### Faculty

<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Humam Farah, MD</td>
<td>Assistant Professor of Medicine</td>
<td>St. Louis University</td>
</tr>
<tr>
<td></td>
<td>Director, Pulmonary and Sleep</td>
<td>St. Louis, MO</td>
</tr>
<tr>
<td></td>
<td>Director, Alpha One and Clinical Research, Hannibal Clinic</td>
<td></td>
</tr>
<tr>
<td>Franck Rahaghi, MD, MHS, FCCP</td>
<td>Director, Pulmonary Hypertension Clinic</td>
<td>Cleveland Clinic Florida Weston, FL</td>
</tr>
<tr>
<td></td>
<td>Director, Pulmonary Education and Rehabilitation</td>
<td></td>
</tr>
<tr>
<td>Arunabh Talwar, MD, FCCP</td>
<td>Director, Pulmonary Hypertension and Advanced Lung Disease Program</td>
<td>North Shore University Hospital, Manhasset, NY</td>
</tr>
<tr>
<td></td>
<td>Associate Professor of Medicine</td>
<td>Hofstra North Shore-LIJ</td>
</tr>
<tr>
<td></td>
<td>School of Medicine, Hofstra University, Hempstead, NY</td>
<td></td>
</tr>
</tbody>
</table>

### FACULTY DISCLOSURES

- **Humam Farah, MD**
  - Speaker – Baxter, Boehringer Ingelheim, Forest

- **Franck Rahaghi, MD, MHS, FCCP**
  - Consultant/Lecturer – Baxter, Grifols, CSL Behring;
  - Lecturer – Forest, Boehringer Ingelheim; Consultant – Intermune;
  - Research – Gilead, Boehringer

- **Arunabh Talwar, MD, FCCP**
  - Consultant – Bayer
LEARNING OBJECTIVES

- Review the 50-year history of alpha1-antitrypsin (AAT) deficiency
- Identify who and when to test for AAT deficiency
- Discuss how to incorporate testing for AAT deficiency into everyday practice
- Describe the new insights into the efficacy of treatment for AAT deficiency

PRE-TEST QUESTION 1

On a scale of 1 to 5, please rate how confident you would be in the diagnosis and management of a patient with Alpha -1 Antitrypsin deficiency.

1. Not at all confident
2. Slightly confident
3. Moderately confident
4. Pretty much confident
5. Very confident
PRE-TEST QUESTION 2

All of the following statements are true except:

1. Alpha-1 Deficiency was discovered in 1963

2. Elastase/Anti-elastase theory for AATD was proposed in 2000

3. We have known since the 1960’s that AAT is secreted in the liver.

4. AAT augmentation therapy was first offered in 1987

5. The American Thoracic Society released their guidelines in 2003, recommending screening for AAT in all COPD patients

CASE

Jaime is a 54 y/o male pilot who reveals a 30 pk year previous history of tobacco use. The spirometry shows very severe obstruction, non reversible with bronchodilators.
PRE-TEST QUESTION 3

What is the likelihood that Jaime would have Alpha-1 Antitrypsin deficiency?

1. 1-5/10000=0.01-0.05%
2. 1-2/1000=0.1-0.2%
3. 1-3/100= 1-3%
4. 4. 10-15/100= 10-15%

CASE

Jaime was known to have COPD for a few years, but no physician had tested him in the past, in spite of the fact that they thought it would be good idea to do so.
PRE-TEST QUESTION 4

Methods for systematically identifying the MAJORITY of patients with AATD include all the following EXCEPT:

1. Using spirometry as a way to identify patients
2. Performing Point of Care testing using Kits on all COPD patients
3. Using reminders from PFT’s or Electronic Medical Records to elicit testing on all COPD patients
4. Making all efforts to test all young patients with emphysema

CASE

✧ After being diagnosed as an AAT deficient patient with ZZ genotype, and a level of 30 mg/dL below the protective threshold of 80 mg/dL, his spirometry is now 30%. Jaime’s practitioner suggested that because of his low FEV1, he should not be given augmentation therapy because it was too late.
**PRE-TEST QUESTION 5**

All of the following benefits have been shown in AATD replacement therapy (Registry or RCT) except:

1. Mortality Benefit of treatment
2. CT Densitometry Benefits
3. Improvement in FEV1 Decline for FEV1 < 30%
4. Improvement in FEV1 Decline in FEV 35-65 range

