and 68% at 1, 3 and 5 years, respectively).[93]

Overall, the existing literature points towards a potential survival advantage for transplantation in patients with very severe disease (FEV_1 < 25% predicted, most of whom will be receiving supplemental oxygen therapy) as this group experiences poor survival without transplantation. A survival benefit of lung transplantation is less clear for patients with better lung function.

Summary

- **Lung transplantation likely provides both quality of life and survival benefits for selected patients with very severe AATD-related emphysema.**

MANAGEMENT OF AATD (OTHER THAN AUGMENTATION THERAPY AND SURGERY)

Should AATD patients be treated with the same usual care as non-AATD COPD?

Principles of non-pharmacological and pharmacological management of COPD[94–96] apply to AATD patients,[6,12] especially those patients who have chronic airflow limitation. This is based on the rationale that these management principles are relevant to COPD patients in general, whatever the underlying cause (AATD-related or non-AATD), as these strategies aim to reduce symptoms, improve quality of life and prevent risk of exacerbations.

Non-pharmacological management

Non-pharmacological therapy is important in the management of patients with AATD-related COPD, in addition to pharmacological, augmentation and surgical approaches. Avoidance of active cigarette smoking, or smoking cessation if the patient is a current smoker, are critical preventive measures.[17] Current smokers should be supported with behavioural counselling, together with pharmacotherapy for nicotine dependence, although side effects of pharmacotherapy need to be managed.[97]

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Vaccination against vaccine-preventable respiratory viral infections is effective in COPD. Annual influenza vaccination is recommended in people aged 65 years and older to lower the risk of influenza-like illness,[98] and in people with COPD to reduce exacerbation rates,[99] with limited, non-randomized data regarding influenza vaccination in patients with AATD.[100] The antibody response to pneumococcal polysaccharides is preserved in AATD, and pneumococcal vaccination protects against community-acquired pneumonia and reduces exacerbation rates in the wider group of all patients with COPD.[101,102]

Exercise and education are important components of the non-pharmacological management of patients with COPD. Pulmonary rehabilitation, consisting of a comprehensive supervised exercise programme combined with education, is highly recommended for symptomatic patients with COPD, to improve exercise and quality of life and reduce exacerbation rates.[103] The benefit from the exercise component of pulmonary rehabilitation appears to be similar in AATD-related and non-AATD-related COPD.[67] Education and self-management support, including COPD action plans,[104] are useful components of chronic disease management for COPD.

Pharmacological management

There are limited data about the use of inhaled therapy, oxygen and treatment of exacerbations in COPD patients with AATD. In one large study, implementation of a management plan associated with increased adherence to pharmacological therapy was shown to reduce exacerbations and unscheduled healthcare use and improve health-related quality of life.[105] A post hoc analysis of another study suggested that inhaled corticosteroid could be useful in patients with AATD-associated COPD who have persistent peripheral blood eosinophilia.[106] Prescription of inhaled therapy, oxygen and treatment of exacerbations in AATD should be considered using similar principles to other patients with COPD.[94–96]

Extrapulmonary manifestations: Management of liver complications

AATD causes chronic hepatitis and its sequelae including liver fibrosis, cirrhosis and hepatocellular carcinoma.[107] In PiZZ individuals, AAT protein misfolding favours polymerization within the endoplasmic reticulum, inhibits its secretion and leads to accumulation in hepatocytes resulting in apoptosis, upregulation of the inflammatory cascade and ensuing fibrogenesis and hepatocarcinogenesis.[108]

The ATS and ERS suggest monitoring liver function annually, acknowledging an evidence-based testing protocol is yet to be established.[1] A recent large study of adults with AATD caused by the PiZZ mutation showed significant liver fibrosis in 20–36% of individuals on non-invasive testing and no evidence of a relationship between lung function and liver fibrosis.[109] While increased age, male sex, elevated liver enzymes and low platelet numbers are associated with increased liver fibrosis, the damage in AATD is mostly clinically silent and often without elevated liver enzymes even in the setting of advanced liver disease.[109,110] Therefore, the diagnosis of AATD-related liver disease may be delayed until the identification of a significant event such as the development of liver cirrhosis or hepatocellular cancer, which are associated with a poor prognosis.[107]

