PROLASTIN®
Alpha$_1$-Proteinase
Inhibitor (Human)
Continuous Commitment.

Testing for Alpha$_1$-Antitrypsin Deficiency

Why, How, and When?

Talecris
BIOTHERAPEUTICS

Contents

Introduction

Alpha$_1$-antitrypsin (AAT) deficiency is the most prevalent, potentially fatal hereditary disease of Caucasians, having a greater prevalence in adults than cystic fibrosis.
It is responsible for up to 3% of chronic obstructive lung disease cases in the US. Affected individuals have an increased risk of liver disease, and a markedly increased risk of severe, early-onset pulmonary emphysema, particularly if they smoke.

The decreased levels of AAT in the plasma and lungs of such individuals increase the potential for lung tissue injury due to relatively unopposed activity of leukocyte elastase, an enzyme carried in polymorphonuclear leukocytes.

In the United States, fewer than 5% of all individuals with AAT deficiency have been detected. Many of the remaining 95% are thought to be suffering from respiratory symptoms, but carrying incorrect diagnoses such as chronic bronchitis, emphysema, or asthma.

The American Thoracic Society and European Respiratory Society have recommended testing for AAT deficiency among all patients with chronic obstructive pulmonary disease (COPD), all adults and adolescents with incompletely reversible asthma, and all individuals with a family history of these diseases.

Modern testing methods allow a complete diagnosis to be established from a few drops of blood.

Affected individuals who are identified will benefit from lifestyle changes (especially smoking cessation), more intense medical intervention, and (in appropriate cases) specific therapy which allows blood levels of AAT to be augmented by intravenous administration of an AAT concentrate such as Prolastin® (Alpha$_1$-Proteinase Inhibitor [Human]).

Prolastin® (Alpha$_1$-Proteinase Inhibitor [Human]) is indicated for chronic replacement therapy of individuals having congenital deficiency of alpha$_1$-PI (alpha$_1$-antitrypsin deficiency) with chronically demonstrable panacinar emphysema. Individuals with selective IgA deficiencies who have known antibody against IgA should not receive Prolastin®, since these patients may experience severe reactions, including anaphylaxis, to IgA which may be present. Please see accompanying Full Prescribing information.

Alpha$_1$-antitrypsin (AAT) deficiency, also known as alpha$_1$-protease inhibitor (A1-PI) deficiency, is caused by abnormalities in the AAT genes. This occurs as a result of inheritance of two defective alpha$_1$-protease inhibitor (PI) alleles.

AAT deficiency occurs predominantly in Caucasians of northern European origin. Its frequency in Europe and North America (1 in 2,000 to 1 in 7,000) is comparable to that of cystic fibrosis.

Some persons with AAT deficiency may have no clinical manifestations. When the disease is clinically manifested, chronic obstructive pulmonary disease (COPD), particularly with panacinar emphysema, is the most prevalent clinical disorder associated with AAT deficiency and the most frequent cause of disability and death.

If an AAT deficient patient smokes, the risk of developing COPD increases, and symptoms often begin by the fourth or fifth decade of life. This onset of symptoms in AAT-replete individuals is much earlier than "usual" COPD.

Liver disease, the second most frequent clinical manifestation of AAT deficiency, typically presents as cholestasis in infancy, but is usually not severe or persistent in the neonate. Although AAT deficiency is the most common cause of chronic liver disease in childhood it develops infrequently. Typically, liver disease presents as cirrhosis or carcinoma of the liver, which affect at least 25% of AAT deficient adults over the age of 50 years.

AAT deficiency appears to be widely underdiagnosed. Based on predicted gene frequencies, only a small proportion of those predicted to have AAT deficiency have been diagnosed, even in the most intensely studied populations.[1]

Figure 1. The number of diagnosed cases does not match the predicted frequency level, indicating that many people with the disorder are still undiagnosed. It has been estimated that fewer than 5% of individuals ("the tip of the iceberg") with alpha1-antitrypsin deficiency have been diagnosed.

Who is Affected

It is estimated that there are 80,000-100,000 Americans who have alpha$_1$-antitrypsin deficiency.[1]

AAT deficiency is responsible for up to 3% of chronic obstructive lung disease cases in the US.[2]

AAT deficiency occurs in approximately 1 in 2,000-7,000 live births in Europe and North America.[2]

- Up to 3% of chronic obstructive lung disease cases
- Between 80,000 and 100,000 Americans affected

Newly diagnosed patients with alpha$_1$-antitrypsin deficiency usually have many questions about the disease. This brochure should help you to answer these questions.

What is Alpha$_1$-Antitrypsin (AAT) Deficiency?

AAT deficiency is a genetic disorder characterized by a marked reduction in serum levels of AAT, a naturally occurring protein.[3]

It is synthesized predominantly by hepatocytes and secreted into the blood, although a small amount is also synthesized and secreted by macrophages in the lung. The normal serum concentration of AAT can rise considerably during inflammatory episodes as part of an acute phase reaction.[4, 5]

Because of its molecular mass, AAT is able to enter the lung by passive diffusion from blood.[6]

In the lung, AAT plays an important role in protecting lung tissue from damage by proteolytic enzymes, particularly leukocyte (neutrophil) elastase.[7, 8, 9]

Under normal conditions, neutrophil elastase may serve a variety of important functions. However, if not neutralized by AAT, neutrophil elastase can destroy healthy lung tissue. Over time, this process can result in emphysema.

