ATOPIC ASTHMA

Assoc. Proff. Vanya Tsvetkova PhD

History

The term “asthma” is derived from the Greek *aazein*, which means to pant

The term “asthma” has been in use for millennia, but the description of the condition that now bears that name has been in place since the writings of Aretæus the Cappadocian about 2000 years ago

Figure 1: Aretæus of Cappadocia. Illustration depicting “Aretæus of Cappadocia,” modified after a lithograph from Johannes Sambucus (1531-1584), Icones Veterum aliquot ac Recentium Medicorum Philosophorumque (Images of Some Ancient and Recent Physicians and Philosophers), 1901.

Asthma has been recognized for more than 3000 years but it is only in the last three to four decades that it has become a serious public health concern

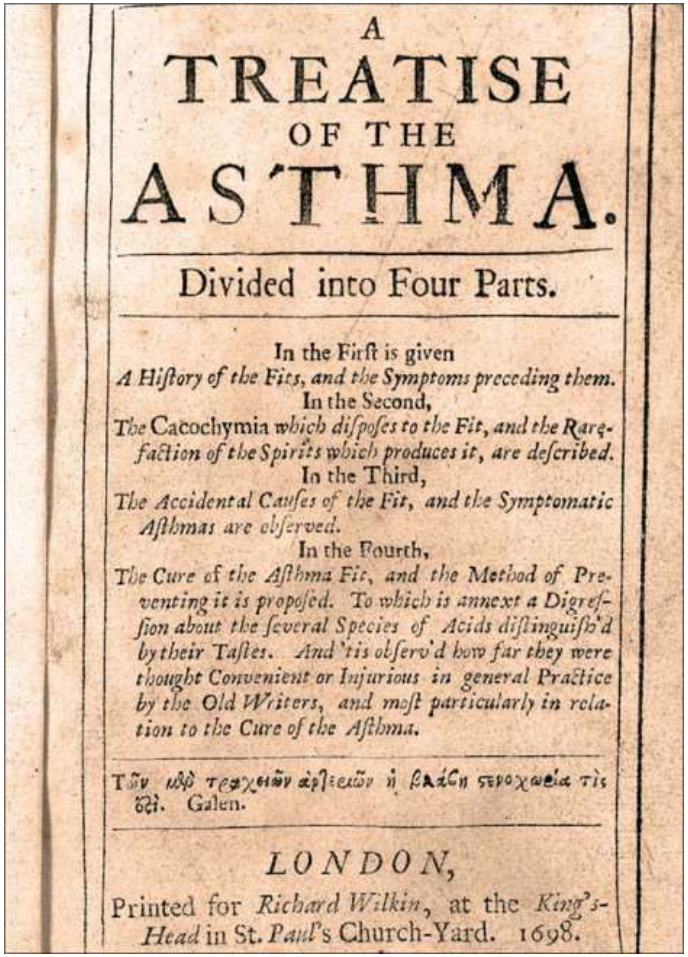
Epidemic of asthma deaths in 1977, affecting New Zealand, more than any other country, that stimulated a great deal of research which continues to this day

Global atlas of asthma

, 2013

In 1698, the English physician John Floyer (1649–1734) published the first book in English on the symptoms, causes, and treatment of asthma

Showed his own experiences of asthma



A
TREATISE
OF THE
ASTHMA.

Divided into Four Parts.

In the First is given
A History of the Fits, and the Symptoms preceding them.
In the Second,
The Cacochymia *which disposes to the Fit, and the Rarefaction of the Spirits which produces it, are described.*
In the Third,
The Accidental Causes of the Fit, and the Symptomatic Asthmas are observed.
In the Fourth,
The Cure of the Asthma Fit, and the Method of Preventing it is proposed. To which is annext a Digression about the several Species of Acids distinguish'd by their Tastes. And 'tis observ'd how far they were thought Convenient or Injurious in general Practice by the Old Writers, and most particularly in relation to the Cure of the Asthma.

Τῶν μὲν τεχνικῶν ἀρετῶν ἡ βελτίστη περὶ χωλὰ τὶς ἕδρα. Galen.

LONDON,
Printed for *Richard Wilkin*, at the *King's-Head* in St. *Paul's* Church-Yard. 1698.

DEFFINITION

Chronic inflammatory disorder of the airways

Usually associated with atopy

Bronchial hyper responsiveness in response to different stimuli

IgE mediated disease

Th2 immune response

Burden of asthma

- Asthma is one of the most common chronic diseases worldwide with an estimated 300 million affected individuals
- Prevalence is increasing in many countries, especially in children
- Asthma is a major cause of school and work absence
- Health care expenditure on asthma is very high
  - Developed economies might expect to spend 1–2 percent of total health care expenditures on asthma.
  - Developing economies likely to face increased demand due to increasing prevalence of asthma
  - Poorly controlled asthma is expensive
  - However, investment in prevention medication is likely to yield cost savings in emergency care

