다양한 증상으로 내원하는 천식환자, 증례별 치료 방법

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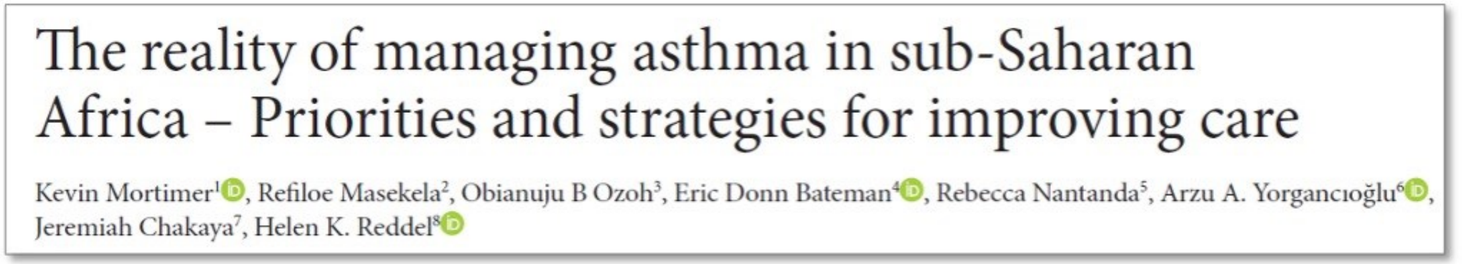
Contents

01. Goals of asthma management and asthma symptoms

Diagnosis of asthma

- Over-diagnosis and under-diagnosis of asthma are common
- Respiratory symptoms are often non-specific
  - Multiple differential diagnoses for dyspnea and cough
- Globally, most clinicians do not have (timely) access to (quality) spirometry
  - Including in high-income countries
- Peak expiratory flow (PEF) is less reliable than spirometry, but better than nothing
  - PEF meters included in WHO-PEN Package of Essential Noncommunicable disease interventions

→ Use PEF if spirometry not available, while we continue to advocate for better diagnostic tools

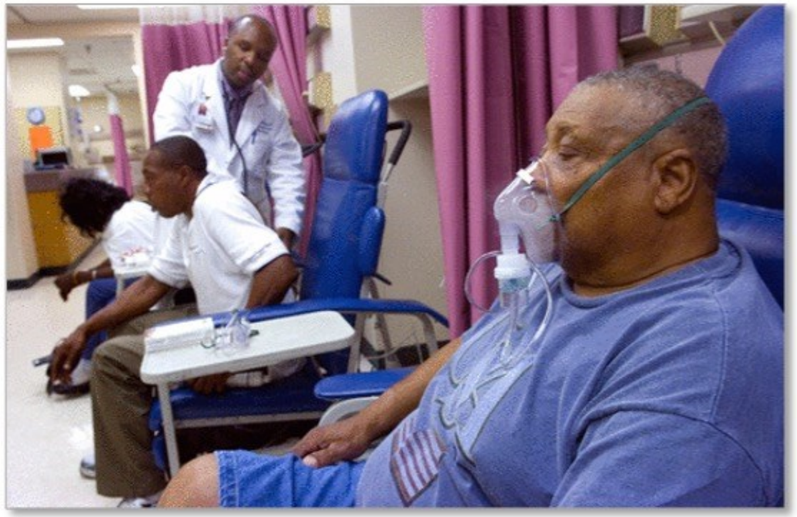

The reality of managing asthma in sub-Saharan Africa – Priorities and strategies for improving care

Kevin Mortimer[1], Refiloe Masekela[2], Obianuju B Ozoh[3], Eric Donn Bateman[4], Rebecca Nantanda[5], Arzu A. Yorgancıoğlu[6], Jeremiah Chakaya[7], Helen K. Reddel[8]

Mortimer et al, JPATS 2022

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



GINA goal of asthma treatment

Box 3-2. Long-term goal of asthma management

The goal of asthma management is to achieve the best possible long-term asthma outcomes for the patient:

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

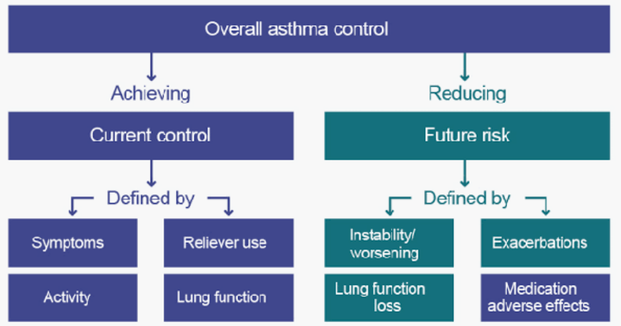
The patient's goals for their asthma may be different from these medical goals; ask the patient what they want from their asthma treatment.

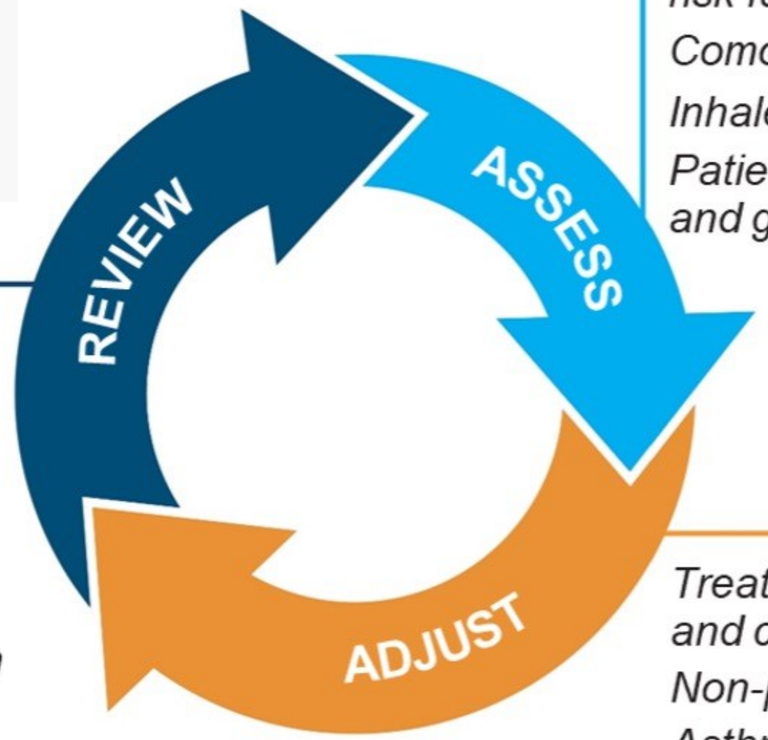
When discussing the best possible asthma outcomes with a patient, consider their goals, their asthma phenotype, clinical features, multimorbidity, risk factors (including severity of airflow limitation), practical issues including the availability and cost of medications, and the potential adverse effects of treatment (Box 3-4, p.54).

Assessing symptom control is NOT enough: the patient's risk factors (Box 2-2B, p.37), including history of exacerbations, should always also be assessed.

Symptom control and risk may be discordant: patients with few or no symptoms can still have severe or fatal exacerbations, including from external triggers such as viral infections, allergen exposure (if sensitized) or pollution.

Asthma treatment is not ‘set and forget’, and not just medications





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

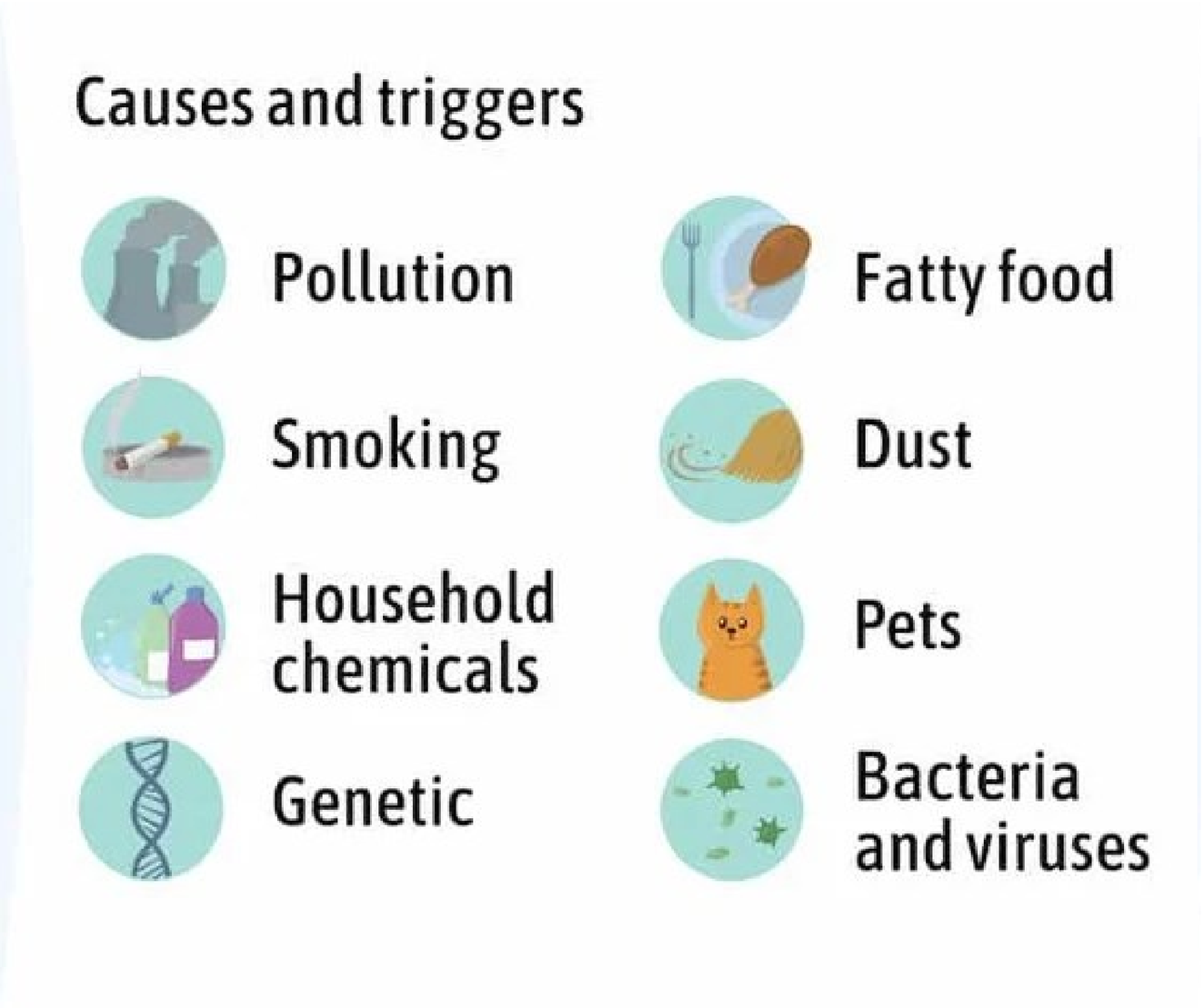
Symptoms of asthma

Respiratory Symptoms

- Shortness of breath
- Chest tightness or pain:
- Wheezing when exhaling:
- Trouble breathing
- Coughing

Systemic Symptoms

- Sleep problems
- Chronic fatigue
- Anxiety, depression



Symptoms of asthma

Patterns of respiratory symptoms that are characteristic of asthma

The following features are typical of asthma and, if present, increase the probability that the patient has asthma.[26]

Respiratory symptoms of wheeze, shortness of breath, cough and/or chest tightness:

- Symptoms are often worse at night or in the early morning.
- Symptoms vary over time and in intensity.
- Symptoms are triggered by viral infections (colds), exercise, allergen exposure, changes in weather, laughter, or irritants such as car exhaust fumes, smoke or strong smells.

The following features decrease the probability that respiratory symptoms are due to asthma:

- Chronic production of sputum
- Shortness of breath associated with dizziness, light-headedness or peripheral tingling (paresthesia)
- Chest pain
- Exercise-induced dyspnea with noisy inspiration.

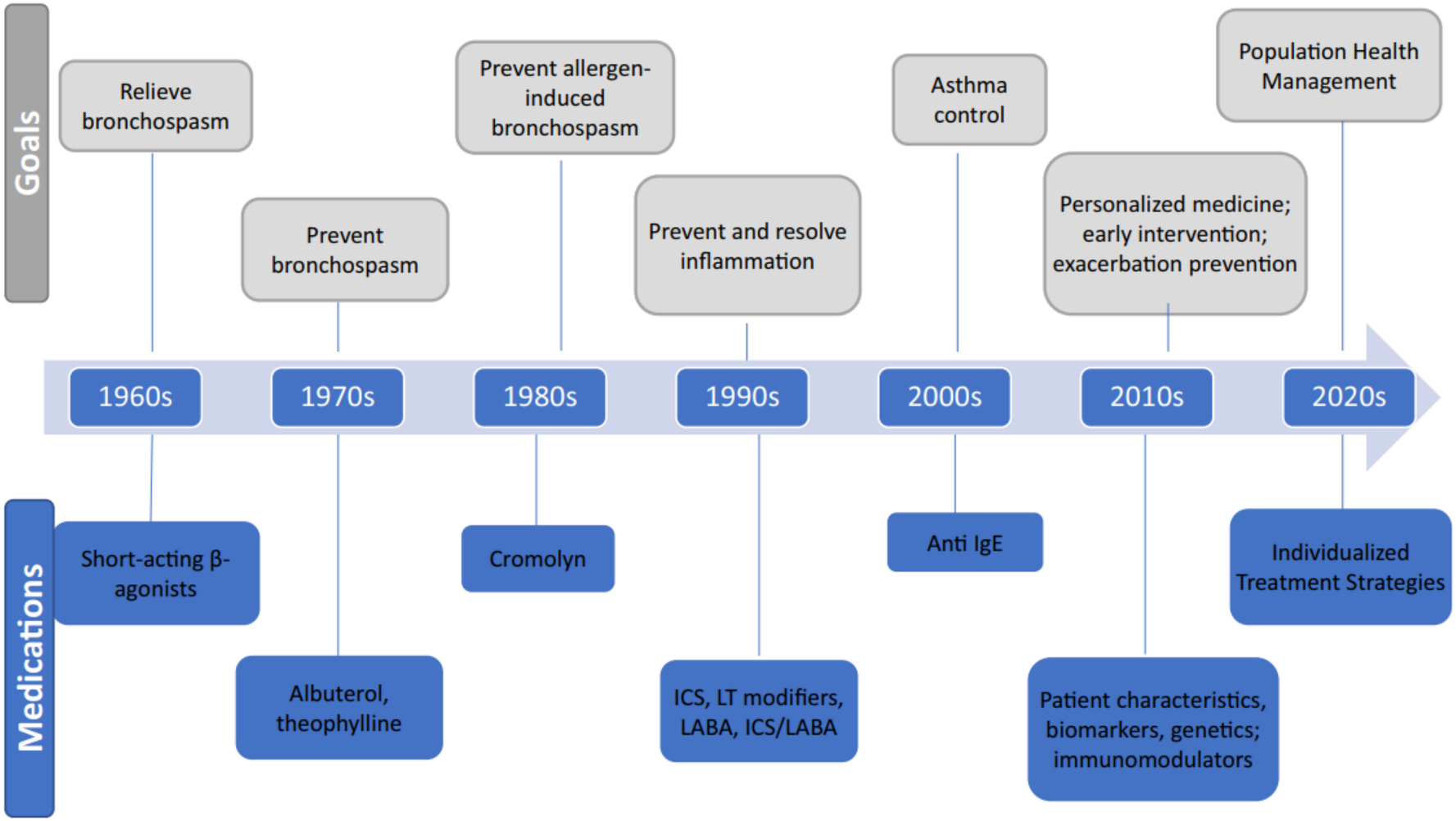
Asthma phenotypes

Cough variant asthma

- Additional information has been added about this clinical phenotype of asthma, which is common in some countries.
- Cough variant asthma may be difficult to distinguish from other causes of chronic cough in clinical practice, as spirometry may be normal and variable airflow limitation may be identified only from bronchial provocation testing.
- Some patients may later also develop wheezing and bronchodilator responsiveness. **The treatment of cough variant asthma is the same as for asthma in general; the cough may return if ICS is stopped.**

- **Allergic asthma**
- **Non-allergic asthma**
- **Adult-onset (late-onset) asthma**
- **Asthma with persistent airflow limitation**
- **Asthma with obesity**

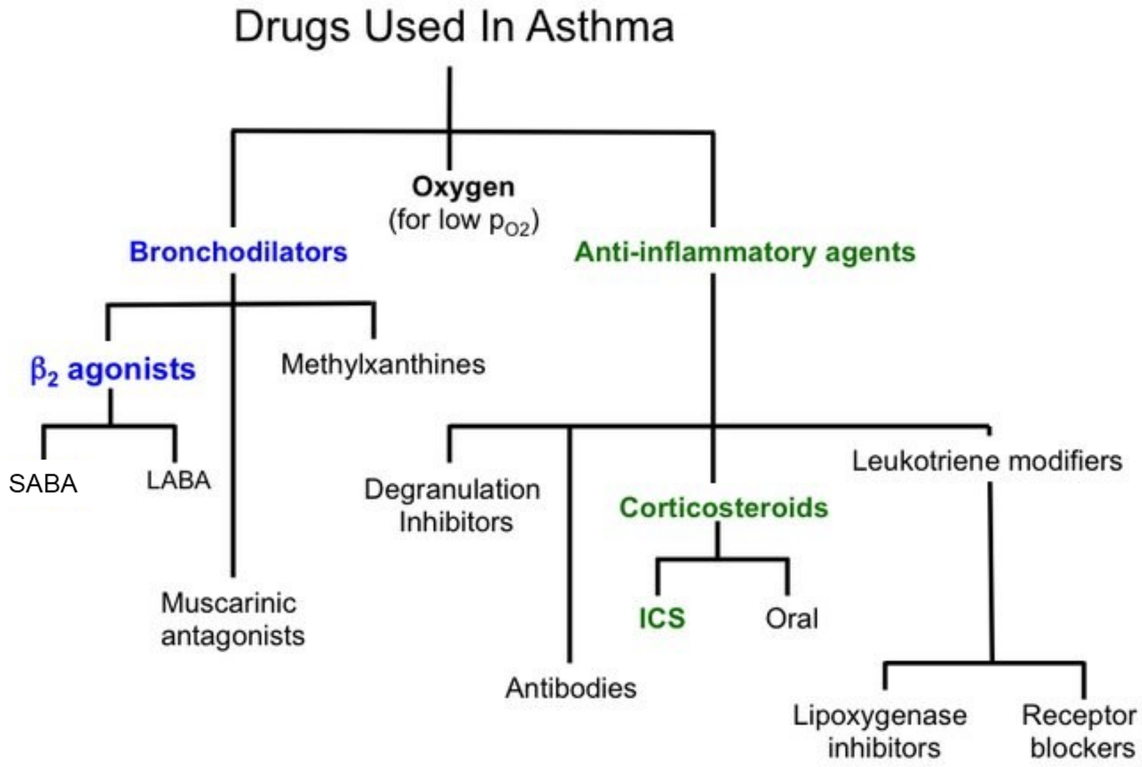
Evolving patterns of asthma management

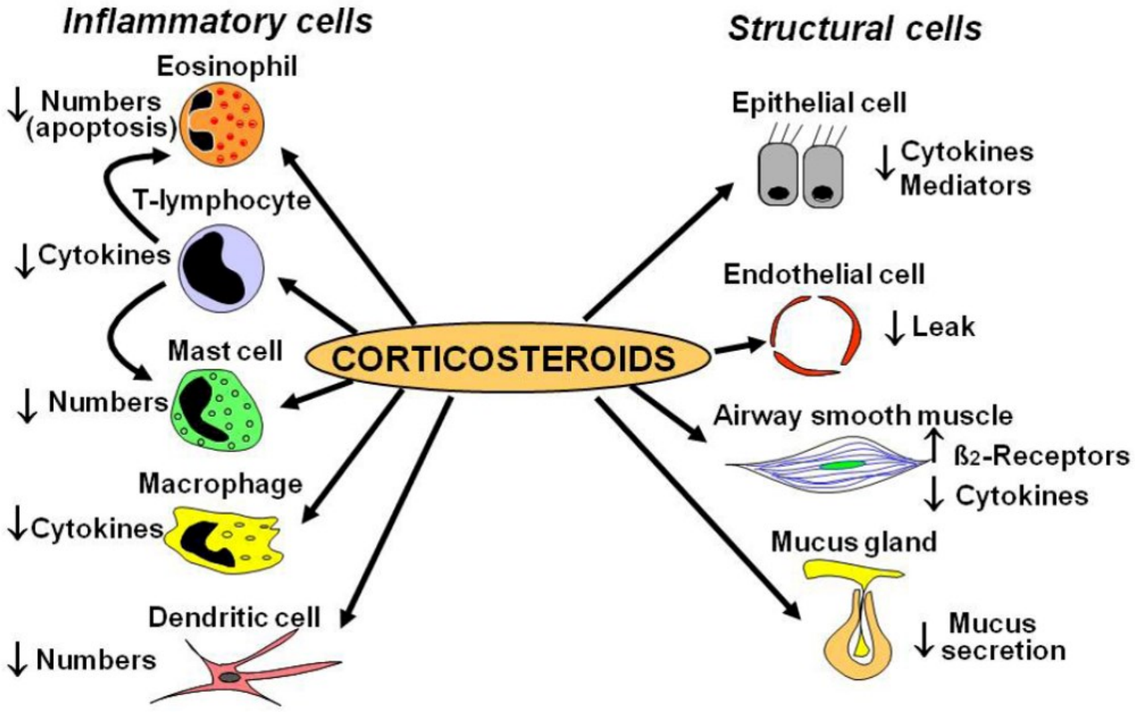


J Allergy Clin Immunol 2018;142:773-80.

About current treatment of asthma: pharmacology

Despite recognizing the heterogeneity of asthma, for most of those given a diagnosis of ‘‘asthma,’’ the standard initial treatment is the same, starting usually with ICSs and/or β2-agonists.

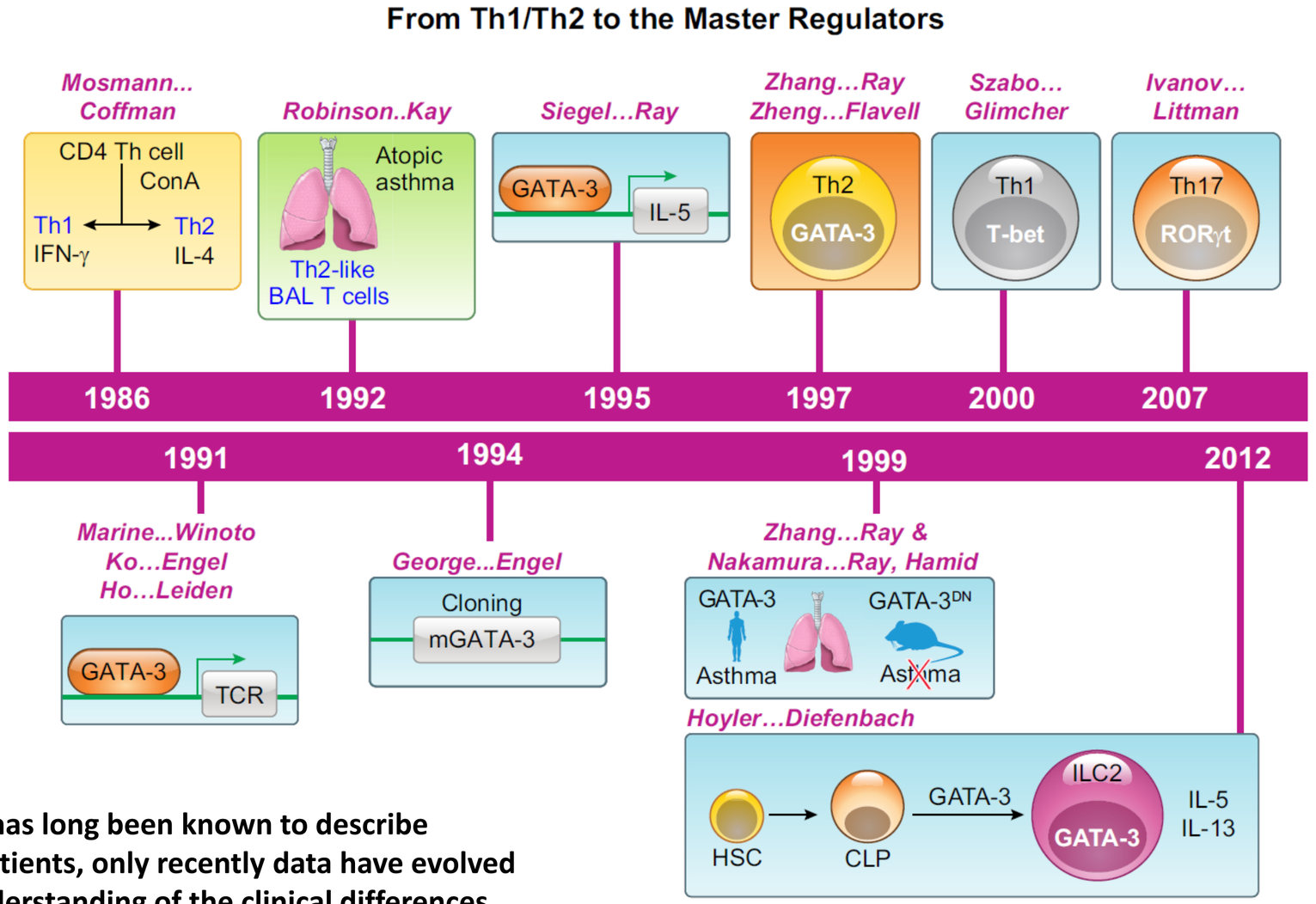




Inflammation is a common pathway in asthmatics
but not all asthmatic patients are optimally responded to steroid

World Journal of Advanced Research and Reviews, 2020, 08(03), 059-070: Pharmaceuticals 2010, 3(3), 514-540

Evolving concept of asthma

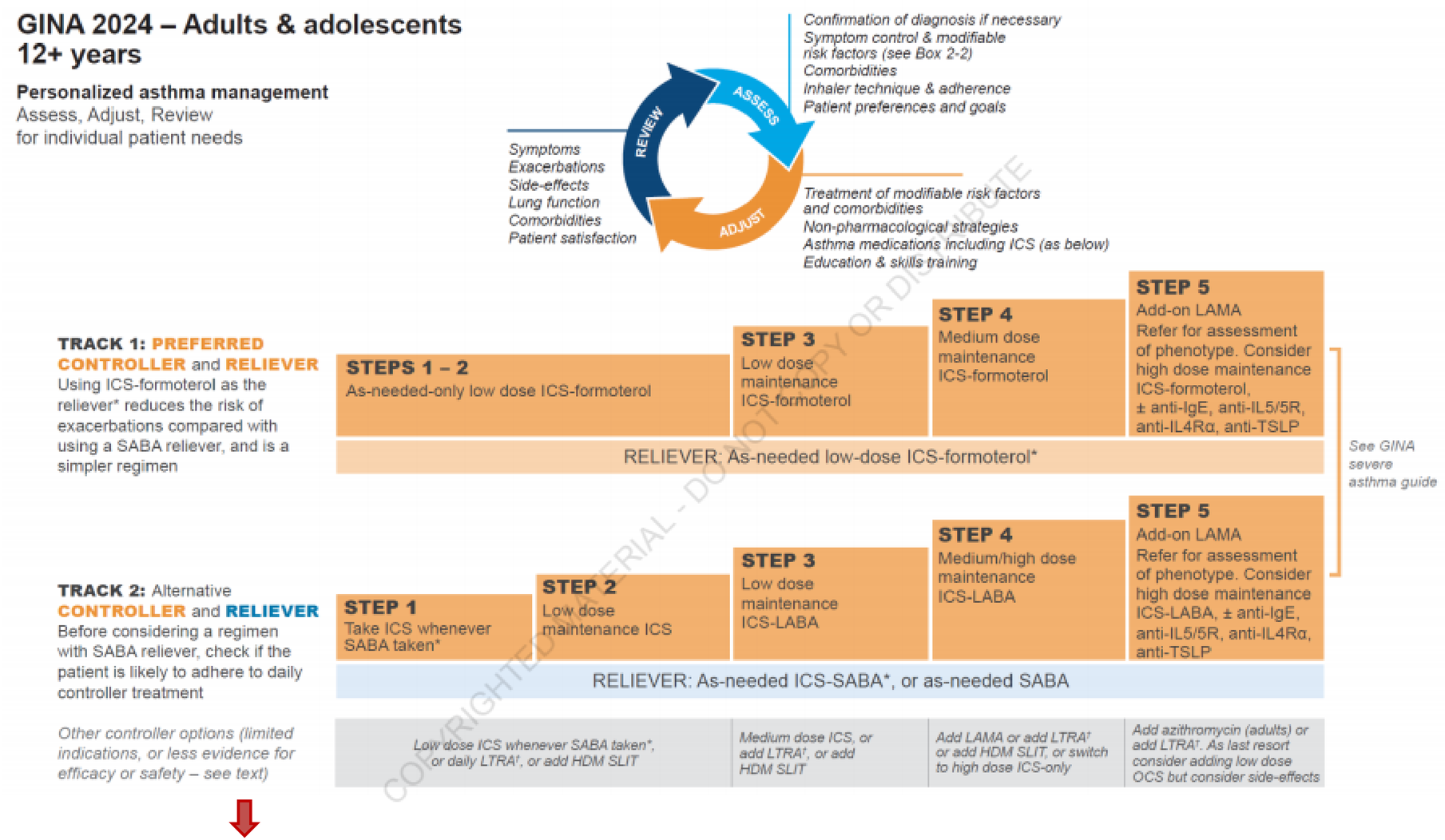


While the term asthma has long been known to describe heterogeneous groupings of patients, only recently data have evolved which enable a molecular understanding of the clinical differences.

Physiol Rev 100: 983–1017, 2020.

Asthma treatment steps for adults and adolescents

Box 4-6. Personalized management for adults and adolescents to control symptoms and minimize future risk

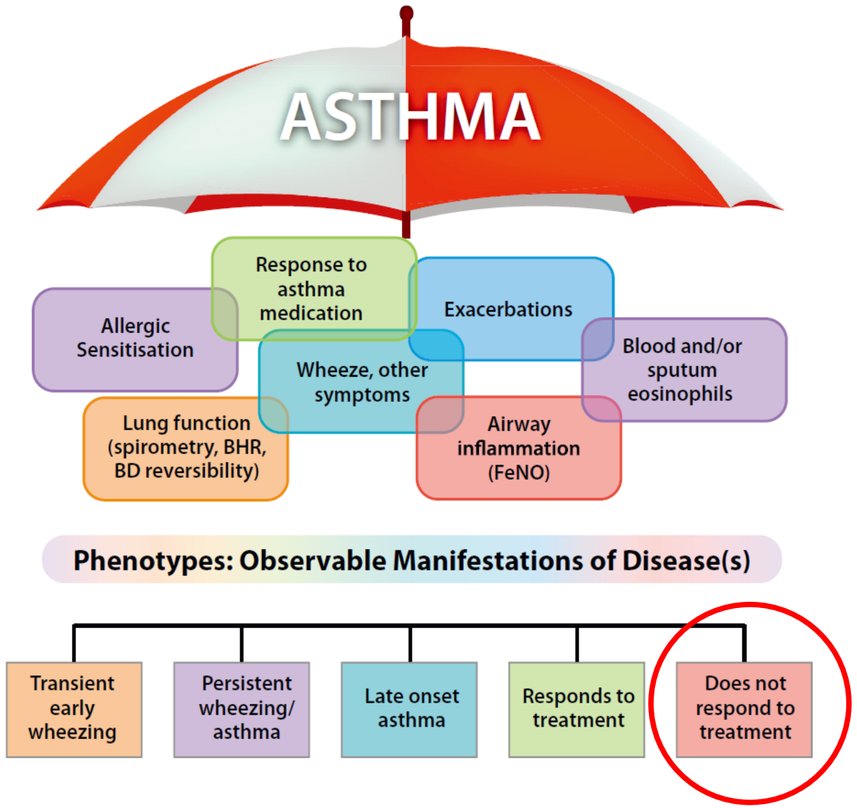


*Anti-inflammatory reliever. †If prescribing LTRA, advise patient/caregiver about risk of neuropsychiatric adverse effects. See list of abbreviations (p.11).

