ASTHMA -UPDATE-

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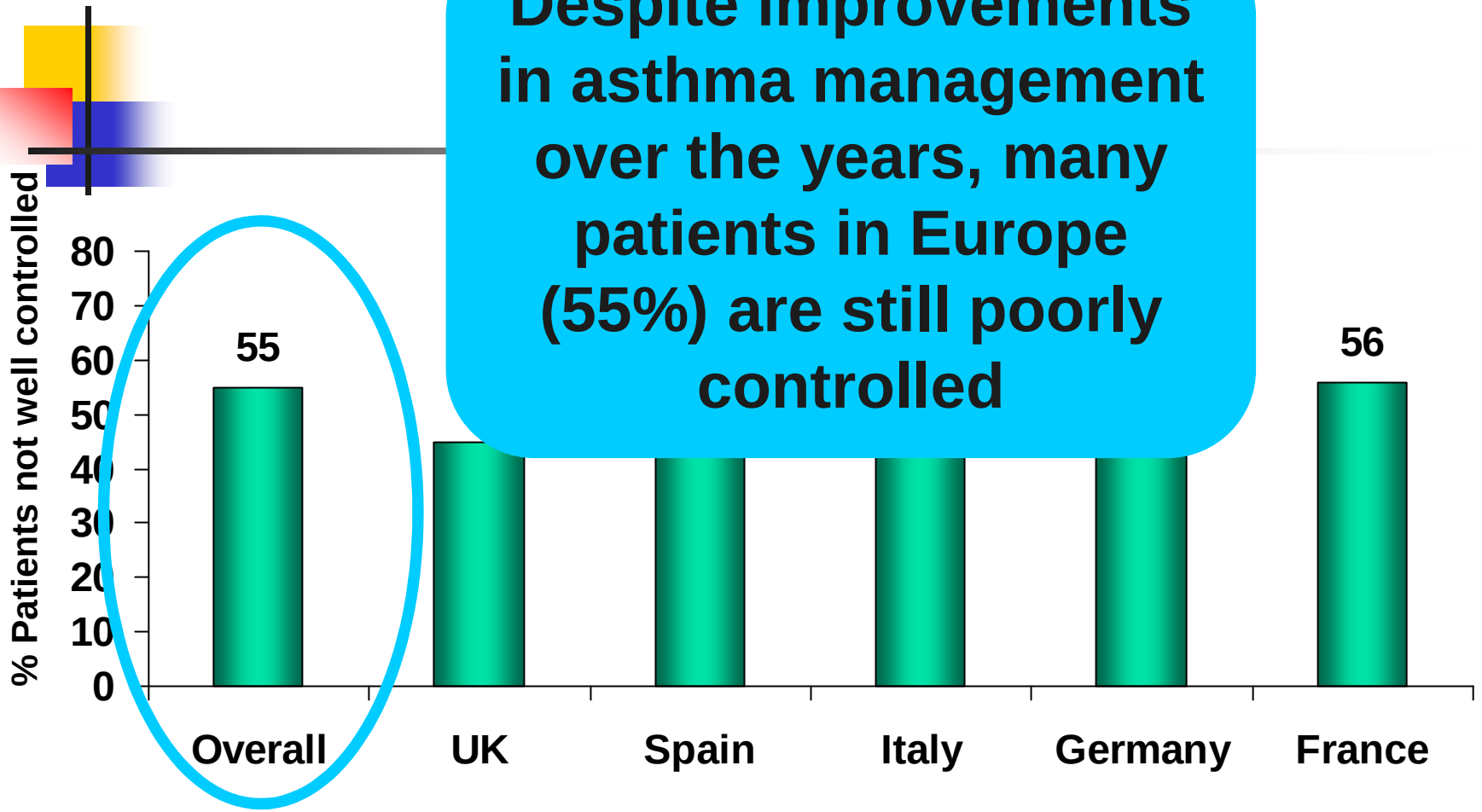
How good is the "world" at treating asthma?

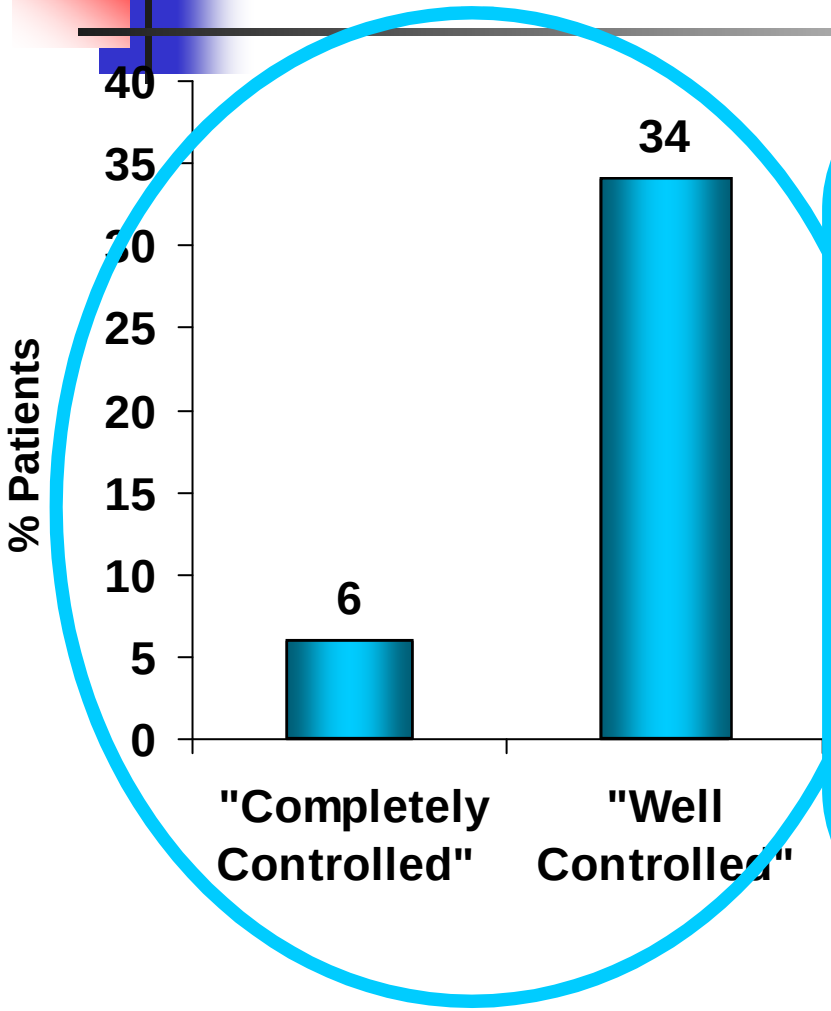
A. Excellent
B. Very good
C. Good
D. OK
E. Poor
F. Abysmal

Despite improvements in asthma management over the years, many patients in Europe (55%) are still poorly controlled



NHWS: A population-based cross-sectional survey conducted in 2006 in 2337 patients diagnosed with asthma in France (n=476), Germany (n=486), Italy (n=223), Spain (n=227) and the UK (n=915)

Patients overestimate their asthma control



40% of Not Well-Controlled patients consider themselves “Well” or “Completely Controlled”

Burden of Asthma

- Asthma has impacted patients in Gulf & Near East:
  - 55% used rescue medications
  - 68% had daytime symptoms
  - 51% missed school
  - 52% awakened at night
  - 77% had Exacerbations

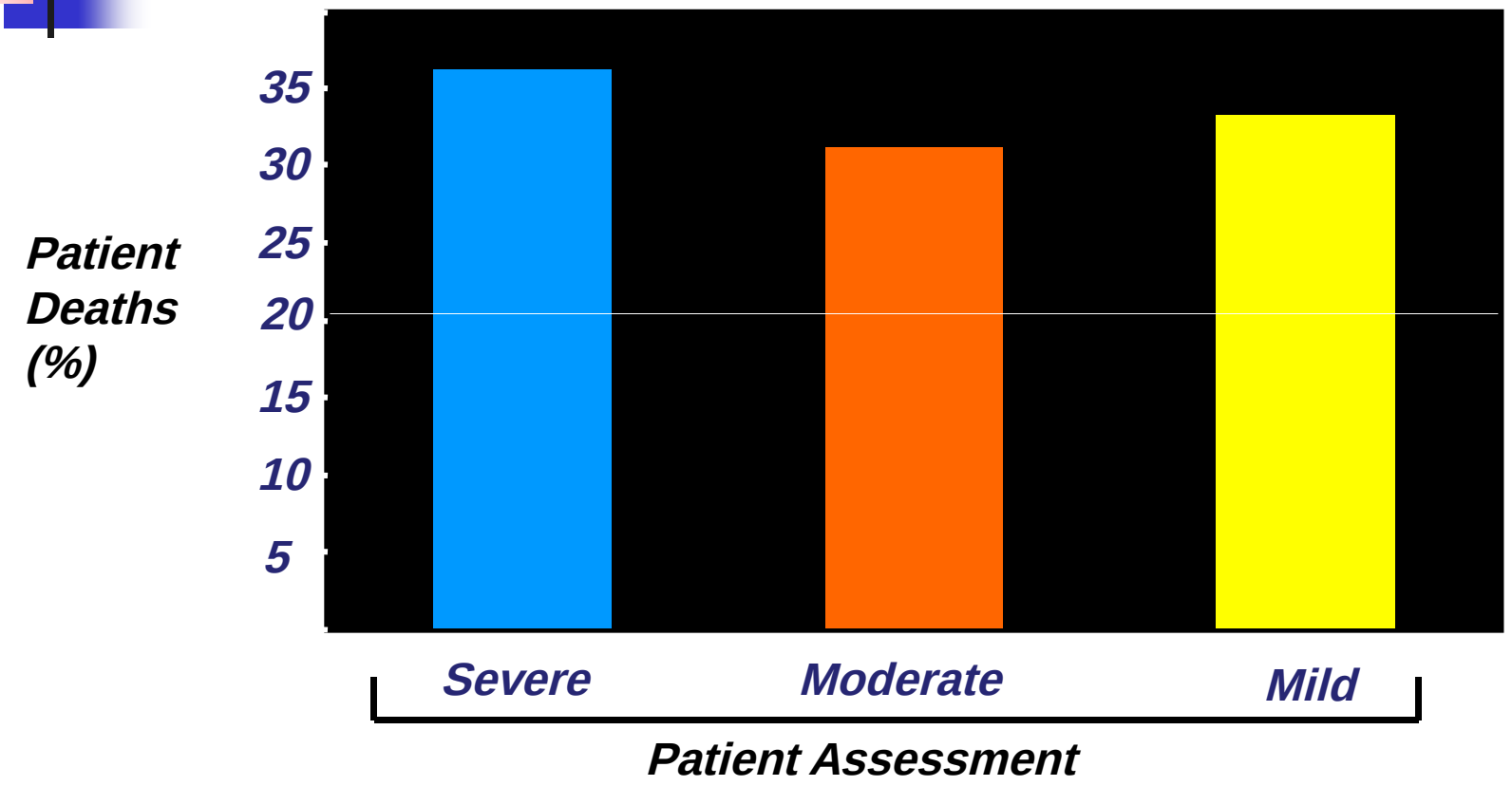
Khadadah M, et al., Asthma Insights and Reality in Gulf and the Near East. Int J Tuber Lung Dis 2009;13(8):1015-1022

