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

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Professional Excellence in Medical Education

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

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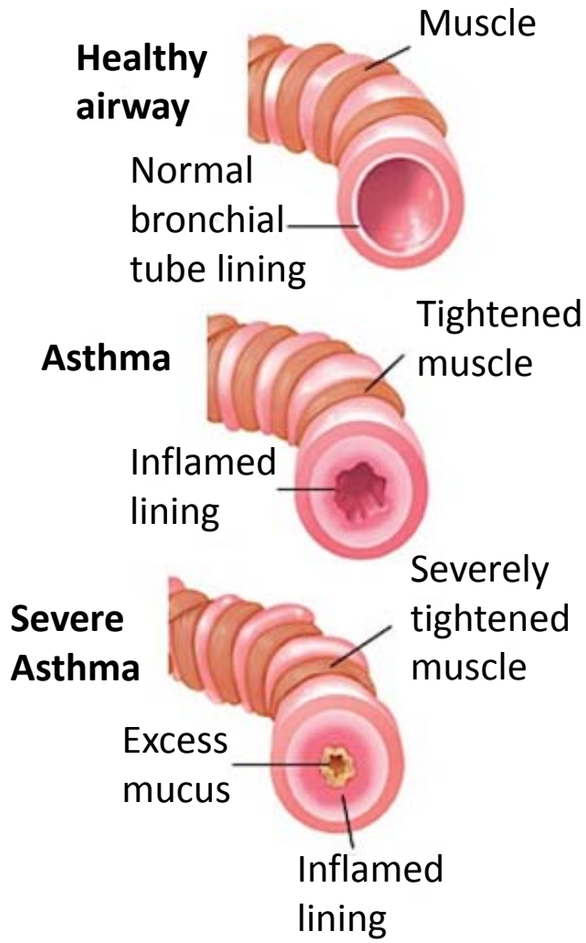
Denver, CO

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

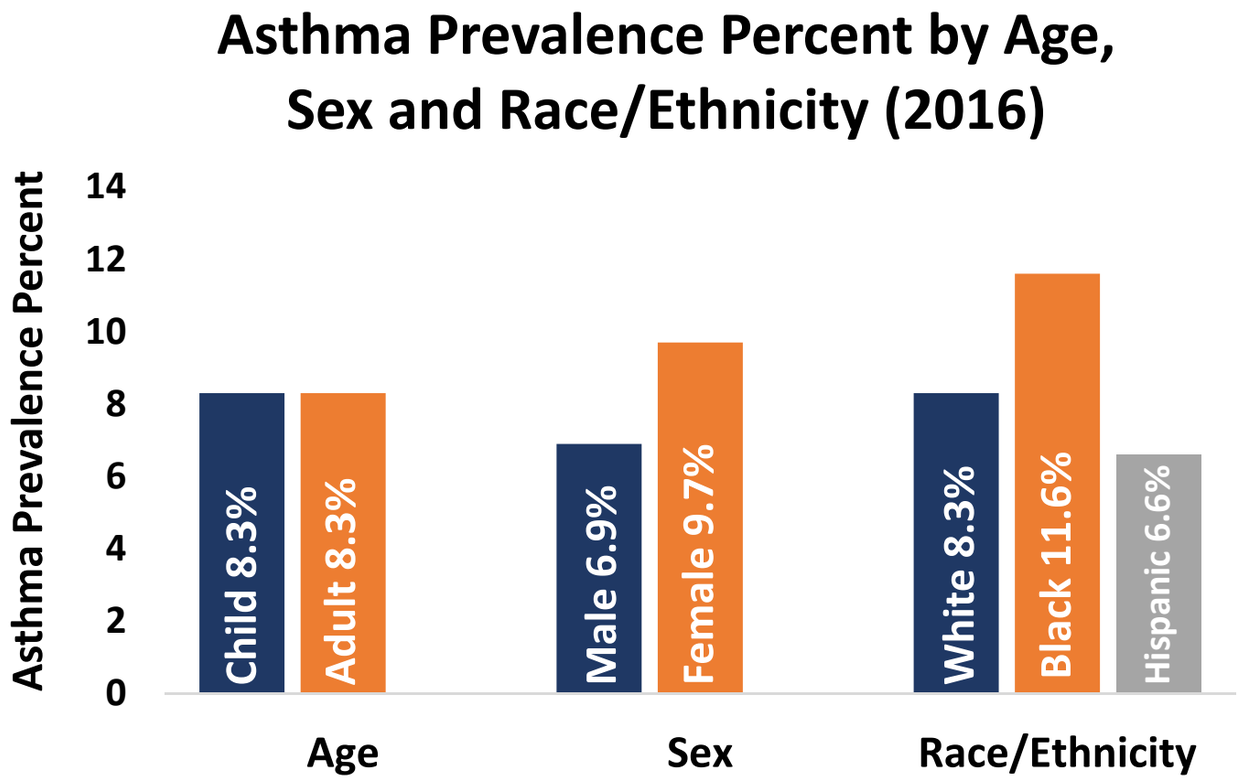
- Asthma is a heterogeneous disease, characterized by chronic airway inflammation and history of respiratory symptoms such as
  - Wheeze
  - Shortness of breath
  - Chest tightness
  - Cough that varies over time and in intensity
  - Variable airflow limitation



Global strategy for asthma management and prevention. Global Initiative for Asthma website. https://ginasthma.org/wp-content/uploads/2018/04/wms-GINA-2018-report-tracked_v1.3.pdf. Updated 2018. Accessed September 2018.

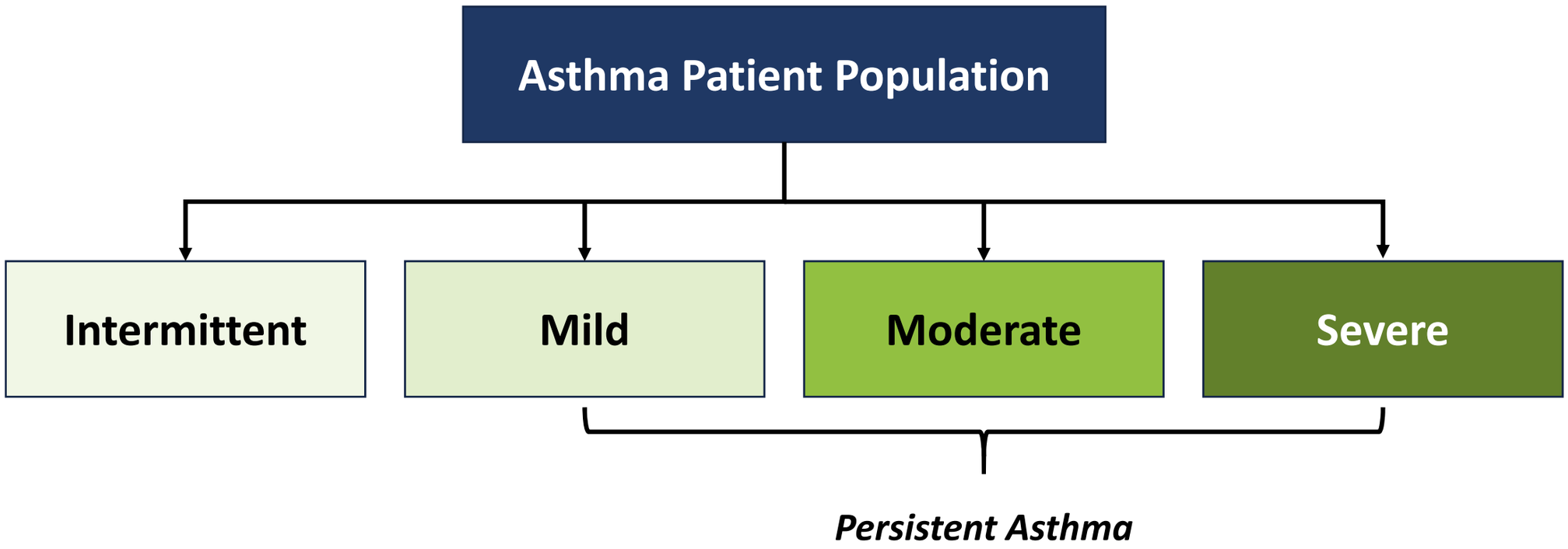
Asthma is a Highly Prevalent Disease

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



Asthma Surveillance data. 2017. Centers for Disease Control and Prevention website. https://www.cdc.gov/asthma/asthmadata.htm. Accessed September 2018.

The Asthma Patient Population is Segmented Based on Disease Severity

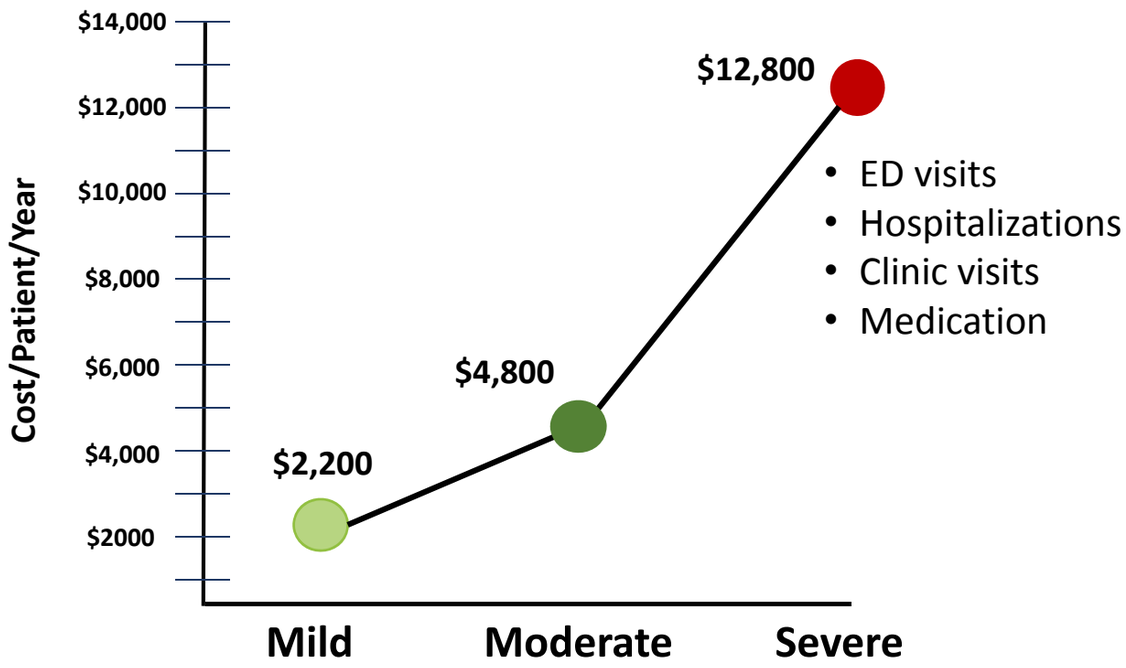


National Asthma Education and Prevention Program Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. National Heart, Lung, and Blood Institute website. https://www.nhlbi.nih.gov/files/docs/guidelines/asthsumm.pdf. Published October 2007. Accessed September 2018.

Severe Asthma

- **Definition**[1]
  - 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**[2]
  - Estimated to affect 5% to 10% of the total asthma population[2]

- **Implications**[3]
  - Severe asthma is associated with higher health care costs



1. Chung KF, Wenzel SE, Brozek JL, et al. *Eur Respir J*. 2014;43(2):343-73.
2. Skloot GS. *Curr Opin Pulm Med*. 2016;22(1):3-9.
3. Barnett SB, Nurmagambetov TA. *J Allergy Clin Immunol*. 2011;127(1):145-52.

Evolution of Asthma Classification

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

Desai M, Oppenheimer J. *Ann Allergy Asthma Immunol.* 2016;116(5):394-401.

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

Howard R, Rattray M, Prosperi M, Custovic A. *Curr Allergy Asthma Rep*. 2015;15(7):38.
Lötvall J, Akdis CA, Bacharier LB, et al. *J Allergy Clin Immunol*. 2011;127(2):355-60.

Asthma Phenotypes

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

Kim H, Ellis AK, Fischer D, et al. *Allergy Asthma Clin Immunol*. 2017;13:48.

Different Phenotypes are Associated with Different Endotypes

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

Skloot GS. *Curr Opin Pulm Med*. 2016;22(1):3-9.

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

1. Lang DM. *Allergy Asthma Proc*. 2015;36(6):418-24. 2. Drazen JM. *J Allergy Clin Immunol*. 2012;129(5):1200-1.
3. De Groot JC, Brinke At, Bel EHD. *ERJ Open Research. 2015;1(1):00024-2015*. 4. Cazzola M, Novelli G. *Pulm Pharmacol Ther*. 2010;23(6):493-500.

Biomarkers for Severe Asthma

Biomarker	Medium	Phenotype/Endotype
IgE	• Serum	• Allergic (early-onset)
Eosinophils	• Blood • Sputum	• IL-5 mediated Eosinophilic (late-onset)–allergic and non-allergic
Neutrophil	• Sputum	• Neutrophilic
Periostin and DPP4	• Serum • Sputum	• IL-13-mediated T2-associated inflammation
Exhaled Nitric Oxide (FeNO)	• Exhaled breath	• IL-13-mediated T2-associated inflammation

Kim H, Ellis AK, Fischer D, et al. *Allergy Asthma Clin Immunol*. 2017;13:48.

