Asthma: Mimickers & Case-Based Management

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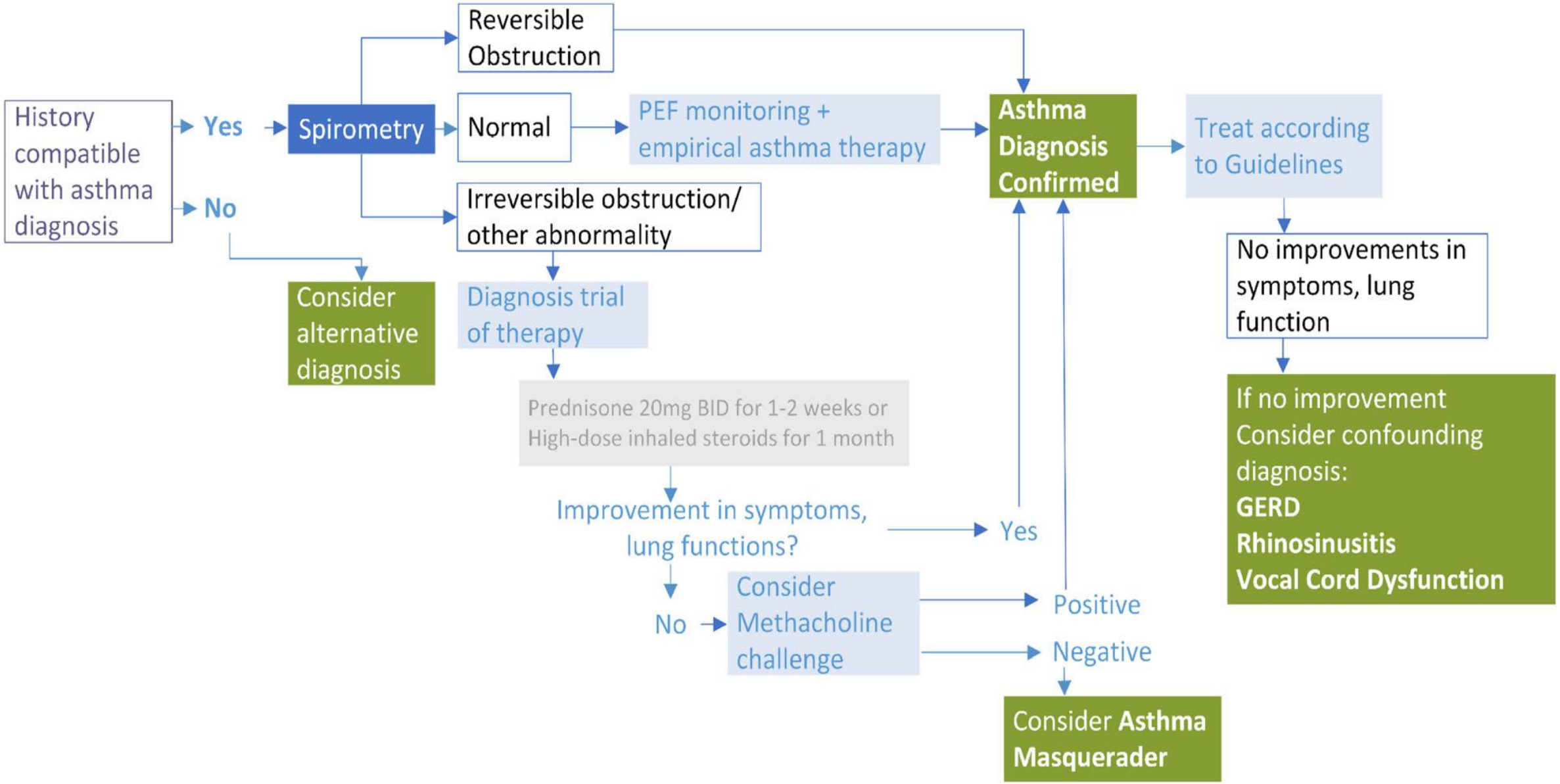
Diagnosis of asthma

- The diagnosis of asthma is based on a history of variable respiratory symptoms and demonstration of variable expiratory airflow limitation
  - Test before treating, wherever possible
  - Symptoms, variability in lung function, and airway hyperresponsiveness are decreased by ICS, so it is often more difficult to confirm the diagnosis after controller treatment is started
- The flow-chart (Box 1-1) has been updated in 2022 to emphasize the different approach for *initial* diagnosis compared with confirming the diagnosis in patients taking controller treatment
  - Diagnostic approaches for patients taking controller treatment are in Boxes 1-3 and 1-4
- At a global level, spirometry before and after bronchodilator is the most useful initial investigation
  - Optimize the conditions for testing, if possible (e.g. when symptomatic, and after withholding bronchodilators)
  - In patients on controller treatment, more than one test is often needed
- GINA will review GRADE evidence from ERS Task Force on diagnosis of asthma *(Louis et al, ERJ 2022)*

Clinical features of asthma and common asthma mimics[4]