Liver biopsy is the gold standard for staging liver fibrosis but is unsuitable for the screening or follow-up of asymptomatic patients due to the risk of complications, pain and sampling error.[111–113] Transient tissue liver elastography, magnetic resonance elastography and ultrasound elastography are increasingly used for non-invasive assessment of liver fibrosis. These modalities have been shown to have similar accuracy compared to others in screening for the presence of significant liver fibrosis in AATD and to identify patients at higher risk of developing liver complications who may benefit from closer surveillance.[47,48,109] In patients with AATD and established cirrhosis, six-monthly targeted testing for hepatocellular carcinoma with ultrasound examination of the liver together with serum alpha fetoprotein has been recommended.[114]

Although i.v. augmentation therapy of pooled human AAT protein is available as a supportive therapy for adults with lung disease, it is not recommended in patients with liver disease as the mechanism of liver injury is the accumulation of defective AAT in hepatocytes rather than anti-protease deficiency. Currently, there is no effective treatment for AATD-related liver disease except for liver transplantation. Recipients express the donor phenotype and therefore they do not experience recurrence of liver disease. In addition, the progression of lung disease is halted, and both adults and children with AATD have excellent overall survival post-liver transplant at 5 years >85%.[115,116] Management also focuses on supportive measures such as nutrition, bone health and mental health to reduce the complications of chronic liver disease. Encouragingly, current research is exploring several innovative small molecule and gene-based strategies which are now in clinical trials and aim to reduce proteotoxicity and maintain protein homeostasis in the liver.[117]

Genetic counselling

It is important that patients and families understand the medical, psychological and familial implications associated with a diagnosis of AATD. Close relatives of individuals with AATD have an increased risk of carrying at-risk alleles and should be offered genetic counselling and testing for AATD.[6,12,51,118] We recommend referral to a genetic counselling service (details of local services are available from the Australasian Society of Genetic Counsellors at hgsa.org.au/asgc), which provides interpretation of family and medical histories, education about inheritance and testing, and counselling to promote informed choices and adaptation to the disease or risk of its development in family members.[119]

Summary

- **Smoking cessation is critically important in all individuals with AATD whether they have COPD.**

- **Patients with AATD-related COPD should be considered for treatment according to the principles of management of COPD in general.**
- **Patients with AATD should be monitored for liver involvement with liver biochemistry; monitoring with ultrasound and non-invasive modes of fibrosis assessment should be considered.**
- **Individuals with AATD-related lung and liver disease should be jointly managed by respiratory physicians and hepatologists.**
- **Referral of individuals with AATD for genetic counselling is recommended.**
- **First-degree relatives of individuals with AATD patient should be offered genetic counselling and testing for AATD.**

How should we monitor disease progression in AATD?

Progression of symptoms and disease markers is highly variable in people with AATD, being influenced by current smoking, presence of asthma and bronchiectasis, and other gene–environmental interactions.[12]

Lung function tests

Lung function, as measured by FEV_1 and DLCO naturally declines with age in the general population; however, decline in lung function can be accelerated in some people with AATD.[36] Although lung function measures are often variable and may not be fully sensitive to changes in people with AATD,[12] they are easy to perform and have reasonable utility in COPD.[94–96] Spirometry and DLCO may be considered for yearly follow-up to detect accelerated physiological decline.

Other tests

Whilst measurement of lung density on CT has been a sensitive tool to detect differences in rate of change of emphysema in research trials,[120] there is insufficient evidence for regular follow-up CT chest scans in the routine management of patients with AATD.

Summary

- **Lung function testing (annual spirometry and DLCO) is suggested for monitoring disease progression in people with AATD-related COPD.**

How should we care for patients heterozygous for AATD?

