World Allergy Forum Symposium: An Update on Severe Asthma

XXVII Congress of the European Academy of Allergology and Clinical Immunology
Monday, 9 June 2008
15.30 – 17.00

Barcelona International Convention Centre
Room 211/212
Barcelona, Spain

Moderators:
G. Walter Canonica, Italy
Roy Gerth van Wijk, The Netherlands

The TENOR Study – the epidemiology of severe asthma
Eugene Bleecker, United States

Severe asthma – determinants and treatment
Klaus Rabe, The Netherlands

Four years’ experience of omalizumab – efficacy and safety
William Storms, United States

The World Allergy Organization (WAO) is an international organization of 77 regional and national allergy and clinical immunology societies. WAO’s mission is to be a global resource and advocate in the field of allergy, advancing excellence in clinical care, education, research and training through a world-wide alliance of allergy and clinical immunology societies.

WAF is an educational program of the World Allergy Organization.
“An Update on Severe Asthma”

Program

Moderators:
G. Walter Canonica
Italy
Roy Gerth van Wijk
The Netherlands

1. Welcome to the World Allergy Forum Symposium and Introduction to “An Update on Severe Asthma”
   G. Walter Canonica and Roy Gerth van Wijk

2. The TENOR Study – the epidemiology of severe asthma
   Eugene Bleecker, United States

3. Severe asthma – determinants and treatment
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4. Four years’ experience of omalizumab – efficacy and safety
   William Storms, United States

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About the World Allergy Organization

World Allergy Organization (WAO)
The World Allergy Organization (WAO) is an international umbrella organization of 77 regional and national allergy and clinical immunology societies. By collaborating with member societies, WAO provides direct educational outreach programs, symposia and lectureships to WAO individual members around the globe.

The World Allergy Organization Mission
To be a global resource and advocate in the field of allergy, advancing excellence in clinical care through education, research and training as a world-wide alliance of allergy and clinical immunology societies.

Programs of the World Allergy Organization

GLORIA Global Resources in Allergy™
www.worldallergy.org/gloria
The GLORIA program promotes good practice in the management of allergic diseases through programs developed by panels of world experts. GLORIA educates medical professionals worldwide through regional and national presentations and local training initiatives. GLORIA educational modules promote the World Allergy Organization’s (WAO) mission – to optimize allergy care worldwide.

GLORIA Modules
Module 1: Allergic Rhinitis
Module 2: Allergic Conjunctivitis
Module 3: Allergic Emergencies
Module 4: Immunotherapy
Module 5: Treatment of Severe Asthma
Module 6: Food Allergy
Module 7: Angioedema
Module 8: Anaphylaxis
Module 9: Diagnosis of IgE Sensitization
Module 10: Chronic Rhinosinusitis and Nasal Polyposis
Module 11: Drug Allergy

World Allergy Forum (WAF)
www.worldallergy.org/waf
WAF symposia are held at major international allergy meetings. Developed by international expert advisory panels, the symposia provide up-to-the-minute presentations on scientific and clinical developments in the field of allergic disease.

Emerging Societies Program
www.worldallergy.org/esp
WAO offers advice on initiating and developing allergy societies throughout the world. This proactive initiative aims to expand and improve the specialty of allergy by supporting colleagues working in the field of allergy worldwide. Through sharing practical experiences and alerting new societies to the criteria required for WAO membership, ESM creates relationships with future World Allergy Organization member societies, and educates WAO’s leadership about the challenges and opportunities faced by colleagues in developing countries.

WAO Seminars & Conferences
www.worldallergy.org/sc
The Seminars & Conferences program invites member societies to apply to host a WAO Invited Lecturer. Complementing WAO’s existing programs, Seminars & Conferences gives Member Societies the opportunity to bid for an international speaker to give a plenary lecture in the scientific program of the Society’s annual meeting, on a topic of the Society’s choice.

World Allergy Organization Journal
www.waojournal.org
World Allergy Organization Journal is the official publication of the World Allergy Organization. An international online-only journal, World Allergy Organization Journal underscores WAO’s commitment to raising awareness and advancing excellence in clinical care, education, research and training in the field of allergy.
**WAO Member Societies**

Albanian Society of Allergology and Clinical Immunology  
American Academy of Allergy, Asthma and Immunology  
American College of Allergy, Asthma and Immunology  
Argentine Association of Allergy and Immunology  
Argentine Society of Allergy and Immunopathology  
Australasian Society of Clinical Immunology and Allergy  
Austrian Society of Allergology and Immunology  
Azerbaijan Society for Asthma, Allergy and Clinical Immunology  
Bangladesh Society of Allergy and Immunology  
Belgian Society of Allergology and Immunology  
Brazilian Society of Allergy and Immunopathology  
British Society for Allergy and Clinical Immunology  
Bulgarian National Society of Allergology  
Canadian Society of Allergy and Clinical Immunology  
Chilean Society of Allergy and Immunology  
China Allergology Society and Chinese Allergists  
(Chinese) Hong Kong Institute of Allergy  
Colombian Allergy, Asthma, and Immunology Association  
Croatian Society of Allergology and Clinical Immunology  
Cuban Society of Allergology  
Czech Society of Allergology and Clinical Immunology  
Danish Society for Allergology  
Egyptian Society of Allergy and Clinical Immunology  
Egyptian Society of Pediatric Allergy and Immunology  
Finnish Society of Allergology and Clinical Immunology  
French Society of Allergology and Clinical Immunology  
Georgian Association of Allergology and Clinical Immunology  
German Society for Allergology and Clinical Immunology  
Hellenic Society of Allergology and Clinical Immunology  
Hungarian Society of Allergology and Clinical Immunology  
Icelandic Society of Allergy and Immunology  
Indian College of Allergy, Asthma and Applied Immunology  
Indonesian Society for Allergy and Immunology  
Israel Association of Allergy and Clinical Immunology  
Italian Association of Territorial and Hospital Allergists  
Italian Society for Allergology and Clinical Immunology  
Japanese Society of Allergology  
Korean Academy of Allergy, Asthma and Clinical Immunology  
Latvian Association of Allergists  
Lebanese Society of Allergy and Immunology  
Malaysian Society of Allergy and Immunology  
Mexican College of Allergy, Asthma and Clinical Immunology  
Mexican College of Pediatricians Specialized in Allergy and Clinical Immunology  
Mongolian Society of Allergology  
Netherlands Society of Allergology  
Norwegian Society of Allergology and Immunopathology  
Panamanian Association of Allergology and Clinical Immunology  
Paraguayan Society of Immunology and Allergy  
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Philippine Society of Allergy, Asthma and Immunology  
Polish Society of Allergology  
Portuguese Society of Allergology and Clinical Immunology  
Romanian Society of Allergology and Clinical Immunology  
Russian Association of Allergology and Clinical Immunology  
Association of Allergy and Clinical Immunology for Serbia and Montenegro  
Singapore Society of Immunology, Allergy & Rheumatology  
Allergy Society of South Africa  
Spanish Society of Allergology and Clinical Immunology  
Swiss Society of Allergology and Immunology  
Allergy and Immunology Society of Thailand  
Turkish National Society of Allergy and Clinical Immunology  
Ukrainian Association of Allergologists and Clinical Immunologists  
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Ecuadorian Society of Allergology and Affiliated Sciences  
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Slovenian Association for Allergology and Clinical Immunology  
Allergy & Immunology Society of Sri Lanka  
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Commonwealth of Independent States (CIS Society)  
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**Affiliate Organizations**

International Association of Asthmology

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Web site: www.worldallergy.org
Dear Colleagues,

World Allergy Forum has been honored to be part of the EAACI program for many years, and it is a great pleasure to bring the 32nd World Allergy Forum symposium to the 2008 EAACI Congress, and to the beautiful city of Barcelona!

Our symposium today is an update on severe asthma; severe asthma is debilitating and frightening for patients, and one of the major management challenges for allergists and pulmonologists. While our understanding of the immunopathology of asthma has increased greatly over the years, until recently new treatment guidelines were able to offer little in the way of advances in the pharmacotherapy of asthma, other than revised recommendations for the use of long-available treatments.

Eugene Bleecker will open today’s program by reporting on the US study into the Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR). We will hear the results of this 3-year, multicenter, observational study of more than 4700 patients, aged 6 years or older, with severe or difficult-to-treat asthma. Klaus Rabe will then discuss determinants and treatment of severe asthma. Concluding the symposium, William Storms will report on over four years of experience with anti-IgE therapy in the treatment of chronic severe asthma. Information will be presented about the safety and efficacy of the most recently introduced therapy for difficult-to-treat allergic asthma. We will hear that in clinical practice, although patients reported improvements in all asthma parameters, this was not reflected by any change in FEV1, a primary endpoint of so many research studies into asthma treatment efficacy.