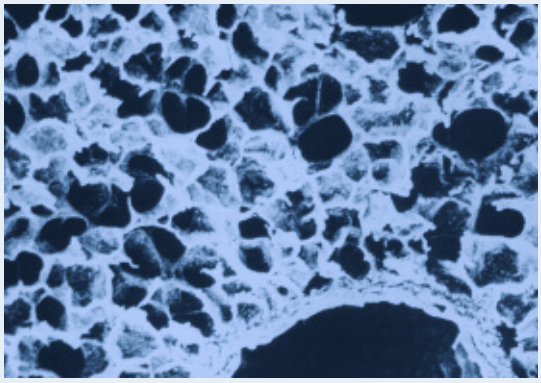
Therefore, the decreased AAT levels in patients with AAT deficiency puts patients at high risk for developing emphysema.[9, 10]

Although lung disease is the most common manifestation of AAT deficiency, the liver is stressed by syntheses of an abnormal AAT. This can lead to neonatal jaundice and persistent childhood liver disease, and to cirrhosis and liver cancer in adults.[11]

When liver disease develops, it usually manifests in infants as jaundice and cirrhosis.[12, 13] However, liver disease may also appear in older children or adults as mild to severe hepatitis or cirrhosis.

Rarely, patients manifest significant lung disease and liver disease concomitantly.

Patients with AAT deficiency also have an abnormally high risk for inflammatory diseases in other sites, especially panniculitis and autoimmune vasculitis, but also joint diseases and hemorrhagic disorders.[6]



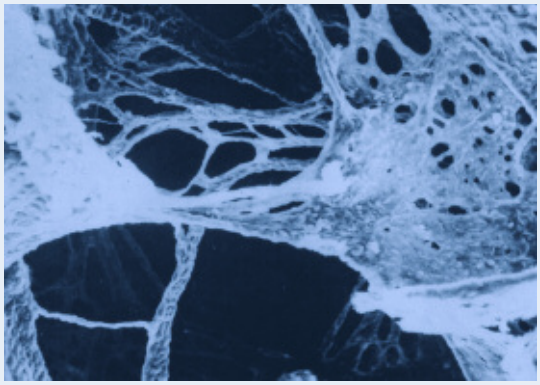


Figure 2. Emphysema is a condition in which there is over-inflation of structures in the lungs known as alveoli or air sacs. This over-inflation results from a breakdown of the walls of the alveoli, as shown in these pictures, which causes a decrease in respiratory function and often, breathlessness.

What are the Symptoms of AAT Deficiency?

Most people diagnosed with AAT deficiency have suffered with years of unexplained and poorly controlled lung problems.[14]

Unfortunately, these individuals are often misdiagnosed as having allergies, asthma, bronchitis, or chronic obstructive pulmonary disease (COPD).

The classic AAT deficient patient may develop symptoms referable to the lungs before age 40.[15] The earliest symptom is usually dyspnea on exertion. Approximately 50% of all patients develop cough and recurrent pulmonary infections.[6] Other symptoms include:

- Shortness of breath following activity
- Decreased exercise tolerance
- Wheezing, with or without an upper respiratory tract infection[14]

Smokers typically develop symptoms about 10 to 15 years earlier than non-smokers and, for a given level of AAT, the destructive processes are more extensive than for non-smokers.[6]

What are the Additional Risk Factors for Lung Disease in AAT Deficiency?

- Cigarette smoking promotes inflammation in the airways and throughout the lung. The influx of inflammatory cells increases the burden of the potentially injurious leukocyte elastase in the lung and increases the risk for lung injury. Smoking may promote lung injury in other ways as well, including reduced effectiveness of the AAT molecule as an inhibitor of leukocyte elastase. Clinically significant lung disease is more prevalent and occurs earlier in cigarette smokers than in lifelong nonsmokers.[6]
- Recurrent respiratory infections also attract inflammatory cells to the lung with potentially injurious consequences in individuals with AAT deficiency.

  These individuals risk additional lung damage during infections owing to the inability to mount an effective acute phase elevation in the AAT level. Thus, their levels of AAT differ from normal even more during respiratory infections than in their baseline states.
- Asthma is associated with an increased inflammatory cell burden in the airways and possibly some familial factors contribute to a severe clinical course.[16]
- Other genetic and/or environmental factors may also increase the risk for lung disease in AAT deficient patients.[17]

Clinical Manifestations of AAT Deficiency

Chronic obstructive pulmonary disease (COPD), due to the presence of chronic bronchitis and emphysema, is the most prevalent clinical disorder associated with AAT deficiency. Chronic bronchitis is defined on a clinical basis as a chronic productive cough, occurring for more than 3 months per year in each of two successive years.

The frequency of asthma in AAT deficient individuals has been reported to be between 4% to 34%.[2]

Bronchiectasis may also occur with AAT deficiency, occurring in 5% to 10% of all patients.[2]

How is AAT Deficiency Inherited?