Burden of Asthma

- Affect as many as 339 million people worldwide.
- Kills around 1000 people every day.
- Mainly in developing countries.
- Most preventable

According to latest report from the global Asthma network 23 may 2018

Pediatric Asthma Deaths: Mild Patients Are Also at Risk



Findings from a cohort study reviewing all pediatric asthma-related deaths (n=51) in the Australian state of Victoria from 1986 to 1989.

Robertson et al. Pediatr Pulmonol. 1992;13:95-100.

Mild Patients Are Also at Risk

- Patients with apparently mild asthma are at risk of serious adverse events
  - 30–37% of adults with acute asthma
  - 16% of patients with near-fatal asthma
  - 15–20% of adults dying of asthma

  had symptoms less than weekly in previous 3 months *(Dusser, Allergy 2007)*

GINA

The BTS / SIGN British Guideline in the Management of Asthma

GINA

- GINA was launched in 1993 as a collaboration between

National Heart, Lung and Blood institute

National institutes of health

WHO

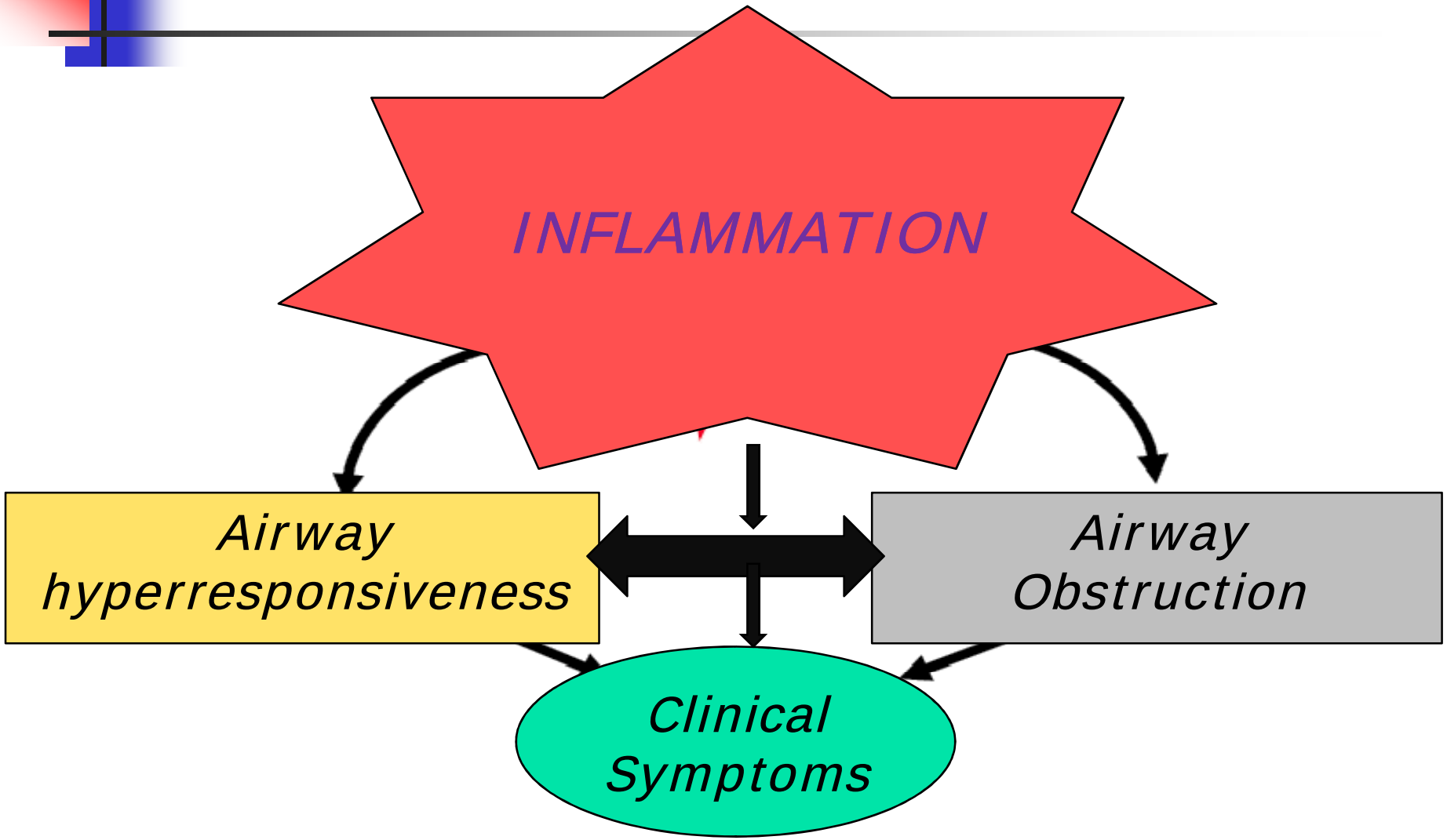
GINA

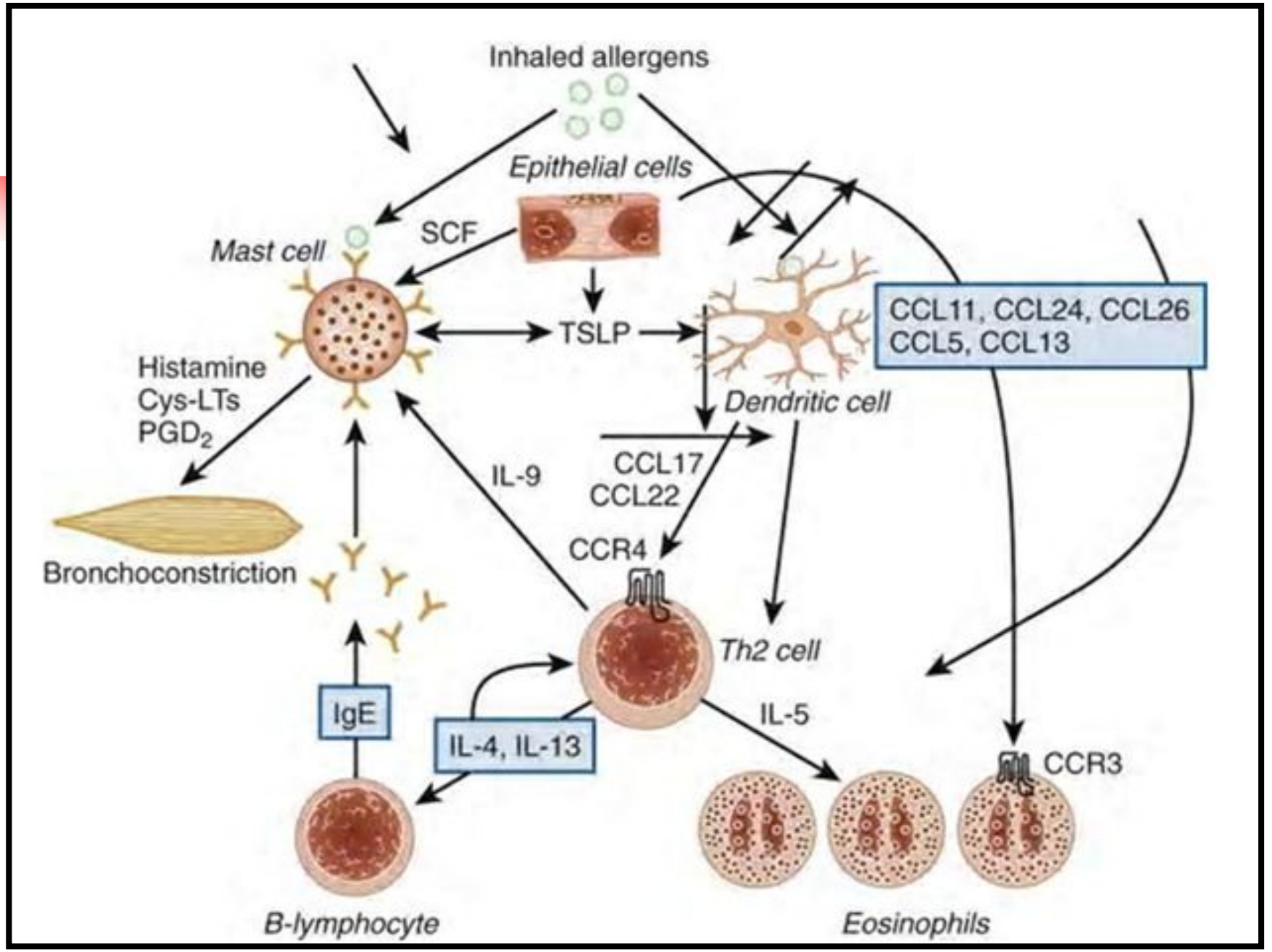
- The Global Initiative for Asthma (GINA) is a medical guidelines organisation which works with public health officials and health care professionals globally to reduce asthma prevalence, morbidity, and mortality.