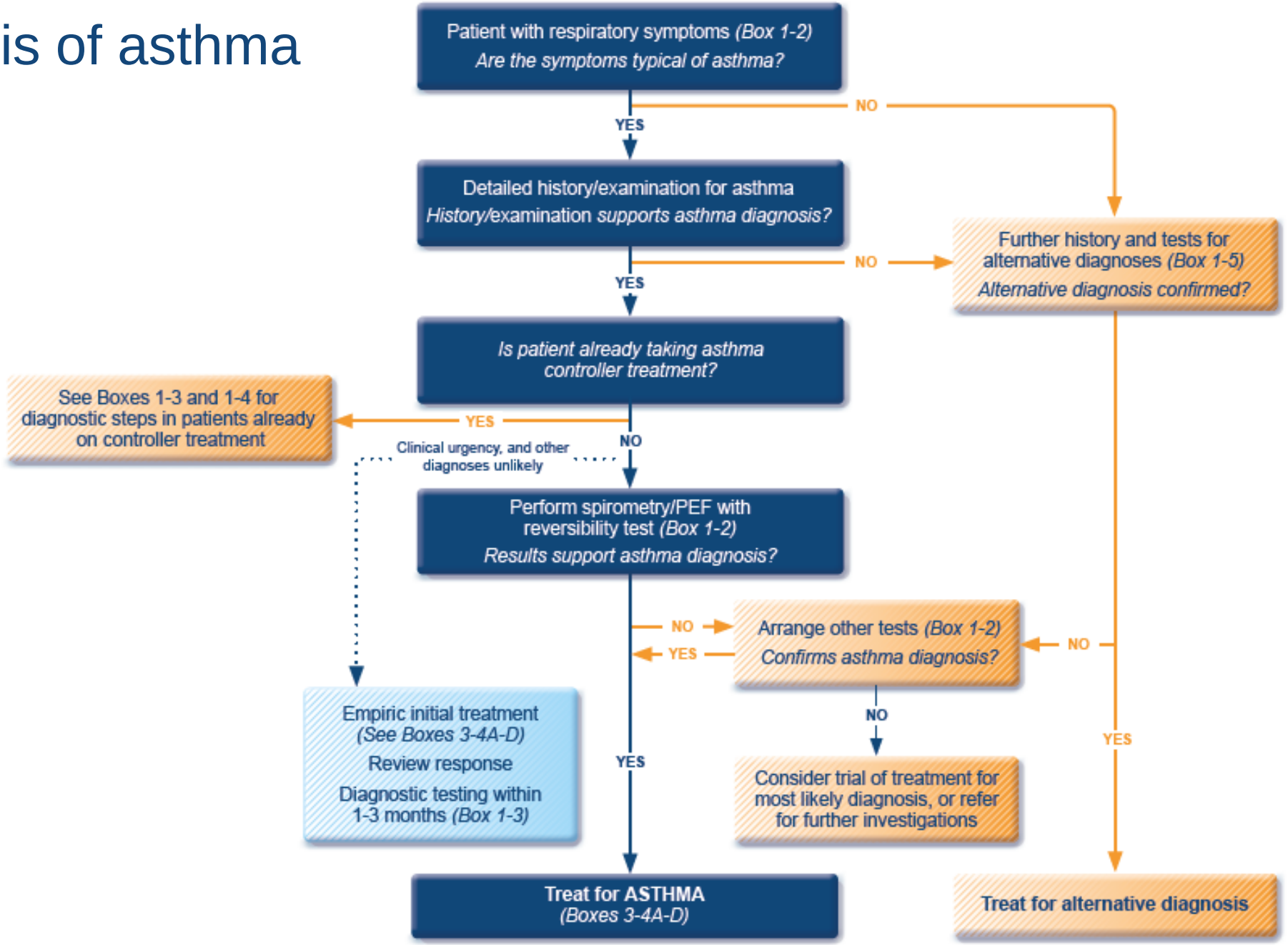
If the patient has these features	... think of asthma
▪ More than one type of respiratory symptom (isolated cough alone is rarely due to asthma) ▪ Recurrent or seasonal respiratory symptoms ▪ Symptoms worse at night or early morning ▪ Symptoms triggered by exercise, allergens, cold air, laughing, viral infections, or by aspirin or β-blockers ▪ Symptoms rapidly relieved by a bronchodilator inhaler ▪ History or family history of allergies (eg, allergic rhinitis; although some asthma is non-allergic) ▪ Symptoms beginning in childhood (although asthma can commence in adult life) ▪ Symptoms during exercise that worsen after the patient stops (almost pathognomonic of asthma)	These clinical features increase the probability of asthma, but common asthma mimics (below) should also be considered. For diagnosis of asthma, objective confirmation of variable expiratory airflow limitation is still needed (see main text)

❖ **Helen K Reddel,** Common conditions that mimic asthma, Medical Journal of Australia, doi: 10.5694/mja2.51467 2022.



❖ Gherasim et al. World Allergy Organization Journal (2018) 11:29

Diagnosis of asthma



Diagnosis in patients already on controller treatment

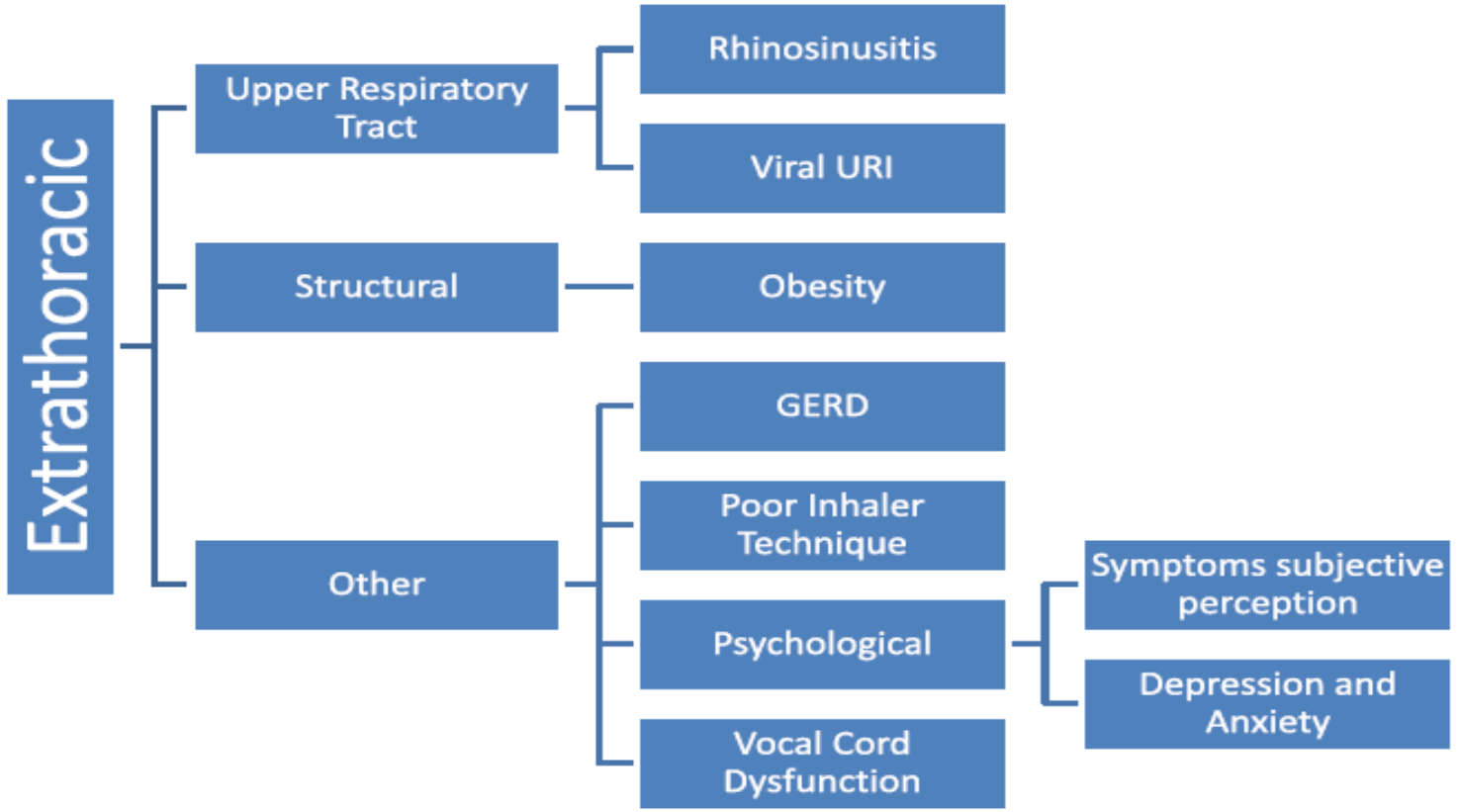
Current status	Steps to confirm the diagnosis of asthma
Variable respiratory symptoms and variable airflow limitation	Diagnosis of asthma is confirmed. Assess the level of asthma control (Box 2-2) and review controller treatment (Box 3-5).
Variable respiratory symptoms but no variable airflow limitation	Consider repeating spirometry after withholding BD (4 hrs for SABA, 24 hrs for twice-daily ICS-LABA, 36hrs for once-daily ICS-LABA) or during symptoms. Check between-visit variability of FEV_1, and bronchodilator responsiveness. If still normal, consider other diagnoses (Box 1-5). *If FEV_1 is >70% predicted*: consider stepping down controller treatment (see Box 1-5) and reassess in 2–4 weeks, then consider bronchial provocation test or repeating BD responsiveness. *If FEV_1 is <70% predicted*: consider stepping up controller treatment for 3 months (Box 3-5), then reassess symptoms and lung function. If no response, resume previous treatment and refer patient for diagnosis and investigation.
Few respiratory symptoms, normal lung function, and no variable airflow limitation	Consider repeating BD responsiveness test again after withholding BD as above or during symptoms. If normal, consider alternative diagnoses (Box 1-5). Consider stepping down controller treatment (see Box 1-5): • *If symptoms emerge and lung function falls*: asthma is confirmed. Step up controller treatment to previous lowest effective dose. • *If no change in symptoms or lung function at lowest controller step*: consider ceasing controller, and monitor patient closely for at least 12 months (Box 3-7).
Persistent shortness of breath and persistent airflow limitation	Consider stepping up controller treatment for 3 months (Box 3-5), then reassess symptoms and lung function. If no response, resume previous treatment and refer patient for diagnosis and investigation. Consider asthma–COPD overlap (Chapter 5).

