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The 2020 NIH Asthma Guidelines Updates Are Here (and they will likely change your practice)

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Conflict of Interest

- **Research support:**
  - American Lung Association
  - Astra Zeneca
  - Novartis
  - Takeda
  - Biocryst
- **Consultant:**
  - NIH

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Objectives

- **Identify the past and current ways of classifying asthma**
- **To apply guideline changes in asthma diagnosis, monitoring, and treatment based on evidence and shared decision making**
- **To determine the strengths and limitations of the new Asthma Management Guidelines**

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Question?

- **What is asthma?**

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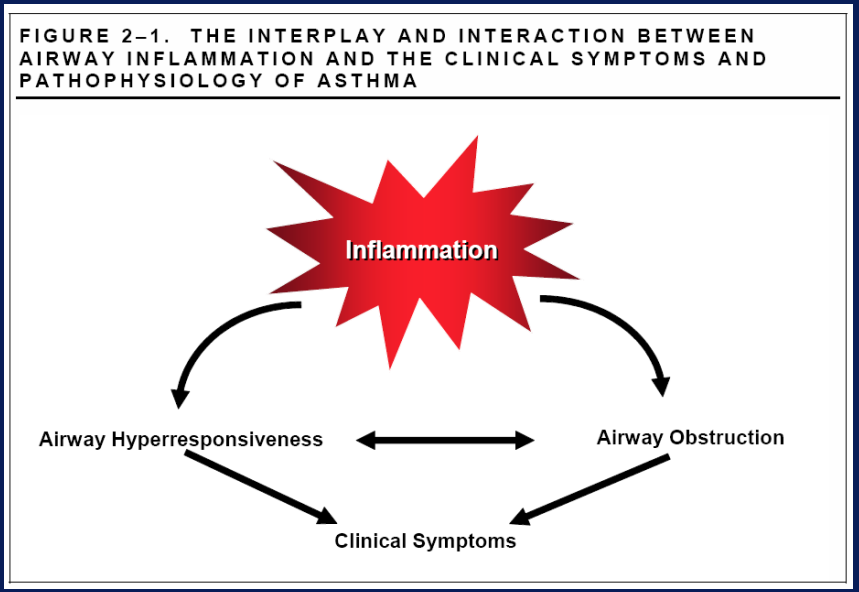
Definition of Asthma

"Asthma is a common chronic disorder of the airways that involves a complex interaction of airflow obstruction, bronchial hyperresponsiveness and an underlying inflammation. This interaction can be highly variable among patients and within patients over time".



2007 NAEPP Guidelines, EPR 3- Section 2, p 12.

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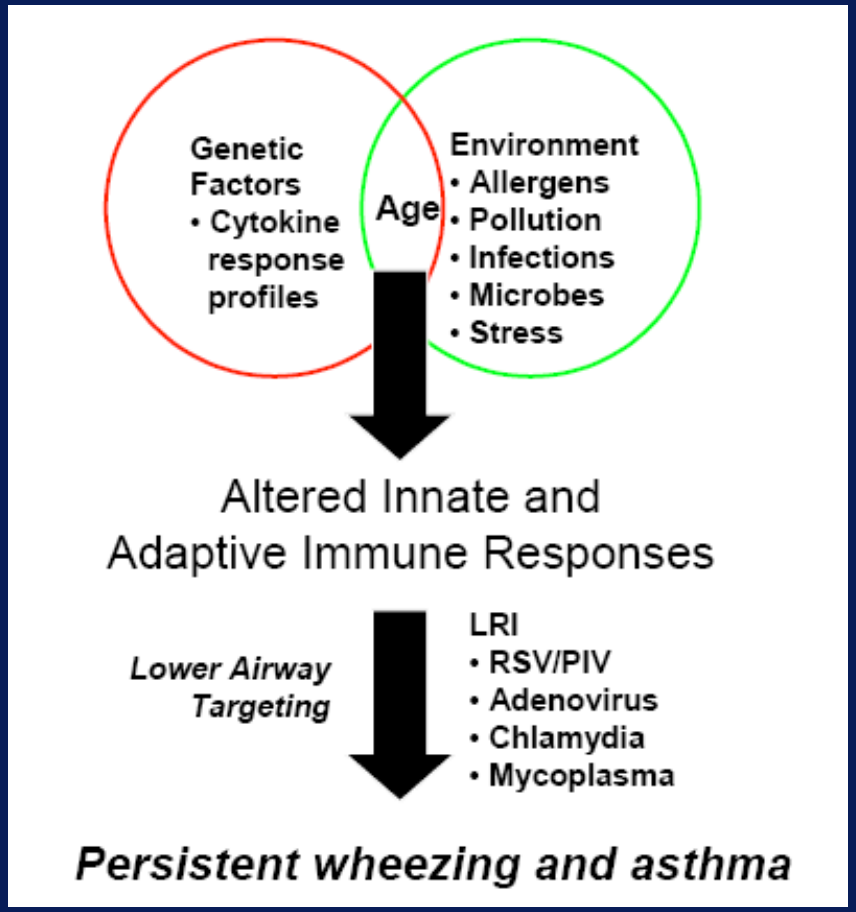
Pathogenesis of Asthma



