Update on COPD & Asthma

Disclosures

- No Pharma Consulting, Research, Lectures
- NHLBI - Asthma Clinical Research Network
- NHLBI AsthmaNet
- NHLBI - COPD Clinical Research Network
- NAEPP Coordinating Committee
- NHLBI SPIROMICS
Update on the Management of COPD

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
### Leading Causes of Deaths in U.S. 2011

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Heart Disease</td>
<td>596,577</td>
</tr>
<tr>
<td>2. Cancer</td>
<td>576,691</td>
</tr>
<tr>
<td>3. Respiratory Diseases (COPD)</td>
<td>142,943</td>
</tr>
<tr>
<td>4. Stroke</td>
<td>128,932</td>
</tr>
<tr>
<td>5. Accidents</td>
<td>126,438</td>
</tr>
<tr>
<td>6. Alzheimer's</td>
<td>84,974</td>
</tr>
<tr>
<td>7. Diabetes</td>
<td>73,831</td>
</tr>
<tr>
<td>8. Influenza &amp; Pneumonia</td>
<td>53,826</td>
</tr>
<tr>
<td>9. Kidney Disease</td>
<td>45,591</td>
</tr>
<tr>
<td>10. Suicide</td>
<td>39,518</td>
</tr>
<tr>
<td>11. All other causes of death</td>
<td>646,137</td>
</tr>
</tbody>
</table>

*Death in the US 2011, CDC, last updated 15 March, 2013*

### 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>
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

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 Surveill Summ 2002; 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


---

**Risk Factors for Frequent Exacerbations**

- Increased Age
- Severity of FEV$_1$ Impairment
- Chronic mucus hypersecretion
- Frequent past Exacerbations
- Daily cough and wheeze
- Persistent symptoms of chronic bronchitis

*Anzueto, Sethi, Martinez
Proc Am Thorac Soc 4:554-564, 2007*
**GOLD (2007) Classification of COPD Severity**

$FEV_1/FVC < 0.70$

**GOLD 1:** (Mild COPD) $FEV_1 > 80\%$ predicted

**GOLD 2:** (Moderate COPD) $FEV_1 50-80\%$ predicted

**GOLD 3:** (Severe COPD) $FEV_1 30-50\%$ predicted

**GOLD 4:** (Very Severe COPD) $FEV_1 <30\%$ predicted

---

**COPD Assessment: A New Model**

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

**GOLD Guidelines 2013**

<table>
<thead>
<tr>
<th>Patient Category</th>
<th>Characteristics</th>
<th>Spirometric Classification</th>
<th>Exacerbations per year</th>
<th>mMRC</th>
<th>CAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Low Risk, Less Symptoms</td>
<td>GOLD 1-2</td>
<td>≤1</td>
<td>0-1</td>
<td>&lt;10</td>
</tr>
<tr>
<td>B</td>
<td>Low Risk, More Symptoms</td>
<td>GOLD 1-2</td>
<td>≤1</td>
<td>≥2</td>
<td>≥10</td>
</tr>
<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>
</tr>
<tr>
<td>D</td>
<td>High Risk, More Symptoms</td>
<td>GOLD 3-4</td>
<td>≥2</td>
<td>≥2</td>
<td>≥10</td>
</tr>
</tbody>
</table>
**COPD Exacerbation Frequency**

- **GOLD II**: 2.68/year
- **GOLD III**: 3.43/year  \[P = 0.029\]

Donaldson et al  
*Thorax* 2002; 57:847-52

- **FEV\(_1\) > 60%**: 1.6/year
- **FEV\(_1\) 40-50%**: 1.9/year
- **FEV\(_1\) < 40%**: 2.3/year

Paggiaro et al  
*Lancet* 1998; 317:773-780

---

**Percentage change in FEV1 over 4 years.**

- Infrequent Exacerbators
- Frequent Exacerbators

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

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

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

Characterized Extensively at:  
Baseline  
3, 6, 12, 18, 24, 30, 36 months

CT scans x 3  
Questionnaires  
6MWT  
Spirometry, Forced oscillatory lung mechanics  
Blood, Urine, Sputum (43%)
Characterization of COPD Heterogeneity in the ECLIPSE Cohort

A

Proportion of subjects (%)

