University at Buffalo The State University of New York

PEDIATRIC ASTHMA MANAGEMENT GUIDELINES: FOCUSED 2020 UPDATES

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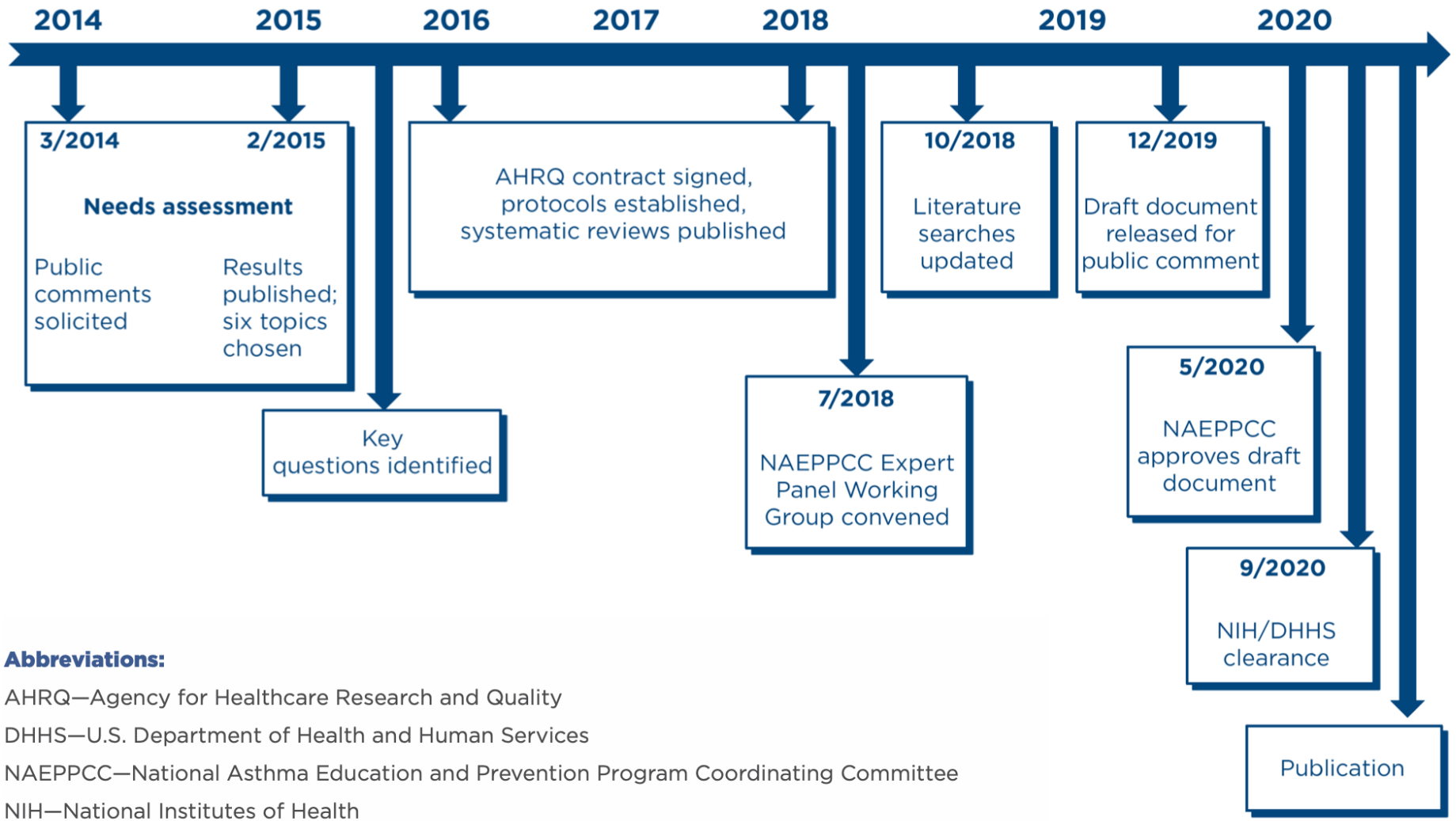
Figure I.a: Timeline for 2020 Asthma Guideline Update



Abbreviations:

AHRQ—Agency for Healthcare Research and Quality

DHHS—U.S. Department of Health and Human Services

NAEPPCC—National Asthma Education and Prevention Program Coordinating Committee

NIH—National Institutes of Health

Overview

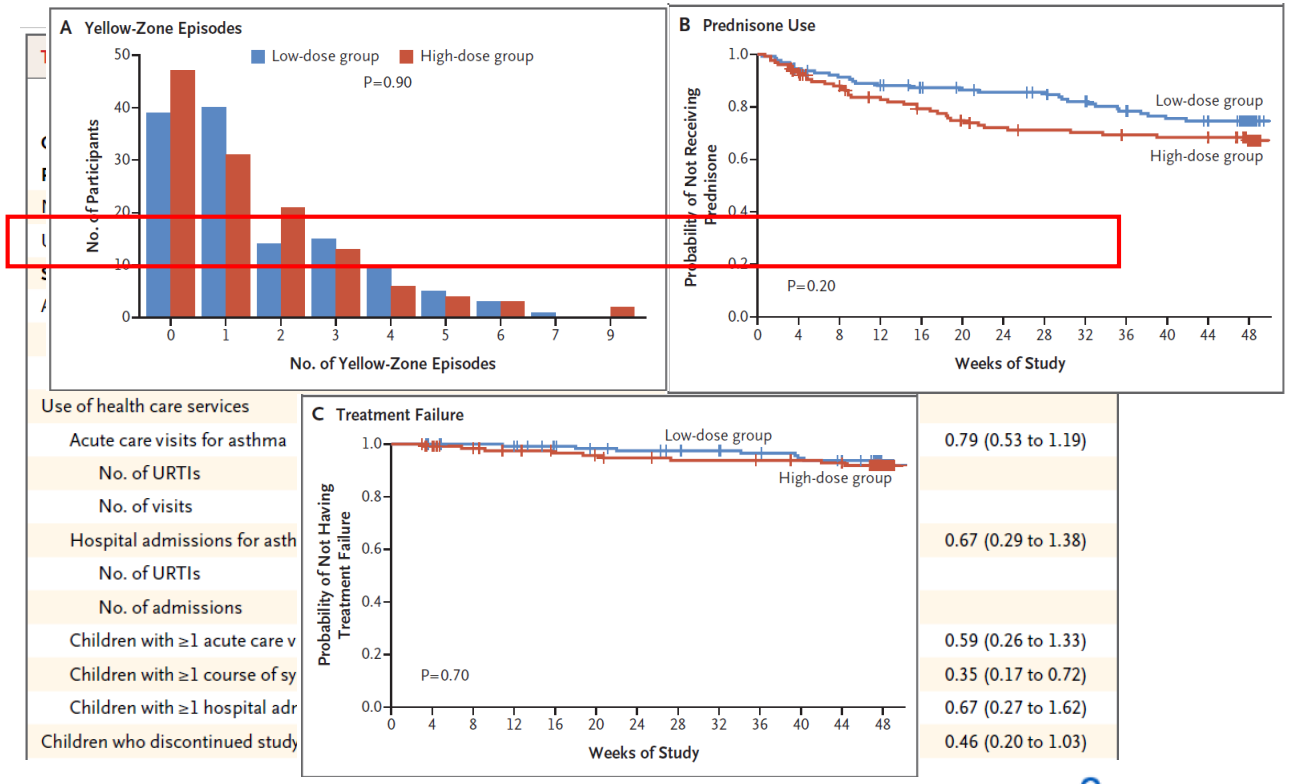
- Priority topics Asthma Expert Panel 4
  1. **Inhaled Corticosteroids**
  2. Long-Acting Muscarinic Antagonists (LAMA)
  3. Indoor Allergen Reduction
  4. **Immunotherapy**
  5. Fractional Exhaled Nitric Oxide (feNO) Testing
  6. Bronchial Thermoplasty
- **Severe asthma**
- **Referral guidelines**

J Allergy Clin Immunol. 2020 Dec;146(6):1217-1270.

Priority Topic #1: Inhaled Corticosteroids

- In children ages 0-4 years old with **recurrent wheezing associated with viral infections and not symptoms in between**:
  - Short (7-10 day) course of daily inhaled corticosteroids along with an as-needed short-acting bronchodilator
  - Recommended at start of a respiratory tract infection

- In people ages 4 years and older with mild to moderate persistent asthma who **use inhaled corticosteroids daily:**
  - Increasing regular inhaled steroid dose for short periods is **NOT recommended** when symptoms increase/peak flow decreases



Ducharme NM, N Engl J Med. 2009 Jan 22;360(4):339-53
Jackson DJ et al, N Engl J Med. 2018 Mar 8;378(10):891-901.