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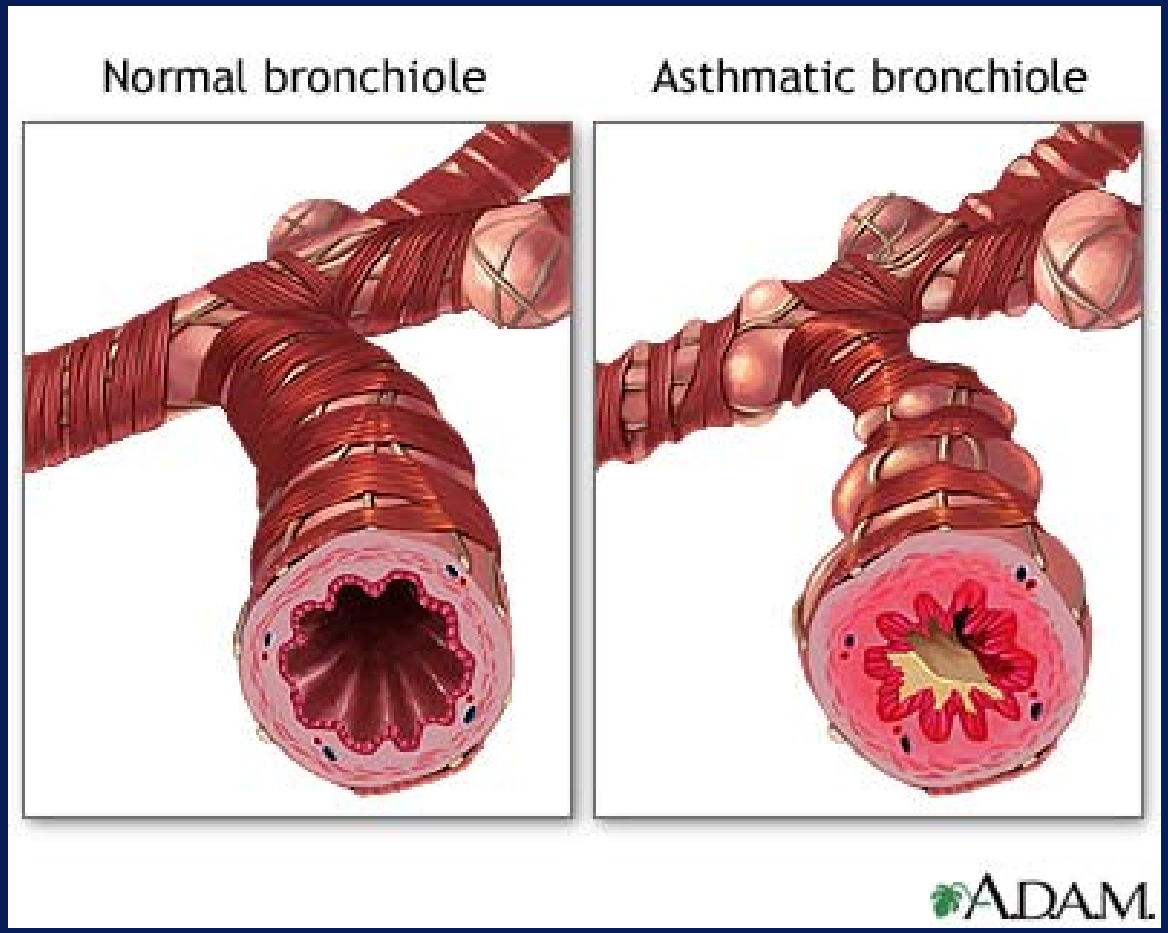
Normal and Asthmatic Bronchiole



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Asthma Is Prevalent: Significant Morbidity and Mortality

34 Million People Have Had an Asthma Diagnosis in Their Lifetime

25 Million People Are Currently Diagnosed With Asthma

11.2 Million People Suffer From Asthma Attacks Annually

Approximately 3500 Asthma-Related Deaths Occur Annually

Approximately 9 People Die From Asthma Each Day

Available at: https://www.cdc.gov/asthma/most_recent_national_asthma_data.htm/. Accessed March 13, 2021.

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Who to refer to a specialist?

- **Patient has had a life-threatening asthma exacerbation**
- **Patient not meeting the goals of asthma therapy after 3 – 6 months**
- **Atypical signs or symptoms**
- **Additional diagnostic testing needed (skin testing, PFTs, bronchoscopy, rhinoscopy)**
- **Patient requires additional education**
- **Patient requires step 4 or higher (consider for step 3)**
- **Patient has had more than two bursts of steroids in past year, or has an exacerbation requiring hospitalization**

2007 NAEPP Guidelines, EPR 3

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Risk factors for death from asthma

FIGURE 5-2a. RISK FACTORS FOR DEATH FROM ASTHMA

Asthma history

Previous severe exacerbation (e.g., intubation or ICU admission for asthma)
Two or more hospitalizations for asthma in the past year
Three or more ED visits for asthma in the past year
Hospitalization or ED visit for asthma in the past month
Using > 2 canisters of SABA per month
Difficulty perceiving asthma symptoms or severity of exacerbations
Other risk factors: lack of a written asthma action plan, sensitivity to *Alternaria*

Social history

Low socioeconomic status or inner-city residence
Illicit drug use
Major psychosocial problems

Comorbidities

Cardiovascular disease
Other chronic lung disease
Chronic psychiatric disease

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All that wheezes is not asthma…

Table 2 **Differential diagnosis of difficult-to-control asthma**
Chronic obstructive pulmonary disease
Bronchiectasis
Vocal cord dysfunction syndrome
Tracheobronchomalacia
Steroid-withdrawal syndrome*
Churg-Strauss syndrome
Aspirated foreign body/endobronchial obstruction
Bronchiolitis obliterans (*e.g.*, in rheumatoid arthritis or ulcerative colitis)
Sarcoidosis
Disseminated strongyloidiasis
Pulmonary thromboembolism
Diastolic dysfunction with congestive heart failure ("cardiac asthma")
**Symptomatic deterioration without objective evidence for worsened airflow obstruction, because of nonrespiratory symptoms associated with oral steroid withdrawal.*