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)

MOA	Compound	IgE	Sputum Eosinophils	Blood Eosinophils	FeNO	Periostin	Other	Biomarker of Choice
Anti-IgE	Omalizumab	✓	✗	✓	✓	✓	• None	IgE
Anti-IL5	Mepolizumab	✓	✓	✓	✓	✗	• None	Blood Eos
	Reslizumab	✗	✓	✓	✓	✗	• None	Blood Eos
	Benralizumab	✗	✗	✓	✓	✗	• EOS + / - (FeNO & blood Eos algorithm to predict sputum Eos or FeNO > 50 ppb)	Blood Eos
Anti-IL4/IL-13	Dupilumab	✓	✓	✓	✓	✗	• TARC • YKL-40 • CEA • Eotaxin-3	Eos or eNO

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

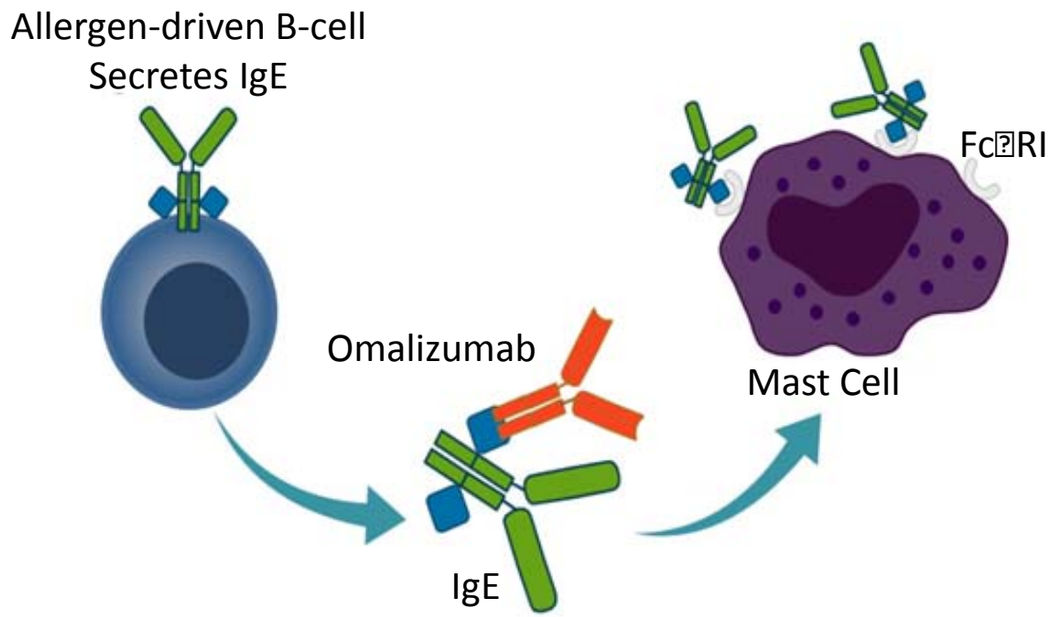
- A high level of unmet need remains in the treatment of severe asthma
- Increased understanding of the role of inflammatory cytokines in asthma pathophysiology has led to the development of multiple cytokine-inhibiting agents that target Th2 and eosinophil (EOS)-driven phenotypes
  - These agents are 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

Bobolea I, Barranco P, Del pozo V, et al. *Allergy*. 2015;70(5):540-6.
National Asthma Education and Prevention Program Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. National Heart, Lung, and Blood Institute website. https://www.nhlbi.nih.gov/files/docs/guidelines/asthsumm.pdf. Published October 2007. Accessed September 2018.

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 ≥6 years of age with
  - A positive skin test or *in vitro* reactivity to a perennial aeroallergen ***and***
  - Symptoms that are inadequately controlled with inhaled corticosteroids

Blocking the IgE Allergic Cascade[2,3]



1. Xolair [package insert]. S. San Francisco, CA: Genentech USA, Inc; East Hanover, NJ: Novartis Pharmaceuticals Corp; 2018.
2. Busse WW, Morgan WJ, Gergen PJ, et al. *N Engl J Med*. 2011;364(11):1005-15.
3. Busse W, Corren J, Lanier BQ, et al. *J Allergy Clin Immunol*. 2001;108(2):184-90.

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

	Omalizumab (n=268)	Placebo (n=257)	p
≥1 exacerbation in steroid-stable phase	14.6%	23.3%	.0009
≥1 exacerbation in steroid-reduction phase	21.3%	32.3%	.0004
≥50% reduction in corticosteroid use	72.4%	54.9%	<0.001

Busse W, Corren J, Lanier BQ, et al. *J Allergy Clin Immunol*. 2001;108(2):184-90.

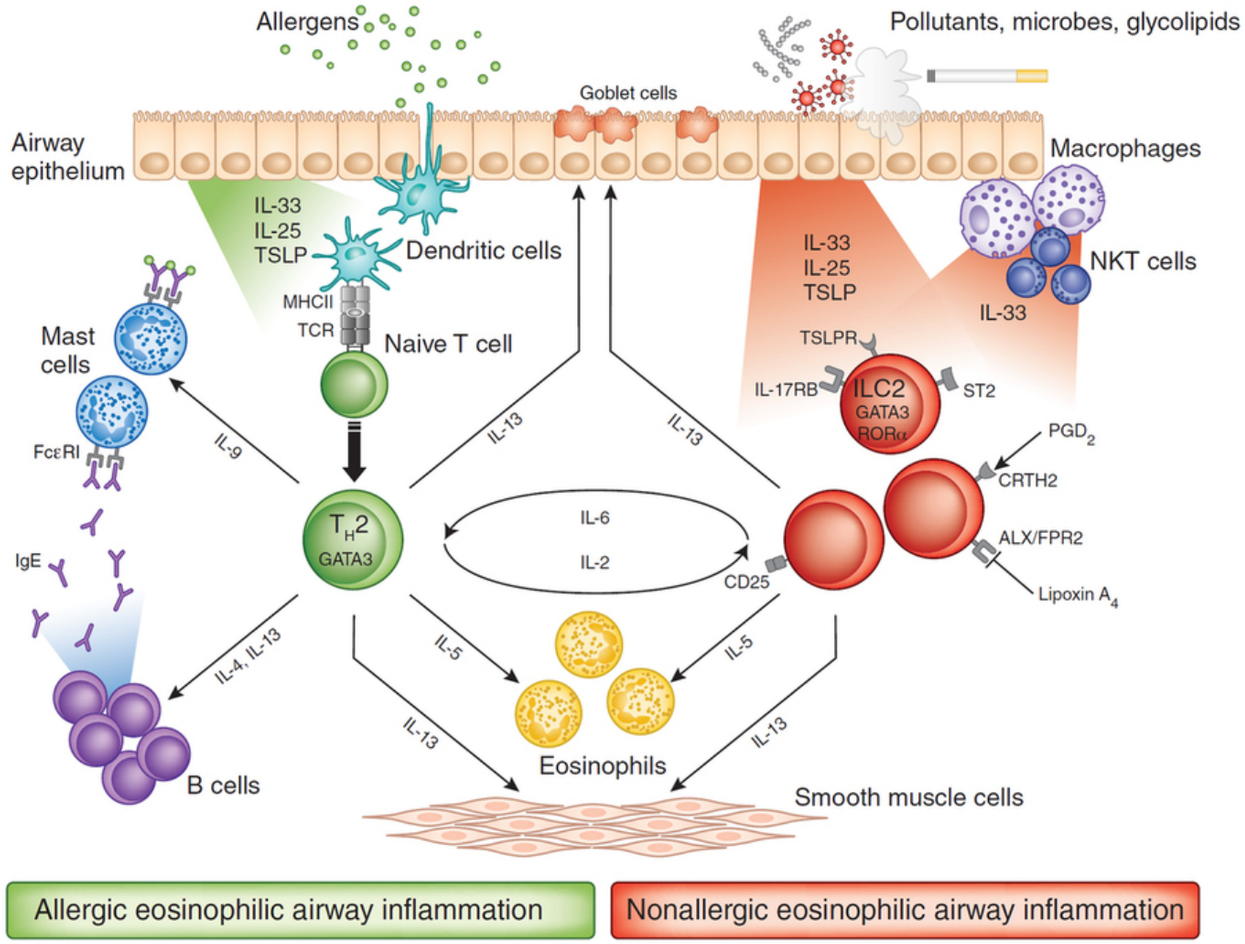
When to Use Omalizumab

- **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

Xolair [package insert]. S. San Francisco, CA: Genentech USA, Inc; East Hanover, NJ: Novartis Pharmaceuticals Corp; 2018.

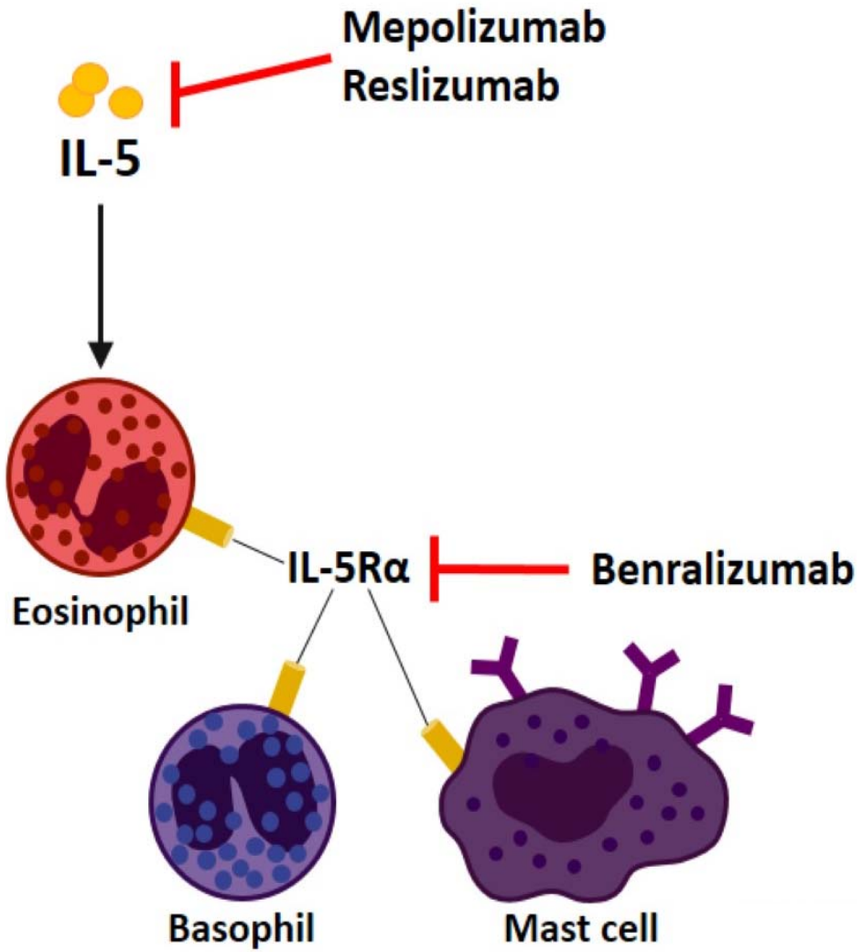
Eosinophils in Asthma

- 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



Brusselle GG, Maes T, Bracke KR. *Nat Med*. 2013;19(8):977-9.

Eosinophilic Asthma: Role of Anti-IL-5 Agents



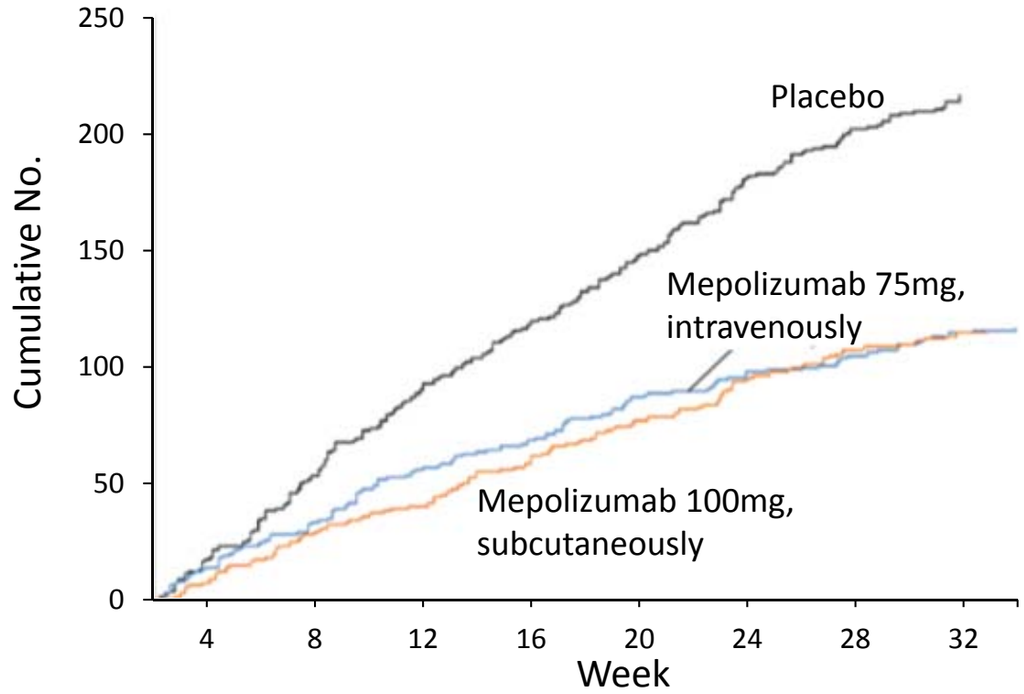
IL-5-targeted agents decrease asthma exacerbations in patients with severe asthma who have high blood eosinophil levels

Dunn RM, Wechsler ME. *Clin Pharmacol Ther.* 2015;97(1):55-65.
Ortega HG, Liu MC, Pavord ID, et al. *N Engl J Med*. 2014;371(13):1198-207.
Castro M, Zangrilli J, Wechsler ME, et al. *Lancet Respir Med*. 2015;3(5):355-66..

