

# A Healthcare Professional's Guide to

Alpha<sub>1</sub> Antitrypsin Deficiency



Alpha-1 UK Support Group  
Registered Charity England & Wales 1146330  
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Research for a Cure

Parts of this brochure were adapted from the  
Alpha-1 Foundation publication  
Alpha-1 Antitrypsin Deficiency Healthcare Provider's Guide.

# Foreword

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*Alpha-1 antitrypsin deficiency (Alpha-1) is one of the most common serious hereditary disorders. Alpha-1 has been identified in virtually all populations, but is most common in individuals of northern European (Scandinavian and British) and Iberian (Spanish and Portuguese) descent. Among patients with Chronic Obstructive Pulmonary Disease (COPD) 1-3% are predicted to have AAT deficiency. It can also cause life threatening liver damage in adults and children, and liver cancer in adults. Despite its prevalence, patients and healthcare professionals have been poorly informed about the disorder. For this and other reasons the overwhelming majority of individuals with AAT deficiency have not been detected. It is estimated that 1 person in every 3,000-5,000 of the UK population has AAT deficiency. However, only around 5% of these people have so far been identified leaving many more individuals undetected, and at risk. The number of people who carry an altered gene is much higher, estimated to be around 3% of the population.*

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The discovery of alpha-1 antitrypsin (AAT) deficiency by Laurell and Eriksson in 1963 provided a foundation for current thinking about the pathogenesis of pulmonary emphysema. Although AAT deficiency has become one of the best understood genetic disorders, at a molecular and cellular level, many questions about the clinical disorder remain unanswered.

The Alpha-1 UK Support Group, together with other organisations, is working with physicians and experts in the treatment and care of Alpha-1 patients to develop better management and clinical guidelines for caring for those affected by AAT deficiency.

## **This Guide**

“A Healthcare Professional’s Guide to Alpha<sub>1</sub> Antitrypsin Deficiency” is a response by the Alpha-1 UK Support Group to the need for the provision of up to date information about screening, diagnosis, and treatment of this disorder. This information is designed to educate doctors, nurses, and patients about AAT deficiency and the resources available.

**Alpha-1 UK Support Group** has also produced four further educational publications for patients, families, and carers of Alpha-1 patients. These are:

- Could Your Asthma or COPD be Hereditary? - A guide to Alpha 1 Antitrypsin Deficiency
- Does Your Child Have Alpha 1 Antitrypsin Deficiency? - A Parent's Guide
- Alpha 1 Antitrypsin Deficiency, Living With Liver Disease - A guide to the assessment and management of A1AD related liver disease
- Are You an Alpha Too? - A children's guide to alpha 1 antitrypsin deficiency

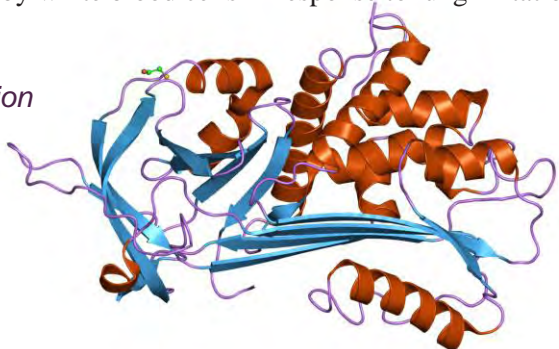
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## *Overview and Disorder Description*

### **What Is Alpha 1 Antitrypsin?**

Alpha-1 antitrypsin (AAT) is a protein that circulates in the bloodstream. Some scientists also call it "alpha 1 proteinase inhibitor." The liver makes most of the circulating AAT. AAT protects the tissues of the body from being damaged by proteolytic enzymes which break down proteins, especially the neutrophil elastase released by white blood cells in response to lung irritation

*A structural representation  
of alpha-1 antitrypsin*



## What is Alpha 1 Antitrypsin Deficiency?

Alpha-1 antitrypsin (AAT) deficiency is a genetic disorder characterised by the production of an abnormal AAT protein. The liver cells cannot secrete the abnormal AAT protein into the bloodstream resulting in marked reductions of circulating AAT levels. Instead, it accumulates within the cells of the liver and, although the mechanisms are not completely known, it is believed that the retained abnormal AAT protein leads to liver injury in some affected patients.

In the lungs, low levels of AAT allow the destructive effects of neutrophil elastase to go unchecked which results in damage to the delicate gas exchange alveoli. Eventually this can lead to early onset emphysema. Thus, persons with AAT deficiency are at high risk of developing life threatening lung and/or liver disease.

### *Epidemiology of AAT*

- Alpha-1 antitrypsin deficiency is one of the most common inherited disorders among white people.
- North-western Europeans are most likely to carry a mutant AAT gene.
- In the UK it is estimated that 1 person in every 3,000-5,000 has AAT deficiency.
- It is a condition that is markedly under diagnosed which probably relates to the fact that some people with very low levels of the protein may not exhibit problems. Furthermore, manifestation of the disease is a mixture of genetic predisposition and environmental factors. For example, a person who is heterozygous (one abnormal gene) may simply have a predisposition to chronic obstructive pulmonary disease (COPD) if they smoke.
- 1-3% of people diagnosed with COPD are thought to have AAT deficiency.

AAT deficiency can appear as a chronic lung disease (e.g. emphysema, chronic bronchitis, COPD, bronchiectasis, and asthma) in adults as early as the third decade of life especially, although not exclusively, in smokers.

Symptomatic AAT deficiency can be diagnosed in adults in all decades. However, some persons with AAT deficiency can live completely normal life spans without significant symptoms, especially if they are non-smokers.

