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Clinical Practice Guidelines

The Diagnosis and Management of Alpha-1 Antitrypsin Deficiency in the Adult

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Abstract

Background: The diagnosis and clinical management of adults with alpha-1 antitrypsin deficiency (AATD) have been the subject of ongoing debate, ever since the publication of the first American Thoracic Society guideline statement in 1989.[1] In 2003, the "American Thoracic Society (ATS)/European Respiratory Society (ERS) Statement: Standards for the Diagnosis and Management of Individuals with Alpha-1 Antitrypsin Deficiency" made a series of evidence-based recommendations, including a strong recommendation for broad-based diagnostic testing of all symptomatic adults with chronic obstructive pulmonary disease (COPD).[2] Even so, AATD remains widely under-recognized. To update the 2003 systematic review and clinical guidance, the Alpha-1 Foundation sponsored a committee of experts to examine all relevant, recent literature in order to provide concise recommendations for the diagnosis and management of individuals with AATD.

Purpose: To provide recommendations for: (1) the performance and interpretation of diagnostic testing for AATD, and (2) the current management of adults with AATD and its associated medical conditions.

Methods: A systematic review addressing the most pressing questions asked by clinicians (clinician-centric) was performed to identify citations related to AATD that were published since the 2003 comprehensive review, specifically evaluating publications between January 2002 and December 2014. Important, more recent publications were solicited from the writing committee members as well. The combined comprehensive literature reviews of the 2003 document and this current review comprise the evidence upon which the committee's conclusions and recommendations are based.

Results: Recommendations for the diagnosis and management of AATD were formulated by the committee.

Conclusions: The major recommendations continue to endorse and reinforce the importance of testing for AATD in all adults with symptomatic fixed airflow obstruction, whether clinically labeled as COPD or asthma. Individuals with unexplained bronchiectasis or liver disease also should be tested. Family testing of first-degree relatives is currently the most efficient detection technique. In general, individuals with AATD and emphysema, bronchiectasis, and/or liver disease should be managed according to usual guidelines for these clinical conditions. In countries where intravenous augmentation therapy with purified pooled human plasma-derived alpha-1 antitrypsin is available, recent evidence now provides strong support for its use in appropriate individuals with lung disease due to AATD.

Abbreviations: alpha-1 antitrypsin deficiency, **AATD;** American Thoracic Society, **ATS;** European Respiratory Society, **ERS;** chronic obstructive pulmonary disease, **COPD;** alpha-1 antitrypsin, **AAT;** proteinase inhibitor genotype with 2 Z alleles, **Pi*ZZ;** COPD related to AATD, **AATD-COPD;** COPD in the absence of AATD, **AAT-replete COPD;** granulomatosis with polyangiitis, **GPA;** polymerase chain reaction, **PCR;** proteinase inhibitor, **Pi;** forced expiratory volume in 1 second, **FEV_1;** computed tomography, **CT;** aspartate aminotransferase, **AST;** alanine aminotransferase, **ALT;** gamma-glutamyltransferase, **GGT;** international normalized ratio, **INR;** U.S. Food and Drug Administration; **FDA;** total lung capacity, **TLC**

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Keywords:

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This article is a statement of the Medical and Scientific Advisory Committee of the Alpha-1 Foundation and has an online data supplement. This is a *clinician-centric* article.

Summary of Recommendations

Testing for Alpha-1 Antitrypsin Deficiency (AATD):

- All individuals with COPD regardless of age or ethnicity should be tested for AATD.
- All individuals with unexplained chronic liver disease should be tested for AATD.
- All individuals with necrotizing panniculitis, granulomatosis with polyangiitis, or unexplained bronchiectasis should be tested for AATD.
- Parents, siblings, and children, as well as extended family of individuals identified with an abnormal gene for AAT, should be provided genetic counseling and offered testing for AATD (see guideline document for special considerations about testing minors).
- For family testing after a proband is identified, AAT level testing alone is **not recommended** because it does not fully characterize disease risk from AATD.
- For diagnostic testing of symptomatic individuals, we **recommend** genotyping for at least the S and Z alleles. Advanced or confirmatory testing should include Pi-typing, AAT level testing, and/or expanded genotyping.

Pulmonary function testing in those with AATD:

- Initial evaluation with complete lung function testing is **recommended**.
- Annual follow-up of adults with at least a spirometry test is **recommended**.

Computed Tomography (CT) scan of the chest in the evaluation in those with AATD:

- In newly diagnosed patients who are symptomatic and/or have abnormal pulmonary function testing, a baseline CT scan of the chest is **recommended**.
- Serial chest CT scanning to monitor progression of disease is **not recommended**.

Monitoring for liver disease in those with AATD:

- Monitoring for liver disease at annual intervals (or more frequently as indicated by clinical circumstances), with physical examination including focused exam for signs of liver disease, liver ultrasound, and laboratory monitoring of AST, ALT, GGT, albumin, bilirubin, INR, and platelets is **recommended**.

Management of lung disease in those with AATD:

- Every effort should be made to prevent exposure to tobacco smoke and facilitate cessation in those who are smoking.
- Lung volume reduction surgery is **not recommended** for individuals with COPD related to AATD.