---

**MALMÖ**
HISTORY OF AATD

1963
Laurell: Univ of Lund, Sweden
• Electrophoresis gels do not have 13 alpha band
• Resident (Eriksson), notes 3 of the 5 patients also have emphysema; Ages 35, 38, and 44 years

Neutrophil Elastase (NE) Discovered
• Elastase – Anti-elastase Hypothesis
• Low AAT leads to emphysema
• Papain, a plant enzyme with elastase properties, can cause emphysema in animals
• AAT keeps elastase activity "in-check"

1967
Sharp: Associates AATD and Liver Disease
• Majority of AAT synthesized by liver; some made by lung epithelial cells and monocytes

1969

1987
US Approval of 1st Augmentation Therapy

1997
WHO Statement

2003
ATS/ERS Guidelines

2011
Ongoing Clinical Trials

Additional US Product Approvals (n = 2)
Laurell Lecture Recognition
WHAT IS ALPHA-1 ANTITRYPSIN (AAT)?

✧ Protease inhibitor primarily synthesized by hepatocytes
  - Some contribution from lung epithelial cells and macrophages

✧ Protects normal body tissue from proteolytic enzyme damage
  - Especially neutrophil elastase (NE) released by white blood cells

✧ Theoretical protective threshold
  \[= 11 \, \mu\text{M/L}\]

Ranes J. Semin Respir Crit Care Med. 2005;26:154-166.

ROLE OF AAT

AAT binds to NE → NE inactivation

✧ Neutrophils release NE to destroy antigens (i.e. pathogens, irritants)

✧ NE can digest lung elastin

✧ AAT released by liver binds and inactivates NE

✧ Elastin maintains bronchial and alveolar wall integrity
  - Prevents airway collapse and obstruction

Schwaiblmair M, Respiration 1997;64(1):10-15
NORMAL AAT INACTIVATION OF NEUTROPHIL ELASTASE

AAT with Reactive Loop

“Mousetrap -like” Closure of AAT on NE

Neutrophil Elastase (NE)

Inactivated NE

©2004 by BMJ Publishing Group Ltd and British Thoracic Society

AAT AND NEUTROPHIL ELASTASE BALANCE

Healthy

Elastase burden

Elastase protection

AAT-deficient

Elastase burden

Elastase protection

Elastase

AAT

Breakdown of lung tissue

Alpha-1 Antitrypsin Deficiency (AAT): 50 Years of Progress

AAT DEFICIENCY PREVALENCE (US)

- Emphysema prevalence: ~3 million
- 2-3% of all emphysema patients have severe AATD
- Emphysema prevalence due to AATD: ~80,000-100,000
- AATD diagnosed: ~7,000 diagnosed with AATD

Estimated <10% diagnosed


AAT DEFICIENCY PREVALENCE*

- Z allele occurs in racial groups worldwide
- Worldwide prevalence estimates
  - Carriers (PI*MS, PI*MZ) = ~116 million
  - Deficient (PI*SS, PI*SZ, PI*ZZ) =~ 3.4 million
  - PI*ZZ: 175,268

*Survey of prevalence studies summarizing data from 373 cohorts in 58 countries.
RANK IN ORDER OF PREVALENCE

- Spina Bifida
- Cystic Fibrosis
- Huntington’s Disease
- AAT deficiency (PI*ZZ)
- Idiopathic Pulmonary Fibrosis

COMPARISON OF PI*ZZ PREVALENCE

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAT deficiency (PI*ZZ)</td>
<td>60,000-100,000¹⁻³</td>
</tr>
<tr>
<td>Cystic Fibrosis</td>
<td>30,000⁴</td>
</tr>
<tr>
<td>Huntington’s Disease</td>
<td>30,000⁵</td>
</tr>
<tr>
<td>Spina Bifida</td>
<td>70,000⁶</td>
</tr>
<tr>
<td>Idiopathic Pulmonary Fibrosis</td>
<td>128,000⁷</td>
</tr>
<tr>
<td>Testicular Cancer</td>
<td>196,000⁸</td>
</tr>
<tr>
<td>Ovarian Cancer</td>
<td>177,000⁸</td>
</tr>
<tr>
<td>Hodgkin’s Lymphoma</td>
<td>164,000⁸</td>
</tr>
</tbody>
</table>

GENETIC ASPECTS

✧ Autosomal Co-dominant
   – Equal incidence among men and women
   – AAT gene located on chromosome 14 segment

✧ > 100 different genetic variants identified
   – Variants classified by protease inhibitor (PI) system and coded “A” to “Z”