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

Mepolizumab Reduced the Rate of Exacerbation vs. Placebo

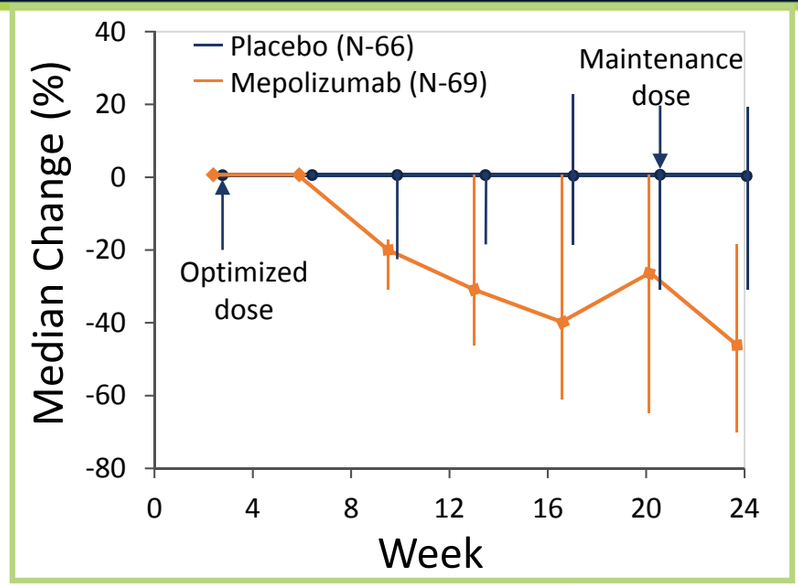


Rate of exacerbation reduced by 47% (95% CI, 29 to 61) in the IV mepolizumab group and by 53% (95% CI, 37 to 65) in the SC group vs. placebo (p<0.001 for both comparisons)

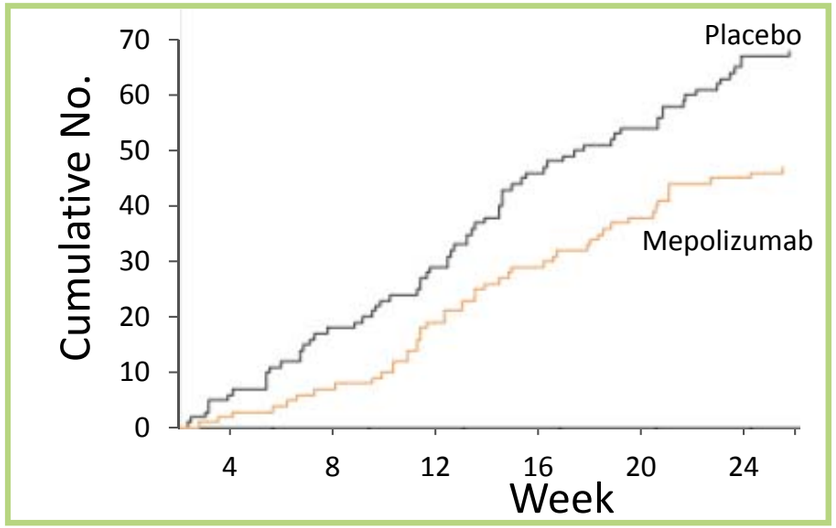
Ortega HG, Liu MC, Pavord ID, et al. *N Engl J Med*. 2014;371(13):1198-207

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



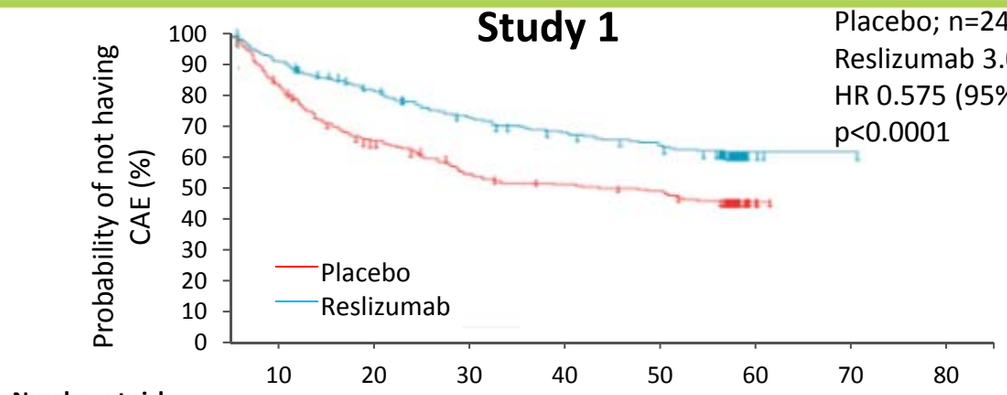
Median percentage reduction in systemic corticosteroid use was 50% in the mepolizumab group vs. 0% in the placebo (p=0.007)

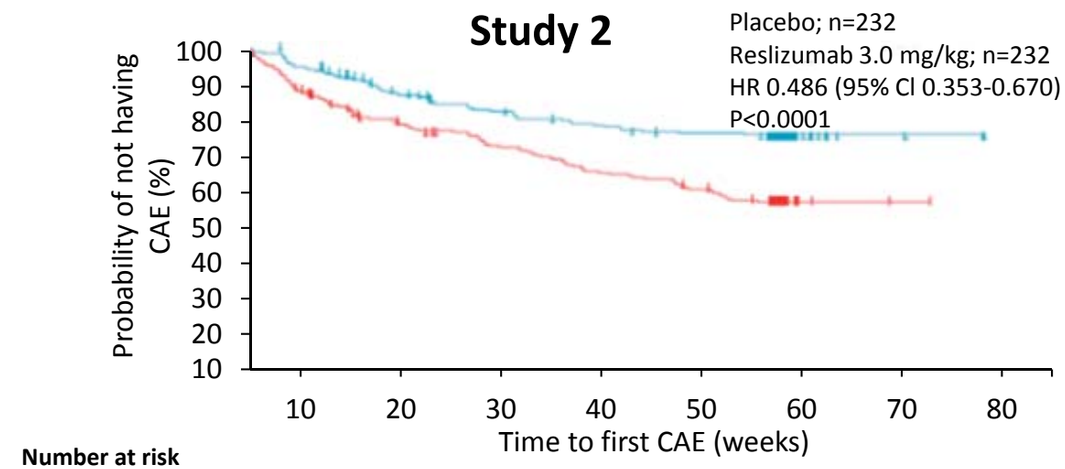


Bel EH, Wenzel SE, Thompson PJ, et al. *N Engl J Med*. 2014;371(13):1189-97.

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





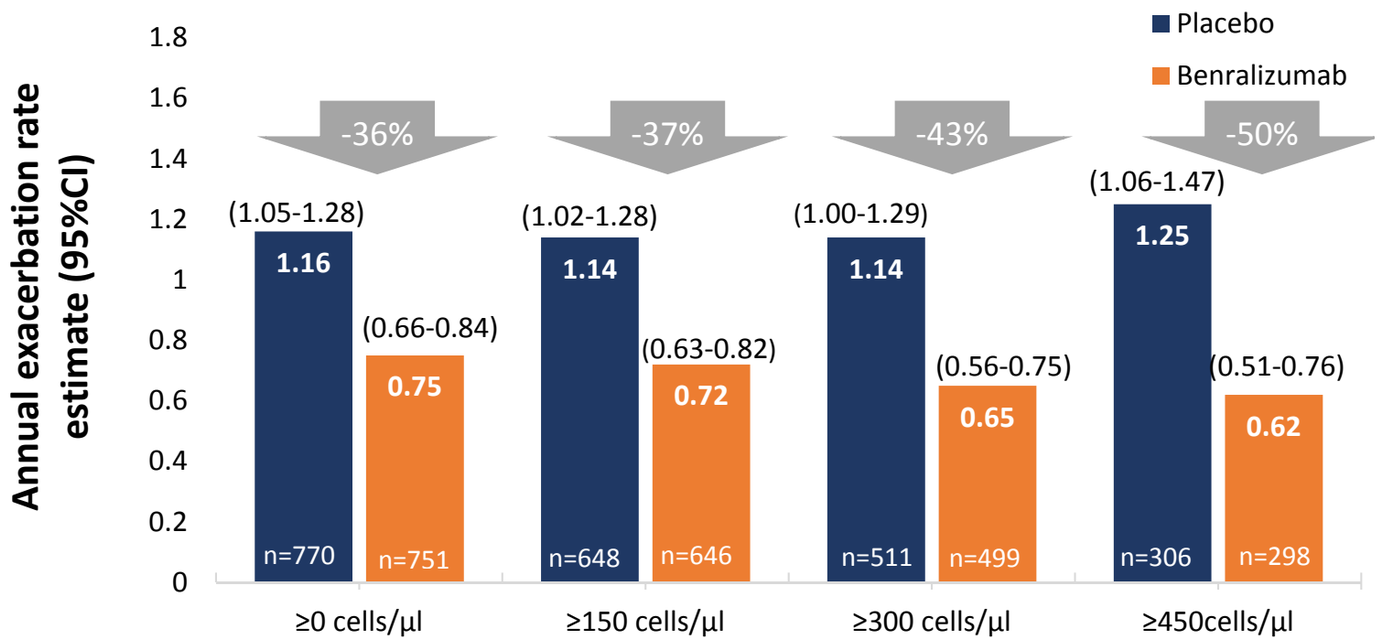
Reslizumab significantly reduced the frequency of asthma exacerbations (p<0.0001 vs placebo) in both studies

Castro M, Zangrilli J, Wechsler ME, et al. *Lancet Respir Med*. 2015;3(5):355-66.

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



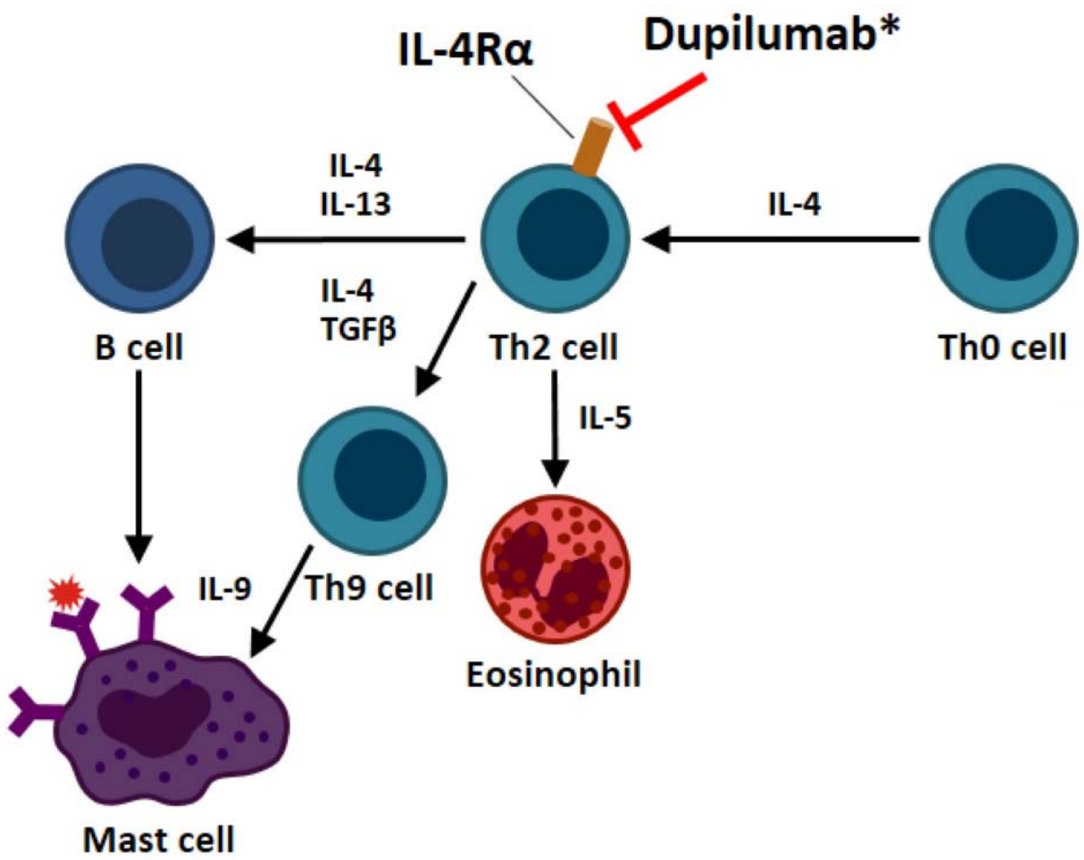
Bleecker ER, Fitzgerald JM, Chanez P, et al. *Lancet*. 2016;388:2115-2127
Fitzgerald JM, Bleecker ER, Nair P, et al. *Lancet*. 2016;388(10056):2128-2141.