Intravenous augmentation therapy in those with AATD is *recommended* for:

- Individuals with an FEV_1 less than or equal to 65% predicted.
  - For those with lung disease related to AATD and an FEV_1 greater than 65%, we **recommend** discussion with each individual regarding the potential benefits of reducing lung function decline with consideration of the cost of therapy and lack of evidence for such benefit.
- Individuals with necrotizing panniculitis.

Intravenous augmentation therapy is *not recommended* for:

- Individuals with the MZ genotype of AATD.
- Individuals with lung disease due to AATD who continue to smoke.
- Individuals with AATD and emphysema or bronchiectasis who do not have airflow obstruction.
- The treatment of liver disease due to AATD.
- Individuals who have undergone liver transplantation.

Additional recommendations regarding dosing of intravenous augmentation therapy:

- Weekly doses higher than the current FDA-approved dose are **not recommended**.
- Monitoring of trough AAT blood levels to evaluate the adequacy of AAT augmentation dosing is **not recommended**.

Introduction

Alpha-1 antitrypsin deficiency (AATD), also known as alpha-1 proteinase inhibitor deficiency, is a genetic condition that leads to increased risk of lung and liver disease and several other conditions. The spectrum of AATD-related disease and the age at clinical onset is quite broad. Individuals with AATD may lead healthy lives without any of these medical conditions, but factors such as smoking, occupational exposure to dust and fumes, and some liver insults can increase the likelihood of disease.

The molecular mechanisms leading to lung disease and liver disease are different. AATD lung disease is due to the relative deficiency in the blood and lungs of the alpha-1 antitrypsin (AAT) protein, a major circulating serine proteinase inhibitor. Although recent evidence suggests a more complicated cascade of proteolytic and inflammatory factors as the cause of emphysema in AATD, unopposed neutrophil elastase activity within the pulmonary interstitium with resultant connective tissue destruction remains an important contributor to the pathogenesis of emphysema. In addition, neutrophil elastase has been implicated in the mucus hypersecretion associated with chronic bronchitis. There is a high prevalence of anatomic bronchiectasis in individuals with AATD, with some individuals manifesting signs and symptoms of clinical bronchiectasis. Overall, the pulmonary manifestations of AATD include the entire spectrum of disorders associated with chronic obstructive pulmonary disease (COPD).

The deficiency of circulating AAT in the most common form of clinically relevant AATD (PI*ZZ type) is caused by the accumulation of AAT protein within hepatocytes, the major site of synthesis of this protein. This accumulation is due to misfolding and polymerization of AAT within the hepatocyte rough endoplasmic reticulum and this accumulation is associated with an increased risk of liver disease. AAT polymers formed or trapped in the lung are pro-inflammatory and may contribute to the pulmonary disease of AATD. While the lung disease of AATD is generally an adult-onset condition, the liver disease of AATD can present from birth through old age. The fulminant liver failure occurring in infants with AATD is thought to have a different mechanism than the cirrhosis seen in some adults with AATD.

Several publications have clarified the likely prevalence of AATD in the United States and Europe as between 1:2500 and 1:5000 PI*ZZ in the entire population and emphasize that only a small minority of affected individuals have been diagnosed.[3,4] In addition, there is often a significant delay in the diagnosis of AATD from the time that symptoms first appear. Finally, there appears to be an increased prevalence of abnormal AAT genotypes among those with COPD or chronic liver disease.

In 2003, the "ATS/ERS: Standards for the Diagnosis and Management of Individuals with Alpha-1 Antitrypsin Deficiency"[2] was published. This 83-page document provided a comprehensive literature review and graded recommendations for identifying and treating individuals with AATD. Unfortunately, despite an accompanying executive summary, the length and density of the document has undermined its widespread clinical application and impact. Both to update the 2003 document with more recently published findings and to encourage review and use of these recommendations more widely, the current committee has sought to provide a much more concise and usable document, backed by online documentation. It is the committee's hope that the clinical impact will be enhanced with this new format.

There are many unmet needs in the clinician community. We recognize that there is need for a clinician-centric, easily accessible, literature-based summary of the current clinical practice among clinician scientists with experience in the evaluation and treatment of AATD. In concert with Voltaire's quote that "perfection must not be the enemy of the good," where gaps in the literature exist, expert opinion may be substituted until a more evidence-based approach can be applied. Educated guidance in this setting is better than no guidance.

Methods

A health sciences librarian (S.K.) used medical subject headings and text words to search for articles referencing AATD or any related synonyms (See online data supplement Table 1). The Ovid platform was used to search MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials , the Database of Abstracts of Reviews of Effects, and the Cochrane Database of Systematic Reviews. The peer-reviewed search was limited to human studies and articles in English or in any language with English abstracts. Literature indexed since the publication of the previous standards document was searched for the period January 2002

through December 2014. The panel reviewed an additional set of older and newer literature identified as important by members of the writing committee. Additionally, members were asked to cite important papers from 2015.

