KEY ADVANCES IN THE TREATMENT AND MANAGEMENT OF ASTHMA

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Chair, Department of Allergy and Clinical Immunology
Respiratory Institute
Cleveland Clinic Foundation
Member, Rock and Roll Hall of Fame
(Roller Level)
Disclaimer

- I have received honoraria from, have carried out clinical research with, and/or have served as a consultant for: Adamis, AstraZeneca, Genentech, GlaxoSmithKline, Merck, Novartis.
- My presentation will not include discussion of off-label uses of FDA approved products, but will include mention of agents that are not FDA approved.

Learning Objectives

- Examine the evidence base for disease monitoring tools and appropriate treatment selection for asthma control
- Discuss appropriate and effective ways to assess asthma control to improve patient adherence, self-management, and overall quality of life in asthma patients
- Analyze different options for improving asthma control in patients with uncontrolled, persistent allergic asthma
- Identify the potential benefits and the role of therapies that target the inflammatory component of allergic asthma
- Assess recent clinical data on the efficacy and safety of current and emerging treatment options for asthma, including the mechanisms of action for biologic drugs
Asthma Control, Management, and Severity

- **Asthma Control, Management, and Severity**

- **Asthma Management**
  - optimal
  - poor

- **Severity**
  - mild
  - severe

- **Burden of Uncontrolled Asthma**

  - **TENOR**: multicenter, prospective, observational study of severe or difficult to treat asthma in the USA.
  - Controlled patients had fewer work/school absences and less health care resource use than uncontrolled patients at all time points. (Sullivan SD, et al. Allergy 2007; 62: 126-33.)
Definitions

• Severity
  – the intrinsic intensity of the disease process
  – Measured most easily and directly in a patient not receiving long term control therapy

• Control
  – The degree to which manifestations of asthma (symptoms, functional impairments, and risks of untoward events) are minimized and the goals of therapy are met.

Asthma Severity and Control: Impairment Domain

Impairment = Frequency and Intensity of Symptoms and Functional Limitations

**Symptoms**
- Nighttime awakenings
- Need for SA β₂-agonists (SABAs) for quick relief
- Work/school days missed
- Ability to engage in normal and desired daily activities
- Quality-of-life assessments

**Lung Function**
- Spirometry
- Peak flow

Adapted from NHLBI Expert Panel Guidelines (EPR-3).

Assessing Asthma Control in Children ≥12 Years of Age and Adults: NAEPP Guidelines

<table>
<thead>
<tr>
<th>Components of Control</th>
<th>Well Controlled</th>
<th>Not Well Controlled</th>
<th>Poorly Controlled</th>
</tr>
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<tbody>
<tr>
<td>Impairment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms</td>
<td>≤2 days/week</td>
<td>&gt;2 days/week</td>
<td>Throughout the day</td>
</tr>
<tr>
<td>Nighttime awakenings</td>
<td>≤2/night</td>
<td>1-3/night</td>
<td>4/night</td>
</tr>
<tr>
<td>Interference with normal activity</td>
<td>None</td>
<td>Some limitation</td>
<td>Extremely limited</td>
</tr>
<tr>
<td>SABA use for symptoms (not prevention of EIB)</td>
<td>≤2 days/week</td>
<td>&gt;2 days/week</td>
<td>Several times per day</td>
</tr>
<tr>
<td>FEV₁ or peak flow</td>
<td>&gt;80% predicted/personal best</td>
<td>60%-80% predicted/personal best</td>
<td>&lt;60% predicted/personal best</td>
</tr>
<tr>
<td>Validated Questionnaires</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATAQ</td>
<td>0 ≤ 0.75</td>
<td>1-2 ≥ 1.5</td>
<td>3-4 N/A</td>
</tr>
<tr>
<td>ACT</td>
<td>≥20</td>
<td>16-19</td>
<td>≤15</td>
</tr>
<tr>
<td>Risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exacerbations</td>
<td>0-1 per year</td>
<td>2-3 per year</td>
<td>&gt;3 per year</td>
</tr>
<tr>
<td>Progressive loss of lung function</td>
<td>Evaluation requires long-term follow-up care</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment-related adverse effects</td>
<td>Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.</td>
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ACQ = Asthma Control Questionnaire; ACT = Asthma Control Test; ATAQ = Asthma Therapy Assessment Questionnaire; EIB = exercise-induced bronchospasm; FEV₁ = forced expiratory volume in 1 second; N/A = not applicable.

