Alpha-1 Deficiency and COPD: Uncovering the Needle in the Haystack to Improve Quality of Life
Faculty

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Disclosures

• **Susan Collazo, RN, MSN, ARNP-BC**
  
  has no financial relationships with commercial interests to disclose.
Learning Objectives

After participating in the proposed educational activities, clinicians should be better able to:

1. Describe effective strategies to identify patients with alpha 1-antitrypsin (AAT) deficiency
2. Recognize the various manifestations of AAT deficiency
3. Incorporate AAT deficiency testing into chronic obstructive pulmonary disease (COPD) management algorithms
4. Recognize the benefits of treatment for AAT deficiency
PRE-TEST QUESTIONS
Pre-test ARS 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 COPD and Alpha-1 Antitrypsin deficiency:

1. Not at all confident
2. Slightly confident
3. Moderately confident
4. Pretty much confident
5. Very confident
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 that is non-reversible with bronchodilators. You diagnose him with severe COPD. On further evaluation you diagnose him as an AAT deficient patient with ZZ genotype, and a level of 30 mg/dL. Patients with Alpha -1 Deficiency are predisposed to COPD A and all of the following except:

1. Vasculitis [c –ANCA positive vasculitis]
2. Cirrhosis
3. Panniculitis
4. Pancreatitits
Methods for systematically identifying the MAJORITY of patients with AATD include all the following EXCEPT:

1. Testing patients with evidence of obstructive lung physiology on spirometry
2. To appreciate that Alpha-1 deficiency is a laboratory diagnosis, not a clinical diagnosis, and a blood level is required to establish this diagnosis
3. Screening patients with Bronchiectasis of unknown etiology
4. Testing only young patients with emphysema
Pre-test ARS Question 4

Which of the following is true of AAT individuals with Emphysema:

1. Emphysema in AATD deficiency is upper lobe predominant
2. On spirometry, partial airway reversibility is common in individuals with AATD
3. Lung volume reduction surgery for emphysema is commonly indicated in AATD with Emphysema
4. AATD patients with COPD rarely have COPD exacerbations
5. 10 % of COPD Patients have AATD
Benefits of SCREENING and subsequently treating for Alpha -1 Antitrypsin deficiency in individuals with Emphysema include all the following EXCEPT:

1. There is an improved rate of FEV1 decline for patients with an FEV 35-65 range once AAT augmentation therapy is started
2. A diagnosis of AATD can favorably affect smoking behavior
3. Because occupational dust exposure is associated with worsening clinical status in individuals with AATD, detection could affect occupational choice
4. Augmentation therapy in AATD is indicated for both COPD and liver cirrhosis
Pre-test ARS Question 6

Which statement is FALSE?

1. ALL COPD patients should be tested for Alpha-1 Antitrypsin Deficiency
2. Replacement therapy is effective in COPD patients with Alpha-1
3. Most Alpha-1 deficient patients tend to be young patients with early emphysema
4. Preferred testing for alpha-1 antitrypsin should include a level, further classification with genotyping, and phenotyping
Jenny is 55 y/o teacher who is having her third bronchitis episode this year. She smoked from 15 y/o to 50y/o and quit 5 years ago. She does not feel that she is SOB and has no sig DOE. Between exacerbations, she does not have sputum production.
Burden of COPD

- COPD is a leading cause of morbidity and mortality worldwide.
- It is consistently in the top 5 leading causes of death in the United States.
- COPD is associated with significant economic burden.
50 Billion

COPD, 2010

- Indirect Mortality Costs, $12.4
- Indirect Morbidity Costs, $8.0
- Direct Health Care Expenditures, $29.5
Prevalence seems to be highest in the Midwest and Southeast states.
COPD, a common preventable and treatable disease, is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases.

Exacerbations and comorbidities contribute to the overall severity in individual patients.
Normal CXR

COPD CXR

Bullae

Flattened diaphragm
Paraseptal Emphysema or Bullous Emphysema

IN AAT patients more Basilar predominance
Assessment of COPD

- Assess symptoms
- Assess degree of airflow limitation using spirometry
- Assess risk of exacerbations
- Assess comorbidities
Diagnosis of COPD

**SYMPTOMS**
- dyspnea
- chronic cough
- sputum production

**EXPOSURE TO RISK FACTORS**
- tobacco
- occupation
- indoor/outdoor pollution

**SPIROMETRY:** Required to establish diagnosis
Assessment of COPD

• COPD Assessment Test (CAT)
  - Eight-item patient questionnaire designed to quantify impact of COPD to patient’s QOL.

