Alpha-1-Antitrypsin Deficiency

Jeff Wilson MD

- A 32 year old man was seen for severe exertional dyspnea which had developed over the previous 1-2 years. He had a ~20 pack year history of smoking. Physical exam revealed a thin man with diminished breath sounds and diffuse wheezing.
- Pulmonary function tests showed severe, irreversible airflow obstruction. His last FEV1 was 0.5L (14% predicted) at age 38. He was unable to stop smoking and died at age 40 from respiratory failure.

- A 68 year old woman was evaluated for a several year history of worsening exertional dyspnea, cough and purulent sputum. She had a 5-10 pack year history of smoking but had quit at age 30. Physical examination revealed bilateral wheezing and basilar crackles. PFTs showed a FEV1 of 0.72L (34% predicted) and chest CT scan revealed bilateral bronchiectasis and panacinar emphysema, most prominent in the lower lobes.

- A 39 year-old woman has no respiratory symptoms. She runs several miles 3 times per week. She is a life-long nonsmoker. Family history is significant for severe Alpha-1-Antitrypsin deficiency in her mother.
- Physical examination is normal.
- Over the next 9 years her lung function tests show evidence of accelerated decline but remain in the low normal range.

- A newborn infant is jaundiced. After one month her bilirubin remains high – total bilirubin 11.2 – with mild elevation of hepatic transaminases. Over the next two months this resolves without specific treatment.

- A 68 year man (ex-smoker) with COPD develops fatigue and weight loss. Evaluation eventually reveals a large liver mass which is biopsied and found to be hepatocellular carcinoma

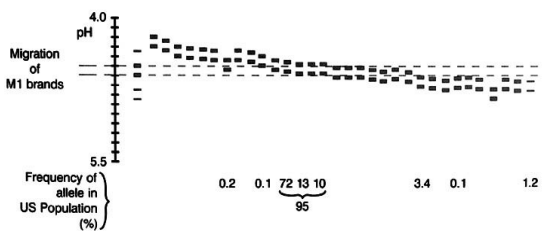
Alpha-1-Antitrypsin

- 394 amino acid glycoprotein – protease inhibitor
- Synthesized primarily in hepatocytes (ER) (>80%) – lessor amounts in monocytes, macrophages, pancreas, lung alveolar cells, and endothelial cells
- Autosomal codominant pattern of inheritance with > 150 alleles described
- Specific substrate – neutrophil elastase – also neutralizes other serine proteases (PR3)

Classification of A1AT Variants – 4 Basic Groups

- Normal (M_{1-3})
- Deficient:
  - Z – (Glu342Lys)
  - S – (Glu264Val)
- Null
- Dysfunctional (F allele)

POLYACRYLAMIDE GEL ISOELECTRIC FOCUSING



From Gadek & Chrystal, in Stanbury et al (eds): *The Metabolic Basis of Inherited Disease*, ed 5.

Quantitative Tests and Interpretation

- Nephelometry – Normal range ~90 – 200 mg/dl and "protective" threshold 50mg/dl or 11uM.
- Radial immunodiffusion - overestimates AAT levels by 35-40%. Normal range 150/200 – 350/400mg/dl and "protective" threshold 80mg/dl
- Interpretation of A1AT levels should take into account it is an acute phase reactant

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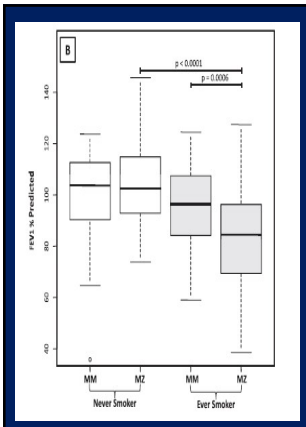
A1AT Threshold Protective Level Concept

Phenotype	Serum Level (mg/dl)	Emphysema Risk
MM	150-350	Background
SS	100-140	Background
MZ (ns)	90-150	Background
SZ	45-80	Moderate (20-25%)
ZZ	15-50	High (80-100%)
Null-Null	0	High (100%)

Measured by radial immunodiffusion



Post-bronchodilator

Risk of COPD in MZ Heterozygotes

• Family-based study of MM and MZ non-index subjects recruited from 51 MZ index probands with COPD

• MZ genotype associated with an elevated odds ratio for COPD of ~5 for all relatives and ~10 for ever-smokers

