

Adding some **FLAIR** to Pediatric Asthma Care: Updates for the General Pediatrician

January 20, 2021

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Center for Pediatric Medicine Asthma Program Director







Office Space, 1999



PAPER SIGNED FOR HOME AND SCHOOL, ASTHMA TEMPLATE FILLED OUT, EDUCATION AND SPACERS PROVIDED AND FLU SHOT ADMINISTERED?

Objectives

- Discuss differences between NHLBI Expert Panel Guidelines and the Global Initiative Report
- Discuss EPR-4 and GINA 2020 report updates and the key studies behind the latest recommendations, specifically concerning use of ICS and ICS/LABA medications



Timeline of Pediatric Asthma Guidelines

First Expert Panel Report (EPR)

Asthma highlighted as an inflammatory disease.

EPR-2 released

Importance of early recognition and intervention recognized.

EPR-3 released

EPR-3 focused on asthma natural course, increased focus on asthma control and emphasis on individual treatment

1989

First Expert Panel Convened

1991

1995

GINA Report released
Collaboration between WHO and NHLBI

1997



2004

GINA Global Burden of Asthma Report

2006-2007

President's Task Force on Environmental Health Risks and Safety Risks to Children forms cabinet-level, multi-agency group to address asthma morbidity and its racial and ethnic disparities

2012

EPR-4 released December 3rd!

Updates in 6 Topic Areas to be embedded in stepwise approach framework

2020

Selection of asthma medications has been based on the national Guidelines for the Diagnosis and Management of Asthma Expert Panel Report 3 (EPR-3) and The Global Initiative for Asthma (GINA) through a **stepwise, control-based approach**.

Goal of asthma care involves not only initial diagnosis and treatment to achieve asthma control, but also long-term regular follow-up care to maintain control

The best treatment for a child with asthma is a therapy that **achieves asthma control, preserves lung function and minimizes side effects**.



Global Initiative for Asthma (ginasthma.org)



The GINA report is a global strategy document



- Regulatory approvals and submissions differ from country to country
- Many recommendations are 'off-label' in various countries, particularly for pediatrics
- Updates published biannually

Addressing New Therapies



- Regulatory agencies often receive more safety data than are in peer-reviewed literature
- Recs based on the best available evidence, after approval by at least one major regulatory agency (e.g. EMA, FDA)

Incorporation of Evidence for New Regimens of Existing Medications



- If satisfied with evidence for safety and effectiveness, may make recs not covered by a regulatory indication in any country at the time

Practical Implications



- Use your own professional judgment
- **Take into account local and national guidelines, payer eligibility criteria, and licensed drug doses**

Focus on Mild Asthma Since 2007

Dusser D et al. Mild Asthma: An Expert Panel Review on Epidemiology, Clinical Characteristics and Treatment Recommendations. *Allergy*:62, 591-604, 2007

- Intermittent + mild persistent asthma affects **50-75%** of asthmatic patients
- Mild asthma is more frequent, more symptomatic and less well controlled in children than in adults
- **30-40%** of asthma exacerbations presenting to ED are in patients with mild asthma
- Inhaled SABA has been first-line treatment for asthma for 50 years
 - This dates from an era when asthma was thought to be a disease solely of bronchoconstriction
 - Patient satisfaction with, and reliance on, SABA treatment is reinforced by its rapid relief of symptoms, its prominence in ED and hospital management of exacerbations, and low cost
 - **Patients commonly believe that “My reliever gives me control over my asthma” and often don’t see the need for additional treatment**

Emphasis on Poor Adherence as a Modifiable Risk Factor

When the reliever is SABA, poor adherence with controller exposes patient to risks of SABA-only tx



Reddel HK, Ampon RD, Sawyer SM, Peters MJ. Risks associated with managing asthma without a preventer: urgent healthcare, poor asthma control and over-the-counter reliever use in a cross-sectional population survey. *BMJ* 2017;7:e016688.

Emphasis on Poor Adherence as a Modifiable Risk Factor

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Dispensing of ≥ 3 canisters per year (average 1.7 puffs/day) is associated with higher risk of emergency department presentations (*Stanford, AAAI 2012*)

Dispensing of ≥ 12 canisters per year is associated with higher risk of death (*Suissa, AJRCCM 1994*)



Our practice is to dispense 1 Albuterol with 0 refills, unless back-to-school, then will dispense 2 Albuterol (1 for home and 1 for school) with 0 refills.

Stanford RH et al. Short-acting β -agonist use and its ability to predict future asthma-related outcomes. *AAAI* 2012.

Suissa S et al. A cohort analysis of excess mortality in asthma and the use of inhaled beta-agonists. *Am J Respir Crit Care Med* 1994.

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Adverse Effects from Regular/Frequent Use of SABA

beta-receptor downregulation, decreased bronchoprotection, rebound hyperresponsiveness, decreased bronchodilator response (*Hancox, Respir Med 2000*)

Hancox RJ et al. Bronchodilator tolerance and rebound bronchoconstriction during regular inhaled beta-agonist treatment. *Respir Med* 2000.

