

## Key points

- ▶ AAT deficiency is one of the most common hereditary disorders in Europe and may lead to early-onset pulmonary disease and liver disease.
- ▶ Despite its prevalence, AAT deficiency is under-recognised; >90% of affected individuals may be undiagnosed.
- ▶ Even among those diagnosed, studies have shown a delay of ~8 years between the appearance of pulmonary symptoms and diagnosis.
- ▶ Clinical symptom development varies and can be affected by smoking, as well as by other genetic factors and gene-environment interactions.
- ▶ Augmentation therapy with AAT is effective in slowing the decline in lung function.



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# Diagnosis and management of $\alpha_1$ -antitrypsin deficiency

## Educational aims

- ▶ To increase awareness of  $\alpha_1$ -antitrypsin (AAT) deficiency and to describe the characteristics of this relatively common inherited disorder that can lead to lung disease.
- ▶ To describe methods of patient identification and diagnosis of AAT deficiency.
- ▶ To familiarise the reader with management and treatment options available to AAT-deficient patients.
- ▶ To explain the role of the respiratory professional in the diagnosis and management of AAT-deficient patients.

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## Summary

$\alpha_1$ -Antitrypsin (AAT) deficiency is a genetic disorder characterised by a low serum level of AAT, which predisposes individuals to early-onset pulmonary disease, most commonly emphysema. Although it is one of the most common inherited conditions leading to lung disease, AAT deficiency is an under-recognised condition. It is believed that only ~5% of AAT-deficient individuals have been diagnosed and the vast majority are therefore unaware that they could benefit from lifestyle changes to reduce morbidity (such as smoking cessation), or from the specific therapy that is available. This review describes the role of respiratory professionals in identifying, diagnosing and managing AAT-deficient patients and outlines the therapeutic options available.

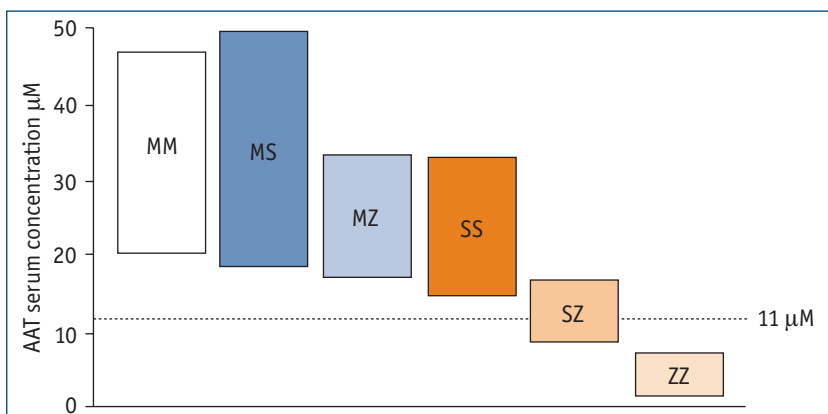
## Pathogenesis

Deficiency of AAT, first described in 1963 [1], is a serious and relatively common genetic disorder affecting the respiratory system. AAT deficiency is the only established genetic risk factor for chronic obstructive pulmonary disease (COPD), and it predisposes to severe panlobular emphysema. It may also cause cirrhosis, liver carcinoma and, less frequently, vasculitis and panniculitis [2].

AAT is produced predominantly in liver hepatocytes and is released into the bloodstream. Diffusion of AAT from the blood enables the protein to enter the lungs, where

it protects alveolar tissue from the proteolytic effect of neutrophil elastase and other damaging proteases. Neutrophil elastase is secreted by neutrophils, which are recruited to the lung in response to infection or inflammation, as part of the innate immune response. Within the lung alveoli, AAT binds neutrophil elastase, resulting in permanent inactivation of the protease.

