Allergic Asthma & Treatment Modalities

Jennifer Petts, DO | Allergy & Immunology | The Iowa Clinic
Disclosures

/ None
Overview

- History of environmental allergies
- Role of allergens in asthma
- Diagnosis of environmental allergies
- Treatment
  - Oral/topical antihistamines
  - Nasal steroids
  - Cromoyln
  - LTRA
  - SLIT vs SCIT
  - Omalizumab
  - Mepolizumab
  - Other biologics
Definitions

- Asthma is a chronic disease with a prevalence of up to ~12% of the United States population, characterized by reversible airflow obstruction, inflammation, and airway hyperresponsiveness.

- Allergic rhinoconjunctivitis is a chronic disease with a prevalence of ~20%, characterized by an IgE mediated reaction to an airborne allergen which the normal population does not have.
Classifying asthma severity and initiating treatment in youths greater than or equal to 12 years of age and adults

<table>
<thead>
<tr>
<th>Components of severity</th>
<th>Classification of asthma severity (≤12 years of age)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intermittent</td>
</tr>
<tr>
<td>Impairment</td>
<td></td>
</tr>
<tr>
<td>Normal FEV₁/FVC</td>
<td></td>
</tr>
<tr>
<td>6 to 19 years 85 percent</td>
<td>≤2 days/week</td>
</tr>
<tr>
<td>20 to 39 years 80 percent</td>
<td>≤2x/month</td>
</tr>
<tr>
<td>40 to 59 years 75 percent</td>
<td>≤2 days/week</td>
</tr>
<tr>
<td>60 to 80 years 70 percent</td>
<td>≤2x/month</td>
</tr>
<tr>
<td>Intermittent</td>
<td></td>
</tr>
<tr>
<td>Persistent</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td></td>
</tr>
<tr>
<td>Interference with normal activity</td>
<td>None</td>
</tr>
<tr>
<td>Lung function</td>
<td></td>
</tr>
<tr>
<td>• Normal FEV₁ between exacerbations</td>
<td></td>
</tr>
<tr>
<td>• FEV₁ &gt;80 percent predicted</td>
<td></td>
</tr>
<tr>
<td>• FEV₁/FVC normal</td>
<td></td>
</tr>
<tr>
<td>• FEV₁ &gt;50 but &lt;60 percent predicted</td>
<td></td>
</tr>
<tr>
<td>• FEV₁/FVC reduced &gt;5 percent</td>
<td></td>
</tr>
<tr>
<td>Risk</td>
<td></td>
</tr>
<tr>
<td>Exacerbations requiring oral systemic glucocorticoids</td>
<td>0 to 1/year (see footnote)</td>
</tr>
</tbody>
</table>

Recommended step for initiating treatment

- Step 1
- Step 2
- Step 3
- Step 4 or 5

In two to six weeks, evaluate level of asthma control that is achieved and adjust therapy accordingly.

Assessing severity and initiating treatment for patients who are not currently taking long-term control medications. The stepwise approach is meant to assist, not replace, the clinical decision-making required to meet individual patient needs. Level of severity is determined by assessment of both impairment and risk. Assess impairment domain by patient’s/caregiver’s recall of previous two to four weeks and spirometry. Assign severity to the most severe category in which any feature occurs. At present, data are inadequate to correlate frequencies of exacerbations with different levels of asthma severity. In general, more frequent and intense exacerbations (eg, requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate greater underlying disease severity. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic glucocorticoids in the past year may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.

FEV₁: forced expiratory volume in one second; FVC: forced vital capacity; ICU: Intensive care unit.

## Asthma Endotypes

<table>
<thead>
<tr>
<th>Endotype</th>
<th>Clinical Features</th>
<th>Proposed Mechanism</th>
<th>Treatment Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic asthma</td>
<td>Allergen-associated symptoms, allergic rhinitis, childhood onset, history of eczema</td>
<td>Th2 dominant</td>
<td>Responds to glucocorticoids and omalizumab</td>
</tr>
<tr>
<td>Allergic bronchopulmonary aspergillosis</td>
<td>Severe mucus production, adult onset, long duration</td>
<td>Colonization of airways by fungi</td>
<td>Responds to glucocorticoids and antifungals</td>
</tr>
<tr>
<td>API-positive preschool wheezer*</td>
<td>&gt;3 episodes per year, family history of asthma</td>
<td>Th2 dominant</td>
<td>Responds to daily inhaled glucocorticoids</td>
</tr>
<tr>
<td>Aspirin-sensitive asthma</td>
<td>Nasal polyposis, often severe asthma, aspirin sensitivity, adult onset</td>
<td>Eicosanoids-related</td>
<td>Responds to antileukotrienes, aspirin desensitization</td>
</tr>
<tr>
<td>Severe late-onset hypereosinophilic asthma</td>
<td>Severe exacerbations, late-onset disease, peripheral blood eosinophilia</td>
<td>Nonatopic, mechanisms unclear</td>
<td>Often dependent on oral glucocorticoids</td>
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<tr>
<td>Exercise-induced bronchospasm</td>
<td>Symptoms related to exercise, frequently in elite athletes</td>
<td>Dehydration of airways</td>
<td>Mixed response to glucocorticoids</td>
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*API, asthma predictive indices: children with repeated wheezing episodes and history of atopic dermatitis, parental asthma, or aeroallergen sensitivity, and peripheral eosinophilia, wheezing unrelated to common cold, or sensitization to food allergen.

