

Managing Virus-Induced Wheezing in Children

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Disclosures:

- ACAAI, Immediate Past-President
- Clinical research:
 - Sunovion
 - Shionoghi
 - Genetech
- Speakers bureau:
 - AstraZeneca
 - Novartis/Genetech

Learning Objectives

- Understand the characteristics of wheezing illnesses in children.
- Discuss the role of viral infections triggering exacerbations of asthma in children.
- Explain treatment options for children with viral induced wheezing.

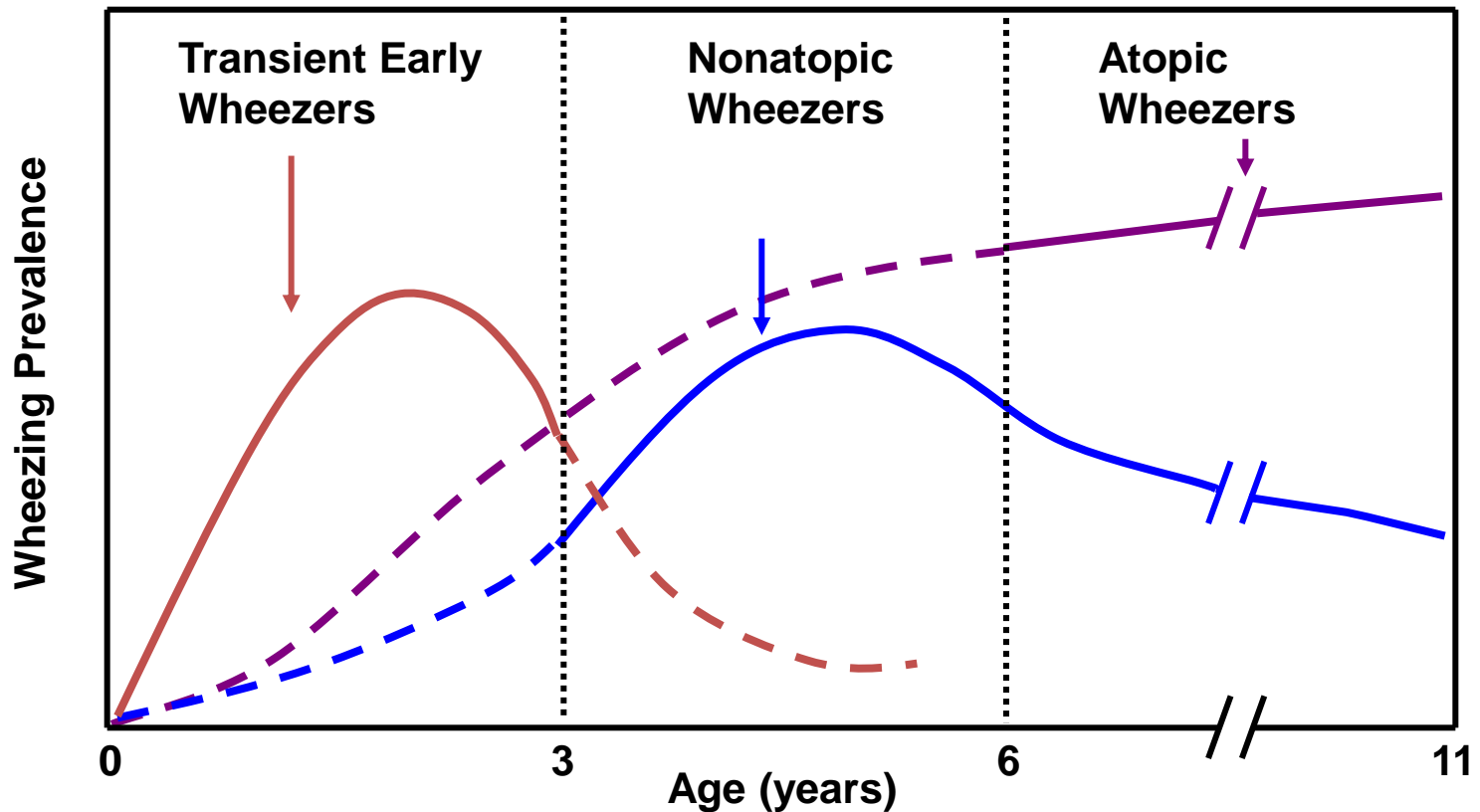
Asthma Definition: Asthma Predictive Index

- Identify high risk children (2 and 3 years of age):
 - ≥ 4 wheezing episodes in the past year (at least one must be MD diagnosed)

PLUS

- One major criterion
 - Parent with asthma
 - Atopic dermatitis
 - Aero-allergen sensitivity
- OR*
- Two minor criteria
 - Food sensitivity
 - Peripheral eosinophilia ($\geq 4\%$)
 - Wheezing not related to infection