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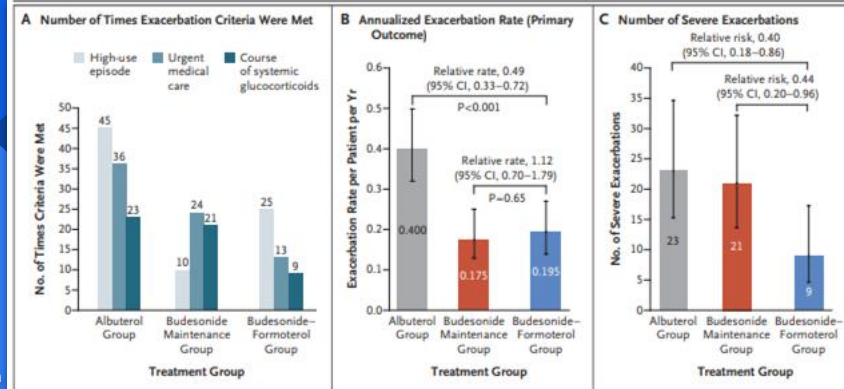
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SYGMA Studies, 2018 (Trial of ICS/LABA in Mild Asthma)

- SYGMA (Symbicort Given as Needed in Mild Asthma)
- Novel START (Novel Symbicort Turbuhaler Asthma Reliever Therapy)
- PRACTICAL (PeRsonalized Asthma Combination Therapy with Inhaled Corticosteroid And fast-onset Long-acting beta agonist.

Novel START



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For safety, GINA no longer recommends SABA-only treatment for Step 1

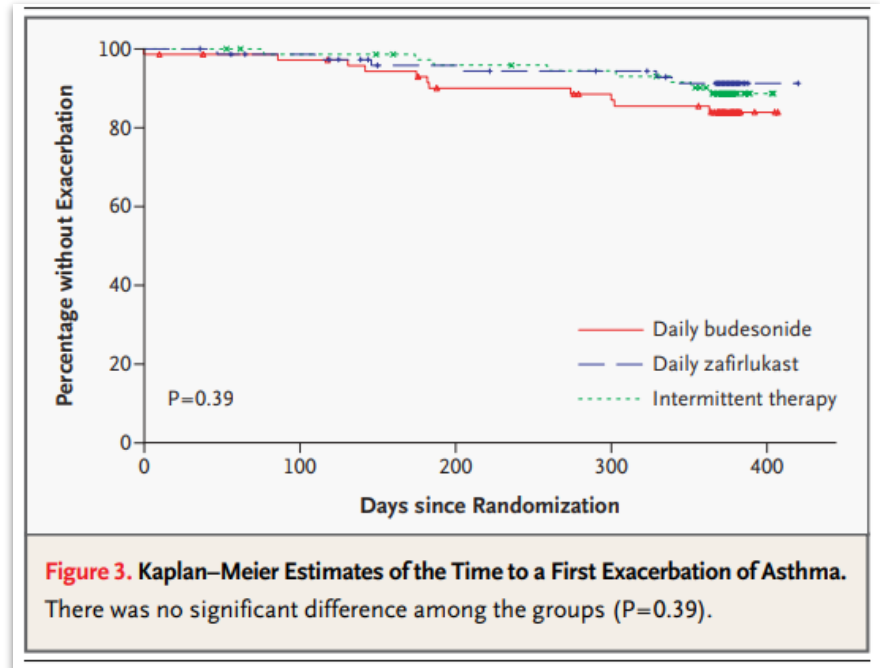
This decision was based on evidence that SABA-only treatment increases the risk of severe exacerbations, and that adding any ICS significantly reduces the risk

- GINA now recommends that all adults **and adolescents** with asthma should receive ICS-containing controller treatment, to reduce the risk of serious exacerbations.
- The ICS can be delivered by regular daily treatment or, in mild asthma, by as-needed low dose ICS-formoterol

