Asthma Medication Refresher

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11/7/2018
Objectives

1. Classify asthma medications according to their mechanism of action.

2. Identify patients indicated for asthma medications or medication combinations.

3. Describe precautions and side effects of newer medications used to treat asthma.

4. Select appropriate asthma medication delivery devices for patients of varying ages and needs.

5. Understand the role of biologic medications in the management of asthma.

6. Identify options for helping with access to asthma medications.
2007

- iPhone most popular phone in U.S.
- Pirates of the Caribbean: at World’s End highest grossing U.S. film
- Umbrella by Rihanna #1 song
- Indianapolis Colt’s def. Chicago Bears in Superbowl
- NIH Guidelines for the Diagnosis and Management of Asthma (EPR-3) published
Control-Based Asthma Management

Symptoms
Exacerbations
Side-Effects
Patient-Satisfaction
Lung Function

Asthma Medications
Non-pharmacologic Strategies
Modify Risk-factors

Review Response
Assess
Treatment Adjustment

Symptoms
Risk Factors
Lung Function
Inhaler Technique
Medication Adherence
Patient Preferences
Asthma Medications

• Quick-Relief Medications (Rescue/Reliever)
  • Used as-needed for **reducing current symptoms** or prevention of exercise-induced bronchoconstriction

• Controller Medications (Maintenance)
  • Reduce airway inflammation and hyperreactivity to **reduce future symptoms** and risks such as exacerbations and decline in lung function

Who Should Use Controller Medications?

Daytime Symptoms or Reliever Use > 2 days per week

Nighttime Awakening from Asthma > 2 days per month
### Assess Control:

#### STEP UP IF NEEDED
(first, check medication adherence, inhaler technique, environmental control, and comorbidities)

#### STEP DOWN IF POSSIBLE
(and asthma is well controlled for at least 3 months)

<table>
<thead>
<tr>
<th>STEP 1</th>
<th>STEP 2</th>
<th>STEP 3</th>
<th>STEP 4</th>
<th>STEP 5</th>
<th>STEP 6</th>
</tr>
</thead>
</table>

**At each step:** Patient education, environmental control, and management of comorbidities

#### Intermittent Asthma
- **Preferred Treatment**
  - SABA* as needed
- **Alternative Treatment**
  - cromolyn, LTRA*, or theophylline
  - medium-dose ICS*

#### Persistent Asthma: Daily Medication
- **Consult with asthma specialist if step 4 care or higher is required. Consider consultation at step 3.**
- **high-dose ICS* + LABA**
  - high-dose ICS* + LABA*
  - high-dose ICS* + oral corticosteroid
  - high-dose ICS* + oral corticosteroid
- **consider omalizumab for patients who have allergies**
  - consider omalizumab for patients who have allergies
- **Consider subcutaneous allergen immunotherapy**
  - for patients who have persistent, allergic asthma.

#### Quick-Relief Medication
- SABA* as needed for symptoms. The intensity of treatment depends on severity of symptoms: up to 3 treatments every 20 minutes as needed. Short course of oral systemic corticosteroids may be needed.
- Caution: Use of SABA >2 days/week for symptom relief (not to prevent EIB*) generally indicates inadequate control and the need to step up treatment.
<table>
<thead>
<tr>
<th>Controller Classes</th>
<th>Clinical Effect</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
<td>Wide range of actions on multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, cytokines) involved in inflammation</td>
<td>Preferred Controller*</td>
</tr>
<tr>
<td>Inhaled Long-acting Beta₂ Agonists</td>
<td>Causes bronchodilation and some inhibition of release of mediators from mast cells</td>
<td>Preferred Add-on</td>
</tr>
<tr>
<td>Leukotriene receptor antagonists</td>
<td>Inhibits physiologic actions of leukotrienes (airway edema, smooth muscle contraction, and activity associated with the inflammatory process)</td>
<td>Alternative or add-on</td>
</tr>
<tr>
<td>Anti-immunoglobulin E monoclonal antibody (Anti-IgE)</td>
<td>Limits release of mediators of the allergic response from mast cells and basophils</td>
<td>Add-on</td>
</tr>
<tr>
<td>Methylxanthines (Theophylline)</td>
<td>Causes bronchodilation via phosphodiesterase III/IV inhibition and reduces airway sensitivity</td>
<td>Alternative or add-on</td>
</tr>
<tr>
<td>Mast Cell Stabilizer (Cromolyn)</td>
<td>Inhibits the release of histamine and leukotrienes from mast cells</td>
<td>Alternative or add-on</td>
</tr>
</tbody>
</table>

*Oral steroids are reserved as add-on therapy or for short courses during exacerbations*
### How does the 2007 standard of care work?