A pair of genes controls the synthesis of AAT. Every person inherits two genes for AAT, one from each parent. The two AAT genes are codominantly expressed, meaning that the patient's phenotype is a result of the expression of the two AAT alleles.

Products of both genes, the AAT protein, can usually be found in the circulation.[10]

Mutations within the critical regions of the genes that translate into the mobile reactive center of the AAT protein may cause conformational changes.

Categorizing According to Phenotype

Each variant is assigned a letter of the alphabet corresponding with their mobility on acid starch gel electrophoresis:

- F (fast)
- M (medium)
- S (slow)
- Z (the most cathodal).[18]

Subsequently discovered variants were also given alphabetic designations in accordance with their relative mobility.

At least 75 different alleles of the AAT gene have been identified and categorized into an arrangement designated using the protease inhibitor (Pi) system.[18, 19]

Since AAT is one of the major **p**rotease **i**nhibitors of human plasma, the symbol **Pi** was chosen for the AAT polymorphism.[18]

The most common normal AAT alleles are referred to as M, and are found in approximately 95% of the U.S. population and other populations of northern European descent. The two most common "deficient" variants are the allele Z, representing about 1% to 2% of the alleles in Caucasians in the U.S., and the allele S, representing about 2% to 4% of these alleles.[6] "Null" alleles result in no AAT in the blood, but account for less than one percent of alleles in the U.S.

Some persons may inherit a single abnormal gene. The most common of these heterozygotes are PiMZ and PiSZ individuals. They have far lower, if any, increased risk of lung disease.

In individuals with AAT deficiency, the serum levels of AAT are 10% to 15% of normal.[6]

In families in which one parent has a very low concentration of AAT (indicating the phenotype PiZZ) and the other parent has a normal value (indicating the phenotype PiMM), all children have intermediate levels, phenotype (PiMZ).

People with a phenotype PiMZ are also called carriers. The AAT level of a carrier may be lower than normal, but it is still high enough to prevent significant health problems. When both parents are carriers, three different phenotypes in children can be observed:

- PiZZ (low levels of AAT)
- PiMZ (intermediate levels of AAT)
- PiMM (normal levels of AAT)

These findings indicate that low levels of AAT are caused by homozygosity of a deficiency gene, intermediate values by heterozygosity, and normal concentration by homozygosity of the "normal" or most common gene.[10]

Blood tests, called phenotyping or genotyping, can determine if a person is a carrier of AAT deficiency.[1]

Categorizing According to AAT Levels

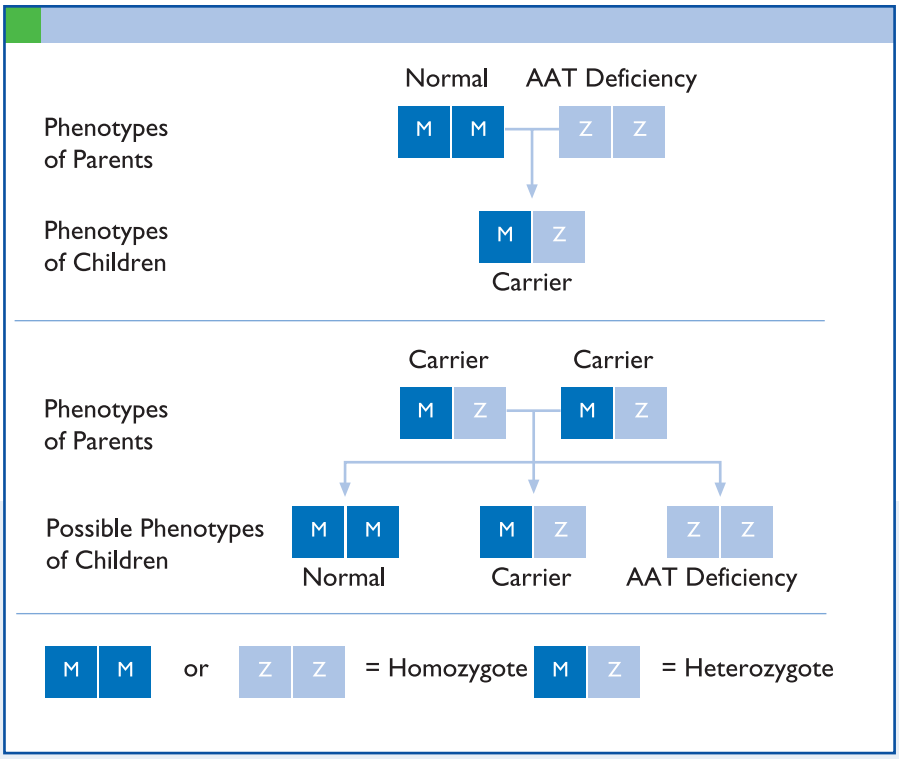


Figure 3. The two parental AAT genes are co-dominantly expressed, meaning that the patient's phenotype is a result of the expression of the two AAT alleles.

