Asthma
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Disclosures

TEACHING
Idaho State University PA and NP Programs
ThriveAP

INDUSTRY AFFILIATIONS
Grifols Pharmaceutical - speaker, consultant
Boehringer Ingelheim Pharmaceuticals – consultant, speaker
Meda Pharmaceuticals – speaker, consultant
Circassia Pharmaceuticals – advisory panel
Genentech Pharmaceuticals - Speaker

CLINICAL RESEARCH
2017 – Sub-I, Genentech Zenyatta Severe Asthma Study
2016 – Sub-I, Biota Human Rhinovirus Study
2015 – Sub-I, Sanofi Traverse Severe Asthma Study
2015 – Sub-I, Sanofi Liberty Severe Asthma Study
2013 – Study Coordinator: MediVector Influenza Study

Brian Bizik does not intend to discuss the use of any off-label use/unapproved use of drugs or devices that he represents

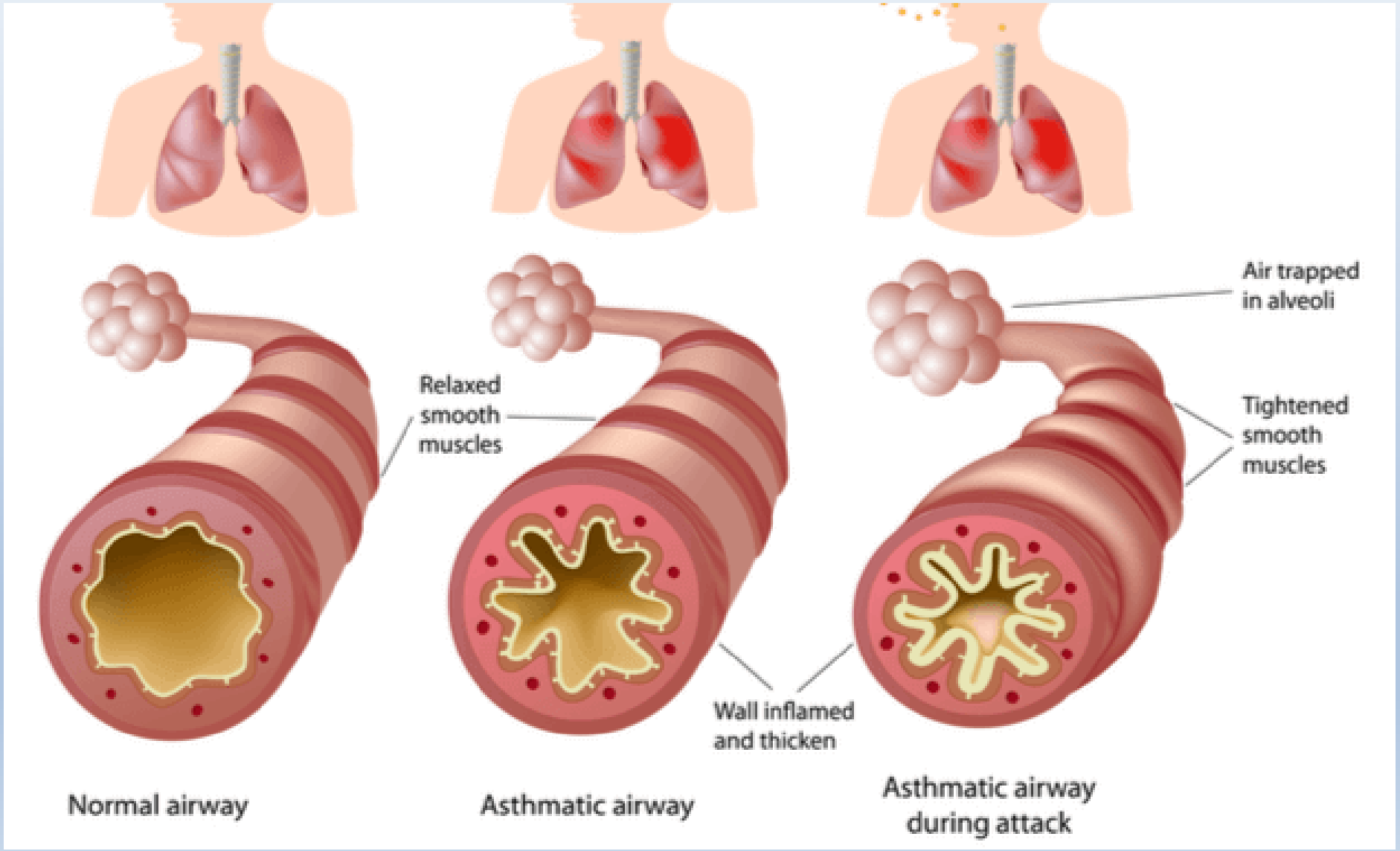
Asthma and COPD

We need to build the big picture first, before anything else. I need these two very different (but sometimes overlapping) diseases to be clear.

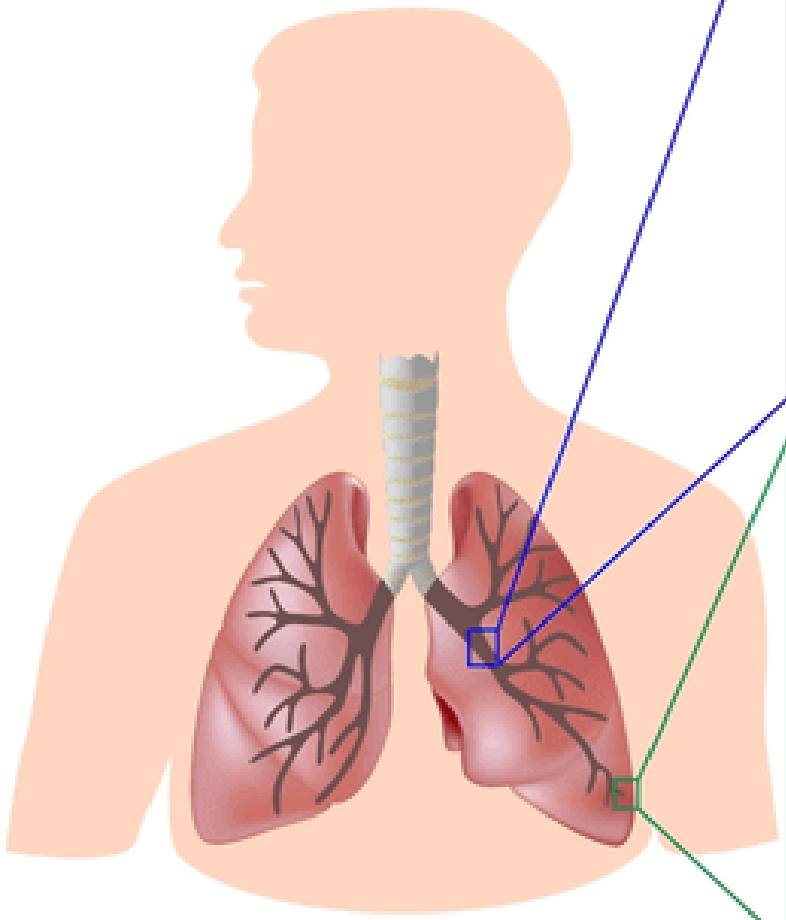
Asthma – bronchoconstriction, airway inflammation, mucous production

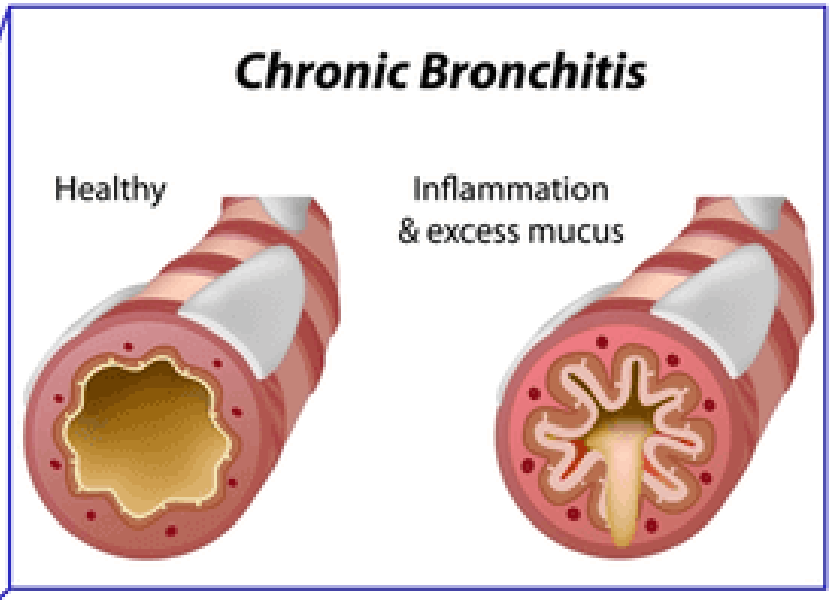
COPD – Tissue destruction, chronic cough, due to exposure

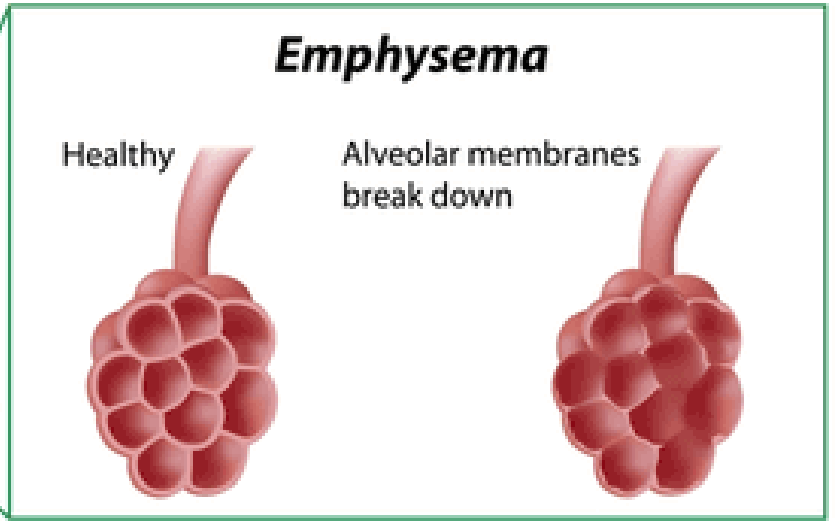
Asthma – Three key features: bronchoconstriction, airway inflammation and mucous production.



COPD – Think of the name. . Any thing chronic, that is obstructive, in the lungs and is terrible







Asthma

OK Big picture - - -

Asthma – the big three

COPD – exposure, tissue destruction

OK – lets focus on asthma now

Asthma

Guidelines

2007 - last time we had anything new in the US till . . . .last year.

GINA – the rest of the world has GINA, the Global Initiative for Asthma, updated every year

Burden of asthma

- Asthma is one of the most common chronic diseases worldwide with an estimated 300 million affected individuals
- Prevalence is increasing in many countries, especially in children
- Asthma is a major cause of school and work absence

- **Every day in America:**
- 40,000 people miss school or work due to asthma.
- 30,000 people have an asthma attack.
- 5,000 people visit the emergency room due to asthma.
- 1,000 people are admitted to the hospital due to asthma.
- 11 people die from asthma

Definition of asthma

Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation, bronchoconstriction and increased mucous production.

It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation.

What are asthma phenotypes and are they important?

Phenotype to Endotype

- Phenotype – the observable properties of an organism that are produced by the interaction of the genotype and the environment.

- Endotype - An "*endotype*" is proposed to be a subtype of a condition *defined* by a distinct pathophysiological mechanism. Criteria for *defining* asthma *endotypes* on the basis of their phenotypes and putative pathophysiology are suggested.

We have now moved to defining phenotypes of this heterogeneous disease

- Clinical:
- Fixed obstruction
- Obese
- Adult onset
- Exacerbation prone
- Treatment resistant

Pathologic:
Eosinophilic
Non-eosinophilic
Pauci-granulocytic

- Triggers
- Occupational
- Aspirin
- Exercise
- Menses

Phenotype suggests a clustering of characteristics, but may not describe underlying pathobiology that create these characteristics

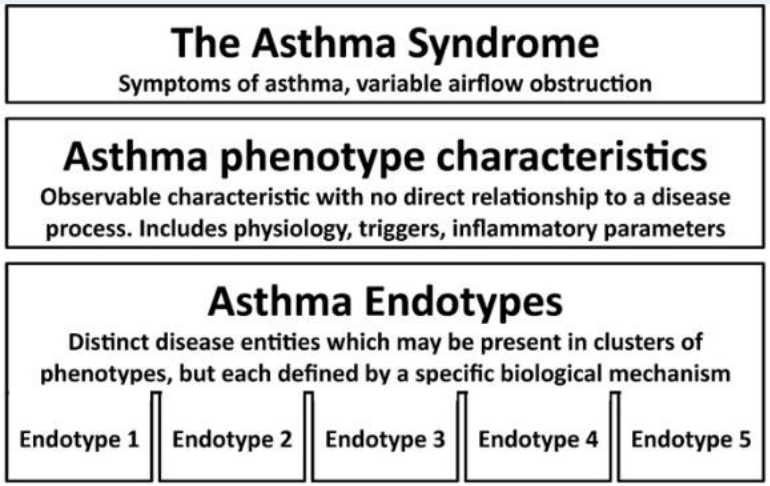
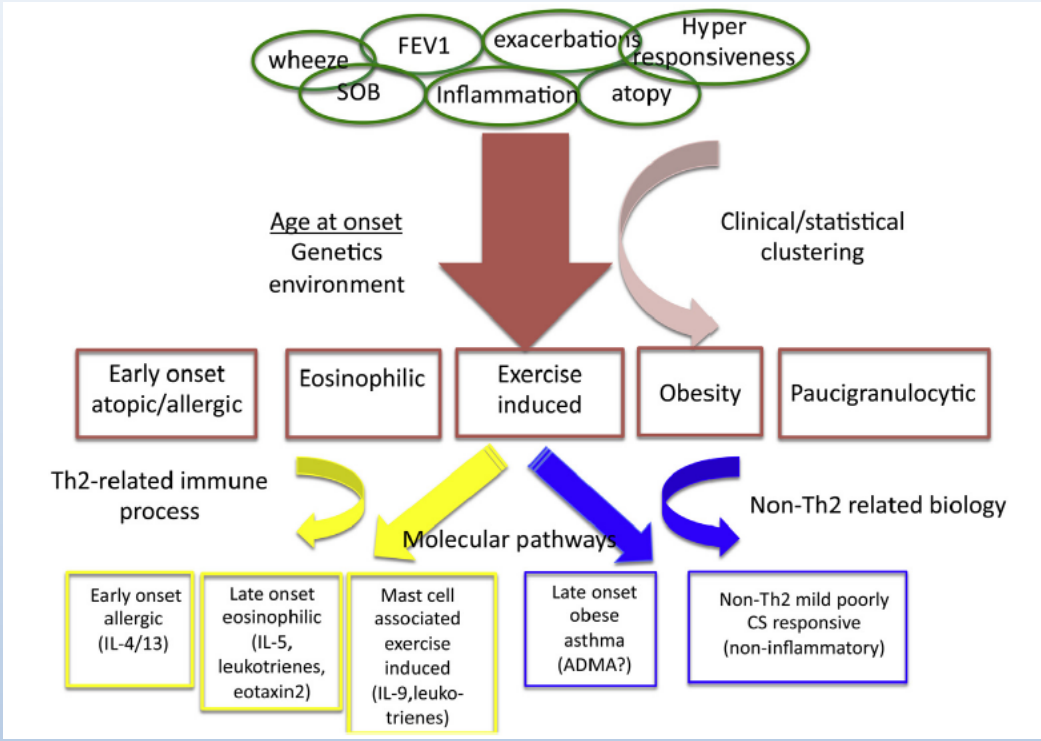


FIG 1. Asthma is made up of different endotypes, each characterized by its pathophysiology.