Definition

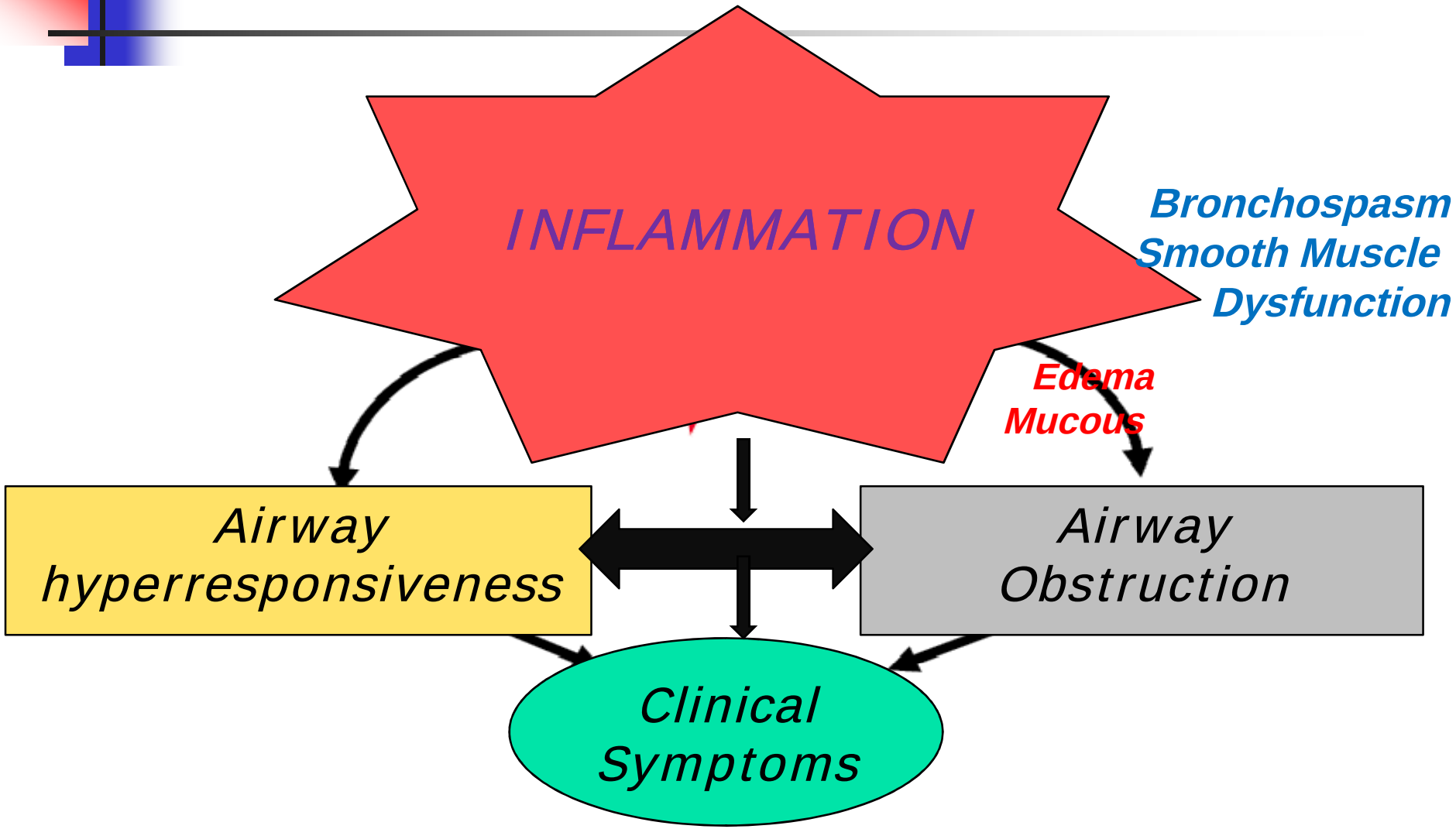
- Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation.

Asthma Pathophysiology

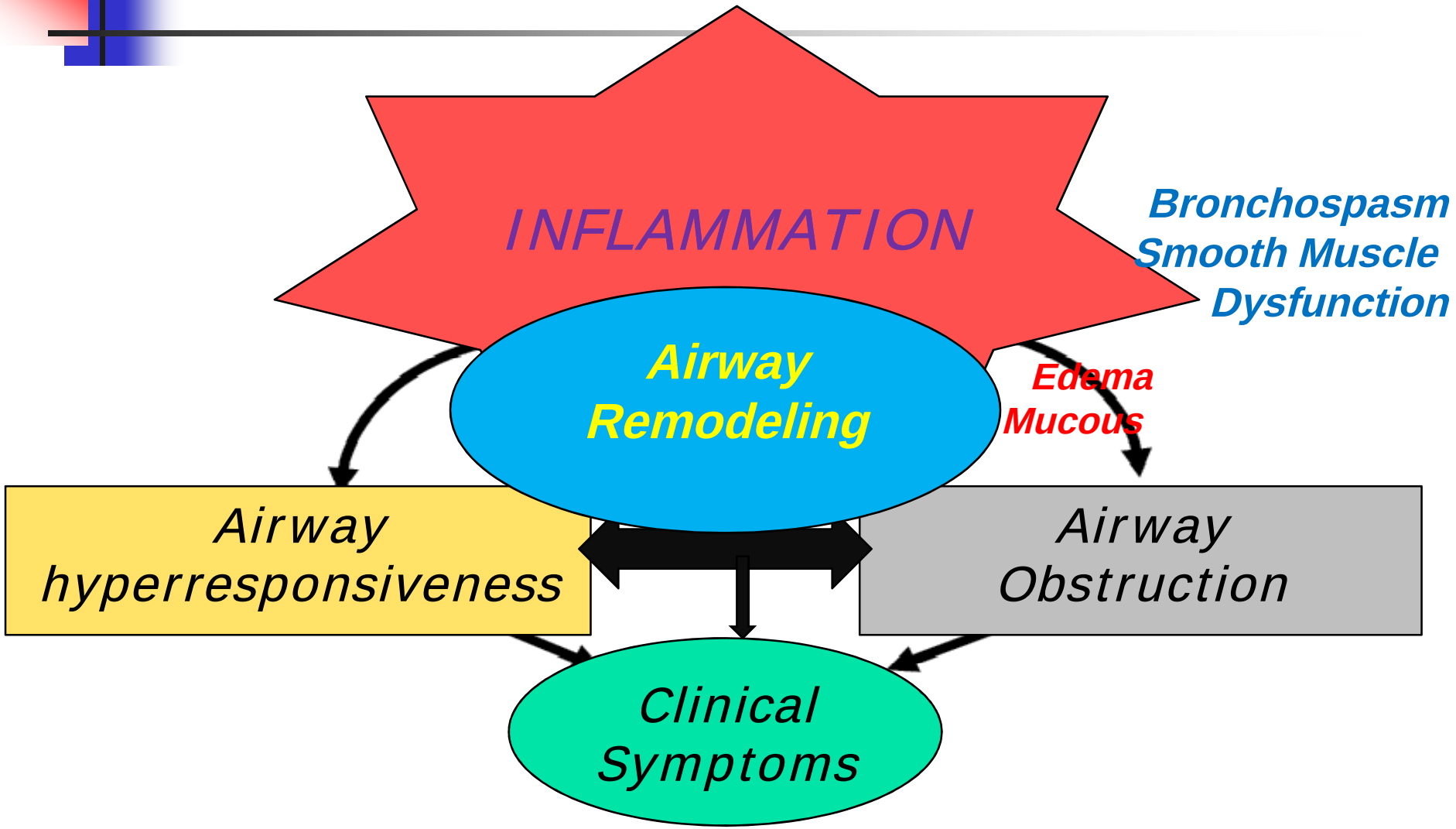



Inhaled allergens
Epithelial cells
SCF
Mast cell
TSLP
CCL11, CCL24, CCL26
CCL5, CCL13
Histamine
Cys-LTs
PGD2
Dendritic cell
IL-9
CCL17
CCL22
CCR4
Bronchoconstriction
Th2 cell
IgE
IL-4, IL-13
IL-5
CCR3
B-lymphocyte
Eosinophils

Asthma Pathophysiology



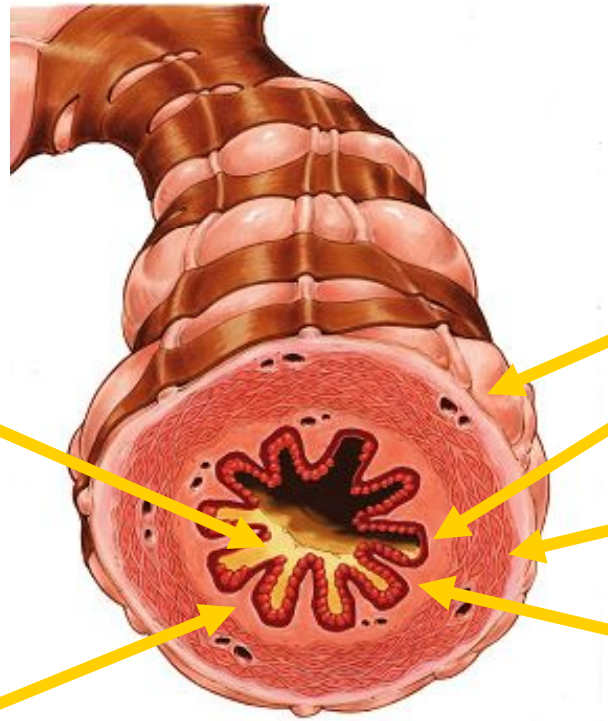
Asthma Pathophysiology



Asthma Pathology

Airway obstruction and symptoms by:

- Bronchoconstriction
- Mucus plugs
- Mucosal oedema



Remodelling:

-Increased vascularity

-Epithelial cell disruption

-Increased airway smooth muscle mass

-Reticular basement membrane thickening

Inflammatory cell infiltration/activation

Definition

- 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.

