Update on COPD & Asthma

UCSF Primary Care Medicine
San Francisco, CA
October 09, 2015

Disclosures

• No Pharma Disclosures

• NHLBI - Asthma Clinical Research Network

• NHLBI - Severe Asthma Research Program
Update on the Management of COPD
To review COPD

- COPD is a leading cause of death worldwide, and mortality is increasing
- COPD = Inflammatory Disease
- Exacerbations are the major complication of COPD
  - Associated with increased loss of lung function
  - And Mortality
- There are effective strategies for decreasing exacerbations

COPD

- Pharmacologic Therapy: ("it's not just for symptoms anymore")
  - Decreasing exacerbations
  - Change natural history?
- Smoking Cessation modifies natural history
  (lung function, mortality)
- O2 therapy
- Pulmonary Rehab: reduces symptoms, depression, health care utilization; improves Q of L, exercise
Question #1: Which of the following is NOT true?

1. COPD mortality has plateaued
2. Hospitalization for exacerbation predicts mortality
3. Most exacerbations are caused by infection
4. There are effective strategies for decreasing exacerbations
Hey Doc, Do I Have COPD???

- **CHRONIC Obstructive Pulmonary Disease**
  - NEED SPIROMETRY: FEV1/FVC < 0.70

- **Physical Exam:**
  - >90% Specificity
  - Poor Sensitivity

- > 55 Pack Years
- Wheezing on Auscultation
- Self-reported wheezing

High Probability For COPD

Likelihood Ratio: 156

Simel and Rennie
Evidence-based Clinical Diagnosis
No benefit of screening adults with no symptoms

No evidence that treating asymptomatic individuals prevents future symptoms, or reduces the subsequent decline in lung function.

Anthonisen et al
JAMA 272:1497-505, 1994

Risk Factors for COPD

• Other:
  - Proteases/inflammation
  - Repetitive bacterial/viral infections
  - Genetics, especially α1-antitrypsin deficiency

Give it to me Straight. Is it BAD?

GOLD 2007

FEV1/FVC < 0.70

GOLD 1: (Mild COPD) FEV1 > 80% predicted
GOLD 2: (Moderate COPD) FEV1 50-80% predicted
GOLD 3: (Severe COPD) FEV1 30-50% predicted
GOLD 4: (Very Severe COPD) FEV1 <30% predicted

GOLD Guidelines 2007

Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-Points (ECLIPSE)

Eur Respir J 2008; 31:869-73

N = 2164 stable COPD
N = 337 “Healthy Smokers”
N = 245 Never Smokers

Characterized Extensively at:
Baseline
3, 6, 12, 18, 24, 30, 36 months
2007 Gold Guidelines Not Good Enough

A

Proportion of subjects (%)

Stage II

Stage III

mMRC score

Mean=1.3

Mean=1.8

Mean=2.3

2007 Gold Guidelines Not Good Enough

C

Proportion of subjects (%)

Stage II

Stage III

Number of exacerbations

Mean=0.6

Mean=1.0

Mean=1.2

Agusti Respir Res 2010; 11:122
COPD Assessment: A New Model

When assessing risk, choose the highest risk according to GOLD grade or exacerbation history.

GOLD Guidelines 2015

<table>
<thead>
<tr>
<th>Patient Category</th>
<th>Characteristics</th>
<th>Spirometric Classification</th>
<th>Exacerbations per year</th>
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<td>A</td>
<td>Low Risk, Less Symptoms</td>
<td>GOLD 1-2</td>
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<td>0-1</td>
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<td>≥2</td>
<td>≥10</td>
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<tr>
<td>C</td>
<td>High Risk, Less Symptoms</td>
<td>GOLD 3-4</td>
<td>≥2</td>
<td>0-1</td>
<td>&lt;10</td>
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<td>D</td>
<td>High Risk, More Symptoms</td>
<td>GOLD 3-4</td>
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### GOLD Guidelines 2015

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**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*
Question #2: Which of the Following Is the Best Predictor of a Future Acute Exacerbations of COPD?

