2nd Edition

GLOBAL ATLAS OF ASTHMA

EAACI
EUROPEAN ACADEMY OF ALLERGY AND CLINICAL IMMUNOLOGY

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April 2021

GLOBAL ATLAS OF ASTHMA

Asthma - definition, epidemiology and risk factors

Mechanisms, phenotypes and endotypes

Diseases associated with asthma

Asthma diagnosis

Major current problems in asthma

Management of asthma

Special considerations

Prevention and control of asthma

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EARLY RELEASE

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Section A

ASTHMA - DEFINITION, EPIDEMIOLOGY AND RISK FACTORS

1 WHAT IS ASTHMA

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KEY MESSAGES

- Asthma is one of the most common chronic inflammatory disorders with two clinically relevant phenotypes, allergic and intrinsic asthma
- Asthma affects patients of all ages. It is a serious challenge to public health and has significant effects on individuals` school, work and social performance
- Asthma symptoms can be treated effectively in most patients, however, at considerable costs, but not treating asthma is even more expensive
- There is no cure. Many patients remain poorly controlled despite available treatment. Today, systemic glucocorticosteroids with their detrimental side effects can be replaced in many patients with targeted, personalised allergen immunotherapy or anti-inflammatory biologicals
- Combined efforts in public health, basic and clinical research need to be upscaled to combat this highly prevalent and increasing disorder.

Epidemiologically asthma is a very common chronic condition. Its prevalence varies worldwide but more than 5% of any population investigated suffer from asthma. In some regions this percentage is even higher. Asthma affects all ages: its allergic phenotype is the most common chronic disease of childhood, adolescence and adulthood and affects patients in their most productive years. People are either personally affected or will know someone who suffers from asthma. Every physician will see patients with asthma during his/her career. Asthma imposes a large burden on individuals and is a serious challenge to public health. Its direct and indirect costs are high but the costs of not treating asthma are even higher. It has detrimental influences on school, work and social performance and productivity. In addition, it is estimated that around 10% of all asthma is caused by or occurs in the workplace. As more people reach old age it is also an important disease of the elderly. Asthma not only leads to limitations in daily life but can end fatally in some cases, especially if untreated.

Pathophysiologically asthma is an inflammatory disorder of the airways. Its characteristic biomarker is eosinophilia. The inflammation leads to widespread airflow limitation with resulting signs and symptoms such as dyspnea, discomfort, wheezing, anxiety and panic and occasionally fatal respiratory arrest. The pathogenesis of asthma is highly complex and as of today incompletely understood (Figure 1).

Based on clinical and laboratory findings different phenotypes have been suggested (Figure 2, Table 1). Whether they all represent different features or severities of a single disease or are separate diseases within the syndrome of asthma remains unclear. The majority of asthma occurs on an IgE-mediated background with sensitisations to inhaled allergens which has been termed allergic asthma. Asthma which occurs in adulthood with a non-allergic background is termed intrinsic asthma. In intrinsic asthma chronic persistent airway inflammation

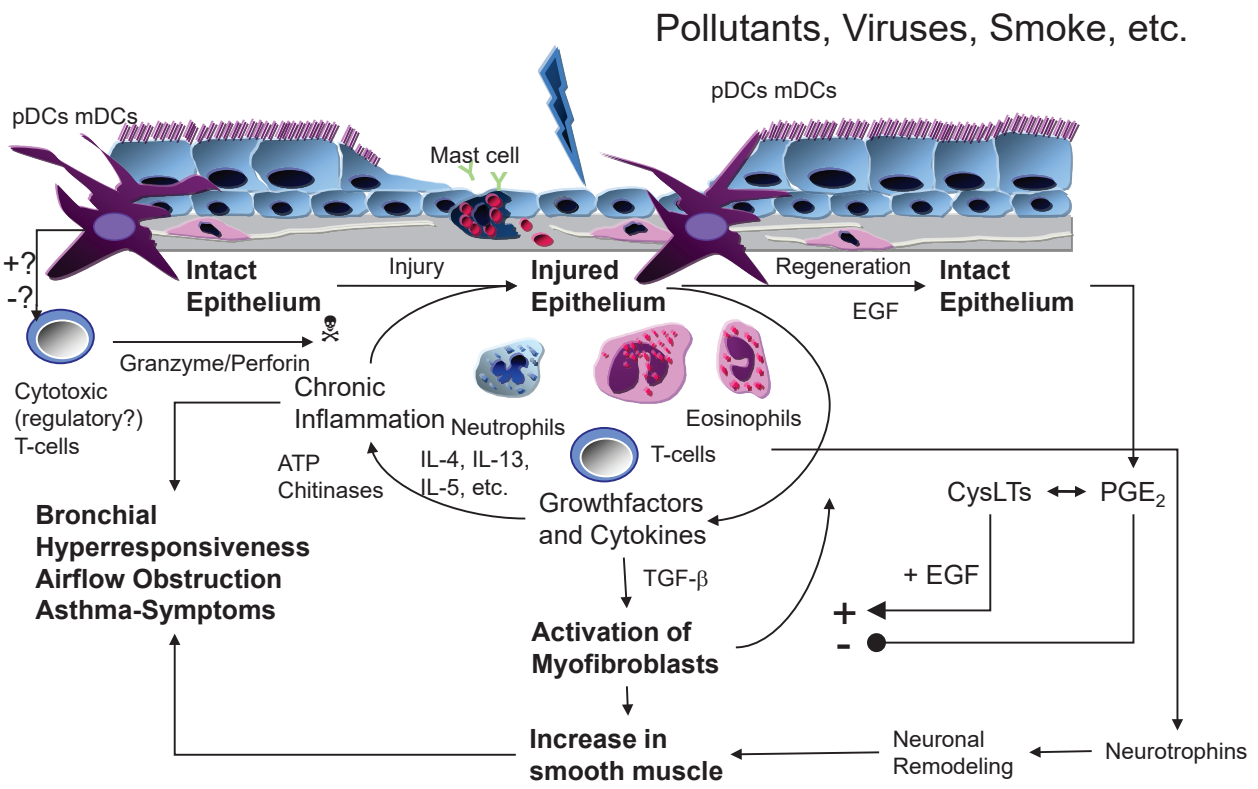

Figure 1 **Pathophysiology of asthma.**
(Adapted from Virchow JC, Pichler WJ. Allergische Atemwegserkrankungen. In: Petter HH, Pichler WJ, Müller-Ladner U, editors. Klinische Immunologie, 3rd ed. Munchen :Urban & Fischer, 2012.)

is unrelated to allergen contact and may have features of autoimmunity.

Long term chronic inflammation has been associated with airway remodeling often associated with a presumably fixed airflow limitation as a result of „scarring" of the airways.

Clinically signs and symptoms of asthma vary between individuals. Episodic shortness of breath, wheezing and the sensation that inspiration is no longer possible due to hyperinflation of the lungs are common. The pathophysiological equivalent in pulmonary function tests are a reduced FEV1 (Forced Expiratory Volume of the first second) and PEF (Peak Expiratory Flow). A circadian peak of symptoms in the early morning hours is typical. Bronchial hyperresponsiveness to non-specific airway irritants such as smoke, cold air, odors, etc. is characteristic and can be tested with bronchoprovocation tests with histamine or methacholine. Levels of circulating total and specific IgE are increased in allergic asthma. Eosinophilia can be found in the blood, the airway mucosa and the bronchoalveolar lavage fluid. In allergic asthma, this eosinophilia is variable and increases with contact to allergen while in intrinsic asthma eosinophilia is persistent. The fraction of NO in exhaled breath (FENO) can be elevated in asthma. Many patients experience worsening airflow obstruction and symptoms following exercise (exercise induced bronchoconstriction - EIB) or inhalation of allergens in the case of allergic asthma. Some suffer from severe attacks upon ingestion of non-steroidal anti-inflammatory drugs (Aspirin exacerbated respiratory disease - AERD). None of these signs or symptoms, however, is characteristic. Asthma, therefore, remains a clinical diagnosis.

Therapeutically there is no cure. In allergic rhinitis allergen immunotherapy (AIT) might prevent the onset of asthma, while in allergic asthma it can improve asthma control. Most patients profit from inhaled corticosteroids (ICS) and long-acting beta-2-agonists (LABAs) which can be supplemented by long-acting muscarinic antago-

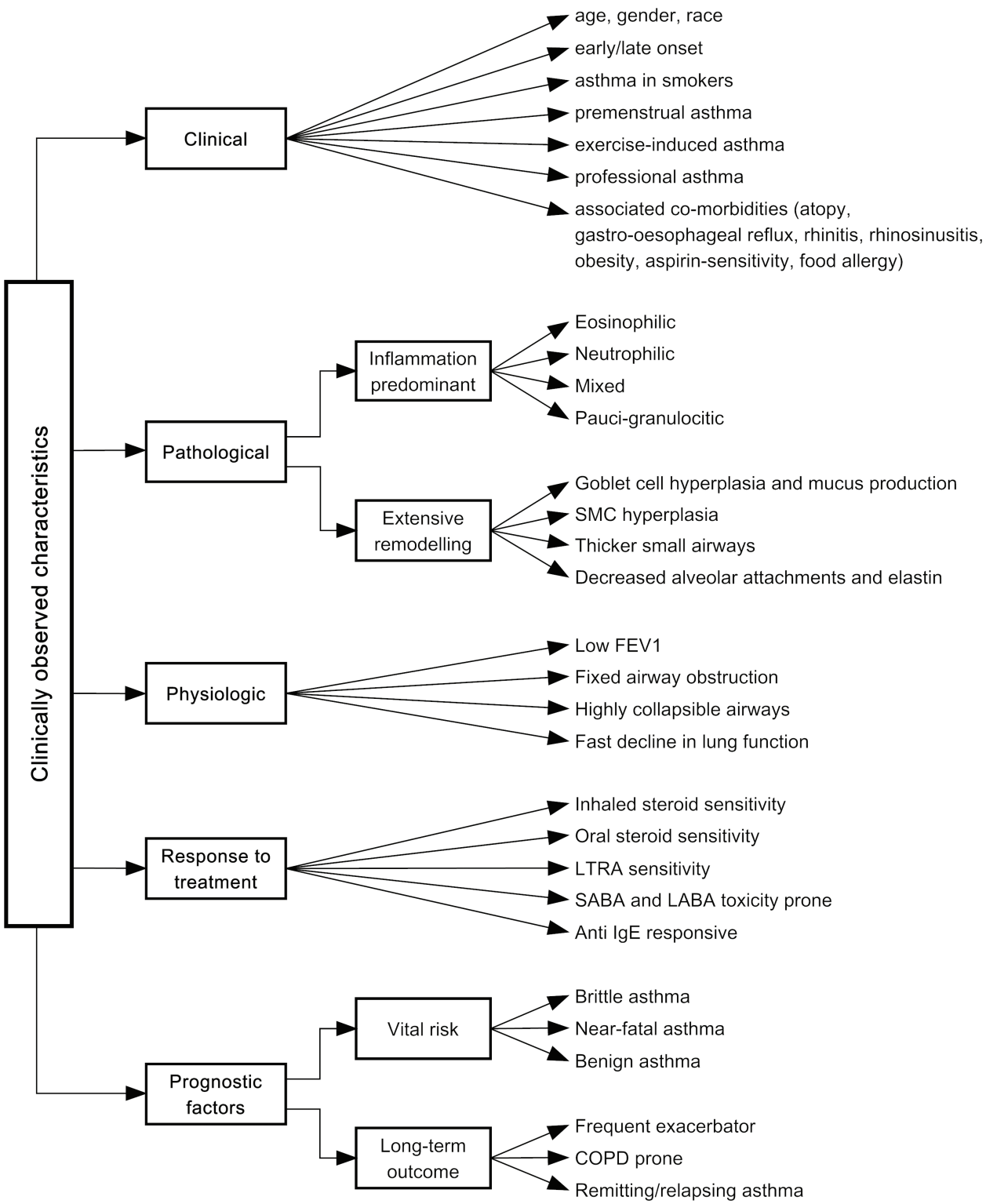

Figure 2 **Clinically observed characteristics and asthma phenotypes.**
(Reproduced from Agache I, Akdis C, Jutel M, et al. Untangling asthma phenotypes and endotypes. Allergy 2012; 67:835-846; with permission from Wiley-Blackwell.)

TABLE 1

Comparison between allergic and intrinsic asthma*		
Clinical features	**Allergic Asthma**	**Intrinsic Asthma**
Onset	Before age 30	After age 40
Family history	+	-
Other atopic manifestations	+	-
Seasonal symptoms	Depending on sensitisation	-
Perennial symptoms	Depending on sensitisation	-
Asthma attacks	+	-
Skin-Prick-Test	+	-
Total IgE	Elevated	Normal
Specific IgE	+	-
Eosinophilia	+ (reactive)	++ (persistent)
Sputum-eosinophilia	+ (reactive)	++ (persistent)
Chronic sinusitis	-	++
Nasal polyps	-	+
Aspirin-induced asthma	Rarely	+
Response to therapy	+	-
Steroid free intervals	+	-
Steroid requirement	-	+

** Adapted from Virchow JC Jr. Intrinsic Asthma, In: Busse WW, Holgate ST, editors. Asthma & Rhinitis, Oxford: Blackwell Science Ltd. 2000*

nist (LAMAs) in more severe cases. Leukotriene antagonists might be useful in young patients with allergic asthma and milder disease. In recent years, monoclonal antibodies directed against IgE, interleukin (IL)-5 and its receptor and antibodies against the IL-4Rα subunit have revolutionised the treatment of severe or therapy refractory cases and have replaced the need to use side effect prone, systemic glucocorticosteroids.

Outlook: Asthma is a common and serious chronic inflammatory disorder of the lungs, which might become an even greater burden in the future due to increasing allergen exposures (climate change), growing urbanisation and increased air pollution. In contrast to this increasing prevalence and burden research in asthma is dramatically underfunded. Recent advances in anti-inflammatory therapy for severe asthma have reduced the need for systemic corticosteroids in the more severely affected. Despite these combined efforts in public health, basic and clinical research need to be upscaled to fight this disorder.

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2 ASTHMA: AN HISTORICAL PERSPECTIVE

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KEY MESSAGES

- 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
- Both attacks and chronic dyspnea are characteristic of asthma
- Treatments of asthma based on bronchial smooth muscle relaxation have been in use for over 200 years, with sympathomimetic reliever treatment introduced in the early 1900s
- The use of glucocorticoids to treat asthma was introduced in the mid-20th century; inhaled corticosteroid treatment was started in the late 1960s
- Bioloigically targeted asthma treatments were introduced in the 1990s
  - Leukotriene modifiers in 1995
  - Anti-IgE in 2003
  - TH2 targeting monoclonal antibodies beginning in 2015

THE TERM "ASTHMA"

The term "asthma" is derived from the Greek aazein, which means to pant. Before the writings of Aretaeus in the 2nd century and well into the 20th century, many physicians and lay people alike used the term "asthma" to refer to any condition characterized by acute nonphysiologic shortness of breath. For example, acute congestive heart failure would often be termed "cardiac asthma." Aretaeus's and, much later, Floyer's (1698) descriptions of asthma largely match those in use today (Figure 1).

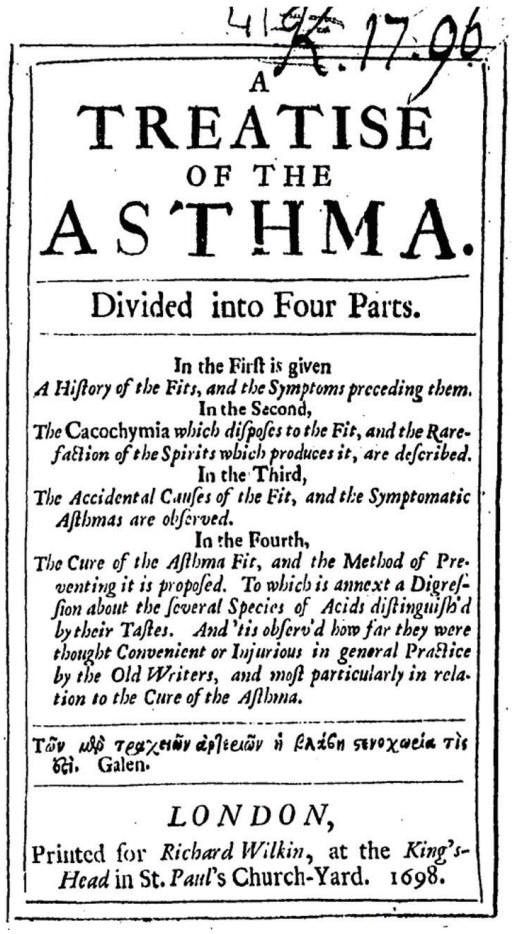
CLINICAL DESCRIPTIONS

There are two key components of the clinical description that have survived two millennia. The first is the acute asthmatic episode, also known as an asthma attack or fit. This is the sudden onset (as quickly as seconds but more usually minutes to hours) of shortness of breath often accompanied by wheezing audible to the patient and those close to him or her; this resolves spontaneously or as a result of treatment. The second is the presence of dyspnea of much less severity between these episodes. Exercise and allergen exposure have been recognized as causes of asthma attacks over this entire recorded history.

The physicians examining patients with asthma were able to appreciate wheezing long before Laennec's treatise on diseases of the chest was published in 1819. With Laennec's work, it became clear that there were many other conditions characterized by wheezing other than asthma.

ASTHMA TREATMENTS

Anticholinergic asthma treatment was known to Floyer. At that time, patients were instructed to inhale smoke from the burning of certain plants containing belladonna alkaloids. The three most commonly used plants were known as the "sinister sisters" because, if taken in excess amounts, they could have severe side effects including death. These were hyoscyamus, stramonium, and belladonna (Figure 2). After a century of disuse, long-acting muscarinic antagonists are being re-introduced into asthma treatment.



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 τραχειῶν ἀρτηριῶν ἡ βλάβη στενοχωρία τὶς ἐστί. Galen.

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

Figure 1 **Title page from Floyer's classic monograph on asthma published in 1696.** This contains a clear description of the condition we now recognize as asthma.

Figure 2 **"Sinister sisters" plants.** Smoking the leaves from these plants has been used as an asthma remedy for decades. A - Hyocyamus, image from http://uic.edu/pharmacy/MedPlTranscriptome/sp8.html; B - Stramonium, image from http://www.missouriplants.com/Blueralt/Datura_stramonium_page.html; C - Belladona, image from http://www.fs.fed.us/wildflowers/ethnobotany/mindandspirit/belladonna.shtml.

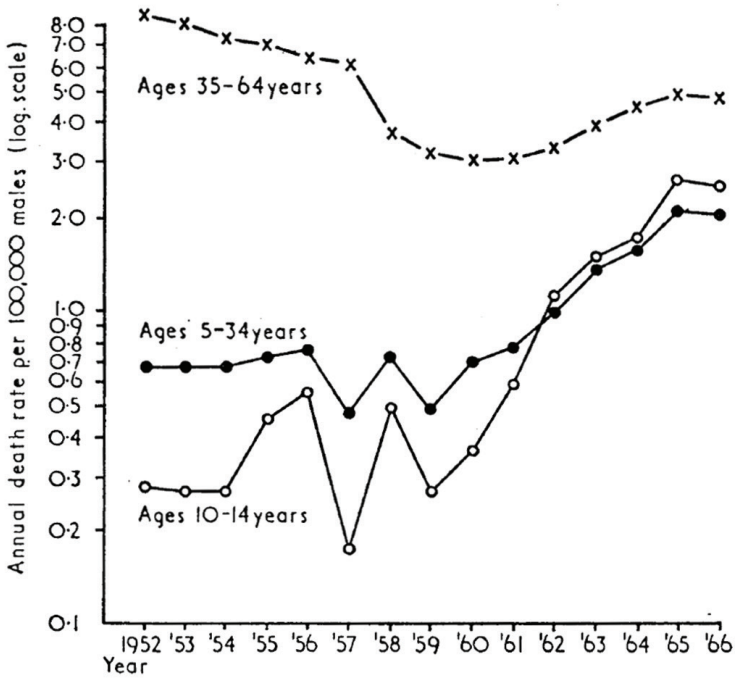


Figure 3 **Asthma deaths in Britain from 1952 to 1966 showing the impact of high potency isoproterenol inhalers, introduced for over the counter sales in the late 1950s and subsequently limited to prescription use in the late 1960s.**
(Reproduced from Br Med J, Speizer FE, Doll R, Heaf P, 1, 335-339, Copyright 1968 with permission from BMJ Publishing Group Ltd.)

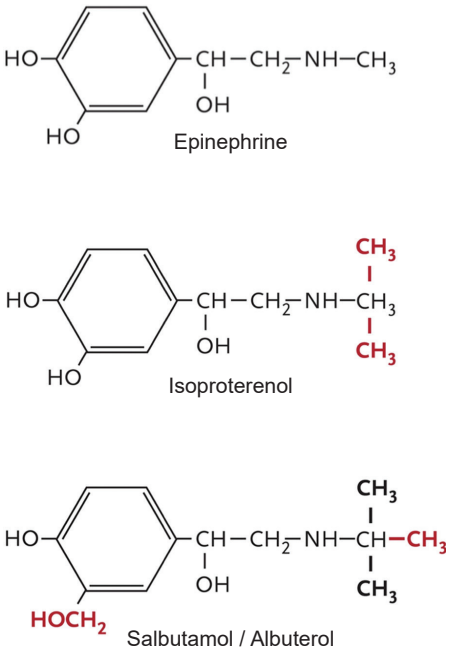


Figure 4 **Chemical structures of epinephrine, the nonselective beta-adrenergic agonist, isoproterenol (isoprenaline), and the selective beta2-agonist, albuterol (salbutamol).** The components of the structure in red show the differences from the preceeding structure.

Sympathomimetic treatment of asthma dates from the original use of ma huang in traditional Chinese medicine, likely over 5000 years ago. The active ingredient in ma huang is ephedra. Epinephrine, first by injection and later by inhalation, became the standard of care for acute asthma treatment. In the 1950s, inhaled isoproterenol (isoprenaline) was introduced for over the counter sales for asthma therapy, but high potency isoproterenol use was associated with asthma deaths (Figure 3). Restriction of this treatment led to a reversal in asthma deaths. In the 1960s, selective β2 agonists (Figure 4), such as albuterol, became available for inhalation and now have become the standard of care. The introduction of inhaled beta agonists with duration of action of over 12 hours occurred in the 1990s. Although these are highly effective therapies, there has been concern about their long-term safety. Large safety studies are ongoing at this time.

GLUCOCORTICOIDS AND ASTHMA

The use of adrenocorticotropic hormone (ACTH) or injections of biologically derived or synthetic steroids as an asthma therapy were introduced in the early 1950s. Because of the severe side effects of systemic steroid use, inhaled glucocorticoids were introduced in asthma treatment in the 1960s (Figure 5).

TARGETED ASTHMA TREATMENTS

Leukotriene modifier treatments - both antagonists of the action of leukotriene D4 at the CysLT1 receptor or inhibitors of the action of the enzyme ALOX-5 were introduced into the marketpace in the mid-1990s. Although their impact on lung function is less than inhaled glucocorticoids, they have a minimal adverse event profile and their oral action has led to their reasonably common use.

Anti-IgE therapy was approved in 2003. It requires subcutaneous drug dosing based on the patient's weight and IgE levels.

Anti TH2 monoclonal antibody treatments

Anti IL-5/IL-5 receptor targeted treatment was introduced for severe asthma in 2015. Mepolizumab was approved by the US FDA in 2015, followed by reslizumab in 2016; both of these molecules

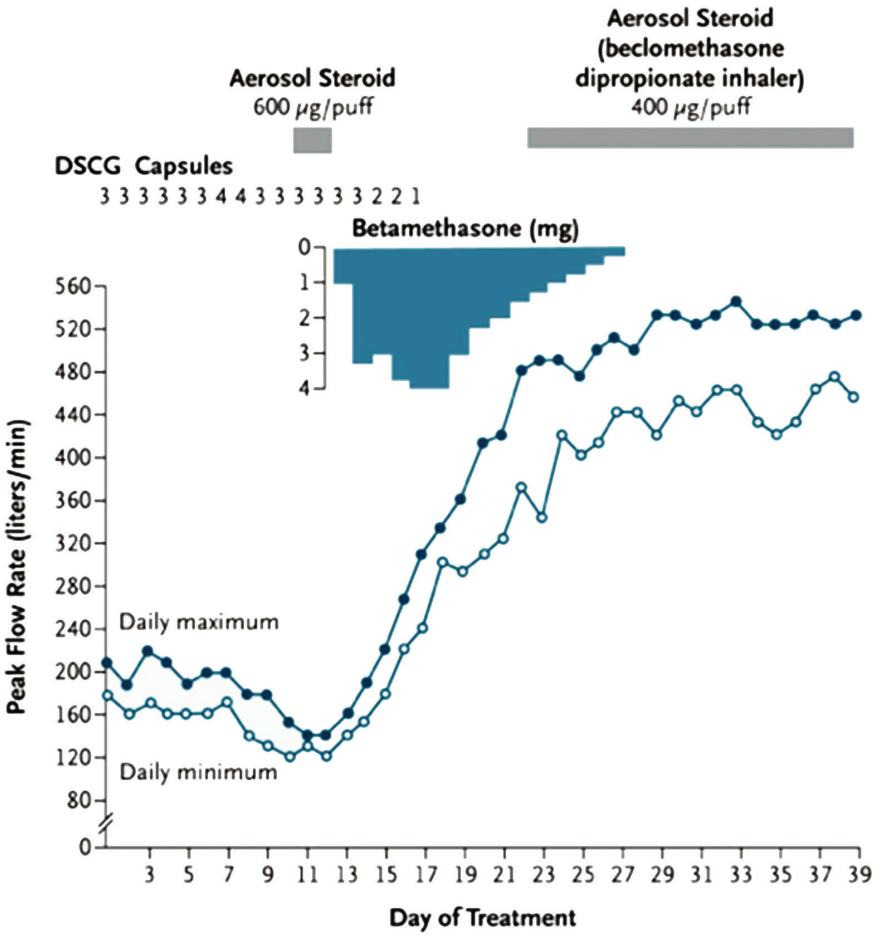


Figure 5 **Data from an early case report of the effects of inhaled glucocorticosteroids in asthma.** DSCG denotes disodium cromoglycate.
(Adapted from Br Med J, Brown HM, Storey G, George WH, 1, 585-590, Copyright 1972 with permission from BMJ Publishing Group Ltd.)

bind IL-5 directly Benralizumab, which binds the IL-5 receptor, was approved for severe asthma treatment in 2019.

Anti-IL4/IL-13 receptor monoclonal antibody treatment for severe asthma, in the form of dupilumab, was approved by the US FDA in 2019.

As of early 2020 there were no studies directly comparing these monoclonal antibody treatments.

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3a THE ASTHMA EPIDEMIC - GLOBAL AND TIME TRENDS OF ASTHMA IN CHILDREN

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ASTHMA CONTEXT

Asthma has been recognized for more than 3000 years but it is only in the last four decades that it has become identified as a serious public health concern. This was precipitated by a new 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. About the same time admissions to hospital for asthma were increasing dramatically in New Zealand, Australia, the United Kingdom, Canada and USA and the highest rates were in New Zealand children. Until three decades ago scientists in these countries believed that asthma affected predominantly people in high income countries and was negligible in developing countries.

Every day around 1150 people die worldwide because of asthma (compared with 1175 from malaria) and most of these deaths are avoidable. Globally, asthma ranks 28th among the leading causes of burden of disease measured by disability–adjusted life years (DALYs), contributing 23.7 million DALYs, with children 5-14 years and people over 60 most affected.

KEY MESSAGES

- Asthma in children is a disease of low and middle income, as well as high income countries
- Asthma in children is more severe in low and middle income countries
- Asthma in children is on the increase in many countries especially in low and middle income countries
- Further asthma surveillance and research is needed

GLOBAL VARIATION

The International Study of Asthma and Allergies in Childhood (ISAAC) was formed in 1991 to examine variation in asthma and allergies around the world by development of the necessary standardised methodology. At the time ISAAC started, there were fewer than 30 centres in the world, where the prevalence of asthma in children had been studied at all, and most had used different methodologies, thus making comparisons between locations difficult. ISAAC, which in the third phase included 237 centres in 98 countries, identified that asthma occurs in all countries studied, with striking variations in the prevalence of asthma symptoms throughout the world – up to 15-fold between countries (Figure 1). Although asthma symptoms were more common in some high income countries, some low and middle income countries also had high levels of asthma symptom prevalence. Among children with asthma symptoms, asthma is more severe in low and middle income than high income countries (Figure 2).

TIME TRENDS

Studies from English-language countries in the 1990s reported increases in asthma prevalence from the 1980s, and therefore continuing increases in prevalence were expected. Indeed, ISAAC found that asthma in children was on the increase in many countries from 1993 to 2003. However, in most high prevalence countries, particularly the English language countries, the prevalence of asthma symptoms changed little during that time, and even declined in some cases. In contrast, symptom prevalence increased in many countries over that time, especially low and middle income countries with large populations (Figure 3). The

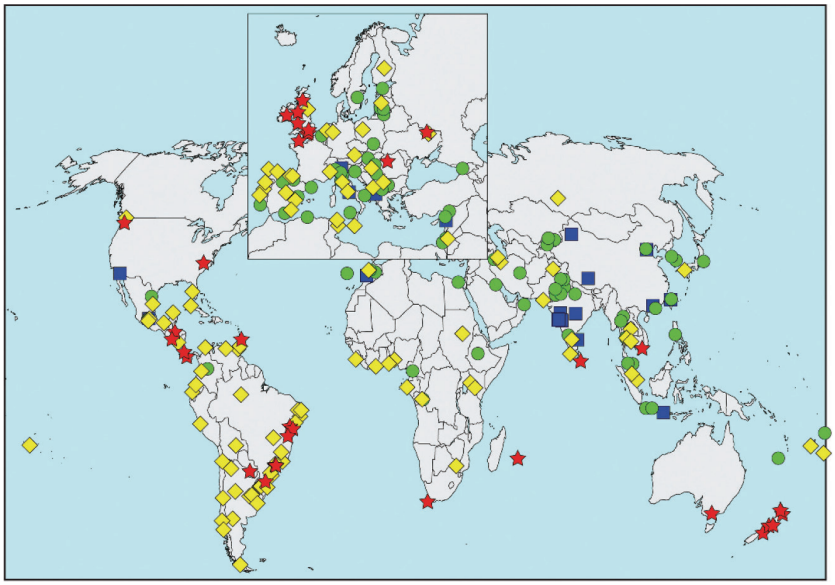

Figure 1 Prevalence of current wheeze according to the written questionnaire in the 13–14 year age group. The symbols indicate prevalence values of <5% (blue square), 5 to <10% (green circle), 10 to <20% (yellow diamond) and >20% (red star).

(Reproduced from Global variation in the prevalence and severity of asthma symptoms: Phase Three of the International Study of Asthma and Allergies in Childhood (ISAAC). Thorax 2009; 64(6): 476-483 with permission from BMJ Publishing Group Ltd.)

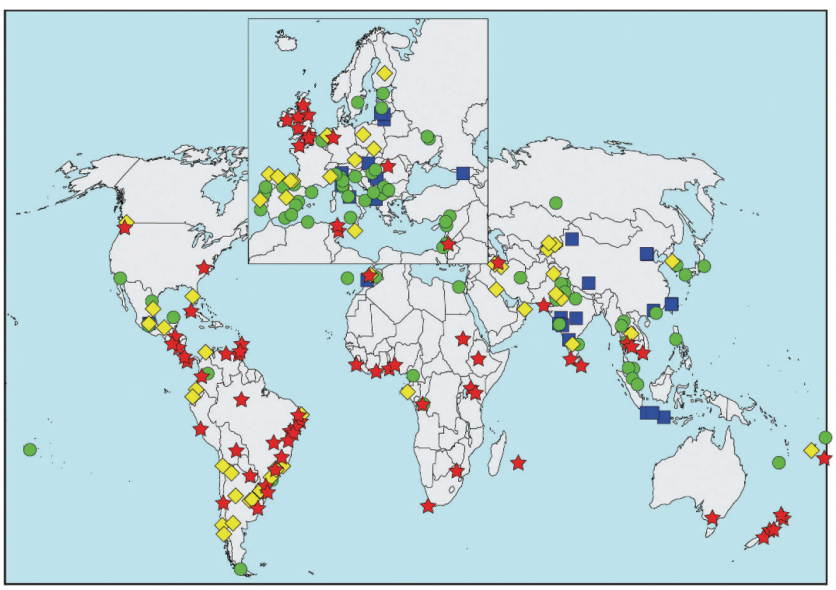

Figure 2 Prevalence of symptoms of severe asthma according to the written questionnaire in the 13–14 year age group. The symbols indicate prevalence values of <2.5% (blue square), 2.5 to <5% (green circle), 5 to <7.5% (yellow diamond) and >7.5% (red star).

(Reproduced from Global variation in the prevalence and severity of asthma symptoms: Phase Three of the International Study of Asthma and Allergies in Childhood (ISAAC). Thorax 2009; 64(6): 476-483 with permission from BMJ Publishing Group Ltd.)

overall percentage of children and adolescents reported to have ever had asthma, increased significantly, possibly reflecting greater awareness of this condition and/or changes in diagnostic practice.

CONCLUSION

The 20-year ISAAC programme found that childhood asthma is a common disease in both high income and lower income countries. It is relatively more severe and increasing in prevalence in many lower income countries. Some environmental factors have been identified as risk factors, therefore it is vital to continue surveillance of asthma, research its causes and reach all asthma sufferers with good management as summarised in the Global Asthma Report 2018. These are the aspirations of the Global Asthma Network, of which Phase I, modelled on ISAAC, has collected new data on these matters which will be published in due course.

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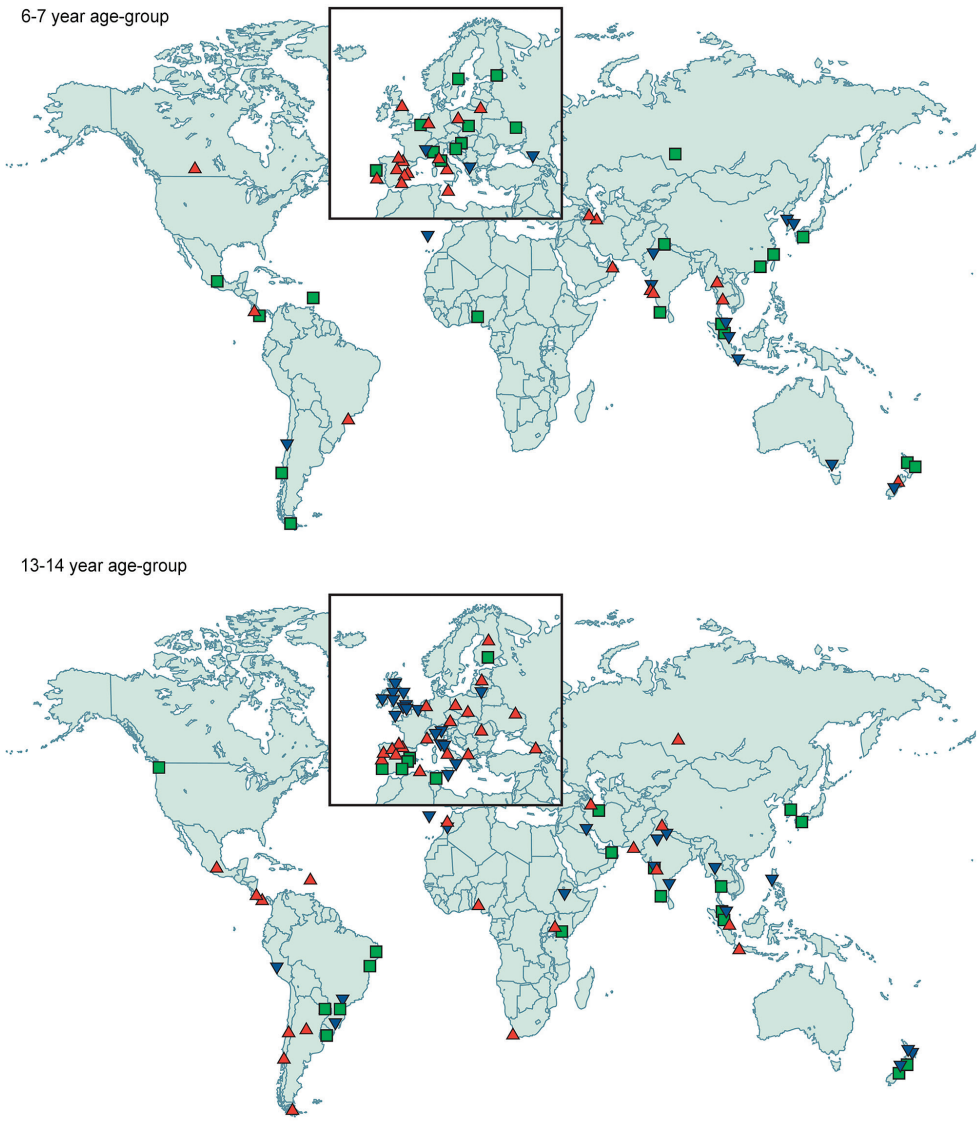

Figure 3 World map showing direction of change in prevalence of asthma symptoms for 6-7 year age-group and 13-14 year age-group. Each symbol represents a centre. Blue triangle=prevalence reduced by ≥1 SE per year. Green square=little change (<1 SE). Red triangle=prevalence increased by≥1 SE per year.
(Reproduced from The Lancet, 368(9537), Asher MI, Montefort S, Björkstén B, et al. , Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys, 733-43, 2006, with permission from Elsevier.)

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3b THE ASTHMA EPIDEMIC - GLOBAL AND TIME TRENDS OF ASTHMA IN ADULTS

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KEY MESSAGES

- Studies have used various data sources and surveys to estimate the prevalence of adult asthma in different countries
- Valid comparison of prevalence estimates across studies is hampered by the lack of a gold standard definition for asthma and by the underlying heterogeneity of adult asthma phenotypes
- Large international surveys conducted some years ago used standardized protocols, and suggested substantial geographical variation in the prevalence of adult asthma
- The Global Burden of Disease (GBD) initiative has provided information on global trends in asthma mortality
- Increases in asthma in higher income nations recorded in the latter half of the 20th century may be slowing or reversing but the picture remains unclear

MEASURING ADULT ASTHMA FOR GLOBAL COMPARISON

The assessment of adult asthma in epidemiological studies is compromised by the lack of a gold standard objective test. Comparisons of the reported prevalence of disease in different countries and over time is hampered by the different definitions of disease used (Table 1). Some epidemiological definitions are more sensitive while others are more specific - and both can lead to misclassification of asthma status. Furthermore, most fail to characterize the wide range of phenotypes of adult asthma, each of which may demonstrate different epidemiological patterns.

SURVEYS USING COMMON PROTOCOLS ACROSS COUNTRIES:

Three major multinational studies, all conducted some years ago, used common protocols to report comparisons of adult asthma prevalence between countries.

The European Community Respiratory Health Survey (ECRHS) assessed the prevalence of asthma symptoms, asthma attacks, and the use of asthma medication in the general population aged 20-44 years in 48 centres in 22 European countries from 1991-4. There was wide variation in the prevalence of current wheeze and 'diagnosed asthma' (a report of an asthma attack or current use of asthma medication). The Global Allergy and Asthma Network of Excellence (GA2LEN) survey of 15-74 year year old subjects in 19 centres in 12 European countries in 2008/09 using similar methods to those in the ECRHS showed, again, marked variation in prevalence of asthma across Europe.

In 2002/2003, the World Health Survey (WHS) assessed the prevalence of wheeze and of asthma diagnosis in adults in over 60 countries, including low and middle income countries. It showed wide variations in the prevalence of wheeze (Figure 1a and 1b) and asthma regardless of overall national income.

The Global Asthma Network should soon publish information on reported asthma and asthma-like symptoms in parents of children taking part in an international study of asthma in children.

SURVEYS REPORTING TIME TRENDS IN PREVALENCE OF ADULT ASTHMA

During the late 20th century marked increases in prevalence of asthma symptoms and diag-

TABLE 1

Factors that should be considered when comparing adult asthma prevalence estimates from different surveys in different locations

	Asthma definition used	Types of error that might occur
1	Questions asking about symptoms of wheeze and/or cough and/or breathlessness ('asthma-like symptoms')	In older adults these symptoms are similar to those that may be reported by people with COPD
2	Have you had **wheeze** in your chest at any time **in the last 12 months?** ('current wheeze')	Translation of 'wheeze' into different languages may be difficult – some languages do not have equivalent terms Even though the question asks about the last 12 months people may recall very recent events more readily The perception and reporting of asthma symptoms differ between subjects who come from diverse socio-cultural backgrounds
3	Have you **ever** had asthma? ('ever asthma')	Adults have poor/inaccurate recall of childhood diseases The term asthma may be applied differently in different populations/cultures
4	Have you been **told by a doctor** you have asthma? ('diagnosed asthma')	In areas or countries with poor healthcare provision people with asthma may not have access to healthcare and may not have a diagnosis Men and smokers who report asthma like symptoms are more likely to be told by healthcare professionals they have COPD than women and non-smokers who report the same symptoms Health care professionals in different countries may use the term 'asthma' in different ways
5	Are you taking any **medication** for the treatment of asthma? ('current medication')	In areas or countries with poor healthcare provision or fee-based provision of asthma medication people with asthma may not get treatments that are readily available elsewhere

noses were reported from repeat surveys conducted within some, mainly higher income, nations with strong evidence that this was related to increased disease in successive birth cohorts. More recent data are confined to developed economies where the prevalence of diagnosed asthma in adults appears to be increasing although the prevalence of asthma symptoms may have stabilized. Surveys that have looked at changes in prevalence and have provided information since 2010 are shown in Figure 2. Neither ECRHS, GA2LEN nor WHS have repeated their surveys.

The Global Burden of Disease project has collated worldwide mortality data from multiple surveys in multiple countries across the world. Since 1990 deaths from asthma (which mainly occur in adults) have decreased, although this decrease is less apparent in countries with lower sociodemographic development. This likely reflects improvements in case fatality rates rather than a decrease in prevalence of disease.

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TABLE 2

Prevalence (in %) of 'wheeze' and 'diagnosed asthma' in the European Community Respiratory Health Survey (ECRHS) and the Global Allergy and Asthma Network of Excellence (GA2LEN)*

Country	Centre	ECRHS		GA²LEN
		wheeze[1]	dg asthma[2]	asthma[3]
Iceland	Reykjavik	18.0	3.4	
Norway	Bergen	24.6	4.3	
Sweden	Göteborg	23.2	5.8	7.1
	Stockholm			8.6
	Umeå	19.8	6.8	11.2
	Uppsala	19.2	6.0	9.5
Finland	Helsinki			7.8
Estonia	Tartu	26.8	2.0	
Denmark	Aarhus	24.1	4.0	
	Odense			8.6
Poland	Katowice			5.2
	Krakow			7.1
	Lodz			6.0
Netherlands	Amsterdam			6.4
	Bergen op Zoom	19.7	4.7	
	Geleen	20.9	4.4	
	Groningen	21.1	4.3	
Belgium	Antwerp city	20.6	4.6	
	Antwerp south	12.8	2.7	
	Ghent			7.6
Germany	Brandenburg			6.3
	Duisburg			10.1
	Erfurt	13.3	2.1	
	Hamburg	21.1	4.4	
Austria	Vienna	14.3	3.1	
France	Bordeaux	15.7	5.5	
	Grenoble	14.6	3.5	
	Montpellier	14.4	5.0	10.3
	Nancy	13.6	3.7	
	Paris	14.5	5.1	
Macedonia	Skopje			5.1
UK	Caerphilly	29.8	8.0	
	Cambridge	25.2	8.4	
	Dundee	28.4		
	Ipswich	25.5	7.8	
	London			11.4
	Norwich	25.7	7.5	
	Southampton			14.2
Ireland	Dublin	32.0	5.0	
	Kilkenny-Wexford	24.0	5.4	
Greece	Athens	16.0	2.9	
Italy	Palermo			10.7
	Pavia	8.5	3.3	
	Turin	10.7	4.5	
	Verona	9.7	4.2	
Spain	Albacete	25.0	3.9	
	Barcelona	19.2	3.1	
	Galdakao	16.2	2.1	
	Huelva	29.2	6.3	
	Oviedo	21.0	3.6	
	Seville	22.6	5.0	
Portugal	Coimbra	19.0	6.0	16.8
	Oporto	17.7	4.3	
Algeria	Algiers	4.2	3.0	
India	Bombay	4.1	3.5	
New Zealand	Auckland	25.2	10.1	
	Christchurch	26.7	11.2	
	Hawkes Bay	24.2	9.0	
	Wellington	27.3	11.3	
Australia	Melbourne	28.8	11.9	
USA	Portland, Oregon	25.7	7.1	

** Reproduced with permission of the European Respiratory Society. Eur Respir J April 1, 1996 9:687-695 and from Jarvis D, Newson R, Lotvall J, et al. Asthma in adults and its association with chronic rhinosinusitis: the GA2LEN survey in Europe. Allergy 2012;67:91-98, Wiley-Blackwell.*

[1] Age and sex standardized prevalence of a positive response to 'Have you had wheezing or whistling in your chest at any time in the last 12 months?' in 20-44 year olds.

[2] dg asthma = diagnosed asthma. Age and sex standardized prevalence of a positive response to at least one of the following: (i) 'Have you had an asthma attack in the last 12 months?', or (ii) 'Are you currently taking medication for the treatment of asthma?' in 20-44 year olds.

[3] Age and sex standardized prevalence of reporting 'ever had asthma' AND reporting at least one of the following symptoms in the last 12 months (i) wheeze or whistling in the chest, (ii) waking with chest tightness, (iii) waking with shortness of breath, and (iv) waking with an attack of coughing in 15-74 year olds.

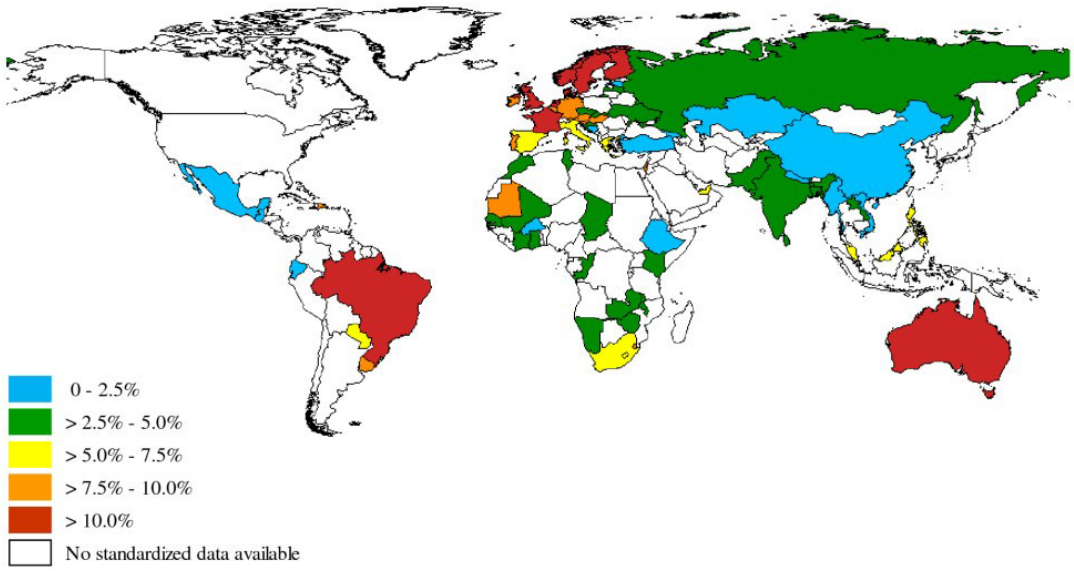

Figure 1 Prevalence of 'clinical asthma' in the World Health Survey in participants aged 18 to 45 years. Clinical asthma defined as a positive response to "Have you ever been diagnosed with asthma?" and/or a positive response to either "Have you ever been treated for asthma?" or "Have you been taking any medications or treatment for asthma during the last 2 weeks?

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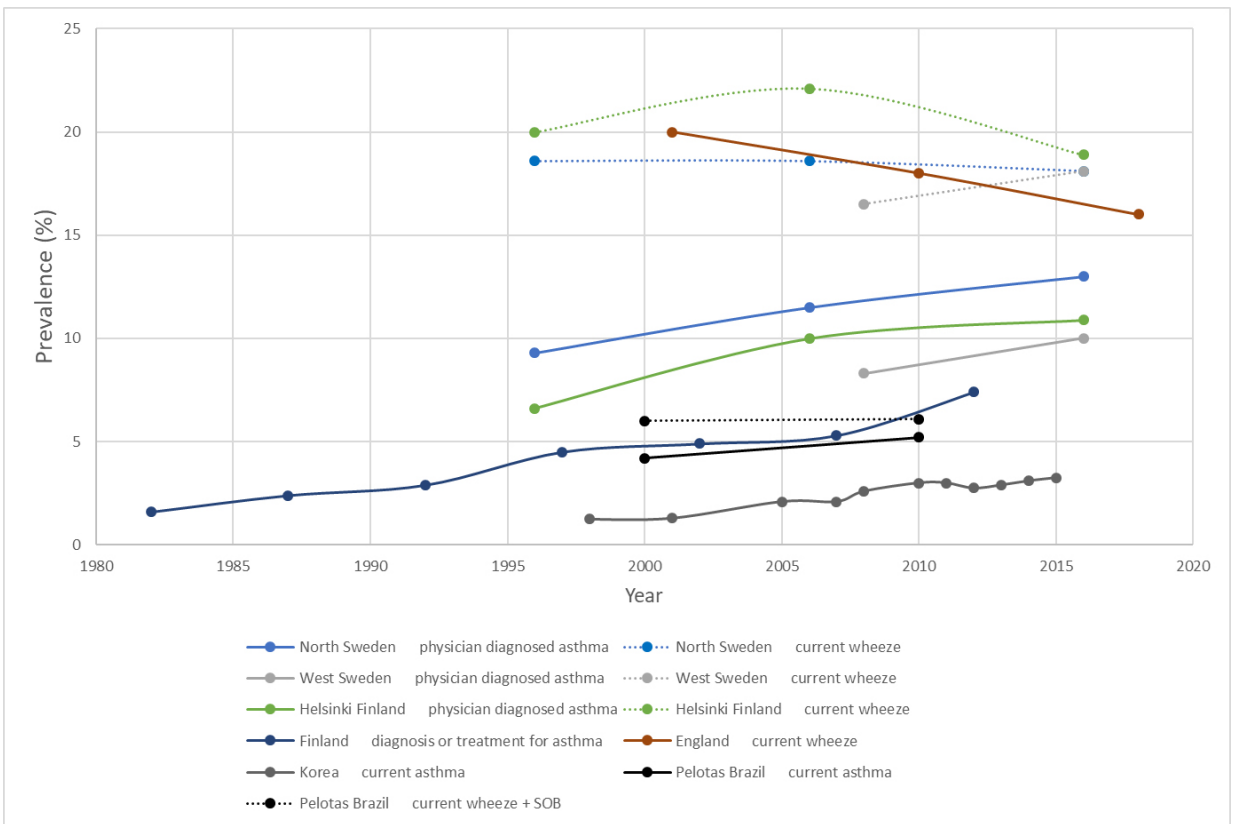

Figure 2 Prevalence of asthma (different definitions used) in adults from repeat surveys in same location and with at least one survey after 2010.

4 DEATH AND DISABILITY DUE TO ASTHMA

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KEY MESSAGES

- Asthma is one of the most common causes of airway disease and is associated with increased mortality and long-term disability
- Predictors of progressive lung dysfunction include eosinophilic inflammation and persistant exposure to environmental factors, especially molds and pollutants, interacting with atopic and genetic predispostion
- Disability is primarily linked to disease severity, decline in lung function, associated comorbidities and social inequalities
- In 2016, more than 1000 patients died every day from asthma in the world
- Mortality from asthma has decreased in the last decades likely following improved awareness of disease biology and therapeutic advances; further effort is needed to minimize asthma-related death and disability

Asthma is a major cause of disability, healthcare resource utilisation and significantly reduces patients' quality of life. Airways inflammation and progressive remodeling represent the pathological substrate underpinning bronchial hyper-reactivity, acute clinical events and enhanced lung function decline. Main predictors of functional lung decline have been identified in large longitudinal cohorts of patients and include age, environmental exposures and genetic background. Disability and global impairment of quality of life result from a complex interplay between primary drivers, namely disease severity and loss of pulmonary function and secondary determinants such as physical deconditioning, treatment non-adherence, associated comorbidities, social impairment and subjective feelings over the disease and its consequences, amongst others (Figure 1). The degree of impairment and disability can be assessed with standardised and validated tools that offer objective and reproducible results over main domains. One main barrier in disability assessment is overestimation or underestimation of the symptomatic burden.

Asthma-related deaths are not frequent, but in many cases, they are preventable. Mortality rate increases exponentially with age, from childhood to advanced ages, when other comorbidities are also present. Other factors, like a lower socio-economic status, history of smoking, atopic status, frequent exacerbations, lower baseline forced expiratory volume in the first second (FEV1) and poor asthma control have been associated with increased asthma mortality. It was estimated that more than 1000 patients died from asthma in the world in 2016 every day. Likely, one of the causes of major impact is that many countries have not a Public Health System ensuring specialist medical supervision. This means that patients with asthma have less awareness of their disease, are not provided with personal asthma action plans, rely on self-administration of short-acting reliever medications and are not receiving appropriate long-term control medications such as inhaled corticosteroids (ICS) ± long-acting β-agonists (LABA). This facilitates severe

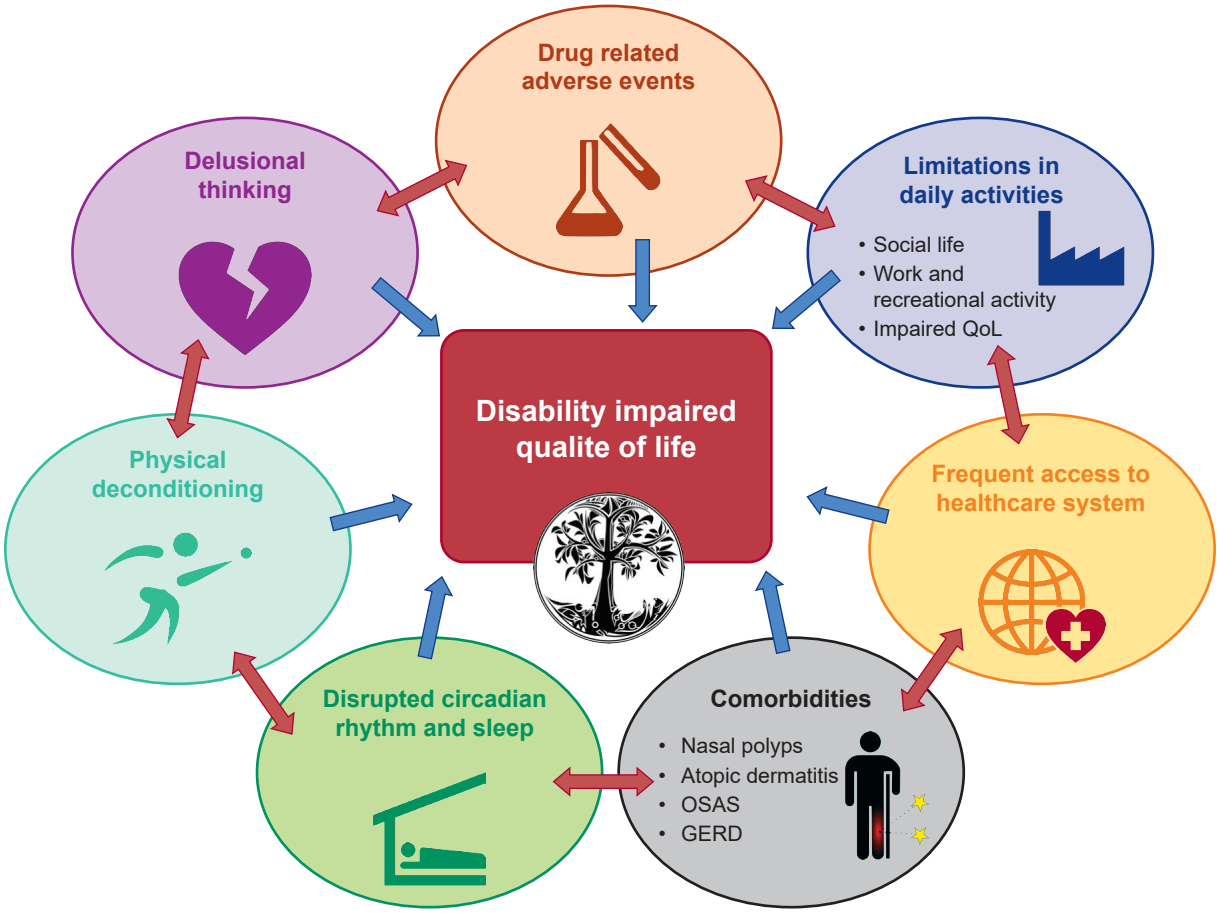

Figure 1 **The complex network of asthma-related burden on the individual.**

asthma exacerbations with a higher risk of disability and death.

On a whole, asthma-related mortality has decreased over the last decades. Comparing the period from 2001 to 2005 to the period from 2011 to 2015, there was a halving of the mortality rate, particularly in the age group from 6 to 35 years . This reduction is related to the introduction of new therapies for asthma and to increased awareness that uncontrolled asthma can lead to disability and death. Some countries in the world seem to be more affected than others: in low and middle-income countries, the highest mortality rates are registered in Fiji, Philippines, South Africa and Mauritius, while the lowest ones are reported in Malaysia, Colombia, Ecuador and Bulgaria. For high-income countries, the highest mortality rates are reported in the Republic of Korea, Uruguay, Venezuela and Puerto Rico the lowest ones in Italy, Netherlands, Austria and Canada. These data show that asthma still represents a major cause of mortality and disability especially in low income countries; further efforts and investments are needed.

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5 SOCIO-ECONOMIC COSTS OF ASTHMA

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The clinical impact of asthma is accompanied by a significant socio-economic burden on patients, their families, and societies at large. Notably, the full economic burden involves both direct costs, such as medication, outpatient visits, and hospital admissions, as well as indirect costs such as work productivity losses. In this chapter, the economic impact of asthma, trends and cost drivers are described.

KEY MESSAGES

- The economic burden of asthma, consisting of direct and indirect costs, is substantial
- Major direct costs include medication, outpatient visits, and hospital admissions
- Major indirect costs include work productivity losses, missing school, and caregiver burden
- Cost enhancing factors include severe, uncontrolled asthma, and comorbidities
- There are large global differences in the socioeconomic burden of asthma

ECONOMIC BURDEN OF ASTHMA: A GLOBAL CHALLENGE

The economic burden of asthma is dependent on the total number of people with asthma multiplied by the mean cost per patient. Multiple studies, mostly from high-income countries where detailed data are often available, have highlighted the significant excess costs due to asthma. Given the large international variability in the detection and diagnosis of asthma, the distribution of its severity, extent of treatment availability, and structure and process of care, most data can however not be directly compared across countries. Therefore, it can be challenging to provide an estimate of the total global economic burden of asthma, yet detailed analyses from individual countries provide useful insights into its cost components and drivers.

DIRECT AND INDIRECT COSTS

The costs of asthma can generally be divided in direct costs and indirect costs. The direct costs of asthma involve costs related to healthcare utilization (e.g. medication, healthcare provider visits, and hospital admissions) to control or monitor asthma. Indirect costs include work productivity losses, missing school in the younger age groups and caregiver burden. Within the work productivity related costs, one can distinguish between absenteeism (missed workdays) and presenteeism (less productive while at work). A detailed population-based study from the United Kingdom estimated the total annual national direct costs of asthma at around £1.1 billion. Of these costs, 74% were attributed to medication and primary care services (60% prescribing, 14% consultations), 13% for disability claims, and 12% for hospital care. A smaller but more detailed Korean cost study provided the mean direct and indirect per patient cost of asthma by severity, ranging from $1361 and $1421 for mild and moderate asthma respectively, to $5141 for severe asthma (Figure 1). Indirect costs add substantially to the total asthma costs, particularly in people with uncontrolled and severe asthma. Of note, in low- and middle-income countries, it has been demonstrated that presenteeism

due to asthma is generally more profound than absenteeism, probably driven by the limited access to care and social security systems.

HIGH COST SUBPOPULATIONS

While the majority of asthma cost studies provide an average number, there are several clearly identified sub-populations where asthma costs are significantly higher than average. In particular, these involve patients with more severe forms of (uncontrolled) asthma and patients with comorbidities (Figure 2). Severe uncontrolled asthma results in more healthcare resource utilization driven by high symptom burden and comorbidities. Another sub-population with higher costs is asthma patients with high burden of comorbidity. In patients with

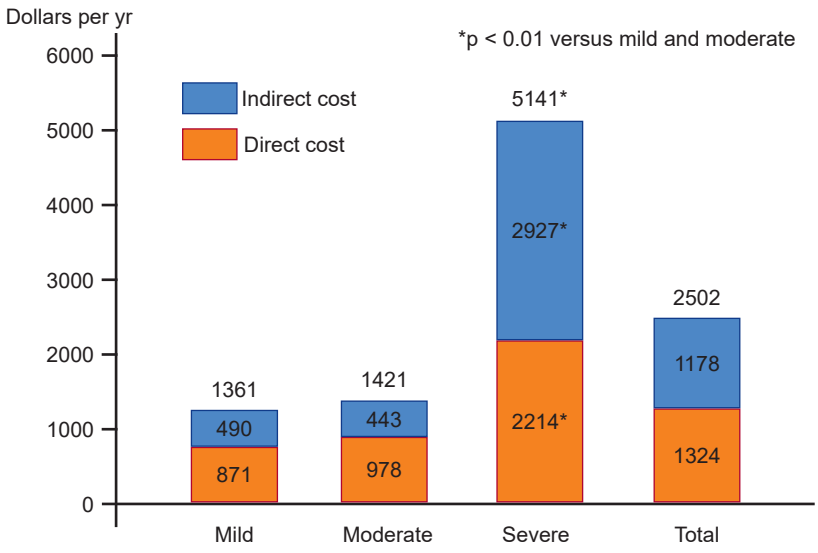

Figure 1 **Asthma direct and indirect costs by severity.**
(Reproduced from Journal of Asthma, Kim SH,et al., Economic costs for adult asthmatics according to severity and control status in Korean tertiary hospitals, 2012; 49(3):303-9 with the permission of Taylor & Francis Ltd.)

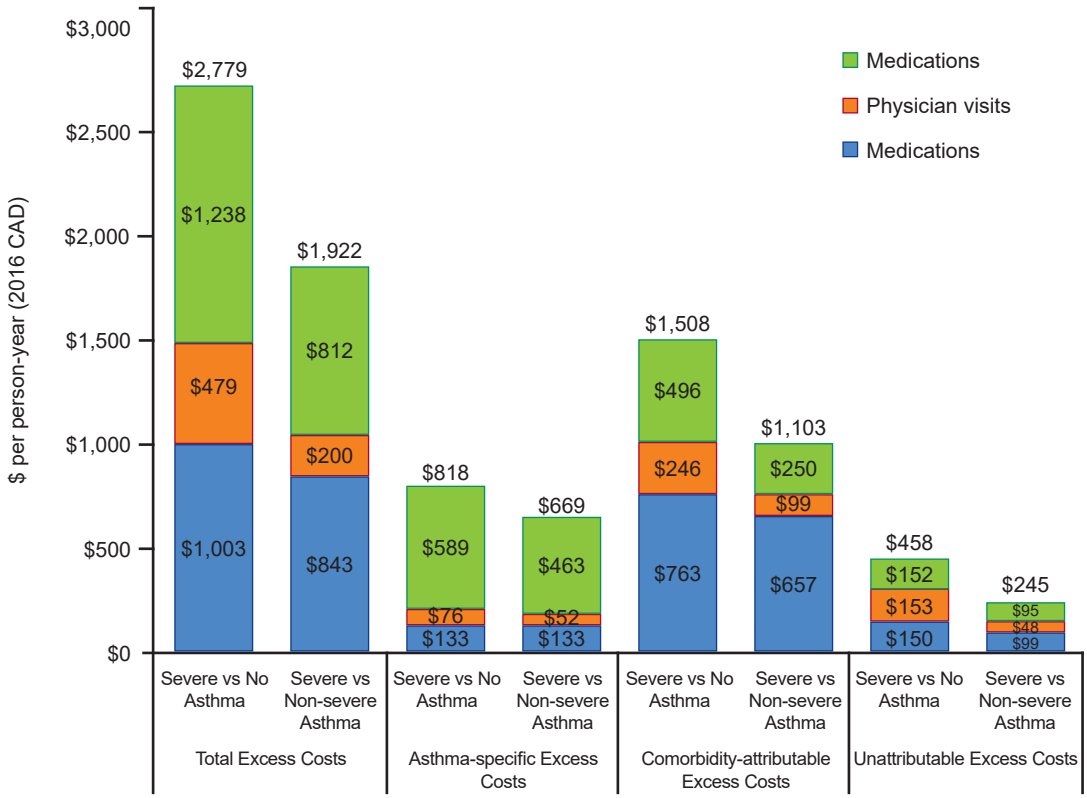

Figure 2 **Excess costs of severe asthma versus no and non-severe asthma.**
(Reproduced from Economic burden of multimorbidity in patients with severe asthma: a 20-year population-based study, Chen W, et al., 74, 1113-1119, 2019, with permission from BMJ Publishing Group Ltd.)

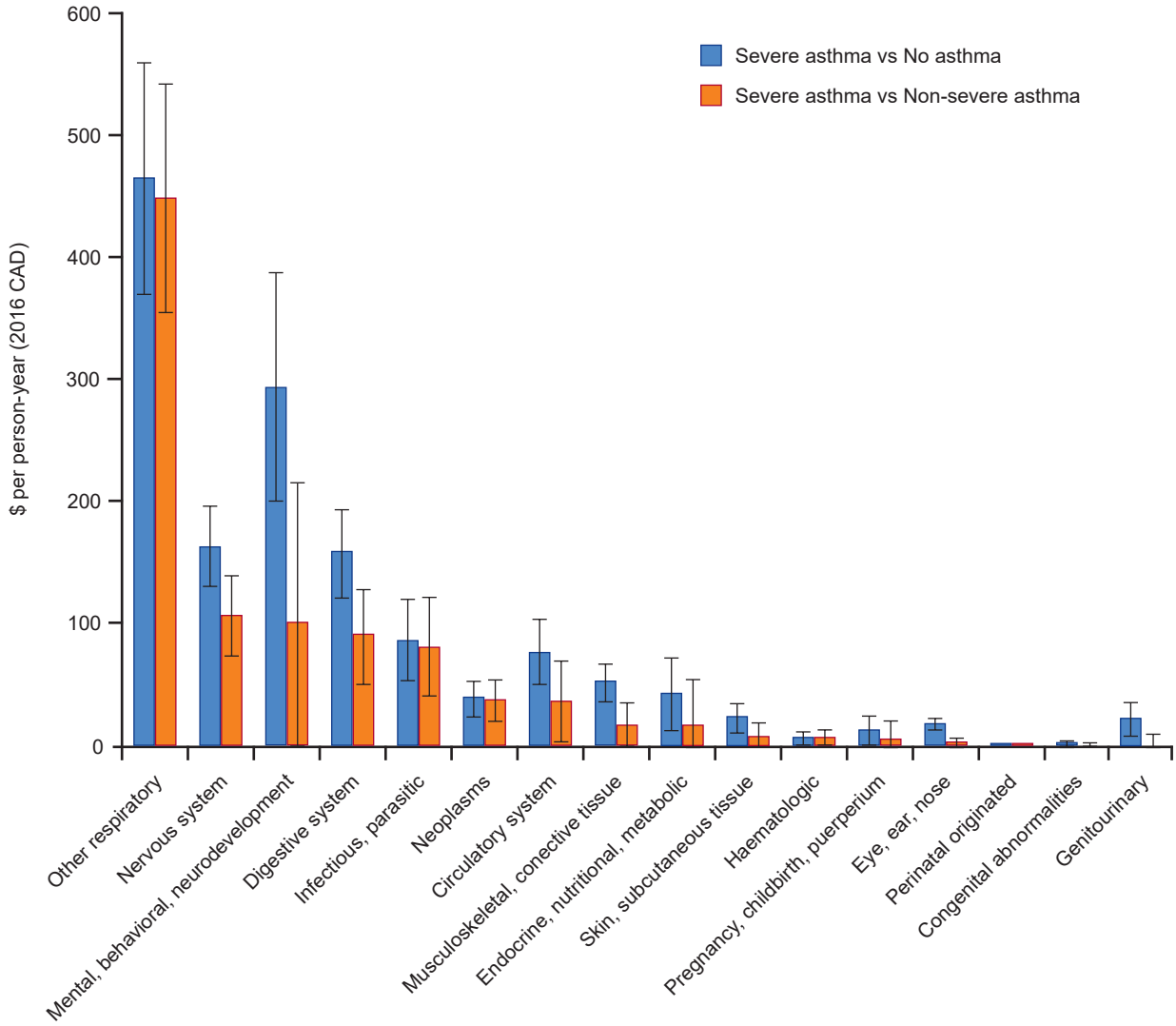

Figure 3 **Excess costs of asthma due to comorbidities.**
(Reproduced from Economic burden of multimorbidity in patients with severe asthma: a 20-year population-based study, Chen W, et al., 74, 1113-1119, 2019, with permission from BMJ Publishing Group Ltd.)

asthma, the prevalence of comorbid conditions is generally higher than in the general population. Most costly comorbidities involve other respiratory complaints (e.g. COPD), mental and nervous system disorders (e.g. depression) and digestive comorbidities (e.g. reflux) (Figure 3). Historically, patients with severe asthma were often fully dependent on oral corticosteroids that can result in costly long-term complications such as osteoporosis. Currently, targeted biologic therapies are available, yet these come at high costs ($15,000-20,000 per year) and are only available in high-resource settings.

TRENDS IN COSTS

While no global estimate exists, models have provided us with estimations of the 20-year projected direct costs of uncontrolled asthma in the United States (in 2018 USD values). Annual costs (around 15 billion) will slightly increase over the years and will costs the US a total of around $300 billion (95%CI: 190-411) over the next 20 years. When also indirect costs are included, the total 20-year costs are estimated at $963 billion (95%CI: 664-1263). In addition to these costs, an estimated 15.46 million (95%CI: 12.77-18.14) quality adjusted life years (QALYs) will be lost (Figure 4).

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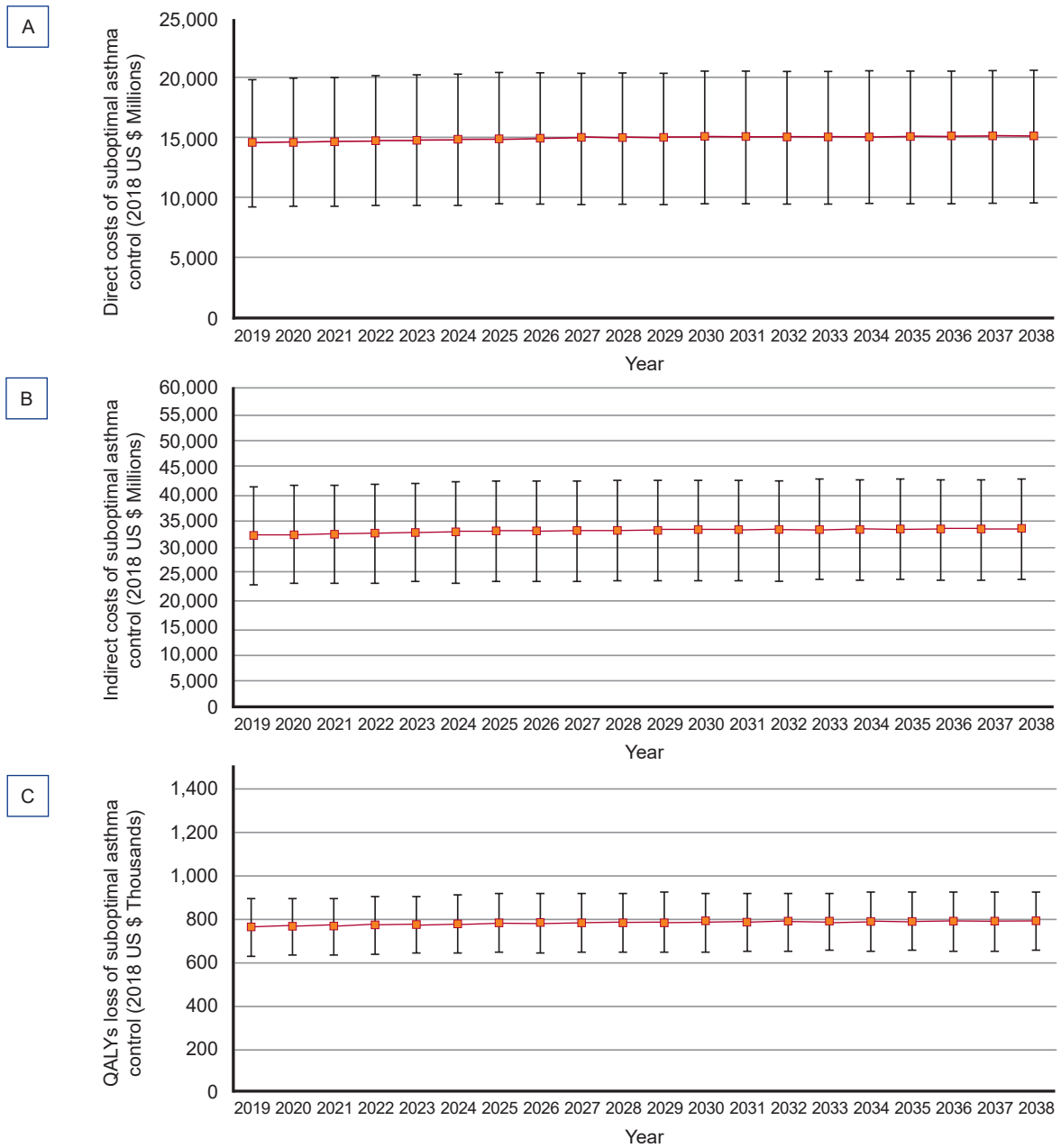

Figure 4 **20-year trends in costs and QALYs of asthma in the USA.**

(Reproduced from the Projected Economic and Health Burden of Uncontrolled Asthma in the United States, Yaghoubi M, et al. Am J Respir Crit Care Med. 2019; 200(9):1102-1112, under the terms of the creative commons attribution non-commercial license 4.0)

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6 NATURAL HISTORY OF ASTHMA

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KEY MESSAGES

- In both children and adults, studies of the natural history of wheezing, allergy and asthma have led to the identification of specific asthma phenotypes
- In infants with recurrent wheeze, the early onset of allergic sensitization is a strong risk factor for persistent asthma symptoms and the development of obstructive changes on lung function testing
- Severe allergic asthma in childhood often leads to continued severe disease later in life
- Asthma that begins in adults can be grouped into clusters with type 2 inflammation, eosinophilia without allergic sensitization, and non-type 2 inflammation
- Adult-onset asthma associated with aspirin sensitivity (AERD) and chronic sinusitis usually does not remit, requires long-term management and is a distinct phenotype

ASTHMA IN CHILDREN

Early attempts to describe the natural history of wheezing in childhood led to the recognition of specific phenotypes of wheezing and asthma. Subsequent studies have affirmed these phenotypes across multiple populations and have started to identify connections with unique sets of risk factors, comorbidities and age of onset and in some cases resolution. Thus, each of these asthma and wheeze phenotypes has its own natural history (Figure 1).

Infants who have recurrent episodic wheeze or cough associated with acute infections have a variable course; these symptoms can resolve during the preschool years or early school years, or symptoms can persist throughout childhood. The probability of persistence and transition to persistent asthma is increased by the coincident occurrence of clinical indicators (e.g. atopic dermatitis), eosinophilia or the development of allergen-specific IgE. Sensitization to aeroallergens by 2-3 years of age is a particularly strong risk factor for persistent asthma, additional acute wheezing illnesses, and the development of airway obstruction during childhood. Conversely, recurrent wheeze in infants in the absence of allergic sensitization or other atopic features is likely to resolve by 6-10 years of age.

Development of allergic sensitization later in childhood can be associated with mild allergic asthma that responds well to standard care. One additional phenotype of childhood asthma has been recognized in girls who are overweight and have early onset of puberty. This phenotype is not strongly linked to allergy and is persistent in nature.

NATURAL HISTORY OF ASTHMA IN ADULTS

Two major natural history patterns in adult asthma emerge: persistence of disease from childhood and adult-onset asthma (Table 1). Many longevity characteristics including allergy and airway obstruction are established in childhood, as discussed above. Adult-onset asthma usually begins in the fourth decade of life in women with low frequency of allergic sensitization and infrequent remission. While the natural history of asthma in adults is

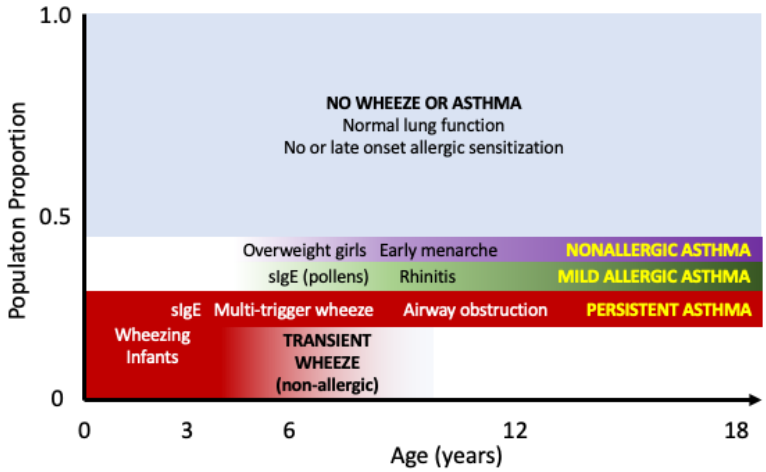

Figure 1 **The natural history of asthma in children is dependent on asthma phenotype.**
sIgE - allergen-specific IgE.

TABLE 1

Natural History Characteristics of Asthma in Adults

	Pattern from Childhood Onset		Adult Onset	
Characteristic	**Mild/ Moderate**	**Severe**	**No CRSwNP**	**CRSwNP**
Allergic sensitization	+++	++	+	–
Remission	+	+	–/+	–
Loss of lung function	–	++	+	++
ICS use	+	++++	++	+++
Exacerbations frequency	+	+++	+	+++

CRSwNP - chronic rhinosinusitis with nasal polyps; ICS - inhaled corticosteroids.

heterogeneous, groups of asthma patients with distinct features and natural history can be identified. In the Severe Asthma Research Program (SARP), five asthma clusters were identified. The first two clusters had childhood asthma which remained mild-to-moderate in severity. A third cluster had adult-onset asthma, a predominance of women, poor disease control, obesity, low frequency of allergic sensitization, compromised lung function and frequent exacerbations. The fourth and fifth clusters were characterized by low lung function, poor disease control, need and use of high dose medication, frequent exacerbations and a variability of allergic sensitization and childhood disease – all characteristics of severe persistent asthma. Predictors for persistent severe asthma include severe childhood disease, female sex, and hay fever.

Amelink et al performed a cluster analysis on 200 patients with adult-onset asthma. Cluster 1 was predominantly women with eosinophilic inflammation and persistent airflow obstruction. Cluster 2 were also women with low sputum eosinophilia, high health care utilization and frequent symptoms and exacerbations. The third cluster was predominantly male with mild-to-moderate but well controlled asthma and normal lung function, but greater frequency of aspirin exacerbated respiratory disease (AERD). Chronic sinusitis with nasal polyps (CRSwNP) and aspirin sensitivity is a unique phenotype found predominantly in adult-onset asthma. Despite a variability in disease severity in this population, remissions are rare and long-term treatment is required.

The natural history of asthma in adults is variable, influenced by childhood disease, and, for those with adult-onset disease, lifetime persistence.

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7 ENVIRONMENTAL RISK FACTORS FOR ASTHMA: AIR POLLUTION, CLIMATE CHANGE

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KEY MESSAGES

- The exposome is defined as the totality of specific and nonspecific environmental exposures to which an individual is exposed from pre-conception onwards and of the consequences at the organs and cells' level
- The external exposome interacts with the epigenome and genome or impacts directly on the internal exposome
- Major external factors include pollutants, diet, allergens, climate change, biodiversity

Environmental changes occurring in the last decades have played a key role in the increasing prevalence of asthma. Better understanding of the complexity of the environmental challenges led to the concept of exposome. The exposome is defined as the totality of specific and nonspecific external environmental exposures (external exposome) to which an individual is exposed from pre-conception onwards and of the consequences at the organs and cells level (internal exposome). The expsosome is being considered to explain inception, development and exacerbations of allergic diseases and asthma. The external exposome interacts with the epigenome and genome or impacts directly on the internal exposome (Figure 1). Major external factors include pollutants, diet, allergens, climate, biodiversity. Climate change, with the fast raise of temperature and long-lived greenhouse gases (GHG), and the projected increase of extreme events, such as thunderstorms and flooding, emerges as one of the most relevant factors for the external nonspecific exposome. On one hand, higher temperature and CO_2 levels result in increased pollen abundance, earlier shifts of airborne pollen seasons, increased pollen and invasive allergenic plant species. On the other hand, extreme events can affect molds levels and therefore the risk of development and exacerbations of asthma, like of flooding, or thunderstorm induced severe asthma outbreaks. The thunderstorm asthma is an outbreak of severe asthma attacks which occurs during the grass, pellitory and olive tree pollen or mold seasons.