IMPACT (**I**mproving **A**sthma **C**ontrol) **T**rial

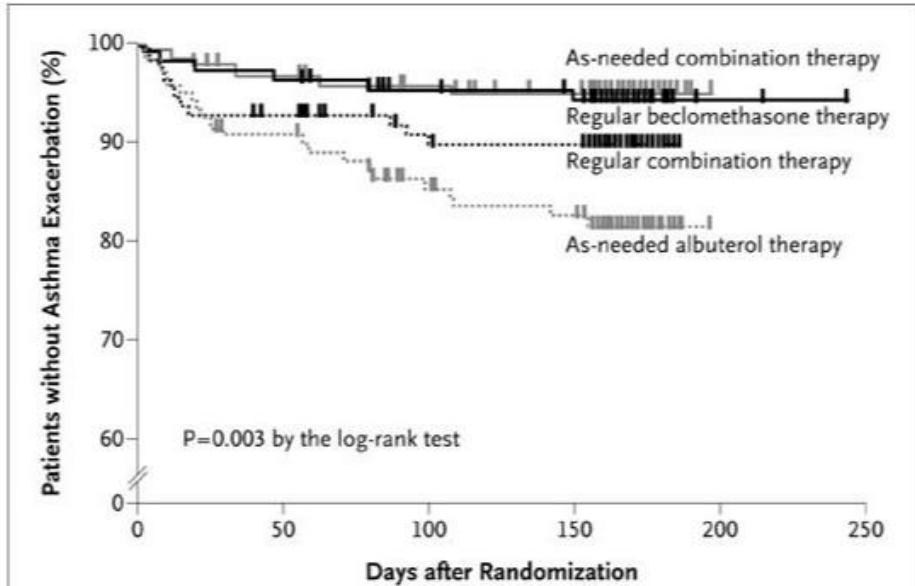
Boushey H et al. Daily versus As-Needed Corticosteroids for Mild Persistent Asthma. *NEJM*. 2005; 352:1519-1528

- 225 randomized adults over 1 year
- Is symptom based intermittent treatment of mild asthma an acceptable alternative to daily therapy?
- 3 parallel treatment arms
- All groups given an action plan that included intermittent ICS, OCS and SABA
- Primary endpoint AM peak expiratory flows
- Daily ICS therapy provided only small, secondary advantages



BEST (**B**eclomethasone plus **S**albutamol **T**reatment) Study

Papi A, et al. Rescue Use of Beclomethasone and Albuterol in a Single Inhaler for Mild Asthma. *NEJM* 2007;356; 20.

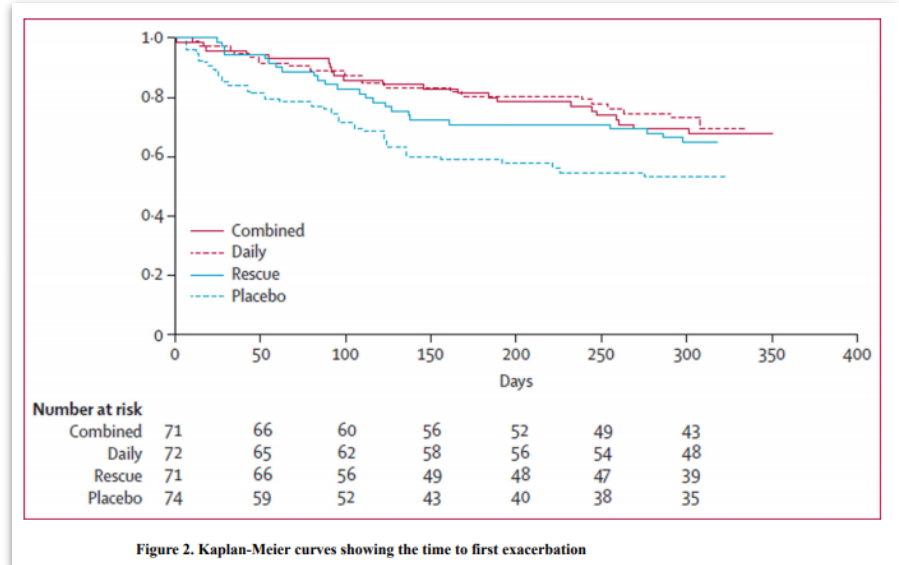


- 450 Italian adults with mild persistent asthma
- Is symptom-based therapy with ICS combined with a SABA as effective as daily controller therapy?
- 4 arms:
 - ICS maintenance + SABA prn - standard therapy
 - ICS/SABA prn
 - SABA prn - placebo
 - ICS/SABA maintenance + SABA prn
- Primary endpoint: PEF

TREXA (Treating Children to Prevent Exacerbation of Asthma) Study

Martinez FD, Chinchilli VM, Morgan WJ, et al. Use of beclomethasone dipropionate as rescue treatment for children with mild persistent asthma (TREXA): a randomised, double-blind, placebo controlled trial. *Lancet*. 2011 Feb 19; 377(9766):650-657

- 5-18 yr olds with mild persistent asthma
- Is symptom-based therapy with inhaled corticosteroid therapy combined with a short-acting beta2-agonist as effective as daily controller therapy?
- 288 patients assigned to 1 of 4 arms
 - Placebo group: BID daily placebo with placebo plus albuterol as rescue
 - Rescue group: BID placebo with beclomethasone plus albuterol as rescue
 - Combined group: BID daily ICS with ICS plus albuterol as rescue
 - Daily group: BID daily ICS with placebo plus albuterol as rescue



Key GINA change 2019

  EDITORIAL
GINA 2019

GINA 2019: a fundamental change in asthma management

Treatment of asthma with short-acting bronchodilators alone is no longer recommended for adults and adolescents