Diagnosis of Asthma

History of variable respiratory symptoms

- Wheezing
- Dyspnea
- Cough With or without sputum production

Other →

-- Chest or substernal pain, Discomfort, or *Tightness*

-- Nocturnal awakenings

Diagnosis of Asthma

- Confirmed variable expiratory airflow limitation
- At least once during diagnostic process when FEV1 is low, confirm that FEV1/FVC is reduced*
- *Adults: increase in FEV1 of >12% and >200 mL from baseline, 10–15 minutes after 200–400 mcg SABA (greater confidence if increase is >15% and >400 mL).*

** (normally >0.75–0.80 in adults, >0.90 in children)*

Lung FunctionTest
SPIROMETRY

Peak Flow-Meters

Frequency of measurement of lung function

Lung function should be assessed :

- ⇨ At diagnosis or start of treatment.
- ⇨ After 3–6 months of controller treatment to assess the patient's personal best FEV_1.
- ⇨ Periodically thereafter according to the severity of asthma

Asthma assessment

- *Asthma Control Test (ACT) :*

  Score ranges from 5-25 (lowest is worse)

- *Asthma Control questionnaire (ACQ):*

  Score ranges from 0-6 (higher is worse)

- *Levels of asthma control*

Asthma Control Test (ACT)

1- In the past 4 weeks, how much of the time did your asthma keep you from getting as much done at work, school or at home?

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

2- During the past 4 weeks, how often have you had shortness of breath?

More than once a day	1	Once a day	2	3 to 6 times a week	3	Once or twice a week	4	Not at all	5	☐

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

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

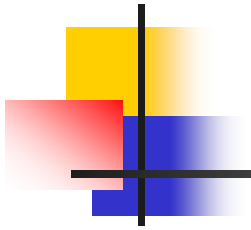
4-During the past 4 weeks, how often have you used your rescue inhaler or nebulizer medication (such as salbutamol)?

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

5-How would you rate your asthma control during the past 4 weeks?

Not controlled at all	1	Poorly controlled	2	Somewhat controlled	3	Well controlled	4	Completely controlled	5	☐

Patient Total Score ☐



Not Well-Controlled defined as:

Asthma Control Test score **≤ 19**

Desfougeres JL et al. Abstract 1589, ERS 2007

Levels of asthma control

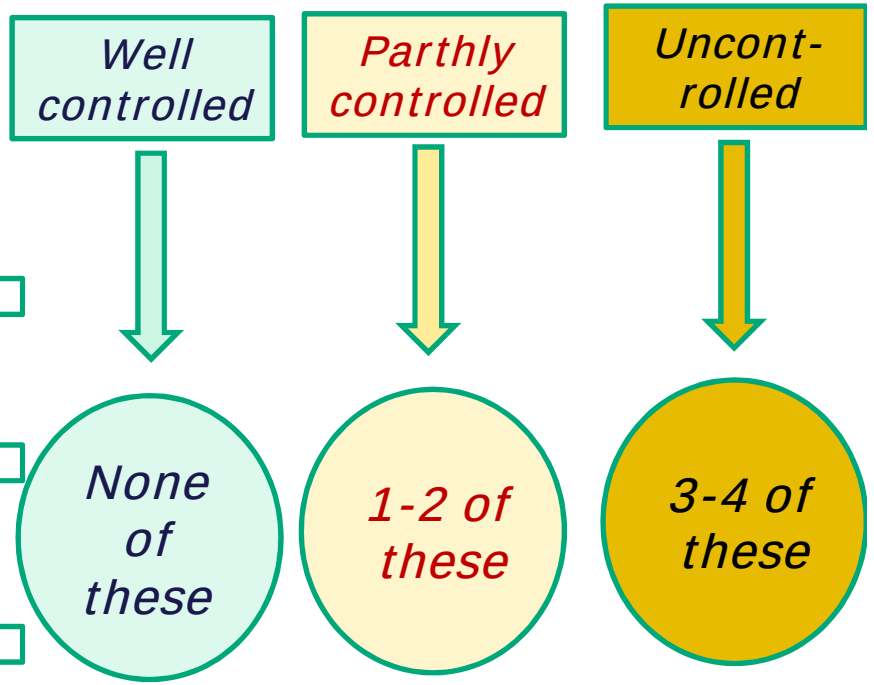
In the past 4 weeks, has the patient had

Daytime symptoms more than twice/week ? Yes ☐ No ☐

Any night waking due to asthma ? Yes ☐ No ☐

Reliever Needed more than twice/week ? Yes ☐ No ☐

Any activity limitation due to asthma ? Yes ☐ No ☐



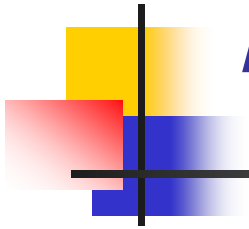
Risk factors for exacerbations

- Uncontrolled asthma symptoms
- **High SABA use (≥**3 canisters/year)
- **Having ≥**1 exacerbation in last 12 months
- Low FEV1; higher bronchodilator reversibility
- Incorrect inhaler technique and/or poor adherence

Risk factors for exacerbations

- Smoking
- Obesity, chronic rhinosinusitis, pregnancy, blood eosinophilia and GERD
- Elevated FeNO in adults with allergic asthma taking ICS
- Ever intubated for asthma

Risk factors for fixed airflow limitation



- No ICS treatment
- Smoking
- Occupational exposure
- Mucus hypersecretion
- Blood Eosinophilia
- Pre-term birth and low birth weight

Assessing asthma severity

Categories of asthma severity

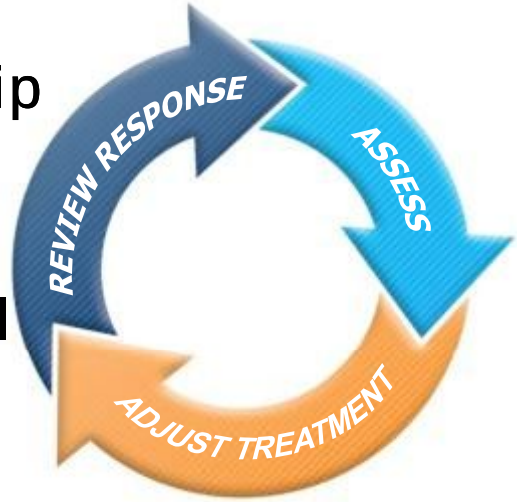
- ☐*Mild asthma: well-controlled with Steps 1 or 2*
- ☐*Moderate asthma: well-controlled with Step 3*
- ☐*Severe asthma: requires Step 4/5 (and may* remain uncontrolled despite this treatment)