<table>
<thead>
<tr>
<th>Group – By treatment in 6 months before randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 No Treatment</td>
</tr>
<tr>
<td>2 Low-Dose ICS</td>
</tr>
<tr>
<td>3 Medium/High-Dose ICS</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Treatment Group</th>
<th>n</th>
<th>Well Controlled (%)</th>
<th>Totally Controlled (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluticasone</td>
<td>1</td>
<td>544</td>
<td>65</td>
<td>31</td>
</tr>
<tr>
<td>Fluticasone-Salmeterol</td>
<td>1</td>
<td>539</td>
<td>71</td>
<td>42</td>
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<tr>
<td>Fluticasone</td>
<td>2</td>
<td>577</td>
<td>52</td>
<td>20</td>
</tr>
<tr>
<td>Fluticasone-Salmeterol</td>
<td>2</td>
<td>583</td>
<td>69</td>
<td>32</td>
</tr>
<tr>
<td><strong>Fluticasone</strong></td>
<td><strong>3</strong></td>
<td><strong>567</strong></td>
<td><strong>33</strong></td>
<td><strong>8</strong></td>
</tr>
<tr>
<td>Fluticasone-Salmeterol</td>
<td><strong>3</strong></td>
<td><strong>568</strong></td>
<td><strong>51</strong></td>
<td><strong>19</strong></td>
</tr>
</tbody>
</table>

All patient’s received *guideline-concordant* step-therapy every 12 weeks to maximum step 5 (High dose ICS/LABA) over 52 weeks.

Severe Uncontrolled Asthma

European Respiratory Society and American Thoracic Society Definition:

“Asthma that requires treatment with high dose inhaled corticosteroids plus a second controller and/or systemic corticosteroids to prevent it from becoming “uncontrolled” or that remains “uncontrolled” despite this therapy.”

Chung KF, et al. *Eur Respir J.* 2014;43:343
Where do we go from here?

- Sherri, 43 yo AA F with worsening asthma
- ACT 7, 2 exacerbations past year requiring OCS
- + FH of asthma
- Bus drive for CTA, two cats (has been with her “forever”), never smoker
- BMI 32 kg/m²
- Currently Taking:
  - Fluticasone/salmeterol (Airduo®) 232/14 mcg, 1 puff twice daily
  - Albuterol MDI prn
  - Omeprazole 20 mg po daily
  - Montelukast 10 mg qHS
  - Loratadine 10 mg prn
Inflammatory Cascade


Allergen | Irritant/Bacteria/Viruses | Oxidative Stress

Goblet Cell

Th2

B

Mast Cell

IgE

ILC2

IL-4

IL-5

IL-13

TSLP

IL25

IL33

Dendritic APC Cell

Airway Epithelium

Clinical Results:
Airway Narrowing/Bronchoconstriction
Airway Hyperresponsiveness
Increased Mucus Production
Airway Smooth Muscle Hyperplasia
Goblet Cell Hyperplasia

Eosinophilic asthma
High/Low Th2 (T2)
Inflammatory Cascade

Clinical Results:
- Airway Narrowing/Bronchoconstriction
- Airway Hyperresponsiveness
- Increased Mucus Production
- Airway Smooth Muscle Hyperplasia
- Goblet Cell Hyperplasia

Phenotype Guided Therapy

- Uses inflammatory cell biomarkers to guide therapy

- Elevated Blood or Sputum Eosinophils
- Elevated Serum IgE
- Elevated $FE_{NO}$ / Periostin?
<table>
<thead>
<tr>
<th>Medication</th>
<th>Biomarker Target</th>
<th>Approved Age</th>
<th>Indication</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omalizumab (Xolair®, 2003)</td>
<td>IgE</td>
<td>≥6 years</td>
<td>High IgE Levels (30-700 IU/mL)+Allergies</td>
<td>75-375 mg SubQ q2-4weeks</td>
</tr>
<tr>
<td>Mepolizumab (Nucala®, 2015)</td>
<td>IL-5</td>
<td>≥12 years</td>
<td>Blood Eos ≥150 cell/µL (90d) ≥300 cell/µL (1y)</td>
<td>30 mg SubQ q4wks</td>
</tr>
<tr>
<td>Reslizumab (Cinqair®, 2016)</td>
<td>IL-5</td>
<td>≥18 years</td>
<td>Blood Eos ≥400 cell/µL</td>
<td>3 mg/kg IV q4wks</td>
</tr>
<tr>
<td>Benralizumab (Fasenra®, 2017)</td>
<td>IL-5R</td>
<td>≥12 years</td>
<td>Blood Eos ≥300 cell/µL</td>
<td>30 mg SubQ q4-8weeks</td>
</tr>
<tr>
<td>Dupilumab (Dupixent®, 2018)</td>
<td>IL-4R/(IL-4/IL-13)</td>
<td>≥12 years</td>
<td>Blood Eos ≥300 cell/µL</td>
<td>400 mg (200 mg x 2) SubQ, followed by 200 mg given every other week*</td>
</tr>
</tbody>
</table>

*Start 600 mg (two 300 mg injections) SubQ, followed by 300 mg given every other week if using concomitant oral corticosteroids or with co-morbid moderate-to-severe atopic dermatitis for which dupilumab is indicated.*
Inflammatory Cascade

**Eosinophilic asthma**

- Allergen
- Irritant/Bacteria/Viruses
- Oxidative Stress

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**Airway Epithelium**

- Dendritic APC Cell
- Goblet Cell

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**Innate Lymphoid Cell Type 2**

- TSLP
- IL25
- IL33

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**Th2**

- IL-4

---

**B**

- IL-4

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**Mast Cell**

- IgE

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**TSLP**

- Histamine
- Prostaglandins
- Leukotrienes

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**Clean-up in IL-5!**
**Mepolizumab – Anti-IL-5 Antibody**

**Percent Reduction in Asthma Exacerbation Rate compared to Placebo**

- **DREAM** (13 months)
  - Eos > 300, 3%, or FENO > 50

- **MENSA** (32 weeks)
  - Eos >150 90d / 300 last year

**ADRs (similar rates to placebo)**
- HA, nasopharyngitis, back pain, fatigue
- Inj. Site Rxn: 9% vs 3% PCB
- Hypersensitivity 1% vs. 2% PCB
- Anaphylaxis rare (0.2%)

