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1ST WAO INTERNATIONAL SCIENTIFIC CONFERENCE

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

DUBAI, UAE
5–8 DECEMBER 2010

Leading up to the XXII World Allergy Congress — Cancún, México, 4–8 December 2011

www.worldallergy.org/2010Dubai
“Asthma Phenotypes and Heterogeneity of Therapeutic Responses: Personalized Medicine in the 21st Century”

Program

Moderators:
Richard F. Lockey, MD FAAAAI
University of South Florida
Tampa, FL, USA

Paul A. Greenberger, MD FAAAAI
Northwestern University
Chicago, IL, USA

   Richard F. Lockey and Paul A. Greenberger

2. Obese vs. Non-Obese
   Louis-Philippe Boulet MD, FCCP, FRCPC
   Laval University Heart & Lung Institute
   Québec, QC, Canada

3. Aspirin Exacerbated Respiratory Disease
   Marek L. Kowalski, MD PhD
   Medical University of Łódź
   Łódź, Poland

4. Allergic vs. Non-Allergic
   Paul M. O’Byrne, MD
   Firestone Institute for Respiratory Diseases, McMaster University
   Hamilton, ON, Canada

Upon completion of this session, participants should be able to:
- Discuss the role of genetic phenotypes in predicting patient responses to asthma therapy;
- Discuss the effect of obesity on asthma severity and symptoms;
- Describe the pathological mechanisms underlying aspirin-induced exacerbations of respiratory disease and thus the selection of appropriate therapy;
- Explain the different treatment strategies available for IgE-mediated and non-IgE mediated allergic asthma and non-allergic asthma

2010-2011 World Allergy Forum 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.

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## 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
- 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
Canadian Society of Allergy and Clinical Immunology
Chinese Society of Allergology
(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 of 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
Georgian Association of Allergology and Clinical Immunology
German Society for Allergology and Clinical Immunology
Hellenic Society of Allergology and Clinical Immunology
Honduran Society of Allergy and Clinical Immunology
Hungarian Society of Allergology and Clinical Immunology
Icelandic Society of Allergy and Immunology
Indian College of Allergy, Asthma and Applied Immunology (ICAAC)
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
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Latvian Association of Allergists
Lebanese Society of Allergy and Immunology
Malaysian Society of Allergy and Immunology
Mexican College of Clinical Immunology and Allergy
Mexican College of Pediatricians Specialized in Allergy and Clinical Immunology
Mongolian Society of Allergy
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
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Romanian Society of Allergology and Clinical Immunology
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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
Algerian Society of Allergy and Immunology
Egyptian Society of Allergy and Clinical Immunology
Ecuadorian Society of Allergy and Immunology
Ecuadorian Society of Allergy and Affiliated Sciences
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Kuwait Society of Allergy and Clinical Immunology
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Swedish Association for Allergology

Regional Organizations

Asia Pacific Association of Allergy, Asthma and Clinical Immunology
Commonwealth of Independent States Society of Immunology and Allergology
European Academy of Allergology and Clinical Immunology
Latin American Society of Allergy and Immunology

Affiliate Organizations

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

For WAO membership information please contact the Secretariat
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Tel: +1 414 276 1791 • Fax: +1 414 276 3349
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Web site: www.worldallergy.org
March 1, 2010

Dear Colleagues,

It is good to bring World Allergy Forum back to the vibrant city of New Orleans, for the 36th Symposium in the World Allergy Organization program, Asthma Phenotypes and Heterogeneity of Therapeutic Responses: Personalized Medicine in the 21st Century.

The focus of World Allergy Organization’s activities for 2010-2011 will be allergic co-morbidities, and so it is fitting that our first presentation, from Louis-Philippe Boulet, will look at asthma in patients with obesity. The presentation will guide us about the factors that could lead to an over-diagnosis of asthma in the obese patient. Does obesity lead to asthma, or are there common genetic/environmental influences that predispose to both asthma and obesity? Why is asthma more difficult to control in the obese patient, and what are the optimal management strategies?

Marek Kowalski is a leading authority on aspirin-exacerbated respiratory disease (AERD). We will hear about the pathomechanisms of AERD and new insights into the role of Staphylococcus aureus enterotoxins in the development of underlying chronic airway inflammation in AERD patients. Several AERD phenotype-specific management strategies will be proposed.