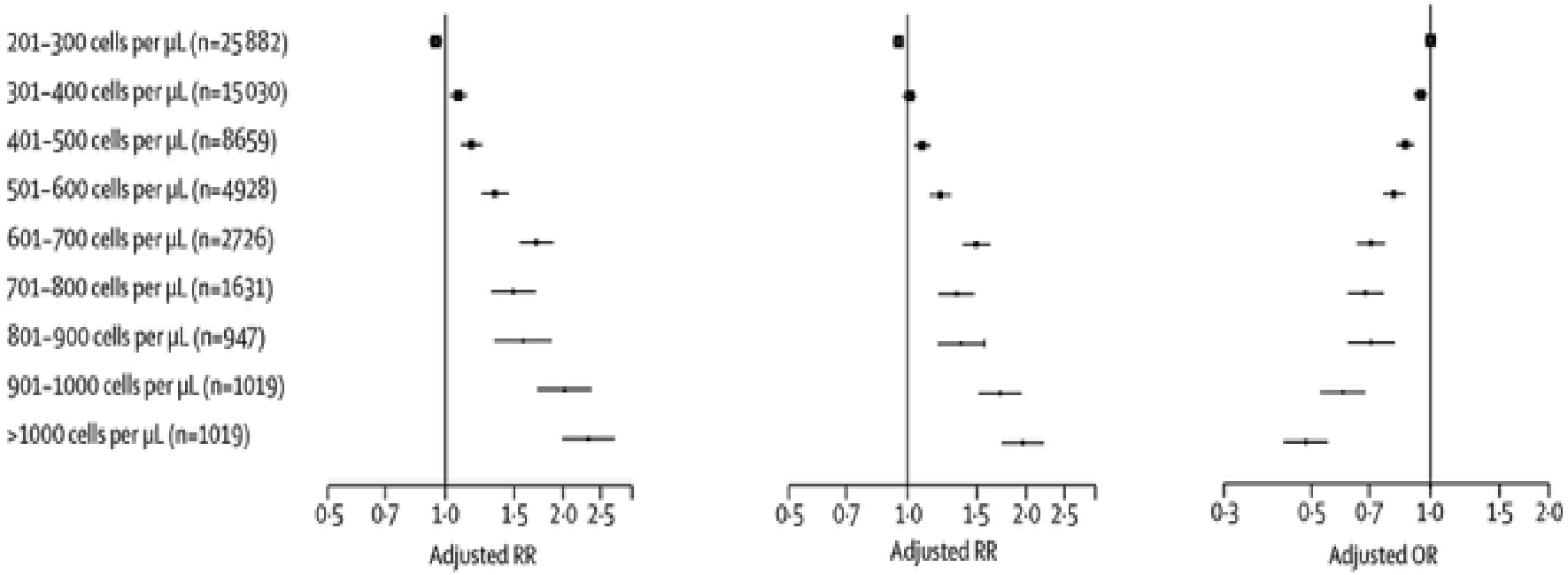


Endotype: underlying biologic or pathobiologic mechanism

Lotvall et al. JACI 2011;127:355-60

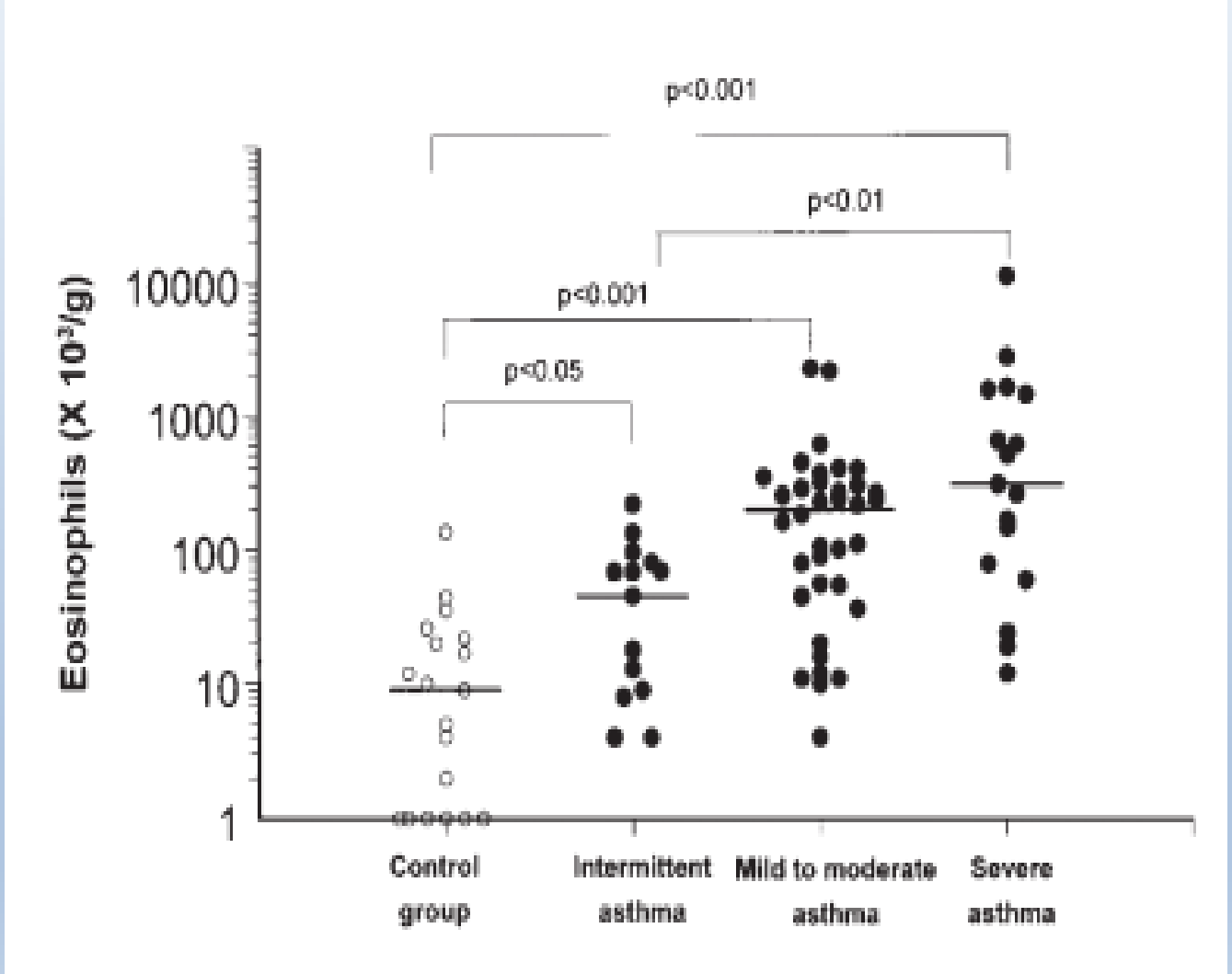
Relationship Between Blood Eosinophil Counts and Asthma Exacerbations

Claims database analysis examining eosinophil counts and exacerbations requiring systemic CS or ER/hospital care (N=61,841)



Price DB, et al. *Lancet Respir Med*. 2015

Sputum Eosinophils are Associated with Asthma Severity



Louis et al, *Am J Respir Crit Care Med*, 2000

Emphasis Shifting from Empiric to Targeted (Precision) Therapy

One size fits all → **Stratified medicine** → **Precision medicine**

- **Evidence-based**
- **One treatment for all**

- **Evidence-based**
- **Different treatments for groups of patients**

- **Evidence-based**
- **Individualized treatment for each patient**

Willis JC, Lord GM. *Nat Rev Immunol*. 2015.

Pause to Reflect

Asthma has different types – for most of you:

1. **The allergic type – needs steroids and montelukast, antihistamines and control nasal symptoms.**

2. **The non-allergic type – steroids probably, but how helpful? Screen for COPD, exercise, vaccines, don’t fear nebulizers, GERD, wt loss.**

Pause to Reflect

Going to go to guidelines soon but lets review the meds, in a new and helpful way!

Asthma Terms/Actions/Inhaler Types

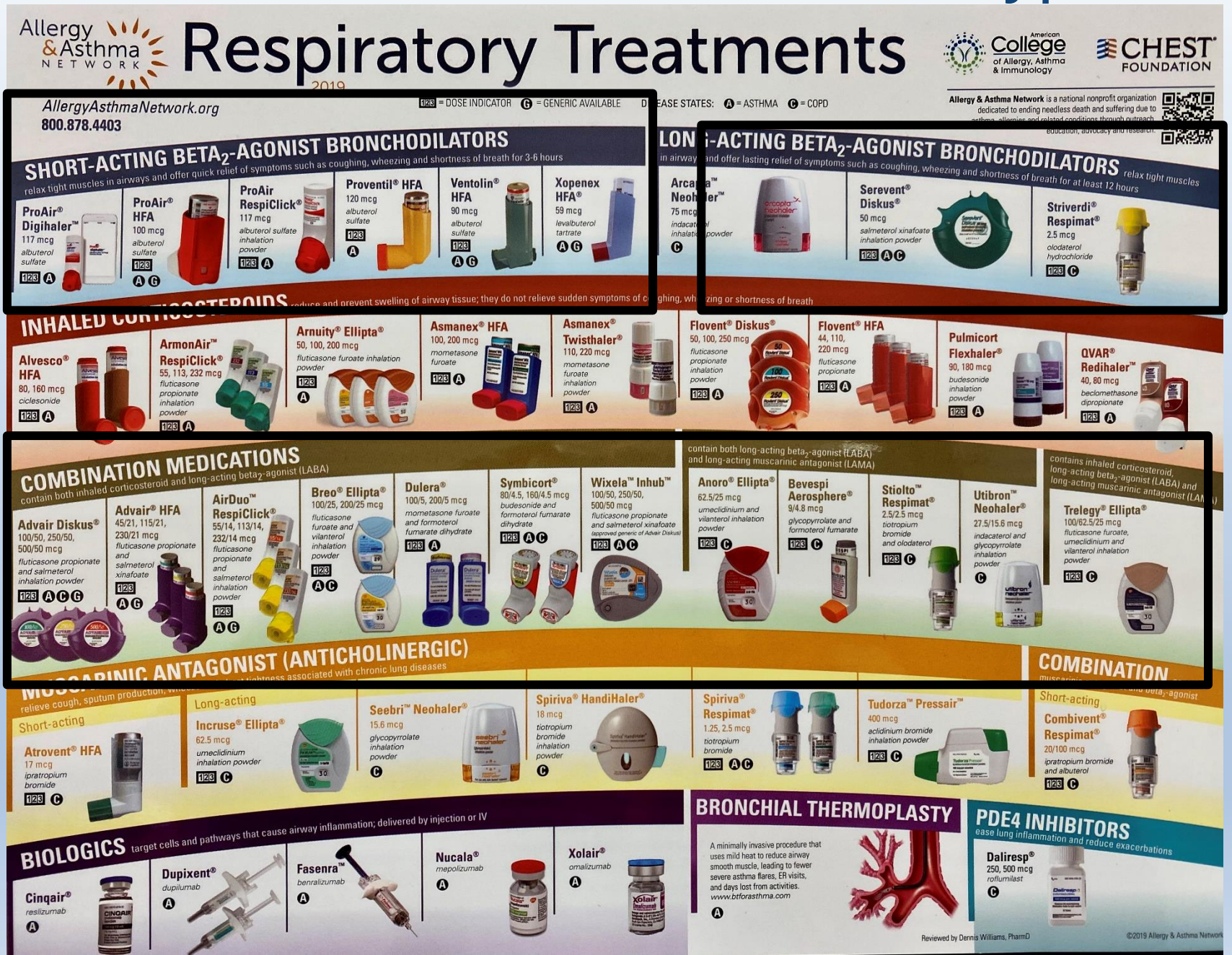
- SABA = Short Acting Beta-Agonist = Albuterol = rescue inhaler = puffer, Proair, Ventolin, Proventil
- LABA = Long Acting Beta-Agonist, Serevent, Salmeterol
- ICS = Inhaled Corticosteroid, Flovent, fluticasone, QVAR, Pulmicort
- LAMA = Long Acting Muscarinic Antagonist, Spiriva, tiotropium
- MDI = Metered Dose Inhaler
- DPI = Dry Powdered Inhaler – Advair, Breo, Trelegy

Asthma Terms/Actions/Inhaler Types

Albuterol – short acting bronchodilator, relaxes smooth muscle. Binds to beta receptors on smooth muscle, causing about a billion things to happen that drop the calcium in the cell and it relaxes.

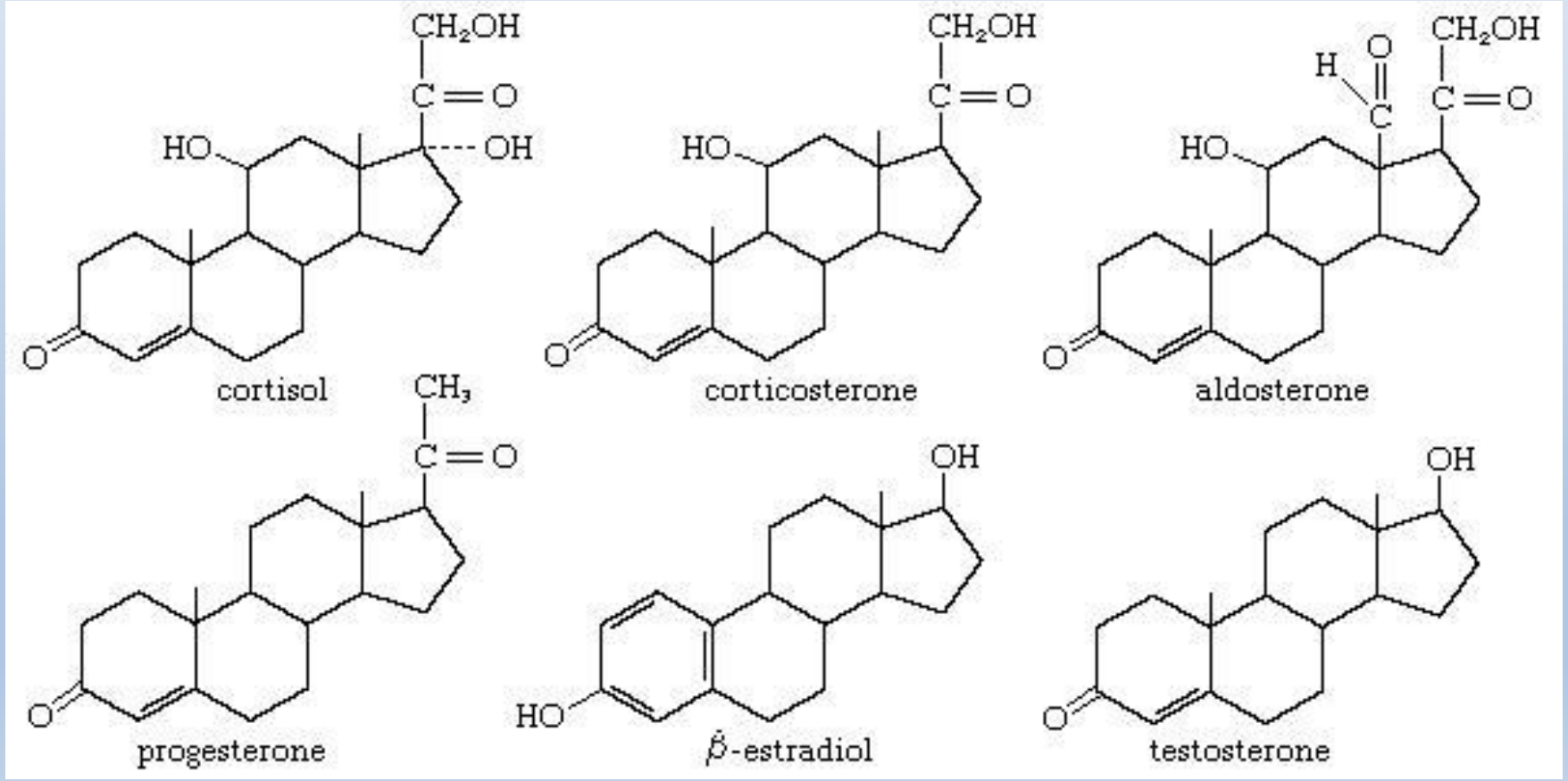
Salmeterol/formoterol/vilanterol – Same thing as above but lasts 12 or 24 hours

Asthma Terms/Actions/Inhaler Types



Asthma Terms/Actions/Inhaler Types

The term “steroid” refers to the structure of the compound, not to the function.



Asthma Terms/Actions/Inhaler Types

Prednisone et al.

Prednisone –

(1S,2R,10S,11S,14R,15S)-14-hydroxy-14-(2-hydroxyacetyl)-2,15-dimethyltetracyclo[8.7.0.0^{2},^{7}.0^{11},^{15}]heptadeca-3,6-diene-5,17-dione

Asthma Terms/Actions/Inhaler Types

Prednisone

Prednisone is metabolized by the liver to prednisolone. A glucocorticoid agonist corticosteroid

One of the first effects is to decreased the leukocyte migration to sites of Inflammation.

Corticosteroids then bind to the glucocorticoid receptor mediates changes in gene expression that lead to multiple downstream effects over hours to days.

Asthma Terms/Actions/Inhaler Types

Prednisone

Glucocorticoids inhibit neutrophil apoptosis and demargination; they inhibit phospholipase A2, which decreases the formation of arachidonic acid derivatives; they inhibit NF-Kappa B and other inflammatory transcription factors; they promote anti-inflammatory genes like interleukin.

Lower doses of corticosteroids provide an anti-inflammatory effect, while higher doses are immunosuppressive.

Asthma Terms/Actions/Inhaler Types

Prednisone

Aaaaarrrghhhh! Stop – too many words on one slide!

The point, it shuts down most of the things that drive inflammation.

So, think this with me. . What if there is a severe:

ATOPIC inflammation – good stuff!

BACTERIAL inflammation – with abx – good stuff

BACTERIAL inflammation – without abx – hmmm?

VIRAL inflammation – hmmm?

Asthma Terms/Actions/Inhaler Types

Prednisone

Taper?

As you know you DON'T have to taper.

In fact, you should not be putting patients on a dose of steroid that requires a taper.

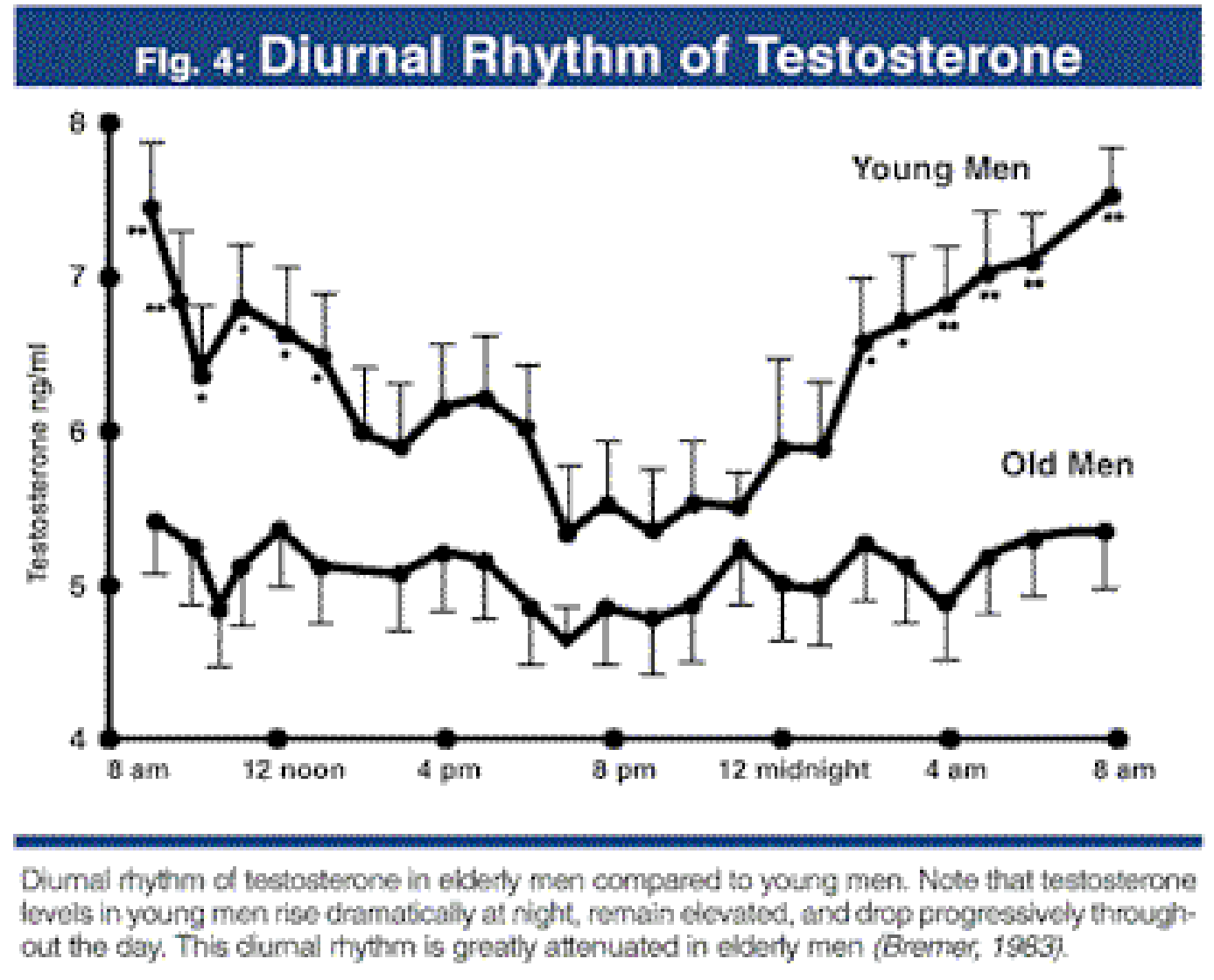
Tapering is NOT because you have to, it's because you can! You can give them less. . .takes half the dose to keep you well as it did to get you well.