Adapted from *Journal of Allergy and Clinical Immunology*, 127(2), Lotvall J, Akdis CA, Bacharier LB, et al. Asthma endotypes: a new approach to classification of disease entities within the asthma syndrome, 355-360, 2011, with permission from Elsevier.
# Asthma Endotypes

## Examples of Asthma Endotypes

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History of ‘hay fever’

- Occasional description of allergic disease occurred in antiquity
- First true description by John Bostock in 1828
- First publication in 1870’s by Blackley (UK, grass) and Wyman (US, ragweed)
History of ‘hay fever’

By 1900: sites to go to avoid exposure established and earliest investigations into immunotherapy

1950’s: first controlled trials of immunotherapy to grass
Asthma Epidemic in Children

- Prior to 1960, asthma was not a common diagnosis.
- 1960’s increased numbers of patients with asthma also with skin testing positive to dust mites.
- This increase was observed first in countries which dust mites were the dominant allergen.
Asthma Epidemic in Children

- In the 1990’s, information regarding prevalence of other perennial allergens in patients with asthma were published
- Cat/dog in army recruits in Sweden/Finland
- Cockroach in US African Americans living in poverty
Diagnosis of Environmental Allergies

/ Skin prick/puncture
/ Skin intradermal
/ Serum specific IgE
/ Immunocap by Phadia
Skin Prick/Puncture

Primary diagnostic test and most appropriate initial test
Skin Prick/Puncture

Benefits
- Quick tests with results available that day
- Patient can visualize results
- Variety of allergens
- In combination with history, predictive value is 97-99%
- Negative results with accuracy of >95%
Intradermal

- Increased sensitivity
- 95% accuracy with negative results
- Increased false positives
- Increased risk of systemic reactions
- NEVER used for food or latex testing due to an unacceptably high rate of anaphylaxis
Serum Specific IgE
/ Limited by what is made commercially depending on the allergen
/ Sensitivity 60-95%
/ Specificity 30-95%

Figure 4-11. ImmunoCAP.
Treatment Options

/ Avoidance
/ Oral/topical antihistamines
/ Nasal steroids
/ Cromolyn
/ Leukotriene Receptor Antagonists (LTRA)
/ Immunotherapy
/ Omalizumab (Xolair)
Importance?
Reducing allergic triggers will aid in management of poorly controlled asthma or reduce the number/dosing of asthma medications.
Basic Environmental Control Measures

- Animal dander
  - No animals in the bedroom
  - Wash hands after touching the animal and do not touch face
  - Air filters and HEPA filters

- Indoor Molds
  - Remove known mold from the home
  - Fix water leaks
  - Avoid humidifiers
Basic Environmental Control Measures

/ Dust mites
/ Encasements for mattress and pillows
/ Wash sheets
/ Reduced humidity
/ Keep clutter out of the bedroom
/ Vacuum regularly

http://www.apartmenttherapy.com/dust-and-dust-mite-proof-your-105222
## Oral Antihistamines

**Table 9-6. Antihistamines in Adults**

<table>
<thead>
<tr>
<th></th>
<th>Onset of Action Based on Wheal-and-Flare Studies (h Hr)</th>
<th>Half-Life (t½, in Hr)</th>
<th>Conditions That May Require Dose Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-generation antihistamines</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorpheniramine</td>
<td>3</td>
<td>27.9 ± 8.7</td>
<td></td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>2</td>
<td>9.2 ±2.5</td>
<td>Hepatic impairment</td>
</tr>
<tr>
<td>Doxepin</td>
<td>13</td>
<td></td>
<td>Hepatic impairment</td>
</tr>
<tr>
<td>Hydroxyzine</td>
<td>2</td>
<td>20 ± 4.1</td>
<td>Hepatic impairment</td>
</tr>
<tr>
<td><strong>Second-generation antihistamines</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cetirizine (a metabolite of hydroxyzine) cleared through urine</td>
<td>1</td>
<td>6.5–10</td>
<td>Renal and hepatic impairment</td>
</tr>
<tr>
<td>Desloratadine (metabolite of loratadine)</td>
<td>2</td>
<td>27</td>
<td>Renal and hepatic impairment</td>
</tr>
<tr>
<td>Fexofenadine *cleared through feces.</td>
<td>2</td>
<td>14.4</td>
<td>Renal impairment</td>
</tr>
<tr>
<td>Levocetirizine (enantiomer of cetirizine)</td>
<td>1</td>
<td>7 ± 1.5</td>
<td>Renal and hepatic impairment</td>
</tr>
<tr>
<td>Loratadine</td>
<td>2</td>
<td>7.8 ± 4.2</td>
<td>Hepatic impairment</td>
</tr>
</tbody>
</table>
Oral Antihistamines