Allergy Asthma Proc. 2012;33(4):305-12

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Don't forget about comorbidities

- **Allergic upper airway disease / sinusitis**
- **GERD**
- **Obesity**
- **OSA**
- **Smoking**
- **Psychiatric disorders**
- **Medications (ACE, NSAIDS, β blockers)**
- **Hormonal influences**

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Consider non-medical therapies

- **Adherence**
- **Education**
- **Adverse environment**

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Asthma Classification – 1997 and 2002 guidelines

Table 3

Asthma Classification and Treatment Based on Severity

Components	Intermittent	Mild Persistent	Moderate Persistent	Severe Persistent
Symptoms	≤ 2 days/week	> 2 days/week	Daily	Throughout the day
Nighttime awakenings	≤ 2/month	3–4/month	> 1/week but not nightly	Nightly
SABA use for symptom control	≤ 2 days/ week	> 2 days/week but not daily; not > 1x on any day	Daily	Several times/day
Interference with normal activity	None	Minor limitation	Some limitation	Extreme limitation
Lung function	Normal FEV_1 during exacerbations; FEV_1 > 80% predicted; FEV_1 /FVC normal	FEV_1 > 80% predicted; FEV_1/FVC normal	FEV_1 60–80% predicted; FEV_1 /FVC reduced 5%	FEV_1 < 60% predicted; FEV_1 /FVC reduced > 5%

Abbreviations: FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; SABA, short-acting beta-agonist

Adapted from: National Asthma Education and Prevention Program Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. *Bethesda, MD: National Heart, Lung, and Blood Institute, US Dept of Health and Human Services; 2007. NIH publication 08-5846.*

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Asthma Classification – 2007 guidelines

Components of Severity		Classification of Asthma Severity (Youths ≥12 years of age and adults)			
		Intermittent	Persistent		
			Mild	Moderate	Severe
Impairment Normal FEV_1/FVC: 8-19 yr 85% 20-39 yr 80% 40-59 yr 75% 60-80 yr 70%	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	≤2x/month	3-4x/month	>1x/week but not nightly	Often 7x/week
	Short-acting $beta_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not >1x/day	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function	• 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 reduced 5%	• FEV_1 <60% predicted • FEV_1/FVC reduced >5%
Risk	Exacerbations requiring oral systemic corticosteroids	0-1/year	≥2/year →		
		← Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category. →			
		Relative annual risk of exacerbations may be related to FEV_1			

2007 NAEPP Guidelines, EPR 3

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Asthma Classification – 2007 guidelines

- **Control for short-term (impairment):**
  - Albuterol use ≤ 2X/week
  - Daytime symptoms ≤ 2X/week
  - Nocturnal symptoms ≤ 2X/month
  - No activity limitation
  - Normal spirometry (FEV1 and FEV1/FVC)
- **Control for long-term (risk):**
  - ED visits or hospitalizations < 2X/year
  - Courses of oral steroids < 2X/year
  - Canisters of albuterol < 2X/ year
  - Stable lung function over time

2007 NAEPP Guidelines, EPR 3

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Definition of severe asthma

- **Treatment with a high dose ICS and LABA (or leukotriene modifier/theophylline) OR oral steroids for > 50% of the previous year and still has one of the following:**
  - Poor symptoms control
  - ≥ 2 steroid bursts in the previous year
  - ≥ 1 hospitalization in the previous year
  - FEV1 ≤ 80% after a bronchodilator

ERS/ATS Guidelines on Severe Asthma. Eur Respir J 2014; 43: 343 - 73

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Classification of asthma

- **Intermittent – Less that the ‘rule of 2’**
- **Mild persistent – more than ‘rule of 2’ but not daily**
- **Moderate persistent – Daily problems**
- **Severe persistent – Can’t control even on high dose therapy**