We look forward to leading discussion with you on these exciting presentations!

With best regards,

G. Walter Canonica
President
World Allergy Organization

Roy Gerth Van Wijk
President
European Academy of Allergology and Clinical Immunology
The Epidemiology of Severe Asthma: The TENOR Study and SARP (NIH)

Eugene R. Bleecker, MD
Thomas H. Davis Professor of Pulmonary Medicine
Section Head, Pulmonary, Critical Care, Allergy and Immunologic Diseases
Co-Director, Center for Human Genomics
Winston-Salem, NC
USA

“Severe Asthma” consists of up to 20% of asthma patients who have frequent and severe symptoms despite aggressive therapy with anti-inflammatory as well as other controller medications. They often have fixed and progressive reductions in pulmonary function that do not reverse completely either after intense acute or long-term therapy. These abnormalities in lung function may reflect structural changes in the airways that have been classified as “airway remodeling”. The varied clinical patterns found in severe asthma may reflect genetic differences that regulate bronchial inflammation and interact with environmental stimuli resulting in the characteristic pathophysiologic abnormalities as well as propensity to airway remodeling. In addition, pharmacogenetic responses may alter expected therapeutic responses and influence asthma severity. Thus, it is important to understand and characterize the clinical and inflammatory phenotypes in patients with severe asthma. Specific disease patterns may emerge during this comprehensive phenotype evaluation (including biomarkers), which would allow us to better understand the pathogenesis, development and treatment of more severe asthma.

The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimes (TENOR) study was a two to three year multi-center observational cohort study of asthmatics described as “difficult to treat” by their physicians, sponsored by Genentech and Novartis. It was not a clinical trial but rather a longitudinal cohort study of 4,756 patients (15% African American, 6.4% Hispanic, and 1.5% Asian or Pacific Islanders) with asthma, aged 6 or older, from 283 clinical centers including managed care, HMO, community and academic centers. Subjects were included if they had physician-characterized difficult-to-treat asthma, and met additional criteria based on frequency of urgent care visits and/or the use of multiple controller medications. In this group of asthmatics, 44.6% met the NHLBI National Asthma Education and Prevention Program (NAEPP) expert panel guidelines for severe persistent asthma, 27.5% for moderate persistent asthma, and 27.8% for mild persistent asthma. All subjects were evaluated initially with comprehensive questionnaires and laboratory testing, and were seen every 6 months during the remaining 2-3 years of the study. Detailed phenotypic information collected includes information on asthma exacerbations, medication use, urgent care visits, quality of life, pulmonary function tests (spirometry with reversibility), total serum IgE levels and history of allergies. Difficult-to-treat or severe asthma is common, representing a significant subset of asthmatics, estimated at 20% of patients with asthma. In addition, these severe asthmatics use disproportionately more healthcare resources.

The NIH (NHLBI) Severe Asthma Research Program (SARP) has characterized over 1000 asthmatics of varying severity (and ~200 normal controls), including over 400 subjects with severe asthma. All subjects underwent detailed clinical, physiologic, inflammatory and in a subset, radiologic phenotyping. In addition, DNA from all SARP subjects is being genotyped using the Illumina 1 million SNP chip for Genome Wide Associations Studies (GWAS) analysis as part of the NHLBI funded STAMPEED project. Investigative bronchoscopies are routinely performed as part of each of the independent SARP research projects.

While the NAEPP expert panel guidelines represent an important approach to classify asthma severity, the guidelines have well recognized problems which limit their use in clinical practice and clinical research. For example, the need to classify severity of patients when they are “off” medications is both impractical and, for the severe of difficult-to-treat asthmatic, can be dangerous. In addition, clinical investigators have recognized that asthmatics labeled “severe” can be characterized by several different clinical patterns of disease expression. In some patients, frequent and severe symptoms occur despite aggressive therapy with anti-inflammatory as well as other controller medications. Other patients with asthma have fixed and progressive reductions in pulmonary function that do not reverse completely either after intense acute or long-term therapy. These abnormalities in lung function may reflect structural changes in the airways that have been classified as “airway remodeling”.

The varied clinical patterns found in difficult-to-treat and severe asthma almost certainly reflect genetic differences interacting with environmental factors that regulate bronchial inflammation resulting in characteristic pathophysiology abnormalities, the propensity for airway remodeling, and different responses to asthma controller therapy. Pharmacogenetic responses may be particularly important in these patients since the more difficult-to-treat asthma patients may not respond as well to controller therapies as do other asthmatics. Thus, it is important to carefully define and characterize the phenotypic characteristics of difficult-to-treat and severe asthma in large population samples throughout the world.
The Epidemiology of Severe Asthma: The TENOR Study and SARP (NIH)

References


Wenzel SE, Schwartz LB, Langmack EI, Halliday JJ, Trudeau JB, Gibbs RL, Chu HW. Evidence that severe asthma can be divided pathologically into two inflammatory subtypes with distinct physiologic and clinical characteristics. AMJ Respir Crit Care Med 1999; 160:1001-1008.

The Epidemiology of Severe Asthma:
The TENOR Study and SARP (NIH)

Professor Eugene R. Bleecker
Thomas H. Davis Professor of Medicine
Head, Pulmonary, Critical Care, Allergy & Immunologic Diseases
Co-Director, Center for Human Genomics
Winston-Salem, NC
USA

Severe Asthma

• Asthma is a heterogeneous disease with related clinical phenotypes

• Severe asthma represents 20% of total asthma population and is difficult to treat with high levels of morbidity, mortality and health care costs

Severe Asthma

• While progress has been made in understanding the pathogenesis of severe asthma, our understanding of the complexity and heterogeneity of this disorder remains limited
What is Severe Asthma: A Tale of Two “Studies”?  

• The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimes (TENOR)

• Severe Asthma Research Program (SARP), NHLBI

TENOR Study Design

• 3-year, multi-center, observational study  
  - Patients continued to receive medications and treatments administered for their asthma as indicated by their physician  
• 4,756 patients enrolled between January and October 2001  
  - aged 6 years or older  
  - 283 sites across the US

Objectives

• Primary objective  
  - Describe natural history of patients considered by physicians to have “severe” or “difficult-to-treat” asthma  
• Secondary objectives  
  - Examine relationship between features of asthma, treatments, and outcomes  
  - Observe frequency of comorbid conditions  
  - Examine the relationship between IgE and disease

IgE=Immunoglobulin E
Inclusion Criteria

• Physician assessed severe or difficult-to-treat asthma
  - Patients with mild or moderate asthma eligible if considered difficult-to-treat by their physician and met the other inclusion criteria
• Received care from their current physician/provider for at least 1 year
• Be at least 6 years old
• Be able to read and understand English

Inclusion Criteria (cont’d)

• In addition, subjects had to meet at least one of the following criteria:
  - During the past 12 months, 2 or more unscheduled care visits for their asthma
  - During the past 12 months, 2 or more oral steroid “bursts”
  - Currently require chronic daily high doses of ICS or ≥5 mg oral prednisone
  - Currently using ≥3 medications to control asthma

Exclusion Criteria

• Subjects with ANY of the following criteria were excluded:
  - Heavy smoker (≥30 pack-years)
  - Primary diagnosis of cystic fibrosis
  - Severe cardiovascular disease (NYHA class II or greater)
  - Cancer (not including non-melanoma skin cancer or subjects whose cancer has been “clear” for >5 years)
  - Severe psychiatric disorder (not including anxiety or depression)
  - Significant systemic disease (<2 to 3 year life expectancy)
  - Known drug abuser
Baseline Demographics

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>&lt;18 Years</th>
<th>13-17 Years</th>
<th>6-12 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrollment (n)</td>
<td>4756</td>
<td>3499</td>
<td>497</td>
<td>770</td>
</tr>
<tr>
<td>Age (years, mean)</td>
<td>39 (±21)</td>
<td>49 (±15)</td>
<td>15 (±11)</td>
<td>19 (±22)</td>
</tr>
<tr>
<td>Weight (kg, mean)</td>
<td>75 (±27)</td>
<td>84 (±22)</td>
<td>67 (±21)</td>
<td>41 (±17)</td>
</tr>
<tr>
<td>BMI (kg/m², mean)</td>
<td>28 (±9)</td>
<td>30 (±8)</td>
<td>25 (±10)</td>
<td>21 (±8)</td>
</tr>
<tr>
<td>Gender (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>62</td>
<td>71</td>
<td>43</td>
<td>34</td>
</tr>
<tr>
<td>Male</td>
<td>38</td>
<td>28</td>
<td>57</td>
<td>67</td>
</tr>
<tr>
<td>Race/Ethnicity (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>75</td>
<td>80</td>
<td>65</td>
<td>60</td>
</tr>
<tr>
<td>Black</td>
<td>15</td>
<td>12</td>
<td>23</td>
<td>25</td>
</tr>
<tr>
<td>Hispanic</td>
<td>6</td>
<td>6</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Asian or Pacific Islander</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>4</td>
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</table>

