Pulmonary Exacerbations: Better Understanding Needed

Michael Tracy, MD
Clinical Assistant Professor
Pediatric Pulmonary
CF Pulmonary Exacerbations

- Definition
- Importance
- Causes
- Treatment
- Research opportunities
A CF pulmonary exacerbation is…

• No universally accepted definition
A CF pulmonary exacerbation is...

- No universally accepted definition

Phrases to avoid:

I’ll know it when I see it.
A CF pulmonary exacerbation is…

- Acute (or Chronic?) worsening of:
  
  - Symptoms
    - increased cough
    - sputum production
    - fever
    - weight loss
    - decreased exercise tolerance
    - missed school or work due to illness
  
  - Clinical findings
    - tachypnea
    - new crackles
    - decreased PFT values ($\downarrow FEV_1$)
    - reduced oxygen level
    - new findings on CXR
## Research definitions of exacerbations

<table>
<thead>
<tr>
<th></th>
<th>Fuchs Criteria (56)</th>
<th>Azithromycin Trial (58)</th>
<th>ISIS Trial (61)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Signs and symptoms</strong></td>
<td>Change in sputum</td>
<td>Major criteria:</td>
<td>O₂ saturation &lt;90% or ≥5% drop</td>
</tr>
<tr>
<td></td>
<td>New/increased hemoptysis</td>
<td>- Decrease ≥10% FEV₁</td>
<td>New infiltrate on X-ray</td>
</tr>
<tr>
<td></td>
<td>Increased cough</td>
<td>- O₂ saturation &lt;90% or ≥5% drop</td>
<td>Hemoptysis</td>
</tr>
<tr>
<td></td>
<td>Increased dyspnea</td>
<td>- New infiltrate on X-ray</td>
<td>Increased work of breathing</td>
</tr>
<tr>
<td></td>
<td>Malaise</td>
<td>- Hemoptysis</td>
<td>Increased cough</td>
</tr>
<tr>
<td></td>
<td>Fatigue/lethargy</td>
<td>- Increased work of breathing</td>
<td>Decreased exercise tolerance</td>
</tr>
<tr>
<td></td>
<td>Temperature ≥38°C</td>
<td>Acute</td>
<td>Increased chest congestion/change in sputum</td>
</tr>
<tr>
<td></td>
<td>Anorexia/weight loss</td>
<td>New/increased adventitial sounds on exam</td>
<td>New/increased adventitial sounds on exam</td>
</tr>
<tr>
<td></td>
<td>Sinus pain/tenderness</td>
<td>- ≥5% weight loss</td>
<td>≥5% weight loss</td>
</tr>
<tr>
<td></td>
<td>Change in sinus discharge</td>
<td>Increased cough</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Change in exam of chest</td>
<td>Decreased exercise tolerance</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Decrease ≥10% FEV₁</td>
<td>Increased chest congestion/change in sputum</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Radiographic changes</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>1 major or 2 minor</td>
<td>1</td>
</tr>
<tr>
<td><strong>Minimum number of</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>criteria</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Symptom duration</strong></td>
<td>Not required</td>
<td>≥3 d for minor criteria</td>
<td>≥3 d</td>
</tr>
<tr>
<td><strong>Antibiotic use</strong></td>
<td>Intravenous antibiotics</td>
<td>Not required</td>
<td>Oral or inhaled or intravenous antibiotics</td>
</tr>
</tbody>
</table>

