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# Pulmonary Exacerbations: Better Understanding Needed

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# 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<sub>1</sub>)
    - reduced oxygen level
    - new findings on CXR

# Research definitions of exacerbations

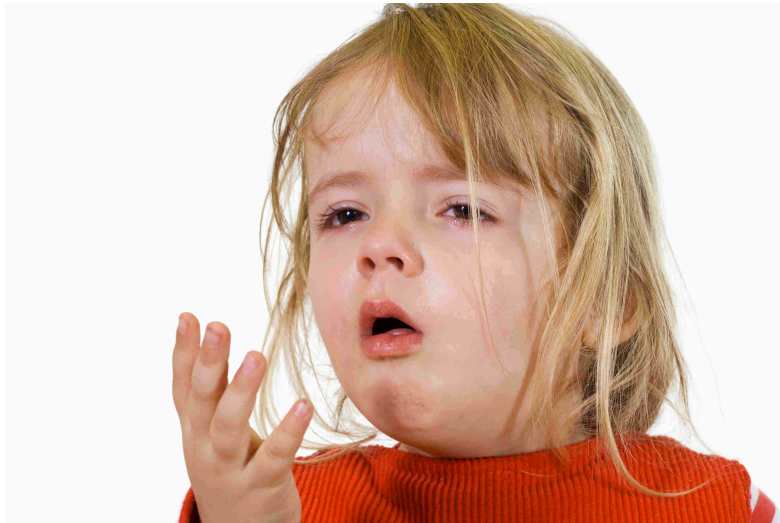
	Fuchs Criteria (56)	Azithromycin Trial (58)	ISIS Trial (61)
Signs and symptoms	Change in sputum New/increased hemoptysis Increased cough Increased dyspnea Malaise Fatigue/lethargy Temperature $>38^{\circ}\text{C}$  Anorexia/weight loss  Sinus pain/tenderness Change in sinus discharge Change in exam of chest Decrease $\geq 10\%$ FEV <sub>1</sub>  Radiographic changes	Major criteria: Decrease $\geq 10\%$ FEV <sub>1</sub> O <sub>2</sub> saturation $<90\%$ or $\geq 5\%$ drop New infiltrate on X-ray Hemoptysis Minor criteria: Increased work of breathing  Acute New/increased adventitial sounds on exam $\geq 5\%$ weight loss Increased cough Decreased exercise tolerance Increased chest congestion/change in sputum	O <sub>2</sub> saturation $<90\%$ or $\geq 5\%$ drop New infiltrate on X-ray Hemoptysis Increased work of breathing Increased cough Decreased exercise tolerance Increased chest congestion/change in sputum New/increased adventitial sounds on exam $\geq 5\%$ weight loss
Minimum number of criteria	4	1 major or 2 minor	1
Symptom duration	Not required	$\geq 3$ d for minor criteria	$\geq 3$ d
Antibiotic use	Intravenous antibiotics	Not required	Oral or inhaled or intravenous antibiotics

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# Different severities of exacerbation

- Mild
  - Outpatient oral antibiotics
- Severe
  - Hospitalization with IV antibiotics



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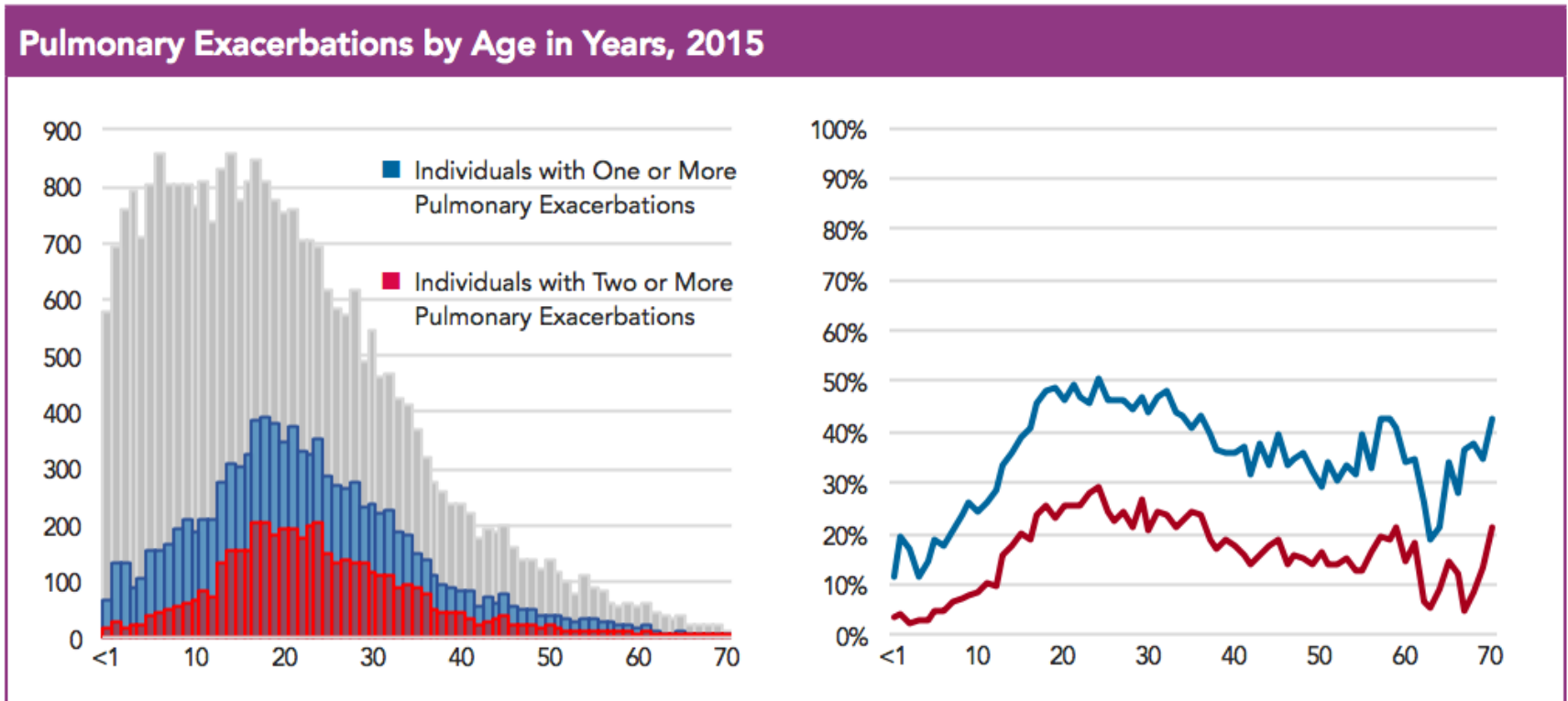
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# Severe exacerbations are bad

