Acute Exacerbations of COPD

Bill Vandivier MD
Director, COPD Center
University of Colorado Anschutz Medical Center

What is an Acute Exacerbation of COPD (AECOPD)?

GOLD Guidelines 2015
• Acute worsening of respiratory symptoms
• Beyond day to day variation
• Results in a change in medical therapy
AECOPD Grades

• Mild AECOPD
  – Not treated
• Moderate AECOPD
  – Ambulatory treatment
• Severe AECOPD
  – Hospital treatment
• Very Severe AECOPD
  – Acute hypercarbic respiratory failure
  – Non-invasive or invasive mechanical ventilation

Vollenweider D.J. Cochrane Review 2012

Why are AECOPDs Important?

• Negatively impact quality of life
• Slow recovery of symptoms and lung function
• Accelerate lung function decline
• Increase mortality
• High socioeconomic costs
AECOPDs Worsen Quality of Life

Change from Baseline SGRQ Versus Patients with no AECOPDs

Xu W. Eur Resp J 35:1022, 2010

Lung Function Recovers Slowly Following an AECOPD

Seemungal T. AJRCCM 161:1608, 2000
**Lung Function Recovers Slowly Following an AECOPD**

- Median recovery of PEFR at 6-7 days (parallels symptoms)
- Day 35
  - PEFR recovery in 75%
  - Symptom recovery in 86%
- Day 90
  - 7% not recovered to PEFR baseline

*Seemungal T. AJRCCM 161:1608, 2000*

---

**Frequent AECOPDs Worsen Lung Function Decline**

Annual Change in FEV1 (ml)

- ≥ 3 AECOPDs/yr
- < 3 AECOPDs/yr

*Xu W. Eur Resp J 35:1022, 2010*
AECOPDs Worsen Mortality

AECOPD Number vs Mortality

- No AECOPD
- 1-2 AECOPD
- 3-4 AECOPD

Soler-Cataluna JJ. Thorax 60:925, 2005

Mortality From Severe AECOPDs 1998-2008

- Nationwide Inpatient Sample of Healthcare Cost and Utilization Project (HCUP-NIS)
- 1998-2008

Chandra D. AJRCCM 185:152, 2012
What Causes AECOPDs?

- Viruses 30%
  - Rhinovirus
  - RSV
  - Influenza A&B
  - Parainfluenza
  - Coronavirus
  - Picornavirus
  - Adenovirus
  - Human metapneumovirus

- Bacteria 40-50%
  - H. influenza
  - S. pneumoniae
  - M. catarrhalis
  - E. coli
  - Klebsiella
  - P. aeruginosa

- Atypical Bacteria 5-10%
  - C. pneumoniae

- Other 10-25%
  - Air Pollution

Viral Infection and AECOPDs

- Investigated role of viral infection in AECOPDs using PCR
- 39% associated with viral infection
- Viral infections associated with
  - more severe symptoms
  - longer duration of illness
  - frequent exacerbations
- Rhinovirus was the most common virus (58%)

Seemungal AJRCCM 164:1618, 2001
**Respiratory Syncytial Virus (RSV) in the Elderly**

**Healthy/High Risk/Hospital**
- RSV: Healthy ~8%
- RSV: High Risk ~10%
- RSV: Hospital ~10%
- FluA: Healthy ~4%
- FluA: High Risk ~4%
- FluA: Hospital ~11%

**RSV versus Influenza:**
- Healthy
  - RSV had less HCU
- High Risk
  - RSV had equal HCU
- Hospital
  - Same LOS
  - Same ICU
  - Same Mortality

*Falsey AR. NEJM 352:1750, 2005*

**Chronic RSV is Associated with a More Rapid Decline in Lung Function**

![Annual Decline in FEV1 (mL/yr)](chart)

Independent of smoking, exacerbation frequency or bacterial load

*Wilkinson TM. AJRCCM 173:871, 2006*
**Watch for the Imposters!!!!**

- Pulmonary embolism
- Chronic aspiration
- Airway tumors
- Churg-Strauss vasculitis
- Hypersensitivity pneumonitis
- Autoimmune bronchiolitis
- Infections with
  - MAC, rapid growers, aspergillosis

