Update on Asthma & COPD

Asthma:
- LABAs have been associated with increased risk of severe asthma exacerbations and asthma-related death
- LABAs should not be used as monotherapy
- LABAs appear to be safe when used together with ICS (in general population)
- Frequent or severe exacerbations lead to loss of fx
- Asthma is a risk factor for Pneumococcal Infection
- Vitamin D may be protective

COPD:
- COPD is a leading cause of death worldwide, and mortality is increasing
- Exacerbations are the major complication of COPD
- Exacerbations are associated with accelerated loss of lung function
- Most exacerbations are caused by infection
- There are effective strategies for decreasing exacerbations

Disclosures
- No Pharma Consulting, Research, Lectures
- NHLBI - Asthma Clinical Research Network
- NHLBI AsthmaNet
- NHLBI - COPD Clinical Research Network
- NAEPP Coordinating Committee
Question #1:
Your patient is a 47 year-old female with moderately-severe asthma not controlled on ICS at 880 mcg/day
• Takes PPI, nasal steroids
• Extensive environmental controls
• Wakes 3-4 nights/week with asthma
• Requires prednisone 2-3 times/year

Question #1:
Which of the following is your best choice?
1. Add a LABA 'til she's better then stop it
2. Increase ICS further because LABAs are dangerous
3. Add a LABA, optimize other therapies, re-assess after 2-3 months of control

The "ß-Agonist Controversy"

FDA announces new Safety Controls for LABAs in Asthma
1) LABAs are contraindicated without ICS or other controller
2) LABAs should only be used long-term in patients whose asthma cannot be controlled with other medications
3) Once asthma control is achieved, LABAs should be discontinued
4) Pediatric and adolescent patients should use combination product (LABA + ICS), to avoid monotherapy

February 10, 2010
The "ß-Agonist Controversy"

The "ß-Agonist Controversy"

- 1992: Canadian Case-Control Study Linked ß-agonist use and death (NEJM 326:501-6, 1992)

The NHLBI's Asthma Clinical Research Network

Comparation of regularly scheduled with as-needed use of albuterol in mild asthma

Suissa et al.

Am J Respir Crit Care Med 149:604-610
**BAGS AM Peak Flow**

![Graph showing AM Peak Flow](image)

*NEJM 335:841-7, 1996*

**β₂-Adrenoceptor (β₂-AR) Variants**

![Diagram showing β₂-AR variants](image)

*Reisheus et al., 1993. AJRCMB: 8:334-339*

**BAGS Genetic Analysis**

**B16 Polymorphisms and AM PEF**

![Graph showing BAGS genetic analysis](image)

*Israel EJ et al., AJRCCM 162:75-80, 2000*

**β-Receptor Genetic Analysis**

**Summary - SABAs**

- There are known sequence variants in the β₂-adrenergic receptor
- Differences in β₂-AR genotypes are associated with altered response to albuterol
- Arg/Arg (β₂-AR-16) - reduction in airflow after chronic albuterol
$\beta$-Receptor Genetic Analysis

Implications - SABAs

- 1/6 (~16%) of the US population is homozygous for Arg ($\beta_2$-AR-16)
- ≥1/5 (~20%) of African Americans are homozygous for Arg ($\beta_2$-AR-16)
- These individuals may benefit from avoiding regularly-scheduled $\beta_2$-agonists

Serevent Nationwide Surveillance Study

- N=25,180
- SM BID vs ALB QID x 16 wks
- >12 yo; regular bronchodilator
- 69% ICS

<table>
<thead>
<tr>
<th></th>
<th>Salmeterol (n=16,787)</th>
<th>Albuterol (n=8393)</th>
<th>RR Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths: Resp &amp; Asthma</td>
<td>12 (0.07%)</td>
<td>2 (0.02%)</td>
<td>3.00 0.105</td>
</tr>
<tr>
<td>Withdrawals: Resp &amp; Asthma</td>
<td>4.88 (2.91%)</td>
<td>3.18 (3.79%)</td>
<td>0.77 0.0002</td>
</tr>
</tbody>
</table>

[Sources: Castle et al, BMJ 306:1034-7, 1993]

Chronology of $\beta$-Agonist Studies

1990 Sears study
1992 Spitzer study
1993 Start of ACRN BAGS publication
1994 Salmeterol approved
1997-1999 SOCS
2003 SMART (GSK)

