Bronchial Asthma

ICP – API 2025

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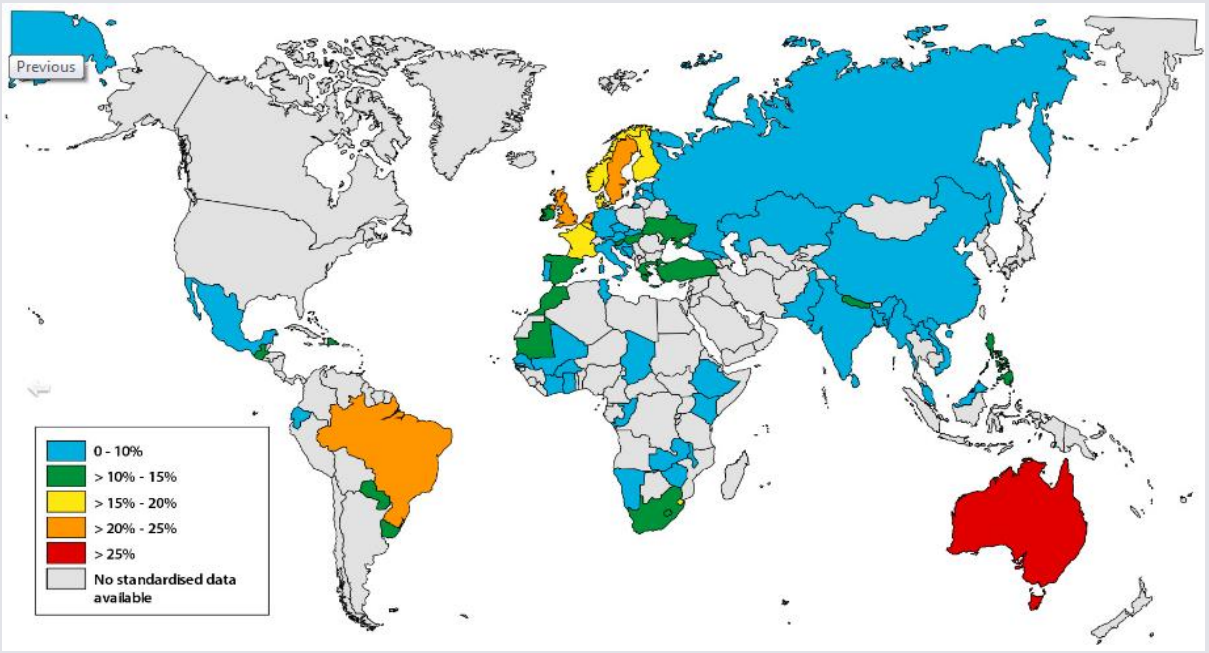
Burden of Asthma : *Problem !*

- **Asthma affects 339 million people worldwide**
- **1 in 10 asthma patients globally live in India**
- **> 20% of total deaths in asthma from India**

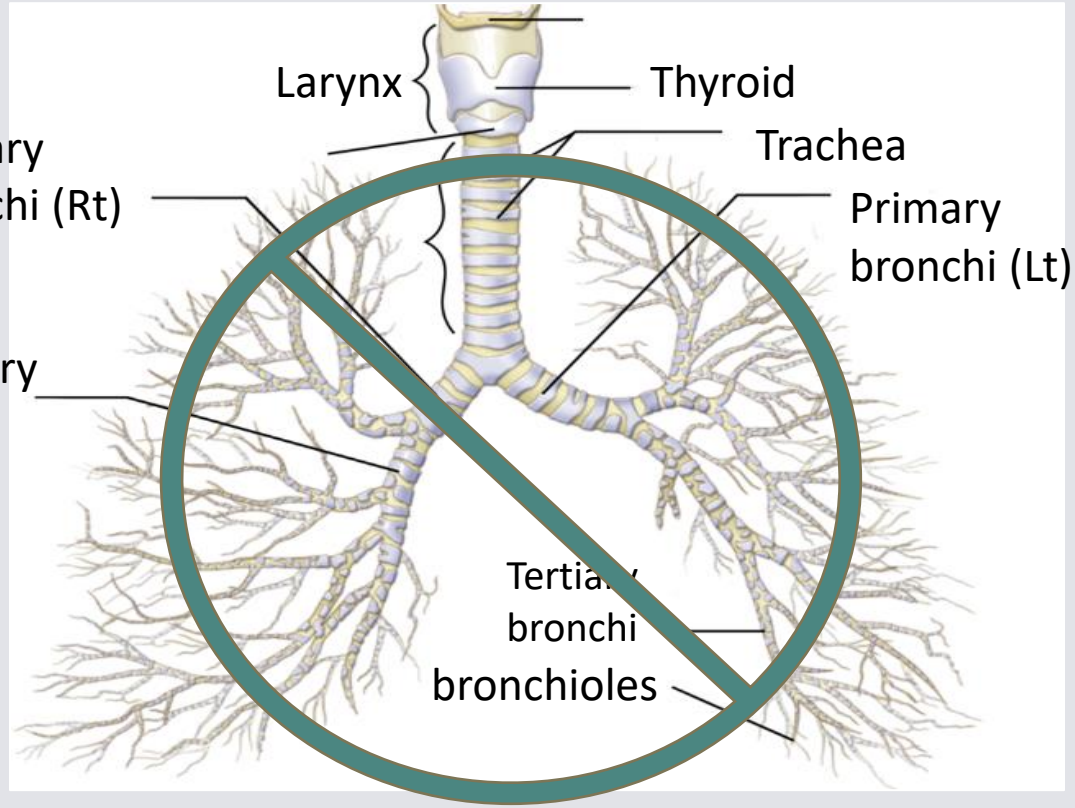
Prevalence of asthma worldwide



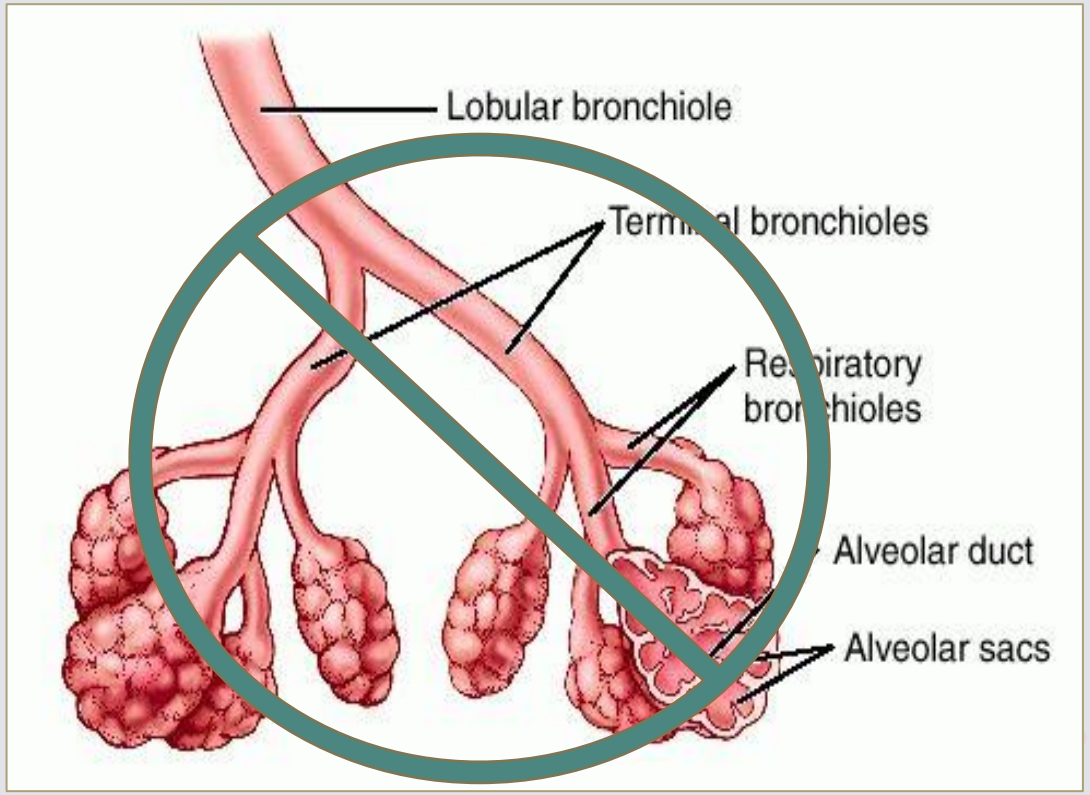
Fletcher JM et al. Primary Care Respiratory Medicine (2020) 30:29 ; https://doi.org/10.1038/s41533-020-0184-0

