Refractory Asthma: Mechanisms and Management

Dr. Pratap Upadhya

22/1/16

- Definitions
- Phenotype
- Mechanism
- Treatment

Refractory Asthma

- Previosly used synonymously with many terms under various guidelines like

"*Refractory* asthma"

"*Severe* asthma"

"*Steroid-dependent and/or resistant* asthma"

"*Difficult to control* asthma"

"*Poorly controlled* asthma"

"*Brittle* asthma"

"*Irreversible* asthma"

Refractory Asthma- Implication

- No definite prevalence, though most estimates keep it around 5-10% of all asthmatics
- Accounts for considerable cost in overall asthma management
- Mostly manageable with proper confirmation of diagnosis, evaluation and optimization of treatment

Definition

1999, an ERS Task Force-

'Difficult/therapy-resistant asthma' defined as poorly controlled asthma with a *continued requirement for short acting B2 agonists despite delivery of a reasonable dose of inhaled corticosteroids (ICS)* and follow-up by a respiratory specialist for a *period of >6 months*

2000 an ATS Workshop-

‘Refractory/severe asthma’

one of two major criteria

(continuous high-dose ICS or oral corticosteroids for >50% of the time during the previous year),

with *two out of seven additional minor* criteria

ATS 2000 severe/refractory

Major characteristics

To achieve control to a level of mild-moderate persistent asthma

1. Treatment with continuous or near continuous (≥50% of year) oral corticosteroids
2. Requirement for treatment with high-dose inhaled corticosteroids (Beclomethasone dipropionate >1260 μg/d)

Minor characteristics

1. Requirement for daily treatment with a controller medication in addition to inhaled corticosteroids, eg, long-acting β-agonist, theophylline, or leukotriene antagonist
2. Asthma symptoms requiring daily short-acting β agonists
3. Persistent airway obstruction (FEV1 <80% predicted; diurnal PEF variability >20%)
4. One or more urgent care visits for asthma per year
5. Three of more oral steroid "bursts" per year
6. Prompt deterioration with ≤25% reduction in oral or inhaled corticosteroid dose
7. Near fatal asthma event in the past

Am J Respir Crit Care Med 2000;162:2341–2351

2007, International workshop, Paris (NAEPP/EPR3)-

‘Severe refractory asthma’

patients who have refractory asthma *after an extensive re-evaluation* on of the correct diagnosis, aggravating comorbidities and environmental factors and an appropriate *observation period of at least 6 months*.

2008,later in 2011, the British Thoracic Society (BTS) and Scottish Intercollegiate Guideline Network (SIGN) guidelines

'Difficult asthma'

persistent symptoms and/or frequent exacerbations in patients with a prior diagnosis of asthma *despite treatment at step 4 or step 5*

IMI, 2011-

Algorithm to distinguish difficult-to-control asthma from severe refractory asthma

ATS/ERS, 2013-

Latest recommendations on the identification, evaluation and treatment of patients with severe refractory asthma

Refractory vs Difficult to treat vs Uncontrolled asthma

Refractory-

Patients with asthma in whom:
Alternative diagnoses have been excluded
Co-morbidities have been treated
Trigger factors have been removed (if possible)
Compliance with treatment has been checked
But still have:
Poor asthma control, or
frequent (2) severe exacerbations per year
Despite :
The prescription of high-intensity treatment, or
Can only maintain adequate control when taking systemic corticosteroids

Bel et al. Thorax 2011;66:910-7

Refractory vs Difficult to treat vs Uncontrolled asthma

Difficult to treat-

'Difficult-to-treat asthma'
was defined as asthma where the poor control is

- **due to a wrong diagnosis or comorbidities,**
- **the inability and unwillingness to adhere to the prescribed treatment regimens or**
- **Adverse psychological and environmental factors**

Elisabeth H Bel et al. Diagnosis and definition of severe refractory asthma: an international consensus statement from the Innovative Medicine Initiative (IMI). Thorax 2011;66:910-17

Refractory vs Difficult to treat vs Uncontrolled asthma

Uncontrolled-

least one of the following:

1. **Poor symptom control: ACQ consistently >1.5, ACT <20 (or "not well controlled" by NAEPP/GINA guidelines)**
2. **Frequent severe exacerbations: two or more bursts of systemic CS (>3 days each) in the previous year**
3. **Serious exacerbations: at least one hospitalization, ICU stay or mechanical ventilation in the previous year**
4. **Airflow limitation: after appropriate bronchodilator withhold FEV1 <80% predicted (in the face of reduced FEV1/FVC defined as less than the lower limit of normal)**

Sub-phenotypes of severe refractory asthma

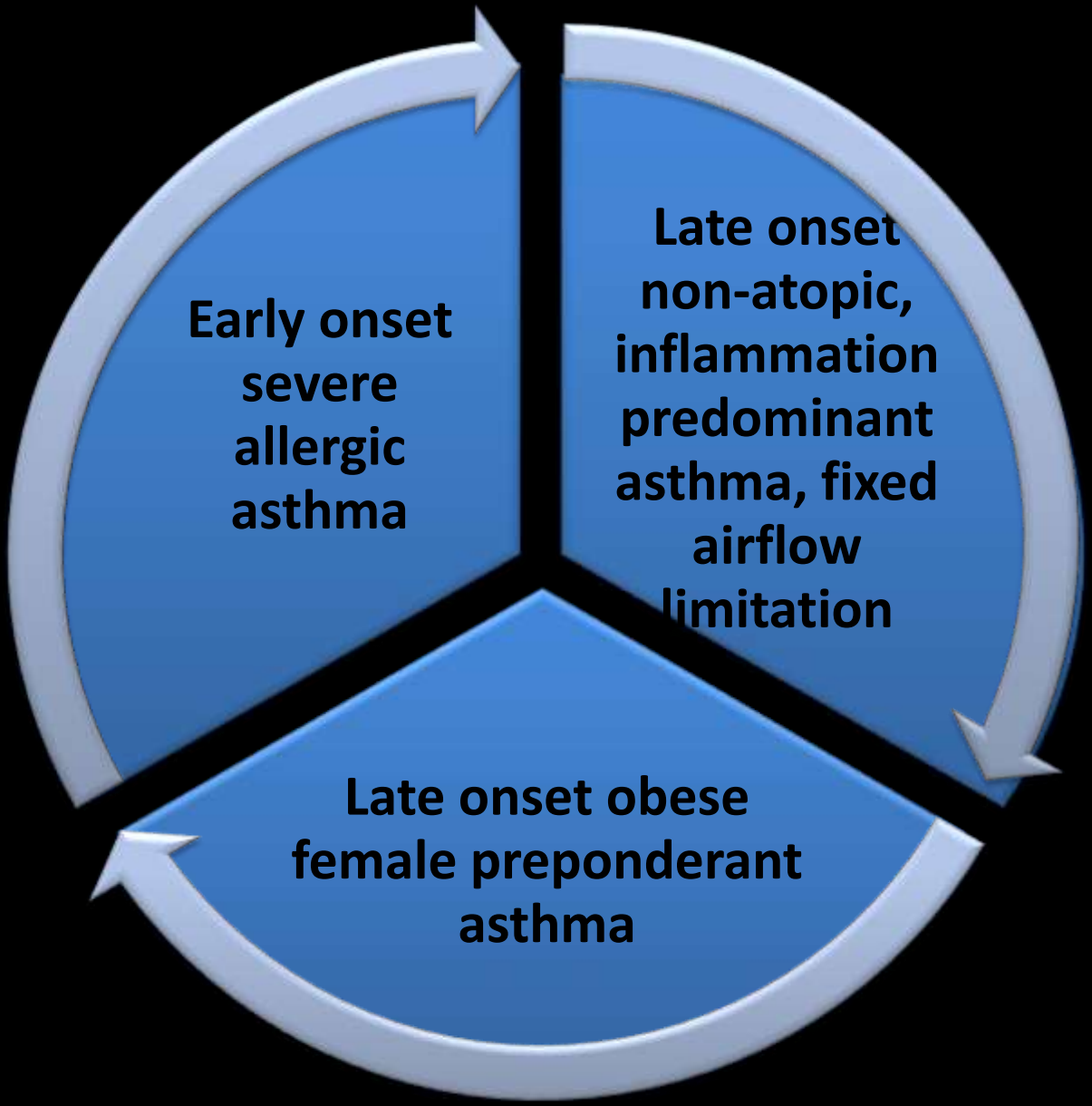
- over the past few years several clinical phenotypes have been identified
- These subtypes characterized by different clinical and physiological features, reflect separate immuno-pathologies

Haldar P, Pavord ID, Shaw DE, et al. Cluster analysis and clinical asthma phenotypes.Am J Respir Crit Care Med 2008; 178: 218–224.
Moore WC, Meyers DA, Wenzel SE, et al. Identification of asthma phenotypes

Identification of Asthma Phenotypes Using Cluster Analysis in the Severe Asthma Research Program

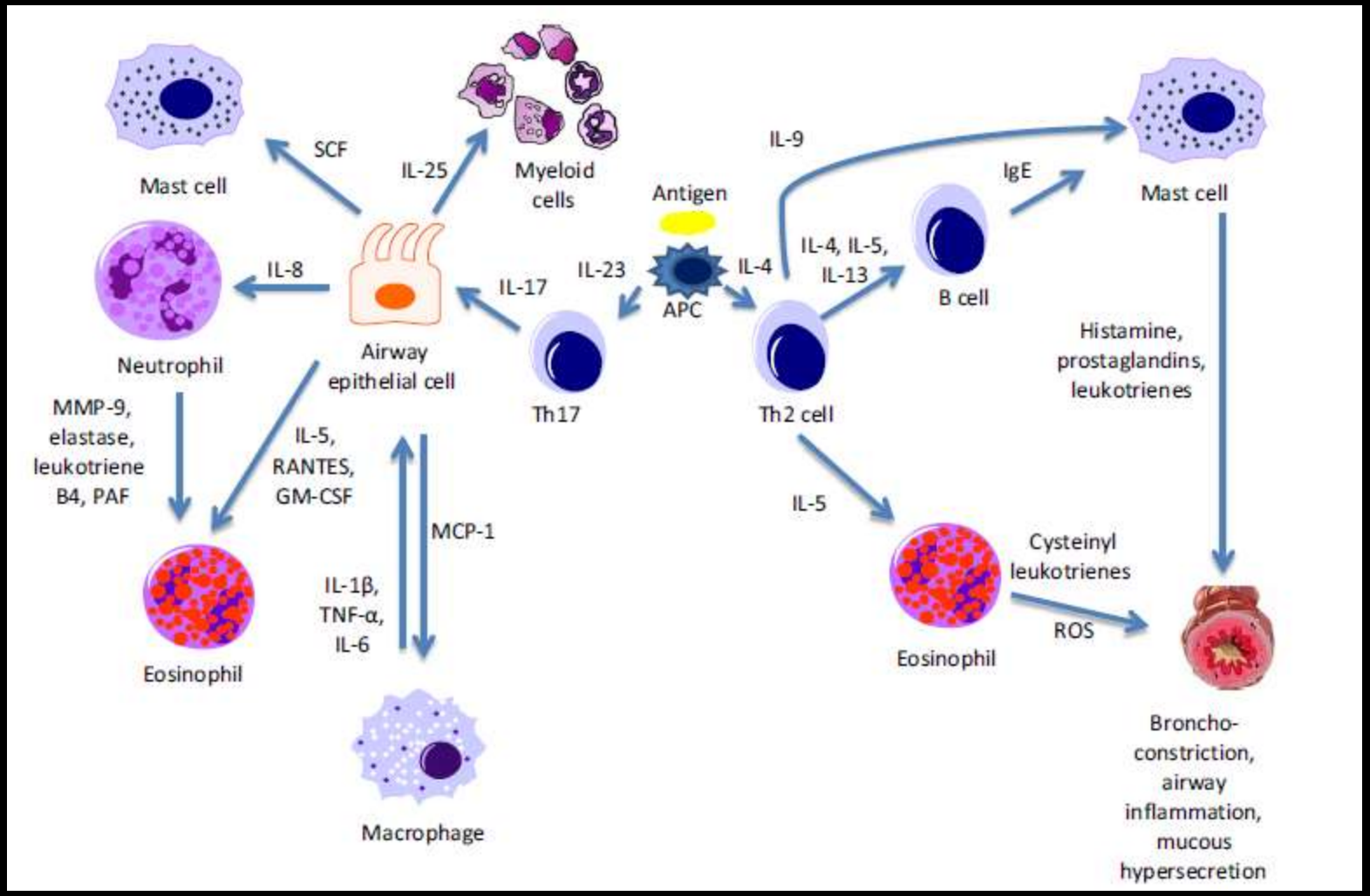
Wendy C. Moore[1,2], Deborah A. Meyers[1,2], Sally E. Wenzel[2], W. Gerald Teague[2], Huashi Li[1], Xingnan Li[1], Ralph D'Agostino, Jr.[3], Mario Castro[2], Douglas Curran-Everett[2], Anne M. Fitzpatrick[2], Benjamin Gaston[2], Nizar N. Jarjour[2], Ronald Sorkness[2], William J. Calhoun[2], Kian Fan Chung[2], Suzy A. A. Comhair[2], Raed A. Dweik[2], Elliot Israel[2], Stephen P. Peters[1,2], William W. Busse[2], Serpil C. Erzurum[2], and Eugene R. Bleecker[1,2], for the National Heart, Lung, and Blood Institute's Severe Asthma Research Program[2*]

[1]Wake Forest University School of Medicine, Center for Human Genomics; [2]The Severe Asthma Research Program, Bethesda, Maryland; and [3]Wake Forest University School of Medicine, Public Health Sciences, Winston-Salem, North Carolina


Early onset severe allergic asthma
Late onset non-atopic, inflammation predominant asthma, fixed airflow limitation
Late onset obese female preponderant asthma

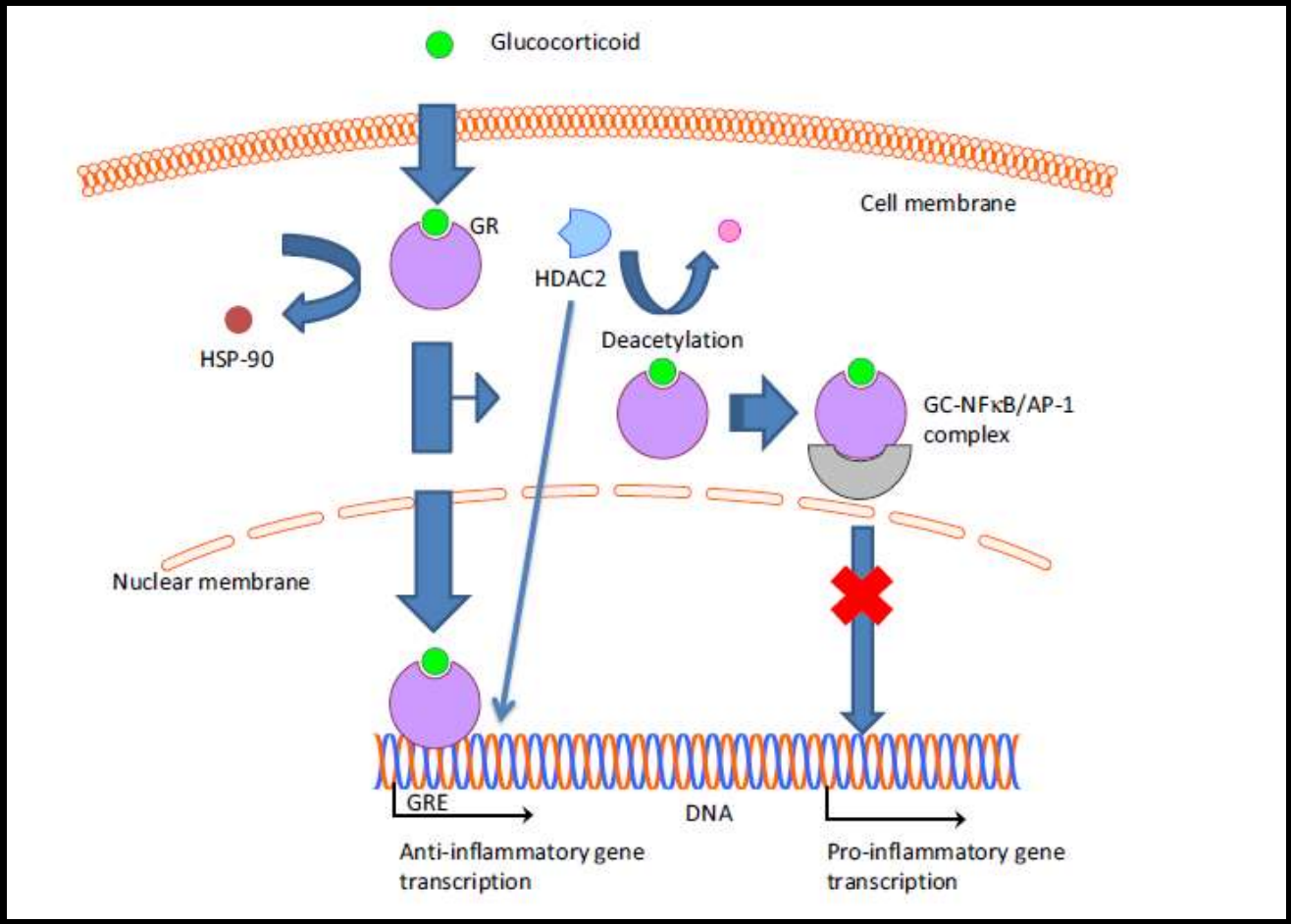
Early onset severe allergic asthma	Late onset non-atopic, inflammation predominant asthma with fixed airflow limitation	Late onset obese female preponderant asthma
➢ <12years ➢ IgE more-IgE mediated reactions more ➢ Anti-IgE therapy more useful	➢ >12years ➢ Persistant eosinophilia ➢ Eosinophillic inflammation-rhino sinusitis and nasal polyposis ➢ Fixed airway obstruction ➢ These 2 comorbidities should be routinely checked ➢ ICS/mepolizumab[anti-IL5] more useful	➢ >23 years ➢ BMI>30 ➢ Treat obesity related comorbidities-OSAS and GERD.

