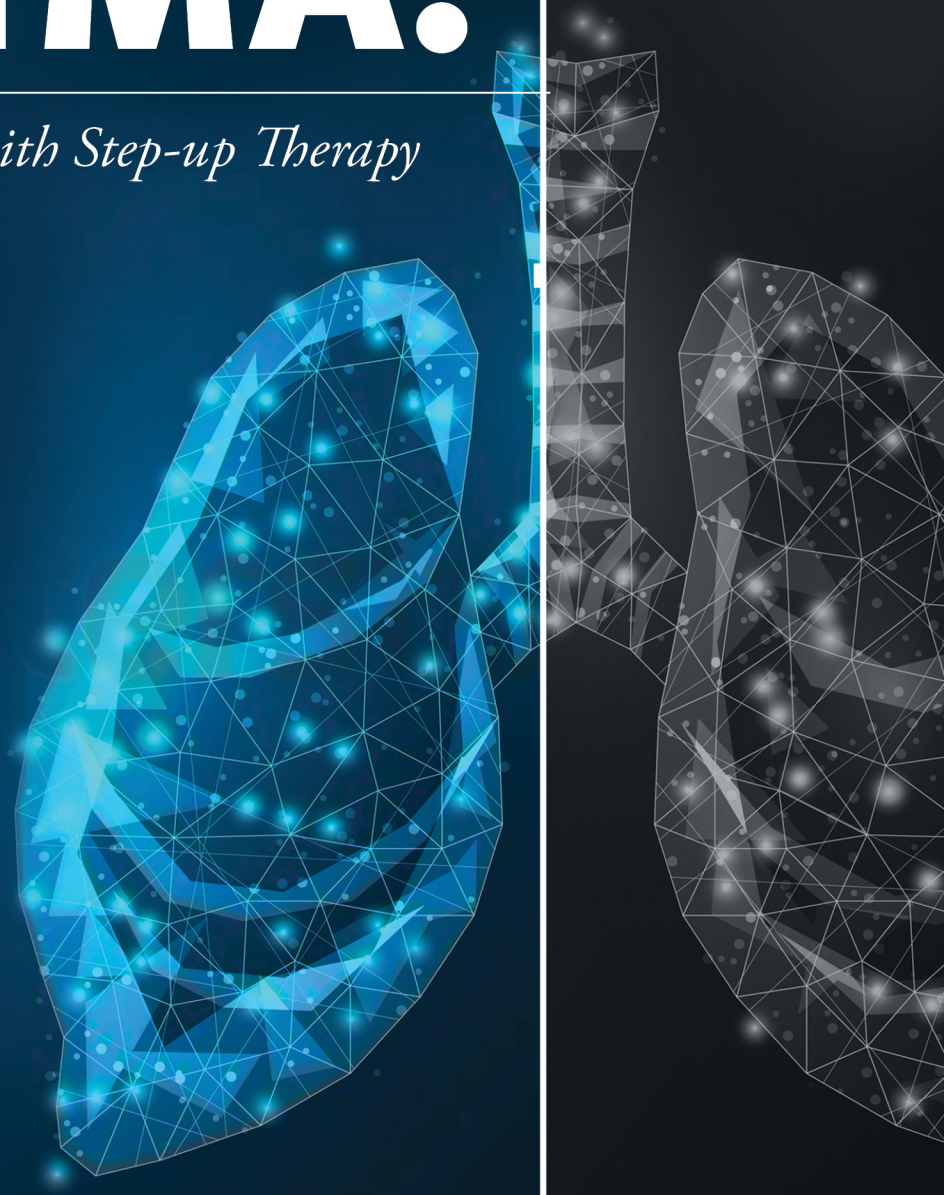
SEVERE ASTHMA:

Reducing Disease Burden with Step-up Therapy



This activity is provided by Med Learning Group.
This activity is co-provided by Ultimate Medical Academy/Complete Conference Management (CCM).
This activity is supported by an independent medical education grant from Regeneron Pharmaceuticals, Inc. and Sanofi Genzyme.

SEVERE ASTHMA:

Reducing Disease Burden with Step-up Therapy

Program Agenda:

I. Introduction to Severe Asthma in Adults and Children
- a. Review of epidemiology and burden of disease
- b. Symptoms and presentation
- c. Burden of disease
- d. The pathogenesis of severe asthma
  - i. Cytokines involved in type 2 inflammation
  - ii. Animated theme – Type 2 inflammation and the pathophysiologic targets of biologics in severe asthma

II. The Phenotypes and Endotypes of Severe Asthma
- a. Using biomarkers to assess the severity of asthma
- b. Identifying phenotypes and endotypes
- c. Animated theme – Using mechanistic features of therapies to identify treatment targets in severe asthma

III. Diagnosis and Management of Severe Asthma
- a. Current guideline recommendations
- b. Differential diagnosis
- c. Goals of therapy
- d. Recognizing the need for treatment intensification

IV. Clinical Trial Data for Available Biologics
- a. Efficacy and safety of:
  - i. Anti-IL-4R agent (dupilumab)
  - ii. Anti-IL-5 and IL-5R agents (mepolizumab, reslizumab, benralizumab)
  - iii. Anti-IgE agent (omalizumab)

V. Personalized Therapy
- a. Identifying patient-specific factors that impact therapy selection
- b. Assessment of quality-of-life
- c. Utilizing biomarkers to select treatment options
- d. Managing common comorbid conditions

VI. Case Study

VII. Conclusions

Severe Asthma: Reducing Disease Burden with Step-up Therapy

PROGRAM CHAIR

Nicola A. Hanania, MD, MS, FRCP(C), FCCP, FACP, FERS, ATSF (PROGRAM CHAIR)
Director, Airway Clinical Research Center
Interim Chief, Pulmonary and Critical Care Medicine
Ben Taub Hospital, Baylor College of Medicine
Houston, TX

SPEAKING FACULTY

Sandra G. Adams, MD
Professor of Medicine, Pulmonary/Critical Care Division, UT Health San Antonio
Staff Physician, South Texas Veterans Health Care System
San Antonio, TX

Theresa W. Guilbert, MD, MS
Director, Asthma Center
Professor, UC Department of Pediatrics
Cincinnati Children's
Cincinnati, OH

Diego J. Maselli, MD, FCCP
Associate Professor of Medicine
Division of Pulmonary Diseases & Critical Care
UT Health
Director, Severe Asthma Program, University Health System
San Antonio, TX

Hassan M. Nasir, DO
Allergy / Immunology Physician
Memorial Healthcare
West Bloomfield, MI

Wanda Phipatanakul, MD, MS
Attending Physician, Division of Immunology
Director, Research Center, Division of Immunology
Professor of Pediatrics, Harvard Medical School
Boston, MA

Michael Wechsler, MD
Professor of Medicine - National Jewish Health
Director, National Jewish Cohen Family Asthma Institute
Denver, CO

PROGRAM OVERVIEW

The case-based virtual live activity will cover the treatment and management of patients with severe asthma.

TARGET AUDIENCE

This CME activity is designed to meet the educational needs of pulmonologists, allergists, primary care physicians, pediatricians, and other health care providers involved in the management of patients with severe uncontrolled asthma.

LEARNING OBJECTIVES

Upon the completion of this program, attendees should be able to:

- Assess disease severity and intensify therapy as needed to manage the symptoms and quality-of-life issues associated with uncontrolled severe asthma in pediatric and adult patients
- Utilize biomarkers and asthma phenotypes to personalize the selection of treatment options for pediatric and adult patients with severe asthma
- Incorporate current treatment recommendations and clinical trial data for the management of severe asthma into clinical practice

ACCREDITATION STATEMENT

Med Learning Group is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. This CME activity was planned and produced in accordance with the ACCME Essentials.

CREDIT DESIGNATION STATEMENT

Med Learning Group will designate each virtual live meeting and simulcast for a maximum of 1.0 AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the live-virtual activity.

NURSING CREDIT INFORMATION

Purpose: This program would be beneficial for nurses involved in the care of patients with severe asthma.
CNE Credits**:** 1.0 ANCC Contact Hour.

CNE ACCREDITATION STATEMENT

Ultimate Medical Academy/CCM is accredited as a provider of nursing continuing professional education development by the American Nurses Credentialing Center's Commission on Accreditation.
Awarded 1.0 contact hour of continuing nursing education of RNs and APNs.

DISCLOSURE POLICY STATEMENT

In accordance with the Accreditation Council for Continuing Medical Education (ACCME) Standards for Commercial Support, educational programs sponsored by Med Learning Group must demonstrate balance, independence, objectivity, and scientific rigor. All faculty, authors, editors, staff, and planning committee members participating in an MLG-sponsored activity are required to disclose any relevant financial interest or other relationship with the manufacturer(s) of any commercial product(s) and/or provider(s) of commercial services that are discussed in an educational activity.

DISCLOSURE OF CONFLICTS OF INTEREST

Faculty Member	Disclosures
Nicola A. Hanania, MD	Discloses that he has received Consulting fees from GSK, Boehringer Ingelheim, Novartis, AstraZeneca, Sanofi, Teva and Amgen. He also has worked on the Speakers Bureau for AstraZeneca and Sanofi, and has received funds for contracted research from GSK, Boehringer Ingelheim, Novartis, Genentech, AstraZeneca, Sanofi and Teva
Sandra G. Adams, MD	Discloses that she provides contracted research with unrestricted educational grants from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKlein, and Sunovion. She is also the President/Founder of WipeDiseases Foundation
Theresa W. Guilbert, MD	Discloses that she has received royalties from the UptoDate preschool wheezing review, fees for advisory board research from Regeneron / Sanofi and AstraZeneca, and has provided contracted research for AstraZeneca, GSK and Sanofi / Regeneron

Diego J. Maselli, MD	Discloses that he has received consulting fees from GSK, AstraZeneca, Regeneron/Sanofi and Amgen. He has also worked on the speakers bureau for GSK, AstraZeneca and Regeneron/Sanofi
Hassan M. Nasir, DO	Discloses that he has worked on the speakers bureau for AstraZeneca and GSK
Wanda Phipatanakul, MD	Has nothing to disclose
Michael Wechsler, MD	Discloses that he has received consulting fees from AstraZeneca, GlaxoSmithKline, Sanofi, Regeneron, Novartis, Genentech, Teva, Boehringer Ingelheim, Equillium and Amgen

CME Content Review

The content of this activity was independently peer reviewed.
The reviewer of this activity has nothing to disclose.

CNE Content Review

The content of this activity was peer reviewed by a nurse reviewer.

Douglas Cox, MSN, MHA, RN
Ultimate Medical Academy/CCM – Lead Nurse Planner

The reviewer of this activity has nothing to disclose

Staff Planners and Managers

The staff, planners, and managers reported the following financial relationships or relationships to products or devices they or their spouse/life partner have with commercial interests related to the content of this CME/CE activity:

Matthew Frese, MBA, General Manager of Med Learning Group, has nothing to disclose.

Christina Gallo, SVP, Educational Development for Med Learning Group, has nothing to disclose.

Douglas Cox, MSN, MHA, RN, UMA/CCM – LNP, has nothing to disclose.
Michael Page, PharmD, RPh, Medical Director for Med Learning Group has nothing to disclose.

Lauren Welch, MA, VP, Accreditation and Outcomes for Med Learning Group, has nothing to disclose.

Marissa Mays-Verman, Program Manager for Med Learning Group, has nothing to disclose.

Daniel DaSilva, Accreditation and Outcomes Coordinator for Med Learning Group, has nothing to disclose.

DISCLOSURE OF UNLABELED USE

Med Learning Group requires that faculty participating in any CME activity disclose to the audience when discussing any unlabeled or investigational use of any commercial product or device not yet approved for use in the United States.

During this lecture, the faculty may mention the use of medications for both FDA-approved and non-approved indications.

METHOD OF PARTICIPATION

There are no fees for participating and receiving CME credit for this live virtual activity. To receive CME/CNE credit participants must:

1. Read the CME/CNE information and faculty disclosures.
2. Participate in the virtual live activity.
3. Complete the online post-test and evaluation.

You will receive your certificate as a downloadable file.

DISCLAIMER

Med Learning Group makes every effort to develop CME activities that are science based.
This activity is designed for educational purposes. Participants have a responsibility to use this information to enhance their professional development in an effort to improve patient outcomes. Conclusions drawn by the participants should be derived from careful consideration of all available scientific information. The participant should use his/her clinical judgment, knowledge, experience, and diagnostic decision making before applying any information, whether provided here or by others, for any professional use.

For CME questions, please contact Med Learning Group at info@medlearninggroup.com

Contact this CME provider at Med Learning Group for privacy and confidentiality policy statement information at http://medlearninggroup.com/privacy-policy/

AMERICANS WITH DISABILITIES ACT

Staff will be glad to assist you with any special needs. Please contact Med Learning Group prior to participating at info@medlearninggroup.com

This activity is provided by Med Learning Group

This activity is co-provided by Ultimate Medical Academy/Complete Conference Management (CCM).

This activity is supported by an independent medical education grant from Regeneron Pharmaceuticals, Inc. and Sanofi Genzyme.

Severe Asthma: Reducing Disease Burden with Step-up Therapy

The BREATHE Initiative

Nicola A. Hanania, MD, MS, FRCP(C), FCCP, FACP, FERS, ATSF
Associate Professor of Medicine,
Director, Airways Clinical Research Center
Baylor College of Medicine
Interim Chief, Section of Pulmonary and Critical Care Medicine
Ben Taub Hospital
Houston, TX

Accreditation

- Med Learning Group is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. This CME activity was planned and produced in accordance with the ACCME Essentials.
- Ultimate Medical Academy/CCM is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission of Accreditation.
- This educational activity is applicable for CME and CNE credit. Please complete the necessary electronic evaluation to receive credit.