Epidemiology

300 million worldwide and patients of:
Childhood
Adolescence
Adulthood

More than 5 percent of each study population

Global atlas of asthma, 2013

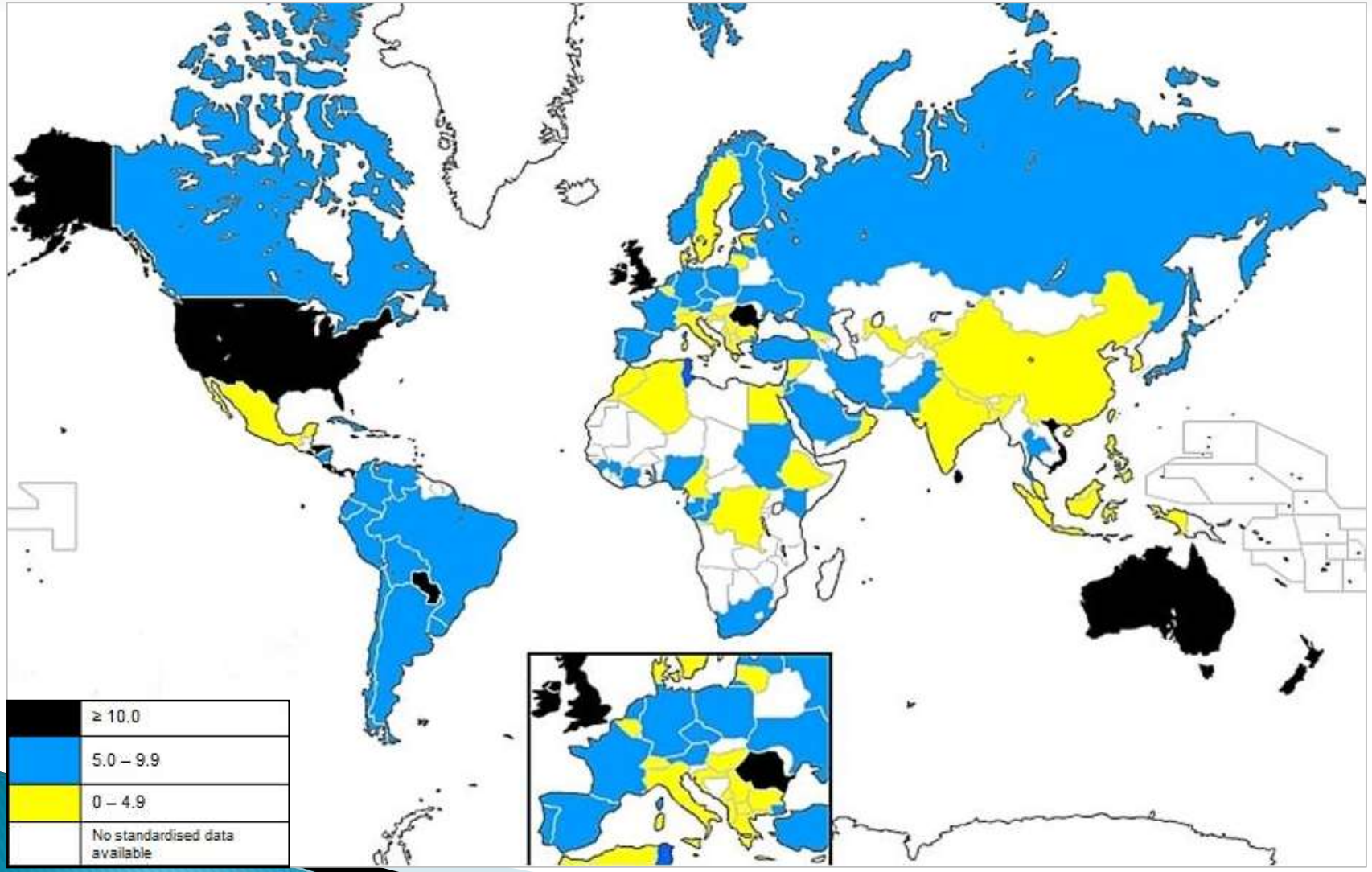
Prevalence

4-6% of the general population

10-15% in children

An estimated 25.9 million people, including almost 7.1 million children, have asthma in USA

Prevalence of asthma in children aged 13-14 years



GINA 2017 Appendix Box A1-1; figure provided by R Beasley

Etiology

Intrinsic factors

Genetic
- Atopy predisposition genes
- Bronchial hyperreactivity predisposition genes

Obesity
Gender

Extrinsic factors

Allergens
indoor – house dust mites, pets, cockroaches, fungal allergens, pollens

Drugs
Infections
Exercise
Cold air
Emotional stress
Indusrtial pollutants
Tobacco smoke