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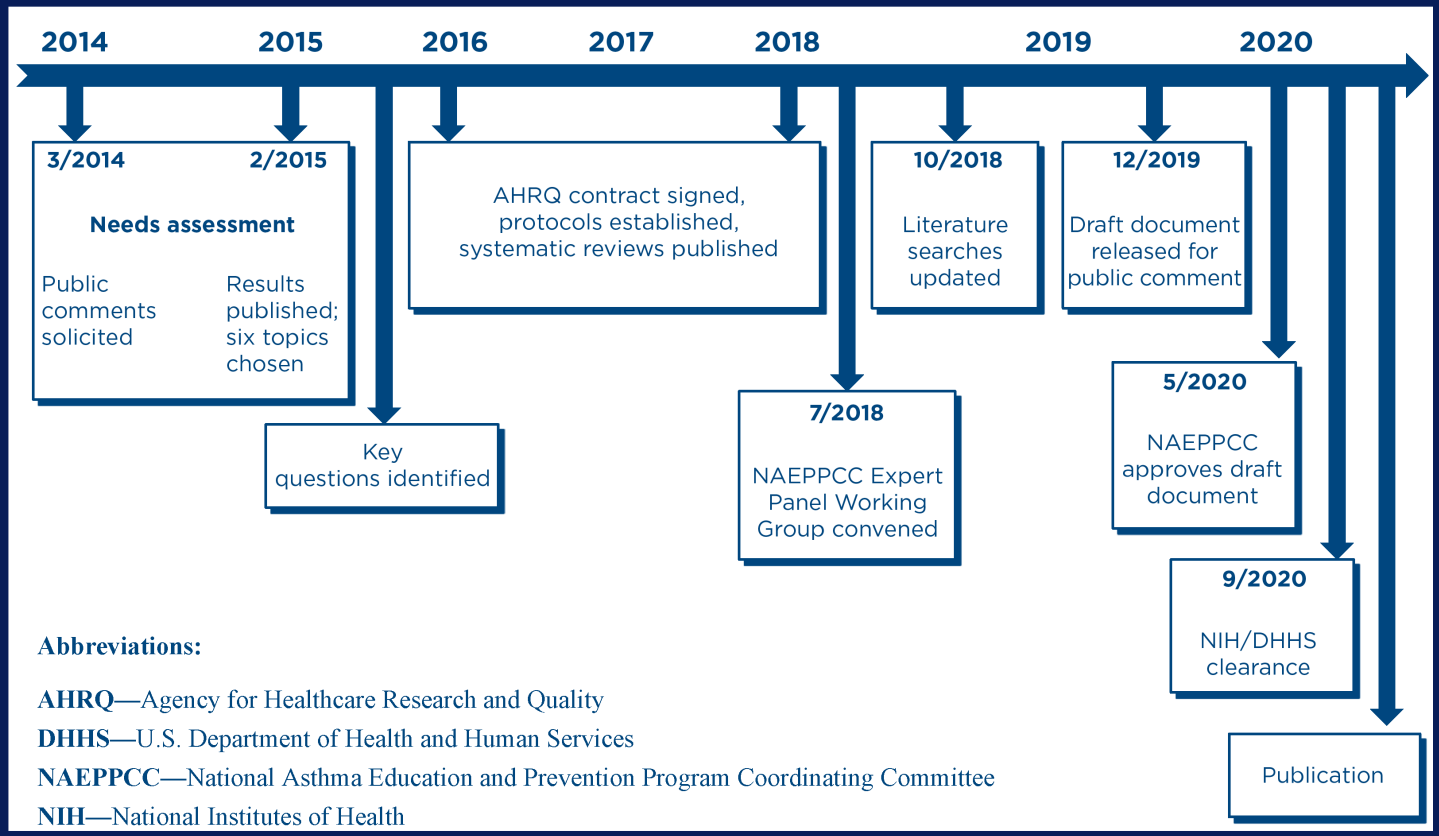
Timeline for Asthma Guidelines 2020 Update



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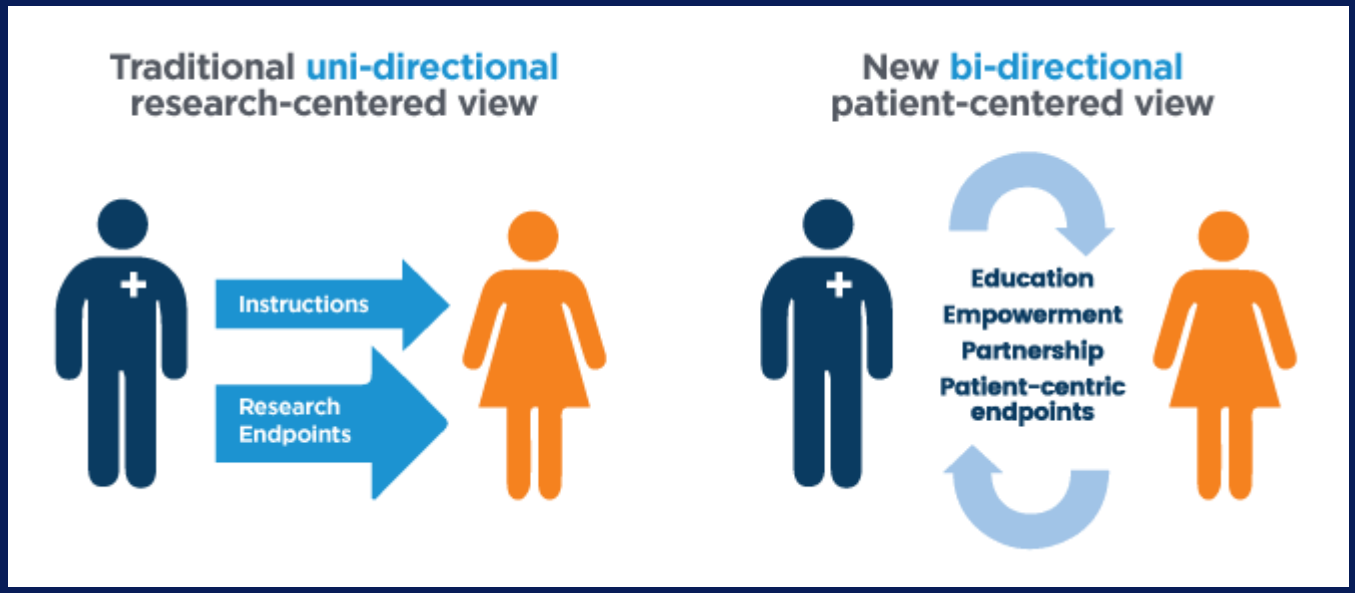
Focused Updates, Not Complete Revision of 2007 Guidelines

- **Improve asthma management and support informed, shared decision making**



- **New guidance in six key areas of asthma diagnosis, management, and treatment**
- **Updates offer 19 recommendations**

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GRADE Methodology

Grading of Recommendations Assessment, Development and Evaluation (GRADE):

- **Framework to determine quality or certainty of evidence and direction and strength of a recommendation.**
- **Used patient-centered outcomes to make judgments:**
  - Critical outcomes: exacerbations, asthma control, asthma-related quality of life
  - Important outcomes: asthma symptoms, rescue med use, others by topic

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GRADE Methodology

- **2 main components to GRADE:**
  - Creation of Evidence Profiles based upon each critical and important outcome.
  - Development of an Evidence to Decision Table for each recommendation.