Respiratory System – *Where Asthma Attacks ?*

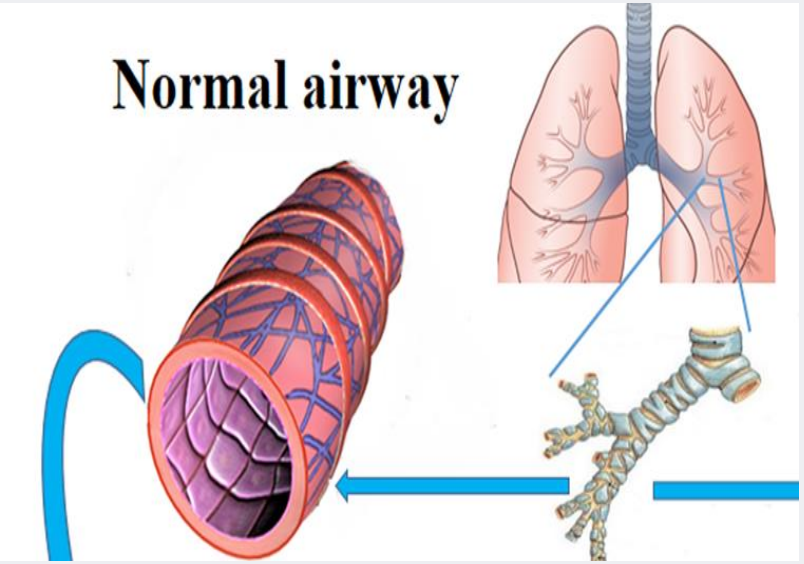
Predominantly affect large airways



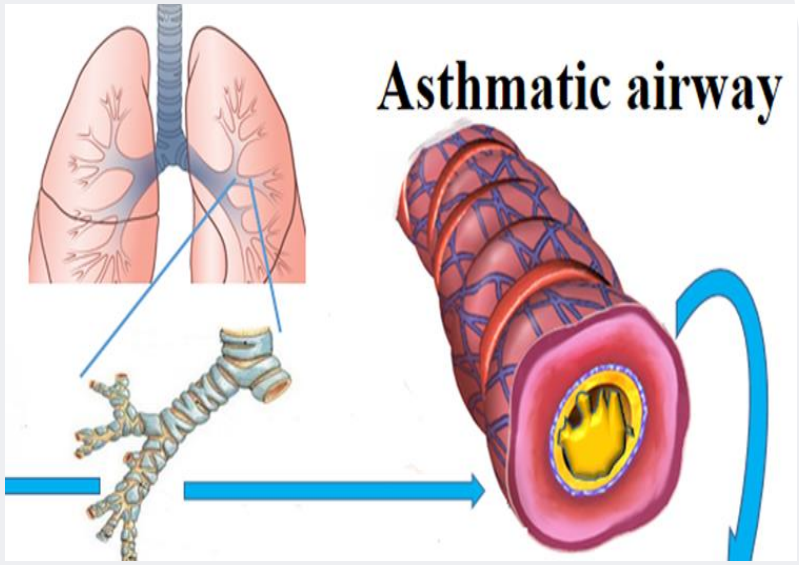
Large airways



Small airways



Defining 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.