- Common & increase with age

# Exacerbations are common & increase with age



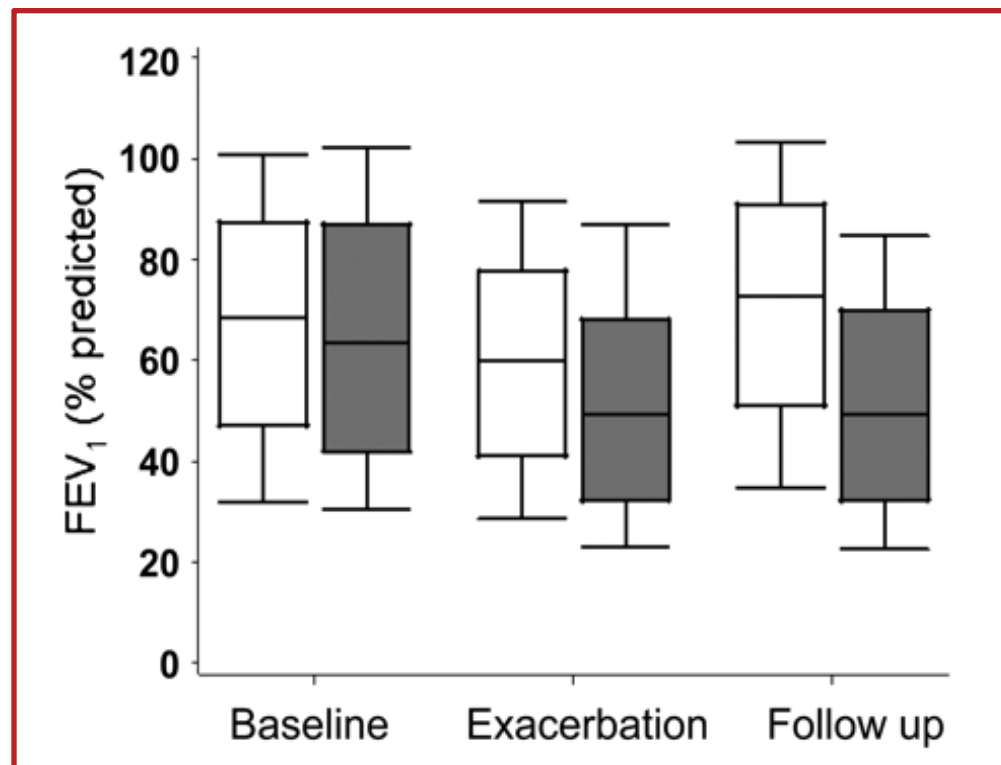
CF Registry Data 2015

# 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<sub>1</sub> when checked at 3 months after treatment



White = response to IV Abx

Gray = no response to IV Abx

# 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

Marshall BC, et al. J Pediatr 2005;146:681

Dobbin CJ et al. AJRCCM 2005;172:99.

Britto MT, et al. Chest 2002;121:64.

Liou TG, et al. Am J Epidemiol 2001;153:345

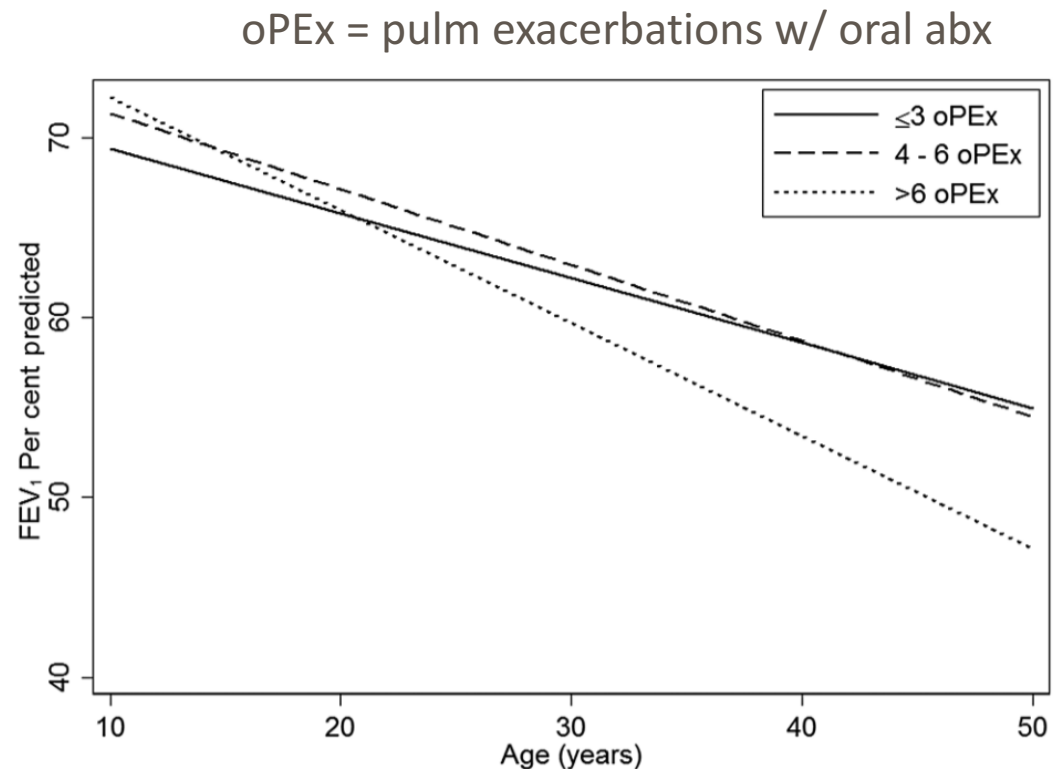
# What about mild exacerbations?