Baseline Demographics (cont'd)

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>&lt;18 Years</th>
<th>13-17 Years</th>
<th>6-12 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>MD assessment of severity (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Moderate</td>
<td>48</td>
<td>46</td>
<td>48</td>
<td>59</td>
</tr>
<tr>
<td>Severe</td>
<td>48</td>
<td>51</td>
<td>48</td>
<td>36</td>
</tr>
<tr>
<td>Ever smoked (%)</td>
<td>24</td>
<td>32</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Clinical measures</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>IgE (IU/mL, mean)</td>
<td>106.6</td>
<td>85.2</td>
<td>223.8</td>
<td>182.5</td>
</tr>
<tr>
<td>FEV₁ (% predicted pre-bronch)</td>
<td>580</td>
<td>28</td>
<td>16</td>
<td>8</td>
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<tr>
<td>&gt;60-&lt;80%</td>
<td>30</td>
<td>32</td>
<td>24</td>
<td>26</td>
</tr>
<tr>
<td>≥80%</td>
<td>47</td>
<td>41</td>
<td>61</td>
<td>66</td>
</tr>
</tbody>
</table>

Asthma Severity in TENOR Patients

![Asthma Severity Graph]

- 6-12 (n=766)
- 13-17 (n=495)
- ≥18 (n=3,455)
- Overall (n=4,756)
Majority of TENOR Patients Identified as Difficult-to-Treat

- Difficult-to-treat: 37%, 38%
- Multiple drugs required: 65%, 66%
- Frequent exacerbations: 42%, 43%
- Severe exacerbations: 32%, 33%
- Unable to avoid triggers: 24%, 25%
- Complex medication regimen: 15%, 16%

Long-Term Controller Use by Age

- 6-12 yrs (n=770)
  - High-dose ICS: 89%
  - Long-term ICS: 54%
- 13 yrs (n=3,986)
  - High-dose ICS: 26%
  - Long-term ICS: 74%
- Overall (n=4,756)
  - High-dose ICS: 68%
  - Long-term ICS: 62%

HCU and Missed Work/School Days by Asthma Severity

- Steroid burst in past 3 months: 57%
- Unscheduled office visit in past 3 months: 56%
- ER visit in past 3 months: 31%
- Missed ≥1 day school or work in past 2 weeks: 19%
- Ever intubated: 17%
- Hospitalization in past 3 months: 0%

*P ≤ 0.05
Demographic and clinical characteristics of children and adolescents with severe or difficult-to-treat asthma

Baseline characteristics, male patients

<table>
<thead>
<tr>
<th>Age group, years</th>
<th>6-8</th>
<th>9-11</th>
<th>12-14</th>
<th>15-17</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients, n (%)</td>
<td>145</td>
<td>382</td>
<td>240</td>
<td>124</td>
<td></td>
</tr>
<tr>
<td>Race/Ethnicity, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>87 (60)</td>
<td>165 (59)</td>
<td>141 (59)</td>
<td>70 (51)</td>
<td>NS</td>
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<tr>
<td>Black</td>
<td>38 (26)</td>
<td>70 (25)</td>
<td>69 (29)</td>
<td>31 (23)</td>
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<tr>
<td>Hispanic</td>
<td>9 (6)</td>
<td>31 (11)</td>
<td>16 (7)</td>
<td>11 (8)</td>
<td></td>
</tr>
<tr>
<td>Asian/PI</td>
<td>3 (2)</td>
<td>3 (1)</td>
<td>3 (1)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>6 (5)</td>
<td>13 (5)</td>
<td>11 (8)</td>
<td>5 (4)</td>
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<tr>
<td>Body mass index, mean ±SD (kg/m²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Mild</td>
<td>16.9±7.4</td>
<td>20.6±5.4</td>
<td>23.6±4.4</td>
<td>25.8±7.1</td>
<td>&lt; .001</td>
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<tr>
<td>Moderate</td>
<td>18 (6)</td>
<td>17 (6)</td>
<td>17 (6)</td>
<td>17 (6)</td>
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<tr>
<td>Severe</td>
<td>44 (46)</td>
<td>44 (46)</td>
<td>44 (46)</td>
<td>44 (46)</td>
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<td>Physiologist specialty, n (%)</td>
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<tr>
<td>Pulmonologist</td>
<td>19 (5)</td>
<td>18 (5)</td>
<td>16 (5)</td>
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<tr>
<td>Allergist</td>
<td>20 (6)</td>
<td>20 (6)</td>
<td>20 (6)</td>
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Baseline characteristics, female patients

<table>
<thead>
<tr>
<th>Age group, years</th>
<th>8-8</th>
<th>9-11</th>
<th>12-14</th>
<th>15-17</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients, n (%)</td>
<td>86</td>
<td>130</td>
<td>171</td>
<td>91</td>
<td></td>
</tr>
<tr>
<td>Race/Ethnicity, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt; .0001</td>
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<tr>
<td>White</td>
<td>62 (70)</td>
<td>60 (57)</td>
<td>115 (67)</td>
<td>72 (80)</td>
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<td>33 (27)</td>
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<td>11 (12)</td>
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<tr>
<td>Hispanic</td>
<td>7 (8)</td>
<td>17 (14)</td>
<td>17 (14)</td>
<td>17 (14)</td>
<td></td>
</tr>
<tr>
<td>Asian/PI</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>3 (2)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1 (1)</td>
<td>4 (3)</td>
<td>2 (1)</td>
<td>4 (4)</td>
<td></td>
</tr>
<tr>
<td>Body mass index, mean ±SD (kg/m²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Mild</td>
<td>19±5.2</td>
<td>21±5.8</td>
<td>24±7.1</td>
<td>26±7.6</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Moderate</td>
<td>4 (5)</td>
<td>4 (5)</td>
<td>9 (5)</td>
<td>2 (2)</td>
<td>NS</td>
</tr>
<tr>
<td>Severe</td>
<td>55 (63)</td>
<td>71 (58)</td>
<td>90 (63)</td>
<td>42 (46)</td>
<td></td>
</tr>
<tr>
<td>Physiologist specialty, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonologist</td>
<td>51 (60)</td>
<td>80 (68)</td>
<td>109 (64)</td>
<td>45 (51)</td>
<td>NS</td>
</tr>
<tr>
<td>Allergist</td>
<td>34 (40)</td>
<td>37 (32)</td>
<td>60 (35)</td>
<td>44 (49)</td>
<td></td>
</tr>
</tbody>
</table>

*White vs. non-White. NS, not significant.

Spirometry by Age and Gender
**Healthcare Utilization by Long-Term Controller Use, Ages 6-11 & 12-17**

**Medication Use by Age**

**Conclusions**

- TENOR is an important database for understanding severe or difficult-to-treat asthma in young patients.
- TENOR data lend support to potential adverse effect of inhaled corticosteroids on growth in young asthma patients.
  - Such concerns about growth delays in children associated with long-term ICS therapy have often been cited as a major factor in non-adherence to asthma guidelines.
- TENOR data support current literature showing association between childhood obesity and asthma.
- Decline in lung function with age is consistent with data from other cohorts of children with asthma followed longitudinally.
  - Evidence suggests that rate of decline is faster in children with airway hyperresponsiveness (AHR) compared to those without AHR.
  - FEV1/FVC ratio falls with increasing duration of severe asthma in children.
Association of control and risk of severe asthma-related events in severe or difficult-to-treat asthma patients


Methods

• Asthma Therapy Assessment Questionnaire (ATAQ)
  • Measures patient-perceived asthma control and symptoms
    - Scores range from 0 (no control problems) to 4 (maximum number of control problems)
• Acute healthcare utilization (HCU) events in previous 3 months
  - Unscheduled office visits/contacts, oral steroid bursts, emergency department visits, overnight hospitalizations
• Relative risks (RRs) of HCU associated with asthma control problems calculated using Poisson regression

Adjusted* Results

Risk of asthma-related healthcare utilization by barrier group based on Poisson regression analysis in the TENOR cohort

*Adjusted for age, gender, obesity, education, physician-assessed severity, number of controller medications, and number of asthma control problems
Conclusions

- The TENOR study provides unique opportunity to evaluate the relationship between baseline levels of asthma control and future clinical events in a large cohort of severe asthma patients.
- The relationship between worse asthma control and higher risk of events was evident regardless of race or gender differences, even after controlling for various clinical and demographic covariates.
- ATAQ is an easy-to-use clinical tool which can be used to identify patients who are at risk of future asthma-related clinical events.

