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GINA 2024: Le novità terapeutiche nell'adolescente

Vincenzo Ragazzo

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GINA 2024: Le novità terapeutiche nell'adolescente

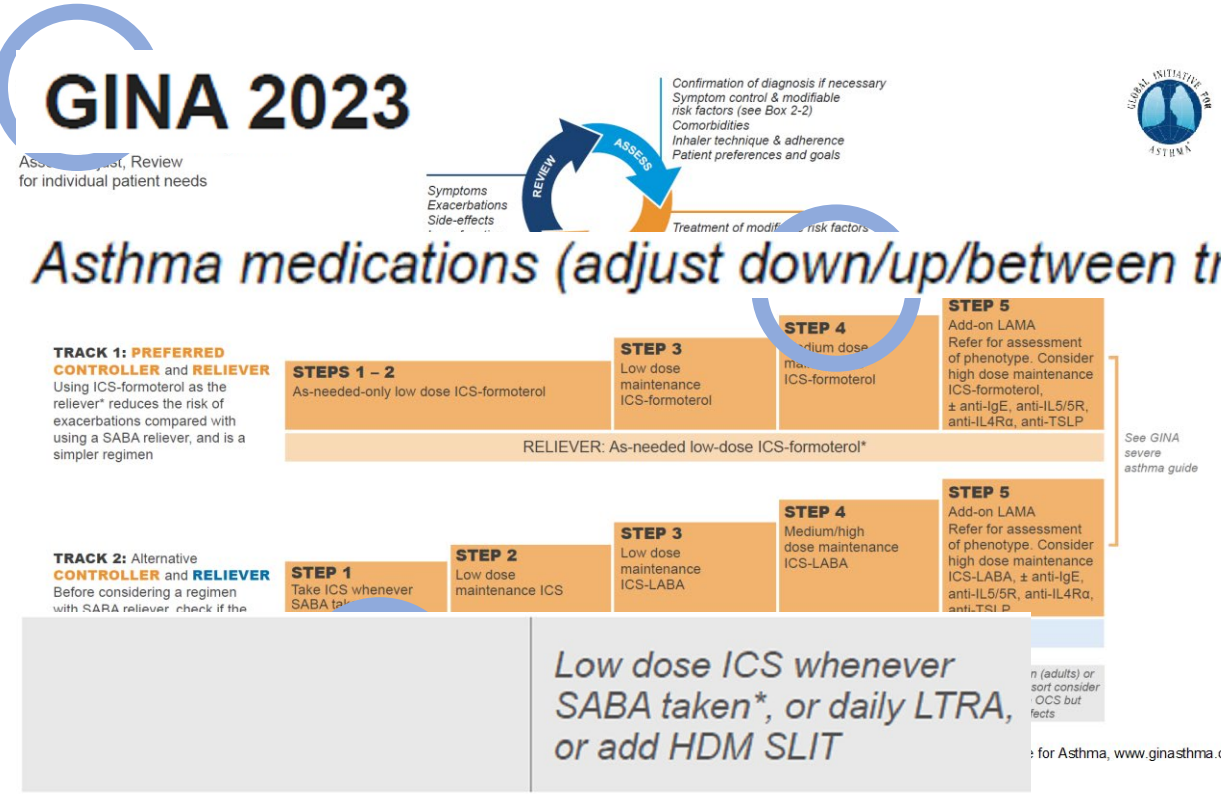
- «SABA»: find the differences!
- Conclusioni

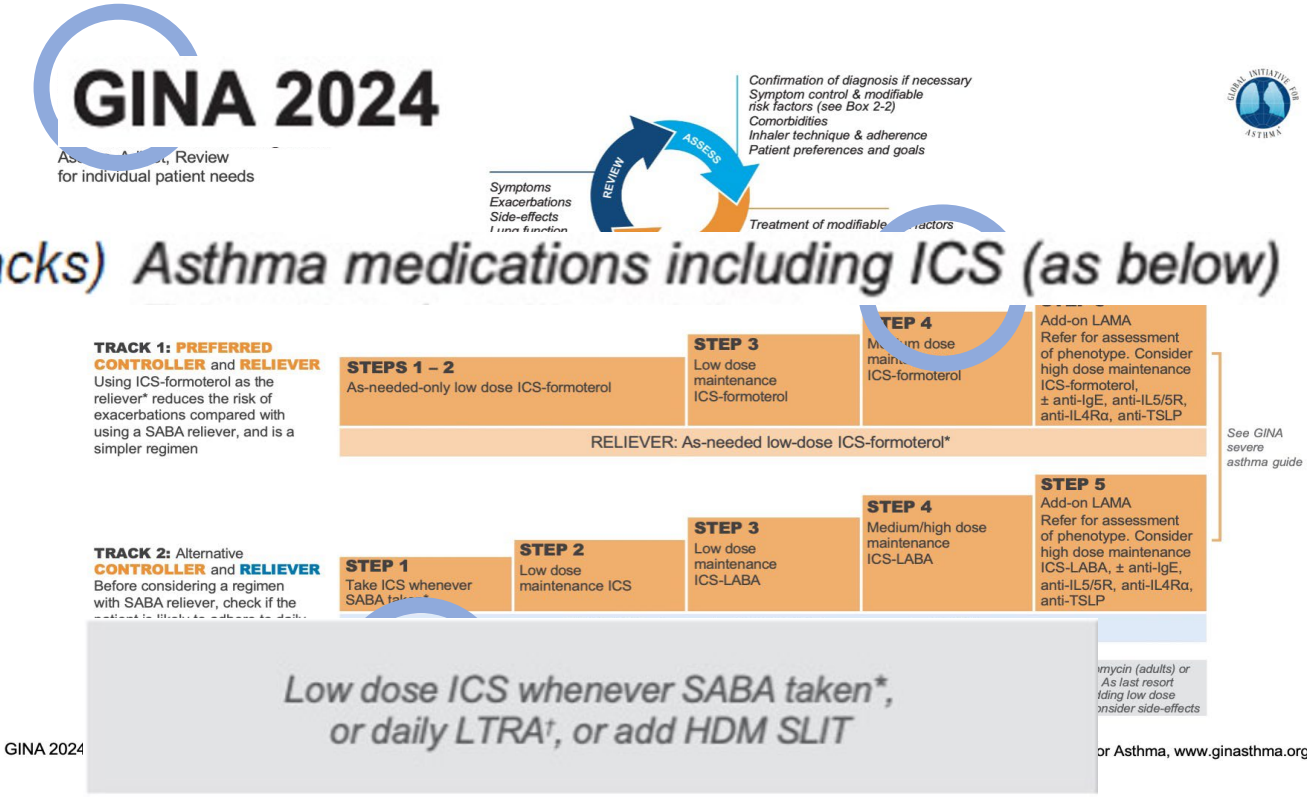
GINA 2024: Le novità terapeutiche nell'adolescente

- «SABA»: find the differences!
- Conclusioni

“SABA”: Find the differences!

Find 3 differences!

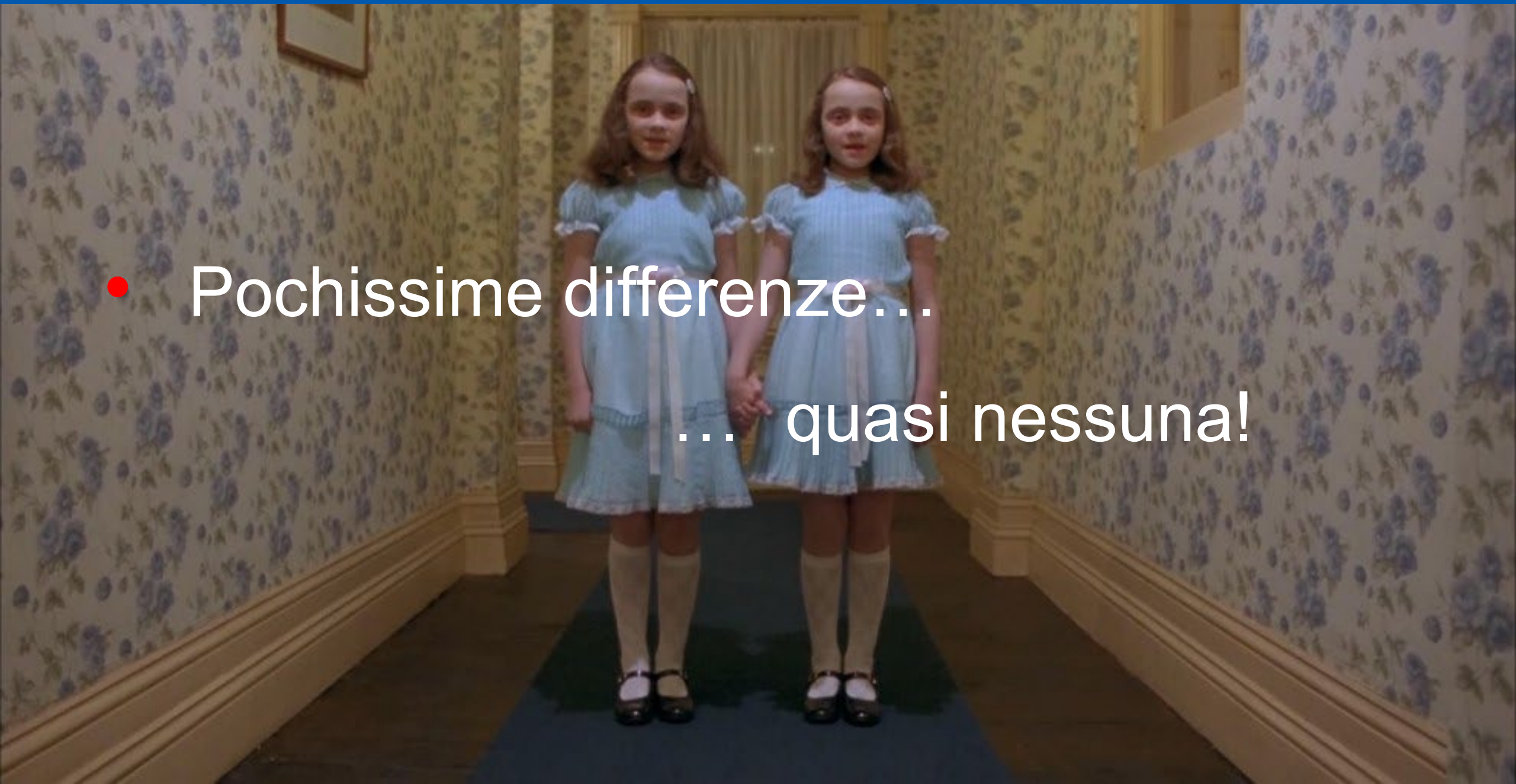




GINA 2024: Le novità terapeutiche nell'adolescente

- «SABA»: find the differences!
- Conclusioni

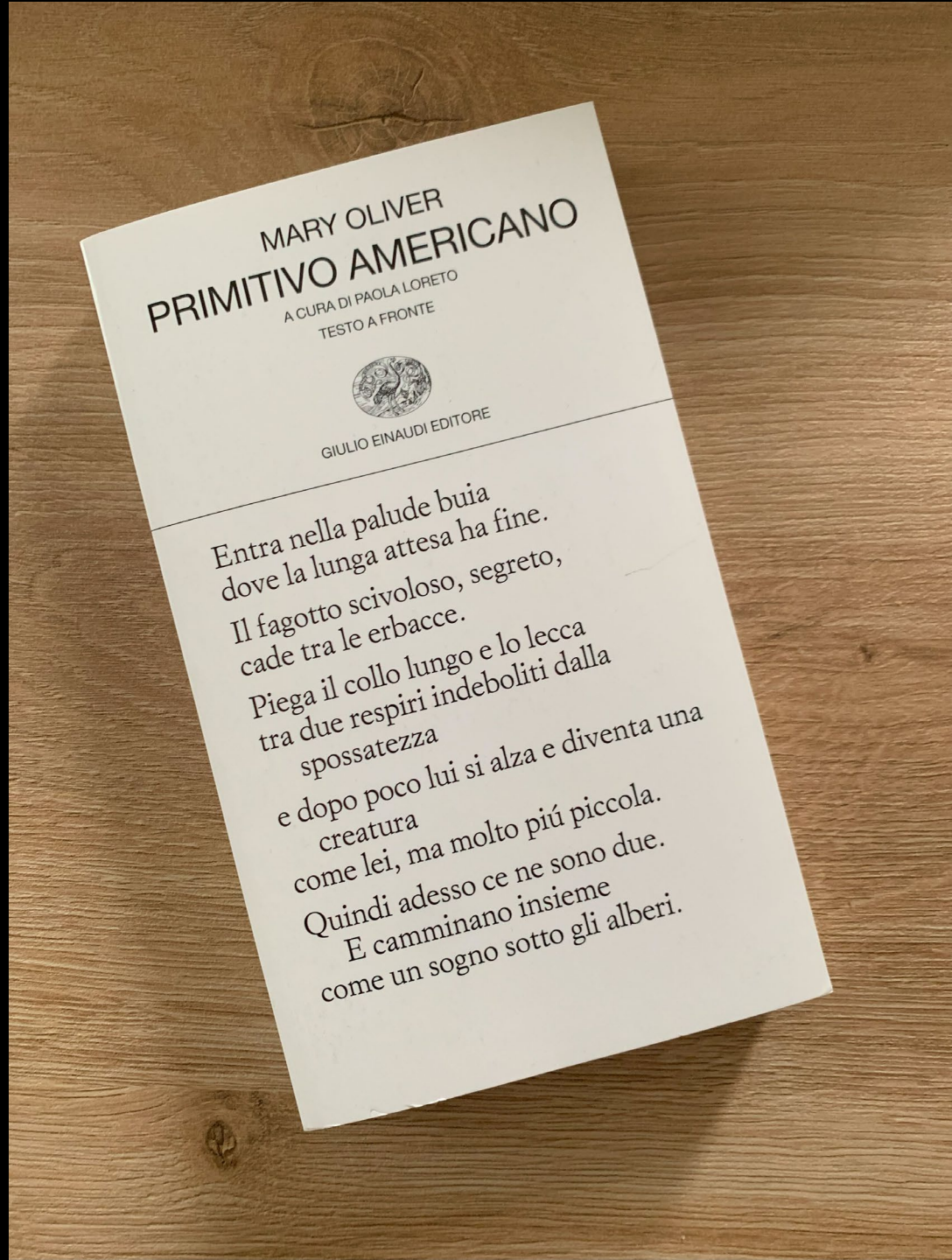
Conclusioni («SABA»)



- Pochissime differenze…

  … quasi nessuna!

Grazie per l’attenzione!



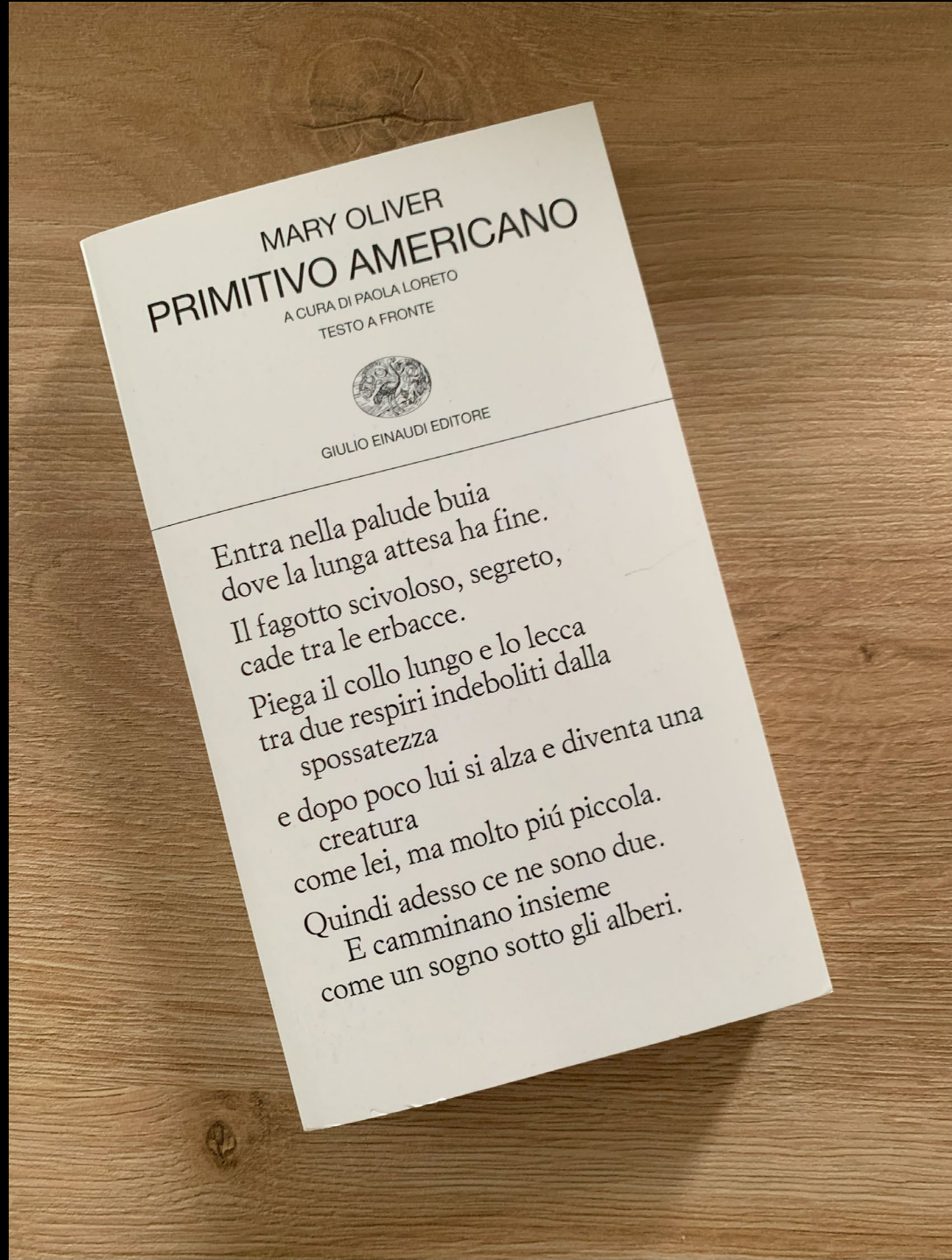
Istruzioni per vivere la vita:

Presta attenzione.

Fatti stupire.

Raccontalo.

Mary Olyver



Presta attenzione

- «SABA»: find the differences!
- Conclusioni

Presta attenzione

- «SABA»: find the differences!
- Conclusioni

Fatti stupire

- «SABA»: find the differences!

Fatti stupire

- «SABA» (Short Acting Brain Activity):

  find the differences!

Raccontalo

- «SABA» (Short Acting Brain Activity): find the differences!
- Un passo indietro
- Ah, l'adolescente...! (quanti dubbi)
- La rivoluzione continua
- Conclusioni

GINA 2024: Le novità terapeutiche nell'adolescente

- «SABA» (Short Acting Brain Activity): find the differences!
- Un passo indietro
- Ah, l'adolescente...! (quanti dubbi)
- La rivoluzione continua
- Conclusioni

Un passo indietro

«Bisogna ritornare sui passi già dati, per ripeterli, e per tracciarvi a fianco nuovi cammini.
Bisogna ricominciare il viaggio.
Sempre».

José Saramago

*For many years, all international guidelines recommended using short-acting β2-agonists (**SABA**) during exacerbations, prescribed **as the only as-needed treatment**… Inhaled SABA has been first-line treatment for asthma for **50 years**!*

GINA 2019: a fundamental change in asthma management

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

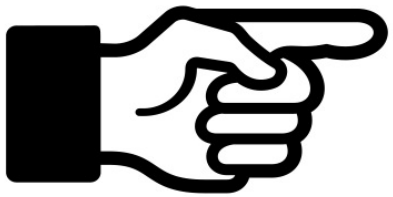
Reddel HK et al. Eur Respir J. 2019; 53: 1901046

Asma «lieve»?

2024

Mild asthma is asthma that is well controlled with **low-intensity treatment** (Step 1-2)

- '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. (Assessment after 2-3 months of asthma treatment)
- In clinical practice and in the general community, the term 'mild asthma' is often used to mean infrequent or mild symptoms, and it is often assumed that these patients are not at risk and do not need ICS-containing treatment.
- For these reasons, GINA suggests that the term 'mild asthma' should generally be avoided in clinical practice if possible or, if used, qualified with a reminder that patients with infrequent symptoms can still have severe or fatal exacerbations, and that this risk is substantially reduced with ICS-containing treatment.



«**apparently mild asthma**» o «**asthma that seems to be mild**»

The risks of **mild asthma** and **SABA-only treatment**

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

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

- **Regular or frequent use of SABA is associated with adverse effects**
  - β-receptor downregulation, decreased bronchoprotection, rebound hyperresponsiveness, **decreased bronchodilator response** *(Hancox, Respir Med 2000)*
  - Increased allergic response, and **increased eosinophilic airway inflammation** *(Aldridge, AJRCCM 2000)*
- **Higher use of SABA is associated with adverse clinical outcomes**
  - Dispensing of ≥3 canisters per year (average 1.7 puffs/day) is associated with higher risk of **emergency department presentations** *(Stanford, AAAI 2012)*
  - Dispensing of ≥12 canisters per year is associated with higher risk of **death** *(Suissa, AJRCCM 1994)*

GINA 2019 – landmark changes in asthma management

- For safety, **GINA no longer recommends SABA-only treatment for Step 1**
- 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

Overuse of SABA

Relieves the acute symptoms, but doesn't address the underlying airway inflammation, or may even make it worse

Underuse of ICS

Poor adherence, many if not most doses are **omitted**, Inhaler technique is **poor**, despite multiple teaching sessions.

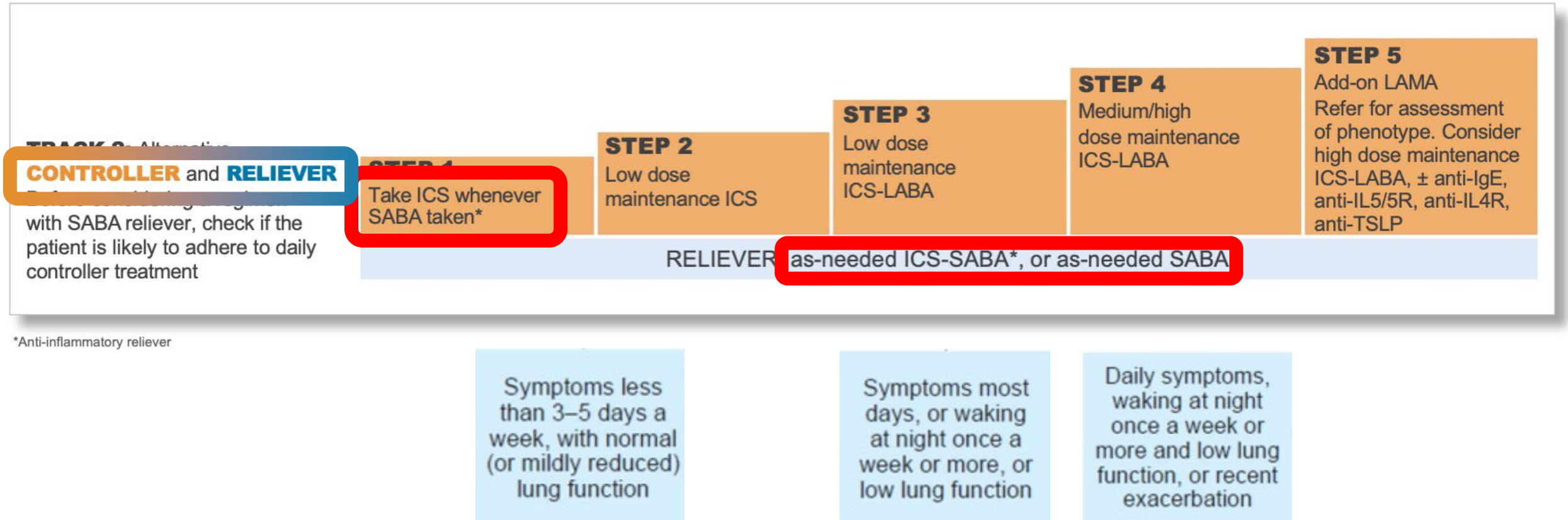
Why not treat with inhaled short-acting beta$_2$-agonists (SABA) alone?