• Modified Medical Research Council Dyspnea Scale (mMRC)
## Modified MRC (mMRC) Questionnaire

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description of Breathlessness</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>I only get breathless with strenuous exercise.</td>
</tr>
<tr>
<td>1</td>
<td>I get short of breath when hurrying on level ground or walking up a slight hill.</td>
</tr>
<tr>
<td>2</td>
<td>On level ground, I walk slower than people of the same age because of breathlessness, or have to stop for breath when walking at my own pace.</td>
</tr>
<tr>
<td>3</td>
<td>I stop for breath after walking about 100 yards or after a few minutes on level ground.</td>
</tr>
<tr>
<td>4</td>
<td>I am too breathless to leave the house or I am breathless when dressing.</td>
</tr>
</tbody>
</table>
What is Jenny’s mMRC

1) 0
2) 1
3) 2
4) 3
5) 4
Spirometry

- Simple procedure easily performed in any clinic or office
- Effort dependant
- Values guide therapy
Spirometry: Obstructive Disease

Volume, liters

Time, seconds

FEV₁ = 1.7L
FVC = 3.3L
FEV₁/FVC = 0.51

Normal

Obstructive
Assessment of Airflow Limitation: Spirometry

- According to the GOLD guidelines, a post-bronchodilator FEV$_1$/FVC < 0.70 confirms the presence of airflow limitation.

- Where possible, values should be compared to age-related normal values to avoid "overdiagnosis" of COPD in the elderly- since FEV$_1$/FVC ratio declines with age.

- i.e. Value in normal subjects 20–30 years old is 87% and falls to 81% by age 50–60
Classification of Severity of Airflow Limitation in COPD*

In patients with FEV$_1$/FVC < 0.70:

GOLD 1: Mild  \( \text{FEV}_1 \geq 80\% \text{ predicted} \)

GOLD 2: Moderate  \( 50\% \leq \text{FEV}_1 < 80\% \text{ predicted} \)

GOLD 3: Severe  \( 30\% \leq \text{FEV}_1 < 50\% \text{ predicted} \)

GOLD 4: Very Severe  \( \text{FEV}_1 < 30\% \text{ predicted} \)

*Based on Post-Bronchodilator FEV$_1$
Jenny

Jenny had a spirometry:

- FEV1 45%
- FVC 80%
- FEV1/FEVC: 0.5
- No BD response
What is her Spirometry Grade

1. Gold 1
2. Gold 2
3. Gold 3
4. Gold 4

Jenny’s Spiro results:
FEV1 45%
FVC 80%
FEV1/FEVC: 0.5
No BD response

GOLD 1: Mild  \( \text{FEV} \_1 \geq 80\% \text{ predicted} \)
GOLD 2: Moderate  \( 50\% \leq \text{FEV} \_1 < 80\% \text{ predicted} \)
GOLD 3: Severe  \( 30\% \leq \text{FEV} \_1 < 50\% \text{ predicted} \)
GOLD 4: Very Severe  \( \text{FEV} \_1 < 30\% \text{ predicted} \)
Combined Assessment of COPD

2x2 table

Risk (GOLD Classification of Airflow Limitation)

Risk (Exacerbation history)

Symptoms (mMRC or CAT score)

- mMRC 0-1
- CAT < 10

- mMRC ≥ 2
- CAT ≥ 10

(C)  (D)

(A)  (B)
What is Jenny’s GOLD Class?

1. GOLDA
2. GOLD B
3. GOLD C
4. GOLD D

- mMRC 0
- GOLD 3
  - Spirometry
- 3 exacerbations
Risk Factors Associated With Repeated Exacerbations

- **1-Older age**
- **2-COPD severity**
  - Greater baseline dyspnea
  - Low FEV$_1$
  - Low PaO$_2$
- **3-History of previous exacerbations**
- **4-Inflammation**
  - Greater airway inflammation
  - Greater systemic inflammation
- **5-Bacterial load (stable phase)**
  - Chronic bronchial hypersecretion
- **6-Comorbidity/ extrapulmonary manifestations**
  - Cardiovascular
  - Anxiety-depression
  - Myopathy
  - Reflux disease
COPD: Assess Genetics