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Validated Tools To Assess Asthma Control

- Asthma Control Questionnaire (ACQ)<sup>1</sup>
- Asthma Control Test (ACT)<sup>2</sup>
- Asthma Therapy Assessment Questionnaire (ATAQ)<sup>3</sup>


Patients on a controller are classified as having “not well controlled” asthma if they have any ONE of the following*:

- Albuterol use >2 days/week
- Asthma symptoms >2 days/week
- Nighttime awakenings 1-3x/week
- Some limitation of normal activity
- FEV<sub>1</sub> between 60%-80% of predicted
- ACT score < 20

*Based on NIH asthma guidelines for adjusting therapy in patients ≥12 years.

Asthma Control Test™ (ACT)

1. In the past 4 weeks, how much of the time did your asthma keep you from getting as much done at work, school or at home?

2. During the past 4 weeks, how often have you had shortness of breath?

3. During the past 4 weeks, how often did your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) wake you up at night, or earlier than usual in the morning?

4. During the past 4 weeks, how often have you used your rescue inhaler or nebulizer medication (such as albuterol)?

5. How would you rate your asthma control during the past 4 weeks?

Algorithm for Attaining Optimal Asthma Control

- Classify Asthma Severity
- Assess Asthma Control:
  - Frequency of symptoms
  - Frequency of rescue bronchodilator
  - Frequency of night/morning symptoms
  - Activity, work, school limitations
  - Patient assessment
  - Pulmonary Function Tests
- Periodic Assessment of Asthma:
  - Assess psychosocial status
  - Assess adherence/compliance
  - Assess medication’s side effects
  - Assess asthma triggers
  - Review action plan
  - Confirm/reconfirm diagnosis of asthma
- Asthma Well-controlled
- Yes
- Maintain or step-down therapy
- No
  - Detailed asthma assessment
  - Step-up therapy

The US Asthma Burden

- 2010: An estimated 25.7 million (8%) with current asthma, compared with 20 million (7%) in 2001
  - African Americans = 10.2%
  - Whites = 7.6%
- Asthma cost the USA about $3,300 per person with asthma each year from 2002 to 2007 in medical expenses.
- 2007: $56 billion in annual costs including medical costs, lost school/work, and early deaths.
- 3630 deaths (2013)
  - [http://www.cdc.gov/asthma/pdfs/asthma_fast_facts_statistics.pdf](http://www.cdc.gov/asthma/pdfs/asthma_fast_facts_statistics.pdf) accessed 1/11/16
  - Akinbami L, Moorman J. National Health Statistics Reports, Number 32, January 12, 2011
Cross-Sectional Study of Uncontrolled Asthma in 35 Primary Care Offices in USA

<table>
<thead>
<tr>
<th></th>
<th>Overall N=2238</th>
<th>Respiratory Visits N=861</th>
<th>Nonrespiratory Visits N=1289</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years), Mean (95% CI)</td>
<td>46.7 (46.0-47.3)</td>
<td>46.3 (45.2-47.3)</td>
<td>46.7 (45.8-47.6)</td>
</tr>
<tr>
<td>Female n (%)</td>
<td>1601 (72%)</td>
<td>602 (70%)</td>
<td>935 (73%)</td>
</tr>
<tr>
<td>Race/ethnicity n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>1483 (68%)</td>
<td>557 (65%)</td>
<td>877 (68%)</td>
</tr>
<tr>
<td>African American</td>
<td>262 (12%)</td>
<td>97 (11%)</td>
<td>154 (12%)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>246 (11%)</td>
<td>119 (14%)</td>
<td>118 (9%)</td>
</tr>
<tr>
<td>Other</td>
<td>206 (9%)</td>
<td>74 (9%)</td>
<td>119 (9%)</td>
</tr>
<tr>
<td>Patient-described severity n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>1061 (47%)</td>
<td>324 (38%)</td>
<td>708 (55%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>971 (43%)</td>
<td>434 (50%)</td>
<td>497 (39%)</td>
</tr>
<tr>
<td>Severe</td>
<td>137 (6%)</td>
<td>79 (9%)</td>
<td>51 (4%)</td>
</tr>
<tr>
<td>Body mass index, Mean (95% CI)</td>
<td>31.0 (30.7-31.3)</td>
<td>31.2 (30.7-31.7)</td>
<td>30.9 (30.5-31.3)</td>
</tr>
<tr>
<td>&gt;30</td>
<td>1043 (46.6%)</td>
<td>410 (47.6%)</td>
<td>598 (46%)</td>
</tr>
</tbody>
</table>
Almost Half of Patients Visiting a Primary Care Physician for a Nonrespiratory Complaint Had Not Well or Poorly Controlled Asthma

