World Allergy Forum Symposium:
Severe Asthma

XXIX Congress of the EAACI
Sunday, 6 June 2010 - 13:30 - 15:00
London, United Kingdom

Moderators:
Richard F. Lockey, United States
Jan Lötvall, Sweden

Phenotypes of severe asthma
Sally Wenzel, United States

Effect of asthma exacerbations on natural history
Robert Lemanske, United States

Severe asthma treatment in children
Ulrich Wahn, Germany

www.worldallergy.org

The World Allergy Organization (WAO) is an international organization of 84 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 through education, research and training as a world-wide alliance of allergy and clinical immunology societies.

WAF is an educational program of the World Allergy Organization.
WAO INTERNATIONAL SCIENTIFIC CONFERENCE

Asthma and Co-morbid Conditions:
Expanding the Practice of Allergy for Optimal Patient Care

5–8 DECEMBER 2010
DUBAI, UAE

KEY REASONS TO ATTEND

Be on the leading edge of medical learning & education!

• Attend state-of-the-art lectures by world experts on Allergy, and Asthma & Co-morbid Conditions
• Participate in practical, clinic-friendly workshops on Food Allergy, Asthma, Spirometry, Rhinoscopy, Broncoscopy, Immunotherapy, Sleep Apnea, and more
• Network with others in your field/areas of interest including: Asthma, Allergy, Immunology, Pediatrics, Pulmonology, Ophthalmology, Dermatology and ENT
• Receive CME credits
• Showcase your own achievements to key international opinion leaders

INVITED SPEAKERS

Carlos E. Baena-Cagnani
Sami Bahna
Neil Barnes
Eric Bateman
Michael Blaiss
Sergio Bonini
Louis-Philippe Boulet
Fulvio Braido
G. Walter Canonica
Thomas B. Casale
Adnan Custovic
Alessandro Fiocchi
Peter Gibson
Paul Greenberger
Tari Haahrtena
Stephen Holgate
Michael A. Kaliner
Pramod Kelkar

Marek Kowalski
Dennis Ledford
Robert Lemanske
Richard F. Lockey
Harold Nelson
Paul O’Byrne
Hae-Sim Park
Ruby Pawankar
Stephen P. Peters
Richard Polosa
Lanny Rosenwasser
Mario Sánchez-Borges
Glenis Scadding
Giovanni Viegi
Myron Zitt

Additional speakers to be invited
Severe Asthma

Program

Moderators:
Richard F. Lockey
University of South Florida
Tampa, FL, United States

Jan Lötvall
Göteborg University
Göteborg, Sweden

1. Welcome to the World Allergy Forum Symposium and Introduction to “Severe Asthma”
   Richard F. Lockey and Jan Lötvall

2. Phenotypes of severe asthma
   Sally Wenzel
   University of Pittsburgh Medical Center NW
   Pittsburgh, PA, United States

3. Effect of asthma exacerbations on natural history
   Robert Lemanske
   University of Wisconsin School of Medicine and Public Health
   Madison, WI, United States

4. Severe asthma treatment in children
   Ulrich Wahn
   Charité Berlin
   Berlin, Germany

Upon completion of this session, participants should be able to:

- Understand the genetic phenotypes that influence disease expression and asthma severity
- Evaluate the long-term effect of severe asthma exacerbations on the natural course of the disease
- Discuss the available treatment strategies for severe asthma in childhood and the factors that influence treatment choice

2010-2011 World Allergy Form Advisory Board

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ABOUT THE WORLD ALLERGY ORGANIZATION

WORLD ALLERGY ORGANIZATION (WAO)
The World Allergy Organization (WAO) is an international umbrella organization of 84 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.

PROGRAMES 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
Module 12: Urticaria

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 (ESP)
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, ESP 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**

All active members of dues-paying Member Societies are Individual Members of the World Allergy Organization (WAO).

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 for Allergy and Clinical Immunology
Brazilian Society of Allergy and Immunopathology
British Society for Allergy and Clinical Immunology
Bulgarian Society of Allergology
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Chilean Society of Allergy and Immunology
Chinese Society of Allergology
(Chinese) Hong Kong Institute of Allergy
Colombian Allergy, Asthma, and Immunology Association
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Finnish Society of Allergology and Clinical Immunology
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Honduran Society of Allergy and Clinical Immunology
Hungarian Society of Allergology and Clinical Immunology
Icelandic Society of Allergology and Immunology
Indian College of Allergy, Asthma and Applied Immunology (ICAAI)
Indonesian Society for Allergy and Immunology
Israel Association of Allergy and Clinical Immunology