Liver disease related to AAT deficiency can manifest at any age. In infancy the liver disease commonly takes the form of “prolonged obstructive jaundice.”

AAT deficiency should be suspected in older children, adolescents, or adults with elevated liver enzymes, prolonged clotting tests, enlarged liver and/or spleen, portal hypertension, oesophageal varices, ascites, chronic active hepatitis, or “cryptogenic” cirrhosis.

AAT deficiency is the leading genetic cause of liver disease in infants and children, and is the second most common indication for liver transplantation in this group.

The risk of hepatocellular carcinoma is increased in persons with AAT deficiency. However, the rate of liver disease progression in affected individuals, even those with severe disease, may be relatively slow; some AAT deficient individuals may lead a relatively normal life even if they have abnormal liver function.

Recent evidence suggests that there is some very slight increased risk of liver and lung disease in persons who are Z allele heterozygotes (Pi MZ) although these issues are still under investigation. Liver disease has not been identified in persons with the rare Pi null/null phenotype who do not produce any AAT protein.

## *Genetics of AAT Deficiency*

The accumulated knowledge about AAT deficiency is the result of many studies conducted worldwide. The two most important genetic aspects of AAT deficiency are:

- (1) the understanding that there are many alleles (gene variations) for the protein, and
- (2) that the clinical manifestations (mainly lung and/or liver disease but also panniculitis or pancreatic problems in some rare cases) result from specific combinations of alleles.

A pair of alleles at the proteinase inhibitor (Pi) locus controls the synthesis of AAT. The genes are inherited as co-dominant alleles (products from both genes can be found in the circulation, except for the null genes). AAT in the serum can be characterised by phenotyping (identifying the expressed AAT proteins in the body); this is accomplished by isoelectric focusing. There are more than 90 different allelic variants of AAT, but many of these are quite rare.

Phenotype	What Does It Mean?
Pi Z (ZZ) (Homozygote)	Patient HAS alpha-1 antitrypsin deficiency
Pi MZ (Heterozygote)	Patient is a CARRIER of alpha-1 antitrypsin deficiency and can pass the altered gene on to his, or her, children
Pi M (MM) (Homozygote)	Patient does not have alpha-1 antitrypsin deficiency

*Please note that phenotyping for AAT deficiency is very complicated. When we refer to the “phenotype” in this disorder we are referring to the protein TYPES. The most common variants of AAT deficiency are discussed in detail below; there are also many other possibilities.*

For this reason it is easier to group the variants into categories:

- (1) normal variants of AAT (those that produce and distribute AAT normally in the serum) and
- (2) deficient variants (those that produce reduced or no AAT levels in the serum) which lead to an increased risk of AAT deficiency related lung, liver, and other problems.

## Common Alleles:

The family of the normal AAT alleles is referred to as M. The M alleles are the most common types of AAT gene and result in normal amounts, and normal functionality, of AAT in the blood. About 93% of the population in the UK has only M alleles. There are other normal alleles, and at least four identified variants of the M allele.

The most prevalent type of deficient allele associated with AAT deficiency is the Z allele. More than 95% of individuals with AAT deficiency have phenotype Pi Z (i.e. express only the Z variant in the plasma). There are at least 20 other rare allele variants that comprise the rest of the 5% of the AAT deficient population. The Z variant is subtly abnormal as an inhibitor of neutrophil elastase. However, the most striking abnormality in affected individuals is that circulating levels of the protein are only 10-15% of normal.

When the livers of these individuals are examined the hepatocytes contain an abnormal accumulation of AAT.

The Pi Z type of AAT cannot be released effectively from liver cells. As a result, the levels in the blood are decreased and the retained AAT increases the risk of injury to the liver.

A Pi allele associated with mild AAT deficiency is the S allele producing the S variant protein. The S mutation is not associated with intracellular accumulation of the protein, and the S protein inhibits elastase almost as normal.

Individuals with Pi S phenotype do not appear to be at an increased risk for lung or liver disease (Pi S individuals who are heterozygous with the Z allele are discussed further below).

Another allelic variation is represented by the null alleles. The null allele expresses no AAT in the blood. Note that in Pi Z individuals isoelectric focusing reveals only an abnormally migrating Pi Z type AAT. These individuals may be either Pi ZZ homozygotes, or Pi Z/null heterozygotes since no AAT attributable to the null gene can be found in the circulation to phenotype it.

There has been no evidence of liver disease in the Pi null/null population. Also, in cases of Pi M phenotypes associated with low levels of AAT there may be a possibility that a null allele might be present. Family studies of the pattern of inheritance, and further documentation, are necessary to distinguish between the possibilities.

## **Common Heterozygotes:**

Pi MS individuals have one normal allele and one S allele. They have nearly normal levels of AAT. They do not appear to be at an increased risk for lung or liver disease. Pi MZ individuals have one normal allele and one Z variant (the classic deficiency variant). They usually have decreased levels of AAT in their circulation; however, their levels can also fall within the normal range.

Although this issue remains under investigation, recent studies suggest that Pi MZ heterozygotes may have a very slight increased risk for developing clinically important lung or liver disease. At present though, it seems prudent to reassure Pi MZ heterozygotes regarding their potential risk for developing lung or liver disease, and to counsel them about the risk of genetic transmission of the deficient allele. You should recommend that the patient avoid tobacco smoking.