GENETIC ASPECTS

<table>
<thead>
<tr>
<th>Heterozygous</th>
<th>Homozygous</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 2 different alleles</td>
<td>• 2 same alleles</td>
</tr>
<tr>
<td>• Expressed as “Pi*MZ”</td>
<td>• Expressed as “Pi*ZZ”</td>
</tr>
</tbody>
</table>

✧ Two alleles that genetically code for the Alpha 1 protein = “phenotype”
✧ Alleles
   – M allele- Normal variant
     • ~95% of US population
   – Z allele
     • Found in 95% of with clinically recognized AATD
     • Ineffective AAT release from hepatocytes (hepatic accumulation, polymerization)
   – S allele (slightly more common than Z)
     • Variant causing mildly decreased AAT levels
   – Null allele
     • Interrupted AAT synthesis due to transcriptional or translational errors
     • No liver accumulation

### DISEASE RISK BY AAT SERUM LEVELS AND PHENOTYPE

<table>
<thead>
<tr>
<th>Units</th>
<th>PI*MM</th>
<th>PI*MS</th>
<th>PI*SS</th>
<th>PI*MZ</th>
<th>PI*SZ</th>
<th>PI*ZZ</th>
<th>Null/Null</th>
</tr>
</thead>
<tbody>
<tr>
<td>11 µmol/L</td>
<td>20-48</td>
<td>18-48</td>
<td>15-33</td>
<td>17-33</td>
<td>8-16</td>
<td>2.5-7</td>
<td>0</td>
</tr>
<tr>
<td>80 mg/dL</td>
<td>150-350</td>
<td>140-350</td>
<td>100-200</td>
<td>90-120</td>
<td>75-120</td>
<td>20-45</td>
<td>0</td>
</tr>
<tr>
<td>Risk</td>
<td>Normal</td>
<td>Low</td>
<td>Low</td>
<td>Moderate</td>
<td>High</td>
<td>High</td>
<td>High</td>
</tr>
</tbody>
</table>


### AATD CLINICAL MANIFESTATIONS

- **Lung Disease**
  - Emphysema
  - Chronic Bronchitis
  - Bronchiectasis
- **Childhood and Adult Liver Disease**
  - Hepatitis, cirrhosis, hepatocellular carcinoma
  - Fulminant liver failure
- **Occasional Systemic Manifestations**
  - Necrotizing panniculitis
  - Vasculitis

*Ranies J. Semin Respir Crit Care Med. 2005;26:154-166.*
CLINICAL PRESENTATION OF AATD--LUNG DISEASE

◼ No unique presenting features
  - Dyspnea (84%)
  - Decreased exercise tolerance
  - Wheezing (76%)
  - Cough (42%)
  - Excess sputum production (46%)
  - Frequent lower respiratory tract infections
  - History of suspected allergies and/or asthma
◼ In NHLBI Registry, 61% had FEV1 reversibility when tested with 3 serial spirometries

Age, Smoking History, or Severity of FEV\textsubscript{1} Decline Should NOT Define Which COPD Patients to Test

![FEV\textsubscript{1} percentage predicted by age for 378 Pi ZZ patients stratified by smoking status](image)

Remember that only a laboratory test can confirm the presence of alpha-1

SELF-REPORTED DIAGNOSES IN SEVERE AATD AAT DEFICIENCY  

(N=1851 Patients with Severe AATD)

Obstructive Lung Disease  
- Asthma  
  - n=199  
  - n=122  
- Emphysema  
  - n=314  
- Chronic Bronchitis  
  - n=159  
- No Lung or Liver Related Symptoms  
  - n=287

Liver Disease  
- n=61

AATD may present in several ways on chest X-rays  
- In advanced disease, AATD produces panacinar, basilar emphysema

INCONSISTENT IMAGING IN AATD

✧ Chest X-rays from 165 ZZ Alpha-1 patients:¹
   – 15% were normal
   – Only 20% showed “classic” emphysema at bases

✧ CTs from 102 ZZ Alpha-1 patients:²
   – 64% showed basal predominance
   – 36% had predominant apical disease


CLINICAL PRESENTATION OF AATD--LIVER DISEASE

✧ Infancy – prolonged jaundice¹
   – Leading genetic cause of liver disease in children²
   – 2nd most common indication for liver transplantation³ in children

✧ Older children and adults¹
   – Elevated liver function tests, abnormal clotting, enlarged liver or spleen, portal hypertension, esophageal varices, ascites, chronic active hepatitis, “cryptogenic” cirrhosis