Italian Association of Territorial and Hospital Allergists
Italian Society of Allergy and Clinical Immunology
Japanese Society of Allergology
Korean Academy of Allergy, Asthma and Clinical Immunology
Latvian Association of Allergists
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Malaysian Society of Allergy and Immunology
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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 Allergy and Clinical Immunology
Paraguayan Society of Immunology and Allergy
Peruvian Society of Allergy and Immunology
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
Allergy and Clinical Immunology Society (Singapore)
Association of Allergy and Clinical Immunology of Serbia and Montenegro
Slovenian Association for Allergology and Clinical Immunology
Allergy Society of South Africa
Spanish Society of Allergology and Clinical Immunology
Allergy & Immunology Society of Sri Lanka
Swiss Society for Allergology and Immunology
Allergy, Asthma and Immunology Society of Thailand
Turkish National Society of Allergy and Clinical Immunology
Ukrainian Association of Allergologists and Clinical Immunologists
Uruguayan Society of Allergology
Venezuelan Society of Allergy and Immunology
Vietnam Association of Allergy, Asthma and Clinical Immunology
Zimbabwe Allergy Society

For WAO membership information please contact the Secretariat

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**Associate Member Societies**

National Association for Private Algerian Allergists
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**Affiliate Organizations**

GA²LEN (Global Allergy and Asthma European Network)
International Association of Asthmology
International Primary Care Respiratory Group (IPCRG)
Southern European Allergy Societies (SEAS)
June, 2010

Dear Colleagues,

In 1996, the International Association of Allergology and Clinical Immunology (now World Allergy Organization) brought together a group of international experts at a hotel just outside London, to form the first World Allergy Forum (WAF) Advisory Board. The Board planned activities for the program’s first year, and invited EAACI to host a symposium on Mechanisms of Action of Rhinitis Therapy at its Congress in Rhodes, Greece. Since then, WAF has flourished to become the longest running educational program of World Allergy Organization, and we are delighted that WAF has been hosted by EAACI every year since the program started in 1997. Thirty six symposia have been presented around the World, focusing on a wide variety of topics of major interest to the international allergy community, and all delivered by internationally renowned experts. WAF attracts some 1,000 attendees each year, and reaches out to many more allergists through posting of the program abstracts and slides on the WAO Website: http://www.worldallergy.org/waf

It is a great pleasure that World Allergy Forum now returns to London, to be part of the 2010 EAACI Congress, and to bring you this 37th World Allergy Forum symposium, Severe Asthma.

The successful management of Severe Asthma is one of the greatest challenges faced by the allergist, as we constantly seek to manage the condition and to limit the long term health effects, and the major impact that this debilitating condition imposes on the life of our patients. In today’s program, Sally Wenzel will provide guidance on current thinking about asthma phenotypes, and consider how these can influence response to therapy, helping us to target pharmacotherapy more effectively. Robert Lemanske will review the effects of asthma exacerbations on the natural history of the disease, discussing the role of viral infections and their effect on lung function, and the possible underlying mechanisms for this effect. Ulrich Wahn’s presentation will discuss inadequately controlled severe asthma in childhood, looking particularly at comorbidity with other allergic conditions and sensitization to panallergens. We hope you will enjoy the session and that it will provide valuable insights into the management of severe asthmatic patients.

World Allergy Organization would like to acknowledge the unrestricted educational grant from Novartis that supports the World Allergy Forum program.

With best regards,

Richard F. Lockey
President
World Allergy Organization

Jan Lötvall
President
European Academy of Allergology and Clinical Immunology
Severe asthma and its phenotypes

Sally E. Wenzel, MD
University of Pittsburgh Medical Center NW
Pittsburgh, PA, United States

Asthma has long been appreciated to be a heterogeneous disease, but the identification of specific phenotypes has been difficult. Severe asthma represents a group of patients with an extreme form of the disease where phenotype characterization may be easier. Additionally, severe asthma itself is likely to be more heterogeneous than milder asthma. Approaches to identifying phenotypes of severe asthma have ranged from biased clinical impressions to searches for biomarkers to relatively unbiased statistical approaches. Perhaps surprisingly, there is considerable overlap among the approaches.

One of the earliest attempts at phenotyping of asthma was the breakdown into allergic/extrinsic and intrinsic (less allergic) forms of asthma. Although this fell out of favor years ago, recent studies have strongly supported a very similar approach based on age at onset of disease. Similar to the previous differentiation, early onset disease (before the age of 12) represents a very homogeneous, highly atop allergic phenotype. This phenotype represents the large majority of all asthmatics, but perhaps only 50-60% of severe asthmatics. This early onset, allergic phenotype has been identified using both biased and unbiased approaches. In this subgroup, there appears to be a strong relationship between genetics, duration of disease and additional “hits” in determining the progression of the disease.

In contrast, later onset asthma (12 or older) represents a much more heterogeneous group of asthmatics. These groups of asthmatics are surprisingly more likely to be severe asthmatics and less likely to be allergic/atopic. These individuals range from women with an age at onset around the time of menopause, to aspirin sensitive asthmatics to post infectious, as well as allergic and occupational asthmatics. These individuals range from women with an age at onset around the time of menopause, to aspirin sensitive asthmatics to post infectious, as well as allergic and occupational asthmatics.

