Management of Pulmonary Exacerbations in Cystic Fibrosis

Jeremiah Lysinger, MD
Director, Montana Cystic Fibrosis Center
Pediatric Pulmonology
Billings Clinic

Pulmonary Exacerbations

- Chronic respiratory symptoms of CF may show a rapid or progressive increase of symptoms
  - Pulmonary Exacerbation
- Large observational study of >11,000 CF pts Rabin et al. Pediat Pulmonol 2004
  - 42% experience exacerbation in 6 mo period
- What is a pulmonary exacerbation in CF?
  - No standard definition
  - Difficult to assess incidence/prevalence
  - Impairs research into treatment

Pulmonary Exacerbations

- Currently considered symptoms requiring antibiotics
  - Depending on source may include
    - Oral
    - IV – home or hospital
- Symptoms usually include some combination of
  - Increased cough
  - Change in sputum
  - Decreased exercise tolerance
  - Decreased appetite
  - Decreased weight
  - Hemoptysis
  - Change in physical exam
  - Decreased spirometry
Everyone Knows an Exacerbation When They See One – Right?

- 28 clinical vignettes presented to CF care providers from large and small centers
  - No absolute treatment consensus for any scenario
  - Variability between care centers
  - Variability within care centers
  - No consistent approach by the individual providers
- Adult providers, younger physicians and centers with more providers more aggressive
- Systemic symptoms, change in SaO2, and change in FEV1 most associated with IV abx


Why Is This Important?

- Negative impact on pt quality of life
- Significant impact on overall cost of care
- Associated with more rapid loss of lung function
- Despite advances in care, exacerbation rate has not changed over last 2 decades
- Many patients show no restoration of lung function after exacerbation
  - Better prevention or treatment needed

Stenbit and Flume. Curr Opin Pulm Med 2011

Adverse Outcomes of Exacerbations

- 446 CF pts assessed prospectively over 3 years stratified based on exacerbation rates
  - Pts with >2 exacerbations per year when compared pts with <1 exacerbation per year showed
    - More rapid decline of 5% loss of lung function (HR 1.55 p=0.02)
    - Increased risk of death or lung transplant (24.7% of pts; HR 4.05 p=0.03)
    - Increased risk of death alone (11% of pts; HR 7.86 p=0.006)

de Boer et al. Thorax 2011
Patients at Risk

- Negative correlation between pulmonary exacerbation rates and FEV1. Goss and Burns. Thorax 2007
- Female pts
  - Also have poorer survival outcomes
- CF related diabetes

Causes of Exacerbations

- Source may be multifactorial
- Multiple causes proposed
  - Slow progression of chronic airway inflammation
  - Acute event leading to rapid increase in mucous production and inflammation
    - Viral process
    - Rapid increase in current bacterial load
    - Change in bacterial biome. Turney et al. Thorax 2011
    - Change in P aeruginosa phenotype. Fothergill et al. J Med Microbiol 2010

Management
General Principles

• Chronic infection and increased bacterial load are felt to create inflammation, increased mucous production, and mucous plugging
• 2 general principles
  - Intensification of airways clearance therapy and chronic therapies – get mucous out
  - Antibiotics – decrease bacterial load and inflammation

Goal of Therapy

• Return to baseline of cough and sputum production
• Reduction of dyspnea and increased appetite and exercise tolerance
• If FEV1 is decreased, attempted return to baseline
  – Frequently not achieved Sanders et al. AJRCCM 2010; Sanders et al. Pediatr Pulmonol 2011
• Pancreatic insufficiency with malnutrition, female sex, ABPA, MRSA, and B cepacia are risk factors

Antibiotics
**Delivery of Antibiotics**

- **Oral antibiotics**
  - Probably adequate for mild exacerbation
  - Option for pt unable to come to hospital
  - Limited options for *P. aeruginosa*
  - Decreased bioavailability
- **IV antibiotics**
  - Diverse options for treating *P. aeruginosa*
  - Significantly improved bioavailability
  - Requires long term access
  - Usually associated with hospitalization
  - Increased toxicity

