Examining Emerging Biologics for Difficult-to-treat or Severe Asthma

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- PIM (Postgraduate Institute for Medicine)

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Assessing the Clinical Benefits and Appropriate Use of Biologics for Difficult-to-treat or Severe Asthma

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Learning Objectives

• Explore techniques to assess asthma severity and symptom control
• Discuss the current management of difficult-to-treat or severe asthma, including guideline recommendations and new and emerging treatments
Asthma Defined

- Asthma is a heterogeneous disease, characterized by chronic airway inflammation and history of respiratory symptoms such as
  - Wheeze
  - Shortness of breath
  - Chest tightness
  - Cough that varies over time and in intensity
  - Variable airflow limitation

Asthma is a Highly Prevalent Disease

26 million people in the US are affected by asthma, including 6 million children

Asthma Prevalence Percent by Age, Sex and Race/Ethnicity (2016)

- Child: 8.3%
- Adult: 8.3%
- Male: 6.9%
- Female: 9.7%
- White: 8.3%
- Black: 11.6%
- Hispanic: 6.6%

The Asthma Patient Population is Segmented Based on Disease Severity

Asthma Patient Population

- Intermittent
- Mild
- Moderate
- Severe

Persistent Asthma

Severe Asthma

• **Definition**
  
  Asthma that, despite patient adherence, requires high-dose ICS plus LABA and/or additional controller medication, or requires oral corticosteroids (OCSs) to prevent it from becoming uncontrolled, or that remains uncontrolled despite this therapy.

• **Prevalence**
  
  Estimated to affect 5% to 10% of the total asthma population

• **Implications**
  
  Severe asthma is associated with higher health care costs

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Evolution of Asthma Classification

1960’s-1970’s: Bronchoconstriction
1980’s-1990’s: Inflammation
Early 2000’s: Identification of phenotypes and clusters
Late 2000’s: Precision medicine: identification of endotypes and mechanisms of disease including T2 vs. non-T2
Present: Precision therapy by endotype

Asthma is Not Just One Disease

Asthma Syndrome
Symptoms of asthma, variable airflow obstruction

Allergy
Lung function
Exacerbations
Airway inflammation
Wheeze, cough, other symptoms

Asthma Phenotype Characteristics
Based on observable features with no direct relationship to a disease process (e.g., gender, age, obesity, ethnicity, smoking history, early vs. late onset, etc.)

Asthma Endotypes
Distinct functional or pathophysiologic mechanisms that may be present in clusters of phenotypes; identified by biomarkers (e.g., blood, sputum, urine, FeNO, exhaled breath)

Endotype 1
Endotype 2
Endotype 3
Endotype 4
Endotype 5

## Asthma Phenotypes

<table>
<thead>
<tr>
<th>Category</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trigger induced</td>
<td>• Allergic</td>
</tr>
<tr>
<td></td>
<td>• Non-allergic</td>
</tr>
<tr>
<td></td>
<td>• Infection</td>
</tr>
<tr>
<td></td>
<td>• Exercise-induced</td>
</tr>
<tr>
<td></td>
<td>• Aspirin-exacerbated respiratory disease (AERD)</td>
</tr>
<tr>
<td>Clinical presentation</td>
<td>• Pre-asthma wheezing in infants; episodic (viral) wheeze; multi-trigger wheezing</td>
</tr>
<tr>
<td></td>
<td>• Exacerbation-prone asthma</td>
</tr>
<tr>
<td></td>
<td>• Asthma associated with apparent irreversible airflow limitation</td>
</tr>
</tbody>
</table>

# Different Phenotypes are Associated with Different Endotypes

<table>
<thead>
<tr>
<th>Category</th>
<th>Histopathology</th>
<th>Proposed Mechanism/Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin sensitive</td>
<td>• Often eosinophilic</td>
<td>• Eicosanoid-related&lt;br&gt;• Leukotriene-related gene polymorphisms</td>
</tr>
<tr>
<td>Allergic bronchopulmonary mycosis (ABPM)</td>
<td>• Bronchiectasis&lt;br&gt;• Eosinophils&lt;br&gt;• Polymorphonucleocytes (PMNs)</td>
<td>• Colonization of airways&lt;br&gt;• Human leukocyte antigen (HLA) and rare cystic fibrosis variants</td>
</tr>
<tr>
<td>Allergic</td>
<td>• Eosinophils&lt;br&gt;• Sub-basement membrane thickening</td>
<td>• Th2 dominant&lt;br&gt;• Th2 pathway&lt;br&gt;• Single nucleotide polymorphisms</td>
</tr>
<tr>
<td>Severe late-onset asthma</td>
<td>• Tissue eosinophilia</td>
<td>• Nonatopic&lt;br&gt;• Genetics unknown</td>
</tr>
</tbody>
</table>

Potential Application of Biomarkers

Barriers to Care in Difficult-to-Treat Asthma\(^1-3\)

- Inadequate treatment response to standard of care
- Incomplete understanding of inflammatory mechanisms
- Phenotypes and endotypes not well-established
- Need for targeted therapies
- Disease heterogeneity

Utility of Biomarkers\(^4\)

- Define populations that will derive the most benefit from a drug
- Predict disease course
- Monitor the effects of therapy and adverse events
- Identify new biological pathways
- Facilitate identification of new drug targets

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**Biomarkers for Severe Asthma**

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Medium</th>
<th>Phenotype/Endotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgE</td>
<td>• Serum</td>
<td>• Allergic (early-onset)</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>• Blood</td>
<td>• IL-5 mediated Eosinophilic (late-onset)—allergic and non-allergic</td>
</tr>
<tr>
<td></td>
<td>• Sputum</td>
<td></td>
</tr>
<tr>
<td>Neutrophil</td>
<td>• Sputum</td>
<td>• Neutrophillic</td>
</tr>
<tr>
<td>Periostin and DPP4</td>
<td>• Serum</td>
<td>• IL-13-mediated T2-associated inflammation</td>
</tr>
<tr>
<td></td>
<td>• Sputum</td>
<td></td>
</tr>
<tr>
<td>Exhaled Nitric Oxide (FeNO)</td>
<td>• Exhaled breath</td>
<td>• IL-13-mediated T2-associated inflammation</td>
</tr>
</tbody>
</table>

**Biologics for Severe and Difficult-to-Treat Asthma and Their Biomarkers**

- Biologic therapies target specific pathologic mechanisms
- Biomarkers used to help specify the therapeutic target(s)

<table>
<thead>
<tr>
<th>MOA</th>
<th>Compound</th>
<th>IgE</th>
<th>Sputum Eosinophils</th>
<th>Blood Eosinophils</th>
<th>FeNO</th>
<th>Periostin</th>
<th>Other</th>
<th>Biomarker of Choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-IgE</td>
<td>Omalizumab</td>
<td>✔</td>
<td>✖</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>None</td>
<td>IgE</td>
</tr>
<tr>
<td>Anti-IL5</td>
<td>Mepolizumab</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✖</td>
<td>None</td>
<td>Blood Eos</td>
</tr>
<tr>
<td></td>
<td>Reslizumab</td>
<td>✖</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✖</td>
<td>None</td>
<td>Blood Eos</td>
</tr>
<tr>
<td>Anti-IL4/IL-13</td>
<td>Benralizumab</td>
<td>✖</td>
<td>✖</td>
<td>✔</td>
<td>✔</td>
<td>✖</td>
<td>EOS + / - (FeNO &amp; blood Eos algorithm to predict sputum Eos or FeNO &gt; 50 ppb)</td>
<td>Blood Eos</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dupilumab</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✖</td>
<td>TARC</td>
<td>Eos or eNO</td>
</tr>
</tbody>
</table>

