Standards for the Diagnosis and Management of Individuals with Alpha-1 Antitrypsin Deficiency: Executive Summary

Prepared by the Alpha-1 Antitrypsin Deficiency Task Force*

Introduction

Since the first American Thoracic Society (ATS) statement regarding the diagnosis and management of severe alpha-1 antitrypsin (AAT) deficiency in 1989[1] and the initial Canadian Thoracic Society standards statement in 1992[2] (which was updated in 2001),[3] significant advances in understanding the cell and molecular biology of AAT and the diagnosis, natural history, and treatment of individuals with AAT deficiency have occurred. These new developments, including completion of several large, longitudinal studies in both Europe and North America and a small randomized controlled trial of augmentation therapy, have provided important new insights that have impacted the clinical management of individuals with severe deficiency of AAT.

In the context of these new developments, a need was felt to re-examine recommendations for optimal management of AAT deficiency, to synthesize current knowledge of diagnosis and management for practicing clinicians, and to identify key remaining questions in need of further investigation. With these purposes in mind, a Task Force to develop a new standards document regarding the diagnosis and management of individuals with severe AAT deficiency was formed in 1998 under the auspices of the ATS and the European Respiratory Society, with additional sponsorship and support by the Alpha-1 Foundation, the American College of Chest Physicians, and the American Association for Respiratory Care. Under a contractual arrangement, the Veterans Administration Technology Assessment Program, Office of Patient Care Services, Veterans Health Administration provided education regarding preparing an evidence-based document and support in conducting literature searches.

In keeping with current standards for developing evidence-based recommendations for optimal care, the current Task Force has undertaken a systematic review of current literature regarding AAT deficiency. Every effort was made to identify the scientific evidence for positions taken and to identify where there was little or no evidence. In the absence of ratable evidence, consensus among members of the Task Force determined the recommendation.

This summary document briefly describes the organization and preparation of the Task Force's report and provides an executive summary of key clinical recommendations. The 3 following sections are the full systematic reviews [not reprinted here in RESPIRATORY CARE] prepared by the 3 individual writing groups that composed the AAT Deficiency Task Force.

Goals, Organization of the Project, and Timeline

The goal of the AAT Deficiency Task Force was to prepare and present for the medical and interested lay communities the reasoned, current views of a large international group of experts regarding the current diagnosis and management of individuals with AAT deficiency, using a systematic review and the evidence-based approach. The Task Force undertook to evaluate the full clinical and management dimensions of this multisystem illness, including the lung, liver, and other organ manifestations. Also, issues relating to the ethical, legal, social, psycho-

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logical, and economic implications of genetic testing for AAT deficiency were addressed.

A Planning Group was assembled in the Fall of 1997 when sponsorship and funding by the major sponsors—the ATS, the European Respiratory Society, and the Alpha-1 Foundation—was finalized. Additional support from the Alpha-1 Foundation, the American College of Chest Physicians, and the American Association for Respiratory Care allowed the Planning Committee to assemble the full membership of the Task Force and to proceed.

As presented in Figure 1, the AAT Deficiency Task Force consisted of an Executive Committee, 3 individual Writing Groups composed of international experts, and a Steering Committee (composed of the Executive Committee and the Chairs of each of the 3 Writing Groups). Preparation of the systematic review was aided by members of the Health Care Technology Assessment Program of the Department of Veterans Affairs, who provided ongoing input and guidance to the project regarding literature searches and evidence-based medicine methods. Administrative assistance was provided by the ATS.

The membership of the Task Force was fully constituted by September 1998, at which point Writing Groups began to review literature and to draft documents for subsequent review by the Steering Committee. The Steering Committee conducted a number of conference calls and 5 face-to-face meetings between Fall 1998 and Fall 2001 to review the evolving documents. Individual Writing Group documents were finalized by the Fall of 2001 for final editing by the Executive Committee and subsequent submission to the sponsoring organizations. Reviews were received in June 2002 and the revised document was re-submitted in Fall 2002 for final approval. Approval was granted by the ATS in December 2002, when an additional review of salient literature led to a final update of the document.

While the Executive Committee has attempted to minimize overlap between the 3 documents, the Task Force's stated goal of preparing 3 individual documents, each complete and with its own emphasis, references, and supportive tables and figures, will inevitably lead to some overlap.

Finally, in the context that research is ongoing and that current understanding of AAT deficiency and optimal management is evolving, the Task Force recognizes the need for periodic review and updating of management recommendations.