**Dosing and Administration**
- **100 mg SQ q4 wks**
  - SQ in upper arm, thigh, or abdomen
  - Administered in healthcare setting

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Reslizumab – Anti-IL-5 Antibody

Exacerbation Rate in Patients with Elevated Eosinophils (≥400 cell/µL)

Percent Reduction in Asthma Exacerbation Rate compared to Placebo

Annual Asthma Exacerbation Rate (95% CI)

Placebo: 1.81 (n=476)
Reslizumab 3.0 mg/kg: 0.84 (n=477)

-54%

ADRs (similar rates to placebo)
- Oropharyngeal pain, myalgia (1-3%)
- Anaphylaxis (0.3%)
- Transient CK elevation? (20%)

Dosing and Administration
- IV Infusion
  - Administered in healthcare setting
  - 3 mg/kg IV q4 wks
  - Infusion over 20-50 minutes
  - Observe for 20 minutes after infusion

SIROCCO (Benralizumab – IL5R antagonist)

**Reduction in AEX Rate vs. Placebo**

- **≥300**
  - Placebo: 1.33 (0.60–0.89)
  - Benralizumab 30 mg SQ Q4W: 0.73 (0.53–0.80)
  - Benralizumab 30 mg SQ Q8W: 0.65

- **<300**
  - Placebo: 1.21 (0.65–1.11)
  - Benralizumab 30 mg SQ Q4W: 0.85
  - Benralizumab 30 mg SQ Q8W: 1

**Blood Eosinophil Count (cell/µL)**

- **≥300**
  - Placebo: 0.96–1.52
  - Benralizumab 30 mg SQ Q4W: 0.78–1.28
  - Benralizumab 30 mg SQ Q8W: 0.65–1.11

**Annual Asthma Exacerbation Rate (95% CI)**


**ADRs (similar rates to placebo)**
- HA, nasopharyngitis, worse asthma
- Inj. Site Rxn: 3% vs 2% PCB
- Hypersensitivity 3% vs. 3% PCB

**Dosing and Administration**
- 30 mg SQ q4 wks x 3 then
- 30 mg SQ q8 ws thereafter
- SQ in upper arm, thigh, or abdomen

Administered in healthcare setting
Inflammatory Cascade

Eosinophilic asthma

- Allergen
- Irritant/Bacteria/Viruses
- Oxidative Stress

Airway Epithelium

Dendritic APC Cell

Goblet Cell

TSLP
IL-25
IL-33

Th2

B

Mast Cell

IL-4

IL-13

Innate Lymphoid Cell Type 2

ILC2

IL-5

Periostin

Eosinophil Maturation

Dupilumab: IL-4R antagonist

IL-13

Sputum Eosinophils

NO

Histamine
Prostaglandins
Leukotrienes

IL-4

IL-5

Sputum Eosinophils


### Table 1: Effect of Dupilumab on Risk of Severe Exacerbations

<table>
<thead>
<tr>
<th>Dose</th>
<th>Favors Dupilumab</th>
<th>Favors Placebo</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td></td>
<td><strong>0.52 (0.41-0.66)</strong></td>
</tr>
<tr>
<td><strong>Eosinophil Count</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 300 cells/m³</td>
<td></td>
<td></td>
<td>0.34 (0.24-0.48)</td>
</tr>
<tr>
<td>≥ 150-&lt;300 cells/m³</td>
<td></td>
<td></td>
<td>0.64 (0.41-1.02)</td>
</tr>
<tr>
<td>&lt;150 cells/m³</td>
<td></td>
<td></td>
<td>0.93 (0.58-1.47)</td>
</tr>
<tr>
<td><strong>FE_{NO}</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 50 ppb</td>
<td></td>
<td></td>
<td>0.31 (0.18-0.52)</td>
</tr>
<tr>
<td>≥ 25-&lt;50 ppb</td>
<td></td>
<td></td>
<td>0.39 (0.24-0.62)</td>
</tr>
<tr>
<td>&lt; 25 ppb</td>
<td></td>
<td></td>
<td>0.75 (0.54-1.05)</td>
</tr>
</tbody>
</table>

### Table 2: Effect of Dupilumab 300 mg q 2wk on Risk of Severe Exacerbations

<table>
<thead>
<tr>
<th>Dose</th>
<th>Favors Dupilumab</th>
<th>Favors Placebo</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td></td>
<td><strong>0.54 (0.43-0.68)</strong></td>
</tr>
<tr>
<td><strong>Eosinophil Count</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 300 cells/m³</td>
<td></td>
<td></td>
<td>0.33 (0.23-0.45)</td>
</tr>
<tr>
<td>≥ 150-&lt;300 cells/m³</td>
<td></td>
<td></td>
<td>0.56 (0.35-0.89)</td>
</tr>
<tr>
<td>&lt;150 cells/m³</td>
<td></td>
<td></td>
<td>1.15 (0.75-1.77)</td>
</tr>
<tr>
<td><strong>FE_{NO}</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 50 ppb</td>
<td></td>
<td></td>
<td>0.31 (0.19-0.49)</td>
</tr>
<tr>
<td>≥ 25-&lt;50 ppb</td>
<td></td>
<td></td>
<td>0.44 (0.28-0.69)</td>
</tr>
<tr>
<td>&lt; 25 ppb</td>
<td></td>
<td></td>
<td>0.79 (0.57-1.10)</td>
</tr>
</tbody>
</table>
Dupilumab