- Side effects
  - Sedation
  - Increased appetite
  - Decreased cognitive performance
  - Dry mouth
  - Urinary retention
  - Prolonged QT intervals
# Topical Antihistamines

**Table 9-6. Antihistamines in Adults**

<table>
<thead>
<tr>
<th>Topical Antihistamines</th>
<th>Onset of Action Based on Wheal- and-Flare Studies (n Hr)</th>
<th>Half-Life ($t_{1/2}$, in Hr)</th>
<th>Conditions That May Require Dose Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azelastine</td>
<td>0.5</td>
<td>22–27.6</td>
<td></td>
</tr>
<tr>
<td>Emedastine</td>
<td>0.25</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Epinastine</td>
<td>0.1</td>
<td>6.5</td>
<td></td>
</tr>
<tr>
<td>Ketotifen</td>
<td>0.25</td>
<td>20–22</td>
<td></td>
</tr>
<tr>
<td>Levocabastine</td>
<td>0.25</td>
<td>35–40</td>
<td></td>
</tr>
<tr>
<td>Olopatadine</td>
<td>0.25</td>
<td>7.1–9.4</td>
<td></td>
</tr>
</tbody>
</table>
Nasal Steroids

- MOST effective medication for treatment of allergic rhinitis
- Low side effect profile
  - Nasal irritation corrected with technique
- Inhibit allergic inflammation
<table>
<thead>
<tr>
<th>Name</th>
<th>United States trade name</th>
<th>Generic available in United States</th>
<th>Available without a prescription in United States</th>
<th>Usual adult dose (per nostril)</th>
<th>Usual pediatric dose (per nostril)</th>
<th>Type of preparation (alcohol content*)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Second-generation (systemic bioavailability &lt;1% or undetectable)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluticasone furoate</td>
<td>Veramyst</td>
<td>No</td>
<td>No</td>
<td>Two sprays once daily</td>
<td>Two sprays once daily</td>
<td>Aqueous suspension pump spray</td>
</tr>
<tr>
<td>Fluticasone propionate</td>
<td>Flonase, Flonase Allergy Relief (OTC)</td>
<td>Yes</td>
<td>Yes</td>
<td>Two sprays once daily or one spray twice daily</td>
<td>One spray once daily</td>
<td>Aqueous suspension pump spray [0.25% alcohol]</td>
</tr>
<tr>
<td>Mometasone</td>
<td>Nasonex</td>
<td>No</td>
<td>No</td>
<td>Two sprays once daily</td>
<td>One spray once daily</td>
<td>Aqueous suspension pump spray</td>
</tr>
<tr>
<td><strong>First-generation (systemic bioavailability 10 to 50%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beclomethasone</td>
<td>Beconase AQ</td>
<td>No</td>
<td>No</td>
<td>One or two sprays twice daily</td>
<td>One spray twice daily</td>
<td>Aqueous suspension pump spray [0.25% alcohol]</td>
</tr>
<tr>
<td>Budesonide</td>
<td>Rhinocort Aqua, Rhinocort Allergy (OTC)</td>
<td>Yes</td>
<td>Yes</td>
<td>Two sprays once daily</td>
<td>Two sprays once daily for children ≥12 years</td>
<td>Pressurized aerosol spray (8% alcohol)</td>
</tr>
<tr>
<td>Flunisolide</td>
<td>Nasarel (brand version no longer available in United States)</td>
<td>Yes</td>
<td>No</td>
<td>Two sprays twice daily</td>
<td>One spray three times per day or two sprays twice daily</td>
<td>Aqueous suspension pump spray (contains propylene glycol, a possible irritant)</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>Nasacort AQ, Nasacort Allergy 24 Hr (OTC)</td>
<td>Yes</td>
<td>Yes</td>
<td>Two sprays once daily</td>
<td>One spray once daily (age 2 to 5 years)</td>
<td>One to two sprays once daily (age 6 to 11 years)</td>
</tr>
</tbody>
</table>
Cromolyn

