Alpha 1-Antitrypsin Deficiency: State of the Art
James K. Stoller, M.D., M.S.

1. Alpha 1-Antitrypsin Deficiency: State of the Art

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Cleveland Clinic

2. Alpha 1-antitrypsin deficiency: state of the art

- History
- Epidemiology of alpha 1-antitrypsin (AAT) deficiency
- Physiology of AAT and pathophysiology of the deficiency state
- Clinical features of individuals with AAT deficiency

3. Alpha 1-antitrypsin deficiency: state of the art (2)

- Natural history of AAT deficiency
- Diagnosis of AAT deficiency
- Treatment of AAT deficiency:
  - Conventional treatment of COPD
  - Augmentation therapy
  - Lung transplantation
  - Lung volume reduction surgery
  - Gene therapy
  - Other

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Alpha 1-Antitrypsin Deficiency: State of the Art
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My disclosures of significant relationships

- Scientific consultant
  - Talecris
  - CSL Behring
  - Boehringer-Ingelheim
  - AsthmaTx
  - Kamada
- Lectures supported
  - Talecris
  - CSL Behring
  - Baxter
  - Grifols

A registry of patients with deficiency of alpha 1-antitrypsin

Division of Lung Diseases

Primary objective of the registry

- To characterize the clinical and laboratory course of severe alpha 1-antitrypsin deficiency, whether or not patient is receiving augmentation therapy

The registry, because of its inherent study design, is not a clinical trial to evaluate the efficacy of alpha 1-antitrypsin augmentation therapy but rather a mechanism to collect and analyze clinical data useful for understanding the natural history of the deficiency under different conditions.
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American Thoracic Society Documents

- Evidence-based, systematic review of current literature regarding the management of individuals with alpha 1-antitrypsin deficiency
- Sponsored by ATS, ERS, ACCP, and AARC and developed by an international group of thought leaders with graded recommendations

Alpha 1-antitrypsin deficiency: state of the art

- History
- Epidemiology of alpha 1-antitrypsin (AAT) deficiency
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- Clinical features of individuals with AAT deficiency

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Medline citations for the term “alpha 1-antitrypsin deficiency”, 1967 – 2010

Total 2706 citations

Alpha 1-antitrypsin deficiency: state of the art

• History
• Epidemiology of alpha 1-antitrypsin (AAT) deficiency
• Physiology of AAT and pathophysiology of the deficiency state
• Clinical features of individuals with AAT deficiency
Prevalence of alpha 1-antitrypsin (AAT) deficiency

- Estimated U.S. prevalence of emphysema 2.1 – 3.1 million (based on NHIS [1985] and NCHS [2000])
- 2 – 3% of all emphysema patients have severe deficiency of AAT (Lieberman et al.)
- Estimated U.S. prevalence of patients with emphysema due to AAT deficiency is 63,000 – 93,000
- Total prevalence of AAT deficiency is higher because some patients do not have emphysema

Prevalence of PI*Z alpha 1-antitrypsin (AAT) deficient patients in screening studies

<table>
<thead>
<tr>
<th>Author (date)</th>
<th>N screened</th>
<th>Population</th>
<th>Prevalence of PI*Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saris NE et al. (1972)</td>
<td>664</td>
<td>College students</td>
<td>1/664 (0.15%)</td>
</tr>
<tr>
<td>O'Brien ML et al. (1978)</td>
<td>107,033</td>
<td>Newborns</td>
<td>1/5,097 (0.02%)</td>
</tr>
<tr>
<td>Dijkman JH et al. (1980)</td>
<td>95,083</td>
<td>Newborns</td>
<td>1/3,801 (0.0263%)</td>
</tr>
<tr>
<td>Kimpen J et al. (1988)</td>
<td>10,329</td>
<td>Newborns</td>
<td>1/1,722 (0.058%)</td>
</tr>
<tr>
<td>Sveger T et al. (1988)</td>
<td>200,000</td>
<td>Infants</td>
<td>1/1,575 (0.06%)</td>
</tr>
</tbody>
</table>