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Direction and Strength of Recommendation

Evidence-to-Decision (EtD) tables determined direction of each recommendation (for or against intervention) and its strength (strong or conditional).

Implications	Strong Recommendation	Conditional Recommendation
For patients	Most would want; only small proportion would not.	Most would want, but many would not.
For clinicians	Most patients should receive intervention. Formal decision aids likely unnecessary.	Different choices appropriate based on individual values and preferences. Decision aids may be helpful.
For policy makers	Recommendation can be adapted as policy or performance measure.	Will require substantial debate and involvement of stakeholders.
For researchers	Supported by credible research. For low/very low certainty of evidence, new research may provide evidence to alter recommendation.	Likely to be strengthened by additional research.

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Topic Areas

1. Intermittent Inhaled Corticosteroids
2. Long-Acting Muscarinic Antagonists
3. Indoor Allergen Mitigation
4. Immunotherapy in the Treatment of Allergic Asthma
5. Fractional Exhaled Nitric Oxide Testing
6. Bronchial Thermoplasty

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Intermittent ICS – Question 1

- **You see a 3 year old child who presents with occasional wheezing. Should you use intermittent ICS during these episodes?**

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Intermittent ICS – Question 1

- **For children ages 0–4 years with recurrent wheezing triggered by respiratory tract infections only *and no wheezing between infections*, the Expert Panel conditionally recommends**
  - a **short course of daily ICS** at the onset of a respiratory tract infection
  - with an inhaled **short-acting beta$_2$-agonist** (SABA) as-needed

  (Conditional recommendation, high certainty evidence)

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Intermittent ICS – Question 2

- **Part 2a**
  - In patients with persistent asthma, does increasing the ICS dose during an asthma worsening help?
    - Yes
    - No

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Intermittent ICS – Question 2a

- **For children ages 4 years and older and adults with mild to moderate persistent asthma *who are likely to be adherent to daily ICS treatment*, the Expert Panel conditionally recommends against a short-term increase in the ICS dose for increased symptoms or decreased peak flow. (Conditional recommendation, low certainty evidence.)**

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Intermittent ICS – Question 2b

- **<u>Mild persistent</u> asthma management guidelines**
- **A 25-year-old with asthma is using albuterol 3-4X/week, wakes up 1X/week, and FEV1 is 83%. What would you do?**
  a) Medium dose ICS/formoterol daily and as needed
  b) LTRA daily (e.g. montelukast)
  c) Albuterol and ICS, both as needed
  d) Daily medium dose ICS

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Intermittent ICS – Question 2b, mild asthma

- **For individuals ≥ age 12 with mild persistent asthma, either of the following two treatments are recommended:**
  - a daily low-dose ICS and as-needed SABA for quick-relief therapy, or
  - intermittent as-needed ICS and SABA used one after the other for worsening asthma.

(Conditional recommendation, moderate certainty evidence.)

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Intermittent ICS – Q3

- **Now the moderate and severe persistent asthma patients – can I use an ICS/LABA as their only inhaler?**

ICS – Formoterol Combination

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Intermittent ICS – Q2b, mod/severe asthma

- **For individuals ages 4 years or older with moderate to severe persistent asthma, preferred treatment is a single inhaler with ICS-formoterol used both daily and as-needed. (Strong recommendation, high certainty evidence for ages ≥ 12 years, moderate certainty evidence for ages 4–11 years.)**
- **For individuals ages 12 years or older with moderate to severe persistent asthma, preferred treatment is a single inhaler with ICS-formoterol used both daily and as-needed compared to daily higher dose ICS-long-acting bronchodilator combination with as-needed SABA. (Conditional recommendation, high certainty evidence.)**
- **BOTTOM LINE – Use ICS/fomoterol as controller and reliever for your moderate to severe persistent asthma patients**

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LAMA therapy in those age ≥ 12

- **3 questions:**
  - Patient on ICS alone, is LAMA as good as adding LABA?
  - Patient on ICS alone, what is a good step up option?
  - Patient on ICS + LABA, will LAMA help?

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LAMA therapy in those age ≥ 12

- **If asthma not controlled by ICS therapy alone, adding a LABA rather than a LAMA to an ICS is recommended. (Conditional recommendation, moderate certainty.)**

ICS + LABA	>	ICS + LAMA

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LAMA therapy in those age ≥ 12

- **If a LABA cannot be used (unable to tolerate, contraindication, inability to use device, unavailability) adding a LAMA to an ICS is an acceptable alternative. (Conditional recommendation, moderate certainty.)**

ICS + LAMA	>	ICS + nothing

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LAMA therapy question

- **A patient is on an ICS-LABA. Adding a LAMA will improve:**
  a) Asthma exacerbations requiring OCS
  b) Asthma quality of life
  c) Rescue albuterol use
  d) None of these

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LAMA therapy in those age ≥ 12

- **If asthma is not controlled with ICS-LABA, adding a LAMA is recommended for many people because it offers a small potential benefit. (Conditional recommendation, moderate certainty.)**

ICS + LABA + LAMA > ICS + LABA

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Indoor Allergen Mitigation

- **Does control of the indoor environment help in asthma? What is best way to do so? Should we do for everyone?**

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Indoor Allergen Mitigation

- **For individuals with asthma with no history of exposure and no allergies (IgE or sensitization) or symptoms after exposure to indoor allergens, environmental interventions in the home are not recommended.**
- **For individuals with asthma who are exposed and allergic to a specific indoor substance using multiple strategies to reduce the allergen is recommended—using only one strategy often does not improve asthma outcomes.**
- **For individuals with asthma who are sensitive to dust mites, impermeable pillow/mattress covers are recommended only as part of a multicomponent intervention.**
- **Integrated pest management in the home is recommended for individuals with asthma who are allergic and exposed to cockroaches, mice, or rats.**

