Assessment Tools and Biomarkers for COPD & Asthma

2/6/2019
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Disclosures

Neither Dr. Manka nor Dr. Finigan have any financial disclosures to report.
Learning Objectives

• Discuss updated clinical practice guidelines to the assessment and management of patients with COPD and asthma, including the role of exacerbations.

• Review emerging evidence related to targeted therapies and potential biomarkers to select personalized treatment in asthma and COPD.

• Review current and emerging therapies for the management of COPD and asthma
Learning Objectives: Asthma

• Discuss assessment and management of asthma
  • Updated Practice Guidelines
  • Role of exacerbations
• Review clinically relevant biomarkers
• Mention emerging therapies for the management of severe asthma.
Learning Objectives: Asthma

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Asthma

- HETEROGENOUS disease
- chronic airway inflammation
- wheeze, shortness of breath, chest tightness
- cough
- VARIABLE expiratory airflow limitation

- Paraphrased from Global Initiative for Asthma (GINA)
Confirm diagnosis of Asthma

- Sneezing
- Nasal Congestion
- Headaches
- Sinus polyps
- Aspirin
- Throat tightness

Dyspnea
cough
Chest
tightness
wheezing

- Allergens/
  Environmental/
  Occupational

- Odors
- Fragrances
- Temperature
- Humidity
- Dust
- Air pollution
- Foods

Upper airway Symptoms

- GERD/
  Aspiration symptoms

Late vs early onset

Exertion Dyspnea
vs.
Exercise induced bronchoconstriction

Nocturnal Symptoms

Smoking

Exertion Dyspnea
vs.
Exercise induced bronchoconstriction

Triggers

Courtesy of Balkissoon R
Consider the differential/Mimickers

- COPD
- CHF "Cardiac wheeze"
- Vocal Cord Dysfunction
- GERD/Aspiration
- Sinus Disease
- Allergies/Allergic rhinitis
- Eosinophilic Pneumonia
- Bronchiolitis
- Bronchiectasis
- Tracheal Stenosis
- Foreign body aspiration
- Eosinophilic Granulomatosis with Polyangiitis

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Stepwise management - pharmacotherapy

3 changes to reduce risk of exacerbations

1. Consider low dose ICS
2. Leukotriene receptor antagonists (LTRA) Low dose theophylline
3. Med/high dose ICS + LTRA (or + theoph)

**Not for children <12 years**

*For children 6-11 years, the preferred Step 3 treatment is medium dose ICS

**For patients prescribed BDP/formoterol or BUD/formoterol maintenance and reliever therapy

† Tiotropium by mist inhaler is an add-on treatment for patients ≥12 years with a history of exacerbations

GINA 2018, Box 3-5 (2/8) (upper part)
Assess Response/Control

- Asthma Control Test
- Asthma Control Questionnaire
- Peak Expiratory Flow Readings
What is Severe Asthma?

**The definition of severe asthma (according to ERS/ATS 2014) (7)**

During treatment with:
- High-dose ICS + at least one additional controller (LABA, montelukast, or theophylline) or
- Oral corticosteroids >6 months/year

...at least one of the following occurs or would occur if treatment would be reduced:
- ACT <20 or ACQ >1.5
- At least 2 exacerbations in the last 12 months
- At least 1 exacerbation treated in hospital or requiring mechanical ventilation in the last 12 months
- \( FEV_1 <80\% \) (if \( FEV_1/FVC \) below the lower limit of normal)
Why is Severe Asthma important?

• Make up 3-10% of asthma population
• Generate 60% of asthma related costs
• More health care expenditures than type 2 diabetes, stroke, and COPD

Difficult to Treat Asthma  True Refractory Asthma
Workup of Severe Asthma

- CT: Chest and Sinus
- GI investigations
- Laryngoscopy
- Bronchoscopy
- Clinical Biomarkers
Laryngoscopy
Laryngoscopy

- Supraglottic index
- Edema
- Erythema
- Secretions
- Hypertrophy

Martin RJ and Good JT. Supraglottic Index Learning Program
http://www.nationaljewish.org/professionals/education/pro-ed/Supraglottic-Index-Learning-Program/silp
Bronchoscopy

