European Respiratory Society statement: diagnosis and treatment of pulmonary disease in α_1-antitrypsin deficiency

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ABSTRACT α_1-antitrypsin deficiency (AATD) is the most common hereditary disorder in adults. It is associated with an increased risk of developing pulmonary emphysema and liver disease. The pulmonary emphysema in AATD is strongly linked to smoking, but even a proportion of never-smokers develop progressive lung disease. A large proportion of individuals affected remain undiagnosed and therefore without access to appropriate care and treatment.

The most recent international statement on AATD was published by the American Thoracic Society and the European Respiratory Society in 2003. Since then there has been a continuous development of novel, more accurate and less expensive genetic diagnostic methods. Furthermore, new outcome parameters have been developed and validated for use in clinical trials and a new series of observational and randomised clinical trials have provided more evidence concerning the efficacy and safety of augmentation therapy, the only specific treatment available for the pulmonary disease associated with AATD.

As AATD is a rare disease, it is crucial to organise national and international registries and collect information prospectively about the natural history of the disease. Management of AATD patients must be supervised by national or regional expert centres and inequalities in access to therapies across Europe should be addressed.

Introduction

It has been over 50 years since the first cases of α_1-antitrypsin deficiency (AATD) were described [1] and much has been learnt about the condition since then, especially in recent years. More than 100 genetic variants have been described and those associated with severe plasma deficiency (<11 μM or 0.5 $g \cdot L^{-1}$) are recognised as increasing susceptibility to the development of emphysema even in never-smokers. The PiZZ homozygous genotype is by far the most prevalent severe deficiency state and its additional extrapulmonary associations with liver cirrhosis, hepatocellular cancer, vasculitis and panniculitis are well recognised. Knowledge has progressed through the development of local, national and international registries and the mechanisms leading to emphysema and cirrhosis and the natural history of the disease are now documented in greater detail. The prevalence of AATD in Europe varies from 1 in 1368 in Denmark to 1 in 58 319 in Poland following migration patterns [2].

The complexity of interpreting the genetic variants, their importance and the role of patient and family screening as well as disease management requires expertise only gained by seeing patients on a regular basis. The role and instigation of augmentation therapy and transplantation need careful and multidisciplinary approaches. The development of new therapies such as gene silencing strategies, small molecule drugs and other anti-inflammatory and anti-proteinase therapies requires the application of novel approaches to the design and implementation of clinical trials to overcome some of the inherent challenges of conducting clinical research in rare diseases. The establishment of patient advocacy organisations and close collaboration with clinicians and other healthcare workers have played, and will continue to play, a key role in the acquisition of new knowledge and the design and delivery of new clinical trials. The views and concerns of patients were sought through the European Lung Foundation together with national AATD patient organisations. These have both added to the development of the current document and are include in the text and summarised verbatim in the online supplementary material.

This European Respiratory Society (ERS) statement provides a broad update on the "state of the art" knowledge in the study and management of pulmonary disease associated with AATD.

Method

The task force co-chairs (R.A. Stockley and M. Miravitlles) led all aspects of project management and selected the panellists, which included 13 specialists with experience in AATD and/or non-deficient chronic obstructive pulmonary disease (COPD) management, basic and clinical research. The co-chairs and panellists discussed the evidence and formulated the statements. All panel members were required to disclose any potential conflicts of interest. At least one third of the panel was free from any such conflicts.

Task force members compiled a list of issues that they considered important and relevant to the diagnosis and management of pulmonary disease in AATD. Our literature search used the previous American Thoracic Society (ATS)/ ERS statement published in 2003 as a starting point [3]. The following databases were searched up until June 2016 with no language restrictions (online supplementary material): MEDLINE, MEDLINE In Process and EMBASE (*via* Ovid), and Cochrane Library (Wiley) CENTRAL, CDSR, HTA, EED and DARE databases. In addition, Conference Proceedings Citation Index *via* Web of Science and British Library's ZETOC were searched for conference proceedings and abstracts. The references of included studies and reviews were checked. The search was confined to α_1-antitrypsin deficiency of homozygous Z genotype, Null genotype or Null/Z genotype, all abbreviated for this document as AATD. The searches and the formulation of statements were supervised by one of the ERS methodologists (D. Rigau).

AATD and lung disease

The initial five cases of AATD reported by Laurell and Eriksson [1] included three patients with emphysematous lung disease and one young and one old person without obvious signs of COPD. Subsequently Eriksson [4] collected a further 33 patients *via* hospital records and hence represented a partially biased cohort. Again variability in the presence and severity of lung disease was noted, although, in general, the patients had early onset of COPD and basal panlobular emphysema. This pattern of disease became recognised as the classical clinical phenotype, leading to predominant testing of younger patients

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presenting with severe lung disease. However, existing guidelines recommend testing all COPD patients irrespective of age and severity [3, 5–7]. The pathophysiology has been thought to reflect the lack of α_1-antitrypsin (AAT) function (a primary serum and lung inhibitor of serine proteinases) protecting the lung tissues from proteolytic destruction, which is largely neutrophil dependent. However, although smoking amplifies neutrophil recruitment to the lung and is recognised as an important risk factor, it fails to explain the diversity of clinical and structural impact in both smokers and never-smokers with AATD.

More recently, the establishment of AATD registries [8, 9] and follow-up data from the 1972 Swedish birth cohort [10] have highlighted the diversity of impact and type of lung disease, including its effect on health status and lung physiology. One of the most comprehensive databases is the UK national registry, which now includes in-depth data and longitudinal follow-up data from over a thousand patients [11]. The clinical features of these patients have highlighted many facets of the disease that are not entirely consistent with a simple AAT–neutrophil proteinase balance concept.

First, there is lack of concordance found between siblings raised with the same environmental background. There is no relationship between the forced expiratory volume in 1 s (FEV_1) of such siblings even though gas transfer is related [12]. This raises two issues, namely, that FEV_1 is a poor surrogate measure for emphysema in these patients, and that other unknown environmental or genetic influences may play a role in determining the outcome.

Secondly, the FEV_1 decline reflects a late physiological change in the disease process only starting to deviate from normal in the fourth decade, whereas gas transfer is reduced much earlier indicating that it may be a more sensitive and specific test of emphysema development [13, 14]. This is supported by the observational monitoring of the Swedish birth cohort, where abnormal gas transfer was present in some patients in their fourth decade while FEV_1 remained within normal ranges [15].

Thirdly, a proportion of never-smokers develop emphysema with reduction in FEV_1 in middle age, whereas some retain normal spirometry into old age [16], and the life expectancy of never-smokers is close to normal [17].

Fourthly, physiological assessment confirms a discordance of lung function with some patients retaining normal gas transfer even with reduced FEV_1 and *vice versa* [18], which reflects (at least in part) the distribution of emphysema [14, 19]. Indeed, the classical basal distribution of emphysema is not always present and a proportion of patients display a pattern of emphysema distribution more typical of non-AATD deficient COPD [19]. These issues have a significant bearing on monitoring patients for stability/progression. As indicated above, the earliest change is a decline in gas transfer, which may be independent of and faster than FEV_1 decline [20]. This is particularly evident in very severe disease when gas transfer impairment and progression is greatest and average FEV_1 decline is least [21, 22].

Finally, patients can demonstrate the same clinical features as non-deficient COPD, including increased evidence of bronchiectasis, chronic bronchitis, bacterial colonisation, frequent exacerbations (but with a greater degree of pulmonary inflammation and associated progression), impaired health status and a degree of reversibility of airflow obstruction [20, 23, 24]. Therefore, the World Health Organization (WHO) guidance for testing every patient with a diagnosis of COPD or adult-onset asthma for AATD should be standard [25].

Statement

- The clinical impact of AATD is highly variable. Heterogeneity in lung disease is only partly explained by exposure to known risk factors, such as cigarette smoke.
- Lung disease in AATD generally presents at a younger age than "usual" COPD and may be misdiagnosed as asthma.
- Although the patients' clinical phenotype may vary they are more likely to have basal emphysema than patients with usual COPD.
- The WHO recommends all patients with a diagnosis of COPD or adult-onset asthma should be tested for AATD.

Laboratory diagnosis and hierarchy of testing

The laboratory diagnosis of AATD has evolved over the past 50 years since the first cases of the disorder were reported, based on a low or absent AAT band seen on paper electrophoresis [1]. We have reviewed the testing hierarchy for the diagnosis of AATD.