BD: bronchodilator; LABA: long-acting $beta_2$-agonist; SABA: short-acting $beta_2$-agonist. 'Variable airflow limitation' refers to expiratory airflow.

If the patient has these features	... consider these asthma mimics
■ Dry cough or difficulty breathing triggered by strong smells, irritants, reflux, exercise ■ Symptoms worse when talking on the phone ■ Associated throat tightness or change in voice ■ Inspiratory stridor ■ Breathlessness worse at peak exercise	Laryngeal hypersensitivity, inducible laryngeal obstruction
■ Onset of shortness of breath, cough, wheeze after 40 years of age ■ Smoker or ex-smoker, or exposed to environmental tobacco smoke or dust/fumes ■ History of repeated chest infections ■ Persistent shortness of breath, which may be getting worse over time ■ Family history of emphysema	Chronic obstructive pulmonary disease (think α-1 antitrypsin deficiency if onset under 35 years of age)
■ History of ischaemic heart disease, hypertension or valvular disease ■ Dyspnoea on lying flat ■ Basal crepitations, ankle oedema, atrial fibrillation	Cardiac failure
■ Dizziness, light-headedness, tingling fingers ■ Symptoms triggered by anxiety ■ Sighing (air hunger)	Panic attacks, hyperventilation
■ Sneezing, itching nose, eyes or ears ■ Blocked nose ■ Throat-clearing	Allergic rhinitis, chronic upper airway cough syndrome (previously called post-nasal drip)
■ Productive cough most days ■ Recurrent chest infections	Bronchiectasis, cystic fibrosis
■ Dyspnoea unresponsive to bronchodilators	Central airway obstruction

❖ **Helen K Reddel,** Common conditions that mimic asthma, Medical Journal of Australia, doi: 10.5694/mja2.51467 2022.

Differential diagnosis of extrathoracic mimickers of asthma



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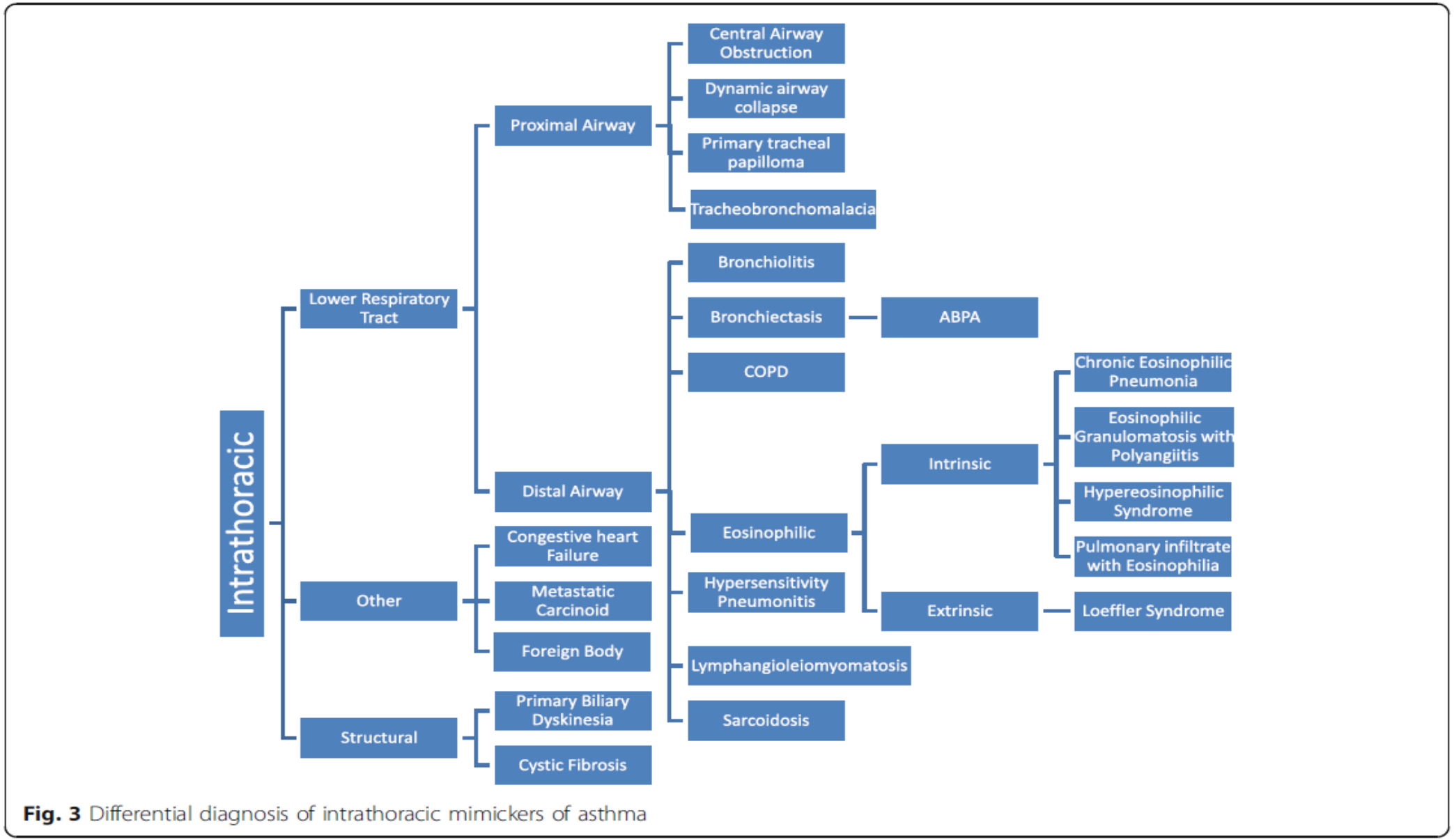
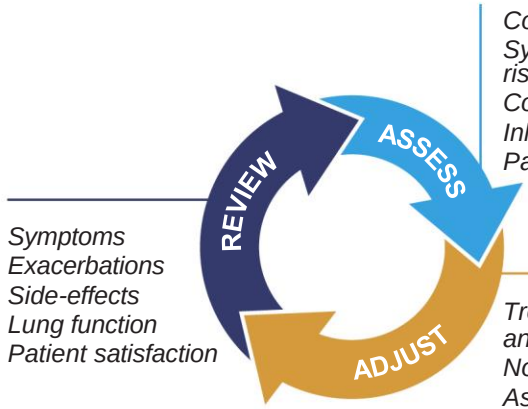