Summary of Main Recommendations Regarding Diagnosis and Management by the Alpha-1 Antitrypsin Deficiency Task Force

Clinical Recognition of Alpha-1 Antitrypsin Deficiency

Available evidence suggests that PI*ZZ (Pi phenotype ZZ) AAT deficiency is frequently under-recognized or misdiagnosed by clinicians. The following features should prompt suspicion by physicians that their patient may be more likely to have AAT deficiency:

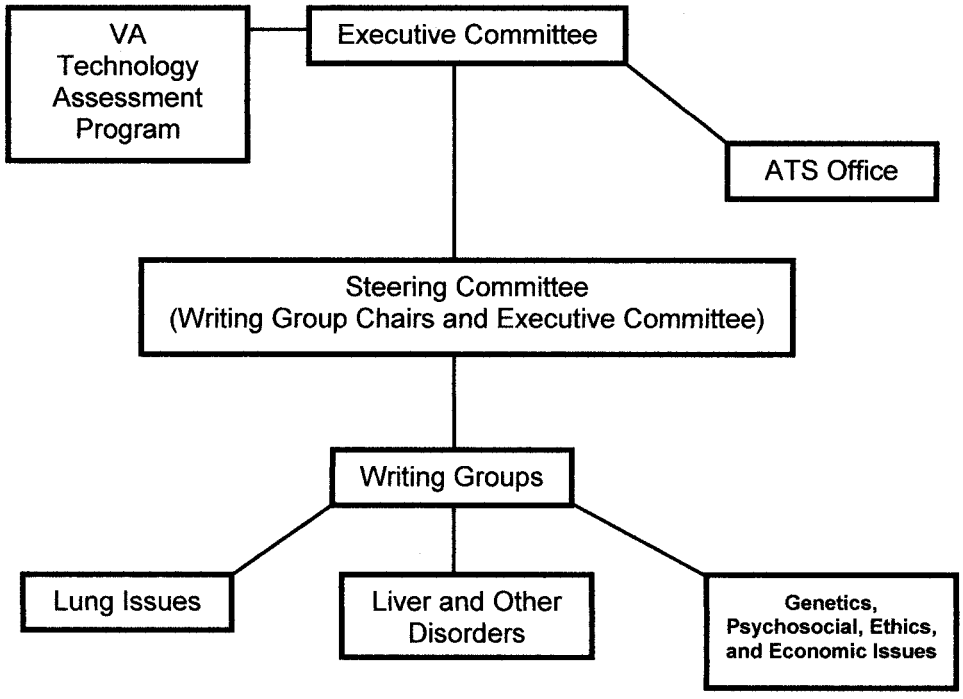

Fig. 1. Structure of the Alpha-1 Antitrypsin Deficiency Task Force.

Table 1. Classification of Recommendations for Genetic Testing*†

A. Genetic testing is recommended
B. Genetic testing should be discussed and could reasonably be accepted or declined
C. Genetic testing is not recommended (ie, testing should not be encouraged)
D. It is recommended that genetic testing not be performed (ie, testing should be discouraged)

*The recommendation type was determined by the Task Force's subjective weighing of all the issues that either supported or opposed genetic testing. The weight attributed to each issue is dependent upon the level of the evidence supporting each issue. Accordingly, the recommendation for genetic testing is informed by both the evidence of each issue and consensus of experts on how strongly each issue supports or opposes testing.
†This classification of recommendations should not be confused with schemes for grading the quality of evidence which, as used in other documents (although not here) may also use letter designations.

- Early onset emphysema (age ≤ 45 years)
- Emphysema in the absence of a recognized risk factor (smoking, occupational dust exposure, etc)
- Emphysema with prominent basilar hyperlucency
- Otherwise unexplained liver disease
- Necrotizing panniculitis
- Anti-proteinase 3 positive vasculitis (C-ANCA [anti-neutrophil cytoplasmic antibody] positive vasculitis)
- Family history of any of emphysema, bronchiectasis, liver disease, or panniculitis
- Bronchiectasis without evident etiology (see below)

Notably, in recognizing the discordance of studies concerning whether bronchiectasis is specifically associated with AAT deficiency, the Task Force recommends discussing AAT testing with individuals who have bronchiectasis without evident etiology, with the understanding that testing could reasonably be accepted or declined.

