BMJ Best Practice

Alpha-1 antitrypsin deficiency

Straight to the point of care

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Summary

Alpha-1 antitrypsin (AAT) deficiency is a genetic disorder with an autosomal inheritance pattern and codominant expression of alleles.

Allele mutations cause ineffective activity of AAT, the enzyme responsible for neutralising neutrophil elastase.

Pulmonary and hepatic manifestations include emphysema, COPD, bronchiectasis, and cirrhosis.

Granulomatosis with polyangiitis (formerly known as Wegener's granulomatosis) and necrotising panniculitis are infrequent complications but can prompt diagnosis.

Plasma AAT levels, protein phenotyping (called PI-typing), and genotyping may be necessary for diagnosis. Rare alleles may require gene sequencing.

Intravenous AAT augmentation therapy benefits some patients.

Definition

Alpha-1 antitrypsin (AAT) deficiency is an autosomal codominant genetic disorder (i.e., one allele is inherited from each parent and each allele is expressed equally). It results from allele mutations in the SERPINA1 gene at the protease inhibitor (PI) locus.[1]

The PI locus is highly polymorphic. Different protein variants have different charges because of amino acid alterations. The charge affects the speed of protein migration on serum electrophoresis.[2] Alleles are assigned a letter from A to Z depending on their relative speed of migration, with A being the fastest and Z the slowest. The allele most widely associated with clinical AAT deficiency is allele Z. The pattern of protein migration observed on serum electrophoresis is called the PI phenotype, which is written in form PI*[allele A] [allele B].[3]

PI* allele mutations cause ineffective activity of the specific protease inhibitor AAT, the enzyme responsible for neutralising neutrophil elastase and preventing inflammatory tissue damage in the lungs.[4] [5] Variants of the enzyme may also polymerise and accumulate in the liver, resulting in hepatic failure in some patients.

AAT is also known as alpha-1 proteinase inhibitor.

Epidemiology

AAT deficiency is frequently under-recognised by clinicians. Direct population-based screening has estimated that prevalence of the PI*ZZ phenotype in the US is 1 in 4455 people.[13] The largest prospective screening study of newborns was performed in Sweden and reported a PI*Z phenotype prevalence of 1 in 1639.[14] One indirect genetic survey in the US determined the frequency of the Z allele and estimated that 59,047 individuals carry the genotype.[15]

Although the two greatest disease-associated alleles (S and Z) have been documented in every racial group, people with northern European ancestry carry the greatest frequencies of these alleles.[3] [16] Z allele frequency is highest (20-40 per 1000) in northwestern Europe and decreases towards the east of the continent.[17] The prevalence of PI*ZZ phenotype in people with COPD is 1 in 408 in northern Europe and 1 in 944 in western Europe.[18]

A self-reported allelic frequency study utilising direct-to-consumer testing investigated the frequency of S and Z alleles in almost 200,000 people. The study demonstrated an allele frequency of 15.1% for PI*S and 6.5% for PI*Z. The PI*ZZ genotype was present in 0.63% of participants, half of whom had been diagnosed with AAT deficiency.[19]

There is limited evidence to suggest that symptomatic lung disease is more prevalent in PI*ZZ males than in PI*ZZ females. However, this result is likely to be confounded by other variables, such as smoking and occupational exposure.[20] [21] [22] [23] The mean age at which smokers with AAT deficiency typically present with symptomatic pulmonary disease is 32 to 41 years.[24]

Liver involvement may be evident in neonates, and is the second most common cause of liver transplant in children.[14] [25] Mortality is high in those with severe liver disease, and death may occur in the first decade of life.[26] Liver disease is also the most common manifestation in non-smoking older adults with AAT deficiency who do not manifest pulmonary symptoms.[27] Liver fibrosis has been detected in 20% to 36% of asymptomatic adults with PI*ZZ AAT deficiency, while the reported prevalence of cirrhosis ranges from 2% to 43%.[6] [28] [29]

Aetiology

Alpha-1 antitrypsin (AAT) deficiency is caused by decreased circulating plasma levels of AAT, due to the inheritance of variant alleles of the SERPINA1 gene.[30] The inheritance pattern is autosomal, and expression of the alleles is codominant. This means that all individuals have twos AAT alleles, and it is the expression of both alleles that contributes to the phenotypic variance. Specifying genotype in the form PI*[allele A][allele B] provides greater precision when referring to the condition of individual patients.[5]

Inflammation of the lung in AAT deficiency is exacerbated by cigarette smoking, which initiates degradation of the extracellular matrix by neutrophil-secreted elastases in the absence of an antiprotease counterbalance. Characterisation of inflammation in transgenic mice and in explanted human lungs has shown that ZZ-phenotype polymers invoke a pro-inflammatory response, suggesting that emphysematous changes in AAT deficiency are the result of more than merely an imbalance between AAT and elastases.[31]

The effect of smoking in heterozygous AAT individuals was quantified in a family-based study in which lung function of PI*MZ individuals was compared with that of PI*MM individuals. There was no difference in lung function (FEV1 % predicted, FEV1/FVC ratio) between PI*MM and PI*MZ never-smokers. Among ever-smokers, lung function was significantly worse in PI*MZ subjects (FEV1/FVC ratio 0.71 versus 0.77,

P=0.001; FEV1 % predicted: 84.6 versus 96.4, P=0.0006). These data suggest an important influence of smoking on lung function in heterozygote individuals.[32] In two large cohorts of patients with COPD, those with the PI*MM phenotype had higher FEV1/FVC than those with the PI*MZ phenotype. Furthermore, among those with low smoking exposure (<20-pack-years), PI*MZ individuals had more severe emphysema on CT scan than PI*MM individuals.[33]

There are limited data on smoking of non-tobacco products and 'vaping' on lung function in people with AAT deficiency, but given the mechanism of inflammation imbalance caused by smoking, they are presumed to carry the same risk for PI*MZ and PI*ZZ individuals.

Pathophysiology

AAT deficiency results from allele mutations in the SERPINA1 gene at the protease inhibitor (PI) locus.[1] Allele mutations cause ineffective activity of the specific protease inhibitor AAT. The mechanism by which AAT plasma levels are decreased depends upon the specific mutation of the protease inhibitor allele.

The Z allele is characterised by a point mutation causing beta-sheet polymerisation of the protein and subsequent aggregation in the liver, where most of the enzyme is produced.[34] In severe deficiency alleles (including the Z allele and the rare Siiyama and Mmalton alleles), approximately 70% of the mutant AAT is degraded within hepatocytes, 15% is secreted, and 15% forms ordered polymers.[30] Retention of polymers in the liver can cause jaundice, hepatitis, cirrhosis and, in severe cases, hepatocellular carcinoma, and death in the first decade of life.

The failure to secrete functional AAT into the circulation also decreases the amount of AAT available for protease activity in the lung, causing unopposed lung damage by neutrophil elastase and other matrix metalloproteinases.[35] [36] [37]

The S allele (the other common abnormal allele) also occurs through a point mutation, but pathogenesis results from the failure of sufficient post-translational processing resulting in intracellular proteolysis and reduced circulating plasma levels.[5]

Reduced serum levels, by whichever mechanism, cause inflammatory responses within the lung to be less controlled, which increases susceptibility to infection and structural damage.[30] This is often initiated by cigarette smoking and involves degradation of the extracellular matrix of the lung by neutrophil-secreted elastases in the absence of an antiprotease counterbalance. Emphysematous changes result.

Classification

Level of functioning AAT enzyme

Serum AAT level measured using the purified standard developed by the US National Institutes of Health (the most common testing method in the US) is classified as follows.[6] [7]

- Normal: normal levels of circulating plasma AAT (>20 micromol/L).
- Deficiency: decreased circulating plasma AAT (<20 micromol/L).
- Null: no detectable circulating plasma AAT.
- Dysfunctional: normal levels of circulating plasma AAT, but the enzyme has reduced activity.

- Protective threshold: AAT levels <11 micromol/L are considered to confer inadequate protection against inflammatory lung disease.

Exact threshold values vary depending on testing method and regional guidance; appropriate regional guidelines should be consulted for interpretation of serum AAT levels.[6] [8] [9] [10]

Alphabetic labelling of alleles[5] [11]

All individuals have two AAT alleles. Each allele, normal or abnormal, has a letter designation between A and Z. The letter assigned to each allele is an indication of migration rate on electrophoresis gel with respect to the other >120 known AAT alleles. "A" represents the fastest-moving variant on electrophoresis gel and "Z" represents the slowest. Specifying phenotype in the form PI*[allele A][allele B] provides greater precision when referring to the condition of individual patients.

The normal allele is designated 'M', so two normal copies would be MM. An example of a carrier phenotype is PI*MZ, and an example of a patient with AAT deficiency is PI*ZZ.

Given the large number of possible alleles, there are hundreds of possible genotypes and phenotypes. The allele most widely associated with clinical AAT deficiency is allele Z. The S allele is another common variant that results in decreased functional AAT expression, although not as severe as with the Z allele.

Clinical AAT deficiency

Any combination of alleles whose expression results in AAT levels below the protective threshold in the lung has an increased likelihood of contributing to pulmonary disease. The PI*ZZ phenotype is one particular manifestation well known to cause pulmonary disease. However, intermediate phenotypes also predispose to disease. For example, PI*MZ individuals have one allele with normal expression of AAT, but one allele that results in significantly decreased amount of functioning protein. The codominant nature of AAT alleles means that the resulting phenotype lies between that expected of a patient with normal AAT levels and that expected of a patient with severe AAT deficiency as seen with PI*ZZ. The Z allele is also the cause of liver disease in AAT deficiency (due to variant protein accumulation). Little evidence exists to support the contribution of other variant AAT proteins to liver disease, except for the rare Mmalton and Siiyama mutations.[12]

Case history

Case history #1

A 39-year-old man presents for the third time in 2 years (to different physicians each time) for evaluation of an intermittent productive cough and increasing dyspnoea on exertion. He has a 15 pack-year smoking history, reports thick, yellow phlegm at times and describes having trouble keeping up when playing with his children. His medical history reveals mild intermittent asthma controlled with a salbutamol inhaler. His symptoms have persisted despite stopping smoking, and his asthma exacerbations have increased in frequency, with some attacks being unresponsive to salbutamol. Physical examination reveals a generally healthy-looking male. During the examination he experiences coughing with subsequent wheezing on auscultation and a long expiratory phase. Cardiac examination is normal. Spirometry demonstrates an FEV1 of 40% of his predicted value.