The quantitative determination of AAT levels in blood is a crucial first test to identify AATD. Original methods, such as radial immunodiffusion and rocket electrophoresis, are no longer used in laboratories.

Nowadays, the measurement of AAT levels in blood is mostly performed by nephelometry or, less commonly, a comparable latex-enhanced immunoturbidimetric assay (table 1) [26].

In the past decade, more reproducible and reliable quantitative techniques based on the use of dried blood samples (DBSs) have become more widely available and have facilitated centralisation of testing [27–29].

AAT is a polymorphic protein with more than 100 genetic variants coded for by two alleles in a codominant manner. Many of these reflect point mutations in the gene sequence leading to amino acid substitutions, which may affect the electrophoretic mobility of the resulting AAT protein. Isoelectric focusing detects these variants, which are given letters A–Z depending on their mobility, *i.e.* faster or slower, compared to the most common (normal variant) labelled M labelled with earlier or later letters, respectively. Other common variants are S and Z, with MM, MS, MZ, SS, SZ and ZZ protein phenotypes accounting for over 99% of all variants in most of population surveys [30]. Although phenotyping can only identify protein that is present in the blood, it remains a routine test for AATD. The rarer null variants that include a variety of gene insertions, deletions and point mutations can result in the absence of AAT production, and null heterozygotes can appear to be normal (Mnull) or abnormal (Znull) based on the electrophoretic pattern of protein phenotyping, although not consistent with expected family inheritance. Other deficient mutations such as M_{Malton}, $M_{Wurzburg}$, $M_{Heerlen}$ also display an M protein electrophoretic phenotype. For these reasons, including the necessity for pre- and post-test genetic counselling, access to central laboratories and/or AATD expertise is essential [31]. Standard manual methods have been improved by semi-automation in the past decade [32] and result in easier and faster testing, although significant expertise is still required for interpretation [33].

The ranges of serum AAT in the general population, determined according to the main genotypes, have been summarised recently [34].

TABLE 1 Laboratory methodologies used in different central national laboratories across Europe for diagnosis of α1-antitrypsin deficiency

Country	Biological sample	First-line method(s)	Second-line method(s)	Further method(s)	Author, year [Ref.]
Ireland	Serum/plasma	AAT level	Phenotyping	Genotyping, sequencing	McElvaney, 2015 [136]
Poland	Serum/DBS	Serum AAT level	Determination of AAT levels on DBS samples, phenotyping, genotyping	Sequencing	Chorostowska-Wynimko, 2015 [137]
Serbia	Blood	Immunonephelometric assay for AAT; genotyping		IEF; DNA sequencing	Beletic, 2014 [138]
France	Serum	Quantification of serum AAT concentration with possible complementary measurement of the elastase inhibitory capacity of serum	Phenotyping, genotyping	Direct sequencing	Balduyck, 2014 [139]
Germany	DBS	AAT level	AAT level by nephelometry, genotyping	Phenotyping, sequencing	Miravitlles, 2010 [31]
Italy	DBS	AAT level, genotyping	Phenotyping	Sequencing	Miravitlles, 2010 [31]
Spain	DBS	AAT level	Genotyping	Phenotyping; sequencing	Miravitlles, 2010 [31]
USA	Blood/serum	AAT level, genotyping	Phenotyping		Bornhorst, 2007 [140]
Italy	DBS	AAT level, genotyping, phenotyping	Sequencing		Ferrarotti, 2007 [141]
Poland		Serum level	Phenotyping	Gene screening	Kaczor, 2007 [142]
Italy	Blood/DBS	Serum level	Phenotyping	Genotyping, sequencing	Corda, 2006 [143]
USA	Blood	AAT level, genotyping	Phenotyping		Snyder, 2006 [144]
USA	Plasma-serum/ DBS	Concentration of AAT protein in plasma or serum (immunoassay)	Phenotype (IEF)	Genotype (PCR), function test (inhibition of leukocyte elastase)	Campbell, 2000 [145]

AAT: α1-antitrypsin; DBS: dried blood spot; IEF: isoelectric focusing.

The optimal threshold level for AAT to discriminate normal PI*MM from other genotypes carrying at least one deficient S or Z allele was 24.4 μM (1.1 $g \cdot L^{-1}$) with 73.4% sensitivity and 88.5% specificity [34]. AAT is an acute phase protein and, despite average concentrations varying with protein phenotype, there is a high degree of overlap, such that plasma level alone is an insufficient parameter to diagnose intermediate deficiency due to M heterozygosity with certainty. The acute phase response known to influence AAT can be partly recognised by the simultaneous quantification of C-reactive protein (CRP). However, these issues are overcome by protein phenotyping or specifically by genotyping, both of which are independent of AAT level.

Genotyping describes the detection of specific AAT gene mutations, mainly S and Z. This approach utilises the principles of PCR and can also detect rare and null variants such as the M_{Malton} [35–37]. However, it can only detect known sequence defects and requires specific primers for each of these, some of which (*e.g.* F and I) are routinely used by some laboratories. The absence of specific primers can lead to false results.

Whole gene sequencing (which is becoming cheaper) will detect stop mutations and help elucidate the nature of rarer variants such as E, F, G, I and P without the need for specific primers, as well as identify currently unrecognised variants. The optimal results of genotyping are obtained when performed in expert laboratories and interpreted in conjunction with the protein level and familial relationships by experienced AATD clinicians/geneticists.

Each specialised laboratory has developed its own flow chart for local or national AATD detection programmes, starting from sample collection (blood, plasma or DBS) [31]. The initial step is usually to measure the AAT plasma level, separating severely deficient subjects (ZZ, Znull, Nullnull and most SZ) from intermediate levels for M heterozygotes (MZ, MS and Mnull) and normal levels (MM). This step is usually followed by protein phenotyping, genotyping or whole gene sequencing depending on availability and/or the need for more detailed interpretation. With ever reducing costs for PCR and gene sequencing, it is likely that genotyping will become the second step in the testing algorithm in the future.

Figure 1 shows a testing algorithm with initial quantitation of the AAT level in blood together with a measure of CRP to determine whether the AAT level could be higher than usual due to a possible acute phase response. Thereafter, protein phenotyping by isoelectric focusing or genotyping, where specific primers for known mutations are available, will identify the most common variants. Whole exon sequencing can be undertaken especially if null variants are expected. The role of intron sequencing is currently uncertain.

Since AATD is hereditary, family testing should be conducted after identification of an index case. Parents of an index case are most commonly PiMZ heterozygotes, but may be informative if available for testing when a null gene is suspected. In reference centres siblings are offered testing as well, because with MZ parents there is a one in two likelihood of being heterozygote and a one in four chance of being PiZZ. Identified PiZZ siblings are offered follow-up as for the initial (index) case. PiMZ siblings should be

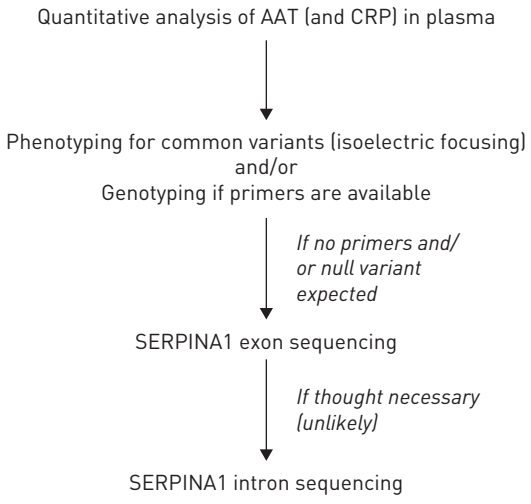


FIGURE 1 Algorithm for laboratory testing of α1-antitrypsin deficiency (AATD). This algorithm describes the current practice of how members of the task force treat patients with AATD and is not provided as a general recommendation. AAT: α1-antitrypsin; CRP: C-reactive protein.

advised against smoking and may be offered testing for their partner as the PiMZ protein phenotype is relatively common (1–3% prevalence) and hence the risk of subsequent PiZZ children who, by this strategy, will be identified and can be monitored during maturation and into adulthood. For the same reason, checking the index patient's partner may detect any deficiency allele and, where present, the children would also have a one in two likelihood of having severe deficiency. Early detection of the deficiency in these children is considered best practice, providing no legal barrier exists for testing (figure 2). More widespread testing (beyond first degree relatives) may be conducted in some families depending on family history of lung disease or parental results (such as one parent being PiZZ).