Clinical Use of Anti-IL-5 Therapies

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

1. Nucala [package insert] Research Triangle Park, NC: GlaxoSmithKline; December 2017.
2. Cinqair [package insert] Frazer, PA: Teva Pharmaceutical Industries; May 2016;
3. Fasenra [package insert] . Wilmington, DE: AstraZeneca Pharmaceuticals LP; November 2017.

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

Hambly N, Nair P. *Curr Opin Pulm Med*. 2014;20(1):87-94.
Barranco P, Phillips-angles E, Dominguez-ortega J, Quirce S. *Ther Clin Risk Manag*. 2017;13:1139-1149.
Regeneron. Tarrytown, N.Y. and Paris, Oct. 19, 2018 /PRNewswire.

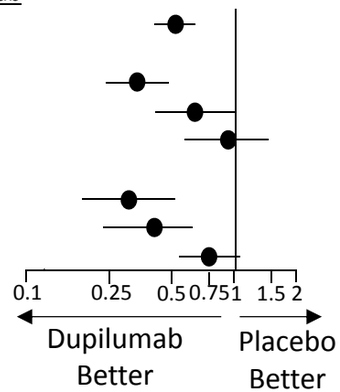
Dupilumab Significantly Lowers Rates of Severe Exacerbation in a Phase 3 Trial

- 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

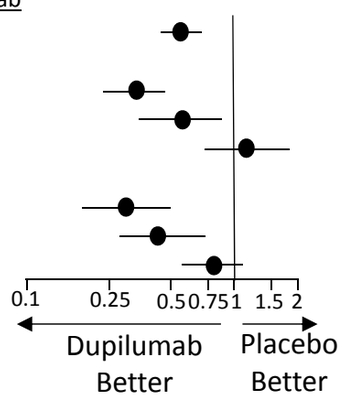
A Dupilumab, 200 mg Every 2 Wk, vs. Matched Placebo

Subgroup	No. of Patients: Placebo	No. of Patients: Dupilumab	Relative Risk vs. Placebo (95% CI)
Overall	317	631	0.52 (0.41-0.66)
Eosinophil count			
≥300 cells/mm^3	148	264	0.34 (0.24-0.48)
≥150 to <300 cells/mm^3	84	173	0.64 (0.41-1.02)
<150 cells/mm^3	85	193	0.93 (0.58-1.47)
FE_{NO}			
≥50 ppb	71	119	0.31 (0.18-0.52)
≥25 to <50 ppb	91	180	0.39 (0.24-0.62)
<25 ppb	149	325	0.75 (0.54-1.05)



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

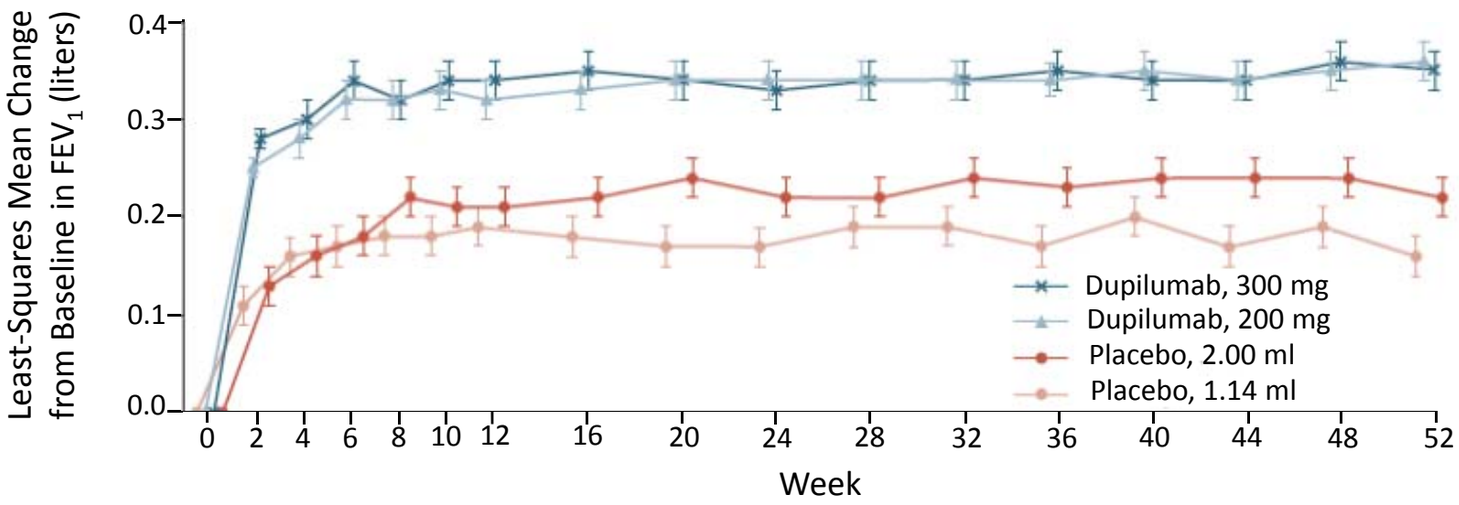
Subgroup	No. of Patients: Placebo	No. of Patients: Dupilumab	Relative Risk vs. Placebo (95%CI)
Overall	321	633	0.54 (0.43-0.68)
Eosinophil count			
≥300 cells/mm^3	142	277	0.33 (0.23-0.45)
≥150 to <300 cells/mm^3	95	175	0.56 (0.35-0.89)
<150 cells/mm^3	83	181	1.15 (0.75-1.77)
FE_{NO}			
≥50 ppb	75	124	0.31 (0.19-0.49)
≥25 to <50 ppb	97	186	0.44 (0.28-0.69)
<25 ppb	144	317	0.79 (0.57-1.10)



Castro M, Corren J, Pavord ID, et al. *N Engl J Med*. 2018;378(26):2486-2496.

Dupilumab Significantly Improved Lung Function

Change in the Prebronchodilator FEV_1 from Baseline over 52-Weeks



No. at Risk

Dupilumab, 300 mg	633	625	614	612	609	598	610	611	593	596	586	579	584	584	570	562	488
Dupilumab, 200 mg	631	610	613	615	604	607	611	605	601	599	589	585	590	577	581	570	477
Placebo, 2.00 ml	321	313	311	313	311	309	313	310	304	296	304	301	301	297	292	290	250
Placebo, 1.14 ml	317	315	307	301	305	301	307	300	303	300	290	286	289	287	288	281	240

The benefit of dupilumab on FEV_1 was greatest among patients with a blood eosinophil count of ≥300 eos/cc at baseline

Castro M, Corren J, Pavord ID, et al. *N Engl J Med*. 2018;378(26):2486-2496.

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

Therapeutic target
Approved therapy
Therapy in clinical development
Injectable
Oral
Inhaled

T2 High Asthma

- Downstream Mediators
  - Immunoglobulin
    - IgE → Omalizumab
  - Cytokines
    - IL-5 → Mepolizumab, Reslizumab, Benralizumab
    - IL-4 → Dupilumab
    - IL-13 → Dupilumab
  - Receptor antagonist
    - DP_2/CRTH2 → Fevipiprant, OC000459
- Upstream Mediators
  - Transcription factor
    - GATA-3 → SB010 DNAzyme
  - Alarmin
    - TSLP → AMG 157

Pepper AN, Renz H, Casale TB, Garn H. *J Allergy Clin Immunol Pract.* 2017;5(4):909-916.

Summary

- 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

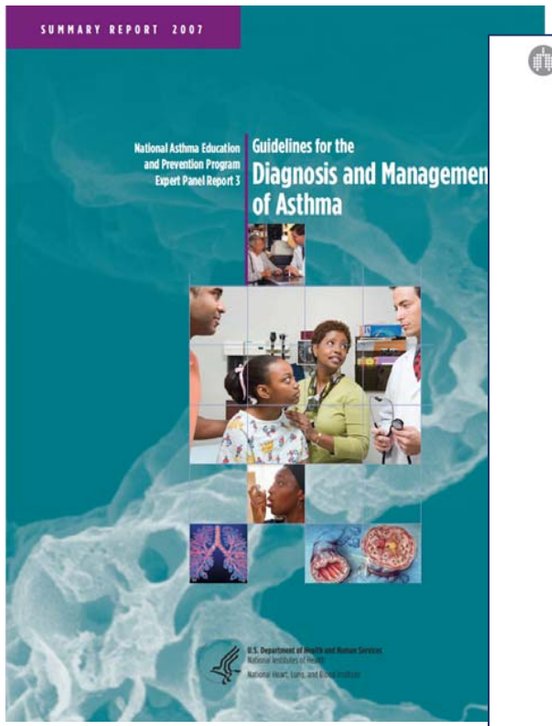
Integrating Emerging Biologic Therapies into Health Plan Asthma Treatment Algorithms

Edmund Pezalla, MD, MPH
CEO
Enlightenment Bioconsult, LLC

Learning Objective

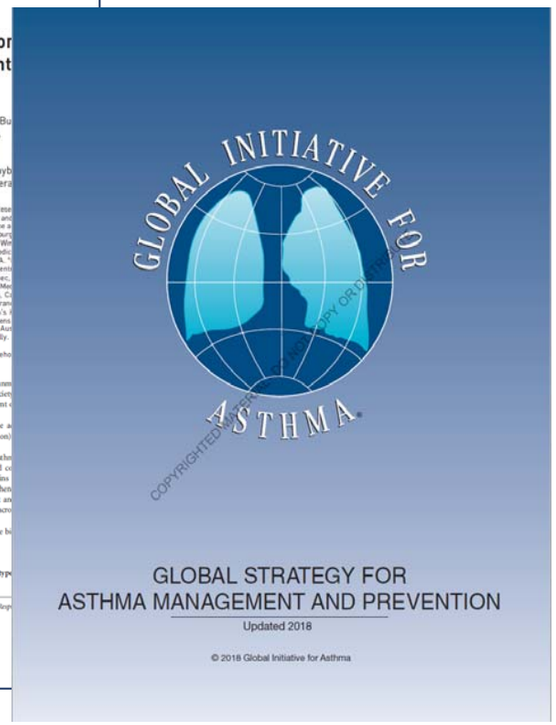
- Discuss the current management of difficult-to-treat or severe asthma, including guideline recommendations and new and emerging treatments

Asthma Treatment Guidelines



National Asthma Education and Prevention Program
2007

ERS/ATS Guidelines on Severe Asthma
2014



Global Initiative for Asthma
2018

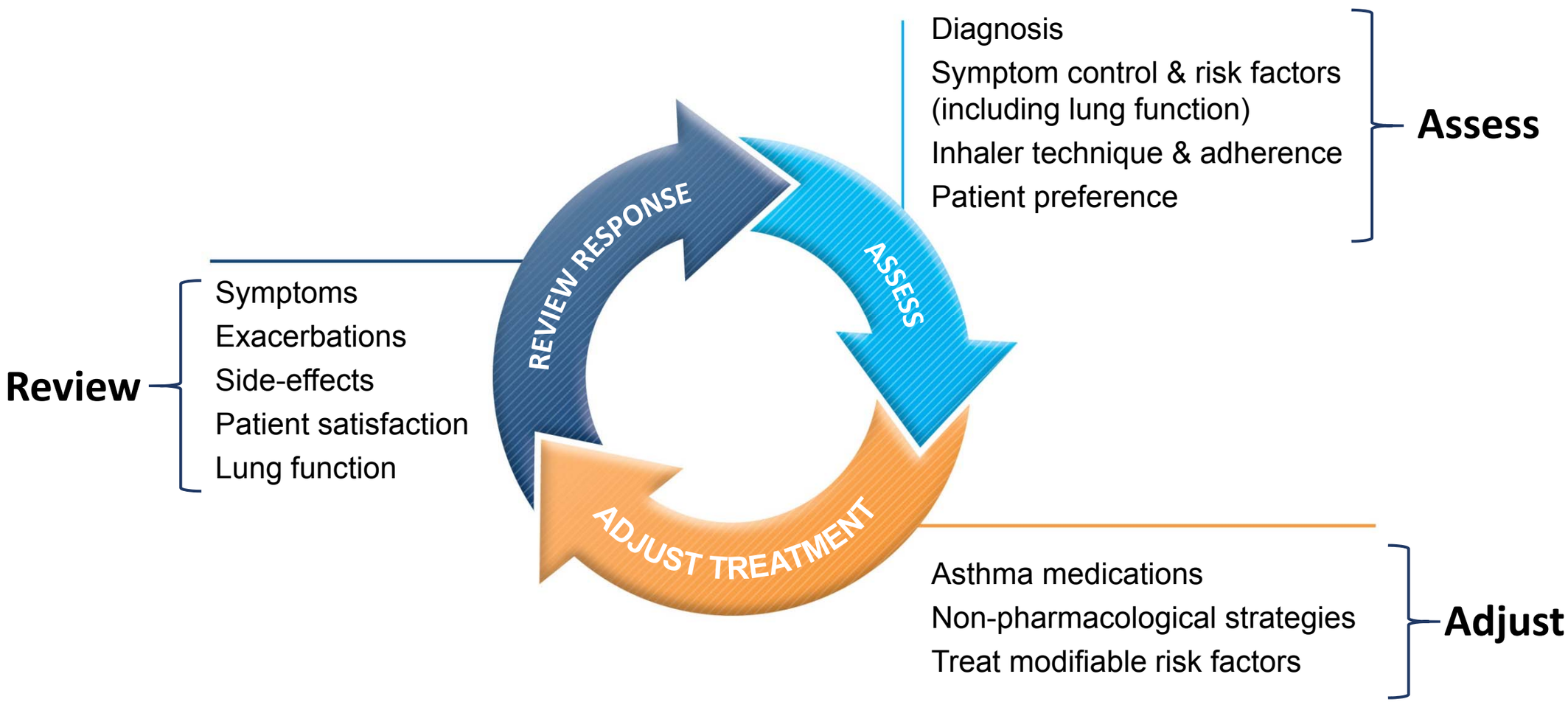
- Understanding of the immuno-pathologic mechanisms of asthma continues to increase
- This has resulted in the introduction of biologic therapies that target specific steps in the dysregulated immune processes underlying the disease
- Due to the fast pace of innovation, treatment guidelines often do 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

National Asthma Education and Prevention Program Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. National Heart, Lung, and Blood Institute website. https://www.nhlbi.nih.gov/files/docs/guidelines/asthsumm.pdf. Published October 2007. Accessed September 2018.
Global strategy for asthma management and prevention. Global Initiative for Asthma website. https://ginasthma.org/2018-gina-report-global-strategy-for-asthma-management-and-prevention/. Updated 2018. Accessed September 2018.

