Il bambino con asma intrinseco

Carlo Capristo
Predictors of remitting, periodic, and persistent childhood asthma

Ronina A. Covar, MD, Robert Strunk, MD, Robert S. Zeiger, MD, PhD, Laura A. Wilson, ScM, Andrew H. Liu, MD, Scott Weiss, MD, MSc, James Tonascia, PhD, Joseph D. Spahn, MD, and Stanley J. Szefler, MD for the Childhood Asthma Management Program Research Group

The Childhood Asthma Management Program (CAMP) in children with mild to moderate persistent asthma.

- 4.3 years treatment
- 4 years follow-up
- 909 participants.

% ADOLESCENTS WITH

- Remitting: 6%
- Periodic: 39%
- Persistent: 55%

JACI 2010
Remission of asthma: The next therapeutic frontier?
Targeting the interleukin pathway in the treatment of asthma

Kian Fan Chung

Lancet 2015; 386: 1086–96

See Editorial page 1014

This is the second in a Series of two papers about Asthma
Experimental Studies, Airway Disease Section, National Heart and Lung Institute, Imperial College London, London, UK and National Institute for Health Research (NIHR), Respiratory Biomedical Research Unit, Royal Brompton & Harefield NHS Trust and Imperial College London, London, UK (Prof Kian Fan Chung DSc)
Asthma is a common heterogeneous disease with a complex pathophysiology. Current therapies based on inhaled corticosteroids and long-acting $\beta_2$ agonists are effective in controlling asthma in most, but not all patients, with a few patients falling into the severe asthma category. Severe asthma is characterised by poor asthma control, recurrent exacerbations, and chronic airflow obstruction despite adequate and, in many cases, high-dose treatments. There is strong evidence supporting the role for interleukins derived from T-helper-2 (Th2) cells and innate lymphoid cells, such as interleukins 4, 5, and 13, as underlying the eosinophilic and allergic inflammatory processes in nearly half of these patients. An anti-IgE antibody, omalizumab, which binds to circulating IgE, a product of B cells from the actions of interleukin 4 and interleukin 13, is used as treatment for severe allergic asthma. Studies examining cytokine blockers such as anti-interleukin-5, anti-interleukin-4Ra, and anti-interleukin-13 monoclonal antibodies in patients with severe asthma with recurrent exacerbations and high blood eosinophil counts despite use of inhaled corticosteroids have reported improved outcomes in terms of exacerbations, asthma control, and forced expiratory volume in 1 s. The US Food and Drug Administration’s recommendation to use an anti-interleukin-5 antibody for the treatment of severe eosinophilic asthma suggests that there will be a therapeutic place for these anti-Th2 agents. Biomarkers should be used to identify the right patients for such targeted approaches. More guidance will be needed as to which patients should receive each of these classes of selective antibody-based treatments. Currently, there is no treatment that targets the cytokines driving asthma associated with non-eosinophilic inflammation and low Th2 expression.
Novel diagnostic approaches and biological therapeutics for intrinsic asthma

María del Carmen Vennera¹-³
César Picado¹-³

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Abstract: Intrinsic asthma has been considered as a specific disease entity for a long time, although many controversies have emerged in relation to this concept. Of note, not finding specific allergen sensitization in an asthmatic patient neither excludes an allergic component nor the essential role that immunoglobulin E may play in asthma. The diagnostic approach should be similar in any patient suspected to have asthma. The atopic status is one among many other questions. Omalizumab, the only monoclonal anti-immunoglobulin E antibody commercialized for asthma, should be tried in patients with uncontrolled severe asthma independent of their atopic status.

Keywords: nonatopic asthma, immunoglobulin E, omalizumab
Novel diagnostic approaches and biological therapeutics for intrinsic asthma

Table 1 Diagnostic approach to asthma

<table>
<thead>
<tr>
<th>Clinical history</th>
<th>Diagnostic tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>General data: age, sex, height, and weight (body mass index), smoking</td>
<td>Spirometry with a bronchodilator test</td>
</tr>
<tr>
<td>Family history: asthma and atopic status</td>
<td>Nonspecific bronchial provocation test</td>
</tr>
<tr>
<td>Personal history: atopic dermatitis, allergic rhinitis, and conjunctivitis, other allergies</td>
<td>Common aeroallergen skin tests</td>
</tr>
<tr>
<td>History of asthma: age of onset, severity at baseline, treatments performed and response, asthma admissions, requirement for mechanical ventilation for asthma</td>
<td>Total serum IgE levels</td>
</tr>
<tr>
<td>Background: chronic rhinosinusitis with or without polyposis; sense of smell</td>
<td>Specific serum IgE levels</td>
</tr>
<tr>
<td>Background intolerance to nonsteroidal anti-inflammatory drugs</td>
<td>Peripheral blood eosinophil count</td>
</tr>
<tr>
<td>Background: gastroesophageal reflux</td>
<td>Sputum eosinophil count</td>
</tr>
</tbody>
</table>

**Abbreviation:** IgE, immunoglobulin E.
Genetics of allergic disease

- Environment sensing
  - TLR2, TLR4, CD14
  - GSTP1, GSTM1 -3, -5, GSTT1

- Atopic Immune Responses
  - HLAG, FCER1A, CD23
  - OPN3/CHML, CYFIP2, IL4, IL4RA, IL12, IL13
  - GATA3, STAT5, STAT6, TBX21, PHF11, IRAK1