The chairs reviewed citations for relevance based on titles and abstracts. Writing groups were established from the principal categories of clinical questions. Chairs and committee members sorted the remaining citations into non-discrete sets for each clinical question. Full text was assessed for risk of bias. If more than one writing committee used the same citation, screening was compared and reconciled.

Through 2014, no definitive randomized controlled trials had been published. A meta-analysis of 2 pilot studies was published and reviewed but was felt to have major methodologic shortcomings. However, just prior to finalizing this document, a large, randomized, placebo-controlled, blinded study of intravenous augmentation therapy was published[5] and this study has been included in our deliberations.

Each recommendation is rated by the strength of the opinion (strong, medium, weak) and the quality of evidence (high, moderate, low). The strength of the recommendation was determined by voting among the writing committee and a strong recommendation, even in the face of weak evidence, reflects a broad consensus among the expert scientists and clinicians within the writing committee. In situations where there was a lack of consensus, a minority opinion was included following the recommendation.

In organizing this document, we have adopted several nomenclature conventions. Individuals with COPD due to AATD are referred to as having *AATD-COPD* and those with COPD without AATD are said to have *AAT-replete COPD*. The clinical questions are divided into 3 groups:

1. Detection, which refers to strategies to identify individuals with AATD among various at-risk populations;

2. Diagnostic Testing, which refers to the actual tests used (e.g., genotyping) and to the sequence of tests deployed to secure a diagnosis of AATD;

3. Clinical Evaluation and Treatment. Within the Treatment section, the order of clinical questions progresses from those regarding general therapy of COPD and liver disease in individuals with AATD to issues regarding the specific management of AATD (e.g., augmentation therapy).

Finally, in the context that the document discusses AATD that is ascertained both in those with symptoms (who may already be under clinical care) and in those without symptoms and not yet recognized, we refer to those with AATD as *individuals* rather than as *patients*. We refer to the infusion of purified pooled human plasma alpha-1 antitrypsin as augmentation therapy. Lastly, the discussion of each clinical question is followed by several key references when appropriate. As this document updates the prior 2003 ATS/ERS standards document, references cited in the body of this document are those published since 2003 whenever possible.

For the complete literature evaluation results and methodology, please refer to the online data supplement for these guidelines.

Questions

1. Should individuals be tested for AATD?

In general, the reason for making a specific diagnosis is that the management of the patient or of family members is impacted by the test result. Examples of relevant impacts include changing how patients are monitored; how patients are counseled, e.g., with regard to lifestyle or genetic risks; or how patients are treated. Testing methods may vary by the specific clinical context in which the testing is done. For example, testing strategies for population-based screening, if appropriate, will differ from those used for targeted detection or clinical case-finding. These general considerations inform many of the specific clinician-centric questions that arise regarding AATD. In the sections that follow, specific testing-related clinical questions are posed, with responses, the related evidence, and the grading of the recommendation.

Should specific populations be tested for AATD?

Background: The goal of testing is to identify individuals and at-risk families for whom interventions might confer benefit. Populations enriched for AATD include families of affected individuals, people with COPD, and people with liver disease. As AATD is a genetic disorder, testing of first-degree relatives is certainly logical. In general, deficient family members are healthy or less severely affected or symptomatic compared to the proband, also called the index case. It is less clear how deep into an affected individual's pedigree such testing

should extend, although identifying additional family members with AATD would prompt a new round of testing of their first-degree relatives. Population-based screenings performed thus far have been of limited size and scope. Prevalence estimates may vary by ancestry and ethnicity of a population.

Genetic counseling provides individuals with the opportunity to make an informed decision about being tested and the potential consequences of results. Genetic counseling can be provided by a well-informed primary provider.

Recommendation 1a: All individuals with COPD, regardless of age or ethnicity, should be tested for AATD (strong recommendation, moderate quality of evidence).
Rationale: High value is placed on understanding the etiology of COPD in a given individual and the potential for providing specific therapy. Low value is placed on the high cost of testing. Testing of adults should not be limited on the basis of age, gender, or race. There are no specific demographic or clinical characteristics that rule out the diagnosis of AATD. For example, while there is a lower prevalence of AATD in African American and Asian populations, such individuals with consistent clinical features should be tested for AATD.
Key references:[6-8]

Recommendation 1b: All individuals with unexplained chronic liver disease should be tested for AATD (strong recommendation, low quality of evidence).
Rationale: High value is placed on understanding disease etiology. Low value is placed on the lack of AATD specific therapy for these conditions.
Key reference:[9]

Recommendation 1c: All individuals with necrotizing panniculitis, granulomatosis with polyangiitis (GPA, formerly Wegener's granulomatosis), or unexplained bronchiectasis should be tested for AATD (strong recommendation, low quality of evidence).
Rationale: High value is placed on understanding disease etiology. Low value is placed on lack of AATD specific therapy for some of these conditions.
Key references:[10-13]

Recommendation 1d: Adult siblings of individuals identified with an abnormal gene for AAT, whether heterozygote or homozygote, should be provided with genetic counseling and offered testing for AATD (strong recommendation, moderate quality evidence).

