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INTEGRITY
CONTINUING EDUCATION

Biologics for the Treatment of Asthma and the Critical Role of Primary Care in Improving Patient Outcomes

This activity is provided by Integrity CE, LLC.
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Learning Objectives

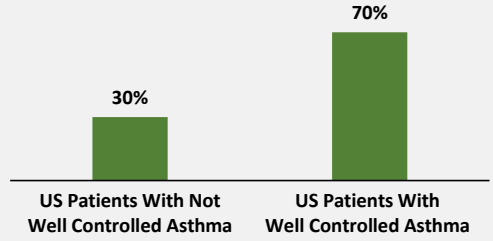
- Identify clinical indicators of uncontrolled asthma and candidates who may benefit from addition of biologic therapy to treatment plans
- Discuss available biologic therapies for asthma management, data supporting their clinical use, and initiation criteria
- Describe multispecialty management strategies for patients with asthma including the critical importance of referral for respiratory specialist evaluation

Burden of Asthma and Current Unmet Needs in Asthma Care

Asthma and Asthma Control in the US

- Current US asthma prevalence increased from 20.3 million patients in 2001 to 25.3 million in 2021
- Patients with asthma with one or more asthma attack in 2020:
  - Children: 42.7%
  - Adults: 40.7%
- Per 10,000 patients in 2019:
  - 46.4 emergency department visits
  - 5.2 hospitalizations

Proportion of US Patients With Well-Controlled Asthma in the US (Practice Fusion Database; N=15,579)



7.59 million patients in the US whose asthma is not well controlled

CDC. Asthma Facts. Available at: https://www.cdc.gov/asthma/most_recent_national_asthma_data.htm;
Davitte J, et al. *NPJ Prim Care Resp Med.* 2023;33.

Why is Frequent Assessment of Control Needed?

- Patients often overrate asthma control
  - 70% with uncontrolled asthma (eg, exacerbations, hospital visits, and additional medication use) did not regard their condition as serious
- Only moderate agreement between physicians' perception of asthma control and overall ACT score (*P*=.5450)
- When assessed by GINA symptom criteria, asthma was well controlled in only 17.8% of 775 patients:

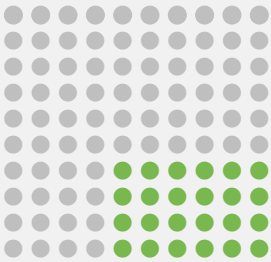
Uncontrolled: 27.7%	**Partly Controlled: 54.5%**	**Well Controlled: 17.8%**
3-4 of: • Daytime symptoms >2/week • Night wakening due to asthma • Reliever needed >2/week • Activity limitation	1-2 of: • Daytime symptoms >2/week • Night wakening due to asthma • Reliever needed >2/week • Activity limitation	Complete absence of: • Daytime symptoms >2/week • Night wakening due to asthma • Reliever needed >2/week • Activity limitation

ACT, Asthma Control Test; GINA, Global Initiative for Asthma.

Fuhlbrigge A, et al. *J Allergy Clin Immunol Pract*. 2021;9(8):3080-3088.e1; Levy ML, et al. *NPJ Prim Care Respir Med*. 2023;33(1):7.

Rate of Asthma Control Reduces at Higher Steps of Care

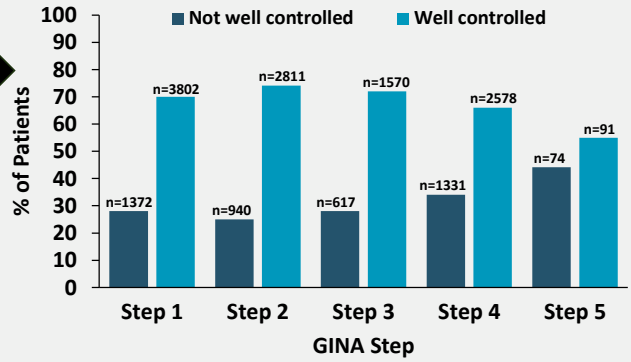
Proportion of Adults With High Intensity Treatment



24%
High intensity treatment
= high dose ICS-LABA or medium dose (ICS-LABA + OCS)

Rate of Asthma Control Lowers at Higher Steps of Care

Asthma Control Status by GINA Step
(Practice Fusion Database; N=15,579)



ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; OCS, oral corticosteroid.

