Early Viral Infections: Their Role in the Development of Asthma

Nelson Rosário MD, PhD

HOSPITAL DE CLÍNICAS
UNIVERSIDADE FEDERAL DO PARANÁ
Viral Infection Is a Common Cause of Wheezing Exacerbations in Children

• In a survey, viruses were detected in up to 85% of wheezing exacerbations, in particular:
  – Rhinovirus
  – Coronavirus
  – Influenza virus
  – Parainfluenza viruses
  – Respiratory syncytial virus (RSV)

• Seasonal correlations between rates of upper respiratory infections (URIs) and hospital admissions for asthma

Healthy Infant

- Lung function
- Tobacco
- INF response
- Fam. Hx.

Wheezing

- Parainfluenza
- RSV
- RV

Resolution

Asthmatic

- Atopy
- Pollutants
- Allergen expos.
- other

Exacerbation

- Rhinovirus
- Influenza
- other

Adapted from Lemanske R
Adjusted odds ratios (95% CI) for factors independently related to current wheeze using logistic regression.
Population-based birth cohort; at age 5 years.

Current wheeze: 22%
28% were sensitized

Protection and Risk Factors for Recurrent Wheezing in Infancy

- Smoking in pregnancy
  \( (\text{OR} = 1.86; \text{CI} 95\% = 1.28–2.70; P = 0.001) \)

- Daycare attendance
  \( (\text{OR} = 1.76; \text{CI} 95\% = 1.33–2.35; P = 0.0001) \)

- Colds >4 months age
  \( (\text{OR} = 0.57; \text{CI} 95\% = 0.42–0.76; P = 0.0001) \)

- Mother >12 years school
  \( (\text{OR} = 0.73; \text{CI} 95\% = 0.55–0.97; P = 0.09) \)

- Dog at home
  \( (\text{OR} = 1.51; \text{CI} 95\% = 1.16–1.96; P = 0.002) \)

- Bronchopneumonia
  \( (\text{OR} = 1.76; \text{CI} 95\% = 1.28–2.42; P = 0.0006) \)

- Asthma in parents
  \( (\text{OR} = 4.19; \text{CI} 95\% = 1.03–16.97; P = 0.04) \)

Chong Neto, Rosario et al. Allergy 2010; 65: 406-7

written questionnaire
N= 3003
recurrent wheezing= 22.6%
**Human rhinovirus associated wheezing during the first and second year of life and asthma risk at 5–7 years of age**

*Single infections.*

Independent of age, sex, and atopic dermatitis.

Independent of aeroallergen sensitization.

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Setting</th>
<th>Age (months)</th>
<th>Index group</th>
<th>Comparator group</th>
<th>Asthma risk at age 5–7 years OR (95% CI)</th>
<th>Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kotaniemi-Syrjänén, 2003 (9)</td>
<td>Inpatients, non-selected population</td>
<td>&lt;24</td>
<td>HRV+ wh+, n = 20*</td>
<td>HRV−, wh+, n = 43</td>
<td>4.1 (1.0–17)</td>
<td>No†</td>
</tr>
<tr>
<td>Kusel, 2007 (41)</td>
<td>Outpatients, birth cohort at atopy risk</td>
<td>&lt;12</td>
<td>HRV+ wh+, n = 34</td>
<td>LRI+ wh−, n = 193</td>
<td>3.2 (1.1–9.5)</td>
<td>Atopy</td>
</tr>
<tr>
<td>Jackson, 2008 (55)</td>
<td>Outpatients, birth cohort at atopy risk</td>
<td>&lt;12</td>
<td>HRV+ wh+, n = 45</td>
<td>HRV+ wh−, n = 214</td>
<td>2.7 (1.4–5.3)</td>
<td>No‡</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12–23</td>
<td>HRV+ wh+, n = 37</td>
<td>HRV+ wh−, n = 222</td>
<td>6.5 (3.1–13.7)</td>
<td>No‡</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval; HRV, human rhinovirus; wh, wheezing; LRI, lower respiratory tract illness.