Goals of asthma management

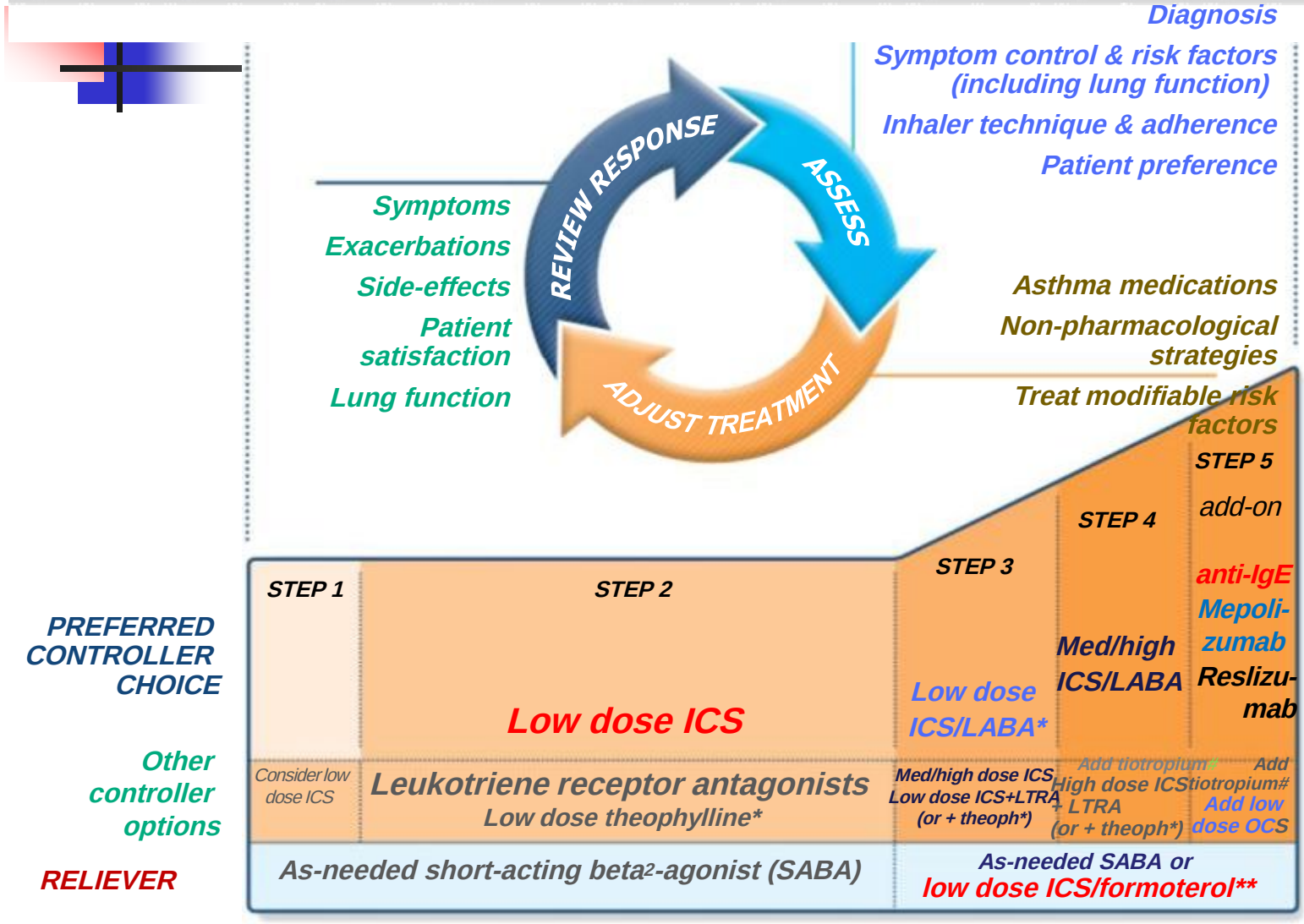
- The long-term goals of asthma management are:
  1. Symptom control: to achieve :
     -- Good control of symptoms
     -- Maintain normal activity levels
  1. Risk reduction: to minimize future risk of:
     -- Exacerbations
     -- Fixed airflow limitation
     -- Side-effects of medication

Treating 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



Stepwise management - pharmacotherapy



*For children 6-11 years, theophylline is not recommended, and preferred Step 3 is medium dose ICS

**For patients prescribed BDP/formoterol or BUD/ formoterol (SMART)

Tiotropium by soft-mist inhaler is indicated as add-on treatment for adults (≥6 yrs) with a history of exacerbations

Omaluzimab SC (≥6 yrs)

Mepolizumab SC - (≥12 yrs) or -

-Reslizumab IV (≥18 yrs) or

Benralizumab SC (≥12 yrs)

anti-IL4 R alpha (dupilumab)

Asthma education Environmental control				
Reliever	As-needed rapid-acting β_2-agonist			
Controller options	Select one	Select one	Add one or more	Add one or both
	Low-dose inhaled ICS	Low-dose ICS + long-acting β_2-agonist	Medium-or high-dose ICS + long-acting β_2-agonist	Anti-IgE Omalizumab
	Leukotriene modifier	Medium-or high-dose ICS	+Leukotriene modifier	Anti- IL-5 **Mepolizumab** **Reslizumab** **Benralizumab**
		Low-dose ICS plus leukotriene modifier	+Tiotropium	Oral Steroid (lowest dose)
		Low-dose ICS + sustained release theophylline	+Theophylline SR	

GINA 2019

landmark changes in asthma management

Step 1 – rationale for changes in GINA 2019

GINA no longer recommends SABA-only treatment for Step 1

- As-needed low dose ICS-formoterol
  - Indirect evidence from SYGMA 1 of large reduction in severe exacerbations vs SABA-only treatment in patients eligible for Step 2 therapy *(O'Byrne, NEJMed 2018)*

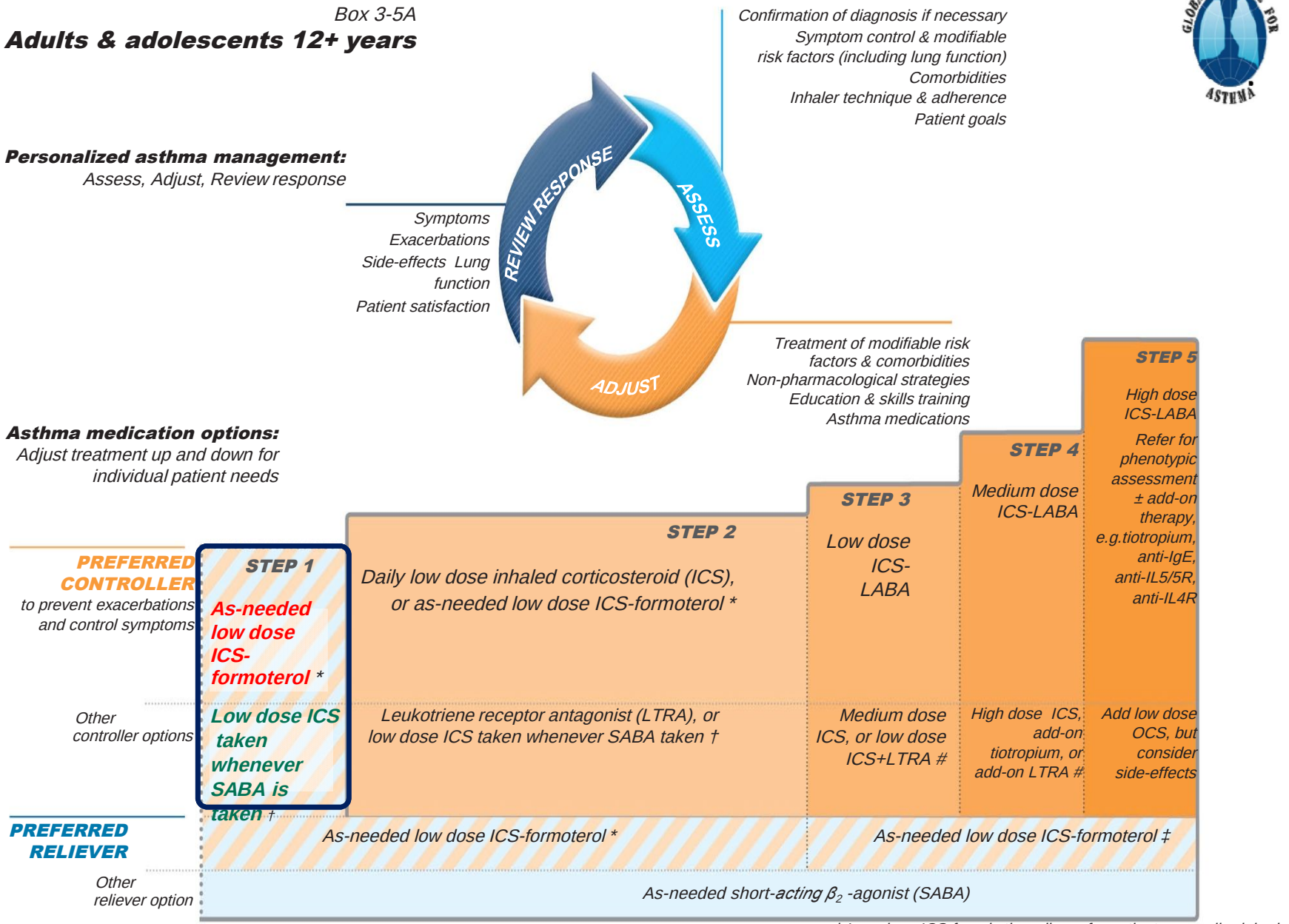
Step 1 – rationale for changes in GINA 2019

- Low dose ICS taken whenever SABA is taken
  - Indirect evidence from studies in patients eligible for Step 2 treatment (BEST, TREXA, BASALT) to preventing severe exacerbations

Daily ICS is no longer listed as a Step 1 option

Box 3-5A

Adults & adolescents 12+ years



* 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

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Step 2 – rationale for changes in GINA 2019

