Asthma “101”

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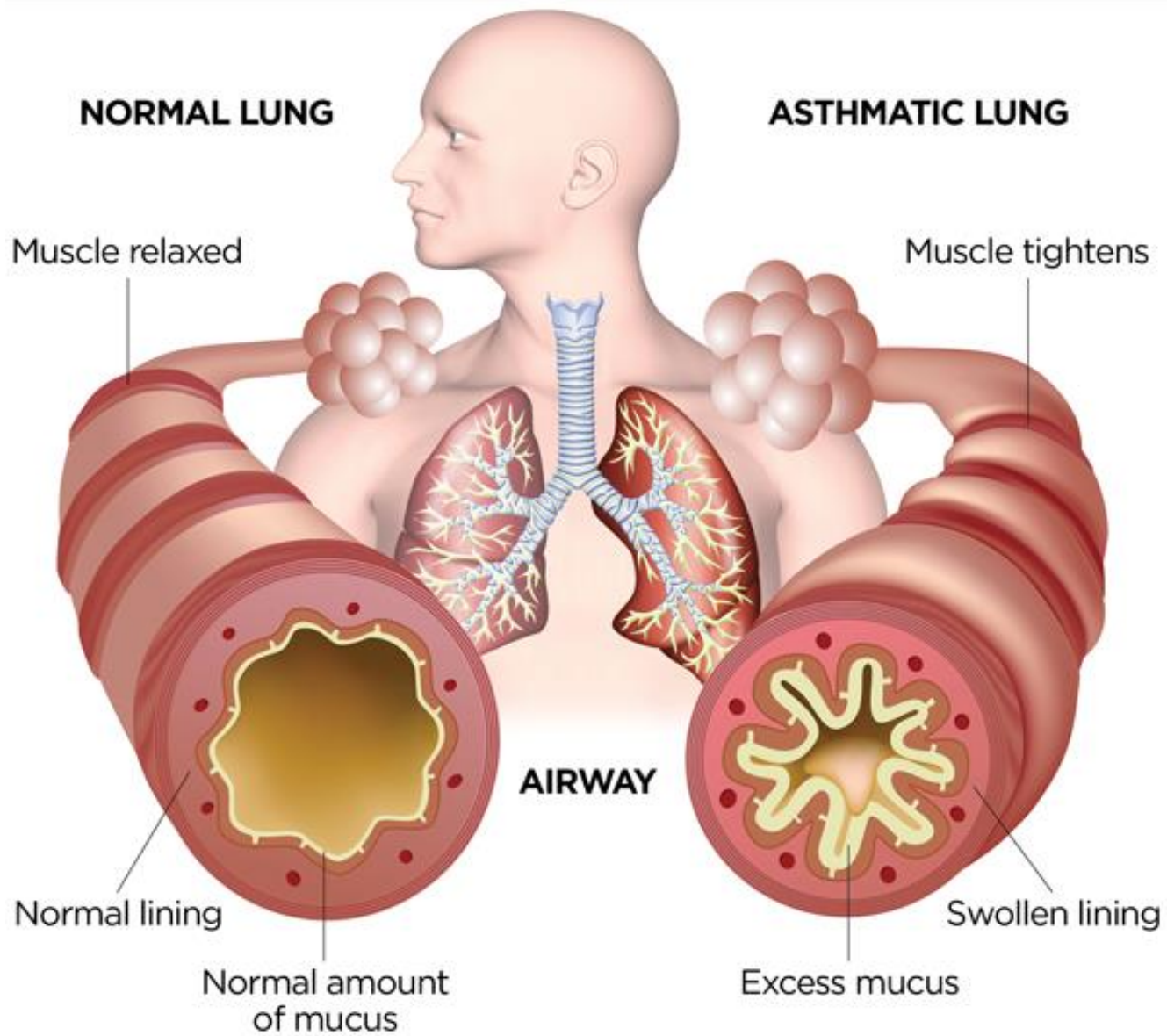
Learning Objectives

- Define asthma and identify high risk patients
- Understand 2020 Focused Updates to the NHLBI Asthma Management Guidelines
- Ensure patients and providers understand and reflect the latest scientific evidence in treatment decisions – CASE REVIEW

Defining Asthma

- Most common chronic non-communicable disease, affecting over 260 million people globally
- *Heterogenous*
- Most of the morbidity and mortality associated with asthma is preventable, particularly with use of inhaled corticosteroids



Asthma and Allergy Foundation of America

ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J. 2014 Apr;43(4):1216.

Is it Asthma? Clinical Attributes

- Perform a careful clinical history and physical exam to exclude asthma mimickers:

  Ask about dyspnea (at rest and in relation to exercise)
  Ask about cough, wheeze, chest tightness, nocturnal awakenings
  Ask about exacerbating factors, environmental and occupational triggers

- Perform spirometry with flow-volume loops before and after bronchodilator to assess for variable expiratory airflow limitation

Asthma: Differential Diagnosis/Mimickers

Clinical clue	Possible diagnosis
PERINATAL AND FAMILY HISTORY	
Symptoms present from birth	Chronic lung disease of prematurity, PCD, CF
Family history of unusual chest disease	CF, Neuromuscular disorders, PCD
Severe upper respiratory tract disease	PCD
SYMPTOMS AND SIGNS	
Persistent moist cough	PBB, Bronchiectasis, Recurrent aspiration, PCD, CF
Excessive vomiting	GERD (w/without aspiration)
Dysphagia	Swallowing problems (w/without aspiration)
Breathlessness with light headedness and peripheral tingling	Dysfunctional breathing, Panic attacks
Inspiratory stridor	Tracheal or laryngeal disorder
Abnormal voice or cry	Laryngeal problems
Focal signs in chest	Developmental anomaly, FB, Post-infective syndrome
Persistent wheeze	Extrinsic intra thoracic airway compression, Airway-malacia, Luminal obstruction, CF, FB
Finger clubbing	CF, Bronchiectasis
Failure to thrive	CF, GERD

CF, cystic fibrosis; FB, foreign body; GERD, gastro-esophageal reflux disease; PBB, protracted bacterial bronchitis; PCD, primary ciliary dyskinesia.