1. Spirometry
2. Symptoms
3. Smoking Status
4. Socio-Economic Status
5. Prior Exacerbation History

“Its déjà vu all over again”
**Predictors of Acute Exacerbations of COPD**

<table>
<thead>
<tr>
<th>Number of Exacerbations</th>
<th>Odds Ratio (95% CI)</th>
<th>Odds Ratio (95% CI)</th>
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<tbody>
<tr>
<td>≥2 vs. 0</td>
<td></td>
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<tr>
<td>1 vs. 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exacerbation in Prior Year</td>
<td>5.7 (4.5-7.3)</td>
<td>2.2 (1.8-2.8)</td>
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<tr>
<td>FEV1 per 100ml decrease</td>
<td>1.1 (1.08-1.1)</td>
<td>1.1 (1.0-1.1)</td>
</tr>
<tr>
<td>SGRC (symptom score) per 4 points</td>
<td>1.1 (1.0-1.1)</td>
<td>1.1 (1.0 - 1.1)</td>
</tr>
<tr>
<td>GERD</td>
<td>2.1 (1.6-2.7)</td>
<td>1.6 (1.2-2.1)</td>
</tr>
<tr>
<td>WBC Count</td>
<td>1.1 (1-1.1)</td>
<td>1.1 (1.0-1.1)</td>
</tr>
</tbody>
</table>

*Hurst NEJM 2010*

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**Acute Exacerbations of COPD**

- Some patients seldom exacerbate
- Some patients exacerbate frequently
- Best predictor of ≥2 AECOPD/year (“Frequent Exacerbator”) = previous frequent exacerbations
- Spirometry does not correlate well with clinical features of disease
- “Frequent Exacerbator” is a stable phenotype
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

A good battle plan that you act on today can be better than a perfect one tomorrow.

— George S. Patton —
The Battle Plan.

- Prevent Acute Exacerbations
- Prevent Progressive Loss of Lung Function
- Improve Symptoms

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
- $18 billion in direct health care costs

Mannino et al. MMWR Surveill Summ 2002; 51:1-16
NHLBI: http://www.nhlbi.gov/resources/docs/02_chtbk.pdf
Question #3: Which of the Following DOES NOT Reduce Acute Exacerbations of COPD?

1. Inhaled Corticosteroids
2. Long Acting Beta Agonist
3. Long Acting Muscarinic Agonists
4. Azithromycin
5. EMR training
Prevention of AECOPD
American College of Chest Physicians & Canadian Thoracic Society Guideline

• PICO (population, intervention, comparator, outcome)

• Literature Search

• Quality Assessment (AGREE II, DART)

• Grading Evidence (GRADEpro)
• Recommendations (CHEST)

Criner et al. CHEST 147:894-942, 2015

Prevention of AECOPD
Recommendations

Non-Pharmacologic Treatments/Vaccinations:

• Influenza Vaccine (Grade 1B)
• Pulmonary Rehab (Grade 1C)
• Smoking Cessation (Grade 2C)
• Pneumococcal Vaccine (Grade 2C)
  Mod-severe-very severe; recent AECOPD≤4 weeks

Criner et al. CHEST 147:894-942, 2015
Prevention of AECOPD
Recommendations

Maintenance Inhaled Therapy:

• LAMA vs PBO (Grade 1A)
• LABA vs PBO (Grade 1B)
• LAMA vs LABA (Grade 1C)
• COMBO Therapy vs MonoTherapy (Grade 1B,C)

Criner et al. CHEST 147:894-942, 2015

Prevention of AECOPD
Recommendations

Oral Therapy:

• Macrolide (Grade 2A)
  (Frequent AECOPD despite Tx)
• Systemic Corticosteroids (Grade 2B)
  (For AECOPD - prevent next 30 days)
• Roflumilast (Grade 2A)
  (Chr Bronchitis, ≥1 AECOPD in year)
• Do not use statins for AECOPD (Grade 1B)

Criner et al. CHEST 147:894-942, 2015
Azithromycin for Prevention of Exacerbations of COPD