FeNO: fractional exhaled nitric oxide; TARC: thymus and activation-regulated chemokine; YKL-40: chitinase-3-like-1; CEA: carcinoembryonic antigen; Eotaxin-3: aka CCL26 (chemokine (C-C motif) ligand 26)
Asthma Biologics Target a Subset of Patients with Overlapping Phenotypes

- A high level of unmet need remains in the treatment of severe asthma
- Increased understanding of the role of inflammatory cytokines in asthma pathophysiology has led to the development of multiple cytokine-inhibiting agents that target Th2 and eosinophil (EOS)-driven phenotypes
  - These agents are expected to be used in biomarker selected populations
  - However, there is significant overlap between the addressable patient populations with little guidance or validated biomarkers to suggest which patients will benefit

Until 2015, Omalizumab Was the Only Biologic Agent Approved for Asthma

• Recombinant humanized mAb against IgE approved in 2003\(^1\)-\(^3\)

• **Indication:**\(^1\) moderate-to-severe persistent asthma in patients \(\geq 6\) years of age with
  • A positive skin test or *in vitro* reactivity to a perennial aeroallergen \textit{and}
  • Symptoms that are inadequately controlled with inhaled corticosteroids

Omalizumab Reduced Exacerbations, Symptoms, and Need for Corticosteroids in Patients with Severe Asthma

- Phase 3 randomized, double-blind, placebo-controlled trial
- n=525 patients with severe allergic asthma requiring daily inhaled corticosteroids
- Randomized to receive subcutaneous omalizumab every 2 or 4 weeks or placebo
- Inhaled corticosteroid doses kept stable over the initial 16 weeks of treatment and tapered during a further 12-week treatment period

<table>
<thead>
<tr>
<th></th>
<th>Omalizumab (n=268)</th>
<th>Placebo (n=257)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1 exacerbation in</td>
<td>14.6%</td>
<td>23.3%</td>
<td>.0009</td>
</tr>
<tr>
<td>steroid-stable phase</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥1 exacerbation in</td>
<td>21.3%</td>
<td>32.3%</td>
<td>.0004</td>
</tr>
<tr>
<td>steroid-reduction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>phase</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥50% reduction in</td>
<td>72.4%</td>
<td>54.9%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>corticosteroid use</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

When to Use Omalizumab

- **Patients:** ≥6 years and older with moderate-to-severe asthma not well controlled on inhaled corticosteroids or ICS/LABA combination
- **Biomarker:** Total serum IgE level of 30 to 700 IU/L
- **Atopy:** Evidence of sensitivity to inhalant allergens (ideally perennial) by skin test or RAST
- **Asthma history:** History of worsening asthma symptoms with exposure to allergens
- **Dosing:** Based on IgE level and body weight
- **Administration:** Every 2-4 weeks via subcutaneous injection in a health care setting
- **Adverse events/monitoring:** Boxed warning for severe anaphylaxis-like reactions; extended monitoring after first 1-3 doses and subsequent monitoring for 30 minutes

Eosinophils in Asthma

- Raised levels of eosinophils are present in 40–60% of asthma patients
  - A reduction in asthma exacerbations follows a reduction in eosinophils
- IL-5 is the principal eosinophilic regulatory cytokine
  - It is involved in the maturation, differentiation, survival and activation of eosinophils
- IL-13 works in concert with IL-4 to influence airway inflammation, remodelling, and recruitment of eosinophils and basophils

Eosinophilic Asthma: Role of Anti-IL-5 Agents

IL-5-targeted agents decrease asthma exacerbations in patients with severe asthma who have high blood eosinophil levels.
Mepolizumab Reduced the Rate of Clinically Significant Exacerbations in Severe Asthma

- Phase 3 randomized, double-blind, placebo-controlled trial
- n=576 patients with ≥2 severe exacerbations in past year despite high dose inhaled corticosteroids
  - Eosinophilia of 300 eos/cc μL in the prior year or 150 eos/cc μL at study entry
  - 25% of patients were on daily prednisone
- Randomized to receive mepolizumab 75 mg IV or 100 mg SC every 4 weeks or placebo
- Primary outcome: rate of exacerbations requiring systemic steroids for ≥3 days or ED visit or hospital admission


Rate of exacerbation reduced by 47% (95% CI, 29 to 61) in the IV mepolizumab group and by 53% (95% CI, 37 to 65) in the SC group vs. placebo (p<0.001 for both comparisons)
Systemic Corticosteroid-Sparing Effect of Mepolizumab in Eosinophilic Asthma

- Phase 3 randomized, double-blind, placebo-controlled trial
- n=135 patients with severe eosinophilic asthma
  - Eosinophilia of 300 eos/cc μL in the prior year or 150 eos/cc μL at study entry
  - All patients had a 6 month history of daily prednisolone (5-35 mg/d)
  - All patients were on high dose inhaled corticosteroids and LABA or other controller
- Randomized to receive mepolizumab 100 mg SC every 4 weeks or placebo for 20 weeks
- Primary outcome: reduction in steroid use

Median percentage reduction in systemic corticosteroid use was 50% in the mepolizumab group vs. 0% in the placebo (p=0.007)

Reslizumab for Inadequately Controlled Asthma

- Two parallel phase 3, double-blind, placebo-controlled trials
- n=953 patients with inadequately controlled asthma and blood eosinophils ≥400 cells/μL
- Randomized to receive reslizumab 3 mg/kg every 4 weeks or placebo for 52 weeks by IV infusion
- Primary outcome: annual frequency of clinical exacerbations

Study 1
- Reslizumab significantly reduced the frequency of asthma exacerbations (p<0.0001 vs placebo) in both studies

Study 2
- Placebo; n=244
- Reslizumab 3.0 mg/kg; n=245
- HR 0.575 (95% CI 0.440-0.750)
- p<0.0001

Study 2
- Placebo; n=232
- Reslizumab 3.0 mg/kg; n=232
- HR 0.486 (95% CI 0.353-0.670)
- P<0.0001

Benralizumab in Eosinophilic Asthma

- Two parallel phase 3, double-blind, placebo-controlled trials
- n=2511 patients with inadequately controlled asthma and ≥2 exacerbations in the prior year
- Stratified by blood eosinophils ≥300 cells/μL vs. <300 cells/μL
- Randomized to receive SC benralizumab 30 mg every 4 weeks, or every 8 weeks or placebo for 48 weeks (Study 1) or 56 weeks (Study 2)
- Primary outcome: annual exacerbation rate ratio

**Pooled Annual Asthma Exacerbation Rate Reduction with Benralizumab Q8W by Eosinophil Ranges**

- Annual exacerbation rate estimate (95%CI)
  - ≥0 cells/μL: 1.16 (0.66-0.84) (36% reduction)
  - ≥150 cells/μL: 1.14 (0.63-0.82) (37% reduction)
  - ≥300 cells/μL: 1.14 (0.56-0.75) (50% reduction)
  - ≥450 cells/μL: 1.25 (0.51-0.76) (50% reduction)