Allergic and non-allergic asthma phenotypes will be discussed by Paul O’Byrne, who will consider the finding that even in “non-allergic” asthmatics, associations have been shown between asthma severity and serum IgE levels. Paul will review how monitoring the airway inflammatory response using induced sputum can determine therapy requirements, and will look at the role of monoclonal antibodies and IL-8 receptor antagonists in severe asthma with persisting eosinophilia and neutrophilia.

It promises to be an excellent session!

World Allergy Organization would like to thank the American Academy of Allergy, Asthma and Immunology for hosting today’s symposium, and to acknowledge the unrestricted educational grant from Novartis that supports the World Allergy Forum program.

With best regards,

Richard F. Lockey, MD FAAAAI
President
World Allergy Organization

Paul A. Greenberger, MD FAAAAI
President
American Academy of Allergy, Asthma and Immunology
An increased prevalence of asthma has been reported in obese subjects, both in adults and children, and particularly in women. In most instances, obesity precedes the development of asthma. However, the mechanisms by which obesity could influence the development of asthma are still uncertain. Various contributing factors have been suggested, such as an alteration in lung function from obesity-related mechanical changes, inflammatory, hormonal or neurogenic mechanisms, an increased prevalence of co-morbid conditions, or common genetic or developmental influences. The possibility of asthma over-diagnosis due to the presence of asthma-like symptoms in the obese has also been suggested but recent evidence suggests that this does not explain the increased prevalence of asthma in subjects with increased Body Mass Index (BMI). It is still unclear if the risk of developing asthma in the obese is related to an increased prevalence of allergic sensitization, or if the pattern of body fat distribution influences the prevalence of associated asthma. Obesity is associated with systemic inflammation and oxidative stress but how these could possibly translate into changes in airway function is uncertain. Furthermore, changes in adipokines serum levels, such as increases in serum leptin and reductions in adiponectin are found in obese asthmatic patients but these changes seem more related to obesity per se than to asthma. Furthermore, although many animal and human studies suggest a positive association between BMI and airway hyperresponsiveness, this has been challenged. An increasing number of studies, however, show that asthma is more difficult to control in the obese, possibly due to a change in its phenotype, associated with a less eosinophilic airway inflammation, a reduced response to asthma medications, or to other contributing factors. Obesity or weight gain are associated with an increased health-care utilization and poorer asthma-related quality of life. Improvements in asthma-related clinical/inflammatory parameters seem less in the obese than in the non-obese following inhaled corticosteroids, and although reports suggest that response to leukotriene antagonists is, less influenced by obesity, additional studies are needed to determine what could be the optimal pharmacological treatment of asthma in the obese. Otherwise, in those with increased BMI, weight reduction has led to a universal improvement of asthma symptoms and a reduction in medication needs. More research is needed to determine the link between asthma and obesity and the optimal management of asthma in the obese.

References


Beuther DA, Sutherland ER. Overweight, obesity, and incident asthma: a metaanalysis of prospective epidemiologic studies. Am J Respir Crit Care Med 2007;175:661-6.


Sutherland ER, Gowan JD, Taylor DK. Dynamic hyperinflation with bronchoconstriction: differences between obese and non-obese women with asthma. Am J Respir Crit Care Med 2008; 177:970-975.


Asthma in the obese vs non-obese

Synopsis

- The links between asthma and obesity
- Pulmonary function and airway inflammation
- Clinical features and asthma control
- Asthma treatment responses
- Remaining questions

Phenotyping asthma

“The general consensus now emerging is that, even in adults, asthma is unlikely to be a single disease entity ... or perhaps, asthma as a symptom is really only the clinical manifestation of several distinct diseases...”

A plea to abandon asthma as a disease concept
The Lancet 2006

“Phenotype” refers to ‘a set of observable characteristics of an individual or group resulting from the interaction of its genotype with its environment’

Oxford English Dictionary
How many subjects with MD-diagnosed asthma had a diagnosis of asthma excluded after thorough investigation?

Obese group: $77/242 = 31.8\%$ (95% CI: 26.3-37.9%).
Non-obese group: $73/254 = 28.7\%$ (95% CI: 23.5-34.6%).