AAT Z VARIANT RETAINED IN HEPATOCYTES

Intracellular Inclusions


CLINICAL PRESENTATION OF AATD--NECROTIZING PANNICULITIS


CLINICAL PRESENTATION OF AATD
RECOGNITION/WARNING SIGNS

- Early-onset emphysema (<45 years of age)
- Emphysema in the absence of recognized risk factor
- Emphysema with prominent basilar hyperlucency
- Otherwise unexplained liver disease
- Necrotizing panniculitis
- Anti-proteinase 3–positive vasculitis
- Family history of:
  - Emphysema, bronchiectasis, liver disease, or panniculitis
- Bronchiectasis without evident etiology

Because AATD presentation is not consistent, it is important to test all COPD patients


NATURAL HISTORY OF EMPHYSEMA IN AATD

- Risk of developing emphysema with AATD not completely understood
  - Some with AATD never develop the disease
- Estimated annual rate of FEV₁ decline
  - PI*ZZ non-smokers = 40-60 mL/yr
  - PI*ZZ smokers = 113 mL/yr¹
- Predictors of greater FEV₁ decline:
  - Smokers, males, age 30-44 years, FEV₁ 35-79% predicted value, decreased serum AAT levels, bronchodilator response.²

FROM A JOINT STATEMENT OF
AMERICAN THORACIC SOCIETY AND
EUROPEAN RESPIRATORY SOCIETY...

AATD is “frequently underdiagnosed or
misdiagnosed by clinicians.”

DIAGNOSIS OF AATD
DELAYS AND MISSED OPPORTUNITIES

✧ Mean delay of 7.2 years between first symptom and
initial AATD diagnosis\(^1\)
  – Survey of 300 AATD patients
  – 44% reported seeing at least 3 physicians before
    initial AATD diagnosis\(^1\)
✧ No improvement in early disease diagnosis between
1968 and 2003\(^2\)

MAJORITY OF AADT PATIENTS DIAGNOSED AT 40-49 YEARS OF AGE*

*All studied patients reported symptomatic lung disease at time of diagnosis
Alpha-1 Antitrypsin Deficiency (AAT): 50 Years of Progress

AGE AT AATD DIAGNOSIS INCREASED IN RECENT YEARS

NUMEROUS PHYSICIANS SEEN BEFORE AATD DIAGNOSIS

ATS DIAGNOSTIC TESTING GUIDELINES*

Type A – Recommend
- Symptomatic adults with:
  - Emphysema
  - COPD
- Incompletely reversible asthma
- Asymptomatic individuals with:
  - Persistent obstruction on PFT and identifiable risk factors
    (patients with FEV1 < 80% predicted and FEV1/FVC less than 0.70)
- All individuals with unexplained liver disease
- Adults with necrotizing panniculitis

Type B – Consider
- Adults with bronchiectasis of unknown source
- Adolescents with persistent airflow obstruction
- Asymptomatic individuals with persistent airflow obstruction and no identifiable risk factors
- Adult C-ANCA-positive vasculitis

*Recommendations, graded from type A to type D, made based on supportive and weighing for and against all issues.

AAT CLINICAL TESTS AVAILABLE

Quantitative (Level)
- Serum level tests (CPT 82103)
  - Rocket immunoelectrophoresis
  - Radial immunodiffusion
  - Nephelometry
  - Immunoassay/double antibody assay

Qualitative (Genetic Profile)
- Phenotyping (CPT 82104)
  - Identification of AAT variants (phenotypes) by isoelectric focusing (IEF)
  - Serum or plasma, some use “dried blot spot” samples
- Genotyping (CPT 83894)
  - Molecular level Dx of genomic DNA
  - Whole blood or buccal swab samples
  - “Dried blot spot” samples
SERUM LEVELS DIFFER DEPENDING ON TEST METHOD

AAT is an acute phase reactant; inflammatory conditions may falsely elevate levels

◊ Radial immunodiffusion
  – Normal range: 150/200–350/400 mg/dl*
  – Protective threshold: 80 mg/dl*

◊ Nephelometry
  – Normal range: 83/120–200/220 mg/dl*
  – Protective threshold: 50 mg/dl*; 11 µM†

* Value obtained by commercially available standards.
† Value obtained by the NHLBI standard.