In individuals with severe AAT deficiency, a structural defect in the AAT protein results in its accumulation in the liver, which can lead to hepatic abnormalities in both adults and children. Insufficient levels of AAT are secreted into the bloodstream and are present in the



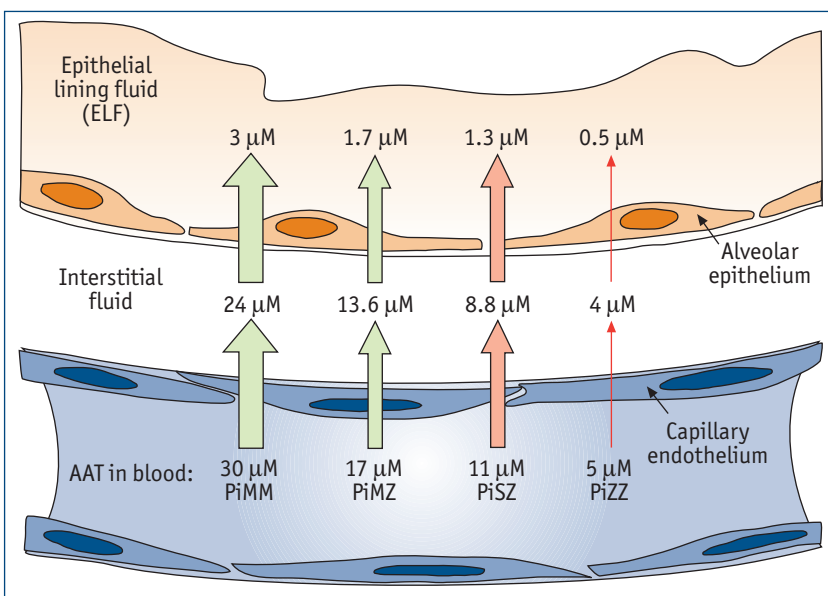
**Figure 1**  
Range of AAT serum levels in various phenotypes. Reproduced from [12], with permission from the publisher.

lung to provide adequate protection against neutrophil elastase. The consequential excess of uninhibited neutrophil elastase in the lungs results in proteolytic damage to the alveoli and pulmonary connective tissue, in particular elastin, which constitutes 10–30% of the fibrous lung structure. Neutrophil elastase also induces the expression of the neutrophil chemoattractant leukotriene B<sub>4</sub>, which is released from airway macrophages, resulting in further neutrophil recruitment and amplified tissue destruction [3]. Individuals with AAT deficiency may be predisposed to early-onset pulmonary disease, most commonly emphysema [4, 5].

## Genetics

AAT deficiency, like cystic fibrosis (CF), is a classic single-gene disorder [6]; the AAT protein is encoded by the protease inhibitor (Pi) locus on chromosome 14, currently referred to as the SERPINA1 gene. In order to be classified as having AAT deficiency, an individual must inherit two

**Figure 2**  
Amounts of AAT that migrate from the blood to the interstitial fluid and to the ELF in individuals with different alleles.



abnormal SERPINA1 alleles. Individuals who have one abnormal and one normal SERPINA1 allele are carriers.

At the protein level, differences in the speed of migration of AAT on gel electrophoresis have been used to identify the protein variants, referred to as the Pi phenotype. The most common variant, with an allele frequency of ~95%, is the normal M-allele variant (PiMM), which is not associated with AAT deficiency [7]. The commonest deficiency variants are S and Z. The frequency of the S allele is highest in southern Europe, peaking in the Iberian peninsula. The S-allele variant is associated with lower-than-normal plasma AAT levels, but only confers a significant risk of developing pulmonary emphysema in smokers and as a heterozygote with the Z allele (PiSZ) [8, 9]. In contrast, the Z allele, most commonly found in northern Europe, is present in ~95% of symptomatic AAT-deficient patients [10]. The Z variant results in more severe AAT deficiency, characterised in the ZZ homozygote by plasma AAT levels of 10% of those found in subjects with the M allele [11]. The Z mutation results in accumulation of AAT in the liver, predisposing the homozygote to juvenile hepatitis, cirrhosis and hepatocellular carcinoma. The resultant lack of circulating AAT protein greatly increases the risk of the homozygote developing panlobular emphysema at an early age. Figure 1 shows AAT serum levels corresponding to the phenotypes of several thousand people who were tested for AAT deficiency [12]. Carriers (*i.e.* PiMZ) have AAT serum levels lower than normal but not below the "protective threshold" of ~11 μM, and their risks of developing clinically significant respiratory symptoms are much lower than the risks associated with severe deficiency.

