

# American Thoracic Society

## GUIDELINES FOR THE APPROACH TO THE PATIENT WITH SEVERE HEREDITARY ALPHA-1-ANTITRYPSIN DEFICIENCY

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### Introduction

In the 25 yr since severe hereditary alpha-1-antitrypsin (AAT) deficiency was first recognized (1), the genetics of inheritance (2) and the clinical manifestations (3) have been described, the responsible gene has been cloned, the molecular bases of the major deficiency states have been defined (4, 5), techniques have been developed for accurate prenatal diagnosis, and augmentation therapy has become available (6, 7). These achievements represent successes by many investigators from different disciplines and from different countries, with important contributions from the National Heart, Lung, and Blood Institute and from private industry.

The purpose of this statement is to provide guidelines for the approach to the individual with severe hereditary AAT deficiency. These guidelines have been developed because the efficacy of the only specific treatment available, augmentation therapy with human AAT, is still unproved in terms of retarding the progression of emphysema, although it has been clearly demonstrated that the treatment augments the existing low levels of AAT in the blood and lungs. Decisions about who should be treated, therefore, must be made with great care. Although the treatment that is presently available does not cure the hereditary deficiency, there is good reason to hope that boosting the levels of AAT in the blood and in the lungs of severely deficient individuals in this manner will retard the ongoing destruction of lung parenchyma. Other approaches to treatment such as the use of recombinant AAT and synthetic antielastases are being developed and may be available in the future.

### Background

AAT deficiency is an autosomal hereditary disorder in which there are low serum and lung levels of AAT, a high risk for the development of panacinar emphysema in the third to fifth decades (8-10), and an increased risk for the development of liver disease, primarily in childhood (11, 12).

AAT, which is synthesized in and secreted by the liver hepatocytes and to a lesser extent by the mononuclear phagocytes, is a serine protease inhibitor that has the primary function of inhibiting neutrophil elastase. All available evidence leads to the concept that emphysema results from an imbalance between

the neutrophil elastase in the lung, which has the capability of destroying elastin and other connective tissue components, and the antielastases that are responsible for protecting the lung from the elastase (13, 14). This concept is called the elastase-antielastase balance hypothesis of emphysema. Two lines of evidence support the validity of this hypothesis. First, human studies have amply demonstrated that individuals with very low serum and lung levels of AAT are at greatly increased risk of developing severe panacinar emphysema, even if they do not smoke. Second, animal studies, carried out in a number of species of small animals, have demonstrated that neutrophil elastase instilled into the respiratory tract is capable of causing extensive destruction of the lung parenchyma similar to human emphysema.

At least 75 alleles of the AAT gene have been identified and categorized into an arrangement designated as the protease inhibitor (Pi) system (4, 5, 9). These alleles can be categorized into four groups on the basis of the AAT levels that occur in the serum: (1) "normal," associated with normal serum levels of AAT with normal function; (2) "deficient," associated with serum AAT levels < 35% of average normal level; (3) "null," in which there is no detectable AAT protein in serum; (4) "dysfunctional," in which the AAT protein is present but does not function normally. The normal and deficient AAT alleles are assigned a letter code (A to Z) on the basis of the electrophoretic mobility of the molecule. The family of normal AAT alleles are referred to as M, e.g., M1(Val<sup>213</sup>), M1(Ala<sup>213</sup>), M2, and M3, and are found in approximately 90% of the U.S. population and other populations of European descent. The most common deficiency allele associated with emphysema is the Z allele, representing 1 to 2% of the Caucasian population in the United States. The AAT phenotype, therefore, is made up of the two parental alleles and is referred to as the Pi phenotype. AAT variants are inherited as codominant alleles. The most common phenotype is PiMM (e.g., PiM2M3), and the most common deficient phenotype associated with a high risk for disease is PiZZ.