Another well-established risk factor for asthma is chemical air pollution. Traffic-related air pollutants including fine particulate matter, nitrogen dioxide and ozone, have been related not only to asthma exacerbation but also to asthma development, with very robust data in children. Pollution exposure is expected to intensify as a consequence of climate change. In addition, air pollution and climate change influence each other through complex interactions in the atmosphere (Figure 2). Increasing levels of GHGs alter the energy balance between the atmosphere and the Earth's surface which, in turn, can lead to temperature changes that change the chemical composition of the atmosphere. Direct emissions of air pollutants (e.g. black carbon), or those formed from emissions such as sulfate and ozone, can also influence this energy balance. Ozone concentrations increase during hot weather and spells due to climate change. Urbanization is also contributing to the increase in outdoor air pollution. Lastly, the frequency and the geographical distribution of extreme phenomena like wildfire and dust storm are increasing. Both

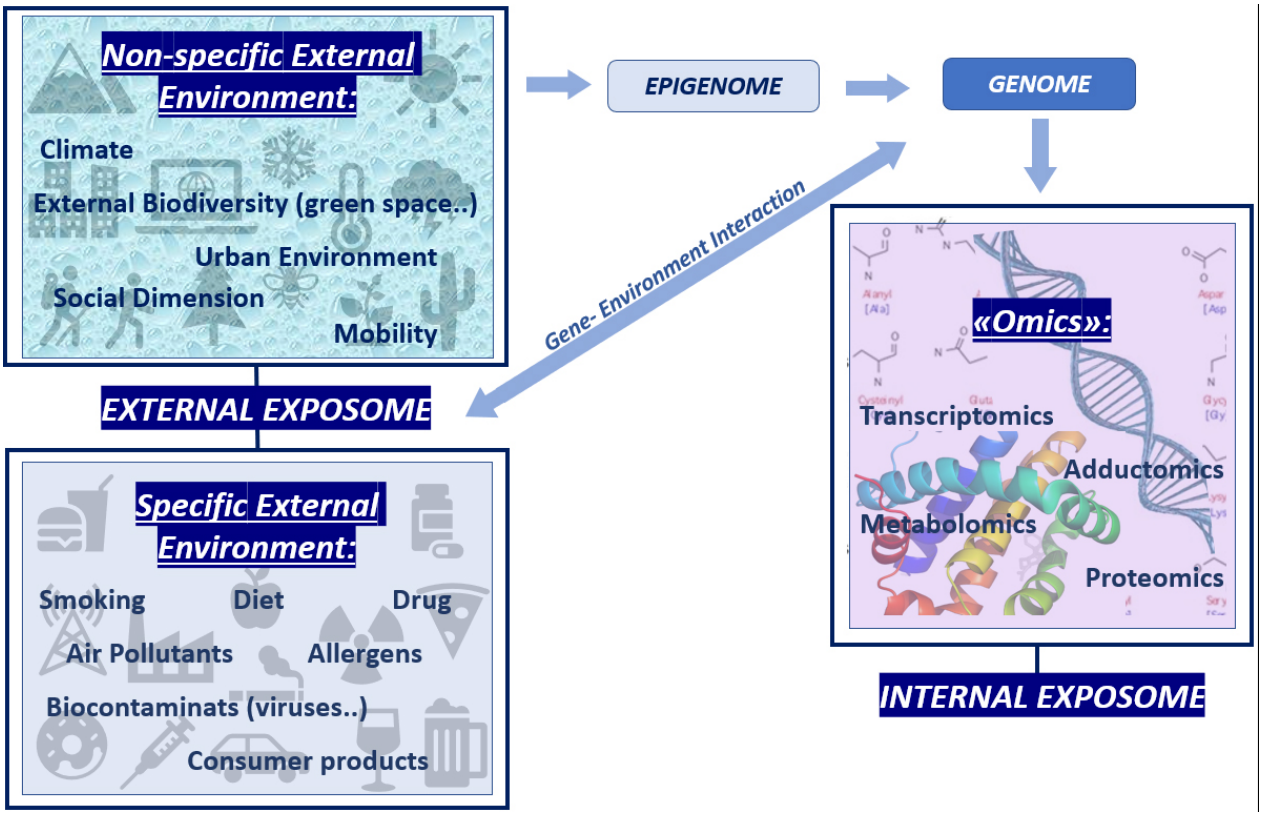

Figure 1 Exposome involved in asthma.

TABLE 1

Effects of air pollutants and temperature on pollen and molds allergenicity and onset of pollen season *

	Pollen/mold	CO_2	O_3	NO_2	Temperature
Allergenicity*	Birch		↑	↑	
	Ragweed	↑	↔	↑	
	Hornbeam			↑	
	Oak			↑	
	Plan tree		↔	↑	
	Aspergillus fumigatus			↑	
Earlier start	Grass	↑			↑
	Birch				↑
	Oak				↑
	Olive tree				↑

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↑, Increase; ↔, no changes.

**Allergen content and/or IgE recognition of exposed samples by patients' sera.*

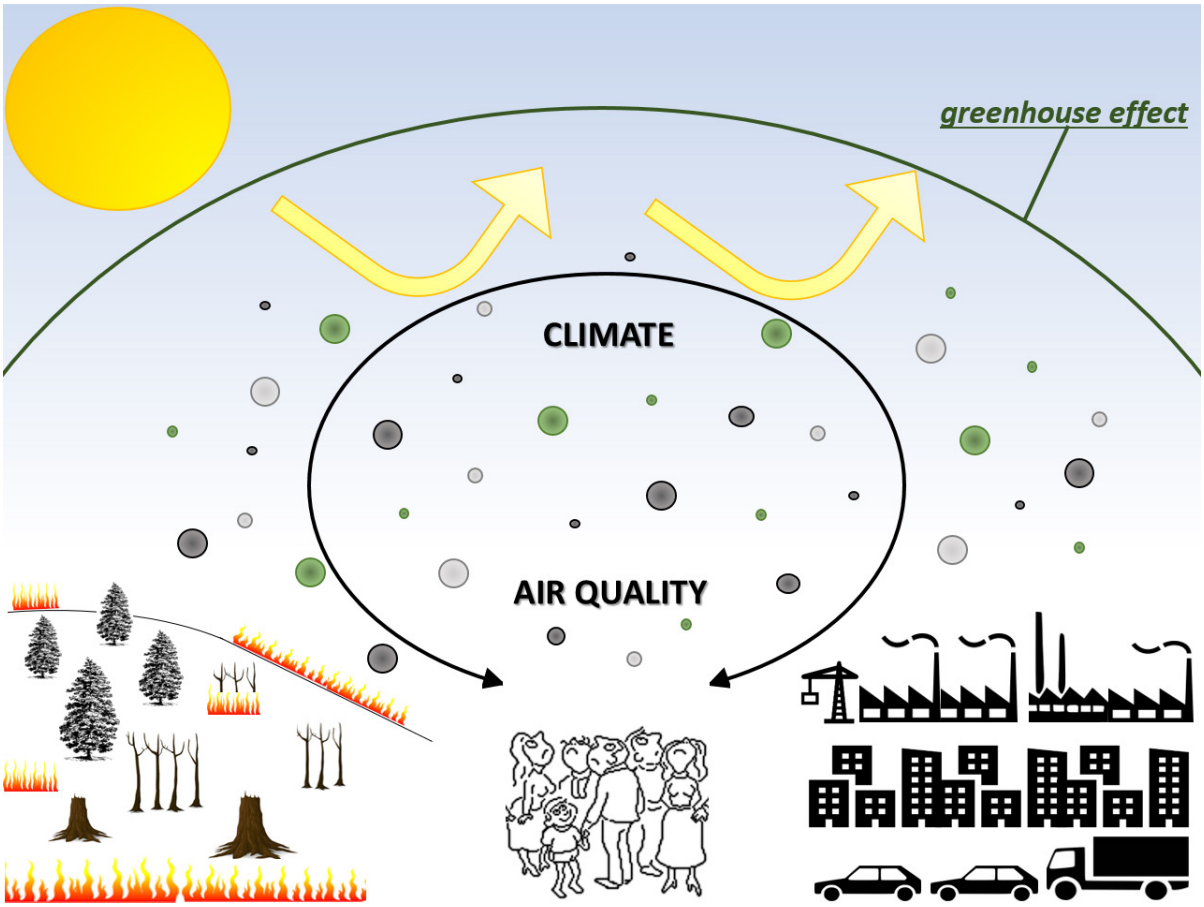

Figure 2 **Air pollution and climate change.**

produce high amount of gases and particulate matter. In addition, air pollutants and temperature variously affect pollen and molds allergenicity and onset of pollen season (Table 1). All of these events pose a huge challenge to asthma, overall in susceptible individuals. In this context, the exposome is an emerging area of research that explores how exposure to environmental factors (climate change, pollution, diet, lifestyle, socioeconomic factors, work, environment, infections etc.) impacts asthma and wellbeing throughout life, starting from conception and pregnancy.

Thus, climate change and air pollution management have consequences on each other and impact asthma. Recent research showed the existence of trade-offs and co-benefits that may be gained from reducing both long-lived GHGs, responsible for climate change, and air pollutants, overall short-lived pollutants, responsible for adverse impacts on human health, including asthma, ecosystems and the climate.

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8 ENVIRONMENTAL RISK FACTORS FOR ASTHMA: ALLERGEN EXPOSURE

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KEY MESSAGES

- Allergen exposure causes exacerbation in patients with atopic asthma through crosslinking of mast cell/basophil surface IgE molecules and/or activation of antigen-specific Th2 cells
- Exposure to high amounts of house dust mite during infancy is a risk for sensitization and development of asthma later in life
- Some allergens can activate both acquired (IgE-mediated) and innate (epithelial-derived cytokine-mediated) immunity, which further highlights the importance of allergen avoidance
- Recent global and regional climate changes may be influencing the distribution and amounts of airborne allergens

An allergen is defined as "a harmless substance capable of triggering a response that starts in the immune system and results in an allergic reaction". In patients with atopic asthma, allergen exposure often exacerbates the asthma through crosslinking of mast cell/basophil surface IgE molecules and/or activation of antigen-specific Th2 cells. More than 900 types of allergens have been reported to date, about half of which are airborne (Table 1).

Six mite species, including *Dermatophagoides pteronyssinus* and *D. farinae*, are the major sources of allergens in house dust in many countries. More than 13 allergenic proteins are reported as mite-derived allergens; *Der f*1 and *Der p*1 originate mainly from the feces of the mites. The growth of mites is strongly dependent on the environment (optimal conditions: >25°C temperature and >75% relative humidity). Therefore, the amount of house dust mite (HDM) allergens is critically influenced by climate, season, housing type, presence/absence of carpeting, pets, plants, vacuum cleaners and others (Figure 1). A previous birth cohort study reported that exposure to *Der p*1 >2 µg/g of dust during infancy was associated with increased prevalence of sensitization to mites by age 5 years, and levels above 10 µg/g were associated with a 4.8-fold relative risk for development of asthma by age 11 years.

Several intervention trials showed that HDM avoidance improved asthma control in sensitised patients. However, such avoidance showed controversial results for primary prevention of sensitization in high-risk children. In addition, a couple of preliminary studies that tried to induce oral tolerance to HDM allergens for primary prevention of sensitization were ineffective, indicating that new approaches are needed in this regard.

Cockroaches infest homes and buildings in many countries. The major allergen of the German cockroach (*Blattella germanica*), *Bla g*1, is contained in their feces, and it causes asthma exacerbation, especially in patients living in urban areas and inner cities. A combination of integrated pest management strategies, such as dust formulations, bait and paint insecticide formulations, improve asthma control.

Mice, cats, dogs and other domestic animals are also sources of allergens for sensitized patients with atopic asthma. The dander, saliva and urine of these animals contain allergenic proteins (Table 1). Interestingly, according to several observation studies, the pres-

TABLE 1

Major allergens associated with asthma*

Origin	Species	Allergen	MW (kDa)	Main source	Function
HDM	*Dermatophagoides farinae*	*Der f* 1	27	feces	Cysteine protease
		Der f 2	15	feces	NPC2 family
	Dermatophagoides pteronyssinus	*Der p* 1	24	feces	Cysteine protease
		Der p 2	15	feces	NPC2 family
Cockroach	*Blattella germanica*	*Bla g* 1	46	feces	Lipid-associated and/or binding protein
		Bla g 2	36	feces	Inactive aspartic protease
Mouse	*Mus musculus*	*Mus m* 1	17	urine	Lipocalin/ urinary prealbumin
Cat	*Felis domesticus*	*Fel d* 1	38	dander	Uteroglobin
Dog	*Canis familiaris*	*Can f* 1	23-25	dander	Lipocalin
Fungi	*Alternaria alternata*	*Alt a* 1	16.4 and 15.3		IL-33 inducer
	Aspergillus fumigatus	*Asp f* 1	18		Mitogillin family
		Asp f 2	37		
Ragweed	*Ambrosia artemisiifolia*	*Amb a* 1	38	pollen	Pectate lyase

HDM: house dust mite; MW: molecular weight; NPC2: Niemann-Pick type C2.

** Reproduced from Jacquet A, Robinson C. Proteolytic, lipidergic and polysaccharide molecular recognition shape innate responses to house dust mite allergens. Allergy 2020;75:33-53; Do DC, Zhao Y, Gao P. Cockroach allergen exposure and risk of asthma. Allergy 2016;71:463-474; Dávila I, Domínguez-Ortega J, Navarro-Pulido A, Alonso A, Antolín-Amerigo D, González-Mancebo E, et al. Consensus document on dog and cat allergy. Allergy 2018;73:1206-1222; and Gadermaier G, Hauser M, Ferreira F. Allergens of weed pollen: an overview on recombinant and natural molecules. Methods 2014;66:55-66.*

ence of dogs in early life reduced the risk of asthma later in life.

Various fungi, including *Aspergillus fumigatus*, *Alternaria alternata* and *Penicillium* species, are well known to induce IgE-sensitization and mast cell/basophil activation, leading to asthma upon exposure. In addition, non-IgE-mediated mechanisms for airway inflammation have also been elucidated: *A. fumigatus*-specific IgG/precipitating antibodies play critical roles in the pathogenesis of allergic bronchopulmonary aspergillosis. Similarly, *Alternaria* is known to induce IL-33-mediated severe asthma exacerbation.

Some pollens, such as those from ragweed (*Ambrosia artemisiifolia*), are well-known to sensitize and often cause asthma with severe rhinitis. Interestingly, however, some other pollens, such as those from Bermuda grass (*Cynodon dactylon*) and Japanese cedar (*Cryptomeria japonica*), also sensitize and frequently cause rhinoconjunctivitis, but rarely cause asthma.

The primary mechanism of involvement of allergen exposure in the pathogenesis of asthma is sensitization to the allergens followed by IgE-driven eosinophilic inflammation. Many of the indoor allergens, such as *Der f*1, *Der p*1 and *A. alternata*, have protease activity. Protease activity itself induces allergic airway inflammation in mice through epithelial-derived cytokine IL-33, independent of acquired immunity via T cells and IgE antibodies. In addition, such epithelial-derived cytokines as IL-33 and thymic stromal lymphopoietin can prime antigen-presenting cells to induce T-cell development towards Th2. Allergen proteases reportedly induce bronchial epithelial barrier dysfunction by degrading tight junction proteins and intercellular adhesion molecules such as zona occludens (ZO)-1 and E-cadherin. Accumulating evidence suggests that the pathogenesis of asthma is not limited to IgE-mediated mechanisms (acquired immunity), but also involves activation/damage of bronchial epithelial cells, leading to release of epithelial-derived cytokines and activation of innate lymphoid cells that then release type 2 cytokines (innate immunity). Some allergens can activate both acquired and innate immunity, which further highlights the importance of allergen avoidance.

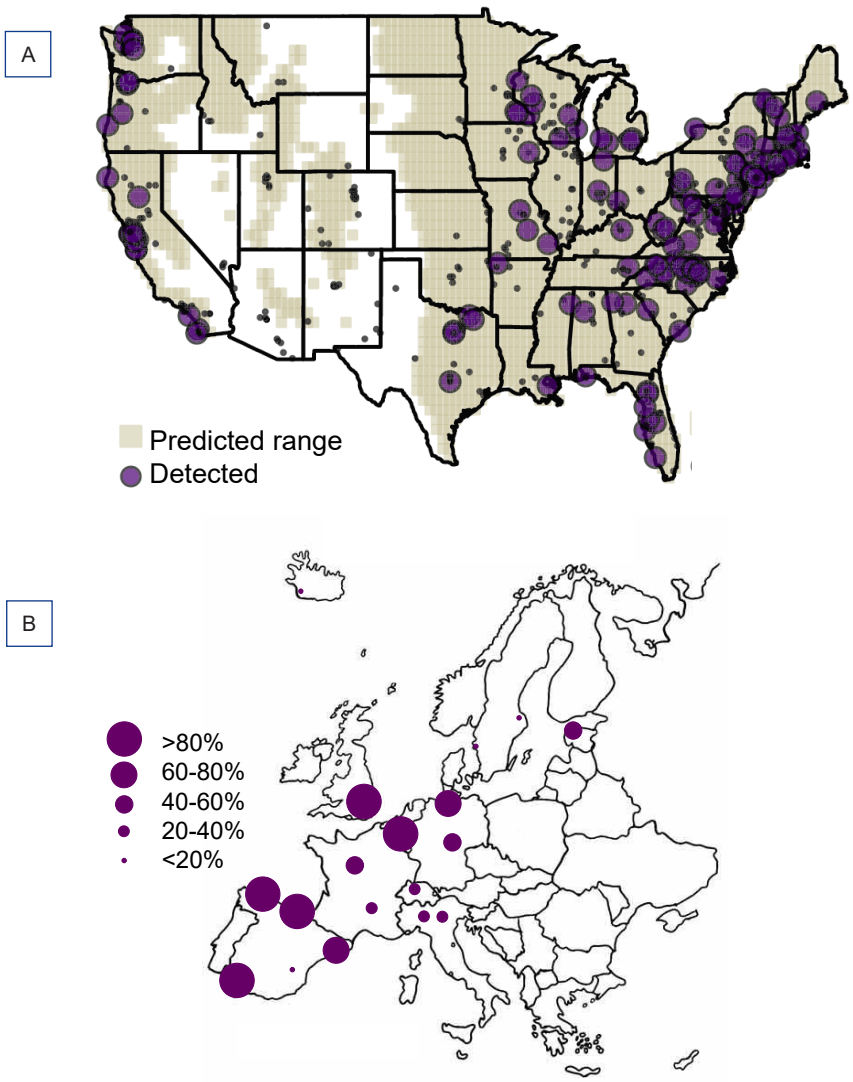

Figure 1 **A. Distributions of house dust mite (Dermatophagoides spp.) range vs. detected range. B. Detection rates of house dust mite antigen (Der p1 > 0.1 µg/g dust) in different cities in Europe.**

(Reproduced from Mol Ecol, Vol 25, Madden AA et al., The diversity of arthropods in homes across the United States as determined by environmental DNA analyses, 6214.6224, 2016 with permission of John Wiley and Sons, and from J Allergy Clin Immunol, Vol 118, Zock JP et al., Distribution and determinants of house dust mite allergens in Europe: the European Community Respiratory Health Survey II, 682-690, 2006 with permission from Elsevier)

Finally, global and regional climate changes that may be influencing the distribution and amounts of airborne allergens and thus may facilitate/exacerbate allergic diseases worldwide.

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9 ENVIRONMENTAL RISK FACTORS FOR ASTHMA: OCCUPATIONAL EXPOSURE

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KEY MESSAGES

- A large number of substances can cause occupational asthma (OA), either high-molecular-weight glycoproteins from vegetal and animal origins or low-molecular-weight agents (i.e., reactive chemicals, metals, and wood dusts)
- OA results from complex interactions between environmental factors and individual susceptibility
- Complete avoidance of exposure to the causal agent remains the optimal treatment, but full recovery is reached in only a minority
- A longer duration of the disease and more severe asthma at the time of diagnosis are associated with a worse outcome, emphasizing the importance of an early and accurate diagnosis
- Preventive strategies should focus on the control of workplace exposures and early identification of the disease

Workplace exposures can induce to the development of asthma either through immunological sensitization to a specific substance encountered at work, which is termed "sensitizer-induced OA" (OA) or through high-level exposure(s) to an inhaled irritant, which is termed irritant-induced OA (IIA).

A large number of substances can cause OA (Table 1), either high-molecular-weight (HMW) (glyco) proteins from vegetal and animal origins or low-molecular-weight (LMW) agents (i.e., reactive chemicals, metals, and wood dusts). HMW proteins and a few LMW agents (e.g., acid anhydrides, platinum salts) induce asthma through the production of specific IgE antibodies. The immunological mechanisms underlying the effects of most LMW agents have not yet been fully characterized.

Similar to non-occupational asthma OA results from complex interactions between environmental factors and individual susceptibility. The physico-chemical properties of inhaled substances, their concentration, and the duration of exposure, as well as the conditions under which this exposure occurs, are relevant factors in the induction of respiratory sensitization (Table 2). Nevertheless, the duration of exposure does not seem to be such a critical factor, as only 40% of patients with OA develop symptoms in the first two years of exposure. In the remaining, the symptoms of OA appear after ten years of exposure . Atopy is the most significant predisposing factor, but only in workers exposed to HMW agents, though it is a weak predictor of the development of OA. For LMW agents, a quantitative structure-activity relationship (QSAR) model has been developed to predict chemical asthma hazard.

Complete avoidance of exposure to the causal agent remains the optimal treatment, but full recovery is reached in only a minority (~30%) of affected subjects. A longer duration of the disease and more severe asthma at the time of diagnosis are associated with a worse outcome, emphasizing the importance of an early and accurate diagnosis. Preventive strategies aimed in reducing the development of immunological sensitization to occupational agents and subsequent OA should focus on the control of workplace exposures and early identification of the disease.

Different clinical phenotypes can be distinguished within the spec-

TABLE 1

Main agents causing occupational asthma		
Agent		**Occupation/industry**
High-molecular weight agents		
Plants	Cereal flour (wheat, rye, barley, buckwheat)	Flour mills, bakers, pastry makers
	Pollen (tomato, bell pepper, broccoli, saffron)	Greenhouse workers
	Ornamental plants	Horticulture, floral workers
	Spices (aniseed, cinnamon, coriander, fennel, nutmeg), beans, seeds (coffee, soybean, linseed, lupine), leaves (tea, chamomile)	Food industry, tea and herbal tea processors
	Natural rubber latex from Hevea tree	Health and dental care workers, laboratory technicians
Animals	Mammals (mice, rats, cows)	Laboratory workers, farmers
	Seafoods (fish, crustaceans, molluscs)	Seafood processers
	Insects (flies, locusts, worms, spiders, predatory mites, parasitoidal wasps, nematodes)	Laboratory workers, fish food producers, fruit growers, biological pest control in greenhouses
	Animal-derived products: - Milk/egg proteins, bovine serum albumin - Carmine from *Dactolylopius coccus*	Food processors, bakers Natural dye producers
Enzymes	Alpha-amylase, maxatase, alcalase, papain, bromelain, pancreatin	Baking product production, bakers, detergent production, pharmaceutical industry, food industry
Low-molecular weight agents		
Isocyanates	Toluene diisocyanate (TDI), methylene diphenyl-diisocyanate (MDI), hexamethylene diisocyanate (HDI)	Polyurethane production, plastic industry, insulation, molding, spray painting
Acid anhydrides	Phthalic, trimellitic, maleic, tetrachlorophthalic anhydrides	Epoxy resin workers
Acrylates	Cyanoacrylates, methacrylates, plain acrylates	Adhesives, dental and orthopedic materials, sculptured fingernails, printing inks, paints and coatings
Amines	Polyamine epoxy resin hardeners	Construction coatings, adhesives, plastic composites manufacturing, pipe relining
Biocides	Formaldehyde, glutaraldehyde, quaternary ammonium compounds, chlorhexidine, triclosan	Health-care workers, cleaners, food industry
Metals	Chromium, nickel, cobalt, platinum	Metal refinery, metal alloy production, electroplating, welding
Persulfate salts	Hair bleach	Hairdressers
Metal working fluids	Uncertain causal agent(s): biocides (benzisotiazoline-3 isothiazolinone, methylene-bismorpholine), microorganisms, metals	Metal cutting and grinding
Woods	Red cedar, iroko, obeche, oak, and others	Sawmill workers, carpenters, cabinet and furniture makers

TABLE 2

Potential risk factors for the development of occupational asthma

Risk factor	Evidence	Agents/settings
Environmental:		
High level of exposure	Strong	HMW agents: flour, enzymes, laboratory animals
	Moderate	LMW agents: Platinum salts, acid anhydrides, isocyanates
Cigarette smoking	Moderate	IgE sensitization: Laboratory animals, snow crab, prawn, salmon, psyllium, green coffee, enzymes, acid anhydrides, platinum, reactive dyes
	Weak	Clinical OA: Laboratory animals, enzymes
Skin exposure	Weak	Isocyanates
Host-related:		
Atopy	Strong	HMW agents
	Weak	LMW agents: Platinum, acid anhydrides
Work-related rhinitis	Strong	Laboratory animals
Pre-existing NSBH	Moderate	HMW agents (laboratory animals, flour, latex)
Genetic markers:		
HLA class II alleles	Moderate	LMW agents: Isocyanates, red cedar, acid anhydrides, platinum salts HMW agents: Laboratory animals, latex
Anti-oxidant enzymes SNPs*	Moderate	Isocyanates
Alpha-T catenin SNPs	Moderate	Isocyanates
TLR4 SNPs	Weak	Laboratory animals
IL-4 receptor α and IL-13 SNPs	Weak	Isocyanates
TNFα, TGFB1, PTGS1 and PTGS2 SNPs	Weak	Isocyanates
Gender (female)	Weak	Snow crab processors

HMW: high-molecular-weight; IL: interleukin; LMW: low-molecular-weight; NSBH: non-specific bronchial hyperresponsiveness; OA: occupational asthma; SNPs: single nucleotide polymorphisms; TLR4: Toll-like receptor-4; TNFα: tumor necrosis factor-α; TGFB: transforming growth factor-β; PTGS: prostaglandin-endoperoxide synthase.

**glutathione-S-transferase and N-acetyltransferase*

trum of IIA: 1) acute-onset IIA (i.e., "Reactive Airways Dysfunction Syndrome" - RADS), characterized by the rapid onset of symptoms within hours of a single exposure to a very high level of almost any irritant substance (i.e., "puffs" or "gassings"); 2) asthma that develops in workers with a history of repeated symptomatic high-level exposures to irritants; and 3) asthma occurring with a delayed onset after chronic exposure to moderate levels of irritants. The risk of developing this IIA depends on the degree and intensity of exposure to toxic irritants. Treatment with inhaled corticosteroids early after the accidental exposure is beneficial, but the duration and dose are still uncertain. The clinical and functional outcomes of acute-onset IIA seems to be similar to those described in subjects with OA after cessation of exposure to the sensitizing agent.

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10 LIFE STYLE RISK AND PROTECTIVE FACTORS FOR ASTHMA

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KEY MESSAGES

- The occurrence of asthma is strongly influenced by environmental factors
- Exposure early in life to a cocktail of microbes from the environment can explain some of the protective effect on asthma and atopy
- Significant risk factors for asthma are active and passive smoking, pollution, indoor moulds and dampness, weight gain or obesity
- Nutrition may also be a source of risk or protective factors

The occurrence of asthma is strongly influenced by environmental factors. Populations with very similar genetic background differ in the prevalence of asthma depending on the area of residence. For example, childhood asthma is almost non-existing in rural areas in China, whereas in regions approximately 200 km away, in the capital of Bejing, the prevalence rose up to 5 percent. Such strong protection is also seen in Karelia which has been divided by the Iron Curtain after World War II into a Finnish and a Russian part. On the Russian side life style has been maintained as in former times, whereas people on the Finnish side have adopted a more westernized lifestyle. The prevalence of asthma in Russian Karelia is very low. In comparison asthma rates in Finnish Karelia are about 5.5 times higher (Figure 1). In the Alpine regions protection is seen within rural areas, i.e. among children being raised on traditional dairy farms as compared to their peers living in the same village but not living on a farm (Figure 2). Both, in the Karelian studies and the farm studies microbial exposures in the environment explain some of this protective effect on asthma and atopy. The protection is not mediated by just one particularly potent protective microbe, but by a cocktail of microbial exposures, which in turn shapes the child's microbiome. (Figure 3) It seems important that children get exposed early in life as this is the time when immune responses and lung tissues mature.

In turn, maternal and postnatal use of antibiotics and antipyretics may increase asthma risk, but reverse causation may bias some studies. Asthmatics are more likely to use antibiotics and antipyretics because of their disease rather than these drugs causing the onset of disease. There is no indication that vaccinations increase asthma risk.

There are other significant risk factors for asthma. The most important is active smoking, particularly by the mother exposing her unborn child in utero or of adolescents and young adults. Not only does the risk of asthma increase, but also remission which occurs in a significant proportion of adolescent asthmatics is jeopardized by taking up active smoking. Passive smoking also increases the asthma risk. The introduction of the smoking ban in Scotland has resulted in significantly reduced rates of asthma admissions to hospitals supporting such public health measures (Figure 4). Pollution by car and truck traffic exhausts has furthermore been implicated as risk factor, particularly for children living 100 – 500 m away from busy motorways. Indoor moulds and dampness have consistently been

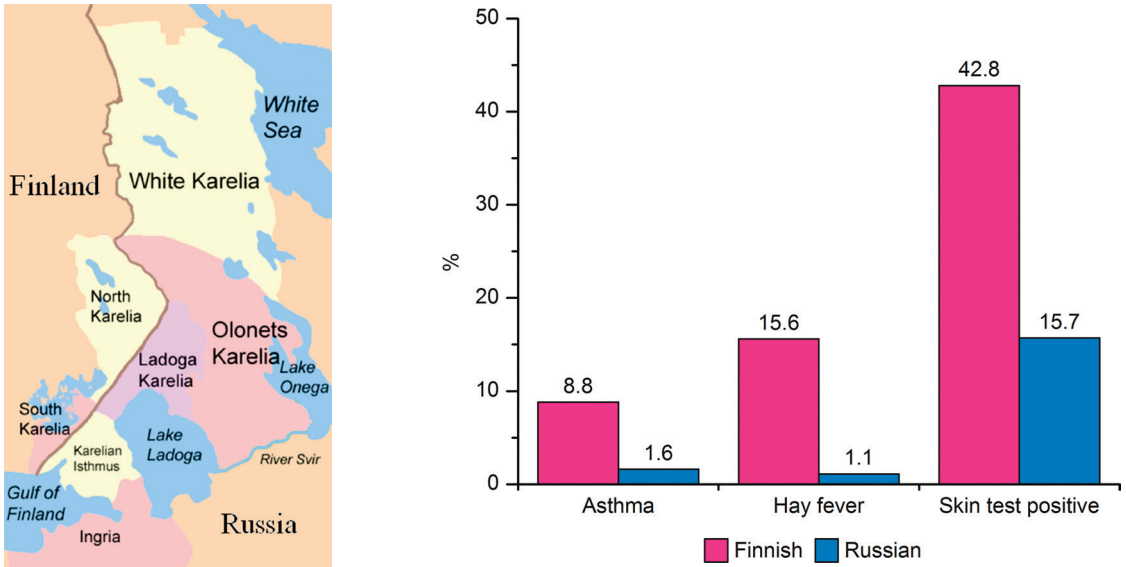

Figure 1 **Prevalence of asthma and atopy in Karelian children.**
(Data from von Hertzen L, Mäkelä MJ, Petäys T, et al. Growing disparities in atopy between the Finns and the Russians: a comparison of 2 generations. J Allergy Clin Immunol. 2006;117:151-157.)

Figure 2 **Protective environment in a traditional farm.**

shown to increase asthma risk but the responsible exposures remain unknown.

Lifestyle factors are furthermore important. Weight gain and obesity have been related to asthma like symptoms and weight loss has been shown to improve symptoms among asthmatic patients. Therefore, nutrition may also be a source of risk factors, but data collected so far have not identified certain foods as particularly asthmagenic.

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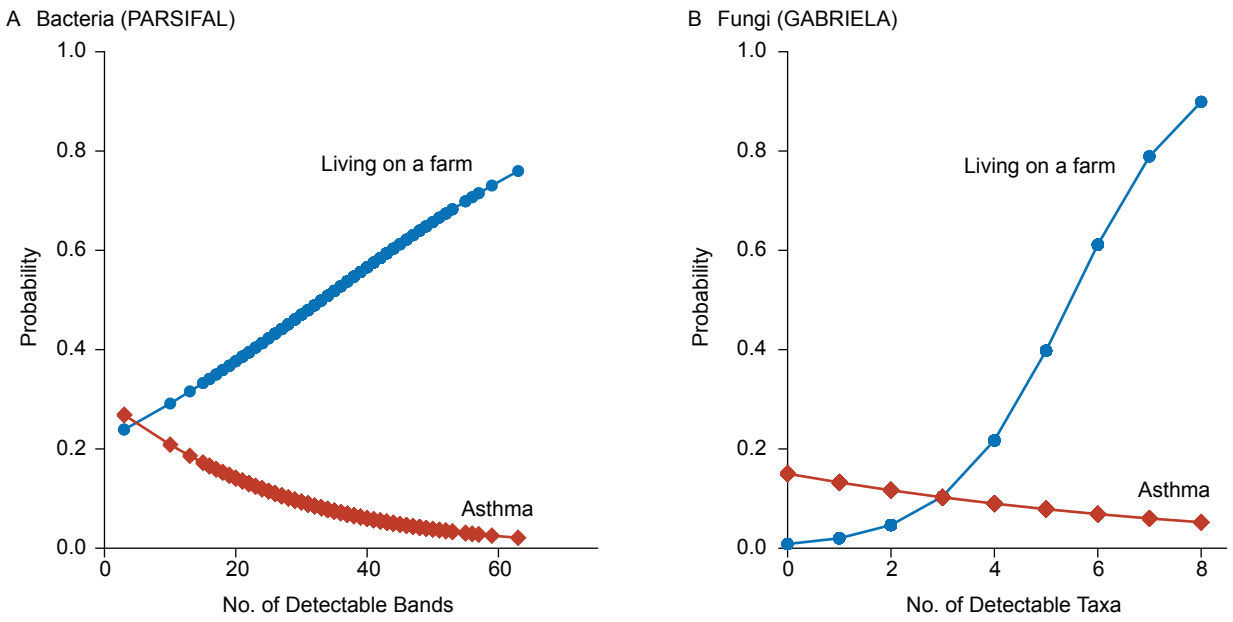

Figure 3 **The diversity of microbial exposure is inversely related to asthma.**
(From N Engl J Med, Ege MJ, Mayer M, Normand, et al. Exposure to environmental microorganisms and childhood asthma, 364, 701-709 Copyright © 2011 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.)

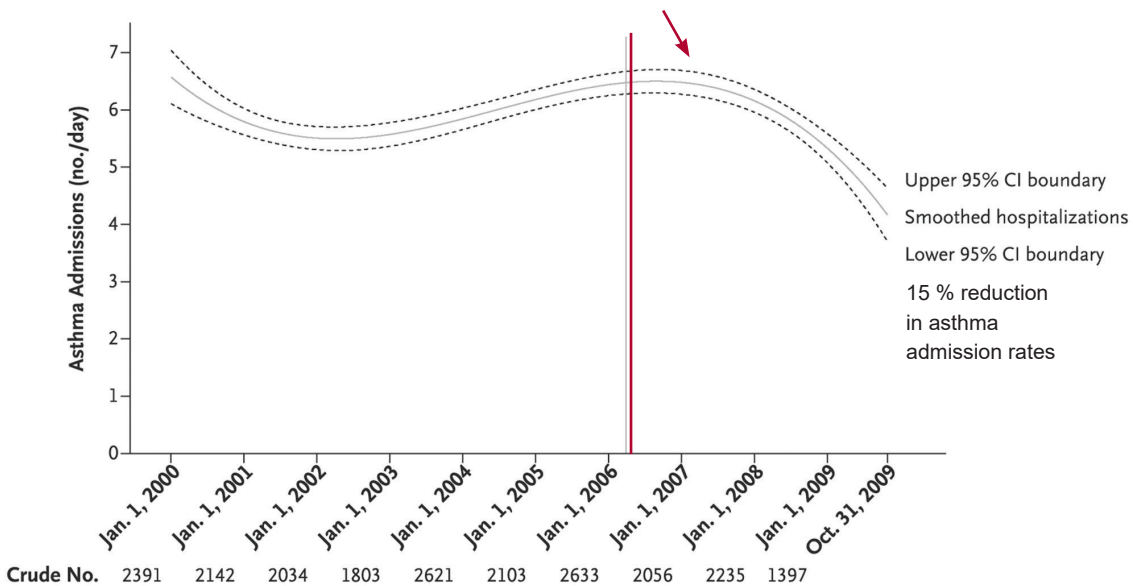

Figure 4 **Decreased hospital admission for asthma after tobacco smoke ban in Scotland.**
(From N Engl J Med, Mackay D, Haw S, Ayres JG, et al. Smoke-free legislation and hospitalizations for childhood asthma, 363, 1139-1145 Copyright © 2010 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.)

11a RISK FACTORS FOR ASTHMA: RHINOVIRUSES

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KEY MESSAGES

- Rhinoviruses (RVs) are the most frequent virus associated with both initiation and exacerbation of asthma
- The immune response against RV in atopic individuals is defective with reduced IFN and increased IL4 production, resembling an 'allergic' response
- A vaccine against RVs could decrease both the pediatric asthma prevalence and the frequency of asthma exacerbations, both in children and in adults

Rhinoviruses (RVs) are the most common human infectious agent. They are responsible for the large majority of upper respiratory infections, even during the first years of life. At the preschool age group, recurrent wheezing is usually not diagnosed as asthma, mostly because a large proportion of children who wheeze at that age will not develop persistent disease. Nevertheless, among children with asthma, the large majority presents their first episode during that time. In several studies, infection with RV, rather than syncytial respiratory virus (RSV), has been shown to be strongly associated with asthma persistence. In the COAST trial, a symptomatic infection with RV during the first year of life was associated with a highly increased risk for wheeze persistence at the age of 3 years.

However, the strongest evidence in regards to the risk of RVs in asthma comes from studies of acute asthma exacerbations. The epidemiological association between a common cold, induced by RV in more than 50% of cases, and the development of an acute asthma exacerbation has been shown more than 30 years ago (Table 1). RVs can reach the lower respiratory tract, infect the bronchial epithelium, replicate locally and induce local inflammation. In asthma patients the bronchial epithelium appears to be often, although not always, deficient in production of type-1 and type-3 interferons (IFN), allowing high virus replication, slower clearance and increased virus-induced cytotoxicity. The immune response against RV in atopic individuals is defective with reduced IFN and increased IL4 production, resembling an 'allergic' response. At the same time the epithelium produces cytokines such as IL25 and IL33, capable of activating type-2 immunity. Following RV epithelial infection growth factors such as TGF-beta, FGF-2 and VEGF are upregulated, promoting airway remodeling. This physiological response is augmented in an atopic environment. Thus, increased susceptibility to RV infection and a cumulative effect of these on airway pathophysiology may explain why repeated infections during early childhood promote the development of persistent asthma (Figure 1).

While RV is the most frequent virus associated with both initiation and exacerbation of asthma, it has not been clear if this was because of their frequency in relation to upper respiratory infections or it is due to specific properties that could make them more predisposed to asthma. In children of any age hospitalized for flu-like illness, RV infection was associated with wheeze (independent of a previous asthma diagnosis), in contrast to influenza infection. In asthmat-

TABLE 1

Prevalence of respiratory viruses in asthma exacerbations in children across the continents (average(range))*

	Europe	Americas	Australasia
Rhinovirus	40 (17-82)	57 (26-77)	42 (33-78)
RSV	12 (1.5-61)	40 (8-68)	16 (7.5-17)
Influenza	3 (0-7)	10 (0-20)	6.5 (1-12)
Corona	2.5 (0-13)	1.5 (0-3)	2 (1.5-2)
Parainfluenza	4 (0-7)	4 (2-6)	8 (7.5-8)

**data from Papadopoulos NG, Christodoulou I, Rohde G, et al. Viruses and bacteria in acute asthma exacerbations – A GA2LEN-DARE systematic review. Allergy 2011;66:458-468*

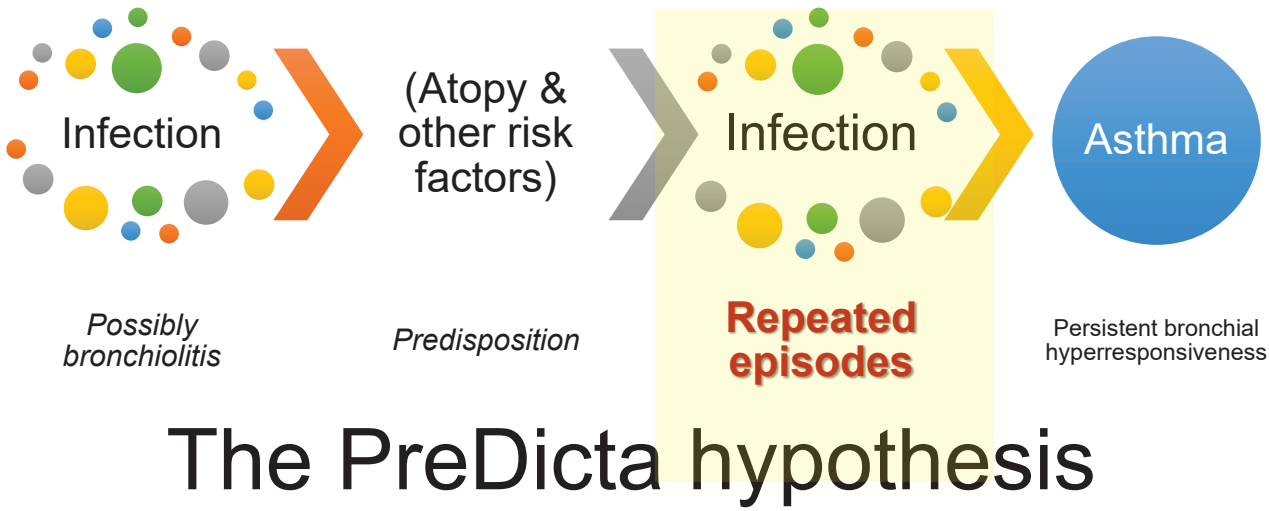

Figure 1 **The PreDicta hypothesis states that following the trigger of a single event, repeated infections on a background of increased susceptibility may condition the immune system towards a continuous hyperreactivity.**

ics, influenza-associated disease was different from a RV-induced exacerbation, suggesting a different pathophysiological background, coined as 'asthma-augmented influenza' (Figure 2).

RVs are key pathogens driving not only symptoms of acute asthma, but also at least part of the disease initiation and persistence. RV infection is particularly asthmagenic and should be targeted specifically, ideally with a vaccine. However, the design of such a vaccine needs to consider the pronounced evolutionary capacity of the RV for immune evasion.

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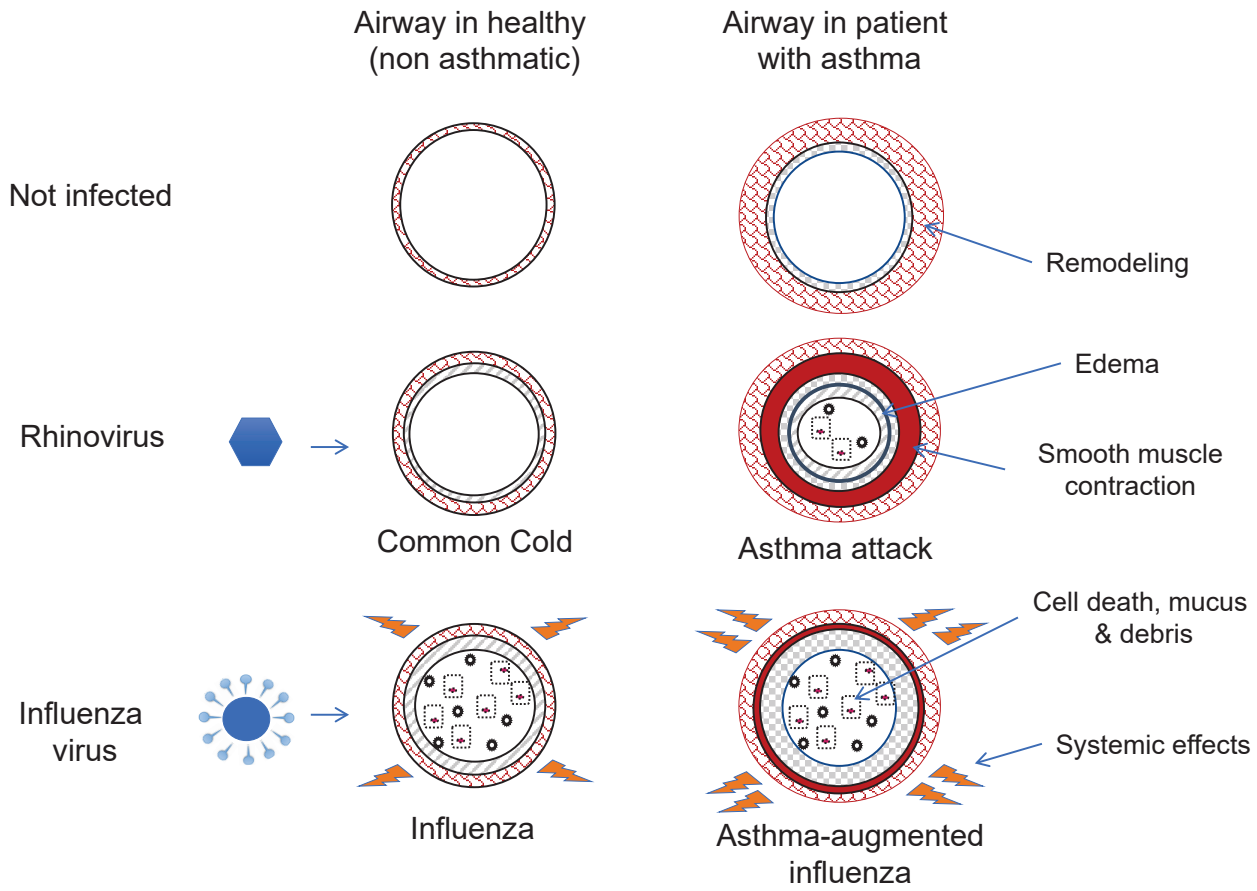

Figure 2 **Distinction between RV-induced asthma exacerbation and asthma-augmented influenza: rhinovirus infection is capable of triggering type-2 inflammation and typical symptoms of exacerbation in an asthmatic background, while influenza virus infection in a person with asthma results in a disease has the characteristics of influenza, of increased severity.**

11b RISK FACTORS FOR ASTHMA – RESPIRATORY SYNCYTIAL VIRUS AND OTHER VIRAL INFECTIONS

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KEY MESSAGES

- Respiratory syncytial virus (RSV) low respiratory tract infection (LRTI) in infancy, especially if severe, is strongly associated with an increased risk of recurrent wheeze of early childhood and asthma development
- RSV-LRTI and non-RSV, non-rhinovirus LRTI confer a similar risk of recurrent wheeze of early childhood and asthma development
- There is evidence of a period of susceptibility to virus induced asthma development around four months of age. An intervention preventing RSV LRTI in infancy significantly reduced recurrent wheeze, however the causal contribution of viral LRTI to asthma development, while likely remains unproven
- Individual development trajectories of the respiratory microbiome in infancy predict the frequency of LRTI and of recurrent wheeze of early childhood, raising the prospect of microbial interventions for asthma prevention
- The respiratory microbiome influences disease activity and exacerbation frequency in established asthma

ASTHMA DEVELOPMENT

Administrative "big" data, epidemiological, clinical, and mechanistic research demonstrates that viral lower respiratory tract infection (LRTI), including bronchiolitis and pneumonia, in infancy is strongly associated with the development of recurrent wheeze of early childhood (RWEC) and childhood asthma, which is known to frequently continue into adult life. Respiratory syncytial virus (RSV) accounts for about 70% of viral bronchiolitis cases. Recent systematic reviews and metanalyses demonstrate an association between RSV LRTI and RWEC, childhood asthma, reduced lung function and increased airway reactivity with a 3-fold increased risk compared to children without infant viral LRTI. Interestingly, comparisons between children with non-RSV, non-rhinovirus LRTI (e.g. due to human metapneumo virus, parainfluenza, human coronaviruses) and RSV LRTI, did not find a difference in the risk of RWEC/asthma development, suggesting that this may be linked with viral LRTI rather than RSV infection specifically.

Several studies indicate that high RSV load and severity of RSV bronchiolitis are associated with increased RWEC/ asthma risk. Potential biological factors leading to high RSV load and severe RSV LRTI include infection with a particularly virulent RSV strain, an aberrant respiratory microbiome, inadequate antiviral immune and excessive inflammatory responses to RSV, environmental exposure (e.g. air pollution, smoke exposure) and reduced lung function. Potentially, these factors also confer an increased RWEC/asthma risk independently of RSV LRTI.

While still a topic of debate, some observations suggest that RSV and/or other respiratory viruses make a causal contribution to asthma development. An insurance data study from the US found the highest risk of asthma at 5 years of age in children who were 4 months old before the peak winter virus season, the age of highest risk for severe RSV bronchiolitis.

This suggests a period of particular susceptibility for virus-induced RWEC/asthma development. Furthermore, a randomised placebo controlled trial (RCT) of RSV prophylaxis with palivizumab, an anti-RSV antibody, for late premature infants demonstrated reduction in wheezing days (by 73%) and RWEC (by 46%) during 10 months of follow-up after the intervention. When this study cohort was reassessed at 6 years of age parents reported a 41% reduction in wheeze/ use of asthma medication in those children who had received RSV prophylaxis, however without any difference in doctor diagnosed asthma, lung function or FeNo levels.

Future studies of quasi-random RSV exposure, adequately powered RCTs and post-introduction studies (cluster randomised trials) of novel RSV prophylaxis or vaccination and mechanistic studies are needed to determine if RSV (and non-RSV) LRTI make a causal contribution to RWEC/asthma development.

ASTHMA EXACERBATIONS

Most acute asthma exacerbations (AAEs) are triggered by respiratory viral infections, mostly by rhino viruses and in allergic asthma, AAEs are most severe if viral infection and allergen exposure coincide. Other respiratory viruses including enteroviruses, RSV, human metapneumoviruses (hMPV), human corona viruses (hCoV), parainfluenza viruses and influenza virus are also associated with AAEs and importantly influenza vaccination, which is effective in people with asthma, can contribute to a reduction in AAEs.

THE RESPIRATORY MICROBIOME IN VIRUS INDUCED ASTHMA DEVELOPMENT AND EXACERBATIONS.

Bacterial culture studies have implicated the neonatal carriage of pathobionts, including *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moxarella catarrhalis*, in the development of childhood asthma. More recently, next generation sequencing has enabled increasing insight into the respiratory microbiome in early childhood and its role in viral LRTIs and asthma development. Breast feeding-associated respiratory microbiome profiles dominated by *Dolosigranulum* and *Corynebacterium* are stable and confer a reduced risk of LRTI and RWEC, whereas less stable profiles dominated by *Haemophilus*, *Streptococcus* or initially by *Moraxella* followed by *Neisseria* and *Prevotella* are less stable and associate with higher numbers of LRTIs (Figure 1). Pathobionts may interact with respiratory viruses in promoting RWEC and asthma development: *Haemophilus*-dominance of the respiratory microbiome has been associated with more severe RSV-LRTI with delayed viral clearance and a heightened CXCL8 (IL-8) inflammatory response.

In established asthma, airway carriage of *H. influenzae* and S. *pneumoniae* is more frequent than in health and commensal bacteria of the *Phylum bacteroidetes* are lacking. The abundance of other airway commensals (*Comamonadaceae*, *phingomonadaceae,Oxalobacteraceae*) correlates with the degree of bronchial hyperresponsiveness, a marker of disease severity.

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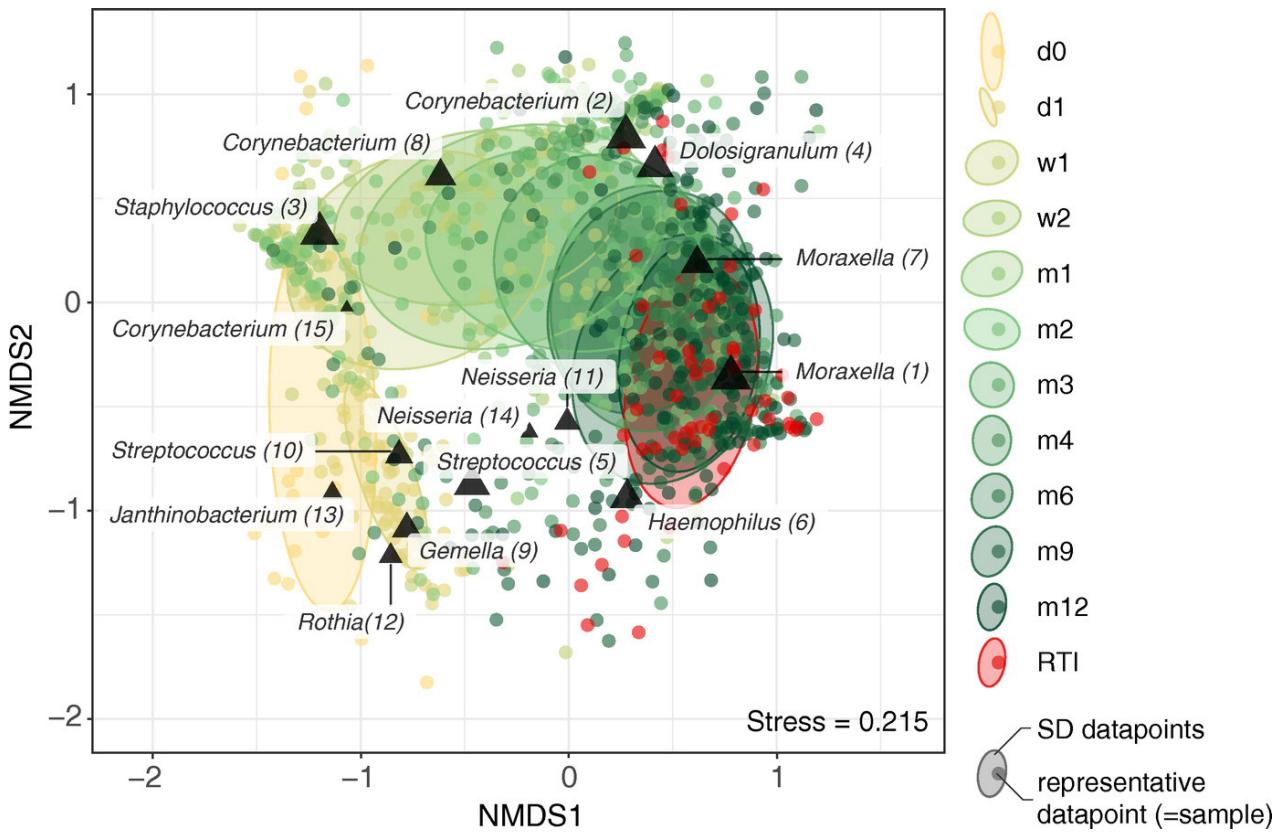

Figure 1 **Nonmetric multidimensional scaling (NMDS) plot visualizing the microbiota succession patterns in the first year of life.** Each point represents the microbial community composition of one sample.
(Reproduced from the American Journal of Respiratory and Critical Medicine (official journal of the American Thoracic Society), Maturation of the Infant Respiratory Microbiota, Environmental Drivers, and Health Consequences. A Prospective Cohort Study, Bosch AATM et al., Volume 196, 1582-1590, 2017 with permission of the American Thoracic Society. Copyright © 2020 American Thoracic Society. All rights reserved.)

11c

INFECTIONS AND ASTHMA- BACTERIA

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KEY MESSAGES

- Airway bacteria are important determinants of asthma inception and exacerbations
- The airway microbiome evolves in early life and usually comprises of limited number of dominant bacterial clusters
- The early life airway microbiome composition is dynamic: changes in bacterial respiratory clusters may precede respiratory infections and may predict future wheezing episodes
- Interactions between airway bacteria and other factors such as respiratory viruses, the gut microbiome, and the immune system are important drivers of asthma pathogenesis
- The airway microbiome is a potential target for future primary, secondary and tertiary asthma prevention strategies

It has been known for many years that respiratory viruses are important determinants of asthma inception and exacerbations. However, emerging data from the past decade have also highlighted the role of airway bacteria in these processes.

BACTERIA AND ASTHMA INCEPTION

A pioneering report, published more than a decade ago, revealed that asymptomatic 1-month-old infants who had upper airway colonization with *Streptococcus pneumoniae*, *Moraxella catarrhalis*, and/or *Haemophilus influenzae* had higher odds for future asthma. Immune cells taken from these children, who eventually developed asthma, produced increased levels of type 2 (T2) cytokines. Hence, it was suggested that aberrant immune response predisposes to airway bacterial colonization, which may lead to T2 airway inflammation and asthma.

A more recent study revealed that the airway microbiome is shaped during the first years of life and is dominated by limited number of genera. These respiratory clusters differ between periods of respiratory health (dominance of *Staphylococcus*, *Corynebacterium*, and *Alloiococcus* dominance; viewed as commensal bacteria) and acute respiratory illnesses (dominance of *Streptococcus*, *Moraxella*, and *Haemophilus* dominance; viewed as pathogenic bacteria (Figure 1). The airway microbiome composition is dynamic with changes into pathogenic bacteria clusters preceding respiratory infections and predicting future wheezing episodes. Early life sensitisation to aeroallergens, in combination with airway microbiome dysbiosis, predicted development of the persistent wheeze phenotype; while the dysbiosis, but without allergic sensitization, predicted development of the transient wheeze phenotype. These associations highlight the importance of bacteria and immune system interactions in asthma inception.

VIRAL AND BACTERIAL INTERACTIONS

The interactions between airway bacteria and viruses are important in asthma inception. This concept may be illustrated by the development of recurrent wheezing and asthma following severe respiratory syncitial virus (RSV) bronchiolitis. Although this is a common sequel, not all children with severe RSV bronchiolitis develop these

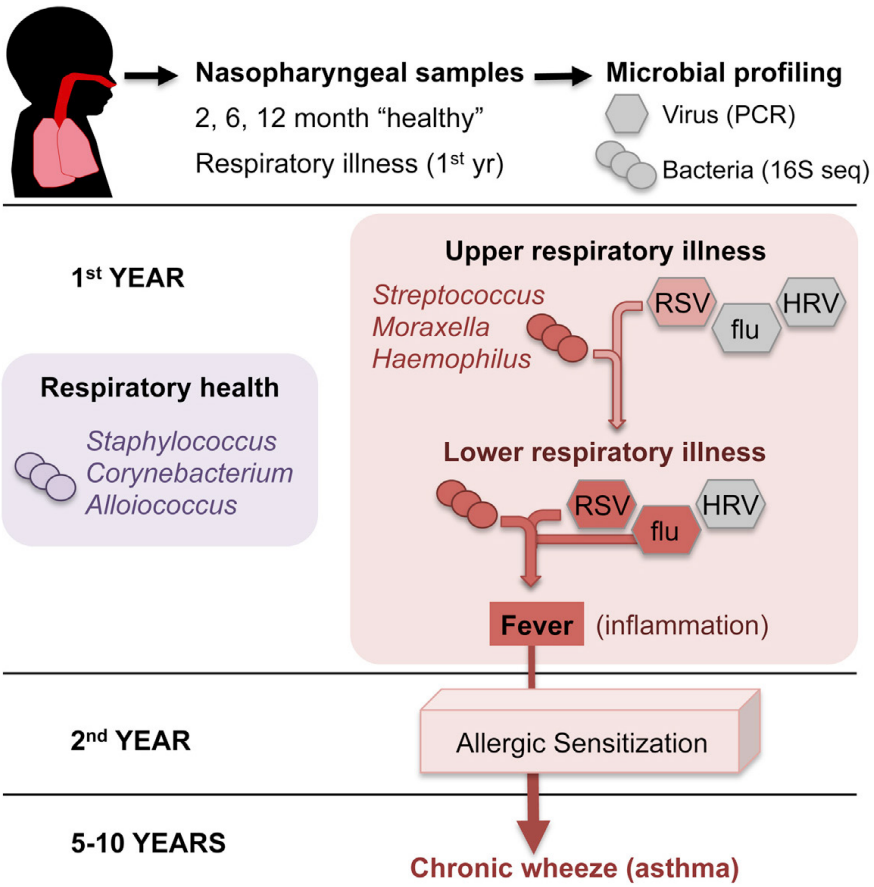

Figure 1 **The airway microbiome is shaped during the first years of life.**
(Reproduced from Teo SM, Mok D, Pham K, et al. The infant nasopharyngeal microbiome impacts severity of lower respiratory infection and risk of asthma development. Cell Host Microbe. 2015;17:704-15)

outcomes; hence it may be that the composition of airway microbiome during the RSV infection contributes to the development of post-RSV recurrent wheezing. Indeed, high abundance of airway *Moraxella* or *Haemophilus* was found to be related to the development of post-RSV wheeze. Furthermore, a small proof-of-concept study (Table 1) revealed that azithromycin therapy during the acute RSV infection, reduced airway *Moraxella* abundance, which in turn was related to lower likelihood to develop post-RSV recurrent wheeze. However, some airway bacteria may be beneficial as higher abundance of airway *Lactobacillus* during RSV illness was associated with a reduced risk of future wheezing.

AIRWAY BACTERIA AND ASTHMA EXACERBATIONS

Although exacerbations of acute episodic wheeze in preschool children were traditionally related to viral infections, dominance of airway bacteria was noted during many of these episodes. Furthermore, two clinical trials in this age group, have shown beneficial effects of azithromycin therapy for the prevention and the treatment of these episodes (Table 1) suggesting a potential mechanistic role of bacteria in these exacerbations. However, it should be noted that other mechanisms (e.g., anti-inflammatory effects) may have mediated these beneficial effects.

On the other hand, some bacteria may actually promote respiratory health. A study among school-age asthmatic children revealed that children whose respiratory microbiome was dominated by the more commensal bacteria *Corynebacterium+Dolosigranulum* were less likely to experience loss of asthma control.

Finally, although airway bacteria have roles in asthma pathogenesis, their roles should be viewed in the broader context of the complex interaction between airway bacteria and the gut microbiome, which has the capacity to shape airway immune response.

TABLE 1

Clinical trials that utilized macrolides for the prevention and treatment of childhood wheezing exacerbations

Reference	Population	Aim /intervention	Outcome
Beigelman A, et al. Randomized trial to evaluate azithromycin's effects on serum and upper airway IL-8 levels and recurrent wheezing in infants with respiratory syncytial virus bronchiolitis. J Allergy Clin Immunol. 135: 1171-8	40 infants (1-18 months) hospitalized with RSV bronchiolitis	#**Secondary prevention**: prevention of recurrent wheeze following severe RSV bronchiolitis (a year of follow-up) # Azithromycin (10mg/kg/d for a week, following by 5 mg/kg/d for another week), or placebo for 14 days, started during the acute RSV bronchiolitis	Azithromycin compared to placebo: #Prolonged time to the third wheezing episode (P =.048) # Fewer days with respiratory symptoms over the subsequent year (36.7 vs 70.1 days, P = .01) #No significant difference in the proportion of participant who developed recurrent wheeze (22% vs. 50%; p=0.07)
Bacharier LB, et al. Early Administration of Azithromycin and Prevention of Severe Lower Respiratory Tract Illnesses in Preschool Children With a History of Such Illnesses: A Randomized Clinical Trial. JAMA. 2015; 314: 2034-2044.	607 preschool children (12- 71 months) with histories of severe episodic wheeze	# **Tertiary Prevention**: prevention of severe lower respiratory tract illnesses # Azithromycin (12 mg/kg/d for 5 days) or placebo, started early during each predefined respiratory tract illnesses	# Azithromycin significantly reduced the risk of progressing to severe lower respiratory tract illnesses (hazard ratio, 0.64 [95% CI, 0.41-0.98], P = .04)
Stokholm J, et al. Azithromycin for episodes with asthma-like symptoms in young children aged 1-3 years: a randomised, double-blind, placebo-controlled trial. Lancet Respir Med. 2016; 4:19-26.	158 preschool children (1-3 years) with histories of recurrent asthma-like symptoms	# **Treatment** of exacerbations of asthma-like symptoms #Azithromycin (10 mg/kg/d for 3 days) or placebo for each episode of asthma-like symptoms lasting at least 3 days	# Azithromycin reduced episode duration by 63% (95% CI 56.0-69/3; p<0.0001). #Earlier treatment was more effective: 83% reduction in episode duration if treatment was initiated before day 6 of the episode compared with 36% reduction if initiated on or after day 6 (p<0.0001).

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12 EMERGING RISK AND PROTECTIVE FACTORS FOR ASTHMA

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KEY MESSAGES

- The individual disease entities subsumed under the asthma syndrome are susceptible to different risk and protective factors
- Changing environments contribute to the heterogeneous pattern of risk and protective factors for asthma
- Old risk factors are replaced by new ones, e.g. environmental tobacco smoking by electronic cigarettes
- Environmental microbiota as well as the human microbiome may contribute to the development of asthma or its prevention
- Climate change enhances many risk factors such as pollen production, allergenicity, heat waves
- Prenatal inflammation is increasingly recognized as a determinant of asthma

The many faces of the asthma syndrome and their secular trends may explain why studies in different settings and populations reveal seemingly inconsistent patterns of risk and protective factors. Moreover, environmental factors vary over time with changing impact on disease manifestation.

New risk factors may replace old ones. The smoking ban in public spaces resulted in a general decrease in environmental smoke exposure and consequently less asthma exacerbations. The recently introduced electronic cigarettes, however, substitute toxic compounds by other reactive compounds with even unknown adverse effects on respiratory health.

Beyond maternal smoking during pregnancy, preconceptional effects of smoke exposure are increasingly coming into focus of research. Transgenerational effects by grandmaternal smoking through the maternal line imply extrachromosomal inheritance and epigenetic effects. Likewise, the higher risk of asthma conferred by the ever more prevalent paternal smoking before age 15 seems to be attributable to changes in extrachromosomal nucleic acids such as micro RNAs (miRNAs), which are transferred to the oocyte during conception.

Though the genetic code itself is considered rather stable with alterations only becoming relevant over generations, there is increasing evidence that its influence on disease can be modified by environmental exposures. These gene-environment interactions might mimic time-dependent phenomena also for actually invariable genetic risk factors. For example, children bearing the risk allele of the childhood onset asthma genotype encoded on chromosome 17q21 are particularly susceptible to environmental exposures as found for wheeze between 3 and 6 years and exposure to animal sheds early in life.

The asthma-protective farm exposures animal shed visits, endotoxins, and consumption of raw milk are currently being specified with respect to particular sets of microorganisms, milk ingredients such as omega-3 polyunsaturated fatty acids (enriched in milk of pasturing cows) and heat-sensitive whey proteins like lactoferrin. The rather consistent asthma-protective effect of unprocessed cow's milk seems a promising candidate for prevention (Figure 1).

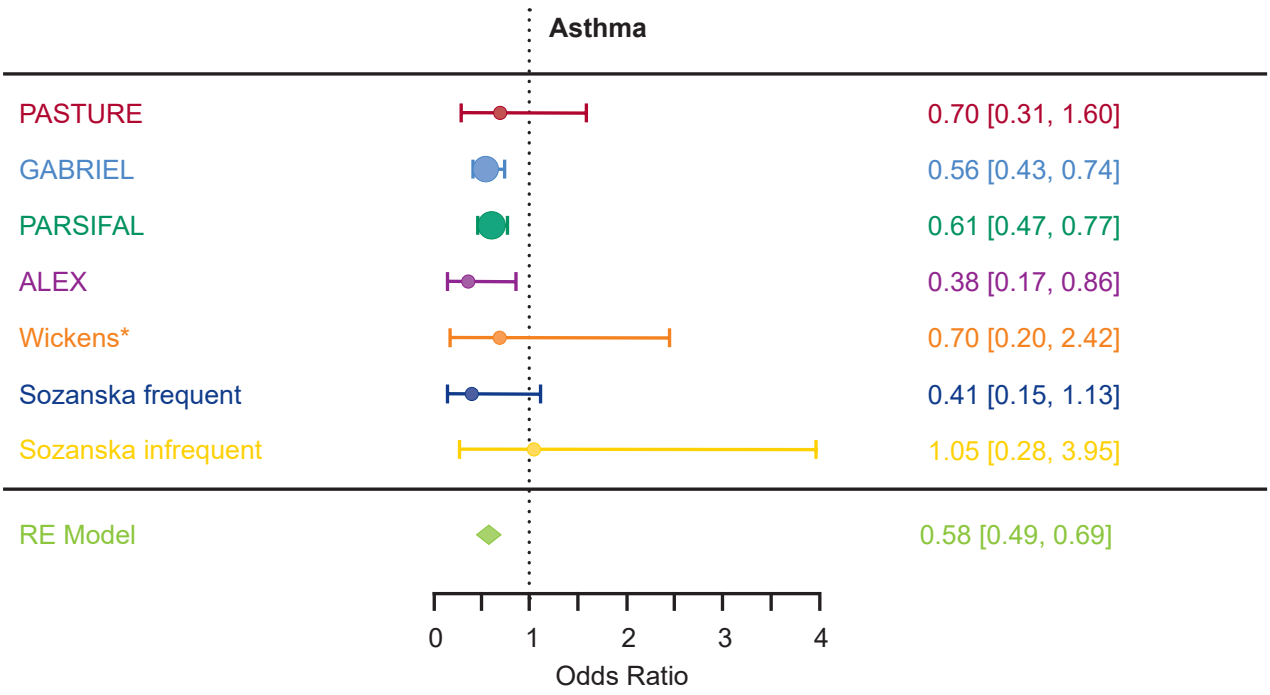

Figure 1 **The asthma-protective effect of consumption of unprocessed farm milk in the first year of life.** The random effects (RE) models considers heterogeneity among the various studies.
(Reprinted from J Allergy Clin Immunol Pract, 8/3, Brick T, Hettinga K, Kirchner B, et al, The Beneficial Effect of Farm Milk Consumption on Asthma, Allergies, and Infections: From Meta-Analysis of Evidence to Clinical Trial, 878-889, Copyright 2020, with permission from Elsevier.)

Environmental microorganisms also influence the human intestinal and lung microbiome, which may affect respiratory health by establishing balance between beneficial and adverse microbiota or, in less favorable constellations, lead to dysbiosis and disease.

Manmade changes to the environment, from spread of pesticides and antibiotics up to climate change, alter the microbiome and impact on plants, animals and directly on human health. Increase in CO2 levels fosters ragweed plant pollen production and allergenicity, whereas the increasing occurrence of thunderstorms and heat spells with high ambient ozone levels translate to more frequent asthma exacerbations.

Another global phenomenon, the current SARS-CoV-2 pandemic particularly affects individuals with airway disease. In contrast to the direct impact of the virus itself, the hygiene measures against the pandemic interfere with the spread of any respiratory infection thereby currently reducing the frequency of asthma exacerbations. Once hygiene measures will be stopped, however, a rebound effect of respiratory tract infections may occur. The anticipated resulting wave of infections may hit a population without continuous immune stimulation over months (or years?) more strongly than ever. Thus, asthma patients need special attention for early countermeasures against respiratory infections and exacerbations with excessive airway inflammation, once hygiene measures are lifted.

Chronic inflammation during pregnancy as observed in pre-eclampsia or in obesity might induce trajectories towards asthma, whereas previous pregnancies might reduce inflammation (Figure 2). Low-grade chronic inflammation may also be involved in the effect of violence and stress during pregnancy and early childhood on subsequent asthma.

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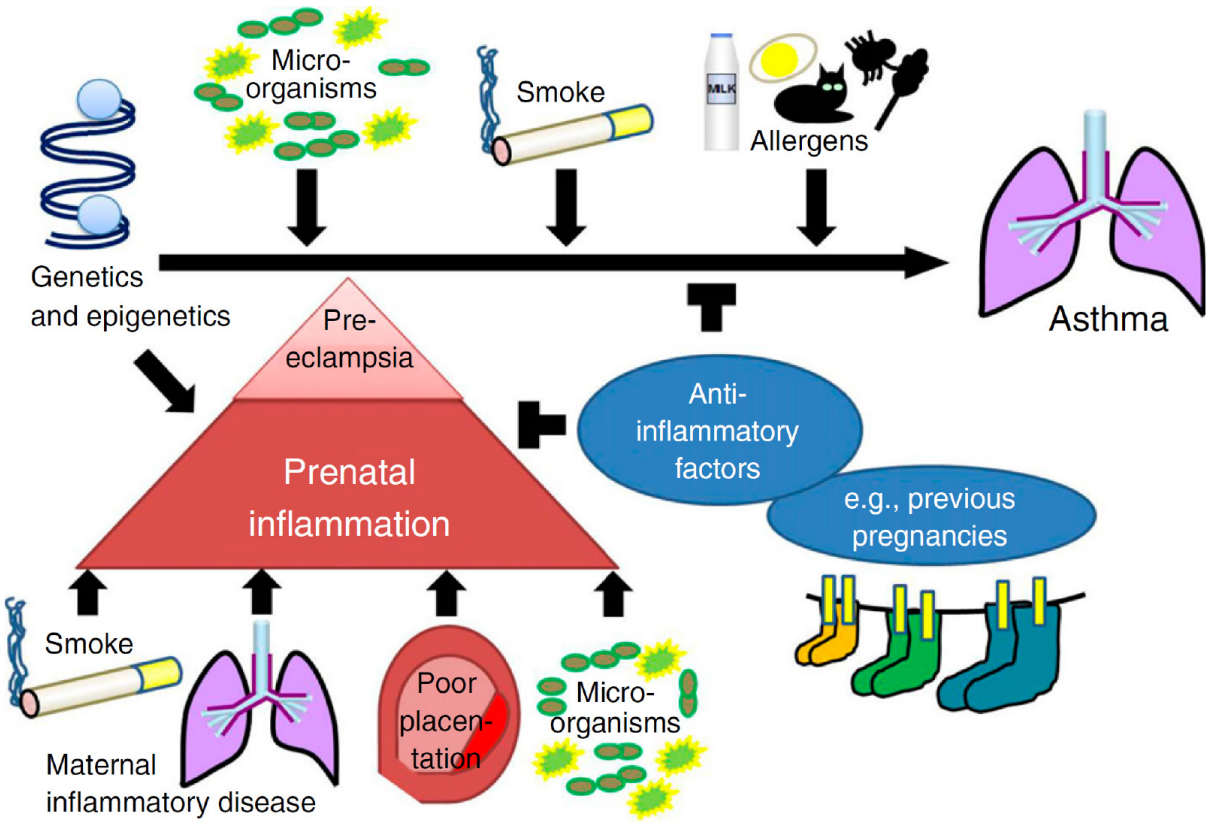

Figure 2 **Prenatal inflammation as a key risk factor of asthma.** Various risk and protective factors operate in the development of asthma before, during and after pregnancy. *(Reproduced from the American Journal of Respiratory and Critical Medicine (official journal of the American Thoracic Society), Asthma and Prenatal Inflammation, Markus Ege, Volume 195, Issue 5, 2017 with permission of the American Thoracic Society.*

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13 RECENTLY DEVELOPING HAZARDS FOR LUNG HEALTH: WILD FIRES AND ELECTRONIC NICOTINE DELIVERY SYSTEMS

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KEY MESSAGES

- Over the past few years, mankind has witnessed an outbreak of new environmental hazards, related to climate change and/or consumption habits
- Electronic nicotine delivery systems use has developed in the past decades, especially among adolescents, males, and for individuals with past/current history of conventional cigarette use. There is increasing knowledge regarding their impact on airway growth and development and on, pre-existing respiratory conditions, such as asthma
- Climate change poses increased risk to lung health. Meteorological conditions linked to asthma exacerbations include temperature extremes and heat waves, precipitation extremes (e.g. rain and thunderstorms) and droughts/dryness (e.g. more windstorms, dust storms and wildfires)

IMPACT OF THE ELECTRONIC NICOTINE DELIVERY SYSTEMS

Electronic nicotine delivery systems (ENDS), including electronic cigarettes (EC), are non-combustible tobacco products. They appeared in China and were commercialized worldwide starting in 2007, providing a potential new tool for cessation of conventional cigarette (CC) consumption. Though difficult to estimate, 1.5% of European adults in 2014 and 1.8% in 2017 reported regular ENDS consumption. Risk factors for consumption are younger age, male sex, and past/current history of CC use. Adolescents, of whom 16% reported current consumption in 2016, are more prone to start ENDS with no history of CC use, raising a concern for the development of nicotine addiction. ENDS are battery-powered handled devices, generating an aerosol of highly variable fine particles (~100 nm), by heating a solution called e-liquid. Although ENDS harm has been estimated at about 5% CC based on experts' opinions, pre-clinical and clinical data suggest higher deleterious effects, among which include cardiovascular, brain and lung damage (Figure 1). Nicotine concentration is often higher to that observed in CC, able to saturate brain receptors and induce rapid addiction. Flavoring agents, which are a major attraction for ENDS consumption, are composed of more than 7,500 compounds.

ENDS consumption has been linked with self-reported respiratory symptoms (cough), and school absenteeism in adolescents. Epidemiological studies have described an impact on asthma symptoms, risk of exacerbations and impaired lung function (Table 1). In 2019, several cases of diffuse pneumonia following consumption were described, possibly linked to lipoid inhalation, together with reports of acute respiratory distress syndrome and deaths (E-cigarette or vaping product use-associated lung injury: EVALI). These reports have raised serious concerns worldwide. ENDS consumption risks needs to be further addressed and users closely monitored in the upcoming years.

IMPACT OF CLIMATE CHANGE

Climate change is impacting the quality of respiratory health. The Intergovernmental Panel on Climate Change predicts with vary-

Component	Potential effects in the lungs
Components of the e-liquid	
Vegetable glycerin, Propylene glycol: *While heated:* Generate formaldehyde, acetaldehyde and acrolein *(temperature-dependent quantity)*	Generation of toxic carbonyl species Potent irritants Impairment of epithelial response and mucus secretion
Tobacco-specific nitrosamines	Potent carcinogens
Metal nanoparticles *Resulting from the heating of device components*	Potential carcinogenic effect, lung toxicity and autoimmune dysfunction.
Nicotine	
	In murine models: Increased susceptibility to respiratory viral infections Epigenetic alterations induced by nicotine exposure during pregnancy, alteration of signaling pathways for lung development. *Possible transgenerational effects with asthma-like disease observed up to 3rd generation.*
Flavoring agents	
Diacetyl	Acute onset bronchiolitis obliterans
Menthol	Bronchial hyperresponsiveness with acute decline of lung function
Aldehydes (Benzaldehyde)	Impaired lung function Development of asthma and exacerbations
All agents Including Acetone, siloxanes, volatile organic compounds, polycyclic aromatic hydrocarbons, etc	Generation of toxic carbonyl species

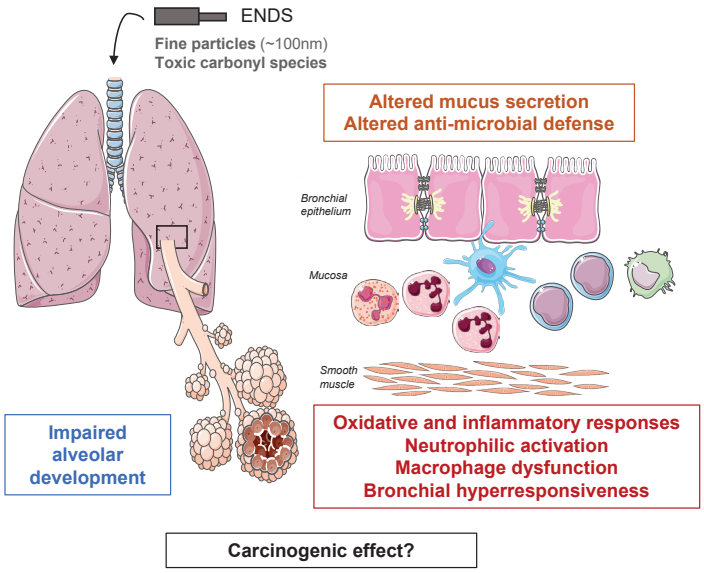

Figure 1 **Potential effects of ENDS components in the lungs.**
ENDS - Electronic nicotine delivery systems.

TABLE 1

Impact of ENDS consumption on asthma parameters

Asthma parameter	ENDS impact
Prevalence (current asthma)	• ENDS consumption associated with more frequent reports of current asthma among adolescents and adults • Graded increased odds of having asthma with increase of ENDS use intensity • Increased perception of ENDS being "harmless products" in asthma patients
Asthma symptoms	• Coughing and symptoms of asthma are among the most-frequent reported symptoms following ENDS use in an analysis of more than 40,000 online forum posts • School absenteeism associated with current ENDS use in high school students
Asthma attacks	• Self-reported asthma attacks in the previous year more frequent among ENDS users and adolescents with second-hand exposure • Case reports of *status asthmaticus* in asthmatic adolescent patients consuming ENDS
Lung function	• *Mouse models:* Decreased functional residual capacity and increased trans-respiratory pressures in mice exposed to ENDS aerosol, hyperresponsiveness to methacholine in mice exposed to glycerin-based ENDS aerosols • No impact of nicotine- and flavor-free ENDS aerosols (70% Propylene glycol, 30% Vegetable glycerin) inhalation on lung function parameters in healthy and asthmatic volunteers • Immediately after ENDS exposure: significant increase of respiratory system resistances (impulse oscillometry system measurements) in healthy and asthmatic volunteers, more pronounced in asthma patients, and decrease of FeNO levels compared to baseline

ENDS: Electronic nicotine delivery systems; FeNO: Fractional exhaled nitric oxide

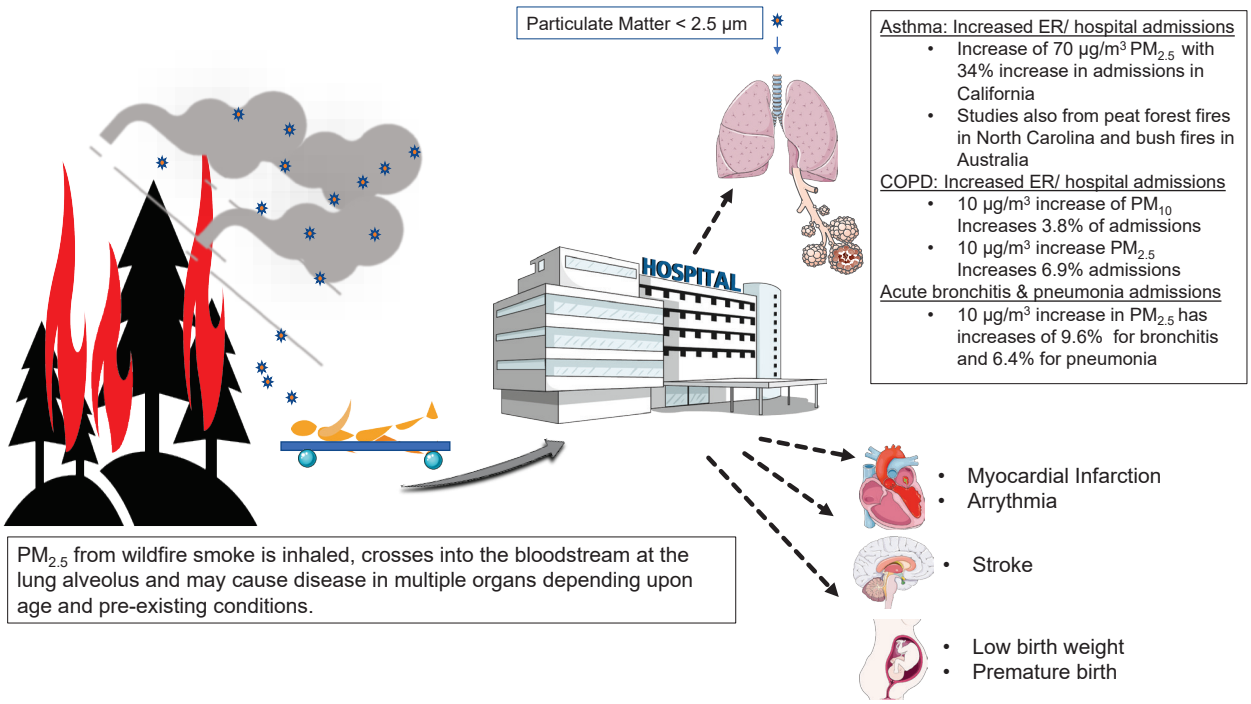

Figure 2 Impact of wildfire smoke on health.
PM - Particulate matter; ER - Emergency room; COPD - Chronic obstructive pulmonary disease.

ing degrees of certainty the changes that will occur due to climate change: higher maximum and minimum temperatures (Virtually Certain); increased frequency, intensity and length of warm spells (Very Likely); precipitation extremes (Likely); and droughts or dryness (Medium Confidence). All of these changes are linked to increased allergies, asthma exacerbations and other respiratory conditions. Precipitation extremes include more rain and thunderstorms. During thunderstorms the pollen ruptures and releases its allergenic contents into the air. Melbourne, Australia experienced the worst epidemic of thunderstorm-related asthma attacks in 2010, which resulted in 9 deaths and 8500 hospitalizations. CO_2 increases associated with climate change spurs the growth of allergenic plants. Increased dryness is associated with windstorms and dust storms, also aggravating respiratory conditions. Climate change is also causing an increase in size, duration and intensity of wildfires, resulting in more particulate matter of 2.5 microns or smaller to be released into the atmosphere and is associated with increased emergency room visits and hospital admissions for respiratory and cardiovascular diseases (Figure 2). All of these alterations associated with climate change are impacting lung health in compounding and unprecedented ways.