---

**Delivery of Antibiotics**

- **Inhaled antibiotics**
  - Traditionally used as maintenance/preventive therapy
  - May offer additional means of delivering antibiotics as outpatient
  - Very high levels of antibiotics in airways
    - Overwhelm resistance
  - Potential for toxicity when used in conjunction with IV antibiotics – no proven benefit

  Flume et al. AJRCCM. 2009

---

**Site of Treatment**

- **Home vs Hospital**
- Treatment of exacerbation not just about antibiotics
  - Airway clearance therapy
  - Addressing nutritional deficits
    - Nutritional needs increased during exacerbation
  - Social issues
  - Comorbidities
    - CFRD, chronic renal insufficiency
  - Education
Site of Treatment

- Advanced therapies not available outside of hospital
  - New IV regimens
- Observational studies have shown better outcomes in hospital vs home 
- Hospital may create social and geographical isolation
- CFF recommends against home IV abx unless resources and support equivalent to hospital can be provided Flume et al. AJRCCM. 2009

Multiple Antibiotics

- 2 antibiotics have traditionally been used in tx of \( P \text{ aeruginosa} \)
- Single antibiotic associated with reduced toxicity and cost
- In vitro synergy not proven to improve clinical outcome Aaron et al. Lancet 2005
- CFF concludes that there is insufficient data to recommend use of a single agent Flume et al. AJRCCM 2009

Multiple Antibiotics

- \( S \text{ aureus} \) may not need 2 agents
- Respiratory cultures may not represent what is most significant pathogen
- Clinical response may not correlate with in vitro sensitivity testing
- Start with what has worked in past and adjust if response is inadequate
  Stenbit and Flume. Curr Opin Pulm Med 2011
Antibiotic Choice and Dosing

- Traditionally, *P. aeruginosa* treated with combination of aminoglycoside and beta-lactam
- Tobramycin most common aminoglycoside
  - Concerns for ototoxicity and nephrotoxicity
- Sometimes avoided because of reported resistance
- New treatment regimens attempt to avoid both

Tobramycin Dosing

- Concentration dependent killing
  - Higher the peak concentration, the more effective the medication
- Toxicity dependent upon time of exposure
- Traditional Q8 dosing achieves peaks of 10-12 with 1-2 hour period when drug below detectable level
- Q24 dosing at ~ 10 mg/kg/dose aims for peak of 25-35 with 9-11 hour period undetectable levels

Tobramycin Dosing

- Pathogen MIC’s to tobramycin
  - Sensitive < 4
  - Intermediate = 8
  - Resistant > 16
- Standard “levels” for assessing once daily tobramycin aim to assess safe trough levels
- CF dosing aims for peak of 25-35 with AUC of 80-110
- Kinetics are critical!!!
- CFF recommends once daily dosing on tobramycin Flume et al. AJRCCM 2009
Beta-Lactam Dosing

- Beta-lactams exhibit time dependent killing
- The length of time above MIC is more critical than concentration above MIC
- Prolonged infusion or continuous infusion beta-lactam abx may be superior to intermittent dosing
- At time of last CFF treatment guidelines, data was insufficient to recommend continuous infusion Flume et al. AJRCCM 2009

Beta-Lactam Dosing

- Studies ongoing about using prolonged or continuous infusion in resistant pathogens
  - Multi-drug resistant PA, mucoid PA
- Continuous infusion requires ability to check drug levels
- Prolonged infusion does not necessarily require drug levels

Q8 hr dosing standard infusion
Q8 hr dosing infused over 4 hours
Q24 hr dosing with 23 hour infusion
Duration of Therapy

- Mucoid and resistant pathogens in areas of poor perfusion theoretically require prolonged tx
- Longer therapy associated with increased toxicity, increased cost and increased risk for allergic reaction
- Median length of treatment in kids is 14.5 days and 16.8 days in adults.