Fig. 3 Differential diagnosis of intrathoracic mimickers of asthma

❖ Gherasim et al. World Allergy Organization Journal (2018) 11:29

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 2-2B)
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/up/between tracks)
Education & skills training

CONTROLLER and **PREFERRED RELIEVER**
(Track 1). Using ICS-formoterol as reliever reduces the risk of exacerbations compared with using a SABA reliever

STEPS 1 – 2	STEP 3	STEP 4	STEP 5
As-needed 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-IL4R, anti-TSLP
RELIEVER: As-needed low-dose ICS-formoterol			

See GINA severe asthma guide

CONTROLLER and **ALTERNATIVE RELIEVER**
(Track 2). Before considering a regimen with SABA reliever, check if the patient is likely to be adherent with daily controller

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-IL4R, anti-TSLP
RELIEVER: As-needed short-acting beta$_2$-agonist				

Other controller options for either track (limited indications, or less evidence for efficacy or safety)	*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 LTRA or HDM SLIT, or switch to high dose ICS*	*Add azithromycin (adults) or LTRA. As last resort consider adding low dose OCS but consider side-effects*

GINA 2022, Box 3-5A

Definition of asthma severity and mild asthma

- By the ATS/ERS Task Force definition, asthma severity is assessed retrospectively from the treatment required to control the patient's asthma, i.e. after at least several months of treatment *(Taylor, ERJ 2008; Reddel, AJRCCM 2009)*
  - By this definition, asthma severity can be assessed only when treatment has been optimized and asthma is well-controlled, except for patients taking high dose ICS-LABA
- Severe asthma is asthma that remains uncontrolled despite optimized treatment with high dose ICS-LABA, or that requires high dose ICS-LABA to prevent it from becoming uncontrolled *(Chung, ERJ 2014)*
  - This definition is widely accepted, and has clinical utility
  - Severe asthma is distinguished from 'difficult-to-treat' asthma that is difficult to treat because of problems such as poor adherence, incorrect inhaler technique and comorbidities
- Mild asthma is currently defined as asthma that is well controlled on low dose ICS or as-needed-only ICS-formoterol
  - The utility and relevance of this definition is much less clear
  - The term 'mild asthma' is often interpreted very differently
  - Patients and clinicians often assume that 'mild asthma' means no risk and no need for controller treatment
  - BUT: up to 30% asthma deaths are in patients with infrequent symptoms *(Dusser, Allergy 2007; Bergstrom, Respir Med 2008)*

Background - the risks of ‘mild’ asthma

- Patients with apparently mild asthma are still at risk of serious adverse events
  - 30–37% of adults with acute asthma
  - 16% of patients with near-fatal asthma
  - 15–27% of adults dying of asthma

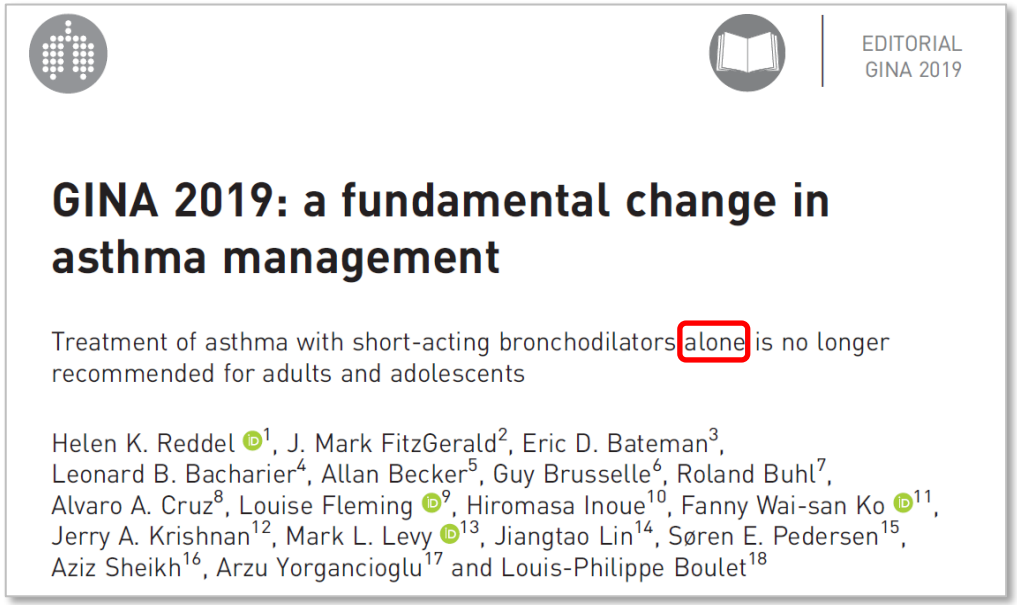
  } had symptoms less than weekly in previous 3 months *(Dusser, Allergy 2007; Bergstrom, 2008)*

- Exacerbation triggers are unpredictable (viruses, pollens, pollution, poor adherence)
- Even 4–5 lifetime OCS courses increase the risk of osteoporosis, diabetes, cataract *(Price et al, J Asthma Allerg 2018)*

SABA: short-acting beta$_2$-agonist

Why not treat with SABA alone?

- Inhaled SABA has been first-line treatment for asthma for 50 years
  - Asthma was thought to be a disease of bronchoconstriction
  - Role of SABA reinforced by rapid relief of symptoms and low cost
- Regular use of SABA, even for 1–2 weeks, is associated with increased AHR, reduced bronchodilator effect, increased allergic response, increased eosinophils *(e.g. Hancox, 2000; Aldridge, 2000)*
  - Can lead to a vicious cycle encouraging overuse
  - Over-use of SABA 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
- The only previous option was daily ICS even when no symptoms, but adherence is extremely poor
- GINA changed its recommendation once evidence for a safe and effective alternative was available



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]