Richard K. Albert, M.D., John Connett, Ph.D., William C. Bailey, M.D., Richard Casaburi, M.D., Ph.D., J. Allen D. Cooper, Jr., M.D., Gerard J. Criner, M.D., Jeffrey L. Curtis, M.D., Mark T. Dransfield, M.D., Melan K. Han, M.D., Stephen C. Lazarus, M.D., Barry Make, M.D., Nathaniel Marchetti, M.D., Fernando J. Martinez, M.D., Nancy E. Madinger, M.D., Charlene McEvoy, M.D., M.P.H., Dennis E. Niewoehner, M.D., Janos Porszasz, M.D., Ph.D., Connie S. Price, M.D., John Reilly, M.D., Paul D. Scanlon, M.D., Frank C. Scirba, M.D., Steven M. Scharf, M.D., Ph.D., George R. Washko, M.D., Prescott G. Woodruff, M.D., M.P.H., and Nicholas R. Anthonisen, M.D., for the COPD Clinical Research Network.

The MACRO Study

(Azithromycin 250mg/day x 1 year)

- NHLBI - COPD Clinical Research Network
- \(N = 1130\)
- Moderately-severe COPD
  \(\text{FEV}_1/\text{FVC} < 70\%; \text{FEV}_1 < 80\%\)
- “Exacerbation Prone”
- Primary Outcome: Time to first AECOPD
Rates of Acute Exacerbations of Chronic Obstructive Pulmonary Disease per Person-Year, According to Study Group.


Macrolides Decrease AECOPD

P < 0.001 by Poisson analysis
P = 0.004 by negative binomial analysis

Macrolides May Increase risk of Cardiovascular Death

Ray WA et al. NEJM 2012
Macrolide Antibiotics and the Risk of Cardiac Arrhythmias
Richard K. Albert$^{1,2}$ and Joseph L. Schueller$^{1,2}$; for the COPD Clinical Research Network

$^{1}$Denver Health, Denver, Colorado; and $^{2}$University of Colorado Denver, Aurora, Colorado

Am J Respir Crit Care Med
2014; 189:1173-1180

- Macrolides can prolong QT and QTc leading to arrhythmias, including torsades de pointes
- Most arrhythmias with macrolides occur in patients with underlying risk factors
- Incidence of arrhythmias in absence of additional risk factors is very low, perhaps 1 in 100,000.

Mosholder, NEJM 2013

Macrolide Antibiotics and the Risk of Cardiac Arrhythmias

"Macrolide-associated arrhythmias can be reduced by not prescribing to patients with comorbidities of concern...the majority of which can be discovered by:
- History
- ECG before initiating therapy
- ECG a short time after initiating therapy"

Am J Respir Crit Care Med
2014; 189:1173-1180

COPD CRN
COPD Clinical Research Network
Roflumilast

- Oral Tablet
- 500 ug Once Daily
- Phosphodiesterase-4 Inhibitor

Side Effects, GI
Diarrhea
Weight Loss
Nausea

Martinez et al. Lancet 2015

Simvastatin for the Prevention of Exacerbations in Moderate-to-Severe COPD

Effect of Corticosteroids on Treatment Failure Rates after AE COPD

2 week = Solumedrol 125mg q6hr x 3d, Prednisone 60mg qd x 4d, 40mg qd x 4d, 20mg qd x 4d

8 week = additional 10mg qd x 5 week, then 5 mg qd x 1 week

Niewoehner et al., NEJM 340:1941, 1999

Short-term vs Conventional Glucocorticoid Therapy in Acute Exacerbations of Chronic Obstructive Pulmonary Disease
The REDUCE Randomized Clinical Trial

- Randomized, noninferiority multicenter trial
- N = 314, ED with AECOPD
- Prednisone, 40 mg/day x 5 days vs
- Prednisone, 40 mg/day x 14 days

Leuppi et al
JAMA 2013; 309:2223-2231
Summary

- Azithromycin prevents COPD Exacerbations
  - Potential Risk of Cardiac Arrhythmias
- Roflumilast offers some benefit in bronchitis patients
- 5 days of corticosteroids -- appropriate time frame
- No indication for statins in preventing AECOPD
**Goals of Treatment**
*For Primary Care Physicians*

- Prevention of Acute Exacerbations
- Prevent Progressive Loss of Lung Function
- Improve Symptoms

**Question #4:**
*Which of the Following Slows Loss of Lung Function in COPD?*

1. Smoking Cessation
2. LABA
3. ICS
4. LAMA
5. All of the above
6. 1, 2, and 3
Question #4: Which of the Following Slows Loss of Lung Function in COPD?