/ Inhaled, nasal and ophthalmic
/ Mast cell stabilization preventing degranulation and release of mediators
/ Half-life of 80-90 min
/ Pregnancy class B (systemic)
Leukotriene Receptor Antagonists (LTRA)

/ Montelukast (Singulair) and Zarfirlukast

/ Clinical uses

/ Exercise-induced bronchospasm

/ Allergic asthma

/ Allergic rhinitis

/ Aspirin-exacerbated respiratory disease (AERD)
Leukotriene Receptor Antagonists (LTRA)

- Attenuate early and late-phase bronchoconstrictor responses
- Improvement in FEV1
- Less need for rescue SABA
- Decrease in asthma exacerbations
- Less effective than corticosteroids
LTRA

- Montelukast: age 6 months, once daily
- Zarfirlukast: 5 years old, twice daily
- Pregnancy class B
- Side effects
  - Diarrhea
  - SI or mood changes
  - Elevated transaminases (Zarfirlukast)
  - Rare association with onset of Churg-Strauss vasculitis
- Drug interactions
  - Montelukast: none
  - Zarfirlukast: Warfarin
Allergen Immunotherapy

- Approved for:
  - Allergic rhinitis/conjunctivitis
  - Allergic asthma
  - Atopic dermatitis

- Goal duration of therapy of 3-5 years

- Efficacy in DBPC

- Two ways to administer:
  - Subcutaneous
  - Sublingual
Allergen Immunotherapy

- Reduce symptoms of allergic rhinoconjunctivitis, atopic dermatitis and asthma
- Decrease medication usage
- Asthma:
  - Decreases bronchial responsiveness
  - Does not alter pulmonary function results
  - Prevent or delay the onset of asthma in patients with allergic rhinitis
Potential Mechanisms and Immunologic Changes Associated with Immunotherapy

- Modified allergic response to allergens over time
- Increase in IgG blocking antibody (initially IgG1, later IgG4)
- Increased numbers of CD4⁺CD25⁺ regulatory T lymphocytes and % of CD8⁺ T cells
- Initial increase (months), then a steady decrease (years) in allergen-specific IgE
- Blunted seasonal rise in allergen-specific IgE
- Decrease in low-affinity FceRI and FceRII (CD23)
- Increased IgA in respiratory secretions
- Reduction in basophil hyper-reactivity
- Increased interferon (IFN)-γ/interleukin (IL)-4 ratio and secretion of IL-10 and transforming growth factor (TGF)-β
- Decreased number of eosinophils, basophils, and mast cells in nose/lung
- Shift of T₇2 cytokines (IL-4, IL-5, and IL-13) to T₇1 cytokines (IFNγ, TGFβ, and IL-10)
Subcutaneous Immunotherapy

- Required build-up phase to reach maintenance
- Injections are given SQ in the posterior aspect of the upper arms

**FIG 2.** Example of color-coded vials of allergen immunotherapy maintenance.
Subcutaneous Immunotherapy

- Risk of systemic reactions
  - Unstable asthma
  - Dosing errors
  - Hx of prior systemic reaction
  - First injections from new vial
  - Accelerated or rush protocols
  - Build-up phase
  - Pollen season
  - B-blocker therapy
  - Theoretical with ACEI therapy
Allergen Immunotherapy

/ Careful administration in:
  / Severe or unstable asthma
  / B-blocker and ACEI
  / Pregnancy
  / Systemic mastocytosis
  / Cardiovascular disease
/ Safe in patients with HIV
/ No evidence of induction/worsening of autoimmune disease
/ Cost effective
Sublingual Immunotherapy (SLIT)

- Alternative approach
- Daily sublingual drops or dissolvable tablets
- Decreased risk of anaphylaxis
- Self administration
Sublingual Immunotherapy (SLIT)

- Proposed in early 1900’s
- 1980’s: clinical trials demonstrated a dose-dependent therapeutic response
- 1998: the World Health Organization recognized SLIT as an emerging therapy
- Performed for years with success in Europe
SLIT

/ FDA approved
/ Rawitek: ragweed, Merck, ages 18-65
/ Grastek: timothy grass, Merck, ages 5-65
/ Oralair: 5 northern grasses, Stallergenes, ages 10-65.
/ Under tongue x 1 min. Swallow. No food or drink x 5 min
/ Initiate 3-4 months prior to pollen season
/ May be used continuously for 3 years, Merck only
/ NOT tested in moderate to severe asthma
SLIT Safety

/ Adverse effects
/ Eosinophilic esophagitis
/ Pregnancy: safety has not been studied

/ Although Europe has used SLIT for many years, their allergens cannot be directly compared to US allergens due to different types of manufacturer processes, dosing and potency.
SLIT vs SCIT

Advantages of SLIT
- Safer
- More convenient
- Ingested vs injected

Disadvantages
- Consistent self administration of SLIT
- Patient education is increased
SLIT vs SCIT

Comparative efficacy:

- 20 adults monosensitized to grass (without asthma). Same reductions in symptoms and medications scores. No placebo arm. SCIT resulted in increased IgG4.