Other presentations

Patients with pulmonary manifestations may also present with fatigue, chest tightness, and/or exercise intolerance. Patients with hepatic manifestations may present with jaundice, scleral icterus, abnormal liver function tests, fatigue, asterixis, hepatic encephalopathy, bleeding/bruising, and/or oesophageal varices. Hepatocellular carcinoma presents with worsening liver function, abnormal liver imaging, rising alpha-fetoprotein levels detected in blood serum, and sometimes pain.

Approach

The major manifestations of AAT deficiency are hepatic and pulmonary.

- Panacinar emphysema and associated obstructive lung disease are the most common manifestations.[38] [39] Evidence suggests that almost 60% of patients develop severe pulmonary disease.[24]
- Bronchiectasis may occur. Up to 95% of patients with PI*ZZ AAT deficiency have radiological evidence of bronchiectasis (but PI*ZZ AAT deficiency has been found in <1% of patients who present with bronchiectasis).[40]
- Liver disease usually initially presents as hepatitis and jaundice, although severe disease may progress to cirrhosis and hepatocellular carcinoma. Liver involvement may also be seen in neonates with AAT deficiency.[9] [38]
- Necrotising panniculitis and granulomatosis with polyangiitis are infrequent complications.

Evidence suggests that AAT deficiency may be under-recognised by physicians as a cause of lung and liver disease.[41] Further evidence demonstrates a significant time difference between the onset of clinical disease and diagnosis, with evaluation by multiple physicians in the interim.[42]

Guidelines recommend a high clinical suspicion and quantitative AAT measurement in the following scenarios:[6] [38] [43] [44]

- Airflow obstruction partially reversible or irreversible with bronchodilators
- All patients with COPD[8] [45]
- All patients with adult-onset asthma[8]
- A personal or family history of c-ANCA vasculitis (granulomatosis with polyangiitis is an infrequent complication of AAT deficiency)
- Liver disease of unknown aetiology
- Bronchiectasis of unknown aetiology, especially when co-existing with panacinar emphysema[38] [40]
- Panniculitis of unknown aetiology (necrotising panniculitis is an infrequent complication of AAT deficiency)
- Adolescents and adults with a sibling who is AAT homozygous
- Asymptomatic people with persistent obstructive pulmonary dysfunction who report smoking or occupational exposure.

Historical factors

Presenting symptoms of pulmonary manifestations are non-specific and may include shortness of breath, shortness of breath on exertion, fatigue, wheezing, cough, and/or chest tightness.

Presenting symptoms of hepatic manifestations are non-specific and may include yellowing of the skin, fatigue, bleeding, bruising, abdominal distension, abdominal pain, and/or confusion.

It is important to consider age, occupation, and smoking history in patients with symptomatic lung disease, as these factors may point to AAT deficiency. The greatest risk factor for emphysema in patients with the PI*ZZ phenotype is smoking. Lung function and survival are both affected.[24] [46] [47] However, some evidence suggests that ex-smokers and people who have never smoked have similar declines in lung function over time, and some smokers may never develop pulmonary symptoms.[42] [48] Occupational or other exposure to gas, fumes, and/or dust has also been associated with decreased pulmonary function in patients with PI*ZZ AAT deficiency. This includes passive smoking and work with

kerosene heaters.[49] [50] [51] [52] There is limited evidence to suggest that symptomatic lung disease is more prevalent in PI*ZZ males than in PI*ZZ females. However, this result is likely to be confounded by other variables, such as smoking and occupational exposure.[20] [21] [22] [23] The mean age at which smokers with AAT deficiency typically present with symptomatic pulmonary disease is 32 to 41 years.[24] Medical history may include asthma and/or granulomatosis with polyangiitis (an infrequent complication of AAT deficiency), and family history may reveal the presence of AAT deficiency in relatives.

Examination findings

General inspection may reveal jaundice, scleral icterus, and/or asterixis if liver disease is present. Abdominal examination may reveal hepatomegaly and/or ascites.

Respiratory examination may reveal wheeze and/or chest hyperinflation if pulmonary disease is present.

Serum AAT measurements

Serum AAT levels should be quantified in individuals with possible AAT deficiency.[1] [8] [53] However, AAT is an acute phase reactant, meaning that normal serum AAT levels can be misleading, especially in the setting of inflammatory processes.[1] [8] Disease states may still be represented by borderline or even normal AAT levels, meaning such results warrant continued suspicion. Serum AAT measurement alone is not recommended for family testing after identification of a proband because it does not fully characterise the risk of disease from AAT deficiency.[38]

Some guidelines suggest genotyping for the S and Z allele is the appropriate first step for diagnostic testing of symptomatic individuals.[38]

Quantitative testing and protective threshold

Low to normal levels of AAT (<35 micromol/L) should increase suspicion and prompt further testing. Commercially available quantitative testing utilises radial immunodiffusion and nephelometry methods. Exact threshold values vary depending on testing method and regional guidance; appropriate regional guidelines should be consulted for interpretation of serum AAT levels.[6] [8][9] [10]

Serum AAT level measured using the purified standard developed by the US National Institutes of Health (the most common testing method in the US) are typically given in micromol/L, while AAT levels measured using commercial standards are typically given in mg/dL to differentiate them.[6] Nephelometry values less than 20 micromol/L (83-120 mg/dL) are considered deficient. Nephelometry levels below 11 micromol/L (50 mg/dL) are considered to confer inadequate protection against inflammatory lung disease; this is referred to as the 'protective threshold'.[7]

Some of the more common phenotypes result in the following serum AAT levels:

- PI*MM: 20-48 micromol/L (150-350 mg/dL)
- PI*MZ: 17-33 micromol/L (90-210 mg/dL)
- PI*SS: 15-33 micromol/L (100-200 mg/dL)
- PI*ZZ: 2.5-7.0 micromol/L (20-45 mg/dL).

Those resulting in levels below the protective threshold are more likely to result in pulmonary disease.

Phenotyping (PI-typing)

Phenotyping can be used when a quick decision is needed, whereas genotyping should be used for definitive diagnosis when available.[1] Low-normal plasma AAT measurements may correspond to

heterozygous phenotypes that may place the individual and family members at risk for associated disease. Patients, and first-degree relatives of patients, with normal-low but protective AAT levels (12-35 micromol/L) should undergo qualitative testing through phenotyping.

Phenotyping involves the separation of AAT variants using isoelectric focusing, and can confirm the identification of characteristic deficient AAT-variant proteins. Phenotyping can reveal the presence of the actual protein variants, such as the Z protein, M (normal) protein, and S protein, as well as less common variants.[8] [53]

Genotyping

Phenotyping can be used when a quick decision is needed, whereas genotyping should be used for definitive diagnosis when available.[1] Genetic testing may be performed when the actual phenotype does not correspond with the phenotype predicted by the serum AAT level.

It will demonstrate the characteristic AAT alleles responsible for the AAT-variant proteins.

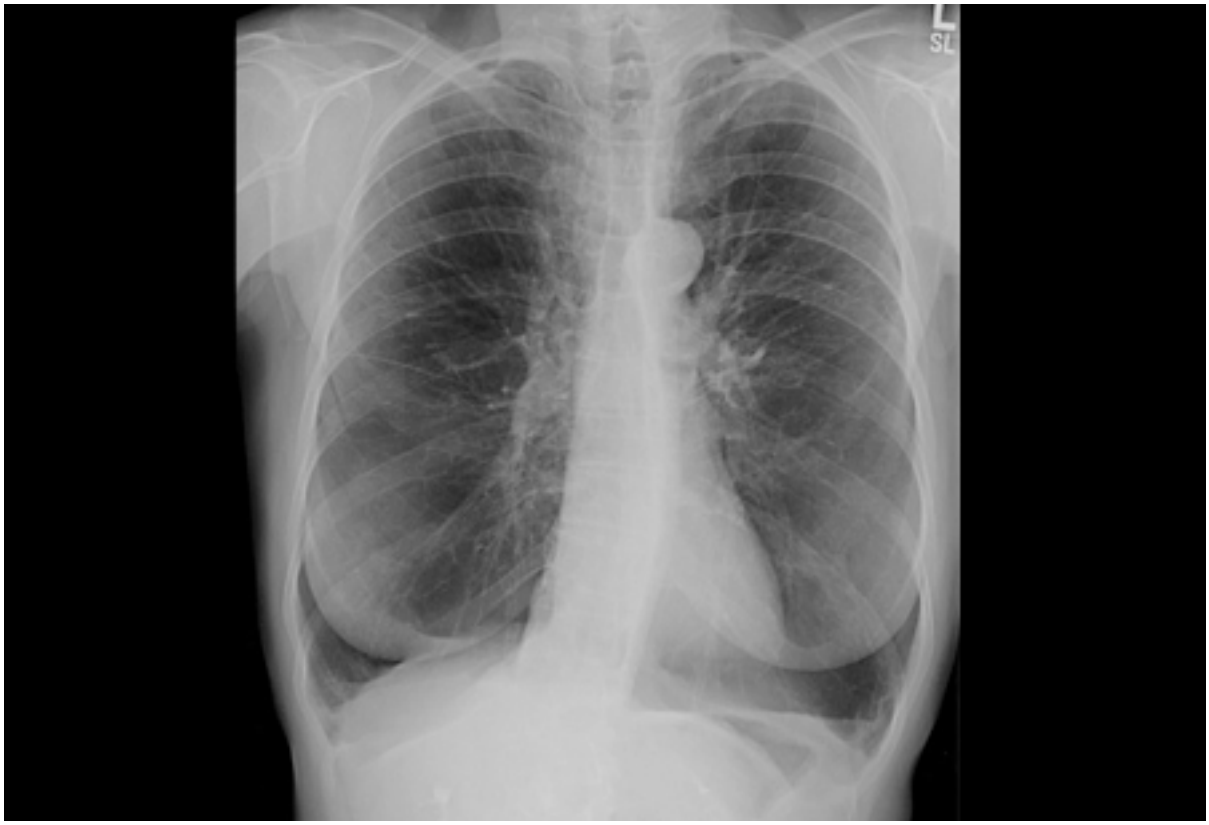
For example, when a low-normal AAT level is detected, further testing with phenotyping is performed to determine the actual AAT protein variants in the serum. If only Z protein is detected, this does not correspond to a low-normal serum AAT level. In this case, additional testing may proceed to genotyping to determine the alleles present in the individual.