These alleles can be categorized into four groups on the basis of the AAT levels that occur in the serum:

- "Normal", associated with normal serum levels of AAT with normal function
- "Deficient", associated with serum AAT levels less than 11 micromolar (usually 10% – 15% of normal)
- "Null", in which there is no detectable AAT protein in serum
- "Dysfunctional", in which the AAT protein is present but does not function normally[19]

How is AAT Deficiency Diagnosed?

When AAT deficiency is suspected, the first step is to measure AAT concentration (or level) in blood or serum. The AAT level is expressed in micromolar (μM) units.

The "threshold" above which there is sufficient AAT to protect the lungs (and below which the individual has an increased risk of developing emphysema compared to the general population) is 11μM.[1]

A follow-up test may be done to determine the actual genes carried by the individual. This testing is only indicated for individuals who have a low AAT level or who have a family history of AAT deficiency.[1]

AAT protein in the blood can be phenotyped by isoelectric focusing in polyacrylamide gels.[6, 18] Genotyping is typically performed from whole blood by polymerase chain reaction, using primers specific for particular point mutations in the DNA.

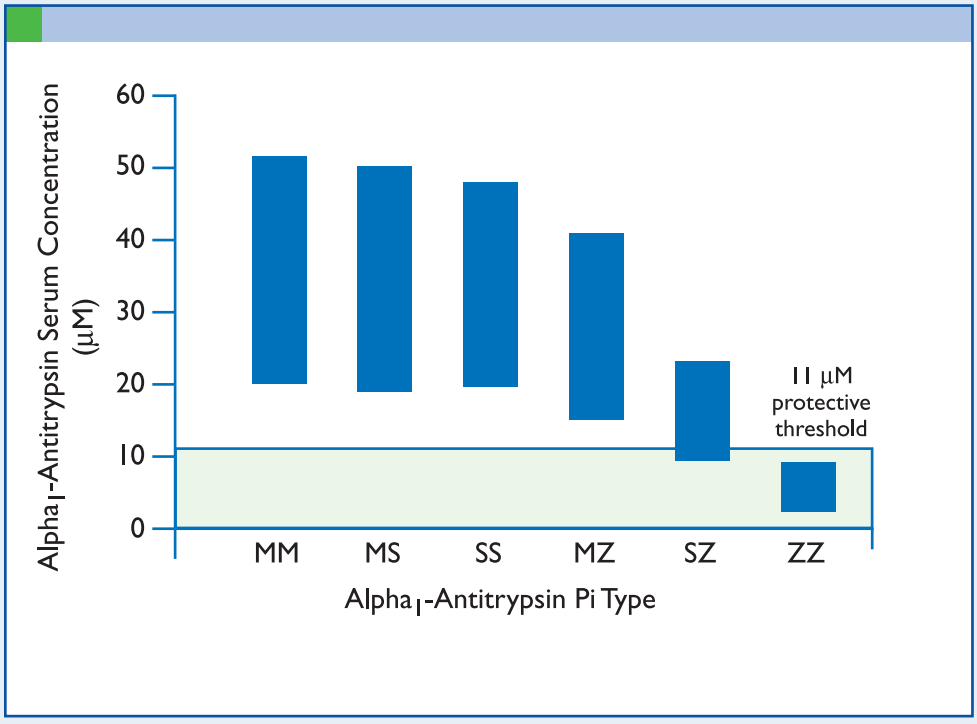


Figure 4. This picture shows the alpha$_1$-antitrypsin levels and the corresponding phenotypes of several thousand people who were tested for alpha$_1$-antitrypsin deficiency.[20]

How are Phenotyping Results Interpreted?

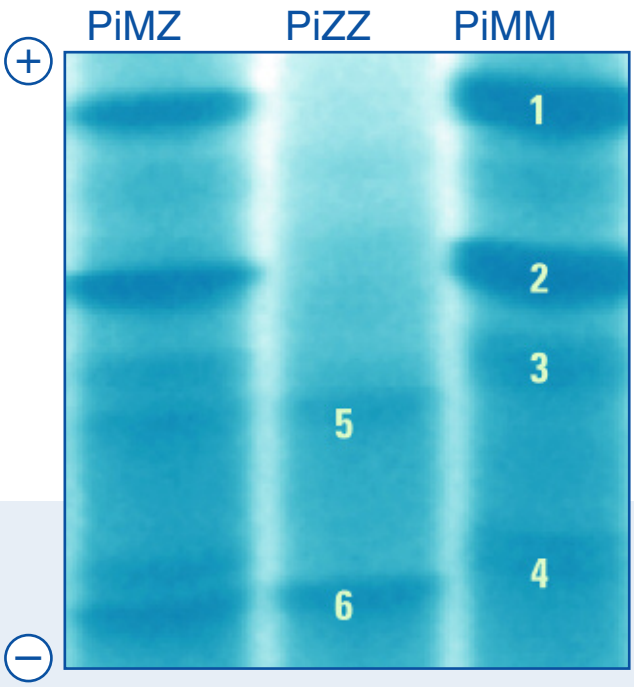


Figure 5. Phenotyping Schematic of alpha$_1$-antitrypsin PI types separated according to their isoelectric point. Isoelectric focusing of alpha$_1$-antitrypsin on a thin-layer polyacrylamide gel. In a pH gradient of 4-5, alpha$_1$-antitrypsin variants migrate as two major bands (1 and 2). Two minor bands (3 and 4) contribute to the microheterogeneity of alpha$_1$-antitrypsin. Major variation in the migration of alpha$_1$-antitrypsin alleles is the result of amino acid substitutions that alter the net charge of the protein and hence the isoelectric point of the protein.