SOCS: Long-Acting $\beta_2$-Agonist Monotherapy in Persistent Asthma

AM PEF (liters/min)

**SOCS - Treatment Failure Rate**

<table>
<thead>
<tr>
<th>Randomized Treatment Period, wk</th>
<th>Treatment Failure Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>7</td>
<td>14</td>
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<tr>
<td>8</td>
<td>16</td>
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<tr>
<td>9</td>
<td>18</td>
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<tr>
<td>10</td>
<td>20</td>
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<tr>
<td>11</td>
<td>22</td>
</tr>
<tr>
<td>12</td>
<td>24</td>
</tr>
<tr>
<td>13</td>
<td>26</td>
</tr>
<tr>
<td>14</td>
<td>28</td>
</tr>
<tr>
<td>15</td>
<td>30</td>
</tr>
</tbody>
</table>

**Summary of Treatment Effects**

**Salmeterol vs Triamcinolone**

- **Pulmonary function**
  - AM Peak Flow: 0.951
  - PM Peak Flow: 0.917
  - FEV\(_1\): 0.048
  - Methacholine PC\(_{20}\): 0.042

- **Symptom control**
  - Asthma symptom scores: 0.321
  - Rescue medication use: 0.452
  - Quality of life: 0.331

**The SMART Study**

- **n = 60,000 x 28-weeks**
- Salmeterol (42mcg BID) + Usual Care
  vs
- Placebo + Usual Care

**Primary Endpoint:**
- Respiratory-related deaths
- Respiratory-related “Life-threatening Experiences”

The SMART Study

Study design

Usual Care + blinded salmeterol MDI (42 μg) BID

No LABA

≥ 12 years of age
No β-blockers

Phone contacts every 4 weeks

Usual Care + blinded placebo MDI BID

Study Visit 1
Day 0

Study procedures reviewed: 6 month
supply of study medication provided

No Significant differences for Primary Endpoint

Higher, not statistically significant, number of asthma-related life-threatening experiences in Salmeterol group

In Caucasians (71%) - no difference between treatment groups

In AA (17%) - statistically significant greater number of events, including deaths in salmeterol group

Table 2. Demographic and Baseline Characteristics for Caucasians and African Americans

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Caucasians (n = 18,642)</th>
<th>African Americans (n = 4,685)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, yr</td>
<td>40.3 (71%)</td>
<td>36.5 (18%)</td>
</tr>
<tr>
<td>Sex, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>11,719 (64)</td>
<td>3,088 (67)</td>
</tr>
<tr>
<td>Male</td>
<td>6,732 (36)</td>
<td>1,545 (33)</td>
</tr>
<tr>
<td>Peak expiratory flow, % predicted (SD)</td>
<td>85.3 (25.40)</td>
<td>78.1 (25.13)</td>
</tr>
<tr>
<td>Baseline ICS use</td>
<td>49 (26%)</td>
<td>38 (20%)</td>
</tr>
<tr>
<td>≥ 1 ED visit in last 12 mo</td>
<td>22 (12%)</td>
<td>41 (22%)</td>
</tr>
<tr>
<td>≥ 1 ED visit in lifetime</td>
<td>59 (32%)</td>
<td>72 (41%)</td>
</tr>
<tr>
<td>≥ 1 hospitalization in last 12 mo</td>
<td>6 (3%)</td>
<td>15 (8%)</td>
</tr>
<tr>
<td>≥ 1 hospitalization in lifetime</td>
<td>30 (16%)</td>
<td>44 (24%)</td>
</tr>
<tr>
<td>≥ 1 intubations for asthma in lifetime</td>
<td>4 (2%)</td>
<td>8 (4%)</td>
</tr>
<tr>
<td>Nocturnal symptoms present</td>
<td>59 (32%)</td>
<td>67 (37%)</td>
</tr>
</tbody>
</table>


The SMART Study

2002 - Interim Analysis; Jan 2003 - Study Stopped:
n=25,858 patients

• No Significant differences for Primary Endpoint

• Higher, not statistically significant, number of asthma-related life-threatening experiences in Salmeterol group

• In Caucasians (71%) - no difference between treatment groups

• In AA (17%) - statistically significant greater number of events, including deaths in salmeterol group