The amount of serum AAT is directly proportional to the amount of AAT that migrates to the interstitium and the epithelial lining fluid (ELF) of the lungs. Overall, ~80% of the AAT in the serum reaches the interstitial fluid, while 10% reaches the ELF (figure 2).

## Epidemiology

AAT deficiency is one of the most common inherited disorders in Western countries, with a prevalence similar to that of CF [13]. In Europe, between one in 1,600 and one in 2,000 individuals are believed to be affected [13]. In a survey of 21 countries, the number of individuals in Europe with severe AAT deficiency has been

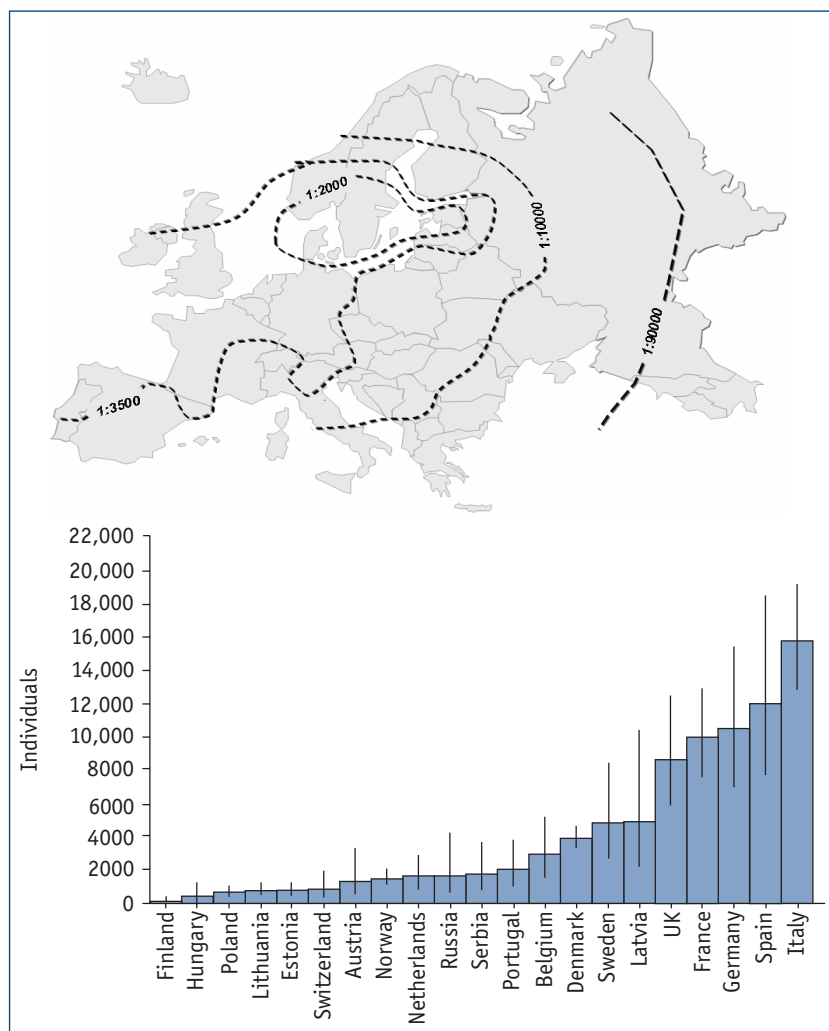
estimated as ~125,000 [13]. The corresponding estimate for the USA is ~100,000 [12]. Some 1–3% of all cases of COPD in the USA may be attributable to severe AAT deficiency [14]. The incidence of severe AAT deficiency peaks in northern European countries, with a decreasing level towards the Mediterranean (figure 3) [13].

