Alpha-1 Antitrypsin Deficiency (AAT; Alpha-1)

Case related questions.

Scenario 1:
Mr. C is a 50-year-old male, former smoker with past medical history of obesity (body mass index 38) coming into clinic for progressive dyspnea on exertion. His primary care doctor had ordered pulmonary function testing (PFT) 5 years ago which showed a mild obstructive ventilatory defect without a bronchodilator response, normal total lung capacity (TLC), and normal diffusing capacity (DLCO). He prescribed him albuterol as needed. He reports the albuterol did not help him much. He had "breathing problems" as a child. He has allergies to dust mites, pollen, and perfumes. He reports he has family members with emphysema.

Question 1: What etiologies of his dyspnea should we consider? What tests would you like to obtain?

Scenario 1 cont.:
Further questioning reveals that Mr. C's dyspnea has been slowly progressing over the past few years, and he has also noticed some mild intermittent wheezing but no significant cough or sputum production. His symptoms get worse around dust. He denies chest pain, orthopnea, paroxysmal nocturnal dyspnea, and lower extremity edema. He stopped smoking 4 years ago but used to smoke 1 pack per day for 6 years (6 pack years). He works in accounting.

His family history is notable for asthma in his father, who was also a smoker, asthma in his 2 older siblings that are non-smokers, and his maternal aunt who had emphysema but never smoked.

His hemoglobin is 14 and his eosinophil absolute count is 310.

Chest x-ray in clinic which reports mild flattening of the diaphragmatic domes and PFTs again reveal mild obstruction without a bronchodilator response.

You decide to treat him as asthma and start him on an inhaled corticosteroid and long-acting beta-agonist given his minimal smoking history.

Question 2: When should we consider Alpha-1 antitrypsin deficiency?

Question 3: Why should we test?

Scenario 1 cont.:
Mr. C comes for a follow-up visit with increasing wheezing and shortness of breath and new thick greenish mucus production. You start him on a course of prednisone 40 mg for 5 days and azithromycin for what seems more like a COPD exacerbation.

Given the suspicion of Alpha-1 antitrypsin deficiency, Mr. C's serum AAT levels are checked, and the results come back normal at 150 mg/dL.

Question 4: What is the appropriate testing for diagnosis of Alpha-1 antitrypsin deficiency?

Question 5: What are the different AAT deficiency genotypes? What do they mean in terms of clinical course (disease progression)?

Scenario 1 cont.:
Mr. C's genotype is also checked, and results return as Pi*MZ. Patients with this genotype can have AAT levels in the normal range, especially if testing is obtained during an acute inflammatory process (infection).

Question 6: What is the importance of smoking cessation in this population?

Scenario 1 cont.:
You repeat PFTs which show a moderate obstructive ventilatory defect with moderate gas transfer defect. You decide to obtain a CT Chest which shows emphysema.

Mr. C has now quit smoking and is interested in learning more about specific treatments for his condition.

Question 7: When should we start augmentation therapy?

Scenario 1 cont.:
Given his diagnosis, Mr. C is concerned about the health of his children and other family members. His daughter, age 35, comes to your clinic. She had her PCP send a phenotype and level. Her results are Pi*MZ and AAT level of 78 mg/dL.

Question 8: What is the importance of family genetic screening?

Alpha-1 Antitrypsin Deficiency (AAT; Alpha-1)

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Educational Objectives:

1. Review the differential diagnosis and initial evaluation for Alpha-1 Antitrypsin deficiency
2. Review diseases commonly associated with Alpha-1
3. Identify patients who may benefit from augmentation therapy
4. Discuss broader epidemiological implications of genetic screening

Scenario 1:
Mr. C is a 50-year-old male, former smoker with past medical history of obesity (body mass index 38) coming into clinic for progressive dyspnea on exertion. His primary care doctor had ordered pulmonary function testing (PFT) 5 years ago which showed a mild obstructive ventilatory defect without a bronchodilator response, normal total lung capacity (TLC), and normal diffusing capacity (DLCO). He prescribed him albuterol as needed. He reports the albuterol did not help him much. He had "breathing problems" as a child. He has allergies to dust mites, pollen, and perfumes. He reports he has family members with emphysema.

Question 1: What etiologies of his dyspnea should we consider? What tests would you like to obtain?

Given Mr. C's presentation with progressive dyspnea, the absence of a response to bronchodilators, and obstruction on PFTs, we need to consider a range of potential etiologies that could explain his symptoms.