The inflammatory process associated with each of these phenotypes differs, with increasing severity of early onset disease associated with increasing neutrophilic inflammation. In contrast, the inflammatory pattern in late onset disease may help to identify specific phenotypes, less dependent on severity.

While these distinct immune-inflammatory phenotypes help to identify specific groups of patients which do, in fact, appear to respond differently to different therapies, it is likely that some commonalities exist as well. Whether these underlying similarities will tie in the common themes of airway reversibility, obstruction and bronchial hyperresponsiveness remain to be determined.

References


Phenotypes of Severe Asthma

Sally Wenzel, MD
Professor of Medicine, Director
University of Pittsburgh Asthma Institute@UPMC/UPSOM

Phenotypic evaluation of severe asthma

- Asthma, particularly severe asthma, is a heterogeneous disease where characteristics are accentuated.
- Phenotype: "Characteristics of an organism resulting from the interaction of its genetic make-up and environment"
  - Implies some elements of phenotype may be fixed, others may not be.
  - Phenotype can be confused with disease characteristic.
- Identifying pathobiologic pathways which contribute to phenotypes likely to improve mechanistic understanding and treatment of asthma.

The "Umbrella" of Severe Asthma

Refractory Asthma
Unresponsive to Rx and Rx of exacerbations

Exacerbations
Low FEV1

Clinical Hallmarks

Different ways to get there

Phenotype A
Phenotype B
Phenotype C
Phenotype D
Early onset "allergic" asthma

- **Associated conditions:**
  - Hx eczema (p=0.0007)

- **Biomarker:** Serum IgE tends to be higher

- **Genetics:** Family hx of asthma early-late

- **Allergic Symptoms** (most or all of time)
  - House dust
  - Furred animals
  - Seasonal pollen

- Concomitant house dust and any of the above:
  - p=0.04
  - p=0.007

- Schematic data from Miranda, JACI 2004

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Unbiased cluster approaches support importance of age at onset

- Two large scale cluster analyses have now been performed and published
  - Haldar et al. AJRCCM 2008
  - Moore et al. AJRCCM 2009

- **Moore study performed on 726 SARP subjects**
  - 304 severe subjects by ARIA criteria
  - Utilized 629 variables which were compressed into 34 weighted variables for final analysis using random forests software
  - Five separate clusters identified
  - Five strongest predictors were pre and post FEV1% predicted and age at onset

- Haldar study of ~370 asthmatics from primary care and 2ndary care populations divided primarily on sputum cell counts/symptoms (without FEV1)

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**Moore:** Five clusters, defined primarily by age at onset/FEV1

- Mild atopic asthma
- Mild to moderate atopic asthma (largest)
- Severe atopic asthma

- Late onset
- Nonatopic
- Females

- "late onset/females" Severe constriction/fewer atopy
- Highest HCU/lowest QOL
Classic atopic/early onset pattern:

- INCREASING AGE/DURATION
- INCREASING SEVERITY
  - Asthma duration
  - Pre-FEV1%
  - Pre-FVC%
- Environmental factors
- Genetics of atopy/allergies
- Air trapping highly reversible, reversible.
- Most allergic: greatest # of skin reactions

Phenotype in relation to genotype

- IL-4, IL-13, STAT6, IL-4Rα polymorphisms long associated with asthma/atopy.
- Concentrated # of SNPs in single exon of IL-4Rα encoding for amino acid changes in receptor.
- Suggested gene involved in adaptive environmental responses.
- Associated with severe exacerbating asthma.
  - Lung function and African racial background
  - Wenzel AJRCCM 2007

Th2/IL-4Rα tracks with atopic clusters

- % subjects with “C” allele at E375A in IL-4Rα
- Overall p<0.009
- n=630
- Mild, Mild-Mod, Severe, Female, Very Severe, Later to Late Onset Less Atopic
Anti-IgE/allergic desensitization in *subgroup* with allergic asthma

No. of hospitalizations due to serious asthma exacerbation

- **Pooled analysis from studies 008 and 009**
  - Omalizumab/Anti-IgE
  - Placebo

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Molecular phenotyping also supports presence of a Th2/atopic phenotype

3 genes expressed *in vitro* in epithelial cells in response to IL-13 applied to *ex vivo* epithelial cells—"cluster" of mild asthmatics with:
- More BHR, atopy, eosinophils and SEM thickening
- Better response to ICS
- Likely associates with increased iNOS expression as well (and increased FeNO)

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IL-13 also increases iNOS expression and activity *in vitro*

Chibana, K. Clin Exp Allergy 2008
**Allergic asthma may also respond to Th2 antagonists**

Pitrakinra is a 14 kDa IL-4 mulein that inhibits assembly of IL3Rγ or IL13Rα into receptor complexes with IL-4Rα.

