Recent Advances in Management of Asthma

DM Seminar

19/02/2021

Dr Kritarth

Brief Outline

- Problem Statement
- Key change in GINA 2019
- Severe Asthma
- Biologics
- Type 2 Low Asthma
- SLIT
- Bronchial Thermoplasty
- Summary

Problem Statement

- Estimated to affect as many as 339 million people worldwide

The Global Asthma Report. The Global Asthma Network; 2018. Available from: http://www.globalasthmareport.org/Global%20Asthma%20Report%202018.pdf . [Last accessed on 2021 Feb 12].

- Second most prevalent chronic respiratory disease
- Second leading cause of morbidity and death

	Overall				Males				Females			
	Death rate per 100 000	Proportion of all-cause deaths, %	DALY rate per 100 000	Proportion of all-cause DALYs, %	Death rate per 100 000	Proportion of all-cause deaths, %	DALY rate per 100 000	Proportion of all-cause DALYs, %	Death rate per 100 000	Proportion of all-cause deaths, %	DALY rate per 100 000	Proportion of all-cause DALYs, %
All chronic respiratory diseases	51·23 (49·61–52·94)	7·00% (6·76–7·23)	1470·03 (1369·68–1566·56)	4·50% (4·20–4·78)	56·45 (54·32–58·08)	7·12% (6·89–7·30)	1529·43 (1432·75–1624·22)	4·37% (4·12–4·60)	45·97 (42·73–49·34)	6·85% (6·37–7·34)	1410·18 (1288·53–1520·29)	4·65% (4·27–5·03)
Asthma	6·48 (4·43–8·39)	0·88% (0·60–1·14)	297·92 (236·69–370·88)	0·91% (0·76–1·09)	6·30 (3·72–8·85)	0·79% (0·47–1·11)	287·50 (220·90–368·68)	0·82% (0·65–1·02)	6·66 (4·55–8·68)	0·99% (0·68–1·29)	308·43 (237·74–388·97)	1·02% (0·82–1·23)
Chronic obstructive pulmonary disease	41·85 (39·64–43·96)	5·72% (5·43–5·97)	1068·02 (994·47–1135·50)	3·27% (2·96–3·56)	46·68 (43·62–49·25)	5·89% (5·50–6·20)	1128·21 (1045·99–1202·19)	3·22% (2·93–3·49)	36·99 (33·63–39·85)	5·51% (5·00–5·91)	1007·37 (916·25–1088·81)	3·33% (2·95–3·71)
Interstitial lung diseases and pulmonary sarcoidosis	1·93 (1·50–2·37)	0·26% (0·20–0·32)	44·04 (36·19–53·43)	0·13% (0·11–0·16)	2·09 (1·60–2·73)	0·26% (0·20–0·35)	47·93 (38·75–62·32)	0·14% (0·11–0·18)	1·78 (1·19–2·37)	0·26% (0·18–0·35)	40·13 (30·41–52·65)	0·13% (0·10–0·17)
Pneumoconiosis	0·28 (0·27–0·30)	0·04% (0·04–0·04)	6·64 (6·18–7·17)	0·02% (0·02–0·02)	0·50 (0·47–0·53)	0·06% (0·06–0·07)	11·82 (10·98–12·75)	0·03% (0·03–0·04)	0·06 (0·05–0·07)	0·01% (0·01–0·01)	1·42 (1·20–1·66)	0·00% (0·00–0·01)
Other chronic respiratory diseases	0·68 (0·60–0·78)	0·09% (0·08–0·11)	53·40 (47·16–59·63)	0·16% (0·15–0·18)	0·89 (0·76–1·06)	0·11% (0·10–0·13)	53·97 (47·38–61·67)	0·15% (0·14–0·18)	0·48 (0·39–0·56)	0·07% (0·06–0·08)	52·83 (45·68–59·90)	0·17% (0·15–0·20)

Data are point estimate (95% uncertainty interval). DALYs=disability-adjusted life-years.

Table 2: **Chronic respiratory disease-attributable deaths and DALYs per 100 000 individuals and as a proportion of all-cause deaths and DALYs, respectively, across all super regions, 2017**

Prevalence and attributable health burden of chronic respiratory diseases, 1990–2017: a systematic analysis for the Global Burden of Disease Study, Lancet 2017

	Percentage of total deaths (95% UI)			Percentage of total DALYs (95% UI)		
	Both sexes	Male	Female	Both sexes	Male	Female
Chronic respiratory diseases	10·9% (10·0–12·0)	10·8% (10·0–11·4)	11·1% (9·4–13·5)	6·4% (5·8–7·0)	6·7% (6·2–7·1)	6·0% (5·3–7·1)
COPD	8·7% (7·8–9·5)	8·7% (7·6–9·7)	8·6% (7·1–10·5)	4·8% (4·3–5·3)	5·2% (4·6–5·7)	4·4 % (3·8–5·3)
Asthma	1·9% (1·2–2·5)	1·6% (0·9–2·6)	2·1% (1·4–3·2)	1·3% (0·9–1·6)	1·2% (0·8–1·6)	1·4% (1·0–1·9)
Interstitial lung disease and pulmonary sarcoidosis	0·28% (0·16–0·40)	0·27% (0·14–0·42)	0·28% (0·15–0·47)	0·14% (0·08–0·20)	0·14% (0·08–0·22)	0·13% (0·07–0·22)
Pneumoconiosis	0·04% (0·03–0·05)	0·05% (0·04–0·07)	0·01% (0·01–0·02)	0·02% (0·01–0·02)	0·03% (0·02–0·04)	0·01% (0·00–0·01)
Other chronic respiratory diseases	0·09% (0·05–0·11)	0·12% (0·06–0·17)	0·04% (0·02–0·07)	0·13% (0·11–0·16)	0·16% (0·12–0·20)	0·10% (0·08–0·12)

DALY=disability-adjusted life-year. COPD=chronic obstructive pulmonary disease. 95% UI=95% uncertainty interval.

Table 1: Percentage of deaths and DALYs due to each cause under the category of chronic respiratory diseases in India, 2016

The burden of chronic respiratory diseases and their heterogeneity across the states of India: the Global Burden of Disease Study 1990–2016. Lancet 2018

- Among India's 1.31 billion people, about 6% of children and 2% of adults have asthma[1]

- It was estimated that an appalling 139.45 billion Indian rupees have been spent on the treatment of asthma in the year 2015 alone[2]

1. The Global Asthma Report. The Global Asthma Network; 2018. Available from: http://www.globalasthmareport.org/Global%20Asthma%20Report%202018.pdf . [Last accessed on 2021 Feb 12].
2. Agarwal R et al, Lung India 2015;32:S342

EDITORIAL
GINA 2019

GINA 2019: a fundamental change in asthma management

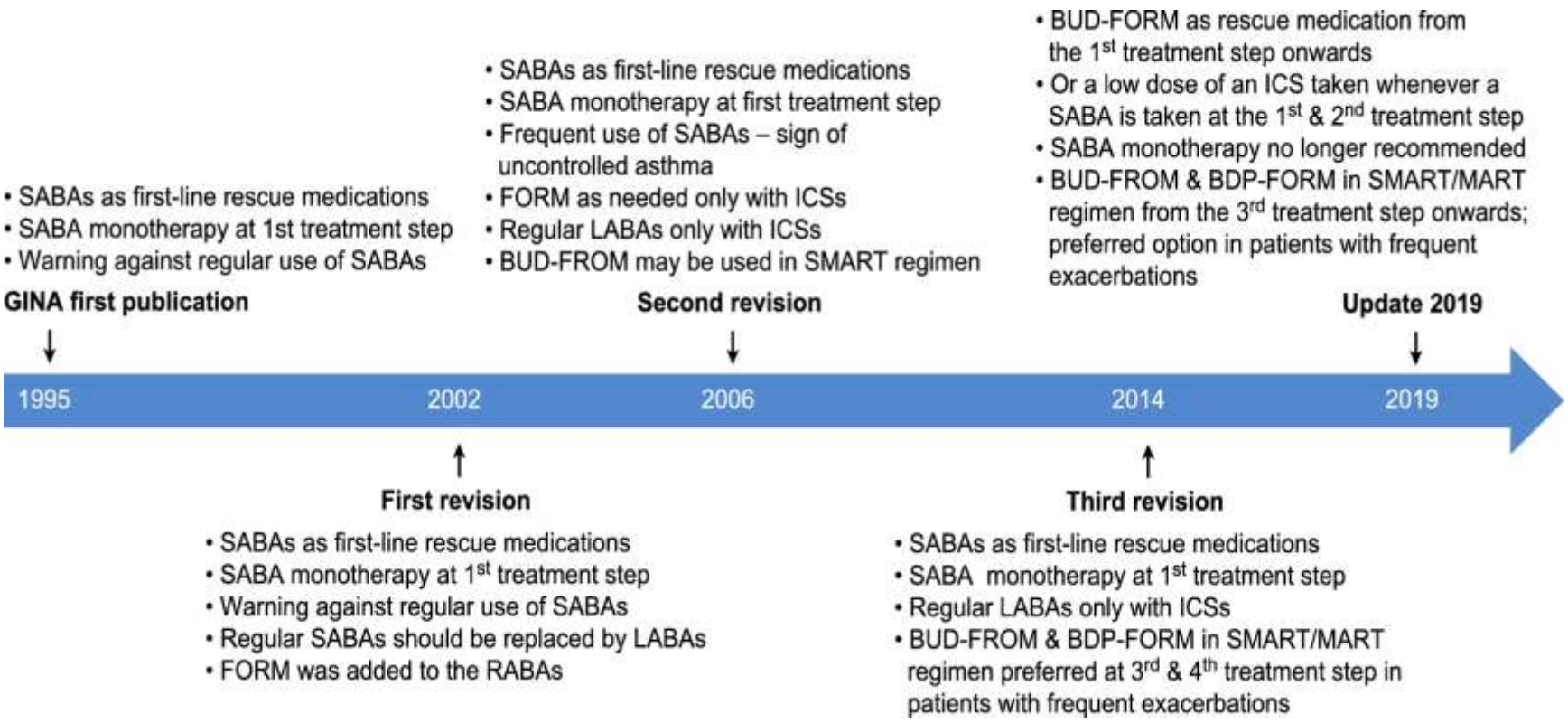
Treatment of asthma with short-acting bronchodilators alone is no longer recommended for adults and adolescents

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

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

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

GINA 2019



Timeline for SABA position changes in asthma management according to the GINA guidelines 1995–2019. ICS inhaled corticosteroids, LABA long acting beta2 agonist, RABA rapid acting beta2 agonist, SABA short acting beta2 agonist, SMART single inhaler maintenance and rescue therapy, MART maintenance and rescue therapy, BUD budesonide, BDP beclomethasone, FORM formoterol

Lipinska et al, Clin Transl Allergy 2020

Box 3-5A

Adults & adolescents 12+ years

Personalized asthma management:
Assess, Adjust, Review response

Confirmation of diagnosis if necessary
Symptom control & modifiable risk factors (including lung function)
Comorbidities
Inhaler technique & adherence
Patient preferences and goals

Symptoms
Exacerbations
Side-effects
Lung function
Patient satisfaction

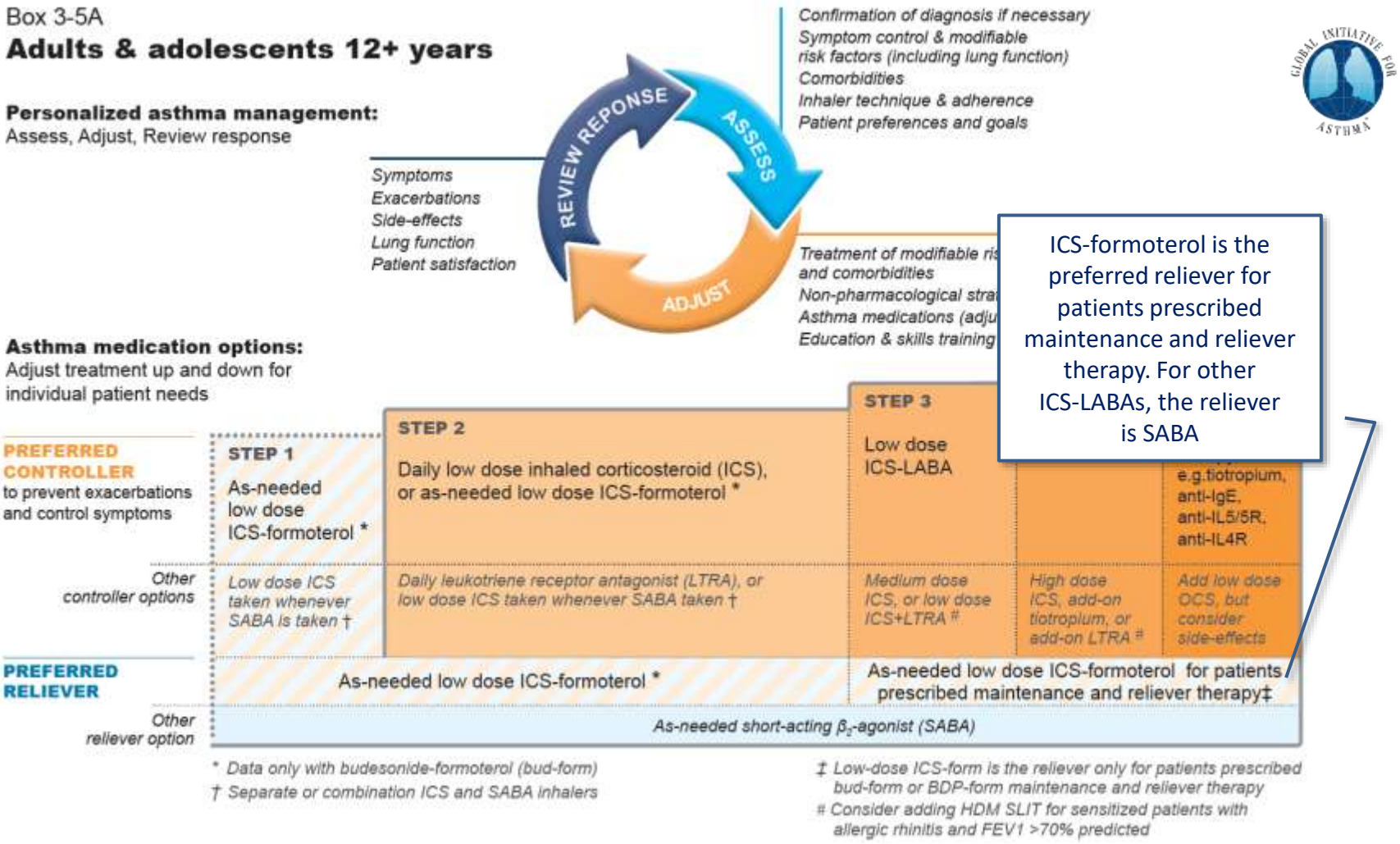
Treatment of modifiable risk factors and comorbidities
Non-pharmacological strategies
Asthma medications (adjust down or up)
Education & skills training