Davitte J, et al. *NPJ Prim Care Resp Med.* 2023;33; Levy ML, et al. *NPJ Prim Care Respir Med*. 2023;33(1):7.

Consequences of Not Assessing Asthma Control: Acute Management of Asthma, Overuse of OCS, and Delayed Referral for Specialist Care

- Asthma is often managed as an acute illness
  - Patients are treated for exacerbations and sent home without follow-up
- Up to 60% of patients with moderate-to-severe/uncontrolled asthma have received long-term OCS
  - OCS are associated with multiple adverse events, including cardiovascular, metabolic, psychiatric, ocular, gastrointestinal, bone-related, increased risk of infection
- Earlier specialist referral is needed
  - 77% of PCPs refer patients with asthma to a specialist after ≥2 exacerbations/year

PCP, primary care provider.

Bleecker ER, et al. *Am J Respir Crit Care Med*. 2020;201(3):276-293; Haughney J, et al. *Adv Ther*. 2023;40(6):2577-2594; Levy ML, et al. *NPJ Prim Care Respir Med*. 2023;33(1):7; Patel B, et al. *Ann Allergy Asthma Immunol*. 2023;131(5):S46-S47; Timmins L, et al. *Ann Fam Med*. 2022;20(4):343-347.

Current Guidelines for Assessment of Control

Asthma Management Cycle for Personalized Care

Personalization of Asthma Management

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

- Confirmation of diagnosis, if necessary
- Symptom control and modifiable risk factors
- Comorbidities
- Inhaler technique and adherence
- Patient preferences and goals

- Treatment of modifiable risk factors and comorbidities
- Nonpharmacological strategies
- Asthma medications
- Education and skills training

GINA. Reports. Available at: https://ginasthma.org/reports

Defining Uncontrolled Asthma, Clinical Indicators and Diagnosis

- Asthma control is defined by current symptom control and risk for future exacerbations
- Symptom control should be assessed at every opportunity
- Poor control increases risk for exacerbations
  - Even those with good symptom control or mild asthma are at risk for worsening disease and exacerbations

GINA. Reports. Available at: https://ginasthma.org/reports; Levy ML, et al. *NPJ Prim Care Respir Med*. 2023;33(1):7.

GINA Symptom Control Assessment Tool

Assessment of Asthma Control

In the past 4 weeks, has the patient had:

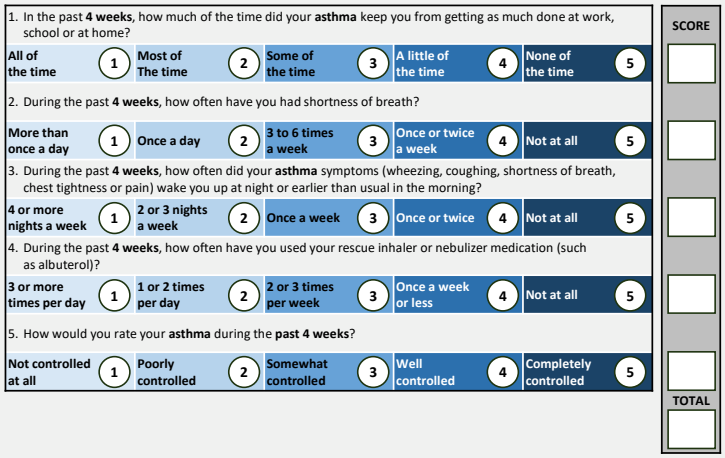
Daytime asthma symptoms more than 2x/week?	Yes/No	None of these: Well Controlled	1–2 of these: Partly Controlled	3–4 of these: Uncontrolled
Any night waking due to asthma?	Yes/No			
SABA* reliever for symptoms more than 2x/week?	Yes/No			
Any activity limitation due to asthma?	Yes/No			

*Based on SABA (as-needed ICS-formoterol reliever not included); excludes reliever taken before exercise.
SABA, short-acting beta-agonist.