The Z variant bands (5 and 6) are located near the cathode (-) and are significantly fainter because of the low serum alpha$_1$-antitrypsin concentration. Serum from heterozygous individuals, such as MZ, demonstrates a more complex pattern due to the individual contribution of each allele to the total alpha$_1$-antitrypsin serum concentration and phenotype.[21]

PiZ Variant

The Z variant can produce a clinically important form of AAT deficiency. When inherited in a homozygous form, the Z allele results in serum levels of less than 11 µM.[22] In addition to being present in a reduced amount, the Z protein does not function normally as an inhibitor of neutrophil elastase.[23] PiZ null heterozygotes also have AAT deficiency.

Brothers and sisters of a patient with AAT deficiency have a 25% chance of also having the deficiency.[10]

PiS Variant

The S variant is slightly more common than the Z variant. However, from a clinical viewpoint, the S variant is less important because in its homozygous form it is associated with AAT serum levels sufficient to protect the lung.[17,24]

Unlike the Z variant, the S variant functions normally as an inhibitor of neutrophil elastase.[25]

PiSZ

Inheritance of one S allele and one Z allele results in AAT levels that are approximately 1/3 to 1/2 of normal. While these levels are thought to be sufficient to protect the lung from injury, it remains controversial whether there is some excessive risk for the development of emphysema in these individuals (particularly if they smoke).[15,26]

PiNull

The null variants represent a rare group of AAT alleles in which no AAT protein attributable to that gene is present in the serum. Inheritance of a null allele from both parents may put the person at very high risk for the development of emphysema.[19]

PiMS

Since PiMS results in only a slightly decreased level of AAT, no health problems related to AAT deficiency would be expected in a PiMS individual.[24]

PiM(null)

This patient inherited a null allele from one parent but does not have AAT deficiency. However, the level of immunoreactive AAT is mildly to moderately reduced. This is associated with a normal phenotype and suggests, but does not prove, that this individual is a heterozygote ("carrier") for AAT deficiency.

Since the null allele does not result in secretion of AAT into the circulation, phenotyping cannot confirm with certainty that this allele is present. Family studies of the pattern of inheritance of low AAT levels are necessary to confirm this possibility.

There is little clinical information about the PiM(null) phenotype, since it is quite uncommon and difficult to detect with certainty. However, there is no clinical evidence that the PiM(null) phenotype is associated with an excess risk of lung or liver disease.

PiMZ

This is the clinical heterozygote for AAT deficiency. Although histologic abnormalities can be seen in the liver of heterozygotes, there is minimal if any predisposition to lung and liver disease in this population.[24]

Many heterozygotes wish to have their spouses tested in order to determine the risk to their children.

Who Should be Tested for AAT Deficiency?

In 1996, the report of the World Health Organization (WHO) recommended that the following individuals should be tested[2]:

- All patients with COPD
- All adolescents and adults with asthma
- All individuals with a family history of AAT deficiency

In 2003, the American Thoracic Society and European Respiratory Society recommended that the following individuals be tested for AAT deficiency[27]:

- COPD (all subjects)
- Early-onset pulmonary emphysema (regardless of smoking history)
- Family members of known AAT-deficient patients
- Dyspnea and cough occurring in multiple family members (same or different generations)
- Liver disease of unknown cause
- Adults with bronchiectasis without evident etiology
- Patients with asthma whose spirometry fails to return to normal with therapy
- Unexplained panniculitis and antiproteinase-3 vasculitis