Total serum IgE levels in a large cohort of patients with severe or difficult-to-treat asthma


IgE by Gender and Age in TENOR

(P<0.001 for children (6-12 years) and adolescents (13-17 years) vs adults (18+ years); P<0.05 for males vs females across all of the 5-year age groups.)
IgE by Race and Gender

<table>
<thead>
<tr>
<th>Race/Male/Female/Overall</th>
<th>Geometric mean IgE levels (IU/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White (n=3,384)</td>
<td>Males: 192, Females: 77, Overall: 127</td>
</tr>
<tr>
<td>Black (n=681)</td>
<td>Males: 180, Females: 120, Overall: 147</td>
</tr>
<tr>
<td>Hispanic (n=290)</td>
<td>Males: 122, Females: 154, Overall: 144</td>
</tr>
<tr>
<td>Asian/Pacific Islander (n=66)</td>
<td>Males: 213, Females: 234, Overall: 224</td>
</tr>
<tr>
<td>Other (n=87)</td>
<td>Males: 144, Females: 90, Overall: 127</td>
</tr>
</tbody>
</table>

*P<0.001 compared with White patients

IgE by Smoking History and Gender in Adult Subjects

<table>
<thead>
<tr>
<th>Smoking History/Male/Female/Overall</th>
<th>Geometric mean IgE levels (IU/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never smoked (n=2,105)</td>
<td>Males: 128, Females: 70, Overall: 83*</td>
</tr>
<tr>
<td>Past smoker (n=1,066)</td>
<td>Males: 136, Females: 67, Overall: 83*</td>
</tr>
<tr>
<td>Current smoker (n=138)</td>
<td>Males: 119, Females: 161, Overall: 161</td>
</tr>
</tbody>
</table>

*P<0.001 compared with current smokers

IgE by Age and Physician-Evaluated Asthma Severity

<table>
<thead>
<tr>
<th>Age/Mild/Moderate/Severe</th>
<th>Geometric mean IgE levels (IU/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children (n=253)</td>
<td>Males: 138, Females: 146, Severe: 280*</td>
</tr>
<tr>
<td>Adolescents (n=228)</td>
<td>Males: 108, Females: 224, Moderate: 238</td>
</tr>
<tr>
<td>Adults (n=1,600)</td>
<td>Males: 84, Females: 82, Severe: 88</td>
</tr>
</tbody>
</table>

*P<0.001 vs children with mild or moderate disease
Conclusions

- TENOR is largest observational study of patients with severe or difficult-to-treat asthma with measured IgE levels
- IgE levels in TENOR patients are elevated compared with non-asthmatic populations
- Decrease across age groups
  - Higher in males than females
- Higher in current smokers
  - Consistent across race and gender
- Association between IgE and severity among children

Risk factors associated with persistent airflow limitation in severe or difficult-to-treat asthma


Results: 1,017 Patients Included

![Graph showing 60% PAFL vs 40% NPAFL]
Asthma Control by PAFL Status

Factors Independently Associated With Persistent Airflow Limitation

Conclusions

• Previous studies of PAFL in severe asthma patients are few and small in size
  - TENOR study allowed for multivariate and subgroup analyses
• PAFL may affect a relatively well-defined subset of asthmatics
• The etiology of PAFL (and asthma) may comprise 2 distinct phenotypes
  - PAFL: less allergic, with more severely obstructed asthma, and characterized by older age and a longer duration of asthma
  - NPAFL: more allergic with poorly controlled asthma
Conclusions

• TENOR confirms the impact of severe and difficult-to-treat asthma on patients and the healthcare system.
• There is a high rate of healthcare utilization among this population, most notably patients requiring hospitalization or ER care in the past 3 months, as well as the high number of patients with a history of intubation.
• Despite being on multiple standard-of-care medications, the TENOR cohort reported high rates of healthcare utilization.
  - Unmet medical need for new therapeutic approaches.

Unmet Needs in Asthma Treatment

• Optimal treatment needs to:
  - Effectively control symptoms and pathogenesis of allergic disease
  - Reduce the incidence of exacerbations and hospitalizations
  - Enhance health status (QoL)
  - Improve patient adherence

What is Severe Asthma: A Tale of Two “Studies”?

• The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimes (TENOR)

• Severe Asthma Research Program (SARP), NHLBI
Severe Asthma Research Program

- NHLBI funded 5-year program to investigate the pathobiology of severe asthma.

- Eight individual R01 awards
  
  Brigham and Women's Hospital  Elliot Israel, M.D.
  Imperial College, London  K. Fan Chung, M.D.
  National Jewish Center  Sally E. Wenzel, M.D.
  University of Texas-Galveston  William J. Calhoun, M.D.
  Cleveland Clinic  Serpil C. Erzurum, M.D.
  Emory University  W. Gerald Teague, M.D.
  University of Virginia  B. Gaston, M.D.
  University of Wisconsin  William W. Busse, M.D.
  Wake Forest University  Eugene R. Bleecker, M.D.
  Washington University  Mario Castro, M.D.

SARP Goals

- Identify and characterize a large number of subjects with severe asthma and differentiate this group from subjects with less severe disease.

- Collaboration of all sites to achieve this goal through sharing of data without compromising individual projects.

Subject Characterization

- Staff administered questionnaires
- Phlebotomy for DNA, serum IgE, blood eosinophils
- Atopy skin testing
- Pulmonary function assessment
  - Bronchodilator reversibility
  - Airway hyperresponsiveness to methacholine
- Collection of noninvasive biomarkers
  - Exhaled nitric oxide
  - Exhaled breath condensate
  - Hypertonic sputum induction
- Investigative bronchoscopy
  - Bronchoalveolar lavage
  - Endobronchial brushings and biopsies

Moore et al. JACI 2007; 119:405-13
American Thoracic Society Workshop
Definition of Severe/Refractory Asthma

Major Characteristics (need at least 1):
• Treatment with continuous or near continuous (≥ 50% of year) oral corticosteroids
• Treatment with high-dose inhaled corticosteroids (ICS)

Minor Criteria (need at least 2):
• Daily treatment with an additional controller medication
• Short-acting beta-agonist on a daily or near-daily basis
• Persistent airway obstruction (FEV1 < 80% predicted)
• ≥ 1 urgent care visits for asthma per year
• ≥ 3 oral steroid “bursts” per year
• Prompt deterioration with ≥ 25% reduction in oral or ICS
• Near-fatal asthma event in the past

Classification of Not-Severe Subjects

• Significant heterogeneity within the group led to application of post hoc definitions of mild and moderate asthma.
• Classification based on medication use and baseline pulmonary function

<table>
<thead>
<tr>
<th>Baseline Lung function</th>
<th>ICS</th>
<th>Corresponding NAEP class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>FEV1 ≥ 80%</td>
<td>None or Low-moderate dose</td>
</tr>
<tr>
<td>Moderate</td>
<td>FEV1 &lt; 80%</td>
<td>Low-moderate dose</td>
</tr>
</tbody>
</table>

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Total Minor Criteria per Subject
Frequency of ATS Workshop Criteria

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Mild (n=164)</th>
<th>Moderate (n=70)</th>
<th>Severe (n=204)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major Criteria</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Oral corticosteroids (OCS)</td>
<td>0.6%</td>
<td>0%</td>
<td>32%</td>
<td>&lt;0.0001†</td>
</tr>
<tr>
<td>2. High dose ICS</td>
<td>0%</td>
<td>0%</td>
<td>98%</td>
<td>&lt;0.0001†</td>
</tr>
<tr>
<td><strong>Minor Criteria</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Daily 2nd controller medication</td>
<td>38%</td>
<td>79%</td>
<td>89%</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>2. Daily SABA for symptoms</td>
<td>27%</td>
<td>44%</td>
<td>75%</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>3. Persistent airflow obstruction</td>
<td>0%</td>
<td>100%</td>
<td>77%</td>
<td>&lt;0.0001†</td>
</tr>
<tr>
<td>4. ≥ 1 urgent care visit/year</td>
<td>16%</td>
<td>31%</td>
<td>54%</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>5. ≥ 3 OCS bursts/year</td>
<td>5%</td>
<td>13%</td>
<td>54%</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>6. Deterioration with reduced CS</td>
<td>32%</td>
<td>60%</td>
<td>78%</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>7. Near Fatal Event</td>
<td>4%</td>
<td>6%</td>
<td>23%</td>
<td>&lt;0.0001†</td>
</tr>
</tbody>
</table>