Mechanism



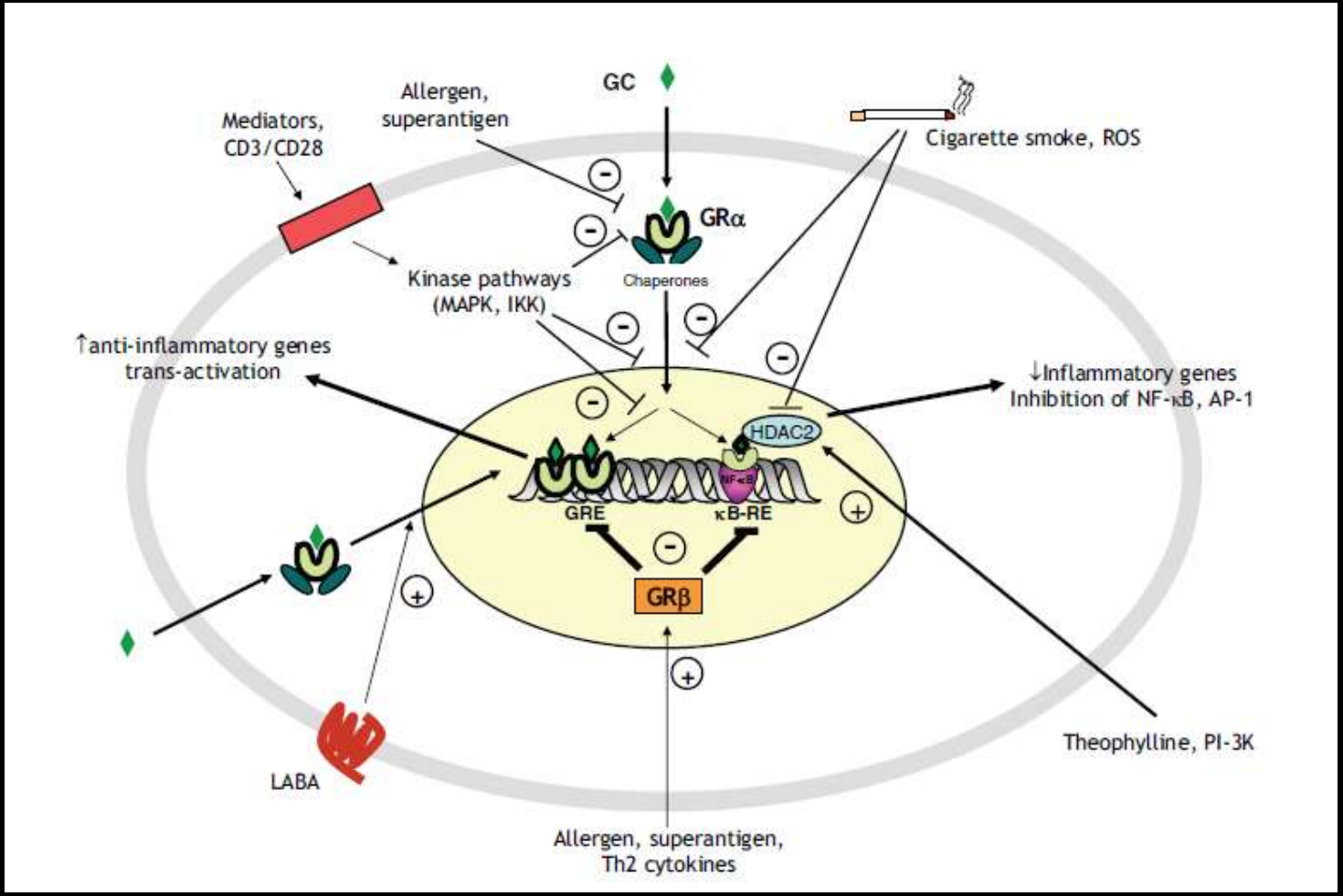
Allergy. 2014 Jul;69(7):817-27. doi:10.1111/all.12412. Epub 2014 Apr 29.

GC-mechanism of action



Allergy. 2014 Jul;69(7):817-27. doi: 10.1111/all.12412. Epub 2014 Apr 29.

Regulation of GC insensitivity



Chest. 2008 Aug;134(2):394-401. doi: 10.1378/chest.08-0440

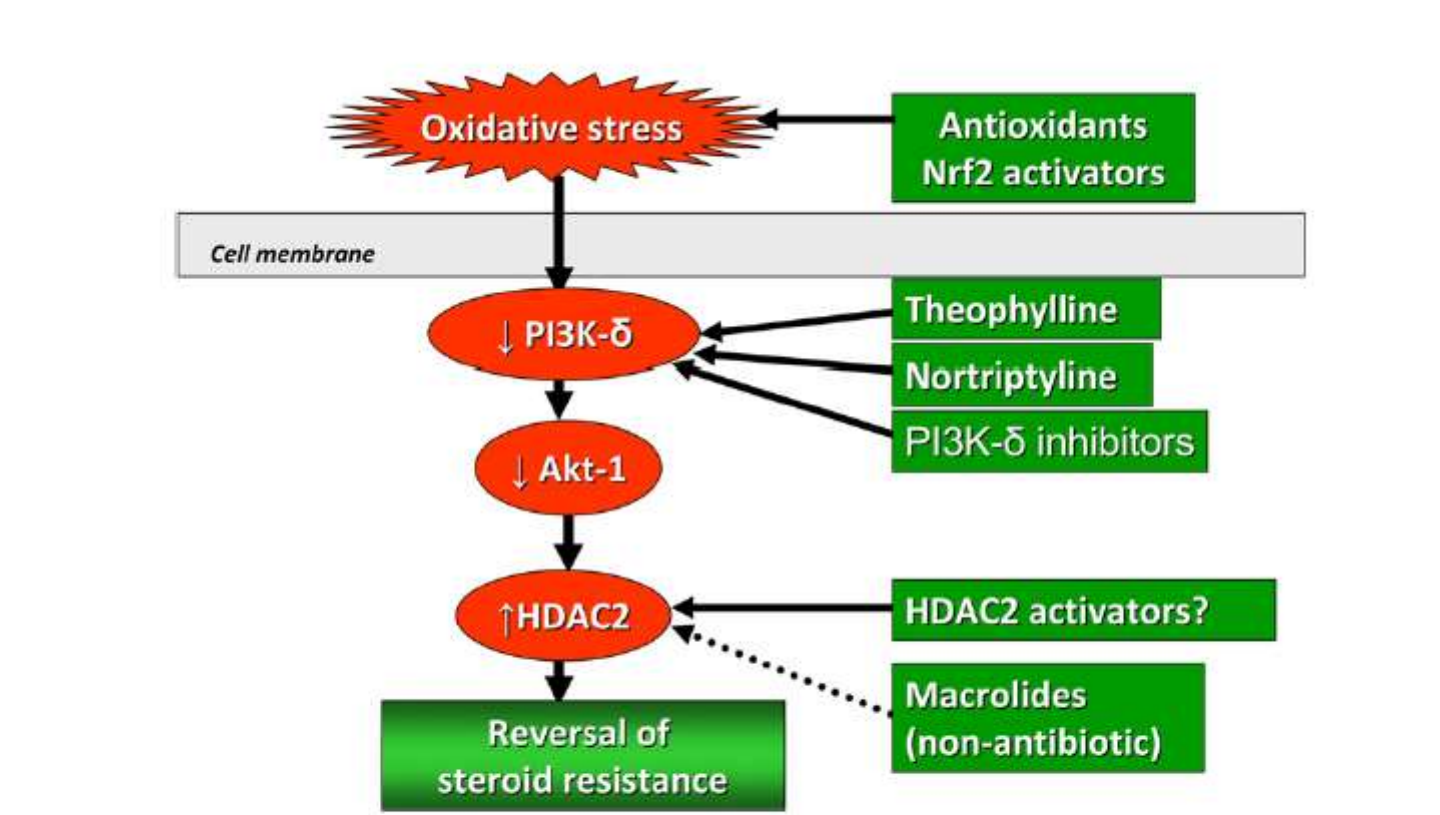
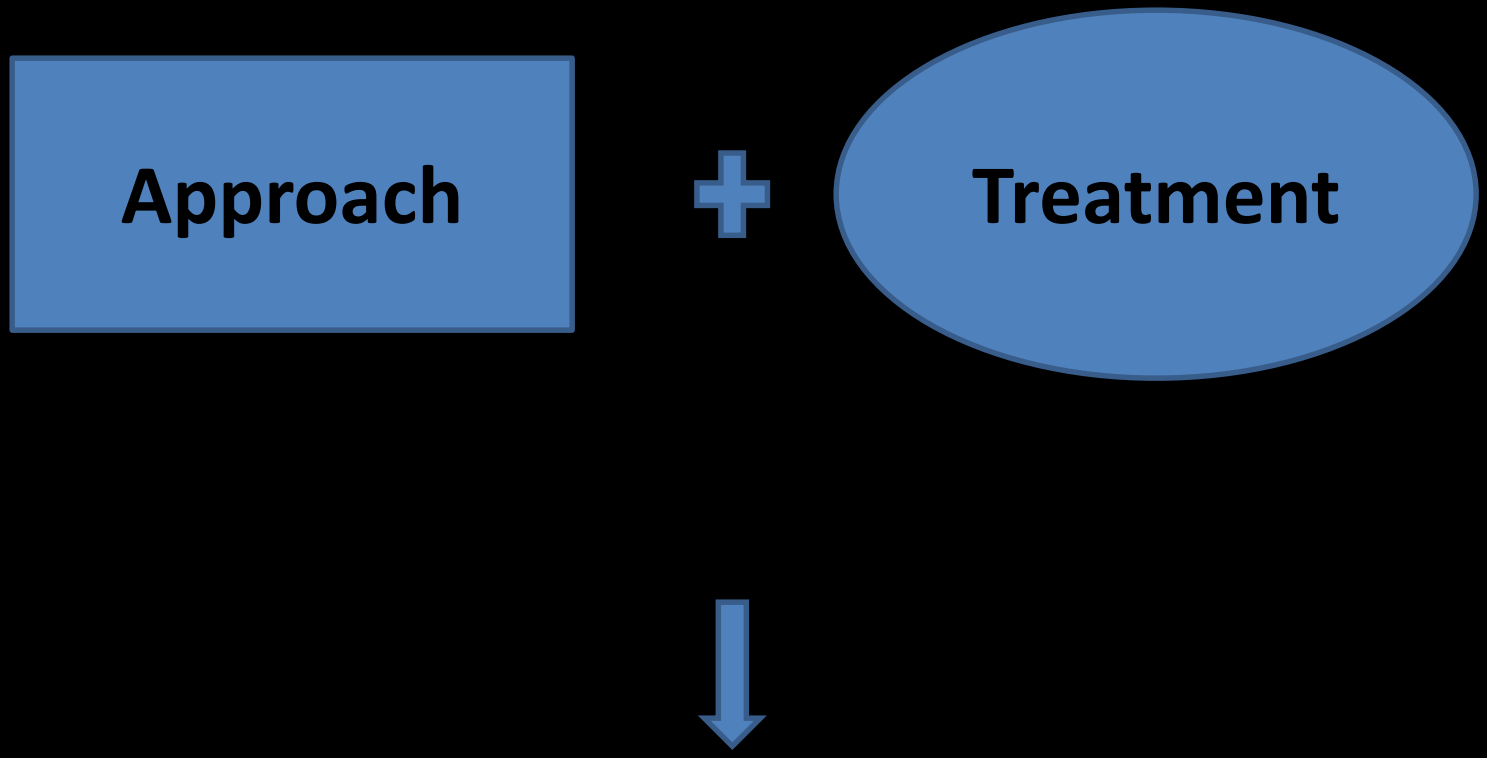


FIG 4. Corticosteroid resistance in some patients with severe asthma is due to a reduction in HDAC2 activity and expression as a result of oxidative stress through activation of PI3Kδ. This can be reversed by antioxidants, including Nrf2 activators, theophylline, nortriptyline, and selective PI3Kδ inhibitors. Macrolides also reverse corticosteroid resistance by acting further down the pathway. In the future, selective HDAC2 activators might be developed.

J Allergy Clin Immunol. 2012 Jan;129(1):48-59. doi: 10.1016/j.jaci.2011.11.006.

Management

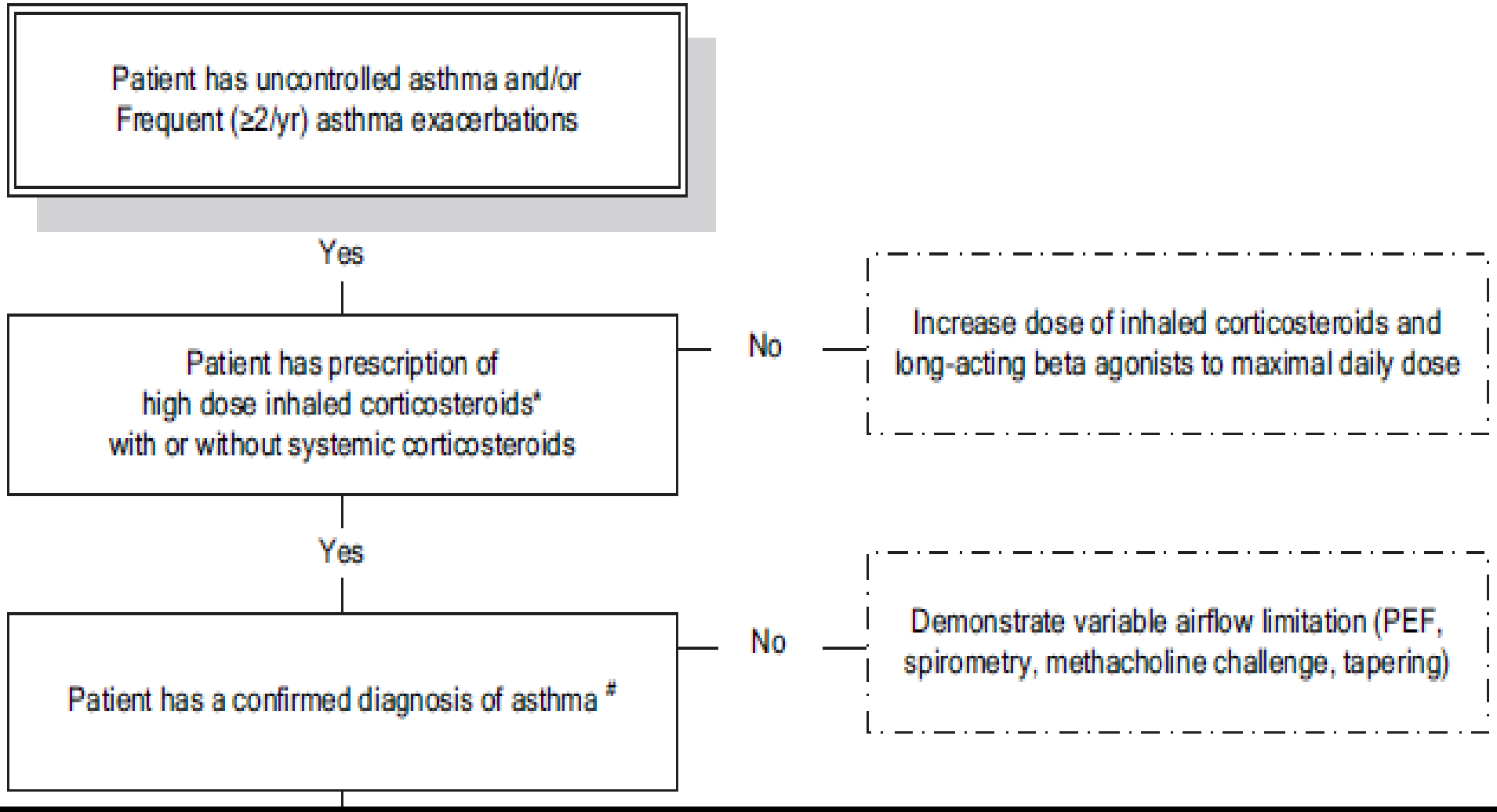


Approach

- Asthma is confirmed by a history of wheeze either spontaneously or on exertion,
- as well as variable airflow limitation by:
  - Variability of PEF (amplitude %mean of twice daily measurements > 8%)
  - Reversibility in FEV1 to 400 µg inhaled salbutamol (>12% predicted and >200 ml)
  - AHR to methacholine (PC20 <8 mg/ml)
  - Fall in FEV1 >12% plus >200 ml when tapering treatment (any one or more of ICS, OCS, LABA & SABA)

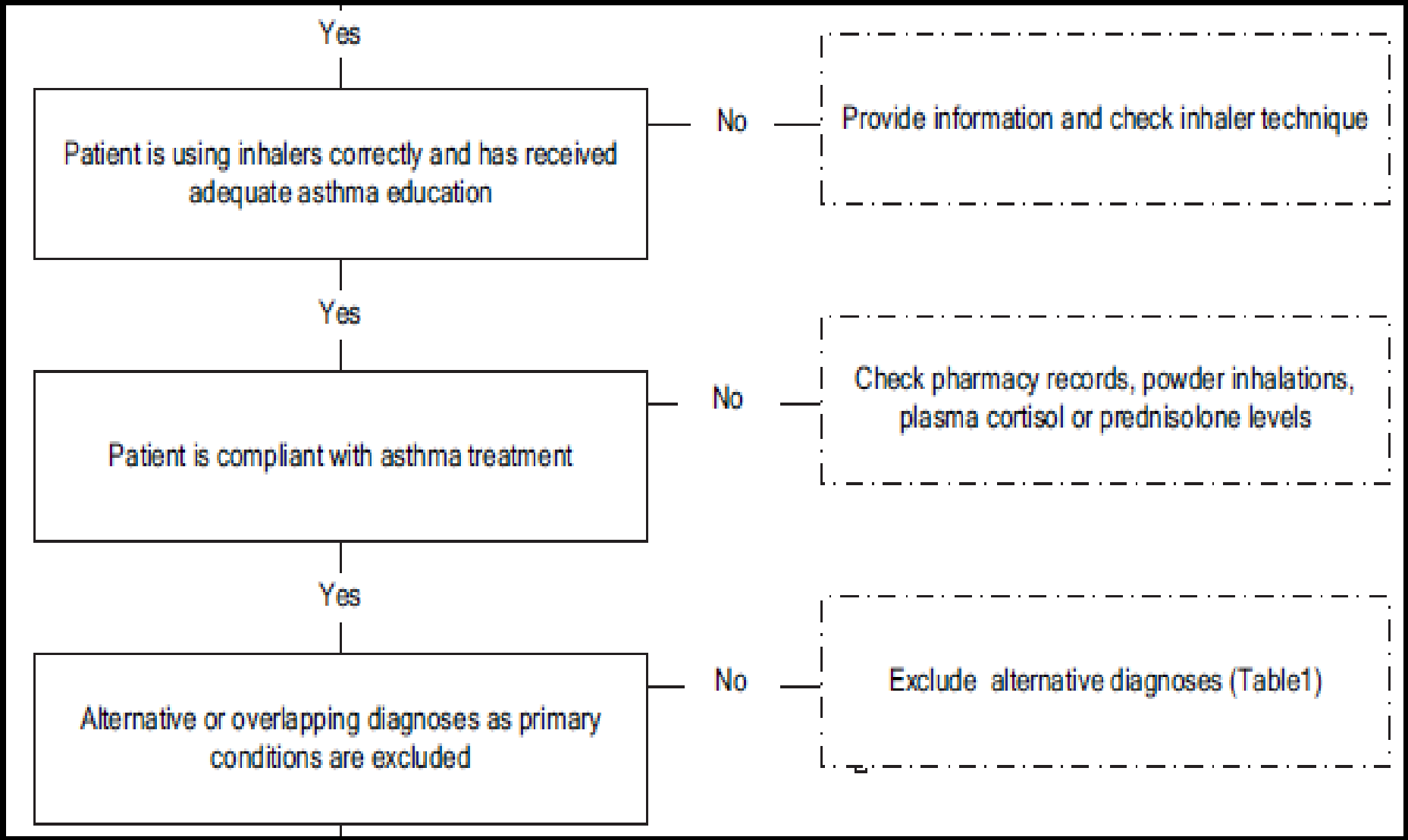
Elisabeth H Bel et al. Diagnosis and definition of severe refractory asthma: an international consensus statement from the Innovative Medicine Initiative (IMI). Thorax 2011;66:910-17