- 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

Change in  $FEV_1$  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)

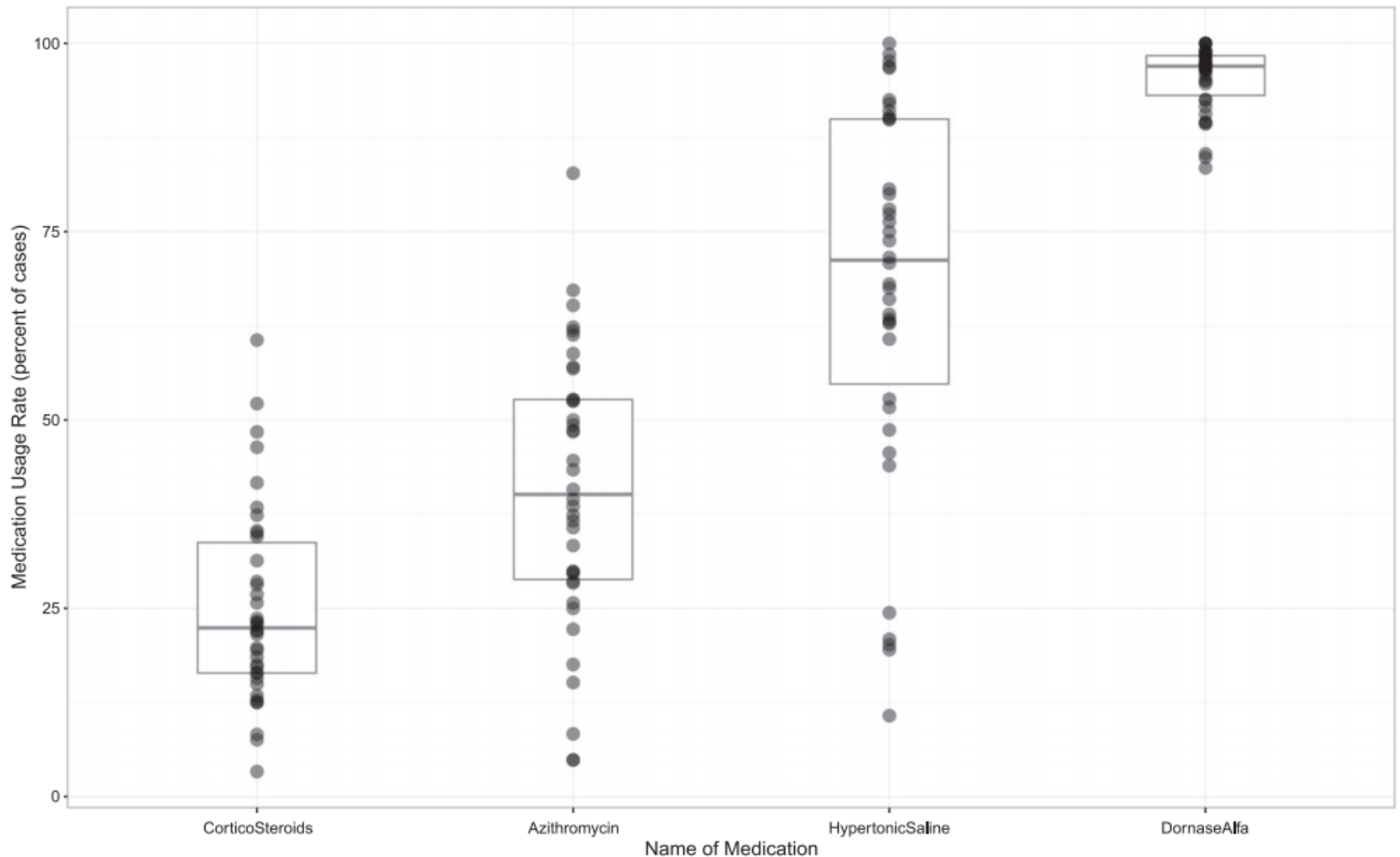


# Treatment: CFF Guidelines 2009

- Chronic therapies for lung health
- Airway clearance therapies

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

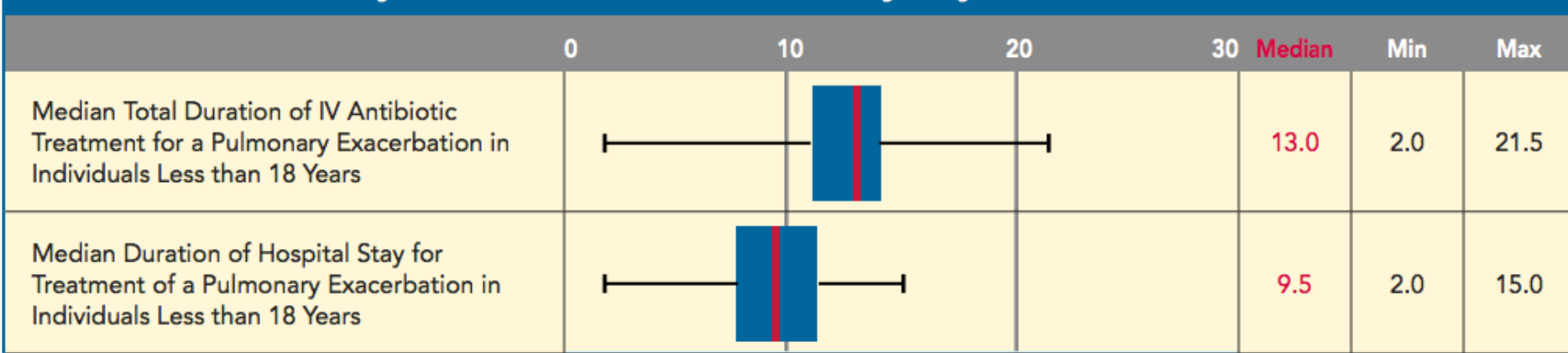
# Variation in usage of chronic therapies