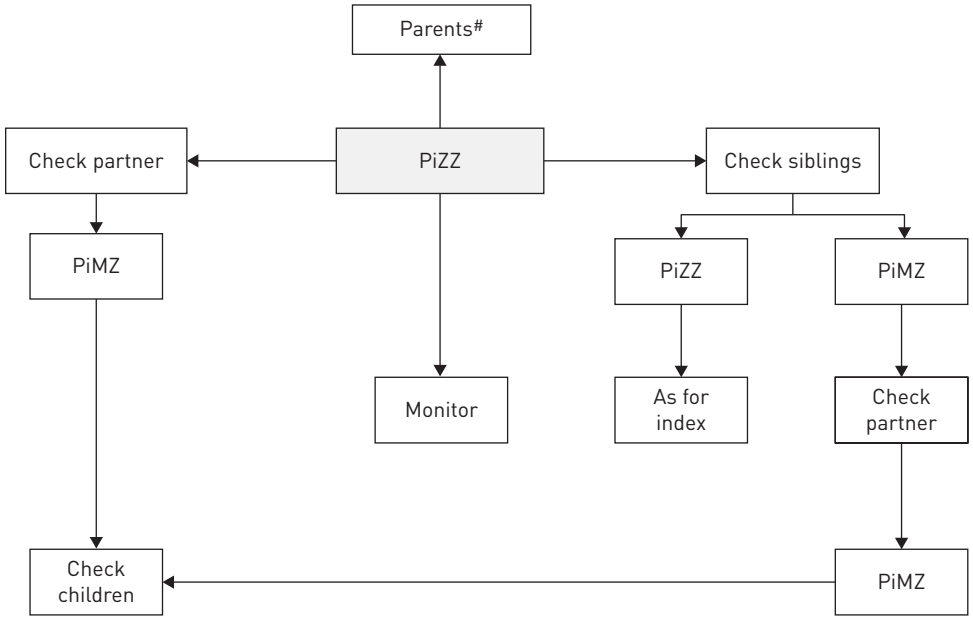
It is imperative that appropriate genetic counselling is provided, both before and after genetic testing, in accordance with national legislation [38]. Patients need to be made aware of all the potential implications of having a genetic test prior to testing in order to be able to give informed consent. Therefore, patients should be referred for expert genetic testing by their doctor.

Statement

- The quantitative determination of AAT levels in blood is a crucial first test to identify AATD. Quantitative deficiency must be supported by qualitative tests to identify the genetic mutation(s) causing AATD.
- Protein phenotyping by isoelectric focusing identifies variants where AAT is present in the sample including the rarer variants F, I and P *etc*.
- Genotyping allows a rapid and precise identification/exclusion of S and Z alleles and other variants, where specific primers are available.
- Gene sequencing remains necessary for those cases where a null variant or a deficient variant other than Z or S is suspected.
- Testing of relatives of identified patients should be considered after appropriate counselling.
- Genetic testing should be carried out only after informed consent is given and in accordance with the relevant guidelines and legislation.

Lung disease progression in AATD

The proportion of individuals with AATD who develop lung disease is largely unknown although cross-sectional studies indicate that perhaps 50% of never-smokers retain spirometric lung function in the normal range in later life [16, 17]. Nevertheless, once established it is generally believed that progression is



FIGUR E 2 Algorithm for familial testing for α1-antitrypsin deficiency (AATD). This algorithm describes the current practice of how members of the task force treat patients with AATD and their first degree relatives and is not provided as a general recommendation. Wider family testing may be indicated in some instances (see text). #: test parents (if available) if a null gene is suspected.

more rapid than in non-AATD patients with COPD, especially in smokers. However, smoking cessation can "normalise" this progression to that of AATD in never-smokers [20].

Conventionally, FEV_1 has been used as the major indicator for the presence, progression and severity of lung disease. However, FEV_1 is a poor surrogate of emphysema, while gas transfer is more specific. Although these two measures correlate in cohort studies, both have to be measured to a high degree of specification and do not provide the same information on the clinical phenotype or the rate of progression or stability. Similarly, the progression of emphysema measured by lung density in computed tomography (CT) continues even when FEV_1 is stable [14, 18, 20, 22].

Monitoring the progression of lung disease in AATD

Physiology/lung function

The complexity of interpretation of results obtained by common lung function measures such as spirometry and carbon monoxide gas transfer is illustrated by the discordance between these two measures as the disease progresses. Rapid FEV_1 decliners can be identified even when lung function is initially found to be in the normal range and rapid decline of gas transfer can occur even when there is severe airflow obstruction and little decline in FEV_1. This raises the issue of the need to monitor all patients (at least for a time) to assess treatment options including augmentation therapy where available. This careful monitoring would include parameters such as FEV_1, diffusing capacity of the lung for carbon monoxide (D_{LCO}) (or D_{LCO}/alveolar volume), 6-min walking distance and health-related quality of life parameters.

CT densitometry

CT densitometry has been established as the most specific and sensitive surrogate end-point for the evaluation of therapeutic benefit of augmentation therapy and represents a paradigm imaging biomarker. Validation of the methodology as an objective and specific measure of emphysema has been extensive [39–44]: cross-sectional studies have shown a close correlation with pathology, lung function indices including FEV_1 and gas transfer [45–47], health status [47] and exercise capacity [48]. Longitudinal observational studies demonstrate that, although the progressive loss of lung density correlates with deteriorating lung function and health status as emphysema worsens [22, 49], CT densitometry is a more sensitive means of detecting emphysema progression than these "traditional" clinical measures [13, 22, 50].

This novel surrogate outcome measure has facilitated the successful completion of several randomised placebo-controlled studies over a compressed time frame and with smaller sample sizes [51–53] than were estimated to be required in studies that used FEV_1 as an end-point [54]. As a consequence of the published evidence, a meeting of the Blood Products Advisory Committee of the Food and Drug Administration [55] concluded in 2009 that it accepted "serial lung density measurements by HRCT as a clinically meaningful end-point to assess efficacy of augmentation therapy with intravenous AAT on emphysema disease progression" and its use as a primary end-point in phase 4 studies.

Notwithstanding this progress, the validity of CT densitometry as evidence of treatment efficacy is still being questioned because of a lack of coexisting signals in conventional surrogate measures, such as lung function or health status. The power calculations that have been used historically to design the latest interventional study predicted that a study of 130 patients over 3 years would be sufficient to demonstrate treatment efficacy if CT densitometry was the outcome [51], whereas the use of FEV_1 as outcome would require at least 550 patients per arm over the same period [54]. Power calculations based on health status as an outcome have not been performed.

Our systematic review of the literature assessed 200 manuscripts (see the online supplementary material). Table 2 shows the results for annual decline in lung density measured as the 15th percentile point (abbreviated as Perc15 or PD15) and expressed as $g{\cdot}L^{-1}$ annual change of density together with FEV_1, D_{LCO} and transfer coefficient of the lung for carbon monoxide (K_{CO}) (the latter two corrected for haemoglobin concentration). The numbers in the table are based on placebo-treated patients in randomised controlled clinical trials, except for the last two rows where the data were collected in follow-up studies. Clearly, there is high variability in the mean values in each of the progression parameters. In the AATD population, only repeatability of lung density is reported in the literature [56]. In fact, variation for the 15th percentile point, corrected for differences in total lung volume between two scans, is minimal (intraclass correlation coefficient 0.96; 95% CI: 0.86–0.99) [56].

A larger set of information on monitoring of emphysema progression comes from non-AATD individuals. In the 2005, the ATS/ERS Task Force document relating to interpretation for lung function tests [57] indicated the optimal method for expressing the short-term variability (measurement noise) is to calculate the coefficient of repeatability.