For recommendations about initial asthma treatment in adults and adolescents, see Box 4-4 (p.75) and Box 4-5 (p.76). See Box 4-2 (p.71) for low, medium and high ICS doses for adults and adolescents. See Box 4-8 (p.84) for Track 1 medications and doses.

No one size fits all in asthma care

- There is no doubt that the **introduction of ICSs and implementation of guidelines have contributed to a marked improvement in all outcomes** including mortality and hospital admissions between the 1980s and the beginning of the 21st century.



- Variability of response and differential response to ICSs or CS
- There Is No One Size Fits All.
- Based on the results of RCTs, a minority of study participants who do not improve or who get worse are often overlooked.

J Allergy Clin Immunol 2019;144:25-33.

02. Intermittent asthma

Intermittent asthma is mild asthma?

Intermittent asthma is characterized by:

1. Daytime symptoms occurring no more than 2 days per week
2. Nighttime symptoms occurring 2 or fewer times per month
3. Use of a rescue inhaler up to 2 days a week
4. No interference with normal daily activities
5. Normal lung function tests between episodes

Key points about intermittent asthma:

- It has very little impact on daily life
- Symptoms are infrequent and short-lived
- Lung function returns to normal between episodes
- It can often be managed with as-needed use of a rescue inhaler alone, without daily controller medications
- It is considered the mildest classification of asthma severity

People with intermittent asthma may go through long periods without any symptoms.
However, they can still experience **asthma attacks** when exposed to triggers, though these attacks are **typically less severe and less frequent** compared to more persistent forms of asthma.

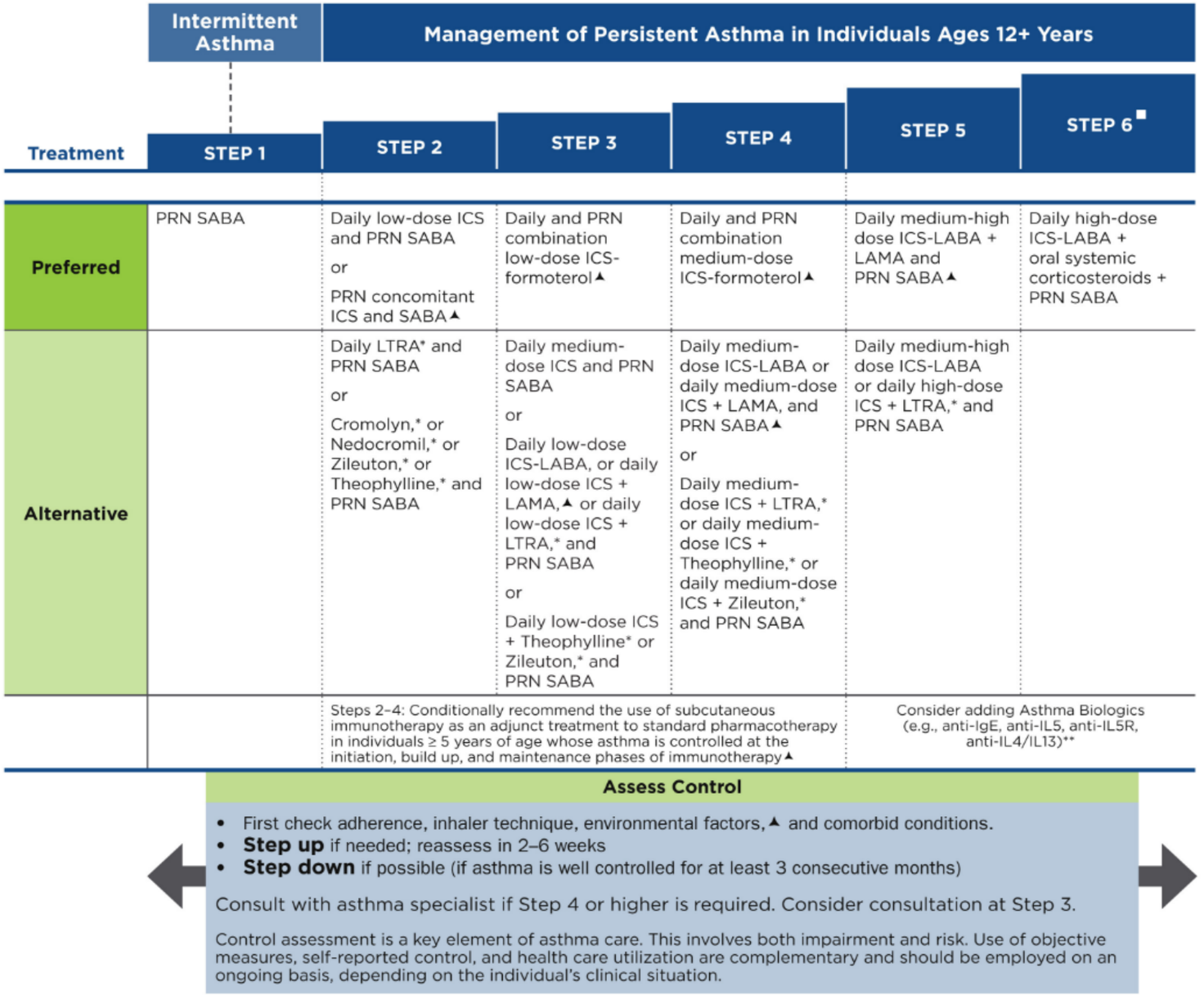
Intermittent asthma is mild asthma?

- **Mild asthma** (GINA 2024)
  - **The term ‘mild asthma’ is a retrospective label, so it cannot be used to decide which patients are suitable to receive Step 1 or Step 2 treatment.**

- Intermittent asthma and mild persistent asthma are both categories used to classify asthma based on the frequency and severity of symptoms

- Mild (Persistent) Asthma:
  Frequency of Symptoms: Symptoms occur more than twice a week, but not daily.
  Nighttime Symptoms: Nighttime awakenings occur 3-4 times a month.
  Symptom Duration: Episodes may affect activity.
  Lung Function: FEV1 is still greater than 80% of the predicted value but there is minor impairment.
  Medication Use: Use of rescue medication or AIR more than twice a week, but not daily.
  Impact on Daily Activity: Minor limitation with normal activities.

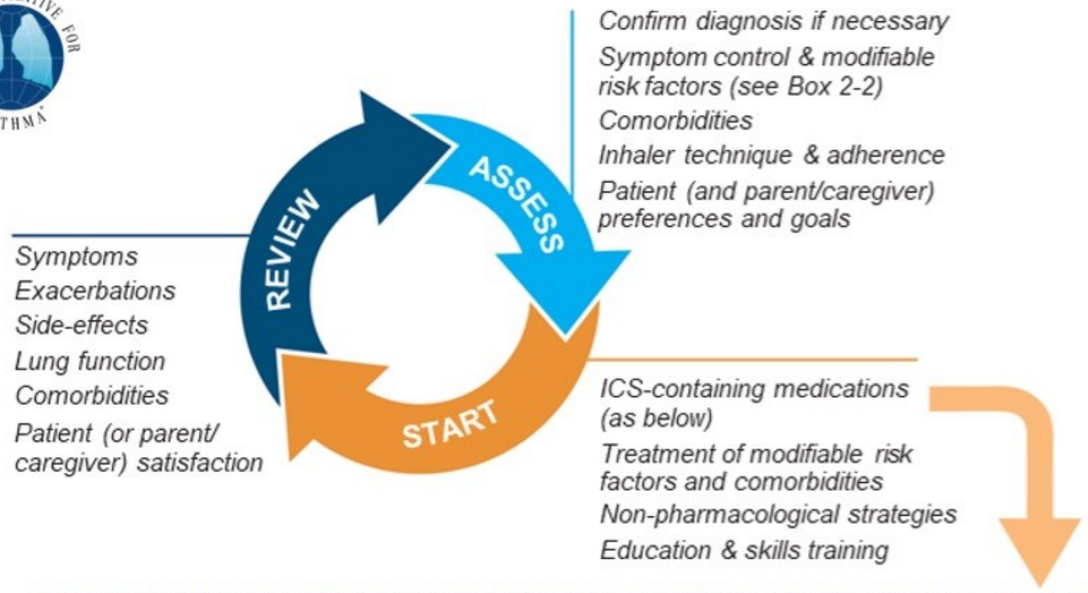
NHLBI EPR-4 Asthma Guidelines 2020



J Allergy Clin Immunol 2020;146:1217-70

GINA 2024 – STARTING TREATMENT

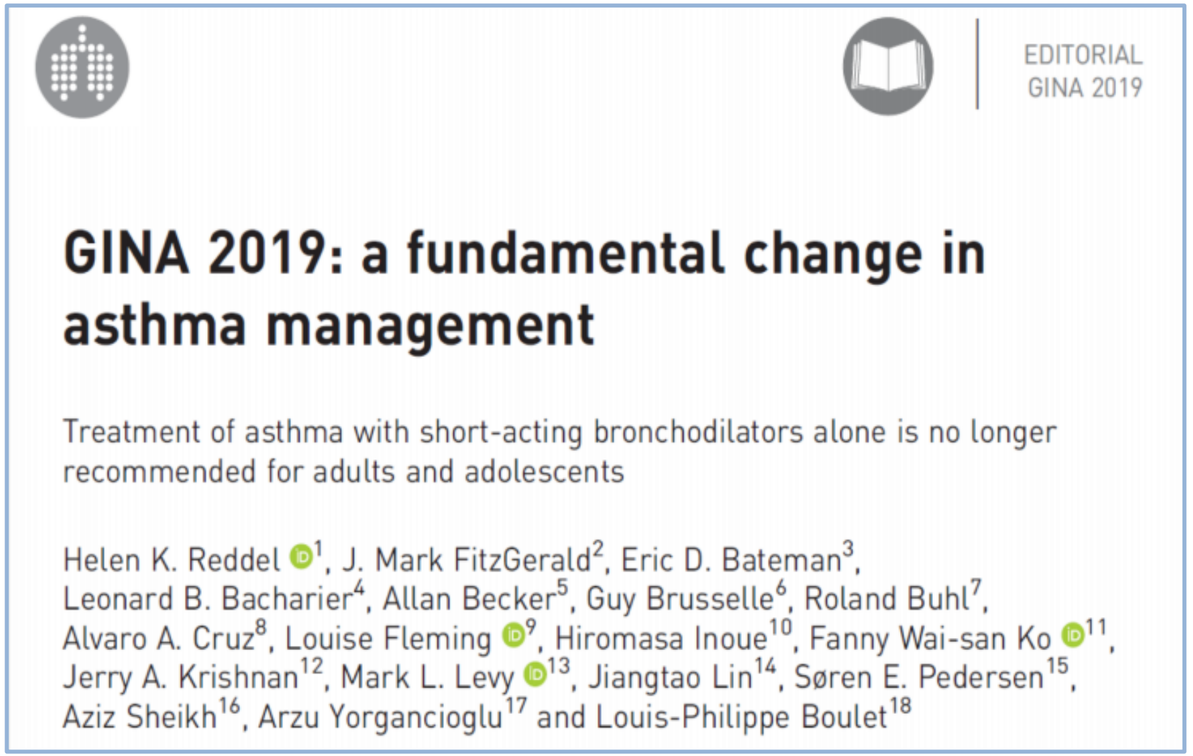
in adults and adolescents 12+ years with a diagnosis of asthma



These recommendations are based on the (little) available evidence and consensus

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	**Persistent Mild**	Low dose ICS + as-needed SABA (or ICS-SABA)	STEP 2	*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*
			Intermittent	Take low dose ICS whenever SABA is taken	STEP 1	

A reminder- a key change in asthma management



EDITORIAL
GINA 2019

GINA 2019: a fundamental change in asthma management

Treatment of asthma with short-acting bronchodilators alone is no longer recommended for adults and adolescents

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

@ERSpublications
GINA no longer recommends treating adults/adolescents with asthma with short-acting bronchodilators alone. Instead, they should receive symptom-driven (in mild asthma) or a daily corticosteroid-containing inhaler, to reduce risk of severe exacerbations. http://bit.ly/310LLzE

Cite this article as: Reddel HK, FitzGerald JM, Bateman ED, *et al.* GINA 2019: a fundamental change in asthma management. *Eur Respir J* 2019; 53: 1901046 [https://doi.org/10.1183/13993003.01046-2019].

Reddel et al. ERJ 2019;53:1901046

GINA emphasized **poor adherence** as a modifiable risk factor for **exacerbations**

- When the reliever is SABA, poor adherence with maintenance controller exposes the patient to risks of SABA-only treatment
- We were aware that **poor adherence is common in mild asthma** in the community, and that this would expose patients to the risks of SABA-only treatment
- High importance given to poor adherence with regular ICS in patients with infrequent symptoms, which would expose them to risks of SABA-only treatment

- 1. Adopted from GINA guideline 2019

AIR (Anti-inflammatory reliever) in GINA 2023

addition

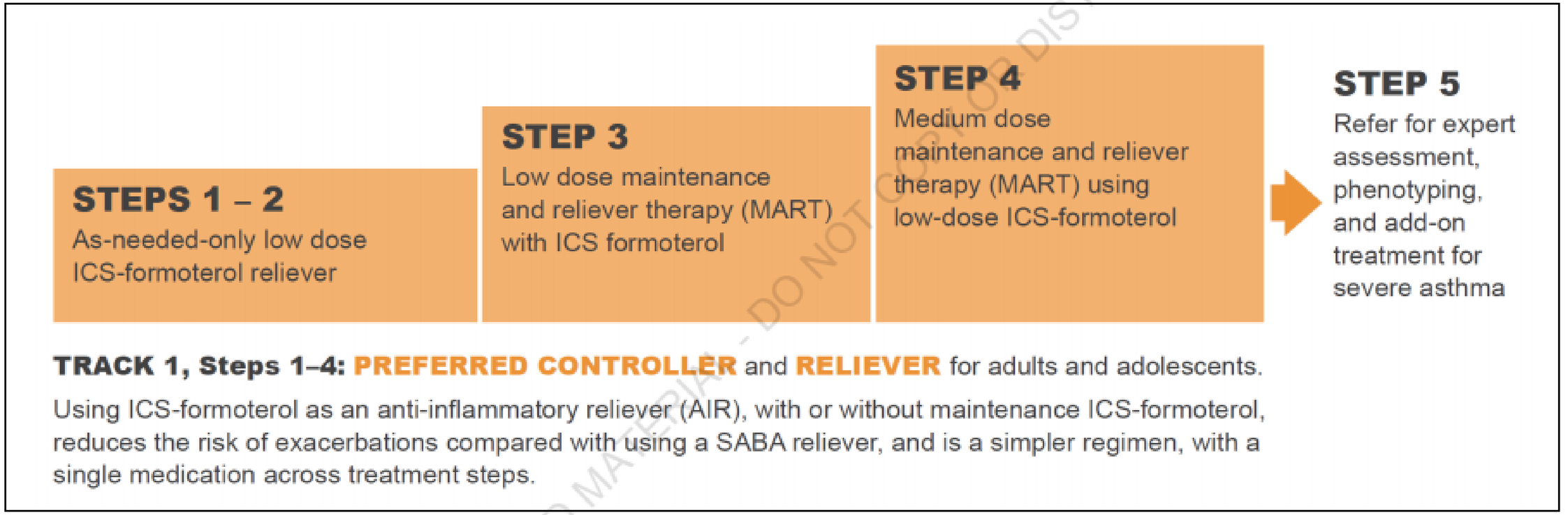
Box 3-4. Terminology for asthma medications

Term	Definition	Notes
Anti-inflammatory reliever (AIR)	Reliever inhaler that contains both a low-dose ICS and a rapid-acting bronchodilator • ICS-formoterol • ICS-SABA	Includes budesonide-formoterol, beclometasone-formoterol and ICS-salbutamol combinations. Patients can also use them as needed before exercise or allergen exposure to prevent asthma symptoms and bronchoconstriction. Non-formoterol LABAs in combination with ICS cannot be used as relievers. The anti-inflammatory effect of as-needed ICS-formoterol was demonstrated by reduction in FeNO in several studies.[171,172,195] Some anti-inflammatory relievers can be used as-needed at Steps 1–2 as the person's sole asthma treatment, without a maintenance treatment ('**AIR-only**' treatment). Almost all evidence for this is with ICS-formoterol. Some ICS-formoterol combinations can be used as both maintenance treatment and reliever treatment at Steps 3–5 (see **MART**, below). For medications and doses see Box 3-15, p.80.

It is important to distinguish between the as-needed use of an anti-inflammatory reliever on its own ('AIR-only') in Steps 1-2, and maintenance and reliever therapy ('MART') with ICS-formoterol in Step 3-5.

Track 1 treatment

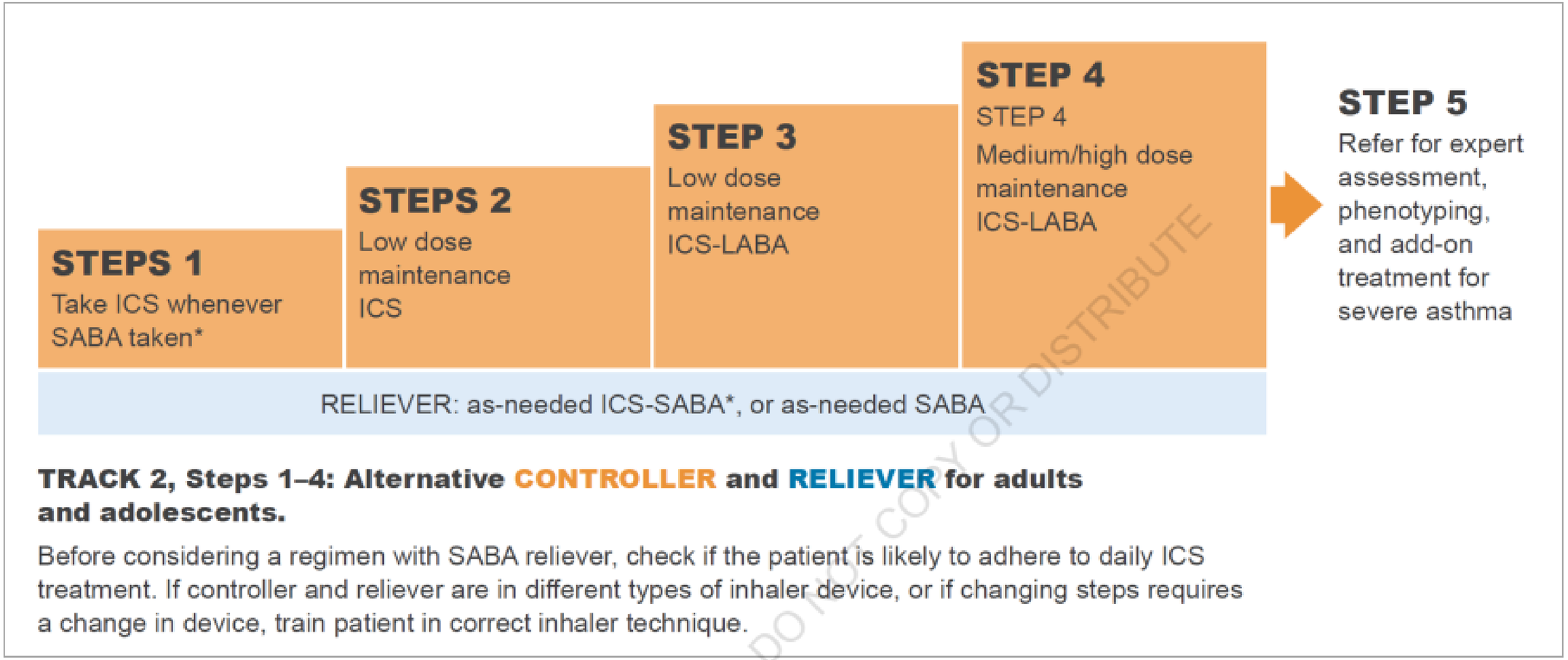
Box 4-7. Track 1 (preferred) treatment Steps 1–4 for adults and adolescents



See Box 4-8 (p.84) for details of medications and doses. AIR: anti-inflammatory reliever; ICS: inhaled corticosteroid; MART: maintenance-and-reliever therapy with ICS-formoterol; SABA: short-acting beta$_2$ agonist

Track 2 treatment

Box 4-9. Track 2 (alternative) treatment Steps 1–4 for adults and adolescents



TRACK 2, Steps 1–4: Alternative CONTROLLER and RELIEVER for adults and adolescents.

Before considering a regimen with SABA reliever, check if the patient is likely to adhere to daily ICS treatment. If controller and reliever are in different types of inhaler device, or if changing steps requires a change in device, train patient in correct inhaler technique.

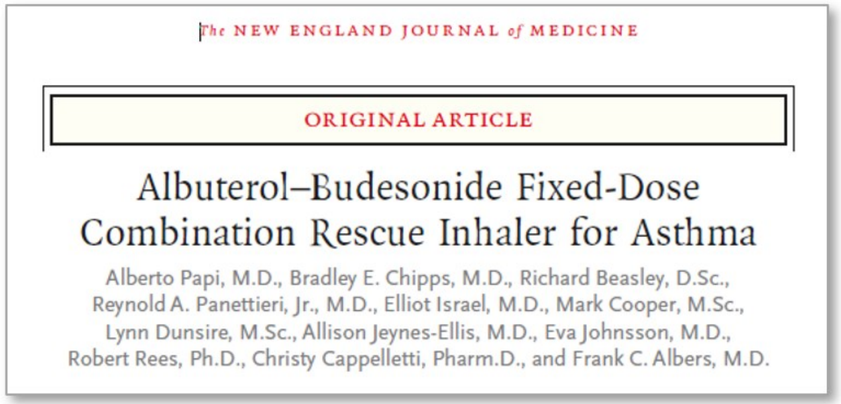
*Anti-inflammatory reliever therapy (AIR); ICS: inhaled corticosteroid; LABA: long-acting beta$_2$ agonist; SABA: short-acting beta$_2$ agonist

Medication and doses of Track 1 AIR therapy

Age	Inhalers: mcg/inhalation metered dose *[delivered dose]* and maximum in any day	Dosing frequency by age group and treatment step (see next page for additional inhaler options and doses)
6–11 years	Budesonide-formoterol 100/6 DPI *[80/4.5]* (maximum total 8 inhalations in any day)	Step 1–2 AIR-only: no evidence to date Step 3 MART: 1 inhalation once daily plus 1 as needed Step 4 MART: 1 inhalation twice daily plus 1 as needed Step 5 MART: not recommended
12–17 years	Budesonide-formoterol 200/6 DPI *[160/4.5]* (maximum total 12 inhalations in any day)	Step 1–2 (AIR-only): 1 inhalation as needed Step 3 MART: 1 inhalation twice (or once) daily plus 1 as needed Step 4 MART: 2 inhalations twice daily plus 1 as needed Step 5 MART: 2 inhalations twice daily plus 1 as needed
≥18 years	Budesonide-formoterol 200/6 *[160/4.5]* DPI or BDP-formoterol 100/6 pMDI or DPI (maximum total 12 inhalations in any day†)	Step 1–2 (AIR-only): 1 inhalation as needed† Step 3 MART: 1 inhalation twice (or once) daily plus 1 as needed Step 4 MART: 2 inhalations twice daily plus 1 as needed Step 5 MART: 2 inhalations twice daily plus 1 as needed
Adults 18 years and older		
Budesonide-formoterol DPI 200/6 *[160/4.5]* (maximum total 12 inhalations in any day*)		Step 1–2 (AIR-only): 1 inhalation as needed Step 3 MART: 1 inhalation twice (or once) daily plus 1 as needed Step 4 MART: 2 inhalations twice daily plus 1 as needed Step 5 MART: 2 inhalations twice daily plus 1 as needed
Budesonide-formoterol pMDI 200/6 *[160/4.5]* (maximum total 12 inhalations in any day*)		Step 1–2 (AIR-only): 1 inhalation as needed Step 3 MART: 1 inhalation twice (or once) daily plus 1 as needed Step 4 MART: 2 inhalations twice daily plus 1 as needed Step 5 MART: 2 inhalations twice daily plus 1 as needed
Budesonide-formoterol pMDI 100/3 *[80/2.25]* (maximum total 24 inhalations in any day*)		Step 1–2 (AIR-only): 2 inhalations as needed Step 3 MART: 2 inhalations twice (or once) daily plus 2 as needed Step 4 MART: 4 inhalations twice daily plus 2 as needed Step 5 MART: 4 inhalations twice daily plus 2 as needed
Beclometasone-formoterol pMDI or DPI 100/6 (GINA suggests maximum total 12 inhalations in any day*)		Step 1–2 (AIR-only): 1 inhalation as needed Step 3 MART: 1 inhalation twice (or once) daily plus 1 as needed Step 4 MART: 2 inhalations twice daily plus 1 as needed Step 5 MART: 2 inhalations twice daily plus 1 as needed

Maximum total dose of formoterol (with ICS) in a single day:
72 mcg metered dose

AIR (Anti-inflammatory reliever): ICS-SABA



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

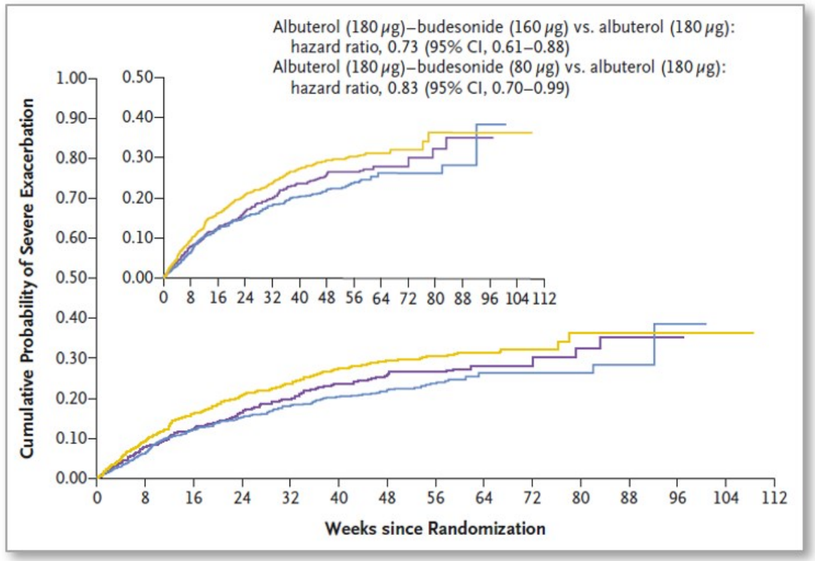
Albuterol–Budesonide Fixed-Dose Combination Rescue Inhaler for Asthma

Alberto Papi, M.D., Bradley E. Chipps, M.D., Richard Beasley, D.Sc., Reynold A. Panettieri, Jr., M.D., Elliot Israel, M.D., Mark Cooper, M.Sc., Lynn Dunsire, M.Sc., Allison Jeynes-Ellis, M.D., Eva Johnsson, M.D., Robert Rees, Ph.D., Christy Cappelletti, Pharm.D., and Frank C. Albers, M.D.

Papi et al, NEJMed 2022 (n=3,132)

In patients taking Step 3–5 maintenance treatment:

- Hazard ratio for probability of severe exacerbations was 0.73 (95% CI 0.61–0.88) with higher dose of as-needed albuterol-budesonide compared with as-needed albuterol
- Most benefit seen in Step 3



From "Albuterol-Budesonide Fixed Dose Combination Rescue Inhaler for Asthma", Papi et al, NEJMed 2022; 386:2071-2083 Copyright © 2023. Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society

- **Airsupra™**
- **ICS-SABA (Budesonide-Albuterol)**
- **FDA 승인 (2023.01.10) - 천식의 악화 위험 감소 및 기관지 수축 예방**
- **국내 미허가**

SABA-ICS may be the preferred choice for patients taking ICS-LABA maintenance that does not contain formoterol.

03. Uncontrolled asthma and severe asthma

Assessment of symptom control

- GINA clarifies that this should not be limited to the most recent 4 weeks; there are no validated tools for assessing symptom control over longer periods than this, and recall-error for symptoms is common.
- GINA continues to emphasize that assessing asthma control is not enough–the patients risk factors for exacerbations (incl. history of exacerbations), for accelerated decline in lung function and for medication AE must also be assessed.

ERS/ATS Definitions for Severe and Uncontrolled Asthma

Severe asthma is estimated to have a prevalence of **5% to 10%** in the asthma population

ERS/ATS Definition of Severe Asthma

Requires ≥1 of the following to maintain asthma control:

- High-dose ICS plus an additional controller
- SCS for ≥50% of the previous year

or

Asthma that remains uncontrolled despite these therapies

ERS/ATS Definition of Uncontrolled Asthma

Meets the criteria for ≥1 of the following:

Poor symptom control

ACQ ≥1.5 or ACT <20

Frequent severe exacerbations

≥2 bursts of SCS (≥3 days each) in previous year

Serious exacerbations

≥1 hospitalization, ICU stay, or mechanical ventilation in previous year

Airflow limitation

FEV_1 <80% predicted after appropriate bronchodilator withheld

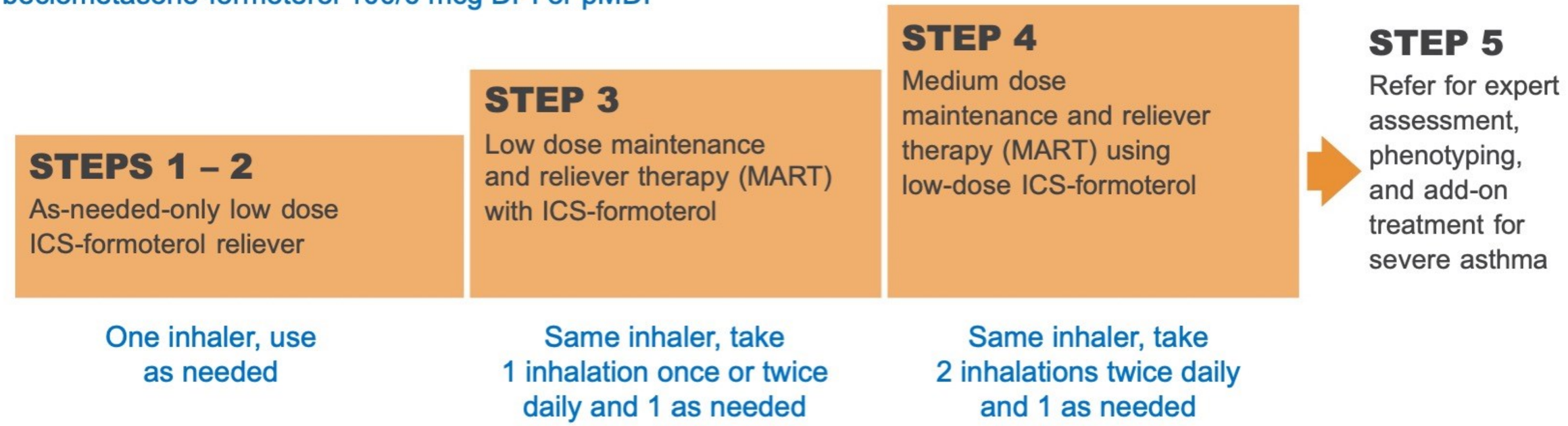
ACQ=Asthma Control Questionnaire; ACT=Asthma Control Test; ATS=American Thoracic Society; ERS=European Respiratory Society; FEV_1=forced expiratory volume in 1 second; ICS=inhaled corticosteroid; ICU=intensive care unit; SCS=systemic corticosteroid.

