Virginia Mason™

Updates in Asthma

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Disclosure

None

Case

81 y/o M with very distant past 10 pack year smoking history (quit in 1975) presents with exertional dyspnea. Stress echo shows no concern for ischemia with normal wall motion and LVEF 65%. He was sent to see Pulmonary to make sure nothing else was going on. He has a known elevated left hemidiaphragm and has for years.

He feels winded while talking sometimes. He wakes up at night sometimes (1/week) coughing and then feeling short of breath. Has some morning sputum. He also admits to some anxiety feeling when he feels like he cannot catch his breath. Benzos have helped with some of the daytime symptoms in the past, but not the night wakening and night cough.

Case

Spirometry	Ref	Pre BD (L)	Pre % ref	Post BD (L)	Post % ref	% change
FEV1/FVC	0.75 (LLN 0.67)	0.65		0.68		
FVC	4.42	1.70	38%	1.90	43%	13%
FEV1	3.29	1.11	34%	1.28	39%	15%

What inhaler would you trial first

SABA (Short-acting beta-agonist – albuterol)

LAMA (Long-acting muscarinic antagonist – Spiriva)

ICS-Famoterol Schedule (Inhaled corticosteroid – Long-acting beta-agonist)

ICS-Famoterol PRN

ICS + SABA

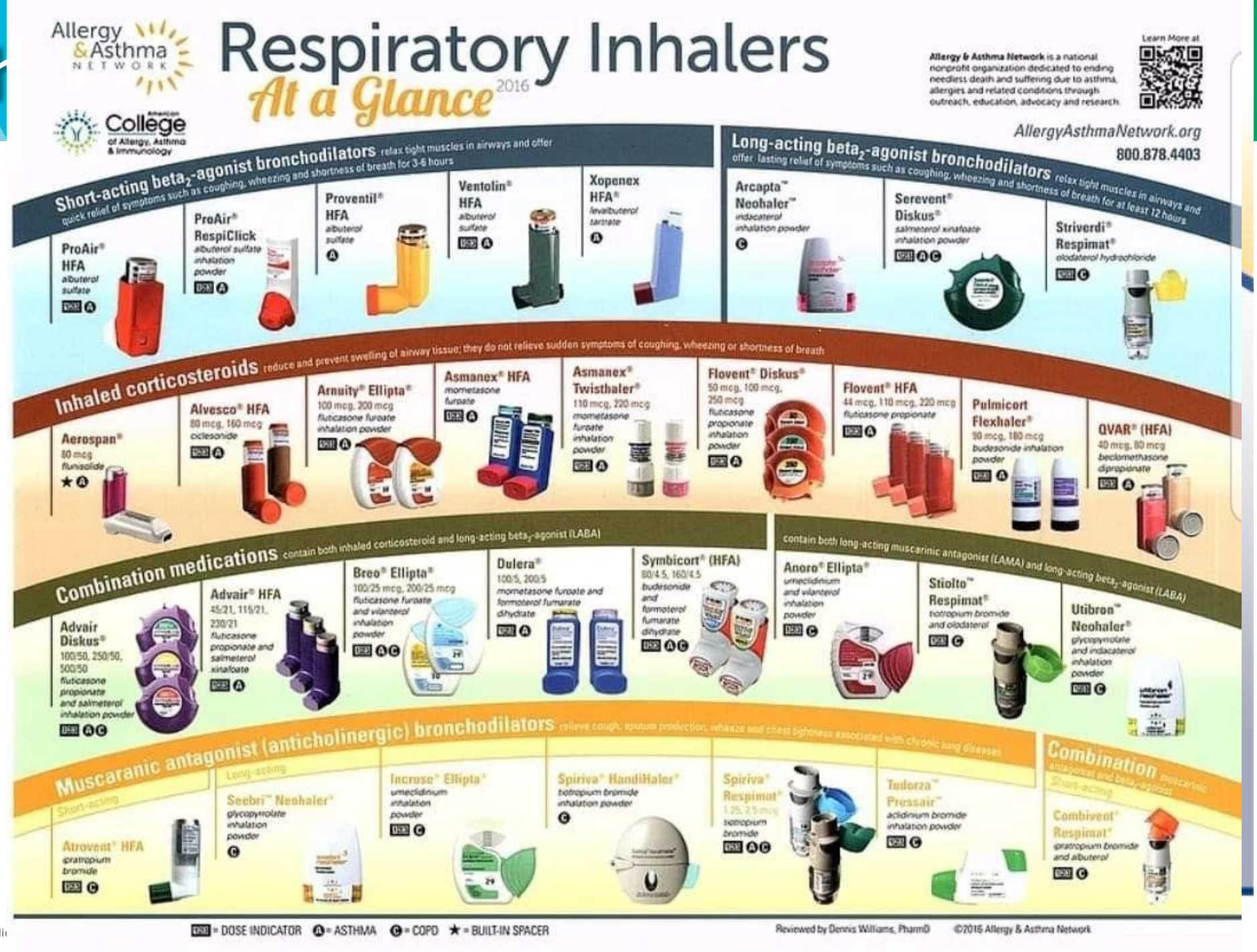
Outline

Asthma:

- Review NIH and GINA (Global Initiative for Asthma) guidelines in effect 2020-2021 Reviewing discrepancies between the two sets of guidelines.
- Highlight recent changes and how this changes inhaler prescribing
- Review when to refer
- Review what is new in Biologics.

- Please interrupt and ask:
  - My favorite inhaler
  - Tricks to get around insurance etc.

Asth



Asthma Guidelines

NIH -> NHLBI -> National Asthma Education Prevention Program Coordinating Committee (NAEPPCC)

GINA

U.S. Department of Health and Human Services
National Institutes of Health

National Heart, Lung, and Blood Institute

Asthma

Definition:

Hx of symptoms (wheeze, SOB, chest tightness, cough) that vary over time, *with* variable expiratory airflow limitation.

Diagnosing obstruction

Spirometry	BD reversibility: FEV1 or FVC >12% and 200 cc improvement
Peak flow diary	1-2 weeks twice-daily PEF (daily amplitude x 100/daily mean, averaged) >20%
Therapeutic trial	“significant” increase in FEV1 or PEF after 4 weeks controller therapy

Asthma

GINA 2021 update:

When possible, confirm diagnosis of asthma before starting controller treatment as confirmation is more difficult once treatment is started.

Key reason to refer to pulmonology is when diagnosis cannot be confirmed.

We will likely move on to methacholine challenge test or other provocation tests.

GINA vs. NAEPPCC

TABLE II. Differences between the GINA and NAEPP approaches to asthma management*

Approach	GINA	NAEPP
Direction	Global	National
Composition	Primarily asthma specialists from representative countries	Multidisciplinary combination of asthma specialists, primary care physicians, health policy experts, implementation and dissemination experts, methodologists, and other health care personnel
Target audience	Template for application for countries to develop their national approach	Provides specific guidance for the national approach in the United States
Challenges	Must consider developing countries with limited resources and access to asthma specialists	Must consider federal regulations as limitations of recommendations
Revision	Annually	Periodically
Scope	Living document approach that regularly reviews current literature and decides on modifications	Decides which questions to address and then evaluates the literature to make evidence-based recommendations using detailed GRADE methodology
Support system	Previously from restricted education grants from the pharmaceutical industry and now from product sales. Commercial sales allow for widespread advertising with multiple products, such as handbooks, documents, and teaching slides	NIH-directed development and distribution, with limited budget for distribution

GRADE, Grading of Recommendations Assessment, Development and Evaluation; *NIH*, National Institutes of Health.

*This comparison is provided to highlight major differences in approach between the 2 groups of experts that provide direction in asthma care, with specific features to consider in applying their information in clinical practice.

13 years ago

Szefler SJ. J Allergy Clin Immunol, 2020

NIH 2020 update – What they covered

- Fractional Exhaled Nitric Oxide Testing
- **Intermittent Inhaled Corticosteroids**
- **Long-Acting Muscarinic Antagonists**
- **Indoor Allergen Mitigation**
- **Immunotherapy in the Treatment of Allergic Asthma**
- Bronchial Thermoplastic

Asthma Diagnosis

Hx of symptoms (wheeze, SOB, chest tightness, cough) that vary over time, *with* variable expiratory airflow limitation.

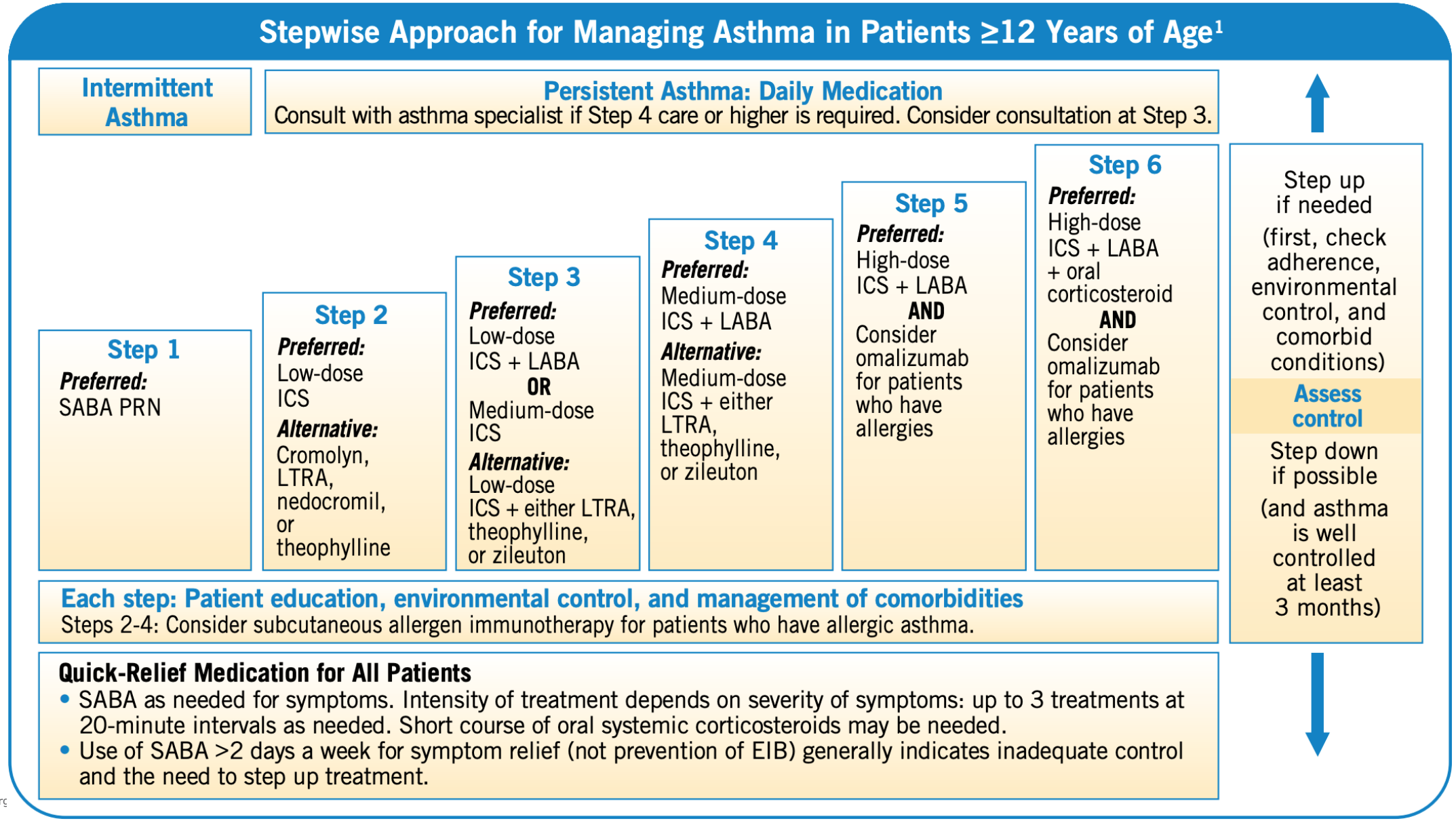
Spirometry	BD reversibility: FEV1 or FVC >12% and 200 cc improvement. Or Large variability on airflow obstruction over time
Peak flow diary	1-2 weeks twice-daily PEF >20%
Therapeutic trial	"significant" increase in FEV1 or PEF after 4 weeks **controller** therapy
Bronchoprovocation	Methacholine or mannitol inhalation challenge. High negative predictive value

Classification of Asthma Severity (Youths ≥12 years of age and adults)

Components of Severity		Step 1	Step 2	Step 3 nt	Step 4
		Intermittent	**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%

Journal of Allergy and Clinical Immunology 2007 120S94-S138DOI: (10.1016/j.jaci.2007.09.029)

NIH 2007 Treatment Recommendations



Intermittent ICS-Formoterol?