Regular low dose ICS with as-needed SABA

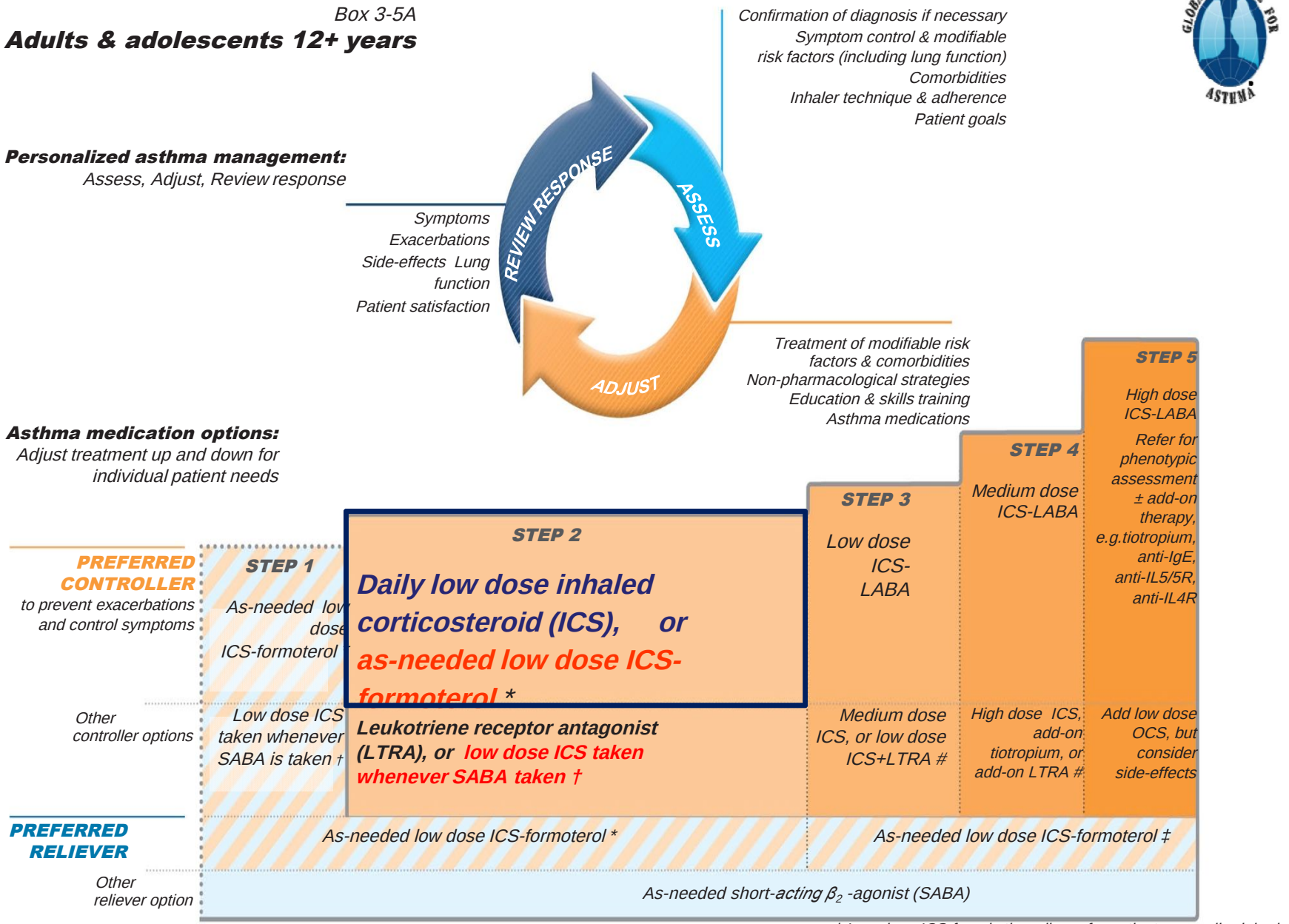
Reduces risks of severe exacerbations, hospitalizations and death

As-needed low dose ICS-formoterol

Direct evidence from two large studies of non-inferiority for severe exacerbations vs daily low dose ICS + as-needed SABA

Box 3-5A

Adults & adolescents 12+ years



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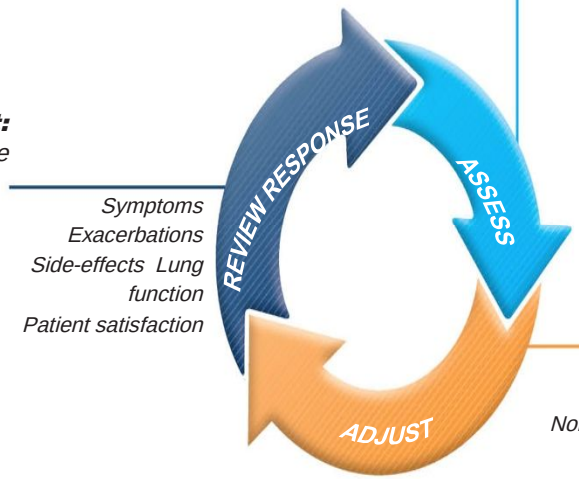
Other changes in GINA 2019 - Steps 3-5 for adults and adolescents

- Step 4 treatment is medium dose ICS-LABA;
- High dose ICS-LABA now in Step 5

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

Step 4 treatment is medium dose ICS-LABA; high dose now in Step 5

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)				

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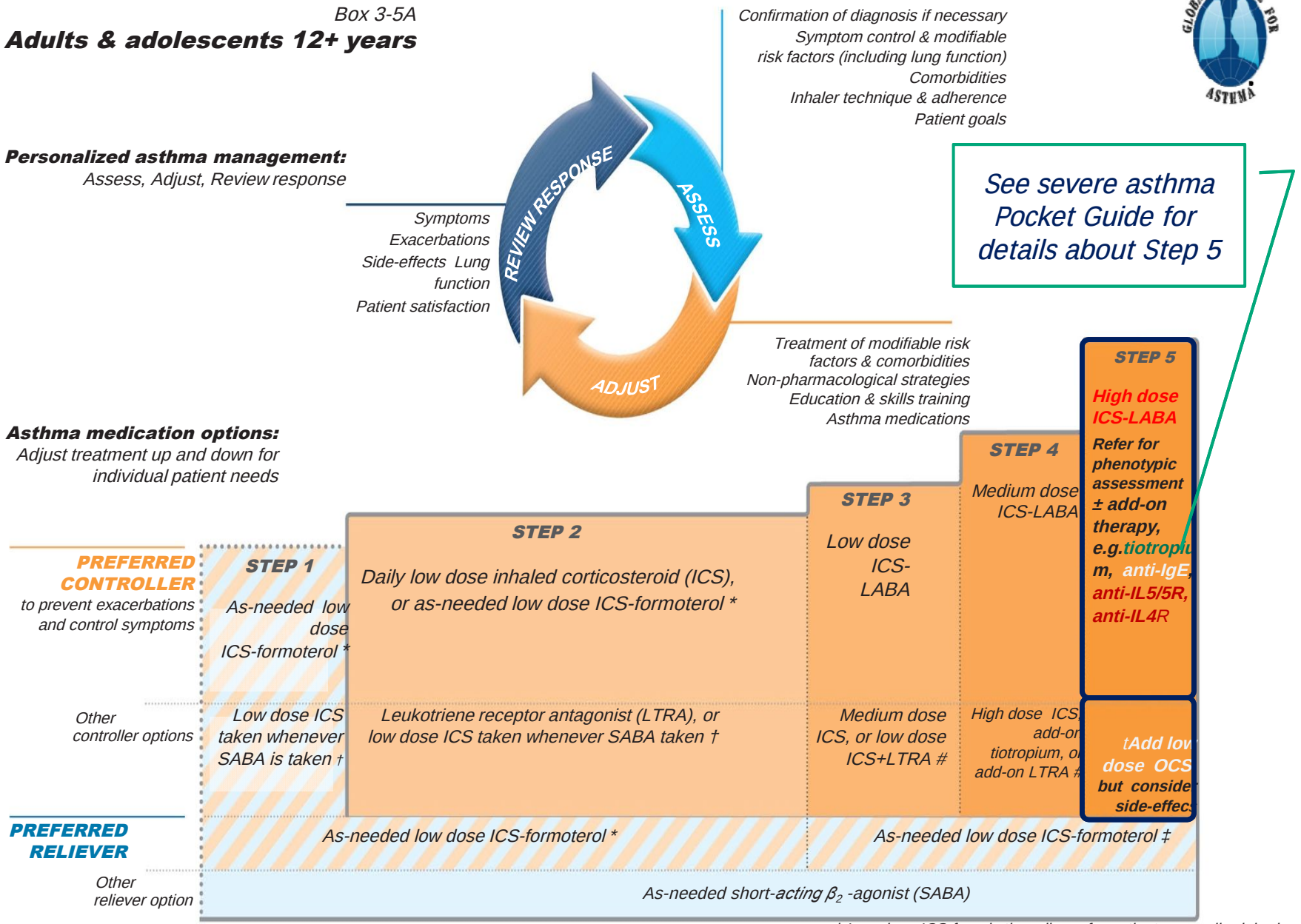
Box 3-5A

Adults & adolescents 12+ years



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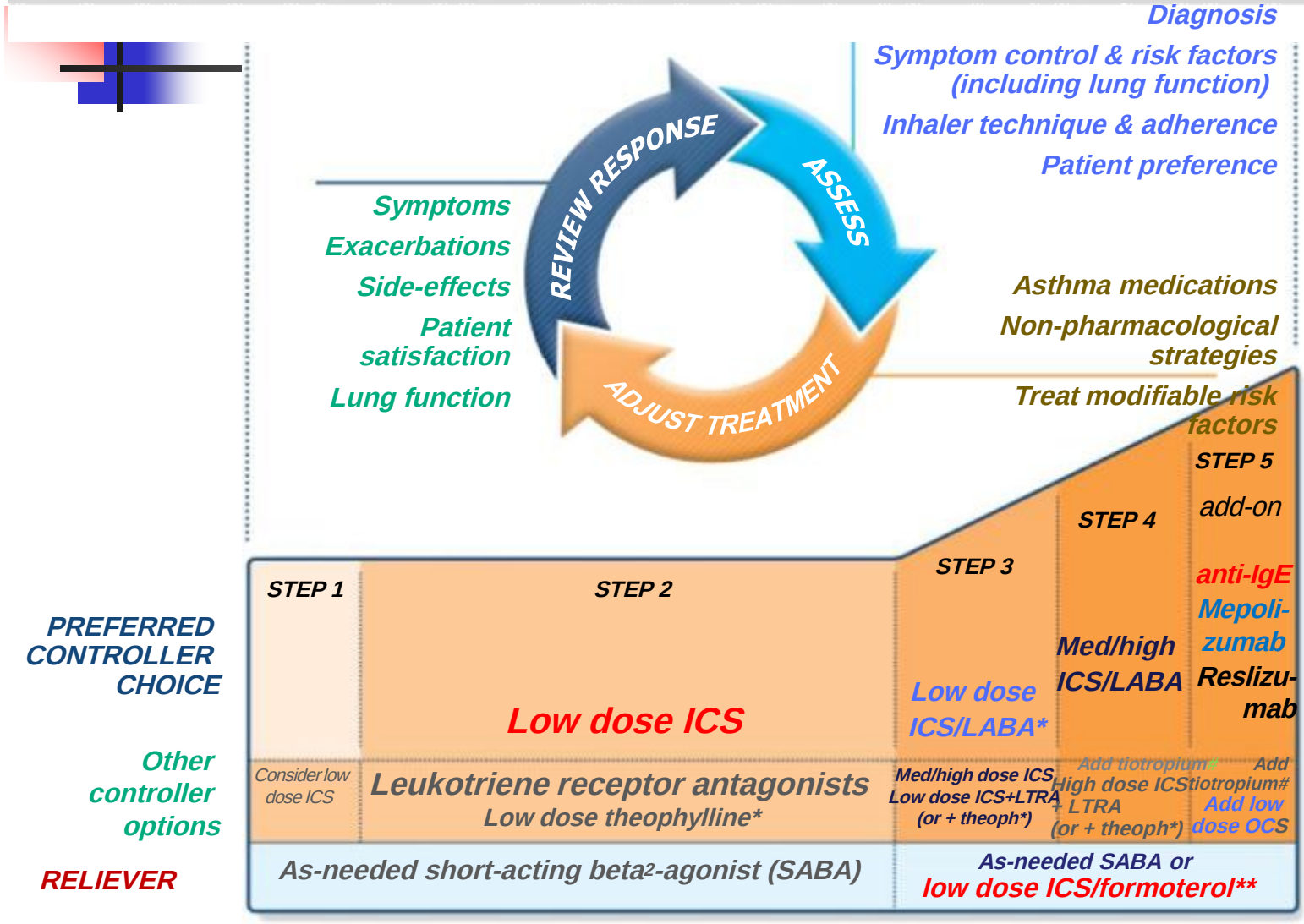
Stepwise management - pharmacotherapy