Table 3. Asthma-Related Deaths, n=25,858, 28-week data

<table>
<thead>
<tr>
<th></th>
<th>Salmeterol n (%)</th>
<th>Placebo n (%)</th>
<th>Relative Risk (95% CI)</th>
<th>Excess Deaths/10K (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Population</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salmeterol: n=13,176</td>
<td>13 (0.10%)</td>
<td>4.37 (1.25,15.34)</td>
<td>8 (3,13)</td>
<td></td>
</tr>
<tr>
<td>Placebo: n=13,179</td>
<td>3.0 (0.02%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salmeterol: n=9,281</td>
<td>6 (0.07%)</td>
<td>5.82 (0.70,48.37)</td>
<td>6 (1,10)</td>
<td></td>
</tr>
<tr>
<td>Placebo: n=9,361</td>
<td>1 (0.01%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salmeterol: n=2,366</td>
<td>7 (0.31%)</td>
<td>7.26 (0.89,58.94)</td>
<td>27 (8,46)</td>
<td></td>
</tr>
<tr>
<td>Placebo: n=2,319</td>
<td>1 (0.04%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The SMART Study
2002 - Interim Analysis: (n=25,858 patients)
• AA patients had more severe asthma (sxs, PEF, prior intubations, ED visits)
• Only 47% of entire study population used ICS
  • Caucasians: 50%
  • African Americans: 38%
• In total population receiving ICS at Baseline, no significant differences between groups
• SMART was not designed to evaluate the effects of ICS on study outcomes

FDA-mandated “Black Box Warning”

WARNING
Long-acting beta2-adrenergic agonists, such as salmeterol, the active ingredient in SEREVENT DISKUS, may increase the risk of asthma-related death. Therefore, when treating patients with asthma, SEREVENT DISKUS should only be used as additional therapy for patients not adequately controlled on other asthma-controller medications (e.g., low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies, including SEREVENT DISKUS.

Data from a large placebo-controlled US study that compared the safety of salmeterol (SEREVENT® Inhalation Aerosol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,176 patients treated for 28 weeks on salmeterol versus 3 deaths out of 13,179 patients on placebo) (see warnings and CLINICAL TRIALS: Asthma: Salmeterol Multi-center Asthma Research Trial).

March 2, 2006

There is a large body of literature demonstrating benefit from long-acting β₂-agonists

Added Salmeterol vs higher-dose Corticosteroid in asthma patients with symptoms on existing inhaled corticosteroid


| N = 429 |
| Symptoms despite BDP 200 mcg BID |
| BDP 500 mcg BID |
| BDP 200 mcg BID + Salmeterol 50 mcg BID

6/25/2010
**New Data on LABAs**

- Bleecker et al. *(Lancet 370:2118-25, 2007)*
  Combinations of β-receptor polymorphisms do not affect responses to ICS + LABAs

- Bleecker et al. *(Am J Respir Crit Care Med Nov 12, 2009, Epub ahead of print)*
  No pharmacogenetic effect of β-receptor variation on salmeterol response

- Wechsler et al. *(Lancet 374:1754-64, 2009)*
  β-receptor polymorphisms had no effect on bronchodilator response, but there was an effect on methacholine reactivity

---

**FACET Study: Formoterol and Budesonide in Moderate Asthma**

- **Kaplan-Meier Survival Curves:**
  Withdrawal for Worsening Asthma

- **Probability**
  * differs from FP 250mcg, SALM and placebo, p<0.002

- **Kaplan-Meier Survival Curves:**
  Withdrawal for Worsening Asthma

- **Probability**
  * differs from FP 250mcg, SALM and placebo, p<0.002

---

**Long Acting Beta Agonist Response by Genotype**

- **The LARGE Trial**
  A Prospective, DB, PC, Cross-over trial

  * Salmeterol, 50mcg BID + BDP, 240mcg BID
  * vs
  * Placebo BID + BDP, 240mcg BID
  * X 18 weeks

- **Primary Outcome = AM PEF**
  Wechsler et al. *(Lancet 374:1754-64, 2009)*
**Long Acting Beta Agonist Response by Genotype**

The LARGE Trial

- n = 474 screened and genotyped
- n = 42 β16 Arg/Arg
  n = 45 β16 Gly/Gly
- Stratified by FEV1 and race
- Ipratropium Bromide for rescue
- FEV1 on ICS ~80%