Asthma medication options:
Adjust treatment up and down for individual patient needs

	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
PREFERRED CONTROLLER to prevent exacerbations and control symptoms	As-needed low dose ICS-formoterol *	Daily low dose inhaled corticosteroid (ICS), or as-needed low dose ICS-formoterol *	Low dose ICS-LABA	Medium dose ICS-LABA	High dose ICS-LABA Refer for phenotypic assessment ± add-on therapy, e.g.tiotropium, anti-IgE, anti-IL5/5R, anti-IL4R
Other controller options	*Low dose ICS taken whenever SABA is taken †*	*Daily leukotriene receptor antagonist (LTRA), or low dose ICS taken whenever SABA taken †*	*Medium dose ICS, or low dose ICS+LTRA #*	*High dose ICS, add-on tiotropium, or add-on LTRA #*	*Add low dose OCS, but consider side-effects*
PREFERRED RELIEVER	As-needed low dose ICS-formoterol *		As-needed low dose ICS-formoterol for patients prescribed maintenance and reliever therapy‡		
Other reliever option	*As-needed short-acting β_2-agonist (SABA)*				

* *Data only with budesonide-formoterol (bud-form)*
† *Separate or combination ICS and SABA inhalers*
‡ *Low-dose ICS-form is the reliever only for patients prescribed bud-form or BDP-form maintenance and reliever therapy*
\# *Consider adding HDM SLIT for sensitized patients with allergic rhinitis and FEV1 >70% predicted*

GINA 2020


Box 3-5A
Adults & adolescents 12+ years
Personalized asthma management:
Assess, Adjust, Review response
Confirmation of diagnosis if necessary
Symptom control & modifiable risk factors (including lung function)
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REVIEW REPONSE
ASSESS
ADJUST
Symptoms
Exacerbations
Side-effects
Lung function
Patient satisfaction
Treatment of modifiable ri
and comorbidities
Non-pharmacological stra
Asthma medications (adju
Education & skills training
ICS-formoterol is the preferred reliever for patients prescribed maintenance and reliever therapy. For other ICS-LABAs, the reliever is SABA
Asthma medication options:
Adjust treatment up and down for individual patient needs
PREFERRED CONTROLLER
to prevent exacerbations and control symptoms
STEP 1
As-needed low dose ICS-formoterol *
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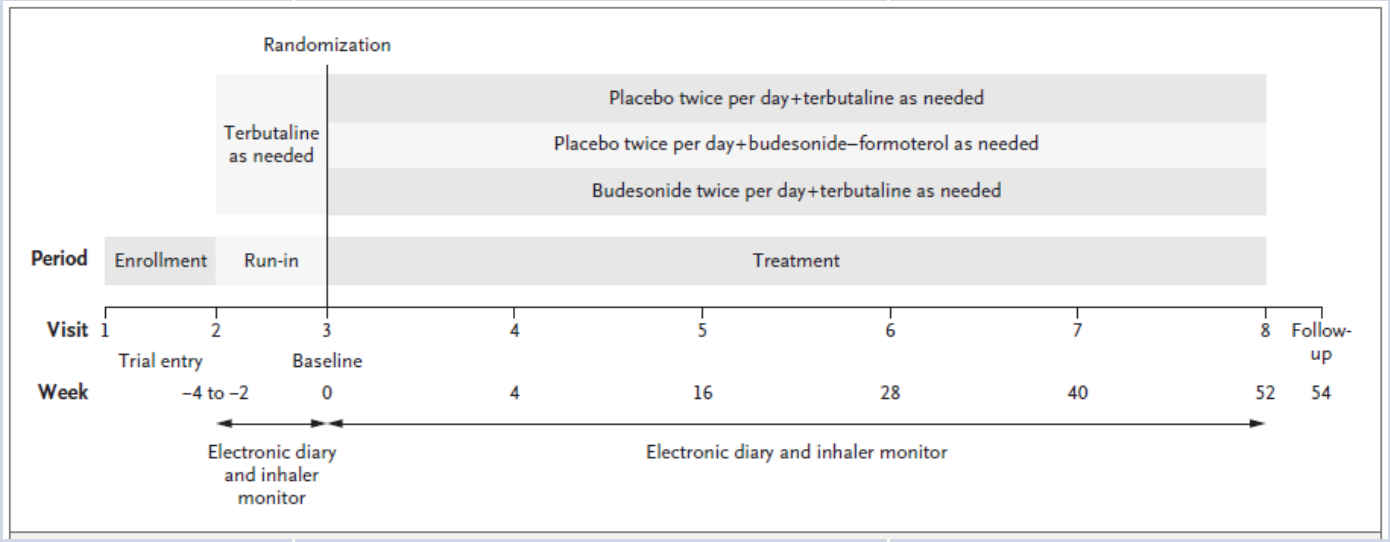
* Data only with budesonide-formoterol (bud-form)
† Separate or combination ICS and SABA inhalers
‡ Low-dose ICS-form is the reliever only for patients prescribed bud-form or BDP-form maintenance and reliever therapy
# Consider adding HDM SLIT for sensitized patients with allergic rhinitis and FEV1 >70% predicted

GINA 2020

Evidence

Population	Intervention	Outcome
N= 3849, 12 years of age or older with mild asthma needing GINA step 2 treatment Double-blind, randomized, parallel group, 52-week, phase 3 trial	Randomly assigned to one of 3 regimens: A = Placebo BD + TERBU as needed B = Placebo BD + BUD-FORM as needed C = BUD BD + TERBU as needed	Primary: Long term efficacy of as needed BUD-FORM vs as needed TERBU; measured by the weeks of well-controlled asthma.



SYGMA 1, *O'Byrne et al, NEJM 2018*

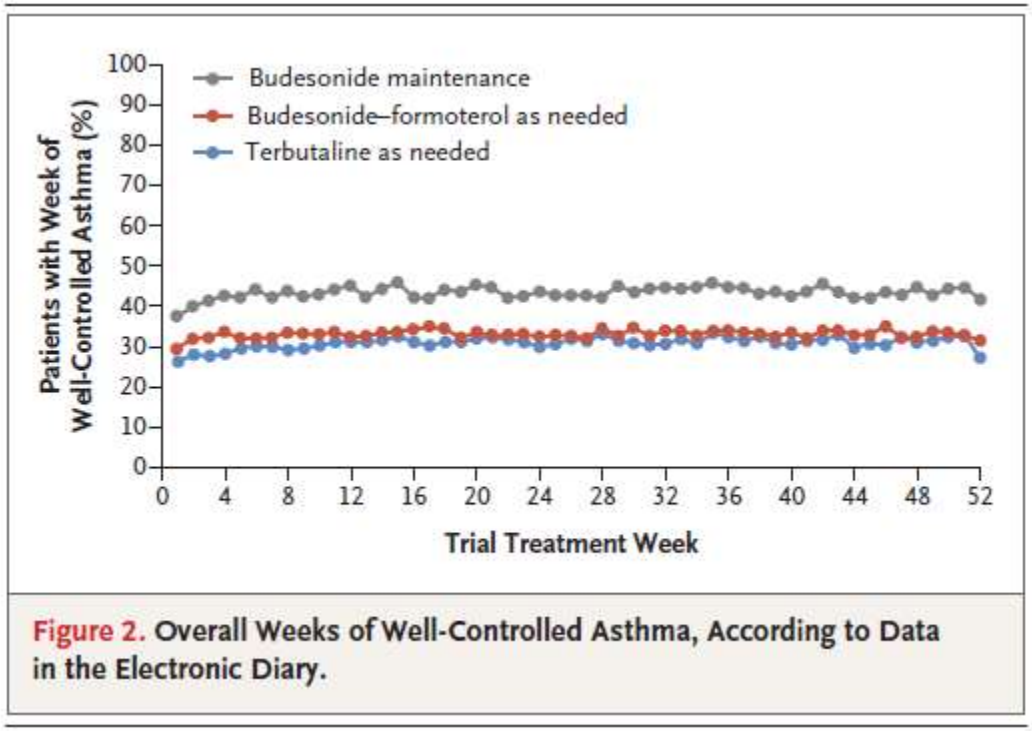


Figure 2. Overall Weeks of Well-Controlled Asthma, According to Data in the Electronic Diary.

With respect to the mean percentage of weeks with well-controlled asthma per patient, BUD-FORM was superior to TERBU (34.4% vs. 31.1% of weeks but inferior to BUD maintenance therapy (34.4% and 44.4%,)

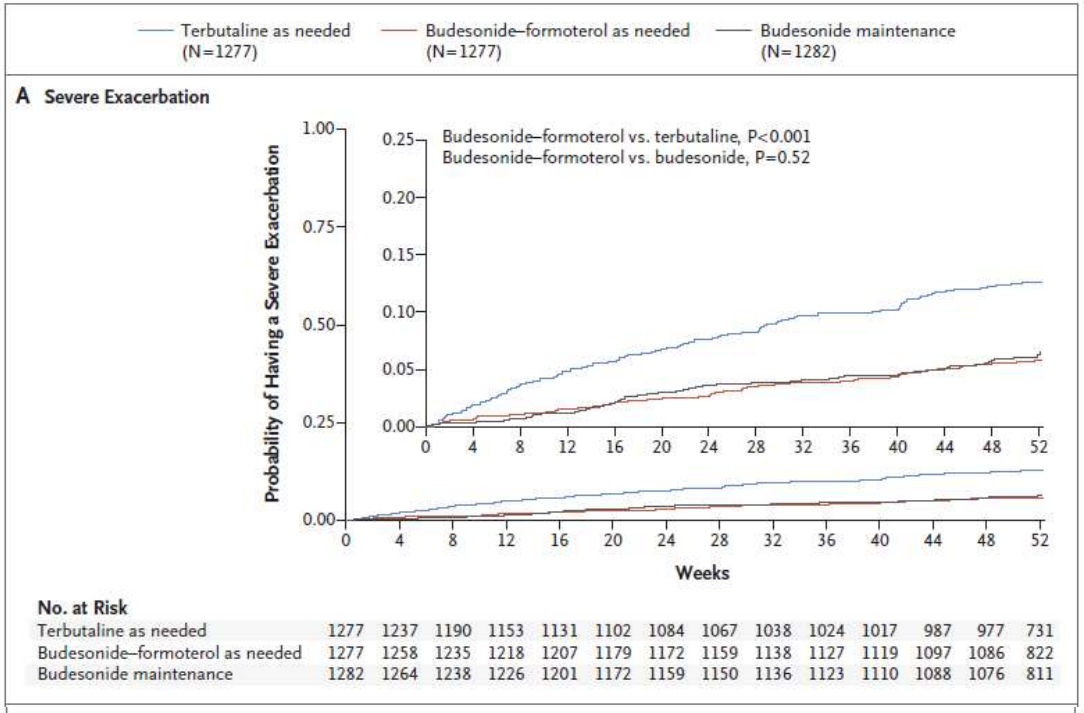
SYGMA 1, *O'Byrne et al, NEJM 2018*

Table 2. Summary of Asthma Exacerbations, According to Treatment Group.

Variable	Terbutaline as Needed (N=1277)	Budesonide–Formoterol as Needed (N=1277)	Budesonide Maintenance Therapy (N=1282)
All severe exacerbations			
Patients with ≥1 exacerbation — no. (%)	152 (11.9)	71 (5.6)	78 (6.1)
Total no. of exacerbations	188	77	89
Annualized exacerbation rate	0.20	0.07	0.09
Comparison between as-needed budesonide–formoterol and other regimen			
Rate ratio	0.36	—	0.83
95% CI	0.27–0.49	—	0.59–1.16
P value	<0.001	—	0.28
Severe exacerbation leading to hospitalization			
Patients with ≥1 exacerbation — no. (%)	15 (1.2)	6 (0.5)	8 (0.6)
Total no. of exacerbations	21	6	8
Severe exacerbation leading to emergency department visit and systemic glucocorticoid use			
Patients with ≥1 exacerbation — no. (%)	29 (2.3)	7 (0.5)	10 (0.8)
Total no. of exacerbations	29	8	10
Severe exacerbation leading to systemic glucocorticoid use for ≥3 days			
Patients with ≥1 exacerbation — no. (%)	141 (11.0)	70 (5.5)	74 (5.8)
Total no. of exacerbations	173	76	84
All moderate or severe exacerbations			
Patients with ≥1 exacerbation — no. (%)	274 (21.5)	131 (10.3)	143 (11.2)
Total no. of exacerbations	372	164	170
Annualized exacerbation rate	0.36	0.14	0.15
Comparison between as-needed budesonide–formoterol and other regimen			
Rate ratio	0.40	—	0.95
95% CI	0.32–0.49	—	0.74–1.21
P value	<0.001	—	0.66

Exacerbation rates with the two BUD-containing regimens were similar and were lower than the rate with TERBU

SYGMA 1, *O'Byrne et al, NEJM 2018*



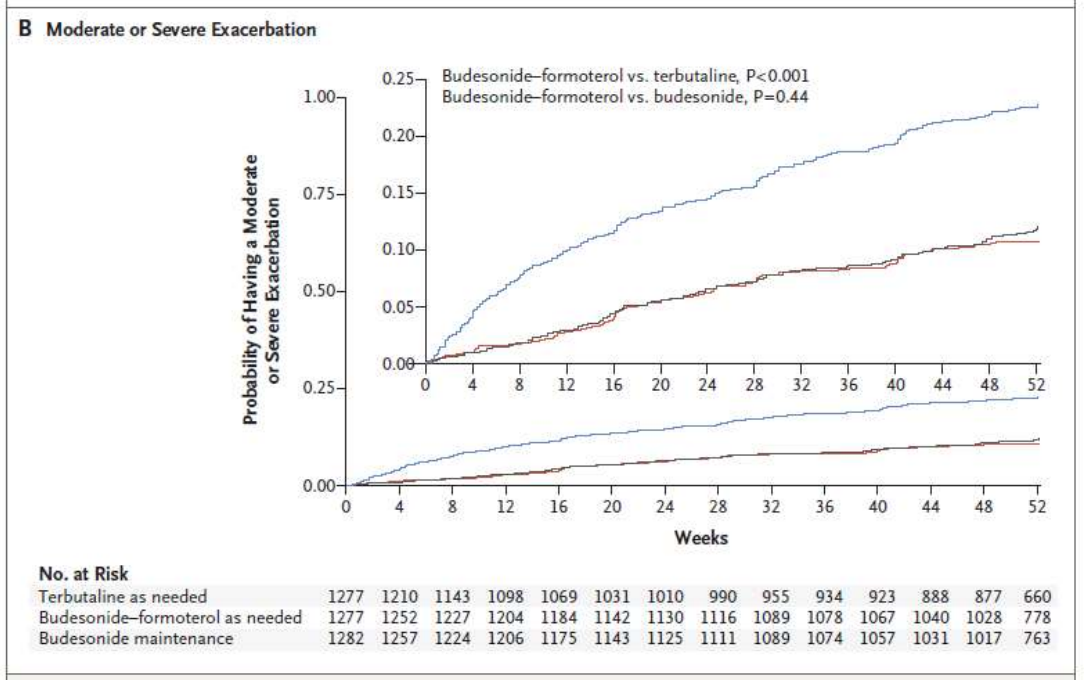


Figure 3. Time to First Exacerbation.