Disclosures

- Please see program overview for specific faculty's disclosures
- During this lecture, speaking faculty may mention the use of medications for both FDA-approved and nonapproved indications.

This activity is supported by an independent medical education grant from Regeneron Pharmaceuticals, Inc. and Sanofi Genzyme

Learning Objectives

- Assess disease severity and intensify therapy as needed to manage the symptoms and quality-of-life issues associated with uncontrolled severe asthma in pediatric and adult patients
- Utilize biomarkers and asthma phenotypes to personalize the selection of treatment options for pediatric and adult patients with severe asthma
- Incorporate current treatment recommendations and clinical trial data for the management of severe asthma into clinical practice

Introduction to Severe Asthma in Adults and Children

Burden of Asthma in the United States

~25 million Americans had asthma in 2019

>11 million people reported having ≥1 **asthma exacerbation** in 2018

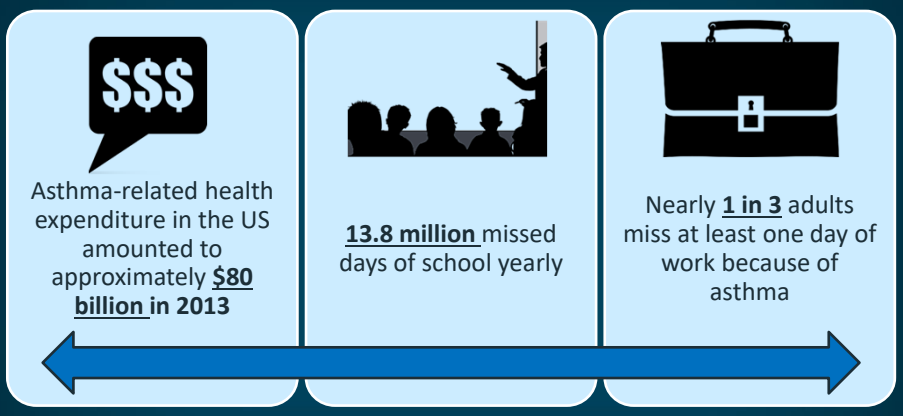
>1.6 million **emergency room visits** in 2018

>178,000 **hospitalizations** in 2018

>3400 **deaths** in 2018

Centers for Disease Control and Prevention (CDC). (www.cdc.gov/asthma/asthmadata.htm). CDC. Asthma attacks (www.cdc.gov/asthma/most_recent_national_asthma_data.htm). CDC. Asthma emergency room visits (www.cdc.gov/asthma/healthcare-use/2018/table_a.html). CDC. Asthma hospitalizations (www.cdc.gov/asthma/healthcare-use/2018/table_b.html). CDC. Asthma deaths (www.cdc.gov/asthma/most_recent_national_asthma_data.htm). All URLs accessed 8/20/2021.

Burden of Asthma in the United States



Nurmagambetov T, et al. *Ann Am Thorac Soc.* 2018;15:348-356. CDC. *MMWR.* 2011;60:547-552. CDC. Asthma statistics fact sheet. (www.cdc.gov/asthma/asthma_stats/AstStatChild_Missed_School_Days.pdf). CDC. Asthma fact sheet. (www.cdc.gov/asthma/impacts_nation/AsthmaFactSheet.pdf)

Multiple Unmet Medical Needs in Asthma

Despite national and international guidelines, asthma control is not optimal with current standard-of-care treatment[1,2]

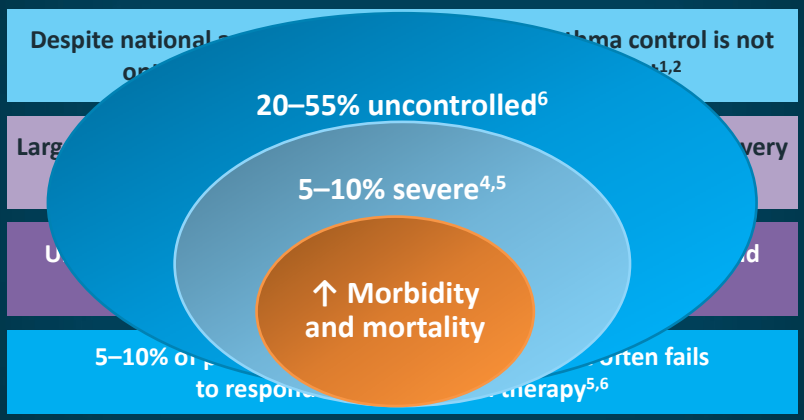
Large number of hospitalizations every year for people with severe asthma

Uncontrolled asthma is associated with significant morbidity and mortality and a high economic burden[3]

5–10% of patients have severe asthma[4,5] that often fails to respond to conventional therapy[5,6]

1. Bateman ED, et al. *Am J Respir Crit Care Med*. 2004;170:836-844. 2. Bateman ED, et al. *Eur Respir J*. 2007;29:56-62. 3. Chipps BE, et al. *J Allergy Clin Immunol*. 2012;130:332-342.e10. 4. Chung KF, et al. *Eur Respir J*. 2014;43:343-373. 5. Holgate ST, Polosa R. *Lancet*. 2006;368:780-793. 6. Partridge MR. *Eur Respir Rev*. 2007;16:67-72.

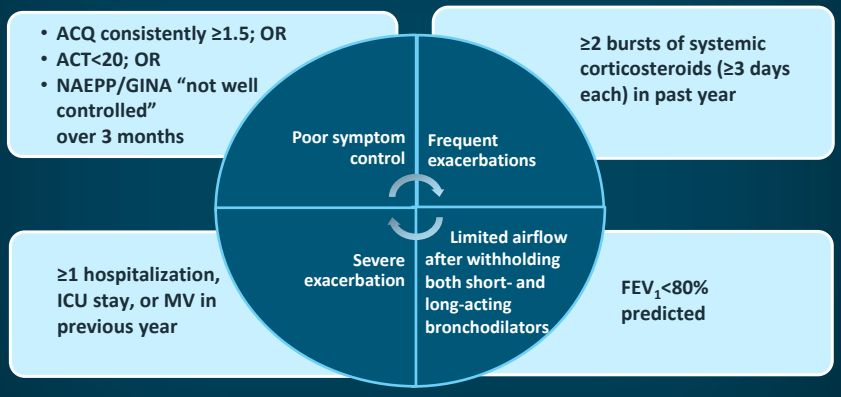
Multiple Unmet Medical Needs in Asthma (continued)



1. Bateman ED, et al. *Am J Respir Crit Care Med*. 2004;170:836-844. 2. Bateman ED, et al. *Eur Respir J*. 2007;29:56-62. 3. Chipps BE, et al. *J Allergy Clin Immunol*. 2012;130:332-342.e10. 4. Chung KF, et al. *Eur Respir J*. 2014;43:343-373. 5. Holgate ST, Polosa R. *Lancet*. 2006;368:780-793. 6. Partridge MR. *Eur Respir Rev*. 2007;16:67-72.

Guidelines (ERS/ATS) Criteria For Identifying Uncontrolled Asthma

Any 1 of following 4 criteria qualifies patient as having uncontrolled asthma



ERS = European Respiratory Society; ATS = American Thoracic Society; ACQ = Asthma Control Questionnaire; ACT = Asthma Control Test; GINA = Global Initiative for Asthma; FEV_1, forced respiratory volume in 1 second; ICU = intensive care unit; MV = mechanical ventilation; NAEPP = National Asthma Education and Prevention Program.

Chung KF, et al. *Eur Respir J*. 2014;43:343-373.

NAEPP: Assessment of Asthma Control
Patients >12 Years of Age and Adults

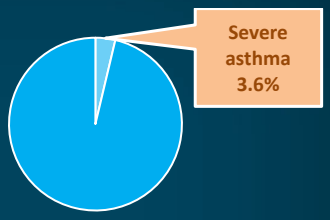
Components of severity		Classification of asthma severity (youths ≥12 of age and adults)		
		Well controlled	Not well controlled	Very poorly controlled
Impairment	Symptoms	≤2 days/week	>2 days/week	Throughout the day
	Nighttime awakenings	≤2x/month	1–3x/week	≥4x/week
	Interference with normal activity	None	Some limitation	Extremely limited
	SABA use for symptom control	≤2 days/week	>2 days/week	Several times per day
	FEV_1 or peak flow	>80% predicted/ personal best	60%–80% predicted/ personal best	<60% predicted/ personal best
	Validated questionnaires • ATAQ • ACQ • ACT	 • 0 • ≤0.75 • ≥20	 • 1–2 • ≥1.5 • 16–19	 • 3–4 • N/A • ≤15
Risk	Exacerbations	0–1/year	≥2/per year	≥2/per year
	Progressive loss of lung function	Evaluation requires long-term follow-up care		
	TRAEs	Medication side effects vary in intensity from none to very troublesome. Intensity levels do not correlate to specific levels of control but should be considered in overall assessment of risk.		

ATAQ = Asthma therapy Assessment Questionnaire; ACQ = Asthma Control Questionnaire; SABA = short-acting $beta_2$-agonist; N/A = not applicable; TRAE = treatment-related adverse event.

Modified from Asthma Care Quick Reference. (www.nhlbi.nih.gov/files/docs/guidelines/asthma_qrg.pdf). Accessed 8/23/2021.

Who Has Severe Asthma?
(continued)

3.6% have severe asthma with high-intensity treatment and poor symptom control despite good adherence and excellent inhaler technique[1,2]

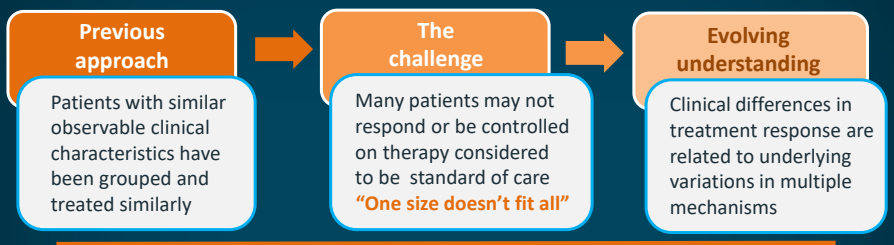


- Estimates of the prevalence of severe asthma vary from 5% to 10% across studies.[3]
- Approximately 2% to 5% of children with asthma have severe disease.[4]

1. GINA report, 2021 (https://ginasthma.org/wp-content/uploads/2021/05/GINA-Main-Report-2021-V2-WMS.pdf). Accessed 8/24/21. 2. Hekking PP, et al. *J Allergy Clin Immunol*. 2015;135:896-902. 3. Chung KF, et al. *Eur Respir J*. 2014;43:343-373. 4. Dharmage SC, et al. *Front Pediatr*. 2019;7:246.

Phenotypes and Endotypes of Severe Asthma

Our Understanding of Asthma Is Changing
Focus Shifting Toward Disease Mechanisms



Heterogeneity in treatment response has inspired discussion of a precision approach to care that tailors treatment to the patient

1. Muraro A, et al. *J Allergy Clin Immunol*. 2016;137:1347-1358. 2. Lötvall J, et al. *J Allergy Clin Immunol*. 2011;127:355-360.

Approach to Asthma Phenotyping: Age

- Age at onset
  - Early onset likely to be atopic/allergic
  - Later onset more heterogeneous

Holgate ST, et al. *Nat Rev Dis Primers*. 2015;1:15025.

Approach to Asthma Phenotyping: + Exposure

- Age at onset
  - Early onset likely to be atopic/allergic
  - Later onset more heterogeneous
- Patient exposures/triggers and host characteristics
  - Age
  - Smoking, other exposures
  - BMI
  - Infection triggers

BMI = body mass index.

Holgate ST, et al. *Nat Rev Dis Primers*. 2015;1:15025.

Approach to Asthma Phenotyping: + Course

- Age at onset
  - Early onset likely to be atopic/allergic
  - Later onset more heterogeneous
- Patient exposures/triggers and host characteristics
  - Age
  - Smoking, other exposures
  - BMI
  - Infection triggers
- Asthma course
  - Frequent exacerbation

Holgate ST, et al. *Nat Rev Dis Primers*. 2015;1:15025.

Approach to Asthma Phenotyping: + Biomarkers

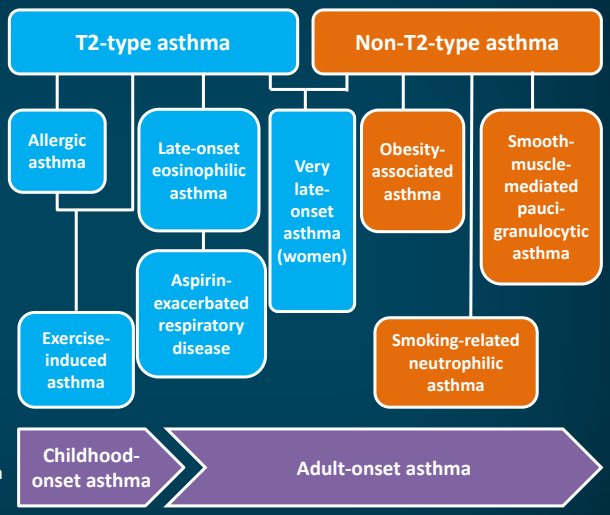
- Age at onset
  - Early onset likely to be atopic/allergic
  - Later onset more heterogeneous
- Patient exposures/triggers and host characteristics
  - Age
  - Smoking, other exposures
  - BMI
  - Infection triggers
- Asthma course
  - Frequent exacerbation
- Biomarkers
  - T2-inflammation
    - Sputum/blood eosinophils
    - FeNO
    - IgE/atopy
  - Absence of T2-inflammation
    - Blood/sputum neutrophils

FeNO = fractional exhaled nitric oxide; IgE = immunoglobulin E.