*Wechsler et al. (Lancet 374:1754-64, 2009)*

**Long Acting Beta Agonist Response by Genotype**

The LARGE Trial

**Methacholine Responsiveness**

PC_{20} (mg/ml)

![Graph showing Methacholine Responsiveness](image)

- P<0.0001
- Placebo/ICS vs LABA/ICS

*Wechsler et al. (Lancet 374:1754-64, 2009)*

**PEF by Genotype in African American Subjects**

![Graph showing PEF by Genotype](image)

*Wechsler et al. (Lancet 374:1754-64, 2009)*
**β-agonist Summary**

- Risk of SABAs appears to segregate by genotype (Arg/Arg vs haplotypes)
- LABAs have been associated with increased risk of severe asthma exacerbations and asthma-related death
- LABAs appear to be safe when used together with ICS (in general population)
- LABAs should not be used as monotherapy

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**Do Exacerbations Contribute to Decline of Lung Function Over Time in Asthma?**

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**β-agonist Summary**

- In Gly/Gly, BHR improved with SM
- In Arg/Arg, BHR did not improve with SM
- In AA with Gly/Gly, SM improved PEF
- In AA with Arg/Arg, SM had no effect
- NAEPP and GINA guidelines recommend LABAs as add-on therapy
- Counsel patients about poorly-controlled asthma, and consider withdrawal of LABAs in patients who are poorly controlled

---

**Asthma Exacerbations Lead to Loss of Lung Function**

- Change in FEV1 (%) over 3 yrs
- *P*<0.001
- *P*=0.57
- *P*=0.042

*O'Byrne et al.* Am J Respir Crit Care Med 179:19-24, 2009
Asthma Exacerbations Lead to Loss of Lung Function

- Change in FEV1 (%) over 3 yrs
- Budesonide
- Placebo
- No Systemic Steroids
- Systemic Steroids

O'Byrne et al. Am J Respir Crit Care Med 179:19-24, 2009

FACET: Changes Associated with Exacerbations


FACET: Changes Associated with Exacerbations


Rescue Use of Beclomethasone and Albuterol in a Single Inhaler for Mild Asthma

**Asthma and Pneumococcal Infections**

- Asthma is an independent risk factor for invasive pneumococcal disease.
  - nested case-control study
  - 2 to 49 years old

  *Talbot et al*  
  *N Eng J Med* 352:2082-90, 2005

- Adults with asthma may be at increased risk for serious pneumococcal disease
  - (OR, 6.7; 95% CI, 1.6-27.3; P = .01)
  - retrospective case-control study
  - Rochester Minnesota (1964-1983)

  *John et al*  

**Asthma and Pneumococcal Vaccination**

October 25, 2008:

The U.S. Centers for Disease Control and Prevention’s (CDC) Advisory Committee on Immunization Practices (ACIP) voted unanimously yesterday to recommend that adults ages 19 to 64 with asthma receive pneumococcal polysaccharide vaccine (PPSV23)

**Asthma and Pneumococcal Infections**

Possible Mechanisms:

- Disrupted airway epithelial barrier
- Increased and aberrant mucus production
- Alterations in innate and adaptive immunity
- Genetic factors
- Immunosuppressive medications
- Increased pneumococcal colonization

**Question #2:**

Which of the following is true?

1. Vitamin D insufficiency is common
2. Vitamin D has immunomodulatory effects
3. Maternal Vit D inversely assoc w/childhood asthma
4. Vit D levels inversely associated with asthma severity
5. All of the above.
**Vitamin D and Asthma**
- Vit D has potent immunomodulatory effects
- Vit D inhibits TH1, ?TH2, induces IL-10, Tregs
- Maternal Vit D intake during pregnancy inversely associated with asthma symptoms in early childhood
  

- Vit D inversely associated with markers of asthma and allergy severity
  - IgE, eosinophils
  - Methacholine reactivity
  - Asthma hospitalization
  - Medication requirements