- 58 birch allergic adults (1/3 with asthma). No difference in therapy.

- 30 children with asthma, DM AR. Randomized SLIT/SCIT/placebo. SCIT significant reduction in asthma symptoms and medications use. Changes with SLIT were minimal and equivalent to placebo.
Biologics: the new frontier
Targets for current and pipeline biologics

The discovery that asthma is a heterogeneous disease has paved the way for new, targeted biologic therapies. Omalizumab, which targets immunoglobulin E (IgE), was the first to be approved over a decade ago and at least six biologics that target interleukins have now reached human trials.

IL-4 specific monoclonal antibodies:
- Dupilumab

IL-13 specific monoclonal antibodies:
- Lebrikizumab
- Tralokinumab

IL-4 is crucial for T\(_{H2}\) cell differentiation.

Along with IL-4, IL-13 stimulates B cells to produce IgE.

IL-5 specific monoclonal antibodies:
- Mepolizumab
- Reslizumab
- Bevacizumab

IL-5 prompts eosinophils to mature and migrate out of the bone marrow. Eosinophils trigger inflammation in the lungs in response to allergens.

IgE specific monoclonal antibodies:
- Omalizumab

When exposed to allergens, IgE binds to receptors on mast cells and triggers the release of histamine, leukotriene and prostaglandins (which promote vascular permeability and smooth muscle contraction) and cytokines such as IL-4 and IL-13 (which induce mucus secretion).
Omalizumab (Xolair)
Omalizumab (Xolair)

- Anti-IgE
- Approved for
  - Age 12+
  - Moderate-to-severe and severe allergic asthma
  - Perennial allergies (DM, M, C, D, Cockroach)
  - IgE level from 30-100 IU/ml
  - Incomplete symptom control with inhaled glucocorticoid treatment
# Omalizumab (Xolair)

## Q4-Week Dosing Table

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<thead>
<tr>
<th>Pretreatment serum IgE (IU/mL)</th>
<th>Body Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pounds</td>
</tr>
<tr>
<td></td>
<td>66-132</td>
</tr>
<tr>
<td></td>
<td>&gt;132-154</td>
</tr>
<tr>
<td></td>
<td>&gt;154-198</td>
</tr>
<tr>
<td></td>
<td>&gt;198-330</td>
</tr>
<tr>
<td>≥ 30-100</td>
<td>150 mg</td>
</tr>
<tr>
<td>&gt; 100-200</td>
<td>300 mg</td>
</tr>
<tr>
<td>&gt; 200-300</td>
<td>300 mg</td>
</tr>
</tbody>
</table>

## Q2-Week Dosing Table

<table>
<thead>
<tr>
<th>Pretreatment serum IgE (IU/mL)</th>
<th>Body Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pounds</td>
</tr>
<tr>
<td></td>
<td>66-132</td>
</tr>
<tr>
<td></td>
<td>&gt;132-154</td>
</tr>
<tr>
<td></td>
<td>&gt;154-198</td>
</tr>
<tr>
<td></td>
<td>&gt;198-330</td>
</tr>
<tr>
<td>≥ 30-100</td>
<td>See adjacent table on left</td>
</tr>
<tr>
<td>&gt; 100-200</td>
<td>225 mg</td>
</tr>
<tr>
<td>&gt; 200-300</td>
<td>225 mg</td>
</tr>
<tr>
<td>&gt; 300-400</td>
<td>225 mg</td>
</tr>
<tr>
<td>&gt; 400-500</td>
<td>300 mg</td>
</tr>
<tr>
<td>&gt; 500-600</td>
<td>375 mg</td>
</tr>
<tr>
<td>&gt; 600-700</td>
<td>375 mg</td>
</tr>
<tr>
<td></td>
<td>DO NOT DOSE</td>
</tr>
</tbody>
</table>

[iowaclinic.com](http://iowaclinic.com)
Omalizumab (Xolair)

- Efficacy in moderate-to-severe asthma
  - Reduced exacerbations from 16 to 26%
  - Reduced hospitalizations from 0.5 to 3%
  - Allowed for a small but significant reduction in inhaled glucocorticoid use
Omalizumab (Xolair)

- Efficacy in severe asthma
  - Decreased daily steroid use (median from 20 mg daily to 5 mg daily)
  - Decreased exacerbation rates
  - Increased quality of life
# Asthma Endotypes