Front. Pediatr., 03 October 2018
Sec Pediatric Pulmonology
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Asthma: Differential Diagnosis/Mimickers

Alternative diagnosis	When to suspect	Useful diagnostic examinations
Cystic fibrosis and bronchiectasis	Daily cough productive of sputum, clubbing, malabsorption and failure to thrive, recurrent chest infections, airways bacterial colonization	Sweat chloride test, Genetic tests, Swab culture, Lung Function tests, Chest CT
Immunodeficiency	Recurrent airway infections, Systemic infections (from a few months of age)	Immunoglobulins and specific tests
Primary ciliary dyskinesia	Neonatal upper airway symptoms, Chronic rhinosinusitis, Recurrent otitis media, Daily wet cough, Laterality defects	Nasal NO, HSVM, EM, Genetic tests, Immunofluorescence, Chest CT
Protracted Bacterial Bronchitis	Cronich wet cough, Poor response to Beta-2 agonists, Good response to prolonged course of antibiotics	Often no need of examinations, Swab culture, Bronchoscopy with BAL
Airway malacia	Monophonic wheeze when the child is active, High risk setting (i.e., pt operated for tracheo-esophageal fistula or vascular ring), Presence of associated stridor	Lung function test (truncated expiratory flow in spirometry), Flexible bronchoscopy, Dynamic CT
Airway foreign body	Abrupt onset of symptoms, History of choking, Unilateral monophonic wheeze, Focal hyperinflation of lung	Bronchoscopy, chest x-ray
Habit cough	Prolonged dry, honking cough; Absence of cough during sleep; Absence of any physical findings	Medical investigations should be avoided
Vocal cord dysfunction	Absence of structural abnormalities, Sudden worsening of "asthma" symptoms, No response to asthma medications	Video of an attack, Laryngoscopy during attack
Bronchiolitis obliterans	History of severe viral respiratory infection in the first 3 years of life	CT scan (characteristic mosaic pattern and air trapping)

CT, computed tomography; EM, eletcron microscopy; HSVM, high speed video microscopy; NO, nitric oxide.

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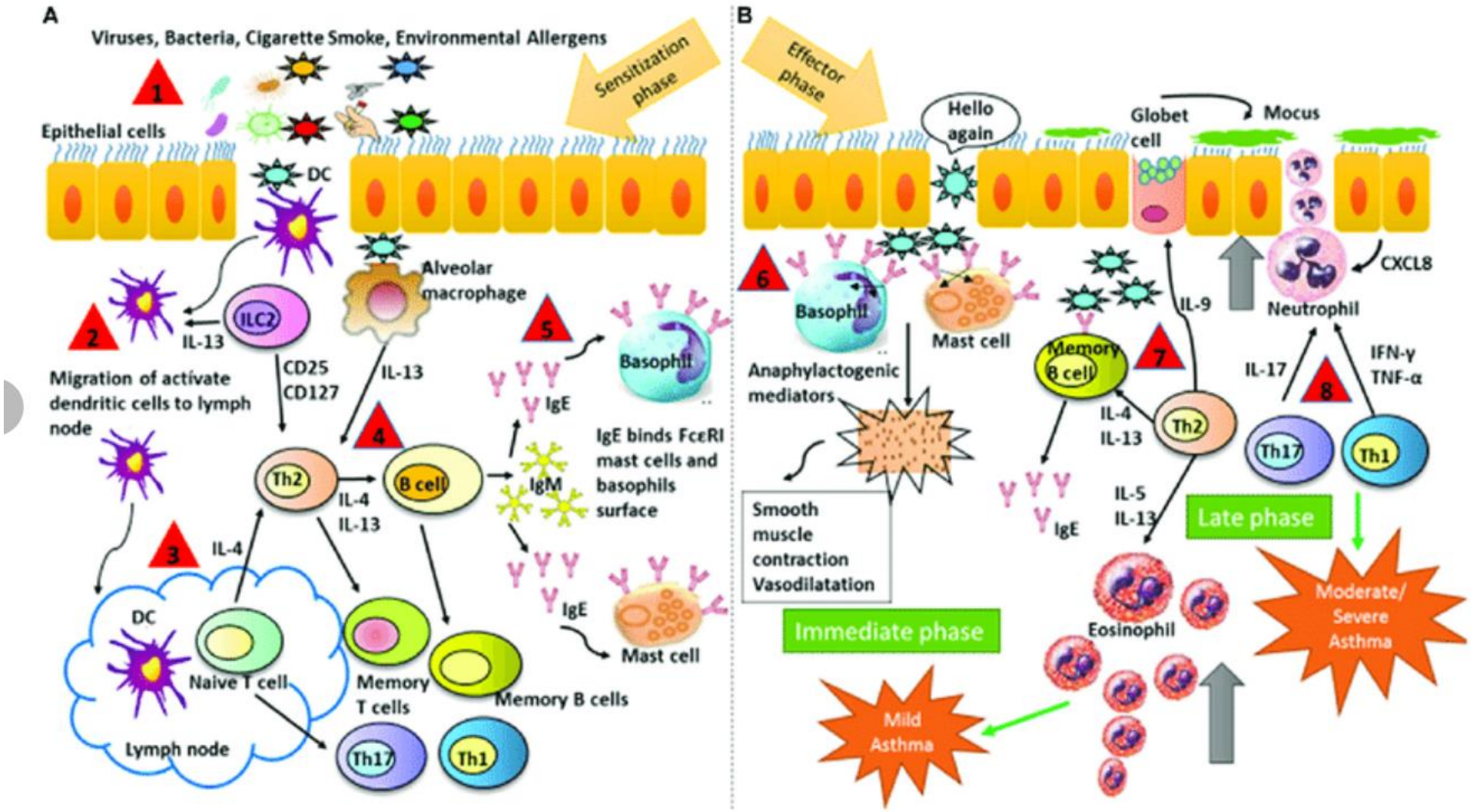
Etiology & Pathogenesis