SYGMA 1, *O'Byrne et al, NEJM 2018*

BUD-FORM used as needed prolonged the time to the first severe exacerbation, as compared with TERBU used as needed

The results in the BUD-FORM group did not differ significantly from those in the BUD maintenance group

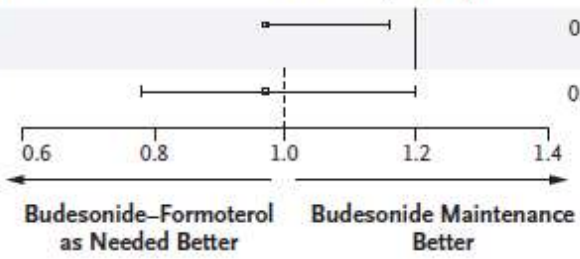
The median metered daily dose of inhaled GC in the BUD-FORM group (57 µg) was 17% of the dose in the BUD maintenance group (340 µg).

Population	Intervention	Outcome
N= 4176, 12 years of age or older with mild asthma needing GINA step 2 treatment Double-blind, randomized, parallel group, 52-week, phase 3 trial	Randomly assigned to one of two regimens: A = Placebo BD + BUD-FORM as needed B = BUD BD + TERBU as needed	Primary: Rate of severe exacerbations

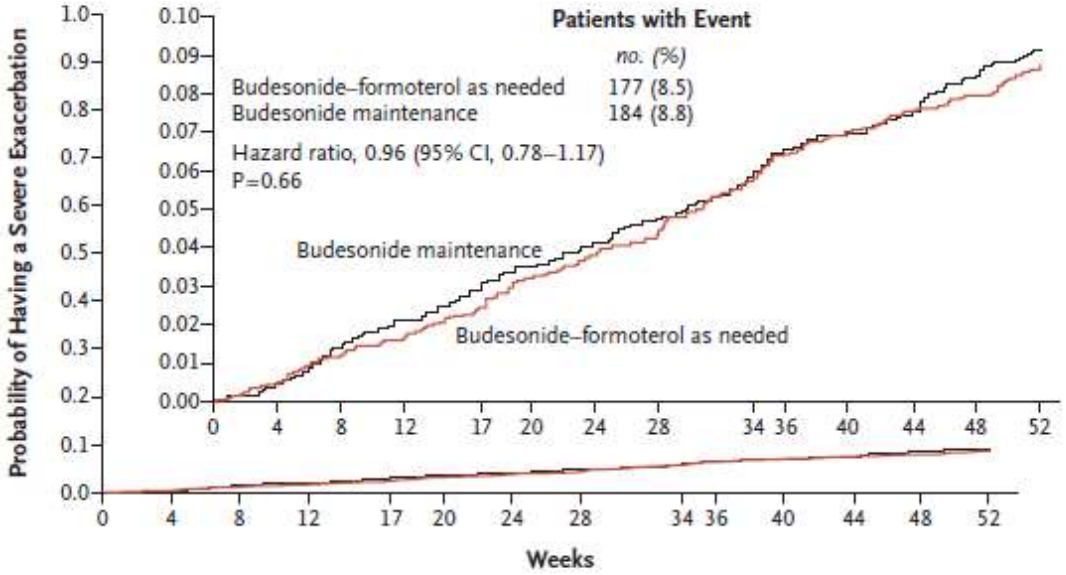
SYGMA 2, *Bateman et al, NEJM 2018*

A Annualized Rate of Severe Asthma Exacerbations

Test	Budesonide–Formoterol as Needed	Budesonide Maintenance	Rate Ratio (95% CI)	P Value
Noninferiority test	2084	2083	0.97 (NA–1.16)	—
Superiority test	2089	2087	0.97 (0.78–1.20)	0.75



B Time to First Severe Exacerbation



No. at Risk

Budesonide–formoterol as needed	2089	2065	2039	2012	1982	1944	1926	1904	1862	1840	1821	1799	1782	1208
Budesonide maintenance	2087	2060	2027	1987	1957	1929	1909	1883	1848	1826	1811	1786	1760	1222

Figure 1. Annualized Rate of Severe Asthma Exacerbations and Time to First Severe Exacerbation.

SYGMA 2, *Bateman et al, NEJM 2018*

Table 2. Severe Asthma Exacerbations and Exacerbation Rate, According to Treatment Group.*

Variable	Budesonide–Formoterol as Needed (N=2089)	Budesonide Maintenance Therapy (N=2087)
Total no. of patient-yr	1998	1981
All severe exacerbations		
Patients with ≥1 exacerbation — no. (%)	177 (8.5)	184 (8.8)
Total no. of exacerbations	217	221
Total no. of exacerbations per patient-yr	0.11	0.11
Severe exacerbation leading to systemic glucocorticoid use for ≥3 days		
Patients with ≥1 exacerbation — no. (%)	171 (8.2)	173 (8.3)
Total no. of exacerbations	209	207
Total no. of exacerbations per patient-yr	0.10	0.10
Severe exacerbation leading to emergency department visit and systemic glucocorticoid use		
Patients with ≥1 exacerbation — no. (%)	25 (1.2)	36 (1.7)
Total no. of exacerbations	26	40
Total no. of exacerbations per patient-yr	0.01	0.02
Severe exacerbation leading to hospitalization		
Patients with ≥1 exacerbation — no. (%)	17 (0.8)	17 (0.8)
Total no. of exacerbations	20	17
Total no. of exacerbations per patient-yr	0.01	0.01

* Patient-years were assessed only during the trial period (i.e., during exposure to the trial medications and placebo).

BUD-FORM used as needed was noninferior to BUD maintenance therapy for severe exacerbations.

SYGMA 2, *Bateman et al, NEJM 2018*

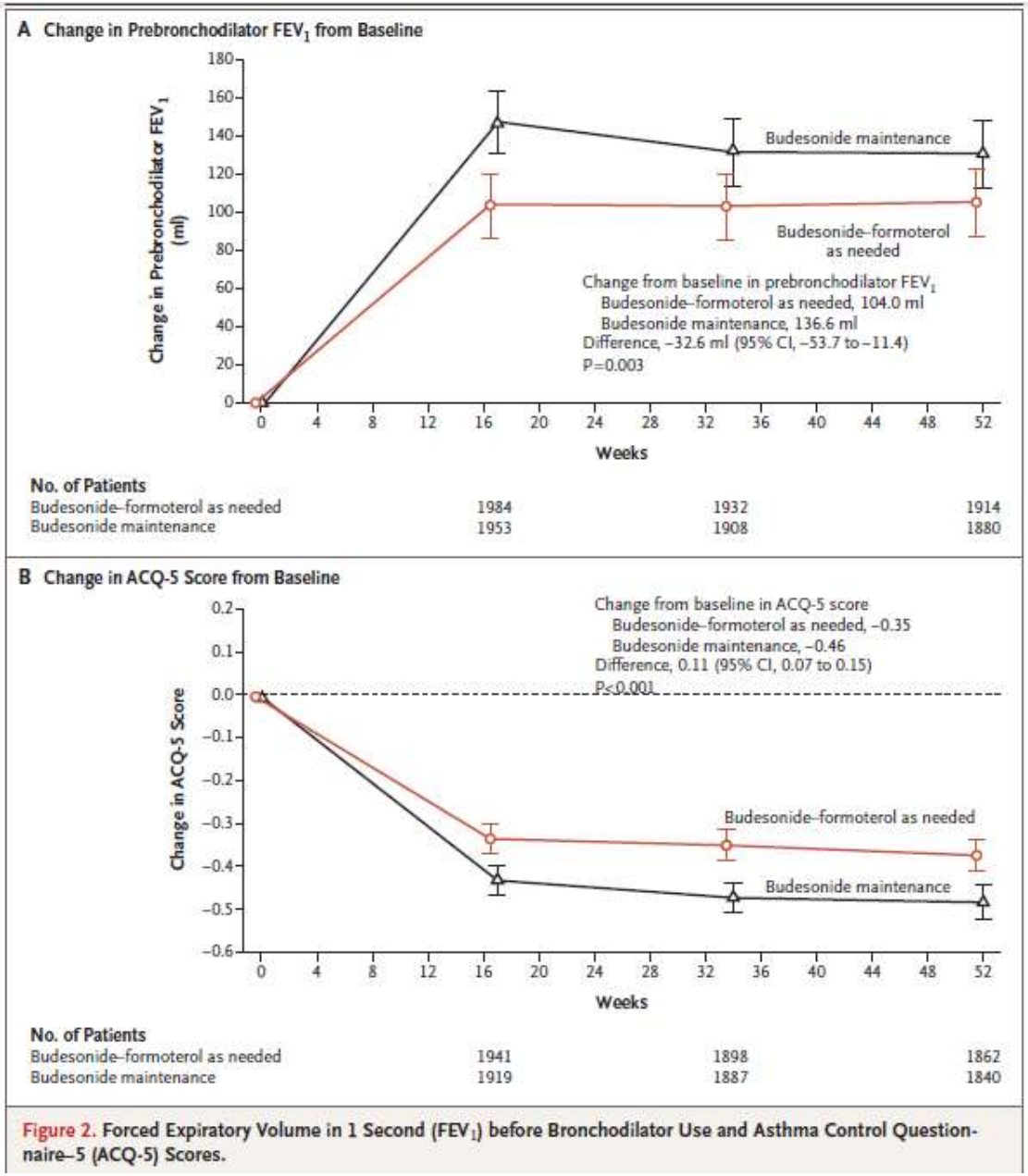


Figure 2. Forced Expiratory Volume in 1 Second (FEV_1) before Bronchodilator Use and Asthma Control Questionnaire–5 (ACQ-5) Scores.

- Change from baseline in the FEV1 both before and after bronchodilator use was less in the BUD-FORM than in the BUD group
- ACQ-5 score decreased over time in each group. Decrease in the BUD-FORM group was less than in the BUD group

SYGMA 2, *Bateman et al, NEJM 2018*

Additional Evidence

Population	Intervention	Outcome	Conclusions
N= 668, 18 to 75 years of age 52-week, randomized, open-label, parallel-group, controlled trial	Randomly assigned to one of 3 treatment groups: A= ALBU as needed B= BUD BD + as-needed albuterol C= BUD–FORM as needed	Primary outcome: Annualized rate of asthma exacerbations.	Annualized exacerbation rate in the BUD–FORM group was lower than that in the ALBU group and did not differ significantly from the rate in the BUD group The number of severe exacerbations was lower in the BUD–FORM group than in both the ALBU group and the BUD group The mean (±SD) dose of inhaled budesonide was 107±109 µg per day in the BUD-FORM group and 222±113 µg per day in the BUD group

START, *Beasley et al, NEJM 2019*

Population	Intervention	Outcome	Conclusions
N= 890, adults aged 18–75 years 52-week, open-label, parallel-group, multicentre, superiority, RCT	Randomly assigned to one of two regimens: A= BUD-FORM as needed B= BUD BD + TERBU as needed	Primary outcome: No. of severe exacerbations per patient per year	Severe exacerbations per patient per year were lower with as-needed BUD-FORM than with maintenance BUD as needed

PRACTICAL, Hardy et al, Lancet 2019

- **Uncontrolled asthma**
  - Frequent symptoms and/or flare-ups (exacerbations)
  - Many of these patients may potentially have mild asthma, i.e. their asthma could be well-controlled with low dose ICS, if taken regularly

- **Difficult-to-treat asthma** (not difficult patients!)
  - Asthma uncontrolled despite prescribing high dose preventer treatment
  - Contributory factors may include incorrect diagnosis, incorrect inhaler technique, poor adherence, comorbidities

European Respiratory Society/American Thoracic Society definition of severe asthma for patients aged ≥6 years*

The definition of severe asthma requires that one or both of the following levels of treatment for the previous year has been needed to prevent asthma from becoming uncontrolled or asthma that remains uncontrolled despite this level of treatment:

- Treatment with guidelines suggested medications for GINA steps 4-5 asthma (high dose inhaled glucocorticoid* and long-acting beta agonist [LABA] or leukotriene modifier/theophylline) for the previous year
- Treatment with systemic glucocorticoid for ≥50% of the year

Uncontrolled asthma is defined as at least one of the following:

- Poor symptom control: ACQ consistently >1.5, ACT <20 (or "not well controlled" by NAEPP/GINA guidelines)
- Frequent severe exacerbations: two or more bursts of systemic glucocorticoids (more than three days each) in the previous year
- History of serious exacerbation: at least one hospitalization, intensive care unit stay, or mechanical ventilation in the previous year
- Airflow limitation: after appropriate bronchodilator withhold FEV_1 <80% predicted (in the face of reduced FEV_1/FVC defined as less than the lower limit of normal)

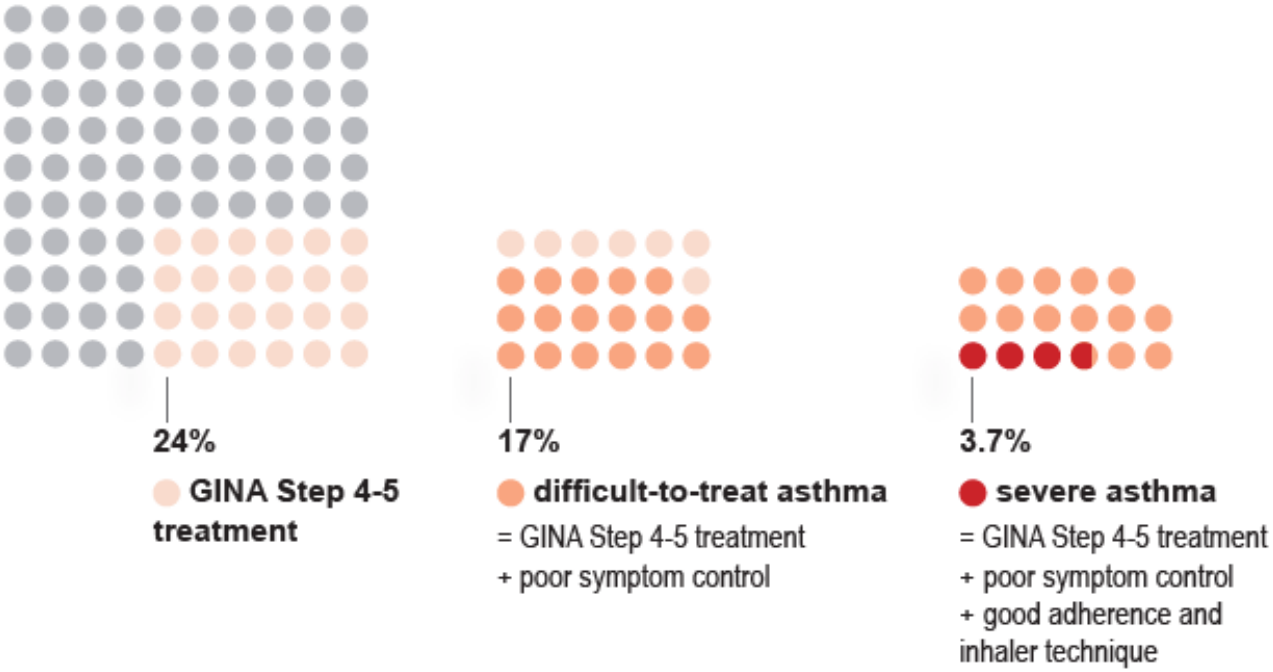
The ERS/ATS definition of high doses of various inhaled glucocorticoids in relation to patient age (in mcg/day):