Reference: Chung KF, et al. *Eur Respir J.* 2014;43(2):343-373.

TRACK 1, Steps 1–4: PREFERRED CONTROLLER and RELIEVER for adults and adolescents.

Using ICS-formoterol as an anti-inflammatory reliever (AIR), with or without maintenance ICS-formoterol, reduces the risk of exacerbations compared with using a SABA reliever, and is a simpler regimen, with a single medication across treatment steps.

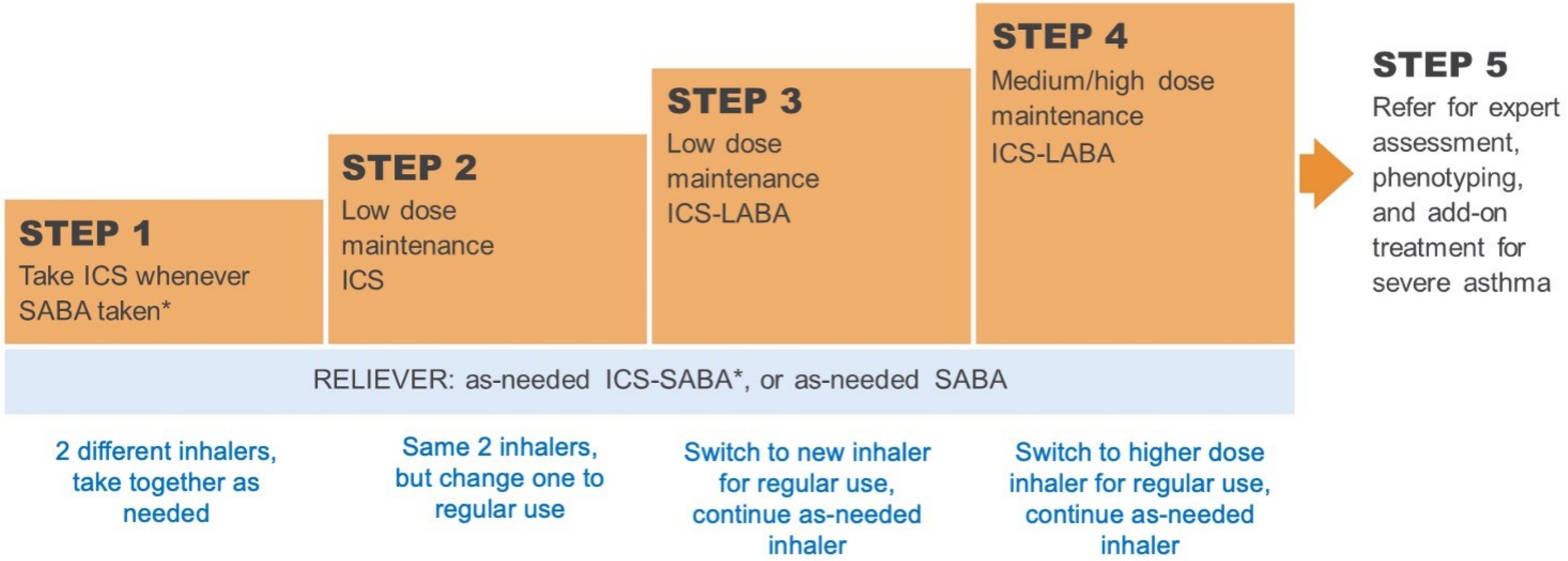
For budesonide-formoterol 200/6 mcg [160/4.5] DPI or pMDI*, or beclometasone-formoterol 100/6 mcg DPI or pMDI



*In some countries, a budesonide-formoterol pMDI with 100/3 [80/2.25] mcg per actuation is available for AIR-only or MART. For this pMDI, the recommended number of inhalations is double those shown above above.

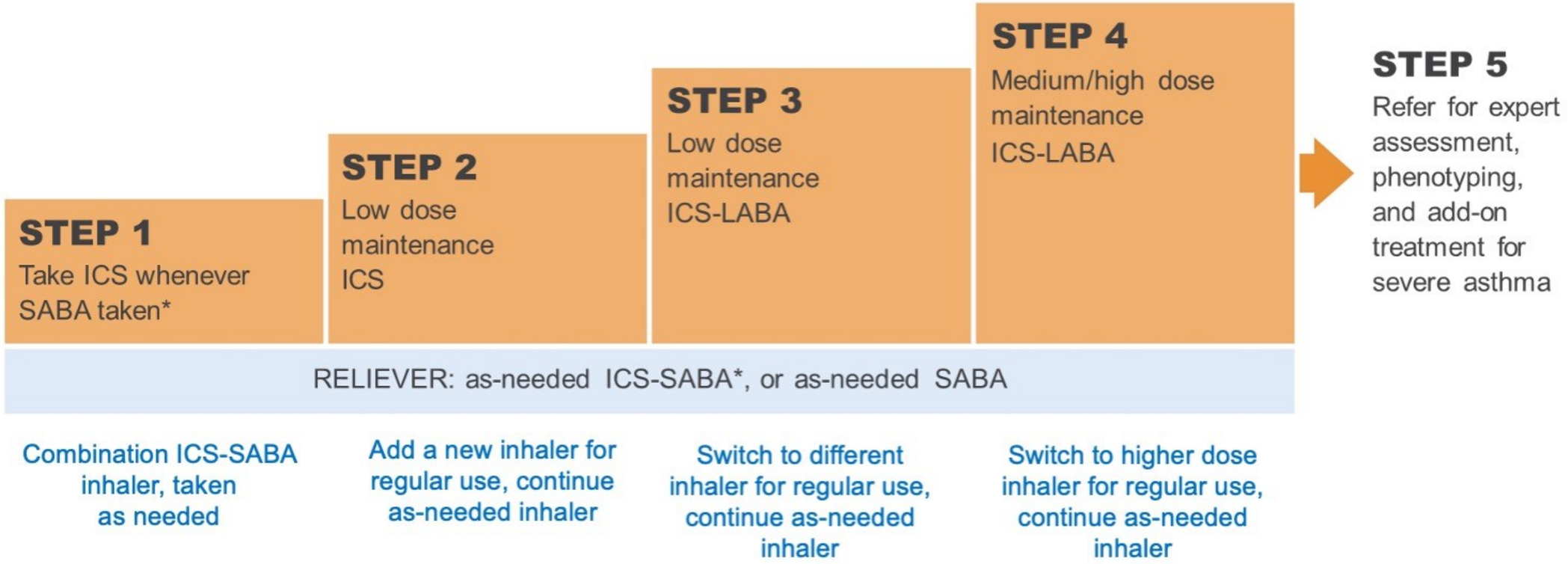
TRACK 2, Steps 1–4: Alternative CONTROLLER and RELIEVER for adults and adolescents, with SABA reliever

Before considering a regimen with SABA reliever, check if the patient is likely to adhere to daily ICS treatment. If controller and reliever are in different types of inhaler device, or if changing steps requires a change in device, train patient in correct inhaler technique.



TRACK 2, Steps 1–4: Alternative CONTROLLER and RELIEVER for adults and adolescents, with ICS-SABA reliever

If maintenance and reliever medications are in different types of inhaler device, or if changing steps requires a change in device, train patient in correct inhaler technique. Make sure the patient knows which inhaler should be taken regularly, and which one as needed.



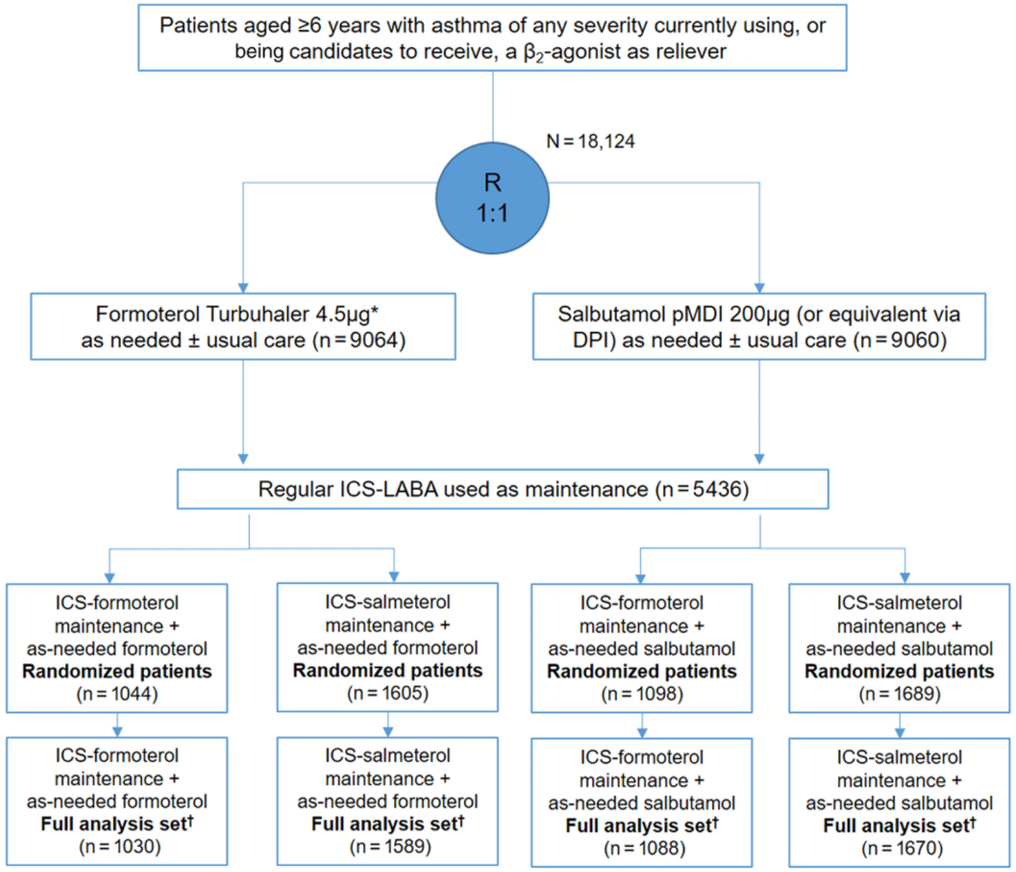
ICS-formoterol as reliever with other ICS-LABAs?

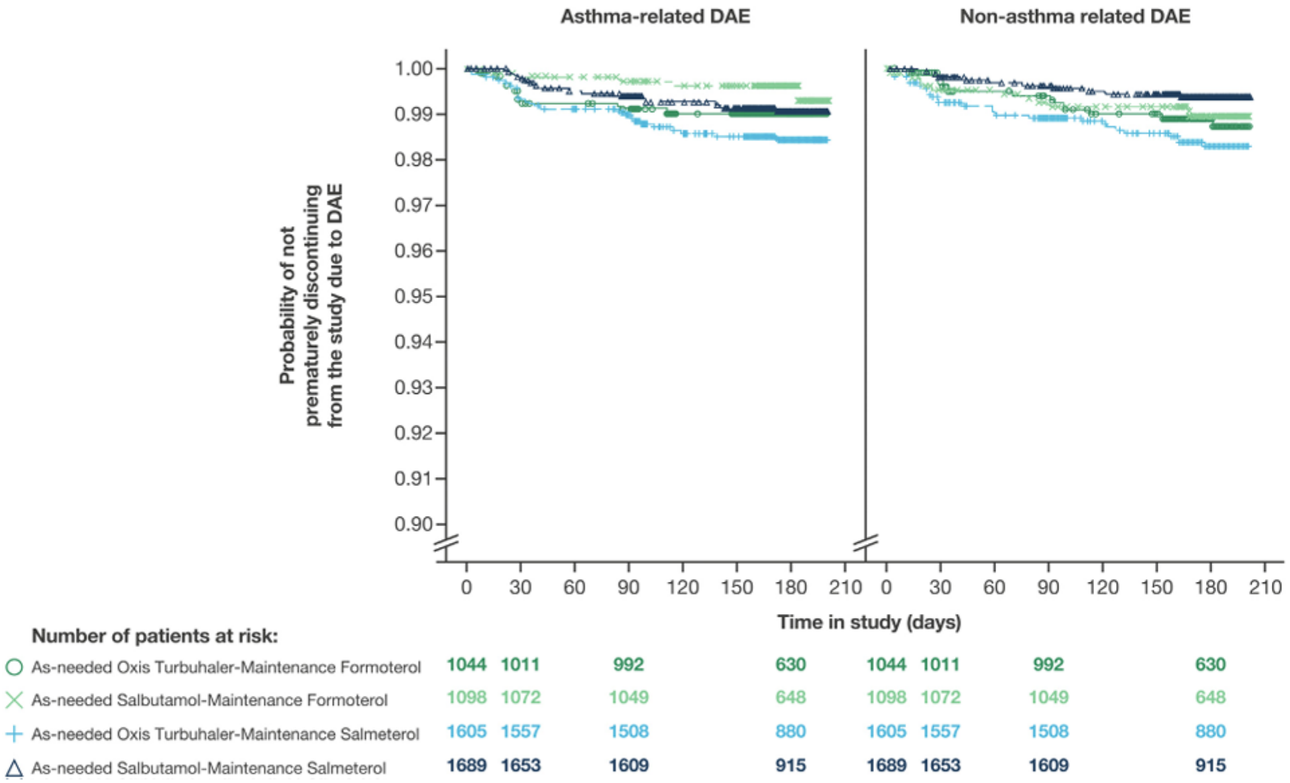
GINA previously recommended against use of ICS-formoterol as the reliever for patients using maintenance treatment ICS-other LABA

Original Article

Safety and Effectiveness of As-Needed Formoterol in Asthma Patients Taking Inhaled Corticosteroid (ICS)-Formoterol or ICS-Salmeterol Maintenance Therapy

Helen Kathryn Reddel, PhD[a], Guy Brusselle, MD[b], Rosa Lamarca, PhD[c], Per Gustafson, MD[d], Gary P. Anderson, PhD[e], and Carin Jorup, MD[f] *Sydney, NSW, and Melbourne, VIC, Australia; Ghent, Belgium; Barcelona, Spain; and Gothenburg, Sweden*

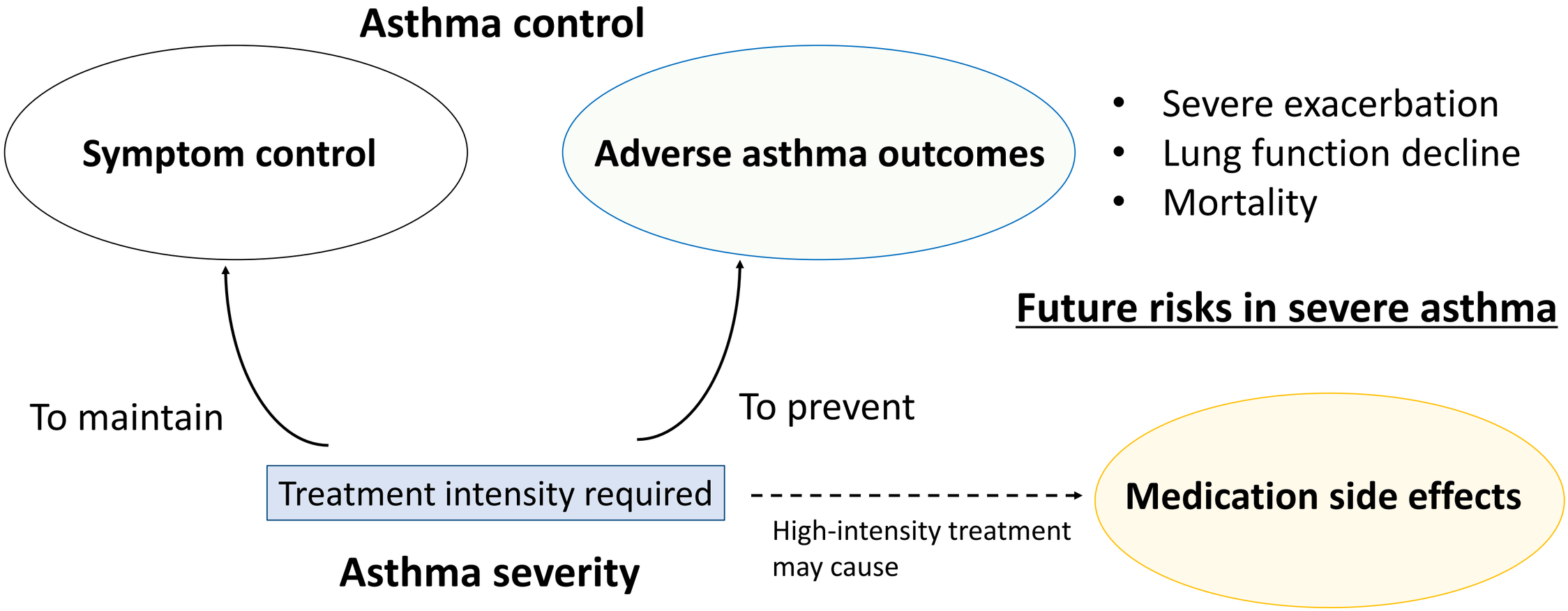




In patients taking maintenance ICS-salmeterol, the use of as-needed formoterol versus as-needed salbutamol was associated with more DAEs, specifically non-serious and non-asthma-related DAEs, than in patients taking maintenance ICS-formoterol.

J Allergy Clin Immunol Pract 2023;11:2104-14

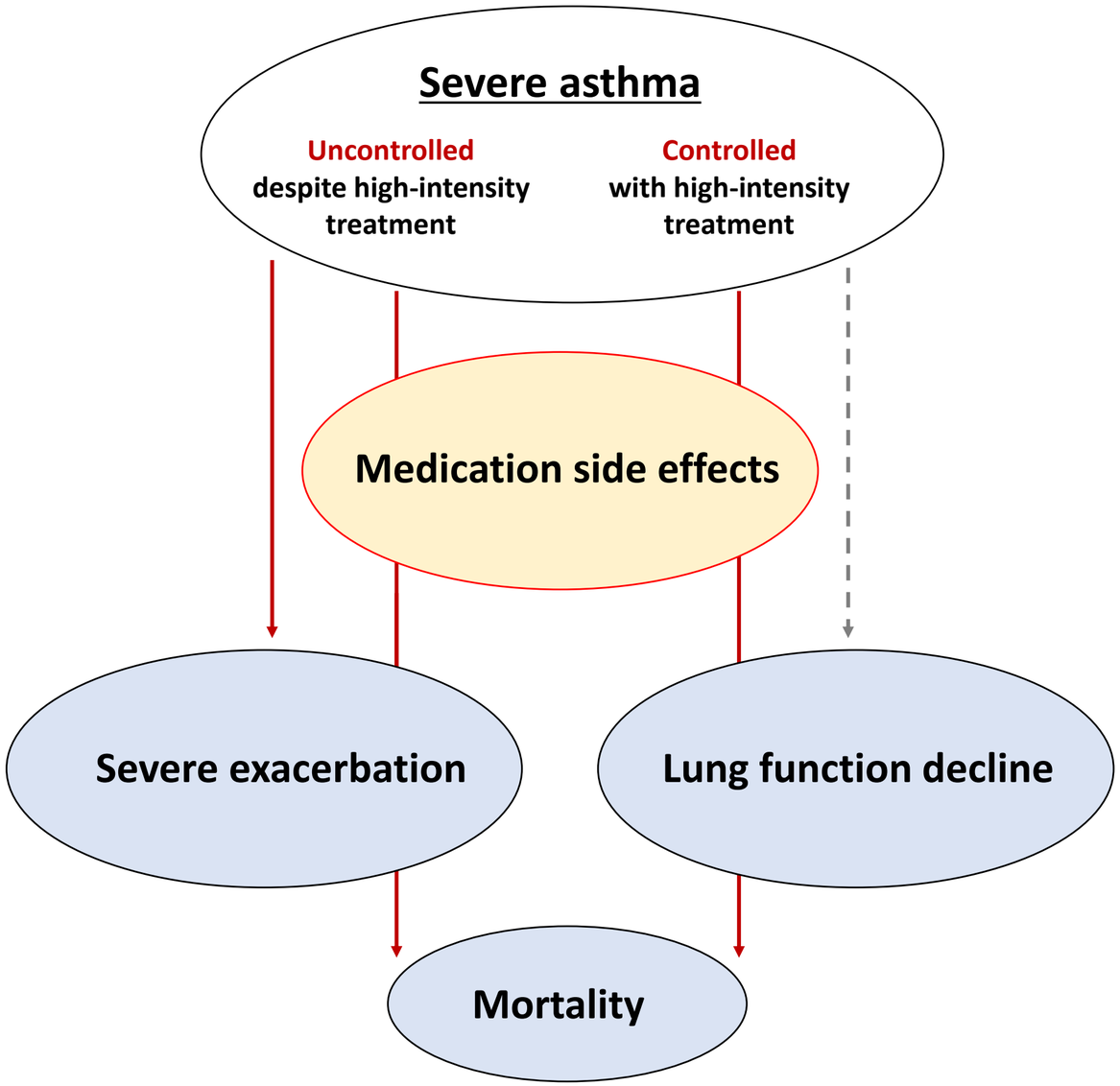
The concept of severe asthma



- Severe exacerbation
- Lung function decline
- Mortality

Future risks in severe asthma

Future risks in severe asthma



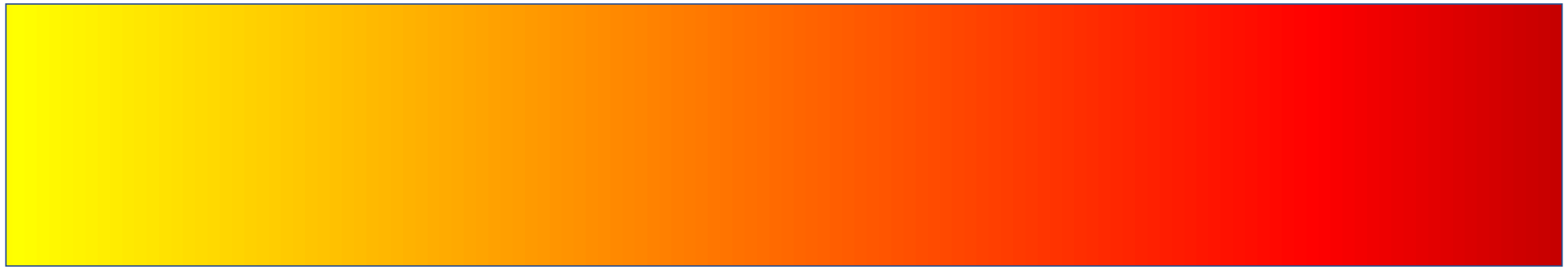
Treatment-related future risks (OCS)

Asthma activity-related future risks

Song WJ et al. Allergy Asthma Immunol Res 2019

Two types of severe asthma: Patient experience

Patient's response



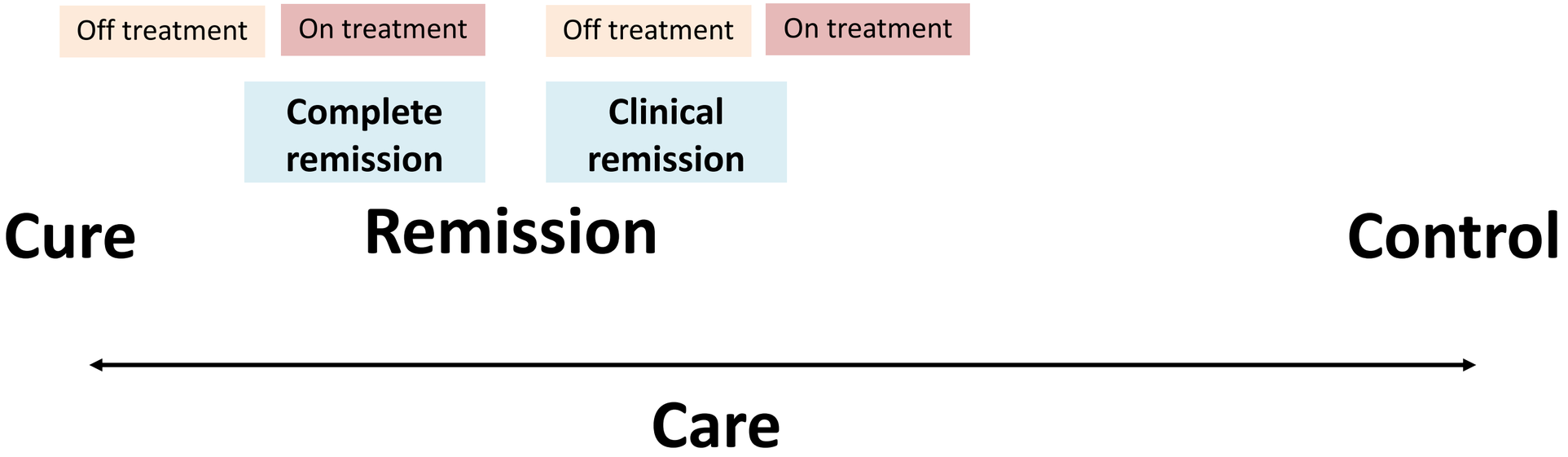
Fine **Very difficult**

Controlled by OCS rescues

= Severe "controlled" asthma

Severe "uncontrolled" asthma

Shifting the therapeutic goal of asthma



Step ladder therapeutic approach

Biologics and treatable trait-based therapeutic approach

The introduction of biologics for the treatment of severe asthma has substantially changed the treatment landscape and provided an unprecedented opportunity to eliminate or nearly eliminate oral corticosteroids for patients

Asthma remission by consensus among clinical experts

Clinical Remission on Treatment

For ≥12 months:
- Sustained absence of significant asthma symptoms based on validated instrument, **and**
- Optimization and stabilization of lung function, **and**
- Patient and HCP agreement regarding disease remission, **and**
- No use of systenic corticosteriod therapy for exacerbation treatment or long-term disease control

Clinical Remission off Treatment

Same criteria maintained without asthma treatment for ≥12 months

Complete Remission on Treatment

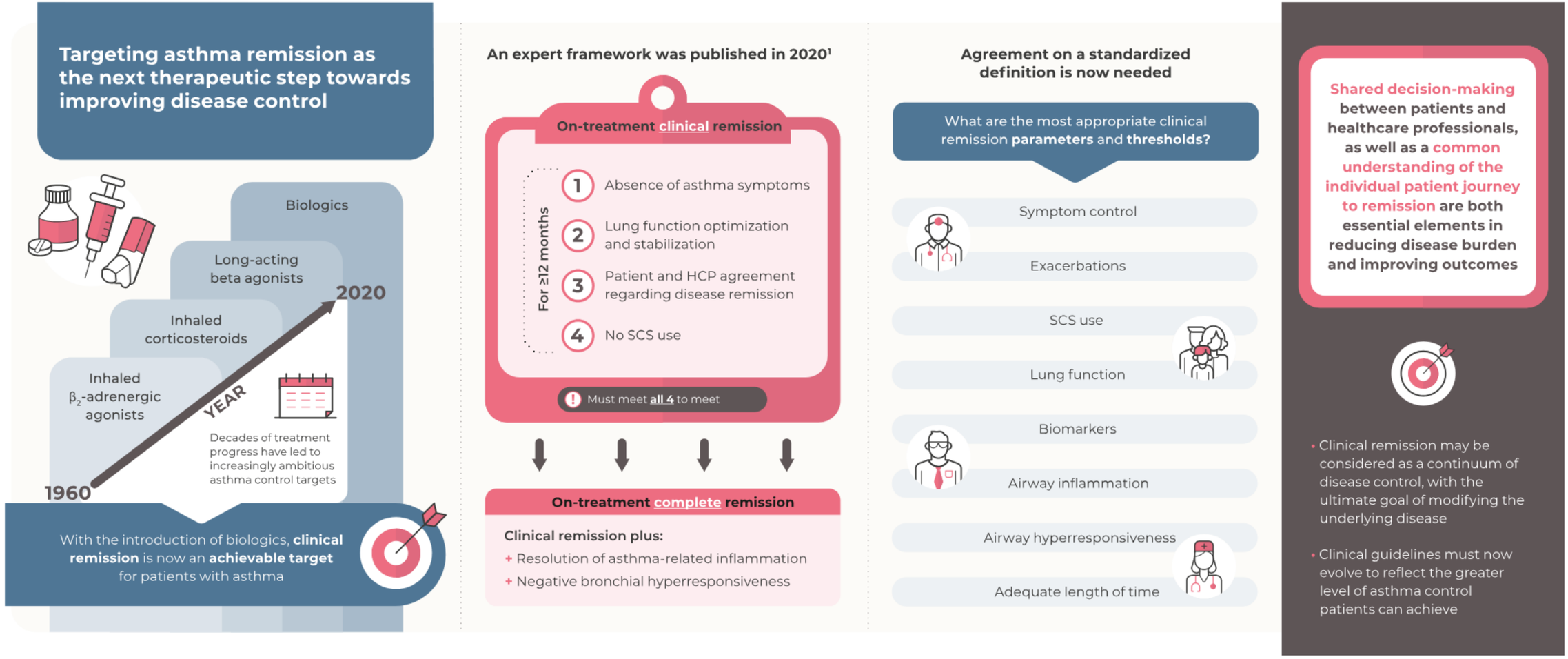
Clinical remission plus the following:
- Current, objective evidence of the resolution of previously documented asthma-related inflammation (eg, reduced blood or sputum eosinophil counts, FENO, and/or other relevant measures), **and**
- In appropriate research settings: Current negative bronchial hyperresponsiveness

Complete Remission off Treatment

Same criteria maintained without asthma treatment for ≥12 months

J Allergy Clin Immunol Pract 2024;12:894-903

The concept of asthma remission on treatment is consistent with GINA long-term goal of asthma treatment



J Allergy Clin Immunol Pract 2024;12:894-903

GP OR SPECIALIST CARE

Investigate and manage difficult-to-treat asthma in adults and adolescents

Consider referring to specialist or severe asthma clinic at any stage

DIAGNOSIS: ***"Difficult-to-treat asthma"***

For adolescents and adults with symptoms and/or exacerbations despite medium or high dose ICS-LABA, or taking maintenance OCS

1 Confirm the diagnosis (asthma/differential diagnoses)

2 Look for factors contributing to symptoms, exacerbations and poor quality of life:

- Incorrect inhaler technique
- Suboptimal adherence
- Comorbidities including obesity, GERD, chronic rhinosinusitis, OSA
- Modifiable risk factors and triggers at home or work, including smoking, environmental exposures, allergen exposure (if sensitized); medications such as beta-blockers and NSAIDs
- Overuse of SABA relievers
- Medication side effects
- Anxiety, depression and social difficulties

3 Optimize management, including:

- Asthma education
- Optimize treatment (e.g. check and correct inhaler technique and adherence; switch to ICS-formoterol maintenance and reliever therapy, if available)
- Consider non-pharmacological interventions (e.g. smoking cessation, exercise, weight loss, mucus clearance, influenza and COVID-19 vaccination)
- Treat comorbidities and modifiable risk factors
- Consider non-biologic add-on therapy (e.g. LABA, LAMA, LM/LTRA, if not used)
- Consider trial of high dose ICS-LABA, if not used

4 Review response after ~3-6 months

Is asthma still uncontrolled?

yes

DIAGNOSIS: ***"Severe asthma"***

If not done by now, refer to a specialist, if possible

no

Consider stepping down treatment, OCS first (if used)

Does asthma become uncontrolled when treatment is stepped down?

yes

Restore previous dose

no

Continue optimizing management

Key

decision, filters

intervention, treatment

diagnosis, confirmation

Assess and treat severe asthma phenotypes

Continue to optimize management as in section **3** (including inhaler technique, adherence, comorbidities, non-pharmacologic strategies)

5 *Investigate* further and provide *patient support*

- Investigate for comorbidities/differential diagnoses and treat/refer as appropriate
  - Consider: CBC, CRP, IgG, IgA, IgM, IgE, fungal precipitins; CXR and/or HRCT chest; DLCO; DEXA scan
  - Skin prick testing or specific IgE for relevant allergens, if not already done
  - Consider screening for adrenal insufficiency in patients taking maintenance OCS or high dose ICS
  - If blood eosinophils ≥300/µl, look for and treat non-asthma causes, including parasites (e.g. Strongyloides serology, or stool examination)
  - If hypereosinophilia e.g. ≥1500/µl, consider causes such as EGPA
  - Other directed testing (e.g. ANCA, CT sinuses, BNP, echocardiogram) based on clinical suspicion
- Consider need for social/psychological support
- Involve multidisciplinary team care (if available)
- Invite patient to enroll in registry (if available) or clinical trial (if appropriate)

6 Assess the *severe asthma phenotype*

Could patient have Type 2 airway inflammation?

yes

Type 2 airway inflammation

- Consider adherence tests
- Consider increasing the ICS dose for 3-6 months
- Consider add-on non-biologic treatment for specific Type 2 clinical phenotypes, e.g. AERD, ABPA, chronic rhinosinusitis, nasal polyposis, atopic dermatitis

Is add-on Type 2 biologic therapy available/ affordable?

yes

no

If add-on Type 2-targeted biologic therapy is NOT available/affordable

- Consider higher dose ICS, if not used
- Consider other add-on therapy (e.g. LAMA, LM/LTRA, low dose azithromycin)
- As last resort, consider add-on low dose OCS, but implement strategies to minimize side-effects
- Stop ineffective add-on therapies

Go to section **10**

no

Type 2 inflammation

- Blood eosinophils ≥150/µl and/or
- FeNO ≥20 ppb and/or
- Sputum eosinophils ≥2%, and/or
- Asthma is clinically allergen-driven

(Repeat blood eosinophils and FeNO up to 3x, at least 1-2 weeks after OCS or on lowest possible OCS dose)

*Note: these are **not** the criteria for add-on biologic therapy (see **8**)*

No evidence of Type 2 airway inflammation

- Review the basics: differential diagnosis, inhaler technique, adherence, comorbidities, side-effects
- Avoid exposures (tobacco smoke, allergens, irritants)
- Consider investigations (if available and not done)
  - Sputum induction
  - High resolution chest CT
  - Bronchoscopy for alternative/additional diagnoses
- Consider trial of add-on treatments (if available and not already tried)
  - LAMA
  - Low dose azithromycin
  - Anti-IL4Rα* if taking maintenance OCS
  - Anti-TSLP* (but insufficient evidence in patients on maintenance OCS)
  - As last resort, consider add-on low dose OCS, but implement strategies to minimize side-effects
- Consider bronchial thermoplasty (+ registry)
- Stop ineffective add-on therapies

Not currently eligible for T2-targeted biologic therapy

Go to section **10**

* *Check local eligibility criteria for specific biologic therapies as these may vary from those listed*

Assess and treat severe asthma phenotypes *cont'd*

Continue to optimize management as in section **3** (including inhaler technique, adherence, comorbidities, non-pharmacologic strategies)

8 Consider *add-on biologic Type 2-targeted* treatments

- Consider add-on Type 2-targeted biologic therapy for patients with exacerbations or poor symptom control on high dose ICS-LABA, who have evidence of Type 2 inflammation*
- Consider **local payer eligibility criteria***, **comorbidities** and **predictors of response** when choosing between available therapies
- Also consider cost, dosing frequency, route (SC or IV), patient preference

Which biologic is appropriate to start first?