COMMON AATD TESTING BARRIERS

◊ Lack of AATD awareness and knowledge
◊ Lack of adherence to guidelines
  – Problem With Guidelines
  – Physician adherence to any guidelines
◊ Unfamiliarity/ Nihilism with treatment options
◊ Office workflow may not be conducive
◊ Testing fatigue
APPROACHES TO INCREASING TESTING

- Campaigns to enhance awareness of AATD among primary care physicians and respiratory therapists using a variety of media, including targeted publications
- Presentations at grand rounds and at national meetings, and in web-based instructional programs
- Distributing free test kits for AATD and providing free, confidential home-based testing for AATD
- Evolving interest in developing a rapid point-of-care test for AATD
- Issuing written recommendations to physicians to test for AATD in the written results of pulmonary tests.
- Clinical decision support within an electronic medical record to prompt physicians to test for AATD in appropriate clinical settings
- Testing for AATD and recognition of affected individuals by RTs and by the physicians with whom they practice will increase.
- Renewing consideration of wide-spread, mandatory newborn screening for AATD

OVERCOMING BARRIERS TO ALPHA 1 TESTING

- Identify barriers to AATD testing in your practice
- Identify where testing can be integrated into workflow
- “Protocolization” of testing alleviates testing degradation and testing fatigue
**ALGORITHM FOR TESTING AT PULMONARY FUNCTION TEST LABORATORIES**

Notify referring physicians of automatic testing at PFT laboratory

Evaluate each patient for candidacy:
FEV₁/FVC<0.7, FEV₁<80%, post-BD

Mention ATS/ERS criteria, discuss merits of AAT testing, obtain consent

If patient agrees, perform testing using kits or send patient to lab (order signed by PFT lab director)

Notify patient of status:
Negative or heterozygote: Via mail with information about status  Positive/deficient: Phone call from PFT lab director to patient (and primary MD)

Deficient patients complete work-up:
Considered for replacement therapy if indicated/continued follow-up

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**GOING WITH THE FLOW**

<table>
<thead>
<tr>
<th>Office Flow</th>
<th>Intervention</th>
<th>Expected Outcome</th>
</tr>
</thead>
</table>
| Pre-Check in | Off site Questionnaire/On-line  
|             | Pre-Visit Questionnaire/Tablets | Auto Alert to MD  
|             | Use Pre-Visit Questionnaire/Tablets  
|             | Check-in Questions asked | Pending testing Orders by Reviewing Nurse/MD  
| Nurse Check in | Alpha-1 Status as a line item in the template | Reminder to MD to order  
| COPD Template | Protocol/Reminders to Lab Tech/RN to screen for need to test | Possible automatic order upon clicking on the line item  
| PFT/Spirometry | Place Alpha-1 on COPD order set  
| Orders/Check-out | Place AAT on Favorite List | Pend lab/ test kit initiation Orders for MD  
|               |                      | Direct offering of Testing through test kits at the point of service  
|               |                      | Check box by MD in COPD Order set  
|               |                      | Presence of AATD in general Favorite list would cause MD to order  
|               |                      | Acceptance of Pended orders by Nurse/ PFT lab screening (Kit or Lab) |

WHY TEST?

1. Because alpha-1 antitrypsin (AAT) deficiency is inherited as an autosomal co-dominant condition, family members of probands are at risk of having AATD and of developing associated disease;
2. Diagnosis of AATD can favorably affects smoking behaviors;
3. Because occupational dust exposure is associated with worsened clinical status in individuals with AATD, detection could affect occupational choice;
4. Specific therapy for AATD is available and has been recommended for individuals with emphysema due to AATD; and,
5. Official society guidelines endorse testing for AATD, establishing a standard of care that warrants compliance.

REPLACEMENT THERAPY

✧ The emphysema link to PiMZ individuals (levels >50 to 60% of normal) is relatively weak
✧ Prevalence appears to increase with PI*SZ individuals (whose levels are approximately 25–35% of normal).
✧ Nevertheless, the PI*SZ risk is clearly less than that for PI*ZZ disease especially in nonsmokers
✧ A level of AAT above the PI*SZ level has been considered appropriate as a target for therapy.
### AUGMENTATION THERAPY

- Increases serum and lung epithelial lining fluid (ELF) levels of AAT
- Indicated for adult patients with AATD and evidence of emphysema/COPD
- 60mg/kg/week IV

**ATS/ERS Standards:** Am J Respir Crit Care Med. 2003;168(7):818-900.

### BENEFITS OF EARLY INTERVENTION

- May slow decline of pulmonary function
- Early identification of at-risk or carrier family members
- Aggressive smoking cessation efforts to reduce risk of related emphysema
- Reassessment and change of occupational/environmental risk factors