* all groups differ, † severe group differs from others, ‡ mild group differs from others

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Subject Characteristics

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Mild (n=164)</th>
<th>Moderate (n=70)</th>
<th>Severe (n=204)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current Age (yrs)</td>
<td>31 ± 12</td>
<td>38 ± 12</td>
<td>41 ± 13</td>
<td>&lt;0.0001†</td>
</tr>
<tr>
<td>Age of asthma onset (yrs)</td>
<td>15 ± 13</td>
<td>18 ± 15</td>
<td>16 ± 16</td>
<td>NS</td>
</tr>
<tr>
<td>Asthma duration (yrs)</td>
<td>17 ± 11</td>
<td>20 ± 14</td>
<td>25 ± 14</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Gender (% females)</td>
<td>72%</td>
<td>56%</td>
<td>64%</td>
<td>NS</td>
</tr>
<tr>
<td>Race (% Caucasian)</td>
<td>69%</td>
<td>66%</td>
<td>67%</td>
<td>NS</td>
</tr>
</tbody>
</table>

Asthma Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mild (n=164)</th>
<th>Moderate (n=70)</th>
<th>Severe (n=204)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICS</td>
<td>58%</td>
<td>100%</td>
<td>97%</td>
<td>&lt;0.0001†</td>
</tr>
<tr>
<td>LABA</td>
<td>48%</td>
<td>80%</td>
<td>89%</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Leukotriene modifier</td>
<td>22%</td>
<td>26%</td>
<td>51%</td>
<td>&lt;0.0001†</td>
</tr>
<tr>
<td>Omalizumab</td>
<td>0.1%</td>
<td>0%</td>
<td>12%</td>
<td>&lt;0.0001†</td>
</tr>
<tr>
<td>Theophyllines</td>
<td>0%</td>
<td>4%</td>
<td>18%</td>
<td>&lt;0.0001†</td>
</tr>
<tr>
<td>Anti-cholinergics</td>
<td>4%</td>
<td>6%</td>
<td>26%</td>
<td>&lt;0.0001†</td>
</tr>
</tbody>
</table>

* all groups differ, † severe group differs from others, ‡ mild group differs from others

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Daily Asthma Symptoms

* all groups differ, † severe group differs from others

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**Health Care Utilization**

![Health Care Utilization Diagram](image1)

* * all groups differ, † severe group differs from others

Moore et al. JACI 2007; 119:405-13

---

**Physiology and Biomarkers**

<table>
<thead>
<tr>
<th></th>
<th>Mild (n=164)</th>
<th>Moderate (n=70)</th>
<th>Severe (n=204)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline Lung Function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV1 % predicted</td>
<td>94 ± 11</td>
<td>66 ± 11</td>
<td>62 ± 22</td>
<td>&lt;0.0001†</td>
</tr>
<tr>
<td>FVC % predicted</td>
<td>100 ± 12</td>
<td>81 ± 13</td>
<td>77 ± 20</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>FEV1/FVC %</td>
<td>80 ± 7</td>
<td>67 ± 10</td>
<td>65 ± 13</td>
<td>&lt;0.0001†</td>
</tr>
<tr>
<td><strong>Best Lung Function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV1 % predicted</td>
<td>102 ± 11</td>
<td>79 ± 12</td>
<td>77 ± 21</td>
<td>&lt;0.0001†</td>
</tr>
<tr>
<td>FVC % predicted</td>
<td>103 ± 13</td>
<td>91 ± 14</td>
<td>91 ± 18</td>
<td>&lt;0.0001†</td>
</tr>
<tr>
<td>Max % change in FEV1</td>
<td>9 ± 7</td>
<td>20 ± 15</td>
<td>20 ± 24</td>
<td>&lt;0.0001†</td>
</tr>
<tr>
<td>PC20 Methacholine (log)</td>
<td>.24 ± .82</td>
<td>-.11 ± .54</td>
<td>-.06 ± .70</td>
<td>.0002‡</td>
</tr>
<tr>
<td>Blood eosinophils (log)</td>
<td>-.72 ± .42</td>
<td>-.63 ± .46</td>
<td>-.75 ± .51</td>
<td>NS</td>
</tr>
<tr>
<td>Serum IgE (log)</td>
<td>2.0 ± .75</td>
<td>2.1 ± .83</td>
<td>2.0 ± .76</td>
<td>NS</td>
</tr>
<tr>
<td>≥ 1 positive skin test (%)</td>
<td>85%</td>
<td>87%</td>
<td>71%</td>
<td>0.0007†</td>
</tr>
</tbody>
</table>

* * all groups differ, † severe group differs from others, ‡ mild group differs from others

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---

**Exhaled NO**

![Exhaled NO Graph](image2)

Mild, n=120; Moderate, n=55; Severe, n=135

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# Co-morbidities

<table>
<thead>
<tr>
<th></th>
<th>Mild (n=164)</th>
<th>Moderate (n=70)</th>
<th>Severe (n=204)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remote Smoking</td>
<td>12%</td>
<td>19%</td>
<td>18%</td>
<td>NS</td>
</tr>
<tr>
<td>(&lt;5 pk yrs)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms with Menses</td>
<td>12%</td>
<td>8%</td>
<td>29%</td>
<td>&lt;0.0001†</td>
</tr>
<tr>
<td>Aspirin Sensitivity</td>
<td>7%</td>
<td>13%</td>
<td>16%</td>
<td>0.01‡</td>
</tr>
<tr>
<td>Gastroesophageal Reflux symptoms</td>
<td>16%</td>
<td>12%</td>
<td>41%</td>
<td>&lt;0.0001†</td>
</tr>
<tr>
<td>History of Sinusitis</td>
<td>37%</td>
<td>33%</td>
<td>54%</td>
<td>0.0001†</td>
</tr>
<tr>
<td>History of Pneumonia</td>
<td>36%</td>
<td>35%</td>
<td>63%</td>
<td>&lt;0.0001†</td>
</tr>
</tbody>
</table>

* all groups differ, † severe group differs from others, ‡ mild group differs from others

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# Risk factors for severe disease

- The strongest single predictors
  - FEV1 % predicted; 36% increase in risk for every 5% fall in FEV1 (P<0.0001)

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
<th>CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of pneumonia</td>
<td>3.30</td>
<td>1.92-5.69</td>
<td>p=0.0001</td>
</tr>
<tr>
<td>Lower number blood basophils</td>
<td>2.55</td>
<td>1.46-4.47</td>
<td>p=0.001</td>
</tr>
<tr>
<td>Asthma symptoms with routine activities</td>
<td>2.28</td>
<td>1.25-4.15</td>
<td>p=0.007</td>
</tr>
<tr>
<td>Lower number positive skin test responses</td>
<td>1.11</td>
<td>1.00-1.22</td>
<td>p=0.04</td>
</tr>
</tbody>
</table>

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# Conclusions

- The ATS Workshop definition did identify a group of subjects with persistent symptoms, disproportionate health utilization and decreased pulmonary function despite high doses of corticosteroids

- Severe asthma was best discriminated by:
  - Cough and shortness of breath, not wheeze
  - Frequent exacerbations requiring OCS
  - Hospitalizations and near-fatal events, not ER visits

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Conclusions

• Although pulmonary function was similar in moderate and severe asthma, decreased FEV1 was an independent risk factor for severe disease
• Severe asthma subjects were less atopic by skin tests and less atopy increased risk for severe disease
• Biomarkers did not differentiate disease severity
• Sinopulmonary infections were reported more frequently in severe asthma and a history of pneumonia increased the risk for severe disease

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SARP Co-investigators

*The Severe Asthma Research Program (SARP) is a multicenter asthma research group funded by the NHLBI and consisting of the following contributors:
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Data Coordinating Center- James R. Murphy*, Douglas Curran-Everett;
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• TENOR Advisory Board:
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• TENOR Investigators and Study Coordinators
• TENOR Collaborators
Severe Asthma – Determinants and Treatment

Prof. Dr. Klaus F. Rabe
Department of Pulmonology
Leiden University Medical Center
The Netherlands

“The term severe refractory asthma (SRA) in adults applies to patients who remain difficult to control despite extensive reevaluation of diagnosis and management following an observational period of at least 6 months by a specialist. Factors that influence asthma control should be recognized and adequately addressed prior to confirming the diagnosis of SRA.”