- SABA treats the symptoms, but not the disease
- People with apparently mild asthma can have severe or fatal exacerbations *(Dusser, 2007)*
  - Up to 27% asthma deaths are in patients with occasional symptoms *(Bergstrom, 2008)*
  - Exacerbation triggers are unpredictable (viral, allergen, pollution, stress)
  - Even 4–5 **lifetime** OCS courses increase the cumulative risk of adverse events including osteoporosis, diabetes, cataract, heart failure, pneumonia *(Price et al, J Asthma Allerg 2018)*
- **Regular** use of SABA, even for 1–2 weeks, is associated with increased AHR, reduced bronchodilator effect, increased allergic response, increased eosinophils *(e.g. Cockcroft 2006)*
  - Can lead to a vicious cycle encouraging overuse
  - Over-use of SABA is associated with ↑ exacerbations and ↑ mortality *(e.g. Suissa 1994, Nwaru 2020)*
- Starting treatment with SABA **trains** the patient to regard it as their primary asthma treatment
  - Poor adherence with ICS is almost inevitable
- There is strong evidence for a more effective and safer alternative than SABA alone, or ICS plus as-needed SABA: **as-needed ICS-formoterol**

The blue one's good because you can just have a couple of squirts and get back to what you were doing

Cole et al, BMJ Open 2013

Better together



*Anti-inflammatory reliever

Symptoms less than 3–5 days a week, with normal (or mildly reduced) lung function

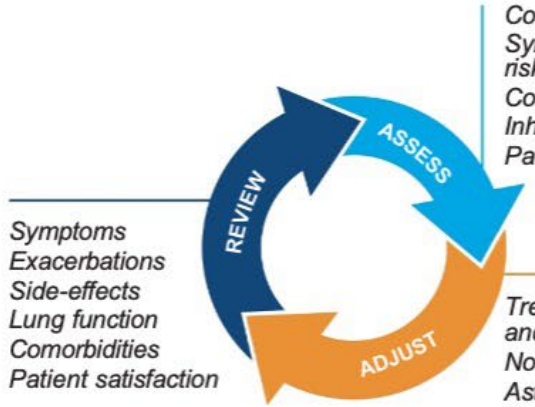
Symptoms most days, or waking at night once a week or more, or low lung function

Daily symptoms, waking at night once a week or more and low lung function, or recent exacerbation

2024

GINA 2024 – Adults & adolescents 12+ years

Personalized asthma management
Assess, Adjust, Review
for individual patient needs



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

Symptoms
Exacerbations
Side-effects
Lung function
Comorbidities
Patient satisfaction

Treatment of modifiable risk factors and comorbidities
Non-pharmacological strategies
Asthma medications including ICS (as below)
Education & skills training

TRACK 1: PREFERRED CONTROLLER and RELIEVER
Using ICS-formoterol as the reliever* reduces the risk of exacerbations compared with using a SABA reliever, and is a simpler regimen

STEPS 1 – 2	STEP 3	STEP 4	STEP 5
As-needed-only low dose ICS-formoterol	Low dose maintenance ICS-formoterol	Medium dose maintenance ICS-formoterol	Add-on LAMA Refer for assessment of phenotype. Consider high dose maintenance ICS-formoterol, ± anti-IgE, anti-IL5/5R, anti-IL4Rα, anti-TSLP

RELIEVER: As-needed low-dose ICS-formoterol*

See GINA severe asthma guide

TRACK 2: Alternative **CONTROLLER and RELIEVER**
Before considering a regimen with SABA reliever, check if the patient is likely to adhere to daily controller treatment

STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
Take ICS whenever SABA taken*	Low dose maintenance ICS	Low dose maintenance ICS-LABA	Medium/high dose maintenance ICS-LABA	Add-on LAMA Refer for assessment of phenotype. Consider high dose maintenance ICS-LABA, ± anti-IgE, anti-IL5/5R, anti-IL4Rα, anti-TSLP

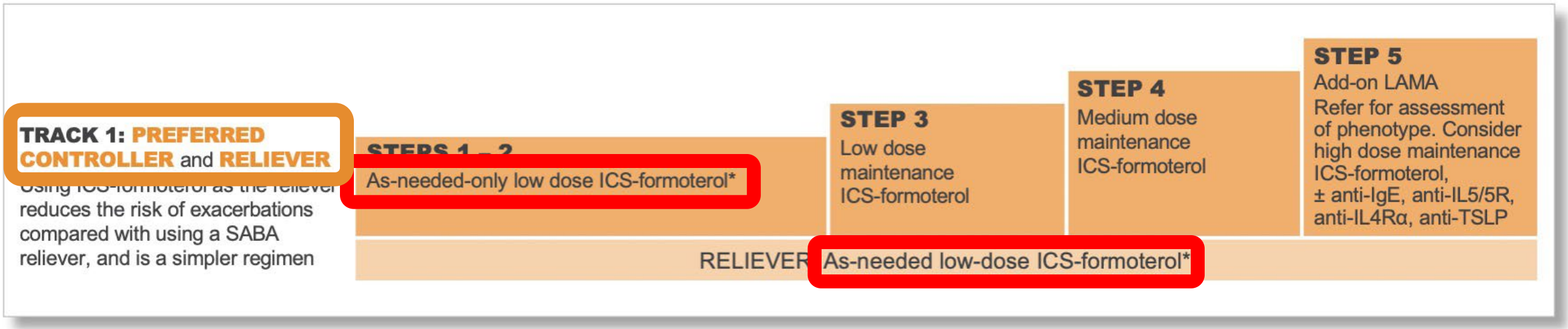
RELIEVER: As-needed ICS-SABA*, or as-needed SABA

Other controller options (limited indications, or less evidence for efficacy or safety – see text)

Low dose ICS whenever SABA taken, or daily LTRA†, or add HDM SLIT*	*Medium dose ICS, or add LTRA†, or add HDM SLIT*	*Add LAMA or add LTRA† or add HDM SLIT, or switch to high dose ICS-only*	*Add azithromycin (adults) or add LTRA†. As last resort consider adding low dose OCS but consider side-effects*

*Anti-inflammatory reliever; †advise about risk of neuropsychiatric adverse effects

GINA 2024 Box 4-6

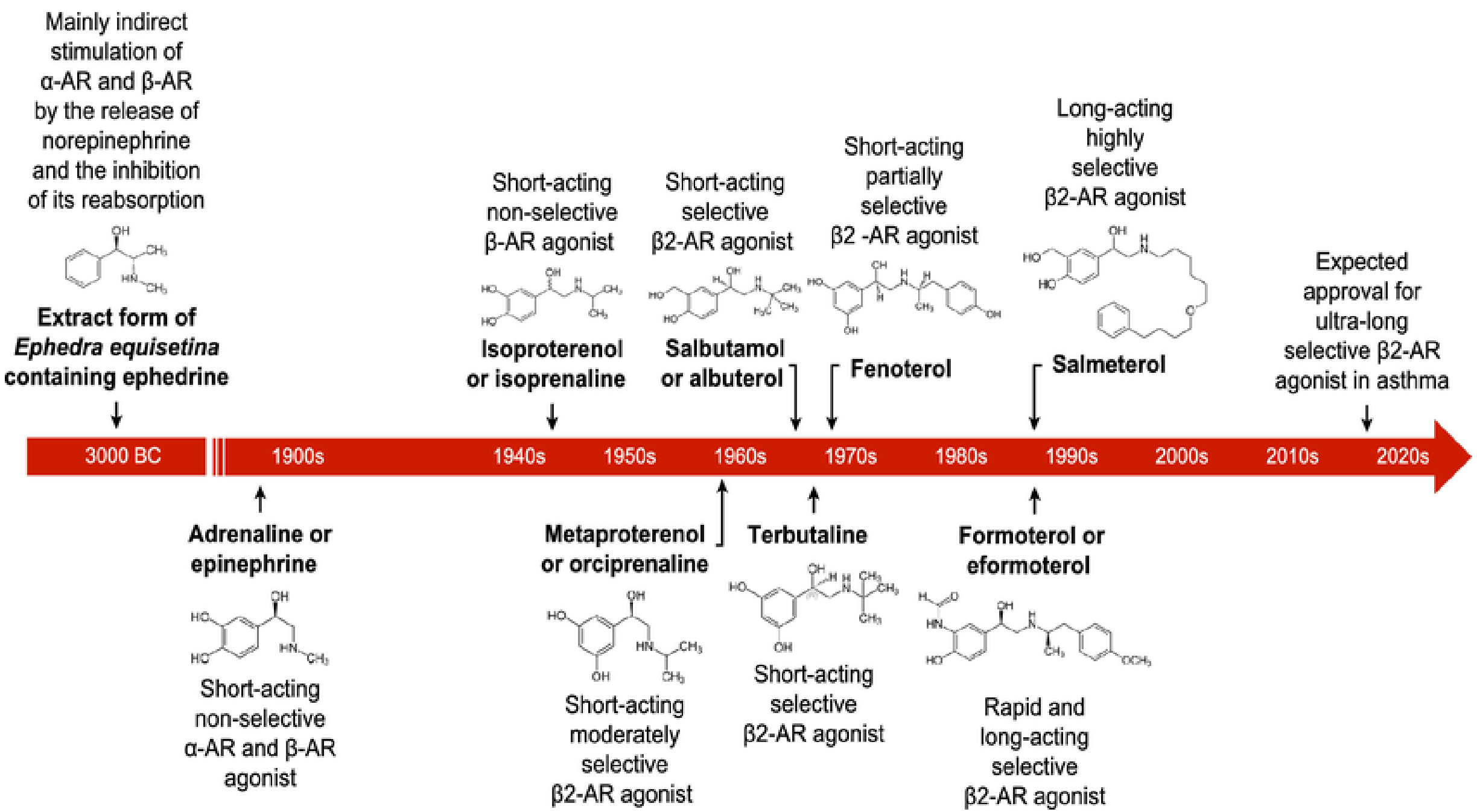


*Anti-inflammatory reliever

Symptoms less than 3–5 days a week, with normal (or mildly reduced) lung function

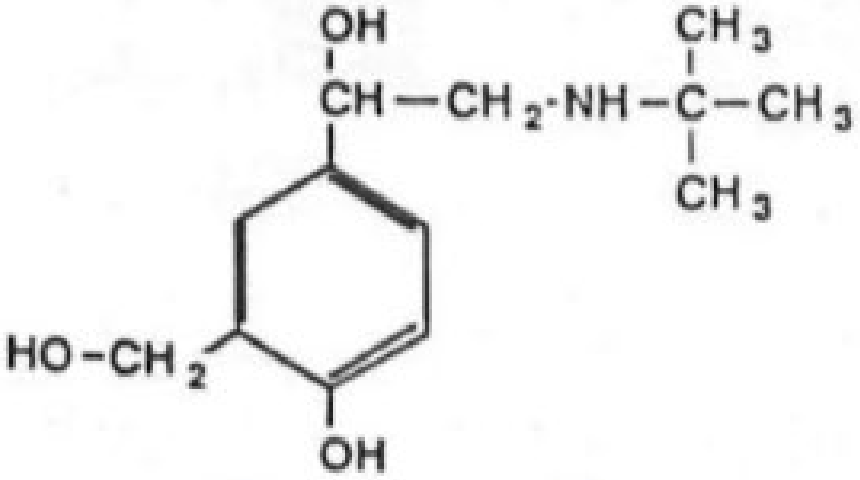
Symptoms most days, or waking at night once a week or more, or low lung function

Daily symptoms, waking at night once a week or more and low lung function, or recent exacerbation

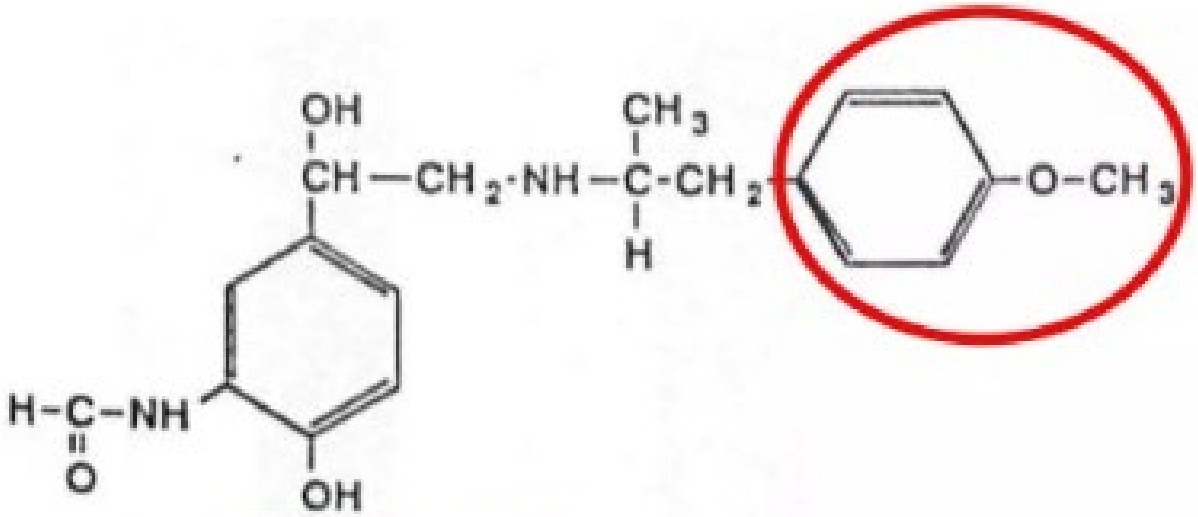


Kuprys-Lipinska et al. Clin Transl Allergy (2020) 10:19

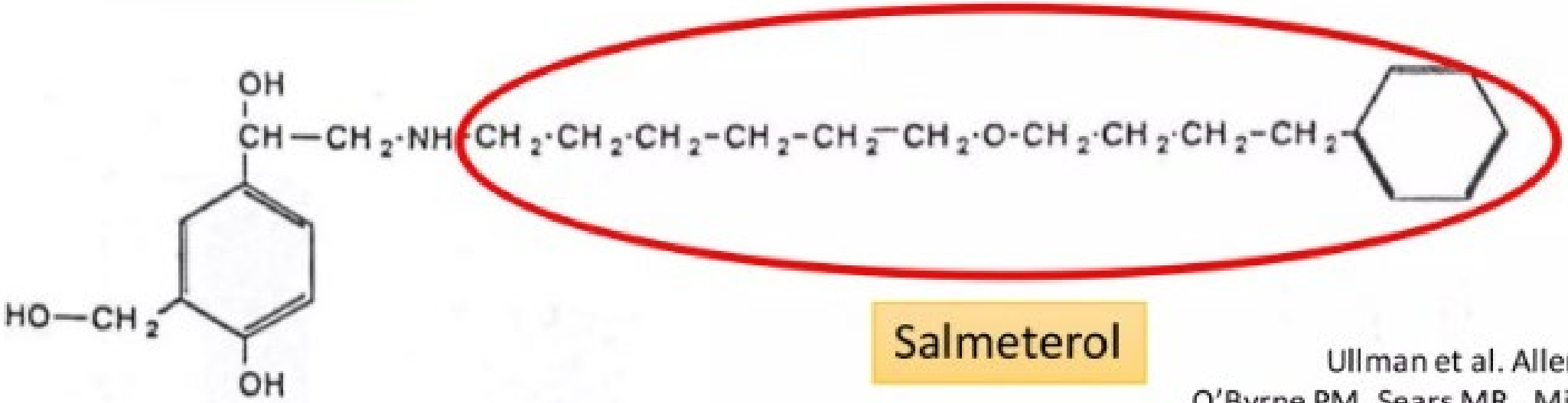
Struttura chimica



Salbutamol



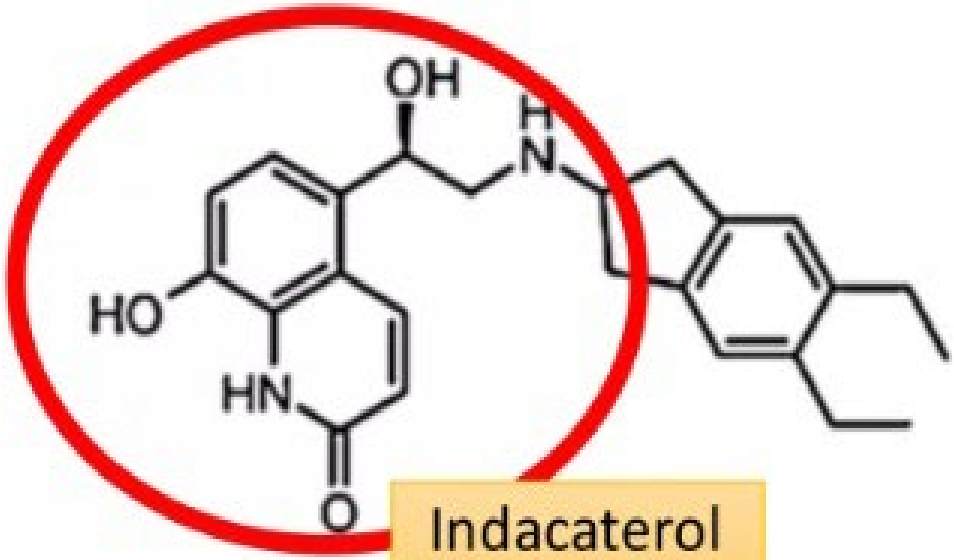
Formoterol



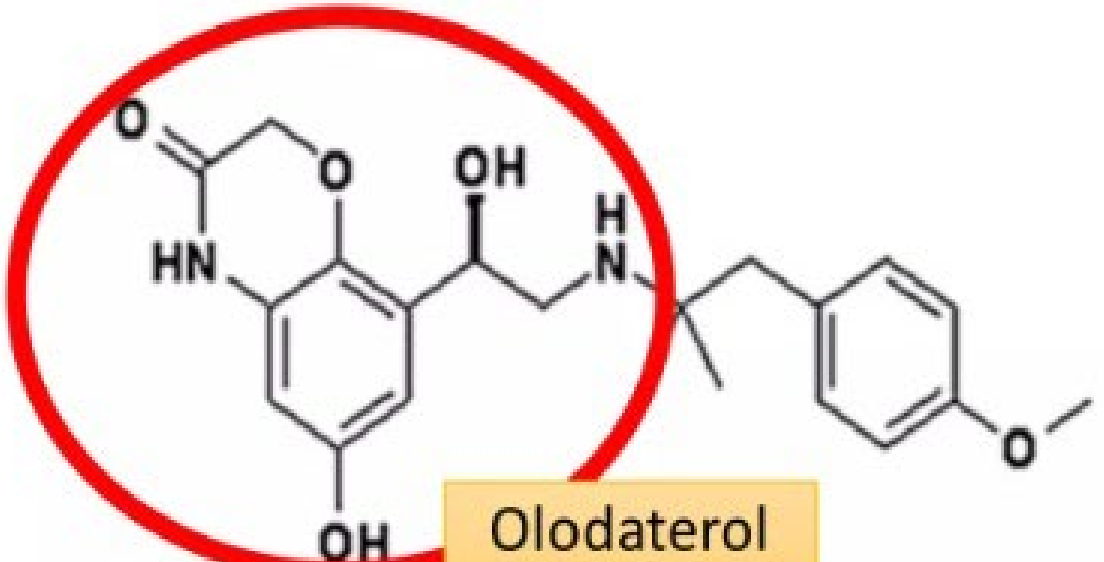
Salmeterol

Ullman et al. Allergy 1992: 47; 384-387
O'Byrne PM. Sears MR . Middleton's 8th edition.

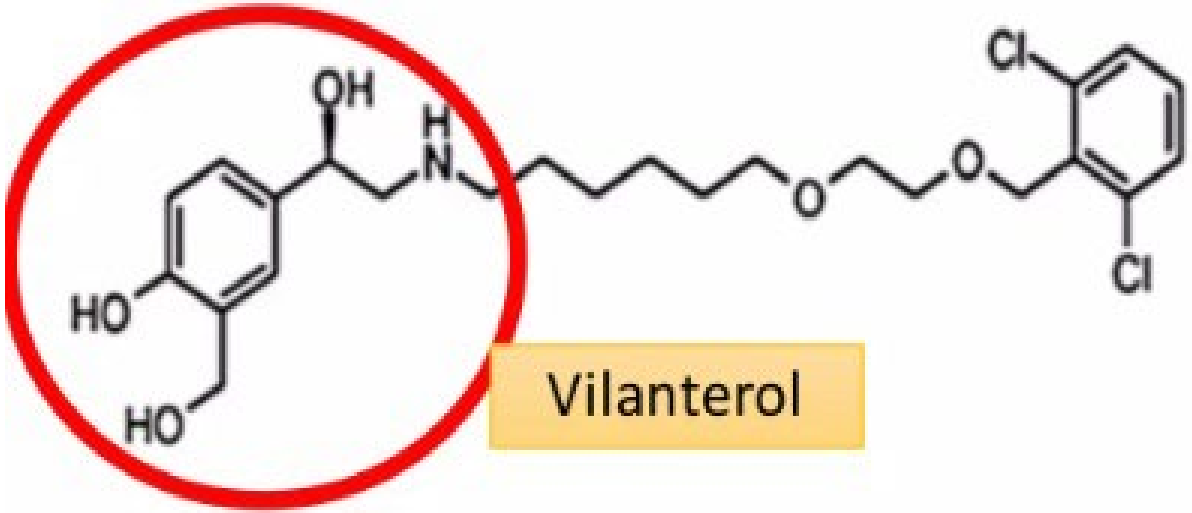
Struttura chimica



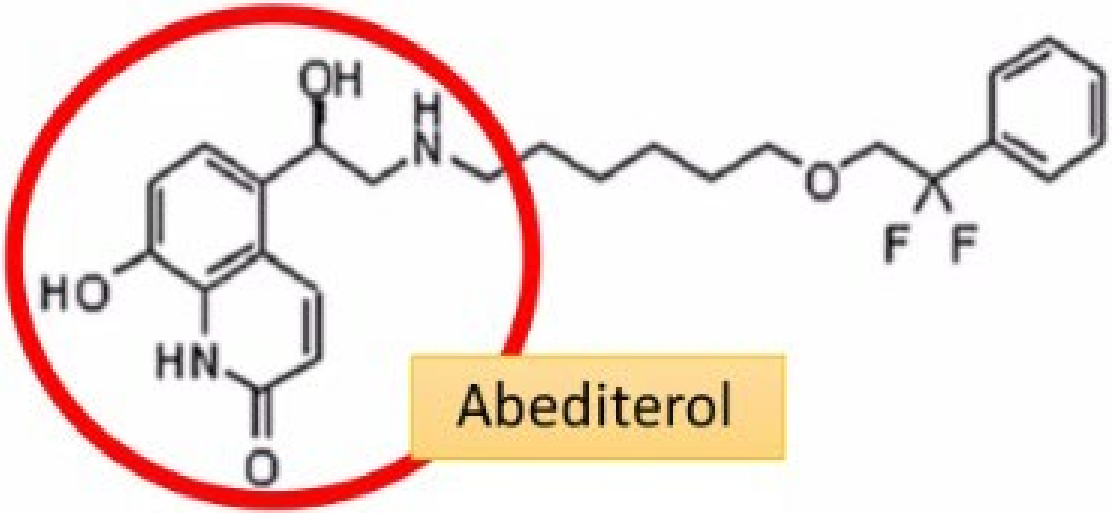
Indacaterol



Olodaterol



Vilanterol

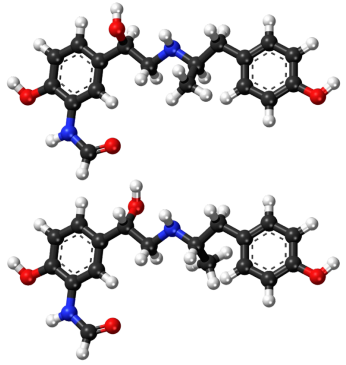


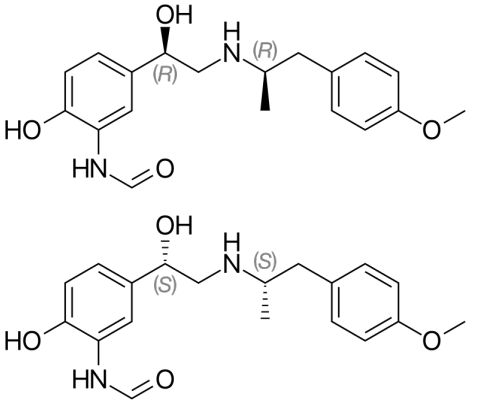
Abediterol

Cazzola et al. Am J Respir Crit Care Med 2013;187:690-696

	ALBUTEROL	FORMOTEROL	SALMETEROL
Lipophilicity	Hydrophilic	Moderately lipophilic	Most lipophilic
Onset of action	Fast	Fast	Delayed
Duration of action	Short	Long	Long
β_2-agonist potency (Efficacy & receptor affinity)	Partial agonist (= Terbutaline)	Full agonist	Partial agonist
Mechanism of action	Accesses active site directly from the aqueous extracellular compartment		

Sorkness CA. In Middleton's Alle





β2-agonists	Selectivity ratio (β1:β2 receptors)	Onset of action (minutes)	Duration of action (hours)
Isoprenaline	1:1	2-5	< 20 minutes
Albuterol	1:1375	2-3	4-6
Fenoterol	1:120	2-4	4-6
Terbutaline	nd	2-4	4-6
Salmeterol	1:85000	30	> 12
Formoterol	1:120	2-3	> 12

Sorkness CA. In Middleton's Allergy: Principles and Practice; 2009:1485-1503.

Nuova terminologia

2024

RELIEVER	Sollievo immediato dai sintomi o premedicazione (sport, esposizione ad allergeni) -> SABA
CONTROLLER	Per la terapia di fondo (***maintenance treatment***), solitamente ICS da soli o in associazione ad altri farmaci, per controllare la malattia (sintomi e rischio futuro)


RELIEVER
OF THE YEAR

RELIEVER

Su cosa si basano le raccomandazioni per l'impiego come reliever nello step 1-2?

Study, first author (year)	Design	Duration	Sites	Population	Participants (intervention *versus* control)[#] n	Primary outcome (analysis)	Intervention	Control
SYGMA 1 O'Byrne (2018)	RCT, parallel-group, double-blind placebo-controlled	52 weeks	261 sites, 18 countries	Adults and adolescents (≥12 years)	2559 (1277 *versus* 1282)	Mean percentage of electronically recorded weeks with well-controlled asthma per patient (noninferiority)[¶]	Budesonide-formoterol 200/6 µg (Symbicort Turbuhaler, AstraZeneca) one inhalation as needed plus twice-daily placebo	Budesonide 200 µg (Pulmicort Turbuhaler, AstraZeneca) twice daily plus terbutaline 500 µg (Turbuhaler) as needed
SYGMA 2 Bateman (2018)	RCT, parallel-group, double-blind placebo-controlled	52 weeks	350 sites, 25 countries	Adults and adolescents (≥12 years)	4176 (2089 *versus* 2087)	Annualised rate of severe exacerbations (non-inferiority)[+]	Budesonide-formoterol 200/6 µg (Symbicort Turbuhaler, AstraZeneca) one inhalation as needed plus twice-daily placebo	Budesonide 200 µg (Pulmicort Turbuhaler, AstraZeneca) twice daily plus terbutaline 500 µg (Turbuhaler) as needed
Novel start Beasley (2019)	RCT, parallel-group, open-label, real-world	52 weeks	16 sites, 4 countries	Adults (≥18 years)	425 (220 *versus* 225)	Annualised rate of asthma exacerbations (superiority)	Budesonide-formoterol 200/6 µg (Symbicort Turbuhaler, AstraZeneca) one inhalation as-needed	Budesonide 200 µg (Pulmicort Turbuhaler, AstraZeneca) twice daily plus albuterol 100 µg (Ventolin pMDI) two inhalations as needed
PRACTICAL Hardy (2019)	RCT, parallel-group, open-label, real-world	52 weeks	15 sites, 1 country	Adults (≥18 years)	885 (437 *versus* 448)	Number of severe exacerbations per patient per year (superiority)	Budesonide-formoterol 200/6 µg (Symbicort Turbuhaler, AstraZeneca) one inhalation as needed	Budesonide 200 µg (Pulmicort Turbuhaler, AstraZeneca) twice daily plus terbutaline 250 µg (Bricanyl Turbuhaler, AstraZeneca) two inhalations as needed

4 RCTs (n=8065 participants), BUD/FOR

Hatter L et al. ERJ Open Res. 2021; 7: 00701-2020

As-needed low-dose ICS-formoterol* in mild asthma (n=9,565)

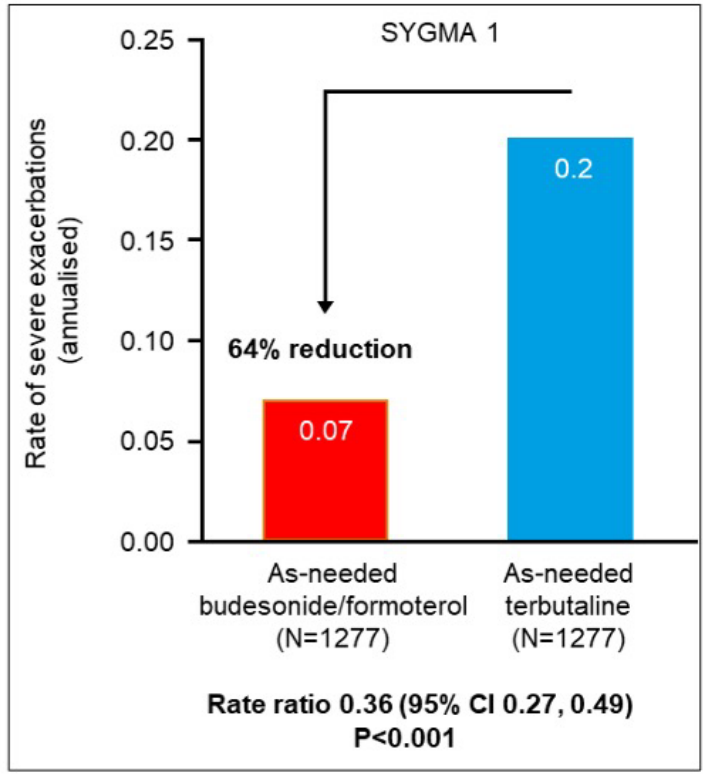
2024

COMPARED WITH AS-NEEDED SABA

- Risk of severe exacerbations reduced by 60–64% (SYGMA 1, Novel START)