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**Pitrakinra decreases allergen induced exacerbation**

3.7-fold reduction in average LAR FEV1 %fall from pre-challenge baseline

<table>
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Wenzel, Lancet. October 2007

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**Inhibition of IL-4Rα pathway improves allergic inflammation**

- Nebulized blockade of IL-4Rα decreased FeNO at baseline and tended to decrease FeNO after allergen challenge
- Supports FeNO as marker of Th2 pathway activation
- Small pharmacogenetic effect observed, as well in association with IL-4Rα polymorphisms

Wenzel, the Lancet Oct 2007
Halder: Clusters based on inflammation and symptoms...age at onset

US data also supports eosinophils more common in late onset dz

Later Onset Severe Asthma

- "Defined" as asthma beginning at age 12 or later
- Much more heterogeneous than early onset (defined as Clusters 3 and 6 in SARP analysis)
- Likely contributed to by:
  - Eosinophilic/aspirin sensitive inflammation
  - Less eosinophilic/neutrophilic
  - Infection
  - Hormones
  - Obesity
  - Occupational exposures: Diesel increasingly recognized
  - Tobacco smoke
  - AND ALLERGIES!
Aspirin Sensitive

- Perhaps best defined phenotype
- Classic definition as asthma exacerbation in response to NSAID but also identified by adult onset and high degree eosinophilia
  - Chronic sinusitis/nasal polyps
  - CAN be associated with better response to anti-LT agts, specifically 5 LO inhibitors
  - Begins to border on "endotype" with specific natural hx, immunopathology and responses to Rx

Aspirin sensitive asthma specifically improves with 5 LOI

- Aspirin sensitive asthma increases between 25-40 yr old: Late onset
- <5% of all asthma, >25% of severe asthma
- Strong association with sinusitis/polyps
- Highly eosinophilic
- More so than early onset
- Implications for Rx
  - 5-lipoxygenase inhibitors (zileuton)
    - Anecdotally (100+ subjects)
    - Superior to ITRA
  - Addicts to ICS/ICS improved outcomes in A/E
  - Improved nasal-sinus symptoms


Specifically targeted eosinophil inhibition: exacerbations decrease

- 12 mo study in severe asthma in subjects with historical sputum eosinophilia>3%
- Decreased eos in sputum, tissue
- 40% reduction in asthma exacerbations
  - and little else
- Based on median age, majority also appear to be late onset phenotype

Infection related

- Many later onset asthmatics report onset after URI
- Late onset with + chlamydia titers had greater FEV1 decline
- Ten Brinke JACI 2001
- Mild-moderate adult patients improved lung function and had decrease in inflammation if PCR+ for mycoplasma
- In severe, mostly adult onset (mean dx=age 29) asthma, improvement in AQLQ (but no change in FEV1)
  - Simpson AJRCCM 2009

Overlap with neutrophilic asthma

- While overall results modest in Simpson Clarithromycin study, best results achieved in group with neutrophilic-type inflammation
  - Simpson AJRCCM 2008
- Clarithromycin decreased both IL-8 and neutrophil elastase
- Suggests more "bronchitic/neutrophil" type of adult onset asthma may respond better

Neutrophilic asthma

- Long associated with more severe asthma, steroid use, lower FEV1 and infection (all additional "phenotypes")
- Also seen in smoking asthma
- But no longitudinal or interventional studies to better define the phenotype
Neutrophilic asthma: Poor response to CS therapy

- Abundant neutrophils (fewer eosinophils) in sputum may limit response to ICS
  - Green, Thorpe 2002
- May be especially important in smoking asthmatics, and maybe obese asthma
  - THOMSON 2004
- Suggests these patients may do better, at least as well with lower dose ICS

Others

- Premenstrual/hormonal
  - Very poorly understood
  - May be overlap with Aspirin Sensitive/late onset
- Exercise induced
  - Defines group where exercise ONLY trigger
  - Is this just mild asthma or a specific phenotype?
- "Obesity"
  - Are there differences in asthma in relation to obesity?
  - Does obesity alter BHR/inflammation or just worsen symptoms, FVC?