- Eosinophils
  - IL1RL1, IL33
  - MYB, WDR36

- Barrier Function
  - FLG, SPINK5, CTNNA3
  - C11orf30, COL29A1, IL13, ORMDL3/GSDML, PENDRIN

- Tissue Response
  - ADAM33, UPAR, NPSR1, PDE4D
  - IRAK1
  - IL13
  - COL29A1, TNC

John W. Holloway JACI 2010
International consensus on (ICON) pediatric asthma

N. G. Papadopoulos\textsuperscript{1}, H. Arakawa\textsuperscript{2}, K.-H. Carlsen\textsuperscript{3}, A. Custovic\textsuperscript{4}, J. Gern\textsuperscript{5}, R. Lemanske\textsuperscript{6}, P. Le Souef\textsuperscript{2}, M. Mäkelä\textsuperscript{8}, G. Roberts\textsuperscript{9}, G. Wong\textsuperscript{10}, H. Zar\textsuperscript{11}, C. A. Akdis\textsuperscript{12}, L. B. Bacharier\textsuperscript{13}, E. Baraldi\textsuperscript{14}, H. P. van Bever\textsuperscript{15}, J. de Blic\textsuperscript{16}, A. Boner\textsuperscript{17}, W. Burks\textsuperscript{18}, T. B. Casale\textsuperscript{19}, J. A. Castro-Rodriguez\textsuperscript{20}, Y. Z. Chen\textsuperscript{21}, Y. M. El-Gamal\textsuperscript{22}, M. L. Everard\textsuperscript{23}, T. Frischer\textsuperscript{24}, M. Geller\textsuperscript{25}, J. Gereda\textsuperscript{26}, D. Y. Goh\textsuperscript{27}, T. W. Guilbert\textsuperscript{28}, G. Hedlin\textsuperscript{29}, P. W. Heymann\textsuperscript{30}, S. J. Hong\textsuperscript{31}, E. M. Hossny\textsuperscript{32}, J. L. Huang\textsuperscript{33}, D. J. Jackson\textsuperscript{34}, J. C. de Jongste\textsuperscript{35}, O. Kalayci\textsuperscript{36}, N. Aît-Khaled\textsuperscript{37}, S. Kling\textsuperscript{38}, P. Kuna\textsuperscript{39}, S. Lau\textsuperscript{40}, D. K. Ledford\textsuperscript{41}, S. I. Lee\textsuperscript{42}, A. H. Liu\textsuperscript{43}, R. F. Lockey\textsuperscript{44}, K. Lødrup-Carlsen\textsuperscript{45}, J. Lötvall\textsuperscript{16}, A. Morikawa\textsuperscript{47}, A. Nieto\textsuperscript{48}, H. Paramesh\textsuperscript{49}, R. Pawankar\textsuperscript{50}, P. Pohunek\textsuperscript{51}, J. Pongracic\textsuperscript{52}, D. Price\textsuperscript{53}, C. Robertson\textsuperscript{54}, N. Rosario\textsuperscript{55}, L. J. Rossenwasser\textsuperscript{56}, P. D. Sly\textsuperscript{57}, R. Stein\textsuperscript{58}, S. Stick\textsuperscript{59}, S. Szefler\textsuperscript{60}, L. M. Taussig\textsuperscript{61}, E. Valovirta\textsuperscript{62}, P. Vichyanond\textsuperscript{53}, D. Wallace\textsuperscript{64}, E. Weinberg\textsuperscript{65}, G. Wennergren\textsuperscript{66}, J. Wildhaber\textsuperscript{67} & R. S. Zeiger\textsuperscript{68}

Keywords
- asthma
- children
- consensus
- guidelines
- wheeze

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Abstract
Asthma is the most common chronic lower respiratory disease in childhood throughout the world. Several guidelines and/or consensus documents are available to support medical decisions on pediatric asthma. Although there is no doubt that the use of common systematic approaches for management can considerably improve outcomes, dissemination and implementation of these are still major challenges. Consequently, the International Collaboration in Asthma, Allergy and Immunology (ICAAI), recently formed by the EAACI, AAAAI, ACAAI, and WAO, has decided to propose an International Consensus on (ICON) Pediatric Asthma. The purpose of this document is to highlight the key messages that are common to many of the existing guidelines, while critically reviewing and commenting on any differences, thus providing a concise reference. The principles of pediatric asthma management are generally accepted. Overall, the treatment goal is disease control. To achieve this, patients and their parents should be educated to optimally manage the disease, in collaboration with healthcare professionals. Identification and avoidance of triggers is also of significant importance. Assessment and monitoring should be performed regularly to re-evaluate and fine-tune treatment. Pharmacotherapy is the cornerstone of treatment. In the optimal use of medication can, in most cases, help patients control symptoms and reduce the risk for future morbidity. The management of exacerbations is a major consideration, independent of chronic treatment. There is a trend towards considering phenotype-specific treatment choices; however, this goal has not yet been achieved.
International consensus on (ICON) pediatric asthma
Is intrinsic asthma synonymous with infection?