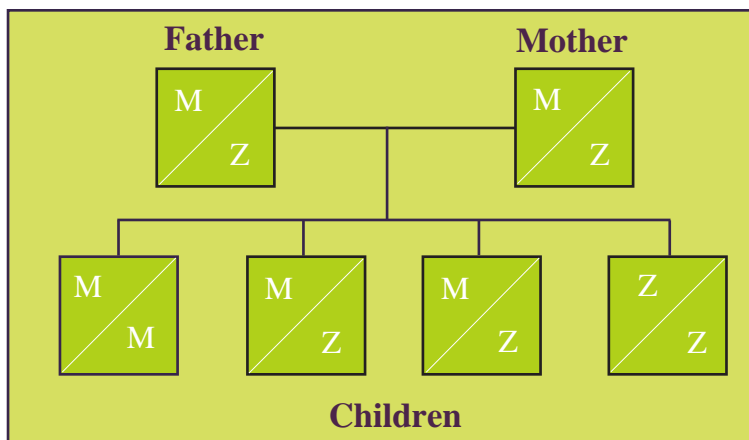
Pi SZ individuals have one allele for the S variant and one for the deficient Z variant. Again there is uncertainty about whether this represents a risk factor as the alpha-1 level is generally higher than the critical threshold thought to increase risk of lung disease. However, research about this is still ongoing. As for persons who are Pi MZ, Pi SZ individuals should be counselled about the risk of genetic transmission of the deficient allele. They should also avoid tobacco smoking.

## Genetic Transmission:

Genetic transmission of AAT deficiency follows simple Mendelian principles. Individuals with AAT deficiency have two deficient alleles for the protein (e.g. Z and/or null allele). Thus, the deficiency is inherited in a similar way to an autosomal recessive condition. Brothers and sisters of deficient individuals have a significant chance of also having the condition. Children of deficient individuals are usually heterozygous (a “carrier”) for the deficiency (assuming the patient’s spouse is Pi M). Among UK Caucasians approximately 3% are carriers. These people may have slightly reduced levels of the protein, but usually have minimal risk of lung or liver disease. Phenotyping is necessary to reliably detect carriers since AAT levels of normal individuals and carriers overlap to some extent.

## For example:

AAT deficiency is a genetic disorder. Look at the figure below to see the possible combinations for children if both parents are carriers of an abnormal AAT gene.



<b>Normal</b>	<b>(MM)</b>	Does not have the disorder and does not carry any altered AAT genes.
<b>Carrier</b>	<b>(MS)</b>	It is not a recognised risk factor but does include an altered AAT gene.
<b>Carrier</b>	<b>(MZ)</b>	Mild to moderate AAT deficiency - very slight increased risk of developing abnormal lung function but usually no increased risk of symptoms and does carry an altered AAT gene.
<b>AAT Deficiency (SS)</b>		It is unlikely that there is a risk for developing disease symptoms. Does carry two altered AAT genes.
<b>AAT Deficiency (SZ)</b>		Moderate deficiency - whether the SZ type increases the risk of lung disease remains unlikely but does include two altered genes.
<b>AAT Deficiency (ZZ)</b>		Severe deficiency - could develop lung and/or liver disease and does include two altered AAT genes.
<b>AAT Deficiency (null/null)</b>		Severe deficiency - could develop lung disease but is not thought to be at risk of liver disease. Does include two altered genes that produce no alpha-1 antitrypsin.



# Diagnosis

## Family History:

A positive family history of AAT deficiency is the greatest risk factor for AAT deficiency. The implications for finding ALL family members who may be carriers are of great importance.

## Identification of Patients:

Adult patients with the following problems should be tested, as recommended by the World Health Organization (WHO):

- COPD
- adult onset diagnosis of asthma
- family history of AAT deficiency
- chronic liver disease

Other conditions possibly indicating an increased risk for AAT deficiency include:

- bronchiectasis
- panniculitis
- unexplained vasculitis, particularly of Wegener's granulomatosis type

It is important to understand that if these conditions are seen in non-smokers of any age, or if COPD occurs at an early age (age 30 to 55) in smokers, the likelihood of AAT deficiency is increased.

## Testing:

In general, testing for Alpha-1 begins by first checking the AAT serum levels. This is followed by phenotyping, if necessary. Phenotyping is performed:

- (1) if the level AAT is abnormal, and/or
- (2) there is a known family history of AAT deficiency, and/or
- (3) there is otherwise unexplained liver disease or emphysema.

Individuals found with a serum level of  $11\mu\text{M}$  or less, or a deficient phenotype, are considered to have AAT deficiency and be at risk for developing lung disease. Newer testing methods utilise a finger stick test that measures both AAT levels and genotype (type of AAT gene in DNA).

## Phenotype & AAT Deficiency Risk

Phenotype	Serum AAT Range ( $\mu\text{M}$ )*
Pi M	20 - 48
Pi MZ (heterozygotes)	12 - 35
Pi S	15 - 33
Pi SZ (heterozygotes)	8 - 19
Pi Z	2.5 - 7.0
Pi null	0

### Assessing Patients At Risk:

After confirming the AAT deficiency status of your patient you may wish to consider the following:

- physical examination
- postero-anterior (PA) and lateral chest x-ray or a high resolution CT of the lungs
- pulmonary function tests including:
  - spirometry (before and after inhaled bronchodilator)
  - lung volumes
  - diffusion capacity
  - arterial blood gases
- liver function tests (ideally performed annually) including:
  - AST
  - ALT
  - alkaline phosphatase
  - total and direct bilirubin
  - albumin, clotting studies (PT, INR, PTT)
  - liver ultrasound examination
  - alpha fetoprotein

# *Treatment*

There are several forms of treatment listed in this guide for the confirmed AAT deficient patient including these four major areas: lifestyle modification, drug therapy for lung problems, specialised therapy for AAT deficiency, and surgical options.