Alpha 1-antitrypsin deficiency is frequently undiagnosed

- Of 20,000 blood donors in St. Louis, 7 PI*Z individuals were identified (prevalence 1/2900)
- This rate predicts 700 PI*Z individuals in St. Louis (population 2 million)
- But, only 28 PI*Z individuals were known to the medical community (4% of expected)
- Most individuals with severe AAT deficiency are unrecognized
Most individuals with alpha 1-antitrypsin deficiency escape detection

- 96% undiagnosed
- 4% diagnosed

No signs or symptoms
Symptomatic but misdiagnosed


Alpha 1-antitrypsin deficiency is under-recognized

- Canada:
  - Expected - 42,372
  - Diagnosed - 144 (0.69% of expected)
- Italy:
  - Expected - 46,086
  - Diagnosed - 100 (0.22% of expected)
- Holland:
  - Expected - 9,740
  - Diagnosed - 136 (1.4% of expected)
- N. Zealand/Australia:
  - Expected - 33,707
  - Diagnosed - 93 (0.28% of expected)
- Spain:
  - Expected - 86,899
  - Diagnosed - 90 (0.10% of expected)
- Sweden:
  - Expected - 79,456
  - Diagnosed - 324 (4.1% of expected)
- UK:
  - Expected - 79,456
  - Diagnosed - 324 (4.1% of expected)

Total: Expected - 305,009; Diagnosed - 1,068 (0.35% of expected)

Survey of A1AT-deficient readers of the alpha 1 news

<table>
<thead>
<tr>
<th>Feature</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>48.8 years</td>
</tr>
<tr>
<td>Smoking status</td>
<td>Ex-smoker 81.2%</td>
</tr>
<tr>
<td></td>
<td>Current smoker 1.3%</td>
</tr>
<tr>
<td>Presence of dyspnea</td>
<td>90.2%</td>
</tr>
<tr>
<td>Mean age at onset of lung symptoms</td>
<td>35 years</td>
</tr>
<tr>
<td>Mean interval between first lung symptom and first diagnosis of A1AT deficiency</td>
<td>7.2 yrs ± 8.3 yrs</td>
</tr>
</tbody>
</table>

Mail survey sent to ~ 850 A1AT-deficient individuals with response by 414 (49%), of whom 304 report severe deficiency (300 PI*ZZ)

Survey of A1AT-deficient readers of the alpha 1 news (2)

Number of doctors seen until first diagnosis of A1AT deficiency

1st doctor made diagnosis 25.1%
2nd doctor 31.2%
3rd doctor 17.6%
4th doctor 9.5%
5th doctor 4.1%
6th doctor 12.5%
At least 3 doctors seen 43.7%

For 304 self-reported severely deficient individuals (300 PI*ZZ)

Diagnosis Year Categories
1: Before 1980
2: 1980 - 1985
3: 1986 - 1990
5: 1996 – 2000
6: Since 2000

N = 1953 (of 5222 [37%]) respondents to a questionnaire administered to mailing list of A1F, Alpha 1-Association, and AlphaNet

Trends in diagnosing alpha 1-antitrypsin deficiency

• There has been no significant decrease in the number of physicians seen before initial diagnosis over time
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Physiology of alpha 1-antitrypsin

- Major production site in liver (2 grams/day) but also made in macrophages (including in lung)
  - Provides > 90% of protection against neutrophil elastase in lower respiratory tract
- Translocated to RER, glycosylated, to Golgi, then secreted into bloodstream
- Normal levels:
  - Serum 20 – 53 µM (100 – 220 mg/dl)
  - Interstitium 10 – 40 µM
  - Epithelial lining fluid 2 – 5 µM (10-fold < serum)

Structure of the AAT molecule

- Single chain 394 amino acid glycoprotein (52 kD)
- 3 carbohydrate side chains at asparagine residues (at positions 45, 83, 247)
- 9 helices and 3 pleated sheets
  - 5-stranded A sheet has reactive center loop
  - Reactive site methionine 358 and serine 359
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**Alpha 1-antitrypsin molecule**

- 3-D structure of α1-antitrypsin (left) and neutrophil elastase (right)
- Reactive loop of α1-antitrypsin (red) combines with active pocket (arrow head) of neutrophil elastase to neutralize neutrophil elastase activity
- Binding is very tight and each molecule commits a suicide action