The measurement of serum levels of AAT is complicated by the fact that many of the commercial standards available overestimate the AAT levels by 35 to 40%. By convention, the serum AAT levels have been expressed in units of mg/dl, and levels of 80 mg/dl have been considered to be the "threshold" serum level above which there is sufficient AAT to protect the lung and below which the individual has an increased risk of emphysema com-

pared with the general population. Recognizing that this level is higher than the true level, investigators in the field now use a true laboratory standard that accurately quantifies the amount of AAT present. To avoid confusion with the historic values that are overestimates, the true values (using pure standards) are expressed in micromolar units. With this true standard, the "threshold" is 11  $\mu$ M, the range for individuals inheriting any combination of normal M alleles is 20 to 48  $\mu$ M, PiZZ homozygotes have levels of 2.5 to 7  $\mu$ M, and PiSS homozygotes have levels of 13 to 33  $\mu$ M. In contrast, individuals who are heterozygous have reduced concentrations with the extent of the reduction depending on the phenotype: PiSZ, 8 to 19  $\mu$ M and PiMZ, 12 to 35  $\mu$ M. Individuals who are Pi null null have, by definition, serum levels of zero. The deficient null alleles are very rare, together representing less than 1% of all AAT alleles. Individuals with the Pi null null phenotypes are at a very high risk of developing emphysema early in life since they have no AAT to protect their lungs.

There is reasonable evidence from epidemiologic studies that there is a threshold above which the lung appears to be able to protect itself adequately. This threshold lies at 11  $\mu$ M, about 35% of the average normal level. It follows from this that individuals who are at greatest risk are PiZZ homozygotes, the null homozygotes, and, occasionally, PiSZ heterozygotes. PiSS homozygotes and other heterozygotes, such as PiMZ and PiMS, do not appear to be at increased risk.

Estimates of the prevalence of the PiZZ phenotype have varied considerably, depending on the population used to derive the estimate, the ethnic mix of the population, and the method of phenotyping. In North America, estimates range from approximately 1:3,500 to 1:1,670 (15). This makes severe hereditary AAT deficiency one of the most common serious genetic conditions.

Much has been learned about the natural history of AAT deficiency since the first patients with this condition were reported by Laurell and Eriksson in 1963 (1). The information is still, however, incomplete. For example, it is not known what proportion of individuals with the PiZZ phenotype do not develop clinically significant emphysema. The information that is available indicates that individuals with a PiZZ phenotype who have smoked cigarettes are at greatly increased risk, become symptomatic earlier, and have a life expectancy that is approximately 10 yr less than nonsmokers with this condition (8). From one large Swedish study, the average age of onset of dyspnea among nonsmokers was 52

yr, and among smokers it was 40 yr, with men and women having very similar ages of onset. In PiZZ individuals who have developed clinically significant airflow obstruction, the rate of decline of FEV<sub>1</sub> has been estimated to be in excess of 100 ml/yr (8).

The liver disease associated with AAT deficiency is much less common than emphysema and probably occurs in < 10% of individuals with the PiZZ phenotype (11, 12), although accurate estimates of this are lacking. Its most common manifestation is hepatitis with jaundice in the neonate. This is usually self-limiting, but in 1 to 3% of AAT-deficient individuals, it progresses to liver cirrhosis and eventually to hepatic failure (11). The risk for significant liver disease appears to be linked to the Z homozygous state with few exceptions. The pathogenesis of the liver disease is not understood, although it is known that intracellular aggregation of the AAT occurs in the hepatocytes of Z homozygotes, likely contributing to the hepatocyte injury.

### Approach to the Individual with Suspected Severe Hereditary AAT Deficiency

#### Clinical Manifestations of AAT Deficiency

A typical smoker with AAT deficiency develops pulmonary symptoms between 30 and 45 yr of age; the disease is usually fatal by 60 yr of age. The commonest method of presentation is dyspnea, especially with exercise. In neonates, jaundice and hepatitis may be presenting signs.

#### How to Make the Diagnosis

In an individual suspected of having AAT deficiency, the first step is to measure serum AAT concentrations. This test is readily available in most hospital clinical pathology laboratories or through a referral laboratory. Phenotyping should be saved for individuals who have a low or borderline AAT concentration. Phenotyping requires skill and experience, so care should be taken to select a laboratory that can provide these features.

The historic problem of standardization of serum AAT levels is discussed above. The association of serum AAT levels with the risk for emphysema compared with that in the general population is summarized in table 1.

In addition to obtaining serum AAT levels and phenotyping, it is recommended that the baseline evaluation should include a postero-anterior and left lateral chest roentgenogram, pulmonary function tests (spirometry or flow-volume curves before and after an inhaled bronchodilator, lung volumes, diffusing capacity), and arterial blood gas and liver function tests (SGOT, total bilirubin, SGPT, alkaline phosphatase).