The link between obesity and asthma

**Common etiologies**
- In utero conditions
- Genetics
- Environmental exposures
- Dietary factors (e.g. antioxidants, omega-3 fatty acids)

**Effects of obesity on lung mechanics**
- FRC
- RV
- Airway closure
- Loss of bronchoprotective mechanisms

**Systemic inflammation**
- Cytokines (TNFα, IL-6)
- Chemokines (IL-8, MCP-1)
- Oxidative mechanisms
- Acute phase reactants
- Other factors (VEGF)

**Energy regulating hormones**
- Leptin
- Adiponectin
- Visfatin

**Co-morbidities**
- Dyslipidemia
- GERD
- SDB
- Type 2 diabetes
- Hypertension

Adapted from Shore 2018

Candidate genes of potential relevance for both obesity and asthma

<table>
<thead>
<tr>
<th>Locus</th>
<th>Candidate Genes</th>
<th>Relevance to Asthma</th>
<th>Relevance to Obesity</th>
</tr>
</thead>
<tbody>
<tr>
<td>5q</td>
<td>ADRB2, NRC1</td>
<td>Controls airway tone</td>
<td>Controls metabolic rate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Modulates inflammation</td>
<td>Modulates inflammation</td>
</tr>
<tr>
<td>6p</td>
<td>TNF HLA gene cluster</td>
<td>Modulates immune and inflammatory responses</td>
<td>Modulates immune and inflammatory responses</td>
</tr>
<tr>
<td>11q13</td>
<td>UF5E, VCP3, TRAF6</td>
<td>Unknown</td>
<td>Thi inflammatory response</td>
</tr>
<tr>
<td></td>
<td>(FGF19)</td>
<td></td>
<td>Unknown</td>
</tr>
<tr>
<td>12q</td>
<td>STAT6, BFG1, IL1A, IL18H</td>
<td>Modulates inflammatory responses</td>
<td>Modulates inflammatory responses</td>
</tr>
<tr>
<td>17q</td>
<td>PRKCA</td>
<td>Role in cellular proliferation and differentiation</td>
<td>Negative feedback inhibitor of adipocyte differentiation and insulin signaling</td>
</tr>
</tbody>
</table>

Beuther et al. AJRCCM 2006
Murphy et al. Am J Hum Genet 2009
Pulmonary function and obesity

- FRC but not RV = ERV
- Tidal volume
- ERV may approach or be exceeded by closing volume
- VC and TLC normal but if marked obesity
- FEV₁ and FVC ↓ with increasing BMI
- Loss of bronchoprotection from deep inspiration

Obesity is associated with a loss of bronchoprotective effect of deep inspiration

Obesity and airway responsiveness

- Obesity associated with increased airway responses in animal models 1,2
  - Increased airway responses in leptin deficient, leptin receptor deficient, and overfed mice
  - Leptin increases allergic and nonallergic airway responses
  - Adiponectin infusion reduces allergic airway responses

- Controversial data in humans:
  - Associated with increased AHR (weak) 3,4
  - Not associated with AHR 5,6

1 Shore et al. JAP 2006
2 Shore et al. Pharm Ther 2007
3 Chinn Thorax 2002
4 Soed J Asthma 2006
5 Schachter et al. Thorax 2001
ASTHMA VS OBESITY: two inflammatory conditions

Asthma
- Chronic airway inflammation
- CD4T H2 lympho
- Mast cells
- Eosinophils
- IL4, IL5, IL13
- RANTES, eotaxin, MCP-1

Obesity
- Chronic low-grade inflammation
- Total leucocytes count α BMI
- Adipose tissue macrophages ↑
- Leptin ↑ (IL6)
- Adiponectin ↓

Markers of systemic inflammation

- Levels of C-reactive protein and fibrinogen were elevated in obese women suggesting systemic inflammation

How can systemic inflammation influence asthmatic inflammation?

- Biomarkers of systemic inflammation increased in obese versus normal-weight individuals (e.g., IL-6 and CRP) - highest levels in the obese asthmatic group, but no difference with non-obese subjects with asthma
- Biomarkers in sputum supernatant (IL-1β, IL-5, IL-6, IL-8) significantly increased in subjects with asthma compared with subjects without asthma - highest in the obese asthmatic group, but no significant differences compared with nonobese
- For CRP, the effects of obesity and asthma were additive.
- No clear evidence of an interaction between obesity-related adipokines and airway inflammation

Sutherland et al. AJRCCM 2008
Systemic inflammation/adipokines and asthma in the obese patient

- C-reactive protein increased in obesity, but not always associated with asthma
- Most human studies using a small precipitin assay did not show an convincing association between adipokines and asthma
- Oxidative stress (e.g., Prasma F2-iso prostane) have been associated with elevated BMI but not asthma

Obesity and airway inflammation

Non-asthmatic subjects with normal AR

Sputum cell counts and lipid index in participants with asthma according to body mass index category