Holgate ST, et al. *Nat Rev Dis Primers*. 2015;1:15025.

Approach to Asthma Phenotyping

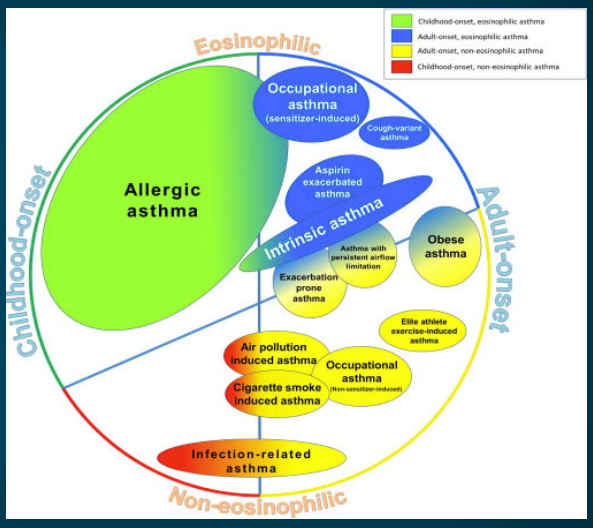
- Age at onset
  - Early onset likely to be atopic/allergic
  - Later onset more heterogeneous
- Patient exposures/triggers and host characteristics
  - Age
  - Smoking, other exposures
  - BMI
  - Infection triggers
- Asthma course
  - Frequent exacerbation
- Biomarkers
  - T2-inflammation
    - Sputum/blood eosinophils
    - FeNO
    - IgE/atopy
  - Absence of T2-inflammation
    - Blood/sputum neutrophils



Holgate ST, et al. *Nat Rev Dis Primers*. 2015;1:15025.

Approach to Asthma Phenotyping

- Age at onset
  - Early onset likely to be atopic/allergic
  - Later onset more heterogeneous
- Patient exposures/triggers and host characteristics
  - Age
  - Smoking, other exposures
  - BMI
  - Infection triggers
- Asthma course
  - Frequent exacerbation
- Biomarkers
  - T2-inflammation
    - Sputum/blood eosinophils
    - FeNO
    - IgE/atopy
  - Absence of T2-inflammation
    - Blood/sputum neutrophils



Holgate ST, et al. *Nat Rev Dis Primers*. 2015;1:15025.

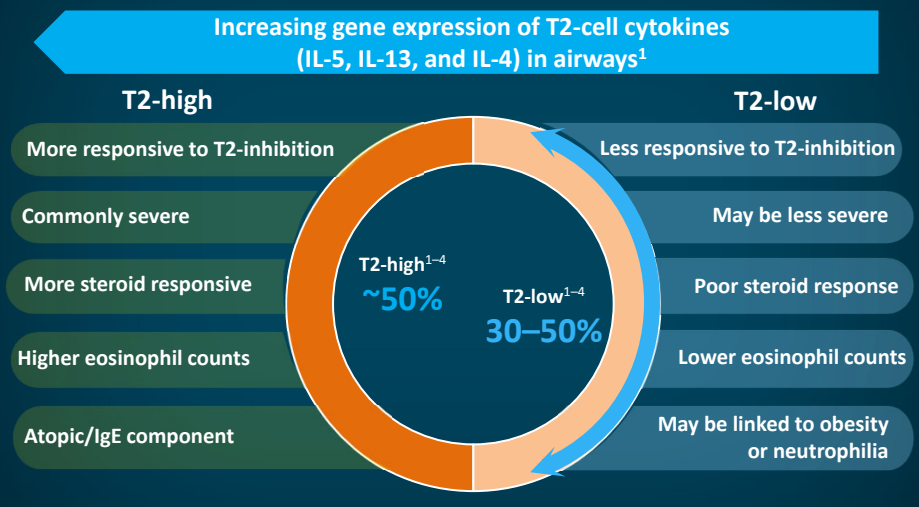
Biomarkers of Type 2 Inflammation in Asthma

Biomarker	T2 Levels			Limitations
	Low	Medium	High	
Total IgE (IU)	<30	31–149	>150	Affected by age; poor predictor of response rate to biologic therapy. Does not correlate well with asthma severity. Elevations are not specific to asthma (also elevated in atopic dermatitis, allergic bronchopulmonary aspergillosis, etc.)
Blood eosinophils (cells/µL)	<150	151–399	>400	Affected by weight, allergen exposure, steroids, and infection; optimal cutoff value varies by therapy. Elevations are not specific to asthma (also in allergic rhinitis, drug reactions, etc.)
Sputum eosinophils	—	—	≥3%	Semi-invasive; confined to research settings
FeNO (ppb)	<25	26–49	>50	Affected by age, weight, sex, smoking, and respiratory infections
Investigational				
Serum periostin (ng/mL)	—	—	≥50	Unknown competing causes of systemic increases; unclear differences between asthma and healthy subjects; studied only in context of anti-IL-13 and anti-IgE therapy
DPP-4	—	—	>Median	One of the newer biomarkers, lacks data from confirmatory studies in asthma

DPP-4 = dipeptidyl peptidase-4; T2 = T-helper cell type 2; ppb = parts per billion.

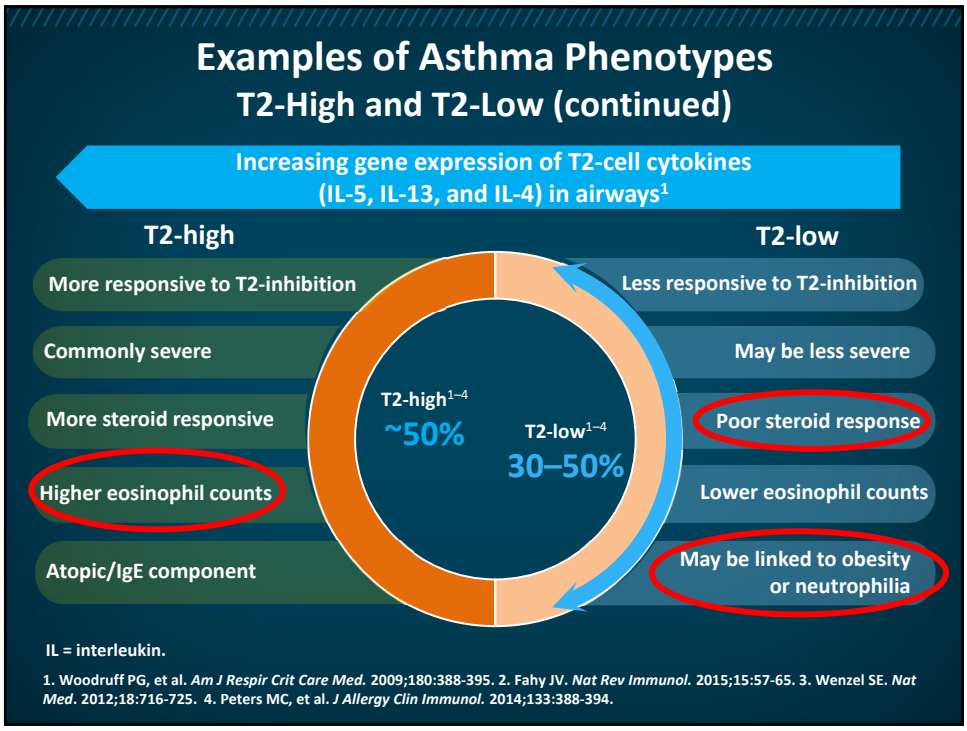
Parulekar AD, et al. *Curr Opin Pulm Med*. 2016;22:59-68. Peters MC, et al. *Curr Allergy Asthma Rep*. 2016;16:71.

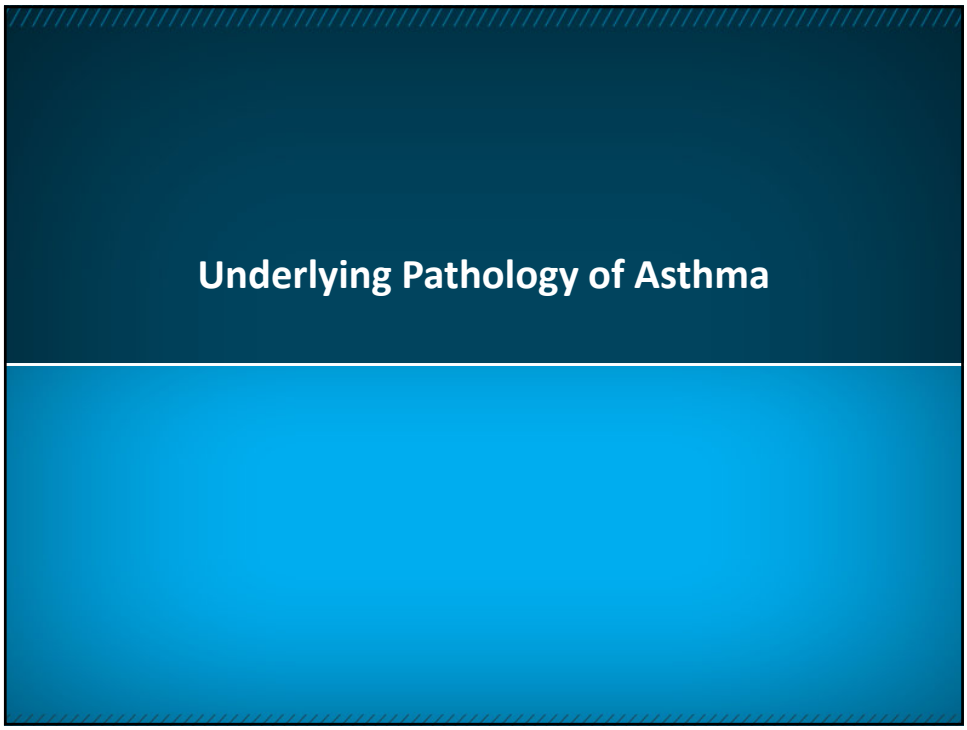
Examples of Asthma Phenotypes
T2-High and T2-Low



IL = interleukin.

1. Woodruff PG, et al. *Am J Respir Crit Care Med.* 2009;180:388-395. 2. Fahy JV. *Nat Rev Immunol.* 2015;15:57-65. 3. Wenzel SE. *Nat Med*. 2012;18:716-725. 4. Peters MC, et al. *J Allergy Clin Immunol.* 2014;133:388-394.


Examples of Asthma Phenotypes
T2-High and T2-Low (continued)
Increasing gene expression of T2-cell cytokines
(IL-5, IL-13, and IL-4) in airways[1]
T2-high
T2-low
More responsive to T2-inhibition
Less responsive to T2-inhibition
Commonly severe
May be less severe
More steroid responsive
Poor steroid response
Higher eosinophil counts
Lower eosinophil counts
Atopic/IgE component
May be linked to obesity or neutrophilia
T2-high[1–4]
~50%
T2-low[1–4]
30–50%
IL = interleukin.
1. Woodruff PG, et al. Am J Respir Crit Care Med. 2009;180:388-395. 2. Fahy JV. Nat Rev Immunol. 2015;15:57-65. 3. Wenzel SE. Nat Med. 2012;18:716-725. 4. Peters MC, et al. J Allergy Clin Immunol. 2014;133:388-394.

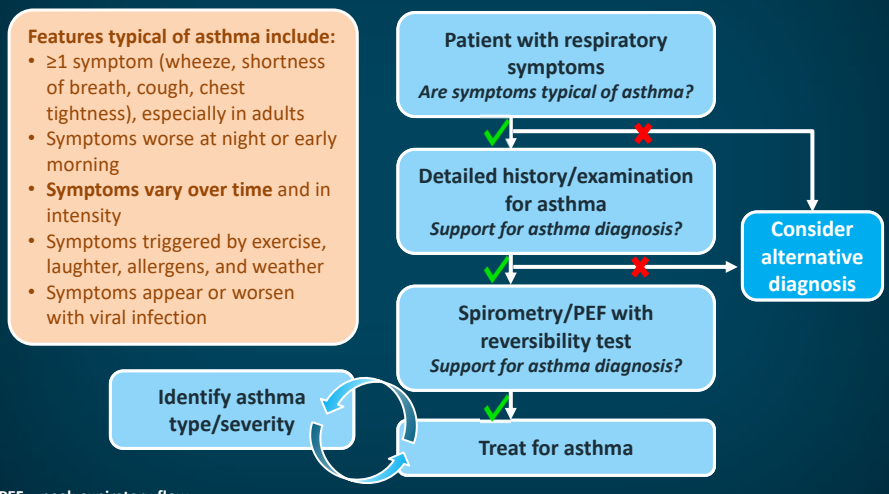

Underlying Pathology of Asthma

Please scan below to view an animation discussing the underlying pathology of Asthma

https://youtu.be/c_kYILD0wKU

Diagnosis and Management of Severe Asthma

Diagnosis of Asthma Is Based on Characteristic Pattern of Respiratory Symptoms

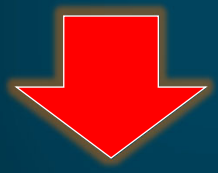


PEF = peak expiratory flow.