Although often regarded as a rare disorder, AAT deficiency is one of the most common inherited disorders in the West, causing considerable morbidity and mortality. This apparent contradiction is explained by the fact that AAT deficiency is, even today, widely under-diagnosed by healthcare providers [5]. In the USA, only ~5,000 cases have been diagnosed, and therefore it is believed that >90% of AAT-deficient individuals have not been identified [14]. In addition to AAT deficiency being under-recognised, there is a long delay before individuals are diagnosed. For instance, a survey of severely AAT-deficient individuals performed in the mid-1990s suggested that, at that time, the diagnosis was made on average 7 years after the first symptoms appeared [15]. The disorder was correctly diagnosed by the first physician to see the patient in only a quarter of cases, and almost half of the patients surveyed saw at least three doctors before they were finally diagnosed. More recent data have shown that the average interval between the onset of pulmonary symptoms and diagnosis was 8.3 years [14]. The diagnostic delay for the entire population is in reality probably much longer, since the patients included in these studies are among the low proportion of those who were eventually successfully diagnosed. The vast majority of AAT-deficient individuals are either not properly diagnosed or are never diagnosed. Reasons for this underdiagnosis include the highly variable clinical symptom development of AAT deficiency; patients can present with respiratory symptoms similar to those seen in COPD or asthma, or have no symptoms at all.

Although many patients are diagnosed in the fourth or fifth decade of life, a considerable number of patients are diagnosed with AAT deficiency in later years. A study of symptomatic AAT-deficient patients by CAMPOS *et al.* [14] showed that 30% of those diagnosed were aged >50 years [14]. A further study showed that older patients experience longer diagnostic delays than younger patients [16].

## Registries

Since guidelines for assessment and diagnosis of individuals with AAT deficiency were first



published in 1989 [17], a number of countries have established detection programmes to identify individuals with AAT deficiency. The countries have then enrolled these individuals in national registries. Most national AAT deficiency identification programmes have adopted targeted detection criteria to identify individuals with a high likelihood of having AAT deficiency (*i.e.* individuals with early-onset COPD, individuals with familial clustering of COPD, relatives of individuals with AAT deficiency, or individuals with low serum AAT levels). A key recommendation of the World Health Organization (WHO) was the establishment of an international registry of AAT-deficient individuals (box 1) [18]. The increase in the number of AAT-deficient individuals included in the Alpha One International Registry (AIR) is shown in figure 4 [19]. Up to March 2006, AIR identified a total of 2,627 people with severe AAT deficiency. This is the largest series of severely affected individuals so far reported. Table 1 shows some of the characteristics of 2,143 of the 2,627 enrolled individuals.

**Figure 3** Distribution of PiZZ prevalence and estimates of numbers of ZZ individuals in 21 European countries. Reproduced from [13], with permission from the publisher.

**Box 1 The Alpha One International Registry (AIR)**

The AIR is a multinational research organisation, founded in 1997 in response to a recommendation from the WHO [18], which aims to continue research into ways of improving patient identification and the treatment of AAT deficiency. Initially, AIR included a group of European countries (the UK, Germany, Denmark, Sweden, the Netherlands, Italy, Spain and Switzerland), together with New Zealand, South Africa, Canada and the USA. Subsequently other countries have joined, including Austria, Belgium, Poland, Finland, Latvia, Lithuania, Australia, Argentina and Brazil. By 2005, AIR included 21 countries over four continents. Each member country holds a national registry of AAT-deficient patients, and sends detailed clinical information about these individuals to an international database in Malmö, Sweden. The information is identified only by a number, and no information can be traced to individuals. Representatives from the member countries meet at least twice annually to discuss AAT research and the progress of AIR. In addition, AIR organises a scientific meeting every 2 years to provide an update on current research into AAT deficiency.