TABLE 2 Annual change in lung density measured as the 15th percentile point (abbreviated as Perc15 or PD15), FEV_1 and gas transfer in placebo-treated patients in randomised controlled trials or studies on the natural course of AATD-associated emphysema

Author, year [Ref.]	Patients n	Follow-up months	Perc15 (PD15) value $g \cdot L^{-1}$	FEV_1 $mL \cdot year^{-1}$	D_{LCO} $mmol \cdot min^{-1} \cdot kPa^{-1}$	K_{CO}[¶] $mmol \cdot min^{-1} \cdot kPa^{-1} \cdot L^{-1}$
Dirksen, 1999 [51]	28	36	−2.57±0.41[#]	−59.1±11.9[#]	−0.16±.04[#]	−0.0162±0.004[#]
Dirksen, 2009 [52]	35	25	−2.241[¶] (−2.90–−1.577)	−23 mL[¶] (−0.043–−0.004)	−0.343[¶] (−0.489–−0.196)	−0.035[¶] (−0.051–−0.020)
Stolk, 2012 [146]	110	14	−1.81±0.5[#]	−50±13[#]	−0.23±0.05[#]	NA
Stolk, 2015 [147]	51	96	NA	−66 ± 60.9[+]	NA	−0.0275±0.00259[+]
Chapman, 2015 [53]	87	24	−2.19±0.23[#]	−2.3±13.1%[§]	−1.5±19.5%[§]	NA
Green, 2016 [111]	76	24	−3.2±0.5	−44.67±8.71	−0.37±0.04	−0.01±0.01

FEV_1: forced expiratory volume in 1s; AATD: α1-antitrypsin deficiency; D_{LCO}: diffusing capacity of the lung for carbon monoxide; K_{CO}: transfer coefficient of the lung for carbon monoxide *i.e.* D_{LCO}/alveolar volume; NA: not available in the manuscript. [#]: mean±SE; [¶]: (95% CI); [+]: mean±SD; [§]: annual decline in % predicted.

Statement

- Annual measurement of lung function including post-bronchodilator FEV_1 and gas transfer provides information about disease progression.
- Lung densitometry, as performed in observational cohort studies and randomised clinical trials is the most sensitive measure of emphysema progression.
- The correlation between change in lung density and any short-term change in measures of pulmonary function is weak. However, in the longer term, CT lung density decline correlates with reduction in FEV_1 and health status.
- The role of CT in the follow-up of patients in routine clinical practice requires further validation.

The risk of lung disease in heterozygotes

The risk in individuals with MZ genotype

The susceptibility of patients with the MZ genotype for developing COPD was explored in a meta-analysis by Hersh *et al.* [58] in 2004. 16 studies were case–control or cross-sectional with the binary outcome of COPD or airflow limitation, and seven were cross-sectional studies with FEV_1 (% of the predicted value) as a continuous outcome. One study included both outcome measures and was included in both analyses [59]. The pooled odds ratio for COPD in heterozygotes compared with normal genotype individuals was significantly increased at 2.31 (95% CI 1.60–3.35), although large heterogeneity was detected among the studies [58]. Cross-sectional studies and those adjusting for smoking status showed lower and nonsignificant risk estimates compared with case–control studies and those not adjusting for smoking status. In the pooled analysis, there was no difference in mean FEV_1 (% predicted) between PiMM and PiMZ individuals. A subsequent case–control study from Norway and a multicentre family-based study from Europe and North America [60] found that the PiMZ genotype was associated with lower FEV_1/(forced) vital capacity ratio and more severe emphysema on chest CT scan. However, the number of MZs in the two groups was small and the study samples were not population based.

A family-based genetic association study by Molloy *et al.* [61] tested for PiMZ COPD risk specifically within families that already had an identified PiMZ COPD subject. The study compared 99 PiMM and 89 PiMZ non-index subjects recruited from 51 index PiMZ probands with COPD GOLD (Global Initiative for Chronic Obstructive Lung Disease) stage II–IV. These results indicated conclusively that PiMZ individuals who smoke have more airflow obstruction and clinical COPD than carefully matched PiMM individuals.

The risk in individuals with SZ genotype

The number of PiSZ individuals worldwide is less than PiMZ; however, the risk for COPD is still not fully elucidated. Dahl *et al.* [62] performed a meta-analysis of the risk of COPD in individuals with the PIS

allele. 21 studies were included and there were six case–control and cross-sectional studies. In the pooled analysis there were 42 PiSZ individuals of whom 27 had COPD. The summary odds ratio for COPD in PiSZ individuals was significantly elevated at 3.26 (95% CI 1.24–8.57) compared with PiMM; however, when a significant outlier was removed from the analysis the odds ratio was no longer significantly increased [63]. Seersholm *et al.* [64], in a study of 94 PiSZ individuals of whom 66 were non-index cases, observed that index PiSZ cases had reduced survival. Data from the Italian and Spanish registries [24, 65] found that PiSZ subjects were older at diagnosis and had more preserved lung function despite higher smoking exposure than PiZZ patients. Similarly, a more recent study [66] suggested that PiSZ subjects were less susceptible to cigarette smoke than PiZZ and that the pattern of emphysema found on the CT scan at diagnosis was similar to that seen in patients with usual COPD rather than the predominantly basal distribution of panlobular emphysema of PiZZ individuals.

Taken together, these data suggest increased susceptibility of the SZ phenotype for the development of COPD in smokers, but more research is needed, including the effect of environmental factors in a similar way to that undertaken for MZ subjects [61].

Rarer mutation heterozygotes (such as FZ, IZ, MMalton and Mnull mutations)

There is a paucity of data for rarer AATD mutations, but some studies are emerging indicating that the F, I and MMalton mutations confer increased susceptibility to COPD when inherited with a Z allele. Although the Null mutations associated with AATD are rare, studies have shown that Null homozygotes have more severe lung disease than PiZZ or PiSZ individuals [67–70] and Mnull individuals have increased lung symptomatology and obstructive lung disease [71].

Statement

- Never-smoking PiMZ subjects do not have an increased risk for COPD.
- Smoking PiMZ and PiSZ subjects have an increased risk of COPD compared to smoking PiMM subjects.
- The role of other heterozygotes remains unknown due to their rarity and potential ascertainment bias from measuring AAT in unusual cases of lung or liver disease.

Role and benefits of screening

There are different approaches to identify individuals with AATD. The first is population-based, in which unselected groups have been tested (screening studies). The second is targeted-detection studies in which patients with an enhanced suspicion of having AATD are tested including those with early-onset COPD (<40 years age), basal panlobular emphysema, family history of COPD or AATD, and those with perinatal jaundice, cirrhosis, vasculitis or panniculitis.

No randomised controlled study determining the efficacy of screening programmes for AATD has been performed. Most screening studies have been selective and did not involve random population samples, but included individuals that are healthier (blood donors) or sicker (hospital outpatients) than the general population. A few population-based studies that randomly screened the general population [72, 73] or large numbers of newborns [10, 74] provided a less biased and more accurate prevalence estimate of specific AATD phenotypes. The newborn studies have also provided valuable insight into the natural history of AATD, with unbiased assessments in the risks of liver and lung diseases. More specifically, these studies have found that individuals tested often had lung function in the normal range at mean ages of 15 years [75] and 30 years [76]. Data collected at age 35 years suggest that at least some have developed a reduction in gas transfer and lung density [15]. This is consistent with the retrograde analysis that highlighted the higher sensitivity of these measures to detect early changes compared to spirometry [14]. The most recent birth cohort information at ages 37 to 40 years showed that two of the four current smokers already had COPD [77].

Potential benefits of systematic screening include genetic counselling, lifestyle recommendations (smoking prevention or cessation, avoidance of high-risk occupations, alcohol intake limitation), and consideration for earlier augmentation therapy. The potential harms include psychological effects, social discriminatory effects and costs. These effects can be addressed, at least partially, by reassurance as never-smokers who are non-index cases with AATD have a normal life expectancy [17, 78].

The largest population-based study published for AATD was carried out in 200 000 newborn children in Sweden between 1972 and 1974 leading to the identification of 127 PIZ individuals and 48 PISZ individuals [10]. The major purpose was to reduce exposure of the child to parental smoking during childhood and adolescence and to prevent active smoking. Neonatal screening reduced the smoking rates in18–20-year-olds compared to age-matched subjects [79], with 6% being current smokers *versus* 17% ($p<0.05$) and 88% being never-smokers *versus* 65% ($p<0.05$), although this failed to affect smoking among

the parents. Similar results were also found in another neonatal screening study in Oregon, with significantly lower smoking initiation rates in subjects who had been diagnosed with AATD than in control subjects (27.3% *versus* 56.9%; p=0.02) [75].

Neonatal screening produced no adverse psychological effects in adolescents identified at birth with AATD, although parental distress and adverse effects were identified in the mother–child relationship [80] and 20 years later the mothers had significantly more anxiety than control mothers [81]. These concerns have inhibited the reintroduction of neonatal screening in Sweden although a clearer understanding of the risks/benefits and natural history of the disease is both helpful and reassuring.

Statement

- Most screening studies have been biased as they did not involve random population samples.
- Population-based screening studies provide less biased prevalence estimates of specific AATD protein and clinical phenotypes as well as valuable insights into the natural history of AATD.
- Neonatal screening has been shown to be effective in reducing the smoking rates for 18–20-year-olds compared to age-matched individuals.
- Screening may have negative psychological effects on parents and on mother–child bonding. However, these negative effects can be addressed by comprehensive genetic counselling and care provision at centres of excellence for AATD.