- **Adverse Reactions**
  - Discontinuation due to adverse events: 5% (vs. 6% pcb)
  - Injection Site Reactions: 17% (vs. 6% pcb)
  - Eosinophilia: 4% (vs. 0.6% pcb)
  - Hypersensitivity <1%

- 2 pre-filled, single use syringes, **for use at home**
- Clear, and colorless to pale yellow solution
- Stored in refrigerator (room temperature 14 days)
- Let syringe come to room temperature (200 mg, 30m; 300 mg, 45m)
- Injected subcutaneously at 45° angle in stomach or thigh (or upper arm)

DUPIXENT. [Prescribing Information]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc.;2018
Greater reduction in exacerbations with omalizumab among patients with high Th2 biomarkers.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Biomarker Target</th>
<th>Mechanism</th>
<th>Eosinophilic / Neutrophilic</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZD1402</td>
<td>IL-4</td>
<td>Inhaled Anti-IL-4R Antibody</td>
<td>Eosinophilic</td>
<td>Phase I</td>
</tr>
<tr>
<td>3511294</td>
<td>IL-5</td>
<td>Anti-IL-5 Antibody</td>
<td>Eosinophilic</td>
<td>Phase I</td>
</tr>
<tr>
<td><strong>Pitrakinra</strong></td>
<td>IL-4/IL-13</td>
<td>Inhaled IL-4/IL-13 Antagonist</td>
<td>Eosinophilic</td>
<td>Phase III</td>
</tr>
<tr>
<td>REGN3500</td>
<td>IL-33</td>
<td>Anti-IL-33 Antibody</td>
<td>Eosinophilic</td>
<td>Phase II</td>
</tr>
<tr>
<td>3772847</td>
<td>IL-33</td>
<td>Anti-IL-33 Antibody</td>
<td>Eosinophilic</td>
<td>Phase II</td>
</tr>
<tr>
<td><strong>Tezepelumab</strong></td>
<td>TSLP</td>
<td>anti-TSLP antibody</td>
<td>Eosinophilic</td>
<td>Phase III</td>
</tr>
<tr>
<td>CSJ117</td>
<td>TSLP</td>
<td>anti-TSLP antibody</td>
<td>Eosinophilic</td>
<td>Phase II</td>
</tr>
<tr>
<td>Fevipiprant</td>
<td>PGD2/CRT2H2</td>
<td>PGD2 antagonist</td>
<td>Eosinophilic</td>
<td>Phase III</td>
</tr>
<tr>
<td>AZD1419</td>
<td>TLR9</td>
<td>TLR9 Agonist</td>
<td>Neutrophilic</td>
<td>Phase II</td>
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<tr>
<td>2245035</td>
<td>TLR9</td>
<td>TLR9 Agonist</td>
<td>Neutrophilic</td>
<td>Phase II</td>
</tr>
<tr>
<td>Brodalumab</td>
<td>IL-17</td>
<td>Anti-IL-17R Antibody</td>
<td>Neutrophilic</td>
<td>Withdrawn</td>
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<td>Etanercept</td>
<td>TNF</td>
<td>TNF-a receptor blocker</td>
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<td>Withdrawn</td>
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<tr>
<td>Anakinra</td>
<td>IL-1</td>
<td>Anti-IL-1R Antibody</td>
<td>Neutrophilic</td>
<td>Phase I/II</td>
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<tr>
<td>Sirukumab</td>
<td>IL-6</td>
<td>Anti-IL-6 Antibody</td>
<td>Neutrophilic</td>
<td>Withdrawn</td>
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<tr>
<td>Navarixin</td>
<td>CXCR2</td>
<td>CXCR2 antagonist</td>
<td>Neutrophilic</td>
<td>Withdrawn</td>
</tr>
</tbody>
</table>
Inflammatory Cascade


Eosinophilic asthma

Airway Epithelium

Allergen

Irritant/Bacteria/Viruses

Oxidative Stress

Dendritic APC Cell

Goblet Cell

TSLP

IL25

IL33

TSLP

IL4

Th2

B

Mast Cell

Releases

Histamine

Prostaglandins

Leukotrienes

IgE

IL-4

IL-13

IL5

NO

Periostin

ILC2

IL-13

Eosinophil Maturation

Tezepelumab:

anti-TSLP antibody

### PATHWAY (Tezepelumab - Phase II)

#### Blood Eosinophil Count (cell/µL)

<table>
<thead>
<tr>
<th>Fe\textsubscript{NO} (ppb)</th>
<th>&lt;250</th>
<th>≥250</th>
<th>Low</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;24</td>
<td>60</td>
<td>62</td>
<td>81</td>
<td>63</td>
</tr>
<tr>
<td>≥24</td>
<td>60</td>
<td>62</td>
<td>83</td>
<td>67</td>
</tr>
<tr>
<td>≥250</td>
<td>61</td>
<td>85</td>
<td>76</td>
<td>67</td>
</tr>
<tr>
<td>&lt;250</td>
<td>85</td>
<td>83</td>
<td>85</td>
<td>67</td>
</tr>
</tbody>
</table>