**ATS/ERS Standards:** Am J Respir Crit Care Med. 2003;168(7):818-900.
WHY AUGMENTATION THERAPY?

Wewers in NEJM 1987;316:1055

IMPORTANCE OF WEEKLY DOSING

AAT Serum Levels During Biweekly Infusions

AAT Serum Levels During Monthly Infusions

*N=22 Day 1-26; N=51 Day 27-end

Days after last infusion

Placebo ○ Active ●

p<0.001

Threshold
# Alpha-1 Antitrypsin Deficiency (AAT): 50 Years of Progress

## Indications
- **Zemaira®**
  - Chronic augmentation and maintenance therapy in patients with AAT-D and emphysema
- **Prolastin-C®**
  - Chronic augmentation and maintenance therapy in patients with AAT-D and emphysema
- **Aralast NP™**
  - Chronic augmentation and maintenance therapy in patients with AAT-D and emphysema
- **GLASSIA™**
  - Chronic augmentation and maintenance therapy in patients with AAT-D and emphysema

## Purity
- **Zemaira®**
  - ≥ 99% (*≥ 0.7 mg functional A1 protein*)
- **Prolastin-C®**
  - ≥ 90% (*≥ 0.7 mg functional A1 protein*)
- **Aralast NP™**
  - 20 mg/kg body weight
- **GLASSIA™**
  - UNKNOWN

## Viral Reduction
- **Zemaira®**
  - Pasteurization (60°C for 10 hours) Nanofiltration
- **Prolastin-C®**
  - Cold ethanol fractionation PEG precipitation Depth Filtration Solvent detergent 15nm nanofiltration Accumulated virus reduction
- **Aralast NP™**
  - Cold ethanol fractionation Solvent detergent 15nm nanofiltration
- **GLASSIA™**
  - Cold ethanol fractionation Solvent detergent 15nm nanofiltration

## Dosing:

<table>
<thead>
<tr>
<th>Product</th>
<th>Dosage</th>
<th>Weekly Pregnancy</th>
<th>Infusion Time</th>
<th>Volume</th>
<th>Transfer Needle</th>
<th>Storage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Zemaira®</strong></td>
<td>60 mg/kg</td>
<td>Weekly Pregnancy</td>
<td>15 minutes</td>
<td>20 mL/kg</td>
<td>Sterile Needle</td>
<td>Room Temperature: Not to exceed 77°F or 25°C</td>
</tr>
<tr>
<td><strong>Prolastin-C®</strong></td>
<td>60 mg/kg</td>
<td>Weekly Pregnancy</td>
<td>15 minutes</td>
<td>20 mL/kg</td>
<td>25 ml vial</td>
<td>Refrigeration: Store at 2-8°C/36-46°F</td>
</tr>
<tr>
<td><strong>Aralast NP™</strong></td>
<td>60 mg/kg</td>
<td>Weekly Pregnancy</td>
<td>40 minutes</td>
<td>20 mL/kg</td>
<td>Double Ended Transfer Needle</td>
<td>Room Temperature: Not to exceed 77°F or 25°C</td>
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<tr>
<td><strong>GLASSIA™</strong></td>
<td>60 mg/kg</td>
<td>Weekly Pregnancy</td>
<td>60-80 minutes</td>
<td>50 mL/g</td>
<td>Double Ended Transfer Needle</td>
<td>Refrigeration: Store at 2-8°C/36-46°F</td>
</tr>
</tbody>
</table>

## Available Units
- 1-gm vial with 20 ml sterile water diluent
- 1-gm vial with 20 ml sterile water diluent
- 0.5-gm and 1-gm vial with 25 or 50 ml diluent
- 1-gm vial in 50 ml fluid- No reconstitution required

## Storage
- **Zemaira®**
  - Room Temperature: Not to exceed 77°F or 25°C
- **Prolastin-C®**
  - Room Temperature: Not to exceed 77°F or 25°C
- **Aralast NP™**
  - Room Temperature: Not to exceed 77°F or 25°C
- **GLASSIA™**
  - Refrigeration: Store at 2-8°C/36-46°F

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**FEV1 DECLINE NHLBI REGISTRY STUDY STRATIFICATION BY FEV1 % PREDICTED**

![FEV1 Decline NHLBI Registry Study Stratification by FEV1 % Predicted](image)