Polymerase chain reaction (PCR) is typically used for genotyping. Rare alleles (e.g., null or deficient variants other than Z or S) may require whole gene sequencing. Gene sequencing may also be considered if no primers are available for PCR.[8] [10]

Specific tests for respiratory disease

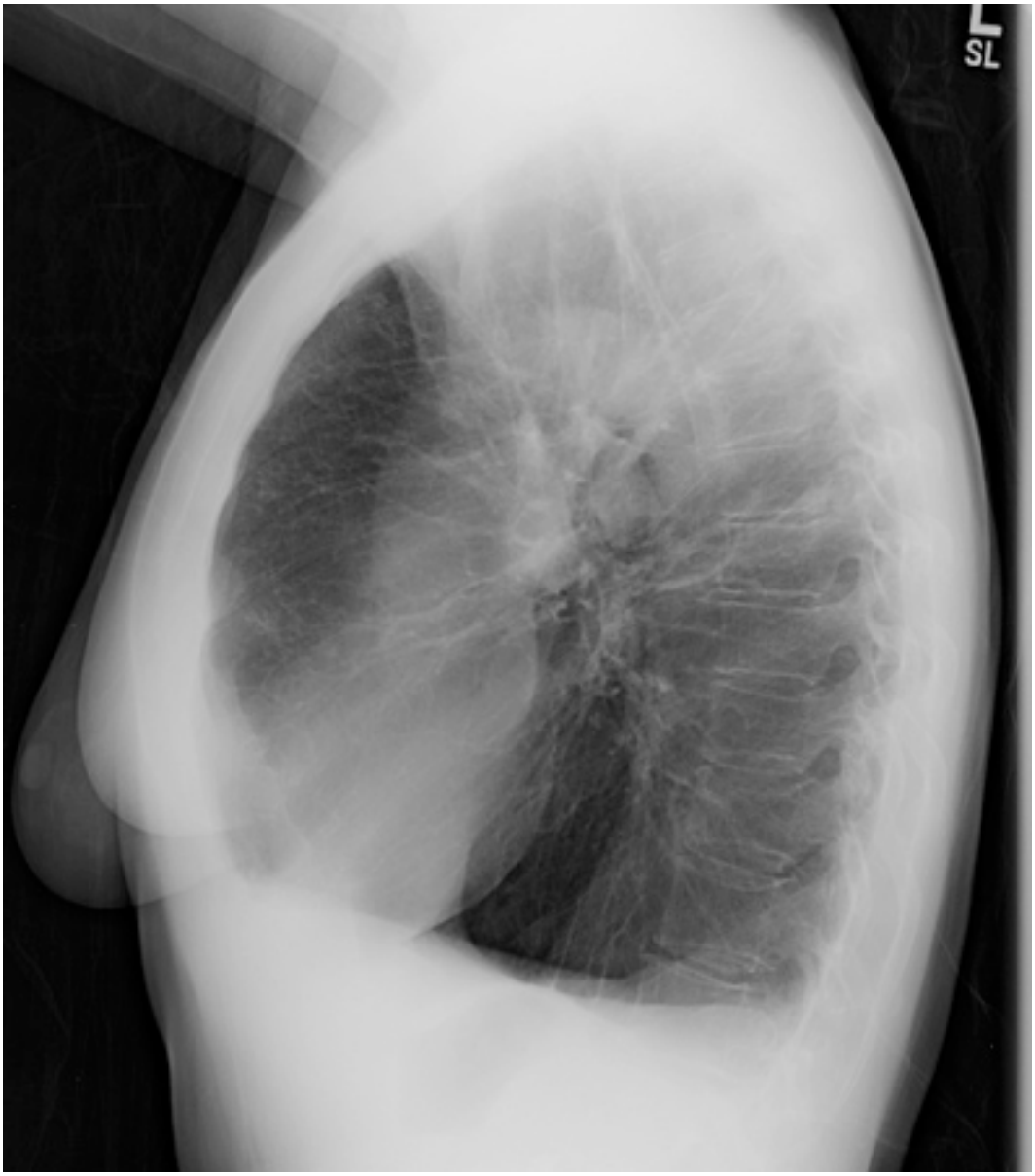
If respiratory disease is present, pulmonary function testing will demonstrate significantly abnormal results including reduced FEV1.

Chest x-ray may reveal large lung volumes and basilar predominant emphysema.



Chest x-ray of AAT deficiency (PA view)

From the personal collection of D. Kyle Hogarth, MD, FCCP; used with permission



Chest x-ray of AAT deficiency (lateral view)

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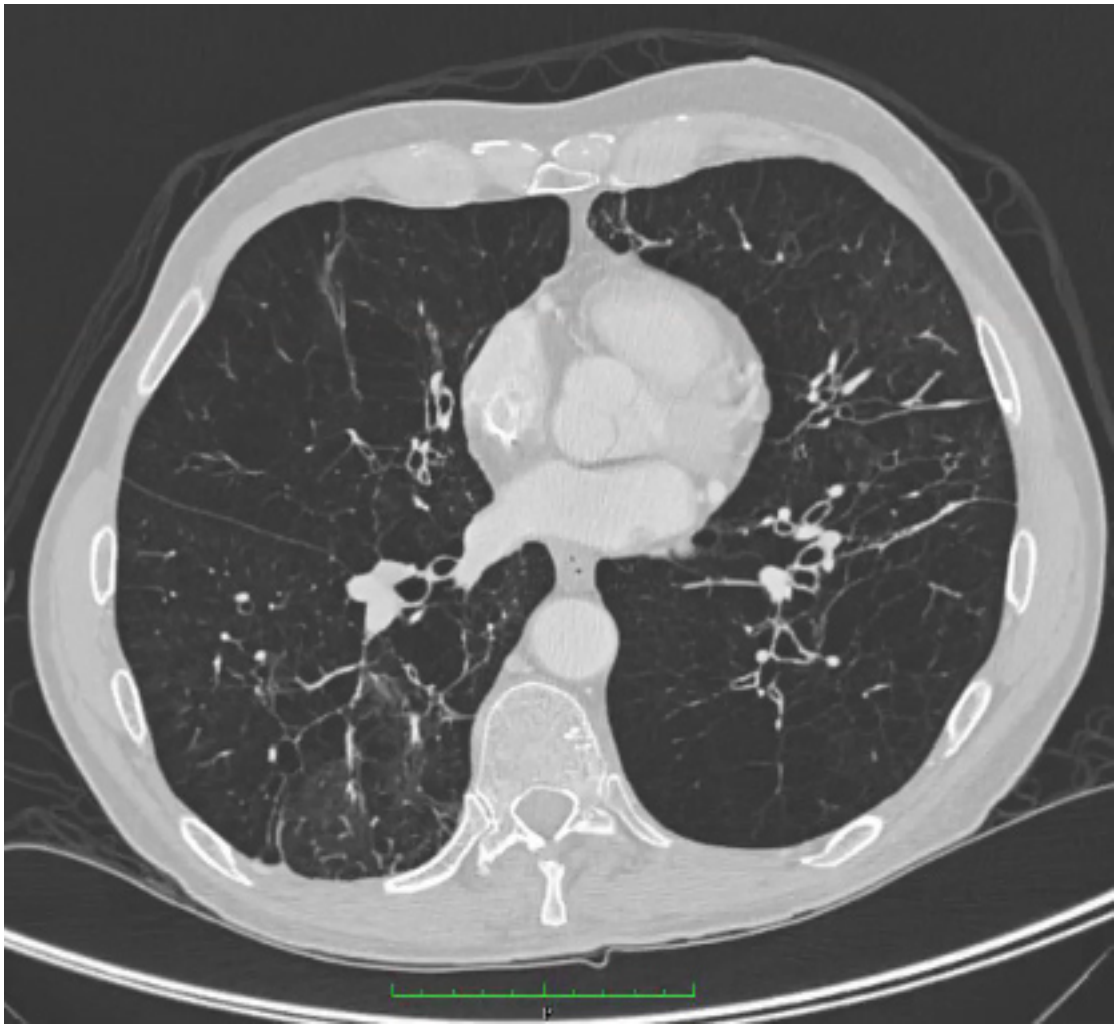
Patients with non-diagnostic results may require a chest computed tomography (CT) scan. CT is more sensitive than chest x-ray or pulmonary function tests for identifying panacinar emphysema and bronchiectasis.[8] [40] However, the absence of emphysematous changes on CT does not rule out AAT deficiency. Panacinar emphysema is predominantly seen in the lower lobes, although upper lobe-only disease has been described. A direct relationship between AAT deficiency and bronchiectasis is less clear as the presence of bronchiectasis on CT may be the result of emphysematous changes.



CT of advanced emphysema in a patient with AAT deficiency

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Exercise testing with arterial blood gas analysis in patients with emphysema is also usually abnormal and demonstrates exercise intolerance.[8] [9]

Specific tests for hepatic disease

Guidelines recommend evaluation of liver function with liver function tests (LFTs) for those diagnosed with AAT deficiency, whether symptomatic or asymptomatic for hepatic disease.[38] [53] Alpha-fetoprotein (AFP) levels are also important as part of any liver disease work-up. However, some data suggest that the sensitivity of LFTs, namely alanine aminotransferase (ALT), is only 11.9% in detecting liver disease in AAT deficiency.[54]

Patients with a phenotype associated with liver disease (e.g., PI*ZZ, PI*Mmalton, PI*Siiyama) require liver imaging, and liver ultrasound is recommended annually.[38] Liver ultrasound may also be used to monitor for signs of portal hypertension and hepatocellular carcinoma. Abdominal CT and/or magnetic resonance imaging (MRI) can also be helpful for assessing patients for liver morphology, cirrhosis, and portal hypertension, particularly in those with obesity.[53]

If hepatocellular carcinoma is present, LFTs may be worsening, and AFP levels may be rising.