This is where the PATIENT controlled taper is nice:

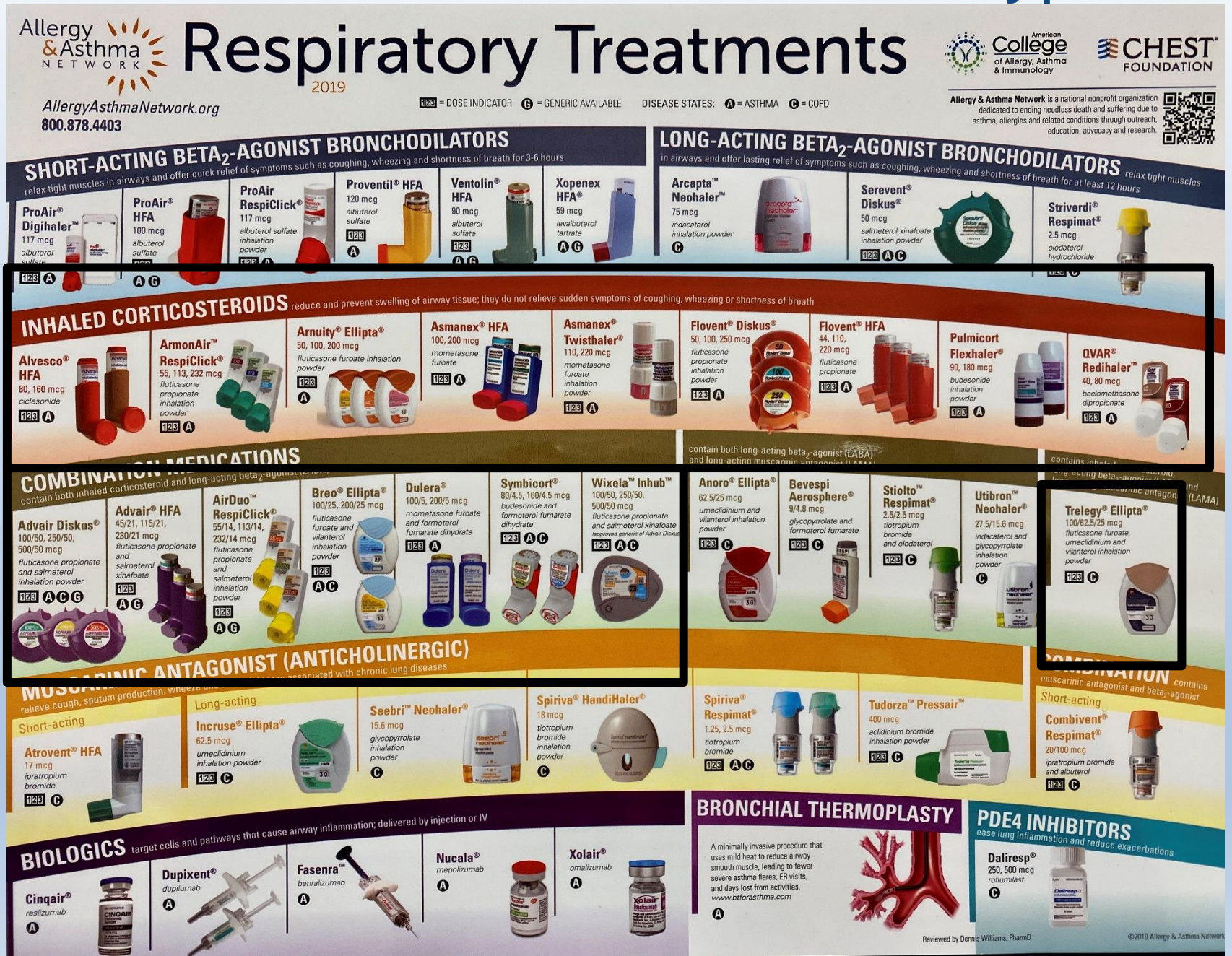
Take 40 mg till you are 50% better
Take 20 mg till you are back to baseline. . . .

Asthma Terms/Actions/Inhaler Types

Prednisone – diurnal variation



Asthma Terms/Actions/Inhaler Types



Asthma Terms/Actions/Inhaler Types

Ipratropium bromide (and other short and long-acting muscarinic antagonists) are often listed as bronchodilators?

Are they? The exert minimal effect on smooth muscle, so are they?

Asthma Terms/Actions/Inhaler Types

Let's look at SAMAs and LAMAs

Ipratropium bromide

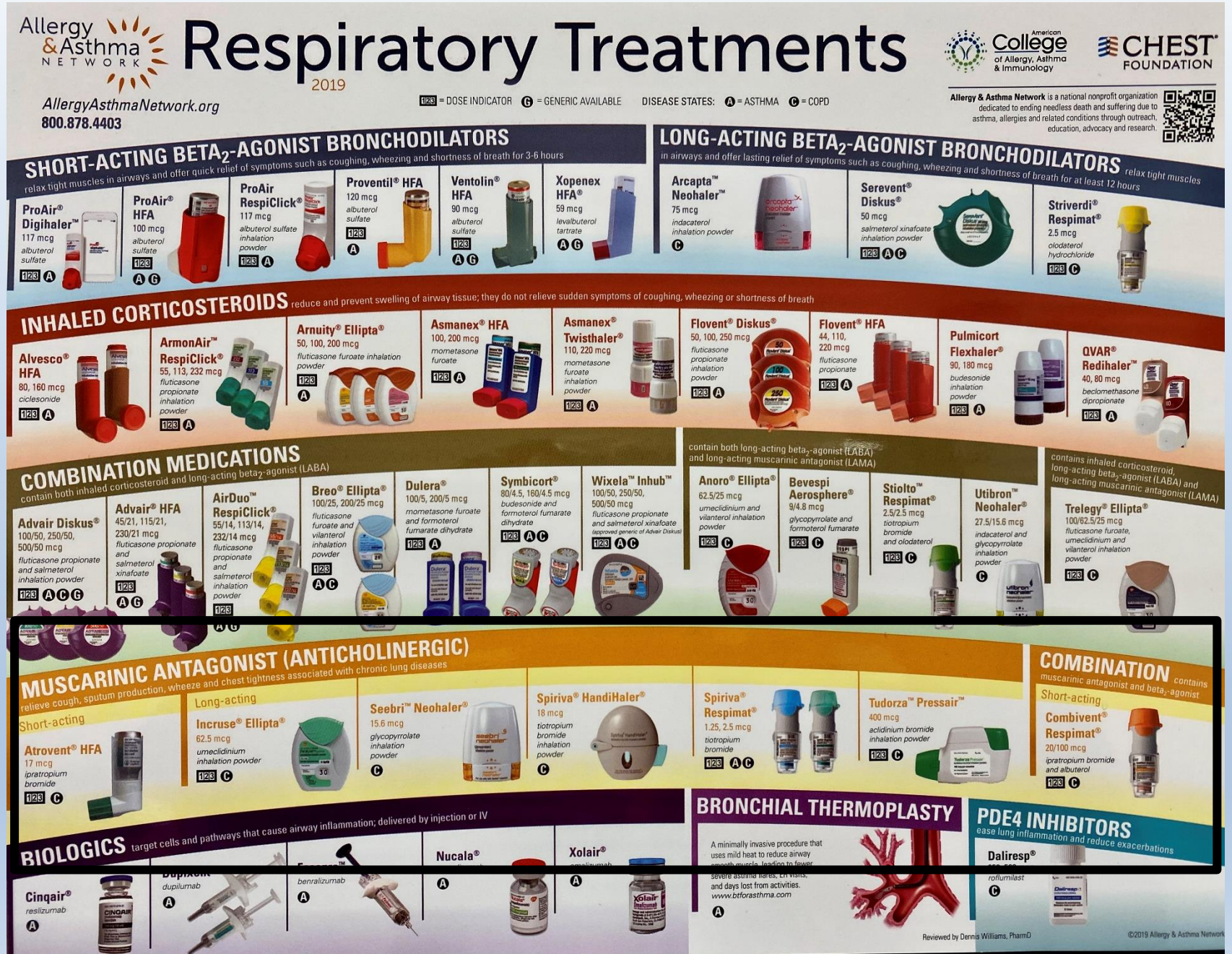
1. Made from the combination of Isopropyl alcohol and atropine. The name comes from these two words. Isopropyl alcohol and atropine
2. Works by INCREASING the degradation of cGMP and by DECREASING Ca2+ in the cells, these all BLOCK contraction. They don't dilate anything really.
3. Onset of action . . . 20 minutes or so. Ipratropium half life is 2 hours.
4. SAMAs and LABAs also effect one big nerve. . . .

Asthma Terms/Actions/Inhaler Types
Let's look at SAMAs and LAMAs

Ipratropium bromide

1. Vagal tone – both LAMAs and SAMAs decrease vagal tone (lungs only). This is why they can be helpful in patients with minimal constriction but have dyspnea.
2. So these are very different than SABAs and LABAs, and when combined work very well.
3. For patients over the age of 2 years and older nebulized therapy should use both (if they need a SVN, they need both)
4. Oh yea, the diffusion of inhaled ipratropium bromide (both nose and lungs) does NOT diffuse into the blood in any significant amount. Yep ☺

Asthma Terms/Actions/Inhaler Types



So those are the players in this very crowded game!

Now we shift gears and move onto GUIDELINES

Since the new US GUIDELINES came out a few months ago we can now say that the world (GINA) and the US (EPR4) GUIDELINES are on the same page about a good deal of things – but still differ a bit.

The FDA – not yet. Maybe not for years. . . .

So what are the main changes in the past few years?

Key changes – *Albuterol use*

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 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”*, so they often don’t see the need for additional treatment

Key changes – *Albuterol use*

- 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)*
  - The MOST consistent factor in asthma death is, over use of albuterol. Don't just "fill the puffer".

Key changes

- 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 symptom-driven or regular low dose ICS-containing controller treatment, to reduce the risk of serious exacerbations
  - This is a population-level risk reduction strategy, e.g. statins, anti-hypertensives

Updates US Guidelines -

- **Effectiveness and safety of bronchial thermoplasty in asthma management**
- **Effectiveness of indoor allergen reduction in asthma management**
- **The role of immunotherapy and asthma management**
  - **Covers both subcutaneous and sublingual immunotherapy**
- **Fraction of exhaled nitric oxide clinical utility in asthma management**

Mensah et al. JACI 2018; 142:744-748

Updates US Guidelines -

Both guidelines note that “formoterol” has a much faster onset of action. This has lead to “PRN” use of inhalers with this LABA

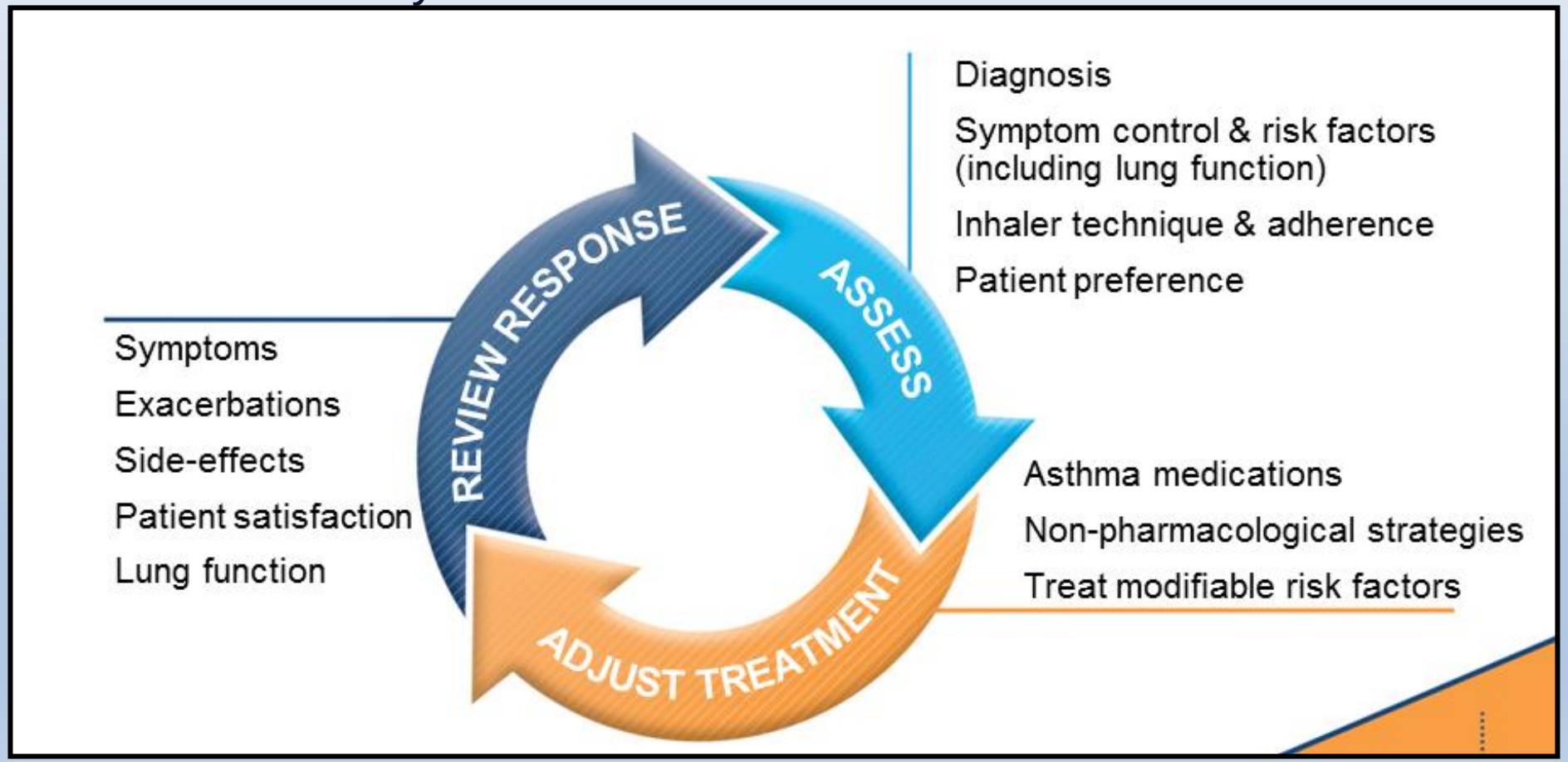
Mensah et al. JACI 2018; 142:744-748

So we now use the GINA and the US Guidelines, both are similar

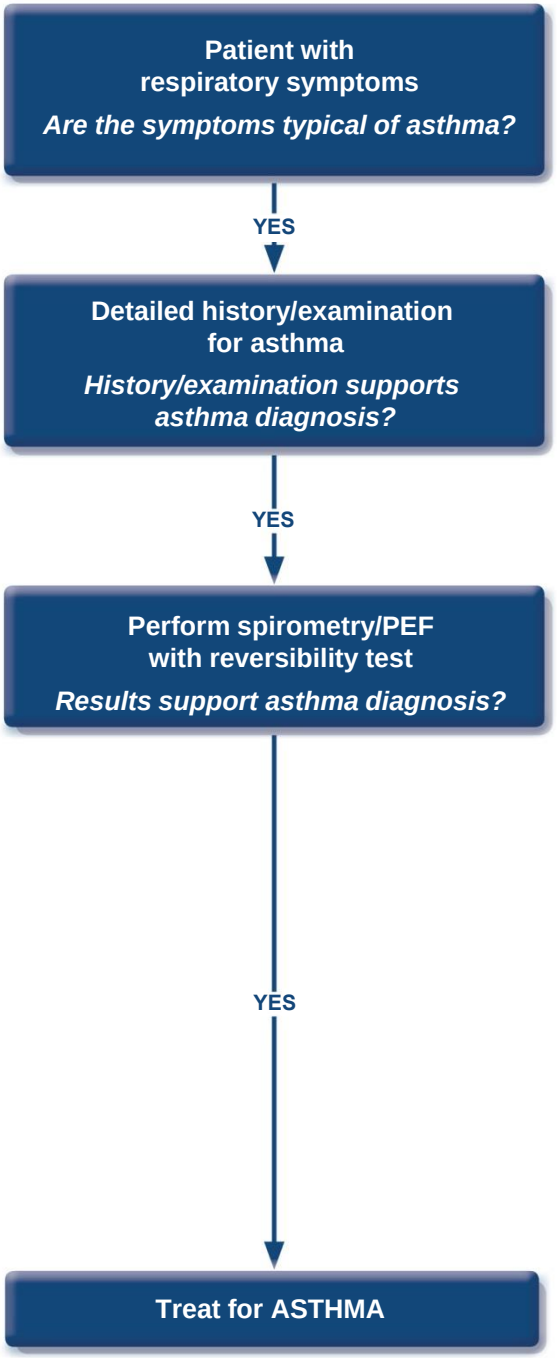
- Using GINA Guidelines – they are the best
- https://www.nhlbi.nih.gov/health-topics/asthma-management-guidelines-2020-updates
- https://ginasthma.org/