	Age 6 to 12 years	Age >12 years
Beclomethasone	≥320 (HFA MDI)	≥1000 (HFA MDI)
Budesonide	≥800* (MDI or DPI)	≥1600[¶] (MDI or DPI)
Ciclesonide	≥160 (HFA MDI)	≥320 (HFA MDI)
Fluticasone propionate	≥500[Δ] (HFA MDI or DPI)	≥1000[◊] (HFA MDI or DPI)
Mometasone	≥500[§] (DPI)	≥800[¥] (DPI)

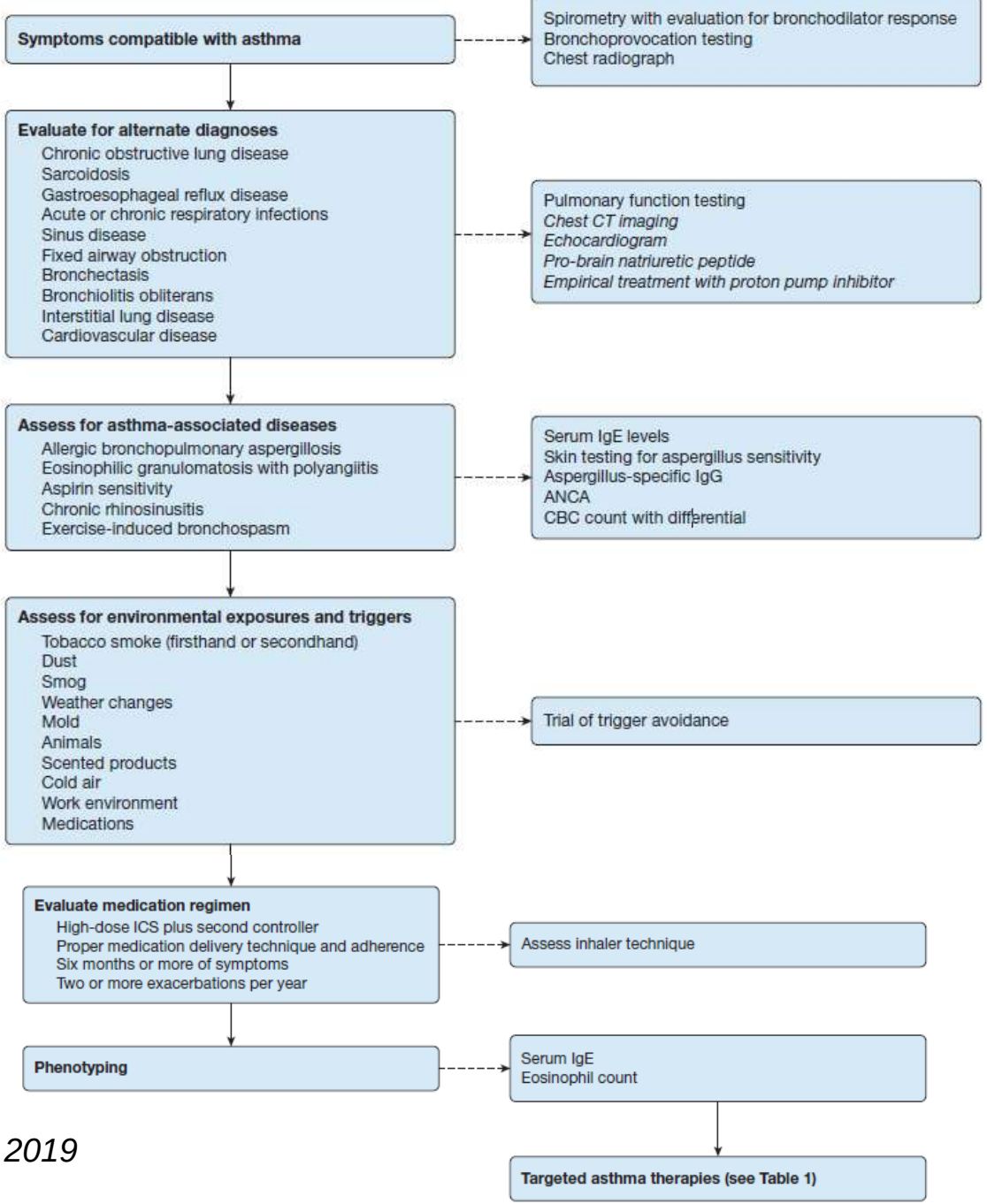
Designation of high doses is provided from manufacturers' recommendations where possible. Equivalent high doses may be expressed differently between countries and some products (eg, beclomethasone) are available in multiple formulations with different dosing recommendations. Medication inserts should be carefully reviewed by the clinician for the equivalent high daily dosage.

How common is severe asthma?

Box 1. What proportion of adults have difficult-to-treat or severe asthma?



These data are from a Dutch population survey of people ≥18 years with asthma[2]



Schoettler et al, CHEST 2019

Overview of evaluation of patients with severe

- Two major risk factors that contribute to severe asthma are genetics and environmental exposures
- modulate immune responses
- often interact in complex manners that are not fully understood
- certain endotypes converge in severe asthma.

Schoettler et al, CHEST 2019

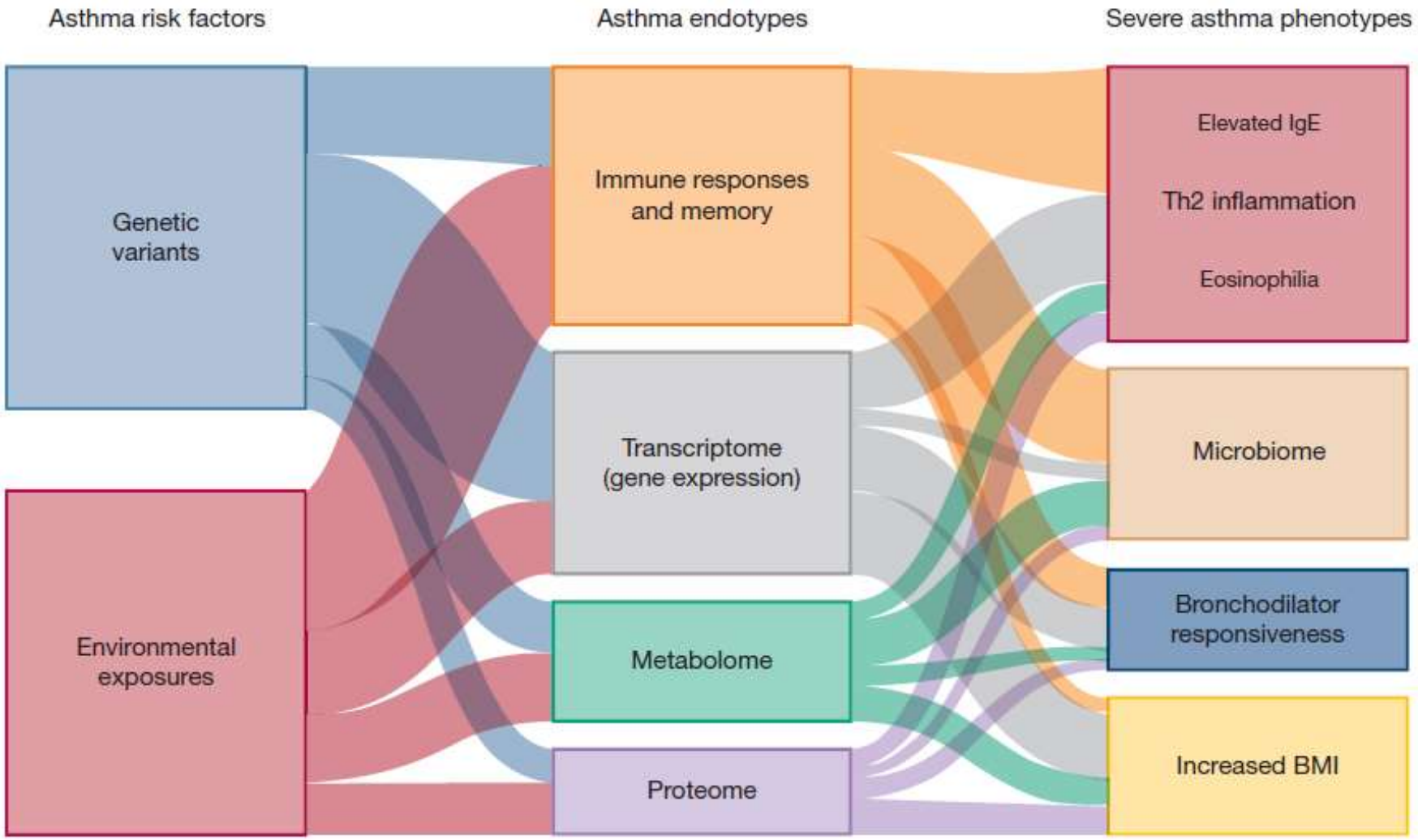
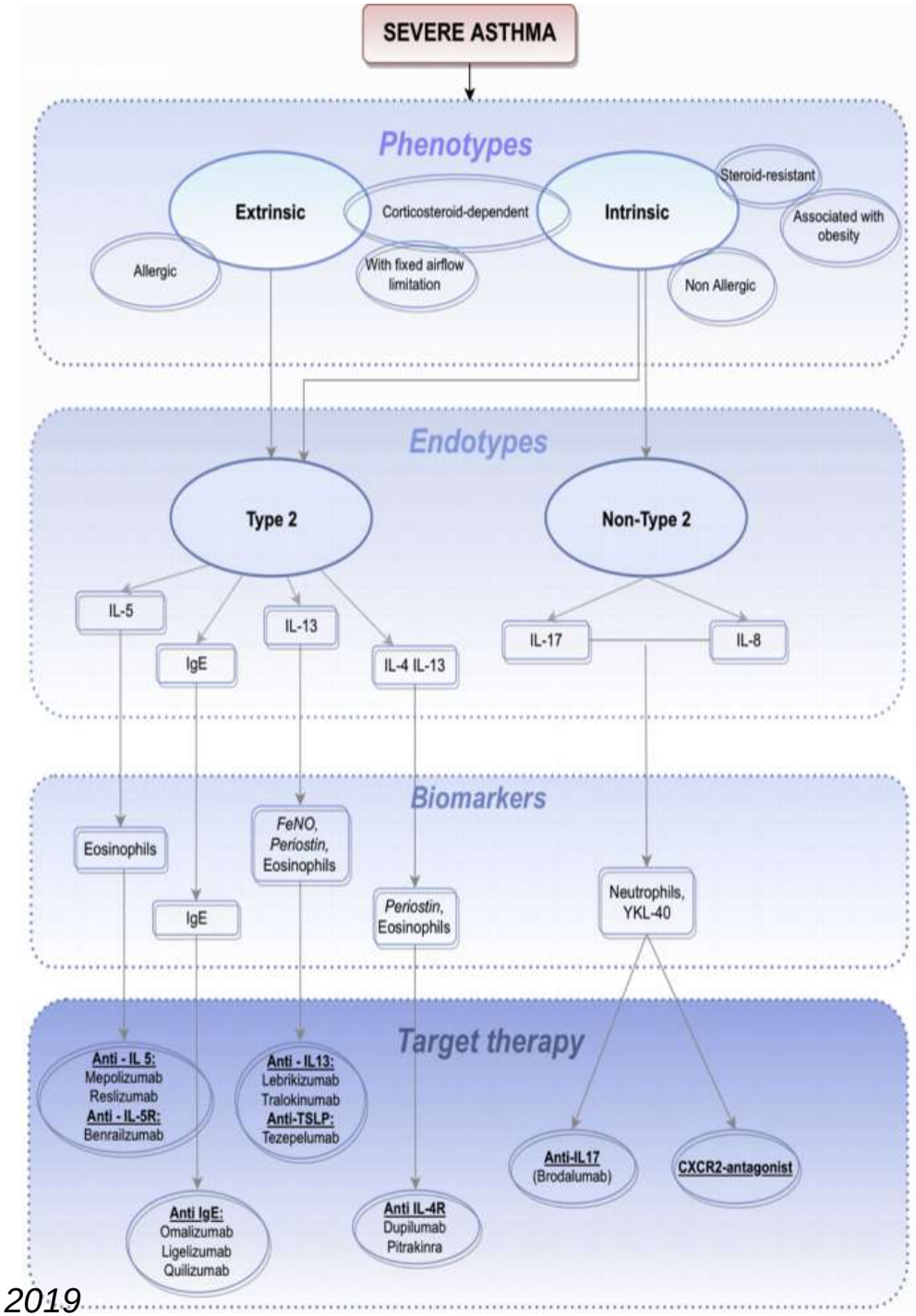
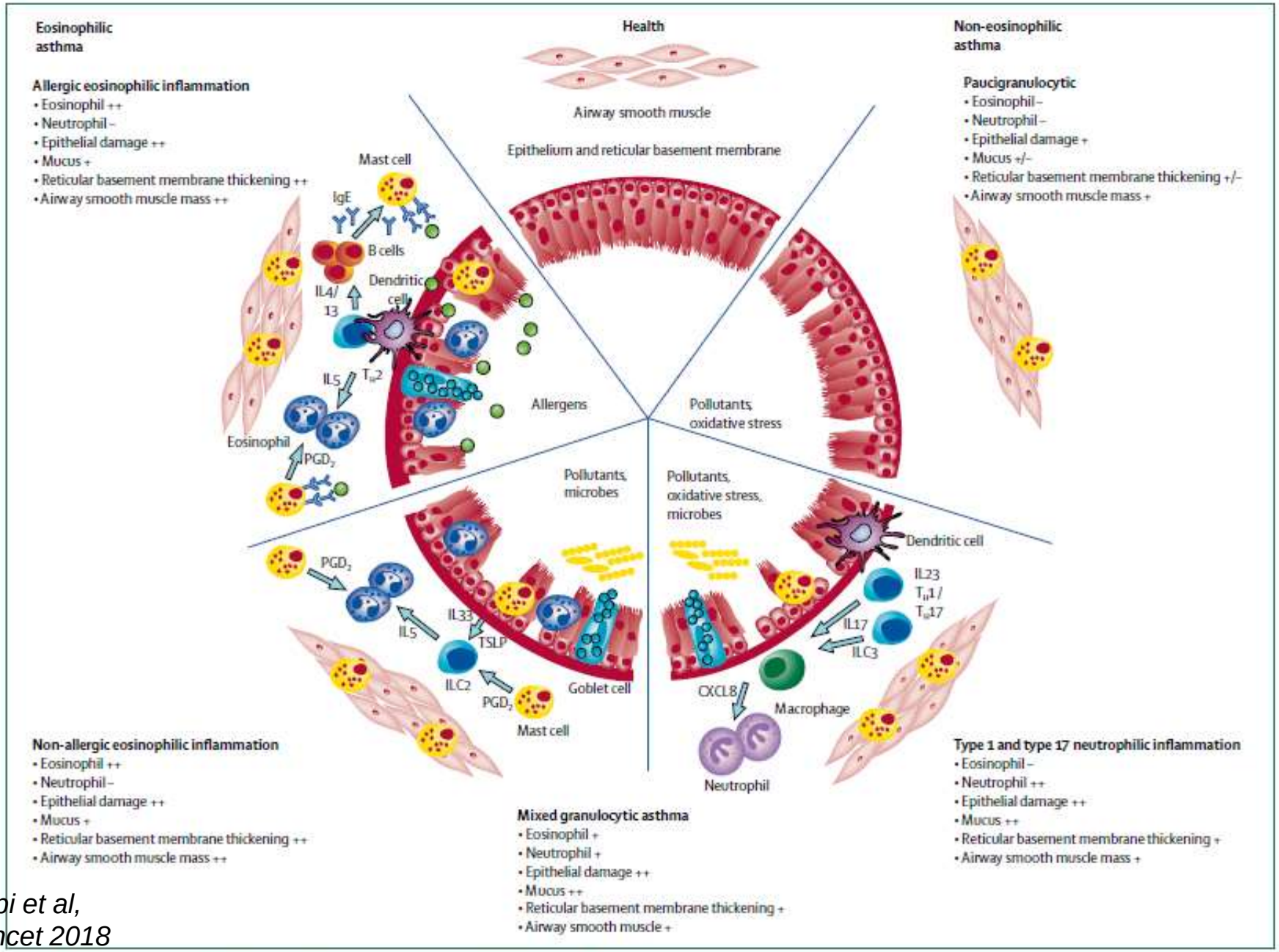


