Asthma Therapy 2017

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BACKGROUND-PREVALENCE

- 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
- Health care expenditure on asthma is very high

In The US

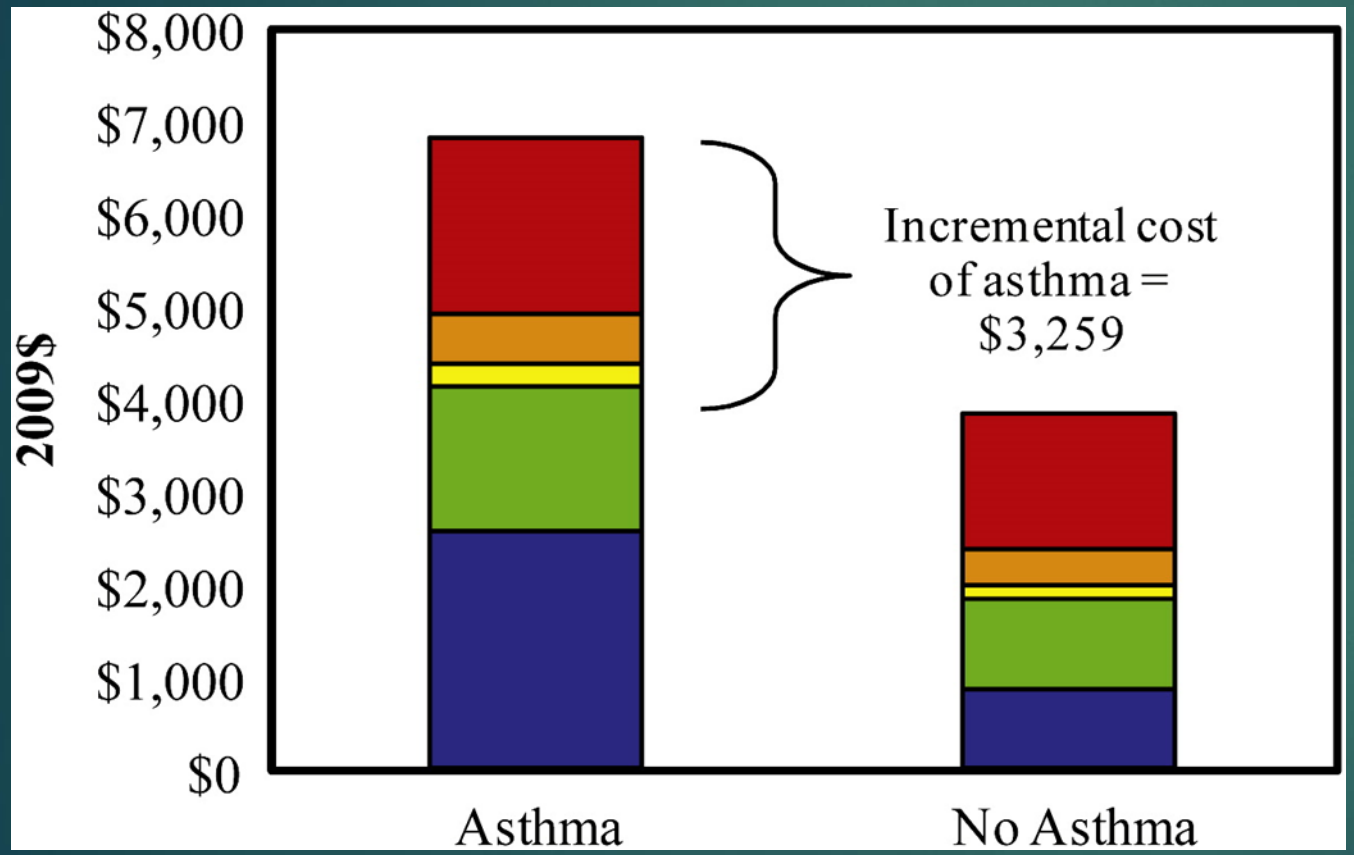
24M
People in the US have asthma[1]

17.7M
Adults have asthma

8.9M
Inadequately controlled asthma

1. Centers for Disease Control and Prevention. Asthma fast stats. http://www.cdc.gov/nchs/fastats/asthma.htm. Accessed September 8, 2016.

BACKGROUND-COST

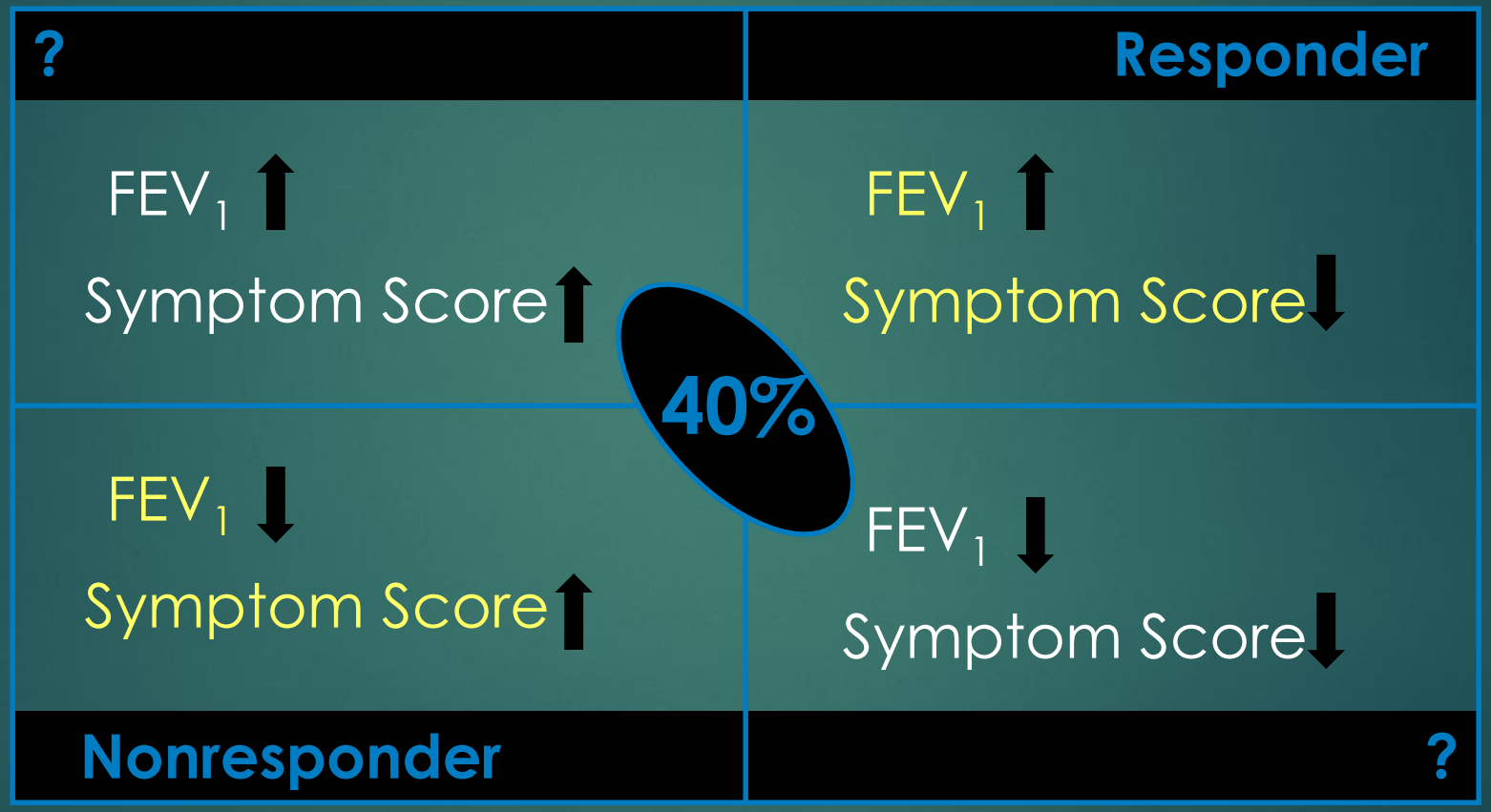


Total Cost of Asthma for the year 2007 was 56 billion dollars

FIG 1. Individual predicted annual medical expenditures by category, 2002-2007,. Red, Inpatient; orange, outpatient; yellow, emergency department; green, office visits; blue, prescription.

Journal of Allergy and Clinical Immunology
Volume 127, Issue 1, Pages 145-152 (January 2011)

Variable Responses in Outcomes Measured:
Responders and Non-responders in Asthma



1. Reprinted from Luskin AT. *J Allergy Clin Immunol.* 2005;115:S539–S545, with permission from the American Academy of Allergy, Asthma, and Immunology.
2. Shingo S et al. *Eur Respir J.* 2001;17:220–224.

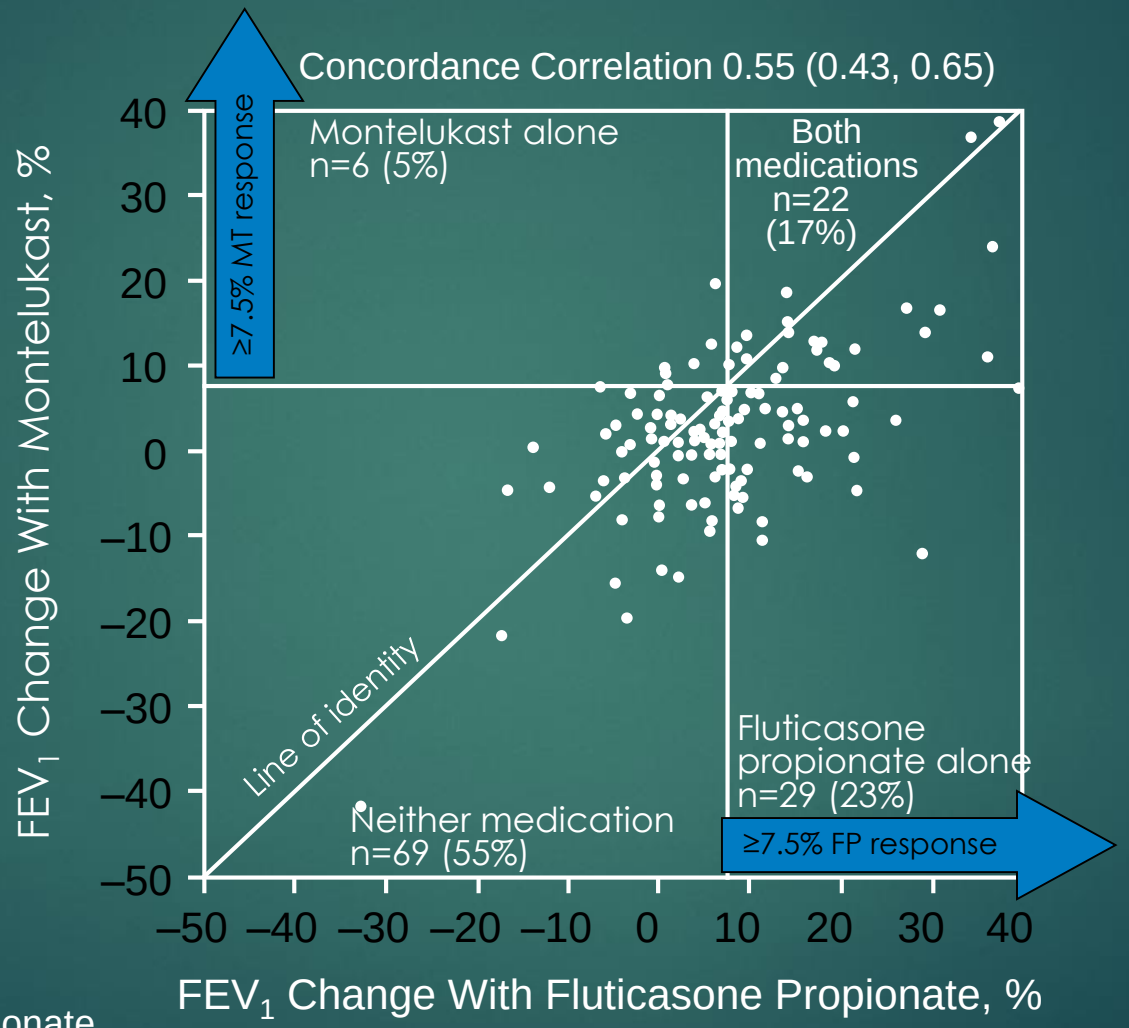
CLIC: Characterizing Response to a Leukotriene Receptor Antagonist and an Inhaled Corticosteroid

- Objective:
  - Are responses to ICSs and LTRAs concordant?
  - Do asthmatic patients who don't respond to one medication respond to the other?
- Design:
  - Multicenter, double-masked, 18-week trial
  - Children aged 6 to 7 years randomized to 1 of 2 crossover sequences, including 8 weeks of fluticasone propionate and 8 weeks of montelukast
- Primary Outcome Variables:
  - Percent change in prebronchodilator FEV_1 from baseline to the end of each treatment period
  - Responses assessed for relationships to baseline asthma phenotype-associated biomarkers
- Other Measured Variables Included:
  - Asthma-free days, rescue β-agonist use, exhaled nitric oxide

ICS=inhaled corticosteroid; LTRA=leukotriene receptor antagonist.