**Function of α1-antitrypsin**

- Neutrophil elastase binds the active site of the α1-antitrypsin molecule
- Entrapment and destruction of neutrophil elastase releases steric energy in α1-antitrypsin
- Catalyzing the elastase to the back side of the molecule - inactivating neutrophil elastase

---

**Mechanisms of Disease**

- **Alpha 1-Antitrypsin Deficiency**
  - **A. Neutropenic Complications**
    - Neutrophil elastase binds the active site of the α1-antitrypsin molecule
    - Entrapment and destruction of neutrophil elastase releases steric energy in α1-antitrypsin
    - Catalyzing the elastase to the back side of the molecule - inactivating neutrophil elastase
Structure of the AAT molecule

- Mutations at the hinge of the reactive loop (Z, Glu 342 → Lys) or at the shutter region (Sihama, Ser 53 → Phe) allow loss of constraints that hold the reactive loop in an exposed position, allowing loop-sheet polymerization.

Mechanism of loop-sheet polymerization


Polymer of Z-type alpha 1-antitrypsin molecules

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Genetics of alpha 1-antitrypsin deficiency

- Autosomal co-dominant inheritance
- PI (Protease Inhibitor) nomenclature, e.g.,
  - PI*allele, e.g., PI*ZZ, PI*MZ
- Over 100 alleles identified to date
- Alleles named by position of migration within an isoelectric field of pH 4.0 – 5.0
  - M allele in middle
  - Z allele closest to pH 5 end due to substitution of lysine for glutamic acid (at position 342) with resultant less negative charge

Concept of a protective threshold serum value* for AAT deficiency

<table>
<thead>
<tr>
<th>Phenotype (PI*)</th>
<th>Serum level (mM)</th>
<th>Serum level (mg/dl)</th>
<th>Emphysema risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI*MM</td>
<td>20 - 53</td>
<td>100 - 220</td>
<td>No increase</td>
</tr>
<tr>
<td>PI*MZ</td>
<td>12 - 35</td>
<td>60 - 150</td>
<td>No increase</td>
</tr>
<tr>
<td>PI*SZ</td>
<td>8 - 19</td>
<td>40 - 110</td>
<td>Mild increase</td>
</tr>
<tr>
<td>PI*ZZ</td>
<td>2.5 - 7</td>
<td>20 - 35</td>
<td>Increased</td>
</tr>
<tr>
<td>PI*Null</td>
<td>Null</td>
<td>0 - 0</td>
<td>Increased</td>
</tr>
</tbody>
</table>

*Proposed protective threshold value = 11 mM or ~57 mg/dl

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Clinical spectrum of alpha 1-antitrypsin deficiency

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Percent</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>74.8%</td>
<td>(184/246)</td>
</tr>
<tr>
<td>Emphysema</td>
<td>44.3%</td>
<td>(100)</td>
</tr>
<tr>
<td>Chronic bronchitis (initial or later)</td>
<td>43.9%</td>
<td>(108)</td>
</tr>
<tr>
<td>Asthma</td>
<td>3.3%</td>
<td>(8)</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>11.3%</td>
<td>(28)</td>
</tr>
<tr>
<td>Liver disease</td>
<td>12.2%</td>
<td>(36)</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>11.8%</td>
<td>(29)</td>
</tr>
<tr>
<td>Neonatal hepatitis</td>
<td>0.4%</td>
<td>(1)</td>
</tr>
<tr>
<td>Hepatoma</td>
<td>3.3%</td>
<td>(3)</td>
</tr>
</tbody>
</table>

N = 246 P/VZ individuals identified from a reference lab roster with follow-up over ≤ 14 y

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Design of the registry
Alpha 1-antitrypsin deficiency registry

- Observational cohort study to evaluate the natural history of alpha 1-antitrypsin deficiency in those receiving vs. not receiving intravenous augmentation therapy
- Not a randomized controlled trial
- Decisions regarding augmentation therapy made by individual managing physicians and participants, not by the registry