Helen K. Reddel¹, J. Mark FitzGerald², Eric D. Bateman³, Leonard B. Bacharier⁴, Allan Becker⁵, Guy Brusselle⁶, Roland Buhl⁷, Alvaro A. Cruz⁸, Louise Fleming⁹, Hiromasa Inoue¹⁰, Fanny Wai-san Ko¹¹, Jerry A. Krishnan¹², Mark L. Levy¹³, Jiangtao Lin¹⁴, Søren E. Pedersen¹⁵, Aziz Sheikh¹⁶, Arzu Yorgancioglu¹⁷ and Louis-Philippe Boulet¹⁸



 @ERSpublications

GINA no longer recommends treating adults/adolescents with asthma with short-acting bronchodilators alone. Instead, they should receive symptom-driven (in mild asthma) or a daily corticosteroid-containing inhaler, to reduce risk of severe exacerbations. <http://bit.ly/310LLzE>

Cite this article as: Reddel HK, FitzGerald JM, Bateman ED, *et al*. GINA 2019: a fundamental change in asthma management. *Eur Respir J* 2019; 53: 1901046 [<https://doi.org/10.1183/13993003.01046-2019>].

Low Long Term ICS Adherence

Barnes CB et al. Asthma and Adherence to Inhaled Corticosteroids: Current Status and Future Perspectives. *Resp Care* 2015;60; 3.

- Avg level of adherence 22-63% (out of 19 adult studies)
- Associated with 24% of asthma exacerbations and 60% of asthma related hospitalizations
- Lack of immediate symptomatic benefit discourages adherence
- Improved adherence with use of ICS/LABA



Safety of Adding LABA to ICS in Children with Asthma

Stempel DA et al. Safety of Adding Salmeterol to Fluticasone Propionate in Children with Asthma. *NEJM* 2016.

- Randomly assigned 6,208 children ages 4-11 years with persistent asthma
- Non-inferiority study, primary endpoint was time to first serious asthma-related event
- No deaths. 2 intubations (both in fluticasone only group). Overall, no difference in “serious adverse events”



FDA Drug Safety Communication: FDA review finds no significant increase in risk of serious asthma outcomes with long-acting beta agonists (LABAs) used in combination with inhaled corticosteroids (ICS)

- 4 large clinical safety trials demonstrated that LABAs, when used with ICS, did not significantly increase the risk of asthma-related hospitalizations, intubations, or deaths as compared to ICS alone
- Since the black box warning for LABAs was removed in 2017 there is already been an expanded use of ICS-LABA combo earlier in treatment to reduce exposure to HD-ICS

Gaining Optimal Asthma Control (GOAL) Study

Bateman ED et al. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma Control study. *Am J Respir Crit Care Med.* 2004

- Can Guideline-Defined Asthma Control be Achieved?
- 1 year randomized, double-blind, parallel-group study of 3,421 patients with uncontrolled asthma
- Fluticasone vs Salmeterol/Fluticasone
- Significantly more patients achieved control with ICS/LABA

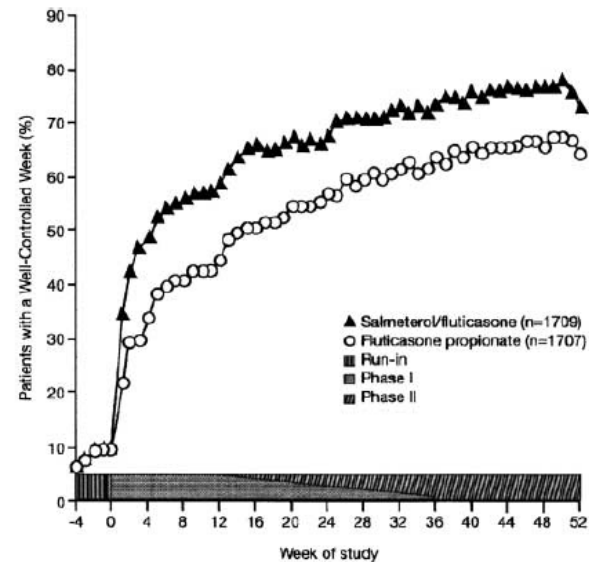


Figure 2. Proportion of patients achieving a well-controlled week (non-cumulative) over Weeks -4 to 52 for all strata combined on treatment with salmeterol/fluticasone or fluticasone propionate.