Control-Based Asthma Management Cycle



Global strategy for asthma management and prevention. Global Initiative for Asthma website. https://ginasthma.org/2018-gina-report-global-strategy-for-asthma-management-and-prevention/. Updated 2018. Accessed September 2018.

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/long-acting b-agonists (LABA)
  - *Severe asthma:* requires moderate or high-dose ICS/LABA ± add-on or remains uncontrolled despite this treatment

Global strategy for asthma management and prevention. Global Initiative for Asthma website. https://ginasthma.org/2018-gina-report-global-strategy-for-asthma-management-and-prevention/. Updated 2018. Accessed September 2018.

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

Components of severity		Classification of asthma severity (age ≥12 y)			
		Intermittent	Persistent		
			Mild	Moderate	Severe
Impairment	Symptoms	≤2 d/wk	>2 d/wk but not daily	Daily	Throughout the day
	Nighttime awakenings	≤2x mo	3-4x mo	>1x wk but not nightly	Often 7x wk
	Short-acting β_2-agonist use for symptom control (not prevention of EIB)	≤2 d/wk	>2 d/wk but not daily and not more that 1x on any day	Daily	Several times per day
	Interference with normal activity	none	Minor limitation	Some limitation	Extremely limited
	Lung function Normal FEV_1: FVC ratio 20-39 y 80% 40-59 y 75% 60-80 y 70%	• Normal FEV_1, between exacerbations • FEV_1, >80% predicted • FEV_1: FVC normal	• FEV_1, > 80% predicted • FEV_1: FVC normal	• FEV_1, >60% but <80% predicted • FEV_1: FVC normal	• FEV_1, <60% predicted • FEV_1: FVC reduced >5%
Risk	**Exacerbations requiring oral systemic corticosteroids**	**0-1/y**	**≥2/y**	**≥2/y**	**≥2/y**
		Consider severity and interval since last exacerbation Frequency and severity may fluctuate over time for patients in any severity category Relative annual risk of exacerbation may be related to FEV_1			
Recommended step for initiating treatment (see Figure 3 for treatment steps)		Step 1	Step 2	Step 3 and consider short course of	Step 4 or 5 oral systemic corticosteroids
		In 2-6 weeks, evaluate level of asthma control that is achieved and adjust therapy accordingly			

National Asthma Education and Prevention Program Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. National Heart, Lung, and Blood Institute website. https://www.nhlbi.nih.gov/files/docs/guidelines/asthsumm.pdf. Published October 2007. Accessed September 2018.

How to Distinguish Between Uncontrolled and Severe Asthma

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

Global strategy for asthma management and prevention. Global Initiative for Asthma website. https://ginasthma.org/2018-gina-report-global-strategy-for-asthma-management-and-prevention/. Updated 2018. Accessed September 2018.

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 yes, did you bring your peak flow chart? _____ 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 $beta_2$-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

These questions are examples and do not represent a standardized assessment instrument. Other examples of asthma control questions: Asthma Control Questionnaire (Juniper); Asthma Therapy Assessment Questionnaire (Volmer); Asthma Control Test (Nathan); Asthma Control Score (Boulet)

National Asthma Education and Prevention Program Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. National Heart, Lung, and Blood Institute website. https://www.nhlbi.nih.gov/files/docs/guidelines/asthsumm.pdf. Published October 2007. Accessed September 2018.

Benchmarks of Good Asthma Control

- ✓ 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		Level of Asthma Symptom Control		
In the past 4 weeks, has the patient had:		**Well-controlled**	**Partly controlled**	**Uncontrolled**
• Daytime asthma symptoms more than twice a week?	Yes❑ No❑	None of these	1-2 of these	3-4 of these
• Any night waking due to asthma?	Yes❑ No❑			
• Reliever needed for symptoms* more than twice a week?	Yes❑ No❑			
• Any activity limitation due to asthma?	Yes❑ No❑			

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

Global strategy for asthma management and prevention. Global Initiative for Asthma website. https://ginasthma.org/2018-gina-report-global-strategy-for-asthma-management-and-prevention/. Updated 2018. Accessed September 2018.

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 FEV_1 at start of treatment, after 3 to 6 months, and then periodically for ongoing risk assessment

Global strategy for asthma management and prevention. Global Initiative for Asthma website. https://ginasthma.org/2018-gina-report-global-strategy-for-asthma-management-and-prevention/. Updated 2018. Accessed September 2018.

Risk Factors for Poor Asthma Outcomes

Exacerbations	Progressive Lung Function Decline	Treatment AEs
• Uncontrolled asthma symptoms • High SABA use (≥3 canisters/year) • ≥1 exacerbation in last 12 months • Low FEV_1; higher bronchodilator reversibility • Incorrect inhaler technique and/or poor adherence • Smoking • Obesity, chronic rhinosinusitis, pregnancy, blood eosinophilia • Elevated fractional exhaled nitric oxide (FeNO) in adults with allergic asthma taking ICS • Ever intubated for asthma	• No ICS treatment • Smoking • Occupational exposure • Mucus hypersecretion • Blood eosinophilia • Pre-term birth • Low birth weight	• Frequent oral steroids • High dose/potent ICS • P450 inhibitors

Global strategy for asthma management and prevention. Global Initiative for Asthma website. https://ginasthma.org/2018-gina-report-global-strategy-for-asthma-management-and-prevention/. Updated 2018. Accessed September 2018.

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

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

- Availability and cost at the population level

Global strategy for asthma management and prevention. Global Initiative for Asthma website. https://ginasthma.org/2018-gina-report-global-strategy-for-asthma-management-and-prevention/. Updated 2018. Accessed September 2018.

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?

Global strategy for asthma management and prevention. Global Initiative for Asthma website. https://ginasthma.org/2018-gina-report-global-strategy-for-asthma-management-and-prevention/. Updated 2018. Accessed September 2018.

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

Global strategy for asthma management and prevention. Global Initiative for Asthma website. https://ginasthma.org/2018-gina-report-global-strategy-for-asthma-management-and-prevention/. Updated 2018. Accessed September 2018.

2018 GINA-Recommended Asthma Pharmacotherapy

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

Global strategy for asthma management and prevention. Global Initiative for Asthma website. https://ginasthma.org/wp-content/uploads/2018/04/wms-GINA-2018-report-tracked_v1.3.pdf/. Updated 2018. Accessed September 2018.

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	STEP 2	STEP 3	STEP 4	STEP 5	STEP 6

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

≥12 years of age		**Intermittent Asthma**	**Persistent Asthma: Daily Medication** Consult with asthma specialist if step 4 care or higher is required. Consider consultation at step 3				
	Preferred Treatment	SABA as needed	Low dose ICS	Low dose ICS + LABA **OR** medium dose ICS	Medium dose ICS + LABA	High-dose ICS + LABA **AND** consider omalizumab for patients who have allergies	High dose ICS + LABA + oral corticosteroids **AND** consider omalizumab for patients who have allergies
	Alternative Treatment		Cromolyn, LTRA, or theophylline	Low dose ICS + either LTRA, theophylline or zileuton	Medium dose ICS + either LTRA, theophylline, or zileuton		
			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.					

National Asthma Education and Prevention Program Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. National Heart, Lung, and Blood Institute website.

Step 5: Treatment of Severe Asthma

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

Global strategy for asthma management and prevention. Global Initiative for Asthma website. https://ginasthma.org/wp-content/uploads/2018/04/wms-GINA-2018-report-tracked_v1.3.pdf/. Updated 2018. Accessed September 2018.

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 ≥12 years with history of exacerbations
  - Add-on anti-IgE (omalizumab) for patients with severe allergic asthma
  - Add-on anti-IL5 (mepolizumab (SC, ≥12 years) or reslizumab (IV, ≥18 years)) or anti-IL5R (benralizumab (SC, ≥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 (≤7.5mg/day prednisone equivalent)**: this may benefit some patients, but has significant systemic side-effects. Assess and monitor for osteoporosis

Global strategy for asthma management and prevention. Global Initiative for Asthma website. https://ginasthma.org/wp-content/uploads/2018/04/wms-GINA-2018-report-tracked_v1.3.pdf/. Updated 2018. Accessed September 2018.

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 FEV_1
- 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

Mepolizumab for the treatment of severe asthma with eosinophilia: effectiveness, value, and value-based price benchmarks. Institute for Clinical and Economic Review. https://icer-review.org/wp-content/uploads/2016/03/CTAF_Mepolizumab_Final_Report_031416.pdf. Published March 14, 2016. Accessed September 2018.

Reviewing Response to Therapy

Reviewing Response to Treatment

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

Global strategy for asthma management and prevention. Global Initiative for Asthma website. https://ginasthma.org/wp-content/uploads/2018/04/wms-GINA-2018-report-tracked_v1.3.pdf/. Updated 2018. Accessed September 2018.

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

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Vice President, Clinical Strategy and
Programs and Industry Relations
Magellan Rx Management

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CEO
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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

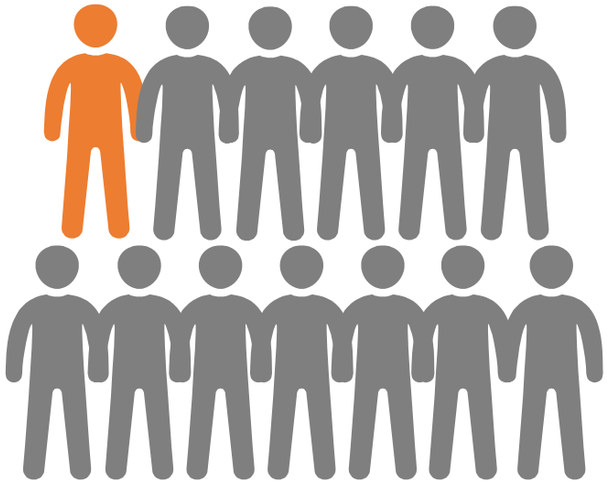
Children

8.3%

~6,100,000

5%-10% have severe asthma

Adults



8.3%

~20,400,000

Centers for Disease Control and Prevention. Current Asthma Prevalence (2016). https://www.cdc.gov/asthma/most_recent_data.htm#modalIdString_CDCTable_0. Updated May 2018. Accessed September 2018.