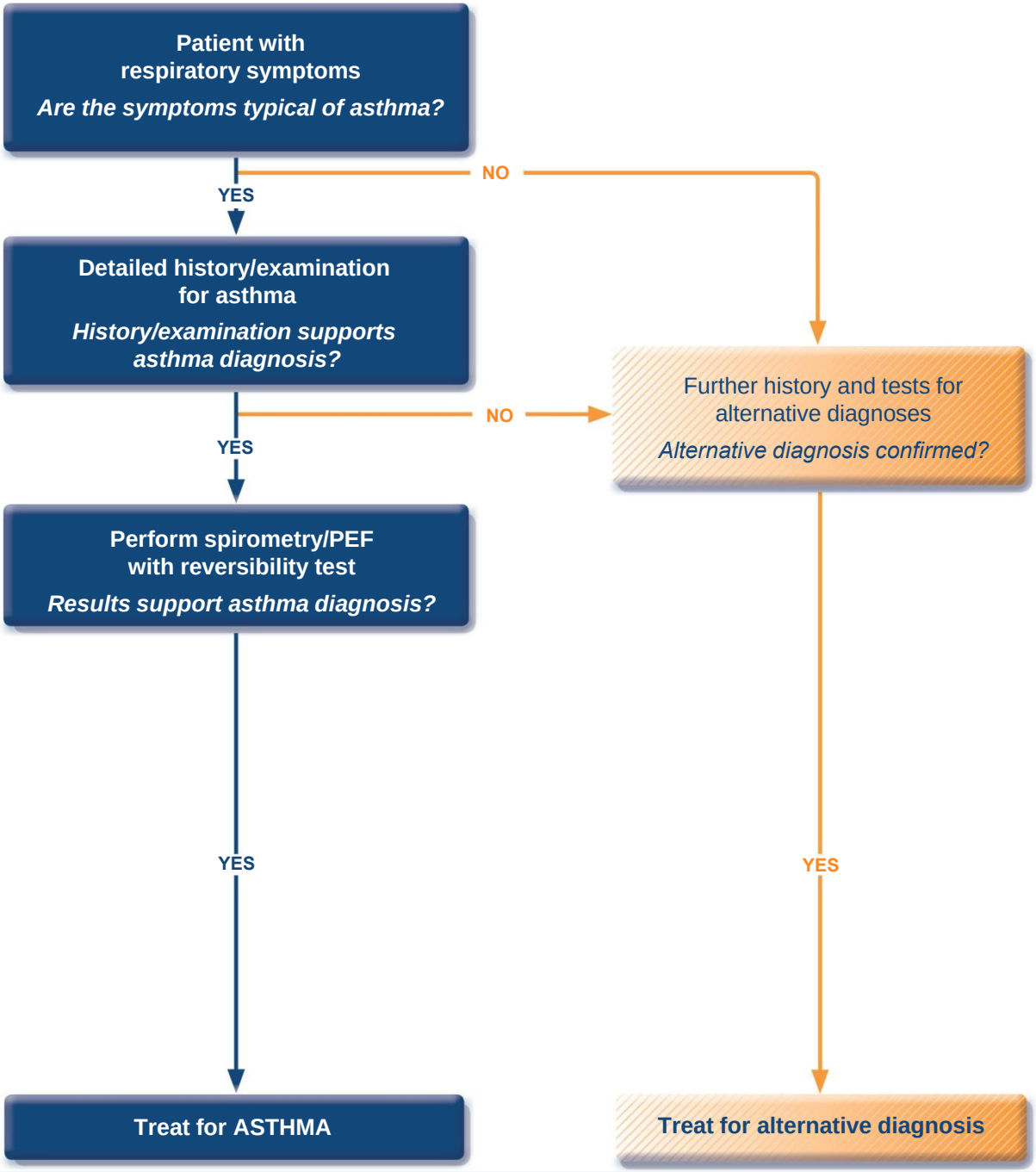
The cycle of asthma

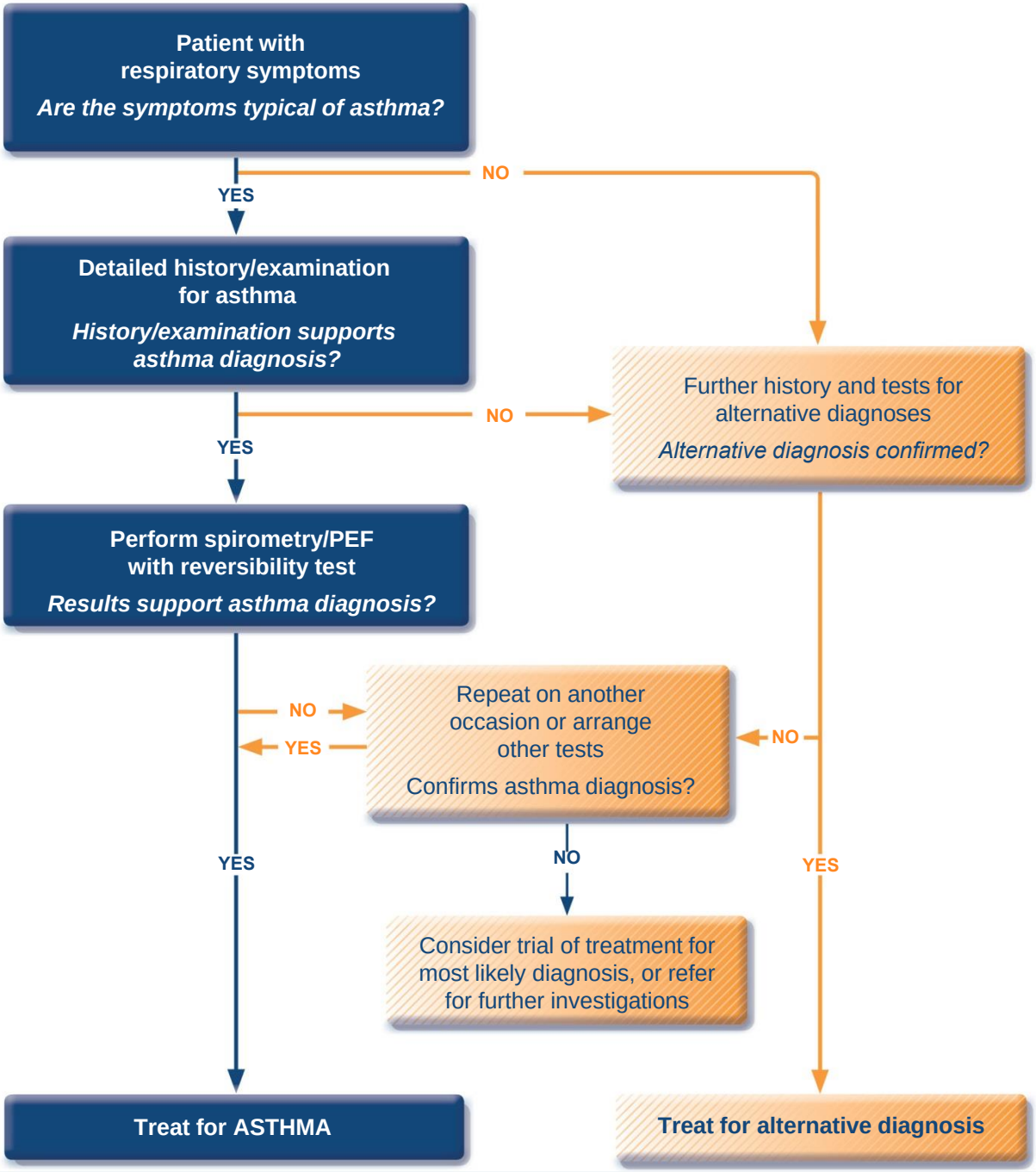
- This is the cycle of asthma. . . .

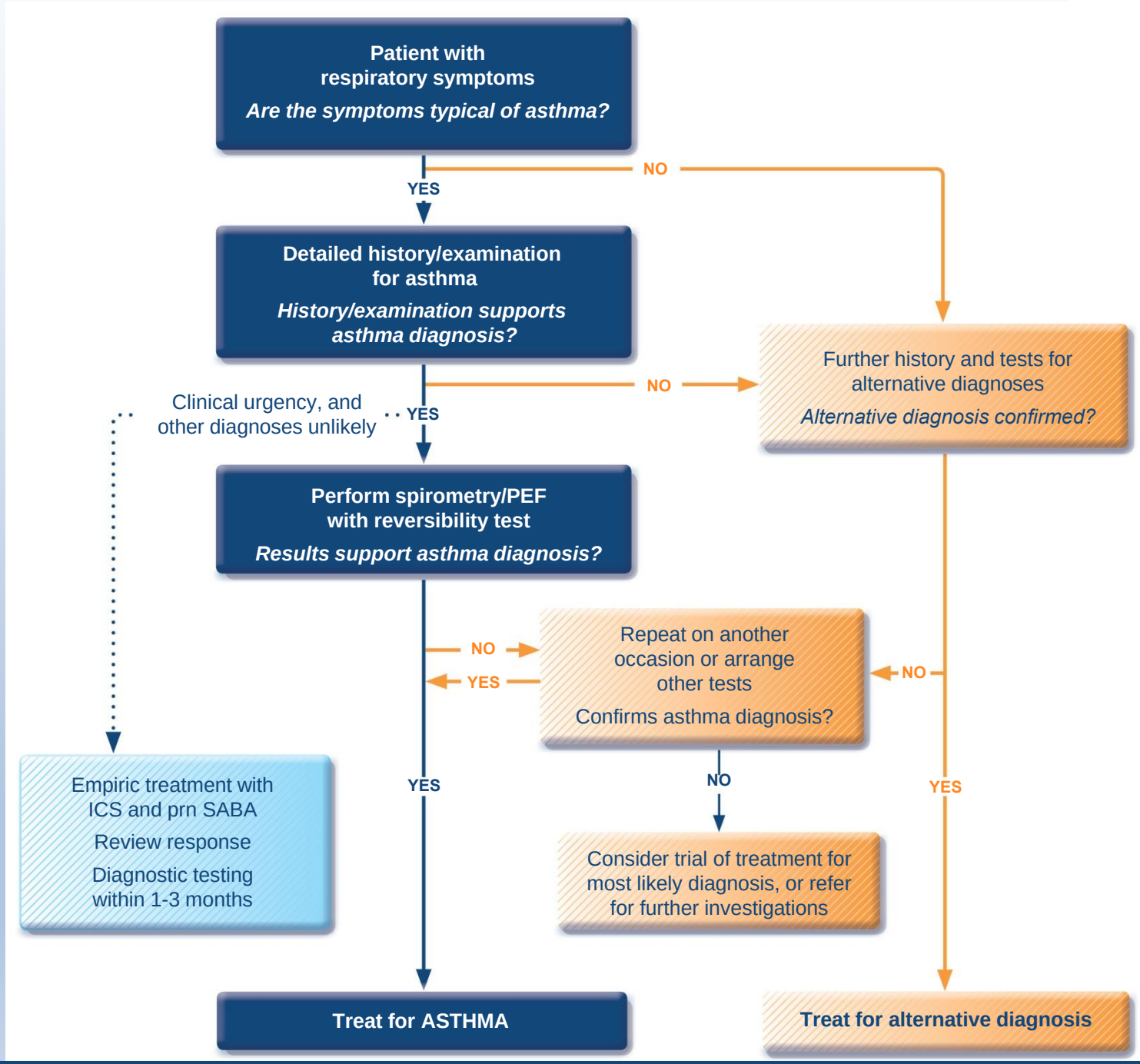


Diagnosis of asthma (be brave!)





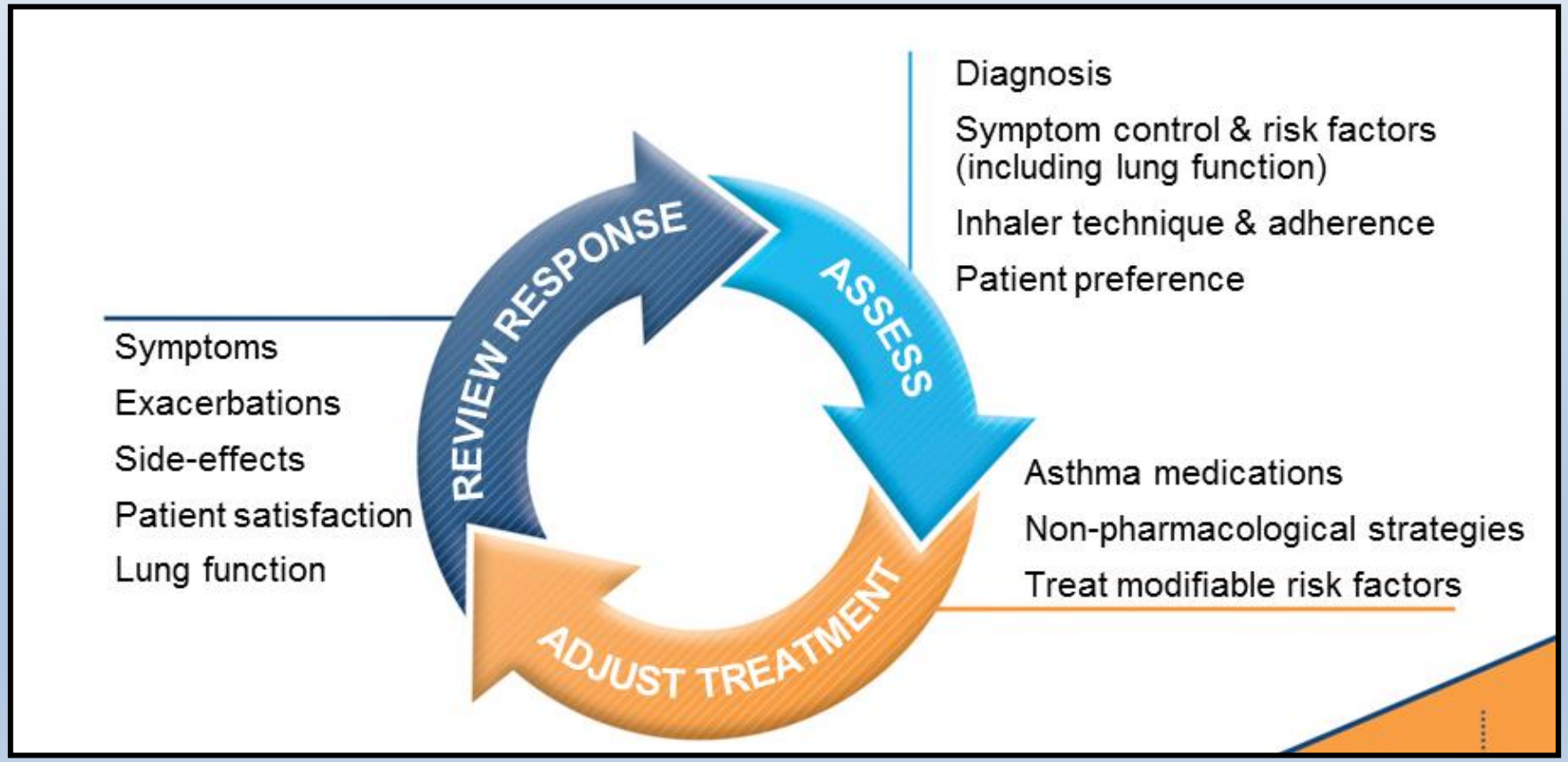




Diagnosis of asthma – variable airflow limitation

- Confirm presence of airflow limitation
  - Document that FEV_1/FVC is reduced (at least once, when FEV_1 is low)
  - FEV_1/ FVC ratio is normally >0.75 – 0.80 in healthy adults, and >0.90 in children
- Confirm variation in lung function is greater than in healthy individuals
  - The greater the variation, or the more times variation is seen, the greater probability that the diagnosis is asthma
  - **Excessive bronchodilator reversibility (adults: increase in FEV_1 >12% and >200mL; children: increase >12% predicted)**
  - Excessive diurnal variability from 1-2 weeks' twice-daily PEF monitoring (daily amplitude x 100/daily mean, averaged)
  - **Significant increase in FEV_1 or PEF after 4 weeks of controller treatment**
  - If initial testing is negative:
    - Repeat when patient is symptomatic, or after withholding bronchodilators
    - Refer for additional tests (especially children ≤5 years, or the elderly)

Assessment of asthma



Keep it simple!

Determine if they are in control or not. . . .

Asthma Control:

- When asthma is well-controlled, patients can
  - ✓ Avoid troublesome symptoms during the day and night
  - ✓ Need little or no reliever medication
  - ✓ Have productive, physically active lives
  - ✓ Have normal or near-normal lung function
  - ✓ Avoid serious asthma flare-ups (also called exacerbations, or severe attacks)
  - ✓ REMEMBER THE RULE OF 2s

Assessment of asthma

1. Asthma control
   - Assess symptom control over the last 4 weeks
   - Assess risk factors for poor outcomes, including low lung function
2. Treatment issues
   - Check inhaler technique and adherence
   - Ask about side-effects
   - Does the patient have a written asthma action plan?
   - What are the patient's attitudes and goals for their asthma?
3. Comorbidities
   - Think of rhinosinusitis, GERD, obesity, obstructive sleep apnea, depression, anxiety
   - These may contribute to symptoms and poor quality of life

Asthma Control Test (ACT)

Q1 During the **past 4 weeks,** how often did your asthma prevent you from getting as much done at work, school or home?

Score:

All of the time	Most of the time	Some of the time	A little of the time	None of the time
1	2	3	4	5

Q2 During the **past 4 weeks,** how often have you had shortness of breath?

Score:

More than once a day	Once a day	3-6 times a week	1-2 times a week	Not at all
1	2	3	4	5

Q3 During the **past 4 weeks,** how often did your asthma symptoms (wheezing, coughing, chest tightness, shortness of breath) wake you up at night or earlier than usual in the morning?