The Big Change

SABA → ICS/LABA

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. Reddel[1], J. Mark FitzGerald[2], Eric D. Bateman[3], Leonard B. Bacharier[4], Allan Becker[5], Guy Brusselle[6], Roland Buhl[7], Alvaro A. Cruz[8], Louise Fleming[9], Hiromasa Inoue[10], Fanny Wai-san Ko[11], Jerry A. Krishnan[12], Mark L. Levy[13], Jiangtao Lin[14], Søren E. Pedersen[15], Aziz Sheikh[16], Arzu Yorgancioglu[17] and Louis-Philippe Boulet[18]

@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].

The risks of SABA only

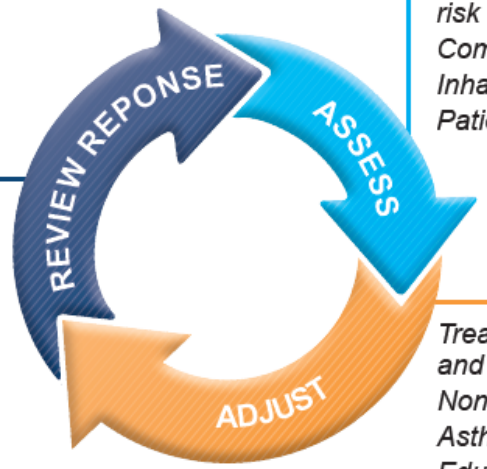
- Regular or frequent use of SABA is associated with adverse effects
  - β-receptor downregulation, decreased bronchoprotection, rebound hyperresponsiveness, decreased bronchodilator response *(Hancox, Respir Med 2000)*
  - Increased allergic response, and increased eosinophilic airway inflammation *(Aldridge, AJRCCM 2000)*
- Higher use of SABA is associated with adverse clinical outcomes
  - 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)*

Hancox et al. *Respir Med* 2000
Aldridge et al. *AJRCCM* 2000
Stanford et al. *AAAI* 2012
Suissa et al. *AJRCCM* 1994

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 risk factors and comorbidities
Non-pharmacological strategies
Asthma medications (adjust down or up)
Education & skills training

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

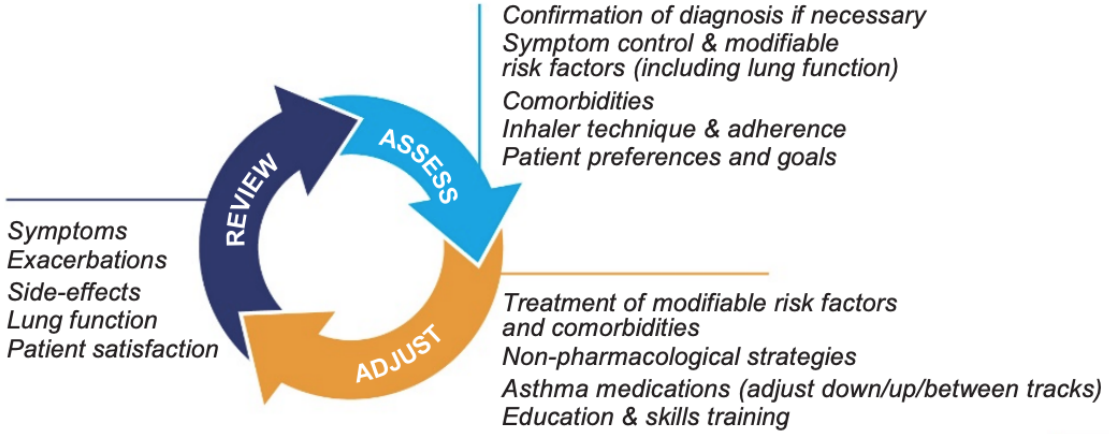
	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
PREFERRED CONTROLLER to prevent exacerbations and control symptoms	As-needed low dose ICS-formoterol *	Daily low dose inhaled corticosteroid (ICS), or as-needed low dose ICS-formoterol *	Low dose ICS-LABA	Medium dose ICS-LABA	High dose ICS-LABA Refer for phenotypic assessment ± add-on therapy, 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 allergic rhinitis and FEV1 >70% predicted*

Treatment	Intermittent Asthma	Management of Persistent Asthma in Individuals Ages 12+ Years				
	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)**	

Adults & adolescents 12+ years

Personalized asthma management
Assess, Adjust, Review
for individual patient needs



CONTROLLER and **PREFERRED RELIEVER**
(Track 1). Using ICS-formoterol as reliever reduces the risk of exacerbations compared with using a SABA reliever

STEPS 1 – 2	STEP 3	STEP 4	STEP 5
As-needed low dose ICS-formoterol	Low dose maintenance ICS-formoterol	Medium dose maintenance ICS-formoterol	Add-on LAMA Refer for phenotypic assessment ± anti-IgE, anti-IL5/5R, anti-IL4R Consider high dose ICS-formoterol
RELIEVER: As-needed low-dose ICS-formoterol			

CONTROLLER and **ALTERNATIVE RELIEVER**
(Track 2). Before considering a regimen with SABA reliever, check if the patient is likely to be adherent with daily controller

STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
Take ICS whenever SABA taken	Low dose maintenance ICS	Low dose maintenance ICS-LABA	Medium/high dose maintenance ICS-LABA	Add-on LAMA Refer for phenotypic assessment ± anti-IgE, anti-IL5/5R, anti-IL4R Consider high dose ICS-LABA
RELIEVER: As-needed short-acting β2-agonist				

Other controller options for either track

	Low dose ICS whenever SABA taken, or daily LTRA, or add HDM SLIT	*Medium dose ICS, or add LTRA, or add HDM SLIT*	*Add LAMA or LTRA or HDM SLIT, or switch to high dose ICS*	*Add azithromycin (adults) or LTRA; add low dose OCS but consider side-effects*

- **Track 1, with low dose ICS-formoterol as the reliever, is the preferred approach**
  - Using ICS-formoterol as reliever reduces the risk of exacerbations compared with using a SABA reliever, with similar symptom control and similar lung function
- **Track 2, with SABA as the reliever, is an alternative approach**
  - Use this if Track 1 is not possible, or is not preferred by a patient with no exacerbations on their current controller therapy
  - Before considering a regimen with SABA reliever, consider whether the patient is likely to be adherent with daily controller – if not, they will be exposed to the risks of SABA-only treatment

Take it one step at a time

STEP 1 → 2

STEP 1	STEP 2
PRN SABA	Daily low-dose ICS and PRN SABA or PRN concomitant ICS and SABA▲
	Daily LTRA* and PRN SABA or Cromolyn,* or Nedocromil,* or Zileuton,* or Theophylline,* and PRN SABA

STEPS 1 – 2

As-needed low dose ICS-formoterol

As-needed low dose ICS-formoterol *

STEP 1

Take ICS whenever SABA taken

STEP 2

Low dose maintenance ICS

RELIEVER: As-needed short-acting β2-agonist

SYGMA 1 and SYGMA 2 trials

Symbicort **G**iven as Needed in **M**ild **A**sthma

Patient: Asthmatics requiring step 2 GINA asthma management (eg. mild persistent asthma), in > 300 sites

- SYGMA 1 (N=3849), Mean age : 39.6yrs SD 16.6
- SYGMA 2 (N=4215) Mean age : 41yrs SD 17.0

Intervention:

A. Placebo BD + Terbutaline PRN
B. Placebo BD + Symbicort (ICS/F) PRN
C. Budesonide BD + Terbutaline PRN

SYGMA 2

SYGMA 1

O'Byrne PM et. al. 2018, NEJM

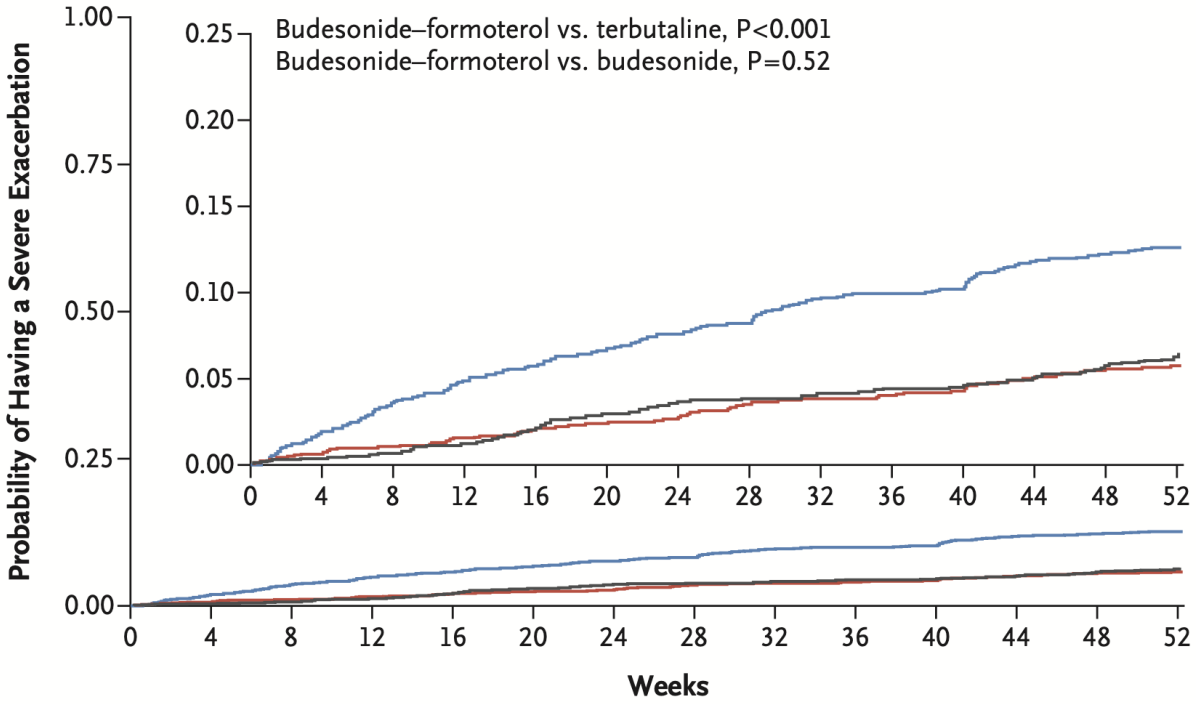
SYGMA 1

Terbutaline as needed (N=1277)