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sputum indices</td>
<td>&lt;20 (n=8)</td>
</tr>
<tr>
<td>TCC (x10^6/ml)</td>
<td>3.2 (0.8-49.5)</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>0.4 (26.7)</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>0.4 (0-53.0)</td>
</tr>
</tbody>
</table>

Cell count

Boulet et al. Unpublished data

Lessard et al. CHEST 2008

Bronchial inflammation

r=0.38 p=0.01

r=0.42 p=0.01
Relationships between obesity and airway inflammation

Van Veen et al. Allergy 2008

Asthma and co-morbidities

Boulet LP. Eur Resp J 2009

Asthma Control & Symptoms Perception

Obese women have poorer asthma control than non-obese women (p > 0.05)

Boulet et al. Unpublished data
**Influence of obesity on asthma control**

% Patients who achieve asthma control with salmeterol+ fluticasone vs fluticasone only

- **SFC controlled**
- **FP controlled**

*Boulet & Frassen. Resp Med 2007*

---

**Placebo-adjusted LS mean Asthma control days by BMI category for montelukast and beclomethasone**

*Peters-Golkin et al. ERJ 2006*

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**BMI category and change in outcome in inhaled glucocorticoid treated-subjects**

<table>
<thead>
<tr>
<th>Variable</th>
<th>BMI &lt; 25</th>
<th>BMI ≥ 25</th>
<th>P Value for difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1 (L)</td>
<td>2.50</td>
<td>2.94</td>
<td>.8/6</td>
</tr>
<tr>
<td>FEV1 (% predicted)</td>
<td>1.68</td>
<td>1.11</td>
<td>.2/3</td>
</tr>
<tr>
<td>Quality of life</td>
<td>0.31</td>
<td>0.24</td>
<td>.4/5</td>
</tr>
<tr>
<td>PC20 FEV1</td>
<td>0.19</td>
<td>0.30</td>
<td>.6/6</td>
</tr>
<tr>
<td>FEF25-75</td>
<td>-6.54</td>
<td>-3.57</td>
<td>.04/05</td>
</tr>
<tr>
<td>Average daily symptoms</td>
<td>-0.03</td>
<td>-0.14</td>
<td>.6/5</td>
</tr>
<tr>
<td>Average daily rescue use</td>
<td>-0.24</td>
<td>-0.20</td>
<td>.4/5</td>
</tr>
</tbody>
</table>

*Adapted from Sutherland ER et al JACI 2009*
Influence of weight loss on asthma: a systematic review

Eneli et al. Thorax 2008

- Few studies have addressed reversibility of obesity in regard to asthma features
- Heterogeneity of interventions
- All 15 studies showed improvements of at least one asthma outcome

Correlation between weight loss & lung function

Aaron et al, Chest 2004

The “obesity” asthma phenotype

Etiology: genetics? change in lung mechanics? fat intake? Systemic inflammation?
Clinical Features: predominant in women more difficult-to-control asthma increased prevalence of co-morbidities
Physiological findings: low ERV (breathing at low lung volumes) increased work of breathing loss of DI protective effect
Inflammatory patterns: less eosinophilic systemic inflammation
Treatment response: reduced, particularly ICS
Outcomes: improves with weight reduction long-term outcome uncertain
Asthma in the obese vs non-obese

Remaining questions

• How can obesity promote the development of asthma?
• Can systemic inflammation influence airway function?
• What is the optimal asthma pharmacological treatment of asthma in the obese?
• What is the natural history of asthma in the obese?

Conclusion

Asthma in the obese is a specific phenotype

– Different clinical features, airway function & inflammatory pattern
– Increased severity, morbidity and poorer control
– Reduced response to standard therapy

More research needed…
The coexistence of hypersensitivity to aspirin with rhinosinusitis/nasal polyps and bronchial asthma has been referred to as “aspirin triad” and more recently the term aspirin-exacerbated respiratory disease (AERD) has been proposed. The incidence of AERD varies from 5% in mild asthmatics up to 24% in more severe groups of patients with asthma. Patients with AERD suffer from persistent asthma of greater than average severity and of higher than ordinary medication requirements, including poor response to steroids. Rhinosinusitis has usually a protracted course and is complicated by mucosal hypertrophy and polyph formation.