Figure 2 – *Interplay between risk factors, endotypes, and phenotypes in severe asthma. Both genetics and environment contribute to asthma risk and interact in complex ways to influence asthma endotypes or biological processes. Size of the lines indicates the relative proportion to severe asthma phenotype.*

Schoettler et al, CHEST 2019



P. Santus et al,
Pharmacological Research 2019



Papi et al, Lancet 2018

Figure 2: **Mechanisms and characteristic pathological features of asthma immunopathology**
Features are divided into eosinophilic (allergic and non-allergic), non-eosinophilic (neutrophilic type 1 and type 17 and paucigranulocytic), and mixed granulocytic inflammation. Reproduced from Russell and Brightling,[12] by permission of Portland Press. IL=interleukin. T_H=T helper. PDG_2=prostaglandin D2. TSLP=thymic stromal lymphopoietin. ILC2=type 2 innate lymphoid cells. CXCL8=C-X-C motif chemokine ligand 8. ILC2=type 3 innate lymphoid cells.

SPECIALIST CARE; SEVERE ASTHMA CLINIC IF AVAILABLE

Assess and treat severe asthma phenotypes *cont'd*

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

6b Consider *add-on biologic Type 2* targeted treatments

- Consider add-on Type 2-targeted biologic for patients with exacerbations or poor symptom control on high dose ICS-LABA, who:
  - have eosinophilic or allergic biomarkers, or
  - need maintenance OCS
- Consider **local payer eligibility criteria** 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?

Anti-IgE

*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

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

- Exacerbations in last year
- Blood eosinophils ≥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-IL4R

*Is the patient eligible for **anti-IL4R***

… for severe eosinophilic asthma?

- Exacerbations in last year
- Blood eosinophils ≥150/µl or FeNO ≥25 ppb

… or because of need for maintenance OCS?

What factors may predict good asthma response to anti-IL4R?

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

Anti-IL4R may also be used to treat

- Moderate/severe atopic dermatitis
- Nasal polyposis

Eligible for none?
Return to section **6a**

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

TABLE 1] Immunomodulatory Biologic Agents Approved for Use in Asthma

Pathway	IgE	IL-4 and IL-13	IL-5		
Mechanism	Blocks IgE-mediated immune stimulation	Binds to IL-4R alpha subunit and blocks IL-4 and IL-13 cytokine-induced inflammatory responses	Block IL-5 binding to the receptor and reduces survival of eosinophils		
Medication	Omalizumab	Dupilumab	Mepolizumab	Benralizumab	Reslizumab
Target	Anti-IgE monoclonal antibody	Anti-IL-4R alpha monoclonal antibody	Anti-IL-5 monoclonal antibody	Anti-IL-5 alpha monoclonal antibody	Anti-IL-5 receptor monoclonal antibody
Considerations	Elevated IgE	Atopic dermatitis and/or eosinophilia	Eosinophilia	Eosinophilia	Eosinophilia
Indications	Add-on therapy for patients ≥ 6 y old with moderate-to-severe persistent asthma inadequately controlled on ICS and a total serum IgE level between 30 and 700 units/mL and a positive allergen test	Moderate to severe asthma in patients ≥ 12 y old; oral corticosteroid-dependent asthma or asthma with severe atopic dermatitis or chronic rhinosinusitis with nasal polyps	Severe asthma in patients ≥ 12 y old with eosinophilia	Severe asthma in patients ≥ 12 y old with eosinophilia	Severe asthma in patients ≥ 18 y old with eosinophilia
Dosing route	Subcutaneous	Subcutaneous	Subcutaneous	Subcutaneous	IV
Dosing interval	Every 2-4 wk depending on pretreatment serum IgE level	Every 2 wk	Every 4 wk	Every 4 wk for the first three doses, then once every 4 or 8 wk	Every 4 wk
Outcomes observed in clinical trials	Reduced exacerbations by approximately 25%-50% in subjects with an FEV_1 between 40% and 80% predicted	Reduced exacerbations by approximately 50% in patients with severe asthma compared with placebo and improvement in FEV_1 Among patients on oral glucocorticoids, 70% had a reduction in the dose, compared with 42% in placebo	Fewer exacerbations compared with placebo and reduced corticosteroid dose in patients requiring maintenance corticosteroids	Reduced exacerbation rate in moderate or severe asthma. In patients with eosinophil counts ≥ 300 cells/μL, rate ratio of < 0.55 for both dosing regimens and improved prebronchodilator FEV_1. Reduced glucocorticoid use with an odds of reduction of 4.09 compared with placebo	Decreased asthma exacerbations by as much as 59%. Improvement in lung function. Improvement in asthma symptoms and asthma-related quality of life

(Continued)

Schoettler et al, CHEST 2019

TABLE 1] *(Continued)*

Pathway	IgE	IL-4 and IL-13	IL-5		
Common (> 3%) or severe side effects	Headache (6%-12%) Arthralgias (3%-8%) **Anaphylaxis (0.3%) – black box warning** **Serum sickness-like reaction** **Cardiovascular events, including transient ischemic attack and ischemic stroke** **Eosinophilic granulomatosis and polyangiitis**	Injection site reaction (10%-18%) Oral herpes simplex infection (4%) Antibody response with neutralizing activity (2%-4%) Conjunctivitis (10%) **Eosinophilic granulomatosis with polyangiitis and eosinophilic pneumonia** **Hypersensitivity reactions**	Headache (19%) Injection site reaction (8%-15%)	Antibody response with neutralizing activity (12%) Headache (8%) Pharyngitis (5%)	Antibody to medication (5%) Transient increased creatine phosphokinase (20%) Oropharyngeal pain (3%) **Increased malignancies observed at 6 mo (diverse types)** **Anaphylaxis (0.3%) – black box warning**

Serious side effects are in bold font.

Schoettler et al, CHEST 2019

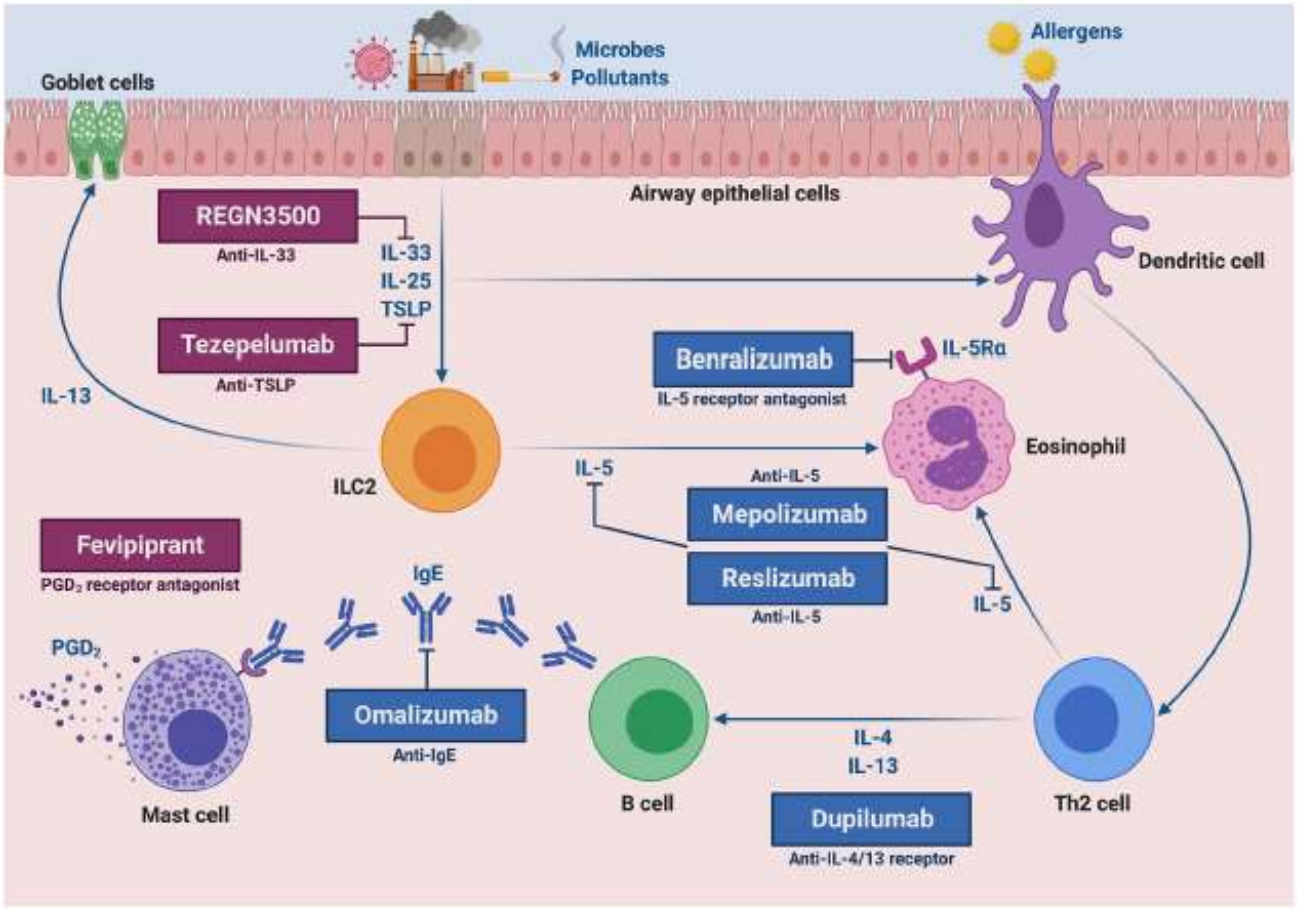


FIGURE 1 | Molecular targets of current and future biological therapies of severe type 2 asthma. The targets of approved add-on biologic treatments (highlighted in blue color) of severe asthma include IgE (omalizumab), IL-5 (mepolizumab and reslizumab), IL-5 receptor (benralizumab), and IL-4/IL-13 receptor complex (dupilumab). Moreover, experimental drugs (highlighted in dark magenta color) such as tezepelumab, REGN3500 and fevipiprant target TSLP, IL-33 and the CRTH2 receptor of PGD_2, respectively. This original figure was created by the authors using "BioRender.com".

Pelaia et al, Front Immunol 2020

TABLE 1 | Licensed biological therapies for severe asthma.

Licensed biological therapies	Targets	Molecular mechanisms of action	Effects in the control of severe asthma
Omalizumab	IgE	Generation of IgE/anti-IgE immune complexes that inhibit IgE-mediated allergic cascade	↓ Exacerbations ↑ Quality of life and symptom control ↑ FEV1
Mepolizumab	IL-5	Prevention of IL-5 binding to IL-5Rα	↓ Blood and sputum eosinophils ↓ Exacerbations ↑ Quality of life and symptom control ↓ OCS intake ↑ FEV1
Reslizumab	IL-5	Prevention of IL-5 binding to IL-5Rα	↓ Blood and sputum eosinophils ↓ Exacerbations ↑ Quality of life and symptom control ↑ FEV1
Benralizumab	IL-5Rα	Blockade of IL-5Rα ADCC-induced eosinophil apoptosis	↓ Blood eosinophils ↓ Exacerbations ↑ Quality of life and symptom control ↓ OCS intake ↑ FEV1
Dupilumab	IL-4Rα	Dual receptor antagonism of IL-4/IL-13	↓ Exacerbations ↓ OCS intake ↑ FEV1

Pelaia et al, Front Immunol 2020

Real-World Effectiveness and the Characteristics of a 'Super-Responder' to Mepolizumab in Severe Eosinophilic Asthma

Population	Intervention	Outcome
N=130, Severe Eosinophilic Asthma Design: Retrospective analysis Patients who did not complete ≥24 weeks of benralizumab treatment were excluded from the analysis.	Benralizumab	Response to treatment: as a reduction of ≥50% in annualised exacerbation rate (AER) or in mOCS dose after 48 weeks of treatment. Super-response: zero exacerbations and no mOCS for asthma.

Kavanagh et al, Chest 2020

All (n=130)	Baseline	48 weeks	P value
Annual exacerbation rate	4.92 (3.35)	1.34 (1.71)	**<0.001**
OCS dose (prednisolone, mg/day, n=74)	10 (5-20)	0 (0-5)	**<0.001**
ACQ-6	2.90 (1.39)	2.15 (1.41)	**<0.001**
Mini-AQLQ	3.46 (1.49)	4.35 (1.51)	**<0.001**
Post-bronchodilator FEV_1 (L)	1.76 (0.69)	1.90 (0.70)	**<0.001**
Post-bronchodilator FEV_1 (% predicted)	63.8 (20.6)	69.4 (21.9)	**<0.001**
Blood eosinophil count ($x10^9$/L)	0.2 (0.1-0.4)	0.0 (0.0-0.0)	**<0.001**
FeNO (ppb)	45 (26-78)	38 (23-71)	0.135
Responder rate[¶]	n/a	112 (86.2)	n/a
Super responder rate[†]	n/a	51 (39.2)	n/a

Table 2: One-year outcomes

Kavanagh et al, Chest 2020

Conclusions:

- In a large real-world SEA cohort, benralizumab led to significant improvements in all clinical outcome measures

- A lack of response was seen in a minority (N=18) and should be investigated

Kavanagh et al, Chest 2020

EMERGING BIOLOGICAL THERAPIES IN CLINICAL DEVELOPMENT

TABLE 2 | New potential targets of emerging anti-asthma therapies.