Adding LABA to ICS for Pediatric Persistent Asthma

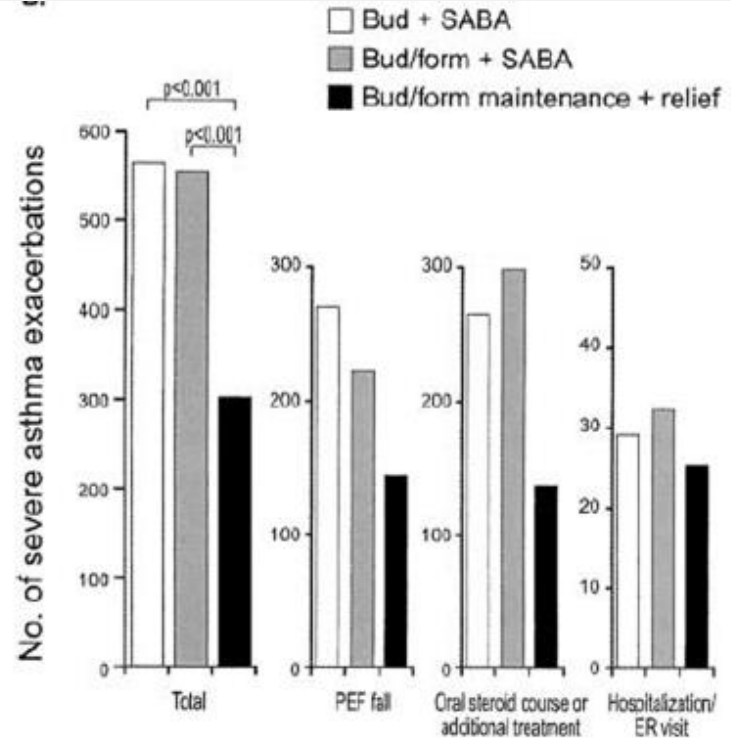
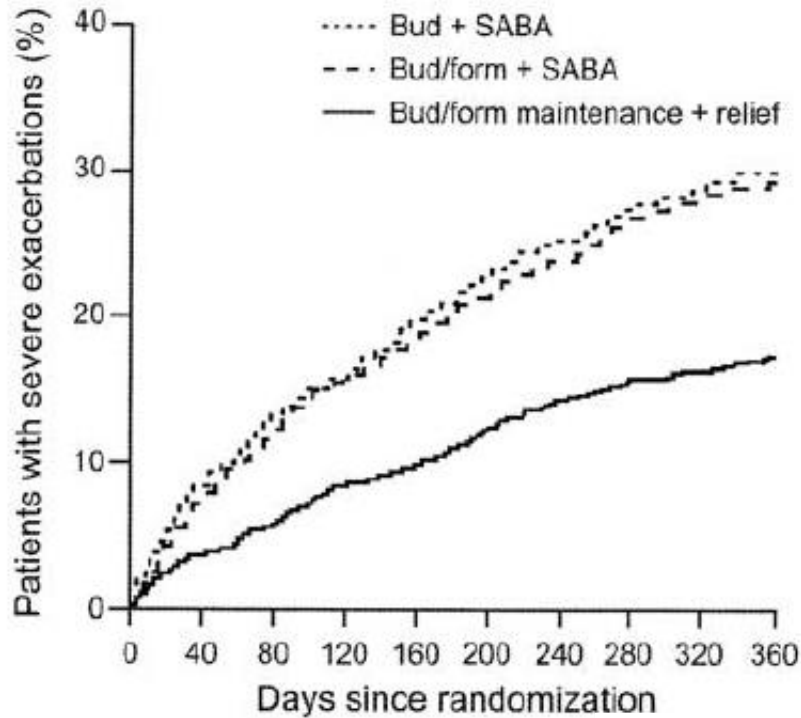
Chauhan B et al. Addition of long-acting beta2-agonists to inhaled corticosteroids for chronic asthma in children. *Cochrane Database Syst Rev* 2015.

- 33 trials reviewed for this systematic review, total of 6381 children, mean age 11
- LABA to ICS not associated with a significant reduction in the rate of exacerbations requiring systemic steroids
- **Superior for improving lung function** compared with the same or higher doses of ICS
- No differences in adverse effects, except greater growth with the use of ICS and LABA compared with a higher ICS dose.

Single-Inhaler Maintenance and Reliever Therapy (SMART)

O'Byrne PM et al.
Budesonide/Formoterol
Combination Therapy as Both
Maintenance and Reliever
Medication in Asthma. *Am J Resp Crit
Care Med* 2005.

- Double, blind randomized study conducted in 246 centers in 22 countries. 2,760 patients with asthma, aged 4-80 years old
- 3 treatment arms
 - Budesonide BID, terbutaline prn
 - Budesonide/formoterol BID, terbutaline prn
 - Budesonide/formoterol BID and prn
- Primary outcome: severe asthma exacerbations

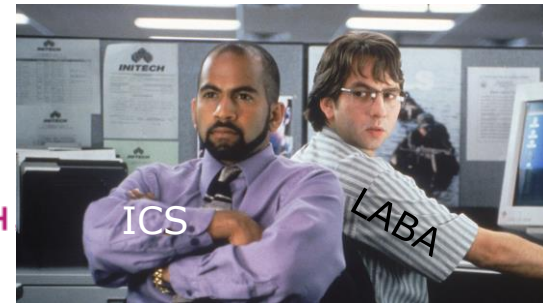


Review and Meta-Analysis of SMART Approach

Sobieraj DM et al. Association of Inhaled Corticosteroids and Long-Acting Beta-Agonists as Controller and Quick Relief Therapy With Exacerbations and Symptom Control in Persistent Asthma: A Systematic Review and Meta-analysis. *JAMA* 2018.