Approach

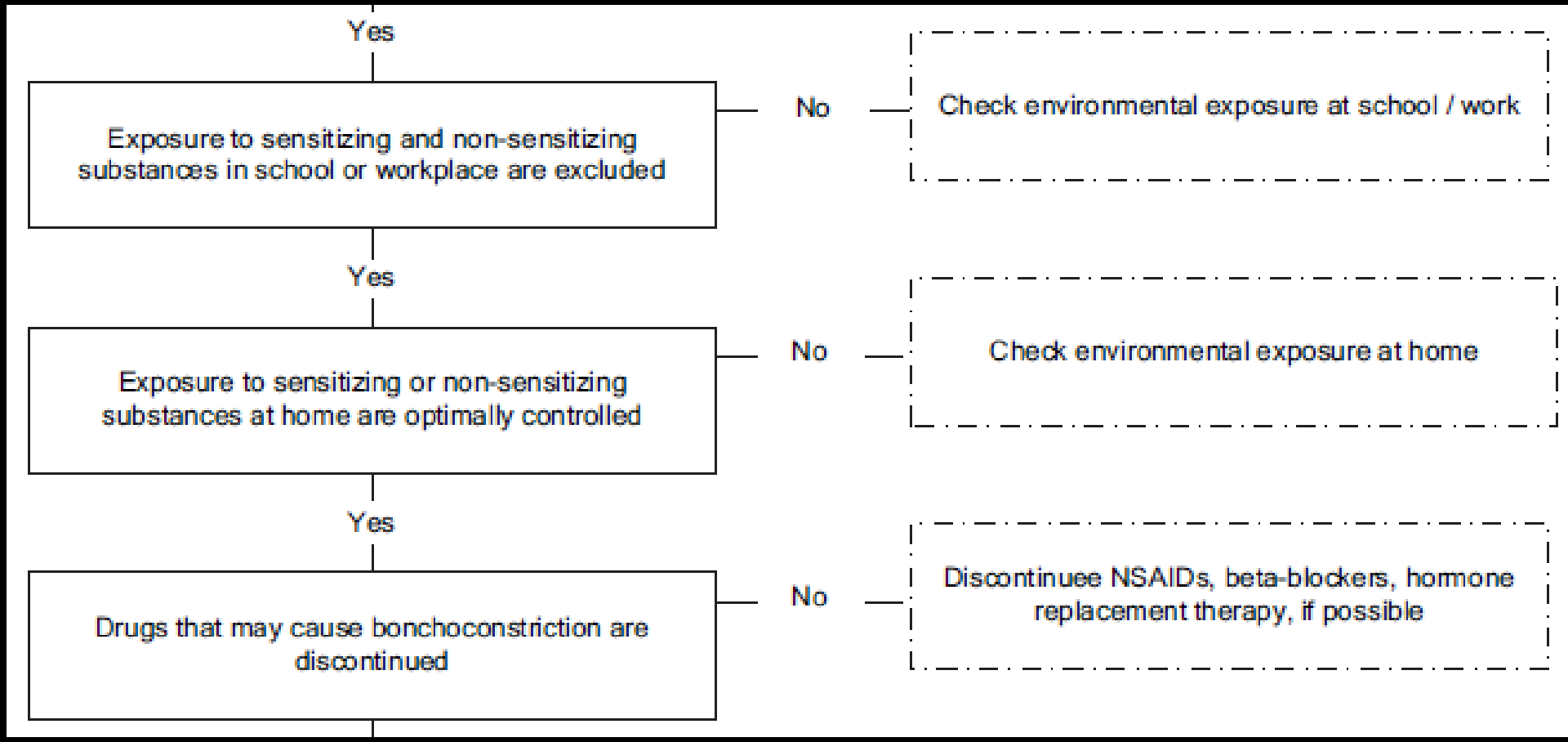


Elisabeth H Bel et al. Diagnosis and definition of severe refractory asthma: an international consensus statement from the Innovative Medicine Initiative (IMI). Thorax 2011;66:910-17

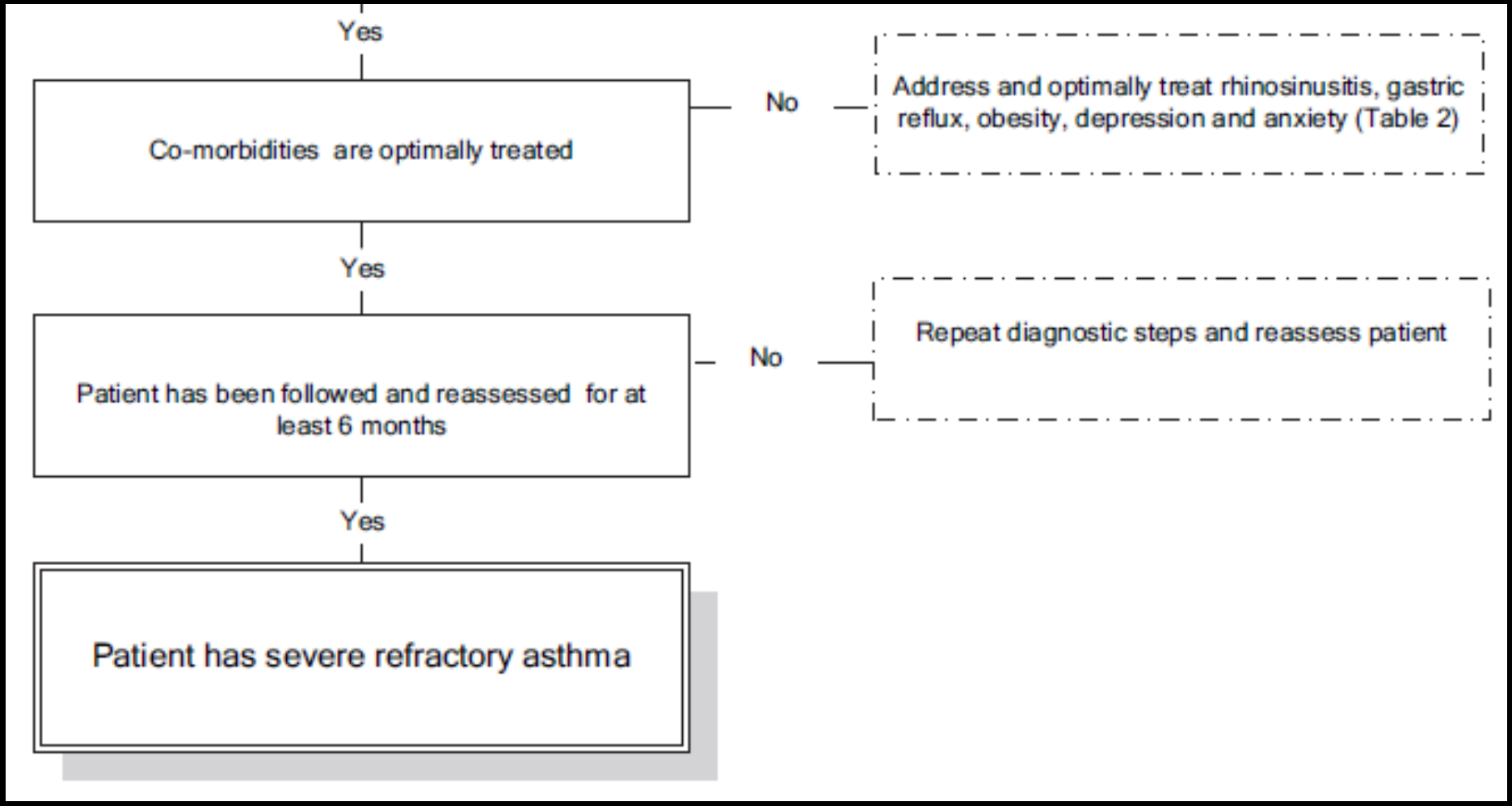
Approach


Yes
Patient is using inhalers correctly and has received adequate asthma education
No
Provide information and check inhaler technique
Yes
Patient is compliant with asthma treatment
No
Check pharmacy records, powder inhalations, plasma cortisol or prednisolone levels
Yes
Alternative or overlapping diagnoses as primary conditions are excluded
No
Exclude alternative diagnoses (Table1)

Approach


Yes
Exposure to sensitizing and non-sensitizing substances in school or workplace are excluded
No
Check environmental exposure at school / work
Yes
Exposure to sensitizing or non-sensitizing substances at home are optimally controlled
No
Check environmental exposure at home
Yes
Drugs that may cause bonchoconstriction are discontinued
No
Discontinuee NSAIDs, beta-blockers, hormone replacement therapy, if possible

Approach


Yes
Co-morbidities are optimally treated
No
Address and optimally treat rhinosinusitis, gastric reflux, obesity, depression and anxiety (Table 2)
Yes
Patient has been followed and reassessed for at least 6 months
No
Repeat diagnostic steps and reassess patient
Yes
Patient has severe refractory asthma

High intensity asthma treatment is defined as:
1000 mcg/day fluticasone equivalent combined with long acting beta-2- agonists or other controllers (adults)
500 mcg/day fluticasone equivalent (school-aged children)
400 mcg/day budesonide equivalent and oral leukotriene receptor antagonists (pre-school children)

Elisabeth H Bel et al. Diagnosis and definition of severe refractory asthma: an international consensus statement from the Innovative Medicine Initiative (IMI). Thorax 2011;66:910-17

Tests to distinguish severe asthma from alternative diagnosis that may mimic asthma

Routine screening test in adults	Exclusion (if test is normal)
Air trapping measured by body plethysmography	Bronchiolitis obliterans
Carbon monoxide diffusion capacity	Emphysema or parenchymal lung disease
Chest HRCT scan	Parenchymal lung disease Bronchiolitis obliterans Bronchiectasis Congestive heart failure
D-dimer	Recurrent pulmonary embolism

Suspected alternative or additional diagnoses in adults	Diagnostic test
Intrabronchial obstruction	Bronchoscopy
Vocal cord dysfunction	Laryngoscopy during attack
Dysfunctional breathing/panic attacks	Blood gases during attack Hyperventilation provocation test
Recurrent microaspiration	Proximal oesophageal pH measurement Bile salts in bronchoalveolar lavage fluid
Cystic fibrosis (CF)	Sweat test
Allergic bronchopulmonary aspergillosis (ABPA)	Aspergillus sp IgE
Emphysema Hypersensitivity pneumonitis Bronchiectasis (including ABPA, CF)	High resolution CT scan
Recurrent pulmonary embolism Pulmonay arterial hypertension	CT pulmonary angiography
Bronchiolitis Sarcoidosis	Transbronchial or thoracoscopic lung biopsy
ChurgeStrauss syndrome	Biopsy of affected organ(s) Antineutrophilic cytoplasmic antibodies

Diagnosis and treatment of recognized comorbidities in severe asthma

Comorbid condition	Test	Treatment
Gastro-oesophageal reflux	3 months empirical therapy trial with proton pump inhibitors or oesophageal pH testing	Lifestyle modifications Proton pump inhibitors Surgery
Obesity with or without obstructive sleep apnoea syndrome	Polysomnography	Weight control Positive airway pressure Oral appliances Surgery
Sinus disease	CT scan Nasendocopy	Nasal irrigation with saline Corticosteroid pray/drops Surgery
Depression/anxiety	Evaluation by mental health professional	Medical treatment or psychotherapy

Treatment

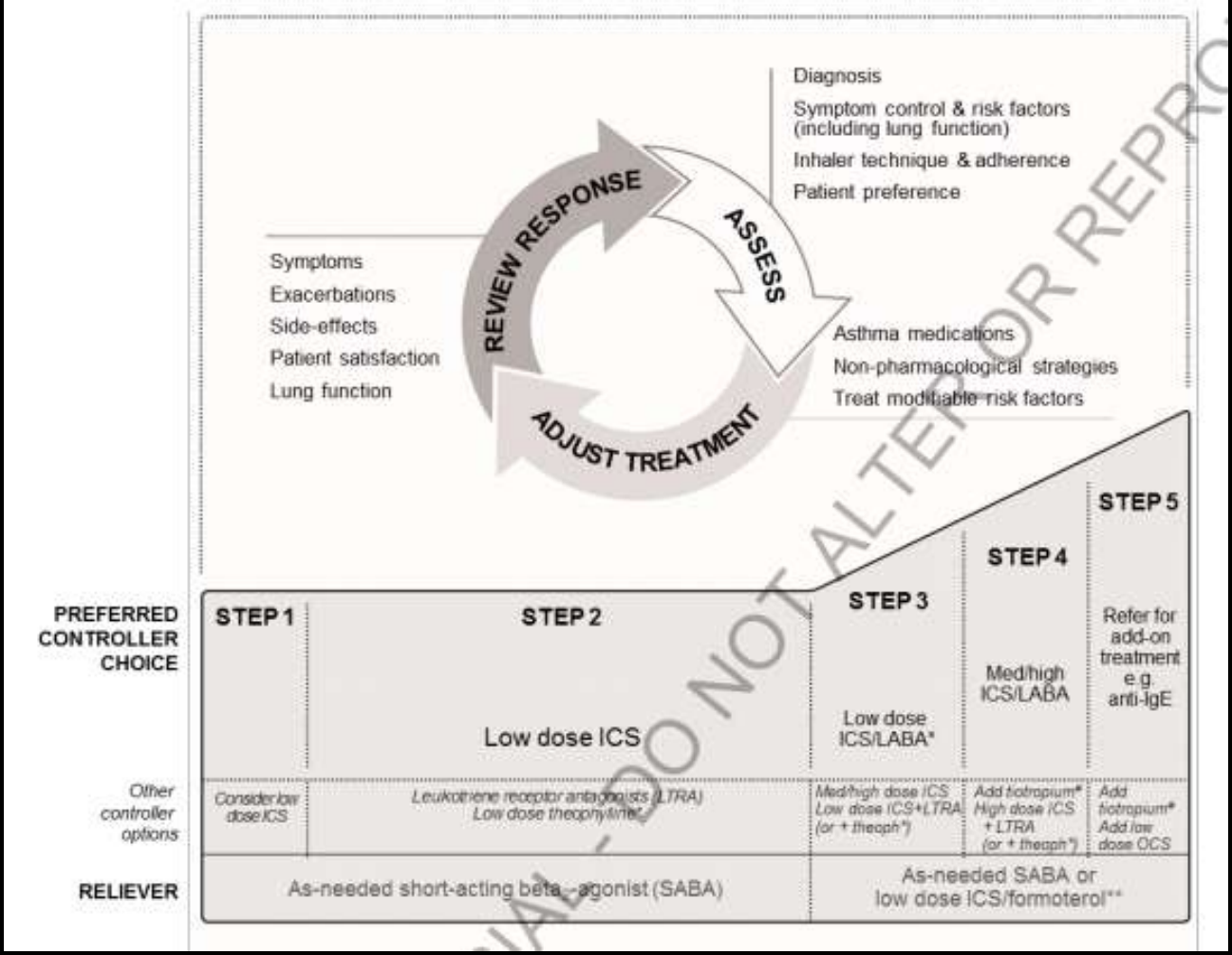
Proposed strategy for the management of asthma in the Indian setting

Reliever medication	Step 1	Step 2	Step 3	Step 4		Step 5
	SABA		SABA or ICS/LABA (SiT)*			
Controller medication						
Preferred choice	None	Low-dose ICS	Low-dose ICS plus LABA	Increase dose of ICS to medium /high-dose ICS. Continue LABA	If symptoms persist Add one or more of the following	Continue the same Add either of the following
Less preferred choices (in no particular order)	None	LTRA	Medium dose ICS Low-dose ICS plus LTRA Low-dose ICS plus methylxanthine	For patients not yet using LABA, add LABA to the earlier therapy and then hike up the dose of ICS	Tiotropium LTRA Methylxanthine	Oral steroids Omalizumab
General measures	Patient education, avoidance of asthma triggers, environmental control and treatment of comorbidities					

*LABA component in SiT should be formoterol, Use of SiT preferred in steps 3-5, ICS: Inhaled corticosteroid, LABA: Long-acting beta-2 agonists, LTRA: Leukotriene receptor antagonist, SABA: Short-acting beta-2 agonists, SiT: Single inhaler therapy

Lung India. 2015 Apr; 32(Suppl 1): S3–S42.

Stepwise approach to control symptoms



Eur Respir J. 2015 Sep;46(3):622-39. doi: 10.1183/13993003.00853-2015. Epub 2015 Jul 23.