Eligibility | *Predictors of asthma response*

Anti-IgE *(omalizumab)*

*Is the patient eligible for **anti-IgE** for severe allergic asthma?**

- Sensitization on skin prick testing or specific IgE
- Total serum IgE and weight within dosage range
- Exacerbations in last year

What factors may predict good asthma response to anti-IgE?

- Blood eosinophils ≥260/µl ++
- FeNO ≥20 ppb +
- Allergen-driven symptoms +
- Childhood-onset asthma +

no / *no*

Anti-IL5 / Anti-IL5R *(benralizumab, mepolizumab, reslizumab)*

*Is the patient eligible for **anti-IL5 / anti-IL5R** for severe eosinophilic asthma?**

- Exacerbations in last year
- Blood eosinophils, e.g. ≥150/µl or ≥300/µl

What factors may predict good asthma response to anti-IL5/5R?

- Higher blood eosinophils +++
- More exacerbations in previous year +++
- Adult-onset of asthma ++
- Nasal polyposis ++

no / *no*

Anti-IL4Rα *(dupilumab)*

*Is the patient eligible for **anti-IL4Rα** for severe eosinophilic/Type 2 asthma?**

- Exacerbations in last year
- Blood eosinophils ≥150 and ≤1500/µl, or FeNO ≥25 ppb, or taking maintenance OCS

What factors may predict good asthma response to anti-IL4Rα?

- Higher blood eosinophils +++
- Higher FeNO +++

no / *no*

Anti-TSLP *(tezepelumab)*

*Is the patient eligible for **anti-TSLP** for severe asthma?**

- Exacerbations in last year

What factors may predict good asthma response to anti-TSLP?

- Higher blood eosinophils +++
- Higher FeNO +++

Eligible for none? Return to section **7**

Choose one if eligible*; trial for at least 4 months and assess response

*Good asthma response?**

yes → Good response to T2-targeted therapy

unclear → Extend trial to 6-12 months*

no → **STOP add-on**

Consider switching to a different Type 2-targeted therapy, if eligible*

no → Little/no response to T2-targeted therapy

No evidence of Type 2 airway inflammation

No evidence of Type 2 airway inflammation. Go to section **10**

* *Check local eligibility criteria for specific biologic therapies as these may vary from those listed*

Monitor / Manage severe asthma treatment

Continue to optimize management

9 Review response

- Asthma: symptom control, exacerbations, lung function
- Type 2 comorbidities e.g. nasal polyposis, atopic dermatitis
- Medications: treatment intensity, side-effects, affordability
- Patient satisfaction

yes

If good response to Type 2-targeted therapy

- Re-evaluate the patient every 3-6 months *
- First, consider decreasing/stopping OCS (and check for adrenal insufficiency), then consider stopping other add-on asthma medications
- Then, if asthma well-controlled for 3-6 months, consider reducing maintenance ICS-LABA dose, but do not stop maintenance ICS-LABA. See text for details.
- Re-evaluate need for ongoing biologic therapy
- Order of reduction of treatments based on observed benefit, potential side-effects, cost and patient preference

no

If no good response to Type 2-targeted therapy

- Stop the biologic therapy
- Review the basics: differential diagnosis, inhaler technique, adherence, comorbidities, side-effects, emotional support
- Consider high resolution chest CT (if not done)
- Reassess phenotype and treatment options
  - Induced sputum (if available)
  - Consider add-on low dose azithromycin
  - Consider bronchoscopy for alternative/additional diagnoses
  - As last resort, consider add-on low dose OCS, but implement strategies to minimize side-effects
  - Consider bronchial thermoplasty (+ registry)
- Stop ineffective add-on therapies
- Do not stop ICS

No evidence of Type 2 airway inflammation. Go to section 10

* *Check local eligibility criteria for specific biologic therapies as these may vary from those listed*

10 Continue to optimize management as in section 3, including:

- Inhaler technique
- Adherence
- Comorbidity management
- Non-pharmacologic strategies
- Patients' social/emotional needs
- Two-way communication with GP for ongoing care

Notes:

Monitor / Manage severe asthma treatment

9 Review response

- Asthma: symptom control, exacerbations, lung function
- Type 2 comorbidities e.g. nasal polyposis, atopic dermatitis
- Medications: treatment intensity, side-effects, affordability
- Patient satisfaction

yes

If good response to Type 2-targeted therapy

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- First, consider decreasing/stopping OCS (and check for adrenal insufficiency), then consider stopping other add-on asthma medications
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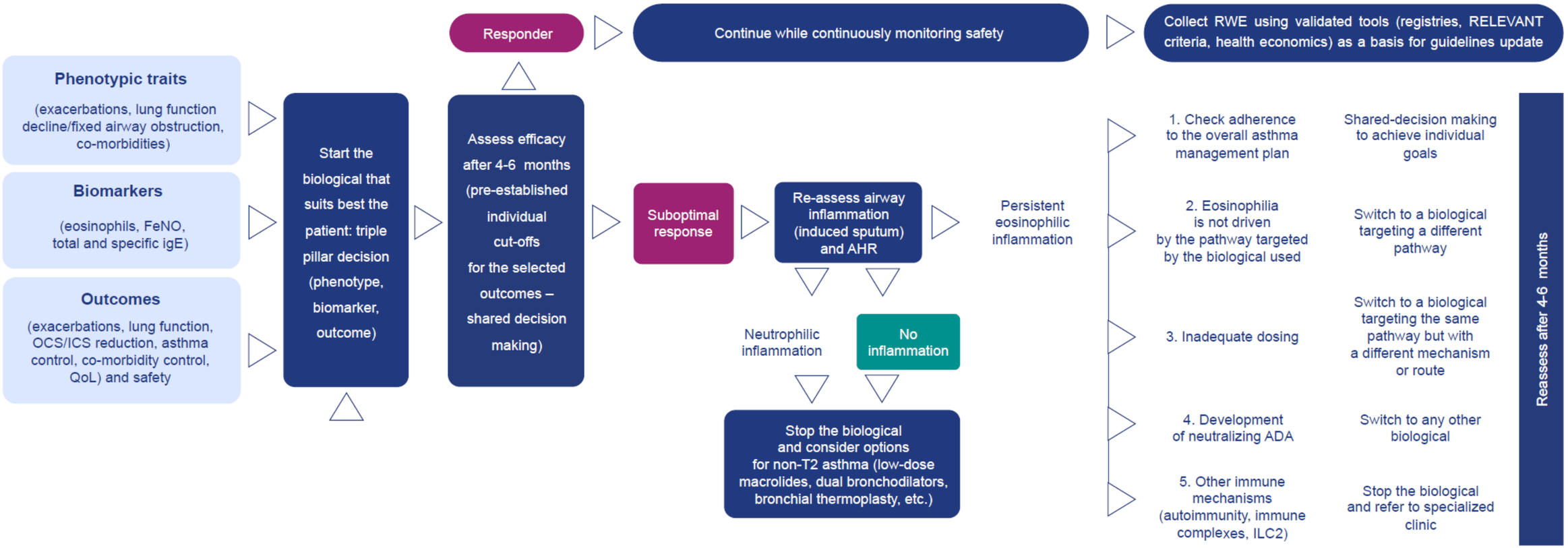
- Re-evaluate need for ongoing biologic therapy
- Order of reduction of treatments based on observed benefit, potential side-effects, cost and patient preference

- Consider bronchial thermoplasty (+ registry)
- Stop ineffective add-on therapies
- Do not stop ICS

No evidence of Type 2 airway inflammation. Go to section 10

* *Check local eligibility criteria for specific biologic therapies as these may vary from those listed*

EAACI biologicals guidelines-recommendations for severe asthma



Allergy. 2021 Jan;76(1):14-44

ERS/ATS Guidelines for Severe Asthma[1,2]

ERS/ATS 2014 Guidelines[1]

- High-dose ICS plus LABA, LTRA, or theophylline and/or continuous or near-continuous OCS use
  - Chronic use of OCS is associated with an increased risk of fracture and cataracts
- Given the complexity of chronic severe asthma due to different underlying mechanisms being involved in different phenotypes of the disease, personalized therapy could lead to improved outcomes and fewer adverse events
- Methotrexate and antifungal agents are not recommended for the treatment of severe asthma

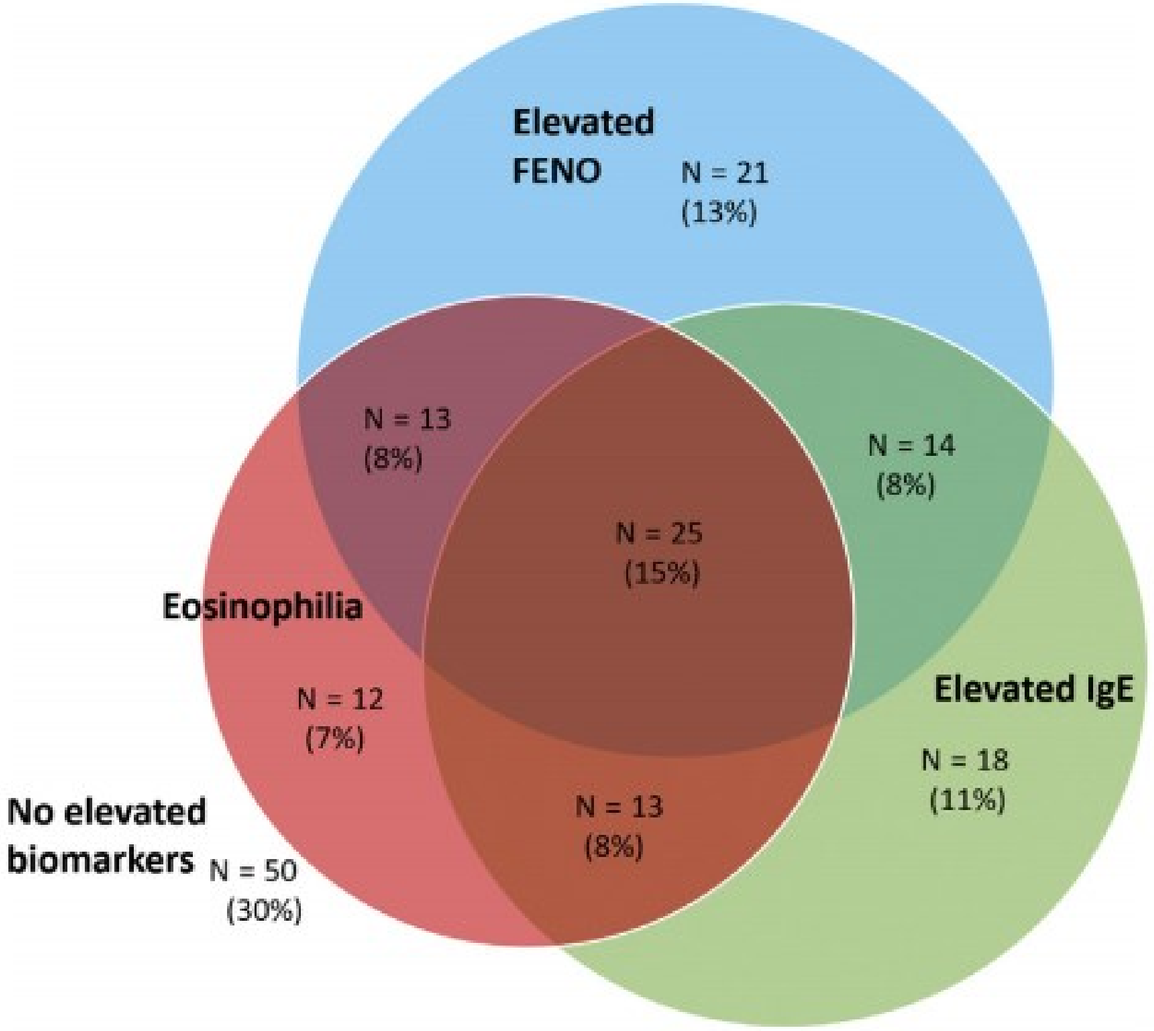
ERS/ATS 2019 Task Force Report[2]

- Suggests a trial of macrolide treatment to reduce asthma exacerbations in adult asthmatics on GINA/NAEPP step 5 therapy that remain persistently symptomatic or uncontrolled
- Suggests against the use of chronic macrolide treatment in children and adolescents with severe uncontrolled asthma
- Recommends anti–IL-5 as add-on therapy for adult patients with severe uncontrolled asthma with eosinophilic phenotype
- Recommends the addition of tiotropium for children, adolescents, and adults with severe uncontrolled asthma despite GINA step 4 or 5 or NAEPP step 5 therapy
- Suggests dupilumab as add-on therapy for adult patients with SEA and for those with severe corticosteroid-dependent asthma regardless of eosinophil levels

LABA=long-acting beta$_2$-agonist; LTRA=leukotriene receptor antagonist; NAEPP=National Asthma Education and Prevention Program; SABA=short-acting beta$_2$-agonist.

References: 1. Chung KF, et al. *Eur Respir J*. 2014;43(2):343-373. **2.** Holguin F, et al. *Eur Respir J*. 2020;55(1):1900588.

The prevalence of subtypes of Type 2 inflammation in severe asthma



70% of patients with severe asthma to have at least 1 T2 biomarker elevated: 31% with a single biomarker elevated and 39% with 2 or more elevated.

J Allergy Clin Immunol Pract 2021;9:1267-75

A surge in the development and approval of biologics to treat severe asthma

Six and counting

The FDA has approved six biologics as treatments for severe asthma and more approvals are expected.

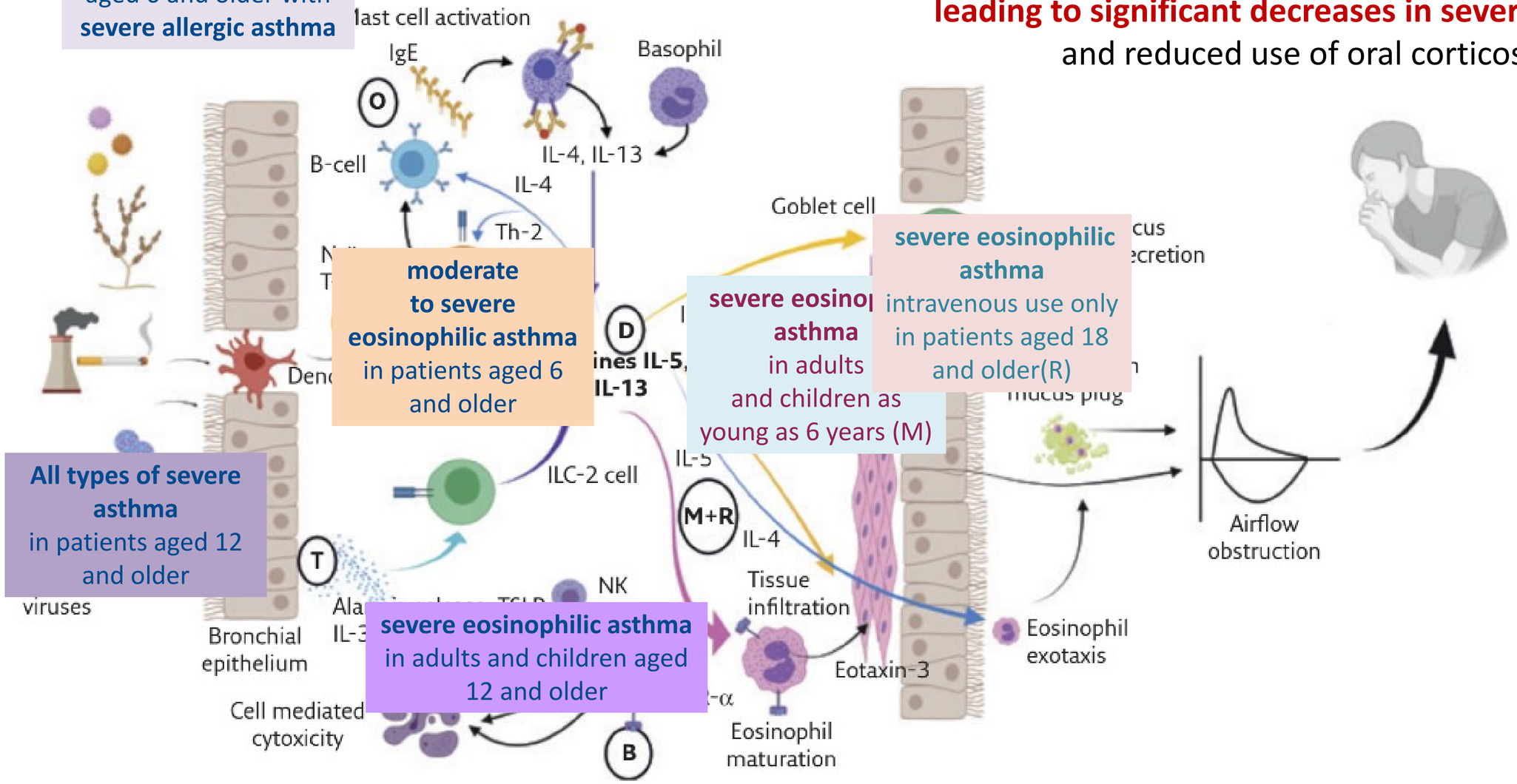
Biologic	Approved by the FDA for severe asthma
Cinquair (reslizumab)	2016
Dupixient (dupilumab)	2018
Fasenra (benralizumab)	2017
Nucala (mepolizumab)	2015
Tezspire (tezepelumab)	2021
Xolair (omalizumab)	2003

MHE June 2022, Volume 32, Issue 6

The sites of action of biologic therapies

adults and children aged 6 and older with **severe allergic asthma**

leading to significant decreases in severe exacerbations
and reduced use of oral corticosteroids



moderate to severe eosinophilic asthma
in patients aged 6 and older

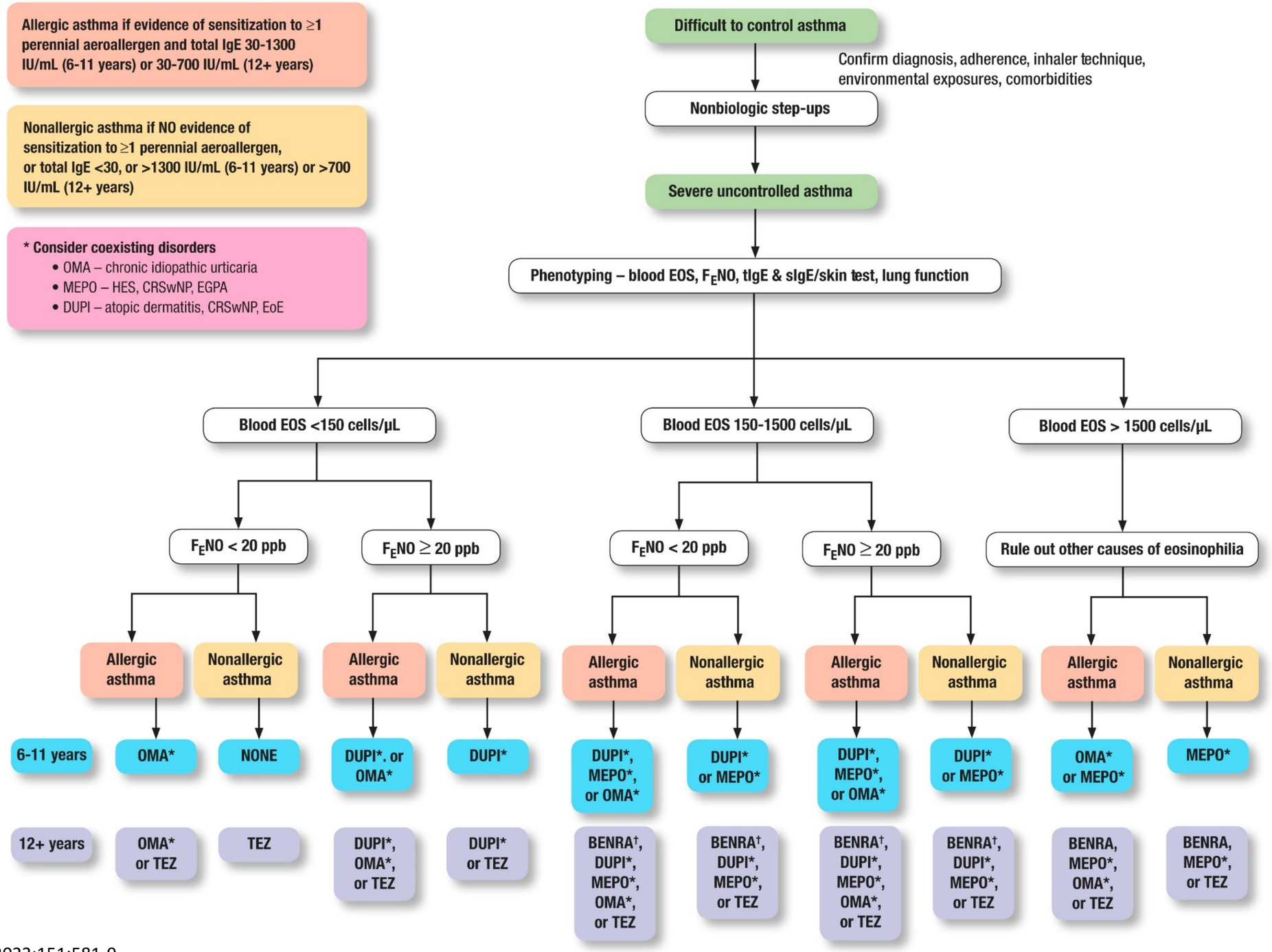
severe eosinophilic asthma
intravenous use only in patients aged 18 and older(R)

severe eosinophilic asthma
in adults and children as young as 6 years (M)

All types of severe asthma
in patients aged 12 and older

severe eosinophilic asthma
in adults and children aged 12 and older

Breathe 2021; 17:210144.



J Allergy Clin Immunol 2023;151:581-9.

RCTs regarding OCS-sparing effects of biologics

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 25, 2014 VOL. 371 NO. 13

Oral Glucocorticoid-Sparing Effect of Mepolizumab in Eosinophilic Asthma

Elisabeth H. Bel, M.D., Ph.D., Sally E. Wenzel, M.D., Philip J. Thompson, M.D., Charlene M. Prazma, Ph.D., Oliver N. Keene, M.Sc., Steven W. Yancey, M.Sc., Hector G. Ortega, M.D., Sc.D., and Ian D. Pavord, D.M., for the SIRIUS Investigators*

ORIGINAL ARTICLE

Oral Glucocorticoid–Sparing Effect of Benralizumab in Severe Asthma

Parameswaran Nair, M.D., Ph.D., Sally Wenzel, M.D., Klaus F. Rabe, M.D., Ph.D., Arnaud Bourdin, M.D., Ph.D., Njira L. Lugogo, M.D., Piotr Kuna, M.D., Ph.D., Peter Barker, Ph.D., Stephanie Sproule, M.Math., Sandhia Ponnarambil, M.D., and Mitchell Goldman, M.D., for the ZONDA Trial Investigators*

ORIGINAL ARTICLE

Efficacy and Safety of Dupilumab in Glucocorticoid-Dependent Severe Asthma

Klaus F. Rabe, M.D., Ph.D., Parameswaran Nair, M.D., Ph.D., Guy Brusselle, M.D., Ph.D., Jorge F. Maspero, M.D., Mario Castro, M.D.,

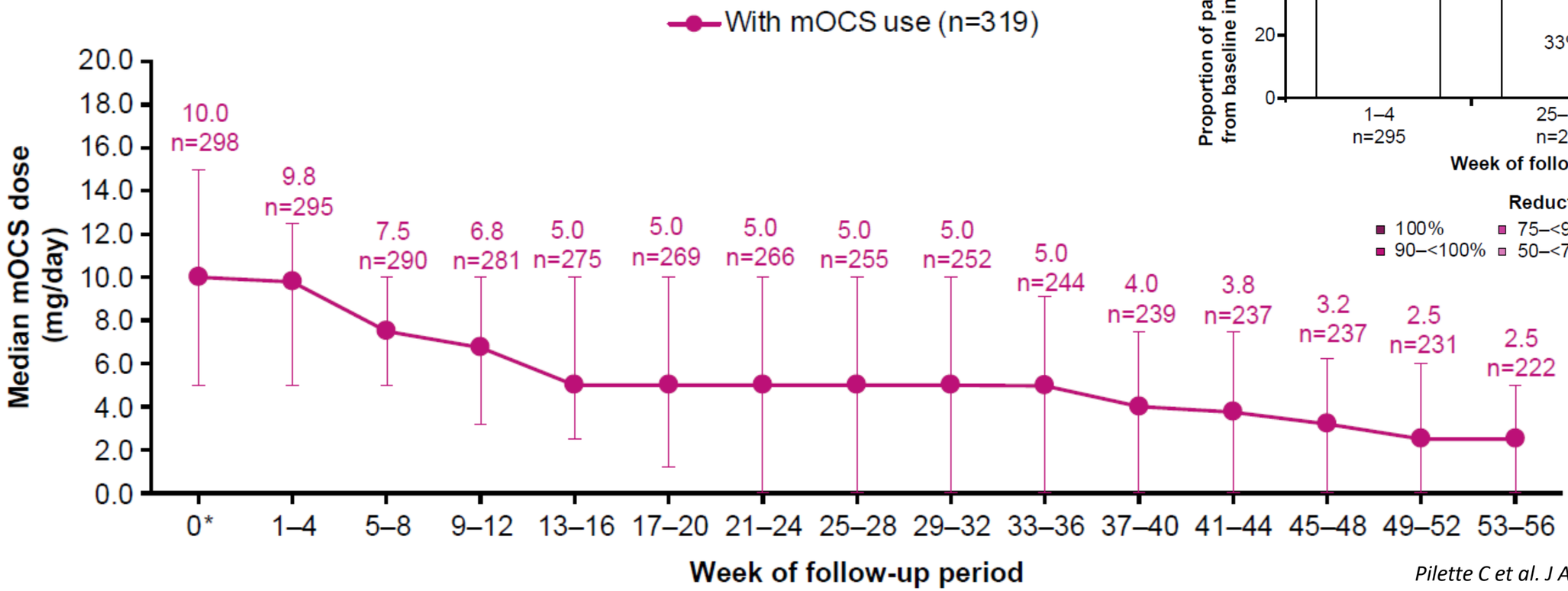
Study name	Intervention dose/ duration	Intervention	Reduction in daily OCS dose from baseline (%)†	*P*-value	Patients achieving reduction in daily OCS dose from baseline by percentage category (%) ≥50% Reduction	≥75% Reduction	≥90% Reduction	100% Reduction
SIRIUS[19]	Mepolizumab 100 mg SC Q4W for 20 weeks‡	Placebo (*n* = 66)	0	—	33	18	11	8
		Mepolizumab (*n* = 69)	50	0.007	54	41	23	14
ZONDA[20]	Benralizumab 30 mg SC Q4W or Q8W for 28 weeks§	Placebo (*n* = 75)	25	—	35	20	12	19
		Benralizumab Q4W (*n* = 72)	75	<0.001	67	53	33	56¶
		Benralizumab Q8W (*n* = 73)	75	<0.001	66	52	37	52¶
LIBERTY ASTHMA VENTURE[54]	Dupilumab 300 mg SC Q2W (after a 600-mg loading dose) for 24 weeks††	Placebo (*n* = 107)	42	—	53	39	31	29
		Dupilumab (*n* = 103)	70	<0.001	80	69	55	52

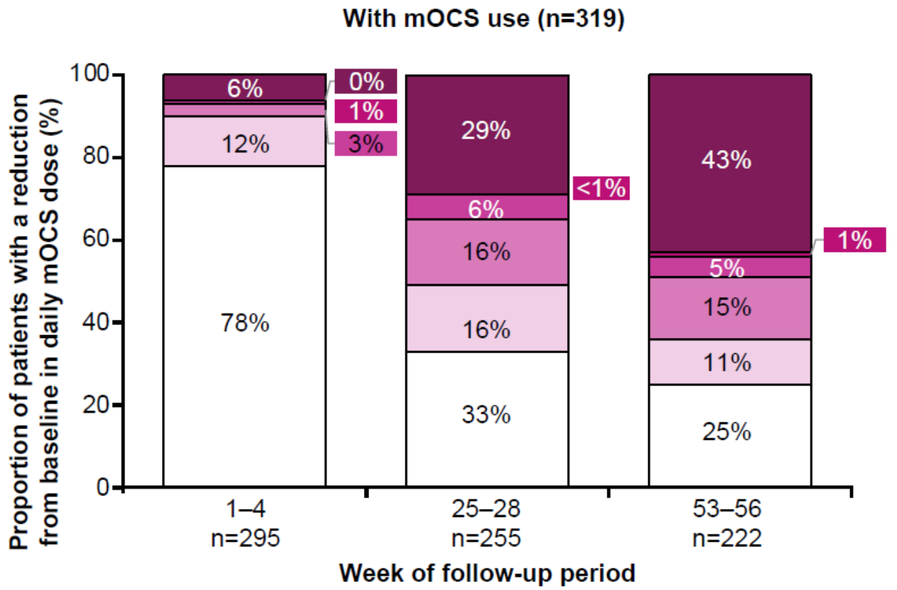
N Engl J Med 2018;378:2475-85; N Engl J Med 2014;371:1189-97; N Engl J Med 2017;376:2448-58; Respirology (2020) 25, 161–172