Modified from GINA report, 2021 (https://ginasthma.org/wp-content/uploads/2021/05/GINA-Main-Report-2021-V2-WMS.pdf). Accessed 8/24/21.

Goals of Asthma Management: Reduce Current Impairment and Future Risk

Improve
- Symptom control (daytime symptoms, night-time awakening)
- Management of comorbidities
- Lung function



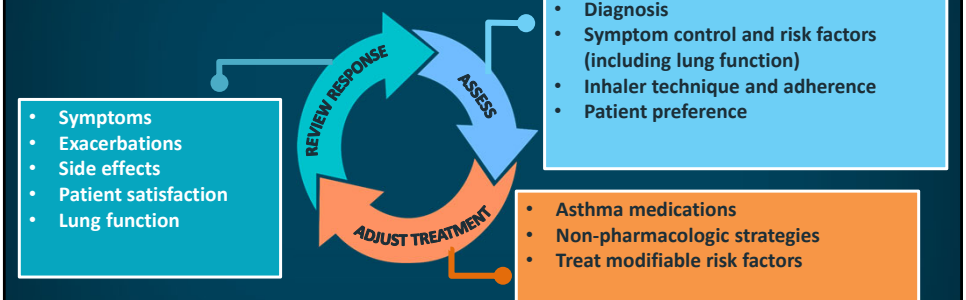
Reduce
- Exacerbations
- Rescue medication
- Treatment related AEs
- Emergency visits

Effective asthma management requires a partnership between patient and healthcare provider to define and achieve treatment goals

AEs = adverse events.

Modified from GINA report, 2021 (https://ginasthma.org/wp-content/uploads/2021/05/GINA-Main-Report-2021-V2-WMS.pdf). Accessed 8/24/21.

GINA Recommends a Control-Based Asthma Management Strategy—A Continuous Process



Modified from GINA report, 2021 (https://ginasthma.org/wp-content/uploads/2021/05/GINA-Main-Report-2021-V2-WMS.pdf). Accessed 8/24/21.

Common Causes of Uncontrolled Asthma

Nonadherence to therapy[1]

Incorrect inhaler technique[1]

Comorbidities and psychosocial factors[1]

Ongoing exposure to asthma triggers[1]

1. GINA report, 2021 (https://ginasthma.org/wp-content/uploads/2021/05/GINA-Main-Report-2021-V2-WMS.pdf). Accessed 8/24/2021. 2. Bourdin A, et al. *Clin Exp Allergy*. 2012;42:1566-1574.

Common Causes of Uncontrolled Asthma (continued)

Nonadherence to therapy[1]

Incorrect inhaler technique[1]

Comorbidities and psychosocial factors[1]

Ongoing exposure to asthma triggers[1]

Understanding a patient's adherence to therapy is always a prerequisite when assessing severe asthma[2]

1. GINA report, 2021 (https://ginasthma.org/wp-content/uploads/2021/05/GINA-Main-Report-2021-V2-WMS.pdf). Accessed 8/24/2021. 2. Bourdin A, et al. *Clin Exp Allergy*. 2012;42:1566-1574.

Managing Allergic and Non-Allergic Triggers of Asthma

Common allergic triggers


House dust mite


Pollen


Mold


Ragweed


Cockroach


Pet dander

Common non-allergic triggers


Ozone


Cigarette smoke


Exercise


Diesel particles


Respiratory infection (viral or bacterial)


Cold air

<u>Diagnostic testing</u>

Allergy skin tests

Blood tests (RAST)—allergen-specific IgE

RAST = radioallergosorbent test.

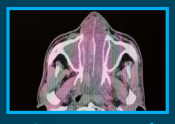
NAEPP. *J Allergy Clin Immunol*. 2007;120(5 suppl):S94-S138. American College of Allergy, Asthma & Immunology (ACAAI) (https://acaai.org/asthma/types-asthma/allergic-asthma) and (https://acaai.org/asthma/types-asthma/nonallergic-asthma). Accessed 8/24/2021.

Treating the Whole Patient
Comorbidities Commonly Associated With Asthma


Atopic dermatitis


GERD


Vocal cord dysfunction


Rhinosinusitis/ nasal polyposis


OSA


Obesity

Comorbidities

- More health-care utilization
- Increased frequency/ severity of exacerbations
- More severe asthma
- Increased systemic inflammation
- Greater reductions in HRQoL

Identification and treatment of comorbid conditions is critical

GERD = gastroesophageal reflux disease; OSA = obstructive sleep apnea; HRQoL = health-related quality of life.

Boulet LP. *Eur Respir J*. 2009;33:897-906. Galli E, et al. *Allergy Asthma Proc*. 2007;28:540-543. Porsbjerg C, Menzies-Gow, A. *Respirology*. 2017;22:651-661. Sundh J, et al. *Respir Med*. 2017;132:154-160.

Proper Inhaler Technique

Poor inhaler technique leads to:

- Poor asthma control
- Increased risk of exacerbations
- Increased adverse effects

- Up to 70–80% of patients are unable to use their inhaler correctly
- Many patients received inadequate education on inhaler technique
- Many healthcare providers are unable to demonstrate how to use inhalers they prescribe
- Patients' inhaler technique has been shown to deteriorate over time
- Assess proper inhaler technique at multiple visits and prior to concluding that a given therapy is ineffective

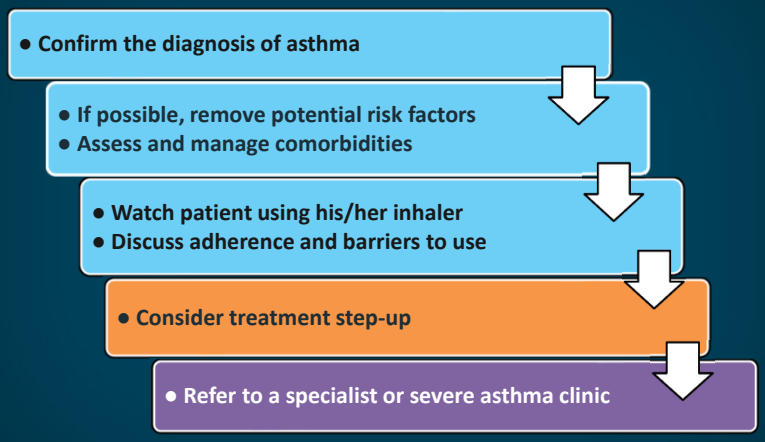
GINA report, 2021 (https://ginasthma.org/wp-content/uploads/2021/05/GINA-Main-Report-2021-V2-WMS.pdf). Accessed 8/24/2021.

Keeping the Team Involved—
Provide Hands-on Inhaler Skills Training: the 4 Cs

Choose
• Choose an appropriate device before prescribing. Consider medication options, arthritis, patient skills, and cost. For ICS by pressurized metered-dose inhaler (pMDI), prescribe a spacer or valved holding chamber • Avoid multiple different inhaler types if possible
Check
• Check technique at every opportunity—"*Can you show me how you use your inhaler at present?*" • Identify errors with a device-specific checklist
Correct
• Give a physical demonstration to show how to use the inhaler correctly • Check again (up to 2–3 times) • Re-check inhaler technique frequently, as errors often recur within 4–6 weeks
Confirm
• Can you demonstrate correct technique for the inhalers you prescribe? • Brief inhaler-technique training improves asthma control

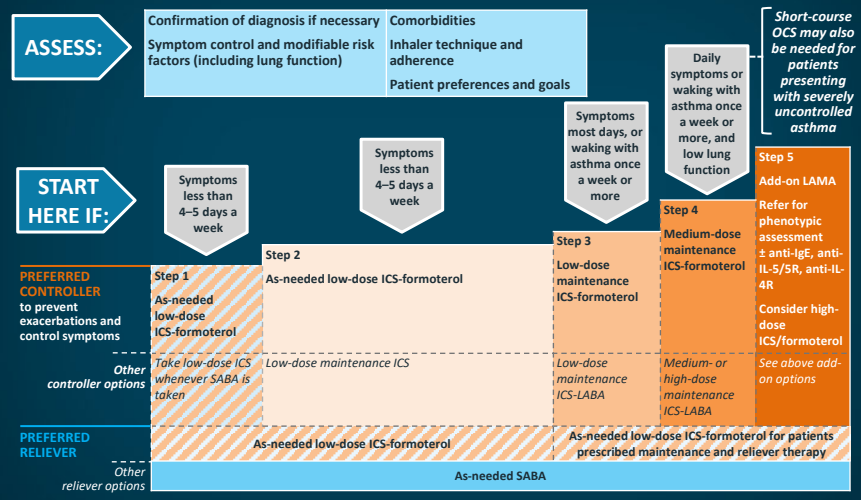
GINA report, 2021 (https://ginasthma.org/wp-content/uploads/2021/05/GINA-Main-Report-2021-V2-WMS.pdf). Accessed 8/24/2021.

GINA: Control-Based Asthma Management Strategy: General Approach



GINA 2021. (https://ginasthma.org/wp-content/uploads/2021/05/GINA-Main-Report-2021-V2-WMS.pdf). Accessed 8/24/2021.

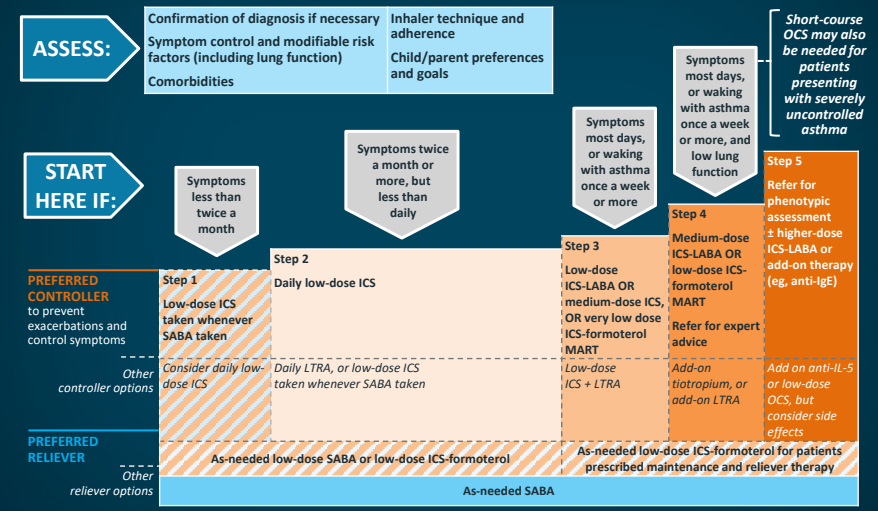
Selecting Initial Controller Treatment in Adults and Adolescents With Diagnosis of Asthma



HDM SLIT = house dust mite sublingual immunotherapy; LAMA = long-acting muscarinic antagonist; LTRA = leukotriene receptor antagonist.

GINA report, 2021 (https://ginasthma.org/wp-content/uploads/2021/05/GINA-Main-Report-2021-V2-WMS.pdf). Accessed 8/24/2021.

Selecting Initial Controller Treatment in Children Aged 6–11 Years With Diagnosis of Asthma



MART = maintenance and reliever therapy.

GINA report, 2021 (https://ginasthma.org/wp-content/uploads/2021/05/GINA-Main-Report-2021-V2-WMS.pdf). Accessed 8/24/2021.

Targeted Therapies for Severe Asthma

Biologic	Target	Key trials	Administration			Approved or studied in other diseases
			Age	Route	Frequency	
Omalizumab[1]	IgE	Study 008/009/ALTO	≥6 years	SC	Q2W/Q4W	Urticaria; nasal polyps; Food allergy
Mepolizumab[2]	IL-5	MENSA/SIRIUS	≥6 years	SC	Q4W	EGPA; HES; CRwNP; COPD
Reslizumab[3]	IL-5	BREATH trials	≥18 years	IV	Q4W	Sinusitis; eosinophilic esophagitis
Benralizumab[4]	IL-5 receptor	SIROCCO/CALIMA/ ZONDA	≥12 years	SC	Q4W/Q8W	COPD
Dupilumab[5]	IL-4 receptor†	LIBERTY QUEST LIBERTY VENTURE SOLO1/SOLO2 CHRONOS	≥12 years	SC	Q2W	Atopic dermatitis, CRwNP; eosinophilic esophagitis; peanut allergy; grass allergy; COPD
Tezepelumab[6]*	TSLP	PATHWAY	≥18	SC	Q2W/Q4W	Atopic dermatitis

*Investigational - phase 3 studies ongoing; †Inhibits IL-4 and IL-13 signaling pathways .

IV = intravenous; Q2W = every 2 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks; QD = once daily; SC = subcutaneous; EGPA = eosinophilic granulomatosis with polyangiitis; HES = hypereosinophilic syndrome; CRwNP = chronic rhinosinusitis with nasal polyps; COPD = chronic obstructive pulmonary disease; TSLP = thymic stromal lymphopoietin.