P. E. Dahlberg and W. W. Busse

Section of Allergy, Pulmonary and Critical Care, Department of Medicine, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA

Summary

Rackemann described the ‘intrinsic asthma’ population over 50 years ago as a unique subgroup that was characterized by onset of progressive loss of lung function beginning later in life, possibly after a respiratory infection. It has also been associated with a female predominance, aspirin-sensitive bronchospasm, and nasal polyposis. While the aetiology is not understood, we propose that persistent respiratory infections play a central role in the development of intrinsic asthma.
Role of viral respiratory infections in asthma and asthma exacerbations

William W Busse, Robert F Lemanske Jr, James E Gern

Lancet 2010; 376: 826–34
Is intrinsic asthma synonymous with infection?

The role of respiratory infections in asthma

INCEPTION
Healthy infant
- RV
- RSV
- PIV

Wheezing illness
Atopy
Resolution
Asthma

PREVENTION
Infant
- Virus infections type
- Frequency/severity age

TH1

UP

EXACERBATION
Child or adult with asthma
- Rhinovirus

Exacerbation of asthma
- Emergency room visits
- Hospitalization

TH1

DOWN

PERSISTENCE
Adult
(Pre-existing asthma?)
- Mycoplasma
- Chlamydia

Persistent asthma

DOWN

UP

TH2

Allergy/Asthma

↓ Allergy/Asthma

↓ TH1
Is intrinsic asthma synonymous with infection?

Healthy

Extrinsic asthma
Inhaled irritants
Vitamin D deficiency
Immune senescence

Acute infection

Chronic pulmonary infection
- Staphylococcus
- Rhinovirus
- Adenovirus
- Atypical bacteria
- Fungus

Intrinsic asthma
- Chronic obstruction with
- Progressive loss of lung function
429 otherwise healthy preterm infants born at a gestational age of 33 to 35 weeks

monthly palivizumab injections (214 infants) or placebo (215 infants) during the RSV season

Cumulative Wheezing Days for 429 Preterm Infants during the First Year of Life.

p=0.01

M. O. Blanken 2013
Novel severe wheezy young children phenotypes: Boys atopic multiple-trigger and girls nonatopic uncontrolled wheeze

Jocelyne Just, PhD, MD,¹ Rahele Gouvis-Echraghi, MD,² Remy Couderc, PhD, PharmD,³ Nathalie Guillemot-Lambert, MD,³ and Philippe Saint-Pierre, PhD⁵ Paris, France

✓ 2 cluster analysis with 20 variables.

✓ 551 children with active asthma, younger than 36 months old.
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The 3 clusters according to the percentage of multiple-trigger wheeze, severity, and atopy

- 2 cluster analysis with 20 variables.
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The 3 clusters according to the percentage of multiple-trigger wheeze, severity, and atopy

*MTW* is defined as wheezing during colds and with other triggers such as house dust, grass, pets, tobacco smoke, exercise, or cold air.
Novel severe wheezy young children phenotypes: Boys atopic multiple-trigger and girls nonatopic uncontrolled wheeze

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Paris, France

The 3 clusters according to the percentage of multiple-trigger wheeze, severity, and atopy

Severity is defined as the percentage of subjects with moderate to severe asthma, according to GINA classification.
Cluster 1, mild episodic viral wheeze (n= 327), consisted of children with wheezing related only to colds (71%), mild disease (76%), and mainly normal chest x-ray results.
Cluster 2, nonatopic uncontrolled wheeze (n = 157), was characterized by moderate to severe disease (91%), uncontrolled wheezing despite high doses of inhaled corticosteroids (55%), parents with asthma, and increased levels of ferritine.
Cluster 3, atopic multiple-trigger wheeze (n = 67), included more children with multiple-trigger wheeze (68%) than did clusters 1 or 2; eczema (75%); a positive result from the Phadiatop Infant test (90%); increased levels of IgE, IgA, and IgG; and abnormal results from chest x-rays.
In soggetti con multi-trigger wheezing le alterazioni infiammatorie e strutturali sono simili indipendentemente dall’atopia.

**Perdita epiteliale**

**Spessore MB**

**Vasi**

**Eosinofili**
# Classification and pharmacological treatment of preschool wheezing: changes since 2008

Brand PLP, ERJ 2014;43:1172

---

**TABLE 2** Distinction between temporal patterns of preschool wheeze and recommendations for controller therapy, as issued in the European Respiratory Society 2008 Task Force report [*].

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Temporal pattern</th>
<th>Proposed first choice of controller therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Episodic viral wheeze</strong></td>
<td>Wheezing during discrete time periods, often in association with clinical evidence of a viral cold, with absence of wheeze between episodes</td>
<td>Montelukast</td>
</tr>
<tr>
<td><strong>Multiple-trigger wheeze</strong></td>
<td>Wheezing that shows discrete exacerbations (as with episodic viral wheeze) but also symptoms between episodes</td>
<td>Inhaled corticosteroids</td>
</tr>
</tbody>
</table>

Daily controller therapy

- In children with MTW, ICS are the first choice for daily controller therapy

- In children with EVW, daily therapy may be considered with either ICS or montelukast if:
  - the attacks are severe (requiring hospital admission or systemic corticosteroids);
  - or the attacks are frequent;
  - or the clinician suspects that interval symptoms are being under reported
Intermittent montelukast in children aged 10 months to 5 years with wheeze (WAIT trial): a multicentre, randomised, placebo-controlled trial

Chinedu Nwokoro, Hitesh Pandya, Stephen Turner, Sandra Eldridge, Christopher J Griffiths, Tom Vulliamy, David Price, Marek Sanak, John W Holloway, Rossa Brughia, Lee Koh, Iain Dickson, Clare Rutterford, Jonathan Grigg

Summary

Background The effectiveness of intermittent montelukast for wheeze in young children is unclear. We aimed to assess whether intermittent montelukast is better than placebo for treatment of wheeze in this age group. Because copy numbers of the Sp1-binding motif in the arachidonate 5-lipoxygenase (ALOX5) gene promoter (either 5/5, 5/x, or x/x, where x does not equal 5) modifies response to montelukast in adults, we stratified by this genotype.