- **Baseline FEV1 % Predicted**
  - <35%
  - 35%-49%
  - 50%-79%
  - ≥80%

- **FEV1 Decline (mL/yr)**
  - No Augmentation
  - Augmentation

- *P=0.03*

Adapted from The Alpha-1-Antitrypsin Deficiency Registry Study Group. *Am J Respir Crit Care Med.* 1998;158:49-59. 58

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NACE - Emerging Challenges in Primary Care: 2014  
Alpha -1 - 29
STUDY OF EFFICACY OF AUGMENTATION THERAPY IN DANISH REGISTRY

<table>
<thead>
<tr>
<th>Initial FEV&lt;sub&gt;1&lt;/sub&gt;</th>
<th>Treated (German)</th>
<th>Untreated (Danish)</th>
<th>Diff</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>n</td>
<td>ΔFEV&lt;sub&gt;1&lt;/sub&gt;</td>
<td>n</td>
<td>ΔFEV&lt;sub&gt;1&lt;/sub&gt;</td>
<td></td>
</tr>
<tr>
<td>≤30% pred</td>
<td>75 -24.2</td>
<td>27 -30.9</td>
<td>6.7</td>
<td>0.6</td>
</tr>
<tr>
<td>31%–65% pred</td>
<td>112 -61.8</td>
<td>58 -82.8</td>
<td>21</td>
<td>0.04</td>
</tr>
<tr>
<td>&gt;65% pred*</td>
<td>11 -162.0</td>
<td>12 -140.0</td>
<td>22</td>
<td>0.7</td>
</tr>
<tr>
<td>Total</td>
<td>198 -53</td>
<td>97 -74.5</td>
<td>21.5</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*In the treated group, these patients were required to have a decline in FEV<sub>1</sub> >120 mL/yr

Seersholm N. Eur Respir J. 1997;10:2260.

CHAPMAN META-ANALYSIS

Chapman KR. J Chronic Obstructive Pulmonary Disease. 2009:6:177-184
### CHANGE OF FEV1 IN PATIENTS WITH FEV1 > 65% THAT DECLINED WHILE NOT RECEIVING THERAPY

<table>
<thead>
<tr>
<th>Time [months]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before augmentation therapy</td>
</tr>
<tr>
<td>72</td>
</tr>
<tr>
<td>60</td>
</tr>
<tr>
<td>48</td>
</tr>
<tr>
<td>36</td>
</tr>
<tr>
<td>24</td>
</tr>
<tr>
<td>12</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>-12</td>
</tr>
<tr>
<td>-24</td>
</tr>
<tr>
<td>-36</td>
</tr>
<tr>
<td>-48</td>
</tr>
<tr>
<td>-60</td>
</tr>
</tbody>
</table>

**“Slow Decliners”**
- n=4
- FEV1 [m³] 3.2
- P < 0.002
- +15.9 m³/y
- -10.6 m³/y

**“Fast Decliners”**
- n=7
- FEV1 [m³] 3.3
- P < 0.002
- -255.7 m³/y
- -52.7 m³/y

---

### LUNG DENSITOMETRY

**Normal lung density**

**Emphysema**

---

THE RAPID TRIAL – NEWLY REPORTED

- Placebo controlled – 2 year CT densitometry follow-up
  - Zemaira (60 mg/Kg)
  - Placebo group crossed over to Rx – followed + 2 years.
- Prespecified (in 2003) primary end point of combined CT densitometry score at TLC and FRC was not significantly different (p=0.027) between treated and placebo.
- CT densitometry at TLC was significantly different (p=0.007)
- None of the other secondary endpoints were different between groups (FEV1, exacerbations, quality of life)
- Placebo patients crossed over to treatment and followed for an additional 2 years showed slowing of decline in CT densitometry at TLC

N.B.: significance is p of 0.025 or better because this was analyzed as a one-sided test

THE RAPID TRIAL

![Graph showing lung density decline over months for A1-PI and Placebo groups](Am J Respir Crit Care Med 187,2013:A6069)
**RATE OF LUNG INFECTIONS IN AATD PATIENTS**

![Bar chart showing the rate of lung infections in AATD patients](chart)


**SURVIVAL FEV1 DECLINE IN INDIVIDUALS WITH SEVERE ALPHA-1 ANTITRYPSIN DEFICIENCY**

![Survival curves for FEV1 decline](chart)