Almost Half of Patients Visiting a Primary Care Physician for a Nonrespiratory Complaint Had Not Well or Poorly Controlled Asthma
Risk Factors For Future Exacerbations

- Poor or Not Well Controlled Asthma
- History of Recent Exacerbation
- Medications
  - Reliever overuse
  - Controller underuse
- Biomarkers for “High Th2 Phenotype”
  - Blood / Sputum Eosinophils
  - Exhaled Nitric Oxide
  - Serum Periostin
Asthma Control Test™ (ACT)

1. In the past 4 weeks, how much of the time did your asthma keep you from getting as much done at work, school or at home?

   - All of the time 1
   - Most of the time 2
   - Some of the time 3
   - A little of the time 4
   - None of the time 5

2. During the past 4 weeks, how often have you had shortness of breath?

   - More than once a day 1
   - Once a day 2
   - 2 to 6 times a week 3
   - Once or twice a week 4
   - Not at all 5

3. During the past 4 weeks, how often did your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) wake you up at night, or earlier than usual in the morning?

   - 4 or more nights a week 1
   - 2 or 3 nights a week 2
   - Once a week 3
   - Once or twice 4
   - Not at all 5

4. During the past 4 weeks, how often have you used your rescue inhaler or nebulizer medication (such as albuterol)?

   - 3 or more times per day 1
   - 1 or 2 times per day 2
   - 2 or 3 times per week 3
   - Once a week or less 4
   - Not at all 5

5. How would you rate your asthma control during the past 4 weeks?

   - Not controlled at all 1
   - Poorly controlled 2
   - Somewhat controlled 3
   - Well controlled 4
   - Completely controlled 5

Odds of Future Exacerbations

adjusted multivariate analysis

N = 2780, age ≥ 12, 18 month prospective study

Dispensed Beta Agonist Cannisters Associated with Health Service Utilization

Risk of having >1 asthma exacerbations within calendar year according to quartiles of controller-to-total prescription ratio.


Elevated Eosinophils Associated with Asthma Disease Burden

- EOS ≥ 400 cells/mm^3 compared with < 400 cells/mm^3
  (EOS cutoff points of 300 cells/mm^3 and 150 cells/mm^3 were not)

- ≥ 2 asthma exacerbations
  - 1.7

- ≥ 2 asthma exacerbations (adjusted)
  - 1.55

- ≥ 1 asthma ED visit or hospitalization
  - 2.39

- ≥ 1 asthma ED visit or hospitalization (adjusted)
  - 2.29

CHAPTER FOUR

A Disease of the Direst Suffering

BRONCHIAL ASTHMA is among the most serious of childhood afflictions—baffling, capricious, expensive, and, in its acute stages, terrifying. It is also a family affliction and a severe one, which is something seldom understood by those who have never lived with an asthmatic child, for rarely does anyone beyond the immediate family or the medical profession see an actual attack or have any idea of the suffering involved. The child known by the outside world is the child between attacks who appears to have little or nothing the matter with him, who can play and carry on like most any healthy youngster, even hike twenty miles in the Alps. It is

“Nobody seemed to think I would live”

Theodore Roosevelt, discussing his asthma during childhood.
Quoted in NY World, Nov. 16, 1902

Asthma Therapies

- Emetics and purges
- Smoke from dried Jimson weed (*datura stramonium*)
- Coffee
- Whiskey and gin
- Landanum
  - Opium and wine

A Patient with Asthma Seeks Medical Advice in 1828, 1928, and 2012

Erika von Mutius, M.D., and Jeffrey M. Drazen, M.D.