Pathogenesis

Highly complex

Inflammatory cells

Over 100 inflammatory mediators

Bronchoconstriction

Plasma exudation

Mucus hypersecretion

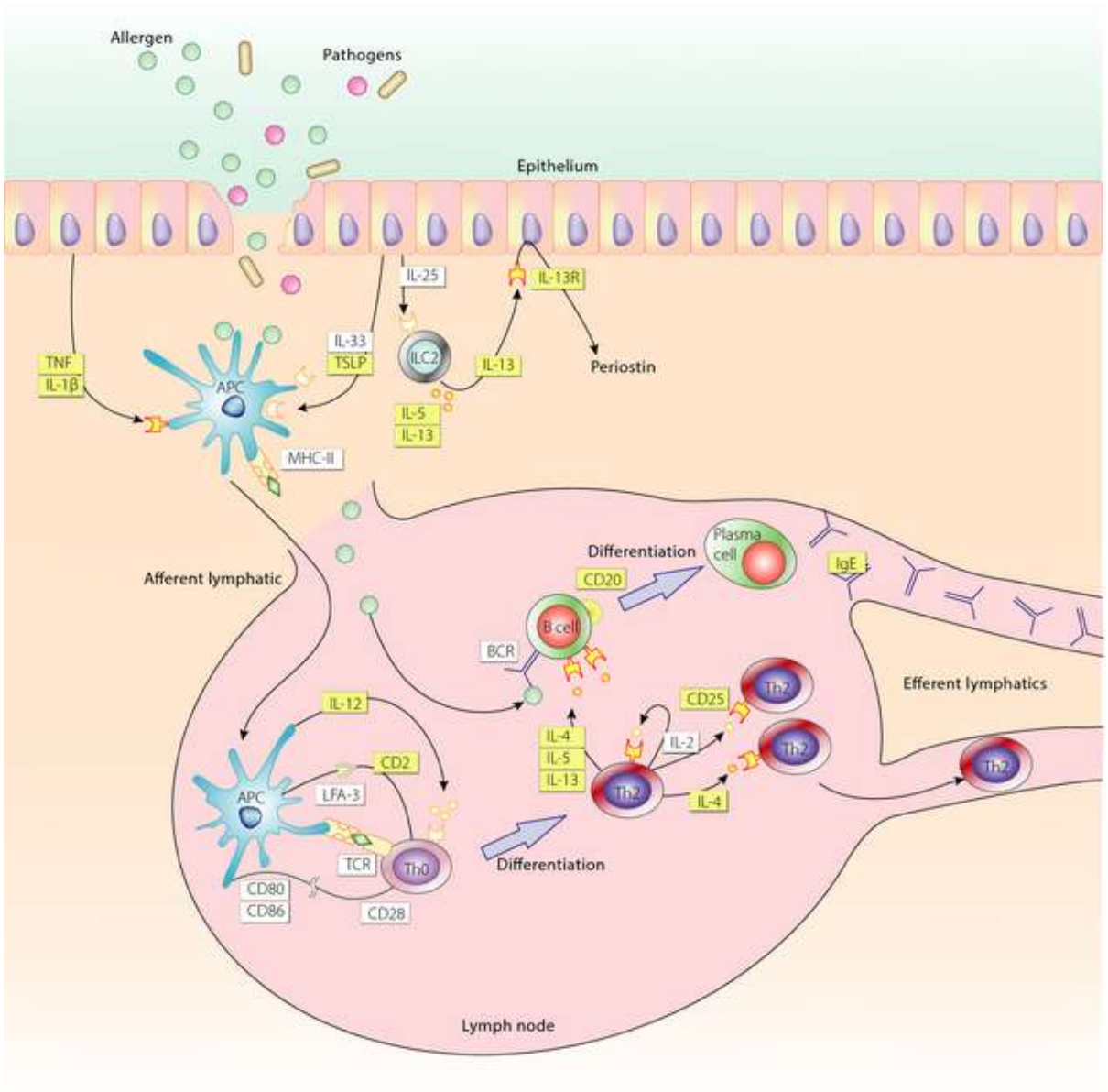
Sensory nerve activation

Inflammation and airway hyperresponsiveness

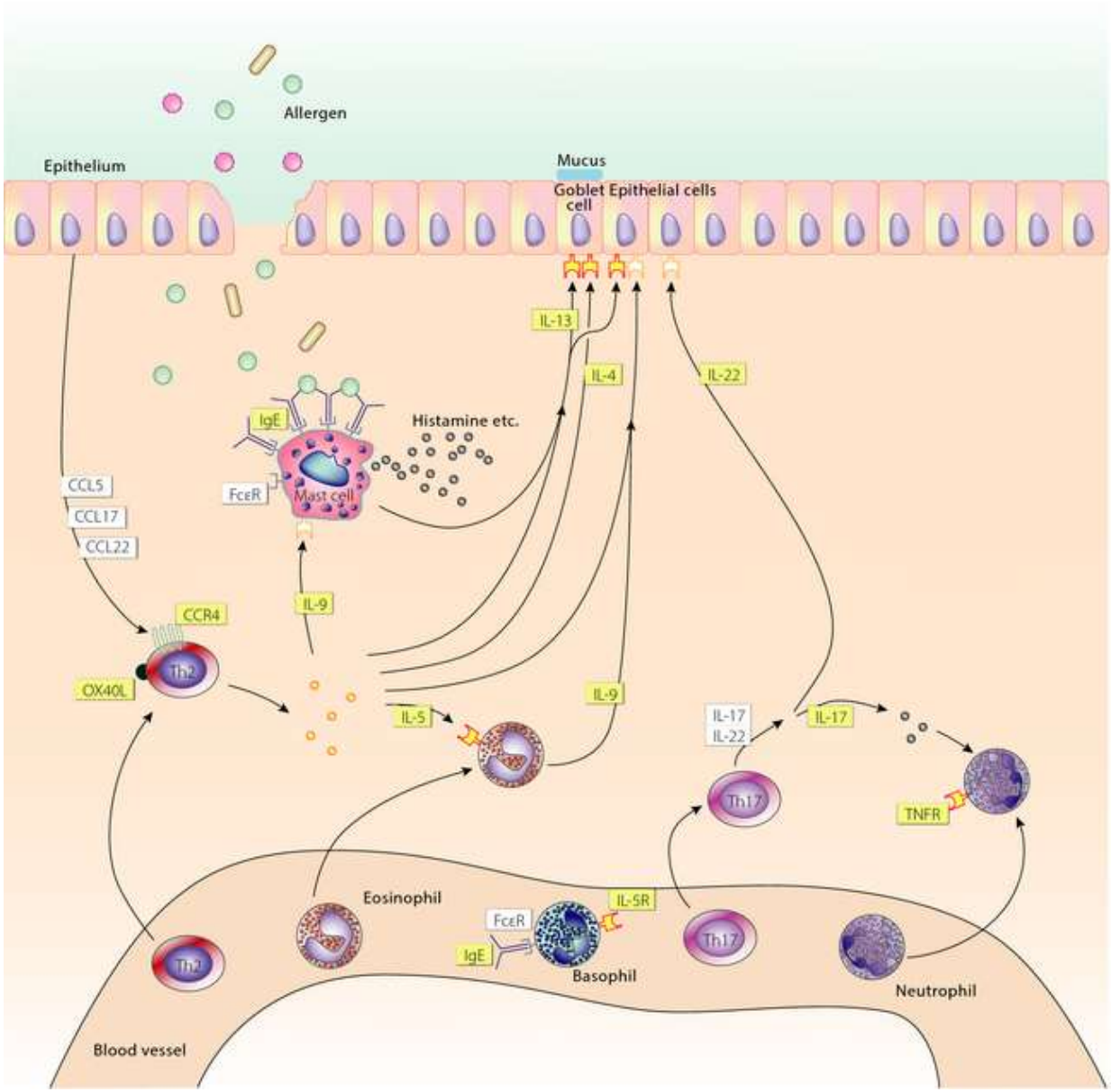
Inflammatory cells: mast cells, macrophages, dendritic cells, eosinophils, neutrophils, T-lymphocytes, B-lymphocytes, basophils, platelets, structural cells

Inflammatory mediators: lipid mediators, cytokines, chemokines

Transcription factors: NF-kB



Allergy
Volume 70, Issue 7, pages 727-754, 2015 DOI: 10.1111/all.12616
http://onlinelibrary.wiley.com/doi/10.1111/all.12616/full#all12616-fig-0001



Allergy
Volume 70, Issue 7, pages 727-754, 2015 DOI: 10.1111/all.12616
http://onlinelibrary.wiley.com/doi/10.1111/all.12616/full#all12616-fig-0002

Pathophysiology

Inflammation of the bronchi

Four types of Cells :
dendritic cells and macrophages
T-helper lymphocytes
mast cells
eosinophils

Bronchial hyperreactivity

Classification

Allergic or Atopic- about 50% prevalence

Related to children and adults to 35-40 years

Nonatopic -10-20% prevalence, related to adults over 45 years

Exercise-induced

Aspirin and NSAID-induced

Viral-induced

Idiopathic

Symptoms

Asthma attack – sudden onset of shortness of breath

Dyspnea of less severity between asthma attack episodes

Dyscomfort

Wheezing

Anxiety and panic

Asthma GINA Classification

Intermitent

Mild persistent

Moderate persistent

Severe persistent

Asthma GINA Classification

Burden	Incidence of symptoms	Nighttime symptoms	FEV1%	FEV1 variability	B2 agonist use
Intermittent	≤ 2 days a week	≤ 2 days a month	≥ 80%	< 20%	≤ 2 days a week
Mild Persistent	≤ 2 daily	3-4 monthly	≥ 80%	20-30%	> 2 daily
Moderate Persistent	daily	> 1 weekly	60-80%	> 30%	daily
Severe Persistent	throughout the day	frequent -6-7 weekly	< 60%	> 30%	several times a day

Clinical “Extent”

Periods of exacerbations and remission

Asthma Attack

Severe asthma attack

Status asthmatics

Asthma Attack

Pathophysiology	*Symptoms*
bronchospasm	difficulty breathing
Inflammation	wheezing
mucus production	coughing, dyspnea

Severe Asthma Attack

The symptoms of a severe asthma attack may include:
Persistent shortness of breath