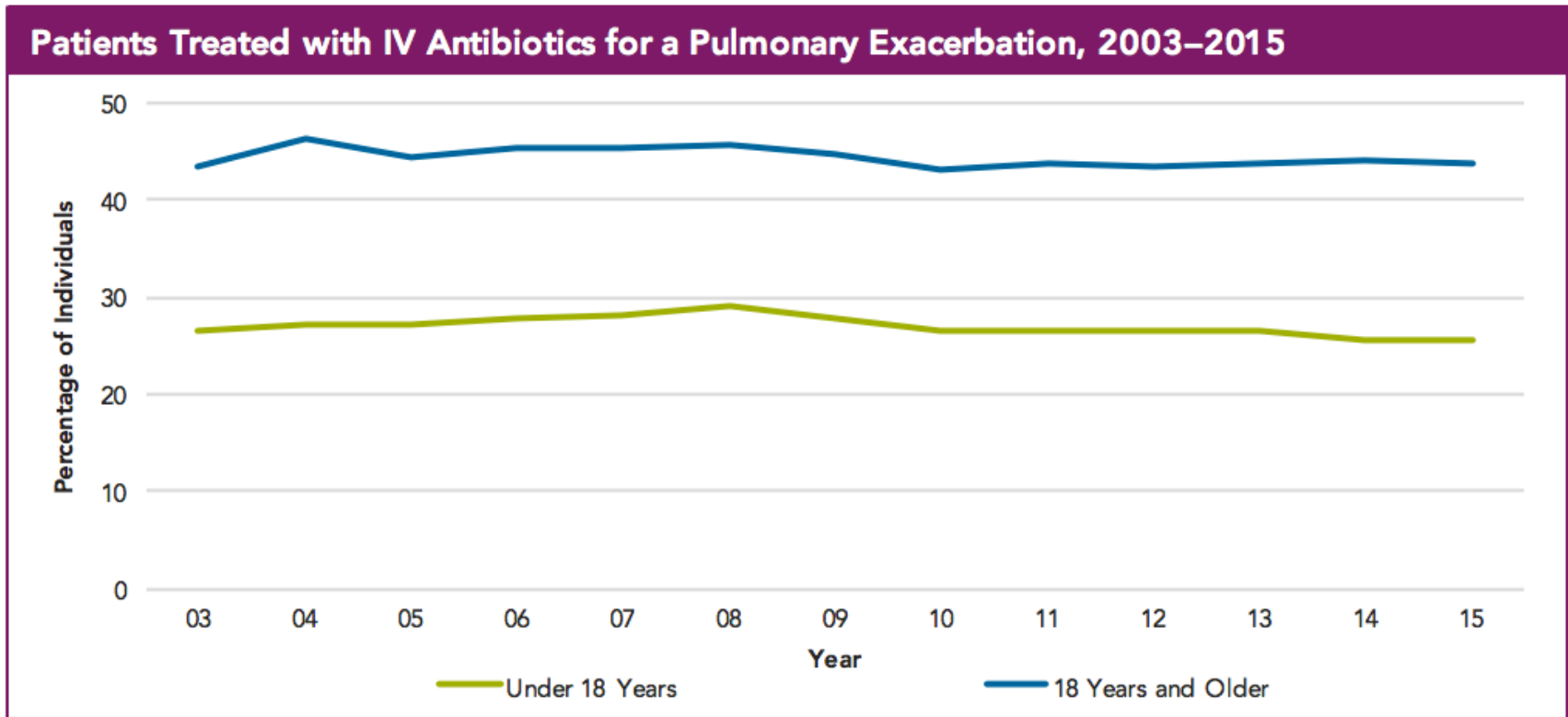
# Duration of IV therapy varies

## 2015 CF Registry Data

### Duration of Pulmonary Exacerbation Treatment in Days, by Center



# No reduction in percentage of patients treated with IV antibiotics



2015 CF Registry Data