Treatment

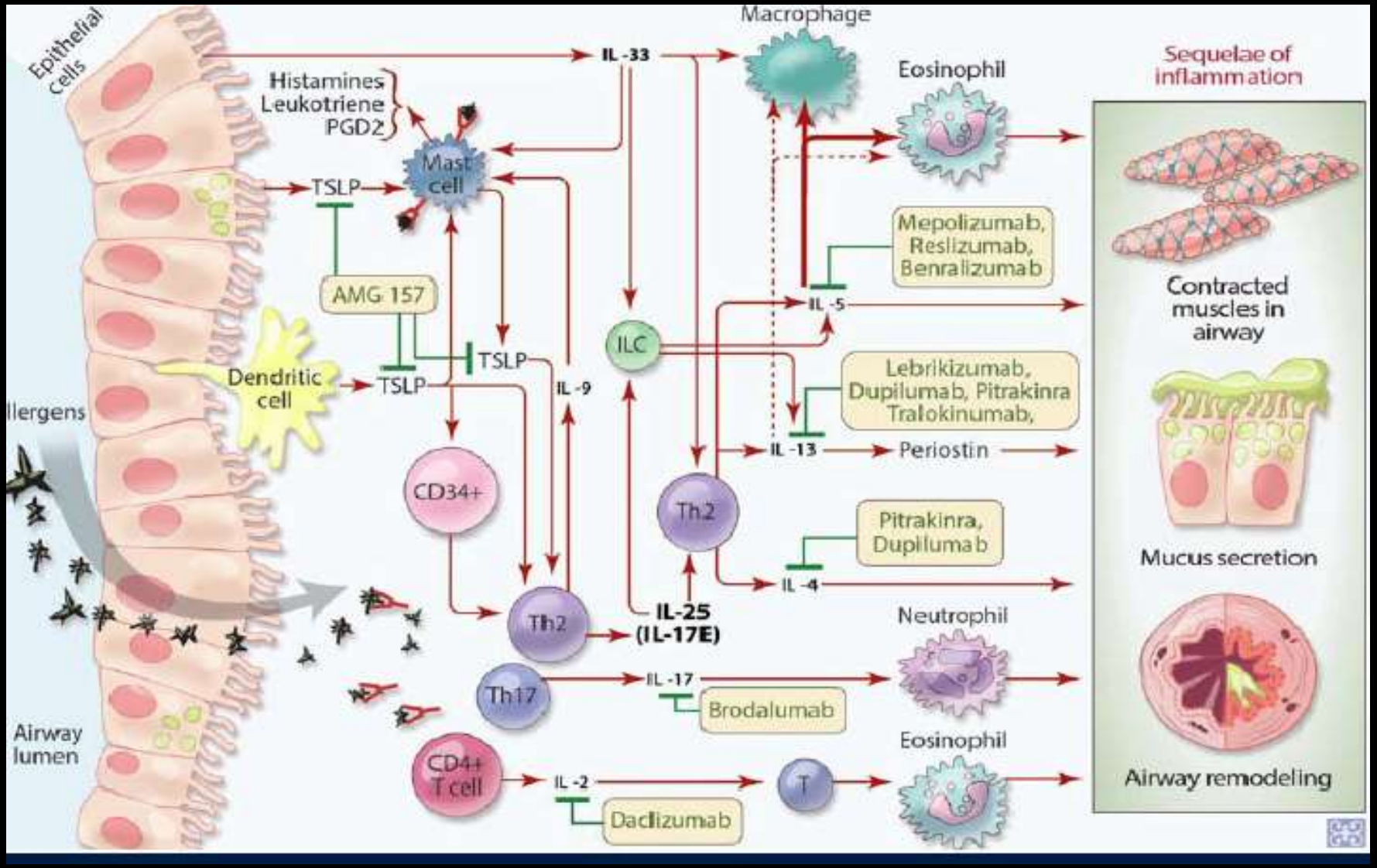
Pharmacological

- Optimal bronchodilatation-tiotropium,others
- Targeted therapy-anti-IL5, anti-IgE, TNF-alpha antagonists, Anti-IL2R chain, Anti-CXCR2, others
- Macrolides
- methotrexate

Non pharmacological

- Bronchial thermoplasty
- High altitude treatment

Targeted therapy



Eur Respir Rev. 2013 Sep 1;22(129):227-35. doi: 10.1183/09059180.00001913

Tiotropium

- Tiotropium resulted noninferiorly to salmeterol and superiorly to placebo in patients with moderate to severe asthma who were not adequately controlled by ICS or ICS/ salmeterol.
- Major benefits were concentrated in the increase in lung function and in the case of patients with severe asthma, in the reduction of exacerbations.

CHEST2015; 147 (2): 388 - 396

[Original Research **Asthma**]

CHEST

What Is the Role of Tiotropium in Asthma?
A Systematic Review With Meta-analysis

Gustavo J. Rodrigo, MD; and José A. Castro-Rodríguez, MD, PhD

BACKGROUND: The role of tiotropium for the treatment of asthma has not yet been clearly defined. The aim of this systematic review was to assess the efficacy and safety of tiotropium in patients with asthma.

METHODS: Randomized placebo-controlled trials were included. Primary outcomes were peak and trough FEV_1 and morning and evening peak expiratory flow (PEF).

RESULTS: Thirteen studies (4,966 patients) were included. Three different therapeutic protocols were identified. Tiotropium as an add-on to inhaled corticosteroids (ICSs) showed statistically and clinically significant increases in PEF (22-24 L/min) and FEV_1 (140-150 mL). Additionally, tiotropium decreased the rate of exacerbations (number needed to treat for benefit [NNTB], 36) and improved asthma control. The use of tiotropium in patients poorly controlled despite the use of medium to high doses of ICS was not inferior to salmeterol. Finally, the use of tiotropium as an add-on to ICS/salmeterol combination increased pulmonary function to a clinically significant magnitude, reduced asthma exacerbations (relative risk, 0.70; 95% CI, 0.53-0.94; $P < .02$; $I^2 = 0\%$; NNTB, 17), and improved asthma control compared with ICS/salmeterol. Tiotropium was well tolerated, and no potential safety signals were observed.

CONCLUSIONS: Tiotropium resulted noninferiorly to salmeterol and superiorly to placebo in patients with moderate to severe asthma who were not adequately controlled by ICS or ICS/salmeterol. Major benefits were concentrated in the increase in lung function and in the case of patients with severe asthma, in the reduction of exacerbations. CHEST 2015; 147(2):388-396

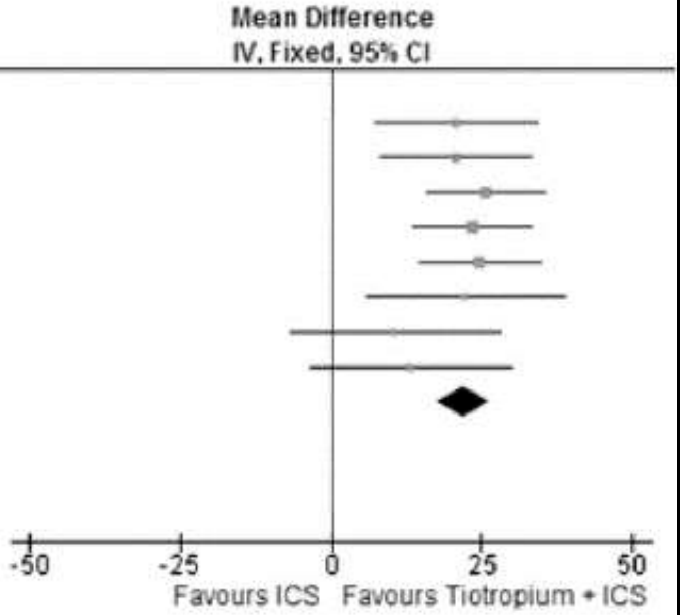
Tiotropium as Add-on to ICS [10]	Tiotropium Plus ICS vs LABA Plus ICS [4]	Tiotropium as Add-on to LABA Plus ICS [3]
9-moderate, 1-mild	All-moderate	Severe

A

Study or Subgroup	Tiotropium + ICS Mean	SD	Total	ICS Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Mild-moderate								
Bateman [18]	-3.9	55	128	-24.8	54.3	125	10.4%	20.90 [7.43, 34.37]
Beeh [24]	25.2	54.7	144	4.39	54.9	142	11.7%	20.81 [8.11, 33.51]
Peters [6]	24.4	50	203	-1.4	50	196	19.6%	25.80 [15.99, 35.61]
Trial 205.418 [26]	13.5	55.1	236	-10.15	54.5	238	19.4%	23.65 [13.78, 33.52]
Trial 205.419 [27]	27.5	50.6	236	2.76	60	235	18.8%	24.74 [14.71, 34.77]
Trial 205.420 [22]	24.3	56.1	90	1.95	55.9	91	7.1%	22.35 [6.03, 38.67]
Trial 205.464 [21]	8.4	55	114	-2.2	55	57	6.2%	10.60 [-6.89, 28.09]
Vogelberg [23]	20.5	53	77	7.27	52.5	74	6.7%	13.23 [-3.60, 30.06]
Subtotal (95% CI)			**1228**			**1158**	**100.0%**	**22.06 [17.71, 26.41]**

Heterogeneity: Chi² = 3.71, df = 7 (P = 0.81); I² = 0%

Test for overall effect: Z = 9.94 (P < 0.00001)

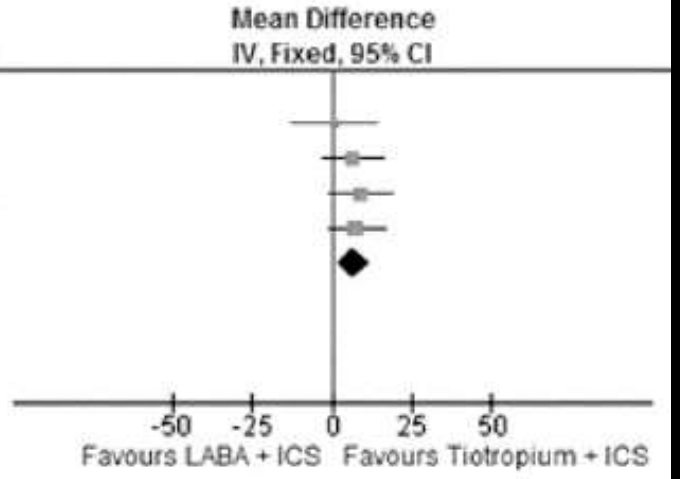


A

Study or Subgroup	Tiotropium + ICS Mean	SD	Total	LABA + ICS Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Mild-moderate								
Bateman [18]	3.9	55	128	3.2	53.7	134	14.9%	0.70 [-12.47, 13.87]
Peters [6]	24.4	50	203	18	50	195	26.7%	6.40 [-3.43, 16.23]
Trial 205.418 [26]	22.5	55.1	236	13.5	55.6	254	26.8%	9.00 [-0.81, 18.81]
Trial 205.419 [27]	27.5	50.6	236	19.8	50.5	247	31.7%	7.70 [-1.32, 16.72]
Subtotal (95% CI)			803			830	**100.0%**	**6.66 [1.59, 11.74]**

Heterogeneity: Chi² = 1.06, df = 3 (P = 0.79); I² = 0%

Test for overall effect: Z = 2.57 (P = 0.01)



A

Study or Subgroup	Tiotropium + LABA + ICS Mean	SD	Total	LABA + ICS Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Severe								
Fardon [4]	55.3	60	25	41.5	69	25	5.4%	13.80 [-22.04, 49.64]
Kerstjens [19]	7.4	25.5	104	-0.5	25.3	103	37.6%	7.90 [0.98, 14.82]
Kerstjens-1 [20]	15.297	55.5	237	-6.996	55.9	222	29.6%	22.29 [12.10, 32.49]
Kerstjens-2 [20]	17.4	60.7	219	-3.2	60.2	234	27.5%	20.60 [9.46, 31.74]
Subtotal (95% CI)			585			584	**100.0%**	**15.96 [7.13, 24.79]**

Heterogeneity: Tau² = 41.58; Chi² = 6.87, df = 3 (P = 0.08); I² = 56%

Test for overall effect: Z = 3.54 (P = 0.0004)

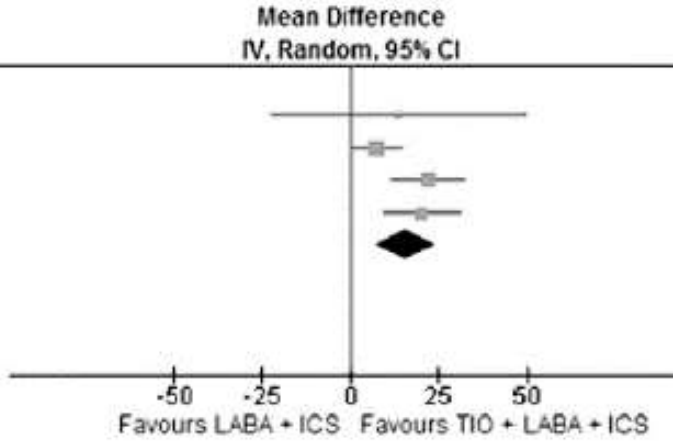


TABLE 4] Tiotropium as Add-on to ICS Plus LABA vs ICS Plus LABA on Asthma Outcomes (Severe Asthma)

Outcome	Studies[a]	No.	Estimate	Effect (95% CI)	I^2 % (*P* Value)
FEV_1 peak (change from baseline) L	4, 19, 20(1), 20(2)	1,169	MD	0.12 (0.09 to 0.16)	26 (.00001)
FEV_1 trough (change from baseline) L	19, 20(1), 20(2)	1,119	MD	0.08 (0.04 to 0.11)	20 (.00001)
Rescue medication use, puffs/d	20(1), 20(2)	912	MD	−0.16 (−0.44 to 0.13)	0 (.28)
AQLQ (change from baseline)	4, 19, 20(1), 20(2)	1,169	MD	0.12 (0.05 to 0.18)	26 (.003)
ACQ-7 (change from baseline)	20(1), 20(2)	912	MD	−0.20 (−0.25 to −0.09)	73 (.98)
ACQ-7 (responder rate)	20(1), 20(2)	907	RR	1.29 (1.13 to 1.46)	0 (.0001)
			NNTB	8 (5 to 15)	
No. patients with at least one episode of asthma exacerbation	19, 20(1), 20(2)	1,119	RR	0.70 (0.53 to 0.94)	0 (.02)
			NNTB	17 (9 to 99)	
Total withdrawals	19, 20(1), 20(2)	1,119	RR	0.96 (0.64 to 1.44)	22 (.85)
Withdrawals due to worsening asthma	19, 20(1), 20(2)	1,119	RR	0.55 (0.18 to 1.66)	0 (.29)
Any AE	19, 20(1), 20(2)	1,119	RR	0.77 (0.59 to 1.01)	15 (.06)
SAE	19, 20(1), 20(2)	1,119	RR	0.71 (0.32 to 1.55)	55 (.39)

See Table 1-3 legends for expansion of abbreviations.

[a]20(1), 20(2) = trials 1 and 2 from Kerstjens et al.[20]

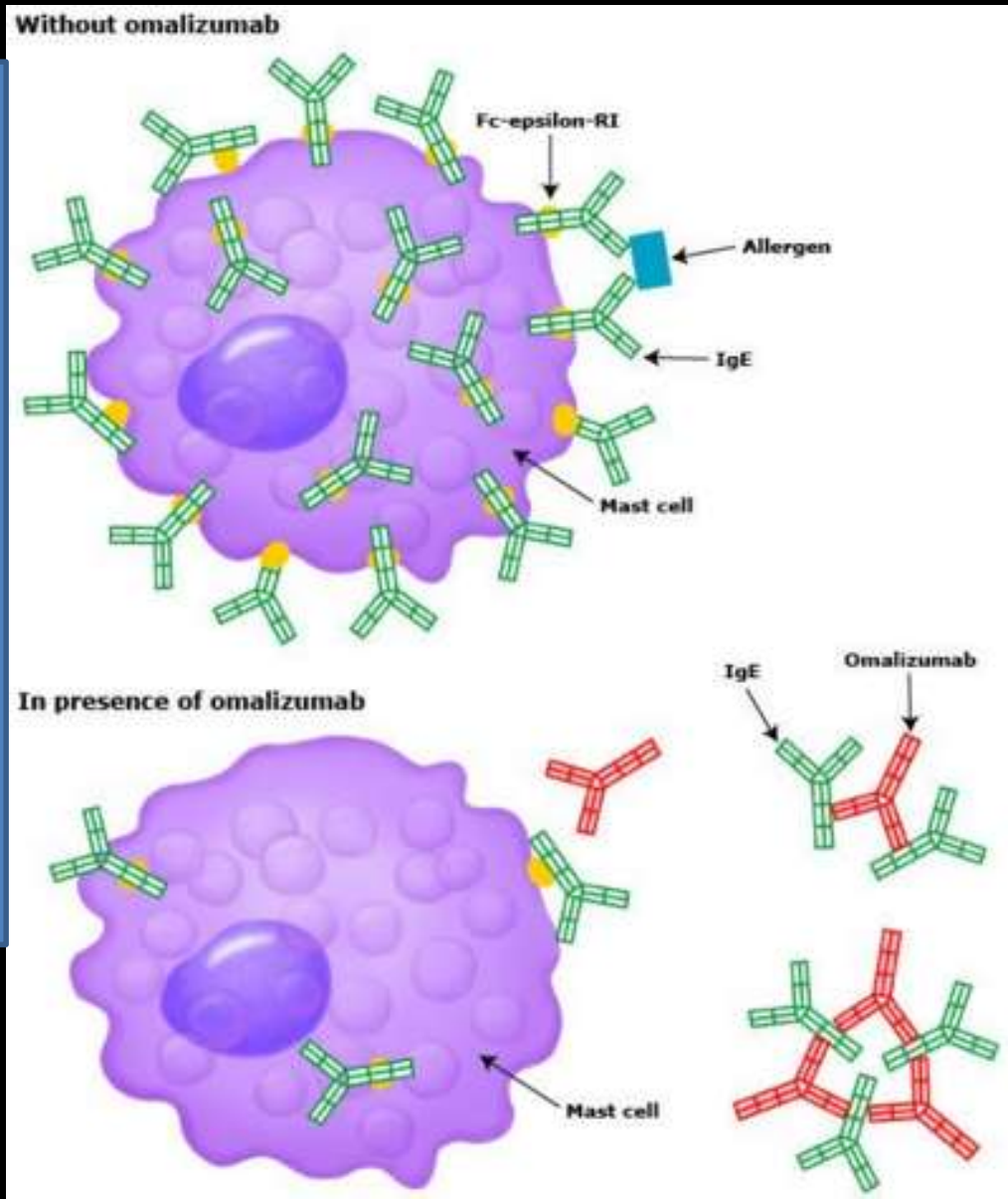
Anti IgE therapy-Omalizumab

Omalizumab is a recombinant humanized IgG1 monoclonal antibody that binds IgE with high affinity and has been developed for the treatment of allergic disease.