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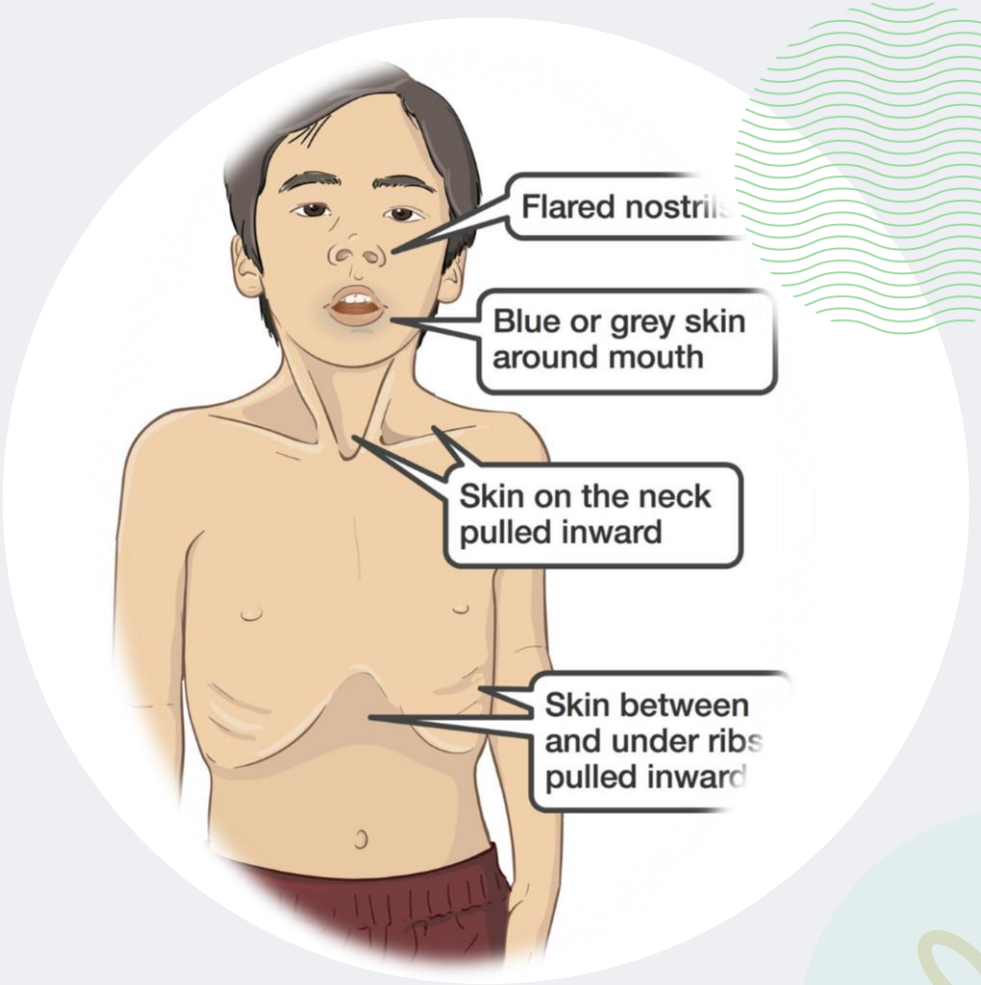
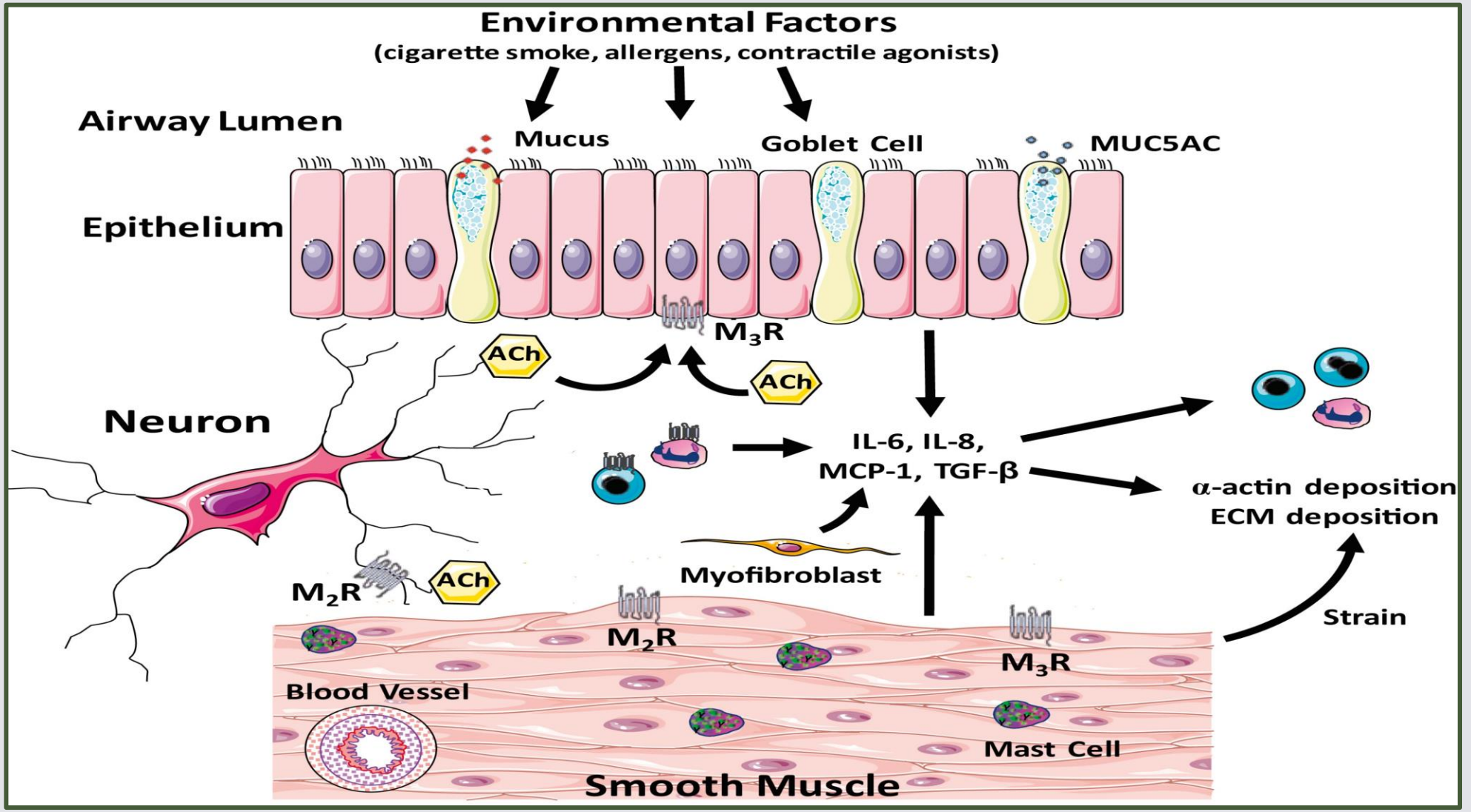
Spot Red Flag Symptoms In Asthma :



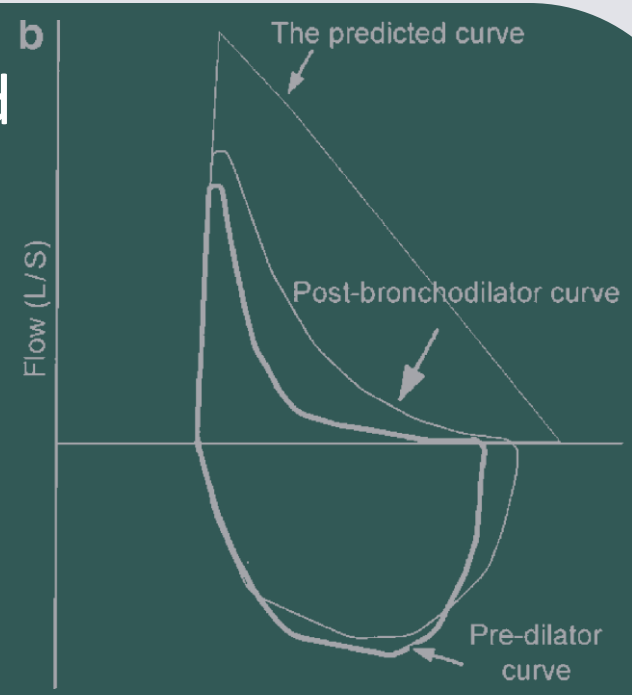
Asthma : Patho-physiology – *Chronic Inflammation*



Tliba O et al JACI 2018

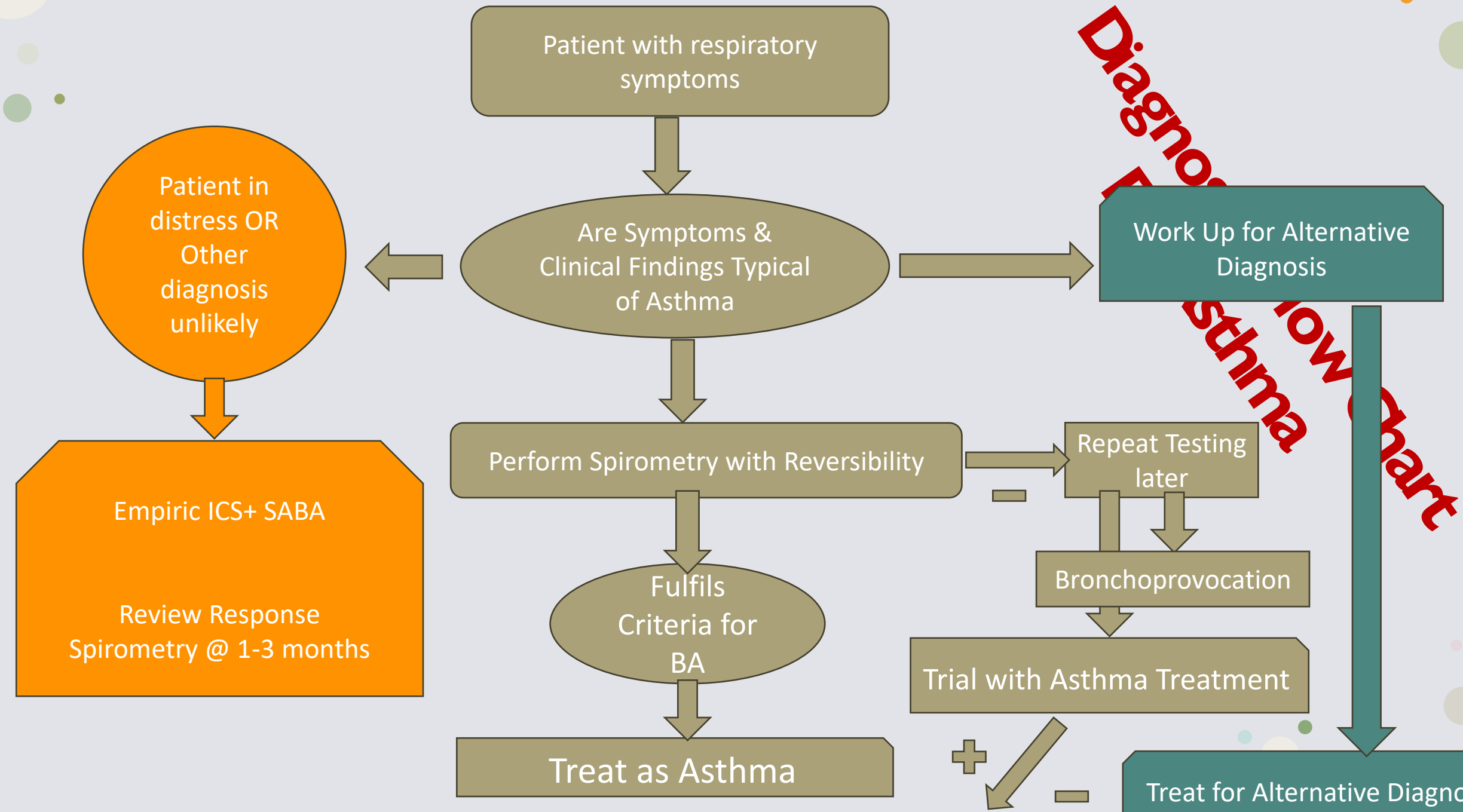
Defining Variability in Asthma : *Key to Diagnosis*