Augmentation therapy for AATD

Since augmentation is currently the only specific therapy for AATD, it has been a topic of intense debate in the literature and the subject of numerous review and opinion articles. In rare diseases such as AATD, the difficulty of recruitment to clinical trials, coupled with the lack of sensitivity to change of typical outcome measures has challenged the development and delivery of clinical trials. Furthermore, there is the unusual situation where augmentation has been advocated (and given) for some time on the basis of biochemical effect (namely raising AAT level) [82] and hence has become established as treatment in many areas of the world, without the level of evidence now expected for respiratory outcomes such as FEV_1, quality of life and mortality. There have been two previous systematic reviews, one focused on randomised controlled trials (RCTs) of augmentation [83] and the other which considered all controlled study designs of augmentation (including nonrandomised studies) and presented analyses of FEV_1 decline [84]. In addition, an individual patient data analysis of the CT densitometry data from two of the randomised controlled trials has been reported [85]. The latter two studies were supportive of augmentation as a treatment capable of reducing, albeit not eliminating, emphysema progression [84, 85]. The meta-analysis conducted by Gøtzsche *et al.* [83] also indicated that CT density decline was lower on augmentation therapy than placebo, but concluded that this did not equate to efficacy. A similar view was also expressed in the more recent update by the same authors [86], following publication of the RAPID trial [53].

In order to obtain all the evidence about augmentation and minimise bias we used standard systematic review methods as described in the online supplementary material. There have been eight RCTs of intravenous augmentation, three against placebo [51–53, 87] and five against another active comparator [88–92], generally a newer brand of augmentation therapy. In addition there have been six observational studies reporting a control group [8, 93–97], largely assessing data from registries, and 11 uncontrolled observational studies [82, 98–108], focused on pharmacokinetics, safety or novel outcomes. There are also two ongoing trials (ClinicalTrials.gov identifiers NCT00242385 and NCT01213043). In the interests of brevity, the published placebo-controlled RCTs are discussed here in detail, whereas other published studies are shown in table 3, which contains a brief summary of study characteristics and results.

The RCTs included a total of 315 patients. The earliest RCT included 58 ex-smoking PiZZ patients with moderate-to-severe emphysema, treated for a minimum of 3 years and randomised to an infusion of AAT at 250 $mg \cdot kg^{-1}$ or human albumin every 4 weeks [51]. FEV_1 was the primary outcome; secondary outcomes included K_{CO}, D_{LCO} and change in lung density measured by CT. There was no difference in physiological decline, but a strong trend towards reduced decline in CT-measured lung density.

The EXACTLE trial included 77 participants with severe AATD treated using weekly infusions of AAT at 60 $mg \cdot kg^{-1}$ or placebo for 2 years, with an optional 6-month extension [52]. Primary outcome was progression rate of emphysema determined by annual CT lung density at total lung capacity (TLC), but this was in part an exploratory study, as the optimum method of image analysis was uncertain at the time. A strong trend toward reduced density deterioration was seen, consistently across the four different analytical methods used. In one of these, conventional statistical significance was reached (p=0.049).

TABLE 3 Studies on augmentation therapy for α1-antitrypsin deficiency

Study design	Author, year [Ref.]	Intervention	Comparator	Primary outcome	Subjects n	Duration of treatment	Effect of treatment
RCT *vs* placebo	Dirksen, 1999 [51]	250 mg·kg^{-1} augmentation 4 weekly	625 mg·kg^{-1} albumin solution	FEV_1 decline	58	⩾3 years	FEV_1 decline NS difference 59 *vs* 79 mL·year^{-1} (p=0.25); reduced CT decline 2.6 *vs* 1.5 g·L^{-1}·year^{-1} (p=0.07)
	Dirksen, 2009 [52]	60 mg·kg^{-1} Prolastin weekly	2% albumin solution	CT densitometry	77	⩾2 years	Reduced CT decline 1.4 *vs* 2.2 g·L^{-1}·year^{-1} (p=0.06)
	Chapman, 2015 [53]	60 mg·kg^{-1} Zemaira weekly	Lyophilised preparation	CT densitometry	180	⩾2 years	Reduced CT decline 1.5 *vs* 2.2 g·L^{-1}·year^{-1} (p=0.03)
RCT *vs* active comparator	Stoller, 2002# [88]	60 mg·kg^{-1} Prolastin weekly	60 mg·kg^{-1} Respitin weekly	Serum AAT level	28	⩾12 weeks	Equivalence for primary outcome, NS difference FEV_1, D_{LCO}, urinary desmosine
	Stocks, 2006# [89]	60 mg·kg^{-1} Prolastin weekly	60 mg·kg^{-1} Zemaira weekly	Serum AAT level	44	⩾10 weeks	Equivalence for primary outcome
	Stocks, 2010# [90]	60 mg·kg^{-1} Prolastin-C weekly	60 mg·kg^{-1} Prolastin weekly	Plasma AAT level	24	10 weeks	Equivalence for primary outcome
	Campos, 2013# [91]	120 mg·kg^{-1} Prolastin-C weekly	60 mg·kg^{-1} Prolastin weekly	Plasma AAT level, safety	30	8 weeks	Equivalence for primary outcome, NS difference in adverse events
	Sandhaus, 2014# [92]	60 mg·kg^{-1} Glassia weekly	60 mg·kg^{-1} Prolastin weekly	Plasma AAT level	50	⩾1 weeks	Equivalence for primary outcome, NS difference FEV_1 or FVC
Observational with control	Seersholm, 1997 [93]	60 mg·kg^{-1} Prolastin or Trypsone weekly	No augmentation	FEV_1 decline	295	1 year	Reduced FEV_1 decline 53 *vs* 75 mL·year^{-1} (p=0.02)
	AAT registry group, 1998 [8]	60 mg·kg^{-1} Prolastin weekly	↓ frequency or no augmentation	FEV_1 decline, survival	1129	12–86 months	Better survival (p=0.001), NS difference in FEV_1 decline overall (p=0.40), if FEV_1 35–49%, decline lower on treatment (73 *vs* 93 mL·year^{-1}, p=0.01)
	Wencker, 2001 [95]	60 mg·kg^{-1} augmentation weekly	Data prior to augmentation	FEV_1 decline	96	⩾12 months	Reduced FEV_1 decline 34 *vs* 49 mL·year^{-1} (p=0.02)
	Stoller, 2003 [94]	Any dosing regimen augmentation	Usual care	Adverse events	1129	12–86 months	83% augmented patients had no adverse events; rate 0.02 events per patient per month
	Tonelli, 2009 [96]	Any dosing regimen augmentation	No augmentation	FEV_1 decline	164	Mean 42 months	Reduced FEV_1 decline 37 *vs* 46 mL·year^{-1} (p=0.05)
	Barros-Tizon, 2012 [97]	60 mg·kg^{-1} Prolastin or Trypsone at any interval	Data prior to augmentation	Exacerbation rate	127	18 months	Reduced exacerbation rate 1.2 *vs* 1 per year (p<0.01), reduced hospitalisation costs

Continued

TABLE 3 Continued

Study design	Author, year [Ref.]	Intervention	Comparator	Primary outcome	Subjects n	Duration of treatment	Effect of treatment
Observational, no control	Wewers, 1987 [82]	60 mg·kg^{-1} augmentation weekly	N/A	Serum AAT level, safety	21	6 months	AAT level improved *vs* baseline, low adverse event rate (*i.e.* safe)
	Schmidt, 1988 [98]	60 mg·kg^{-1} augmentation weekly	N/A	Serum AAT level	20	6 months	AAT level maintained at 35% of normal (equivalent to PiMZ)
	Barker, 1994 [99]	60 mg·kg^{-1} Prolastin weekly¶	N/A	Functional status	14	12–48 months	12 out of 14 patients stabilised self-reported functional status
	Miravitlles, 1994 [101]	60 mg·kg^{-1} Prolastin weekly^{+}	N/A	Safety, AAT level	13	Up to 6 years	No significant adverse events; 10 out of 13 trough AAT >50 mg·dL^{-1}
	Barker, 1997 [100]	120 mg·kg^{-1} Prolastin fortnightly	N/A	AAT level, safety	23	20 weeks	Trough levels inadequate with fortnightly dosing, treatment safe
	Schwaiblmair, 1997 [102]	60 mg·kg^{-1} Prolastin weekly	N/A	FEV_1	20	3 years	FEV_1 decline 36 mL·year^{-1}
	Wencker, 1998 [103]	60 mg·kg^{-1} Prolastin weekly	N/A	FEV_1 decline, safety	443	3.1–82.8 months	FEV_1 decline 57 mL·year^{-1} on treatment, which was deemed safe
	Campos, 2009 [106]	Any form of augmentation	N/A	Compared age >60 years to <60 years	1062	1 year	Older subjects exhibited more indolent disease with fewer exacerbations
	Campos, 2009 [105]	Any form of augmentation	N/A	Exacerbations	922	1 year	Mean exacerbations 2.4 per year, 17 days per episode
	Vidal, 2010 [108]	60 mg·kg^{-1} Trypsone weekly	N/A	Safety	23	24 weeks	1 out of 555 infusions had a treatment related adverse event
	Subramanian, 2012 [107]	60 mg·kg^{-1} Prolastin weekly	N/A	PET CT	10	12 weeks	NS difference in PET signal on treatment