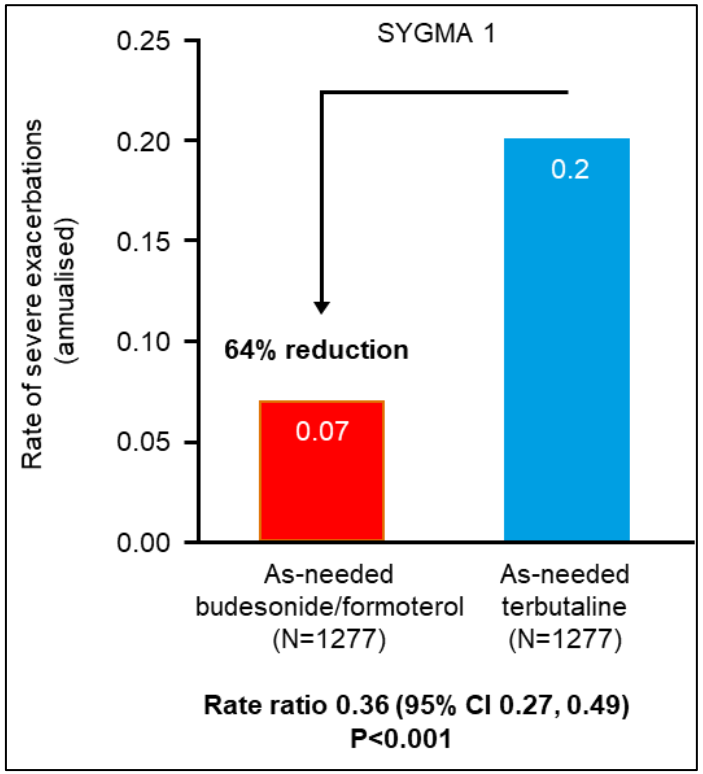
As-needed low dose ICS-formoterol in mild asthma (n=9,565)

COMPARED WITH AS-NEEDED SABA

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

COMPARED WITH MAINTENANCE LOW DOSE ICS

- The risk of severe exacerbations was similar (SYGMA 1 & 2), or lower (Novel START, PRACTICAL)
- Small differences in other asthma outcomes, favoring maintenance ICS, but all were less than the minimal clinically important difference
  - ACQ-5 mean difference 0.15 (MCID 0.5)
  - FEV_1 mean difference ~54 mL
  - FeNO mean difference ~10ppb (Novel START, PRACTICAL)
  - No evidence of progressive worsening over 12 months
- In Novel START and PRACTICAL, outcomes were independent of baseline features including blood eosinophils, FeNO, lung function, and exacerbation history
- Average ICS dose was ~50–100mcg budesonide/day

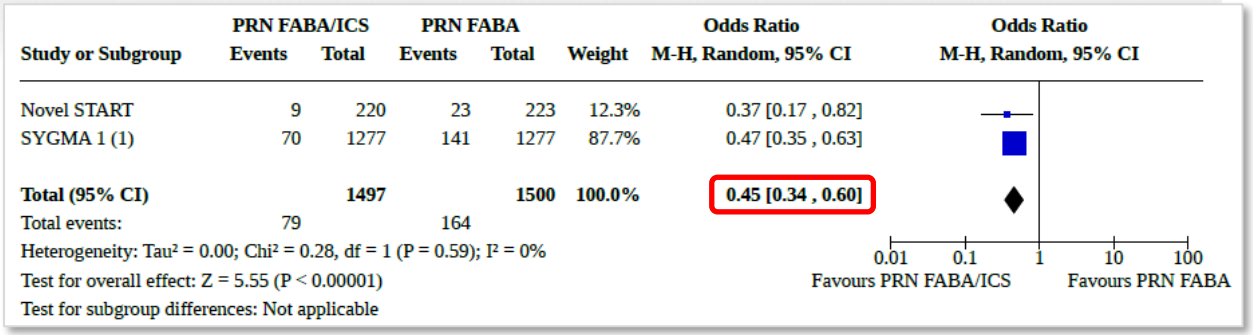


O'Byrne et al, NEJM 2018

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

New evidence for as-needed ICS-formoterol in mild asthma

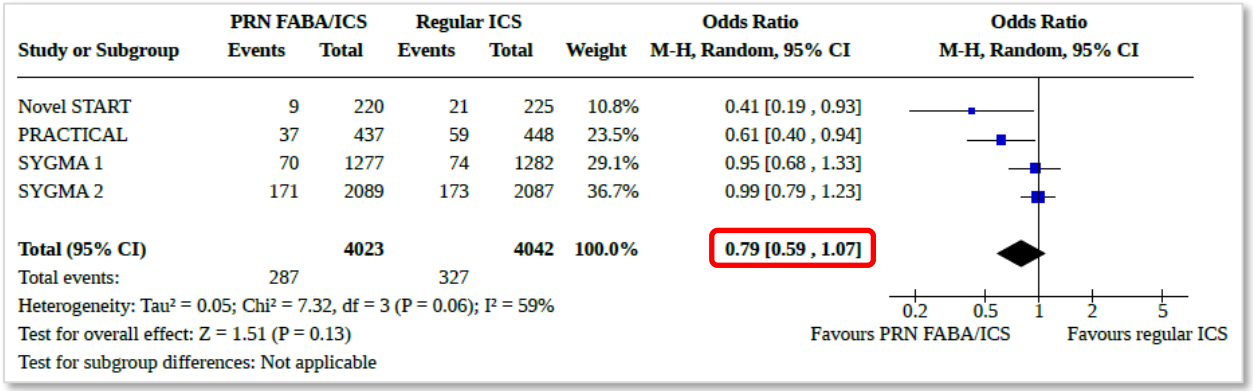
- Meta-analysis of all four RCTs, n=9,565
  (Crossingham, Cochrane 2021)
  - 55% reduction in severe exacerbations compared with SABA alone
  - Similar risk of severe exacerbations as with daily ICS + as-needed SABA



Study or Subgroup	PRN FABA/ICS Events	Total	PRN FABA Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Novel START	9	220	23	223	12.3%	0.37 [0.17 , 0.82]
SYGMA 1 (1)	70	1277	141	1277	87.7%	0.47 [0.35 , 0.63]
Total (95% CI)		**1497**		**1500**	**100.0%**	**0.45 [0.34 , 0.60]**
Total events:	79		164			

Heterogeneity: Tau² = 0.00; Chi² = 0.28, df = 1 (P = 0.59); I² = 0%
Test for overall effect: Z = 5.55 (P < 0.00001)
Test for subgroup differences: Not applicable

Odds Ratio M-H, Random, 95% CI
0.01 0.1 1 10 100
Favours PRN FABA/ICS Favours PRN FABA



Study or Subgroup	PRN FABA/ICS Events	Total	Regular ICS Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Novel START	9	220	21	225	10.8%	0.41 [0.19 , 0.93]
PRACTICAL	37	437	59	448	23.5%	0.61 [0.40 , 0.94]
SYGMA 1	70	1277	74	1282	29.1%	0.95 [0.68 , 1.33]
SYGMA 2	171	2089	173	2087	36.7%	0.99 [0.79 , 1.23]
Total (95% CI)		**4023**		**4042**	**100.0%**	**0.79 [0.59 , 1.07]**
Total events:	287		327			

Heterogeneity: Tau² = 0.05; Chi² = 7.32, df = 3 (P = 0.06); I² = 59%
Test for overall effect: Z = 1.51 (P = 0.13)
Test for subgroup differences: Not applicable

Odds Ratio M-H, Random, 95% CI
0.2 0.5 1 2 5
Favours PRN FABA/ICS Favours regular ICS

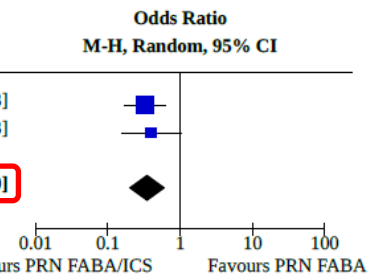
New evidence for as-needed ICS-formoterol in mild asthma