RWD regarding OCS-sparing effects of biologics

REALITI-A Study: Real-World Oral Corticosteroid-Sparing Effect of Mepolizumab in Severe Asthma

Charles Pilette, MD[a,b], Giorgio Walter Canonica, MD[c,d], Rekha Chaudhuri, MD[e,f], Geoffrey Chupp, MD[g], F. Eun-Hyung Lee, MD[h], Jason Kihyuk Lee, MD[i], Carlos Almonacid, MD, PhD[j], Tobias Welte, MD[k], Rafael Alfonso-Cristancho, MD[l], Rupert W. Jakes, PhD[m], Aoife Maxwell, PhD[n], Robert G. Price, MSc[o], and Peter Howarth, MD[p] *Brussels, Belgium; Milan, Italy; Toronto, Ontario, Canada; Madrid, Spain; Hannover, Germany; Glasgow, London, Hertfordshire, and Middlesex, United Kingdom; and New Haven, Conn; Atlanta, Ga; and Collegeville, Pa*





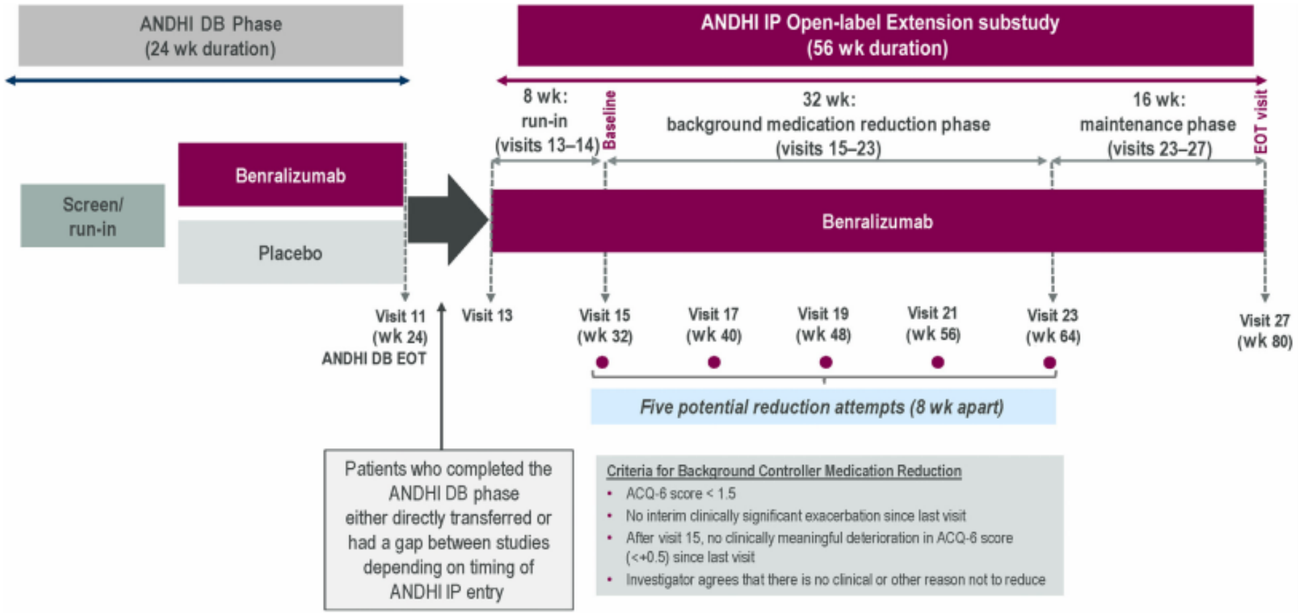
Pilette C et al. J Allergy Clin Immunol Pract 2022

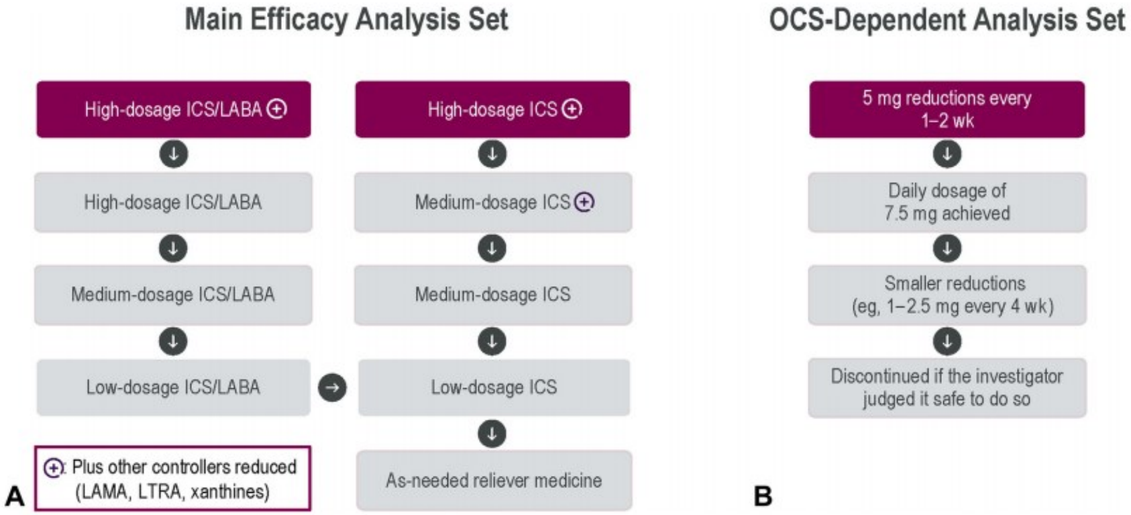
Standard-of-care background medication reduction with biologics

Original Article

Severe Asthma Standard-of-Care Background Medication Reduction With Benralizumab: ANDHI *in Practice* Substudy

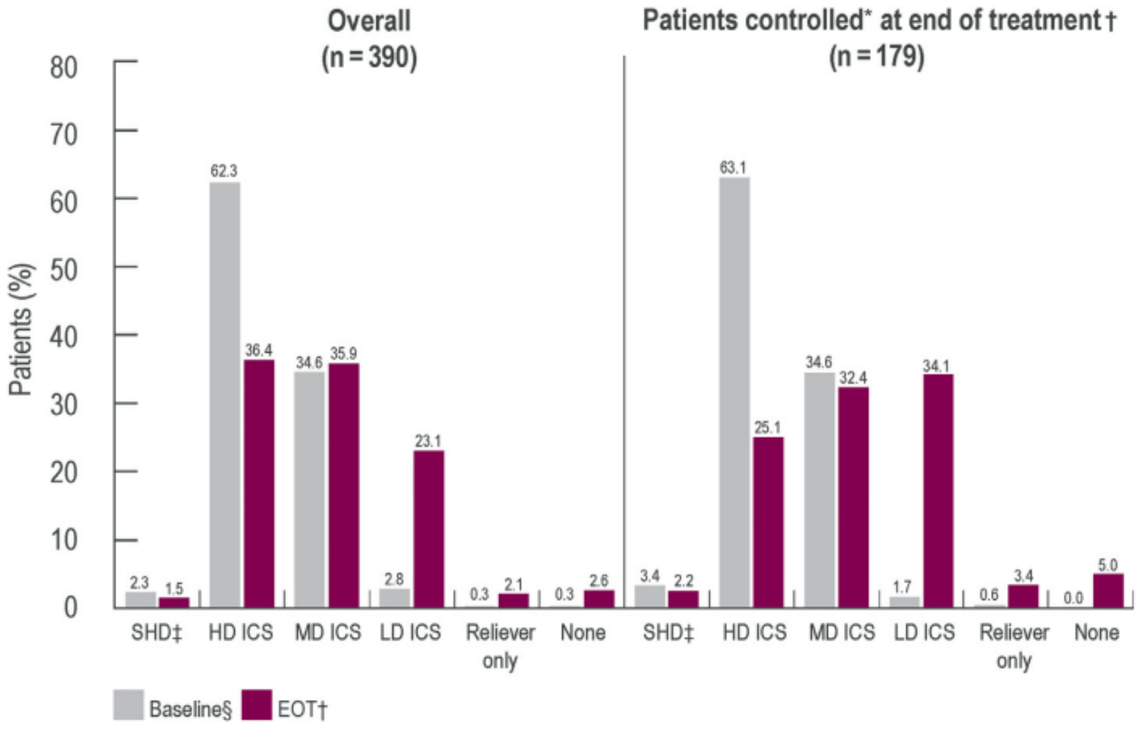
Renaud Louis, MD[a,*], Tim W. Harrison, MD[b,c,*], Pascal Chanez, MD, PhD[d], Francesco Menzella, MD[e], George Philteos, MD[f], Borja G. Cosio, MD, PhD[g], Njira L. Lugogo, MD[h], Gustavo de Luiz, MD[i], Annie Burden, MSc[j], Timothy Adlington, MS[j], Nanna Keeling, MPharm[k], Justin Kwiatek, PharmD[l], and Esther Garcia Gil, MD[m]; on behalf of the ANDHI Study Investigators *Liège, Belgium; Nottingham and Cambridge, United Kingdom; Marseille, France; Montebelluna, Italy; Saskatoon, Canada; Palma de Mallorca, Màlaga, and Barcelona, Spain; Ann Arbor, Mich; Gothenburg, Sweden; Wilmington, Del*

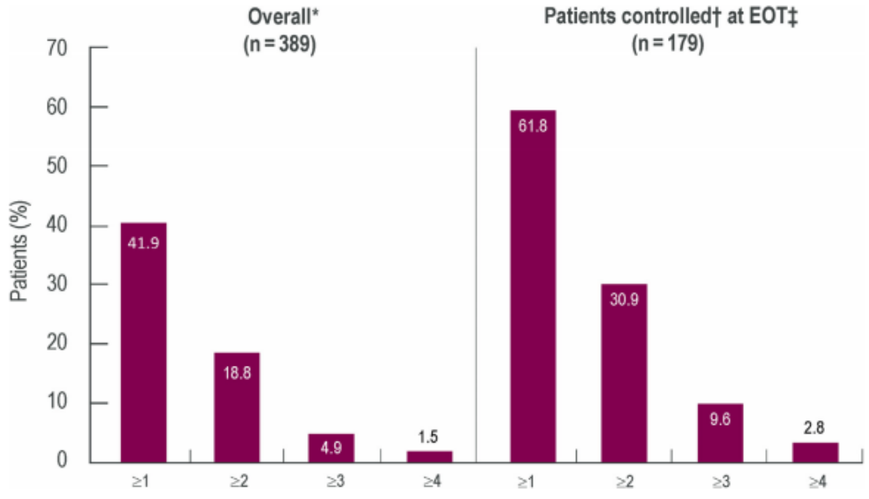


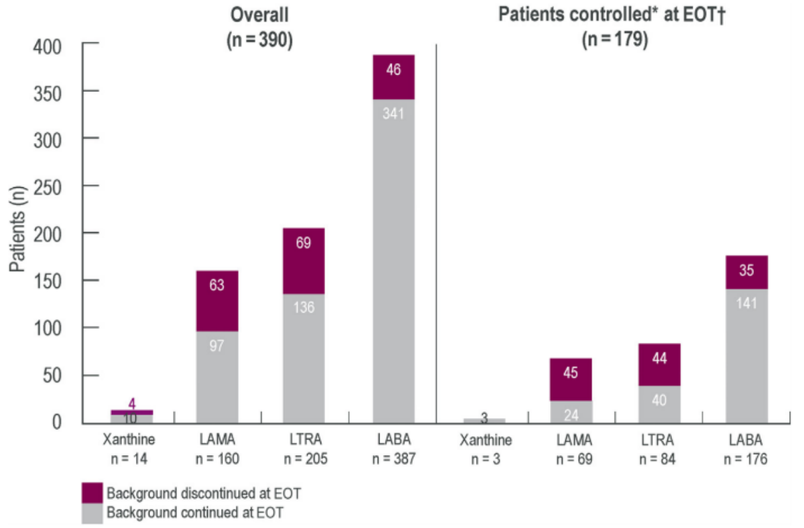


J Allergy Clin Immunol Pract 2023;11:1759-70

Standard-of-care background medication reduction with biologics



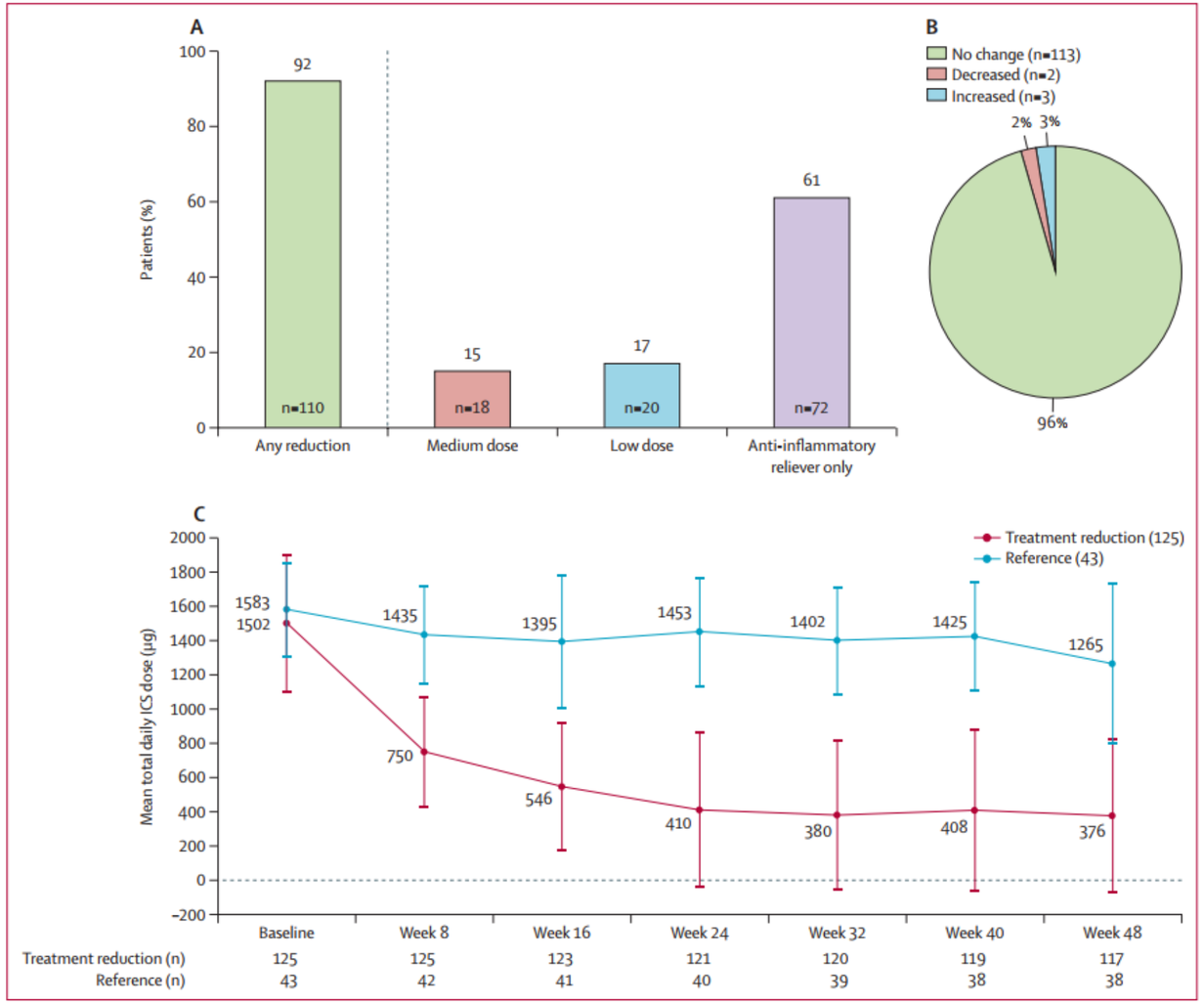




Standard-of-care background medications, including OCS, ***can be tapered and adapted GINA steps reduced for patients with severe eosinophilic asthma*** *treated with benralizumab while maintaining symptom control in a clinical setting.*

J Allergy Clin Immunol Pract 2023;11:1759-70

ICS reduction with biologics in severe asthma: SHAMAL study



Lancet 2024; 403: 271–81

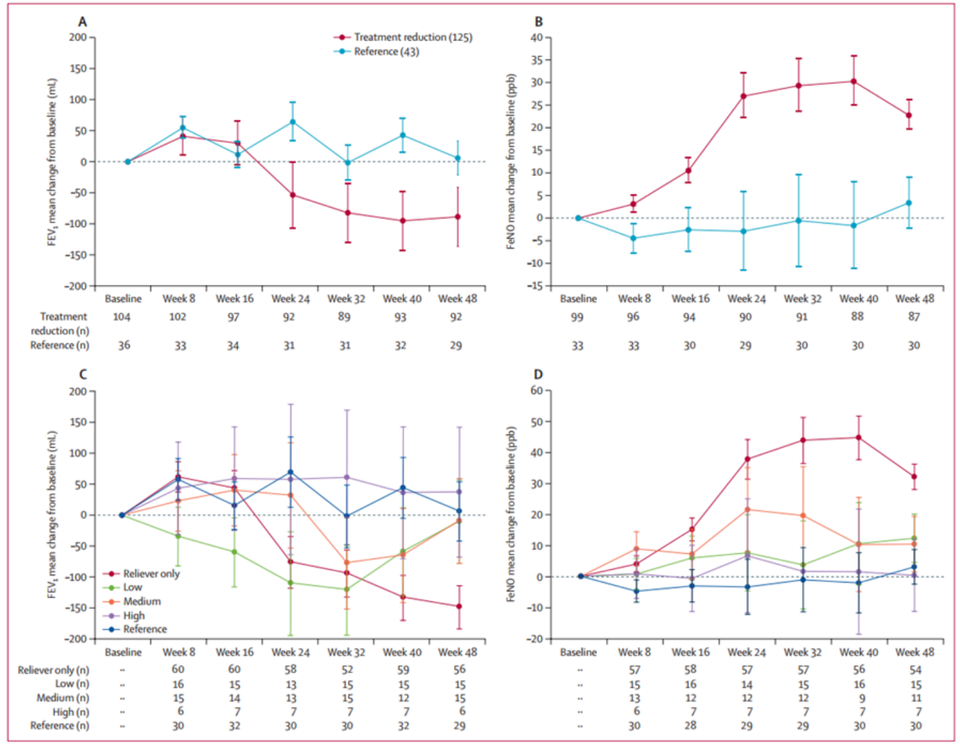
Reduction of daily maintenance inhaled corticosteroids in patients with severe eosinophilic asthma treated with benralizumab (SHAMAL): a randomised, multicentre, open-label, phase 4 study

*David J Jackson, Liam G Heaney, Marc Humbert, Brian D Kent, Anat Shavit, Lina Hiljemark, Lynda Olinger, David Cohen, Andrew Menzies-Gow, Stephanie Korn, on behalf of the SHAMAL Investigators**

Summary

Background Stepwise intensification of inhaled corticosteroids (ICS) is routine for severe eosinophilic asthma, despite some poor responses to high-dose ICS. Dose reductions are recommended in patients responding to biologics, but little supporting safety evidence exists.

Lancet 2024; 403: 271–81
Published Online
December 7, 2023
https://doi.org/10.1016/



04. Cough-variant asthma

Cough-variant asthma (CVA)

- Common causes of an isolated non-productive cough
  - Cough-variant asthma
  - Chronic upper airway cough syndrome, chronic sinusitis
  - GERD, post-infectious cough, inducible laryngeal obstruction, eosinophilic bronchitis
  - ACEI-induced cough…

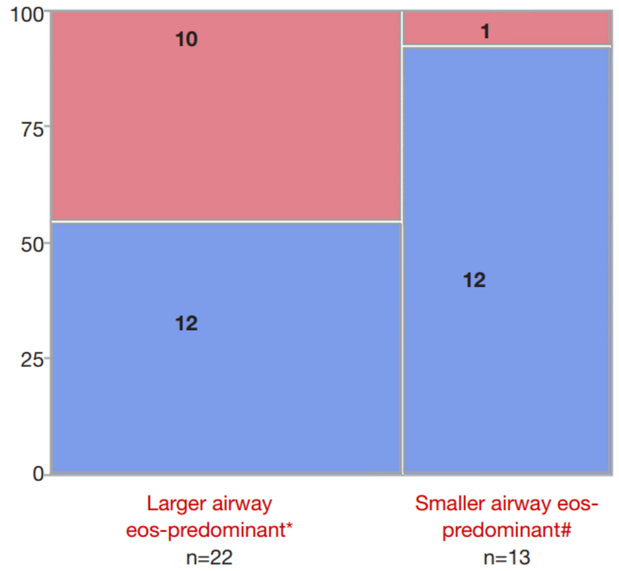
- CVA is a subtype of bronchial asthma characterized primarily by chronic cough. Unlike typical asthma, it has the following features:
  - **Dry cough as the sole or predominant symptom**
  - Absence or minimal presence of typical asthma symptoms (wheezing, shortness of breath)
  - Symptoms may worsen at night or early morning.

Asthmatic cough

	Asthma	Cough-variant asthma	Eosinophilic bronchitis
Symptoms	Dyspnea, cough, wheeze	Isolated cough	Cough, often associated with upper airway symptoms
Variable airflow obstruction	+	±	-
Methacholine provocation test	+	+/±	-
Cough reflex hypersensitivity	- ~ ↑	- ~ ↑	↑
Response to bronchodilator	+	+/±	unknown
Response to corticosteroid	+	+	+
Sputum eosinophilia	usually	usually	always
BAL eosinophilia	↑	↑	↑
Bronchial biopsy eosinophilia	↑	↑	↑
Mast cell within airway smooth muscle bundle	↑	→	→
Atopy	60-80%	40-80%	20-70%

Unlike typical asthma, CVA may show normal pulmonary function test results, requiring careful diagnosis.

Cough-variant asthma (CVA)



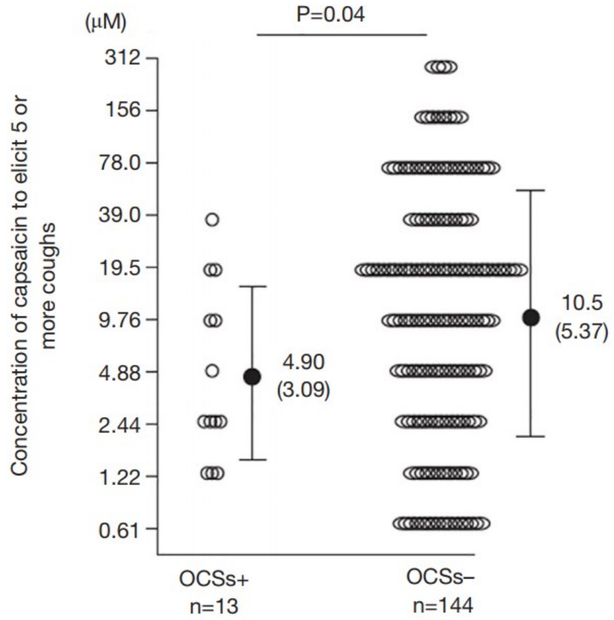
Cough variant asthma (n=11)

Classic asthma (n=24)

P=0.02
(Fisher's exact test)

* early phase eos%>late phase eos%

early phase eos%<late phase eos%



Inflammatory subtypes
(Simpson *et al.* Respirology 2006)

At enrollment

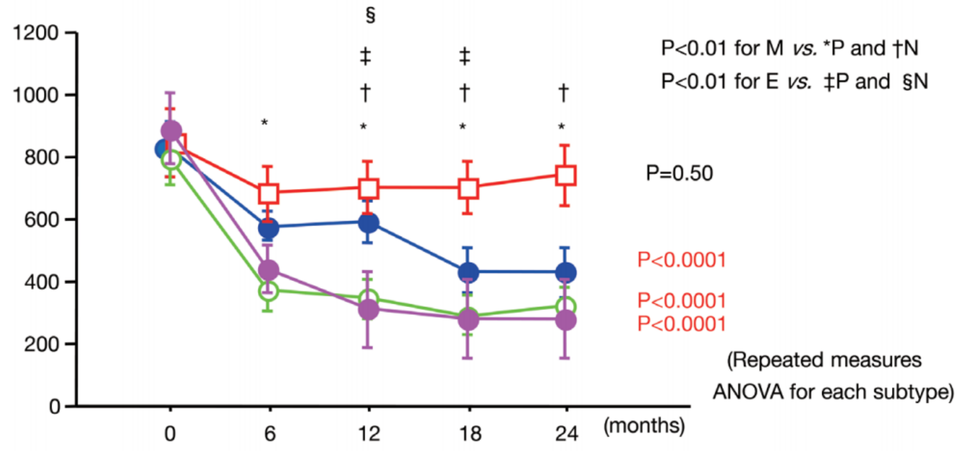
- Mixed granulocytic n=12
- Eosinophilic n=28
- Neutrophilic n=31
- Paucigranulocytic n=27

At 24 m: patients being weaned off ICS

Mixed: 2/11 (18%)
Eos: 5/21 (24%)
Neu: 11/27 (41%)
Pauce: 13/19 (68%)

P=0.01
P=0.02

Maintenance ICS dose
(beclomethasone equivalent)



P<0.01 for M *vs.* *P and †N
P<0.01 for E *vs.* ‡P and §N

P=0.50

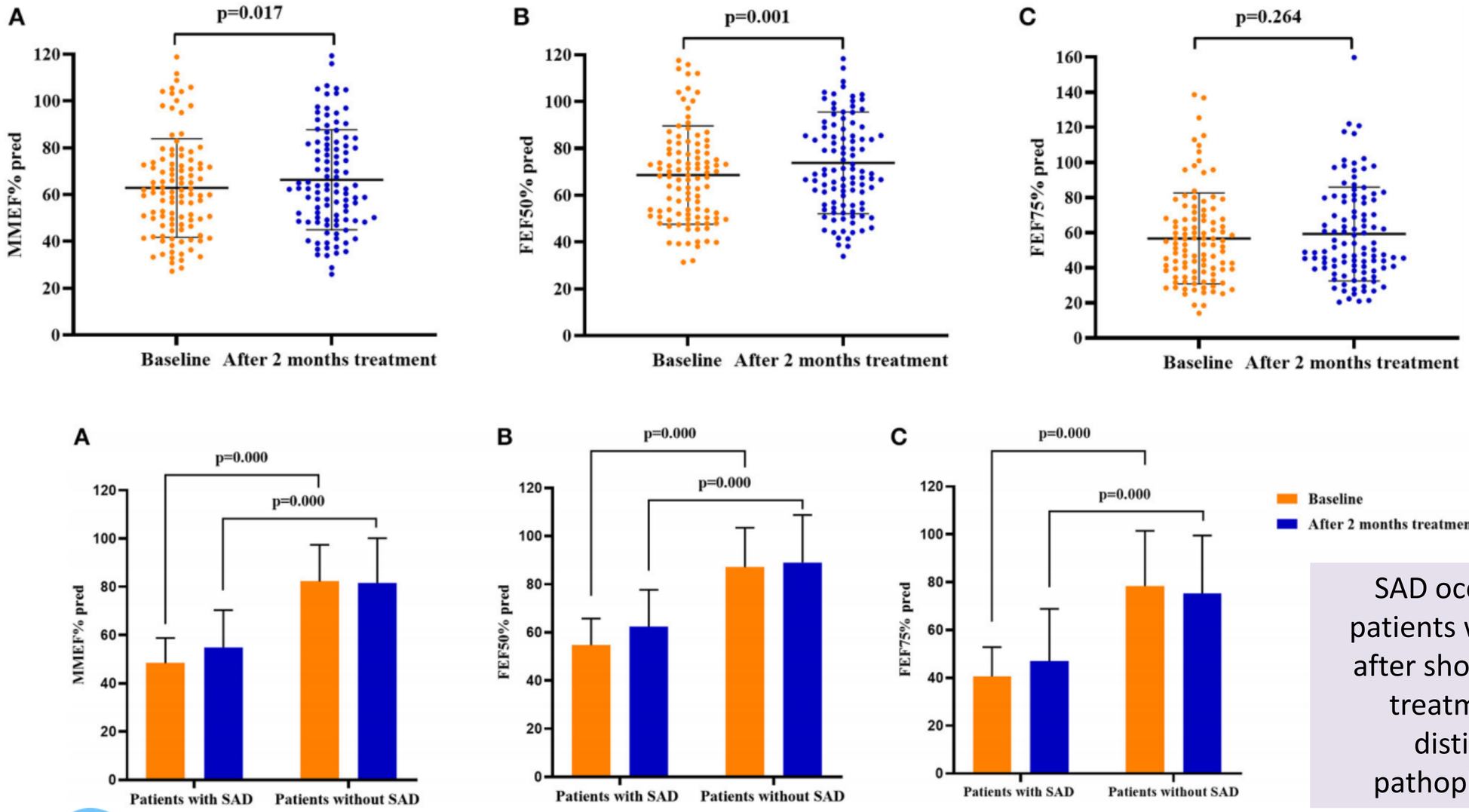
P<0.0001

P<0.0001
P<0.0001

(Repeated measures ANOVA for each subtype)

J Thorac Dis 2021;13(5):3197-3214

Cough-variant asthma (CVA) and small airway dysfunction (SAD)



SAD occurred in over half of patients with CVA and persisted after short-term anti-asthmatic treatment, which showed distinctive clinical and pathophysiological features.

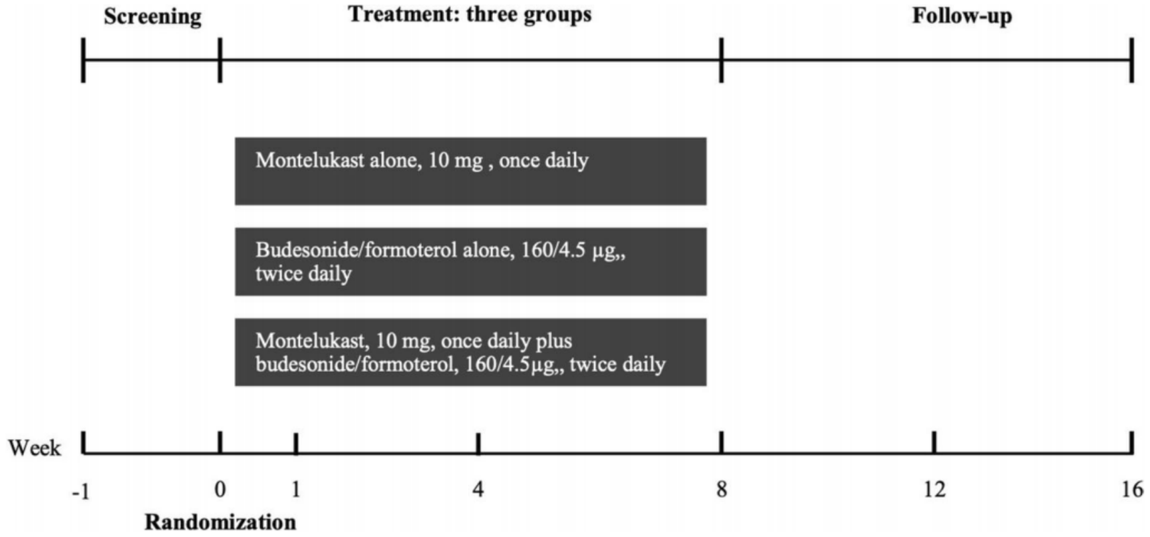
Front. Physiol. 2021;12:761622.