J Immunol 1993; 151:2623.

Mechanism

Binds to the third constant domain of the IgE heavy chain, which is the **same site at which IgE normally binds to both high and low affinity IgE receptors on mast cells, basophils, and other cell types**



Omalizumab

Indications	Side effects	Dose
ALL: ➢ Twelve years of age and older ➢ Moderate to severe persistent asthma ➢ Asthma symptoms that are inadequately controlled with inhaled glucocorticoids ➢ A total serum IgE level between 30 and 700 international units/mL (IU/mL), ➢ Allergic sensitization to a perennial ag.	➢ Hypersensitivity reactions ➢ Utricaria, anaphylaxis ➢ Cardiovascular ➢ Malignancy-solid tumors ➢ Parasitic infection	➢ s/c ➢ 0.016mg/kg/ IU/mL of IgE per month ➢ 3-6m trial ➢ Every 2-4weeks

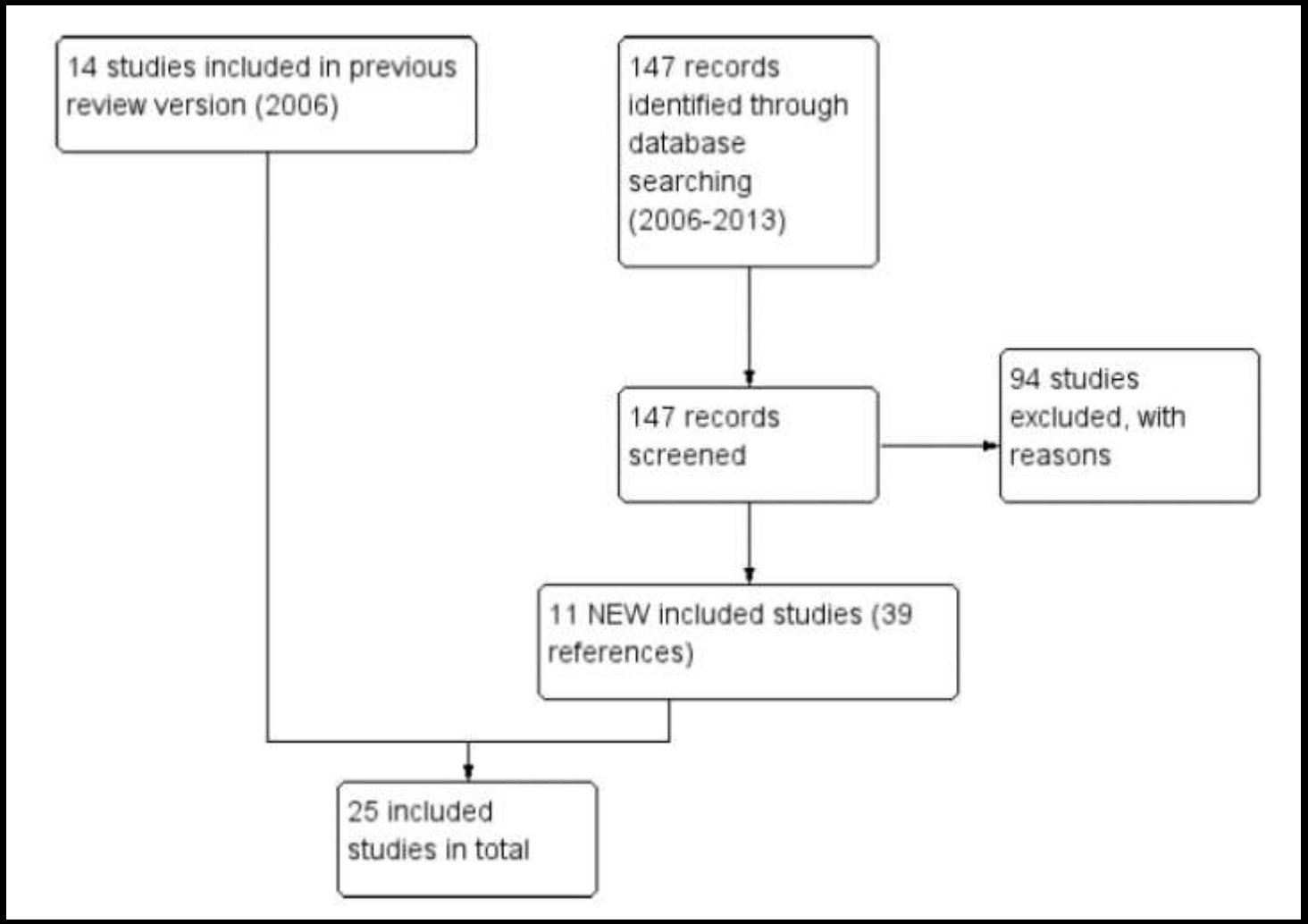
Med Lett Drugs Ther 2003; 45:67.

Omalizumab for asthma in adults and children (Review)

Normansell R, Walker S, Milan SJ, Walters EH, Nair P

THE COCHRANE

- Only double-blind randomised controlled trials (RCTs) were considered for inclusion.
- 25 trials included



Primary outcome	Secondary outcome
Asthma exacerbation Steroid reduction/termination	1-Asthma symptoms. 2. Health-related quality of life. 3. Rescue medication use. 4. Measures of lung function: forced expiratory volume in one second (FEV1), peak expiratory flow (PEF). 5. Adverse events.

Results

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Subcutaneous omalizumab+ steroid versus placebo + steroid (stable steroid)				
Number of participants with at least one exacerbation All asthmatic participants (16 to 60 weeks)	262 per 1000	163 per 1000 (130 to 176)	OR 0.55 (0.46 to 0.65)	3261 (10 studies)	⊕⊕⊕◯ moderate[1]	
Number of participants with at least one exacerbation Moderate to severe asthma (16 to 60 weeks)	274 per 1000	159 per 1000 (137 to 185)	OR 0.5 (0.42 to 0.6)	2889 (7 studies)	⊕⊕⊕◯ moderate[1]	
Number of participants with at least one exacerbation Severe asthma (16 to 32 weeks)	145 per 1000	145 per 1000 (78 to 252)	OR 1 (0.5 to 1.99)	277 (2 studies)	⊕⊕◯◯ low[2]	
Mortality 16 to 60 weeks	2 per 1000	0 per 1000 (0 to 3)	OR 0.19 (0.02 to 1.67)	4245 (9 studies)	⊕⊕◯◯ low[3,4]	
Hospitalisations 28 to 60 weeks	31 per 1000	5 per 1000 (2 to 13)	OR 0.16 (0.06 to 0.42)	1824 (4 studies)	⊕⊕⊕◯ moderate[5]	
Adverse event-serious 16 to 60 weeks	64 per 1000	47 per 1000 (37 to 58)	OR 0.72 (0.57 to 0.91)	5713 (15 studies)	⊕⊕⊕◯ moderate[6]	

Subcutaneous omalizumab + steroid versus placebo + steroid (steroid reduction) for asthma in adults and children

Patient or population: adults and children with asthma
Settings:
Intervention: subcutaneous omalizumab + steroid versus placebo + steroid (steroid reduction)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Subcutaneous omalizumab+ steroid versus placebo + steroid (steroid reduction)				
Number of participants achieving complete inhaled steroid withdrawal 28 to 32 weeks	212 per 1000	402 per 1000 (350 to 457)	OR 2.5 (2 to 3.13)	1634 (4 studies)	⊕⊕◯◯ low[1]	
>50% reduction in inhaled steroid usage 28 to 32 weeks	560 per 1000	761 per 1000 (720 to 798)	OR 2.5 (2.02 to 3.1)	1634 (4 studies)	⊕⊕⊕◯ moderate[2]	
Exacerbations requiring hospitalisation 28 weeks	20 per 1000	3 per 1000 (1 to 11)	OR 0.11 (0.03 to 0.48)	1405 (3 studies)	⊕⊕⊕◯ moderate[3]	

OPEN

SUBJECT AREAS:
DRUG DEVELOPMENT
DRUG SAFETY

Received
20 May 2014

Accepted
9 January 2015

Published
3 February 2015

Correspondence and requests for materials should be addressed to B.W. (wubin621011@126.com) or H.S. (huahaoshen@163.com)

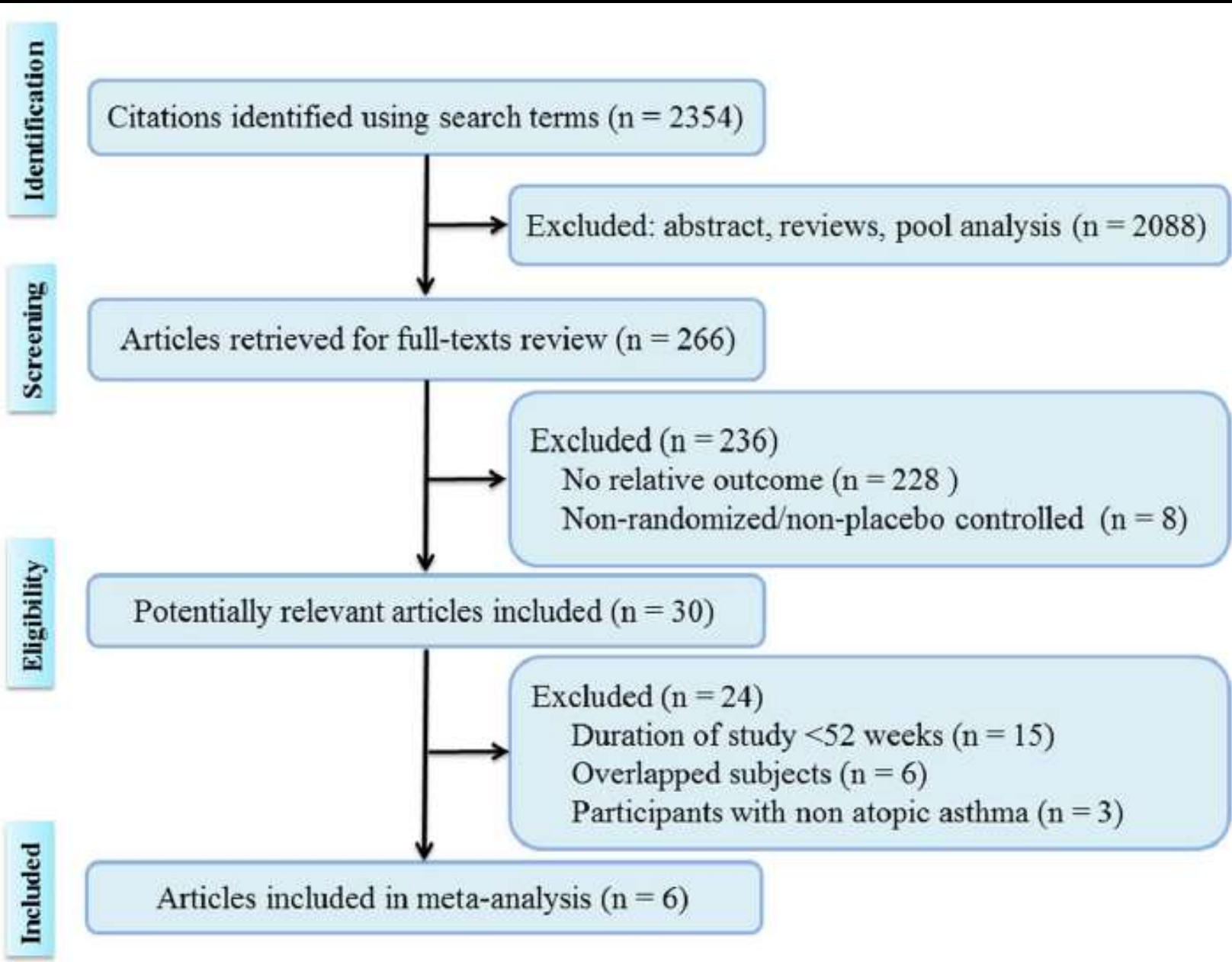
* These authors contributed equally to this work.

Long-term efficacy and safety of omalizumab in patients with persistent uncontrolled allergic asthma: a systematic review and meta-analysis

Tianwen Lai[1,2]*, Shaobin Wang[1]*, Zhiwei Xu[1], Chao Zhang[1], Yun Zhao[1], Yue Hu[1], Chao Cao[1], Songmin Ying[1,4], Zhihua Chen[1], Wen Li[1], Bin Wu[2] & Huahao Shen[1,3]

[1]Department of Respiratory and Critical Care Medicine, Second Affiliated Hospital, Institute of Respiratory Diseases, Zhejiang University School of Medicine, Hangzhou, China, [2]Department of Respiratory and Critical Care Medicine, Affiliated Hospital, Institute of Respiratory Diseases, Guangdong Medicine College, Zhanjiang, China, [3]State Key Lab. for Respiratory Diseases, Guangzhou, China, [4]Department of Pharmacology, Zhejiang University School of Medicine, Hangzhou, China.

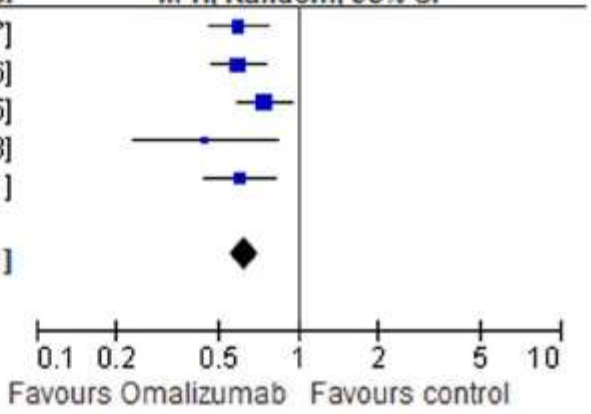
Currently, limited information is available to clinicians regarding the long-term efficacy of omalizumab treatment for allergic asthma. In this report, we aimed to (i) systematically review the evidence regarding the long-term efficacy of omalizumab in patients with persistent uncontrolled allergic asthma, and to (ii) discuss the cost-effectiveness evidence published for omalizumab in this patient population. A comprehensive search for randomized controlled trials (RCTs; ≥52 weeks) was performed, and six studies met our final inclusion criteria (n = 2,749). Omalizumab was associated with significant improvements in quality of life and the Global Evaluation of Treatment Effectiveness. Omalizumab also allowed patients to completely withdraw from inhaled corticosteroid therapy and did not increase the overall incidence of adverse events. However, there was insufficient evidence that omalizumab reduced the incidence of exacerbations, and the cost-effectiveness of omalizumab varied across studies. Our data indicated that omalizumab use for at least 52 weeks in patients with persistent uncontrolled allergic asthma was accompanied by an acceptable safety profile, but it lacked effect on the asthma exacerbations. Use of omalizumab was associated with a higher cost than conventional therapy, but these increases may be cost-effective if the medication is used in patients with severe allergic asthma.


Identification
Citations identified using search terms (n = 2354)
Excluded: abstract, reviews, pool analysis (n = 2088)
Screening
Articles retrieved for full-texts review (n = 266)
Excluded (n = 236)
No relative outcome (n = 228)
Non-randomized/non-placebo controlled (n = 8)
Eligibility
Potentially relevant articles included (n = 30)
Excluded (n = 24)
Duration of study <52 weeks (n = 15)
Overlapped subjects (n = 6)
Participants with non atopic asthma (n = 3)
Included
Articles included in meta-analysis (n = 6)

Study or Subgroup	Favours Omalizumab Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Buhl 2002 [47]	61	254	93	229	22.6%	0.59 [0.45, 0.77]
Busse 2011 [49]	63	208	108	211	27.3%	0.59 [0.46, 0.76]
Lanier 2003 [45]	78	245	92	215	28.5%	0.74 [0.59, 0.95]
Lanier 2009 [48]	17	421	19	207	4.1%	0.44 [0.23, 0.83]
Niven 2008 [46]	45	115	32	49	17.5%	0.60 [0.44, 0.81]
Total (95% CI)		**1243**		**911**	**100.0%**	**0.63 [0.55, 0.71]**
Total events	264		344			

Heterogeneity: Tau² = 0.00; Chi² = 3.65, df = 4 (P = 0.46); I² = 0%

Test for overall effect: Z = 7.19 (P < 0.00001)



Study or Subgroup	Favours Omalizumab Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
3.1.1 The overall incidence of adverse events						
Buhl 2002 [47]	161	254	151	229	9.2%	0.96 [0.84, 1.10]
Busse 2011 [49]	82	208	100	211	3.3%	0.83 [0.67, 1.04]
Lanier 2003 [45]	203	245	177	215	22.1%	1.01 [0.93, 1.09]
Lanier 2009 [48]	380	421	194	207	65.5%	0.96 [0.92, 1.01]
Subtotal (95% CI)		**1128**		**862**	**100.0%**	**0.97 [0.93, 1.01]**
Total events	826		622			

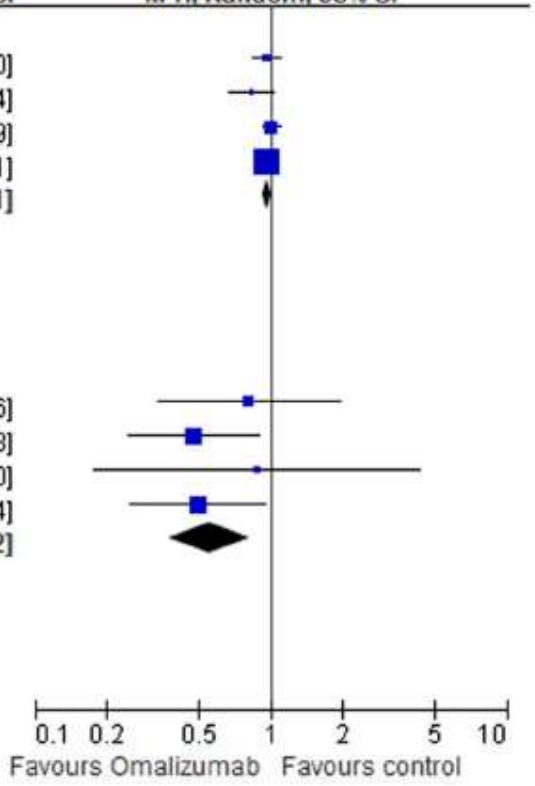
Heterogeneity: Tau² = 0.00; Chi² = 3.08, df = 3 (P = 0.38); I² = 3%

Test for overall effect: Z = 1.60 (P = 0.11)