Score:

4 or more times a week	2-3 nights a week	Once a week	Once or twice	Not at all
1	2	3	4	5

Q4 During the **past 4 weeks,** how often have you used your reliever inhaler (usually blue)?

Score:

3 or more times a day	1-2 times a day	2-3 times a week	Once a week or less	Not at all
1	2	3	4	5

Q5 How would you rate your **asthma control** during the **past 4 weeks?**

Score:

Not controlled	Poorly controlled	Somewhat controlled	Well controlled	Completely controlled
1	2	3	4	5

Total Score

What does your score mean?

Score: 25 – WELL DONE

- Your asthma appears to have been UNDER CONTROL over the last 4 weeks.
- However, if you are experiencing any problems with your asthma, you should see your doctor or nurse.

Score: 20 to 24 – ON TARGET

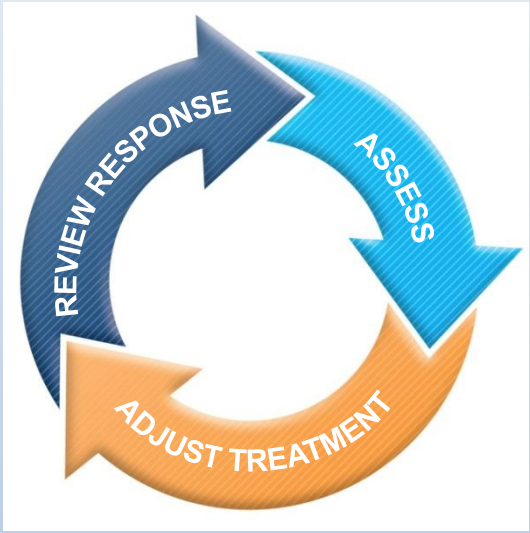
- Your asthma appears to have been REASONABLY WELL CONTROLLED during the past 4 weeks.
- However, if you are experiencing symptoms your doctor or nurse may be able to help you.

Score: less than 20 – OFF TARGET

- Your asthma may NOT HAVE BEEN CONTROLLED during the past 4 weeks.
- Your doctor or nurse can recommend an asthma action plan to help improve your asthma control.

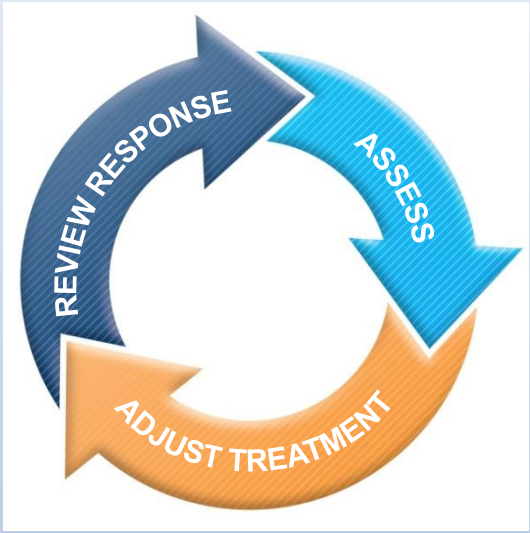
Treating to control symptoms and minimize risk

- Establish a patient-partnership
- Manage asthma in a continuous cycle:
  - **Assess**
  - **Adjust** treatment (pharmacological and non-pharmacological)
  - **Review** the response
- Teach and reinforce essential skills
  - Inhaler skills
  - Adherence
  - Guided self-management education
    - Written asthma action plan
    - Self-monitoring
    - Regular medical review



Treating to control symptoms and minimize risk

- BUT! Treatment with a controller is more than just reducing symptoms – remember its about reducing exacerbations and reducing risk



Referred to as steps or stages but they are the same

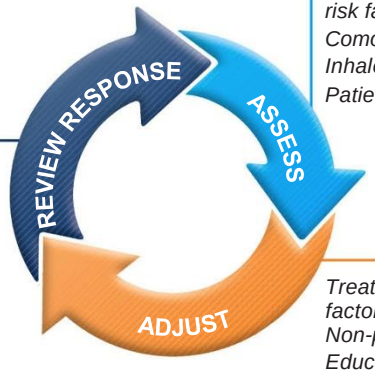
- Stage 1 = Mild Intermittent
- Stage 2 = Mild Persistent
- Stage 3 = Moderate Persistent
- Stage 4/5 = Severe Persistent

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 goals



Symptoms
Exacerbations
Side-effects
Lung function
Patient satisfaction

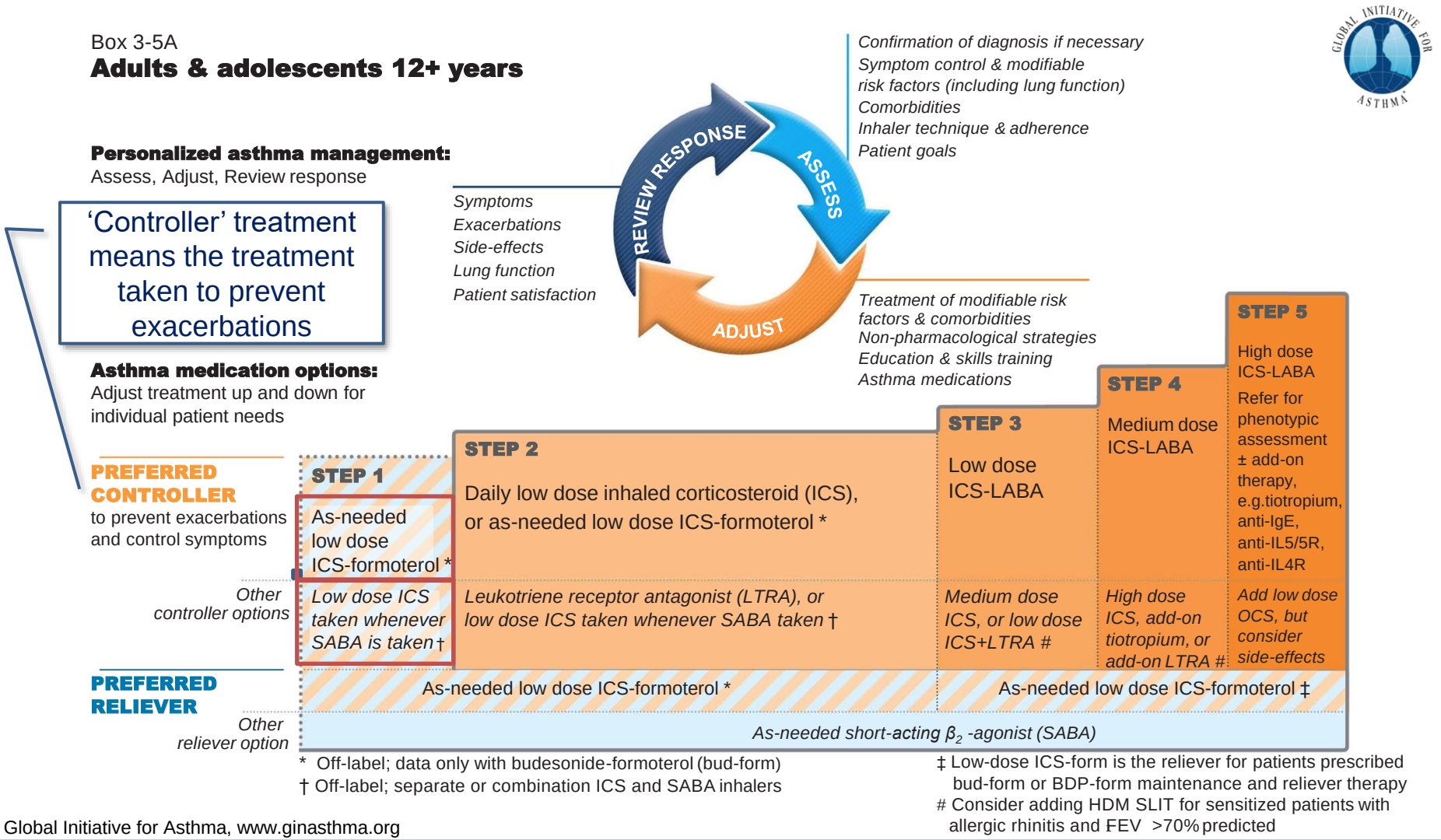
Treatment of modifiable risk factors & comorbidities
Non-pharmacological strategies
Education & skills training
Asthma medications

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 †*	*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 ‡		
Other reliever option	*As-needed short-acting β_2 -agonist (SABA)*				

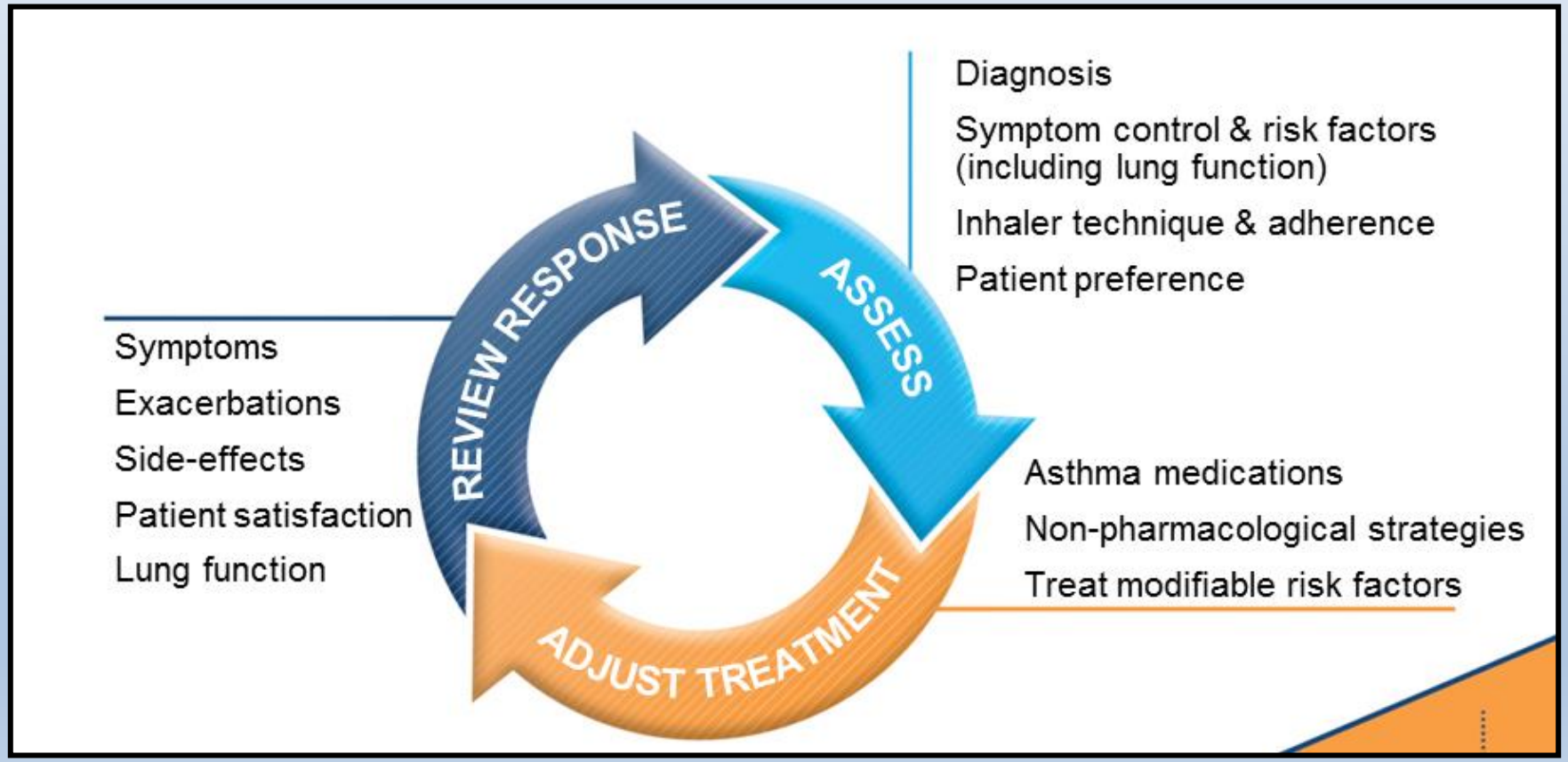
* Off-label; data only with budesonide-formoterol (bud-form)
† Off-label; separate or combination ICS and SABA inhalers
‡ Low-dose ICS-form is the reliever for patients prescribed bud-form or BDP-form maintenance and reliever therapy
# Consider adding HDM SLIT for sensitized patients with allergic rhinitis and FEV >70% predicted

For your test and boards, Step 1 is SABA only



* Off-label; data only with budesonide-formoterol (bud-form)
† Off-label; separate or combination ICS and SABA inhalers
‡ Low-dose ICS-form is the reliever for patients prescribed bud-form or BDP-form maintenance and reliever therapy
# Consider adding HDM SLIT for sensitized patients with allergic rhinitis and FEV >70% predicted

Step 1 to Step 2



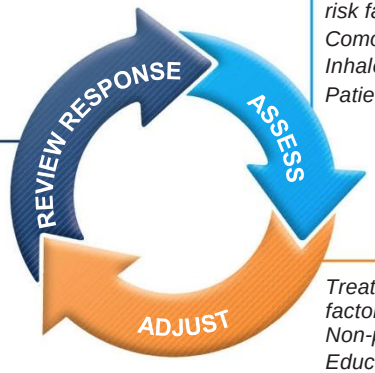
Box 3-5A

Adults & adolescents 12+ years

Personalized asthma management:
Assess, Adjust, Review response

'Controller' treatment means the treatment taken to prevent exacerbations

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



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

Symptoms
Exacerbations
Side-effects
Lung function
Patient satisfaction

Treatment of modifiable risk factors & comorbidities
Non-pharmacological strategies
Education & skills training
Asthma medications

	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 †*	*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 ‡		
Other reliever option	*As-needed short-acting β_2 -agonist (SABA)*				

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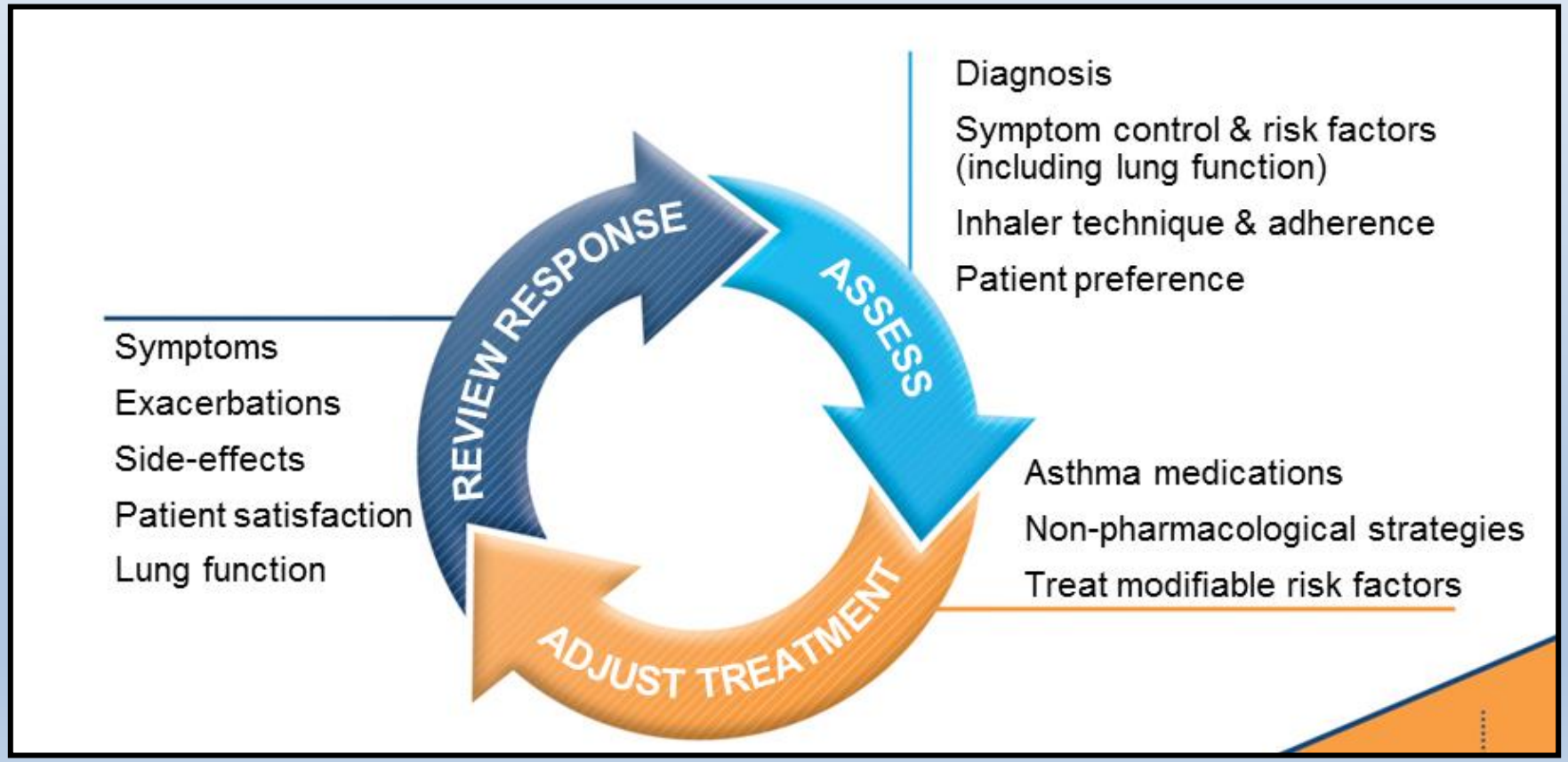
# Consider adding HDM SLIT for sensitized patients with allergic rhinitis and FEV >70% predicted

Start to look for ALLERGY symptoms, SINUSITIS symptoms, GERD symptoms

Step 2 to Step 3



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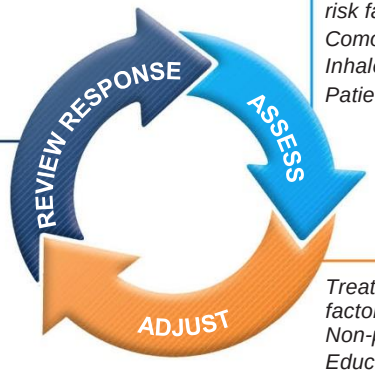