Cough-variant asthma (CVA)

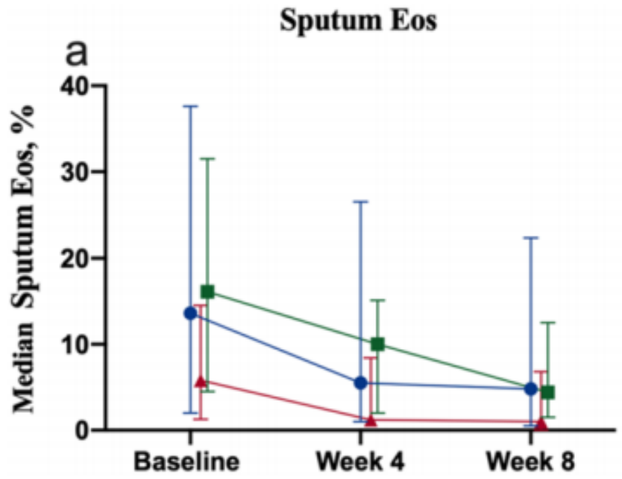
RESEARCH Open Access

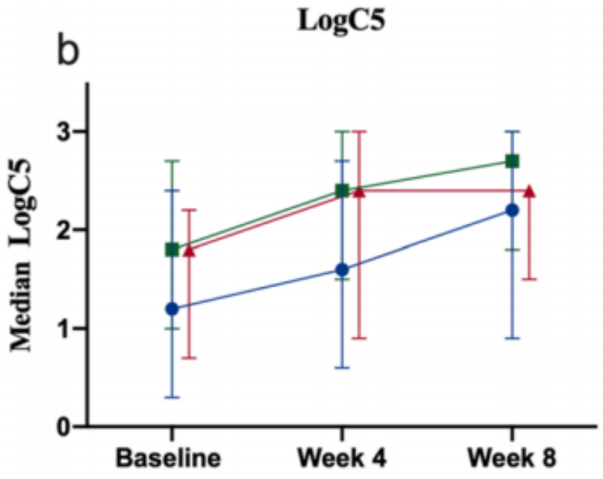
Effects of treatment with montelukast alone, budesonide/formoterol alone and a combination of both in cough variant asthma

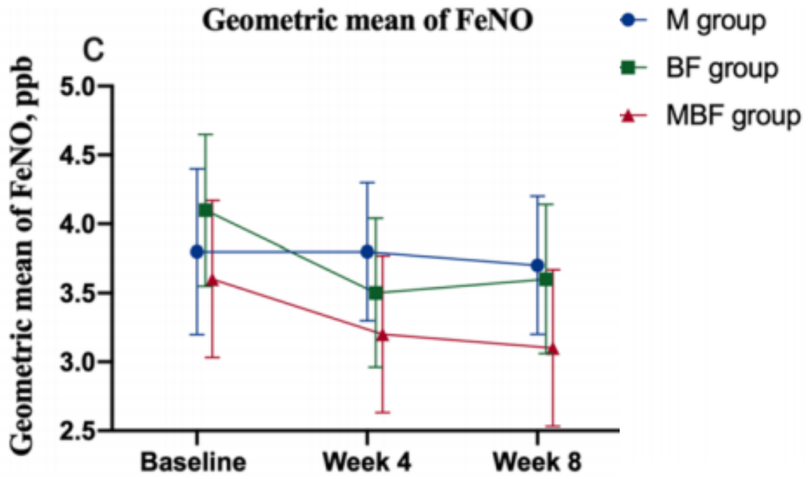
Fang Yi†, Chen Zhan†, Baojuan Liu, Hu Li, Jianmeng Zhou, Jiaman Tang, Wen Peng, Wei Luo, Qiaoli Chen and Kefang Lai*



Montelukast can effectively improve cough symptoms, cough reflex sensitivity and eosinophilic airway inflammation in patients with CVA.



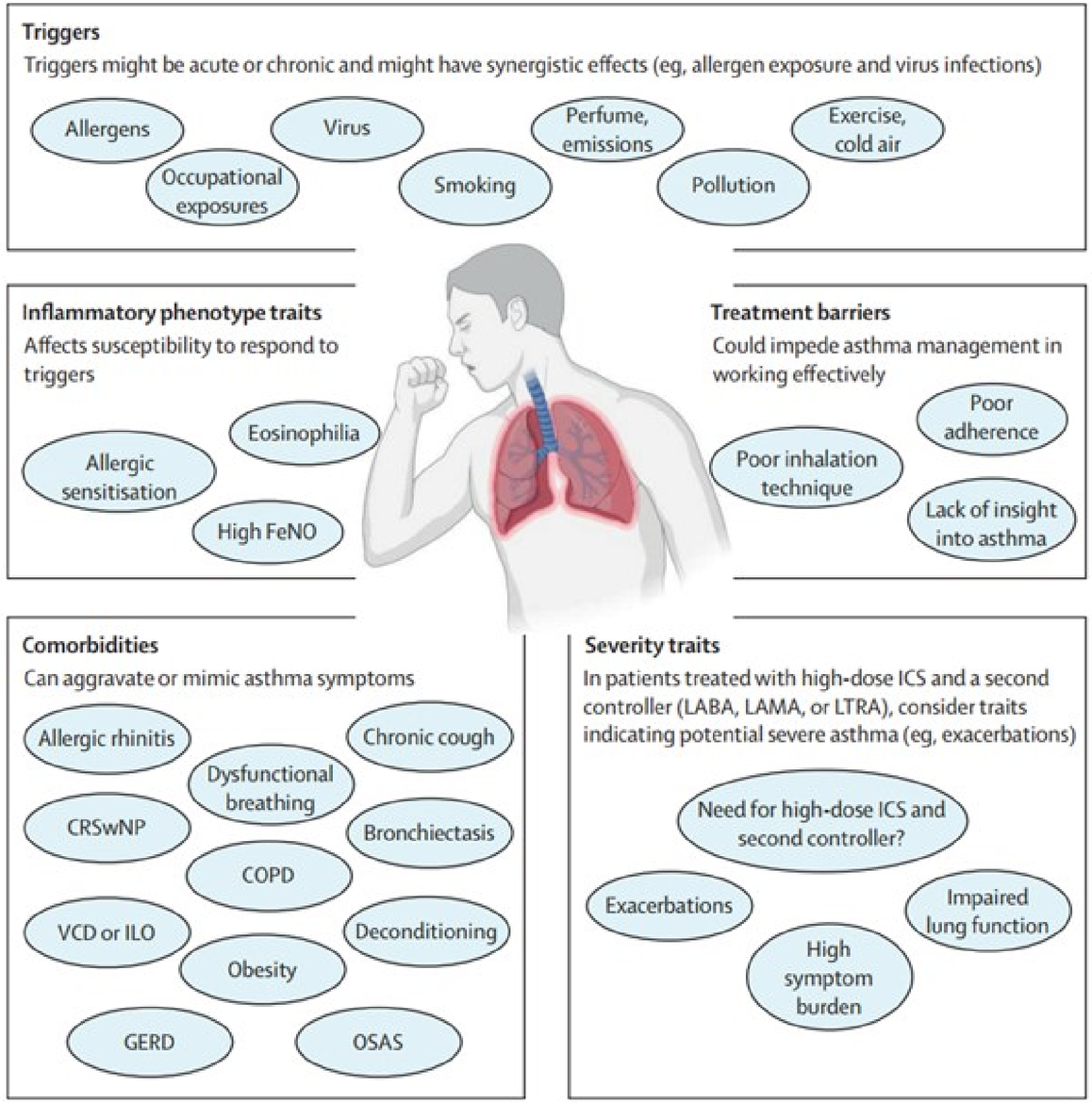




Respir Res. 2022 Oct 10;23(1):279.

05. Asthma with comorbidities

Factors contributing to poor asthma control

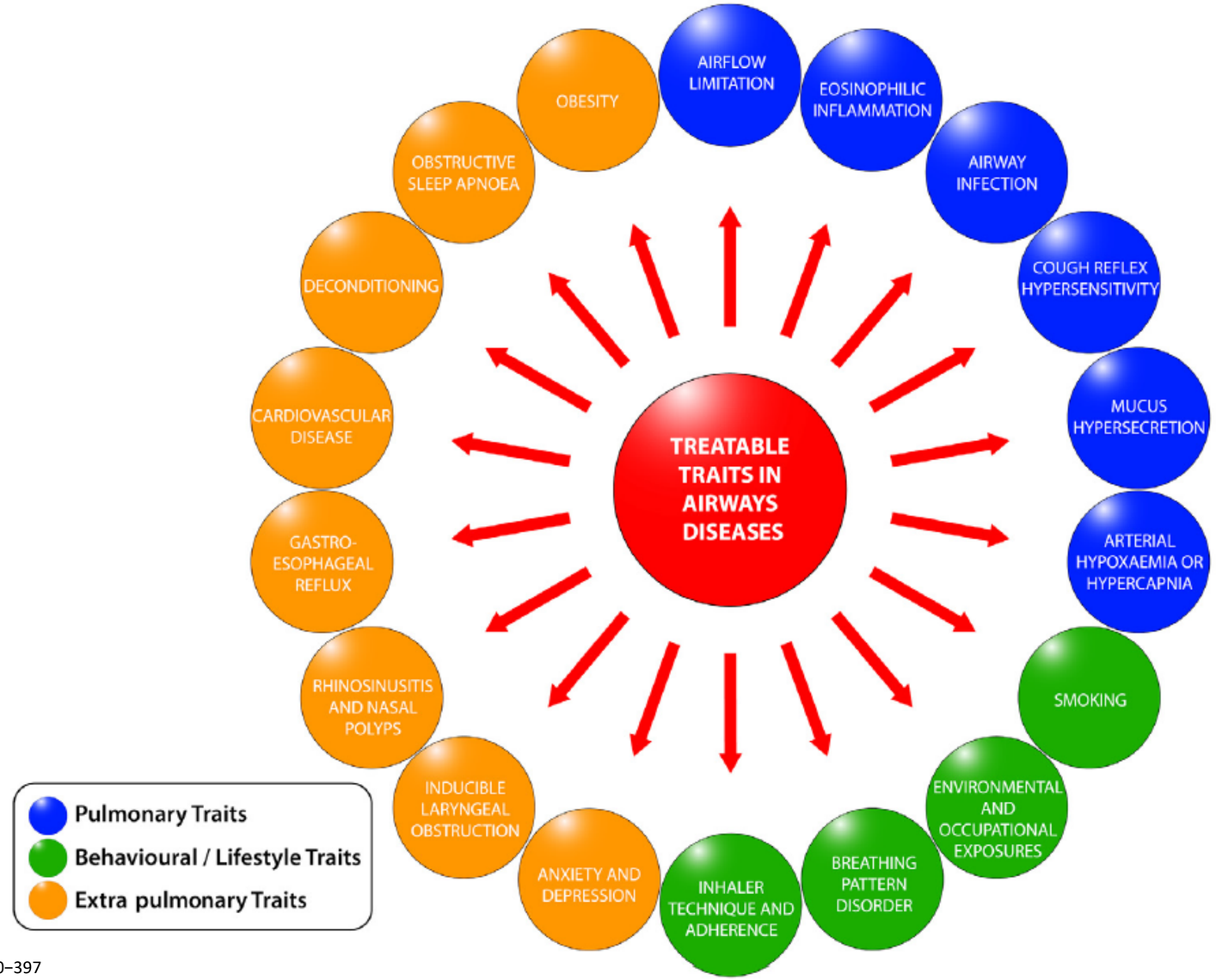


Asthma phenotypes

- **Cough-variant asthma**
- **Allergic asthma**
- **Non-allergic asthma**
- **Adult-onset (late-onset) asthma**
- **Asthma with persistent airflow limitation**
- **Asthma with obesity**

Lancet 2023; 401: 858–73

A schematic of identified treatable traits in asthma

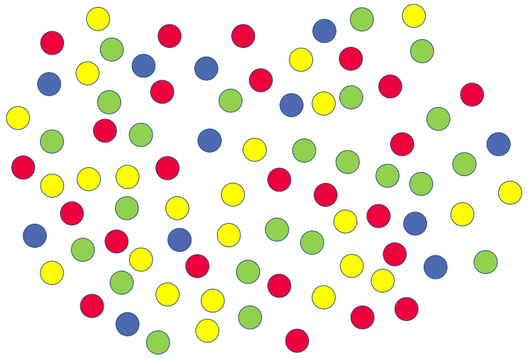


Ann Allergy Asthma Immunol 128 (2022) 390–397

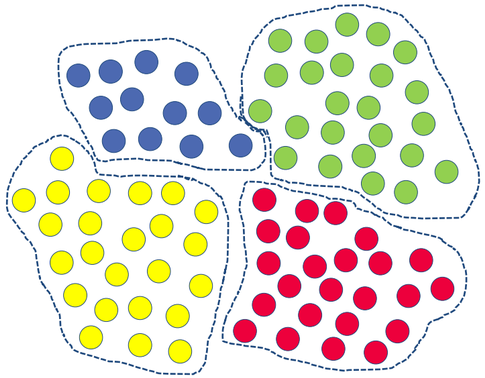
Asthma is heterogeneous and may benefit from a personalised treatment

- **All patients are different** and can present with a wide range of symptoms and underlying factors
- The concept of a clinical **phenotype attempted to group patients** with similar clinically relevant characteristics
- In reality, however, airways diseases are **complex** and **heterogeneous**
- Different clinical characteristics can occur in varying proportions in any given patient

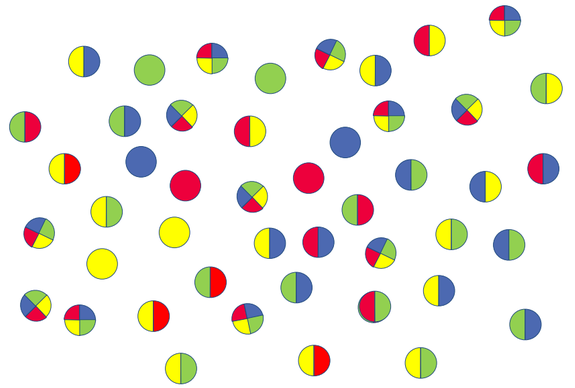
Individual patients



Phenotypes



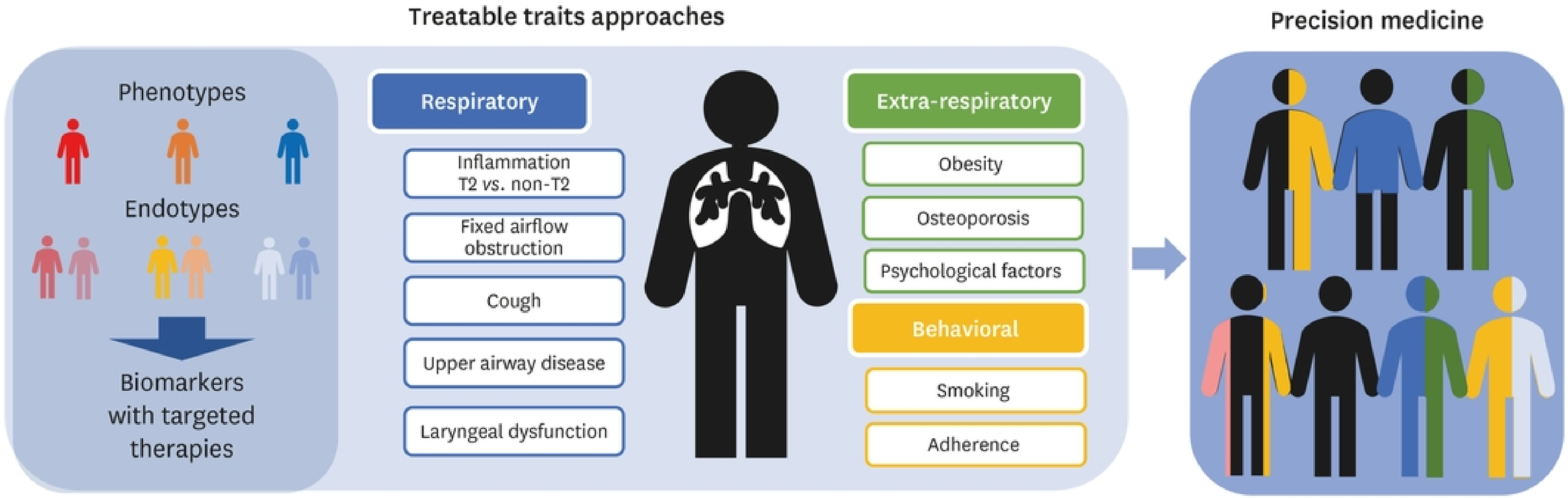
Treatable traits



1. Agustí A. *Thorax*. 2014;69(9):857–864.

Date of preparation: November 2020 NP-GBL-RS-PPT-200002

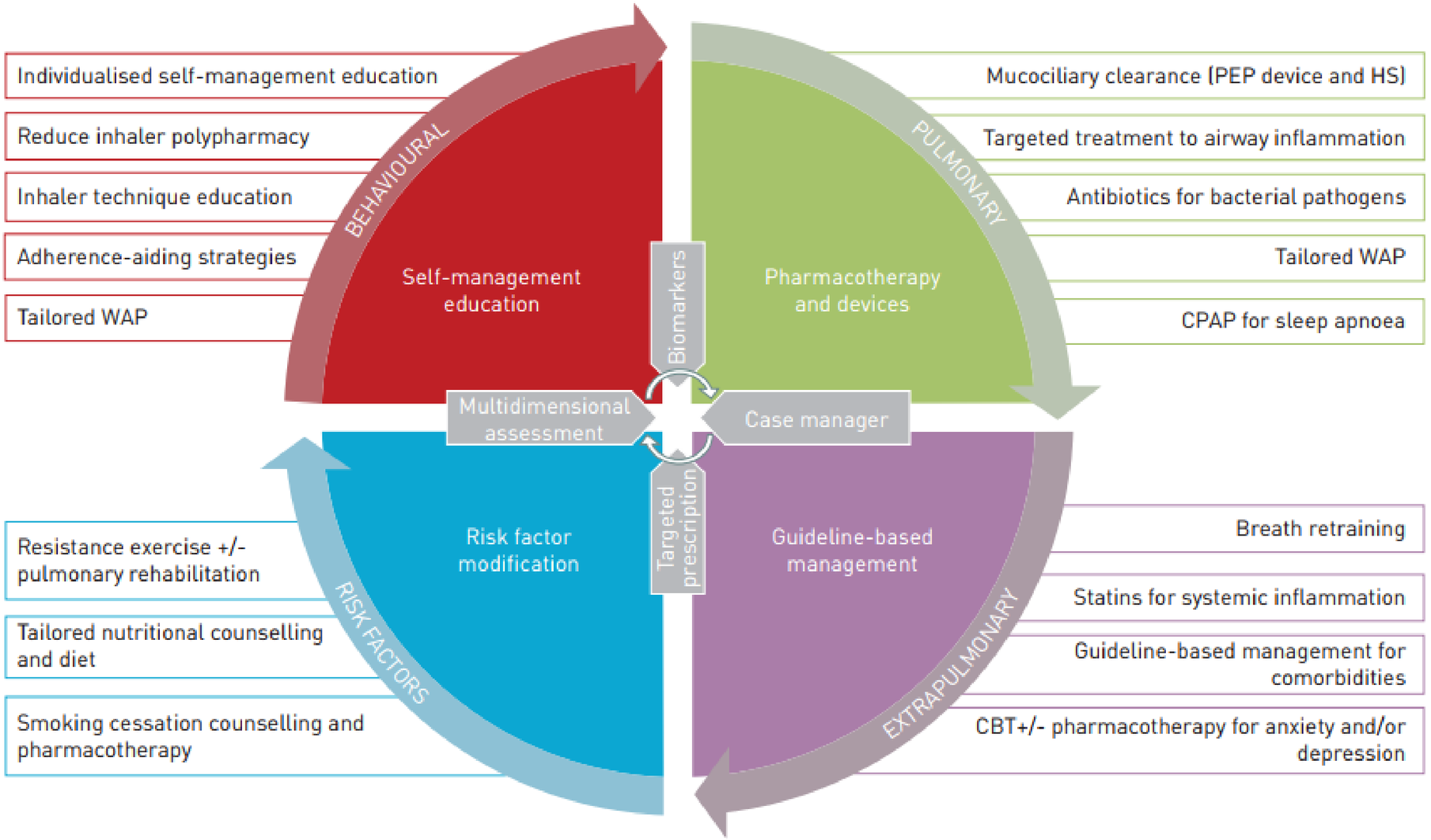
Beyond multiple biomarkers; Integrating with treatable traits



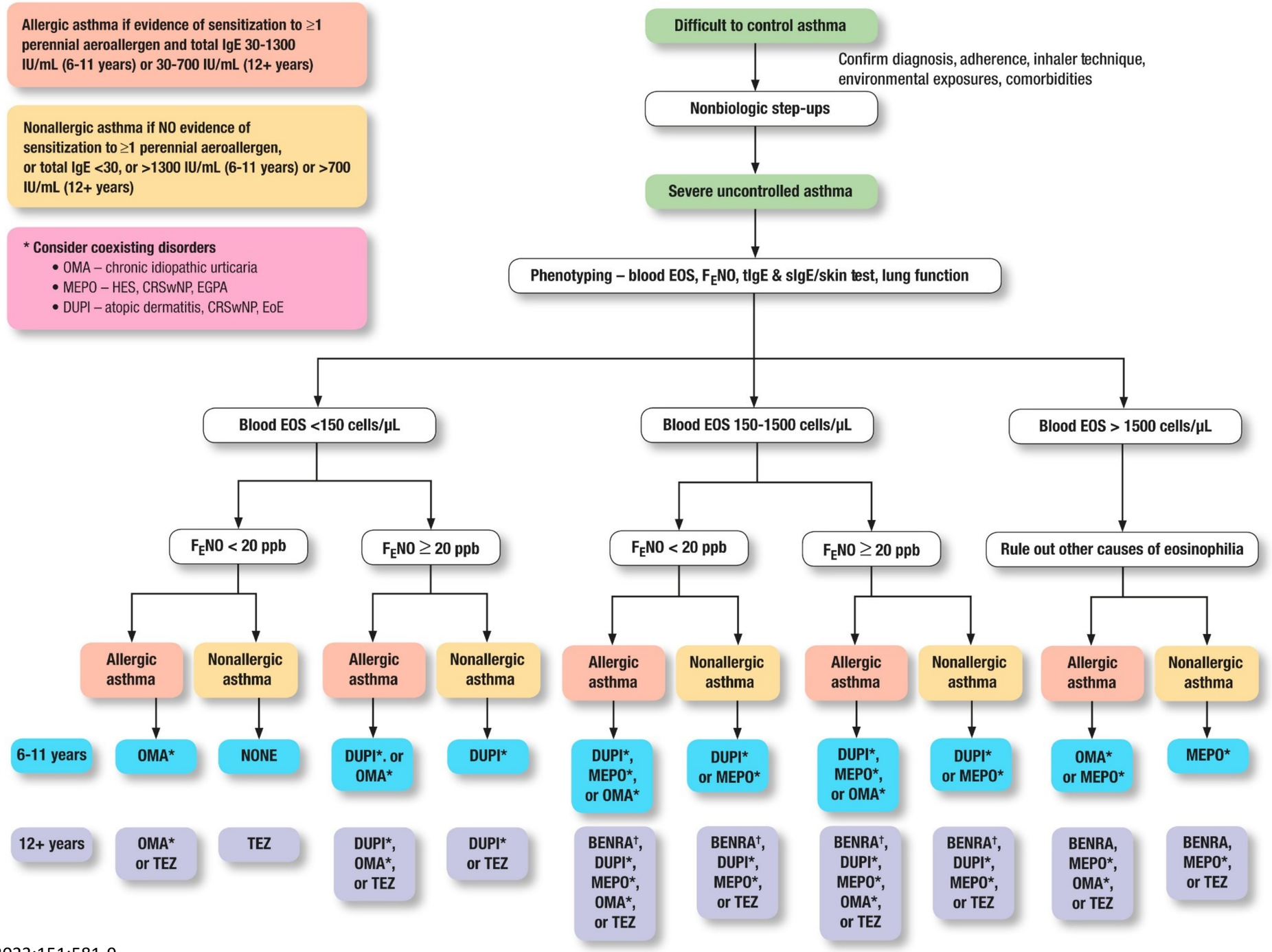
Allergy Asthma Immunol Res. 2022 Sep;14(5):447-464.

Traits should have clinical impact, connectivity, and patient impact

Treatable traits are not mutually exclusive

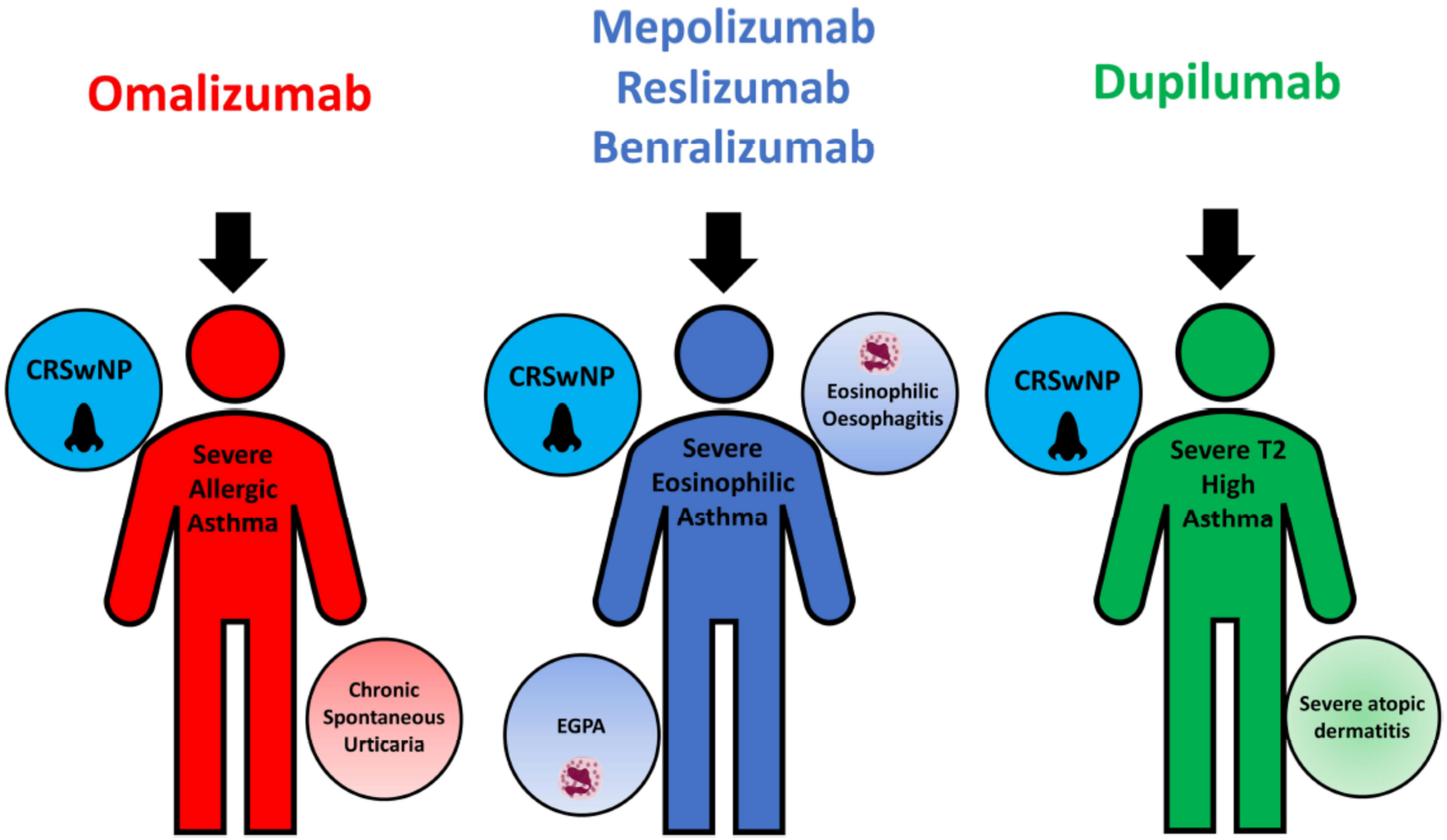


Eur Respir J 2019; 53: 1802058; Eur Respir J 2020; 55: 1901509



J Allergy Clin Immunol 2023;151:581-9.

A proposed algorithm for biomarker with co-morbidity approach to the use of current biologics

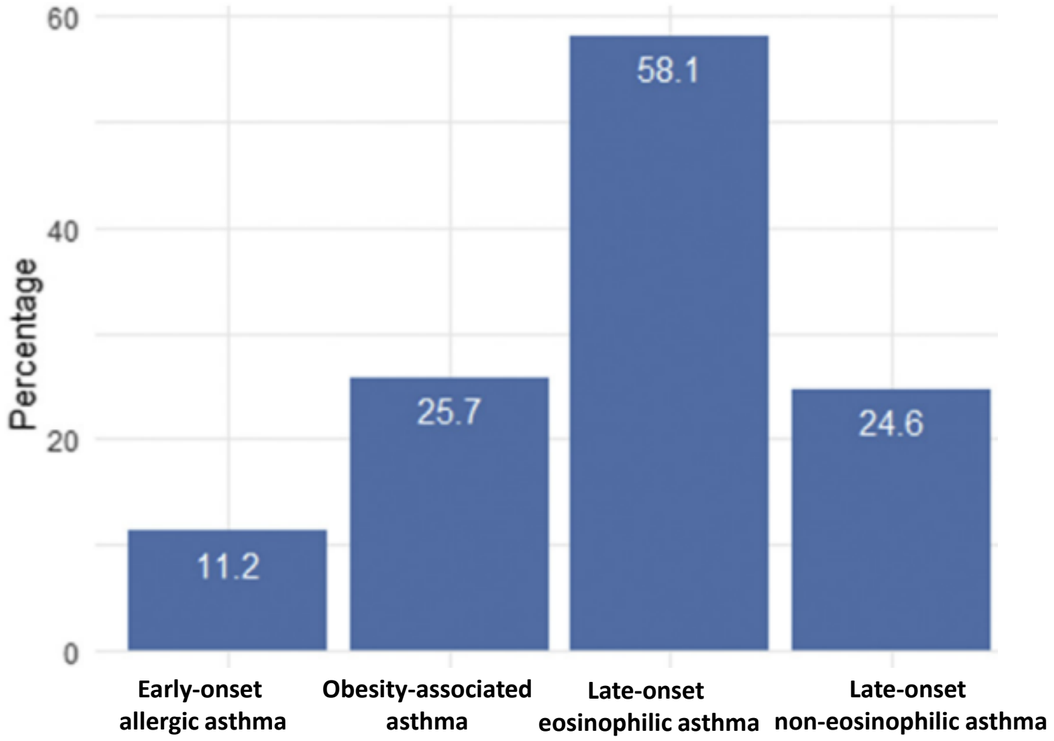


Journal of Inflammation Research 2021:14

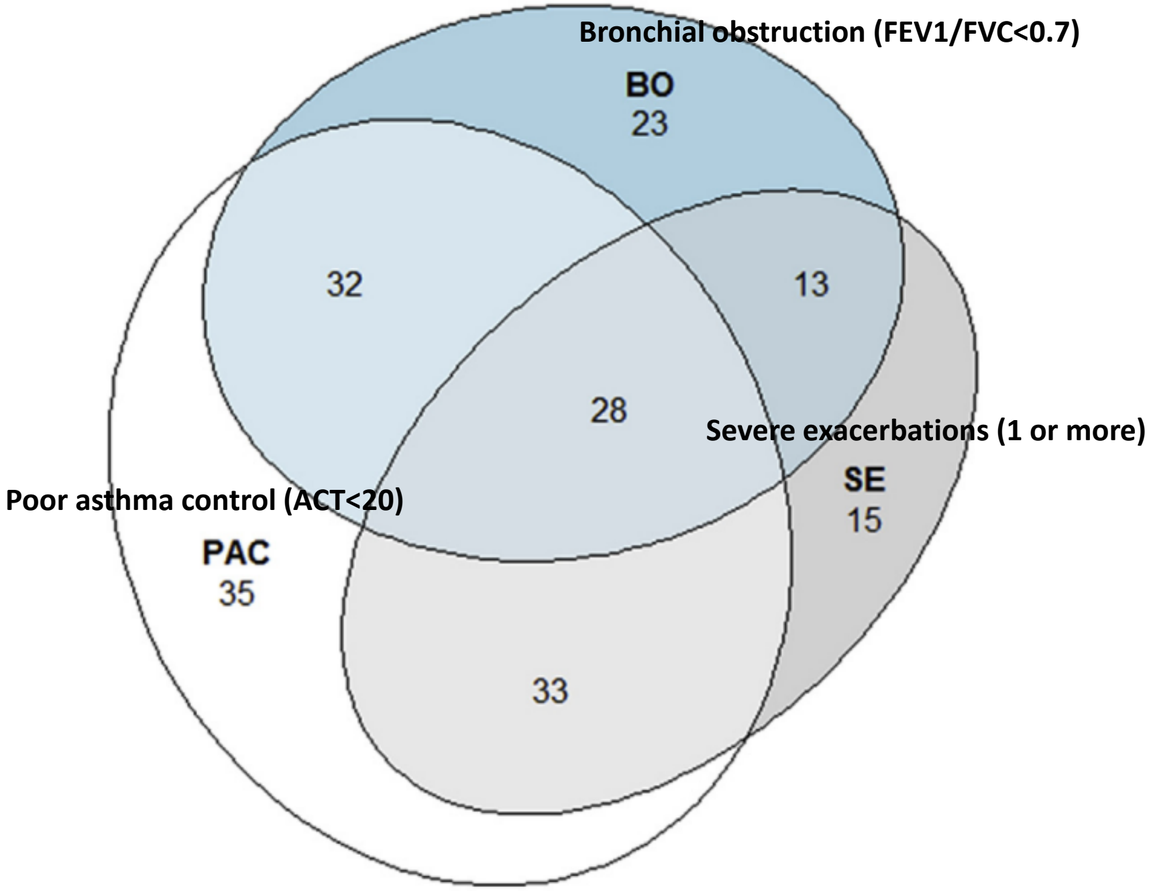
06. Asthma with fixed airflow obstruction

Severe asthma

Phenotypic distribution (in Spain)



Proportional Venn diagram for therapeutic objectives



Luis Pérez de Llano et al. Respir Med. 2019 May;151:49-54.