Martín-Orozco Santiago, Elena et al. 05/23/2017; Regulatory T Cells in Allergy and Asthma Vol 5 DO 10.3389/fped.2017.00117 Frontiers in Pediatrics

Asthma Phenotypes

Allergic Asthma – (environmental)

- Most common - 40-50% of patients with asthma
- Tests – allergy testing, CBC w/ diff (eosinophil (eos) count), total IgE, FeNO
- Treatment – control allergies, decrease exposures, IT, biologics

Exercise Induced Asthma

- Detailed history about when symptoms occur most frequently or consistently
- Test – exercise test (eg running on a treadmill or clinic hallway) and checking lung function after to determine if exercise induces a drop in lung function
- Tx – depends on severity, as needed SABA most common

(Martinez ED, NEJM 1995;332:133-138) Saveije JACI 2012;130:325-31) (Belgrave JACI 2013:132:575-83)

Asthma Phenotypes

Aspirin Sensitive Asthma

- asthma will flare with aspirin or NSAID use
- Less common, may also have chronic rhinitis and/or nasal polyps
- Tests – CBC w/ diff (eos count)
- Tx – leukotriene modifiers, polyp removal, biologics

Neutrophilic Asthma

- most common among those with severe asthma
- Tests – sputum sample
- Tx – consider addition of macrolides

(Martinez ED, NEJM 1995;332:133-138) Saveije JACI 2012;130:325-31) (Belgrave JACI 2013:132:575-83)

The Asthma Predictive Index

Major criteria

- Parent with asthma
- Physician diagnosed atopic dermatitis
- Sensitization to ≥1 aeroallergen

Minor criteria

- Wheezing unrelated to colds
- Blood eosinophils >4%
- Sensitization to food allergens

Indications for spirometry

- Evaluation of patients presenting with dyspnea (typically >5 yrs)
- Evaluating disease severity and monitoring response to treatment

Obstructive vs Restrictive Patterns

MEASUREMENT	OBSTRUCTIVE PATTERN	RESTRICTIVE PATTERN
Forced vital capacity (FVC)	Decreased or normal	Decreased
Forced expiratory Volume in 1 s (FEV1)	Decreased	Decreased or normal
FEV1/FVC ratio	Decreased	Normal
Total lung capacity	Normal or increased	Decreased

Al-Ashkar et al., Pulmonary Function Tests. *Cleveland Journal of Medicine Vol 70, Number 10.* October 2003

EPR-3 Classifying Asthma Severity by Age

Components of Severity			Intermittent			Persistent											
						Mild			Moderate			Severe					
Age in years			0-4	5-11	≥12	0-4	5-11	≥12	0-4	5-11	≥12	0-4	5-11	≥12			
Impair-ment	Daytime symptoms		≤2 days/week			≥2 days/week but not daily			daily			Throughout the day					
	Nocturnal symptoms		0	≤2 x/mo		1-2x/mo	3-4x/mo		3-4x/mo	≥1 x/wk		≥2x/wk	Often, 7x/wk				
	SABA use		≤2 days/wk			≥2 days/wk			daily			Several times/day					
	Interferes with normal activity		none			minor			some			extremely					
	PFTs	FEV_1	n/a	>80%		n/a	>80%		n/a	60-80%		n/a	<60%				
		FEV_1/FVC		>85%	Nl		>80%	Nl		75-80%	↓ by 5%		<75%	↓ by >5%			
Risk	Exacerbations requiring systemic steroids		0-1x/yr			≥2 x/6 mos **or** 4x/yr **+** Risk factors	→										
							>2x/yr →										
Recommended Step for Initiating Therapy			Step 1			Step 2			Step 3	Step 3 Medium-dose ICS option	Step 3	Step 3	Step 3 (medium dose ICS option) or Step 4	Step 4 or 5			

Asthma Guidelines

1. Inhaled Corticosteroids
2. Fractional exhaled nitric oxide (FeNO) in diagnosis, medication selection and monitoring of treatment response in asthma
3. Remediation of indoor allergens (house dust mites/pets) in asthma management
4. Long-acting antimuscarinic agents (LAMA) in asthma management as add-ons to inhaled corticosteroids
5. Immunotherapy and the management of asthma
6. Bronchial thermoplasty (BT) in adult severe asthma

Inhaled Corticosteroids

- **Intermittent use of inhaled corticosteroids (ICS) for children ages 0 to 4, with a current wheeze triggered by respiratory infections only and no wheezing in between -** short course of daily ICS at the first onset of respiratory tract infection with a long-acting beta agonist

- **ICS in individuals 12 years of age and older with mild persistent asthma.** Either of the following two treatments are recommended as part of step two therapy:

  - A daily low dose inhaled corticosteroid with as needed SABA (short acting beta agonist) for quick relief. (GINA no longer recommends SABA by itself)
  - Intermittent use of as needed ICS and SABA – use one right after the other for worsening asthma

Inhaled Corticosteroids

- **Individuals ages 4 or older with moderate to severe persistent asthma.** The recommended treatment is a single inhaler with ICS and formoterol, also known as SMART therapy.
- **Individuals ages 12 or older with moderate to severe persistent asthma.** The recommended treatment is a single inhaler with ICS and formoterol.
- **Should a short-term increase of inhaled corticosteroid be used in children greater than 4 years of age? Should it be used in adults with mild to moderate persistent asthma who are adherent to daily ICS?**

Combination Budesonide-Formoterol as Needed in Mild Asthma (O'Byrne et al., 2018)