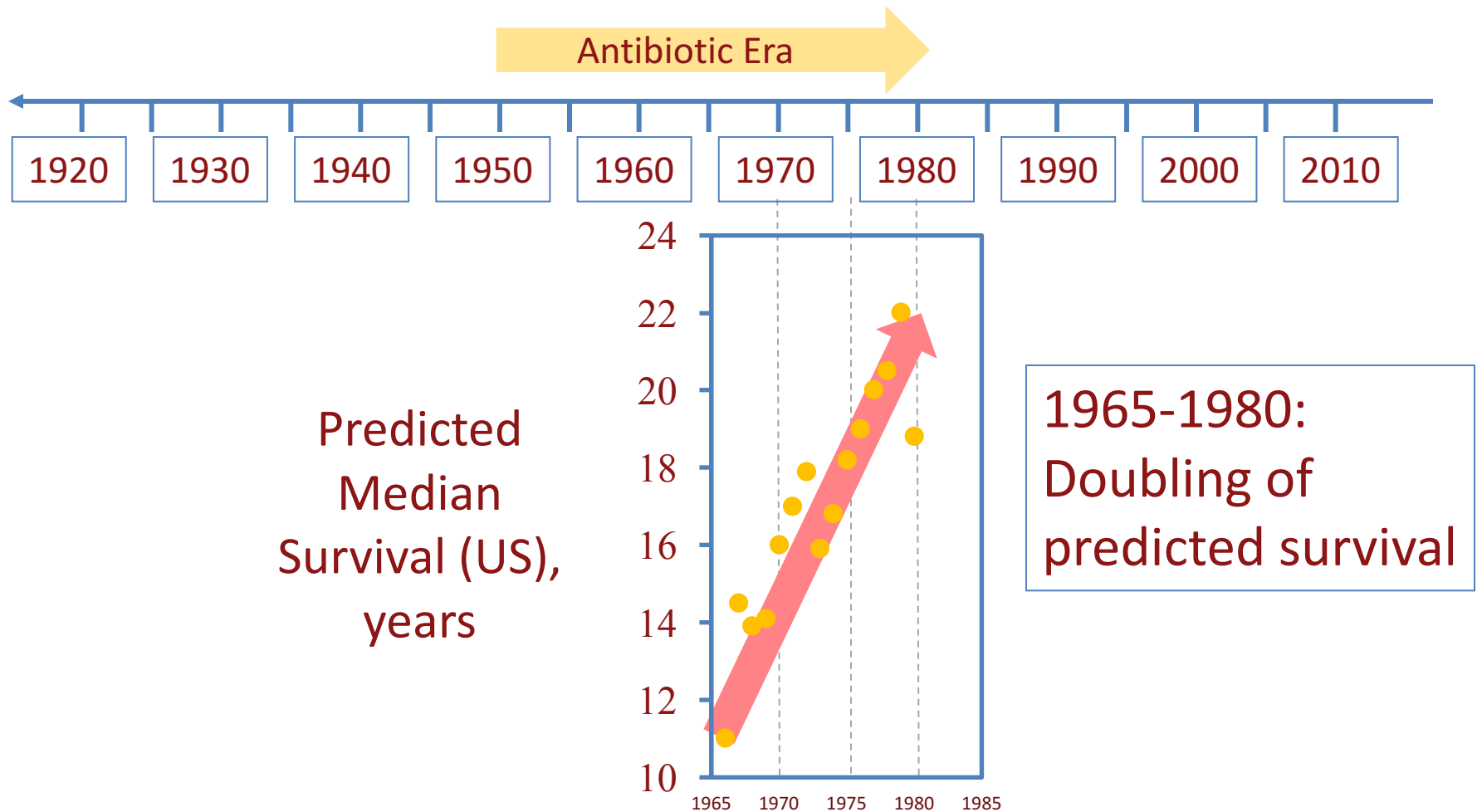
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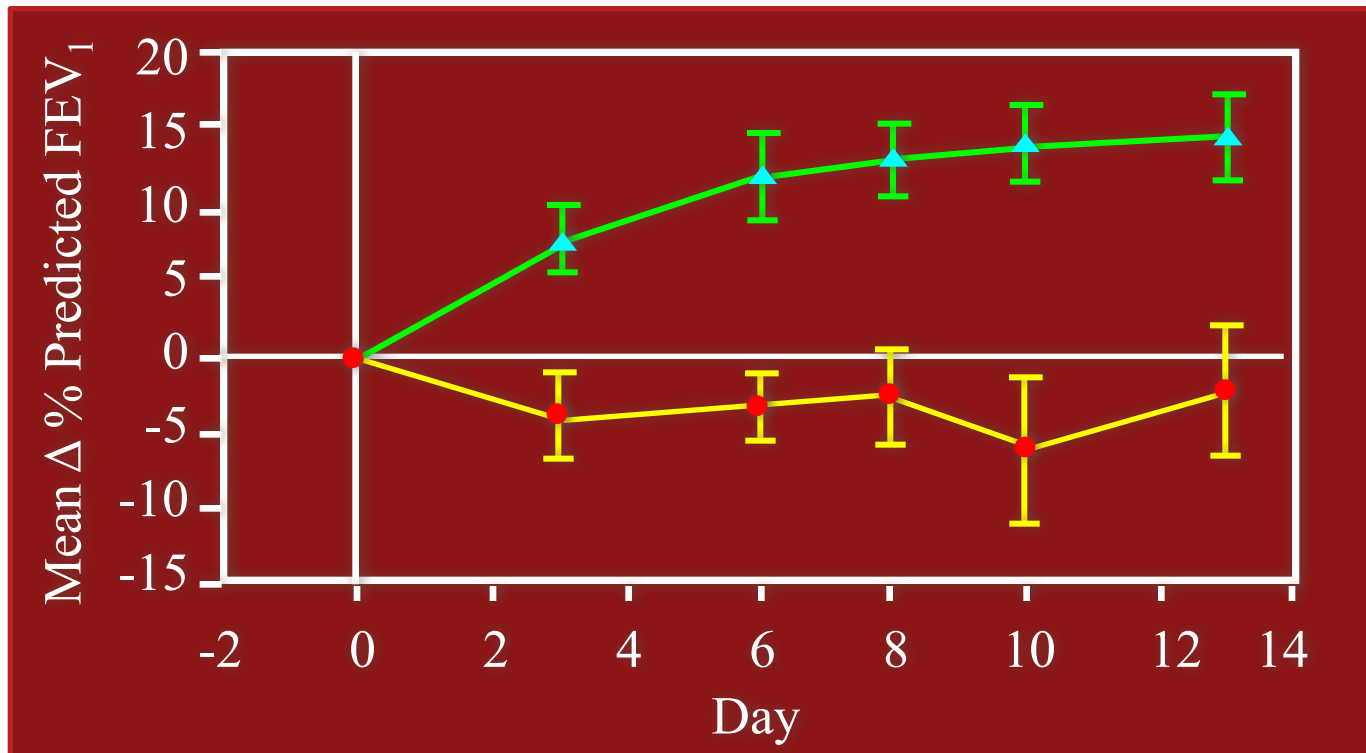
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# Antibiotics help