### Clinical Use of Anti-IL-5 Therapies

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Dosing and Administration</th>
<th>Biomarker</th>
<th>Serious Adverse Event(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mepolizumab</td>
<td>Add-on maintenance treatment of patients with severe asthma ≥12 years and with an eosinophilic phenotype</td>
<td>100 mg administered once every 4 weeks by SC injection in a health care setting</td>
<td>Blood eosinophils &gt;300 cells/mL in the past 12 months or &gt;150 cells/mL in the past 6 weeks</td>
<td>Risk of anaphylaxis and herpes zoster virus</td>
</tr>
<tr>
<td>(November 2015)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reslizumab</td>
<td>Add-on maintenance treatment of patients with severe asthma ≥18 years and with an eosinophilic phenotype</td>
<td>3 mg/kg once every 4 weeks administered by IV infusion over 20-50 min in a health care setting</td>
<td>Blood eosinophils &gt;300 cells/mL in the past 12 months or &gt;150 cells/mL in the past 6 weeks</td>
<td>Risk of anaphylaxis and malignancy</td>
</tr>
<tr>
<td>(March 2016)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benralizumab</td>
<td>Add-on maintenance treatment of patients with severe asthma ≥12 years and with an eosinophilic phenotype</td>
<td>30 mg every 4 weeks by SC injection for the first 3 doses, followed by once every 8 weeks in a health care setting</td>
<td>Blood eosinophils &gt;150 cells/mL within the past 3 months</td>
<td>Risk of hypersensitivity reactions and parasitic infection</td>
</tr>
<tr>
<td>(November 2017)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Anti-IL-4/IL-13 Agents for the Treatment of Severe Asthma

- Dupilumab targets a receptor mediating both IL-4 and IL-13 and appears to be effective in patients with severe, uncontrolled asthma
- October 19, 2018 approved for patients ≥12 years:
  - Moderate and severe asthma patients with eosinophilic phenotype
  - Oral corticosteroid-dependent asthma, regardless of phenotype

Dupilumab Significantly Lowers Rates of Severe Exacerbation in a Phase 3 Trial

- Phase 3, randomized, double-blind, placebo-controlled trial
- n=1902 patients ≥12 years of age with uncontrolled asthma stratified by baseline blood eosinophil level
- Randomized to receive add-on SC dupilumab at a dose of 200 or 300 mg every 2 weeks or placebo for 52 weeks
- Primary outcomes: Annualized rate of severe asthma exacerbations and the absolute change from baseline to week 12 in FEV$_1$ before bronchodilator use

### Risk of Severe Asthma Exacerbations

#### A  Dupilumab, 200 mg Every 2 Wk, vs. Matched Placebo

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Placebo</th>
<th>Dupilumab</th>
<th>Relative Risk vs. Placebo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>317</td>
<td>631</td>
<td>0.52 (0.41-0.66)</td>
</tr>
<tr>
<td>Eosinophil count</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥300 cells/mm$^3$</td>
<td>148</td>
<td>264</td>
<td>0.34 (0.24-0.48)</td>
</tr>
<tr>
<td>150 to &lt;300 cells/mm$^3$</td>
<td>84</td>
<td>173</td>
<td>0.64 (0.41-1.02)</td>
</tr>
<tr>
<td>&lt;150 cells/mm$^3$</td>
<td>85</td>
<td>193</td>
<td>0.93 (0.58-1.47)</td>
</tr>
<tr>
<td>FENO</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥50 ppb</td>
<td>71</td>
<td>119</td>
<td>0.31 (0.18-0.52)</td>
</tr>
<tr>
<td>≥25 to &lt;50 ppb</td>
<td>91</td>
<td>180</td>
<td>0.39 (0.24-0.62)</td>
</tr>
<tr>
<td>&lt;25 ppb</td>
<td>149</td>
<td>325</td>
<td>0.75 (0.54-1.05)</td>
</tr>
</tbody>
</table>

#### B  Dupilumab, 300 mg Every 2 Wk, vs. Matched Placebo

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Placebo</th>
<th>Dupilumab</th>
<th>Relative Risk vs. Placebo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>321</td>
<td>633</td>
<td>0.54 (0.43-0.68)</td>
</tr>
<tr>
<td>Eosinophil count</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥300 cells/mm$^3$</td>
<td>142</td>
<td>277</td>
<td>0.33 (0.23-0.45)</td>
</tr>
<tr>
<td>150 to &lt;300 cells/mm$^3$</td>
<td>95</td>
<td>175</td>
<td>0.56 (0.35-0.89)</td>
</tr>
<tr>
<td>&lt;150 cells/mm$^3$</td>
<td>83</td>
<td>181</td>
<td>1.15 (0.75-1.77)</td>
</tr>
<tr>
<td>FENO</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥50 ppb</td>
<td>75</td>
<td>124</td>
<td>0.31 (0.19-0.49)</td>
</tr>
<tr>
<td>≥25 to &lt;50 ppb</td>
<td>97</td>
<td>186</td>
<td>0.44 (0.28-0.69)</td>
</tr>
<tr>
<td>&lt;25 ppb</td>
<td>144</td>
<td>317</td>
<td>0.79 (0.57-1.10)</td>
</tr>
</tbody>
</table>

Dupilumab Significantly Improved Lung Function

The benefit of dupilumab on FEV$_1$ was greatest among patients with a blood eosinophil count of ≥300 eos/cc at baseline.

Approved and Agents with Published Human Data in Late-Phase Development for Severe Asthma

• Asthma is a heterogenous disease yet we have been treating it as one

• Identification of multiple phenotypes and associated biomarkers (IgE, eosinophils, etc.) may help better align patients and targeted therapy

• Treatment with biologic agents targeting IgE and Th2 cytokines IL-4, IL-5, and IL-13 are efficacious and safe asthma therapies
Integrating Emerging Biologic Therapies into Health Plan Asthma Treatment Algorithms

Edmund Pezalla, MD, MPH
CEO
Enlightenment Bioconsult, LLC
Learning Objective

• Discuss the current management of difficult-to-treat or severe asthma, including guideline recommendations and new and emerging treatments
Understanding of the immuno-pathologic mechanisms of asthma continues to increase

This has resulted in the introduction of biologic therapies that target specific steps in the dysregulated immune processes underlying the disease.

Due to the fast pace of innovation, treatment guidelines often do not reflect the most recently introduced treatment options.
General Principles of Asthma Management

- Assess asthma severity and degree of control
  - **Severity**: the intrinsic intensity of the disease process
  - **Control**: the degree to which the manifestations of asthma are minimized by therapy

- Assess impairment and risk
  - **Impairment**: the frequency and intensity of symptoms and functional limitations
  - **Risk**: the likelihood of asthma exacerbations, progressive decline in lung function or adverse effects from medication

- Employ a control-based management approach to treatment
  - Continuously review the response to treatment and adjust as needed to achieve/maintain control

- Consider patient characteristics, phenotype, preferences, and practical issues (e.g., adherence, cost, etc.) when selecting therapy and evaluating response

- Establish a partnership between the person with asthma and health care providers


Control-Based Asthma Management Cycle

Assess
- Diagnosis
  - Symptom control & risk factors (including lung function)
  - Inhaler technique & adherence
  - Patient preference

Adjust
- Asthma medications
- Non-pharmacological strategies
- Treat modifiable risk factors

Review
- Symptoms
- Exacerbations
- Side-effects
- Patient satisfaction
- Lung function

Assessing Asthma Status
Assessing Asthma Severity

• How:
  • Asthma severity is assessed retrospectively from the level of treatment required to control symptoms and exacerbations

• When:
  • All patients should have an initial severity assessment based on current impairment and future risk in order to determine type and level of initial therapy needed
  • Re-assess severity after patient has been on controller treatment for several months

• Severity categories:
  • *Mild asthma*: well-controlled with as-needed short-acting b-agonists (SABA) or low dose inhaled corticosteroids (ICS)
  • *Moderate asthma*: well-controlled with low-dose ICS/LABA
  • *Severe asthma*: requires moderate or high-dose ICS/LABA ± add-on or remains uncontrolled despite this treatment