- BAL
  - Eosinophils and neutrophils
  - Acute infection
- Endobronchial biopsies
  - tissue eosinophilia
  - Airway remodeling
- Brushings
  - Chronic infection
Workup of Severe Asthma

• CT: Chest and Sinus
• GI investigations
• Laryngoscopy
• Bronchoscopy

• Clinical Biomarkers
  • Eosinophils
  • IgE
  • FENO
  • Sputum neutrophils
    • Periostin*
    • Dipeptidyl Peptidase-4. *
Learning Objectives: Asthma

• Discuss assessment and management of asthma
  • Updated Practice Guidelines
  • Role of exacerbations

• Review clinically relevant biomarkers

• Mention emerging therapies for the management of severe asthma.
Eosinophils

• 40–60% of asthma is eosinophilic

• Symptom severity is increased in eosinophilic asthma

• Elevated Sputum eosinophils are associated with increased risk of exacerbation

• Increased blood eosinophils (>400 cells/µL) associated with higher risk of severe exacerbations and lower likelihood of asthma control.


Eosinophils

- Sputum Eos: >2-3%
  - Risk of bronchospasm
- Blood Eos: >300-400 cells/µL
  - Interpret with caution
  - Moderate sensitivity and specificity of detecting sputum eos >3%
- IL-5 Driven
- Related biologic agents:
  - mepolizumab, reslizumab, benralizumab.
  - dupilumab
Immunoglobulin E

- Mediates type 1 hypersensitivity reactions
- Key role in allergic asthma
- Binds receptors on mast cells and basophils drives Th-2 inflammation
- Generation of antigen-specific IgE requires class switching, which is driven by IL-4 and IL-13.
- Related biologic agents: omalizumab
Exhaled Nitric Oxide

- Nitric oxide is a free radical molecule
- Epithelial vasodilation and bronchodilation
- Activated through IL-13 and IL-4
- Elevated NO in asthmatics vs healthy controls
- FeNO >50 ppb is associated with a good response to ICS
- Related biologic agents: omalizumab, dupilumab
Exhaled Nitric Oxide

• More popular and clinical available

• 2018 GINA updates:
  • FeNO can support the decision to start ICS, but cannot safely be recommended for deciding against treatment with ICS
  • Children/adolescents: FENO-guided treatment led to exacerbations than treatment based on current guidelines
  • Adults: no significant difference in exacerbations
Sputum Neutrophils

• 20% of asthma patients have sputum neutrophils >61%
• Across literature: 40-76% sputum neutrophils considered abnormally high
• Blood neutrophils do not correlate to sputum
• Sputum neutrophilia associated with poor response to corticosteroids
• No biologic targeted therapy

Periostin* and Dipeptidyl Peptidase-4*

- Periostin
  - Extracellular matrix protein
  - IL-13
  - Elevated airway levels in asthmatics vs healthy controls
  - Anti-IL-13 agents showed improved asthma outcomes only in patients with elevated serum periostin levels

- DPP-4
  - Found in bronchial epithelial cells
  - Stimulated by IL-13
  - Increased serum DPP-4 predicted a reduction in asthma exacerbations with use of anti-IL-13 agent
Learning Objectives: Asthma

• Discuss assessment and management of asthma
  • Updated Practice Guidelines
  • Role of exacerbations