- Meta-analysis of four all RCTs, n=9,565
  (Crossingham, Cochrane 2021)
  - 55% reduction in severe exacerbations compared with SABA alone
  - Similar risk of severe exacerbations as with daily ICS + as-needed SABA
  - ED visits or hospitalizations
    - 65% lower than with SABA alone
    - 37% lower than with daily ICS

Analysis 1.3. Comparison 1: As required fixed dose combination inhaler versus as required short acting beta agonist, Outcome 3: Exacerbations requiring hospital admission or emergency department / urgent care visit

Study or Subgroup	PRN FABA/ICS Events	PRN FABA/ICS Total	PRN FABA Events	PRN FABA Total	Weight	Odds Ratio M-H, Random, 95% CI
Novel START (1)	13	220	36	223	67.2%	0.33 [0.17 , 0.63]
SYGMA 1	6	1277	15	1277	32.8%	0.40 [0.15 , 1.03]
Total (95% CI)		**1497**		**1500**	**100.0%**	**0.35 [0.20 , 0.60]**
Total events:	19		51			

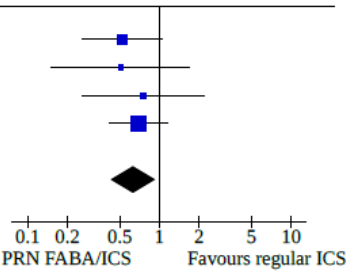
Heterogeneity: Tau² = 0.00; Chi² = 0.11, df = 1 (P = 0.74); I² = 0%
Test for overall effect: Z = 3.80 (P = 0.0001)
Test for subgroup differences: Not applicable



Analysis 2.3. Comparison 2: Fixed dose combination inhaler as required versus regular inhaled steroid plus as required short acting beta agonist, Outcome 3: Exacerbations requiring hospital admission or emergency department / urgent care visit

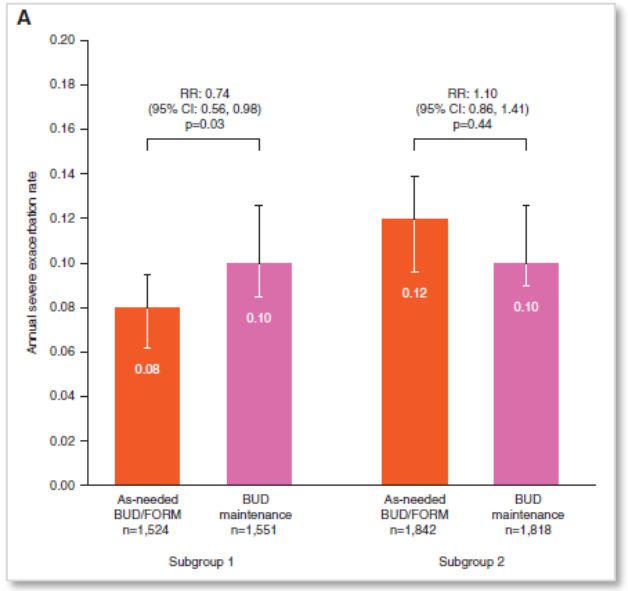
Study or Subgroup	PRN FABA/ICS Events	PRN FABA/ICS Total	Regular ICS Events	Regular ICS Total	Weight	Odds Ratio M-H, Random, 95% CI
Novel START	13	220	24	225	27.4%	0.53 [0.26 , 1.06]
PRACTICAL	4	437	8	448	9.3%	0.51 [0.15 , 1.70]
SYGMA 1	6	1277	8	1282	12.0%	0.75 [0.26 , 2.17]
SYGMA 2	25	2089	36	2087	51.3%	0.69 [0.41 , 1.15]
Total (95% CI)		**4023**		**4042**	**100.0%**	**0.63 [0.44 , 0.91]**
Total events:	48		76			

Heterogeneity: Tau² = 0.00; Chi² = 0.60, df = 3 (P = 0.90); I² = 0%
Test for overall effect: Z = 2.47 (P = 0.01)
Test for subgroup differences: Not applicable

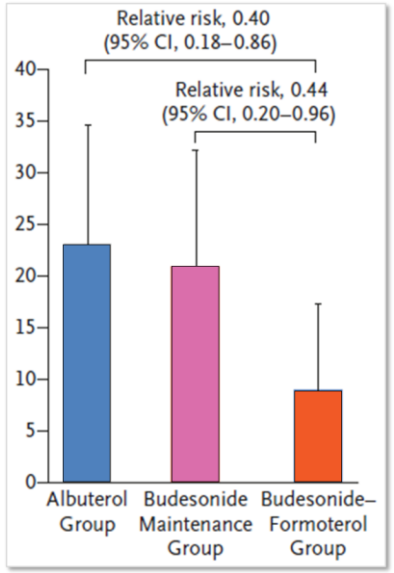


New evidence for as-needed ICS-formoterol in mild asthma

- Meta-analysis of four all RCTs, n=9,565
  (Crossingham, Cochrane 2021)
  - 55% reduction in severe exacerbations compared with SABA alone
  - Similar risk of severe exacerbations as with daily ICS + as-needed SABA
  - ED visits or hospitalizations
    - 65% lower than with SABA alone
    - 37% lower than with daily ICS
- Analysis by previous treatment
  - Patients taking SABA alone had lower risk of severe exacerbations with as-needed ICS-formoterol compared with daily ICS + as-needed SABA *(Bateman, Annals ATS 2021; Beasley, NEJMed 2019)*



Bateman 2021



Beasley 2019

Key changes to GINA severe asthma guide in 2022

- Additional investigations
  - Consider screening for adrenal insufficiency if patient is on maintenance OCS or high dose ICS-LABA
  - For patients with eosinophils ≥300/µl, investigate for non-asthma causes including *Strongyloides* (often asymptomatic), before considering biologic therapy
  - For patients with hypereosinophilia, e.g. ≥1500/µl, investigate for conditions such as EGPA
- Assessment of inflammatory phenotype
  - If blood eosinophils or FeNO not elevated, repeat up to 3 times, at least 1–2 weeks after stopping OCS, or on lowest possible OCS dose
- Treatment options for patients with no evidence of Type 2 inflammation on repeated testing
  - Consider add-on treatment with LAMA or low-dose azithromycin if not already tried
  - Can also consider anti-IL4R* (if on maintenance OCS) or anti-TSLP* (but insufficient evidence with maintenance OCS)
- Consider maintenance OCS only as last resort, because of serious cumulative adverse effects