### NAEPP Approach to Classification of Asthma Severity (Age ≥12 Years)

<table>
<thead>
<tr>
<th>Components of severity</th>
<th>Intermittent</th>
<th>Persistent Mild</th>
<th>Persistent Moderate</th>
<th>Persistent Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Impairment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms</td>
<td>≤2 d/wk</td>
<td>&gt;2 d/wk but not daily</td>
<td>Daily</td>
<td>Throughout the day</td>
</tr>
<tr>
<td>Nighttime awakenings</td>
<td>≤2x mo</td>
<td>3-4x mo</td>
<td>&gt;1x wk but not nightly</td>
<td>Often 7x wk</td>
</tr>
<tr>
<td>Short-acting β₂-agonist use for symptom control (not prevention of EIB)</td>
<td>≤2 d/wk</td>
<td>&gt;2 d/wk but not daily and not more that 1x on any day</td>
<td>Daily</td>
<td>Several times per day</td>
</tr>
<tr>
<td>Interference with normal activity</td>
<td>none</td>
<td>Minor limitation</td>
<td>Some limitation</td>
<td>Extremely limited</td>
</tr>
<tr>
<td>Lung function</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal FEV₁: FVC ratio</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20-39 y 80%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40-59 y 75%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60-80 y 70%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Normal FEV₁ between exacerbations</td>
<td></td>
<td>• FEV₁ &gt; 80% predicted</td>
<td></td>
<td>• FEV₁ &lt; 60% predicted</td>
</tr>
<tr>
<td>• FEV₁ &gt; 80% predicted</td>
<td></td>
<td>• FEV₁: FVC normal</td>
<td></td>
<td>• FEV₁: FVC reduced &gt;5%</td>
</tr>
<tr>
<td>• FEV₁: FVC normal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exacerbations requiring oral systemic corticosteroids</td>
<td>0-1/y</td>
<td>≥2/y</td>
<td>≥2/y</td>
<td>≥2/y</td>
</tr>
<tr>
<td>Considers severity and interval since last exacerbation</td>
<td></td>
<td>Frequency and severity may fluctuate over time for patients in any severity category</td>
<td></td>
<td>Relative annual risk of exacerbation may be related to FEV₁</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommended step for initiating treatment (see Figure 3 for treatment steps)</th>
<th>Step 1</th>
<th>Step 2</th>
<th>Step 3</th>
<th>Step 4 or 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>In 2-6 weeks, evaluate level of asthma control that is achieved and adjust therapy accordingly</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

How to Distinguish Between Uncontrolled and Severe Asthma

- Watch patients using their inhalers
- Discuss adherence and barriers
- Confirm the diagnosis of asthma
- Remove potential risk factors
- Assess and manage comorbidities
- Consider treatment step-up
- Refer to a specialist of severe asthma clinic

- Compare inhaler technique and correct errors
- Recheck frequently
- Have a discussion about barriers to adherence
- If lung function is normal during symptoms, consider halving ICS dose and repeating lung function after 2–3 weeks
- Risk factors (e.g., smoking, β-blockers, NSAIDs, allergen exposure, etc.)
- Comorbidities (e.g., rhinitis, obesity, GERD, etc.)
- Consider step-up to next treatment level
- Use shared decision making, and balance potential benefits and risks
- Refer if uncontrolled after 3–6 months of therapy
- Refer earlier if symptoms are severe or questionable diagnosis

### Sample Patient Asthma Severity Self-Assessment

**Your Asthma Control**

- How many days in the past week have you had chest tightness, cough, shortness of breath, or wheezing (whistling in your chest)?
  - 0
  - 1
  - 2
  - 3
  - 4
  - 5
  - 6
  - 7

- How many nights in the past week have you had chest tightness, cough, shortness of breath, or wheezing (whistling in your chest)?
  - 0
  - 1
  - 2
  - 3
  - 4
  - 5
  - 6
  - 7

- Do you perform peak flow readings at home? Yes No

- If you did your peak flow chart, was it yes No

- How many days in the past week has asthma restricted your physical activity?
  - 0
  - 1
  - 2
  - 3
  - 4
  - 5
  - 6
  - 7

- Have you had any asthma attacks since your last visit? Yes No

- Have you had any unscheduled visits to a doctor, including to the emergency department, since your last visit? Yes No

- How well controlled is your asthma, in your opinion? Very well controlled Somewhat controlled Not well controlled

- Average number of puffs per day of quick-relief medication (short-acting beta-agonist)

**Taking your medicine**

- What problems have you had taking your medicine or following your asthma action plan?

- Please ask the doctor or nurse to review how you take your medicine.

**Your questions**

- What questions or concerns would you like to discuss with the doctor?

- How satisfied are you with your asthma care? Very satisfied Somewhat satisfied Not satisfied

---

| ✔ No coughing or wheezing |
| ✔ No shortness of breath or rapid breathing |
| ✔ No waking up at night |
| ✔ Normal physical activities |
| ✔ No school absences or missed work due to asthma |
| ✔ No missed time from work for parent or caregiver |
## Assessment of Asthma Control

### A. Symptom control

<table>
<thead>
<tr>
<th>In the past 4 weeks, has the patient had:</th>
<th>Level of Asthma Symptom Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Daytime asthma symptoms more than twice a week?</td>
<td>Well-controlled</td>
</tr>
<tr>
<td></td>
<td>Yes ☐ No ☐</td>
</tr>
<tr>
<td>• Any night waking due to asthma?</td>
<td>Yes ☐ No ☐</td>
</tr>
<tr>
<td>• Reliever needed for symptoms* more than twice a week?</td>
<td>Yes ☐ No ☐</td>
</tr>
<tr>
<td>• Any activity limitation due to asthma?</td>
<td>Yes ☐ No ☐</td>
</tr>
</tbody>
</table>

*Excludes reliever taken before exercise, because many people take this routinely

Assessment of Risk Factors for Poor Asthma Outcomes

Assess risk for

- Exacerbations
- Progression of lung function decline
- Medication side effects

Timing

- Assess at the time of diagnosis and then periodically throughout treatment
- Measure FEV₁ at start of treatment, after 3 to 6 months, and then periodically for ongoing risk assessment
## Risk Factors for Poor Asthma Outcomes

<table>
<thead>
<tr>
<th>Exacerbations</th>
<th>Progressive Lung Function Decline</th>
<th>Treatment AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Uncontrolled asthma symptoms</td>
<td>• No ICS treatment</td>
<td>• Frequent oral steroids</td>
</tr>
<tr>
<td>• High SABA use (≥3 canisters/year)</td>
<td>• Smoking</td>
<td>• High dose/potent ICS</td>
</tr>
<tr>
<td>• ≥1 exacerbation in last 12 months</td>
<td>• Occupational exposure</td>
<td>• P450 inhibitors</td>
</tr>
<tr>
<td>• Low FEV₁; higher bronchodilator reversibility</td>
<td>• Mucus hypersecretion</td>
<td></td>
</tr>
<tr>
<td>• Incorrect inhaler technique and/or poor adherence</td>
<td>• Blood eosinophilia</td>
<td></td>
</tr>
<tr>
<td>• Smoking</td>
<td>• Pre-term birth</td>
<td></td>
</tr>
<tr>
<td>• Obesity, chronic rhinosinusitis, pregnancy, blood eosinophilia</td>
<td>• Low birth weight</td>
<td></td>
</tr>
<tr>
<td>• Elevated fractional exhaled nitric oxide (FeNO) in adults with allergic asthma taking ICS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Ever intubated for asthma</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Selecting and Adjusting Asthma Therapy
Choosing Between Controller Options: Population Level Decisions

Choosing Between Treatment Options at a Population Level
(e.g., national formularies, health maintenance organizations, national guidelines)

The ‘preferred treatment’ at each step is based on:

- Efficacy
- Effectiveness
- Safety
- Availability and cost at the population level

Based on group mean data for symptoms, exacerbations and lung function (from RCTs, pragmatic studies and observational data)

Choosing Between Controller Options: Patient Level Decisions

Decisions for Individual Patients

Use shared decision making with the patient/parent/carer to discuss the following:

1. Preferred treatment for symptom control and for risk reduction
2. Patient characteristics (phenotype)
   - Does the patient have any known predictors of risk or response? (e.g., smoker, history of exacerbations, blood eosinophilia)
3. Patient preference
   - What are the patient’s goals and concerns for their asthma?
4. Practical issues
   - **Inhaler technique**: Can the patient use the device correctly after training?
   - **Adherence**: How often is the patient likely to take the medication?
   - **Cost**: Can the patient afford the medication?