New potential targets	New potential drugs	Molecular mechanisms of action	Effects in the control of severe asthma
TSLP	Tezepelumab	Prevention of TSLP binding to its receptor complex	↓ Blood eosinophils ↓ FeNO ↓ Exacerbations ↑ FEV1
IL-33	REGN3500	Prevention of IL-33 binding to ST2 receptor	↑ Quality of life and symptom control
PGD2	Fevipiprant	Selective antagonism of CRTH2 receptor	Weak FEV1 increase

Pelaia et al, Front Immunol 2020

Characteristic	Eosinophilic asthma	Neutrophilic asthma
Biology of granulocytes	Eosinophils: - long-lived haematopoietic cells. - reside predominantly in mucosal tissues (e.g. airways). - absent in sputum and airways in health.	Neutrophils: - short-lived haematopoietic cells. - predominantly circulating in blood. - present in sputum and airways in health.
Role in pathogenesis	Inflammatory eosinophils in the airways of patients with asthma are pathogenic and associate with exacerbations.	Role of neutrophils in the airways of patients with asthma is unknown; neutrophils are beneficial in airway infection.
Non-invasive biomarkers	Elevated FeNO Blood eosinophils correlate with sputum eosinophils in asthma.	None. Non-invasive biomarkers (e.g. VOC) are not available in clinical practice. Blood neutrophil levels do not correlate with sputum neutrophil levels in asthma.
Heterogeneity of phenotype	Moderate heterogeneity within eosinophilic asthma: allergic versus non-allergic; early-onset versus late-onset.	Huge heterogeneity within neutrophilic asthma; multiple associated factors e.g. smoking, air pollution, obesity, infection.
Differential diagnosis	Limited: eosinophilic COPD; eosinophilic pneumonia; ABPA; EGPA.	Very broad: e.g. COPD; bronchiectasis; cystic fibrosis; diffuse panbronchiolitis; bacterial and fungal infections; tuberculosis; NTM infection.
Therapeutic targets	Clearly delineated: - corticosteroids. - type-2 cytokines and their receptors: IL-5, IL-5R and IL-4R. - IgE in allergic eosinophilic severe asthma. - epithelial alarmins (e.g. TSLP, IL-33).	Less well defined: [see Table 3] - pro-inflammatory cytokines such as IL-1β, IL-6, TNF, IL-17, IL-17R, IL-23 - CXC chemokines or their receptors - β-tryptase, G-CSF, GM-CSF - epithelial alarmins (e.g. TSLP; IL-33)

Hinks et al, ERJ 2020

How common is type-2 low asthma?

- A normal sputum eosinophil count is seen in 25% of patients with untreated symptomatic asthma and 40-50% of patients with asthma treated with high doses of ICS

- Type-2 low asthma may be more common in mild-to-moderate disease, with estimates of 64-73% with a single sputum sample, and even with repeated sampling this may be approximately half of asthmatics

Hinks et al, ERJ 2020

- Sputum neutrophilia is often defined as ≥61% or ≥73% neutrophils on a cytospin. The optimal cut-off might differ according to local air pollution levels

- For sputum eosinophilia several definitions have been used including cut-offs of 1%, 2%, 3%

- However for the purposes of identifying non-eosinophilic asthma a lower cut off for sputum eosinophils of <2% may be more specific, and has been adopted in recent clinical trials and GINA guidelines.

Hinks et al, ERJ 2020

What are the clinical characteristics of type-2 low asthma, beyond an absence of type-2 biomarkers?

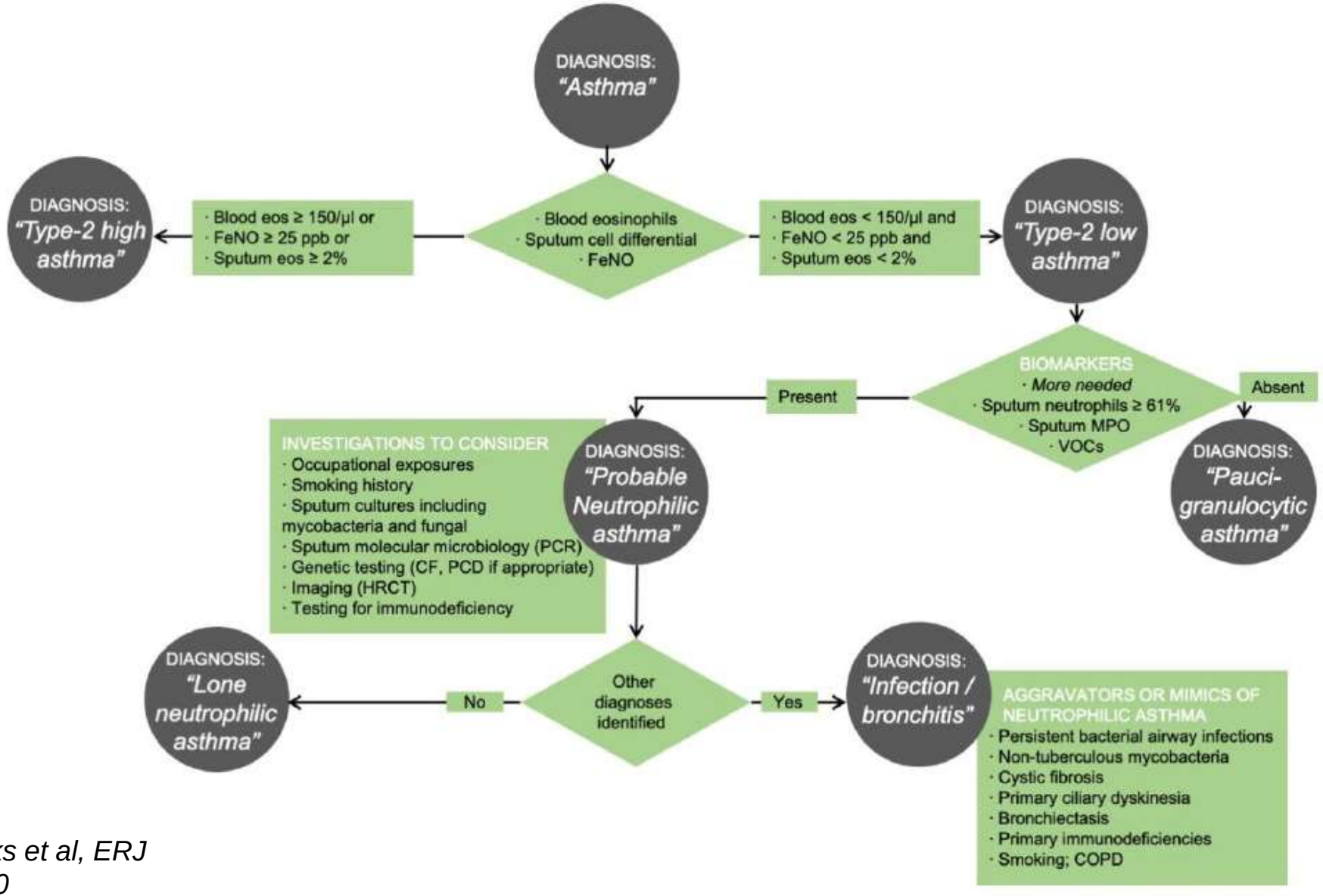
A characteristic feature is a lack of response to systemic corticosteroids

Hinks et al, ERJ 2020

Non-eosinophilic asthma is associated with

- female sex
- obesity
- non-atopic status
- adult onset symptoms
- smoking
- occupational exposures to low-molecular weight compounds
- and elite athletics

Hinks et al, ERJ 2020



Hinks et al, ERJ 2020

Suggested algorithm for defining type-2 low asthma in clinical practice.

- In difficult-to-treat and severe asthma systemic corticosteroid prescribing is common, with up to 60% of treatment refractory asthmatics in a UK series receiving oral corticosteroids

- In symptom-predominant asthma phenotypes, or those with fixed airflow limitation, overtreatment with systemic corticosteroids can occur with inappropriate escalation of oral corticosteroids

Hinks et al, ERJ 2020

- Adjusting ICS doses based on sputum eosinophil or FeNO effectively decreases exacerbations

Petsky HL et al, Thorax 2018

Composite type-2 biomarker strategy versus a symptom–risk-based algorithm to adjust corticosteroid dose in patients with severe asthma: a multicentre, single-blind, parallel group, randomised controlled trial

Population	Intervention	Comparison	Outcome
N=301, Adults (18–80 years of age) with severe asthma (GINA steps 4 and 5) and FENO of less than 45 ppb at 12 specialist severe asthma centres across England, Scotland, and Northern Ireland	Biomarker based (FeNO, eosinophils and periostin) adjustment of GC dose	Randomly assigned (4:1) to either the biomarker strategy group or the control group	Proportion of patients with any reduction in oral or inhaled GC dose at any point over the 48 weeks of the study

LG Heaney et al, Lancet 2020

Interpretation

Study could not show a greater proportion of patients on a lower GC dose by means of a biomarker-based strategy in severe asthma compared with GC adjustment based on symptoms and previous exacerbation history

LG Heaney et al, Lancet 2020

Treatable trait	Phenotype	Potential Biomarkers	Investigations	Therapeutic option	Comments
Fixed airflow obstruction	Persistent airflow obstruction despite ICS+LABA use.		Spirometry with reduced post-bronchodilator FEV_1/FVC ratio.	Long acting antimuscarinics.	Effect small and may worsen cough so assess response and discontinue if no benefit.
Chronic bacterial airway colonisation	Persistent mucopurulent cough, frequent infective exacerbations. Bacterial colonisation with potentially pathogenic bacteria (e.g. *Haemophilus influenzae*).	Typical organisms on sputum culture. Pathogenic specific quantitative PCR.	Sputum culture. Exclude mycobacteria with sputum culture. Consider CT to exclude bronchiectasis.	Long term, low dose azithromycin.	Research needed into optimal patient selection, duration of therapy, potential use of other macrolides.
Cough reflex hypersensitivity	Female predominant, adult onset.	Capsaicin hypersensitivity.		Discontinue ACEi, treat GORD.	Research needed into cough suppressants including P2X3 inhibitors.
Airway hyper-reactivity	Marked airway hyperreactivity and inadequate response to other therapies.	Paucigranulocytic.	Reversibility / bronchial hyper-responsiveness testing, CT to exclude bronchiectasis and tracheo-bronchomalacia.	Consider bronchial thermoplasty in highly-selected patients.	Optimal phenotype, long term outcomes and efficacy of retreatment remain to be defined.
Steroid over use	Non-eosinophilic, patient reports symptoms are slow to improve after initiation of systemic steroids.		Peripheral blood eosinophil count.	Consider a steroid holiday: cautiously stopping systemic steroids.	Care to avoid iatrogenic adrenal insufficiency.
Vocal cord dysfunction (ILO)	Episodic, symptoms predominantly inspiratory, inspiratory stridor, minimal response to pharmacotherapy.	Flattened inspiratory flow loop, normal expiratory spirometry.	Laryngoscopy during provocation.	Specialist speech and language therapy.	Often coexists with asthma, triggers include inhalational irritants, exercise, and psychosocial disorders.

Table 2 Current therapeutic options in type-2 low asthma

Hinks et al, ERJ 2020

Table 3 Potential future therapeutic targets in type-2 low asthma

Pathway	Pathobiological Mechanism	Potential Biomarkers	Potential Therapeutics
IL-1β	Activation of the NLRP3 inflammasome → NF-kB → cytokines including IL-1β and neutrophil chemokines	IL-1β IL-1R NLPR3	Anti-IL-1β (e.g. canakinumab) IL-1β receptor antagonists (e.g. anakinra) NLRP3 small-molecule inhibitors
IL-17A/F	Th17 / γδ T17 / ILC3 / MAIT cells → IL-17A & IL-17F → epithelial derived neutrophil chemoattractants and antimicrobial defence	IL-17A, IL-17F IL-23A RORγt	Anti-IL-17RA (e.g. brodalumab) Anti-IL-23 (e.g. risankizumab) DNAzymes Small-molecule inhibitors
Alarmins	Epithelial tissue damage → release of alarmins TSLP / IL-33 / IL-25		Anti-TSLP (e.g. tezepelumab)
Resolvins	Lipoxin A4 promotes resolution of inflammation via ALX/FPR2 Increased serum amyloid A inhibits resolvin signalling via ALX/FPR2	Low LXA4 High SAA	LXA4 or analogues Specialized proresolving mediator precursors
Colony stimulating factors	Apoliporoteins (e.g. APOA1) → ABCA1 inhibit G-CSF-induced neutrophilia	G-CSF GM-CSF	Neutralising antibodies APOA1 mimetic peptide
Type I interferons	Stable state: high ISG → type-2-independent inflammation Acute viral infection: deficient type-I/III IFN → increased viral replication	Blood ISG expression Low IFN-α / -β / -λ	 Inhaled IFN-β
IL-6	IL-6: obesity / granulocytes → IL-6 → steroid-resistant inflammation IL-6 trans-signalling: bacteria → TLRs → granulocytes shed soluble IL-6R + IL-6 → local epithelial cell inflammation	IL-6 sIL-6R	Anti-IL-6 (e.g. clazakizumab) Anti-IL-6R (e.g. tocilizumab) Antimicrobials
Mast cells	IgE cross-linking → Mast cell degranulation → mediators including histamine, tryptase, chymase, carboxypeptidase	Tryptase Chymase	Anti-β-tryptase mAb KIT inhibitors (e.g. imatinib)
IFN-γ	Th1 / ILC1 / NK cells → IFN-γ → CXCL10 → neutrophilia & ↓ SLPI	TNF IFN-γ, CXCL10, SLPI Tbet	Soluble TNFR (e.g. etanercept) Small-molecule inhibtors (JAK1) DNAzyme (Tbet)
CXCL8 (IL-8)	CXCL8 → CXCR2 → neutrophil recruitment	CXCL8	Small-molecule inhibitors

Hinks et al, ERJ 2020

- Few studies have investigated proteomics in severe asthma

- Despite little difference in clinical characteristics, current smoker asthmatics were distinguishable from ex smoker asthmatics subjects at the sputum proteomic level when sputum supernatants were compared

- Smokers in this study had increased levels of colony-stimulating factor 2 protein in their sputum, and ex-smokers had increased levels of CXCL8, neutrophil elastase, and azurocidin 1

K Takahashi et al, ERJ 2018

- Neutrophilic asthma is associated with airway colonisation by bacteria including Haemophilus influenzae and Moraxella catarrhalis, which might induce Th17 responses

- Microbiome studies have also linked neutrophilic asthma with the presence of H. influenzae and of a reduced microbial diversity, suggesting dominance of a single airway pathogen

- Larger microbiome studies are needed to determine the exact role these bacteria play