• Review clinically relevant biomarkers

• Mention emerging therapies for the management of severe asthma.
<table>
<thead>
<tr>
<th>Inflammatory Phenotype</th>
<th>Common Clinical Features</th>
<th>Biomarkers in Patients Receiving High-Dose ICS</th>
<th>Add-on Pharmacologic Maintenance Therapies</th>
<th>Additional Strategies to Consider*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type 2 (Th2) inflammation</strong></td>
<td>IL-4, IL-5, IL-13 mediated inflammation with high eosinophils or FENO</td>
<td>Early onset, allergic, with elevated IgE level; Later onset, obesity, female sex, variable airflow obstruction; Exacerbations; Nasal polyps</td>
<td>Blood eosinophil count $\geq 300/\mu$L; FENO $\geq 20$ ppb; Sputum eosinophils $\geq 2%$</td>
<td><strong>Anti–IgE</strong> (If IgE $= 30-700$ IU/mL and IgE-mediated hypersensitivity to a perennial allergen) Anti–IL-5</td>
</tr>
<tr>
<td><strong>Non-Type 2 inflammation</strong></td>
<td>Neutrophilic airway inflammation</td>
<td>Poor response to ICS; Purulent sputum; Bronchiectasis; Low lung function</td>
<td>Sputum PMNs $\geq 40-60%$</td>
<td><strong>No phenotype-specific treatment currently available</strong> Treat infections Consider macrolide antibiotics</td>
</tr>
<tr>
<td><strong>Paucigranulocytic (noninflammatory) asthma</strong></td>
<td>Fixed or variable airflow obstruction</td>
<td>No Th2 biomarkers and sputum PMNs $\leq 40-60%$</td>
<td>No phenotype-specific treatment currently available</td>
<td><strong>Nonpharmacologic strategies (including pulmonary rehabilitation)</strong></td>
</tr>
<tr>
<td><strong>Possible Th2 inflammation</strong></td>
<td>Mixed eosinophilic and neutrophilic inflammation</td>
<td>Features of both eosinophilic and neutrophilic airway inflammation</td>
<td>Th2 and neutrophilic markers</td>
<td>Trial of macrolide antibiotics† for 3-6 months</td>
</tr>
</tbody>
</table>

* Assumes that alternative diagnoses have been excluded, comorbidities have been identified and managed, patient-related factors and environmental exposures have been addressed, inhaled therapy and adherence have been optimized, and non-biologic therapy has been considered or tried (see Roadmap for details).
† Not approved by the U.S. Food and Drug Administration for the treatment of asthma.

**Abbreviations:** ABPA, allergic bronchopulmonary aspergillosis; AERD, aspirin-related respiratory disease; FENO, fractional nitric oxide concentration in exhaled breath; ICS, inhaled corticosteroid; IgE, immunoglobulin E; IL, interleukin; PMN, polymorphonuclear leukocyte; Th2, T-helper 2.
Treatment updates: Benralizumab

• Anti- IL-5 Rα, found on eosinophils and basophils
• FDA approved in eosinophilic asthma in November 2017
• Unique MOA: Neutralizing and cytotoxic effects
• Now included in GINA Management 2018 update
Treatment updates: Benralizumab

Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β₂-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial

Eugene R Bleeker, J Mark FitzGerald, Pascal Chanez, Alberto Papi, Steven F Weinstein, Peter Barker, Stephanie Spyro, Geoffrey Gilmartin, Magnus Aurøllius, Viktoria Werkström, Mitchell Goldman, on behalf of the SIROCCO study investigators

Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial

J Mark FitzGerald, Eugene R Bleeker, Panameswaran Nad, Stephanie Korn, Ken Olda, Marek Lommatzsch, Gary T Ferguson, William W Busse, Peter Barker, Stephanie Spyro, Geoffrey Gilmartin, Viktoria Werkström, Magnus Aurøllius, Mitchell Goldman, on behalf of the CALIMA study investigators

↓ annual asthma exacerbation rate
In patients with peripheral eos >300 Cells/μL treated with Benralizumab
Compared to placebo
Treatment updates: Dupilumab

- Anti IL-4Rα
- Inhibits IL-4 and IL-13 activity
- Approved for moderate and severe asthma Oct 2018
  - Eosinophilic
  - Oral corticosteroid dependent regardless of phenotype

Image courtesy of Wechsler ME
Treatment updates: Dupilumab

↓ annualized rate of severe asthma exacerbations by 48%

↑ FEV1 from baseline
In dupilumab group vs Placebo.