# Antibiotics improve lung function

Antibiotic vs. Placebo Parenteral Therapy on Mean Change in FEV<sub>1</sub>



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



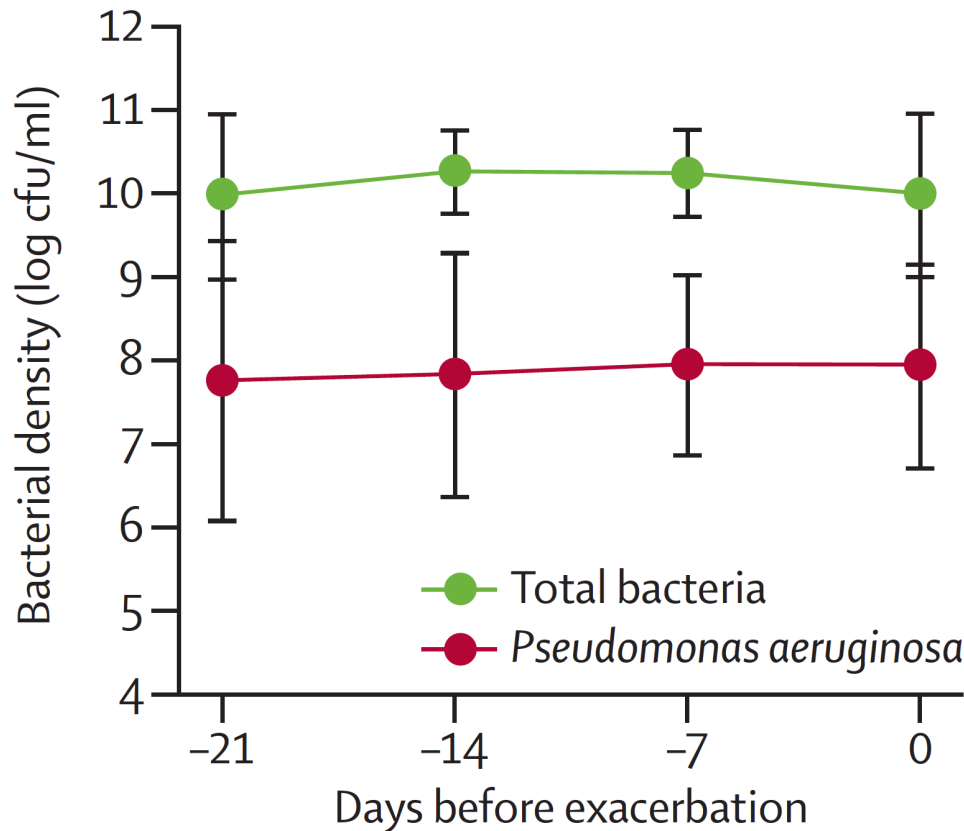
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# Bacterial density with exacerbations