- Alpha-1 Antitrypsin Deficiency in 1-3% of patients with COPD
- Only <10% found mostly attributed to lack of screening by providers
- In spirometry, partial airway reversibility is common in AATD patients
WHAT IS ALPHA-1 ANTIMTryPSIN (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 µM/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

Neutrophil Elastase (NE)

Inactivated NE

“Mousetrap-like” Closure of AAT on NE

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AAT AND NEUTROPHIL ELASTASE BALANCE

Elastase burden
Elastase protection
Elastase burden
Elastase protection
Elastase
AAT
AAT
Breakdown of lung tissue

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

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

Adapted from ATS/ERS Statement. Am J Respir Crit Care Med. 2003;168.818.
Age, Smoking History, or Severity of FEV1 Decline Should NOT Define Which COPD Patients to Test

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

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.*
Serum Testing for AATD

Quantitative (Level)
Serum level tests (CPT 82103)
Nml=100-300mg/dl
Increase risk for lung disease =<80ml/dl

Qualitative (Genetic Profile)

• Phenotyping (CPT 82104)
  – Identification of AAT variants (phenotypes) by isoelectric focusing (IEF)
  – Detects risk for AATD

• Genotyping (CPT 83894)
  – Molecular level Dx of genomic DNA
  – Whole blood or buccal swab samples

To obtain a free Alpha-1 Test Kit (finger-stick test) from the Alpha-1 Research Registry at (877) 886-2383, which is associated with the Alpha-1 Association. The test sample can be submitted directly to the Registry at the Medical University of South Carolina. The test screens for the most common Z and S genotypes.
CLINICAL PRESENTATION OF AATD RECOGNITION/WARNING SIGNS

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

- 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

## 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  
• Pending testing Orders by Reviewing Nurse  
• MD Initiation of testing |
| Nurse Check in | • Use Pre-Visit Questionnaire/Tablets  
• Check-in Questions asked | • Pending testing Orders by Reviewing Nurse  
• MD |
| COPD Template | • Alpha-1 Status as a line item  
In the template | • Reminder to MD to order  
• Possible automatic order upon clicking on the line item |
| PFT/Spirometry | • Protocol/Reminders to Lab Tech/  
RN to screen for need to test | • Pend lab/ test kit initiation Orders for MD  
• Direct offering of Testing through test kits at the point of service |
| Orders/Check-out | • Place Alpha-1 on COPD order set  
• Place AAT on Favorite List | • 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) |

Jenny

- Since she had an obstructive PFT, Jenny was tested for Alpha-1 using a kit and was found to have levels of 30 mg/dL and to be a ZZ
Manage Stable COPD: Goals of Therapy

- Quality of life goals:
  - Relieve symptoms
  - Improve exercise tolerance
  - Improve health status

- Natural history of the disease:
  - Prevent disease progression
  - Prevent and treat exacerbations
  - Reduce mortality
Smoking Cessation

- Greatest capacity to influence the natural history of COPD.
- Pharmacotherapy and nicotine replacement increase long-term smoking abstinence rates.
- Even a brief (3-minute) period of counseling to urge a smoker to quit results in smoking quit rates of 5-10%.
Effects of smoking on FEV1
Therapeutic Options: Do it

- All COPD patients benefit from regular physical activity and should repeatedly be encouraged to remain active.

- United States Advisory Committee on Immunization Practices (ACIP): PPSV23 for COPD patients, asthma and smokers 19-65 years.
# COPD Medications