**Increased Risk for AECOPD**

- Cough, sputum and wheeze
- Hx of AECOPD - antibiotic or steroid use within past year
- Severity of obstruction
- Increased Age
- Duration of COPD
- Prior use of COPD meds
- Bacterial colonization
- Comorbid conditions (e.g. cardiovascular)
- Poor quality of life
AECOPD Risk Associated with Cough and Sputum

Burgel, P-R. Chest 135:975, 2009

AECOPD Risk Associated with Lung Function

Donaldson GC Thorax 61:164, 2006
COPD Treatment Model

Preventing AECOPDs

GOLD Guidelines 2015
Pulmonary Rehabilitation Reduces Hospital Use

Influenza Vaccination Decreases AECOPD Risk

- Influenza vaccination reduces AECOPDs
- Protection occurs ≥ 3-4 weeks after vaccination
- Influenza vaccination causes local effects that are transient, but it does not increase AECOPDs
**Pneumovax 23 Decreases Pneumonia Risk in COPD**

Age < 65y

- Vaccinated: 91
- Control: 114

FEV₁ < 40%

- Vaccinated: 132
- Control: 114

Alfageme I. Thorax 61:189, 2006

**Macrolides Prevent AECOPDs**

Erythromycin 250 BID

Azithromycin 250 Daily

Seemungal AJRCCM 178:1139, 2008

Albert RK NEJM 365:689, 2011
**MACRO Trial**  
*NEJM 365;689 2011*

- **Objective:** Determine whether Azithromycin decreases COPD exacerbations
- **Design:** 1142 patients studied over 1 year  
  Azithromycin (250mg per day) versus Placebo
- **Results**
  - **Time to first exacerbation:** 266 days vs. 174 days (P<0.001)
  - **Exacerbations per year:** 1.48 vs. 1.83 (P=0.001)
  - **QOL:** improved 2.8 units (P=0.004)
  - **Increased hearing loss:** 25% vs. 20% (P=0.04)

**TORCH Trial**  
*NEJM 356;775 2007*

- **Objective:** Determine whether Advair decreases mortality
- **Design:** 6,112 patients studied over 3 years  
  Placebo  Serevent  Fluticasone  Advair (500/50)
- **Results**
  - **Mortality:** Advair reduced mortality by 2.6% (17.5%) vs  
    Placebo (P=0.052)
  - **Placebo (15.2%), Serevent (13.5%), Fluticasone (16%), Advair (12.6%)**
  - **Advair vs Placebo**
    - reduced exacerbations (25%), hospitalizations (17%),
    - increased lung function, QOL and PNAs (6%)
**Uplift Trial**
*NEJM 359;1543 2008*

- **Objective:** Determine the effects of Spiriva on the long-term decline in lung function
- **Design:** 5993 patients studied over 4 years
  Spiriva vs Placebo
- **Results**
  - Decreased exacerbations (~15%), related hospitalizations (~15%) and respiratory failure (~33%)

---

**Inspire Trial**
*AJRCCM 177;19 2008*

- **Objective:** Efficacy of Spiriva vs. Advair (500/50) to prevent AECOPDs
- **Design:** 1,323 patients studied over 2 years
  Spiriva + Placebo
  Advair + Placebo
- **Results**
  - No difference in exacerbation rates
  - **Spiriva:** improved lung function but had a higher withdrawal rate
  - **Advair:** slightly better QOL, more PNAs, lower mortality (3% vs 6%)
POET-COPD Trial

NEJM 364;1093 2011

- **Objective:** Efficacy of Spiriva vs. Serevent to prevent AECOPDs
- **Design:** 7,376 patients studied over 1 year
  Spiriva vs Serevent
- **Results for Spiriva**
  - Increased the time to the first exacerbation (185 vs. 165 d)
  - Reduced the risk for an AECOPD by 17%
  - Increased time to the first severe AECOPD
  - Reduced the annual number of moderate and severe AECOPDs

Other Therapies

- **Phosphodiesterase-4 inhibitor (Roflumilast)**
  - Increases FEV₁ by ~50ml
  - Very small increase QOL
  - No effect on symptoms
  - Decrease AECOPDs (OR = 0.78)
Summary of Therapies to Reduce AECOPD Risk