Genetic Testing for AAT Deficiency

Recognizing that identifying individuals as having AAT deficiency can expose them to risks (eg, of psychologic burden or genetic discrimination), the Task Force recommends that clinicians weigh these risks and discuss them with those for whom testing (by serum level or phenotype) is being considered. In evaluating the strength of the Task Force's recommendation to test various individuals for AAT deficiency, the Task Force recognized 4 clinical purposes for which testing for AAT deficiency might be undertaken: **1. Diagnostic testing** (ie, to identify symptomatic or otherwise affected individuals), **2. Predispositional testing** (ie, to identify asymptomatic individuals who may be at high risk of having AAT deficiency), **3. Assessment of carrier status in relation to reproduction**, and **4. Population screening**.

Recommendations for genetic testing in specific situations were graded from **type A to type D** (see Table 1). Each recommendation type was based on the level of supportive evidence for each issue regarding testing (eg, the penetrance of AAT deficiency, population prevalence of AAT deficiency, clinical impact, accuracy of genetic testing, efficacy of treatment, psychological and social effects, and economic costs) and the weighing by the Task Force of the issues for or against testing. In the context of this grading scheme, recommendations for the 4 types of genetic testing are as follows:

1. Diagnostic Testing

A **type A recommendation** for diagnostic testing was made in the following settings:

- Symptomatic adults with emphysema, chronic obstructive pulmonary disease (COPD), or asthma with airflow obstruction that is incompletely reversible after aggressive treatment with bronchodilators. (Notably, in populations where the prevalence of AAT deficiency is known to be much lower than the general North American and Northern European prevalence, a Type B recommendation for diagnostic testing in this setting is offered.)
- Individuals with unexplained liver disease, including neonates, children, and adults, particularly the elderly
- Asymptomatic individuals with persistent obstruction on pulmonary function tests with identifiable risk factors (eg, cigarette smoking, occupational exposure, etc)
- Adults with necrotizing panniculitis

A **type B recommendation** for diagnostic testing was made in the following settings:

- Adults with bronchiectasis without evident etiology
- Adolescents with persistent air flow obstruction
- Asymptomatic individuals with persistent airflow obstruction and no risk factors
- Adults with C-ANCA-positive (anti-proteinase 3-positive) vasculitis

A **type C recommendation** for diagnostic testing was made for:

- Adults with asthma in whom airflow obstruction is completely reversible

2. Pre-dispositional Testing

A **type A recommendation** was made for:

- Siblings of an individual with AAT deficiency

A **type B recommendation** was made for:

- Individuals with a family history of COPD or liver disease not known to be attributed to AAT deficiency

• Distant relatives of an individual who is homozygous for AAT deficiency
• Offspring or parents of an individual with homozygous AAT deficiency
• Siblings, offspring, parents, or distant relatives of an individual who is heterozygous for AAT deficiency

A **type D recommendation** was made for pre-dispositional fetal testing.

3. Assessment of Carrier Status in Relation to Reproduction

A **type B recommendation** was made for:
• Individuals at high risk of having AAT deficiency-related diseases
• Individuals who are not at risk themselves of having AAT deficiency but who are partners of individuals who are homozygous or heterozygous for AAT deficiency

4. Population Screening

A **type D recommendation** was made for population screening of either neonates, adolescents, or adults (ie, population screening is not recommended currently). However, a possible exception (**type B recommendation**) regarding population screening may apply in countries satisfying 3 conditions: (1) the prevalence of AAT deficiency is high ($\geq \sim$1/1,500), (2) smoking is prevalent, and (3) adequate counseling services are available.

A **type C recommendation** was made for population screening of smokers with normal spirometry.

Liver Disease

Regarding the occurrence of liver disease in individuals with AAT deficiency, the Task Force offers the following findings and recommendations:

• Liver disease is a complication of the intrahepatocytic accumulation of unsecreted, polymerized AAT that forms characteristic periodic acid-Schiff-positive inclusions in individuals with the Z allele and several others (eg, S_{iiyama}, M_{malton}). Other deficiency alleles (eg, null variants, S) do not predispose to liver disease.

• Serum phenotyping by isoelectric focusing performed by a reliable laboratory is the accepted "gold standard" for diagnosing AAT deficiency. Liver biopsy is not indicated for purposes of establishing the diagnosis of AAT deficiency; the role of liver biopsy is confined to staging of liver disease in individuals with clinically overt liver disease. The incidental finding of periodic acid-Schiff-positive globules in a liver biopsy should prompt suspicion of the Z allele or other rare deficiency alleles associated with intra-hepatocyte inclusions.

• Most PI*ZZ AAT-deficient individuals are clinically healthy throughout childhood but have liver enzyme abnormalities in early life. The PI*ZZ phenotype is a common cause of neonatal cholestasis. Despite spontaneous resolution in a majority of such individuals, AAT deficiency is a frequent indication for liver transplantation in childhood. Cirrhosis in PI*ZZ AAT-deficient individuals may become clinically apparent at any age, with the peak incidence occurring in elderly never-smokers who have survived without developing severe emphysema.