The inability to speak in full sentences

Breathlessness even while lying down

Bluish tint to lips

Severe Asthma Attack

Agitation, confusion, or an inability to concentrate

Hunched shoulders and strained abdominal and neck muscles

A need to sit or stand up to breathe more easily

Diagnosis

Medical History

Recurrent episodes of dyspnea

Chest tightness

Wheezing

Coughing

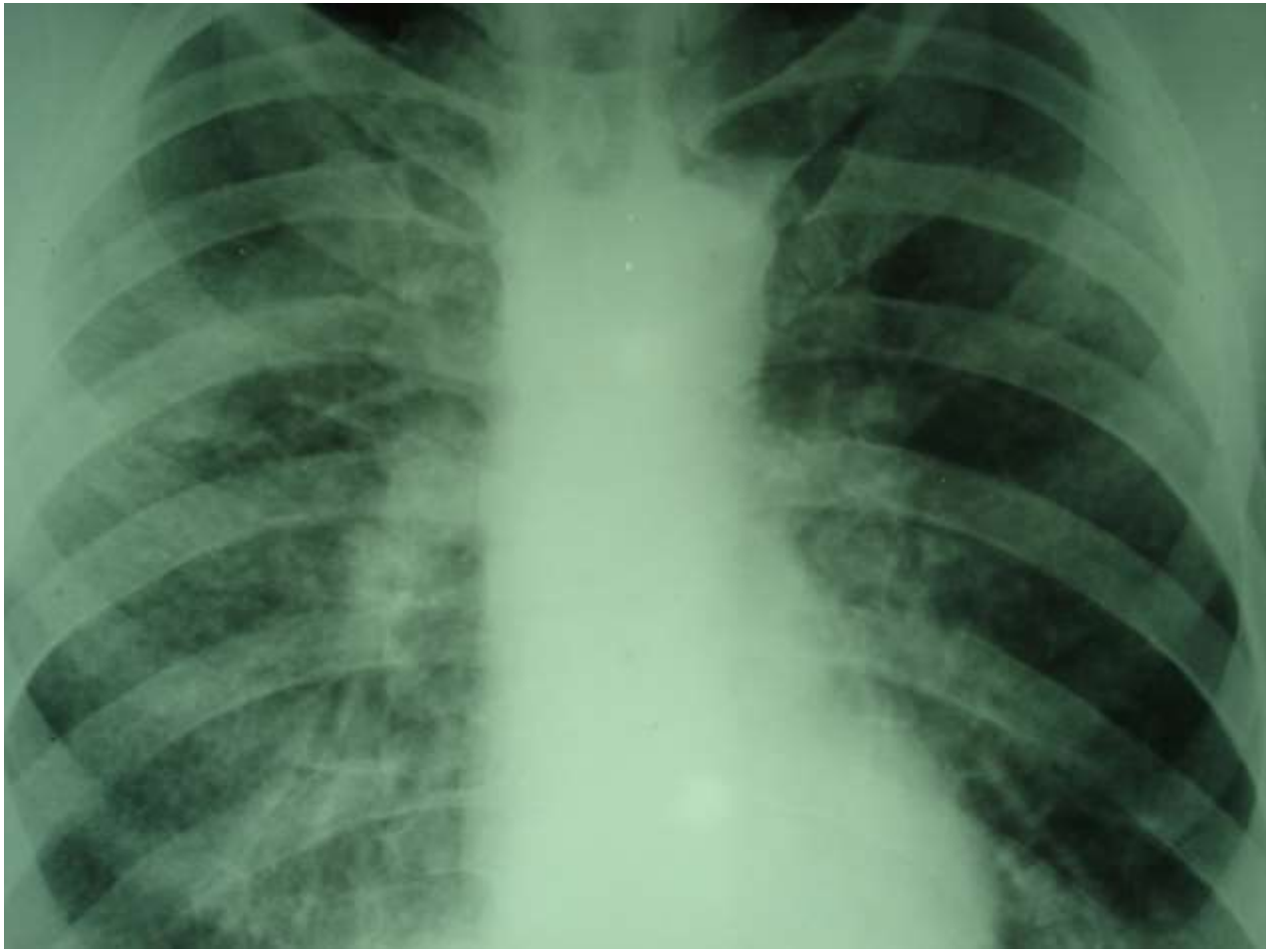
Physical examination

Hyperexpansion of the thorax

Use of accessory muscles

Sounds of wheezing during normal breathing

Prolonged phase of forced exhalation



Diagnosis

Recurrent symptoms

Increased Airway reactivity upon exposure to stimuli

Reversible airway obstruction on pulmonary function testing or response to challenge with methacholine

Diagnosis

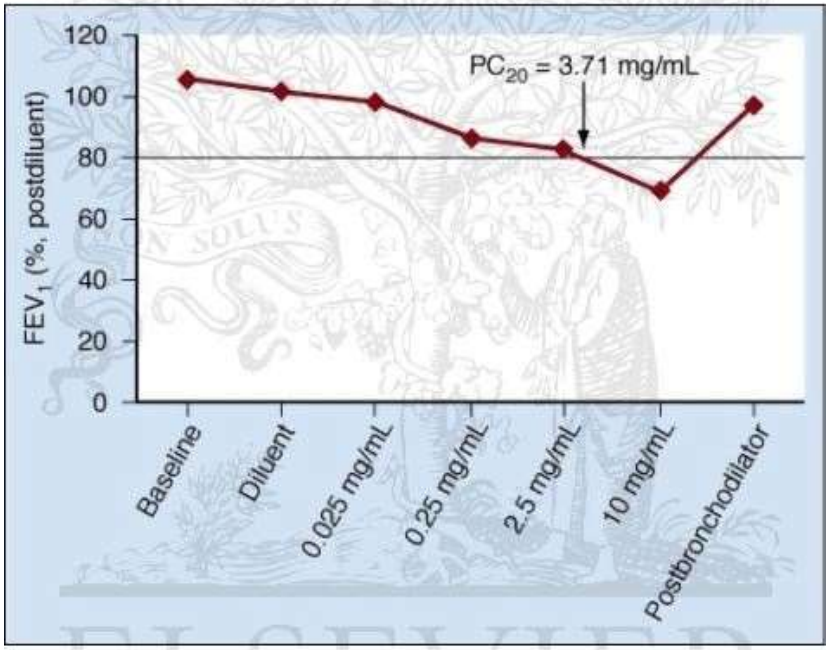
Pulmonary function testing

Measurement of nonspecific bronchial hyperresponsiveness

Chest x-ray

Daily monitoring of Peak expiratory flow (PEF)

Methacholine test



ZONES OF ASTHMA

The Green zone – total asthma control
PEF 80%–100%

The Yellow zone – warning, loss of control
PEF 50%–80%

The Red zone – emergency
PEF <50%

Lab Tests

Allergy testing

Evaluation of daily variations

Lab tests:

Arterial blood gas (ABG)

Total IgE (elevated values in allergic asthma)