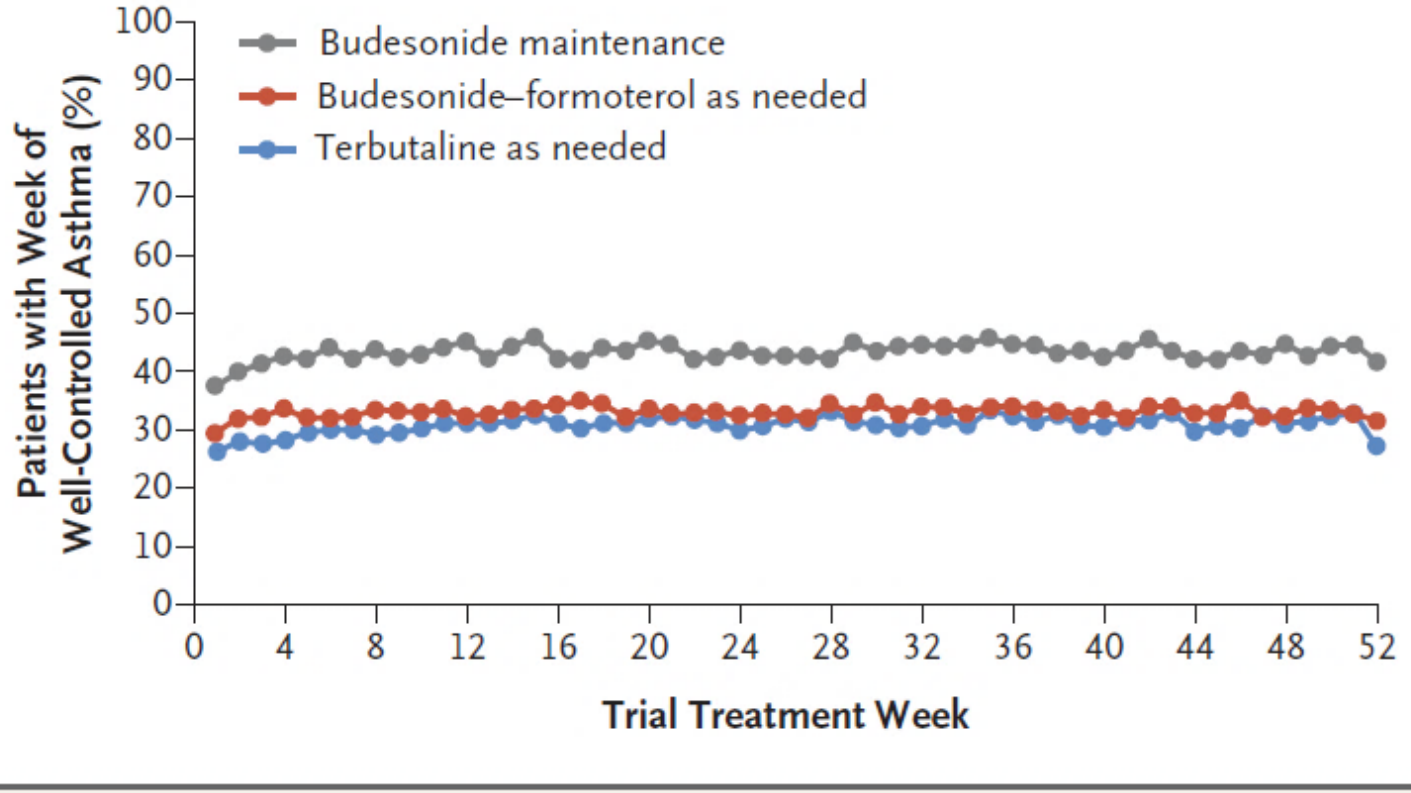


Figure 2. Overall Weeks of Well-Controlled Asthma, According to Data in the Electronic Diary.

O'Byrne, P. M., FitzGerald, J. M., Bateman, E. D., Barnes, P. J., Zhong, N., Keen, C., . . . Reddel, H. K. (2018). Inhaled Combined Budesonide-Formoterol as Needed in Mild Asthma. *N Engl J Med, 378*(20), 1865-1876. doi:10.1056/NEJMoa1715274

Q&A

- **Why is this preferred?**
  - Because using low dose ICS-formoterol as reliever reduces the risk of severe exacerbations compared with regimens with SABA as reliever, with similar symptom control
- **How is it used?**
  - ICS-formoterol should be administered as maintenance therapy with 1-2 puffs once or twice daily and 1-2 puffs as needed for asthma symptoms
  - Maximum number of puffs per day is 8 (36mcg formoterol) for kids 4-11 years, and 12 puffs (54mcg formoterol) in those greater than 12 years
- **When should it not be used?**
  - ICS-formoterol should not be used as the reliever in patients prescribed a different ICS-LABA for their controller therapy

Fractional exhaled Nitric Oxide (FeNO)

- **For patients ages 5 or older.** Fractional exhaled nitric oxide (FeNO) may support a diagnosis of asthma

- FeNO testing may be used as part of ongoing asthma monitoring and management when there is uncertainty and adjusting therapy using clinical and laboratory assessment.

- For patients ages 5 or older, FeNO testing should not be used in isolation to assess asthma control or to predict future exacerbations or assess the severity of an exacerbation

- In children ages 4 years and younger who have recurrent episodes of wheezing, FeNO measurement does not predict the development of future asthma

Allergen Mitigation

- **Individuals with asthma, with no history of exposure and no IgE sensitization or allergy, or symptoms after exposure to indoor allergens-** Environmental control is not recommended
- **Individuals with asthma who are exposed and allergic to a specific indoor allergy and substance-** Using multiple strategies to reduce the allergen is recommended.
- **Individuals with asthma who are sensitive to house dust mites-** Dust mite-proof pillow and mattress covers are recommended, but only as part of a multi-component intervention strategy
- **Individuals with asthma who are allergic and exposed to cockroaches, mice or rats.** Pest management in the home is recommended

Long acting muscarinic antagonist (LAMA)

(in patients >12 years)

- In patients with uncontrolled asthma with ICS therapy alone, or with ICS therapy alone, adding a LABA rather than a LAMA and ICS is recommended