COMPARED WITH MAINTENANCE LOW DOSE ICS plus as-needed SABA

- Risk of severe exacerbations similar (SYGMA 1 & 2), or lower (Novel START, PRACTICAL)
- No clinically important differences in symptom control or FEV_1 (all 4 studies) or in FeNO (Novel START, PRACTICAL), and no worsening in these outcomes over 12 months
- Patients used the as-needed inhaler on ~30% of days very low ICS dose
- Outcomes for severe exacerbations and ACQ-5 were independent of baseline characteristics including blood eosinophils, FeNO, lung function, history of exacerbations (Novel START, PRACTICAL)
- Embedded qualitative research demonstrated most patients preferred as-needed combination treatment over regular daily treatment *(Baggott 2020 & 2022; Foster 2020 & 2022)*

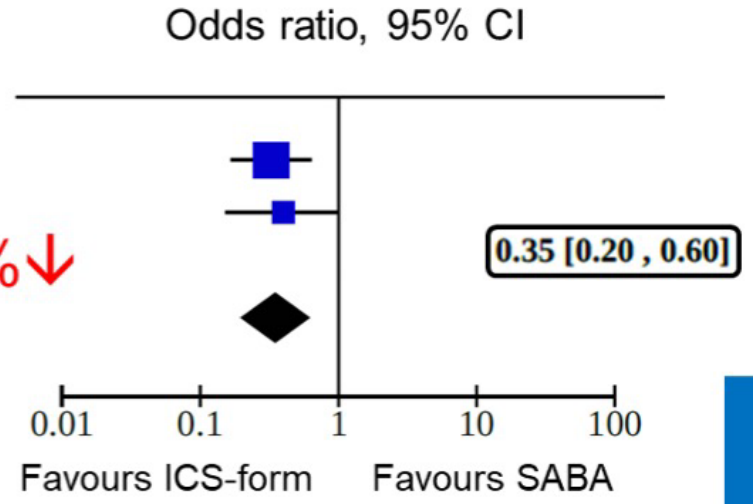


O'Byrne et al, NEJM 2018

*Budesonide-formoterol 200/6 [160/4.5] mcg, 1 inhalation as needed for symptom relief

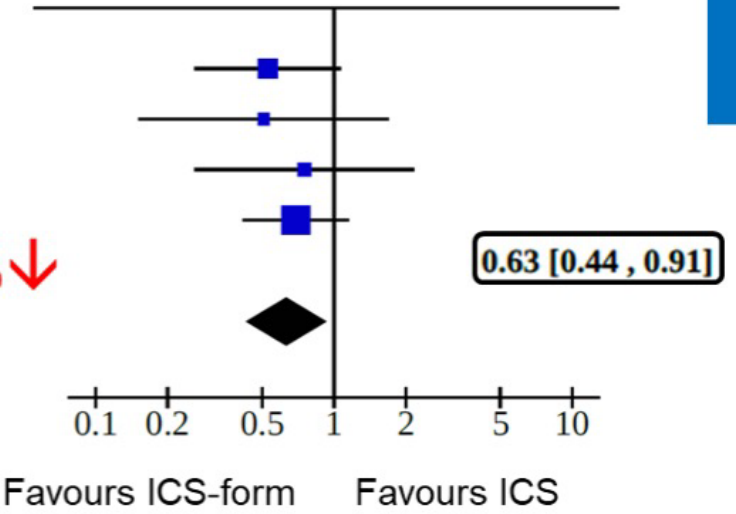
As-needed-only ICS-formoterol reduces emergency visits and hospitalisations in patients with mild asthma

2024



As-needed ICS-formoterol compared with as-needed SABA

65%↓



As-needed ICS-formoterol compared with daily ICS + as-needed SABA

37%↓

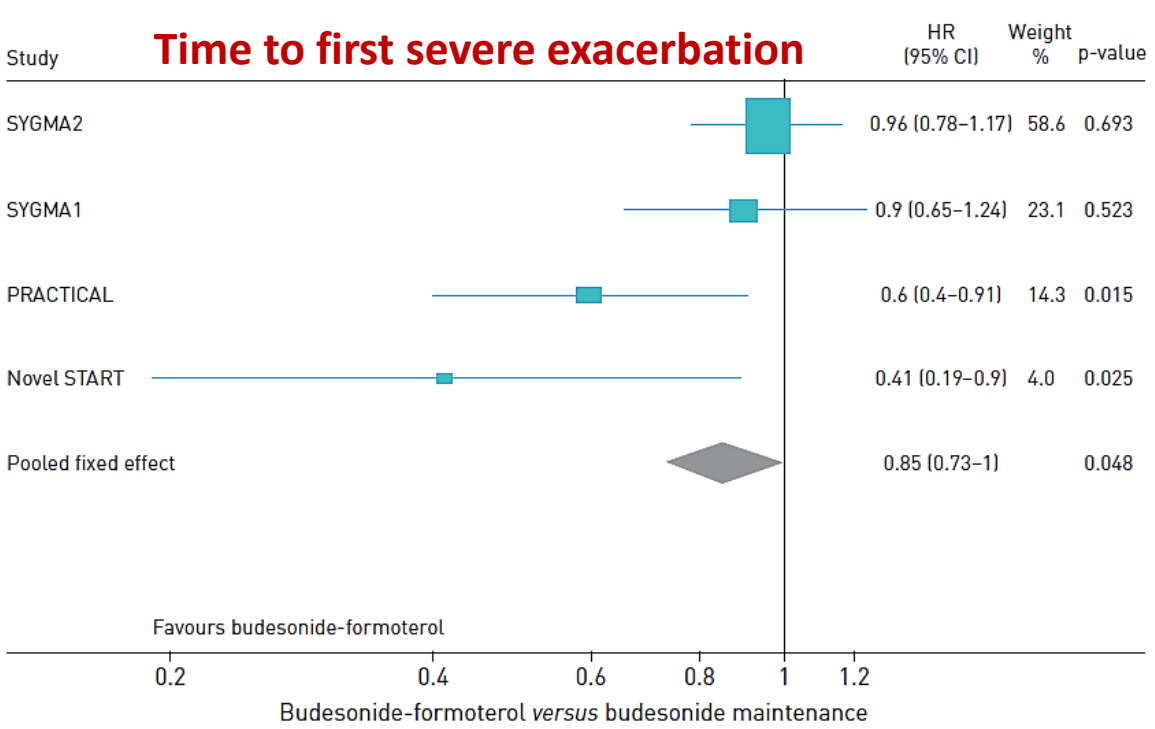
Approved by regulators in ~50 countries
Recommended in asthma guidelines of ~32 countries

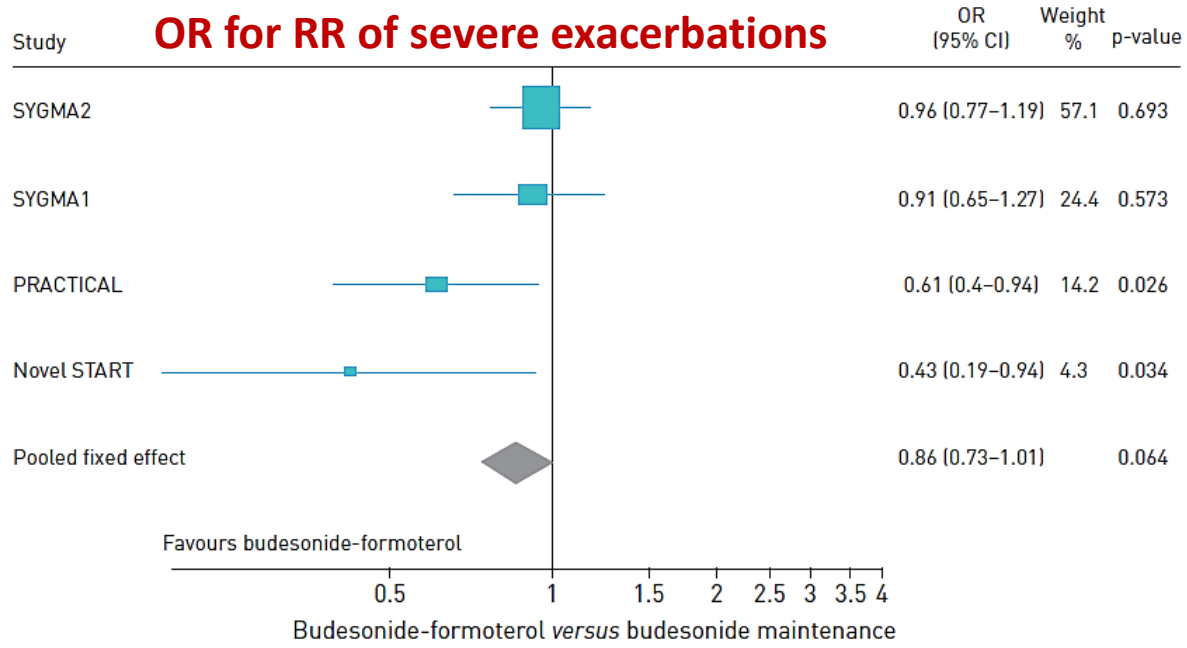
From Crossingham et al, Cochrane Database Syst Rev 2021 (n=9565)

ICS-formoterol reliever *versus* ICS and short-acting β_2-agonist reliever in asthma: a systematic review and meta-analysis

Hatter L et al. ERJ Open Res. 2021; 7: 00701-2020

- **As-needed ICS-formoterol** was associated with a **prolonged time to first severe exacerbation** (hazard ratio 0.85, 95% CI 0.73–1.00; p=0.048) and **reduced daily ICS dose** (mean difference −177.3 µg, 95% CI −182.2 -172.4 µg). **Asthma symptom control was worse** in the as-needed group (Asthma Control Questionnaire-5 mean difference 0.12, 95% CI 0.09–0.14), although this did not meet the minimal clinically important difference of 0.50 units. There was no significant difference in serious adverse events (OR 1.07, 95% CI 0.84–1.36).
- *As-needed ICS-formoterol offers a therapeutic alternative to maintenance low-dose ICS plus SABA in asthma and **may be the preferred option** when **prevention of severe exacerbation is the primary aim of treatment***





European Respiratory Society short guidelines for the use of as-needed ICS/formoterol in mild asthma

ERS

PICO 1

*Is **as-needed ICS/formoterol** (single inhaler) **without maintenance** treatment the preferred treatment **compared** **with** **regular low-dose ICS** **maintenance treatment plus as-needed SABA** in adult/adolescent patients with mild asthma (i.e. GINA treatment steps 1 or 2)?*

Recommendations

- We suggest that *adult patients* with asthma on GINA [1] treatment steps 1 or 2 use as-needed ICS/formoterol in a single inhaler without maintenance treatment instead of regular ICS maintenance treatment plus as-needed SABA. (Conditional recommendation for the intervention; low certainty of evidence.)
- We suggest that *adolescent patients* with asthma on GINA [1] treatment steps 1 or 2 use either as-needed ICS/formoterol in a single inhaler or regular ICS maintenance treatment plus as-needed SABA. (Conditional recommendation for the intervention; low certainty of evidence.)

Limited data is available in adolescents compared with adults, therefore the Task Force suggested either treatment option for adolescent patients as the balance between the two options is very close.

Papi A et al. Eur Respir J. 2023; 62: 2300047

European Respiratory Society short guidelines for the use of as-needed ICS/formoterol in mild asthma

ERS

PICO 2

*Is **as-needed ICS/formoterol** (single inhaler) **without maintenance** treatment the preferred treatment **compared with as-needed SABA** without maintenance treatment in adult/adolescent patients with mild asthma (i.e. GINA treatment steps 1 or 2)?*

Recommendation

- We recommend that *adu*
  as-needed ICS/formoterc
  the intervention; low cer

The Task Force concluded th
with adult data and that the e

One driver of the ERS recommendation was that the panel placed a relatively **higher value on the outcomes related to exacerbations**, and a relatively **lower value on the small differences in asthma control**, since, as above, **severe attacks – but not minor symptoms – kill patients**.

Bush A et al. Eur Respir J. 2024; 63: 2400408

Papi A et al. Eur Respir J. 2023; 62: 2300047

Mart
Museo di arte
moderna e contemporanea
di Trento e Rovereto

GINA Track 1, Steps 3–5: Maintenance and reliever therapy (MART) with low-dose ICS-formoterol

- MART with ICS-formoterol reduces the risk of severe exacerbations requiring oral corticosteroids, compared with other regimens plus SABA reliever, with similar symptom control
  - 32% reduction compared with same dose ICS-LABA *(Sobieraj, JAMA 2018)*
  - 23% reduction compared with higher dose ICS-LABA *(Sobieraj, JAMA 2018)*
  - 17% reduction compared with conventional best practice *(Cates et al, Cochrane 2013)*
- Not just an anti-inflammatory effect
  - Formoterol as reliever reduces risk of severe exacerbations compared with SABA reliever, but greater reduction if the reliever is ICS-formoterol *(Rabe, Lancet 2006)*
- MART is more effective than ICS-LABA plus SABA reliever in both eosinophilic and non-eosinophilic asthma
  - Benefit of MART further increased with higher blood eosinophils *(Brusselle et al, ERJ 2021)*
- MART is approved in ~120 countries

Which formulations and doses of ICS-formoterol can be used as anti-inflammatory relievers in AIR-only or MART?

- **Budesonide-formoterol**
  - Adults and adolescents: 200/6 mcg metered dose [160/4.5 delivered dose] by D
  - Children 6–11 years: 100/6 mcg metered dose [80/4.5 delivered dose] by DPI or
- **Beclometasone-formoterol**
  - Adults: 100/6 mcg metered dose by DPI or pMDI, 1 inhalation per dose no data
- Use of higher or lower dose formulations than these is **not** recommende
- The maximum total dose of formoterol **in any one day** (reliever plus maint formulation is 72 mcg [54 mcg delivered dose] for adults/adolescents, and for children 6–11 years
- ICS-formoterol is the only ICS-LABA that can be used as an anti-inflam

*In some countries, a budesonide-formoterol pMDI with 100/3 [80/2.25] mcg per actuation is available for adults [40/2.25] per actuation is available for children. For these pMDIs, the recommended number of inhalations is double that for the formulations above.

AIR: anti-inflammatory reliever; BDP: beclometasone dipropionate; DPI: dry powder inhaler; MART: maintenance and reliever therapy with ICS-formoterol; pMDI: pressurized metered dose inhaler

Which formulations and doses of ICS-formoterol can be used as anti-inflammatory relievers in AIR-only or MART?

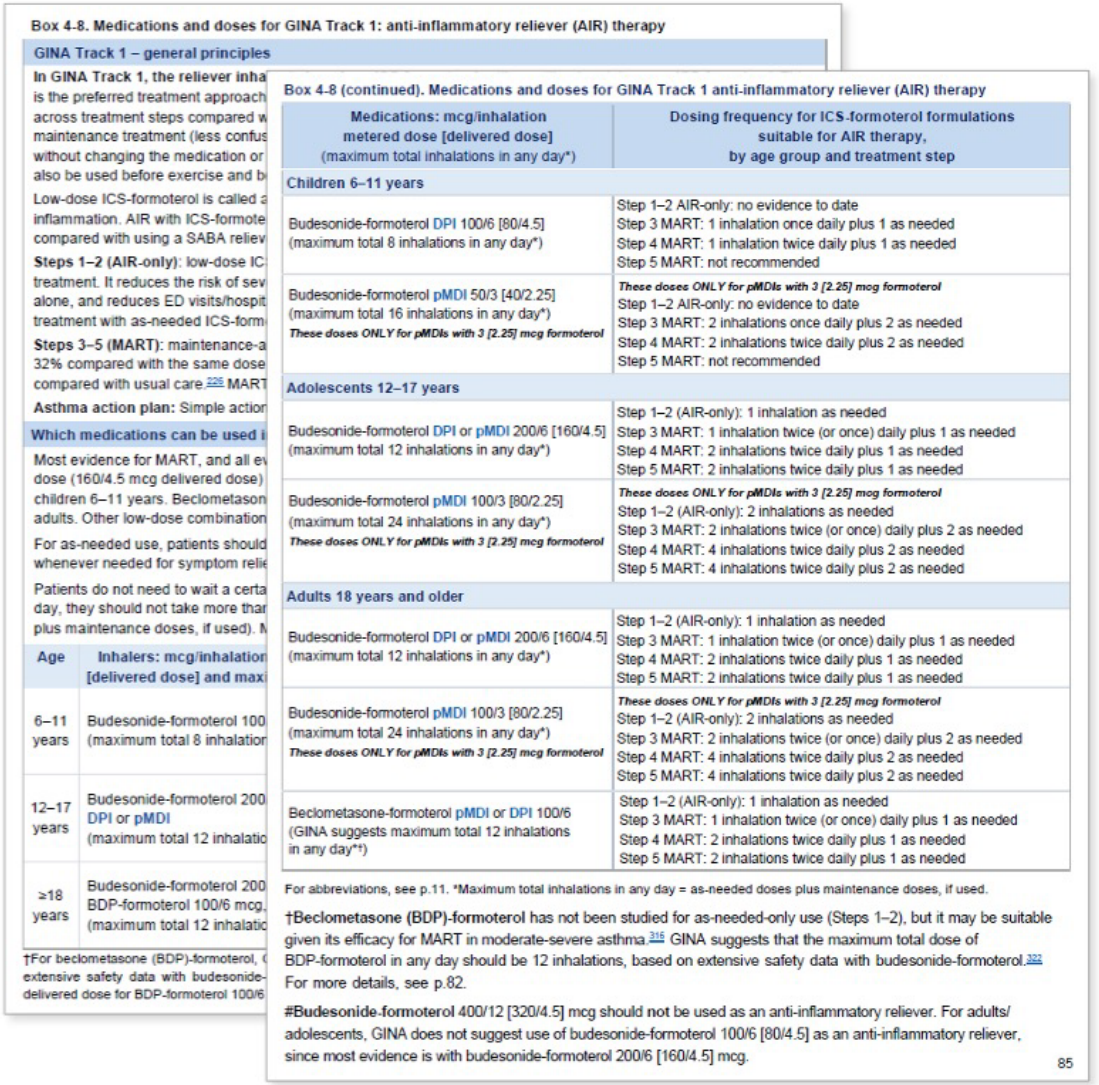
- **Budesonide-formoterol**
  - Adults and adolescents: 200/6 mcg metered dose [160/4.5 delivered dose] by DPI or pMDI, 1 inhalation per dose
  - Children 6–11 years: 100/6 mcg metered dose [80/4.5 delivered dose] by DPI or pMDI, 1 inhalation per dose*
- **Beclometasone-formoterol**
  - Adults: 100/6 mcg metered dose by DPI or pMDI, 1 inhalation per dose; no data in adolescents or children to date
- Use of higher or lower dose formulations than these is **not** recommended*
- The maximum total dose of formoterol **in any one day** (reliever plus maintenance doses, if used) with any formulation is 72 mcg [54 mcg delivered dose] for adults/adolescents, and 48 mcg [36 mcg delivered dose] for children 6–11 years
- ICS-formoterol is the only ICS-LABA that can be used as an anti-inflammatory reliever

*In some countries, a budesonide-formoterol pMDI with 100/3 [80/2.25] mcg per actuation is available for adults and adolescents, and a pMDI with 50/3 mcg [40/2.25] per actuation is available for children. For these pMDIs, the recommended number of inhalations is double that for the formulations above.

AIR: anti-inflammatory reliever; BDP: beclometasone dipropionate; DPI: dry powder inhaler; MART: maintenance and reliever therapy with ICS-formoterol; pMDI: pressurized metered dose inhaler

GINA Track 1: medications & doses for anti-inflammatory reliever therapy

- Evidence to date is with budesonide-formoterol and beclometasone (BDP)-formoterol
- For patients ≥12 yrs: maximum total in any one day is 12 inhalations of budesonide-formoterol 200/6 [160/4.5] mcg
  - Extensive safety data to maximum total of 72 mcg formoterol metered dose [54 mcg delivered dose]
  - GINA suggests the same maximum total dose can be used with BDP-formoterol
- **Very few patients ever need this much!**
- See **GINA 2024 Box 4-8** for more details about recommended formulations and doses
- Do not use ICS-formoterol as the reliever with other maintenance ICS-LABAs *(Reddel et al, JACI IP 2023)*



Box 4-8. Medications and doses for GINA Track 1: anti-inflammatory reliever (AIR) therapy

GINA Track 1 – general principles

In GINA Track 1, the reliever inha
is the preferred treatment approach
across treatment steps compared w
maintenance treatment (less confus
without changing the medication or
also be used before exercise and b

Low-dose ICS-formoterol is called a
inflammation. AIR with ICS-formote
compared with using a SABA reliev

Steps 1–2 (AIR-only): low-dose IC
treatment. It reduces the risk of sev
alone, and reduces ED visits/hospit
treatment with as-needed ICS-form

Steps 3–5 (MART): maintenance-a
32% compared with the same dose
compared with usual care.[226] MART

Asthma action plan: Simple actior

Which medications can be used i

Most evidence for MART, and all ev
dose (160/4.5 mcg delivered dose)
children 6–11 years. Beclometason
adults. Other low-dose combination

For as-needed use, patients should
whenever needed for symptom relie

Patients do not need to wait a certa
day, they should not take more thar
plus maintenance doses, if used). N

Age	Inhalers: mcg/inhalation [delivered dose] and maxi
6–11 years	Budesonide-formoterol 100 (maximum total 8 inhalation
12–17 years	Budesonide-formoterol 200 DPI or pMDI (maximum total 12 inhalatio
≥18 years	Budesonide-formoterol 200 BDP-formoterol 100/6 mcg, (maximum total 12 inhalatio

†For beclometasone (BDP)-formoterol, (extensive safety data with budesonide- delivered dose for BDP-formoterol 100/6

Box 4-8 (continued). Medications and doses for GINA Track 1 anti-inflammatory reliever (AIR) therapy

Medications: mcg/inhalation metered dose [delivered dose] (maximum total inhalations in any day*)	Dosing frequency for ICS-formoterol formulations suitable for AIR therapy, by age group and treatment step
Children 6–11 years	
Budesonide-formoterol DPI 100/6 [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
Budesonide-formoterol pMDI 50/3 [40/2.25] (maximum total 16 inhalations in any day*) ***These doses ONLY for pMDIs with 3 [2.25] mcg formoterol***	***These doses ONLY for pMDIs with 3 [2.25] mcg formoterol*** Step 1–2 AIR-only: no evidence to date Step 3 MART: 2 inhalations once daily plus 2 as needed Step 4 MART: 2 inhalations twice daily plus 2 as needed Step 5 MART: not recommended
Adolescents 12–17 years	
Budesonide-formoterol DPI or 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*) ***These doses ONLY for pMDIs with 3 [2.25] mcg formoterol***	***These doses ONLY for pMDIs with 3 [2.25] mcg formoterol*** 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
Adults 18 years and older	
Budesonide-formoterol DPI or 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*) ***These doses ONLY for pMDIs with 3 [2.25] mcg formoterol***	***These doses ONLY for pMDIs with 3 [2.25] mcg formoterol*** 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

For abbreviations, see p.11. *Maximum total inhalations in any day = as-needed doses plus maintenance doses, if used.

†**Beclometasone (BDP)-formoterol** has not been studied for as-needed-only use (Steps 1–2), but it may be suitable given its efficacy for MART in moderate-severe asthma.[316] GINA suggests that the maximum total dose of BDP-formoterol in any day should be 12 inhalations, based on extensive safety data with budesonide-formoterol.[322] For more details, see p.82.

#**Budesonide-formoterol** 400/12 [320/4.5] mcg should not be used as an anti-inflammatory reliever. For adults/adolescents, GINA does not suggest use of budesonide-formoterol 100/6 [80/4.5] as an anti-inflammatory reliever, since most evidence is with budesonide-formoterol 200/6 [160/4.5] mcg.

85

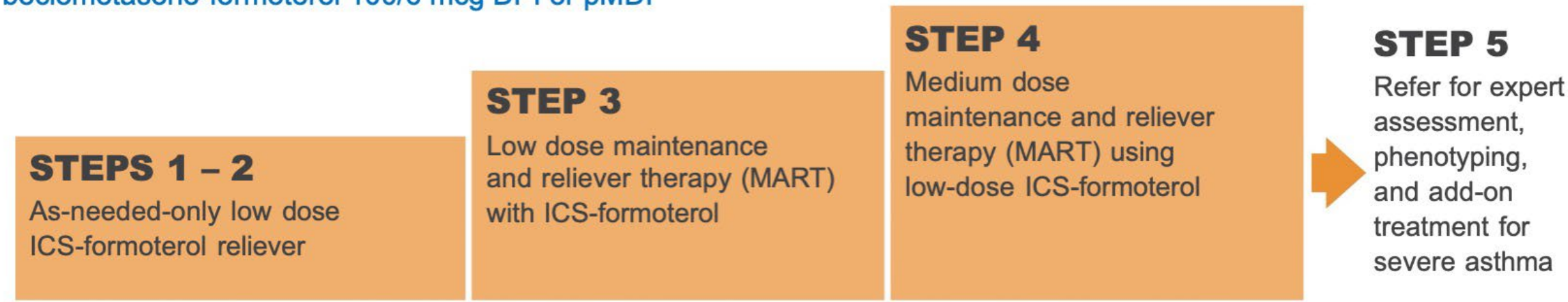
Medications: mcg/inhalation metered dose *[delivered dose]* (maximum total inhalations in any day*)	**Dosing frequency for ICS-formoterol formulations suitable for AIR therapy, by age group and treatment step**
Adolescents 12–17 years	
Budesonide-formoterol **DPI** 200/6 *[160/4.5]* (maximum total 12 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

Inhaled corticosteroid (alone or in combination with LABA)	Total daily ICS dose (mcg) – see notes above		
	Low	Medium	High
Adults and adolescents (12 years and older)			
Beclometasone dipropionate (pMDI, standard particle, HFA)	200–500	>500–1000	>1000
Beclometasone dipropionate (DPI or pMDI, extrafine particle, HFA)	100–200	>200–400	>400
Budesonide (DPI, or pMDI, standard particle, HFA)	200–400	>400–800	>800
Ciclesonide (pMDI, extrafine particle, HFA)	80–160	>160–320	>320
Fluticasone furoate (DPI)	100		200
Fluticasone propionate (DPI)	100–250	>250–500	>500
Fluticasone propionate (pMDI, standard particle, HFA)	100–250	>250–500	>500
Mometasone furoate (DPI)	Depends on DPI device – see product information		
Mometasone furoate (pMDI, standard particle, HFA)	200–400		>400

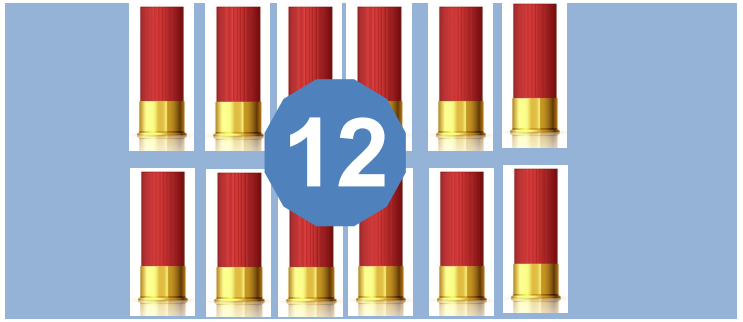
TRACK 1, Steps 1–4: PREFERRED CONTROLLER and RELIEVER for adults and adolescents.

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.