GINA. Reports. Available at: https://ginasthma.org/reports

Numerical Tools for Assessing Asthma Symptom Control: Asthma Control Test

- Consists of 4 symptom/reliever questions and patient self assessment of asthma control
- Scores range from 5-25
- Higher scores are better controlled, 16-19 are not well controlled, and 5-15 are very poorly controlled



1. In the past **4 weeks**, how much of the time did your **asthma** keep you from getting as much done at work, school or at home?									SCORE
All of the time	1	**Most of The time**	2	**Some of the time**	3	**A little of the time**	4	**None of the time**	5	
2. During the past **4 weeks**, how often have you had shortness of breath?									
More than once a day	1	**Once a day**	2	**3 to 6 times a week**	3	**Once or twice a week**	4	**Not at all**	5	
3. During the past **4 weeks**, how often did your **asthma** symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) wake you up at night or earlier than usual in the morning?									
4 or more nights a week	1	**2 or 3 nights a week**	2	**Once a week**	3	**Once or twice**	4	**Not at all**	5	
4. During the past **4 weeks**, how often have you used your rescue inhaler or nebulizer medication (such as albuterol)?									
3 or more times per day	1	**1 or 2 times per day**	2	**2 or 3 times per week**	3	**Once a week or less**	4	**Not at all**	5	
5. How would you rate your **asthma** during the **past 4 weeks**?									
Not controlled at all	1	**Poorly controlled**	2	**Somewhat controlled**	3	**Well controlled**	4	**Completely controlled**	5	TOTAL

Thomas M, et al. *Prim Resp Care J.* 2009;18:41-49.

Assess Lung Function and Risk for Asthma Exacerbations

- Assess risk factors at diagnosis and periodically, particularly for patients experiencing exacerbations
- Measure FEV_1 at diagnosis, after 3-6 months of ICS treatment, then periodically for ongoing risk management

Risk Factors for Exacerbations
Uncontrolled asthma symptoms
SABA/reliever overuse
Inadequate ICS due to lack of prescribing, adherence, or inhaler technique
Other medical conditions such as obesity, GERD, etc.
Exposures to irritants such as tobacco smoke
Psychosocial risk factors
Low lung function
T2 inflammation

FEV_1, forced expiratory volume in 1 second; T2, type 2.

GINA. Reports. Available at: https://ginasthma.org/reports

Case Study #1: Introduction and Background

- 14-year-old male diagnosed with asthma at age 8
- Currently managed with medium dose ICS + LABA
  - Was stepped up 3 months ago after experiencing 2 exacerbations in the past year
- Recently experienced another exacerbation that did not require emergency care

Case Study #1: Assessment of Asthma Control

Daytime asthma symptoms more than 2x/week?	✓ Yes
Any night waking due to asthma?	✓ Yes
SABA reliever for symptoms more than 2x/week?	✓ Yes
Any activity limitation due to asthma?	✓ Yes

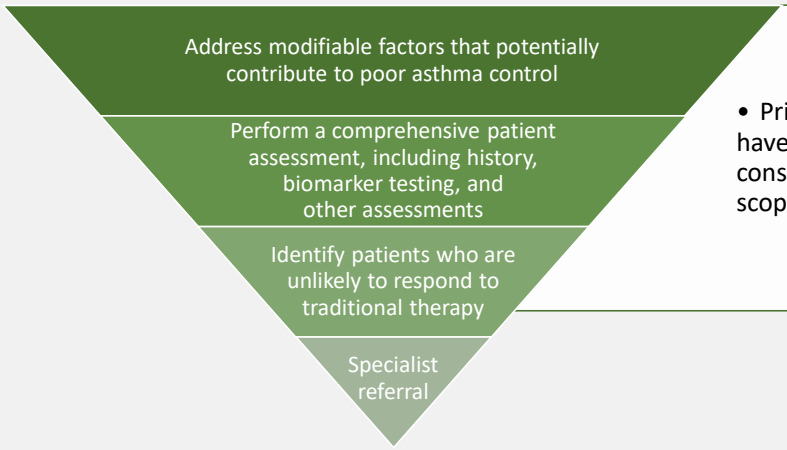
- ACT Score: 16
- Lung function: FEV_1 77% predicted

What is the level of control for this patient?