The mechanism of the aspirin-induced reaction is not immunological, but seems to be related to inhibition by aspirin (or other NSAID) of cyclooxygenase-1, leading to release of mast cell derived mediators and enhanced production of leukotrienes. The pathomechanism of persistent eosinophilic inflammation of the lower and upper airway mucosa, a typical feature for AERD, is not related to intake of aspirin, but may result from inherited and/or acquired AA metabolism abnormalities including overproduction of cysteinyl leukotrienes and deficiency of anti-inflammatory lipoxins. More recently, an immunological response to Staphylococcus aureus enterotoxins has been implicated in the development of underlying chronic inflammation in the airways of patients with AERD.

Although management of asthma and rhinosinusitis in a patient with AERD follows general guidelines, several AERD phenotype specific measures should be considered. Careful avoidance of ASA and other NSAIDs in sensitive patients is important, since aspirin may be a cause of severe asthmatic attacks. For the majority of aspirin-hypersensitive patients an alternative anti-inflammatory drug can be found, and selective COX-2 inhibitors (e.g. celecoxib) are well tolerated by patients with AERD. Management of chronic rhinosinusitis includes topical steroids, which are quite effective in controlling symptoms of rhinitis and slow down recurrence of nasal polyps in most patients. Various nasal surgical procedures may be needed to relieve chronic rhinosinusitis and to remove nasal polyps, although patients with AERD respond less well to surgical intervention. Inhaled glucocorticosteroids, often in combination with long acting beta-2 agonists, are the most effective drugs for controlling asthmatic inflammation and asthma symptoms in aspirin-sensitive patients. Although leukotriene receptor antagonists and synthesis inhibitors have been shown to be of clinical benefit in patients with AERD, the magnitude of improvement does not exceed that observed in ASA-tolerant patients. A more specific approach to AERD is aspirin given orally after desensitization. In a subgroup of patients ingestion of aspirin after desensitization results in alleviation of chronic symptoms from both upper and lower airway and in a decreased need for nasal/sinus surgery.

References
Aspirin Exacerbated Respiratory Disease

World Allergy Forum
2010 AAAAI Annual Meeting

Marek L. Kowalski, M.D., Ph.D.
Department of Immunology, Rheumatology and Allergy
Medical University of Łódź, Poland

Aspirin-induced asthma – the oldest known asthma phenotype

- Patient J.M., 40 years old
- The disease began 11 years ago (in 1912) with symptoms of rhinitis related to polypoid mucosal hypertrophy and associated with frequent "colds" and coughing, but without fever.
- He had several polypectomies which relieved symptoms temporarily ...
- Few years later he experienced an acute asthma attack at night after ingesting a tablet of aspirin ...
- He suffers a severe asthma with several attacks during day and night ...


The milestones in the history of aspirin sensitivity

- 1902 – R. Hirschberg the first case of ASA-sensitivity reported
- 1922 - F. Widal "ASA-triad"
- 1967 - M.Samter ASA-sensitivity as a clinical entity
- 1975 - A. Szczeklik "prostaglandin inhibition" theory of AIA
Aspirin Exacerbated Respiratory Disease

NSAIDs - Induced symptoms
- Hyperplastic CRS with nasal polyps
- Moderate to severe asthma

Aspirin triad: Widal’s Syndrome, Santor’s Syndrome; Aspirin-Induced Asthma

Prevalence of aspirin sensitivity among patients with asthma

AERD as a severe asthma phenotype

- Higher medication requirements, including dependence on oral GCS (Szczeklik A. et al. 2000)
- Irreversible airway obstruction
- More likely to have been intubated and to have a steroid burst in the previous three months (Mascola K et al. 2005)
- Frequent exacerbations (Koga T. et al. 2006)
- Association with near fatal asthma (Plaza W. et al. 2002)

Risk factors for severe asthma

GR > 2.6
Pathomechanisms of Aspirin Exacerbated Respiratory Disease

I. Acute symptoms precipitated by ASA and NSAIDs

ASA / NSAID's → COX → Leukotrienes
- Tryptase
- Histamine
- ECP
- 15-HETE

EOS
Mast cell

Bronchial
Nasal
Occular
symptoms

II. Chronic symptoms and underlying airway inflammation

Unrelated to ASA or other NSAIDs intake !!!