AJRCCM 2014;189:419-27

U.S. A1AT Epidemiology

- Frequency of "Z" allele 1-2% in Whites, lower in Blacks and ~absent in Asian populations

  Ther Adv Respir Dis 2010;4(2):63-71

- Estimated ~50-100,000 PiZZ individuals in the U.S. - less than 10% diagnosed

  Am Rev Resp Dis 1989;140:961

Alpha-1-antitrypsin in Montana

Between 2017 – 2022:

- 61 Medicaid claims with A1AT code
- 106 ED visits
- 140 hospitalizations

Population - 1,142,746

- Frequency Z allele 1% - 114 ZZ individuals
- Frequency Z allele 2% - 457 ZZ individuals

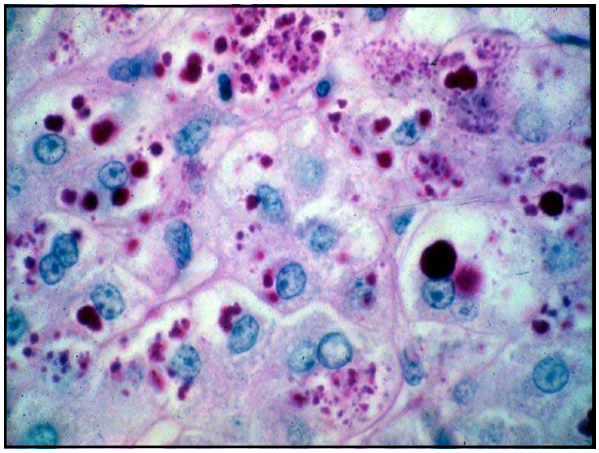
Elastase/Anti-Elastase Balance Hypothesis of Emphysema

- Risk of emphysema is increased in A1AT deficient individuals
- Imbalance between neutrophil elastase in the lung and the elastase inhibitor A1AT – "toxic loss of function"
- Cigarette smoking is associated with the recruitment of inflammatory cells into the lung - increasing the elastase burden and oxidizing the active binding site of the A1AT molecule
- Polymers of the "Z" allele are chemotactic for neutrophils – "toxic gain of function"

Liver Disease in A1AT Deficiency

- Occurs nearly exclusively in carriers of the "Z" allele – usually homozygotes
- Associated with accumulation of mutant A1AT protein in the endoplasmic reticulum of hepatocytes – in association with ineffective intracellular degradation mechanisms – "toxic gain of function"
- Infants - jaundice in ~10% and elevated ALT in ~3/4 of infants with ZZ genotype. Usually resolves during childhood – but liver disease mortality 2-3%
- Adults - increased risk of cirrhosis and liver cancer

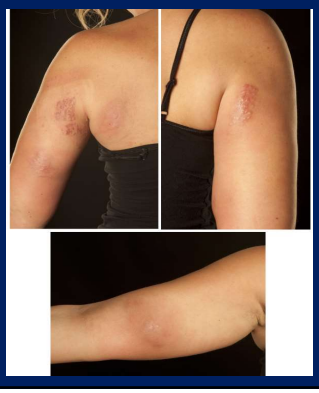
COPD 2013;10(S1):35-43 NEJM 2020; 382:1443-55



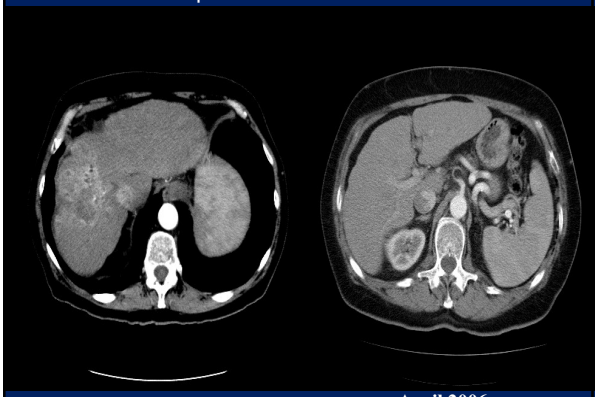
Clinical Presentation of A1AT Deficiency

- Majority of patients present with respiratory symptoms – dyspnea, cough and wheezing
- Smokers with severe A1AT deficiency typically present at a relatively young age (age 30-40), and are frequently diagnosed with asthma
- Unexplained liver disease 2nd most common presentation. ANCA vasculitis and panniculitis less common
- Commonly a long delay in diagnosis from time of initial symptoms