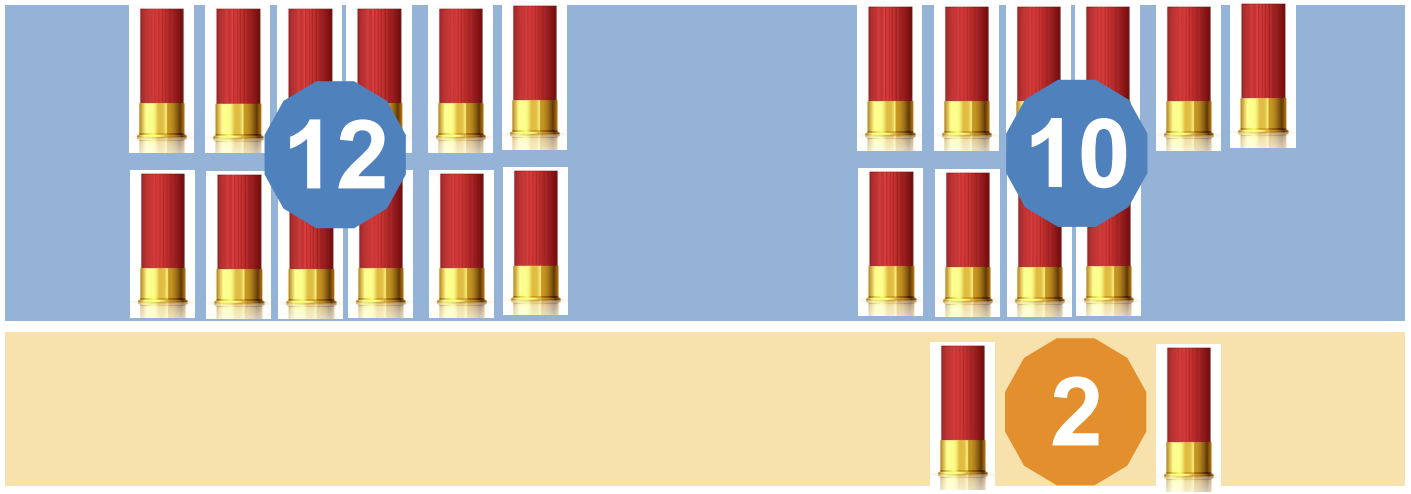


STEPS 1 – 2

As-needed-only low dose ICS-formoterol reliever

One inhaler, use as needed

Symptoms less than 3–5 days a week, with normal (or mildly reduced) lung function



STEPS 1 – 2

As-needed-only low dose ICS-formoterol reliever

One inhaler, use as needed

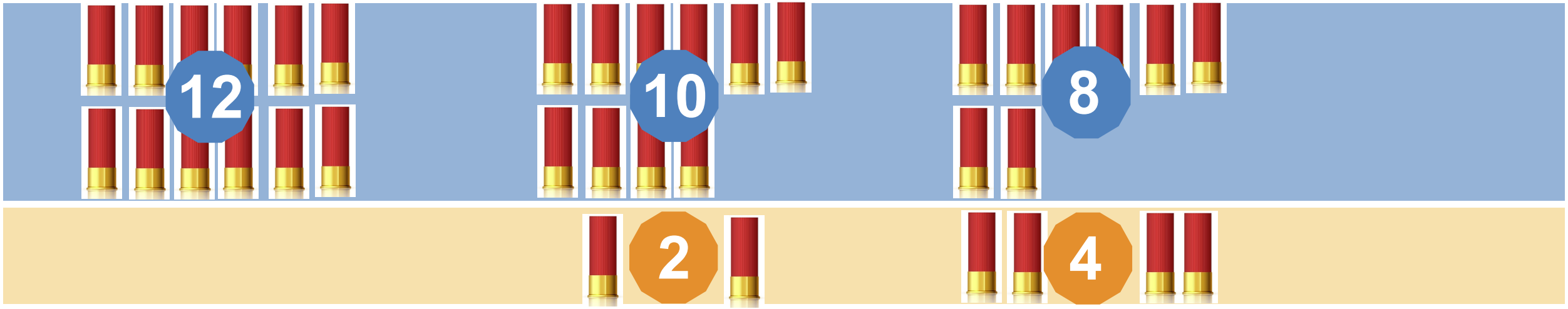
Symptoms less than 3–5 days a week, with normal (or mildly reduced) lung function

STEP 3

Low dose maintenance and reliever therapy (MART) with ICS-formoterol

Same inhaler, take 1 inhalation once or twice daily and 1 as needed

Symptoms most days, or waking at night once a week or more, or low lung function



STEPS 1 – 2

As-needed-only low dose ICS-formoterol reliever

One inhaler, use as needed

Symptoms less than 3–5 days a week, with normal (or mildly reduced) lung function

STEP 3

Low dose maintenance and reliever therapy (MART) with ICS-formoterol

Same inhaler, take 1 inhalation once or twice daily and 1 as needed

Symptoms most days, or waking at night once a week or more, or low lung function

STEP 4

Medium dose maintenance and reliever therapy (MART) using low-dose ICS-formoterol

Same inhaler, take 2 inhalations twice daily and 1 as needed

Daily symptoms, waking at night once a week or more and low lung function, or recent exacerbation

STEP 5

Refer for expert assessment, phenotyping, and add-on treatment for severe asthma

MART ACTION PLAN

My Symbicort (budesonide/formote Turbuhaler 200/6 Asthma Action Plan

Anti-inflammatory Reliever
With or without Maintenan

NORMAL MODE

- MY SYMBICORT ASTHMA T
  - ☐ Symbicort Turbuhaler 200/
- RELIEVER
  - I should take 1 inhalation of my whenever needed for relief of symptoms
  - I should always carry my Symb use as a reliever when needed
- MY REGULAR MAINTENANC EVERY DAY IS : *(enter number o no regular daily treatment prescribe*
  - _____ Inhalation(s) in the m
  - _____ Inhalation(s) in the e
- MY ASTHMA IS STABLE IF:
  - I do not wake up at night or because of asthma
  - My asthma has not interfere activities (e.g housework, sc

OTHER INSTRUCTIONS
(e.g. what to do before exercise, when to

Allergy & Asthma NETWORK

(Example of action plan template for budesonide/formoterol. A similar action plan could be constructed for other ICS/formoterol formulations, eg, mometasone/formoterol)

My Asthma Action Plan

For Single Inhaler Maintenance and Reliever Therapy (SMART) with budesonide/formoterol

Name: _____ **Action plan provided by:** _____

Date: _____ **Doctor:** _____

Usual best PEF: _____ L/min *(if used)* **Doctor's phone:** _____

Normal mode

My SMART Asthma Treatment is:

☐ budesonide/formoterol 160/4.5 (12 years or older)

☐ budesonide/formoterol 80/4.5 (4-11 years)

My Regular Treatment Every Day:

(Write in or circle the number of doses prescribed for this patient)

Take [1, 2] inhalation(s) in the morning

and [0, 1, 2] inhalation(s) in the evening, every day

Reliever

Use 1 inhalation of budesonide/formoterol whenever needed for relief of my asthma symptoms

I should always carry my budesonide/formoterol inhaler

My asthma is stable if:

- I can take part in normal physical activity without asthma symptoms

AND

- I do not wake up at night or in the morning because of asthma

Other Instructions

_____

_____

Asthma Flare-up

If over a Period of 2-3 Days:

- My asthma symptoms are getting worse OR NOT improving

OR

- I am using more than 6 budesonide/formoterol reliever inhalations a day (if aged 12 years or older) or more than 4 inhalations a day (if aged 4-11 years)

I should:

☐ Continue to use my regular everyday treatment PLUS 1 inhalation budesonide/formoterol whenever needed to relieve symptoms

☐ Start a course of prednisolone

☐ Contact my doctor

Course of Prednisolone Tablets:

Take _____ mg prednisolone tablets per day for _____ days OR

_____

_____

☐ If I need more than 12 **budesonide/formoterol inhalations (total)** in any day (or more than 8 inhalations for children 4-11 years), I **MUST** see my doctor or go to the hospital the same day.

Asthma Emergency

Signs of an Asthma Emergency:

- Symptoms getting worse quickly
- Extreme difficulty breathing or speaking
- Little or no improvement from my budesonide/formoterol reliever inhalations

If I have any of the above danger signs, I should dial _____ for an ambulance and say I am having a severe asthma attack.

While I am waiting for the ambulance start my asthma first aid plan:

- Sit upright and stay calm.
- Take 1 inhalation of budesonide/formoterol. Wait 1-3 minutes. If there is no improvement, take another inhalation of budesonide/formoterol (up to a maximum of 6 inhalations on a single occasion).
- If only albuterol is available, take 4 puffs as often as needed until help arrives.
- Start a course of prednisolone tablets (as directed) while waiting for the ambulance.
- Even if my symptoms appear to settle quickly, I should see my doctor immediately after a serious attack.

Modified from Australian action plan with permission from National Asthma Council Australia and AstraZeneca Australia

Review Date: October 2024

NHS Frimley Clinical Commissioning Group

s daily (as below) you are strongly
be reconsidered.

EMERGENCY

GENCY
is not relieving my

difficulty breathing.
o speak in full

.....
usual best).

calm.
Duoresp.

ement take another puff
2 minutes up to a
in total until help

ncy actions
getting worse
medical attention by
use further reliever
arrives.

espiratory review at my
ymptoms improve.

SIMRI ACTION PLAN

PIANO D'AZIONE DELL'ASMA

Nome e cognome:

Data:

Prossimo controllo:

Contatti del centro

COME TI SENTI?

Tutto okay!

Tutti i seguenti sono presenti:

- Respiro bene
- Non tossisco e non "fischio"
- Ho dormito bene stanotte: non mi sono mai svegliato!
- Riesco a giocare senza problemi.

Allora prendo queste medicine **tutti i giorni**:

COSA?	QUANTO?	QUANDO?

Non mi sento molto bene...

Almeno uno dei seguenti è presente:

- Tossisco, fischio, ho difficoltà a respirare
- Ho dovuto utilizzare la mia terapia al bisogno già 3 (o più) volte questa settimana
- Mi sono svegliato stanotte, non riesco a dormire per la tosse.

Allora **aggiungo** queste medicine se ho un nuovo episodio acuto entro un mese **aumento** la mia terapia di fondo e **anticipo** l'appuntamento col mio dottore:

COSA?	QUANTO?	QUANDO?

Sto male...

Almeno uno dei seguenti è presente e **non ho alcun beneficio dalla terapia al bisogno**

- Respiro molto velocemente e a fatica
- Uso tutti i muscoli del corpo per far entrare l'aria nei polmoni
- Non riesco a parlare

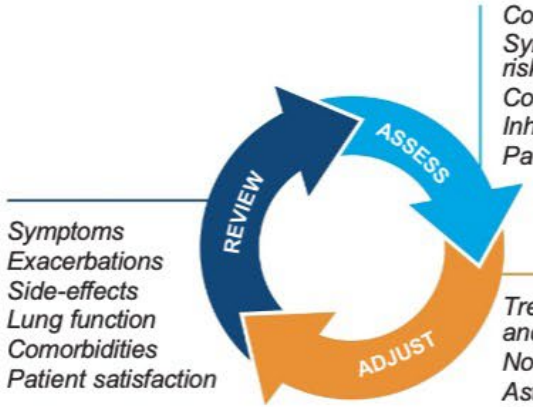
Prendo queste medicine e chiamo il mio dottore:

COSA?	QUANTO?	QUANDO?

Se i sintomi non migliorano, ma peggiorano, le labbra diventano viola o sembra che i sintomi dell'asma siano fuori controllo, chiamo il **112** e mi reco subito al **Pronto Soccorso**!

GINA 2024 – Adults & adolescents 12+ years

Personalized asthma management
Assess, Adjust, Review
for individual patient needs



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

Symptoms
Exacerbations
Side-effects
Lung function
Comorbidities
Patient satisfaction

Treatment of modifiable risk factors and comorbidities
Non-pharmacological strategies
Asthma medications including ICS (as below)
Education & skills training

TRACK 1: PREFERRED CONTROLLER and RELIEVER
Using ICS-formoterol as the reliever* reduces the risk of exacerbations compared with using a SABA reliever, and is a simpler regimen

STEPS 1 – 2	STEP 3	STEP 4	STEP 5
As-needed-only low dose ICS-formoterol	Low dose maintenance ICS-formoterol	Medium dose maintenance ICS-formoterol	Add-on LAMA Refer for assessment of phenotype. Consider high dose maintenance ICS-formoterol, ± anti-IgE, anti-IL5/5R, anti-IL4Rα, anti-TSLP

RELIEVER: As-needed low-dose ICS-formoterol*

See GINA severe asthma guide

TRACK 2: Alternative **CONTROLLER and RELIEVER**
Before considering a regimen with SABA reliever, check if the patient is likely to adhere to daily controller treatment

STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
Take ICS whenever SABA taken*	Low dose maintenance ICS	Low dose maintenance ICS-LABA	Medium/high dose maintenance ICS-LABA	Add-on LAMA Refer for assessment of phenotype. Consider high dose maintenance ICS-LABA, ± anti-IgE, anti-IL5/5R, anti-IL4Rα, anti-TSLP

RELIEVER: As-needed ICS-SABA*, or as-needed SABA

Other controller options (limited indications, or less evidence for efficacy or safety – see text)

Low dose ICS whenever SABA taken, or daily LTRA†, or add HDM SLIT*	*Medium dose ICS, or add LTRA†, or add HDM SLIT*	*Add LAMA or add LTRA† or add HDM SLIT, or switch to high dose ICS-only*	*Add azithromycin (adults) or add LTRA†. As last resort consider adding low dose OCS but consider side-effects*

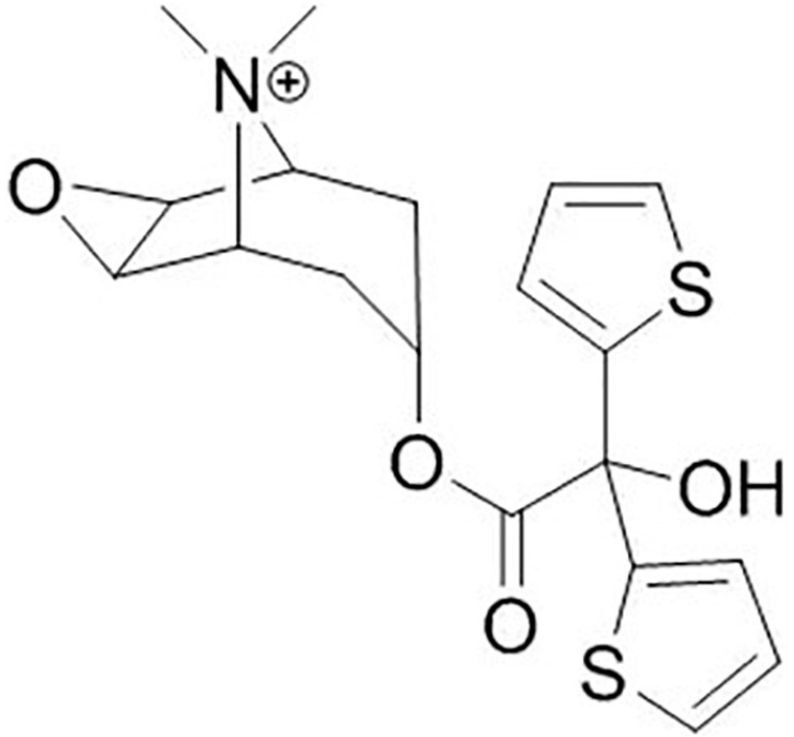
*Anti-inflammatory reliever; †advise about risk of neuropsychiatric adverse effects

GINA 2024 Box 4-6

Tiotropio

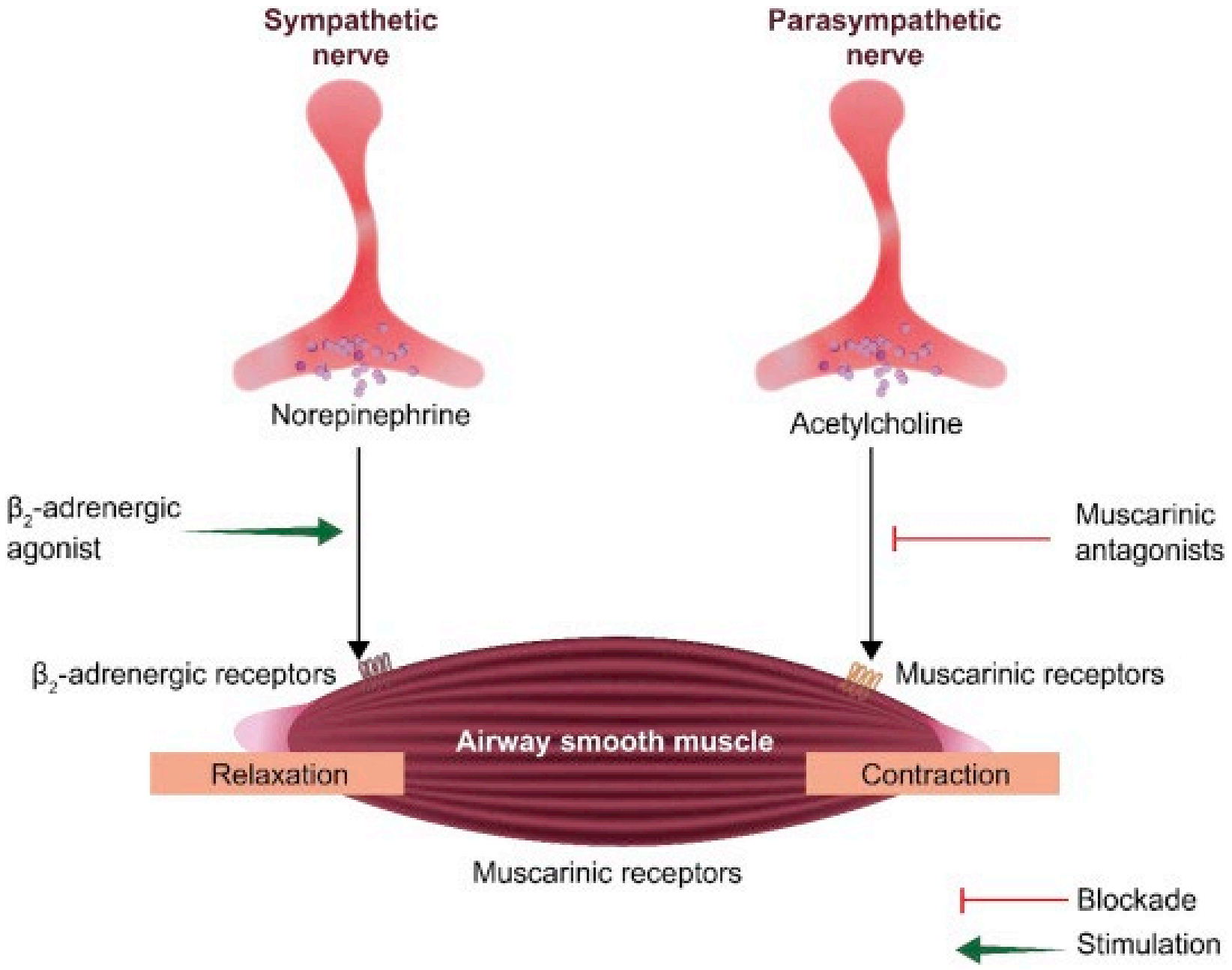
- In **1989** the tiotropium bromide (bromide salt) was **patented** and then **approved for medical use** in the form of inhalation powder in **2002** as LAMA bronchodilator drug.

- Tiotropium bromide is a quaternary ammonium derivative, structurally related to ipratropium bromide, but with a significantly **higher affinity for muscarinic receptors** within the airways.



Santamaria F et al. Front Pediatr. 2022, 19;10:896865

Tiotropio


Sympathetic nerve
Parasympathetic nerve
Norepinephrine
Acetylcholine
β2-adrenergic agonist
Muscarinic antagonists
β2-adrenergic receptors
Muscarinic receptors
Airway smooth muscle
Relaxation
Contraction
Muscarinic receptors
Blockade
Stimulation

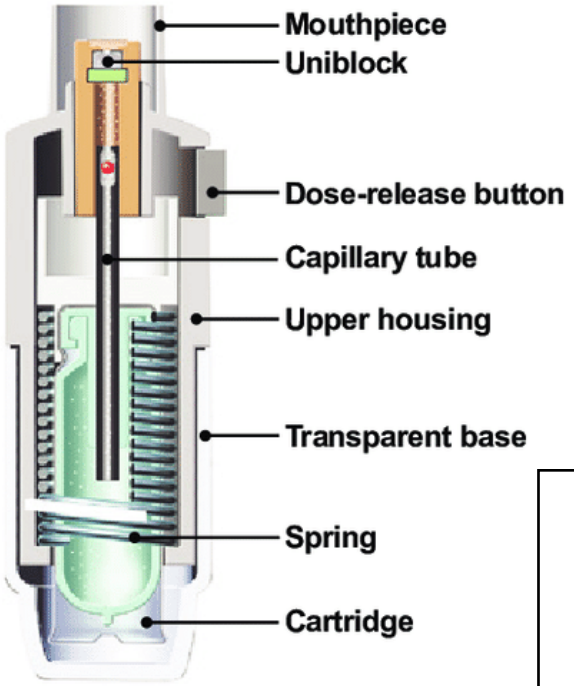
Tiotropio

- Tiotropium bromide **reversibly binds to the M1, M2, and M3 receptors of the airway smooth muscles**, and **blocks the effects of the acetylcholine** released by parasympathetic nerve endings **through a competitive and reversible inhibition**, with faster dissociation rates from M2 than from M1 or M3 receptors.

- Tiotropium bromide has a **maximum effect occurring at 30-60 min**, and since the cholinergic transmission is blocked approximately for **35 h**, its principal anti-asthmatic property is the **long-acting bronchodilation**, which allows a **once daily administration**.

Santamaria F et al. Front Pediatr. 2022, 19;10:896865

Soft Mist Inhaler



Tiotropio

frontiers | Frontiers in Pediatrics

REVIEW
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Update on Long-Acting Anticholinergics in Children and Adolescents With Difficult and Severe Asthma

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Tiotropio

Author	Study design	Age group (years)	Asthma severity	Daily dose and treatment duration	Primary outcome	Main findings
Vogelberg et al. (28)	Phase 2, double-blind, placebo-controlled, dose- ranging, incomplete crossover study	Adolescents (12–17)	Moderate persistent asthma	5 µg 2.5 µg 1.25 µg 12 weeks	Peak FEV1 (0–3 h): 5 µg: 113 mL $p = 0.004$ 2.5 µg: 57 mL $p = 0.148$ 1.25 µg: 67 mL $p = 0.066$	Improvement of lung function vs. placebo. Safe and well tolerated
Hamelmann et al. (29)	Phase 3, double-blind, placebo-controlled, parallel-group trial	Adolescents (12–17)	Moderate symptomatic asthma	5 µg 2.5 µg 48 weeks	Peak FEV1 (0–3 h): 5 µg: 174 mL (95% CI, 76–272 mL) $p < 0.001$ 2.5 µg: 134 mL (95% CI, 34–234 mL) $p < 0.01$	Improvement of lung function vs. placebo. Safe and well tolerated
Huang et al. (36)	Phase 3, double-blind, placebo-controlled study	School-age children and adolescents (6–14)	Moderate symptomatic asthma	1.25 µg 12 weeks	FEV1% at week 12 and FVC at week 8 $p < 0.05$. Other indicators $p < 0.01$	Improvement of lung function vs. placebo. Decreased need for SABA Night symptoms improvement
Hamelmann et al. (30)	Phase 3, double-blind, placebo-controlled, parallel-group study	Adolescents (12–17)	Severe symptomatic asthma	5 µg 2.5 µg 12 weeks	Peak FEV1 (0–3 h): 5 µg: 90 mL (95% CI, –19 –198 mL) $p = 0.104$ 2.5 µg:111 mL (95% CI, 2–220 mL) $p = 0.046$	Improvement of lung function only at 2.5 µg vs. placebo.

Tiotropio

- **Based on the evidence** from literature data on asthma, **indications** for administration of tiotropium bromide inhalation spray include the long-term, once-daily, **maintenance treatment of moderate-to-severe asthma that is not adequately controlled on ICS**.

- The drug was approved by the **US Food and Drug Administration** in **2015 in patients with asthma aged ≥12 years**, and more recently in February **2017 in pediatric patients aged ≥ 6 years**.

- The approved **doses** are **2.5 mg in the United States** and **5 mg in the European Union**.

Santamaria F et al. Front Pediatr. 2022, 19;10:896865

Tiotropio

- Tiotropium bromide is the **only LAMA** licensed for asthma longterm treatment of **patients aged ≥ 6 years** who continue to have symptoms despite controller medication administration.
- **Most relevant changes** are reported in spirometry when patients are administered **5 mg** rather than other doses.
- In the phase III RCT of a large group of children and adolescents, Szefler and coworkers concluded that the effects of tiotropium bromide as an add-on treatment were **not influenced by Th 2 phenotype**, indicating that the decision of adding tiotropium does **not require the evaluation of Th 2** and that tiotropium **is effective regardless of allergic status**.

Santamaria F et al. Front Pediatr. 2022, 19;10:896865
Szefler SJ et al. J Allergy Clin Immunol Pract. 2019, 7:1088–90

Tiotropio

- An **important limitation** is also the **difference in treatment duration (12 or 48 weeks)**, which hampers establishment of the **long-term effectiveness** of the medication.

- Treatment with tiotropium bromide as an add-on medication appears to be **well tolerated** by children and adolescents with suboptimal control of moderate-to-severe asthma, **is safe** and **no fatal events** have been reported so far.

- **However, longterm safety should be evaluated** in future studies including **longer periods of treatment**.

Santamaria F et al. Front Pediatr. 2022, 19;10:896865

E il montelukast?

Other controller options (limited indications, or less evidence for efficacy or safety – see text)	Low [illegible] daily LTRA†, [illegible]	[illegible] add LTRA†, [illegible] add [illegible]	Add LAMA or add LTRA† or add HDM SLIT, or switch to high dose ICS-only	Add azithromycin (adults) or add LTRA†. [illegible] last resort consider adding low dose OCS but consider side-effects

*Anti-inflammatory reliever; †advise about risk of neuropsy[illegible]

†If prescribing LTRA, advise patient/caregiver about risk of neuropsychiatric adverse effects.

E il montelukast?

2020

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Drug Safety Communications

FDA requires Boxed Warning about serious mental health side effects for asthma and allergy drug montelukast (Singulair); advises restricting

- La possibilità che durante il trattamento con montelukast possano verificarsi eventi neuropsichiatrici, anche se rara, deve essere chiaramente comunicata ai pazienti e/o ai genitori/caregiver.
- I pazienti e/o genitori/caregiver devono essere istruiti sulla necessità di informare prontamente il proprio medico o il medico della persona che si sta assistendo in caso di:
  - cambiamenti nel comportamento e nell'umore, compresi alterazione dell'attività onirica inclusi incubi, insonnia, sonnambulismo, ansia, agitazione comprendente comportamento aggressivo o ostilità, depressione, iperattività psicomotoria (comprendente irritabilità, irrequietezza, tremore),
  meno frequentemente: alterazione dell'attenzione, compromissione della memoria, tic, allucinazioni, disorientamento, pensieri e comportamento suicida (propensione al suicidio), sintomi ossessivo-compulsivi e disfemia.
- In caso si verifichino tali disturbi, i medici prescrittori devono valutare attentamente i rischi e i benefici relativi al proseguimento del trattamento con montelukast. I casi vanno valutati singolarmente ed è responsabilità del prescrittore valutare se proseguire il trattamento.