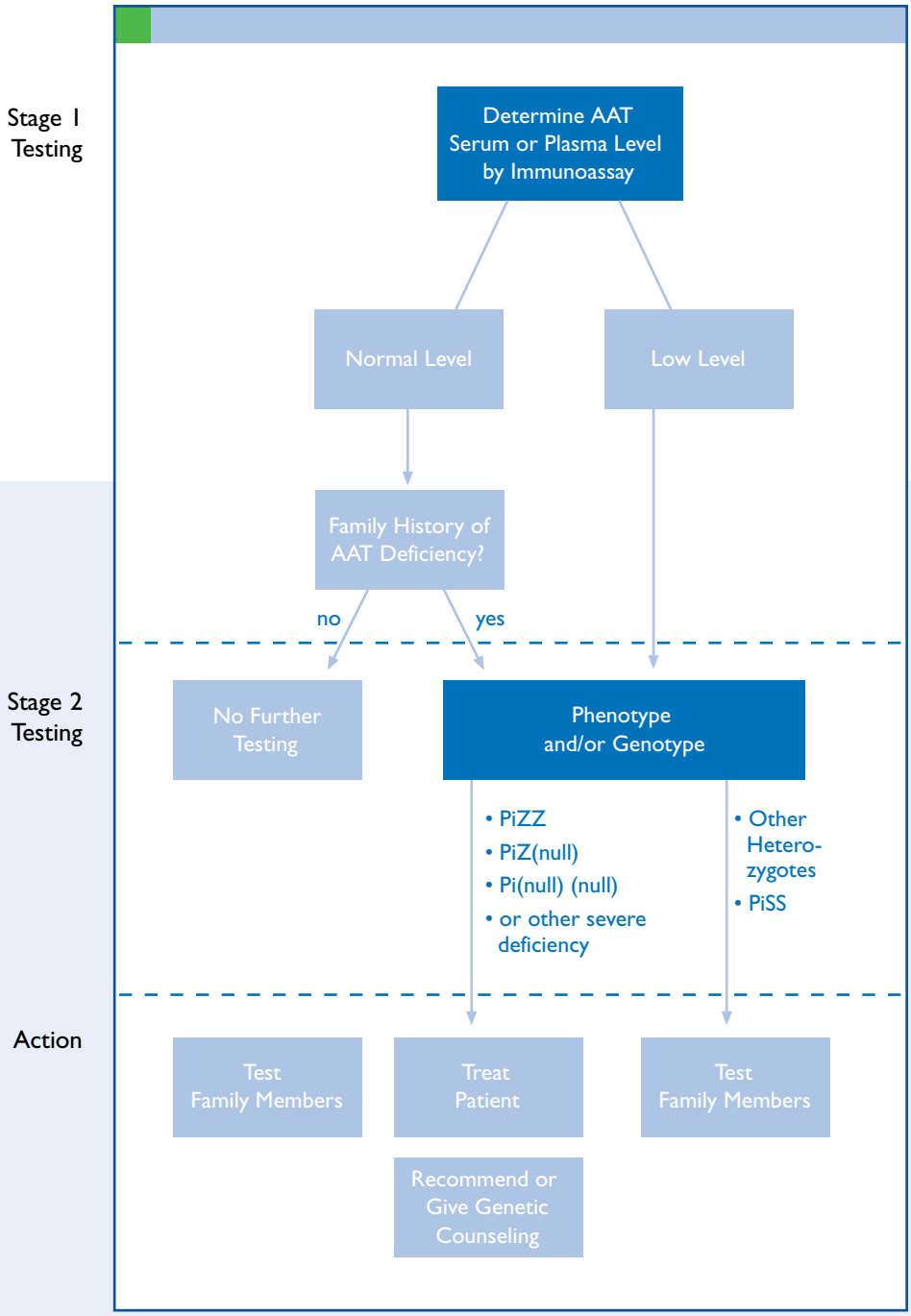


Figure 6. Decision Tree Suggested algorithm for testing for AAT deficiency.

Stage 1 is determination of the concentration, or "level" of AAT in the blood. If normal, testing should proceed only if the patient has a family history of the disease.

Stage 2 (phenotyping and/or genotyping) should be performed in individuals with low levels of AAT, as determined in Stage 1, or individuals with a family history of the disease. Stage 2 testing will conclusively identify individuals with the disease, carriers of the disease, and individuals with rare AAT alleles.

Recommended courses of action are also shown.

Who is Performing the Tests for AAT Deficiency?

The Talecris AlphaKit allows testing to be performed with only a few drops of blood dried onto filter paper, thus providing convenient and state-of-the-art testing.

The Talecris AlphaKit is a blood collection kit (Figure 7), which contains all of the materials required to obtain and ship the blood sample. The dried blood is not biohazardous and can be shipped by regular mail in the preaddressed envelope supplied. Results are usually returned within 10 working days.

In the US, analysis of samples collected using the Talecris AlphaKit is performed at an academic research laboratory. The laboratory performs a highly automated immunoassay for AAT deficiency on the submitted sample.

The laboratory will measure the AAT level in the dried blood sample, followed by genotyping and phenotyping, if appropriate.

Figure 7. The Talecris AlphaKit. This blood collection kit contains a data form attached to specially manufactured filter paper, a device for obtaining a blood sample by fingerstick, instructions for obtaining and handling the blood sample, and a return envelope.

Laboratory policy allows samples from individuals who have low levels of AAT by immunoassay or who have a family history of AAT deficiency to be phenotyped by isoelectric focussing in polyacrylamide gels. However, you may submit a sample of EDTA-anticoagulated whole blood (purple-top tube) to a variety of reference laboratories for testing.

For more information on this program or any other questions about testing, call:

Talecris Clinical Communications at: 1-800-520-2807.

To order free Talecris AlphaKits directly, call: 1-800-562-7222

How Can You Manage AAT Deficiency?

- Your patient must stop smoking immediately!
- Your patient should get pneumococcal and annual influenza vaccines.
- Respiratory illnesses should be treated promptly and aggressively.
- Other supportive measures, including the use of bronchodilators, supplemental oxygen, and inhaled steroids, may be considered for patients with airway hyperactivity.
- Augmentation therapy with Prolastin® ($Alpha_1$-Proteinase Inhibitor [Human]) is available. It is indicated for chronic therapy of individuals having congenital AAT deficiency with clinically demonstrable panacinar emphysema.[28]

With any plasma-derived products, the theoretical risk of virus transmission cannot be ruled out. Individuals with selective IgA deficiencies who have known antibody against IgA should not receive Prolastin®, since these patients may experience severe reactions, including anaphylaxis, to IgA which may be present. Please see accompanying Full Prescribing information.