1. Omalizumab (Xolair®) prescribing information (PI), 2021 (www.gene.com/download/pdf/xolair_prescribing.pdf). 2. Mepolizumab (Nucala®) PI, 2021 (https://gskpro.com/content/dam/global/hcpportal/en_US/ Prescribing_Information/Nucala/pdf/NUCALA-PI-PIL-IFU-COMBINED.PDF). 3. Reslizumab (Cinqair®) PI, 2020 (www.cinqair.com/globalassets/cinqair/prescribinginformation.pdf). 4. Benralizumab (Fasenra®) PI, 2021 (www.azpicentral.com/fasenra/fasenra.pdf). 5. Dupilumab (Dupixent) PI, 2021 (www.regeneron. com/sites/default/files/Dupixent_FPI.pdf). 6. Corren J, et al. *N Engl J Med.* 2017;377:936-946. URLs accessed 8/2021.

Current Inflammatory Targets; Monoclonal Antibodies for IgE, IL-4, IL-5, and IL-13

Please scan below to view an animation discussing the Current Inflammatory Targets; Monoclonal Antibodies for IgE, IL-4, IL-5, and IL-13

https://youtu.be/BIZGM6e0MKg

Clinical Trial Data for Available Biologics

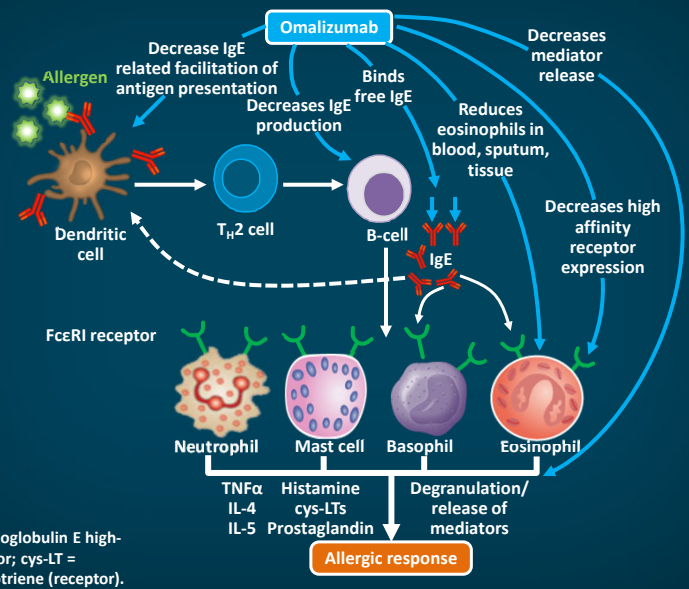
Case 1: Brittany

- 32-year-old woman with a history of eczema and childhood asthma, improved and not requiring meds in her teenage years, but symptoms returned and have been present since her mid-20s
  - Using rescue inhaler 3–4 times/day for cough/wheezing/shortness of breath
  - No nighttime awakenings
- Taking ICS/LABA and LAMA (technique good on assessment)
  - Leukotriene-receptor modifier; antihistamines and nasal steroid for allergies
- Already addressed/completed all environmental control measures
- Labs
  - FEV_1 = 62% (postbronchodilator) with 8% improvement
  - IgE = 390 IU/mL
  - FeNO = 28 ppb
  - Perennial allergen testing: + mold, oak, ragweed, cat dander, and dust mites
  - CBC normal, absolute eosinophil count of 100 cells/microliter

Which biologic(s) would be most appropriate for Brittany?

CBC = complete blood count.

Targeting IgE



FcεRI = immunoglobulin E high-affinity receptor; cys-LT = cysteinyl leukotriene (receptor).

Modified from Edwards M, et al. *Eur Res J*. 2017;49:1602448. Holgate S, et al. *Resp Med*. 2009;103:1098-113.

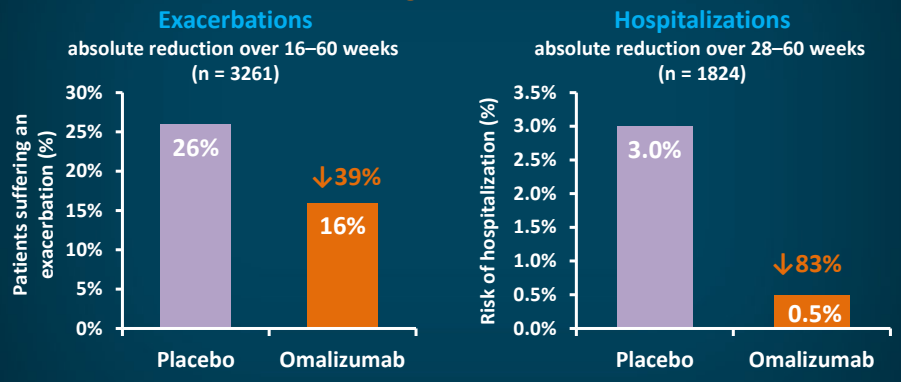
Omalizumab

- For patients with asthma uncontrolled despite high-dose ICS and LABA and who are adherent to therapy and demonstrate good inhaler technique
- Mechanism of action
  - Inhibits serum IgE by binding to its constant region, preventing interaction with high- and low-affinity IgE receptors
- Efficacy
  - **Reduces free serum IgE by >95%**
  - Results in reduction of receptor density on the mast cells or basophils, leading to decreased allergen-stimulated mediator response
- Administration
  - Always done in healthcare setting by trained healthcare staff

Al Said A, et al. *Ther Adv Chronic Dis*. 2017;8:31-45.

Efficacy of Omalizumab (anti-IgE) in Moderate-to-Severe Allergic Asthma (Cochrane Review)

Meta-analysis of 25 studies (N = 6382) comparing omalizumab to PBO through June 2013

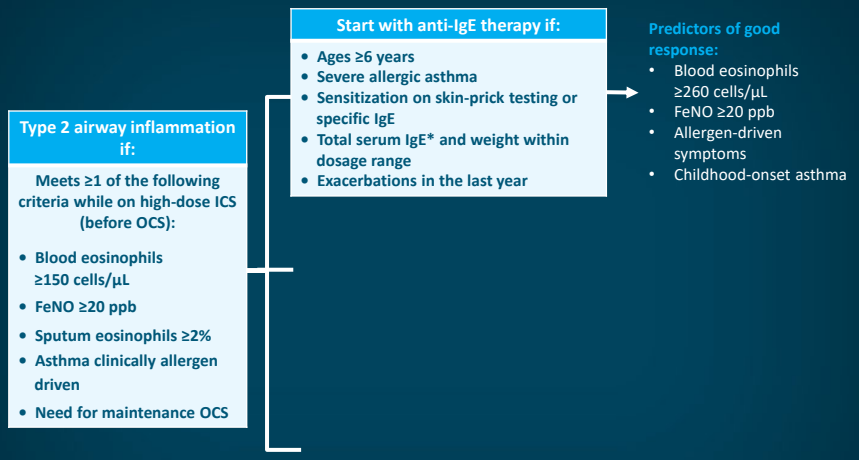


Omalizumab-treated patients also significantly more likely to completely withdraw ICS

PBO = placebo.

Normansell R, et al. *Cochrane Database Syst Rev*. 2014;1:CD003559.

GINA: Identifying Patients and Selecting Biologics



*Baseline IgE levels do not predict likelihood of response.

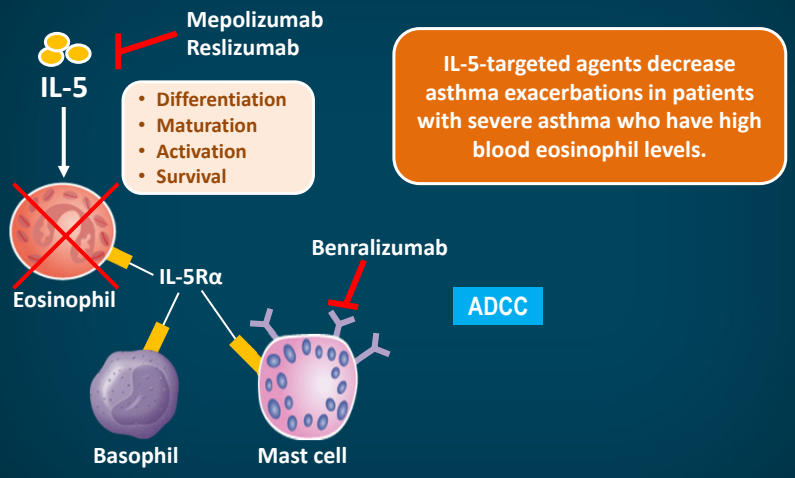
GINA 2019. Difficult-to-treat severe asthma in adolescents and adult patients: diagnosis and management (https://ginasthma.org/wp-content/uploads/2019/04/GINA-Severe-asthma-Pocket-Guide-v2.0-wms-1.pdf). Accessed 8/24/2021.

Case 2: Brian

- 56-year-old man with adult-onset asthma diagnosed 5 years ago
- Presence of nasal polyps, no significant allergy symptoms, no GERD
- Intermittent dyspnea and wheezing with nonproductive cough, worse over the last 6–9 months
  - No changes at home: no pets; environmental measures controlled at home
- Compliant with ICS/LABA/LAMA and good inhaler technique
- Labs
  - IgE = 12 IU/mL
  - FeNO = 22 ppb
  - Allergens negative
  - CBC with absolute eosinophil count of 400 cells/microliter

Which biologic(s) would be most appropriate for Brian?

Targeting IL-5



ADCC = antibody-dependent cell-mediated cytotoxicity.

Ortega HG, et al. *N Engl J Med*. 2014;371:1198-1207. Castro M, et al. *Lancet Respir Med*. 2015;3:355-366.

Mepolizumab

- Mechanism of action
  - Selectively inhibits eosinophilic inflammation
  - Reduces the number of eosinophils in sputum and blood
- Efficacy
  - May lead to **reduction in exacerbations and need for treatment with systemic glucocorticoids**
- Safety
  - Adverse events: nasopharyngitis, headache, URTI, sinusitis

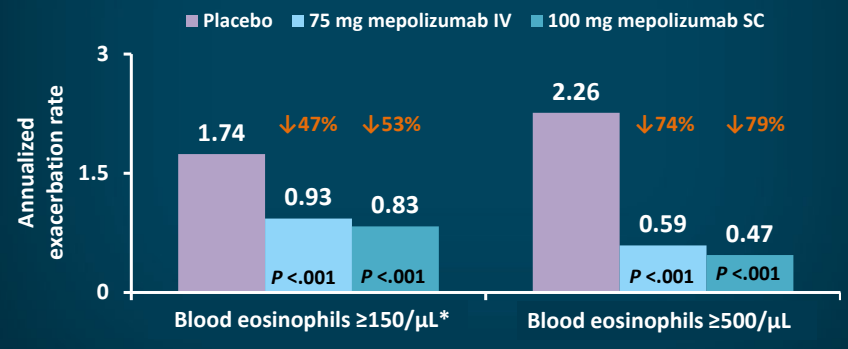
- **Approved as add-on maintenance therapy for severe eosinophilic asthma**
- **Subcutaneous dosing is 40 mg Q4W for ages 6–11 years and 100 mg Q4W for ages ≥12 years**

URTI = upper respiratory tract infection.

Ortega HG, et al. *N Engl J Med*. 2014;371:1198-1207. Mepolizumab (Nucala®) PI 2021 (https://gskpro.com/content/dam/global/hcpportal/en_US/Prescribing_Information/Nucala/pdf/NUCALA-PI-PIL-IFU-COMBINED.PDF). Accessed 8/24/2021.

Efficacy of Mepolizumab in Severe Eosinophilic Asthma

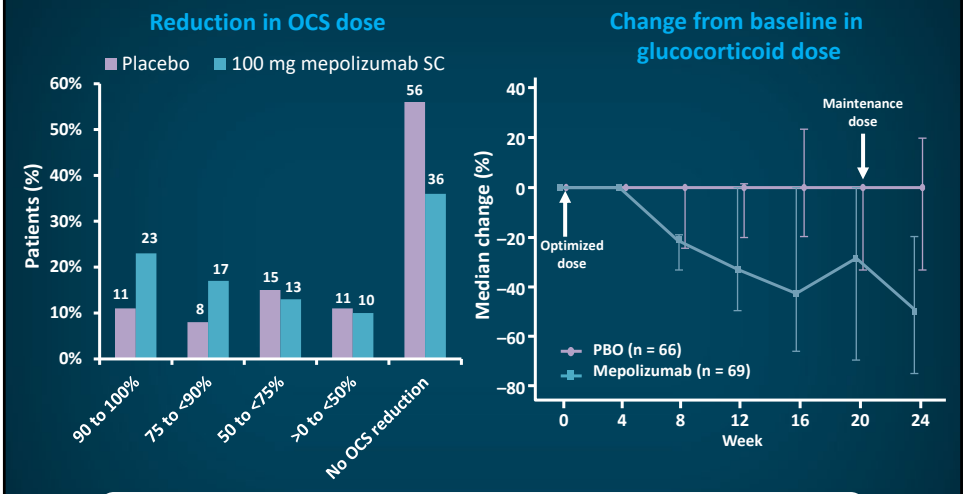
576 patients aged ≥12 years with severe, eosinophilic asthma received mepolizumab add-on therapy to ICS + ≥1 controller regimen



*Eosinophil count ≥150/µL at screening or ≥300/µL within previous year.

Ortega HG, et al. *N Engl J Med*. 2014;371:1198-1207.