Density does not increase before or at onset of exacerbations

Stressmann FA, et al. J Cyst Fibros 2011; 10: 357

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**

Asner S, et al. J Cyst Fibros 2011;11:433

Hiatt PW, et al. Pediatrics 1999;103:619

van Ewijk BE, et al. J Cyst Fibros 2005;4:31

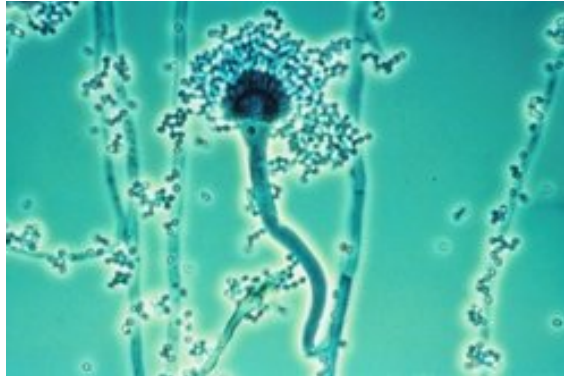
Aaron SD, et al. AJRCCM 2004;169:811

# Possible infectious causes of exacerbations



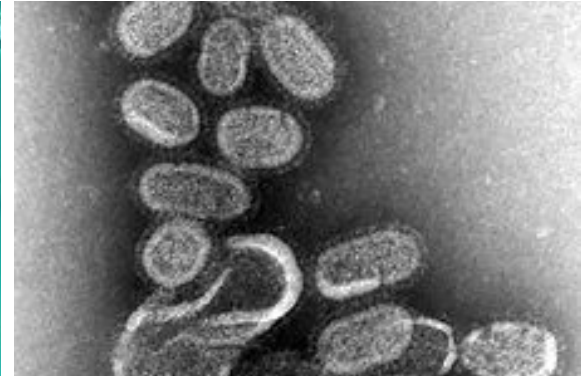
## Bacteria

- 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

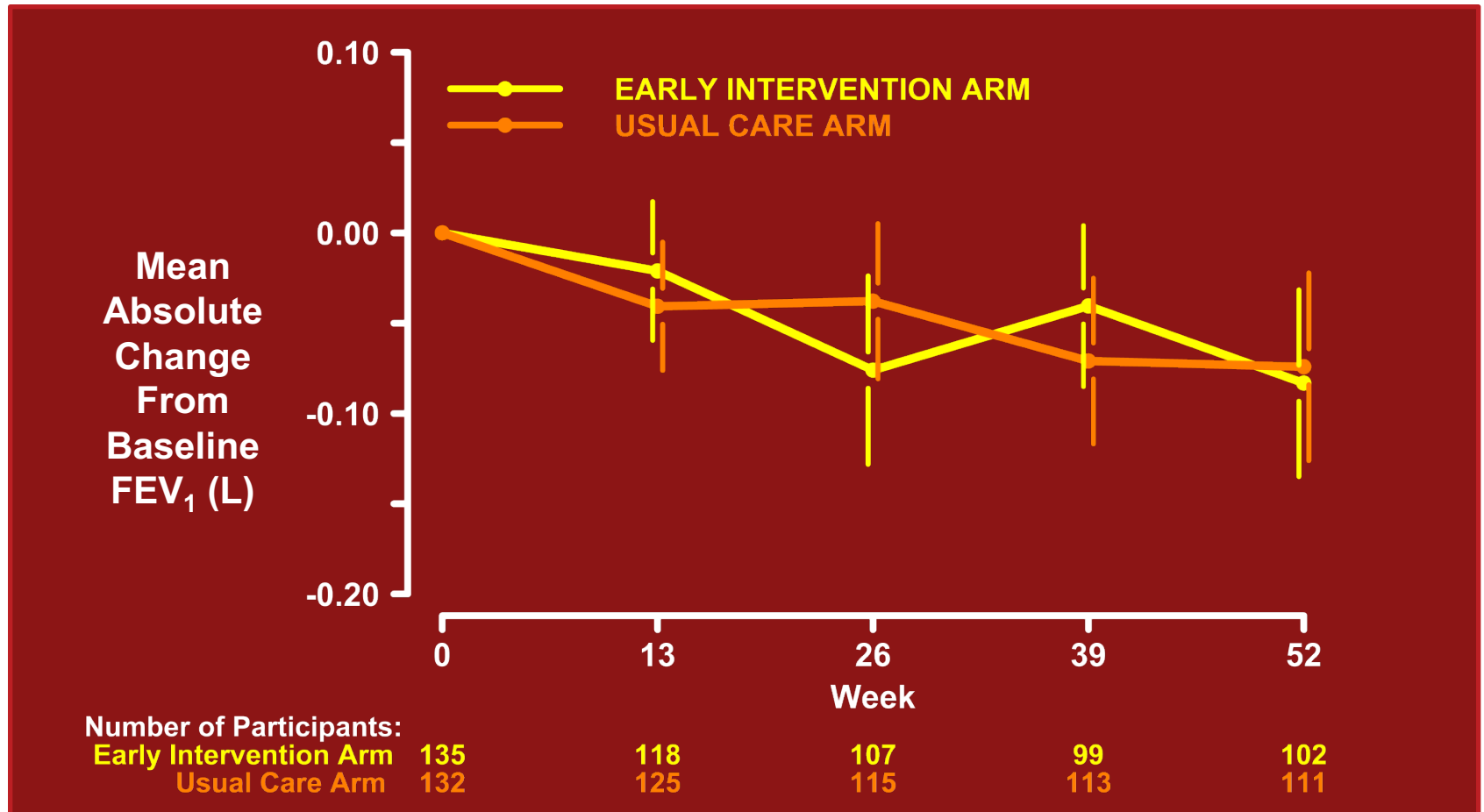
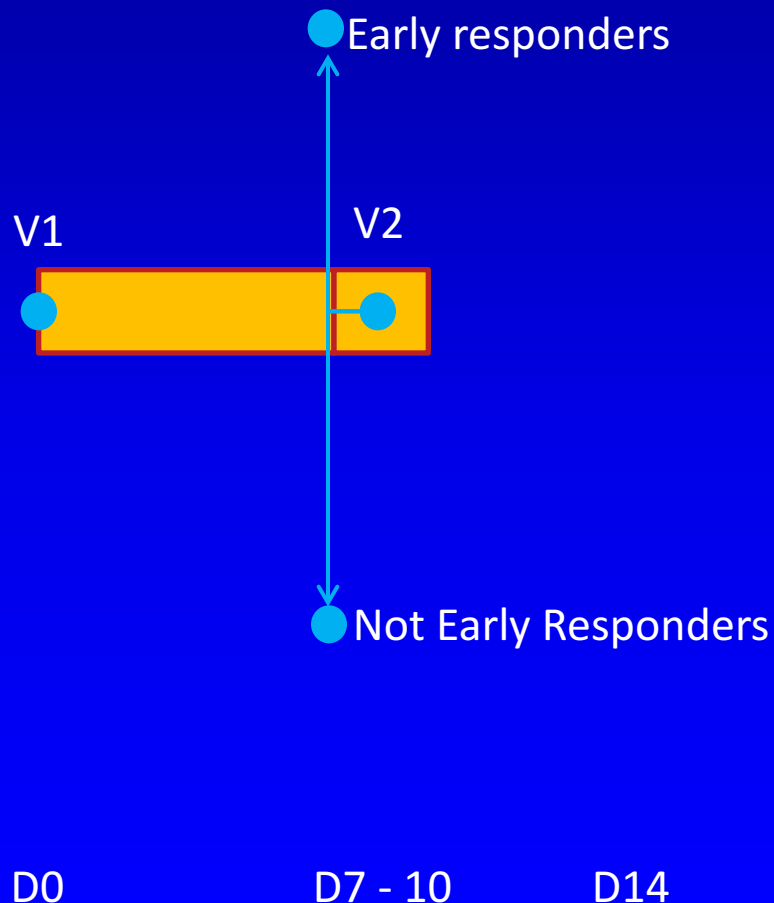