- Pneumonia Vaccination (23 and 13)
- Influenza Vaccination
- Pulmonary Rehabilitation
- Long-acting Beta Agonists
- Long-acting Anticholinergics
- Inhaled Corticosteroids
- Macrolide Antibiotics
- PDE4 Inhibitors
- Treat OSA, chronic aspiration and GERD

Treating AECOPDs

- Bronchodilators
- Corticosteroids
- Antibiotics
- Noninvasive Ventilation
**Bronchodilators for AECOPDs**

- No RCTs for short-acting bronchodilators
- No RCTs for long-acting bronchodilators
- Weak evidence to support combining Beta agonists with anti-cholinergics
- Nebulizer and metered dose inhalers are equivalent

**Steroids for AECOPDs**

- **Steroid Effects**
  - Reduce treatment failure (OR=0.48)
  - Reduce relapse rate at 1 month (OR=78)
  - No effect on mortality (OR=1.00)
  - Faster early (72h) increase in FEV₁
  - Shorter hospital LOS (-1.22d)
  - No difference in ICU LOS
  - Increased hyperglycemia

*Walters J. Cochrane Review 2014*
Steroids for Moderate AECOPDs

Outpatients

Prednisolone for Outpatient AECOPDs

- 147 ER discharges
- Treatment
  - Pred 40mg x 10d
- Relapse
- Results – Prednisol.
  - Increased time to relapse
  - Decreased 30d treatment failure (27% vs. 43%)
  - Rapid improvement in FEV₁ and dyspnea

Aaron S. NEJM 348:2618, 2003
Steroids for Severe AECOPDs

Hospitalized, Non-ventilated Patients

VA Cooperative Study

- 271 severe AECOPD
- Treatments
  - Solumedrol 125q6h – 2wk taper
  - Solumedrol 125q6h – 8wk taper
  - Placebo
- Treatment Failure
- Results
  - Short or long-term solumedrol decreased treatment failure
  - Short and long-term solumedrol were equally effective

Niewoehner D. NEJM 340:1941, 1999
**Prednisolone for Severe AECOPDs**

- **58 severe AECOPDs**
  - Non-acidotic
- **Treatments**
  - Prednisolone 30mg x 14d
  - Placebo
- **Results - Prednisolone**
  - Improved FEV$_1$ faster
  - Shorter LOS (7 vs. 9 days)

*Davies L. Lancet 354:456, 1999*

---

**Treatment Length for Severe AECOPDs**  
*REduce Trial*

- **314 severe AECOPDs**
- **Non-inferiority design**
- **Time to next AECOPD**
- **Treatment**
  - Pred 40mg x 5 days
  - Pred 40mg x 10 days
- **Results**
  - No difference in time to next AECOPD
  - 11-14% required ventilation

*Leuppi JAMA 309:2223, 2013*
Steroid Dose and Route Severe AECOPDs

- **Objective:** Compare the outcomes of patients treated with low-dose oral steroids (~30mg/d) vs. high-dose IV steroids (~300mg/d)
- **Design:** Observational study of 79,985 patients in 2006 ICU patients excluded
- **Primary Outcome:** Treatment Failure = ICU transfer, intubation, death, 30 day readmission
- **Results:**
  - Overall - no difference in mortality or treatment failure
  - **Propensity-matched analysis:** Low-dose oral steroids decreased treatment failure, length of stay and cost.

*Lindenauer JAMA 303:2359, 2010*

Prednisolone versus Budesonide for Severe AECOPDs

- **Treatments**
  - Prednisolone 30mg BID
  - Budesonide 2gm QID
  - Placebo
- **Results - Budesonide**
  - Equal effect on FEV1
  - No clinical deterioration
  - Less hyperglycemia

*Maltais F. AJRCCM 165:698, 2002*
Steroids for Very Severe AECOPDs

Hospitalized, Ventilated Patients

- **354 Severe AECOPDs**
  - Required ventilation
- **Treatment**
  - Solumedrol 2mg/kg/d
  - Placebo
- **Results – Solumedrol**
  - Decreased ventilation
  - ~Decreased ICU LOS
  - Decrease NIV failure

Alia  AIM 171:1939, 2011

- **217 Severe AECOPDs**
  - Required ventilation
- **Treatment**
  - Prednisone 1mg/kg/d
  - Placebo
- **Results – Prednisone**
  - No improvements