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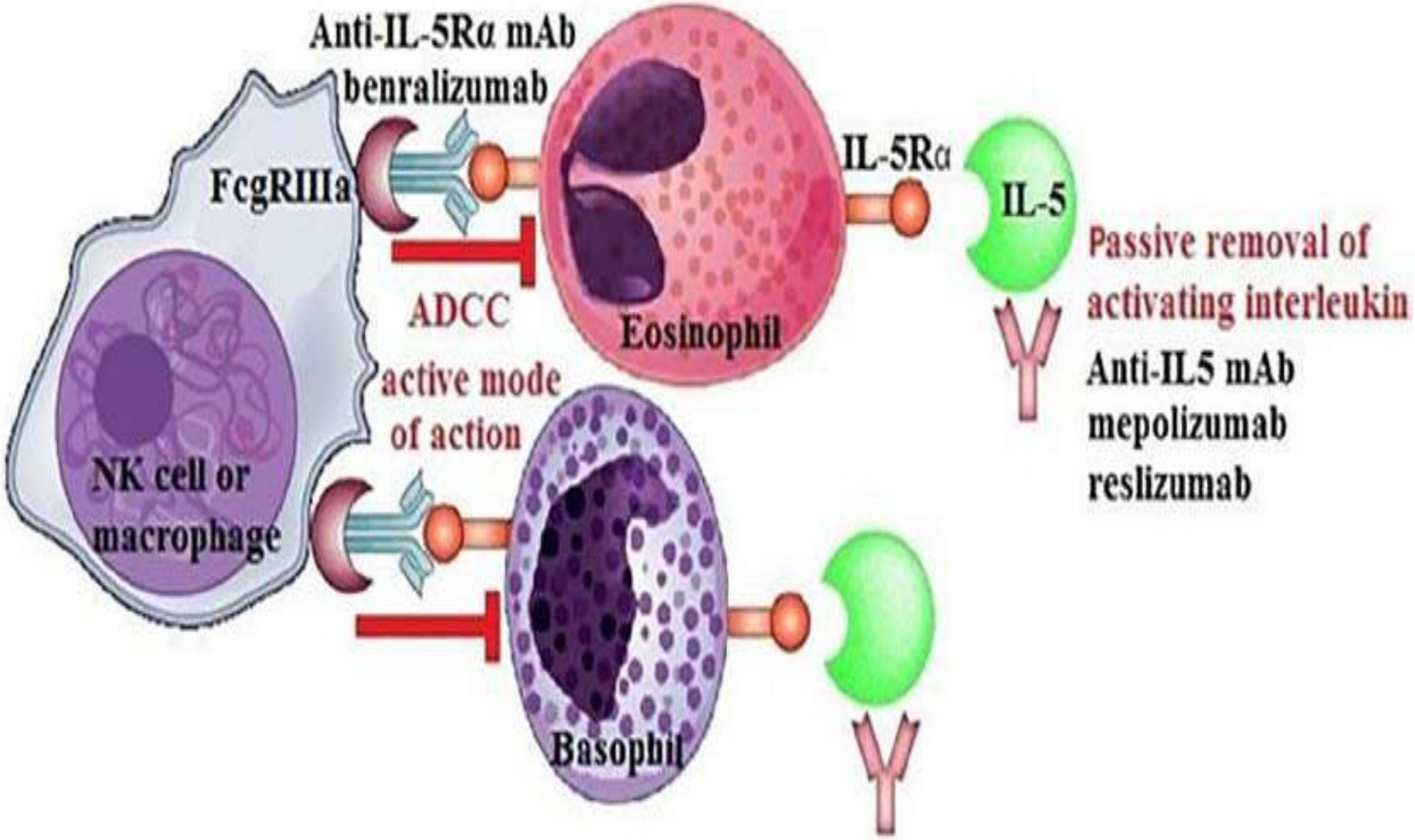

Anti-IL-5Rα mAb
benralizumab
FcgRIIIa
ADCC
Eosinophil
IL-5Rα
IL-5
Passive removal of
activating interleukin
Anti-IL5 mAb
mepolizumab
reslizumab
active mode
of action
NK cell or
macrophage
Basophil

Monoclonal Antibodies in Severe Asthma

	Omalizumab	Mepolizumab	Reslizumab
Target	**IgE**	**IL-5**	**IL-5**
Putative mechanism	Inhibits activation of basophils and mast cells	Inhibits activation and migration of eosinophils	Inhibits activation and migration of eosinophils
Indication (in addition to asthma inadequately controlled with inhaled corticosteroids and one additional medication	Positive skin test or in vitro reactivity to a perennial aeroallergen in patient inadequately controlled with inhaled corticosteroids	Blood eosinophil count of ≥ 150 cells/μL at initiation or ≥ 300 cells/μL in the past 12 months	Blood eosinophil count of ≥400 cells/μL at initiation of the treatment
Recommended dose	3 mg/kg IV every 4 weeks	100 mg subcutaneous injection every 4 weeks	3 mg/kg IV every 4 weeks
Phase 3 Outcome	Reduction in exacerbations and reduced steroid use[1]	Reduction in exacerbations, reduced oral steroid dose and improved quality of life[2]	Reduction in exacerbations and improvement of FEV_1[3]

1. Busse W et al. *J Allergy Clin Immunol* 2001:108:184-190
2. Bel, EH et al. *N Engl J Med* 2014; 371:1189-1197; Ortega HG et al. *N Engl J Med* 2014;371:1198-1207.
3. Bjermer L et al. *Chest* 2016 Oct;150(4):789-798; Castro M et al. *Lancet Respir Med* 2015;3:355-366.

The Medical Xchange

Table 1. Anti-Interleukin-5 Antibodies for Eosinophilic Asthma

	Benralizumab (Fasenra)	Mepolizumab (Nucala)[a]	Reslizumab (Cinqair)
Formulation	30 mg/mL soln in single-dose prefilled syringes	100 mg lyophilized powder in single-dose vials	100 mg/10 mL soln in single-use vials
Route	SC	SC	IV
Metabolism	Degradation by proteolytic enzymes	Degradation by proteolytic enzymes	Degradation by proteolytic enzymes
Half-life	~15 days	16-22 days	~24 days
Dosage	30 mg SC q4 wks × 3, then q8 wks	100 mg SC q4 wks	3 mg/kg IV q4 wks
FDA-approved age	≥12 years	≥12 years	≥18 years
Cost[b]	$4752	$2868	$2580[c]

[a] Mepolizumab is also FDA-approved for treatment of eosinophilic granulomatosis with polyangiitis in adults.

[b] Approximate WAC for a single dose. WAC = wholesaler acquisition cost or manufacturer's published price to wholesalers; WAC represents a published catalog or list price and may not represent an actual transactional price. Source: AnalySource® Monthly. February 5, 2018. Reprinted with permission by First Databank, Inc. All rights reserved. ©2018. www.fdbhealth.com/policies/drug-pricing-policy/.

[c] Cost for a 70-kg patient (3 vials).

Anti-IgE (**Omalizumab**)

- **Anti-IgE is a treatment option limited to patients with elevated serum levels of IgE.**
- **for patients with severe allergic asthma who are uncontrolled on ICS**
- **Improved asthma control is reflected by fewer symptoms, less need for reliever medications, and fewer exacerbations.**

REMEMBER TO...

- *Provide guided self-management education*
- *Treat modifiable risk factors and comorbidities*
- *Advise about non-pharmacological therapies and strategies*
- *Consider stepping up if ... uncontrolled symptoms, exacerbations or risks, but check diagnosis, inhaler technique and adherence first*
- *Consider stepping down if ... symptoms controlled for 3 months + low risk for exacerbations. Ceasing ICS is not advised.*

SLIT as an add-on option for some patients

REMEMBER TO...

- *Provide guided self-management education*
- *Treat modifiable risk factors and comorbidities*
- *Consider adding SLIT in adult HDM-sensitive patients with AR who have exacerbations despite ICS treatment, provided FEV1 > 70 % predicted*
- *Consider stepping down if ... symptoms controlled for 3 months + low risk for exacerbations. Ceasing ICS is not advised.*

Changes in GINA 2019 – children 6-11 years

- Step 1

  Low dose ICS whenever SABA taken (indirect evidence), or

  Daily low dose ICS.