As serum liver tests may sometimes yield inconclusive results, the European Association for the Study of the Liver recommends considering liver biopsy in patients with otherwise unexplained, recurrently elevated liver enzymes.[1]

History and exam

Key diagnostic factors

productive cough (common)

- The National Heart, Lung, and Blood Institute (NHLBI) Registry of Individuals with Severe Deficiency of AAT reported 50% of patients with cough.[55] Many patients meet criteria for chronic bronchitis, manifested as chronic cough for 3 months in 2 successive years.[52]

shortness of breath on exertion (common)

- Patients with respiratory disease may present with shortness of breath on exertion.

current cigarette smoker (common)

- The greatest risk factor for emphysema in patients with the PI*ZZ phenotype is smoking. Lung function and survival are both affected.[24] [46][47] Some evidence suggests that ex-smokers and people who have never smoked have similar declines in lung function over time.[48] Some smokers may never develop pulmonary symptoms.[42]

exposure to gas, fumes, and/or dust (uncommon)

- Occupational or other exposure to inhaled toxins has been associated with decreased pulmonary function in patients with PI*ZZ AAT deficiency. This includes passive smoking and work with kerosene heaters.[49] [50] [51] [52]

hepatomegaly (uncommon)

- Patients with liver manifestations may present with hepatomegaly.

ascites (uncommon)

- Patients with liver manifestations may present with ascites.

confusion (uncommon)

- Patients with liver manifestations may present with hepatic encephalopathy.

Other diagnostic factors

aged 32-41 years (common)

- This is the mean age at which smokers with AAT deficiency typically present with symptomatic pulmonary disease.[24]

male sex (common)

- At least one study has shown an increase in symptomatic lung disease in PI*ZZ males.[20] However, this result is likely to be confounded by other variables, such as smoking and occupational exposure.[21] [22] [23]

wheezing (common)

- The NHLBI registry implies that bronchodilator-responsive wheezing is more prevalent in patients with deficient AAT than in patients with normal AAT and COPD.[55] However, it is neither sensitive nor specific for AAT-deficiency lung disease.[9]
- Pulmonary function tests (PFTs) can differentiate between asthma and AAT deficiency disease because asthma is fully reversible with bronchodilation, whereas in AAT deficiency the reversibility is incomplete.[56]

chest hyperinflation (common)

- May indicate the presence of respiratory disease.

scleral icterus/jaundice (uncommon)

- AAT deficiency causing liver failure will normally present as jaundice, indicating hepatitis.[57] Liver disease will only occur in patients with phenotypes that are associated with intrahepatic polymerisation of the AAT variant: notably the Z, Mmalton, and Siiyama.[12]

asterixis (uncommon)

- May indicate the presence of liver disease.

Risk factors

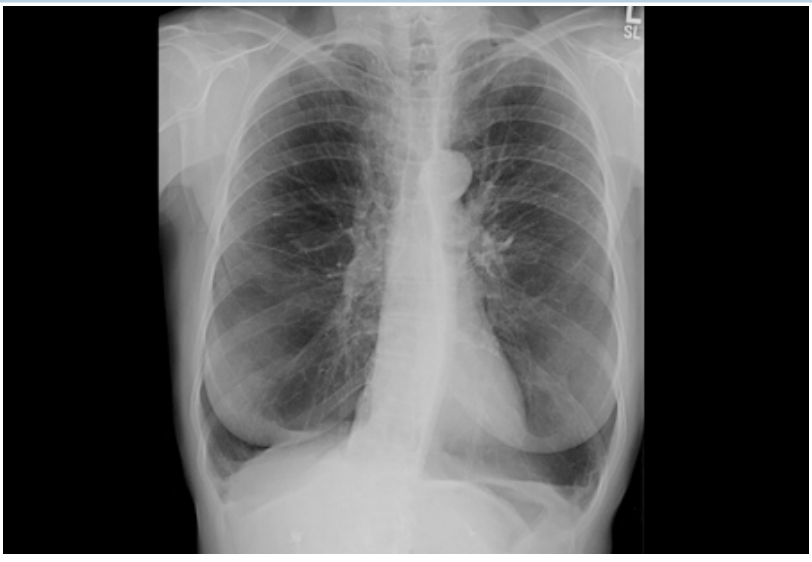
Strong

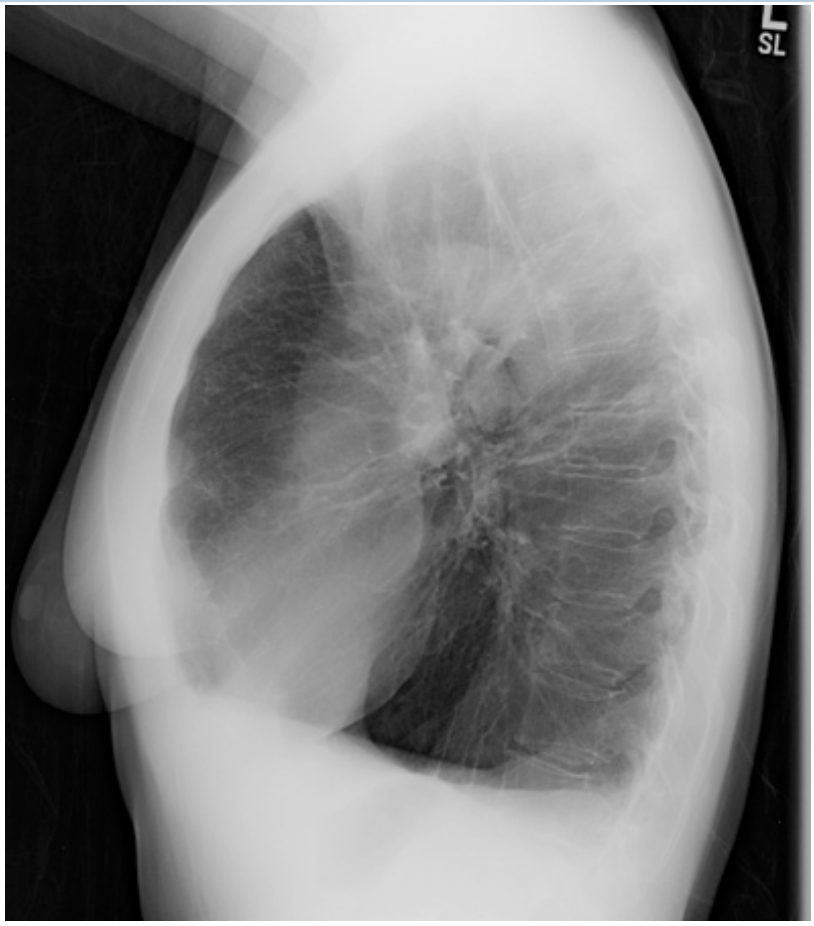
famliy history of AAT deficiency

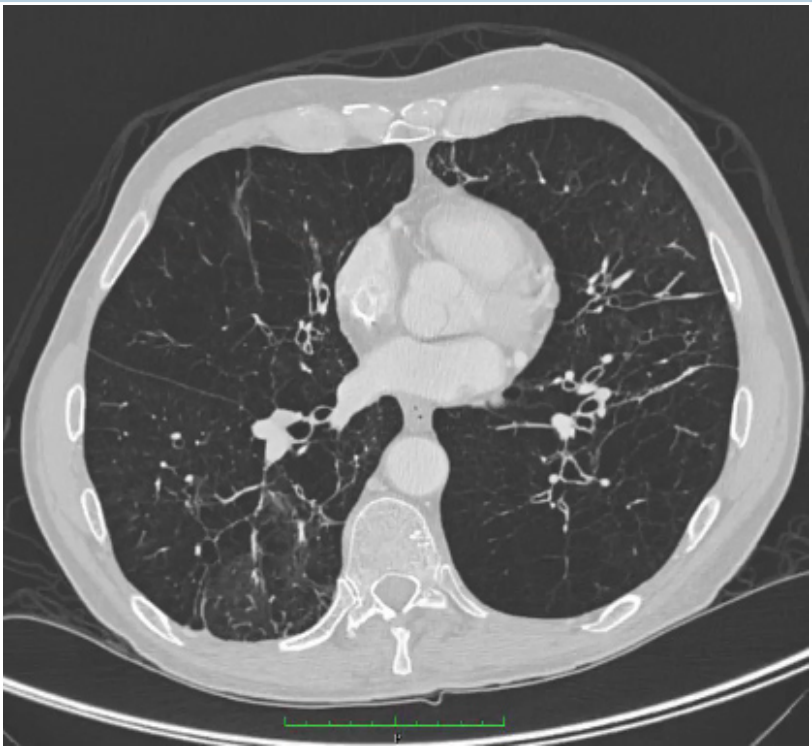
- The inheritance pattern of AAT deficiency is autosomal, and expression of the alleles is codominant. Knowledge that one or both parents are AAT deficient should increase suspicion of AAT deficiency, for example in an individual with early-onset emphysema.

Investigations

1st test to order

Test	Result
plasma AAT level • Serum AAT levels should be measured when the clinician has increased suspicion of disease.[8] [53] • Disease states may still be represented by borderline or even normal AAT levels, meaning that such results warrant continued suspicion. • Levels below 11 micromol/L (80 mg/dL) confer inadequate protection against inflammatory lung disease.[7] • Exact threshold values vary depending on testing method and regional guidance; appropriate regional guidelines should be consulted for interpretation of serum AAT levels.[6] [8] [9] [10] • AAT is an acute phase reactant and can be artificially elevated in some clinical settings (e.g., exacerbation of COPD).[30]	**reduced plasma level <20 micromol/L**
pulmonary function testing • Significantly abnormal results are usual, including reduced FEV1, which is only partially reversible with bronchodilation.	**significantly reduced FEV1, FVC, and FEV1/FVC; increased TLC; impaired CO-diffusing capacity**
chest x-ray • Emphysematous changes may be evident if pulmonary disease is present.  *Chest x-ray of AAT deficiency (PA view)* *From the personal collection of D. Kyle Hogarth, MD, FCCP; used with permission*	**large lung volumes and basilar predominant emphysema**

Test	Result
 *Chest x-ray of AAT deficiency (lateral view)* *From the personal collection of D. Kyle Hogarth, MD, FCCP; used with permission*	
chest CT • CT is more sensitive than chest x-ray or pulmonary function tests for identifying panacinar emphysema and bronchiectasis.[8] [40] Panacinar emphysema is predominantly seen in the lower lobes, although upper lobe-only disease has been described.	**panacinar emphysema and/or bronchiectasis**