Priority Topic #1: Inhaled Corticosteroids

- In people ages 12 and older with **mild** asthma:
  - Either daily low-dose ICS and PRN SABA for quick-relief therapy or ICS and SABA used concomitantly PRN for individuals ages 12 years and older with mild persistent asthma

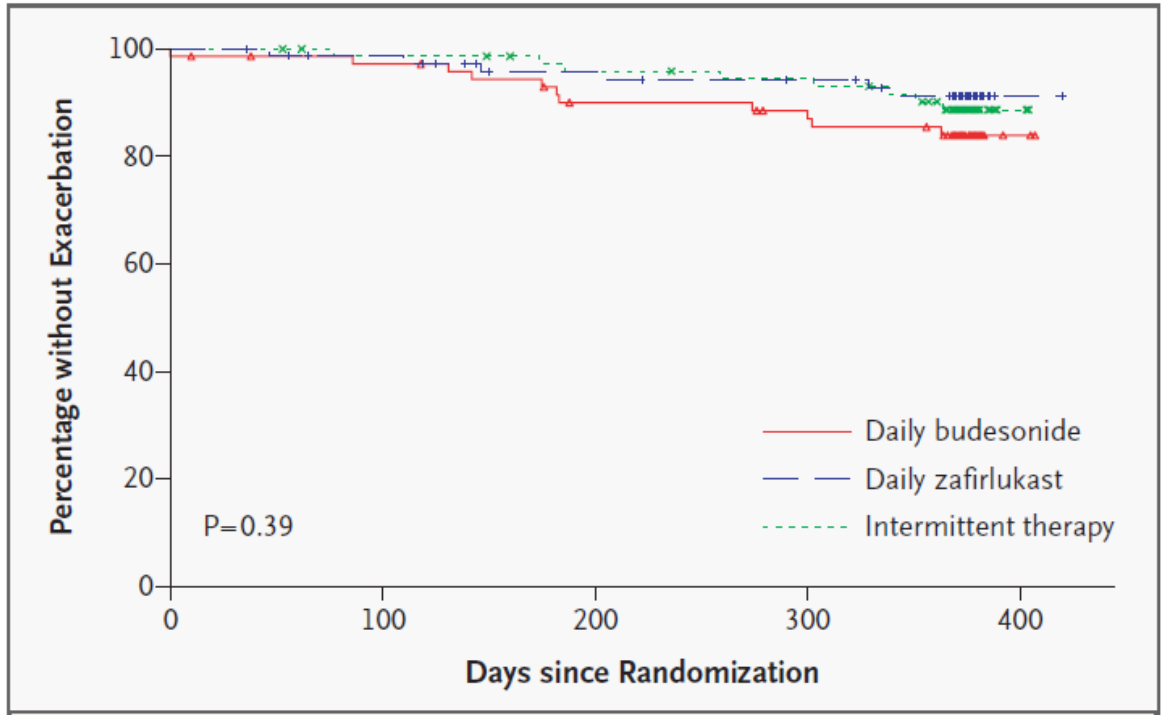


Figure 3. Kaplan–Meier Estimates of the Time to a First Exacerbation of Asthma.
There was no significant difference among the groups (P=0.39).