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14 PERINATAL AND EARLY LIFE INFLUENCES ON ASTHMA DEVELOPMENT

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KEY MESSAGES

- The two most promising targets for primary prevention in asthma are early postnatal aeroallergen sensitization and severe lower respiratory tract infections
- There is also increasing evidence of a modulatory role for the gastro-intestinal tract microbiome that can directly and indirectly modulate immunoinflammatory responses in the airways
- Prenatal exposures impacting the pregnant mother clearly influence susceptibility to early sensitization, respiratory infections, and asthma development in offspring
- The transplacental "immune training" effects have been replicated in animal models, including with a microbial-derived immunomodulatory agent approved for human use

Identification of environmental exposures that are associated with risk for development of early onset asthma represent the "holy grail" for an increasing body of researchers who share the goal of primary asthma prevention. The two most promising targets revealed to date are early postnatal aeroallergen sensitization and severe lower respiratory tract infections (LRTI) during infancy, which can act independently or in synergy to drive asthma pathogenesis. The basis for susceptibility to these risk-associated exposures involves transient immune dysregulation, resulting in inflammation-driven perturbation of normal lung function development, particularly during infancy when lung growth rates are maximal (Figure 1).

The overall extent and degree of variability of developmentally-associated immune dysregulation within the infant population is incompletely understood, but recent findings indicate that an important component concerns capacity to express Types 1/3 interferon (IFN) genes, which is severely constrained at birth (but to variable degrees) in all subjects (Fig 2). Of particular interest, subjects in the lowest tercile with respect to production capacity at birth are at highest risk for mild-moderate LRTI during infancy and a diagnosis of asthma at 5yrs, especially if they also develop aeroallergen sensitization, whilst ultra-high producer are at highest risk for emergency hospitalization for severe infant LRTIs, suggesting a biphasic relationship between innate IFN response capacity and risk for early asthma development.

Ongoing expression of the atopy-associated Th2 high immunophenotype beyond early childhood drives disease progression/consolidation directly, and also indirectly via increasing susceptibility to the exacerbation-triggering by viral infections, evidenced by the success of omalizumab in multiple pediatric clinical trial settings targeting exacerbations.

Human rhinovirus is prominent amongst the list of viral pathogens driving early asthma development, but it is clearly not unique. In this regard, increasing attention is also being given to the role of bacterial pathogens, including to the concept that they can play an "enabling" role via disturbance of immunological homeostasis in the nasopharynx to facilitate virus

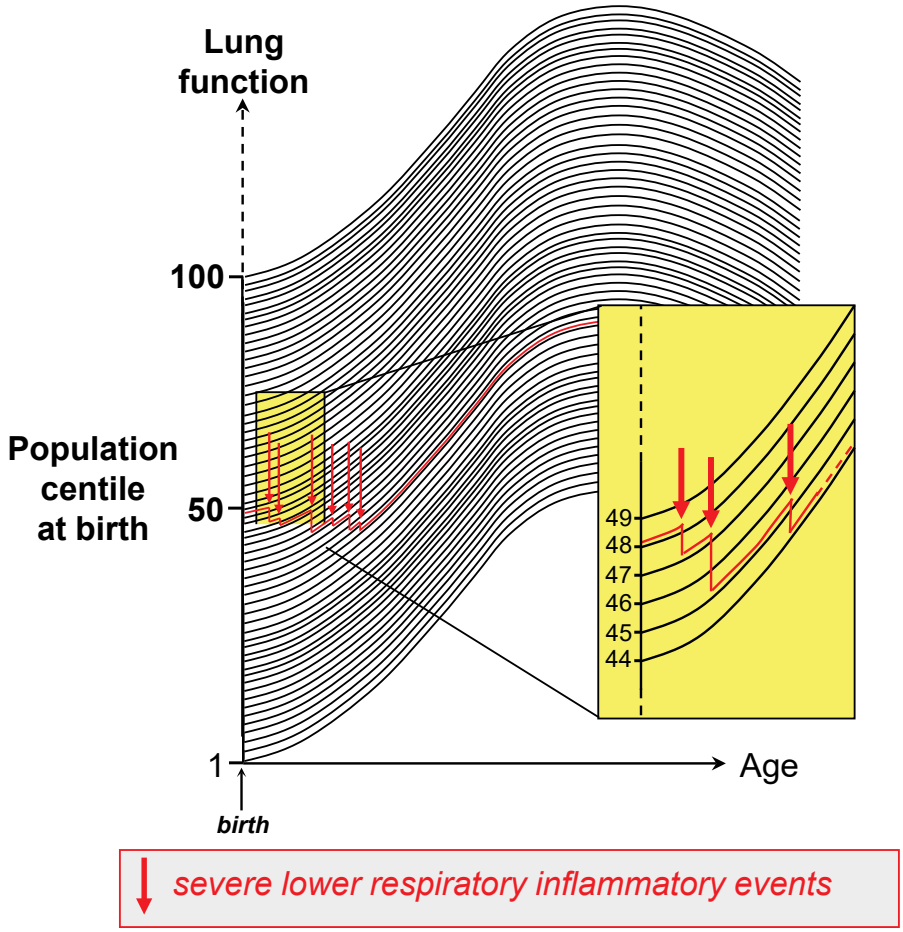

Figure 1 **Establishing trajectories for maturation of respiratory function during childhood.** Respiratory function can be expressed as population centiles, and during the preschool years individual children typically track on the same respiratory function centile (darklines) defined by their personal centile at birth. Experiencing recurrent inflammatory events of sufficient intensity and duration to perturb ongoing growth/differentiation of lung tissues can result in non-reversible tissue remodeling, accompanied by stepwise dropping to progressively lower levels of lung function. The figure exemplifies an infant who is in the 49th centile at birth, who after three such severe events has declined to the 44th centile. *(Reproduced from: Walker ML, Holt KE, Anderson GP, Teo SM, Sly PD, Holt PG, Inouye M. Elucidation of pathways driving asthma pathogenesis: Development of a systems-level analytic strategy. Frontiers in Immunology 2014; 5: Article 447; doi:10.3389/fimmu.2014.00447)*

ingress, and/or via direct amplification of virus-induced airway tissue damage. Early postnatal nasopharyngeal colonization with bacterial pathogens, particularly in subsequently atopic children, constitutes a major asthma risk factor. There is also increasing evidence of a modulatory role for the gastro-intestinal tract microbiome through elaboration of diffusible signals that can directly and indirectly modulate immunoinflammatory responses in the airways, including via effects on migratory T-regulatory cells.

In addition to these postnatal exposures, prenatal exposures impacting the pregnant mother clearly influence susceptibility to early sensitization, respiratory infections, and asthma development in offspring, as illustrated by the studies on traditional farming families in Europe/USA. Notably, prenatal exposure to farm-associated benign/diverse microbial signals is protective for all three disease phenotypes, and protection levels are improved by continuing postnatal exposure. The underlying mechanism(s) are incompletely understood but include promotion of precocious maturation of innate immune functions exemplified by expression of microbi-

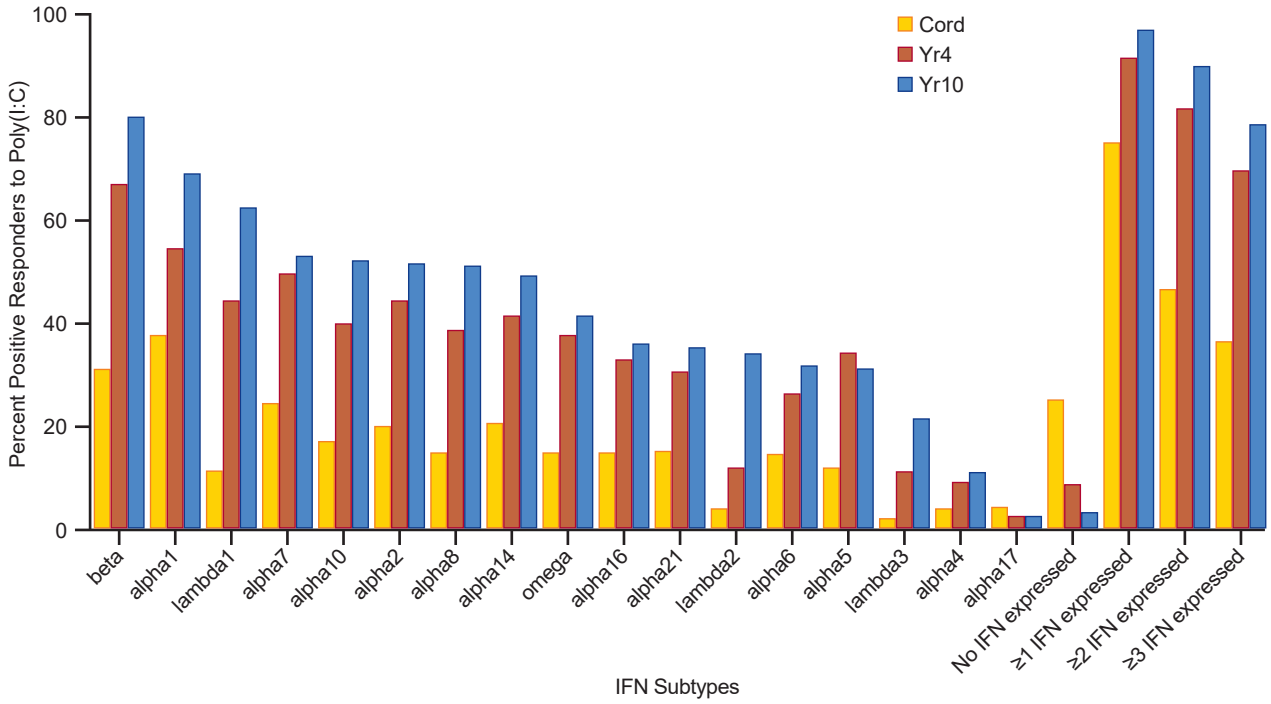

Figure 2 Postnatal development of Types1/3 IFN production capacity in the CAS cohort. Data shown are % subject PBMC samples exhibiting IFN subtype-specific gene expression above detection limits, stratified by subject age. Sample numbers for cord: n=151; 4yrs: n=160; 10yrs: n=125.
(Reproduced from: Holt PG, Mok D, Panda D, Renn LA, Fabozzi G, de Klerk NH, Kusel MMH, Serralha M, Hollams EM, Holt BJ, Sly PD, Rabin RL. Developmental regulation of type 1 and type 3 IFN production and risk for infant infections and asthma development. J Allergy Clin Immunol; 2019; 143(3): 1176-1182 e5)

al sensing receptors on myeloid cells, equipping the newborn with capacity to immediately recognize/respond to both pathogens and to the non-pathogenic microbial signals required to drive functional maturation of the immune system. This effect is bolstered by ongoing postnatal farm/microbial exposure of the offspring, consolidating disease resistance.

There is rapidly growing interest in clinical translation of results from research in this area. In this regard, these transplacental "immune training" effects have been replicated in animal models, including with a microbial-derived immunomodulatory agent approved for human use (OM85-Bronchovaxom). Preventive trials in infants with the same microbial agent, sponsored respectively by NIH (ORBEX; https://clinicaltrials.gov/ct2/show/NCT02148796) and the Australian NHMRC (OMPAC; https://www.anzctr.org.au;#362459 – which recently reported reduced LRTI rates) have already been initiated, and related approaches are in development in a number of centres.

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15 PSYCHOLOGICAL FACTORS AND ASTHMA

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Since the beginning of the 20th century it has been recognised that asthma is a condition in which psychological factors have a major role. Clinicians recognise that emotional stress can precipitate or exacerbate asthma and that a patient's psychological status may affect their asthma control, by impacting on symptom presentation and treatment adherence (Figure 1). Thus, the relationship between asthma and psychological factors can be described as bi-directional.

KEY MESSAGES

- Asthma is associated with significant psychological burden and psychiatric co-morbidity
- Psychological distress may play a role in the perception of asthma symptoms and asthma treatment (eg adherence, health seeking behaviours) which in turn impacts on prognosis, morbidity and mortality
- There is global consistency in the relationship between asthma and mental disorders
- Adopting a bio-psychosocial approach when consulting with a patient with asthma ensures that the wider consequences of asthma and not just their physical symptoms are addressed
- Psychological interventions are used to augment pharmacological management of asthma but there is currently limited evidence of their effectiveness

PSYCHOLOGICAL STATUS AND PSYCHIATRIC CO-MORBIDITY IN PATIENTS WITH ASTHMA

Asthmatics tend to report high levels of negative emotions, and asthma exacerbations have been linked temporally to periods of heightened emotionality. The prevalence of depressive disorders is probably higher in people with asthma relative to the general population: a wide range of prevalence estimates have been reported, with some exceeding 40%. Interestingly a relationship between depression and asthma is evident in families as well as in individuals; familial studies suggest that the prevalence of each disorder is higher in the family members of index cases with the other.

Patients with bipolar affective disorders also appear to have a higher risk than the general population of developing IgE-mediated allergic conditions, including asthma. Similarly, there is an increased prevalence of anxiety disorders in asthma, affecting as many as one third of asthmatic children and adolescents, and 24% of adults with asthma.

Unfortunately, the literature on the prevalence of psychological and psychiatric disorders in asthmatics is complicated by unclear disease definitions, differences in nomenclature, small samples and a focus on outpatient or inpatient populations rather than the community.

The World Mental Health Survey goes some way to address these methodological problems and provides standardised data for 17 countries worldwide (Figure 2). The pooled estimates of age- and sex-adjusted odds of mental disorders among patients with asthma comparative to those without asthma were 1.6 (95%CI=1.4,1.8) for depressive disorders and 1.5 (95%CI=1.4,1.7) for anxiety disorders. This study also demonstrated a relationship between asthma and alcohol use disorders (OR 1.7 (95%CI=1.4, 2.1). Although the prevalence of mental disorders and asthma varies greatly

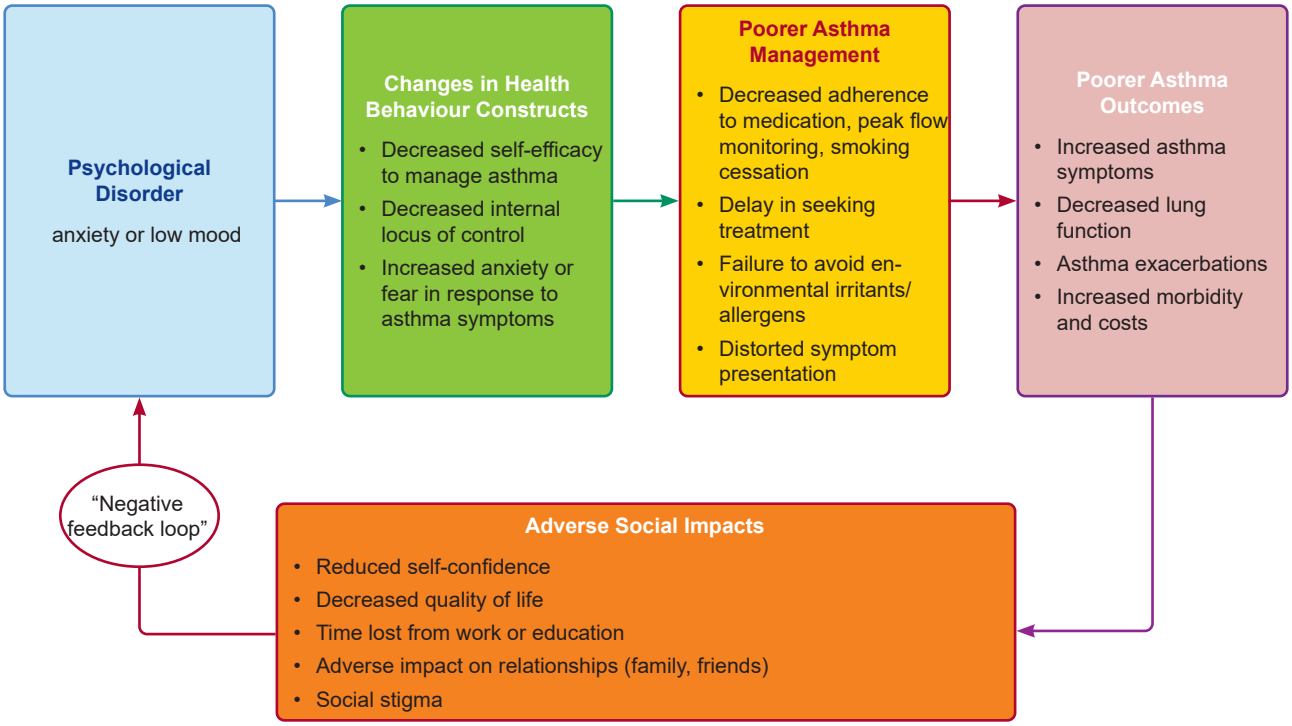

Figure 1 **How low mood or anxiety might impact on asthma.**

between countries, the association of the two showed much less cross-sectional variability. This consistency is fascinating given that the countries included differ significantly in their culture, organisation of health services and stage of socioeconomic development. It indicates that wherever setting clinicians work, they need to be aware of the significant overlap of asthma with psychological and psychiatric disorders.

WHAT LINKS PSYCHOLOGICAL DISTRESS AND ASTHMA?

Early psychosomatic models supported a role for psychological distress in contributing to variable asthma morbidity among those with existing disease, but growing knowledge of patho-physiological pathways suggests a role for psychological factors also in the genesis of asthma. Asthma and major depressive disorders have similar patterns of dysregulation of key biological systems including the neuro-endocrine stress response, cytokines, and neuropeptides. Twin-pair studies provide additional evidence of a genetic link between atopic and depressive symptoms. Further work is needed to unravel these relationships.

PSYCHOLOGICAL INTERVENTIONS FOR ASTHMA

Recognising the relationship between asthma and psychological factors psychological interventions are sometimes used to complement the pharmacological management of asthma. Many different therapies have been tried, including behavioural therapies, cognitive therapies, cognitive-behavioural therapy (CBT), relaxation techniques, psycho-dynamic psychotherapies and counselling (both for the individual and for the family). However, unlike pharmacological therapies for asthma, we still have limited evidence of the effectiveness of these psychological interventions in children or adults.

This paucity of evidence arises because studies of psychological interventions for asthma have often not been randomised, and those studies that have used randomised controlled methodology have lacked power to confirm the utility of the intervention. Furthermore, combining studies in systematic reviews and meta-analyses is limited by the diversity of interventions used, and the variety of different outcomes measured. In a Cochrane review published in 2016, patients receiving CBT had improved quality of life, better asthma control and less anxiety when compared to those receiving usual care. In other reviews biofeedback has been found to improve peak expiratory flow rate (PEFR), and relaxation therapy to reduce medication use. In a review of psychological interventions for children, relaxation

TABLE 1

Odds Ratio (age - sex adjusted) for mental disorders amongst adults with asthma versus without asthma

Country	Weighted asthma prevalance %	Major Depression OR	Dysthymia OR	General Anxiety OR	Panic Disorder OR	Social Phobia OR	Post traumatic stress disorder OR	Alcohol Use Disorder OR
Americas								
Colombia	3.0	3.8	7.5	0.6	2	1.1	-	8.9
Mexico	2.2	1.2	0.7	-	0.7	2.9	3.6	1.6
United States	11.6	1.4	1.7	1.7	1.3	1.0	1.3	1.8
Asia and South Pacific								
Japan	5.4	1.2	0.9	1.7	0.8	3.8	4.3	1.6
Beijing, PRC	2.3	2.5	2.8	2.9	-	5.0	-	0.9
Shanghai, PRC	5.1	1.4	-	-	-	-	-	0.8
New Zealand	17.2	1.5	1.5	1.7	1.5	1.1	1.8	1.5
Europe								
Belgium	5.8	1.2	0.2	4	-	0.9	0.5	0.9
France	7.5	1.5	2.6	2.8	0.8	2.1	3.3	0.6
Germany	4.5	2.1	5.4	-	4.1	1.0	-	1.8
Italy	4.6	2.2	1.6	-	0.4	3.2	2.8	-
The Netherlands	8.5	1.4	1.6	0.6	3.0	1.4	5.5	2
Spain	5.7	2.7	2.5	2.8	1.6	8.1	3.8	2.9
Ukraine	1.8	2.7	3.6	1.2	6.0	0.8	4.1	5.4
Middle East and Africa								
Lebanon	1.2	-	-	-	-	-	-	-
Nigeria	0.6	-	-	-	-	-	-	-
Israel	7.2	1.4	1.1	1.2	1.7	-	0.6	1.7
South Africa	5.8	2.1	-	2.7	2.6	3.1	0.8	1.4

Odds Ratio (OR) is not listed if fewer than 25 respondents have asthma or if the cross classification of mental disorder and asthma is null. PRC - People's Republic of China. (Data from Scott KM, Von Korff M, Ormel J, et al. Mental disorders among adults with asthma: results from the World Mental Health Survey. Gen Hosp Psychiatry 2007;29:123-133.)

therapy improved PEFR. Low confidence in the evidence remains so care is needed when endorsing psychological interventions on the basis of current literature.

Clinicians' observations of positive benefit for individuals from psychological interventions may challenge the formal review of the literature. In part this discrepancy may arise because in clinical practice psychological treatments are often reserved for distressed patients with severe or poorly controlled asthma whereas trials often recruit patients with milder and more controlled asthma, and have often failed to screen participants for psychological distress at inclusion, resulting in study populations that are less able to benefit (ceiling effect) from psychological intervention. Well designed trials are urgently needed.

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Section B

MECHANISMS, PHENOTYPES AND ENDOTYPES

1 GENETICS OF ASTHMA

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KEY MESSAGES

- Asthma is a heterogeneous disease caused by the interaction between genetic and environmental factors
- Asthma-associated genetic loci may highlight disease mechanisms and targets for novel drugs
- > 100 asthma-associated independent single nucleotide polymorphisms have been identified in the last years
- Childhood-onset asthma is associated with the most independent loci, while adult-onset-and moderate-to-severe-asthma are associated with a subset of these loci
- Several asthma associated genes are connected to barrier function biology as well as the HLA region
- Genomics-based drug repurposing can be explored in future studies
- Studies in populations of other than European ethnicities are urgently needed

Asthma is a heterogeneous disease with multiple underlying pathogenetic mechanisms and clinical trajectories.

A breakthrough in the asthma genetics field occurred after the introduction of large-scale genome-wide association studies (GWAS). A review of GWAS allowed the identification of numerous independent single-nucleotide polymorphisms (SNPs) that are associated with asthma (Figure 1 and Table 1). Research on genetic predictors of asthma over the last few years has focused on discriminating traits of different asthma phenotypes such as childhood- vs. adult-onset and moderate-to-severe vs. difficult-to-treat asthma. At the same time, data on the genetic predictors for the development of allergic sensitization, allergic rhinitis, and atopic dermatitis have also been collected (Table 2). Such findings allowed the identification of commonalities regarding genetic predisposition between asthma and other diseases (Figure 2). For example, there is evidence that 17q21 is a risk locus for the development of childhood asthma. Interestingly, the same locus is associated with the development of Crohn's disease, ulcerative colitis, type 1 diabetes, and rheumatoid arthritis.

Bioinformatics also helped to unravel genes shared between asthma and diseases such as arterial hypertension, celiac disease, and mental health disorders. Such genes are pleiotropic, with the same gene being able to affect several pathogenetic pathways. Understanding of these complex mechanisms will allow the development of targeted drugs that are likely to be effective for multiple diseases at the same time.

The majority of GWAS to date focus on Caucasian populations, albeit ethnicity plays an important role in modulating the course of the disease. Expansion of GWAS maps will allow a more accurate construction of polygenic risk prediction models and population-matched GWAS' statistics. Indeed, this is absolutely necessary if one considers that asthma is a global disease across all races and continents. GWAS of asthma drug (corticosteroid, bronchodilator) response have also advanced our knowledge by surprisingly

Figure 1 **Independent single nucleotide polymorphisms associated with asthma.**

TABLE 1

Target asthma gene list

Targeted Asthma Genes	Genes Name	Clinical Trial
ADORA1	Adenosine A1 receptor	Launched
CHI3L1	Chitinase 3 like 1	Preclinical
TNFSF4	Tumor necrosis factor superfamily member 4	Phase II
CHIT1	Chitinase 1	Phase I
PDCD1	Programmed cell death 1	Launched
IL1RL1	Interleukin 1 receptor like 1	Phase II
IL7R	Interleukin 7 receptor	Phase I
TSLP	Thymic stromal lymphopoietin	Phase III
ITPR3	Inositol 1,4,5-trisphosphate receptor type 3	Preclinical
TNF	Tumor necrosis factor	Launched
GATA3	GATA binding protein 3	Phase II
PRKCQ	Protein kinase C theta	Phase II
IL2RA	Interleukin 2 receptor subunit alpha	Launched
MAP3K11	Mitogen-activated protein kinase kinase kinase 11	Phase II
STAT6	Signal transducer and activator of transcription 6	Launched
IL4R	Interleukin 4 receptor	Launched

showing that associated loci did not overlap with those of asthma inception, thus indicating distinct mechanistic pathways. To date, the largest evidence base relates to 4 genes: FCER2 - response to corticosteroids, ABCC1 and LTC4S - response to antileukotriene agents, ADRB2.- response to beta-agonists. Of particular interest are markers of response to biological agents, which will make it possible to stratify for treatment with expensive drugs, until now used for uncontrolled patients with asthma. Loci influencing the metabolism and pharmacokinetics of drugs for asthma are also described (cytochromes P450 (CYP) genes 3A4 (CYP3A4), 3A5 (CYP3A5), and 3A7 (CYP3A7)). Most of the available finds are preliminary and require validation.

Today we know that environmental factors (eg air pollution, smoking, antibiotic use, presence of pets, the use of unprocessed cow's milk) as well as social activity (regular exercise) can modify genetically determined characteristics, changing the course of the disease. Along these lines, epigenetic processes (DNA methylation, posttranslational histone modifications, nucleosome occupancy, small and long non-coding RNAs) have attracted great interest and are believed to be quite important in customizing therapy. Epigenome-wide association studies (EWAS) play a pivotal role in this field.

Integration of GWAS data with several -omic datasets including the microbiome, proteome, metabolome and epigenome currently represents one of the greatest challenges and opportunities. Interconnections may highlight molecular biomarkers and new pharmacological targets but also

TABLE 2

Top genes associated with asthma and other allergic diseases				
GENES	**Atopic dermatitis**	**Allergic rhinitis**	**Allergic sensitization**	**Asthma**
CLEC16A	+	+		+
C11ORF30	+	+	+	+
IL1RL1/IL18R1	+	+	+	+
HLADQB1/DQA1		+	+	+
IL5/IL13	+			+
WDR36/TSLP		+		+
ORMDL3/GSDML		+		+

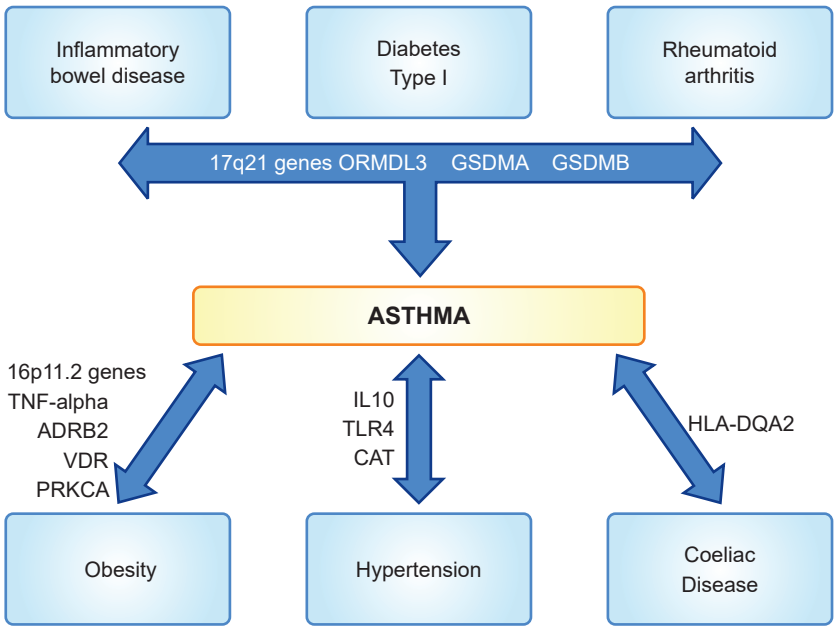

Figure 2 Overlap of genes involved in the development of asthma and other chronic diseases. *ORMDL3, GSDMB, GSDMB (17q21 genes); TNFα - tumor necrosis factor alpha; ADRB2 - β2-adrenergic receptor; VDR - vitamin D receptor; PRKCA - protein kinase C alpha; IL10 - Interleukin 10; TLR4 - Toll-like receptor 4; CAT - catalase coding gene; HLA-DQA2 - Major histocompatibility complex, class II, DQ alpha 2.*

shape personalized treatment, for example through optimization of treatment duration and prevention of side effects.

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2 EPIGENETICS OF ASTHMA

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KEY MESSAGES

- Asthma is a complex airway disease with genetic and environmental influences
- Environmental interaction may result in epigenetic changes that increase the risk of asthma development
- Epigenetic damaging changes include DNA methylation, histone modifications and non-coding RNA-associated gene silencing
- In utero changes to the epigenome may be initiated through exposure to prenatal adverse environments
- Reversal of epigenetic changes can be explored as targeted treatments for specific phenotypes of asthma

Asthma is characterized by chronic airway inflammation leading to respiratory symptoms and poses major health and economic burdens. It is a heterogenous disease that can manifest under many different phenotypes. In addition to genetic and environment factors that predispose an individual to develop asthma, epigenetic changes that regulate gene expression independently of changes in DNA sequence can also drive asthma pathogenesis. Together, these factors lead to chronic airway inflammation and asthma symptoms.

Epigenetic mechanisms involve three processes: DNA methylation, histone modification and non-coding RNA expression (Figure 1). Methylation of DNA and modification of histones via acetylation and methylation causes changes in the chromatin packing of the gene, which then alters the accessibility of pro-inflammatory transcription factors to DNA resulting in changes in gene expression profiles. Non-coding RNA, including microRNA (miRNA), small hairpin RNA and long non-coding RNA serve as post-transcriptional regulators of gene expression where their presence alters gene expression by sequestration or direct degradation of mRNAs.

Epigenetic modifications resulting from environmental interactions with the airway epithelium may be a key driver of asthma development. Accumulated epithelial epigenetic changes may result in epithelial barrier dysfunction, immune dysregulation and remodelling events that are all predisposing factors to asthma development and severity (Table 1). In addition, the recent finding of epithelial memory in airway epithelial basal cells suggests that altered gene expression, most likely via epigenetic modifications, allows these cells to retain memory of their altered status even during differentiation.

Epigenetic modifications such as histone acetylation, DNA methylation and miRNA expression are found consistently in airway epithelial cells, other structural cells such as airway smooth muscle cells and fibroblasts, and in airway immune cells. These epigenetic profiles are also reflected in the blood and nasal mucosa of patients with asthma. These modifications affect the inflammatory and immunologic profile seen in asthma and the proliferation and differentiation status of epithelial and other structural cells resulting in phenotype-specific disease development.

The manifestation of asthma is a multi-pronged event with many different triggers that determine its onset and severity. The accumulation of epigenetic modifications contributes to disease manifestation through the interaction

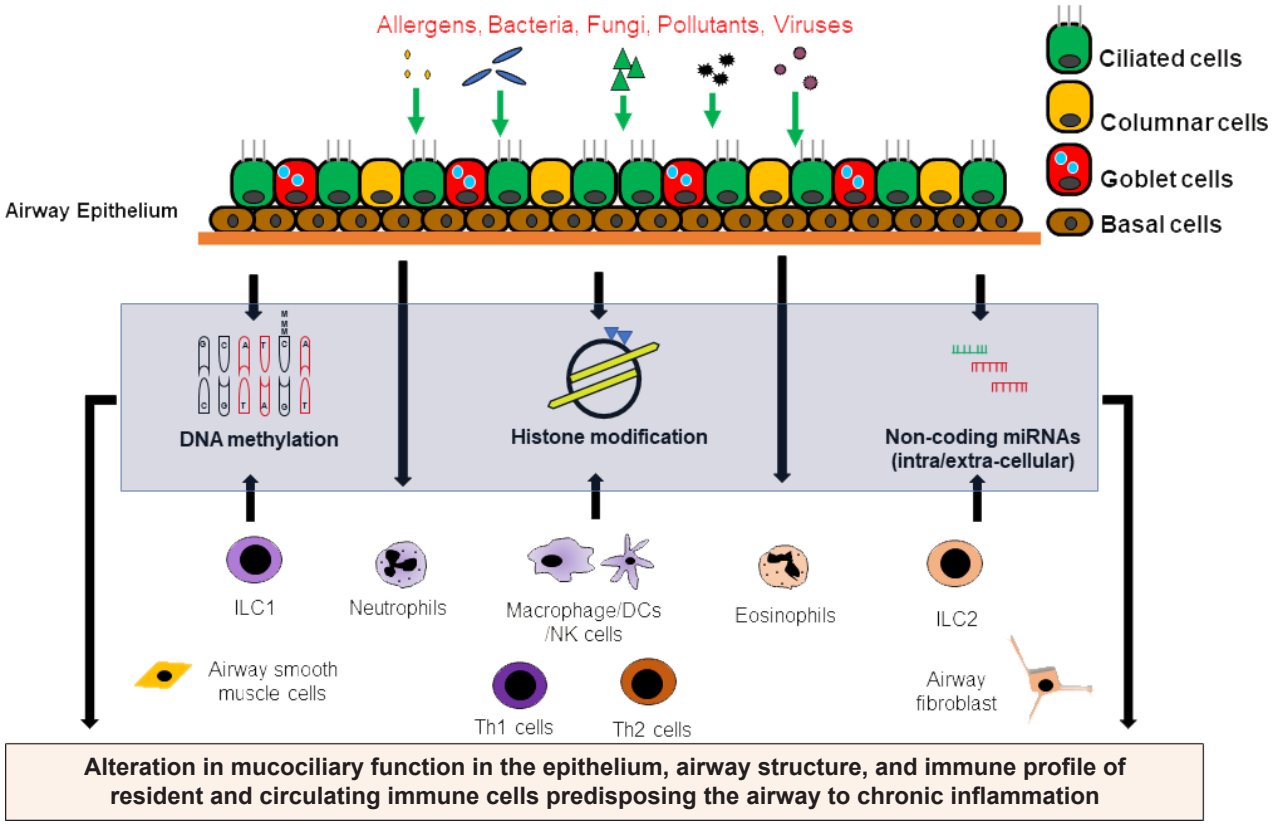

Figure 1 **Epigenetic modifications in the airways.** The airway epithelium serves as the first point of contact with environmental triggers that occur in utero through to adulthood. These may have short- and long-term effects on airway gene expression profiles through DNA methylation, histone modification and non-coding RNA expression. These epigenetic changes alter the accessbility of the genome to transcriptoin factors or the transcription and translation of inflammatory and immunomodulatory mRNAs resulting in chronic airway inflammation. Changes in the airway epithelium can then further influence the epigenetic profile of other airway and immune cells via antigen presentation and cytokine production. The accumulation of these changes leads to alterations in the mucociliary barrier, airway structure, and immune profiles that promote chronic airway inflammation and remodeling, thus contributing to the development of asthma and to increasing its severity.

of a myriad of environmental triggers such as smoking exposure in utero increasing the risk of asthma. Exposure to allergens such as house dust mites and pollen cause rapid epigenetic modifications. In addition, microbial infections, including bacterial, viral, and fungal pathogens, may also result in alteration in DNA methylation, histone modifications and non-coding RNA changes that result in specific types of chronic airway inflammation. Air pollution contains dust and chemicals that also trigger epigenetic modifications in the airway and these triggers may interact with the airway microbiome to further alter the epigenome of susceptible individuals.

The epigenome represents a key mechanism that underlies the airway changes occurring during asthma development and those associated with asthma severity. Drugs targeting different epigenetic processes have been developed for cancer and other chronic inflammatory diseases and may be re-purposed for treating asthma particularly in patients with severe disease where there is extensive remodelling and in whom anti-T2 biologicals are ineffective.

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TABLE 1

Snapshot of recent studies on epigenetic modifications contributing to asthma development and phenotypes (Mar 2019 – Feb 2020)

Epigenetic modifications	Genes affected	Cell types/effects
DNA Methylation	*FOXP3*[1]	Regulatory T cells
	Gene sets from EWAS[2]	Atopy, IgE levels
	IFNγ[2]	Th2 skewed differentiation
	MAPK1[3]	Reduced methylation upon exposure to Bisphenol A increased asthma prevalence
	Methylation of SNPs[4]	Atopic asthma risk
Histone Modification	*ORMDL3* acetylation by p300[5]	Asthma remodeling
	Ets2 mediated deacetylation of IL6[6]	Suppresses IL6 expression
	IL4 promoter acetylation[7]	Increase Th2 inflammation
Non-coding RNA	Downregulated Let-7, miR-24, miR-27, miR-193b, miR-375; Upregulated miR-21, miR-223, miR-146a, miR-142-5p, miR-142-3p, miR-146b, miR-155[8,9]	Decrease Th1 cytokines, increase Th2 differentiation
	Downregulated miR-1[10]	Eosinophilia
	miR-203a-3p[11]	TGFβ1 pathway and EMT in asthma
	Downregulated miR-224[12]	Increase TLR2 signaling following PM2.5 exposure
	Downregulated miR-192-5p[13]	Airway remodeling
	miR-124 and lncRNA NEAT1[14]	Increase exacerbation risk
	Downregulated miR-30[15]	Fibrosis
	Downregulated miR-218-5p[16]	Eosinophilic inflammation

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3 PHARMACOGENETICS OF ASTHMA

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KEY MESSAGES

- As many as one-half of asthmatics do not respond to one or more of the three major medication classes used to treat asthma: inhaled corticosteroids, β2-agonists, and leukotriene antagonists
- Pharmacogenetics is the study of how heredity influences medication response
- Pharmacogenomics more broadly studies both DNA and RNA elements and regulatory mechanisms impacting treatment response
- Pharmaco-genetics and -genomics research have identified genetic variants, messenger RNAs, microRNAs, DNA methylation marks, and systems biology pathways associated with response to each asthma medication class
- The future of pharmacogenetics lies in translating research evidence into clinical practice with the goal of providing personalized therapy for each patient

Wide variation exists in how patients respond to asthma treatment medications. It is estimated that as many as one-half of asthmatic patients do not respond to treatment with β2-agonists, leukotriene antagonists, or inhaled corticosteroids (Figure 1).

Pharmacogenetics is the study of the role of genetic determinants in the variable, inter-individual response to medications. Asthma medication treatment response is commonly quantified as an improvement in lung function measurements (e.g., peak expiratory flow, forced expiratory volume in one second (FEV1), airway hyper-responsiveness), decrease in exacerbations (e.g., asthma-related emergency department visits or hospitalizations, oral corticosteroid bursts), or asthma symptom control (e.g., Asthma Control Test, Asthma Control Questionnaire, asthma-related school absences).

Since 1999, pharmacogenetic studies have identified several genes associated with response to the most common asthma treatment medications, including short-acting β2-agonists, long-acting β2-agonists, inhaled corticosteroids, and leukotriene antagonists (Table 1). Initially, candidate gene and genome-wide association approaches were used, and more recently, whole genome sequencing has been used to identify rare variants associated with treatment response. Anti-leukotrienes were the first class of medications studied in asthma pharmacogenetics. *ALOX5* and *MRP1* have been associated with all three measures of leukotriene antagonist treatment response in children and adults. Most studies on the pharmacogenetics of β2-agonists have focused on the *ADBR2* gene which encodes the beta-2 adrenergic receptor, and the most consistent results for inhaled corticosteroid response has been seen for the *FCER2* gene which encodes the low-affinity IgE receptor. Many of these genetic findings have been experimentally validated, but more *in vitro* and *in vivo* validation studies are needed.

Pharmacogenetics is encompassed within the broader field of pharmacogenomics that studies both DNA and RNA elements and regulatory mechanisms affecting treatment response. Since 2014, transcriptomic, epigenetic, and systems biology approaches have identified

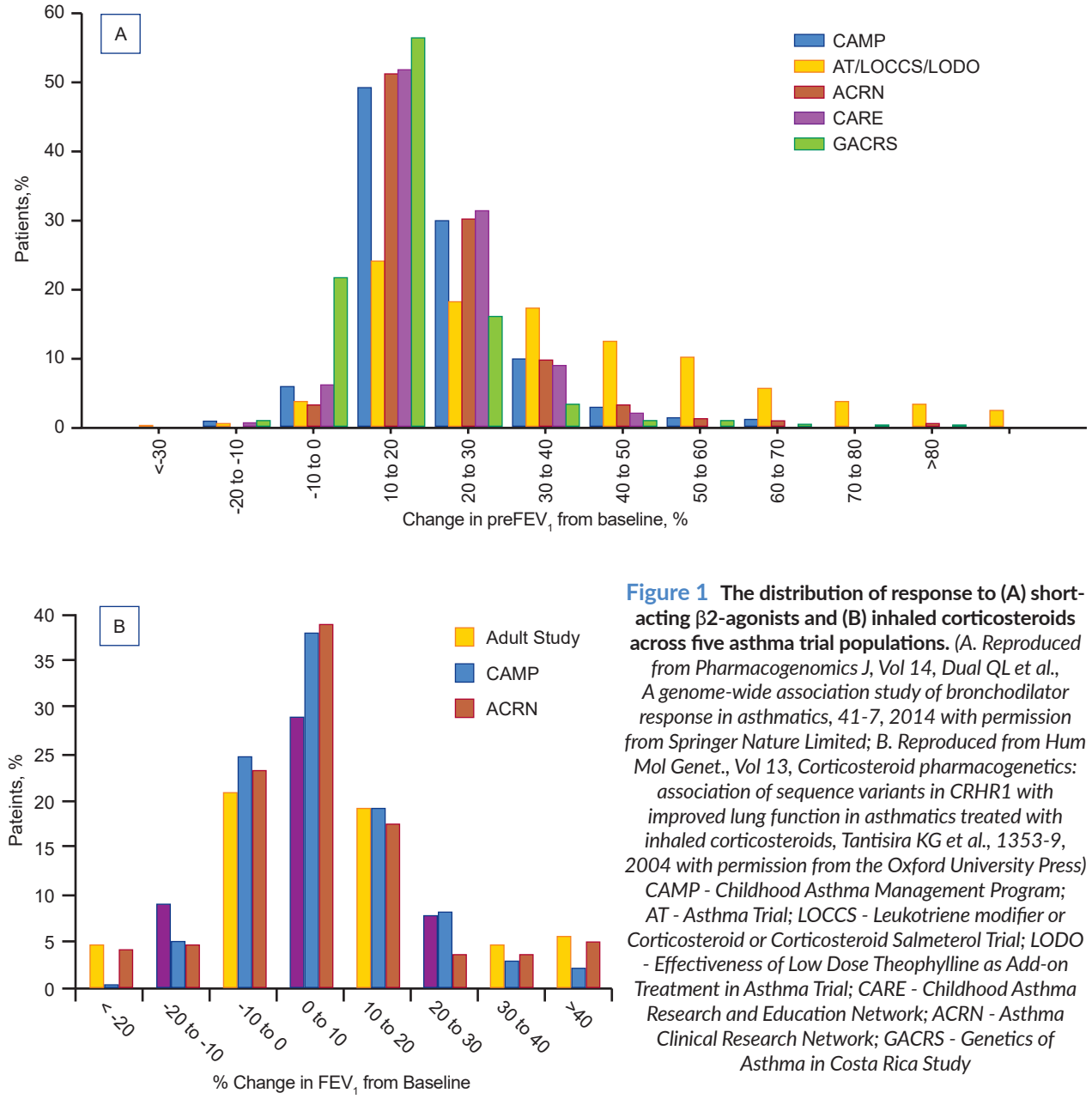

Figure 1 The distribution of response to (A) short-acting β2-agonists and (B) inhaled corticosteroids across five asthma trial populations. *(A. Reproduced from Pharmacogenomics J, Vol 14, Dual QL et al., A genome-wide association study of bronchodilator response in asthmatics, 41-7, 2014 with permission from Springer Nature Limited; B. Reproduced from Hum Mol Genet., Vol 13, Corticosteroid pharmacogenetics: association of sequence variants in CRHR1 with improved lung function in asthmatics treated with inhaled corticosteroids, Tantisira KG et al., 1353-9, 2004 with permission from the Oxford University Press) CAMP - Childhood Asthma Management Program; AT - Asthma Trial; LOCCS - Leukotriene modifier or Corticosteroid or Corticosteroid Salmeterol Trial; LODO - Effectiveness of Low Dose Theophylline as Add-on Treatment in Asthma Trial; CARE - Childhood Asthma Research and Education Network; ACRN - Asthma Clinical Research Network; GACRS - Genetics of Asthma in Costa Rica Study*

novel genes, messenger RNAs, microRNAs, and DNA methylation marks associated with asthma treatment response (Table 2). For example, in an epigenome-wide DNA methylation study, hypomethylation of cg00066816 upstream of *IL12B* and hypermethylation of cg04256470 upstream of *CORT* were associated with response to inhaled corticosteroids and corresponding changes in gene expression in children. In addition, systems biology approaches, such as Passing Attributes between Networks for Data Assimilations (PANDA), have identified differentially connected gene-regulatory networks, including differential regulation by transcription factors *NFKB1* and *JUN* and their respective downstream genes *CEBPD* and *TMEM53*, important to inhaled corticosteroid response (Figure 2).

Over the past two decades, pharmaco-genetics and -genomics have elucidated new genetic and omic factors contributing to asthma treatment response. Asthma is a complex disease where individual genetic variants have small effect sizes that only partially explain

treatment heterogeneity. Pharmacogenetic results have been difficult to replicate due to small cohort sizes and differences in study designs, outcomes, and patient populations. Currently, there is not enough evidence for genetic or omic testing as part of asthma management, and more research is needed on the pharmaco-genetics and -genomics of asthma biologics. Going forward, integrative omic approaches have the potential to achieve higher predictive capacities, and large-scale discovery and validation studies are necessary to bridge the results into clinical practice.

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TABLE 1

Genes associated with asthma treatment response identified through candidate gene, genome-wide association, and whole genome sequencing approaches

Medication class and phenotype	Genes
Short-acting β2-agonists (SABA)	
Bronchodilator response	*AC9, ADAMTS3, ADCY9, ADCYAP1R1, ADRB2, ARG1, ARG2, ASB3/SOCS, CLOCK, COL22A1, COX18, CRHR2, DNAH5, FGF14, GSNOR, IGF2R, IL2RA, IL6, IL6R, IL15RA, KLF6, NCOA3, NFKB1, PAPPA2, PLCB1, PRKCQ, SLC22A15, SLC24A4, SPATA13-AS1, SPATS2L, SPON1, THRB, ZNF432*
Long-acting β2-agonists (LABA)	
Lung function: ΔFEV1	*ADCY9, ADRB2*
Exacerbations	*ADRB2*
Asthma symptom control	*ADRB2*
Inhaled corticosteroids (ICS)	
Lung function	
ΔFEV1	*ALLC, APOBEC3B, APOBEC3C, ARG1, CA10, COL2A1, CRHR1, CTLA4, CTNNA3, FCER2, GLCCI1, HDAC1, NK2R, SERPINE1, STIP1, TBXT (T gene), TBX21, VEGF*, 17q12-21 locus, rs6924808 (chromosome 6), rs1353649 (chromosome 11)
Airway responsiveness	*ACOT4, ALG8, BRWD1, H33Q, NAPRT1, NK2R, SPATA20, TBX21*, 17q12-21 locus
Exacerbations	*CMTR1, CRHR1, FCER2, GLCCI1, MAGI2, NR3C1, P2RX7, ST13, TRIM24*, 17q12-21 locus
Asthma symptom control	*CRHR1, CYP3A4, DUSP1, FBXL7, FCER2, LOC728792, NK2R, TBX21, RMST*
Combined ICS and LABA	
Lung function: ΔFEV1	*HSPA8, NOS3*
Asthma symptom control	*CHRM2*
Leukotriene antagonists	
Lung function	
ΔFEV1	*ABCC1, ALOX5, CHRM2, GLT1D1, LTA4H, LTC4S, MLLT3, MRP1, MRPP3, PTGDR*
Bronchodilator response	*ALOX5AP, LTA4H*
Exacerbations	*ALOX5, LTC4S, LTA4H, MRP1*
Asthma symptom control	*ALOX5, MRP1*

TABLE 2

Genes, messenger RNAs, microRNAs, and pathways associated with asthma treatment response identified through epigenetic, transcriptomic, and systems biology approaches in asthma pharmacogenomics

Medication class and phenotype	Messenger RNA	MicroRNA	DNA methylation	Systems biology
SABA: Bronchodilator response		microRNA 16		
ICS				
Lung function: ΔFEV1	*CRISPLD2*	microRNA 21	*BOLA2*	*CEBPD, TMEM53*
Exacerbations			*IL12B, CORT*	
Combined phenotype				*FAM129A*
Other			VNN1, OTX2, DNHD1, LDHC, PRRC1	*GAB1*
Leukotriene antagonist: ΔFEV1				PI3K pathway

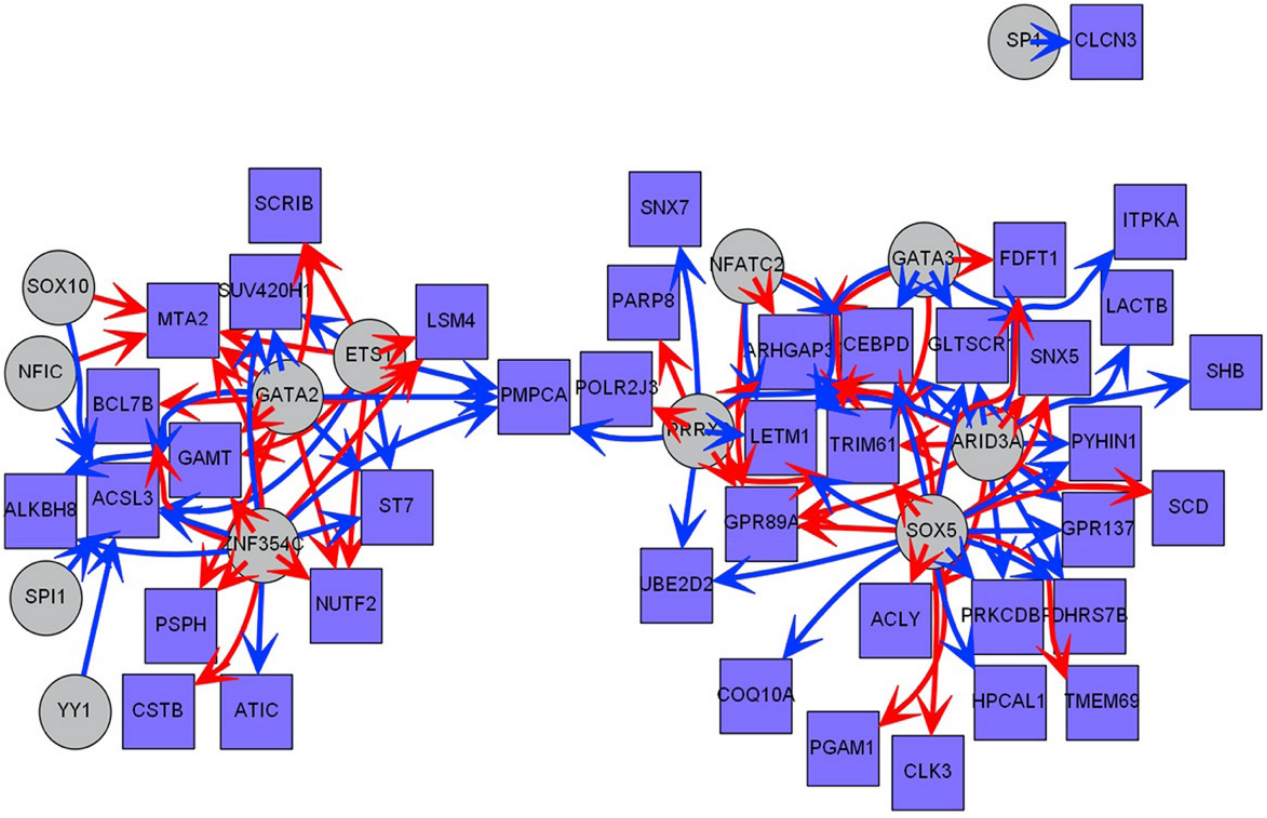

Figure 2 **Differential connectivity between two gene regulatory networks comparing inhaled corticosteroid good responders to poor responders.** The top 50 transcription factor-gene pairs as determined by the absolute difference of the edge weights between the two networks are shown. The red edges are for the network of good responders; the blue edges are for the network of poor responders. *(Reproduced from J Allergy Clin Immunol., Vol 141, Qiu W et al., Differential connectivity of gene regulatory networks distinguishes corticosteroid response in asthma, 1250-8, 2018 with permission from Elsevier)*

4 THE UNDERLYING PATHOLOGY OF ASTHMA

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Asthma is a chronic inflammatory disease classified into distinct phenotypes and endotypes. Over the last decade, progress has been made in understanding the heterogeneity of asthma and the mechanisms underpinning its pathophysiology. In asthma, a myriad of inflammatory changes at the cellular level affects the airways and leads to tissue remodeling.

KEY MESSAGES

- Distinct immune pathways drive the pathophysiology of asthma
- Type-2 inflammation propagate eosinophilic inflammation and allergic hyperresponsiveness through innate and adaptive immune response
- Non-type 2 inflammation constitutes an unmet need both as pathogenetic pathways and treatment approach; a potential role of Th-1 and Th-17 pathways is suggested
- Airway remodeling includes structural, mechanical and inflammatory alterations
- Propagators of airway remodeling correlate with the degree of disease severity

THE PATHOLOGY BEHIND ASTHMA: DISTINCT INFLAMMATORY PATHWAYS

Cellular inflammation in asthma has been divided into two distinct subtypes: type 2 (T2)-high inflammation and type 2-low (or non-type 2) inflammation. The pathophysiological pathways driving each have been partly elucidated.

TYPE 2- HIGH AND TYPE 2-LOW AIRWAY INFLAMMATION

In T2-high asthma, innate and adaptive immune responses propagated by the innate lymphoid cells type 2 (ILC2) and Th2 cells, respectively, lead to the production of the effector cytokines IL-5 and IL-13. IL-5 is responsible for eosinophilic recruitment, maturation and survival. The release of chemokines and other mediators from eosinophils further contributes to tissue remodeling. IL-13 has a pleotropic effect and is associated with goblet cell hyperplasia, mucus production and airway smooth muscle cells hyperresponsiveness. IL-4 is another important cytokine that helps with the differentiation of T cells into TH2 cells and subsequent potentiation of eosinophilic inflammation. It also promotes the switch of B cells into the IgE secreting isotype, production of IgE and, the propagation of an allergen driven hypersensitivity response through mast cell degranulation (Figure 1). Epithelial derived cytokines (thymic stromal lymphopoietin/TLSP, IL-25 and IL-33) further augment T2 response through the downstream production of the aforementioned cytokines (Table 1).

While advances have been made in elucidating the pathology behind T2 inflammation in asthma, little is known about the T2 low counterpart. A potential role of Th-1 and Th-17 pathways has been suggested. Stimuli including smoking, pollutants, viral and bacterial infections inflect changes on airway epithelial cells leading to the activation of Th-17 cells and innate lymphoid cells type 3 (ILC3) and the production of pro-neutrophilic cytokines including IL-17 and IL-22. These in turn lead to smooth muscle proliferation in airways and collagen deposition.

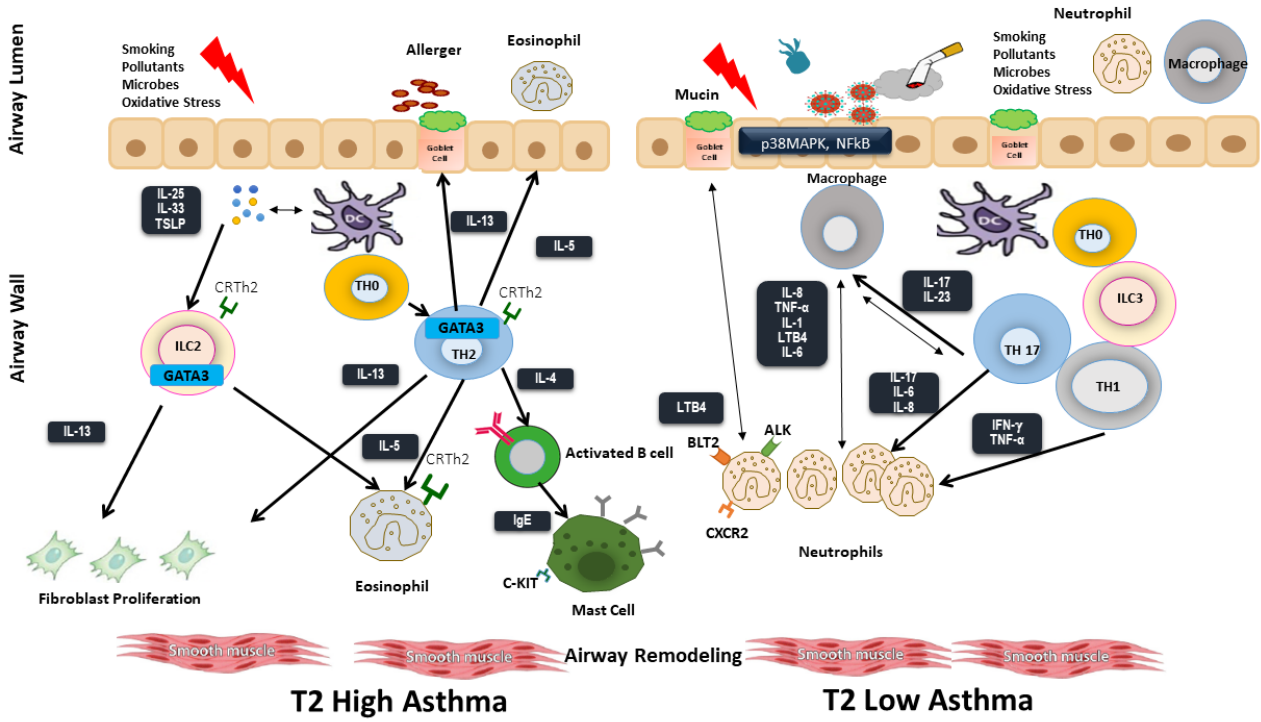

Figure 1 **The immunopathology of T2 high and T2 low asthma.**

TSLP - thymic stromal lymphopoietin; Th - T helper cells (0, 1, 2, 17); CRTH2 - chemoattractant receptor homologous molecule expressed on Th2 cells; GATA3 - GATA transcription factor 3; ILC2 - group 2 innate lymphoid cells; ILC3 - group3 innate lymphoid cells; TSLP - thymic stromal lymphopoietin; LTB4 - leukotriene B4.

Another pathway implicated in non-T2 inflammation is the Th-1 pathway via the production of interferon-γ which increases airway hyperresponsiveness. Few patients with non-T2 asthma demonstrate minimal or no inflammation in their airways (Figure 1 and Table 1).

AIRWAY REMODELING

Histopathological changes in asthma lead to changes at the level of airway mucosa and submucosa and are collectively grouped under the umbrella of tissue remodeling (Figure 2).

The major structural and inflammatory alterations in airways leading to tissue remodeling are highlighted in table 2.

TABLE 1

Key inflammatory drivers of asthma		
Type of Cells	**Inflammatory Changes**	**Mode of Action**
Epithelial cells	Increased epithelial derived cytokines: TSLP, IL-25 and 33	Activation of ILC2
Lymphocytes	Increased Th2 cells	T2 high inflammation with increased IL-4,5,13 and IgE producing plasma cells
	Increased Th1 and Th17 cells	T2 low inflammation with increased IL-17, IL-22, IFN-γ and TNF-α
Eosinophils	IL-5 mediated accumulation in the lung	T2 high inflammation Tissue remodeling
Mast cells and Basophils	Increased binding of IgE	Allergen specific hypersensitivity reaction through degranulation of mast cells

TSLP, thymic stromal lymphopoietin; IL, interleukin; Th, T helper cells (1,2,17); ILC2, innate lymphoid cells type 2; IFN-γ, interferon- γ; TNF-α, tumor necrotic factor- α; IgE, immunoglobulin E

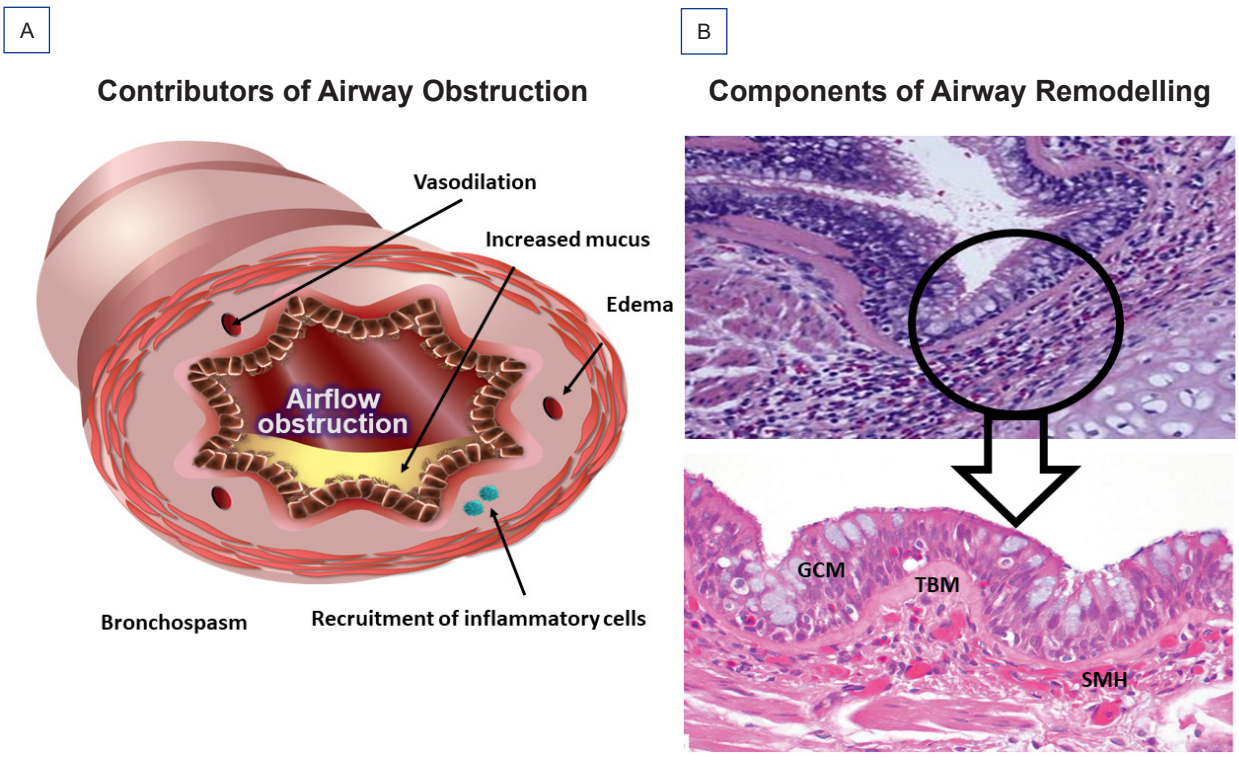

Figure 2 **(A) Schematic representation of features of airway obstruction in asthma and (B) Histopathology of airway remodeling in asthma.**

GCM - goblet cell metaplasia; TBM - thickening of basement membrane; SMH - smooth muscle cell hypertrophy.

As previously discussed, cytokines produced through T2 and non-T2 pathways contribute to airway remodeling. In addition, other remodeling factors like TGF-β have been implicated in disease progression. Genes like mesenchymal epithelial transition (MET) and the metalloproteinase MMP-10 were associated with extracellular matrix (ECM) organization and increased submucosal thickening. Moreover, epithelial damage through the downregulation of cytoskeletal proteins like Ezrin correlate with decreased epithelial barrier function and increased severity of asthma. Changes in basement membrane composition and thickness through the upregulation of fibulin-1c contribute as well to airway remodeling.

TABLE 2

Components of airway obstruction and remodeling in asthma

Airway Obstruction	Airway Remodeling
Bronchoconstriction	Smooth muscle cells hypertrophy and hyperresponsiveness
Mucous plugs	Metaplasia and hyperplasia of goblet cells
Inflammatory exudate	Epithelial cell disruption
Mucosal and submucosal edema	Increased submucosal vascularity
Inflammatory cell infiltration and activation	Reticular basement membrane thickening
Reduction in airway caliber	Changes in composition of extra cellular matrix and submucosal fibrosis
Airflow limitation	Increased submucosal collagen deposition

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5 THE UNDERLYING MECHANISMS OF ASTHMA– OVERVIEW

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KEY MESSAGES

- Asthma is a common disease with the greatest prevalence in developed countries, and rapidly increasing prevalence in low- and middle-income countries as they adopt aspects of Western living
- Asthma is a strongly heritable disease involving many susceptibility genes interacting with strong environmental factors
- Asthma is a heterogeneous disease comprising different clinical phenotypes and causal endotypes implicating a combination of inflammatory and remodelling pathways
- Most asthma is driven through Type 2 immunoinflammatory pathways that are effectively suppressed by inhaled corticosteroids
- For difficult to treat asthma, the targeting of responsible Type 2 cytokines and their receptors provides a new mechanism-driven stratified approach to asthma

Asthma is a heterogeneous disease characterised by chronic airway inflammation. It is defined by the history of wheeze, shortness of breath, chest tightness and cough that vary over time and intensity together with variable expiratory airflow limitation. It is the most common inflammatory disease of the lungs affecting more than 339 million worldwide and presents a substantial global health and economic burden. The highest prevalence of asthma is reported in the developed world, although in low- and middle-income countries, it is increasing linked to adoption of a Western lifestyle.

The most common form of asthma begins in childhood in association with atopy and other allergic conditions, however in adults, new-onset asthma is often non-allergic, though maybe associated with NSAID hypersensivity (Aspirin Exacerbated Respiratory Disease), obesity or occupational exposures.

Asthma involves inflammation and remodelling of the large-conducting airways, spreading to smaller airways as the disease becomes more severe. It has strong genetic drivers with over 100 candidates identified, many of which are preferentially expressed in the epithelium and structural cells as well as those linked to innate and adaptive immunity. Equally, there are many environmental drivers of asthma that may operate directly (e.g. viruses, allergens) or indirectly by altering the airway microbial content (microbiome).

The chronic inflammatory response in asthma is characterised by increased infiltration and activation mast cells and eosinophils orchestrated by Type 2 (T2) helper lymphocytes and/or T2 innate T cells through the secretion of T2 cytokines IL-3, -4, -5, -9, -13 and GM-CSF and production of allergen-specific IgE. A second key component of asthma, especially in more severe disease, is the generation of epithelial derived cytokines (IL-33, IL-25 and TSLP) by a stressed epithelium through environmental insults such as viral infection, alteration in the bacterial/fungal microbiome and air pollution exposure reducing epithelial barrier functions both physically (leakiness) and functionally as a

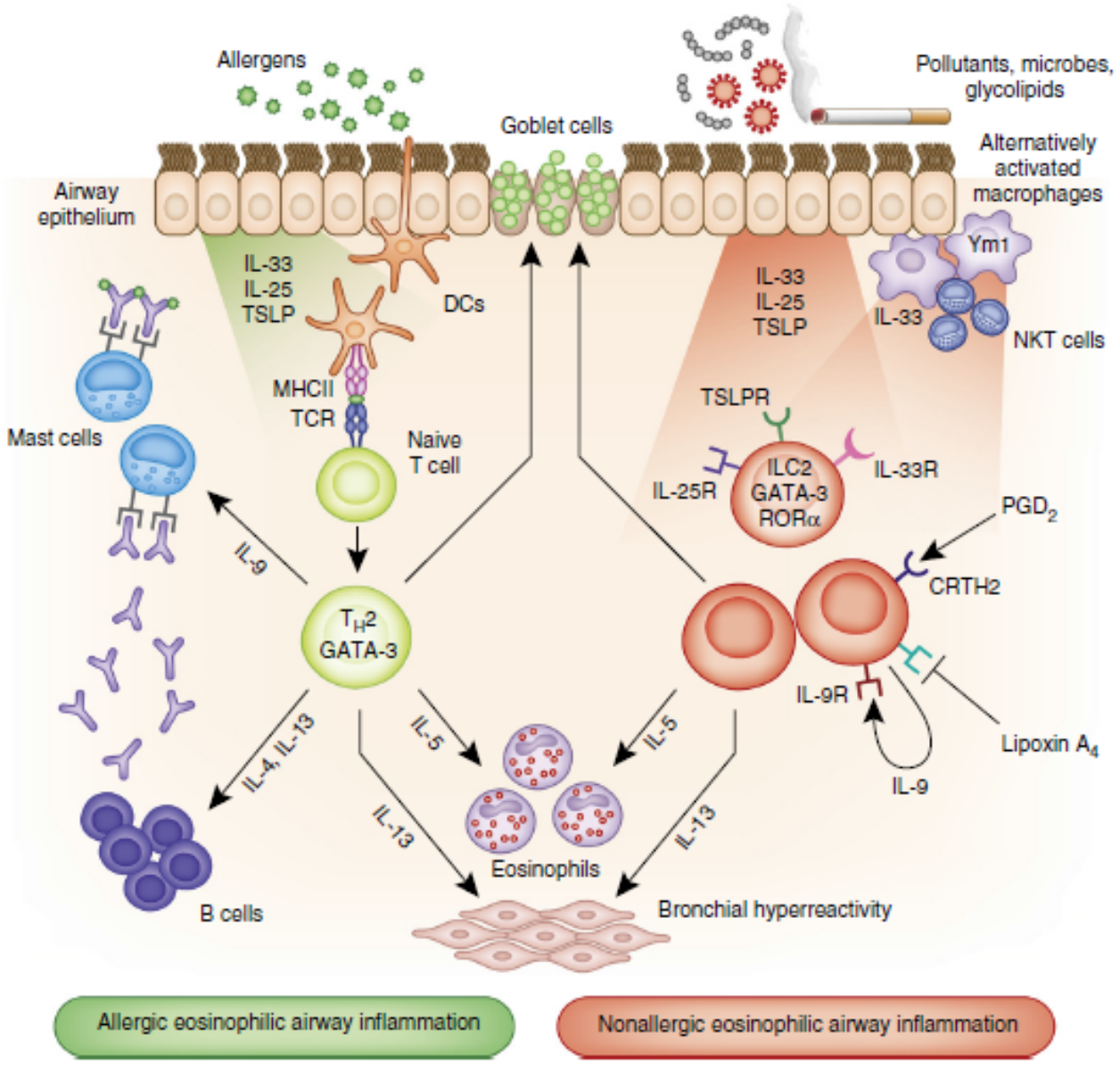

Figure 1 **Two different pathways lead to eosinophilic airway inflammation in asthma.** In allergic asthma, dendritic cells present allergens to CD4+ T cells, inducing Th2 cells, which produce IL-4, IL-5 and IL-13, and leading to IgE switching in B cells, airway eosinophilia and mucous hypersecretion. In non-allergic eosinophilic asthma, air pollutants, microbes induce the release of epithelium-derived cytokines, including IL-33, IL-25 and TSLP, which activate innate Type 2 lymphocytes (ILC2s) in an antigen-independent manner via their respective receptors (IL-17RB, ST2 and TSLPR). Activated ILC2s produce high amounts of IL-5 and IL-13, promoting eosinophilia, mucus hypersecretion and airway hyperresponsiveness. *(Adapted from Brusselle GG, Maes T, Bracke KR. Eosinophils in the spotlight: Eosinophilic airway inflammation in nonallergic asthma. Nat Med. 2013; 19: 977-9)*

CRTH2 - chemoattractant receptor-homologous molecule expressed on TH2 cells; ALX/FPR2 - receptor for lipoxin A4; FcεRI - high-affinity receptor for IgE; GATA3 - GATA-binding protein 3; PGD2 - prostaglandin D2; RORα - retinoic acid receptor–related orphan receptor a.

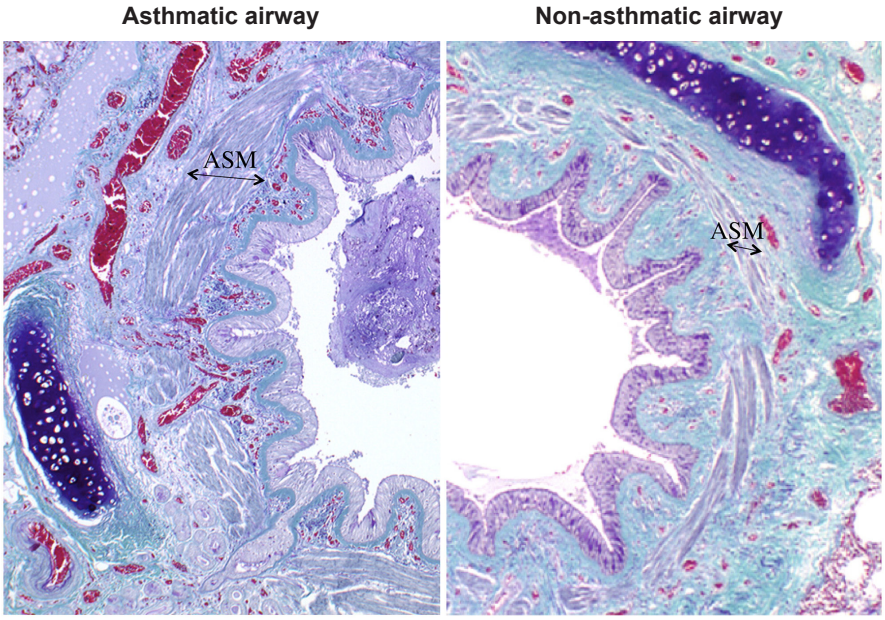

Figure 2 Remodelling of the airway in severe asthma. Note the increase in smooth muscle, vascular congestion of the mucosa, thickening of the *lamina retiularis* of the subepithelial basement membrane and goblet cell metaplasia with mucus plug formation. *(Reproduced from J Allergy Clin Immunol., Vol 141, Qiu W et al., Differential connectivity of gene regulatory networks distinguishes corticosteroid response in asthma, 1250-8, 2018 with permission from Elsevier)*

source of mediators (Figure1). The epithelial derived cytokines help set the stage for enhanced immune-inflammatory responses including macrophage/monocytes and neutrophils.

While variable airflow obstruction is the common feature of asthma it comprises different processes – spiral smooth muscle contraction linked to increased airway responsiveness, hypersecretion of viscid mucus, angiogenesis and oedema and activation of sensory neural pathways (Figure 2). Combinations of these pathobiological pathways gives rise to different asthma phenotypes that, in turn, are shaped by the range of inflammatory pathways or endotypes.

While most asthma cases can be managed by a combination of anti-inflammatory drugs (*controllers* - especially inhaled corticosteroids) and when needed, bronchodilators (*relievers* – especially inhaled β2-adrenergic agonists), difficult to control asthma requires a different approach which target the individual components of the T2 immunoinflammatory response. Biologicals administered systemically are especially valuable difficult to treat and severe asthma, especially in patients with ongoing evidence of T2 inflammation under chronic oral corticosteroids. Such biologicals include monoclonal antibody blockade of IgE (e.g. omalizumab), IL-4r/-13 receptor α (e.g. dupilimab) and IL-5 (e.g. mepolizumab and reslizumab) or its functions (e.g. IL5r – benralizumab). Biologicals are also being developed against some of the epithelial derived cytokines (TSLP and IL-33 and its receptor ST2). So far it has not been possible to totally reverse asthma once it has developed, though allergen-directed immunotherapy does seem to mimic some aspects of natural remission in upregulating of regulatory T lymphocytes.

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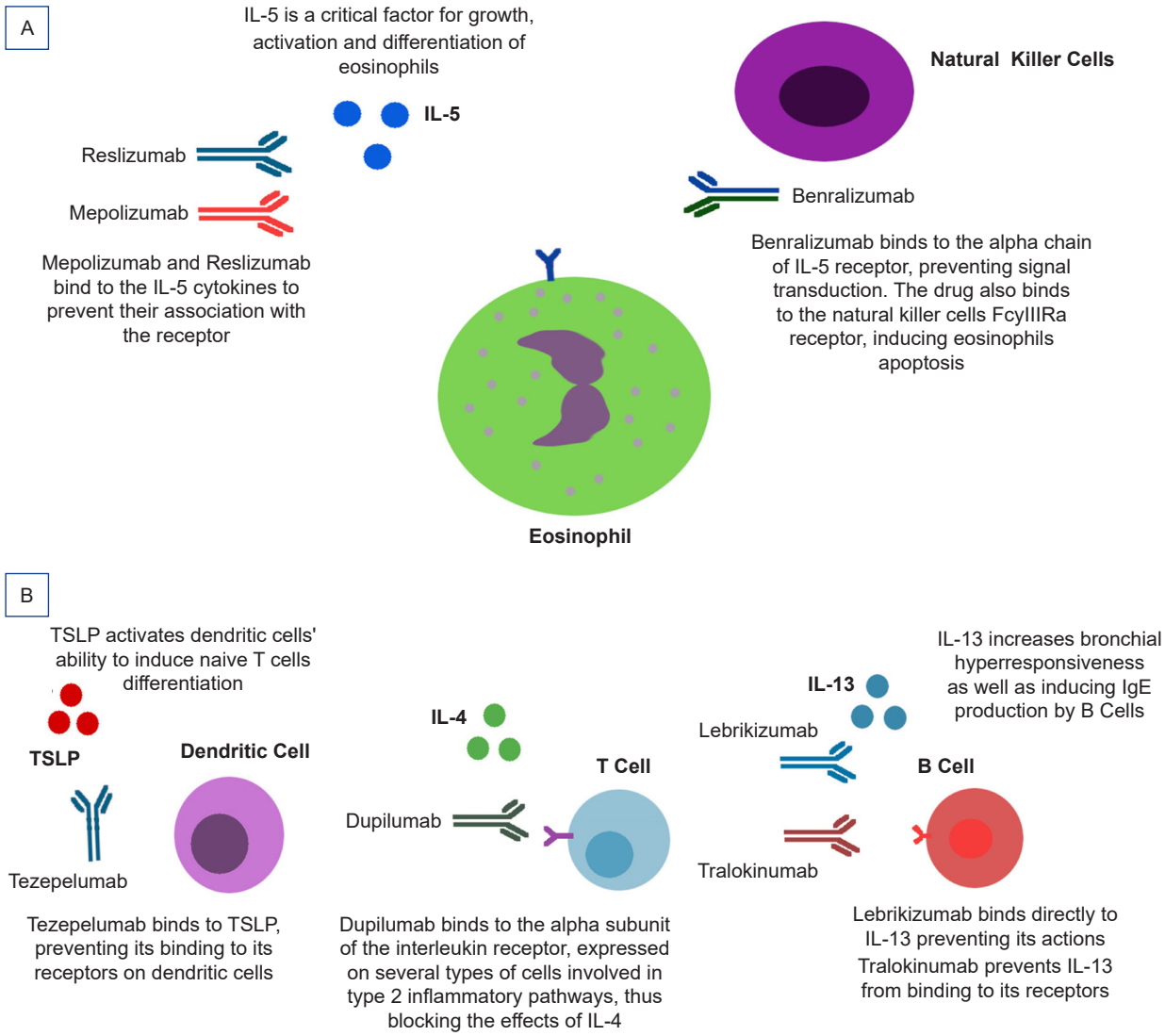

Figure 3 **Mechanism of action of agents used in the treatment of severe asthma.** (A) IL-5 is a critical factor for growth, differentiation and activation of eosinophils. Mepolizumab and reslizumab act as antibodies to IL-5 cytokines, binding to them and preventing their association with the receptor. Benralizumab is an IL-5 receptor blocker. It binds to the alpha chain of the IL-5 receptor (IL-5Rα), expressed on eosinophils. The antibody's Fc domain binds to the FcγRIIIa domain, expressed on natural killer cells, which induces eosinophils' apoptosis. (B) TSLP is an important cytokine in the inflammatory cascade, as it activates dendritic cells, inducing inflammatory reactions through their effects on T cells differentiation. Tezepelumab inhibits TSLP effects by binding to the cytokine. IL-4 is a potent inducer for Th2 cells differentiation, existing on several types of immune cells. Dupilumab binds to the alpha subunit of IL-4 receptor, inhibiting its effects. Lebrikizumab binds to IL-13 cytokines, and tralokinumab binds to its receptor on B cells, inhibiting its effects on IgE production. (*Reproduced from: Edris A, De Feyter S, Maes T, Joos G, Lahousse L. Monoclonal antibodies in type 2 asthma: a systematic review and network meta-analysis. Respir Res. 2019; 20: 179*)

6a THE INNATE IMMUNE RESPONSE IN ASTHMA: INNATE LYMPHOID CELLS

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KEY MESSAGES

- Innate lymphoid cells (ILCs) are divided into three different subsets, types 1, 2 and 3, which are considered to be the innate counterparts of Th1, Th2 and Th17 lymphocytes
- Group 2 ILCs (ILC2s) are involved in the pathophysiology of eosinophilic asthma, mainly through their production of IL-5 and IL-13, which mediate eosinophil infiltration and goblet cell hyperplasia in the airway
- Inducers of ILC2 activation and proliferation include epithelial-derived cytokines (IL-25 and IL-33), lipid mediators (PGD2, LTE4 and LTD4) and neuropeptides (neuromedin U, vasoactive intestinal peptide and calcitonin gene-related peptide)
- Thymic stromal lymphopoietin (TSLP) mediates ILC2 survival and confers corticosteroid resistance
- Inhibitors of ILC2 activation and proliferation include epithelial-derived cytokines (type I interferons), type 1 cytokines (IFNγ and IL-27), lipid mediators (PGI2 and PGE2), neurotransmitters (cholinergic and β2-adrenergic agonists) and IL-10

Innate lymphoid cells (ILCs) are hematopoietic cells that have a lymphoid morphology but lack antigen receptors. There are three main subsets of ILCs, types 1, 2 and 3; they are considered to be the innate counterparts of Th1, Th2 and Th17 lymphocytes, respectively. Among them, ILC2s are the predominant ILC population in the lungs at steady state.