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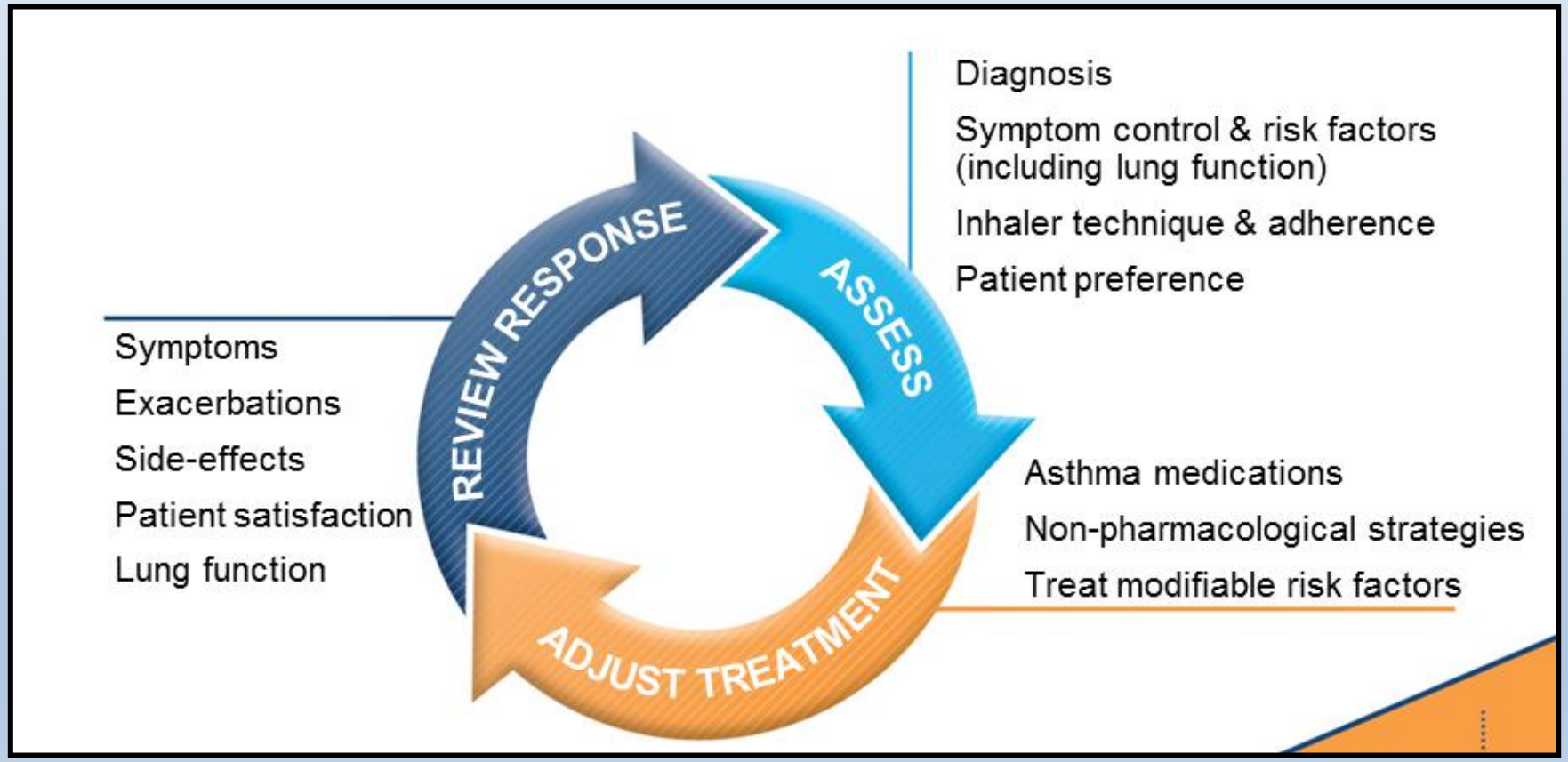
Again: co-morbid conditions, check inhaler technique, add in a spacer. If older. . can they inhale?

Step 3 to Step 4&5



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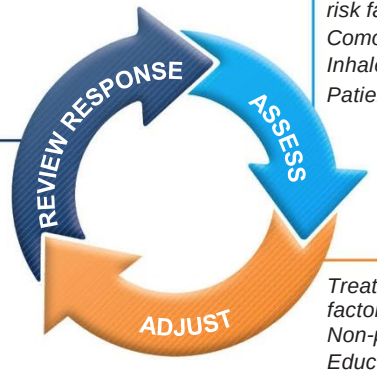

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# Consider adding HDM SLIT for sensitized patients with allergic rhinitis and FEV >70% predicted

High dose, add in tiotropium, check inhaler technique but please refer these patients, biologics are life changing

AGES 12+ YEARS: STEPWISE APPROACH FOR MANAGEMENT OF ASTHMA

	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▲ 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.

Treatment	STEP 1	STEP 2	STEP 3	STEP 4	ST
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 me dose ICS LAMA a PRN SA
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	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 +	Daily me dose ICS or daily ICS + LT PRN SA

Pause to Reflect

US and World (GINA) Guidlines

1. **Mostly agree, GINA says everyone gets s steroid**
2. **Both note that formoterol is fast and can be used in a combination (Symbicort) as a PRN medicine in the right patient**
3. **If atopic add in Montelukast**
4. **Step up aggressively**
5. **Move to biologics/specialty referral**

Reviewing response and adjusting treatment

- How often should asthma be reviewed?
  - 1-3 months after treatment started, then every 3-12 months
  - During pregnancy, every 4-6 weeks
  - After an exacerbation, within 1 week
- Stepping up asthma treatment
  - *Sustained step-up*, for at least 2-3 months if asthma poorly controlled
    - Important: first check for common causes (symptoms not due to asthma, incorrect inhaler technique, poor adherence)
  - *Short-term step-up*, for 1-2 weeks, e.g. with viral infection or allergen
    - May be initiated by patient with written asthma action plan
  - *Day-to-day adjustment*
    - For patients prescribed low-dose ICS/formoterol maintenance and reliever regimen*
- Stepping down asthma treatment
  - Consider step-down after good control maintained for 3 months
  - Find each patient's minimum effective dose, that controls both symptoms and exacerbations

Treating modifiable risk factors

- Provide skills and support for guided asthma self-management
  - This comprises self-monitoring of symptoms and/or PEF, a written asthma action plan and regular medical review
- Encourage avoidance of tobacco smoke
  - Provide smoking cessation advice and resources at every visit
- GERD
  - Treat or refer for this. It good deal of people have asthma improve once this is controlled
- Nasal congestion and post-nasal drip
  - Treat this aggressively. REMEMBER that older individual especially have cholinergic, not allergic rhinitis. Ipratropium Nasal is wonderful for this.

Check adherence with asthma medications

- Poor adherence:
  - Is very common: it is estimated that 50% of adults and children do not take controller medications as prescribed
  - Contributes to uncontrolled asthma symptoms and risk of exacerbations and asthma-related death
- Contributory factors
  - Unintentional (e.g. forgetfulness, cost, confusion) and/or
  - Intentional (e.g. no perceived need, fear of side-effects, cultural issues, cost)
- How to identify patients with low adherence:
  - Ask an empathic question, e.g. "*Do you find it easier to remember your medication in the morning or the evening?*", or "*Would you say you are taking it 3 days a week, or less, or more?*"
  - Check prescription date, label date and dose counter
  - Ask patient about their beliefs and concerns about the medication

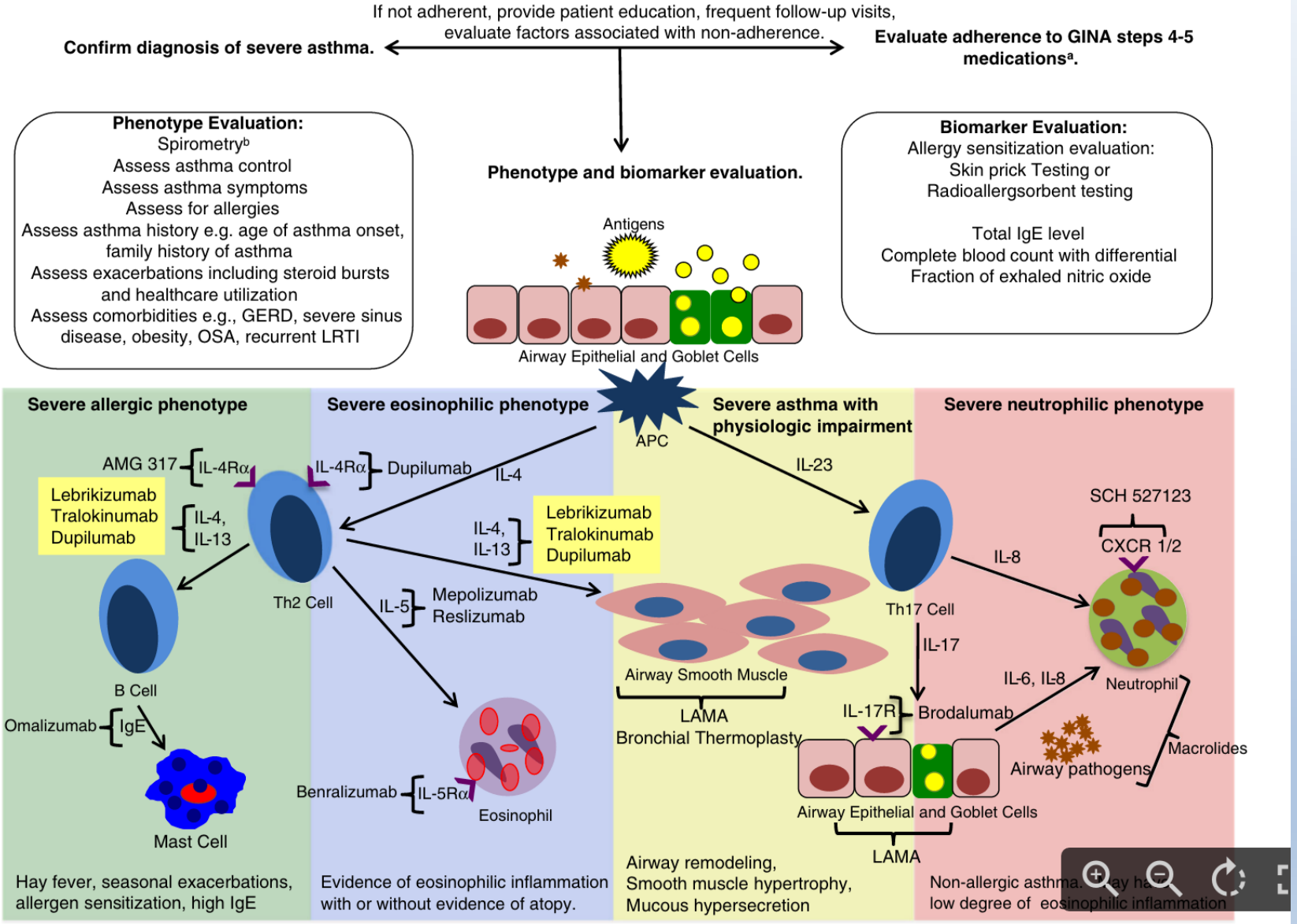
The Exacerbation -

- Prednisone – treat aggressively. No need to taper for most.
  - Kids – ok to treat QD! 0.5 mg/kg or more.
  - Adults – 40 mg minimum, many need more. Dose in AM with food. Sugar changes are transient.
  - Bump up therapy - short term combination therapy etc.
- The opportunity
  - Exacerbations often represent failures in chronic asthma care, and they provide opportunities to review the patient's asthma management
- At follow-up visit(s), check:
  - The patient's understanding of the cause of the flare-up
  - Modifiable risk factors, e.g. smoking
  - Adherence with medications, and understanding of their purpose
  - Inhaler technique skills
  - Written asthma action plan

A Note on Nebulizers

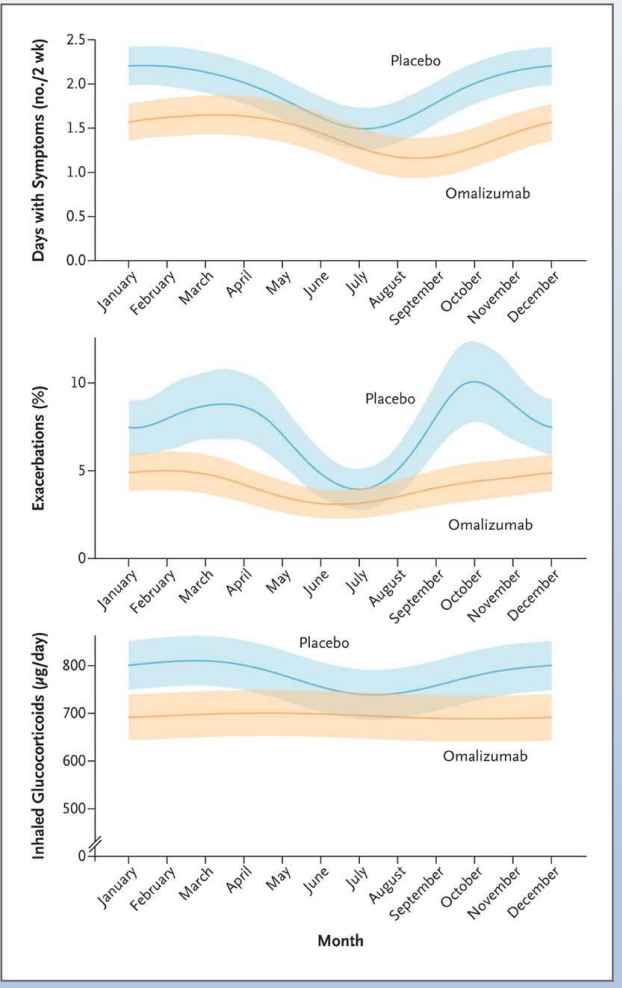
- Nebulizers are a known quantity – this can be helpful
- Avoid reliance on them for those school age and older but don't be afraid to keep them around
- If using budesonide its ok to add albuterol/ipratropium in the same treatment
- Over 2 years should be both albuterol/ipratropium, under 2 it's anyone's guess.
- OK to give ½ treatment before bed etc
- Move your senior patients with asthma or COPD to nebulized budesonide with Brovana or Perforomist (these are nebulized LABAs) if they are struggling or have poor inspiratory capacity

Biologics for Severe Asthma Therapy



Opina et al. Curr Allergy Asthma Rep (2017) 17:10

Omalizumab Decreases Seasonal Asthma Exacerbations



Busse WW et al. N Engl J Med 2011; 364:1005-1015

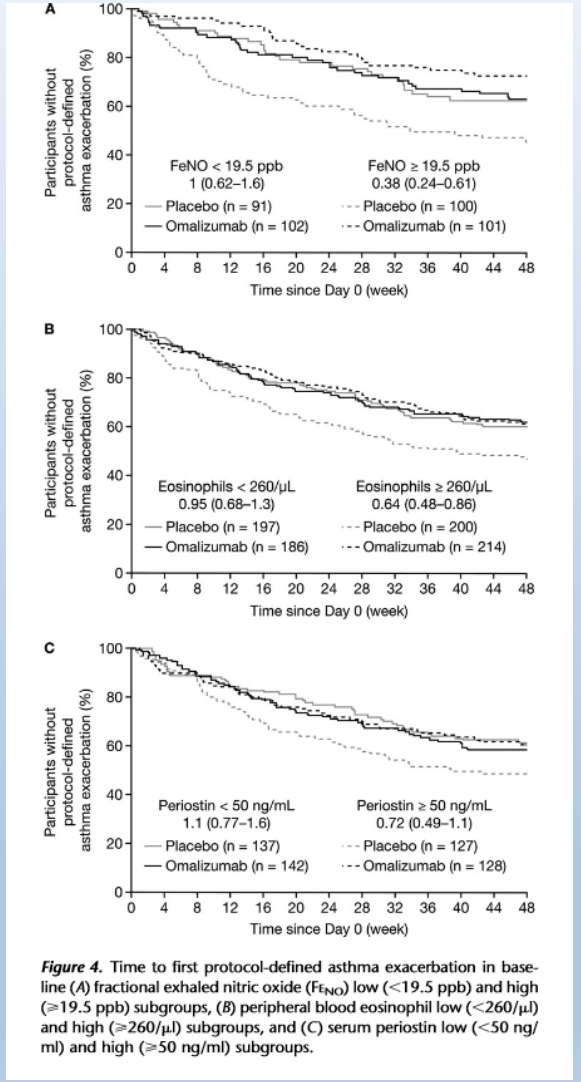


Figure 4. Time to first protocol-defined asthma exacerbation in baseline (*A*) fractional exhaled nitric oxide (Fe_{NO}) low (<19.5 ppb) and high (≥19.5 ppb) subgroups, (*B*) peripheral blood eosinophil low (<260/μl) and high (≥260/μl) subgroups, and (*C*) serum periostin low (<50 ng/ml) and high (≥50 ng/ml) subgroups.