**Low rates of diagnosis**

AAT deficiency is a common hereditary disorder affecting not only Caucasian northern Europeans, but also individuals in many other ethnic and geographical groups [20]. However, healthcare providers do not routinely test subjects who present with COPD or asthma for AAT deficiency.

One of the major problems for clinicians is that AAT deficiency can cause similar respiratory symptoms to those seen in COPD or asthma. Initial symptoms include cough, excess sputum production and wheezing. Symptoms can be intermittent to begin with, and if wheezing is the predominant symptom, patients are often told that they have asthma. Dyspnoea is the clinical symptom that is eventually the most characteristic of AAT deficiency; over time, patients often find that it limits even mild activity. Conversely, many subjects with severe AAT deficiency may exhibit no clinical symptoms [10]. In the USA, it is estimated that only 40,000–60,000 of the ~100,000 individuals with AAT deficiency have symptomatic emphysema [12, 21]. In terms of patient identification, if COPD is seen in non-smokers of any age, or if emphysema occurs earlier than expected in smokers, then the probability of AAT deficiency as the underlying cause is increased [22].

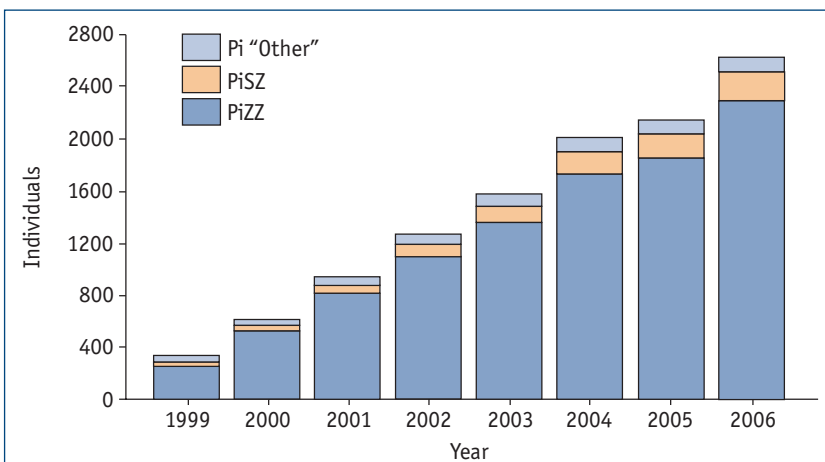
**Genetic and/or environmental modifiers of emphysema risk**

In the case of COPD, while the principal environmental risk factor is smoking, there is generally considerable variability in the susceptibility of individuals to develop symptomatic disease. Although AAT deficiency is a single-gene disease, as described above, the phenotype of the disorder is likely to be the consequence of a number of genes. The highly variable clinical symptom development associated with AAT-deficient individuals may be influenced by genetic factors (*e.g.* modifier genes), environmental exposure or a combination of genetic and environmental factors [23]. For example, male sex has been found to be a significant risk factor for airflow obstruction: males with severe AAT deficiency were found in a recent study to have a significantly lower % predicted forced expiratory volume in one second (FEV<sub>1</sub>) than females (55 *versus* 75%, respectively,  $p < 0.0001$ ) [24]. This trend was seen even in nonsmokers. The same study demonstrated that, in addition to sex, asthma was a risk factor for severe COPD; % pred FEV<sub>1</sub> values were lowest in men with a history of asthma before age 16 (27 *versus* 55% for women who reported asthma in childhood;  $p = 0.03$ ) [24].