Test	Result
 *CT of advanced emphysema in a patient with AAT deficiency* *From the personal collection of D. Kyle Hogarth, MD, FCCP; used with permission*	
LFTs • Liver function evaluation is required whether symptomatic or asymptomatic.[38] [53] • Worsening LFTs may indicate hepatocellular carcinoma.	**elevated aminotransferase, bilirubin, alkaline phosphatase**

Other tests to consider

Test	Result
phenotyping • Phenotyping can be used when a quick decision is needed, whereas genotyping should be used for definitive diagnosis when available.[1] • Performed if AAT levels are <20 micromol/L. • Low-normal plasma AAT measurements may correspond to heterozygous phenotypes that may place the individual and family members at risk for associated disease. Patients, and first-degree relatives of patients, with normal-low but protective AAT levels (12-35 micromol/L) should also undergo qualitative testing through phenotyping.	**characteristic AAT-variant proteins**
genotyping • Phenotyping can be used when a quick decision is needed, whereas genotyping should be used for definitive diagnosis when available.[1] Genetic testing may be performed when the actual phenotype does not correspond with the phenotype predicted by the serum AAT level. • Polymerase chain reaction is typically used for genotyping.[8] [10]	**characteristic AAT alleles responsible for the AAT-variant proteins**
gene sequencing • Rare alleles (e.g., null or deficient variants other than Z or S) may require whole gene sequencing. Gene sequencing may also be considered if no primers are available for genotyping.[8] [10]	**characteristic mutations in the SERPINA1 gene**
exercise testing with ABG analysis • With exercise, these results are typical of people with emphysema.	**reduced PaO_2 and elevated A-a gradient**
alpha-fetoprotein • Rising alpha-fetoprotein levels may indicate hepatocellular carcinoma.	**elevated in cases of hepatocellular carcinoma**
liver ultrasound • Patients with a phenotype associated with liver disease (e.g., PI*ZZ, PI*Mmalton, PI*Siiyama) require liver imaging, and liver ultrasound is recommended annually.[38] [53]	**abnormal liver imaging**
abdominal CT • If hepatocellular carcinoma is present, abdominal CT may demonstrate abnormal liver imaging with typical hypervascular pattern. • CT can also be helpful for assessing signs of liver cirrhosis and portal hypertension, particularly in those with obesity.[53]	**abnormal liver imaging**
abdominal MRI • MRI can be helpful for assessing signs of liver cirrhosis and portal hypertension, particularly in those with obesity.[53]	**abnormal liver imaging**
liver biopsy • As serum liver tests may sometimes yield inconclusive results, the European Association for the Study of the Liver recommends considering liver biopsy in patients with otherwise unexplained, recurrently elevated liver enzymes.[1]	**abnormal hepatocellular cytoplasmic eosinophilic globules**

Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
Asthma	• Clinically indistinguishable.	• Pre-and post-bronchodilator spirometry: reversibility of obstruction is moderate in AAT deficiency emphysema, while obstruction is usually fully reversible in asthma.
COPD	• Long periods of cigarette smoking, advanced age.	• Obstructive, non-reversible pattern on spirometry, predominantly upper lobe changes on chest x-ray/CT.
Bronchiectasis	• Copious daily mucopurulent sputum, history of cystic fibrosis, history of primary ciliary dyskinesia, history of immunodeficiency, history of congenital disorders of the bronchial airways (e.g., Young's syndrome, Mounier-Kuhn syndrome, Williams-Campbell syndrome, pulmonary sequestration, yellow nail syndrome).	• Marked dilation of airways on CT. • Tests for possible causes may demonstrate the CFTR gene or ciliary dysfunction on biopsy.
Viral hepatitis	• Positive for risk factors (e.g., blood transfusion, intravenous drug use, overseas travel).	• Viral hepatitis serology including hepatitis A, B, and C antibodies.
Alcohol-related liver disease	• History of excess alcohol consumption, withdrawal symptoms when off alcohol, alcohol tolerance.	• Reduced carbohydrate-deficient transferrin (CDT), altered gamma-GT, AST, and ALT.

Screening

General population

As AAT deficiency is incurable, and many patients (especially non-smokers) have normal lifespans, AAT deficiency is not routinely screened for.[6] [38] [58]

Neonatal screening can improve modifiable risks such as smoking, but can also adversely affect parental stress and parent-child relationships.[8] [10]

Predispositional testing

Genetic counselling and screening is recommended for adult siblings of individuals with an abnormal AAT variant, whether heterozygous or homozygous.[38] Children, parents, and distant relatives should receive genetic counselling and have screening discussed, but may reasonably accept or refuse screening.

Carrier testing in a reproductive setting

Genetic screening should be discussed with individuals at high risk of AAT deficiency, and with partners of those with AAT deficiency.[6]

Chronic obstructive pulmonary disease

Testing for AAT deficiency should be performed in all patients with COPD.[38] [59]

Asthma

The relationship between asthma and AAT deficiency is unclear, and screening recommendations vary.[8] [9] [10] [38] [39]

The American Thoracic Society/European Respiratory Society recommendations suggest screening patients with asthma who have persistent airflow obstruction despite aggressive bronchodilator therapy.[6] The WHO recommends all patients with adult-onset asthma be tested for AAT deficiency.[8] [43]

One suggested algorithm for AAT deficiency screening in asthma recommends genotyping for S and Z alleles first. If either is detected, then serum AAT measurement should be performed.[60]

Approach

All patients with AAT deficiency should stop smoking and avoid pollution to help protect against respiratory manifestations. There is evidence demonstrating the rate of forced expiratory volume in the first second of expiration (FEV1) decline is worse in smokers compared with non-smokers; however, no significant difference is demonstrated between ex-smokers and non-smokers.[48]

AAT deficiency from the PI*ZZ mutations (and the rare PI*Mmalton, PI*Siiyama mutations) puts patients at risk for liver disease, these patients require hepatitis A and hepatitis B vaccination.[6] [38]

AAT deficiency manifestations are treated using the same modalities as COPD/liver disease of other aetiology.

Patients with airflow obstruction and low plasma AAT levels may benefit from intravenous AAT (also known as alpha-1 proteinase inhibitor) augmentation therapy.[45]

Pulmonary manifestations

Lung disease in AAT deficiency should be treated with the same modalities as COPD of other aetiologies.[38] [45] [61] Although the precise regimen is patient-specific and dependent on disease severity, therapies include short- and long-acting bronchodilators, inhaled corticosteroids, antibiotics, pulmonary rehabilitation, vaccination, smoking cessation, pollutant avoidance, oxygen, and oral corticosteroids.

Intravenous augmentation therapy for obstructive disease

Patients with plasma AAT levels <11 micromol/L have inadequate protection against inflammatory lung disease.[7] If they have coexisting airflow obstruction they may benefit from intravenous AAT augmentation therapy, although evidence examining its effectiveness is limited.[8] [62] [63]

Data for treating moderate obstructive disease (FEV1 31% to 65% of expected) are derived from two large observational studies (of patients >18 years with AAT deficiency) that reported reduced mortality and rate of decline in FEV among patients receiving augmentation therapy.[63] [64] [65] Consideration of observational studies is warranted given the low incidence of AAT deficiency; these studies have been instrumental in shaping current treatment recommendations.

One meta-analysis, that included randomised clinical studies and the observational data described above, found a reduced decline in FEV1 among all patients receiving augmentation therapy (23%); augmentation was associated with a 26% reduction in rate of FEV1 decline in the subset of patients with baseline FEV1 30% to 65% of predicted.[66] Subsequent meta-analyses of two small randomised controlled trials detected a significant difference in lung density on CT scan between AAT-treated patients (FEV1 between 25% and 80% of predicted; median 46%) and patients receiving placebo.[67] [68] Neither meta-analysis reported a difference in decline in FEV1.[67] [68]

Evidence suggests that augmentation therapy reduces the frequency of exacerbations and reduces total hospital cost per patient with AAT deficiency; however, the overall cost-effectiveness of therapy is unclear, given the high cost of AAT concentrates.[69]

Patient selection

Guidelines recommend intravenous augmentation therapy in those with AAT deficiency with an FEV1 less than or equal to 65% predicted, and that it should continue indefinitely.[38] However, some experts believe that individuals with mild airflow obstruction should receive augmentation therapy, citing the difficulty in detecting statistically significant efficacy in this cohort given the slow rate of decline of control patients.[70] The Global Initiative for Chronic Obstructive Lung Disease advises that never-smokers or ex-smokers with FEV1 between 35% and 60% predicted are most suitable for AAT augmentation therapy.[45] The Canadian Thoracic Society guidelines suggest that augmentation therapy may be considered for non-smoking or ex-smoking patients with COPD, with FEV1 25% to 80%, who are otherwise optimised pharmacologically and non-pharmacologically (i.e., pulmonary rehabilitation).[39]

Clinical trial and registry data are almost exclusively from patients with PI*ZZ phenotype; in clinical practice, people with PI*Z/null or PI*null/null genotypes are also evaluated for AAT augmentation. Other genotypes are not considered at risk or likely to benefit from AAT augmentation.[45] Although there is evidence that Z allele heterozygotes may have an increased risk of developing mild COPD, AAT augmentation therapy is not indicated because COPD does not develop in the absence of smoking and smoking cessation is, therefore, thought to be sufficient to prevent progression.[45]

If patients have low plasma AAT but normal lung function, they should not be treated with augmentation therapy as they have no manifestation of the disease. If patients have low plasma AAT and mild airflow obstruction (FEV1 >85%), hepatitis vaccination and lifestyle changes (smoking cessation, pollution avoidance) are encouraged, and their lung function is monitored. If they lose lung function at an accelerated rate (a change in FEV1 of >120 mL per year), or if FEV1 is <65%, augmentation therapy can be started.[38] [64]

The UK National Institute for Health and Care Excellence does not recommend AAT replacement therapy for patients with AAT deficiency.[71]

The RAPID trial was a large, randomised, placebo-controlled study looking at progression of emphysema as measured by CT densitometry.[72] In this study, augmentation therapy led to less loss of lung parenchyma over time as measured at total lung capacity.