#### Percent Reduction in Asthma Exacerbation Rate compared to Placebo

<table>
<thead>
<tr>
<th>Fe\textsubscript{NO} (ppb)</th>
<th>Low-dose</th>
<th>Medium-dose</th>
<th>High-dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;24</td>
<td>-43</td>
<td>-46</td>
<td>-59</td>
</tr>
<tr>
<td>≥24</td>
<td>-62</td>
<td>-62</td>
<td>-56</td>
</tr>
<tr>
<td>≥250</td>
<td>-72</td>
<td>-79</td>
<td>-62</td>
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<tr>
<td>&lt;250</td>
<td>-77</td>
<td>-79</td>
<td>-65</td>
</tr>
<tr>
<td>≥250</td>
<td>-78</td>
<td>-79</td>
<td>-65</td>
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</table>

#### Th2 Status

<table>
<thead>
<tr>
<th>Fe\textsubscript{NO} (ppb)</th>
<th>Low</th>
<th>High</th>
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</thead>
<tbody>
<tr>
<td>&lt;24</td>
<td>60</td>
<td>62</td>
</tr>
<tr>
<td>≥24</td>
<td>61</td>
<td>85</td>
</tr>
<tr>
<td>≥250</td>
<td>85</td>
<td>83</td>
</tr>
<tr>
<td>&lt;250</td>
<td>85</td>
<td>85</td>
</tr>
</tbody>
</table>

*P < 0.05
Tezepelumab

- **Adverse Reactions**
  - Discontinuation due to adverse events: 1.1% (vs. 0.7% pcb) in PATHWAY
  - Inj. Site Reactions (1mL): 2.5%, 2.8%, 1.4%, 3.4% in L, M, H, Placebo grps
  - Inj. Site Reactions (1.5mL): 2.1%, 2.8%, 3.4%, 2.7% in L, M, H, Placebo grps
  - Hypersensitivity/Anaphylaxis/Neutralizing Antibodies – None reported
  - No other treatment emergent SAEs

- **Currently Recruiting Phase III Studies:**
  - NAVIGATOR (ClinicalTrials.gov Identifier: NCT03347279)
  - SOURCE (ClinicalTrials.gov Identifier: NCT03406078)

Inflammatory Cascade

What about noneosinophilic asthma?
Long Acting Muscarinic Antagonist (Tiotropium)

- Cause bronchodilation and reduce mucous secretion by inhibiting muscarinic cholinergic receptors on airway smooth muscle, glands, and nerves
- Dosing (Spiriva Respimat®) - Patients 12 years of age and older
  - 1.25 mcg 2 puffs daily
- Place in Therapy
  - Add-on to Med/High-Dose ICS + LABA (Step 4 or 5) therapy
- ADR: dry mouth, metallic taste, AUR
- Caution:
  - NAG, Bladder obstruction
# Antimuscarinic/Anticholinergic Medications

<table>
<thead>
<tr>
<th>Tiotropium Plus:</th>
<th>Low-Medium Dose ICS</th>
<th>Low-Medium Dose ICS</th>
<th>Low-Dose ICS</th>
<th>High Dose ICS/LABA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparator</td>
<td>Placebo</td>
<td>Adjunct LABA</td>
<td>Medium-Dose ICS</td>
<td>Placebo</td>
</tr>
<tr>
<td>Number of RCTs/pts</td>
<td>(n=5)/2563</td>
<td>(n=4)/~2000</td>
<td>(n=1)/210</td>
<td>(n=3)/1197</td>
</tr>
<tr>
<td>Exacerbation requiring steroid</td>
<td><strong>Favors Tiotropium</strong></td>
<td>N/D</td>
<td>N/D</td>
<td><strong>Favors Tiotropium</strong></td>
</tr>
<tr>
<td>Exacerbation requiring Hospitalization</td>
<td><strong>Favors Tiotropium</strong></td>
<td>N/D</td>
<td>N/D</td>
<td>N/D</td>
</tr>
<tr>
<td>Asthma Control</td>
<td><strong>Favors Tiotropium</strong></td>
<td><strong>Favors LABA</strong></td>
<td>N/D</td>
<td><strong>Favors Tiotropium</strong></td>
</tr>
<tr>
<td>FEV\textsubscript{1} Change</td>
<td><strong>Favors Tiotropium</strong></td>
<td>N/D</td>
<td><strong>Favors Tiotropium</strong></td>
<td><strong>Favors Tiotropium</strong></td>
</tr>
<tr>
<td>QOL</td>
<td>N/D</td>
<td><strong>Favors LABA</strong></td>
<td>N/D</td>
<td>N/D</td>
</tr>
<tr>
<td>AEs</td>
<td>N/D</td>
<td>N/D</td>
<td>N/D</td>
<td>N/D</td>
</tr>
<tr>
<td>Cochrane Review #</td>
<td>CD011397</td>
<td>CD011438</td>
<td>CD011437</td>
<td>CD011721</td>
</tr>
</tbody>
</table>

- N/D: Not determined
- **Favors Tiotropium**: Tiotropium is favored over the comparator
- **Favors LABA**: LABA is favored over the comparator

Cochrane Review #:
- CD011397
- CD011438
- CD011437
- CD011721
Macrolides Antibiotics?