Personal cigarette smoking, passive smoke exposure, particularly as a child, and mineral dust exposure are all environmental factors that can affect symptom development and progression of lung disease [25–27]. Personal smoking has the most pronounced effect on the clinical manifestation of AAT deficiency (see below) and, since the susceptibility of AAT-deficient individuals to the effects of cigarette smoke varies, this would suggest that individuals could also be genetically predisposed to developing certain disease characteristics. This is an example of a gene–environment interaction. To illustrate this point, AAT-deficient individuals who smoke develop obstructive lung disease at an earlier

**Figure 4**

Cumulative increase of the AIR. By March 2006, a total of 2,627 AAT-deficient individuals (2,285 PiZZ, 218 PiSZ and 124 other rare AAT-deficient phenotypes) were included in the register. Reproduced from [19], with permission from the publisher.



age than nonsmoker or ex-smoker AAT-deficient individuals, and the deterioration in lung function is more rapid [28, 29]. However, the age of onset of airflow obstruction and symptom development varies between AAT-deficient smokers, some of whom have normal lung function.

## The pivotal role of respiratory professionals

The substantial burden associated with AAT deficiency was highlighted recently in a North American survey of almost 2,000 individuals with AAT deficiency [30]. Data compiled from these individuals showed that 50% of respondents considered their health status to be less than good, with 81% reporting COPD with symptoms of asthma, chronic bronchitis and emphysema, usually in combination. Overall, quality of life was diminished and 16% of those surveyed had received, or were awaiting, lung or liver transplants.

Respiratory professionals frequently care for symptomatic individuals who might be AAT-deficient and can therefore play a role in increasing the number of individuals who are tested for AAT deficiency. The methods for investigating and diagnosing AAT deficiency are, initially, laboratory tests such as immunoassays and nephelometry, which measure serum AAT levels. AAT genotype testing can be performed using PCR. Over the past few years, screening for AAT deficiency has been made easier and more convenient by using dried blood-spot specimens on filter paper, thus avoiding the need to take blood intravenously [31, 32].

## Clinical recommendations from the ERS and ATS

The publication of a standards document regarding management of individuals with AAT

**Table 1** Characteristics of AAT-deficient subjects included in the AIR.

Subjects n	2,143
Male %	55
Mean age years	49.8
Ascertainment %	
Lung/liver disease	68.8
Family screening	19.2
AAT deficiency phenotype	
PiZZ	86.2
PiSZ	8.5
Rare AAT deficiency alleles	5.3
Smoking status %	
Never	30
Former	60
Current	10

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deficiency has important consequences for respiratory specialists. The guidelines of the European Respiratory Society (ERS) and the American Thoracic Society (ATS), published in 2003 [12], recommend testing for AAT deficiency in all symptomatic adults with COPD, emphysema or asthma with airflow obstruction that is incompletely reversible. They also recommend testing of asymptomatic individuals with persistent obstruction on pulmonary function tests and risk factors for the disorder (*e.g.* smoking), together with other groups of individuals (box 2) [12].

The hereditary nature of AAT deficiency has consequences for testing. A positive diagnosis for a defective gene in one individual is likely to mean that close relatives have the disease or are carriers of the disorder. The ATS/ERS guidelines state that family members should be made aware of their increased risk for AAT deficiency and the genetic test, as well as the implications of a positive test result, should be explained. Informed consent should then be obtained from individuals before they are tested.

### Box 2. ERS and ATS guidelines.

Current recommendations include the diagnostic testing of the following individuals:

Symptomatic adults with:

    Emphysema

    COPD

    Asthma with airflow obstruction that is incompletely reversible after aggressive treatment with bronchodilators.

Asymptomatic individuals with persistent obstruction on pulmonary function testing with identifiable risk factors (*e.g.* cigarette smoking, occupational exposure).

Individuals with unexplained liver disease (including neonates, children and adults, particularly the elderly).

Adults with necrotising panniculitis.

Siblings of individuals with AAT deficiency.