Greatest treatment benefit in Patients with eos >300 cells/µL And FeNO >25 ppb.
Conclusions

• Discuss assessment and management of asthma
  • Updated Practice Guidelines: 3 new changes
  • Role of exacerbations

• Review clinically relevant biomarkers:
  • Eosinophils, IgE, FeNO, and Sputum Neutrophils

• Mention emerging therapies for the management of severe asthma.
  • Benralizumab and Dupilumab
Thank You

mankal@njhealth.org
CASE PRESENTATION

Dr. Jay Finigan
Case Presentation

72-year-old female with:
• constant cough productive of yellow sputum worse in the past 6 months
• mild exertional shortness of breath for 3 years; slowly progressive
• not exercising; decreased her gardening
• + chest tightness with the shortness of breath; no wheezing
• her PCP gave her albuterol a year ago. Using the albuterol 3-4x/day
• no hospitalizations/urgent care visits in the past year for her breathing
• no antibiotics or prednisone in the past year

PCP = primary care provider
Past History
• Coronary artery disease
• Type 2 diabetes
• Hypertension
• Gastroesophageal reflux disease
• Sinus surgery

Medications
Aspirin daily, losartan daily, metformin twice a day

Social History
• Married
• Smoked age 18–64, 1 pack a day
• 4 glasses of wine a week
• No illicit substance abuse
• Retired school teacher
• No occupational or environmental chemical exposures
Case Presentation, Cont...

Family History
• Father
  – Coronary artery disease, COPD
• Mother
  – Lung cancer
• No other respiratory disease in the family

Physical Exam
• Vitals: Temp: 37.6° Celsius, HR: 89, RR: 18, BP: 135/79, SaO₂: 91% on room air, weight: 160lbs, height: 5’4”, BMI: 27.5
• General: No apparent distress
• HEENT: Sclera clear, EOMI, mouth clear of lesion, no adenopathy, no sinus tenderness
• Lungs: Rhonchi bilaterally, symmetric, no crackles
• Cardiac: RRR no murmur/rub/gallop
• Abdomen: Non-tender, no distention, no rebound
• Extremities: No cyanosis or clubbing, No lower extremity edema

HR = heart rate; RR = respiratory rate; BP = blood pressure; SaO₂ = arterial oxygen saturation; BMI = body mass index; HEENT = head, ears, eyes, nose, throat; EOMI = extraocular movements intact; RRR = regular rate and rhythm.
EVALUATION OF SUSPECTED COPD
COPD-Definition

• COPD is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases.
• Mix of emphysema and airways disease that varies patient to patient.
Evaluation of COPD

• Presence and severity of *spirometric obstruction*.
• Nature and magnitude of *symptoms*.
• History of moderate to severe *exacerbations*.
• Presence of *comorbidities*.
Evaluation for Suspected COPD

Screening for COPD is not recommended but case finding is.
Evaluation for Suspected COPD

- **SYMPTOMS**
  - Shortness of breath
  - Chronic cough
  - Sputum

- **RISK FACTORS**
  - Host factors
  - Tobacco
  - Occupation
  - Indoor/outdoor pollution

**SPIROMETRY:** Required to establish diagnosis
Spirometry in COPD

• Reproducible and objective measurement of physiologic lung function

• Criterion for chronic airflow limitation
  – Post-bronchodilator ratio of $\text{FEV}_1/\text{FVC} < 0.70$

$\text{FEV}_1 =$ Forced expiratory volume, 1 second; $\text{FVC} =$ Forced vital capacity

### COPD Assessment Tool


<table>
<thead>
<tr>
<th>Stage</th>
<th>Severity</th>
<th>Post bronchodilator FEV₁</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOLD 1</td>
<td>Mild</td>
<td>FEV₁ ≥ 80% predicted</td>
</tr>
<tr>
<td>GOLD 2</td>
<td>Moderate</td>
<td>50% ≤ FEV₁ &lt; 80% predicted</td>
</tr>
<tr>
<td>GOLD 3</td>
<td>Severe</td>
<td>30% ≤ FEV₁ &lt; 50% predicted</td>
</tr>
<tr>
<td>GOLD 4</td>
<td>Very Severe</td>
<td>FEV₁ &lt; 30% predicted</td>
</tr>
</tbody>
</table>