Patterns of Wheezing in Children



Hypothetical Prevalence of Wheezing Over Time for Childhood Wheezing Phenotypes

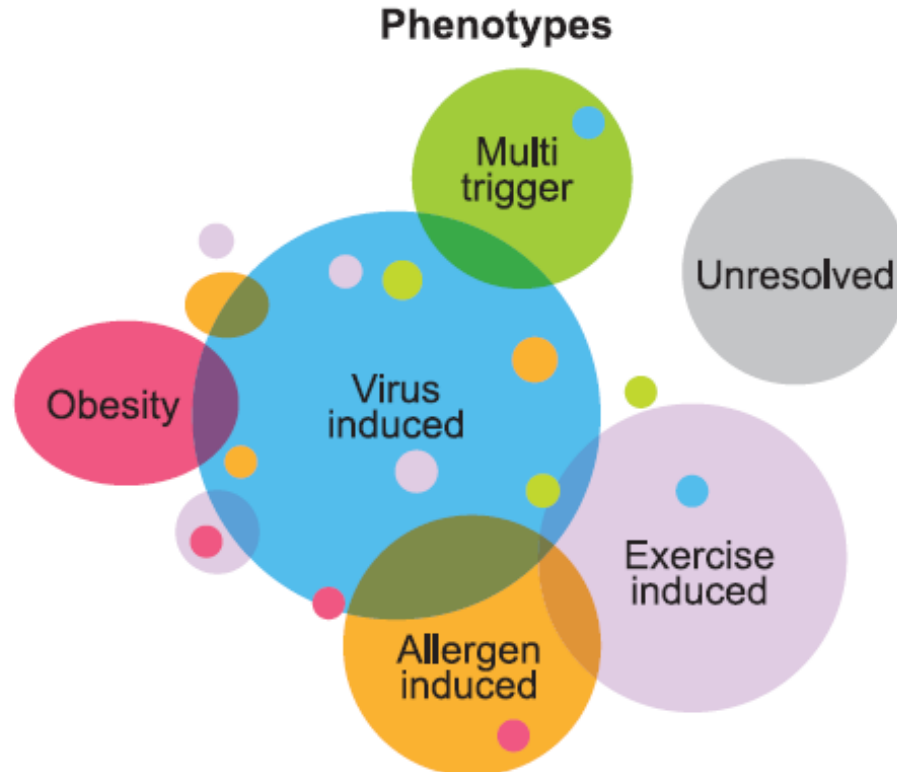
Phenotypic Expressions of Childhood Wheezing Disorders

1. Viral induced wheezing
2. Severe intermittent wheezing
3. Exercise bronchospasm/asthma
4. Persistent asthma
5. Severe asthma

POSITION PAPER

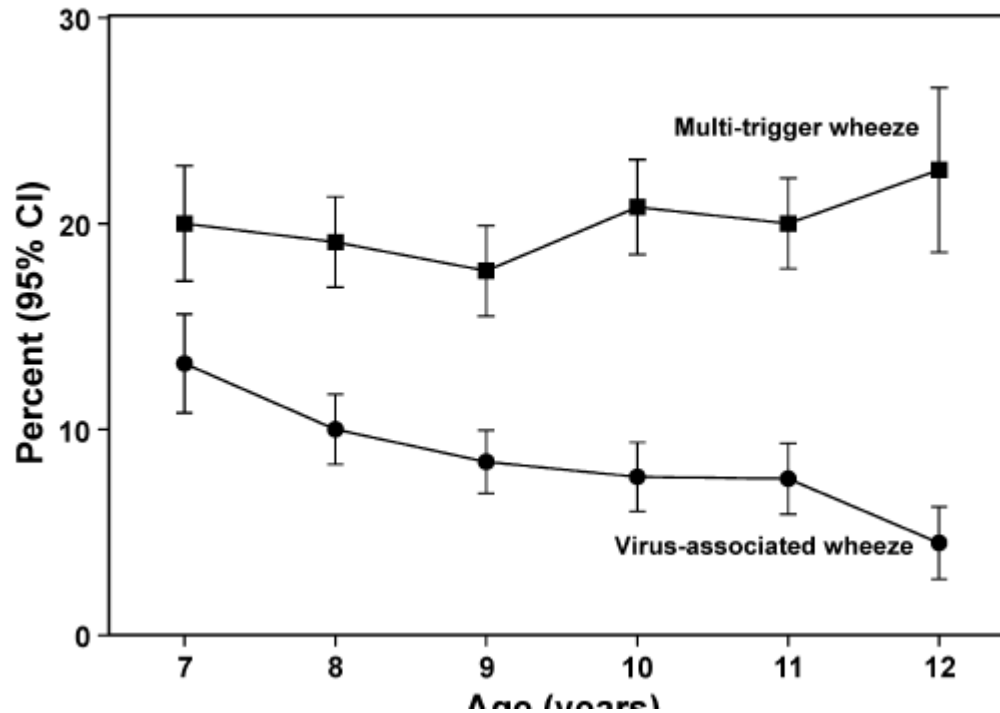
International consensus on (ICON) pediatric asthma

N. G. Papadopoulos¹, H. Arakawa², K.-H. Carlsen³, A. Custovic⁴, J. Gern⁵, R. Lemanske⁶,
P. Le Souef⁷, M. Mäkelä⁸, G. Roberts⁹, G. Wong¹⁰, H. Zar¹¹, C. A. Akdis¹², L. B. Bacharier¹³,
E. Beroldi¹⁴, H. B. von Boven¹⁵, L. de Blic¹⁶, A. Bønnelykke¹⁷, W. Busch¹⁸, T. B. Cook¹⁹