Hinks et al, ERJ 2020

Sublingual Immunotherapy for Asthma

Objective	Population
To assess the efficacy and safety of SLIT compared with placebo or standard care for adults and children with asthma	66 studies, involving 7944 people Most double-blind and placebo-controlled, and recruited participants with mild or intermittent asthma, often with comorbid allergic rhinitis 23 studies recruited adults and teenagers; 31 recruited only children; 3 recruited both; and 9 did not specify

Fortescue R et al, Cochrane Database of Systematic Reviews 2020

Summary of findings 1. Sublingual immunotherapy versus control for asthma

Sublingual immunotherapy versus control for asthma

Patient or population: adults and children with asthma
Settings: outpatient
Intervention: sublingual immunotherapy
Comparison: placebo or usual care

Weight mean duration of all included studies: 54 weeks (Fadel 2010, Li 2016, and Rodriguez 2012 not included in calculation as duration not reported)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	SLIT				
Exacerbation requiring ED or hospital visit **Weighted mean duration of studies: 31 weeks**	250 per 1000	104 per 1000 (32 to 286)	OR 0.35 (0.10 to 1.20)	108 (2 RCTs)	⊕⊝⊝⊝ Very low[a,b,c]	
Quality of life	No meta-analysis possible	Not applicable	-	-	Not applicable	9 studies reported quality of life outcomes, but we were unable to perform a meta-analysis. See Analysis 1.2. Whilst the direction of effect favoured SLIT in most studies reporting quality of life, the effect was often uncertain and of small magnitude.
Serious adverse events **Weighted mean duration of studies: 56 weeks**	20 per 1000	16 per 1000 (10 to 25)	RD −0.0004, (−0.0072 to 0.0064)	4810 (29 RCTs)	⊕⊕⊕⊝ Moderate[d,e,f]	
Exacerbation requiring OCS **Weighted mean duration of studies: 58 weeks**	61 per 1000	46 per 1000 (28 to 75)	OR 0.75 (0.45 to 1.24)	1364 (5 RCTs)	⊕⊝⊝⊝ Very low[a,b,c]	

Fortescue R et al, Cochrane Database of Systematic Reviews 2020

All adverse events **Weighted mean duration of studies: 62 weeks****	465 per 1000	634 per 1000 (565 to 699)	OR 1.99 (1.49 to 2.67)	4251 (27 RCTs)	⊕⊕⊕⊕ High[d,e]	
Bronchial provocation	Mean bronchial provocation in control group was 1020 µg (PD20) and 4.75 mg/mL (PC20).	Mean bronchial provocation in intervention group was 0.99 standard deviations higher (0.17 higher to 1.82 higher).	-	200 (5 RCTs)	⊕⊕⊖⊖ Low[g,h]	4 studies reported outcome as PC20 and 1 study as PD20. We combined the different scales using standardised mean differences.
ICS use	Mean ICS use in control group was 255 µg.[l]	Mean ICS use in intervention group was 17 µg/d lower (61.19 lower to 26.93 higher).	-	778 (3 RCTs)	⊕⊕⊖⊖ Low[l,k]	Both treatment and control groups in the studies included in this analysis showed significantly decreased ICS use at end of the study compared with baseline.

*The basis for the **assumed risk** (e.g. median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**'All adverse events' was not a prespecified outcome, but we have included it here, as substantial data contributed to this outcome. We have left out the asthma symptom scores outcome, as we were able to perform only a limited narrative analysis.

CI: confidence interval; **ED:** emergency department; **FEV_1:** forced expiratory volume in 1 second; **ICS:** inhaled corticosteroids; **OCS:** oral corticosteroids; **OR:** odds ratio; **PC20:** provocative concentration of methacholine required to produce a 20% fall in FEV_1; **PD20:** provocative dose of methacholine required to produce a 20% fall in FEV_1; **RCT:** randomised controlled trial; **RD:** risk difference; **SLIT:** sublingual immunotherapy

GRADE Working Group grades of evidence

Fortescue R et al, Cochrane Database of Systematic Reviews 2020

Conclusions

- Evidence for important outcomes such as exacerbations and QoL remains too limited to draw meaningful conclusions about the efficacy of SLIT for people with asthma

- Trials mostly recruited mixed populations with mild and intermittent asthma and/or rhinitis and focused on non-validated symptom and medication scores

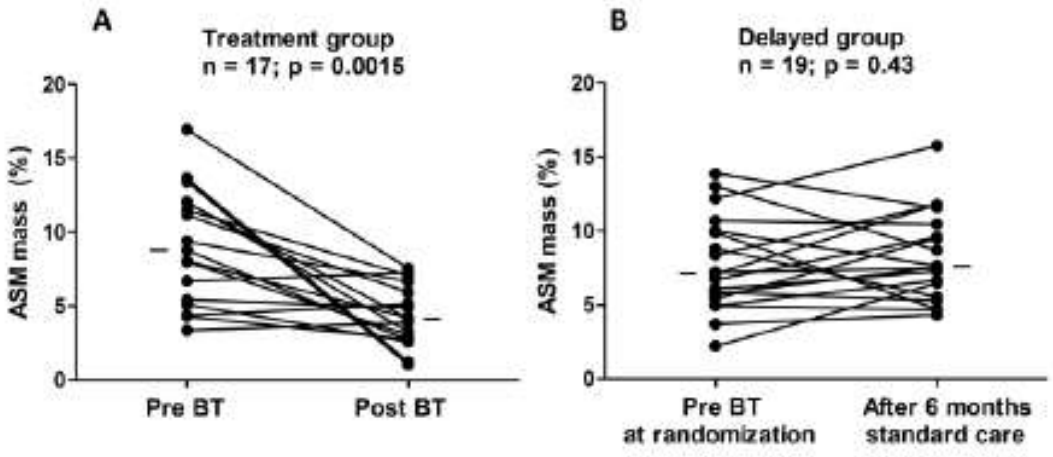
- SLIT may be a safe option for people with well-controlled mild-to-moderate asthma and rhinitis who are likely to be at low risk of serious harm; role of SLIT for people with uncontrolled asthma requires further evaluation

Fortescue R et al, Cochrane Database of Systematic Reviews 2020

Bronchial Thermoplasty Induced Airway Smooth Muscle Reduction and Clinical Response in Severe Asthma: The TASMA Randomized Trial

Population	Intervention	Comparison	Outcome
N=40, Severe asthma patients between 18 and 65 years old Design: RCT in two centers (UK/ sNetherlands each)	BT	Patients were randomized into A= immediate BT treatment and B= 6 months delayed BT treatment control group (1:1 ratio, n=20 per group).	1.To assess the effect of BT on ASM mass 2. To identify patient characteristics that correlate with BT-response.

Goorsenberg et al, AJRCCM 2020



A) ASM mass % in the immediate group before and after BT showing a median ASM mass % of 8.75% pre BT versus 4.14% post BT (53% decrease)

B) ASM mass % in the delayed group before and after 6 months standard care with a median of ASM mass % of 7.08% at randomization versus 7.56% after 6 months standard care (7% increase)

Goorsenberg et al, AJRCCM 2020

Table 4 Associations between ACQ-6 and AQLQ improvement and baseline characteristics (n=35)

	ACQ-6 change		AQLQ change	
	rho	p-value	rho	p-value
Asthma age of onset	-0.20	0.25	0.30	0.08
Total IgE†	-0.53	0.001*	0.24	0.17
Blood eosinophils x10^9/L†	-0.46	0.006*	0.48	0.004*
Pre-SABA FEV_1% predicted‡	-0.02	0.89	0.20	0.26
Reversibility FEV_1‡	-0.13	0.48	0.21	0.25
PC20 (mg/ml)§	0.30	0.08	-0.09	0.61
FeNO (ppb)‖	-0.28	0.19	0.21	0.33
ASM mass (%) desmin	0.07	0.69	-0.009	0.96
ASM mass (%) α-SMA	0.18	0.29	-0.05	0.79

ASM mass at baseline, ASM mass after BT and ASM change were not associated with ACQ and/or AQLQ improvement

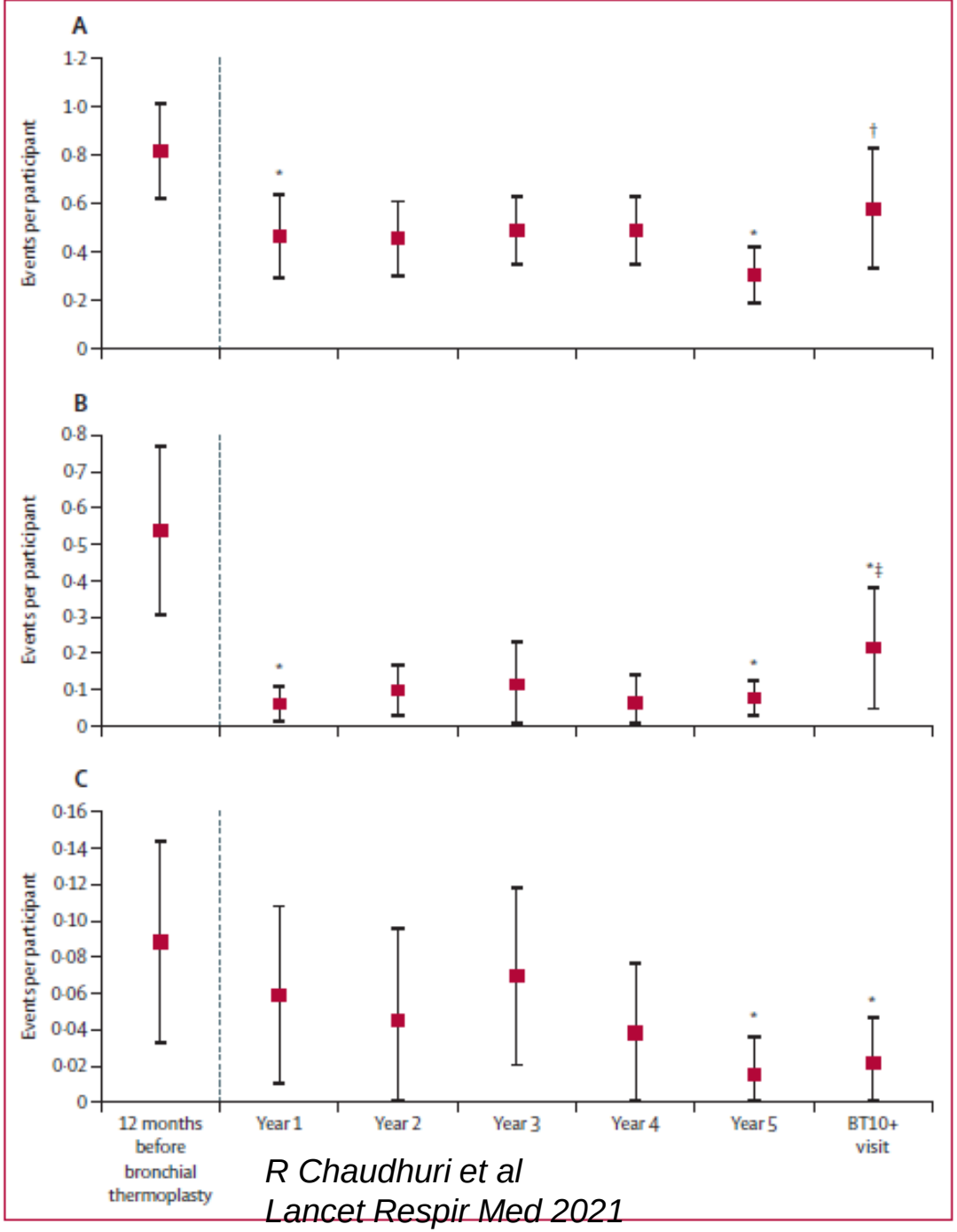
Associations were found between ACQ improvement and baseline blood eosinophil count and total IgE count

Goorsenberg et al, AJRCCM 2020

Safety and effectiveness of bronchial thermoplasty after 10 years in patients with persistent asthma (BT10+): a follow-up of three randomised controlled trials

Population	Intervention	Comparison	Outcome
N=192	BT	A. **Treated**: Subjects that received BT in a prior study (**AIR, RISA, or AIR2**) B. **Control**: Subjects that participated in prior study (AIR) or (RISA) but did not receive BT. C. **Sham**: Subjects that participated in the AIR2 study, were blinded and did not receive the treatment.	A. **Primary Safety Endpoint**: Absence of clinically significant post-treatment respiratory changes defined as bronchiectasis and bronchostenosis from Baseline (pre-BT) CT. B. **Primary Effectiveness**: Endpoints at 10 or more years following the subjects' last BT procedure; Asthma Exacerbations, ER Visits, Hospitalizations, and respiratory Serious Adverse Events.

R Chaudhuri et al
Lancet Respir Med 2021



R Chaudhuri et al
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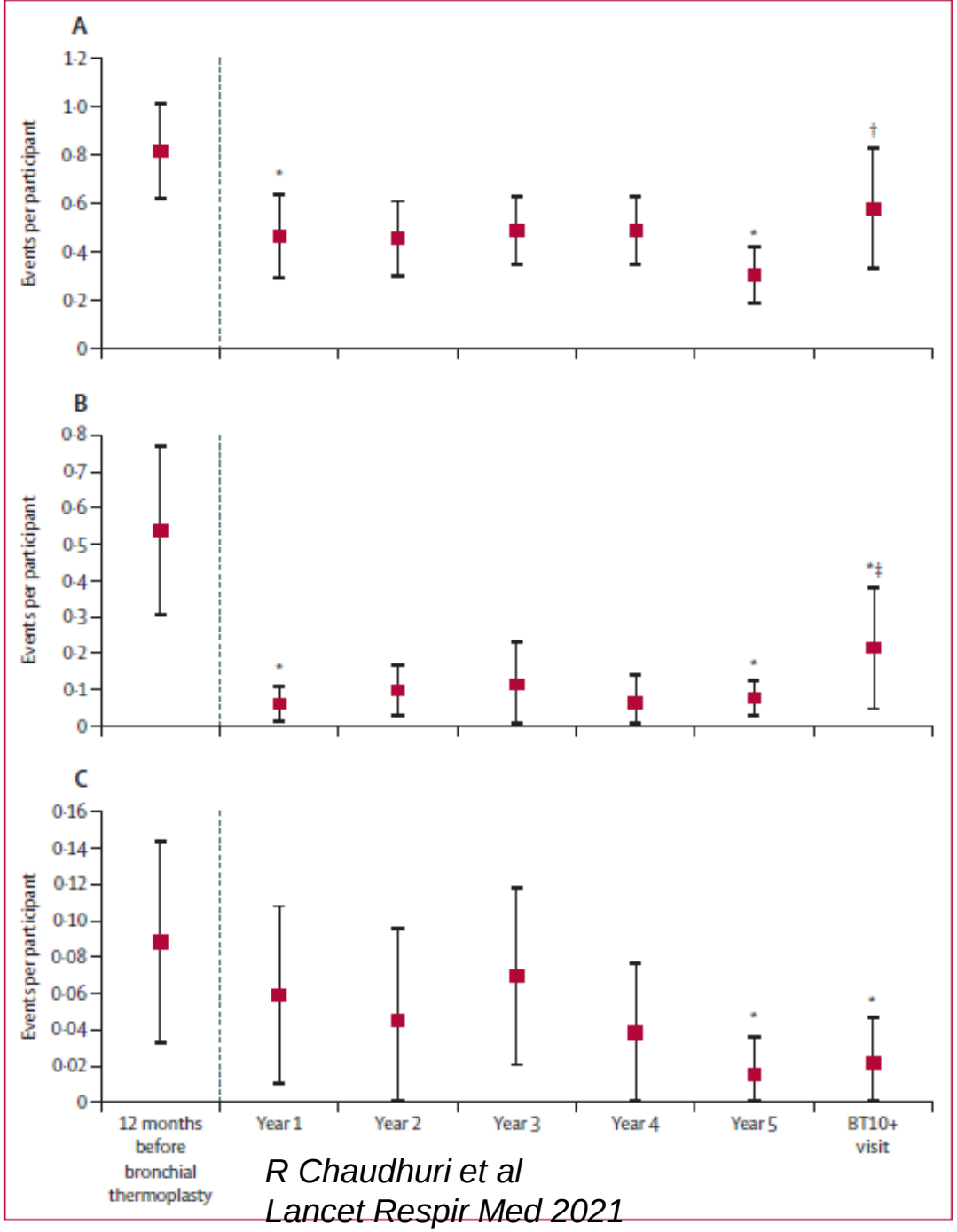
Figure 2: Severe asthma exacerbations in participants treated with bronchial thermoplasty (A), hospital emergency department visits (B), and admissions to hospital for asthma (C) in the BT10+ study