Szefler SJ et al. *J Allergy Clin Immunol.* 2005;115:233–242.

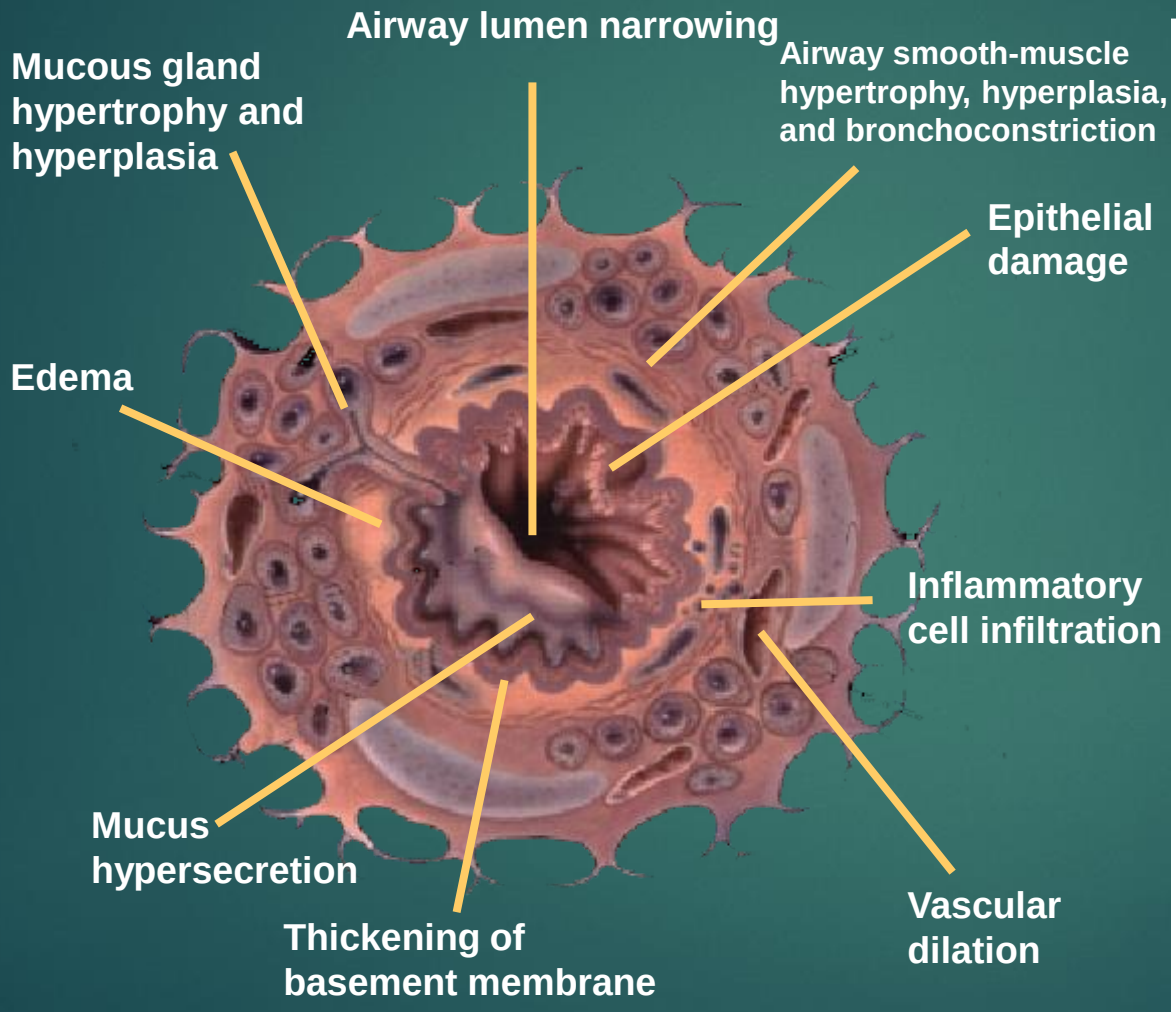
CLIC Primary Outcome: FEV_1 Response



MT=montelukast; FP=fluticasone propionate.

Reprinted from Szefler SJ et al. *J Allergy Clin Immunol.* 2005;115:233–242, with permission from the American Academy of Allergy, Asthma, and Immunology.

AIRWAY INFLAMMATION



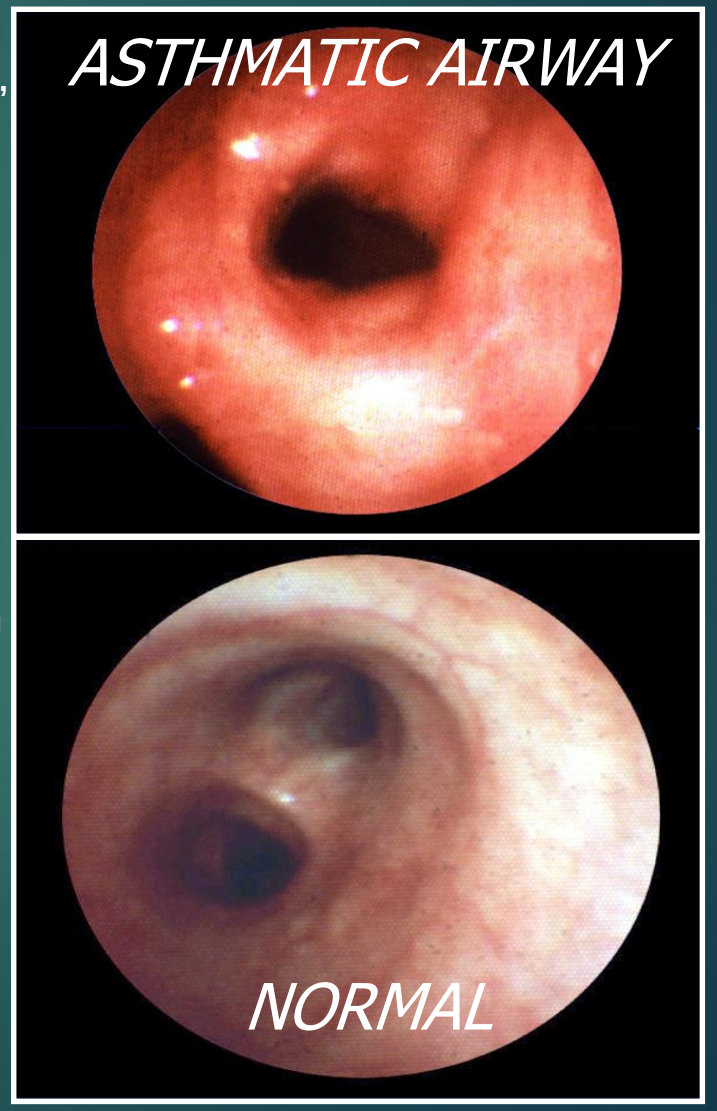
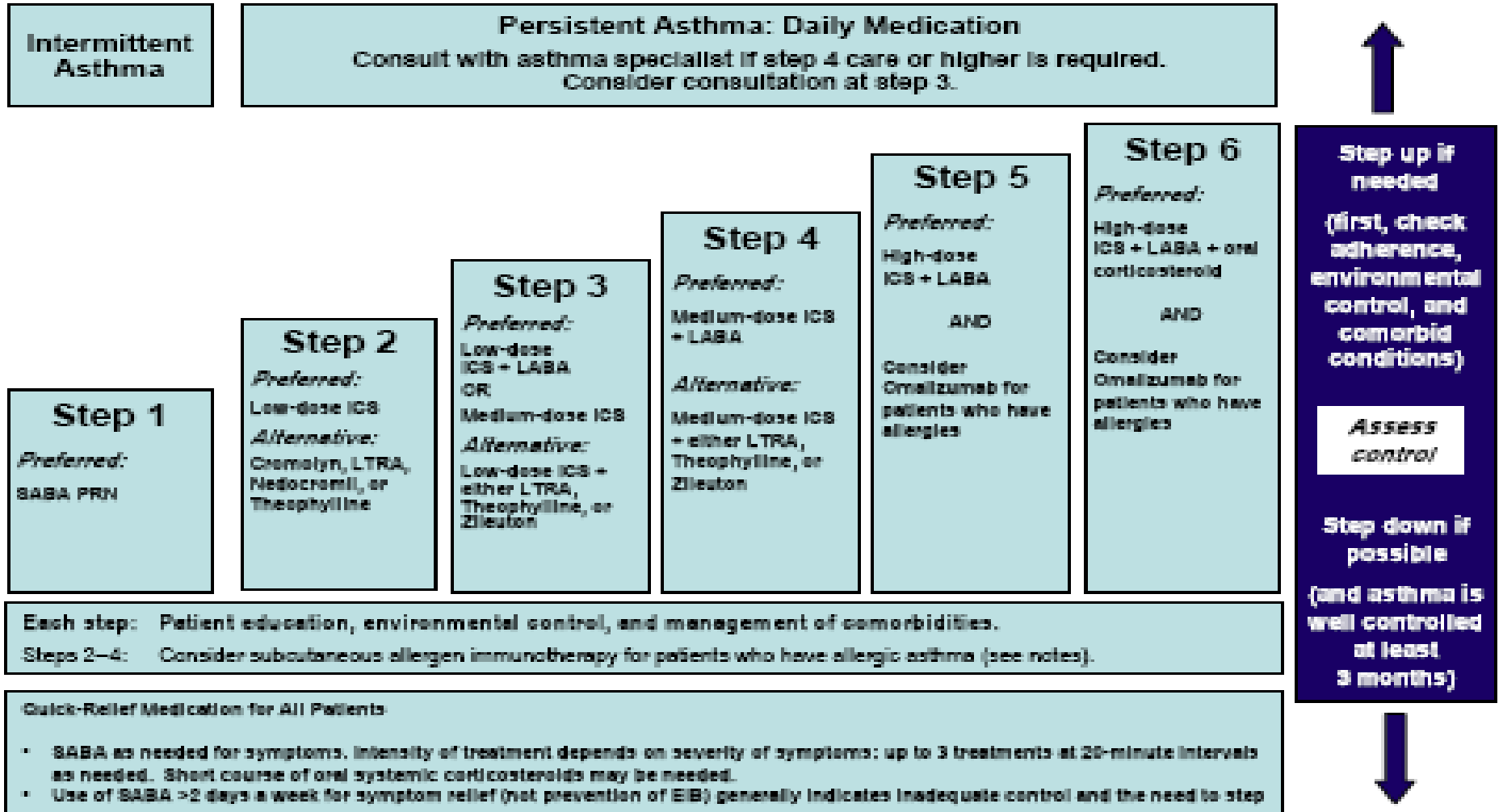


FIGURE 4–5. STEPWISE APPROACH FOR MANAGING ASTHMA IN YOUTHS ≥12 YEARS OF AGE AND ADULTS



NAEPP, NHLBI, NIH. *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma.* August 2007