Stage II
Mean = 1.3

Stage III
Mean = 1.8

Stage IV
Mean = 2.3

mMRC score

Characterization of COPD Heterogeneity in the ECLIPSE Cohort

B

Proportion of subjects (%)

Stage II
Mean = 405.4

Stage III
Mean = 356.1

Stage IV
Mean = 289.2

Distance walked (Metres)

Agusti Respir Res 2010; 11:122
Characterization of COPD Heterogeneity in the ECLIPSE Cohort

C

Proportion of subjects (%)

Mean = 0.6

Number of exacerbations

Stage IV

Stage III

Stage II

Agusti Respir Res 2010; 11:122

Characterization of COPD Heterogeneity in the ECLIPSE Cohort

D

Proportion of subjects (%)

Mean = 42.5

Mean = 54.0

Mean = 61.5

SGRQ-C Total score

Agusti Respir Res 2010; 11:122
**Acute Exacerbations of COPD**

- Some patients seldom exacerbate
- Some patients exacerbate frequently
- Best predictor of ≥2 AECOPD/year ("Frequent Exacerbator") = previous frequent exacerbations

**ECLIPSE**
- "Frequent Exacerbator" is a stable phenotype
- Risk of exacerbations increases with decreasing FEV1
- GERD doubles risk of AECOPD
- WBC associated with risk of AECOPD

**Targets of Treatment**

- Symptoms
- Exacerbations
- Frequent Exacerbators
- Smoking Cessation
- Progressive Loss of Lung Function
- Systemic Inflammation
Question #2:
Which of the Following DOES NOT Reduce Acute Exacerbations of COPD?

1. ICS
2. LABA
3. LAMA
4. Azithromycin
5. Chocolate

Prevention of AECOPD
American College of Chest Physicians & Canadian Thoracic Society Guideline

- PICO (population, intervention, comparator, outcome)
- Guidelines International Network
- National Guideline Clearinghouse
- PubMed
- Cochrane Library
- Quality Assessment (AGREE II, DART)
- Meta-Analyses
- Grading Evidence (GRADEpro)
- Recommendations (CHEST)

Criner et al. CHEST 147:894-942, 2015
Prevention of AECOPD  
Am Coll Chest Physicians & Canadian Thoracic Society Guideline - Recommendations  

Non-Pharmacologic Treatments/Vaccinations:  
• Pneumococcal Vaccine (Grade 2C)  
• Influenza Vaccine (Grade 1B)  
• Smoking Cessation (Grade 2C)  
• Pulmonary Rehab (Grade 1C)  
  *Mod-severe-very severe; recent AECOPD*

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

Maintenance Inhaled Therapy:  
• LABA vs PBO (Grade 1B)  
• LAMA vs PBO (Grade 1A)  
• LAMA vs LABA (Grade 1C)  
• SAMA vs SABA (Grade 2C)  
• SAMA + SABA vs SABA (Grade 2B)  

*Criner et al. CHEST 147:894-942, 2015*
Prevention of AECOPD
Am Coll Chest Physicians & Canadian Thoracic Society Guideline - Recommendations

Maintenance Inhaled Therapy:

- LABA vs SAMA (Grade 2C)
- LAMA vs SAMA (Grade 1A)
- SAMA + LABA vs LABA (Grade 2C)

Criner et al. CHEST 147:894-942, 2015
Prevention of AECOPD
Am Coll Chest Physicians & Canadian Thoracic Society Guideline - 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

Natural History of COPD
- Patients with COPD lose lung function faster than normals
- Smoking cessation decreases rate of loss
- Patients with reversibility lose lung function faster than those without reversibility
- Patients with emphysema lose lung function faster than those with chronic bronchitis
Question #3: 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); FEV₁ = 63%

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

Results:
• 22% of smoking intervention & 5% of usual care pts were sustained “quitters”
• Ipratropium made no difference
• Smoking cessation slowed the fall in FEV₁

Effect of Smoking Cessation on FEV₁

Effects of a Smoking Cessation Intervention on 14.5-year Mortality

Anthonisen et al
Effects of a Smoking Cessation Intervention on 14.5-year Mortality

Anthonisen et al
Changes in FEV1 over time in COPD

N = 2163 with COPD
40-75 years old
>10 Pack Years
FEV1/FVC < 0.7
FEV1 <0.8
Followed x 3 years