RCT: randomised controlled trial; FEV_1: forced expiratory volume in 1 s; NS: nonsignificant; CT: computed tomography; D_{LCO}: diffusing capacity of the lung for carbon monoxide; AAT: α1-antitrypsin; FVC: forced vital capacity; N/A: not applicable; PET: positron emission tomography. #: crossover study (either wholly or as follow on for the placebo group); ¶: some patients changed to 120–180 mg·kg^{-1}, 2–3 weekly $^{+}$: changed to 240 mg·kg^{-1}, 4 weekly.

Secondary outcomes included patient-reported exacerbation frequency, D_{LCO} and quality of life. No trends in these measures were seen between active treatment and placebo, although there was a reduction in hospital admissions for exacerbations in the active treatment arm.

The most recently performed study (RAPID) included 180 patients with emphysema secondary to AATD and FEV_1 of 35–70% predicted [53]. Patients received either weekly infusions of AAT at 60 $mg \cdot kg^{-1}$ or placebo for 2 years, with a 2-year open label extension for some participants [87]. This study was the first to be powered to detect a treatment effect on the annual rate of decrease in lung density measured by CT scan; secondary outcomes included exacerbation rate, change in FEV_1 % predicted, quality of life using the St George's Respiratory Questionnaire (SGRQ) and change in D_{LCO}. The CT imaging protocol obtained scans at full inspiration (TLC) and at relaxed expiration (functional residual capacity (FRC)). While the chosen primary end-point was a combination of CT lung density (PD15) measured at TLC and FRC (which failed to achieve statistical significance), the separate imaging series at TLC and FRC were included as secondary outcomes. The main finding was a reduced rate of lung density decline, as measured by CT scanning, in the treated patients. This treatment effect was statistically significant when quantified using CT imaging obtained at full inspiration (TLC), as in previous studies (discussed earlier). During the open label extension, the patients previously on placebo exhibited a change in CT density decline, becoming similar to that seen in patients treated in the randomised phase. However, as in previous RCTs in this area, no significant effect was seen on other outcome measures, such as lung function and quality of life [87]. A supplementary report to the trial has also detailed reduced circulating desmosine, indicating an effect of augmentation on body elastin breakdown [109].

Augmentation is considered safe across the larger number of studies where this is reported. Adverse event rates were similar between treated and placebo groups in both EXACTLE [52] and RAPID [53], but were not reported in the earlier RCT [51].

The consistency of the trial data with respect to CT density decline, and the fact that CT density has been shown in cross-sectional and longitudinal studies to relate well to other clinical outcomes, such as mortality and quality of life [47, 110], indicates that it is a clinically relevant measure. Moreover decline in CT density has also been shown to relate to mortality [111], indicating that the RCT results with respect to CT density decline are consistent with the longer observational work suggesting a mortality benefit [8]. Survival was also reported in the most recent RCT (one death on augmentation, three on placebo), but the low mortality rate prevented any conclusion.

While many of the observational studies imply a benefit of treatment on the rate of FEV_1 decline, the potential for bias is greater than in a RCT and the data should be interpreted with caution. The effect of augmentation on exacerbations of AATD lung disease remains uncertain, with inconsistent effects in those RCTs which reported them [52, 53], and reduced rates in one retrospective observational study [97]. Longer duration trials, with use of symptom diaries, and/or selection for frequent exacerbations might help to confirm any treatment effect on clinical symptoms, but again such studies would require large sample sizes and the inclusion of a placebo control group would probably be considered unethical given the evident benefit on CT density decline.

Statement

- Several randomised clinical trials in severe AATD have shown intravenous augmentation therapy to reduce the progression of emphysema as assessed by CT densitometry.
- There is no evidence to support efficacy of AAT augmentation therapy in PiSZ, PiMZ or current smokers of any protein phenotype.
- Clinical trials have used fixed doses of AAT determined by body weight. Whether individualising dosage based on trough levels for each patient has any benefit requires confirmation.

Patient assessment and management steps

This stepwise approach describes the current practice of how members of the task force assess and treat patients with AATD and is not intended as a general recommendation.

1) Identify patient with severe AAT deficiency.

2) Ensure smoking is stopped if the patient was a smoker.

3) Identify and modify any other potential risk factor(s).

4) Optimise current COPD therapy.

5) Assess patient in an expert reference centre.

6) Instigate augmentation therapy if indicated.

7) Continue monitoring.

Lung volume reduction surgery in AATD

Patients with severe emphysema suffer breathlessness in part due to emphysematous hyperinflation. It is well established that targeted resection of these areas, in selected patients with COPD, can result in significant improvements in quality of life and mortality. The previous ATS/ERS statement concluded that bilateral lung volume reduction surgery (LVRS) offered short-term benefit only and was not recommended for AATD-related emphysema until more data was available [3]. Stoller *et al.* [112] reported outcomes from a National Emphysema Treatment Trial study in 10 AATD patients having bilateral LVRS (five with upper lobe predominant emphysema). The authors identified a higher mortality than medical treatment and a trend towards reduced magnitude and duration of beneficial effect compared with usual COPD. Specifically with respect to unilateral LVRS in AATD, Dauriat *et al.* [113] compared outcomes in 17 patients with AATD *versus* 35 individuals with non-AATD-related COPD, finding improvements in both groups in terms of FEV_1, dyspnoea score and arterial oxygen tension at 3–6 months. There was a loss of effect on walking distance, but preserved FEV_1 and dyspnoea score at 12 months in the AATD group.

These studies were performed a decade or more ago, since when there have been significant advances in patient selection, surgery and the advent of RCTs utilising devices to achieve medical lung volume reduction without the need for surgery (*i.e.* endobronchial valves (EBV), endobronchial coils, lung sealant, thermal vapour). Patient selection is currently advocated through a multidisciplinary team approach including a physician, surgeon, radiologist and interventional bronchoscopist with a special interest in lung volume reduction (LVR). It is recognised that patients being considered are, by definition, those with advanced disease and thus at higher risk, hence risk/benefit analysis is central to the multidisciplinary team assessment. Early outcomes from surgical LVR are now improved, probably a reflection of improved patient selection, multidisciplinary team approach and the fact that most cases involve minimally invasive video assisted thoracoscopic surgery (VATS) and a unilateral rather than a bilateral procedure. Whether this has an influence on long-term outcomes is unknown. However, mortality rate is 3% over 20 years post LVRS [114], with benefit in both lower and upper lobe disease and very low mortality from unilateral VATS [115].

The range of treatments in development may allow specific patterns of emphysema to be treated. The two best evaluated devices are endobronchial coils and EBV. Coils have been evaluated in patients with emphysema and significant improvements have been shown in 6-min walking distance, FEV_1 and quality of life. Some patients with emphysema associated with AATD have been treated with coils, but no results have been provided for this specific subgroup of patients. Studies have shown that morbidity is increased and therefore personalised risk/benefit analysis is critical [116, 117]. EBVs are unidirectional valves placed bronchoscopically in the airways supplying the target lobe. In common with LVRS, the success of this approach remains optimal patient selection; in the case of an EBV the absence of collateral ventilation between target and non-target lobe is vital to a successful outcome. The most recent RCT demonstrated significant improvements in 6-min walking distance, FEV_1 and quality of life at 6 months, and also demonstrated that centres need to be aware of potential morbidity of pneumothorax related to non-target lobe expansion and be proactive in performing valve maintenance to a high standard [118]. The study also included some AATD individuals treated with an EBV. However, owing the rarity of AATD large studies are not currently available to provide detailed assessment of coils, EBV or LVRS in AATD alone. Unlike EBV, coils can be used in patients with homogeneous emphysema, irrespective of collateral ventilation, but there is no specific data in AATD. The promising results from EBV therapy have meant that specialist LVR units no longer exclude appropriate AATD individuals from these therapies, although more research is required.