Steroid Reduction with Mepolizumab

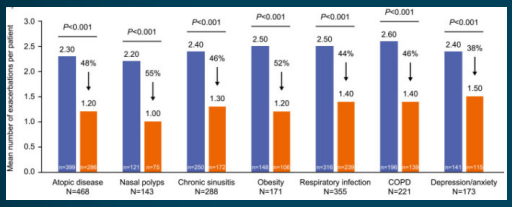


Overall OCS dose was reduced by 50% with mepolizumab vs no reduction with PBO (*P*= .007)

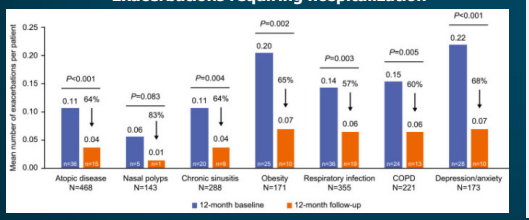
Bel EH, et al. *N Engl J Med*. 2014;371:1189-1197.

Real-World Effectiveness of Mepolizumab in Patients With Severe Asthma and Associated Comorbidities

Exacerbations



Exacerbations requiring hospitalization



- Retrospective analysis of 639 patients with asthma
- Most common comorbidities: atopic diseases (73%), respiratory infections (56%), chronic sinusitis (45%)
- During the follow-up vs baseline period:
  - In most subgroups, reductions seen in exacerbations and exacerbations requiring hospitalization
- 39% to 47% of patients achieved ≥ 50% OCS dose reduction

COPD, chronic obstructive pulmonary disease; OCS, oral corticosteroid.

Casale T, et al. *Ann Allergy Asthma Immunol*. 2021;S1081-1206(21)00382-3.

Reslizumab

- Indicated as add-on maintenance treatment for severe asthma of eosinophilic phenotype
- Mechanism of action
  - IL-5 antagonist reslizumab binds to the alpha chain of IL-5 receptor on eosinophil surface, inhibiting proliferation of eosinophils
- Adverse events
  - Most common includes oropharyngeal pain

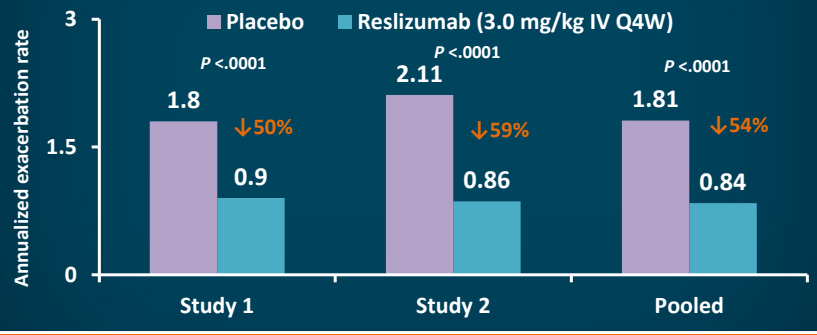
Approved as add-on maintenance therapy for patients ≥18 years old with severe eosinophilic asthma; dosing at 3 mg/kg IV Q4W

Hom S, Pisano M. *P T*. 2017;42:564-568. Reslizumab (Cinqair®) PI 2020 (www.cinqair.com/globalassets/cinqair/prescribinginformation.pdf). Accessed 8/24/2021.

Reslizumab in Moderate-to-Severe Eosinophilic Asthma

2 multicenter trials involving 953 patients ≥12 years with eosinophilic asthma (≥400 cells/µL) inadequately controlled by medium-to-high dose ICS-based therapy

Reduced exacerbation rate vs PBO



Lung function, asthma control, and QoL were also significantly improved in both studies

QoL = quality of life.

Castro M, et al. *Lancet Respir Med*. 2015;3:355-366.

Benralizumab

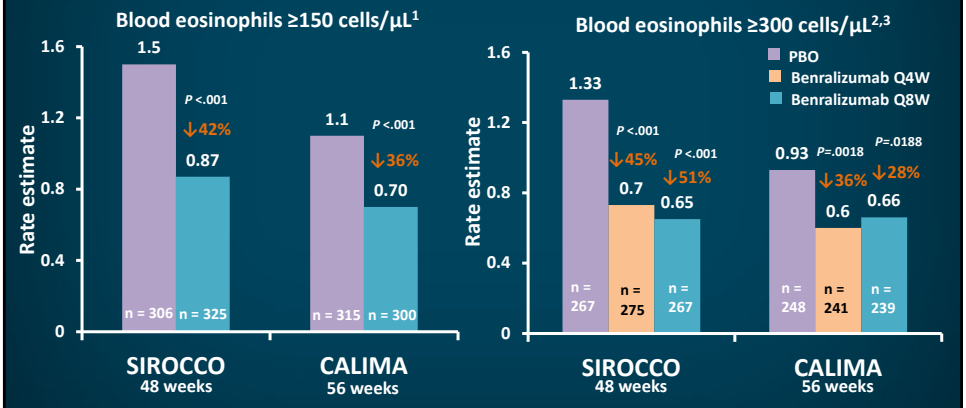
- Humanized IgG1κ mAb
- Indicated for add-on maintenance treatment of patients ≥12 years of age with severe asthma and with eosinophilic phenotype[1]
- WINDWARD program: 6 phase 3 studies included in program to evaluate the safety and efficacy of benralizumab[2]
  - SIROCCO
  - CALIMA
  - ZONDA
  - BORA
  - BISE
  - GREGALE

1. Benralizumab (Fasenra®) PI 2021. (www.azpicentral.com/fasenra/fasenra.pdf). Accessed 8/24/2021. 2. Pelaia C, et al. *Drug Des Devel Ther*. 2018:12:619-628.

Benralizumab Efficacy in Severe Uncontrolled Asthma

Benralizumab (30 mg Q4W or Q8W) as add-on therapy to high-dose ICS/LABA (SIROCCO[1]) or medium-to-high dose ICS/LABA (CALIMA[2])

Annual asthma exacerbation rate (AER)

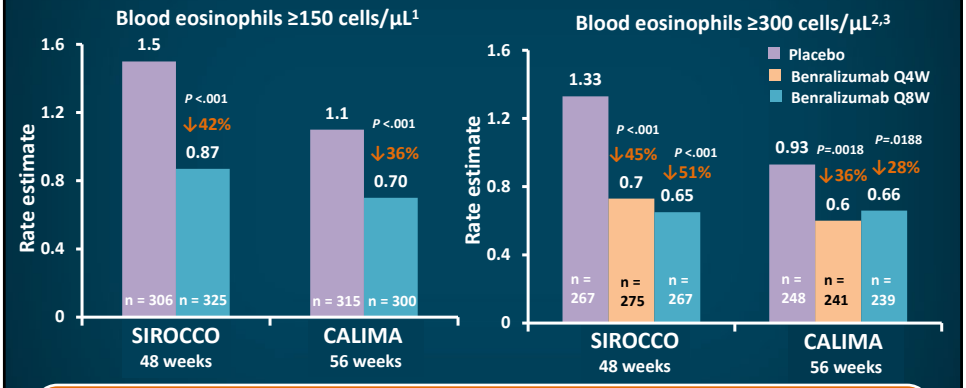


1. Goldman M, et al. *Curr Med Res Opin*. 2017;33:1605-1613. 2. Bleecker ER, et al. *Lancet*. 2016;388:2115–2127. 3. FitzGerald JM, et al. *Lancet*. 2016;388:2128-2141.

Benralizumab Efficacy in Severe Uncontrolled Asthma

Benralizumab (30 mg Q4W or Q8W) as add-on therapy to high-dose ICS/LABA (SIROCCO[1]) or medium-to-high dose ICS/LABA (CALIMA[2])

Annual asthma exacerbation rate (AER)



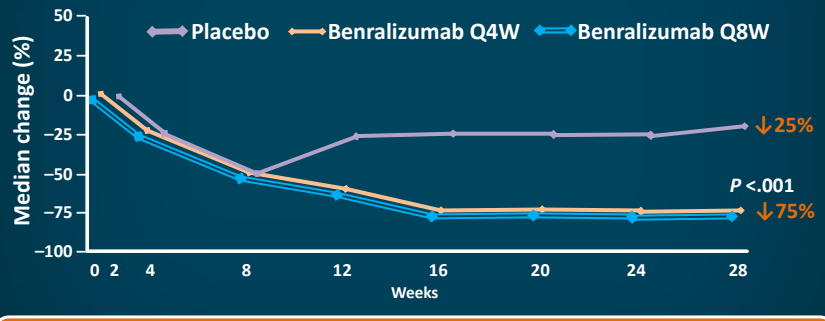
Pooled analysis: Benralizumab ↓AER, ↑FEV_1, and improved symptoms; subanalyses suggested OCS use and nasal polyposis were associated with ↑ response.[4]

1. Goldman M, et al. *Curr Med Res Opin*. 2017;33:1605-1613. 2. Bleecker ER, et al. *Lancet*. 2016;388:2115–2127. 3. FitzGerald JM, et al. *Lancet*. 2016;388:2128-2141. 4. FitzGerald JM, et al. *Lancet Respir Med*. 2018;6:51-64.

Benralizumab: OCS-Sparing Effect in Patients with Severe Eosinophilic Asthma in ZONDA Phase 3 Trial

220 patients ≥18 years old with severe asthma currently on OCS-based therapy randomized to receive placebo or benralizumab for 28 weeks

OCS dose reduction



Annual exacerbation rate and time to first asthma exacerbation also improved in both benralizumab groups vs placebo

Nair P, et al. *N Engl J Med*. 2017;376:2448-2458.

Elimination of Oral CS with Benralizumab: *The PONENTE Trial*

- N = 598 patients
- Assessed efficacy and safety of daily OCS dosage reduction after initiation of benralizumab 30 mg
- Four weeks after benralizumab initiation, patients began an OCS dosage-reduction algorithm with rapid down-titration

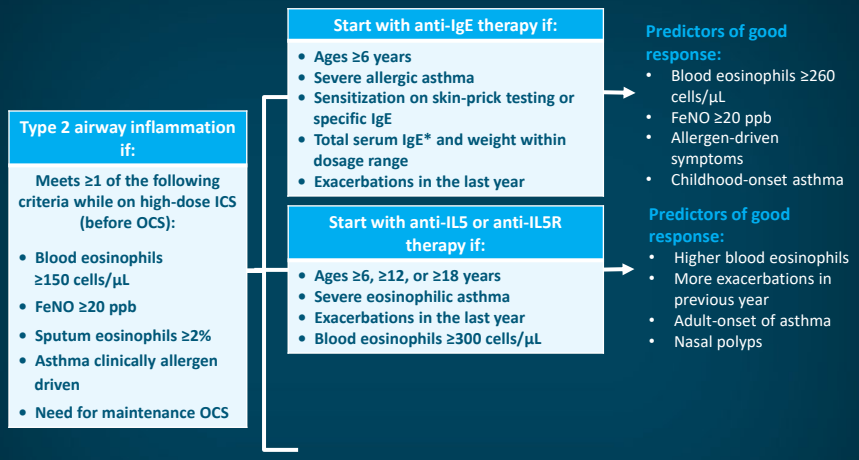
RESULTS

- 62.2% eliminated OCS use
- 80.6% eliminated use or reduced daily OCS dosage to ≤ 5 mg
- OCS reductions were achieved irrespective of baseline eosinophil count
- Lower percentage of patients had exacerbations during the OCS reduction phase than in the previous year (25.8% vs 84.4%)

OCS, oral corticosteroid.

Menzies-Gow A, et al. *J Allergy Clin Immunol*. 2021;147:L45.

GINA: Identifying Patients and Selecting Biologics



*Baseline IgE levels do not predict likelihood of response.

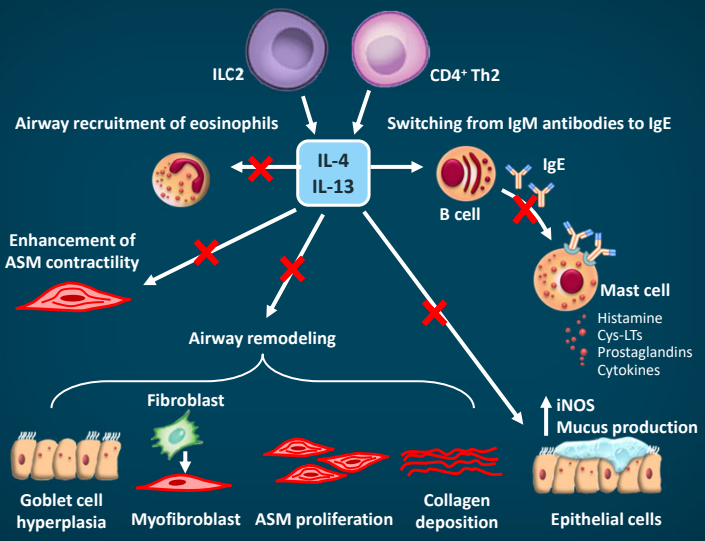
GINA 2019. Difficult-to-treat severe asthma in adolescents and adult patients: diagnosis and management (https://ginasthma.org/wp-content/uploads/2019/04/GINA-Severe-asthma-Pocket-Guide-v2.0-wms-1.pdf). Accessed 8/24/2021.

Case 3: Barry

- 21-year-old with severe asthma
- 3 exacerbations within the past year
- Medications
  - ICS/LABA/LAMA, prednisone 20 mg/day
- Labs
  - FeNO = 30 ppb
  - CBC with absolute eosinophil count of 300 cells/microliter

Which biologic(s) would be most appropriate for Barry?