Specific IgE

Blood eosinophils

Eosinophils in sputum

Nitric oxid (NO) in exhaled air

arterial blood gas analysis

pH	PaCO2	HCO3-	PaO2
↑	↓	↓ (weak)	↓

Alveolar hyperventilation with hypoxemia

arterial blood gas analysis

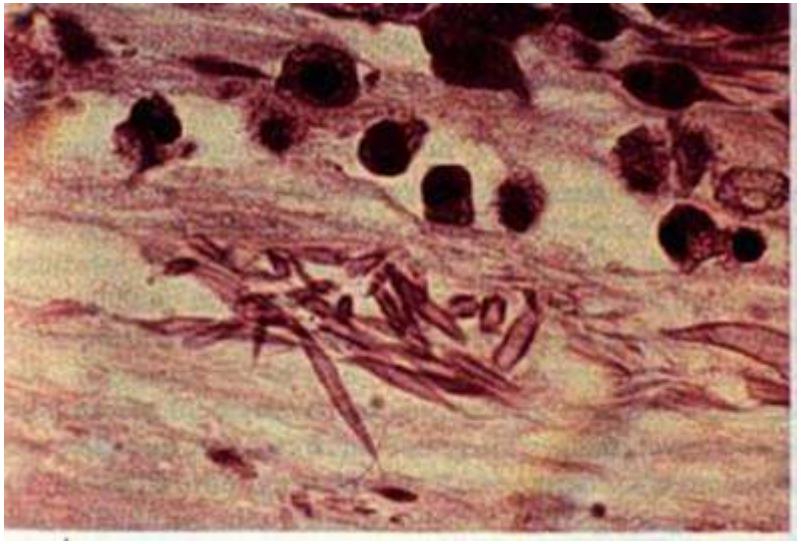
pH	PaCO2	HCO3-	PaO2
↓	↓	↓ (substentially)	↓

Acute ventilatory failure with hypoxemia

Sputum

Eosinophils

Charcot-Leyden crystals



Differential Diagnosis

- Chronic obstructive pulmonary disease
- Nonatopic bronchial asthma
- Heart failure
- Foreign body aspiration
- Pulmonary embolism
- Gastroesophageal reflux disease
- Churg-Strauss syndrome
- Cystic fibrosis

Treatment

Avoid exposure to triggers:

Pat dander

House dust mites

Pollens

Molds

Cockroach

Treatment

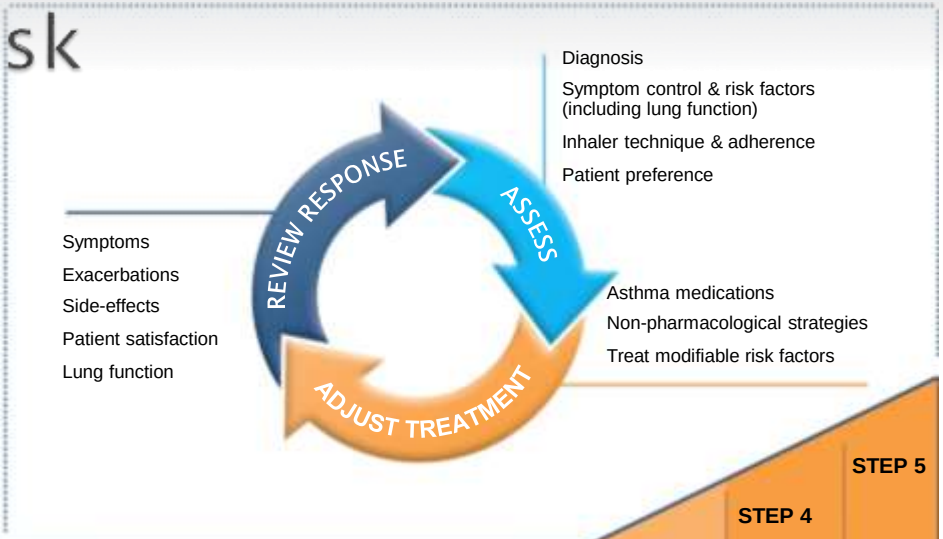
Targets:

Allergic inflammation

Bronchial obstruction

Mucus hypersecretion

Stepwise approach to control asthma symptoms and reduce risk



	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
PREFERRED CONTROLLER CHOICE		Low dose ICS	Low dose ICS/LABA**	Med/high ICS/LABA	Refer for add-on treatment e.g. tiotropium,*† anti-IgE, anti-IL5*
Other controller options	*Consider low dose ICS*	*Leukotriene receptor antagonists (LTRA) Low dose theophylline**	*Med/high dose ICS Low dose ICS+LTRA (or + theoph*)*	*Add tiotropium*† High dose ICS + LTRA (or + theoph*)*	*Add low dose OCS*
RELIEVER	As-needed short-acting beta$_2$-agonist (SABA)		As-needed SABA or low dose ICS/formoterol#		

REMEMBER TO...

- Provide guided self-management education (self-monitoring + written action plan + regular review)
- Treat modifiable risk factors and comorbidities, e.g. smoking, obesity, anxiety
- Advise about non-pharmacological therapies and strategies, e.g. physical activity, weight loss, avoidance of sensitizers where appropriate
- Consider stepping up if … uncontrolled symptoms, exacerbations or risks, but check diagnosis, inhaler technique and adherence first
- Consider adding SLIT in adult HDM-sensitive patients with allergic rhinitis who have exacerbations despite ICS treatment, provided FEV1 is >70% predicted
- Consider stepping down if … symptoms controlled for 3 months + low risk for exacerbations. Ceasing ICS is not advised.

SLIT added as an option

Treatment

Long-term controller medications:

Inhaled corticosteroids

Long acting beta agonists

Combination inhalers

Leukotriene modifiers

Methylxanthines

Inhaled corticosteroids

Generic Name	***Brand Name***
beclomethasone	Becotide
budesonide	Pulmicort
fluticasone	Flixotide

Long acting beta agonists

LABAs

Albuterol Sulfate

Formoterol Fumarate

Salmeterol Xinafoate

The FDA has recommended LABAs be used ONLY in conjunction with inhaled steroids in asthma

Combination inhalers

Generic Name	***Brand Name***
salmeterol/fluticasone propionate	Seretide
formoterol/budesonide	Symbicort
formoterol/fluticasone propionate	Flutiform
vilanterol/fluticasone furoate	Relvar
formoterol/beclomethasone	Foster

Leukotriene modifiers

Forms

Singulair

10 mg tabl.

5 mg Chewable tabl.

4 mg Chewable tabl.