In mice, administration of environmental antigens as *Alternaria* and protease allergens induces asthma-like eosinophilic airway inflammation through activation of ILC2s, even without acquired immunity, indicating that ILC2s are involved in innate-type eosinophilic airway inflammation. In humans, the numbers of ILC2s in both the bronchoalveolar lavage and induced sputum were significantly higher in eosinophilic asthma patients compared to controls. Of note, the number of ILC2s in induced sputum was significantly higher in steroid-resistant, severe eosinophilic asthma patients compared to mild asthma patients, whereas the numbers of Th2 cells were comparable. These findings indicate that ILC2s may be involved in the pathophysiology of eosinophilic asthma and the induction of steroid resistance.

ILC2s are activated by signals from surrounding cells, including airway epithelial cells and immune cells, upon exposure to external stimuli. Following activation they produce their signature type-2 cytokines IL-5 and IL-13. These type-2 cytokines induce infiltration of eosinophils, goblet cell hyperplasia in the airway, and disruption of tight junctions between epithelial cells, thus compromising the integrity of the bronchial epithelium. Two epithelial-derived cytokines, IL-33 and IL-25 were the first described activators of ILC2s. Lipid mediators such as prostaglandin (PG) D2, leukotriene (LT) E4 and LTD4, and neuropeptides such as neuromedin U, calcitonin gene-related peptide and vasoactive intestinal peptide were recently reported to induce activation and proliferation of ILC2s in the airway. Another epithelial-derived factor, thymic stromal lymphopoietin (TSLP),

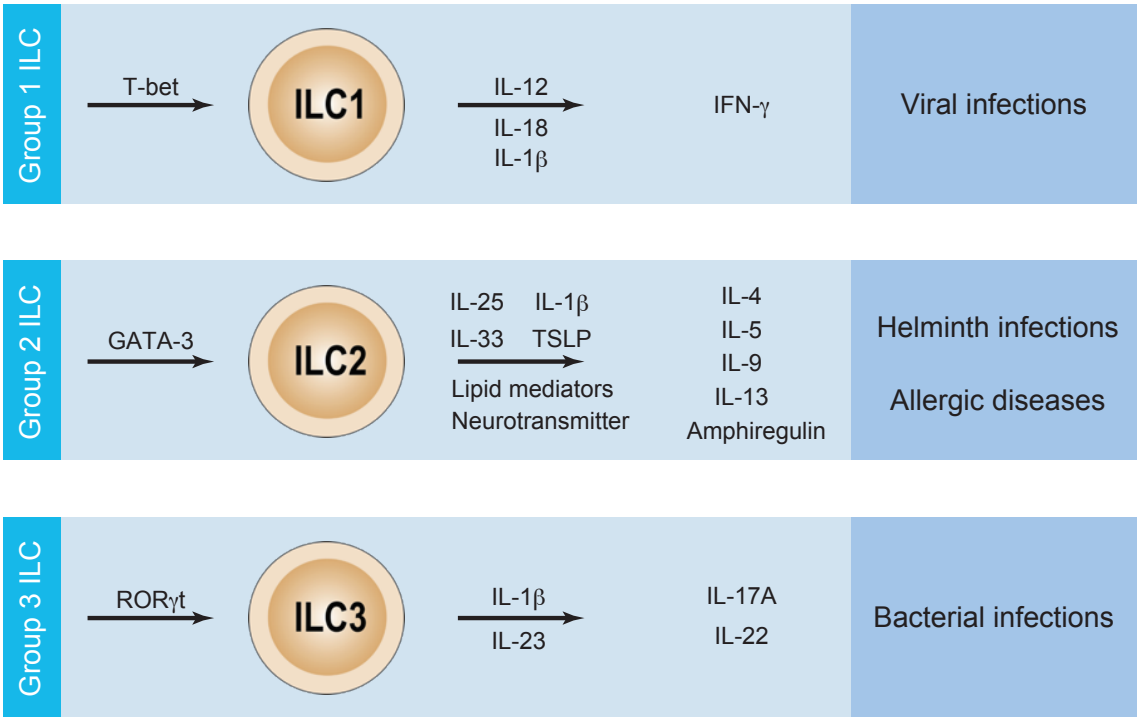

Figure 1 **Classification of innate lymphoid cells.**

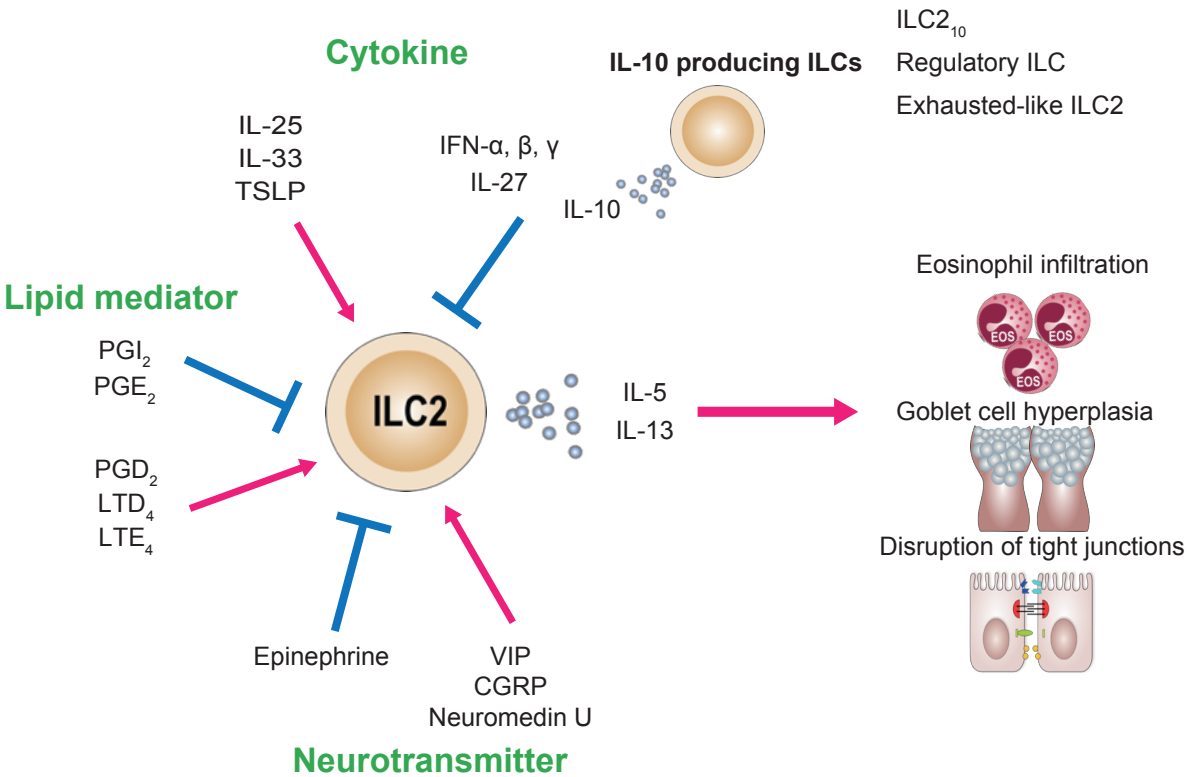

Figure 2 **Regulation of ILC2-mediated inflammation in the airways.**

is involved in ILC2 survival rather than activation, yet it can also amplify IL-33-mediated activities. Moreover, TSLP induces steroid resistance of ILC2s by promoting STAT5 phosphorylation and Bcl-xL expression, ultimately leading to corticosteroid resistance in asthma. Anti-TSLP treatment significantly alleviated asthma exacerbation in steroid-resistant asthma patients.

On the other hand, several cytokines involved in type 1 immunity inhibit activation and proliferation of ILC2s. Both type I and II interferons and IL-27 suppressed ILC2 function during bronchial inflammation in a STAT1-dependent manner. Lipid mediators such as PGI2 and PGE2, and neurotransmitters such as epinephrine also inhibit activation of ILC2s, with decreased secretion of IL-5 and IL-13 as well as reduced airway inflammation and hyperresponsiveness. IL-10 secreted by regulatory T cells (Tregs) also inhibits activation of ILC2s. Interestingly, recent studies have shown that IL-10–producing ILCs may be derived from ILC2s. These cells have been given various names, including $ILC2_{10}$ cells, regulatory ILCs or exhausted-like ILC2s. Up to now the role of these cells in asthma pathophysiology remains unclear.

While there is growing evidence of involvement of ILC2s in the pathophysiology of eosinophilic asthma, little is known about the roles of other ILC subsets in asthma. There is a possible involvement of ILCs in non-eosinophilic asthma. In mice, ILC3s are reportedly involved in obesity-related asthma. However, in humans, possible involvement of ILC3s in non-allergic asthma remains unclear.

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6b THE INNATE IMMUNE RESPONSE IN ASTHMA - MACROPHAGES

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KEY MESSAGES

- Several subsets of macrophages co-exist in the lungs
- The role of macrophages in murine models is unclear due to the lack of tools to target specific populations
- In patients with asthma, lung macrophages have altered functions
- Macrophages are targeted by several therapies used by patients with asthma

The lung is continuously challenged by a variety of foreign substances, including pathogens and allergens. Maintenance of homeostasis requires a system that can precisely calibrate the extent of inflammatory responses in the lung. Macrophages fulfill this function. In steady-state conditions, two populations of macrophages co-exist in the lung: the well-studied alveolar macrophages (AMs), that rely upon GM-CSF for their development, and interstitial macrophages (Table 1). Upon inflammation, the release of CCL2 by lung epithelial cells allows the recruitment of monocytes, which contribute to the pool of AMs (Figure 1). These monocyte-derived macrophages are transcriptionally very similar to resident AMs.

Despite the growing knowledge on lung macrophage ontogeny, their functions still remain enigmatic. The main reason for this is that the experimental lung field currently lacks the technical tools to specifically deplete different populations of macrophages. The widely used suicide strategies to target macrophages in mice have yielded opposite results showing that, depending on the asthma model used, lung macrophages can display pro- or anti-inflammatory responses.

Even if the role of lung macrophages in asthma is still debated in mice, one certainty in this field is that macrophages from asthmatic patients are functionally different from those of healthy individuals (Figure 2). Phagocytosis of particulate matters and of lung-colonizing bacteria is impaired in lung macrophages from adults and children with asthma. This can have important consequences and could contribute to the bacterial-induced disease exacerbations, which characterize the severe forms of asthma. Patients with severe uncontrolled asthma present an accumulation of neutrophils with or without eosinophils in the airways. As neutrophils die, they need to be cleared from the lungs by macrophages through efferocytosis. The capacity to perform efferocytosis is strongly reduced in macrophages of severe asthmatic patient1. It is not clear if this contributes in any way to asthma pathophysiology, but the accumulation of neutrophils corpses could lead to the accumulation of noxious substances that would perpetuate inflammation and contribute to tissue damage.

Lung macrophages are also a major source of pro-inflammatory cytokines like IL-1β, TNFα, or IL-6. In asthmatics, macrophages produce these cytokines in greater amounts. At the same time, the amounts of anti-inflammatory cytokines like IL-10 are reduced in AMs from asthmatic patients. The shift of the balance towards pro-inflammatory mediator production suggests that AMs might contribute to chron-

TABLE 1

Markers allowing the identification of the different lung macrophage populations in mice and humans

Markers	Mouse		Human	
	Alveolar	Interstitial	Alveolar	Interstitial
CCR2	-	low		
CD11b	-	+	+	+
CD11c	+	-/low	+	+
CD64	+	+	+	+
CD86	+	+	+	low
CX3CR1	-	+		
Mertk	+	+		
MHCII	Low	+		
Siglec F	+	-		
CD14			-	+
CD16			+	Int
CD169			+	-
CD206			+	Int
HLA-DR			+	+

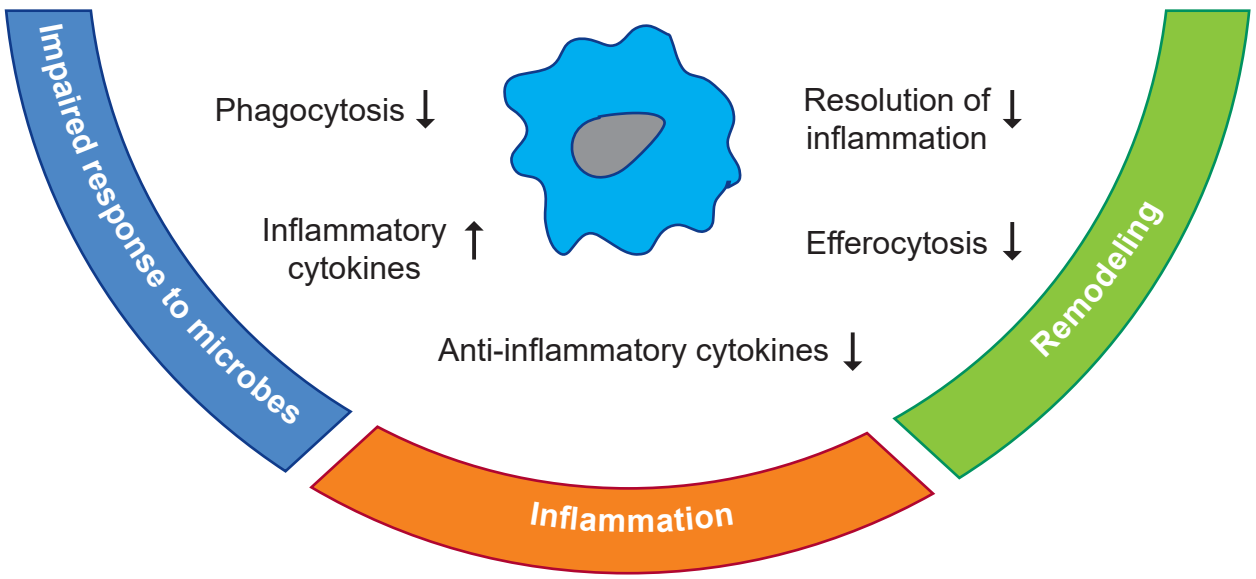

Figure 1 **During homeostasis (left), alveolar macrophages (AM) reside in the alveolar space and require GM-CSF derived from alveolar epithelial cells for their development.** Following exposure to allergens (right), alveolar epithelial cells produce CCL2 that allows the recruitment of monocytes to the lung where they will differentiate into monocyte-derived alveolar macrophages. Lung macrophages produce inflammatory mediators and contribute to chronic inflammation.

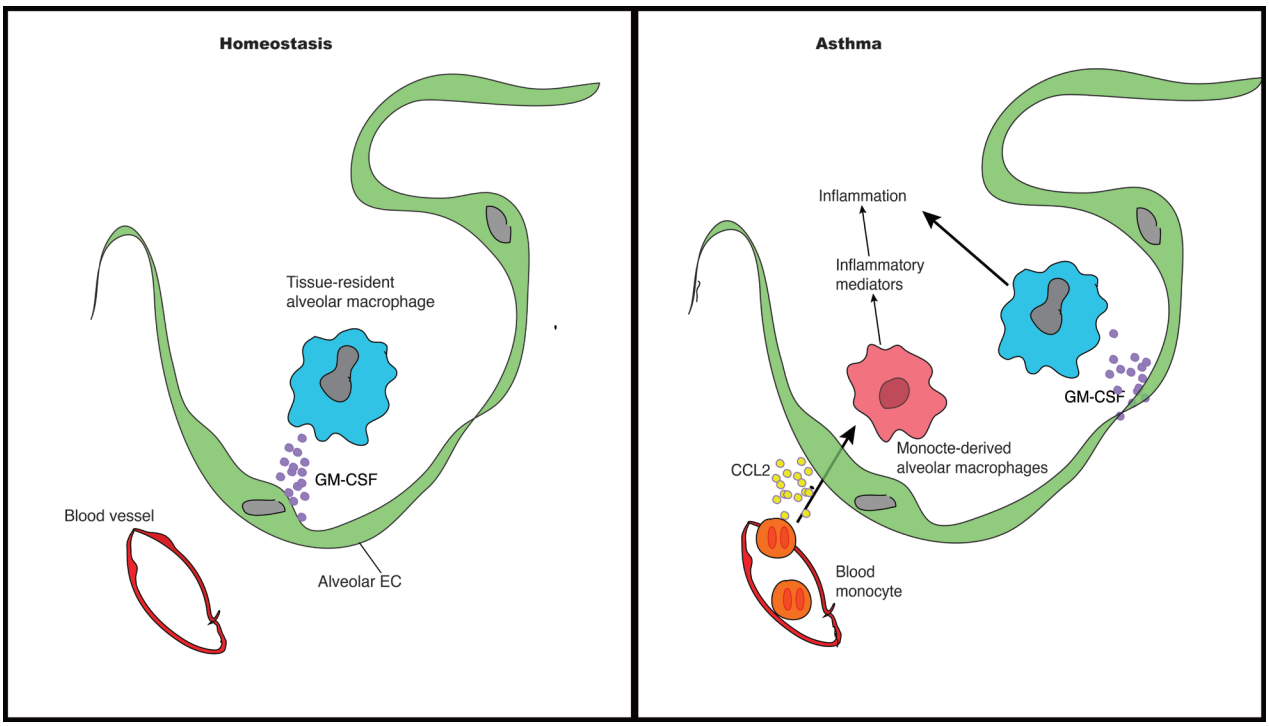

Figure 2 **In the lung, alveolar macrophages perform different functions during homeostasis.** These are altered in asthma, leading to deficient handling of colonizing bacteria, pulmonary inflammation and tissue remodeling.

ic airway inflammation (Figure 1). AMs, under the influence of the strong Th2 environment present in asthmatic lungs, turn on a gene program that leads to the development of tissue repair, remodeling and fibrosis. In addition, these macrophages represent a permissive niche for the development of pathogens, found to be associated with asthma exacerbations.

Because macrophages are very abundant cells in the lungs, and because their altered functions might contribute to chronic inflammation and exacerbations, they represent an attractive therapeutic target in asthma. Several drugs used in asthma, like corticosteroids or leukotriene antagonist, can decrease the production of pro-inflammatory mediators by alveolar macrophages. However, with the recent evidence that different macrophage population co-exist, many of the earlier findings will need to be revisited to allow to assign specific phenotypes and functions to specific types of macrophages. In the future, this may help in the development of targeted therapies.

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6c MAST CELLS IN ASTHMA

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KEY MESSAGES

- Mast cells play critical pathogenetic roles in both allergic and non-allergic asthma
- Mast cell density in bronchial biopsies correlate with asthma severity
- Mast cell mediators contribute to inflammation, airway hyperreactivity, mucus secretion and airway remodeling
- Novel interventions targeting mast cells, mast cells mediators, or their activation pathways should be explored for future asthma therapies

More than 90% of asthma in children and 50% in adults is classified as allergic asthma. Mast cells (MCs) are involved in the pathogenesis of both allergic and nonallergic asthma. Mast cells are the effector cells of immediate type hypersensitivity reactions and contribute to upper and lower airway inflammation and symptoms in allergic patients. They are derived from hematopoietic progenitors from the yolk sac in embryo and from the bone marrow in children and adults and mature under the influence of SCF/KIT. Their function in innate immune system include first line defense against pathogens, neutralization of toxins, as well as recruitment of other immune cells. Based on their location and protease content, at least 2 pools of mast cells are observed: connective tissue mast cells (CTMC) carrying tryptase, chymase, CPA3 and cathepsin G and mucosal mast cells (MMC) carrying primarily tryptase in their granules. Both types are found in the human lung. In healthy individuals they reside in lamina propria and around blood vessels, while in asthma MCs infiltrate airway smooth muscle, epithelium and mucosal glands.

Mast cells release a variety of mediators (Table 1) through IgE or non-IgE dependent triggers (Table 2) which contribute to inflammation and pathogenesis of asthma. Interestingly, alveolar mast cells have low IgE receptor expression, which is upregulated in allergic asthma. The biologic effects of mast cell mediators include bronchial smooth muscle contraction, mucus production, airway remodeling and recruitment of other inflammatory cells. Increased numbers of mast cells may be seen in bronchial biopsies of asthmatic subjects (allergic and non-allergic), which correlate with airway hyper-responsiveness. Mast cell mediators have been detected in bronchial secretions, as well as systemically after allergen challenge in patients with allergic asthma. Furthermore, patients with aspirin exacerbated respiratory disease have a baseline hyperactivated mast cell phenotype with increased levels of systemic mast cell mediators, including PGD2 and LTE4, which further increase upon exposure to NSAIDs.

In clinical practice, the efficacy of anti-IgE monoclonal antibodies (e.g. omalizumab), leukotriene antagonists and mast cell stabilizers (e.g. cromolyn) as well as improvements with allergen immunotherapy emphasizes mast cell involvement in early- and late-phase asthma responses. New investigational approaches targeting mast cells or their mediators including anti-tryptase antibodies or mast cell cytoreduction by KIT selective tyrosine kinase inhibitors, have shown promise in preliminary animal or human studies of asthma.

TABLE 1

Effect of selected mast cell mediators in the asthmatic inflammation

Mediator	Effect in asthma
Histamine	Bronchoconstriction, vascular permeability, chemotaxis, mucus secretion
PGD2	Bronchoconstriction, chemotaxis
CysLTs	Bronchoconstriction, mucus production, vascular permeability
LTB4	Chemotaxis
PAF	Bronchoconstriction, vascular permeability
Tryptase	Possibly fibrosis and tissue remodeling
Chymase	Extracellular matrix degradation and turnover
IL4	Tissue remodeling, Th2 cytokine production
IL5	Eosinophil migration
IL6	Enhances Ig production, mucus secretion, ASM contractility
IL33	Inflammatory cytokine production
IL13	Mucus production, ASM contractility
TNF	Th2 cytokine production, adhesion of inflammatory cells, ASM contractility
TSLP	Th2 cytokine induction
TGFβ1	Airway fibrosis
VEGF	Angiogenesis
FGF2	Fibrosis

TABLE 2

Selected triggers of mast cell activation

Trigger	Receptor
IgE	FcεRI and FcεRII
IgG	FcγRI
Complement C3a and C5a	C3aR, C5aR
Cationic peptides	MRGPRX2
Stem cell factor	KIT
Microbial components, PAMPs	TLRs
Endogenous peptides	SPR, MRGPRX2
Epithelial-derived cytokines (TSLP, IL-33)	TSLP receptor, ST2
Purines (adenosine, ATP)	P2X, P2Y, adenosine receptors

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6d

BASOPHILS

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KEY MESSAGES

- Basophils are the least common granulocytes, representing less than 1% of peripheral blood leukocytes
- Recent studies have revealed previously unappreciated roles for basophils, distinct from those played by tissue-resident mast cells, in a variety of immune responses including allergy
- When activated through an IgE-dependent or -independent pathway basophils release pro-allergic factors, including histamine, proteases, lipid mediators, Th2 cytokines and chemokines
- The accumulation of basophils was detected in the lung and sputum of asthmatic patients
- Studies using mouse models demonstrated a crucial role for basophils in the pathogenesis of asthma

Basophils are the rarest granulocytes, which account for less than 1 % of peripheral blood leukocytes. Blood-circulating basophils share some features with tissue-resident mast cells, including basophilic granules in the cytoplasm and surface expression of the high-affinity IgE receptor FcεRI. Therefore, basophils had been erroneously considered as minor relatives of mast cells for a long time and analyzed in clinics as surrogates of less-accessible tissue-resident mast cells for diagnosis of allergen sensitization in allergic patients. Even though the evolutional conservation of basophils in many animal species suggested beneficial roles for basophils *in vivo*, the paucity of useful analytical tools had hampered the advance of basophil research. Recent studies using newly-developed tools, including basophil-deficient mice, have illustrated non-redundant functions of basophils in various immune responses, such as allergic reactions and protective immunity against parasitic infections in mouse models.

Basophils infiltrate the lung tissue of asthmatic patients and their number correlates with airway responsiveness, especially in fatal asthma episodes. Moreover, the number of activated basophils is increased in the sputum of patients with eosinophilic asthma, compared with those with non-eosinophilic asthma, suggesting a possible role for basophils in eosinophilic asthma. Basophils are activated through IgE-dependent and -independent stimuli, including allergens, cytokines (IL-3, and IL-33) and Toll-like receptor ligands (Figure 1). Activation of basophils leads to the rapid release of their granule contents, including histamine and proteases, and the synthesis of lipid mediators (leukotriene C4), Th2 cytokines (IL-4 and IL-13) and chemokines. These mediators are associated with symptoms and signs of asthma, including cough, bronchoconstriction and airway hyperresponsiveness. Intriguingly, anti-IgE therapy results in the rapid reduction of FcεRI density on basophils rather than mast cells, with reduced mediator release from basophils, suggesting an important contribution of basophils to the exacerbation of a certain type of asthma in an IgE-independent manner.

Studies using mouse models of asthma demonstrated that basophils play indispensable roles in the development of asthma pa-

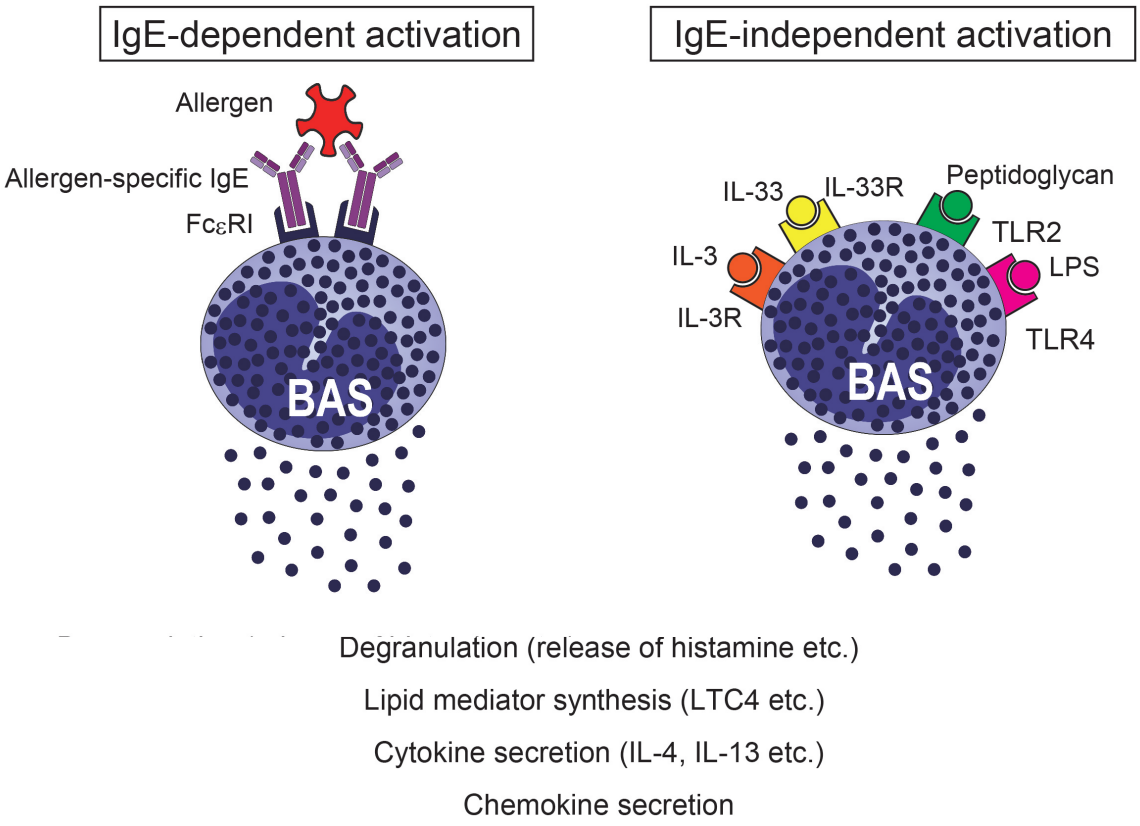

Figure 1 **IgE-dependent and –independent activation of basophils.** Basophils are activated via multiple pathways. In the IgE-dependent activation, basophils are activated by allergens through cross-linking of allergen-specific IgE on the cell surface, leading to the release of granule contents(degranulation) and de novo synthesis of lipid mediators, cytokines and chemokines. In the IgE-independent activation basophils are activated by cytokines (IL-3 and IL-33) or Toll-like receptor ligands (ligands for TLR2 and TLR4).

thology. In an ovalbumin-induced asthma model, basophils infiltrate the lung and amplify Th2 cytokine production from memory T cells. In an allergenic protease-induced asthma model, IL-4 released from IL-33-activated basophils promotes the activation of group 2 innate lymphoid cells, leading to the enhanced infiltration of eosinophils and the exacerbation of asthma (Figure 2). The positive correlation between basophil and eosinophil numbers in sputum of asthmatic patients suggests a key role for human basophils in the recruitment of eosinophils to the lung and the induction of human asthma pathology. Therefore, basophils could be a good target cells for the treatment of eosinophilic asthma.

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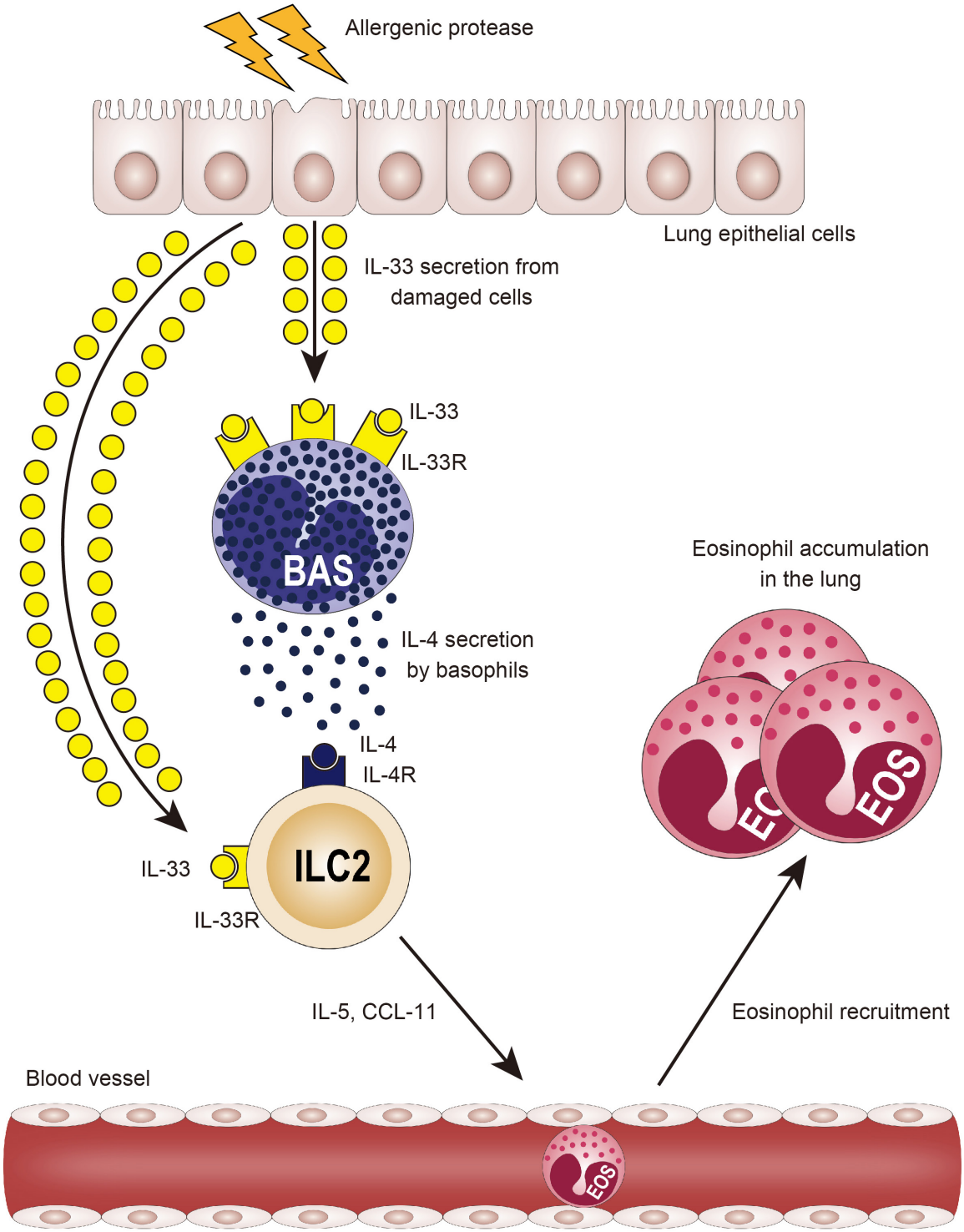

Figure 2 Proposed role of basophils in the pathogenesis of asthma, on the basis of the findings in an allergenic protease-induced mouse model of asthma. Inhalation of allergenic protease induces IL-33 release from damaged lung epithelial cells. Basophils are recruited to the lung and produce IL-4 in response to IL-33. IL-33 and basophil-derived IL-4 cooperatively activate group 2 innate lymphoid cells (ILC2) to produce IL-5 and CCL11 (eotaxin-1), leading to the enhanced migration of eosinophils (EOS) to the lung.

6e

DENDRITIC CELLS IN ASTHMA

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KEY MESSAGES

- Dendritic cells (DCs) are the first immune cells that come into contact with inhaled stressors at the mucosal surface and continuously sample luminal content with their trans-epithelial dendrites
- The dynamic interactions between inhaled antigens, damaged epithelium, and the cytokine milieu result in activation of either proinflammatory or tolerogenic phenotype of airway DCs
- Different types of activated DCs can further polarize T cells into an allergic or tolerogenic response
- Understanding the interplay between epithelial cells, DCs, and other immune cells in asthmatic airway inflammation will enable the identification of novel therapeutic targets in asthma

Dendritic cells (DCs) are the crucial component of the innate immunity of the airways accounting for initiating numerous immune responses in asthma. DCs comprise cells of different developmental lineages classified as plasmacytoid DCs (pDCs), myeloid (conventional) DCs (mDCs), and monocyte-derived DCs (Figure 1). In contrast with pDCs and mDCs, monocyte-derived DCs were, to date, reported only in the steady-state in the lungs; therefore, their role in asthma remains elusive.

Different DC subsets may act as either activators or regulators of immune responses. Within the lungs, DCs are located mainly at the basolateral side of epithelium, where they can recognize and sample inhaled antigens (such as infectious agents, allergens and pollutants) from the airway lumen (Figure 2). In fact, DC polarization towards either immune-stimulatory or immune-modulatory activities is triggered by their direct interaction with the antigen. In addition, the polarisation process is modulated by the neighboring epithelial cells and is largely influenced by the local cytokine microenvironment (Figure 2).

Recently, our understanding of epigenetic reprogramming of innate immune cells allowed us to define mechanisms of innate immune memory, which may be associated with more intense (trained immunity) or less intense (trained tolerance) response to second antigen challenge after return to steady-state. It has yet to be determined whether this mechanism is also involved in regulating DC function in asthma. However, indirect evidences showed that allergen re-stimulation of atopic host causes reactivation of Th2 inflammation by monocyte-derived DCs.

After antigen uptake, activated DCs migrate to lymph nodes wherein they process and present antigen-derived peptides on their surface in the context of MHC molecules in order to induce naïve T cell differentiation and memory cells' clonal expansion (Figure 3). mDCs are involved mainly in the development of Th2, Th1, and Th9 immune responses dependent on the local microenvironment. Importantly, in asthmatic patients, airway epithelium-derived cytokines TSLP, IL-25, and IL-33 polarize mDCs into promoting type 2 immune responses, leading to eosinophilia, enhanced IgE secretion, increased mucus production, and remodeling. On the other hand, DCs from asthmatic individuals upregulate the TSLP receptor and express Th2 promot-

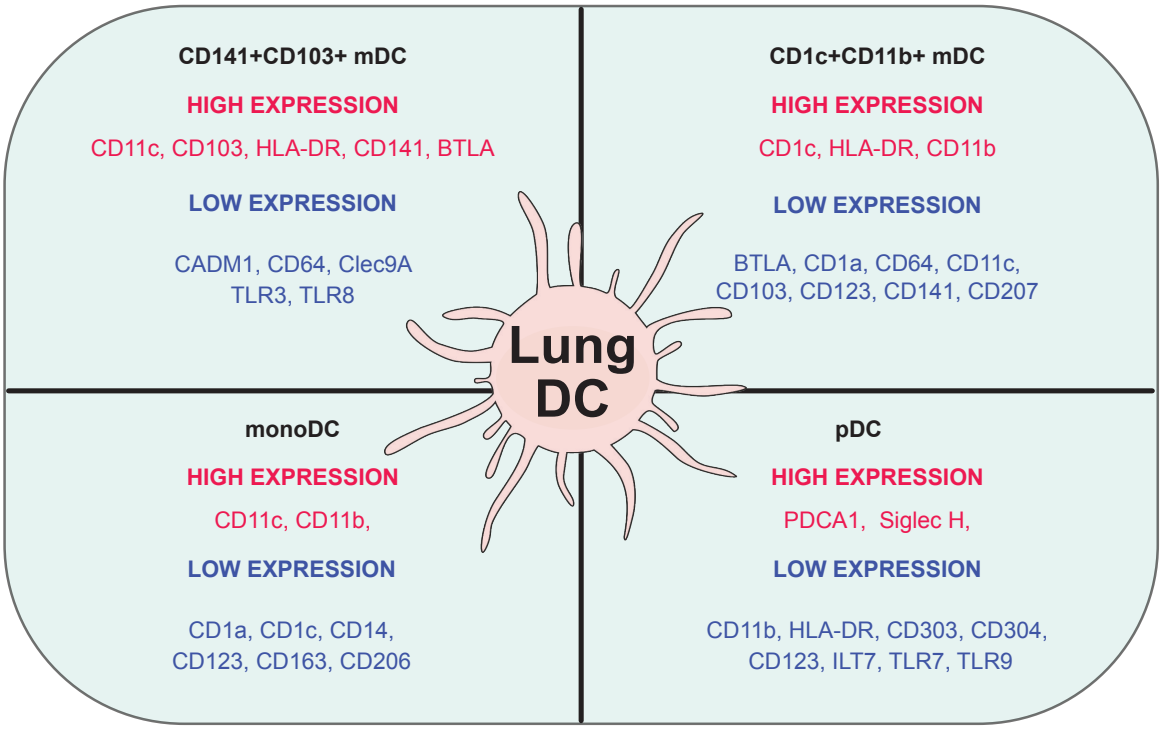

Figure 1 **Subpopulations of lung dendritic cells.**

ing costimulatory molecules and soluble factors such as OX40L and CCL17, respectively.

Additionally, activated mDCs play a crucial role in the chronic phase of asthmatic inflammation and in asthma exacerbations by releasing inflammatory cytokines and chemokines that attract other inflammatory cells to inflamed lungs. Interestingly, prolonged exposure to endotoxins and farm dust reduces epithelial responsiveness and favors the maintenance of mDCs in an immature (inactivated or semi-activated) tolerogenic state.

In contrast to mDCs, pDCs are more involved in anti-viral immunity and may act as rather tolerogenic agents inducing regulatory T cells and release of anti-inflammatory IL-10 and TGF-beta. Notably, depletion of pDCs in mice model of allergic lung inflammation increased Th2 immune responses and, consequently, lung inflammation. Conversely, the transfer of allergen-primed pDCs into mice before challenge significantly decreased the number of inflammatory cells in BALF.

In summary, DCs play a crucial role in orchestrating numerous immune responses underlying asthmatic airway inflammation. Their phenotype and function are significantly regulated by epithelial cells, with epithelium-derived cytokines specifically dictating the fate of ate DCs and their mobilization from the periphery. Given the multifaceted roles of DCs in airway inflammation, therapies targeting different pathways regulated by DCs can contribute to more efficient asthma management.

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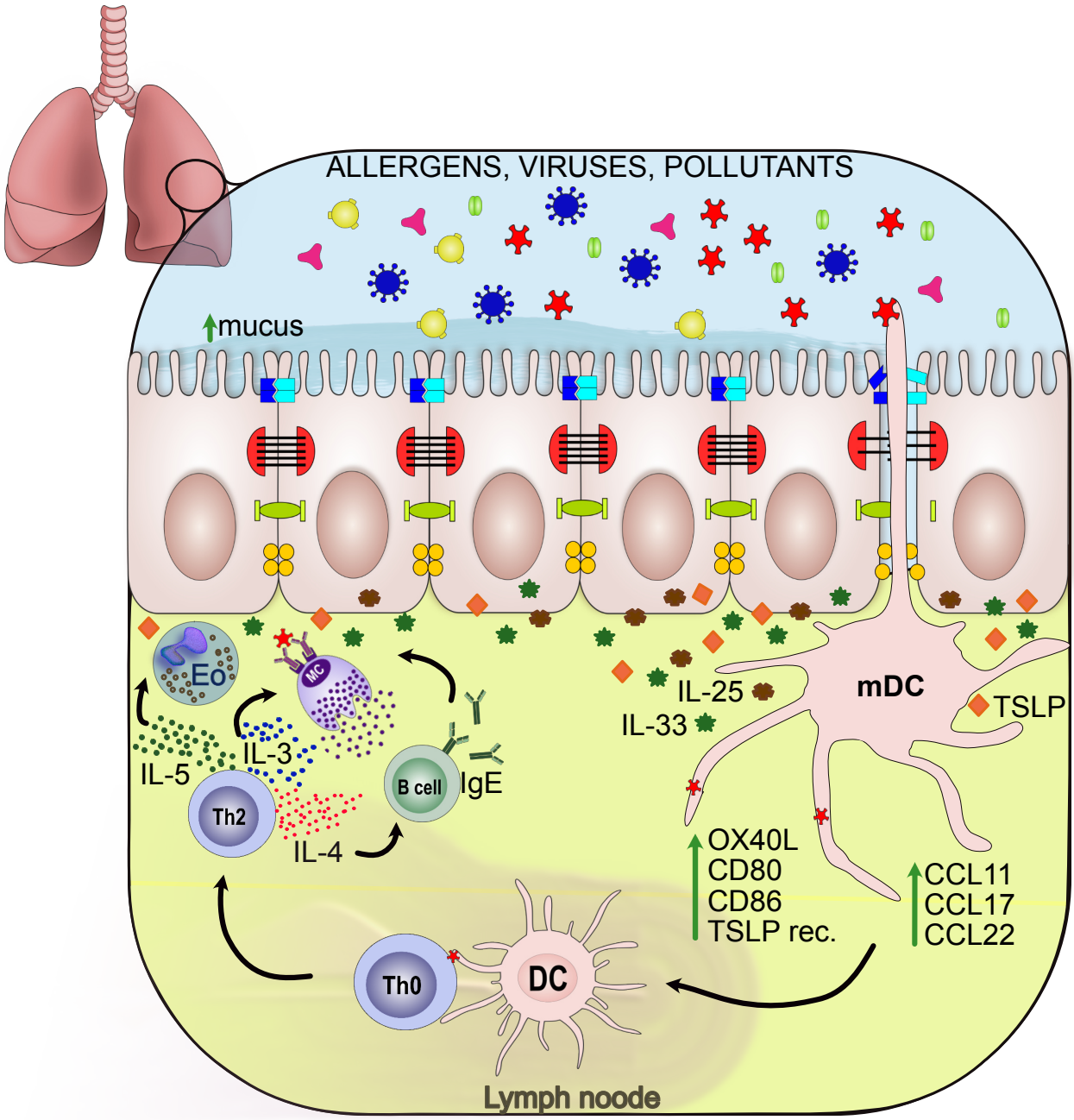

Figure 2 **The role of dendritic cells in the induction of Th2-driven lung inflammation in asthma.** DCs acquire antigen from the mucosal side and become primed by epithelial cell-derived cytokines. Activated DCs process antigen and present immunogenic peptides in the context of MHC class II molecules to T cells in the lymph node. Induced Th2 cells release high levels of IL-3, IL-4, IL-5, and IL-13, leading to eosinophilia, enhanced IgE production, mast cell activation, and mucus overproduction.

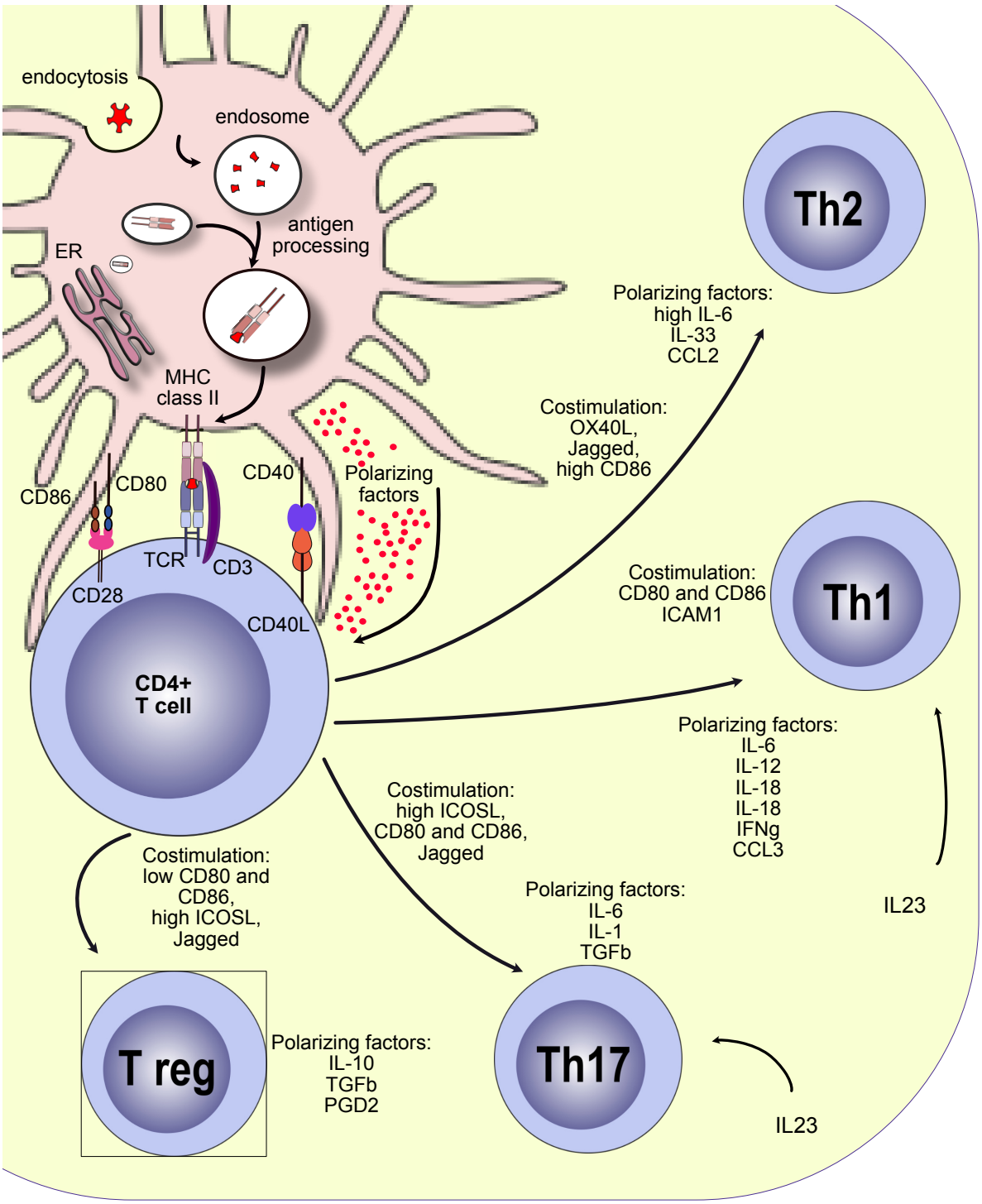

Figure 3 **Antigen presentation and T cell polarization by dendritic cells in the lymph node.** T cell activation requires two signals. The first one is antigen-specific and derived by the interaction of immunogenic peptide of the antigen presented in the context of MHC class II protein with T cell receptor (TCR). The second signal, referred to as costimulatory, is induced by costimulatory molecules (checkpoint molecules) such as CD80/CD86 and CD28, CD40 and CD40L, ICOS and ICOSL, among others. The direction of T cell polarization depends on DC costimulatory molecules and released soluble mediators.

7a THE ADAPTIVE IMMUNE RESPONSE IN ASTHMA - B CELLS

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KEY MESSAGES

- B cells contribute to the pathogenesis of asthma through the production of allergen-specific IgE antibodies
- B cells may also contribute to the pathogenesis of asthma through presentation of allergen-derived peptides, thereby initiating T cell responses
- B cells can promote induction of allergen tolerance through the production of neutralizing antibodies, in particular of the IgG4 isotype
- B cells also contribute to induction of allergen tolerance through the production of anti-inflammatory cytokines

B cells play a key role in adaptive immune responses through several mechanisms including antibody production, antigen presentation and cytokine production.

The available data on the role of B cells in the pathogenesis of asthma remains relatively limited and is largely focused on their role in the production of allergen-specific IgE antibodies. While it is clear that allergen-specific IgE is a key factor in the pathogenesis of allergic asthma, the cellular and molecular mechanisms of the regulation of IgE production and the immunological memory of IgE responses remain still elusive. Much of our knowledge of B cells in the context of allergic airway inflammation comes from murine models. While these models provide valuable mechanistic insight, the translation to human disease remains often challenging.

In order to produce IgE antibodies, B cells must undergo class-switch recombination (CSR) to IgE. This process can take place through direct switching fom IgM (which is expressed by naïve B cells) to IgE as well as through sequential CSR in which naïve B cells first switch to an IgG or IgA intermediate and upon subsequent allergen exposure switch further to IgE (Figure 1). While direct CSR is thought to result in the generation of low affinity IgE antibodies, sequential CSR appears to generate high affinity IgE. It still remains incompletely understood whether there exists a population of IgE-switched memory B cells or that the immunological memory of the IgE response resides in long-lived IgE-producing plasma cells or memory B cells expressing another isotype.

It has long been thought that IL-4-producing T_H2 cells are the key drivers of IgE CSR. However, recent findings indicate that follicular helper T (T_{FH}) cells are indispensable for IgE CSR. A subset of $GATA3^+$ T_{FH} cells co-expressing IL-4, IL-5 and IL-13 is required for eliciting high affinity anaphylactic allergen-specific IgE, derived from sequentially switched B cells. Low affinity non-anaphylactic IgE can be generated independently of IL-13. CSR typically takes place in secondary lymphoid organs but there is evidence that in patients with asthma and allergic rhinits that CSR can also occur in the mucosa.

Besides their contribution to the pathogenesis of asthma through the production of IgE antibodies, B cells also play a role in the induction of allergen tolerance (Figure 2). This appears to be mainly mediated through the production of neutralizing antibodies, in particular of the IgG4 isotype and

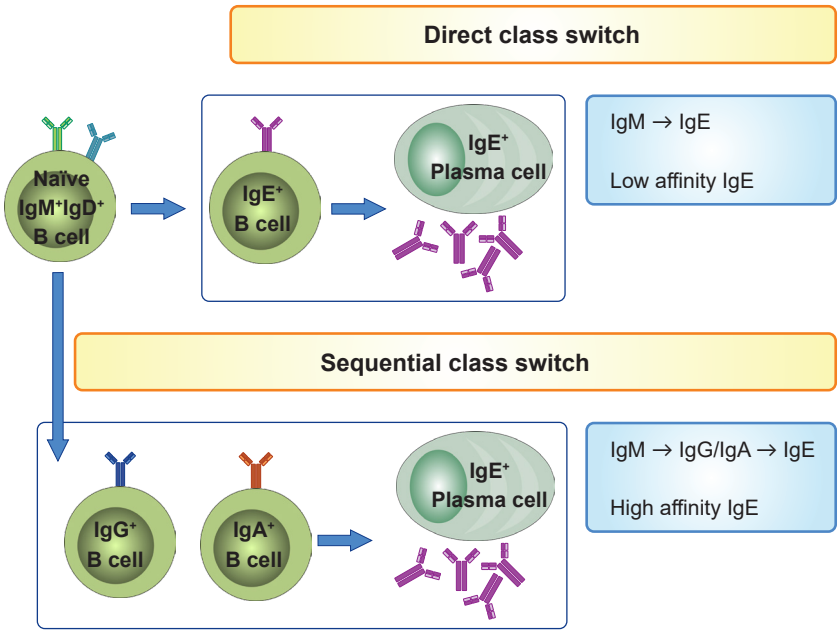

Figure 1 **IgE Class switch recombination.** IgM⁺IgD⁺ Naïve B cells can switch to IgE through direct and sequential class switch recombination.

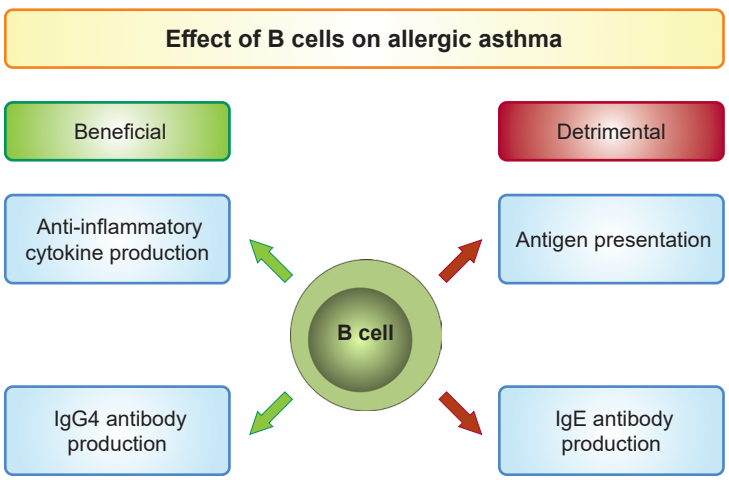

Figure 2 **The role of B cell responses in the development of asthma.**

through anti-inflammatory cytokine production, such as IL-10. In this context regulatory B cells, which dampen inflammatory responses, are worth mentioning.

The role of B cells in the induction of allergen-specific primary and recall responses has been studied in several murine models and it appears that the contribution of B cells greatly differs depending on the model system that is used. While B cells are not necessary for allergy development in the OVA model, they efficiently present house dust mite allergens and are capable of initiating T cell responses (Figure 2).

Taken together, our current knowledge on the role of B cells in asthma largely centers around their classical function of antibody production. However there is mounting evidence that cytokine production and antigen presentation by B cells may also be involved in the regulation of asthma pathogenesis.

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7b THE ADAPTIVE IMMUNE RESPONSE IN ASTHMA - T CELLS

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Asthma is a syndrome encompassing different phenotypes/endotypes that is characterized by reversible airflow obstruction, bronchial airway hyperresponsiveness (BHR) and chronic airway inflammation. Patients can be broadly classified as type 2 (T2) and non-T2 asthma according to T2 biomarkers and clinical features. Severe uncontrolled asthma patients present frequent exacerbations and airway remodeling, contributing to disease chronicity. A key feature of allergic asthma is the recurrence of symptoms upon allergen exposure, highlighting the role of allergen-specific adaptive immune responses. Many studies convincingly demonstrated that different T cell subsets play key roles in the pathophysiology of asthma (Table 1).

KEY MESSAGES

- Bronchial epithelial barrier disruption and the production of epithelial derived cytokines in response to environmental insults contribute to the generation of allergen-specific T helper type 2 (T_H2) cells
- Allergen-specific T_H2 cells constitute key players in type 2 (T2) asthma. T_H2 cells contribute to the IgE class-switching in B cells, leading to the sensitization of mast cells and basophils, as well as to the chronic inflammation
- Different T cell subsets besides T_H2 such as T_H1, T_H17, T_H9, T_H22, natural killer T (NKT) cells, γδ and CD8 T cells, or regulatory T cells (T_{REG}) contribute to the perpetuation or suppression of immune responses in asthma
- Dendritic cells (DCs) may polarize T cells towards T2 inflammatory responses or T_{REG}-mediated immune homeostasis depending on the integration of pro-inflammatory and tolerogenic signals
- T_{REG} are the cornerstone of allergen-specific immune tolerance induction. These cells are decreased in asthmatic patients and their levels inversely correlate with asthma severity

THE ROLE OF T_H2 CELLS IN ASTHMA

In T2 asthma, T_H2 cells represent the key T cell subset in the orchestration of adaptive immune responses leading to chronic inflammation. In allergic asthma, during sensitization, airway DCs uptake allergens and migrate to the draining lymph nodes where processed allergen peptides are presented to naïve CD4+ T cells in the context of major histocompatibility complex II (MHC-II) molecules, thus inducing their activation, proliferation and T_H2 polarization (Figure 1). T_H2 polarization is conditioned by epithelial derived cytokines (IL-25, IL-33 or TSLP) produced by bronchial epithelial cells activated by environmental exposure. Epithelial-derived cytokines activated DCs increase the expression of Notch-receptor ligand and OX40-L, which together with IL-4 promote the differentiation of allergen-specific T_H2 cells (Figure 1). In cooperation with B cells, DCs also generate T2 follicular T helper cells (T_{FH}) that support IgE class-switching in B cells (Figure 1). Different T_H2 subsets are generated, including effector (T_{EFF}), central memory (T_{CM}) and tissue-resident memory (T_{RM}) T cells, which contribute to the perpetuation of T2 inflammation. During the effector phase, allergen-specific

TABLE 1

CD4⁺ T cell subpopulations and their role in asthma

CD4⁺ T cell	Polarising cytokines	Effector cytokines	Function	Role in asthma
T_H1	IL-12	IFN-γ	Protection against intracellular pathogens Activation of tissue cells Apoptosis of tissue cells	Bronchial epithelial cell apoptosis Epithelial shedding
T_H2	IL-4	IL-4, IL-13, IL-5, IL-9, IL-31	Effector T cell activation, IgE class switch in B cells and IgE local and systemic production, Mast cells activation, Eosinophil and inflammatory cells recruitment to the airways, Goblet cell hyperplasia, Smooth muscle cell contraction	Airway Inflammation, Mucus production, BHR, Airway remodelling
T_H9	TGF-β , IL-4	IL-9	Mast cell recruitment, survival, differentiation and activation	Mucus production, Airway inflammation
T_H17	IL-1β, IL-6, IL-23, TGF-β	IL-17A, IL-17E, IL-6, IL-8, IL-22, IL-26	Defence against extracellular pathogens Neutrophilic chemotaxis and activation	Neutrophilic inflammation
T_H22	TNF-α, IL-6	IL-22	Wound healing Epithelial hyperplasia Tissue reorganization	Epithelial cell barrier homeostasis Airway inflammation
T_{FH}	IL-21	IL-4, IL-21	Germinal centre formation Class-switching and affinity maturation B cell differentiation IgE class-switching	Airway inflammation
T_{REG}	IL-2, TGF-β	IL-10, IL-35, TGF-β	Suppress innate & adaptive responses Inhibit IgE production Promote IgG4 production Prevention of airway remodelling Prevention of smooth muscle contraction	Inhibits pathophysiology of asthma and promotes tissue homeostasis

memory T_H2 cells are activated by airway DCs via IgE-facilitated presentation. Activated memory T_H2 cells produce large amounts of T2 cytokines (IL-4, IL-13, IL-5, IL-9), amplifying the inflammation and contributing to the chronicity of asthma (Figure 1).

OTHER T CELL SUBSETS INVOLVED IN ASTHMA

In the airways of non-T2 asthma patients and in some severe allergic asthma patients, other CD4⁺ T cells such as T_{H1}, T_{H17}, T_{H9}, T_{H22} and T_{REG} also play crucial roles in aggravating or suppressing excessive immune responses (Table 1). Different subsets of NKT cells, γδ or CD8 T cells may also contribute to the inflammation in different asthma endotypes. T_{REG} are a heterogeneous population including natural (nT_{REG}), inducible (iT_{REG}), Type 1 (Tr1) and helper type 3 (T_H3) regulatory T cells characterized by distinct phenotypes and functional immunosuppressive properties (Table 2). The generation and maintenance of functional T_{REG} is a hallmark of allergen-specific immune tolerance. T_{REG} keep immune homeostasis by different mechanisms involving a wide range of surface-bound and soluble molecules (Figure 2). T_{REG} are decreased in asthmatic patients and their numbers inversely correlated with the severity of

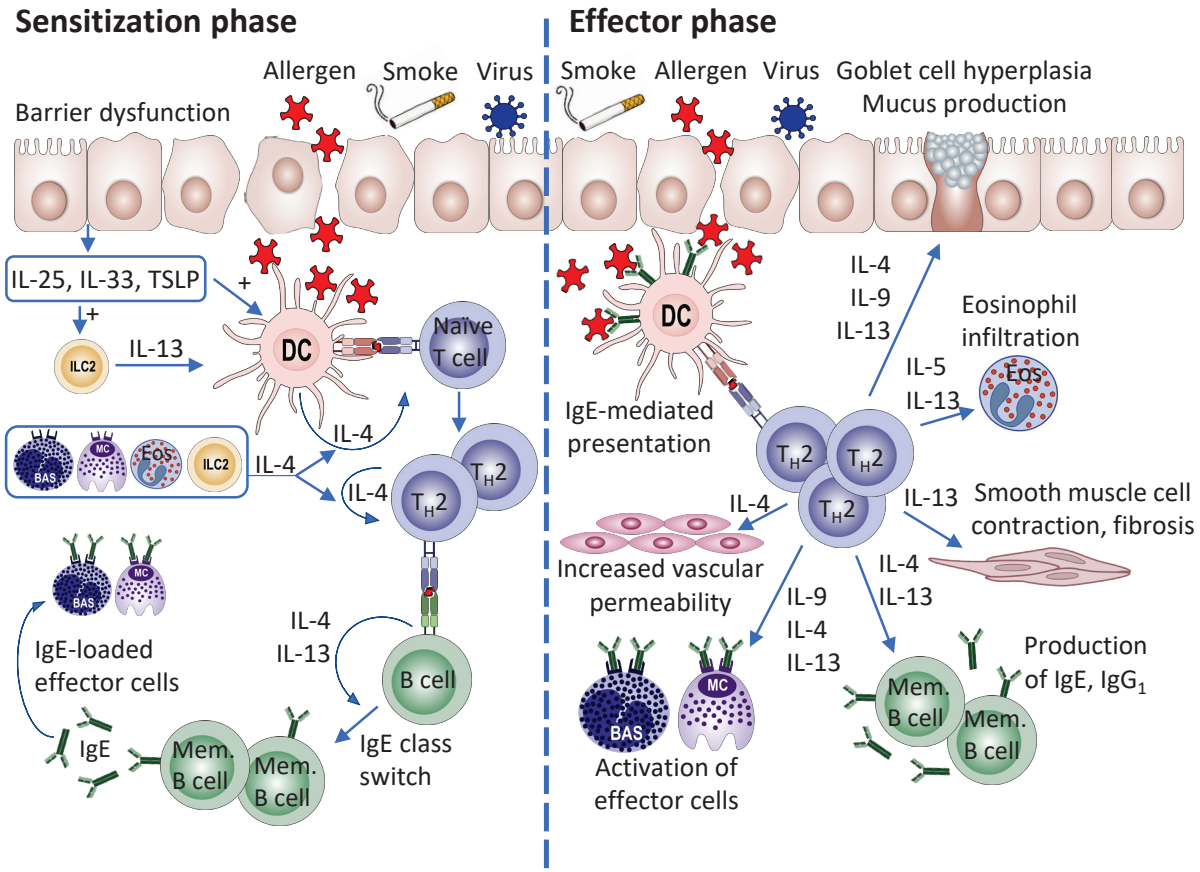

Figure 1 **The role of T_H2 cells in sensitization and effector phases of allergic asthma.** Upon environmental factors encounter, epithelial cell-derived cytokines (IL-25, IL-33 and TSLP) activate ILC2 and condition DCs to polarize allergen-specific T_H2 cells. T_H2 promote the IgE class switch at the B cell level by mechanisms partially depending on IL-4 and IL-13. IgE secreted by differentiated plasma cells sensitize mast cells and basophils. During the effector phase, allergen-specific memory T_H2 cells activated by DCs via IgE-facilitated presentation produce type 2 cytokines that contribute to eosinophilia, airway recruitment and activation of inflammatory cells, local production of IgG_1 and IgE, mucus production, goblet cell hyperplasia, increase in vascular permeability, airway remodeling and contraction of smooth muscle cells. *TSLP - Thymic stromal lymphopoietin; Bas - Basophil; MC - Mast cell; Eos - Eosinophil; ILC2 - Type 2 Innate lymphoid cells.*

TABLE 2

Treg phenotypes and function

Treg subset	Tissue generation	Phenotype	Main function
nTreg	Thymus	$CD4^+CD25^+FOXP3^+$	Prevention of autoimmunity Induction of transplant tolerance
iTreg	Induced in the periphery	$CD4^+CD25^+FOXP3^+$	Peripheral tolerance to allergens Prevention of autoimmunity Tumor immunity
Tr1		$CD4^+CD25^-Foxp3^-$	Peripheral tolerance to allergens Prevention of autoimmunity
T_H3		$CD4^+CD25^-Foxp3^+$	Oral tolerance Peripheral tolerance to allergens

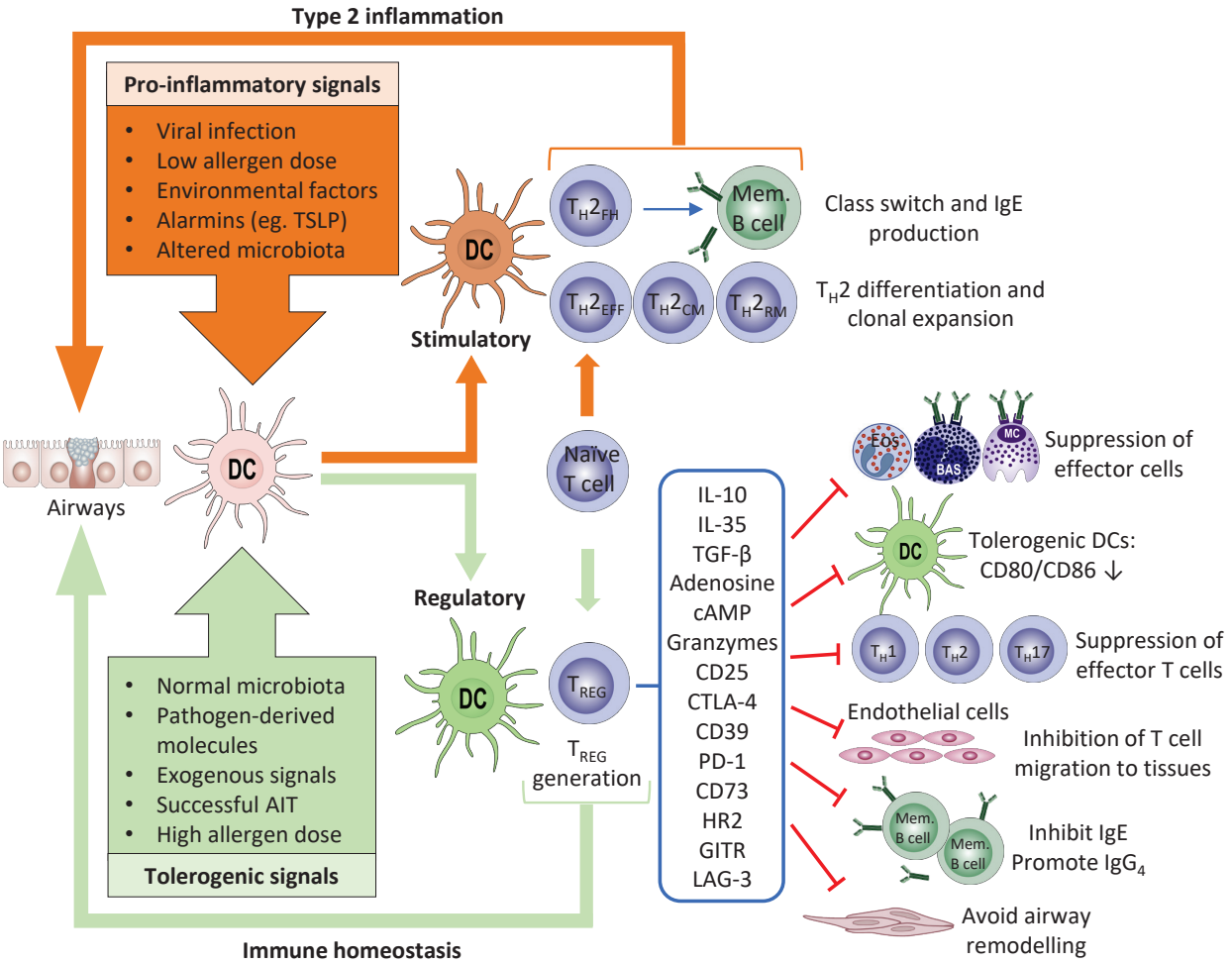

Figure 2 **Balance between type 2 inflammation and immune tolerance in asthma.** Under pro-inflammatory conditions, immature DCs differentiate into stimulatory DCs and trigger effector type 2 immune responses. Under tolerogenic conditions, DCs acquire regulatory phenotypes that promote the generation of functional T_{REG} that suppress and immunomodulate all the indicated features by using a plethora of surface-bound and soluble molecules.
AIT - Allergen-specific immunotherapy; TSLP - Thymic stromal lymphopoietin; CTLA-4 - Cytotoxic T lymphocyte-associated protein 4; cAMP - Cyclic adenosine monophosphate; HR2 - Histamine receptor 2; LAG-3 - Lymphocyte-activation gene 3; IL - Interleukin; GITR - Glucocorticoid-induced tumor necrosis factor receptor; TGF-β - Transforming growth factor-beta; PD-1 - Programmed cell death protein 1; T_H2_{FH} - Type 2 follicular helper T cells, T_H2_{EFF} - Type 2 effector T cells, T_H2_{CM} - Type 2 central memory T cells and T_H2_{RM} - Type 2 tissue-resident memory T cells

T2 inflammation. Treatment of severe asthma with Omalizumab, a humanized monoclonal anti-IgE antibody, increases the frequency of T_{REG} in asthmatic children, which correlates with better asthma control.

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7c THE ADAPTIVE IMMUNE RESPONSE IN ASTHMA - REGULATORY T AND B CELLS

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KEY MESSAGES

- Th2-like immune responses are the major underlying mechanism in a high percentage of asthma patients
- T regulatory cells (Tregs) and B regulatory cells (Bregs) are the key players in maintaining immune tolerance to allergens
- IL-10, TGFβ, IL-35, CTLA-4, PD1 are important molecules that play a key role in immune tolerance induction by suppressing Th2 and ILC2 responses and decreasing eosinophil, basophil and mast cell activation
- Tregs and Bregs can induce the production of the noninflammatory immunoglobulin IgG4 with a blocking role for IgE binding to allergens
- Allergen specific immunotherapy can induce immune tolerance in allergic asthma through Tregs and Bregs

Asthma is a heterogeneous chronic inflammatory disease of the airways driven by multiple different pathogenic mechanisms. In the majority of cases the chronic airway inflammation is driven by a T helper cell type 2 (T2) response. The mechanisms for non Th2-mediated asthma are less well understood but could involve Th17 cells, altered micro-RNA expression and NLRP3.

T2 asthma pathogenesis involves type 2 T-helper cells (Th2) and type 2 innate lymphoid cells (ILC2s) (Figure 1). Both of these cells produce T2 cytokines: IL-4, IL-5 and IL-13. IL-4 and IL-13 are implicated in IgE induction in B cells. The produced IgE will then bind to Fc ε R receptors on mast cells and basophils, which causes degranulation of these cells and the release of various compounds triggering an allergic response and airway hyperresponsiveness. Blocking of IL-4 and IL-13 inhibits eosinophils and Th2 cell migration to inflamed tissues through downregulating the VLA-VCAM-1 molecules on these cells and on the endothelium. LC2s and Th2 cells can also produce IL-5, which induces eosinophil activation. Eosinophils can in turn produce Th2 cytokines, growth factors, and release reactive oxygen species that can trigger tissue damage and inflammation. All of these responses represent default physiologic mechanisms of anti-helminth immunity.

One of the key players that normally regulates the immune responses of the body are T regulatory cells (Tregs). Tregs are capable of suppressing other cells of the immune system, keep within a normal range the response of all T cell subsets, ILC subsets, macrophages, dendritic cells, NK cells, mast cells, basophils, eosinophils, epithelium and endothelium, and suppress inflammatory ques from these cells. When Tregs fail to effectively suppress an excessive type-2 response, asthma and allergic rhinitis can develop. There are three main types of Tregs: natural Tregs (nTregs), induced Tregs (iTregs) and type 1 regulatory (Tr1) cells (Figure 2). The first two are characterized by the expression of the transcription factor FOXP3 and the surface marker CD25, the high affinity IL-2 receptor. Tr1 cells are characterized by the expression of CD49b and LAG3. Tregs mainly exert their functions by producing the cytokines IL-10, TGFβ and IL-35 (Figure 2). These molecules are the key players in

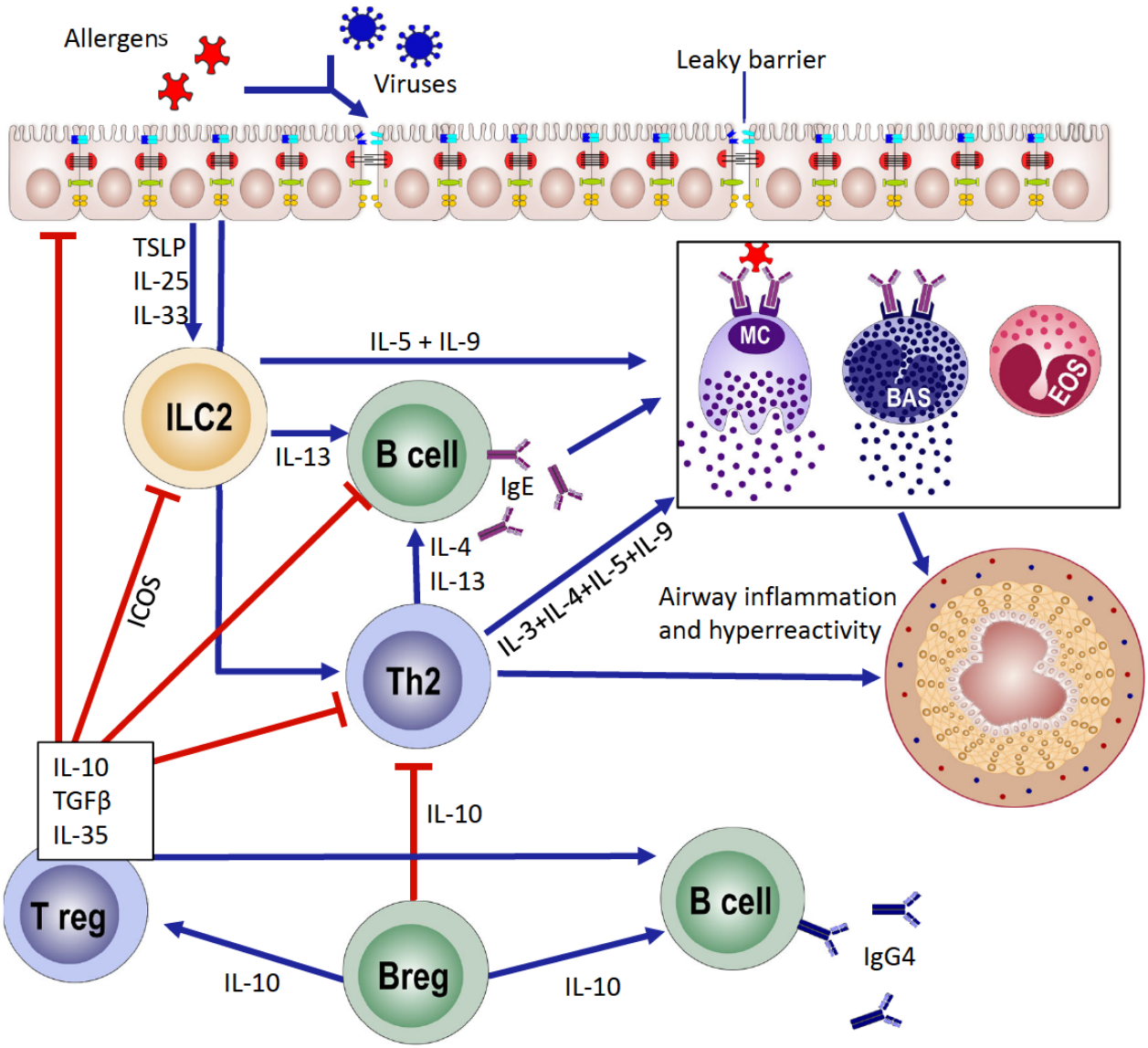

Figure 1 **Pathogenic mechanisms of asthma and the suppressive mechanisms of Tregs and Bregs on these processes.** Tregs and Bregs are able to suppres the immune system in different manners, mainly mediated by the cytokines IL10, TGFβ and IL35. The red lines indicate the suppressive effects Tregs and Bregs have on, ILC2, TH2, Epithelial cells, IgE production, while they increase the production of IgG4.

suppressing Th2 type responses. Furthermore, by the expression of CD25 Tregs are able to prevent IL-2 from binding to other T cells and thereby prevent proliferation. Another important molecule on Tregs is CTLA4, which acts as an inhibitory molecule when bound to CD80 and CD86 on the surface of antigen presenting cells. In a similar way LAG3 is able to have regulatory effects by regulating TCR-mediated signal transduction, and this is essential for the functioning of Tr1 cells. Lastly ICOS plays a role in regulating suppressive functions of Tregs and it was shown that ICOS is needed for the suppression of ILC2s.

Besides Tregs there is another important suppressive cell in the adaptive immune system: B regulatory cells (Bregs) (Figure 2). Like Tregs, Bregs are capable of producing high amounts of IL-10. Furthermore, they can also produce IL-35 and TGFβ. There are three main types of B regulatory cells in humans: a) B10 cells,

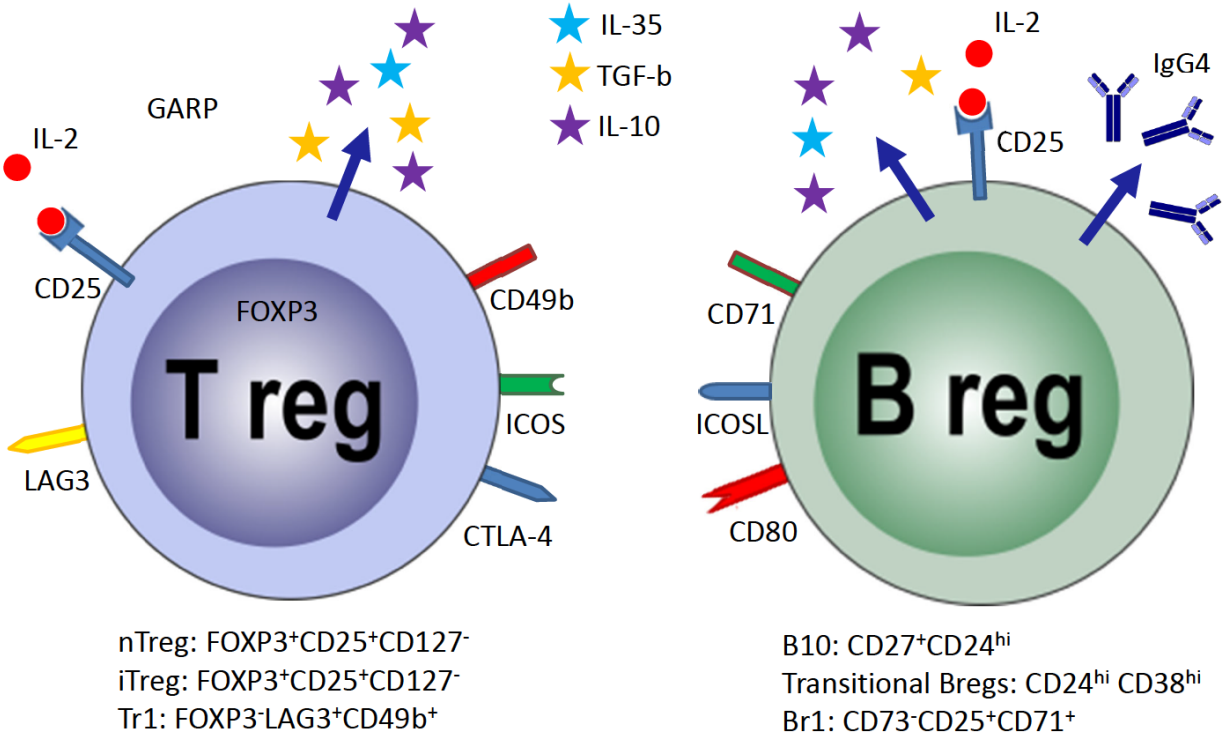

Figure 2 **Surface markers and mechanisms of suppression by Tregs and Bregs.**

$CD27^{+}CD24^{hi}$; b) immature transitional Bregs, $CD24^{hi}CD38^{+}$; c) Br1 cells, $CD73^{-}CD25^{+}CD71^{+}$. Br1 cells are mostly implicated as a protective cell in allergic diseases, are capable of suppressing IgE production and favor the production of the anti-inflammatory IgG4. IgG4 can inhibit IgE from allergen binding and may reduce allergic responses by preventing FcεR-mediated activation of granulocytes. Additionally, IgG4 is considered as noninflammatory immunoglobulin since it is not able to activate the complement system.

Allergen immunotherapy (AIT) is an essential treatment in allergic asthma, particularly with a disease modifying effect that induces an allergen-specific immune tolerance. AIT is effective by restoring immune tolerance to allergens via several mechanisms such as decreasing activation of mast cells and basophils, inducing Tregs and Bregs and increasing allergen-specific IgG4. Most of the Treg and Breg effects and their cytokines have been reported in the early course of both subcutaneous and sublingual AIT.

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8 METABOLIC PATHWAYS IN ASTHMA

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KEY MESSAGES

- Metabolic reprograming of epithelial cells, dendritic cells, macrophages and ILC2 at the sensitization stage as well as during chronic inflammation is crucial for orchestrating the adaptive immunity (Th2 cells, Treg cells, B cells) and for the effector cells function such as mast cells, eosinophils and neutrophils
- Metabolic shifts were reported for neutrophilic, severe and steroid-resistant asthma and for T regulatory cells
- Untargeted and targeted metabolomics identified several metabolic biomarker candidates (adenosine, arginine, acetate, threonine, glutamate, fatty acids, bile acids, sphingolipids), pointing at abnormal amino acids and lipid metabolism in asthma

IMMUNOMETABOLISM

All cells in human body including immune cells constantly perform energetically demanding intracellular processes in order to function properly. These processes include transcription, translation, synthesis of nucleotides, proteins and lipids, enzymatic reactions, support for the cytoskeleton, differentiation, proliferation or migration. To be competent to perform all those duties, the cell needs tightly regulated metabolic processes, shifting nutrients into different pathways, using up energy or producing energy - a process called metabolic reprogramming. Main metabolic processes in the cell include catabolic processes such as glycolysis, Krebs (TCA) cycle, oxidative phosphorylation (OXPHOS) and fatty acid oxidation (FAO), which produce energy in the form of ATP and anabolic processes involving all form of energy expenditure, such as nucleotide, protein and fatty acid synthesis (Figure 1). Other potent intracellular mechanisms connected to and regulating these metabolic pathways are HIF-1a, mTOR, ER stress, inflammasome and ubiquitination pathways.