Current Guidelines Recommend a Stepped Approach to Asthma Therapy

Stepping up should be regarded as a “Therapeutic Trial”

- Day-to-day adjustment
- Short-term step-up (1-2 weeks)
- Sustained step-up (2-3 months)

Before stepping therapy, check:

- Diagnosis
- Adherence
- Inhaler technique
- Modifiable risk factors

### 2018 GINA-Recommended Asthma Pharmacotherapy

**Global strategy for asthma management and prevention. Global Initiative for Asthma website.**


<table>
<thead>
<tr>
<th>Preferred Controller Choice</th>
<th>Other Controller Options</th>
<th>Reliever</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1</td>
<td>Consider low dose ICS</td>
<td>As-needed SABA</td>
</tr>
<tr>
<td>Step 2</td>
<td>Leukotriene receptor antagonists (LTRA)</td>
<td>Leukotriene receptor antagonists (LTRA)</td>
</tr>
<tr>
<td>Low Dose ICS</td>
<td>Low dose theophylline</td>
<td>Low dose theophylline</td>
</tr>
<tr>
<td>Step 3</td>
<td>Med/high dose ICS+LTRA (or + theophylline)</td>
<td>Add low dose ICS</td>
</tr>
<tr>
<td>Medium/High Dose ICS/LABA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Step 4</td>
<td>Add tiotropium med/high dose ICS+LTRA (or + theophylline)</td>
<td></td>
</tr>
<tr>
<td>Step 5</td>
<td>Refer for add-on treatment (e.g., tiotropium, anti-IgE, anti-IL-5/5R)</td>
<td>Add low dose ICS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Step 1:** Consider low dose ICS

**Step 2:** As-needed SABA

**Step 3:** Med/high dose ICS+LTRA (or + theophylline)

**Step 4:** Add tiotropium med/high dose ICS+LTRA (or + theophylline)

**Step 5:** Refer for add-on treatment (e.g., tiotropium, anti-IgE, anti-IL-5/5R)
# NAEPP Recommended Pharmacotherapy

## 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)

## Step 1 to Step 6

<table>
<thead>
<tr>
<th>Step</th>
<th>Intermittent Asthma</th>
<th>Persistent Asthma: Daily Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preferred Treatment</strong></td>
<td>SABA as needed</td>
<td>Consult with asthma specialist if step 4 care or higher is required. Consider consultation at step 3</td>
</tr>
<tr>
<td></td>
<td>Low dose ICS</td>
<td>Low dose ICS + LABA</td>
</tr>
<tr>
<td></td>
<td>Low dose ICS + LABA or medium dose ICS</td>
<td>Medium dose ICS + LABA</td>
</tr>
<tr>
<td></td>
<td>Medium dose ICS + LABA</td>
<td>High-dose ICS + LABA AND consider omalizumab for patients who have allergies</td>
</tr>
<tr>
<td></td>
<td>High-dose ICS + LABA + oral corticosteroids AND consider omalizumab for patients who have allergies</td>
<td></td>
</tr>
<tr>
<td><strong>Alternative Treatment</strong></td>
<td>Cromolyn, LTRA, or theophylline</td>
<td>Low dose ICS + either LTRA, theophylline or zileuton</td>
</tr>
<tr>
<td></td>
<td>Low dose ICS + either LTRA, theophylline or zileuton</td>
<td>Medium dose ICS + either LTRA, theophylline, or zileuton</td>
</tr>
<tr>
<td></td>
<td>Consider subcutaneous allergen immunotherapy for patients who have persistent, allergic asthma.</td>
<td></td>
</tr>
</tbody>
</table>

## 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.

---

### Step 5: Treatment of Severe Asthma

<table>
<thead>
<tr>
<th>Preferred Controller Choice</th>
<th>Other Controller Options</th>
<th>Reliever</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1 Low Dose ICS</td>
<td>Consider low dose ICS</td>
<td>As-needed SABA</td>
</tr>
<tr>
<td>Step 2 Leukotriene receptor antagonists (LTRA) Low dose theophylline</td>
<td>Leukotriene receptor antagonists (LTRA) Low dose theophylline</td>
<td>As-needed SABA or low dose ICS/formoterol</td>
</tr>
<tr>
<td>Step 3 Med/high dose ICS+LTRA (or + theophylline)</td>
<td>Med/high dose ICS+LTRA (or + theophylline)</td>
<td>Add leucotriene receptor antagonist (LTRA) Low dose theophylline</td>
</tr>
<tr>
<td>Step 4 Medium/High Dose ICS/LABA</td>
<td>Add tiotropium med/high dose ICS/LTRA (or + theophylline)</td>
<td>Add tiotropium med/high dose ICS/LTRA (or + theophylline)</td>
</tr>
<tr>
<td>Step 5 Refer for add-on treatment (e.g., tiotropium, anti-IgE, anti-IL-5/5R)</td>
<td>Add low dose ICS</td>
<td>Add low dose ICS</td>
</tr>
</tbody>
</table>

Management of Severe Asthma

- Preferred option is referral to a specialist for consideration of add-on treatment
  - If symptoms remain uncontrolled or exacerbations persist despite Step 4 treatment, check inhaler technique and adherence before referring
  - Add-on tiotropium for patients $\geq 12$ years with history of exacerbations
  - Add-on anti-IgE (omalizumab) for patients with severe allergic asthma
  - Add-on anti-IL5 (mepolizumab (SC, $\geq 12$ years) or reslizumab (IV, $\geq 18$ years)) or anti-IL5R (benralizumab (SC, $\geq 12$ years) for severe eosinophilic asthma

- Other add-on treatment options at Step 5 include:
  - **Sputum-guided treatment**: available in specialized centers; reduces exacerbations and/or corticosteroid dose
  - **Add-on low dose oral corticosteroids ($\leq 7.5$mg/day prednisone equivalent)**: this may benefit some patients, but has significant systemic side-effects. Assess and monitor for osteoporosis

Framework for Assessing the Choice of an IL-5 Antagonist for Treatment of Severe Asthma

Individuals with severe asthma with eosinophilic inflammation → Treatment with an IL-5 antagonist (mepolizumab, reslizumab, benralizumab) → Harms
- Systemic reaction
- Injection site reaction
- SAEs
- Other AEs

Intermediate Outcomes
- Decreased exacerbations
- Improve FEV₁
- Improve peak flow
- Reduce OCS use

Health Care Utilization Outcomes
- Decreased ED visits
- Decreased hospital days

Clinical & Patient-Centered Outcomes
- Mortality
- Days in school
- Days at work
- Nocturnal symptoms
- Quality of Life

Reviewing Response to Therapy
How often should response to asthma therapy be reviewed?