Burden of Asthma in the United States

11.0 million Physician office visits with asthma as primary diagnosis [1]

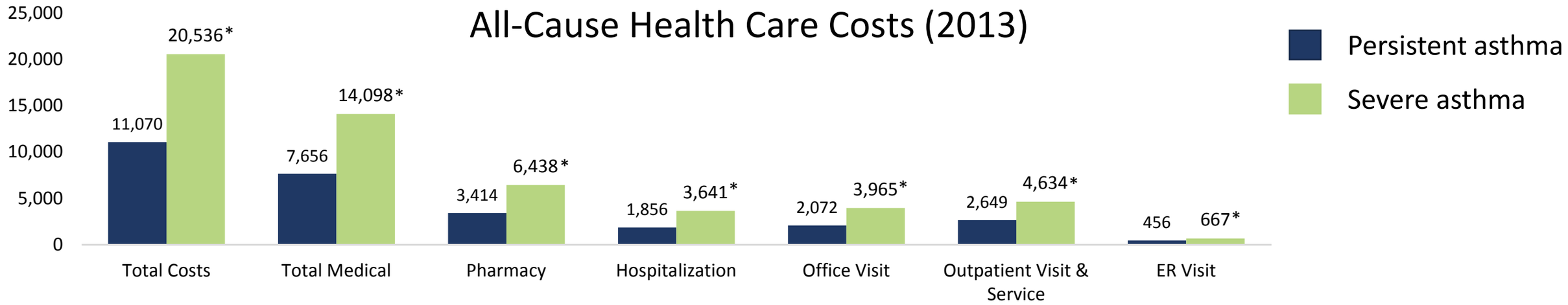
1.7 million ED visits with asthma as primary diagnosis[1]

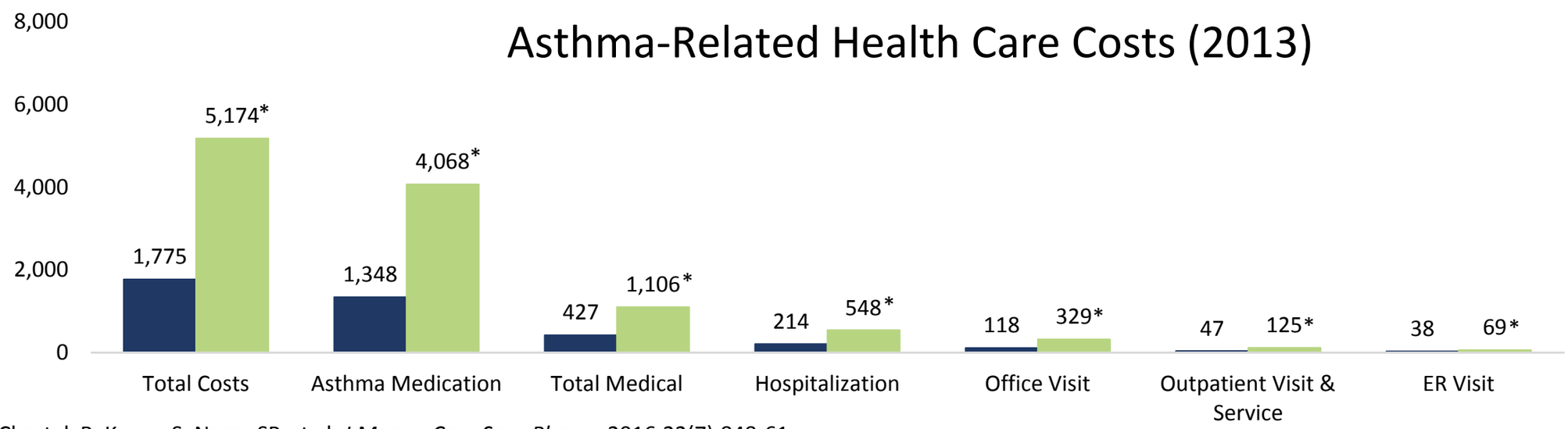
3,518 Deaths with asthma as underlying cause[1]

$81.9 billion Cost of asthma in the United States[2]

1 Centers for Disease Control and Prevention. Current Asthma Prevalence (2016). https://www.cdc.gov/asthma/most_recent_data.htm#modalIdString_CDCTable_0. Updated May 2018. Accessed September 2018. 2 Nurmagambetov T, Kuwahara R, Garbe P. *Ann Am Thorac Soc*. 2018;15(3):348-356.

Severe Asthma Presents a Significant Clinical and Economic Burden





Chastek B, Korrer S, Nagar SP, et al. *J Manag Care Spec Pharm*. 2016;22(7):848-61.

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

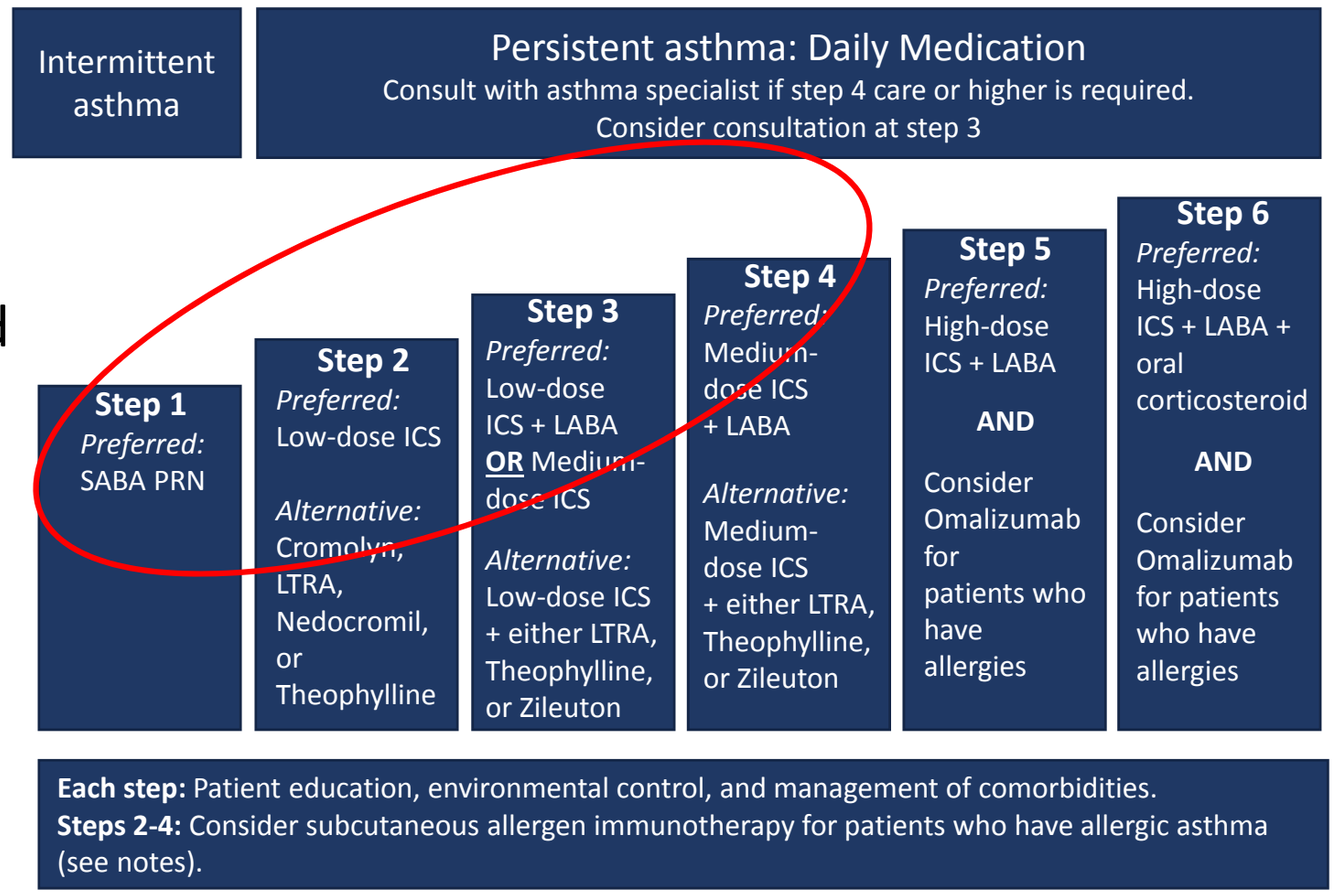
Impact

- 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

Chastek B, Korrer S, Nagar SP, et al. *J Manag Care Spec Pharm*. 2016;22(7):848-61.

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



National Asthma Education and Prevention Program. Expert Panel Report 3. https://www.nhlbi.nih.gov/files/docs/guidelines/asthsumm.pdf. Published October 20007. Accessed September 2018.
Global Initiative for Asthma. Global strategy for asthma management and prevention, 2018. https://ginasthma.org/2018-gina-report-global-strategy-for-asthma-management-and-prevention. Accessed September 2018.

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

Target	Treatment	Status
IgE	Omalizumab	Approved 2003
IL-5	Mepolizumab Reslizumab	Approved 2015 Approved 2016
IL-5R	Benralizumab	Approved 2017
IL-4/IL-13	Dupilumab	Approved 2018
TSLP	Tezepelumab	Phase 3
CRTh2	Fevipiprant	Phase 3

IgE=immunoglobulin E; IL=interleukin; IL-5R=interleukin-5 receptor; TSLP=thymic stromal lymphopoietin; CRTh2=chemoattractant receptor on Th2 cells

Mccracken JL, Tripple JW, Calhoun WJ. *Curr Opin Allergy Clin Immunol*. 2016;16(4):375-82.

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

Costill D. *Managed Care Connect*. https://www.managedhealthcareconnect.com/article/severe-asthma-new-biologics-improve-standard-care-increase-costs. March 12, 2018. Accessed September 2018.

Estimated Total Potential Budget Impact of an IL-5 Antagonist

		Analytic Horizon = 1 Year			Analytic Horizon = 5 Years		
	Eligible Population (thousands)	Number Treated (thousands)	Annual BI per Patient* ($)	Total BI (millions)	Number Treated (thousands)	Weighted BI per Patient* ($)	Average BI per Year (millions)
Mepolizumab	**320**	**6.4**	**$31,388**	**$201.1**	**32.0**	**$93,043**	**$596.1**

*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.

Mepolizumab for the treatment of severe asthma with eosinophilia: effectiveness, value, and value-based price benchmarks. Institute for Clinical and Economic Review. https://icer-review.org/wp-content/uploads/2016/03/CTAF_Mepolizumab_Final_Report_031416.pdf. Published March 14, 2016. Accessed September 2018.

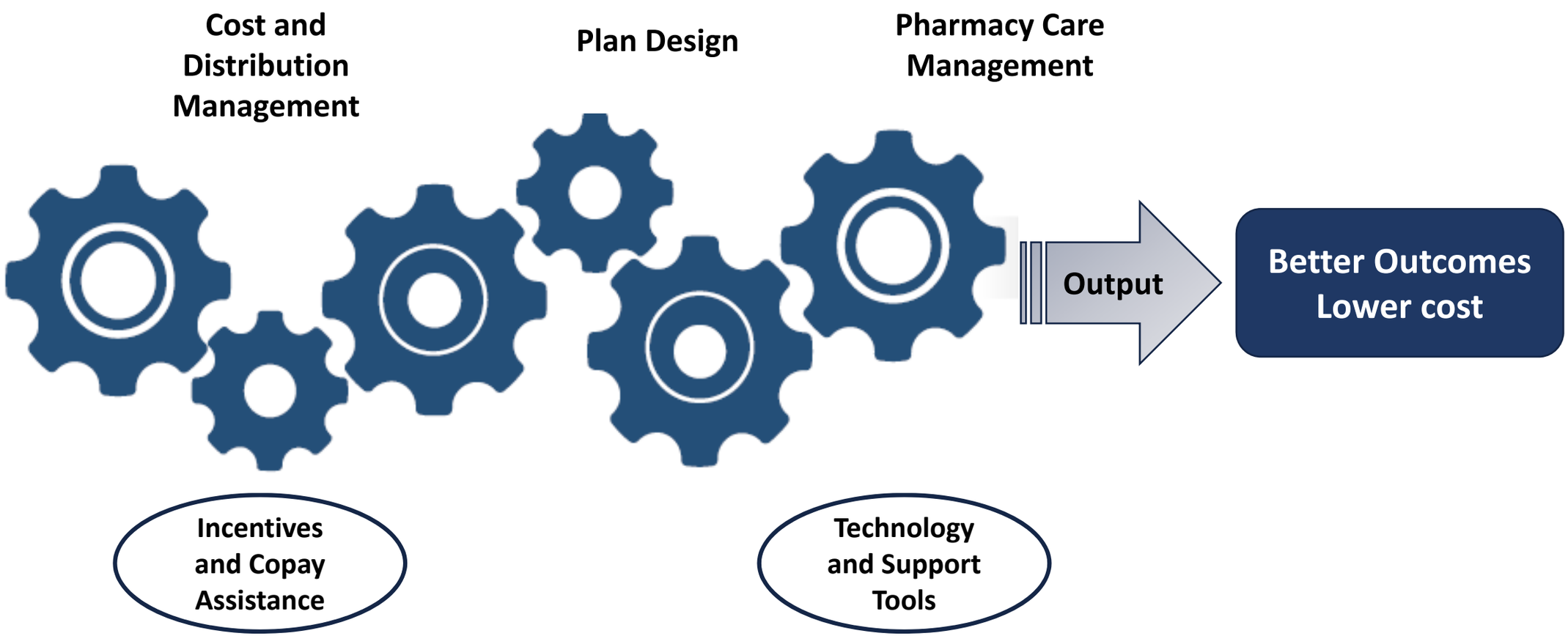
Representative Payer Policies for Biologic Asthma Therapies

	Aetna	Anthem	Cigna	Humana	UHC	Health Net	BSBC	CVS / Caremark
Mepolizumab								
Covered?	Yes	Yes	Yes	Medical benefit	–	–	–	–
Tier	5	Non-formulary	3	Non-formulary	–	–	–	–
PA	Yes	–	Yes	Yes	–	–	–	–
Step therapy	–	Yes	-	-	–	–	–	–
Eosinophil level	–	≥150 cells/µL ≥300 cells/µL	-	≥300 cells/µL	–	–	–	–
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

Mepolizumab for the treatment of severe asthma with eosinophilia: effectiveness, value, and value-based price benchmarks. Institute for Clinical and Economic Review. https://icer-review.org/wp-content/uploads/2016/03/CTAF_Mepolizumab_Final_Report_031416.pdf. Published March 14, 2016. Accessed September 2018.

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



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

Starner CI, Alexander GC, Bowen K, Qiu Y, Wickersham PJ, Gleason PP. *Health Aff* (Millwood). 2014;33(10):1761-9.