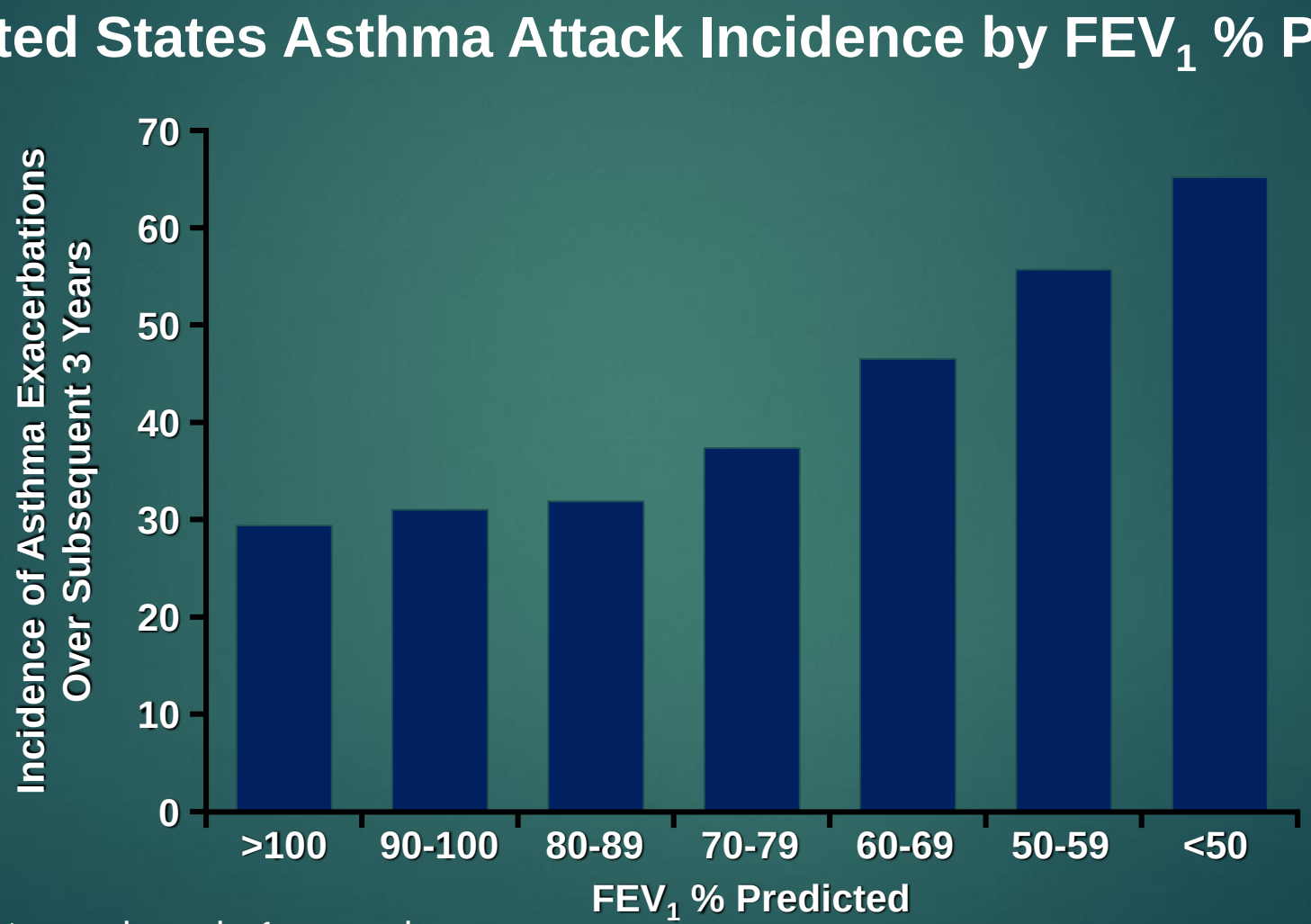
Classification of Asthma Severity

- **Current Impairment:**
  - Symptoms
    - Nighttime awakenings
    - Need for SABA (quick reliever)
    - Work/School days missed
    - Ability to engage in normal daily activities or in desired activities
    - Quality-of-life assessments
  - Lung Function: Spirometry (not peak flow)

Classification of Severity: Risk

- Risk based on:
  - History, observation and clinical judgment
- Predictors:
  - Airflow obstruction (severity and persistence)
  - Two or more ED visits or hospitalizations in the past year, intubation or ICU admission in the last 5 years
  - Patient is frightened by their asthma
  - Demographics: female, non-white, non-use of ICS, current smoking
  - Psychosocial factors: Depression, increased stress, socioeconomic factors
  - Attitudes and beliefs about taking medications

FEV_1 Can Predict the Risk of Exacerbation

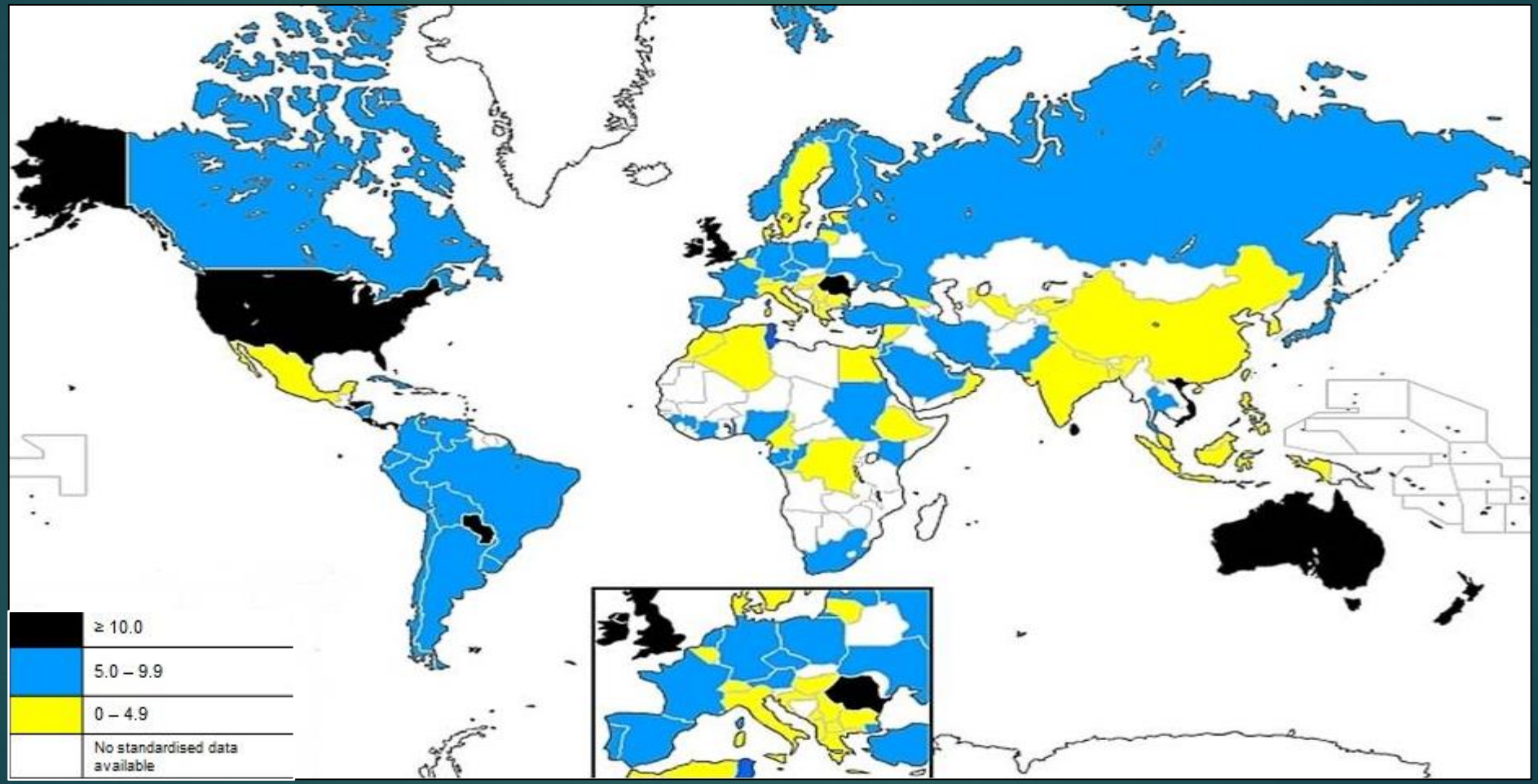


FEV_1 = forced expiratory volume in 1 second.

Adapted with permission from Kitch BT et al. *Chest*. 2004;126:1875-1882.

Global Initiative for Asthma (GINA) 2017 update

Prevalence of asthma in children aged 13-14 years



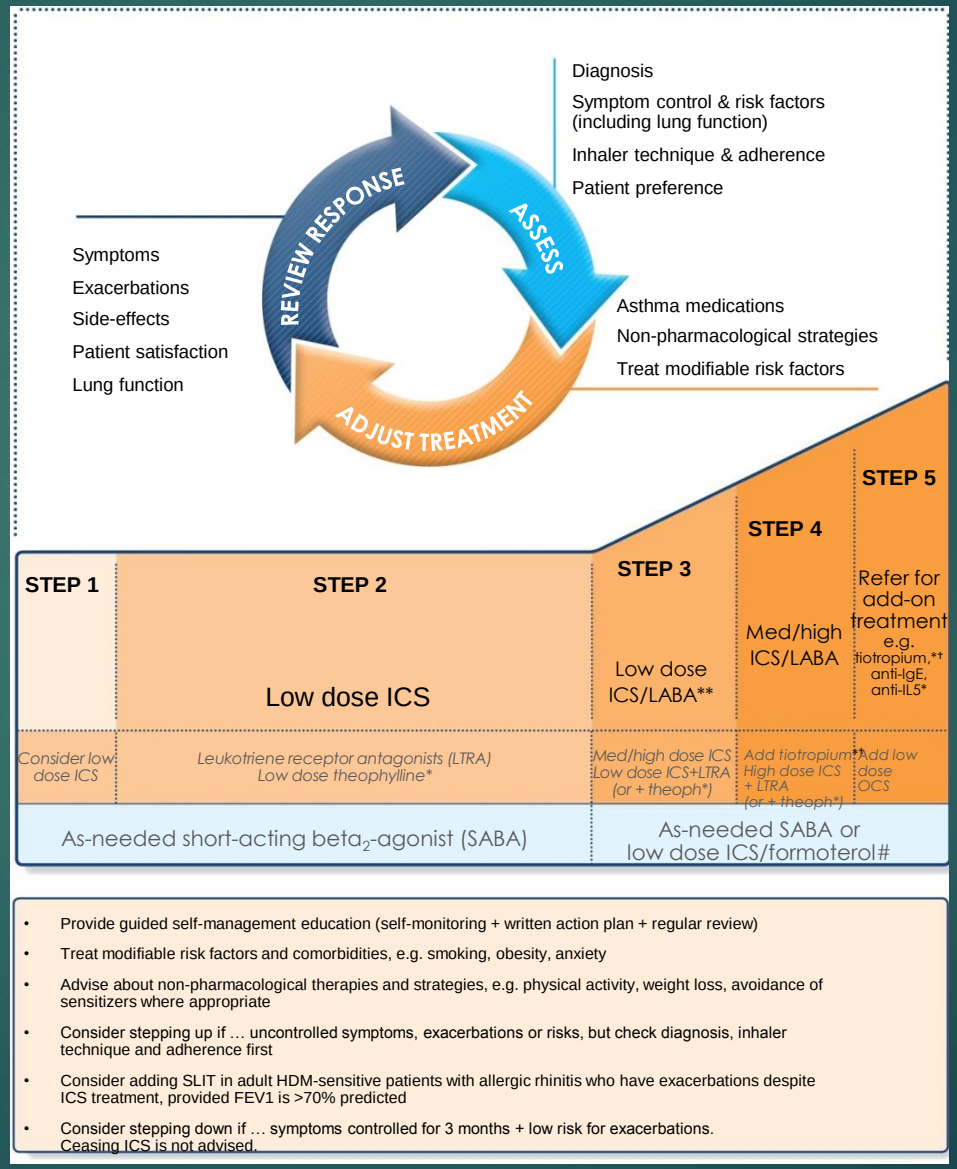
GINA 2017 Appendix Box A1-1; figure provided by R Beasley

Definition of asthma

Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation.

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.

Stepwise approach to control asthma symptoms and reduce risk



SLIT added as an option

GINA 2017, Box 3-5 (1/8)

Diagnosis of Asthma

- The diagnosis of asthma should be based on:
  - A history of characteristic symptom patterns
  - Evidence of variable airflow limitation, from bronchodilator reversibility testing or other tests
- Document evidence for the diagnosis in the patient's notes, preferably before starting controller treatment
  - It is often more difficult to confirm the diagnosis after treatment has been started
- Asthma is usually characterized by airway inflammation and airway hyperresponsiveness, but these are not necessary or sufficient to make the diagnosis of asthma.

Diagnosis of Asthma-Symptoms

- *Increased* probability that symptoms are due to asthma if:
  - More than one type of symptom (wheeze, shortness of breath, cough, chest tightness)
  - Symptoms often worse at night or in the early morning
  - Symptoms vary over time and in intensity
  - Symptoms are triggered by viral infections, exercise, allergen exposure, changes in weather, laughter, irritants such as car exhaust fumes, smoke, or strong smells
- *Decreased* probability that symptoms are due to asthma if:
  - Isolated cough with no other respiratory symptoms
  - Chronic production of sputum
  - Shortness of breath associated with dizziness, light-headedness or peripheral tingling
  - Chest pain
  - Exercise-induced dyspnea with noisy inspiration (stridor) (PVFMD=VCD)

Risk factors for poor asthma outcomes

Risk factors for exacerbations include:

- Ever intubated for asthma
- Uncontrolled asthma symptoms
- Having ≥1 exacerbation in last 12 months
- Low FEV_1 (measure lung function at start of treatment, at 3-6 months to assess personal best, and periodically thereafter)
- Incorrect inhaler technique and/or poor adherence
- Smoking
- Elevated FeNO in adults with allergic asthma
- Obesity, pregnancy, blood eosinophilia

Risk factors for fixed airflow limitation include:

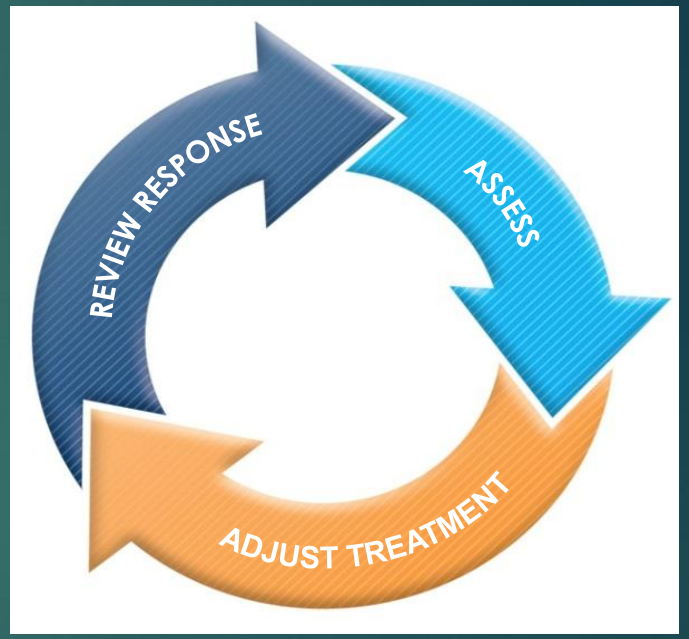
- No ICS treatment, smoking, occupational exposure, mucus hypersecretion, blood eosinophilia