- If a LABA cannot be used, adding a LAMA to ICS is an acceptable alternative

- If asthma is not controlled with ICS-LABA, then adding a long acting muscarinic is recommended for many people because it offers a small potential benefit

Immunotherapy

- **Individuals with mild to moderate asthma who have demonstrated a sensitization to the allergen and evidence of worsening asthma symptoms after exposure.** Immunotherapy is recommended as an adjunct treatment to standard pharmacotherapy

- **The evidence does not support using sublingual immunotherapy to specifically treat allergic asthm**

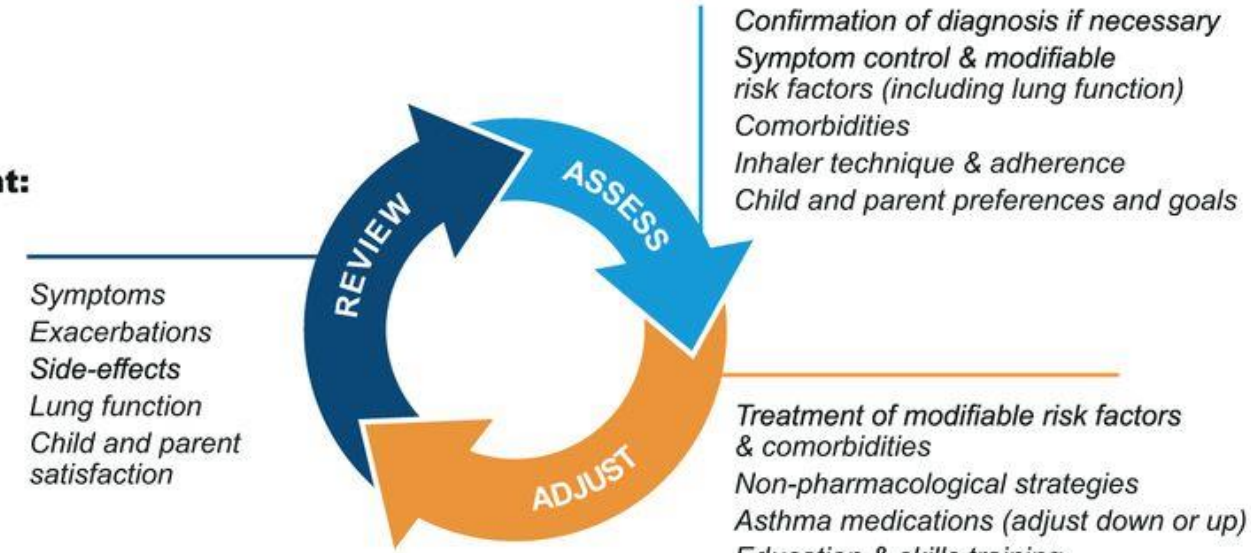
Bronchial Thermoplasty

- **Most individuals 18 years and older with uncontrolled asthma should not undergo bronchial thermoplasty because the benefits are small, the risks are moderate, and long-term outcomes are uncertain**.

Treatment

Children 6-11 years

Personalized asthma management:
Assess, Adjust, Review



Asthma medication options:
Adjust treatment up and down for individual child's needs

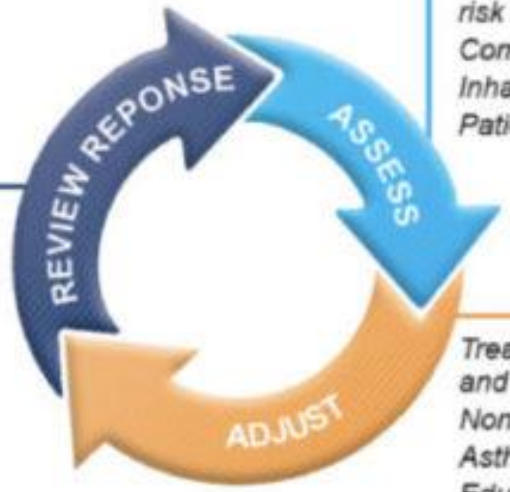
	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
PREFERRED CONTROLLER to prevent exacerbations and control symptoms	Low dose ICS taken whenever SABA taken	Daily low dose inhaled corticosteroid (ICS) (see table of ICS dose ranges for children)	Low dose ICS-LABA, OR medium dose ICS, OR very low dose* ICS-formoterol maintenance and reliever (MART)	Medium dose ICS-LABA, OR low dose† ICS-formoterol maintenance and reliever therapy (MART). Refer for expert advice	Refer for phenotypic assessment ± higher dose ICS-LABA or add-on therapy, e.g. anti-IgE
Other controller options	*Consider daily low dose ICS*	*Daily leukotriene receptor antagonist (LTRA), or low dose ICS taken whenever SABA taken*	*Low dose ICS + LTRA*	*Add tiotropium or add LTRA*	*Add-on anti-IL5, or add-on low dose OCS, but consider side-effects*
RELIEVER	*As-needed short-acting beta2-agonist (or ICS-formoterol reliever for MART as above)*				

**Very low dose: BUD-FORM 100/6 mcg*
†Low dose: BUD-FORM 200/6 mcg (metered doses).

Box 3-5A

Adults & adolescents 12+ years

Personalized asthma management:
Assess, Adjust, Review response



Confirmation of diagnosis if necessary
Symptom control & modifiable risk factors (including lung function)
Comorbidities
Inhaler technique & adherence
Patient preferences and goals

Symptoms
Exacerbations
Side-effects
Lung function
Patient satisfaction

Treatment of modifiable ris
and comorbidities
Non-pharmacological stra
Asthma medications (adju
Education & skills training

ICS-formoterol is the preferred reliever for patients prescribed maintenance and reliever therapy. For other ICS-LABAs, the reliever is SABA

Asthma medication options:
Adjust treatment up and down for individual patient needs