Elements Typically Found in the Asthma Benefit Design

Asthma Benefit

Incentive Programs
- Members
- Prescribers

Special Pharmacy Integration

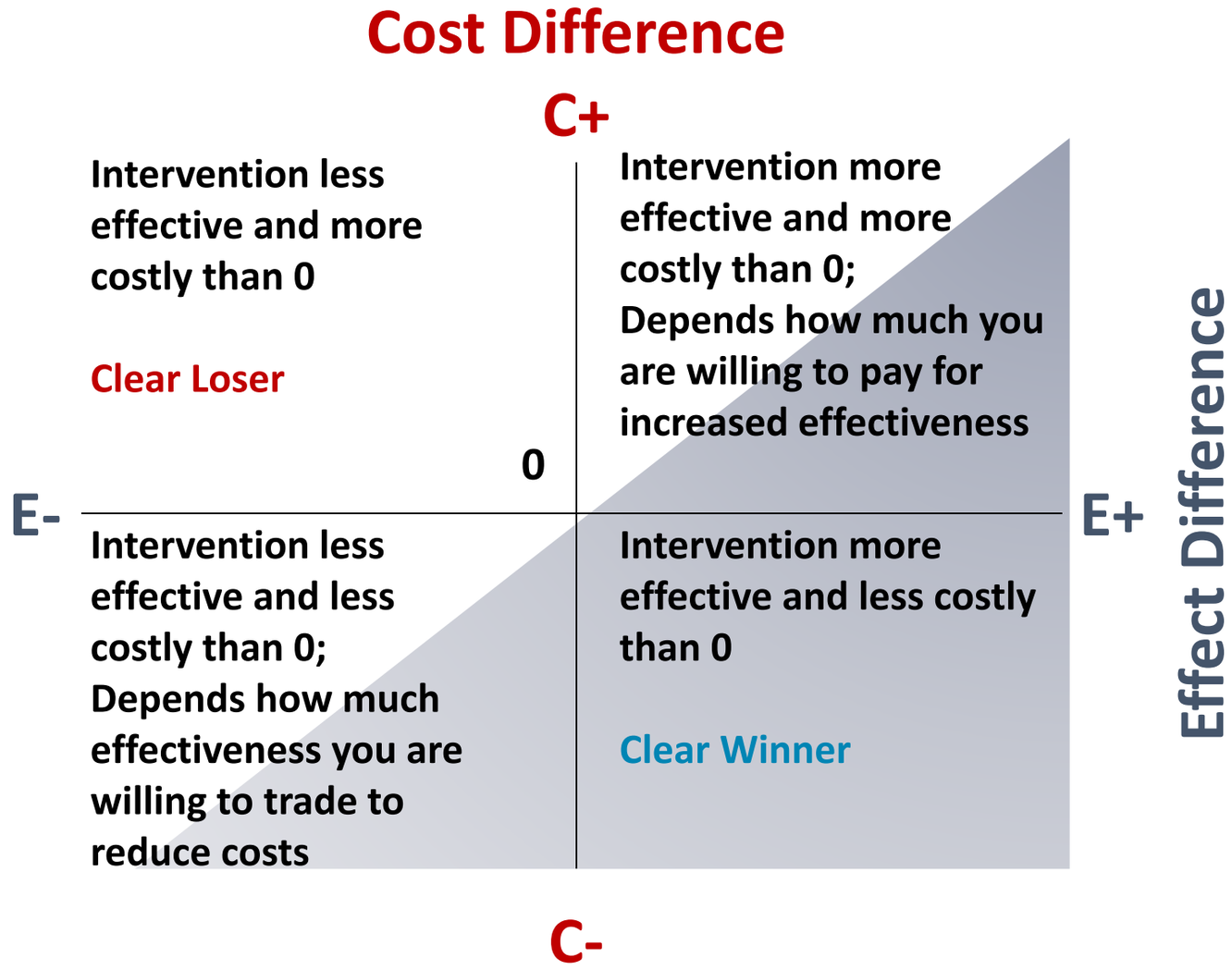
Coordination
- Data management
- Integrated IT

Case Management
- Efforts to increase patient ownership of their care

Patient Access Support Programs
- Patient assistance
- Copay coupons

Value = Cost Effectiveness

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



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

Tier 1 Generic	Tier 2 Preferred	Tier 3 Non-preferred	Tier 4 Specialty
$	$$	$$$	$$$$
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**

2018 Aetna Pharmacy Drug Guide. Formulary Navigator. https://fm.formularynavigator.com/FBO/41/premier_pdf.pdf. Published September 2018. Accessed September 2018.

Formulary Design Example

Pharmacy Benefit		
Tier	**Drug**	**Cost**
Preferred generic		$5
Non-preferred generic		$10
Preferred brand		$50
Non-preferred brand		$100
Preferred specialty		10%
Non-preferred specialty		20%

Medical Benefit		
Tier	**Drug**	**Cost**
Non-specialty		NA
Preferred specialty		10%
Non-preferred specialty		20%

Traditional Versus Potential Value-based Contracting

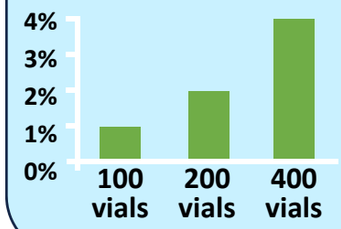
- Value-based contracts ensure the use of medication is leading to an offset in hospitalization/ emergency room utilization and other medical costs associated with poor asthma control

Traditional Contracting

Flat, Volume or Share-Based

Concessions may depend on volume or share

Rebate %s for Purchased Brand A



ILLUSTRATIVE

Value-Based Contracting

Indication-Based

Rebate specific to an indication

Regimen-Based

Rebate paid when two products used in combination

"Outcomes" Based

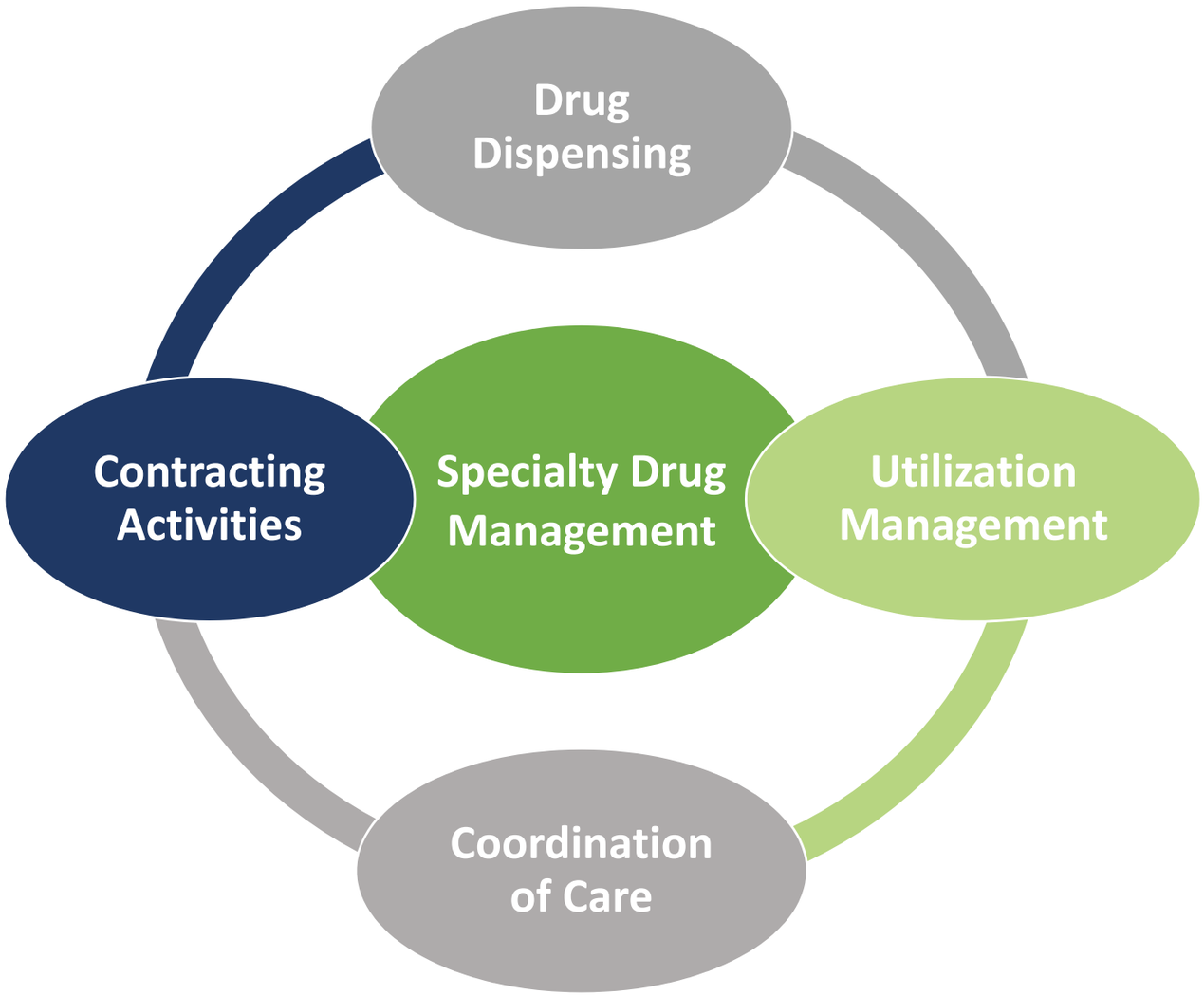
Concessions depend on how 'well' the drug works for a patient/cohort

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

Increasing Data & Complexity

Long G, Mortimer R, Sanzenbacher G. *J Med Econ*. 2014;17(12):883-93.

Successful Asthma Pharmacy Management Requires Finding the Appropriate Balance



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Benefit Design (Cost Share) & Formulary

Summary

- 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.

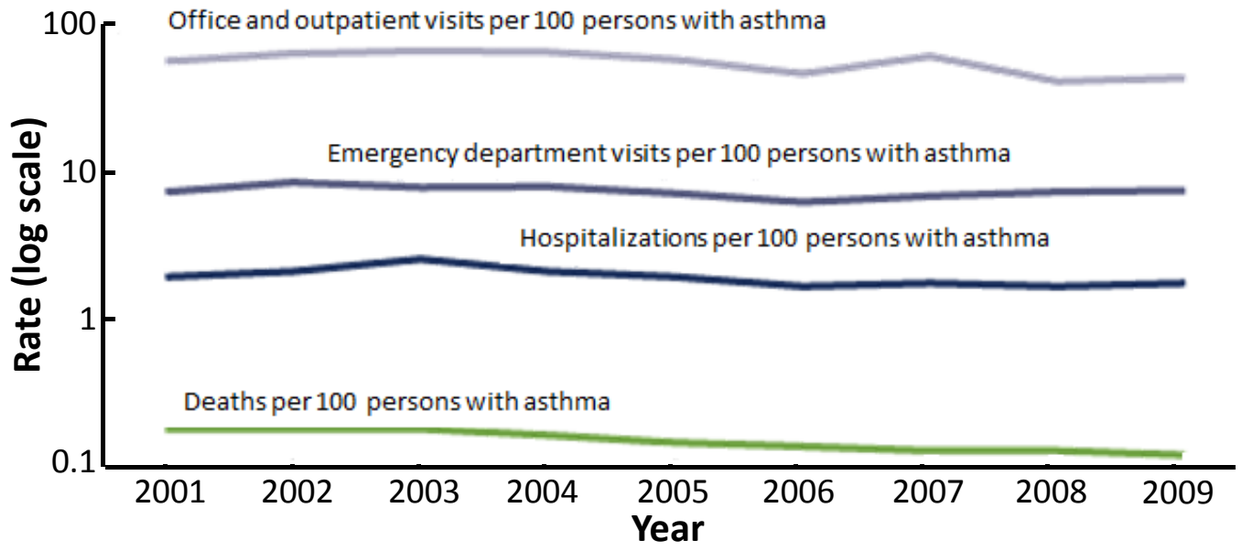
Learning Objective

- 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 has lead 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