Cumulative enrollment in registry
Alpha 1-antitrypsin deficiency registry

Sex and race (N=1129)
Alpha 1-antitrypsin deficiency registry

<table>
<thead>
<tr>
<th>Sex</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>627</td>
<td>55</td>
</tr>
<tr>
<td>Female</td>
<td>502</td>
<td>45</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Race</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>1120</td>
<td>99</td>
</tr>
<tr>
<td>Other</td>
<td>9</td>
<td>1</td>
</tr>
</tbody>
</table>
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### Age (years)

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-30</td>
<td>50</td>
</tr>
<tr>
<td>31-40</td>
<td>309</td>
</tr>
<tr>
<td>41-50</td>
<td>419</td>
</tr>
<tr>
<td>51-60</td>
<td>232</td>
</tr>
<tr>
<td>&gt;60</td>
<td>119</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1129</strong></td>
</tr>
</tbody>
</table>

Mean age ± SD = 46 ± 11

### Employment

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Employment full-time</td>
<td>478</td>
</tr>
<tr>
<td>Employment part-time</td>
<td>123</td>
</tr>
<tr>
<td>Retired or unemployed (medical)</td>
<td>339</td>
</tr>
<tr>
<td>Retired or unemployed (other)</td>
<td>91</td>
</tr>
<tr>
<td>Homemaker</td>
<td>71</td>
</tr>
<tr>
<td>Other/Unknown</td>
<td>27</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1129</strong></td>
</tr>
</tbody>
</table>

### Alpha 1-antitrypsin levels

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>N</th>
<th>Mean (µM)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZZ</td>
<td>992</td>
<td>5.8</td>
<td>2.0 – 10.2</td>
</tr>
<tr>
<td>SZ</td>
<td>10</td>
<td>10.5</td>
<td>9.1 – 11.0</td>
</tr>
<tr>
<td>Nullgranite falls</td>
<td>3</td>
<td>0.0</td>
<td>---</td>
</tr>
<tr>
<td>ZMmarion</td>
<td>3</td>
<td>7.0</td>
<td>4.7 – 9.2</td>
</tr>
<tr>
<td>MheerlenNull</td>
<td>2</td>
<td>8.5</td>
<td>8.2 – 8.9</td>
</tr>
<tr>
<td>Pheerlen/Z</td>
<td>3</td>
<td>1.2</td>
<td>0.5 – 2.0</td>
</tr>
<tr>
<td>Mheerlen/Null</td>
<td>1</td>
<td>1.0</td>
<td>---</td>
</tr>
</tbody>
</table>
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Lung function test results
Alpha 1-antitrypsin deficiency registry

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>Mean (µM)</th>
<th>Standard deviation</th>
<th>Minimum value</th>
<th>Maximum value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC (liters)*</td>
<td>1066</td>
<td>3.7</td>
<td>1.3</td>
<td>1.0</td>
<td>7.8</td>
</tr>
<tr>
<td>FVC % predicted*</td>
<td>1108</td>
<td>75.6</td>
<td>24.9</td>
<td>22.7</td>
<td>150.2</td>
</tr>
<tr>
<td>FEV1 (liters)*</td>
<td>1095</td>
<td>1.7</td>
<td>1.1</td>
<td>0.3</td>
<td>6.3</td>
</tr>
<tr>
<td>FEV1 % predicted*</td>
<td>1108</td>
<td>42.5</td>
<td>29.6</td>
<td>7.4</td>
<td>134.8</td>
</tr>
<tr>
<td>DLCO (mlCO/min/mmHg)</td>
<td>878</td>
<td>16.9</td>
<td>8.5</td>
<td>1.1</td>
<td>47.8</td>
</tr>
<tr>
<td>DLCO % predicted**</td>
<td>878</td>
<td>50.4</td>
<td>22.6</td>
<td>2.6</td>
<td>118.5</td>
</tr>
</tbody>
</table>

* Maximum value post-bronchodilator
* Maximum value pre-bronchodilator


FEV1 percent of predicted normal
Alpha 1-antitrypsin deficiency registry

Self-reported medical history of patient:
lung diseases (N = 1115)
Alpha 1-antitrypsin deficiency registry