A Comparison of Virus-Associated and Multi-Trigger Wheeze in School Children

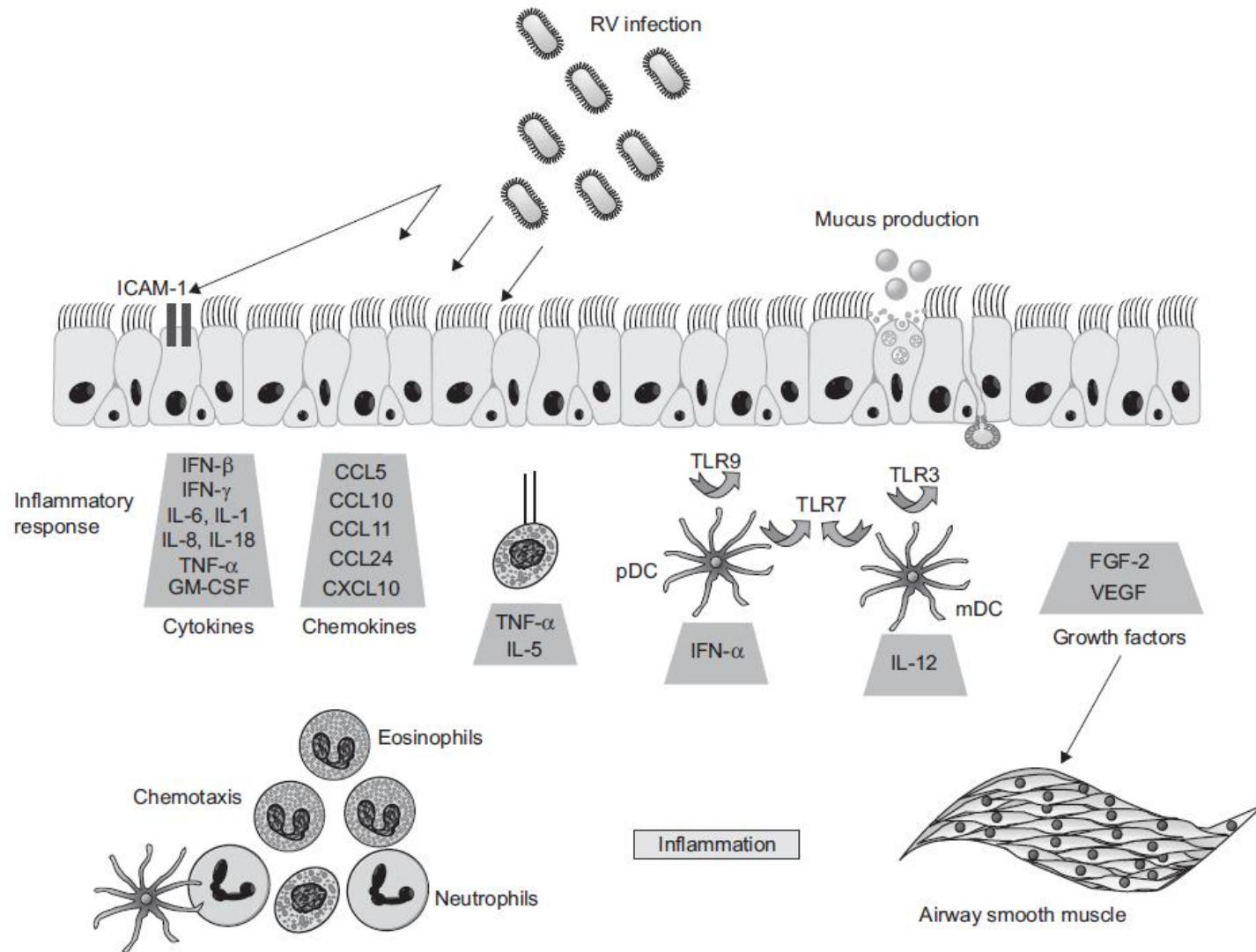
HEATHER J. WASSALL, M.Sc.,¹ ANNE M. DEVENNY, M.B.,¹ SULEMAN DAUD KHAN, M.B.,¹
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Viral-induced Wheeze more of a problem in younger ages

Childhood asthma and infection: virus-induced exacerbations as determinants and modifiers

P. Xepapadaki and N.G. Papadopoulos



Viral Infections are a Common Trigger of Wheezing Exacerbations in Children

- Viruses were detected in up to 85% of wheezing exacerbations in children
 - Rhinovirus
 - Coronovirus
 - Influenza virus
 - Parainfluenza virus
 - Respiratory syncytial virus (RSV)
- Seasonal correlations between rates of URI and hospital admissions for asthma.

Wheezing Rhinovirus Illnesses in Early Life Predict Asthma Development in High-Risk Children

Daniel J. Jackson^{1,2}, Ronald E. Gangnon^{3,4}, Michael D. Evans³, Kathy A. Roberg¹, Elizabeth L. Anderson¹, Tressa E. Pappas¹, Magnolia C. Printz¹, Wai-Ming Lee¹, Peter A. Shult⁵, Erik Reisdorf⁵, Kirsten T. Carlson-Dakes¹, Lisa P. Salazar¹, Douglas F. DaSilva¹, Christopher J. Tisler¹, James E. Gern¹, and Robert F. Lemanske, Jr.^{1,2}

Departments of ¹Pediatrics, ²Medicine, ³Biostatistics and Medical Informatics, and ⁴Population Health Sciences, University of Wisconsin–Madison; and the ⁵Wisconsin State Laboratory of Hygiene, Madison, Wisconsin

- 259 children in COAST cohort followed prospectively.
- Viral etiologies were identified in 90% of wheezing illnesses.
- Respiratory syncytial virus (RSV) or rhinovirus (RV) or both associated with increased risk of asthma at 6 yo.

Wheezing Rhinovirus Illnesses in Early Life Predict Asthma Development in High-Risk Children