## **Lifestyle Modification**

Individuals with AAT deficiency should NEVER smoke. Evidence shows that smoking tobacco products significantly increases the risk and severity of emphysema in AAT deficient individuals, and may decrease life span by ten years or more. Exercise and nutritional plans can help maintain a healthier body which places less stress on the lungs. These three issues are explored in further detail below:

### **1. Smoking Cessation**

This is the first priority in managing patients with AAT deficiency. Lifelong non-smokers will have a good chance of avoiding serious lung disease, even with AAT deficiency, and are likely to have a normal life span.

Current smokers should stop smoking upon diagnosis since the most severe lung function impairment is seen in current or former smokers. Smoking attracts large numbers of white blood cells to the lungs and speeds the development of lung disease. The lungs of AAT deficient patients do not have the normal defences against neutrophil elastase from the white blood cells.

### **2. Avoiding Environmental Pollution**

Formal studies do show a small influence on lung function so, it is probably advisable for Alpha-1 patients to avoid occupational and environmental pollutants that can be inhaled (including pollen, dust, agricultural sprays, smoke etc.). These substances can cause further irritation of the lungs and worsen the current condition of patients with disease.

Patients should avoid both indoor and outdoor air pollution such as particulates smaller than 10  $\mu\text{m}$  (found in higher industrialised urban regions), and exposure to chemicals. It is also important to realise that your patient(s) may encounter pollutants and infections both at home and at work so recommend precautions in both places.

## ■ In the Workplace

Patients should avoid exposure to inorganic or organic dust (i.e. coal, hay, etc.) or irritating gasses (i.e. chlorine, isocyanates, etc.). Your patients should seek the healthiest possible work environment with clean indoor air and proper ventilation.

Recommend wearing protective clothing i.e. gloves etc. when handling any type of chemical compounds since they may be absorbed through the skin, and could further damage an already compromised liver. Advise patients to read labels carefully and to be aware of potential dangers from these substances.

## ■ In the Home

Advise your patients to avoid certain household chemicals including:

- respiratory irritants such as products in aerosols and sprays - air fresheners and perfumes can also be a problem
- chlorine and ammonia (found in common household cleaning products)
- pesticides

Since bacterial and viral infections are harmful to the lungs recommend that your patients try to avoid contact with sick or infectious people. Remind them that handwashing with an antibacterial soap, or gel, is the single most effective way to avoid both contracting and spreading infectious diseases.

## 3. Development of an Exercise Programme

Although formal studies are lacking, routine exercise can improve mental outlook, stamina and physical well being. Exercise is essential to all those with Alpha-1. Patients should start exercising slowly and increase levels over time as tolerance increases. Some physicians recommend the use of a small pulse oximeter during exercise.

A Pulmonary Rehabilitation course is highly recommended for Alpha-1 patients. These can help an individual with pulmonary disease through exercise, breathing retraining, education, smoking cessation, and nutritional advice. Many participants find that their exercise tolerance increases dramatically over the course.

## 4. Alcohol Consumption

Excessive alcoholic consumption can damage the liver even in normal people. However, there is no evidence to suggest that moderate consumption (within government guidelines) increases the risk of liver damage for ZZ patients. Those who already have clinical evidence of AAT related liver damage should be warned of the potential dangers.

## 5. Development of a Nutrition Programme

Although there is a lack of formal research regarding the effects of specific nutritional recommendations, proper eating habits may help to preserve lung and liver function. It is important for your patient to maintain an ideal body weight whether he/she has lung/liver disease or not.

Nutritional needs may need to be supported in those patients exhibiting liver complications due to AAT deficiency. Sodium and protein intake can become a concern in those with liver failure. Fat absorption may be altered and it may be necessary to supplement the diet with Vitamins A, D, E, and K.

A special formula is often recommended for an infant experiencing feeding difficulties which result in poor growth and a failure to thrive.



Recommend to your patients that they should establish, or maintain, good eating habits. If your patient has lung and/or liver problems it may help to work closely with a nutritionist or dietician who will be able to set up an appropriate, individual nutritional plan. Those who are overweight should be encouraged to lose the excess; not only will they be healthier, but having less weight to carry around will alleviate breathlessness to some extent.

In the other extreme, Alpha-1 patients can suffer dramatic weight loss due to a combination of general lack of appetite and using many times more calories than a healthy person just to breathe. These patients may not only need nutritional advice but also to have their protein intake increased; meal supplements will add easy to digest calories along with vital vitamins and minerals which may be lacking due to a poor appetite.

## **5. Reducing Stressors**

Persons with AAT deficiency report benefits with stress reduction techniques. There are many relaxation techniques that help in reducing stress. Here are a few:

- breathing exercises
- muscle relaxation
- biofeedback
- positive thinking
- improving sleep patterns
- yoga
- meditation

## **Drug Therapy for Lung Problems**

This is one of the most important types of medical therapy for the newly diagnosed individual with AAT deficiency.

### **1. Vaccinations (influenza/pneumonia)**

It is important for your patient to have a yearly influenza vaccination and a pneumococcal vaccination every five years. Since his/her lungs are vulnerable to pollutants and infections the use of these prophylactic vaccinations is of the utmost importance. Furthermore, your patient may find this the easiest and most convenient type of therapy available.

### **2. Aggressive Treatment of Lung Infections**

Prompt and aggressive treatment of exacerbations is recommended due to the increased neutrophil elastase burden during infection. It is important for you to recommend to your patients that they take action immediately they suspect a lung infection.



Here is a list of common symptoms they should be advised about:

- fever
- increased shortness of breath
- increased coughing (may not be productive)
- chills with fever
- changes in color of sputum

Because the lungs attract more leukocytes when a bacterial infection is present, and the leukocytes release neutrophil elastase, it is important to control lung inflammation and begin treatment as soon as possible. Patients should keep antibiotics and oral steroids in the home and the antibiotics should be taken for episodes where the sputum becomes green.