4 mg Oral Granule

Use

To prevent and treat asthma

To prevent exercise-induced asthma

Relief of symptoms of allergic rhinitis age 6 months of age and older

Leukotriene modifiers

Generic Name	*Brand Name*
montelukast	Singulair
zafirlukast	Accolate

Methylxanthines

Methylxanthines act as bronchodilators by relaxing bronchial smooth muscle and helps the constricted airways to dilate

Methylxanthines are bronchodilators used in the treatment of asthma and chronic obstructive pulmonary disease (COPD)

Generic Name	***Brand Name***
theophylline	Theo-24
theophylline	Uniphyl
theophylline	Quibron-T
theophylline	Theo-Dur
dyphylline	Dilor
aminophylline	Phyllocontin

Quick-relief (rescue) medications:

Short acting beta agonists

Ipratropium (Atrovent)

Oral and intravenous corticosteroids

Allergy medications:

Anti IgE therapy (Omalizumab)(Xolair)

Allergen specific immunotherapy

Biologics

Eosinophils targeted

mepolizumab

reslizumab

Benralizumab

IL-4/IL-13 targeted

lebrikizumab

tralokinumab

dupilumab

pitrakinra

Allergic asthma

Omalizumab - ↓ IgE ↓ expression of FcεR1on Ba, Mcs

Eosinophils targeted

Benralizumab

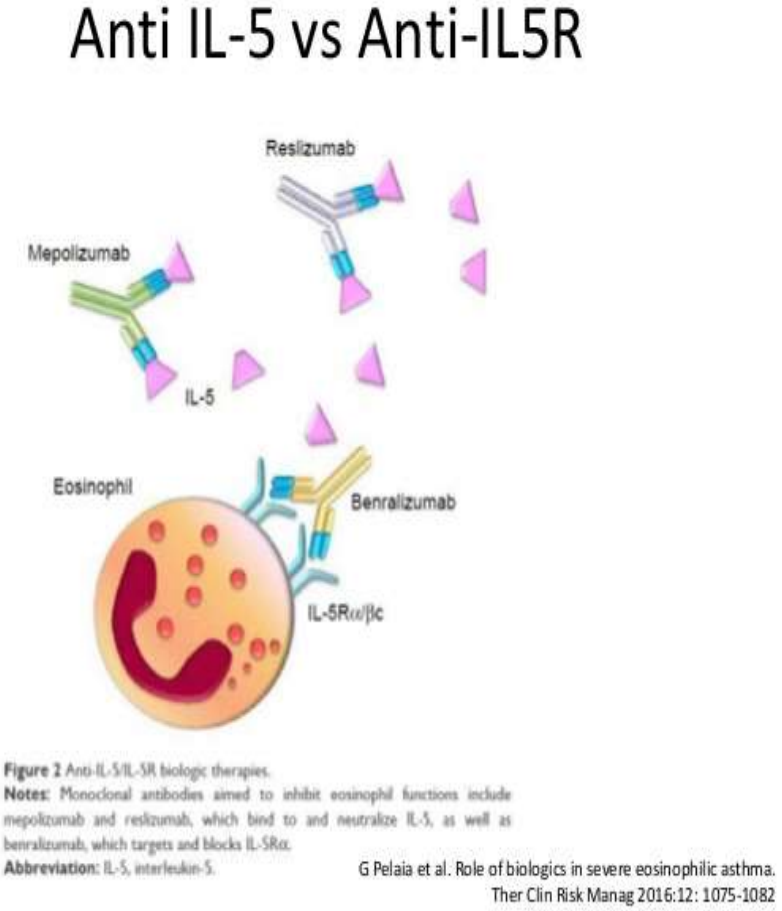
interleukin-5 receptor α-directed cytolytic monoclon antibody that directly depletes eosinophils

Mepolizumab

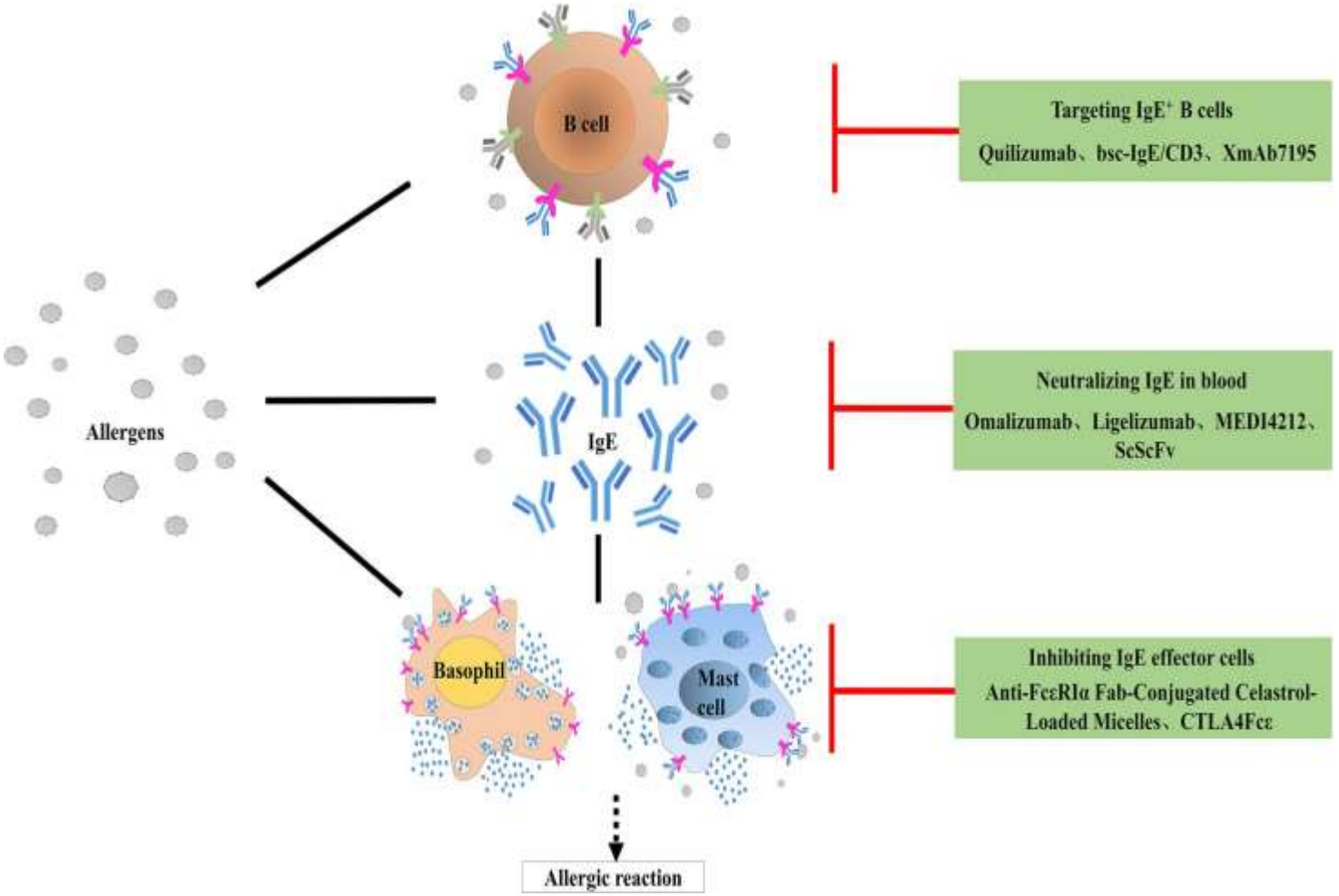
targets human IL-5;prevent interaction with the α-chai of the IL-5 receptor