Dyspnea on exertion can be a presentation of Chronic Obstructive Pulmonary Disease (COPD), which would be a likely diagnosis given his smoking history and prior obstruction on PFTs. Occupational exposures may be relevant in determining airway diseases related to the workplace (e.g. hypersensitivity pneumonitis, occupational asthma, pneumoconiosis).

A new diagnosis of adult-onset asthma can occur. According to National Health and Nutrition Examination Survey (NHANES) data 2001-2018, prevalence of an adult asthma diagnosis in the USA is estimated to be 5.5% vs 2.7% in childhood.[1] Moreover, there may be patients with a missed diagnostic opportunity as a child as suggested in this case. Other things to include on a differential diagnosis include heart failure, coronary artery disease/angina, other obstructive airway diseases, such as bronchiectasis (cystic fibrosis (CF) and non-CF) and constrictive bronchiolitis, and sarcoidosis. It is also important to consider other etiologies for emphysema (alpha-1 antitrypsin disease).

A frequently used heuristic is that bronchodilator response equates to likely asthma, and if there is no bronchodilator response, the diagnosis is COPD. However, in population and trial registries, only 31-42% of patients with severe asthma did have a bronchodilator response (BDR). Interestingly, one-fourth to half of patients with COPD can also have a BDR.[2,3] This is without considering other covariates that frequently alter bronchodilator response results (e.g. not withholding controller medications, race-based equations, inappropriate technique, too many prior attempts).[4]

This highlights the importance of avoiding premature bias and continued re-evaluation of pulmonary diagnosis throughout time with patients.

You order a complete blood count (CBC) with differential, chest x-ray, and repeat pulmonary function testing.

Scenario 1 cont.:
Further questioning reveals that Mr. C's dyspnea has been slowly progressing over the past few years, and he has also noticed some mild intermittent wheezing but no significant cough or sputum production. His symptoms get worse around dust. He denies chest pain, orthopnea, paroxysmal nocturnal dyspnea, and lower extremity edema. He stopped smoking 4 years ago but used to smoke 1 pack per day for 6 years (6 pack years). He works in accounting.

His family history is notable for asthma in his father, who was also a smoker, asthma in his 2 older siblings that are non-smokers, and his maternal aunt who had emphysema but never smoked.

His hemoglobin is 14 and his eosinophil absolute count is 310.

Chest x-ray in clinic which reports mild flattening of the diaphragmatic domes and PFTs again reveal mild obstruction without a bronchodilator response.

You decide to treat him as asthma and start him on an inhaled corticosteroid and long-acting beta-agonist given his minimal smoking history.

Question 2: When should we consider Alpha-1 antitrypsin deficiency?

Mr. C's family history of lung disease and minimal smoking history should give you concern about the diagnosis of Alpha-1 antitrypsin deficiency. Adult-onset asthma with airflow obstruction and lack of bronchodilator response is another concerning finding. Alpha-1 antitrypsin (AAT; Alpha-1) deficiency is often missed and initially diagnosed as asthma and/or COPD.

Alpha-1 antitrypsin deficiency is an autosomal co-dominant genetic disease caused by mutations in the SERPINA1 gene leading to impaired production of AAT, a protease inhibitor that regulates enzymes such as elastase, trypsin, chymotrypsin, and thrombin. In AAT deficiency, unchecked alveolar neutrophil elastase activity results in progressive lung damage.

The 2003 Guidelines from the American Thoracic Society/European Respiratory Society recommend considering Alpha-1 antitrypsin deficiency in patients with one or more of the following characteristics[4]:

Grade A Recommendation (Genetic testing recommended):

- Symptomatic adults with emphysema, COPD, or asthma with airflow obstruction that is incompletely reversible after aggressive treatment with bronchodilators
- Individuals with unexplained liver disease (including neonates, children, adults, and the elderly)
- Asymptomatic individuals with persistent obstruction on PFTs with identifiable risk factors (cigarette smoking, occupational exposure)
- Adults with necrotizing panniculitis
- Siblings of an individual with AAT deficiency

Grade B Recommendation (Genetic testing should be discussed and could reasonably be accepted or declined):

- Adults with bronchiectasis without evident etiology
- Adolescents with persistent airflow obstruction
- Asymptomatic individuals with persistent airflow obstruction and no risk factors
- Adults with c-ANCA (anti-neutrophil cytoplasmic autoantibody) positive (anti-proteinase 3-positive) vasculitis

Clinical factors that should raise your suspicion of AAT deficiency:

1. Early onset emphysema (age 45 or younger)
2. Emphysema in the absence of recognized risk factors (e.g., smoking, occupational dust exposure, etc.)
3. Emphysema with prominent basilar hyperlucency on imaging
4. Unexplained liver disease
5. Necrotizing panniculitis
6. Anti-proteinase 3-positive vasculitis (c-ANCA vasculitis)
7. Family history of emphysema, bronchiectasis, liver disease, and/or panniculitis

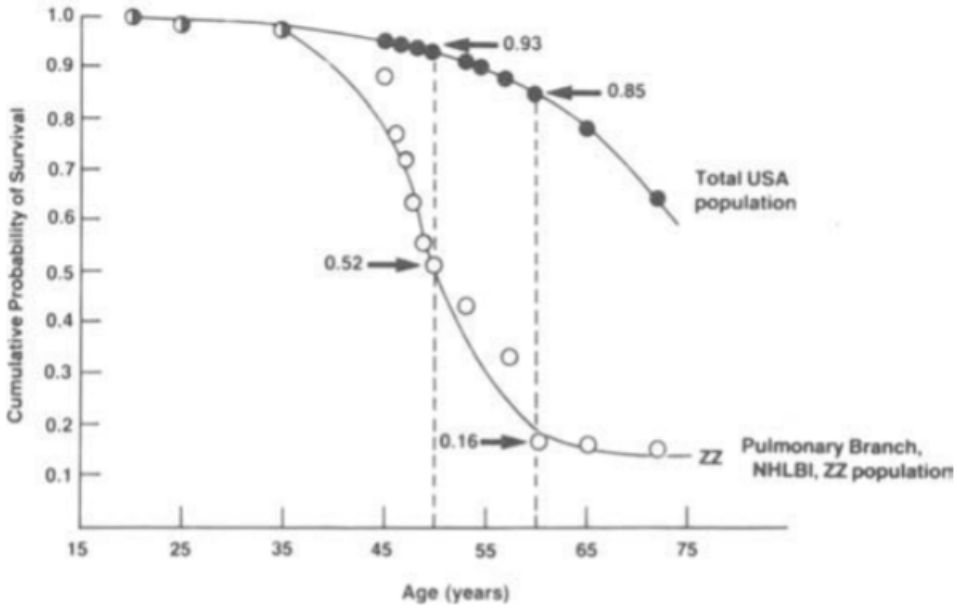
The World Health Organization recommends testing for AAT deficiency in every patient with COPD diagnosis or adult-onset asthma.[5] This has been supported by COPD Global Initiative for chronic obstructive Lung Disease (GOLD) guidelines for over a decade.[6]

Despite this strong recommendation throughout the years, Alpha-1 screening efforts are inadequate, ranging from 5.6% to 39.5%.[7,8] In one UK cohort, only 2.2% of COPD patients diagnosed before the age of 60 had any record of being tested for Alpha-1.[9] In North America, the prevalence of Alpha-1 antitrypsin deficiency is estimated to be about 1 per 3000 to 5000 people, similar to that of cystic fibrosis.[10,11,12] Alpha-1 antitrypsin deficiency is not only a rare disease, but a disease that is rarely diagnosed.[13]

It is also worth considering Alpha-1 in patients with bronchiectasis without evident etiology. However, there is no consensus in the literature as to whether bronchiectasis is specifically associated with Alpha-1, so it requires a risk/benefit conversation with patients prior to testing.[4]

Question 3: Why should we test?

Figure 1: Survival and A1AT[14]



Patients with Alpha-1, specifically Pi*ZZ and pulmonary symptoms have a lower probability of survival than the general population.

- 52% vs 92% at age 50
- 16% vs 85% at age 60

There is an average delay of 8 years before Alpha-1 diagnosis, with patients seeing an average of 2.7 physicians before arriving at a correct diagnosis.[15] A delayed diagnosis is associated with significantly worse overall survival and transplant-free survival.[16]

Scenario 1 cont.:
Mr. C comes for a follow-up visit with increasing wheezing and shortness of breath and new thick greenish mucus production. You start him on a course of prednisone 40 mg for 5 days and azithromycin for what seems more like a COPD exacerbation.

Given the suspicion of Alpha-1 antitrypsin deficiency, Mr. C's serum AAT levels are checked, and the results come back normal at 150 mg/dL.

Question 4: What is the appropriate testing for diagnosis of Alpha-1 antitrypsin deficiency?

While there is some variability in testing between countries, traditionally, the first step to testing was determining Alpha-1 antitrypsin (AAT) levels.

This test is commonly performed using a technique called nephelometry.[17] Normal AAT nephelometry levels range between 83-220 mg/dL.[4] Deficiency is charactered by plasma levels of less than 20micromol/L.