- **AMAZES**
  - Azithromycin 500 mg three times per week added to ICS/LABA (n=420) x 48 weeks
  - Diarrhea / *Drug resistance*
  - Excluded pt with Hearing Loss / QT prolongation

- **AZISAST** *(AZIthromycin in Severe ASThma)*
  - Azithromycin 250 mg daily x 5 days then 250 mg three times per week added to ICS/LABA x 26 weeks
  - Primary outcome: Asthma exacerbation or LRTI
  - **Beneficial for noneosinophilic asthma (blood eosinophil count < 200 cell/µL)**

Vitamin D?

- Low vitamin D (25[OH]D) are associated with increased risk of asthma exacerbation in both children and adults
- Vitamin D inhibits production of IL-17 (noneosinophilic asthma)

### Asthma Phenotype/Endotype

#### Th2-High/Type 2 (e.g. eosinophilic asthma)

- **Biomarkers:** Eosinophils, IgE, FeNO
- **Cellular**
  - Epithelium, airway barrier dysfunction, eosinophils, airway smooth muscle cells, mast cells, NKT, Th2 vs. ILC
- **Key Cytokines**
  - IL-4, IL-5, IL-9, IL-13, IL-25, IL-33, TSLP, GM-CSF
- **Approved**
  - Anti-IL-4/13, Anti-IL-5, Anti IL-5r, Anti-IgE
- **Studied**
  - Anti-IL-13, Anti-IL-4Rα, CRTH2/PGD2, Anti-TSLP, Anti-IL-33

#### Th2-Low/Non-Type 2 (e.g. non-eosinophilic asthma)

- **Biomarkers:** Neutrophils, Mixed granulocytes, Paucigranulocytosis
- **Cellular**
  - Epithelium, airway barrier dysfunction, airway smooth muscle cells, neutrophils, NK/NKT, Th1, Th17, ILC1/3, impaired macrophage efferocytosis, CD8+ cells
- **Key Cytokines**
  - IL-8, IL-17, IL-22, IL-23, IFNγ, TNFα, CXCR2, IL-10 deficiency, IL-6
- **Approved**
  - None
- **Studied**
  - Macrolide antibiotics, TLR9, anti-IL-17RA, TNFα antagonist, anti-IL-23, anti-IL-1, Vitamin D, statins, PPARγ agonists, anti-CXCR2

---

### Example Phenotype-Endotype Pairs

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Clinical Characteristic</th>
<th>Biomarkers</th>
<th>Endotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early onset, mild-moderate, allergic</td>
<td>Mild asthma, good lung function, early onset, low inflammation, ICS responsive</td>
<td>IgE, FeNO, IL-4, 5</td>
<td>Th2/T2 inflammation, IgE-mediated Eosinophilia</td>
</tr>
<tr>
<td>Early onset, severe, allergic</td>
<td>Severe uncontrolled, poor lung function</td>
<td>Mixed</td>
<td>Th2 and Th1 inflammation Neutrophilia</td>
</tr>
<tr>
<td>Late onset, allergic</td>
<td>Severe uncontrolled, poor lung function, nasal polyps/sinusitis, chronic rhinosinusitis, ICS responsive</td>
<td>IgE, FeNO, IL-4, 5</td>
<td>Th2/T2 inflammation Eosinophilia Leukotrienes if ASA induced</td>
</tr>
<tr>
<td>Late onset, nonallergic</td>
<td>Mixed severity, obstruction, reversibility Female, Obese, GERD require high ICS doses</td>
<td>IL-8, IL-17, TNFα, IFNγ or lack of biomarkers</td>
<td>Non-Th2 inflammation Neutrophilia Paucigranulocitic Oxidative stress pathways</td>
</tr>
</tbody>
</table>

Comorbidities / Underlying Disorder

- Atopy / Allergic Rhinitis
- Rhinosinusitis
- GERD
- Aspirin / NSAIDS / Nasal Polyps
- ACE inhibitor
- COPD
- CHF
- Anxiety / Panic Disorder / Vocal cord dysfunction
- Foreign Body
- Infection / ABPA

Aaron SD, et al. JAMA. 2017;317:269
# Sublingual Immunotherapy (SLIT)

<table>
<thead>
<tr>
<th></th>
<th>Grasitek</th>
<th>Oralair</th>
<th>Ragwitek</th>
<th>Odactra</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Allergy Covered</strong></td>
<td>Timothy Grass Orchard Kentucky Blue Perennial Rye Sweet Vernal Fescue Redtop</td>
<td>Timothy Grass Orchard Kentucky Blue Perennial Rye Sweet Vernal</td>
<td>Ragweed pollen</td>
<td>House dust-mite</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>Start 12 weeks prior Continue during season</td>
<td>Start 16 weeks prior Continue during season</td>
<td>Year-round</td>
<td>Start 12 weeks prior Continue during season</td>
</tr>
<tr>
<td><strong>Approved Ages</strong></td>
<td>5-65</td>
<td>10-65</td>
<td>18-65</td>
<td>18-65</td>
</tr>
<tr>
<td><strong>Studied in patients with asthma?</strong></td>
<td>Excluded</td>
<td>Excluded</td>
<td>Low-dose ICS FEV1&gt;70% predicted</td>
<td>At most Medium-dose ICS</td>
</tr>
</tbody>
</table>

All SLIT products contraindicated in patients with severe uncontrolled asthma
Sherri visited the asthma/allergy specialist