- Respiratory Symptoms variability : Historically defined
  - Wheeze, SOB, Cough or Chest tightness: mostly >1 symptom
  - Variable over time and intensity
  - Mostly or worse in night or at wakening
  - Triggered by exercise, laughing or allergen / cold air exposure
  - Viral infections : precipitate of worsen symptoms
- Lung Function variability : Spirometry based
  - Obstruction : Once FEV1 is low and FEV1 /FVC ration < LLN
  - Reversibility : ↑ FEV_1 / FVC > 12% and 200 ml or in children 12% after bronchodilator or @ 4 weeks of ICS therapy
  - More variation and more reversibility and on repeated testing – more confident diagnosis
  - Reversibility may be absent during exacerbation / viral infection



> 10% improvement (ERS 2022)

Diagnosis Flow Chart Asthma



Diagnosis of Asthma in Resource limited Settings

- GINA recommends confirmation of asthma diagnosis with lung function testing, whenever possible, before commencing long-term treatment
  - Spirometry-based testing if available
  - Peak expiratory flow (PEF)
    - >20% increase in PEF, 15 minutes after 2 puffs of salbutamol = asthma likely (WHO-PEN)
    - Improvement of symptoms and PEF after 4 weeks ICS treatment
- Access to affordable diagnostic equipment and skills training needs to be substantially scaled up in low- and middle-income countries

Differential Diagnosis in Asthma

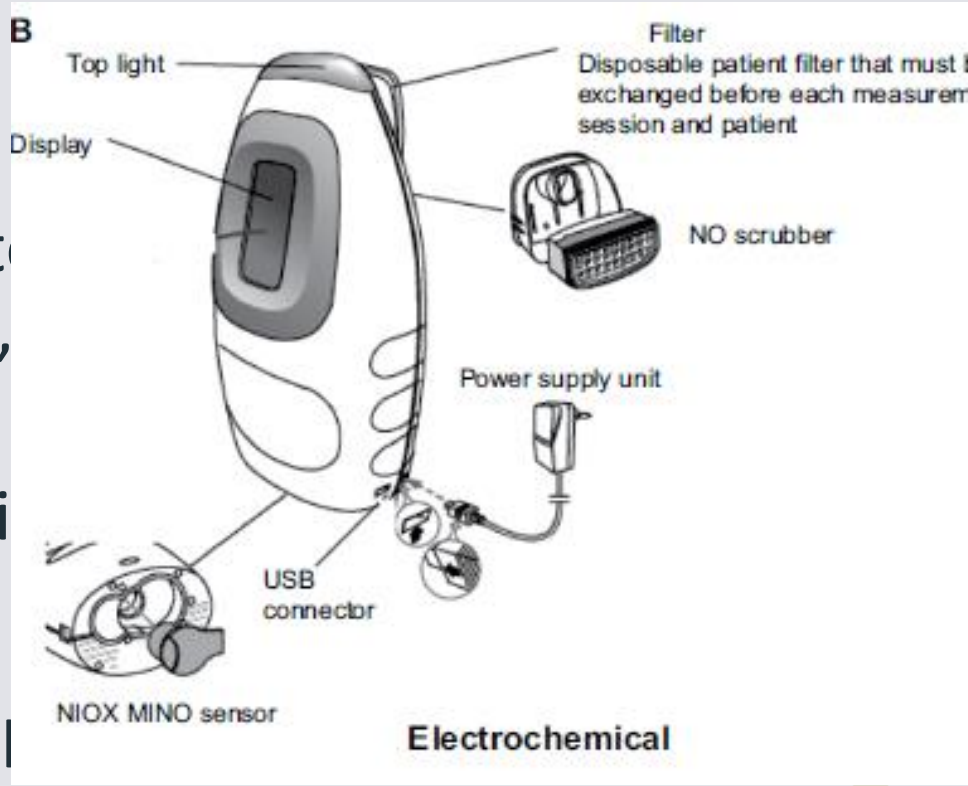
Symptoms	Differential Diagnosis
Sneezing, itching, blocked nose, throat-clearing	Chronic upper airway cough syndrome
Cough, sputum, SOB on exertion, smoking or noxious exposure	COPD
Sudden onset of symptoms, unilateral wheeze	Inhaled foreign body
Recurrent infections, productive cough	Bronchiectasis
Dyspnea with exertion, nocturnal symptoms, ankle edema	Cardiac failure
Cardiac murmurs	Congenital heart disease
Excessive cough and mucus production, gastrointestinal symptoms	Cystic fibrosis

Allergy Tests in Asthma :

- To confirm presence of atopy : But only increases the probability that a patient with respiratory symptoms has allergic asthma, but this is not specific for asthma nor is it present in all asthma phenotypes
- SPT with common environmental allergens is simple, rapid to perform, inexpensive and has a high sensitivity
- Measurement of sIgE is no more reliable than skin tests and is more expensive, for uncooperative patients or with skin disease
- Presence of a positive skin test or positive sIgE, does not mean that the allergen is causing symptoms – must be confirmed by the patient's history