<table>
<thead>
<tr>
<th>Disease</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD*</td>
<td>929</td>
<td>83</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>466</td>
<td>42</td>
</tr>
<tr>
<td>Asthma</td>
<td>390</td>
<td>35</td>
</tr>
<tr>
<td>Allergies affecting respiratory tract</td>
<td>323</td>
<td>29</td>
</tr>
<tr>
<td>Bullous lung disease</td>
<td>93</td>
<td>8</td>
</tr>
<tr>
<td>Pleural disease</td>
<td>75</td>
<td>7</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>48</td>
<td>4</td>
</tr>
</tbody>
</table>

*COPD includes: Emphysema (77%), Chronic bronchitis (35%), and Bronchiectasia (2%)

Data as of 02/28/93
Symptom history (N = 1129)

Alpha 1-antitrypsin deficiency registry

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usual cough</td>
<td>479</td>
<td>42</td>
</tr>
<tr>
<td>Usual phlegm</td>
<td>520</td>
<td>46</td>
</tr>
<tr>
<td>Increased cough &amp; phlegm</td>
<td>560</td>
<td>50</td>
</tr>
<tr>
<td>Wheezing with U.R.I.</td>
<td>852</td>
<td>76</td>
</tr>
<tr>
<td>Wheezing with dyspnea</td>
<td>573</td>
<td>51</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>947</td>
<td>84</td>
</tr>
</tbody>
</table>

Smoking accelerates onset of dyspnea in A1AT deficient patients

<table>
<thead>
<tr>
<th>Series (date)</th>
<th>N</th>
<th>Onset of dyspnea</th>
<th>Smoker</th>
<th>Non-smoker</th>
<th>No dyspnea (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black (1978)</td>
<td>22 PIZZ1</td>
<td>--</td>
<td>51</td>
<td>18%</td>
<td></td>
</tr>
<tr>
<td>Larsson (1978)</td>
<td>168 PIZZ2</td>
<td>40</td>
<td>54</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Tobin (1983)</td>
<td>166 PIZZ</td>
<td>41</td>
<td>48</td>
<td>14%</td>
<td></td>
</tr>
<tr>
<td>Janus (1985)</td>
<td>33 PIZZ</td>
<td>32</td>
<td>51</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Brantley (1988)</td>
<td>120 PIZZ</td>
<td>--</td>
<td>--</td>
<td>2%</td>
<td></td>
</tr>
</tbody>
</table>

1) Never smokers only

2) Only patients with COPD (169/246 and 33/69, respectively)

FEV1 percent of predicted by smoking and augmentation therapy history

Box plots show range, quartiles, and median

FEV1 is maximal pre-bronchodilator value

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Alpha 1-antitrypsin deficiency: state of the art
- Natural history of AAT deficiency
- Diagnosis of AAT deficiency
- Treatment of AAT deficiency
  - Conventional treatment of COPD
  - Augmentation therapy
  - Lung transplantation
  - Lung volume reduction surgery
  - Gene therapy
  - Other

30 year follow-up of alpha 1-antitrypsin deficient individuals
- Question: what is the status of 30 year olds with severe deficiency of AAT who were identified at birth?
- Design: observational
- Methods: follow-up of birth cohort (127 PI*Z, 2 PI*Z null, 54 PI*SZ, 1 PI*S null) at mean age 30.5
  - Response by 107 (of 128 [84%] PI*Z) and 45 (of 55 [82%] PI*SZ)
  - Compared with 197 individuals with normal AAT levels

30 year follow-up of alpha 1-antitrypsin deficient individuals (2)
- Smoking status
  - PI*Z individuals were more likely to be lifelong non-smokers than normals (78.5% vs. 66.5%, p < 0.05)
- Lung function (in 90/107 PI*Z and 84/197 normals)
  - Normal in PI*Z individuals (FEV1, 101% predicted [range 98 – 104%]) and normals (FEV1, 96% predicted [93-98% pred])
  - Mean FEV1/FVC 0.82 vs. 0.84 (normals)
32 year follow-up of alpha 1-antitrypsin deficient individuals