- 1-3 months after treatment started, then every 3-12 months
- During pregnancy, every 4-6 weeks
- After an exacerbation, within 1 week

Stepping up asthma treatment

- **Sustained step-up**, for at least 2-3 months if asthma poorly controlled
- **Short-term step-up**, for 1-2 weeks (e.g., with viral infection or allergen)
- **Day-to-day adjustment**

Stepping down asthma therapy

- Consider step-down after good control maintained for 3 months
- Find each patient’s minimum effective dose, that controls symptoms and minimizes risk of exacerbations

Summary

• Evaluate patients based on their current level of asthma control, disease impairment and risk

• Patients with severe asthma may require additional evaluation and referral

• Patients with allergic asthma not well controlled with high-dose ICS and an additional controller can be considered for treatment with omalizumab

• Patients with severe eosinophilic asthma not controlled with ICS/LABA may benefit from an inhibitor of IL-5 (mepolizumab, reslizumab, or benralizumab), IL-4/IL-13 (dupilumab)
Faculty Idea Exchange

Jeffrey Dunn, PharmD, MBA
Vice President, Clinical Strategy and Programs and Industry Relations
Magellan Rx Management

Edmund Pezalla, MD, MPH
CEO
Enlightenment Bioconsult, LLC

Steven G. Avey, MS, RPh, FAMCP
Vice President
Specialty Pharmacy Programs
MedImpact Healthcare Systems, Inc.

Michael Wechsler, MD
Professor of Medicine
Director, NJH Cohen Family Asthma Institute
Department of Medicine
National Jewish Health
Medical and Pharmacy Benefit Design Strategies for Biologic Therapies

Jeffrey Dunn, PharmD, MBA
Vice President, Clinical Strategy and Programs and Industry Relations
Magellan Rx Management
Learning Objective

• Examine the implications for managed care of treating difficult-to-treat or severe asthma, including medical costs and resource utilization
Asthma Epidemiology in the United States

Children

8.3%
~6,100,000

Adults

8.3%
~20,400,000

5%-10% have severe asthma

Burden of Asthma in the United States

1.7 million ED visits with asthma as primary diagnosis

3,518 Deaths with asthma as underlying cause

11.0 million Physician office visits with asthma as primary diagnosis

$81.9 billion Cost of asthma in the United States

Severe Asthma Presents a Significant Clinical and Economic Burden

**All-Cause Health Care Costs (2013)**

- Total Costs: $11,070
- Total Medical: $7,656
- Pharmacy: $3,414
- Hospitalization: $1,856
- Office Visit: $2,072
- Outpatient Visit & Service: $2,649
- ER Visit: $456


**Asthma-Related Health Care Costs (2013)**

- Total Costs: $5,174
- Asthma Medication: $1,348
- Total Medical: $427
- Hospitalization: $214
- Office Visit: $118
- Outpatient Visit & Service: $47
- ER Visit: $38

Managed Care Perspective on the Burden of Severe Asthma

**Severe Asthma**

- Limited response to standard of care therapy
- Increased morbidity/mortality
- Increased office and ED visits
- Increased hospitalization
- Poor quality of life

**Impact**

- Account for more than 50% of health spending in asthma
  - High demand for care
  - High utilization of care
- Need for utilization management strategies
  - To guide appropriate use of targeted biologic therapy
  - To ensure predictable spend

At Present, Relatively Inexpensive Inhalation Therapies Dominate the Asthma Category

- According to current guidelines, treatment of asthma involves a stepwise approach
- Most asthma is controlled with non-specific anti-inflammatories (steroids) and bronchodilators on relatively inexpensive inhalation therapies
  - Short- and long-acting bronchodilators
  - Inhaled corticosteroids
  - Leukotriene modifiers
  - Anticholinergics


The Increasing Number of Biologic Agents for Severe Asthma Requires Careful Consideration of the Asthma Pharmacy Benefit

- The overall spend on traditional asthma therapies covered in the pharmacy benefit is decreasing
  - Reductions are mainly driven by increased competition and rebate strategies
- With the growing number of biologics on the market and more in the pipeline, asthma treatment is becoming increasingly targeted and patient-specific
  - Consequently, asthma spending trends are beginning to increase through the medical benefit

### Biologic Agents for Severe Asthma and Their Targets

<table>
<thead>
<tr>
<th>Target</th>
<th>Treatment</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgE</td>
<td>Omalizumab</td>
<td>Approved 2003</td>
</tr>
<tr>
<td>IL-5</td>
<td>Mepolizumab</td>
<td>Approved 2015</td>
</tr>
<tr>
<td></td>
<td>Reslizumab</td>
<td>Approved 2016</td>
</tr>
<tr>
<td>IL-5R</td>
<td>Benralizumab</td>
<td>Approved 2017</td>
</tr>
<tr>
<td>IL-4/IL-13</td>
<td>Dupilumab</td>
<td>Approved 2018</td>
</tr>
<tr>
<td>TSLP</td>
<td>Tezepelumab</td>
<td>Phase 3</td>
</tr>
<tr>
<td>CRTh2</td>
<td>Fevipiprant</td>
<td>Phase 3</td>
</tr>
</tbody>
</table>

IgE=immunoglobulin E; IL=interleukin; IL-5R=interleukin-5 receptor; TSLP=thymic stromal lymphopoietin; CRTh2=chemoattractant receptor on Th2 cells
Payers Are Concerned About the Budget Impact of New and Emerging Biologics for Asthma

- Payers are cautiously optimistic about the role of the IL-5s and IL-4s, but their impact on the budget is a concern
- Payers recognize the potential benefit of these agents, but highlight biologics only address a small subset of asthma patients
- The Phase 3 trial endpoints are relevant (reduction in exacerbations, hospitalizations, ED visits, etc), but concerns remain about overprescribing
- The positioning of these agents in the treatment algorithm also remains unclear
  - Overlap between omalizumab and the IL-5s and IL-4/IL-13s
  - Payers are unable to accurately project the budget impact of these agents

### Estimated Total Potential Budget Impact of an IL-5 Antagonist

**Analytic Horizon = 1 Year**

<table>
<thead>
<tr>
<th>Mepolizumab</th>
<th>Eligible Population (thousands)</th>
<th>Number Treated (thousands)</th>
<th>Annual BI per Patient* ($)</th>
<th>Total BI (millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mepolizumab</td>
<td>320</td>
<td>6.4</td>
<td>$31,388</td>
<td>$201.1</td>
</tr>
</tbody>
</table>

**Analytic Horizon = 5 Years**

<table>
<thead>
<tr>
<th>Mepolizumab</th>
<th>Number Treated (thousands)</th>
<th>Weighted BI per Patient* ($)</th>
<th>Average BI per Year (millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mepolizumab</td>
<td>32.0</td>
<td>$93,043</td>
<td>$596.1</td>
</tr>
</tbody>
</table>

*Weighted budget impact (BI) calculated by subtracting cost offsets from drug costs for one-year horizon. For 5-year horizon, drug costs and cost offsets apportioned assuming 20% patients in uptake target initiate therapy each year. Those initiating in Year 1 receive full drug costs and cost offsets, those initiating in Year 2 receive 80% of drug costs and cost offsets, etc.

