Asthma exacerbations are a major cause of disease morbidity and costs. For both children and adults, viral respiratory infections are the major cause of these exacerbations. The mechanisms underlying these episodes are complex and involve multiple cells and factors. With the use of biologics to treat more severe asthma and exacerbation-prone patients, greater insight has been gained into the targets, and consequently, the mechanisms by which respiratory viruses, particularly the common cold virus – rhinovirus, lead to exacerbations. The following discussion on biologic targets for exacerbations will focus on major risk factors in this process: IgE, allergic sensitization, deficiencies in innate immunity, particularly interferon generation, and the multiple cells and pathways involved. The unfolding of this new information has not only provided greater insight to this major cause of asthma morbidity, and its loss of control, but also is identifying new targets whose targeted control promises to lead to improved outcomes and the attenuation or prevention of exacerbations.

**What are key biologic targets in asthma exacerbations?**

**What role does IgE play in asthma exacerbations?**

**What is the effect of IgE antibody to dust mite allergen and risk for wheezing among asthmatic children infected with rhinovirus?**

**What is the effect of omalizumab on asthma exacerbations on a seasonal basis?**

**What role do innate immune responses play in asthma exacerbations?**
Total Serum IgE Levels

Is dendritic cell (pDC) generation of IFN-α antiviral impaired in patients with allergic asthma?

What is the relationship between IgE and virus-induced IFN-α generation?

What effect does omalizumab have on seasonal exacerbations of asthma in PROSE?

What effect does omalizumab treatment have on in vitro generation of IFN-α from isolated PBMC incubated with RV?

What is the effect of restoring IFN-α generation to asthma exacerbations?
Is there a difference in bronchial epithelial cell generation of interferon between normal and asthma?


Impaired IFN-β production in asthma


What is the alveolar macrophage expression of interferon-β to RV in severe asthma?

What is the comparative of TLR7 protein generation by AM to RV in severe asthma?

[Graph showing TLR7 Protein generation by AM compared to RV in Healthy vs. Severe asthma.]


Is there a relationship between TLR7 expression by AM and frequency of exacerbation in severe asthma?

[Graph showing correlation between TLR7 mRNA expression and number of exacerbations.]


What is the comparative AM expression of miRNAs in healthy and severe asthma subjects?

[Graph showing relative expression of miR-375 in Healthy vs. Severe asthma.]


Alteration of alveolar macrophage generation of interferons

[Diagram showing miRNAs downregulation of TLR7 in RV compared to AM.]

What is the relationship of blood eosinophils to severe asthma exacerbations?

<table>
<thead>
<tr>
<th>Blood Eosinophils</th>
<th>Adjusted RR</th>
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<tbody>
<tr>
<td>0-299 cells/µl</td>
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<tr>
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<td>≥4000 cells/µl</td>
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- Evaluated mepolizumab (75, 250 and 750 mg) vs. placebo
- 621 adult patients on high doses of ICS and with one or more of the following
  - 2 or more exacerbations in previous year
  - Sputum eosinophils ≥3%
  - FeNO ≥50 ppb
  - Blood eosinophils ≥500/microliter

Increased susceptibility factors for exacerbations
What is the effect of a RV infection on asthma, eosinophils, IL-33 and IL-5?


How may anti-IL-5 affect virus-induced asthma exacerbations?

What are key biologic targets that may promote asthma exacerbations?