- 16 randomized clinical trials, 22,748 patients
- SMART was associated with reduced risk of asthma exacerbations in patients 12 yrs and up
- Evidence limited for patients 4-11 years old, but also suggests similar efficacy

Fanta C and Lange-Vaidya N. "There is No Longer a Role for Inhaled Steroids Alone in the Treatment of Asthma." Asthma Grand Rounds Presentation. Brigham and Women's Hospital. Boston, Massachusetts. June 5, 2020.



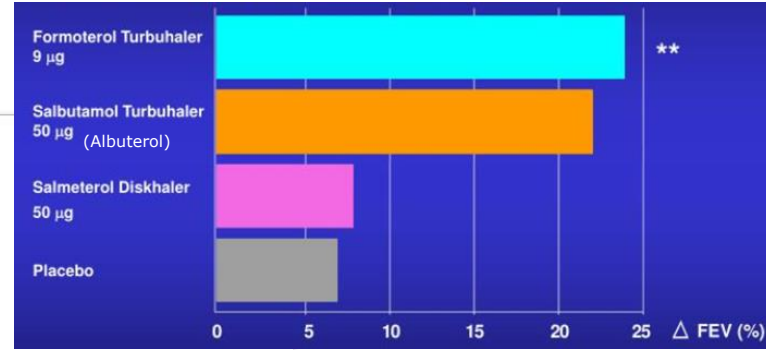
Key GINA Updates 2020

Use of single inhaler strategy/SMART approach

“Temporal Personalization” providing anti-inflammatory treatment to the patient at the time inflammation is developing



Comparison 3 minutes after inhalation of bronchodilators

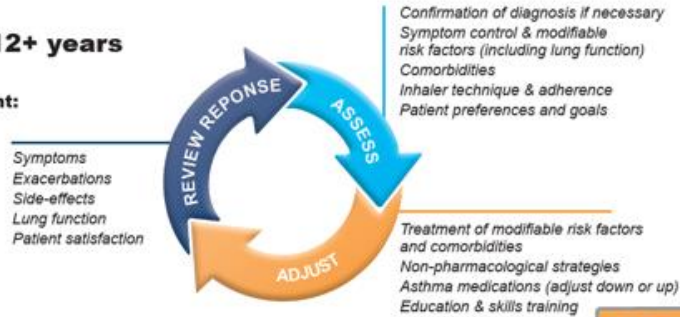


Box 3-5A

Adults & adolescents 12+ years

Personalized asthma management:

Assess, Adjust, Review response



Asthma medication options:

Adjust treatment up and down for individual patient needs

	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
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	Medium dose ICS-LABA	High dose ICS-LABA
Other controller options	Low dose ICS taken whenever SABA is taken †	Daily leukotriene receptor antagonist (LTRA), or low dose ICS taken whenever SABA is taken †	Medium dose ICS, or low dose ICS+LTRA ‡	High dose ICS, add-on tiotropium, or add-on LTRA ‡	Refer for phenotypic assessment ± add-on therapy, e.g. tiotropium, anti-IgE, anti-IL5/5R, anti-IL4R
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 allergic rhinitis and FEV1 >70% predicted

Politek MJ et al. Comparison of formoterol, salbutamol and salmeterol in methacholine-induced severe bronchoconstriction. *Eur Respir J* 1999.

My Symbicort® Asthma Action Plan

Symbicort® Maintenance And Reliever Therapy



Name: _____

Date: _____

GP: _____

Usual best PEF: _____ L/min

GP phone: _____

Normal mode

■ MY SYMBICORT ASTHMA TREATMENT IS:

- Symbicort 100/6 µg OR
- Symbicort 200/6 µg

■ MY REGULAR TREATMENT EVERY DAY:

Take _____ inhalation(s) in the morning
and _____ inhalation(s) in the evening, every day

■ RELIEVER:

Use Symbicort 1 inhalation whenever needed for relief of my asthma symptoms

I should always carry my Symbicort Turbuhaler

■ MY ASTHMA IS STABLE IF:

- I can take part in normal physical activity without asthma symptoms
- AND
- I do not wake up at night or in the morning because of asthma

OTHER INSTRUCTIONS:

Asthma flare-up

■ IF OVER A PERIOD OF 2–3 DAYS:

- My asthma symptoms are getting worse OR not improving OR
- I am using more than 6 Symbicort reliever inhalations a day,

I should:

- Continue to use my regular everyday treatment PLUS 1 inhalation Symbicort whenever needed to relieve symptoms
- Start a course of prednisolone
- Contact my doctor

COURSE OF PREDNISOLONE TABLETS:

Take 2 x 25 mg or _____ mg prednisolone tablets per day for _____ days OR

■ IF I NEED MORE THAN 12 SYMBICORT INHALATIONS (TOTAL) IN ANY DAY,

I must see my doctor or go to hospital the same day

Asthma emergency

■ SIGNS OF AN ASTHMA EMERGENCY:

- Symptoms getting worse quickly
- Extreme difficulty breathing or speaking
- Little or no improvement from Symbicort reliever inhalations.