• PFTs: FEV₁ 75% predicted, post-bd FEV₁ 90% predicted
• Biomarkers
  • FeNO: 43 ppb
  • WBC 7.1 cells/mm³; Eos 2.9% (210 cells/µL)
  • Total IgE: 50 IU/mL
  • Allergen-specific IgE +: dust mites, cat dander
Shared Decision Making for Severe Asthma

• American College of Chest Physicians/American College of Asthma and Immunology

• Interactive shared decision making tool for severe asthma treatments

• Informative handouts for patients
  • Anti-IgE
  • Anti-IL5
  • LAMA Therapy
  • Macrolides
  • Oral Steroids
  • Bronchial Thermoplasty

http://severeasthmatreatments.chestnet.org/
## Delivery Devices

### Devices (2007):
- Metered-Dose Inhaler (MDI)
  - Metered-dose
  - Autohaler
- Dry Powder Inhalers (DPI)
  - Diskus
  - Twisthaler
  - Flexhaler
  - Turbohaler
  - Aerolizer
- Nebulized solutions

### Devices (NOW):
- Metered-Dose Inhaler (MDI)
  - Metered-dose
  - Autohaler (pirbuterol dsc 2014)
  - Redihaler – NEW DEVICE!
- Dry Powder Inhalers (DPI)
  - Diskus
  - Twisthaler
  - Flexhaler
  - Turbohaler
  - Aerolizer (formoterol dsc 2015)
  - Neohaler (COPD)
  - Ellipta – NEW DEVICE!
  - Respiclick – NEW DEVICE!
  - Pressair (COPD) – NEW DEVICE!
- Soft Mist Inhaler
  - Respimat – NEW DEVICE!
- Nebulized solutions
Patients with less stable asthma are more likely to misuse MDIs and have poor hand-lung coordination.


Fig. 1. - Distribution of asthma instability score (AIS) according to inhalation technique and coordination. □: misusers, poor coordinators; □: misusers, good coordinators; □: good users. n=3709 (91% of the eligible population). Analysis of variance: p<0.0001.
<table>
<thead>
<tr>
<th>Device</th>
<th>Essential Step</th>
<th>Make ≥1 errors (n, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MDI</strong></td>
<td>Remove the mouthpiece cover</td>
<td>6 (3.1)</td>
</tr>
<tr>
<td></td>
<td>Shake the device vigorously before use</td>
<td>82 (42.5)</td>
</tr>
<tr>
<td></td>
<td>Trigger and simultaneously breathe in</td>
<td>130 (67.4)</td>
</tr>
<tr>
<td><strong>Aerolizer</strong></td>
<td>Open the dust cap and the mouthpiece</td>
<td>2 (2.4)</td>
</tr>
<tr>
<td></td>
<td>Insert the capsule in the well and close</td>
<td>5 (6)</td>
</tr>
<tr>
<td></td>
<td>Push the buttons to pierce the capsule</td>
<td>12 (14.5)</td>
</tr>
<tr>
<td></td>
<td>Breathe in rapidly and deeply</td>
<td>4 (4.8)</td>
</tr>
<tr>
<td><strong>Diskus</strong></td>
<td>Slide the lever until it clicks</td>
<td>7 (6.8)</td>
</tr>
<tr>
<td></td>
<td>Breathe in rapidly and deeply</td>
<td>4 (3.9)</td>
</tr>
<tr>
<td><strong>Turbohaler</strong></td>
<td>Hold the inhaler upright</td>
<td>37 (25.3)</td>
</tr>
<tr>
<td></td>
<td>Turn the grip until it clicks</td>
<td>35 (24)</td>
</tr>
<tr>
<td></td>
<td>Breathe in rapidly and deeply</td>
<td>20 (13.7)</td>
</tr>
</tbody>
</table>

Less dependence on hand-lung coordination = less errors

## Spacers and Valved Holding Chambers

<table>
<thead>
<tr>
<th>One year outcomes</th>
<th>Favors MDI + Spacer</th>
<th>Favors MDI + No Spacer</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe Exacerbations</td>
<td></td>
<td></td>
<td>0.93 (0.76-1.13)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.87 (0.53-1.42)</td>
</tr>
<tr>
<td>Overall Asthma Control</td>
<td></td>
<td></td>
<td>0.83 (0.73-0.96)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.63 (0.47-0.83)</td>
</tr>
<tr>
<td>Oral Candidiasis</td>
<td></td>
<td></td>
<td>0.88 (0.60-1.29)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.60 (0.28-1.29)</td>
</tr>
</tbody>
</table>

- Beclomethasone (n=2090)
- Fluticasone (n=444)

**Love Them?**

**Wash them monthly?**

**Do not use them?**

39–67% of nurses, doctors, and respiratory therapists are unable to adequately describe or perform critical steps of inhaler use.

Clinicians’ ability to use inhalers is typically ___ years behind the introduction of new devices.

Fink JB and Rubin BK. *Respir Care*. 2005;50:1360
**What Clinicians Need to Know About Each Inhaler**

1. How to select an inhaler
2. Advantages and Limitations
3. How to use / Ease of use
4. Cost
5. How to maintain

---

**Questions Clinicians Should Answer for Their Patients**

1. What should the drug do?
2. Why is it being prescribed?
3. How do I know the drug is working?
4. How do I know if the drug is not working?
5. What are expected adverse effects?
6. What are unexpected or less common adverse effects?
7. How do I take it?
8. How will it taste, feel, etc?
9. When do I take it?
10. How much do I take?
11. How often do I take it?
12. When should dose or frequency change?
13. When should I call for help?