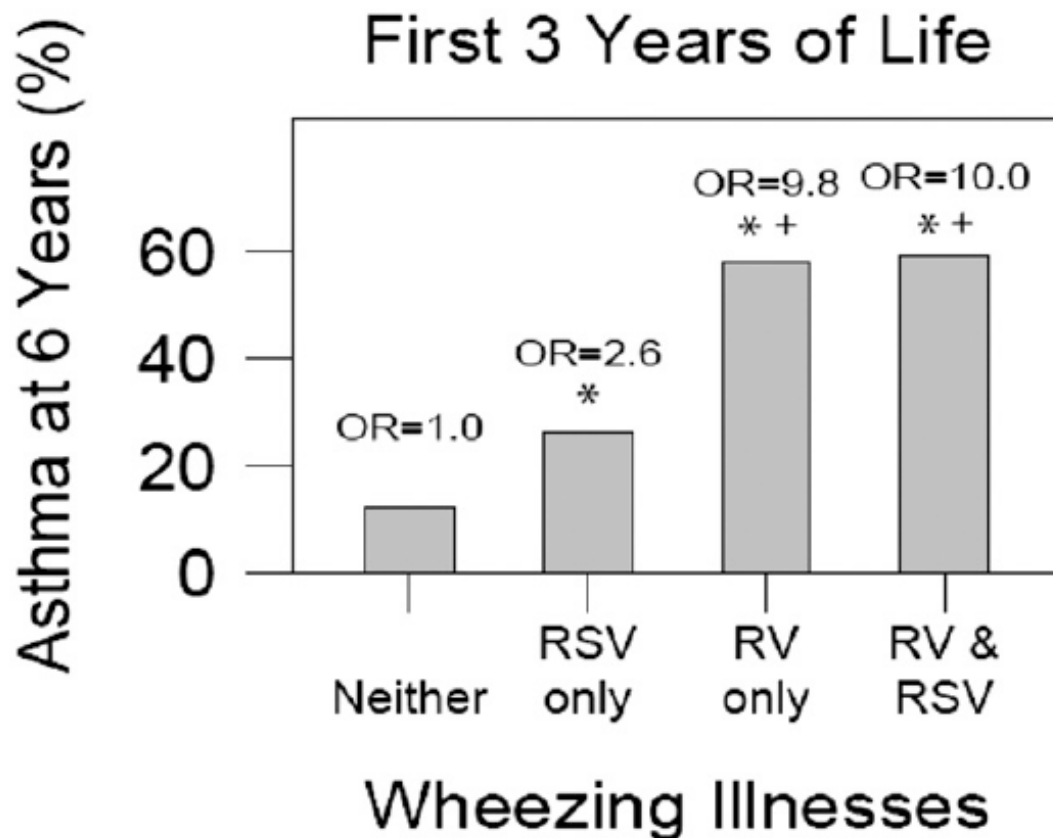


Figure 2. Risk of asthma at age 6 years in children who wheezed during the first 3 years of life with rhinovirus (RV), respiratory syncytial virus (RSV), or both (* $P < 0.05$ vs. Neither; + $P < 0.05$ vs. RSV only).

RV Infections and the Development of Asthma

- RV infections can produce more than upper airway illnesses during infancy.
- Children who develop asthma by 6 years of age have a significantly increased burden of viral wheezing illnesses in early life.
- Pulmonary function abnormalities at 6 years of age are most significantly associated with early childhood wheezing illnesses due to RV (not RSV).
- Of all outpatient wheezing viral illnesses in early life, those due to RV are most significant.
- Why is RV most critical type of viral infection affecting wheezing illnesses in children?

In Vitro Immune response to Viruses

- Wark, et al also found that bronchial epithelial cells from asthmatics had deficient innate immune responses to rhinovirus 16.
- Viral RNA expression in vitro was increased in cells from asthmatics compared to controls.
- Cells from asthmatics produced >2.5 times less INF- β mRNA after viral infection than controls.
- Contoli, et al reported that cells from asthmatics had reduced INF- λ in vitro compared to controls.

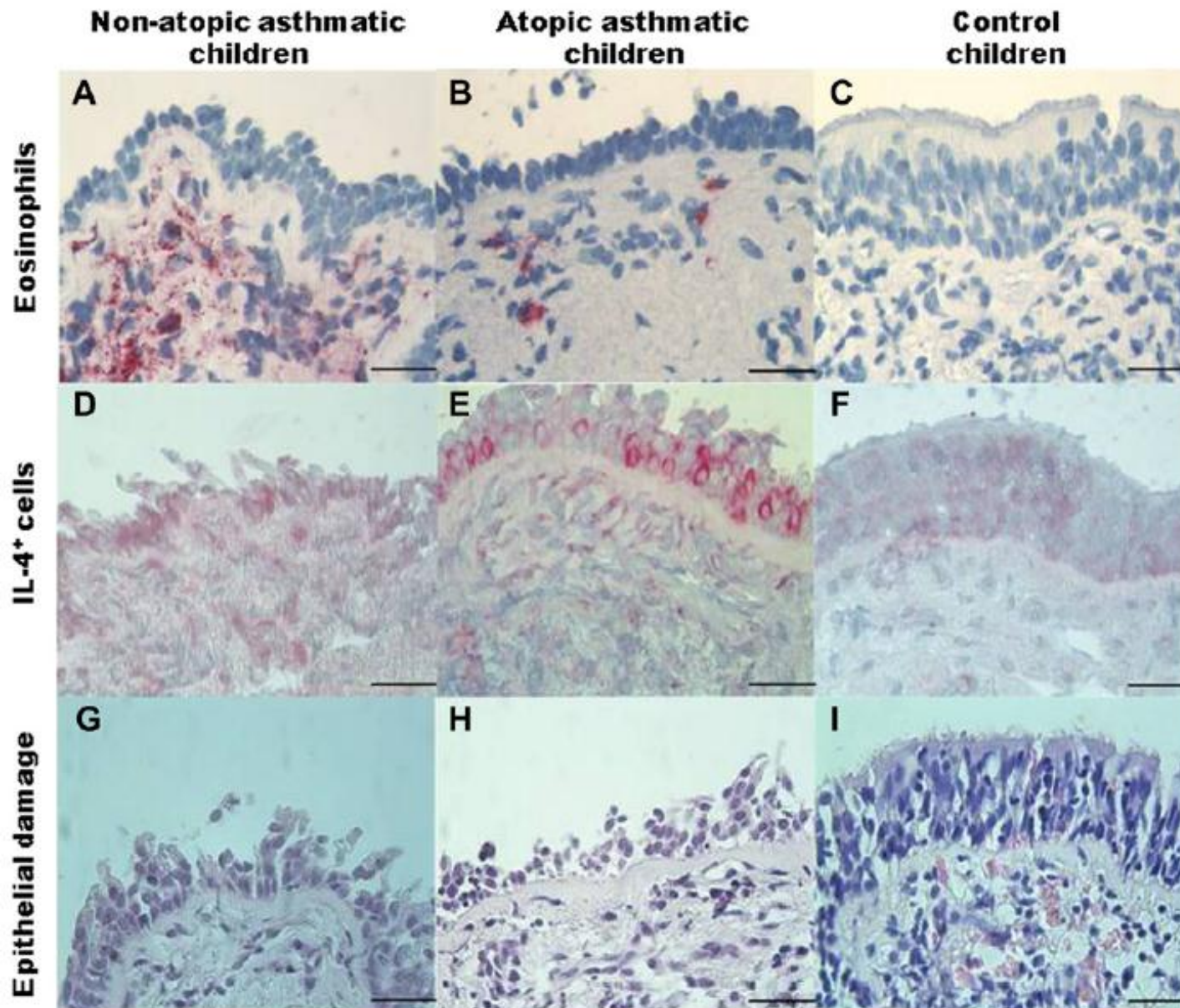
Wark et al. Asthmatic bronchial epithelial cells have a deficient innate immune response to infection with rhinovirus. *J Exp Med* 2005;201:937-947.