### Useful weblinks

The Alpha One International Registry  
[aatregistry.org](http://aatregistry.org)

ATS/ERS Statement: Standards for the diagnosis and management of individuals with AAT deficiency  
[www.ersnet.org/ers/lr/browse/viewPDF.aspx?id\\_attach=7550](http://www.ersnet.org/ers/lr/browse/viewPDF.aspx?id_attach=7550)

## Avoiding additional risk factors

For individuals diagnosed with AAT deficiency, respiratory professionals can impart essential information to avoid the risk factors for the disorder. This in turn may translate into substantial health benefits. Cigarette smoking causes inflammation in the lung, resulting in an increase in neutrophil elastase and the risk of pulmonary damage. Each cigarette smoked results in the utilisation of all the AAT present in the lungs at the time, and for AAT-deficient patients, whose protection against neutrophil elastase is already compromised, the exposure to cigarette smoke increases the risk of pulmonary damage and the development of significant symptoms of lung disease. In terms of life expectancy, PiZZ individuals who smoke cigarettes are reported to die 20 years earlier than PiZZ nonsmokers [33]. Although cigarette smoking is recognised as a controllable risk factor, it is clear that, in many cases, it is not an easily avoidable one. Encouragingly, evidence suggests that if smokers are diagnosed as being severely AAT deficient, this may motivate them to quit [34, 35].

Respiratory professionals can also provide advice on the avoidance of environmental pollutants: particulates smaller than 10  $\mu\text{m}$  can cause lung irritation and worsen the clinical condition of AAT-deficient patients [36]. For AAT-deficient individuals, exposure to bacterial and viral infections can also pose a threat, since microbial infection results in the release of neutrophil elastase and amplified inflammation and airway damage. COPD exacerbations are most commonly caused by respiratory infections (bacterial and/or viral). These are episodes of acute respiratory distress in patients with moderate-to-severe disease. Symptoms typically include increased dyspnoea, cough and production of purulent sputum with increased inflammation of the airways. If they are serious enough, exacerbations may require hospitalisation and long recovery periods. In order to evade microbial infection, respiratory professionals should advise their patients to avoid adults and children who are unwell, and also to be extra vigilant about personal hygiene (hand-washing). In the event of a lung infection, aggressive treatment with antibiotics is recommended.

The benefits of factors such as a balanced diet rich in protein and vitamins, and breathing exercises, should also be emphasised. Taking suitable exercise is important for this patient population, and it can ultimately help to reduce

hospitalisation and mortality rates. The Global Initiative for Chronic Obstructive Lung Disease guidelines recommend pulmonary rehabilitation for all patients with COPD [37]. Pulmonary rehabilitation improves patient symptoms during physical activities by increasing strength, endurance and exercise tolerance. This, in turn, allows the patient to become more independent and self-reliant, which helps restore a feeling of wellbeing and enhance quality of life.

## Treatment

Although there is no cure for AAT deficiency, early diagnosis remains important because as soon as the diagnosis is established AAT-deficient individuals can benefit from the effective therapy that is available. Nonspecific treatments include inhaled bronchodilators, corticosteroids and supplemental oxygen. Augmentation (replacement) therapy, available in a number of European countries, is a specific therapy for AAT deficiency. This is a once-weekly *i.v.* infusion of an AAT preparation that supplements existing levels of AAT in the blood and the lungs, bringing the level of AAT above the protective concentration of 11  $\mu\text{M}$ . Of course, for the reasons described above, it is critical that patients stop smoking cigarettes and avoid environmental pollutants before commencing augmentation therapy. Studies have shown that augmentation therapy has clinical efficacy to slow the rate of decline in lung function, especially in individuals with airflow obstruction of moderate degree [38–40]. On the basis of the results of these studies, the ERS/ATS statement recommends the use of augmentation therapy for symptomatic individuals with established airflow obstruction due to AAT deficiency [12]. A large survey of AAT-deficient individuals found that augmentation therapy was used by 74% of respondents with severe AAT deficiency [30].