A. FEV\(_1\) <50% Predicted  
- Never (n=489)  
- Partially (n=965)  
- Always (n=316)  
**P<.001 logrank test**

B. FEV\(_1\) ≥50% Predicted  
- Never (n=715)  
- Partially (n=71)  
- Always (n=74)  
**P<.41 logrank test**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category</th>
<th>Subjects</th>
<th>Deaths</th>
<th>RR</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Augmentation Therapy</td>
<td>Overall</td>
<td>Never on</td>
<td>326</td>
<td>41</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ever on</td>
<td>722</td>
<td>106</td>
<td>0.64</td>
<td>(0.43, 0.94)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

### Future Interventions in AATD

#### Decrease

**Inflammatory/ NE Burden**

1. Smoking cessation
2. Environmental Intervention
3. Vaccination
4. Early/ aggressive treatment of inflammation and infection.

#### Treatment

1. IV augmentation
2. Gene Therapy
3. Gene Correction Therapy
4. Anti-polymer drugs
5. Molecular chaperone
6. iPS cells
7. Aerosolized rAAT
   - Human
   - Transgenic
   - Yeast
   - Plant

### Summary

- AATD is difficult to identify based on clinical symptoms alone
- AATD is a lab diagnosis
- Testing/screening important to identify patients
- One test once in a lifetime will identify AATD
- Optimal therapy for AATD includes lifestyle changes, symptom management and augmentation therapy
RESOURCES

✧ Alpha-1 Organizations
  – Alpha-1 Foundation - www.alphaone.org
  – AlphaNet – www.alphanet.org
  – Alpha-1 Association – www.alpha1.org
  – Alpha One Registry – www.alphaoneregistry.org

✧ Alpha-1 Testing
  – Labcorp – www.labcorp.com
  – Quest Diagnostics – www.questdiagnostics.com

✧ Specialty Labs
  – Alpha-1 Antitrypsin Genetic Research Lab – www.alphaone.ufl.edu

POST-TEST QUESTIONS
POST-TEST QUESTION 1

All of the following statements are true except:

1. Alpha-1 Deficiency was discovered in 1963
2. Elastase/Anti-elastase theory for AATD was proposed in 2000
3. We have known since the 1960’s that AAT is secreted in the liver.
4. AAT augmentation therapy was first offered in 1987
5. The American Thoracic Society released their guidelines in 2003, recommending screening for AAT in all COPD patients

CASE:
Jaime is a 54 y/o male pilot who reveals a 30 pk year previous history of tobacco use. The spirometry shows very severe obstruction, non reversible with bronchodilators.

What is the likelihood that Jaime would have Alpha-1 Antitrypsin deficiency?

1. 1-5/10000=0.01-0.05%
2. 1-2/1000=0.1-0.2%
3. 1-3/100= 1-3%
4. 4. 10-15/100= 10-15%
POST-TEST QUESTION 3

Methods for identifying the majority of patients with AATD include all the following EXCEPT:

1. Using spirometry as a way to identify patients
2. Performing Point of Care testing using Kits
3. Using reminders from PFT’s or Electronic Medical Records to elicit testing
4. Making all efforts to test all young patients with emphysema

POST-TEST QUESTION 4

Methods for systematically identifying the MAJORITY of patients with AATD include all the following EXCEPT:

1. Using spirometry as a way to identify patients
2. Performing Point of Care testing using Kits on all COPD patients
3. Using reminders from PFT’s or Electronic Medical Records to elicit testing on all COPD patients
4. Making all efforts to test all young patients with emphysema
POST-TEST QUESTION 5

On a scale of 1 to 5, please rate how confident you would be in the diagnosis and management of a patient with Alpha-1 Antitrypsin deficiency.

1. Not at all confident
2. Slightly confident
3. Moderately confident
4. Pretty much confident
5. Very confident

POST-TEST QUESTION 6

Which of the statements below describes your approach to participating in diagnosing and treating Alpha-1 Antitrypsin deficiency?

1. I do not participate in the diagnosis and treatment of Alpha-1 Antitrypsin deficiency, nor do I plan to this year.
2. I did not participate in the diagnosis and treatment of Alpha-1 Antitrypsin deficiency before this course, but as a result of attending this course I’m thinking of doing this now.
3. I do participate in the diagnosis and treatment of Alpha-1 Antitrypsin deficiency and I now plan to change my treatment methods based on completing this course.
4. I do participate in the diagnosis and treatment of Alpha-1 Antitrypsin deficiency and this course confirmed that I don’t need to change my methods.