1. Smoking Cessation
2. LABA
3. ICS
4. LAMA
5. All of the above
6. 1, 2, and 3

Decline in FEV1 in COPD

Fletcher and Peto
BMJ, 1977;1:1645-1648
Smoking Cessation: the Lung Health Study
Anthonisen et al. JAMA 272:1497 (1994)
n = 5887 smokers; ages 35-60 (mean 48); FEV\(_1\) = 63%

Research Question:
Does smoking intervention, ± ipratropium change the course of “mild” COPD

Effect of Smoking Cessation on FEV\(_1\)

Effects of a Smoking Cessation Intervention on 14.5-year Mortality

Anthonisen et al

Therapy Reduces Lung Decline
(TORCH)

Celli et al
A 4-Year Trial of Tiotropium in Chronic Obstructive Pulmonary Disease

Donald P. Tashkin, M.D., Bartolome Celli, M.D., Stephen Senn, Ph.D., Deborah Burkhart, B.S.N., Steven Kesten, M.D., Shailendra Menjoge, Ph.D., and Marc Decramer, M.D., Ph.D., for the UPLIFT Study Investigators

Tiotropium Reduces Lung Decline

Tashkin et al
NEJM 359:1543-54, 2008
Update on the Management of Asthma

Definition of Asthma

- Obstruction that is reversible either spontaneously or with treatment; [NAEPP-EPR, 1991]

- Chronic inflammatory disorder (MCs, Eos, Tcells, Macs, PMNs, Epi); variable obstruction; [NAEPP-EPR2, 1997]

- Variable symptoms, obstruction, BHR; inflammation; interaction [NAEPP-EPR3, 2007]
Definition of Asthma

• Chronic inflammatory disorder; many different cells; BHR; variable/reversible symptoms and obstruction; phenotypes? [GINA, 2011]

• Heterogeneous: Chronic airway inflammation; variable/reversible symptoms and obstruction; Different phenotypes or clusters [GINA, 2014]

FIGURE 16. STEPWISE APPROACH FOR MANAGING ASTHMA IN YOUTHS ≥12 YEARS OF AGE AND ADULTS

Intermittent Asthma

Persistent Asthma: Daily Medication
Consult with asthma specialist if step 4 care or higher is required. Consider consultation at step 3.

Step 1
Preferred: SABA PRN

Step 2
Preferred: Low-dose ICS
Alternative: Cromolyn, LTRA, Montelukast, or Theophylline

Step 3
Preferred: Medium-dose ICS + LABA
Alternative: Low-dose ICS + either LTRA, Theophylline, or Zileuton

Step 4
Preferred: Medium-dose ICS + LABA
AND
Consider Oralomizumab for patients who have allergies

Step 5
Preferred: High-dose ICS + LABA and/or oral corticosteroids
AND
Consider Oralomizumab for patients who have allergies

Step 6
Preferred: Oralomizumab
AND
Assess control
Step down if possible (and asthma is well controlled at least 3 months)

Each step: Patient education, environmental control, and management of comorbidities.
Steps 2–4: Consider subcutaneous allergen immunotherapy for patients who have allergic asthma (see notes)

Quick-Relief Medications for All Patients

• SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-minute intervals as needed. Short course of oral systemic corticosteroids may be needed.
• Use of SABA ≥2-days a week for symptom relief (not prevention of EIB) generally indicates inadequate control and the need to step up treatment.