□ Well controlled
□ Partly controlled
□ Uncontrolled

Recommendations for Management of Patients With Uncontrolled Asthma

The Primary Care Clinician Role in Assessment and Testing



- Primary care providers have a distinct advantage in considering the entire scope of patient care

Trevor JL, Chipps BE. *Am J Med*. 2018;131(5):484-491.

Optimize Management and Address Modifiable Factors Leading to Poor Asthma Control

Check inhaler technique	• Watch patient use of their inhaler(s) and demonstrate the correct method; recheck up to 3 times and at each visit
Discuss adherence and barriers to use	• Have empathetic discussion to identify poor adherence that includes patient beliefs, cost of medications, and refill frequency
Assess and manage comorbidities	• Check for and manage comorbidities that may contribute to symptoms, eg, rhinitis, obesity, GERD, obstructive sleep apnea, depression, anxiety
Remove potential risk factors	• Check for and address risk factors or inducers, including smoking, beta-blockers, NSAIDs, occupational or domestic allergen exposure

Consider step-up if asthma remains uncontrolled despite good adherence and correct inhaler technique
Use shared decision-making, and balance potential benefits and risks

GERD, gastroesophageal reflux disease; NSAIDs, nonsteroidal anti-inflammatory drugs.

GINA. Reports. Available at: https://ginasthma.org/reports

Importance of Asthma Phenotypes and Biomarkers in Patients Who Are Consistently Uncontrolled

Asthma Phenotypes	Associated Testing/Biomarkers
Allergic asthma	Allergy testing, elevated serum IgE, elevated blood eosinophils
Nonallergic asthma	Tests do not indicate markers of allergic inflammation
Eosinophilic asthma	Elevated blood eosinophils and elevated FeNO
Neutrophilic asthma	Elevated neutrophils in sputum
Exercise-induced asthma	Symptoms triggered by exercise
Aspirin sensitive phenotype	Symptoms triggered after taking aspirin or NSAID

- Identification of specific asthma endotype and phenotype can help improve disease management
- Current strategies for asthma management focus on individualizing treatment based on patient phenotype

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

AAAAI. Available at: https://www.aaaai.org/tools-for-the-public/conditions-library/asthma/asthma-is-a-disease-of-different-phenotypes

Assess the Asthma Phenotype

Could the patient have T2 inflammation?

- Blood eosinophils >150 cells/µL **and/or**
- FeNO >20 ppb **and/or**
- Asthma is clinically allergen driven

T2 inflammation present?

- Consider adherence tests
- Consider increasing ICS dose for 3-6 months
- Consider add-on nonbiologic for specific T2 phenotype (AERD, chronic sinusitis, atopic dermatitis, etc)
- Consider add-on biologic therapy

AERD, aspirin-exacerbated respiratory disease; ppb, parts per billion.

GINA. Reports. Available at: https://ginasthma.org/reports

Consider Step Up in Therapy: GINA Track 2 Stepwise Management for Patients ≥12 Years Old

TRACK 2: Alternative **CONTROLLER** and **RELIEVER**
Before considering a regimen with SABA reliever, check if the patient is likely to adhere to daily controller treatment

STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
Take ICS whenever SABA taken	Low-dose maintenance ICS	Low-dose maintenance ICS-LABA	Medium/high-dose maintenance ICS-LABA	Add-on LAMA Refer for assessment of phenotype Consider high-dose maintenance ICS-LABA, ± anti-IgE, anti-IL5/5R, anti-IL4Rα, anti-TSLP

RELIEVER: As-needed SABA, or as-needed ICS-SABA*

Other controller options (limited indications, or less evidence for efficacy or safety)

*Anti-inflammatory reliever.
HDM, house dust mite; IL, interleukin; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; SLIT, sublingual immunotherapy; TSLP, thymic stromal lymphopoietin.