AIFA AGENZIA ITALIANA DEL FARMACO

discuss with a health care
vior or mood-related changes

ry problems
sive-compulsive symptoms
sness
valking
ing
al thoughts and actions
or shakiness
e sleeping

- things that are not really there)
- irritability
- uncontrolled muscle movements

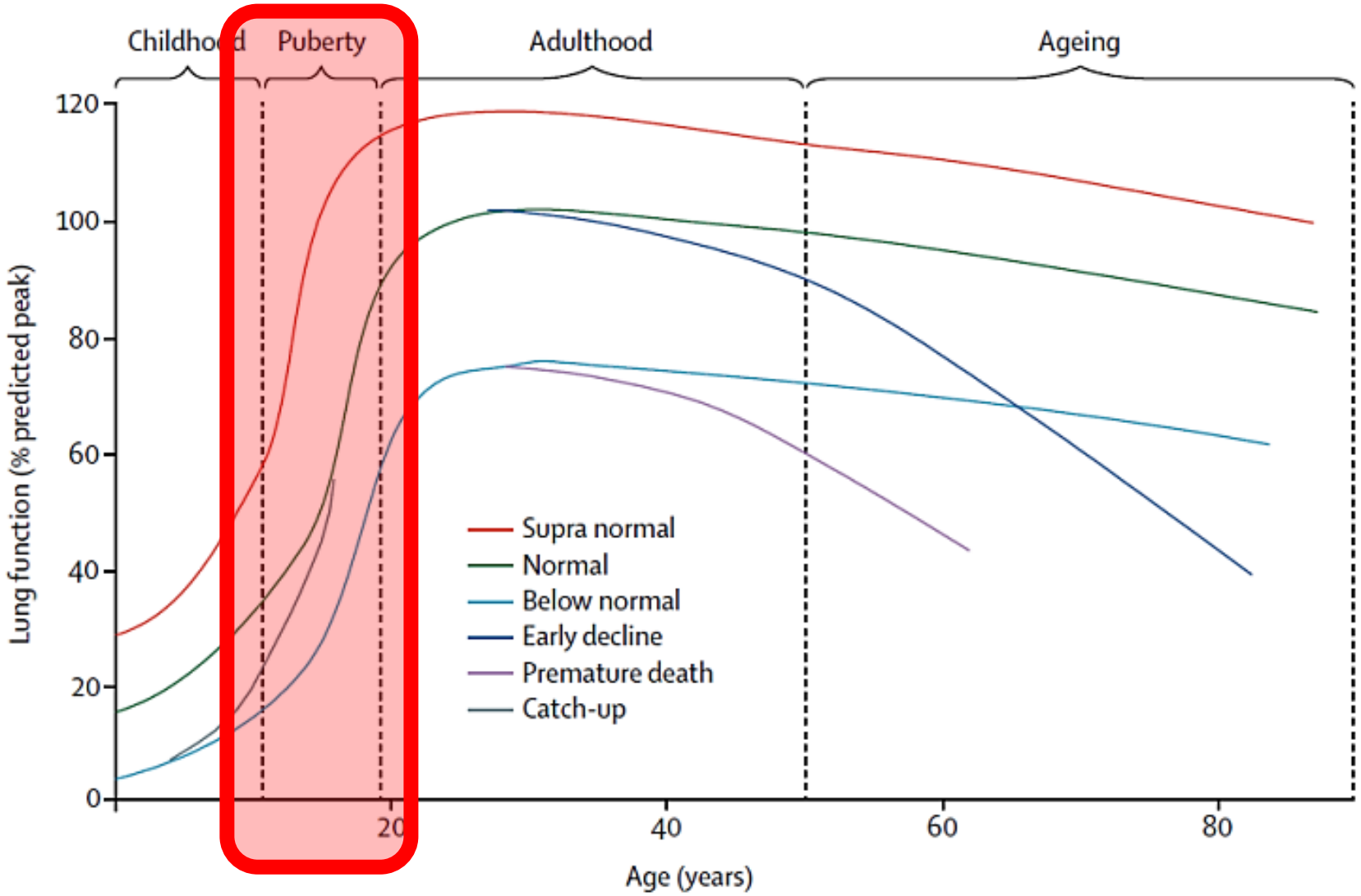
GINA 2024: Le novità terapeutiche nell'adolescente

- «SABA» (Short Acting Brain Activity): find the differences!
- Un passo indietro
- Ah, l'adolescente…! (quanti dubbi)
- La rivoluzione continua
- Conclusioni

Ah, l’adolescente…!

Vi propongo alcune riflessioni…

Le traiettorie della funzione polmonare

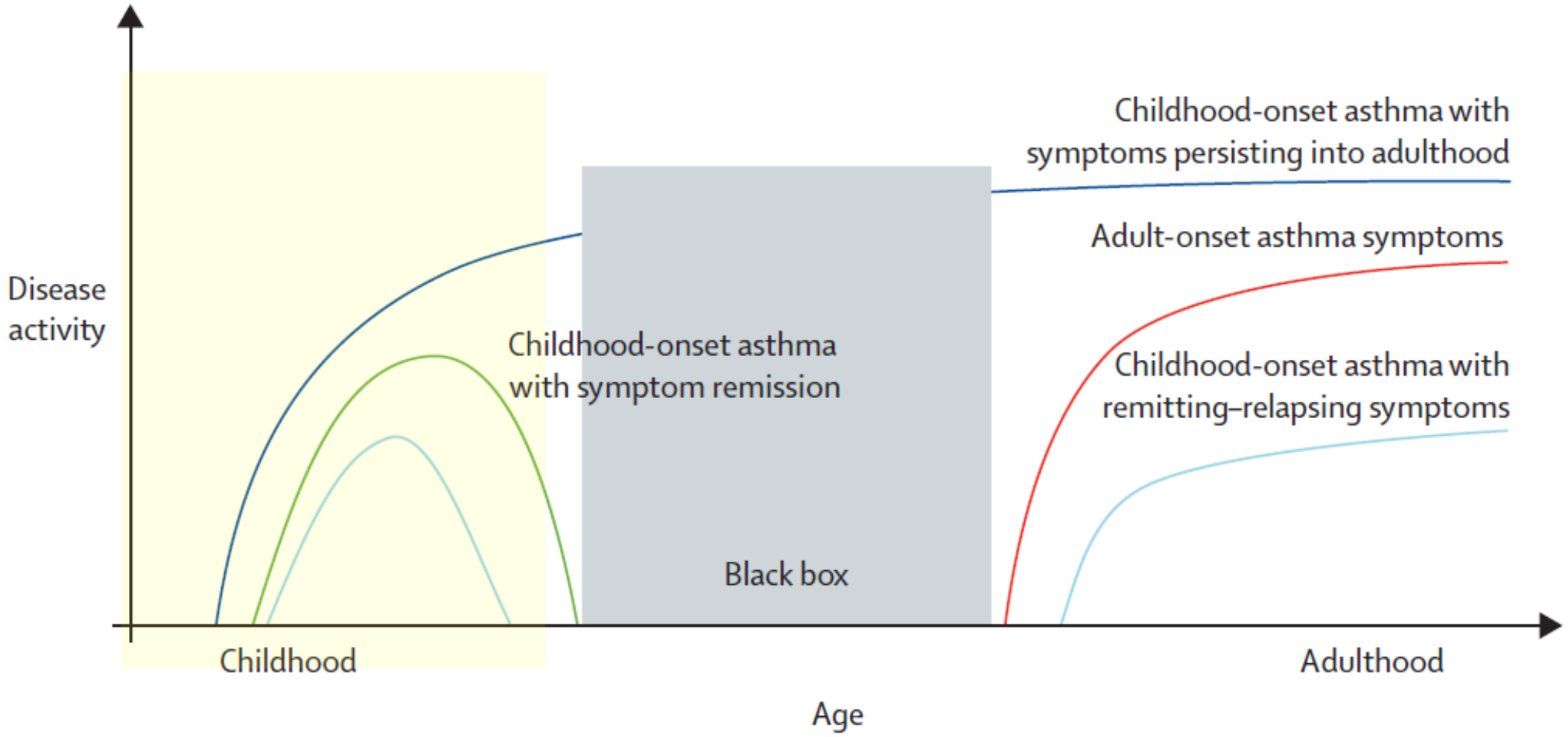


Agustí A et al. ***Pathogenesis of COPD: understanding the contributions of gene-environment interactions across the lifespan****. Lancet Respir Med. 2022; 10: 512-24*

L’esempio del prematuro e della displasia broncopolmonare

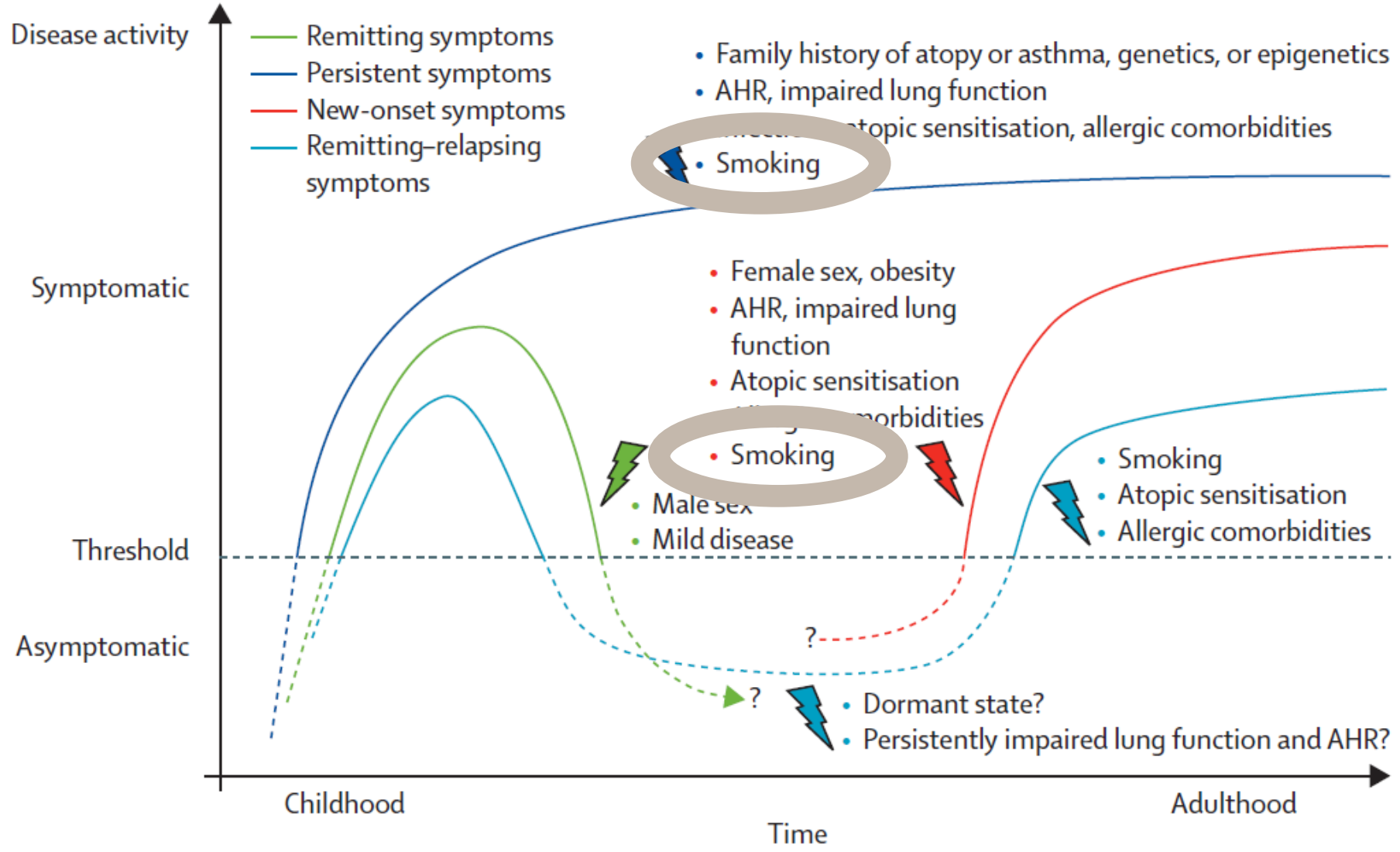
Baraldi E, Filippone M. ***Chronic lung disease after premature birth****. N Engl J Med. 2007; 357: 1946-55*

Gli passerà?

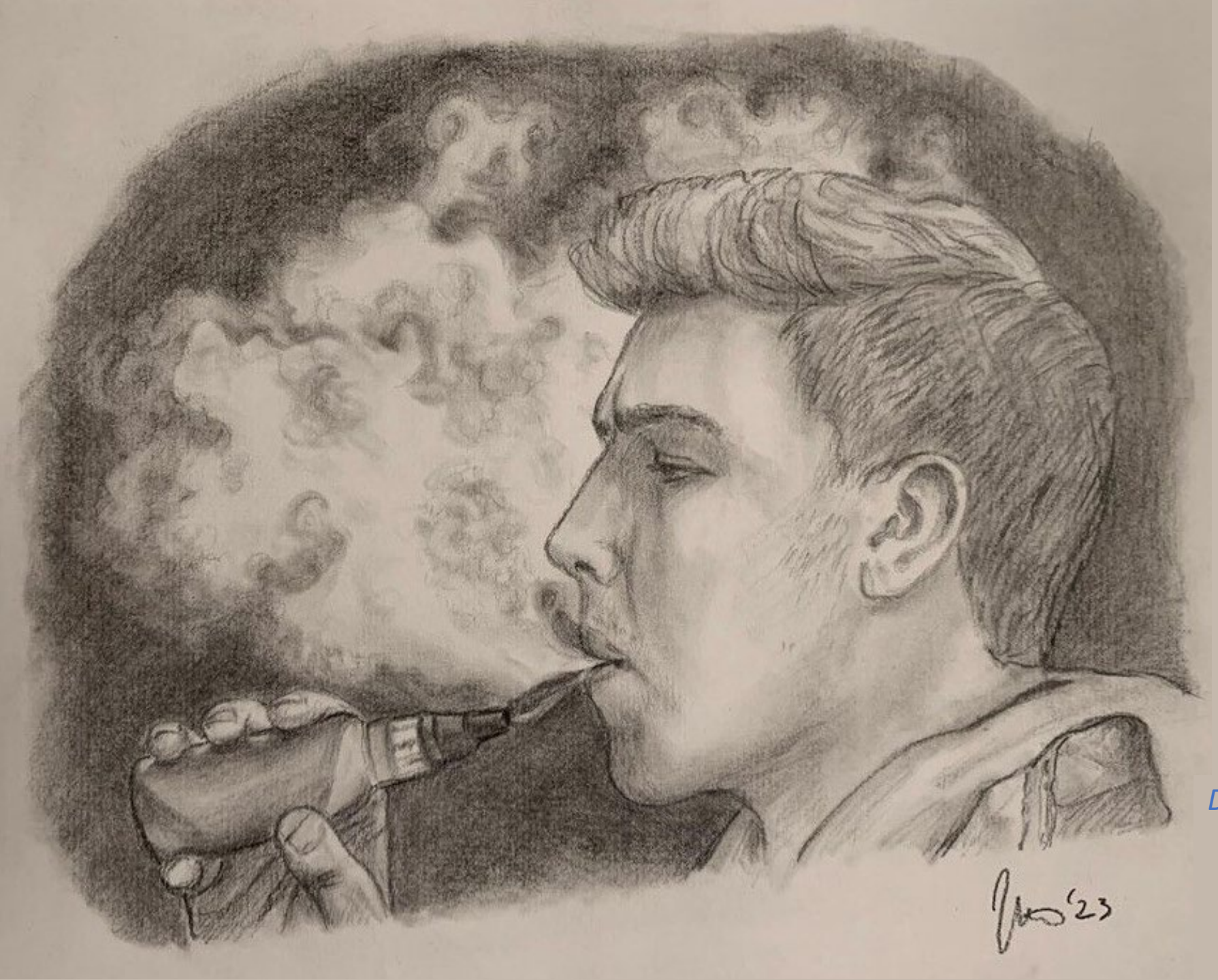


Fuchs O et al. ***Asthma transition from childhood into adulthood.*** *Lancet Respir Med. 2017; 5:224-34*

Siamo in grado di predire il futuro?



Fuchs O et al. ***Asthma transition from childhood into adulthood.*** *Lancet Respir Med. 2017; 5:224-34*

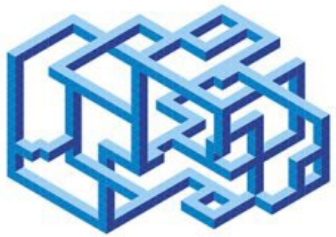


Di Cicco M, Beni A, Ragazzo V, Peroni D.

New threats for pediatric respiratory health: beware of vaping.

Ped Respir J. 2023; 1: 16-25

Massimo Ammaniti



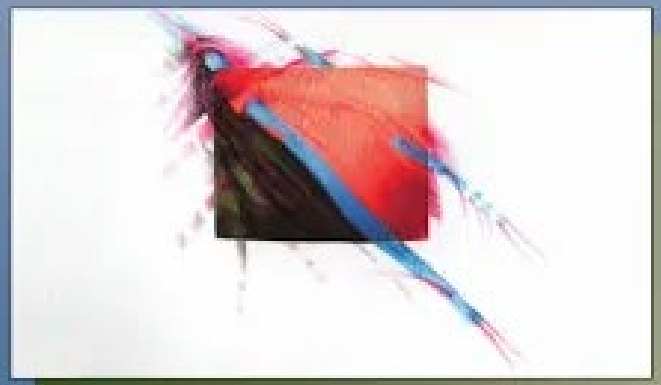
I PARADOSSI DEGLI ADOLESCENTI

Raffaello Cortina Editore

Scelte estreme in adolescenza

Le ragioni emotive
dei processi di radicalizzazione

a cura di
Alfio Maggiolini e Mauro Di Lorenzo



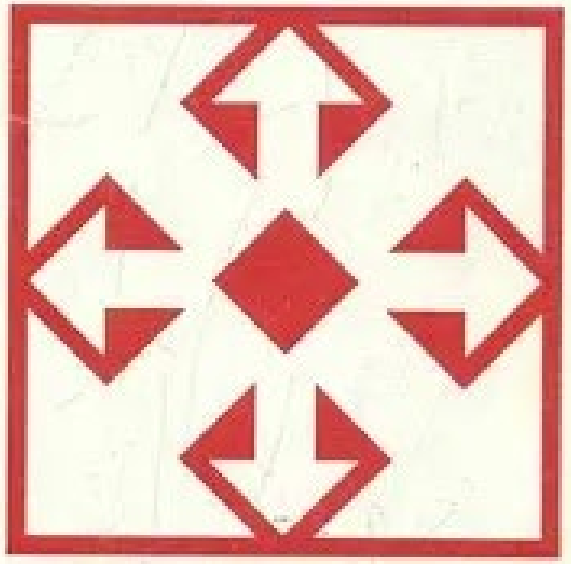
Adolescenza, educazione e affetti
Collana diretta da G. Pietropolli Charmet

FrancoAngeli

Fondazione Rui "Progetto Educazione"

Gerardo Castillo

L'adolescenza e i suoi problemi



Le Monnier

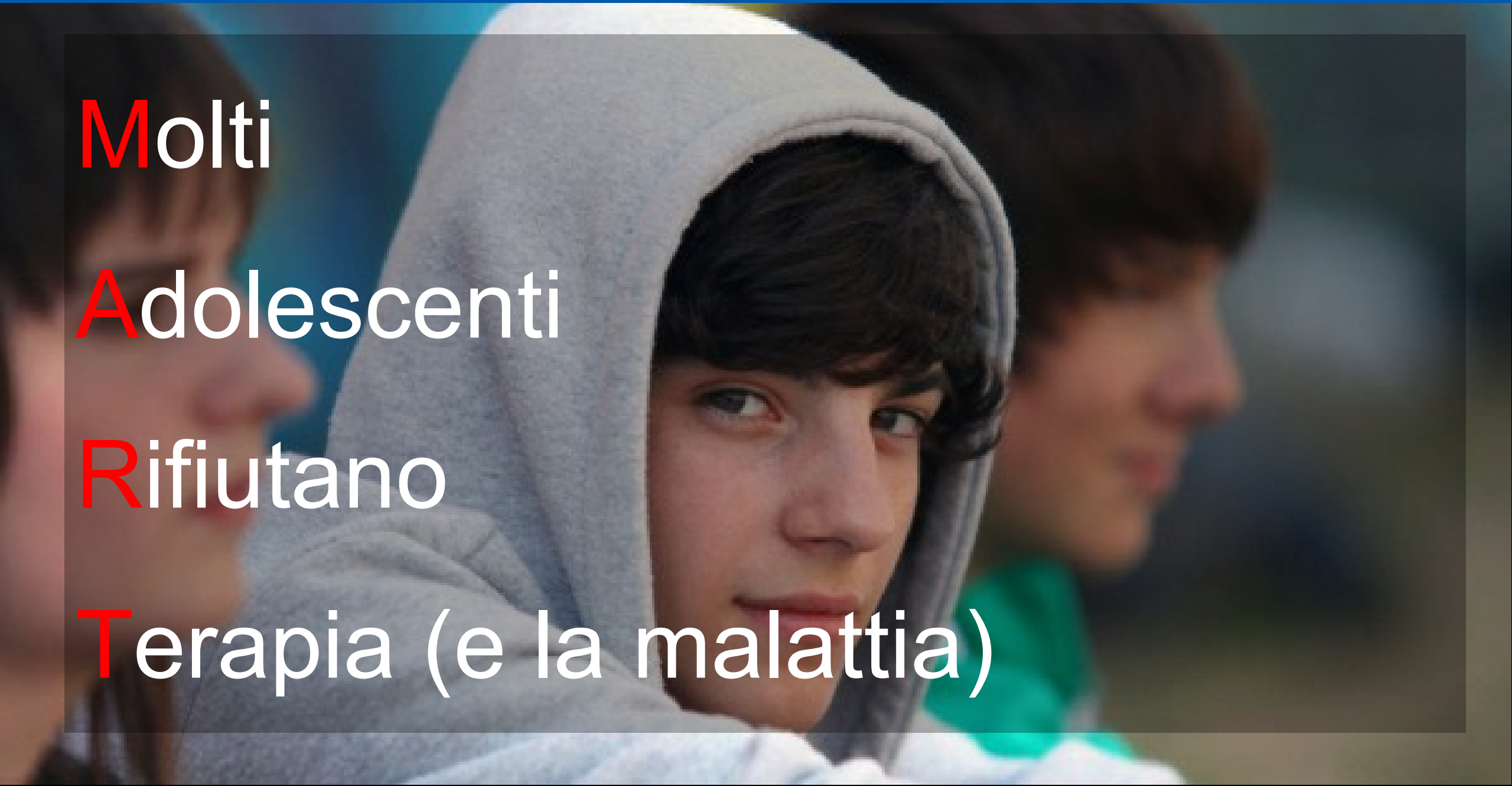
L’adolescente e il suo desiderio di essere contemporaneamente come tutti gli altri e come nessun altro.

Jacques Drillon

Ah, l’adolescente…!

«MART»

«MART»



Molti

Adolescenti

Rifiutano

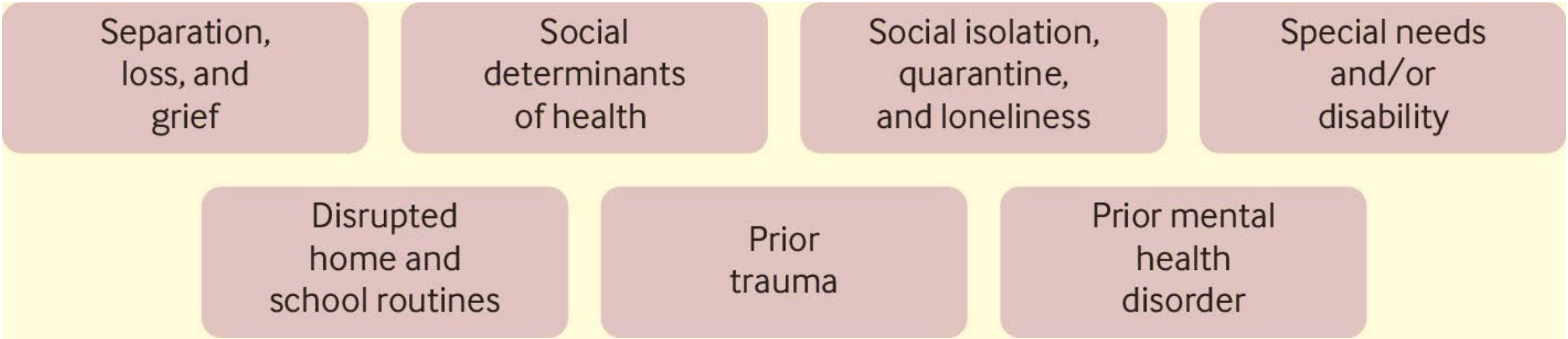
Terapia (e la malattia)

La vera emergenza pediatrica dopo alla pandemia da SARS-CoV2

SANITÀ INTERNAZIONALE | 5 Ottobre 2021 12:46

Unicef allerta: «Con pandemia 1 adolescente su 7 soffre di disturbi mentali»

Adolescenti ancora più a rischio di disturbi mentali: 89 milioni di maschi e 77 milioni di femmine. Ansia e depressione in cima alla lista, vediamo quali sono i fattori di rischio e quelli protettivi