EPR-3, NHLBI, 2011
described an early-onset, symptom-predominant group with minimal eosinophilic disease. Cluster 4 described an eosinophilic inflammation–predominant group with few symptoms, late-onset disease, and a greater proportion of males.

Discriminant function modeling identified the majority of input parameters used in the cluster analysis of both populations to be significant determinants of cluster membership (Table E1 of the online supplement). The discriminant function model of primary-care and refractory asthma clusters required seven of eight input parameters (excluding atopic status) and five of seven parameters (excluding atopic status and sex), respectively. The accuracy of the discriminant function models for predicting cluster membership was 94.6% (primary care) and 96.8% (refractory asthma).

Cluster analysis was performed from baseline data in 68 patients of the prospective study dataset. Three clusters were identified (Table E2); all were comparable with clusters observed in the larger refractory asthma population. The original study demonstrated a significant reduction in severe exacerbation frequency in the sputum arm, with no significant difference in corticosteroid usage between the groups. The present cluster-specific analysis revealed that all of the benefit for preventing exacerbations occurred in the inflammation-predominant cohort (3.53 [SD, 1.18] vs. 0.38 [SD, 0.13] exacerbation/patient/yr, \(P = 0.002\)) (Table 4). In addition, sputum-guided therapy allowed successful downtitration of corticosteroid therapy in early symptom-predominant asthma (Table 4; mean difference, 1,829 mg beclomethasone equivalent/d [95% confidence interval, 307–349 mg]; \(P = 0.02\)), without compromising asthma control.

A univariate ANOVA with the cluster model as a covariate identified both treatment grouping and the cluster model as significant determinants for observed differences in exacerbation frequency (\(P = 0.002\), study groups; \(P = 0.03\), cluster model), but only the cluster model was a significant determinant for differences in inhaled corticosteroid dose (\(P = 0.07\) for treatment groups and \(P = 0.005\) for cluster model).

DISCUSSION

The need for classifying asthma heterogeneity has gained urgency with the parallel development of better tools for measuring disease characteristics that highlight disparity in clinical, physiologic, and pathologic markers, together with novel and specific molecular therapies that are only likely to be efficacious in particular subgroups of asthma. This study is the first to apply principles of cluster analysis for the identification of clinical asthma phenotypes. We have further shown that phenotypes constructed in this way exhibit clinically relevant differences in outcome, with management strategies that use a measure of eosinophilic inflammation for titrating corticosteroid therapy.

Asthma classification is complicated by the multidimensional nature of the disease. This prompted our consideration of cluster analysis techniques for this purpose. We selected the k-means clustering algorithm as it maximizes separation between clusters, thereby offering the greatest scope for identifying distinct groups within the population. Both familiar and previously uncharacterized asthma subgroups were identified that are more representative of multidimensionality.

Asthma Phenotypes

Haldar AJRCCM 2008

Core abnormality

Airway smooth muscle dysfunction

Type 2 inflammation

Other types of inflammation

Disease modifiers

Asthma endotype

\(T_{H2}\)-high asthma

\(T_{H2}\)-low asthma

Inhaled corticosteroids and inhibitors of type 2 inflammation

Treatment options

Unmet therapeutic need

Fahy, NRI, 2015
Not all asthma is the same!!

(Heterogeneity)

(Phenotypes)

SO WHAT?
Question #5 - Asthma

True or False?

Inhaled Corticosteroids are effective (at some dose) in all asthmatics.

1. True
2. False
Patients (≥15 Years) Not Controlled on PRN Beta-Agonists

FEV<sub>1</sub>: Distribution of Individual Patient Responses

Malmstrom et al.
Ann Intern Med. 130:487-495, 1999
A Large Subgroup of Mild-to-Moderate Asthma Is Persistently Noneosinophilic

- Asthma is a heterogeneous disease
- ~50% of asthmatics - poor response to steroids
- Eosinophilic airway inflammation not ubiquitous
- Prior ACRN data (n=995; 2.7 SI; ≥2% eos):

Sputum Eosinophil Percentage (No ICS)