PeoplE HAVE SUFFERED FROM ASTHMA FOR MILLENNIA, although the clinical presentation of asthma has probably changed little, there are many more people who now bear its consequences than there were 200 years ago. As a result of an intense interest in the condition, our understanding of its pathobiology, how to diagnose it, and — most important — how to treat it has evolved dramatically over the past two centuries. To illustrate this change, we provide three fictional reports of consultations performed for essentially the same patient, who has what we in 2012 would refer to as asthma. (A timeline of the major advances in the treatment of asthma from 1812 through 2012 is available with the full text of this article at NEJM.org.) The first report is from 1828, the year that the New England Journal of Medicine and Surgery and Collateral Branches of Science joined with the Medical Intelligencer to form the Boston Medical and Surgical Journal. The second is from 1928 when the title of the...
Asthma is Heterogeneous

- Not a single disease entity
- It’s a syndrome characterized by multiple phenotypes
  - Age
  - Gender
  - Race/ethnicity
  - Disease pattern
    - Remission/relapse
    - Persistence
### Two Barbaras

<table>
<thead>
<tr>
<th>Barbara 1</th>
<th>Barbara 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 48 year old African American woman with 15 year history of asthma – poorly controlled.</td>
<td>• 48 year old woman</td>
</tr>
<tr>
<td>• 2-3 exacerbations/year.</td>
<td></td>
</tr>
<tr>
<td>• Frequent reliance on oral steroid.</td>
<td></td>
</tr>
<tr>
<td>• Co-morbid conditions:</td>
<td></td>
</tr>
<tr>
<td>– Allergic rhinitis</td>
<td></td>
</tr>
<tr>
<td>– GE reflux</td>
<td></td>
</tr>
<tr>
<td>– Obesity</td>
<td></td>
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</table>
Two Barbaras

Barbara 1
• 48 year old African American woman with 15 year history of asthma – poorly controlled.
• 2-3 exacerbations/year.
• Frequent reliance on oral steroid.
• Co-morbid conditions:
  – GERD reflux
  – Obesity

Barbara 2
• 48 year old Caucasian woman with 15 year history of rhinosinusitis, requiring 3 sinus surgeries.
• 12 year course of asthma.
• Frequent reliance on oral steroid.
• 3 episodes of respiratory reaction to ASA/NSAID, one requiring ICU management.

Two Barbaras

Barbara 1
• PE:
  – Chest: clear
  – Otherwise unremarkable
• Skin testing: wheal/flare reactions to tree, grass, ragweed, weed, dust mites, cockroach, cat dander.
• ACT = 5

Barbara 2
Two Barbaras

Barbara 1
- PE:
  - Chest: clear
  - Otherwise unremarkable
- Skin testing: wheal/flare reactions to tree/grass/ragweed/weed pollens, dust mites, cockroach, cat dander.
- ACT = 5

Barbara 2
- PE:
  - Chest: End expiratory wheeze in all lung fields.
  - HEENT: Nasal polyps
- Skin testing: no wheal/flare reactions at prick or intradermal level.
- CT scan: pansinusitis.
- ACT = 5

Two Barbaras

Barbara 1
- Disposition:
  - Avoidance measures
  - Maintain current asthma regimen with high dose ICS/LABA, anti-leukotriene, and optimize regimen for GE reflux.
  - Therapeutic trial of anti-IgE.
  - Dramatic improvement in course of asthma.
# Two Barbaras

**Barbara 1**
- **Disposition:**
  - Aeroallergen avoidance measures
  - Maintain current asthma regimen with high dose ICS/LABA, antileukotriene, and optimize regimen for GE reflux.
  - Therapeutic trial of anti-IgE.
    - Dramatic improvement in course of asthma.

**Barbara 2**
- **Disposition:**
  - Avoidance of ASA/NSAIDs
  - Maintain current regimen for asthma with high dose ICS/LABA, antileukotriene.
  - Sinus surgery.
  - Aspirin desensitization
    - Improved symptoms
    - Reduced medication reliance
    - Reduced need for sinus surgery

---

# Asthma is Heterogeneous

- Not a single disease entity
- It’s a syndrome characterized by multiple phenotypes
  - Age
  - Gender
  - Race/ethnicity
  - Disease pattern
    - Remission/relapse
    - Persistence
Aspirin Exacerbated Respiratory Disease