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta&lt;sub&gt;2&lt;/sub&gt;-agonists</td>
<td>- Short-acting beta&lt;sub&gt;2&lt;/sub&gt;-agonists (Albuterol)</td>
</tr>
<tr>
<td></td>
<td>- Long-acting beta&lt;sub&gt;2&lt;/sub&gt;-agonists (Indacatrol, salmeterol)</td>
</tr>
<tr>
<td>Anticholinergics</td>
<td>- Short-acting anticholinergics (ipratropium)</td>
</tr>
<tr>
<td></td>
<td>- Long-acting anticholinergics (Tiotropium, Aclidinuim bromide)</td>
</tr>
<tr>
<td>Combination short-acting</td>
<td>- Combination short-acting beta&lt;sub&gt;2&lt;/sub&gt;-agonists + anticholinergic in</td>
</tr>
<tr>
<td>beta&lt;sub&gt;2&lt;/sub&gt;-agonists</td>
<td>- Combination long-acting beta&lt;sub&gt;2&lt;/sub&gt;-agonists + corticosteroids in</td>
</tr>
<tr>
<td></td>
<td>- Combination of Ultra long acting beta2-agonists+corticosteroids in one</td>
</tr>
<tr>
<td></td>
<td>- Combination of Long acting beta2 agonists and Long acting anticholinergic</td>
</tr>
<tr>
<td>Methylxanthines (Theophyline)</td>
<td></td>
</tr>
<tr>
<td>Inhaled corticosteroids</td>
<td>- Inhaled corticosteroids</td>
</tr>
<tr>
<td></td>
<td>- Combination long-acting beta&lt;sub&gt;2&lt;/sub&gt;-agonists + corticosteroids in</td>
</tr>
<tr>
<td></td>
<td>- Combination of Ultra long acting beta2-agonists+corticosteroids in one</td>
</tr>
<tr>
<td></td>
<td>- Combination of Long acting beta2 agonists and Long acting anticholinergic</td>
</tr>
<tr>
<td>Systemic corticosteroids</td>
<td></td>
</tr>
<tr>
<td>Phosphodiesterase-4</td>
<td>- Phosphodiesterase-4 inhibitors (Roflumilast)</td>
</tr>
<tr>
<td>inhibitors (Roflumilast) }</td>
<td></td>
</tr>
</tbody>
</table>
• Short-acting beta-agonist (SABA) and long-acting beta-agonist (LABA) are both used for COPD.
• LABAs though reduce exacerbations and related hospitalizations and improve symptoms and health status.

Regular treatment with inhaled corticosteroids (ICS) improves symptoms, lung function and quality of life and reduces frequency of exacerbations for COPD patients with an FEV$_1$ < 60% predicted.
Annual risk of exacerbations was decreased (0.99 vs 1.32) \( p = 0.026 \)

Combination Therapy

- An inhaled corticosteroid combined with a long-acting beta$_2$-agonist is more effective than the individual components in improving lung function and health status and reducing exacerbations in moderate to very severe COPD.
- Combination therapy is associated with an increased risk of pneumonia. (Torch study)
- Addition of a long-acting beta$_2$-agonist/inhaled glucorticosteroid combination to an anticholinergic (tiotropium) appears to provide additional benefits.
Phosphodiesterase-4 Inhibitors
Roflumilast

- In patients with severe and very severe COPD (GOLD 3 and 4) and a history of exacerbations and chronic bronchitis
- 17% reduction in exacerbation

*Calverley PM* *Lancet.* 2009 Aug 29;374(9691):685-94
Manage Stable COPD: Pharmacologic Therapy

RECOMMENDED FIRST CHOICE

<table>
<thead>
<tr>
<th>Exacerbations per year</th>
<th>mMRC 0-1 CAT &lt; 10</th>
<th>mMRC &gt; 2 CAT &gt; 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>SAMA prn or SABA prn</td>
<td>LABA or LAMA</td>
</tr>
<tr>
<td>1</td>
<td>SAMA prn or SABA prn</td>
<td>LABA or LAMA</td>
</tr>
<tr>
<td>≥2</td>
<td>ICS + LABA or LAMA</td>
<td>ICS + LABA and/or LAMA</td>
</tr>
</tbody>
</table>

GOLD 1
GOLD 2
GOLD 3
GOLD 4
# Manage Stable COPD: Pharmacologic Therapy

<table>
<thead>
<tr>
<th>Patient</th>
<th>Recommended First choice</th>
<th>Alternative choice</th>
<th>Other Possible Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>SAMA prn or SABA prn</td>
<td>LAMA or LABA or SABA and SAMA</td>
<td>Theophylline</td>
</tr>
<tr>
<td>B</td>
<td>LAMA or LABA</td>
<td>LAMA and LABA</td>
<td>SABA and/or SAMA Theophylline</td>
</tr>
<tr>
<td>C</td>
<td>ICS + LABA or LAMA</td>
<td>LAMA and LABA or LAMA and PDE4-inh. or LABA and PDE4-inh.</td>
<td>SABA and/or SAMA Theophylline</td>
</tr>
<tr>
<td>D</td>
<td>ICS + LABA and/or LAMA</td>
<td>ICS + LABA and LAMA or ICS+LABA and PDE4-inh. or LAMA and LABA or LAMA and PDE4-inh.</td>
<td>Carbocysteine SABA and/or SAMA Theophylline</td>
</tr>
</tbody>
</table>
What would we choose for Jenny?