#### Treatment

The general principles of management of the individual with severe hereditary AAT deficiency are very similar to those for individuals with cigarette smoking-related chronic airflow

TABLE 1  
THRESHOLD PROTECTIVE LEVEL CONCEPT BASED ON EPIDEMIOLOGIC ASSESSMENT OF AAT LEVELS AND THE RISK FOR THE DEVELOPMENT OF EMPHYSEMA

Phenotype	Serum Levels		Emphysema Risk Compared with That in the General Population
	True Levels* (μM)	Commonly Quoted Levels† (mg/dl)	
MM‡	20-48	150-350	No increase
MZ§	12-35	90-210	No increase
SS	15-33	100-140	No increase
SZ	8-19¶	75-120¶	Mild increased risk
ZZ	2.5-7	20-45	High risk
Null-null	0	0	Extremely high risk

\* True levels based on the laboratory standard used by the registry.

† Based on a commonly used commercial standard; these levels are of historic interest only and are 35 to 40% overestimates of the true levels.

‡ Includes all combinations of normal M-family alleles, including M1 (Val<sup>121</sup>), M1 (Ala<sup>113</sup>), M2, and M3 alleles.

§ Includes all combinations of normal M-family alleles with the Z allele.

¶ Includes all combinations of null alleles.

|| The threshold protective level of 11 μM (80 mg/dl with a commonly used commercial standard) is based on the knowledge that it is very unusual for SZ heterozygotes to develop emphysema.

obstruction. These include: (1) avoidance of respiratory irritants, especially active cigarette smoking, and (2) maximal supportive therapy, including bronchodilators, cardiovascular conditioning, and O<sub>2</sub>, if clinically indicated. Specific therapy for this condition, discussed in more detail below, involves augmentation with human plasma-derived AAT (Prolastin).

#### Respiratory Irritants

As it seems likely that all respiratory irritants have the potential of increasing the elastase burden in the lungs and, therefore, of aggravating the disease, the most important step in management is to reduce the burden of respiratory irritants as much as possible. The most important of these is undoubtedly active cigarette smoking. Every attempt should be made to encourage the individual to stop smoking, if a smoker, or not to start or restart if a nonsmoker or exsmoker. Although there are no specific data to suggest that other exposures play a role in the pathogenesis of the emphysema, it is rational to suggest to AAT-deficient individuals that other respiratory irritants should be minimized as much as possible, including exposure to involuntary smoke and occupational exposure to dusts and gases. Lower respiratory tract infection should be treated promptly with the goal in mind of reducing the inflammatory cell burden in the lungs.

#### Maximal Supportive Therapy

For reasons that are not totally understood, airway hyperresponsiveness and some degree of reversibility are often seen in individuals with severe hereditary AAT deficiency. Consequently, a trial of maximal bronchodilator therapy is recommended to optimize airway function. No rigid guidelines can be given for treatment, but consideration should be given for combining bronchodilators with different modes of action, e.g., beta agonists, theophyllines, and anticholinergics. The value of corticosteroids has not been tested in these patients. An exercise program is always help-

ful to optimize cardiovascular function and conditioning. The use of supplemental oxygen should be considered if the criteria for long-term O<sub>2</sub> therapy are met.

#### Augmentation Therapy

Experience to date with augmentation therapy using human AAT has demonstrated that the treatment is safe and effective in terms of providing serum levels of AAT above the threshold protective levels of AAT and functional antineutrophil elastase capacity in the epithelial lining fluid of the lower respiratory tract (6, 7). Prolastin is heat-treated in solution at 60° C for 10 h. These conditions are capable of destroying the HIV and hepatitis viruses. To date, no instances of transmission of viral diseases have been recorded in individuals receiving Prolastin.

Augmentation therapy with human AAT should be reserved for individuals with PiZZ, PiZ null, or Pi null null phenotypes and a few rare phenotypes associated with AAT serum levels < 11 μM (e.g., Pi Malton Malton). It is *not* indicated for use in individuals who have cigarette smoking-related emphysema with normal AAT phenotypes or with deficient phenotypes (e.g., heterozygotes, PiMZ, PiMS, etc.) but levels of AAT above the 11 μM threshold. It is also not indicated in individuals with deficient phenotypes who have the liver disease associated with AAT deficiency but who do not have evidence of lung disease. The following guidelines are suggested for patients whose plasma concentration of AAT is < 11 μM.