Childhood - Early Adulthood

3rd - 4th Decade

may be unremarkable

vasomotor rhinosinusitis asthma aspirin reaction
	polyposis eosinophilia


Aspirin Desensitization – Barbara

2

Day One Day Two Day Three

<table>
<thead>
<tr>
<th>Time</th>
<th>8:00 AM</th>
<th>9:00 AM</th>
<th>10:00 AM</th>
<th>11:00 AM</th>
<th>12 Noon</th>
<th>1:00 PM</th>
<th>2:00 PM</th>
<th>3:00 PM</th>
<th>4:00 PM</th>
<th>5:00 PM</th>
<th>6:00 PM</th>
</tr>
</thead>
</table>
| FEV1 (liters) | 30mg | 100mg | 150mg | 60mg | 325mg | 100mg | 650mg | 60mg | * = nebulized beta agonist

* 29%

26%
Desensitization: NB
Intranasal Ketorolac and Oral Aspirin

Indications for ASA Desensitization

- Unacceptably high doses of systemic corticosteroids required for control of AERD
- Refractory rhinosinusitis mandating repeated polypectomies and sinus surgery procedures
- ASA/NSAID needed for cardiovascular or musculo-rheumatic condition

Lee RU, Stevenson DD. Allergy, Asthma & Immunology Research. 2011;3(1):3-10.
Studies Supporting Therapeutic Utility of Aspirin Desensitization Treatment


Aspirin Desensitization

172 patients desensitized to ASA, then treated with 1300 mg ASA daily

- 17 improved clinical course
- 24 failed to respond
- 16 discontinued due to side effects
- 115 dropped out

Aspirin Desensitization

126 patients desensitized to ASA, then treated with 1300 mg ASA daily for > 1 year

- 87%
- 13%

☐ improved clinical course
☐ failed to respond


The US Asthma Burden - Disparities

• In 2011, the asthma prevalence rate for African Americans was 47% higher than for Caucasians.
• 1 in 6 African American children have asthma.
• For African Americans, the rate of emergency department visits is 330% higher and the rate of hospitalizations is 220% higher compared to whites
• African Americans are three times more likely to die from asthma.
• Racial/ethnic differences in asthma prevalence, morbidity, and mortality are highly correlated with poverty, urban air quality, indoor allergens, and inadequate medical care.

www.aafa.org; accessed April 19, 2014
Montelukast vs Beclomethasone:
Distribution of Individual Responses for FEV₁

<table>
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<th>Change From Baseline in FEV₁, %</th>
<th>Percentage of Patients</th>
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<tbody>
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<td>&gt;80</td>
<td>30%</td>
</tr>
<tr>
<td>&gt;60 to 70</td>
<td>25%</td>
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<tr>
<td>&gt;40 to 50</td>
<td>20%</td>
</tr>
<tr>
<td>&gt;20 to 30</td>
<td>15%</td>
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<tr>
<td>&gt;10 to 20</td>
<td>10%</td>
</tr>
<tr>
<td>&gt;0 to 10</td>
<td>5%</td>
</tr>
<tr>
<td>&gt;–20 to –10</td>
<td>0%</td>
</tr>
<tr>
<td>&gt;–40 to –30</td>
<td>5%</td>
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Montelukast 10 mg qd (n=635)
Beclomethasone 168 mcg (4 puffs) bid* (n=625)

At the time of these studies, the approved daily dose of beclomethasone was 6 to 20 puffs or 252 to 840 mcg/d.

Asthma is More Common With Atopy, Atopy is More Common With Asthma

- NHANES III (1988-94)
- Allergy skin testing to 10 allergens administered to > 10,000 individuals 6-59 years old.

PAR = 29.3%

What's NEW?

The Asthma Syndrome
Symptoms of asthma, variable airflow obstruction

Asthma phenotype characteristics
Observable characteristic with no direct relationship to a disease process. Includes physiology, triggers, inflammatory parameters

Asthma Endotypes
Distinct disease entities which may be present in clusters of phenotypes, but each defined by a specific biological mechanism

Asthma Endotypes
Distinct disease entities which may be present in clusters of phenotypes, but each defined by a specific biological mechanism

Biomarker Analysis
- eNO
- Serum periostin
- Blood EOS
- Sputum EOS
- Serum IgE
- Skin +/or invitro testing
- Others...

High likelihood of salutary response

Non-responder

Personalized Care

• Heterogeneity of asthma leads to differential responses to treatment.
• Several studies imply that genetic factors and biomarkers -- perhaps in combination, can direct asthma pharmacotherapy.
Biologic Agents for Asthma

• Anti-IgE
  – Omalizumab

• Anti-IL5
  – Mepolizumab
  – Reslizumab
  – Benralizumab

• Anti-IL4/Anti-IL13
  – Tralokinumab
  – Dupilumab

• Others…
Omalizumab: Patient Selection

• Moderate-severe persistent asthma that is poorly or not well controlled on combination controller therapy.
• Positive skin or in vitro test to perennial aeroallergen.
• IgE level = 30-700 IU/ml.