Assessing Asthma Severity

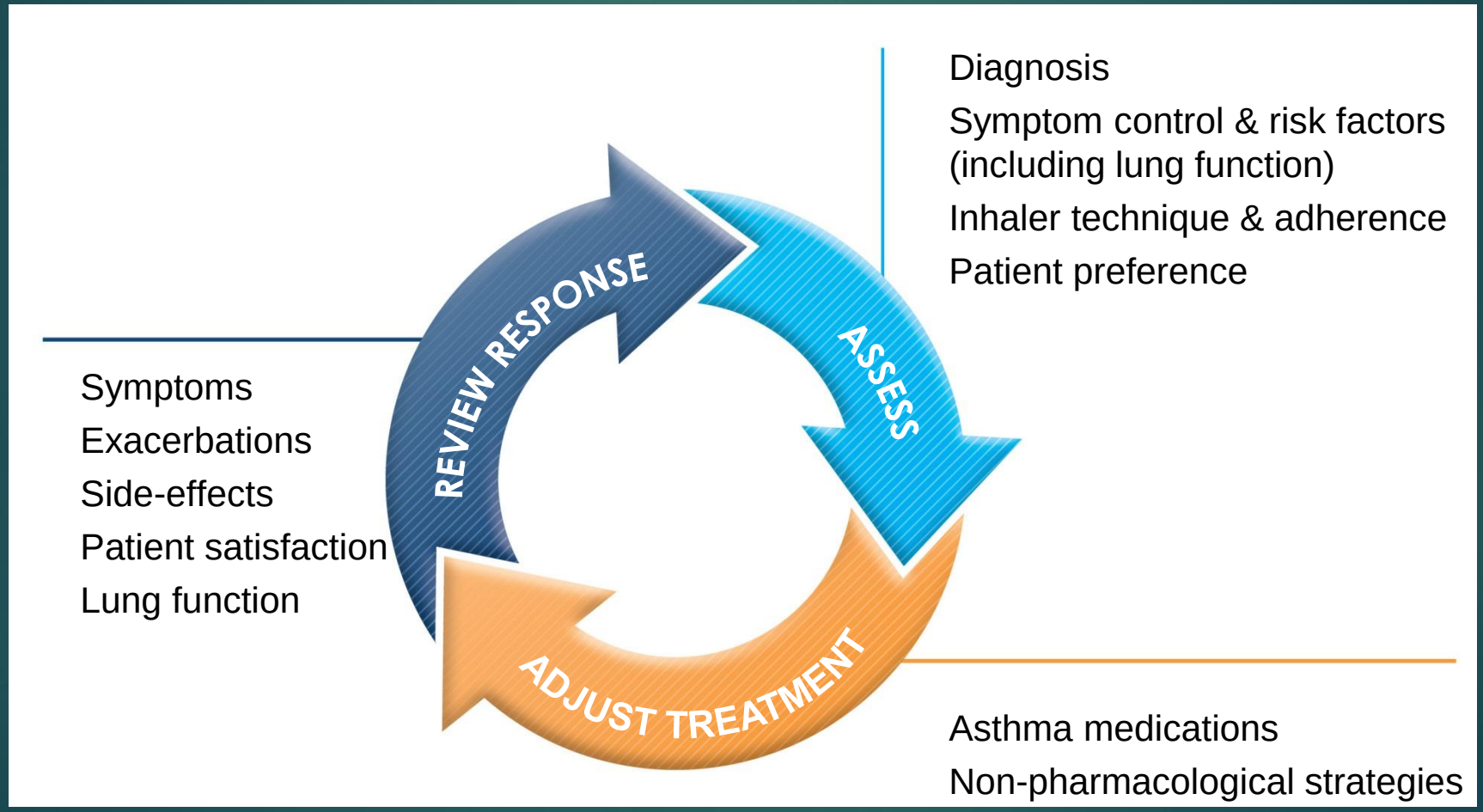
- How?
  - Asthma severity is assessed retrospectively from the level of treatment required to control symptoms and exacerbations
- When?
  - Assess asthma severity after patient has been on controller treatment for several months
  - Severity is not static – it may change over months or years, or as different treatments become available
- Categories of asthma severity
  - *Mild asthma:* well-controlled with Steps 1 or 2 (as-needed SABA or low dose ICS)
  - *Moderate asthma:* well-controlled with Step 3 (low-dose ICS/LABA)
  - *Severe asthma:* requires Step 4/5 (moderate or high dose ICS/LABA ± add-on), or remains uncontrolled despite this treatment

Treat to Control Symptoms and Minimize Risk

- Establish a patient-doctor 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



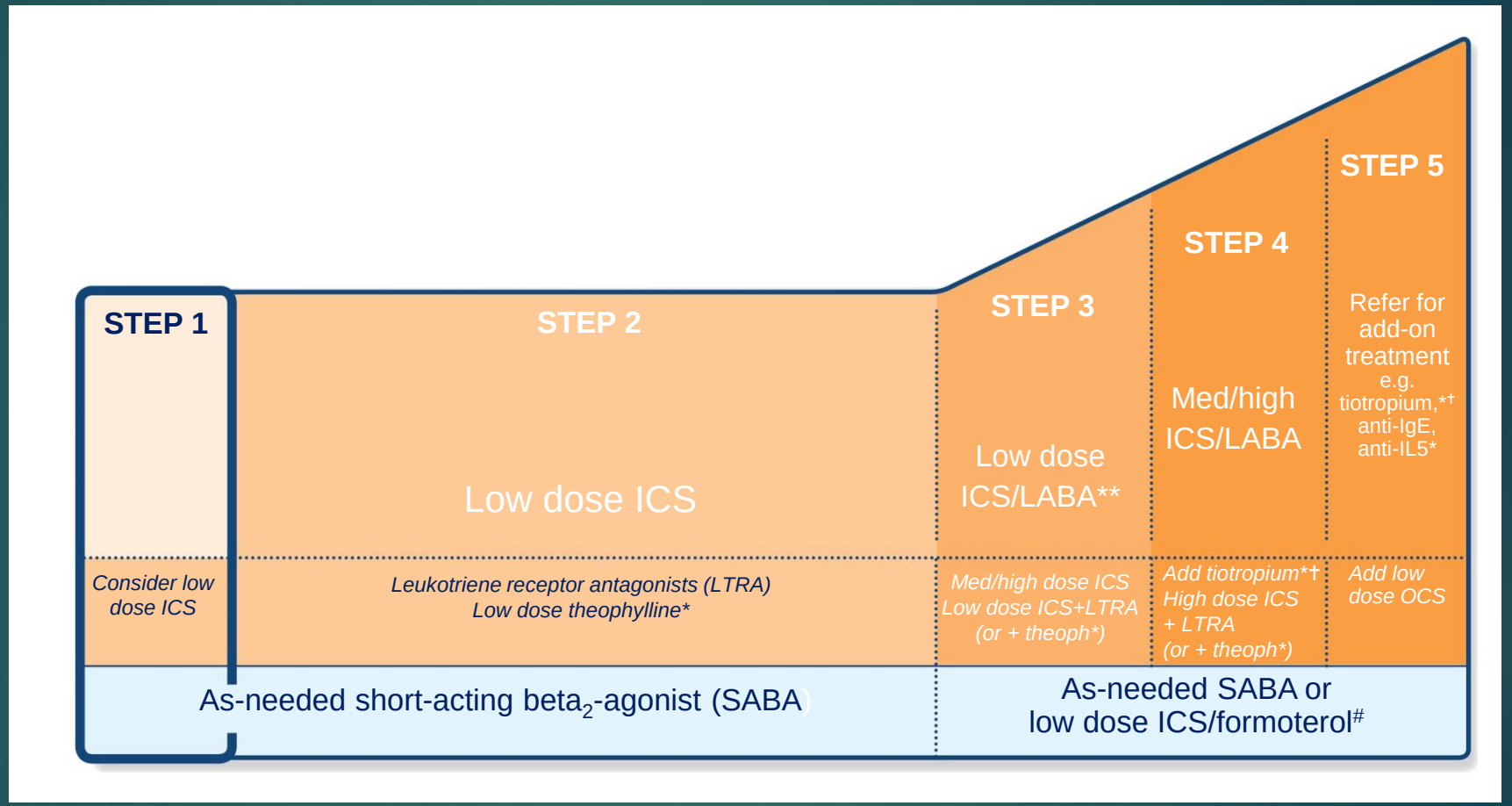
The Asthma Management Cycle



Choosing Controller Options- Individual Patient Decisions

- **Decisions for individual patients**
  - Use shared decision-making with the patient/parent/carer to discuss the following:
- Preferred treatment for symptom control and for risk reduction
- Patient characteristics (phenotype)
  - Does the patient have any known predictors of risk or response? (e.g. smoker, history of exacerbations, blood eosinophilia)
- Patient preference
  - What are the patient's goals and concerns for their asthma?
- Practical issues
  - Inhaler technique - can the patient use the device correctly after training?
  - Adherence: how often is the patient likely to take the medication?
  - Cost: can the patient afford the medication?

Step 1 – as-needed inhaled short-acting beta$_2$-agonist (SABA)

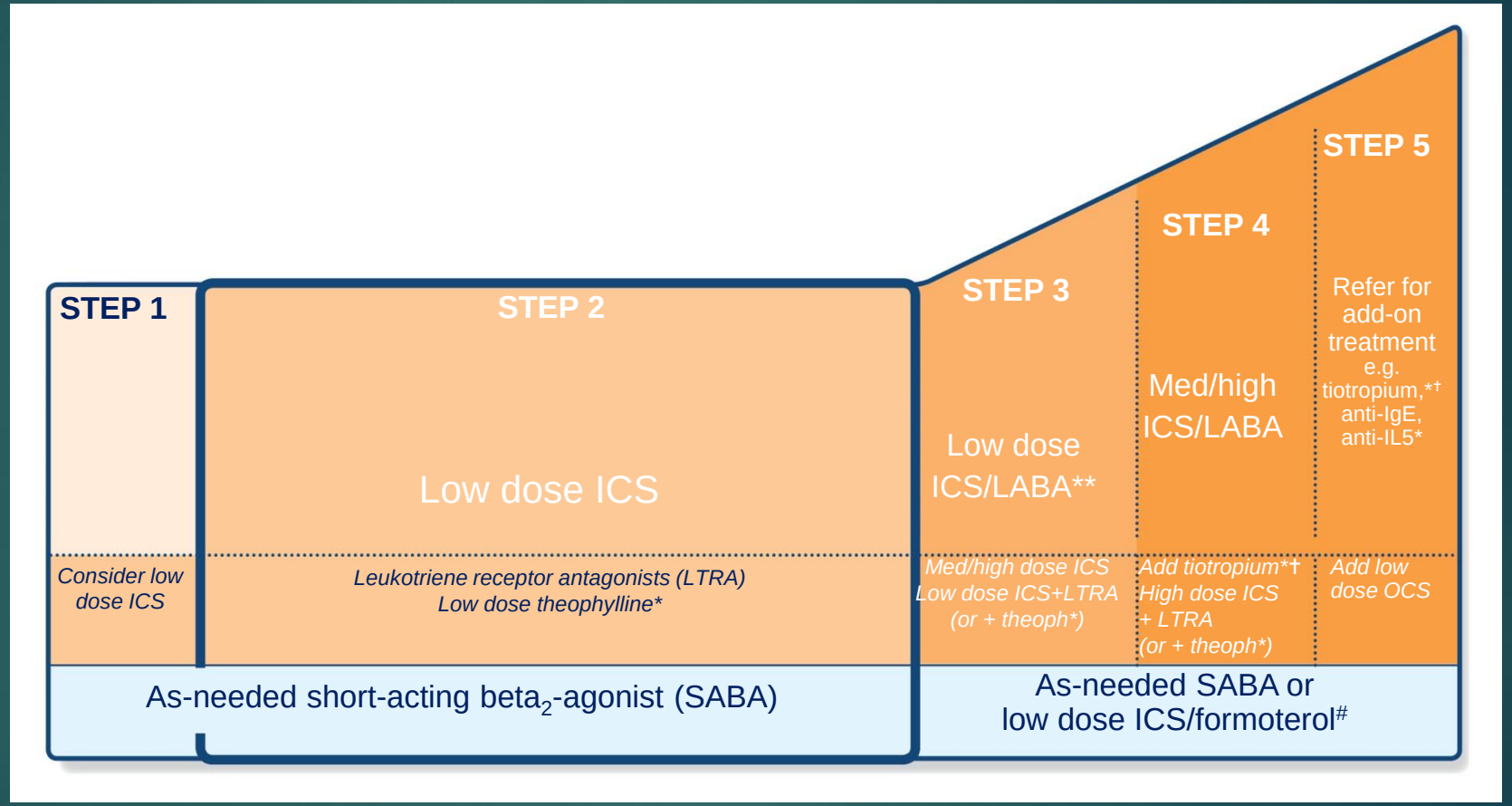


Not for children <12 years
**For children 6-11 years, the preferred Step 3 treatment is medium dose ICS
#For patients prescribed BDP/formoterol or BUD/ formoterol maintenance and reliever therapy
† Tiotropium by mist inhaler is an add-on treatment for patients ≥12 years with a history of exacerbations