We, along with some experts, recommend testing the phenotype in conjunction with the AAT level.[18] Most commercial phenotype tests available in the USA will result with the genotype and a corresponding AAT level.

AAT is an acute phase reactant, meaning that blood levels of the protein can rise by 75–100% in response to inflammation, injury, or infection.[19] Some genotypes may express borderline to normal AAT levels.

Genotyping is conducted via PCR and detects specific gene mutations including rare and null variants. However, genotyping is limited in that it can only identify known sequence defects and requires specific primers – if primers are not available, it can lead to false negative results.[17] Finally, whole gene sequencing can be used to identify rarer variants and stop mutations, but tends to be more expensive. [17]

Table: AAT Testing Options[4]

Test	Purpose[1]	Method[1]	Notes[1,2]
Serum AAT level	Quantitative: measures circulating AAT	Nephelometry	Levels may be altered •**May not detect carriers of the Z allele**
Genotyping	Qualitative: identifies known alleles	PCR-based assay using genomic DNA, extracted from circulating mononuclear blood cells	•New or rare alleles may not be detected (only known defects)
Pi type (Phenotyping)	Qualitative: identifies specific AAT variants	IEF (isoelectric focusing)	•Technically challenging to perform and interpret •Limited access to testing •May detect new or rare variants
Gene Sequencing	Provides all nucleotides in gene	Gene sequencing	•Identifies rare or unidentified alleles •More costly and time consuming

AAT, alpha1 antitrypsin; DBS, dried blood spot; IEF, isoelectric focusing; PCR, polymerase chain reaction; RID, radial immunodiffusion; WBC, white blood cell.

Scenario 1 cont.:
Mr. C's genotype is also checked, and results return as Pi*MZ. Patients with this genotype can have AAT levels in the normal range, especially if testing is obtained during an acute inflammatory process (infection).

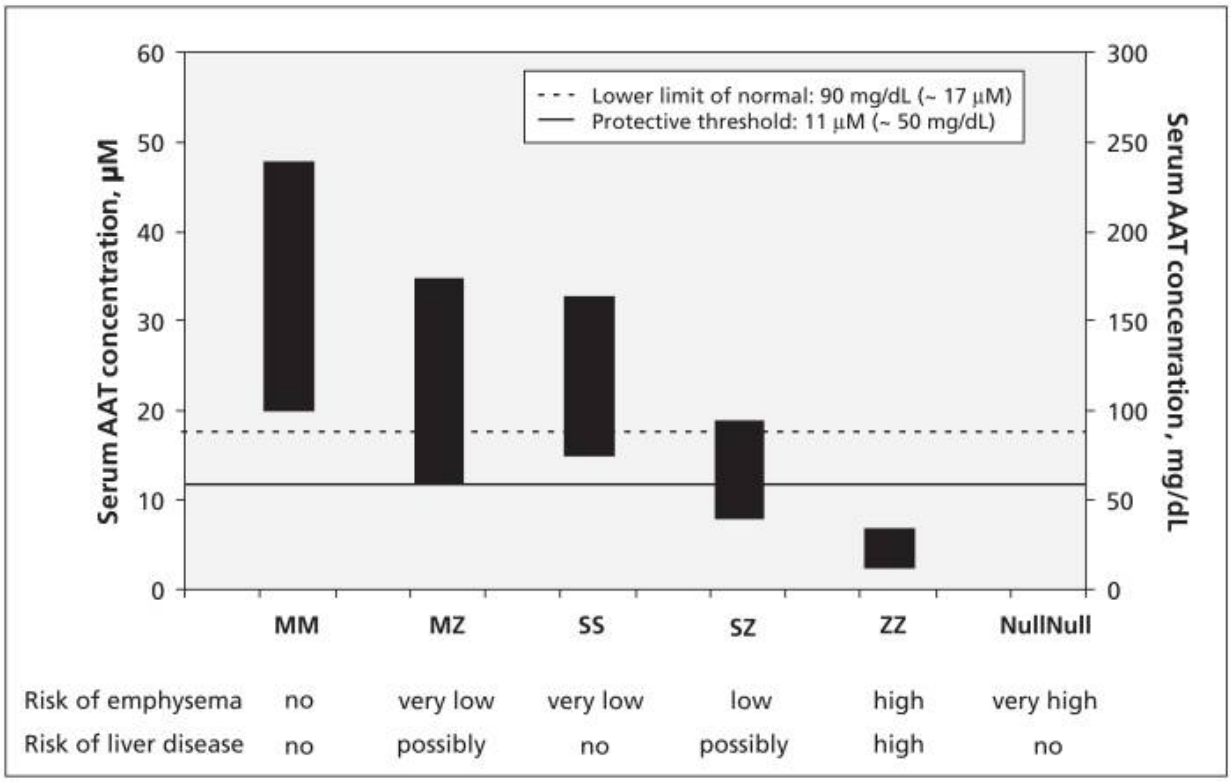
Question 5: What are the different AAT deficiency genotypes? What do they mean in terms of clinical course (disease progression)?