	STEP 1	STEP 2	STEP 3		
PREFERRED CONTROLLER to prevent exacerbations and control symptoms	As-needed low dose ICS-formoterol *	Daily low dose inhaled corticosteroid (ICS), or as-needed low dose ICS-formoterol *	Low dose ICS-LABA		e.g.tiotropium, anti-IgE, anti-IL5/5R, anti-IL4R
Other controller options	*Low dose ICS taken whenever SABA is taken †*	*Daily leukotriene receptor antagonist (LTRA), or low dose ICS taken whenever SABA taken †*	*Medium dose ICS, or low dose ICS+LTRA #*	*High dose ICS, add-on tiotropium, or add-on LTRA #*	*Add low dose OCS, but consider side-effects*
PREFERRED RELIEVER	As-needed low dose ICS-formoterol *		As-needed low dose ICS-formoterol for patients prescribed maintenance and reliever therapy‡		
Other reliever option	*As-needed short-acting β_2-agonist (SABA)*				

* *Data only with budesonide-formoterol (bud-form)*
† *Separate or combination ICS and SABA inhalers*

‡ *Low-dose ICS-form is the reliever only for patients prescribed bud-form or BDP-form maintenance and reliever therapy*
\# *Consider adding HDM SLIT for sensitized patients with*

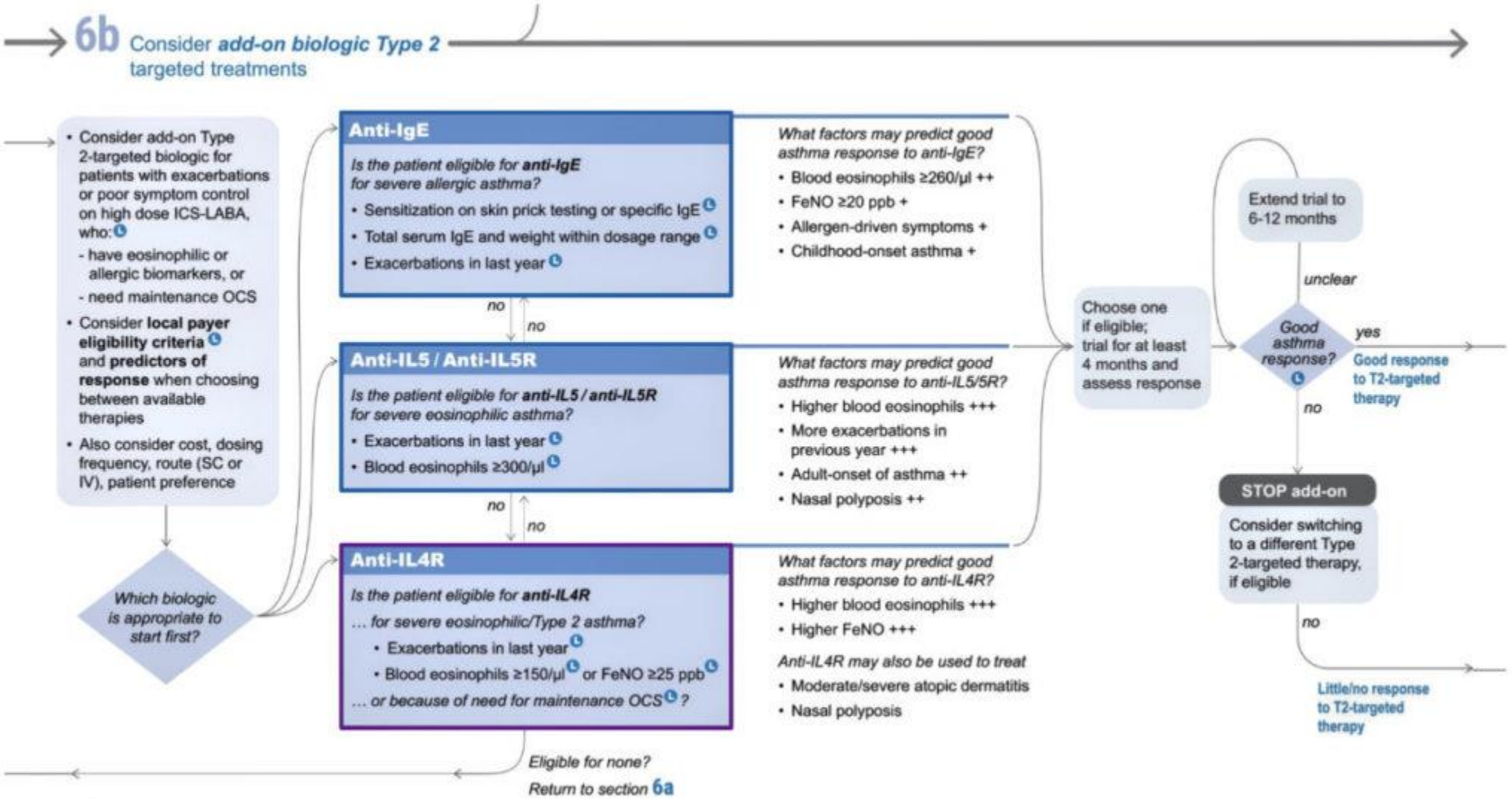
	0–4 years of age			5–11 years of age			≥12 years of age		
Daily Dose	**Low**	**Medium***	**High***	**Low**	**Medium***	**High***	**Low**	**Medium***	**High***
MEDICATION									
Beclomethasone MDI†	N/A	N/A	N/A	80–160 mcg	>160–320 mcg	>320 mcg	80–240 mcg	>240–480 mcg	>480 mcg
40 mcg/puff				1–2 puffs 2x/day	3–4 puffs 2x/day		1–3 puffs 2x/day	4–6 puffs 2x/day	
80 mcg/puff				1 puff 2x/day	2 puffs 2x/day	≥3 puffs 2x/day	1 puff am, 2 puffs pm	2–3 puffs 2x/day	≥4 puffs 2x/day
Budesonide DPI†	N/A	N/A	N/A	180–360 mcg	>360–720 mcg	>720 mcg	180–540 mcg	>540–1,080 mcg	>1,080 mcg
90 mcg/inhalation				1–2 inhs† 2x/day	3–4 inhs† 2x/day		1–3 inhs† 2x/day		
180 mcg/ inhalation					2 inhs† 2x/day	≥3 inhs† 2x/day	1 inh† am, 2 inhs† pm	2–3 inhs† 2x/day	≥4 inhs† 2x/day
Budesonide Nebules	0.25–0.5 mg	>0.5–1.0 mg	>1.0 mg	0.5 mg	1.0 mg	2.0 mg	N/A	N/A	N/A
0.25 mg	1–2 nebs†/day			1 neb† 2x/day					
0.5 mg	1 neb†/day	2 nebs†/day	3 nebs†/day	1 neb†/day	1 neb† 2x/day				
1.0 mg		1 neb†/day	2 nebs†/day		1 neb†/day	1 neb† 2x/day			
Ciclesonide MDI†	N/A	N/A	N/A	80–160 mcg	>160–320 mcg	>320 mcg	160–320 mcg	>320–640 mcg	>640 mcg
80 mcg/puff				1–2 puffs/day	1 puff am, 2 puffs pm– 2 puffs 2x/day	≥3 puffs 2x/day	1–2 puffs 2x/day	3–4 puffs 2x/day	
160 mcg/puff				1 puff/day	1 puff 2x/day	≥2 puffs 2x/day		2 puffs 2x/day	≥3 puffs 2x/day
Flunisolide MDI†	N/A	N/A	N/A	160 mcg	320–480 mcg	≥480 mcg	320 mcg	>320–640 mcg	>640 mcg
80 mcg/puff				1 puff 2x/day	2–3 puffs 2x/day	≥4 puffs 2x/day	2 puffs 2x/day	3–4 puffs 2x/day	≥5 puffs 2x/day