<table>
<thead>
<tr>
<th>Endotype</th>
<th>Clinical Features</th>
<th>Proposed Mechanism</th>
<th>Treatment Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic asthma</td>
<td>Allergen-associated symptoms, allergic rhinitis, childhood onset, history of eczema</td>
<td>Th2 dominant</td>
<td>Responds to glucocorticoids and omalizumab</td>
</tr>
<tr>
<td>Allergic bronchopulmonary aspergillosis</td>
<td>Severe mucus production, adult onset, long duration</td>
<td>Colonization of airways by fungi</td>
<td>Responds to glucocorticoids and antifungals</td>
</tr>
<tr>
<td>API-positive preschool wheezer*</td>
<td>&gt;3 episodes per year, family history of asthma</td>
<td>Th2 dominant</td>
<td>Responds to daily inhaled glucocorticoids</td>
</tr>
<tr>
<td>Aspirin-sensitive asthma</td>
<td>Nasal polyposis, often severe asthma, aspirin sensitivity, adult onset</td>
<td>Eicosanoids-related</td>
<td>Responds to antileukotrienes, aspirin desensitization</td>
</tr>
<tr>
<td><strong>Severe late-onset hypereosinophilic asthma</strong></td>
<td>Severe exacerbations, late-onset disease, peripheral blood eosinophilia</td>
<td>Nonatopic, mechanisms unclear</td>
<td>Often dependent on oral glucocorticoids</td>
</tr>
<tr>
<td>Exercise-induced bronchospasm</td>
<td>Symptoms related to exercise, frequently in elite athletes</td>
<td>Dehydration of airways</td>
<td>Mixed response to glucocorticoids</td>
</tr>
</tbody>
</table>

*API, asthma predictive indices: children with repeated wheezing episodes and history of atopic dermatitis, parental asthma, or Aeroallergen sensitivity, and peripheral eosinophilia, wheezing unrelated to common cold, or sensitization to food allergen.

Adapted from *Journal of Allergy and Clinical Immunology*, 127(2), Lotvall J, Akdis CA, Bacharier LB, et al. Asthma endotypes: a new approach to classification of disease entities within the asthma syndrome, 355-360, 2011, with permission from Elsevier.
Mepolizumab (Nucala)
Mepolizumab

- Humanized monoclonal antibody against interleukin-5
- Approved in November 2015 for treatment of eosinophilic asthma (>150/microL)
- Age 12+
- Severe asthma
- 100 mg SQ every 4 weeks
Targets for current and pipeline biologics

The discovery that asthma is a heterogeneous disease has paved the way for new, targeted biologic therapies. Omalizumab, which targets immunoglobulin E (IgE), was the first to be approved over a decade ago and at least six biologics that target interleukins have now reached human trials.

IL-4 specific monoclonal antibodies:
- Dupilumab

IL-4 is crucial for $T_{H2}$ cell differentiation

IL-13 specific monoclonal antibodies:
- Lebrikizumab
- Tralokinumab

Along with IL-4, IL-13 stimulates B cells to produce IgE

IgE specific monoclonal antibodies:
- Omalizumab

When exposed to allergens, IgE binds to receptors on mast cells and triggers the release of histamine, leukotriene and prostaglandins (which promote vascular permeability and smooth muscle contraction) and cytokines such as IL-4 and IL-13 (which induce mucus secretion).
Figure 1. Study Design and Enrollment and Outcomes.