Consider referral to specialist for patients with asthma that remains uncontrolled despite good adherence and correct inhaler technique

GINA. Reports. Available at: https://ginasthma.org/reports

Case Study #1: Additional Assessment

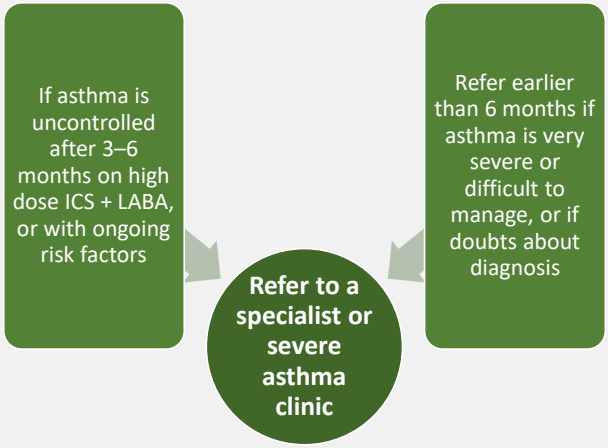
Modifiable Risk Factors	No risk factors identified
Inhaler Technique	Patient presented correct inhaler technique
Adherence	Patient and parent report good adherence to treatment plan
Comorbidities	None
BEC	210 cells/µL
Total serum IgE	100 kU/L; specific IgE (RAST) was negative

BEC, blood eosinophil count; RAST, radioallergosorbent test.

What is your next step for this patient?

- □ Step-up to high dose ICS + LABA
- □ Consider alternative or biologic therapy
- □ Refer to specialist for evaluation

Specialist Referral Based on Asthma Control



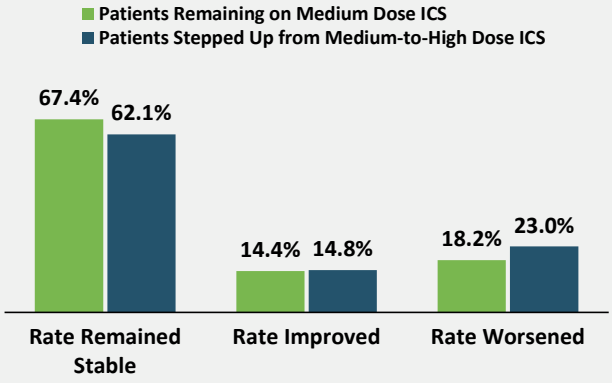
- Referral for specialist care also recommended for:
  - Difficulty confirming diagnosis
  - Suspected occupational asthma
  - Any risk factors for asthma-related death
  - Evidence of treatment-related side effects
  - Symptoms suggesting complications or subtypes of asthma

Bell, E. New biologic drugs for asthma: What PCPs need to know. Available at: https://www.healio.com/news/pediatrics/20200117/new-biologic-drugs-for-asthma-what-pcps-need-to-know; GINA. Reports. Available at: https://ginasthma.org/reports

The Role of Biologics in Asthma Management

Asthma Status Before and After ICS Step-Up

Effect of Step-up in ICS Therapy On Exacerbation Rate Over 1 Year vs No Step-up; UK Database Study (n=58,616 patients)[1]



Patients With Moderate-to-Severe Asthma:

- Considerable proportion of patients remain symptomatic, despite the use of ICS[2]
- Minimal additional clinical benefit with high dose ICS[1,3]
- 80% to 90% of the maximum obtainable benefit achieved with low dose ICS[3]

1. Pavord ID, et al. *J Allergy Clin Immunol Pract*. 2023;11(2):532-543. **2.** Kankaanranta H, et al. *Respir Res*. 2004;5(1):17; **3.** Beasley R, et al. *Am J Respir Crit Care Med*. 2019;199(12):1471-1477.