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Immunotherapy for asthma

- **Should I use subcutaneous immunotherapy (SCIT) for asthma? What about sublingual immunotherapy (SLIT)?**

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Immunotherapy for asthma

- **Subcutaneous immunotherapy is recommended as an adjunct treatment to standard pharmacotherapy for individuals with mild-moderate allergic asthma who have demonstrated allergic sensitization and evidence of worsening asthma symptoms after exposure to relevant antigen(s). (Conditional recommendation, moderate certainty evidence.)**

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Immunotherapy for asthma

- **In patients with mild asthma, the evidence supports SLIT with house dust mite**
  a) True
  b) False

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Immunotherapy for asthma

- **Evidence reviewed did not support using sublingual immunotherapy to specifically treat allergic asthma. (Conditional recommendation, moderate certainty evidence.)**

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FENO Testing in Asthma

- **Can FENO help to diagnose asthma? Will it predict wheezing toddlers who will develop asthma? Should it be routinely used in choosing medications or monitoring response?**

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FENO Testing in Asthma

- **FeNO measurement may support a diagnosis of asthma in those age ≥ 5 for whom the diagnosis is uncertain even after a complete history, physical examination, and spirometry testing including bronchodilator responsiveness. (Conditional recommendation, moderate certainty evidence.)**
- **May be used as part of ongoing asthma monitoring and management when there is uncertainty in adjusting therapy using clinical and laboratory assessment. (Conditional recommendation, low certainty evidence.)**
- **Should not be used in isolation to assess asthma control, predict a future asthma exacerbation, or assess the severity of an exacerbation. (Strong recommendation, low certainty evidence.)**
- **In children ages 4 years and younger who have recurrent episodes of wheezing, FeNO measurement does not predict the future development of asthma. (Strong recommendation, low certainty evidence.)**

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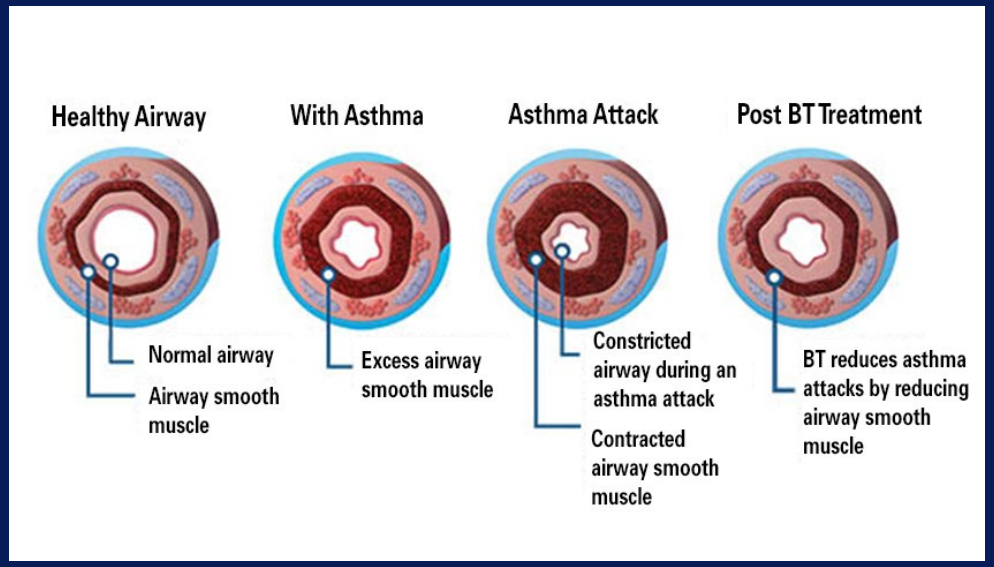
Bronchial Thermoplasty

- **In adult patients with uncontrolled asthma, should I perform bronchial thermoplasty?**



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Bronchial Thermoplasty

- **Most individuals 18 years and older with uncontrolled asthma should not undergo bronchial thermoplasty because benefits are small, risks are moderate, and long-term outcomes are uncertain. (Conditional recommendation, low certainty evidence.)**
- **Some individuals with persistent asthma may be willing to accept the risks of bronchial thermoplasty and, therefore, might choose this intervention after shared decision making with their health care provider.**

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Stepwise table ages 0-4

Figure I.b: Stepwise Approach for Management of Asthma in Individuals Ages 0–4 Years

	Intermittent Asthma	Management of Persistent Asthma in Individuals Ages 0–4 Years				
Treatment	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5	STEP 6
Preferred	PRN SABA and At the start of RTI: Add short course daily ICS▲	Daily low-dose ICS and PRN SABA	Daily low-dose ICS-LABA and PRN SABA▲ or Daily low-dose ICS + montelukast,* or daily medium-dose ICS, and PRN SABA	Daily medium-dose ICS-LABA and PRN SABA	Daily high-dose ICS-LABA and PRN SABA	Daily high-dose ICS-LABA + oral systemic corticosteroid and PRN SABA
Alternative		Daily montelukast* or Cromolyn,* and PRN SABA		Daily medium-dose ICS + montelukast* and PRN SABA	Daily high-dose ICS + montelukast* and PRN SABA	Daily high-dose ICS + montelukast*+ oral systemic corticosteroid and PRN SABA
			For children age 4 years only, see Step 3 and Step 4 on Management of Persistent Asthma in Individuals Ages 5–11 Years diagram.			