It is now increasingly recognized that abnormal metabolic reprogramming of innate and adaptive immune cells in asthma, caused by extrinsic (allergens, viruses, pollutants, detergents, diet, gut and lung dysbiosis) and intrinsic (obesity, stress) factors might be a driver of cellular dysfunctions and defective immune responses. Metabolic reprograming of epithelial cells, dendritic cells, macrophages and ILC2 at the sensitization stage as well as during chronic inflammation is crucial for orchestration adaptive immunity (Th2 cells, Treg cells, B cells) and effector cells such as mast cells, eosinophils and neutrophils in asthma and in chronic inflammatory diseases (Table 1). For example, NLRP3 inflammasome, which has been linked with neutrophilic, severe and steroid-resistant asthma, can be activated by several metabolites such as palmitate, uric acid, cholesterol crystals, mtDNA and ROS, is inhibited by other metabolites such as PGE_2, or ketone bodies, as well as it can modulate metabolic pathways such as glycolysis (Table 1). Toll-like receptor signals that promote Treg cell proliferation increase PI(3)K-Akt-mTORC1 signaling, glycolysis and expression of Glut1, impairing the suppressive capacity of Treg cells. Conversely, the transcription factor Foxp3 opposes this signaling to diminish glycolysis while increasing oxidative metabolism in favor of their suppressive functions (Table 1).

Figure 1

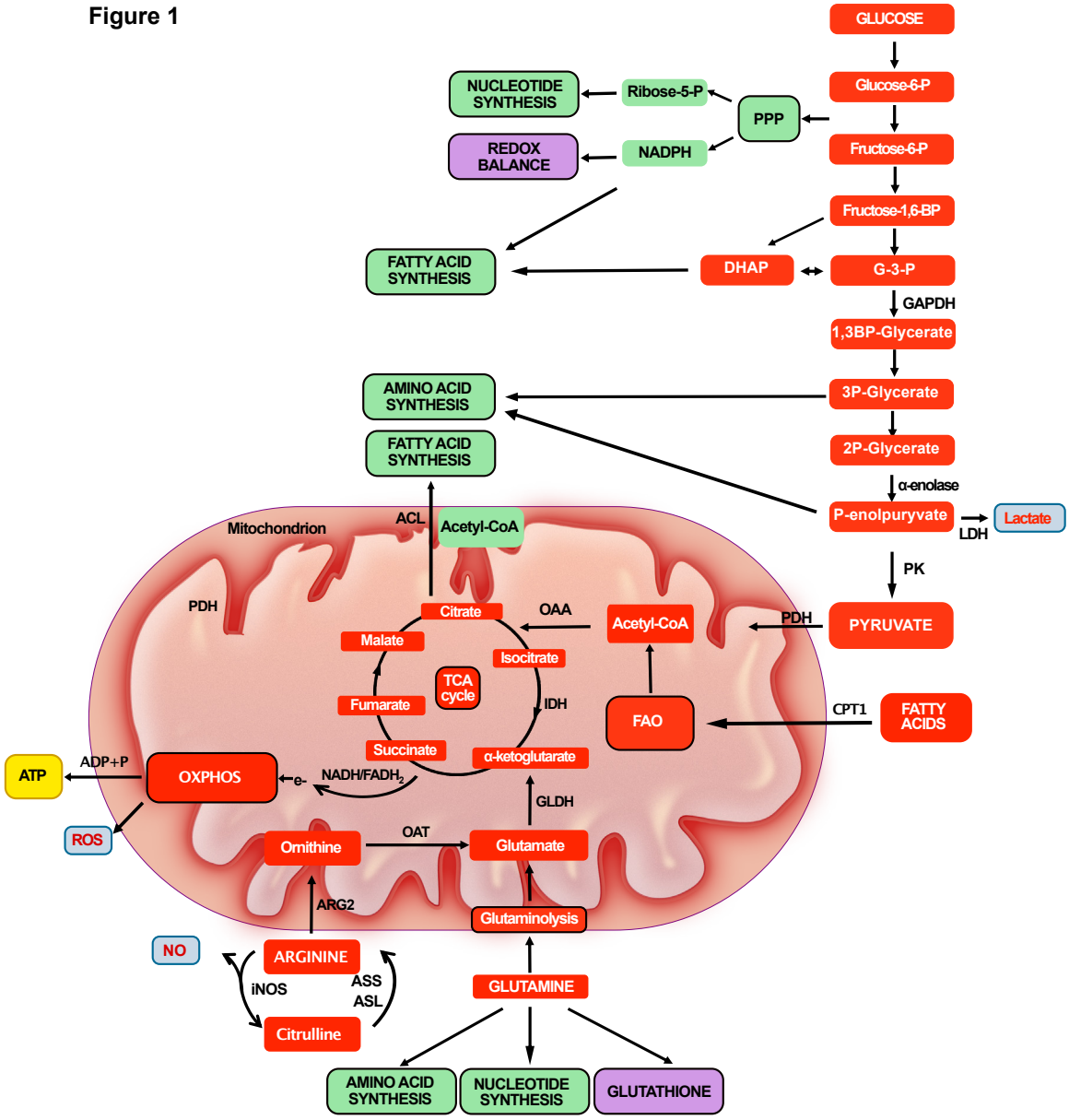

Figure 1 Metabolism of the cell. Catabolic and anabolic metabolic pathways are connected and switched on an off depending on the energy demand and the availability of the nutrient. Catabolic pathways and metabolites are depicted in red boxes, anabolic pathways are shown in green, redox mechanisms in violet. ROS, NO and lactate are side- and end-products of energy production in the form of ATP (yellow box).

1,3BP-Glycerate - 1,3-biphosphoglycerate; 2P-Glycerate - 2-phosphoglycerate; 3P-Glycerate - 3-phos- phoglycerate; acetyl-CoA - acetyl-co-enzyme A; ACL - ATP-citrate lyase; ADP - adenosine diphosphate; ARG2 - arginase 2; ASL - arginino- succinate lyase; ATP - adenosine triphosphate; ASS - argininosuccinate synthetase; CPT1 - carnitine palmitoyltransferase 1; DHAP - dihydroxyacetone phosphate; P-enolpyruvate - phosphoenolpyruvate; FADH2 - reduced flavin adenine dinucleotide; FAO - fatty acid oxidation; Fructose-1,6-BP - fructose-1,6-biphosphate; Fructose-6-P - fructose-6-phos- phate; G-3-P - glycer-aldehyde 3-phosphate; GLDH - glutamate dehydrogenase; Glucose-6-P - glucose-6-phosphate; HK - hexokinase; IDH - isocitrate dehydrogenase; iNOS - induced NO synthase; LDH - lactate dehydrogenase; NADH - reduced nicotin- amide adenine dinucleotide; NADPH - reduced nicotinamide adenine dinucleotide phosphate; NO - nitric acid; OAA - oxaloacetate; OAT - ornithine aminotransferase; OXPHOS - oxidative phosphorylation; PDH - pyruvate dehydrogenase; PK - pyruvate kinase; PPP - pentose phosphate pathway; Ribose-5-P - ribose-5-phosphate; SDH - succinate dehydrogenase; TCA - tricarboxylic acid

TABLE 1

Immunometabolism, metabolomics and metabolic biomarkers in asthma

Main findings summary	References
Allergens induce ROS and NO overproduction by bronchial epithelium	Aguilera-Aguirre L. et al. *J Immunol* 2009; Stefanska J et al. *Exp Lung Res*; Wieczfinska J. et al 2012; *Antioxid Redox Signal* 2015
Increased glycolysis in bronchial epithelium increase IL-33, IL-13 and CCL20 in mouse lungs upon allergen exposure and allergic inflammation	Qian X. et al. *JACI* 2018
Increased mitochondrial arginine metabolism and enhanced OXPHOS in epithelium in asthma	Xu W. et al. *JCI* 2016; Xu W. et al. *Plos One* 2017
Increased glycolysis, PPP, NADPH production in activated DCs especially by allergen-priming. Activated DCs maintain a high glycolytic activity and suppress FAO and OXPHOS through the actions of mTOR and HIF-1α	Everts B. et al. *Nat Immunol* 2014; Cheng SC. et al, *Science* 2014; Fukahori S. et al. *Clin Exp Allergy* 2010
mTOR regulates metabolic reprogramming of antigen presenting cells in the lung	Sinclair C. et al. *Science* 2017
HIF1α controls glycolysis in ILC2. Arginine metabolism is a checkpoint of ILC2 proliferation. Autophagy inhibits FAO and promote glycolysis in ILCs	Li Q. et al. *Immunity* 2018; Monticelli LA. et al. *Nat Immunol* 2016; Galle-Treger L. et al. *JACI* 2020
Activation of FCεR1 on mast cells leads to truncated glycolysis, increase in PPP and increase in nucleotide and lipid mediators' production	Ryu H. et al. *Br. J Pharmacol* 2008
Distinct metabolic profile of macrophages depending on the localization in the lung	Lavrich KS et al. *AjPLCMP* 2017; Mould KJ. et al. *AMRCMB* 2017
Eosinophils display greater metabolic flexibility compared to neutrophils, with the potential to use glycolysis, glucose oxidation, and oxidative phosphorylation	Porter L. et al. *Front Immunol* 2018
HIF1α increases in allergic inflammation together with M2 polarization of macrophages and recruitment of eosinophils. This process is Glutathione S-transferases omega class 1 (GSTO1-1)-dependent	Sokulsky LA. et al. *Clin Exp Allergy* 2020
Arg 2 and arginase metabolism control allergic airway inflammation	Asosingh K. et al. *JCI Insight* 2020
Metabolism of host and microbiota-origin tryptophan controls Treg responses	Hu Q. et al. *Hum Vaccin Immunother* 2020
Foxp3 and Toll-like receptor signaling balance anabolic metabolism of Treg cell which decides of their suppression capabilities	Gerriets VA. et al. *Nat Immunol* 2016
Pyruvate kinase M2 promotes expression of proinflammatory mediators in house dust mite-induced allergic airways disease	van de Wetering C. et al *J Immunol* 2020
NLRP3 inflammasome modulates glycolysis. Palmitate, uric acid, cholesterol crystals, mitochondrial ROS activate NLRP3 inflammasome; ketone bodies and PGE_2 inhibits NLRP3	Finucane OM. et al. *Sci Rep* 2020; Hughes MM. et al. *Imm Rev* 2018
NLRP3 inflammasome is implicated in severe and neutrophilic asthma	Tan TH and Hagner S. et al. *Allergy* 2019; Simpson JL. at al *ERJ* 2014; Kim RY. et al. *AJRCCM* 2017; Rossios C. et al. *JACI* 2018

TABLE 1

continued

Main findings summary	References
Altered metabolism of fatty acids, sphingolipids and eicosanoids in asthma	Sokolowska M. et al, *Allergy* 2020; Rodriguez-Perez N. et al. *Allergy* 2017; Sokolowska et al. *JACI* 2017, Obese D. et al. *Allergy* 2018; Venter C. et al. *Allergy* 2019; Radzikowska U. et al. *Nutrients* 2019
Arginine metabolism endotypes relates to asthma severity	Xu W. et al *Plos One* 2017
Altered fatty acids, bile acids, amino acid metabolites in asthma	Crestani E. et al. *JACI* 2020
Candidate metabolite biomarkers in asthma	Bowler RP. et al. *Ann Am Thorac Soc* 2017; Villaseñor A. et al. *Clin Exp Allergy* 2017; Zhu Z. et al. *Exp Rev Resp Med* 2019; Kelly RS. *Chest* 2017
R- salbutamol regulates glycerophospholipid metabolism. Metabolic response to bronchodilators.	Liu F. et al. *Cells* 2020; Kelly R.S. *Metabolites* 2019
Short chain fatty acids from microbiota and foods have protective effects in asthma	McLoughlin R. et al. *EBio Medicine* 2019; Roduit C. et al. *Allergy* 2020
Complex effects of other microbial metabolites (histamine, biogenic amines, tryptophan) in asthma	Barcik W. et al. *Allergy* 2019; Barcik W. et al. *Immunity* 2020, Sokolowska M et al. *Asthma Res Pract* 2018
Abnormal lipid metabolism in asthmatic BEC during detergent exposure	Wang M. et al. *JACI* 2019

**Evidence from animal and human studies*

SYSTEMIC METABOLISM AND METABOLIC BIOMARKERS

Metabolic changes on the cellular level of the host cells and microbiota are reflected on the systemic level in the circulation, urine, induced sputum, BAL and exhaled air. Untargeted and targeted metabolomics performed by GC-MS, LC-MS or nuclear resonance, are used in search of biomarkers of different asthma endotypes, as well as response to treatment. To date there are several metabolic biomarker candidates (adenosine, arginine, acetate, threonine, glutamate, fatty acids, bile acids, sphingolipids), confirmed in more than one study, pointing at abnormal amino acids and lipid metabolism in asthma (Table 1). Increased and altered fatty acid synthesis leads eventually to increased production of active lipid mediators, such as eicosanoids (prostaglandins, leukotrienes, thromboxanes), other oxylipins, sphingolipids and bile acids by many cells involved in type-2 and non-type 2 inflammation and airway hyperresponsiveness. Abnormal fatty acids metabolism is also involved in the pathogenesis of different asthma phenotypes and endotypes, as well as is connected with asthma exacerbations.

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9 THE DEFECTIVE BRONCHIAL EPITHELIAL BARRIER AND EPITHELIAL BARRIER HYPOTHESIS IN ASTHMA

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KEY MESSAGES

- The epithelial barrier hypothesis suggests that after 1960s biological and chemical insults from the environment disrupting the integrity of the mucosal and skin epithelial barrier by degrading the intercellular barrier proteins, particularly tight (TJ) and adherence junctions, have substantially increased
- This hypothesis has been proposed to explain the epidemic development of asthma, allergies, inflammatory bowel disease, metabolic and autoimmune diseases and diseases that affect the central nervous system
- The astmatic bronchial epithelial barrier shows defects in TJ integrity and leakiness in bronchial biopsies and primary epithelial cells cultures of asthma patients
- Particulate matter, diesel exhaust, ozone, cigarette smoke, cleaning products, detergents, surfactants, processed foods and food emulsifiers, nanoparticles and microplastics open the epithelial barrier
- Proteases in allergens have been shown to cause the degradation of junctional proteins in cell culture experiments and *in vivo* mouse models
- Either type 1 or type 2 inflammation beneath the epithelial barrier opens TJ barrier
- Th2 cells, ILC2s and their secreted cytokines IL-4 and IL-13 open bronchial epithelial TJ barrier

EPITHELIAL BARRIER OPENING AGENTS AND EPITHELIAL BARRIER DEFECT-RELATED DISEASES

The epithelial barrier constitutes the first line of physical, chemical and immunological defences and protects against environmental factors. The structure and the function of the epithelial barrier differs between the skin and mucosas. From the nasal cavity to the bronchi, respiratory barrier is very thin, lined by pseudostratified columnar ciliated epithelium with a continuous physical clearance by cilia and mucus. Proteases in allergens, particulate matter, diesel exhaust, ozone, cigarette smoke, cleaning products, detergents, surfactants, processed foods and food emulsifiers, nanoparticles, and microplastics open epithelial barrier in respiratory gastrointestinal mucosas and skin (Figure 1). Defects in the epithelial barrier, the so-called leaky epithelium, have been demonstrated in affected organs in asthma, chronic rhinosinusitis, allergic rhinitis, atopic dermatitis, eosinophilic esophagitis, celiac and inflammatory bowel disease leading to the development of the "**epithelial barrier hypothesis**" in the pathogenesis of these diseases. Apparently, epithelial barrier hypothesis is gaining more attention in several systemic autoimmune and metabolic conditions such as diabetes, obesity, multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, and autoimmune hepatitis. In addition, remote inflammatory responses due to a 'leaky gut barrier' have been observed in Alzheimer's disease, Parkinson's disease, chronic depression and autism spectrum disorders.

TYPE 1 OR TYPE 2 IMMUNE RESPONSE OPEN EPITHELIAL BARIER

Immunomodulatory cross-talk between epithelial and immune cells in

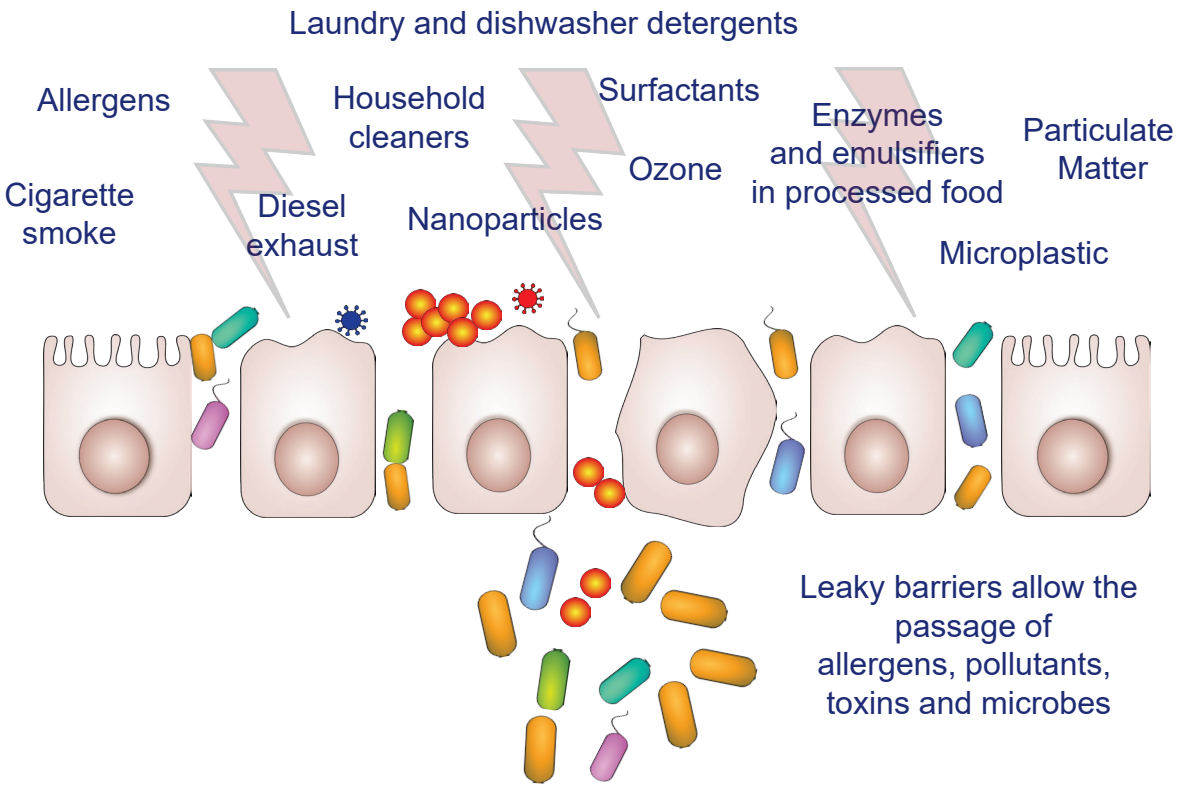

Figure 1 **Multiple environmental factors have been shown to damage epithelial barriers.**

tissues control barrier homeostasis along with defensive barrier functions. A wide variety of innate and adaptive immune cells populate the tissues with barrier functions and epithelial cells mediate innate and adaptive immune responses. Upon damage to epithelial barrier integrity and/or epithelial cells; subsequent adaptive and innate immune responses are activated through the production of cytokines and chemokines. Either type 1 or type 2 inflammation beneath the epithelial barrier opens the tight junction (TJ) barrier. Th2 cells, ILC2s and their secreted cytokines IL-4 and IL-13, which together open epithelial TJ barrier; have been shown to significantly degrade the bronchial epithelial barrier in air-liquid interface cultures of human bronchial and skin epithelial cells and in several mouse models. IL-13 has been found to be sufficient in this activity alone and causes disrupted protein expression of TJ proteins and mRNA reduction, which was restored by its neutralization.

MECHANISMS OF DEFECTIVE EPITHELIAL BARRIER HYPOTHESIS

The epithelial barrier hypothesis includes mechanisms described by the hygiene, "old friends" and biodiversity hypotheses. The immune regulatory role of infectious agents on the innate immune response, T_H1-T_H2 balance, and other complex immune regulatory responses play a role also in epithelial barrier hypothesis. Once the epithelial barrier is leaky, microbial dysbiosis, epithelial translocation of the commensals, decreased biodiversity and colonizing opportunistic pathogens prevail and multiple immune regulatory mechanisms start to take place to suppress tissue inflammation in barrier damaged tissues (Figure 2). Microbiome that normally floats on the surface of skin and mucosal epithelium moves deeper and translocates beneath epithelial cells and a chronic inflammation in the epithelial cells and subepithelial tissue develops together with the immune response against microbiome components.

CALL FOR ACTION

This article also calls for international rapid action on the control of epithelial barrier-attacking environmental pollutants to prevent asthma, other allergic diseases, auto immune and metabolic diseases listed above. Extensive education of consumers, unions, safety and health agencies are urgently needed. The production of epithelial barrier damaging substances should be substantially reduced, dose studies should be performed,

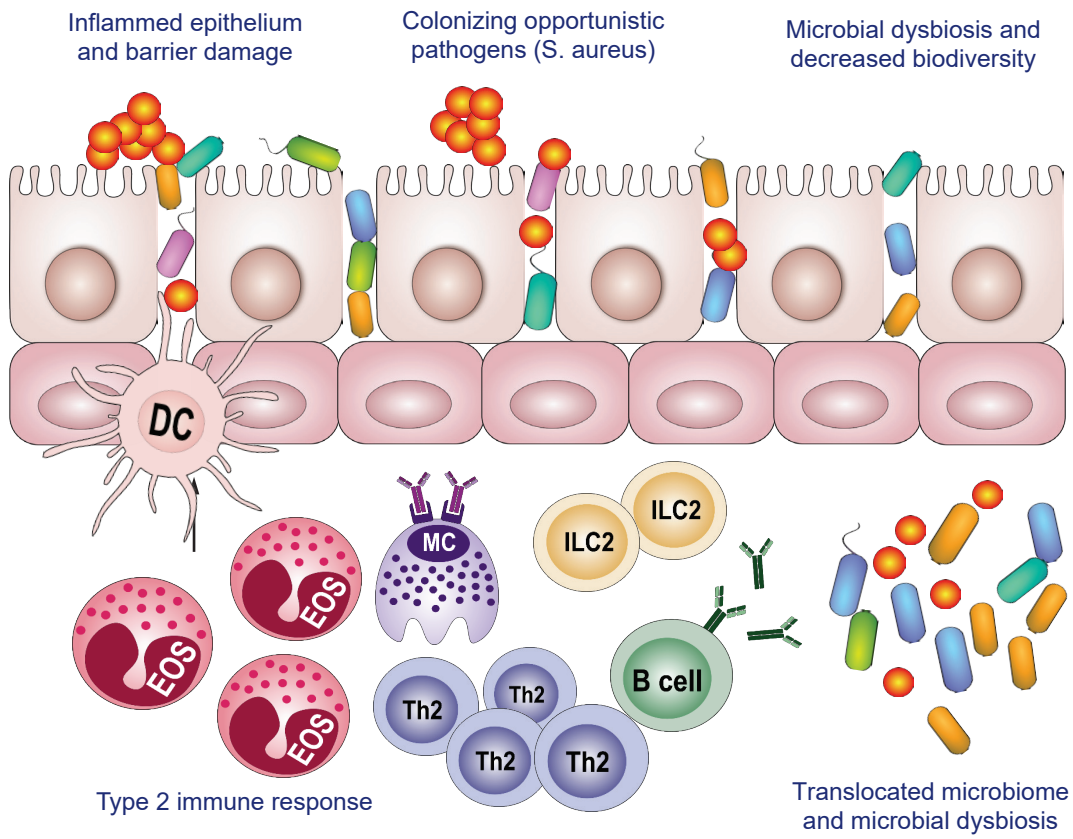

Figure 2 Mechanisms of epithelial barrier dysfunction. In asthma, CRS, allergic rhinitis and atopic dermatitis, type 2 immune response develops towards translocated microbiome and colonized opportunistic pathogens: Microbiome that normally floats on the surface of skin and mucosal epithelium goes deeper between and beneath epithelial cells. Opportunistic pathogens such as *S aureus* colonize and microbial dysbiosis occurs.

their recycle and reuse should be implemented, legal actions and extreme control should be initiated.

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10 THE AIRWAY SMOOTH MUSCLE

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KEY MESSAGES

- Airway smooth muscle (ASM) plays a pivotal role in airway hyperresponsiveness
- ASM increased mass play contributes to airway remodelling and is correlated with the severe and fatal asthma phenotype
- ASM increased mass originates from increased proliferation and recruitment of fibrocytes from the blood
- ASM has a potent role as immunomodulators of airway inflammation in asthma
- ASM are targets of mainstay therapy as beta-2 agonists, antimuscarinic agents, and glucocorticoids, as well as a target for novel promising therapies that could result into decrease of their excessive mass and restored phenotype

Asthma is characterized by intermittent airflow obstruction and airway inflammation. Airway smooth muscle (ASM) cells play an active role in both conditions.

ASM cells exist in the tracheobronchial tree wall from the trachea to the terminal bronchioles representing a normal component. However, the exact physiological role of ASM is still unclear and under debate. While some argue for a homeostatic role in maintaining bronchial tone and consecutively in lung ventilation, others consider that it represents an evolutionary leftover, with no useful function in the lung, analogous to the intestinal appendix.

In asthma, ASM cells play a crucial role in airway hyperresponsiveness through their excessive contractile response to a relatively minor provocation from various stimuli. Underlying mechanisms include excessive of contractile mediators', i.e., from mast cells, increased vagal tone, cytokine-potentiated increased in intracellular free calcium that enhances ASM cell contractility as well as ASM impaired relaxation and increased ASM mass.

Increased ASM mass contributes to airway remodelling and has been a hallmark of asthma and correlated especially with the severe and fatal asthma phenotypes. Both increased ASM cell size (hypertrophy) and increased cell number (hyperplasia) have been described in patients with asthma (figure 1). The exact mechanism driving ASM increased mass is still elusive and under debate, including an increased in-situ local proliferation due to increased grown factors, i.e., transforming growth factor (TGF-β1) and migration and differentiation of fibrocytes, the only blood-derived mesenchymal progenitors identified as a possible source of ASM in asthma originated from bone marrow (figure 2).

Importantly, increasing evidence suggests that ASM also plays a pivotal role in the chronic airway inflammation seen in asthma (figure 3). ASM actively contribute by releasing and expressing numerous inflammatory mediators, including pro-inflammatory cytokines as IL-1β and IL-6, T2 cytokines as IL-5, cytokines as IL-33 and TSLP, chemokines as IL-8, RANTES, eotaxins 1 and 2, IP-10 and TARC.

ASM expresses cell adhesion molecule receptors that bind inflammatory cells like eosinophils and neutrophils. CD4+ T lymphocytes and mast cells have been identified in close interaction with ASM

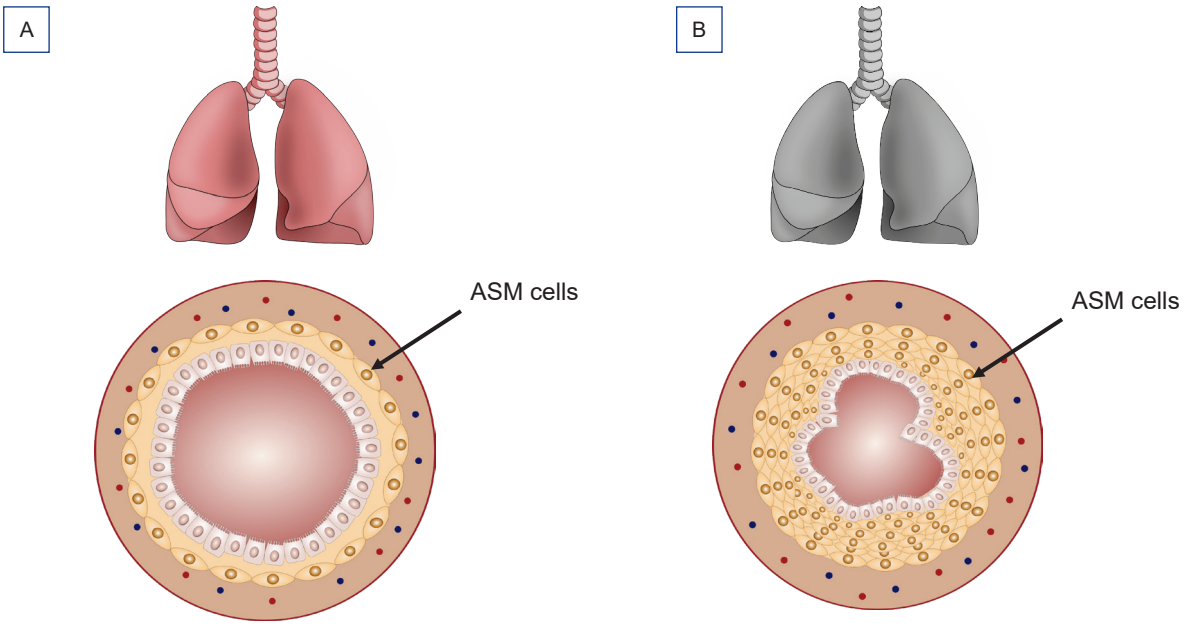

Figure 1 Schematic figure presenting a normal bronchus in healthy lungs (A) and a bronchus from the lungs of a patient with asthma (B). A clear increase of airway smooth muscle (ASM) cells mass is seen (black arrow) result in airway narrowing.

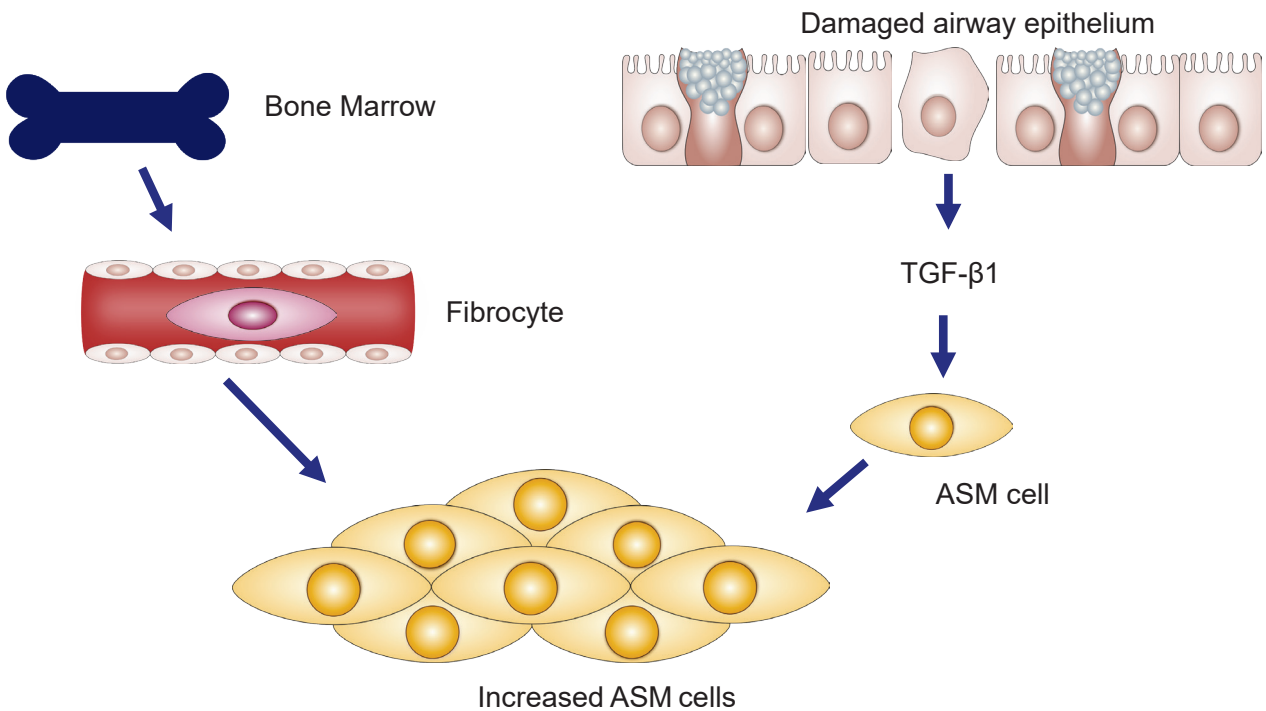

Figure 2 Simplified schematic figure presenting the potential origin of ASM cell increase mass, leading to remodelling in asthmatic airways. Increased ASM mass could origin from increased proliferation after stimulation from damaged airway epithelium in asthma, i.e., via the release of TGF-β1 or by recruitment of fibrocytes from bone marrow via blood circulation.

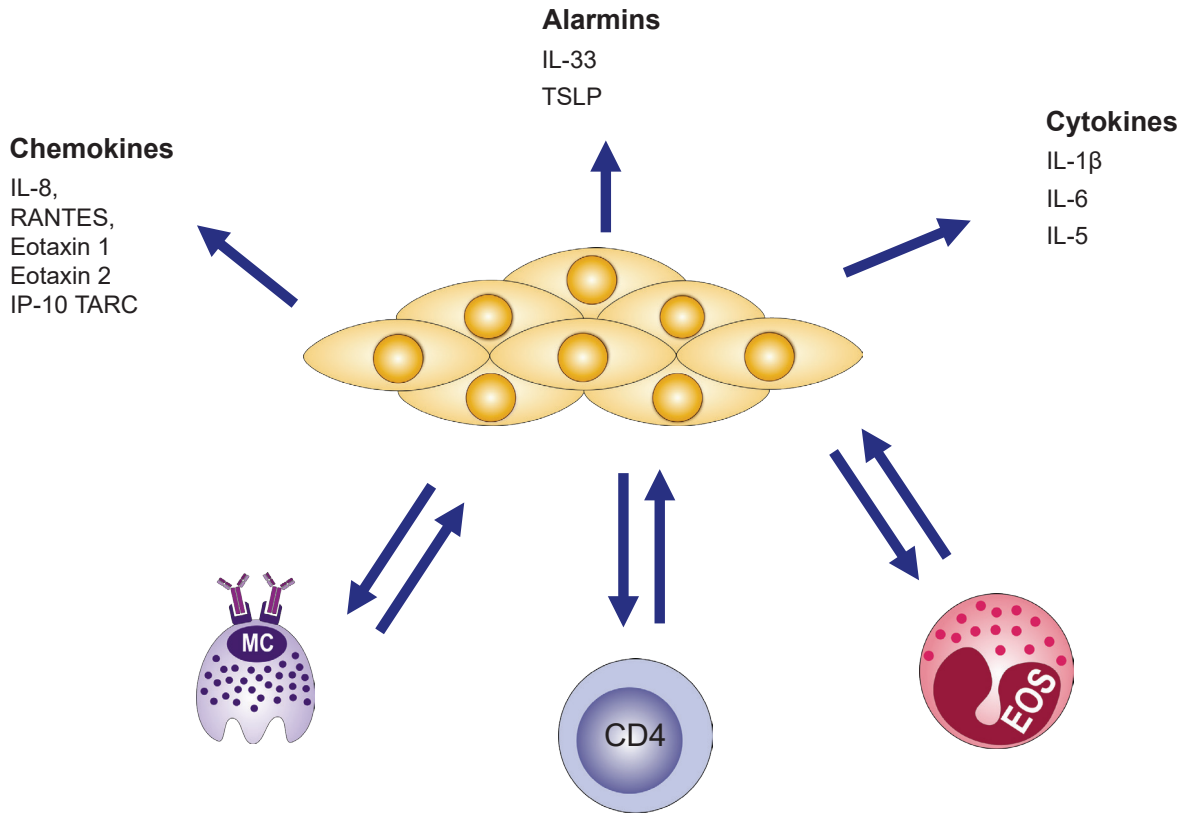

Figure 3 **ASM cells are potential immunomodulators of inflammation in asthmatic airways by secreting a variety of mediators and interact with key cells of airway inflammation.**

in asthmatic airways. Local inflammatory milieu modifies above ASM's inflammatory response. Finally, ASM has been found to express major histocompatibility complex class II, proposing the capacity to act as complementary antigen-presenting cells as well.

ASM cells are considered an important therapeutic target. ASM response to mainstay asthma therapies, as bronchodilation through targeting beta-2-adrenoceptor (β_2AR) and M_3 muscarinic acetylcholine receptor (M_3R) expressed on ASM and glucocorticoids through the glucocorticoid receptor alpha isoform inhibits ASM growth and inflammatory mediator production and release. ASM are also targets for novel therapies as bronchial thermoplasty (BT) licensed for patients with severe asthma. BT applies thermal energy to the airway wall via a bronchoscope to reduces ASM mass. Future therapeutic interventions targeting ASM include prostaglandin type 2 receptor (DP2) and bitter taste receptors (TAS2Rs) agonists as both are expressed in ASM.

In conclusion, although ASM's physiological role is still under debate, they play a pivotal role in asthma pathogenesis. The factors and the underlying mechanisms are still elusive, pointing out the need for more studies. Understanding their role will expand further their value as therapeutic targets.

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11 MUCUS ABNORMALITIES AND MUCUS PLUGGING IN ASTHMA AND CHRONIC RHINOSINUSITIS

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KEY MESSAGES

- Mucus is often altered in chronic airway diseases in which type 2 immune cells like eosinophils, ILC2s and Th2 cells are common. The mucus is often very tenacious and sticky, with high elastic and viscous properties
- Mucus plugging is a very common observation in fatal asthma. In severe asthmatics with persistent airway obstruction, mucus plugging is very common as well, and associated with peripheral blood eosinophilia
- Currently, mucus plugging of the airways in asthma and sinus filling with rubbery allergic mucin in chronic rhinosinusitis represents a large unmet need

The function of the airway epithelium is to protect the host from invading pathogens, that can be contained in inhaled air. For this function, the epithelial cells not only produce antimicrobial peptides, and orchestrate immunity via secretion of cytokines; they also form mucin-rich mucus that forms a gel-like layer on top of the cilia and are crucial for the functioning of the mucociliary blanket by capturing microbes and inhaled spores and conidia, and allowing antimicrobial peptides to kill their targets.

Mucus quality is often severely altered in patients with chronic rhinosinusitis (CRS) and asthma, changing its aspect from a fluid hydrogel into a highly elastic and viscous substance. Patients with asthma often describe the quality of their mucus as sticky or having the aspect of dried-out glue, and many have trouble coughing up this dry mucus, sometimes leading to mucus plugging of the airways (Figure 1). When coughed up, these plugs have a branched morphology, almost as the cast of the airways (often found in the medium sized 3^{d}-8th generation airways). Autopsy studies in fatal asthma have clearly documented the central role of airway plugging with pathologic mucus in the pathophysiology of death from asthma. Mucus plugs in asthmatics are often very chronic and when seen under a microscope contain dead cells and debris, fibrin, extracellular DNA, Periodic acid Schiff reacting mucus, and sometimes Charcot-Leyden Crystals (CLCs), hexagonal bi-pyramidal protein crystals made up of the eosinophil-derived protein galectin-10. In CRS with nasal polyposis (CRSwNP) the mucus can be very rich in fibrin, and often contains a lot of extracellular DNA and CLCs, leading to a rubbery aspect, referred to as peanut butter or hard clay, that is also very hard to sneeze up, and hard to remove by sinus surgery (Figure 2).

The pathophysiology of abnormal mucus in asthma and CRSwNP is very complex, and involves several cell types and cytokines (Figure 3). Not only the quantity, but above all the quality of the mucus is altered. In asthma and CRSwNP, the predominant mucin is MUC5AC, produced from either goblet cells under the influence of IL-4 and/or IL-13 and EGF receptor ligands, or from submucosal serous glands. Another mucin, MUC5B is lower compared with healthy mucus. In fatal asthma, the MUC5AC rich mucus does not detach from the goblet cells, causing tethering, and loss of mucociliary function

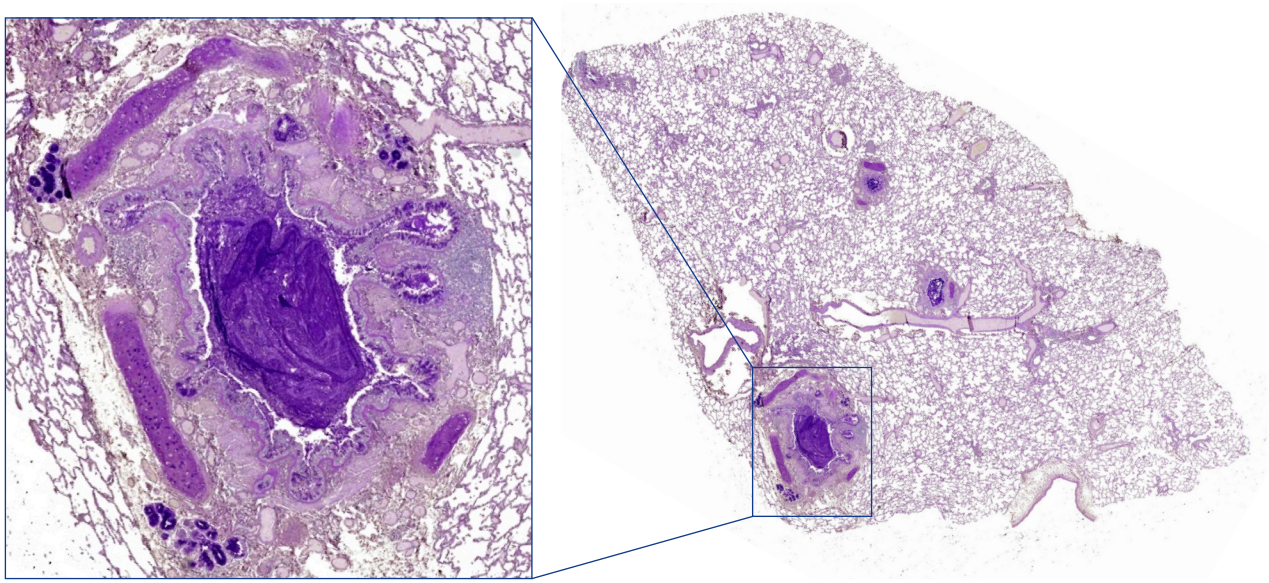

Figure 1 **Mucus plugs stained with Periodic Acid Schiff reagent, in a patient dying of asthma.**
Case provided by Dr. W. Finkbeiner, UCSF.

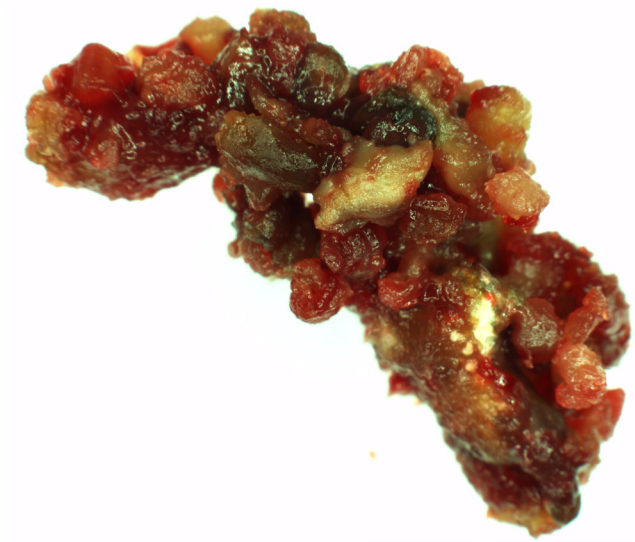

Figure 2 **Rubbery mucus filling up an entire sinus removed by sinus surgery.**
This mucus has a very rubbery aspect.
Case provided by Dr S. Vlaeminck, Hospital Menen, Belgium.

that can further lead to near total airway obstruction. In asthmatics, persistently low lung function and a concentration of more than 300 eosinophils/microliter in peripheral blood despite maximum therapy with inhaled corticosteroids, confers a 60-70% risk of finding mucus plugs. Eosinophils contribute to mucus stiffening by producing eosinophil peroxidase that reacts with H_2O_2 and thiocyanate (HCN) to form hypothyocyanic acid that can crosslink mucus polymers by formation of disulfide bridges. Neutrophils can also cause these crosslinks via myeloperoxidase. Mucus crosslinking subsequently increases the elasticity of the mucus gel. Eosinophils also contribute to mucus plugging by releasing galectin-10 that forms CLCs, and by releasing extracellular DNA when eosinophils undergo EETosis. Charcot-Leyden Crystals are very prominent in cases of asthma with concomitant sensitization to *Aspergillus* as seen in allergic bronchopulmonary aspergillosis (ABPA, Figure 4). Whereas CLCs where initially seen just as markers of eosinophil death, it is now clear that they can stimulate inflammation and further mucus production, and can even be dissolved using specific gal-10 antibodies. CLCs are also very prominent in the tenacious mucus that is often found in patients with CRSwNP, particularly –but not exclusively- when there is fungal colonization and/or sensitization, and here CLCs promote neutrophil extracellular trap formation (NETosis).

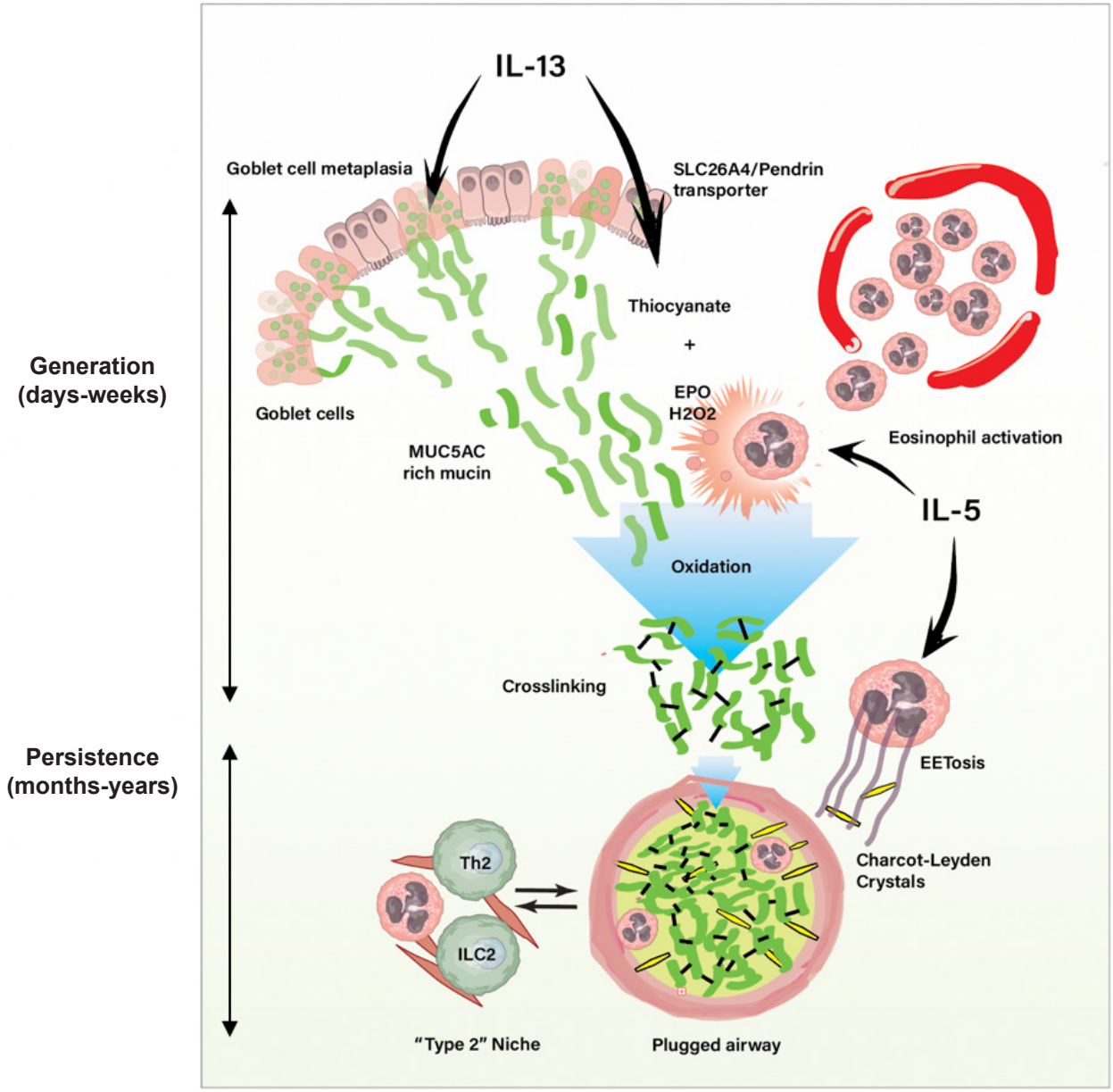

Figure 3 An T2/eosinophilic centric view on mucus plugging.

Currently, few therapeutics directly target mucus impaction and plugging. Patients often mention that they feel considerably less dyspneic when they can expectorate the plugs at the end of an exacerbation. N-acetylcysteine has the potential to reverse disulfide crosslinks in mucus hydrogels, but is not well tolerated in high inhaled or oral doses needed to achieve this effect. This has led to a search for other reducing agents that could be given via inhalation to reduce mucus elasticity. Eosinophils contribute in many ways to plugging, yet it is unclear if and how eosinophil selective therapies like antibodies to IL-5 or its receptor change mucus plugging. An antibody to IL-4Ra (dupilumab) has the potential to reduce mucus production, but its effects on mucus plugging are currently unknown. Other possibilities that need further clinical investigation is use of inhaled DNAse and antibodies that dissolve CLCs. Although these compounds might not benefit every asthmatic, they might be beneficial in highly selected patients with plugs identified by innovative imaging techniques.

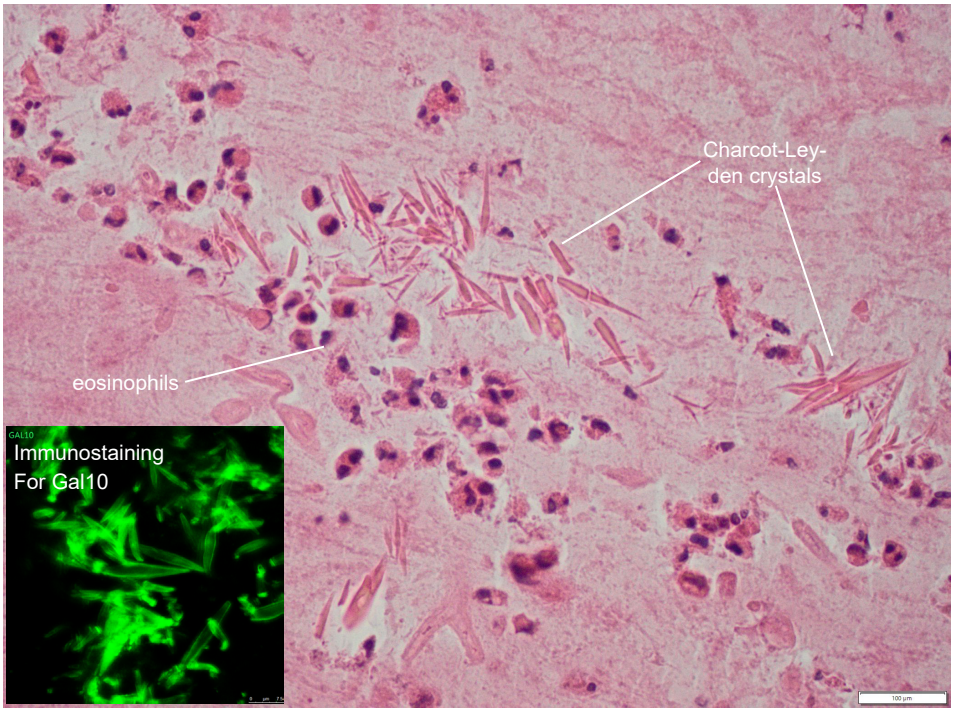

Figure 4 **Mucus plug of ABPA patient stained with H&E, revealing allergic mucin.** Numerous CLCs and eosinophils can be seen. CLCs are made up from galectin-10, as shown by this immunostaining in native mucus.
Case provided by Dr. J. Van Dorpe and Dr E. Van Braeckel, Ghent University Hospital.

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12 NEURO-IMMUNE MECHANISMS IN ASTHMA

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KEY MESSAGES

- Immune responses are controlled by neuronal mechanisms leading to neurogenic inflammation triggered by neuropeptides
- Neuronal response is affected by the immune system leading to neuronal hyperreactivity triggered by various mediators released from effector cells e.g. histamine and by proinflammatory cytokines (TNF-α)
- Neurogenic inflammation contributes to the development of allergy and asthma symptoms, especially of the airway hyperreactivity
- Viral infection of the airway induces changes in neuronal innervation that might lead to asthma development and exacerbations
- Asthma therapies target stress hormone receptors such as corticoid and β2-adrenergic receptors

Neuro-immune interactions play an important role in allergic disorders. The nervous system has a significant impact on airway inflammation and vice versa the immune system is affecting the local innervation of the lung (Table 1).

Neuroinflammation is an important risk factor in the pathogenesis of allergic diseases and asthma. Vagal sensory neurons represent the dominant afferent innervation to the airways and lungs. Especially the non-myelinated subset of afferent nerves – the C-fibers – are involved in pathophysiological features of asthma such as airway hyperreactivity. The influence of local neuronal control of inflammatory mechanisms is called neurogenic inflammation (Figure 1). A stimulation of TRP receptors on sensory nerves in the airways through pollution, chemicals, cold air and other triggers induces the local release of sensory neuropeptides such as the tachykinin substance P (SP) via local axon reflex. Accordingly, asthma patients show increased levels of SP in bronchoalveolar lavage (BALF) fluid, sputum and plasma. Neuropeptides promote airway inflammation, bronchoconstriction (Figure 2) and mucus secretion in patients with asthma, all relevant mechanisms for asthma pathogenesis.

The immune system affects the neuronal system as well. In chronic allergic inflammation, various inflammation mediators such as histamine and PGE2 are released from mast cells, T cells and dendritic cells. These mediators increase the sensitivity of the neurons with release of neuropeptides, NGF and BDNF. While these processes normally have a protective and healing function, like inflammation-induced hyperalgesia, chronic inflammation can lead to a "vicious circle" in which the neurogenic inflammation continues to build up.

The mechanisms of neurogenic inflammation are specifically used by pathogens. Viral pathogens such as the RSV virus specifically increase neurogenic inflammation by increasing the production of nerve growth factors and neuropeptides in the airways (Figure 3). Through increased sneezing and coughing stimuli, this leads to an improved distribution of the pathogen, to its spread and thus to infection of other hosts. If an RSV infection occurs in an early phase of life, in which the plasticity of the peripheral nervous system

TABLE 1

Neuronal changes seen in asthma

Neuronal innervation	Mediator	Observed changes
Sensory innervation	tachykinins, neuropeptides	• Enhanced levels in asthma • Upregulated in cell bodies of ganglia • Increased mechano-sensitivity of sensory A fibers • Increased sensitivity of sensory c fibers • Enhanced response to irritation
Cholinergic innervation	acetylcholin	• Enhanced acetylcholin release • Loss of function of the inhibitory M2 muscarinic receptors
Adrenergic innervation	noradrenaline, neuropetide Y	• Increased adrenergic activity

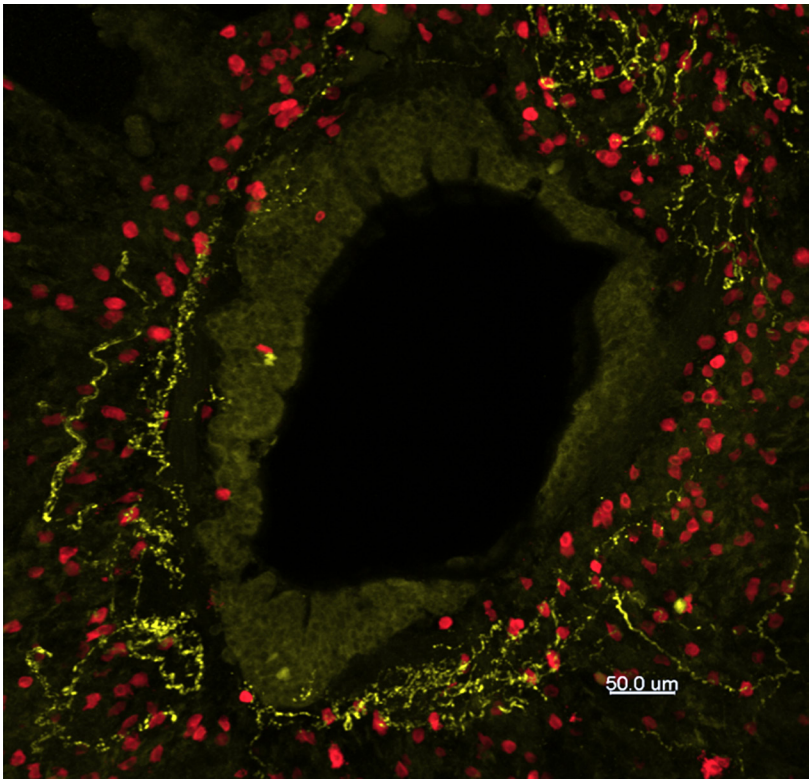

Figure 1 **Local neural control in the airways.** Human airway. Network of mast cells (red) and neurons (yellow).

is still very high, this can lead to irreversible changes in the innervation. In fact, early childhood RSV infection is one of the most important risk factors for later developing asthma and may increase severity of exacerbations.

The mechanisms of the central nervous system control of the (immunological) homeostasis by stress hormone release involves the two central mediators cortisol and adrenaline. The agonistic stimulation of corticoid receptors and β2-adrenergic receptors is thereby the central building block of pharmacological therapy in asthma. B2-adrenergic receptor therapy lead to a relaxation of the constricted bronchial muscles and thus controls acute asthma symp-

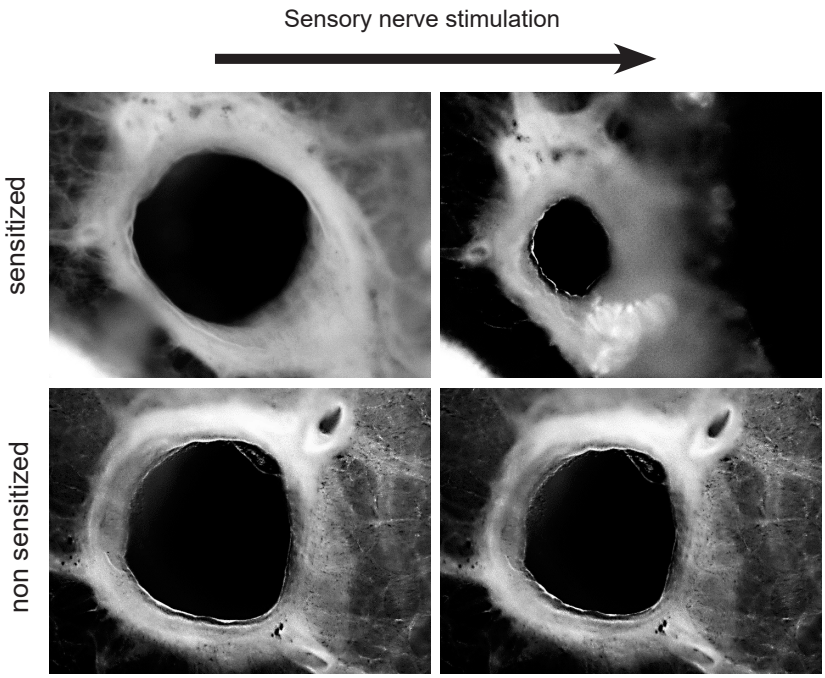

Figure 2 **Airway constriction in response to the sensory nerve stimulus capsaicin in sensitized versus non sensitized airways.**

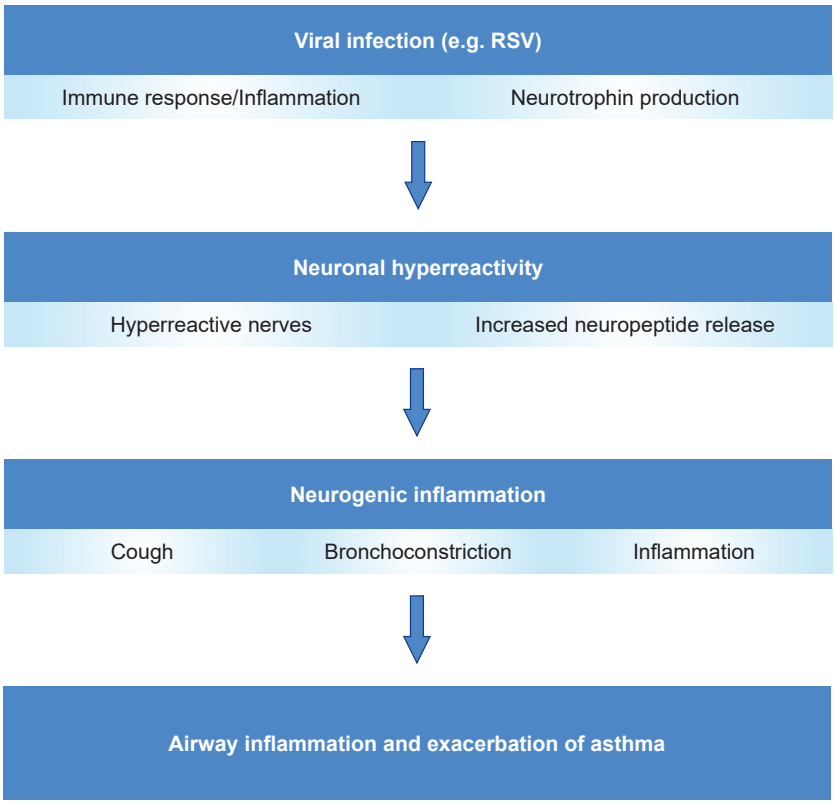

Figure 3 **Virus effects on neuro-immune mechanisms in the airways.**

toms. Cortisone acts anti-inflammatory, lowers hyperreactivity of the bronchi and reduces mucus secretion.

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13 THE MICROBIOME IN ASTHMA

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KEY MESSAGES

- The upper and lower airway microbial composition has a significant impact on asthma development
- The microbiota at sites distant to the lungs can also influence immune responses within the respiratory tract. The gut-lung axis is especially relevant
- Both the upper and lower airway and the gut microbiome may associate with different asthma phenotypes

Since the groundbreaking study revealing the close correlation between reduced diversity of microbial exposures and childhood asthma almost a decade ago, we have gained increasing knowledge about microbial influences on asthma development, disease progression and treatment efficacy.

Previously considered to be a sterile environment, it is now evident that lung colonization goes along with microbial colonization of all other internal and external body surfaces. Representing first contact with external environment, the first months of life after birth are crucial for the formation of a stable microbial community conferring health to the human body. There is increasing scientific evidence suggesting an essential impact of the airway microbial composition on asthma development and disease phenotype. Presence of bacteria such as *Moraxella* species, *Haemophilus* species or *Streptococcus* species in the oropharynx of infants at one month of age were associated with increased risk for asthma development later in life, but additionally contribute to asthma exacerbations in adults (Table 1). This knowledge has contributed to the concept that airway colonization with specific bacteria strains might contribute to asthma development, while other microbes may protect against disease development (Figure 1A).

The microbiota at sites distant to the lungs can also influence immune responses within the respiratory tract. The concept of a common mucosal immune system might be especially relevant to the gut-lung axis. It is well recognized that the gut microbiota is different in healthy compared to asthmatic patients, both in adults and children, with microbial diversity often being reduced in asthmatics.

TABLE 1

Bacterial families associated with protection or aggravation of asthma

Mucosal site	Higher abundance in healthy individuals	Higher abundance in asthmatic patients
Oropharynx		*Moraxella catarrhalis*, *Haemophilus influenzae*, *Streptococcus pneumoniae*
Lung	Bacteroidetes, Actinobacteria	Proteobacteria, Firmicutes
Gut	*Faecalibacterium prausnitzii*, *Sutterella wadsworthensis*, *Bacteroides stercoris*, *Akkermansia muciniphila*	*Eggerthella lenta*

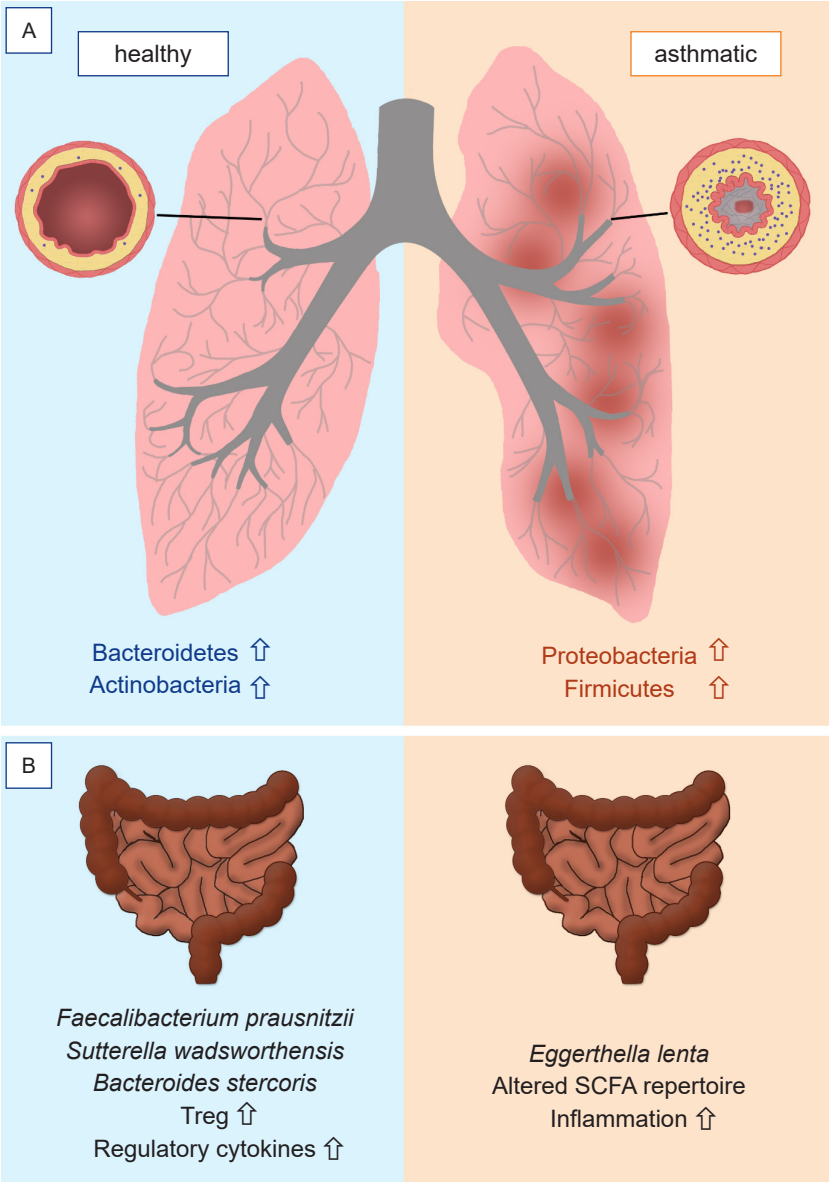

Figure 1 Microbiota composition in health and asthmatic disease. Bacteria found in higher abundance in (A) lower airways and (B) the intestine.

While certain strains are present in higher abundance in healthy individuals, other bacterial strains are found at higher levels in asthmatic patients (Figure 1B). In line with above mentioned knowledge about lung-colonization, it is well established that early life seems to represent an important window of opportunity. Gut colonization with beneficial microbiota might also contribute to asthma prevention. Furthermore, gut-microbiota derived metabolites have a direct influence on lung immunology, which has been most clearly shown for microbial-derived short chain fatty acids (SCFA). Additionally, the gut microbiome may associate with different asthma phenotypes, as recently demonstrated for obese asthmatics that display microbial changes associated with asthma and obesity.

With regards to therapy, asthma medication is known to affect microbiota composition, but it is currently unknown if specific microbial changes can improve responses to anti-inflammatory therapies in asthma patients. Local and systemic asthma therapeutics influence lung microbiota, with corticosteroids having a prominent impact (Figure 2). Direct microbiota modulation might also influence disease presentation. As lung inflammation was shown to alter gut microbiota composition, experimental studies as well as large clinical studies have recently revealed that modulation of gut microbiota by antibiotic treatment with azithromycin influences allergic airway inflammation in asthma. Thus, microbiota modulation could represent an intriguing (add-on) asthma therapy, which needs to be evaluated in detail in future experimental and clinical studies (Table 2).

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TABLE 2

Knowledge gaps and need for future research efforts	
What do we know?	**What do we need to analyze?**
Lung microbial colonization influences asthma development and disease phenotype	What is the impact of early life upper airway microbiota composition on the development of asthma?
	What are the relevant environmental factors shaping the microbiota profile?
	Can the lung microbial composition be modulated by dietary factors?
The gut microbiome influences lung immunology and asthmatic disease	Are other microbial niches like the skin decisive for asthma presentation?
	Which gut microbiota shape the airway antiviral responses?
Local and systemic asthma treatment changes microbial compositions	What is the best strategy to beneficially modulate microbial composition for asthma prevention and treatment?
	Can we efficiently modulate the microbiota also in late childhood or adulthood?

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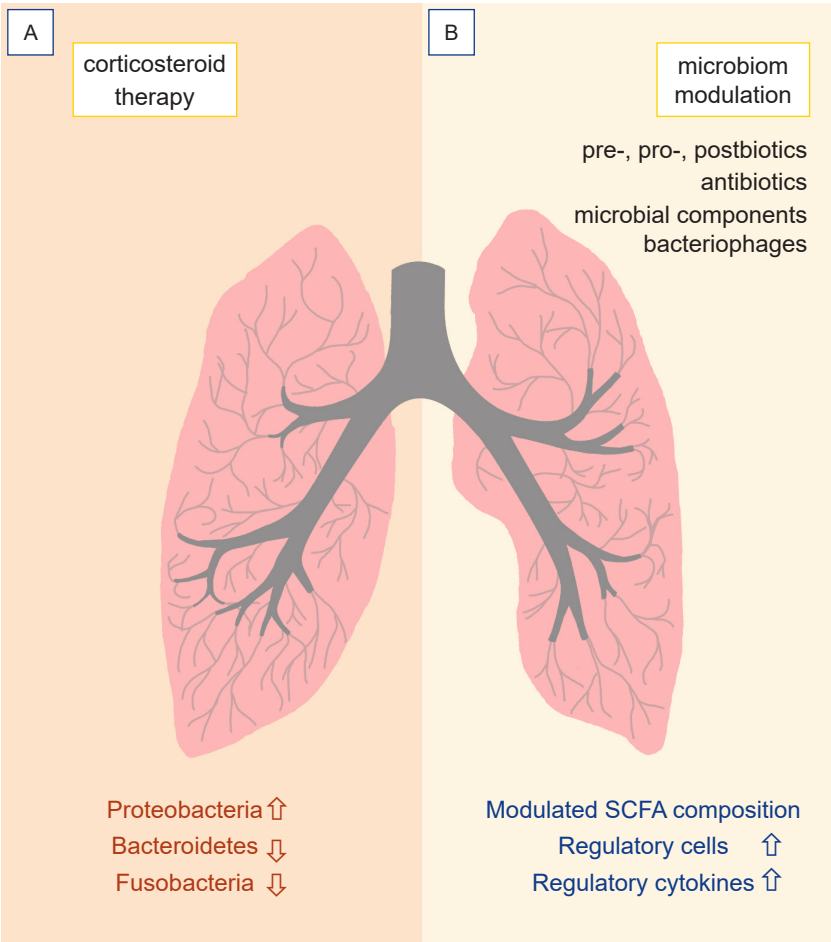

Figure 2 **Microbiota and asthma treatment.** (A) Asthma therapy changes airway and gut microbiome. (B) Microbiota modulation might represent a novel treatment option for asthma.

14 ASTHMA PHENOTYPES AND ENDOTYPES

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KEY MESSAGES

- Asthma is as an umbrella term encompassing several different subtypes, or phenotypes, of patients
- There is less consensus on identification of the underlying specific phenotypes, molecular phenotypes or endotypes
- To be considered a phenotype, multiple different characteristics, from clinical to physiologic to immune-inflammatory, should be consistently observed in similar patients
- For an endotype a specific molecular pathway should be identified as critical, if not essential, to the manifestation of that phenotype
- Asthma phenotypes and endotypes can now be distinguished by the presence or absence of Type-2 molecular processes
- Further research is needed both for Type 2 Hi and Type 2 Lo endotypes

The term *asthma* is now accepted as an umbrella term encompassing several different subtypes, or phenotypes, of patients who meet clinical criteria for asthma (appropriate symptoms in the face of reversible airway obstruction). Despite this general acceptance, there is less consensus on identification of the underlying specific phenotypes, molecular phenotypes or endotypes. To be considered a phenotype or molecular phenotype, multiple different characteristics, from clinical to physiologic to immune-inflammatory, should be consistently and concurrently observed in similar patients. To achieve the status of endotype, a specific molecular pathway should be identified as critical, if not essential, to the manifestation of that phenotype.

Recently, patients have been identified on the basis of clinical characteristics, often termed treatable traits, including factors such as reversible airflow limitation, eosinophilia, and infection-prone (Table 1). Like clinically defined phenotypes (frequent exacerbators, adult onset), these traits can be contributed to by a variety of factors, such that they perform less well for identifying underlying mechanisms. Even eosinophilia is likely to be caused by several different processes.

However, this basic understanding that not all asthma associates with eosinophilia contributed greatly to the successful development of targeted biologic therapies based around the Type-2 pathways, IL-4, 5 and 13 driven. This targeted approach, combined with multiple 'omic studies, confirmed that, depending on severity, ~40-70% of asthma patients exhibited evidence of Type-2 inflammation in association with their clinical presentation (Figure 1). Biomarkers, including blood/sputum eosinophils and fraction exhaled nitric oxide (FeNO) were tracked with lung immune processes and predicted responses to Type-2 targeted therapies (Table 2). These observations contributed to the current characterization of asthma into Type-2 Hi or Type-2 Lo *molecular phenotypes* (Table 2). In adults, Type-2 Hi asthma is associated with more severe, both corticosteroid responsive and dependent disease (Figure 2). It is typically exacerbation prone but allergies may play a less important or even non-existent role in many.

TABLE 1

From Characteristics to Endotypes			
Characteristics/Traits	**Clinical Phenotypes**	**Molecular Phenotypes**	**Endotypes**
Age at onset	Early vs late onset	Type-2 Late onset Type-2 allergic/early onset	Type-2 Hi Late onset asthma
Eosinophilia	Eosinophil Hi vs Lo	Type-2 Hi vs Lo	
Inhalant allergies	Allergic vs non-allergic	Type-2 Hi Allergic/early onset	
Exacerbations	Exacerbation-prone	Type-2 Hi vs Lo	
Airflow limitation	Reversible vs fixed	Type-2 Hi vs Lo	
Corticosteroid responsiveness	Systemic corticosteroid dependency	Type-2 Hi Late onset Type-2 + additional factors	
Obesity	Obese late onset asthma	Type-2 Lo/IL-6 Hi late onset	
Neutrophilia	Bronchitic/neutrophilic	Type-2 Lo	

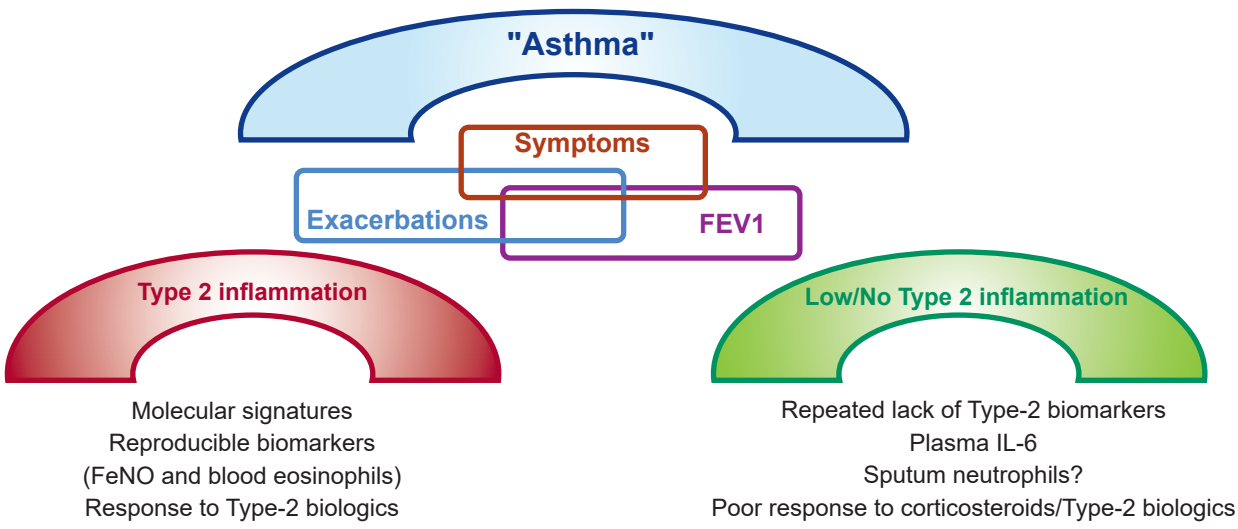

Figure 1 **The emergence of two molecular parasols under the asthma umbrella: Type-2 Hi and Lo.**

Type-2 Lo asthma, defined by the absence of Type-2 biomarkers and poor response to Type-2 targeted therapies, remains poorly defined but may include infection-prone, autoimmunity, obesity- and/or smoking-related disease. Definitive molecular pathways for Type-2 Lo asthma are lacking, but could include IL-6, inflammasome and interferon pathways. Finally, Type-2 Hi biomarkers are even more predominant in asthmatic children than adults. Yet, their relative importance to a Type-2 Hi molecular phenotype or actual disease in children is less clear.

Whether certain Type-2 Hi asthma patients represent the first true asthma endotypes is controversial. Some patients with Type-2 biomarkers may respond better to biologics targeted to the IL-5 pathway, while others respond better to those targeted to IL-4/13. The reasons for this are unknown, but could relate to underlying differences in immune-cell drivers of the phenotypes (Th2, Type-2 innate lymphoid cells (ILC2), non-lymphoid cells), as well as the importance of epithelial cells to the clinical presentations. Increasing data suggest adult-onset asthma, particularly in association with nasal polyps, may respond better to Type-2 biologics than childhood onset asthma, even when matched for Type-2 biomarkers. These adult onset patients, with robust eosinophilia, nasal polyposis, less commonly

TABLE 2

Biomarkers for Molecular Phenotypes		
Biomarker	**Pathway (s)**	**Molecular phenotype**
Sputum eosinophils	IL-5 from Th2/ILC2s, eosinophilic chemokines, lipids	Type-2 Hi late onset
Blood eosinophils	IL-5	Type-2 Hi late onset
FeNO	IL-4/13 upregulation of Inducible NO synthase in airway epithelial cells	Type-2 Hi early and late onset
Sputum neutrophils	IL-8/others	Type-2 Lo asthma?
Plasma IL-6	Metabolic/inflammasome/IL-6	Type-2 Lo asthma?

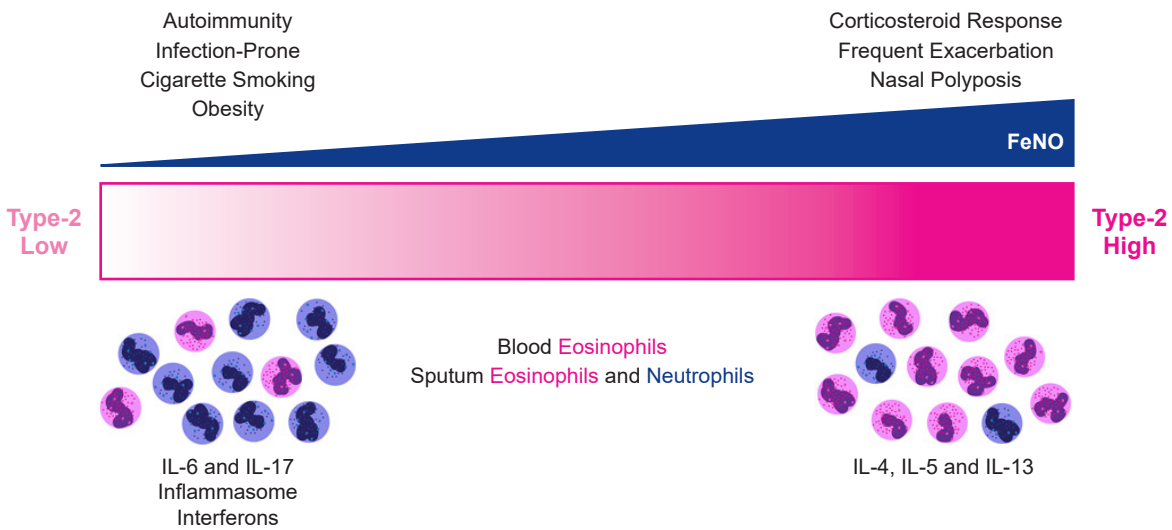

Figure 2 **Spectrum of underlying immunity in patients with asthma.** In many cases there is likely to be overlap between immune pathways, with more complicated immunity leading to the most severe disease.

aspirin sensitivity, and profound responses to Type-2 therapies, are likely as close to achieving the status of an asthma endotype as currently exists. Finally, despite the substantial clinical impact of these Type-2 targeted therapies, none of these therapies, even in the best-responding patients, have yet been shown to be "cures", with the clinical disease recurring upon stopping treatment.

In summary, asthma phenotypes can now be distinguished by the presence or absence of Type-2 molecular processes, which critically identify effective treatment approaches, at least for Type-2 Hi disease. Much remains to be understood regarding underlying endotypes of Type-2 Hi patients. Any mechanistic pathways to determine molecular phenotypes of Type-2 Lo asthma await identification.

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Section C

DISEASES ASSOCIATED WITH ASTHMA

1 ATOPY AND ASTHMA

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KEY MESSAGES

- Atopy is the inherited predisposition to synthesize specific IgE to common environmental allergens. Atopy is a trait rather than a disease
- A diagnosis of atopic asthma requires an indicative clinical history for a relevant aeroallergen *plus* identification of confirmatory allergen-specific IgE in vivo or in vitro
- All asthmatic patients should be investigated for atopy. The diagnosis of allergic asthma offers the opportunity for adjunct allergen immunotherapy (AIT) with the potential to improve asthma control and decrease exacerbations and asthma medication use
- AIT is currently underused, disadvantaging millions of patients with allergic asthma
- Identification of a key role for atopy in patients with severe asthma could also favour biologicals targeting IgE/IL-4/IL-13 rather than IL-5/IL-5R

Atopy is the inherited predisposition to synthesize specific IgE to common environmental aeroallergens (Figure 1). Approximately 45% of the population is atopic, but atopy is a trait rather than a disease. The presence of IgE-sensitization may not translate into a clinical presentation of an allergic disease such as asthma. Young children with eczema can develop the "atopic march", i.e. atopic dermatitis/food allergy in childhood followed by asthma/allergic rhinitis from adolescence. Meta-analysis of recent large birth cohorts indicated <7% children progressed from atopic dermatitis to asthma later in life. Both atopy and asthma are multigenic, with modulating roles for the microbiome, the environment and epigenetics (Figure 2). Recently, specific DNA methylation profiles in airway epithelium were mapped in children with atopy and asthma in epigenome-wide association studies.