Recommendation 1e: Parents, children, minor siblings, and the extended family of individuals identified with an abnormal gene for AAT should be provided genetic counseling and offered testing for AATD (weak recommendation, low quality of evidence).
Rationale for 1d and 1e: High value is placed on knowledge gained for family members to allow for risk modification (smoking avoidance) and proper monitoring. Low value is placed on the potential negative aspects of genetic testing (anxiety, insurability, feelings of guilt).
Remarks: The role of testing in the pediatric age group, especially in children without overt liver disease, is not well studied and not supported by current literature or experience. Parental testing is a potential alternative to testing of younger children to predict risk of deficient genotype. The range of serum AAT levels among individuals with specific genotypes is quite broad and therefore overlap between different genotypes can exist. Thus, family testing should be done with a genotype. The services of an AATD-aware genetic counselor may be appropriate.

The Genetic Information Non-discrimination Act was passed in 2008. This act is intended to protect individuals' insurability (with respect to health insurance, but not life insurance) and employment from discrimination based on genetic information. Counseling family members about the benefits versus risks of genetic testing should occur. Testing of family members should be offered at each clinic visit until all who want testing have received it. Options for confidential testing of family members are available and should be discussed as appropriate. Specific information on such programs is available on the Alpha-1 Foundation website (www.alpha1.org).
Key references:[7,14,15]

Should AAT levels be used for the primary diagnosis of AATD?

Background: More than 95% of all severely AAT deficient individuals have either the ZZ or SZ genotype. Recent evidence indicates that MZ individuals who smoke are at increased risk for airflow obstruction. In this context the Z allele is the single most frequent genetic risk factor for airflow obstruction. The most sensitive and specific method for identification of

individuals at risk for inherited airflow obstruction is direct identification of the Z allele by genotyping (e.g., by using polymerase chain reaction [PCR] probes for the Z allele). Genotyping panels that also include the S allele identify SZ individuals. Genotyping for the S and Z alleles is greater than 99% specific and sensitive for these alleles.

AAT levels are insufficient to identify at risk individuals because the AAT level changes with inflammation, pregnancy, and in children. General recommendations of the American College of Medical Genetics[16] suggest that confirmatory testing should be considered using a second method. In AATD testing, the most widely used confirmatory methods are proteinase inhibitor (Pi) typing and/or AAT genotyping. More advanced testing, such as expanded genotyping for rare AAT alleles and gene sequencing, may also be considered confirmatory testing. The type of primary AAT testing must reflect the clinical circumstance under which the testing is done (targeted detection versus screening).

Recommendation 1f: For family testing after a proband is identified, AAT level testing alone is not recommended because it does not fully characterize disease risk from AATD.

Recommendation 1g: For diagnostic testing of symptomatic individuals, we recommend genotyping for at least the S and Z alleles. Advanced or confirmatory testing should include Pi-typing, AAT level testing, and/or expanded genotyping.

Rationale: High value is placed on accurate testing and minimization of false negative results. Low value is placed on the cost of testing. Positive results should be confirmed using an independent testing method. Test kits that use a combination of 2 or more methods (e.g., level and genotyping) have advantages over a single testing methodology. The range of serum AAT levels among individuals with specific genotypes is sufficiently broad that there is overlap between different genotypes. Thus, serum AAT levels cannot discriminate between different genotypes and additional AAT testing is needed. Finally, the rare Null genotypes (genotypes that lead to the production of no or truncated AAT protein) should always be considered when there is discordance between level, and genotype or Pi-type, especially since unintended paternity/maternity issues can arise in this setting.

Key references:[17,18]

2. Should the clinical evaluation of individuals with AATD be different from those without AATD?

Differences in clinical evaluation between patient groups are justifiable only to the extent that the results will impact the specific management of the patient. AATD is associated with an increased risk of a variety of conditions such as emphysema, bronchiectasis, liver disease, GPA, and panniculitis. Thus, the clinical evaluation of an individual with AATD should pay special attention to the early detection and follow-up of associated conditions. Emphasis on these known conditions might lead to different clinical approaches such as a focus on diffusing capacity or chest CT of the patient with COPD associated with AATD compared to the workup of the patient with AAT-replete COPD.

Should complete pulmonary function testing be part of the evaluation of individuals with AATD?

Background: While more readily available, spirometry alone (forced expiratory measurements of volume and flow) may not accurately reflect the degree of parenchymal destruction associated with AATD-related pulmonary emphysema. There are well-documented cases of individuals with significant emphysema and little or no impairment in spirometry. Measurements of static lung volumes and gas transfer (diffusing capacity) can enhance the detection and assessment of extent of, usually panlobular, emphysema.

Recommendation 2a: Initial evaluation with complete lung function testing is recommended for all individuals with AATD (weak recommendation, low quality evidence).

Minority opinion: Spirometry may be sufficient in asymptomatic individuals with AATD.

Rationale: High value is placed on establishing an initial assessment of all aspects of pulmonary function. Low value is placed on the cost of the testing. Although they reflect different aspects of the same pathological process (emphysema), expiratory flow (forced expiratory volume in 1 second, [FEV_1]), hyperinflation, and diffusing capacity are not always well correlated with one another, and these should be determined when assessing the overall severity of pulmonary impairment in individuals with pulmonary symptoms and AATD.