Treatment Options for Alpha-1

There are many components to treating Alpha-1. The goal is to maintain better lung function. This can be done through smoking cessation, asthma medications (if necessary), infection control, good nutrition, environment modifications, exercise, and stress management. However, there is a specific pharmacologic treatment that helps restore through augmentation therapy the natural balance of enzymes in the lungs and protects from the damage caused by neutrophil elastase. The treatment is Prolastin®, Alpha$_1$-Proteinase Inhibitor (Human).

What is Prolastin®, Alpha$_1$-Proteinase Inhibitor (Human)?

Prolastin®, Alpha$_1$-Proteinase Inhibitor (Human), derived from human plasma, is a concentrated form of AAT. Given as prescribed, Prolastin® raises the blood and lung levels of AAT. This may help lessen damage to the lungs caused by the enzymatic activity of neutrophil elastase. Because Prolastin® therapy augments existing levels of AAT, it is known as "augmentation" or "replacement" therapy.

Benefits of taking Prolastin®

Prolastin® is not a cure for AAT deficiency. However, it may help to slow the loss in lung function that characterizes this disease. Prolastin® is only approved for chronic therapy in individuals with emphysema due to congenital Alpha-1 and is not approved for the treatment of emphysema due to other causes, such as smoking. Prolastin® is not indicated for use in patients other than those with PiZZ, PiZ(null), or Pi(null)(null) phenotypes. In addition, Prolastin® cannot be used to treat individuals with liver disease due to Alpha-1.

Figure 8. Prolastin® Alpha$_1$-Proteinase Inhibitor (Human)

How is Prolastin® given?

The recommended dosage of Prolastin® is 60 mg/kg body weight administered intravenously, once a week.

Safety record of Prolastin®

Prolastin® has an excellent safety profile. Multiple steps are incorporated into the manufacturing process of Prolastin® to reduce the risk of viral transmission. Since Prolastin® was introduced in 1988, over 2 million doses have been administered with no confirmed reports of viral transmission.

What are the risks with Prolastin®?

Prolastin® is very well tolerated with side effects happening in only 1.16% of infusions during clinical trials. The most commonly reported side effects are delayed fever, light-headedness, and dizziness.

For complete prescribing information, please refer to package insert.

Where Can My Patient or I Get Further Information

Each newly diagnosed patient should be encouraged to contact Talecris Biotherapeutics and/or patient organizations for more information and support.

Talecris Biotherapeutics

Talecris Biotherapeutics offers a free service that provides pertinent information concerning insurance coverage and reimbursement issues. Among other benefits, this service will assist in the preparation of supporting documentation requested from the insurance company regarding the use of Prolastin®.

Toll free: 1-800-520-2807, 8:30 AM – 5:00 PM EST

In addition, Talecris can provide you or your patient with additional educational material designed to meet your patient's need for information.

For information on how to access Prolastin® for your patient and enroll him or her in Talecris Direct® please call 1-800-305-7881.

Alpha-1 Association

The Alpha-1 Association is a patient group that was formed to provide support and education for individuals and their families affected by AAT deficiency.

The Alpha-1 Association acts as a clearing-house for information to assist healthcare professionals and individuals with AAT deficiency and acts as an advocate for people with AAT deficiency.

Through this organization, a patient will meet other people with AAT deficiency who can provide support to him or her. Some groups meet informally as part of a national support group network. There are chapters all over the country, with new ones being formed.

Toll free: 1-800-4ALPHA1 (425-7421), or 612-703-9979, or visit them at: www.alpha1.org

Alpha-1 Foundation

The Alpha-1 Foundation is the only national research organization solely dedicated to developing the means to cure and control AAT deficiency and to improve the quality of life for those with the disorder.

The Alpha-1 Foundation also provides general AAT deficiency information, research opportunities and referrals to specialist physicians and clinical resources centers.

Toll free: 1-877-2-Cure-A1 (228-7321),
or visit them at: www.alphaone.org

American Lung Association

The American Lung Association can provide information and support, especially if your patient is trying to quit smoking. Since 1904, the American Lung Association has been working to ensure that all Americans breathe more easily.

Their mission is to prevent and fight lung disease through education, community service, advocacy and research, seeking better treatments and cures.