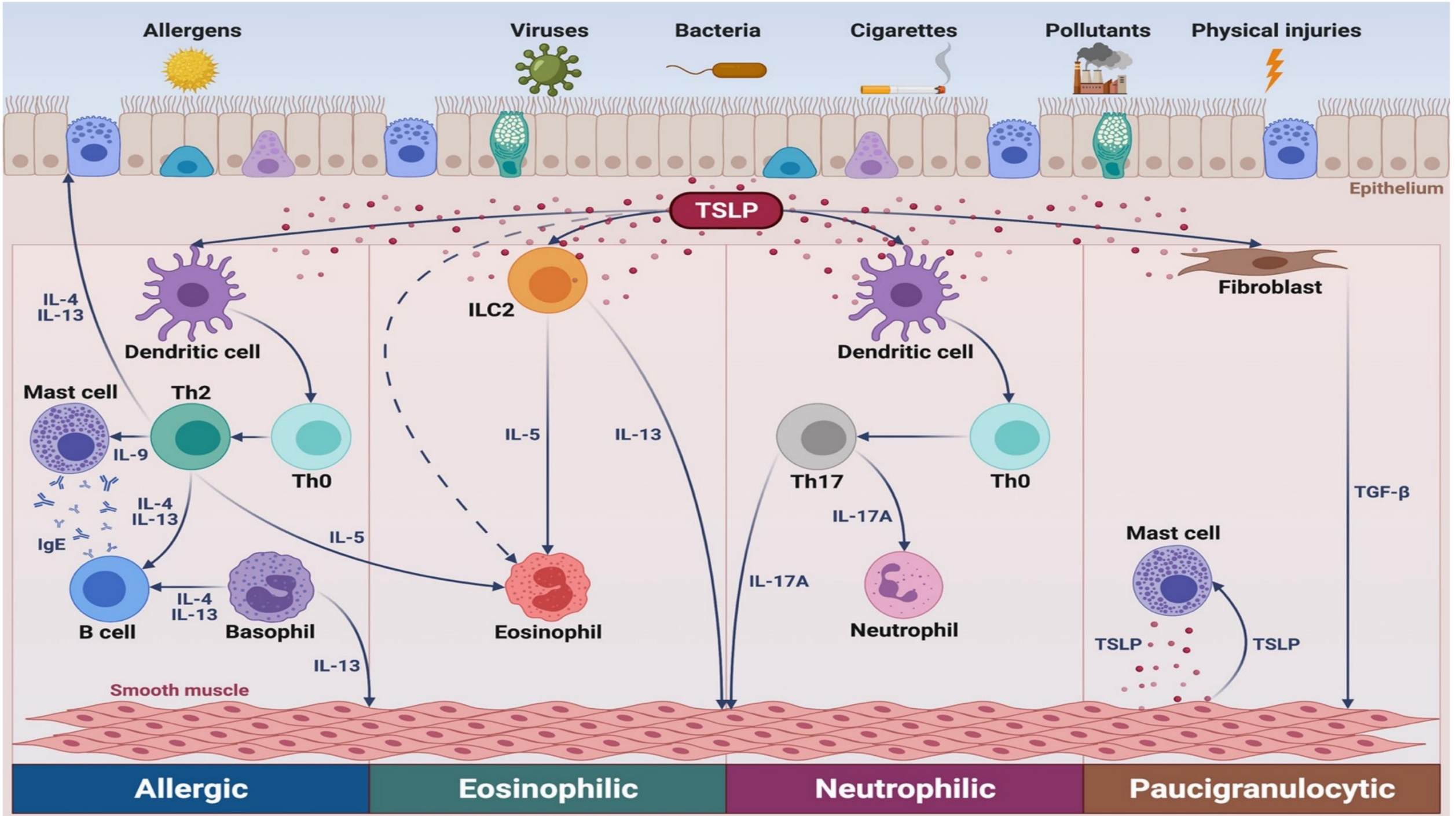
**Check local eligibility criteria for specific biologic therapies*

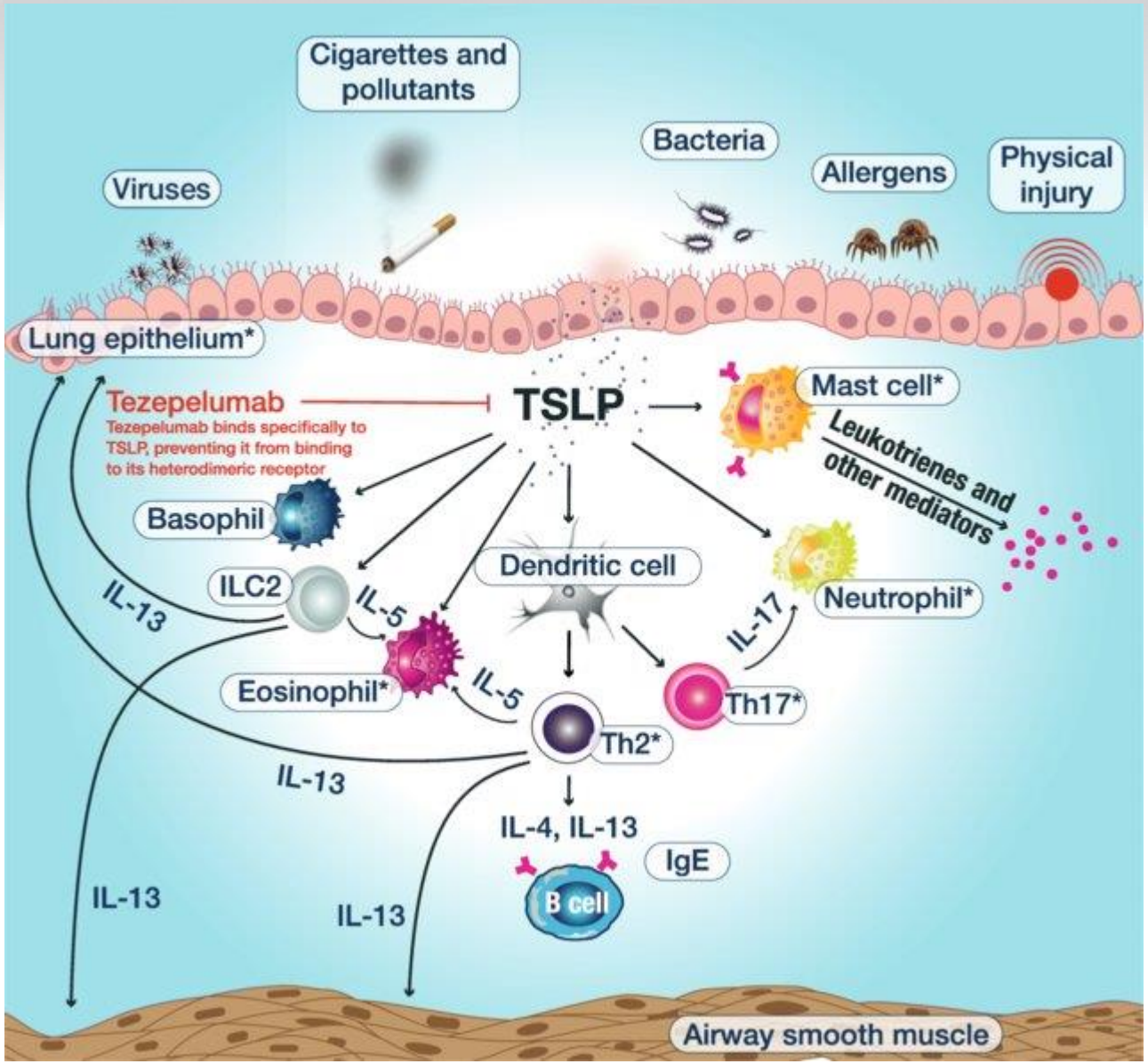
Key changes to GINA severe asthma guide in 2022 (continued)