3.1.2 Serious adverse events						
Buhl 2002 [47]	9	254	10	229	19.6%	0.81 [0.34, 1.96]
Busse 2011 [49]	13	208	28	211	38.5%	0.47 [0.25, 0.88]
Lanier 2003 [45]	3	245	3	215	6.0%	0.88 [0.18, 4.30]
Lanier 2009 [48]	17	421	17	207	35.9%	0.49 [0.26, 0.94]
Subtotal (95% CI)		**1128**		**862**	**100.0%**	**0.55 [0.37, 0.82]**
Total events	42		58			

Heterogeneity: Tau² = 0.00; Chi² = 1.42, df = 3 (P = 0.70); I² = 0%

Test for overall effect: Z = 2.98 (P = 0.003)



Conclusion

1) Use of omalizumab for at least 52weeks in severe asthmatic patients is effective and is accompanied by an acceptable safety profile
2) Subgroup analyses provided further evidence for the current asthma guideline recommendations to consider omalizumab in steps 5 or 6 for patients with persistent allergic asthma that remains uncontrolled in spite of treatment with highdose ICS plus LABAs and/or a third controller (including OCS)
3) Costs increased, but the use of omalizumab could be cost-effective if the drug is used to treat patients with severe allergic asthma

Mepolizumab
For severe eosinophilic asthma
Dose Ranging Efficacy And safety with Mepolizumab in severe asthma *(DREAM) trial*

- A multicentre, double-blind, placebo-controlled trial at 81 centres in 13 countries enrolled 621 patients were aged 12–74 years, and had a history of recurrent severe asthma exacerbations, and had signs of eosinophilic inflammation
- They were randomly assigned to receive one of three doses of intravenous mepolizumab (75 mg, 250 mg, or 750 mg) or matched placebo (100 mL 0·9% NaCl)
- The primary outcome measure was the rate of clinically significant asthma exacerbations over 12 months

Pavord et al. Lancet 2012;380:651-59

Mepolizumab for severe eosinophilic asthma Dose Ranging Efficacy And safety with Mepolizumab in severe asthma *(DREAM) trial*

- The rate of clinically significant exacerbations was reduced by 39%-48% (different doses) compared with placebo
- Small effects on FEV1 and QOL scores, which generally did not differ significantly from those reported with placebo

Pavord et al. Lancet 2012;380:651-59

Macrolids

- The non-eosinophilic asthma phenotype responds poorly to currently available anti-inflammatory therapy
- Macrolides have immunomodulatory and anti-inflammatory effects in addition to their antibacterial effects.
- Maintenance treatment with macrolides such as azithromycin has been proved to be effective in chronic neutrophilic airway diseases including cystic fibrosis, bronchiectasis and recently COPD

McGrath et al. Am J Respir Crit Care Med 2012;185:612-9

Azithromycin for prevention of exacerbations in severe asthma (AZISAST)

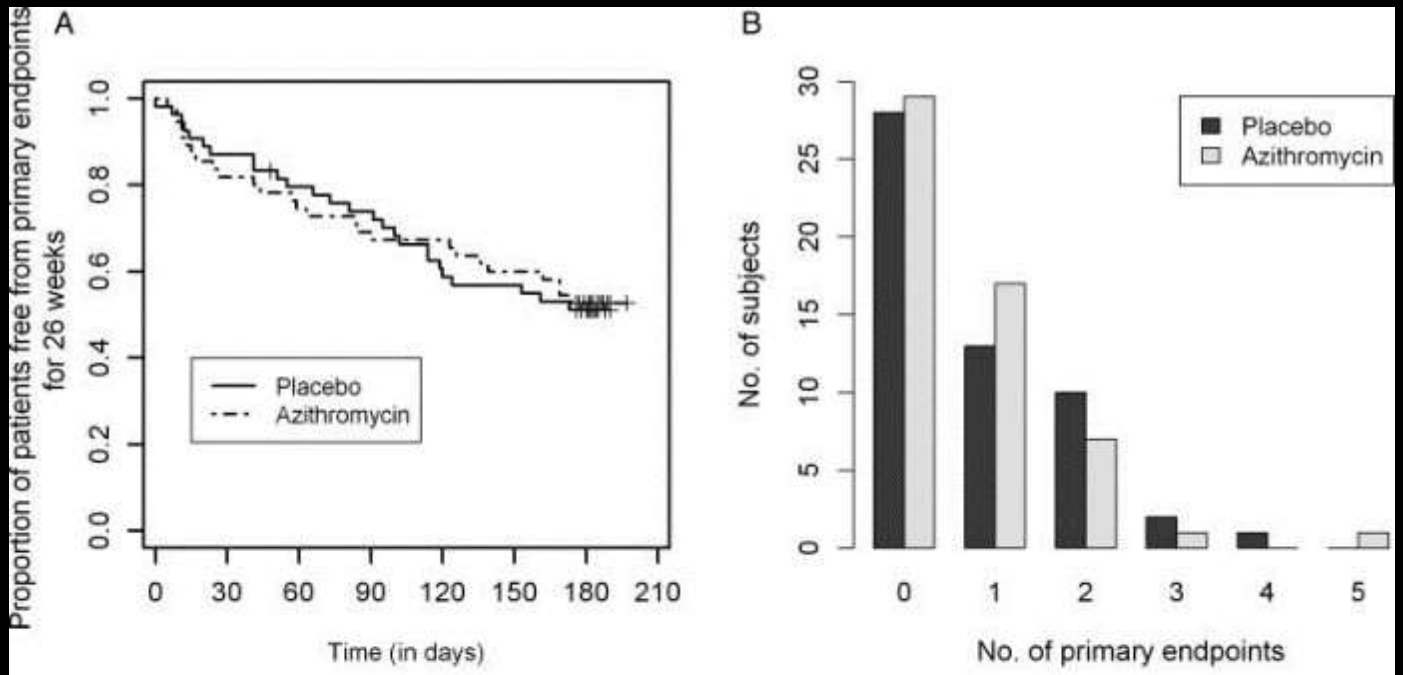
- A randomised double-blind placebo-controlled trial in subjects with severe asthma
- Subjects received low-dose azithromycin (n=55) or placebo (n=54) as add-on treatment to ICS/LABA for 6 months
- The primary endpoints (PFPs) were the rate of severe exacerbations and LRTI requiring treatment with antibiotics during the 26-week treatment phase

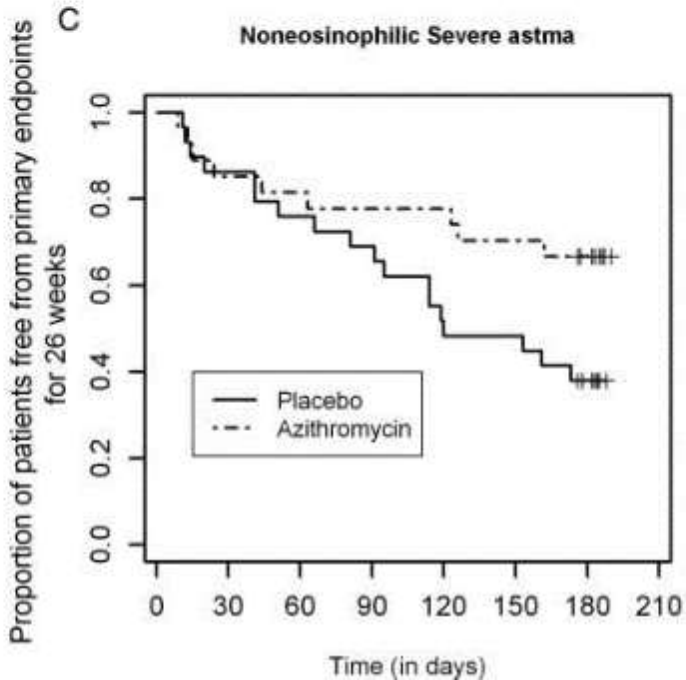
Brussel et al. Thorax 2013;68:322-39

Azithromycin for prevention of exacerbations in severe asthma (AZISAST)

- The rate of PEPs during 6 months was not significantly different between the two treatment groups
- In a predefined subgroup analysis according to the inflammatory phenotype, azithromycin was associated with a significantly lower PEPs rate than placebo in subjects with noneosinophilic severe asthma (blood eosinophilia ≤200/ml)
- Azithromycin significantly improved QOL score but there were no significant differences in the asthma contol or lung function

Brussel et al. Thorax 2013;68:322-39


A
Proportion of patients free from primary endpoints for 26 weeks
0.0
0.2
0.4
0.6
0.8
1.0
0
30
60
90
120
150
180
210
Time (in days)
Placebo
Azithromycin
B
No. of subjects
0
5
10
15
20
25
30
0
1
2
3
4
5
No. of primary endpoints
Placebo
Azithromycin


C
Noneosinophilic Severe astma
Proportion of patients free from primary endpoints for 26 weeks
0.0
0.2
0.4
0.6
0.8
1.0
0
30
60
90
120
150
180
210
Time (in days)
Placebo
Azithromycin

Drug	Evidence for efficacy	No. of patients	Significant reduction in OCS dose	Improvements in other parameters	Common side effects for agent
Thiopurines (AZT)	Hodges et al.[17] (CS)	10	No	Increase in airway conductance.	■ GI upsets (diarrhoea, nausea, vomiting) ■ Flu-like symptoms
	Hodges et al.[17] (CS)	13	No	–	
Macrolides (TAO)	Ball et al.[23] (DBPC)	15	Yes	Improvement in AHR.	■ Steroid related side effects (for TAO)
	Kamada et al.[24] (DBPC)	18	Yes	Improvement in AHR, asthma symptoms.	
	Nelson et al.[25] (DBPC)	57	Yes	Reduction in hospital admissions, ER attendances and OCS boosts.	
Cyclosporin A	Alexander et al.[38] (CS)	30	Not assessed	Improvements in PEF, FEV_1. Reduction in asthma exacerbations.	■ Hypertrichosis ■ Hypertension ■ Paraesthesias ■ GI upsets (nausea, diarrhoea) ■ Flu-like symptoms
	Lock et al.[36] (DBPC)	36	Yes	Improvements in morning PEF.	
	Nizankowska et al.[37] (DBPC)	32	No	Reduction in symptoms scores and reliever use.	
Gold	Klaustermeyer et al.[49] (DBPC)	8	No	–	■ GI upsets (abdominal pain, diarrhoea) ■ Pruritic rash
	Nierop et al.[45] (DBPC)	28	Yes	Improvements in symptom scores, FEV_1. Reductions in OCS boosts.	
	Bernstein et al.[46] (DBPC)	279	Yes	–	
MTX	Mullarkey et al.[52] (CS)	13	Yes	–	■ LFT abnormalities ■ GI upsets (abdominal pain, nausea, diarrhoea) ■ Oral ulcers and stomatitis
	Dyer et al.[54] (CS)	10	Yes	–	
	Shiner et al.[53] (DBPC)	60	Yes	Reduction in asthma exacerbations.	
	Erzurum et al.[55] (DBPC)	17	No[a]	–	
	Trigg et al.[56] (CS)	12	No	–	
	Taylor et al.[57] (CS)	9	No	–	
	Stewart et al.[58] (DBPC)	21	No[a]	Improvements in subjective and physician symptom scores.	
	Coffey et al.[59] (DBPC)	11	Yes	–	
	Kanzow et al.[60] (DBPC)	21	No[a]	–	
	Ogirala et al.[61] (DBPC)	19	No	Improvements in FEV_1, PEF, AHR. Reduction in hospital admissions and ER attendances.	
	Hedman et al.[62] (CS)	12	Yes	Reduction in reliever use.	
	Comet et al.[63] (DBPC)	46	Yes	–	

Respir Med. 2008 Nov;102(11):1499-510. doi: 10.1016/j.rmed.2008.09.006.

Wenzel [99]	Severe	309	R, db, pc, p	Golimumab, anti TNF-α, 24 weeks	FEV1, exacerbations AQLQ, PEFR	FEV1 unchanged, no reduction in exacerbations, AQLQ, PEFR Adverse profile side-effects
Pavord [56]	Severe, with ≥2 exacerbations in past year	621	R, db, pc, p	Mepolizumab (75, 250 or 750 mg infusions at 4 weeks), anti-IL-5, 52 weeks	Rate of exacerbations	All doses reduced exacerbations by 39–52% No effect on ACQ, AQLQ or FEV1
Haldar [157]	Severe	61	R, db, pc, p	Mepolizumab, anti-IL5, 50 weeks	Exacerbations, symptoms, FEV_1, AQLQ, AHR, sputum and blood eosinophils	Reduced exacerbations Improved AQLQ Reduced eosinophils
Nair [58]	Severe	20	R, db, pc, p	Mepolizumab, anti-IL5, 50 weeks	Exacerbations, oral steroid reduction	Reduced exacerbations, eosinophils and OCS dose
Kips [159]	Severe	26	R, db, pc, p	SCH55700, anti-IL-5, 12 weeks	Sputum and blood eosinophils, symptoms, FEV1	Reduced blood sputum eosinophils No other significant outcomes
Castro [57]	Poorly controlled on high-dose inhaled CS	53	R, db, pc, p	Reslimuzab, anti-IL-5, 12 weeks	ACQ, FEV1, Sputum eosinophils	Improved ACQ score Reduction in sputum eosinophils Improved FEV1
Corren [160]	Moderate-severe	294	R, db, pc, p	AMG317, anti-IL-4Rα antibody, blocks IL-4 and IL-13, 12 weeks	ACQ scores, exacerbations	No effect on ACQ or exacerbations
Corren [59]	Moderate-severe	219	R, db, pc, p	Lebrikizumab, anti-IL13 antibody, 24 weeks	Change in pre-bronchodilator FEV1	Improved FEV1, compared with placebo, with greatest changes in high levels of periostin or F_{ENO} group (post hoc analyses) No effect on ACQ-5 or diary measures Exacerbations were 60% lower in treated group with high Th2
Piper [60]	Moderate-to-severe	194	R, db, pc, p	Tralokinumab (150, 300, or 600 mg), IL-13 neutralising monoclonal antibody, 3 months	Change from baseline in ACQ-6 at week 13	No change in ACQ-6 at 13 weeks FEV1 increase of 0.21 L *versus* 0.06 L with placebo ($p=0.072$) β_2-agonist use decrease of -0.68 versus -0.10 with placebo ($p=0.020$) Better response in those with higher IL-13 levels in sputum
Humbert [161]	Severe, CS-dependent	44	R, db, pc, p	Masitinib (3, 4.5 and 6 $mg \cdot kg^{-1} \cdot day^{-1}$), c-kit and PDGFR tyrosine kinase inhibitor, 16 weeks	OCS dose ACQ, FEV1	No difference in OCS dose ACQ improved, no difference in FEV1
Busse [162]	Moderate-to-severe		R, db, pc, p	Daclizumab, IL-2Rα chain antibody, 20 weeks	Change in FEV1 (%) Asthma exacerbations	Improved FEV1 Reduction in day-time asthma scores, use of SABA Prolonged time to severe exacerbations Reduction in blood eosinophils
Nair [163]	Severe asthma	34	R, db, pc, p	SCH527123, CXCR2 receptor antagonist, 4 weeks	Changes in sputum and neutrophil activation markers	Reduction in blood and sputum neutrophil Reduction in mild exacerbations No reduction in ACQ score ($p=0.053$)

ERS/ATS GUIDELINES ON SEVERE ASTHMA | K.F. CHUNG ET AL.
Eur Respir J 2014; 43: 343–373 | DOI: 10.1183/09031936.00202013

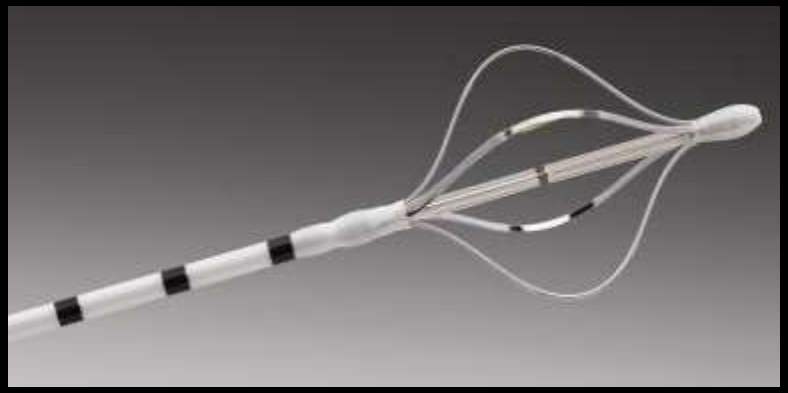
BRONCHIAL THERMOPLASTY-

BT is a novel, minimally invasive therapeutic intervention for patients with severe persistent asthma that is uncontrolled despite the use of ICS and LABA.

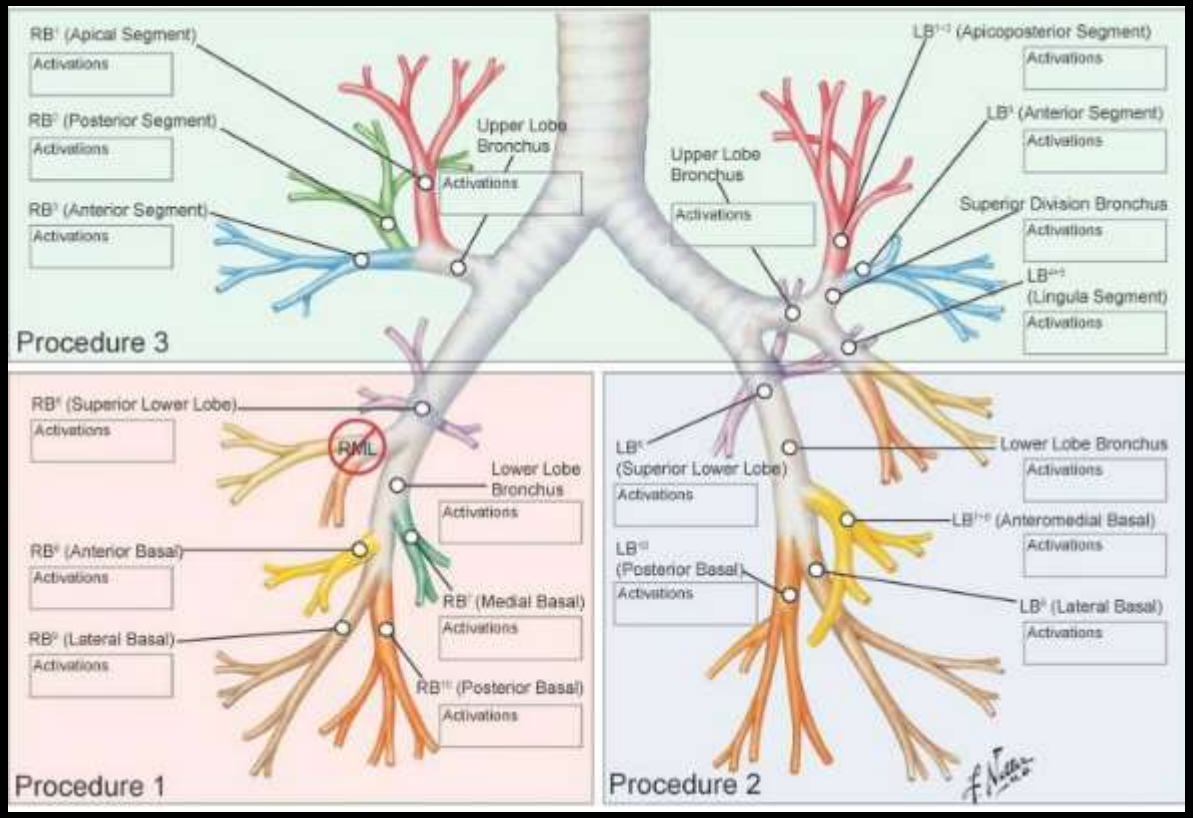
First approved by the United States Food and Drug Administration (FDA) in 2010, BT delivers targeted thermal energy to the airway walls with the goal of reducing ASM mass.