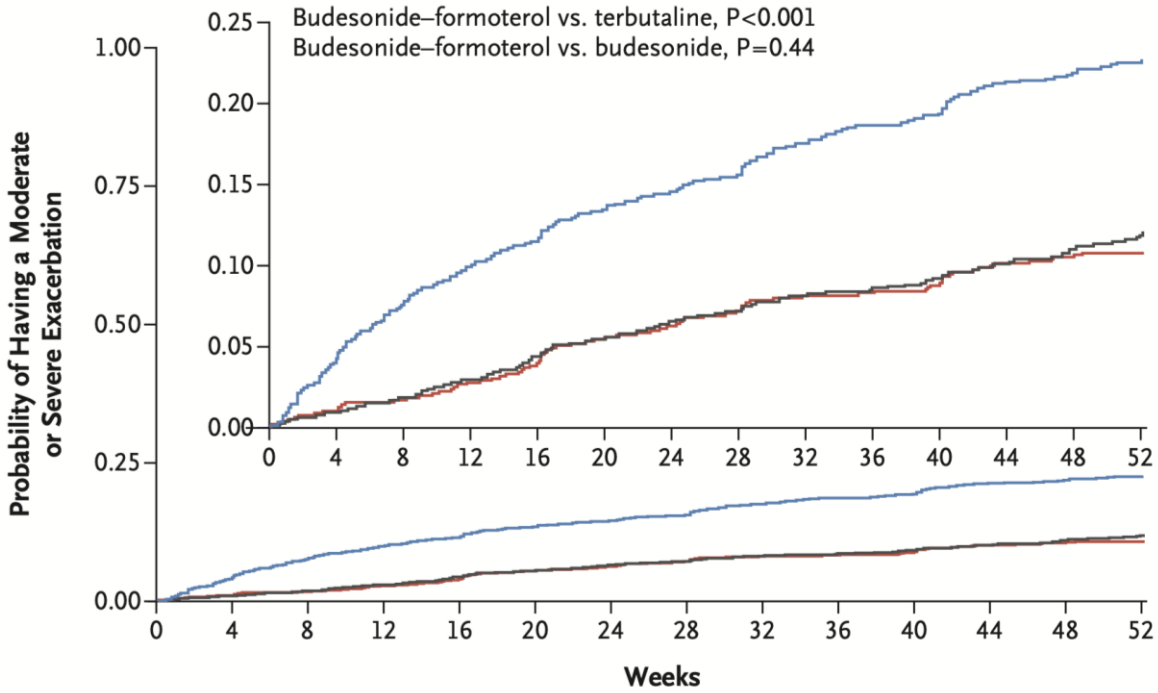
Budesonide–formoterol as needed (N=1277)

Budesonide maintenance (N=1282)

Severe Exacerbation



Moderate or Severe Exacerbation



O'Byrne PM et. al. NEJM 2018

SYGMA 1

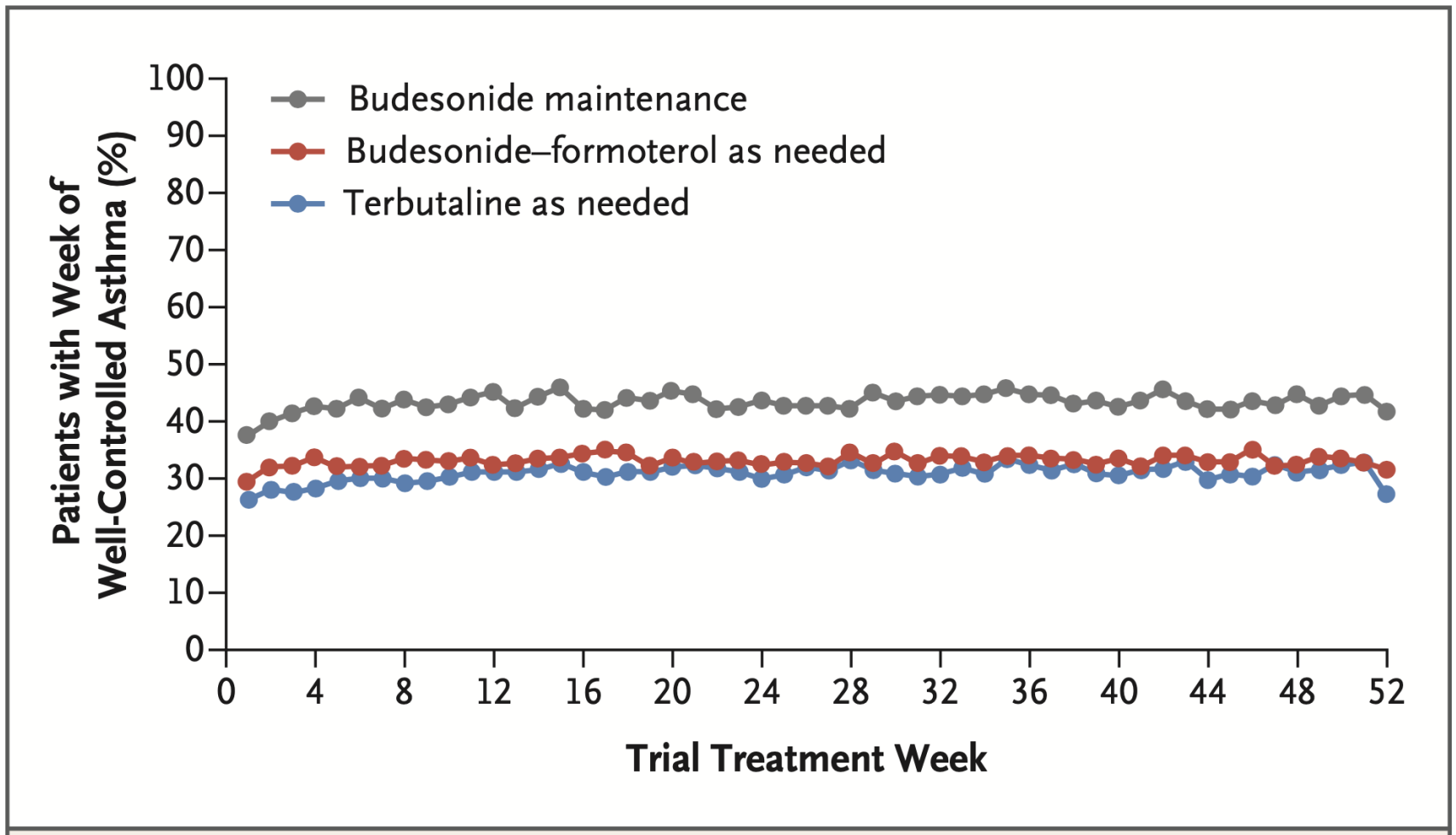


Figure 2. Overall Weeks of Well-Controlled Asthma, According to Data in the Electronic Diary.

O'Byrne PM et. al. NEJM 2018

SYGMA 1: Take away

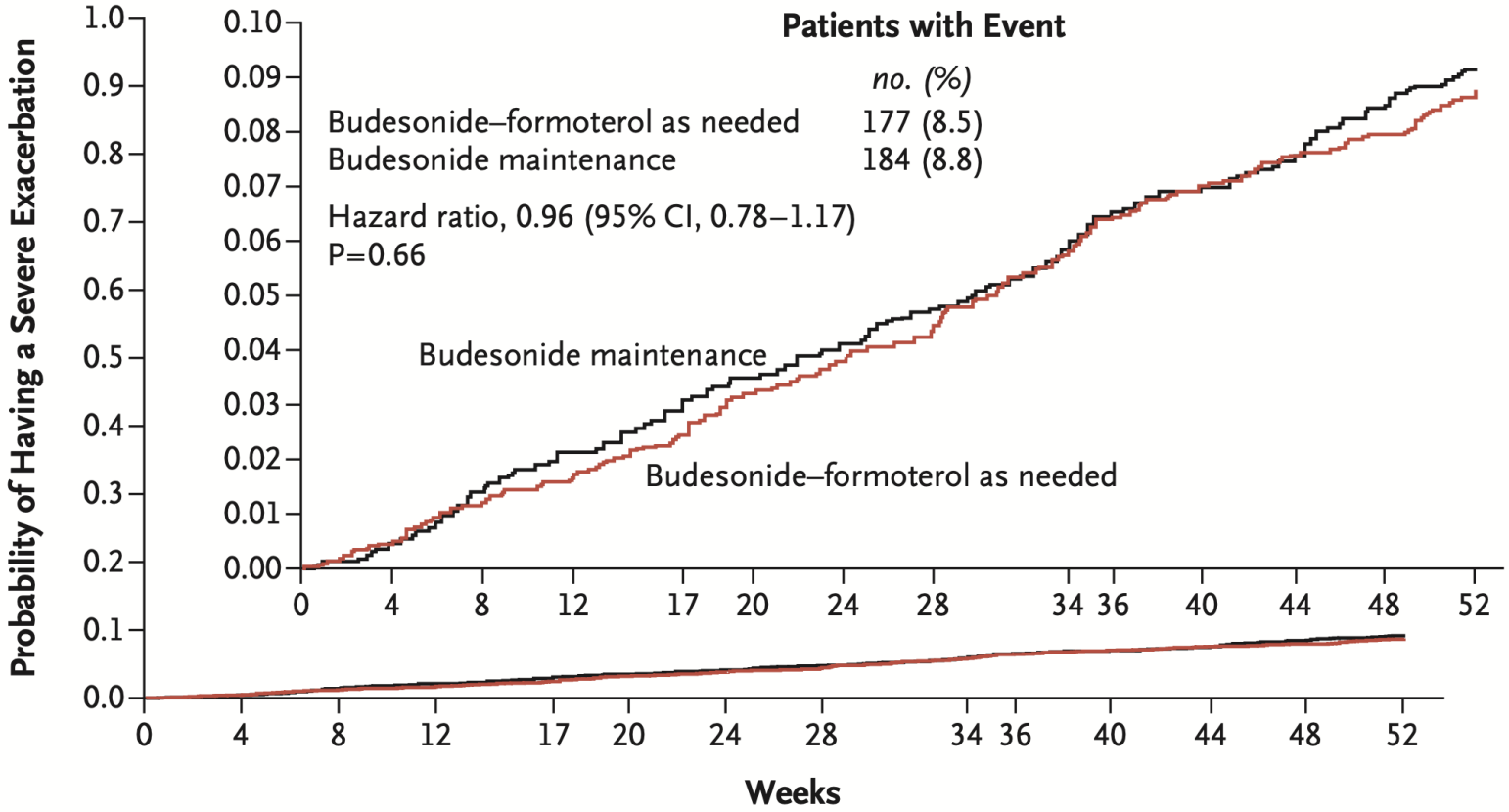
- Improved asthma control with intermittent ICS-F over SABA
- Daily ICS was better for symptom control
- ICS-F noninferior for prevention of acute exacerbations compared to daily ICS and both better than SABA alone
- ICS-F resulted in lower cumulative ICS exposure than ICS daily