Vestbo et al, ECLIPSE

Effect of Corticosteroids on Expiratory Airflows in AE COPD

Prednisone 60qd x 3d, 40qd x 3d, 20qd x 3d
Placebo

* = p<0.05, # = p<0.01
Thompson et al. AJRCCM 154:407, 1996
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

Rate of Treatment Failure (%)

Month

8 week
2 week
Placebo

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
Time to Reexacerbation of COPD

Leuppi et al.
JAMA 2013;309(21):2223-2231

Corticosteroid Dose in Critically-ill Patients with AECOPD

- Retrospective cohort study
- N = 17,239 patients, 473 hospitals
- Admitted to ICU with ICD-9 491.21
- Treated with steroids day 1 or 2
- Classed as:
  - High Dose: >240 mg/day methylprednisolone
  - Low Dose: ≤240 mg/day methylprednisolone

Kiser et al.
Am J Respir Crit Care Med 2014; 189:1052-64
Corticosteroid Dose in Critically-ill Patients with AECOPD

- 64% received high-dose (median=312 mg/day)
- 36% received low-dose (median = 98 mg/day)
- Lower Dose Group
  - Hospital Mortality: OR 0.85; P = 0.06
  - Fewer days in ICU
  - Fewer days in Hospital
  - Shorter length of mechanical ventilation
  - Less insulin
  - Less frequent fungal infections
  - Lower hospital costs

Kiser et al.
Am J Respir Crit Care Med
2014; 189:1052-64

Inhaled corticosteroids and pneumonia in chronic obstructive pulmonary disease

Lancet Respir Med 2014; 2: 919-32
Withdrawal of Inhaled Glucocorticoids and Exacerbations of COPD

Helgo Magnussen, M.D., Bernd Disse, M.D., Ph.D., Roberto Rodriguez-Roisin, M.D., Anne Kirsten, M.D., Henrik Watz, M.D., Kay Tezelaff, M.D., Lesley Towse, B.Sc., Helen Finningan, M.Sc., Ronald Dahl, M.D., Marc Decramer, M.D., Ph.D., Pascal Chauze, M.D., Ph.D., Emiel F.M. Wouters, M.D., Ph.D., and Peter M.A. Calverley, M.D., for the WISDOM Investigators

- DB, Randomized, non-inferiority
- \([\text{SM + TIO + FP}] \text{ vs } [\text{SM + TIO}] + \text{withdrawal of FP}\)
- Run-in on triple therapy x 6 weeks
- Stepwise reduction of FP (1000→0) over 12 weeks
- Followup over 1 year
- n=2485
Withdrawal of ICS and AECOPD (WISDOM)

• Among patients with moderate-severe COPD (with hx of exacerbations) and taking a LABA and LAMA, withdrawal of ICS was non-inferior to continuation of ICS for the endpoint of time to first exacerbation

• Secondary endpoints of lung function and QoL were significantly worse at one year

• Excluded for: Asthma, CHF, Oxygen, Oral Steroids

Magnussen et al

STATCOPE: SimvaSTATin in the Prevention of COPD Exacerbations
(Simvastatin 40mg/day x 1 year)

• NHLBI - COPD Clinical Research Network

• N = 1130; Simvastatin + Usual Care vs Usual Care

• Moderately-severe COPD
  \( \text{FEV}_1/\text{FVC} < 70\%; \text{FEV}_1 < 80\% \)

• “Exacerbation Prone”

• Primary Outcome: Time to first AECOPD
• The rate of AECOPD did not vary between simvastatin and placebo (HDL increased and LDL decreased)

• Lung function, QoL, Mortality did not differ

• Patients already taking statins or with indication for statin were excluded

• Statins remain indicated for many COPD patients for primary and secondary prevention of CV disease.
Role of NIPPV in stable COPD unresolved

Cochrane review of 7 studies (n=245) failed to suggest benefit

N=195, stable, severe, PaCO2 >52, pH >7.35

NIPPV ≥6 hrs overnight; titrated in hosp at BL and Q3 months.
Non-invasive positive pressure ventilation for the treatment of severe stable chronic obstructive pulmonary disease: a prospective, multicentre, randomised, controlled clinical trial

• All-cause mortality at 1 year:
  NIPPV – 12%
  Control – 33%
  HR 0.24 (95% CI 0.11-0.29; p<0.001)

• Significant improvement in PaCO2, pH, SaO2, HCO3, FEV1, QoL

• Unblinded, 9-years to recruit, hospital admissions to titrate, other trials negative

Update on the Management of Asthma
Definition of Asthma

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

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

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

Interplay and Interaction between Airway Inflammation and the Clinical Symptoms and Pathophysiology of Asthma

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]
Question #4 - 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

FEV₁: Distribution of Individual Patient Responses


Asthma Phenotypes

• Allergic Asthma
• Non-allergic Asthma
• Late-onset Asthma
• Asthma with Fixed Airflow Limitation
• Asthma with Obesity
Not all asthma is the same!!