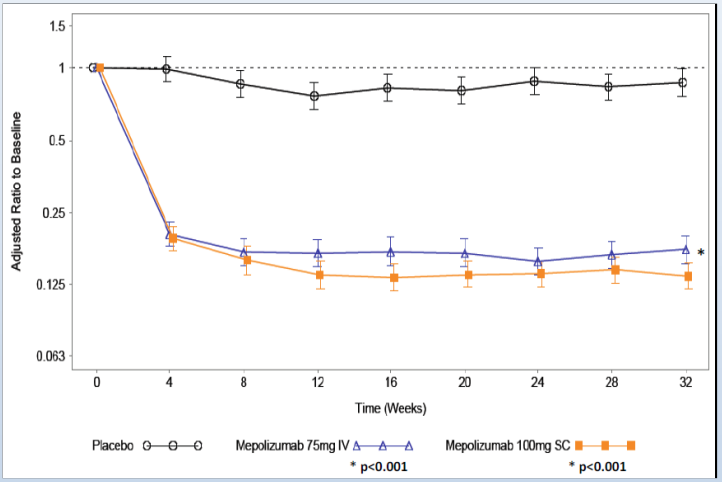
Hanania et al. AJRCCM. 2012;187:804-811

FeNO: 53% (95% [CI], 37–70; P=0.001) versus 16% (95% CI,32 to 46; P 0.45)

Eosinophils eosinophils,32% (95%CI,1148; 0.005)versus 9%(95%CI,24to 34;P 0.54)

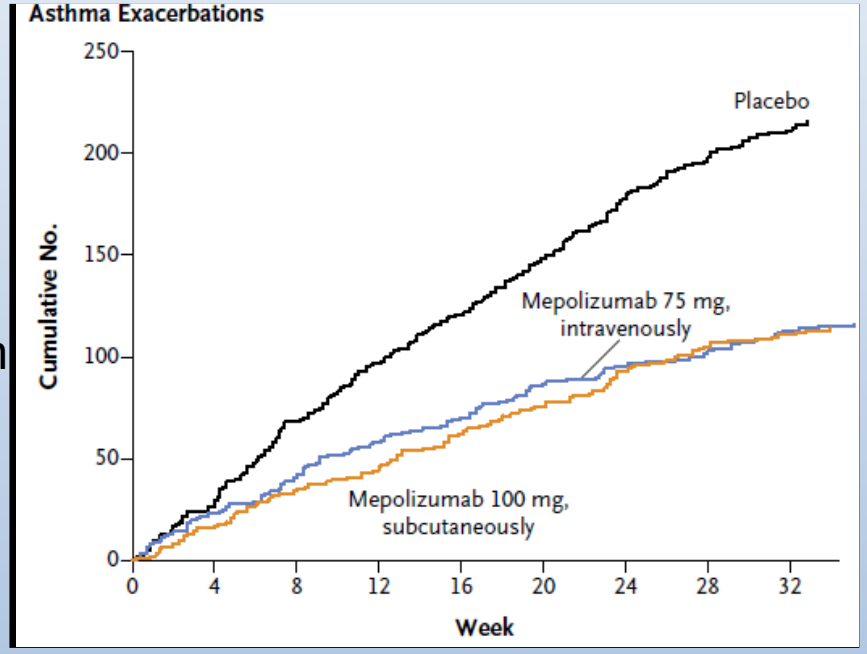
Periostin 30% (95% CI, 2 to 51 P=0.07)versus 3% (95% CI,43 32;P=0.94).

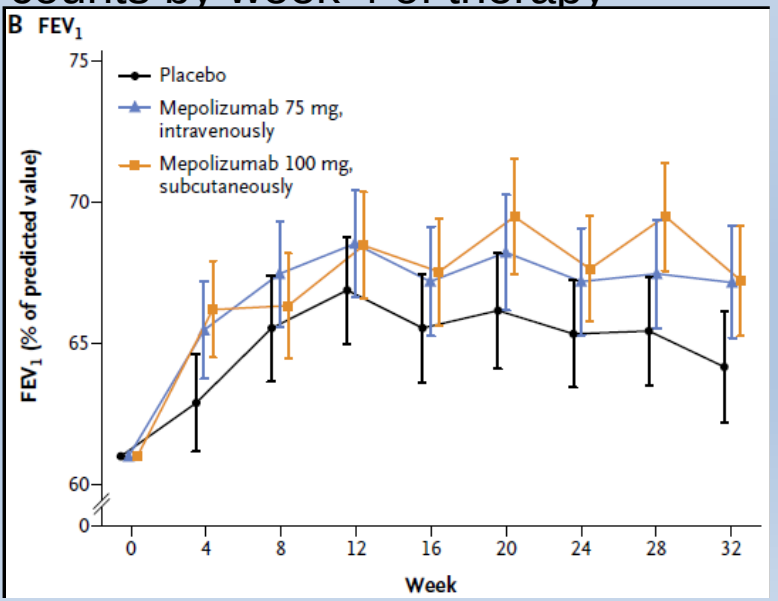
Mepolizumab Significantly Decreased Blood Eosinophils, Exacerbations and Improved Lung Function



Mepolizumab significantly reduces eosinoph counts by week 4 of therapy

Asthma Exacerbations were reduced by 47% with IV mepolizumab and 53% with SC mepolizumab





At week 32, the mean increase from baseline FEV1 was 100ml greater in the IV mepo grp (p=0.02) and 98ml greater in the SC group (p=0.03)

Ortega HG et al. NEJM 2014. 371:1198-1207

Benralizumab in Severe Eosinophilic Asthma

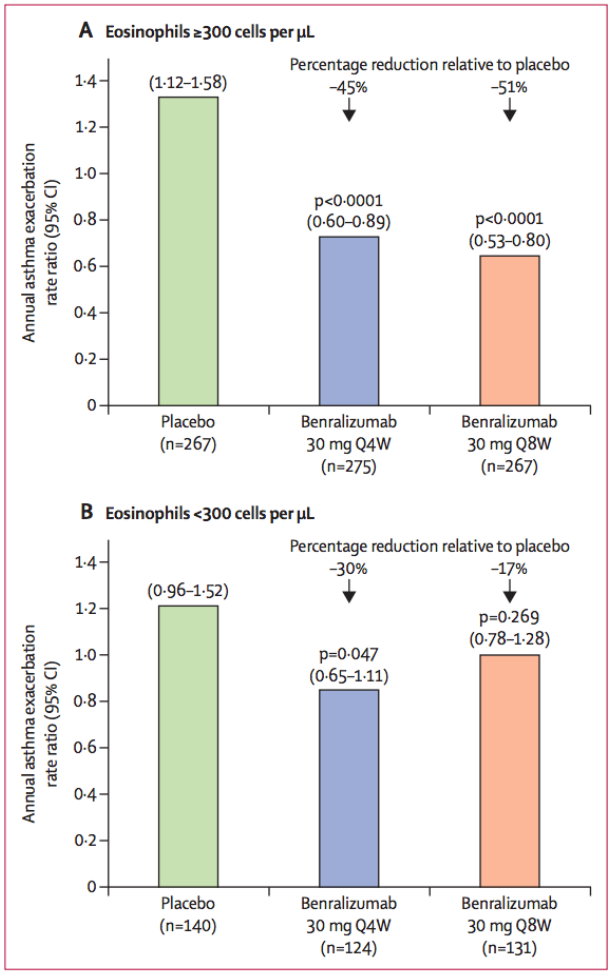


***Figure 2*: Annual asthma exacerbation rate estimates at 48 weeks according to baseline blood eosinophil concentrations**
Data for patients with baseline blood eosinophils (A) ≥300 cells per µL and (B) <300 cells per µL in the full analysis set are shown. Estimates were calculated using a negative binomial model, with adjustment for treatment, region, oral corticosteroid use at time of randomisation, and previous exacerbations. Q4W=every 4 weeks. Q8W=every 8 weeks (first three doses Q4W).

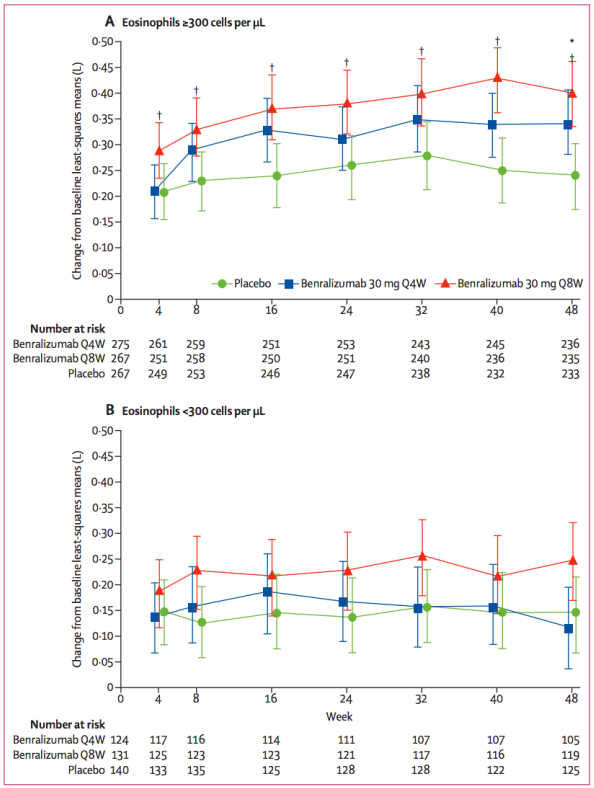


***Figure 3*: Change from baseline in prebronchodilator forced expiratory volume in 1 s according to baseline blood eosinophil concentrations**

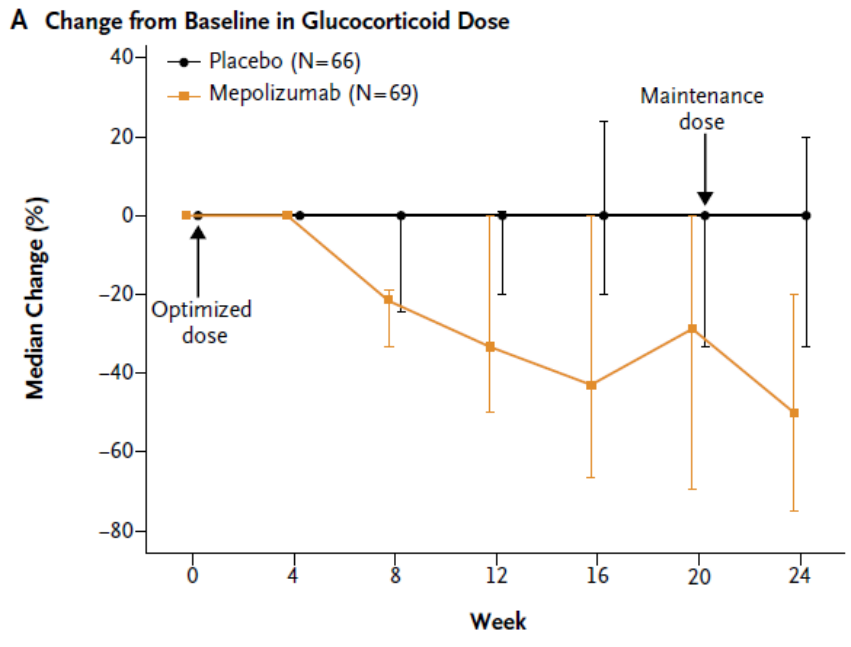
Bleecker et al. Lancet.2016: 2115-27

	SIROCCO		CALIMA[26]	
	Benralizumab Q4W	Benralizumab Q8W	Benralizumab Q4W	Benralizumab Q8W
Annual rate of exacerbations	↓ 45%	↓ 51%	↓ 36%	↓ 28%
Prebronchodilator FEV_1 (L)	↑ 0·106	↑ 0·159	↑ 0·125	↑ 0·116
Total asthma symptom score (score 0–6)*	↓ 0·08†	↓ 0·25	↓ 0·12†	↓ 0·23

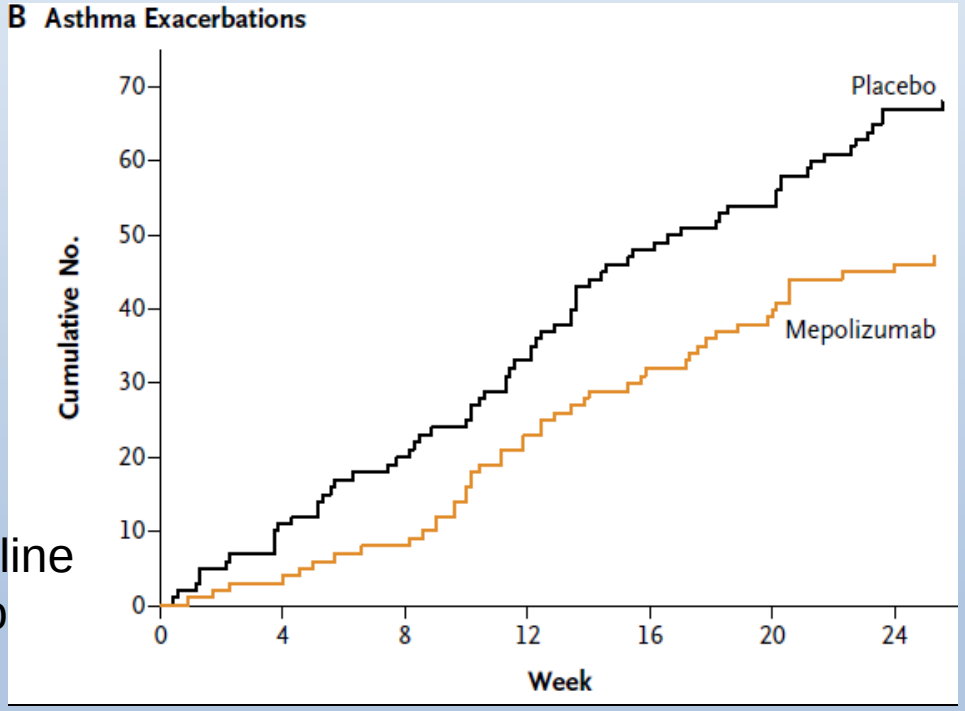
All results are differences from placebo; week 48 results for SIROCCO and week 56 results for CALIMA. FEV_1=forced expiratory volume in 1 s. Q4W=every 4 weeks. Q8W=every 8 weeks (first three doses Q4W). *Reduced score suggests improvement. †Non-significant.

***Table 5*: Efficacy results for patients who received high-dosage inhaled corticosteroids plus long-acting β_2-agonists with baseline blood eosinophils at least 300 cells per µL in the CALIMA and SIROCCO studies**

Mepolizumab Decreased OCS Dose and Reduced Exacerbations Despite Significant Reduction in OCS Use

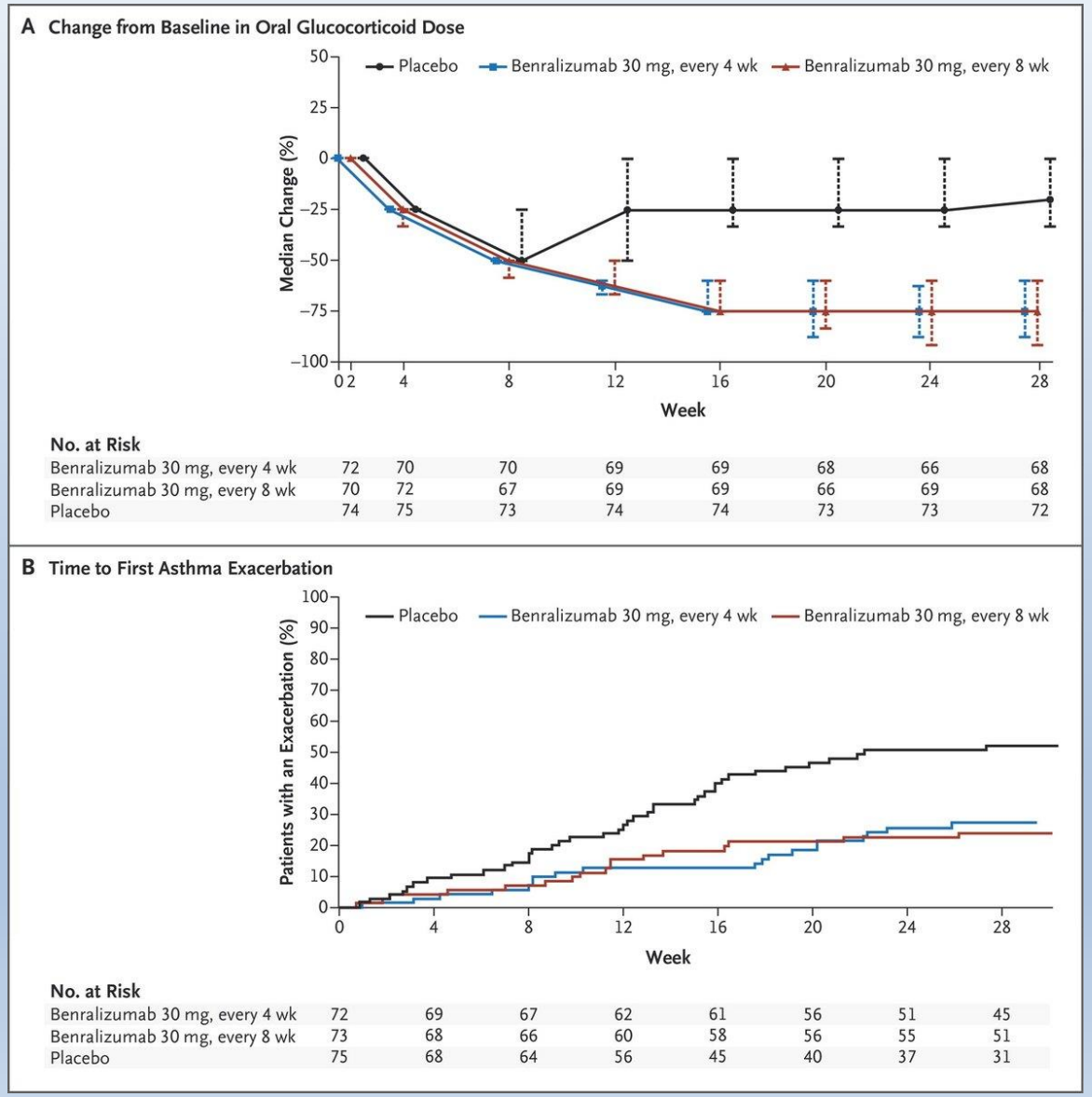


At 24 weeks, mean % reduction from baseline OCS dose was 50% in mepo group and no reduction in the placebo group