Methods We did this multicentre, parallel-group, randomised, placebo-controlled trial between Oct 1, 2010, and Dec 20, 2013, at 21 primary care sites and 41 secondary care sites in England and Scotland. Children aged 10 months to 5 years with two or more wheezy episodes were allocated to either a 5/5 or 5/x+x/x ALOX5 promoter genotype stratum, then randomly assigned (1:1) via a permuted block schedule (size ten), to receive intermittent montelukast or placebo given by parents at each wheezy episode over a 12 month period. Clinical investigators and parents were masked to treatment group and genotype strata. The primary outcome was number of unscheduled medical attendances for wheezing episodes. Analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT01142505.

Findings We randomly assigned 1358 children to receive montelukast (n=669) or placebo (n=677). Consent was withdrawn for 12 (1%) children. Primary outcome data were available for 1308 (96%) children. There was no difference in unscheduled medical attendances for wheezing episodes between children in the montelukast and placebo groups (mean 2.0 [SD 2.6] vs 2.3 [2.7]; incidence rate ratio [IRR] 0.88, 95% CI 0.77–1.01; p=0.06). Compared with placebo, unscheduled medical attendances for wheezing episodes were reduced in children given montelukast in the 5/5 stratum (2.0 [2.7] vs 2.4 [3.0]; IRR 0.80, 95% CI 0.68–0.95; p=0.01), but not in those in the 5/x+x/x stratum (2.0 [2.5] vs 2.0 [2.3]; 1.03, 0.83–1.29; p=0.79, pinteraction=0.08). We recorded one serious adverse event, which was a skin reaction in a child allocated to placebo.

Interpretation Our findings show no clear benefit of intermittent montelukast in young children with wheeze. However, the 5/5 ALOX5 promoter genotype might identify a montelukast-responsive subgroup.

Funding Medical Research Council (UK) and National Institute for Health Research.

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Intermittent montelukast in children aged 10 months to 5 years with wheeze (WAIT trial): a multicentre, randomised, placebo-controlled trial

**Table 3: Secondary outcomes**

<table>
<thead>
<tr>
<th></th>
<th>Montelukast group (n=652)</th>
<th>Placebo group (n=656)</th>
<th>Point estimate (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children with one or more USMA</td>
<td>426 (65%)</td>
<td>456 (70%)</td>
<td>OR 0.83 (0.66–1.04)</td>
<td>0.10</td>
</tr>
<tr>
<td>Time to first USMA (days)*</td>
<td>147 (50–365)</td>
<td>130 (38–)†</td>
<td>HR 0.89 (0.78–1.02)</td>
<td>0.09</td>
</tr>
<tr>
<td>Need for rescue oral corticosteroids (courses per child)‡</td>
<td>0.26 (0.7)</td>
<td>0.33 (0.9)</td>
<td>IRR 0.75 (0.58–0.98)</td>
<td>0.03</td>
</tr>
<tr>
<td>Wheeze episodes‡</td>
<td>2.7 (2.9)</td>
<td>2.6 (3.0)</td>
<td>IRR 1.02 (0.91–1.16)</td>
<td>0.68</td>
</tr>
<tr>
<td>Duration of wheeze episodes (days)</td>
<td>5.2 (4.0)</td>
<td>5.4 (3.8)</td>
<td>IRR 0.97 (0.89–1.06)</td>
<td>0.53</td>
</tr>
<tr>
<td>Duration of hospital admission (days per admission)</td>
<td>1.8 (1.3)</td>
<td>1.7 (1.1)</td>
<td>IRR 1.05 (0.94–1.18)</td>
<td>0.40</td>
</tr>
<tr>
<td>Symptomatic days per wheeze episode</td>
<td>4.9 (3.5)</td>
<td>4.8 (3.8)</td>
<td>IRR 0.96 (0.88–1.05)</td>
<td>0.36</td>
</tr>
</tbody>
</table>

Data are n (%), median (IQR), or mean (SD), unless otherwise indicated. USMA—unscheduled medical attendance for wheeze episodes. OR=odds ratio. HR=hazard ratio. IRR=incidence rate ratio. *Seven participants were missing dates for USMA and seven participants had their first medical attendance on the day of randomisation and were hence excluded. †The 75th percentile could not be calculated for this IQR because more than 25% of children never had a USMA. ‡Analysis included all children. 446 children had no diary data and these participants were considered to have no wheeze and cold episodes. When the analysis was repeated with these patients treated as missing, there was no difference in the IRR between treatment and placebo.
Intermittent montelukast in children aged 10 months to 5 years with wheeze (WAIT trial): a multicentre, randomised, placebo-controlled trial

<table>
<thead>
<tr>
<th>Montelukast group (n=652)</th>
<th>Placebo group (n=656)</th>
<th>Adjusted incidence rate ratio (95% CI)</th>
<th>p value</th>
<th>p Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary analysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>USMA episodes</td>
<td>2.0 (2.6)</td>
<td>2.3 (2.7)</td>
<td>0.88 (0.77–1.01)</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>Subgroup analysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>USMA in 5/5 stratum</td>
<td>2.0 (2.7)</td>
<td>2.4 (3.0)</td>
<td>0.80 (0.68–0.95)</td>
<td>0.01</td>
</tr>
<tr>
<td>USMA in 5/x+x/x stratum</td>
<td>2.0 (2.5)</td>
<td>2.0 (2.3)</td>
<td>1.03 (0.83–1.29)</td>
<td>0.79</td>
</tr>
</tbody>
</table>

Data are mean (SD), unless otherwise indicated. We obtained primary outcome data from the phone call that took place every 2 months. USMA=unscheduled medical attendance for wheeze.