Assess Control

- First check adherence, inhaler technique, environmental factors,▲ and comorbid conditions.
- **Step up** if needed; reassess in 4–6 weeks
- **Step down** if possible (if asthma is well controlled for at least 3 consecutive months)

Consult with asthma specialist if Step 3 or higher is required. Consider consultation at Step 2.

Control assessment is a key element of asthma care. This involves both impairment and risk. Use of objective measures, self-reported control, and health care utilization are complementary and should be employed on an ongoing basis, depending on the individual's clinical situation.

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Stepwise table ages 5 - 11

Figure I.c: Stepwise Approach for Management of Asthma in Individuals Ages 5–11 Years

	Intermittent Asthma	Management of Persistent Asthma in Individuals Ages 5–11 Years				
Treatment	**STEP 1**	**STEP 2**	**STEP 3**	**STEP 4**	**STEP 5**	**STEP 6**
Preferred	PRN SABA	Daily low-dose ICS and PRN SABA	Daily and PRN combination low-dose ICS-formoterol▲	Daily and PRN combination medium-dose ICS-formoterol▲	Daily high-dose ICS-LABA and PRN SABA	Daily high-dose ICS-LABA + oral systemic corticosteroid and PRN SABA
Alternative		Daily LTRA,* or Cromolyn,* or Nedocromil,* or Theophylline,* and PRN SABA	Daily medium-dose ICS and PRN SABA or Daily low-dose ICS-LABA, or daily low-dose ICS + LTRA,* or daily low-dose ICS +Theophylline,* and PRN SABA	Daily medium-dose ICS-LABA and PRN SABA or Daily medium-dose ICS + LTRA* or daily medium-dose ICS + Theophylline,* and PRN SABA	Daily high-dose ICS + LTRA* or daily high-dose ICS + Theophylline,* and PRN SABA	Daily high-dose ICS + LTRA* + oral systemic corticosteroid or daily high-dose ICS + Theophylline* + oral systemic corticosteroid, and PRN SABA
		Steps 2–4: Conditionally recommend the use of subcutaneous immunotherapy as an adjunct treatment to standard pharmacotherapy in individuals ≥ 5 years of age whose asthma is controlled at the initiation, build up, and maintenance phases of immunotherapy▲			Consider Omalizumab**▲	

Assess Control

- First check adherence, inhaler technique, environmental factors,▲ and comorbid conditions.
- **Step up** if needed; reassess in 2–6 weeks
- **Step down** if possible (if asthma is well controlled for at least 3 consecutive months)

Consult with asthma specialist if Step 4 or higher is required. Consider consultation at Step 3.

Control assessment is a key element of asthma care. This involves both impairment and risk. Use of objective measures, self-reported control, and health care utilization are complementary and should be employed on an ongoing basis, depending on the individual's clinical situation.

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Stepwise table ages ≥ 12

Figure I.d: Stepwise Approach for Management of Asthma in Individuals Ages 12 Years and Older

Treatment	Intermittent Asthma: STEP 1	Management of Persistent Asthma in Individuals Ages 12+ Years: STEP 2	STEP 3	STEP 4	STEP 5	STEP 6 ■
Preferred	PRN SABA	Daily low-dose ICS and PRN SABA or PRN concomitant ICS and SABA▲	Daily and PRN combination low-dose ICS-formoterol▲	Daily and PRN combination medium-dose ICS-formoterol▲	Daily medium-high dose ICS-LABA + LAMA and PRN SABA▲	Daily high-dose ICS-LABA + oral systemic corticosteroids + PRN SABA
Alternative		Daily LTRA* and PRN SABA or Cromolyn,* or Nedocromil,* or Zileuton,* or Theophylline,* and PRN SABA	Daily medium-dose ICS and PRN SABA or Daily low-dose ICS-LABA, or daily low-dose ICS + LAMA,▲ or daily low-dose ICS + LTRA,* and PRN SABA or Daily low-dose ICS + Theophylline* or Zileuton,* and PRN SABA	Daily medium-dose ICS-LABA or daily medium-dose ICS + LAMA, and PRN SABA▲ or Daily medium-dose ICS + LTRA,* or daily medium-dose ICS + Theophylline,* or daily medium-dose ICS + Zileuton,* and PRN SABA	Daily medium-high dose ICS-LABA or daily high-dose ICS + LTRA,* and PRN SABA	
		Steps 2–4: Conditionally recommend the use of subcutaneous immunotherapy as an adjunct treatment to standard pharmacotherapy in individuals ≥ 5 years of age whose asthma is controlled at the initiation, build up, and maintenance phases of immunotherapy▲			Consider adding Asthma Biologics (e.g., anti-IgE, anti-IL5, anti-IL5R, anti-IL4/IL13)**	

Assess Control

- First check adherence, inhaler technique, environmental factors,▲ and comorbid conditions.
- **Step up** if needed; reassess in 2–6 weeks
- **Step down** if possible (if asthma is well controlled for at least 3 consecutive months)

Consult with asthma specialist if Step 4 or higher is required. Consider consultation at Step 3.

Control assessment is a key element of asthma care. This involves both impairment and risk. Use of objective measures, self-reported control, and health care utilization are complementary and should be employed on an ongoing basis, depending on the individual's clinical situation.