Cell membrane phospholipids

ASA → PLA → Arachidonic acid → 5-LOX → 5-LOX → LTA₄ → LTD₄ → LTE₄

COX-1
PGH₂
EP-R
PGG₂

EOS
Mast cell

Asthma
Rhinorrhea
Role of infections in the pathogenesis of AERD

- Viral hypothesis (A. Szczeklik; 1988)
  - Flu-like symptoms precede the development of aspirin-sensitivity
  - Chronic viral respiratory tract infection may both initiate and perpetuate chronic airway inflammation in AERD

- Enterotoxin hypothesis (C. Bachert; 2005)
  - Staphylococcus aureus enterotoxins (SAE) are potent superantigens and inflammatory cell activators
  - Specific IgE to SAE have been found in nasal polyp tissue
  - IgE to SAE are associated with eosinophilic inflammation in rhinosinusitis

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**IgE to SAEs in ASA-sensitive and ASA-tolerant polyps**

<table>
<thead>
<tr>
<th>Concentration of SAE-specific IgE in nasal polyps</th>
<th>Correlation of SAE-IgE with ECP and IL-5 in nasal polyps</th>
</tr>
</thead>
<tbody>
<tr>
<td>![Graph showing IgE concentrations](C. Perez-Nova et al. Int. Archs All. Imm. 2004)</td>
<td>![Graph showing correlation](Y. Ish et al. Clin Exp Allergy 2004)</td>
</tr>
</tbody>
</table>

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**IgE to Staphylococcus aureus enterotoxins in serum and asthma severity - LODZ Study**

<table>
<thead>
<tr>
<th>Severe and non-severe asthmatics</th>
<th>ASA-tolerant and ASA-sensitive asthmatics</th>
</tr>
</thead>
<tbody>
<tr>
<td>![Graph showing IgE concentrations](N. Jowiszewski, C. Bachert et al. Allergy 2010 in press)</td>
<td>![Graph showing IgE concentrations](N. Jowiszewski, C. Bachert et al. Allergy 2010 in press)</td>
</tr>
</tbody>
</table>
Diagnosis of respiratory type of hypersensitivity to NSAIDs

- History
- Aspirin challenge
  - Oral
  - Inhaled
  - Intranasal
- In vitro testing
  - Cellular activation tests
    - BAT
    - ASPITest (15-HETE)
  - Urinary LTE4
- Genetic testing

Management of ASA-sensitive rhinosinusitis/asthma

Avoidance of NSAIDs
- Recommendations for selective COX-2 inhibitors

Pharmacologic treatment
- Intranasal / inhaled glucocorticosteroids
- Leukotriene antagonists – as effective as in ASA-tolerant patients

Sinus surgery / polypectomy
- Less effective in ASA-sensitive

Aspirin desensitization
- Clinical use: risks / benefits

Arachidonic acid

COX-1

COX-2

PGE, PGI2, TXB2

Prostaglandins

Cytoprotection
Regulation

Inflammation
**Cox-2 inhibitors and in AERD**

- Aspirin-induced asthma is a COX-1 dependent phenomenon
- Preferential Cox-2 inhibitors are tolerated by 80-90% of ASA-sensitive asthmatics
- Selective COX-2 inhibitors are generally well tolerated
- COX-2 selective NSAIDs can be used by ASA-sensitive asthmatics, but tolerance tests is recommended before an alternative drug is prescribed

---

**Clinical efficacy of leukotriene receptor inhibitors in ASA hypersensitive and ASA-tolerant patients**

- Add on therapy study: 3 months treatment with montelukast 10 mg
- Add on therapy study: 2 months treatment with zafirlukast 20 mg

---

**Endoscopic Sinus Surgery and CRS outcomes in ASA-sensitive and ASA-tolerant patients**

**Patients**
- 19 ASA-sensitive and 104 ASA-tolerant patients with CRS were recruited to prospective study
- Patients were subjected to ESS and followed for a mean of 11.7 months after surgery

**Results**
- Similar proportions of ASA sensitive and ASA-tolerant patients had improved:
  - Endoscopic scores
  - Quality of Life scores
- Larger proportions of ASA sensitive patients reported increased medication use

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Reference: Fagot S. et al., C E A 2001;31:1365.
Reference: Kowalski ML et al., 2008.
Aspirin desensitization in patients with AERD

- 1923 F. Vidal reported „desensitization“ to aspirin
- 1976 C. R. Zeiss & R.F. Lockey described refractory period to aspirin
- 1981 D.D. Stevenson reported clinical benefits of prolonged treatment with aspirin after desensitization

Daly oral ASA after desensitization (300-2400mg) in some patients may lead to:
- Improvement in asthma symptoms
- Improvement in rhinosinusitis symptoms
- Decreased need for sinus surgery/polypectomy