One registry study demonstrated a survival benefit of augmentation therapy in patients with severe AAT deficiency, and this was uncoupled from any effect on FEV1 stabilisation/decline.[73]

Augmentation therapy regimen and adverse effects

Weekly infusions of purified AAT from pooled human plasma are sufficient for increasing AAT in lung fluid and for protective levels of plasma AAT.[74] [75] Regimens of alternate doses and administration intervals have proven ineffective.[62] [76] [77]

The most common reactions to AAT augmentation infusion are fever, chills, dyspnoea, dizziness, and fainting.[63] [64] Augmentation therapy carries a risk of anaphylaxis if an individual's IgA level is near zero, so it is recommended that serum IgA level is measured before considering therapy.[70]

Lung transplantation

Reserved for patients with end-stage lung disease (typically when FEV1 is <25% or there are signs of chronic CO_2 retention).[10]

Around 5% of lung transplants are performed on patients with emphysema secondary to AAT deficiency.[78] A registry study conducted in the UK reported 1 year survival of 74%, 5 year survival of

53%, and 10 year survival of 45%. Lung transplantation was associated with significantly improved quality of life, but not increased survival, compared with matched controls.[79] Augmentation post-transplant may be performed in research or data-collection settings.

Hepatic manifestations

Liver disease in AAT deficiency should be treated with the same modalities as liver disease of alternate aetiologies.[6] [61]

The precise regimen is patient-specific and dependent on disease severity. It may include monitoring for coagulopathy or worsening LFTs; diuretics for ascites; oesophagogastroduodenoscopy to detect and manage varices; and liver transplantation. There is no role for augmentation therapy in the treatment of liver manifestations of AAT deficiency.[38]

AAT deficiency accounts for approximately 1% of all liver transplants. A characterisation of liver transplantation in AAT-deficient patients in 3 transplant centres revealed a 5-year survival rate of 80% for patients with the ZZ phenotype and 79% for patients with the SZ phenotype.[80]

Alcohol consumption in individuals with AAT deficiency may increase the risk of liver manifestations, especially in patients with PI*ZZ phenotypes.[6] Patients with liver disease should be advised to avoid alcohol or at least limit their alcohol intake to <60 g/day (although there is no evidence that ethanol consumption affects progression of disease).[6] [9]

Treatment algorithm overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Ongoing (summary)		
low plasma AAT		
	1st	**smoking cessation, pollution avoidance**
	adjunct	**hepatitis vaccination**
with pulmonary manifestations	**plus**	**standard COPD treatment**
	adjunct	**AAT augmentation therapy**
	adjunct	**lung transplant**
with hepatic manifestations	**plus**	**standard liver disease treatment**
	plus	**alcohol avoidance**

Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Ongoing

low plasma AAT

1st **smoking cessation, pollution avoidance**

» All patients with AAT deficiency should stop smoking and avoid pollution to help protect against respiratory manifestations. There is evidence demonstrating the rate of forced expiratory volume in the first second of expiration (FEV1) decline is worse in smokers compared with non-smokers; however, no significant difference is demonstrated between ex-smokers and non-smokers.[48]

adjunct **hepatitis vaccination**

Treatment recommended for SOME patients in selected patient group

» Patients with AAT deficiency and a phenotype associated with liver disease (e.g., PI*ZZ, PI*Mmalton, PI*Siiyama) also require hepatitis A and hepatitis B vaccination to help protect against hepatic manifestations.[6] [38]

with pulmonary manifestations

plus **standard COPD treatment**

Treatment recommended for ALL patients in selected patient group

» Lung disease in AAT deficiency should be treated with the same modalities as COPD of alternate aetiologies.[38] [45] [61]

» Although the precise regimen is dependent on the patient and the severity of their disease, therapies include short- and long-acting bronchodilators, inhaled corticosteroids, antibiotics, pulmonary rehabilitation, oxygen, and oral corticosteroids.

adjunct **AAT augmentation therapy**

Treatment recommended for SOME patients in selected patient group

Primary options

» alpha1-proteinase inhibitor: 60 mg/kg by intravenous infusion once weekly

» Patients with plasma AAT levels <11 micromol/L have inadequate protection against inflammatory lung disease.[7] If they have coexisting airflow obstruction they may benefit from intravenous AAT augmentation therapy,

Ongoing

although evidence examining its effectiveness is limited.[8] [62] [63]

» Guidelines recommend intravenous AAT augmentation therapy in those with AAT deficiency with an FEV1 ≤65% predicted, and that it should continue indefinitely.[38] However, some experts believe that individuals with mild airflow obstruction should receive augmentation therapy, citing the difficulty in detecting statistically significant efficacy in this cohort given the slow rate of decline of control patients.[70] The Global Initiative for Chronic Obstructive Lung Disease advises that never-smokers or ex-smokers with FEV1 between 35% and 60% predicted are most suitable for AAT augmentation therapy.[45] The Canadian Thoracic Society guidelines suggest that augmentation therapy may be considered for non-smoking or ex-smoking patients with COPD and with FEV1 25% to 80% who are otherwise optimised pharmacologically and non-pharmacologically (i.e., pulmonary rehabilitation).[39]

» Clinical trial and registry data are almost exclusively from patients with PI*ZZ phenotype; in clinical practice, people with PI*Z/null or PI*null/null genotypes are also evaluated for AAT augmentation. Other genotypes are not considered at risk or likely to benefit from AAT augmentation.[45] Although there is evidence that Z allele heterozygotes may have an increased risk of developing mild COPD, AAT augmentation therapy is not indicated because COPD does not develop in the absence of smoking and smoking cessation is, therefore, thought to be sufficient to prevent progression.[45]

» If patients have low plasma AAT but normal lung function, they should not be treated with augmentation therapy as they have no manifestation of the disease.

» If patients have low plasma AAT and mild airflow obstruction (FEV1 >85%), hepatitis vaccination and lifestyle changes (smoking cessation, pollution avoidance) are encouraged, and their lung function is monitored. If they lose lung function at an accelerated rate (a change in FEV1 of >120 mL per year), or if FEV1 is <65%, augmentation therapy can be started.[38] [64]

» One registry study demonstrated a survival benefit of augmentation therapy in patients with severe AAT deficiency, and this was uncoupled from any effect on FEV1 stabilisation/decline.[73]

Ongoing

» The National Institute for Health and Care Excellence in the UK does not recommend AAT replacement therapy for patients with AAT deficiency.[71]

» Weekly infusions of purified AAT from pooled human plasma are sufficient for increasing AAT in lung fluid and for protective levels of plasma AAT.[74] [75]

» Augmentation therapy carries a risk of anaphylaxis if an individual's IgA level is near zero, so it is recommended that serum IgA level is measured before considering therapy.[70]

adjunct **lung transplant**

Treatment recommended for SOME patients in selected patient group

» Reserved for patients with end-stage lung disease (typically when FEV1 is <25% or there are signs of chronic CO_2 retention).[10]

» Around 5% of lung transplants are performed on patients with emphysema secondary to AAT deficiency.[78] The 5-year survival rate following transplant is approximately 50%.[81] [82] [83] Median survival is 6.3 years.[83]

with hepatic manifestations

plus **standard liver disease treatment**

Treatment recommended for ALL patients in selected patient group

» Liver disease in AAT deficiency should be treated with the same modalities as liver disease of alternate aetiologies.[6] [61]

» The precise regimen is patient-specific and dependent on disease severity. It may include monitoring for coagulopathy or worsening LFTs; diuretics for ascites; oesophagogastroduodenoscopy to detect and manage varices; and liver transplantation.

» AAT deficiency accounts for approximately 1% of all liver transplants. A characterisation of liver transplantation in AAT-deficient patients in 3 transplant centres revealed a 5-year survival rate of 80% for patients with the ZZ phenotype and 79% for patients with the SZ phenotype.[80]

plus **alcohol avoidance**

Treatment recommended for ALL patients in selected patient group

» Alcohol consumption in individuals with AAT deficiency may increase the risk of liver manifestations, especially in patients with PI*ZZ phenotypes.[6] Patients with liver disease should

Ongoing

be advised to avoid alcohol or at least limit their alcohol intake to <60 g/day (although there is no evidence that ethanol consumption affects progression of disease).[6] [9]

Emerging

Inhaled AAT augmentation therapy

Initial studies indicate that inhaled AAT augmentation therapy may provide sufficient AAT to reach normal concentrations in the lung fluid.[84] Difficulties of using this modality include poor equality of distribution in lung tissue, and penetration of AAT into interstitial tissue.[85] [86]

Recombinant AAT augmentation/leukoprotease inhibitors

Recombinant AAT has been developed and seems efficacious in vitro.[87] Research evaluating the effectiveness of INBRX-101 (a recombinant human AAT-Fc fusion protein) was completed in one phase 1 trial with encouraging data regarding safety and tolerability as well as maintaining normal levels of AAT in the plasma.[88] Larger studies are starting now in the US and Europe.[87] INBRX-101 has been granted orphan drug designation in the US. Orally bioavailable synthetic inhibitors of neutrophil elastase (e.g., alvelestat) have also been developed and studies are under way.[89] [90] Alvelestat has received fast-track designation by the US Food and Drug Administration (FDA).

Gene therapy

Cytomegalovirus vectors have been used to transduce AAT DNA into muscle cells with sustained AAT production for 15 weeks; retroviral transfection of AAT cDNA to lung epithelium has yielded subtherapeutic AAT levels.[91] [92] Multiple other modalities to alter genetic sequences are being explored in early works. More work is needed in this area, especially given the mutagenic risks with some viral vectors.

Post-transcription message modification (mRNA editing)

Several companies are utilising technology to alter the transcribed Z DNA messenger RNA into the correct M message to be translated by the normal protein manufacturing mechanisms.

Post-transcriptional gene silencing

RNA interference mediated via small interfering RNA (siRNA) is being examined to prevent the AAT polymerisation in the liver, and subsequent liver disease.[93] ARO-AAT, an RNA interference trigger, has received fast-track designation from the US FDA and is currently undergoing phase 2/3 trials.[94]

Lung volume reduction surgery (LVRS)

In small studies those managed medically have better outcomes than those undergoing surgery.[95] LVRS is more effective in those with emphysema who are not AAT-deficient; further studies in patients with AAT deficiency are needed.[10] [38]

Endobronchial valves

In the US, two endobronchial valves have been approved for emphysema. The EMPROVE study had a sub-study of 20 AAT patients who had similar results as non-AAT deficient patients.[96] [97] [98] The European Respiratory Society statement states that endobronchial valves may be considered in select patients with AAT deficiency, but further studies are needed.[8] The Thoracic Society of Australia and New Zealand position statement does not recommend their use outside of clinical trials.[10]

Primary prevention

There is no primary prevention for AAT deficiency; however, severe pulmonary and hepatic manifestations may be prevented with smoking cessation, air-pollution avoidance, alcohol avoidance, and hepatitis vaccination.