Statement

- Surgical volume reduction and EBV placement may be considered in selected patients with AATD, but further studies are needed to confirm the role of such therapies.
- The optimal results of these techniques are obtained when a careful appraisal of risks and benefits are performed by a multidisciplinary team experienced in LVR and AATD.

Lung transplantation for emphysema associated with AATD

Severe AATD-related emphysema accounted for 5.4% of all lung transplants performed between 1995 and 2014 [119]. Since the last ATS/ERS statement [3], there have been several publications reporting outcomes in many established transplant centres in different countries, but all studies have been retrospective. De Perrot *et al.* [120] reported a higher early mortality from sepsis in AATD and lower 10-year survival

in AATD post-transplantation compared with usual non-deficient COPD, and, similarly, Thabut *et al.* [121] have shown that patients with AATD had less survival benefit than patients with non-deficient COPD. This may relate to associated excess inflammation at times of infection in post-transplant AATD individuals [122, 123], due to the lack of the normal anti-inflammatory role of AAT [124]. However, this higher, early mortality for AATD post-transplant has not been confirmed, for example Burton *et al.* [125] reported no differences in early or late mortality for AATD compared with non-deficient COPD.

In terms of survival compared with non-transplanted AATD patients, Tanash *et al.* [126] observed that transplantation increased survival considerably from 5 to 11 years compared with non-transplanted AATD patients matched for FEV_1, age, sex and smoking history. The most common cause of death was pulmonary infection among the transplant patients and respiratory failure among the controls. In contrast, a UK study [127] also matched transplanted and non-transplanted AATD individuals for FEV_1, age and sex, but found that AATD patients who underwent lung transplant had lower gas transfer and quality of life pre-transplant compared with non-transplant patients. Further matching adjusted for quality of life (SGRQ), gas transfer factor and pre-transplant rate of lung function decline showed that transplantation did not increase post-surgical survival although quality of life was much improved. These controversial results underscore that the survival benefit of lung transplant is complex to assess and studies that compare matched patients with and without transplant are (by nature) biased [128]. Consequently, survival benefit remains unclear and thus the main indication for transplantation relates to improvement in quality of life.

The evaluation of comorbidities is crucial in the assessment of candidates for lung transplantation, and hepatic evaluation is particularly critical in AATD [129]. Some centres perform systematic liver biopsy in candidates, although the detection of liver disease *per se* does not preclude lung transplant in these patients. There are experiences of combined liver and lung transplantation with satisfactory results.

Statement

- The survival benefit of lung transplant in AATD patients is not clear.
- In general, patients with AATD have improved quality of life following lung transplantation.
- Referral timing, rate of decline in lung function, health status and social support differ from patient to patient, and will have an influence on the evaluation for transplant.
- The role of post-transplant augmentation therapy in particular needs to be explored.

New lines of research in AATD

There are several aspects of lung disease in AATD that require further research. The main topics identified by the group are: 1) biomarkers of emphysema progression in AATD; 2) biomarkers of response to augmentation therapy; 3) research on the minimum clinically important difference in rate of decline in lung density; 4) personalised augmentation therapy, with individualised selection of therapeutic regimen according to the patient needs; 5) development of genetic and regenerative therapies; 6) other types of treatment, such as biochemical inhibitors of neutrophil proteinases; 7) development of specific patient-reported outcomes for patients with emphysema associated with AATD; and 8) efficacy of augmentation therapy after lung transplant in AATD patients.

Organisation of care: reference centres and registries

Due to the low prevalence and underdiagnosis, AATD is considered a rare disease. It is almost impossible for an individual clinician or a single centre to accumulate enough expertise in diagnosis and management of the disease. Therefore, the care for patients with AATD is best organised in reference centres that can provide the highest standard of care and advice to the individuals affected and their families while also contributing to knowledge accumulation. An optimised format of service provision by a reference centre in AATD as outlined in figure 3, although other models may be applicable.

The European Commission also recommends the development of reference centres for rare diseases. The establishment of European reference networks (ERNs) for rare diseases should therefore serve as research and knowledge centres, updating and contributing to the latest scientific findings, treating patients from other member states and ensuring the availability of subsequent treatment facilities where necessary. The definition of ERNs should also reflect the need for services and expertise to be distributed across the European Union (EU). In a document released by the European Commission in 2006, the criteria for reference centres of rare diseases are clearly specified (table 4) [130].

Reference centres must establish a registry of their activity and collect information prospectively about the natural history of the patients being monitored. These data can be shared at national and international levels and be the foundation of the registries of AATD. The development of registries is crucial as the only

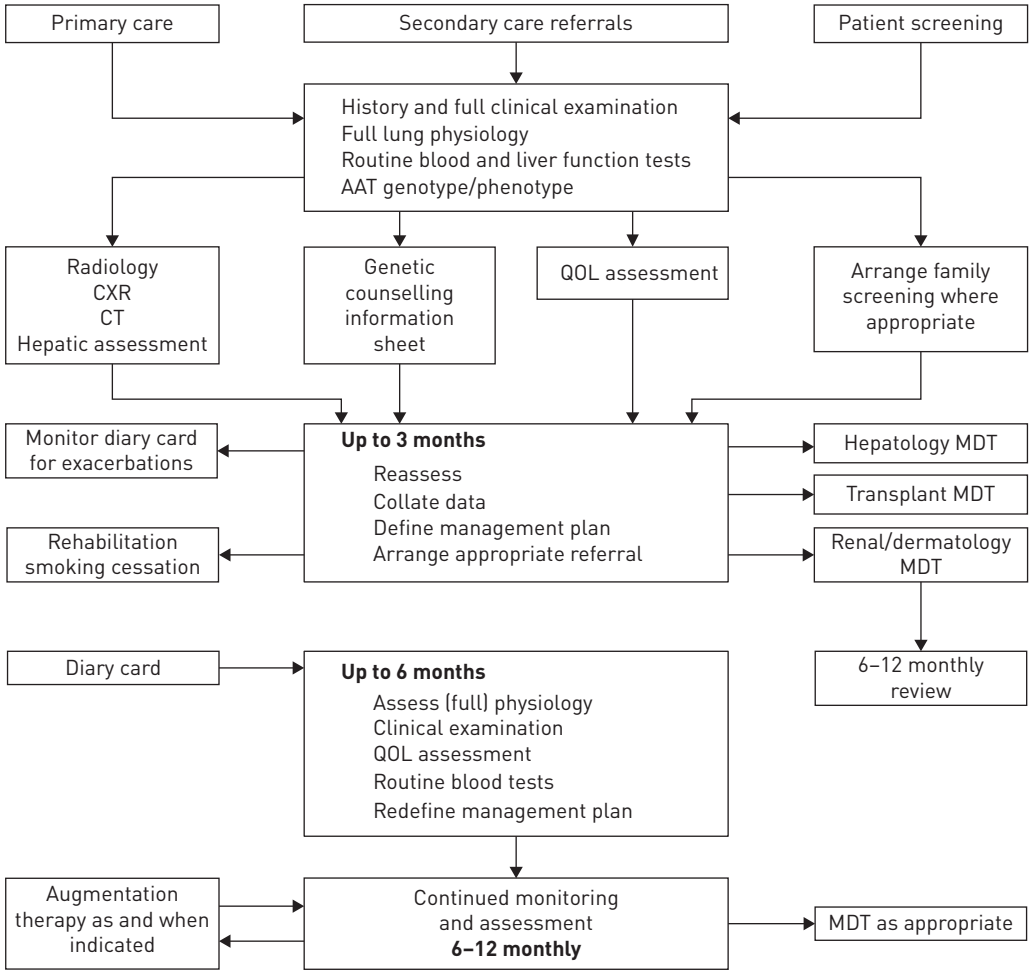


FIGURE 3 Proposal for service provision by a reference centre in α1-antitrypsin deficiency (AATD). This algorithm describes the current practice of how members of the task force treat patients with AATD and is not provided as a general recommendation. AAT: α1-antitrypsin; CXR: chest radiography; CT: computed tomography; QOL: quality of life; MDT: multidisciplinary team.