McGrath et al (ACRN)
Am J Respir Crit Care Med 185:612–619, 2012

TH2 Genes Overexpressed in Asthma

Woodruff et al
Am J Respir CCM 180:388, 2009
Th2 Status Predicts Corticosteroid Response

The NEW ENGLAND JOURNAL of MEDICINE

Oral Glucocorticoid-Sparing Effect of Mepolizumab in Eosinophilic Asthma

- N=135, prednisone x ≥6 months, eosinophils >300
Oral Glucocorticoid-Sparing Effect of Mepolizumab in Eosinophilic Asthma

Elisabeth H. Bel, M.D., Ph.D., Sally E. Wenzel, M.D., Philip J. Thompson, M.D., Charlene M. Prazma, Ph.D., Oliver N. Keene, M.Sc., Steven W. Yancey, M.Sc., Hector G. Ortega, M.D., Sc.D., and Ian D. Pavord, D.M., for the SIRIUS Investigators®

A Change from Baseline in Glucocorticoid Dose

B Asthma Exacerbations
A Large Subgroup of Mild-to-Moderate Asthma Is Persistently Noneosinophilic

- Asthma is a heterogeneous disease
- ~50% of asthmatics - poor response to steroids
- Eosinophilic airway inflammation not ubiquitous
- Prior ACRN data (n=995; 2.7 SI; ≥2% eos):

Sputum Eosinophil Percentage (No ICS)

McGrath et al (ACRN)
Am J Respir Crit Care Med 185:612-619, 2012
Steroids in Eosinophil Negative Asthma (SIENA)

Co-Primary Research Questions:

1. Does the response to ICS differ between subjects who are persistently EOS- and those who are EOS+?

2. Does the response to LMA differ between subjects who are persistently EOS- and those who are EOS+?
SIENA: Schematic

N = 384

Single-blind Placebo
Run-in

EOS+

LMA + Int ICS
ICS + Int ICS
ICS + Int ICS

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(See Appendix A for list of Questionnaires)

Alternative Treatment?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tiotropium Bromide Step-Up Therapy for Adults with Uncontrolled Asthma

Stephen P. Peters, M.D., Ph.D., Susan J. Kunselman, M.A., Nikolina Icicovic, M.A.S., Wendy C. Moore, M.D., Rodolfo Pascual, M.D., Bill T. Ameredes, Ph.D., Homer A. Boushey, M.D., William J. Calhoun, M.D., Mario Castro, M.D., Reuben M. Cherniack, M.D., Timothy Craig, D.O., Loren Denlinger, M.D., Ph.D., Linda L. Engle, B.S., Emily A. DiMango, M.D., John V. Faly, M.D., Eliot Israel, M.D., Nizar Jarjour, M.D., Shamsah D. Kazani, M.D., Monica KRAFT, M.D., Stephen C. Lazarus, M.D., Robert F. Lemanske, Jr., M.D., Niaa Lugogo, M.D., Richard J. Martin, M.D., Deborah A. Meyers, Ph.D., Joe Ramsdell, M.D., Christine A. Sorkness, Pharm.D., E. Rand Sutherland, M.D., Stanley J. Szelfer, M.D., Stephen I. Wasserman, M.D., Michael J. Walter, M.D., Michael E. Wechsler, M.D., Vernon M. Chinchilli, Ph.D., and Eugene R. Bleecker, M.D., for the National Heart, Lung, and Blood Institute Asthma Clinical Research Network
**Tiotropium Step-Up for Uncontrolled Asthma**

![Graph showing Morning PEF (liters/min)]

- Tiotropium: P=0.26
- Double-Glucocorticoid: P<0.001
- Salmeterol: P<0.001

*Peters et al.*

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**International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma**

*Eur Respir J; 43:343-73, 2014*
International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma

Recommendations:

- In adults with severe asthma – use sputum eos in experienced centers
- In severe allergic asthma – therapeutic trial of omalizumab
- Do not use methotrexate for asthma
- Do not use azithromycin for asthma

_Eur Respir J; 43:343-73, 2014_

Recommendations:

- Use anti-fungals for ABPA
- Do not use anti-fungals without ABPA
- Consider bronchial thermoplasty only as part of a study

_Eur Respir J; 43:343-73, 2014_
NAEPP GUIDELINES

“If there is a clear and positive response for at least 3 months, a careful step down in therapy should be attempted to identify the lowest dose required to maintain control. (Evidence D)”

Evidence D = Panel Consensus Judgment

National Asthma Education and Prevention Program.