O'Byrne PM et. al. NEJM 2018

SYGMA 2

- Placebo BD + Symbicort PRN
- Budesonide BD + Terbutaline PRN

B **Time to First Severe Exacerbation**



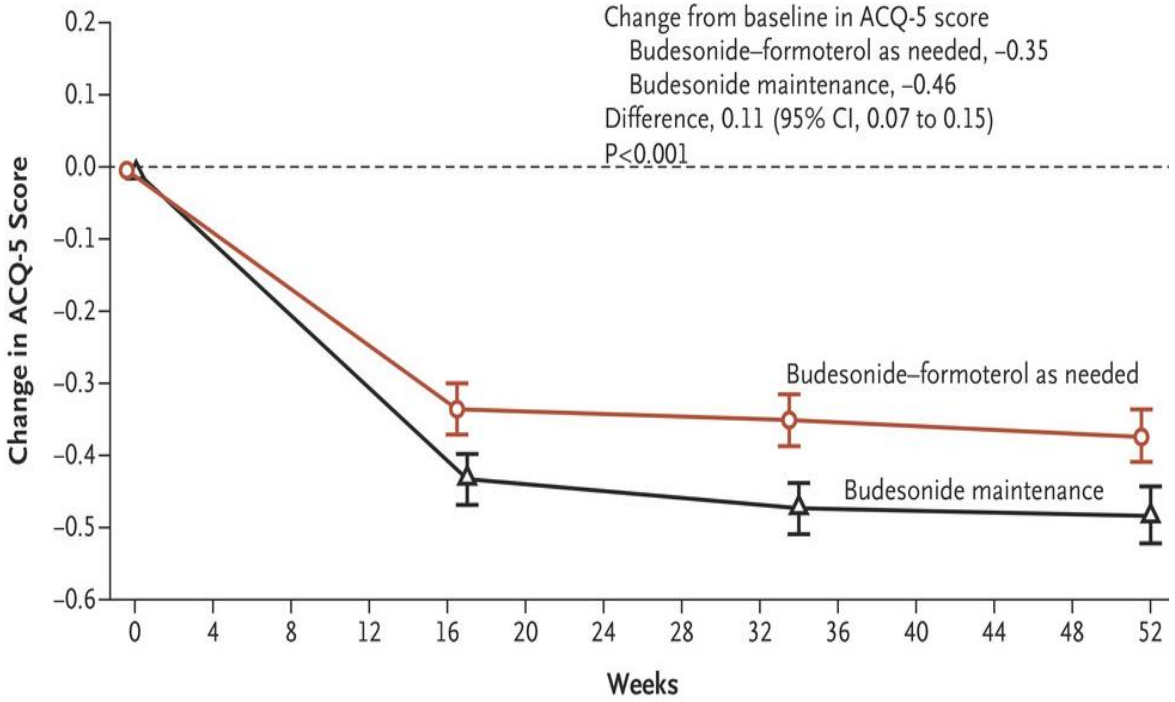
No. at Risk

Budesonide–formoterol as needed	2089	2065	2039	2012	1982	1944	1926	1904	1862	1840	1821	1799	1782	1208
Budesonide maintenance	2087	2060	2027	1987	1957	1929	1909	1883	1848	1826	1811	1786	1760	1222

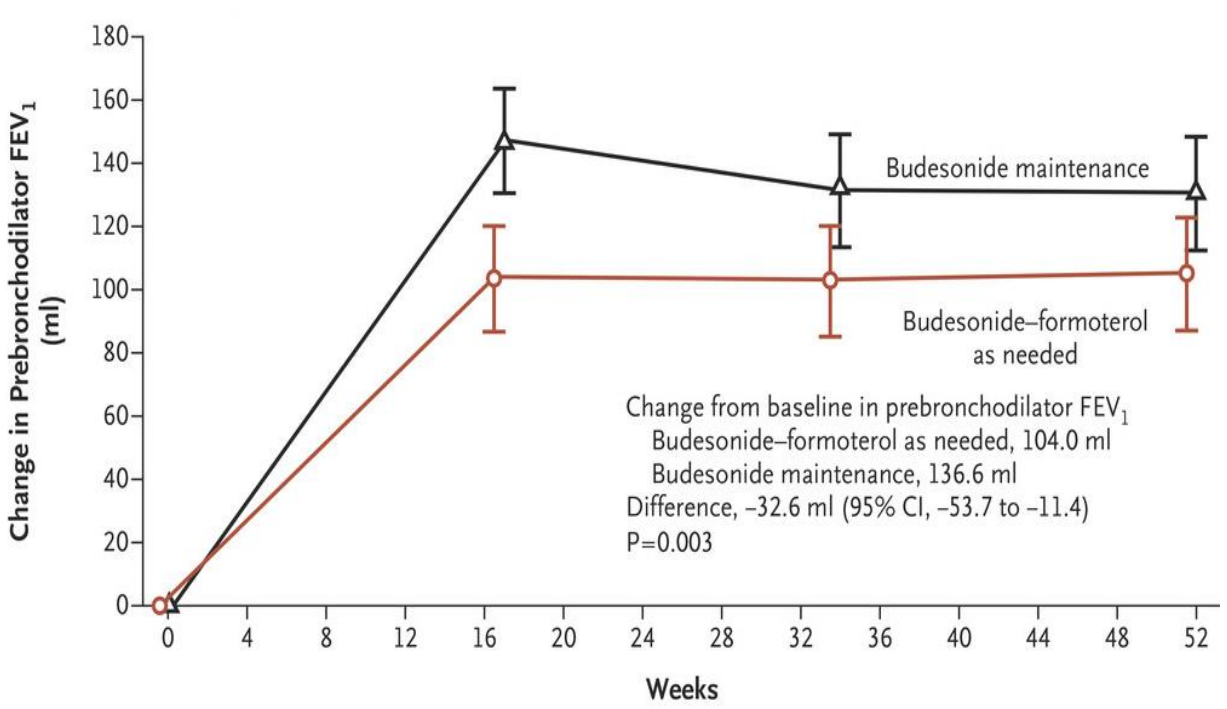
Bateman ED et. al, NEJM 2018

SYGMA 2

Change in ACQ-5 Score from Baseline



Change in Prebronchodilator FEV1 from Baseline



SYGMA 2: Take away

- ICS-F PRN vs. ICS maintenance: noninferior in time to exacerbation
- Benefit of ICS-F PRN: ¼ of the ICS exposure
- Benefit of daily ICS: better QoL, change in FEV1

NIH rational for why Step 1 is still SABA

- Post Hoc Analysis of Three studies
  - O'Byrne et al. Am J Resp Crit Care. 2005
  - Scicchitano et al. Curr Med Res Opin. 2004
  - Rabe et al CHEST 2016

- 1239 Participants aged > 12 yrs.

Confirmed ICS-F schedule and PRN reduced overall exacerbation

In subgroup analysis: Mildest asthmatics (SABA use <1/day) had marginal and statistically nonsignificant benefit

Jenkins CR et al. BMC Pulm Med 2017

Step 1 – 2:

STEP 1 → 2

STEP 1	STEP 2
PRN SABA	Daily low-dose ICS and PRN SABA or PRN concomitant ICS and SABA▲
	Daily LTRA* and PRN SABA or Cromolyn,* or Nedocromil,* or Zileuton,* or Theophylline,* and PRN SABA

STEPS 1 – 2

As-needed low dose ICS-formoterol

As-needed low dose ICS-formoterol *

STEP 1

Take ICS whenever SABA taken

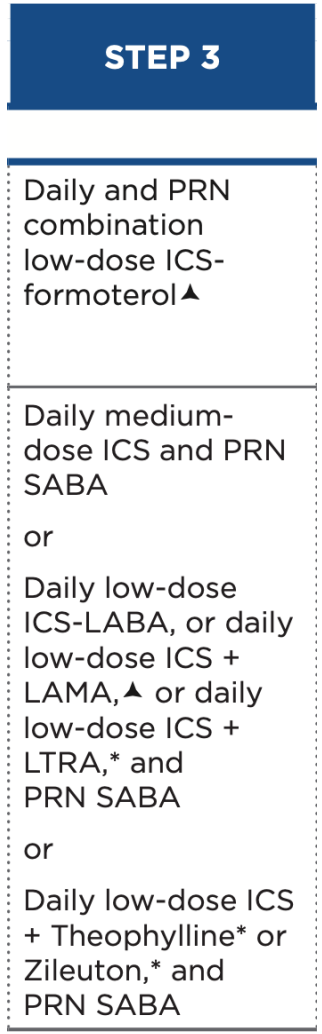
STEP 2

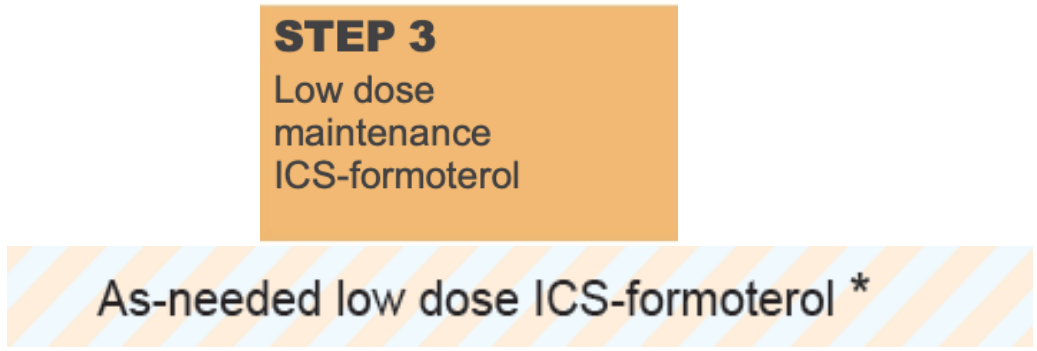
Low dose maintenance ICS

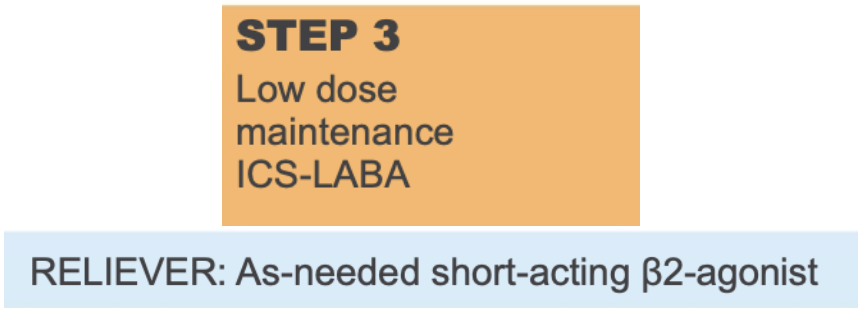
RELIEVER: As-needed short-acting β2-agonist