Role of FeNO in Asthma

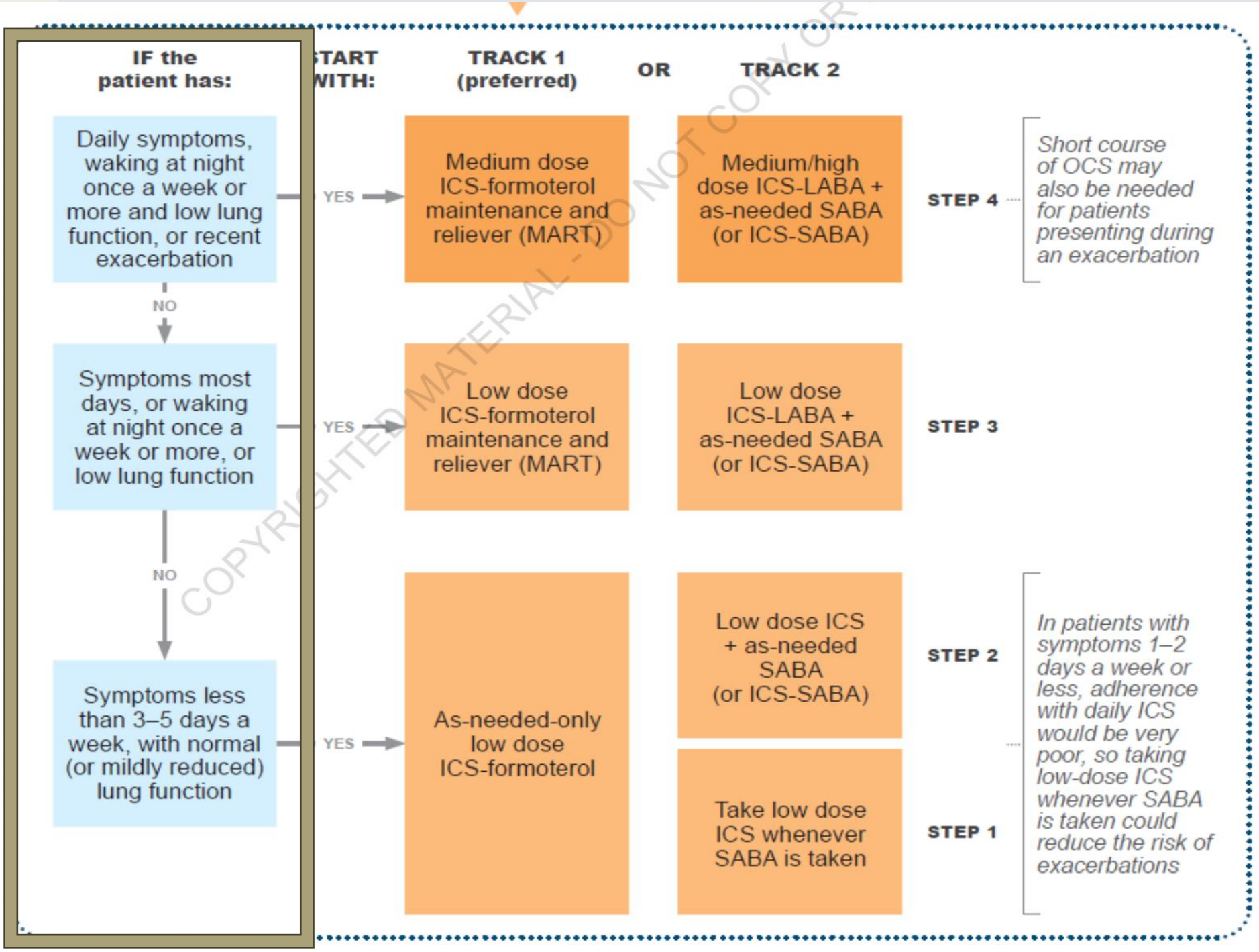
- Modestly associated with levels of sputum and blood eosinophils
- Not to rule in or rule out a diagnosis of asthma
- While FeNO is higher in T 2 asthma, also elevat asthma conditions (e.g. eosinophilic bronchitis, allergic rhinitis, eczema)
- Not elevated in T2 low asthma (e.g. neutrophili
- FeNO is lower in smokers
- May be increased or decreased during viral resp infections



Treatment

- Long-term symptom control, which may include:
  - Few/no asthma symptoms, quickly relieved
  - No sleep disturbance
  - Unimpaired physical activity
- Long-term asthma risk minimization, which may include:
  - No exacerbations
  - Improved or stable personal best lung function
  - No requirement for maintenance oral corticosteroids
  - No medication side-effects

*Anti-inflammatory reliever (AIR)


IF the patient has:
START WITH:
TRACK 1 (preferred)
OR
TRACK 2
Daily symptoms, waking at night once a week or more and low lung function, or recent exacerbation
YES
Medium dose ICS-formoterol maintenance and reliever (MART)
Medium/high dose ICS-LABA + as-needed SABA (or ICS-SABA)
STEP 4
Short course of OCS may also be needed for patients presenting during an exacerbation
NO
Symptoms most days, or waking at night once a week or more, or low lung function
YES
Low dose ICS-formoterol maintenance and reliever (MART)
Low dose ICS-LABA + as-needed SABA (or ICS-SABA)
STEP 3
NO
Symptoms less than 3–5 days a week, with normal (or mildly reduced) lung function
YES
As-needed-only low dose ICS-formoterol
Low dose ICS + as-needed SABA (or ICS-SABA)
STEP 2
Take low dose ICS whenever SABA is taken
STEP 1
In patients with symptoms 1–2 days a week or less, adherence with daily ICS would be very poor, so taking low-dose ICS whenever SABA is taken could reduce the risk of exacerbations
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Treatment

Asthma is often inappropriately treated as a recurrent acute disease, with no treatment in between

- Burden to patients, family, health system, economy
- Risk of asthma mortality
- Cumulative risk of adverse effects of oral corticosteroids, with even 4–5 lifetime courses *(Price, 2018)*
- Asthma morbidity and mortality are largely preventable

Assessments: Asthma Control

Symptom Control

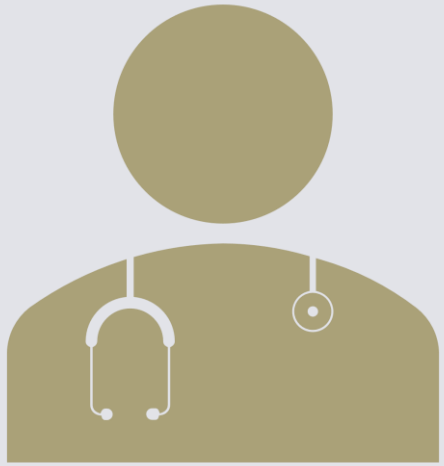
Symptom Control :