Boushey HA, N Engl J Med. 2005 Apr 14;352(15):1519-28

Priority Topic #1: Inhaled Corticosteroids

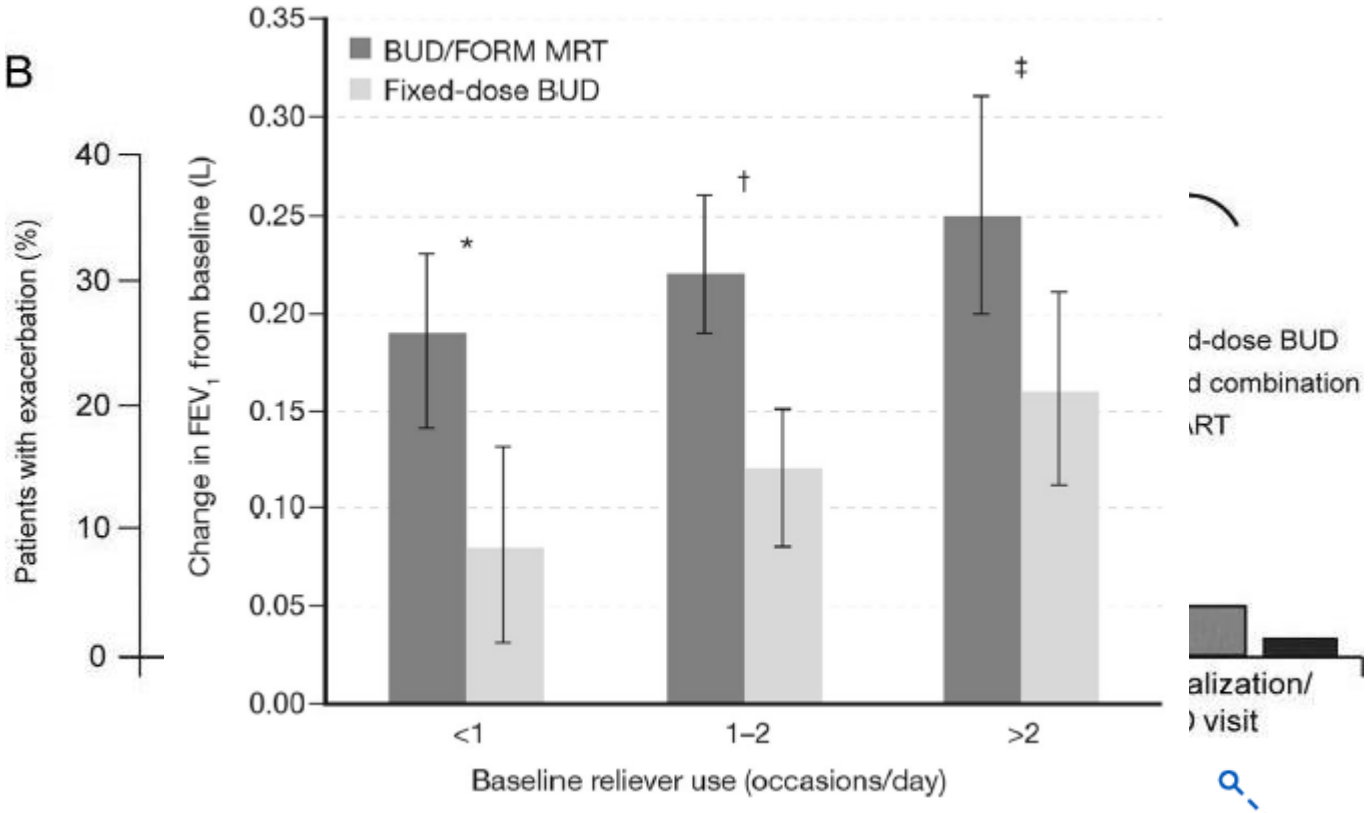
- Strong recommendation for ICS-formoterol in a **single inhaler as both daily controller and reliever therapy** compared to either *higher-dose ICS* as daily controller therapy and SABA for quick-relief therapy or same-dose ICS-LABA as daily controller therapy and SABA for quick-relief therapy in individuals ages 4 years and older with moderate to severe persistent asthma (Step 3 for low-dose ICS and Step 4 for medium-dose ICS)
- Conditional recommendation for ICS-formoterol in a **single inhaler used as both daily controller and reliever therapy** compared to higher-dose ICS-LABA as daily controller therapy and SABA for quick-relief therapy in individuals ages 12 years and older with moderate to severe persistent asthma (Step 4)

Single Maintenance and Reliever Therapy (SMART)

- The recommendation that combination inhaled corticosteroid (ICS)–**formoterol** reliever therapy is preferred to short-acting β agonist (SABA) reliever therapy across the spectrum of asthma severity is arguably one of the greatest paradigm shifts in the management of asthma in decades
- **But what about the black box warning?**
  - Black box warning issued by FDA on all preparations containing LABA in May, 2006
  - SMART study:
    - Clinical trial in adults, most on LABA ALONE
    - Increased risk asthma-related death (13/13,176 vs 3/13,179)
  - Recent meta-analyses (Salpeter, 2006; Rodrigo, 2009) found differences smaller but still statistically significant in kids

Are LABA's effective?

- Several recent trials (Rabe 2006, Bousquet 2007, Papi 2015, Bisgard, Jenkins 2017) and 2 meta-analyses (Cates 2013, Kew 2013)
- ICS/LABA for rescue -> decreased use of SABA, fewer exacerbations compared to ICS alone or ICS/LABA control only
- Lower total ICS dose when compared to high daily dose ICS



Bisgard H et al, Chest. 2006Dec;130(6):1733-43.
Jenkins C et al., BMC Pulm Med. 2017 Apr 20;17(1):65.

Rationale: Combination ICS/LABA Inhalers for Rescue

- Formoterol ***(not Salmeterol)*** has an onset of action (~5 min) similar to albuterol, with longer duration
- Benefits include
  - Ability to titrate ICS dose up during exacerbation
  - Single inhaler for control and rescue
  - Potential for better control with less total ICS

Overview

- Priority topics Asthma Expert Panel 4
  1. Inhaled Corticosteroids
  2. Long-Acting Muscarinic Antagonists (LAMA)
  3. Indoor Allergen Reduction
  4. **IMMUNOTHERAPY**
  5. Fractional Exhaled Nitric Oxide (feNO) Testing
  6. Bronchial Thermoplasty
- Severe asthma
- Referral guidelines

J Allergy Clin Immunol. 2020 Dec;146(6):1217-1270.