The Spectrum of Biologics Approved for Moderate-to-Severe Asthma: Opportunities for Achieving Better Control

Biologic*	Target	Indication	Age (years)	Predictors of Response
Omalizumab	IgE	Moderate-to-severe persistent asthma with a + skin test or in vitro reactivity to perennial aeroallergen	≥6	FeNO (≥20 ppb) Serum IgE (30–150 IU/mL) BEC (>260 cells/µL)
Mepolizumab **Reslizumab** **Benralizumab**	IL-5 IL-5 IL-5Rα	Severe asthma and with eosinophilic phenotype	≥6 ≥18 ≥6	BEC (>150 cells/µL) BEC (400 cells/µL) BEC (>150 cells/µL)
Dupilumab	IL-4Rα	Moderate-to-severe asthma characterized by eosinophilic phenotype or OCS-dependent asthma	≥6	FeNO (≥25 ppb) BEC (>150 cells/µL)
Tezepelumab	TSLP	Severe asthma	≥12	FeNO (≥25 ppb) BEC (>150 cells/µL)

*Listed in order of approval date.

GINA. Reports. Available at: https://ginasthma.org/reports; Package inserts for Cinqair, Dupixent, Fasenra, Nucala, Tezspire, Xolair.

Clinical Trial Efficacy of Biologics Approved for Moderate-to-Severe Asthma

Agent*†	Exacerbations	ACQ	FEV_1	QOL	OCS Use
Benralizumab	↓	ACQ-6 ✓	↑	↑	↓
Dupilumab	↓	ACQ-5 ✓	↑	↑	↓
Mepolizumab	↓	ACQ-5 NS	↑	↑	↓
Omalizumab	↓	ACQ-7 ✓	↑↓	↑	↑↓
Reslizumab	↓	ACQ-7 ✓	↑	↑	—
Tezepelumab	↓	ACQ-6 ✓	↑	↑	↑↓

*Listed alphabetically; †No strong safety signals for any biologic vs placebo in clinical trials; ✓, statistically significant; —, no trial evidence shown; ↑↓, mixed findings.

ACQ, Asthma Control Questionnaire.

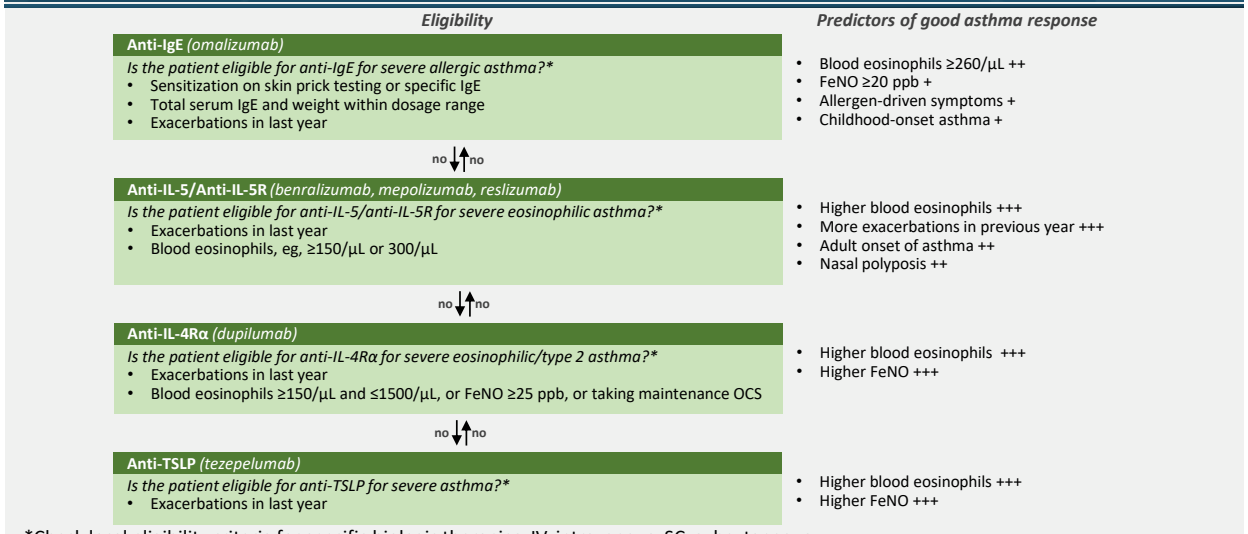
Buhl R, et al. *J Allergy Clin Immunol Pract.* 2022;10:422-432; Castro M, et al. *Lancet Respir Med.* 2015;3:355-366; Castro M, et al. *N Engl J Med.* 2018;378:2486-2496; Fitzgerald JM, et al. *Lancet.* 2016;388:2128-2141; Henriksen DP, et al. *Allergy Asthma Clin Immunol.* 2020;16:49; Lugogo NK, et al. *Clin Ther.* 2016;38:2058-2070; Menzies-Gow A, et al. *N Engl J Med.* 2021;284:1800-1809; Pavord ID, et al. *J Allergy Clin Immunol Pract.* 2022;10:410-419; Wechsler ME, et al. *Lancet Respir Med.* 2022;10:11-25.