1. SABA
2. LAMA+SABA
3. ICS+LABA+SABA
4. ICS+LABA+SABA+PDE5
Advantages of Early Diagnosis in AATD

- Careful follow-up of individuals without symptoms
- Lifestyle changes
  - Reduction of risk factors
    - Smoking (If you have severe AAT deficiency, smoking can shorten your life by as much as 20 years)
    - Liver toxins
    - Immunizations
- Alpha-1 specific therapy or Augmentation Therapy
<table>
<thead>
<tr>
<th></th>
<th>Zemaira®</th>
<th>Prolastin-C®</th>
<th>Aralast NP™</th>
<th>GLASSIA™</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indications</strong></td>
<td>Chronic augmentation and maintenance therapy in patients with AAT-D and emphysema</td>
<td>Chronic augmentation and maintenance therapy in patients with AAT-D and emphysema</td>
<td>Chronic augmentation and maintenance therapy in patients with AAT-D and emphysema</td>
<td>Chronic augmentation and maintenance therapy in patients with AAT-D and emphysema</td>
</tr>
<tr>
<td><strong>Purity</strong></td>
<td>≥ 90% * (≥ 0.7 mg functional A1 protein)</td>
<td>≥ 90% (≥ 0.7 mg functional A1 protein)</td>
<td>≥ 0.55 mg (functional A1 protein)</td>
<td>UNKNOWN</td>
</tr>
<tr>
<td><strong>Viral Reduction</strong></td>
<td>Pasteurization (60°C for 10 hours) Nanofiltration</td>
<td>Cold ethanol fractionation PEG precipitation Depth Filtration Solvent detergent 15nm nanofiltration</td>
<td>Cold ethanol fractionation Solvent detergent 15nm nanofiltration</td>
<td>Cold ethanol fractionation Solvent detergent 15nm nanofiltration</td>
</tr>
<tr>
<td><strong>Dosing: mg/kg body wt</strong></td>
<td>60 mg/kg Weekly Infusion time: 15 minutes Volume: 20 mL/g Color coded transfer needle 0.08 mL/kg body weight per minute</td>
<td>60 mg/kg Weekly Infusion time: 15 minutes Volume: 20 mL/g Transfer needle Sterile needle 0.08 mL/kg body weight per minute</td>
<td>60 mg/kg Weekly Infusion time: 40 minutes Volume: 25ml with 0.5 gm vial 50ml with a 1 gm vial Double ended transfer needle 0.08 mL/kg body weight per minute</td>
<td>60 mg/kg Weekly Infusion time: 60-80 min Volume: 50ml/g Double ended transfer needle Not to exceed 0.04 mL/kg body weight per minute</td>
</tr>
<tr>
<td><strong>Available Units</strong></td>
<td>1-gm vial with 20 ml sterile water diluent</td>
<td>1-gm vial with 20 ml sterile water diluent</td>
<td>0.5-gm and 1-gm vial with 25 or 50 ml diluent</td>
<td>1-gm vial in 50 ml fluid- No reconstitution required</td>
</tr>
<tr>
<td><strong>Storage</strong></td>
<td>Room Temperature: Not to exceed 77°F or 25°C</td>
<td>Room Temperature: Not to exceed 77°F or 25°C</td>
<td>Room temperature: Not to exceed 77°F or 25°C</td>
<td>Refrigerate: Store at 2-8° C/36-46° F</td>
</tr>
</tbody>
</table>

*Average batch purity by SDS-PAGE, range 94-100%
†Based on recommended dosage as stated in the product package inserts of 60 mg/kg body weight at the infusion rate of 0.08 mL/kg/min.
FEV1 Decline NHLBI Registry Study
Stratification by FEV1 % Predicted

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

Am J Respir Crit Care Med 187;2013:A6069
Survival FEV1 Decline in Individuals with Severe Alpha-1 Antitrypsin Deficiency

### A. FEV₁ <50% Predicted

- Never (n=162)
- Partially (n=285)
- Always (n=316)

Survival curves show a significant difference between the groups with a logrank test p-value of <.001.

### B. FEV₁ ≥50% Predicted

- Never (n=215)
- Partially (n=71)
- Always (n=74)

Survival curves show a trend but no significant difference with a logrank test p-value of <.41.