### **3. Aggressive Evaluation of Liver Complications**

It is important for patients, or parents (in the case of children), to be aware of any indication of complications related to liver disease. Here is a list of common symptoms that may require therapy:

- increased abdominal swelling
- coughing up or vomiting bright red blood
- blood in toilet or nappy
- blackish, purplish or dark coloured stools
- confusion, irritability, unusual crying, disorientation, lethargy
- little or no urine
- dark (tea coloured) urine
- lack of energy, easily fatigued
- fever
- no appetite/refusal to eat or drink
- itching or increased itching
- oedema/swelling of the legs

It is very important to inform patients to carefully read the labels on over the counter medications, and to be certain to mention if alternative medicine (e.g. Milk Thistle) or vitamin supplements are being taken.

## **4. Bronchodilators**

Bronchodilators may be useful in relieving the lung symptoms of AAT deficiency. Depending on the specific medical history, and present condition of the patient, you may advise the use of these medications as in usual COPD.

## **5. Corticosteroids**

Inhaled corticosteroids can be useful as a preventative treatment for exacerbations in AAT deficiency and oral corticosteroids may be helpful during the exacerbations.

## **6. Supplementary Oxygen**

For people who need supplementary oxygen it has been shown to be lifesaving. Oxygen can be important for individuals with low blood oxygen levels whilst exercising, whilst sleeping, during active infections, and/or with progressive destruction of the lung tissue.

For some Alpha-1 patients oxygen is especially important when travelling by air because cabin pressure changes with altitude. A “fitness to fly” test is necessary for anyone with significant lung impairment who is thinking of air travel. It may be necessary for them to arrange oxygen provision for the flight, and if so, they will also need a letter stating that they are fit to fly with oxygen.

## **7. Specialised Therapy for AAT Deficiency**

There is a treatment for AAT deficiency called augmentation therapy. However, it is not a cure; it will not reverse the lung damage that has occurred nor will it treat, or prevent, AAT deficiency related liver problems.

Augmentation therapy, a derivative of human plasma, is the only specific treatment currently available for AAT deficiency. It is used to increase the concentration of AAT in the blood and lungs. However, long term controlled clinical trials have never been done to show that augmentation therapy alters the course of lung disease. As a result the National Institute for Health and Clinical Excellence (NICE) have issued guidelines that augmentation therapy is not recommended for general use in the UK. It is however prescribed on a named patient basis for some patients with Alpha-1 related panniculitis.

This therapy is widely available in the US and many European countries, and it is hoped that eligible Alpha-1 patients in the UK will be able to receive the treatment before too long. At the present time there are also ongoing trials of an inhaled form of augmentation therapy which could potentially be an alternative for some patients in the future.

If augmentation therapy becomes available for UK patients the criteria for eligibility will follow the strict criteria that are being established for overseas patients already receiving the treatment.

## **Clinical Criteria for Use**

Currently, augmentation therapy can only be prescribed for patients with AAT deficiency related emphysema (and some cases of panniculitis). This is not a treatment option for AAT deficiency related liver disease.

Augmentation therapy cannot be recommended for individuals with normal lung function. It should be reserved for those patients with lung problems that are progressing in spite of stopping smoking and who have phenotypes Pi Z, Pi Z/null, Pi null, and/or patients who have AAT serum levels < 11  $\mu$ M. It is not given to those individuals with mildly deficient phenotypes.

## **Safety of Augmentation Therapy**

Augmentation therapy is prepared from pooled human plasma that has been screened for known viruses including Hepatitis A, B and C, and tested for HIV and Aids. As an additional precaution against transmission of infectious agents the product is heat treated during the manufacturing process. For further protection, administration of the hepatitis B vaccine is recommended prior to therapy.

## **Known Side Effects**

- There are relatively few side effects reported; headaches, myalgias, arthalgias, and low back pain are the most frequent complaints by patients on therapy, but these usually require no treatment, or just occasional analgesic use. For patients with severe COPD, or heart failure, worsening of shortness of breath may occur if the infusion is given too quickly.
- It is important to be aware that patients who have both AAT deficiency and IgA deficiency can develop acute anaphylaxis when given augmentation therapy. Therefore these patients should NOT receive the treatment.

## Surgical Options

Lung surgery may be an option for some people with certain types of COPD. This could involve removing a section of the lung that is no longer working in order to give the remaining lung more room to expand. This is called lung volume reduction surgery (LVRS). This type of surgery works best in people who have disease that is worse in the upper lobes of their lungs. For this reason it often isn't suitable for AAT patients whose emphysema is usually in the lower lobes, or equally spread throughout the lungs.

Lung/liver transplantation is becoming a viable option for some patients. As experience with new surgical techniques (particularly single lung transplantation) increases, transplantation may become more attractive to AAT deficient patients with end stage lung or liver disease.

If oesophageal varices become a problem any of the techniques described below may be used to correct the cause of bleeding.

- Banding – an endoscopy is carried out and a small band is placed around the base of the varices to help control the bleeding.
- Injection sclerotherapy – following an endoscopy a substance is injected into the varices to make the blood clot and scar tissue to form which helps to stop the bleeding.
- Sengstaken tube with a balloon on the end – this is another option if bleeding cannot be stopped using an endoscopy. The tube is passed down the throat into the stomach and the balloon is inflated putting pressure on the varices and stopping the bleeding.
- A transjugular intrahepatic portosystemic stent shunt (TIPSS) – this procedure may be used if bleeding cannot be controlled using the above methods. A stent is passed across the liver to join the portal vein and the hepatic vein. This creates a new route for the blood to flow through thereby relieving the pressure that causes the varices.