---

Increasing strength of clinical evidence to support increased susceptibility to infection

**Association between asthma and viral infections**
- Up to 85% of asthma exacerbations in children are due to viral URI
- RSV and RV bronchiolitis in infancy associated with increased risk of asthma

**Frequency and severity of respiratory infections**
- Higher rates of influenza attributable morbidity and CAP
- More frequent and more severe LRTI
- More severe infant bronchiolitis associated with higher risk of asthma development

**Susceptibility to infections outside of the respiratory tract**
- Increased rates of otitis media and gastroenteritis in infancy
- Delayed clearance of viral skin infections

**Colonization and infection latency**
- Higher rates of latent infections
- Bacterial colonization of the airways at 1 month of age associated with asthma at age 5 years

**Invasive infections**
- Increased risk of invasive pneumococcal disease
- Higher incidence of rhinoviremia

---

James KM et al. J Allergy Clin Immunol 2012;130:343-501
Human Rhinovirus

- Enhances epithelial cell cytotoxicity.
- Induces mucin production.
- Delays epithelial repair.
- Induces cytokine and chemokine release to recruit secondary effector cells.
- Promotes the production of growth factors.
- Atopy enhances the clinical effect of HRV and both prolong and enhance airway hyperresponsiveness.

Human Rhinovirus (HRV) may contribute to airway remodeling in asthma
Factors linked to severe HRV infections

<table>
<thead>
<tr>
<th>Host characteristics</th>
<th>Immunologic</th>
<th>Environment and lifestyle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic lung diseases</td>
<td>Low interferon responses</td>
<td>Tobacco smoke</td>
</tr>
<tr>
<td>Asthma</td>
<td>IFN-α</td>
<td>Pollutants (NO₂)</td>
</tr>
<tr>
<td>COPD</td>
<td>IFN-β</td>
<td></td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>IFN-γ</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>IFN-λ</td>
<td></td>
</tr>
<tr>
<td>Preschool children</td>
<td>Allergy</td>
<td>Diet</td>
</tr>
<tr>
<td>Elderly</td>
<td>Eosinophilia</td>
<td>Vitamin D</td>
</tr>
<tr>
<td>Genetics</td>
<td>Epithelial integrity</td>
<td>Probiotics</td>
</tr>
<tr>
<td>Gender (young boys)</td>
<td>Immune compromise</td>
<td>Stress</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Day care attendance</td>
</tr>
</tbody>
</table>

Hx of ≥ 4 wheezing episodes with at least one physician diagnosed. In addition, at least one of the major conditions or at least two of the minor conditions.

Modified asthma predictive index

<table>
<thead>
<tr>
<th>Major criteria</th>
<th>Minor criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parental history of asthma</td>
<td>Allergic sensitization to milk, egg, or peanuts</td>
</tr>
<tr>
<td>MD-diagnosed atopic dermatitis</td>
<td>Wheezing unrelated to colds</td>
</tr>
<tr>
<td>Allergic sensitization to at least one aeroallergen</td>
<td>Blood eosinophils ≥4%</td>
</tr>
</tbody>
</table>

Original asthma predictive index

<table>
<thead>
<tr>
<th>Major criteria</th>
<th>Minor criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parental history of asthma</td>
<td>MD-diagnosed allergic rhinitis</td>
</tr>
<tr>
<td>MD-diagnosed atopic dermatitis</td>
<td>Wheezing unrelated to colds</td>
</tr>
<tr>
<td></td>
<td>Blood eosinophils ≥4%</td>
</tr>
</tbody>
</table>

Community-based cohort of 198 children at high atopic risk was followed from birth to 5 ys.

Childhood Asthma Study (CAS) Perth, Australia

- 815 episodes of acute respiratory illness (33% lower respiratory infections)
- Postnasal aspirates + in 69% (RV 48.3%; VSR 10.9%)
- Current wheeze at 5 ys.: 28.3%
- Association with LRTI: risk > 3X, specially if atopic < 2 years.

Predictors of current wheeze at 5 ys of age in relation to time of atopic sensitization

Acute severe LRI caused by RV or RSV in the 1st year of life are important contributors to current asthma and persistent wheeze in 5 y/o children, particularly in those who are sensitized during infancy.

<table>
<thead>
<tr>
<th>Type of LRI</th>
<th>0</th>
<th>1</th>
<th>\geq 2</th>
<th>p-value</th>
<th>Odd Ratio (95%) CI</th>
<th>OR (95%) CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole LRI</td>
<td>1.0</td>
<td>4.2</td>
<td>4.2</td>
<td>0.006</td>
<td>(1.5-11.8)</td>
<td>(0.2-9.9)</td>
</tr>
<tr>
<td>Any wheezy or febrile LRI</td>
<td>1.0</td>
<td>3.9</td>
<td>3.9</td>
<td>0.007</td>
<td>(1.4-10.5)</td>
<td>(0.1-3.9)</td>
</tr>
<tr>
<td>Any wLRI associated with rhinovirus or RSV</td>
<td>0.8</td>
<td>4.1</td>
<td>4.1</td>
<td>0.02</td>
<td>(1.3-12.6)</td>
<td>(0.1-6.4)</td>
</tr>
<tr>
<td>Any wLRI associated with rhinovirus</td>
<td>1.6</td>
<td>3.2</td>
<td>3.2</td>
<td>0.03</td>
<td>(1.1-9.5)</td>
<td>(0.3-18.5)</td>
</tr>
<tr>
<td>Any wLRI associated with RSV</td>
<td>1.6</td>
<td>3.6</td>
<td>3.6</td>
<td>0.06</td>
<td>(1.0-13.3)</td>
<td>Insufficient number</td>
</tr>
</tbody>
</table>

wLRI: Wheezy lower respiratory tract illness
### Association between type of Acute Respiratory Illness caused by RSV and rhinovirus and type of wheeze