Asthma remains a major socioeconomic healthcare burden affecting ~350 million people globally. Asthma is heterogeneous, with endotypes and treatable traits. The main genetic predictor for childhood asthma is a family history of atopic disease. Asthma prevalence in children is approximately 40% for those with two atopic parents, 25% with one atopic parent and 10% with non-atopic parents. Dual parental atopy is strongly linked to multiple allergic diseases in children, including asthma, atopic dermatitis and allergic rhinitis. Atopy is usually associated with childhood-onset Type 2-inflammatory asthma, but has low prevalence in late-onset adult asthma. Birth cohort meta-analyses indicate that multiple early life sensitizations, especially to perennial aeroallergens, enhances the risk for asthma, including severe asthma at school age. Respiratory viruses remain important cofactors, acting synergistically with atopy to promote asthma susceptibility and exacerbations. Controversy remains whether the initiating event for asthma in children is atopy or viral infection; a birth cohort study in children at high risk for atopy suggested that rhinovirus-induced wheeze did not increase the risk of asthma. Atopic asthma in children with early rhinovirus-wheeze was

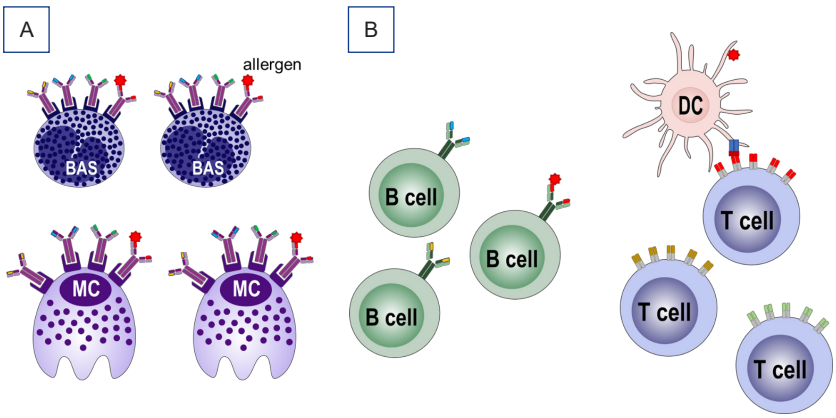

Figure 1 Allergen recognition by immune cells. A. Mast cells and basophils have IgE with multiple distinct antigen specificities bound to their surface, and only those IgE molecules specific for the allergen can cross-link it. B. B-cells and T-cells each have a unique antigen receptor. B cells with an allergen-specific surface IgE can bind allergen. T cells with a specific T-cell receptor can bind peptides processed from whole allergen by antigen presenting cells presented by MHC molecules.

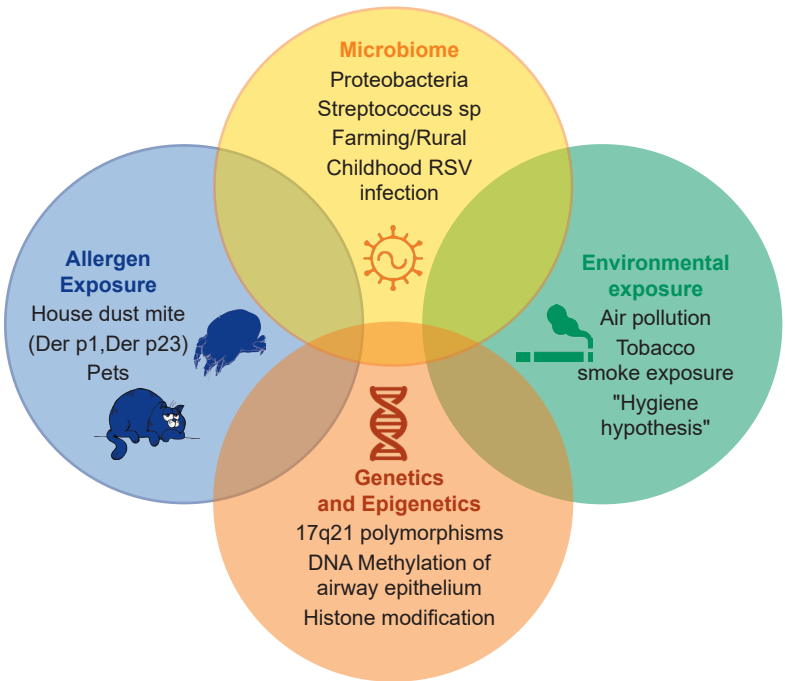

Figure 2 Exposures that may impact atopy development. Susceptibility for the development of atopic disease is multigenic and likely to be influenced by a multitude of factors, including modulating roles for the microbiome, environmental exposures (including allergens and air pollution) and epigenetics.

associated with epigenetic DNA methylation changes, including some in the promoter region of the *SMAD3* gene.

All asthmatic patients should be investigated for atopy. Diagnosis of allergic asthma requires a convincing indicative clinical history of asthma symptoms upon allergen exposure *plus* identification of confirmatory specific IgE. In the clinic, intracutaneous skin prick testing with standardized allergen extract detects the presence of allergen-specific IgE via IgE-sensitized mast cell degranulation. Alternatively, *in vitro* serum immunoassays provide more quantitative results (Figure 3). Component-resolved diagnostics and basophil activation tests add precision, but are rarely available in the clinic. Investigation of the IgE-sensitization molecular profile to house dust mite allergens (*Dermatophagoides pteronyssinus*) indicated that polymolecular sensitization, parental allergic rhinitis and mite exposure levels favour early asthma onset. Der p 1 or Der p 23 sensitization at age 5 have also predicted school-age asthma.

The mainstay of asthma treatment is inhaled corticosteroids (pharmacotherapy). A diagnosis of allergic asthma should lead a clinician to consider allergen immunotherapy (AIT) as add-on to regular asthma pharmacotherapy. AIT is the only current treatment that can alter the natural history of an allergic disease. For safety, spirometry lung function (FEV1) >70% predicted is advised. Many patients may normalize lung function by AIT treatment allowing down-titration of pharmacotherapy. AIT is currently underused, disadvantaging millions of patients with allergic asthma (Figure 4). Identification of a prominent atopic phenotype in patients with severe asthma could also inform algorithms to favour biologicals targeting IgE, IL-4 and/or IL-13 rather than IL-5/IL-5R.

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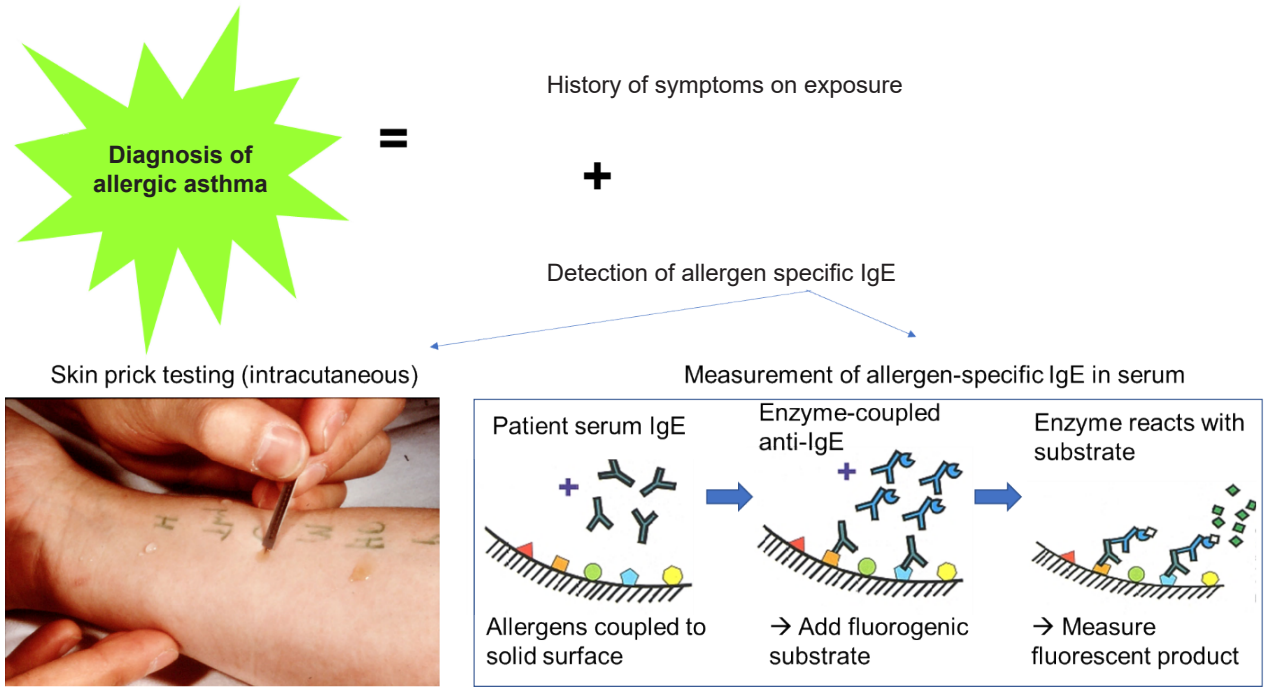

Figure 3 The diagnosis of allergic asthma. The diagnosis requires both a clinically relevant history of symptoms on exposure to allergen as well as evidence of atopic sensitization: the identification of allergen-specific IgE, either by intracutaneous skin prick testing with standardized allergen extract or by measurement of allergen-specific IgE in serum.

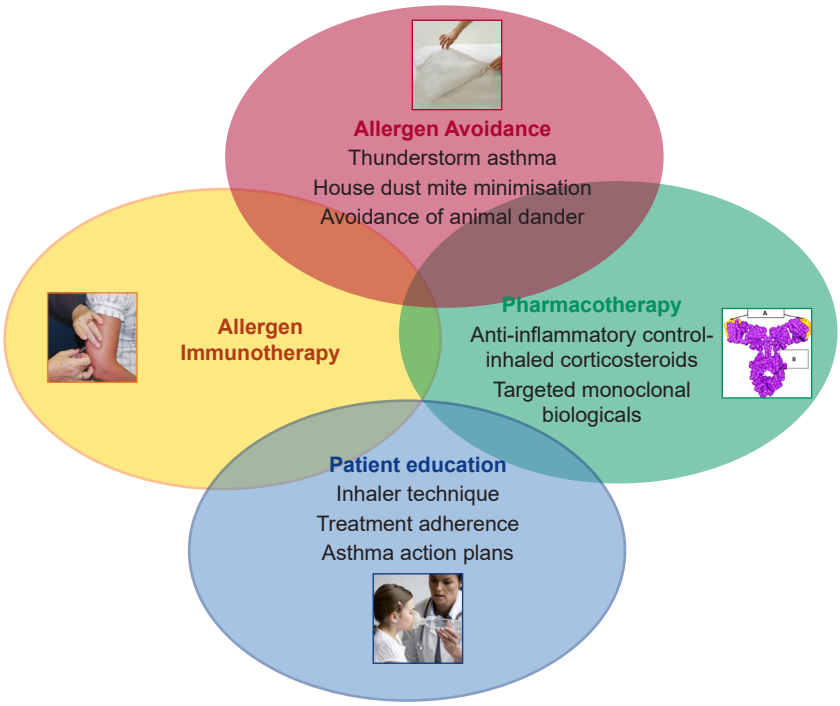

Figure 4 Identification of a predominantly atopic asthma phenotype should lead a clinician to consider adjunctive measures in addition to usual asthma therapies. These include allergen immunotherapy, allergen avoidance strategies and potentially targeted monoclonal biologicals for patients with severe asthma, for example anti-IgE therapy (pictured here).

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2 ALLERGIC RHINITIS

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KEY MESSAGES

- The association of allergic rhinitis (AR) to asthma is common, and vice versa
- Cross-specialty diagnostic is recommended to improve the management of both diseases
- Treatment of clinically-relevant allergic sensitization in AR is recommended to reduce the risk of asthma development

Allergic rhinitis (AR) is an IgE-mediated disease characterized by one or more symptoms including nasal congestion, rhinorrhea, sneezing and itching. AR global prevalence continues to increase, with over 600 million individuals affected worldwide. Allergic Rhinitis and its Impact on Asthma (ARIA) suggests categorizing AR as intermittent or persistent, motivated by the fact that aeroallergens may be present seasonally in one area and year-round elsewhere. "Intermittent" applies to symptoms occurring on fewer than 4 days a week or for less than 4 consecutive weeks, while "persistent" refers to symptoms present more than 4 days per week and for more than 4 consecutive weeks. Additionally, ARIA classifies severity of AR as mild if patients do not show any of the following characteristics: sleep disturbance, impairment of daily activities, and impairment of school/work. If such characteristics are present, however, AR severity is considered moderate to severe.

Studies of both adult and pediatric populations provide evidence for increased risk of asthma development in individuals with AR. The association is common, with up to 90% of asthmatics having comorbid AR, and 10–40 % of individuals with AR showing symptoms of asthma. Untreated AR contributes to asthma severity and loss of control, with moderate to severe AR causing a 12.7-fold increase in the odds of having uncontrolled asthma, compared to those without AR.

ARIA has proposed that AR and allergic asthma may be manifestations of one syndrome in two parts of the respiratory tract, with more severe AR corresponding directly to more severe asthma. AR and sensitization to an inhalant allergen can be causal factors in atopy-prone individuals to development of asthma, and therefore represent an earlier clinical manifestation of the disease (Figure 1). Hence, early detection of either manifestation seems crucial to improve patient care and promote interdisciplinary action where necessary. Nasal and conjunctival allergen challenges are likely to improve diagnostic specificity for both AR and allergic asthma, and is also helpful for the detection of local allergic rhinitis (Figure 2). Currently, AR is underdiagnosed in asthma patients by 30%.

Pharmacologic treatment of comorbid AR in asthmatic patients is essential, as it reduces asthma-related healthcare utilization (e.g. emergency room visits and hospitalizations) by up to 80%, while intranasal glucocorticoids as the most effective pharmacotherapy. Systemic leukotriene receptor antagonists might be another option. Reduction of allergen exposure represents an intuitive approach; however, single interventions often show limited long-term effectiveness, especially for persistent AR. Thus, multifaceted patient ed-

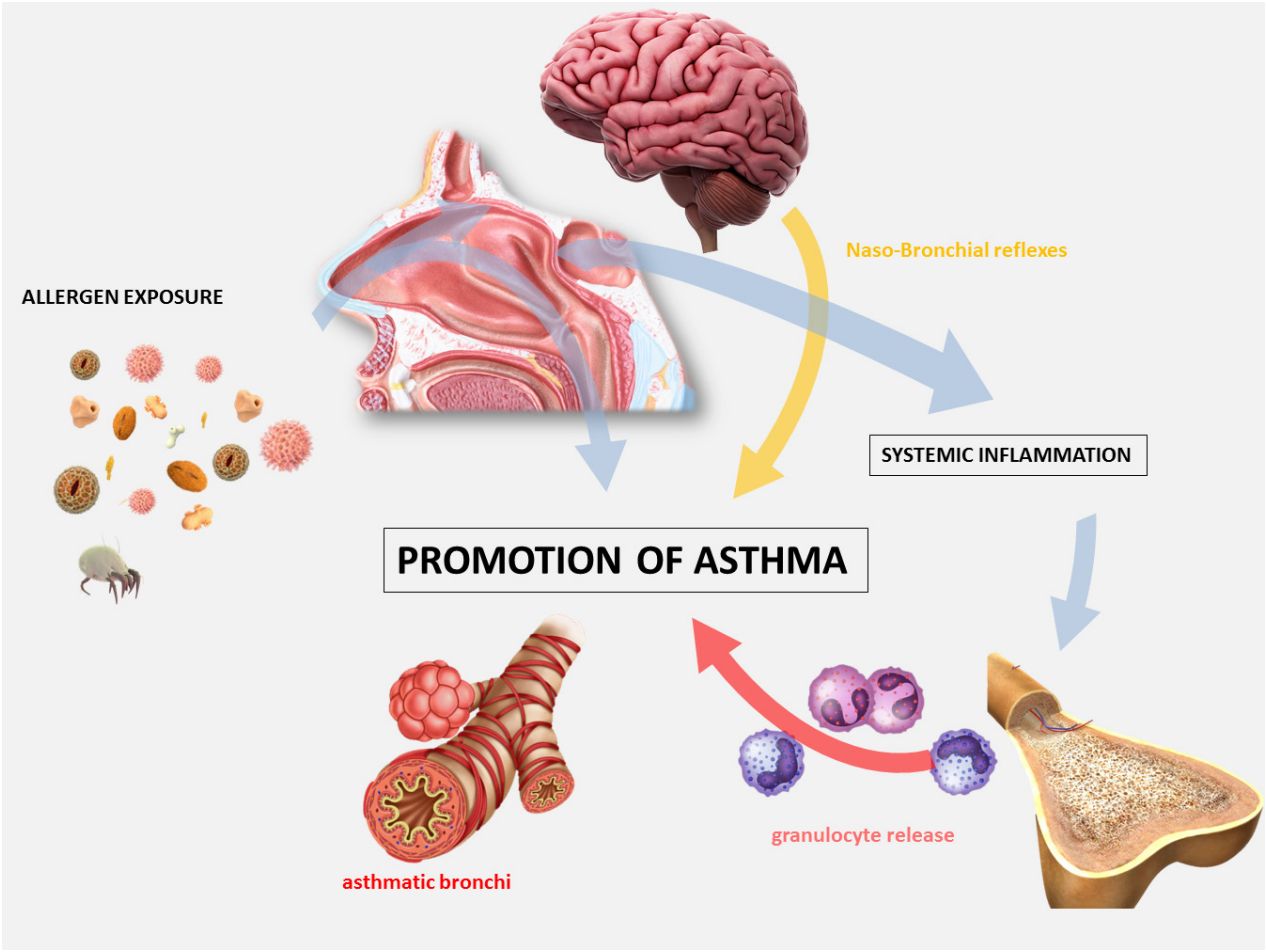

Figure 1 Eosinophil release: mechanisms explaining the naso-bronchial interaction and systemic inflammation in asthma and rhinitis. Airborne allergens trigger Type-2 inflammation in nasal and bronchial mucosa. In addition, nasal inflammation amplifies asthma symptoms via indirect mechanisms: 1) activation of central nervous reflexes with bronchial obstruction (yellow), 2) inflammatory cytokines promoting maturation of the granulocyte progenitors in the bone marrow into inflammatory granulocytes, e.g. eosinophils, which are then released into the peripheral blood. Type-2 chemoattractants lead to accumulation of granulocytes in the lung tissue.

ucation approaches regarding environmental control and allergen avoidance are recommended.

Allergen immunotherapy (AIT) includes both sublingual immunotherapy (SLIT) and subcutaneous immunotherapy (SCIT). AIT not only improves symptoms of AR, but improves asthma symptoms and reduces asthma medication use in subjects with concurrent AR. AIT for AR may prevent new allergen sensitizations and the occurrence of allergic asthma.

In conclusion, most individuals with asthma have AR, AR is associated with higher risk of asthma development and correlates with severity of asthma, and pharmacologic AR treatment and/or AIT can reduce asthma morbidity.

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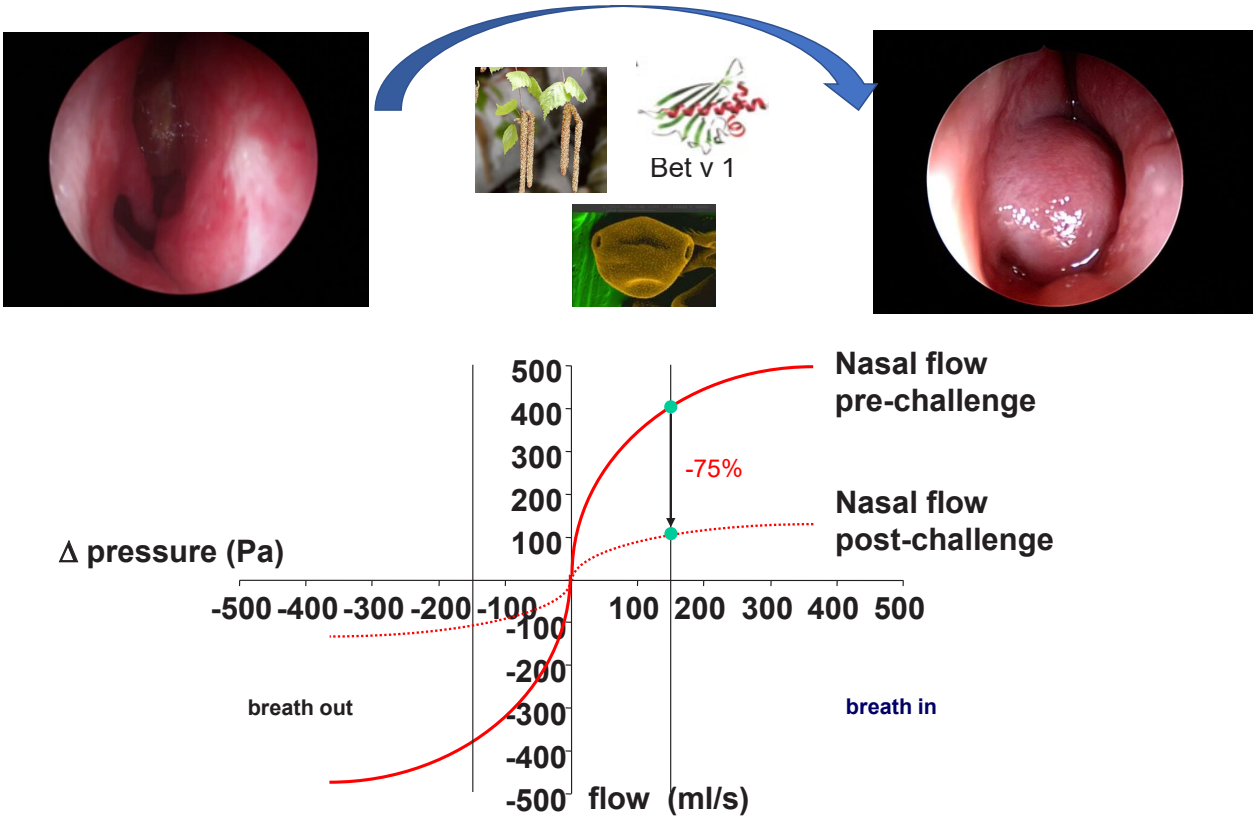

Figure 2 **Nasal allergen challenge.** It can be used to detect airway IgE mediated mucosal reactions in rhinitis by measuring the variation of the peak nasal inflammatory flow.

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3 CHRONIC RHINOSINUSITIS

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KEY MESSAGES

- The prevalence of chronic rhinosinusitis (CRS) in asthmatic patients increases as the severity of the asthma increases
- CRS with a T2 inflammatory background and CRS with nasal polyps are more likely to be associated with asthma
- Treating CRS improves asthma control

Chronic rhinosinusitis (CRS) is a significant health problem and affects 5-12% of the general population. CRS is defined as "inflammation of the nose and the paranasal sinuses characterized by two or more symptoms, one of which should be either nasal blockage / obstruction / congestion and the others can be nasal discharge (anterior / posterior nasal drip), facial pain/pressure, and/or reduction or loss of smell". The symptoms must be complemented by either: (1) endoscopic signs of nasal polyps, mucopurulent discharge, edema and mucosal obstruction (Figure 1) and/or (2) sinus CT findings consistent with mucosal inflammation (Figure 2). The major phenotypes are CRS with nasal polyps (CRSwNP) or without polyps (CRSsNP). CRSsNP represents the majority of patients. Other phenotypes are aspirin exacerbated respiratory disease, and allergic fungal rhinosinusitis.

Endotyping of the tissue removed from the sinuses shows that the amount of T2 inflammation varies by phenotype and by geographic location. In the US and Western Europe about 80% of CRSwNP are T2 inflammation, whereas in China T2 inflammation represents about 50% of patients with polyps. The distinction between T1 and T2 inflammation is more of a blend then an absolute division and may better be described as T2 high and low. Endotype analysis shows similarities between the inflammatory processes described in asthma and those in CRS (Figure 3). This concept explains why treatments targeting specific aspects of the inflammation are effective in both diseases.

CRS is associated with asthma. The association ranges from 10 to 70%, with those with T2 inflammation and nasal polyps having the highest prevalence of asthma. In patients with CRS and no asthma, the chance of developing asthma in the next 4 years reaches 5%. Conversely, patients newly diagnosed with asthma are 2.5 times more likely to develop CRS than matched controls. The more severe the asthma, the greater the amount of mucosal inflammation observed on CT scans. CRS is considered a cause for uncontrolled asthma.

Treating CRS improves asthma. While many systemically administered anti-inflammatory treatments like oral steroids and biologics affect both the upper and lower airway simultaneously, these treatments do not distinguish whether the treatment of the upper airway has a direct effect on asthma. Treatments that directly improve CRS, such as topical intranasal corticosteroids and functional endoscopic sinus surgery, appear to indirectly improve asthma control, without a known direct effect on the lung function, supporting a relationship between the upper and lower airway. Hypotheses to explain these observations include post-nasal drainage with micro-aspiration or laryngeal stimulation, activation

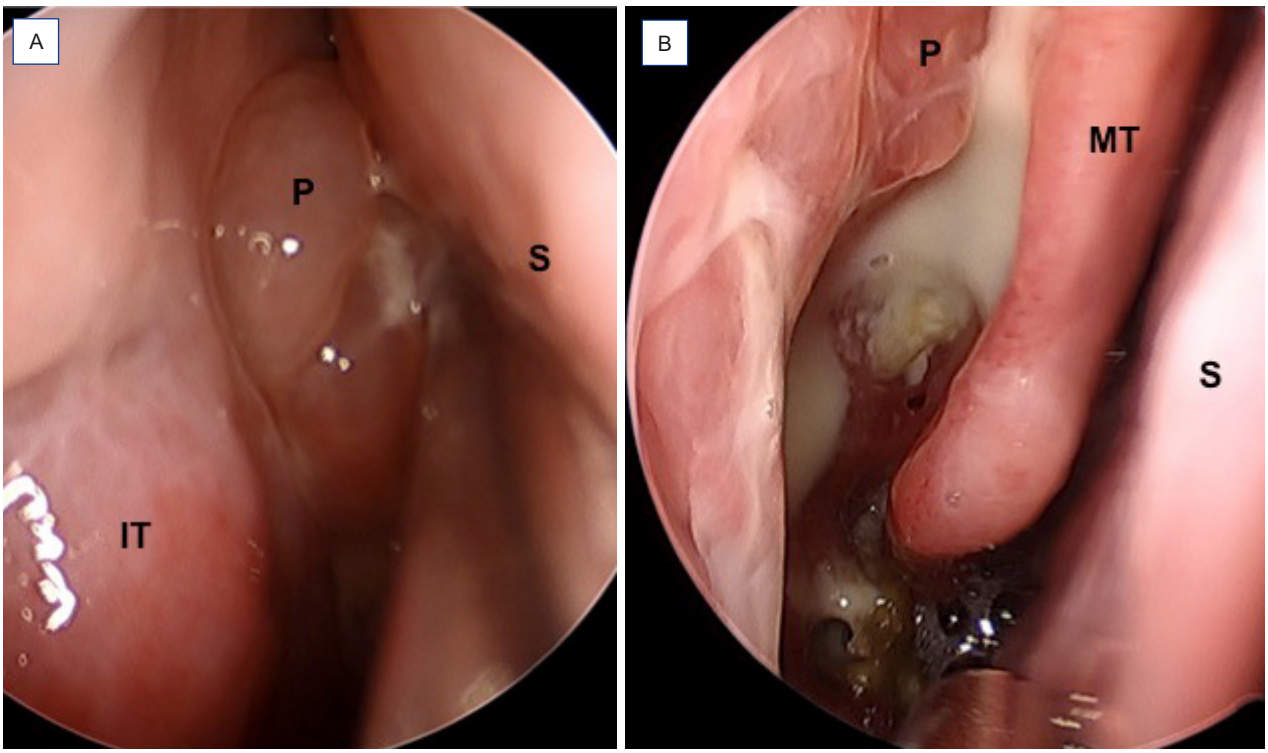

Figure 1 **Nasal endoscopic exam of CRS.** Panel A: Right nasal cavity polyp in patient with CRSwNP. Panel B: Right middle meatal muco-purulence in patient with acute exacerbation of CRS.
P - polyp; S - septum; IT - inferior turbinate; MT - middle turbinate.

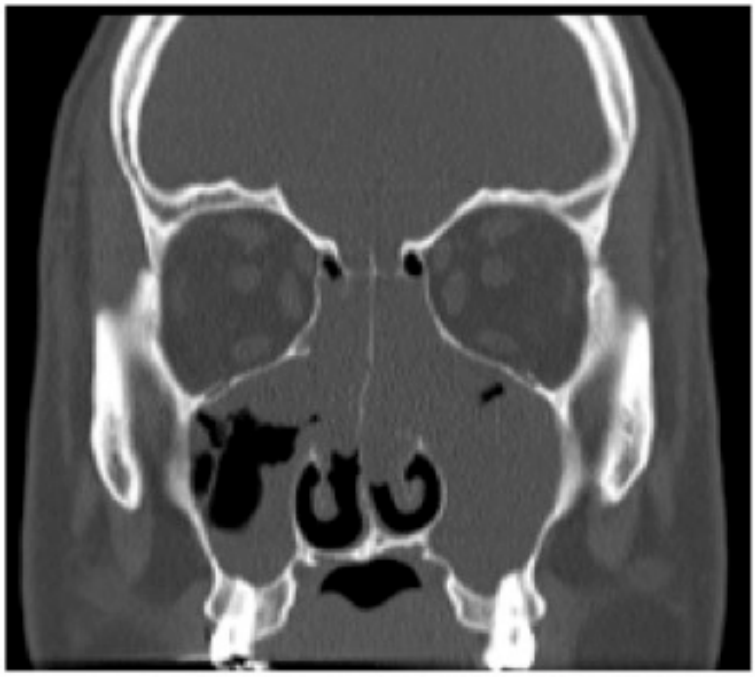

Figure 2 **Sinus CT scan of a patient with CRSwNP.** Coronal view.

of a nasal bronchial reflex, a shift from nasal to mouth breathing, and systemic absorption of mediators or chemotactic factors from inflammatory process in nose or sinuses producing lower airway effects.

CRS and asthma are comorbidities that share pathology and causality. Clinicians should consider a diagnosis of CRS in asthmatics not responding well to treatment.

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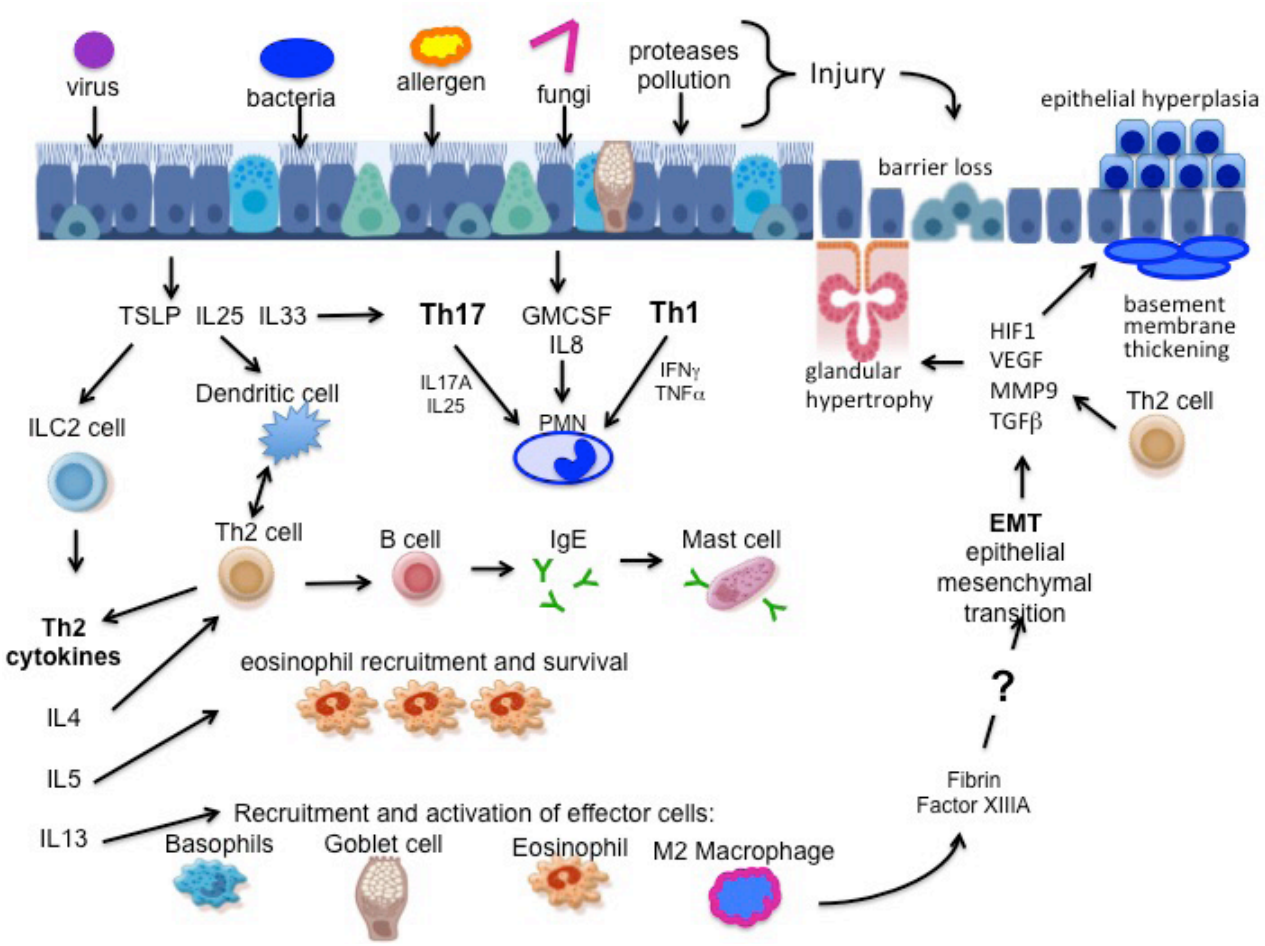

Figure 3 **Pathogenesis of CRSwNP and CRSsNP.**

TSLP - thymic stromal lymphopoetin; ILC2 - group 2 innate lymphoid cells; Th1 - type 1; Th2 - type 2; Th17 - type 17; HIF1 - hypoxia inducible factor-1; VEGF - vascular endothelial growth factor; MMP9 - matrix metallopepsidase-9; TGFβ - transforming growth factor-beta; IFNγ - interferon-gamma; TNFα - tumor necrosis factor-alpha; PMN - polymorphonucleocytes.

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4 ASTHMA AND OBESITY – THE TWIN EPIDEMICS

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KEY MESSAGES

- Asthma incidence and burden are increased in obesity
- Cluster analysis identifies an obese asthma phenotype predominantly in women with late onset severe asthma, high symptom expression, high dose inhaled corticosteroids, a normal eosinophil count, and an airway inflammatory pattern that is either mixed granulocytic or neutrophilic
- Obesity can worsen asthma outcomes by several different mechanisms including altered pulmonary mechanics, production of adipokines and pro-inflammatory cytokines and via co-morbidities (eg. depression, GERD)
- Assessment includes measurement of body mass index and waist circumference measurement
- Management seeks to achieve 5-10% weight loss, with specific weight loss recommendations based on the degree of obesity

Obesity is a progressive and relapsing condition characterized by abnormal or excessive accumulation of fat. Obesity is becoming increasingly common and it is associated with an increased risk of asthma.

Asthma incidence is increased in obesity. A meta-analysis of 333,102 adults reported that obesity doubles the odds of developing asthma. The odds increase with the severity of obesity. The prevalence of obesity is further increased in people with severe asthma, with an Australian study finding that 45% of those prescribed omalizumab are obese compared to 27% in non-severe asthma.

Obesity amplifies the burden of asthma. Asthma with obesity is associated with poorer asthma control, more frequent exacerbations, poorer quality of life, increased use of oral steroids, increased urgent visits to healthcare and lower lung function.

TABLE 1

Clinical Cluster Obese Asthma
Characteristics
Late-onset
Female
Obese
High symptom burden
High ICS use
Airway inflammation (neutrophil or mixed granulocyte)

The obese asthma phenotype was consistently identified in studies adopting a cluster analysis approach. This phenotype involves obese women with late onset severe asthma, with a high symptom expression, use of high dose inhaled corticosteroids, a normal eosinophil count, and an airway inflammatory pattern that is either mixed granulocytic or neutrophilic (Table 1). The obese asthma phenotype seems to be mediated by non-T2 mechanisms and features lower levels of FeNO and normal blood eosinophils.

Obesity can worsen asthma outcomes by several different mechanisms, such as altered pulmonary mechanics (e.g lung restriction, premature airway closure), production of adipokines and pro-inflammatory cytokines (e.g. IL-6, TNF-α) by adipose tissue and the associated systemic inflammatory response, and via co-morbidities such as depression and GERD.

THE MANAGEMENT OF OBESITY IN SEVERE ASTHMA

1. **BMI and waist circumference should both be measured to classify obesity.** Waist circumference is a good predictor of visceral adiposity, with abdominal obesity associated with an increased risk of a number of diseases including cardiovascular disease, diabetes and cancer (Table 2).
2. **People with moderate-severe asthma should be advised that a modest 5-10% weight loss can improve their overall health and** was associated with **clinically important improvements in asthma control in 58%, and asthma-related quality of life in 83%**, of overweight and obese adults with asthma.
3. **Weight loss recommendations vary depending on the degree of obesity (Figure 1).** An additive approach is recommended, with more invasive approaches reserved for those with the highest BMIs. Lifestyle change should be recommended to all obese people with asthma. This includes reducing energy intake, increasing physical activity and counselling for behaviour change. A very-low calorie diet (VLCD) can be considered for those with a BMI>30 if required. Referral to a specialist service to receive advice regarding bariatric surgery may be considered in people with a BMI>40, or >35 in the presence of at least two significant obesity-related comorbidities.

TABLE 2

Interpretation of Waist Circumference*		
Risk of metabolic complications	**Waist circumference (cm) Men**	**Waist circumference (cm) Women**
Increased	≥ 94	≥ 80
Substantially increased	≥ 102	≥ 88

** Recommendations based on Obesity: Preventing and Managing the Global Epidemic, 2000, WHO and reproduced from the Severe Asthma Toolkit. Below are sex-specific recommendations for waist circumference in Caucasians, relating to risk of metabolic complications.*

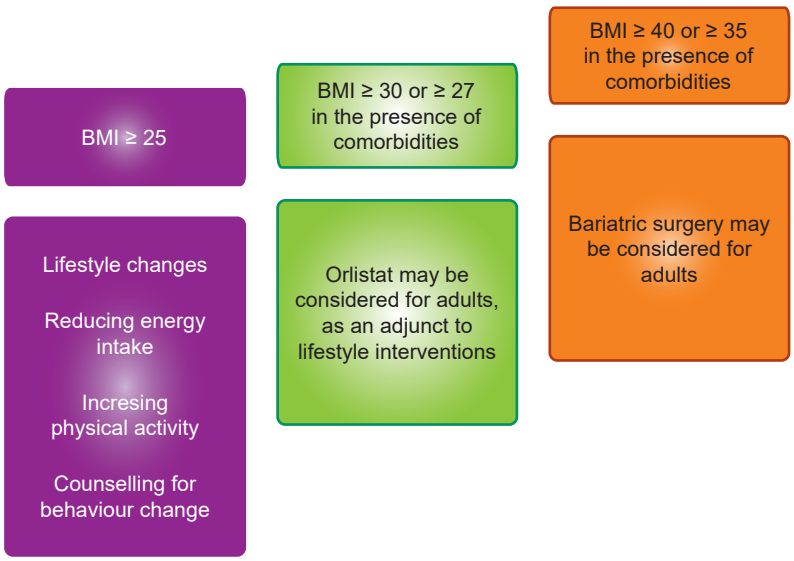

Figure 1 The Obesity Step-up Approach. Recommendations based on the Australian Clinical Practice Guidelines for the Management of Overweight and Obesity (2013), copyright and reproduced with permission from the Severe Asthma Toolkit.

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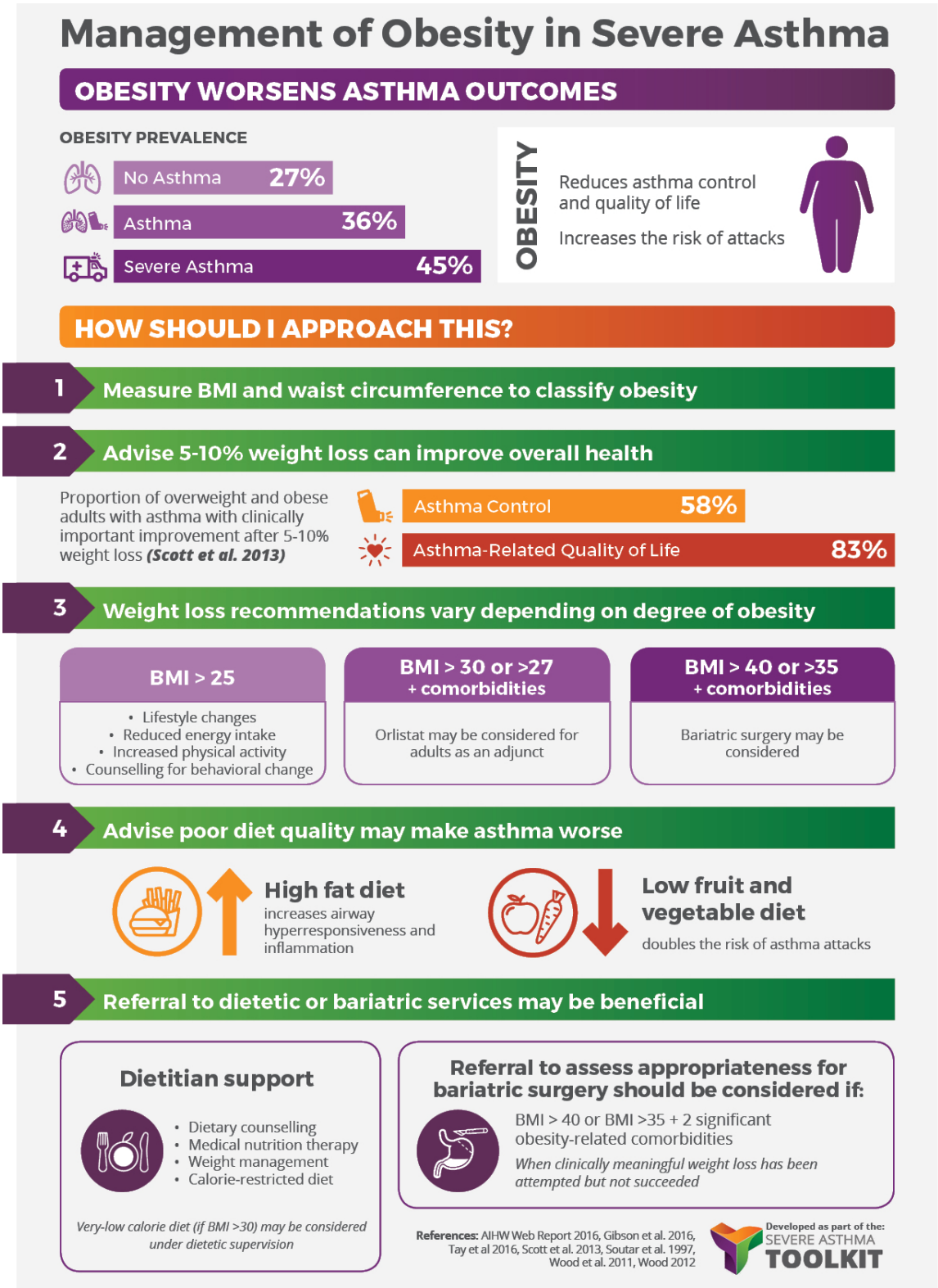

Figure 2 **Management of Obesity in Severe Asthma.** Copyright and reproduced with permission from the Severe Asthma Toolkit.

5 NSAID-EXACERBATED RESPIRATORY DISEASE (N-ERD)

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DEFINITION AND CLINICAL CHARACTERISTICS OF N-ERD

NSAID-Exacerbated Respiratory Disease (N-ERD) is a distinct clinical syndrome observed in 5-10% of adult patients with asthma and characterized by history of acute dyspnea, usually accompanied by nasal symptoms (rhinorrhea and/or nasal congestion), within two hours after ingestion of aspirin (ASA) or other nonsteroidal-anti-inflammatory drugs (NSAIDs), which are potent cyclooxygenase-1 (COX-1) inhibitors. These patients suffer from chronic, usually severe asthma and severe chronic rhinosinusitis (CRS) with recurrent nasal polyps (CRSwNP). The syndrome was previously called Aspirin-Exacerbated Respiratory Disease, Aspirin-triad, Samter trias or Aspirin-Sensitive Asthma. Patients with N-ERD are quite heterogeneous with respect of asthma severity, presence of atopic sensitization (up to 70% may be atopic) and general responsiveness to asthma and CRSwNP treatment. N-ERD is frequently associated with increased risk for severe asthma, frequent exacerbations and sudden death. Chronic urticaria, alcohol intolerance and hearing loss can be associated (Figure 1).

KEY MESSAGES

- Non-steroidal anti-inflammatory drugs Exacerbated Respiratory Disease (N-ERD) is a distinct asthma phenotype with coexisting chronic rhinosinusitis (CRS), nasal polyps and hypersensitivity to aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs)
- N-ERD is a heterogenous syndrome, usually characterized by an increased risk for uncontrolled upper and lower airway disease
- Patients with N-ERD require comprehensive and multidisciplinary diagnostic approach
- Management of asthma and CRS in N-ERD is similar to treatment of other forms of asthma and CRS
- Aspirin desensitization may be an effective option for some N-ERD patients

PATHOGENESIS OF N-ERD AND HYPERSENSITIVITY TO NSAIDS

The mechanism of hypersensitivity to NSAIDs in asthmatic patients is not immunological, but is related to the inhibition of COX-1, an enzyme that converts arachidonic acid into prostaglandins, thromboxanes and prostacyclin. According to the "prostaglandin/cyclooxygenase theory" proposed by Andrew Szczeklik, inhibition of COX-1 by ASA or other NSAID deprives the system of protective prostaglandin E2 (PGE2) and triggers the activation of inflammatory cells (mast cells, eosinophils and platelets) with subsequent excessive release of inflammatory mediators, including cysteinyl leukotrienes (Figure 2). Baseline abnormalities of arachidonic acid metabolism involve PGE2 deficiency, increased generation of PGD2 and over- production of leukotrienes. Inflammation occurs via type 2 cysLT receptor (CysLT2R), and IL-33 pathways. Persistent viral infections, *Staphylococcus aureus* enterotoxins and underlying genetic predisposition may also have important role in the pathogenesis of the chronic eosinophilic inflammation typically present in the upper and lower airway mucosa of N-ERD patients. even without NSAID intake.

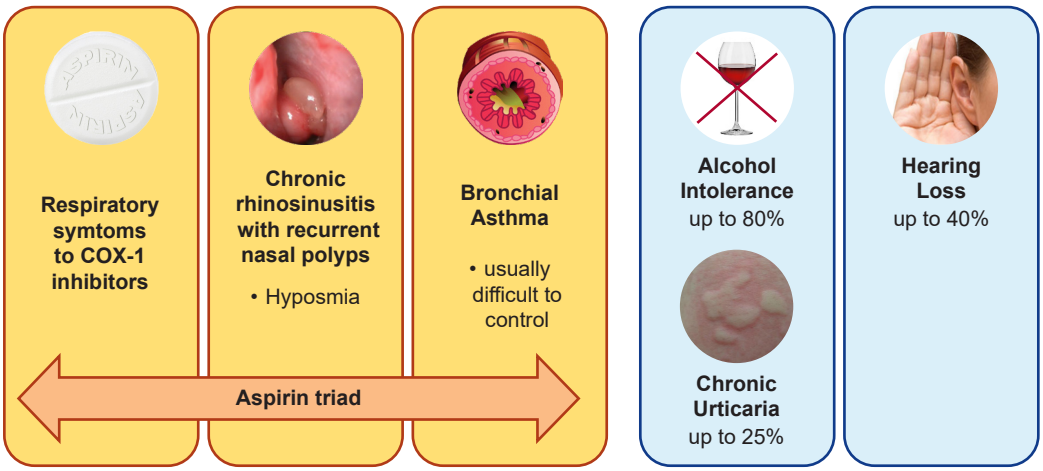

Figure 1 Clinical characteristics of NSAID-Exacerbated Respiratory Disease.

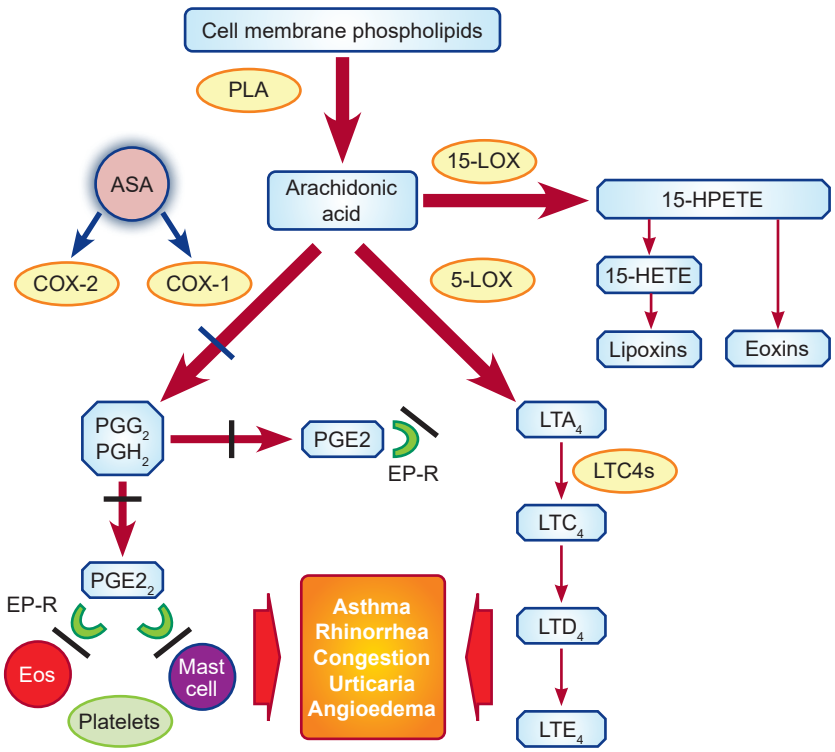

Figure 2 Patho-mechanism of aspirin–induced hypersensitivity reactions in N-ERD.

DIAGNOSIS OF NSAID HYPERSENSITIVITY

In majority of patients the diagnosis of hypersensitivity is based on a history of respiratory symptoms induced by the ingestion of ASA or other NSAIDs. Confirmation by controlled ASA challenge may be necessary in some patients. Oral aspirin provocation is the gold standard for the diagnosis, but bronchial or nasal provocation with lysine-ASA may be valuable alternative diagnostic tools. A simple diagnostic algorithm has been proposed by the EAACI Task Force (Figure 3). Several *in vitro* cell activation tests have been evaluated, but none can be recommended for routine diagnosis.

MANAGEMENT OF N-ERD

Careful avoidance of ASA and other potent COX-1 inhibitors NSAIDs is necessary to prevent severe asthma exacerbation. As alternative to NSAIDs acetaminophen or selective COX-2 inhibitors are recommended (Table 1). Management of asthma and CRSwNP in a patient with N-ERD is similar to treatment of other forms of asthma and CRS. Inhaled glucocorticosteroids, often in combination with long acting beta-2 agonists are effective in controlling asthmatic inflammation and symptoms, but in some patients chronic treatment with oral prednisone may be necessary. Addition of a leukotriene modifiers as montelukast or zileuton to standard anti-inflammatory therapy may be effective in relieving symptoms and improving respiratory function in some patients with N-ERD, but the degree of improvement is similar to ASA

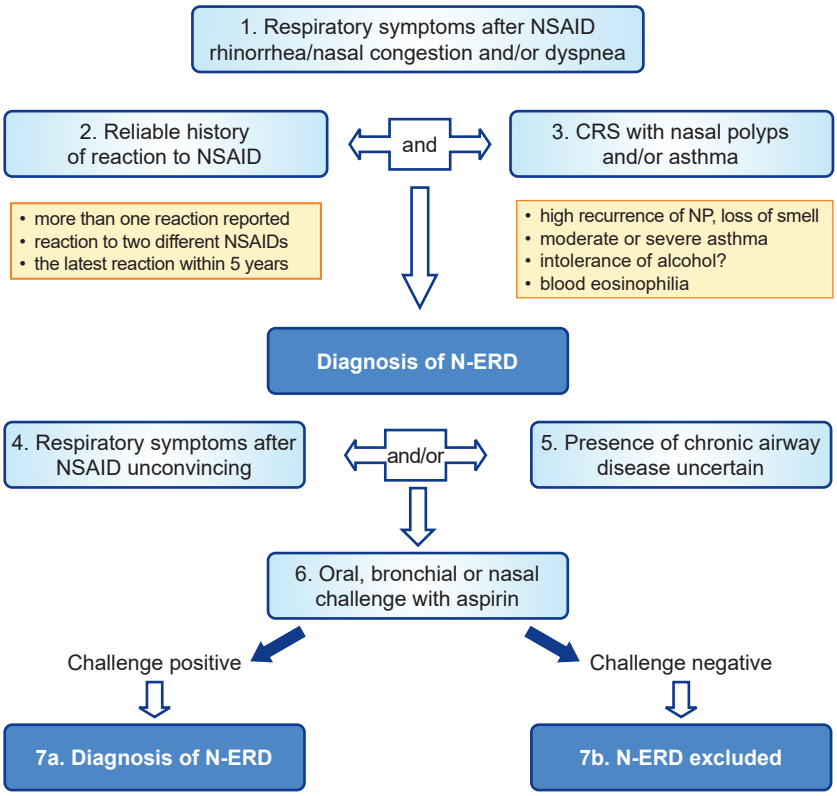

Figure 3 **Algorithm for diagnosis of N-ERD proposed by the EAACI Task Force.** *(Reproduced from Kowalski ML, Agache I, Bavbek S, et al. Diagnosis and management of NSAID-Exacerbated Respiratory Disease (N-ERD)-a EAACI position paper. Allergy. 2019;74:28-39, with permission from Wiley-Blackwell.)*

TABLE 1

NSAIDs tolerated in patients with N-ERD*	
Group A: NSAIDs cross-reacting in majority of hypersensitive patients (60–100%)	
Diclofenac	Etololac
Fenoprofen	Flurbiprofen
Ibuprofen	Indomethacin
Ketoprofen	Ketorolac
Meclofenamate	Mefenamic acid
Nabumetone	Naproxen
Piroxicam	Sulindac
Group B: NSAIDs cross-reacting in minority of hypersensitive patients (2–10%)	
acetaminophen (doses below 1000 mg)	
meloxicam	
nimesulide	
Group C: NSAIDs well tolerated by all hypersensitive patients*	
selective cyclooxygenase inhibitors (celecoxib, parvocoxib)	
trisalicylate, salsalate	

**Single cases of hypersensitivity have been reported*

tolerant asthmatics. Topical nasal glucocorticosteroids are preferred for controlling symptoms of CRS and may slow down recurrence of nasal polyps. Biologicals (anti-IgE, anti-IL5 or anti-IL4/13R) have been shown to be effective to prevent asthma exacerbation and nasal polpys recurrence in N-ERD. Surgical procedures (polypectomy, functional endoscopic sinus surgery or ethmoidectomy) are usually needed at certain stage of the CRS disease.

The special approach for these patients ASA desensitization. Most patients with N-ERD can be desensitized to ASA. Continuous ASA ingestion may result in alleviation of chronic upper and lower airway symptoms, reduction in hospitalization and emergency room visits, and in decreased need for nasal/sinus surgery. However, only a fraction of patients with N-ERD will benefit from ASA desensitization and at present it is not possible to identify the responders before the procedure is implemented.

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6 GASTRO-ESOPHAGEAL REFLUX DISEASE AND ASTHMA

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KEY MESSAGES

- Gastro-esophageal reflux disease (GERD) is an increase of retrograde movement of gastric content into the esophagus
- Ten to 20% of the general adult population in western countries and 5% of subjects in the Asia Pacific region suffer from GERD
- Asthma and/or upper airway complaints or problems are associated with GERD
- Just as GERD may aggravate asthma, so too, could asthma or asthma therapy aggravate GERD
- Treatment includes lifestyle changes and, where necessary, H2 blockers, proton pump inhibitors and prokinetics
- Double-blind controlled studies demonstrate that treatment of asymptomatic GERD in adults and children does not improve asthma

Gastroesophageal reflux disease (GERD) is an increase of retrograde movement of gastric content into the esophagus. Laryngopharyngeal reflux is reflux which reaches the larynx. GERD is present when the frequency and duration of acid reflux exceeds defined parameters, as quantified by a pH probe placed in the esophagus. Regardless of its more formal definition, it is a disease in and of itself, often associated with esophageal complications such as esophageal erosion and stricture and Barrett's esophagus, the latter of which can lead to adenocarcinoma of the esophagus. Factors which contribute to or cause GERD are illustrated in Figure 1.

Ten to 20% of the general adult population in western countries and 5% in the Asia Pacific region suffer from symptoms of GERD. The presence of GERD in some pediatric studies is between 2-8%. Typical symptoms (table 1), particularly in adults, include esophageal burning and discomfort (heartburn) as well as regurgitation of gastric content into the posterior pharynx (water brash). Other symptoms include belching, indigestion, nausea, vomiting, odynophagia, dysphagia, and halitosis. Throat tightness, throat clearing, cough, chest tightness, postnasal drip, and hoarseness are all potential symptoms of GERD, particularly with laryngeal pharyngeal reflux. Cough, associated with laryngopharyngeal GERD, is usually described as originating in the laryngopharynx, whereas cough, associated with asthma, usually originates in the chest; however, this distinction is subjective as can be differentiating the symptoms of cough from throat clearing. The same symptoms can occur in children, however, recurrent regurgitation, with or without vomiting, weight loss or poor weight gain, irritability, and behavioral problems may occur.

Asthma and/or upper airway complaints or problems are associated with GERD. Epidemiologic studies demonstrate a variable prevalence in subjects with asthma of between 12 to 85%. The variability is largely dependent on the method used to define GERD. Conversely, asthma also appears to be more common in individuals with GERD. Two hypotheses are proposed to explain this association; asthma bronchospasm is attributed to aspiration or reflux of gastric contents into the trachea whereas the second implicates vagal reflex-

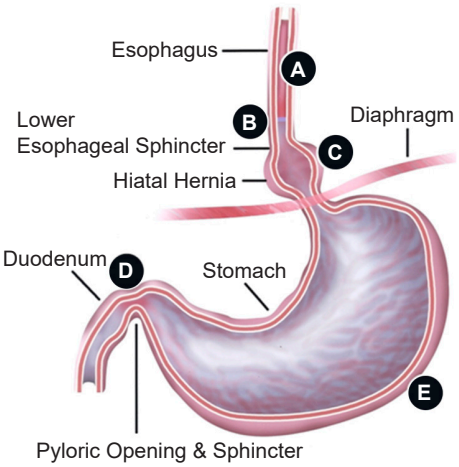

Figure 1 Factors which contribute to or cause GERD.

A. Defective clearance of esophageal contents secondary to reduced salivary and esophageal submucosal gland secretion and ineffective peristalsis

B. Lower esophageal dysfunction with prolonged and inappropriate relaxations of the sphincter with reduction in basal lower esophageal sphincter pressure and tone

C. A hiatal hernia may compromise lower esophageal function causing gastric contents to be trapped above the diaphragm exacerbating reflux

D. Delay of gastric emptying may increase gastric contents available for reflux into the esophagus

E. Various illnesses, such as asthma, which is associated with chronic cough and expiratory straining during breathing, can increase intra-abdominal pressure, pushing gastric contents into the esophagus

TABLE 1

GERD Symptoms and Signs *	
Gastroesophageal	Heartburn, chest/epigastric/cervical pain, water brash, belching, indigestion, nausea/vomiting/hematemesis
Respiratory	Cough, wheeze, dyspnea, hemoptysis
Laryngeal	Hoarseness, throat clearing, sighing dyspnea, irritation, globus, voice changes, soreness
Nasal	Congestion, itching, sneezing, soreness
Sinuses	Headache, pressure, purulent discharge
Ears	Otalgia
Teeth	Loss of dental enamel

** Reproduced from Theodoropoulos DS, Lockey RF, Boyce HW Jr. Gastroesophageal reflux and asthma: a review of pathogenesis, diagnosis, and therapy. Allergy. 1999;54:651-661, with permission from Wiley-Blackwell.*

es mediated through stimulation of esophageal mucosal receptors by a low pH and distention. Both mechanisms probably contribute to asthma in varying degrees.

Double-blind, controlled studies demonstrate that treatment of asymptomatic GERD does not improve asthma in adults or children; however, other controlled studies show that GERD-treated subjects with asthma and symptomatic GERD experience improved asthma quality-of-life and a reduced number of asthma exacerbations while there are questionable effects on asthma symptoms, albuterol use, and pulmonary function. A Cochrane review of controlled studies in both adults and children with asthma indicates that treating GERD does not increase asthma control but does decrease the use of albuterol; it benefited a subset of affected patients.

Just as GERD may aggravate asthma, so too, could asthma or asthma therapy aggravate GERD or GERD-associated symptoms. Beta agonists and theophylline reduce esophageal sphincter tone, systemic glucocorticosteroids increase gastric acid production, and inhaled corticosteroids induce cough and cause chronic laryngeal irritation and hoarseness, the latter of which are also associated with GERD. Asthma also is associated with chronic cough and wheezing, both of which increase intra-abdominal pressure, which can theoretically result in pushing gastric contents up through the lower esophageal sphincter into the esophagus aggravating GERD.

Diagnosis of GERD is primarily based on a detailed history since it is impossible to confirm the diagnosis with a pH probe and/or endoscopy in all individuals with this disease. When complications are suspected, a gastroenterologist consultation is indicated (Figure 2).

Treatment (Figure 3) includes lifestyle changes, i.e., avoiding large meals, maintaining ideal weight, not eating meals three hours before retiring, not lying down within two hours after meals, elevating the head of the bed with 6-inch blocks or using a foam wedge to elevate the trunk and head. Avoiding acid-containing foods, carbonated beverages and fatty foods also may be beneficial. Medications include H2 blockers, proton pump inhibitors and prokinetic agents, the latter for individuals with delayed gastric emptying. GERD commonly resolves by age 4 years in most children. When such resolution does not occur, treatment is similar to adults. Rarely, anti-reflux surgery is indicated.

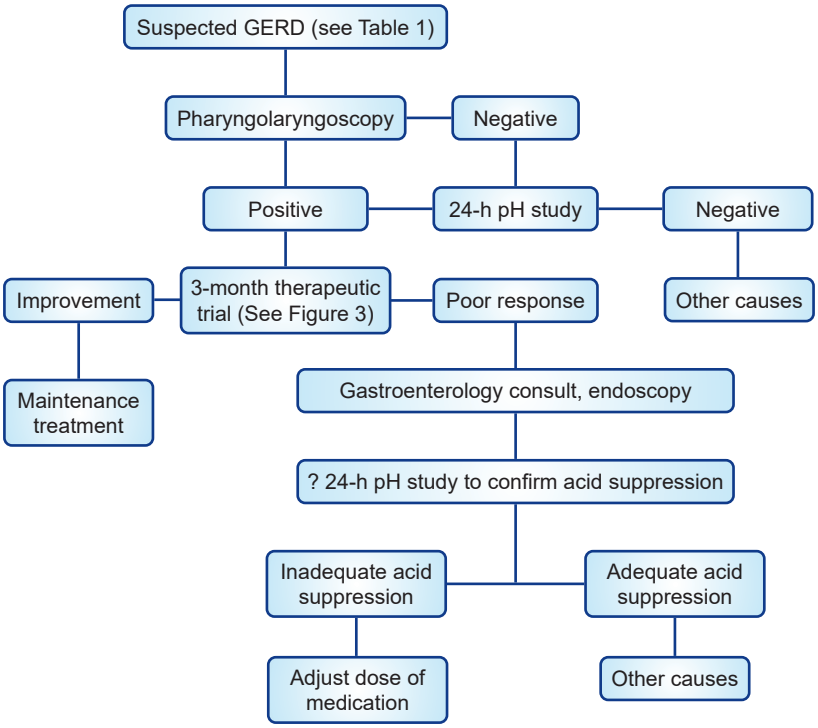

Figure 2 Diagnosis of GERD. *(Modified from Theodoropoulos DS, Lockey RF, Boyce HW Jr. Gastroesophageal reflux and asthma: a review of pathogenesis, diagnosis, and therapy. Allergy. 1999;54:651-661, with permission from Wiley-Blackwell.)*

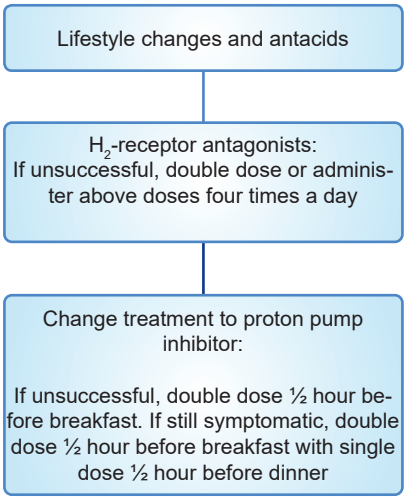

Figure 3 Maintenance treatment for GERD. *(Modified from Theodoropoulos DS, Lockey RF, Boyce HW Jr. Gastroesophageal reflux and asthma: a review of pathogenesis, diagnosis, and therapy. Allergy. 1999;54:651-661, with permission from Wiley-Blackwell.)*

Another problem, laryngopharyngeal reflux, believed to be secondary to the regurgitation of gastric content into the laryngeal pharynx, can result in laryngopharyngeal and upper airway symptoms. Laryngopharyngeal reflux is also a co-morbid condition for asthma, if for no other reason, for the cough associated with such reflux. Also, upper airway disease is commonly associated with asthma, and documented GERD is associated with a variety of different laryngeal and upper airway symptoms.

In summary, regardless of whether there is a true association with GERD, i.e., that GERD can exacerbate asthma, or the converse, that asthma can exacerbate GERD, both seem reasonable because of the close association of the esophagus with the trachea and lungs and the similar embryologic derivation of the nervous system shared by both. Regardless, treating symptomatic GERD in any patient, particularly those with asthma, is essential to prevent complications from GERD, as well as to increase the quality-of-life of the patient with or without asthma.

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7 CARDIOVASCULAR DISEASES AND ASTHMA

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KEY MESSAGES

- Asthma is independently associated with cardiovascular diseases
- It has been suggested that asthma is a comorbidity rather than a cause of cardiovascular diseases
- Inflammation plays a pivotal role in both cardiovascular diseases and asthma
- Targeting pro-inflammatory cytokines highly expressed in patients with asthma and cardiovascular diseases might significantly improve clinical outcomes in both conditions

The clinical evidence supporting the hypothesis that asthma confers high risk of various cardiovascular pathologies to patients is not unequivocal. However, emerging data indicate a link between the two chronic inflammatory diseases (Figure 1). It has been documented that asthma is independently associated with ischemic heart disease, not independently associated with heart failure or atrial fibrillation and associated with lower rates of cerebrovascular disease. A history of asthma is often associated with higher left ventricular mass index, mainly in those with pre-hypertension and hypertension. In addition, there is evidence that asthma exacerbation is associated with a significantly increased risk of cardiovascular diseases (e.g., acute myocardial infarction and ischemic stroke) particularly in the first 1-week period after the asthma exacerbation. Apparently, late-onset asthma confers a greater risk of cardiovascular diseases. Furthermore, recent evidence suggests that cigarette smoking is not rare in adult-onset asthma and smokers with asthma have higher rates of cardiovascular comorbidities. The influence of gender on the association between asthma and cardiovascular diseases risk is not clear although it is well known that oestrogens contrast onset and progression of heart disease by acting on organs associated with both the central and peripheral control of cardiovascular function through specific receptors located in these organs.

Systemic inflammation might be a potential link between asthma and cardiovascular diseases. The release of cytokines is central to almost every stage of the immune response in asthma, and consequent systemic dysregulation of inflammatory homeostasis may explain the potential higher risk of developing cardiovascular diseases (Figure 2). Inflammatory biomarkers such as high-sensitivity C-reactive protein, interleukin-6, tumor necrosis factor-α, interleukin-8, and fibrinogen, which are elevated in asthmatic patients likely because of the local lung inflammation leading to an overspill systemic effect, are also increased in cardiovascular diseases. Chronic airway inflammation might contribute to systemic inflammation and increase vulnerability to vascular diseases, although inflammatory regulation in asthma is different to the one typically observed in atherosclerosis. Nevertheless, targeting pro-inflammatory cytokines highly expressed in patients with asthma and cardiovascular diseases might significantly improve clinical outcomes. Also the excessive release, mostly from eosinophils, of cysteinyl leukotrienes, which are strongly proinflammatory cytokines found in high concentrations in asthmatic

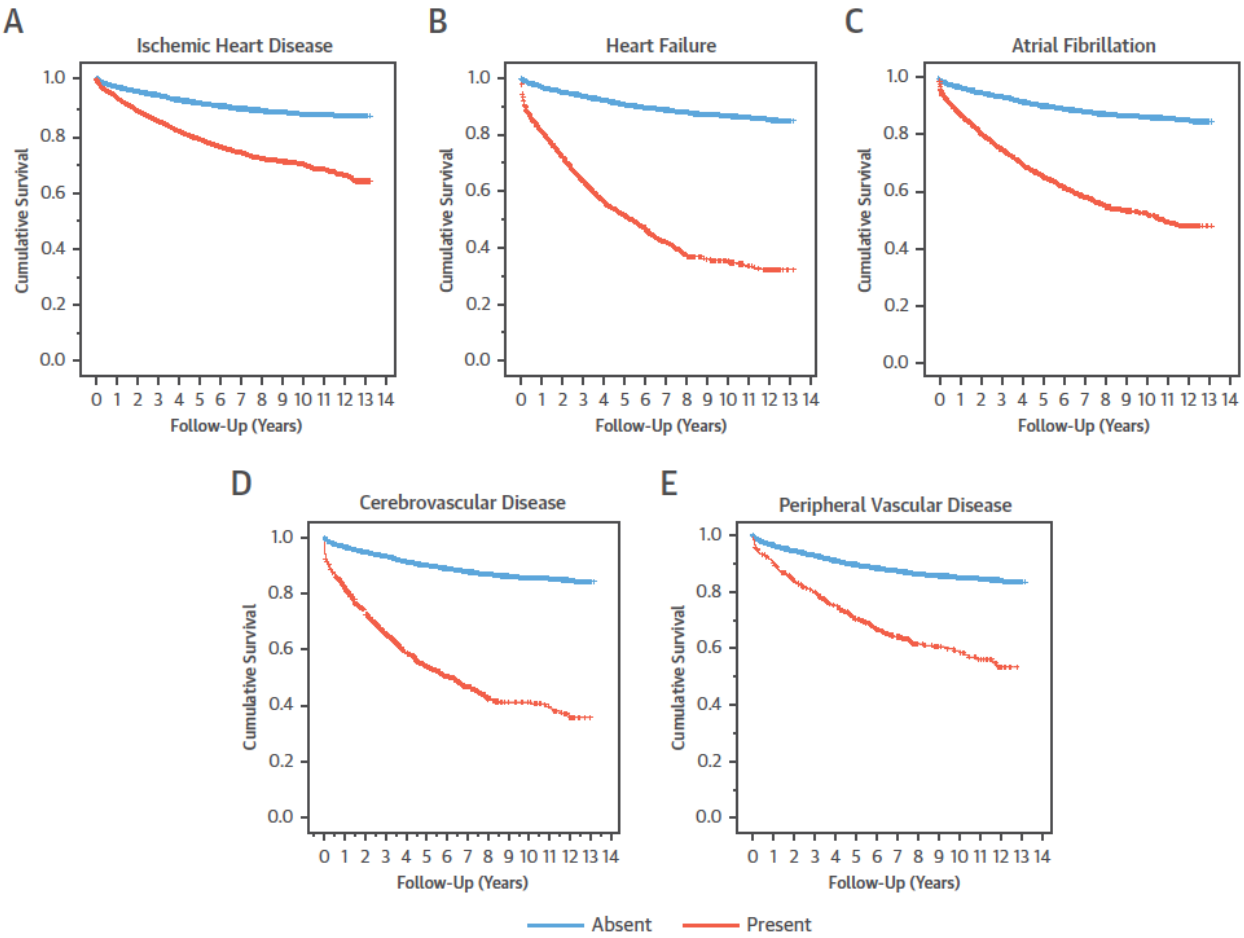

Figure 1 **Impact of cardiovascular diseases on all-cause mortality in asthma.** *(Reproduced from J Am Coll Cardiol., Vol 73, Carter P, et al., Association of Cardiovascular Disease With Respiratory Disease, 2166-2177, 2019 with permission from Elsevier)*

bronchioles and also active in atherosclerotic plaque, may contribute to the development of arteriosclerosis and coronary vasospasm.

Phenomena occurring in asthma such as inflammation, infection, oxidative stress, impaired functions of the anticoagulant protein C system, attenuated fibrinolysis, and increased activation of blood platelets are all potential mechanisms leading to the acceleration of atherosclerosis. Several risk factors that link late-onset asthma and cardiovascular diseases, such as obesity, stress, and oestrogen-modulated inflammation, are linked to inflammation.

Management for asthma with an excessive use of β2-agonists, discontinuation of β-blockers, and aspirin or non-steroidal anti-inflammatory drugs in patients with aspirin-exacerbated respiratory disease may play a role to the subsequent cardiovascular event risks. Inhaled bronchodilators are independently associated with an increased risk of atrial fibrillation. In particular, the use of high doses of β2-agonists for asthma expands the risk of arrhythmias. This probably happens also because the majority of patients with severe asthma have electrolyte disturbances, a well-known cause of cardiac arrhythmia disturbances in patients with chronic stable asthma and with asthma attacks. Excessive β2-agonist use is also associated with an increased risk of myocardial infarction, congestive heart failure, cardiac arrest and sudden cardiac death. Furthermore, concerns have been raised about possible associations of muscarinic antagonists with cardiovascular morbidity and mortality in asthmatic patients, but data in literature are contradictory.

In any case, it has been suggested that asthma is a comorbidity rather than a cause of cardiovascular diseases. This is a fascinating

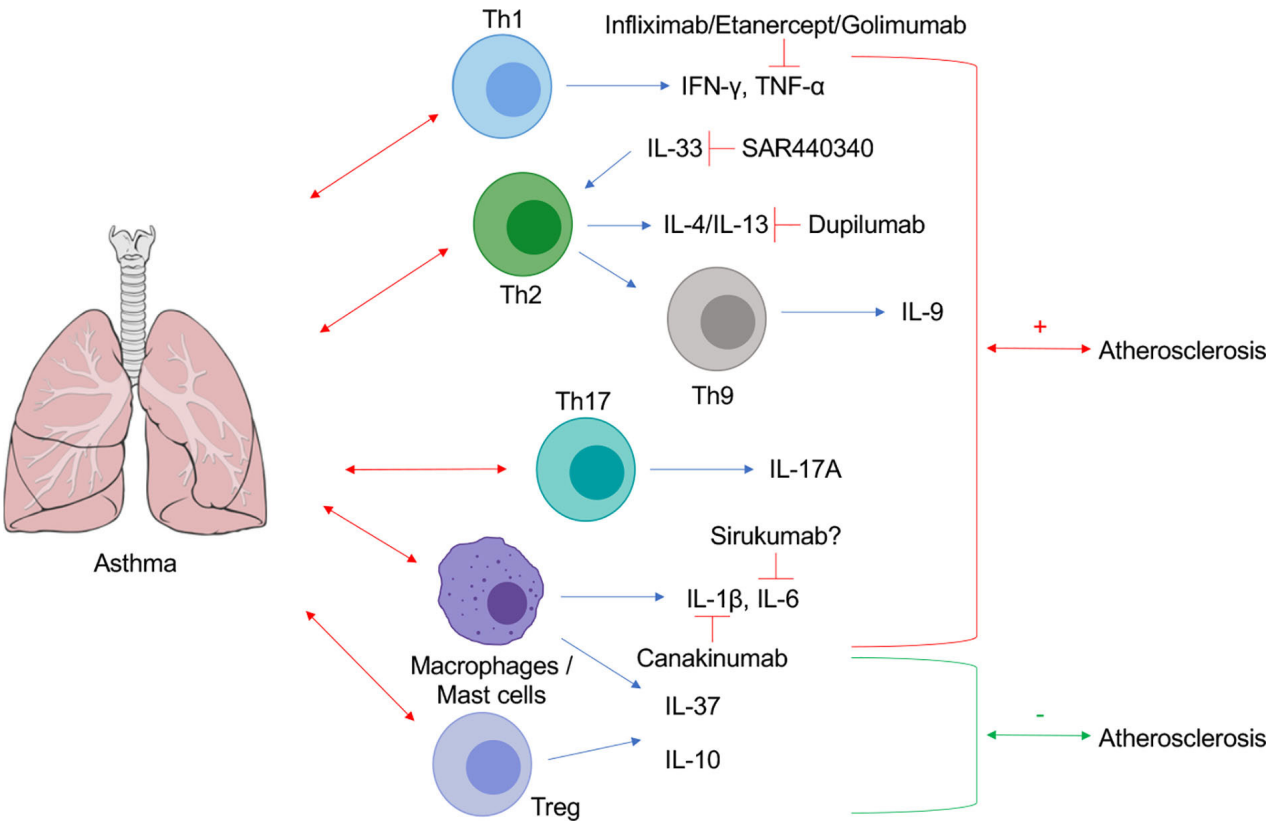

Figure 2 **Possible cytokine contributions at the interplay between asthma and atherosclerosis.** *(Reproduced from Front Pharmacol., Cytokines at the Interplay Between Asthma and Atherosclerosis?, Gurgone et al., 11:166, 2020 under the terms of the creative commons attribution non-commercial license 4.0)*

hypothesis, but there is still no solid documentation to support it. Nonetheless, cardiovascular diseases have been proven to worsen the outcomes in patients with asthma, with a prevalent role of cardiac failure in the genesis of oedema-induced bronchoconstriction. Moreover, it is likely that the initial presentation with symptoms suggesting asthma (dyspnoea presumably) is quite frequently the presentation of a cardiovascular disease.

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8 FOOD ALLERGY AND ASTHMA

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KEY MESSAGES

- Food allergy and asthma often co-exist in patients as part of the "atopic march"
- Respiratory symptoms can be a manifestation of a food allergy reaction
- Asthma is a risk factor for severe anaphylaxis in food allergic patients
- It is vital that food allergic patients with co-morbid asthma have their disease controlled to decrease the risk of adverse reactions
- Patients with pollen sensitizations that trigger asthma may also have cross-reactions to foods (pollen food syndrome)

Food Allergy (FA) is an adverse reaction to food mediated by the immune system. It is an increasing problem with estimated prevalence rate between 6-11%. IgE mediated food allergy causes acute (usually within minutes to 2 hours) symptoms with reactions characterised by involvement of various organ systems, including dermatologic (urticaria, pruritus, angioedema), gastrointestinal (abdominal pain, vomiting), respiratory (nasal congestion, rhinorrhea, cough, wheezing, dyspnoea) and cardiovascular (hypotension). Common food allergens are milk, egg, peanut, tree nuts, fish, shellfish, wheat, soy and sesame seed (Figure 1).

Food allergy and asthma often co-exist in patients as part of the "atopic march," which refers to the natural history of developing co-morbid allergic disease (Figure 2). The atopic march classically begins with atopic dermatitis and is followed by food allergy, asthma and allergic rhinitis. There has been significant interest and research in understanding the genetic and epigenetic factors that predispose to the T2 skewed immune response that drives these diseases.

Respiratory symptoms can be a manifestation of an allergic reaction to a food allergen, even in the absence of cutaneous symptoms. Patients with asthma and food allergies are at risk for severe reactions when exposed to known food allergens. Reviews of fatal food anaphylaxis cases have shown asthma (especially if uncontrolled) to be a major risk factor. Asthma symptoms have been reported even to inhalation exposure to airborne food particles, e.g. seafood and milk, during cooking in food allergic patients.

Patients with asthma can also experience other adverse reactions to additives in foods. For example, a small percentage of asthmatic patients are sensitive to sulfites, which trigger respiratory symptoms. In addition, occupational asthma can be triggered by inhalation of food products, such as flour (known as Baker's asthma). Patients sensitized to pollen may experience seasonal asthma. Many will have cross-sensitisation to plant foods and develop oral allergy syndrome (pollen food syndrome) with symptoms when consuming raw fruits, nuts and vegetables (Figure 3).

Given the new landscape of emerging food allergy treatment, it is vital that patients with co-morbid asthma have their asthma controlled to decrease the risk of adverse reactions to treatment.

Figure 1 **Food allergy reactions can trigger asthma and respiratory symptoms.**

Figure 2 **The atopic march.**

Oral immunotherapy (OIT) for peanut is becoming available in some countries. A risk of OIT is an allergic reaction given the exposure to their known food allergen. In order to minimize the risk of a severe reaction, pre-existing asthma must be well-controlled before starting or escalating this therapy.

Food allergy is a common and increasingly prevalent co-morbidity in patients with asthma, with a complex interplay from both a pathogenesis and a treatment perspective. These two conditions should be carefully managed together in order to optimize patient care.