As with all surgery the outcome depends on a number of issues specific to each person. There are no guarantees for the extent to which there will be an improvement in medical condition.

## Other Issues

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*Once your patient is diagnosed as having AAT deficiency he/she may feel overwhelmed and have many questions. To provide a more comprehensive approach to talking with your patient about the ramifications of an AAT deficiency diagnosis, beyond a purely medical discussion, it may be helpful to review the following material.*

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The purpose of this section is to give you several scenarios that may arise when dealing with an AAT deficient patient. Each scenario is merely a starting point. Contacting the resources at the end of this guide will provide your patient(s) with more in-depth support, and strategies for addressing each situation, from the perspective of a person living with AAT Deficiency. These topics include:

1. psychological and family support
2. employment
3. confidentiality

### 1. Psychological and Family Support

The most useful step the patient can take is to reach out for support and contact one of the resources listed at the end of this guide. These organisations exist to help people affected by AAT deficiency throughout the UK and beyond. Patients, their families, friends and carers can speak to, and even meet, other people with AAT deficiency. This can provide valuable support, and will also provide a source of additional information.

Remember to reassure your patient that you are there to assist them along the way and will answer any questions that come up. Getting actively involved with the overall treatment of the patient, which will extend into other aspects of the patient's life, is of the utmost importance.

**Q:** Should I encourage my patient to discuss AAT deficiency testing with other family members?

**A:** We recommend, after discussion with you about the discriminatory issues surrounding AAT deficiency, that they inform family members about the genetic aspects of AAT deficiency and encourage them to seek genetic counselling. Those who have symptoms, as noted in the WHO recommendations, should be encouraged to be tested.

Other family members should be urged to educate themselves about the disorder, and be vigilant for the development of symptoms.

### **Example:**

If both parents are carriers each child has a 1 in 4 chance of inheriting AAT deficiency, a 1 in 2 chance of being a carrier of AAT deficiency, or a 1 in 4 chance of having both normal genes.

## **2. Employment**

**Q:** Can your patient continue to work?

**A:** The answer to this question usually depends on two conditions:

- (1) the present state of your patient's health, and/or
- (2) the possibility of unwanted airborne exposures (i.e. dust, fumes or other environmental hazard) at work.

It is good for Alpha-1 patients to work, if at all possible. If your patient is in acceptable health and has no occupational exposure to dust and fumes, or other contraindications, then they can continue to work. Otherwise, you may suggest the possibility of him/her changing jobs to reduce these exposures.

If your patient is too ill to work and needs financial advice about insurance policies or claiming disability benefits then we recommend that they should be referred to the Citizens Advice Bureau.

## **5. Confidentiality**

Establishing and maintaining confidentiality in the doctor-patient relationship is always the best way to have the trust of your patients. Breaching this trust can produce devastating results. You should discuss the following confidentiality issues with your patient:

**Q:** Who will know the patient's AAT deficiency diagnosis?

**A:** The results of the test will be included in a patient's medical record. Although generally treated as confidential, inform the patient that doctors, nurses and other health professionals involved in their care will have access to the information. Insurance companies may ask for details, with signed permission, (although at present genetic testing cannot be used to set insurance premiums). There may also be legal reasons why access can be given.

**Q:** To whom should (or must) the patient disclose the AAT deficiency diagnosis?

**A:** Patients must make their own decisions about discussing this information. However it is highly recommended that the patient tells his/her blood relatives about the risk and urge them to seek testing. Patients should inform future healthcare providers, and inform insurance companies if there is a change in policy or they are seeking new cover (although at present genetic testing cannot be used to set insurance premiums).

### Notes:

Finding out about an AAT deficiency diagnosis can be an overwhelming and potentially upsetting experience. It is important for the patient to share this information with his/her family, and to seek professional psychological counselling if necessary. Each newly diagnosed patient should be encouraged to seek more information and support. It is recommended that your patient get more information as soon as possible after diagnosis by talking with persons living with AAT deficiency, and to identify support for himself/herself and family members.

## Counselling

The objectives of this guide are to increase physician awareness of AAT deficiency and also to promote screening of patients at risk. It is important for you to be able to explain the disorder in a clear and concise manner and encourage testing of your patients at risk. Through a simple blood test you can identify affected patients (results take around six weeks). Following are scenarios that were developed to assist you in encouraging screening, giving test results, and explaining the various aspects of an AAT deficiency diagnosis.

### Promoting Screening

#### Objective: Request Blood Sample

*“As one of my patients with a diagnosis of (emphysema, COPD, bronchiectasis, liver disease etc.) I am advising you to consider being tested for the genetic disorder alpha-1 antitrypsin deficiency.*

*“AAT deficiency is believed to affect as many as one in every 3,000-5,000 people in the UK making it one of the most common genetic disorders in the country. Since AAT deficiency was only recently discovered there is much to learn about its frequency, severity, treatment, and prevention. I am advising you to consider this test because this information will be important to help me take better care of you as a patient. By taking the test you will learn whether or not you have this genetic disorder. Early detection of AAT deficiency is very important because there are medical interventions I can prescribe that may help to prevent, or prolong the time before, further damage to your lungs/liver occurs. I can discuss these interventions with you.*

*“The only way to be tested for AAT deficiency is to have a blood test which may cause a little mild discomfort and possibly a bruise. The results generally require a six week period of time to come back. Once they are back I will ask you to come in for a follow up visit to discuss the findings.*

*“There are ways your life could be affected by learning information that may be discovered by positive genetic testing. There may be additional risks, including emotional distress, which I cannot predict at this time. All of these issues should be carefully considered prior to being tested. Your choice to be tested is totally voluntary and you are free to refuse to be tested at any time. As your doctor I would be happy to answer any questions concerning AAT deficiency and your possible risk.”*