Step 1 – as-needed reliever inhaler

- Preferred option: as-needed inhaled short-acting beta$_2$-agonist (SABA)
  - SABAs are highly effective for relief of asthma symptoms
  - However …. there is insufficient evidence about the safety of treating asthma with SABA alone
  - This option should be reserved for patients with infrequent symptoms (less than twice a month) of short duration, and with no risk factors for exacerbations
- Other options
  - Consider adding regular low dose inhaled corticosteroid (ICS) for patients at risk of exacerbations

Step 2 – low-dose controller + as-needed inhaled SABA



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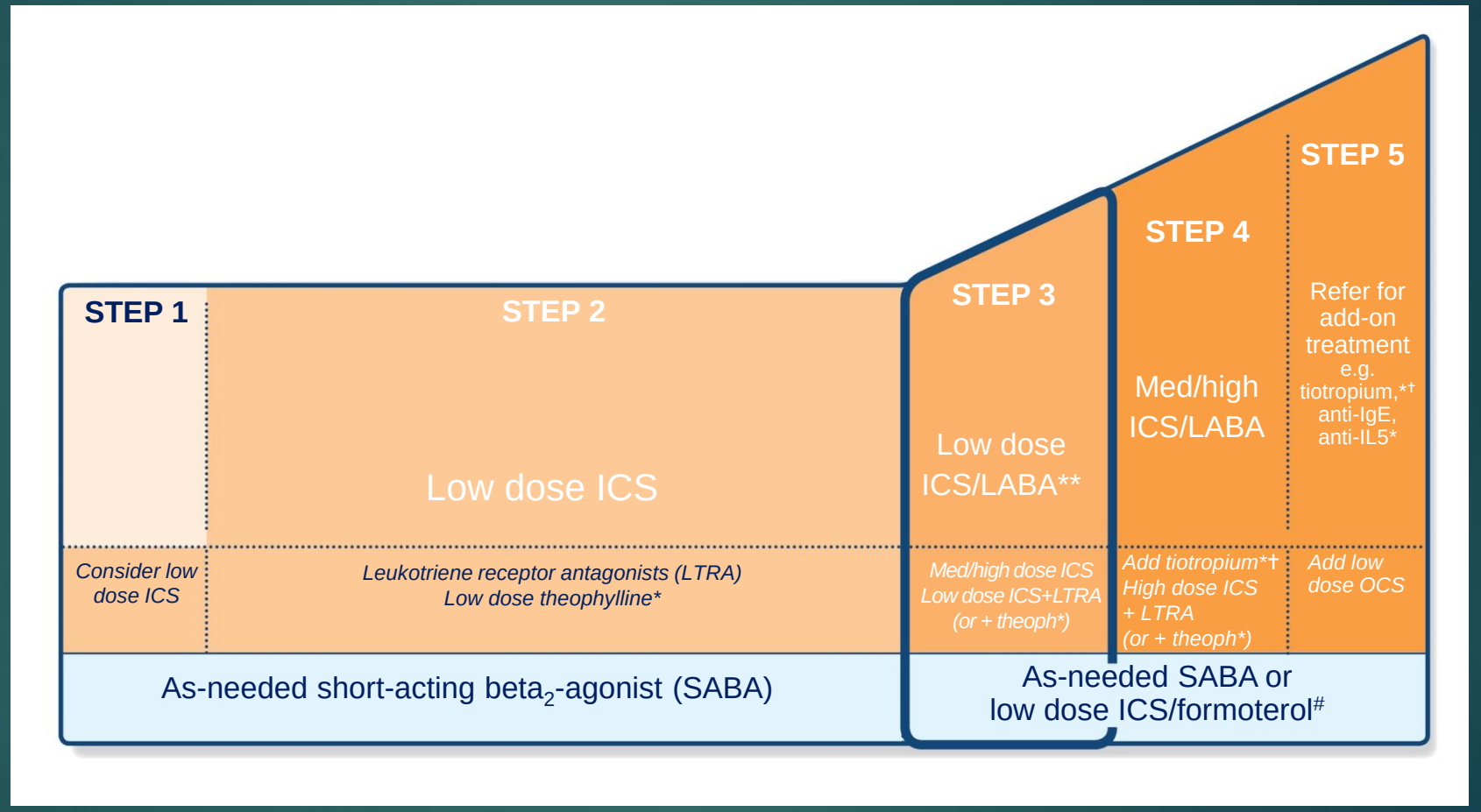
† Tiotropium by mist inhaler is an add-on treatment for patients ≥12 years with a history of exacerbations

Step 2 – Low dose controller + as-needed SABA

- Preferred option: regular low dose ICS with as-needed inhaled SABA
  - Low dose ICS reduces symptoms and reduces risk of exacerbations and asthma-related hospitalization and death
- Other options
  - Leukotriene receptor antagonists (LTRA) with as-needed SABA
    - Less effective than low dose ICS
    - May be used for some patients with both asthma and allergic rhinitis, or if patient will not use ICS
  - Combination low dose ICS/long-acting beta$_2$-agonist (LABA) with as-needed SABA
    - Reduces symptoms and increases lung function compared with ICS
    - More expensive, and does not further reduce exacerbations
  - Intermittent ICS with as-needed SABA for purely seasonal allergic asthma with no interval symptoms
    - Start ICS immediately symptoms commence, and continue for 4 weeks after pollen season ends

Step 3 – one or two controllers + as-needed inhaled reliever



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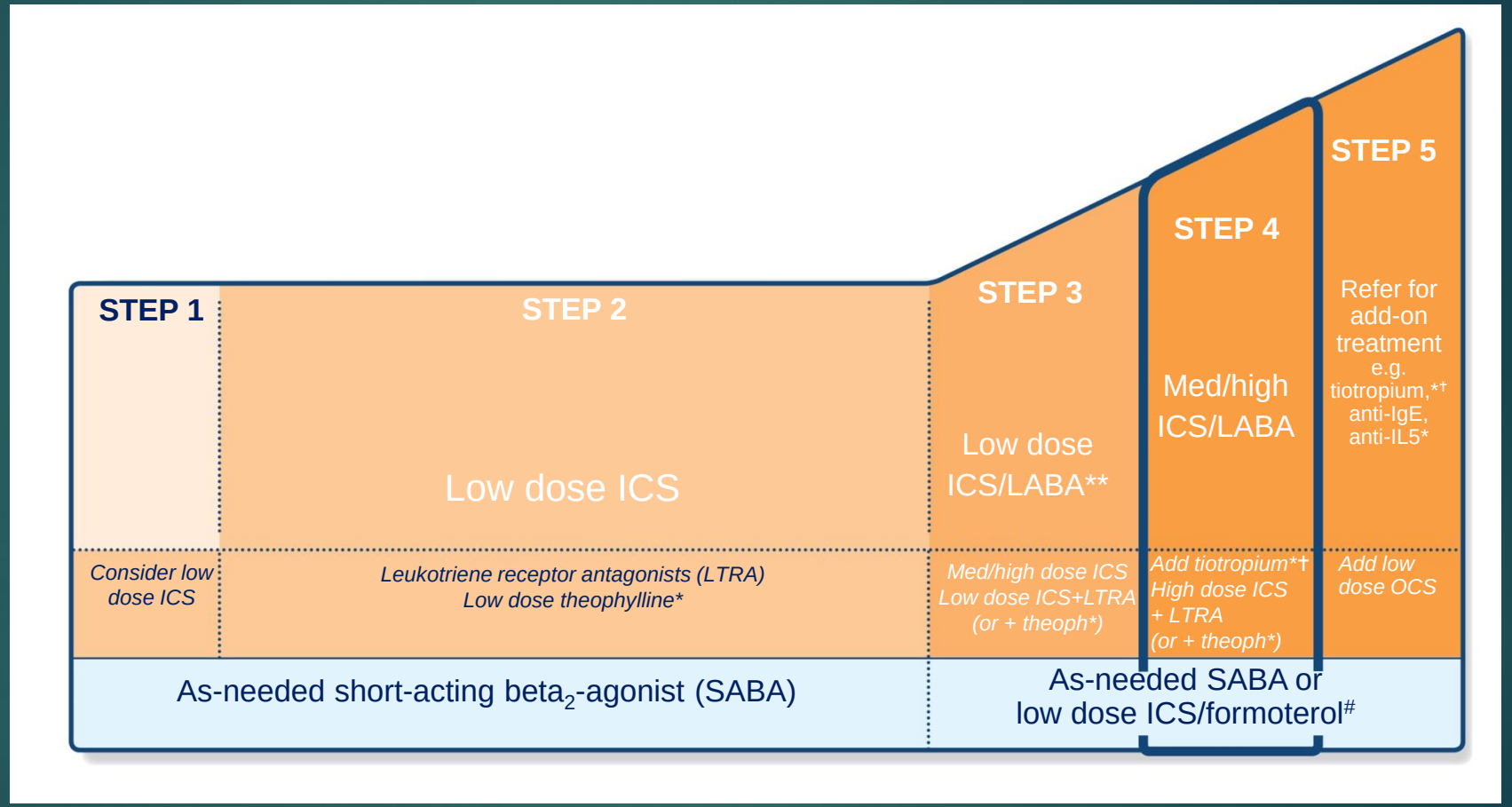
#For patients prescribed BDP/formoterol or BUD/ formoterol maintenance and reliever therapy
† Tiotropium by mist inhaler is an add-on treatment for patients ≥12 years with a history of exacerbations

Step 3 – one or two controllers + as-needed inhaled reliever

- Before considering step-up
  - Check inhaler technique and adherence, confirm diagnosis
- Adults/adolescents: preferred options are either combination low dose ICS/LABA maintenance with as-needed SABA, OR combination low dose ICS/formoterol maintenance and reliever regimen*
  - Adding LABA reduces symptoms and exacerbations and increases FEV_1, while allowing lower dose of ICS
  - In at-risk patients, maintenance and reliever regimen significantly reduces exacerbations with similar level of symptom control and lower ICS doses compared with other regimens
- Children 6-11 years: preferred option is medium dose ICS with as-needed SABA
- Other options
  - Adults/adolescents: Increase ICS dose or add LTRA or theophylline (less effective than ICS/LABA)
  - Adults: consider adding SLIT (see Non-pharmacological interventions)
  - Children 6-11 years – add LABA (similar effect as increasing ICS)

*Approved only for low dose beclometasone/formoterol and low dose budesonide/formoterol