Should individuals with AATD have follow-up pulmonary function testing to monitor for progression of disease?

Background: Some individuals with AATD have normal pulmonary function at the time of diagnosis. The natural history of these individuals is not completely understood, though some data suggest that PI*ZZ never smokers who are asymptomatic have a normal expected survival.[19]

Recommendation 2b: Follow-up of adults with AATD with normal baseline spirometry should include annual spirometry (strong recommendation, low quality evidence).
Minority opinion: No study has assessed the value of annual spirometry (e.g., compared with other testing strategies) as the optimal method or interval for monitoring.
Rationale: High value is placed on detecting the accelerated rate of lung function loss early in the disease process. Low value is placed on the cost of lung function testing. As AATD lung disease is characterized by accelerated lung function loss, the early detection of the development of obstructive lung disease allows proper risk avoidance, implementation of COPD management, and consideration of specific therapy for AATD. Since the lung disease associated with AATD often starts as purely parenchymal destruction, more complete pulmonary function testing (including measures of diffusing capacity) may be considered.
Key references:[20]

Should a baseline computed tomography (CT) scan of the chest be included in the evaluation of those with AATD? Should individuals with AATD get chest CT scans at regular intervals to assess disease status?

Background: Studies have demonstrated that decreased lung density on chest CT directly reflects the lung tissue loss in pulmonary emphysema and correlates with mortality. In addition, clinical studies have shown a slowing of the rate of this density loss with intravenous augmentation therapy administration compared with placebo infusions. However, CT scanning exposes individuals to radiation. Furthermore, how the clinician should respond to the results of the CT scan in regard to clinical management remains unclear.

Current lung cancer screening guidelines recommend regular low-dose chest CTs starting at age 55 and continuing for 20-25 years (depending on the recommendation source) for individuals with a significant smoking history and for individuals who have stopped smoking within a specified interval since abstinence was achieved. Our recommendations are not intended to conflict with these guidelines.

Recommendation 2c: In newly diagnosed patients who are symptomatic and/or have abnormal pulmonary function testing, we recommend a baseline CT scan of the chest (weak recommendation, low quality evidence).
Minority opinion: While CT scans can show associated conditions in AATD (e.g., anatomic bronchiectasis, atypical mycobacterial infection, emphysema), whether detection of these findings impacts therapy in patients without suggestive clinical features is unclear. Furthermore, whether the benefits of clinical vigilance for these findings offset the radiation risk and cost of CT scans also remains unclear.
Rationale: A baseline CT may identify pulmonary emphysema even in the presence of a normal, complete pulmonary function test. The availability of a baseline study for comparison with future studies, especially when early panlobular disease can be difficult to detect without a comparator, can be helpful in later evaluations.

Recommendation 2d: We do not recommend serial chest CT scanning to monitor progression of disease (strong recommendation, low quality evidence).
Rationale: High value is placed on evidence-based data and cost. Chest CTs have shown a high frequency of radiographic (95%) and clinical (27%) bronchiectasis in a large study of individuals with AATD. However, no study to date has demonstrated improved clinical outcomes based on the knowledge provided by chest CTs. Occasionally, individuals with AATD and normal spirometry have symptoms referable to emphysema or bronchiectasis for which CT can establish a diagnosis.
Key references:[11,21,22]

Should individuals with Alpha-1 be monitored for the liver complications of AATD?

Background: Adults with AATD have an increased risk of cirrhosis and of hepatocellular carcinoma. Liver complications of AATD are relatively common, and may be found histologically in many older adults. Liver disease is generally restricted to ZZ and SZ individuals, though other rare genotypes are at risk (e.g., Mmalton and Siiyama). The role of concomitant hepatosteatosis,

liver toxins including ethanol, and infectious agents, such as the hepatitis virus in the promotion of liver disease in AATD has been suggested but there are meager supporting data. There are few data in AATD to define the age at which to begin adult screening or define the optimal testing frequency.

Recommendation 2e: We recommend that individuals with AATD be monitored for liver disease at annual intervals (or more frequently as indicated by clinical circumstances), with physical examination including a focused exam for signs of liver disease, liver ultrasound, and laboratory monitoring of aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyltransferase (GGT), albumin, bilirubin, international normalized ratio (INR), and platelets (strong recommendation, low quality of evidence).

Minority opinion: Clinical liver disease in AATD has a bimodal distribution in children and adults. Clinically significant liver disease is rare in adults less than 40 years of age.

Rationale: High value is placed on evidence-based data. Low value is placed on cost. There are very few data regarding evaluation of AATD separately from other liver diseases. Individuals with AATD have frequent, often transient elevations of transaminases. However, measurements of synthetic function (albumin) and correlates of splenomegaly (e.g., platelet count, liver ultrasound) are more specific for cirrhosis. Abnormal tests should prompt an abdominal ultrasound. The American Association for the Study of Liver Disease recommends a hepatic ultrasound every 6 months to monitor for hepatocellular carcinoma in individuals with a greater than 2% per year risk of hepatocellular carcinoma.[23] This is likely to include any patient with cirrhosis, but may also include non-cirrhotic patients with significant injury, significant inflammation, or comorbidities. There are no prospective studies of this recommendation in AATD. Occasionally, individuals with normal laboratory values have symptoms referable to cirrhosis. Liver ultrasound, elastography, and biopsy can be helpful in these individuals.