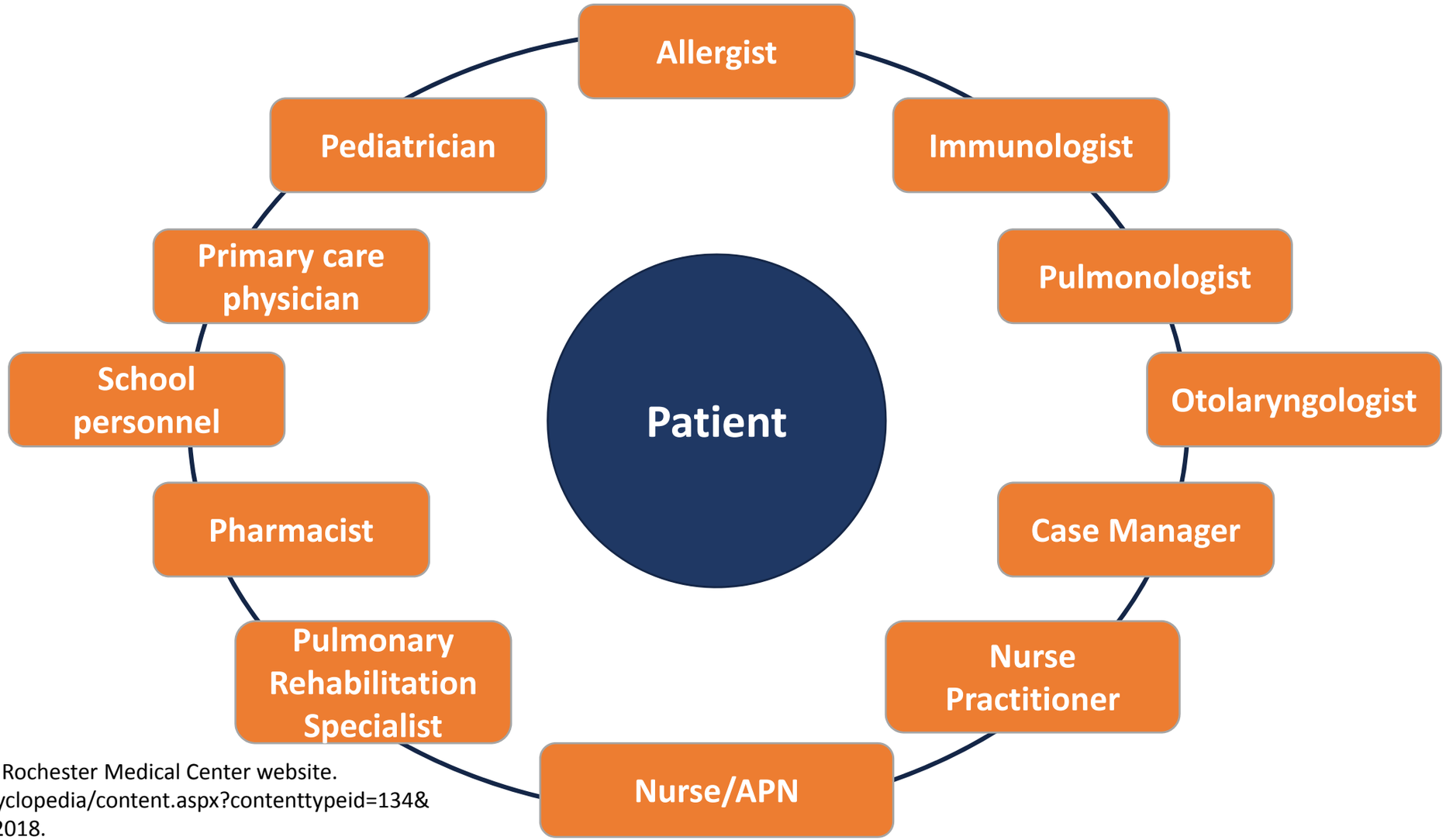
Burke H, Davis J, Evans S, Flower L, Tan A, Kurukulaaratchy RJ. *ERJ Open Res.* 2016;2(3):00039-2016.
Akinbami LJ, Moorman JE, Bailey C, et al. *NCHS Data Brief*. 2012;(94):1-8.

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

Nagakumar P, Thomas H. *Paed Child Health*. 2017;27(7):318-23.

Providing Asthma Care is a Team Sport



Your Asthma Care Team. University of Rochester Medical Center website. https://www.urmc.rochester.edu/encyclopedia/content.aspx?contenttypeid=134&contentid=253. Accessed September 2018.

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?

Ramratnam SK, Bacharier LB, Guilbert TW. *J Allergy Clin Immunol Pract.* 2017;5(4):889-898.

Importance of Regular Follow Up by the Team

- 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

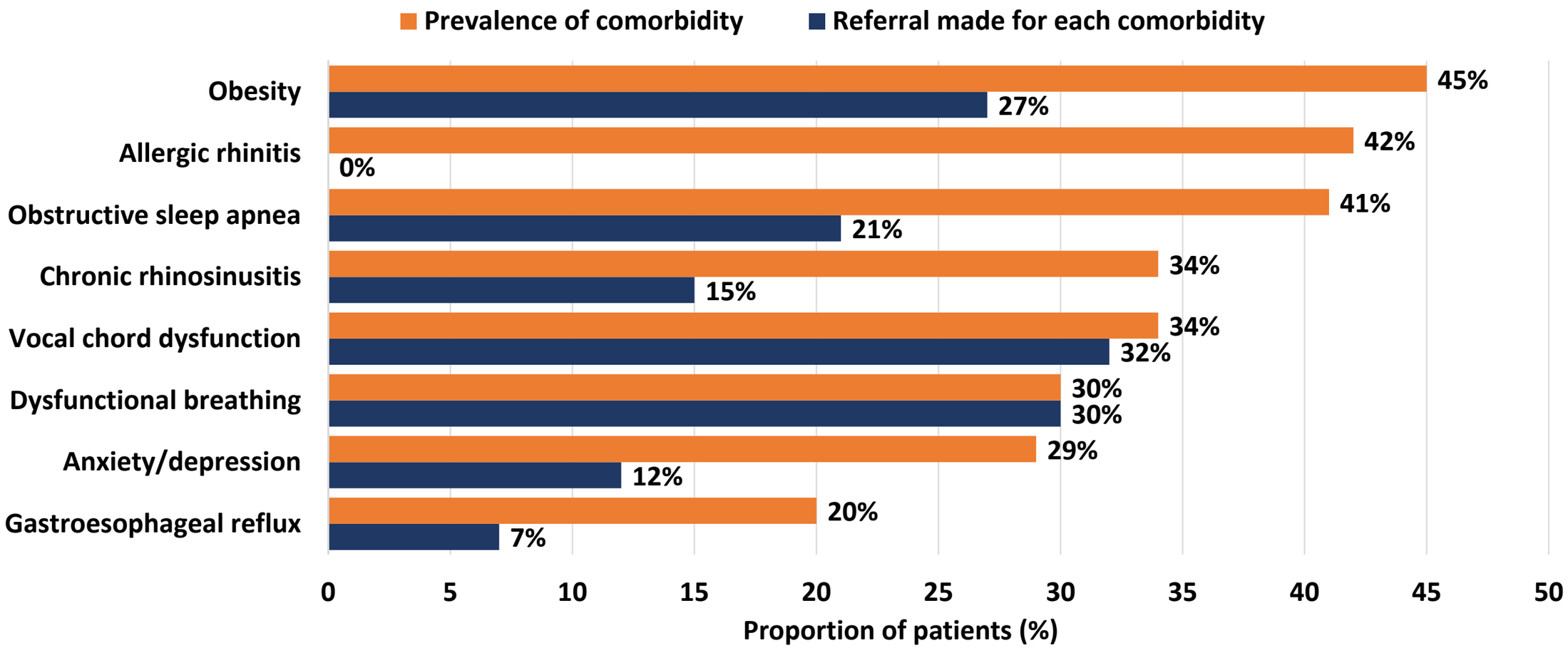
Ramratnam SK, Bacharier LB, Guilbert TW. *J Allergy Clin Immunol Pract.* 2017;5(4):889-898.

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

Price D, Bjermer L, Bergin DA, Martinez R. *J Asthma Allergy*. 2017;10:209-223.

Specialist Referral Increased the Likelihood of Diagnosis of Common Asthma Comorbidities



Tay TR, Lee J, Radhakrishna N, et al. *J Allergy Clin Immunol Pract*. 2017;5(4):956-964.e3.

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

Adapted from: Mechanic R. Will care management improve the value of U.S. health care? The Health Industry Forum website. http://healthforum.brandeis.edu/research/pdfs/CareManagementPrincetonConference.pdf. Accessed September 2018.

Common Elements of Successful Care Management

Success Factor	Description
Communication	• Patient satisfaction increases when the health care team explains information clearly, tries to understand the patient's experience, and provides viable treatment/management options
In-person encounters	• Face-to-face interaction is necessary for effective care management • Care management relying solely on telephone and/or electronic encounters has not been shown to be successful
Training and personnel	• Programs with specially trained care managers working as part of a multidisciplinary team are most successful
Physician involvement	• Placing care managers with physicians in primary care practices may help facilitate physician involvement
Informal caregivers	• 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
Coaching	• Involves teaching patients and their caregivers how to recognize early warning signs of worsening disease

Goodell S, Bodenheimer T, Berry-Millet R. Care management of patients with complex health care needs. Robert Wood Johnson Foundation. https://www.rwjf.org/content/dam/farm/reports/issue_briefs/2009/rwjf49853. Published December 2009. Accessed September 2018.

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

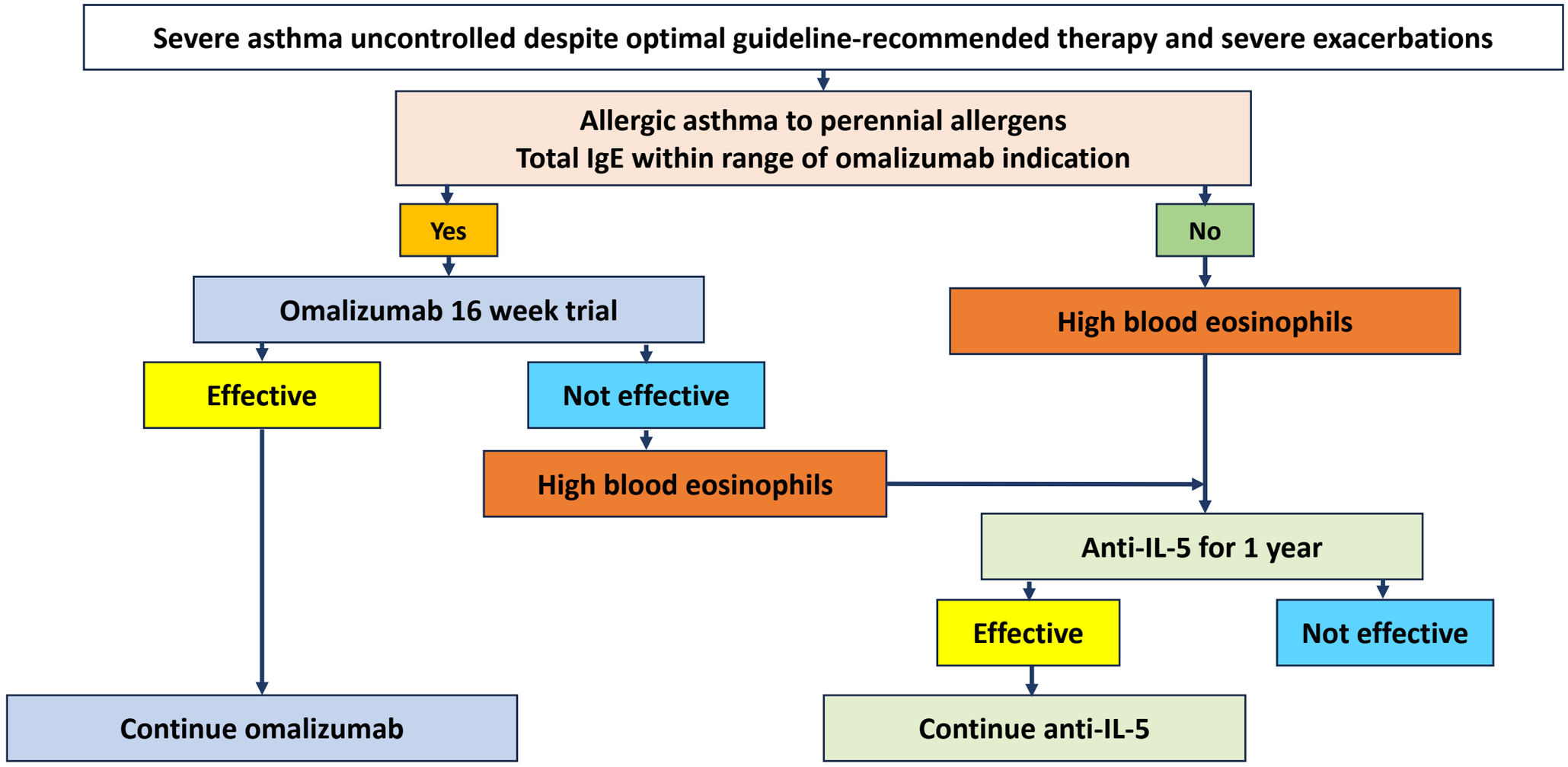
- Review progress toward goals
- Manage therapy interruptions

Patient Education

- Treatment expectations
- Medication administration
- Support programs

Hagerman J, Freed S, Rice G. Specialty pharmacy: a unique and growing industry. American Pharmacists Association website. http://www.pharmacist.com/specialty-pharmacy-unique-and-growing-industry. Published July 1, 2013. Accessed September 2018.

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



Bousquet J, Brusselle G, Buhl R, et al. *Eur Respir J.* 2017;50(6).

Significant Savings Come From Providing Coordinated Care Management

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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

Patient Education	Drug Administration	Drug Dosing	Monitoring

• Therapy expectations
• Dosing
• Adverse events
• Follow up
• Shipping and storage requirements
• Patient access/insurance
	• Train patients and caregivers
	  • Drug preparation
	  • Proper administration techniques
	  • Proper handling, storage, and disposal
		• Individualization of dosing
		• Dosing frequency
			• Adherence support
			• Concurrent medications
			• Adverse events
			• Drug interactions
			• Comorbidities

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 FEV_1 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