Lung transplantation surgery is a treatment option for AAT-deficient patients with end-stage pulmonary emphysema. It is performed as either a single- or double-lung transplant, or more rarely as a heart-lung transplant. The number of lung transplants has increased considerably over the past 15 years, and each year ~150 patients with pulmonary emphysema due to severe AAT deficiency receive lung transplants [41]. Lung transplants have been found to improve quality of life, with a survival half-life after transplantation (double- and single-lung transplants) of 3.8 years and a statistical 5-year

survival rate for both procedures of ~50%. Another surgical procedure, lung volume reduction (LVR) surgery, is being investigated for selected advanced emphysema patients with marked hyperinflation and incapacitating dyspnoea. Although LVR surgery is not an alternative to lung transplantation, it can be used as a bridging procedure until a lung transplant is available, or it may be performed to reduce symptoms and improve exercise tolerance. This surgical procedure, first described in 1957 [42], aims to resect 20–30% of the most damaged lung tissue, which is identified using perfusion scintigraphy or computed tomography (CT) scanning of the thorax. In a prospective study, LVR was shown to result in significant improvements in dyspnoea, exercise tolerance, lung function, respiratory mechanics and quality of life, even in patients with severe AAT deficiency [43]. However, these were only short-term benefits, returning to baseline at 6–12 months post-operatively, and therefore it is questionable whether the risk of this type of surgical intervention is justified for AAT-deficient patients.

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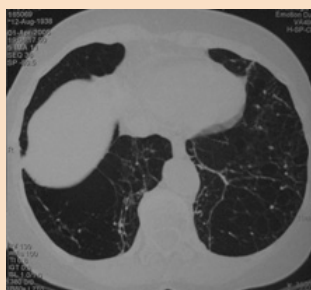
## Conclusion

AAT deficiency remains a common, under-recognised cause of pulmonary problems in which respiratory professionals can play a fundamental role. The majority of AAT-deficient patients remain undiagnosed; even in recent years, there has been no improvement in the time taken to diagnose the condition, and therefore many AAT-deficient patients have not received optimal care. However, recommendations from the ERS and ATS to test all symptomatic individuals with COPD should result in the detection of greater numbers of individuals with the disorder. The role of respiratory specialists in establishing the diagnosis of AAT deficiency is especially important, since effective treatment, such as augmentation therapy, is available. In addition, respiratory specialists can advise on interventions such as smoking cessation, which can reduce morbidity. Enhanced awareness of the disorder among healthcare providers should translate into more appropriate management of AAT deficiency.

### Educational questions

- AAT is a protein predominantly synthesised in the:
  - Lungs.
  - Liver.
  - Blood.
- Which of the following is the 'protective threshold' value for serum AAT?
  - 11  $\mu\text{M}$ .
  - 5  $\mu\text{M}$ .
  - 22  $\mu\text{M}$ .
- AAT deficiency affects approximately how many people in Europe?
  - 10,000.
  - 50,000.
  - 125,000.
- What percentage of individuals with AAT deficiency are believed to be diagnosed?
  - >75%.
  - 30–50%.
  - <10%.
- On average, how long has it been reported that a diagnosis of AAT deficiency lags behind the onset of the first pulmonary symptoms?
  - 2 years.
  - 8 years.
  - 14 years.
- Treatment of AAT deficiency may include:
  - Inhaled corticosteroids.
  - Supplementary oxygen.
  - Augmentation therapy.

### Case Study



A 69-year-old white female patient who has never smoked was diagnosed with pulmonary emphysema in 1986. Her pulmonary function tests at that time were: FEV<sub>1</sub> 43% predicted; and diffusing capacity of the lung for carbon monoxide 36% pred. She was treated with inhaled corticosteroids and  $\beta_2$ -agonists. In April 2006, she presented with evidence of respiratory failure. A CT scan (see figure) showed a pattern of marked bibasilar panacinar emphysema. She began long-term oxygen therapy in June 2006. A full 20 years after the primary diagnosis of pulmonary emphysema, the patient was finally diagnosed with AAT deficiency type PiZZ. She has received weekly replacement therapy with intravenous AAT 60 mg · kg<sup>-1</sup> since November 2006.

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## Suggested answers

1. b
2. a
3. c
4. c
5. b
6. a, b, c

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