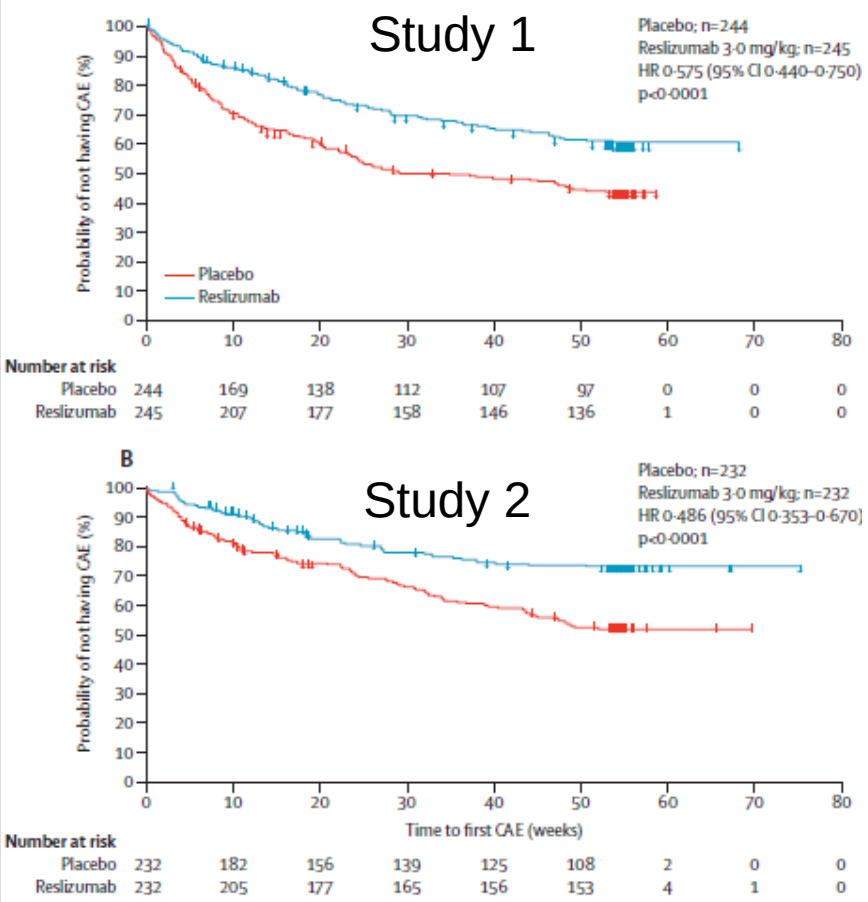
Relative reduction of 32% in exacerbations Compared with placebo (p=0.04)

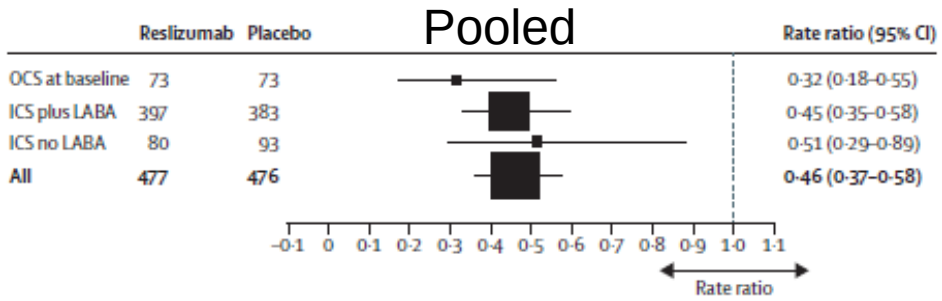
Steroid Sparing Effects of Benralizumab in Severe Eosinophilic Asthma



Nair et al. NEJM 2017

Reslizumab in Severe Eosinophilic Asthma

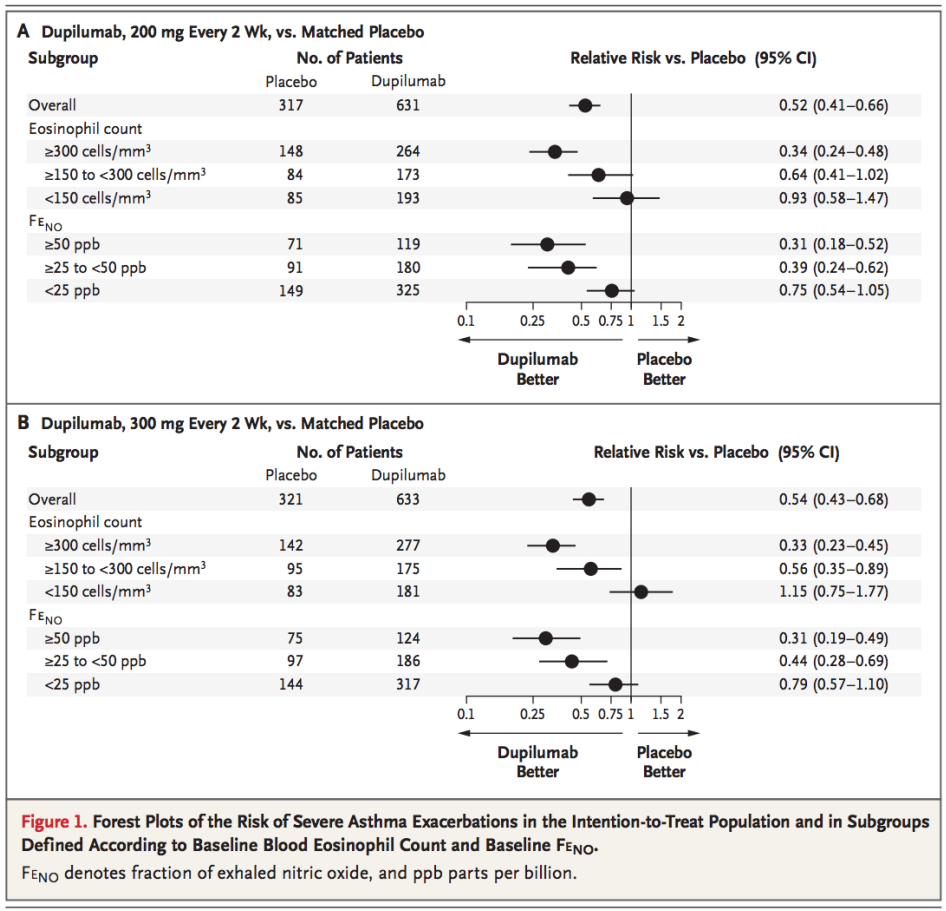




- In two studies, the probability of not having an exacerbation by week 52 with placebo was 44% (95% CI 38–51) and 52% (95% CI 45–58), and with Reslizumab it was 61% (95% CI 55–67) and 73% (95% CI 67–79), respectively
- Reslizumab reduced the risk for asthma exacerbation compared with placebo in both studies ($P < 0.0001$)

Castro et al. Lancet Respir Med. 2015:3:355-66

Dupilumab Significantly Decreases OCS and Exacerbations in Moderate to Severe asthma



A Dupilumab, 200 mg Every 2 Wk, vs. Matched Placebo

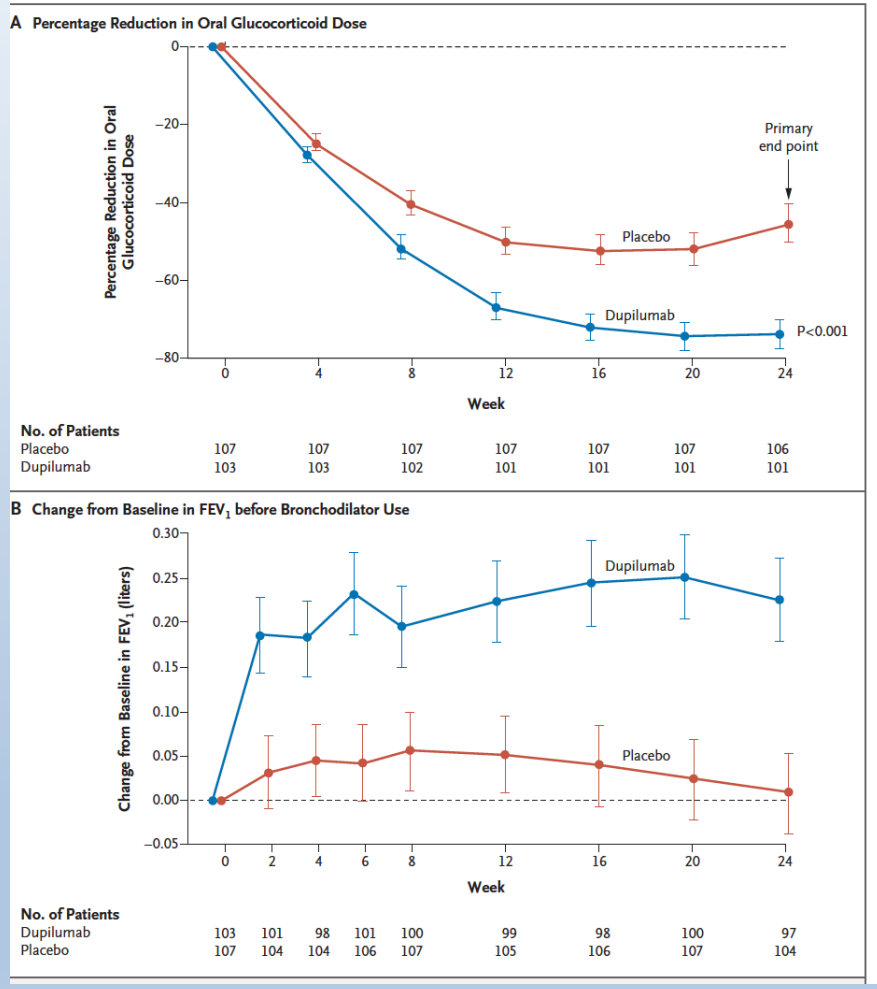
Subgroup	No. of Patients		Relative Risk vs. Placebo (95% CI)
	Placebo	Dupilumab	
Overall	317	631	0.52 (0.41–0.66)
Eosinophil count			
≥300 cells/mm³	148	264	0.34 (0.24–0.48)
≥150 to <300 cells/mm³	84	173	0.64 (0.41–1.02)
<150 cells/mm³	85	193	0.93 (0.58–1.47)
Fe_{NO}			
≥50 ppb	71	119	0.31 (0.18–0.52)
≥25 to <50 ppb	91	180	0.39 (0.24–0.62)
<25 ppb	149	325	0.75 (0.54–1.05)

B Dupilumab, 300 mg Every 2 Wk, vs. Matched Placebo

Subgroup	No. of Patients		Relative Risk vs. Placebo (95% CI)
	Placebo	Dupilumab	
Overall	321	633	0.54 (0.43–0.68)
Eosinophil count			
≥300 cells/mm³	142	277	0.33 (0.23–0.45)
≥150 to <300 cells/mm³	95	175	0.56 (0.35–0.89)
<150 cells/mm³	83	181	1.15 (0.75–1.77)
Fe_{NO}			
≥50 ppb	75	124	0.31 (0.19–0.49)
≥25 to <50 ppb	97	186	0.44 (0.28–0.69)
<25 ppb	144	317	0.79 (0.57–1.10)

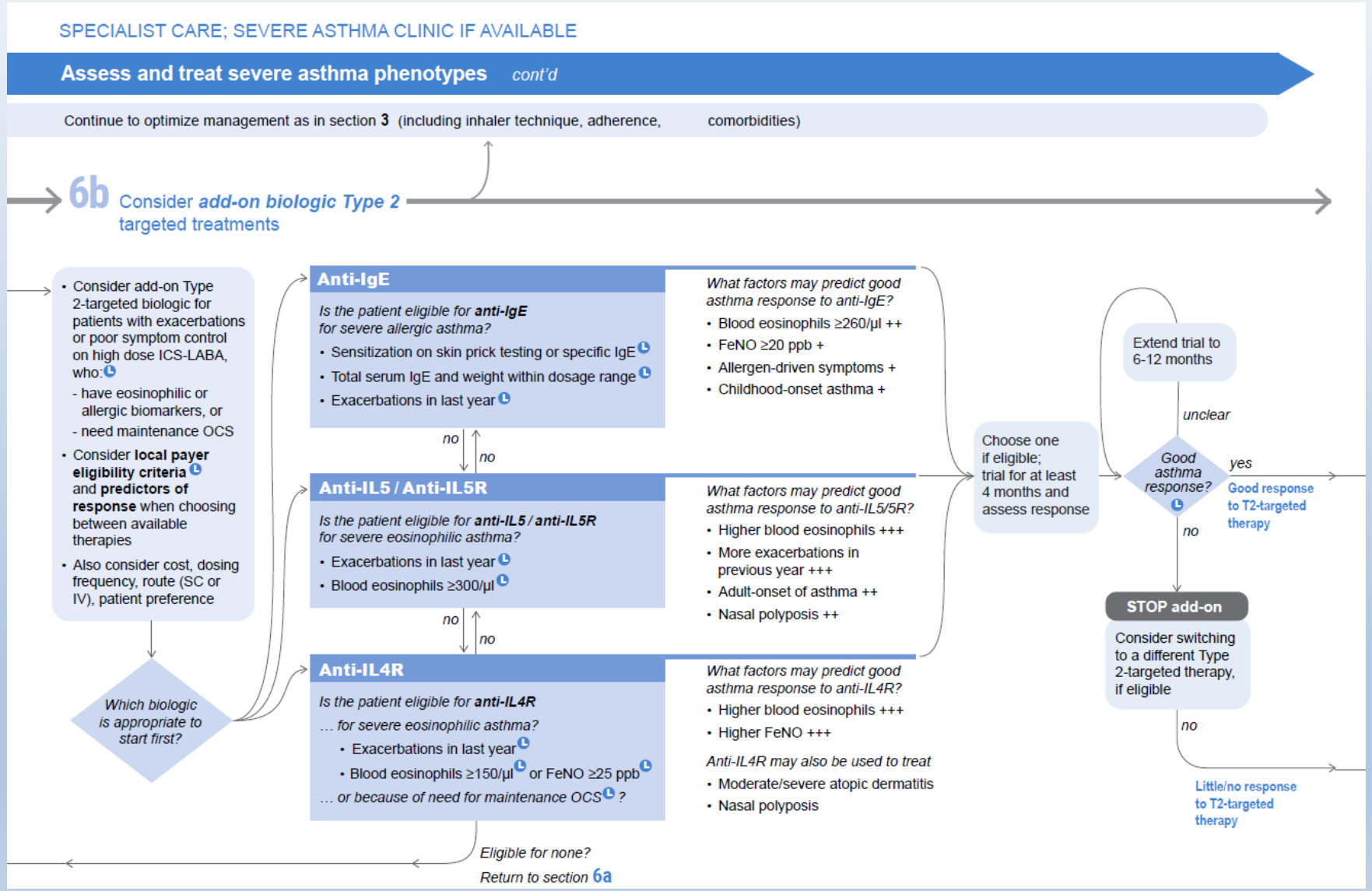
Figure 1. Forest Plots of the Risk of Severe Asthma Exacerbations in the Intention-to-Treat Population and in Subgroups Defined According to Baseline Blood Eosinophil Count and Baseline Fe_{NO}.

Fe_{NO} denotes fraction of exhaled nitric oxide, and ppb parts per billion.



Rabe, C et al. N Engl J Med 2018;378:2475 and Castro et al. NEJM 378;26:2486

GINA Severe Asthma Algorithm



Couple points to throw in -

- Lung function/steroids and height
  - Growth velocity may be lower in the first 1-2 years of ICS treatment, but this is not progressive or cumulative. ▪ Long-term outcomes showed a difference of only 0.7% in adult height (LESS height loss than untreated asthma)

- Patients with *apparently mild asthma* are at risk of serious adverse events (this is the percent that had symptoms “once a week or less” in the 6 months before the event)
  - 30–37% of adults with acute asthma
  - 16% of patients with near-fatal asthma
  - 15–20% of adults dying of asthma

Asthma Action Plan for Home & School

Allergy & Asthma Network

Name: **Birthdate:**

Asthma Severity: ☐ Intermittent ☐ Mild Persistent ☐ Moderate Persistent ☐ Severe Persistent
☐ He/she has had many or severe asthma attacks/exacerbations

☺ Green Zone
Have the child take these medicines every day, even when the child feels well.

Always use a spacer with inhalers as directed.

Controller Medicine(s): _____

_____

Controller Medicine(s) Given in School: _____

Rescue Medicine: Albuterol/Levalbuterol _____ puffs every four hours as needed

Exercise Medicine: Albuterol/Levalbuterol _____ puffs 15 minutes before activity as needed

😐 Yellow Zone
Begin the sick treatment plan if the child has a cough, wheeze, shortness of breath, or tight chest. Have the child take all of these medicines when sick.

Rescue Medicine: Albuterol/Levalbuterol _____ puffs every 4 hours as needed

Controller Medicine(s):

☐ Continue Green Zone medicines: _____

☐ Add: _____

_____

☐ Change: _____

If the child is in the **yellow** zone more than **24** hours or is getting worse, follow **red** zone and call the doctor right away!

☹ Red Zone
If breathing is hard and fast, ribs sticking out, trouble walking, talking, or sleeping.
Get Help Now

Take rescue medicine(s) now

Rescue Medicine: Albuterol/Levalbuterol _____ puffs every _____

Take: _____

_____

If the child is not better right away, call 911
Please call the doctor any time the child is in the red zone.

Asthma Triggers: (List)

School Staff: Follow the Yellow and Red Zone plans for rescue medicines according to asthma symptoms.
Unless otherwise noted, the only controllers to be administered in school are those listed as "given in school" in the green zone.

☐ Both the asthma provider and the parent feel that the child may carry and self-administer their inhalers
☐ School nurse agrees with student self-administering the inhalers

Asthma Provider Printed Name and Contact Information:	Asthma Provider Signature: Date:

Parent/Guardian: I give written authorization for the medications listed in the action plan to be administered in school by the nurse or other school members as appropriate. I consent to communication between the prescribing health care provider/clinic, the school nurse, the school medical advisor and school-based health clinic providers necessary for asthma management and administration of this medication.

Parent/guardian signature:	School Nurse Reviewed:

An Asthma Action Plan:

https://www.allergyasthmanetwork.org/cms/wp-content/uploads/2014/07/Asthma-Action-Plan-English.pdf

Inhaler technique videos:

https://www.bing.com/videos/search?q=how+to+use+a+ventolin+inhaler+properly&&view=detail&mid=42D0422123954963F5E942D0422123954963F5E9&&FORM=VRDGAR

https://www.bing.com/videos/search?q=how+to+use+a+spacer+with+inhaler&&view=detail&mid=4ADA5870C49C9363B0D44ADA5870C49C9363B0D4&&FORM=VRDGAR

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