Toll free: 1-800-Lung-USA (586-4872),
or visit them at: www.lungusa.org

References

1. Buist S: Alpha$_1$-antitrypsin deficiency – diagnosis, treatment, and control: Identification of patients. *Lung* 1990; Suppl: 543 – 551.
2. Bulletin of the World Health Organization: Alpha$_1$-antitrypsin deficiency: *Memorandum from a WHO meeting* 1997; 75 (5): 397 – 415.
3. Lauresll CB, Eriksson S: The electrophoretic alpha$_1$-globulin pattern of serum in alpha$_1$-antitrypsin deficiency. *Scandinav J Clin & Lab Investigation* 1963; 15: 132 – 140.
4. Morse JO: Alpha$_1$-antitrypsin deficiency (first of two parts). *N Engl J Med* 1978; 299: 1045 – 1048.
5. Kueppers F, Black LF: Alpha$_1$-antitrypsin and its deficiency. *Am Rev Respir Dis* 1974; 110: 176 – 194.
6. Gadek JE, Crystal RG: Alpha$_1$-antitrypsin deficiency. In: Stanbury JB, Wynbgaarden JB, Fredrickson DS, Goldstein JI, Brown MS, eds. *The Metabolic Basis of Inherited Disease*. 5th ed. New York: McGraw-Hill, 1982; 1450 – 1467.
7. Janoff A, et al: Experimental emphysema induced with purified human neutrophil elastase: Tissue localization of the instilled protease. *Am Rev Respir Dis* 1977; 115: 461 – 478.
8. Travis J, Salvesen GS: Human plasma proteinase inhibitors. *Annu Rev Biochem* 1983; 52: 655 – 709.
9. Kueppers F: Inherited differences in alpha$_1$-antitrypsin. In: Litwin SD, ed. *Genetic Determinants of Pulmonary Diseases*. New York: Marcel Dekker; 1978: 23 – 74.
10. Eriksson S: Pulmonary emphysema and alpha$_1$-antitrypsin deficiency. *Acta Medica Scandinavice* 1964; 175, fasc. 2: 197 – 205.
11. Eriksson S, et al: Risk of cirrhosis and primary liver cancer in alpha$_1$-antitrypsin deficiency. *N Engl J Med* 1986; 314: 736 – 739.
12. Sharp HL, et al: Cirrhosis associated with alpha$_1$-antitrypsin deficiency: A previously unrecognized inherited disorder. *J Lab Clin Med* 1969; 73: 934 – 939.
13. Sveger T: Liver Disease in alpha$_1$-antitrypsin deficiency detected by screening of 200,000 infants. *N Engl J Med* 1976; 294 (24): 1316 – 1321.
14. Stoller JK, Smith P, et al: Physical and social impact of Alpha$_1$-antitrypsin deficiency: results of a survey. *Cleve Clinic J Med* 1994; 61: 461 – 467.
15. Brantly ML, Paul LD, et al: Clinical features and natural history of the destructive lung disease associated with alpha$_1$-antitrypsin deficiency of adults with pulmonary symptoms. *Am Rev Respir Dis* 1988; 138: 327 – 336.
16. Silverman E, Pierce J, et al: Variability of pulmonary function in alpha$_1$-antitrypsin deficiency: Clinical correlates. *Ann Intern Med* 1989; 111: 982 – 991.
17. Seersholm N, Kok-Jensen A: Clinical features and prognosis of life time nonsmokers with severe alpha$_1$-antitrypsin deficiency. *Thorax* 1998; 53: 265 – 268.
18. Fagerhol MK, Cox DW: The Pi polymorphism: genetic, biochemical, and clinical aspects of human alpha$_1$-antitrypsin. *Adv Hum Genet* 1981; 11: 1 – 62, 371 – 372.
19. Brantly M, Nukiva T, Crystal R: Molecular basis of alpha$_1$-antitrypsin deficiency. *Am J Med* 1988; 84 (suppl 6A): 13 – 31.
20. Campbell E: Data on file, 1999.
21. Brantly M: Alpha$_1$-antitrypsin genotypes and phenotypes. In: Crystal R, ed. Alpha$_1$-Antitrypsin Deficiency *(Series: Lung Biology in Health and Disease, vol. 88)*. New York: Marcel Dekker, 1996; 45 – 59.

22. Wewers MD, Casolaro MA, Sellers SE, et al: Replacement therapy for alpha$_1$-antitrypsin deficiency associated with emphysema. *N Engl J Med* 1987; 316: 1055 – 1062.

23. Ogushi F, Fells GA, et al: Z-type alpha$_1$-antitrypsin is less competent than M1- type alpha$_1$-antitrypsin as an inhibitor of neutrophil elastase. *J Clin Invest* 1987; 80: 1366 – 1374.

24. Morse JO: Alpha$_1$-antitrypsin deficiency (second of two parts). *N Engl J Med* 1978; 299: 1099 – 1105.

25. Ogushi F, Hubbard R, Fells G, et al: Evaluation of the S-type of Alpha$_1$-antitrypsin as an in vivo and in vitro inhibitor of neutrophil elastase. *Am Rev Respir Dis* 1988; 137: 364 – 370.

26. Hutchison DCS, Tobin MJ, Cook PJL: Alpha$_1$-antitrypsin deficiency: clinical and physiological features in heterozygotes of Pi type SZ: a survey by the British Thoracic Association. *Br J Dis Chest* 1983; 77: 28 – 34.

27. American Thoracic Society/European Respiratory Society Statement: Standards for the Diagnosis and Management of Individuals with Alpha$_1$-Antitrypsin Deficiency. *Am J Respir Crit Care Med* 2003; 168: 818 – 900.

28. Buist S, Burrows B, Cohen AIR, et al: American Thoracic Society – Guidelines for the approach to the patient with severe hereditary alpha$_1$-antitrypsin deficiency. *Am Rev Respir Dis* 1969; 140: 1494 – 1497.

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