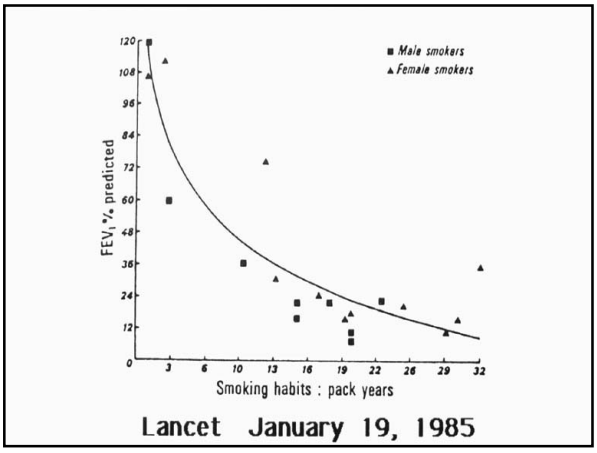
Panniculitis



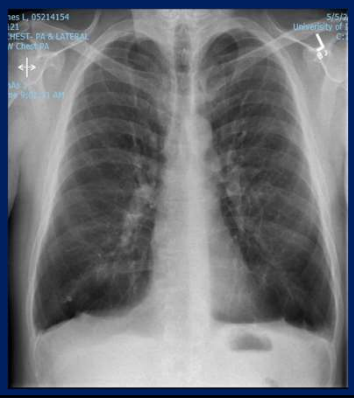
Hepatocellular Carcinoma

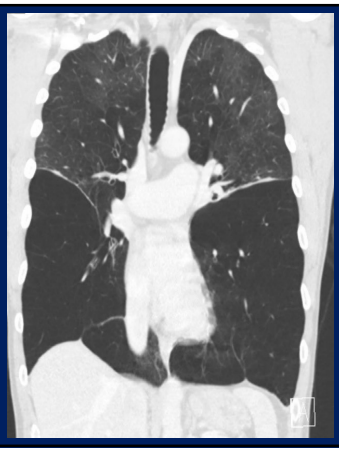


August 2007 April 2006



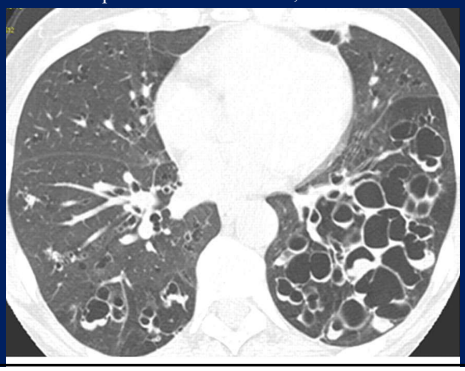
Lower Lobe Predominance of Emphysema in Severe A1AT Deficiency





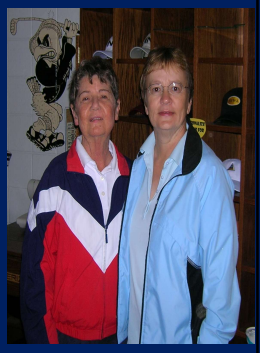
Bronchiectasis in Alpha-1-Antitrypsin Deficiency

Am J Respir Crit Care Med 2007;176:1215-21



Delay in Diagnosis is Common

- 1994 patient mail survey – mean time from onset of symptoms to diagnosis - 7.2 years and 44% saw ≥ 3 physicians
  Cleveland Clin J Med 1994;61:461-67
- 2003 mail survey – mean time from onset of symptoms to diagnosis – 5.6 years
  Chest 2005;128:1989-1994
- 2013 – diagnostic delay of 6 and 7 years in Italy and Germany respectively
  Respir Med 2013;107:1400-08



Who Should be Tested for A1AT Deficiency?

- Individuals with irreversible airflow obstruction (COPD) – especially when it seems out of proportion to their age and/or smoking history
- Individuals with unexplained liver disease
- Individuals with unexplained bronchiectasis
- Individuals with panniculitis and C-ANCA positive vasculitis
- Family members of individuals with A1AT deficiency

*Testing should always be preceded by a discussion of the risks/benefits

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Pre-dispositional Testing and Screening for A1AT Deficiency

- Testing of siblings of homozygous – PiZZ – individuals is recommended
- Testing other family members of homozygous individuals and all family members of heterozygotes – PiMZ - should be discussed
- Testing should be discussed with partners of individuals with A1AT Deficiency
- Screening of newborns/adolescents is not currently recommended (controversial).