Omalizumab: Anti-IgE

• RDBPC study, N = 850.
  – Omalizumab (IgE and Body Weight) vs placebo q 2 or 4 weeks.
• Inclusion criteria
  – Label criteria for omalizumab
  – Inadequately controlled asthma on high dose ICS/LABA.
• 25% relative rate of reduction in exacerbations.

Omalizumab: Anti-IgE

### Table 2: Protocol-Defined Asthma Exacerbations Over the 48-Week Treatment Period

<table>
<thead>
<tr>
<th>Analysis of Primary End Point</th>
<th>Omalizumab Group (n = 427)</th>
<th>Placebo Group (n = 421)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of protocol-defined asthma exacerbations, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>275 (64.4)</td>
<td>242 (57.5)</td>
</tr>
<tr>
<td>1</td>
<td>94 (22.0)</td>
<td>107 (25.4)</td>
</tr>
<tr>
<td>2</td>
<td>31 (7.3)</td>
<td>34 (8.1)</td>
</tr>
<tr>
<td>3</td>
<td>16 (3.7)</td>
<td>23 (5.5)</td>
</tr>
<tr>
<td>≥4</td>
<td>11 (2.6)</td>
<td>15 (3.6)</td>
</tr>
<tr>
<td>Rate of protocol-defined asthma exacerbations per patient</td>
<td>0.66</td>
<td>0.88</td>
</tr>
<tr>
<td>Incidence rate ratio (95% CI):</td>
<td>P value</td>
<td></td>
</tr>
<tr>
<td>0.75 (0.61-0.92)</td>
<td>0.006</td>
<td></td>
</tr>
</tbody>
</table>


### Biomarkers (High/Low) and Exacerbation Rates in Subjects Receiving Omalizumab

#### FeNO

- <19.5 ppb
- ≥19.5 ppb

#### Eosinophils

- <260 μL
- ≥280 μL

#### Periostin

- <50 ng/mL
- ≥50 ng/mL

Percent reduction in protocol-defined asthma exacerbation rate (mean, 95% CI)

- n = 193, P = 0.49
- n = 201, P = 0.001
- n = 383, P = 0.54
- n = 414, P = 0.009
- n = 279, P = 0.94
- n = 255, P = 0.87

Exacerbation rates

<table>
<thead>
<tr>
<th></th>
<th>Low FeNO at baseline</th>
<th>High FeNO at baseline</th>
<th>Low eosinophils at baseline</th>
<th>High eosinophils at baseline</th>
<th>Low periostin at baseline</th>
<th>High periostin at baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omalizumab</td>
<td>0.60</td>
<td>0.50</td>
<td>0.65</td>
<td>0.70</td>
<td>0.73</td>
<td>0.66</td>
</tr>
<tr>
<td>Placebo</td>
<td>0.71</td>
<td>1.07</td>
<td>0.72</td>
<td>1.03</td>
<td>0.72</td>
<td>0.93</td>
</tr>
</tbody>
</table>

Mepolizumab: Anti-IL5

- RDBPC study, N = 576.
  - Mepolizumab 100 mg SQ or 75 mg IV vs placebo q 4 weeks.
- Inclusion criteria
  - 2 exacerbations required oral steroid in past 12 months
  - EOS ≥ 150 at screening or ≥ 300 in past 12 months
- rate of exacerbations reduced 53% compared with placebo

Reslizumab: Anti-IL5

- Two duplicate RDBPC studies, N = 953.
  - IV reslizumab 3 mg/kg vs placebo q 4 weeks
- Inclusion criteria
  - 1 or more exacerbations required oral steroid in past 12 months
  - EOS ≥ 400 during screening and inadequately controlled asthma.
- Reduced exacerbations: Study 1: RR = 0.50; Study 2: RR = 0.41

Biomarker Analysis
• eNO
• Serum periostin
• Blood EOS
• Sputum EOS
• Serum IgE
• Skin +/- or invitro testing
• Others…

High likelihood of salutary response

Non-responder