GINA GUIDELINES

“Controller treatment may be stopped if the patient’s asthma remains controlled on the lowest dose of controller and no recurrence of symptoms occurs for 1 year (Evidence D)”

Evidence D = Panel Consensus Judgment

Global strategy for asthma management and prevention: GINA executive summary.
Eur Respir J. 2008 Jan;31(1):143-78.
Is There Really A Difference Between Asthma And COPD?

Pathophiology in COPD versus Asthma

**COPD**
- Loss of elastic recoil
- Changes in small airways
- “Inflammation”
- Fixed airway obstruction

**Asthma**
- Inflammation
- Bronchial hyperresponsiveness
- Varying airway obstruction
Inflammation in COPD versus Asthma

**COPD**
- Predominant Cells:
  - Macrophages
  - Neutrophils
  - CD-8 T-Lymphocytes
- Predominant Cytokines:
  - Interleukin 8
  - Leukotriene B4
  - Tumor Necrosis Factor alpha

**Asthma**
- Predominant Cells:
  - Eosinophils
  - Activated Mast Cells
  - CD-4 T Lymphocytes
- Predominant Cytokines:
  - Interleukin 4
  - Interleukin 5
  - Interleukin 13

Calverley, Barnes. AJRCCM 2000; 161:341-344

COPD Asthma Overlap

<table>
<thead>
<tr>
<th>Risks</th>
<th>Outcomes</th>
</tr>
</thead>
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<tr>
<td>• Genetic patterns&lt;br&gt;• Maternal smoking&lt;br&gt;• Childhood diseases&lt;br&gt;• Allergy&lt;br&gt;• IgE&lt;br&gt;• Eosinophilia&lt;br&gt;• Exhaled nitric oxide&lt;br&gt;• TH2-related inflammation&lt;br&gt;• Rhinitis</td>
<td>Asthma&lt;br&gt;• Low lung function&lt;br&gt;• Episodic wheezing&lt;br&gt;• Nocturnal symptoms&lt;br&gt;• BHR&lt;br&gt;• Eosinophilia&lt;br&gt;• GERD&lt;br&gt;• Limited reversibility of airway obstruction&lt;br&gt;• Hyperinflation&lt;br&gt;• Abnormal body composition&lt;br&gt;• Coexisting cardiac conditions&lt;br&gt;• Infections&lt;br&gt;• Dyspnea</td>
</tr>
<tr>
<td>• Genetic patterns&lt;br&gt;• Aging&lt;br&gt;• Smoking&lt;br&gt;• Maternal smoking&lt;br&gt;• Exposure to smoke from biomass fuels&lt;br&gt;• Occupational hazards&lt;br&gt;• Poor nutrition&lt;br&gt;• BHR&lt;br&gt;• Emphysema&lt;br&gt;• BPD</td>
<td>ACOS&lt;br&gt;• Low lung function&lt;br&gt;• Episodic wheezing&lt;br&gt;• Nocturnal symptoms&lt;br&gt;• BHR&lt;br&gt;• Eosinophilia&lt;br&gt;• GERD&lt;br&gt;• Limited reversibility of airway obstruction&lt;br&gt;• Hyperinflation&lt;br&gt;• Abnormal body composition&lt;br&gt;• Coexisting cardiac conditions&lt;br&gt;• Infections&lt;br&gt;• Dyspnea</td>
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Asthma Summary

• Asthma not a single disease but a heterogeneous group of diseases
• Patients respond differently to medications based upon underlying “endotype/phenotype”
• “Th2-High” or Allergic Asthma responds to corticosteroids
• Treatments for “Th2-Low” or Non-Allergic Asthma remain unclear