1.Daytime

2 Nocturnal

3 Activity

4 SABA* use (2 /week)



- About Past 4 weeks
- Every Visit
- Direct Questioning
- Tools :
  - ACT or ACQ

Well Controlled, Partially Controlled Uncontrolled

* Not for patients on AIR

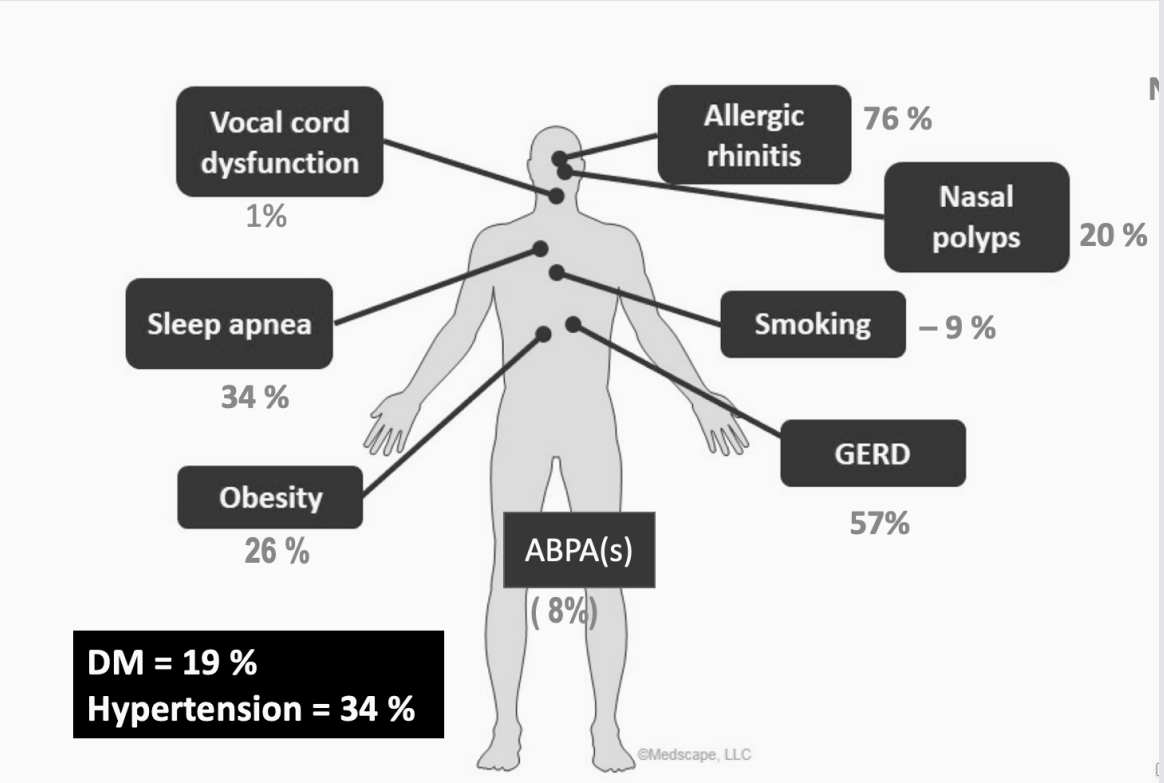
Future Risk for Exacerbations

- Past exacerbation in last 1 year
- Poor adherence
- Incorrect technique
- Chronic sinusitis
- Smoking

Low FEV_1 is a strong predictor of Exacerbations

- Medication: High SABA & Low ICS use
- Others: Pregnancy, Food allergy and multimorbidity
- Exposures : Allergen / Pollution / Smoke
- Psychosocial : Poor support
- Type 2 Inflammation: ↑AEC & FeNO
- Severe Exacerbation : Intubated or ICU

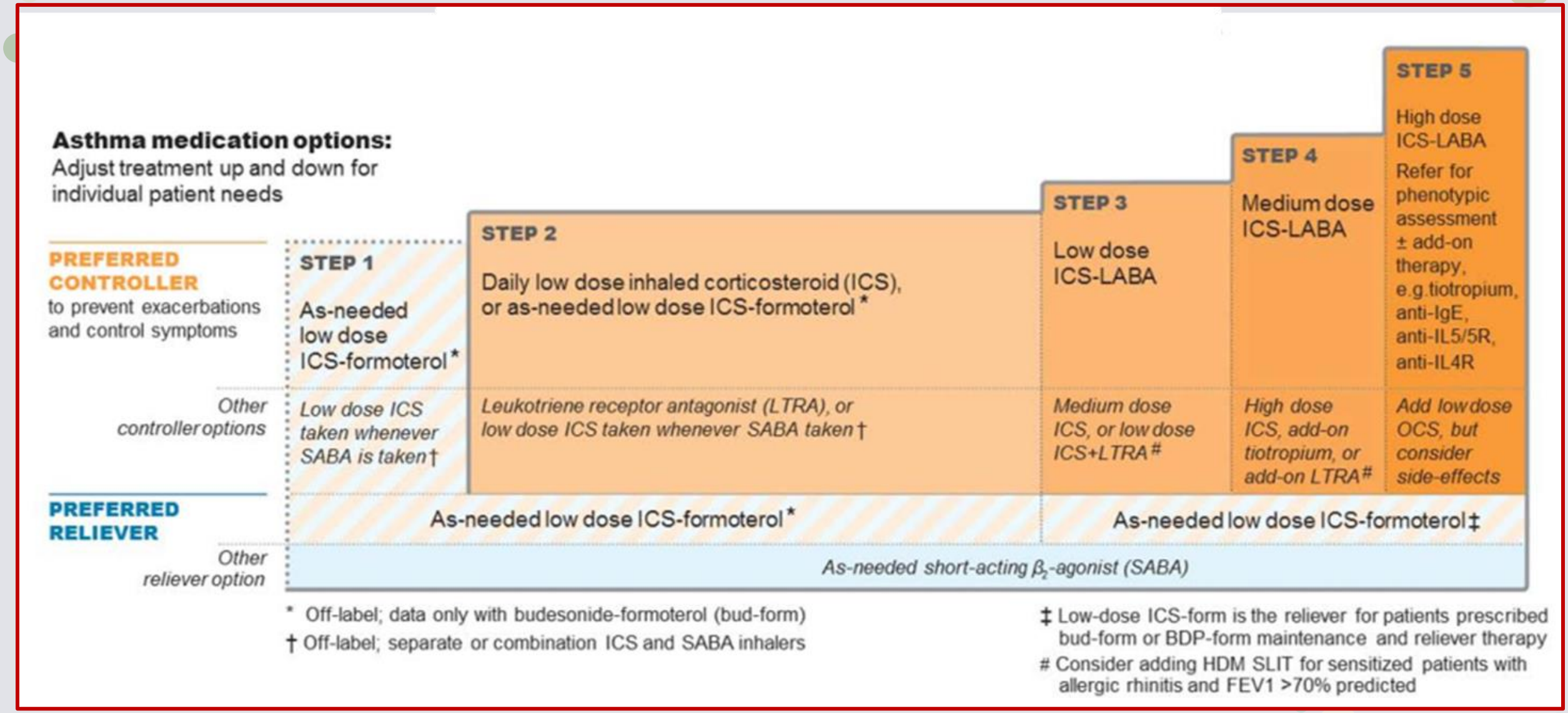
Assessments: Multimorbidities



- Pulmonary :
  - Rhinitis
  - Rhinosinusitis
- Extra-Pulmonary :
  - Obesity
  - GERD
  - OSA
  - Anxiety / Depression

Talwar D, Lung India 2022;39:393-400.

Treatment


Asthma medication options:
Adjust treatment up and down for individual patient needs
PREFERRED CONTROLLER
to prevent exacerbations and control symptoms
Other controller options
PREFERRED RELIEVER
Other reliever option
STEP 1
As-needed low dose ICS-formoterol *
Low dose ICS taken whenever SABA is taken †
STEP 2
Daily low dose inhaled corticosteroid (ICS), or as-needed low dose ICS-formoterol *
Leukotriene receptor antagonist (LTRA), or low dose ICS taken whenever SABA taken †
STEP 3
Low dose ICS-LABA
Medium dose ICS, or low dose ICS+LTRA #
STEP 4
Medium dose ICS-LABA
High dose ICS, add-on tiotropium, or add-on LTRA #
STEP 5
High dose ICS-LABA
Refer for phenotypic assessment ± add-on therapy, e.g.tiotropium, anti-IgE, anti-IL5/5R, anti-IL4R
Add low dose OCS, but consider side-effects
As-needed low dose ICS-formoterol *
As-needed low dose ICS-formoterol ‡
As-needed short-acting β2-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 FEV1 >70% predicted

Oral bronchodilators not Recommended

- Salbutamol tablets/syrup, and oral theophylline are **not recommended**
  - Slow onset of action
  - Less effective for symptom relief than inhaled bronchodilators
  - More adverse effects
  - They do not treat the airway inflammation that is characteristic of asthma

Defining Doses of ICS for Asthma Treatment

Inhaled corticosteroid	Total daily dose (mcg)		
	Low	Medium	High
Beclometasone dipropionate (CFC)	200–500	>500–1000	>1000
Beclomethasone 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)	**100–250**	**>250–500**	**>500**
Mometasone furoate	110–220	>220–440	>440
Triamcinolone acetonide	400–1000	>1000–2000	>2000