Definitions of ACO

- The terms ‘asthma-COPD overlap’ (ACO) or ‘asthma+COPD’ are simple descriptors for patients who have features of both asthma and COPD.
- These terms do not refer to a single disease entity. They include patients with several clinical phenotypes that are likely caused by a range of different underlying mechanisms.
- The term ACO has been preferred to asthma-COPD overlap syndrome (ACOS), as there is no single disease or “syndrome.”
- In 2015, the Global Initiative for Asthma (GINA) and the Global Initiative for COPD (GOLD) released a joint statement : ACOS
- In 2017, the American Thoracic Society and the National Heart, Lung, and Blood Institute published a joint workshop report on ACO.

Global strategy for asthma management and prevention updated 2022

Definitions of ACO

- **In contrast, the 2020 GOLD Strategy update abandoned use of the term "asthma COPD overlap" arguing that asthma and COPD are different disorders that may share common features such as eosinophilia or some degree of reversibility.**

> In addition, we no longer refer to asthma & COPD overlap (ACO), instead we emphasize that asthma and COPD are different disorders, although they may share some common traits and clinical features (e.g., eosinophilia, some degree of reversibility).

Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Manage ment, and Prevention of Chronic Obstructive Lung Disease. https://www.goldcopd.org (Accessed on December 02, 2019).

Why are the labels ‘asthma’ and ‘COPD’ still important?

- **There are extremely important differences in treatment recommendations for asthma and COPD.**

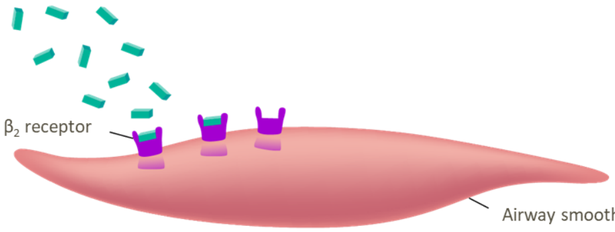
ICS vs Long-acting bronchodilator (LABA/LAMA)

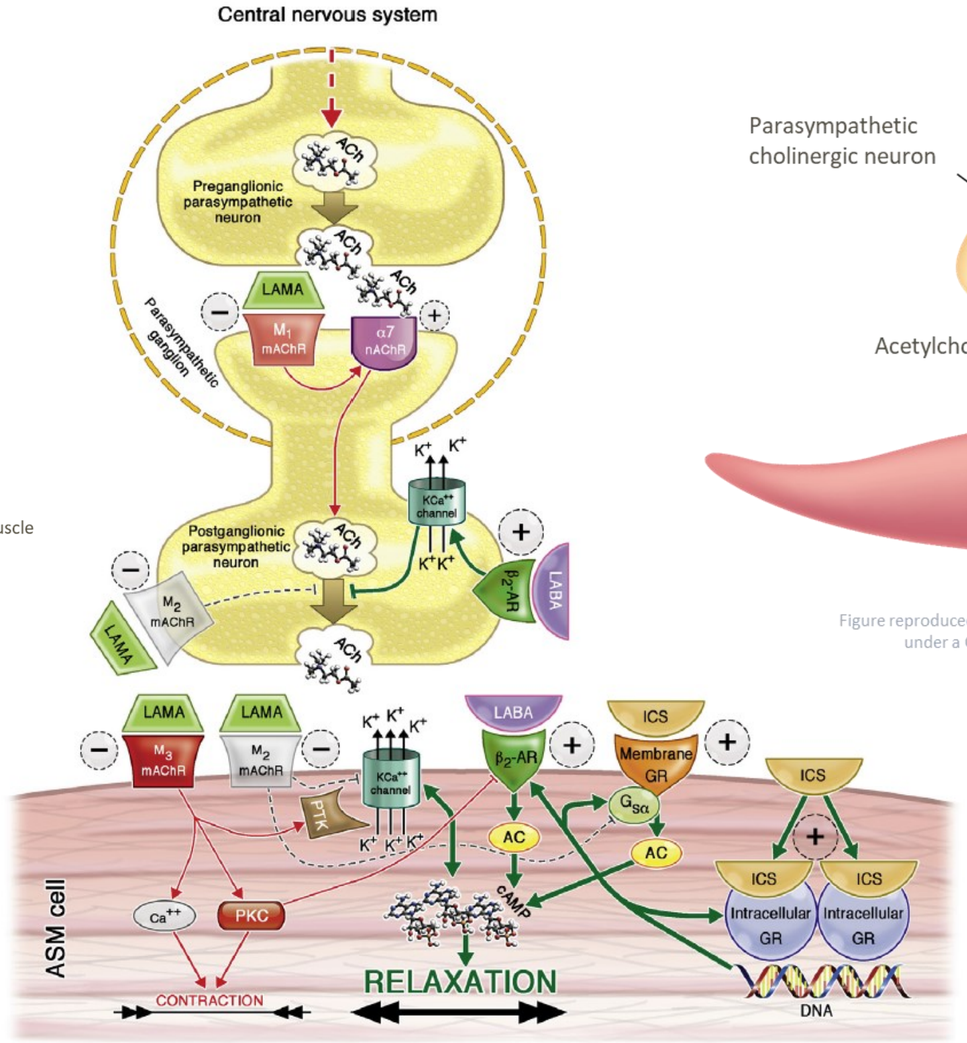
- **Patients with diagnoses of both asthma and COPD are at increased risk of hospitalization or death if they are treated with LABA compared with ICS-LABA.**

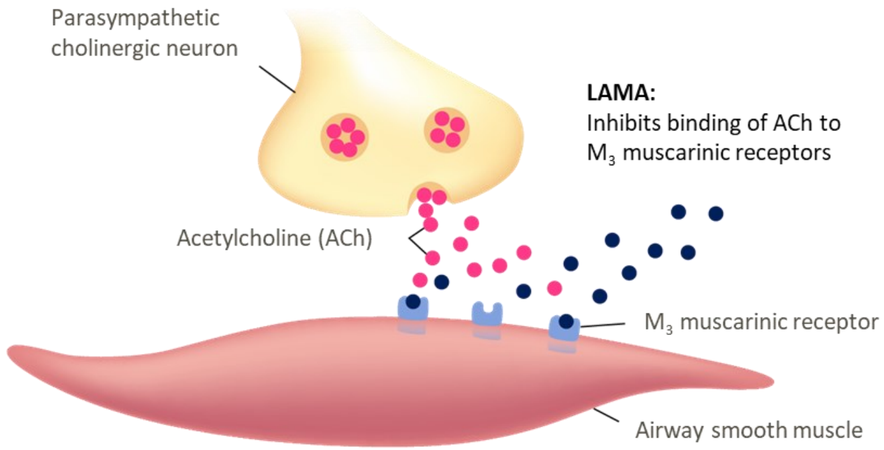
The pharmacological optimization of bronchodilation and the rationale for triple therapy (ICS-LABA-LAMA) in airway disorders

LABA[1–3]
promotes bronchodilation

LABA:
Activates β_2 receptors





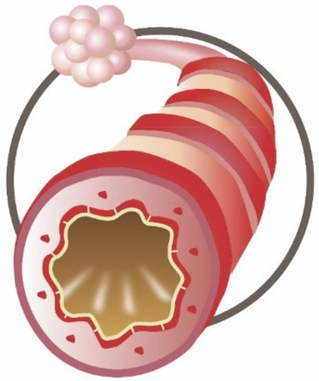


LAMA:
Inhibits binding of ACh to M_3 muscarinic receptors

Pharmacological Reviews January 2020, 72 (1) 218-252;
J Allergy Clin Immunol 2020;146:1288-91.

ICS/LAMA/LABA triple therapy combines molecules with three complementary modes of action to alleviate asthma symptoms

ICS[1,2]

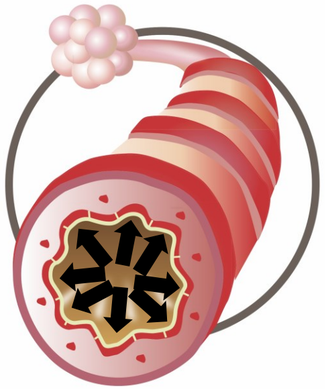


ANTI-INFLAMMATORY EFFECT IN THE AIRWAYS

LABA[3–5]

RELAXES AIRWAY SMOOTH MUSCLE STIMULATES BRONCHO DILATION

LAMA[6–8]



REDUCES AIRWAY SMOOTH MUSCLE CONTRACTION PREVENTS BRONCHO CONSTRICTION

THIS TRIPLE COMBINATION REDUCES INFLAMMATION AND PROVIDES MAXIMAL BRONCHODILATION, WITH THE ADDITIONAL POWER OF LAMA, TO ADDRESS UNDERTREATED BRONCHOCONSTRICTION[1–8]

ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist.

1. Biggadike K et al. J Med Chem 2008; 51:3349–3352. 2. Daley-Yates PT et al. Br J Clin Pharmacol 2021; 87(2):483–493. 3. Slack RJ et al. J Pharmacol Exp Ther 2013; 344:218–230. 4. Hanania N et al. Chest 2012; 142:119–127. 5. Kempsford R et al. Pulm Pharmacol Ther 2013; 26(2):256–264. 6. Feldman G et al. Int J Chron Obstruct Pulmon Dis 2016; 11:719–730. 7. Laine DI. Exp Rev Clin Pharmacol 2010; 3:43–53. 8. Laine DI. J Med Chem 2009; 52:2493–2505.

Multiple-Inhaler ICS-LABA-LAMA Triple Therapy (MITT)

LAMA

LABA/LAMA

ICS/LABA

ICS/LABA

ICS

LAMA

ICS/LABA/LAMA

Triple therapy combinations of ICS-LABA-LAMA in a single inhaler (SITT)

Drug Class	Generic Name	Form	Dose
LABA/LAMA/ ICS	Formoterol/tiotropium/ciclesonide	Inhalation powder	12/18/400 μg once-a-day
	Formoterol/glycopyrronium/beclomethasone dipropionate (TRIMARAN and TRIGGER)	Inhalation spray	5/11/87 μg twice-a-day
	Vilanterol/umeclidinium/fluticasone furoate (CAPTAIN)	Inhalation powder	22/65/92 μg once-a-day
	Formoterol/glycopyrronium/budesonide (KALOS)	Inhalation aerosol	9.6/14.4/320 μg twice-a-day
	Indacaterol/glycopyrronium/mometasone furoate (IRIDIUM and ARGON)	**Inhalation powder**	**150/50/80 or 160 μg once-a-day**

- Several triple therapy combinations of ICS-LABA-LAMA in a single inhaler (SITT) have been marketed
- 2021 GINA recommends adding a LAMA in patients aged ≥18 years who, despite being adherent to inhaled LABA combined with medium or high doses ICS, still experience symptoms or exacerbations

Allergy. 2021 Sep 3. doi: 10.1111/all.15076. Epub ahead of print; Pharmacol Rev 72:218–252, January 2020

Cochrane Library

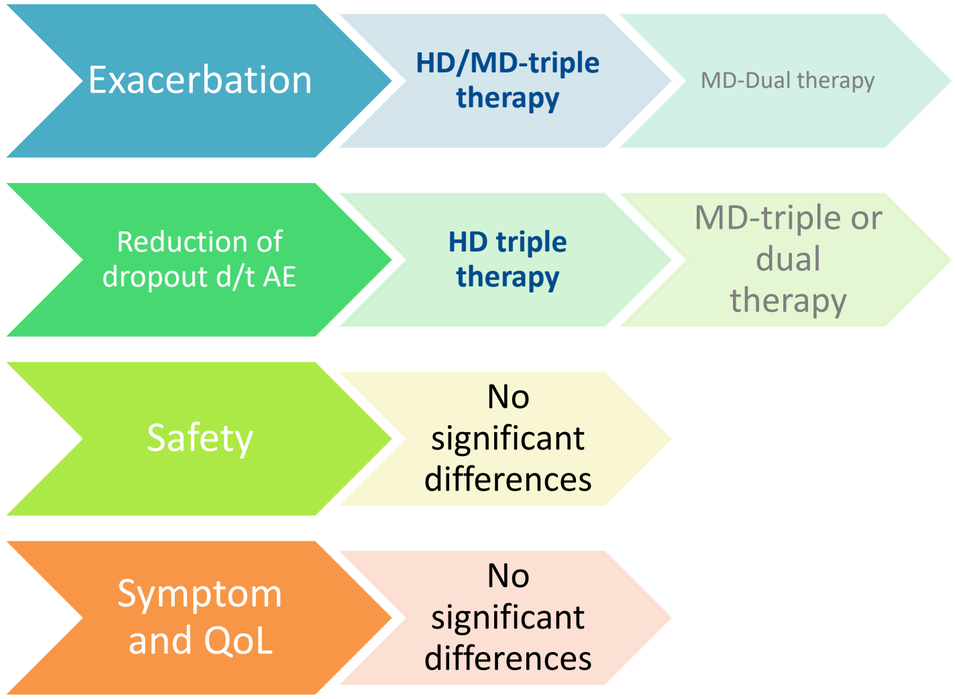
Cochrane Database of Systematic Reviews

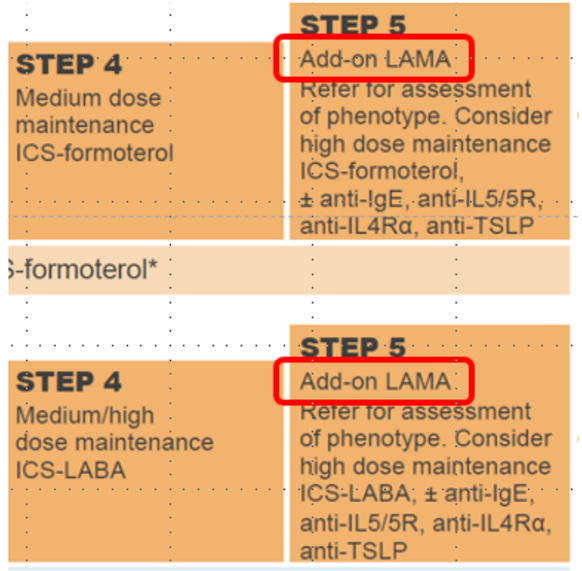
Effectiveness and tolerability of dual and triple combination inhaler therapies compared with each other and varying doses of inhaled corticosteroids in adolescents and adults with asthma: a systematic review and network meta-analysis (Review)

Oba Y, Anwer S, Maduke T, Patel T, Dias S

Effectiveness and tolerability of dual and triple therapy in uncontrolled asthma

- Current guidelines recommend a higher-dose ICS or adding LAMA when asthma is not controlled with medium-dose ICS/LABA combination therapy.
- To assess the effectiveness and safety of dual and triple therapies
- HD-ICS/LABA is unlikely to result in any significant benefit or harm compared to MD-ICS/LABA





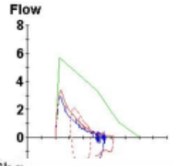
Cochrane Database of Systematic Reviews 2022, Issue 12. Art. No.: CD013799

CASE 1 (Switching from HD ICS+LABA to HD ICS+LABA+LAMA)

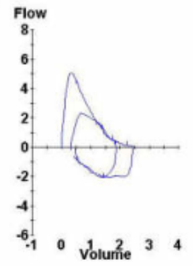
72/F

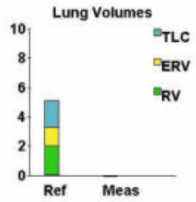
10 yrs ago, Dyspnea and persistent cough despite the medication and SABA rescue med under the diagnosis of asthma
Chronic rhino-sinusitis, NO specific allergen sensitization, Blood EOS: 470/μl, Elevated total Ig E

		Ref	Pre	% Ref	Post	% Ref	%Chg
Spirometry							
FVC	Liters	3.02	1.79	59	2.08	69	17
FEV.5	Liters	1.95	0.79	40	0.90	46	14
FEV.5/FVC	%	68	44		43		
FEV1	Liters	2.21	1.09	49	1.22	55	12
FEV1/FVC	%	73	61		58		
FEV3	Liters		1.48		1.75		18



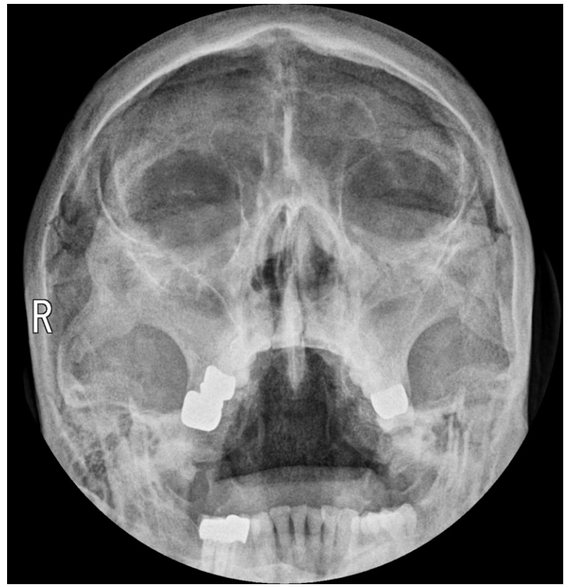
		Ref	Pre	% Ref	Post	% Ref	%Chg
Spirometry							
FVC	Liters	3.57	2.45	69			
FEV.5	Liters	1.87	1.41	76			
FEV.5/FVC	%	68	58				
FEV1	Liters	2.53	1.76	70			
FEV1/FVC	%	71	72				
FEV3	Liters		2.23				
FEV3/FVC	%	97	91				
FEF25-75%	L/sec	2.58	1.18	46			
IsoFEF25-75	L/sec	2.58	1.18	46			
FEF75-85%	L/sec	0.54	0.29	53			
FEF25%	L/sec		4.55				
FEF50%	L/sec	3.16	1.81	57			
FEF75%	L/sec	1.04	0.44	42			
PEF	L/sec	6.96	5.27	76			
FET25-75%	Sec	0.54	1.04	193			
FET100%	Sec		6.70				
FIVC	Liters	3.57	1.99	56			
FIF50%	L/sec		2.04				
PIF	L/sec		2.06				
FEF/FIF50			0.89				
MVV	L/min	113	61	54			
f	BPM		55				





Vt	Liters	0.29
f	BPM	94

BDR: Positive
MBPT: positive (Pc20 : 0.10 mg/ml)



CASE 1 (Switching from HD ICS+LABA to HD ICS+LABA+LAMA)

MD ICS-LABA (FLU-SAL) bid

-Persistent cough and intermittent dyspnea (ACT = 10-13)

- Exacerbation required OCS use

HD ICS-LABA (FLU-SAL) bid

- Mild improving but persistent exacerbation required OCS use

HD ICS-LABA (FLU-VI) once daily

- wax and wane (ACT = 10-11)
- more frequent exacerbations

HD ICS-LABA (FLU-VI) + TIO : no interval change

About 1 yr ago, HD ICS-LABA-LAMA (MF-IND-GLY) once daily

- No exacerbation and NO OCS use for 1 yr
- ACT: 23

CASE 2 (Switching from LD/MD ICS+LABA to HD ICS+LABA)

28세 남자

호흡곤란

약 2년 전부터 시작되었고, 체중 증가로 보다 악화
1년 전에 COVID-19 걸리고 나서 더 심해진 것 같다고 호소

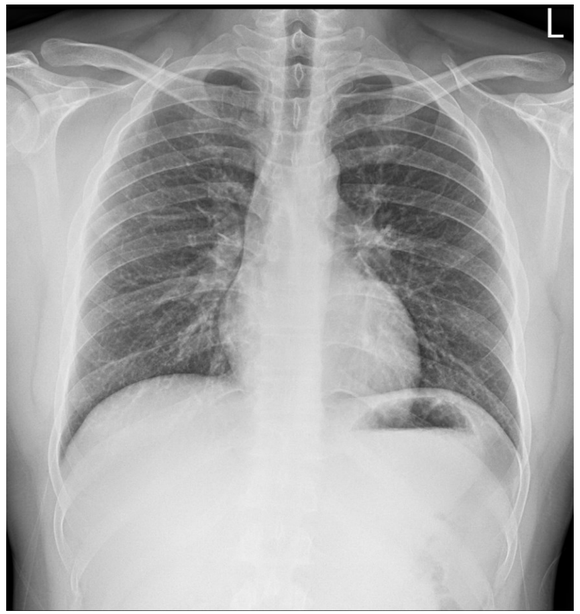
호흡곤란의 양상: 기관지가 좁아진 것 같고, 빨대를 물고 숨을 쉬는 기분
악화인자: 운동, 찬공기, 메밀 들어 간 음식 먹으면 기침이 나면서 불편함

가족력: 어머니- 알레르기 비염

외부 병원에서 알레르기 검사 하고 동물 털에 알레르기가 있다고 알고 있었고, 천식 가능성 있다는 말도 들어서
1년 전 쯤 부터 Beclomethasone+Formoterol (100/6) pMDI as-needed therapy 사용해 봤고,

최근 악화 있어서 다른 병원에서 Beclomethasone+Formoterol (100/6) nexhaler 로 처방 받아서 하루 두 번 꾸준히 사용하라고 들었지만 증상 호전이 더디다.

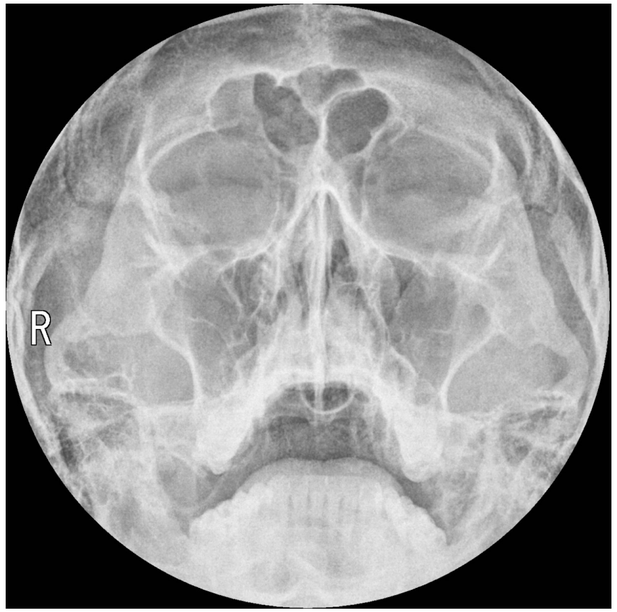
CASE 2 (Switching from AIR-only, LD/MD ICS+LABA to HD ICS+LABA)



Blood EOS: 10.7% (640/uL), ECP: 60.4
Total IgE: 308 IU/mL

MAST
Cat (고양이) : Class 5
Dog(개) : Class 5
Housedust mite-farinae (집먼지 진드기) : Class 4
Housedust mite-pteronyssinus (집먼지 진드기) : Class 4
Birch (자작나무): class 3

FeNO: 74 ppb



BDR: Positive
SPIROMETRY (BTPS)

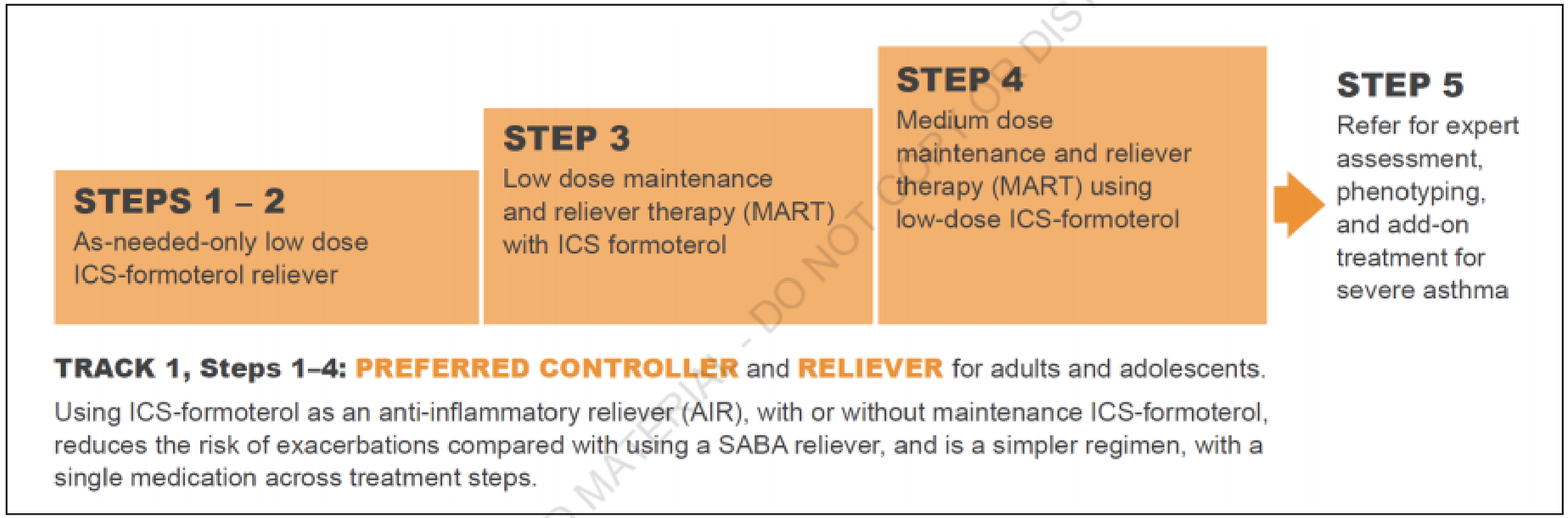
	Pre	Pre (%PRED)	Post	Post (%PRED)	% change
FVC (L)	5.05	96	5.46	104	8
FEV1 (L)	3.46	83	4.15	99	20
FEV1/FVC (%)	69		76		
FEF25-75% (L/sec)	2.25	50	3.32	74	48

MBPT: positive (Pc20 : 0.16 mg/ml)
ACT = 10-11

CASE 2 (Switching from AIR-only, LD/MD ICS+LABA to HD ICS+LABA)

Track 1, pMDI preference
Step 4 for 2 months: ACT 16, no exacerbation
Step 5 for 1 month: ACT 22

Box 4-7. Track 1 (preferred) treatment Steps 1–4 for adults and adolescents



See Box 4-8 (p.84) for details of medications and doses. AIR: anti-inflammatory reliever; ICS: inhaled corticosteroid; MART: maintenance-and-reliever therapy with ICS-formoterol; SABA: short-acting $beta_2$ agonist

CASE 3 (switching from MITT to SITT)

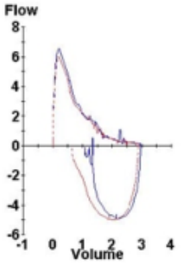
74/M

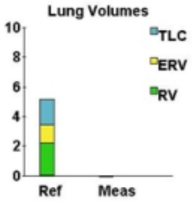
2 yrs ago, Dyspnea and persistent dry cough despite regular MD ICS/LABA (FLU-VI) use under the diagnosis of asthma

Multiple Myeloma Dx and management at IMHO

No allergy, normal total Ig E, Never smoker, No Eosinophilia, FeNo; 5 ppb

		Ref	Pre	% Ref	Post	% Ref	%Chg
How Long:		Quit: No			Stopped:		
Spirometry							
FVC	Liters	3.47	2.98	86	2.90	84	-3
FEV.5	Liters	1.69	1.33	78	1.28	75	-4
FEV.5/FVC	%	68	45		44		
FEV1	Liters	2.32	1.73	75	1.71	74	-1
FEV1/FVC	%	69	58		59		
FEV3	Liters		2.42		2.36		-2
FEV3/FVC	%	97	81		81		
FEF25-75%	L/sec	2.22	0.70	31	0.72	32	3
IsoFEF25-75	L/sec	2.22	0.70	31	0.78	35	11
FEF75-85%	L/sec	0.35	0.24	70	0.24	68	-2
FEF25%	L/sec		3.43		2.81		-18
FEF50%	L/sec	2.97	1.35	46	1.12	38	-17
FEF75%	L/sec	0.90	0.31	34	0.28	31	-10
PEF	L/sec	6.84	6.52	95	6.00	88	-8
FET25-75%	Sec	0.54	2.15	399	2.03	376	-6
FET100%	Sec		6.60		6.44		-2
FIVC	Liters	3.47	1.89	54	2.26	65	20
FIF50%	L/sec		4.88		4.88		-0
PIF	L/sec		4.93		5.00		1
FEF/FIF50			0.28		0.23		-17
MVV	L/min	104	62	59			
f	BPM		60				

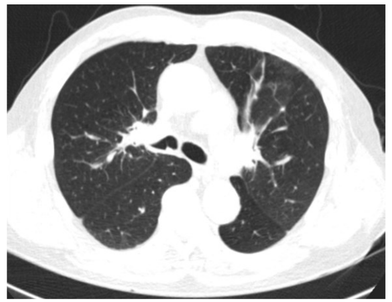


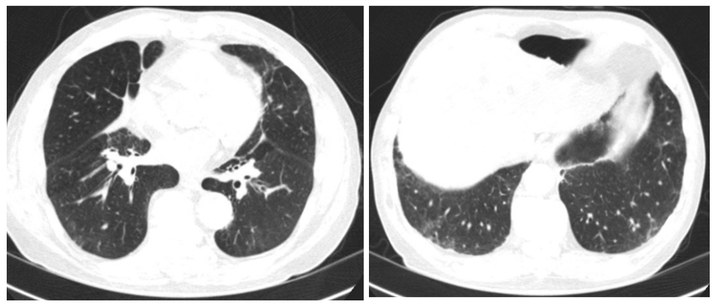


BDR: Negative

MBPT: positive (Pc20 : 8.0 mg/ml)