Indications for ASA-desensitization

- Aspirin sensitive asthma/rhinosinusitis
  - Patients with aggressive polypoid CRS
  - Patients do not responding to pharmacological treatment
  - Corticosteroid-induced side effects

- ASA-sensitive patients with
  - Coronary heart disease
  - Antiphospholipic syndrome
  - Chronic inflammatory diseases (AR; CA)

Overlapping phenotypes in AERD

- ASA-induced reactions
- Arachidonic acid abnormalities
- Eosinophilia
- Autoimmunity
- Nasal Polyps
- Chronic Rhinosinusitis
- Infections
- Severe/non severe asthma
Allergic vs. Non-Allergic Asthma

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Firestone Institute for Respiratory Diseases, McMaster University
Hamilton, ON, Canada

Asthma is frequently characterized as “allergic” and “non-allergic”. Allergic asthmatic patients are, in general, younger and have a better response to conventional therapy, particular to inhaled corticosteroids (ICS). Allergic asthma has been very well characterized and airway dendritic cells, Th2 cells, mast cells, basophils, and eosinophils are important in its pathobiology. Non-allergic asthmatic patients are often adult onset; it is associated with non-allergic co-morbidities, such as rhinosinusitis and gastroesophageal reflux, and is less responsive to ICS treatment. Exposure to small molecular weight occupational sensitizers is an important cause of non-allergic asthma and airway neutrophils are prominent. However, some studies have shown associations between asthma severity and serum IgE levels, even in “non-allergic” patients.

Therapy directed against IgE for asthma (omalizumab) had been demonstrated to improve asthma control, reduce asthma exacerbations and allow ICS dose reduction in allergic patients. It has not been evaluated in “non-allergic” patients. The use of other currently available asthma treatments does not distinguish between allergic and non-allergic patients. A more useful characterization for determining the treatment requirements of more severe asthmatic patients is to measure the airway inflammatory response, using induced sputum. Measuring sputum eosinophils had allowed the monitoring of doses of ICS treatment and a reduction in severe asthma exacerbations. Also, an anti-IL-5 mAb (mepolizumab) has been shown to allow prednisone reduction and reduce severe exacerbations in patients with severe asthma and a persisting airway eosinophilia. A similar approach in patients with a persisting airway neutrophilia may be possible with antagonists of the IL-8 receptor (CXCR2 antagonists).

References
Beek KH, Kjaall M, Buhl R. Elevation of total serum immunoglobulin E is associated with asthma in nonallergic individuals. *Eur Respir J* 2000; 16:609-14
Allergic vs. Non-Allergic Asthma

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Potential for Conflict of Interest

• **Advisory Boards**: AstraZeneca, GlaxoSmithKline, Merck, Nycomed, Resisentia, Topigen.
• **Speakers Fees**: AstraZeneca, Chiesi, GlaxoSmithKline, Nycomed, Ono Pharma.
• **Grants-in-Aid**: AstraZeneca, Alexion, Boehringer Ingelheim, Genentech, GlaxoSmithKline, Medimmune, Merck, Pfizer, Schering Plough, Wyeth.

Allergic vs. Non-Allergic Asthma

<table>
<thead>
<tr>
<th><strong>Allergic Asthma</strong></th>
<th><strong>Non-Allergic Asthma</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Childhood onset</td>
<td>Adult onset</td>
</tr>
<tr>
<td>Allergic triggers</td>
<td>Triggers often unknown</td>
</tr>
<tr>
<td>IgE mediated</td>
<td>Non-IgE mediated</td>
</tr>
<tr>
<td>Allergic co-morbidities</td>
<td>Non-allergic comorbidities</td>
</tr>
<tr>
<td>Th2 dependent</td>
<td>T-cell dependence unclear</td>
</tr>
<tr>
<td>Mast cells, basophils, eosinophils involved.</td>
<td>Neutrophils involved</td>
</tr>
<tr>
<td>Responsive to ICS</td>
<td>Not responsive to ICS</td>
</tr>
</tbody>
</table>
What is Non-Allergic Asthma?