Panel A shows the design of the study. Patients who received 75 mg of mepolizumab intravenously also received placebo subcutaneously, patients who received 100 mg of mepolizumab subcutaneously also received placebo intravenously, and patients who received placebo received placebo both intravenously and subcutaneously. Panel B shows the screening, randomization, treatment, and follow-up of the patients.
### Table 1. Characteristics of the Patients at Baseline in the Intention-to-Treat Population.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (N=191)</th>
<th>Mepolizumab Intravenous (N=191)</th>
<th>Mepolizumab Subcutaneous (N=194)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (range) — yr</td>
<td>49 (12-76)</td>
<td>50 (13-82)</td>
<td>51 (12-81)</td>
</tr>
<tr>
<td>Female sex — no. (%)</td>
<td>107 (56)</td>
<td>106 (55)</td>
<td>116 (60)</td>
</tr>
<tr>
<td>Body-mass index</td>
<td>28.0±5.6</td>
<td>27.7±5.7</td>
<td>27.6±6.2</td>
</tr>
<tr>
<td>Former smoker — no. (%)</td>
<td>57 (30)</td>
<td>52 (27)</td>
<td>50 (26)</td>
</tr>
<tr>
<td>Duration of asthma — yr</td>
<td>19.5±14.6</td>
<td>19.8±14.0</td>
<td>20.5±12.9</td>
</tr>
<tr>
<td>Use of oral glucocorticoids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maintenance use — no. (%)</td>
<td>44 (23)</td>
<td>48 (25)</td>
<td>52 (27)</td>
</tr>
<tr>
<td>Mean daily dose (range) — mg‡</td>
<td>15.1 (5-80)</td>
<td>12.0 (1-40)</td>
<td>12.6 (2-50)</td>
</tr>
<tr>
<td>Allergic rhinitis — no. (%)</td>
<td>95 (50)</td>
<td>91 (48)</td>
<td>95 (49)</td>
</tr>
<tr>
<td>FEV₁ Before bronchodilatation — liters§</td>
<td>1.86±0.63</td>
<td>1.86±0.70</td>
<td>1.73±0.666</td>
</tr>
<tr>
<td>Percent of predicted value before bronchodilatation¶</td>
<td>62.4±18.1</td>
<td>61.4±18.3</td>
<td>59.3±17.5</td>
</tr>
<tr>
<td>Reversibility — %</td>
<td>27.4±20.8</td>
<td>25.4±19.6</td>
<td>27.9±24.0</td>
</tr>
<tr>
<td>FEV₁/FVC ratio — %</td>
<td>64±13</td>
<td>64±13</td>
<td>63±13</td>
</tr>
<tr>
<td>Morning peak expiratory flow — liters/min</td>
<td>277±106</td>
<td>289±112</td>
<td>255±108</td>
</tr>
<tr>
<td>Score on Asthma Control Questionnaire***</td>
<td>2.28±1.39</td>
<td>2.12±1.13</td>
<td>2.26±1.27</td>
</tr>
<tr>
<td>Score on St. George’s Respiratory Questionnaire††</td>
<td>46.9±19.8</td>
<td>44.4±19.4</td>
<td>47.9±19.4</td>
</tr>
<tr>
<td>Geometric mean IgE on log₂ scale — U/ml</td>
<td>150±1.5</td>
<td>180±1.5</td>
<td>150±1.5</td>
</tr>
<tr>
<td>Geometric mean blood eosinophil count on log₂ scale — cells/μl</td>
<td></td>
<td></td>
<td>320±938</td>
</tr>
<tr>
<td>Asthma exacerbations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe episodes in previous year — no./patient</td>
<td>3.6±2.8</td>
<td>3.5±2.2</td>
<td>3.8±2.7</td>
</tr>
<tr>
<td>Necessitating hospitalization in previous year — no. (%)</td>
<td>35 (18)</td>
<td>41 (21)</td>
<td>33 (17)</td>
</tr>
<tr>
<td>History of asthma-related intubation — no. (%)</td>
<td>3 (2)</td>
<td>10 (5)</td>
<td>8 (4)</td>
</tr>
</tbody>
</table>

* Plus-minus values are means (or geometric means) ±SD. There were no significant between-group differences at baseline. More detailed data are provided in Table S3 in the Supplementary Appendix. FEV₁ denotes forced expiratory volume in 1 second, and FVC forced vital capacity.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ The listed value is the prednisone equivalent.

§ Reversibility was measured at baseline.

¶ The percent of the predicted value before bronchodilation was assessed at the screening visit.

*** Scores on the Asthma Control Questionnaire range from 0 to 6, with higher scores indicating worse control; a change of 0.5 points is the minimal clinically important difference.

†† Scores on St. George’s Respiratory Questionnaire range from 0 to 100, with higher scores indicating worse function; a change of 4 points is considered to be clinically relevant.

§§ Values below the lower limit of quantification (LLQ) were replaced by a value that was 50% of the LLQ.
Figure 2. Asthma Exacerbations and FEV₁ at 32 Weeks.