**Post-bronchodilator FEV₁/FVC < 0.7**

**Spirometrically confirmed diagnosis**

**Assessment of airflow limitation**
Risk of Exacerbation and Poor Outcome Increases with Worsening Airflow Limitation

<table>
<thead>
<tr>
<th>Severity of COPD*</th>
<th>Exacerbations (per year)†‡¶</th>
<th>Hospitalizations (per year)†¶</th>
<th>3-year Mortality†‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOLD 1 (Mild)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>GOLD 2 (Moderate)</td>
<td>0.7 – 0.9</td>
<td>0.11 – 0.2</td>
<td>11%‡</td>
</tr>
<tr>
<td>GOLD 3 (Severe)</td>
<td>1.1 – 1.3</td>
<td>0.25 – 0.3</td>
<td>15%†</td>
</tr>
<tr>
<td>GOLD 4 (Very Severe)</td>
<td>1.2 – 2.0</td>
<td>0.4 – 0.54</td>
<td>24%†</td>
</tr>
</tbody>
</table>

* Post bronchodilator FEV1
† Placebo arm of the Toward a Revolution in COPD Health (TORCH) study
‡ Placebo arm of the Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) study
¶ Placebo arm of the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study

COPD Assessment Tool

Spirometrically confirmed diagnosis → Assessment of airflow limitation → Exacerbation history

Post-bronchodilator FEV₁/FVC < 0.7

<table>
<thead>
<tr>
<th>FEV₁ (% predicted)</th>
<th>GOLD 1</th>
<th>GOLD 2</th>
<th>GOLD 3</th>
<th>GOLD 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 80</td>
<td></td>
<td>50-79</td>
<td>30-49</td>
<td>&lt; 30</td>
</tr>
</tbody>
</table>

Property of Presenter
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Definition of Exacerbation

• **Acute** worsening of respiratory symptoms.
  - More than day-to-day variation
• Leads to change in medication use or frequency of use.
• Frequency and severity of exacerbations is important.
• Best predictor of future exacerbations is a history of earlier exacerbations.
• Hospitalization for exacerbation is associated with a poor prognosis and increased risk of death.
• At a population level, severity of obstruction is associated with increased risk of exacerbation and death.
  – 22% of GOLD 2 vs. 47% for GOLD 4
  – However, FEV1 is too variable to be a useful predictor for a specific patient.
Exacerbations more common with increasing obstruction

COPD Assessment Tool

Spirometrically confirmed diagnosis

Assessment of airflow limitation

Post-bronchodilator FEV₁/FVC < 0.7

FEV₁ (% predicted)

GOLD 1  ≥ 80
GOLD 2  50-79
GOLD 3  30-49
GOLD 4  < 30

Exacerbation history

≥ 2
or
≥ 1 leading to hospital admission
0 or 1 (not leading to hospital admission)

C  D
A  B


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COPD Assessment Tool

Spirometrically confirmed diagnosis

Assessment of airflow limitation

Post-bronchodilator FEV₁/FVC < 0.7

Assessment of symptoms

Exacerbation history

≥ 2 or
≥ 1 leading to hospital admission

0 or 1 (not leading to hospital admission)

GOLD 1: ≥ 80
GOLD 2: 50-79
GOLD 3: 30-49
GOLD 4: < 30

A

B

C

D

Assessment of Symptoms: Modified Medical Research Council (mMRC) questionnaire

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

### COPD Assessment Test (CAT)

For each item below, place a mark (x) in the box that best describes you currently. Be sure to only select one response for each question.

<table>
<thead>
<tr>
<th>Example:</th>
<th>I am very happy</th>
<th>I am very sad</th>
</tr>
</thead>
<tbody>
<tr>
<td>I never cough</td>
<td>0 1 2 3 4 5</td>
<td>I cough all the time</td>
</tr>
<tr>
<td>I have no phlegm (mucus) in my chest at all</td>
<td>0 1 2 3 4 5</td>
<td>My chest is completely full of phlegm (mucus)</td>
</tr>
<tr>
<td>My chest does not feel tight at all</td>
<td>0 1 2 3 4 5</td>
<td>My chest feels very tight</td>
</tr>
<tr>
<td>When I walk up a hill or one flight of stairs I am not breathless</td>
<td>0 1 2 3 4 5</td>
<td>When I walk up a hill or one flight of stairs I am very breathless</td>
</tr>
<tr>
<td>I am not limited doing any activities at home</td>
<td>0 1 2 3 4 5</td>
<td>I am very limited doing activities at home</td>
</tr>
<tr>
<td>I am confident leaving my home despite my lung condition</td>
<td>0 1 2 3 4 5</td>
<td>I am not at all confident leaving my home because of my lung condition</td>
</tr>
<tr>
<td>I sleep soundly</td>
<td>0 1 2 3 4 5</td>
<td>I don’t sleep soundly because of my lung condition</td>
</tr>
<tr>
<td>I have lots of energy</td>
<td>0 1 2 3 4 5</td>
<td>I have no energy at all</td>
</tr>
</tbody>
</table>