Table 1: Characteristics of nonallergic asthmatics

<table>
<thead>
<tr>
<th>IgE &lt;50 U·mL⁻¹</th>
<th>IgE &gt;150 U·mL⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects n</td>
<td>62</td>
</tr>
<tr>
<td>Age yrs</td>
<td>39±13</td>
</tr>
<tr>
<td>Sex M/F</td>
<td>38/62</td>
</tr>
<tr>
<td>Caucasian race</td>
<td>96</td>
</tr>
<tr>
<td>Occupational exposure to inhalants</td>
<td>13</td>
</tr>
<tr>
<td>Current smokers</td>
<td>18</td>
</tr>
<tr>
<td>Cigarettes/day</td>
<td>15±5</td>
</tr>
<tr>
<td>Free smoke</td>
<td>18</td>
</tr>
<tr>
<td>ECS usage</td>
<td>47</td>
</tr>
</tbody>
</table>

Data presented as percentage unless otherwise stated. IgE: immunoglobulin E; ECS: inhaled corticosteroid; *p=0.04.

Airway Inflammation in Non-Allergic Asthma

Pharmacology of Allergen-Induced Responses

**TRUE POSITIVES**
- All conventional ICS
- LABAs
- Combination ICS/LABA
- SABAs
- Anti-LTs
- Anti-IgE
- Theophylline

**TRUE NEGATIVES**
- Esterase-sensitive steroids
- PAF antagonists
- Inhaled anti-LTs
- Thromboxane antagonists

**POSSIBLY TRUE NEGS**
- β selectin inhibitors
- ? VLA-4 antagonists
- ? ISS

---

Pharmacology of Allergen-Induced Responses

**FALSE POSITIVES**
- Anti-CD11a
- PGE₂
- ? PDE4 antagonists
- PGE₁ analogue
- ? Heparin derivatives

**FALSE NEGATIVES**
- Mepolizumab

---

![Graph](image)

**% Change in FEV₁**
- Placebo
- Budesonide
- Montelukast
- Combination

*Leigh R, et al., Am J Respir Crit Care Med 2002; 166:1212-7*
Lord Kelvin (1824-1907)

“When you can measure what you are speaking about and express it in numbers, you know something about it; but when you cannot measure it, when you cannot express it in numbers, your knowledge is of a meager and unsatisfactory kind.”

Induced Sputum

Freddy Hargrave

---

Severe Exacerbations (number)

Time (months)

BTS management group

Sputum management group

GREEN R, et al. LANCET 2002; 360: 1115-21
**Prednisone Reduction**

![Graph showing prednisone reduction as % of maximum possible reduction.](image)

- **n=9** for mepolizumab
- **n=10** for placebo

*P < 0.05*


**Asthma Exacerbations**

![Graph showing asthma exacerbations.](image)

- No. at Risk
  - Mepolizumab: 9, 9, 8, 7, 7, 7, 7
  - Placebo: 10, 9, 7, 5, 4, 3, 2


**Refractory Eosinophilic Asthma**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mepolizumab (n=12)</th>
<th>Placebo (n=12)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (no. of subjects)</td>
<td>14</td>
<td>14</td>
<td>0.80</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>15</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>48</td>
<td>50</td>
<td>0.54</td>
</tr>
<tr>
<td>Mean</td>
<td>23-49</td>
<td>24-72</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at onset of symptoms (yr)</td>
<td>26</td>
<td>26</td>
<td>0.99</td>
</tr>
<tr>
<td>Mean</td>
<td>2-53</td>
<td>2-57</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass (kg)</td>
<td>29.4±4.7</td>
<td>29.1±3.9</td>
<td>0.92</td>
</tr>
<tr>
<td>Positive sputum (no. of patients)</td>
<td>6/7</td>
<td>6/8</td>
<td>0.78</td>
</tr>
<tr>
<td>Total sputum (no. of patients)</td>
<td>27/6±247</td>
<td>19±6±64</td>
<td>0.75</td>
</tr>
</tbody>
</table>

Conclusions

- IgE is necessary for the clinical expression of allergic asthma, but may have a role in all asthmatic patients.
- Occupational asthma is a common cause of "non-allergic asthma"
- Allergen-induced airway responses have been extensively studied, involve Th2 responses, mast cells, basophils and eosinophils.
- Small molecular weight occupational sensitizers (particularly isocyanates) cause neutrophilic airway inflammation
Conclusions

- Omalizumab is the only specific therapy for allergic asthma.
- Measuring sputum inflammatory cells is useful in establishing therapeutic responses to ICS.
- Refractory eosinophilic asthma is improved by treatment with mepolizumab.
- CXCR2 antagonists will be useful to establish the role of neutrophils in “non-allergic” asthma
We look forward to welcoming you to the 2011 World Allergy Congress!

¡Deseamos darte la bienvenida al Congreso Mundial de Alergía 2011!

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