This citation from a recent report on severe asthma in adults summarizes some of the relevant aspects of the presentation. The definition of the disease is based on clinical parameters and the management is directly influenced by risk factors and determinants that very individually influence the course of the disease. The estimate for the prevalence lies between 5 and 10% of the population with asthma and by now a number of risk factors have been identified. Tobacco smoking, female gender, and obesity are some of the determinants that have been described although the precise contribution is not always certain. There is good evidence that severe asthma can be described by various phenotypes and for clinical practice it seems advisable to differentiate individuals that have a more rapid decline in lung function from those that present with frequent exacerbations. For those patients with frequent exacerbations respiratory viruses seem to play an important role as well as allergen exposure and occupational sensitizers. Furthermore, trigger factors such as nonsteroidal anti-inflammatory drugs are important for a subset of individuals with severe asthma. Patients with a rapid decline in lung function appear to have a different risk factor profile with persistent (eosinophilic) inflammation, persistence of inflammation of the upper airways, and structural changes of the lungs. The common abnormality lies in a poor corticosteroid response which is likely to be multi-factorial and is still insufficiently understood.

The management of severe asthma relies nevertheless on the use of inhaled corticosteroids and bronchodilators and a limited number of studies have addressed the use of high doses of corticosteroids above those routinely recommended. Leukotriene receptor antagonists are included in several guidelines although their benefit is questionable. Alternative immunosuppressive therapies have been disappointing so far and there is an urgent need for alternative pharmacological developments. There is limited data available on the use of anti-TNF therapies for severe asthma and large scale trials are now underway. The monoclonal antibody omalizumab has demonstrated efficacy in this patient group.

Given the complexity of the disease the role of non-pharmacological strategies including education and instructions in medication use need to be stressed. Severe asthma is undoubtedly frequently associated with a range of co-morbid conditions and the management strategies need to include pharmacological and non-pharmacological approaches. Finally, clinical trials in the future should be performed in well phenotyped patients since severe asthma is likely not a homogeneous entity and the role of allergic sensitization, the onset of the disease, and the clinical course vary greatly between patient populations which will inevitably reflect on the efficacy of novel interventions.

References


An Update on Severe Asthma – XXVII EAACI Congress

Severe Asthma – Determinants and Treatment

Klaus F. Rabe

Department of Pulmonology
Leiden University Medical Center

Bronchial Asthma: Pathophysiology

Eder W et al., NEJM 2006;355:2226-2235

Asthma: State of the Art

Eder W et al., NEJM 2006;355:2226-2235
Bronchial Asthma: Pathophysiology

- Cartilage
- Smooth muscle
- Airway plug
- Subepithelial fibrosis

A restructured airway in severe asthma (T. Bai 2000)

Asthma: State of the Art

Eder W et al., NEJM 2006;355:2226-2235

Bronchial Asthma: Pathophysiology

Airway Remodeling and Inflammation in Symptomatic Infants with Reversible Airflow Obstruction

RBM thickening and the eosinophilic inflammation characteristic of asthma in older children and adults is not present in symptomatic infants with reversible airflow obstruction, even in the presence of atopy.


Airway Remodeling and Inflammation in Symptomatic Infants with Reversible Airflow Obstruction

![Graph showing comparison of RBM thickness across different groups.]


Bronchial Asthma: Pathophysiology

Tolerance
- Intact Barrier
- Mucociliary Clearance
- Epithelial tight junctions
- DC immature
- T cells
- B cells

Responsiveness
- Barrier disrupted
- Impaired Mucociliary Clearance
- Epithelial damage
- DC activated
- Numbers increased
- Th2 cells
- Numbers increased
- Less apoptosis
- Prolonged survival

Bronchial Asthma: Pathophysiology

Severe - Difficult to Control Asthma
Pathophysiology, Prevalence, Risk Factors and Clinical Presentation

- Definition
- Prevalence
- Phenotypes
- Risk Factors
GINA-based Definition of Asthma Severity

<table>
<thead>
<tr>
<th>Step 2</th>
<th>Step 3</th>
<th>Step 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms &lt;once-daily + awakenings &lt;1/week + FEV₁ &gt;80% predicted</td>
<td>Mild persistent</td>
<td>Moderate persistent</td>
</tr>
<tr>
<td>Step 3 Awakenings 1/week OR FEV₁ 60–80% predicted</td>
<td>Moderate persistent</td>
<td>Severe persistent</td>
</tr>
<tr>
<td>Step 4 Symptoms daily OR awakenings 4/week OR FEV₁ &lt;60% predicted</td>
<td>Severe persistent</td>
<td>Severe persistent</td>
</tr>
</tbody>
</table>

Global Initiative for Asthma (GINA) 2002. NIH Publication No. 02-3659

Severe - Difficult to Control Asthma
Pathophysiology, Prevalence, Risk Factors and Clinical Presentation

- Definition
- Prevalence
- Phenotypes
- Risk Factors

Phenotypes of Severe Asthma: Decline of Lung Function

## Associated Factors of Airflow Obstruction in Patients with Severe Asthma

<table>
<thead>
<tr>
<th>Factor</th>
<th>Adjusted OR*</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sputum eosinophils ≥ 2%</td>
<td>7.7</td>
<td>(2.4 – 25.1)</td>
</tr>
<tr>
<td>PC_{20} histamine ≤ 1.0 mg/ml</td>
<td>3.9</td>
<td>(1.2 – 13.0)</td>
</tr>
<tr>
<td>Adult-onset of asthma</td>
<td>3.3</td>
<td>(1.2 – 9.0)</td>
</tr>
<tr>
<td>Exhaled NO ≥ 10 ppb</td>
<td>1.9</td>
<td>(0.8 – 4.8)</td>
</tr>
<tr>
<td>Reversibility FEV₁ ≥ 9%</td>
<td>1.7</td>
<td>(0.8 – 3.6)</td>
</tr>
<tr>
<td>Total IgE &gt; 100 IU/ml</td>
<td>1.7</td>
<td>(0.8 – 3.7)</td>
</tr>
<tr>
<td>Blood eosinophil count &gt; 45.0x10⁶/l</td>
<td>1.5</td>
<td>(0.6 – 3.6)</td>
</tr>
<tr>
<td>Sputum neutrophils ≥ 64%</td>
<td>1.4</td>
<td>(0.5 – 4.6)</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>1.3</td>
<td>(0.6 – 2.8)</td>
</tr>
<tr>
<td>Atopic</td>
<td>0.8</td>
<td>(0.4 – 1.9)</td>
</tr>
</tbody>
</table>

*OR adjusted for age, gender, and asthma duration


---

## Severe - Difficult to Control Asthma

Pathophysiology, Prevalence, Risk Factors and Clinical Presentation

![Image](image1.png)

Wenzel S, AJRCCM 2005;172:149-160

---

## Sputum Induction in Severe Asthma by a Standardized Protocol: Predictors of Excessive Bronchoconstriction

<table>
<thead>
<tr>
<th>Type of Cell</th>
<th>Percentage (Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous cells</td>
<td>31.0 ± 26.2</td>
</tr>
<tr>
<td>Epithelial cells</td>
<td>7.2 ± 11.2</td>
</tr>
<tr>
<td>Macrophages</td>
<td>19.3 ± 13.8</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>65.7 ± 20.8</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>5.9 ± 11.0</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>1.9 ± 1.8</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD
Differential cell counts are expressed as percentage of non-squamous cells

PARAPLU-study, LUMC Leiden: AJRCCM 164:749-753 (2001)
**Phenotypes of Severe Asthma: Chronic Sinusitis**

<table>
<thead>
<tr>
<th></th>
<th>Limited sinus disease</th>
<th>Extensive sinus disease</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>68</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>42.7 ± 13.1</td>
<td>50.4 ± 14.8</td>
<td>0.02</td>
</tr>
<tr>
<td>Age at onset asthma, yr</td>
<td>11.5 (0.5 – 68)</td>
<td>35.0 (1.0 – 63)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Asthma duration, yr</td>
<td>23.0 (2 – 63)</td>
<td>12.0 (2 – 43)</td>
<td>0.01</td>
</tr>
<tr>
<td>Maintenance oral steroids, %</td>
<td>26.9</td>
<td>38.1</td>
<td>0.33</td>
</tr>
<tr>
<td>Nasal corticosteroids, %</td>
<td>30.9</td>
<td>57.1</td>
<td>0.03</td>
</tr>
<tr>
<td>Dose ICS, mg/day</td>
<td>1600 (1600–6400)</td>
<td>1600 (1600–3600)</td>
<td>0.50</td>
</tr>
<tr>
<td>Aspirin or NSAID sensitive, %</td>
<td>31.6</td>
<td>80.0</td>
<td>0.05</td>
</tr>
<tr>
<td>Nasal polyps, %</td>
<td>8.1</td>
<td>36.8</td>
<td>0.002</td>
</tr>
<tr>
<td>Positive RAST, %</td>
<td>63.2</td>
<td>47.6</td>
<td>0.20</td>
</tr>
</tbody>
</table>