Panel A shows the numbers of asthma exacerbations in patients receiving either intravenous or subcutaneous mepolizumab or placebo. The rate of exacerbations was reduced by 47% (95% confidence interval [CI], 28 to 60) among patients receiving intravenous mepolizumab and by 53% (95% CI, 36 to 65) among those receiving subcutaneous mepolizumab, as compared with those receiving placebo (P<0.001 for both comparisons). Panel B shows the mean forced expiratory volume in 1 second (FEV₁) as a percentage of the predicted value. At week 32, there was greater improvement from baseline in the two mepolizumab groups than in the placebo group — a 100-ml greater increase in the intravenous-mepolizumab group than in the placebo group (P=0.02) and a 98-ml greater increase in the subcutaneous-mepolizumab group than in the placebo group (P=0.03). The I bars indicate 95% confidence intervals.
Table 3. Summary of Adverse Events.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (N = 191)</th>
<th>Mepolizumab Intravenous (N = 191)</th>
<th>Mepolizumab Subcutaneous (N = 194)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All adverse events</td>
<td>158 (83)</td>
<td>161 (84)</td>
<td>152 (78)</td>
</tr>
<tr>
<td>Nonasthma event</td>
<td>157 (82)</td>
<td>161 (84)</td>
<td>152 (78)</td>
</tr>
<tr>
<td>Worsening of asthma</td>
<td>29 (15)</td>
<td>18 (9)</td>
<td>13 (7)</td>
</tr>
<tr>
<td>Drug-related event, per investigator assessment†</td>
<td>30 (16)</td>
<td>33 (17)</td>
<td>39 (20)</td>
</tr>
<tr>
<td>Leading to study withdrawal</td>
<td>4 (2)</td>
<td>0</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>During treatment</td>
<td>27 (14)</td>
<td>14 (7)</td>
<td>16 (8)</td>
</tr>
<tr>
<td>Drug-related event, per investigator assessment†</td>
<td>1 (1)</td>
<td>0</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Fatal</td>
<td>1 (1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Most common adverse events‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>46 (24)</td>
<td>45 (24)</td>
<td>33 (17)</td>
</tr>
<tr>
<td>Headache</td>
<td>33 (17)</td>
<td>46 (24)</td>
<td>39 (20)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>27 (14)</td>
<td>22 (12)</td>
<td>24 (12)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>18 (9)</td>
<td>11 (6)</td>
<td>18 (9)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>18 (9)</td>
<td>14 (7)</td>
<td>9 (5)</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>15 (8)</td>
<td>12 (6)</td>
<td>7 (4)</td>
</tr>
<tr>
<td>Injection-site reaction</td>
<td>6 (3)</td>
<td>5 (3)</td>
<td>17 (9)</td>
</tr>
</tbody>
</table>

* A more detailed listing of adverse events is provided in Table S4 in the Supplementary Appendix.
† The status was assigned by investigators while they were unaware of the study-group assignments.
‡ The most common adverse events were those that were reported in at least 5% of the patients in any study group.
Resiluzmab

- Monoclonal anti-IL-5 antibody
- Approved by FDA for add-on therapy
- Not available yet
- Age 12+
- Blood eosinophils >400/microL
- Administered IV 3 mg/kg Q4 weeks
- Reduces asthma exacerbations by 50% in studies
- 0.3% risk of anaphylaxis
Targets for current and pipeline biologics

The discovery that asthma is a heterogeneous disease has paved the way for new, targeted biologic therapies. Omalizumab, which targets immunoglobulin E (IgE), was the first to be approved over a decade ago and at least six biologies that target interleukins have now reached human trials.
Resiluzmab

- Decrease asthma exacerbations even with the complete stoppage of the inhaled steroid and LABA
- Side effects: injection-site reactions, nausea, headache, nasopharyngitis
- Further studies planned
- In research for atopic dermatitis
Dupilumab

- Fully humanized monoclonal antibody
- Binds to alpha subunit of IL-4 receptor
- Inhibits IL-4 and IL-13
- Moderate-to-severe asthma
- Peripheral blood eosinophilia ≥300 cells/microL
- On medium-to-high dose inhaled glucocorticoids + LABA
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IgE specific monoclonal antibodies:
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When exposed to allergens, IgE binds to receptors on mast cells and triggers the release of histamine, leukotriene and prostaglandins (which promote vascular permeability and smooth muscle contraction) and cytokines such as IL-4 and IL-13 (which induce mucus secretion).
Anti-IL-13 antibodies

- IL-13
  - Promotes IgE production
  - Eosinophil chemoattractants
  - Contractility of airway smooth muscle
- Preliminary clinical studies have showed no benefit
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IL-4 is crucial for T_{H2} cell differentiation
Along with IL-4, IL-13 stimulates B cells to produce IgE

IL-13 specific monoclonal antibodies:
• Lebrikizumab
• Tralokinumab

IL-5 specific monoclonal antibodies:
• Mepolizumab
• Resilizumab
• Benralizumab

IL-5 prompts eosinophils to mature and migrate out of the bone marrow. Eosinophils trigger inflammation in the lungs in response to allergens.

IgE specific monoclonal antibodies:
• Omalizumab
When exposed to allergens, IgE binds to receptors on mast cells and triggers the release of histamine, leukotrienes and prostaglandins (which promote vascular permeability and smooth muscle contraction) and cytokines such as IL-4 and IL-13 (which induce mucous secretion).
Influenza Vaccines in Egg Allergic Patients

- No longer a contraindication
- AAP, CDC/ACIP, AAAAI/ACAAI
- All patients ≥6 months of age with egg allergy, including those with a history of anaphylaxis, receive annual immunization with an influenza vaccine according to the indications for all other patients without egg allergy.
- No additional wait time is needed
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/ Tao Le, Bret Haymore, Vivian Hernandez-Trujillo and Gerald Lee. ACAAI Review for the Allergy & Immunology Boards, 2013 edition
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