- Question: what is the status of 32 year olds with severe deficiency of AAT who were identified at birth?
- Design: observational
- Methods: follow-up of birth cohort (126 PI*Z, 2 PI*Z null, 54 PI*SZ, 1 PI*S null) at mean age 32
  - Response by 25 of 128 ([20%] PI*Z) and 11 of 55 ([20%] PI*SZ)
  - Compared with 17 PI*MM individuals

32 year follow-up of alpha 1-antitrypsin deficient individuals (2)

- Very few smokers in the cohort (1 current, 1 former PI*ZZ, 3 former PI*SZ)
- Lung function normal (PI*ZZ/PI*SZ/PI*MM)
  - FEV1% pred. - 109% / 104% / 112%
  - FEV1/FVC ratio - 0.84 / 0.82 / 0.85
  - KCO % pred. - 110% / 111% / 111%
  - CT scans normal in all groups
    - PD15 (g/L) 81 / 85 / 75 (p > 0.05)
    - Relative area < -910 HU 30 / 24 / 35

FEV1 slope values by smoking status from available studies

<table>
<thead>
<tr>
<th>Author/yr</th>
<th>N</th>
<th>Never smokers</th>
<th>Ex-smokers</th>
<th>Current smokers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Janus (1985)</td>
<td>21</td>
<td>-80 (±38)</td>
<td>-61 (±43)</td>
<td>-316 (±43)</td>
</tr>
<tr>
<td>Hutchison (1987)</td>
<td>82</td>
<td>-66 (±55)</td>
<td>-44 (±56)</td>
<td>-67 (±46)</td>
</tr>
<tr>
<td>Wu (1988)</td>
<td>80</td>
<td>-61 (±100)</td>
<td>-81 (±70)</td>
<td>-61 (±170)</td>
</tr>
<tr>
<td>Seersholm (1995)</td>
<td>161</td>
<td>-86 (±107)</td>
<td>-58 (±80)</td>
<td>-132 (±105)</td>
</tr>
<tr>
<td>Seersholm (1997)*</td>
<td>196</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Seersholm (1997)*</td>
<td>97</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>NHLBI registry (1998)*</td>
<td>1129</td>
<td>-67 (CI 56-78)</td>
<td>-54 (CI 46-63)</td>
<td>-109 (CI 87-137)</td>
</tr>
<tr>
<td>Pitulainen (1999)</td>
<td>608</td>
<td>-47 (CI 41-53)</td>
<td>-41 (CI 36-48)</td>
<td>-70 (CI 58 - 82)</td>
</tr>
</tbody>
</table>

*Parenthesis indicate SEM
*Parenthesis indicate 95% CI
*Denotes not on augmentation therapy
*Denotes on augmentation therapy
Natural history of alpha 1-antitrypsin deficiency (PiZZ)

- N = 246 patients with PiZZ (homozygous) alpha 1-antitrypsin deficiency
- COPD develops in 184/246 (75%)
  - Onset by age 40 in 21/54 (39%)
- Death in 91/246 (37%) over follow-up period

<table>
<thead>
<tr>
<th>Cause</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory failure from COPD</td>
<td>54</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>2</td>
</tr>
<tr>
<td>Cirrhosis and complications</td>
<td>12</td>
</tr>
<tr>
<td>Other</td>
<td>23</td>
</tr>
</tbody>
</table>

Larsson C. Acta Med Scand 1978; 204, 343

Overall mortality
Alpha 1-antitrypsin deficiency registry

Mortality rate by initial percent predicted post-BD FEV₁
Alpha 1-antitrypsin deficiency registry
Underlying causes of death (N=118)‡

<table>
<thead>
<tr>
<th>Condition</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emphysema</td>
<td>85</td>
<td>72%</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>12</td>
<td>10%</td>
</tr>
<tr>
<td>Malignancy</td>
<td>3</td>
<td>3%</td>
</tr>
<tr>
<td>Diverticulitis</td>
<td>3</td>
<td>2%</td>
</tr>
<tr>
<td>Sepsis/Infection</td>
<td>2</td>
<td>2%</td>
</tr>
<tr>
<td>Trauma/Accident</td>
<td>2</td>
<td>2%</td>
</tr>
<tr>
<td>Other*</td>
<td>12</td>
<td>10%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>118</td>
<td>100%</td>
</tr>
</tbody>
</table>