Priority Topic #4: Immunotherapy

- Immunotherapy is an asthma management strategy in which people with allergies are exposed to low doses of an allergen.
- Allergy shots (i.e. subcutaneous immunotherapy)
  - Recommended for people who have allergic asthma
  - Whose symptoms worsen after exposure to certain allergens
- Sublingual immunotherapy - placing drops or tablets containing allergens under the tongue
  - NOT recommended for treatment of allergic asthma

Immunotherapy for Pediatric Asthma

- Cox et al – Florida Medicaid Database review showed that even 6 months of immunotherapy improved the economic burden of asthma
- Subcutaneous (‘SHOTS’) immunotherapy has substantial evidence for efficacy in lessening asthma symptoms and even preventing onset of asthma in toddlers with rhinitis
- Unfortunately evidence for a role of Sublingual Immunotherapy can not yet support its recommendation as add on treatment for asthma, although there is an impact of grass SLIT on pediatric rhinitis symptoms.
- Patients being started on omalizumab and dupilumab should be considered for allergy testing as these biologics will change skin tests over time, and when they are controlled SCIT could be considered as a long term immunomodulatory therapy

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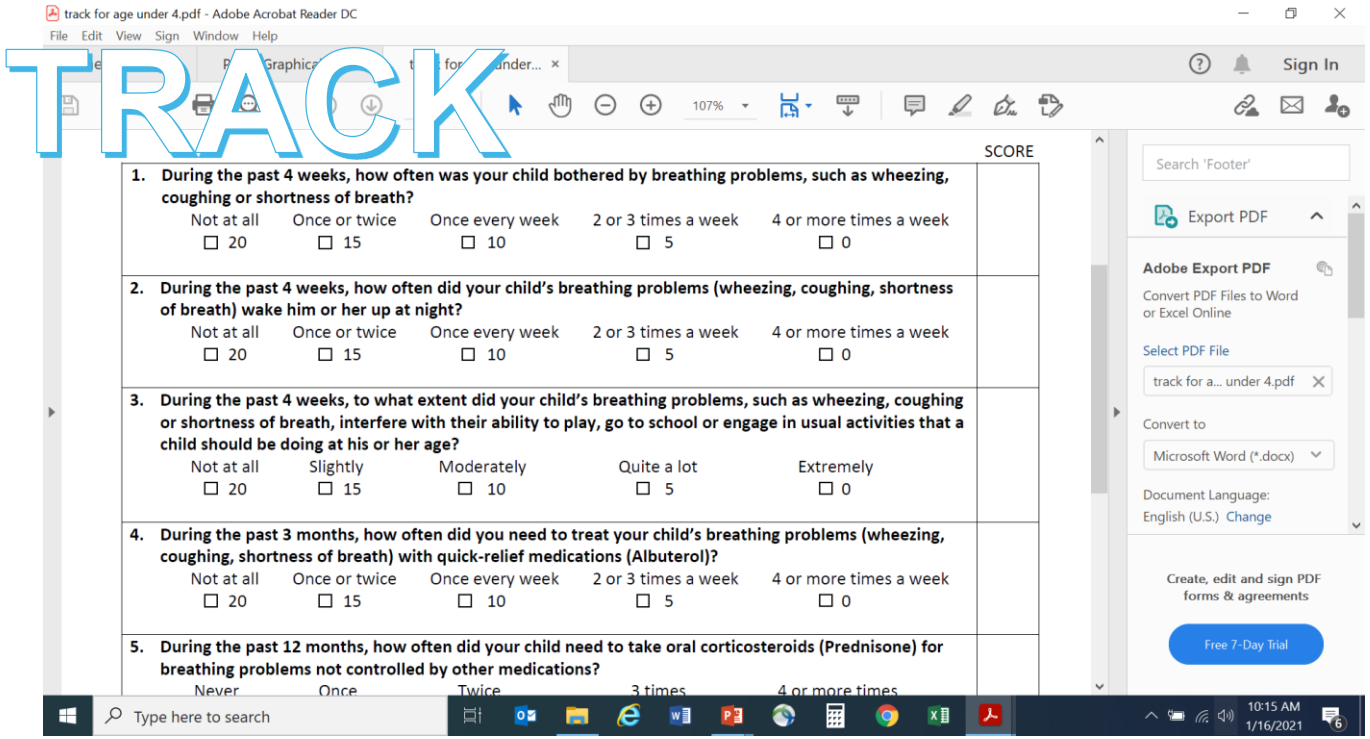
Management starts with education

EPR3 highlighted the need for comprehensive and continual education of parents in trigger controls, medication use and following a plan, identification of exacerbations early ,routine assessment of control and adjustment of treatment plan- THIS IS STILL KEY



2020 guidelines update suggests environmental advice be focused on known triggers for the patient.