Step 4 – two or more controllers + as-needed inhaled reliever



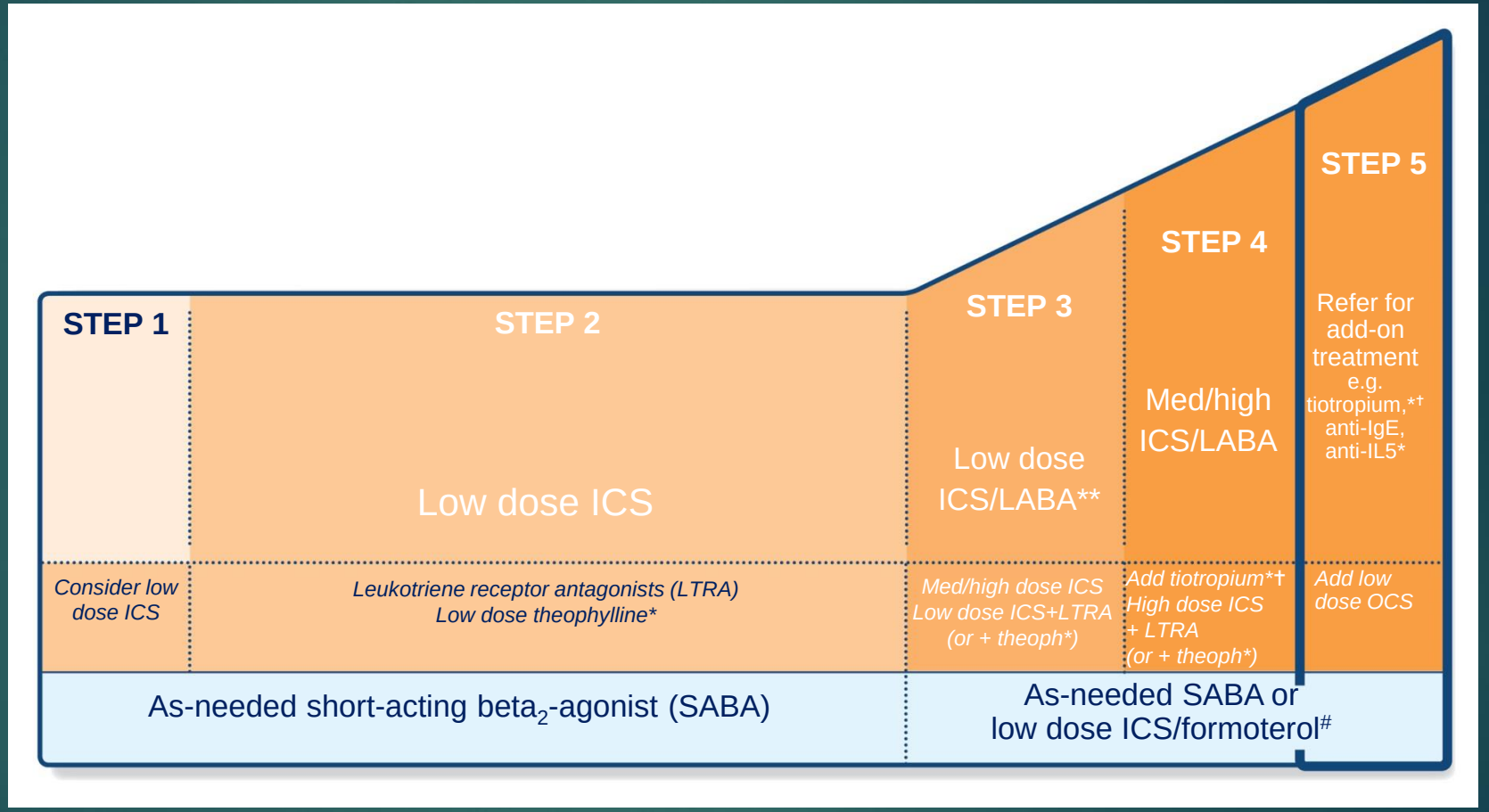
*Not for children <12 years
**For children 6-11 years, the preferred Step 3 treatment is medium dose ICS
#For patients prescribed BDP/formoterol or BUD/ formoterol maintenance and reliever therapy
† Tiotropium by mist inhaler is an add-on treatment for patients ≥12 years with a history of exacerbations

Step 4 – two or more controllers + as-needed inhaled reliever

- Before considering step-up
  - Check inhaler technique and adherence
- Adults or adolescents: preferred option is combination low dose ICS/formoterol as maintenance and reliever regimen*, OR combination medium dose ICS/LABA with as-needed SABA
- Children 6–11 years: preferred option is to refer for expert advice
- Other options (adults or adolescents)
  - Tiotropium by mist inhaler may be used as add-on therapy for patients aged ≥12 years with a history of exacerbations
  - Adults: consider adding SLIT (see Non-pharmacological therapy)
  - Trial of high dose combination ICS/LABA, but little extra benefit and increased risk of side-effects
  - Increase dosing frequency (for budesonide-containing inhalers)
  - Add-on LTRA or low dose theophylline

*Approved only for low dose beclometasone/formoterol and low dose budesonide/formoterol

Step 5 – higher level care and/or add-on treatment



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#For patients prescribed BDP/formoterol or BUD/ formoterol maintenance and reliever therapy
† Tiotropium by mist inhaler is an add-on treatment for patients ≥12 years with a history of exacerbations

Step 5 – higher level care and/or add-on treatment

- Preferred option is referral for specialist investigation and consideration of add-on treatment
  - If symptoms uncontrolled or exacerbations persist despite Step 4 treatment, check inhaler technique and adherence before referring
  - Add-on tiotropium for patients ≥12 years with history of exacerbations
  - Add-on anti-IgE (omalizumab) for patients with severe allergic asthma
  - Add-on anti-IL5 (mepolizumab (SC) or reslizumab (IV)) for severe eosinophilic asthma (≥12 yrs)
- Other add-on treatment options at Step 5 include:
  - Sputum-guided treatment: this is available in specialized centers; reduces exacerbations and/or corticosteroid dose
  - Add-on low dose oral corticosteroids (≤7.5mg/day prednisone equivalent): this may benefit some patients, but has significant systemic side-effects. Assess and monitor for osteoporosis
  - See ERS/ATS Severe Asthma Guidelines (Chung et al, ERJ 2014) for more detail

Low, medium and high dose inhaled corticosteroids Adults and adolescents (≥12 years)

Inhaled corticosteroid	Total daily dose (mcg)		
	Low	Medium	High
Beclometasone dipropionate (CFC)	200–500	>500–1000	>1000
Beclometasone dipropionate (HFA)	100–200	>200–400	>400
Budesonide (DPI)	200–400	>400–800	>800
Ciclesonide (HFA)	80–160	>160–320	>320
Fluticasone furoate (DPI)	100	n.a.	200
Fluticasone propionate (DPI or HFA)	100–250	>250–500	>500
Mometasone furoate	110–220	>220–440	>440
Triamcinolone acetonide	400–1000	>1000–2000	>2000

- This is not a table of equivalence, but of estimated clinical comparability
- Most of the clinical benefit from ICS is seen at low doses
- High doses are arbitrary, but for most ICS are those that, with prolonged use, are associated with increased risk of systemic side-effects

Low, medium and high dose inhaled corticosteroids Children 6–11 years

Inhaled corticosteroid	Total daily dose (mcg)		
	Low	Medium	High
Beclometasone dipropionate (CFC)	100–200	>200–400	>400
Beclometasone dipropionate (HFA)	50–100	>100–200	>200
Budesonide (DPI)	100–200	>200–400	>400
Budesonide (nebules)	250–500	>500–1000	>1000
Ciclesonide (HFA)	80	>80–160	>160
Fluticasone furoate (DPI)	n.a.	n.a.	n.a.
Fluticasone propionate (DPI)	100–200	>200–400	>400
Fluticasone propionate (HFA)	100–200	>200–500	>500
Mometasone furoate	110	≥220–<440	≥440
Triamcinolone acetonide	400–800	>800–1200	>1200

- This is not a table of equivalence, but of estimated clinical comparability
- Most of the clinical benefit from ICS is seen at low doses
- High doses are arbitrary, but for most ICS are those that, with prolonged use, are associated with increased risk of systemic side-effects

Indications for considering referral, where available

- Difficulty confirming the diagnosis of asthma
  - Symptoms suggesting chronic infection, cardiac disease etc
  - Diagnosis unclear even after a trial of treatment
  - Features of both asthma and COPD, if in doubt about treatment
- Suspected occupational asthma
  - Refer for confirmatory testing, identification of sensitizing agent, advice about eliminating exposure, pharmacological treatment
- Persistent uncontrolled asthma or frequent exacerbations
  - Uncontrolled symptoms or ongoing exacerbations or low FEV_1 despite correct inhaler technique and good adherence with Step 4
  - Frequent asthma-related health care visits
- Risk factors for asthma-related death
  - Near-fatal exacerbation in past
  - Anaphylaxis or confirmed food allergy with asthma

Indications for considering referral, where available

- Significant side-effects (or risk of side-effects)
  - Significant systemic side-effects
  - Need for oral corticosteroids long-term or as frequent courses
- Symptoms suggesting complications or sub-types of asthma
  - Nasal polyposis and reactions to NSAIDS (may be aspirin exacerbated respiratory disease)
  - Chronic sputum production, fleeting shadows on CXR (may be allergic bronchopulmonary aspergillosis)
- Additional reasons for referral in children 6-11 years
  - Doubts about diagnosis, e.g. symptoms since birth
  - Symptoms or exacerbations remain uncontrolled
  - Suspected side-effects of treatment, e.g. growth delay
  - Asthma with confirmed food allergy

Guided asthma self-management and skills training

Essential components are:

- Skills training to use inhaler devices correctly
- Encouraging adherence with medications, appointments
- Asthma information
- Guided self-management support
  - Self-monitoring of symptoms and/or PEF
  - Written asthma action plan
  - Regular review by a health care provider

‘Guided self-management education’

- Highly effective in improving asthma outcomes
  - Reduced hospitalizations, ED visits, symptoms, night waking, time off work, improved lung function and quality of life
- Three essential components:
  - Self-monitoring of symptoms and/or PEF
  - Written asthma action plan
    - Describe how to recognize and respond to worsening asthma
    - Individualize the plan for the patient’s health literacy and autonomy
    - Provide advice about a change in ICS and how/when to add OCS
    - If using PEF, base action plan on personal best rather than predicted
  - Regular medical review

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Management of severe asthma

- Optimize dose of ICS/LABA
  - Complete resistance to ICS is rare
  - Consider therapeutic trial of higher dose
- Consider low dose maintenance oral corticosteroids
  - Monitor for and manage side-effects, including osteoporosis
- Add-on treatments without phenotyping
  - Tiotropium - reduces exacerbations (history of exacerbations, age ≥12 years)
  - Theophylline, LTRA – limited benefit

Management of Severe Asthma

- Phenotype-guided treatment
  - Severe allergic asthma: add-on omalizumab (anti-IgE)
  - Severe eosinophilic asthma: add-on mepolizumab or reslizumab (anti-IL5)
  - Sputum-guided treatment to reduce exacerbations and/or steroid dose
  - Aspirin-exacerbated respiratory disease: consider add-on LTRA
- Non-pharmacological interventions
  - Consider bronchial thermoplasty for selected patients
  - Comprehensive adherence-promoting program
- For detailed guidelines, see Chung *et al*, ERJ 2014

Definitions: Difficult to Treat vs Refractory Asthma

- Difficult to treat asthma
  - Patient is capable of control with currently available treatments
    - Poor adherence
    - Psycho-social issues
    - Socioeconomic issues
    - Cultural barriers
- Refractory Asthma
  - Poor control of asthma despite compliance with high dose ICS, other controllers or can maintain control only with OCS

Refractory Asthma

- Alternative diagnosis excluded
- Comorbidities have been treated
- Triggers have been removed
- Compliance with therapy has been checked
  - Remain poorly controlled, frequent or severe exacerbations, despite high intensity therapy* or require OCS for control
    - *EPR-3 Step 5/6
    - *GINA step 5

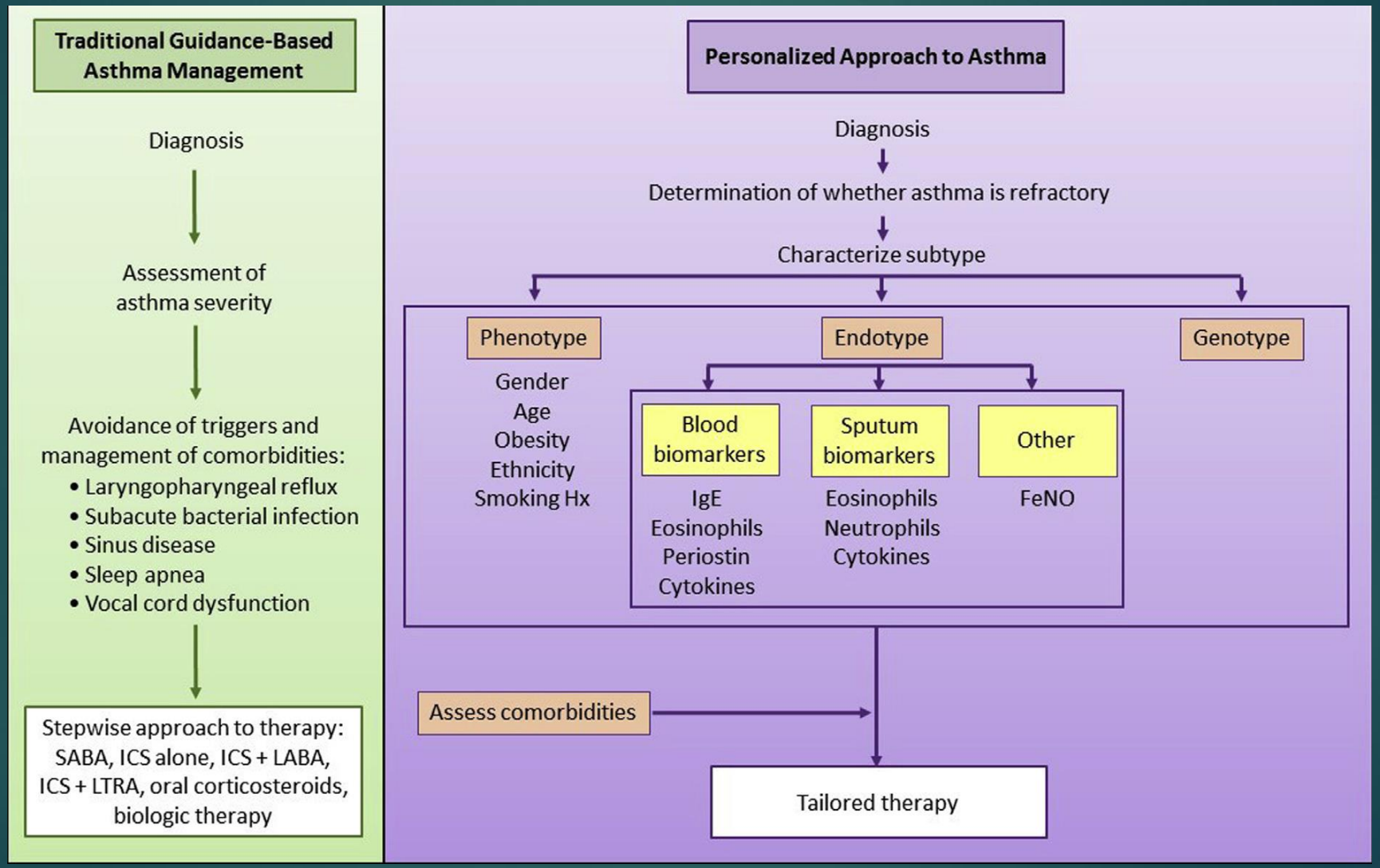
Bei EH, et al, Thorax, 2011;66:910-17

Refractory Asthma

- Difficult to treat asthma
  - 17.4%
- Refractory Asthma
  - 3.6%
- ATS Workshop(2000): 5% of patients with asthma have high medication requirements to maintain good control or have persistent symptoms, airflow obstruction or exacerbations despite high dose medications
  - High HCU, morbidity,mortality and cost associated with asthma care