Fixed Airflow obstruction





CASE 3 (switching from MITT to SITT)

MD ICS-LABA (FLU-VI) once daily

-Persistent cough (ACT = 11)

HD ICS-LABA (FLU-VI) + TIO

- Poor adherence
- ER visit

2 months ago, switched to HD ICS-LABA-LAMA (MF-IND-GLY) once daily

- cough resolved
- ACT: 24

CASE 4

ER visit
46-year-old female

C.C: Fever

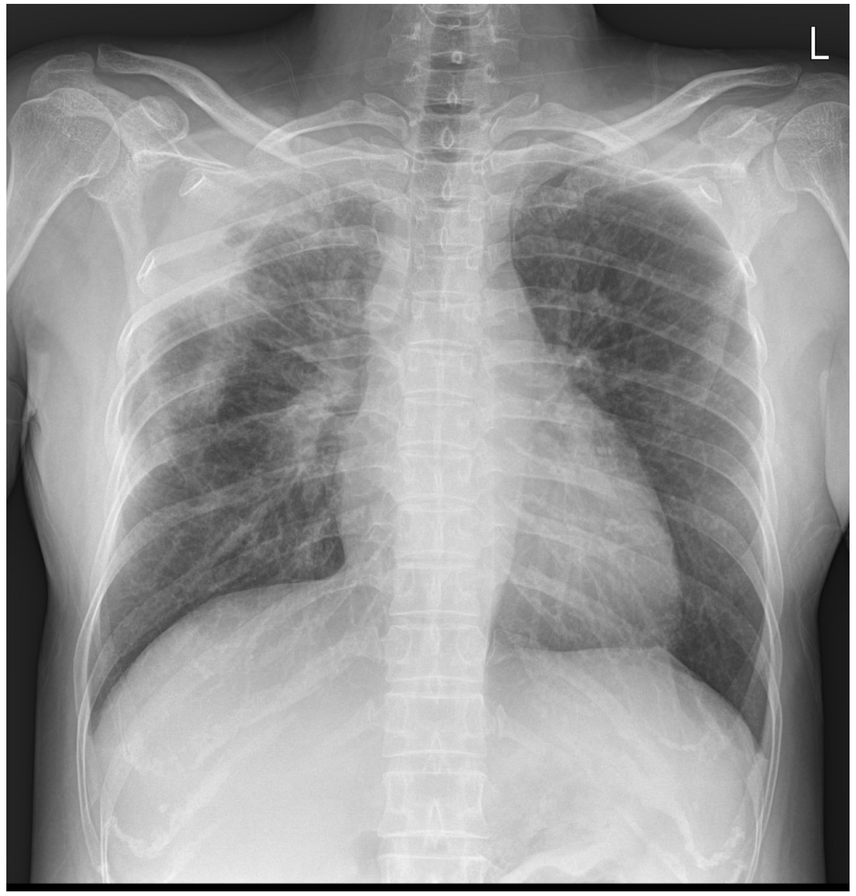
Onset: 16 days ago
Associating symptoms: cough with sputum, dyspnea

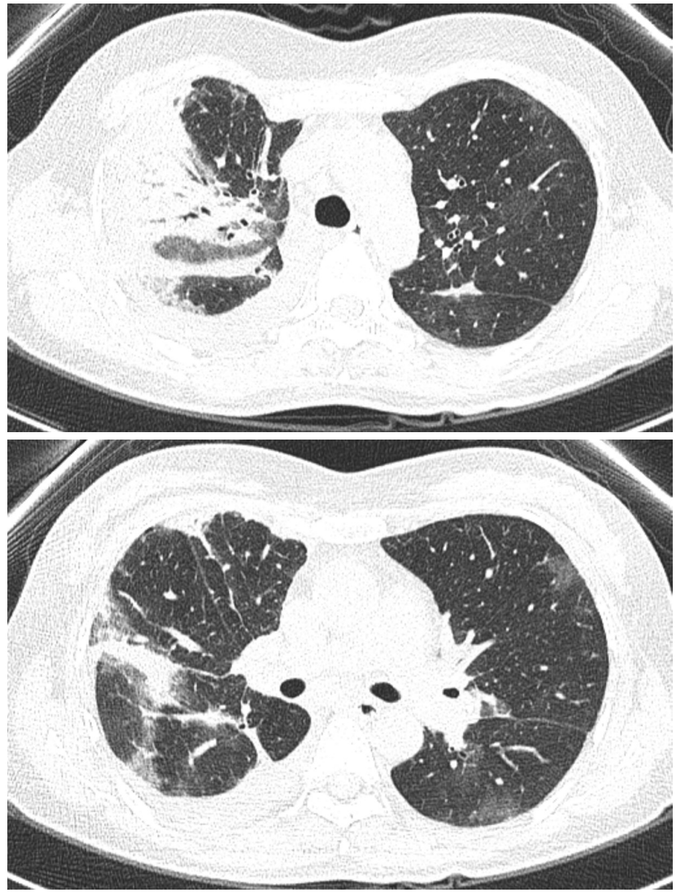
Vital sign: BT: 38.4 C, BP 140/90 mmHg, HR: 98 bpm, RR: 22/min

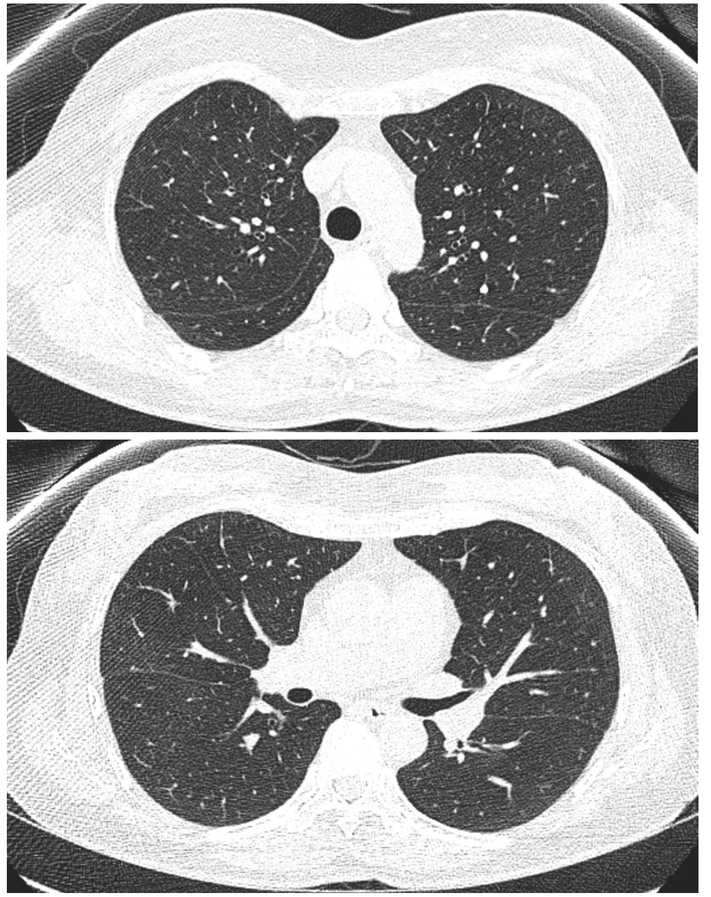
Past history: Recurrent respiration tract infection, Frequent admission to hospital
Allergic rhinitis, but no treatment

Present Illness: She was diagnosed with pneumonia at a local clinic and was continuously treated with antibiotics, but there was no improvement, so she was transferred to our ER.

CASE 4







CBC: 6170-10.1-299K (EOS. 23%, 1420/ul)
BAL cell analysis: EOS 79%

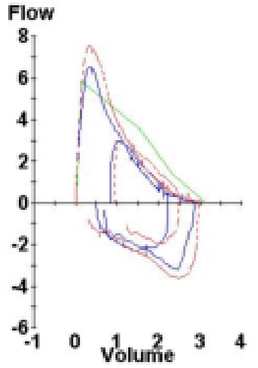
OCS treatment and dramatically improved

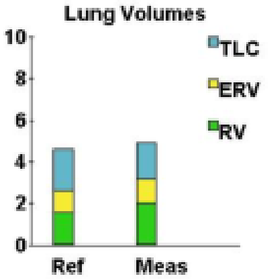
After treatment

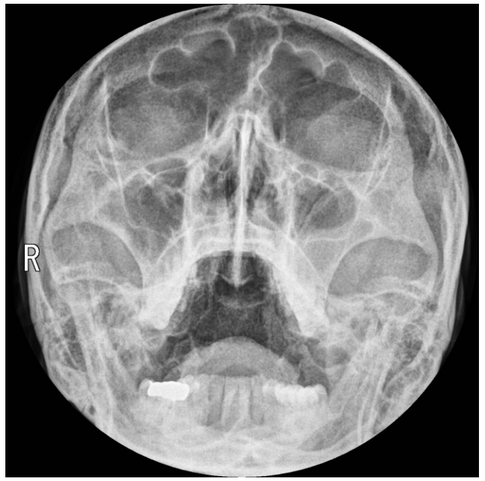
CASE 4

Allergy (MAST): DF/DP class 3 +

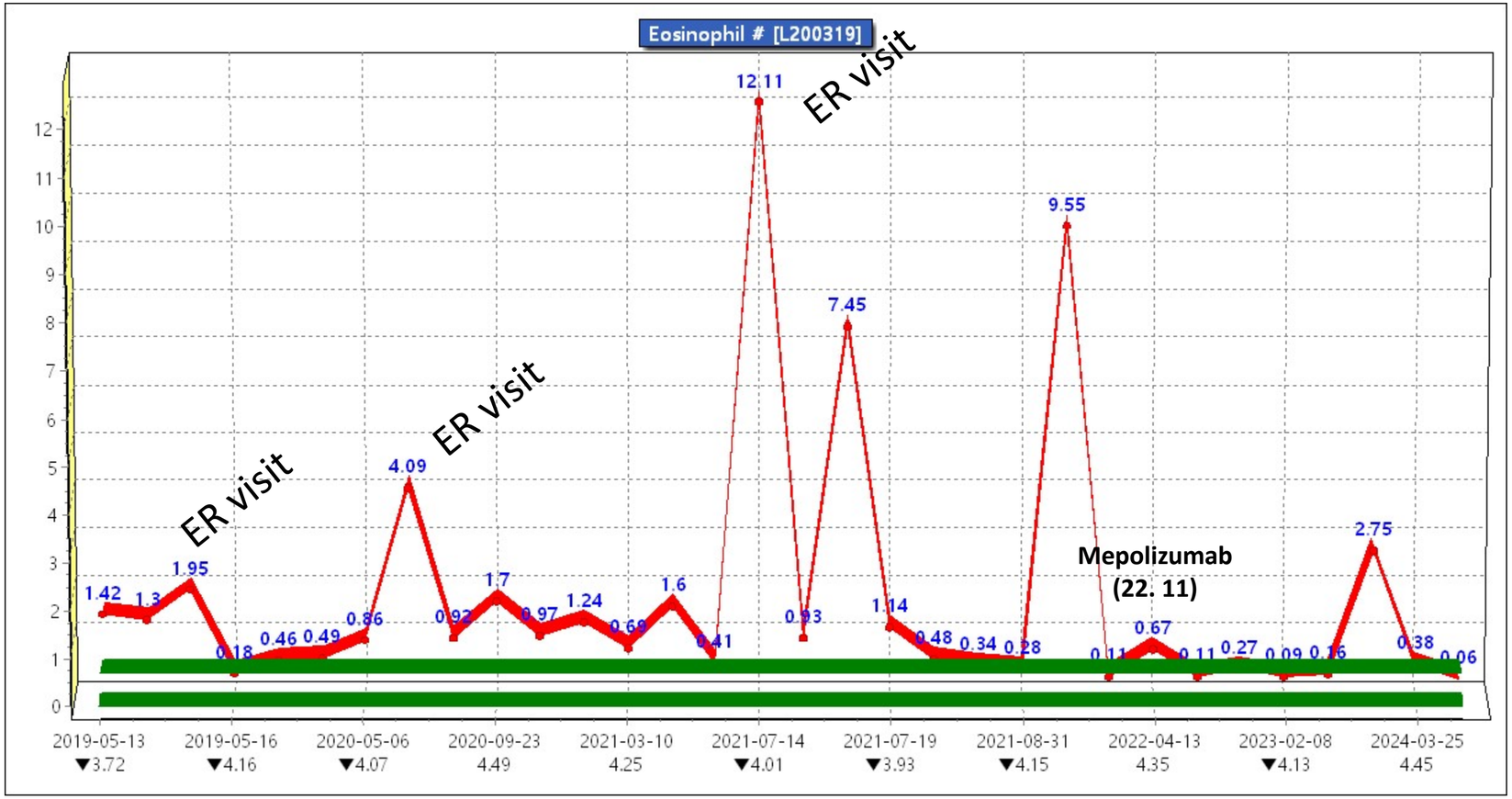
Spirometry		Ref	Pre	% Ref	Post	% Ref	%Chg
FVC	Liters	3.15	2.86	91	2.98	95	4
FEV.5	Liters	2.02	1.57	78	1.69	84	7
FEV.5/FVC	%	68	55		57		
FEV1	Liters	2.40	2.01	84	2.15	90	7
FEV1/FVC	%	76	70		72		
FEV3	Liters		2.57		2.72		6
FEV3/FVC	%	97	90		91		
FEF25-75%	L/sec	2.84	1.27	45	1.47	52	16
IsoFEF25-75	L/sec	2.84	1.27	45	1.76	62	39
FEF75-85%	L/sec	0.87	0.30	35	0.35	41	17
FEF25%	L/sec		5.50		6.08		10
FEF50%	L/sec	3.48	1.85	53	2.14	61	16
FEF75%	L/sec	1.35	0.41	31	0.64	47	54
PEF	L/sec	5.80	6.50	112	7.49	129	15
FET25-75%	Sec	0.45	1.15	256	1.02	228	-11
FET100%	Sec		6.49		6.54		1
FIVC	Liters	3.15	2.36	75	2.67	85	13
FIF50%	L/sec		2.18		2.43		11
PIF	L/sec		3.19		3.59		12
FEF/FIF50			0.85		0.88		4
MVV	L/min	101	68	67			
f	BPM		65				







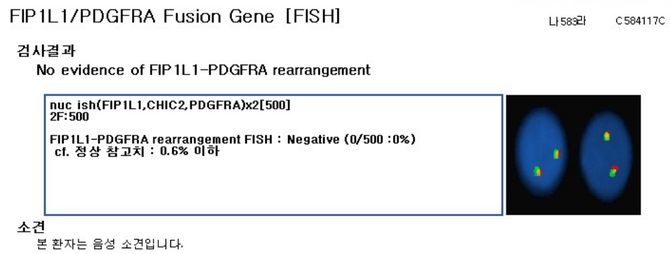
CASE 4



OCS/SCS burst or low dose OCS maintenance

No parasite infection
No other organ involvement
BM biopsy: W.N.L
Chromosomal study: normal

FIP1L1/PDGFRA fusion gene study: negative


FIP1L1/PDGFRA Fusion Gene [FISH]

검사결과
No evidence of FIP1L1-PDGFRA rearrangement

nuc ish(FIP1L1,CHIC2,PDGFRA)x2[500]
2F:500

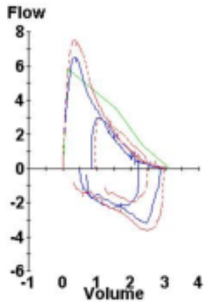
FIP1L1-PDGFRA rearrangement FISH : Negative (0/500 :0%)
cf. 정상 참고치 : 0.6% 이하

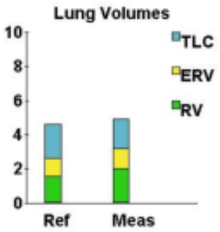
소견
본 환자는 음성 소견입니다.

High dose ICS-LABA, low dose OCS, anti-histamine, LTRA, INCS

CASE 4

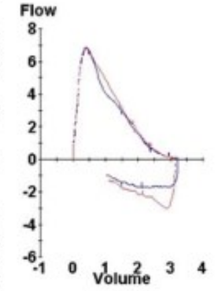
Spirometry		Ref	Pre	% Ref	Post	% Ref	%Chg
FVC	Liters	3.15	2.86	91	2.98	95	4
FEV.5	Liters	2.02	1.57	78	1.69	84	7
FEV.5/FVC	%	68	55		57		
FEV1	Liters	2.40	2.01	84	2.15	90	7
FEV1/FVC	%	76	70		72		
FEV3	Liters		2.57		2.72		6
FEV3/FVC	%	97	90		91		
FEF25-75%	L/sec	2.84	1.27	45	1.47	52	16
IsoFEF25-75	L/sec	2.84	1.27	45	1.76	62	39
FEF75-85%	L/sec	0.87	0.30	35	0.35	41	17
FEF25%	L/sec		5.50		6.08		10
FEF50%	L/sec	3.48	1.85	53	2.14	61	16
FEF75%	L/sec	1.35	0.41	31	0.64	47	54
PEF	L/sec	5.80	6.50	112	7.49	129	15
FET25-75%	Sec	0.45	1.15	256	1.02	228	-11
FET100%	Sec		6.49		6.54		1
FIVC	Liters	3.15	2.36	75	2.67	85	13
FIF50%	L/sec		2.18		2.43		11
PIF	L/sec		3.19		3.59		12
FEF/FIF50			0.85		0.88		4
MVV	L/min	101	68	67			
f	BPM		65				

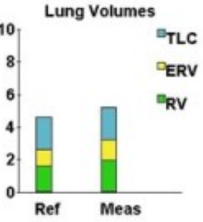




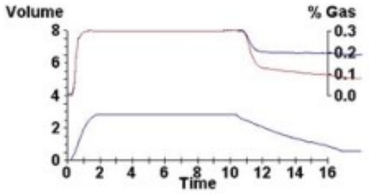
low dose ICS-LABA, anti-histamine

Spirometry		Ref	Pre	% Ref	Post	% Ref	%Chg
FVC	Liters	3.10	3.23	104	3.16	102	-2
FEV.5	Liters	2.00	1.86	93	1.93	97	4
FEV.5/FVC	%	68	57		61		
FEV1	Liters	2.35	2.38	101	2.44	104	3
FEV1/FVC	%	75	73		77		
FEV3	Liters		2.93		2.96		1
FEV3/FVC	%	97	91		94		
FEF25-75%	L/sec	2.78	1.70	61	2.07	74	21
IsoFEF25-75	L/sec	2.78	1.70	61	2.02	73	19
FEF75-85%	L/sec	0.83	0.38	45	0.49	59	30
FEF25%	L/sec		5.75		6.16		7
FEF50%	L/sec	3.43	2.64	77	2.99	87	13
FEF75%	L/sec	1.30	0.60	46	0.78	60	30
PEF	L/sec	5.75	6.89	120	6.78	118	-2
FET25-75%	Sec	0.45	0.95	212	0.78	172	-18
FET100%	Sec		6.87		6.74		-2
FIVC	Liters	3.10	2.22	71	2.06	66	-7
FIF50%	L/sec		1.63		2.01		24
PIF	L/sec		1.74		3.01		74
FEF/FIF50			1.62		1.49		-8
MVV	L/min	100	83	83			
f	BPM		70				





Lung Volumes							
TLC	Liters	4.61	5.23	113			
VC	Liters	3.10	3.23	104			
IC	Liters	2.04	1.95	96			
FRC PL	Liters	2.74	3.28	120			
ERV	Liters	1.02	1.23	120			
RV	Liters	1.61	1.99	124			
RV/TLC	%	35	38				
Vtg	Liters		3.37				
VE	L/min	4.9	23.6	480			
Vt	Liters		0.19				
f	BPM		124				



Diffusing Capacity				
DLCO	mL/mmHg/min	18.4	15.5	84
DL Adj	mL/mmHg/min	18.4	15.5	84
DLCO/VA	mL/mHg/min/L	4.12	3.60	87
DL/VA Adj	mL/mHg/min/L		3.60	
VA	Liters		4.30	
IVC	Liters		2.92	
TLC Sb	Liters	4.61	4.30	93
RV Sb	Liters	1.61	1.38	86
RV/TLC Sb	%	35	32	

CASE 5

62세 남자

7-8년 전부터 지속되는 호흡곤란 및 기침

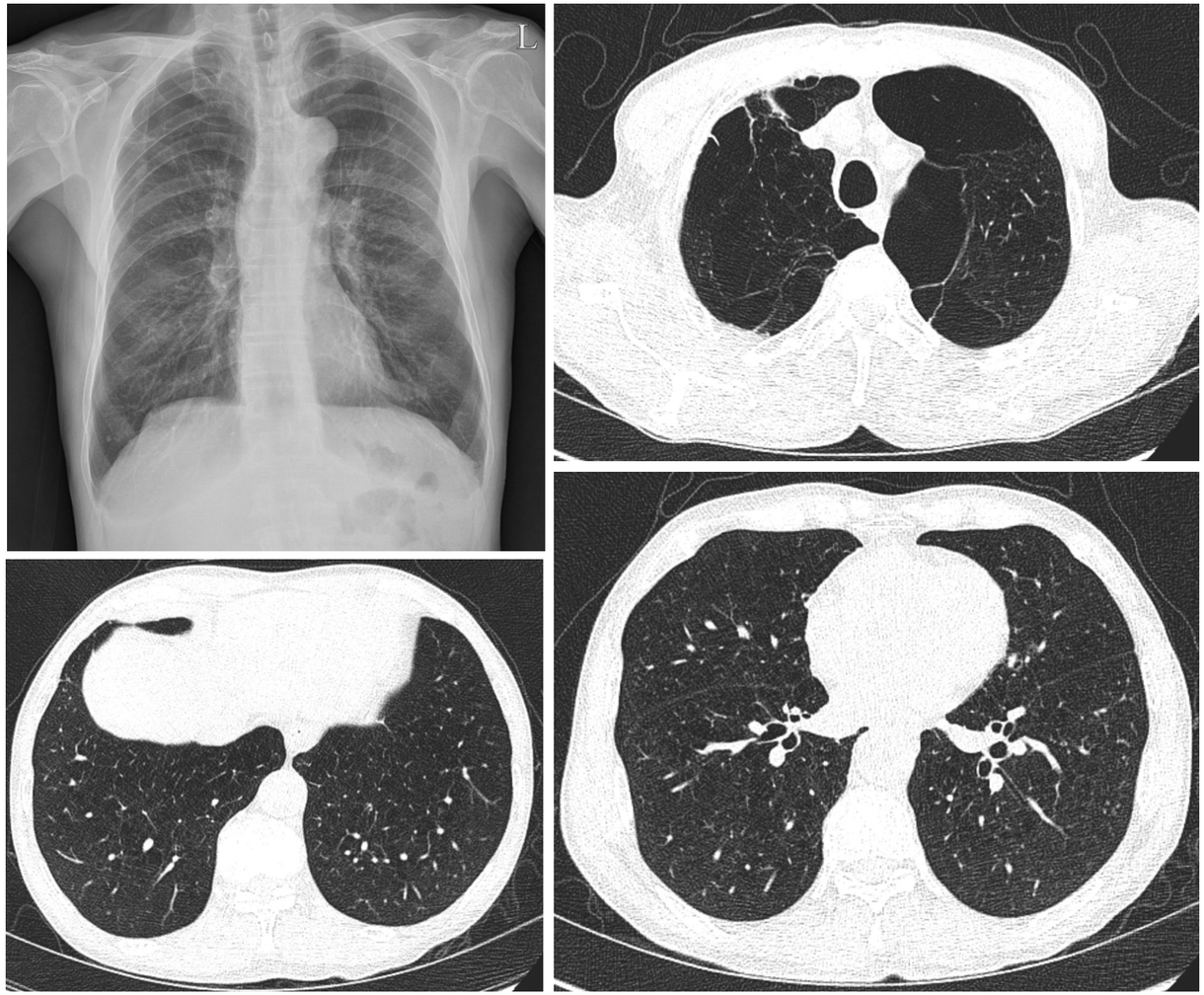
7년 전부터 개인 의원에서 천식이라고 진단을 받고 경구 약제로만 불규칙적인 치료

과거 흡연력: 약 10년 전 금연 시작 (30 갑년), 양봉업 15년

가족력: 아버지-천식

진찰 소견: 호흡음 감소

CASE 5



- **PFT**

1st visit
FVC: 3.35 L (100%)
FEV_1 : 1.77L (76%)
FEV_1/FVC: 53%
DLco: 71%
BDR: FEV1 230 ml (15%)

- **FeNO: 72 ppb**
- **MAST**
  - Aspergillus Class 3
- **CBC** 4600-13.4-308K (Eos 9.2%, 400)
- **Total Ig E** (IU/mL [ref. ~100 IU/mL]): 702.2

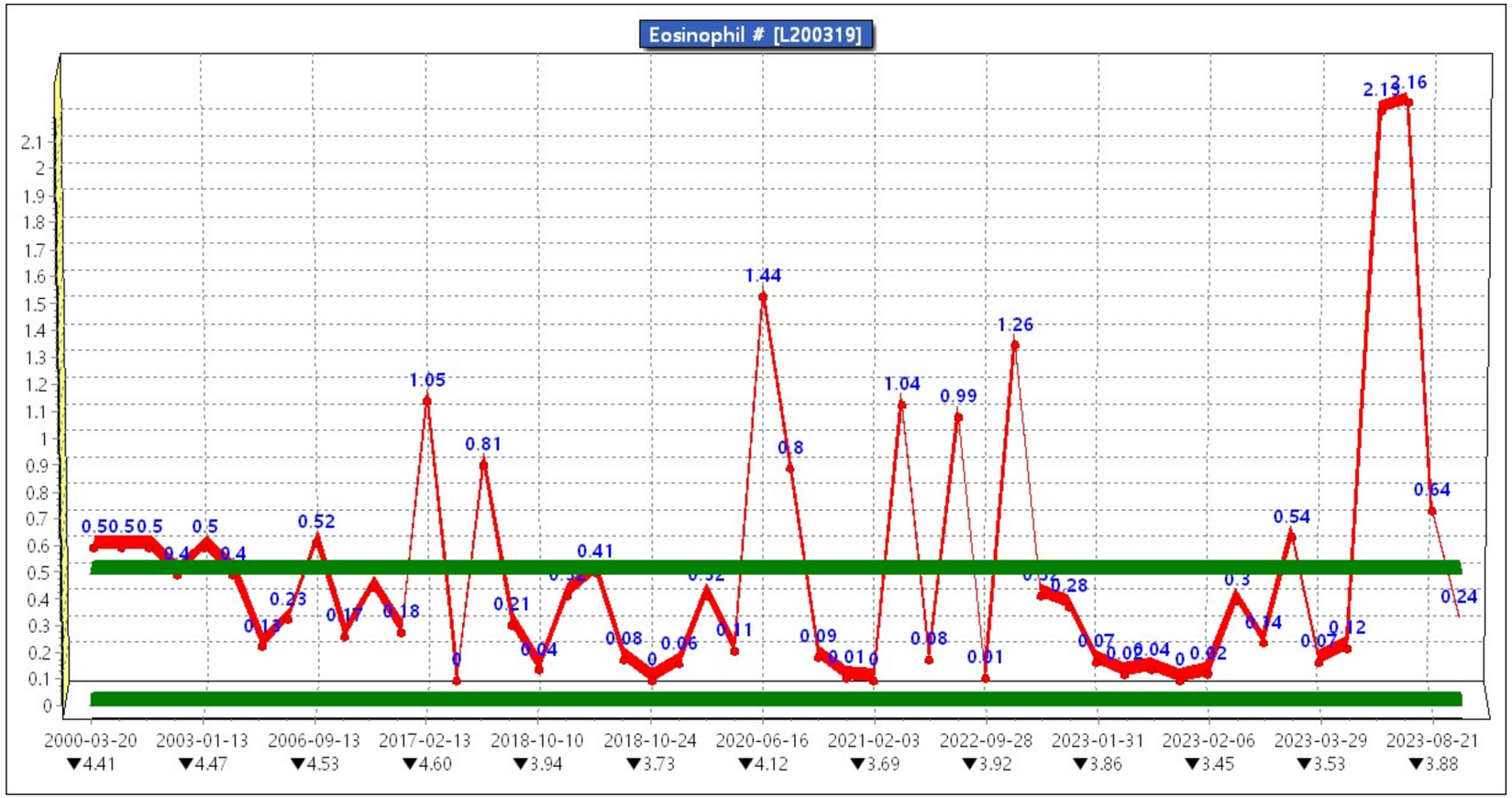
CASE 5

MD ICS+LABA+LAMA -->> HD ICS+LABA+LAMA
Long term low dose OCS use and burst HD OCS
Persistent dyspnea

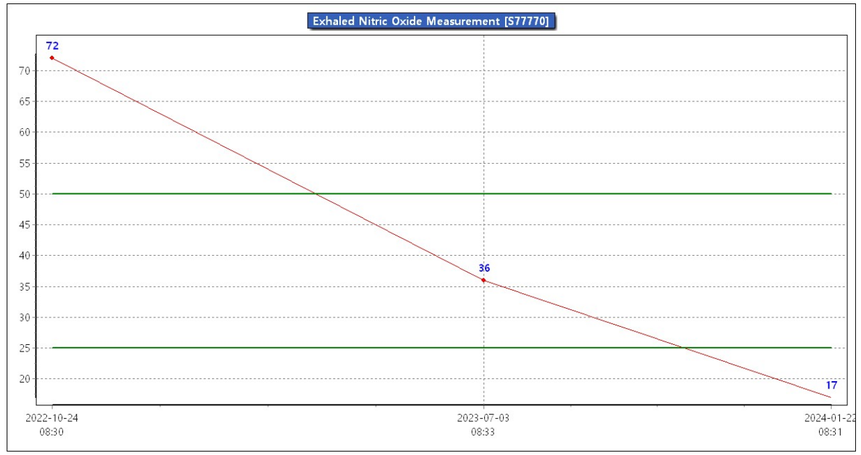
1st visit	Follow-up (3 months)	Follow-up (20 months)
FVC: 3.35 L (100%)	FVC: 3.16 L (94%)	FVC: 3.09 L (93%)
FEV_1 : 1.77L (76%)	FEV_1 : 1.57L (68%)	FEV_1 : 1.53L (67%)
FEV_1/FVC: 53%	FEV_1/FVC: 50%	FEV_1/FVC: 49%
DLco: 71%	DLco: 74%	DLco: 63%
BDR: FEV1 230 ml (15%) FVC 430 ml (15%)	BDR: FEV1 120 ml (8%) FVC 140 ml (5%)	BDR: FEV1 190 ml (15%) FVC 320 ml (11%)

- **Recurrent exacerbation > 2 times/ year**
- **Admission or ER visit 1 time/year**
- **Consider add on-Duphilumab**

CASE 5



Duphilumab



- **FeNO: 72 ppb -->> 36 ppb -->> 17 ppb**

Summary

- Over-diagnosis and under-diagnosis of asthma are common.
- Asthma presents with a wide range of non-specific symptoms.
- Once asthma is properly diagnosed, pharmacological treatment that includes **Inhaled Corticosteroids (ICS)** is essential, regardless of the symptoms
- Asthma remission can be a new long-term therapeutic goal for all patients with asthma.
- High-dose ICS: only suggested for short-term use (3–6 months) to minimize AE potential.
- Many of the recently developed biological formulations have been confirmed to have a steroid-sparing effect in the treatment of asthma.
- The identification of various comorbidities and treatable traits in asthma, and the subsequent individualized treatment approach, can increase the success rate of asthma management.

Thank you for your attention

Questions?