Follow up visits should be structured to include key information- exacerbations, symptoms, compliance, barriers, and goals of the patient

Don't try to achieve all education in a single visit, but have a plan for adding information at each follow up

Delivery matters

Triggers for hospitalization in pediatric asthma

- Infection- RV(48%),RSV(6%), Entero, paraflu,Mycoplasma
  - Insufficient asthma control and allergen sensitization predicted rehospitalization due to RV in the same winter [Abe et al , Ped Allergy &Immunology 30(7)]
- Allergens- Alternaria, mite, cat, household dampness or mold
- Air pollution- PM2.5 ,NO2 and black carbon, cooking fires, ET and MS
- Poor urban zip code,? Due to poor controller use , race impact
- Low Vitamin D status

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Severe asthma definition

- Asthma which requires treatment with guidelines suggested medications for GINA steps 4–5 asthma (**high dose ICS and LABA or leukotriene modifier/theophylline**) for the previous year or systemic CS for ≥ 50% of the previous year to prevent it from becoming ‘‘uncontrolled’’ or which remains ‘‘uncontrolled‘‘ despite this therapy
- Uncontrolled asthma defined **as at least one of the following**:
  - Poor symptom control: ACQ consistently 1.5 ≥ **ACT < 20** (or ‘‘not well controlled’’ by NAEPP/GINA guidelines)
  - Frequent severe exacerbations: **TWO** or more bursts of systemic CS (3 days each) in the previous year
  - Serious exacerbations: at least **ONE** hospitalization, ICU stay or mechanical ventilation in the previous year
  - Airflow limitation: after appropriate bronchodilator withhold FEV1 ,80% predicted (in the face of reduced FEV1/FVC defined as less than the lower limit of normal)
  - Controlled asthma that worsens on tapering of these high doses of ICS or systemic CS (or additional biologics)

European Respiratory Journal 2014 43: 343-373

Definition of high daily dose of various inhaled corticosteroids in relation to patient age

Inhaled corticosteroid	Threshold daily dose in µg considered as high	
	Age 6–12 years	Age >12 years
Beclomethasone dipropionate	⩾800 (DPI or CFC MDI) ⩾320 (HFA MDI)	⩾2000 (DPI or CFC MDI) ⩾1000 (HFA MDI)
Budesonide	⩾800 (MDI or DPI)	⩾1600 (MDI or DPI)
Ciclesonide	⩾160 (HFA MDI)	⩾320 (HFA MDI)
Fluticasone propionate	⩾500 (HFA MDI or DPI)	⩾1000 (HFA MDI or DPI)
Mometasone furoate	⩾500 (DPI)	⩾800 (DPI)
Triamcinolone acetonide	⩾1200	⩾2000

Beclomethasone HFA/Qvar (40/80 mcg)
Ciclesonide/Alvesco (80/160 mcg)
Mometasone/Asmanex (110/220 mcg)

Budesonide DPI (90/180 mcg)
Fluticasone/Flovent (44/110/220 mcg)

European Respiratory Journal 2014 43: 343-373

Masqueraders of asthma

- Dysfunctional breathing
  - Vocal cord dysfunction
- Anatomic
  - Tracheobronchomalacia
  - Tracheoesophageal fistula
  - Central airway compression (i.e., double aortic arch)
- Suppurative lung diseases
  - Cystic fibrosis
  - Primary ciliary dyskinesia
- Interstitial lung disease
  - Bronchiolitis obliterans
- Other
  - Foreign body aspiration
  - Chronic aspiration
  - Congenital heart disease

Diagnostic evaluation

- Lung function test
- CBD with differential
- IgE, specific IgE
- Sweat test
- CT scan of the chest
- Flexible bronchoscopy and BAL
- Sleep Study

