Risk Factors for Recurrent Early Wheezing in Childhood: Viral Infections

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"Healthy" Infant or Young Child

Virus Infection
HRV or RSV

Upper or Lower Respiratory Illness

Resolution

"Predisposed" Infant or Young Child

- Underlying allergic inflammation
- Impaired epithelial barrier
- Impaired anti-viral response (interferons)

Virus Infection
HRV or RSV

Lower Respiratory Illness

Airway damage
Airway remodeling

HRV Infection(s)

Recurrent Wheezing

ASTHMA

Jackson & Lemanske, Immunology & Allergy Clin of North America, 2010
Viral Infections and Asthma

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

RSV
Respiratory Syncytial Virus Bronchiolitis in Infancy Is an Important Risk Factor for Asthma and Allergy at Age 7

Sigurs N et al. AJRCCM 161:1501, 2000
RSV Infections and Recurrent Wheezing

Stein RT et al. Lancet
354:541, 1999
Viral Pathogens other than RSV
## Prevalence of Common Respiratory Viral Infections

### Common colds
1. Rhinoviruses
2. Coronavirus (winter)
3. Parainfluenza viruses
4. Enteroviruses (summer)
5. Influenza A, B, C (winter)
6. RSV (winter)
7. Metapneumoviruses (winter)
8. Bocavirus (winter?)

### Wheezing Infants
1. RSV (winter)
2. Rhinoviruses
3. MPV (winter)
4. Coronavirus
5. Parainfluenza viruses
6. Influenza viruses
7. Adenoviruses
8. Bocavirus (winter?)
Rhinovirus
Viruses other than RSV: *Rhinovirus*

- RV infections leading to hospitalization during infancy were an early predictor of the subsequent development of asthma.
  

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

Kusel MM et al. JACI 119:1105, 2007
COAST
Childhood Origins of Asthma

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

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Funded by the NHLBI
Research Design and Methods

- Target enrollment: 300 families
- At least one parent with allergies or asthma
- Prospective (developmental) evaluation of
  - Immune system
    - Child (annually from birth) and parent
    - Cytokine response profiles; antigen-specific IgE
  - Respiratory infections (nasal aspirates)
  - Wheezing phenotypes (questionnaires)
  - Airway physiological evaluation (ages 4-7 yrs)
    - Impulse oscillometry, spirometry, eNO, meth. challenge
  - Environmental evaluation (diet, allergens, pets)
- Genotype evaluation
- Minimum 12-14 year follow-up
COAST Evaluations

Nasal lavage specimens collected at symptomatic illnesses

Birth  | 1 yr  | 2 yr  | 3 yr  | 4 yr  | 5 yr  | 6 yr

Nasal Washes collected at “Well Child Visits”

Persistent Wheezing Evaluation
[JACI 116:571, 2005]

Asthma Evaluation
[AJRCCM 178:667, 2008]

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

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

Lemanske RF et al. JACI 116:571, 2005
What viral infections in early life are associated with the development of asthma at age 6 years?
Etiology of Wheezing Illnesses in Early Childhood

Asthma at 6 Years

- RV  Rhinovirus
- RSV  Respiratory syncytial virus
- PIV  Parainfluenza
- Flu  Influenza
- CV  Coronavirus
- MPV  Metapneumovirus
- AdV  Adenovirus
- EnV  Enterovirus

Did RV or RSV wheezing illnesses during years 1-3 impact the risk of asthma at age 6?
RV Wheezing vs. RSV Wheezing in First 3 Years and Asthma at Age 6 Years

First 3 Years of Life

Asthma at 6 Years (%)

- Neither: OR=1.0
- RSV only: OR=2.6
- RV only: * OR=9.8
- RV & RSV: * OR=10.0

RV Wheezing & Allergic Sensitization in Year 3 and Asthma at Age 6 Years

Third Year of Life

Asthma at 6 Years (%)

OR=1.0

No whz RAST-

OR=3.5

No whz RAST+

OR=26.6

Whz RAST-

OR=79.9

Whz RAST+

Which comes first?
Allergic sensitization or wheezing illnesses?
Does sensitization lead to viral wheezing, or does viral wheezing lead to sensitization?