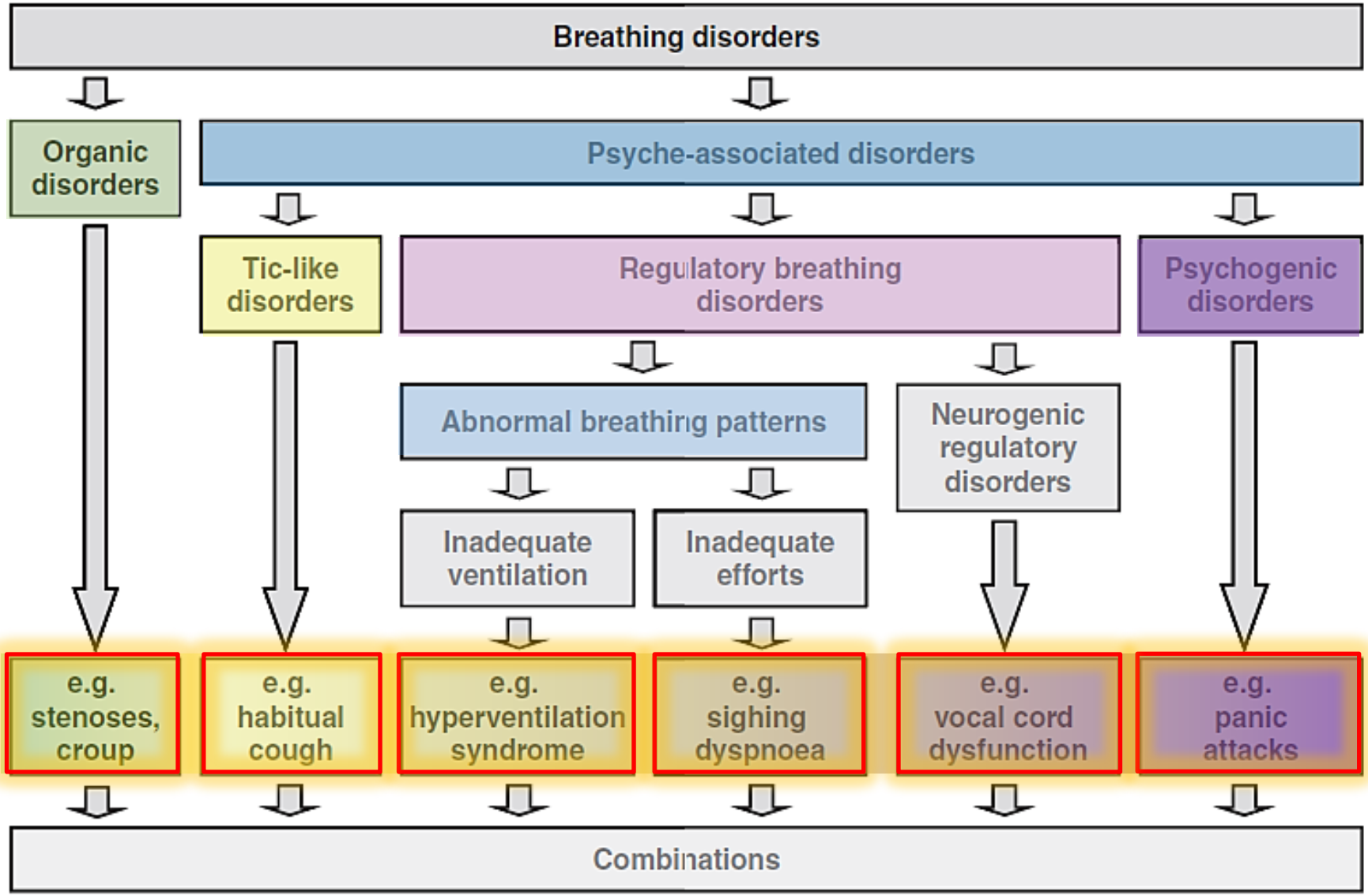


Factors contributing to child and adolescent vulnerability during the covid-19 pandemic.

thebmj

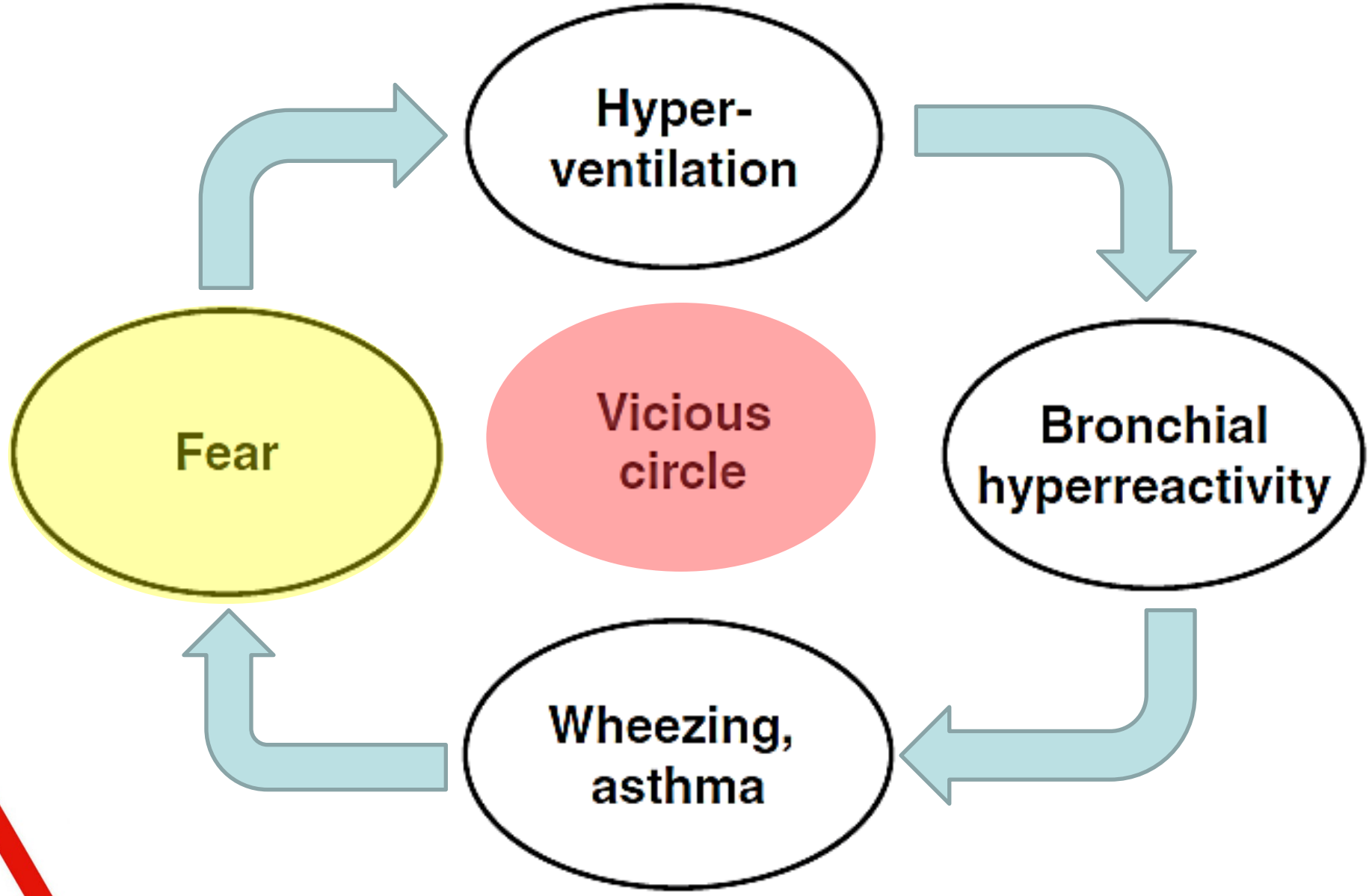
Elizabeth A Rider et al. BMJ 2021;374:bmj.n1730

Disturbi di origine psicogena o funzionale



Niggemann B. Pediatr Allergy Immunol 2010: 21: 895–899.

Diagnosi differenziale: disturbi di origine psicogena o funzionale



Niggemann B. Pediatr Allergy Immunol 2010: 21: 895–899.

Ah, l’adolescente…!

SALBUTAMOLO PER AEROSOL
IMPORTANZA DELLA NEBULIZZAZIONE CONTINUA DI ALTE DOSI

Continua →

0.05 mg/kg ogni 20' > > 0.15 mg/kg/ora

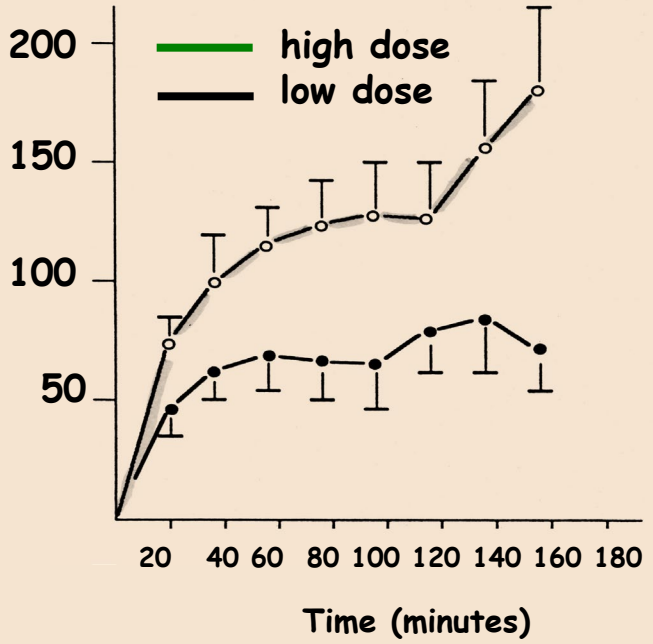
Robertson J. Pediat. 1985; 106: 672

0.15 mg/kg ogni 20' > > 0.05 mg/kg ogni 20' per 2 ore

Schuh Pediatrics 1989; 83: 513

nebulizzazione continua di 0.3 mg/kg/ora > > 0.3 mg/kg/ in 20'

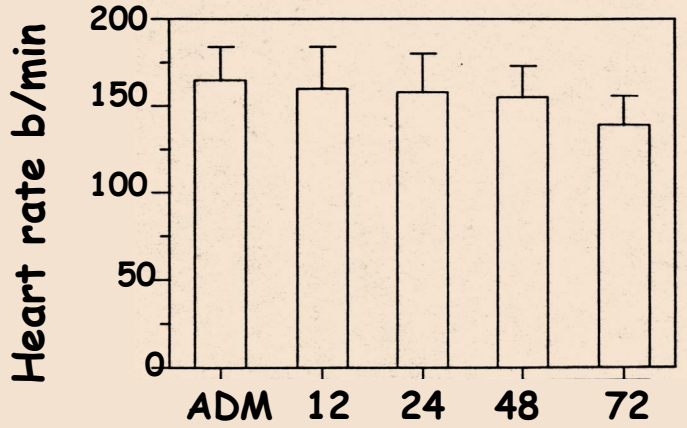
Papo Crit. Care Med. 1993; 21: 1479



Mean percentage of improvement of forced expiratory volume in 1 second from baseline in high-compared with loy-dose groups

ALB

SALBUTAMOLO PER AEROSOL
IMPORTANZA DELLA NEBULIZZAZIONE CONTINUA DI ALTE DOSI



Heart rates during continuous nebulization of albuterol.
ADM, admission

10 - 20 mg/ora

Craig Ped. Emerg. Care. 1996; 12: 1

Dose iniziale raccomandata

- 0.15 mg/Kg (0.03 ml)
- minimo 2.5 mg (0.5 ml)
- massimo 5.0 mg (1 ml)
- al di sotto dei 6 mesi 1.25 mg se tachicardia inaccettabile (> 200) da eseguire se necessario ogni 20'

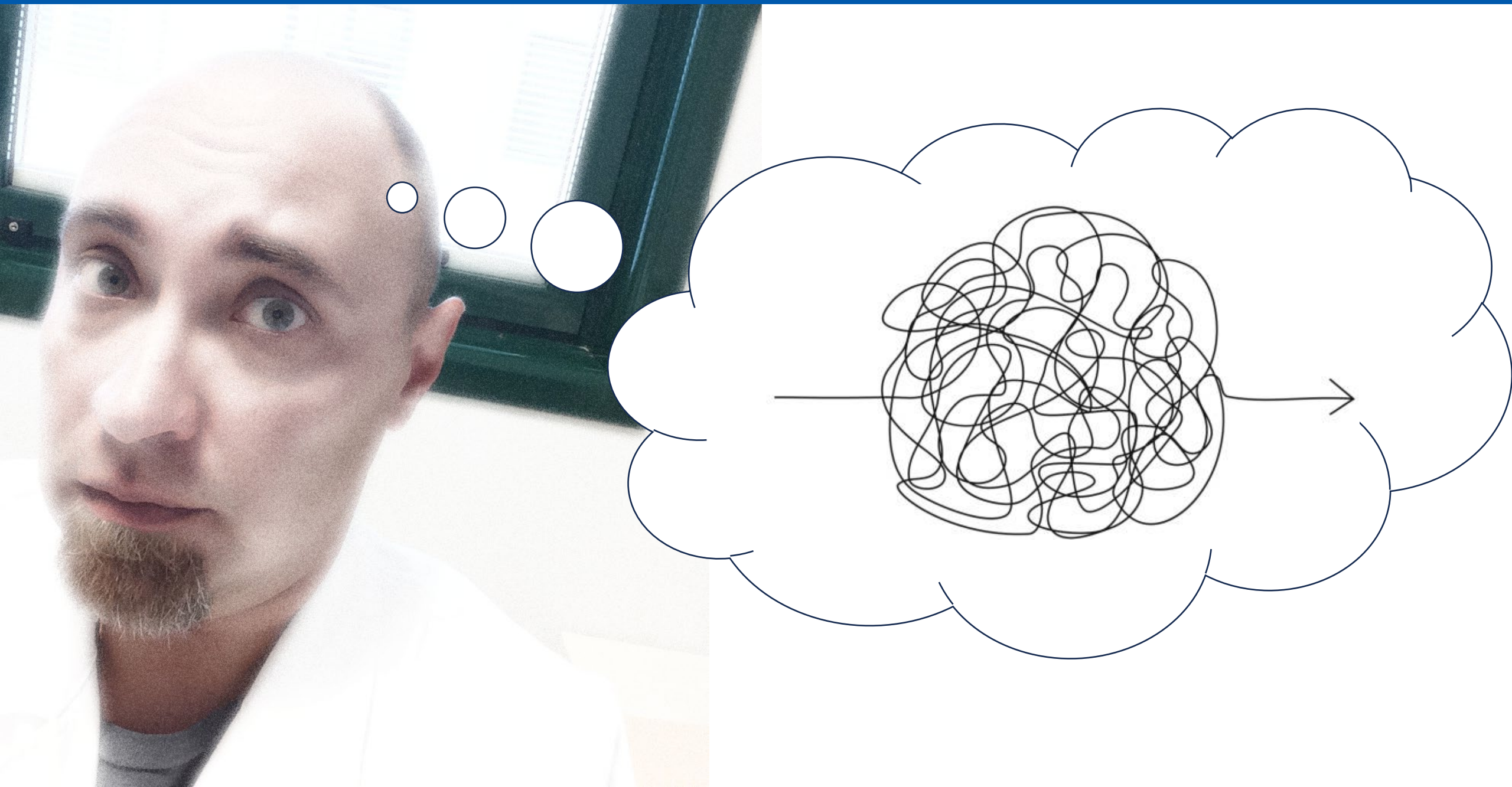
0.5 mg/kg ogni 20 - 30' per 24 ore sono sicuri

Katz Pediatrics 1993; 92: 666

Segue →

ALB

MART… Mumble… Mumble…



MART… Mumble… Mumble…

- Sarà davvero capace di **decidere quando** fare la terapia (AIR-only / MART)?
- Dopo anni passati a convincere genitori e pazienti della sicurezza del salbutamolo spray… **chissà quante inalazioni farà**?
- Massimo 12 dosi al giorno… il **sovradosaggio** è dietro l'angolo!
- Certo che passare alle **polveri** (i preparati disponibili sono quasi tutti polveri secche) dopo anni di spray/distanziatore… mi convince poco!

MART… Mumble… Mumble…

- Ma tutte queste **opzioni (track) alternative** non creeranno un po' di **confusione**?
- I **pediatri di famiglia** si districheranno fra i **diversi schemi terapeutici** ed i **diversi ruoli degli stessi farmaci**?
- L'**AIR-only** e la **MART** sono davvero **l'unico modo di evitare l'abuso di SABA e lo scarso impiego di ICS**?
- Stiamo scegliendo **«il meno peggio»**?

GINA 2024: Le novità terapeutiche nell'adolescente

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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

SPECIALIST CARE; SEVERE ASTHMA CLINIC IF AVAILABLE

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

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

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**

7 Consider ***other*** treatments

* *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

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:

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

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

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- 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

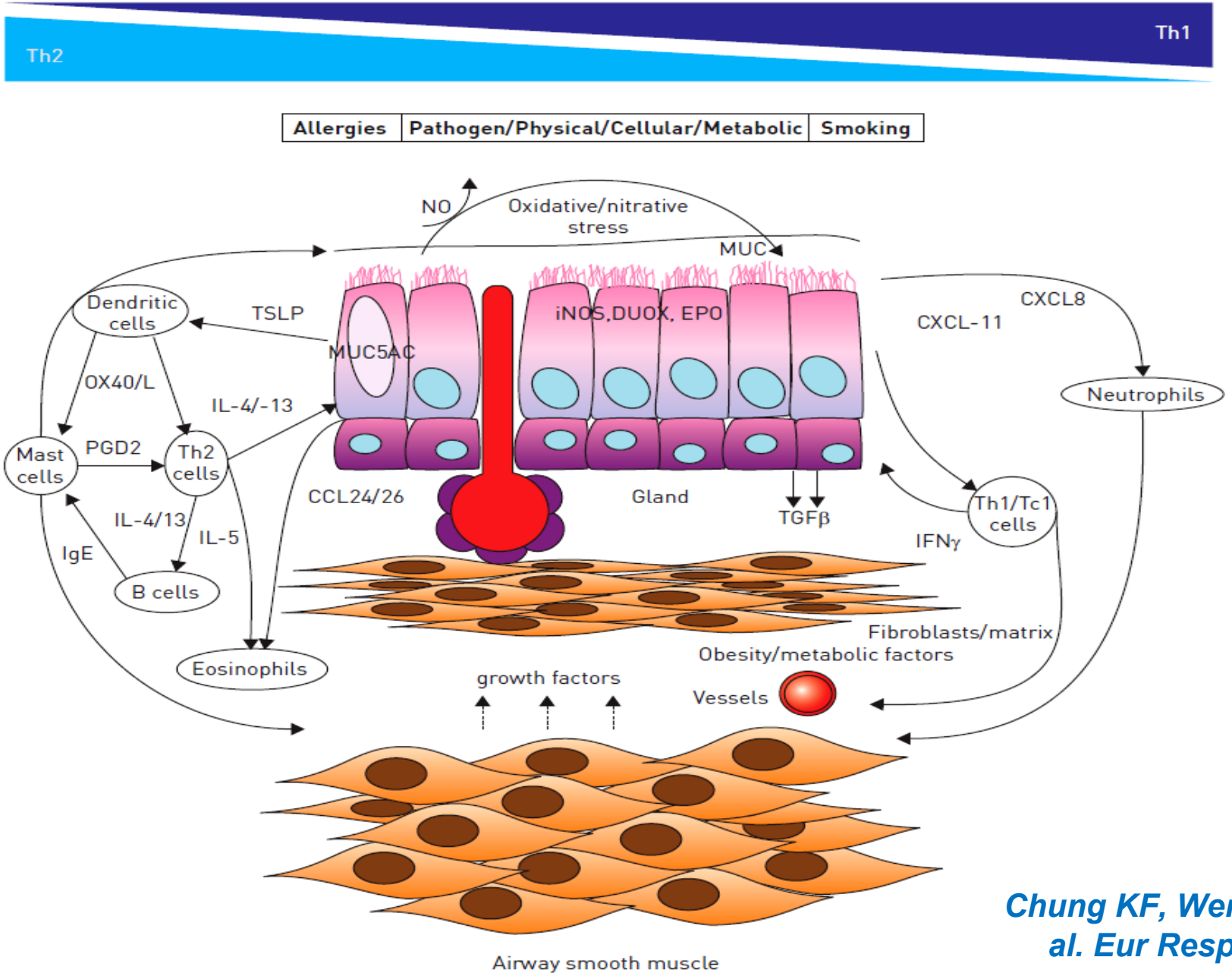
yes

- 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*

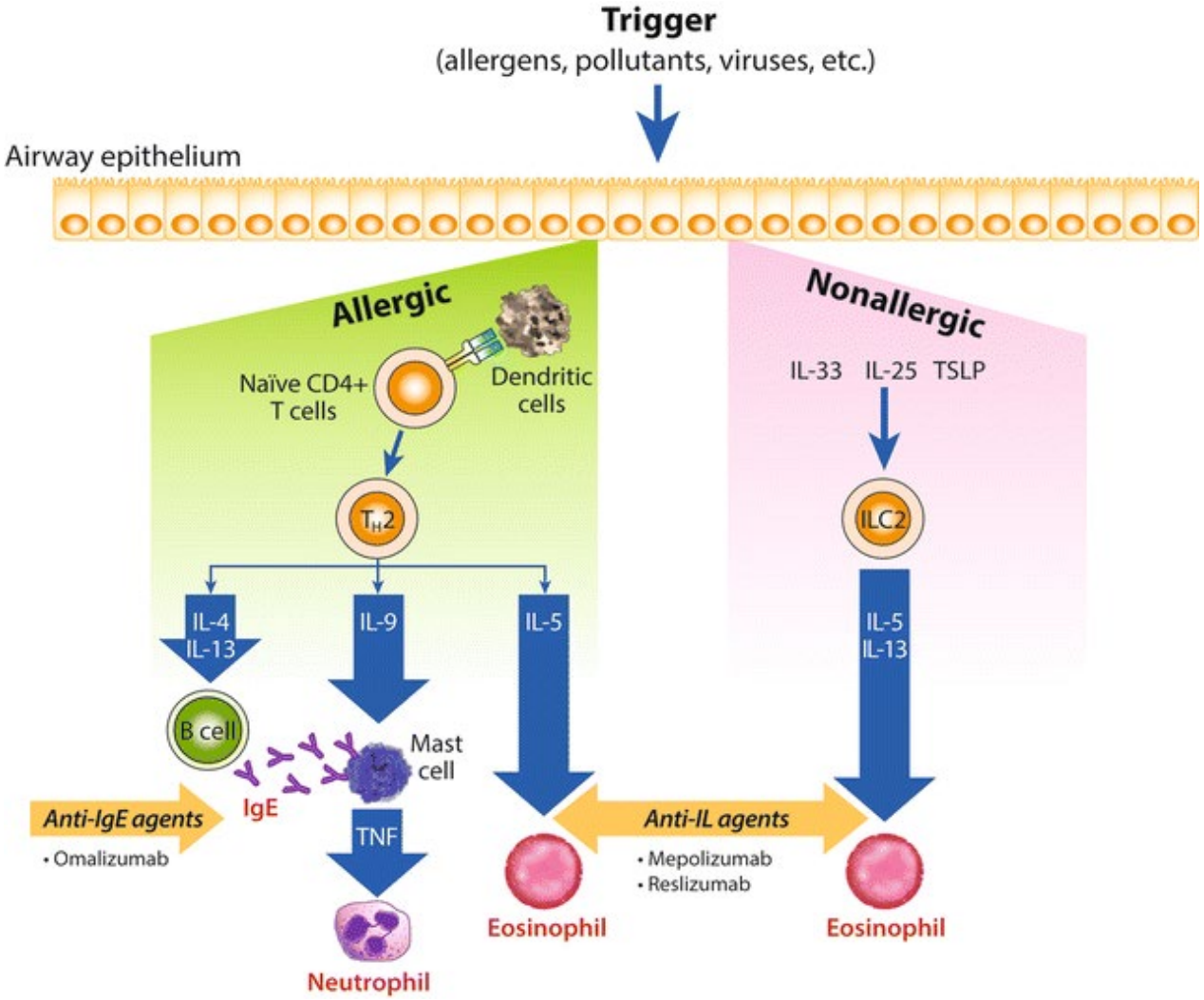
“Le diverse flogosi”



Chung KF, Wenzel SE, Brozek JL et al. Eur Respir J. 2014; 43: 343-73

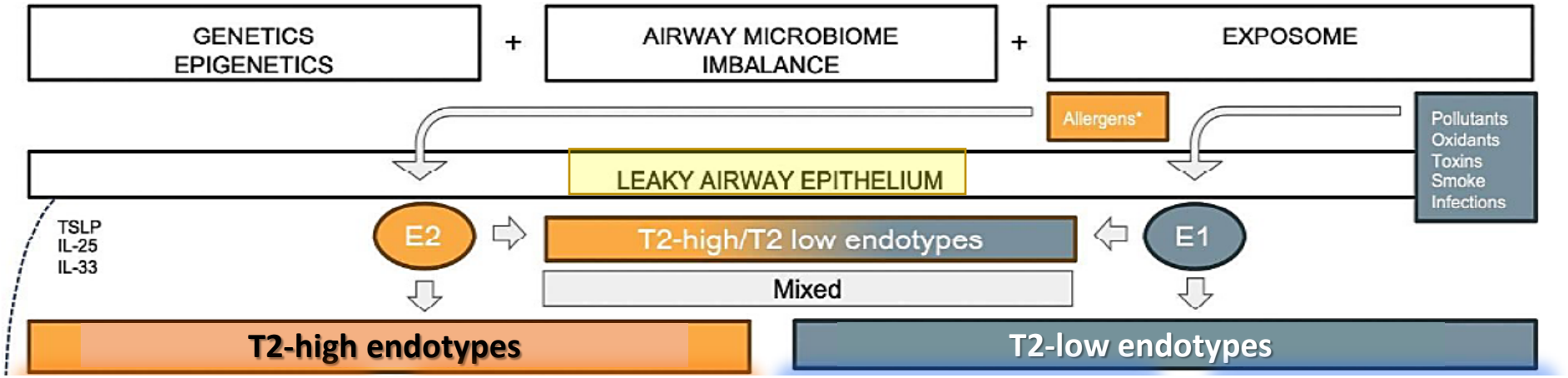
Gli endotipi dell'asma

Asthma phenotyping recently evolved to the **concept of endotypes**, relying on identified/suspected pathobiological mechanisms to phenotype patients.