• Aside from low plasma AAT levels, laboratory and other clinical features of affected individuals are indistinguishable from those with cirrhosis of any etiology.

• Male gender appears to confer an increased risk for developing cirrhosis in PI*ZZ AAT-deficient individuals, but firm evidence supporting other risk factors such as viral hepatitis or alcohol use does not exist.

• In heterozygotes carrying the Z allele, there is a much smaller risk for cirrhosis, for which toxic liver injury from alcohol and viruses (especially hepatitis C) may be risk factors.

• In heterozygotes with active liver or vasculitic disease, the plasma AAT level is frequently normal; performing isoelectric focusing is required for diagnosing such individuals who may be PI*Z heterozygotes.

• Other than liver transplantation for individuals with advanced AAT deficiency-related liver disease, specific therapy for liver disease is not currently available; notably, intravenous augmentation therapy with alpha-1 antiprotease does not confer benefits for liver disease.

• In the absence of firm evidence regarding optimal follow-up and preventive strategies, the Task Force suggests that clinical management of individuals with AAT deficiency-related liver disease should include: hepatitis A and B vaccinations, regular assessment by physical examination, liver function tests, and ultrasound examination. In older individuals (eg, age $\geq$ 50 years) with decompensated cirrhosis due to AAT deficiency and increased risk for hepatoma, periodic computed tomography imaging of the liver is recommended because of the insensitivity of other tests (eg, alpha fetoprotein measurement).

• Regular assessment of simple liver function tests is recommended in elderly individuals with AAT deficiency who lack liver symptoms.

Other Conditions

• Besides the conditions of emphysema and chronic liver disease, available evidence suggests a relationship between AAT deficiency, necrotizing panniculitis, and C-ANCA-positive vasculitis (eg, Wegener's granulomatosis); available evidence does not confirm suggested associations with other vascular conditions (eg, intracranial aneurysms, abdominal aortic aneurysms), pancreatitis, or celiac disease.

Efficacy of Augmentation Therapy

• Recognizing that supportive evidence of efficacy comes from concordant observational studies but not from a randomized controlled clinical trial, the Task Force recommends intravenous augmentation therapy for individuals with established airflow obstruction from AAT deficiency. Evidence that augmentation therapy confers benefit (eg, slowed rate of forced expiratory volume in the first second [FEV_1] decline and decreased mortality) is stronger for individuals with moderate airflow obstruction (eg, FEV_1 35–60% of predicted) than for those with severe airflow obstruction. Augmentation therapy is not currently recommended for individuals without emphysema, and benefits in individuals with severe (eg, $FEV_1 \leq 35\%$ of predicted) or mild (eg, $FEV_1 \geq 50-60\%$ of predicted) airflow obstruction are less clear.

• Insufficient evidence regarding the benefits of augmentation therapy in patients who have undergone lung transplantation for AAT deficiency precludes a firm recommendation. However, it has been observed that inflammation results in free elastase activity in epithelial lining fluid in individuals who have undergone lung transplantation (eg, during acute rejection and infection). In the context of available data regarding this issue, this observation leads the Task Force to favor augmentation therapy for lung transplant recipients during such episodes.

General Management of Obstructive Lung Disease

Optimal management of stable individuals with AAT deficiency should include many of the interventions recommended for AAT-replete individuals with emphysema, including:

• Inhaled bronchodilators

• Preventive vaccinations against influenza and pneumococcus

• Supplemental oxygen when indicated by conventional criteria, including during commercial air travel

• Pulmonary rehabilitation for individuals with functional impairment

• Consideration of lung transplantation for selected individuals with severe functional impairment and airflow obstruction

• During acute exacerbations of COPD, management should again include usual therapies for AAT-replete individuals (eg, brief courses of systemic corticosteroids, ventilatory support when indicated). However, in the context that acute infection poses the threat of increased elastolytic burden in individuals with AAT deficiency, the Task Force favors early antibiotic therapy for all purulent exacerbations.

The scant evidence regarding the efficacy of lung-volume reduction surgery (with possible resection of lower lobes) in individuals with AAT deficiency suggests that improvement in dyspnea, lung function, and functional status is possible. However, well-studied, robust selection criteria for ideal candidates remain elusive and the duration of lung-volume reduction surgery benefit appears shorter than in individuals with AAT-replete COPD.

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