Reslizumab

disrupts eosinophil maturation and promotes programmed cell death

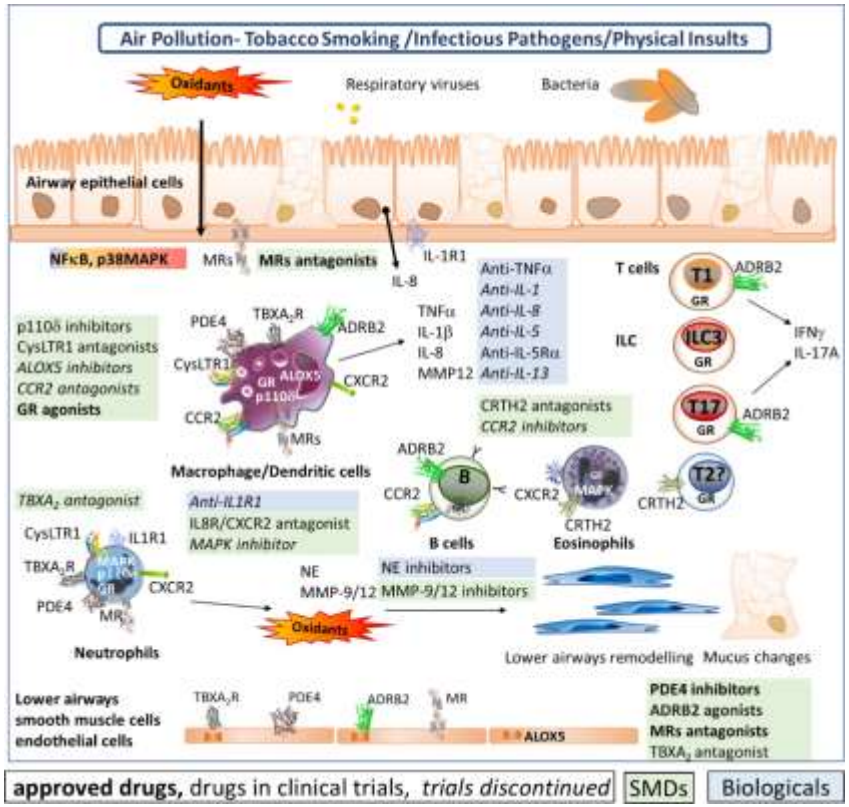


Anti IgE



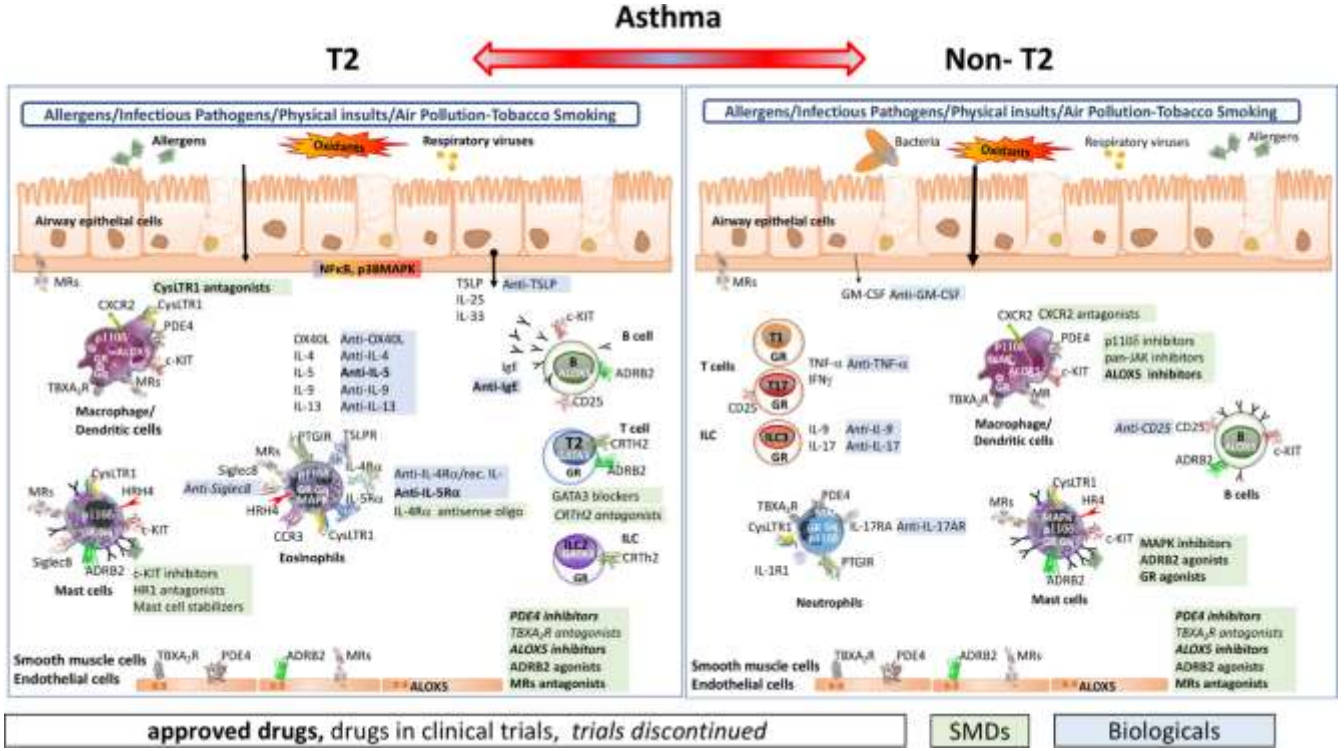
Hu et al. Clin Transl Allergy (2018) 8:27

Comparing biologicals and small molecule drug therapies for chronic respiratory diseases: An EAACI Taskforce on Immunopharmacology position paper



Allergy, Volume: 74, Issue: 3, Pages: 432-448, First published: 24 October 2018, DOI: (10.1111/all.13642)

Comparing biologicals and small molecule drug therapies for chronic respiratory diseases: An EAACI Taskforce on Immunopharmacology position paper



Allergy, Volume: 74, Issue: 3, Pages: 432-448, First published: 24 October 2018, DOI: (10.1111/all.13642)