Targeting IL-4/IL-13

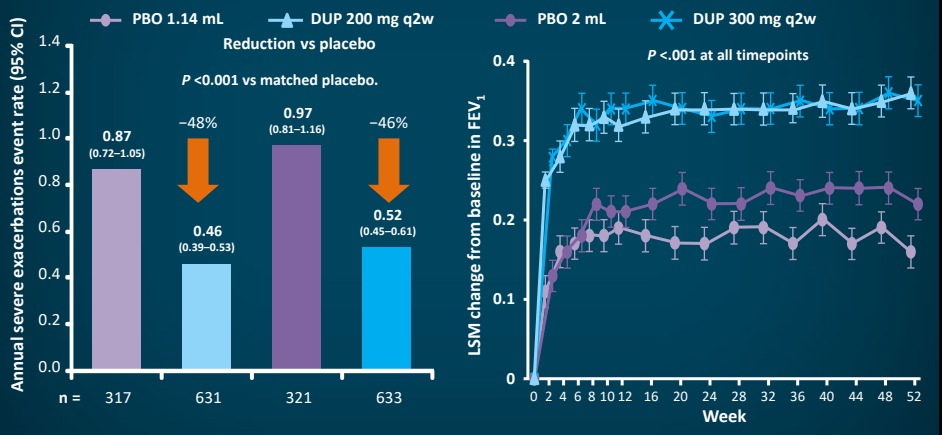


iNOS = inducible nitric oxide synthase; LTs = leukotrienes; ASM = airway smooth muscle cell.

Vatrella A, et al. *J Asthma Allergy*. 2014;7:123-130.

Efficacy of Dupilumab in Patients with Asthma

Phase 3 LIBERTY ASTHMA QUEST: 1902 patients ≥12 years with uncontrolled, moderate-to-severe asthma treated with dupilumab for 52 weeks

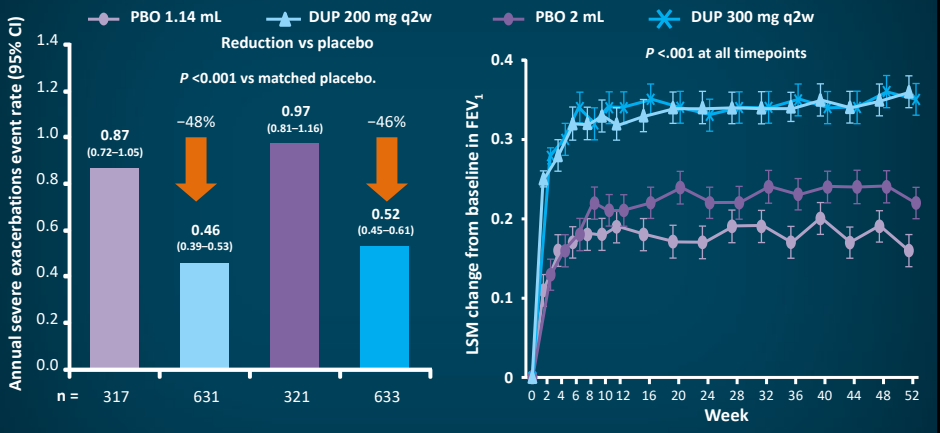


DUP = dupilumab; PBO = placebo; CI = confidence interval; ITT = intent-to-treat; LSM = least squares mean; SE = standard error.

Castro M, et al. *N Engl J Med*. 2018;378:2486-2496 and supplement.

Efficacy of Dupilumab in Patients with Asthma

Phase 3 LIBERTY ASTHMA QUEST: 1902 patients ≥12 years with uncontrolled, moderate-to-severe asthma treated with dupilumab for 52 weeks



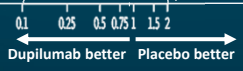
Dupilumab Q2W more consistent and efficacious at improving time to first exacerbation, asthma control scores, quality of life, and FeNO values across patient subgroups

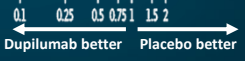
Castro M, et al. *N Engl J Med*. 2018;378:2486-2496 and supplement.

Dupilumab in Patients With Uncontrolled Asthma

LIBERTY ASTHMA QUEST Phase 3 Trial: Subgroup Efficacy

Subgroup	PBO	DUP 200 mg Q2W	RR vs PBO (95% CI)	PBO	DUP 300 mg Q2W	RR vs PBO (95% CI)
Overall	317	631	0.52 (0.41–0.66)	321	633	0.54 (0.43–0.68)
Eosinophil count (cells/mm³)						
≥300	148	264	0.34 (0.24–0.48)	142	277	0.33 (0.23–0.45)
≥150–<300	84	173	0.64 (0.41–1.02)	95	175	0.56 (0.35–0.89)
>150	85	193	0.93 (0.58–1.47)	83	181	1.15 (0.75–1.77)
FeNO (ppb)						
≥50	71	119	0.31 (0.18–0.52)	75	124	0.31 (0.19–0.49)
≥25-<50	91	180	0.39 (0.24–0.62)	97	186	0.44 (0.28–0.69)
<25	149	325	0.75 (0.54–1.05)	144	317	0.79 (0.57–1.10)



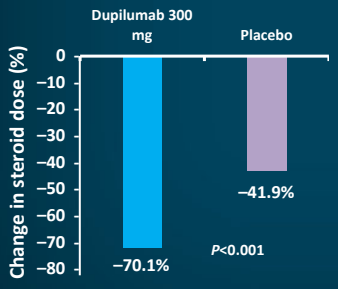


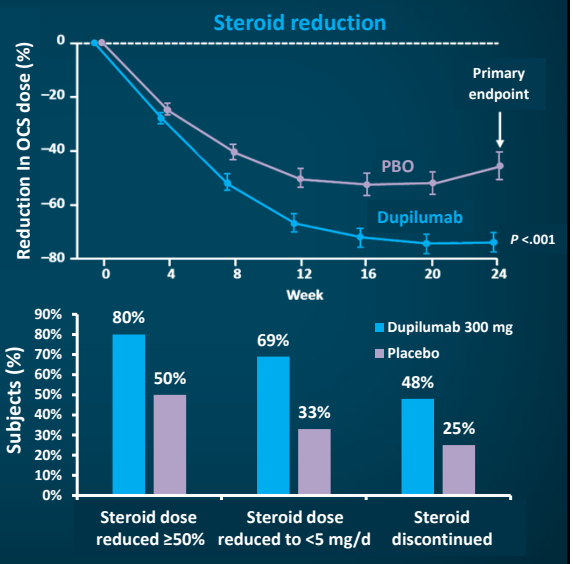
RR = relative risk.

Castro M, et al. *N Engl J Med.* 2018;378:2486-2496.

Dupilumab in Steroid-Dependent Asthma
VENTURE Phase 3 Trial

Changes in steroid dose in 210 patients aged ≥12 years with OCS-dependent severe asthma

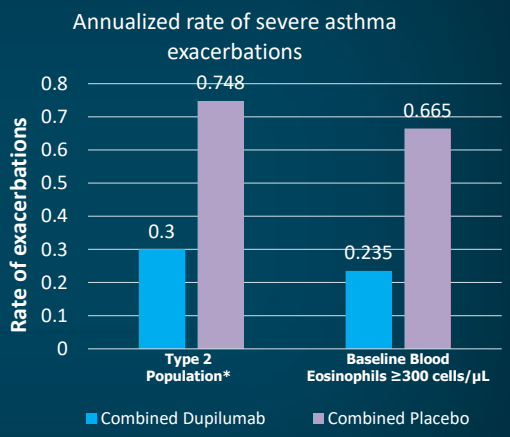




Rabe KF, et al. *N Engl J Med*. 2018;378:2475-2485.

Dupilumab in Children With Severe Asthma

- Participants: children aged 6 to < 12 years with uncontrolled, moderate to severe asthma
- Currently receiving high-dose ICS alone or medium- to high-dose ICS with a second controller
- SC dupilumab 100 mg (≤30 kg) or 200 mg (>30 kg) added on every 2 weeks
- In patients with a type 2 phenotype, dupilumab reduced exacerbation rate by 59.3% (*P* < .0001)
- Overall rates of TEAEs in dupilumab vs placebo groups were 83% vs 80%



*Baseline blood eosinophils ≥ 150 cells/µL or FeNO ≥ 20 ppb.
ICS, inhaled corticosteroid; SC, subcutaneous; ppb, parts per billion; TEAE, treatment-emergent adverse event.
Bacharier LB, et al. ATS 2021. Abstract 1204.

LIBERTY ASTHMA TRAVERSE Study
Long-Term Treatment With Dupilumab

Open-label extension study evaluated long-term safety, tolerability, and efficacy of add-on dupilumab in adults/adolescents rolled over from a previous dupilumab study

Long-term maintenance of OCS reduction and efficacy[1]
- Sustained reductions from baseline in OCS use
- Maintained low exacerbation rates and improvements in FEV1

Sustained efficacy and improvements in asthma control and HRQoL[2]
- ACQ-5 scores exceeded the clinically meaningful response threshold in 85% of patients
- By week 48 of the OLE, 77% of patients showed clinically meaningful improvements in the mean AQLQ score

Long-term efficacy[3]
- Sustained efficacy for up to 3 years in patients with T2-high asthma identified by either elevated FeNO or blood eosinophils (≥ 150 eosinophils/µL or FeNO ≥ 25 ppb at baseline)

Long-term exacerbations and lung function assessment[4]
- Greater pre-bronchodilator FEV1 improvements at the end of QUEST maintained these improvements and had fewer exacerbations during TRAVERSE

ACQ-5, 5-item Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; FEV1, forced expiratory volume in 1 second; HRQoL, health-related quality of life; OLE, open-label extension; ppb, parts per billion.

1. Sher L, et al. *Am J Respir Crit Care Med*. 2021;203:A1441. 2. Wechsler M, et al. *Am J Respir Crit Care Med*. 2021;203:A1452. 3. Wechsler M, et al. *Am J Respir Crit Care Med*. 2021;203:A1201. 4. Hanania NA, et al. *Am J Respir Crit Care Med*. 2021;203:A1443.

GINA: Identifying Patients and Selecting Biologics

Type 2 airway inflammation if:

Meets ≥1 of the following criteria while on high-dose ICS (before OCS):
- Blood eosinophils ≥150 cells/µL
- FeNO ≥20 ppb
- Sputum eosinophils ≥2%
- Asthma clinically allergen driven
- Need for maintenance OCS

Start with anti-IgE therapy if:
- Ages ≥6 years
- Severe allergic asthma
- Sensitization on skin-prick testing or specific IgE
- Total serum IgE* and weight within dosage range
- Exacerbations in the last year

Predictors of good response:
- Blood eosinophils ≥260 cells/µL
- FeNO ≥20 ppb
- Allergen-driven symptoms
- Childhood-onset asthma

Start with anti-IL5 or anti-IL5R therapy if:
- Ages ≥6, ≥12, or ≥18 years
- Severe eosinophilic asthma
- Exacerbations in the last year
- Blood eosinophils ≥300 cells/µL

Predictors of good response:
- Higher blood eosinophils
- More exacerbations in previous year
- Adult-onset of asthma
- Nasal polyps

Start with anti-IL4R if:
- Ages ≥12
- Severe eosinophilic asthma or need for maintenance OCS
- Exacerbations in last year
- Blood eosinophils ≥150 cells/µL or FeNO ≥25 ppb

Predictors of good response:
- Higher blood eosinophils
- Higher FeNO

May also be used to treat:
- Moderate-to-severe atopic dermatitis
- Nasal polyps

***Baseline IgE levels do not predict likelihood of response.**

GINA 2019. Difficult-to-treat severe asthma in adolescents and adult patients: diagnosis and management (https://ginasthma.org/wp-content/uploads/2019/04/GINA-Severe-asthma-Pocket-Guide-v2.0-wms-1.pdf). Accessed 8/24/2021.

Systematic Review of Biologic Therapies

In a systematic review of 19 randomized controlled trials, biologics benralizumab (3), dupilumab (3), mepolizumab (3), omalizumab (5), and reslizumab (5), investigators evaluated reductions in severe asthma exacerbation rates, use of oral corticosteroids, and adverse events.

Treatment	Changes in exacerbation rates (per 1000 patients/year)	Range	Evidence grade
Benralizumab	705 fewer exacerbations	420–915	High
Dupilumab	894 fewer exacerbations	655–1086	High
Mepolizumab	870 fewer exacerbations	592–1079	High
Omalizumab	290 fewer exacerbations	152–396	High
Reslizumab	972 fewer exacerbations	756–1134	High

Agache I, et al. *Allergy.* 2020;75:1023-1042.

Systematic Review of Therapies (continued)

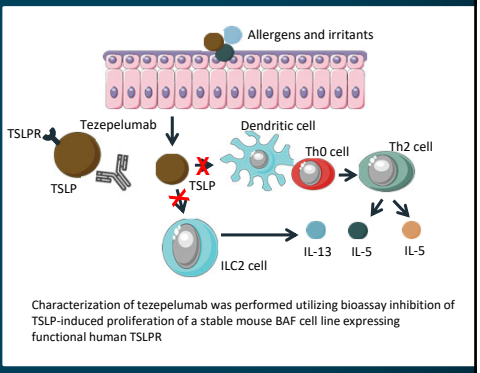
All biologics reduce exacerbation rates. Benralizumab, dupilumab, and mepolizumab had a high certainty of evidence for reducing use of oral corticosteroid use.

However, with a low certainty of evidence, benralizumab, mepolizumab, and reslizumab were associated with a slight increase in drug-related adverse events or any serious drug-related adverse events.