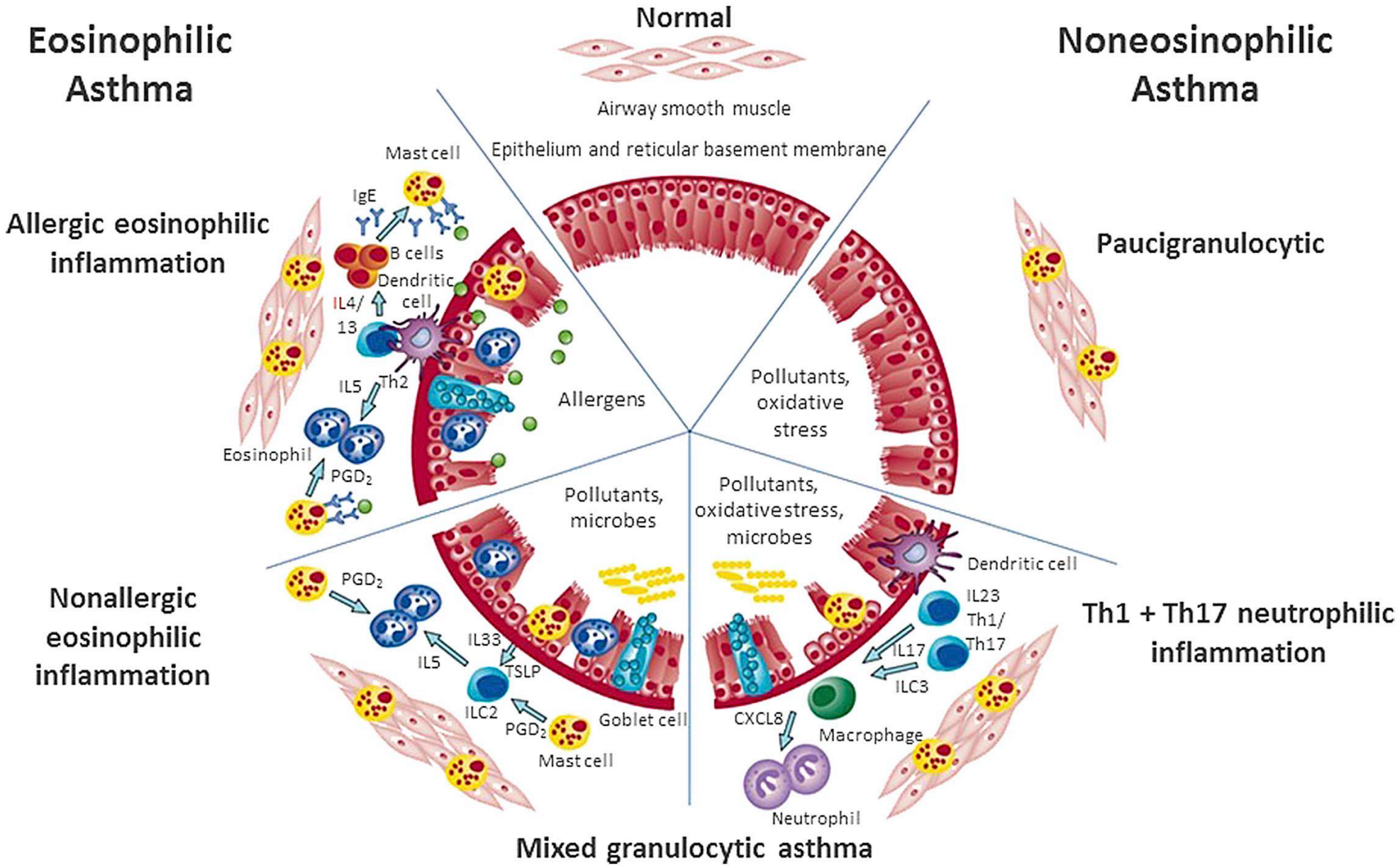
Kim H et al. Asthma biomarkers in the age of biologics. Allergy Asthma Clin Immunol. 2017; 13: 4
Kuruvilla ME et al. Understanding Asthma Phenotypes, Endotypes, and Mechanisms of Disease. Clin Rev Allergy Immunol. 2019; 56: 219-33

Gli endotipi dell'asma



Andrenacci B et al. Severe pediatric asthma endotypes: current limits and future perspectives. Expert Rev Respir Med. 2023; 17: 675-690

Gli endotipi dell'asma



W.W. Busse - Allergology International 68 (2019) 158e166

«Magic Arsenal»

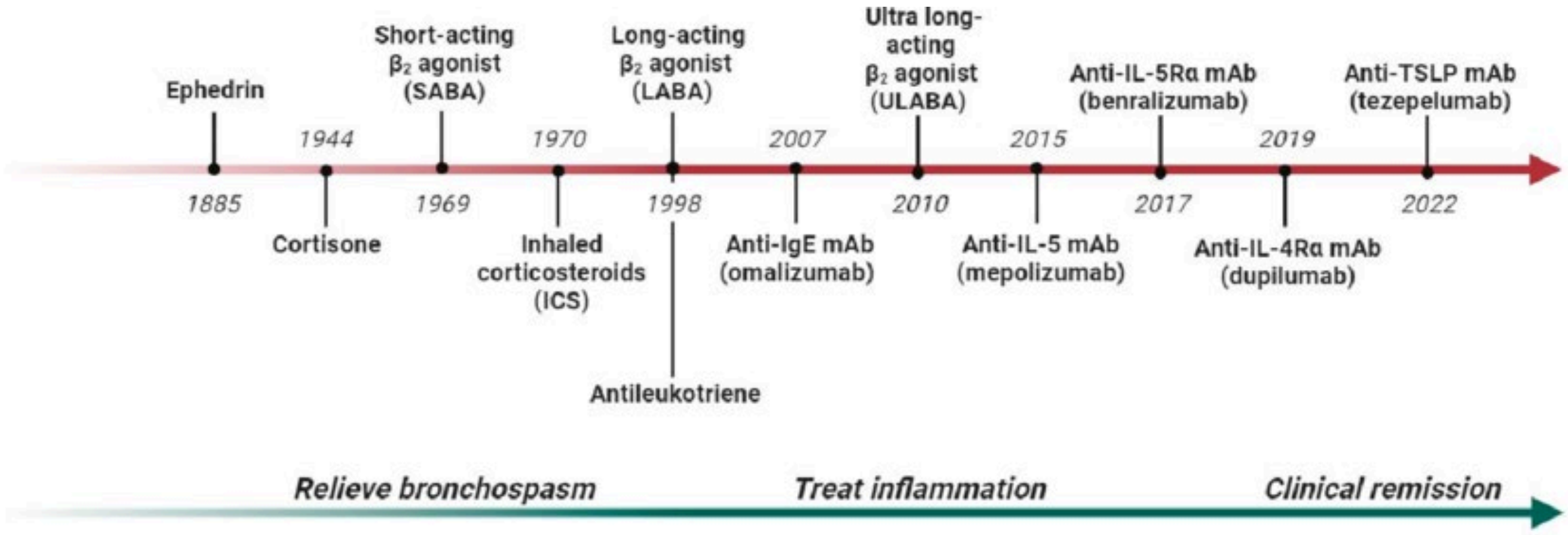
Allergy 2007: 62: 605–610

DOI: 10.1111/j.1398-9995.2007.01390.x

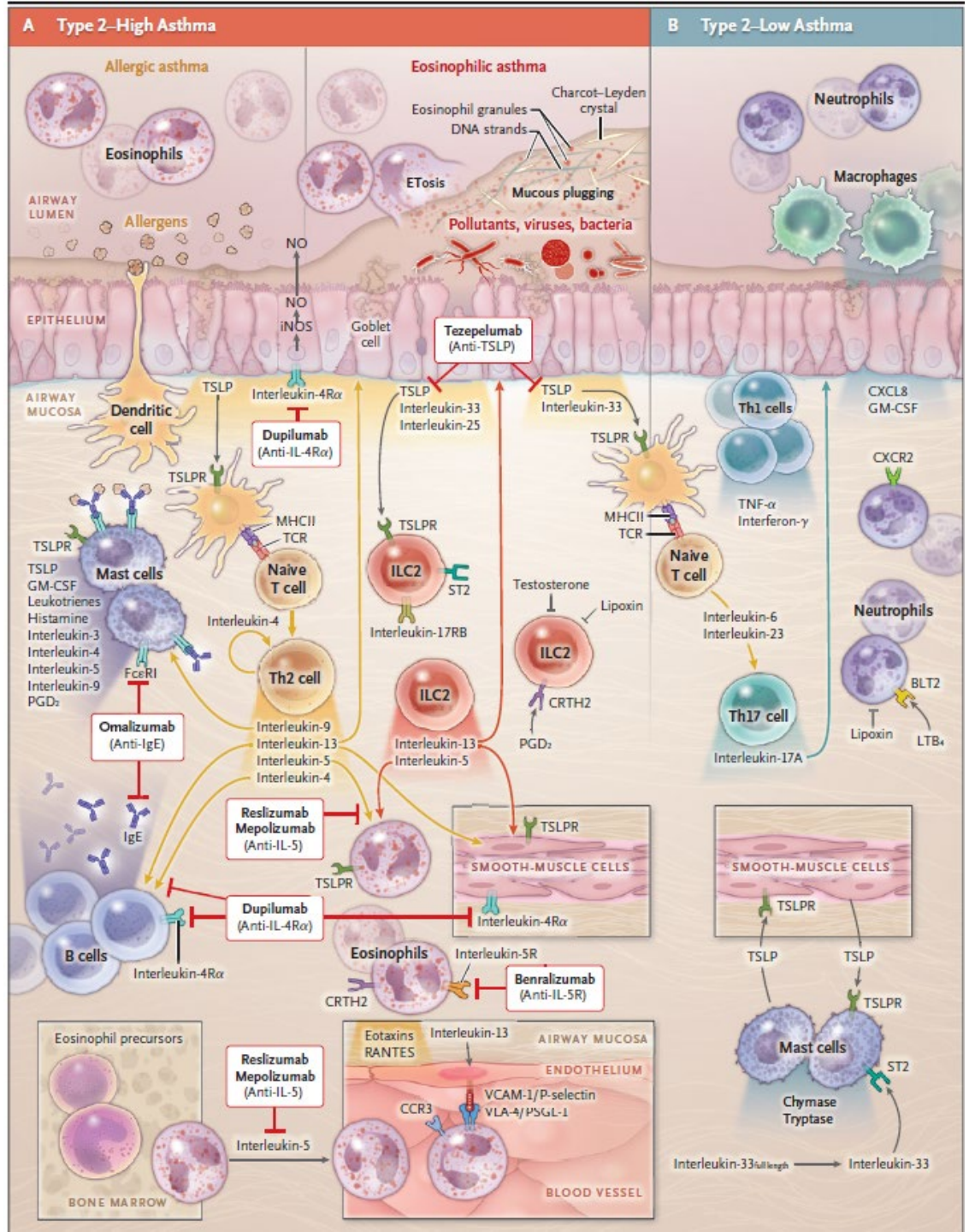
Review article

Asthma treatment: 'magic bullets which seek their own targets'

F. Tarantini, I. Baiardini, G. Passalacqua, F. Braido, G. W. Canonica
Allergy & Respiratory Diseases, DIMI – University of Genoa, Genova, Italy

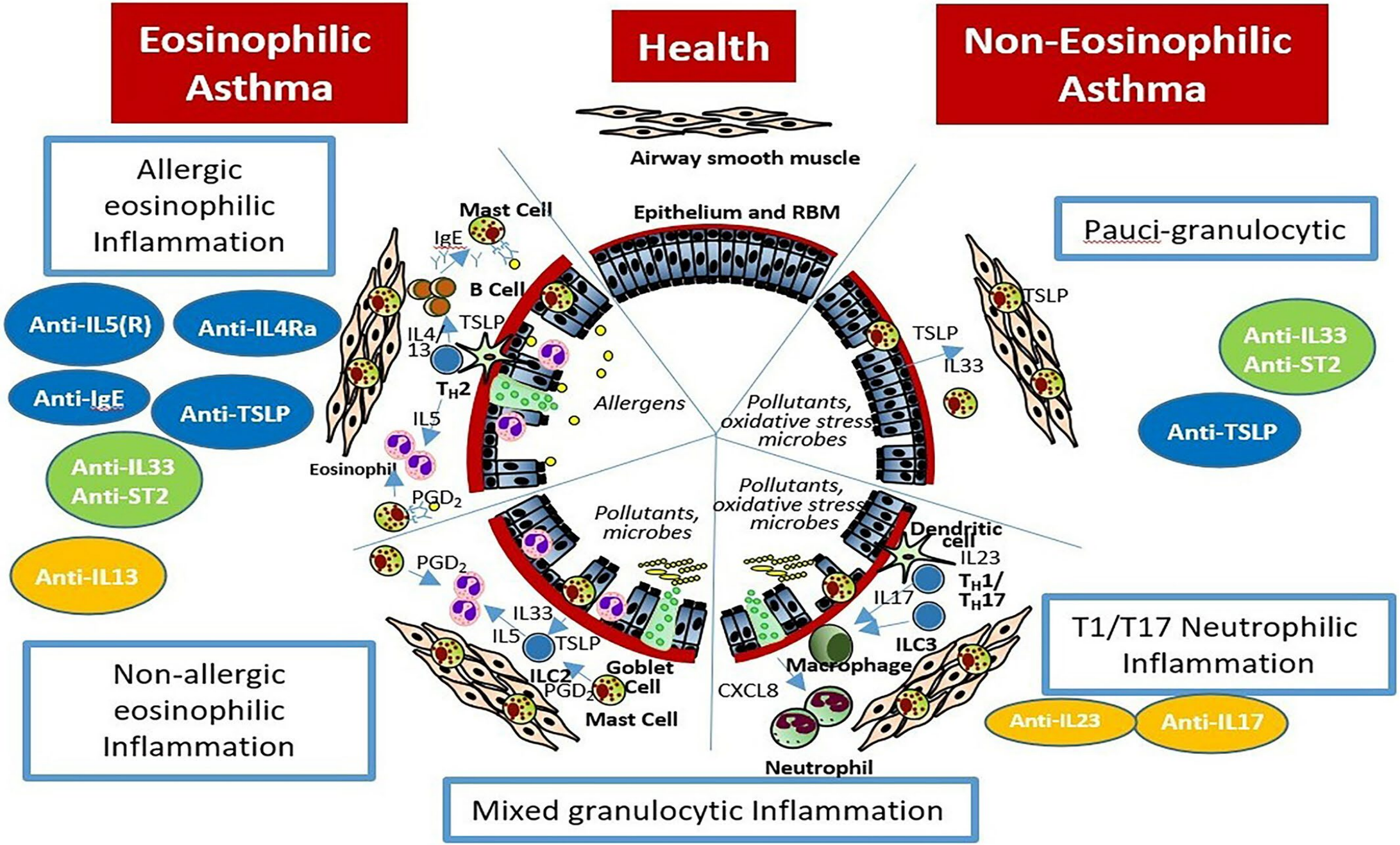


Nolasco S. J. Pers. Med. 2023, 13, 1459.



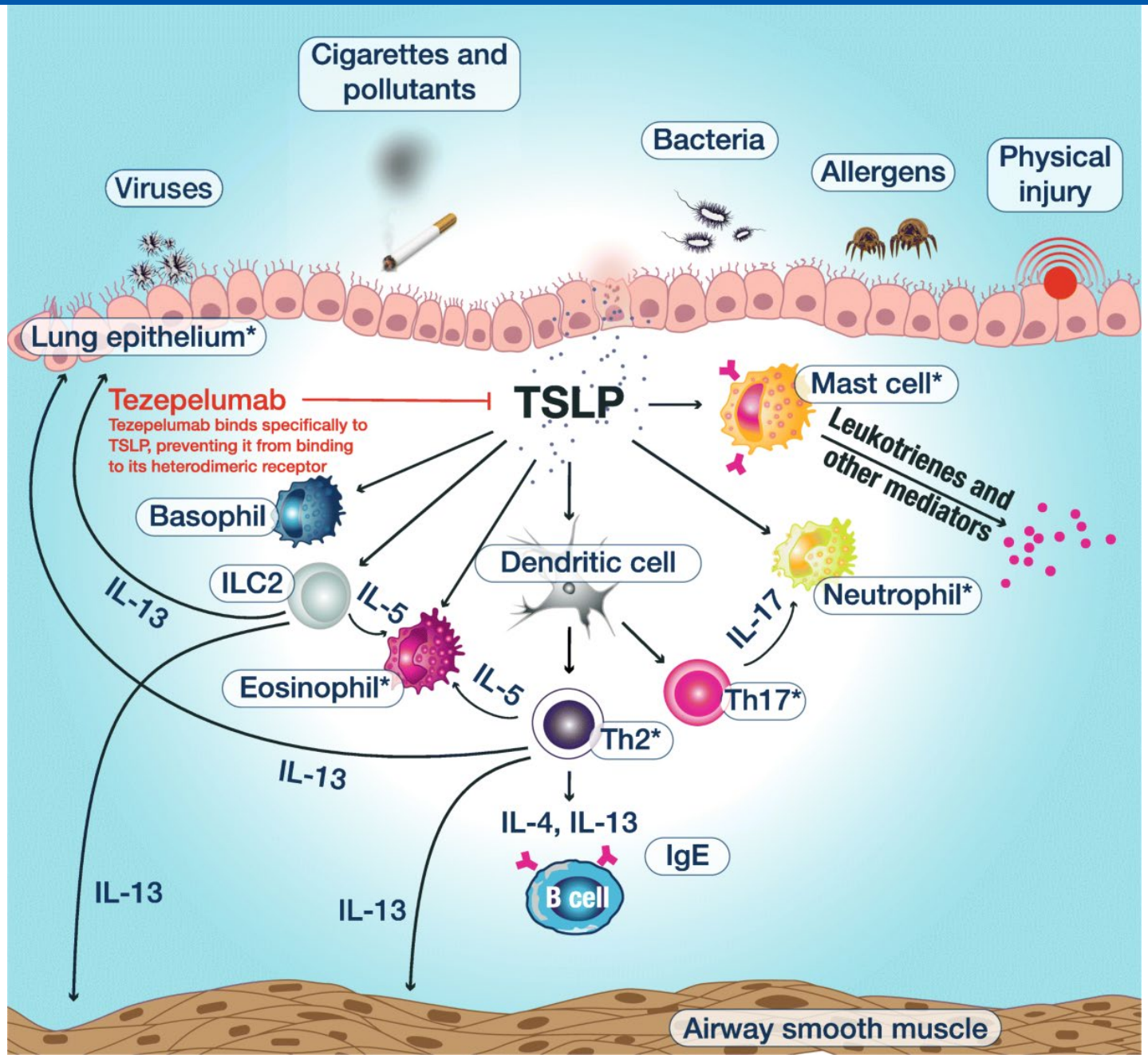
Brusselle G et al.

N Engl J Med 2022;386:157-71.



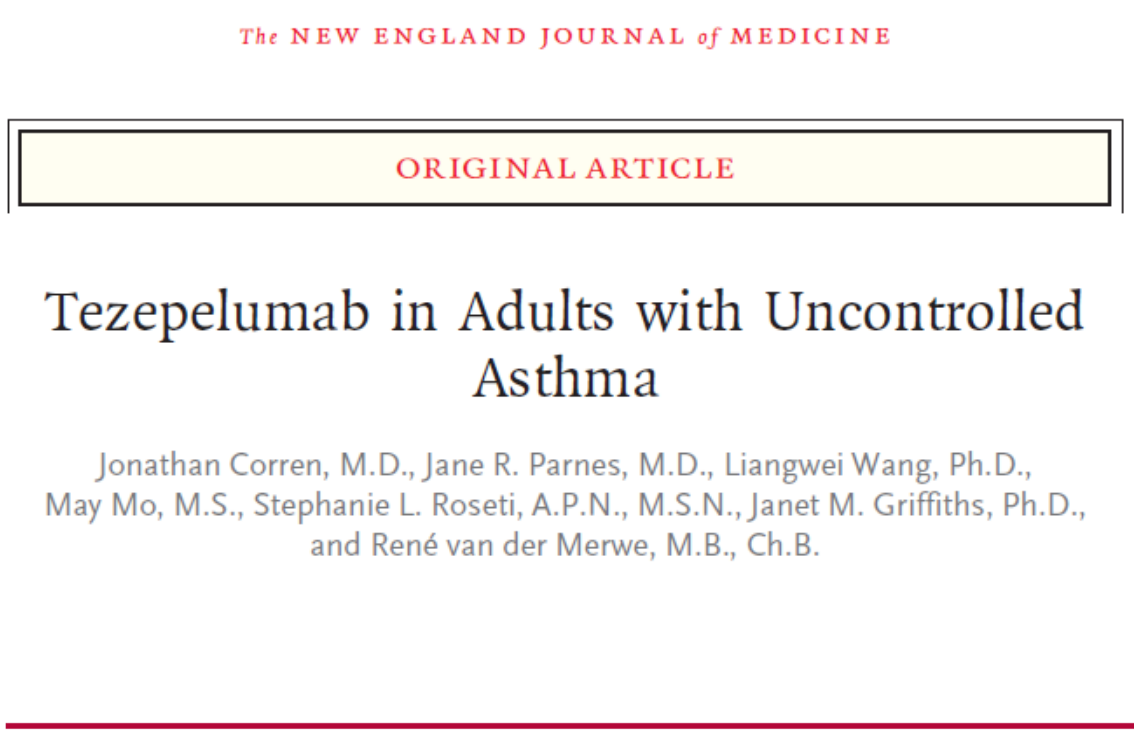
Respirology, Volume: 28, Issue: 8, Pages: 709-721, First published: 24 May 2023, DOI: (10.1111/resp.14520)

Tezepelumab



Emson et al. Respiratory Research, 2020; 21: 265

Tezepelumab


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tezepelumab in Adults with Uncontrolled Asthma

Jonathan Corren, M.D., Jane R. Parnes, M.D., Liangwei Wang, Ph.D., May Mo, M.S., Stephanie L. Roseti, A.P.N., M.S.N., Janet M. Griffiths, Ph.D., and René van der Merwe, M.B., Ch.B.

Among patients treated with long-acting beta-agonists and medium-to-high doses of inhaled glucocorticoids, those **who received tezepelumab** **had lower rates of clinically significant asthma exacerbations** than those who received placebo, **independent of baseline blood eosinophil counts** (**PATHWAY**).

N Engl J Med 2017; 377:936-46


Effect of tezepelumab on airway inflammatory cells, remodelling, and hyperresponsiveness in patients with moderate-to-severe uncontrolled asthma (CASCADE): a double-blind, randomised, placebo-controlled, phase 2 trial

Sarah Diver, Latifa Khalfaoui*, Claire Emson*, Sally E Wenzel, Andrew Menzies-Gow, Michael E Wechsler, James Johnston, Nestor Molfino, Jane R Parnes, Ayman Megally, Gene Colice†, Christopher E Brightling†*

The improvements in asthma clinical outcomes observed in previous studies with tezepelumab are probably driven, at least in part, by reductions in eosinophilic airway inflammation, as shown here by reduced airway eosinophil counts regardless of baseline blood eosinophil count. **Tezepelumab also** **reduced airway hyperresponsiveness** to mannitol, indicating that **TSLP blockade might have additional benefits in asthma beyond reducing type 2 airway inflammation** (**CASCADE**).

Lancet Respir Med 2021; 9:1299-1312

Tezepelumab

The NEW ENGLAND JOURNAL of MEDICINE

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Tezepelumab (N=528)	Placebo (N=531)	Total (N=1059)
Age — yr	49.9±16.3	49.0±15.9	49.5±16.1
Male sex — no. (%)	193 (36.6)	194 (36.5)	387 (36.5)
White race — no. (%)†	332 (62.9)	327 (61.6)	659 (62.2)
Body-mass index‡	28.7±7.1	28.3±6.9	28.5±7.0

Åsa Hellqvist, M.Sc., Karin Bowen, M.Sc., Primal Kaur, M.D.,
Gun Almqvist, M.Sc., Sandhia Ponnarambil, M.D., and Gene Colice, M.D.

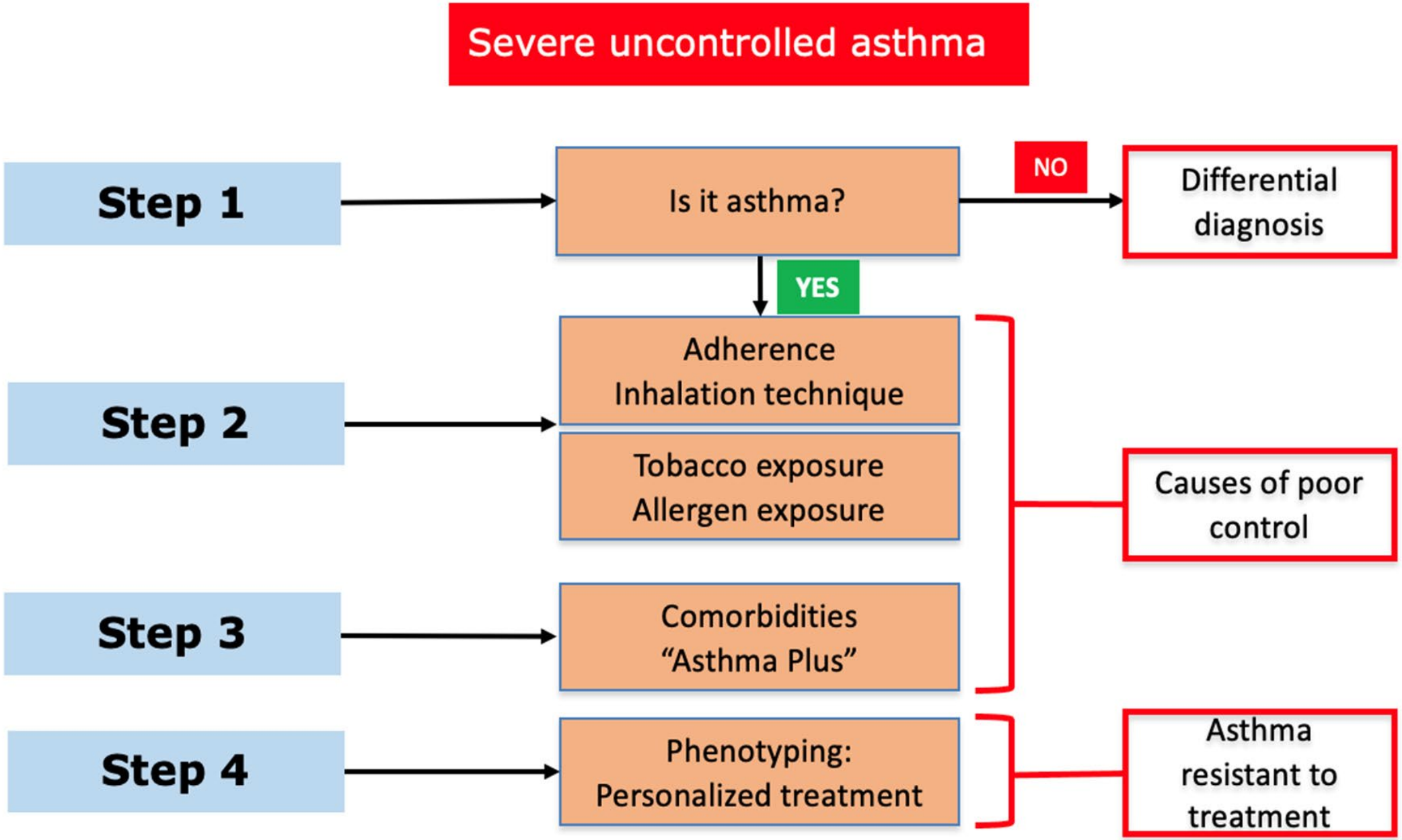
controlled asthma who
ad **fewer exacerbations** and
hma control, and **health-**
an those who received placebo

N Engl J Med 2021; 384:1800-9

Tezepelumab treatment was **well tolerated for up to 2**
stained, clinically meaningful
acerbations in individuals with
hma. These findings are
s randomised, placebo-
how **the long-term safety and**
epelumab in individuals with
hma (**DESTINATION**).

	NAVIGATOR randomised tezepelumab (n=528)	NAVIGATOR randomised placebo (n=531)	SOURCE randomised tezepelumab (n=74)	SOURCE randomised placebo (n=76)
Age, years	49·9 (16·3)	49·0 (15·9)	53·5 (12·1)	53·4 (11·9
Sex				
Female	335 (63%)	337 (63%)	49 (66%)	45 (59%)
Male	193 (37%)	194 (37%)	25 (34%)	31 (41%)

Lancet Respir Med. 2023; 11:425-43



Sardon-Prado, O. et al. J. Clin. Med. 2023, 12, 5846

«Profiling»

Clinica

IgE

FeNO

Eosinofili

Comorbidità

I biomarcatori dell'asma

Biomarker	*Sample type*	*Associated asthma endotype*	*Proposed use*
Eosinophil	Serum, sputum	T2-high	Disease phenotyping Severity of clinical symptoms Monitoring of asthma control Prediction of treatment response
Neutrophil	Sputum	T2-high/T2-low	Disease phenotyping Under investigation
IgE	Serum	T2-high	Disease phenotyping Severity of clinical symptoms
Periostin	Serum	T2-high	Disease phenotyping Severity of clinical symptoms Diagnosis Prediction of treatment response
FeNO	Exhaled air	T2-high	Disease phenotyping Severity of clinical symptoms Monitoring of asthma control
IL-17	Serum	T2-low	Disease phenotyping
EBC	Exhaled air	Not yet determined	Under investigation
VOCs	Exhaled air	Not yet determined	Under investigation

EBC, exhaled breath condensate; FeNO, fractional exhaled nitric oxide; IgE, immunoglobulin E; IL, interleukin; T2, type 2; VOCs, volatile organic compounds.