Contoli et al. Role of deficient type III interferon- λ production in asthma exacerbations. *Nat Med*. 2006;12:1023-1026.

Deficient antiviral immune responses in childhood: Distinct roles of atopy and asthma

Simonetta Baraldo, PhD,^{a*} Marco Contoli, MD, PhD,^{b*} Erica Bazzan, PhD,^a Graziella Turato, PhD,^a Anna Padovani, BSc,^b Brunilda Marku, MD,^b Fiorella Calabrese, MD,^a Gaetano Caramori, MD, PhD,^b Andrea Ballarin, MD,^a Deborah Snijders, MD,^c Angelo Barbato, MD,^c Marina Saetta, MD,^{a‡} and Alberto Papi, MD^{b‡} *Padua and Ferrara, Italy*

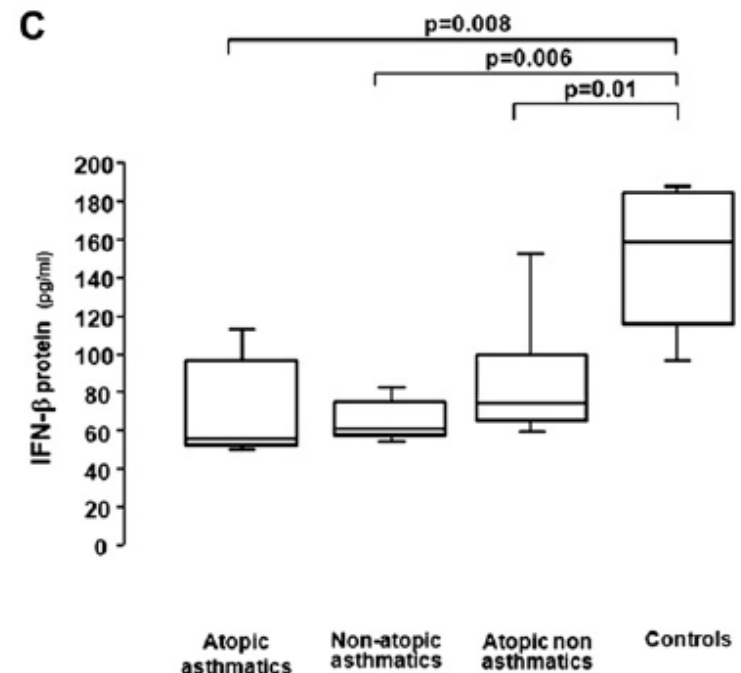
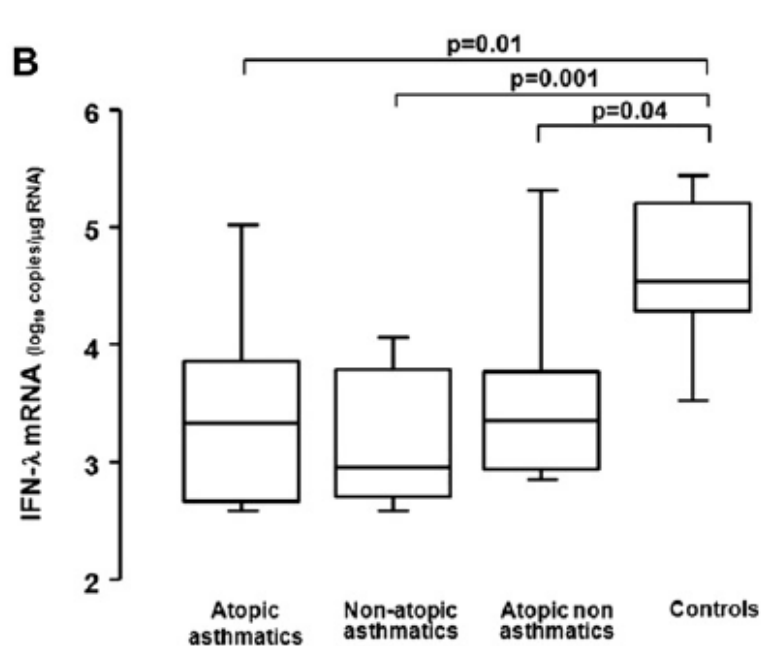
- Bronchial biopsy in 4 groups of children (n=47)
- Rhinovirus type 16 in vitro induction of IFN- λ mRNA and IFN- β protein levels were reduced in atopic asthmatics, nonatopic asthmatics, atopic nonasthmatic compared to nonatopic nonasthmatic children.
- Increased viral RNA levels paralleled the deficient interferon induction.