---

**Leading Causes of Deaths**
**U.S. 1998**

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Heart Disease</td>
<td>724,269</td>
</tr>
<tr>
<td>2. Cancer</td>
<td>538,947</td>
</tr>
<tr>
<td>3. Cerebrovascular disease (stroke)</td>
<td>158,060</td>
</tr>
<tr>
<td>4. Respiratory Diseases (COPD)</td>
<td>114,381</td>
</tr>
<tr>
<td>5. Accidents</td>
<td>94,828</td>
</tr>
<tr>
<td>6. Pneumonia and influenza</td>
<td>93,207</td>
</tr>
<tr>
<td>7. Diabetes</td>
<td>64,574</td>
</tr>
<tr>
<td>8. Suicide</td>
<td>29,264</td>
</tr>
<tr>
<td>9. Nephritis</td>
<td>26,295</td>
</tr>
<tr>
<td>10. Chronic liver disease</td>
<td>24,936</td>
</tr>
<tr>
<td>11. All other causes of death</td>
<td>469,314</td>
</tr>
</tbody>
</table>

---

**Percent Change in Age-Adjusted Death Rates (US, 1965-1998)**

<table>
<thead>
<tr>
<th>Proportion of 1965 Rate</th>
<th>CHD</th>
<th>Stroke</th>
<th>Other CVD</th>
<th>COPD</th>
<th>All other causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1965 - 1998</td>
<td>-59%</td>
<td>-64%</td>
<td>-35%</td>
<td>+163%</td>
<td>-7%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Year 1965</th>
<th>Year 1975</th>
<th>Year 1985</th>
<th>Year 1995</th>
</tr>
</thead>
<tbody>
<tr>
<td>-59%</td>
<td>-64%</td>
<td>-35%</td>
<td>+163%</td>
</tr>
<tr>
<td>-7%</td>
<td>-7%</td>
<td>-7%</td>
<td>-7%</td>
</tr>
</tbody>
</table>
COPD Exacerbations (AECOPD): The Major Complication of COPD

- Characterized by episodic increases in dyspnea, sputum production and cough
- 16 million office visits/year
- 500,000 hospitalizations/year
- 110,000 deaths/year

Mannino et al. MMWR 51:1-16
NHLBI: http://www.nhlbi.gov/resources/docs/02_chtbk.pdf

COPD Exacerbations (AECOPD): The Major Complication of COPD

- $18 billion in direct health care costs
- Most patients experience a transient or permanent decrease in Quality Of Life
- 50% are readmitted to the hospital within 6 months


Question #3:

Which of the following is true?

1. Acute Exacerbations of COPD:
2. Are usually triggered by infection
3. Accelerate the loss of lung function
4. Can be prevented or attenuated
5. All of the above

COPD Exacerbations

- “Exacerbations are to COPD what myocardial infarctions are to coronary artery disease”
- “They are the acute, often trajectory-changing, and sometimes deadly manifestations of a chronic disease”

- Gerard J Criner, MD
  Temple University School of Medicine
  Philadelphia, PA, USA
Hospitalized Severe AECOPD and Mortality: Severity of AECOPD

- 1- no AECOPD
- 2- AECOPD ED
- 3- AECOPD Hosp
- 4- AECOPD Readmit

N = 305 men with COPD x 5 years

Soler-Cataluna Thorax 2005

Postmortem Analysis of Major Cause of Early Death in Hospitalized AECOPD

n=43 autopsies; 2005-2007

- 21%
- 14%
- 37%

Risk Factors for Frequent Exacerbations

- Increased Age
- Severity of FEV₁ Impairment
- Chronic mucus hypersecretion
- Frequent past Exacerbations
- Daily cough and wheeze
- Persistent symptoms of chronic bronchitis

COPD Exacerbation Frequency

- GOLD II 2.68/year
- GOLD III 3.43/year

P = 0.029

Donaldson et al Thorax 2002; 57:847-52

- FEV₁ > 60% 1.6/year
- FEV₁ 40-50% 1.9/year
- FEV₁ < 40% 2.3/year


Pathogenesis of AECOPD

- Most exacerbations caused by infection
- 15 - 20% due to environmental factors
- ~50% caused by bacterial infection
- Viruses detectable in 40-60% of AECOPD (6-19% of controls)

Pathogenesis of AECOPD

- Bacteria
- Viruses
- Non-infective
- Macrophages
- Neutrophils
- Epithelial cells
- Oxidative Stress


Sethi & Murphy; NEJM 2008; 359:2355-65
**How do Infections Trigger Exacerbations?**

- Increases in Bacterial Load?
- Acquisition of New Bacterial Strains?