IF I HAVE ANY OF THE ABOVE DANGER SIGNS, I SHOULD DIAL 000 FOR AN AMBULANCE AND SAY I AM HAVING A SEVERE ASTHMA ATTACK.

■ WHILE I AM WAITING FOR THE AMBULANCE START MY ASTHMA FIRST AID PLAN:

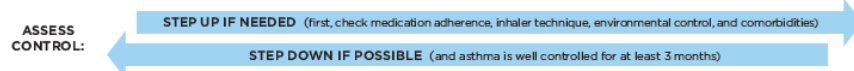
- Sit upright and stay calm
- Take 1 inhalation of Symbicort. Wait 1–3 minutes. If there is no improvement take another inhalation of Symbicort (up to a maximum of 6 inhalations).
- If only Ventolin® is available, take 4 puffs as often as needed until help arrives
- Start a course of prednisolone tablets (as directed) while waiting for the ambulance
- Even if my symptoms appear to settle quickly, I should see my doctor immediately after a serious asthma attack

EPR-3



STEPWISE APPROACH FOR MANAGING ASTHMA LONG TERM

The stepwise approach tailors the selection of medication to the level of asthma severity (see page 5) or asthma control (see page 6). The stepwise approach is meant to help, not replace, the clinical decisionmaking needed to meet individual patient needs.



		STEP 1	STEP 2	STEP 3	STEP 4	STEP 5	STEP 6
At each step: Patient education, environmental control, and management of comorbidities							
0-4 years of age		Intermittent Asthma		Persistent Asthma: Daily Medication			
	Preferred Treatment ¹	SABA* as needed	low-dose ICS*	medium-dose ICS*	medium-dose ICS* + either LABA* or montelukast	high-dose ICS* + either LABA* or montelukast	high-dose ICS* + either LABA* or montelukast + oral corticosteroids
	Alternative Treatment ^{1,4}		cromolyn or montelukast				
	Quick-Relief Medication	<ul style="list-style-type: none"> ▪ SABA* as needed for symptoms; intensity of treatment depends on severity of symptoms. ▪ With viral respiratory symptoms: SABA every 4-6 hours up to 24 hours (longer with physician consult). Consider short course of oral systemic corticosteroids if asthma exacerbation is severe or patient has history of severe exacerbations. ▪ Caution: Frequent use of SABA may indicate the need to step up treatment. 					
5-11 years of age		Intermittent Asthma		Persistent Asthma: Daily Medication			
	Preferred Treatment ¹	SABA* as needed	low-dose ICS*	low-dose ICS* + either LABA,* LTRA,* or theophylline ⁶⁾	medium-dose ICS* + LABA*	high-dose ICS* + LABA*	high-dose ICS* + LABA* + oral corticosteroids
	Alternative Treatment ^{1,4}		cromolyn, LTRA,* or theophylline ³	OR medium-dose ICS	medium-dose ICS* + either LTRA* or theophylline ⁴	high-dose ICS* + either LTRA* or theophylline ⁶	high-dose ICS* + either LTRA* or theophylline ⁶ + oral corticosteroids
	Quick-Relief Medication	<ul style="list-style-type: none"> ▪ SABA* as needed for symptoms. The intensity of treatment depends on severity of symptoms: up to 3 treatments every 20 minutes as needed. Short course of oral systemic corticosteroids may be needed. ▪ Caution: Increasing use of SABA or use >2 days/week for symptom relief (not to prevent EIB*) generally indicates inadequate control and the need to step up treatment. 					
≥12 years of age		Intermittent Asthma		Persistent Asthma: Daily Medication			
	Preferred Treatment ¹	SABA* as needed	low-dose ICS*	low-dose ICS* + LABA* OR medium-dose ICS*	medium-dose ICS* + LABA*	high-dose ICS* + LABA* AND consider omalizumab for patients who have allergies ¹¹	high-dose ICS* + LABA* + oral corticosteroid ¹⁴ AND consider omalizumab for patients who have allergies ¹¹
	Alternative Treatment ^{1,4}		cromolyn, LTRA,* or theophylline ³	low-dose ICS* + either LTRA,* theophylline, ⁹ or zileuton ¹¹	medium-dose ICS* + either LTRA,* theophylline, ⁹ or zileuton ¹¹		
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Priority Areas Addressed in Update