Step 1 – Different Approach

- ***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

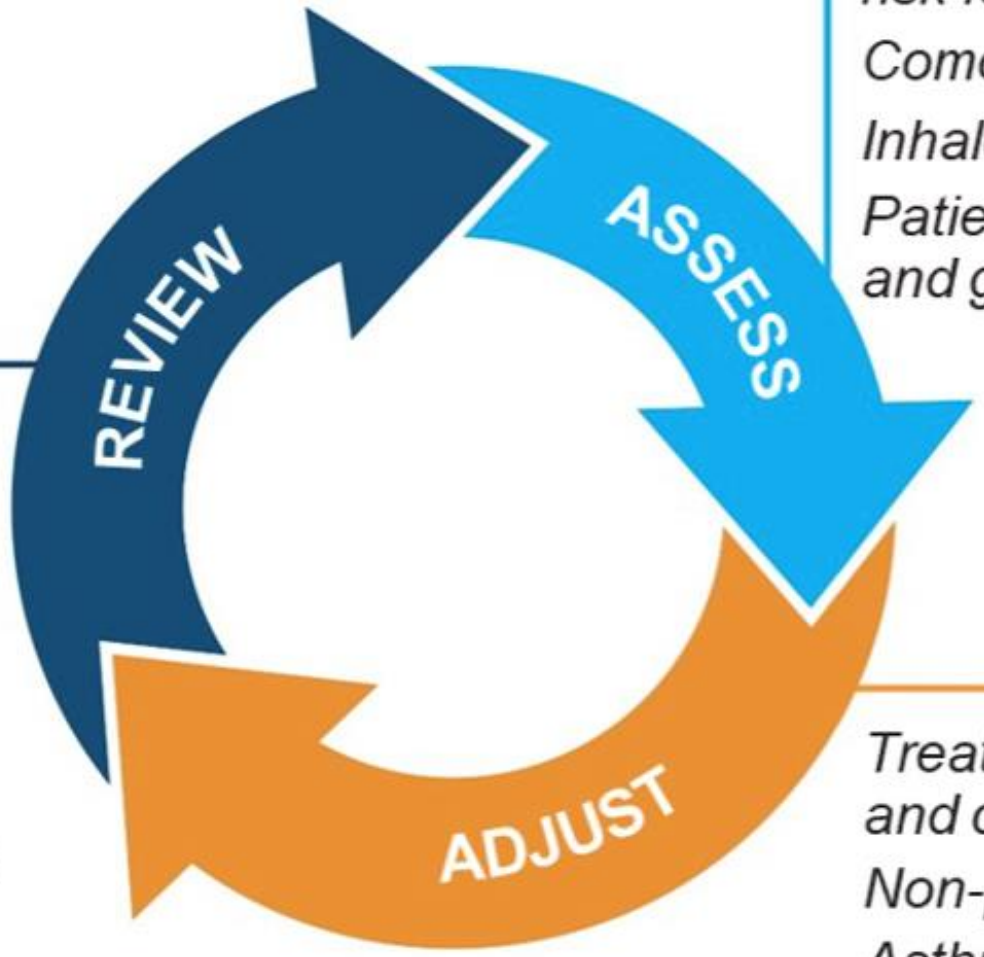
- GINA now recommends that ***all adults and adolescents with asthma should receive symptom-driven or regular low dose ICS-containing controller treatment,*** to reduce the risk of serious exacerbations
  - ***This is a population-level risk reduction strategy***, e.g. statins, anti-hypertensives

- ***Evidence***
  - 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)*
- ***Values and preferences***
  - High importance given to reducing exacerbations
  - High importance given to avoiding conflicting messages about goals of asthma treatment between Step 1 and Step 2
  - ***High importance given to poor adherence with regular ICS*** in patients with infrequent symptoms, which would expose them to risks of SABA-only treatment

***Step 2* – 2 'Preferred' Controller Options**

- As-needed low dose ICS-formoterol (off-label; all evidence with budesonide-formoterol)
- Evidence
  - Direct evidence from two large studies of ***non-inferiority for severe exacerbations vs daily low dose ICS + as-needed SABA*** *(O'Byrne, NEJMed 2018, Bateman, NEJMed 2018)*
  - Direct evidence from one large study of 64% reduction in severe exacerbations vs SABA-only treatment *(O'Byrne, NEJMed 2018)*
  - Symptoms reduced; one study showed reduced exercise-induced bronchoconstriction
- Values and preferences
  - High importance was given ***to preventing severe exacerbations, avoiding need for daily ICS in patients with mild or infrequent symptoms***, and safety of as-needed ICS-formoterol in maintenance and reliever therapy, with no new safety signals
  - Lower importance given to small non-cumulative differences in symptom control (ACQ-5 difference 0.15 vs MCID 0.5) and lung function compared with daily ICS
  - ***Makes use of normal patient behavior (seeking symptom relief) to deliver controller***

Asthma Treatment is NOT SET & FORGET



Confirmation of diagnosis if necessary
Symptom control & modifiable risk factors (see Box 2-2)
Comorbidities
Inhaler technique & adherence
Patient (and parent/caregiver) preferen and goals

Symptoms
Exacerbations
Side-effects
Lung function
Comorbidities
Patient (and parent/ caregiver) satisfaction

Treatment of modifiable risk factors and comorbidities
Non-pharmacological strategies
Asthma medications including ICS
Education & skills training, action plan

Assessing Response & Adjusting Treatment

- How often should asthma be reviewed?
  - 1-3 months after treatment started, then every 3-12 month:
  - 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

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

When To Consider Biologicals in Asthma ?

GINA Step 5 Asthma: Severe Asthma

Consider an add-on targeted biologic for patients with severe asthma who have:

- Exacerbations ± poor symptom control despite optimized high-dose ICS-LABA
- Worsening symptoms when high-dose treatment is decreased
- Allergic or eosinophilic biomarkers
- Those who need maintenance OCS

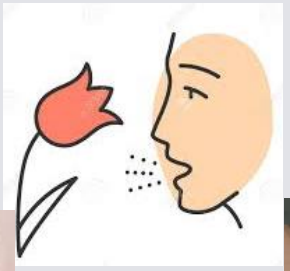
Expansive !

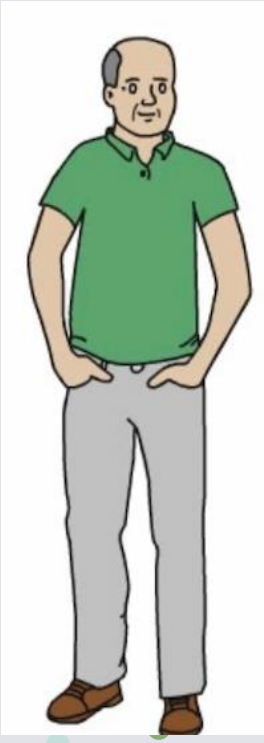
Patients with Severe Asthma Suitable for Biologicals

Type 2 Severe Asthma : Atopic / Eosinophilic Phenotype

Type 2 Inflammation

- Age of onset of asthma: Childhood / Early adulthood
- Allergic comorbidities : Atopic dermatitis, AR, CSwNP, ABPA, EGA
- Oral steroids responsive