**Isolation of New Strains of Bacteria Increases Risk of Exacerbations of COPD**

<table>
<thead>
<tr>
<th>New Strain</th>
<th>RR of Exacerbation (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Pathogen</td>
<td>2.15* (1.83-2.53)</td>
</tr>
<tr>
<td>*Haemophilus influenza</td>
<td>1.69* (1.37-2.09)</td>
</tr>
<tr>
<td>*Moraxella catarrhalis</td>
<td>2.96* (2.39-3.67)</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>1.77* (1.14-2.75)</td>
</tr>
<tr>
<td>*Pseudomonas aeruginosa</td>
<td>0.61 (0.21-1.82)</td>
</tr>
</tbody>
</table>

* Statistically significant increased risk of exacerbation

Sethi et al. NEJM 347:465-71, 2002

**Model of Pathogenesis of Bacterial AECOPD**

- Acquisition of new bacterial strain
- Pathogen virulence and host lung defense
- Change in airway and systemic inflammation
- Elevations of infecting strain
- Increase in respiratory symptoms, with or without systemic symptoms
- Strain-specific immune response, with or without antibiotics

Sethi et al. NEJM 358:2355-65, 2008
VICIOUS CIRCLE HYPOTHESIS

Initiating factors
e.g., smoking, childhood respiratory disease

Impaired innate lung defense

Airway Epithelial Injury

Microbial Colonization

Increased Proteolytic Activity

Altered Protease-Anti-protease Balance

Progression of COPD

Inflammatory Response

Microbial Antigens

Sethi et al. NEJM 358:2355-65, 2008

Prevention of Exacerbations

- Immunizations (Influenza, Pneumococcal)
- Inhaled Corticosteroids
- Long-acting Beta-adrenergic Agonists (LABA)
- Long-acting anticholinergics
- LABA + Inhaled Corticosteroids
- Macrolide antibiotics?

Loss of Lung Function
(Lung Health II)

Change from Baseline FEV₁ (ml)
(after bronchodilator)

Follow-up (years)

COPD Exacerbations
(Lung Health II)

Respiratory Exacerbations
(per 100 person-years)

28.2

p = 0.005

21.1

NEJM 2000; 343:1902-1909
COPD Exacerbations (ISOLDE - stratified by FEV₁)

![Graph showing FEV₁ levels and exacerbation rates](image)


Effects of Inhaled Corticosteroids in COPD: Meta-Analysis

Relative Risk of Exacerbations in Patients With COPD Treated With Inhaled Corticosteroids vs Placebo

<table>
<thead>
<tr>
<th>Author</th>
<th>Relative Risk</th>
<th>Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vestbo et al</td>
<td></td>
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<tr>
<td>Bourbeau et al</td>
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<td>Burge et al</td>
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<tr>
<td>Lung Health Study</td>
<td></td>
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<tr>
<td>Weir et al</td>
<td></td>
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<tr>
<td>Paggiaro et al</td>
<td></td>
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<tr>
<td>Overall</td>
<td></td>
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</tr>
</tbody>
</table>


Salmeterol reduces rate of COPD Exacerbations

![Graph showing exacerbation rates](image)


Salmeterol/Fluticasone combination reduces Exacerbations in COPD

<table>
<thead>
<tr>
<th>Placebo (N = 1524)</th>
<th>Salmeterol (N = 1521)</th>
<th>Fluticasone (N = 1534)</th>
<th>Combination (N = 1533)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual Rate</td>
<td>1.13</td>
<td>0.97</td>
<td>0.93</td>
</tr>
</tbody>
</table>

Rate Ratio (95% CI) 0.75 (0.69-0.81) p<0.001 (≈25% reduction)

Calverley et al., TORCH
**Tiotropium Reduces Exacerbations and Hospitalizations vs Ipratropium**

![Graph showing probability of no exacerbations and hospitalizations over days on treatment for Tiotropium vs Ipratropium.](image)


**Long-term Erythromycin reduces Exacerbations in COPD**

![Graph showing time to first exacerbation for macrolide vs placebo.](image)

*Seemungal et al., Am J Respir Crit Care Med 178:1139-47, 2008*

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**The MACRO Study**

(Azithromycin 250mg/day x 1 year)

- **NHLBI - COPD Clinical Research Network**
- **N = 1130**
- **Moderately-severe COPD**
  - FEV₁/FVC < 70%; FEV₁ <80%
- **“Exacerbation Prone”**
- **Primary Outcome:** Time to first AECOPD
- **Completion:** June, 2010