01

Intermittent ICS Therapy



02

LAMAs as Add-on Therapy

03

Bronchial Thermoplasty in Severe Adult Asthma

04

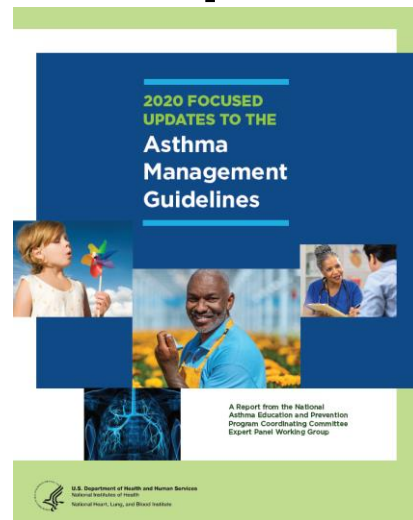
FeNO in Diagnosis, Medication Selection, Monitoring and Tx

05

Multicomponent Interventions for Indoor Allergens

06

Immunotherapy



322 Pages!





EPR-4 is a GRADE (Grading of Recommendations, Assessment, Development and Evaluation) paper to help treat any individual with asthma in any clinical context.

“Therefore, the Expert Panel merged the new recommendations into the framework of the comprehensive approach to asthma management summarized in the EPR-3 step diagrams.”



Implications	Strong recommendation	Conditional recommendation
For individuals with asthma	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	Most individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the intervention. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Different choices will be appropriate for individuals consistent with their values and preferences. Use shared decision-making. Decision aids may be useful in helping individuals make decisions consistent with their risks, values, and preferences.



	2007 Guideline	2020 Guideline
Management of Acute Exacerbation due to viral URI in children 0-4 years with h/o recurrent wheezing	<ul style="list-style-type: none"> Mild symptoms: SABA Q4-6 hrs x 24 hrs, longer with physician consult Moderate-severe: Consider short course OCS 	Conditional Rec: Short course of daily ICS and prn SABA starting at onset of respiratory illness
Treatment of Mild Persistent Asthma in patients 12 yrs+ (Step 2)	Daily LD-ICS + prn SABA	Conditional Rec: Either LD-ICS + prn SABA OR prn ICS + SABA
Treatment of Moderate Persistent Asthma in patients 12 yrs+ (Step 3)	Daily MD-ICS + prn SABA or LD-ICS/LABA + prn SABA	Strong Rec: Combo ICS/formoterol as both daily controller and quick relief therapy
Treatment of Mod-Severe Persistent Asthma in 4 yrs+ (Step 4)	Daily MD-ICS/LABA + prn SABA or daily HD-ICS + prn SABA	Conditional Rec: Combo ICS/formoterol as both daily controller and quick relief therapy





Excerpt from EPR-4 Comment Letter

January 2020

AAFA asks the NAEPP to develop a robust educational program for providers and patients, as clinicians and educators will be responsible for helping recalcitrant patients to this major change in medication recommendations and raise their comfort level in using the SMART regimen.

AAFA surveyed its asthma patient community to ask about their comfort regarding taking controller medication as rescue/reliever medication. Out of the patients who responded (n=43), 91% are taking both long-term controller and quick-relief medications. Of those taking both medications, 71% stated they felt not comfortable at all or somewhat uncomfortable using “ICS therapy as rescue medications”. While we acknowledge this question was a bit misleading (since the proposed guidelines would use ICS + reliever as the as-needed therapy), it does demonstrate the potential resistance from patients. Clinicians and educators will be responsible for helping patients understand this major change in medication recommendations and help raise their comfort level in taking ICS on an as needed basis with a short acting bronchodilator. And we encourage the NAEPP to develop a robust and comprehensive educational program for both providers and patients around this issue.



Figure 11. 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 beta₂-agonist; SABA, inhaled short-acting beta₂-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.

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.

Abbreviations: ICS, inhaled corticosteroid; LABA, long-acting beta₂-agonist; LTRA, leukotriene receptor antagonist; SABA, inhaled short-acting beta₂-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.

Intermittent Asthma

Management of Persistent Asthma In Individuals Ages 12+ Years

Treatment	STEP 1	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.

Abbreviations: ICS, inhaled corticosteroid; LABA, long-acting beta₂-agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; SABA, inhaled short-acting beta₂-agonist

[▲] Updated based on the 2020 guidelines.

* Cromolyn, Nedocromil, LTRAs including Zileuton and montelukast, and Theophylline were not considered for 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.

** The AHRQ systematic reviews that informed this report did not include studies that examined the role of asthma biologics (e.g. anti-IgE, anti-IL5, anti-IL5R, anti-IL4/IL13). Thus, this report does not contain specific recommendations for the use of biologics in asthma in Steps 5 and 6.

■ Data on the use of LAMA therapy in individuals with severe persistent asthma (Step 6) were not included in the AHRQ systematic review and thus no recommendation is made.

In Conclusion

Asthma is a **heterogeneous** disorder characterized by airway inflammation, airway hyperresponsiveness, and variable airflow limitation

Guidelines are only a first step to approaching a goal of personalized medicine, in which **therapy is tailored** to individual patients to maximize efficacy, and minimize toxicity and burden of treatment.



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<http://healthcare.partners.org/streaming/live/bwh/partnersasthmagrandrounds.html>



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