Conclusions and Recommendations

- Phenotyping severe asthma patients extremely important
- However, important to distinguish characteristic from phenotype
- Linking molecular, genetic and clinical phenotypes (and their characteristics) likely to vastly improve our understanding of severe asthma
Despite the availability of medications that provide substantial benefits on the impairment aspects of asthma control, asthma exacerbations (a major feature of the long term risk domain) continue to occur in both children and adults. Exacerbations contribute to the morbidity and mortality of asthma based on their frequency and severity and resultant impact on quality of life and overall health care costs. In addition, recent data in adult patients suggest that frequent exacerbations may be associated with an increased rate of loss of lung function, further underscoring their importance to overall risk. Many exacerbations in both children and adults are caused by viral respiratory tract illnesses, most commonly due to rhinovirus. For many asthmatic patients, the disease has its roots in early childhood, and loss of lung function can be demonstrated in children with persistent wheezing during the first six years of life. Since both rhinovirus and RSV are frequent causes of these wheezing episodes, which have been associated with asthma development, further insights into mechanisms underlying these relationships is needed. This presentation will review data concerning viral induced wheezing episodes, asthma exacerbations, loss of lung function, asthma development, and potential mechanisms surrounding these outcomes.

References
Effect of Asthma Exacerbations on Natural History

Robert F. Lemanske, Jr., M.D.
Professor of Pediatrics and Medicine

Disclosure Slide

- Employment
  - University of Wisconsin-Madison
- Financial Interests
  - Speaker: Merck, GSK, AstraZeneca
  - Consultant: Merck, GSK
- Research Interests
  - NHLBI
- Organizational Interests
  - AAAAI, ATS, AAP, SPR
- Gifts
  - Nothing to Disclose
- Other Interests
  - Nothing to Disclose

The Natural History of Asthma

- Genetic Factors (Atopy)
- Remission
- Relapse or Disease Persistence/Progression
- New Onset
- Allergens
- Inflammation and Remodeling
### Preschool Wheezing: Natural History

- 50% of children are reported to have wheezed in the first year of life
- 40% of these children will experience continued wheeze in later childhood

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### When does asthma begin?

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### When Does Inflammation Begin in Childhood Asthma?

- BAL in wheezing children < 3 yrs old
  - ↑ inflammatory cells
  - ↑ inflammatory mediators (leukotrienes)
- Bronchial biopsies in wheezing infants and toddlers with reversible airflow obstruction
  - No ↑ thickness of laminar reticularis
  - No ↑ in inflammatory cells
Inflammation in Preschool Wheezers

- Endobronchial biopsies obtained in preschool wheezing children (age 3 mos to 5 yrs)
  - 16 confirmed wheezers (video questionnaire)
  - 14 reported wheezers
  - 10 controls (stridor)
- Variables evaluated:
  - Reticular basement membrane thickness
  - Density of subepithelial inflammatory cells

RBM Thickening: Preschool Wheezers vs Childhood Difficult Asthma

Saglani S et al. AJRCCM 176:858, 2007

Possible Differences in Loss of Lung Function in Asthma vs Normal Subjects over a Lifetime

Saglani S et al. AJRCCM 176:858, 2007
**Persistent Wheezing & Lung Function**

- Children with lung function measured at median age of 15 months showed differences based on wheezing history & other characteristics (high risk = + API)

![Graphs showing lung function measurements based on wheezing history and other characteristics.](Borrego_Thorax_2009)

**Persistent Wheezing & Lung Function**

- The Manchester Asthma & Allergy Study suggests that lung function [specific airway resistance (sRaw)] is abnormal by age 3 years in persistent wheezers

![Graphs showing lung function measurements by age.](Lowe_AJAC_2005)

**Estimated prevalence of wheezing identified by latent class analysis in 6265 children**

![Graph showing estimated prevalence of wheezing by age.](Henderson_J_et_al_Thorax_63-974_2008)
Strength and Direction of Associations between Derived Phenotypes and Clinical Outcomes

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Asthma</th>
<th>Atopy</th>
<th>FEV1</th>
<th>FEF25-75</th>
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What contributes to this loss of lung function?

Viral Infections and Asthma

20% of all children have at least 1 episode of LRI associated with wheezing in the first year of life, and 70% of these are associated with viral infections

RSV and Asthma

- 60% of children have evidence of being infected with RSV by age 1 year, and nearly 100% by age 2 years.
- < 5% of children with RSV LRI are hospitalized
- Immunopathobiology of RSV infections may influence:
  - Th1/Th2 balance
  - Neural circuitry
  - Inflammation (remodeling)
Viral Pathogens other than RSV

Prevalence of Common Respiratory Viral Infections

<table>
<thead>
<tr>
<th>Common colds</th>
<th>Wheezing Infants</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Rhinoviruses</td>
<td>1. RSV (winter)</td>
</tr>
<tr>
<td>2. Coronaviruses (winter)</td>
<td>2. Rhinoviruses</td>
</tr>
<tr>
<td>3. Parainfluenza viruses</td>
<td>3. MPV (winter)</td>
</tr>
<tr>
<td>4. Enteroviruses (summer)</td>
<td>4. Coronaviruses</td>
</tr>
<tr>
<td>5. Influenza A, B, C (winter)</td>
<td>5. Parainfluenza viruses</td>
</tr>
<tr>
<td>6. RSV (winter)</td>
<td>6. Influenza viruses</td>
</tr>
<tr>
<td>7. Metapneumoviruses (winter)</td>
<td>7. Adenoviruses</td>
</tr>
<tr>
<td>8. Bocavirus (winter?)</td>
<td>8. Bocavirus (winter?)</td>
</tr>
</tbody>
</table>

Rhinovirus
**Viruses other than RSV: Rhinovirus**

- RV infections leading to hospitalization during infancy were an early predictor of the subsequent development of asthma.
  