- Participants had 0·82 severe exacerbations per participant (AIR2 data only) 12 months before BT compared with 0·47 during the first year after BT and 0·31 during year 5 after BT, both of which were significantly reduced compared with 12 months before BT

- During the 12 months before the BT10+ visit, there were 0·58 severe exacerbations per participant, which was significantly more than during year 5 after BT but not significantly different from year 1 after BT



R Chaudhuri et al
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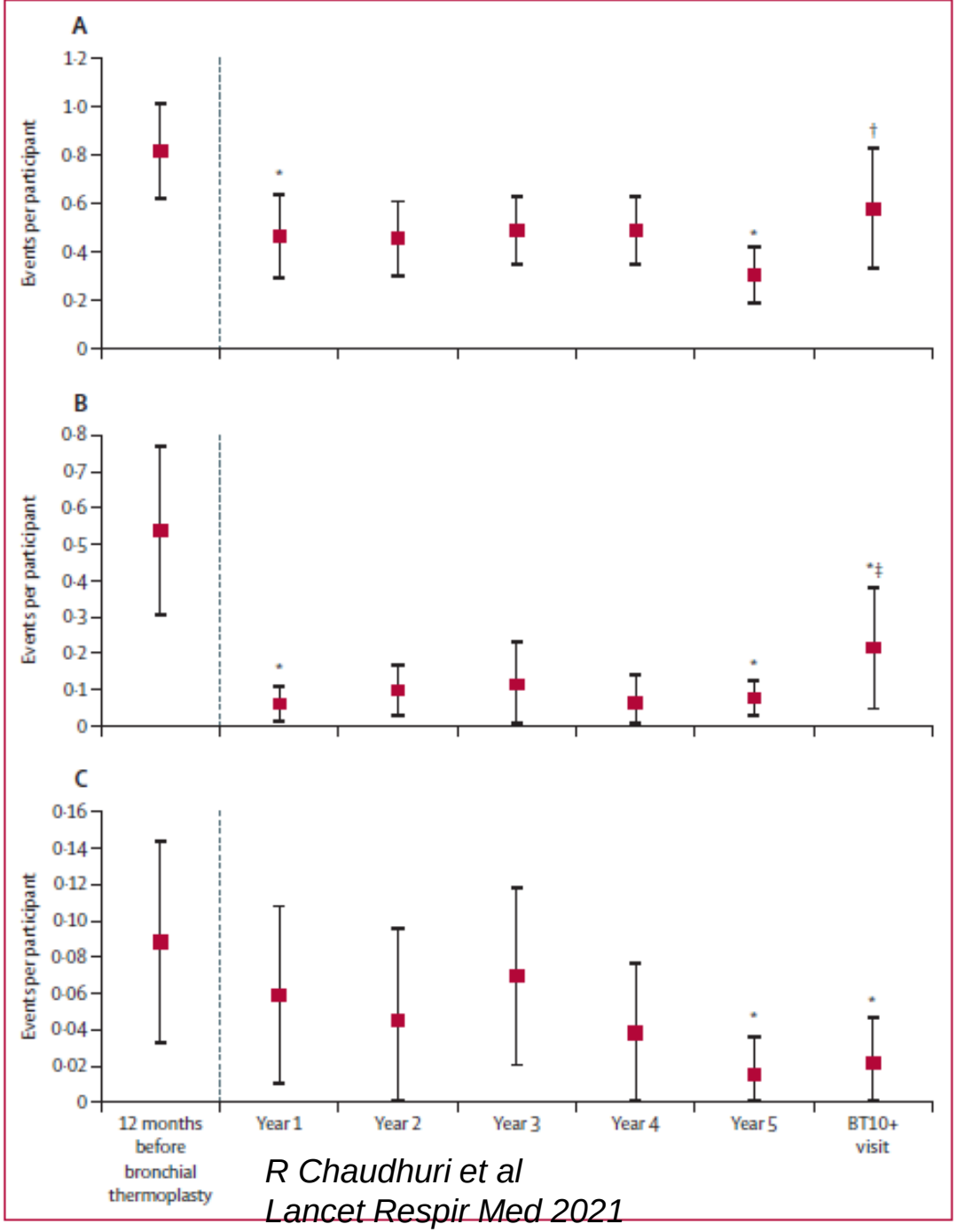
Figure 2: Severe asthma exacerbations in participants treated with bronchial thermoplasty (A), hospital emergency department visits (B), and admissions to hospital for asthma (C) in the BT10+ study

- Compared with the 12 months before BT, the number of hospital emergency department visits per participant was lower at year 1 after BT, year 5 after BT, and during the 12 months before the BT10+ visit

- However, the rate of hospital emergency department visits was significantly higher during the 12 months before the BT10+ visit than during year 1 and year 5 after BT



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Lancet Respir Med 2021

Figure 2: Severe asthma exacerbations in participants treated with bronchial thermoplasty (A), hospital emergency department visits (B), and admissions to hospital for asthma (C) in the BT10+ study

Compared to the 12 months before BT, the rates of admissions to hospital for asthma were lower at year 5 and during the 12 months before the BT10+ visit

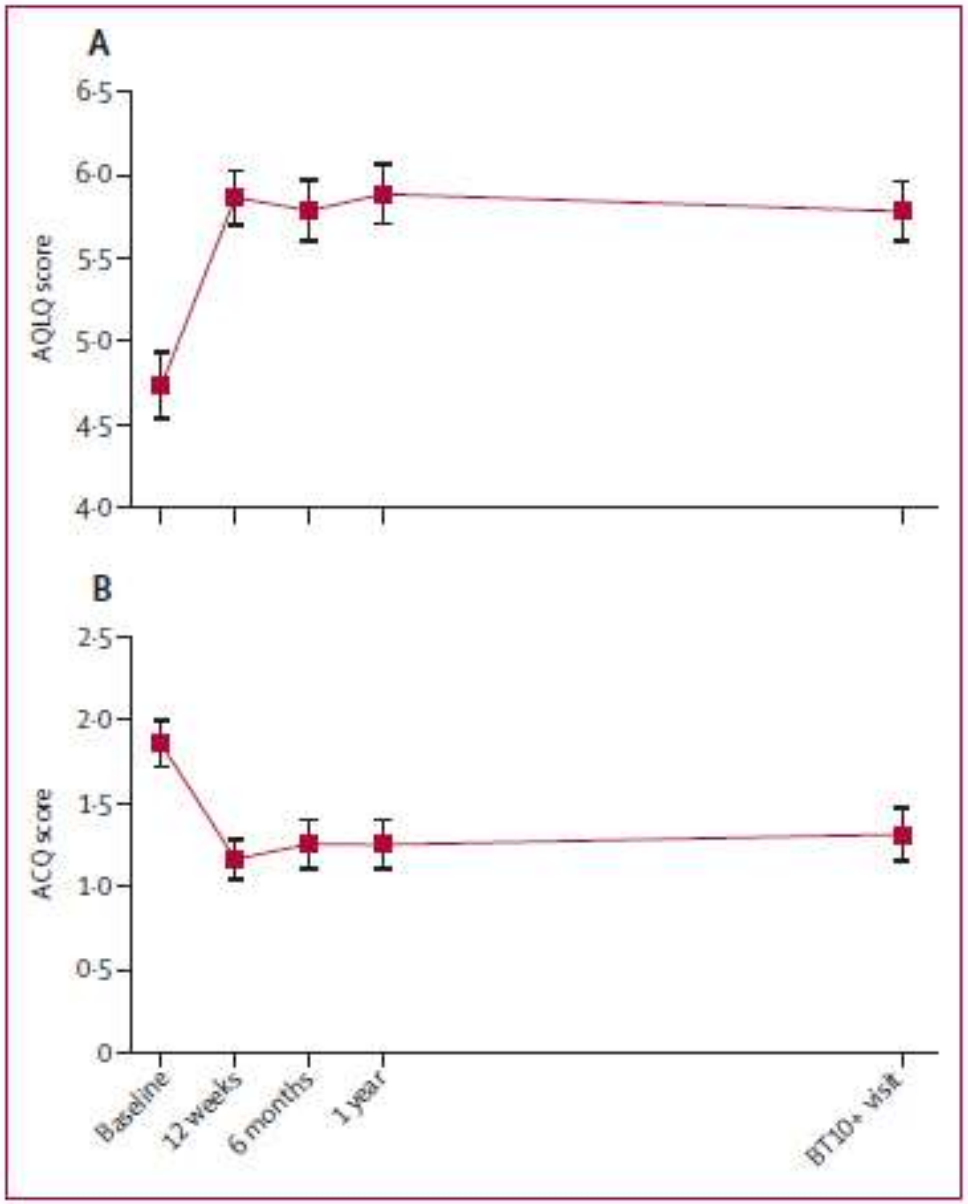

Figure 3: AQLQ (A) and ACQ (B) scores over time in participants treated with bronchial thermoplasty
Datapoints represent mean and 95% CIs.

- Mean AQLQ scores increased from 4·73 to 5·86 by 12 weeks after BT, and this improvement was sustained for 10 years or more after treatment
- ACQ scores dropped from 1·86 to 1·17 by 12 weeks after BT, and improvements in these scores also persisted for 10 years or more

R Chaudhuri et al, Lancet Respir Med 2021

	Sham (n=24)	Bronchial thermoplasty (n=99)
Bronchiectasis observed at baseline	3/21 (14%; 3·0–36·3)	7/96 (7%; 3·0–14·4)
Bronchiectasis observed at BT10+ visit	2/21 (10%; 1·2–30·4)	13/97 (13%; 7·3–21·8)
Bronchiectasis observed at BT10+ visit and not baseline	0/18 (0; 0–18·5)	6/89 (7%; 2·5–14·1)

Data are n/N (%; 95% CI). Sham participants receiving bronchial thermoplasty after participation in the AIR2 study were excluded. Baseline high-resolution CT information for one AIR2 bronchial thermoplasty participant was missing but this participant had a high-resolution CT at the BT10+ study visit.

Table 2: **Results of high-resolution pulmonary CT at the BT10+ study visit (AIR2 participants only)**

- All but one instance of bronchiectasis was classified as mild; one case was classified as moderate
- Clinical symptoms of bronchiectasis (chronic cough, increased sputum, and recurrent infections) were not present in these participants

R Chaudhuri et al, Lancet Respir Med 2021

Interpretation

Efficacy of bronchial thermoplasty is sustained for 10 years or more, with an acceptable safety profile

Bronchial thermoplasty is a long-acting therapeutic option for patients with asthma that remains uncontrolled despite optimised medical treatment

R Chaudhuri et al, Lancet Respir Med 2021

Safety and Effectiveness of Bronchial Thermoplasty When FEV_1 Is Less Than 50%

Population	Intervention	Comparison	Outcome
N=68	BT	Group 1: those with a baseline prebronchodilator FEV1 % predicted < 50% (n = 32) or Group 2: those with an FEV1 > 50% (n = 36)	Effectiveness: 6 months post-BT by the change in ACQ score from baseline. Safety: Adverse event noted if: 1. For any reason, a patient stayed in hospital beyond the elective 24-hour admission 2. Patient attended the ED or readmitted to hospital, for any reason in the 30 days after any BT treatment

Langton D et al, CHEST 2020

TABLE 4] Response to Treatment at 6 Months: Cohorts Compared

Parameter	Group 1 (FEV_1 < 50%)	Group 2 (FEV_1 ≥ 50%)	*P* Value
Change in ACQ	−1.5 ± 1.0	−1.7 ± 1.3	NS
Change in SABA, puffs/d	−8 (14)	−8 (6)	NS
Change in exacerbations/6 mo	−2.2 ± 3.6	−3.9 ± 3.7	.053
Change in OCS, mg/d	−4.8 ± 6.7	−2.5 ± 6.5	NS
Percent change in FEV_1	15.4 ± 28.8	2.8 ± 24.9	.058

See Table 1 legend for expansion of abbreviations.

- In both cohorts improvements were observed in ACQ score, the weaning of oral corticosteroids, exacerbation frequency, and reduction in reliever medication requirement
- The magnitude of the improvements was not statistically different between the two groups

Langton D et al, CHEST 2020

Safety Outcomes

- Of the 204 procedures performed, there were 10 occasions (4.9%) when patients stayed in hospital longer than the electively planned 24-hour stay
- The reasons for the longer hospital stays were asthma (7), lobar collapse in the treated area (2), and a pneumomediastinum (1)
- On 4 of these 10 occasions, patients were observed in an ICU; assisted ventilation was never required
- Of these 10 occasions, 9 were related to group 2 (FEV1 > 50%) and only 1 occasion was related to a group 1 patient

Langton D et al, CHEST 2020

- There were 9 occasions when patients were readmitted to hospital for any cause within 30 days of a procedure (4.4% readmission rate)
- Reasons included lower respiratory tract infection (4), asthma exacerbation in (3), urinary retention(1), and melena(1)
- Of these nine events, 5 were related to group 1 patients and 4 to group 2
- All patients made a complete recovery from their adverse event
- There were no deaths for any reason during follow-up

Langton D et al, CHEST 2020

Conclusions

BT can confidently be offered to patients with asthma with an FEV1 30% to 50% predicted without risk of more frequent or more severe adverse events, and with the expectation of the same degree of response as patients with better lung function

Langton D et al, CHEST 2020

Summary

- Asthma represents one of the most rapid and active area of research
- Personalized medicine represents the future
- Focus is on endotypes and phenotypes, biomarkers, novel treatments such as biologicals, bronchial thermoplasty and real-life studies