Hekking PP, JACI, 2015;135:896-902

Approaches to Asthma Management



Katial RK, JACI in Prac,2017;5:S1-S14

SARP Clusters

- Early Onset
  - Clusters 1, 2 and 4 (mild, moderate & severe)
  - Atopic
  - Cluster 4-Lower lung function, more reversible
  - HCU (46% OCS $\geq$ 3, 23% hospitalization)
- Late Onset
  - Cluster 3 and 5
  - Cluster 5 fixed obstruction, high HCU
  - Cluster 3 very late onset, obese

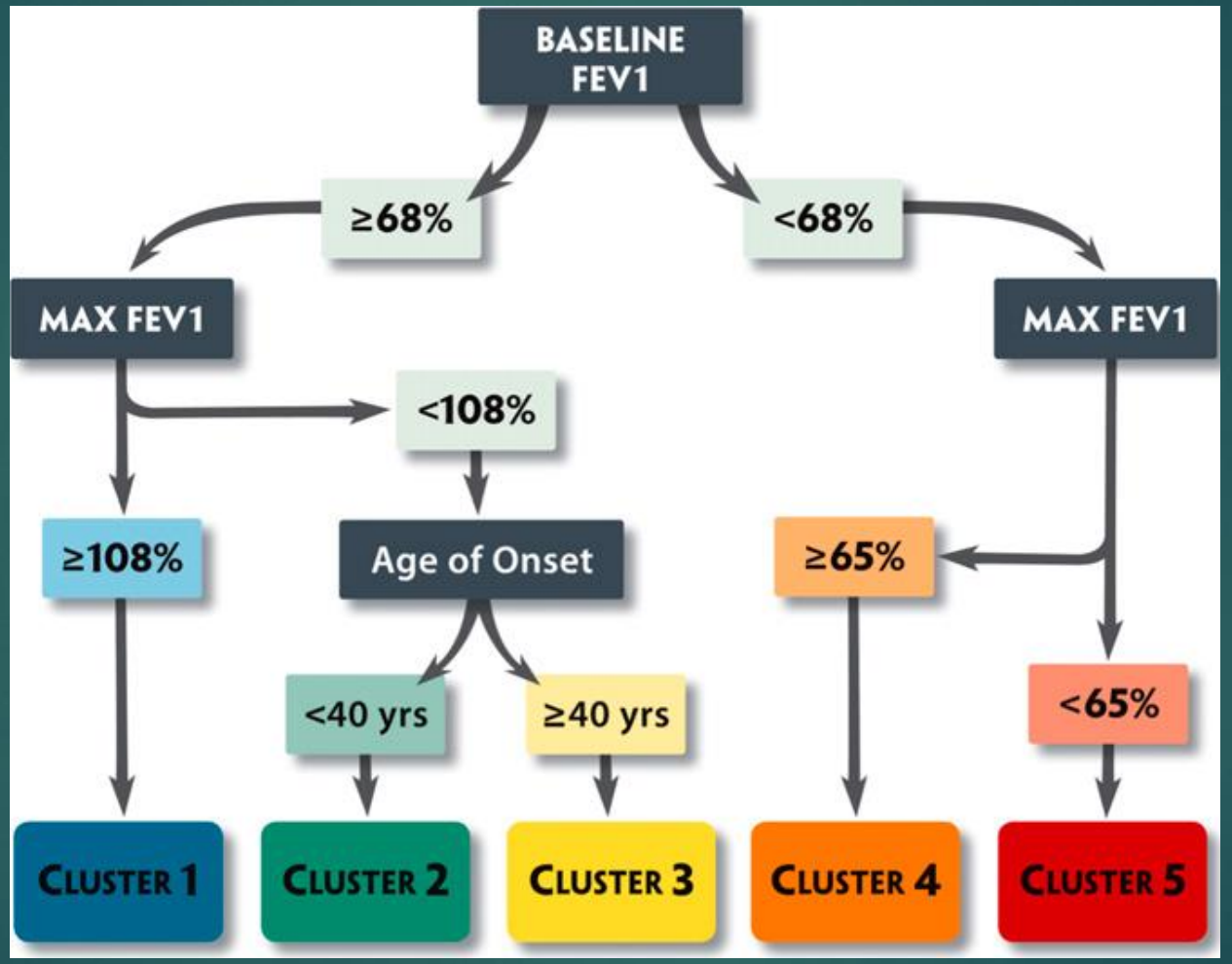
Moore WC, Annals ATS,2013;10:S118-124

SARP Clusters

	Spectrum of Early-Onset Allergic Asthma			Spectrum of Late-Onset Adult Asthma	
	Mild	Moderate	Severe	Fixed Airflow	Very Late Onset, Obese
	Cluster 1	Cluster 2	Cluster 4	Cluster 5	Cluster 3
% of all subjects in group	15	44	17	16	8
Severe, %	<25		70–80		50
Current age, decades	20s	20–30s	30–40s	40–50s	40–50s
African American, %	30	30	30	20	20
Female sex, %	80	67	53	63	71
Obese with BMI > 30, %	24	31	44		>50
Asthma onset					
Age, median (IQR), yr*	9 (5–17)	7 (2–18)	4 (1–13)	20 (5–32)	41 (33–49)
Relevant life events	School aged	Preschool–school aged	Toddler–school-aged	Teens–adults	Adults
Asthma duration, yr	10–15	15–25	>20		<10
Atopy measures					
⩾1 pos SPT, %	85	78	83	66	64
Baseline FEV_1% predicted*	103 (97–109)	83 (76–90)	59 (48–66)	44 (32–52)	75 (67–81)
Maximal FEV_1% predicted*	113 (108–117)	95 (88–99)	77 (68–83)	57 (48–68)	82 (78–90)
Summary Lung Function	Normal	Reversible to normal	Obstructed, more reversible	Obstructed, less reversible	Borderline normal
Medications, % subjects					
High-dose ICS	10	28	63	78	49
OCS	11	10	39	47	17
Taking ⩾3 controllers	19	29	56	67	54
Health care utilization, past yr, % subjects					
⩾3 exacerbations with OCS	11	19	46	42	36
Hospitalization for asthma	7	9	23	28	15

