Reducing/Eliminating Asthma Exacerbations: Immunopathologic Features of Asthma Exacerbations

Mario Castro MD, MPH
Asthma & Airway Translational Research Unit
Washington University School of Medicine
St. Louis, Missouri, USA

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Causes of Asthma Exacerbations

- Poor underlying control
- Environmental factors
  - VRIs
  - Allergen exposure
  - Air pollution
  - Bacterial infections
  - Stress
  - Exercise/cold air
  - Occupational exposure
**Asthma Exacerbations**

- Viruses cause asthma exacerbations in adults and children
- RVs cause ~60% of virus-induced exacerbations of asthma
- The response to viral infection is shaped by the host's antiviral response
- Worsening of airway inflammation during exacerbations may be related to accelerated loss of lung function and structural changes

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**Viruses Detected During Asthma Exacerbations in Children**

<table>
<thead>
<tr>
<th>Virus</th>
<th>PCR</th>
<th>Culture</th>
<th>Immuno-fluorescence</th>
<th>Antibody rise by ELISA</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Picornaviruses</td>
<td>146</td>
<td>47</td>
<td></td>
<td></td>
<td>147</td>
</tr>
<tr>
<td>Coronavirus</td>
<td>17</td>
<td>14</td>
<td></td>
<td>21</td>
<td>38</td>
</tr>
<tr>
<td>Influenza viruses</td>
<td>14</td>
<td>10</td>
<td></td>
<td>20</td>
<td>21</td>
</tr>
<tr>
<td>Parainfluenza viruses</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>18</td>
<td>21</td>
</tr>
<tr>
<td>RSV</td>
<td>6</td>
<td>6</td>
<td>12</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>1</td>
<td>8</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

*1,088 school-age children, viruses detected 80% of exacerbations; all of 147 picornaviruses identified as RV by further testing.*

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**Viruses Detected in Symptomatic Asthma Exacerbations in Adults**

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Number</th>
<th>Percent of all episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV</td>
<td>76</td>
<td>33.2</td>
</tr>
<tr>
<td>HCV OC43</td>
<td>21</td>
<td>9.2</td>
</tr>
<tr>
<td>HCV 229E</td>
<td>15</td>
<td>6.6</td>
</tr>
<tr>
<td>Influenza B</td>
<td>2</td>
<td>0.9</td>
</tr>
<tr>
<td>Parainfluenza</td>
<td>5</td>
<td>2.2</td>
</tr>
<tr>
<td>RSV</td>
<td>2</td>
<td>0.9</td>
</tr>
<tr>
<td>Chlamydia psittaci</td>
<td>3</td>
<td>1.3</td>
</tr>
<tr>
<td>Dual infection</td>
<td>5</td>
<td>2.2</td>
</tr>
</tbody>
</table>

*130 adults with 280 exacerbations.*

RV = rhinovirus; HCV = human coronavirus; RSV = respiratory syncytial virus.
Pathophysiology of T2-High Asthma

High eosinophil levels cause:  
- Recruitment and activation of immune and structural cells  
- Airway inflammation  
- Airway wall fibrosis, thickening, and remodeling  
- Inadequately controlled asthma symptoms and increased...
Inflammatory Responses During an Asthma Exacerbation

Correlation with increase in β-agonist: r = 0.55, p = 0.03 and reactivity r = -0.41, p = 0.04

Castro et al. AJRCCM 2004:169:842-849

T cell subsets in the Airway During an Asthma Exacerbation

CD8 correlation with decrease in FEV1: r = -0.76, p = 0.02 and reactivity r = -0.66, p = 0.05

Castro et al. AJRCCM 2004:169:842-849

RANTES Expression in the Airway Epithelium following Steroid Withdrawal

Castro et al. AJRCCM 2004:169:842-849
The Role of the Respiratory Immune System

- Viral infections (esp. RV) frequently cause exacerbations of asthma
- Possible mechanisms
  - Extension into the lower airway
  - Inflammation with lymphocytes, eosinophils, neutrophils

Mechanisms of VRI-Induced Asthma Exacerbations

- A Th2 bias may also limit the respiratory immune system’s ability to effectively clear virus
- This may lead to greater viral replication, lysis of epithelial cells, airway inflammation, and asthma exacerbations

Poor Viral Clearance May Also Lead to Exacerbations

Cell counts in bronchial biopsy specimens of subjects with and without asthma at baseline and days 4 and 6 of experiment. A, CD45 cells. B, Epithelial neutrophils. C, Subepithelial neutrophils. D, CD68 cells. E, CD4 cells. Data are presented as the number of positive cells per square millimeter of subepithelium or per 0.1 mm² of epithelium.

Interferon Response & Respiratory Virus Control in Asthma

After IAV infection, viral loads were increased 2-fold in HBECs from asthmatics compared to controls (P < .05) but not following RSV infection.

Virus-induced Goblet Cell Hyperplasia

Mucin Products and Goblet Cell Hyperplasia

- Increase in mucin products have been described in mild-moderate asthma - MUC2, MUC5B, and MUC5AC (Ordonez AJRCCM 2001;163:517)
- In severe asthma, there appears to be a marked increase in goblet cells and mucin products as well

Airway Epithelial Remodeling with Steroid Withdrawal

Airway Remodeling in Asthma

- Individuals with asthma have a more rapid decline in FEV1 with age than normals
- Despite long term therapy with steroids, some asthmatics develop irreversible airflow obstruction and persistent airway hyperreactivity
- Repetitive injury and repair of airways caused by chronic inflammation results in structural changes
- Healing of the airways involves replacement with normal cells or replacement by connective tissue/scar
Decline in Lung Function in Asthma
(15 years follow up)

Exacerbations
-Leads to Remodeling?

- Bai et al. studied 93 asthmatics prospectively for ≥5 yrs (median 11 yrs)
- 60% experienced at least one severe exacerbation*
- Exacerbators experienced greater decline in FEV₁ - difference 16.9 ml/yr
- One exacerbation per yr associated with 30 ml greater decline in FEV₁

Inhaled Steroid Treatment
as Regular Therapy in Early Asthma (START)

- 7,165 patients (5-66 yo) with persistent asthma <2 yrs randomized to budesonide vs. placebo for 3 yrs
- Mean followup: 2.47 yr Bud; 2.44 yr placebo
- Drop-out rates: 27.5% Bud; 28.6% placebo
- Added ICS: 12.5% Bud; 23.6% placebo
Inhaled Steroid Treatment as Regular Therapy in Early Asthma (START)

O’Byrne et al AJRCCM 2009;179:19-24

- Mean yr decline in FEV₁ in placebo grp with SARE vs w/o: 66 vs 34 ml
- Mean yr decline in FEV₁ in Bud grp with SARE vs w/o: 27 vs 21 ml

Exacerbations and Airway Remodeling

- Viruses are a common cause of asthma exacerbations leading to AHR and GCM
- Exacerbations are associated with the influx of CD4 and CD8 lymphocytes
- Worsening of airway inflammation during exacerbations may accelerate loss of lung function
- ICS may prevent progressive loss of lung function in those with severe exacerbations
- Promising therapy such as biologics and thermoplasty may modify airway remodeling

Washington University in St. Louis
Asthma and Airway Translational Asthma Research Unit (AATRU)