‡ Medical records available to review in 120 subjects; underlying cause of death could not be determined for 2 cases reviewed
* Other causes include coronary artery disease, MI, drug reaction/toxicity (unrelated to augmentation therapy), pancreatitis, hepatitis, septal fibrosis of the liver, perforated abdominal viscera, biliary tract obstruction, connective tissue disease, ITP, monoclonal gammopathy, depression

Underlying causes of death among never smokers with alpha 1-antitrypsin deficiency

- Cause of death (N=93):
  - Emphysema: 45% (v.s. 72% in registry)
  - Cirrhosis: 28% (v.s. 10% in registry)
  - Malignancy: 14%
  - Other (e.g., cardiovascular): 13%

- N = 93 decedents (16%)
- Post-mortem exam available in 19% (N = 18)

Alpha 1-antitrypsin deficiency: state of the art

- Natural history of AAT deficiency
- Diagnosis of AAT deficiency
- Treatment of AAT deficiency
  - Conventional treatment of COPD
  - Augmentation therapy
  - Lung transplantation
  - Lung volume reduction surgery
  - Gene therapy
  - Other
Alpha 1-Antitrypsin Deficiency: State of the Art
James K. Stoller, M.D., M.S.
Clinical features that should prompt suspicion of alpha 1-antitrypsin deficiency

- Pulmonary
  - Early onset emphysema (e.g., age <45 years)
  - Emphysema in a non- or trivial smoker
  - Chest X-ray with basilar hyperlucency
  - Family history of emphysema and/or liver disease

Clinical features that should prompt suspicion of alpha 1-antitrypsin deficiency (2)

- Hepatic
  - Pediatric hepatitis and/or cirrhosis
  - Unexplained cirrhosis in adults
  - Hepatoma
- Dermatologic
  - Panniculitis
- Vasculitis
  - C-ANCA (antiproteinase 3-positive) vasculitis

Recommendations for alpha 1-antitrypsin (AAT) testing in the standards document

- Symptomatic individuals with persistent obstructive defects on PFTs, e.g.,
  - Emphysema
  - COPD
  - Asthma with incompletely reversible airflow obstruction
Alpha 1-Antitrypsin Deficiency: State of the Art
James K. Stoller, M.D., M.S.

Recommendations for alpha 1-antitrypsin (AAT) testing in the standards document* (2)

• Asymptomatic individuals with persistent obstructive pulmonary dysfunction and:
  - Smoking exposure
  - Occupational exposure
• Individuals with unexplained liver disease (newborns, children, adults)
• Adults with necrotizing panniculitis

Recommendations for alpha 1-antitrypsin (AAT) testing in the standards document* (3)

• Individuals (adults and adolescents) with a family member with AAT homozygosity (e.g., Pi*ZZ)
  - Siblings

Alpha 1-antitrypsin deficiency: state of the art

• Natural history of AAT deficiency
• Diagnosis of AAT deficiency
• Treatment of AAT deficiency
  - Conventional treatment of COPD
  - Augmentation therapy
  - Lung transplantation
  - Lung volume reduction surgery
  - Gene therapy
  - Other

* Am J Respir Crit Care Med (October 2003)
Efficacy criteria for augmentation therapy for alpha 1-antitrypsin deficiency

- Biochemical efficacy criteria
  - Raise serum and lung AAT levels above the "protective threshold" (11 µM in serum)
  - Preserve functional activity of infused AAT to neutralize neutrophil elastase
- Clinical efficacy criteria
  - To prevent or slow the rate of decline of lung function
  - To enhance survival, functional status, and quality of life
  - Safety

Following treatment, serum levels of α1-antitrypsin levels rise well above the protective threshold value and decline with a serum half life of approx. 3-5 days.

At the end of one week, serum levels at the nadir remain above the protective threshold value.