STEP 3:

Single
Maintenance
And
Reliever
Therapy







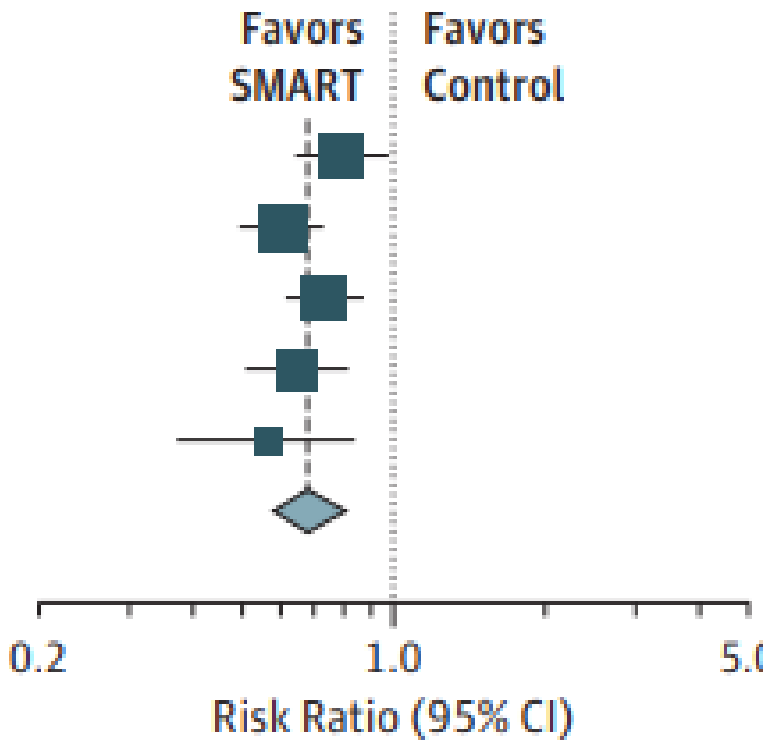
SMART: **S**ingle **M**aintenance **A**nd **R**eliever **T**herapy.

Association of SMART with exacerbations requiring systemic corticosteroids, hospitalization, or ED visits among patients aged 12 years or older vs **same doses** of inhaled corticosteroids and LABA controller therapy

Source	Total No. of Participants
Vogelmeier et al,[23] 2012	1067
Rabe et al,[25] 2006	1107
Atienza et al,[24] 2013	1049
Papi et al,[26] 2013	852
Patel et al,[27] 2013	151
Overall (random-effects model)	4226

Heterogeneity: $I^2 = 29\%$, $P = .23$

Test for overall effect: $t_4 = -6.44$, $P < .001$



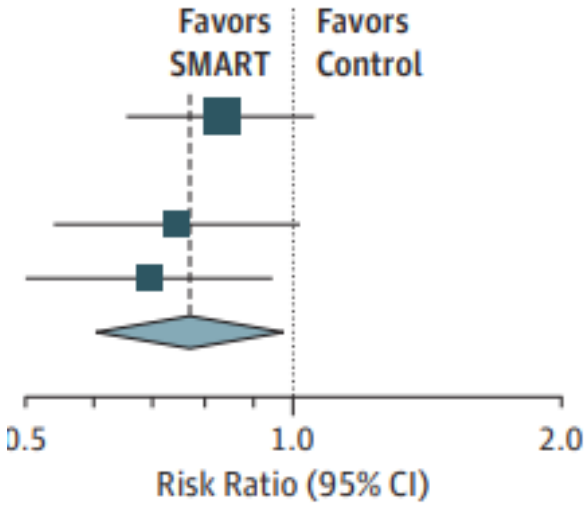
Sobieraj DM, NEJM, 2018

SMART: **S**ingle **M**aintenance **A**nd **R**eliever **T**herapy.

Association of SMART with exacerbations requiring systemic corticosteroids, hospitalization, or ED visits among patients aged 12 years or older vs **higher doses** of inhaled corticosteroids and LABA controller therapy

Source	Total No. of Participants
Bousquet et al,[32] 2007	1151
Kuna et al,[33] 2007	
Comparison 1	552
Comparison 2	552
Overall (random-effects model)	2254

Heterogeneity: $I^2 = 0\%$, $P = .64$
Test for overall effect: $t_2 = -4.71$, $P = .04$



Fda.gov

Sobieraj DM, NEJM, 2018

Caveats about intermittent therapy and SMART

Majority of studies with budesonide-formoterol.

Max dose 12 puffs/day for age >12.

Cannot do with ICS/salmeterol

Cannot do intermittent with ICS-vilanterol DPI (Breo) or other DPI's due to short shelf life.

Patients must be able to recognize and respond to asthma symptoms

- "Just in time"
- The patient that never takes their SABA because "I'm never that bad" is not a good candidate.

ICS/Formoterol ≠ ICS/Salmeterol

Symbicort = Budesonide/formoterol

Dulera = Mometasone/formoterol

Advair = Fluticasone/Salmeterol

LAMA

NAEPPCC

STEP 3

Daily and PRN combination low-dose ICS-formoterol▲

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

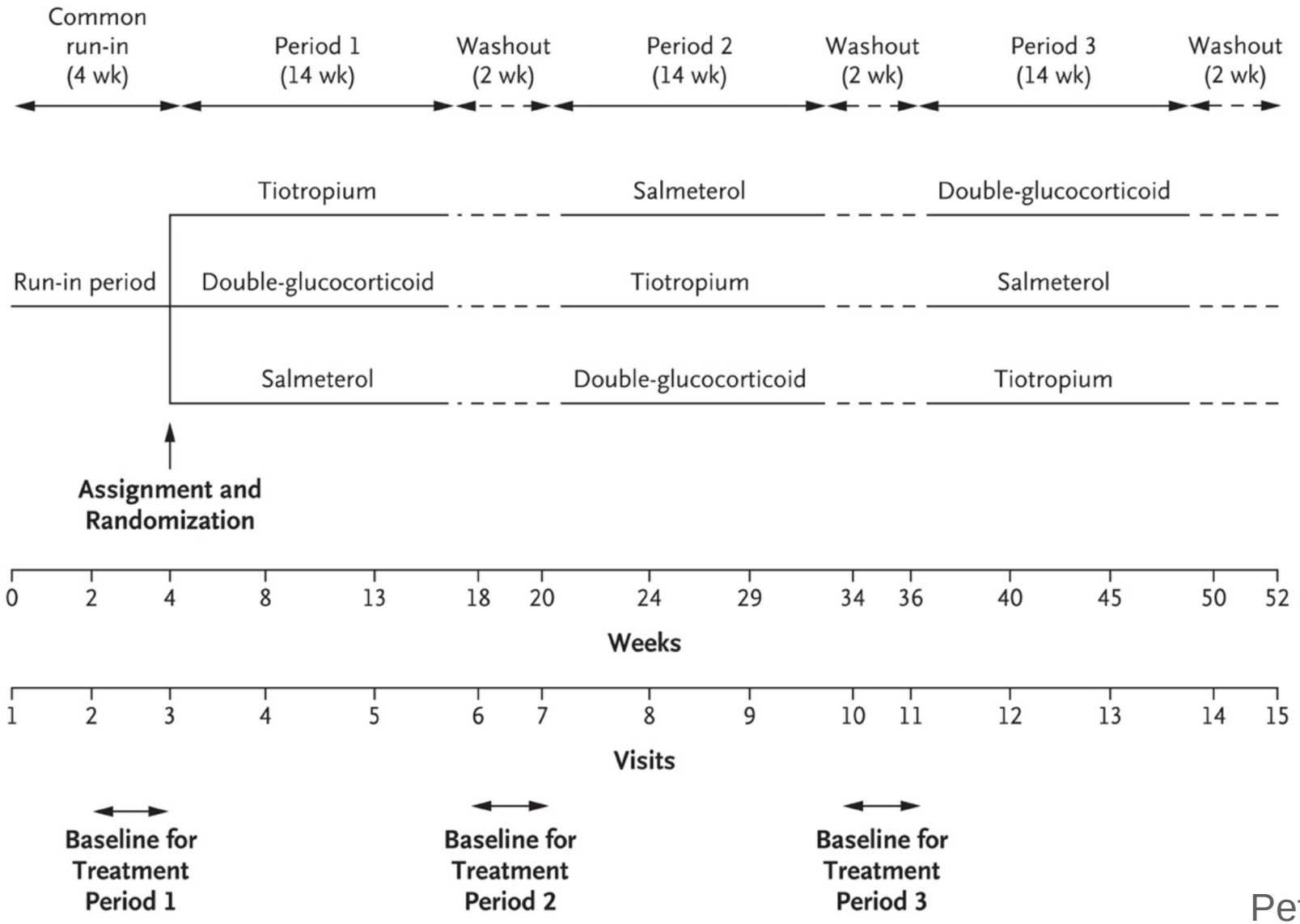
GINA

STEP 4

Medium dose ICS-LABA

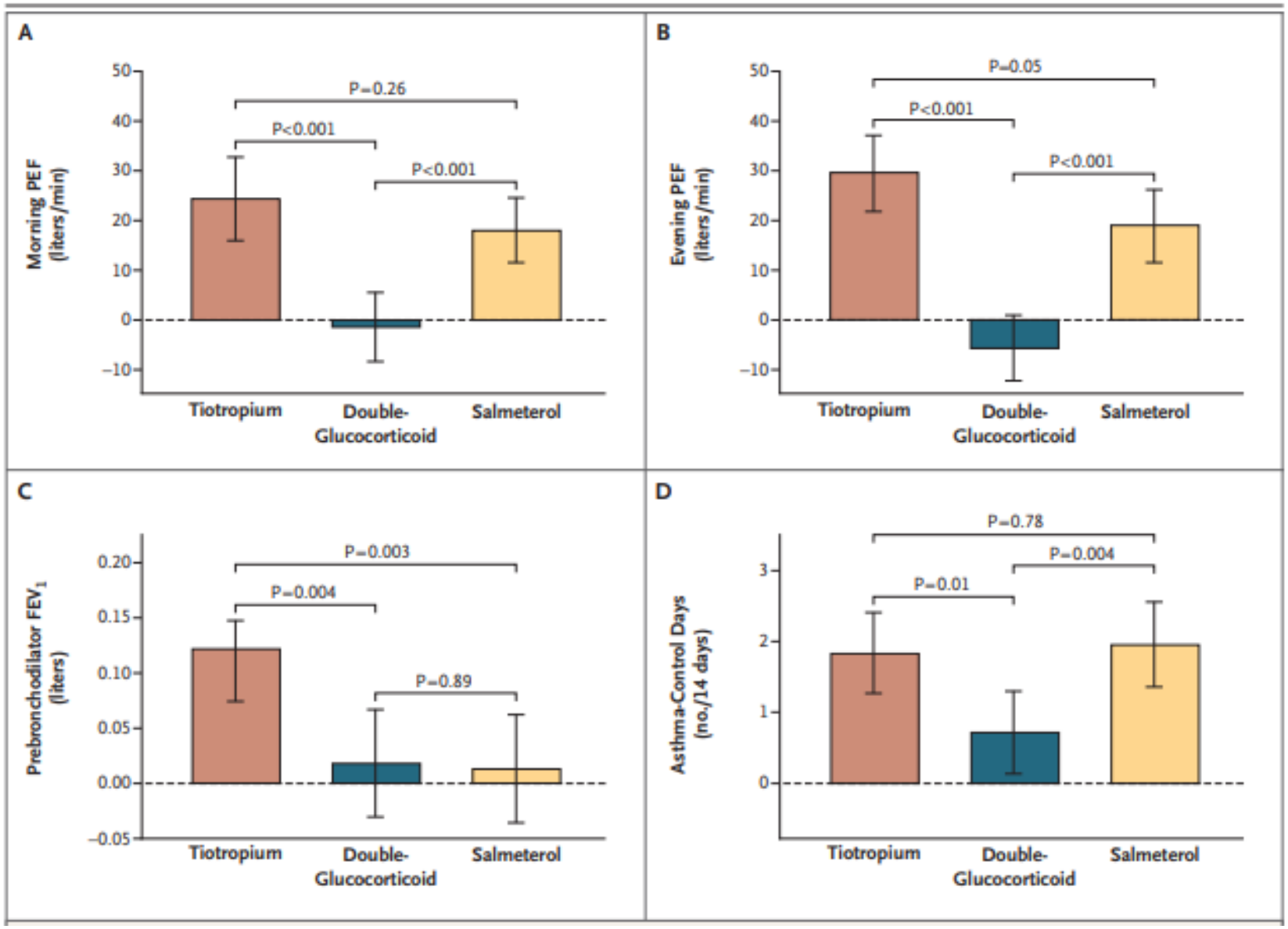
High dose ICS, add-on tiotropium, o add-on LTRA #