Research definitions of exacerbations

<table>
<thead>
<tr>
<th>Fuchs Criteria (56)</th>
<th>Azithromycin Trial (58)</th>
<th>ISIS Trial (61)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Signs and symptoms</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in sputum</td>
<td>Major criteria:</td>
<td>O₂ saturation &lt;90% or ≥5% drop</td>
</tr>
<tr>
<td>New/increased hemoptysis</td>
<td>Decrease ≥10% FEV₁</td>
<td>New infiltrate on X-ray</td>
</tr>
<tr>
<td>Increased cough</td>
<td>O₂ saturation &lt;90% or ≥5% drop</td>
<td>Hemoptysis</td>
</tr>
<tr>
<td>Increased dyspnea</td>
<td>New infiltrate on X-ray</td>
<td>Increased work of breathing</td>
</tr>
<tr>
<td>Malaise</td>
<td>Hemoptysis</td>
<td>Increased cough</td>
</tr>
<tr>
<td>Fatigue/lethargy</td>
<td>Minor criteria:</td>
<td>Decreased exercise tolerance</td>
</tr>
<tr>
<td>Temperature ≥38°C</td>
<td>Increased work of breathing</td>
<td>Increased chest congestion/change in sputum</td>
</tr>
<tr>
<td>Anorexia/weight loss</td>
<td>New/increased adventitial sounds on exam</td>
<td>New/increased adventitial sounds on exam</td>
</tr>
<tr>
<td>Sinus pain/tenderness</td>
<td>≥5% weight loss</td>
<td>≥5% weight loss</td>
</tr>
<tr>
<td>Change in sinus discharge</td>
<td>Increased cough</td>
<td></td>
</tr>
<tr>
<td>Change in exam of chest</td>
<td>Decreased exercise tolerance</td>
<td></td>
</tr>
<tr>
<td>Decrease ≥10% FEV₁</td>
<td>Increased chest congestion/change in sputum</td>
<td></td>
</tr>
<tr>
<td>Radiographic changes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Minimum number of criteria | 4 | 1 major or 2 minor | 1 |
| Symptom duration | Not required | ≥3 d for minor criteria | ≥3 d |
| Antibiotic use | Intravenous antibiotics | Not required | Oral or inhaled or intravenous antibiotics |

Different severities of exacerbation

- **Mild**
  - Outpatient oral antibiotics

- **Severe**
  - Hospitalization with IV antibiotics
Severe exacerbations are bad

• Common & increase with age
Exacerbations are common & increase with age

Pulmonary Exacerbations by Age in Years, 2015

- Individuals with One or More Pulmonary Exacerbations
- Individuals with Two or More Pulmonary Exacerbations

CF Registry Data 2015
Severe exacerbations are bad

- Common & increase with age
- Decreased lung function
Decreased lung function may follow exacerbations

- 25% of patients did not respond to IV antibiotic therapy
  - Did not recover to baseline FEV$_1$ when checked at 3 months after treatment

White = response to IV Abx
Gray = no response to IV Abx

Sanders DB, et al. AJRCC 2010;182:627
Severe exacerbations are bad

- Common & increase with age
- Decreased lung function
- CF-related diabetes $\rightarrow$ more frequent exacerbations
- Sleep & neurobehavioral performance worse
- Negative impact on quality of life
- Associated with survival

What about mild exacerbations?

• More common
  – 73% of exacerbations are treated with oral antibiotics

• Much less is known

Mild exacerbations may also be bad

- Associated with short-term loss of FEV$_1$ & have a negative effect on lung function over time

$$oPEx = \text{pulm exacerbations w/ oral abx}$$

Change in FEV1 based on cumulative number of oPEx events

Treatment: CFF Guidelines 2009

- Site of treatment (home vs hospital)
- Chronic therapies for lung health
- Airway clearance therapies
- Systemic steroids
- Simultaneous use of inhaled and IV antibiotics
- Number of antibiotics to treat Pseudomonas
- Aminoglycoside dosing
- Continuous infusion beta-lactam antibiotics
- Duration of antibiotics
- Synergy testing (routine)

Flume, PA et al. AJRCCM. 2009;180:802
Treatment: CFF Guidelines 2009

- Chronic therapies for lung health
- Airway clearance therapies

Only 2 criteria were determined to meet Grade B (moderate certainty of benefit)