**Age.** The present recommendation is that augmentation therapy should not be offered to individuals younger than 18 yr of age, except in the rare instance when obstructive lung disease is already present. Decisions about an upper age limit should be made on an individual basis.

**Lung function level.** It is recommended that treatment not be started while lung function is still in the normal range since a proportion of individuals with a high risk phenotype ap-

pear to escape without developing clinically significant airflow obstruction. Augmentation therapy should be considered, however, when lung function is in the abnormal range. Clearly, when making the decision about whether to start augmentation therapy, consideration should be given to the patient's age. With the evidence available, it is not appropriate to define a lower limit for lung function at this time since it is considered unethical to withhold treatment that may have benefit even in very severe end-stage disease. It is important to stress that there is no reason to expect that lung function will *improve* on augmentation therapy, but rather that the progression of disease will be retarded.

**Compliance.** Because augmentation therapy requires frequent infusions, one of the considerations in deciding to initiate augmentation therapy should be the willingness and ability of the patient to undergo the therapy. The present recommendation for augmentation therapy with human AAT (Prolastin) is that the product be administered by weekly infusion. Studies are currently underway to evaluate other regimens, for example, monthly infusions (16). For many patients, a home infusion program may be a realistic option.

**Safety.** The record of safety of Prolastin is excellent.<sup>1</sup> It is important to remember, however, that it is prepared from pooled plasma. As noted above, preparation includes heating to 60° C for at least 10 h to reduce the potential risk for transmission of infectious agents. However, no procedure has been found to be totally effective in removing viral infectivity from plasma fractionation products. The conditions of heat treatment used in the manufacture of Prolastin are capable of inactivating the hepatitis virus and HIV; to date, no cases of hepatitis, either non-A, non-B, or hepatitis B, or HIV seroconversion have been demonstrated in individuals receiving Prolastin. Despite this, the following recommendation from the Prolastin package insert should be followed until further information is available.

"It is recommended that in preparation for receiving Prolastin, recipients be immunized against Hepatitis B using a licensed

Hepatitis B Vaccine, according to the manufacturer's recommendations. Should it become necessary to treat an individual with Prolastin, and time is insufficient for adequate antibody response to vaccination, individuals should receive a single dose of Hepatitis B Immune Globulin (Human), 0.06 ml/kg body weight, intramuscularly, at the time of administration of the initial dose of Hepatitis B Vaccine."

Although it is not anticipated that the Prolastin preparation bears any risk for infection with HIV, it is recommended that HIV screening be carried out prior to starting augmentation therapy.

#### NIH Registry

FDA approval of human AAT (Prolastin) was based on clinical studies that demonstrated that weekly infusions were safe, maintained serum AAT levels above the at-risk threshold, and boosted levels of antineutrophil elastase activity in the epithelial lining fluid recovered by bronchoalveolar lavage. It was not based on a controlled clinical trial of its efficacy in changing the natural history of the progression of emphysema because it was clear that such a trial would pose insurmountable problems of logistics and cost.

Because a controlled clinical trial could not be carried out, the Division of Lung Diseases of the National Heart, Lung, and Blood Institute has begun a registry of patients with severe AAT deficiency. The primary objective of this registry is to characterize the clinical and laboratory course of individuals with this deficiency whether or not the patient is undergoing long-term augmentation therapy. Subjects eligible for entry into the registry must be 18 yr of age or older with severe hereditary AAT deficiency and serum levels < 11  $\mu$ M. Patients must be willing to give informed consent for enrollment in the registry and must be willing to undergo the designated evaluations. Subjects need to be close enough to a clinical center to participate in annual follow-up.

The registry was not designed as a randomized clinical trial to evaluate the efficacy of augmentation therapy. Nevertheless, the case finding and identification of individuals with this deficiency throughout the country and the gathering of data in these patients by standardized techniques will provide cohorts of well-characterized patients, which will be an invaluable resource for future studies. Clinical centers participating in the registry are listed below.

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<sup>1</sup> Early in 1989, a small number of patients receiving two lots of Prolastin developed a syndrome of fever, back and chest pain, and, in some cases, cyanosis immediately after the start of infusion. This was traced to a contaminant in the sucrose added to stabilize the alpha-1-antitrypsin during its preparation. To date, no other significant adverse effects have been reported.

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