The thermal energy is delivered using the Alair System (Boston Scientific, Natick, MA, USA). The catheter is introduced via the working channel of the flexible bronchoscope.

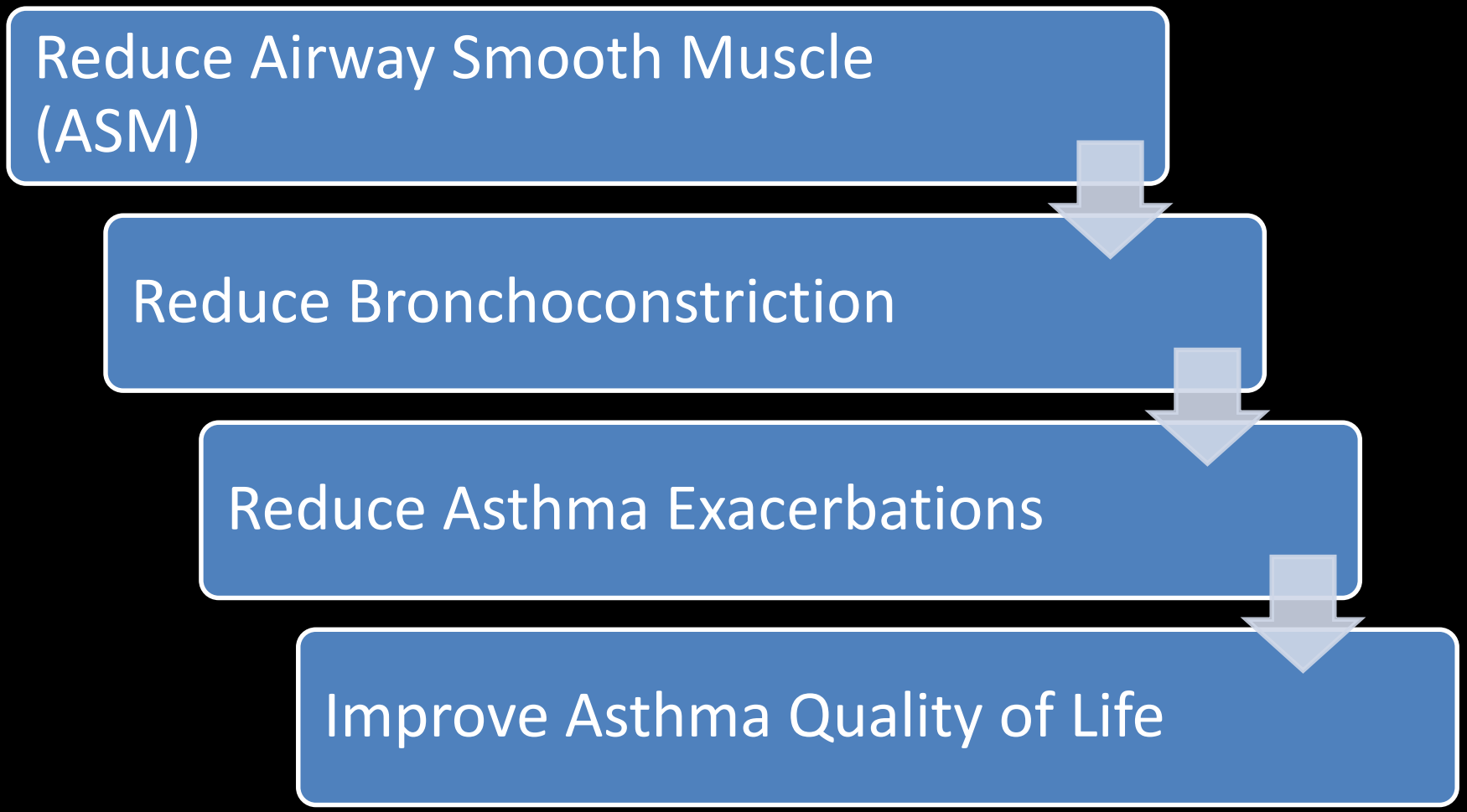
The distal tip contains an expandable four-electrode basket, which is serially deployed in the airways.

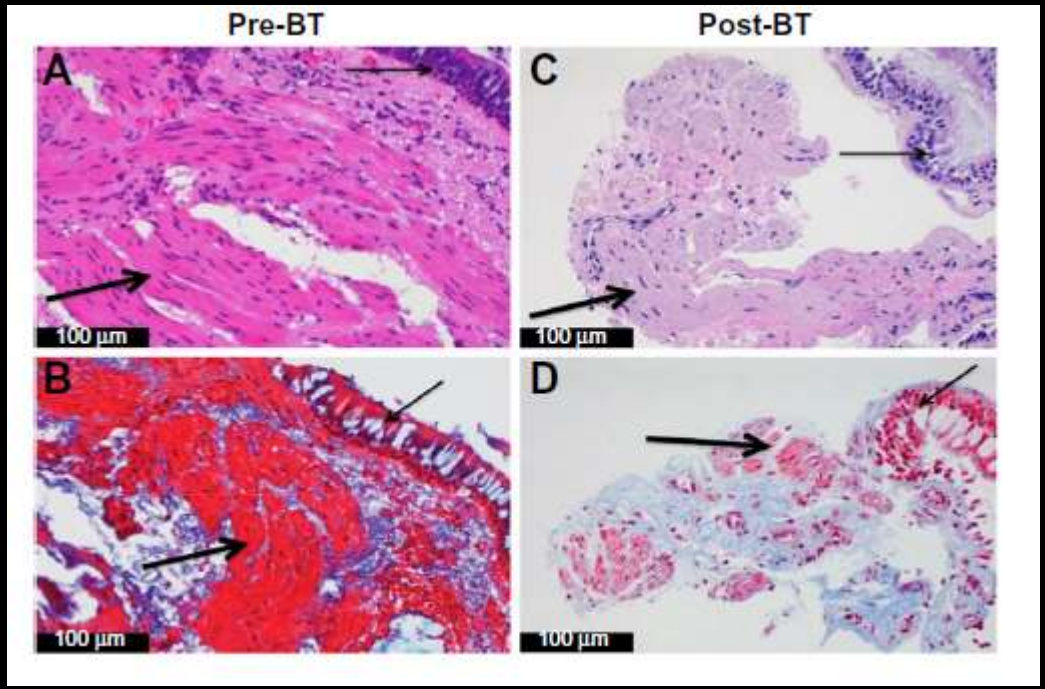



ALAIR®
FOR BRONCHIAL
THERMOPLASTY



- BT is performed by a BT-certified pulmonologist in 3 outpatient visits, typically scheduled 3 weeks apart.
- Temperature controlled energy (65o C) is delivered to airway wall for 10 seconds per activation
- 4/segment


Reduce Airway Smooth Muscle (ASM)
Reduce Bronchoconstriction
Reduce Asthma Exacerbations
Improve Asthma Quality of Life


Pre-BT
Post-BT
A
C
B
D
100 µm
100 µm
100 µm
100 µm

The Journal of International Medical Research
2011; 39: 10 – 22 [first published online as 39(1) 3]

Meta-analysis of the Efficacy and Safety of Bronchial Thermoplasty in Patients with Moderate-to-severe Persistent Asthma

Q WU[1], Y XING[1], X ZHOU[2] AND D WANG[1]

[1]Department of Internal Medicine, Macau University of Science and Technology, Macau, China; [2]Department of Internal Medicine, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China

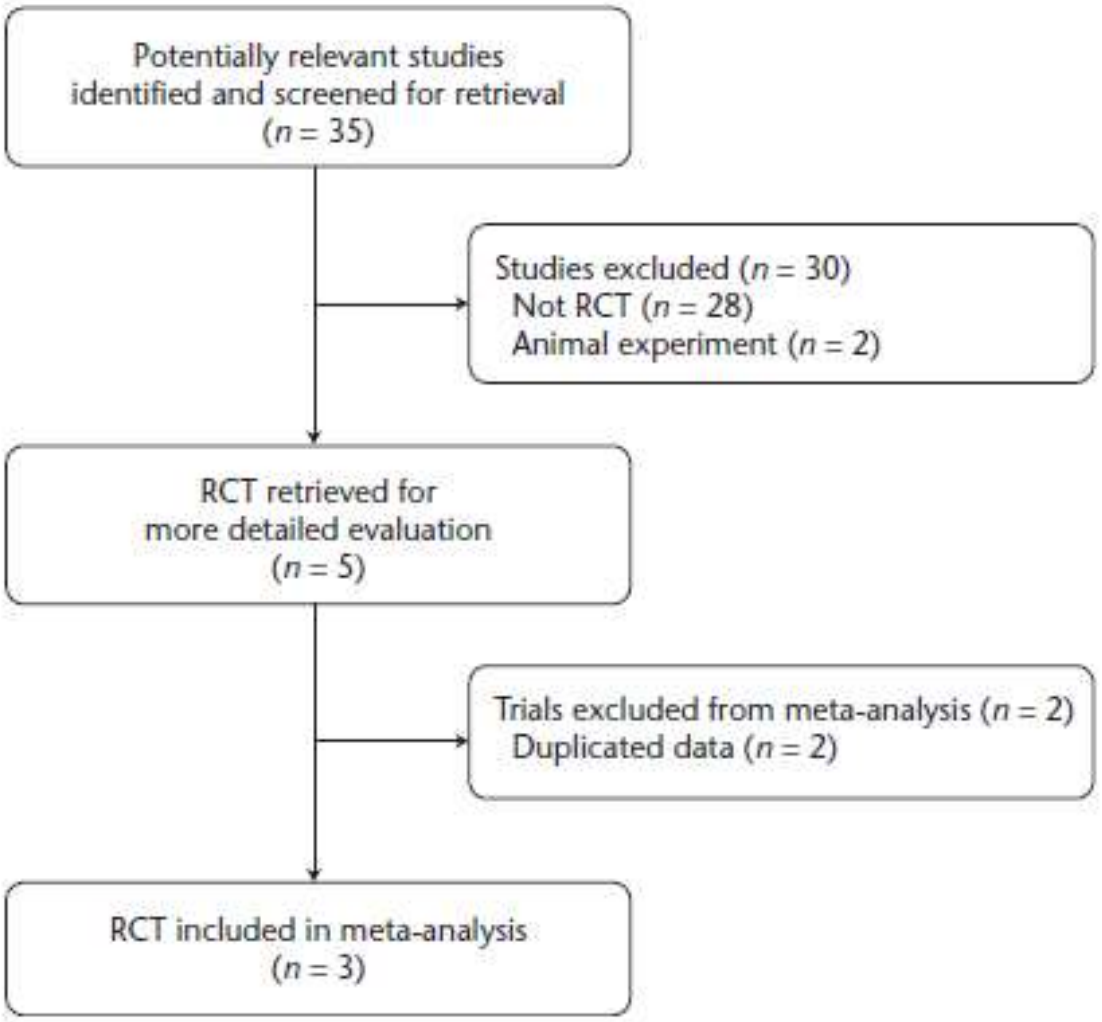


FIGURE 1: Flow diagram showing the trial selection process for the randomized control trials (RCT) included in the present meta-analysis to assess the efficacy and safety of bronchial thermoplasty in patients with moderate-to-severe persistent asthma

J Int Med Res. 2011;39(1):10-22.

TABLE 1:
Principal characteristics of the studies included in a meta-analysis to assess the efficacy and safety of bronchial thermoplasty in patients with moderate-to-severe persistent asthma[12,13,25]

Study (year)	Design	JADAD scale[16–18]	Duration, weeks	Variables	Inclusion criteria	Sample size	Intervention	Control-group intervention
Pavord *et al.*[25] (2007)	Multicentre, randomized, controlled, parallel-group study.	3	52	Change in OCS and ICS; use of rescue medication; morning and evening PEF; FEV_1; asthma symptom score; symptom-free days; AQLQ scores; safety; adverse events; pulmonary function.	Patients aged 18 – 65 years; requirement for high-dose ICS (> 750 µg fluticasone propionate per day or equivalent) and LABA (at least 100 µg salmeterol per day or equivalent); pre-bronchodilator FEV_1 ≥ 50% of predicted; demonstrable airway hyper-responsiveness by challenge with methacholine; uncontrolled symptoms despite taking maintenance medication.	32		
Cox *et al.*[12] (2007)	Randomized, controlled, parallel-group study.	3	52	AQLQ scores; morning PEF; rescue medication; nocturnal awakening caused by asthma symptoms; adverse events; rates of mild and severe exacerbations.	Persons 18 – 65 years of age; moderate or severe persistent asthma, requiring daily therapy with ICS equivalent to a dose of ≥ 200 µg of beclomethasone and LABA, at a dose of ≥ 100 µg of salmeterol or equivalent, to maintain reasonable asthma control. Airflow obstruction, assessed as a pre-bronchodilator FEV_1 of 60 – 85% of the predicted value.	101	Three bronchial thermoplasty procedures ≥ 3 weeks apart. Regular maintenance medications of inhaled LABA and ICS.	Regular maintenance medications of inhaled LABA and ICS.
Castro *et al.*[13] (2010)	Multicentre, randomized, double-blind, sham-controlled clinical trial.	5	52	AQLQ scores; percentage of symptom-free days; symptom scores; rescue medication use; morning PEF; FEV_1; numbers of severe asthma exacerbations; respiratory-related unscheduled physician office visits; emergency department visits; hospitalizations; days missed from work/ school; adverse events.	Eligible patients were adults (18 – 65 years of age) diagnosed with asthma who required regular maintenance medications of inhaled corticosteroids (ICS 1000 µg/day beclomethasone or equivalent) and LABA > 100 µg/day salmeterol or equivalent. Key inclusion criteria were: patients on stable maintenance asthma medications for at least 4 weeks before entry, baseline AQLQ score ≤ 6.25, pre-bronchodilator FEV_1 > 60% of predicted, airway hyper-responsiveness, and at least 2 days of asthma symptoms during the 4-week baseline period.	288		Three sham bronchoscopy procedures, each separated by ≥ 3 weeks. Regular maintenance medications of inhaled LABA and ICS.

OCS, oral corticosteroids; ICS, inhaled corticosteroids; PEF, peak expiratory flow; FEV_1, forced expiratory volume in 1 s; AQLQ, Asthma Quality of Life Questionnaire; LABA, long-acting β_2-agonist.

J Int Med Res. 2011;39(1):10-22.