The most common genotype is MM, which produces normal serum levels of alpha-1 antitrypsin. Most people with severe deficiency are homozygous for the Z allele (ZZ).

See Figure 2 for relative risks of lung and liver disease based on genotype.

Liver disease usually presents in the first four decades of life, while lung disease presents later.

Figure 2: AAT Phenotypes, AAT Levels, and Risk of Disease[20]



Scenario 1 cont:
Mr. C is lost to follow up and comes back 7 years later to your clinic. Despite the confirmed diagnosis of alpha-1 antitrypsin deficiency, Mr. C has resumed smoking occasionally and reports his breathing has gotten worse.

Question 6: What is the importance of smoking cessation in this population?

The development of emphysema in patients with AAT deficiency is thought to be caused by a protease-antiprotease imbalance. AAT is a vital component of antiprotease defenses in the alveolar spaces as it inhibits the activity of neutrophil elastase which works to breakdown elastin and other extracellular matrix components in the lungs. If AAT is reduced, neutrophil elastase (protease activity) overpowers the antiprotease activity leading to destruction of the lungs, particularly in the lower respiratory tract. Cigarette smoke worsens this imbalance as it further inactivates AAT as well as recruits inflammatory cells leading to increased proteolytic destruction.[4,17]

Smoking cessation is incredibly important in this population. Several studies have shown that patients with AAT deficiency who smoke are not only at increased risk of developing COPD but are more likely to develop symptoms earlier on and with increased severity. These patients have been shown to have lower Force Expiratory Volume in 1 second (FEV1), a more rapid decline in FEV1, and an increased mortality rate. It is very important to encourage patients to quit smoking as soon as possible as early smoking cessation has been shown to decrease the rate of FEV1 decline and portends better prognosis.[4]

Identifying AAT genotype may play a beneficial role in encouraging smoking cessation. The Z genotype has been shown to inhibit neutrophil elastase at a slower rate than the M phenotype, placing patients with the Z genotype at higher risk for lung destruction. Patients with the Z phenotype should be strongly encouraged to abstain from smoking as they are at higher risk for developing emphysema.

Scenario 1 cont.:
You repeat PFTs which show a moderate obstructive ventilatory defect with moderate gas transfer defect. You decide to obtain a CT Chest which shows emphysema.

Mr. C has now quit smoking and is interested in learning more about specific treatments for his condition.

Question 7: When should we start augmentation therapy?

Patients should have all of the following:

- Age ≥18
- A1AT level <57 mg/dL or 11 micromol/L
- Genotype associated with alpha-1 antitrypsin deficiency
- FEV1 ≤65% predicted but ≥30% predicted (<30% hasn't been studied)
- No contraindications to therapy. Contraindications include current smoker, IgA deficiency, and/or allergies/anaphylaxis to a component of the AAT formulation

There are no specific recommendations to follow AAT levels at any interval after augmentation therapy has been initiated.

Goals of AAT augmentation include:

- Modest slow in lung function decline
- Possible effect on exacerbations (though not consistently seen in studies)
- Possible survival benefit

Early referral to a lung transplant capable facility should be considered.

Scenario 1 cont.:

Given his diagnosis, Mr. C is concerned about the health of his children and other family members. His daughter, age 35, comes to your clinic. She had her PCP send a phenotype and level. Her results are Pi*MZ and AAT level of 78 mg/dL.

Question 8: What is the importance of family genetic screening?

Screening family members allows for early identification of AAT deficiency before symptoms develop. This enables preventive measures to be taken, such as the following:

- Avoiding smoking and exposure to secondhand smoke
- Limiting exposure to occupational and environmental pollutants
- Making informed decisions about lifestyle and career choices

Early detection is particularly crucial because tobacco smoking often begins during adolescence, and avoiding smoking can significantly impact lung health in AAT deficiency patients.

For family members who smoke, a diagnosis of AAT deficiency can be a powerful motivator for quitting. In one study, 78% of current smokers reported a high likelihood of smoking cessation if diagnosed with AAT deficiency.[21]

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