ASTHMA SPECIALIST REFERRAL GUIDELINES

REFER TO PEDIATRIC ALLERGY/IMMUNOLOGY

- Asthmatic child with **other uncontrolled atopic diseases,** like allergic rhinitis, food allergy or atopic dermatitis.
- Asthmatic child that is **not well controlled on daily therapy** – consider biologic medications; patient may also be a candidate for allergen immunotherapy
- Asthmatic child with **frequent infections** – for immune workup
- Anaphylaxis or confirmed food allergy in a patient with asthma
- Need for additional diagnostic tests (i.e. allergy skin testing)

REFER TO PEDIATRIC PULMONOLOGY

- Difficulty confirming a diagnosis of asthma
- History of a life-threatening asthma exacerbation (i.e. intensive care unit admission, mechanical ventilation for asthma)
- Asthma in a child who has other issues like sleep apnea, failure to thrive, bronchopulmonary dysplasia, congenital heart disease, or another comorbidity that can affect the clinical course, allergic bronchopulmonary aspergillosis (ABPA), inducible laryngeal obstruction (also called vocal cord dysfunction)
- Need for additional diagnostic tests (bronchoscopy, complete pulmonary function tests)

ASTHMA SPECIALIST REFERRAL GUIDELINES

REFER TO EITHER SPECIALTY

- Hospitalization for asthma, more than two courses of oral glucocorticoids in a year or the inability to discontinue oral glucocorticoids
- Poor asthma control after 3-6 months of active therapy and appropriate monitoring
- Presence of complicating comorbidity [i.e. aspirin-exacerbated respiratory disease (AERD), nasal polyposis, chronic rhinosinusitis]
- Patient is a potential candidate for therapy with biologics (benralizumab, dupilumab, mepolizumab, omalizumab, reslizumab)
- Need for STEP 4 care or higher in a child age 5 and up (may consider referral at STEP 3)
- Need for STEP 3 care or higher in a child under five years old (may consider referral at STEP 2)

CONTACT INFORMATION

If you have any questions, or concerns, please do not hesitate to call us.

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Pediatric Pulmonology and Sleep Medicine: 716.323.0110

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.

Abbreviations: ICS, inhaled corticosteroid; LABA, long-acting beta$_2$-agonist; SABA, inhaled short-acting beta$_2$-agonist; RTI, respiratory tract infection; PRN, as needed

▲ Updated based on the 2020 guidelines.

* Cromolyn and montelukast were not considered for this update and/or have limited availability for use in the United States. The FDA issued a Boxed Warning for montelukast in March 2020.

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.

- Use SABA as needed for symptoms. The intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-minute intervals as needed.
- In Steps 3 and 4, the preferred option includes the use of ICS-formoterol 1 to 2 puffs as needed up to a maximum total daily maintenance and rescue dose of 8 puffs (36 mcg).▲
- **Caution:** Increasing use of SABA or use >2 days a week for symptom relief (not prevention of EIB) generally indicates inadequate control and may require a step up in treatment.

Abbreviations: ICS, inhaled corticosteroid; LABA, long-acting beta$_2$-agonist; LTRA, leukotriene receptor antagonist; SABA, inhaled short-acting beta$_2$-agonist

▲ Updated based on the 2020 guidelines.

* Cromolyn, Nedocromil, LTRAs including montelukast, and Theophylline were not considered in this update and/or have limited availability for use in the United States, and/or have an increased risk of adverse consequences and need for monitoring that make their use less desirable. The FDA issued a Boxed Warning for montelukast in March 2020.

** Omalizumab is the only asthma biologic currently FDA-approved for this age range.

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.

- Use SABA as needed for symptoms. The intensity of treatment depends on the severity of symptoms: up to 3 treatments at 20-minute intervals as needed.
- In steps 3 and 4, the preferred option includes the use of ICS-formoterol 1 to 2 puffs as needed up to a maximum total daily maintenance and rescue dose of 12 puffs (54 mcg).▲
- **Caution:** Increasing use of SABA or use >2 days a week for symptom relief (not prevention of EIB) generally indicates inadequate control and may require a step up in treatment.

Priority Topic #2: Long-Acting Muscarinic Antagonists (LAMA)

- If inhaled corticosteroids do NOT control asthma, may add a long-acting bronchodilator such as a LABA or a LAMA.
- For children under 12 and most people 12 or older with asthma that is NOT controlled by an inhaled corticosteroid alone:
  - Adding LABA rather than LAMA to inhaled corticosteroid is preferred
- For people 12 years and older:
  - If a LABA cannot be used, a LAMA may be used with inhaled corticosteroid treatment instead of continuing inhaled corticosteroid alone
- For people 12 years old and older whose asthma is NOT controlled with an inhaled corticosteroid plus a LABA:
  - Adding a LAMA is recommended

Priority Topic #3: Indoor Allergen Reduction

- For people with asthma who are sensitive to indoor substances (e.g. house dust mites):
  - Using multiple strategies to reduce allergen is recommended
  - Air purifiers, HEPA vacuum cleaners, pillow/mattress covers that prevent dust mites from going through them.
  - Using only one strategy often does NOT improve asthma outcomes.
- Integrated pest management
  - Recommended for those who are allergic and exposed to cockroaches, mice, or rats
- Strategies are NOT recommended for people who are NOT allergic to indoor substances.