(Heterogeneity)

(Phenotypes)

Eosinophils

Charcot-Leyden Crystals
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*
Increase in FEV$_1$ after Fluticasone is seen only in TH$_2$-high group

Woodruff et al
Am J Respir CCM 180:388, 2009

- Annual exacerbation rates in eosinophilic vs non-eosinophilic asthmatics
- Poorly-controlled, med-high ICS/LABA, OCS x 2-3 in prior year
- N= 604
Anti-IL5R is effective in reducing exacerbation rates among eosinophilic poorly controlled asthmatics on med-high dose ICS

Efficacy is better among those with blood eos >300

N=135, prednisone ≥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

Median Change (%)

0 4 8 12 16 20 24

Week

- Placebo (N=66)

- Mepolizumab (N=69)

Optimized dose

Maintenance dose

B Asthma Exacerbations

Cumulative No.

0 10 20 30 40 50 60 70

Week

Placebo

Mepolizumab
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)**

  - 36% All Subjects at Baseline
  - 56% Repeated Measures Subjects at Baseline
  - 53% Repeated Measures Subjects Over Time

McGrath et al (ACRN)
Am J Respir Crit Care Med 185:612-619, 2012
Alternative Treatment?

Tiotropium Bromide Step-Up Therapy for Adults with Uncontrolled Asthma

Stephen P. Peters, M.D., Ph.D., Susan J. Kunselman, M.A.,
Nikolina Icitovic, M.A.S., Wendy C. Moore, M.D., Rodolfo Pascual, M.D.,
Bill T. Amenedes, Ph.D., Homer A. Boushey, M.D., William J. Calhoun, M.D.,
Mario Castro, M.D., Reuben M. Chemiack, M.D., Timothy Craig, D.O.,
Loren Denlinger, M.D., Ph.D., Linda L. Engle, B.S., Emily A. DiMango, M.D.,
John V. Falty, M.D., Elliot 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., Njira 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. Szefler, 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

Peters et al.
**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**

<table>
<thead>
<tr>
<th>V Wk</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SI</strong></td>
<td><strong>SI</strong></td>
<td><strong>SI</strong></td>
<td><strong>SI</strong></td>
<td><strong>SI</strong></td>
<td><strong>SI</strong></td>
<td><strong>SI</strong></td>
<td><strong>SI</strong></td>
<td><strong>SI</strong></td>
<td><strong>SI</strong></td>
<td><strong>SI</strong></td>
</tr>
<tr>
<td>Consent H&amp;P</td>
<td>Spiro w/Albuterol</td>
<td>SPI</td>
<td>Spiro w/Albuterol</td>
<td>SPI</td>
<td>Spiro w/Albuterol</td>
<td>SPI</td>
<td>Spiro w/Albuterol</td>
<td>SPI</td>
<td>Spiro w/Albuterol</td>
<td>SPI</td>
</tr>
<tr>
<td>(Mch)</td>
<td>CBC, IgE</td>
<td>ImmunoCAP</td>
<td>SI</td>
<td>Periostin eNO</td>
<td>Eosinophils Genetics Blood Diary Review Review Elig &amp; Compliance Questionnaires</td>
<td>Albuterol Maximum Reversibility Spirometry Maximum Reversibility Spiro (SI) Periostin (eNO)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albuterol PE</td>
<td>Spirometry PE</td>
<td>Spirometry PE</td>
<td>Spirometry PE</td>
<td>Spirometry PE</td>
<td>Spirometry PE</td>
<td>Spirometry PE</td>
<td>Spirometry PE</td>
<td>Spirometry PE</td>
<td>Spirometry PE</td>
<td>Spirometry PE</td>
</tr>
<tr>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
</tr>
</tbody>
</table>

(See Appendix A for list of Questionnaires)
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

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

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