Tiotropium as add on to ICS



Peters SP, et al. NEJM, 2010

Tiotropium as add on to ICS



Peters SP, et al. NEJM, 2010

NIH recommendations for LAMA:

- Persistent asthma, uncontrolled: Do not replace LABA with LAMA
- Persistent asthma, uncontrolled: Add LAMA to ICS-LABA
- Persistent asthma, uncontrolled: As add on to ICS vs. placebo

Stepping up and down

Before Stepping up on therapy confirm that all modifiable risk factors have been addressed:

- Nasal disease
- environmental exposures
- obesity
- reflux

GINA emphasizes in 2021 that once asthma is well controlled for 2-3 months consider stepdown in therapy.

Action Plan:

IF YOUR ASTHMA IS WELL CONTROLLED

You need your reliever inhaler less than 3 times per week, you do not wake up with asthma and, and your asthma does not limit your activities (including exercise) (If used, peak flow over ____L/min)

Your controller medication is: _____ (name) _____ (strength)

Take: _____ puffs/tablet _____ times EVERY DAY

☐ Use a spacer with your controller inhaler

Your reliever/rescue medication is: _____ (name) _____ (strength)

Take _____ puffs if needed to relieve asthma symptoms like wheezing, coughing, shortness of breath

☐ Use a spacer with your reliever inhaler

Other medications: _____ (name) _____ (strength) _____ (how often)

_____ (name) _____ (strength) _____ (how often)

Before exercise take: _____ (name) _____ (strength) _____ (how many puffs/tablets)

IF YOUR ASTHMA IS GETTING WORSE

You need your reliever more often than usual, you wake up with asthma, or you cannot do your normal activities (including exercise) because of your asthma (If used, peak flow between ____ and ____L/min)

Take your reliever/rescue medication: _____ (name) _____ (strength) _____ (how often)

☐ Use a spacer with your controller inhaler

Take your controller medication: _____ (name) _____ (strength)

Take: _____ puffs/tablet _____ times EVERY DAY

☐ Use a spacer with your reliever inhaler ☐ Contact your doctor

Other medications: _____ (name) _____ (strength) _____ (how often)

IF YOUR ASTHMA SYMPTOMS ARE SEVERE

You need your reliever again more often than every 3-4 hours, your breathing is difficult, or you often wake up with asthma (if used, Peak Flow under____L/min)

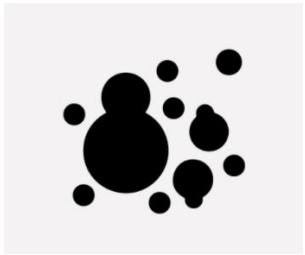
Take your reliever/rescue medication: _____ (name) _____ (strength) _____ (how often)

Take prednisone/prednisolone: _____ (name) _____ (strength)

Take: _____ tablet _____ times every day

CONTACT A DOCTOR TODAY OR GO TO THE EMERGENCY DEPARTMENT

Indoor allergens



Mold

Cockroaches

Animal dander

Dust mites

Case question

47 F with moderate persistent asthma. She is on SMART therapy and is normally on steroids about once every other year for exacerbation. She is asking you of it is worthwhile for her to buy the newest, $1,000 HEPA filter for her house as she heard it can help asthmatics. Her symptoms are the same in an out of the house and when she travels.

A: Tell her it’s a great idea

B: Send her for allergy testing

C: Tell her to save that money for her co-pay on inhalers, because, lets be honest, even when covered by insurance inhaler prices can be ridiculous.

Case question

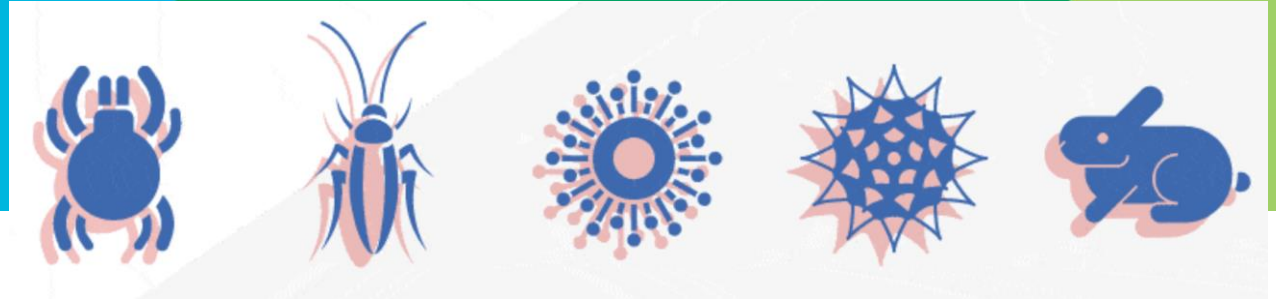
47 F with moderate persistent asthma. She is on ICS-F maintenance and PRN and is normally on steroids about once every other year for exacerbation. She is asking you of it is worthwhile for her to buy the newest, $1,000 HEPA filter for her house as she heard it can help asthmatics. Her symptoms are the same in an out of the house and when she travels.

A: Tell her it's a great idea

B: Send her for allergy testing

C: Tell her to save that money for her co-pay on inhalers, because, lets be honest, even when covered by insurance inhaler prices can be ridiculous.

Indoor allergens



Remove specific allergen exposure ONLY when there is evidence of sensitization and exposure. Use removal strategies as part of a multicomponent allergen-specific mitigation

If History is Negative – Do Nothing more

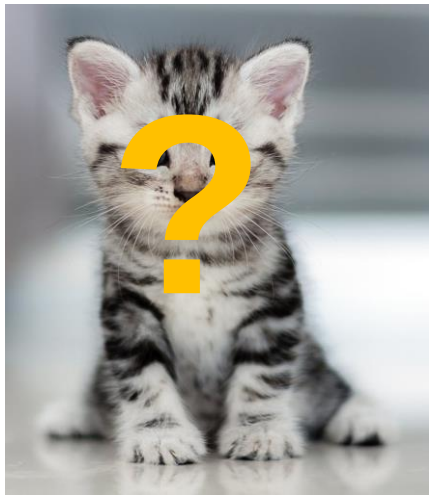
History of asthma symptoms aggravated by mold, dust, or furry animals?

→ Allergy Testing

Indoor allergens

Remove specific allergen exposure ONLY when there is evidence of sensitization and exposure. Use removal strategies as part of a multicomponent allergen-specific mitigation

Acaricides



When to refer

When unable to confirm the diagnosis of asthma

If occupational asthma is suspected

If stepping up to Step 4 /5 → immunotherapy and biologics

Frequent exacerbations

Pt at risk for asthma related deaths (hospitalizing, ER visits, poor compliance)

Pt needing oral steroids more that one a year

Eosinophilic Asthma

Aspirin exacerbated respiratory disease

When to refer

- Comorbid Condition
  - Obesity
  - Acid reflux
  - OSA
  - Sinus disease
- Differential Diagnosis
  - Vocal cord dysfunction
  - Panic disorder a/w dysfunctional breathing
  - COPD
  - Bronchiectasis
  - Tracheobronchomalacia
  - Atypical pneumonia
  - Bronchiolitis obliterans

Allergic Asthma - immunotherapy

WHAT: Therapeutic administration of exogenous aeroallergens to a person who demonstration sensitization with the goal of attenuating the individuals asthmatic response to subsequent exposure to those aeroallergens.

WHO: Asthma that becomes symptomatic after a specific exposure

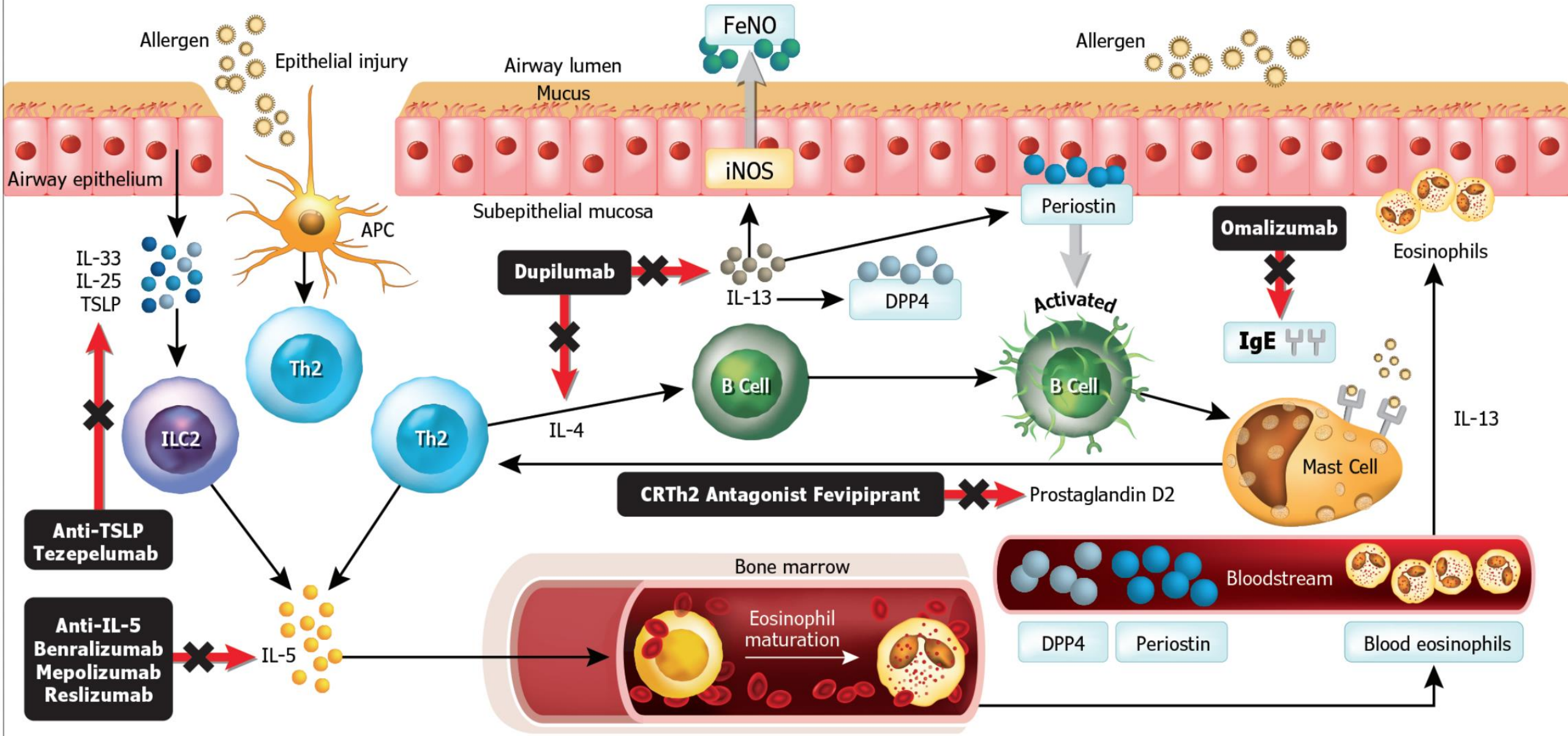
1. Skin Test + - or -
2. Laboratory testing to measure level of antigen-specific IgE