Deficient antiviral immune response in children with asthma

IFN- λ mRNA induction

IFN- β protein induction



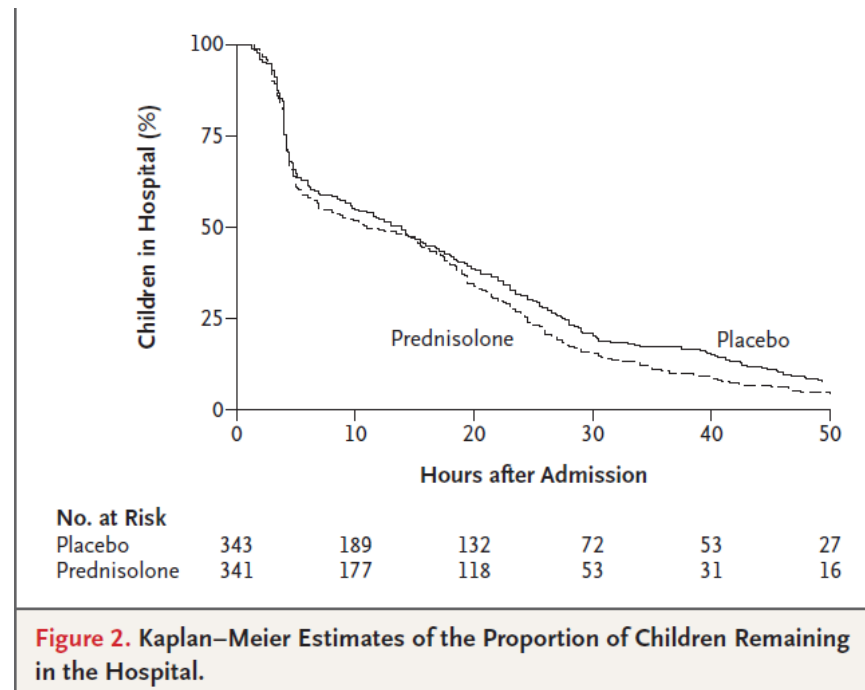
Deficient antiviral immune response in children with asthma

Conclusions:

- Deficient interferon responses to rhinovirus infection was present in children, particularly those with asthma and atopy.
- Suggests that deficient immune response to viral infections may not be limited to atopic asthma, but also in others with TH-2 conditions.

Oral Prednisolone for Preschool Children with Acute Virus-Induced Wheezing

- Randomized, double-blind, placebo-controlled trial comparing a 5-day course of oral prednisolone (10 mg daily for children 10–24 months and 20 mg daily for older children) versus placebo in 700 children between the ages of 10 and 60 months hospitalized for viral-induced asthma exacerbation.



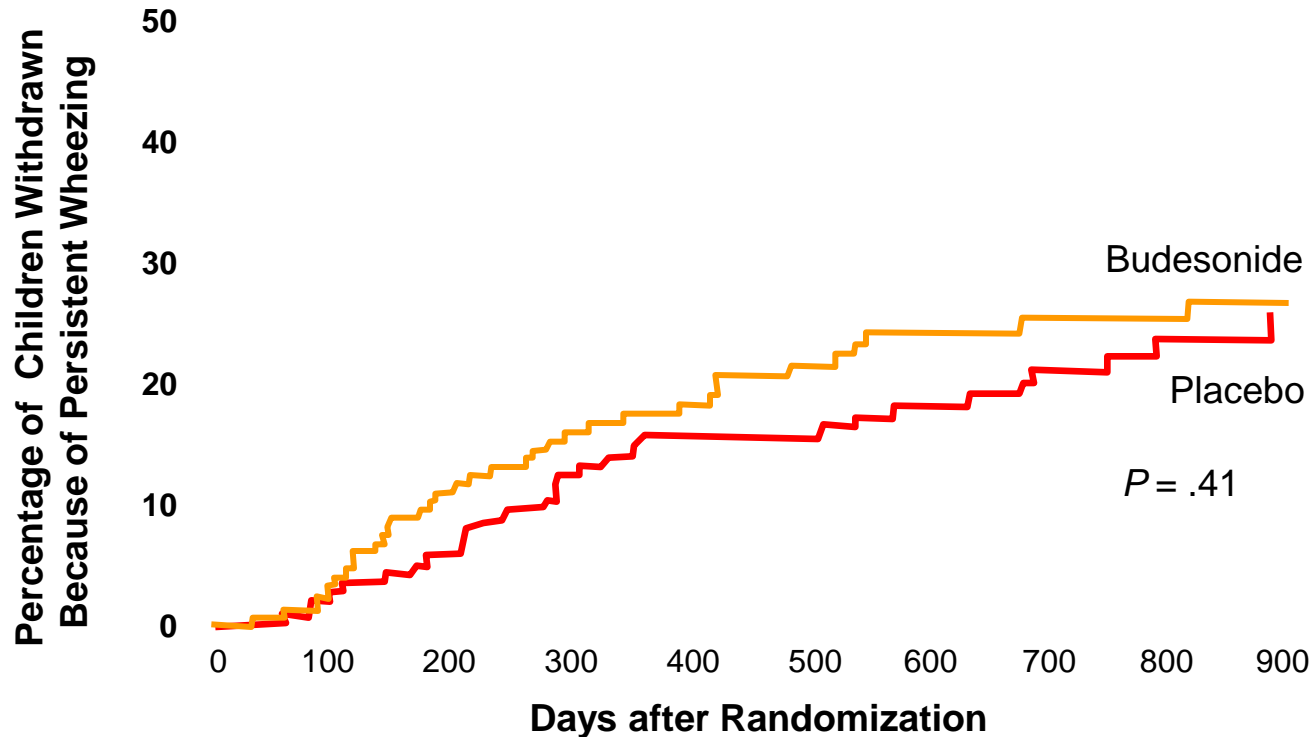
- No difference in 7-day symptom scores, albuterol use, or readmission
- Primarily non-atopic and 60% first time wheezers

Intermittent Inhaled Corticosteroids in Infants with Episodic Wheezing

Hans Bisgaard, M.D., D.M.Sci., Mette Northman Hermansen, M.D.,
Lotte Loland, M.D., Ph.D., Liselotte Brydensholt Halkjaer, M.D.,
and Frederik Buchvald, M.D., Ph.D.