  Kozanemi-Syrjanen A. et al. JACI 111:56, 2003

- Significant association between wheezing outpatient RV (and RSV) illnesses in infancy and persistent wheezing at 5 years of age
  - These findings were restricted to those children with early allergic sensitization (≤ 2 yrs of age)
  - Multivariate analyses using other risk factors eliminated association with asthma

  Kusel MM et al. JACI 119:1105, 2007

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**COAST**

**Childhood Origins of Asthma**

A prospective study in a high risk cohort designed to evaluate the interactions among age, patterns of immune dysfunction, and virus infections with respect to the subsequent development of asthma and allergic diseases

PI: Rob Lemanske, MD
Co-Is: Jim Germ, MD
Carole Ober, PhD
Ron Gangnon, PhD
Wai-Ming Lee, PhD
Kathy Robeck, RN, MS

Funded by the NHLBI

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**COAST Evaluations**

Nasal lavage specimens collected at symptomatic illnesses

Nasal Washes collected at "Well Child Visits"

Persisent Wheezing Evaluation

Asthma Evaluation

[JACI 116:571, 2008]

Timing, severity & etiology of respiratory illnesses determined throughout childhood
Risk Factors for Third Year Wheezing

- Passive smoke exposure (OR=2.1)
- Older siblings (OR=2.5)
- Allergic sensitization to food protein at age 1 year (OR=2.0)
- Any moderate to severe respiratory illness without wheezing during infancy (OR=3.6)
- At least one wheezing illness during infancy with:
  - RSV (OR=3.0)
  - Non RSV/RSV pathogens (OR=3.9) during infancy
  - Rhinovirus (RV, OR=10)
- When viral etiology was considered, first-year wheezing illnesses caused by RV infection were the strongest predictor of subsequent third year wheezing (OR = 6.6; p<0.0001).

Lemanske RF et al. JACI 116:571, 2005

What viral infections in early life are associated with the development of asthma at age 6 years?

Asthma Diagnosis – Age 6 Years

- Physician diagnosis of asthma
- A step-up plan during illness
- Frequent albuterol or asthma-controller medication usage
- Oral prednisone use for an asthma exacerbation

*28% (73 of 259) of children in COAST had asthma at age 6 years
Did RV or RSV wheezing illnesses during years 1-3 impact the risk of asthma at age 6?
How do viral wheezing illnesses in early life influence lung function later in childhood?

Asthma Diagnosis and Lung Function at Age 6 Years
**Forced Expiratory Volume in 1 Second (FEV₁) Percent Predicted**

![Box plot showing FEV₁ %Pred for different groups: Neither, RSV Only, RV Only, Both.](image)

- **p = 0.005**
- **(n=86)**  **(n=19)**  **(n=20)**  **(n=23)**

---

**Mechanisms**

---

**Do wheezing RV infections in early life cause asthma?**
**Host Factors**

- ↓ antiviral responses
- ↓ lung function
- Genetic polymorphisms

Abnormal Host

\[ \text{Asthma} \]

**Mechanisms**

- Airway epithelial cells¹
  - Normal: apoptosis
  - Asthma: viral replication
- Immune dysregulation²⁻⁴
  - Altered innate immune responses
    - Type 1-3 interferons (α, β, γ, λ)
- Genetic polymorphisms⁵⁻⁶
  - CD14, 159 and Toll 3 receptors

3. Copenhagen CC et al. ARDSCH 170:275, 2004

**Virus Factors**

- Lung/Airway damage
- Virulent strains?
**Virus Factors: Rhinovirus**

- Rhinoviruses are the most prevalent human pathogen
- May produce a range of respiratory tract illnesses
- Seasonal: early fall and late spring in temperate climates
- Until recently, 101 strains identified and categorized genetically into 2 groups: A and B
- Recently, a new Group C has been identified
- Virulence patterns currently under investigation

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**Phylogenetic Analysis of New Strains Compared to Group A and B HRVs**

![Phylogenetic Tree](image)

- Non HRV-A and B strains detected in over 50% of children with more than 5 moderate to severe respiratory illnesses during infancy

---

**The Natural History of Asthma**

- Genetic Factors (Atopy)
- New Onset
- Allergens
- Family hx asthma
- Total IgE: elevated
- Infection: virus, bacteria
- Inflammation and Remodeling
- Relapse or Disease Progression
- Remission

---

Guidelines referring to asthma treatment recommend avoidance of potential allergic triggers and the stepwise approach of classical anti-inflammatory therapy.