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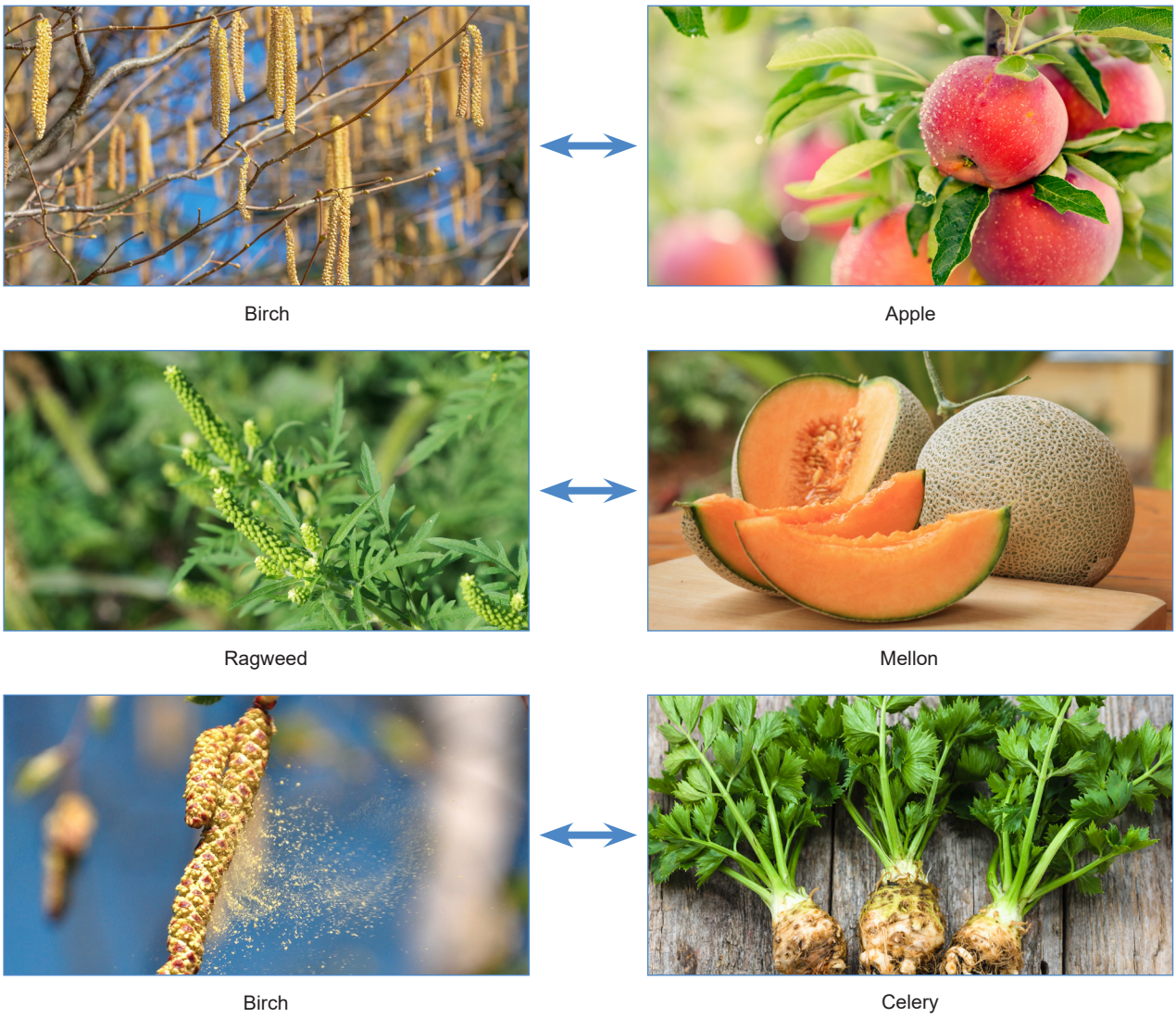

Figure 3 **Oral allergy syndrome cross reactivity.**

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9 ATOPIC DERMATITIS

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KEY MESSAGES

- Atopic dermatitis (AD) is a prevalent, clinically heterogeneus disease
- Diagnosis is still made according to clinical criteria, but with a future role for biomarkers
- The complex AD pathogenesis is based on alterations in the epidermal barrier, immune system and microbiome
- The European S3 guidelines propose a therapeutic algorithm including emollients, topical and systemic therapy
- The study landscape of AD is evolving, with many potential novel targets to be approved

Atopic dermatitis (or atopic eczema, AD) is a non-communicable inflammatory skin disease that affects around 3% of adults and 25% of children worldwide. In Europe, the incidence increases from South to North. Most frequently, AD starts in the first year of life and it may persist life-long, affecting the quality of life of patients and their families to a level similar to cancer. AD has also a deeper impact on patients social functioning scores than hypertension in adults and epilepsy or diabetes in children.

Main symptoms of AD are a devastating itch and a dry skin. The pathogenesis of AD is based upon an interaction of 1) an impaired epidermal barrier that might be driven by genetic predisposition, most frequently in the fillagrin gene; 2) a type 2 dominated immune reaction against environmental or self-antigens with increased levels of cytokines such as Interleukin-4, 5, or 13 – this results in decreased innate immunity and defective epidermal barrier, as well as influx of eosinophils; and 3) an altered skin microbiome, with *S. aureus* colonisation and infection (Figure 1). Clinically, AD is characterised by erythematous, dry and scaly skin with papules, nodules, erosions and crusts. Chronic lesions are characterised by lichenification. Predilection lesion sites are depending on the age, frequently affected being the extremities, head, neck, and shoulder. The combination between variable affected sites, severity, and age results in an impressive heterogeneity of AD phenotypes (Figure 2). Accordingly, differential diagnosis of AD with other forms of eczema such as nummular eczema, microbial or dishydrotic eczema may be challenging. In fact, all these diseases belong to a group of inflammatory skin diseases with a dominant type 2 immunity that is characterised by infiltration with eosinophils, mast cells – just as asthma. In line with this, atopic comorbidities are frequent in AD – primarily asthma, allergic rhinoconjunctivitis, or nasal polyps. However, AD may generally be regarded a systemic disease with further possible comorbidities such as inflammatory bowel diseases or cardiovascular diseases.

Today, AD is diagnosed according to critieria defined by Hanifin and Rajka, the UK Working Party, or the American Academy of Dermatology, all of which define a number of typical clinical hallmarks as a checklist, itch being the key major criterium. Objective biomarkers of AD that might corroborate correct diagnosis (e.g.

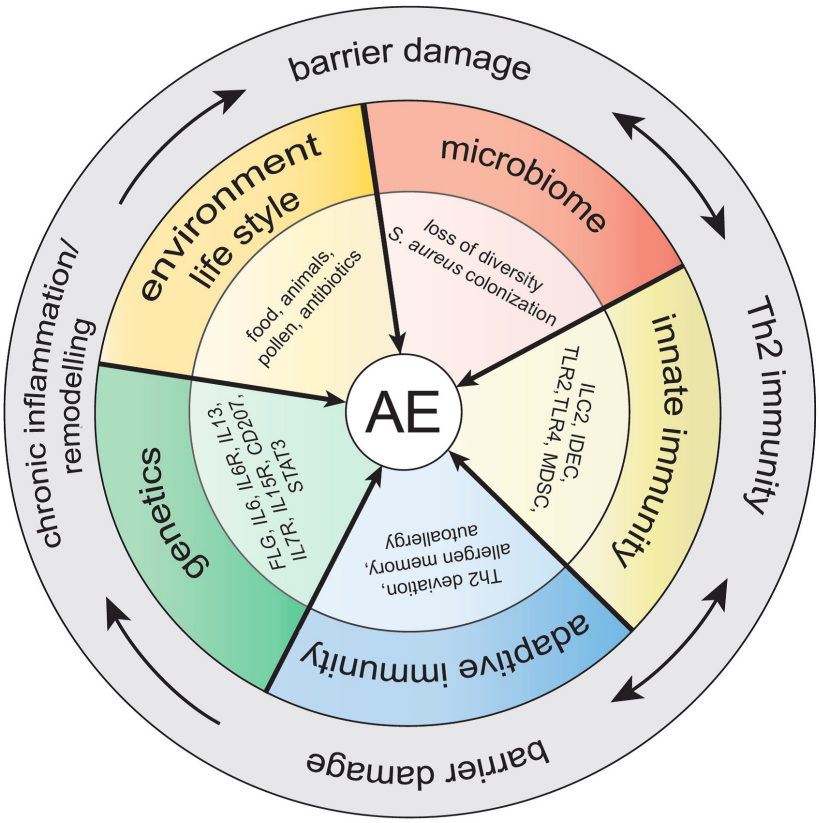

Figure 1 **Pathogenesis of AD.** The complex interplay between the defective epithelial barrier, innate and adaptive T2 response, environmental triggers and disturbed microbiome.

NOS2/CCL27, CCL26), reflect the severity (e.g. CCL17), or stratify an endotype predicting individual disease course or therapeutic response are not yet validated. In the future, molecular diagnostics will be complemented by artificial intelligence-guided machine learning algorithms, thus the diagnostics of AD is expected to change profoundly.

The therapeutic options of AD are Also rapidly changing. The European S3 guideline recommends basic strategies such as emollients and avoidance of trigger factors. Active therapies are recommended depending on disease severity, ranging from topical steroids or other topicals immune modulators to conventional systemics such as ciclosporine or methotrexate (Table 1). In 2017, the first biological specifically targeting type 2 immunity was approved to treat moderate to severe AD, namely the IL-4 receptor inhibitor dupilumab. Today, numerous further biologics or small molecules, most frequently JAK inhibitors, are tested in clinical trials. Thus, there will be multiple options to treat AD in the near future – making it even more important to implement precision medicine in the field.

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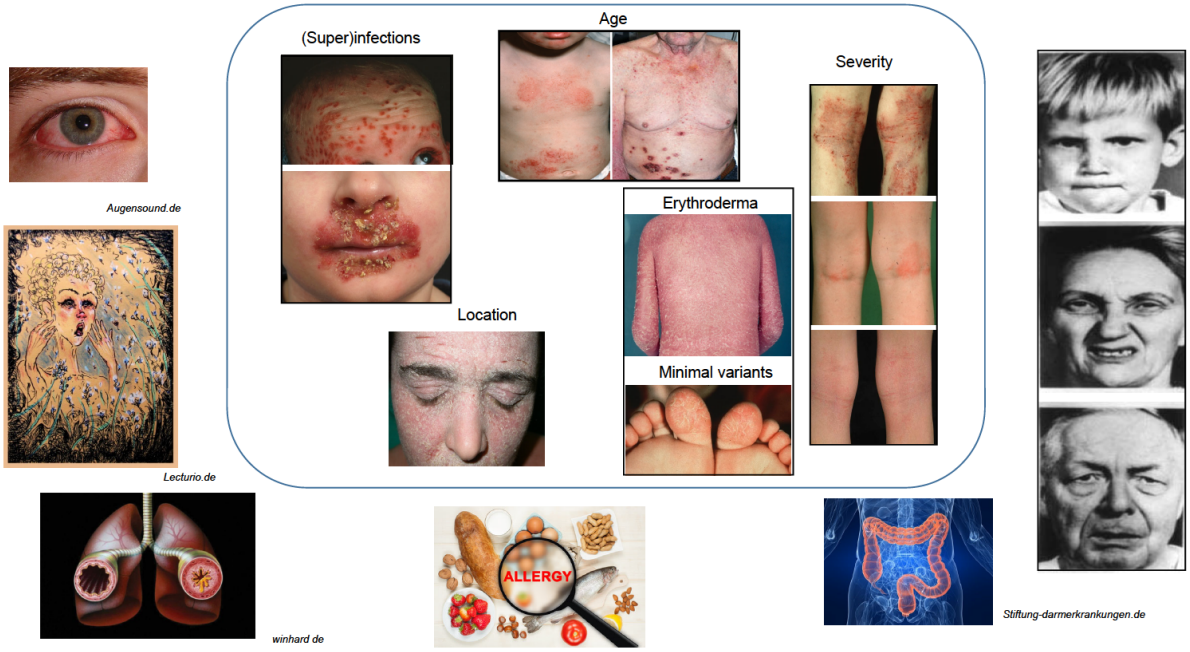

Figure 2 **Clinical spectrum of AD.** Various lesions and locations depending on age and several potential co-morbidities such as asthma or food allergy. *(Reproduced from Trends Immunol., Vol 36, Eyerich K, et al., The Multi-Modal Immune Pathogenesis of Atopic Eczema, 788-801, 2015 with permission from Elsevier)*

Treatment recommendation for atopic eczema: adult

- For every phase, *additional* therapeutic options should be considered
- Add antiseptics / antibiotics in cases of superinfection
- Consider compliance and diagnosis, if therapy has insufficient effect
- Refer to guideline text for restrictions, especially for treatment marked with [1]
- Licensed indication are marked with [2], off-label treatment options are marked with [3]

SEVERE: SCORAD >50 / or persistent eczema	Hospitalization; systemic immunosuppression: cyclosporine A [2], short course of oral glucocorticosteroids[2], dupilumab [1,2] , methotrexate[3], azathioprin [3], mycophenolate mofetil [3]; PUVA [1]; alitretinoin [1,3]
MODERATE: SCORAD 25-50 / or recurrent eczema	Proactive therapy with topical tacrolimus [2] or class II or class III topical glucocorticosteroids [3], wet wrap therapy, UV therapy (UVB 311 nm, medium dose UVA1), psychosomatic counseling, climate therapy
MILD: SCORAD <25 / or transient eczema	Reactive therapy with topical glucocorticosteroids class II [2] or depending on local cofactors: topical calcineurin inhibitors [2], antiseptics incl. silver [2], silver coated textiles [1]
BASELINE: Basic therapy	Educational programmes, emollients, bath oils, avoidance of clinically relevant allergens (encasings, if diagnosed by allergy tests)

Figure 3 **Therapeutic algorithm for AD according to the European S3 guideline.** *(Reproduced from J Eur Acad Dermatol Venereol., Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part II, Wollenberg et al., Vol 32, 850-878, 2018 with permission from John Wiley & Sons)*

10 CHRONIC URTICARIA

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KEY MESSAGES

- Chronic urticaria is an illness characterized by itchy wheals, angioedema or both. It may be spontaneous, inducible or a mixture
- Chronic spontaneous urticaria may be autoimmune or idiopathic. There is increasing evidence for IgE autoallergy in some patients. Cutaneous mast cell degranulation is the primary event and histamine is a key mediator of symptoms
- Systemic symptoms may be seen in severe chronic urticaria including malaise, indigestion and arthralgia. Bronchial hyperreactivity has been reported in some patients with chronic spontaneous and inducible patterns of urticaria but evidence for this is low
- Angioedema is present in 40-60% of patients with chronic spontaneous urticaria but does not cause significant airways obstruction
- Bradykininergic angioedema presenting as recurrent angioedema without wheals in hereditary angioedema and angiotensin converting enzyme inhibitor-induced angioedema may be fatal

Urticaria is a condition characterized by the development of wheals (hives) (Figure 1), angioedema (Figure 2) or both. Wheals present as superficial itchy, red or pale swellings anywhere on the skin of variable size, often surrounded by reflex erythema. Itch is a key symptom that may be intense and distressing, sometimes interfering with sleep. The wheals have a fleeting nature. They typically disappear within 24 hours but new ones may appear elsewhere. Angioedema is characterized by erythematous or skin coloured swelling of the lower dermis or subcutis or below mucous membranes and the patient may feel pain rather than itch. Resolution of angioedema is often slower than for wheals and can take up to 72 hours. Histaminergic angioedema may be seen in 40-60% of patients with chronic spontaneous urticaria and must be distinguished from recurrent bradykininergic angioedema without wheals because this may rarely cause asphyxiation. Chronic urticaria is defined as wheals, angioedema or both for 6 weeks or more. It may be spontaneous, inducible or a mixture (Table 1). Acute urticaria resolves within 6 weeks. Anaphylaxis may also present acutely with wheals and/or angioedema.

Around 30% of patients with chronic spontaneous urticaria have functional autoantibodies that release histamine from skin mast cells and basophils. Co-morbidities in chronic spontaneous urticaria include autoimmune diseases such as thyroid autoimmunity and systemic lupus erythematosus and psychiatric disorders (Table 2).

Chronic urticaria is not usually associated with asthma and is hardly ever due to IgE-mediated allergies. However, in undetected food allergy, such as wheat-dependent cofactor-augmented anaphylaxis and alpha-gal (red meat) syndrome, the symptoms may, in milder cases, manifest as repeated episodes with urticaria and/or angioedema before presenting with a more severe anaphylactic

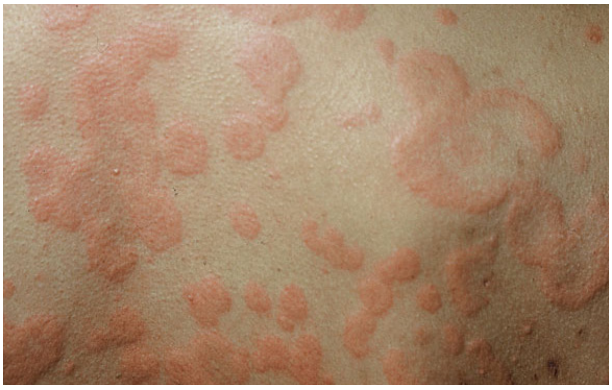

Figure 1 **Multiple small itchy wheals in chronic spontaneous urticaria.**
The authors would like to acknowledge Professor Niels Veien from Aalborg, Denmark for permission to use the clinical pictures from his online database, Danderm.

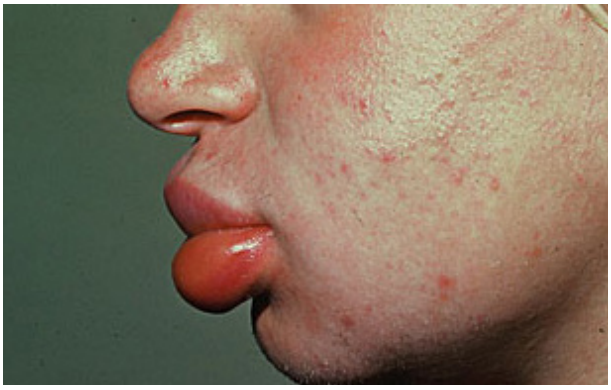

Figure 2 **Angioedema of lips.**
The authors would like to acknowledge Professor Niels Veien from Aalborg, Denmark for permission to use the clinical pictures from his online database, Danderm.

TABLE 1

Classification of urticaria
Urticaria
• Acute (up to 6 weeks of continuous activity) • Chronic (6 weeks or more of continuous activity) ▪ Spontaneous ▪ Inducible ◆ Physical » Symptomatic dermographism » Delayed pressure urticaria » Cold urticaria » Solar urticaria » Vibratory angioedema » Heat urticaria ◆ Others » Cholinergic urticaria » Aquagenic urticaria » Food and exercise dependent urticaria and anaphylaxis » Contact urticaria
Angioedema
• With weals (histaminergic) • Without weals ▪ Histaminergic (spontaneous and inducible) ▪ Bradykinergic ◆ C1 esterase inhibitor deficiency » Hereditary and acquired » Hereditary with normal C1 esterase inhibitor » Angiotensin converting enzyme inhibitor induced

TABLE 2

Co-morbidities with chronic spontaneous urticaria
Autoimmune disease
• Thyroid autoimmunity • Connective tissue disease e.g. SLE, rheumatoid disease • Vitiligo • Type 1 insulin dependent diabetes mellitus
Psychiatric disease
• Sleep-wake disorders • Mood disorders (including depression)
Atopic disease
• Atopic dermatitis • Rhinoconjunctivitis

reaction. The same may be true in children with milder reactions to foods. These pitfalls have to be considered when evaluating patients with more severe urticaria/angioedema i.e. the relation to food intake and co-factors such as exercise, drugs, alcohol or infections. In addition, anti IgE biologicals such as omalizumab is used to treat both asthma and chronic spontaneous urticaria.

Cholinergic urticaria might be occasionally associated with bronchospasm, even in patients without a history of asthma. There is a report as well on bronchial hyperreactivity in chronic urticaria. Furthermore, there is a relationship between chronic urticaria and hypersensitivity to nonsteroidal anti-inflammatory drugs manifested as non-steroidal anti-inflammatory exacerbated respiratory disease (N-ERD).

Most angioedema is histaminergic due to mast cell degranulation. By contrast, there is a small, but very important group of patients who present with angioedema without wheals due to kinin generation. These include hereditary angioedema, acquired angioedema associated with lymphoproliferative disease or autoantibodies against C1 esterase inhibitor, and angiotensin converting enzyme inhibitor (ACEI)-induced angioedema. Kinin-induced angioedema often affects the respiratory tract from the lips to the larynx and may be fatal. The specific bradykinin 2 receptor antagonist, icatibant, or C1 inhibitor offer specific treatment for patients with C1 inhibitor deficiency presenting acutely with with respiratory tract involvement.

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11 EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS

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KEY MESSAGES

- Eosinophilic granulomatosis with polyangiitis (EGPA), is a systemic necrotizing granulomatous vasculitis of small- and medium-size vessels, classified as an antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis
- Late-onset asthma is a key feature of EGPA, and in most of cases precedes the occurrence of vasculitic manifestations
- The diagnosis of EGPA relies on the co-existence of asthma, hypereosinophilia, and on the demonstration of a small-vessel necrotizing vasculitis
- Antineutrophil cytoplasmic antibodies (ANCA), mainly anti-myeloperoxidase, are detected in only 20-40% of patients, and identify different phenotypes of EGPA

Eosinophilic granulomatosis with polyangiitis (EGPA), formerly called Churg-Strauss syndrome, is a systemic necrotizing granulomatous vasculitis of small- and medium-size vessels, classified as an antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. EGPA is the least common of the ANCA-associated vasculitis (AAV), with an annual incidence of 0-4 per million population. The main histologic features of EGPA are small-vessel granulomatous or non-granulomatous lesions, and extravascular necrotizing granuloma, usually associated with eosinophilic infiltrates.

Asthma is the key feature of EGPA, and precedes the systemic manifestations in almost all the patients (mean interval of 9 years). EGPA associated asthma appears at approximatively at 35-40 years of age, it is often severe, glucocorticoid-dependent, and worsens before the appearance of systemic disease. EGPA is also characterized by frequent ear, nose and throat (ENT), pulmonary, and peripheral neurologic manifestations. Maxillary sinusitis is very common and the majority of patients have a history of nasal polyposis and/or allergic rhinitis, that are not destructive as those observed in granulomatosis with polyangiitis (Wegener's, GPA). Lung infiltrates are common and generally transient, may involve one or both lungs, rapidly disappear following corticosteroid treatment and don't have the excavated aspect observed in patients with GPA (Figure 1). Alveolar hemorrhage due to lung vessels vasculitis is uncommon (~5% of cases). Peripheral neuropathy, mainly multiple mononeuritis, affects 45-75% of patients, while central nervous system involvement (<10%) is rarer, and includes mainly strokes and pachymeningitis. Renal involvement is less frequent and on average less severe than that observed in other AAV, and includes focal or diffuse crescentic glomerulonephritis, and less frequently eosinophilic infiltrates or renal vasculitis. Cardiac involvement (pericarditis, myocarditis) is common and is the leading cause of death. Cutaneous (purpura and skin nodules), gastrointestinal (abdominal pain, diarrhea, nausea, bowel perforation) and ophthalmologic (rare) manifestations are also part of the clinical spectrum of the disease.

Only 20-40% of EGPA have detectable ANCA, mainly anti-myeloperoxidase (MPO) antibodies. The ANCA status identifies two

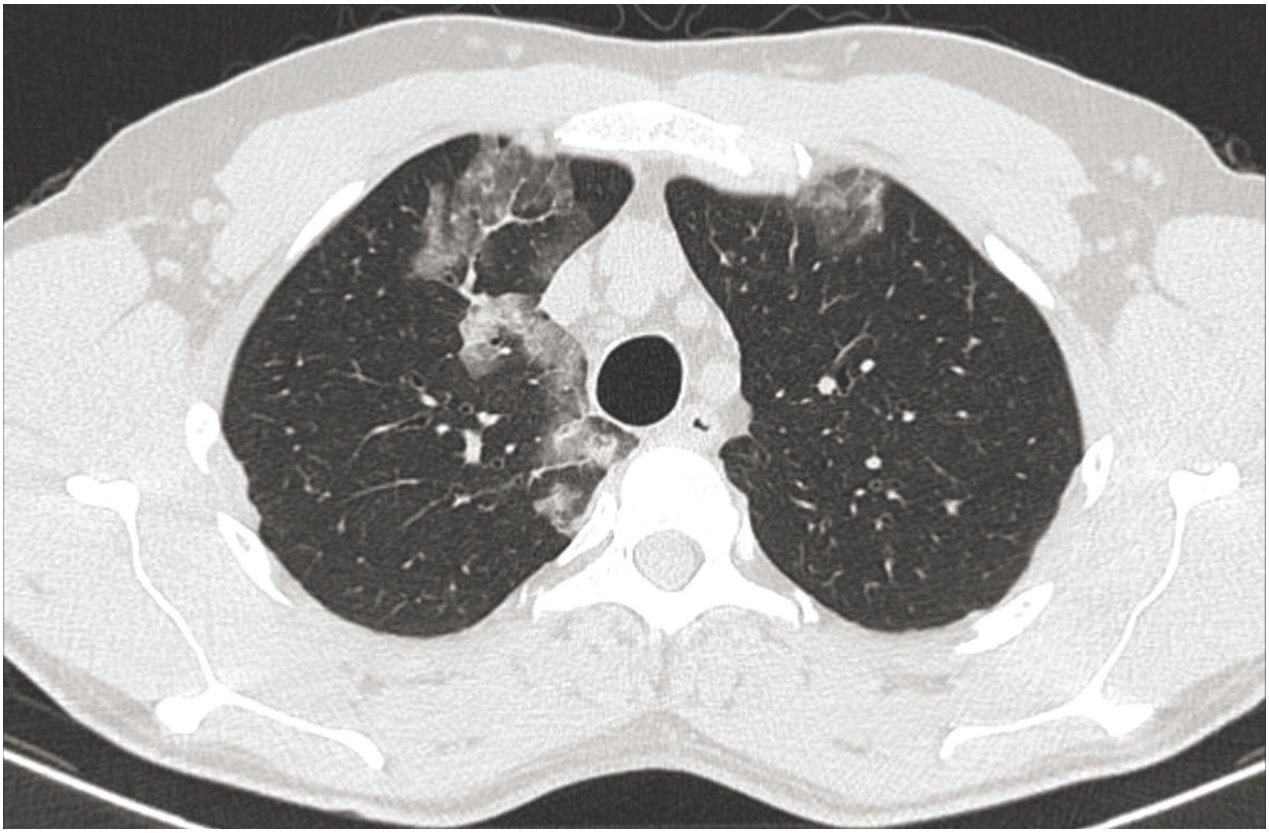

Figure 1 **Computed tomography scan showing pulmonary infiltrates in an EGPA patient.** *(courtesy of Xavier Puéchal).*

phenotypes of patients. Positive ANCA patients develop more peripheral neuropathy, glomerulonephritis, alveolar hemorrhage and central nervous involvement, while ANCA negative are at higher risk to have cardiomyopathy and lung infiltrates. Eosinophilia is almost always present, and often>1500/mmc at diagnosis (mean eosinophil count at diagnosis 7500/mmc). Increased serum IgE is reported in more then 70% of patients. Histology can confirm the diagnosis in about 70% of cases. Skin, muscle or nerves are the most commonly biopsied sites.

The diagnosis of EGPA is clinical. The 1990 ACR classification criteria (Table 1), and revised Chapel Hill Consensus Conference Nomenclature (Table 2), are intended for classification purposes and are most often applied to enroll patients in clinical studies.

Treatment of EGPA relies on remission-induction and maintenance phases, and should be adapted to disease severity. Corticosteroids, immunosuppressors (cyclophosphamide, azathioprine, methotrexate), and targeted therapies (mepolizumab), are currently used.

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TABLE 1

1990 American College of Rheumatology classification criteria for EGPA *	
Criterion	**Definition**
Asthma	History of wheezing or diffuse high-pitched rales on expiration
Eosinophilia	Eosinophilia >10% of white blood cell differential count
Mononeuropathy or polyneuropathy	Development of mononeuropathy, multiple mononeuropathies, or polyneuropathy (i.e., glove/stocking distribution) attributable to vasculitis
Pulmonary infiltrates, non-fixed	Migratory or transitory pulmonary infiltrates on radiographs (not including fixed infiltrates), attributable to systemic vasculitis
Paranasal sinus abnormality	History of acute or chronic paranasal sinus pain or tenderness or radiographic opacification of the paranasal sinuses
Extravascular eosinophils	Biopsy including artery, arteriole, or venule, showing accumulations of eosinophils in extravascular areas

** formerly (Churg-Strauss)*

A patient with vasculitis can be classified as having EGPA when at least four of the six criteria are fulfilled.

TABLE 2

Definition of EGPA in 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides (CHCC2012)	
CHCC2012 name	**CHCC2012 definition**
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA)	Eosinophil-rich and necrotizing granulomatous inflammation often involving the respiratory tract, and necrotizing vasculitis predominantly affecting small to medium vessels, and associated with asthma and eosinophilia. ANCA is more frequent when glomerulonephritis is present.

12 HYPEREOSINOPHILIC SYNDROMES

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KEY MESSAGES

- The distinction between primary and secondary hypereosinophilic syndromes (HES) is a crucial step for the therapeutic choice
- Several genetic alterations have been identified in primary HES
- Th2 cytokines, specifically IL-5, play a central role in the pathogenesis of secondary HES
- New strategies targeting IL-5 or directly eosinophils represent promising therapeutic tools in HES patients

Eosinophils are important effector cells in both innate and adaptive immune responses. Hypereosinophilic syndromes (HES) consist of a group of disorders characterized by an abnormal accumulation of eosinophils in blood or peripheral tissues. Specifically, HES are defined by the increase of the circulating absolute eosinophil count greater than 1500/mL on at least two separate detections. The clinical manifestions of HES are highly variable, ranging from asymptomatic eosinophilia to severe tissue damage and end-organ failure.

HES can be divided into primary and secondary forms. The great majority of primary forms of HES are caused by malignant disorders that directly cause uncontrolled eosinophil lineage expansion, such as chronic eosinophilic leukemia or the myeloid variant of HES. In these forms genetic alterations have been described at level of several trascription factors as KIT, JAK2, V617F, ETV6-ASBL1 and FIPIL1-PDGRF. The secondary form of HES include: 1) the T cell lymphocytic variant in which the IL-5-producing cells are an aberrant clonal population of T cells; 2) HES associated with parasitic infestations; 3) organ-restricted HES such as Eosinophilic Granulomatosis with Polyangitiis (EGPA), Microscopic Polyangiitis (MP), and Granulomatosis with Polyangiitis (GP). EGPA, MP and GP belong to the group of anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (Figure 1).

The diagnosis of the different variant of HES is a crucial point because the treatment options are different, even if treatment directed towards the underlying etiology is not always possible. HES should be treated aggressively with corticosteroid and immunosuppressors to reduce the morbidity and mortality resulting from organ damage by activated eosinophils. Patients with FIP1L1/PDGFRA fusion-positive HES respond very well to imatinib mesylate, a tyrosine kinase inhibitor, despite the aggressive phenotype of the disease.

The understanding of cellular and molecular mechanisms as well as the critical role of specific cytokines involved in the pathogenesis of HES opens the way to new therapeutic strategies by using biological. Several recently introduced monoclonal antinodies (mAbs) have shown potential benefit in reducing or depleting circulating and tissue eosinophils either by targeting interleukin (IL)-5, the main cytokine involved in the maturation and activation of eosinophils, or by depleting the cells via antibody-dependent cellular cytotoxicity (ADCC). The available mAbs targeting IL-5 are mepolizumab and reslizumab whereas benralizumab, by binding the α chain of IL-5 receptor, is able to

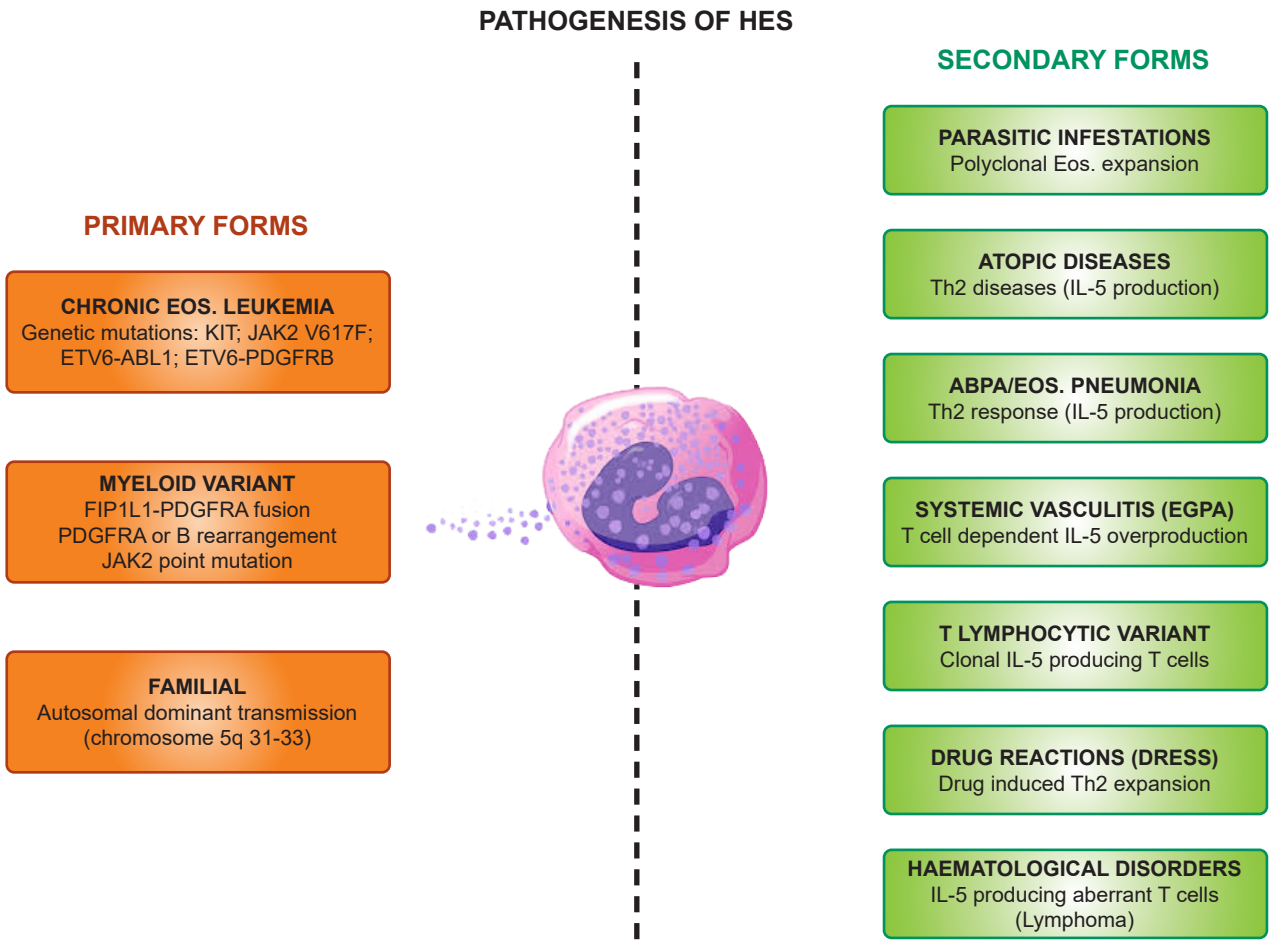

Figure 1 **The distinction between primary and secondary forms of HES.** It is essential for the therapeutic choice.

induce ADCC process. The better diagnosis of the different forms of HES could allow selective therapeutic strategies for the different variants of HES using both traditional and/or biological drugs.

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13 PRIMARY IMMUNODEFICIENCY AND ASTHMA

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KEY MESSAGES

- Recurrent respiratory infections in the context of primary immune deficiencies (PID) are a true mimic of asthma, thus basic testing for PID at an early stage is highly recommended
- Severe asthma in the context of severe or recurrent infections / extremely elevated serum IgE titers / systemic features should evoke the possibility of underlying PID
- Recurrent cough and dyspnoea not responding to asthma treatment should prompt to diffusion capacity testing, PID screening and chest CT scanning to exclude interstitial lung disease in the context of PID
- All asthma manifestations at the end of the spectrum (excessively severe, not responding to treatment, aberrant clinical context, unusual clinical features) should raise the suspicion of PID

Primary Immunodeficiencies (PIDs) comprise a heterogeneous group of over 400 inherited disorders in which one or more components of the immune system fail. This results in a blended phenotype of severe and/or recurrent infection, auto-immunity, auto-inflammation, severe allergy and malignancy. This variable presentation explains the tremendous global underdiagnosis of PIDs. The exact incidence is unknown, but it is estimated that 1:2500 suffer from one or another form of PID with variable mortality and morbidity. Most PIDs manifest in early childhood, but some only manifest in adulthood. Hence, awareness is of crucial importance across all age groups (Table 1). Early diagnosis is unequivocally important to prevent irreversible organ damage.

The recent PID classification by the International Union of Immunological Societies includes 10 categories of PID. The most common group, representing 60% of all PIDs, are the humoral immune deficiencies, with quantitative or qualitative defects in the antibody response. In this group, common variable immunodeficiency (CVID) is the most prevalent clinically relevant antibody deficiency, a condition that is being progressively unveiled at the molecular level as a heterogenous group of monogenic disorders. Although all organ systems can be affected by PID, the respiratory system is often involved, especially in primarily antibody deficiency syndromes but also in most other PIDs. Respiratory complications are a major contributor to the morbidity and mortality of PIDs.

Three major respiratory manifestations/complications should evoke a diagnosis of PID in the context of asthma/asthma-like symptoms (Figure 1):

1. recurrent lower respiratory tract infections, misdiagnosed as asthma
2. severe refractory asthma or frequently exacerbating asthma despite good adherence to state-of-the-art asthma therapy
3. chronic/recurrent symptoms of dyspnea and coughing (more than wheezing) not responding to asthma therapy

Patients with PIDs often suffer from recurrent banally looking viral/bacterial (esp. with encapsulated bacteria) lower respiratory tract infections, mimicking the intermittent signs and symptoms of asthma.

TABLE 1

Jeffrey Modell Foundation Warning Signs for Primary Immunodeficiency

WARNING SIGNS CHILDREN	WARNING SIGNS ADULTS
1. Four or more new ear infections within one year	1. Two or more new ear infections within one year
2. Two or more serious sinus infections within one year	2. Two or more new sinus infections within one year, in the absence of allergy
3. Two or more months on antibiotics with little effect	3. One pneumonia per year for more than one year
4. Two or more pneumonias within 1 year	4. Chronic diarrhea with weight loss
5. Failure of an infant to gain weight or grow normally	5. Recurrent viral infections (warts, condyloma, herpes, colds)
6. Recurrent, deep skin or organ abscesses	6. Recurrent need for intravenous antibiotics to clear infections
7. Persistent oral thrush or fungal infection on skin	7. Recurrent, deep abscesses of the skin or internal organs
8. Need for intravenous antibiotics to clear infections	8. Persistent oral thrush or fungal infection on skin or elsewhere
9. Two or more deep-seated infections including septicemia	
10. A family history of primary immunodeficiency	

A diagnosis of PID should be suspected if 2 or more of these warning signs are present . Auto-immune features (e.g. cytopenia/ endocrinopathy), recurrent fever, granulomatous complications and generalized lymphoproliferation should also evoke the diagnosis of underlying PID

Reference: www.info4PI.org

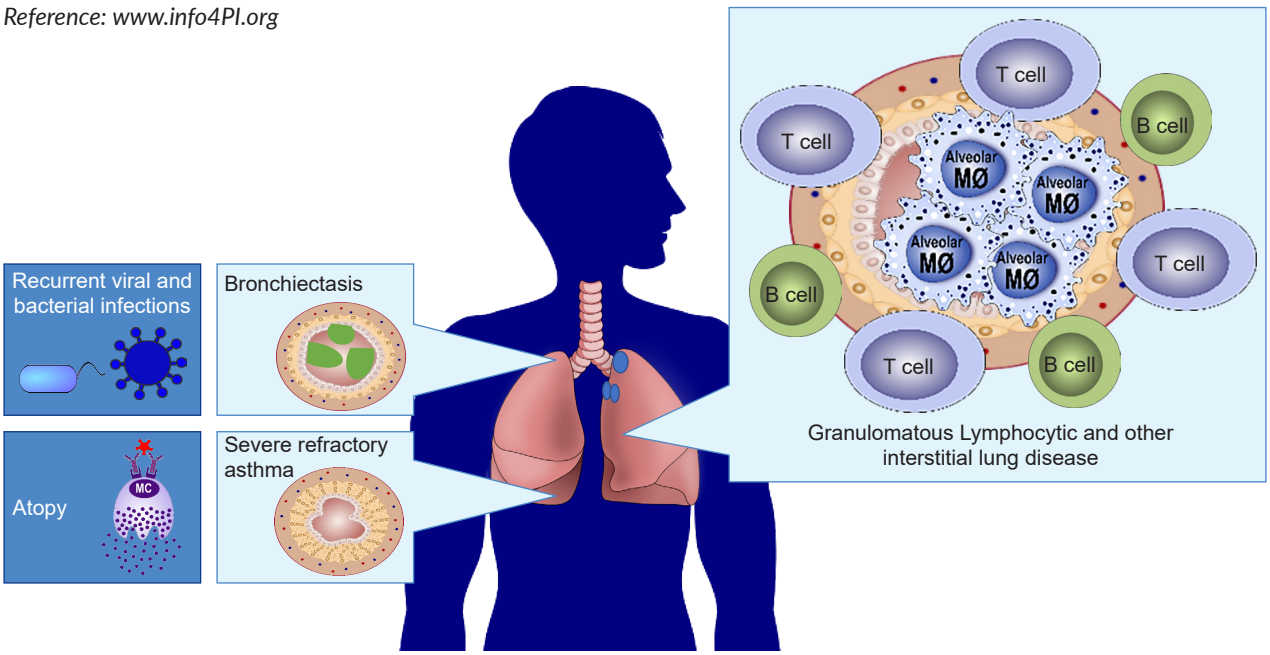

Figure 1 **Asthma and mimics of asthma in PID.**

This is particularly true in young children, for whom performing respiratory function testing for correct asthma diagnosis is challenging.

Recurrent viral infections triggering asthma exacerbations further confound the diagnosis of PID. Indeed, most children referred for suspected PID have previously received asthma treatment for a long time with no or limited success, whereas their symptoms rapidly respond to the institution of adequate therapy for PID (immunoglobulin substitution +/- antibiotics). Therefore, prompt diagnosis and correct treatment are important, since chronic complications such as bronchiectasis are common in CVID and in other primary antibody deficiencies, but also in patients with combined immunodeficiencies, granulocyte defects and complement defects. The activated phosphoinositide 3-kinase (PI3K) δ syndrome (APDS)

deserves special mentioning as a monogenic autosomal dominant condition associated almost invariably with recurrent severe pulmonary infections and the development of bronchiectasis at a young age in up to 60% of cases. Additionally, patients with APDS have increased susceptibility to herpes virus infections, immune dysregulation, lymphoproliferation (e.g. lymphoma). Children with severe recurrent respiratory infections and bronchiectasis should always be studied for APDS and for combined immunodeficiencies, if antibody deficiency and other typical causes, such as cystic fibrosis, have been excluded especially since targeted therapy is available.

Severe refractory asthma is a feature of several PIDs. For instance, severe asthma has been associated with antibody subclass deficiency and specific polysaccharide antibody deficiency, although the pathophysiology is incomplete understood. Severe allergic asthma is also a feature of several PIDs other than antibody deficiencies. For instance, it is present in about a third of patients with autosomal recessive Dedicator of cytokinesis 8 (DOCK8) deficiency, a combined immunodeficiency characterized by recurrent *Staphylococcal* skin infections, severe atopy, elevated IgE and recurrent severe viral infections. Allergic asthma is also a prominent manifestation of autosomal dominant STAT3 and Netherton syndrome.

A third scenario of PID lung involvement mimicking asthma is represented by the immune-mediated complications associated with PIDs, notably interstitial lung disease (ILD), the most common form being granulomatous-lymphocytic interstitial lung disease (GLILD). GLILD presents with cough and breathlessness. Impaired diffusion is the hallmark on lung function testing. Reticular changes with ground-glass appearance can be seen on lung imaging. Thoracic lymphadenopathies complete the picture. Autoimmune phenomena and lymphoproliferation or granulomatous complications can be found (e.g. inflammatory bowel disease). Histologically, granuloma, lymphocytic interstitial pneumonia and follicular bronchiolitis are observed. GLILD is a common feature of CVID and some specific PIDs, such as CTLA4 deficiency and lipopolysaccharide (LPS)-responsive and beige-like anchor protein (LRBA) deficiency.

Thus, in patients with asthma falling outside the Gauss curve of asthma manifestations, i.e. 1/ not responding to standard treatment; 2/ particularly severe and/or accompanied by extrapulmonary manifestations such as severe food allergy, severe skin infections or other recurrent infections; 3/ not fitting asthma diagnostic criteria (e.g. non-reversible spirometry, aberrant diffusion capacity, atypical course), PID should be suspected. A chest X-ray and, chest CT scan will aid in diagnosis, especially of bronchiectasis and of interstitial lung disease. Further diagnostics in the form of diffusion lung capacity testing is advised when interstitial lung disease like GLILD is suspected.

Basic PID evaluations include measurement of serum immunoglobulins (IgG, IgA, IgM with/without IgG subclasses and specific antibody measurement), lymphocyte immunophenotyping, neutrophil and complement function studies. However, broad genetic testing using next generation sequencing approaches is often necessary to obtain a molecular diagnosis and to allow for targeted treatment for APDS, CTLA-4 or LRBA deficiency.

Prompt initiation of treatment (immunoglobulins, antibiotics, chest physiotherapy, immunosuppressive drugs for GLILD) is mandatory. Nonetheless, respiratory complications are responsible for major morbidity and mortality in PID patients. When in doubt, discussing with a PID expert is key.

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14 DRUG ALLERGY

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KEY MESSAGES

- Drug allergy includes different entities induced by different immunological mechanisms
- The diagnosis of drug allergy is often challenging
- Drug provocation test (DPT) is the gold standard, but it is not risk-free and requires expertise
- New and validated in vitro tests are necessary for diagnosis
- Loss of sensitization may occur for different drugs inducing immediate reactions

Drug allergy (DA) is defined as adverse effects of drugs for which an immunological mechanism is demonstrated. They comprise 5–10% of adverse drug reactions.

Clinically, drug allergy is classified depending on the timing of the symptoms' onset into:

- Immediate reactions (IRs): symptoms occur up to 6 h after the drug intake, typically within the first hour.
- Non-immediate reactions (NIRs): symptoms occur any time from 1 h after the drug administration, commonly after more than six hours or even days after the start of the administration.

Drugs can induce any type of immunological reactions, but the most common ones are IgE-mediated mechanism for IRs and T-cell-dependent mechanism for NIRs.

There are also non-specific mechanisms underlying IRs, based on a pharmacological off-target effect of drugs (eg quinolones or NSAID) acting on receptors (MRGPRX2) or abnormal activation of enzymes (eg cyclooxygenase) or of the effector cells (Figure 1).

Skin is the most commonly affected organ in both IRs and NIRs, although systemic involvement can also occur. Less commonly, isolated internal organ involvement may also occur (Figure 1).

Correct diagnosis is important to avoid the negative impact of avoidance. The allergological workup should be carried out 4–6 weeks after the resolution of the reaction (Figure 2). Diagnosis starts with a detailed clinical history, which is often unreliable and can lead to either over- or under-diagnosis. Skin tests (STs) are the most readily available means to confirm sensitization. For IR the evaluation starts with skin prick tests, and, if negative, intradermal tests are used. For NIR patch tests and/or late reading intradermal tests should be performed. However, their diagnostic value has not been fully established for all drugs. *In vitro* tests can be useful during the acute phase of the reaction to evaluate the involved mechanism, and, after resolution, to identify the culprit drug, particularly for severe life-threatening reactions (Table 1). Searching for genetic markers may be helpful to detect the expression of a particular HLA allele that has been associated to specific forms of drug allergy. The drug provocation test (DPT) is the gold standard to identify the culprit drug. It may also be useful for choosing alternatives to the incriminated drug. As it is time-consuming and not risk-free, it must always be performed by experienced personnel in a specialized setting.

Acute reactions must be treated promptly and appropriately, and the administration of all sus-

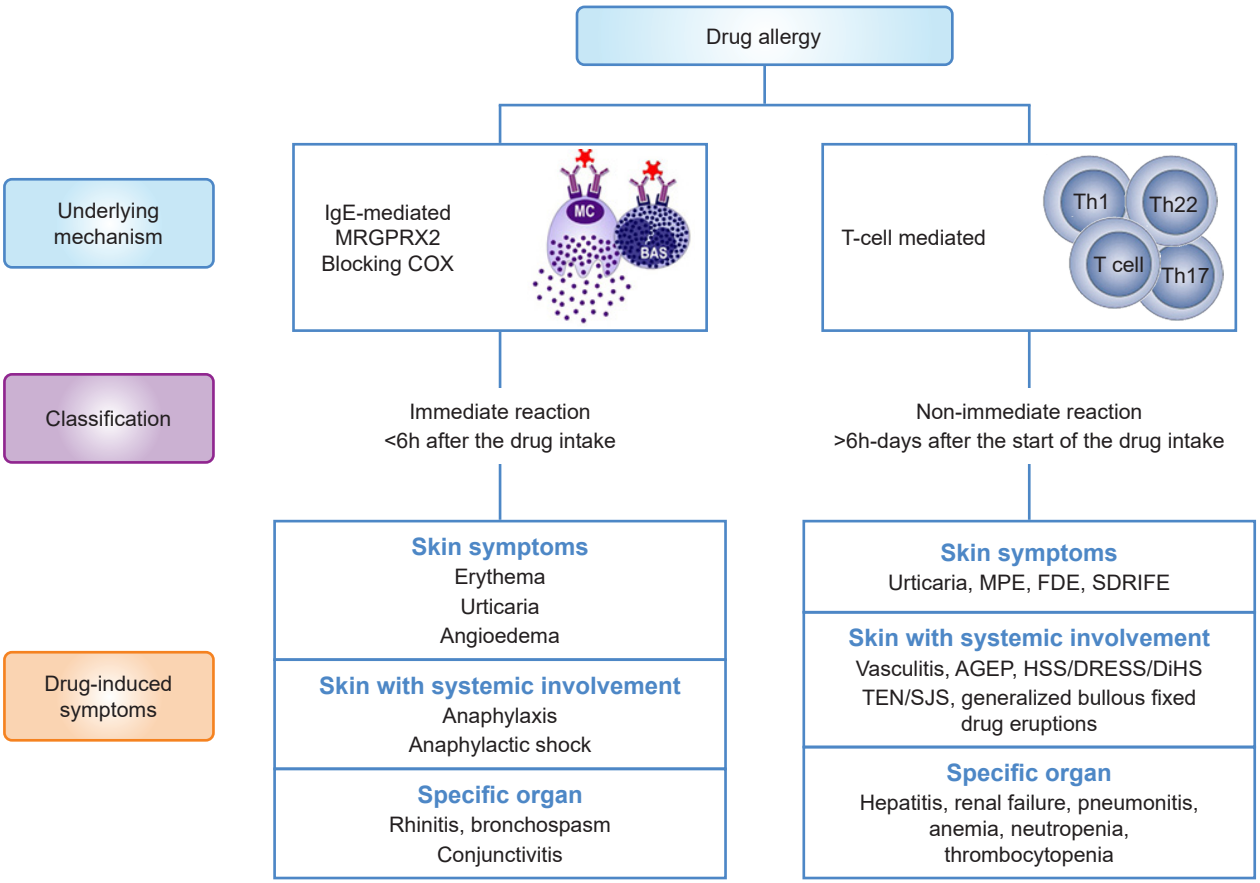

Figure 1 **Underlying mechanisms, drug induced-symptoms, and classification of drug allergic reactions.**
AGEP - Acute generalized exanthematous pustulosis; COX - Cyclooxygenase enzyme; FDE - Fixed drug eruption; HSS/DRESS/DiHS - Hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome; MPE - Maculopapular exanthema; MRGPRX2 - MAS Related G Protein-Coupled Receptor X2; SDRIFE - Symmetrical drug-related intertriginous and flexural exanthema; TEN/SJS - Toxic epidermal necrolysis/Stevens–Johnson syndrome.

pected drugs must be stopped. After the allergological work-up, patients must avoid the drug to which allergy diagnosis is confirmed. If other drugs from the same group are needed, tolerance must be assessed by DPT before recommending their administration as cross-reactivity can occur. When the culprit is essential and no alternatives exist, desensitization should be considered.

For IRs drug sensitivity might wane over time. However, it is recommended to permanently avoid the culprit and cross-reactive drugs if anaphylaxis occurred, as allergic patients negatively tested may re-become positive. For NIRs, T-cell memory seems to be even stronger than for IRs.

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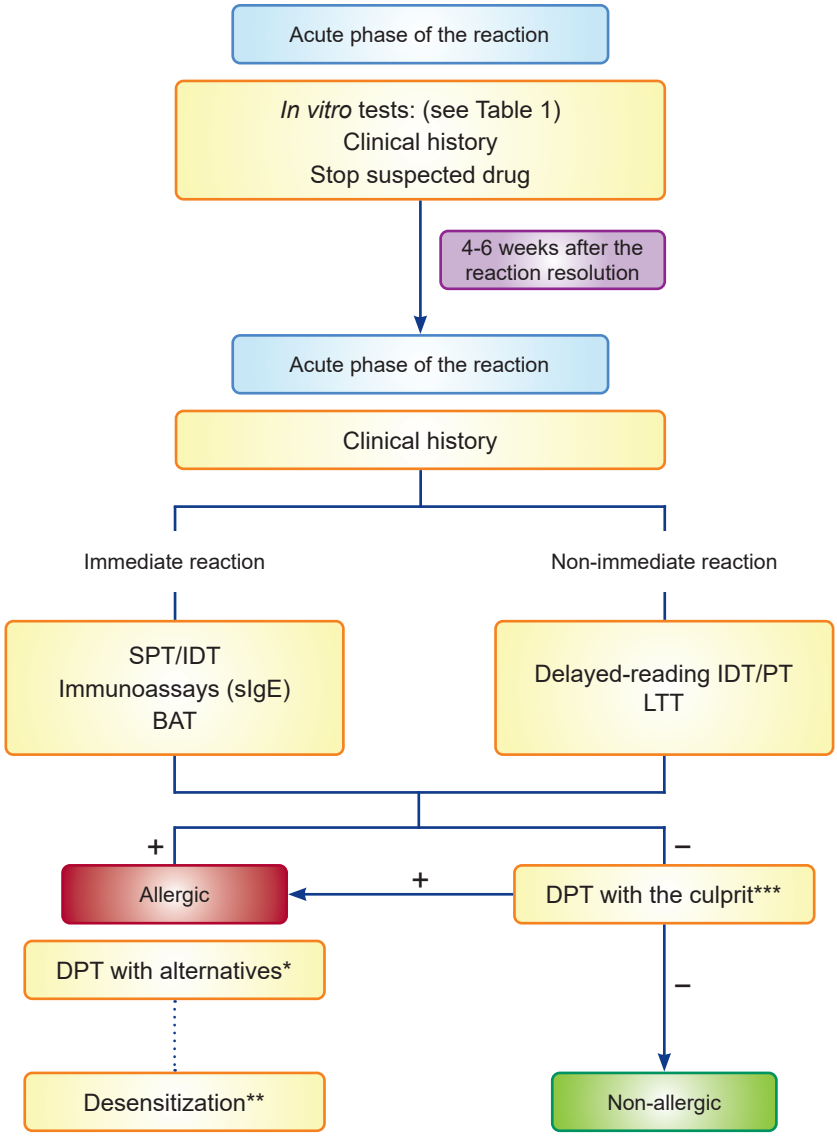

Figure 2 Allergological workup for the evaluation of suspected drug allergic reaction. *When other drugs from the same group are needed, as cross-reactivity can exist. **When the culprit is essential and no alternatives exist. **When reaction is not severe and no internal organs are involved. *BAT - Basophil activation test; IDT - Interdermal test; LTT - lymphocyte transformation tests; PT - Patch test; SPT - Skin prick test; DPT - Drug provocation test.*

TABLE 1

In vitro tests used for diagnosing both IRs and NIRs during the acute phase of the reaction and after the resolution phase		
	Immediate reactions	**Non-immediate reactions**
After resolution	Histamine in serum Tryptase in serum Mediator release assays (histamine and leukotrienes)*	Skin biopsy Quantification of cytokines, chemokines and adhesion molecules in peripheral blood
After resolution phase	Drug-specific IgE in serum Basophil activation test	Lymphocyte transformation/activation Enzyme-linked immunosorbent spot assay Cell markers and cytokine release

**If NSAIDs involved.*

15 ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

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Allergic Bronchopulmonary Aspergillosis (ABPA) is an endotype of asthma and cystic fibrosis that results from antigens from *Aspergillus fumigatus* (Af) that grow saprophytically in the bronchial mucus and produce a CD4+ Th2 biased inflammatory response. While not causing invasive aspergillosis that occurs in neutropenic patients, ABPA causes pulmonary infiltrates, peripheral blood and sputum eosinophilia, inspissated mucus plugs (Figure 1) and bronchiectasis, an irreversible condition of the larger airways.

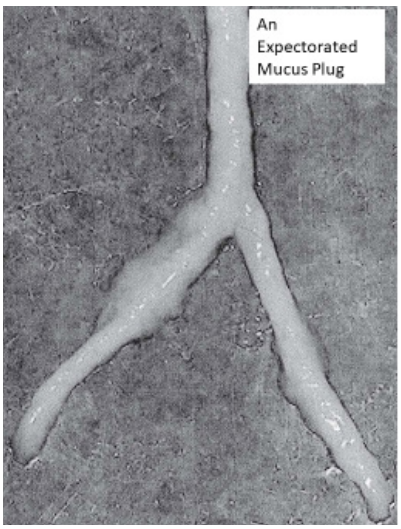

Figure 1 A bronchial plug expectorated by a patient with Allergic Bronchopulmonary Aspergillosis. Note that the shape is a cast of bronchi.

KEY MESSAGES

- Allergic Bronchopulmonary Aspergillosis (ABPA) is an endotype of asthma and cystic fibrosis that causes pulmonary infiltrates, bronchiectasis and peripheral blood eosinophilia and requires oral corticosteroids as primary treatment
- Spores of *Aspergillus fumigatus* inhaled from indoor or outdoor air evade pulmonary defenses and grow as hyphae triggering intense Th2 biased allergic inflammation
- The chest radiographic infiltrates usually involve the upper lobes or middle lobe and resemble a non-hospital acquired pneumonia, which too often results in antibiotic administration instead of treatment directed at the tenacious mucus that causes plugging of bronchi
- Untreated ABPA results in new areas of bronchiectasis and parenchymal lung damage, both of which are irreversible
- About 25% of patients with persistent severe asthma have sensitization to *Aspergillus fumigatus* and as high as 80-90% of such patients have sensitization to either *Aspergillus* species or other fungi (allergic bronchopulmonary mycosis)
- Specialty care by allergist-immunologists or pulmonologists is especially important in providing an earlier diagnosis and effective treatment

Smaller airways can be destroyed by bronchiolitis obliterans, and there may be concomitant eosinophilic pneumonia.

The diagnosis of ABPA often is overlooked for years which leads to repeated non-hospital associated pneumonias or silent pulmonary infiltrates that produce new areas of bronchiectasis. Some of the ways in which APBA can present are listed in Table 1. It is very important to make the diagnosis of ABPA early to avoid bronchiectasis and injury to the lung parenchyma that occurs otherwise.

In susceptible patients with asthma or cystic fibrosis, once the spores of *Aspergillus fumigatus*, which measure 2-3.5 µm, are in-

TABLE 1

Presentations of Allergic Bronchopulmonary Aspergillosis
Inspissated mucus that is difficult to remove during bronchoscopy (eg. The 10 minute bronchoscopy for diagnosis lasts 30 minutes and little mucus is extracted)
Unexplained (idiopathic) bronchiectasis
Asymptomatic pulmonary infiltrates on chest radiographs or computerized tomography of the lungs
Pulmonary infiltrate (s) with peripheral blood eosinophilia
Worsening severity of asthma or uncontrolled or partly controlled asthma
Acute severe asthma (status asthmaticus)
Peripheral blood eosinophilia
Minimal cough or wheeze (or no known asthma)

haled from either outdoor or indoor air, they grow as hyphae in the bronchial mucus and in terminal airways. They evade defenses against them. Spores (conidia) react with toll like receptor (TLR) 4 and produce pro-inflammatory cytokines TNFα, IL1β, IL12, and IFNγ. In contrast, hyphae bind to TLR 2, which leads to T lymphocyte regulatory response, IL10 and a low levels of TNFα. Furthermore, *Aspergillus fumigatus* is able to produce many enzymes including proteases that stimulate production of MUC5AC. Considered perhaps the ideal gel forming mucin, MUC5AC is produced by goblet cells in the bronchial epithelium and in the submucosa.

The worldwide prevalence of ABPA in patients with asthma, primarily from data ascertained from pulmonary clinics is 2.5%, whereas in patients with cystic fibrosis, it ranges from 1-15%. About 25% of patients with asthma have anti-*Aspergillus* IgE antibodies, either by immediate skin testing or *in vitro* measurements (>0.35 kUA/L). The diagnostic criteria for ABPA require the presence of these antibodies so that in their absence, the ABPA diagnosis can be excluded with a high level of confidence. Some populations of patients with asthma may be at higher risk.

Approximately 80-90% of patients with persistent asthma have anti-fungal IgE antibodies, but most cases of allergic bronchopulmonary mycosis (ABPM) are attributable to *Aspergillus fumigatus* (Figure 2).

ABPA classically includes bronchiectasis (called proximal or central) or seropositive, because there is no bronchiectasis on the high resolution computerized tomography (CT) examination of the lungs. Proximal bronchiectasis refers to abnormal bronchial wall widening in the inner 2/3 of the chest CT fields. The CT examination often reveals high attenuation mucus, which is mucus that is clearly denser than the chest wall or paraspinal skeletal muscle. The criteria for diagnosis of ABPA are presented in Table 2. Note that there is a difference between the Northwestern University (Chicago, Illinois) (Rosenberg/Patterson) criteria, where the cut off of total IgE concentration is > 417 kU/L (IU/mL) and International Society (ISHAM), which suggested > 1000 kU/L (IU/mL). A doubling of the total serum IgE typically helps identify ABPA exacerbations.

There are 5 stages of ABPA: Acute (stage 1) with chest roentgenographic infiltrates and elevated total serum IgE which responds to oral corticosteroids (OCS); Remission (stage 2) when the infiltrates have cleared and the patient has not required OCS for 6 months; Exacerbation (stage 3) which is similar to stage 1 in presentation and response; Corticosteroid dependent asthma (stage 4) where asthma has become more severe and requires OCS to achieve control and patients may or may not have additional exacerbations of ABPA; End-stage fibrocavitary (stage 5) with advanced bronchiectasis, cavitary lung disease harboring non-tuberculous mycobacteria or *Pseudomonas* species, or fibrosis.

Management of ABPA requires early identification, avoidance of sources of molds in the home or workplace, monitoring of the total serum IgE concentration, OCS as initial therapy and for exacerbations, adjunctive administration of anti-fungals such as voriconazole or itraconazole and consideration of biologicals that target the Th2 pathway. Specialty care (allergy/immunology and or pulmonology) is advisable for patients with ABPA.

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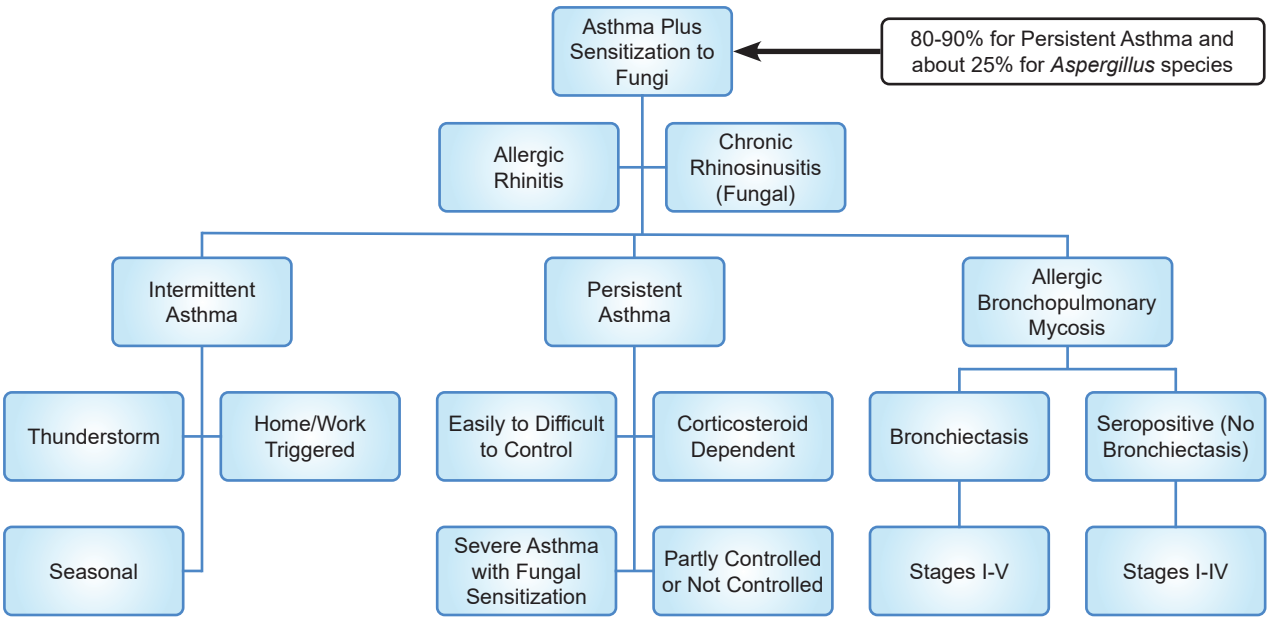

Figure 2 **Some Pertinent "Fungal" Phenotypes and Endotypes of Asthma.**

TABLE 2

Diagnostic Criteria of Allergic Bronchopulmonary Aspergillosis	
Classical Criteria	Asthma
	Chest roentgenographic infiltrates (upper lobes or middle lobe)
	Immediate cutaneous reactivity to Aspergillus or anti-Aspergillus IgE >0.35kUA/L
	Elevated total serum IgE concentration >417 kU/L (IU/mL)*
	Elevated serum anti-Aspergillus fumigatus IgE and/or IgG antibodies#
	Serum precipitating antibodies
	Proximal (central) bronchiectasis
	Peripheral blood eosinophilia
Minimal Essential Criteria	Asthma
	Immediate cutaneous reactivity to Aspergillus or anti-Aspergillus IgE >0.35kUA/L
	Elevated total serum IgE concentration >417 kU/L (IU/mL)
	Elevated serum anti-Aspergillus fumigatus IgE and/or IgG antibodies#
	Proximal bronchiectasis
International Society for Human and Animal Mycology	Predisposing conditions 1. Bronchial asthma 2. Cystic fibrosis
Obligatory criteria (both should be present)	Type I Aspergillus skin test positive (immediate cutaneous hypersensitivity to *Aspergillus* antigen) or elevated IgE levels against Af
	Elevated total IgE levels (>1,000 IU/mL) unless the patient meets all other criteria
Other criteria (must meet 2 of 3)	Presence of precipitating antibodies or IgG antibodies against Af in serum
	Radiographic pulmonary opacities consistent with ABPA
	Total eosinophil count > 500 cells/μL in steroid naïve patients (may be historical)

**The threshold of >1000kU/L (1000 IU/mL) has been proposed by the International Society for Human and Animal Mycology -see below for comparison*

#compared with sera from patients with asthma and immediate cutaneous reactivity to Aspergillus but who do not meet sufficient criteria for ABPA

16 COEXISTING ASTHMA AND COPD

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KEY MESSAGES

- Asthma and COPD are diseases with distinct epidemiologic, clinical, pathophysiologic characteristics in the large majority of cases and require specific management algorithms
- Asthma and COPD may coexist in a significant proportion of adult patients > 40 years of age
- The coexistence of asthma and COPD is characterized by combined risk factors, particularly smoking, chronic rather recurrent respiratory symptoms, poorly reversible airflow limitation, and increased risk of exacerbations
- Patients with coexisting asthma and COPD are treated according to the respective guidelines
- Exacerbations or respiratory symptoms are more frequent in patients with concomitant asthma and COPD compared with patients with single disease, but are treated as asthma or COPD exacerbations

Asthma and chronic obstructive pulmonary disease (COPD) are distinct clinical entities. Asthma usually starts early in life, mainly in atopic subjects, and is characterised by recurrent and variable respiratory symptoms, particularly wheezing, chest tightness and cough, that almost is usually reversible to pharmacologic treatment. By contrast, COPD almost invariably starts after the age of 40, in smokers, and is characterised by chronic symptoms, particularly dyspnoea, and airway obstruction, both poorly reversible to pharmacologic treatment.

Both asthma and COPD are associated with chronic airway inflammation, but with very different characteristics (Figure 1). The pathology of airways and lung from patients with coexisting asthma and COPD have not been described in details.

History, clinical presentation and spirometry showing reversibility of airflow limitation, confirms a diagnosis of asthma, whereas history, clinical presentation and spirometry showing poorly reversible airflow limitation confirms the diagnosis of COPD (Table 1).

Differential diagnosis between asthma and COPD becomes more difficult in elderly patients, in whom some features of asthma and COPD may coexist, such as smoking and atopy, poorly reversible airflow limitation and/or airway responsiveness, symptoms, imaging, and even pathological findings (eg blood and/or sputum eosinophilia) may overlap and thus may not provide solid information to distinguish the two clinical entities.

Reversibility to inhaled corticosteroids alone, or in combination with long-acting bronchodilators, measurements of lung volumes and diffusion capacity, analysis of sputum and FeNO, and imaging of the chest may suggest whether asthma or COPD is the predominant cause of airflow limitation in these patients (Table 2).

In patients with the above characteristics the best approach is to make a diagnosis of coexisting asthma and COPD, and treat the patient according to guidelines for both asthma and COPD. Because of its complexity and heterogeneity, at the population level, asthma, particularly severe asthma, may be difficult to recognize in a patient

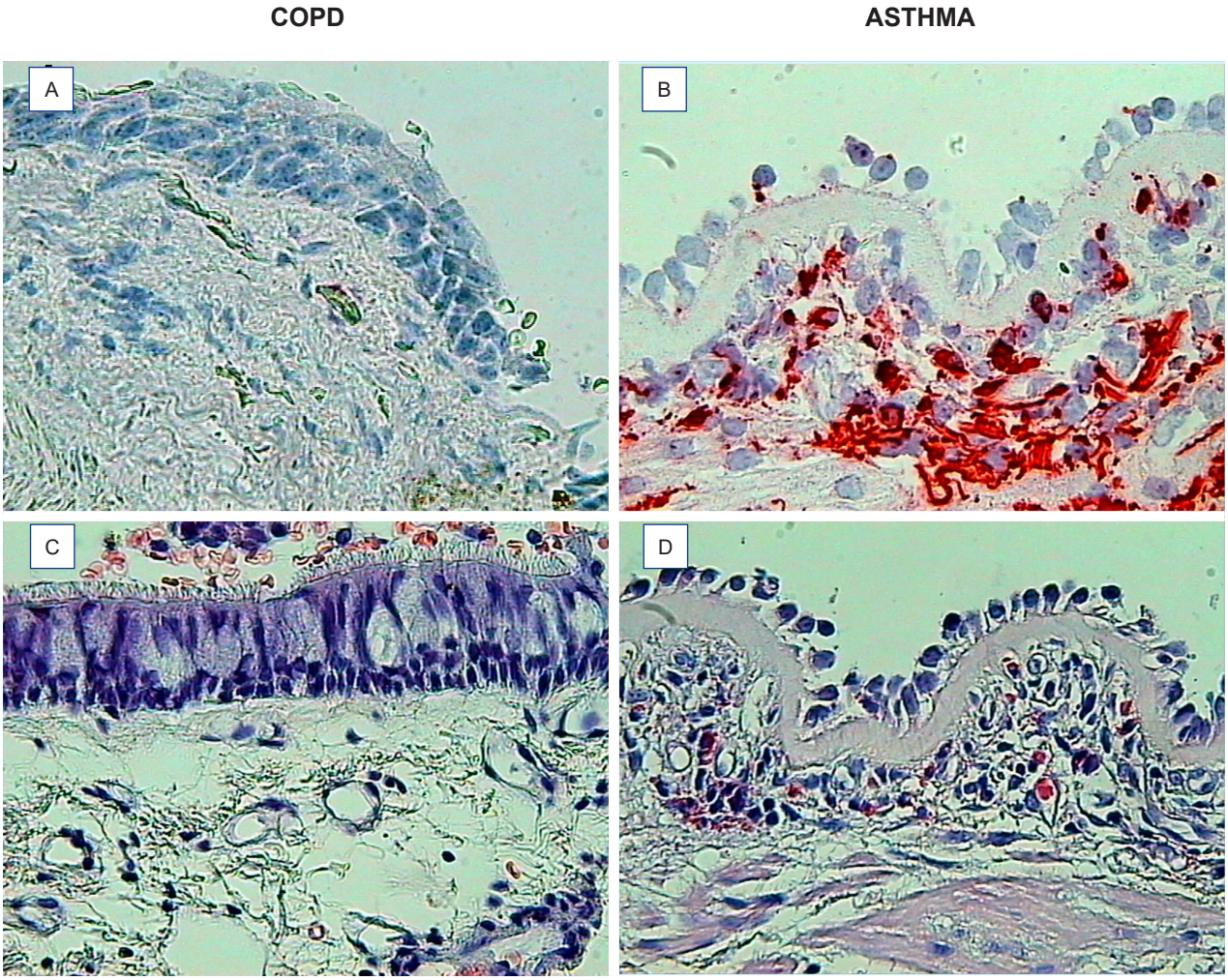

Figure 1 (A) and (B): Photomicrographs showing bronchial biopsy specimens immuno-stained with anti–EG-2 (eosinophil cationic protein) from a patient with fixed airflow obstruction and a history of COPD (A) and from a patient with fixed airflow obstruction and a history of asthma (B). The two patients had a similar degree of fixed airflow obstruction. In (B), there is prominent eosinophilia beneath the destroyed epithelium that is not present in (A). (C) and (D): Photomicrographs showing bronchial biopsy specimens stained with H&E from a patient with fixed airflow obstruction and a history of COPD (C) and from a patient with fixed airflow obstruction and a history of asthma (D). The two patients had a similar degree of fixed airflow obstruction. In (D), there is a thicker reticular layer of the epithelial basement membrane compared with (C). *(Reprinted with permission of the American Thoracic Society. Copyright © 2020 American Thoracic Society. All rights reserved. The American Journal of Respiratory and Critical Care Medicine is an official journal of the American Thoracic Society)*

with COPD, but efforts should be made using clinical judgment in the individual patient, particularly to identify treatable traits and their potential sensitivity to novel effective anti-asthma therapies, like monoclonal antibodies (anti-IgE, anti-IL5 or anti-IL5R, anti-IL4Rα). If properly used, these antibodies may help maintain asthma control in patients uncontrolled by pharmacological therapy, whereas they are not effective in COPD.

The presence of concomitant chronic diseases contributes to the severity of patients with asthma, COPD and concomitant asthma and COPD.

The most frequent concomitant chronic diseases of mild asthma are atopic disorders and gastroesophageal reflux. In more severe asthma polyposis, obesity, arteri-

TABLE 1

History, symptoms and results of pulmonary function tests in the differential diagnosis between asthma and COPD

	ASTHMA	COPD	COEXISTING ASTHMA AND COPD
Onset	Mainly in childhood	In mid to late adult life	Mostly in late adult life
Smoking	20-30% smokers	Almost invariably smokers	Almost invariably smokers
Chronic cough and sputum	10%	20-30%	20-30%
Dyspnoea on effort	Variable and reversible to treatment	Constant, poorly reversible and progressive Occasional wheezing	Constant, poorly reversible and progressive Occasional wheezing
Nocturnal symptoms	Relatively common	Relatively uncommon	Relatively common
Fixed Airflow limitation	May be present together with increased diurnal variability	Invariably present, occasionally associated with diurnal variability	Invariably present, occasionally associated with diurnal variability
Response to bronchodilator	Good	Poor	Poor
Airway hyper-responsiveness	In most patients, with or without airflow limitation	Usually not measured due to airflow limitation	Usually not measured due to airflow limitation

TABLE 2

Ancillary tests in asthma, COPD, and coexisting asthma and COPD

ANCILLARY TEST	ASTHMA	COPD	COEXISTING ASTHMA AND COPD
Reversibility to glucocorticosteroids	Usually present	Usually absent	Frequently present
Vital Capacity, Residual Volume (RV), total lung capacity (TLC)	Usually normal but RV may be increased but reversible to bronchodilator	Usually > RV with/out > TLC, not reversible to bronchodilators or steroids	Usually > RV with/out > TLC, not reversible to bronchodilators or steroids
Diffusion capacity	Normal	Decreased	Decreased
Airway hyperresponsiveness	Increased	Usually not measured due to airflow limitation	Usually not measured due to airflow limitation
Allergy tests	Often positive	Often negative	Often positive
Imaging of the chest	Usually normal	Usually abnormal	Usually abnormal
Sputum	Eosinophilia	Neutrophilia	Neutrophilia + eosinophilia (10%)
Exhaled NO	Increased	Usually normal	Increased

al hypertension, diabetes, chronic heart failure are frequently encounterd. In general, co-morbidities may become important in severe asthma, whereas they play a less important role in the clinical manifestations of mild to moderate asthma. Smoking modifies the airway pathology of asthmatics to a COPD-like pattern and reduces the response to treatment. The most frequent concomitant chronic diseases of COPD are those caused by the same risk factors of COPD, particularly smoking: cardiovascular diseases (arterial hypertension, chronic heart failure, ischemic heart disease, cerebrovascular diseases), metabolic diseases (diabetes, obesity or cachexia, hyper-dyslipidaemia),

endocrine (osteoporosis), neurological (depression, anxiety, cognitive dysfunction). In patients with concomitant asthma and COPD the concomitant chronic diseases combine and may become major determinant of the severity of the patient, and thus they need to be properly diagnosed and treated.

In asthma, primary controller medications are inhaled steroids (ICS) or formoterol/ICS given prn or given both as controller and reliever. Asthmatics are never treated with long-acting bronchodilators alone as controller. In COPD primary controller medications are long acting bronchodilators, and patients are never treated with ICS alone. In COPD, ICS can be added to long acting bronchodilators only if they are not adequately controlled by single or double long-acting bronchodilators, and/or if they are at risk of frequent exacerbations and/or have blood eosinophilia. In the absence of specific clinical trials conducted in patients with coexisting asthma and COPD, these patients are treated according to both asthma and COPD guidelines, ie with combination therapy with single or double bronchodilator and ICS as inhaled controller medication, and short acting inhaled bronchodilator as rescue medication. In addition, in patients who present with COPD and severe asthma, novel biological treatment (anti-IgE, anti-IL-5, anti-IL5R, anti-IL-4Rα) could also be considered.

Exacerbations or respiratory symptoms are more frequent in patients with concomitant asthma and COPD compared with patients with single disease, but are treated as asthma or COPD exacerbations. More severe exacerbations, or exacerbations that do not respond to the increased use of rescue medications, require a 5-10 days course of systemic, preferably oral, corticosteroids and/or antibiotics, if there is evidence of bacterial infection. Because of the complexity of these patients, and of the frequent comorbidities, it is mandatory to investigate carefully the cause of the exacerbations of respiratory symptoms, as might be due acute independent events (e.g. pneumonia, pulmonary embolism, anaemia, etc.) or exacerbations of concomitant of concomitant diseases (e.g. decompensated heart failure, ischemic heart disease, arrhythmias, anxiety, etc.). Severe exacerbations of respiratory symptoms require medical attention or and in some patients hospital and/or intensive care unit admission.

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Section D

ASTHMA DIAGNOSIS

1 LUNG FUNCTION IN ASTHMA

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Asthma was originally described as a symptom-driven disease, however, currently, a diagnosis of asthma is a unifying description of several pathophysiological mechanisms, reflecting the potential complexity of the disease in an individual. No single test can objectively document the presence of asthma.

KEY MESSAGES

- The fraction of exhaled nitric oxide (FeNO) is a relevant biomarker in asthma, which can be used for phenotyping and monitoring
- Spirometry (FEV_1 and FVC) should be measured at each contact with health care providers
- Small airway obstruction needs measurement with forced oscillation technique (FOT) and impulse oscillometry (IOS)
- Airway hyperresponsiveness (AHR) can be measured with direct and indirect methods
- Asthma is characterised by AHR, but one test might not be enough, whereas using more than one test most asthma patients show documentation for variable airway obstruction

FRACTION OF EXHALED NITRIC OXIDE (FENO)

The fraction of exhaled nitric oxide (FeNO) is produced by the epithelial cells in the airways after stimulation, for example by type 2 (T2) cytokines IL4 and IL13. T helper 2 (Th2) inflammation is associated with a high level of FeNO. FeNO correlates with eosinophils in sputum, BAL, bronchial biopsies and blood. FeNO is recommended to define the inflammatory T2 endotype of asthma. A raised level of FeNO in patients with asthma increases the likelihood of a positive response on indirect bronchial challenge testing with agents like mannitol and to treatment with inhaled corticosteroids (ICS). The receiver operating characteristic (ROC) curve for FeNO discriminating between asthmatics with and without exercise induced broncho-constriction (EIB) had an area under the curve (AUC) of 0.771 (95%CI: 0.64–0.87), while sputum eosinophils of ≥3% had an AUC of 0.774 (95%CI: 0.66–0.8) and blood eosinophils of ≥0.300 10^9/L an AUC of 0.687 (95%CI: 0.54–0.83) (Table 1). Due to the inconsistencies, FeNO is not suitable for diagnosing asthma, but the relationship with asthma, eosinophilic inflammation, airway hyperresponsiveness (AHR) and responsiveness to steroid suggests that FeNO is valuable in endotyping and monitoring disease.

LUNG FUNCTION

In asthma, a normal level of lung function is the goal of any treatment. The lung function should be measured at the debut of asthma

TABLE 1

FeNO sensitivity and specificity			
	20-30	30-40	≥40
Sensitivity	64%	53%	41%
Specificity	81%	84%	94%

Values collected from different, but similar, publications

symptoms, or when the patient has increased asthma symptoms.

Spirometry with forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) can be measured in all asthma patients able to cooperate. Each measurement consists of at least two maximal expiratory manoeuvres from total lung capacity to residual volume, with a variation of less than 5%. The highest FEV_1 and FVC should be reported and expressed as a percentage of predicted values (%pred), using predicted equations based on age, ethnicity, sex and height. The FEV_1/FVC ratio ≤ 70% indicate airway obstruction.

Reversibility testing can be performed with inhaled SABA or ICS. FEV_1 is measured before and after administration of the drug for 15 minutes (SABA) or 15 days (ICS), and the reversibility is calculated as follows:

$$\frac{FEV_1 \text{ after} - FEV_1 \text{ before}}{FEV_1 \text{ before}}$$

A positive test is defined as an increase in FEV_1 of at least 200 ml or 12%.

Peak flow (PEF) measures the airflow in the larger airways. Its variability should be measured for ≥2 weeks, both morning and evening. A significant variability is defined as a day-to-day variation of at least 20% ((max – min)/max).

In patients unable to cooperate for FEV_1, the use of the forced oscillation technique (FOT) and impulse oscillometry (IOS) is recommended. Furthermore, FOT and IOS can differentiate small airway obstruction from large airway obstruction, and it is more sensitive than the spirometric measurement of peripheral airway disease, where FEF_{25-75} is performed.

AIRWAY HYPER-RESPONSIVENESS (AHR)

Airway hyperresponsiveness (AHR) is a characteristic finding in patients with asthma, based on excessive sensitivity of the airways in patients with asthma compared with non-asthmatic subjects to different unspecific stimuli. AHR reflects a dysfunction of the airway smooth muscles with considerable variability in the intensity . AHR is associated with both T2-high and T2-low inflammation and the selection of test to be used depends on the patient tested and the question to be solved. In case of FEV_1 < 60% predicted value AHR testing is not advised. Asthma symptoms combined with a positive AHR test is characteristic for the disease asthma. The cut-off values of the different challenge tests are defined due to the variation of the lung function test used (Table 2). Concerning FEV_1, the mean variation (+2SD) when measuring before and after the challenge never exceeds 9%. Therefore, a reduction in FEV_1 of 10% is an abnormal response, a cut-off which have been examined in different set up.