Flume, PA et al. AJRCCM. 2009;180:802
Variation in usage of chronic therapies

Duration of IV therapy varies

2015 CF Registry Data

<table>
<thead>
<tr>
<th>Duration of Pulmonary Exacerbation Treatment in Days, by Center</th>
<th>0</th>
<th>10</th>
<th>20</th>
<th>30 Median</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Total Duration of IV Antibiotic Treatment for a Pulmonary Exacerbation in Individuals Less than 18 Years</td>
<td></td>
<td>10</td>
<td>20</td>
<td>13.0</td>
<td>2.0</td>
<td>21.5</td>
</tr>
<tr>
<td>Median Duration of Hospital Stay for Treatment of a Pulmonary Exacerbation in Individuals Less than 18 Years</td>
<td></td>
<td>10</td>
<td>20</td>
<td>9.5</td>
<td>2.0</td>
<td>15.0</td>
</tr>
</tbody>
</table>
No reduction in percentage of patients treated with IV antibiotics

2015 CF Registry Data
Antibiotics help

Predicted Median Survival (US), years

1965-1980: Doubling of predicted survival

LiPuma, NACFC Plenary Session II, 2014
Antibiotics improve lung function

Antibiotic vs. Placebo Parenteral Therapy on Mean Change in FEV$_1$

Since antibiotics help, are bacteria the main cause of exacerbations?
Bacterial density with exacerbations

Density does not increase before or at onset of exacerbations

Dickson, RP et al. Lancet 2014; 384: 691
Pathophysiology of Exacerbations

• Complex relationship
  – Host defense
  – Airway microbiology
  – Sputum production
  – Airflow obstruction

• Inciting events
  – Viral infections, including RSV
  – Acquisition of new pathogens
  – Majority of PE’s not due to acquisition of new strains of *Pseudomonas*, but clonal expansion of existing strains

Slide Courtesy of C. Goss

Aaron SD, et al. AJRCCM 2004;169:811
Possible infectious causes of exacerbations

Bacteria
- Microbiome - Many species undetected
- New strain OR changing strain?

Fungi
- Aspergillus
- Interactions with bacteria

Viruses
- Associated w/ 30-40% Pulmonary Exacerbations
Clinical research approaches

• The early Intervention in CF Exacerbation Study (eICE)
  – Home Monitoring of Lung Function vs Standard Care

• Earlier identification of acute pulmonary exacerbation will improve lung function in CF
Early intervention → no difference in lung function

- No demonstrable impact on lung function in CF over 52 weeks

![Graph showing mean absolute change from baseline FEV1 (L) over 52 weeks for early intervention and usual care arms.](Figure Courtesy of C. Goss)
Clinical research approaches

• The early Intervention in CF Exacerbation Study (eICE)
  – Home Monitoring of Lung Function vs Standard Care

• Treatment Approaches
  – STOP: Standardized Treatment of Pulmonary Exacerbations Pilot Study
  – STOP 2: Treatment of pulmonary exacerbations in people with CF
STOP2: Treatment Duration Tailored to Patient’s Initial Response to Therapy

- Treat early responders differently than ‘delayed’ responders at V2 (Day 7-10)
- Those with early robust response will be less concerned about stopping too soon, but also know they will not be treated for too long
- Those with delayed response will know they will not stop too soon

Figure Courtesy of C. Goss
STOP2: Treatment Duration Tailored to Patient’s Initial Response to Therapy

- Early responders
  - D0 - D14
- Delayed responders
  - D21 - D28
- Primary Endpoint: Change in FEV$_1$ 2 weeks after treatment

Figure Courtesy of C. Goss
Conclusions

• Pulmonary exacerbations remain a common and important problem

• We need better definitions & understanding of causes → that can then direct treatments

• More research needed!
What you can do

• Reduce risk of exacerbations
  – Chronic therapies for lung health
  – Airway clearance therapies
  – CFTR modulator therapies

• Communicate with your CF care team
  – New symptoms of concern
  – Barriers to adherence
Thank you

• Ask about ongoing research in our Center!