Table 2: Treatment response in the primary analysis, and by 5/5 and 5/x+x/x strata
Wheeze in young children: WAITing for pharmacogenomics?

In *The Lancet Respiratory Medicine*, Chinedu Nwokoro and colleagues’ WAIT trial assesses the effectiveness of intermittent montelukast for treatment of wheezing episodes in 1358 children aged 10 months to 5 years who had had two or more wheeze episodes, with at least one episode in the preceding 3 months. There was no difference in the primary outcome of unscheduled medical attendances for wheezing episodes between children in the montelukast and placebo groups (mean 2.0 [SD 2.6] vs 2.3 [2.7]; incidence rate ratio [IRR] 0.88, 95% CI 0.77–1.01; p=0.06). However, the subgroup of patients who carried the wild type (common) genotype of the 5-lipoxygenase (ALOX5) gene promoter, which encodes a key enzyme in the leukotriene synthesis pathway, had significantly reduced unscheduled severe medical attendances for wheezing episodes (2.0 [2.7] vs 2.4 [3.0]; IRR 0.80, 95% CI 0.68–0.95; p=0.01).

intervention? The answer requires replication of the present study and additional long-term follow up studies, but the concept is exciting.

Additional support for a salutary effect of montelukast in the present study was provided by results of the secondary outcomes. In the entire study group, need for rescue oral corticosteroids was substantially decreased with 0.26 uses per child in the montelukast group versus 0.33 in the placebo group. This difference between the active and placebo treatment groups was statistically significant (p=0.03) and clinically relevant, irrespective of the genotype. Additionally, time to first hospital admission was longer in children in the montelukast group than in those in the placebo group (p=0.04).

Although the results are encouraging, they should be viewed with caution. The findings are concordant with some pharmacogenetic studies of the effect of
Non-atopic intrinsic asthma and the 'family tree' of chronic respiratory disease syndromes

P. G. Holt and P. D. Sly

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Non-atopic intrinsic asthma and the 'family tree' of chronic respiratory disease syndromes

P. G. Holt and P. D. Sly

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Intrinsic asthma: is it intrinsic to the smooth muscle?

J. L. Black* and M. Roth†

*School of Medical Sciences (Pharmacology) and Woolcock Institute of Medical Research, University of Sydney, Sydney, Australia and †Pulmonary Cell Research, Pneumology, University Hospital Basel, Basel, Switzerland

Summary

The traditional view of the pathophysiology of asthma is that its characteristic features are secondary to a major allergic or immunological dysfunction. However, this does not explain intrinsic asthma, which can occur in the absence of atopy. An alternative view is that an abnormality in the airway smooth muscle cell, which is capable of producing inflammatory, immunological and growth factors as well as molecules, which facilitate interaction with inflammatory cells, is the primary or instigating event. Evidence is rapidly accumulating that the smooth muscle is abnormal, in that it proliferates faster, produces more chemokines and cytokines as well as a different profile of extracellular matrix proteins than its non-asthmatic counterpart. These abnormalities may arise from altered calcium homoeostasis leading to increased mitochondrial biogenesis and/or decreases in the levels of key transcription factors such as CCAAT enhancer binding protein—α. Conditions under which smooth muscle is ablated, such as bronchial thermoplasty, may help us to understand more about the contribution of an airway smooth muscle dysfunction to asthma aetiology.
Intrinsic asthma: is it intrinsic to the smooth muscle?

J. L. Black* and M. Roth†

*School of Medical Sciences (Pharmacology) and Woolcock Institute of Medical Research, University of Sydney, Sydney, Australia and †Pulmonary Cell Research, Pneumology, University Hospital Basel, Basel, Switzerland

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Cite this as: J. L. Black and M. Roth, Clinical & Experimental Allergy, 2009 (39) 962–965.
Effect of Bronchoconstriction on Airway Remodeling in Asthma

A Study Timeline

- Screening visit
- First bronchoscopic examination
- Minimum 14 days
- Inhalation challenges
- Day 0
- Day 2
- Day 4
- Minimum 14 days
- Day 8
- Second bronchoscopic examination
Effect of Bronchoconstriction on Airway Remodeling in Asthma

![Graph showing changes in FEV₁ from baseline over time for different treatments.](image)
Effect of Bronchoconstriction on Airway Remodeling in Asthma

**A**
Change in BAL Eosinophils (percentage points)

**B**
Change in BAL ECP (ng/ml)

**C**
Change in Epithelial TGF-β (percentage points)

**D**
Change in K67+ Positive Cells (no. of cells/mm of epithelial length)
Effect of Bronchoconstriction on Airway
Genetic approach identifies distinct asthma pathways in overweight vs normal weight children

M. Butsch Kovacic¹,², L. J. Martin²,³, J. M. Biagini Myers¹, H. He³, M. Lindsey¹, T. B. Mersha¹ & G. K. Khurana Hershey¹

¹Division of Asthma Research; ²Division of Biostatistics and Epidemiology; ³Division of Molecular Genetics, Cincinnati Children’s Hospital Medical Center, Cincinnati, OH, USA

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Keywords
allergy; children; interaction; overweight.