Licari A et al. ***Asthma Endotyping and Biomarkers in Childhood Asthma.*** *Pediatr Allergy Immunol Pulmonol. 2018; 31: 44-5.*

Name	Target	Mechanism of Action	Authorized (Age)		Indication	Dosage S.Q.	Comorbidities Treatable	Predictors Response	Clinical Outcomes					Adverse Effects
			F						E	C	P.F.	QoL	OCS	
OMALIZUMAB	IgE	E binding eptor binding t cells, basophils, plasmacytoid cells; dritic plasmacytoid ree IgE and downregulation of ession.	≥		Uncontrolled allergic SA with sensitization to perennial pneumoallergens and in range according to weight and IgE.	nd total IgE: 5 mg 300 mg. 0 mg 00 mg/2–4 w. inge. nistration.	Idiopathic chronic urticaria. Nasal polyposis.	Eos ≥ 260/µL FeNO > 20 ppb	↓	↑	=↑	↑	↓	Local reaction. Headache. Fever (6–12 years). Anaphylaxis (very rare).
MEPOLIZUMAB	IL-5	-5 binding prevents α-receptor.	≥6	≥6	SA uncontrolled and Eos ≥ 150/µL or ≥300/µL in the last year.	6–11 y: 40 mg. ≥12 y: 100 mg/4 w. Prefilled syringe or autoinjector (pen). Home administration.	Nasal polyposis. EGPA. HES.	↑ Eos ↑ E Nasal polyposis OCS	↓	↑	↑	↑	↓	Local reaction. Headache. Nasal congestion. Anaphylaxis (very rare).
BENRALIZUMAB	IL-5Rα	Binding to IL-5Rα Rapid apoptosis of Eos by cytotoxicity mechanism.	≥12	No	SA uncontrolled and Eos ≥ 150/µL or ≥300/µL in the last year.	30 mg/8 w (first 3 doses every four w). Prefilled syringe or autoinjector (pen). Home administration.		↑ Eos ↑ E Nasal polyposis OCS ↓ PF	↓	↑	↑	↑	↓	Local reaction. Headache. Pharyngitis. Anaphylaxis (very rare).
DUPILUMAB	IL-4Rα	locking hway sation	≥6	≥12	SA uncontrolled and Eos ≥ 150/µL and ≤1500/µL and/or FeNO ≥ 25 ppb and/or need for OCS.	FDA: 6–11 y ≤ 30 kg:100 mg/2 w or 300 mg/4 w. 6–11 y > 30 kg: 200 mg/2 w or 300 mg/4 w. FDA and EMA ≥ 12 y: 200 mg/2 w (first dose 400 mg). Prefilled syringe or autoinjector (pen). Home administration.	AD. Nasal polyposis. EEo.	↑ Eos ↑ FeNO	↓	↑	↑	↑	↓	Local reaction. Transient elevation of eosinophilia. EGPA (very rare). Anaphylaxis (very rare).
TEZEPELUMAB	TSLP	ting TSLP binding. s of the cade.	≥12	≥12	SA T2 or non-T2 with exacerbations.	210 mg/4 w. Prefilled syringe or autoinjector (pen).		↑ Eos ↑ FeNO T2 low	↓	↑	↑	↑	=	Local reaction. Pharyngitis. Arthralgias. Lumbar pain. Nasal congestion. Anaphylaxis (very rare).

IL-5Rα receptor α-subunit, IL-4Rα: IL-4 receptor α-subunit, SA: severe asthma, S.Q: subcutaneous, FDA: Food and Drug Administration, EMA: European Medicines Agency, EGPA: eosinophilic granulomatosis with polyangiitis, HES: hypereosinophilic syndrome, AD: atopic dermatitis, EEo: eosinophilic esophagitis, FeNO: fractional exhaled nitric oxide, ppb: parts per billion, Eos: peripheral blood eosinophils, OCS: oral corticosteroids, PF: pulmonary function, E: exacerbations, C: control, QoL: quality of life, w: week, y: year.

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Name	Target	Mechanism of Action	Authorized (Age) FDA	Authorized (Age) EMA	Indication	Dosage S.Q.	Comorbidities Treatable	Predictors Response	Clinical Outcomes E	C	P.F.	QoL	OCS	Adverse Effects
OMALIZUMAB	IgE	E binding eptor binding t cells, basophils, plasmacytoid cells; dritic plasmacytoid ree IgE and downregulation of ssion.	≥6	≥6	Uncontrolled allergic SA with sensitization to perennial pneumoallergens and in range according to weight and IgE.	By weight and total IgE: FDA: 75–375 mg IgE (KU/L): 6–11 y: 30–1300 mg. : 30–700 mg. EMA: 75–600 mg IgE (KU/L): ≥6 y: 30–1300 mg/2–4 w. ation.	Idiopathic chronic urticaria. Nasal polyposis.	Eos ≥ 260/µL FeNO > 20 ppb	↓	↑	=↑	↑	↓	Local reaction. Headache. Fever (6–12 years). Anaphylaxis (very rare).
MEPOLIZUMAB	IL-5	-5 binding prevents α-receptor.			SA uncontrolled and Eos ≥ 150/µL or ≥300/µL in the last year.	w. pen). ation.	Nasal polyposis. EGPA. HES.	↑ Eos ↑ E Nasal polyposis OCS	↓	↑	↑	↑	↓	Local reaction. Headache. Nasal congestion. Anaphylaxis (very rare).
BENRALIZUMAB	IL-5Rα	Binding to IL-5Rα Rapid apoptosis of Eos by cytotoxicity mechanism.	≥12	No	SA uncontrolled and Eos ≥ 150/µL or ≥300/µL in the last year.	30 mg/8 w (first 3 doses every four w). Prefilled syringe or autoinjector (pen). Home administration.		↑ Eos ↑ E Nasal polyposis OCS ↓ PF	↓	↑	↑	↑	↓	Local reaction. Headache. Pharyngitis. Anaphylaxis (very rare).
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TEZEPELUMAB	TSLP	ting TSLP binding. s of the cade.	≥12	≥12	SA T2 or non-T2 with exacerbations.	210 mg/4 w. Prefilled syringe or autoinjector (pen).		↑ Eos ↑ FeNO T2 low	↓	↑	↑	↑	=	Local reaction. Pharyngitis. Arthralgias. Lumbar pain. Nasal congestion. Anaphylaxis (very rare).

IL-5Rα receptor α-subunit, IL-4Rα: IL-4 receptor α-subunit, SA: severe asthma, S.Q: subcutaneous, FDA: Food and Drug Administration, EMA: European Medicines Agency, EGPA: eosinophilic granulomatosis with polyangiitis, HES: hypereosinophilic syndrome, AD: atopic dermatitis, EEo: eosinophilic esophagitis, FeNO: fractional exhaled nitric oxide, ppb: parts per billion, Eos: peripheral blood eosinophils, OCS: oral corticosteroids, PF: pulmonary function, E: exacerbations, C: control, QoL: quality of life, w: week, y: year.

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MEPOLIZUMAB	IL-5	-5 binding prevents α-receptor.	≥6	≥6	SA uncontrolled and Eos ≥ 150/µL or ≥300/µL in the last year.	6–11 y: 40 mg. ≥12 y: 100 mg/4 w. Prefilled syringe or autoinjector (pen). Home administration.	Nasal polyposis. EGPA. HES.	↑ Eos ↑ E Nasal polyposis OCS	↓	↑	↑	↑	↓	Local reaction. Headache. Nasal congestion. Anaphylaxis (very rare).
BENRALIZUMAB	IL-5Rα	Binding to IL-5Rα Rapid apoptosis of Eos by cytotoxicity mechanism.	≥12	No	SA uncontrolled and Eos ≥ 150/µL or ≥300/µL in the last year.	30 mg/8 w (first 3 doses every four w). Prefilled syringe or autoinjector (pen). Home administration.		↑ Eos ↑ E Nasal polyposis OCS ↓ PF	↓	↑	↑	↑	↓	Local reaction. Headache. Pharyngitis. Anaphylaxis (very rare).
DUPILUMAB	IL-4Rα	locking hway sation			SA uncontrolled and Eos ≥ 150/µL and ≤1500/µL and/or FeNO ≥ 25 ppb and/or need for OCS.	kg:100 mg/2 w 4 w. kg: 200 mg/2 w 4 w. MA ≥ 12 2 w 00 mg). ringe tor (pen). inistration.	AD. Nasal polyposis. EEo.	↑ Eos ↑ FeNO	↓	↑	↑	↑	↓	Local reaction. Transient elevation of eosinophilia. EGPA (very rare). Anaphylaxis (very rare).
TEZEPELUMAB	TSLP	ting TSLP binding. s of the cade.	≥12	≥12	SA T2 or non-T2 with exacerbations.	210 mg/4 w. Prefilled syringe or autoinjector (pen).		↑ Eos ↑ FeNO T2 low	↓	↑	↑	↑	=	Local reaction. Pharyngitis. Arthralgias. Lumbar pain. Nasal congestion. Anaphylaxis (very rare).

IL-5Rα receptor α-subunit, IL-4Rα: IL-4 receptor α-subunit, SA: severe asthma, S.Q: subcutaneous, FDA: Food and Drug Administration, EMA: European Medicines Agency, EGPA: eosinophilic granulomatosis with polyangiitis, HES: hypereosinophilic syndrome, AD: atopic dermatitis, EEo: eosinophilic esophagitis, FeNO: fractional exhaled nitric oxide, ppb: parts per billion, Eos: peripheral blood eosinophils, OCS: oral corticosteroids, PF: pulmonary function, E: exacerbations, C: control, QoL: quality of life, w: week, y: year.

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TEZEPELUMAB	TSLP	ating TSLP binding. s of the cade.			SA T2 or non-T2 with exacerbations. n).			↑ Eos ↑ FeNO T2 low	↓	↑	↑	↑	=	Local reaction. Pharyngitis. Arthralgias. Lumbar pain. Nasal congestion. Anaphylaxis (very rare).

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Sardon-Prado, O. et al. J. Clin. Med. 2023, 12, 5846

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MEPOLIZUMAB	IL-5	-5 binding prevents α-receptor.	≥6	≥6	SA uncontrolled and Eos ≥ 150/μL or ≥300/μL in the last year.	6–11 y: 40 mg. ≥12 y: 100 mg/4 w. Prefilled syringe or autoinjector (pen). Home administration.	Nasal polyposis. EGPA. HES.	↑ Eos ↑ E Nasal polyposis OCS	↓	↑	↑	↑	↓	Local reaction. Headache. Nasal congestion. Anaphylaxis (very rare).
BENRALIZUMAB	IL-5Rα	Binding to IL-5Rα Rapid apoptosis of Eos by cytotoxicity mechanism.	≥12	No	SA uncontrolled and Eos ≥ 150/μL or ≥300/μL in the last year.	30 mg/8 w (first 3 doses every four w). Prefilled syringe or autoinjector (pen). Home administration.		↑ Eos ↑ E Nasal polyposis OCS ↓ PF	↓	↑	↑	↑	↓	Local reaction. Headache. Pharyngitis. Anaphylaxis (very rare).
DUPILUMAB	IL-4Rα	locking hway sation	≥6	≥12	SA uncontrolled and Eos ≥ 150/μL and ≤1500/μL and/or FeNO ≥ 25 ppb and/or need for OCS.	FDA: 6–11 y ≤ 30 kg:100 mg/2 w or 300 mg/4 w. 6–11 y > 30 kg: 200 mg/2 w or 300 mg/4 w. FDA and EMA ≥ 12 y: 200 mg/2 w (first dose 400 mg). Prefilled syringe or autoinjector (pen). Home administration.	AD. Nasal polyposis. EEo.	↑ Eos ↑ FeNO	↓	↑	↑	↑	↓	Local reaction. Transient elevation of eosinophilia. EGPA (very rare). Anaphylaxis (very rare).
TEZEPELUMAB	TSLP	ating TSLP binding. s of the cade.	≥12	≥12	SA T2 or non-T2 with exacerbations.	210 mg/4 w. Prefilled syringe or autoinjector (pen).		↑ Eos ↑ FeNO T2 low	↓	↑	↑	↑	=	Local reaction. Pharyngitis. Arthralgias. Lumbar pain. Nasal congestion. Anaphylaxis (very rare).

IL-5Rα receptor α-subunit, IL-4Rα: IL-4 receptor α-subunit, SA: severe asthma, S.Q: subcutaneous, FDA: Food and Drug Administration, EMA: European Medicines Agency, EGPA: eosinophilic granulomatosis with polyangiitis, HES: hypereosinophilic syndrome, AD: atopic dermatitis, EEo: eosinophilic esophagitis, FeNO: fractional exhaled nitric oxide, ppb: parts per billion, Eos: peripheral blood eosinophils, OCS: oral corticosteroids, PF: pulmonary function, E: exacerbations, C: control, QoL: quality of life, w: week, y: year.

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BENRALIZUMAB	IL-5Rα	Binding to IL-5Rα Rapid apoptosis of Eos by cytotoxicity mechanism.	≥12	No	SA uncontrolled and Eos ≥ 150/µL or ≥300/µL in the last year.	30 mg/8 w (first 3 do every four w). Prefilled syringe or autoinjector (pen). Home administration.		↑ E Nasal polyposis OCS ↓ PF	↓	↑	↑	↑	↓	Local reaction. Headache. Pharyngitis. Anaphylaxis (very rare).
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↑ Eos
↑ E
Nasal polyposis
OCS

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↑ Eos
↑ FeNO
T2 low

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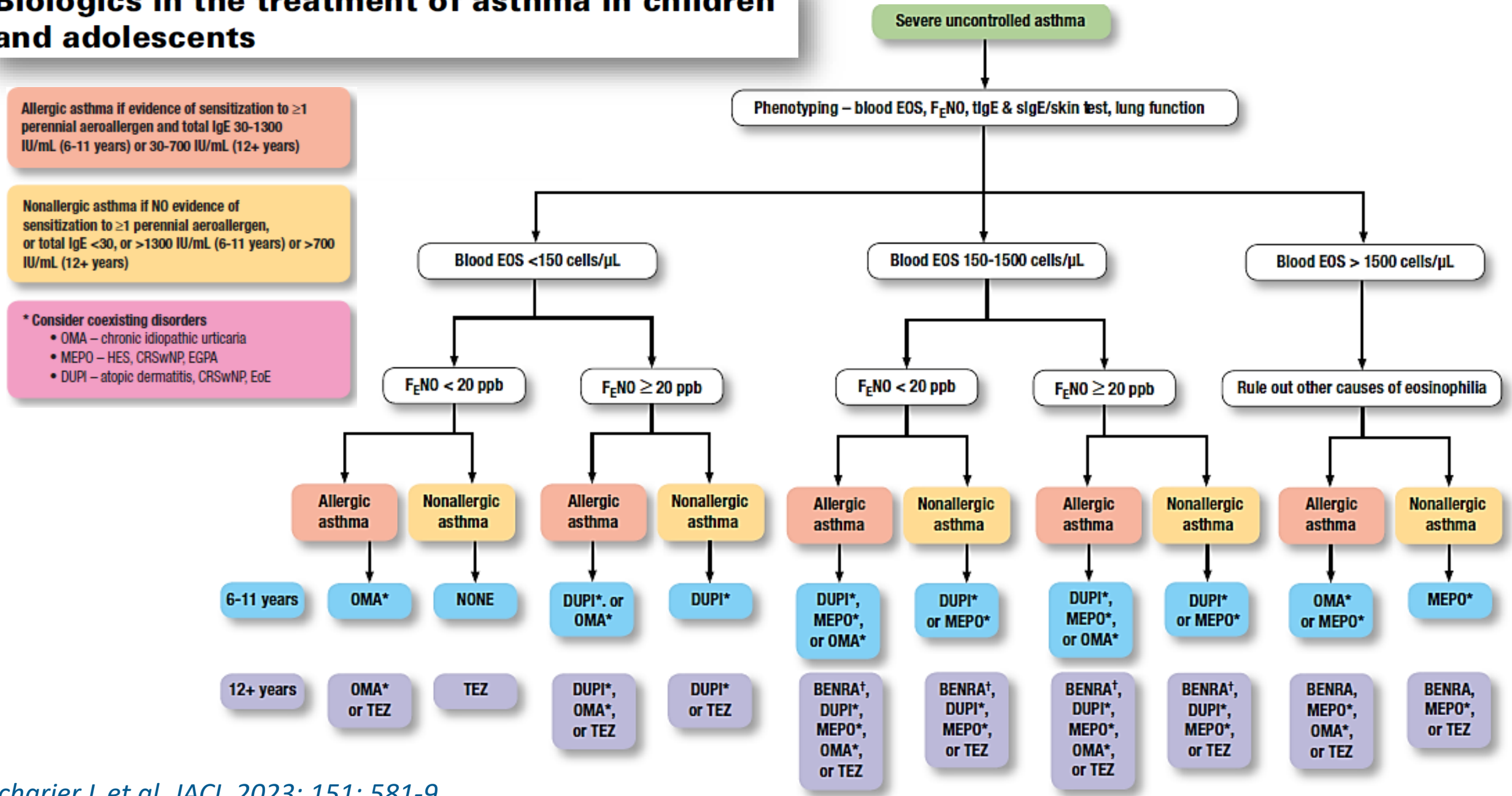
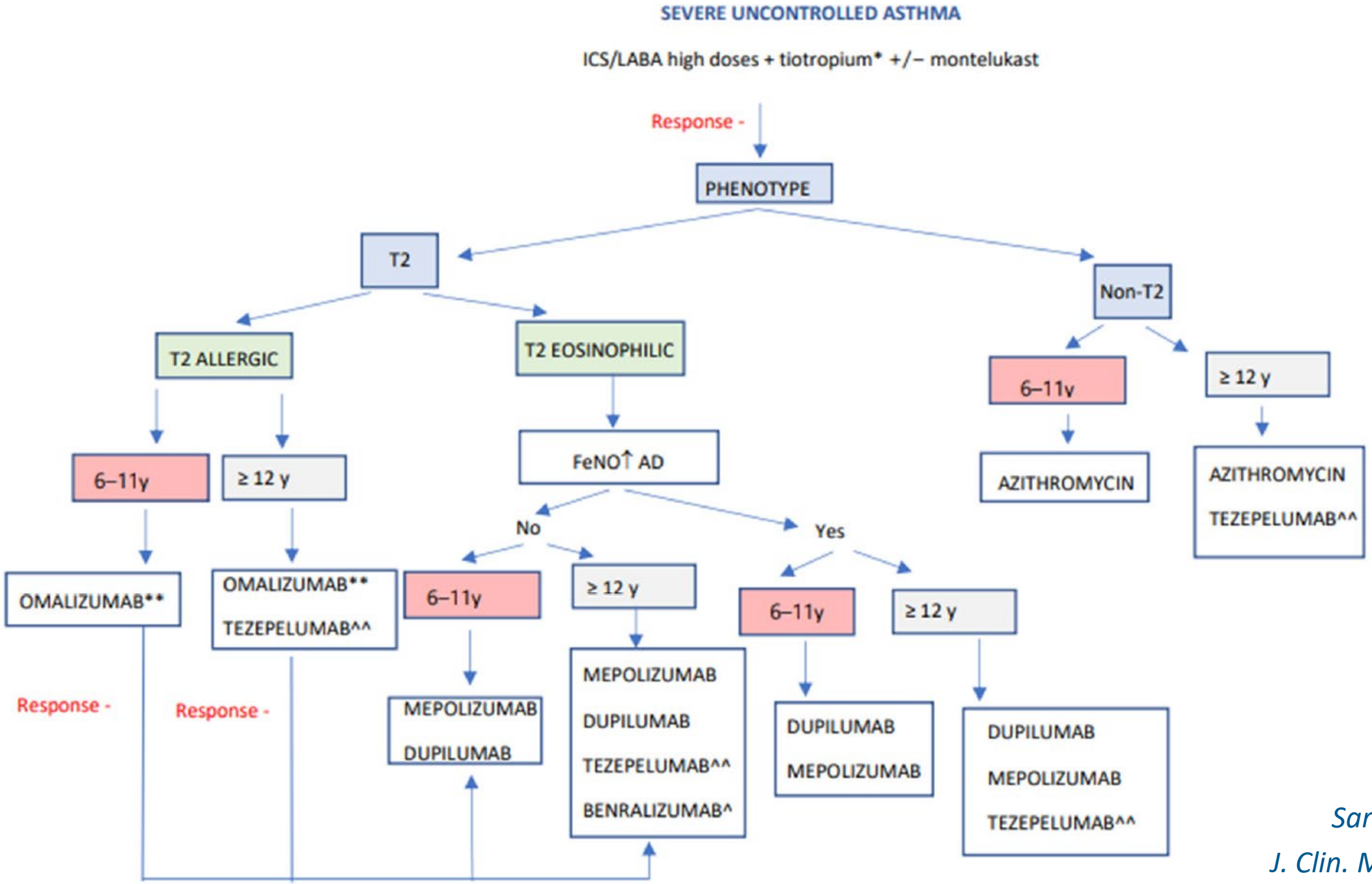
Biologics in the treatment of asthma in children and adolescents



Bacharier L et al. JACI. 2023; 151: 581-9



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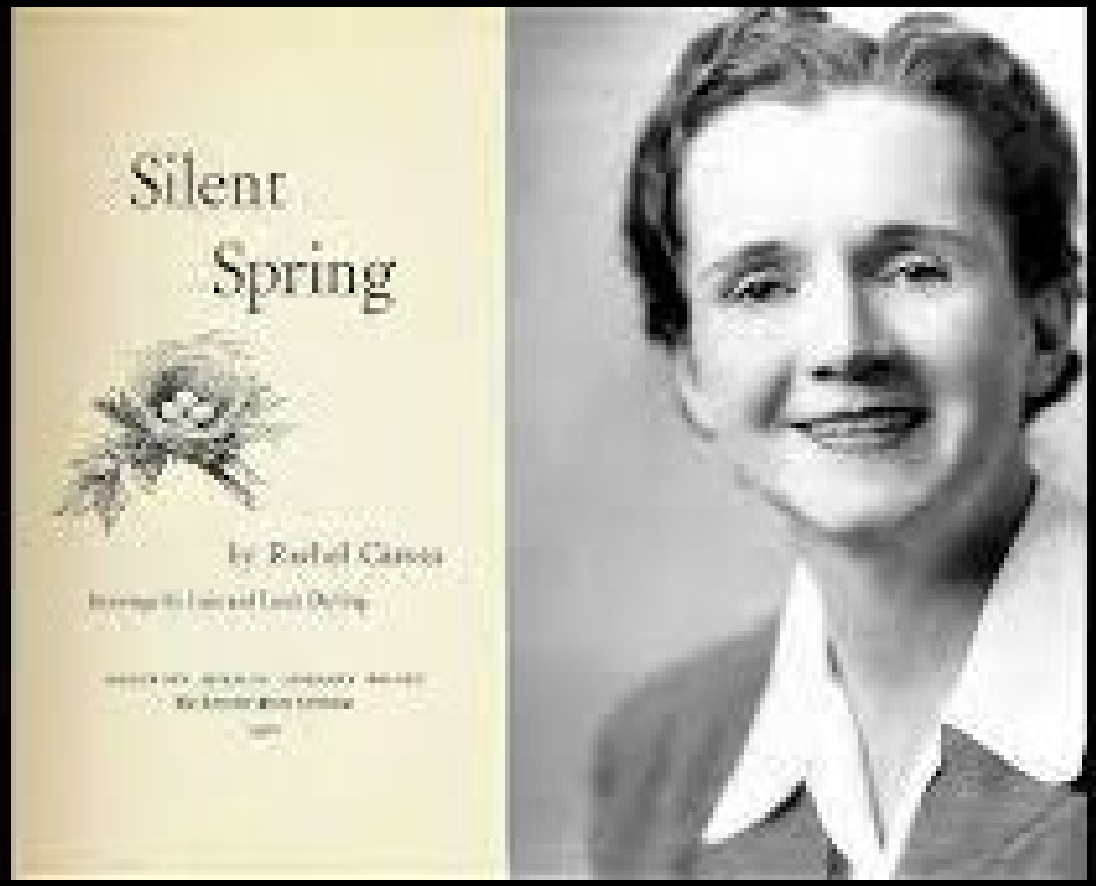
GINA 2024: Le novità terapeutiche nell'adolescente

- «SABA» (Short Acting Brain Activity): find the differences!
- Un passo indietro
- Ah, l'adolescente…! (quanti dubbi)
- La rivoluzione continua
- Conclusioni

Conclusioni

- E’ necessario evitare l’abuso del solo SABA
- Somministrare ICS ogni volta che si somministra un beta2 agonista
- Semplificare lo schema terapeutico è essenziale per aumentare l’aderenza alla terapia (specie nell’adolescente!)
- Con MART attenzione ai sovradosaggi
- Fornire tante alternative terapeutiche potrebbe risultare poco pratico (soprattutto per i medici!)
- Fondamentale selezionare correttamente il paziente e rivalutare periodicamente la terapia con i biologici nell’asma grave

Diversi silenzi



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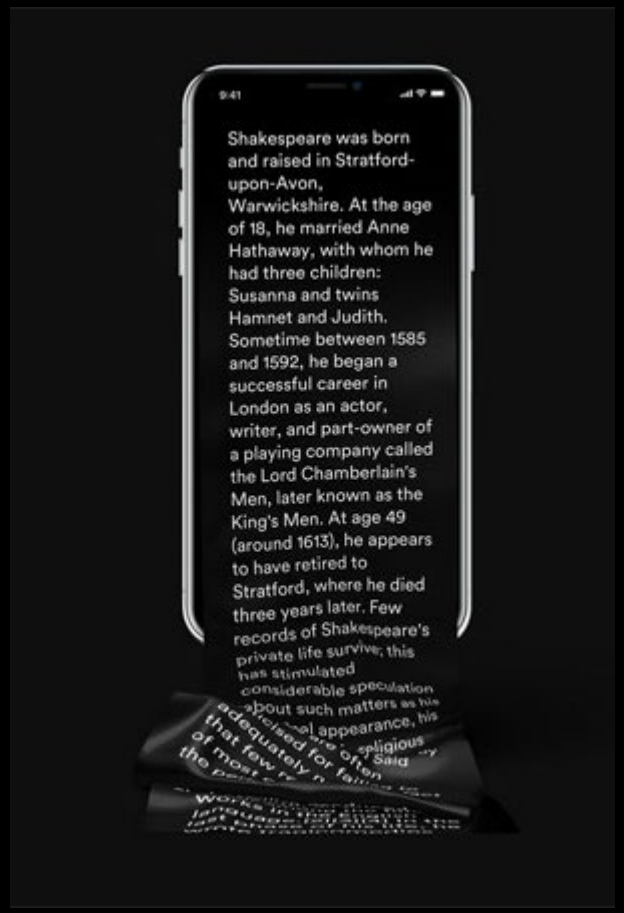

VINCE CARLO PARADA
MARK JEFFERSON MATIAS
MARK ANGELO BATAC

POST PRODUCTION

Producer	JOHN JOSEPH TAN
	MARK JOSEPH LLONA
Post Specialist	RYAN BRUIZ
Assistant Editor/Online Editor	RYAN BRUIZ
Colorist	TWEENIE NOCHE
Assistant Colorist	JOHN BRIAN LAGDAMEO
Head of Technology	KENNEDY RECATO DY
Operations Supervisor	JOHN DEXTER LIM
Software Developer	RONALD DAVIS CABATAÑA
Technical Engineers	ANTONIO VENTURA
	ALYSSA CAY FELICIANO
Digital Cinema Specialists	MARK JOSEPH LOTERTE
	EARL JEROME TUAZON
I/O Group	RAYMARCK RUEBANO