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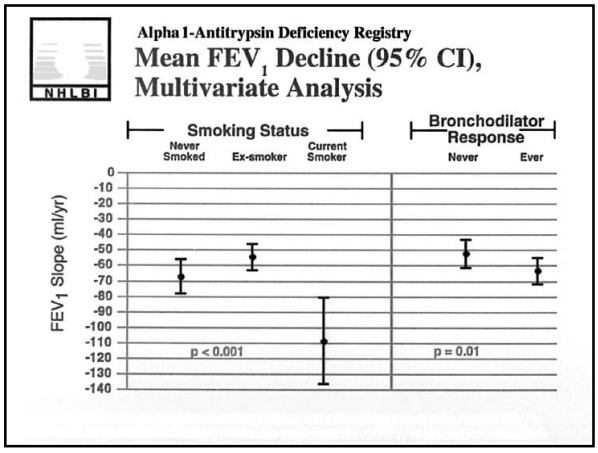
Impacts of Establishing a Diagnosis

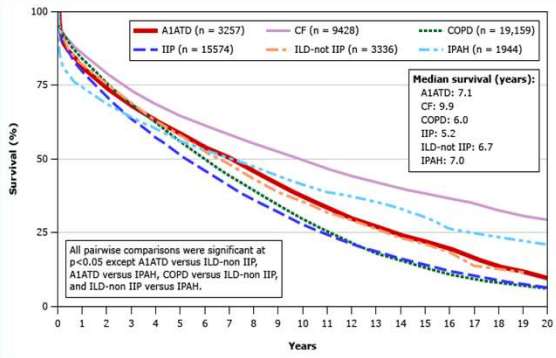
- The need to test family members
- Opportunity to favorably affect smoking behavior
- Opportunity to counsel deficient individuals regarding hazardous (dust exposure) careers
- Opportunity to consider specific (augmentation) therapy for individuals with severe deficiency
- Opportunity to counsel good liver health habits

Annals ATS 2016;13(4):S317-325

Treatment of A1AT Deficiency

- Smoking cessation and avoidance of other environmental respiratory irritants
- Bronchodilators/oxygen
- Exercise
- Vaccinations
- Transplantation/LVR
- Augmentation therapy
- New Therapies
- Modest(or less) ETOH
- Maintain normal body weight



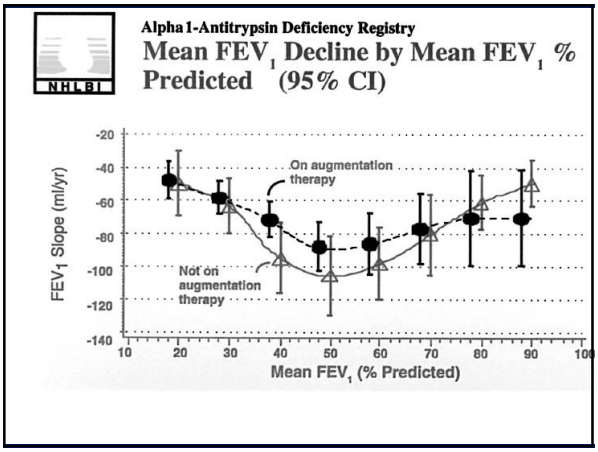


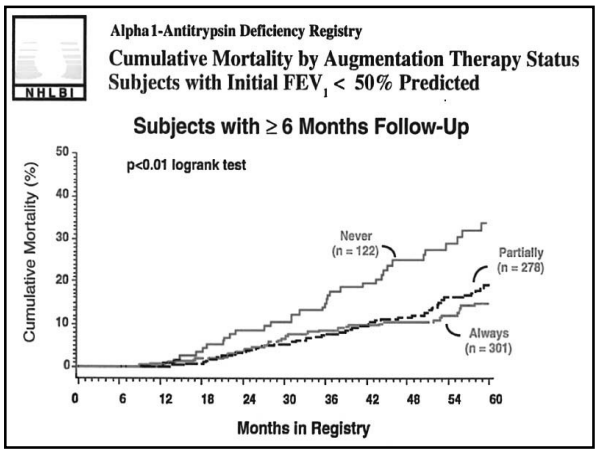
Journal Heart and Lung Transplantation 2019;28 (10):1015-66