**Phenotypes of Severe Asthma**

**Persistent Eosinophilic Airway Inflammation in Severe Asthma is not Resistant to High Dose of Parenteral Corticosteroids**

Severe - Difficult to Control Asthma
Pathophysiology, Prevalence, Risk Factors and Clinical Presentation

- Definition
- Prevalence
- Phenotypes
- Risk Factors

Bronchial Asthma: Relevance of Chlamydia

Severe - Difficult to Control Asthma
Pathophysiology, Prevalence, Risk Factors and Clinical Presentation

Sudden-Onset Asthma Exacerbations: Predictors

<table>
<thead>
<tr>
<th>Parameters</th>
<th>MOR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trigger of current exacerbations</td>
<td>1.0</td>
<td>--</td>
</tr>
<tr>
<td>Upper respiratory infection</td>
<td>2.7</td>
<td>0.008</td>
</tr>
<tr>
<td>Respiratory allergens (dust, pets, pollen, etc.)</td>
<td>3.8</td>
<td>0.04</td>
</tr>
<tr>
<td>Tobacco smoke</td>
<td>6.9</td>
<td>0.001</td>
</tr>
<tr>
<td>Exercise</td>
<td>4.0</td>
<td>0.001</td>
</tr>
<tr>
<td>Psychosocial stress</td>
<td>1.6</td>
<td>0.13</td>
</tr>
<tr>
<td>Other</td>
<td>1.9</td>
<td>0.05</td>
</tr>
<tr>
<td>Salmeterol during the past 4 weeks</td>
<td>1.8</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Severe - Difficult to Control Asthma
Pathophysiology, Prevalence, Risk Factors and Clinical Presentation

- Sleep apnoea
- Psychopathology
- Sinus disease
- Gastric reflux
- Recurrent infections

---

Rhinovirus infecting epithelial cells

Angiogenic growth factors: Tissue remodeling

IL-6: Acute inflammatory response

GM-CSF: Primes neutrophils & eosinophils for enhanced activation

IL-8: Neutrophil recruitment

IL-16: Lymphocyte chemoattractant and growth regulator

RANTES: Eosinophil & T lymphocyte chemoattractant

Upregulation of ICAM-1

---

Severe - Difficult to Control Asthma
Pathophysiology, Prevalence, Risk Factors and Clinical Presentation

Asthma Death, CD8+ T Cells, and Viruses

- AD group
- AUC
- C group

---

Severe - Difficult to Control Asthma
Pathophysiology, Prevalence, Risk Factors and Clinical Presentation

- Asthma Death
- CD8+ T Cells
- Viruses

Asthma: State of the Art

Severe - Difficult to Control Asthma
Pathophysiology, Prevalence, Risk Factors and Clinical Presentation

- Mechanisms
- Proliferation – ASM abnormalities
- Phenotypes
- Risk Factors - Death
Omalizumab became available for use in the United States in 2003. This presentation summarizes the experience at a clinic in Colorado, USA. Initially, omalizumab was given to the most severe chronic asthma patients in the clinic. There were about 25 severe patients started on omalizumab in the fall of 2003. In the spring and summer of 2004 these patients were evaluated and almost all of them had a major improvement in their asthma. At that point more patients were treated with omalizumab and as the word spread to other physicians in the community, pulmonologists and primary physicians referred patients directly for treatment with omalizumab. With these referrals and increasing numbers from the clinic population, over 125 patients have been treated.

Over 125 patients with asthma have been treated with omalizumab in the past 4.5 years in the clinic; 90% of the patients improved in their overall asthma control, quality of life, medication use, etc. About 10% of patients did not improve. This presentation will show the changes in the asthma quality of life scores, spirometry, and reduction in medication usage. Some individual case reports will be used as examples in the presentation. Since some of the patients had other allergic conditions such as eczema or urticaria, those conditions were noted to be improved significantly along with their asthma. The safety of omalizumab will also be summarized. With over 5,000 injections given there was only one serious systemic reaction; this reaction was generalized pruritus, coughing, and an asthma exacerbation. There were a very small number of patients who had arthralgias, muscle aches, or other systemic symptoms; in some of these patients, the treatment was stopped.

One of the interesting findings has been that the patients’ spirometry did not improve; however their quality of life, symptoms, exercise ability, and general well being improved dramatically in spite of the unchanged FEV1. Patients noted that their usual asthma triggers no longer caused them to have asthma attacks. This included both the allergic triggers and non-allergic triggers and it was interesting to note that the improvement in non-allergic triggers were mentioned by patients very frequently (cigarette smoke, pollution, paint fumes, particulates, etc.). This indicated that omalizumab blocked both the allergic and non-allergic asthma triggers.

Another ancillary finding was that patients with food allergies noted that these food allergies did not bother them as much as they had previously.

In summary, omalizumab has been an important adjunctive therapy in patients with severe asthma.
Four Years of Asthma Experience With Omalizumab (Xolair)

William W. Storms, MD
Clinical Professor, University of Colorado Health Sciences Center
Practicing Allergist, Colorado Springs, CO
Member:
National Asthma Education and Prevention Program
Coordinating Committee (NAEPP)
US Olympic Committee Sports Medicine Committee

Wm. Storms, MD
Disclosure Slide

RESEARCH STUDIES:
AlconLabs, Altana/Nycomed, Amgen, AstraZeneca, BMS, Genentech, GSK, Johnson & Johnson, Medpointe, Merck, Novartis, Sanofi-Aventis, Schering

CONSULTANT:
Adams, AlconLabs, Altana/Nycomed, AstraZeneca, Consumer Reports, Consumers Union, Critical Therapeutics, Efficas, Exelixis, Genentech, Greer, GSK, Hoffman-LaRoche, Isis, Ivax, King, Medpointe/Meda, Merck, Nexcuria, Novartis, Pharmaxis, Sanofi-Aventis, Schering, Sepracor, Strategic Biosciences, Strategic Pharmaceutical Advisors, TEVA, Collequium, TREAT Foundation, UCB, Wyeth

SPEAKER’S BUREAU:
Abbott, AlconLabs, AstraZeneca, Boehringer, Genentech, Medpointe, Merck, Novartis, Pfizer, Sanofi-Aventis, Schering, UCB

Allergen sensitivity: an important evaluation

“The Expert Panel recommends that, given the importance of allergens and their control to asthma morbidity and asthma management, patients who have persistent asthma should be evaluated for the role of allergens as possible contributing factors....”

—2007 NHLBI Guidelines for Managing Asthma

- Determine the patient’s exposure to allergens, especially indoor inhalant allergens
- Assess sensitivity to allergens by using:
  - Skin or RAST/in vitro testing to determine the presence of specific IgE antibodies
GINA asthma treatment guidelines include anti-IgE therapy at step 5

<table>
<thead>
<tr>
<th>Step 1</th>
<th>Step 2</th>
<th>Step 3</th>
<th>Step 4</th>
<th>Step 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma education</td>
<td>Environmental control</td>
<td>As needed rapid-acting (\beta_2)-agonist</td>
<td>As needed rapid-acting (\beta_2)-agonist</td>
<td>Add one or more</td>
</tr>
<tr>
<td>Controller options</td>
<td>Select one</td>
<td>Select one</td>
<td>Add one or more</td>
<td>Add one or more</td>
</tr>
<tr>
<td>Low-dose ICS</td>
<td>Low-dose ICS plus LABA</td>
<td>Medium- or high-dose ICS plus LABA</td>
<td>Oral corticosteroid (lowest dose)</td>
<td></td>
</tr>
<tr>
<td>Leukotriene modifier</td>
<td>Leukotriene modifier</td>
<td>Anti-IgE treatment</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*for children older than 5 years, adolescents and adults

\(\beta_2\) = \(\beta_2\)-agonist

*Leukotriene modifier or synthesis inhibitor

GINA Workshop Report 2006
Storms Clinic Xolair Patient Results

125 patients with evaluable results (on drug at least 4 months)

- 114 patients improved (91%)
- 11 patients unimproved (9%)
  » After 3-12 month trial of Xolair