Patient discussions

Patients with a phenotype associated with liver disease (e.g., PI*ZZ, PI*Mmalton, PI*Siiyama) are urged to undergo hepatitis vaccination.

Lifestyle counselling is recommended.[1] All patients who smoke should be urged to stop as soon as possible, using pharmacological assistance if necessary. There are limited data on smoking of non-tobacco products and 'vaping' on lung function in people with AAT deficiency, but given the mechanism of inflammation imbalance caused by smoking, it is presumed to carry the same risk for PI*MZ and PI*ZZ individuals.

Patients with liver disease should be advised to avoid alcohol or at least limit their alcohol intake to <60 g/day (although there is no evidence that ethanol consumption affects progression of disease).[6] [9]

Monitoring

Monitoring

Patients with lung disease require pulmonologist evaluation for any exacerbations of COPD. Initial evaluation should include full pulmonary function testing (volumes, flows, diffusion).[38] A baseline CT of the chest is recommended. When well controlled, patients require annual follow-up with spirometry testing in order to assess pulmonary function changes. Annual CT is not suggested.

Individuals with liver disease require regular evaluations with liver function tests, whether symptomatic or asymptomatic.[38] Annual liver ultrasound is recommended.

Complications

Complications	Timeframe	Likelihood
hepatocellular carcinoma (HCC)	**variable**	**medium**
The risk of HCC is relatively high in PI*ZZ patients with cirrhosis.[38] Alpha-fetoprotein (AFP) levels and LFTs should be monitored, and abdominal CT performed if levels are rising. Treatment is guided by staging and prognosis and may include resection or liver transplantation.[101]		
necrotising panniculitis	**variable**	**low**
Necrotising panniculitis (multifocal, erythematous, non-pruritic cutaneous lesions, which ulcerate in the centre and discharge seropurulent exudate) can be caused by AAT deficiency, although this is uncommon.[10] The prevalence in AAT deficient patients has been estimated at 1 in 1000.[43] There is no clear age group but it is more likely between age 30 and 60 years. Tests include skin biopsy and AAT deficiency testing. There is no role for corticosteroids or antibiotics; rather, smoking cessation and AAT augmentation are the mainstays of therapy.[38]		
granulomatosis with polyangiitis	**variable**	**low**
Multiple studies have demonstrated an association between c-ANCA (particularly in granulomatosis with polyangiitis) and AAT deficiency.[102] [103] The mechanism by which this complication occurs is thought to involve a protective property of AAT against the serine protease proteinase-3 (PR-3). Additionally, the PI*ZZ variant may have a damaging effect on vasculitis processes once they are initiated.[104] Granulomatosis with polyangiitis generally affects middle-aged patients, and may present with haemoptysis, haematuria, shortness of breath, cough, sinus disease, purpuric rash, abnormal chest x-ray/CT scan, abnormal urine analysis, and abnormal kidney function. Tests include lung or kidney biopsy, ANCA test, and AAT deficiency testing.		

FOLLOW UP

Prognosis

There is no cure for the disease but many individuals, especially non-smokers, have normal lifespans.[6] [58]

Lung disease

Between 50% and 72% of deaths in AAT deficiency are caused by respiratory failure, which comprises a greater percentage of deaths than liver failure.[24] [63] [99]

Evidence suggests the median age of death in AAT deficiency is 40 years in smokers and 65 years in non-smokers, owing to early-onset emphysema and progressive lung disease.[24]

FEV1 should be used as a predictor of survival in these patients, as correlation has been established between 2-year mortality and FEV1 >35%.[100] Rates of decline of FEV1 range from 47 to 80 mL/year in people who have never smoked, 41 to 81 mL/year in ex-smokers, and 61 to 316 mL/year in smokers.[46][47] [48] AAT augmentation therapy is effective in slowing radiographical evidence of lung disease, and also in providing mortality benefit.[62] [63]

The 5-year survival rate following lung transplant is approximately 50%.[81] [82] [83] Median survival is 6.3 years.[83]

Liver disease

Patients who are PI*ZZ and do not manifest pulmonary symptoms are more likely to experience cirrhosis and ultimately liver failure.[27]

Liver fibrosis has been detected in 20% to 36% of asymptomatic adults with PI*ZZ AAT deficiency, while the reported prevalence of cirrhosis ranges from 2% to 43%.[6] [28] [29] The prevalence of cirrhosis is higher in older PI*ZZ adults who have never smoked; one third of patients with advanced age and a homozygous phenotype will die of complications related to portal hypertension and primary liver cancer.[6]

Diagnostic guidelines

United Kingdom

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (https://www.nice.org.uk/guidance/ng115)

Published by: National Institute for Health and Care Excellence **Last published:** 2019

British Thoracic Society guideline for bronchiectasis in adults (https://www.brit-thoracic.org.uk/quality-improvement/guidelines)

Published by: British Thoracic Society **Last published:** 2018

Europe

EASL Clinical Practice Guidelines on genetic cholestatic liver disease (https://easl.eu/publication-category/clinical-practice-guidelines)

Published by: European Association for the Study of the Liver **Last published:** 2024

Portuguese consensus document for the management of alpha-1-antitrypsin deficiency (https://www.sciencedirect.com/science/article/pii/S2531043718301351)

Published by: Portuguese Pulmonology Society **Last published:** 2018

European Respiratory Society statement: diagnosis and treatment of pulmonary disease in alpha 1-antitrypsin deficiency (https://erj.ersjournals.com/content/50/5/1700610)

Published by: European Respiratory Society **Last published:** 2017

Guidelines for the diagnosis and management of alpha-1 antitrypsin deficiency (https://www.archbronconeumol.org/es-pdf-S157921290760007X)

Published by: Spanish Society of Pulmonology and Thoracic Surgery **Last published:** 2006

International

Global strategy for diagnosis, management, and prevention of COPD (https://goldcopd.org/2025-gold-report)

Published by: Global Initiative for Chronic Obstructive Lung Disease **Last published:** 2024

Standards for the diagnosis and management of individuals with alpha-1 antitrypsin deficiency (https://www.atsjournals.org/doi/10.1164/rccm.168.7.818)

Published by: American Thoracic Society; European Respiratory Society **Last published:** 2003

North America

Diagnosis and management of alpha-1 antitrypsin deficiency in the adult (https://journal.copdfoundation.org/jcopdf/id/1115/The-Diagnosis-and-Management-of-Alpha-1-Antitrypsin-Deficiency-in-the-Adult)

Published by: Medical and Scientific Advisory Committee of the Alpha-1 Foundation **Last published:** 2016

Alpha-1 antitrypsin deficiency targeted testing and augmentation therapy: a Canadian Thoracic Society clinical practice guideline (https://cts-sct.ca/guideline-library)

Published by: Canadian Thoracic Society **Last published:** 2012

Oceania

Diagnosis and treatment of lung disease associated with alpha one-antitrypsin deficiency (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7078913)

Published by: Thoracic Society of Australia and New Zealand **Last published:** 2020

Treatment guidelines

United Kingdom

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (https://www.nice.org.uk/guidance/ng115)

Published by: National Institute for Health and Care Excellence **Last published:** 2019

British Thoracic Society guideline for bronchiectasis in adults (https://www.brit-thoracic.org.uk/quality-improvement/guidelines)

Published by: British Thoracic Society **Last published:** 2018

Europe

EASL Clinical Practice Guidelines on genetic cholestatic liver diseases (https://easl.eu/publication-category/clinical-practice-guidelines)

Published by: European Association for the Study of the Liver **Last published:** 2024

Portuguese consensus document for the management of alpha-1-antitrypsin deficiency (https://www.sciencedirect.com/science/article/pii/S2531043718301351)

Published by: Portuguese Pulmonology Society **Last published:** 2018

European Respiratory Society statement: diagnosis and treatment of pulmonary disease in alpha 1-antitrypsin deficiency (https://erj.ersjournals.com/content/50/5/1700610)

Published by: European Respiratory Society **Last published:** 2017

Guidelines for the diagnosis and management of alpha-1 antitrypsin deficiency (https://www.archbronconeumol.org/es-pdf-S157921290760007X)

Published by: Spanish Society of Pulmonology and Thoracic Surgery **Last published:** 2006

International

Global strategy for diagnosis, management, and prevention of COPD (https://goldcopd.org/2025-gold-report)

Published by: Global Initiative for Chronic Obstructive Lung Disease **Last published:** 2024

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Published by: American Thoracic Society; European Respiratory Society **Last published:** 2003

North America

Diagnosis and management of alpha-1 antitrypsin deficiency in the adult (https://journal.copdfoundation.org/jcopdf/id/1115/The-Diagnosis-and-Management-of-Alpha-1-Antitrypsin-Deficiency-in-the-Adult)

Published by: Medical and Scientific Advisory Committee of the Alpha-1 Foundation **Last published:** 2016

Alpha-1 antitrypsin deficiency targeted testing and augmentation therapy: a Canadian Thoracic Society clinical practice guideline (https://cts-sct.ca/guideline-library)

Published by: Canadian Thoracic Society **Last published:** 2012

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Published by: Thoracic Society of Australia and New Zealand **Last published:** 2020