Available studies of clinical efficacy of augmentation therapy

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Date</th>
<th>Design</th>
<th>Outcome measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seersholm et al.</td>
<td>1997</td>
<td>Observational cohort, concurrent controls</td>
<td>FEV, decline</td>
</tr>
<tr>
<td>NHLBI registry</td>
<td>1998</td>
<td>Observational cohort, concurrent controls</td>
<td>FEV, decline, Survival</td>
</tr>
<tr>
<td>Tonelli et al.</td>
<td>2009</td>
<td>Observational cohort, concurrent controls</td>
<td>FEV, decline, Survival</td>
</tr>
<tr>
<td>Dirksen et al.</td>
<td>1999</td>
<td>Randomized controlled trial</td>
<td>FEV, decline, Lung density (CT)</td>
</tr>
<tr>
<td>Dirksen et al.</td>
<td>2008</td>
<td>Randomized controlled trial</td>
<td>FEV, decline, Lung density (CT)</td>
</tr>
</tbody>
</table>
Summary of current evidence of clinical efficacy of intravenous augmentation therapy

- In several large observational cohort studies, augmentation therapy recipients experienced a slower rate of FEV₁ decline than non-recipients, especially in those with moderate airflow obstruction (e.g., FEV₁ 35-60% predicted).
- In the NHLBI registry, augmentation therapy recipients experienced improved survival.

Summary of current evidence of clinical efficacy of intravenous augmentation therapy (2)

- In two available randomized controlled clinical trials, augmentation therapy recipients did not experience a slower rate of FEV₁ decline, but a trend (p=0.049 to 0.084, depending on analytic method) toward a slower rate of loss of lung density by CT was evident.
- In a web-based survey, augmentation therapy recipients experienced fewer infections than non-recipients, though no decrease in exacerbation frequency was observed in the most recent randomized controlled trial of augmentations.

Summary of current evidence of clinical efficacy of intravenous augmentation therapy (3)

- Two recent controversial meta-analyses (i.e., Cochrane and pooled analysis of the two randomized trials) have drawn inquiry.
Conclusions regarding the clinical efficacy of augmentation therapy for alpha 1-antitrypsin (AAT) deficiency in the standards document

- "Recognizing that supportive evidence of efficacy comes from concordant observational studies but not from a randomized controlled clinical trial, the Task Force recommends intravenous augmentation therapy for individuals with established airflow obstruction from AAT deficiency"

Am J Respir Crit Care Med 2003;168:818-900

Conclusions regarding the clinical efficacy of augmentation therapy for alpha 1-antitrypsin (AAT) deficiency in the standards document (2)

- "Evidence that augmentation therapy confers benefit (e.g., slowed rate of FEV₁ decline and decreased mortality) is stronger for individuals with moderate airflow obstruction (e.g., FEV₁, 35-60% predicted) than for those with severe airflow obstruction. Augmentation therapy is not currently recommended for individuals without emphysema, and benefits in individuals with severe (e.g., FEV₁ ≤35% predicted) or mild (e.g., FEV₁ ≥50 - 60% predicted) airflow obstruction are less clear"

Am J Respir Crit Care Med 2003;168:818-900

New and emerging treatments for alpha 1-antitrypsin deficiency

- Augmentation therapy
  - New routes of administration (e.g., inhaled, continuous infusion)
  - New agents (e.g., recombinant yeast-derived alpha 1-antitrypsin)
- Other neutrophil elastase inhibitors (e.g., small molecule oral agents)
New and emerging treatments for alpha 1-antitrypsin deficiency (2)

- Prevention of polymer formation (e.g., small peptides that insert into Z molecule, preventing polymerization)
- Elastin protection (e.g., inhaled hyaluronan)
- Hepatic secretagogues (e.g., 4-phenylbutyrate)
- Gene therapy (e.g., adeno-associated virus vector with intramuscular delivery)

Alpha 1-antitrypsin deficiency: conclusions

- Alpha 1-antitrypsin deficiency is common but under-recognized
- Delayed diagnosis is associated with adverse effects, especially because effective interventions are available

Alpha 1-antitrypsin deficiency: conclusions (2)

- Although definitive supportive data are not available (e.g., from randomized controlled trials), the weight of evidence supports the biochemical and clinical efficacy of intravenous augmentation therapy
- Promising new therapies are currently being actively investigated
Alpha 1-Antitrypsin Deficiency: State of the Art
James K. Stoller, M.D., M.S.

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