Jones et al. ERJ 2009; 34 (3) 648-54.
Update in GOLD- 2016- less reliance on obstruction only

GOLD 3 or 4 criteria for lung function

C

GOLD 3 or 4 criteria for lung function

D

≥ 2 Exacerbation/yr OR
≥ 1 Exacerbation w/hospital

mMRC 0-1 CAT < 10

A

mMRC 0-1 CAT < 10

B

mMRC ≥ 2 CAT ≥ 10

≤ 1 Exacerbation/yr
• Spirometry
  – FEV₁/FVC: 0.55 (normal ≥ 0.70)
  – FEV₁: 45% of predicted (normal ≥ 80%)
  – FVC: 74% of predicted (normal ≥ 80%)

• mMRC 2

<table>
<thead>
<tr>
<th>FEV₁ (% predicted)</th>
</tr>
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<tbody>
<tr>
<td>GOLD 1</td>
</tr>
<tr>
<td>GOLD 2</td>
</tr>
<tr>
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<tr>
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<td>&lt; 30</td>
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</tbody>
</table>

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Other Tests During Initial Evaluation

- Alpha-1 antitrypsin level and phenotype
- Chest imaging to rule out other causes of symptoms
  - Screening CT if indicated
- Lung volumes and diffusion capacity
- Arterial blood gas and oxygen assessment
  - Hypercapnea and hypoxia
- Composite scores
  - BODE score: body mass index, obstruction, dyspnea, and exercise
Case Presentation

• 44 y.o. w/♂ smoker c/o some shortness of breath with walking. Never sought medical attention until he reported to ER “unable to catch breath”
• Treated for acute asthma, discharged
## PFTs

### Lung Volumes

<table>
<thead>
<tr>
<th></th>
<th>Pred</th>
<th>Pre</th>
<th>%Pred</th>
<th>Post</th>
<th>%Pred</th>
<th>%change</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLC</td>
<td>6.99</td>
<td>10.32</td>
<td>150</td>
<td>10.62</td>
<td>154</td>
<td>3</td>
</tr>
<tr>
<td>IC</td>
<td>2.98</td>
<td>2.94</td>
<td>98</td>
<td>2.91</td>
<td>97</td>
<td>-1</td>
</tr>
<tr>
<td>TGV</td>
<td>3.90</td>
<td>7.37</td>
<td>189</td>
<td>7.70</td>
<td>198</td>
<td>4</td>
</tr>
<tr>
<td>ERV</td>
<td>2.27</td>
<td>1.17</td>
<td>51</td>
<td>1.59</td>
<td>76</td>
<td>36</td>
</tr>
<tr>
<td>RV</td>
<td>1.62</td>
<td>6.20</td>
<td>382</td>
<td>6.12</td>
<td>377</td>
<td>-1</td>
</tr>
<tr>
<td>SVC</td>
<td>5.20</td>
<td>4.11</td>
<td>75</td>
<td>4.80</td>
<td>87</td>
<td>9</td>
</tr>
<tr>
<td>RV / TLC</td>
<td>23.6</td>
<td>60.1</td>
<td>255</td>
<td>57.6</td>
<td>244</td>
<td>-4</td>
</tr>
<tr>
<td>TGV / TLC</td>
<td>56.59</td>
<td>71.46</td>
<td>125</td>
<td>72.55</td>
<td>120</td>
<td>2</td>
</tr>
</tbody>
</table>