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Edited by: Stephan Weidinger

Abstract
The pathogenesis of asthma in the context of excess body weight may be distinct from asthma that develops in normal weight children. The study’s objective was to explore the biology of asthma in the context of obesity and normal weight status using genetic methodologies. Associations between asthma and SNPs in 49 genes were assessed, as well as, interactions between SNPs and overweight status in child participants of the Greater Cincinnati Pediatric Clinic Repository. Asthma was significantly associated with weight (OR = 1.38; P = 0.037). The number of genes and the magnitude of their associations with asthma were notably greater when considering overweight children alone vs normal weight and overweight children together. When considering weight, distinct sets of asthma-associated genes were observed, many times with opposing effects. We demonstrated that the underlying heterogeneity of asthma is likely due in part to distinct pathogenetic pathways that depend on preceding/comorbid overweight and/or allergy. It is therefore important to consider both obesity and asthma when conducting studies of asthma.
<table>
<thead>
<tr>
<th>Primary Genetic Predisposition</th>
<th>BEFORE Asthma Diagnosis</th>
<th>AFTER Asthma Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergy</td>
<td>![Allergy]</td>
<td>![Allergy] 90% of Asthmatic Children are Allergic</td>
</tr>
<tr>
<td></td>
<td>![Allergy]</td>
<td>![Allergy] 38% of Allergic Asthmatic Children Are Overweight</td>
</tr>
<tr>
<td>Asthma</td>
<td>![Asthma]</td>
<td>![Asthma] 10% of Asthmatic Children are Non-allergic</td>
</tr>
<tr>
<td>Obesity</td>
<td>![Obesity]</td>
<td>![Obesity] 44% of Non-allergic Asthmatic Children Are Overweight</td>
</tr>
</tbody>
</table>
TWO NOVEL SEVERE ASTHMA PHENOTYPES IDENTIFIED DURING CHILDHOOD USING A CLUSTERING APPROACH

Three independent clusters of asthma were identified.

- Severe asthma with bronchial obstruction
- Mild asthma
- Asthma with severe exacerbations and multiple allergies
Table II: Features of children according to cluster analysis in the entire population (n=315)

<table>
<thead>
<tr>
<th></th>
<th>Cluster 1</th>
<th>Cluster 2</th>
<th>Cluster 3</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>“Asthma with severe exacerbations and multiple allergies” (n=103)</td>
<td>“Severe asthma with bronchial obstruction” (n=72)</td>
<td>“Mild asthma” (n=140)</td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>8.8 (8.5;9.2)</td>
<td>10.3 (10.0;10.6)</td>
<td>8.3 (8.0;8.5)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>17.1 (16.6;17.5)</td>
<td>20.0 (19.1;21.0)</td>
<td>16.7 (16.3;17.0)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Maternal asthma (%)</td>
<td>25 (33)</td>
<td>8 (13)</td>
<td>16 (13)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Paternal asthma (%)</td>
<td>25 (29)</td>
<td>11 (18)</td>
<td>11 (9)</td>
<td>.001</td>
</tr>
<tr>
<td>Number of sensitizations to food allergens, median (range)</td>
<td>0.3 (0.2;0.5)</td>
<td>0.0 (0.0; 0.0)</td>
<td>0.1 (0.0;0.1)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Number of sensitizations to inhaled allergens, median (range)</td>
<td>3.0 (2.6;3.5)</td>
<td>1.9 (1.5;2.3)</td>
<td>1.2 (1.0;1.5)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Total IgE (kU/L), median (range)</td>
<td>805 (657;952)</td>
<td>485 (365;605)</td>
<td>450 (323;577)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>IgG (g/L), median (range)</td>
<td>9.9 (9.6;10.4)</td>
<td>11.7 (11.2;12.3)</td>
<td>8.6 (8.1;9.0)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>IgA (g/L), median (range)</td>
<td>1.3 (1.2;1.4)</td>
<td>1.8 (1.6;1.9)</td>
<td>1.1 (1.0;1.2)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>IgM (g/L), median (range)</td>
<td>1.1 (1.0;1.2)</td>
<td>1.3 (1.1;1.4)</td>
<td>0.9 (0.9;1.0)</td>
<td>.0001</td>
</tr>
<tr>
<td>Blood eosinophils (1/mm³)</td>
<td>734 (650;817)</td>
<td>514 (421;607)</td>
<td>454 (395;515)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Blood basophils (1/mm³)</td>
<td>42 (34;50)</td>
<td>3 (4;14)</td>
<td>24 (18;23)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Blood lymphocytes (1/mm³)</td>
<td>3036 (2889;3182)</td>
<td>3030 (2852;3208)</td>
<td>2691 (2561;2820)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Blood neutrophils (1/mm³)</td>
<td>2767 (2540;2993)</td>
<td>3423 (3082;3765)</td>
<td>3250 (3009;3492)</td>
<td>.001</td>
</tr>
<tr>
<td>Blood monocytes (1/mm³)</td>
<td>505 (474;536)</td>
<td>550 (511;588)</td>
<td>515 (483;541)</td>
<td>.08</td>
</tr>
<tr>
<td>Baseline FEV₁ (% predicted)</td>
<td>89 (86;92)</td>
<td>82 (78;86)</td>
<td>97 (95;100)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Asthma duration ≥ 5y (%)</td>
<td>91 (88)</td>
<td>49 (68)</td>
<td>93 (66)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>≥ 1 hospitalization for asthma exacerbation (%)</td>
<td>67 (65)</td>
<td>7 (10)</td>
<td>20 (14)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>
Obesity and asthma: beyond $T_h^2$ inflammation