NIH recommendations: Immunotherapy

SCIT as adjunct to standard Tx for moderate allergenic asthma (Conditional, moderate)

Conditional recommendation against SLIT in asthma treatment

Figure 7. Cytokines, Biomarkers, and New Biologic Therapies



CHEST, Severe Asthma Reference Guide. CME 2018

High IgE? Significant allergy history?

Omalizumab

Reduces free IgE by 96%

-> reduction in Mast cell degranulation

-> evidence for reduced fall season asthma exacerbation in children which are likely driven by respiratory viral infections

Indication: Add-on maintenance treatment for moderate-to-severe persistent asthma > 6yrs with positive skin test or in vitro reactivity to perennial aeroallergens. Inadequately controlled by ICS

Similar patients in who you would send for immunotherapy.

High Eos?: treat w/ anti- IL-5, IL-5Ra, IL-4Ra

Mepolisumab: anti-IL-5
Reslizumab: anti-IL-5
Benralizumab: anti-iL-5Ra
Dupilumab: anti-IL-4Ra

Step 4-5 therapy in place without symptom control.
- Medium dose ICS-F. + LAMA +/- LTRA

Maintenance oral steroids for asthma

First Steps:
Detailed history of exacerbation history x 1 yr
Obtain full lung function testing
Identify co-morbid factors to be able to further treat these as well.

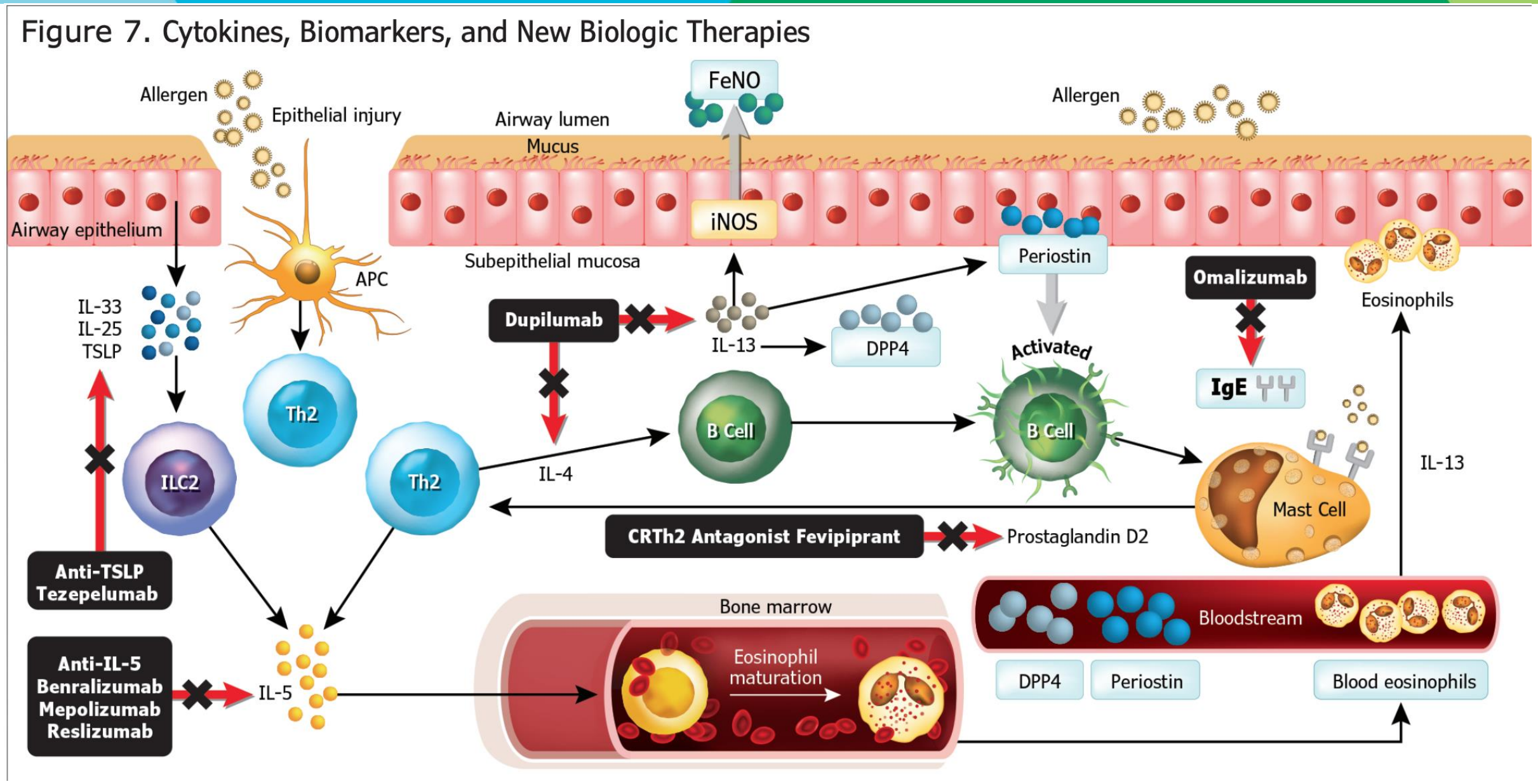
Medication	Mechanism	Delivery	Benefit
Omalizumab	Anti – IgE: Indirect contribution via cytokines (downward effect on IL-4, IL-5, IL-13)	SC q2-4 weeks	Use in allergenic asthma with IgE Has the most safety data in children
Mepolizumab	IL-5: Eosinophil recruitment and subsequent production of TGFBeta1	SC q2 weeks	Review shows: 50% reduction in exacerbations Strong data: - nasal polyposis
Reslizumab		IV monthly	Review shows: 50% reduction in exacerbations
Benralizumab		SC q4 weeks x 3 → q8 weeks	Review shows: 50% reduction in exacerbations Strong data: - improvement in lung function Strongest data: - reduce daily oral steroids
Dupilumb	IL-4: Increased synthesis of alpha-smooth muscle actin and collagen III. And induction if TGF-Beta IL-13: Induction of TGF-beta release by airway epithelial cells	SC q2 weeks	Strongest data: - reducing exacerbations Strongest data: - improvement in lung function Strongest data: - reduce daily oral steroids Strongest data: - nasal congestion, nasal polyposis

No Eos? No IgE? … No Problem!

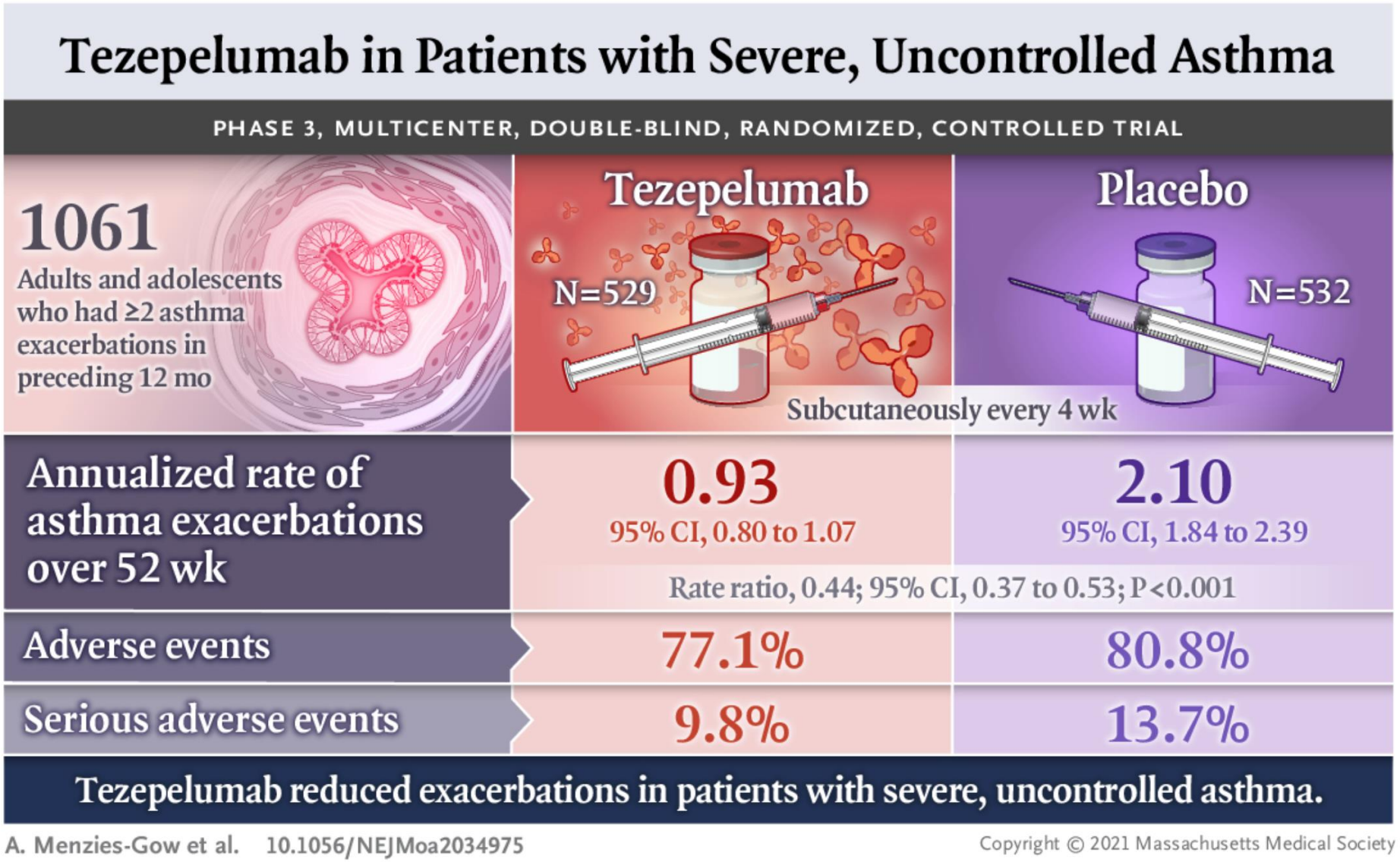
Tezepelumab

A human monoclonal antibody that blocks thymic stromal lymphopoietin, an epithelial-cell–derived cytokine implicated in the pathogenesis of asthma.