Demographics

Female: 69%
Male: 31%
Mean Age - 53 yrs (range: 8-82)
  • Age 8-19: 4 pts
  • 20-29: 5 pts
  • 30-39: 12 pts
  • 40-49: 29 pts
  • 50-59: 31 pts
  • 60-69: 30 pts
  • 70-79: 15 pts
  • 80-89: 2 pts

Patient Improvement

• Inhaled/oral steroids significantly reduced
  • (75-90% reduction in dose)
• Significant reduction/discontinued use of rescue
  • (either neb or MDI)
• Significant increase in ability to exercise
  • (6 patients have had significant weight loss.)
• Reduction in upper/lower respiratory infections
  • (sinusitis, bronchitis)
• Improved Quality of Life by 76%
  • (AQLQ-Juniper)
Patients Who Stopped Xolair In The Past 4 Years

- 10 treatment failures (8%)
  • (after 6 months)

- 15 pt due to insurance change
  • (all saw significant improvement)

- 7 stopped after one injection
  • No data acquired

Frequency of Injections

- 1/3 of patients receive twice a month injections; 2/3 receive once a month injections

- Most patients receive two injections at each visit

Total Number of Injections and Reactions to Injections

As of June 2008: 4,000 patient visits for Xolair

- 7,500 injections given
- Rare local reactions
- Very rare systemic reactions 4/4000 (0.1%):
  – One acute pruritus, cough and asthma; hospitalized
  – Two patients with subacute arthralgias
  – One patient with muscle pain, malaise, fever
Xolair Patient Quality of Life  
(mini AQLQ Juniper)  
98 patients completed surveys  
(0 to 70; 70 is perfect)  
Mean score before starting Xolair...29  
Mean score after 3-6 months........52  
77% improvement

“I would have had to quit work completely without Xolair”  
“I’m not afraid of dying from an asthma attack anymore”  
“This is much, much better than when I first was put on Advair”  
“I feel alive.”  
“You have given me a life I never imagined was possible.”

Rhinosinusitis Disability Index Score  
(Benninger)  
• 16 Patients with pre/post RSDI scores  
Mean Pre-Xolair score: 56  
Mean Post-Xolair score: 33  
Gross change: 23 points  
% improvement: 42%
Depression
Patient Health Questionnaire-9
scores: 0-4 no depression
10-14: moderate
20-27: severe depression

- 84 patients on Xolair more than 4 months completed questionnaire retrospectively
  - Pre-Xolair Average 10 (moderate depression)
  - Post Xolair Average 4 (no depression)

Spontaneous Responses to Depression Questionairre

- “I felt like I could never leave my house”
- “I never realized how sad my life was before”
- “I didn’t travel because I didn’t want to have a problem in another country”
- “I’ve had my will prepared since I was a young adult”
- “I was sure I wasn’t going to live another year”
- “I didn’t know if I’d wake up in the morning”
- “I knew I was going to die from my asthma”

FEV 1 Change Before and After Xolair

- Pre-Xolair: 68% predicted (on ICS+-LABA+-LTRA)+/-pred)
- Post-Xolair: 73% predicted (on much less medication)

This is not surprising, based on the clinical studies. FEV 1 does not change much, but patients show enormous improvement
Case Studies

- Patients were chosen based on history of combination therapy (Advair), with a history of exacerbations.
- Patients had inadequate quality of life in spite of multiple medications
- Patients had a history of exacerbations** and many had frequent prednisone bursts
- All patients had allergic sensitivities based on skin testing or RAST tests

Xolair Patient: BA
56 year old male with lifetime history of triad asthma (nasal polyps, asthma, aspirin sensitivity); 5 sinus surgeries requires frequent urgent office visits and steroid bursts.

<table>
<thead>
<tr>
<th>Asthma meds:</th>
<th>Pre-Xolair</th>
<th>19 Months Later</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Advair 500/50 BID</td>
<td>• Advair 100/50 one puff every other day</td>
<td></td>
</tr>
<tr>
<td>• Singular 10mg QD</td>
<td>• Alupent (MDI) rarely once a month</td>
<td></td>
</tr>
<tr>
<td>• Alupent for rescue 3-5 times per week (MDI)</td>
<td>• Rarely</td>
<td></td>
</tr>
<tr>
<td>• Frequent oral steroids</td>
<td>• Unrestricted, no longer requires antidepressants</td>
<td></td>
</tr>
<tr>
<td>• Daily</td>
<td>• Has missed 3 days of work this year</td>
<td></td>
</tr>
<tr>
<td>• activity extremely restricted, requires antidepressants due to steroid use</td>
<td>• No sinus surgery since Xolair</td>
<td></td>
</tr>
<tr>
<td>• has missed 21 days of work this year</td>
<td>• 84% (unchanged)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• 79%</td>
<td>• 66.5</td>
</tr>
</tbody>
</table>

Xolair Patient: NAC
69-year-old female. Xolair Started 3/04

- Dx: COPD, chronic bronchitis, asthma; on O2 daily
- **FEV<sub>1</sub> generally 20% predicted
- On high doses of beta agonists:
  - oral Volmax (BID) Cornbivent MDI (2puffs QID)
  - nebulized albuterol (BID) Foradil (BID)
- Using nebulized triamcinolone (BID); monthly bursts of prednisone**
- Positive skin tests to both seasonal and perennial allergens
- Severely limited lifestyle
- IgE 15 IU/mL**
- Xolair dose 150mg q 4 weeks
Xolair Pt: NAC
69-year-old female. Xolair Started 3/04

• Dx: COPD, chronic bronchitis, asthma; on O2 daily
• FEV<sub>1</sub> generally 20% predicted
• On high doses of beta agonists:
  oral Volmax (BID) Combivent MDI (2 puffs QID)
  nebulized albuterol (BID) Foradil (BID)
• Using nebulized triamcinolone (BID); monthly bursts of prednisone**
• Positive skin tests to both seasonal and perennial allergens
• Severely limited lifestyle
• IgE 15 IU/mL**
• Xolair dose 150 mg q 4 weeks

Xolair Pt: NAC, 6 months later
69-year-old female. Xolair Started 3/04

• Uses Foradil q am only and Pulmicort 2 puffs in am only
• Combivent prn (1-2 times daily)
• No need for nebulized meds at all
• Denies any chest symptoms except with weather fronts or “hurrying”
• Able to do all daily activities without symptoms
• Continues on O<sub>2</sub> 2 liters
• No prednisone; no asthma exacerbations
• Exercises daily on the treadmill

Xolair Pt: PJN
16 yo male Xolair Started 1/05 (age 14)

• Moderate/severe persistent asthma since age 6. Severe eczema requiring bursts of oral steroids. Severe allergic conjunctivitis requiring steroid drops
• Failure on immunotherapy
• FEV<sub>1</sub> 77% predicted in spite of daily Advair
  Requires daily rescue beta agonists
• Severely limited quality of life
  Patient is embarrassed to wear short sleeved shirts or shorts due to eczema
• Is below 5th percentile for height on growth chart
• IgE 9920 IU/mL**
• Xolair dose 375 mg Q 2 weeks (highest dose for weight)
Xolair Pt: PJN
16 yo male  Xolair Started 1/05 (age 14)

Patient and parents state “it’s a miracle”
Advair dose decreased and finally discontinued (d/c 6-05)
Has had no asthma flares since starting Xolair
FEV1 increased to 93% of predicted
Eczema is almost totally cleared
Minimal flare during pollen season controlled with Protopic pm
Has had not required any topical or oral steroids for eczema, conjunctivitis or asthma
Quality of life greatly improved
Growth is now at 10% on growth chart

Xolair Pt: CDB
46-Year-old Female Xolair Started 8-04

Lifetime history of severe persistent asthma
Shortness of breath daily
Frequent exacerbations requiring prednisone
Severely restricted quality of life
Medications:
- Albuterol 3-4 times daily
- Advair 500/50
- Prednisone 10mg daily
- Singular 10mg QD
- IgE 1,536.5 IU/mL**
Xolair dose 375mg Q 2wks (highest dose for weight)

Her Pulmonologist stopped her prednisone
Patient has no chest symptoms needs albuterol less than once a week
Patient states she can “breath through my nose for the first time in my life”

Medications:
- Advair 100/50 1 puff every day
- Albuterol < once a month
- Astelin pm for nasal symptoms
- Singular once a day
Has had no colds or asthma exacerbations
Feels “great”; able to do all activities without restrictions
Potential Xolair Patient

The patient on multiple daily controllers who does not meet the Asthma Guidelines for control, based on:

1. FEV1 <80% predicted
2. QOL questionnaire
3. Symptoms
4. Short-acting beta-agonist use
5. Two or more steroid bursts or urgent visits in the past year