Luiz O.S. Leiria$^a$, Milton A. Martins$^b$, Mário J.A. Saad$^a,^*$

$^a$ Department of Internal Medicine, Faculty of Medical Sciences, State University of Campinas, Campinas, SP, Brazil
$^b$ Department of Medicine, School of Medicine, University de São Paulo, São Paulo, SP, Brazil

**ABSTRACT**

Obesity is a major risk factor for asthma. Likewise, obesity is known to increase disease severity in asthmatic subjects and also to impair the efficacy of first-line treatment medications for asthma, worsening asthma control in obese patients. This concept is in agreement with the current understanding that some asthma phenotypes are not accompanied by detectable inflammation, and may not be ameliorated by classical anti-inflammatory therapy. There are growing evidences suggesting that the obesity-related asthma phenotype does not necessarily involve the classical $T_h^2$-dependent inflammatory process. Hormones involved in glucose homeostasis and in the pathogeneses of obesity likely directly or indirectly link obesity and asthma through inflammatory and non-inflammatory pathways. Furthermore, the endocrine regulation of the airway-related pre-ganglionic nerves likely contributes to airway hyperreactivity (AHR) in obese states. In this review, we focused our efforts on understanding the mechanism underlying obesity-related asthma by exploring the $T_h^2$-independent mechanisms leading to this disease.
Does obesity produce a distinct asthma phenotype?
Lugogo, JAP 2010; 108:729

Relationship between serum adipokines and asthma

<table>
<thead>
<tr>
<th>Year</th>
<th>Population</th>
<th>Age</th>
<th>n</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>Turkey, asthma clinic</td>
<td>Children</td>
<td>135</td>
<td>Leptin increased in asthmatics</td>
</tr>
<tr>
<td>2004</td>
<td>Turkey, pediatric clinic</td>
<td>Children</td>
<td>43</td>
<td>Leptin increased in asthmatics</td>
</tr>
<tr>
<td>2004</td>
<td>Sweden, birth cohort</td>
<td>Children</td>
<td>138</td>
<td>No relationship between leptin and asthma</td>
</tr>
<tr>
<td>2006</td>
<td>US, population-based</td>
<td>Adults</td>
<td>5,876</td>
<td>Leptin increased in asthmatics, more in women</td>
</tr>
<tr>
<td>2008</td>
<td>Korea, university clinic</td>
<td>Children</td>
<td>240</td>
<td>No relationship between adiponectin/leptin and asthma</td>
</tr>
<tr>
<td>2008</td>
<td>Germany, population-based</td>
<td>Children</td>
<td>462</td>
<td>Leptin associated with asthma in girls</td>
</tr>
<tr>
<td>2008</td>
<td>US, population cohort</td>
<td>Adults</td>
<td>2,890</td>
<td>Adiponectin lower in female asthmatics</td>
</tr>
<tr>
<td>2009</td>
<td>Korea, university clinic</td>
<td>Adults</td>
<td>90</td>
<td>No relationship between adiponectin/leptin and asthma</td>
</tr>
<tr>
<td>2009</td>
<td>Finland, population cohort</td>
<td>Children and adults</td>
<td>2,620*</td>
<td>No relationship between adiponectin/leptin and asthma</td>
</tr>
</tbody>
</table>

Although the data are sometimes conflicting, there does not appear to be a strong relationship between serum levels of leptin/adiponectin and the presence of asthma sufficient to explain the relationship between asthma and obesity

Grazie D. Peroni
Decreased response to inhaled steroids in overweight and obese asthmatic children

Erick Forno, MD, MPH, Rachel Lescher, MD, Robert Strunk, MD, Scott Weiss, MD, MS, Anne Fuhlbrigge, MD, MPH, and Juan C. Celedón, MD, DrPH for the Childhood Asthma Management Program Research Group Boston, Mass, and St Louis, Mo

A  Prednisone bursts

B  ER visits / admissions

J ALLERGY CLIN IMMUNOL MARCH 2011
Using established asthma medications: the problem of corticosteroid insensitivity

- obesity,
  - Sutherland ER, AJRCCM 2008; 178: 682-687.
- smoking,
- low vitamin D levels,
  - Xystrakis E, J Clin Invest 2006
  - Gupta A, AJRCCM 2011
- non-eosinophilic
  (low-Th2 inflammation) mainly in adults.

ERS/ATS Guidelines, ERJ 2014;43:343-373
Obesity, asthma, and oxidative stress.
Holguin F JAP 2010; 108: 754

Visceral fat
Adipokine imbalance

Obesity

Reduced antioxidant defenses, co-morbidities
Metabolic syndrome

Phenotypical changes in inflammatory cells

Airway oxidative stress

Reduced capacity to respond to acute pro-inflammatory or pro-oxidative insults?