The frequency of MZ individuals in Australia and New Zealand is similar to the 2–5% reported in other populations with significant European descent but it may be greater than this among New Zealand Māori and lower among Australian Aboriginal peoples.[7,121,122] Serum AAT levels are reduced to approximately 60% of those found in MM individuals.[4] The risk of COPD in MZ compared with MM individuals has previously been investigated with mixed results but more recent studies have provided strong evidence of increased risk in cigarette-smoking members of this population.[37,38,123,124]

The frequency of SZ individuals is much lower than that of MZ individuals[122] and serum AAT levels are reduced to around 40% of those found in MM individuals.[4] The risk of COPD is not yet well defined but studies suggest that it is increased in SZ individuals compared to their MM counterparts and more so in cigarette smokers.[39,125] The risk of COPD in individuals heterozygous for other AATD mutations is unclear because of their rarity.

The clinical management of individuals heterozygous for AATD remains unclear. While smoking avoidance and cessation should be strongly encouraged, there is no evidence, at present, for ongoing monitoring of those who continue to smoke. In those with COPD, there is no evidence for a differing approach from usual care or for AAT augmentation therapy.

Summary

- **Smoking cessation should be strongly encouraged in individuals heterozygous for AATD but regular follow-up is not advised.**
- **In COPD patients heterozygous for AATD, we advise usual COPD care.**

What support groups are available for people with AATD?

A person's quality of life can be seriously affected when they are diagnosed with AATD. Studies of people with non-communicable lung conditions have found there are many unmet needs that impairs their well-being.[126,127] There are many types of support available including psychological, social and multidisciplinary care to help people self-manage their disease. Support that is instituted in a timely manner and appropriate for that person can significantly improve their everyday life.[128]

The Alpha-1 Association of Australia (AAA) (alpha1.org.au) provides information and support for people with this disease and their families. Online discussions forums offer people with AATD the opportunity to receive peer support, discuss challenges and problems and engage in advocacy. Additional opportunities for face-to-face support facilitated by the Lung Foundation of Australia can be found through their patient support groups (lungfoundation.com.au).

Summary

- **The AAA and the Lung Foundation of Australia offer support for people with AATD and their families.**

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Should we make use of registries for people with AATD?

We support better understanding of the disease through the establishment of national registries for people with AATD in Australia and New Zealand. In other countries, they provide large data sets to research the natural history of the disease and to evaluate new therapies.[66,68,69] This approach has the potential for substantive improvements in the understanding and treatment of lung disease in AATD.

Summary

- **We support the establishment of national registries for people with AATD in Australia and New Zealand.**

CONCLUDING STATEMENT

AATD remains underdiagnosed and testing should be carefully considered in patients with chronic airflow obstruction, adult-onset asthma and bronchiectasis. Increased recognition and diagnosis of the disease and establishment of national registries can facilitate greater understanding of its natural history and research into disease-specific therapies. At testing and diagnosis, patients and their families require access to appropriate genetic counselling services and explanation of the available support services. Patients should be considered for treatment according to the principles of management of COPD in general and monitored for evidence of liver disease while AAT augmentation therapy could be considered in non-smoking patients.

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Abbreviations: AAA, Alpha-1 Association of Australia; AAT, alpha1-antitrypsin; AATD, AAT deficiency; ATS, American Thoracic Society; CRP, C-reactive protein; CT, computed tomography; DLCO, diffusion capacity of the lung for carbon monoxide; ERS, European Respiratory Society; FEV_1, forced expiratory volume in 1 s; FRC, functional residual capacity; GRADE, Grading of Recommendations, Assessment, Development and Evaluations; IEF, isoelectric focusing; IPF, idiopathic pulmonary fibrosis; ISHLT, International Society for Heart and Lung Transplantation; LVRS, lung volume reduction surgery; NETT, National Emphysema Treatment Trial; Pi, protease inhibitor; RCT, randomized controlled trial; SGRQ, St George's Respiratory Questionnaire; TLC, total lung capacity; TSANZ, Thoracic Society of Australia and New Zealand.

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Supplementary Information

Additional supplementary information can be accessed via the *html* version of this article at the publisher's website.

Appendix S1 Alpha1-antitrypsin deficiency position paper working group: principles for addressing conflict of interest.

Appendix S2 GRADE evidence profiles for selected studies of AAT augmentation therapy.

Appendix S3 Search strategy for AAT augmentation therapy systematic review.

Appendix S4 AAT augmentation therapy systematic review flow chart of study selection.

Appendix S5 Overview of included studies.