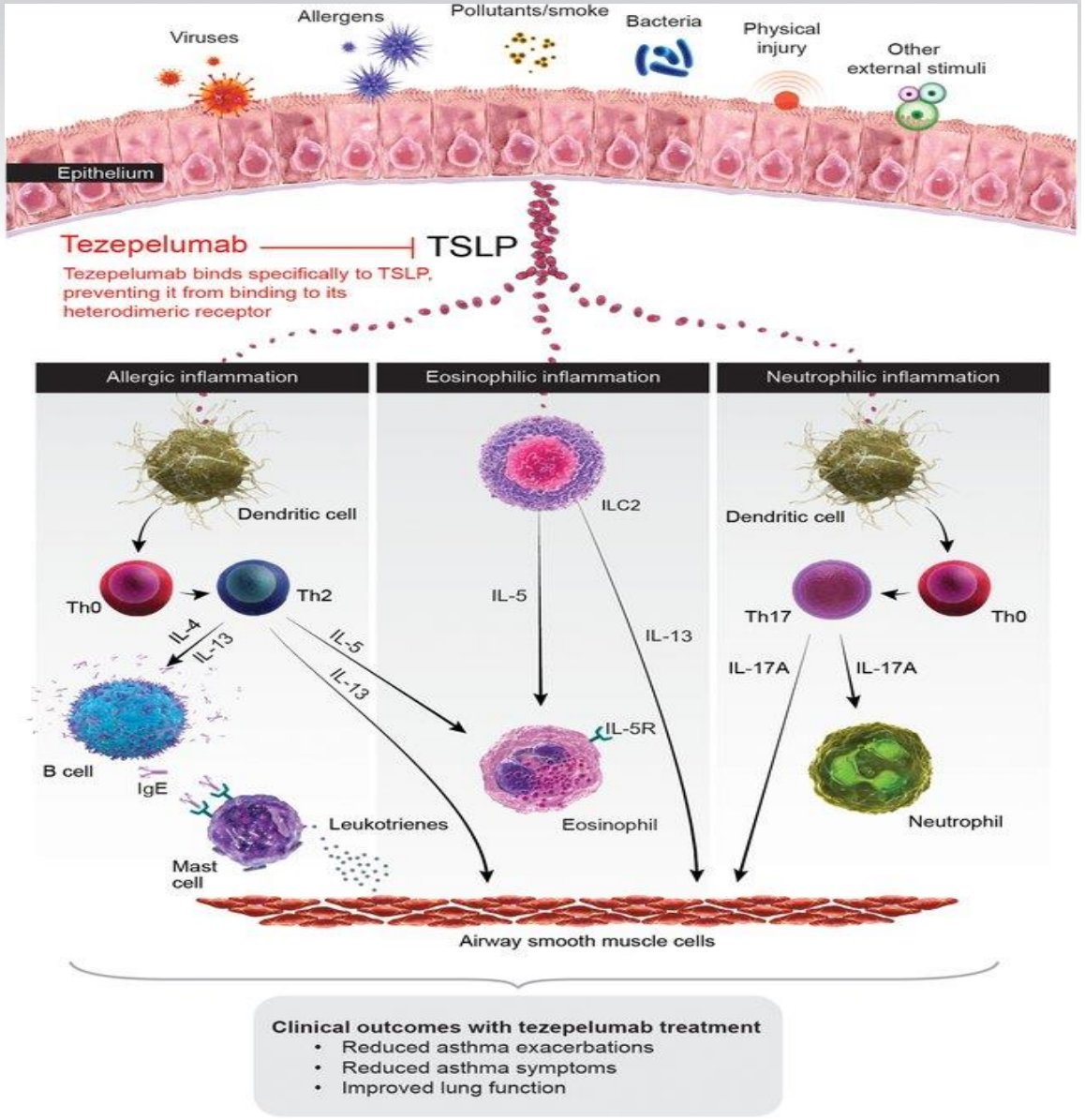
- Anti-IL4R* (dupilumab) for severe eosinophilic/Type 2 asthma
  - Not suggested if blood eosinophils (current or historic) >1500/µl
  - Dupilumab now also approved for children ≥6 years with severe eosinophilic/Type 2 asthma, not on maintenance OCS *(Bacharier, NEJMed 2021)*
- Anti-TSLP* (tezepelumab) now approved for severe asthma (age ≥12 years)
  - Greater clinical benefit with higher blood eosinophils and/or higher FeNO
  - Insufficient evidence in patients taking maintenance OCS

Class	Name	Age*	Asthma indication*	Other indications*
Anti-IgE	Omalizumab (SC)	≥6 years	Severe allergic asthma	Nasal polyposis, chronic spontaneous urticaria
Anti-IL5 Anti-IL5R	Mepolizumab (SC) Reslizumab (IV) Benralizumab (SC)	≥6 years ≥18 years ≥12 years	Severe eosinophilic/Type 2 asthma	Mepolizumab: EGPA, CRSwNP, hypereosinophilic syndrome
Anti-IL4R	Dupilumab (SC)	≥6 years	Severe eosinophilic/Type 2 asthma, or maintenance OCS	Moderate-severe atopic dermatitis, CRSwNP
Anti-TSLP	Tezepelumab (SC)	≥12 years	Severe asthma	

**Check local eligibility criteria for specific biologic therapies; TSLP: thymic stromal lymphopoietin*


Allergens
Viruses
Bacteria
Cigarettes
Pollutants
Physical injuries
Epithelium
TSLP
IL-4
IL-13
Dendritic cell
ILC2
Dendritic cell
Fibroblast
Mast cell
Th2
IL-9
Th0
IL-5
IL-13
Th17
Th0
IL-17A
TGF-β
IgE
IL-4
IL-13
IL-5
Mast cell
B cell
IL-4
IL-13
Basophil
Eosinophil
IL-17A
Neutrophil
TSLP
TSLP
IL-13
Smooth muscle
Allergic
Eosinophilic
Neutrophilic
Paucigranulocytic





Clinical outcomes with tezepelumab treatment

- Reduced asthma exacerbations
- Reduced asthma symptoms
- Improved lung function

Interim advice about asthma severity descriptors

1. Severe asthma: GINA continues to support the current definitions of severe asthma, and difficult-to-treat asthma
2. ‘Mild asthma’: GINA suggests that this term should generally be avoided in clinical practice if possible, because it is used and interpreted in different ways
   - If used, emphasize importance of ICS-containing treatment to reduce risk of severe or fatal exacerbations
3. For population-level observational studies: report the controller and reliever treatment not the ‘Step’, and don’t impute severity
   - e.g. ‘patients prescribed low dose ICS-LABA with as-needed SABA’, not ‘Step 3 patients’ and not ‘moderate asthma’
4. For clinical trials: describe the included patients by their asthma control and treatment (controller and reliever), and don’t impute severity
5. GINA proposes holding a stakeholder discussion about the definition of mild asthma, to obtain agreement about the implications for clinical practice and clinical research of the changes in knowledge about asthma pathophysiology and treatment since the current definition of asthma severity was published