Reduced corticosteroid effectiveness

Increased asthma severity
And increased susceptibility to develop asthma

Grazie D. Peroni
Another Piece to the Puzzle of the “Obese Female Asthma” Phenotype.

- Although the importance of sex in this association is still controversial in children, there is now growing evidence that obese women of childbearing age are at higher risk of being diagnosed with asthma than equally obese men of the same age.

- “late-onset obese female asthma” appears to be more often nonatopic, steroid resistant, and difficult to control than other types of asthma, it is likely to become one of the greatest challenges of asthma management in the next decade.
What mechanism could explain this sex disparity? First, there might be an interaction between obesity and female reproductive hormones.

A second explanation might be that BMI is not an adequate measure of obesity.

In men, BMI has a better correlation with lean mass than with percent body fat, whereas in women the reverse is true. Adipose tissue produces many cytokines and hormones such as leptin and adiponectin. And changes in these adipokines can promote airway hyperresponsiveness and may thus contribute to asthma in the obese.
Another Piece to the Puzzle of the “Obese Female Asthma” Phenotype.

A third possibility relates to altered chest wall mechanics, which might be different between obese males and females.

- Compliance of the chest wall is reduced by adipose tissue around the rib cage, which is typically the case in obese women.
- Functional residual capacity and expiratory reserve volume decrease exponentially with increasing BMI, such that morbidly obese patients breathe near their residual volume. In this setting, expiratory flow is close to the maximal limit, and even the slightest bronchoconstriction may lead to expiratory flow limitation and symptoms of asthma.

Bel  AJRCCM 2013;188:263
Another Piece to the Puzzle of the “Obese Female Asthma” Phenotype.

Thus, asthma symptoms may occur merely as a consequence of this alteration in mechanical forces without any evidence of airway inflammation or airway hyperresponsiveness.
Another Piece to the Puzzle of the “Obese Female Asthma” Phenotype.

- A third possibility relates to altered chest wall mechanics, which might be different between obese males and females.
  - Compliance of the chest wall is reduced by adipose tissue around the rib cage, which is typically the case in obese women.
  - Functional residual capacity and expiratory reserve volume decrease exponentially with increasing BMI, such that morbidly obese patients breathe near their residual volume.

In this setting, expiratory flow is close to the maximal limit, and even the slightest bronchoconstriction may lead to expiratory flow limitation and symptoms of asthma.
Insulin resistance, metabolic syndrome, and lung function in US adolescents with and without asthma
Diet-induced weight loss in obese children with asthma: a randomized controlled trial. *Jensen CEA 2013;43:775*

**Background**
- Obesity is highly prevalent in asthmatic children and associated with worse clinical outcomes.
- Energy restriction to induce weight loss in asthmatic children has not been investigated in a randomized controlled trial (RCT).

**Objective**
- To assess if:
  1. weight loss can be achieved in obese asthmatic children using a dietary intervention; and
  2. changes in asthma outcomes occur following diet-induced weight loss.
Diet-induced weight loss in obese children with asthma: a randomized controlled trial. *Jensen CEA 2013;43:775*

- Obese asthmatic children, aged 8–17.
- Randomized to a wait-list control (WLC) \((n = 15)\) or dietary-intervention group \((n = 13)\) for 10 weeks.
- Lung function, Asthma Control Questionnaire and sputum and systemic inflammation.

![Graph showing changes in BMI z-score and total % body fat]
Diet-induced weight loss in obese children with asthma: a randomized controlled trial. *Jensen CEA 2013;43:775*

Change (∆) in BMI \( z \)-score correlated with ∆CRP \( (r =0.47, P =0.012) \) and ∆exhaled nitric oxide (eNO) \( (r =0.46, P =0.034) \)

![Graph showing changes in BMI z-score and total % body fat](image)
Diet-induced weight loss in obese children with asthma: a randomized controlled trial. *Jensen CEA 2013;43:775*

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- Lung function, Asthma Control Questionnaire and sputum and systemic inflammation.

Change from baseline in (a) Expiratory Reserve Volume (ERV) and (b) Juniper's Asthma Control Questionnaire (ACQ) score.

![Graph showing changes in ERV and ACQ scores](image)
Diet-induced weight loss in obese children with asthma: a randomized controlled trial. *Jensen CEA 2013;43:775*

Dietary intervention can induce acute weight loss in obese asthmatic children with subsequent improvements in static lung function and asthma control.
Novel diagnostic approaches and biological therapeutics for intrinsic asthma

Take home messages

- asthma is a very heterogeneous disease
- there are more similarities than differences between extrinsic and intrinsic asthma
- advances in knowledge have led to identification of different phenotypes based on various clinical and biopathological characteristics
- evolution of “cluster” analysis contributes to better identification of phenotypes
- atopy status is one of the different characteristics that may be present in several phenotypes
- not finding a specific allergen does not mean absence of atopy
- intrinsic status is associated with more severe asthma
- although identification of atopic status may not be a criterion for classification of asthma, it may help to guide treatment and prevention of exposure to the proposed cause

María del Carmen Vennera¹⁻³
César Picado¹⁻³

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GRAZIE PER L'ATTENZIONE

Thesis 2016
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16-17 Dicembre 2016

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