## Representative Payer Policies for Biologic Asthma Therapies

<table>
<thead>
<tr>
<th></th>
<th>Aetna</th>
<th>Anthem</th>
<th>Cigna</th>
<th>Humana</th>
<th>UHC</th>
<th>Health Net</th>
<th>BSBC</th>
<th>CVS / Caremark</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mepolizumab</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Covered?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Medical benefit</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Tier</td>
<td>5</td>
<td>Non-formulary</td>
<td>3</td>
<td>Non-formulary</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>PA</td>
<td>Yes</td>
<td>–</td>
<td>Yes</td>
<td>Yes</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Step therapy</td>
<td>–</td>
<td>Yes</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Eosinophil level</td>
<td>–</td>
<td>≥150 cells/μL</td>
<td>≥300 cells/μL</td>
<td>≥300 cells/μL</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

|                |        |        |       |          |     |            |      |               |
| **Omalizumab** |        |        |       |          |     |            |      |               |
| Covered?       | Yes   | In some plans | Yes   | In some plans | –   | Yes        | –    | Yes           |
| Tier           | 4     | 3      | 2     | 5        | –   | –          | –    | –             |
| PA             | Yes   | Yes    | Yes   | Yes      | –   | –          | –    | –             |
| IgE level      | 30-1,500 IU/mL | ≥30 IU/mL | 30-700 IU/mL | 30-1,500 IU/mL | ≥30 IU/mL | –    | –             |

PA=prior authorization; ‘–’ ‘not listed in coverage policy

Costs Can Be Effectively Managed by Aligning Distribution, Plan Design and Pharmacy Care Management

Cost and Distribution Management

Plan Design

Pharmacy Care Management

Incentives and Copay Assistance

Technology and Support Tools

Output

Better Outcomes
Lower cost
Basic Tenets of the Specialty Drug Benefit

**Utilization Management**
- Reduce costs by aggressively managing drug utilization

**Preferred Drug Management**
- Establish preferred products and formulary tiers
- Use cost sharing to drive use of preferred products, but not limit adherence

**Contract Management**
- Aggressively negotiate rebates
- Incent providers to utilize the most cost-effective drugs

**Channel Management**
- For pharmacy, optimize the distribution network
- Optimize site of care

**Care Management**
- Provide counseling and education to patients and caregivers
- Incent coordinated care

Elements Typically Found in the Asthma Benefit Design

- **Incentive Programs**
  - Members
  - Prescribers

- **Patient Access Support Programs**
  - Patient assistance
  - Copay coupons

- **Case Management**
  - Efforts to increase patient ownership of their care

- **Special Pharmacy Integration**

- **Coordination**
  - Data management
  - Integrated IT
Value = Cost Effectiveness

- Efficacy
- Price
- Cost per event avoided
- Cost per % improvement
- Helps compare agents
  - When there are no head-to-head trials

Cost Difference

<table>
<thead>
<tr>
<th>C+</th>
<th>Intervention more effective and more costly than 0; Depends how much you are willing to pay for increased effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Clear Loser</td>
</tr>
<tr>
<td>E-</td>
<td>Intervention less effective and less costly than 0; Depends how much effectiveness you are willing to trade to reduce costs</td>
</tr>
<tr>
<td>E+</td>
<td>Intervention more effective and less costly than 0; Clear Winner</td>
</tr>
<tr>
<td>C-</td>
<td>Intervention less effective and more costly than 0</td>
</tr>
</tbody>
</table>

Effect Difference
Elements of the Asthma Benefit Design: Formulary Tiers

- Trend is toward multi-tier formularies
- Patient cost is dependent on the formulary tier
  - Tier 1: lowest cost
  - Tier 2: slightly higher cost
  - Tier 3: higher cost
  - Tier 4 (specialty drugs): highest cost
- Formulary positioning depends on the demonstrated value of the drug as assessed by the plan sponsor

<table>
<thead>
<tr>
<th>Tier 1 Generic</th>
<th>Tier 2 Preferred</th>
<th>Tier 3 Non-preferred</th>
<th>Tier 4 Specialty</th>
</tr>
</thead>
<tbody>
<tr>
<td>$</td>
<td>$$</td>
<td>$$$</td>
<td>$$$$$</td>
</tr>
</tbody>
</table>

- Least expensive, including all generics and select brands
- Brand name drugs proven to be most effective in their class
- Non-preferred brand names not considered to be the most effective as well as preferred specialty drugs
- The most expensive drugs; typically non-preferred, branded specialty drugs

### Formulary Design Example

<table>
<thead>
<tr>
<th>Pharmacy Benefit</th>
<th>Medical Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tier</strong></td>
<td><strong>Tier</strong></td>
</tr>
<tr>
<td>Preferred generic</td>
<td></td>
</tr>
<tr>
<td>$5</td>
<td></td>
</tr>
<tr>
<td>Non-preferred generic</td>
<td>$10</td>
</tr>
<tr>
<td>Preferred brand</td>
<td>$50</td>
</tr>
<tr>
<td>Non-preferred brand</td>
<td>$100</td>
</tr>
<tr>
<td>Preferred specialty</td>
<td>10%</td>
</tr>
<tr>
<td>Non-preferred specialty</td>
<td>20%</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Traditional Versus Potential Value-based Contracting

- Value-based contracts ensure the use of medication is leading to an offset in hospitalization/emergency room utilization and other medical costs associated with poor asthma control.

**Traditional Contracting**

- Flat, Volume or Share-Based
  - Concessions may depend on volume or share
  - Rebate %s for Purchased Brand A

**Value-Based Contracting**

- Indication-Based
  - Rebate specific to an indication

- Regimen-Based
  - Rebate paid when two products used in combination

- “Outcomes” Based
  - Concessions depend on how ‘well’ the drug works for a patient/cohoot

<table>
<thead>
<tr>
<th>Quantity</th>
<th>Rebate % for Purchased Brand A</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 vials</td>
<td>4%</td>
</tr>
<tr>
<td>200 vials</td>
<td>3%</td>
</tr>
<tr>
<td>400 vials</td>
<td>2%</td>
</tr>
</tbody>
</table>

Increasing Data & Complexity

*Drug manufacturers will increasingly find themselves involved in such arrangements with payers when applicable.*

Successful Asthma Pharmacy Management Requires Finding the Appropriate Balance

- Drug Dispensing
- Contracting Activities
- Specialty Drug Management
- Coordination of Care
- Utilization Management

+ Benefit Design (Cost Share) & Formulary
• The treatment landscape for severe asthma is evolving rapidly with the recent introduction of three novel products and several others in late-stage development

• While many patients stand to gain with the growth in the number of therapeutic options, these benefits will come at a higher cost

• To ensure patient access to these innovative therapies, the asthma pharmacy benefit must evolve to maintain a balance between access, appropriate use, and cost management
Care Coordination Strategies to Enhance Patient Outcomes with Difficult-to-treat or Severe Asthma

Steven G. Avey, MS, RPh, FAMCP
Vice President
Specialty Pharmacy Programs
MedImpact Healthcare Systems, Inc.
Learning Objective

• Employ care planning strategies to increase the delivery of coordinated, multidisciplinary care for patients with difficult-to-treat or severe asthma
The Asthma Paradox

- Advances in the understanding of asthma pathogenesis have led to advancements in therapy and symptom management.

- However, asthma morbidity and mortality remain relatively unchanged.

- Patients with severe forms of asthma face substantial medical risks, marked reductions in quality of life, and other significant disease-related burdens.

Asthma Health Care Encounters and Asthma Deaths

- Office and outpatient visits per 100 persons with asthma.
- Emergency department visits per 100 persons with asthma.
- Hospitalizations per 100 persons with asthma.
- Deaths per 100 persons with asthma.


Multidisciplinary Asthma Care

- **Multidisciplinary care** creates a team of health care professionals working together to improve quality of care and achieve efficiencies in care delivery.

- Evidence suggests that achieving asthma control often requires several clinic visits to enable a comprehensive work-up, eliminate aggravating factors, and assess therapeutic responses.