## **Giving Test Results**

### **Alternative A**

#### **Objective: Explain a Negative Test Result (Pi M) for AAT Deficiency**

*“After reviewing the results of the blood test we performed at your last visit, to determine if you had the inherited genetic disorder alpha-1 antitrypsin deficiency, I am pleased to inform you that the results were negative. This means that you have enough alpha-1 antitrypsin in your blood, and this indicates that you do not have the disorder.”*

### **Alternative B**

#### **Objective: Explain a Carrier Test Result (Pi MZ or Pi MS) for AAT Deficiency**

*“After reviewing the results of the blood test we performed at your last visit to determine if you have the inherited genetic disorder alpha-1 antitrypsin deficiency, I must inform you that the results were positive for a special state of the disorder known as the carrier state.*



*Carriers (heterozygotes) have one normal gene and one gene for the disorder. This combination of genes does not\* typically cause health problems. Currently the risk of lung or liver problems for yourself appears to be low.*

*“However it is recommended that you should inform your blood relatives of the test result because of the genetic nature of the disorder. Since AAT deficiency is passed genetically from parents to child it is possible that your blood relatives could be carriers such as yourself, or have AAT deficiency. Another important aspect of this test result is that you can pass on the gene to your children. It is also very important that you avoid all tobacco smoke, either from smoking yourself or passive smoking.”*

\*Although this issue remains under investigation, recent studies suggest that Pi MZ heterozygotes may have an increased risk for developing slightly lower lung function or possibly liver disease. At present though, it seems prudent to reassure Pi MZ heterozygotes regarding their potential risk for developing serious problems.

## **Alternative C**

### **Objective: Explain a Positive Test Result (Pi Z) for AAT Deficiency and its Consequences Adult Patient - Pulmonary Disease**

*“After reviewing the results of the blood test we performed at your last visit to determine if you had the inherited genetic disorder alpha-1 antitrypsin deficiency, I must inform you that the results were positive for the disorder. The amount of alpha-1 antitrypsin in your blood is low, and it is slightly different from the normal type. This test result explains some of the health problems that you are experiencing (or have experienced) including [symptoms specific to this patient, i.e. coughing, wheezing, shortness of breath etc.].*

*“I know that this can be upsetting news due to the impact that having this disorder may have on your health. However, with lifestyle modifications such as not smoking, exercise, nutrition, drug therapy, medical treatments and preventive measures, Alpha-1 patients can, and do, lead full lives and enjoy relatively stable lung function. Before we go into the explanation of what this means and the questions you may have let me review the information we have about Alpha-1 at the present.”*

## **A. Explain**

- the course of alpha-1 antitrypsin deficiency
- the progression of alpha-1 antitrypsin deficiency
- consequences, including the genetic risk to the patient’s family

- B. Schedule the next patient visit; and**
- C. Complete the Treatment Checklist**
- D. Provide information**

## **Alternative D**

### **Objective: Explain a Positive Test Result Pediatric Patient - Liver Disease**

*“After reviewing the results of the blood test we performed at your last visit to determine if your child had the inherited genetic disorder alpha-1 antitrypsin deficiency, I must inform you that the results were positive for the disorder. The amount of alpha-1 antitrypsin in your child’s blood is low, and it is slightly different from the normal type. However, your child’s liver disease is not due to this low level of AAT in the bloodstream. Research studies indicate that these liver complications are the result of the abnormal protein becoming trapped in the liver instead of being released into the bloodstream as it should be.*

*“This build up of AAT in the individual liver cells causes damage. At this time there is no specific treatment for liver disease associated with AAT deficiency. Clinical care is primarily supportive management of any liver dysfunction and the prevention of complications. Each child is an individual and treatment is highly individual. The majority of children diagnosed with AAT deficiency have a low rate of disease progression and lead a relatively normal life for extended periods of time, and they often grow out of liver problems as they get older. A very small percentage of liver affected children do need a liver transplant at some point but it is difficult to say if your child will definitely need a liver transplant at this stage.”*

## **Explain**

- the course of alpha-1 antitrypsin deficiency
- the progression of alpha-1 antitrypsin deficiency
- consequences, including the genetic risk to the patient’s siblings (if appropriate) and other family members

- B. Schedule the next patient visit; and**
- C. Complete the Treatment Checklist**
- D. Provide information**

## *Treatment Checklist for AAT Deficiency*

Many patients will experience emotional upset and anxiety due to their diagnosis. It may be necessary to schedule an additional visit in order to complete the discussion about recommended medical treatment and lifestyle changes.

- ☐ Discuss testing (with subsequent follow up).
- ☐ Discuss requirement for lung function tests (FEV1, etc.).
- ☐ Discuss need for liver evaluation or referral to a liver specialist (Paediatric or Adult).
- ☐ Discuss need for lung evaluation or referral to a respiratory specialist.
- ☐ Discuss the use of drug therapy for lung problems.
- ☐ Use of bronchodilators.
- ☐ Use of corticosteroids.
- ☐ Aggressive treatment of lung infections.
- ☐ Discuss aggressive treatment of liver complication symptoms.
- ☐ Discuss need for vaccinations:
  - ☐ Influenza (annual).
  - ☐ Pneumococcal (every five years).
- ☐ Assess smoking status and give a strong message to quit if patient smokes any form of tobacco including cigars and cigarettes.
- ☐ Discuss risk of occupational and environmental exposures including second hand tobacco smoke and dusts.
- ☐ Avoid being around individuals who are ill with the 'flu or a cold etc.
- ☐ Discuss alcoholic beverage consumption.
- ☐ Discuss developing an exercise programme.
- ☐ Discuss developing a nutrition plan.
- ☐ Discuss reducing stressors.
- ☐ Discuss referring patient to a counsellor (if necessary).
- ☐ Refer patients to the resources listed at the end of this guide.
- ☐ Discuss requirement of follow up visits.
- ☐ Discuss use of supplementary oxygen (if necessary).
- ☐ Discuss surgery options (if appropriate).