Identification of Patients Who May Benefit From Biologic Therapies

Case Study #2: Introduction and Background

- 21-year-old female currently on high dose ICS + LABA
- Required OCS to maintain control while on medium dose ICS + LABA
- Diagnosed with asthma at age 19
- Reports persistent symptoms, nighttime awakenings, and impact on daily activities

GINA 2023: Biologic Eligibility Criteria and Predictors of Response



*Check local eligibility criteria for specific biologic therapies. IV, intravenous; SC, subcutaneous.

GINA. Reports. Available at: https://ginasthma.org/reports

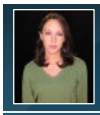
Consideration of Comorbidities When Selecting Biologic Therapy

Biologics Approved for Asthma With Indications for Potential Comorbid Conditions

	Omalizumab	Mepolizumab	Dupilumab
AD			✓
CRSwNP	✓	✓	✓
CSU	✓		
EGPA		✓	
EoE			✓
HES		✓	

EoE, eosinophilic esophagitis.

Adrish M, et al. *Respirology*. 2022;27(11):926-928.



Case Study #2: Findings From the Patient's Work-up

- No comorbid conditions or modifiable risk factors present
- Patient demonstrates correct inhaler technique and reports adherence

ACT	14
FEV_1	70% predicted with 15% reversibility, 290 mL
BEC	305 cells/μL
FeNO	50 ppb
Total serum IgE	100 kU/L; specific IgE (RAST) was negative

Patient Engagement and Shared Decision-Making

Topics for Shared Decision-Making Discussions

Preferred treatment

- Based on evidence for symptom control and risk reduction

Patient characteristics or phenotype

- Does the patient have any features predictive of future risk or treatment response (eg, smoker, history of exacerbations, blood eosinophilia)?
- Any modifiable risk factors or comorbidity that may affect treatment outcomes?

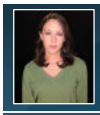
Patient views

- What are the patient's goals, beliefs, and concerns about asthma and medications?

Practical issues

- Which treatment options are available to the patient?
- Inhaler technique—can the patient use the inhaler correctly after training?
- Adherence—how often is the patient likely to take the medication?
- Cost to patient—can the patient afford the medication?

GINA. Reports. Available at: https://ginasthma.org/reports



Case Study #2: Selection of Biologic

Which biologic do you select for this patient?

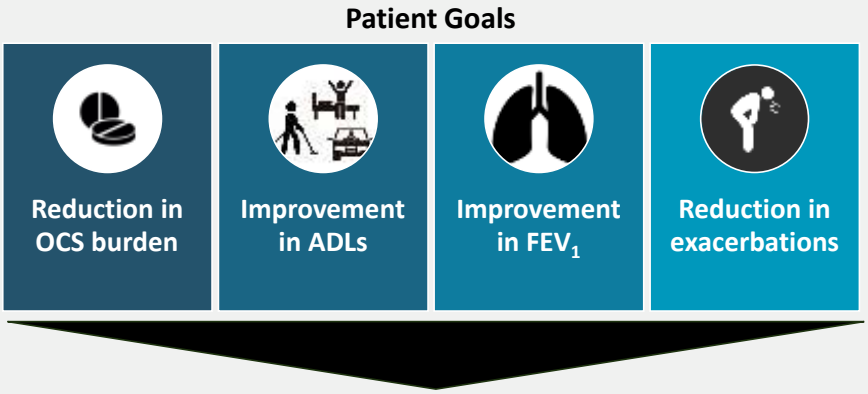
Biologic Therapies and Predictors of Response