- Single randomized, double-blind study
- 411 infants with 3-d history of wheezing
- Infants treated with budesonide, 400 mcg/d, or placebo for 2 weeks
- Primary outcome variables
 - Number of symptom-free days
 - Number of days free from rescue medication use
 - Number of episodes
 - Number of treatments with open-label budesonide

Intermittent ICS Treatment in Infants: Withdrawal Due to Persistent Wheezing



No. at Risk

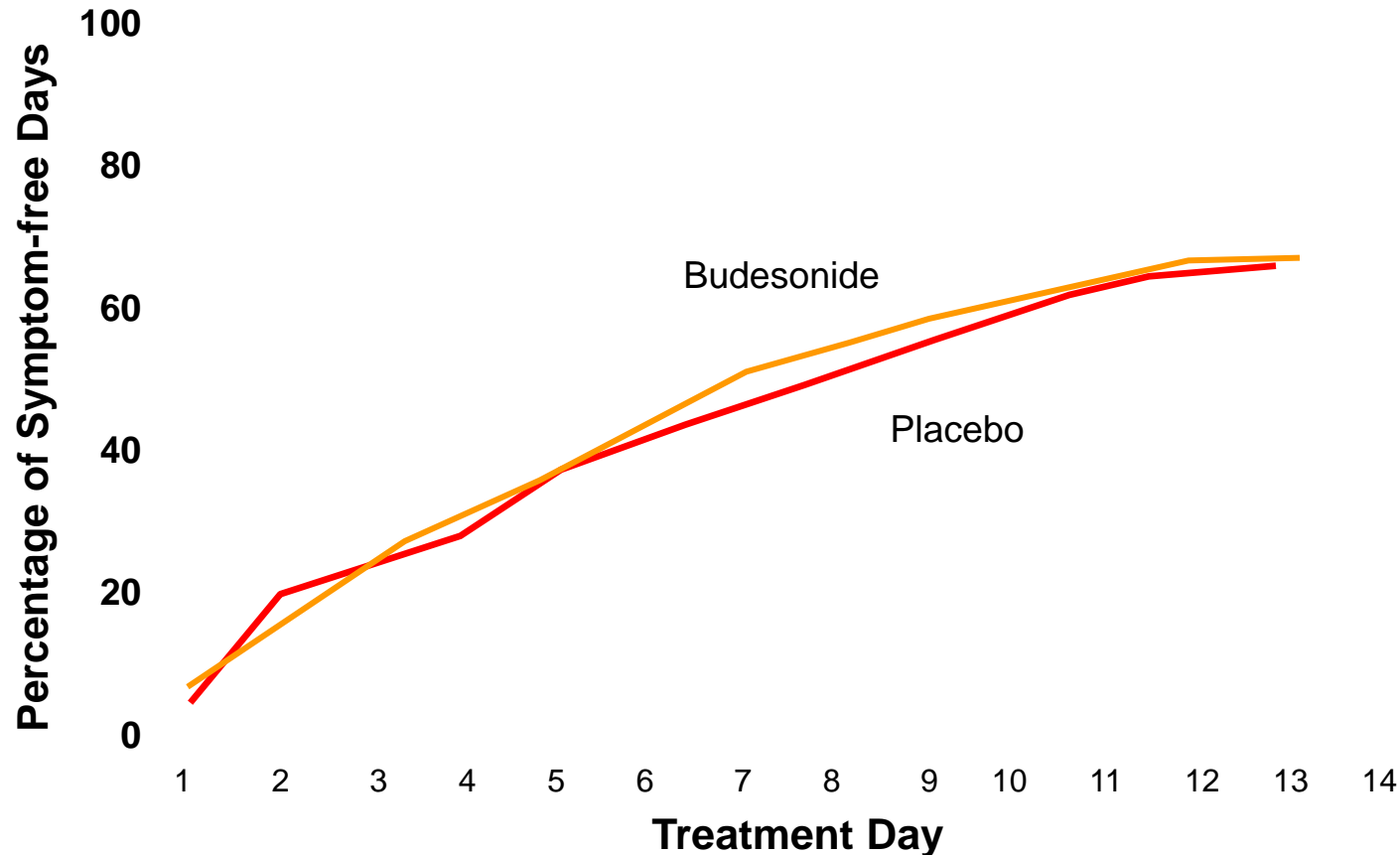
Budesonide	149	115	78	27
Placebo	145	114	92	27

Progression from episodic to persistent wheezing. Results were not significant.

ICS = inhaled corticosteroid

Bisgaard H, et al. *N Engl J Med.* 2006;354:1998-2005.

Intermittent ICS Treatment in Infants: Symptom-Free Days



Percentage of symptom-free days during the 2-week period for all children who received at least 1 study treatment. Results were not significant.

ICS = inhaled corticosteroid

Bisgaard H, et al. *N Engl J Med.* 2006;354:1998-2005.

Intermittent ICS Treatment in Infants: Conclusions

- Intermittent ICS had no effect on the progression from episodic to persistent wheezing in children.
- Intermittent ICS had no short-term benefit during episodes of wheezing in children (1st 3 years of life)
- These results suggest caution against the use of short courses of ICS for episodic wheezing.
- Regular ICS should be reserved for children with persistent wheezing

ICS = inhaled corticosteroid

Bisgaard H, et al. *N Engl J Med.* 2006;354:1998-2005.

Montelukast Reduces Asthma Exacerbations in 2- to 5-Year-Old Children with Intermittent Asthma

Hans Bisgaard, Stefen Zielen, María Luz Garcia-Garcia, Sebastian L. Johnston, Leen Gilles, Joris Menten, Carol A. Tozzi, and Peter Polos

- PREVIA study: 12 mo, multicenter to investigate to role of LTRA in preventing viral-induced asthma exacerbations in children 2-5 yo (n=549).
- Definition of exacerbation: Any 3 consecutive days with:
 - Daytime symptoms (average score of 4 daily symptom questions of ≥ 1 each day), AND
 - ≥ 2 beta-agonist treatments each day OR
- Inhaled corticosteroid rescue (on ≥ 3 consecutive days) or oral corticosteroids (≥ 1 day) OR
- Hospitalization due to asthma

Montelukast Reduces Asthma Exacerbations in 2- to 5-Year-Old Children with Intermittent Asthma