No Eos? No IgE? … No Problem!

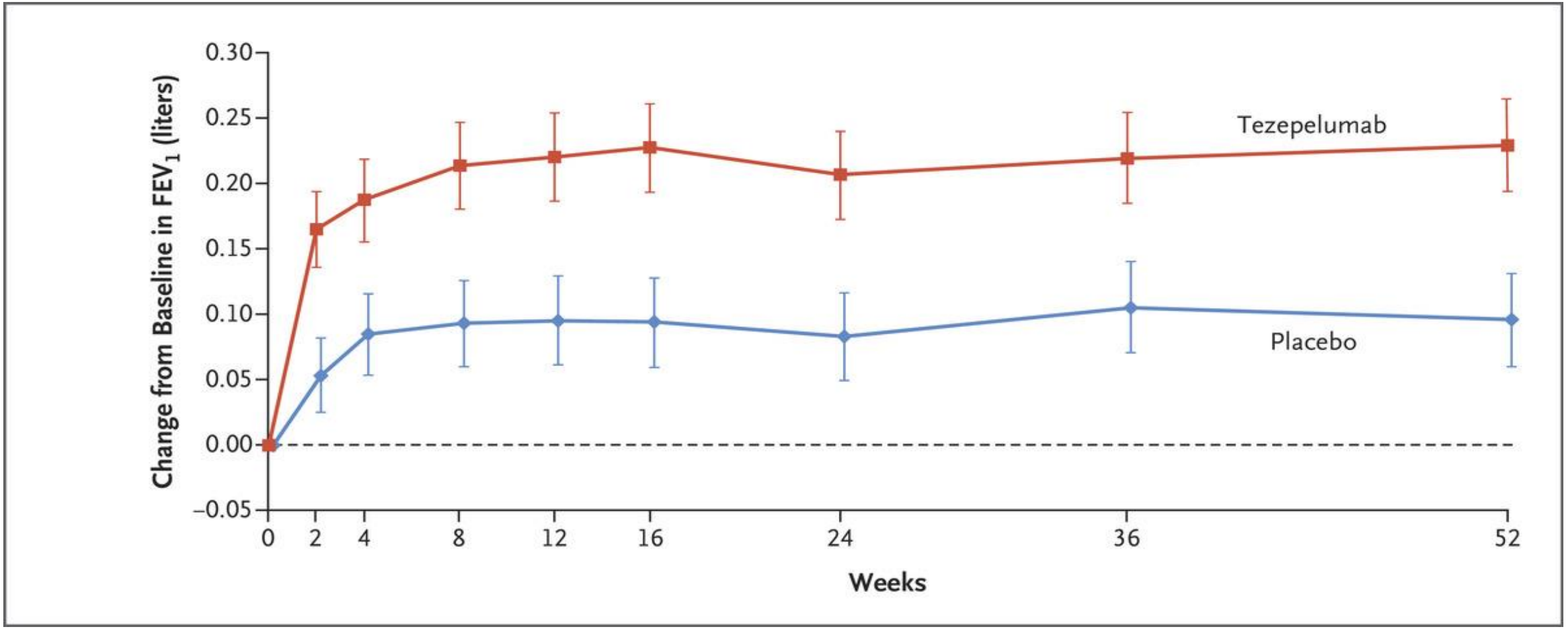


The new option: Tezepelumab

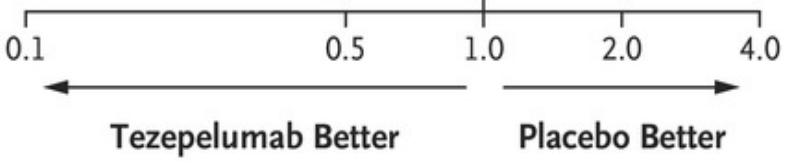


Menzies-Gow, J. et al. NEJM 2021

Change in baseline FEV1



Subgroup	Tezepelumab	Placebo	Rate Ratio (95% CI)
	no. of patients/annualized rate of asthma exacerbations		
Overall	528/0.93	531/2.10	0.44 (0.37–0.53)
Eosinophil count at baseline (cells/μl)			
<300	309/1.02	309/1.73	0.59 (0.46–0.75)
≥300	219/0.79	222/2.66	0.30 (0.22–0.40)
Eosinophil count at baseline (cells/μl)			
<150	138/1.04	138/1.70	0.61 (0.42–0.88)
150 to <300	171/1.00	171/1.75	0.57 (0.41–0.79)
300 to <450	99/0.92	95/2.22	0.41 (0.27–0.64)
≥450	120/0.68	127/3.00	0.23 (0.15–0.34)
Eosinophil count at baseline (cells/μl)			
<150	138/1.04	138/1.70	0.61 (0.42–0.88)
≥150	390/0.89	393/2.24	0.39 (0.32–0.49)
FENO at baseline (ppb)			
<25	213/1.07	220/1.57	0.68 (0.51–0.92)
≥25	309/0.82	307/2.52	0.32 (0.25–0.42)
FENO at baseline (ppb)			
<25	213/1.07	220/1.56	0.68 (0.51–0.92)
25 to <50	158/0.87	151/2.20	0.40 (0.28–0.56)
≥50	151/0.75	156/2.83	0.27 (0.19–0.38)
Allergic status at baseline			
Positive for any perennial allergens	339/0.85	341/2.03	0.42 (0.33–0.53)
Negative for all perennial allergens	184/1.09	177/2.21	0.49 (0.36–0.67)



Adverse Event	Tezepelumab 210 mg Q4W (N=528)	Placebo (N=531)
Most common adverse events*		
Nasopharyngitis	113 (21.4)	114 (21.5)
Upper respiratory tract infection	59 (11.2)	87 (16.4)
Headache	43 (8.1)	45 (8.5)
Asthma	27 (5.1)	59 (11.1)
Bronchitis	25 (4.7)	33 (6.2)
Bronchitis bacterial	24 (4.5)	17 (3.2)
Urinary tract infection	22 (4.2)	22 (4.1)
Hypertension	23 (4.4)	22 (4.1)
Back pain	21 (4.0)	
Arthralgia	20 (3.8)	13 (2.4)
Influenza-like illness	19 (3.6)	22 (4.1)
Sinusitis	19 (3.6)	40 (7.5)
Pharyngitis	17 (3.2)	15 (2.8)
Gastroenteritis	17 (3.2)	16 (3.0)
Viral upper respiratory tract infection	17 (3.2)	14 (2.6)
Rhinitis allergic	16 (3.0)	17 (3.2)
Rhinitis	14 (2.7)	17 (3.2)

*Shown are adverse events that occurred in ≥3% of patients who received tezepelumab.

Menzies-Gow, J. et al. NEJM 2021

COVID-19 and Asthma

- Are people with asthma at increased risk of COVID-19, or severe COVID-19?
  - No increased risk of acquiring COVID-19 and no increased risk of severe COVID-19 in people with well-controlled, mild-to-moderate asthma.
- Are people with asthma at increased risk of COVID-10-related death?
  - If well controlled, NO (*Williamson, Nature 2020, Liu et al JACI IP 2021*)
  - Risk of COVID-19 death increased in ppl who had recently needed oral corticosteroids (OCS) for their asthma (*Williamson, Nature 2020*) and in hospitalized patient with severe asthma (*Bloom, Lancet Respir Med 2021*).
- Are ICS protective in COVID-19?
  - In one study of hospitalized patients aged >/= 50 with COVID-19, ICS use in those with asthma was associated with lower mortality than patients without underlying respiratory conditions (Bloom, Lancet RM 2021)

COVID-19 and Asthma

- Reduced exacerbations seen world wide during the pandemic.
- Good asthma control is of utmost importance at this time

In a nutshell:

Try to find objective data for diagnosis

Avoid frequent SABA use without ICS (if using SABA up to once a day)

Start ICS/LABA sooner - SMART for Step 3 (With ICS-F not ICS-S)

Add on LAMA - Be sure to refer at this point.

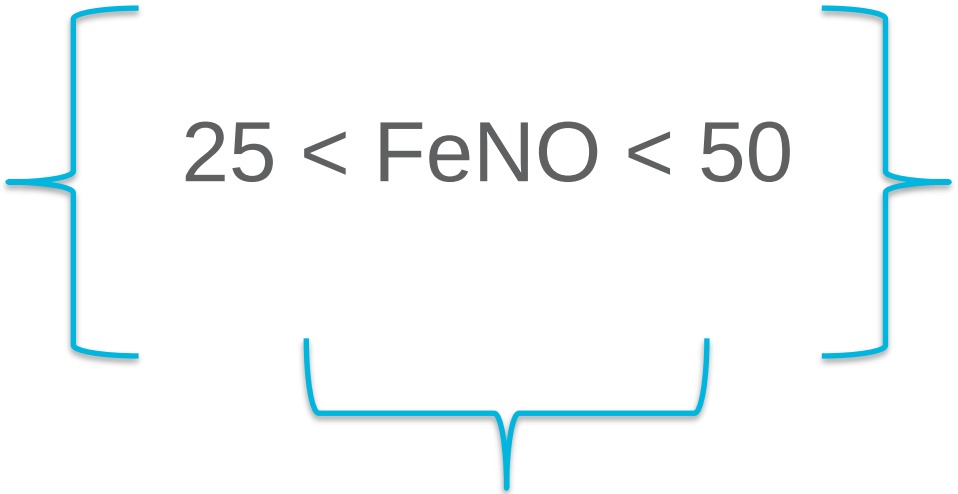
Immunotherapy and Biologics are becoming more mainstream

Importance of maintenance ICS for moderate to severe asthmatics during COVID.

Virginia Mason™

Each Person.
Every Moment.
Better Never Stops.

Role of FeNO



- ICS should not be withheld solely based on low FeNO levels.
- Ages > 5, if asthma diagnosis uncertain, used FeNO as adjunct to the evaluation process

Risk factors for asthma-related deaths

- A history of near-fatal asthma requiring intubation and mechanical ventilation[557]
- Hospitalization[557,558] or emergency care visit for asthma in the past year
- Currently using or having recently stopped using oral corticosteroids (a marker of event severity)[557]
- Not currently using inhaled corticosteroids[90,557]
- Over-use of SABAs, especially use of more than one canister of salbutamol (or equivalent) monthly[89,107,559]
- Poor adherence with ICS-containing medications and/or poor adherence with (or lack of) a written asthma action plan[100]
- A history of psychiatric disease or psychosocial problems[100]
- Food allergy in a patient with asthma[452,560]
- Several comorbidities including pneumonia, diabetes and arrhythmias were independently associated with an increased risk of death after hospitalization for an asthma exacerbation.[[558]