Anti-IgE *(omalizumab)*	• Blood eosinophils ≥260/µL ++ • FeNO ≥20 ppb + • Allergen-driven symptoms + • Childhood-onset asthma +
Anti-IL-5/Anti-IL-5R *(benralizumab, mepolizumab, reslizumab)*	• Blood eosinophils ≥260/µL ++ • FeNO ≥20 ppb + • Allergen-driven symptoms + • Childhood-onset asthma +
Anti-IL-4Rα *(dupilumab)*	• Higher blood eosinophils +++ • Higher FeNO +++ • Maintenance OCS
Anti-TSLP *(tezepelumab)*	• Higher blood eosinophils +++ • Higher FeNO +++

Patient Test Results

BEC	305 cells/µL
FeNO	50 ppb
Total serum IgE	100 kU/L; specific IgE (RAST) was negative
Other	No comorbidities Required OCS to maintain control on medium dose ICS + LABA

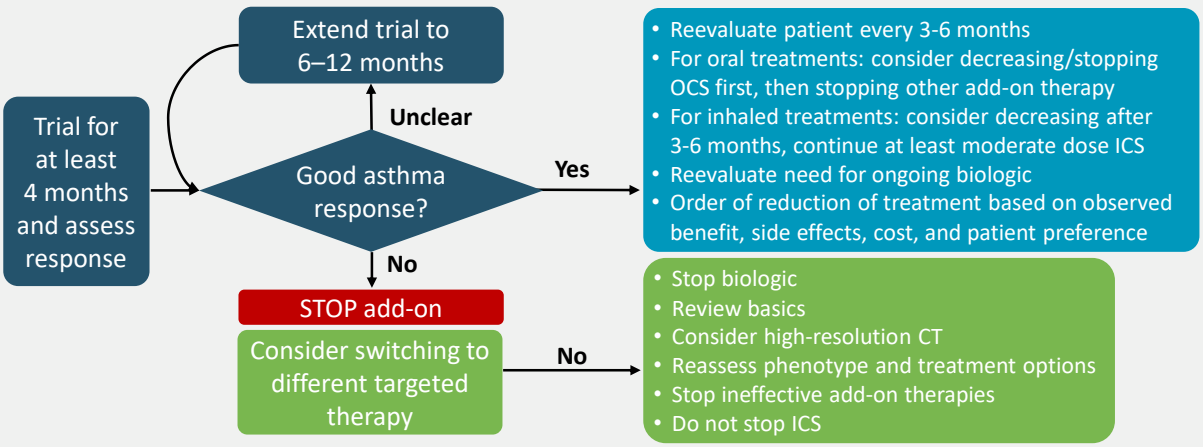
What Does Treatment Success Look Like?



Patient satisfaction determines whether treatment is successful

ADLs, activities of daily living.

Implementing a Trial of Biologic Therapy – GINA 2023



CT, computed tomography.

GINA. Reports. Available at: https://ginasthma.org/reports

Conclusion

Summary and Key Points

- Assess asthma symptom control at every opportunity
- Specialist referral
  - Early in the disease course
  - For uncontrolled asthma despite good adherence and correct inhaler technique
  - Utilize the EHR for consultation, referral, and ongoing interdisciplinary management
  - Include a comprehensive assessment, with phenotype/biomarker testing
- Biologics
  - Not just for “severe” asthma
  - Be familiar, even if not prescribing
- Engage patients with shared decision-making

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Questions and Answers

Thank You!