Asthma is considered to be severe, if it remains inadequately controlled by pharmacotherapy as determined by validated tests like the asthma control test (ACT) for children. Inadequate control includes an unacceptable number of emergency room visits or hospital admissions. A definition by impaired lung function alone has been shown not to be very helpful in children.

A more allergological appreciation of severity may refer to the frequently observed comorbidity with other allergic manifestations of the nose, the skin or concomitant food allergy, which may frequently be related to sensitization to panallergens inducing both airway as well as other allergic symptoms.

Anti-IgE has been demonstrated to be of additional value in children older than 6 years, with a good safety profile. Beside its potential to improve asthma control in all age groups this intervention seems to be of special value in children and adolescents, since this group of patients is frequently allergic to multiple allergens, with a strong impact on quality of life.

In addition anti-IgE might prove to be particularly helpful for those children who due to severe asthma and polysensitization are not eligible for immunotherapy.
Severe asthma treatment in children

Ulrich Wahn
Department for Paediatric Pneumonology and Immunology
Charité, Berlin

Many children with SAA suffer from

- Allergic Rhinitis
- Atopic Dermatitis
- Sensitization to Pan-Allergens
- Taking multiple anti-asthma drugs for years

Severe / Uncontrolled Asthma

1. Current impairment
   - Symptoms
   - $\text{Beta}_2$-Agonists
   - Activity levels
   - Lung function

2. Future risks
   - recurrent exacerbations
Severe Asthma

- impaired lung function
- no sufficient control by standard treatment (ACT)
- Exacerbations (Emergency room, hospital)
- Comorbidity, multiple allergies

Prevalence of wheeze persists after 5 years of age in atopic children

Wheezing at school age (5–7 years):
- - Non-atopic
- - Atopic

Prevalence (%)

Age (years)

Early sensitisation and allergen exposure to perennial allergens * and lung function at school age

* Sensitisation / exposure to mites and/or cats up to the age of 3 years
Prevalence of asthma at **age 7**, stratified for sensitization pattern and family history

<table>
<thead>
<tr>
<th>Sensitization Pattern</th>
<th>Negative Family History for Asthma/Atopy</th>
<th>Positive Family History for Asthma/Atopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>No sensitization</td>
<td>3/183</td>
<td>3/158</td>
</tr>
<tr>
<td>Transient sensitization</td>
<td>0/47</td>
<td>1/14</td>
</tr>
<tr>
<td>Late sensitization</td>
<td>0/29</td>
<td>0/3</td>
</tr>
<tr>
<td>Persistent sensitization</td>
<td>1/13</td>
<td>16/70</td>
</tr>
</tbody>
</table>

* p-value of Chi tests: *p*<0.05
** *p*<0.001 in comparison to no sensitization/negative family history

---

**Standard Therapy**

- Allergen Elimination
- Pharmacotherapy according to Guidelines
- Immunotherapy (in most cases contraindicated)
- Anti-IgE

---

**Recognized plateau effect in efficacy – but increased risk of adrenal suppression**

<table>
<thead>
<tr>
<th>Daily dose of inhaled fluticasone propionate (µg)</th>
<th>Percentage affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>100</td>
<td>20%</td>
</tr>
<tr>
<td>200</td>
<td>60%</td>
</tr>
<tr>
<td>500</td>
<td>100%</td>
</tr>
</tbody>
</table>

LDSSST = low-dose synthet test

**Allergic airway disease**

<table>
<thead>
<tr>
<th>Monospecific Allergy</th>
<th>Multiple Allergies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trees</td>
<td>Trees + Grasses + Ragweed</td>
</tr>
<tr>
<td>Grasses</td>
<td></td>
</tr>
<tr>
<td>Ragweed</td>
<td>- Anti-IgE?</td>
</tr>
<tr>
<td></td>
<td>- Combination of anti-IgE and SIT</td>
</tr>
</tbody>
</table>

**SYMPTOM LOAD**

(Grass pollen season)

- Symptom load (median)
- P = 0.001
- P = 0.02
- P = 0.01

- SIT birch + Placebo
- SIT birch + Omalizumab
- SIT grass + Placebo
- SIT grass + Omalizumab

* = Wilcoxon test (2-sided)

**Omalizumab inhibits the asthmatic early and late phase reaction**

- Placebo
- Omalizumab

FEV (% Ausgangswert)

Vor Behandlung → Nach 56-tägiger Behandlung

Tagesdiagramm (Stunden)
Efficacy and safety of omalizumab in children with moderate-to-severe persistent allergic (IgE-mediated) asthma