Duration of Therapy

- The CFF reports that there is insufficient data to recommend an optimal duration of therapy Flume et al. AJRCCM 2009
- Cochrane review reports similar findings Plummer and Wildman. Cochrane Database of Systematic Reviews 2011
- 2010 study showed that pulmonary function response to IV antibiotics essentially complete within 2 weeks
  - Average time to highest FEV1 8.7 days
  - 93.7% of pts had peak FEV1 within 13 days VanDevanter et al. Respiratory Research 2010

Corticosteroids

- Not routinely recommended in care of CF
- However, certain patients may have:
  - Reactive component
  - Asthma
  - ABPA
- Short course of corticosteroids may be indicated in certain patients
- Larger studies needed Flume et al. AJRCCM 2009
Airway Clearance Therapy and Respiratory Care

Airway Clearance Therapy

- Recommended that ACT be intensified with exacerbation Flume et al. AJRCCM 2009
  - home or hospital
- Increased
  - Length of treatment
  - Frequency of treatment
- ▲ Respiratory medication frequency

Standard Respiratory Therapy

- Standard compliant teenage/adult patient
  - Vest for 15-20 minutes twice daily
    - Huff coughs between each 5 min cycle
  - Pulmozyme 2.5 mg nebs 1-2 x per day
  - 7% hypertonic saline twice daily
- Most patients aren't fully compliant with regimen
  - Skipped huff coughs, vest in bed, skipped treatments
Hospital Exacerbation RT

- Vest and/or IPV four times a day
  - Minimum of 20 min
  - Full huff coughs between each cycle
- Pulmozyme 2.5 mg neb twice daily
- Hypertonic saline neb twice daily
  - Try to step concentration of HTS up if tolerated
- Possibly PEP/Acapella before vest or during treatments
- Twice weekly spirometry

Education

- Exacerbation is opportunity to teach pt about new devices/ACT techniques and to reinforce proper technique
- IPV
- Autogenic drainage
- Proper huff coughs
- Appropriate neb delivery
- Good opportunity to introduce HTS

Chronic Therapies
Chronic Therapies

- Chronic therapies should be continued during exacerbation. Flume et al. AJRCCM 2009
- High dose ibuprofen and inhaled abx may be exception
- Opportunity to reinforce and educate proper use and mechanism of chronic therapies

CFRD

- Opportunity to diagnose, educate and improve management
- Insulin requirement frequently ↑ during exacerbation
  - Fine tune control in hospital
- Certain pts require corticosteroids
  - New insulin requirement
  - Significant change in insulin requirement

Nutrition
**Nutrition**

- Exacerbation frequently associated with weight loss
- Exacerbation associated with increased caloric need
- Malnutrition associated with decreased lung function and increased exacerbation rate
- Opportunity to assess caloric need and nutritional deficiencies

- Opportunity to educate pt/family
- Recommend aggressive nutritional intervention to improve BMI, recover weight loss, and support ↑ nutritional needs with exacerbation
  - CF dietitian consult
  - High protein, high fat, high cal supplements
  - Possible g-tube placement
  - Assess for CFRD
  - Assess for vitamin (fat soluble) deficiencies

**Social**
Social

• Exacerbations may be related to social issues
  – Poor insurance coverage
  – Cost prohibitive medications
  – Inadequate time for complex treatments
  – Depression
  – School/work
  – Neglect
  – Drug abuse

Social

• Exacerbation may be opportunity to address issues
• Hospitalization may allow sanctuary from social issues
• Possibility for intervention
• Opportunity to identify and enroll in support program
• Opportunity to assess social impacts on other systems

Questions?
References

1. Flume PA, Mogayzel PJ Jr, Robinson KA, et al. Cystic fibrosis pulmonary guidelines: treatment of pulmonary exacerbations. Am J Respir Crit Care Med 2009; 180:802-808.