	0–4 years of age			5–11 years of age			≥12 years of age		
Daily Dose	**Low**	**Medium***	**High***	**Low**	**Medium***	**High***	**Low**	**Medium***	**High***
MEDICATION									
Fluticasone MDI†	176 mcg	>176–352 mcg	>352 mcg	88–176 mcg	>176–352 mcg	>352 mcg	88–264 mcg	>264–440 mcg	>440 mcg
44 mcg/puff	2 puffs 2x/day	3–4 puffs 2x/day		1–2 puffs 2x/day	3–4 puffs 2x/day		1–3 puffs 2x/day		
110 mcg/puff		1 puff 2x/day	≥2 puffs 2x/day		1 puff 2x/day	≥2 puffs 2x/day		2 puffs 2x/day	3 puffs 2x/day
220 mcg/puff								1 puffs 2x/day	≥2 puffs 2x/day
Fluticasone DPI†	N/A	N/A	N/A	100–200 mcg	>200–400 mcg	>400 mcg	100–300 mcg	>300–500 mcg	>500 mcg
50 mcg/inhalation				1–2 inhs† 2x/day	3–4 inhs† 2x/day		1–3 inhs† 2x/day		
100 mcg/inhalation				1 inh† 2x/day	2 inhs† 2x/day	>2 inhs† 2x/day		2 inhs† 2x/day	≥3 inhs† 2x/day
250 mcg/inhalation						1 inh† 2x/day		1 inh† 2x/day	≥2 inhs† 2x/day
Mometasone DPI†	N/A	N/A	N/A	110 mcg	220–440 mcg	>440 mcg	110–220 mcg	>220–440 mcg	>440 mcg
110 mcg/inhalation				1 inh†/day	1–2 inhs† 2x/day	≥3 inhs† 2x/day	1–2 inhs† pm	3–4 inhs† pm or 2 inhs† 2x/day	≥3 inhs† 2x/day
220 mcg/inhalation					1–2 inhs†/day	≥3 inhs† divided in 2 doses	1 inh† pm	1 inh† 2x/day or 2 inhs† pm	≥3 inhs† divided in 2 doses

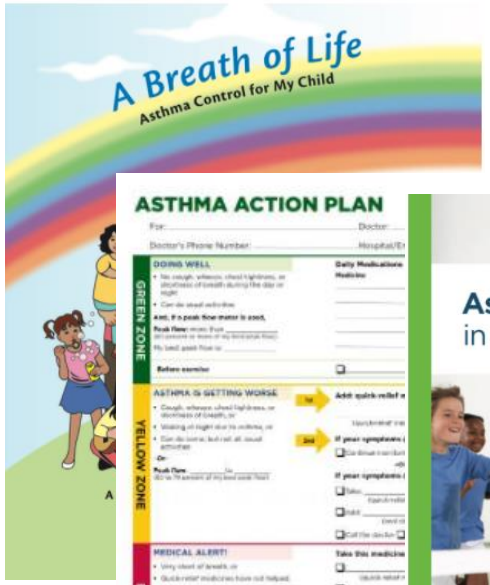
Diagnosis and Management of Difficult to Treat or Severe Asthma in Adults/Adolescents

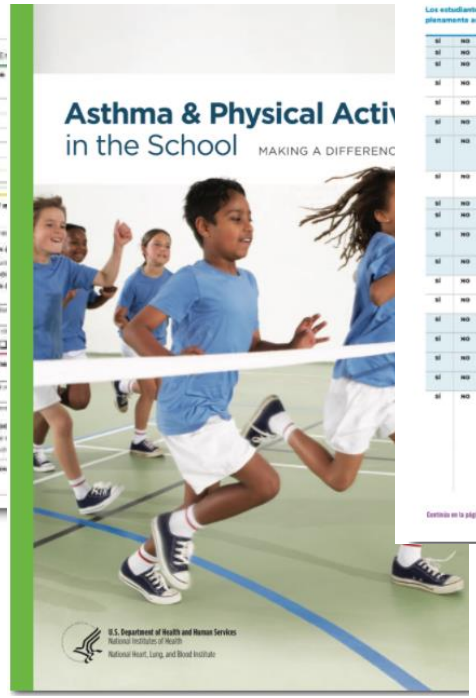
- Screening patients on maintenance OCS or high dose ICS-LABA for adrenal insufficiency
- For patients with eosinophils ≥300/µl, investigate non-asthma causes before starting biologics.
- If patients have hypereosinophilia, check for other conditions, such as EGPA
- Assess for the inflammatory phenotype
- Updated treatment options for those without evidence of Type 2 inflammation.
- OCS should only be used as a last resort option. For patients with hypereosinophilia, e.g. ≥1500/µl, investigate for conditions such as EGPA