A1AT Augmentation

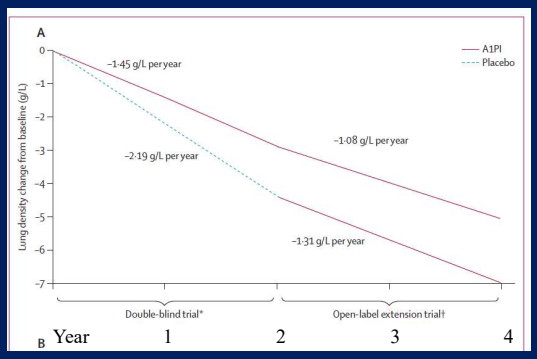
- FDA approved in 1987 based on pharmacokinetic and safety data
- Derived from pooled human serum
- Weekly infusions for life
- Cost - > $100,000/yr – weight-based dosing (60mg/kg/week)
- Cost per year of life saved estimated at ~14,000 to > 100,000$ using NIH Registry survival data
- No reported cases of viral transmission

Chest 2000; 117:875-880





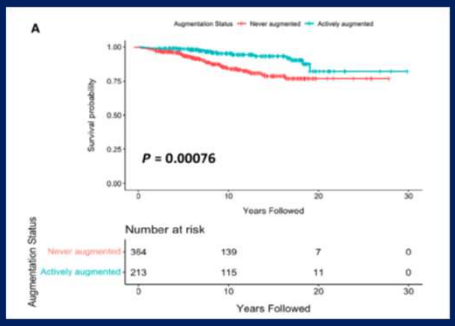
Changes in Lung Density with Augmentation Therapy



No difference in QOL, FEV1, exacerbations

Lancet 2015: 386:360-68

Multinational Registry Analysis – Ireland, Austria and Switzerland

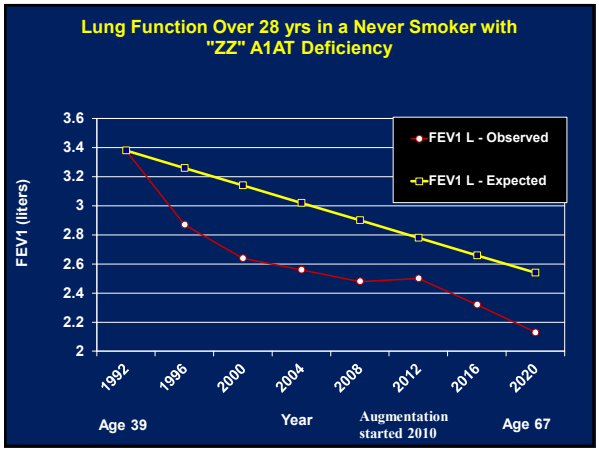


Augmentation independently associated with higher survival

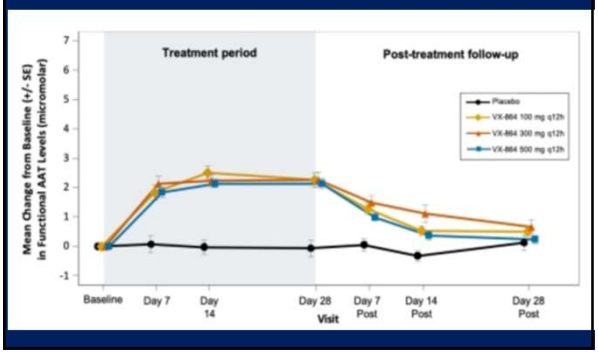
AJRCCM 2023;208(9):964-74

A1AT Augmentation Therapy Patient Selection Guidelines

- Presence of severe A1AT deficiency - (PiZZ, Z-null or null-null, FZ, etc phenotypes)
- Serum A1AT levels <50mg/dl or 11um (immunodiffusion assay)
- Abnormal lung function - (airflow obstruction/emphysema) – progressive despite smoking cessation



VX-864 study – small molecule promoting folding of mutant Z protein



A1AT Deficiency - Conclusions

- Severe A1AT deficiency most frequently presents as irreversible airflow obstruction which is generally out of proportion to the patients age and smoking history
- The condition is underdiagnosed – look for it
- Identification of AIAT deficiency aids smoking cessation, allows for early identification of the condition in family members and may result in delayed disease progression via augmentation therapy