Key references:[24,25]

3. Should the diagnosis of AATD alter medical management?

Differences in treatment between conditions are justified only when pathobiologic differences between the conditions produce different natural histories, prognoses, or differential responses to treatment. In the context of AATD, differences between managing patients with AAT-replete COPD and those with AATD relate to the specific pathogenetic role of the deficiency of AAT in predisposing to COPD. The specific questions and recommendations that follow represent those frequently asked by clinicians regarding whether to treat AATD patients differently from those with AAT-replete COPD.

Should usual medical management of COPD be altered in those with COPD due to AATD?

Background: The rate of lung function decline in smokers with AATD-COPD is considerably higher than that seen in AAT-replete COPD. This is likely due to the combined effects of cigarette smoke in reducing the anti-proteinase activity of the AAT molecule and promotion of pulmonary inflammatory infiltration.

There are no reliable data that suggest a differential treatment response to bronchodilators, inhaled corticosteroids, pulmonary rehabilitation, supplemental oxygen therapy, or immunizations in individuals with AATD-COPD and AAT-replete COPD. One study involving a small number of individuals with AATD-COPD found that treatment with an inhaled long-acting beta-agonist/glucocorticoid combination significantly improved FEV_1 as would be expected in AAT-replete COPD. Also, one study[26] found that in contrast to AAT-replete COPD patients undergoing transplant, AATD-COPD individuals receiving double lung transplantation experienced a more rapid FEV_1 decline than single lung transplant recipients. Multiple studies have shown that survivorship following lung transplantation is similar in AAT-replete and AATD-COPD (Banga et al[26] and International Society for Heart and Lung Transplantation data[27]).

Similarly, at the time of this writing, there is no specific therapy for AATD-associated liver disease. Management of liver disease is not altered by the diagnosis of AATD.

There are data to suggest that any benefit from lung volume reduction surgery is shorter-lived in individuals with AATD-COPD than those with AAT-replete COPD. In addition, there is often a basal predominance of the emphysema in AATD lung disease or generalized emphysema with a low diffusing capacity, making lung volume reduction surgery more technically difficult

and with a higher mortality (National Emphysema Treatment Trial study[28]).

Recommendation 3a: We recommend every effort be made to prevent exposure to tobacco smoke and facilitate cessation in those who are smoking (strong recommendation, high quality evidence).
Rationale: High value is placed on observational data from well-designed registries and biochemical understanding of AATD. Data suggest that identification of AATD at birth is associated with a lower rate of smoking initiation and that the diagnosis of AATD in adults is associated with a greater willingness to attempt quitting and greater success in quitting.
Key references:[29,30]

Recommendation 3b: We do not recommend lung volume reduction surgery for individuals with AATD-COPD (weak recommendation, low quality evidence).
Rationale: High value is placed on the multicenter treatment experience. Low value is placed on case reports of significant long-lasting improvement in some individuals. AATD-COPD characteristically has lower lobe-predominant, panacinar/panlobular emphysema that has been shown to respond less well to surgical lung volume reduction than in individuals with upper lobe-predominant heterogeneous COPD. While some individuals with AATD-COPD have upper lobe-predominant heterogeneous disease, no current data suggest that these individuals respond comparably to those with AAT-replete COPD. Newer therapies of bronchoscopic lung volume reduction are being evaluated in AATD.
Key references:[31]

Should AATD individuals with COPD be treated with intravenous augmentation therapy?

Background: Intravenous administration of purified preparations of pooled donor-derived human AAT has been shown to augment levels of AAT and the AAT-related anti-elastase capacity of serum and lung epithelial lining fluid. The current U.S. Food and Drug Administration (FDA)-approved intravenous augmentation therapy dose for chronic administration is 60mg/kg body weight, administered weekly.

Recommendation 3c: Intravenous augmentation therapy is recommended for individuals with AATD and an FEV_1 in the range of 30%-65% predicted (strong recommendation, high quality evidence).
Rationale: This recommendation places a high value on treating individuals with moderate obstruction, a group with well-documented benefit. It also places high value on the finding that intravenous augmentation therapy is associated with lower levels of elastin degradation products in individuals with AATD and on lower rates of loss of CT lung density in individuals with AATD-COPD receiving augmentation therapy compared with those receiving placebo. It weighs the cost of therapy against these expected benefits.
Key references:[5,32]

Recommendation 3d: For individuals with FEV_1 less than 30% predicted, intravenous augmentation therapy is recommended (weak recommendation, low quality of evidence).
Rationale: High value is placed on the potential to prolong survival in this group, the finding that intravenous augmentation therapy is associated with lower levels of elastin degradation products in individuals with AATD, and lower rates of loss of CT lung density in individuals with AATD-COPD receiving augmentation therapy. Low value is placed on the cost of this therapy.