Figure Courtesy of C. Goss

# Clinical research approaches

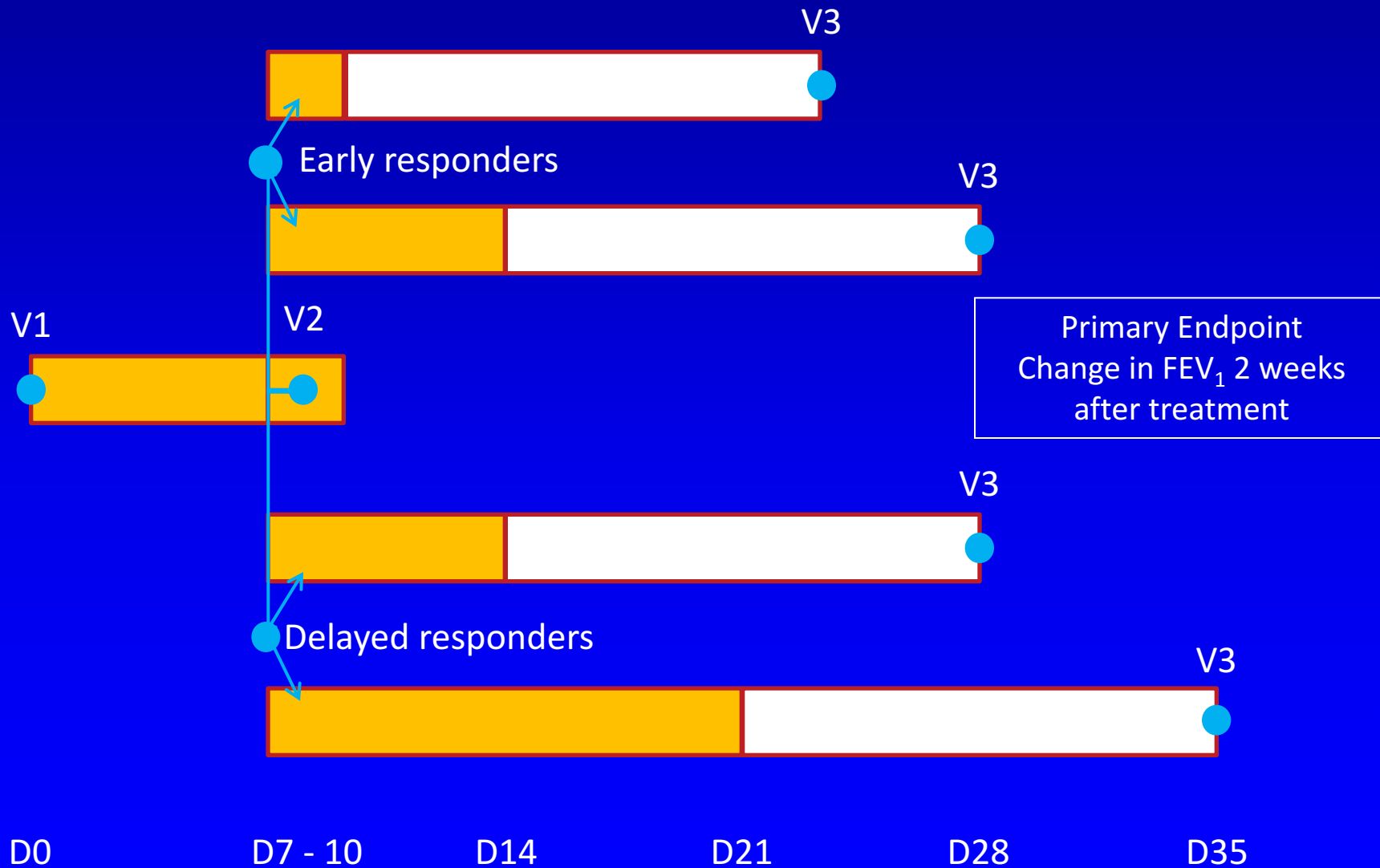
- The early Intervention in CF Exacerbation Study (eICE)
  - Home Monitoring of Lung Function vs Standard Care
- Treatment Approaches
  - STOP: Standardized Treatment of Pulmonary Exacerbations Pilot Study
  - STOP 2: Treatment of pulmonary exacerbations in people with CF

# 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

# STOP2: Treatment Duration Tailored to Patient's Initial Response to Therapy



# 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!