<table>
<thead>
<tr>
<th></th>
<th>Any ARI caused by RSV OR (95% CI) P</th>
<th>Any ARI caused by rhinovirus OR (95% CI) P</th>
<th>Nonwheezy LRI caused by RSV OR (95% CI) P</th>
<th>Nonwheezy LRI caused by rhinovirus OR (95% CI) P</th>
<th>Wheezy LRI caused by RSV OR (95% CI) P</th>
<th>Wheezy LRI caused by rhinovirus OR (95% CI) P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current asthma</td>
<td>1.5 (0.7-3.2) 0.3</td>
<td>1.1 (0.6-3.2) 0.9</td>
<td>1.1 (0.4-2.9) 0.9</td>
<td>0.7 (0.4-1.3) 0.3</td>
<td>2.1 (0.5-8.1) 0.3</td>
<td>2.9 (1.2-7.1) 0.02</td>
</tr>
<tr>
<td>Transient wheeze</td>
<td>1.2 (0.6-2.3) 0.6</td>
<td>1.6 (0.6-3.9) 0.3</td>
<td>1.7 (0.8-4.0) 0.2</td>
<td>1.3 (0.8-1.9) 0.3</td>
<td>1.7 (0.4-6.3) 0.5</td>
<td>0.9 (0.4-2.2) 0.9</td>
</tr>
<tr>
<td>Late-onset wheeze</td>
<td>1.5 (0.6-4.1) 0.4</td>
<td>0.8 (0.3-2.9) 0.8</td>
<td>0.6 (0.1-2.8) 0.5</td>
<td>0.6 (0.2-1.5) 0.3</td>
<td>0.7 (0.1-7.0) 0.8</td>
<td>0.7 (0.1-3.2) 0.6</td>
</tr>
<tr>
<td>Persistent wheeze</td>
<td>1.1 (0.5-2.4) 0.7</td>
<td>0.8 (0.3-2.1) 0.6</td>
<td>1.1 (0.7-1.6) 0.8</td>
<td>1.1 (0.7-1.6) 0.8</td>
<td>2.7 (0.7-9.8) 0.04</td>
<td>2.9 (1.2-7.0) 0.02</td>
</tr>
<tr>
<td>Current wheeze</td>
<td>1.2 (0.6-2.4) 0.6</td>
<td>0.7 (0.3-1.8) 0.5</td>
<td>0.7 (0.3-1.7) 0.4</td>
<td>0.8 (0.5-1.2) 0.3</td>
<td>2.5 (1.0-11.3) 0.05</td>
<td>2.5 (1.1-5.9) 0.03</td>
</tr>
</tbody>
</table>

Transitório: episódios nos 3 primeiros anos; início tardio: entre 3-5 anos; ativo: sibilos nos 12 meses; persistente: desde primeiros 3 até 5 anos

Immunologic risk factors for virus-induced wheezing

- 285 children with a parental hx of asthma and/or respiratory allergies.
- Mononuclear cells obtained at birth (umbilical cord blood) and at 1 year
- Incubated with phytohemagglutinin, RSV, or RV, and supernatants were analyzed for IL-5, IL-10, IL-13, and IFN-g.

The TH2 response, could have beneficial effects during viral respiratory infections. Low IL-13 and IFN-γ production at birth are indicators of an immature immune system.

RV wheezing episodes are risk factors for asthma development.

259 were still followed at the age of six.

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)

Wheezing Illnesses

Jackson DJ, AJRCCM 2008:178:667
“Childhood Origin of ASThma (COAST)“

n=238; followed prospectively from birth to 8 ys. of age (1,3,6,8 ys); Parents with asthma and/or positive PST.

Viral respiratory infection: culture and RT-PCR in nasopharynx aspirates.

Spirometry and impulse oscillometry annually.

Specific IgE FEIA.

RV wheezing illnesses in early life are associated with a subsequent diagnosis of asthma and lower lung function in childhood.