Recommendation 3e: For those with FEV_1 greater than 65%, we recommend discussion with each individual regarding the potential benefits of reducing lung function decline with consideration of the cost of therapy and lack of evidence for such benefit (strong recommendation, low quality of evidence).
Rationale: This recommendation to discuss the pros and cons of augmentation therapy places a high value on treating high-risk individuals early in the course of their disease to avoid an accelerated rate of lung function decline and its consequences. It also places high value on the finding that intravenous augmentation therapy is associated with lower levels of elastin degradation products in individuals with AATD and on lower rates of loss of CT lung density in individuals with AAT-replete COPD receiving augmentation therapy. Factors such as age, a rapid decline in FEV_1, decreasing diffusing capacity, or progression of emphysema on imaging studies can be important to inform a decision regarding treatment.

Recommendation 3f: Weekly doses of intravenous augmentation therapy higher than the current

FDA-approved dose are not recommended (weak recommendation, low quality of evidence).
Rationale: High value is placed on the few studies evaluating clinical and biochemical outcomes with different intravenous augmentation therapy regimens. Dosing schedules other than what is currently approved (e.g., 120mg/kg every 2 weeks) appear to provide less complete biochemical protection against lung destruction in some individuals. Higher doses (i.e., 120mg/kg/week) appear to be safe and increase AAT levels towards more physiologic values but clinical efficacy has not been proven. Some value is placed on the cost of intravenous augmentation therapy.
Note: Short-term lifestyle considerations may prompt alternate dosing regimens, such as allowing an individual to enjoy a two-week vacation at a distant location by administering a *double dose* just before departure. There have been no dose-ranging studies completed to establish the appropriate dose based on clinical endpoints.
Key references:[33]

Recommendation 3g: Intravenous augmentation therapy is not recommended for affected individuals with lung disease who continue to smoke (weak recommendation, low quality evidence).
Minority opinion: There is no current evidence that augmentation does not benefit individuals with AATD-COPD who continue to smoke.
Rationale: High value is placed on the proven benefits of tobacco cessation in the natural history of COPD (decreased FEV_1 decline and decreased mortality), the high cost of therapy, and relative lower benefits of intravenous augmentation therapy in active smokers, as cigarette smoke causes oxidative inactivation of the elastase inhibiting capacity of AAT *in vitro* and *in vivo*.

Recommendation 3h: Monitoring of trough AAT levels to document adequate AAT augmentation dosing is not recommended (strong recommendation, moderate quality evidence).
Rationale: High value is placed on the lack of studies addressing doses of intravenous augmentation therapy other than 60mg/kg weekly for the treatment of AATD-COPD. Low value is placed on the low cost of AAT level measurements.
Remarks: Potential costs and benefits should be discussed with the individual patient; actions will be driven by individual and physician judgment as well as by cost considerations. Intravenous augmentation therapy is an expensive intervention that is associated with significant inconvenience from regular IV infusions. Augmentation slows the progression of anatomic emphysema as assessed by CT densitometry in clinical trials. There is currently no high-quality evidence that intravenous augmentation therapy lessens the incidence or severity of exacerbations in AATD-related lung disease. One large observational cohort study in which the majority of individuals had FEV_1 <30% predicted found that intravenous augmentation therapy improved survival in individuals with AATD with airflow obstruction.
Key references:[34,35]

Should AATD individuals without emphysema be treated with intravenous augmentation therapy?

Recommendation 3i: We do not recommend intravenous augmentation therapy in individuals with bronchiectasis without airflow obstruction (weak recommendation, low quality evidence).
Rationale: High value is placed on the cost and lack of specific evidence of benefit in this setting. Although intravenous augmentation therapy has been shown to decrease inflammatory markers in sputum and lung epithelial lining fluid and to enhance anti-elastase capacity, low value is placed on the concept that decreasing the neutrophil elastase burden that characterizes the secretions of bronchiectatic airways will decrease symptoms and disease progression.
Recommendation 3j: Intravenous augmentation therapy is not recommended for the treatment of liver disease due to AATD (strong recommendation, low quality of evidence).
Rationale: High value is placed on our current understanding of mechanisms underlying liver disease related to AATD. While the AATD-related lung disease is caused by a deficiency of circulating AAT, the liver disease associated with AATD is thought to be due to an over-abundance of polymerized AAT protein trapped within hepatocytes. Therefore, augmenting the circulating levels of AAT would seem unlikely to be of benefit. Clinical experience treating individuals with both lung and liver disease with intravenous augmentation therapy suggests that liver disease neither improves nor worsens with this therapy.

Recommendation 3k: We recommend intravenous

augmentation therapy for the treatment of necrotizing panniculitis in individuals with AATD (strong recommendation, low quality of evidence).

Rationale: High value is placed on improving this often serious dermatologic condition. Several case reports have documented the relative effectiveness of intravenous augmentation therapy in preventing or controlling the skin lesions associated with this condition. Higher doses of intravenous augmentation therapy than those approved for the treatment of lung disease due to AATD may be needed. Low value is placed on the high cost of therapy.