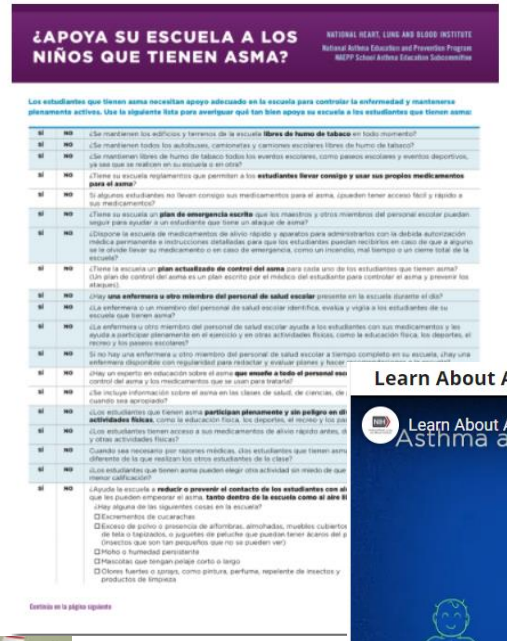
Biologics

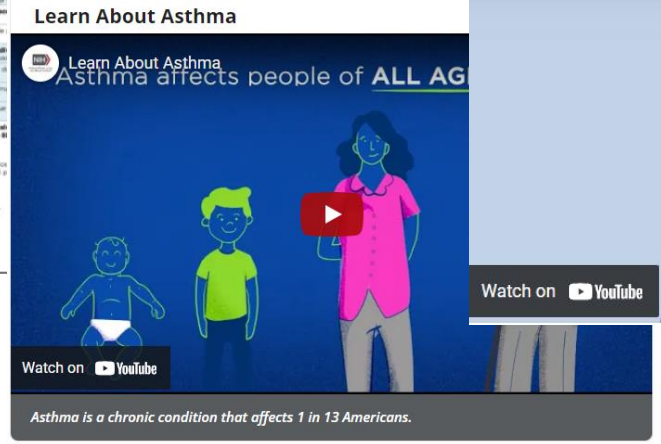

6b Consider add-on biologic Type 2 targeted treatments
• Consider add-on Type 2-targeted biologic for patients with exacerbations or poor symptom control on high dose ICS-LABA, who:
- have eosinophilic or allergic biomarkers, or
- need maintenance OCS
• Consider local payer eligibility criteria and predictors of response when choosing between available therapies
• Also consider cost, dosing frequency, route (SC or IV), patient preference
Which biologic is appropriate to start first?
Anti-IgE
Is the patient eligible for anti-IgE for severe allergic asthma?
• Sensitization on skin prick testing or specific IgE
• Total serum IgE and weight within dosage range
• Exacerbations in last year
no
no
Anti-IL5 / Anti-IL5R
Is the patient eligible for anti-IL5 / anti-IL5R for severe eosinophilic asthma?
• Exacerbations in last year
• Blood eosinophils ≥300/µl
no
no
Anti-IL4R
Is the patient eligible for anti-IL4R
… for severe eosinophilic/Type 2 asthma?
• Exacerbations in last year
• Blood eosinophils ≥150/µl or FeNO ≥25 ppb
… or because of need for maintenance OCS?
Eligible for none?
Return to section 6a
What factors may predict good asthma response to anti-IgE?
• Blood eosinophils ≥260/µl ++
• FeNO ≥20 ppb +
• Allergen-driven symptoms +
• Childhood-onset asthma +
What factors may predict good asthma response to anti-IL5/5R?
• Higher blood eosinophils +++
• More exacerbations in previous year +++
• Adult-onset of asthma ++
• Nasal polyposis ++
What factors may predict good asthma response to anti-IL4R?
• Higher blood eosinophils +++
• Higher FeNO +++
Anti-IL4R may also be used to treat
• Moderate/severe atopic dermatitis
• Nasal polyposis
Choose one if eligible; trial for at least 4 months and assess response
Extend trial to 6-12 months
unclear
Good asthma response?
yes
Good response to T2-targeted therapy
no
STOP add-on
Consider switching to a different Type 2-targeted therapy, if eligible
no
Little/no response to T2-targeted therapy

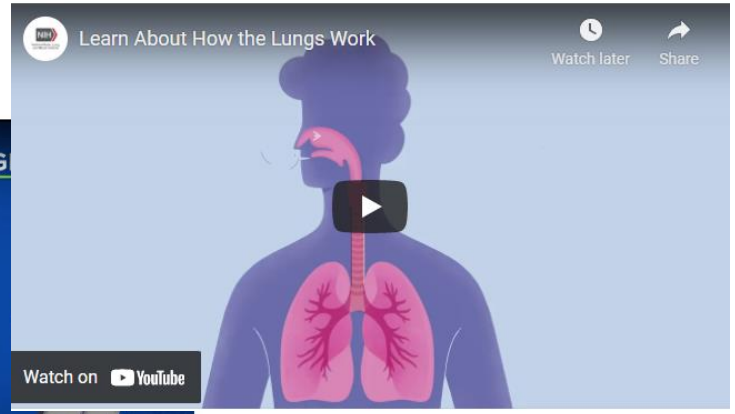
Parent/Caregiver resources











- Downloadable Printables
- Educational videos
- Social media links

NHLBI.NIH.GOV/BREATHEBETTER

Inhaler Technique

https://vimeo.com/454633544