TABLE 4 Criteria required for reference centres for rare diseases

Appropriate capacity to diagnose, monitor and manage patients with evidence of good outcomes when applicable
Sufficient capacity to provide expert advice, diagnosis or confirmation of diagnosis, to produce and adhere to good practice guidelines and to implement outcome measures and quality control
Demonstration of a multidisciplinary approach
High level of expertise and experience documented through publications, grants or honorary positions, teaching and training activities
Strong contribution to research
Involvement in epidemiological surveillance, such as registries
Close links and collaboration with other expert centres at the national and international levels and a capacity to network
Close links and collaboration with patient associations where they exist
Perform education, information, communication activities to empower patients
Although an ENCR should fulfil most of the above criteria, the comparative relevance of these various criteria will be influenced (in part) by the particular disease or group of diseases covered

ENCR: European national centre of excellence. Reproduced from [130].

TABLE 5 Description of access to care for α1-antitrypsin deficiency patients in some Eastern and Western European countries

	Country			α1-antitrypsin deficient subjects			
	Population million[#]	National centres n	Location of national centres	Patients monitored	Access to augmentation	Patients receiving augmentation therapy n	Reimbursement[¶] (status in January 2017)
East European centres							
Bulgaria	7.09	0	0	By university clinics on individual basis	No access	0	Not covered by public health insurance
Croatia	4.22	0	0	By university clinics on individual basis	No access	0	Not covered by public health insurance
Czech Republic	10.55	1	Thomayer Hospital Prague	By national centre (63 PiZZ patients)	Unrestricted	21	100% covered by public health insurance
Hungary	9.81	4	Plan to set up 4 national centres at universities (2016)	By national centres	No access	0	Not covered by public health insurance
Latvia	1.95	1	Centre of TB and Lung Disease, Riga East University Hospital	By national centre (~20 PiZZ patients)	Limited access	1	Not covered by public health insurance
Poland	38.59	1	National Institute of Tuberculosis and Lung Diseases in Warsaw, The Childrens Memorial Health Institute in Warsaw	By national centre (70 patients)	No access	0	Not covered by public health insurance
Romania	19.34	1	Marius Nasta Institute of Pneumology, Bucharest	By national centre (7 patients)	No access	0	Not covered by public health insurance
Russia	143.44	0	0	By university clinics on individual basis	No access	7	Not covered by public health insurance
Serbia	8.80	0	0	By university clinics on individual basis (~20 patients)	No access	0	Not covered by public health insurance
Slovakia	5.43	3	Plan to set up of centres (Kosice, Bratislava, Vysne Hagy)	By national centres	Limited access	1	Every single patient has to be individually agreed with health insurance
Slovenia	2.09	0	0	N/A	No access	0	Not covered by public health insurance
West European centres							
Austria	8.49	8	Vienna, Salzburg, Graz, Hörgas-Enzenbach, Wels-Grieskirchen, Natters, Klagenfurt, Hohenems	By general practitioners	Unrestricted	130	100% covered by public health insurance
Belgium	11.48	N/A	All over the country	University hospitals and local hospitals by pneumologists	Unrestricted	56	100% covered by public health insurance, but only for patients who started therapy before 2010 No reimbursement for new patients after 2010
Denmark	5.70	1	Copenhagen	By university clinic, follows up patients on individual basis	No access	0	Not covered by public health insurance

Continued

TABLE 5 Continued

	Country			α1-antitrypsin deficient subjects			
	Population million[#]	National centres n	Location of national centres	Patients monitored	Access to augmentation	Patients receiving augmentation therapy n	Reimbursement[¶] (status in January 2017)
France	64.73	N/A	All over the country	By university hospitals, local hospitals, private practices	Unrestricted (to PiSZ and PiZZ)	>300	100% covered by public insurance
Germany	80.68	60	All over the country	By university hospitals, local hospitals, private practices	Unrestricted	>1000	100% covered by health insurance
Italy	59.80	>20	All over the country	University hospitals and local hospitals by pneumologists	Unrestricted	115	100% covered by public health insurance
Ireland	4.72	1	Dublin	By national centre	Limited access	23	Not covered by public health insurance
The Netherlands	15.1	1	Leiden University Med Center	By national centre	No access	0	Not covered by public health insurence
Portugal	10.29	27	All over the country	By university hospitals and local hospitals by pneumologists	Unrestricted	118	100% covered by public health insurance
Spain	46.05	>40	All over the country	By university hospitals and local hospitals by pneumologists	Unrestricted	170	100% covered by public health insurance
UK	65.20	5	Birmingham, Edinburgh, Cambridge, Coventry, London	Major centres by experts and local hospitals by pneumologists	No access but some named patients with panniculitis (off label indication)	0	Full if approved for Individual Funding Request by local commissioners (in NHS England)

Data were provided by: Karin Schmid-Scherzer (Austria); Jacques Hutsebaut (Belgium); Kosta Kostov (Bulgaria); Neven Tudoric (Croatia); Jan Chlumsky (Czech Republic); Asger Dirksen (Denmark); Gabriel Thabut (France); Claus Vogelmeier (Germany); Attila Somfay (Hungary); Noel G. McElvaney (Ireland); Ilaria Ferrarotti (Italy); Alvils Krams (Latvia); Jan Stolk (the Netherlands); Joanna Chorostowska-Wynimko (Poland); Maria Sucena (Portugal); Ruxandra Ulmeanu (Romania); Kirill Zykov (Russia); Branislava Milenkovic (Serbia); Ivan Solovic (Slovakia); Marc Miravitlles (Spain); Robert A. Stockley (UK). N/A: data not available. [#]: information from www.worldometers.info; [¶]: status in January 2017.

way to achieve the successful accumulation of knowledge about the clinical characteristics, evolution, natural history and response to treatment of patients with rare diseases, such as AATD.

Europe was pioneer in the development of national registries for AATD. As early as the 1970s Sweden [15] and Denmark [78] initiated their registries, followed by other countries such as the Netherlands, Spain, Italy, Germany, Ireland, the UK and more recently Switzerland, Latvia, Estonia, Czech Republic, Poland, Austria, Belgium and France, among others. However, the low prevalence of the disease stimulated the organisation of an international registry, not restricted to Europe, but with predominance of European countries, the Alpha One International Registry (AIR), which was founded in 1997 [9] following the recommendation from the WHO to establish such a registry of AATD [25]. AIR has been a successful platform for the development of clinical trials with new and existing therapies for the disease and has contributed to increase the awareness of the disease among healthcare professionals across Europe [131].

Statement

- According to the European Council, management of patients with AATD should be supervised by reference centres of excellence at a national or regional level.
- The systematic collection of data concerning clinical characteristics and natural history of patients with AATD in national and international registries will enhance knowledge about the evolution of this disease and its optimal management.
- For many AATD individuals a respiratory service is the first point of diagnosis. The operational pathway includes varying assessments and follow-up depending on personalising the patients' risk and defining the respiratory phenotype. Links to multidisciplinary teams will ensure the best quality of care.

Access to optimal care and augmentation therapy for AATD in Europe

In Europe, healthcare policy is largely a devolved matter and decisions related to provision of healthcare services, disease management and prescription medicines rest with national, regional or local policy makers, health technology assessment (HTA) agencies and payers. This results in different standards of care for AATD and contributes to geographical inequalities in access to optimal healthcare services, clinical expertise and effective therapies. Notably, access to high-cost, rare disease therapies, such as augmentation therapy for AATD, can vary significantly across jurisdictions [132]. Augmentation therapy is fully reimbursed in some countries such as Germany, Italy, Spain, Portugal, France and others, but not reimbursed in the majority of Eastern European countries and in some Western European countries such as the UK, Ireland, Denmark or Sweden (table 5).

Increasing efforts are being made by policy makers to ensure that patients with rare diseases such as AATD have timely, better and more equitable access to high quality care. Examples of these initiatives include: the European Council recommendation on an action in the field of rare diseases, that required all EU member states to adopt national plans and policies for rare diseases by the end of 2013 [133]; the European Network of HTA agencies (EUnetHTA) that aims to assist in the development of reliable, timely, transparent and transferable information to contribute to HTAs in European countries [134]; and the European Medicine Agency's adaptive pathways pilot for medicine development and data generation, which allows for early and progressive patient access to a medicine [135].

In the absence of harmonised legislation that regulates AATD healthcare provision and access to augmentation therapy and other specific treatments across Europe, only multi-stakeholder collaboration and continuous improvement of the available evidence-base for efficacy and cost-effectiveness of AATD therapies is likely to achieve greater equity in implementation of best practice.

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