Agache I, et al. *Allergy.* 2020;75:1023-1042.

Tezepelumab is an Anti-TSLP mAb

- TSLP is a cytokine predominantly secreted by epithelial cells[1]
- TSLP plays a role in allergic inflammation[2,3]
  - Levels of TSLP correlate with severity of disease symptoms in asthma[4]
- Tezepelumab functionally antagonizes the action of TSLP at its receptor (TSLPR), thereby reducing its pro-inflammatory activity[5,6]



Characterization of tezepelumab was performed utilizing bioassay inhibition of TSLP-induced proliferation of a stable mouse BAF cell line expressing functional human TSLPR

mAb, monoclonal antibody; TLSP, Thymic stromal lymphopoietin.

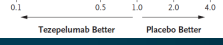
1. Corren J, et al. *N Engl J Med*. 2017;377:936–946. 2. Soumelis V, Liu YJ. *Springer Semin Immunopathol*. 2004;25:325–333. 3. Soumelis V, et al. *Nat Immunol*. 2002;3:673–680. 4. Ying S, et al. *J Immunol*. 2005;174:8183–8190 5. Gauvreau GM, et al. *N Engl J Med*. 2014;370:2102–2110 & Appendix. 6. Verstraete K et al. *Nat Commun*. 2017;8:14937

NAVIGATOR: Tezepelumab in Adults and Adolescents with Severe, Uncontrolled Asthma

- Human monoclonal antibody that binds specifically to TSLP
- Study participants: patients received medium to high dose ICS and ≥ 1 additional controller medication, with or without oral GC
- Design: patients randomized to receive tezepelumab (210 mg) or placebo SC every 4 weeks for 52 weeks

Primary endpoint: annualized rate of asthma exacerbations over a period of 52 weeks

Subgroup	Tezepelumab	Placebo	Rate Ratio (95% CI)
	no. of patients/annualized rate of asthma exacerbations		
Overall	528/0.93	531/2.10	0.44 (0.37–0.53)
Eosinophil count at baseline (cells/μl)			
<300	309/1.02	309/1.73	0.59 (0.46–0.75)
≥300	219/0.79	222/2.66	0.30 (0.22–0.40)
Eosinophil count at baseline (cells/μl)			
<150	138/1.04	138/1.70	0.61 (0.42–0.88)
150 to <300	171/1.00	171/1.75	0.57 (0.41–0.79)
300 to <450	99/0.92	95/2.22	0.41 (0.27–0.64)
≥450	120/0.68	127/3.00	0.23 (0.15–0.34)
Eosinophil count at baseline (cells/μl)			
<150	138/1.04	138/1.70	0.61 (0.42–0.88)
≥150	390/0.89	393/2.24	0.39 (0.32–0.49)
FENO at baseline (ppb)			
<25	213/1.07	220/1.57	0.68 (0.51–0.92)
≥25	309/0.82	307/2.52	0.32 (0.25–0.42)
FENO at baseline (ppb)			
<25	213/1.07	220/1.56	0.68 (0.51–0.92)
25 to <50	158/0.87	151/2.20	0.40 (0.28–0.56)
≥50	151/0.75	156/2.83	0.27 (0.19–0.38)
Allergic status at baseline			
Positive for any perennial allergens	339/0.85	341/2.03	0.42 (0.33–0.53)
Negative for all perennial allergens	184/1.09	177/2.21	0.49 (0.36–0.67)

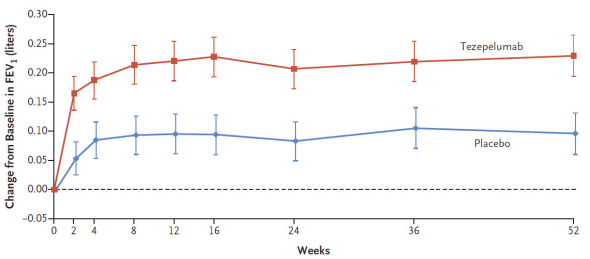


GC, glucocorticoid; ICS, inhaled corticosteroid; SC, subcutaneously; TLSP, Thymic stromal lymphopoietin.

Menzies-Gow A, et al. *N Engl J Med*. 2021;384:1800-1809.

NAVIGATOR: Secondary Endpoint and Safety Findings

Change from Baseline to Week 52 in Prebronchodilator FEV1



Safety Findings

- 77.1% of the patients in the tezepelumab group and 80.8% of those in the placebo group reported an adverse event
- Most common adverse events:
- Nasopharyngitis, upper respiratory tract infection, headache, and asthma

Menzies-Gow A, et al. *N Engl J Med*. 2021;384:1800-1809.

Personalized Therapy and Case Studies

Factors Impacting Biologic Therapy Selection

- Patient characteristics (eg, BMI, age)
- Asthma phenotype and endotype
- Concurrent comorbidities
- Safety and efficacy profile
- Patient preference
- Route of administration (IV vs SC)
- Frequency of dosing
- Adherence considerations (self-administration vs office visits)
- Cost (insurance coverage, prior authorization)
- Clinician's experience

Common Patient Concerns for Treatment Selection

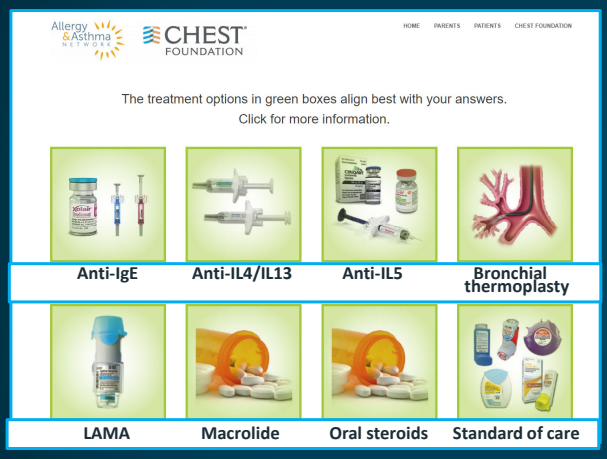
Treatment
- Frequency and route
- Safety and side effects
- Long-term effectiveness
- Unawareness and fear

Patient
- Perceived ineffectiveness
- Perceived need for control
- Time demands and scheduling conflicts

Socioeconomic
- Financial burden
- Insurance coverage

If these concerns are not addressed, they can impact adherence and outcomes

CHEST Foundation: SDM Tool



http://asthma.chestnet.org/sdm-tool/

- Patient identifies his/her preferences and values
- Clinician provides patient's biomarkers
- This narrows down patient's personalized options

SDM = shared decision-making.

CHEST Foundation (http://asthma.chestnet.org/sdm-tool/). Accessed 8/24/2021.

Treatment of T2-Low Asthma

- ~40% to 50% of asthma patients **do not** have type 2 inflammation
- Severe, uncontrolled asthma without evidence for type 2 inflammation referred to as "Type 2 (T2)-low asthma"
- Potential targets for T2-low asthma:
  - IL-17 indirectly recruits neutrophils
  - IL-8 chemoattractant for neutrophils
  - Macrolide antibiotics
- Bronchial thermoplasty

Fajt ML, Wenzel SE. *Allergy Asthma Immunol Res*. 2017;9:3-14.

Summary Points

- Addressing **modifiable risk factors** can improve symptom control in many patients with severe asthma
- Phenotyping and endotyping using clinical, physiologic, and biologic biomarkers will allow for a more precise approach to severe disease
- Growing number of treatment options available for patients with severe asthma
- Clinical trials have shown that several targeted biologic therapies can **improve symptoms, decrease exacerbations, and improve quality of life** in various severe asthma cohorts
  - Five biologic therapies are FDA-approved to treat severe T2-high asthma
- Coordinated **multidisciplinary care** is essential for the optimization of outcomes for patients with severe asthma

Thank you!

Severe Asthma: Reducing Disease Burden with Step-Up Therapy

Resource	Address
Aaron S, Boulet LP, Reddel HK, Gershon AS. Underdiagnosis and overdiagnosis of asthma. *Am J Respir Crit Care Med*. 2018;198(8):1012-1020.	https://pubmed.ncbi.nlm.nih.gov/29756989/
Agache I, Beltran J, Akdis C, et al. Efficacy and safety of treatment with biologicals (benralizumab, dupilumab, mepolizumab, omalizumab and reslizumab) for severe eosinophilic asthma. A systematic review for the EAACI Guidelines - recommendations on the use of biologicals in severe asthma. *Allergy*. 2020;75(5):1023-1042.	https://pubmed.ncbi.nlm.nih.gov/32034960/
Bagnasco D, Caminati M, Ferrando M, et al. Anti-IL-5 and IL-5Ra: Efficacy and safety of new therapeutic strategies in severe uncontrolled asthma. *Biomed Res Int*. 2018;2018:5698212.	https://pubmed.ncbi.nlm.nih.gov/30519580/
Busse WW. Biological treatments for severe asthma: A major advance in asthma care. *Allergol Int*. 2019;68(2):158-166.	https://pubmed.ncbi.nlm.nih.gov/30792118/
Chest Foundation. Shared decision-making tool. Accessed July 25, 2021.	https://asthma.chestnet.org/sdm-tool/
Chung KF. Diagnosis and management of severe asthma. *Semin Respir Crit Care Med*. 2018;39(1):91-99.	https://pubmed.ncbi.nlm.nih.gov/29427989/
Corren J. New targeted therapies for uncontrolled asthma. *J Allergy Clin Immunol Pract*. 2019;7(5):1394-1403.	https://pubmed.ncbi.nlm.nih.gov/31076057/
Delgado J, Dávila IJ, Domínguez-Ortega J; Severe Asthma Group (SEAIC). Clinical recommendations for the management of biological treatments in severe asthma patients: A consensus statement. *J Investig Allergol Clin Immunol*. 2021;31(1):36-43.	https://pubmed.ncbi.nlm.nih.gov/32856593/
Dunn R, Busse PJ, Wechsler ME. Asthma in the elderly and late-onset adult asthma. *Allergy*. 2018;73(2):284-294.	https://pubmed.ncbi.nlm.nih.gov/28722758/

Farne H, Wilson A, Powell C, Bax L, Milan SJ. Anti-IL5 therapies for asthma. *Cochrane Database Syst Rev*. 2017;9(9):CD010834.	https://pubmed.ncbi.nlm.nih.gov/28933516/
Fuchs O, Wilson A, Powell C, Bax L, Milan SJ. Asthma transition from childhood into adulthood. *Lancet Respir Med*. 2017;5(3):224-234.	https://pubmed.ncbi.nlm.nih.gov/27666650/
Henriksen DP, Bodtger U, Sidenius K, et al. Efficacy of omalizumab in children, adolescents, and adults with severe allergic asthma: A systematic review, meta-analysis, and call for new trials using current guidelines for assessment of severe asthma. *Allergy Asthma Clin Immunol*. 2020;16:49.	https://pubmed.ncbi.nlm.nih.gov/32565844/
Israel E, Reddel HK. Severe and difficult-to-treat asthma in adults. *N Engl J Med*. 2017;377(10):965-976.	https://pubmed.ncbi.nlm.nih.gov/28877019/
Lambrecht B, Hammad H, Fahy JV. The cytokines of asthma. *Immunity*. 2019;50(4):975-991.	https://pubmed.ncbi.nlm.nih.gov/30995510/
McGregor M, Krings JG, Nair P, Castro M. Role of biologics in asthma. *Am J Respir Crit Care Med*. 2019;199(4):433-445.	https://pubmed.ncbi.nlm.nih.gov/30525902/
Morais-Almeida M, Aguiar R, Martin B, et al. COVID-19, asthma, and biological therapies: What we need to know. *World Allergy Organ J*. 2020;13(5):100126.	https://pubmed.ncbi.nlm.nih.gov/32426090/
Patel S, Casale TB, Cardet JC. Biological therapies for eosinophilic asthma. *Expert Opin Biol Ther.* 2018;18(7):747-754.	https://pubmed.ncbi.nlm.nih.gov/29938543/
Pelaia C, Crimi C, Vatrella A, Tinello C, Terracciano R, Pelaia G. Molecular targets for biological therapies of severe asthma. *Front Immunol*. 2020;11:603312.	https://pubmed.ncbi.nlm.nih.gov/33329598/
Pijnenburg MW, Fleming L. Advances in understanding and reducing the burden of severe asthma in children. *Lancet Respir Med*. 2020;8(10):1032-1044.	https://pubmed.ncbi.nlm.nih.gov/32910897/
Rogliani P, Calzetta L, Matera MG, et al. Severe asthma and biological therapy: When,	https://pubmed.ncbi.nlm.nih.gov/32048241/

which, and for whom. *Pulm Ther*. 2020;6(1):47-66.	
Schoettler N, Strek ME. Recent advances in severe asthma: From phenotypes to personalized medicine. *Chest*. 2020;157(3):516-528.	https://pubmed.ncbi.nlm.nih.gov/31678077/

Resources and Societies

Resource	Address
Allergy and Asthma Network.	https://allergyasthmanetwork.org/
American Academy of Allergy, Asthma & Immunology.	https://acaai.org/asthma
American Association for Respiratory Care.	https://www.aarc.org/
American Lung Association.	https://www.lung.org/lung-health-diseases/lung-disease-lookup/asthma
Association of Asthma Educators.	https://www.asthmaeducators.org/
Asthma and Allergy Foundation of America.	https://www.aafa.org/
Centers for Disease Control and Prevention.	https://www.cdc.gov/asthma/default.htm