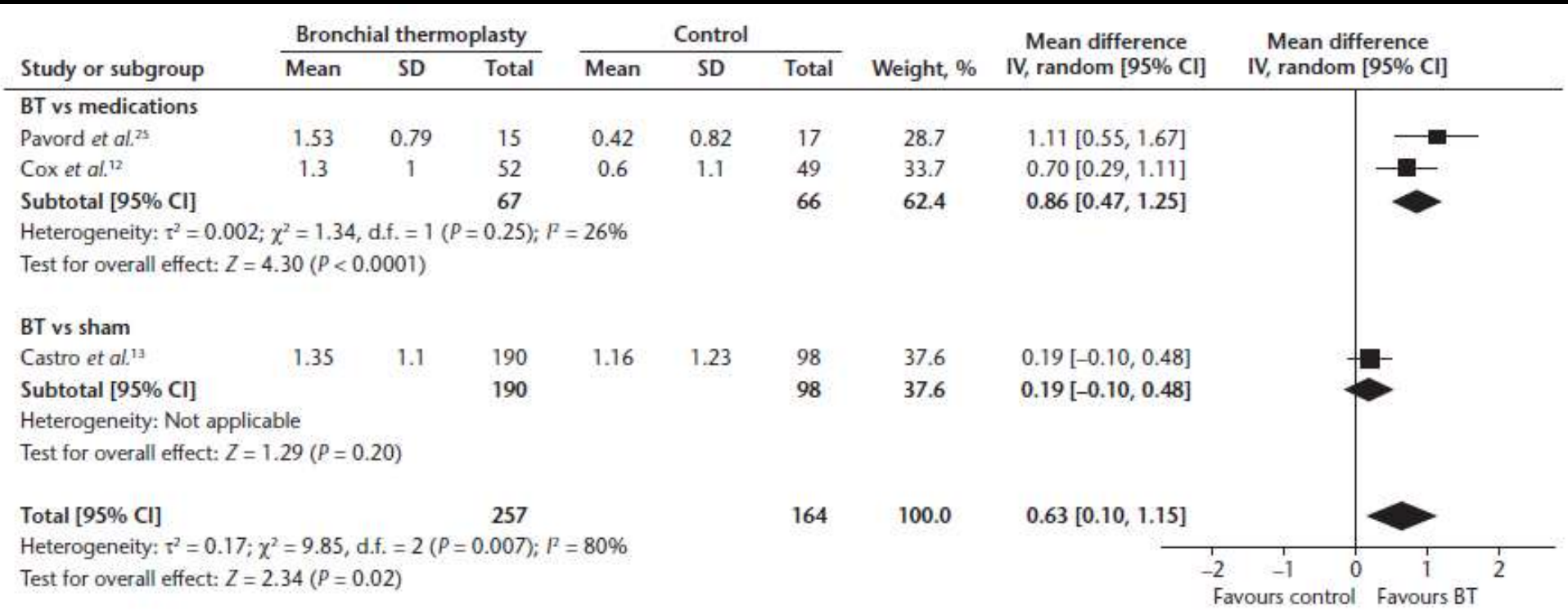


FIGURE 2: Forest plots showing that the mean improvements in the Asthma Quality of Life Questionnaire scores from baseline to the study end, in a meta-analysis of three trials that assessed the efficacy and safety of bronchial thermoplasty (BT), were greater with BT than with medications or sham BT treatment[12,13,25]

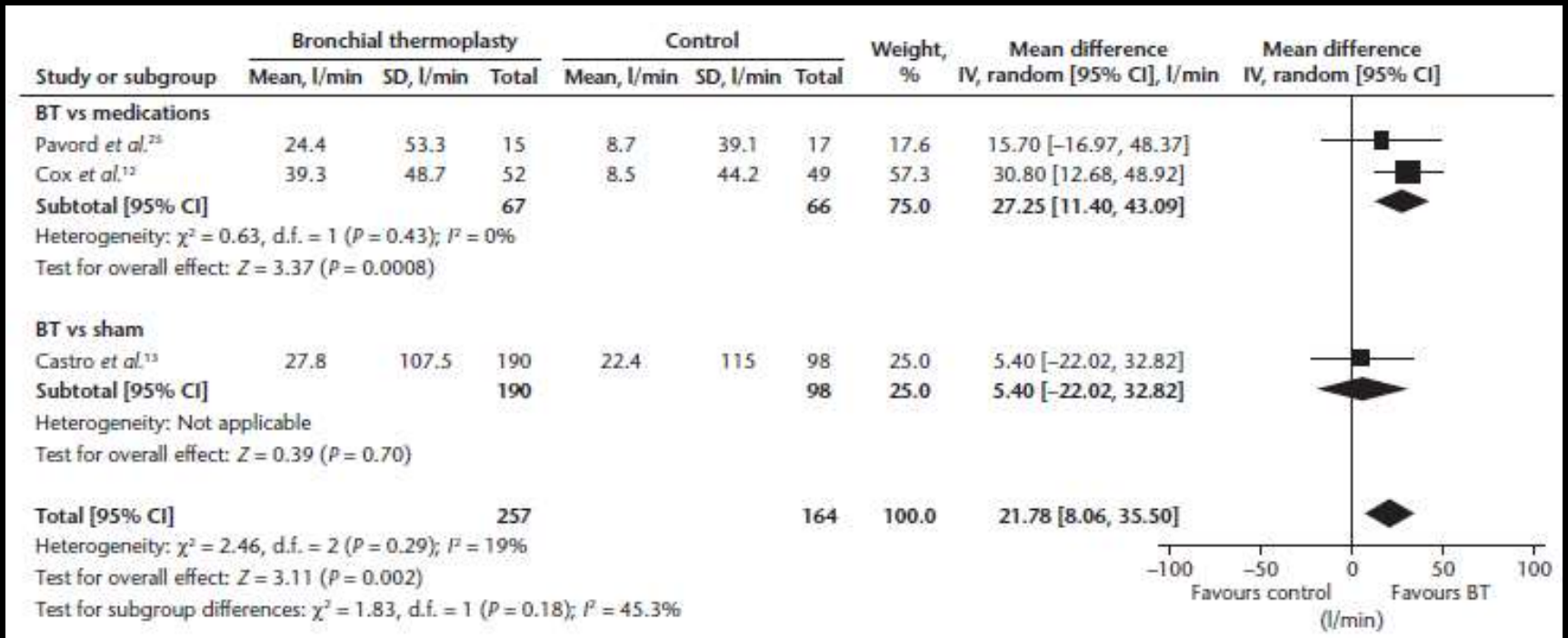


FIGURE 3: Forest plots showing that the mean improvements in the peak expiratory flow from baseline to the end of each study were greater with bronchial thermoplasty (BT) than with medications or sham BT treatment, in three trials included in a meta-analysis of BT treatment[12,13,25]

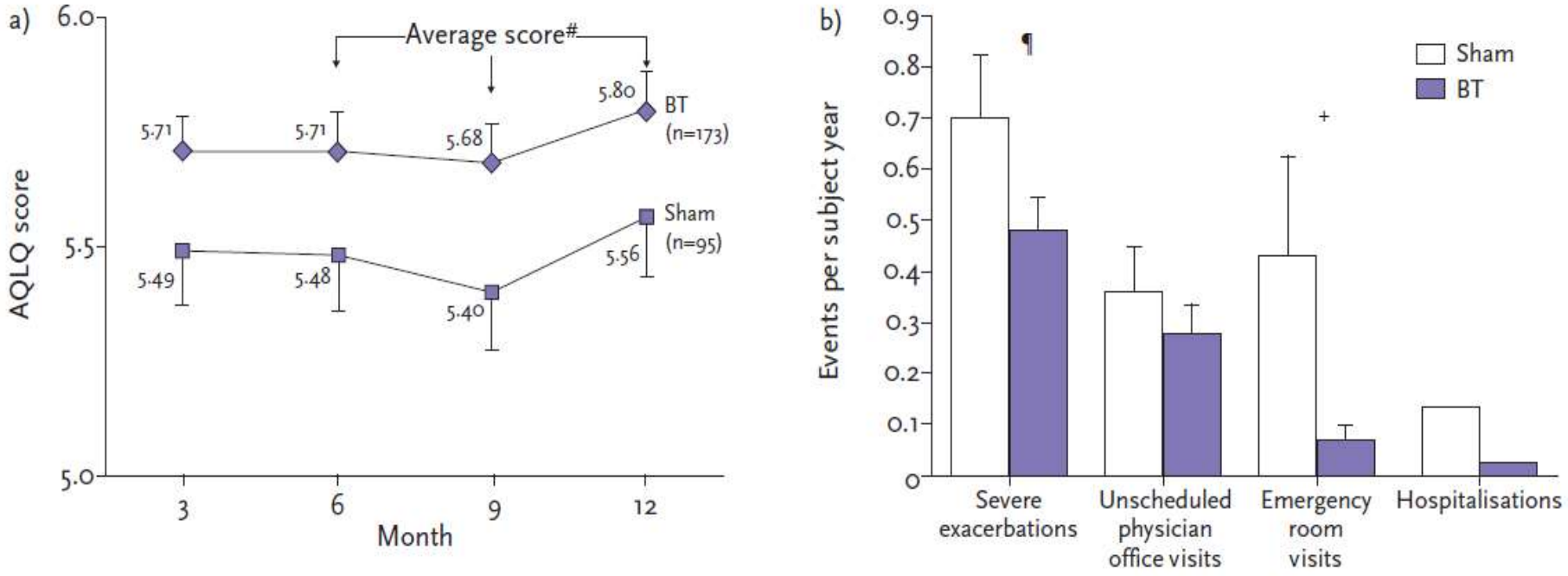
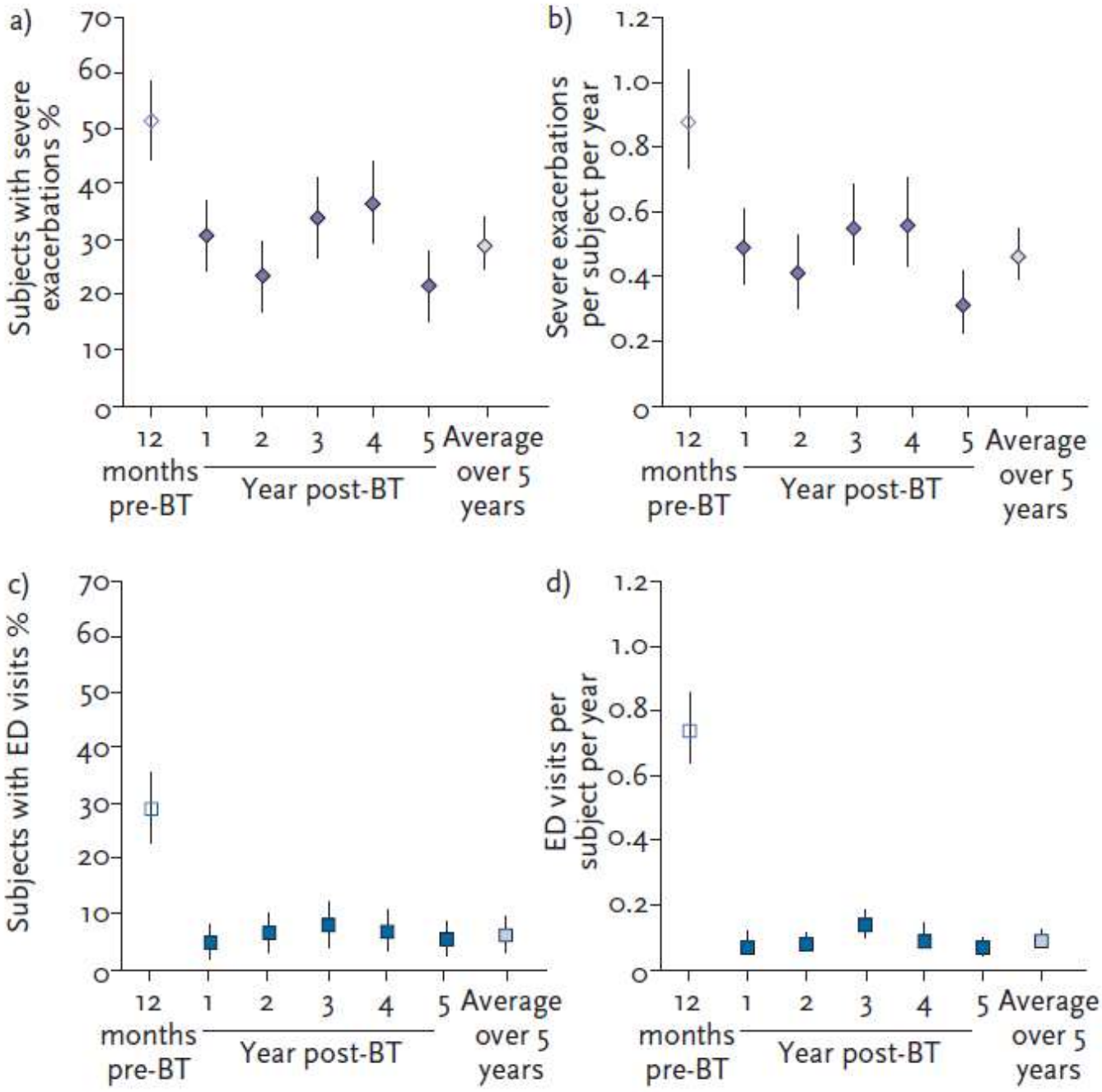
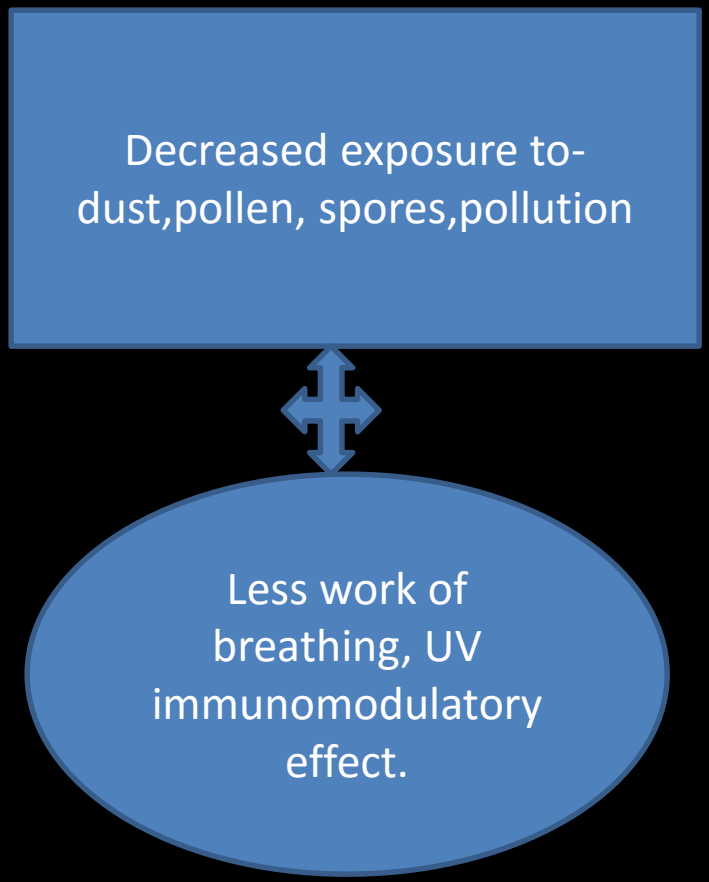


Figure 2

a) Total Asthma Quality of Life Questionnaire (AQLQ) score over 12 months after treatment with bronchial thermoplasty (BT) in the per protocol population and b) mean ± SEM healthcare utilisation events during the post-treatment period. Severe exacerbations were defined as exacerbations requiring treatment with systemic corticosteroids or doubling of the inhaled corticosteroids dose. #: Posterior probability of superiority 97.9%; ¶: posterior probability of superiority 95.5%; +: posterior probability of superiority 99.9%. Reproduced from [15] with permission from the publisher.


a)
Subjects with severe exacerbations %
70
60
50
40
30
20
10
0
12 months pre-BT
1
2
3
4
5
Year post-BT
Average over 5 years
b)
Severe exacerbations per subject per year
1.2
1.0
0.8
0.6
0.4
0.2
0
12 months pre-BT
1
2
3
4
5
Year post-BT
Average over 5 years
c)
Subjects with ED visits %
70
60
50
40
30
20
10
0
12 months pre-BT
1
2
3
4
5
Year post-BT
Average over 5 years
d)
ED visits per subject per year
1.2
1.0
0.8
0.6
0.4
0.2
0
12 months pre-BT
1
2
3
4
5
Year post-BT
Average over 5 years

High altitude treatment



Eur Respir J 2012; 40: 1374–1380
DOI: 10.1183/09031936.00195211

High-altitude treatment in atopic and nonatopic patients with severe asthma

Lucia H. Rijssenbeek-Nouwens*, Karin B. Fieten*, Adriaan O. Bron*, Simone Hashimoto#, Elisabeth H. Bel# and Els J. Weersink#

prospective observational cohort study, 137 adults with severe refractory asthma (92 with allergic sensitisation), referred for high-altitude (1,600 m) treatment in Davos Switzerland, were consecutively included.

At admission and 12 weeks-

TABLE 3 Values at baseline and after 12 weeks of high-altitude treatment in patients with and without house dust mite (HDM) sensitisation

	HDM-sensitised patients			Non-HDM-sensitised patients			Significance between groups p-value
	Baseline	12 weeks	p-value	Baseline	12 weeks	p-value	
Subjects n		68			69		
ACQ score[#]	3.0±1.0	1.6±1.2	<0.001	3.3±1.0	1.8±1.0	<0.001	0.965
AQLQ score[¶]	4.0±0.9	5.6±1.0	<0.001	3.8±0.9	5.3±1.1	<0.001	0.952
SNOT-20 score[+]	2.2±0.8	1.5±1.1	<0.001	2.2±0.76	1.6±1.0	<0.001	0.412
Patients on OCS	29 (43)	15 (22)	<0.001	41 (59)	26 (38)	<0.001	0.87
OCS mg·day^{-1}	0 (0–60)	0 (0–40)	<0.001	5.0 (0–110)	0 (0–40)	<0.001	0.668
ICS μg·day^{-1}	1600 (200–8000)	1600 (0–8000)	0.533	1600 (0–8000)	1600 (0–8000)	0.40	0.584
FEV_1 % pred	88.4±20.4	94.2±20.1	0.001	86.5±26.2	92.8±23.1	0.004	0.838
6MWD m	516±178	636±219	<0.001	430±182	575±197	<0.001	0.360
Total IgE kU·L^{-1}	376 (7–5000)	245 (6–4682)	0.003	94 (5–1781)	58 (5–1961)	0.039	0.211
Blood eosinophils per μL of blood	235 (0–1050)	210 (50–570)	0.033	200 (0–880)	200 (0–630)	0.207	0.025
F_{ENO} ppb	27.6 (5–209)	18.4 (3–70)	<0.001	16 (5–224)	16 (1–61)	0.058	0.033

TABLE 9 Potential phenotype-targeted therapies in severe asthma[#]

Characteristic	Associations	Specifically targeted treatments
Severe allergic asthma	Blood and sputum eosinophils High serum IgE High F_{ENO}	Anti-IgE (adults and children) Anti-IL-4/IL-13 Anti-IL-4 receptor
Eosinophilic asthma	Blood and sputum eosinophils Recurrent exacerbations High F_{ENO}	Anti-IL-5 Anti-IL-4/IL-13 Anti-IL-4 receptor
Neutrophilic asthma[¶]	Corticosteroid insensitivity Bacterial infections	Anti-IL-8 CXCR2 antagonists Anti-LTB4 (adults and children) Macrolides (adults and children)
Chronic airflow obstruction	Airway wall remodelling as increased airway wall thickness	Anti-IL-13 Bronchial thermoplasty
Recurrent exacerbations	Sputum eosinophils in sputum Reduced response to ICS and/or OCS	Anti-IL5 Anti-IgE (adults and children)
Corticosteroid insensitivity	Increased neutrophils in sputum[¶]	p38 MAPK inhibitors Theophylline (adults and children) Macrolides (adults and children)

ERS/ATS GUIDELINES ON SEVERE ASTHMA | K.F. CHUNG ET AL.
Eur Respir J 2014; 43: 343–373 | DOI: 10.1183/09031936.00202013

Recommendations-ERS/ATS GUIDELINES ON SEVERE ASTHMA 2013/Severe refractory asthma: an update [2013]

Bronchial Thermoplasty Very low	bronchial thermoplasty is performed in adults with severe asthma only in the context of an Institutional Review Board approved independent systematic registry or a clinical study (recommendation, quality evidence)
Methotrexate low	do not use methotrexate in adults or children with severe asthma
Macrolide Antibiotics Very low	do not use macrolide antibiotics in adults and children with severe asthma for the treatment of asthma

Anti fungal agents **Very low**	-suggest antifungal agents in adults with severe asthma and recurrent exacerbations of ABPA -clinicians do not use antifungal agents for the treatment of asthma in adults and children with severe asthma without ABPA irrespective of sensitisation to fungi (i.e. positive skin prick test or fungus-specific IgE in serum)