Moore WC, Annals ATS,2013;10:S118-124

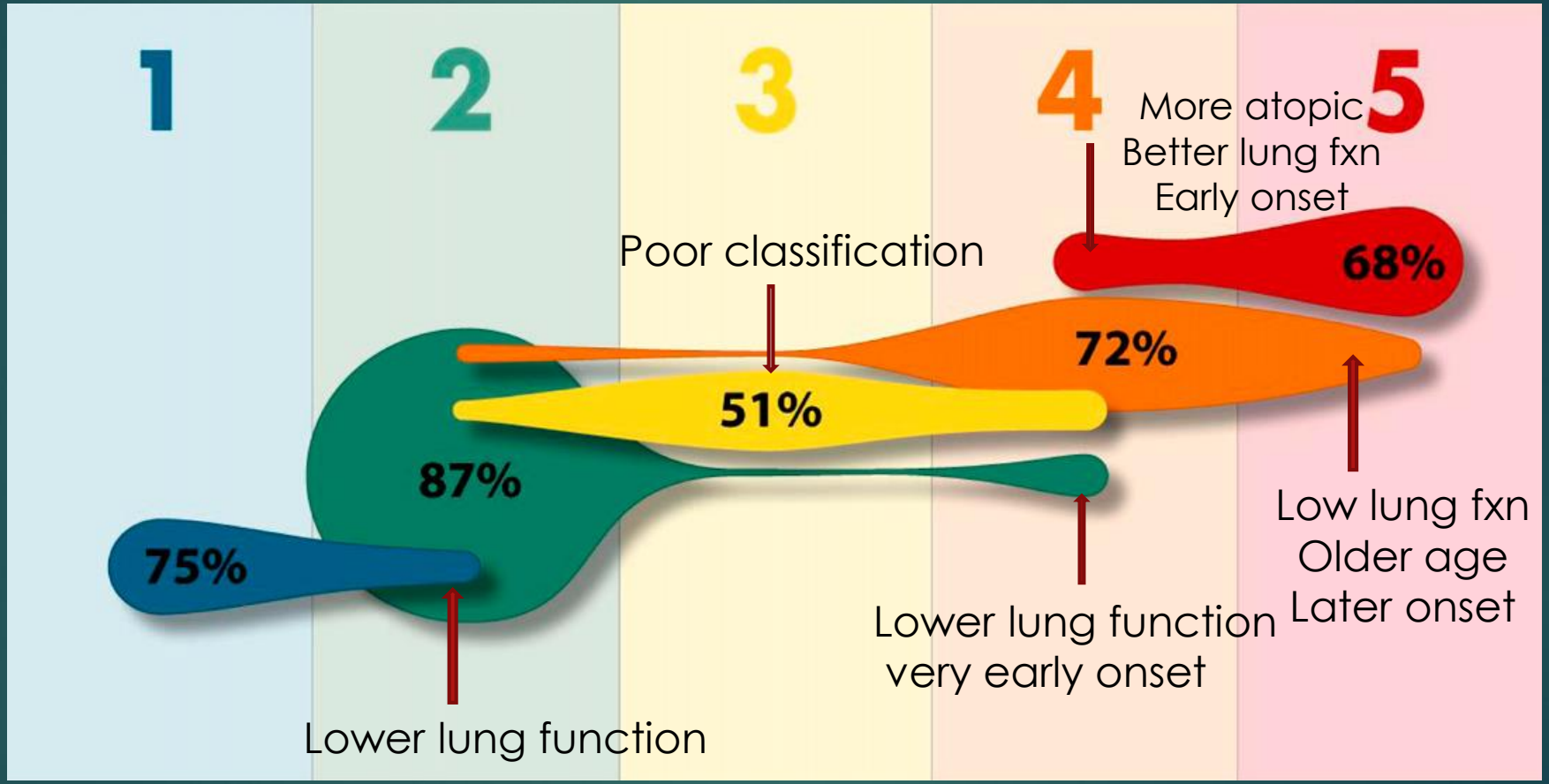
SARP 3 Variable Assignment



Baseline FEV1(BD withhold), Max FEV1 (6-8 puffs albuterol), age of onset

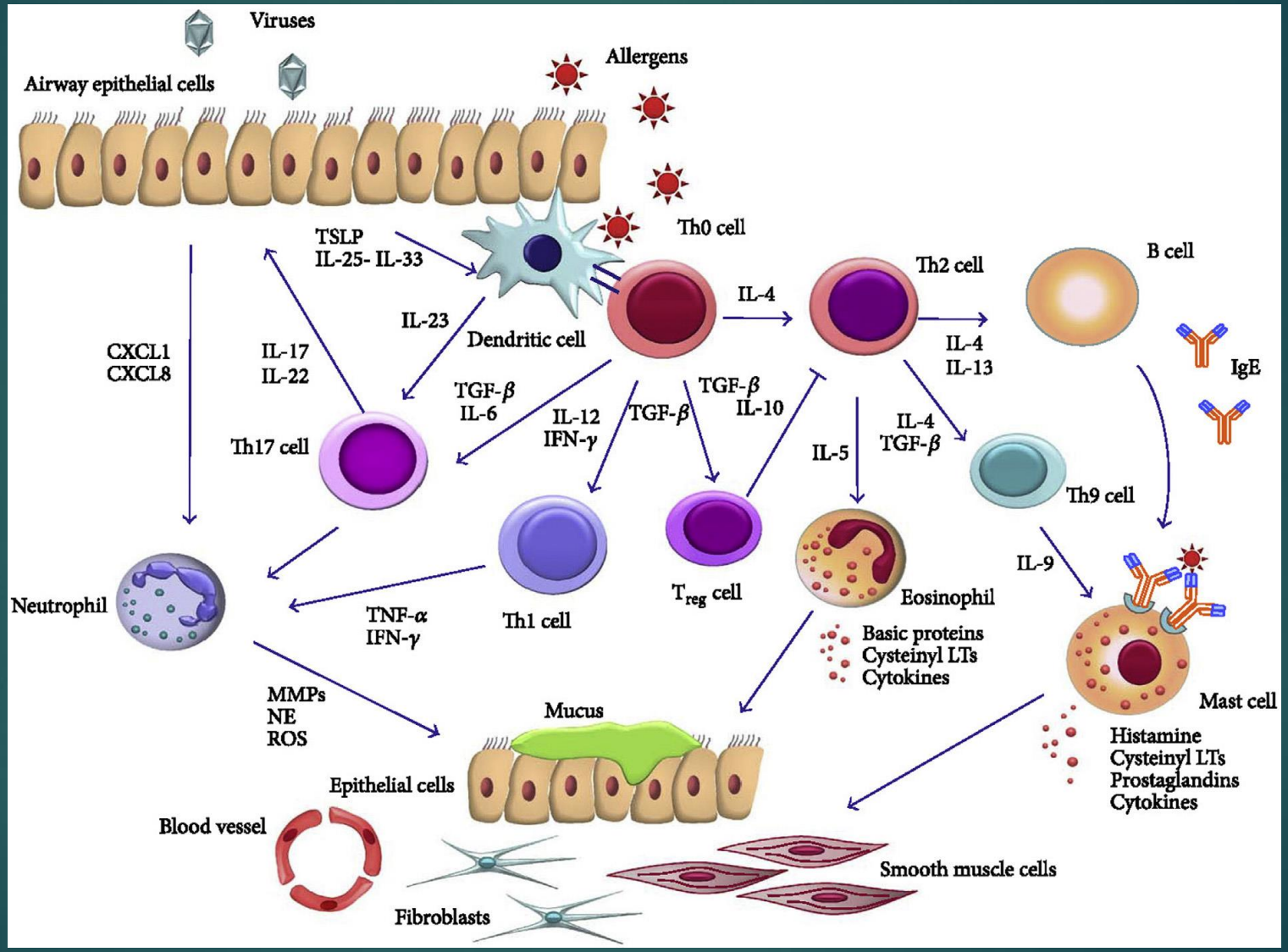
Moore WC, Annals ATS,2013;10:S118-124

Misclassification



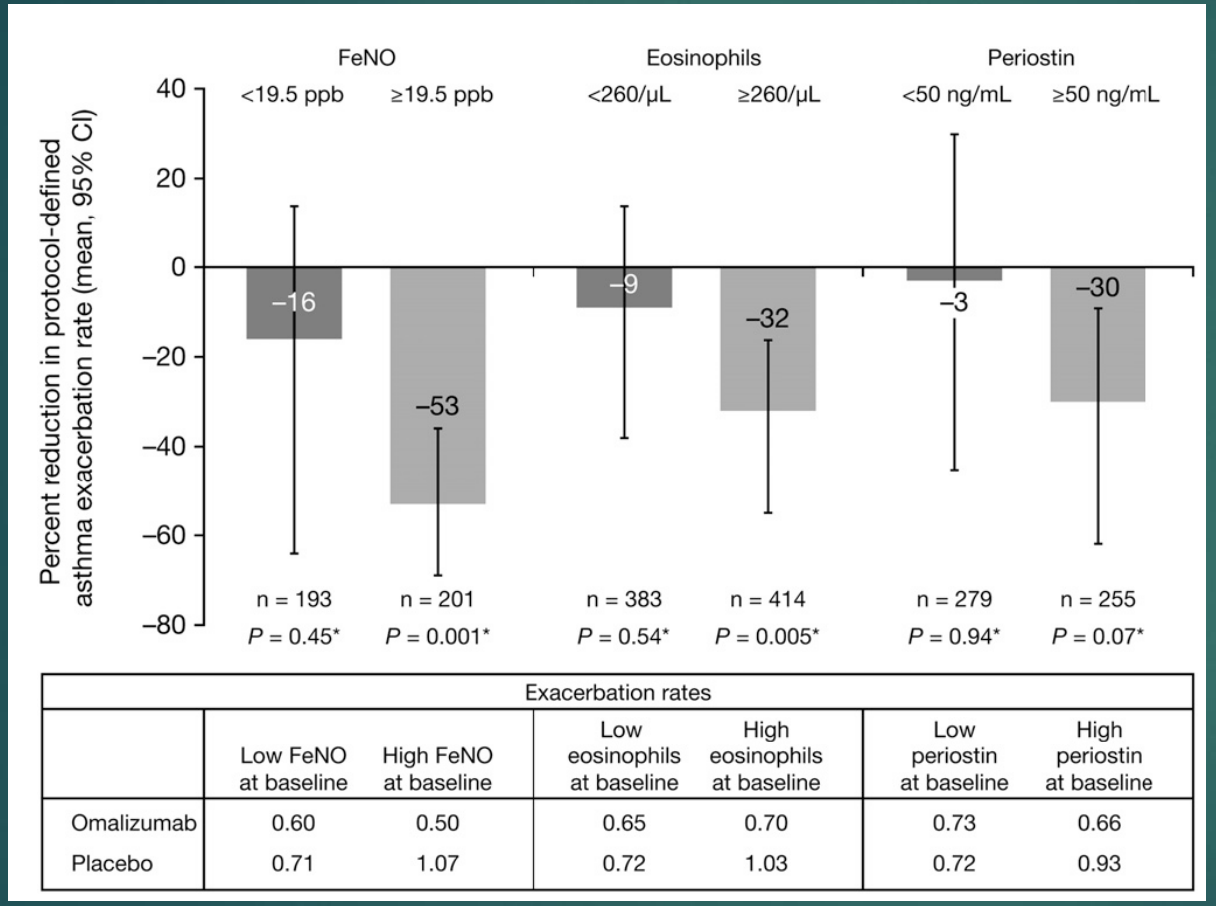
Moore WC, Annals ATS,2013;10:S118-124

Pathobiology

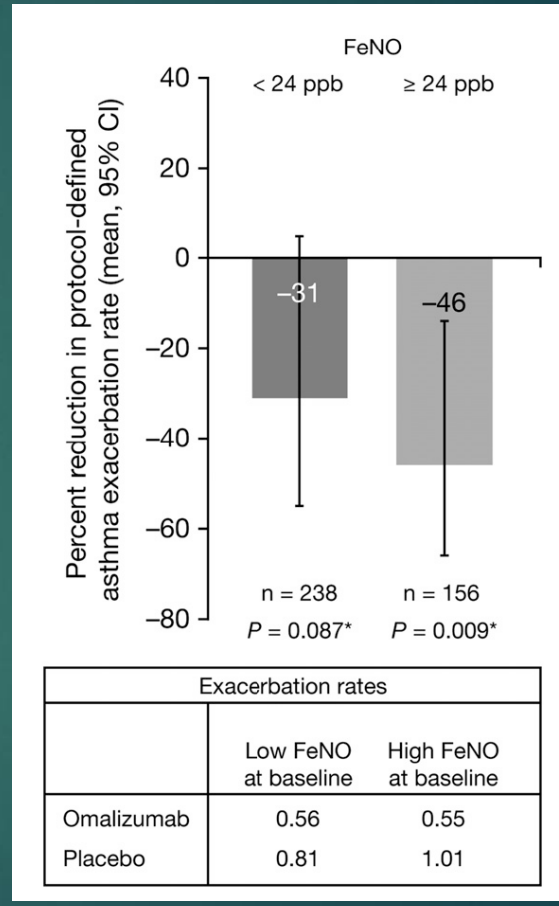


Katial RK, JACI in Prac,2017;5:S1-S14

Biomarkers of Response



Exacerbation rates						
	Low FeNO at baseline	High FeNO at baseline	Low eosinophils at baseline	High eosinophils at baseline	Low periostin at baseline	High periostin at baseline
Omalizumab	0.60	0.50	0.65	0.70	0.73	0.66
Placebo	0.71	1.07	0.72	1.03	0.72	0.93



Exacerbation rates		
	Low FeNO at baseline	High FeNO at baseline
Omalizumab	0.56	0.55
Placebo	0.81	1.01

Asthma exacerbation rates in high and low biomarker groups; P values for omalizumab vs placebo for each biomarker subgroup

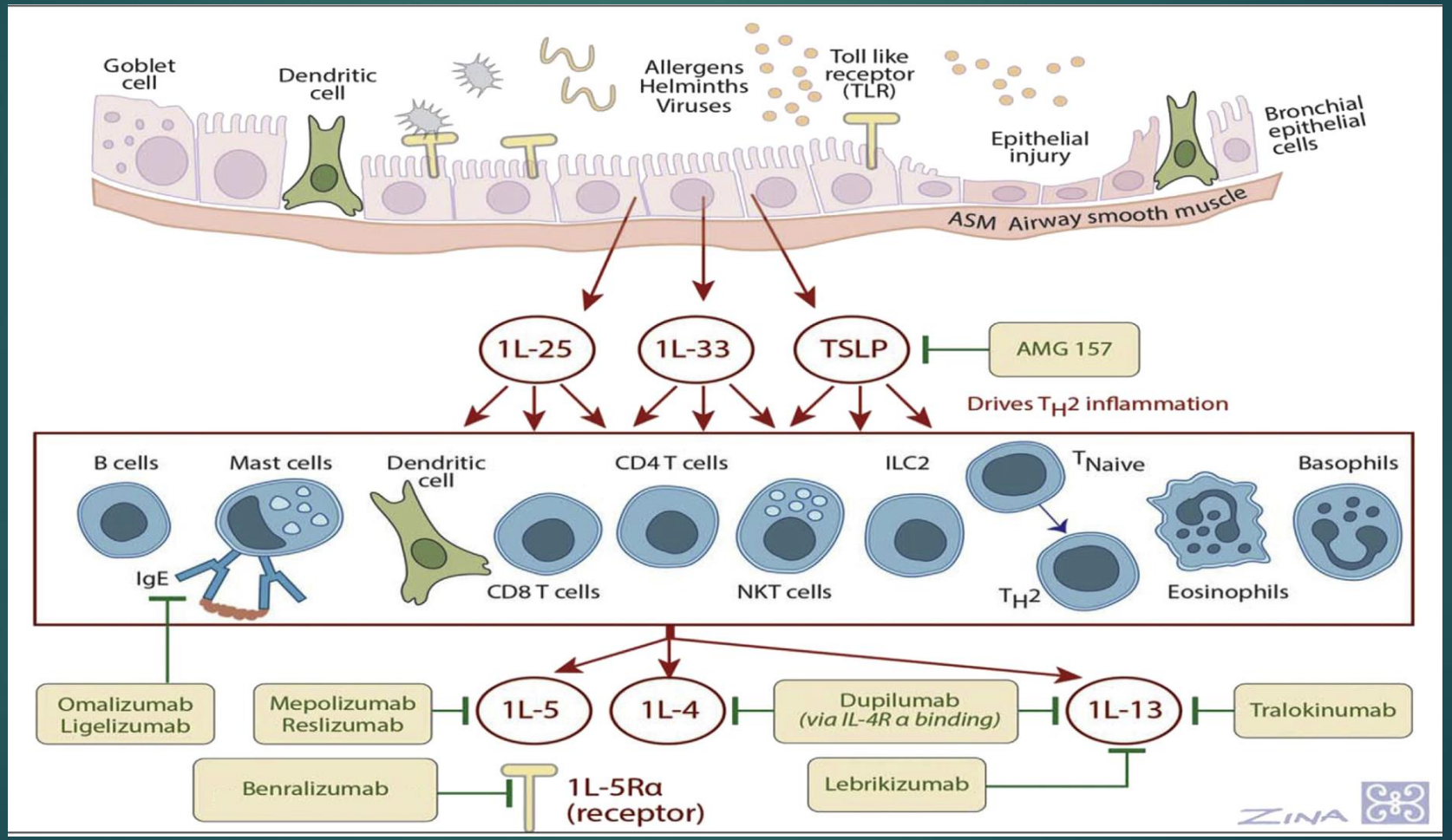
Hanania NA Am J Respir Crit Care Med 2013;187:804-11

Biomarkers Summary

- High Th2 biomarkers
  - FeNO (>24 ppb)
  - Eosinophils (>260/uL)
  - Periostin (>50 ng/mL)
- Significant reduction in asthma exacerbations compared to subjects with biomarkers below the cut offs

Hanania NA Am J Respir Crit Care Med 2013;187:804-11

Targets in Type2 Inflammation



Katial RK, JACI in Prac,2017;5:S1-S14

Anti-eosinophil strategies

Drug	Status	Dosing	Frequency	Route	Eos Cutoff	Exac Rate Red	FEV1 change
mepolizumab	A	100 mg	Q4 wks	SC	150/uL or 300	53%	98ml
reslizumab	A	3mg/kg	Q 4 wks	IV	400/uL	50-59%	90-126 ml
benralizumab	P	30 mg	Q 4 or Q 8wks	SC	300/uL	28-51%	106-159 ml

Katial RK, JACI in Prac,2017;5:S1-S14

Thank You

Questions?

http://ginasthma.org/2017-gina-report-global-strategy-for-asthma-management-and-prevention/
http://ginasthma.org/2017-pocket-guide-for-asthma-management-and-prevention/