## *AAT Deficiency Resources, Groups and Community Organisations*

Throughout the world there are many specialised centres for research into alpha-1 antitrypsin deficiency. In the UK the primary centre is the **ADAPT** Project (Antitrypsin Deficiency Assessment and Programme for Treatment) at Queen Elizabeth Hospital Birmingham. Here patients usually attend on an annual basis and the team help manage and advise about the condition. In addition they undertake further research and the development of new treatments for Alpha-1 lung affected patients.

Patients are monitored in depth by specialist lung function tests, liver function tests, physical examinations and psychological and health questionnaires.

The team are happy to work with patients' GPs and Consultants by sending full reports and discussing recommendations for treatment options. If your patient has phenotype Pi Z, PiSZ, Pi Z/null, Pi null null, and/or has AAT serum levels  $< 11 \mu\text{M}$  you may consider referring him/her for assessment.

### **ADAPT Project**

Lung Function and Sleep Department  
Outpatients, Ground Floor  
Queen Elizabeth Hospital Birmingham  
Mindelsohn Way  
Edgbaston  
Birmingham  
B15 2WB



Telephone: **0121 371 3885**

Fax: **0121 371 3887**

Many patients, their families, carers, and friends, benefit from being in touch with others who are living, and coping, with the same issues. The following are organisations that can bring AAT deficient patients together to share experiences, hints and tips for making life easier, as well as keeping them up to date with research and new treatments as they become available.

## **Alpha-1 UK Support Group**

50 Wenning Lane  
Emerson Valley  
Milton Keynes  
Buckinghamshire  
MK4 2JF



Website: **[www.alpha1.org.uk](http://www.alpha1.org.uk)**

Email: **[infoalpha1uk@gmail.com](mailto:infoalpha1uk@gmail.com)**

**Patron Prof. R.A.Stockley MD, D.Sc., F.R.C.P. (ADAPT)**

We are registered UK charity providing support and education for patients, families, carers and friends who are affected directly or indirectly by alpha-1 antitrypsin deficiency. We provide social network discussion groups for patients, focusing on how better to cope with their condition, aiming towards improving quality of life. We help inform and educate the medical community and general public through generating awareness of alpha-1 antitrypsin deficiency genetic lung, liver and skin disease. We campaign for better access to treatment for Alpha-1 patients.

## **British Lung Foundation**

73-75 Goswell Road  
London  
EC1V 7ER

Website: **[www.blf.org.uk](http://www.blf.org.uk)**

BLF Helpline: **03000 030 555**



One person in five in the UK is affected by lung disease. Millions more are at risk. We are here for every one of them, leading the fight against lung disease. We support people affected by lung disease, so that no one has to face it alone. We promote greater understanding of lung disease and we campaign for change in the nation's lung health. We fund vital research so that new treatments and cures can help save lives.

## **British Liver Trust**

2 Southampton Road  
Ringwood  
BH24 1HY



Website: **[www.britishlivertrust.org.uk](http://www.britishlivertrust.org.uk)**

Free Helpline: **0800 652 7330**

General enquiries: **01425 481320**

Fax: **01425 481335**

General Email: **[info@britishlivertrust.org.uk](mailto:info@britishlivertrust.org.uk)**

The British Liver Trust is the leading liver charity in the UK for all adult liver conditions. The Trust works to pioneer liver health and reduce the impact of liver disease through awareness, care and research.

## **Children's Liver Disease Foundation**

36 Great Charles Street  
Birmingham  
B3 3JY



Telephone: **0121 212 3839**

Website: **[www.childliverdisease.org](http://www.childliverdisease.org)**

Enquiries: **[info@childliverdisease.org](mailto:info@childliverdisease.org)**

Formed in 1980, Children's Liver Disease Foundation (CLDF) is a unique national charity dedicated to fighting all liver diseases of childhood. Based in Birmingham, CLDF provides:

- a comprehensive information hub for patients, their families, allied and healthcare professionals and the general public
- a tailored support service for young people with liver disease and their families
- the lead charity supporting medical research into all aspects of childhood liver diseases
- the voice for young people, their families and adults diagnosed with liver disease in childhood

## **What is ADAPT?**

**ADAPT** (Antitrypsin Deficiency Assessment and Programme for Treatment) has been established by research doctors, who have an international reputation for their research into the causes of emphysema, in collaboration with the pharmaceutical company **GRIFOLS**.

**ADAPT**'s mission is to rapidly collect important information about how AAT deficiency affects patients and their families, in addition to being helpful to patients in the understanding and effects of AAT deficiency on their lungs. The information will be critical to the design of clinical studies into the effects of treatment of the disease.

ADAPT Project  
Lung Function and Sleep Department  
Outpatients, Ground Floor  
Queen Elizabeth Hospital Birmingham  
Mindelsohn Way  
Edgbaston  
Birmingham  
B15 2WB

Telephone: 0121 371 3885  
Fax: 0121 371 3887



**ADAPT**





Website: [alpha1.org.uk](http://alpha1.org.uk) - Email: [infoalpha1uk@googlemail.com](mailto:infoalpha1uk@googlemail.com)

Patron Professor R. A. Stockley MD, D.Sc., F.R.C.P.

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