Changes in GINA 2019 – children 6-11 years

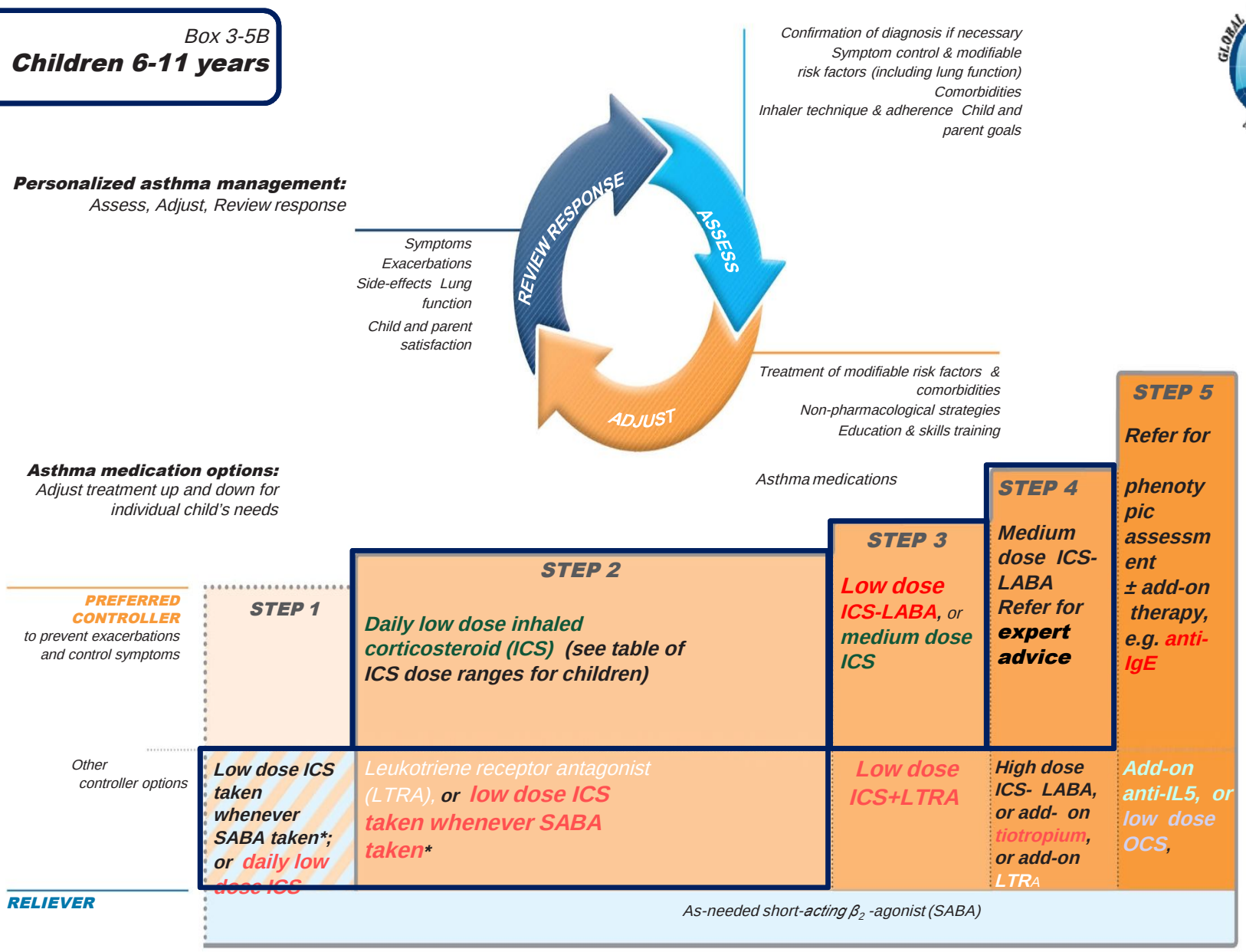
- Step 2
  - Preferred controller is daily low dose ICS
  - As-needed low dose ICS taken whenever SABA is taken, but only one study in children *(Martinez, Lancet 2011)*
  - Studies of as-needed ICS-formoterol are needed; since maintenance and reliever therapy with low dose budesonide-formoterol in children 4-11 years reduced exacerbations by 70-79% compared with ICS and ICS-LABA *(Bisgaard, Chest 2006)*

Changes in GINA 2019 – children 6-11 years

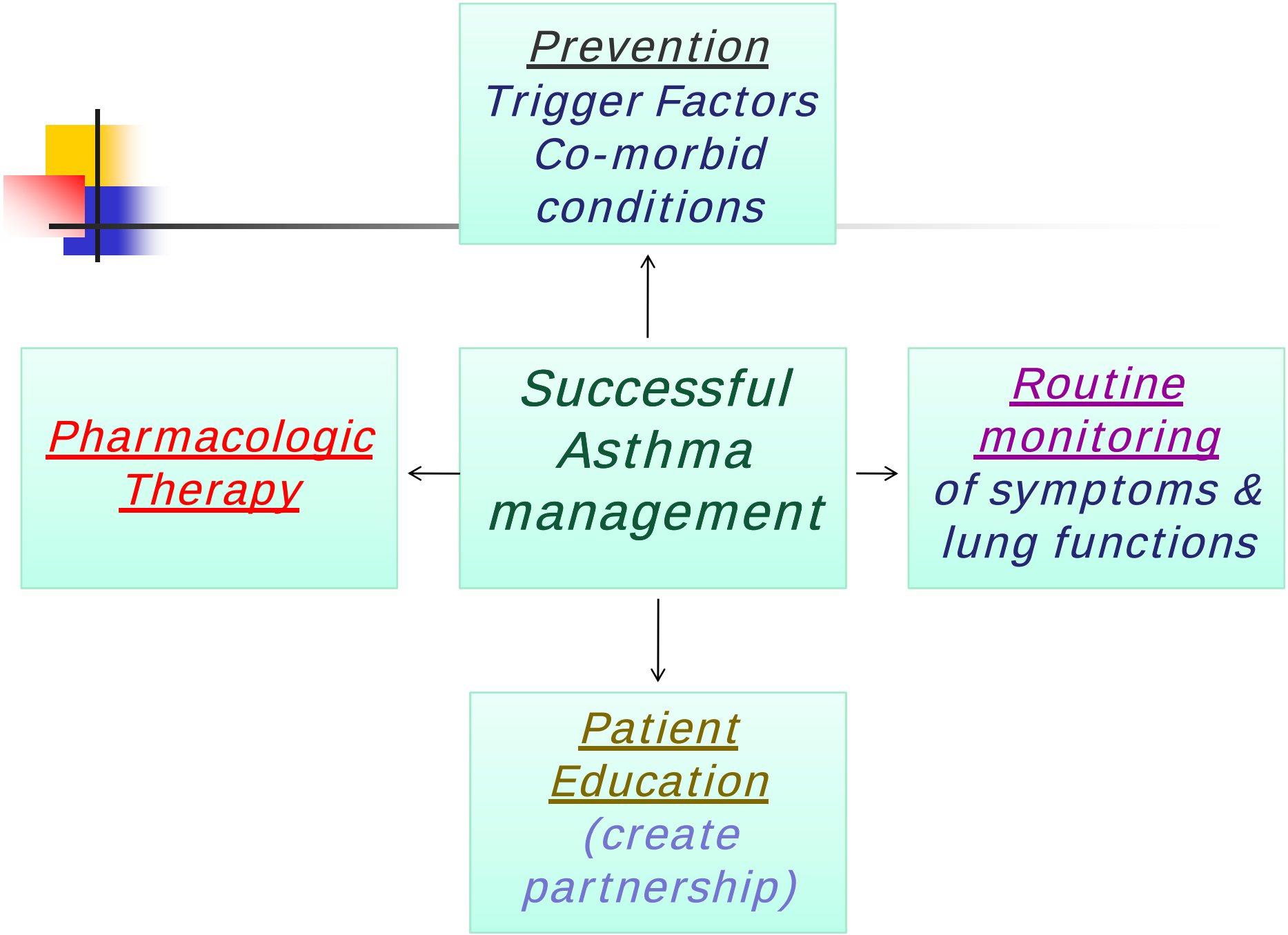
- Step 3
  - Low dose ICS-LABA or medium dose ICS are 'preferred' controller treatments
  - No safety signal with ICS-LABA in children 4-11 years *(Stempel, NEJMed 2017)*
- Step 4
  - Medium dose ICS-LABA, but refer for expert advice

Box 3-5B

Children 6-11 years



* Off-label; separate ICS and SABA inhalers; only one study in children


Prevention
Trigger Factors
Co-morbid conditions
Pharmacologic Therapy
Successful Asthma management
Routine monitoring of symptoms & lung functions
Patient Education (create partnership)

Non-Pharmacologic Therapy

- Breast feeding should be encouraged for its many benefits.
- Parents should be advised of the many adverse effects that smoking, particularly increased risk of persistent asthma.
- Weight reduction is recommended in obese patients with asthma to improve asthma control.

Asthma Management Approach for Children 5 Years and Younger

Asthma education, Environmental control, and As needed rapid-**acting β2** agonists in all steps

STEP 1	STEP 2	STEP 3	STEP 4
As needed SABA	Low-dose ICS Or Montelukast	Double Low-dose ICS Or Low-dose ICS + Montelukast	Increase ICS frequency + Montelukast Add intermett. ICS or theophylline or OCS

Effectiveness
of Medical Therapy

=

Medication Efficacy

X

Adherence

Dosing frequency

Side effects

Patient education

Ease of use

Thank You !