Key articles

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Images

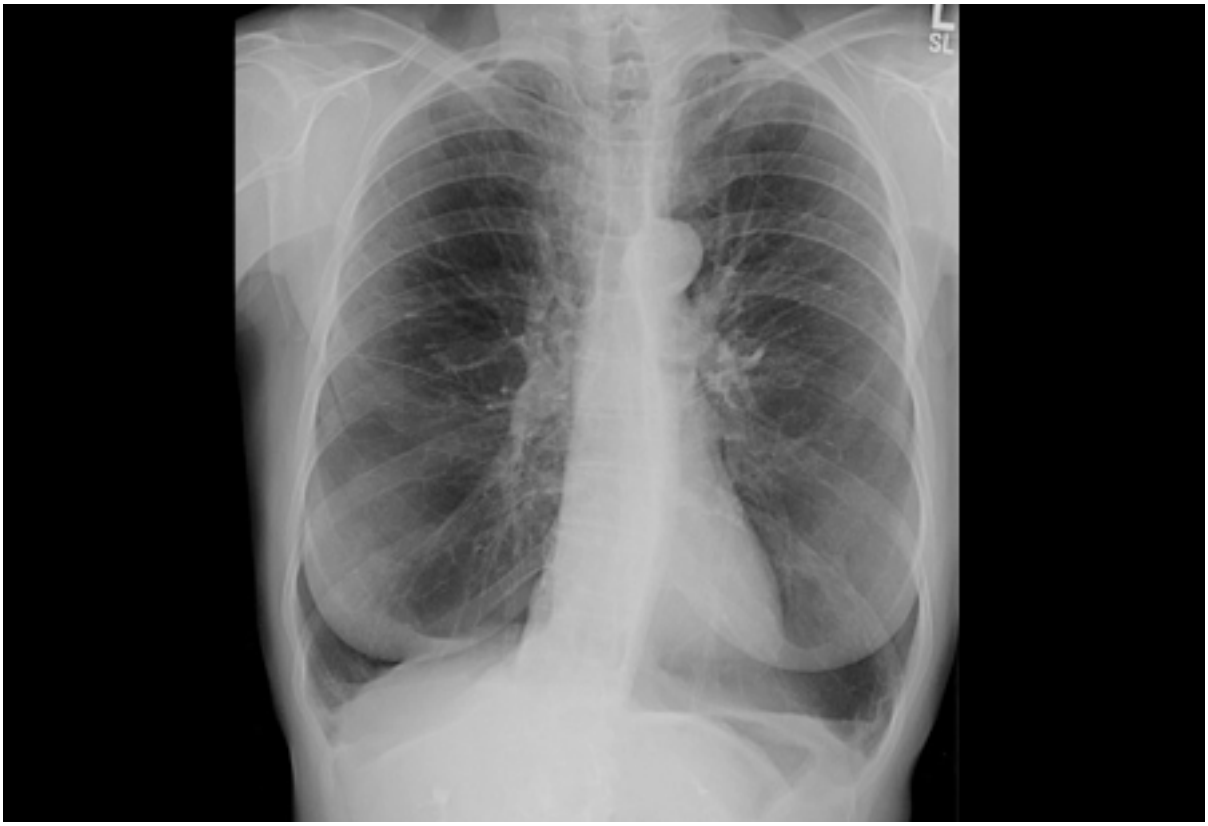

Figure 1: Chest x-ray of AAT deficiency (PA view)

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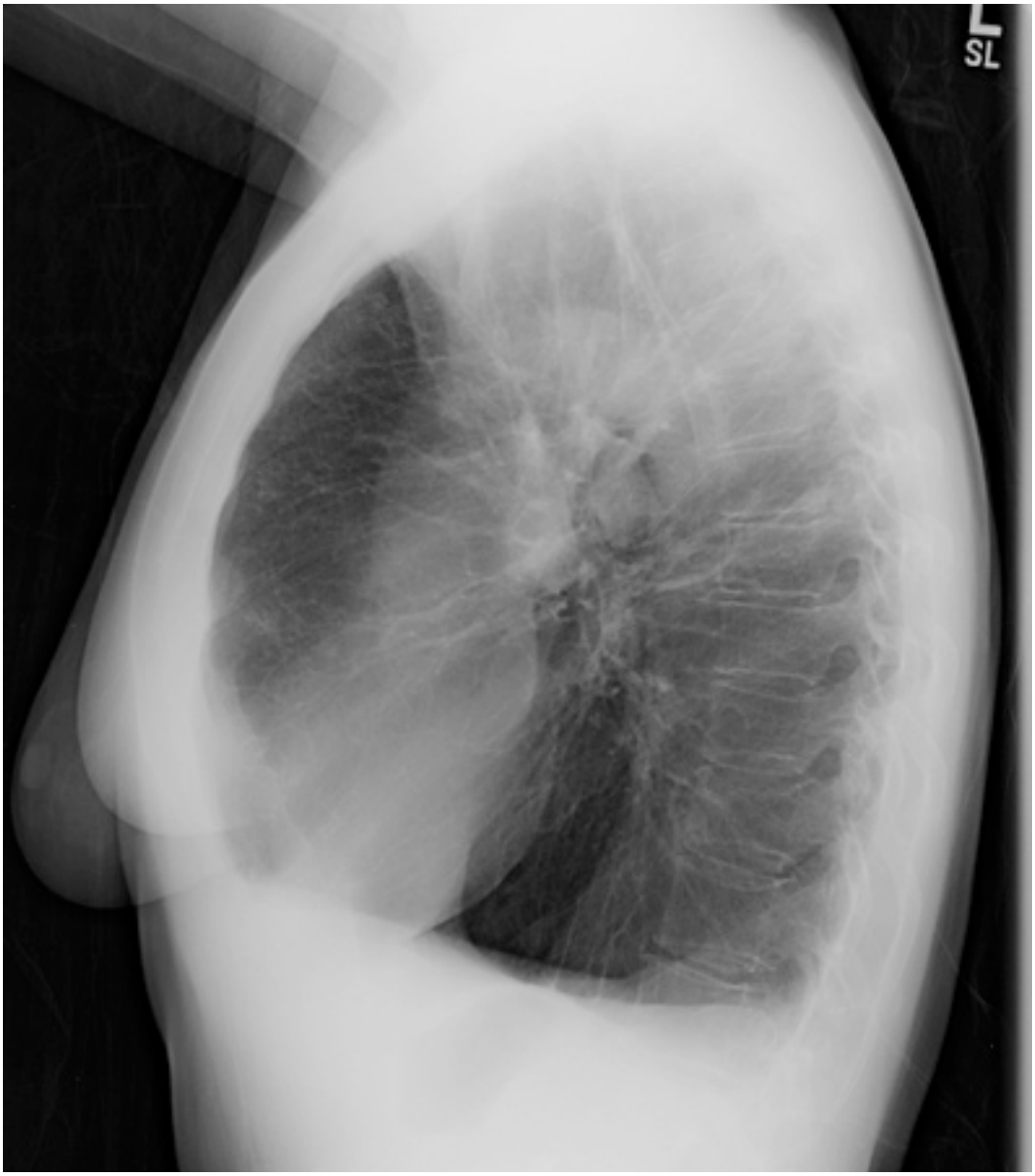

Figure 2: Chest x-ray of AAT deficiency (lateral view)

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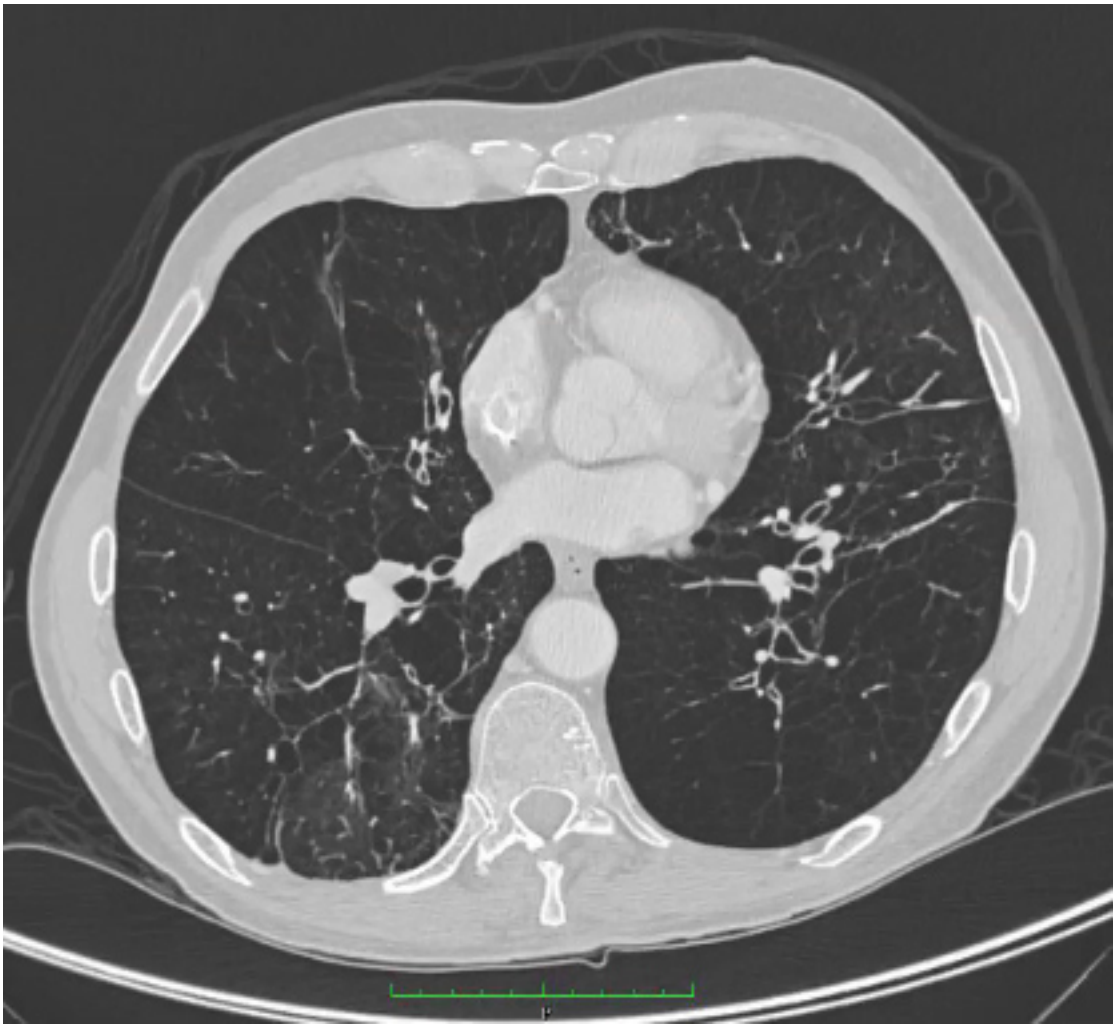

Figure 3: CT of advanced emphysema in a patient with AAT deficiency

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This approach is in line with the guidance of the International Bureau of Weights and Measures Service.

Figure 1 – BMJ Best Practice Numeral Style

5-digit numerals: 10,000

4-digit numerals: 1000

numerals < 1: 0.25

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