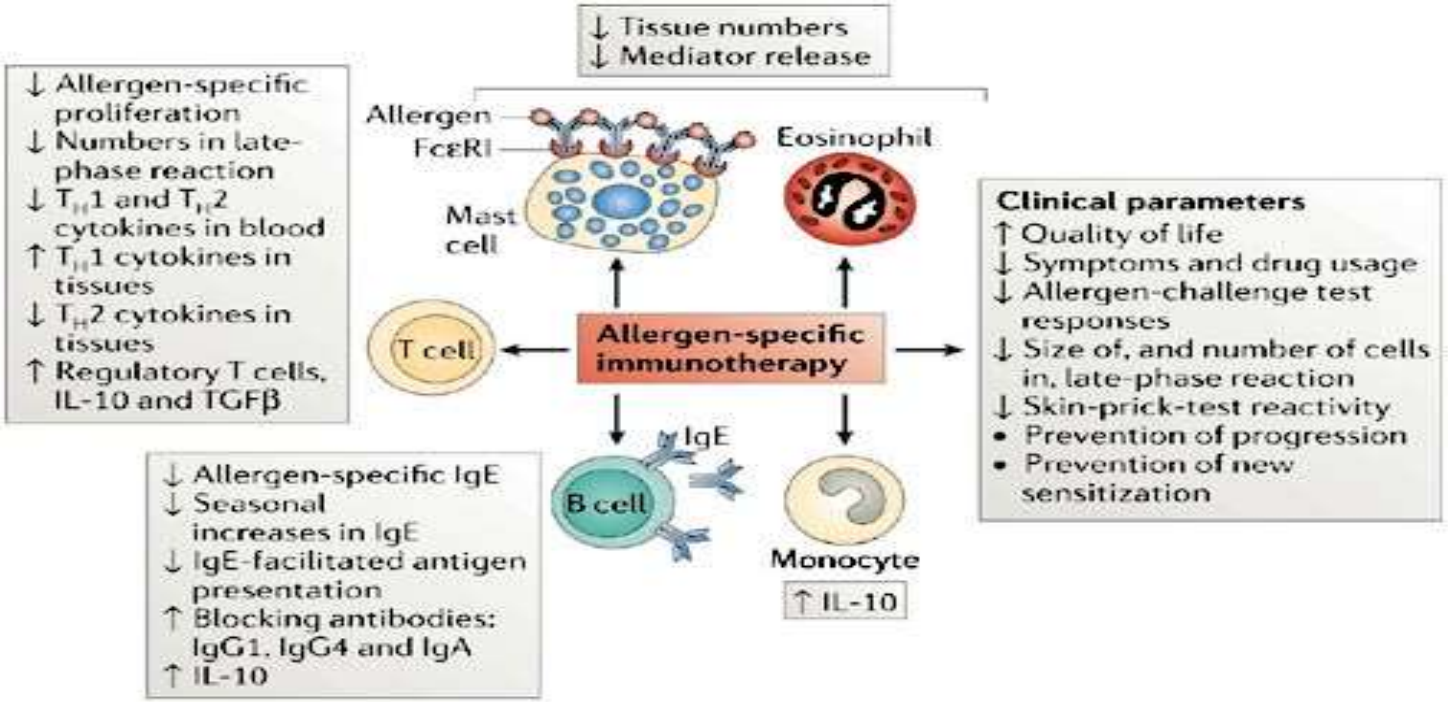
Key changes in GINA 2017 – role of SLIT

REMEMBER TO...

- Provide guided self-management education
- Treat modifiable risk factors and comorbidities
- Advise about non-pharmacological therapies and strategies
- Consider stepping up if … uncontrolled symptoms, exacerbations or risks, but check diagnosis, inhaler technique and adherence first
- Consider adding SLIT in adult HDM-sensitive patients with allergic rhinitis who have exacerbations despite ICS treatment, provided FEV_1 is 70% predicted
- Consider stepping down if … symptoms controlled for 3 months + low risk for exacerbations. Ceasing ICS is not advised.

SLIT: sublingual immunotherapy

Allergen Specific Immunotherapy



Clinical Case

- A 57 year old female hospitalized at endocrinology clinic for diabetes and asthma as accompanying disease
- Non-smoker
- Age at onset of respiratory symptoms – before six years
- Hospitalizations for various diseases: Thyroiditis Hashimoto, Myocardial infarction, Hypertension, Bronchial asthma

Treatment

- Foster inhaler (100 mcg beclometasone dipropionate/ 6 mcg of formoterol fumarate dihydrate) 2x 3 inh for 3 years regularly
- Poorly controlled on maximum doses of inhaled CS
- Poor quality of life

Therapeutic indications of ICS/LABA

Regular treatment of asthma where use of a combination product (inhaled corticosteroid and long-acting $beta_2$-agonist) is appropriate:

- patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled rapid-acting $beta_2$-agonist
- patients already adequately controlled on both inhaled corticosteroids and long-acting $beta_2$- agonists

Treatment approaches with ICS/LABA

A. Maintenance therapy: Foster is taken as regular maintenance treatment with a separate as needed rapid-acting bronchodilator

B. Maintenance and reliever therapy: Foster is taken as regular maintenance treatment and as needed in response to asthma symptoms.

Maintenance therapy

Patients should be advised to have their separate rapid-acting bronchodilator available for rescue use at all times

Dose recommendations for adults 18 years and above:

- One or two inhalations twice daily
- The maximum daily dose is 4 inhalations

Maintenance and reliever therapy

Patients take their daily maintenance dose and in addition as needed in response to asthma symptoms. Patients should be advised to always have Foster available for rescue use

Foster maintenance and reliever therapy should especially be considered for patients with :

- not fully controlled asthma and in need of reliever medication
- asthma exacerbations in the past requiring medical intervention
- close monitoring for dose-related adverse effects is needed in patients who frequently take high numbers of Foster as-needed inhalations

Dose recommendations for adults 18 years and above:

- The recommended maintenance dose is 1 inhalation twice daily (one inhalation in the morning and one inhalation in the evening).
- Patients should take 1 additional inhalation as needed in response to symptoms. If symptoms persist after a few minutes, an additional inhalation should be taken

The maximum daily dose is 8 inhalations

Patients requiring frequent use of rescue inhalations daily should be strongly recommended to seek medical advice. Their asthma should be reassessed and their maintenance therapy should be reconsidered

Clinical findings

Symptoms suspicious of adrenal insufficiency

- Fatigue
- Weakness
- Episodic abdominal pain

Laboratory findings

- early morning cortisol levels : **46.0** (131–642)
- evening cortisol levels : **28.0** (61–429)

Discussion

- ICS are a form of exogenous glucocorticosteroids that can suppress the endogenous production of glucocorticosteroids, a condition known as adrenal suppression
- ICS may trigger features of adrenal insufficiency with a spectrum of presentations varying from vague symptoms of fatigue to potentially life threatening acute adrenal crises

In conclusion

- Few studies have addressed the risk of adrenal insufficiency (AI) with inhaled glucocorticoids
- AI is a life-threatening disorder due to impairment of the hypothalamic-pituitary-adrenal (HPA) axis

Key changes in GINA 2017 – ICS and growth in children

Height should be checked at least yearly, as poorly-controlled asthma can affect growth *[Pedersen 2001]*, and growth velocity may be lower in the first 1-2 years of ICS treatment *[Loke, 2015].*

Consider referral if there is growth delay

- Choice of controller treatment
  - Discuss relative benefits and risks with parents or carers, including the importance of maintaining normal physical activity
  - Effects of ICS on growth velocity are not progressive or cumulative *[Kelly 2012, Loke 2015].*
  - The one study that examined long-term outcomes showed a difference of only 0.7% in adult height *[Kelly 2012, Loke 2015]*

Thank you