Guilbert T et al J Allergy Clin Immunol 2011;128:532-8
HRV wheezing illnesses in the first 3 years: greater risk for asthma at age 6 (OR=9.8) compared to infants who wheezed with RSV (OR=2.6)

Guilbert T et al J Allergy Clin Immunol 2011;128:532-8
• 630 infants with bronchiolitis or URIs.
• 162 (26%) had HRV infection.
• 35% had HRVA, 6% HRVB, and 30% had HRVC.
• 104 (64%) had HRV infection alone.
• Maternal and family history of atopy = more severe HRV-associated illness
• Maternal history of atopy/asthma = more severe HRV associated bronchiolitis (OR, 2.39 P < .02).

Miller EK et al J Allergy Clin Immunol 2011;127:883-91
Duration of hyperreactivity after a single URTI

Non-atopic

duration = 7.3 ± 1 weeks

Atopic

duration = 7.0 ± 2 weeks

Non atopic wheezers have airway pathology comparable to asthma

Basement membrane thickening and eosinophils

Turato G, AJRCCM 2008;178:476
Neonatal bronchial hyperresponsiveness precedes acute severe viral bronchiolitis in infants

Bo L. K. Chawes, MD, PhD, * Porntiva Poirisrisak, MD, PhD, ** Sebastian L. Johnston, MD, PhD, and Hans Bisgaard, MD, DMSc

Copenhagen and Gentofte, Denmark, and London, United Kingdom

Bronchial responsiveness (BR) and lung function (LF) in 1-month-old neonates (before any respiratory symptoms) who later develop acute severe bronchiolitis with those who do not. n = 402

Using the raised-volume rapid thoracoabdominal compression technique and 15% decrease in transcutaneous oxygen pressure [methacholine PD15]
Acute severe bronchiolitis before 2 ys of age:
(34) 8.5% hospitalized,
(21) 62% and
(6) 7% associated with RSV
Comparison of lung function at age 1 month in children who later have acute severe bronchiolitis versus healthy control subjects

<table>
<thead>
<tr>
<th>Lung function, age 1 mo</th>
<th>Control subjects (n = 366) vs:</th>
<th>Acute severe bronchiolitis (n = 34)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean difference (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>FEV(_{0.5}) (z score)</td>
<td>-0.17 (-0.52 to 0.19)</td>
<td>.36</td>
</tr>
<tr>
<td>FEF(_{50}) (z score)</td>
<td>-0.28 (-0.65 to 0.08)</td>
<td>.13</td>
</tr>
<tr>
<td>logPD(_{15}) (PtcO(_2) [(\mu)mol])</td>
<td>-0.69 (-1.24 to -0.15)</td>
<td>.01</td>
</tr>
</tbody>
</table>
Early RV infection is strongly associated with asthma symptoms and/or persistence later in childhood, more than RSV.

The duration of such associations awaits further follow-up of cohorts.

Synergistic interaction between viral infection and allergic sensitization. More severe viral illnesses in infancy have been linked to increased risk of developing asthma. Current drugs for the prevention and treatment of virus-induced exacerbation of asthma are poorly effective.

Ahanchian et al. BMC Pediatrics 2012, 12:147
<table>
<thead>
<tr>
<th>Process</th>
<th>Preventive strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhinoviral transmission</td>
<td>Hand hygiene, isolation</td>
</tr>
<tr>
<td>Attachment to respiratory epithelium</td>
<td>HRV neutralizing antibodies, anti-receptor antibodies</td>
</tr>
<tr>
<td></td>
<td>Second generation antihistamines, zinc vaccines</td>
</tr>
<tr>
<td>Entry, RNA and protein synthesis</td>
<td>Anti-rhinoviral therapies (Pleconaril, Ruprintrivir)</td>
</tr>
<tr>
<td>Enhancing immunity</td>
<td>Balanced diet, interferons, immunostimulants, probiotics, breast milk, Echinacea, garlic, zinc, ginseng</td>
</tr>
</tbody>
</table>
Strategies for the primary prevention of asthma: prevention of either allergic sensitization or of sLRI in high risk children.

Intervention measures that can lower the frequency and/or intensity of sLRI in early life amongst the high risk atopic subgroup of children are likely to be successful at preventing asthma.
There are currently no strategies available for the successful prevention of respiratory tract illnesses caused by rhinovirus.

- Respiratory tract illnesses caused by RV are highly frequent in children attending day care.
- It is possible that avoidance of day care in early life could be used as prevention of asthma.
- Although day care attendance is associated with increased incidence of wheezing LRIs in early life, it is either unrelated to asthma risk or might be associated with protection against the development of asthma.

Martinez FD J Allergy Clin Immunol 2011;128:939-45

Thank you
Obrigado