<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>
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<td>722</td>
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Alpha-1 COPD is Treatable!

Reduce Risk

Reduce Symptoms

Reduce Complications

Reduce Lung Destruction

Education

Smoking cessation
Immunize
Reduce other exposures

Bronchodilators
Inhaled steroids
Pulmonary rehabilitation

Treat exacerbations
Supplemental oxygen

Augmentation therapy


= therapies shown to improve survival
Indications for Long-term Oxygen Therapy (LTOT) in COPD

UNITED STATES

PaO₂ <55 mmHg or SaO₂ < 88% (room air)
PaO₂ 56–59 mmHg or SaO₂ 89%–90%, with
(one or more):

- Pulmonary hypertension
- Evidence of cor pulmonale or edema due to heart failure
- Elevated hematocrit (>56%)

Jenny

- Jenny’s Saturation was 95% at rest, but stayed above 92% with walking desaturation study.

Does Jenny need supplemental oxygen?
Jenny

All of these are appropriate recommendations for Jenny except:

1. Pulmonary Rehabilitation
2. No bronchodilators needed because she does not have bronchodilator response
3. Flu Shot every year
4. Pneumonia Vaccination
5. AAT replacement therapy
Jenny

- Jenny was placed on LABA+ Steroid Combo with SABA PRN, she was sent to Pulmonary Rehabilitation, received vaccination and;
- Was treated with 60mg/kg of AAT replacement therapy on a weekly basis. Her sister is coming for testing as are her children.
Pathways for new therapies

• Newer long acting/ultra-long acting of existing agents (LABs, LAMAs, LABA/LAMA and LABA/ICS fixed dose combinations in a single device)
• Novel anti-inflammatory agents (the inflamed phenotype)
• Regenerative therapy (retinoids and stem cells)
POST-TEST QUESTIONS
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 that is non-reversible with bronchodilators. You diagnose him with severe COPD. On further evaluation you diagnose him as an AAT deficient patient with ZZ genotype, and a level of 30 mg/dL. Patients with Alpha -1 Deficiency are predisposed to COPD A and all of the following except:

1. Vasculitis [c – ANCA positive vasculitis]
2. Cirrhosis
3. Panniculitis
4. Pancreatitis
Methods for systematically identifying the MAJORITY of patients with AATD include all the following EXCEPT:

1. Testing patients with evidence of obstructive lung physiology on spirometry
2. To appreciate that Alpha-1 deficiency is a laboratory diagnosis, not a clinical diagnosis, and a blood level is required to establish this diagnosis
3. Screening patients with Bronchiectasis of unknown etiology
4. Testing only young patients with emphysema
Which of the following is true of AAT individuals with Emphysema:

1. Emphysema in AATD deficiency is upper lobe predominant
2. On spirometry, partial airway reversibility is common in individuals with AATD
3. Lung volume reduction surgery for emphysema is commonly indicated in AATD with Emphysema
4. AATD patients with COPD rarely have COPD exacerbations
5. 10 % of COPD Patients have AATD
Benefits of SCREENING and subsequently treating for Alpha -1 Antitrypsin deficiency in individuals with Emphysema include all the following EXCEPT:

1. There is an improved rate of FEV1 decline for patients with an FEV 35-65 range once AAT augmentation therapy is started
2. A diagnosis of AATD can favorably affect smoking behavior
3. Because occupational dust exposure is associated with worsening clinical status in individuals with AATD, detection could affect occupational choice
4. Augmentation therapy in AATD is indicated for both COPD and liver cirrhosis
Post-test ARS Question 5

Which statement is FALSE?

1. ALL COPD patients should be tested for Alpha-1 Antitrypsin Deficiency
2. Replacement therapy is effective in COPD patients with Alpha-1
3. Most Alpha-1 deficient patients tend to be young patients with early emphysema
4. Preferred testing for alpha-1 antitrypsin should include a level, further classification with genotyping, and phenotyping
Post-test ARS Question 6

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

1. Not at all confident
2. Slightly confident
3. Moderately confident
4. Pretty much confident
5. Very confident
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 COPD and AAT deficiency, nor do I plan to this year.
2. I did not participate in the diagnosis and treatment of COPD and AAT 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 COPD and AAT 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 COPD and AAT deficiency and this course confirmed that I don’t need to change my methods.