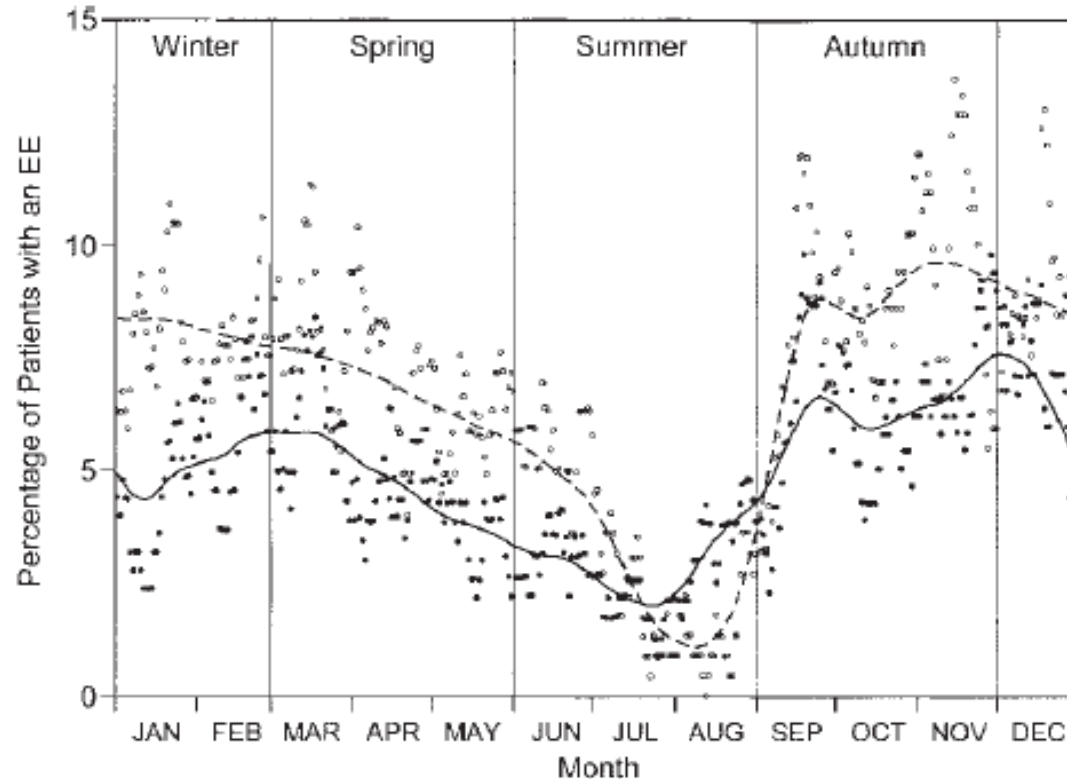
Hans Bisgaard, Stefen Zielen, María Luz Garcia-Garcia, Sebastian L. Johnston, Leen Gilles, Joris Menten, Carol A. Tozzi, and Peter Polos

TABLE 4. NASAL ASPIRATE TESTS CONDUCTED AT EIGHT STUDY CENTERS

	Montelukast (n = 46)	Placebo (n = 45)*	Total (n = 91)
Number of nasal aspirates	65	93	158
All tests negative	27 (41.5%)	55 (59.1%)	82 (51.9%)
At least one test positive	38 (58.6%)	38 (40.8%)	76 (48.1%)
Rhinoviruses	24 (37.0%)	19 (20.1%)	43 (27.6%)
Coronaviruses	5 (7.8%)	9 (9.9%)	14 (9.0%)
Respiratory syncytial virus	5 (7.8%)	8 (8.8%)	13 (8.3%)
Influenza virus	4 (6.2%)	4 (4.4%)	8 (5.1%)
Enteroviruses	2 (3.1%)	2 (2.2%)	4 (2.6%)
Parainfluenza viruses	2 (3.1%)	1 (1.1%)	3 (1.9%)
<i>Mycoplasma pneumoniae</i>	1 (1.5%)	1 (1.1%)	2 (1.3%)
Adenoviruses	0 (0.0%)	1 (1.1%)	1 (0.6%)
Human metapneumovirus	0 (0.0%)	1 (1.1%)	1 (0.6%)
<i>Chlamydia pneumoniae</i>	0 (0.0%)	0 (0.0%)	0 (0.0%)

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LTRA reduced exacerbations Autumn through Spring

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Hans Bisgaard, Stefen Zielen, María Luz Garcia-Garcia, Sebastian L. Johnston, Leen Gilles, Joris Menten, Carol A. Tozzi, and Peter Polos

- LTRA reduced rate of exacerbation episodes by 32% ($p \leq 0.001$).
- Average rate of exacerbation episodes was 1.60/yr on LTRA compared to 2.34/yr on placebo.
- LTRA reduced courses of ICS by 40% and increased the number of days without asthma.
- LTRA did not affect the average duration or severity of exacerbations

International consensus on (ICON) pediatric asthma

Box 4

Key points in asthma exacerbation treatment

Bronchodilation: inhaled salbutamol, 2–10 puffs; or nebulized, 2.5–5 mg, every 20' for the first hour, and according to response thereafter

Ipratropium, 2–8 puffs; or nebulized, 0.25–0.5 mg, can be added to salbutamol

If there is no improvement, children should be referred to a hospital

Oxygen supplementation: aim at $\text{SaO}_2 > 95\%$

Systemic corticosteroids: oral prednisolone, 1–2 mg/kg/24 h, usually for 3–5 days

At the hospital or ICU, if necessary, consider:

IV beta-2 agonists, IV aminophylline, IV magnesium sulfate, helium–oxygen mixture

Summary

- Virus triggered exacerbations are a major concern in children with asthma.
- Rhinovirus is the major agent but its antigenic diversity prevents vaccine development.
- Corticosteroids are a mainstay of chronic treatment, but have not been shown to be as effective at preventing or treating viral-induced wheezing.
- LTRA do have a modest effect on viral-induced wheezing in children.