Priority Topic #5: Fractional Exhaled Nitric Oxide (feNO) Testing

- FeNO tests measure the amount of nitric oxide.
  - Byproduct of inflammation in air you breathe out
  - Should not be used alone to assess asthma control or predict clinical course of disease
- In patients 5 years and older: FeNO testing is recommended (NOT in isolation)
  - When either diagnosis or approach to therapy is uncertain.
  - Recommended in uncontrolled persistent asthma on ICS or an ICS with LABA, montelukast or omalizumab
- In children 4 years and younger who have recurrent episodes of wheezing:
  - FeNO measurement does NOT reliably predict the future development of asthma

TABLE 5. GENERAL OUTLINE FOR F_{ENO} INTERPRETATION: SYMPTOMS REFER TO COUGH AND/OR WHEEZE AND/OR SHORTNESS OF BREATH*

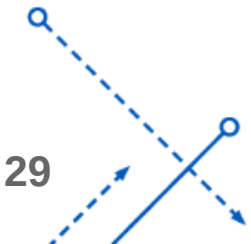
	F_{ENO} < 25ppb (<20 ppb in children)	F_{ENO} 25–50 ppb (20–35 ppb in children)	F_{ENO} > 50 ppb (>35 ppb in children)
		Diagnosis	
Symptoms present during past 6+ wk	Eosinophilic airway inflammation unlikely Alternative diagnoses Unlikely to benefit from ICS	Be cautious Evaluate clinical context Monitor change in F_{ENO} over time	Eosinophilic airway inflammation present Likely to benefit from ICS
		Monitoring (in Patients with Diagnosed Asthma)	
Symptoms present	Possible alternative diagnoses Unlikely to benefit from increase in ICS	Persistent allergen exposure Inadequate ICS dose Poor adherence Steroid resistance	Persistent allergen exposure Poor adherence or inhaler technique Inadequate ICS dose Risk for exacerbation Steroid resistance
Symptoms absent	Adequate ICS dose Good adherence ICS taper	Adequate ICS dosing Good adherence Monitor change in F_{ENO}	ICS withdrawal or dose reduction may result in relapse Poor adherence or inhaler technique

Definition of abbreviations: F_{ENO} = fraction of exhaled nitric oxide; ICS = inhaled corticosteroid.

*The interpretation of F_{ENO} is an adjunct measure to history, physical exam, and lung function assessment. *See* text and Tables 3 and 4 for other details.

Priority Topic #6: Bronchial Thermoplasty

- Bronchial thermoplasty: FDA-approved medical procedure
  - Treats severe persistent asthma
  - Uses heat to reduce the smooth muscle around the airways that tighten during asthma exacerbations
- Patients 18 years and older with uncontrolled, moderate to severe persistent asthma:
  - Should NOT undergo bronchial thermoplasty
  - Benefits are small, risks are moderate
  - Long-term outcomes are uncertain
- Some people with moderate to severe persistent asthma who have troublesome symptoms may be willing to accept risks of bronchial thermoplasty
  - Intervention may be chosen after shared decision making with health care provider



Where are the eleven additional topics?

- There were 11 additional topics identified but NOT selected for update.
  - NHLBI council concluded there was insufficient new information at the time to support an update
  - Adherence, asthma action plans, asthma heterogeneity, biologic agents
  - Biomarkers (other than FeNO), classification of asthma severity, long-acting beta-agonist safety
  - Physiological assessments, prevention of asthma onset, step down from maintenance therapy
  - Role of community health workers in asthma management

- Asthma biologic therapy was considered an “emerging” therapeutic option but not selected as a priority topic.

Limitations

- Recommendations are based on an initial search of literature that concluded in March-April 2017.
  - Conducted by Evidence Practice Centers of the Agency for Healthcare Research and Quality
- Systematic reviews were updated through October 2018 by expert panel and were considered in making recommendations.
- Incomplete characterization of study participants.
  - Particular issue in the allergen mitigation interventions
  - Allergic status of participants was often not reported or included
- Study design concerns – risk of bias, small sample size, and limited information about harms and benefits of interventions if used in clinical/community settings