Pulmonary Exacerbations: Better Understanding Needed

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Pediatric Pulmonary Medicine
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>Fuchs Criteria (56)</th>
<th>Azithromycin Trial (58)</th>
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<td><strong>Signs and symptoms</strong></td>
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<tr>
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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

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 → 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 FEV₁ & have a negative effect on lung function over time

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

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)
Variation in usage of chronic therapies

Duration of IV therapy varies

2015 CF Registry Data

<table>
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<tr>
<th>Duration of Pulmonary Exacerbation Treatment in Days, by Center</th>
<th>0</th>
<th>10</th>
<th>20</th>
<th>30</th>
<th>Median</th>
<th>Min</th>
<th>Max</th>
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<td></td>
<td></td>
<td>13.0</td>
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No reduction in percentage of patients treated with IV antibiotics
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

Aaron SD, et al. AJRCCM 2004;169:811

Slide Courtesy of C. Goss
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
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

V1 V2 V3
Early responders

Primary Endpoint
Change in FEV$_1$ 2 weeks after treatment

D0 D7 - 10 D14 D21 D28 D35

Delayed responders

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!