Fink JB and Rubin BK. *Respir Care*. 2005;50:1360
<table>
<thead>
<tr>
<th>Redihaler: Breath-Activated MDI</th>
<th>Respiclick: Breath-Activated DPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone HFA (QVAR Redihaler)</td>
<td>Fluticasone propionate (ArmonAir Respiclick)</td>
</tr>
<tr>
<td></td>
<td>Fluticasone/Salmeterol (Airduo Respiclick)***</td>
</tr>
<tr>
<td></td>
<td>Albuterol sulfate (Proair Respiclick)</td>
</tr>
</tbody>
</table>

1. OPEN CAP – HOLD UPRIGHT
2. BREATH OUT FULLY
3. PLACE MOUTHPIECE IN MOUTH
4. FORM GOOD SEAL WITH LIPS
5. INHALE DEEPLY
6. REMOVE INHALER WHILE HOLDING BREATH 5-10 SECONDS
7. BREATH OUT SLOWLY AWAY FROM INHALER
8. CLOSE CAP

- Do not shake
- Do not use with spacer
- Do not clean with water
1. Slide the cover down until you hear a click
2. Hold the Ellipta level and away from your mouth
3. Gently breathe out. Never exhale into the Ellipta
4. Seal lips around the mouthpiece
5. Inhale rapidly and deeply. Continue to take a full, deep breath.
6. Do not block the air vent with your fingers
7. Hold your breath for up to ten seconds
8. Resume normal breathing
9. Close the Ellipta

- Do not shake
- Do not use with spacer
- Do not clean with water
Preparing New Respimat
1. Hold the cap in one hand and press the safety catch on the side of the inhaler. With the other hand pull off the clear base
2. Write the discard date on the inhaler. The discard date is 3 months from the date you prepare the new Respimat
3. Take the Respimat cartridge out of the box
4. Push the narrow part of the cartridge into the inhaler
5. Push the cartridge on a firm surface to make sure it is correctly inserted

Priming New Respimat
1. Hold the Respimat inhaler upright
2. Turn the clear base in the direction of the white arrows until it clicks
3. Flip the cap until it snaps fully open
4. Point the inhaler towards the ground
5. Press the dose release button
6. Close the orange cap
7. Repeat steps 1-6 three more times
8. Re-prime once if inhaler not used for more than 3 days; Re-prime 4 times if inhaler not used for more than 21 days

Using Respimat
1. Hold the Respimat upright
2. Turn the clear base in the direction of the white arrows until it clicks
3. Flip the cap until it snaps fully open
4. Hold the Respimat away from your mouth and gently breathe out
5. Seal your lips around the end of the mouthpiece w/ covering vents
6. Point the Respimat inhaler to the back of your throat
7. While inhaling slowly and deeply through your mouth press the dose release button
8. Continue to breathe in slowly and deeply.
9. Hold your breath for up to ten seconds
10. Close the cap until you use the inhaler again

Respimat: Soft-Mist Inhaler
Ipratropium/Albuterol (Combivent Respimat)
Tiotropium (Spiriva Respimat 1.25 mcg and 2.5 mcg)
Tiotropium/Olodaterol (Stiolto Respimat – COPD)
Olodaterol (Striverdi Respimat – COPD)
Neohaler – Dry Powder Inhaler

Indacaterol (ArcaNeohaler®) - COPD
Glycopyrrolate (Seebri Neohaler®) - COPD
Indacaterol and glycopyrrolate (Utibron Neohaler®) - COPD

Pressair – Dry Powder Inhaler

INSERT  PIERCE  INHALE  INSPECT

TUDORZA® PRESSAIR® [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2017
Overcoming Cost Barriers

Insurance Issues
• Check formulary (preferred drug, quantity limits)
• Consider copay cards
• Consider requesting tiering exception

NeedyMeds https://www.needymeds.org/
• Resources to help locate assistance programs to afford medications
• Links to Medication Assistance Programs and medications with copay programs

Rx Outreach https://rxoutreach.org/
• Non-profit online pharmacy, discounts on many common medications
• Proair Respiclick ($35), Airduo ($90)

Online drug discount programs (e.g. GoodRx)

Patient Advocate Foundation https://www.copays.org/ (Asthma program currently closed)
• Financial assistance with prescription drug co-payments

Patient Access Network https://panfoundation.org (Asthma program currently closed)
• Financial assistance programs for Co-pays, Premiums and Travel for Medical Care

Good Days https://www.mygooddays.org/ (Asthma program currently closed)
• Financial assistance with prescription drug co-payments

National Heart Lung and Blood Institute https://www.nhlbi.nih.gov/
• Provides free treatment, evaluation, and transportation to individuals eligible for NIH clinical trials

Clinicaltrials.gov
Other Resources (organizations)


Respiratory Health Association [https://resphealth.org/](https://resphealth.org/)


The American Academy of Allergy, Asthma & Immunology (AAAAI) [https://www.aaaai.org/](https://www.aaaai.org/)

Asthma and Allergy Foundation of America [http://www.aafa.org/](http://www.aafa.org/)

Centers for Disease Control and Prevention [https://www.cdc.gov/asthma/default.htm](https://www.cdc.gov/asthma/default.htm)
Asthma Medication Refresher

Paul M Stranges, PharmD, BCPS, BCACP, AE-C
11/7/2018