- COAST cohort
- Ages 0 – 6 yrs
- Does sensitization lead to viral wheezing, or does viral wheezing lead to sensitization?
- Analysis of transitions between 4 states.

Jackson et al. AJRCCM, in press
Does sensitization lead to viral wheezing, or does viral wheezing lead to sensitization?

If viral wheeze causes sensitization:

\[ 2 \rightarrow 4 > 1 \rightarrow 3 \]

If sensitization causes viral wheeze:

\[ 3 \rightarrow 4 > 1 \rightarrow 2 \]

No causality:

\[ 2 \rightarrow 4 = 1 \rightarrow 3 \]
\[ 3 \rightarrow 4 = 1 \rightarrow 2 \]

Jackson et al. AJRCCM, in press
Sensitization Leads to Viral Wheeze (the reverse does not appear to be true)

Jackson et al. AJRCCM, in press
How does allergic sensitization alter the host response to viral respiratory infections?
Hypothesis: Allergy Inhibits Innate Immune Responses

Cross-linking of FcεRI

Type I & Type III IFN

More frequent and severe virus-induced wheezing

Prolonged inflammation

Possible airway remodeling and/or loss of lung function
Do wheezing RV infections in early life influence subsequent lung function?
Effect of Treatment on SARE-related Changes in Post-bronchodilator FEV$_1$

![Graph showing changes in FEV$_1$ over time for different treatment groups.]

O’Byrne PM et al. AJRCCM 179:19, 2009
Mean 3 Year Change in Post-bronchodilator FEV$_1$

O’Byrne PM et al. AJRCCM 179:19, 2009
Influence of Viral Etiology for Wheezing on Lung Function

Guilbert T et al. JACI 128:532, 2011
Effects of Asthma Exacerbation Severity on Lung Function

Pre-bronchodilator Spirometry

- No Wheezing
- Mild-Moderate Wheezing
- 1 Severe Exacerbation
- 2+ Severe Exacerbations

FEV0.5(L) vs Year

FEV1(L) vs Year
Mechanisms
Do wheezing RV infections in early life cause asthma?
Host Factors

↓ antiviral responses

↓ lung function

Genetic polymorphisms

“A Normal” Virus → Abnormal Host → Asthma
Mechanisms

- **Airway epithelial cells**\(^1\)
  - Normal: apoptosis
  - Asthma: viral replication

- **Immune dysregulation**\(^1-4\)
  - Altered innate immune responses
    - Type 1-3 interferons (\(\alpha, \beta, \gamma, \lambda\))
    - Fc\(\varepsilon\) R1 numbers and bridging on antigen-presenting cells\(^4\)

- **Genetic polymorphisms**\(^5\)
  - CD14\_159 and Toll 3 receptors

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3. Copenhaver CC et al. AJRCCM 170:175, 2004
4. Gill M et al. JI 184:5999, 2010
**Virus Factors**

Lung/Airway damage

Virulent strains?

Asthma
Virus Factors: Rhinovirus

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

Sequencing and Analyses of All Known Human Rhinovirus Genomes Reveals Structure and Evolution
HRV-C and Asthma Exacerbations

• Prospective population-based surveillance
  Nashville TN and Rochester NY
  1052 children age <5 yrs hospitalized with ARI or fever
  HRV-C vs. HRV-A:
  • ↑ discharge diagnosis of asthma (55% vs 36%, \( P = .022 \))

• ED Asthma Study (2-16 y/o)
  Perth, Australia
  HRV C detected in 59% of children:
  • ↑ severity in HRV C vs. A or B

1 Miller EK et al. JACI 2009
2 Bizzintino J et al. ERJ 2011
HRV infections and illnesses in COAST during infancy
HRV infection of infant occurs year-round.
HRV Strain
Virulence
Genetic Factor
- Atopy (Immune Dysregulation)
  - (Innate immunity)
  - (Interferons)

Environmental Factors
- Viral LRIs (RV and RSV)

Developmental Component

Persistent Wheezing

Asthma
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