Key references:[9,36]

Recommendation 3l: Intravenous augmentation therapy is not recommended for individuals who have undergone liver transplantation (strong recommendation, high level of evidence).

Rationale: High value is placed on the fact that a successful liver transplantation for severe AATD liver disease should lead to normal circulating levels of a normal AAT protein. The successfully transplanted normal donor liver will synthesize and release normal quantities of AAT to the blood.

Recommendation 3m: Intravenous augmentation therapy is not recommended for individuals with the MZ genotype who have COPD (strong recommendation, low quality evidence).

Rationale: High value is placed on the cost of therapy and the lack of evidence to support such therapy in this group. There are no data that intravenous augmentation therapy improves outcomes in those with the MZ or other heterozygote genotypes that include a normal M gene. There is neither a biologic rationale nor evidence to support treating these individuals. The primary treatment of individuals with the MZ genotype and COPD is smoking cessation and other evidence-based therapies for COPD.

Key references:[37,38]

Conclusions and Future Directions

The formal evidence that supports the recommendations in these guidelines includes observational studies; case-control studies; small, randomized controlled trials; and a single, well-powered randomized controlled trial, which was published during the final preparation of these guidelines. This last trial demonstrated that augmentation therapy provided a statistically significant reduction in emphysema progression evaluated by CT densitometry performed at total lung capacity (TLC) but not at TLC plus functional residual capacity. Even so, there remain gaps in available studies to address important management issues. Therefore, the clinical observations and opinions of experts in the diagnosis and management of AATD played a prominent role in crafting this document and the recommendations that are offered. Acknowledging these limitations, the writing committee and the Medical and Scientific Advisory Committee of the Alpha-1 Foundation believe that this document will provide meaningful guidance for clinicians caring for individuals with this widely under-diagnosed condition.

Until universal neonatal screening for AATD is adopted, the true prevalence of this condition and its natural history will not be fully understood. As additional well-powered studies of therapies for AATD are published and perhaps newer, more convenient therapies are developed and tested using accepted clinical endpoints, many of the expert-based recommendations in this document may be replaced by fully evidence-based documentation. The authors look forward to that time.

Alpha-1 antitrypsin deficiency is the major, known genetic risk factor for chronic obstructive lung disease and a prominent genetic risk factor for liver disease. It is the committee's hope that providing clear guidance will improve detection of individuals with AATD and promote evidence-based treatment of those who are diagnosed.

Limitations

In this attempt to offer clinician-centric recommendations regarding the care of individuals with AATD, several important limitations are noteworthy. First, because AATD is an uncommon disease, formidable challenges exist in assembling large cohorts for adequately powered randomized clinical trials upon which to base the most rigorous clinical conclusions. As such, some uncertainty persists regarding key clinical questions such as the cost-effectiveness of intravenous augmentation therapy and the optimal strategies for targeted detection of affected individuals. Clinical recommendations require synthesizing the literature and studies from disparate settings and sources. Second, because progress in uncommon diseases like AATD requires close collaborations between clinical leaders, academic

leaders, the patient community, government, and pharma, engagement of the authors with patient organizations like the Alpha-1 Foundation would disqualify them from participating in writing clinical practice guidelines under current medical society criteria. We have addressed this perceived conflict through disclosure and we highlight the paradox that the very engagement that permits the expertise needed to write this document and to receive and understand the questions that clinicians pose is a curious disqualifier.

Drugs for intravenous augmentation therapy are marketed in the United States and Europe by a number of different manufacturers. The cost of this therapy is very high. Intravenous augmentation therapy was approved in the United States based on its *biochemical efficacy*--its ability to increase serum and lung levels of AAT above putative *protective threshold* values. Numerous observational studies have provided evidence that individuals receiving this therapy for their AATD-related lung disease show a decreased rate of lung function decline and one large study showed an improvement in survival compared to AATD-affected individuals who never received intravenous augmentation therapy. Several small, randomized pilot trials provided suggestive trends toward effectiveness and the community of clinicians caring for lung-affected individuals with AATD, as well as affected individuals themselves, rely on this therapy to supplement the usual treatment of COPD. In fact, the degree of acceptance of intravenous augmentation therapy by these communities within the United States and other countries has made it virtually impossible to perform placebo-controlled trials to formally evaluate effectiveness. Even so, relying heavily on enrollment in countries where there is limited or no availability of augmentation therapies, a single, adequately powered, randomized, placebo-controlled, blinded efficacy study has now been published.[5]

Because AATD is an uncommon genetic condition, it becomes difficult to provide high-level literature support for the various treatments that are commonly prescribed for individuals with AATD. Even the usual medications used to treat COPD and liver disease in the general population are being used "off label" in the AATD community, since virtually all studies leading to the approval of these therapies excluded individuals with AATD. Most bronchoscopic lung volume reduction therapies being investigated in the United States (and available in Europe) have excluded individuals with AATD as well. A final qualification is that the cost-effectiveness of intravenous augmentation therapy has been difficult to address since the overall benefit is still under study.[39]

Declaration of Interest

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