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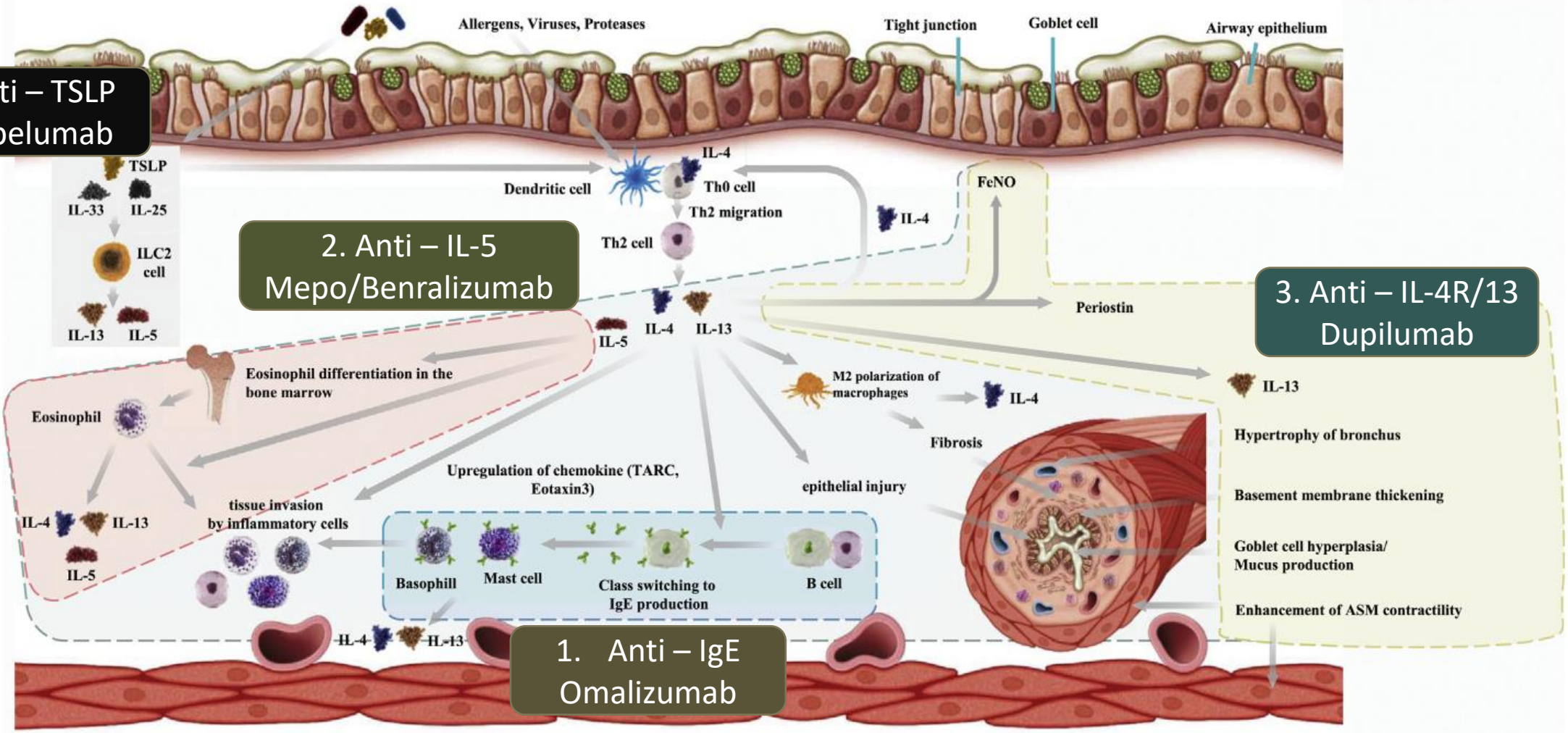
Choosing Appropriate Biologicals - *Drivers*

4. Anti – TSLP
Tezepelumab

2. Anti – IL-5
Mepo/Benralizumab

3. Anti – IL-4R/13
Dupilumab

1. Anti – IgE
Omalizumab



K. Matsunaga et al. / Allergology International 69 (2020) 187e196

Choosing Biologicals in SA : Match Expectations with Research

SA Outcomes	Omalizumab	Mepolizumab	Benralizumab
Reduction in Exacerbations	25% reduction	~ 50 %	40 -70 %
Reduction in maintenance dose of OCS	50% dose reduction in those at 15 mg/day baseline	50% dose reduction 2- 6 months	50 - 80%
FEV_1	2.1%	100 ml	**100 -160 ml @ 4 weeks**
QoL	SGRQ Asthma diaries	ACQ5 + 0.4 SGRQ +7 points	ACQ < 0.5 SGRQ +8.1 points
Real World Data	Reduction in AE in 42% vs 63 % & 28% vs 48% @ baseline	**Reduction in AE ~ 50%** Reduction in mOCS ~ 50%	**All improved with 70% exacerbation free** @2years
Comorbidities	CRwNP Chronic Idiopathic Urticaria	EGPA (300 mg/ month) CRSwNP	WIP

Assessing Effectiveness of Biologicals : *FU@ 6 months*

Initial Trial for 4 months Minimum

Good /Response

Continue

No standard criteria for good response, but consi

- Symptom burden
- Exacerbations
- Treatment side effects
- Lung function
- Treatment intensity
- Patient satisfaction/concerns

Poor response

- Stop biologic
- Switch to a different biologic or T2-targeted therapy

Unclear response

- Extend trial to 6-12 mo

Stepping Down Treatment in Asthma

- Consider stepping down when symptoms are well-controlled and lung function stable for ≥3 months
  - If patient has exacerbation risk factors, e.g. severe exacerbation in past year, step down only with close supervision
- Choose an appropriate time
- Treat each step as a therapeutic trial
  - Engage the patient in the process
  - Document asthma status
  - Provide clear instructions and an action plan
  - Sufficient medication to resume previous dose
  - Monitor symptoms and/or PEF
  - Schedule a follow-up visit
- Do not stop ICS-containing treatment
  - In severe asthma, do not stop maintenance ICS-LABA

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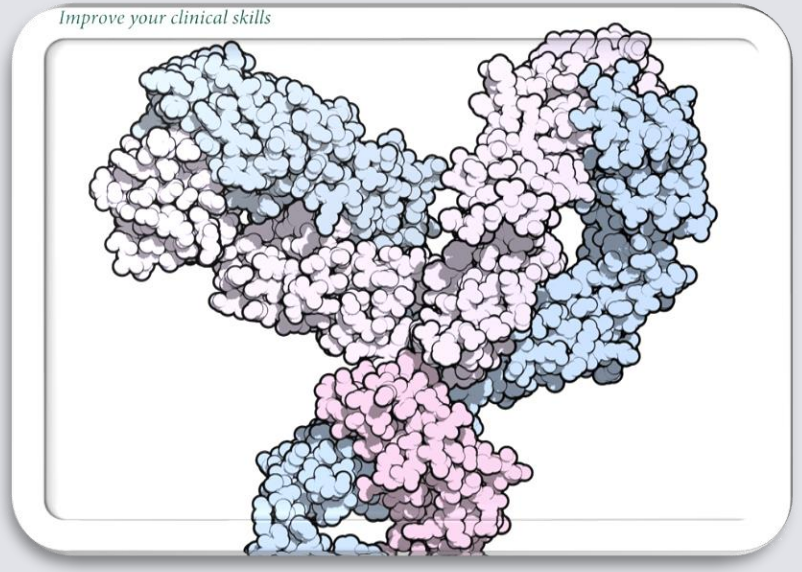
Take Home Messages

- Asthma is a chronic inflammatory airway disease.
- Diagnostic approach simple: Medical history-variability in PFT's.
- Consider BHR where diagnosis remains controversial.
- Biomarkers and particular FeNO reach applicability, validity and utility in different aspects.
- ICS the cornerstone of treatment.
- As needed treatment for step 1&2. More closer to patients needs.
- Phenotypes and endotypes drive our treatment decision strategies.
- Severe asthma a continuous challenge.
- Biologics for T2 related process…but limited treatments exist for the T2 low.
- Continuously Assess, Adjust & Review asthma cases on FU @ 1-3 months

Thank You



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