IA05: the largest controlled study of omalizumab in paediatric allergic asthma

IA05: Inclusion Criteria

- Moderate-to-severe allergic (IgE-mediated) asthma*
- Perennial allergy (skin-prick positive or RAST)
- ≥12% increase in FEV₁ after taking short-acting β₂-agonist
- Past medical history of exacerbations
- Inadequate asthma symptom control (day or night) despite ICS dose equivalent to fluticasone DPI ≥200 µg/day (with or without other controller asthma medications)
- Pre-specified severe subgroup: high-dose (fluticasone ≥500 µg/day) ICS plus LABA

*LMTB 2002 criteria
RAST = radioallergosorbent test
FEV₁ = forced expiratory volume in 1 second
DPI = dry powder inhaler

Medical history and current medical conditions illustrate atopic burden

<table>
<thead>
<tr>
<th>Condition</th>
<th>IA05 safety population (n=628)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic rhinitis</td>
<td>276 (43.9%)</td>
</tr>
<tr>
<td>Perennial rhinitis</td>
<td>116 (18.5%)</td>
</tr>
<tr>
<td>Seasonal allergy</td>
<td>108 (17.2%)</td>
</tr>
<tr>
<td>Food allergy</td>
<td>105 (16.7%)</td>
</tr>
<tr>
<td>Eczema</td>
<td>97 (15.4%)</td>
</tr>
<tr>
<td>Gastroesophageal reflux</td>
<td>91 (14.5%)</td>
</tr>
<tr>
<td>Seasonal rhinitis</td>
<td>77 (12.3%)</td>
</tr>
<tr>
<td>Dermatitis atopic</td>
<td>63 (10.0%)</td>
</tr>
<tr>
<td>Drug hypersensitivity</td>
<td>62 (9.9%)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>58 (9.2%)</td>
</tr>
<tr>
<td>Allergic conjunctivitis</td>
<td>57 (9.1%)</td>
</tr>
</tbody>
</table>

Novartis data on file
IA05: Study Design

Primary endpoint: clinically significant asthma exacerbation rate (24 weeks)

Definition
- Worsening of asthma symptoms, as judged clinically by the investigator, requiring
  - doubling of the baseline ICS dose for at least 3 days and/or
  - treatment with rescue systemic (oral or IV) corticosteroids
- 88% of patients with exacerbations treated with OCS

Exacerbations reduced and efficacy maintained over time (mITT)
Meaningful reductions in severe exacerbations and hospitalizations over 52 weeks

<table>
<thead>
<tr>
<th>mITT</th>
<th>High-dose ICS + LABA subgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td>% reduction compared with placebo</td>
<td></td>
</tr>
<tr>
<td>Severe exacerbations*</td>
<td>50%; p=0.004</td>
</tr>
<tr>
<td>Hospitalization rate</td>
<td>47%; p=0.08</td>
</tr>
</tbody>
</table>

- In a severe adult population, pooled analyses showed 56% reduction in severe exacerbations* (p=0.001) and 52% reduction in hospitalizations (p=0.041).1

*Clinically significant exacerbation where, in addition, FEV1 or PEF <80% personal best

1. Novartis data on file

Consistent reduction in exacerbations irrespective of baseline FEV1 (high-dose ICS + LABA subgroup)

Percent predicted FEV1

- FEV1 <80% predicted (n=103)
- FEV1 ≥80% predicted (n=132)

Decreased risk of exacerbations
Increased risk of exacerbations

Rate ratio (logarithmic scale)

AEs of special interest: Summary

- One anaphylactic reaction in each treatment group; neither case due to study medication
- No malignancy in omalizumab-treated children
- No thrombocytopenia
- No serum sickness
In the EU, omalizumab indication recently extended to include children (6–<12 years) with severe persistent allergic asthma

- Add-on therapy to improve asthma control in patients (>6 years) with
  - severe persistent allergic asthma
  - positive skin test or in-vitro reactivity to a perennial allergen
  - frequent daytime symptoms or night-time awakenings
  - multiple documented severe asthma exacerbations despite daily high-dose ICS, plus a LABA
  - In patients ≥12 years: reduced lung function (FEV₁ <80%)

- Omalizumab treatment should only be considered for patients with convincing IgE-mediated asthma

FEV₁ = forced expiratory volume in 1 second; ICS = inhaled corticosteroid
LABA = long-acting β₂-agonist

Omalizumab for the management of paediatric asthma: Conclusions

- Paediatric asthma remains a significant problem
  - treatment may include allergen avoidance, pharmacotherapy and, if appropriate, specific immunotherapy

- Targeting IgE is a rational approach in the treatment of paediatric allergic (IgE-mediated) asthma

- Omalizumab has been shown to reduce clinically significant and severe asthma exacerbations in children

- Omalizumab has a favourable safety profile in children
We look forward to welcoming you to the 2011 World Allergy Congress!

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