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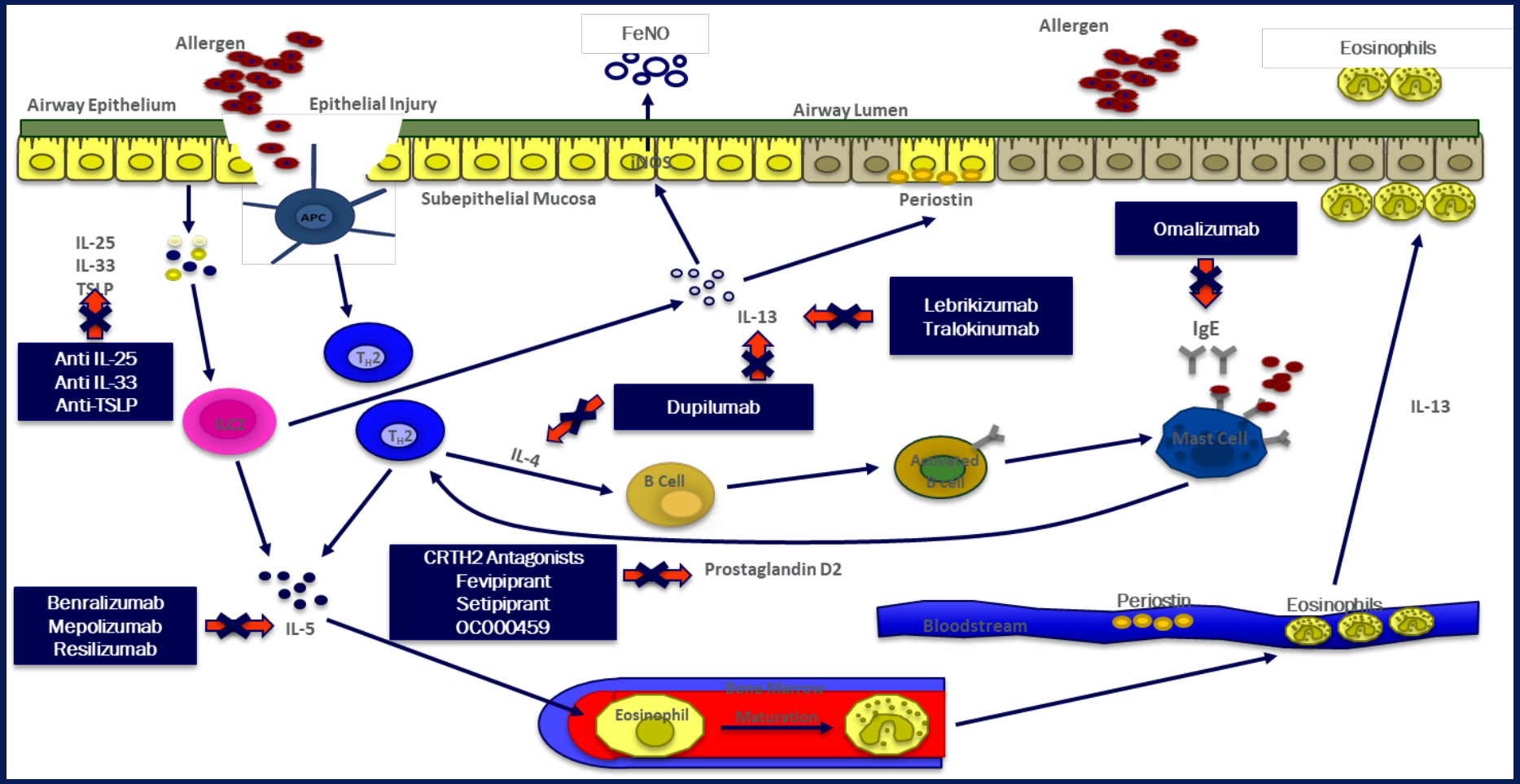
Novel therapies targeting T2 high asthma



Parulekar A et al. *Curr Opin Pulm Med* 2017

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Comparison of FDA approved meds

	Age	Target	Route	Frequency	Dose	Biomarker
Omalizumab	>6	IgE	SC	Q2-4W	weight/IgE	IgE/eos/FENO
Mepolizumab	>6	IL-5	SC	Q4W	fixed	eos > 150
Reslizumab	>18	IL-5	IV	Q4W	weight	eos > 400
Benralizumab	>12	IL-5R	SC	Q8W	fixed	eos > 300
Dupilumab	>12	IL-4/IL-13	SC	Q2W	fixed	eos/FENO

	Exacerbation rate reduction	FEV1 improvement	OCS reduction	Symptoms / QOL
Omalizumab	50%	mixed	Yes	Yes
Mepolizumab	53 - 58%	0.1L	Yes	mixed
Reslizumab	50 - 59%	0.13L	No	mixed
Benralizumab	50 - 70%	0.16L	Yes	mixed
Dupilumab	50 - 80%	0.12-0.25L	Yes	Yes

Wang, FP. Clinic Rev Allerg Immunol (2018) 54: 318.
Assaf, SM. Curr Opin Allerg Immunol (2019) 19(4):379

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Biologics in asthma - $$$

- **Average cost/year (Lexicomp average wholesale price)**
  - Reslizumab $28,890
  - Omalizumab $4200 – $62,448
  - Mepolizumab $42,540
  - Benralizumab $34,728
  - Dupilumab $43,440

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Conclusion

- **NIH Asthma guideline and primary care:**
  - Use an ICS for URI in toddlers with intermittent wheeze
  - Do not increase ICS during an asthma flare
  - Use ICS and albuterol intermittently in mild persistent asthma
  - Use ICS/formoterol for rescue and maintenance in moderate/severe asthma
  - Triple therapy (ICS/LABA/LAMA) works a bit
  - Offer subcutaneous immunotherapy for mild/moderate asthma
  - Targeted, multicomponent allergen avoidance should be used

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Questions?

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