### Forced Expiration

<table>
<thead>
<tr>
<th></th>
<th>Pred</th>
<th>Pre</th>
<th>%Pred</th>
<th>Post</th>
<th>%Pred</th>
<th>%change</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC</td>
<td>5.20</td>
<td>3.53</td>
<td>68</td>
<td>5.33</td>
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### Additional Studies

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Imaging
What’s the diagnosis
What’s the next test?
Alpha-1 Antitrypsin (AAT)

- Glycoprotein coded for by single gene on long arm of chromosome 14
- Synthesis predominantly in hepatocytes, but also expressed by many other cells
- Transported to blood where it bathes all tissues
- Prototype SERPIN
- Primary target: neutrophil elastase
Alpha-1 Antitrypsin (AAT)

- 52 kDa glycoprotein
- Acute phase reactant
- Main anti-inflammatory protein
- At least 200 different mutations of *serpina1* gene
- About 1/2 of known mutations are associated with deficiency or dysfunction
- Mutations may affect the amount synthesized, secreted, and/or its function
- The frequency of the Z allele suggests a selective advantage
Lung Disease

Protease/Antiprotease Balance

ELASTASE Burden

ANTIELASTASE Protection

ELASTASE Burden

ANTIELASTASE Protection

NORMAL

Alpha-1
AAT Deficiency (AATD)

- Genetic/Hereditary condition causing decreased levels of AAT in blood and tissues
- Usually estimated to be 100,000 people in the US and a similar number in Europe (likely wrong!)
- Over 20 million carriers of a single AATD gene in the US
- Predisposes to lung, liver, other disease
- AAT replacement available as treatment but recommend specialist input.
Co-dominant expression

Alpha-1 Antitrypsin Blood Levels
Serum AAT Levels by Phenotype

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<tr>
<th>Phenotype</th>
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<th>MS</th>
<th>SS</th>
<th>MZ</th>
<th>SZ</th>
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<td>28%</td>
<td>19%</td>
<td>13%</td>
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Disease Associated with Alpha-1

• Others
  – Necrotizing panniculitis
  – Vasculitis (especially Granulomatosis with Polyangiitis (GPA))
  – Hepatocellular Carcinoma
  – Susceptibility to atypical TB
  – Susceptibility to chronic active hepatitis
The Lung in AATD

Silverman EK & Sandhaus RA 2009; NEJM 360:2749-2757
Disease Mechanisms

- **Lung disease**
  - Lack of protease inhibitor
  - Pro-inflammtory state

- **Liver disease**
  - Excess of protease inhibitor

- **Vasculitis**

- **Polymerization of Alpha-1**
  - Decreases inhibitory activity
  - Pro-inflammatory
Treatment: Alpha-1

Estimated loss of lung density by CT
Comorbidities

- Comorbidities are common in COPD and can impact quality of life and mortality.
- Cardiovascular disease
- Skeletal muscle loss and dysfunction
- Metabolic syndrome
- Osteoporosis
- Depression
- Anxiety
- Lung Cancer
Special Considerations

• Lung Volume Reduction Surgery
• Transplant
Emerging Therapies in COPD
Emerging Therapies in COPD

- Angiotensin receptor blockers
- Decreased CS-induced emphysema and airway wall thickness in mice
- Decreased emphysema progression in an observational MESA study
Losartan in CS-induced Injury

Decreased emphysema and airway wall thickness

Mice exposed to CS 2 hrs/d, 5d/wk, 7 wks

Mechanism tied to decreased TGF-β signaling

Podowski M et al. JCI 2012
Angiotensin Pathway in Patients

ARB/ACEI Associated with Decreased Progression of Emphysema in Patients

MESA Study - observational study - 4472 enrolled (fewer got full CT scanning).

12% on ACEI, 6% on ARB

Parikh MA et al. Annals ATS 2017
Losartan in COPD

- Current study of Losartan in COPD underway: LEEP.
- COPD patients randomized to losartan vs. placebo daily for 48 weeks.
- Main outcome is emphysema progression on CT.
Thank you!

• Questions?