Abroug  ERJ 43:717, 2013
**High vs Lower Dose Steroids for Very Severe AECOPDs**

<table>
<thead>
<tr>
<th>Model</th>
<th>Total Cohort</th>
<th>Propensity-Matched Cohort</th>
<th>OR 95% CI p value</th>
<th>OR 95% CI p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Propensity score and covariate adjustment a (n=17,239)</td>
<td>Matched sample adjusted for unbalanced covariates b (n=9,498)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In Hospital Mortality</td>
<td>0.76 (0.65-0.89) &lt; 0.01</td>
<td>0.85 (0.71-1.01) 0.06</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linear Regression Coefficient</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU length of stay (days)</td>
<td>-0.27 (-0.38, -0.16) &lt; 0.01</td>
<td>-0.31 (-0.46, -0.16) &lt; 0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital length of stay (days)</td>
<td>-0.46 (-0.64, -0.29) &lt; 0.01</td>
<td>-0.44 (-0.67, -0.21) &lt; 0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Cost ($)</td>
<td>-2,155 (-3,777, -533) &lt; 0.01</td>
<td>-2,559 (-4,508, -609) &lt; 0.01</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Unbalanced Covariates: Hospital Region, Antibiotic use hospital day 1 or 2

*Kiser T. AJRCCM 189:1052, 2014

**Summary of Steroid Dosing for AECOPDs**

- **Moderate AECOPD**: Prednisone 40mg/d x 5d
- **Severe AECOPD**: Solumedrol/Prednisone 40mg/d x 5d, Budesonide 1-2gm QID
- **Very Severe AECOPD**: Solumedrol 2mg/kg/d x 5-10d
Antibiotics for AECOPDs

Effect of Antibiotics on Treatment Failure

• Mild to Moderate AECOPD (OR=0.75)
  • No significant effect when analysis restricted to current antibiotics

• Severe AECOPDs (OR=0.77)
  • No effect on mortality and hospital LOS

• Very Severe AECOPDs (OR=0.19)

Vollenveider D.J. Cochrane Review 2012

Antibiotics for Mild-Mod AECOPDs

• 300 Mod AECOPD
  – FEV₁ > 50%

• Clinical Cure Day 9-10

• Treatment
  – Augmentin TID x 8d
  – Placebo TID x 8d

• Results – Augmentin
  – Cure 74% vs 60%
  – Time to next AECOPD 233d vs. 160d

Lior AJRCCM 186:716, 2012
Antibiotics for Severe AECOPDs

- **Objective:** Compare the outcomes of patients treated with antibiotics in the first 2 hospital days
- **Design:** Observational study of 84,621 patients in 2006
  - ICU patients excluded
  - Primary outcome was treatment failure
- **Results:**
  - Overall – antibiotic-treated patients had decreased mechanical ventilation, mortality and lower readmission.
  - Propensity-matched analysis: Lower treatment failure in antibiotic-treated patients.

Rothberg M. JAMA 303:2035 2010

Antibiotics for Very Severe AECOPDs

- **93 subjects with very severe AECOPD**
- **Primary Outcome:**
  - Death, additional antibiotics or both
- **Treatment**
  - Ofloxacin 400mg or placebo daily x 10d
- **Results**
  - Decreased mortality, more antibiotics or both
  - Decreased hospital LOS and mechanical ventilation

Summary of Antibiotics for AECOPDs

- **Use antibiotics for**
  - Moderate to severe AECOPDs
    - increased sputum volume and purulence ± SOB
  - Very severe AECOPDs
- **Antibiotics**
  - Aminopenicillin ± clavulanic acid, macrolide or tetracycline
  - Add gram-negative coverage for
    - Frequent AECOPDs, FEV$_1$ < 50%, mech ventilation

_GOLD Guidelines 2015_

Non-invasive Ventilation

- Reduced need for endotracheal intubation by 65%
  - Increased efficacy as pH decreases
- Decreased mortality by 55%
- Shortened LOS by 2 days

_Quon et al. Chest 133:756, 2008_
**Summary**

**AECOPDs**

1. Have a large impact on the course of COPD
2. They are caused by bacteria and viruses
3. Risk for AECOPDs is increased by chronic cough, sputum, reduced lung function and prior AECOPDs
4. AECOPDs can be prevented
5. Treatments include bronchodilators, antibiotics and steroids