Providing Asthma Care is a Team Sport

Key Questions Addressed by the Multidisciplinary Team

• Is the diagnosis right?
• Why is there poor symptom control?
• Is there a comorbid condition that can impact treatment or treatment response?
• Is the patient receiving/taking their medication?
• What psychological and behavioral factors may be affecting the acceptance/response to therapy?
• Is dysfunctional breathing present?
• Is the inhaler device/technique right?
• Is the patient avoiding allergens, tobacco smoke, and other triggers?

• Regular follow-up and longitudinal assessment of outcomes of patients with severe asthma are important to ensure that
  • Maintenance therapy is reduced to the minimal amount required to achieve control of asthma symptoms
  • Asthma symptoms improve after all modifiable factors have been addressed
  • The basics of inhaler technique, adherence, and allergen exposure are being maintained
  • Monitor the patient over time to determine if medications are working optimally

When to Refer to a Specialist

- Patients with severe or difficult-to-treat asthma are frequently referred to a pulmonologist, allergist or other respiratory specialist for systematic evaluation and advanced treatment
  - Testing and management of comorbidities, including allergies
  - Current treatment with non-biologics is not effective
  - Initiation of treatment with targeted biologic therapies

Specialist Referral Increased the Likelihood of Diagnosis of Common Asthma Comorbidities

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Prevalence of comorbidity (%)</th>
<th>Referral made for each comorbidity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity</td>
<td>45</td>
<td>27</td>
</tr>
<tr>
<td>Allergic rhinitis</td>
<td>42</td>
<td>27</td>
</tr>
<tr>
<td>Obstructive sleep apnea</td>
<td>41</td>
<td>21</td>
</tr>
<tr>
<td>Chronic rhinosinusitis</td>
<td>34</td>
<td>15</td>
</tr>
<tr>
<td>Vocal chord dysfunction</td>
<td>34</td>
<td>32</td>
</tr>
<tr>
<td>Dysfunctional breathing</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Anxiety/depression</td>
<td>29</td>
<td>12</td>
</tr>
<tr>
<td>Gastroesophageal reflux</td>
<td>20</td>
<td>7</td>
</tr>
</tbody>
</table>

Defining Care Management

- **Care management**: A set of activities designed to improve patient care and reduce the need for medical services by enhancing *coordination between health care professionals*

- **Goal**: Improve coordination of care while providing safe, effective, non-duplicative care in the most cost-effective manner

- **Challenge**: Identifying patients most likely to benefit from care management

- **Ultimate goal of treatment and care management**: Help each asthma patient attain the highest level of health with their condition, reduce the number of exacerbations, and reduce the risk of co-morbidities

### Common Elements of Successful Care Management

<table>
<thead>
<tr>
<th>Success Factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Communication</td>
<td>• Patient satisfaction increases when the health care team explains information clearly, tries to understand the patient’s experience, and provides viable treatment/management options</td>
</tr>
<tr>
<td>In-person encounters</td>
<td>• Face-to-face interaction is necessary for effective care management</td>
</tr>
<tr>
<td></td>
<td>• Care management relying solely on telephone and/or electronic encounters has not been shown to be successful</td>
</tr>
<tr>
<td>Training and personnel</td>
<td>• Programs with specially trained care managers working as part of a multidisciplinary team are most successful</td>
</tr>
<tr>
<td>Physician involvement</td>
<td>• Placing care managers with physicians in primary care practices may help facilitate physician involvement</td>
</tr>
<tr>
<td>Informal caregivers</td>
<td>• Patients with complex health care needs, particularly those with physical or cognitive functional decline, often need the assistance of informal caregivers to actively participate in care management</td>
</tr>
<tr>
<td>Coaching</td>
<td>• Involves teaching patients and their caregivers how to recognize early warning signs of worsening disease</td>
</tr>
</tbody>
</table>

Components of Care Management

Assess Safety
- Adverse events
- Allergies
- Drug interactions

Verify Clinical Appropriateness
- Route of administration
- Strength/dose
- Dosing frequency
- REMS

Adherence
- Access assistance
- Initial fill
- Refills

Monitoring
- Review progress toward goals
- Manage therapy interruptions

Patient Education
- Treatment expectations
- Medication administration
- Support programs

Identifying Patients with Severe Asthma Most Likely to Benefit From Care Management

Severe asthma uncontrolled despite optimal guideline-recommended therapy and severe exacerbations

Allergic asthma to perennial allergens
- Total IgE within range of omalizumab indication

Yes
- Omalizumab 16 week trial
  - Effective
    - Continue omalizumab
  - Not effective
    - High blood eosinophils

No
- High blood eosinophils
  - Anti-IL-5 for 1 year
    - Effective
      - Continue anti-IL-5
    - Not effective
      - Continue anti-IL-5

Significant Savings Come From Providing Coordinated Care Management

Total Medical & Pharmacy Cost = Price $$$ + Care Management
Role of Specialty Pharmacy

- Specialty pharmacists can help determine coverage and service levels for individual health plans or specific products, and reimbursement rates.
- Specialty pharmacists have a good appreciation of unique factors of value to managed care:
  - Market dynamics
  - Good appreciation of all therapies available to treat each disease
  - Cost
  - Clinical effectiveness and medical evidence
  - Legislated mandate
  - Medical necessity
  - Preventive value
**Specialty Pharmacy is Well-Positioned to Support Care Management Activities**

<table>
<thead>
<tr>
<th>Patient Education</th>
<th>Drug Administration</th>
<th>Drug Dosing</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Therapy expectations</td>
<td>• Train patients and caregivers</td>
<td>• Individualization of dosing</td>
<td>• Adherence support</td>
</tr>
<tr>
<td>• Dosing</td>
<td>• Drug preparation</td>
<td>• Dosing frequency</td>
<td>• Concurrent medications</td>
</tr>
<tr>
<td>• Adverse events</td>
<td>• Proper administration techniques</td>
<td></td>
<td>• Adverse events</td>
</tr>
<tr>
<td>• Follow up</td>
<td>• Proper handling, storage, and disposal</td>
<td></td>
<td>• Drug interactions</td>
</tr>
<tr>
<td>• Shipping and storage requirements</td>
<td></td>
<td></td>
<td>• Comorbidities</td>
</tr>
<tr>
<td>• Patient access/insurance</td>
<td></td>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>
Specialty Pharmacy Care

• Coordinate with nurses or physicians who give biologic injections for asthma
• Patient outreach depending on severity of their asthma (every 3 to 6 months)
  • Monitor FEV₁ levels where possible
  • Monitor for adverse events and comorbidities
  • Monitor for good adherence and coach patients that are not conforming to their regimens
  • Collect information on Quality of Life where possible (ie, number of days missed at school or work, etc)
  • Utilize the Asthma Control Test (ACT) to determine asthma control where possible
Improved Outcomes Through Quality Care

Member Experience
- Member diagnosed with chronic disease
- Years go by managing disease
- Member slowly stops taking medications, following up with providers, and having labs tested
- Unnecessary hospitalizations and procedures

Value of Coordinated Care
- Member is identified early using analytic software
- Care Team outreach by nurse/pharmacist provides motivational interviewing and education
- Evidence-Based recommendations sent to member and provider
- Member is empowered to manage their disease coordination with provider leads to change

Costly Complications Minimized or Avoided
- Systemic complications • Redundant/Unnecessary testing • ER visits • Hospital admissions • High-cost medications
Summary

- Asthma patients benefit from care delivered by a coordinated multidisciplinary care team.
- Care management is a set of activities designed to improve patient care and reduce the need for medical services by enhancing coordination of care.
- Care coordination is the organization of care activities between a multidisciplinary team of providers to facilitate the appropriate delivery of health care service.
- Significant cost savings arise from providing optimal clinical support and care management.
- Specialty pharmacy is well-positioned to support care management programs.