The challenge tests depend on the mechanism behind the response, of which methacholine provocation works directly on the smooth muscles and histamine challenge works directly via nervous irritant receptors and a vagal reflex. A positive response of 20% reduction in FEV_1 should be calculated and AHR are defined as PC_{20} or PD_{20} depending of methods. Challenge test performed with both methacholine and histamine can be done with both tidal breathing and single breath generated with different devices. There is no standardised method when performing direct challenge testing, which is a problem when results between different lung function testing labs are compared . The response to indirect AHR tests has been associated with the intensity of the airway inflammation. Mannitol bronchial provocation is performed with an Osmohale Kit^R. This is a standardised, safe and easy-to-use test. A positive response is defined as a 15% reduction in FEV_1 and AHR is defined as a PD_{15} ≤ 635 mg. In clinical setting, a response of 10–14% after inhalation of mannitol can be used as some support of the diagnosis of asthma, whereas this is not possible in research. Exercise induces bronchospasm is present in almost all asthmatics. The exercise test consists of steady running on a 10% sloping treadmill for 6-8 min. The speed should be adjusted to maintain the heart rate at 80% of the participant's maximum heart rate. FEV_1 should be measured before testing, and after 0, 3, 5, 10 and 15 min. A decrease in lung function of ≥15% is defined as exercise-induced asthma (EIA). Eucapnic hyperventilation (EVH) was developed as a standardised laboratory test for EIA, and is more effective and sensitive test than exercise testing. In the EVH test, dry air with a CO_2 content of 5% is inhaled for 6 min with 85% of the maximum voluntary ventilation. FEV_1 is measured after 0, 5, 10, 15 and 20 min post-test. AHR is defined as a response of a 10% or greater reduction in FEV_1—at two separate measurements. Inhalation of hypertonic saline increases the osmolarity of the periciliary fluid, which triggers mediator release from the inflammatory cells, followed by indirect bronchoconstriction. Hypertonic saline (4.5%) is inhaled as an aerosol from a nebuliser for periods of increasing duration (e.g. 0.5, 1, 2, 4 and

TABLE 2

Different bronchial challenge tests: Sensitivity and specificity		
Agent	**Sensitivity**	**Specificity**
Methacholine	High	Moderate
Histamine	High	Moderate
4.5% Saline	Moderate	High
Mannitol	Moderate	High
Exercise test	Low	High
EVH	Moderate	High
AMP	Moderate	High

8 min). A 15% decrease in FEV_1 of the initial value is defined as AHR. Lastly, AMP indirectly stimulates smooth muscle cells through the release of inflammatory mediators from mast cells into the respiratory tract, and it represents an indirect pharmacological test, with a PC_{20}, indicating AHR in asthma (200–400 mg/ml) (Table 2).

For the diagnosis of asthma, when analysing the different challenge tests in patients suspected for asthma, some degree of overlap between the test results exists, and a combination of tests (PEF variation, reversibility, methacholine, mannitol) has a diagnostic value as high as 82%.

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2 BRONCHIAL ALLERGEN PROVOCATION

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KEY MESSAGES

- Current guidelines suggest allergen provocation to prove the clinical relevance of a an allergen
- Bronchial allergen provocations (BAP) are safe in experienced hands
- In house dust mite allergy nasal provocations have a high positive predictive value, however negative provocations do not exclude an allergy
- The specific IgE significantly predicts an early asthmatic reaction upon BAP
- In asthma research low dose allergen provocations are useful to reproduce the natural allergen exposure

Bronchial allergen provocations (BAP) are useful in diagnostics of allergic asthma, for the assessment of asthma biomarkers, for the study of the mechanisms of allergic airway inflammation, and for the evaluation of the efficacy of anti-allergic and anti-asthmatic agents.

It is well-known that bronchial allergen provocation (BAP) in sensitised asthmatic individuals provokes an early asthmatic reaction (EAR) within 10 minutes, which resolves within 1–2 hours. About 50-70 percent of individuals with asthma experience a more sustained late asthmatic reaction (LAR) which peaks within 6-9 hours and resolves within 24 hours. The LAR is associated with an increase of bronchial hyperreactivity (BHR) which may last for several days. Thus, the understanding of EAR to inhaled allergens changed as allergens besides acute bronchospasm initiate a series of inflammatory events that lead to enhanced BHR and increased asthma severity.

In house dust mite (HDM) driven allergic asthma current EAACI guidelines suggest allergen provocations to prove the relevance of HDM sensitization, e.g., before the start of a allergen immunotherapy with HDM. Especially for BAP concerns about the safety of the method exist. We could show in a group of 425 children and adolescents with HDM allergy that BAP is a save method even in an outpatient setting. Nasal provocation testing (NPT) is a safe and reproducible technique in diagnostics of allergic rhinitis. For the prediction of allergic asthma NPT had a sensitivity of 72 percent and a positive predictive value of 89 percent. However, for negative NPTs, BAP is still the method to prove or to rule out a house dust mite allergy.

Specific IgE against *Dermatophagoïdes pteronyssinus* (D pter) and *Dermatophagoïdes farinae* (D far) and the fractional exhaled nitric oxide (FeNO) were significant predictors of an EAR in BAP. Specific IgE to D far had an accuracy of 78 und 88 percent in ROC analyses, respectively. In another study using logistic regression models the ImmunoCAP ^{10}log D pter significantly predicted the individual probability of an EAR with an accuracy of 89 percent (Figure 1). The predictive value of eNO for an EAR was slightly lower than the specific IgE with an accuracy of 78 and 71 percent, respectively.

BAPs is a frequently used tool for the evaluation of the efficacy of anti-asthmatic medication. The advantage is that only a relative

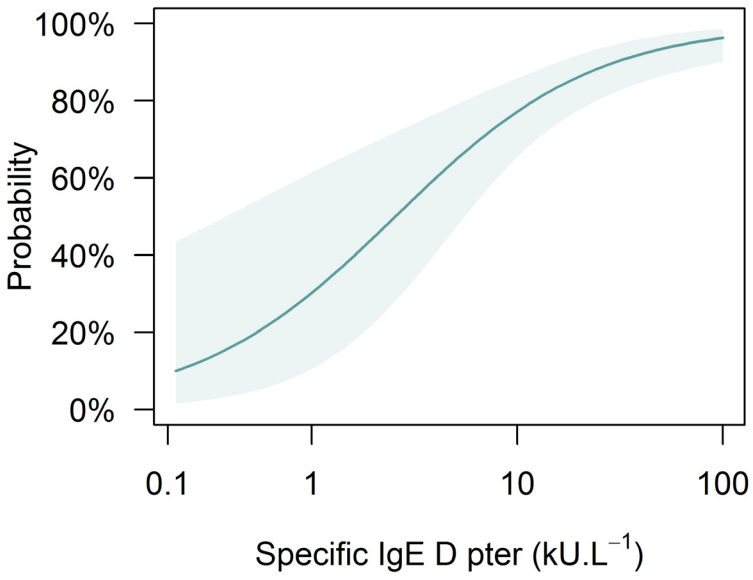

Figure 1 **The figure shows the increasing probability of an early asthmatic response with increasing ImmunoCAP D pter concentrations.** The probability of an EAR was estimated as 19% at 3.5 kU.L^{-1} and 90% at 96 kU.L^{-1}.
(Reproduced from Immunotherapy, Comparison of two different assays and the predictive value of allergen components in house dust mite allergy, Schulze J, et al., Vol 9, 1253-53, 2017 with permission from Future Science Group)

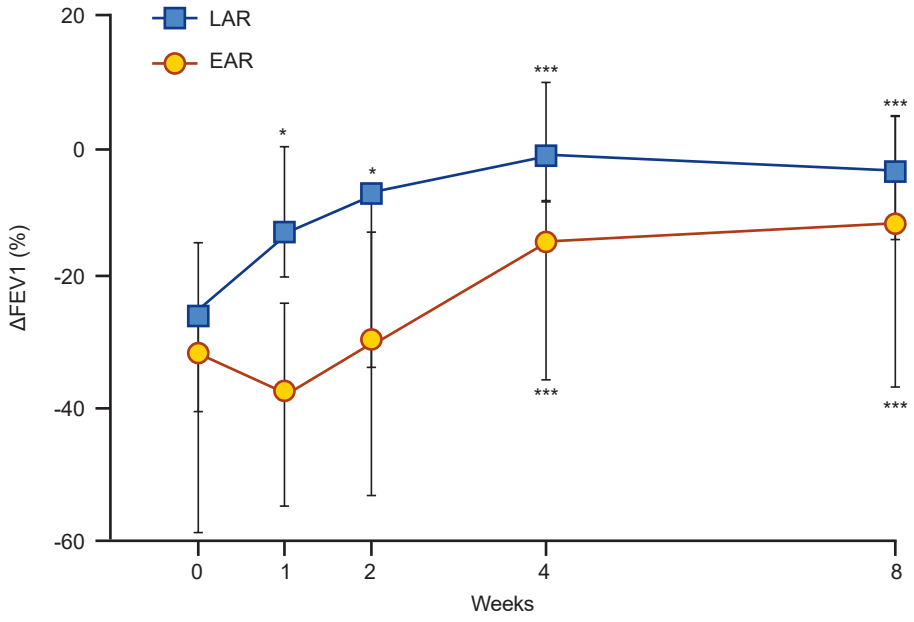

Figure 2 **Early and late allergic response (EAR, LAR) after bronchial allergen provocation (BAP): LAR is significantly improved after 1 week of omalizumab treatment, EAR after 4 weeks of treatment.**
(Reproduced from Allergy, Omalizumab effectively protects against early and late allergic responses in asthma after 4 weeks, Trischler J et al., Vol 72, 1912-15, 2017 with permission from John Wiley & Sons)

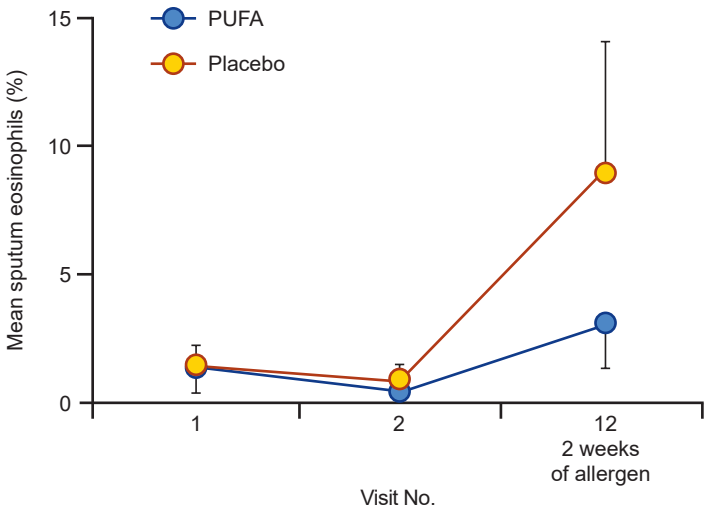

Figure 3 Changes of eosinophil counts in sputum after 2 weeks of low allergen provocation, comparison of verum (n-3 polyunsaturated fatty acids) and placebo.

("Reproduced from Int Arch Allergy Immunol , Effect of n-3 polyunsaturated fatty acids in asthma after low-dose allergen challenge, Schubert R et al., Vol 148, 321-9, 2009 with permission from Karger Publishers

small number of subjects is needed and the method is not dependent of environmental conditions like the seasonal pollen count.

In classical provocation models the dose of the allergen that causes a 20 percent fall in FEV_1 (PD20 allergen) is determined using an incremental allergen challenge. Then the PD20 is compared before and after the treatment with an anti-asthmatic or anti-allergic drug (Figure 2).

Low allergen challenges reproduces the natural allergen exposure. In this model the PD5 is repeated on 5 consecutive days. The procedure induces allergic airway inflammation with increasing eosinophils in sputum and increasing eNO levels (Figure 3). At the same time no asthma symptoms occur, represented by nighttime symptoms or Salbutamol use. High allergen challenges using the PD15 threshold in repeated provocations are designed to induce asthma symptoms and increase rescue medication use. Because of moderate to severe asthma reactions can occur this model should be restricted to experienced centres.

In conclusion, BAP increases our understanding of allergic and asthmatic mechanisms and they are an important tool in the research of new anti-allergic or anti-asthmatic agents.

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3 IMAGING IN ASTHMA

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KEY MESSAGES

- Chest radiography is often the initial imaging modality in asthma, but it is frequently normal even during an acute exacerbation
- When abnormal, the most common chest radiography findings in asthma are bronchial wall thickening and hyperinflation
- Computed tomography (CT) imaging is not routinely recommended in the evaluation of asthma; however, CT imaging may be indicated to evaluate for alternative diagnoses
- In the research setting, quantitative analyses of CT and magnetic resonance imaging (MRI) scans can provide objective ways to measure airway remodeling, air trapping, and ventilation defects

CHEST RADIOGRAPHY

Chest radiographs are generally the initial imaging modality in asthma management. Although not necessary for the diagnosis of asthma, chest radiographs may help identify alternative diagnoses that are associated with wheezing such as anatomic abnormalities, emphysema, left-sided heart failure, or tracheobronchial obstruction (Table 1).

Chest radiographs are generally normal in patients with asthma, even during an acute exacerbation, and the absence of radiograph findings does not rule out a diagnosis of asthma. When abnormal, common, albeit subjective and nonspecific findings that are consistent with a diagnosis of asthma are bronchial wall thickening and hyperinflation. During an acute asthma exacerbation, rare, but sometimes serious, complications such as pneumothorax and pneumomediastinum can also be identified on chest radiograph and should be carefully evaluated for in each patient (Table 1).

COMPUTED TOMOGRAPHY AND ALTERNATIVE DIAGNOSES

CT imaging is occasionally indicated in the workup of asthma when the asthma diagnosis is either unclear or conditions associated with asthma are being considered.

Common findings on CT scans in asthma include bronchial wall thickening, luminal narrowing, endobronchial mucus plugging, and air-trapping (Figures 1 and 2 and Table 1). Bronchial wall thickening is particularly common in asthma, and, when quantified, has been shown to be directly correlated with asthma severity.

Bronchiectasis is another common finding in asthma (present in 30-40% of patients with severe asthma), and its presence is associated with both the duration of asthma and poor lung function.

CT imaging can be particularly useful when asthma-associated diagnoses such as allergic bronchopulmonary aspergillosis (ABPA), chronic eosinophilic pneumonia, and eosinophilic granulomatosis with polyangiitis (EGPA) are being considered. ABPA involves segmental and subsegmental bronchiectasis, frequently in the upper lobes, with mucoid impaction. Chronic eosinophilic pneumonia is associated with peripheral non-segmental ground-glass opacities that are generally predominant in the upper or middle lobes. EGPA is characterized by peripheral-predominant or random consolidations that are often transient and migratory.

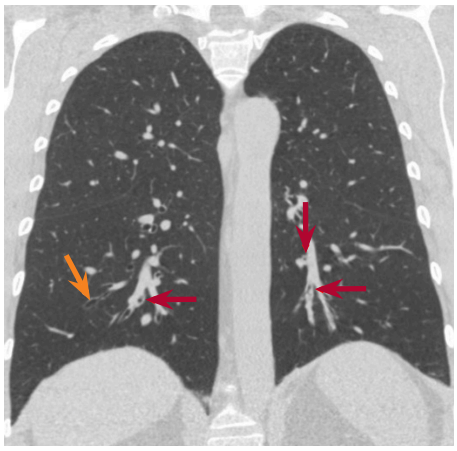

Figure 1 A sample coronal CT image in a patient with severe asthma demonstrates both subsegmental bronchi airway wall thickening (red arrows) as well as focal dilation of a subsegmental bronchus (orange arrow).

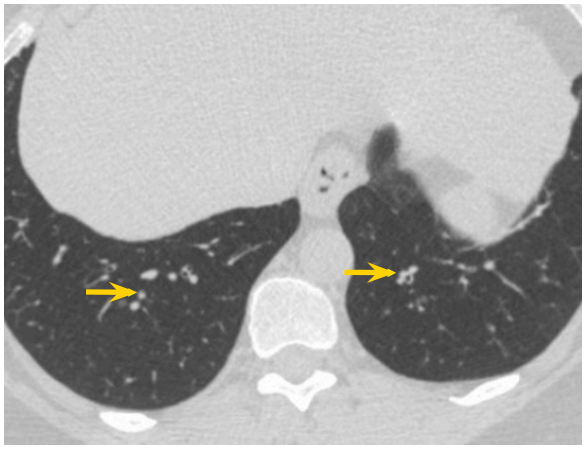

Figure 2 A sample axial CT image in a patient with severe asthma, which is focused on the basilar segments, shows foci of endobronchial mucus impaction (yellow arrows).

TABLE 1

Imaging modalities in asthma

Imaging Modality	Findings	Indications	Disadvantages
Chest radiography	• Many chest radiographs are normal in patients, even during an acute exacerbation • Common radiograph findings include bronchial wall thickening and hyerinflation	• Useful in examining for other conditions that can be misdiagnosed as asthma including anatomic abnormallties, left-sided heart failure, emphysema, and tracheobronchial obstruction • Useful in diagnosing complications including atelectasis, pneumothorax, and pneumomediastinum	• Not clearly indicated for the diagnosis of asthma as findings are non-specific
Computerized tomography	• Many CT scans are normal, even during an acute exacerbation • Common findings include bronchial wall thickening, air-trapping, bronchiectasis, and mucus plugging	• Indicated if alternative diagnoses associated with asthma such as allergic bronchopulmonary aspergillosis (ABPA), chronic eosinophilic pneumonia, or eosinophilic granulomatosis with polyangiltis (EGPA) are being considered • Quantitative CT scans increasingly being used in research settings and have been shown to be associated with important clinical outcomes	• Not clearly indicated for the diagnosis of asthma itself • Cost and radiation exposure (although newer scanners limit exposure)
Magnetic resonance imaging	• Uses inhaled polarized gases and can help identify the regional distribution of ventilation abnormalities	• At this point, nearly exclusively used in the research setting.	High cost and facility expertise required.

QUANTITATIVE IMAGING IN THE RESEARCH SETTING

In the research setting, quantitative CT is increasingly being used to objectively describe airway measurements, the degree of air-trapping and hyperinflation, as well as lung mechanics (Figure 3 and Table 1). Quantitative CT measurements have been associated with asthma severity, longitudinal lung function decline, and the occurrence of future exacerbations. Additionally, magnetic resonance imaging (MRI), particularly with the use of hyperpolarized gases, can help determine the location of ventilation defects in asthma. Although promising, these imaging modalities remain primarily confined to the research setting until further evidence of clinical utility is demonstrated, and costs and automation improve.

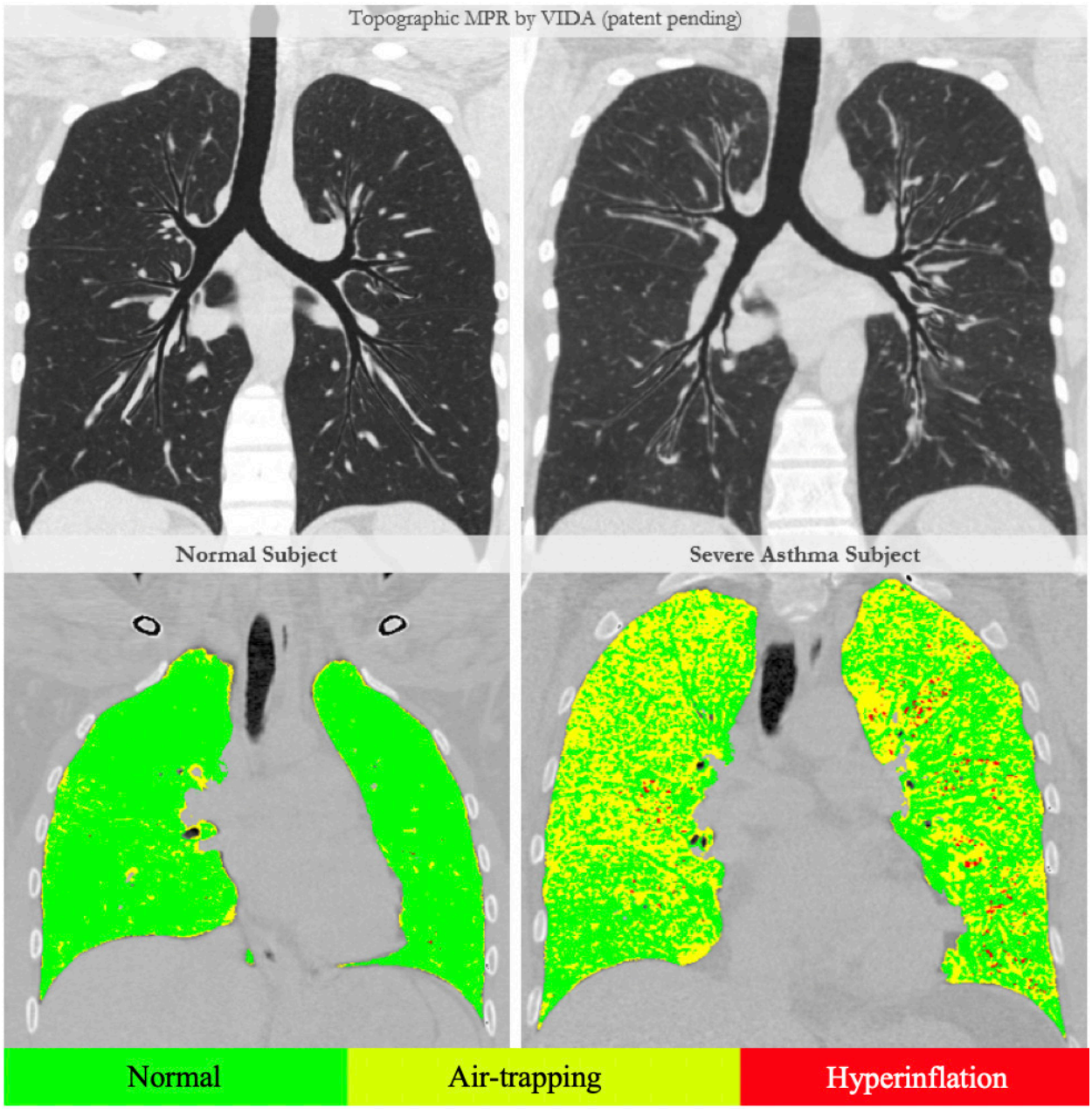

Figure 3 Sample axial images from a patient without asthma (left) compared with a patient with severe asthma (right) using pulmonary imaging analytic software. Bottom images demonstrate differences in areas of air trapping and hyperinflation as elucidated by the imaging software.
(Produced by VIDA Diagnostics, Inc. Coralville, IA)

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4 SPUTUM MEASUREMENTS

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KEY MESSAGES

- Quantitative cytometry on saliva-free, DTT-dispersed sputum provides reliable and repeatable total and differential cell counts in sputum
- Sputum induction with hypertonic saline, after pre-treatment with salbutamol, is safe when performed with careful monitoring of FEV_1
- Raised eosinophils indicates response to steroids and anti-IL5 biologics, while raised neutrophils generally indicates airway infection and poor steroid response
- In addition to cell counts, sputum examination provides opportunities to examine various proteins, growth factors, mediators, gene expression, cell activation markers, exosomes, micro RNA, and to study microbiome, all relevant to the stratified management of airway diseases

Quantitative sputum cytometry provides a relatively non-invasive method to assess the cellular component of airway inflammation. The method of sputum collection is well described and standardised. A low output ultrasonic nebulizer that produces aerosols of less than 5 µm median mass aerodynamic diameter (MMAD) is recommended. Newer vibrating mesh nebulizers with output of flow rate of ~0.2 mL/min and particle size <0.3 µm are also safe and effective. Hypertonic saline inhalation is safe in patients with FEV_1 as low as 0.9L. Spontaneously expectorated sputum, when available, provides just as useful information as induced sputum. Sputum collection is successful in almost all patients with smoker's bronchitis and COPD, in 80% of patients with asthma, and in 60% of patients with a dry chronic cough. Sputum processing and the quantification of cell counts are also standardized and normal values have been established. The most important technical factors to ensure good quality slides are to select sputum plugs from saliva under an inverted microscope, to process not more than 300 mg of sputum, and to adequately disperse with freshly prepared DTT. A schema of the Hamilton protocol is shown in Figure 1.

Sputum cell counts are valid, reliable and reproducible. They are responsive to change of clinical status and monitoring them helps to adjust anti-inflammatory medications in patients with a variety of airway diseases such as asthma, smoker's bronchitis and chronic cough. Sputum counts help to increase corticosteroids in exacerbations associated with an eosinophilic bronchitis, limit the use of corticosteroids in exacerbations associated with a non-eosinophilic bronchitis and indicate the use antibiotics in exacerbations associated with a neutrophilic bronchitis. Sputum cytology also helps to identify patients with an "eosinophil-phenotype" for targeted therapy with anti-eosinophil strategies. Such targeted treatment strategies help to significantly reduce asthma exacerbations and hospitalizations due to exacerbations of COPD. Sputum examination provides additional useful information in patients with airway diseases. For example, macrophages containing haemosiderin can be useful in detecting left ventricular dysfunction and macrophages containing lipid

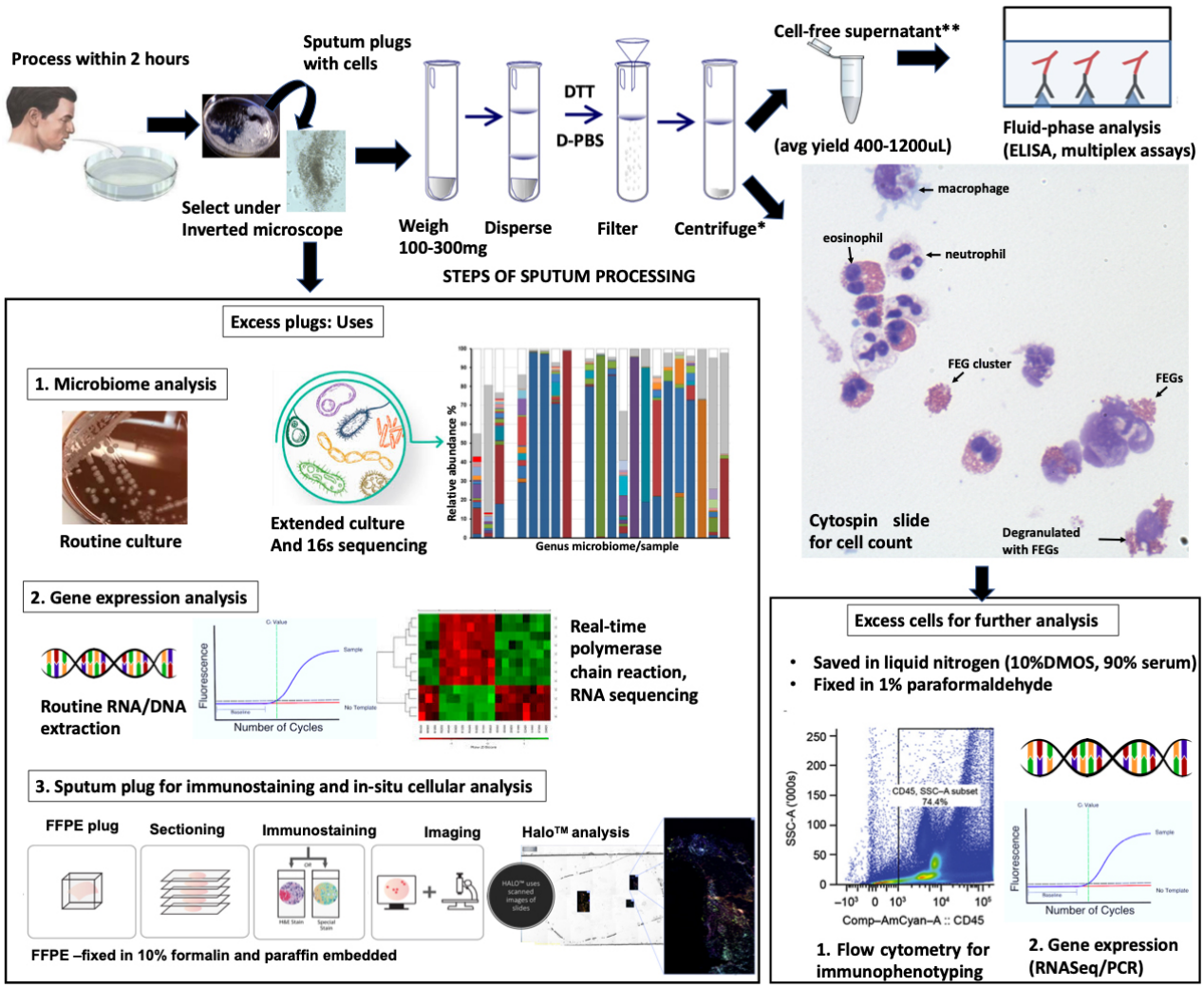

Figure 1 The figure depicts steps of sputum processing including selection under inverted microscope and DTT/PBS dispersal to yield a cell free supernatant and cell pellet used for cytospin slide. The cytospin slides are stained with Wright's stain and 400 cells are counted to report the cell differential. Representative cytospin slide image given here: macrophages, neutrophils, intact eosinophils and free eosinophil granules. Sputum eosinophil% reported was 80% and many free granules for this particular induced sputum. Excess sputum plugs are used for research purposes, and have been validated for microbiome, gene expression and immunocytochemistry. Excess cells from the sputum cell pellet after processing of cytospin slides are again used for research purposes for cellular analysis (rare cells using flow cytometry) and/or gene expression. Please refer to Table 1 for details and reference to particular studies).

*N.B. *care should be taken for centrifuge speed to be less than 350g, to reduce lysis of eosinophils; **best practice includes addition of protease inhibitor cocktail (Roche).*

The sputum processing showed here is based on those detailed by Pizzichini et al Eur Respir J 1996; 9:1174 – 80; also designated as protocol number 1 in compiled article by Kelly et al Eur Respir J 2002: 20May;Supple 37, 24s-39s).

are suggestive of oropharyngeal reflux with microaspiration, both of which can complicate or confuse assessment of airway disease. Representative cytospins are shown in Figure 2.

Over the past decade, measurements in sputum have been extended beyond cell counts. These include but are not limited to cytokines, mediators, growth factors and other proteins, immunoglobulins, and exosomes in the cell-free supernatant, flow cytometry of the cellular fraction, gene expression signatures in RNA extracts, including Covid-19 related genes, deep se-

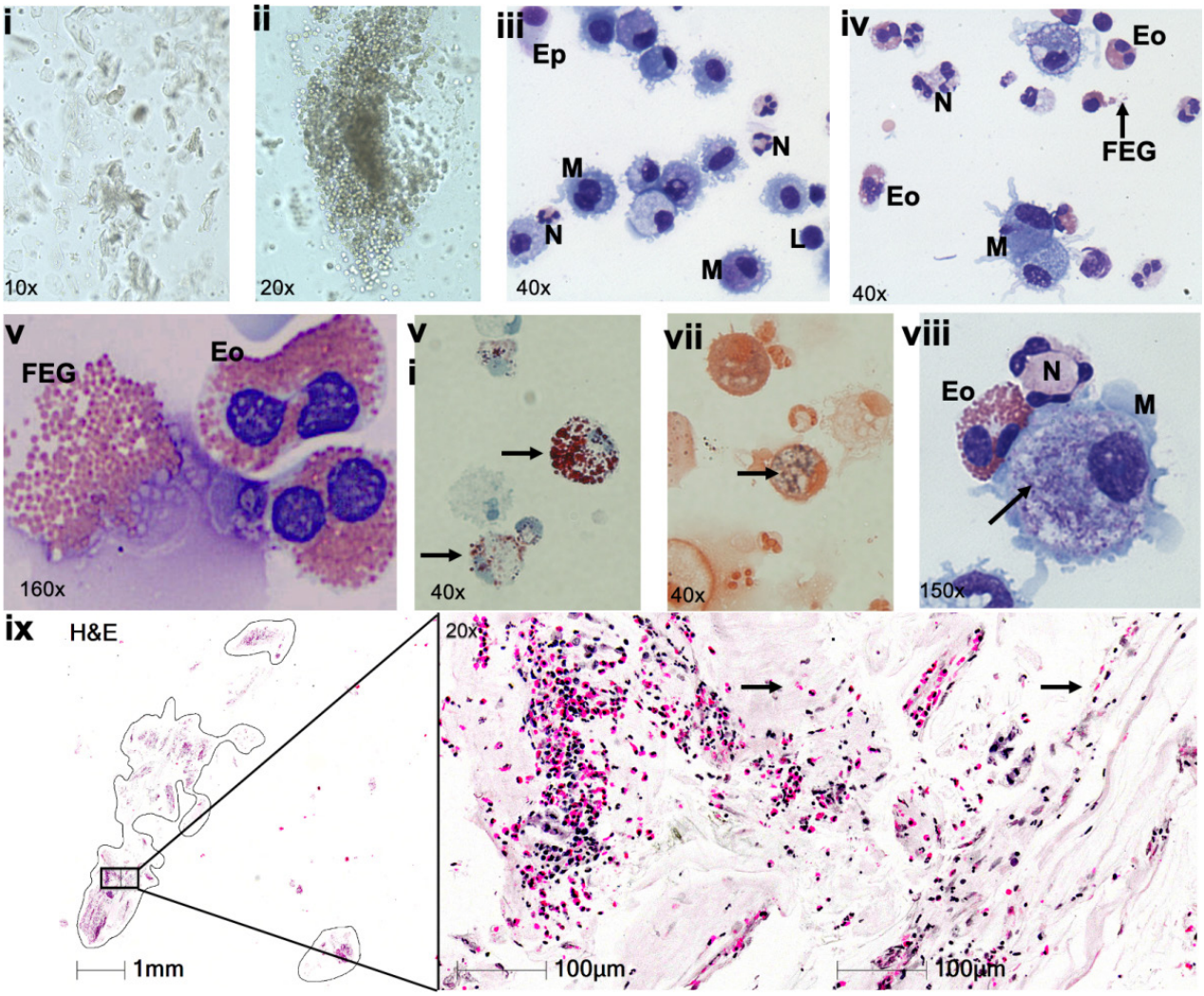

Figure 2 **Cellular components of sputum analysis and staining.** Light microscope image (i) showing squamous cell contamination in unselected sputum plugs (ii) sputum plugs with cells selected under an inverted microscope; cytospin stained (Wright stain) light microscope image of a (iii) healthy sputum showing macrophages (M), epithelial cells (Ep), Lymphocytes (L) and neutrophils (N); and (iv) eosinophilic asthmatic showing intact eosinophils (Eo) and free eosinophils granules (FEGs) (indicated by black arrow), and (v) 160x magnification of an activated eosinophil with shape change and eosinophil cytolysis with release of FEGs. Representative images of macrophages (v) lipids by Oil red and (vi) hemosiderin and (vii) smoker's inclusions (indicated by black arrows). (ix) Scanned image of formalin-fixed paraffin - embedded sputum plug, sectioned and stained with hematoxylin and eosin (H&E immunohistochemistry protocol) for patient whose sputum cell differential using standard sputum processing protocol was 25% eosinophils with many granules. Higher magnification of selected slide (black box) shows intact eosinophils in the sectioned plugs and granules (eosin stain without any nuclei, indicated by arrows)

(acknowledgment: Molecular Phenotyping and Imagine Core Facility, St Joseph's Healthcare, Hamilton, ON, Canada).

quencing and extended microbial cultures, immunohistochemistry etc. These are summarized in Table 1. The European Respiratory Society task force on sputum examination, in 2002, provided detailed reports on every aspect of induction, processing, measurements, promises and pitfalls. It is time that these documents are revisited and updated.

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TABLE 1

Possible measurements in sputum to assess airway inflammation

End-point analysis	Sample type	Methods used	Reference
Cell differential with total cell count	DTT dispersed selected sputum plugs – cellular fraction (cytospin)	Inverted microscope; Wright stain; light microscope	Pizzichini et al. Eur Respir J 1996;9:1174-1180
Free eosinophil granules	DTT dispersed selected sputum plugs – cellular fraction (cytospin)	Inverted microscope; Wright stain; light microscope	Pizzichini et al. Am J Respir Crit Care Med. 1997;155:1501-1508
Fluid-phase mediators (IL-5, IL-8, ECP, MBP, Eicasonoids, tryptase)	Cell-free supernatants (comparative analysis of different processing techniques)	Radioimmunoassay, ELISA	Kelly et al. Eur Respir J 2002;Supple 37:24s-39s
Micro-RNA	Selected sputum plugs	Trizol solubilised and processed Agilent 8 x 15K mouse microRNA array slides (#AMADID21828, AZ, USA)	Li et al. J Allergy Clin Immunol. 2015;136:462-473
Eosinophil peroxidase	DTT dispersed selected sputum plugs – cell free supernatant	Non-commercial ELISA	Nair et al. Allergy 2013;68:1177-1184
IL-5 and IL-8	DTT dispersed selected sputum plugs – cell free supernatant	Validation of commercial ELISA, alkaline phosphatase vs. Multiplex (Eve Technologies, AB, Canada)	Kim et al. J Immunol Methods 2018;454:76-79
Immunoglobulins IgG (IgG_{1-4}), IgM, IgA, IgE	DTT dispersed selected sputum plugs – cell free supernatant	Multiplex Discovery assay (Eve Technologies, AB, Canada)	Ho et al. Allergy 202;75: 2105-2108
Antinuclear antibodies	DTT dispersed selected sputum plugs – cell free supernatant	Human ANA Line Immunoassay strip (IMTEC-ANA-LIA-Maxx; Human Worldwide, Germany) and ANAs using HEp-2 immunostaining (Immco Diagnostics, Inc. NY, USA).	Mukherjee et al. J Allergy Clin Immunol 2018;141:1269-1279
Anti-neutrophil cytoplasmic antibodies	DTT dispersed selected sputum plugs – cell free supernatant – immunoprecipitated with Protein A/G beads	ImmuGlo COMVI c1pANCA IFA kit (Immco Diagnostics, Inc.Buffalo, NY)	Mukherjee et al. Am J Respir Crit Care Med 2019;199:158-170
Anti-EPX antibodies	DTT dispersed selected sputum plugs – cell free supernatant – immunoprecipitated with Protein A/G beads	Non-commercial ELISA	Mukherjee et al. J Allergy Clin Immunol 2018;141:1269-1279
Extracellular DNA and neutrophil extracellular traps	Cell-free supernatant and sputum smears on slides	Quant-iT PicoGreen dsDNA Assay Kit. PLP/sucrose fixed slides stained with SYTOX Green Nucleic Acid Stain (0.5 µM; Invitrogen, CA, USA)	Lachowicz-Scroggins et al. Am J Respir Crit Care Med 2019;199:1076-1085 Wright et al. Respirology 2016;21:467-475
Post translational modifications (halogenated tyrosine residues)	Cell-free supernatants dispersed by DTT (unselected plugs)	micro array ELISA	Jin et al. J Immunol Methods 2014;403:17-25

End-point analysis	Sample type	Methods used	Reference
Sputum gene expression for Th2 high and low subtypes	Processed cells (as per Gershman et al. Eur Respir J 1996;9:2448-53)	RLT lysis buffer and RNAeasy RNA kit (Qiagen, CA, USA), Taqman quantitative PCR	Peters et al. J Allergy Clin Immunol 2014;133:388-394
Sputum 6-gene signature (transcriptomics)	Selected sputum plugs (not processed) stored in RLT buffer	RNAeasy RNA kit (Qiagen, CA, USA), TaqMan real-time qPCR methods (Applied Biosystems, Foster City, Calif	Fricker et al. J Allergy Clin Immunol 2019;144:51-60.e11
Sputum RNA exosome	Cell free supernatant	Electron microscopy with negative ion capture, nanoparticle tracking analysis	Sanchez Vidaurre S et al. J Allergy Clin Immunol 2017; 140:1459-1461
$CD4^+$ lymphocytes, Innate lymphoid cells and intracellular cytokine staining	DTT dispersed-processed cell pellets in 1% paraformaldehyde	Flow cytometry FACS LSR II flow cytometer (Becton, Dickinson Instrument Systems)	Smith et al. J Allergy Clin Immunol 2016;137:75-86.e8
Cell sorting and macrophage isolation	Sputum from cystic fibrosis patients	FACS Aria II (BD Biosciences)	Hisert et al. Am J Respir Cell Mol Biol 2019;61:42-50
Macrophage isolation for invitro	Processed sputum cells in culture	In vitro culture, in-house protocol	Bølling et al. Exp Lung Res 2018;44:312-322
Secreted mucins (MUC2, MUC5AC, and MUC5B)	raw sputum, centrifuged for supernatant	Commercial ELISA (USCN Life Science Inc., China)	Sibilia et al. Ann Am Thorac Soc 2016;13:636-842
Mucus Rheology	Induced sputum unprocessed plugs	Passive microbead rheology (Rheometer, AR1500ex, TA Instruments, New Castle, Delaware)	Hill et al. PLoS One 2014;9:e97980
Immune complex deposition	Formalin fixed paraffin embedded sputum plugs (unprocessed, selected)	Routine H&E, Immunocytochemistry and HALO™ software analysis	Mukherjee et al. Am J Respir Crit Care Med 2019;D101: A7084-A7084 Mukherjee et al. Eur Resp J (in press, 2020)
Microbiome	DTT dispersed sputum	chloroform extraction and DNA recovery with EZ-10 Spin columns (Bio Basic, Ontario, Canada); 16S sequencing (Illumina MiSeq 16s Metagenomic Sequencing Library Preparation Protocol)	Taylor et al. J Allergy Clin Immunol 2018;141:94-103.e15.

Abbreviations: PLP- Periodate-lysine-paraformaldehyde; DTT – dithiothreitol; ELISA – enzyme linked immunosorbent assay

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5 EXHALED NITRIC OXIDE

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Nitric Oxide (NO) is present in exhaled breath and has been implicated as a biomarker of type 2 (T2) inflammation in asthma. It can be measured and used in the diagnosis, monitoring and treatment of asthma. Fractional exhaled NO (FeNO) levels have been shown to predict adult sputum eosinophilia as well as blood eosinophilia. However, exhaled NO and eosinophils are not always concordant as they are driven by different T2 cytokine pathways.

NO is derived from the L-argine amino acid which acts a substrate for the enzyme NO synthase (NOS). An inducible form of this enzyme (iNOS) is produced in response to airway inflammation and as host defence to infections. Proinflammatory cytokines, in particular interleukin-13 can upregulate iNOS expression resulting in increased production of NO (Figure 1). The FeNO can then be measured in the subject's breath providing an indication of the level of T2 inflammation occurring.

KEY MESSAGES

- Increased exhaled nitric oxide levels are associated with type 2 inflammation
- Measurement of exhaled nitric oxide is non-invasive, safe and available at the point of care
- Exhaled nitric oxide has a role in the diagnosis of asthma when combined with other clinical characteristics
- Exhaled nitric oxide can be used to predict response to inhaled corticosteroids (ICS) and monitor adherence to ICS

MEASURING EXHALED NO

FeNO can be measured with non-invasive point of care tests, which are safe in asthmatic patients. The NO levels are measured in a single breath exhaled directly into the analyser at 50 ml/s for around 6 seconds (regulated through exhaling against an expiratory resistance whilst a computer graphic provides feedback to the subject). The process is repeated twice to ensure reproducibility. The exhaled NO levels are measured in parts per billion (ppb) and can be obtained in real time.

FeNO IN THE DIAGNOSIS OF ASTHMA

FeNO can provide an important adjunct in the diagnosis of asthma. However, defining a normal range is problematic and has led to multiple 'cut-off' levels being used in the guidelines (table 1). In the UK the National Institute of Health and Care Excellence (NICE) guidance suggests using FeNO in combination with clinical symptoms and lung function tests in the initial diagnosis of asthma for inhaled corticosteroid (ICS)-naïve patients. NICE uses a cut off >40 ppb in adults and >35 ppb in children (Table 1).

FeNO progressively increases with age and is also affected by height and gender, although the latter may be confounded by height. Furthermore, FeNO levels can be raised by multiple factors including dietary intake. For example, eating nitrogen rich foods, such as lettuce, can temporarily increase FeNO levels by more than 60%. It is important to always consider alternative causes for a raised FeNO level and where appropriate repeat the recording at a future time point. FeNO levels can be lowered by smoking (although T2 asthmatic smokers still have higher FeNO levels than non-asthmatic smokers).

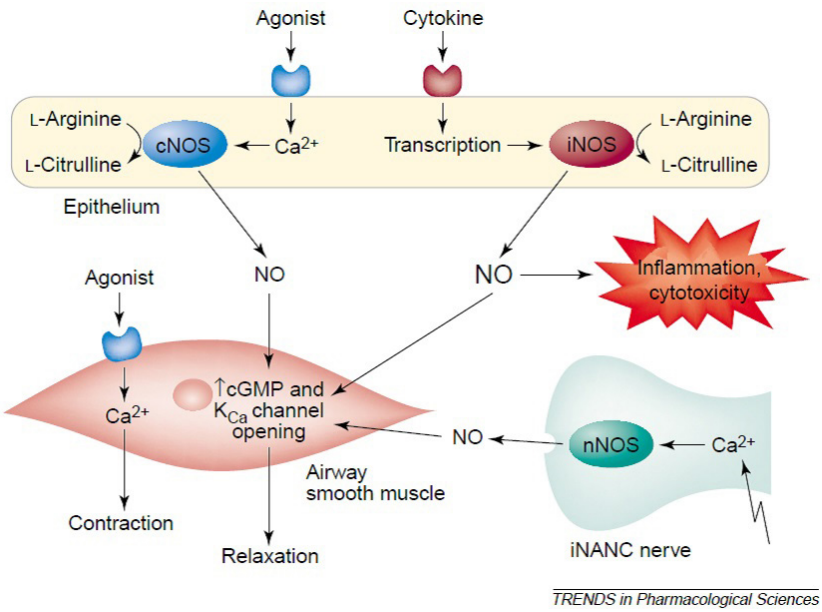

Figure 1 **Production of nitric oxide in asthma.**

cGMP - cyclic guanosine monophosphate; cNOS - constitutive nitric oxide synthase; iNANC - inhibitory non-adrenergic non-cholinergic; iNOS - inducible nitric oxide synthase; nNOS - neuronal nitric oxide synthase; NO - nitric oxide

(Reproduced from Trends in Pharmacological Sciences, 24, Meurs, H., Maarsingh, H. & Zaagsma, J. Arginase and asthma: novel insights into nitric oxide homeostasis and airway hyperresponsiveness., 450-455, 2003, with permission from Elsevier)

TABLE 1

FeNO cut-offs according to different guidelines		
	Positive cut off values for FeNO in asthma	
	Adults	Children
NICE (2017)	>40 ppb	>35 ppb
Scottish Consensus (2019)	>40 ppb ICS naïve patients >25 ppb Patients taking ICS	
GINA (2020)	≥ 20 ppb	
ATS/ERS (2011)	>50 ppb	>35 ppb

ATS: American Thoracic Society; ERS: European Respiratory Society; FeNO: fractional exhaled nitric oxide; GINA: Global Initiative for Asthma; NICE: National Institute for Health and Care Excellence.

PREDICTION OF RESPONSE TO ICS

A raised FeNO is indicative of airway inflammation that is likely to respond to inhaled corticosteroids. Studies have shown an increased response to ICS treatment the higher the baseline FeNO.

FeNO TO MONITOR ADHERENCE TO THERAPY

The suppression of FeNO through ICS therapy allows for its use in the monitoring of ICS therapy. One study used a FeNO suppression test to demonstrate a significant and rapid fall in FeNO after seven days directly observed ICS treatment distinguishing poor adherence from refractory disease.

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6 EXHALED BREATH CONDENSATE

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KEY MESSAGES

- Exhaled breath condensate reflects the airway lining fluid and contains many inflammatory and oxidative stress biomarkers
- It is a safe and non-invasive research tool for investigating the inflammation of asthma
- Larger studies with standardized methodologies using sensitive analytical techniques are needed before it can be clinically useful

Asthma is a heterogeneous disease with different endotypes that are characterized by inflammation of the airways. Since the diagnosis and clinical follow-up of asthma is still a challenge especially in preschool children, a non-invasive method reflecting the airway inflammation which could provide clinically useful biomarkers would be extremely useful. In this respect, exhaled breath condensate (EBC) emerged as a promising tool to monitor airway inflammation.

EBC is a biofluid obtained by cooling the warm humid exhaled breath through a condenser (Figure 1). This system requires just tidal breathing. The samples are collected as fluid or frozen material. It contains various molecules such as cytokines, chemokines, lipid mediators and oxidative stress products that are central in the pathogenesis of asthma. The composition of EBC is presumed to reflect the airway lining fluid.

The results of the EBC studies are unfortunately inconsistent. Compared to the healthy controls, EBC obtained from asthmatic individuals usually contains higher levels of eicosanoids such as cysteinyl leukotrienes, LTB4 or 8-isoprostane, oxidative stress markers and nitric oxide metabolites such as 3-nitrotyrosine, nitrite and, nitrate. While some pro-inflammatory cytokines such as IL-4, IL-6, IL-16, and MCP-1 have been found at higher levels in asthma, the major cytokines of Th2 inflammation IL-5 and IL-13, are usually not present in detectable levels in the EBC of asthmatic children. There are also conflicting results on the acidity and anti-inflammatory mediators such as lipoxin A4 or annexin A5 in the EBC obtained from asthmatic children. Studies that investigated the potential of EBC in the long term follow up of asthma control and in prediction of asthma exacerbations have failed to produce positive results.

Even though it has been more than twenty years since the introduction of EBC in the research field, it is still far from being useful as a clinical tool. There are a number of reasons for this. First of all, the results obtained with the measurement of inflammatory mediators have usually been inconsistent partly due to the heterogeneity among study populations and the methodology used. Many studies have evaluated small sample sizes, used different collecting systems and different methods for analytical measurements that impedes the standardisation of EBC analyses as a diagnostic tool. Secondly, in many studies, the detection rate of mediators remained below detection limits either due to the low concentration of the mediators or to the dilution by the water vapor to varying degrees or to lack of sensitive analytical methods. In addition, it is still unclear how asthma can be distinguished from other chronic pulmonary diseases by the EBC content.

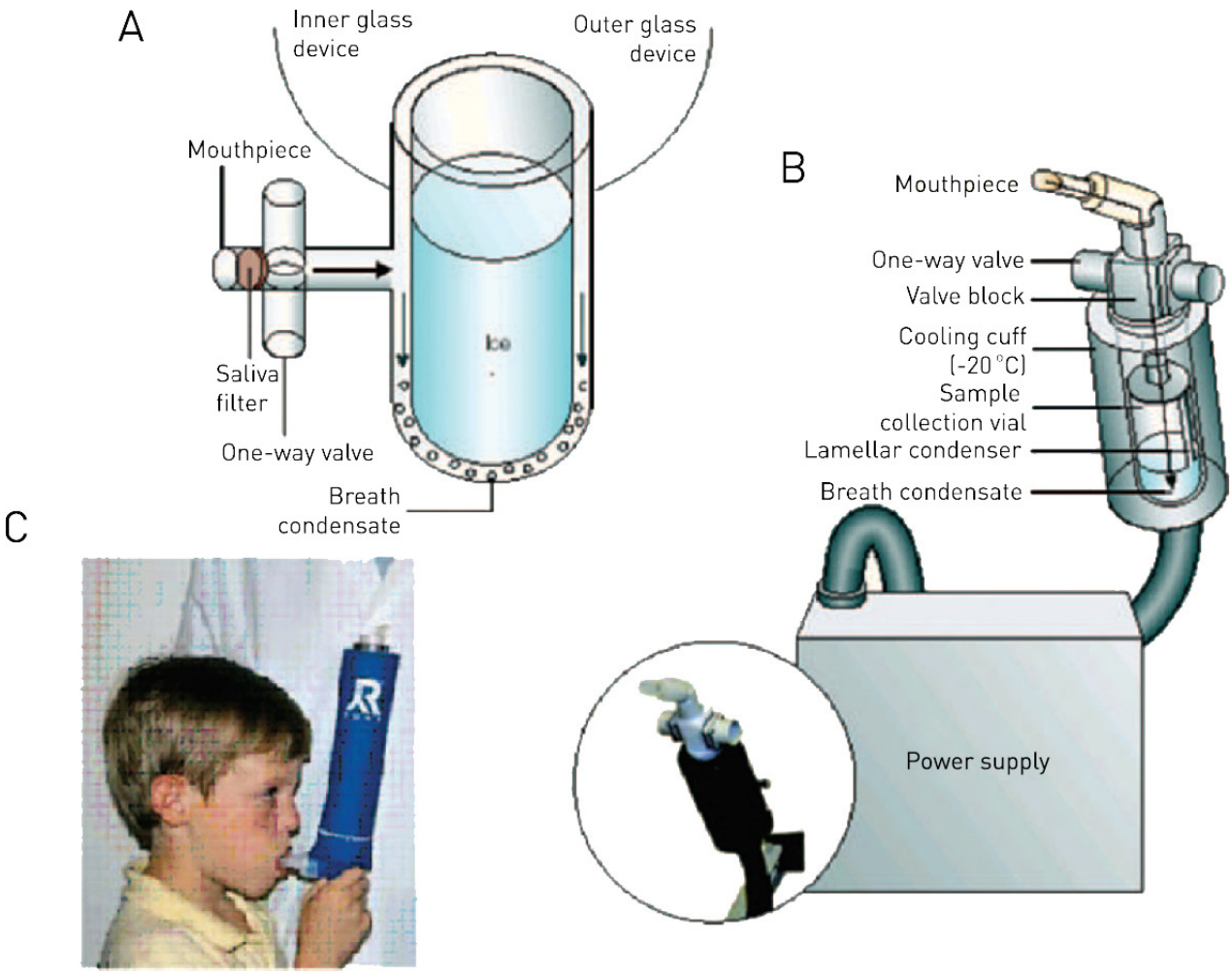

Figure 1 **The principle of collecting the exhaled breath condensate.**
Picture taken from Montuschi P. Analysis of exhaled breath condensate in respiratory medicine: methodological aspects and potential clinical applications. Ther Adv Respir Dis. 2007 Oct;1(1):5-23. DOI:10.1177/1753465807082373

EBC still remains to be a research tool for inflammatory lung diseases such as asthma. In order to be clinically useful, larger studies with standardized methodologies that cluster multiple variables by using omics approaches are needed.

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7 BIOMARKERS

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A biomarker is defined as a characteristic that can be objectively measured as an indicator of a normal, or pathogenic processes, or response to a therapeutic intervention. Biomarkers are useful for diagnosing diseases, assessing their severity, estimating disease prognosis, and predicting responsiveness to therapies.

KEY MESSAGES

- "Companion diagnostics," which can predict therapeutic efficacy, are important for applying biologics to increase their therapeutic effects and to decrease the overall cost of drugs
- Several biomarkers (blood and sputum eosinophils, exhaled nitric oxide (FeNO) and exhaled volatile organic compounds) can be used to identify a "T2-high" endotype with areas under the ROC curve ranging from 0.68 to 0.98
- Blood eosinophils > 400 cells/μL and/or FeNO ≥50 ppb indicate higher risk of asthma exacerbations, whereas blood eosinophils > 400 cells/μL, blood eosinophils ≥ 300 cells/μL and FENO ≥ 25 ppb, serum periostin ≥ 95 ng/mL or a mixed granulocytic pattern in induced sputum seem to be associated with a greater risk of FEV1 decline over time
- Blood eosinophil count and FeNO are used as biomarkers for predicting the efficacy of recently available biologicals for asthma such as anti–IL-5, anti–IL-5 receptor or anti–IL-4 receptor α-chain antibodies

BIOMARKERS TO IDENTIFY ASTHMA ENDOTYPES

Endotypes are biologically related asthma subtypes. From a very general point of view, we can distinguish two groups of asthma endotypes: "T2-high" and "T2-low". This rather simple classification has been shown successful to direct therapy more specifically than relying only on clinical features. However, there is not a clear definition of what we mean by "T2-high" and this concept varies depending on the reference standard used: eosinophilia in sputum, broncho-alveolar lavage (BAL), bronchial biopsy or in blood, or a transcriptomics signature consistent with increased expression of T2 inflammatory mediators (i.e. cytokines). Moreover, both "T2-high" and "T2-low" endotypes are heterogeneous, encompassing a variety of subendotypes representative of distinct pathobiological mechanisms. The most scrutinized biomarkers in asthma are those related to a "T2-high response" with few studies evaluating biomarkers to identify a "T2-low response". Table 1 summarizes the performance of the most frequently analyzed. Serum dipeptidyl peptidase-4 (DPP-4) does not correlate with other T2 biomarkers such as periostin, IgE, FeNO or blood Eos. Urine eicosanoids were found to be significantly associated with T2 biomarkers, but more data are needed. Higher circulating YKL-40 levels consistently associates with clusters of patients displaying evidence of T2-low inflammation, but it was unable to discriminate between T2-high and T2-low endotypes. Combinations of markers did not show a significant improvement in the diagnostic accuracy compared with single ones, except in one study.

TABLE 1

Biomarkers used to identify asthma endotypes

Biomarker	Endotype	Sample	Performance according to the reference standard
Eos	T2-high	Blood	AUC 0.89 (Sputum Eos) Wagener et al. Thorax 2015 AUC 0.71 (Sputum Eos) Jia et al. JACI 2012 AUC 0.83 (Sputum Eos) Westerhof et al. Eur Respir J 2015 AUC 0.69 (34 IL-13 genes transcriptomic signature in bronchial brushing) Pavlidis et al. ERJ 2018 AUC 0.78 (Sputum Eos). Meta-analysis. Korevaar et al. Lancet Respir Med 2015
Eos	T2-high	Sputum	AUC 0.78 (34 IL-13 genes transcriptomic signature in bronchial brushing) Pavlidis et al. ERJ 2018
Eos	T2-high	Nasal	AUC 0.89 (Sputum Eos) de Farias et al. Respirology 2017 AUC 0.84 (Sputum Eos) Amorim et al. Clin Exp Allergy 2010
EPX	T2-high	Nasal	AUC 0.89 (Sputum Eos) Rank et al. Allergy 2016
FENO	T2-high	Breath	AUC 0.78 (Sputum Eos) Wagener et al. Thorax 2015 AUC 0.79 (Sputum Eos) Jia et al. JACI 2012 AUC 0.82 (Sputum Eos) Westerhof et al. Eur Respir J 2015 AUC 0.68 (34 IL-13 genes transcriptomic signature in bronchial brushing) Pavlidis et al. ERJ 2018 AUC 0.74 (Sputum Eos). Meta-analysis. Korevaar et al. Lancet Respir Med 2015
Periostin	T2-high	Serum	AUC 0.55 (Sputum Eos) Wagener et al. Thorax 2015 AUC 0.84 (Sputum Eos) Jia et al. JACI 2012 AUC 0.55 (34 IL-13 genes transcriptomic signature in bronchial brushing) Pavlidis et al. ERJ 2018
Total serum IgE	T2-high	Serum	AUC 0.62 (Sputum Eos) Jia et al. JACI 2012 AUC 0.62 (34 IL-13 genes transcriptomic signature in bronchial brushing) Pavlidis et al. ERJ 2018 AUC 0.63 (Sputum Eos). Meta-analysis. Korevaar et al. Lancet Respir Med 2015.
EVOC	T2-high	Breath	AUC 0.79 (Sputum Eos) Ibrahim et al. Thorax 2011 AUC 0.98 (Sputum Eos) Plaza et al. J Investig Allergol Clin Immunol 2015 AUC 0.71 (Sputum Eos) Schleich et al. Am J Respir Crit Care Med 2019
	T2-low		AUC 0.98 (Sputum Eos) Plaza et al. J Investig Allergol Clin Immunol 2015 AUC 0.71 (Sputum Eos) Schleich et al. Am J Respir Crit Care Med 2019
TS	T2-high vs T2-low	Sputum	AUC 0.89 (Sputum cellularity) Baines et al. JACI 2014

Eos = Eosinophils; EPX = Eosinophil peroxidase; AUC = Area under the ROC curve; IgE: Immunoglobulin E; EVOC = Exhaled volatile organic compounds; TS = Transcriptomic signature of 6 genes (CLC, CPA3, DNASE1L3, IL1B, ALPL, C-X-C motif).

BIOMARKERS TO PREDICT FUTURE RISK OF ASTHMA

There is a need for biomarkers to predict future risk in asthma patients (mainly severe exacerbations and accelerated FEV1 decline). Several longitudinal studies have found conflicting results according to the duration of follow-up, the characteristics of the included population, the severity of the disease or the therapeutic strategies employed. Figure 1 lists biomarkers identified as predictors of adverse asthma outcomes.

BIOMARKERS TO PREDICT RESPONSE TO THERAPY

"Companion diagnostics," which can predict therapeutic efficacy, are important for applying biologicals to increase their therapeutic effects and to decrease the overall cost of drugs. Although no companion diagnostic has been officially set for omalizumab, an anti–IgE monoclonal antibody (mAb), several T2 biomarkers—FeNO, blood eosinophil count, and serum periostin—have been reported to be positively correlated with omalizumab's ability to reduce exacerbations. Blood eosinophil count is the best-established biomarker for predicting the efficacy of anti–IL-5 or anti–IL-5 receptor mAb such as

TABLE 2

Companion diagnostics for biologicals for asthma (based on the results of phase 3 studies)

Drug	Biomarker	Value	Efficacy
Omalizumab	Independent of biomarkers		Decrease of exacerbation Improvement of FEV1 Improvement of asthma symptoms Glucocorticoid-sparing effect
Mepolizumab	Blood eosinophil	≥ 150 cells/µL	Decrease of exacerbation Improvement of asthma symptoms Glucocorticoid-sparing effect
Reslizumab	Blood eosinophil	≥ 400 cells/µL	Improvement of FEV1 Improvement of asthma symptoms Glucocorticoid-sparing effect
Benralizumab	Blood eosinophil	≥ 150 cells/µL	Decrease of exacerbation Improvement of FEV1 Improvement of asthma symptoms Glucocorticoid-sparing effect
Dupilumab	FeNO	≥ 25 ppb	Improvement of FEV1 Decrease of exacerbation Glucocorticoid-sparing effect
	Blood eosinophil	≥ 150 or 300 cells/µL	Improvement of FEV1 Decrease of exacerbation Glucocorticoid-sparing effect

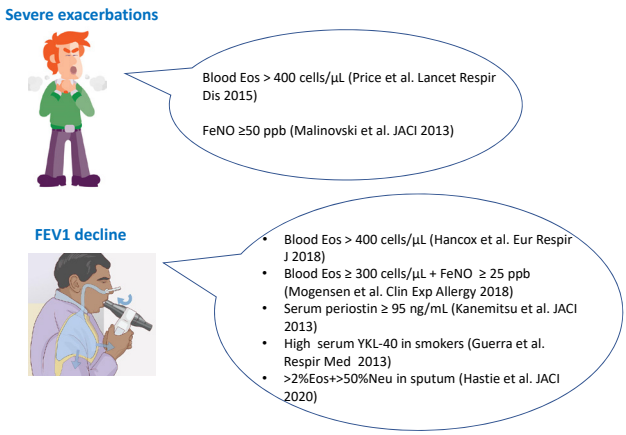

Figure 1 Biomarkers to predict asthma related adverse outcomes. Evidence from longitudinal studies.

mepolizumab, reslizumab, and benralizumab, whereas FeNO and IgE are less effective in predicting their efficacy. In the phase 3 studies, the criterion "blood eosinophil count ≥ 150 cells/µL" was critical to predict the efficacy of mepolizumab and benralizumab, whereas blood eosinophil count ≥ 400 cells/µL was set as the criterion for reslizumab.

In the phase 3 study with dupilumab, the anti–IL-4 receptor α-chain mAb that blocks both IL-4 and IL-13 signals, both high baseline FeNO (≥ 25 ppb) and high blood eosinophil count (≥ 150 cells/µL or ≥ 300 cells/µL) were able to predict its efficacy. The value of each biological as companion diagnostic is summarized in Table 2.

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8 OMICS

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KEY MESSAGES

- Omics represents a key tool for precision medicine
- New biomarkers will allow better diagnosis strategies
- Integration of omic and clinical data will lead to personalised medicine
- Deeper knowledge of the mechanisms underlying allergy and asthma will converge into novel patient management approaches

Omics technologies are based on the acquisition and analysis of a large data volumes, using fast and automated high-performance methods. They have brought along a paradigm shift in the development of research strategies. Genomics, Epigenomics, Transcriptomics, Proteomics and Metabolomics are by now widely applied to identify biological variants, to characterize complex biochemical systems, to study pathophysiological processes and to define new biomarker strategies (Figure 1). Each omics discipline provides different information on the regulation of gene expression in health and diseases such as asthma (Figure 2).

GENOMICS

Genomics is the study of the DNA and its associated alterations of a specific tissue/cell. Genomic studies in asthma focused on candidate gene approaches (specific genes linked to asthma outcomes). In 2007, the first genome-wide association study (GWAS) enabled the detection of previously undescribed genes. Today, 38 loci have been associated with asthma; among these, 17q12-21 is the most consistent cluster of genes. This locus harbours the *ORMDL3* (orosomucoid-like 3) and *GSDMB* (gasdermin B) genes, underlying airway remodeling and responsiveness in asthma.

EPIGENOMICS

Epigenetic modifications consisting of DNA methylation and post-translational histone modifications contribute to the control of gene expression by modulating DNA accessibility and protein interactions. They can therefore mediate the interaction with the environment, also in the context of asthma. In a series of epigenome-wide association studies (EWAS), differentially methylated CpGs associated with asthma were identified, with stronger effects, better correlations with gene expression changes and increased reproducibility when nasal epithelial cells rather than blood samples were used.

TRANSCRIPTOMICS

Transcriptomics is the science that studies the transcriptome, i.e. the sum of all RNA transcripts present in one or a population of cells (mRNA, rRNA, tRNA, miRNA and other non-coding RNAs). As the transcriptome is different among cell populations and varies with environmental conditions, choosing the appropriate sample compartment and disease phenotypes are key elements for transcriptomic analyses. Analysing the transcriptome of different biological samples (sputum, nasal brushings, and endobronchial brushings/biopsies) in the U-BIOPRED project identified a set of differentially expressed genes (DEG) associated with asthma severity that could be potential biomarkers.

PROTEOMICS

Proteomics approaches range from high-throughput mass-spectrometry based methods that mainly identify more abundant proteins, to targeted methods focused on smaller sets of proteins such as Western blotting or multiplex assays (Luminex, Simoa, OLINK, etc.). Proteomics can capture molecular information on proteotypes that cannot be retrieved otherwise, e.g. on post-translational modifications, protein interactions and localization. In a proteomics study using asthma patient's sputum, molecular subphenotypes were identified corresponding to the known eosinophilic, neutrophilic and atopic asthma phenotypes, and further studies are expected to yield more information.

METABOLOMICS

Metabolomics focusses on the study of compounds defined as metabolites that encompass the metabolism of a living organism/tissue/cell. Characterization of the metabolic profile has the potential to capture metabolic alterations in asthma and has revealed alterations in cellular energy, amino acid, oxidative stress, fatty acid, sphingolipid and phospholipid metabolism. For example, the lipid mediator sphingosine-1-phosphate (S1P) regulated by ORMDL3 has been associated with increased bronchiolitis severity, and nitric oxide (NO) with airway inflammation and asthma severity.

CONCLUSIONS

Combined omics analyses provide a system biology view of complex diseases such as asthma. Table 1 shows some relevant omic biomarkers and their role in asthma. In the next years integration of omics and non-omics data has the potential of

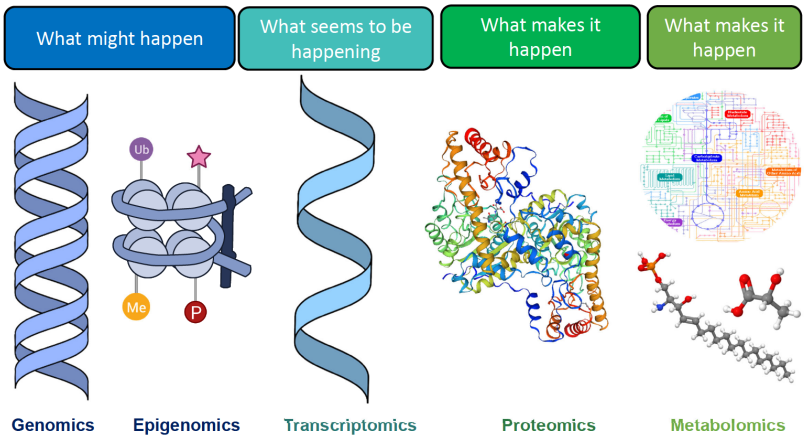

Figure 1 **Omic sciences and their aim.**

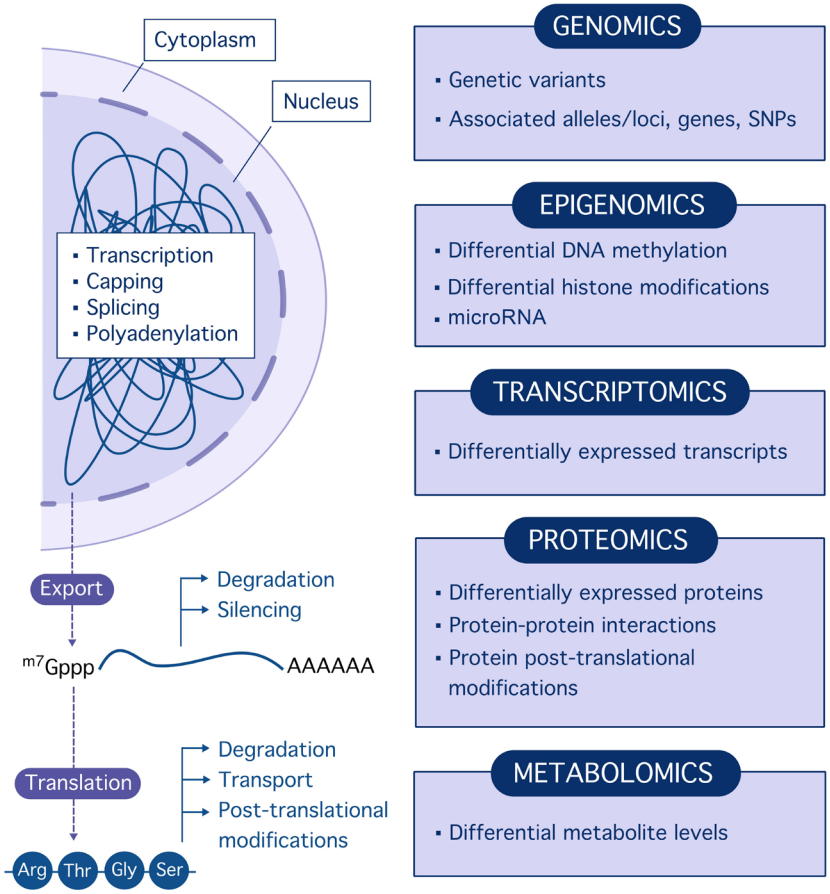

Figure 2 **Gene expression and the type of information that can be obtained on its regulation in the different omics disciplines.**

TABLE 1

Omics biomarkers in asthma

Omic science	Biomarkers/biological pathways	Description	Reference
Genomics	17q12-21 (GRB7, IKZF3, ZPBP2, GSDMB, ORMDL3, GSDMA)	Chilhood-onset asthma	Abdel-Aziz et al. (2020)
	2q12 (IL18R1, IL1RL1, IL1RL2)	IL1RL1 encodes the receptor for IL33 (proinflammatory danger signal expressed in damaged airway epithelium)	Willis-Owen et al. (2018)
Epigenomics	PDE6A, METTL1, CES4A, GJA4, SPP2, CDHR3, GRK5, FBXL7, LINC00704, ANKRD31, C22orf31, SUCNR1, NTRK1, PLEC, PCSK6, CAPN14, SYNPO, TSHR, NCF2, PCSK6, NUP98, BANF2, EFNA5, C15orf54, LRRFIP1, ZPLD1, CDH26, CUOX1, ADCK1, C15orf54	Top 30 EWAS linked to atopic asthma	Forno et al. (2019)
	LDLRAD3, ATXN7L1, METTL1, LINC00703, PCSK6, CDC45, LOC152225, C15orf54, CUOX1, EPPK1	Top 10 DMRs linked to allergic asthma	Yang et al. (2017)
	EPX, SORCS2, TREM2, FAM168A, SBNO2, ACOT7, LINC01140, RASSF2, GABBR1, ZBTB48, RGS3, COL15A1	Top 12 DMRs linked to allergic asthma	Cardenas et al. (2019)
Transcriptomics	Leukocyte gene signature Lung injury gene signature	Adult asthma cohort	Hekking et al. (2018)
	T-helper cell type 2 cytokines Lack of corticosteroid response	Epithelial brushings and bronchial biopsies	Kuo et al. (2017)
Proteomics	NGAL, G3P, HV320, TCO1, MYH13, LDHA, TPIS, MYH7, CFAB, AL3B1, ILEU, CLUS, LG3BP, PROL4	Sputum protein profile for Eosinophilic asthma	Schofield et al. (2019)
	LYSC	Sputum protein profile for Highly atopic asthma	
	TKT, CATA, PEDF, LG3BP, BP1B1, MUC1, CFAB, ALDOA, ZG16B, IGHG1, HEMO, A1AT, FIBG, TKT, TALDO	Sputum protein profile for Neutrophilic asthma	
Metabolomics	Sphingosine-1-phosphate	Associated with increased bronchiolitis and asthma severity	Zhu, Zhaozhong et al. (2019)
	Nitric oxide	Increased airway inflammation Asthma severity	Kelly, Rachel et al. (2017)

DMRs: differentially methylated regions, EWAS: epigenome-wide association studies

changing current asthma practices with a deeper understanding of the underlying mechanisms and a high impact on personalized diagnosis and intervention.

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Section E

MAJOR CURRENT PROBLEMS IN ASTHMA

1 UNMET NEEDS IN ASTHMA

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KEY MESSAGES

- The greatest unmet need is to reduce asthma deaths, by facilitating access to affordable high quality controller medications in low-middle income countries
- Asthma exacerbations are burdensome for patients and the healthcare system, and they have multiple different triggers. Exacerbation risk needs to be reduced based on the evidence from recent treatment advances in mild asthma facilitating the understanding of the underlying mechanisms
- Increased support for personalisation of asthma treatment across the spectrum of asthma severity is advocated, by better characterisation of asthma patients and by standardised recording of all asthma-related outcomes, both in clinical trials and in clinical practice
- There is a great need for better communication about asthma, not only between people with asthma and their healthcare providers, but also with their family, friends and the broader community, to promote understanding of the impact of asthma

Asthma is a condition of paradoxes – highly prevalent in many countries but rare in others, well-known to run in families but with no clear genetic risk factors, able to be controlled in most patients with medications that have been available for decades yet still responsible globally for over 420,000 deaths a year and 23.7 million disability-adjusted life years (DALYs), and with the medications most widely used to treat asthma symptoms (short-acting beta2-agonists, SABA) known to increase the risks of severe asthma exacerbations and deaths even at modest levels of use.

From a global perspective, the most important unmet need is to reduce deaths in adults and in children, particularly in low and middle income countries where, despite major gains in the past 30 years, asthma mortality rates are still 8 times higher than in high income countries. Key to meeting this objective is providing wide access to affordable high-quality inhaled corticosteroid (ICS)-containing medications, within a healthcare system framework that facilitates correct and timely asthma diagnosis together with efficient delivery of asthma care and monitoring of outcomes. Introduction of free or subsidised ICS in many countries has been associated with marked improvement in asthma outcomes, but processes to ensure equitable access are still needed.

A closely related need is to reduce severe exacerbations in both children and adults, and to reduce the need for oral/systemic corticosteroids, because of increasing evidence about their harm. The environmental triggers and background risk factors for exacerbations are diverse, but there are some distinctive patterns that suggest specific (albeit complex) underlying mechanisms and potential treatment targets (Table 1). These include the well-recognised 'back to school' epidemics of asthma exacerbations among children in autumn each year, with childhood hospitalisation remaining an unpleasant memory for many patients through into adult life. Patients with poorly con-

TABLE 1

Strategies for preventing asthma exacerbations and minimising their impact	
Prevention of asthma exacerbations	
Recognise who is at risk	• Patients with uncontrolled asthma symptoms • Patients with other potentially modifiable risk factors, independent of asthma symptom control, e.g. SABA over-use, poor adherence with ICS, environmental exposures (smoking, air pollution, allergens, occupational), comorbidities (allergic rhinitis, obesity, chronic rhinosinusitis, confirmed food allergy, pregnancy), major psychological or socioeconomic problems, low lung function, sputum or blood eosinophilia • Patients with a history of one or more exacerbations in the last year, or ever in ICU
Treat to minimise risk of exacerbations	Therapeutic strategies that reduce the risk of severe exacerbations • Low dose ICS more than halves the risk of asthma death, halves the risk of severe exacerbation, even in patients with symptoms once a week or less • In mild asthma, as-needed low dose ICS-formoterol reduces the risk of severe exacerbation by two-thirds compared with SABA alone; and to a similar extent as daily ICS at less than a quarter of the dose • Combination ICS-LABA reduces the risk of severe exacerbations by 17% compared with the same dose of ICS • In patients at risk, maintenance and reliever therapy with ICS-formoterol reduces the risk of severe exacerbations by 32% vs same dose ICS-LABA and by 23% vs higher dose ICS or ICS-LABA • For patients with exacerbations despite GINA step 4-5 treatment, severe exacerbations can also be reduced by add-on tiotropium or by add-on low dose azithromycin • For patients with severe asthma, targeted add-on biologicals (benralizumab, dupilumab, mepolizumab, omalizumab, reslizumab) reduces the rate of severe exacerbations by 30 to 50 %
	Targeted management of modifiable risk factors • Adherence-promoting strategies (e.g. shared decision-making, inhaler reminders, monitoring of prescription filling) • Reducing exposure to environmental tobacco smoke, outdoor pollutants and allergens • Diet high in anti-oxidants • Bariatric surgery in the extreme obese • Sputum cytology-guided treatment (in moderate-severe asthma)
Provide patients with a written asthma action plan	• In combination with self-monitoring of symptoms and/or PEF (PEF only in adults) and regular medical review, written asthma action plan reduces risk of exacerbations • See GINA 2020 report, Box 4-2 for specific regimen changes suitable for 'yellow zone' of written asthma action plan
Downsize the impact of asthma exacerbations	
Improve acute management	• Avoid over-use of SABA; no benefit from giving them regularly rather than as-needed in hospital/ICU • Puffer and spacer preferred option to nebuliser with the exception of life-threatening exacerbations
Minimise side-effects of treatment	• Consider the serious short-term and long-term side-effects of oral corticosteroids (OCS). Optimise inhaled therapeutic regimen, adherence, inhaler technique and action plan to reduce need for OCS • If OCS are needed, prescribe morning dosing to reduce insomnia and avoid suprarenal inhibition • Advise about tapering SABA use as soon as possible
Provide emotional and social support	• Exacerbations can be terrifying for patients and their families, and may contribute to long-term anxiety. Arrange follow-up visit to ensure the patient has recovered from the exacerbation, and provide advice about how to prevent future exacerbations; provide mental health support if needed • See www.healthtalk.org/asthma and www.healthtalkaustralia/severe-asthma to understand patient experiences of exacerbations

GINA: Global Initiative for Asthma, www.ginasthma.org; ICS - inhaled corticosteroids; ICU - intensive care unit; LABA - long-acting beta2-agonists; OCS - oral corticosteroids; PEF - peak expiratory flow; SABA - short-acting beta2-agonists

trolled symptoms are more likely to experience exacerbations, but severe exacerbations can occur even in apparently mild or controlled disease. Recent evidence from almost 10,000 patients with mild asthma, showing that severe exacerbations can be reduced by two-thirds with as-needed budesonide-formoterol compared with SABA alone, and to a similar or greater extent as with regular ICS, regardless of patients' baseline inflammatory status, demands investigation of how these findings can improve the current understanding of the mechanisms of asthma and of exacerbations.

Across the spectrum of asthma severity, patients and clinicians need more evidence about how best to choose between available treatment options to meet individual patient needs. Although most attention has been given to phenotype-guided treatment in severe asthma, treatment can already be personalised to some extent even in mild-moderate asthma by taking into account patients' individual risk factors and comorbidities and their individual preferences and treatment goals, and by incorporating both pharmacologic and non-pharmacologic interventions. However, to make progress towards the ultimate goal of precision medicine in asthma, two key elements are needed in clinical trials and in daily practice: extensive baseline characterisation of patients, and standardisation of asthma-related outcomes. At present, the tools that seem most likely to radically advance knowledge about the heterogeneous mechanisms of asthma, and to inform the choice of therapy (or developments of new therapies), are those that assess biomarkers in exhaled breath, "breathomics". There is a particular need for evidence about early identification of patients who are later found to be relatively refractory to ICS, to allow fast-tracking to specialist investigation, multidisciplinary care and potential biologic therapy; and treatment options for severe non-T2 asthma and other clinical phenotypes such as asthma with persistent airflow limitation, and asthma with mucus hypersecretion.

Finally, there are substantial unmet needs around communication about asthma to patients, healthcare professionals, families and the broader community. Asthma needs to be destigmatised, but at the same time its physical, emotional, social and economic burden on patients and their families should be fully acknowledged. One example is the meticulously-prepared resources on healthtalk.org/asthma and healthtalkaustralia.org/severe-asthma. These provide, in patients' own voices, their unique perspectives on asthma and its unmet needs.

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2 ASTHMA EXACERBATIONS

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KEY MESSAGES

- Acute asthma exacerbations are potentially life-threatening events that require prompt treatment to prevent serious outcomes
- Respiratory virus infections are the commonest trigger for asthma exacerbations
- There is a clear relationship between eosinophilic inflammation and asthma exacerbation risk
- Exacerbations are associated with poor adherence to or poor inhaler technique with ICS, overuse of short-acting β2-agonists and comorbidities including obesity, gastro-oesophageal reflux and chronic sinusitis
- Patient education alongside pharmacological management are central to asthma exacerbation prevention
- In severe asthma, exacerbations can be substantially reduced by targeting T2 inflammation with biologicals against IgE, IL-5, IL-5R and IL-4R

The Global Initiative for Asthma (GINA) defines asthma exacerbations as "*episodes characterised by a progressive increase in symptoms of shortness of breath, cough, wheezing or chest tightness and progressive decrease in lung function*". Exacerbations constitute the greatest immediate risk to patients, are associated with accelerated decline in lung function over time, have an adverse impact on health-related quality of life and are associated with a significant financial burden to healthcare systems. Airflow obstruction during exacerbations stems from a combination of concentric smooth muscle contraction, airway wall oedema, airway inflammatory cell infiltration and luminal obstruction with mucus and cellular debris (Figure 1).

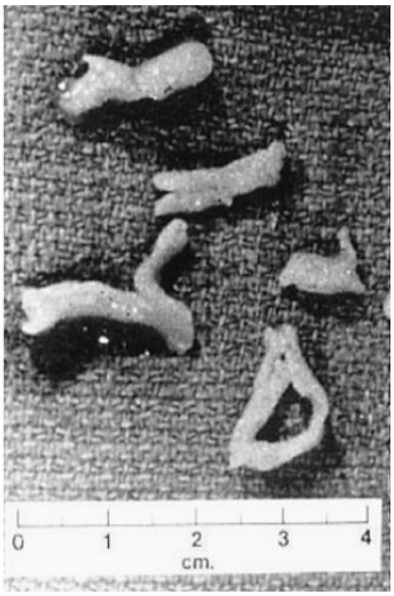

Figure 1 Airway casts recovered from an asthma patient during an acute exacerbation.
(Reproduced from Ann Allergy, Vol 67, Lang DM et al., Safety and possible efficacy of fiberoptic bronchoscopy with lavage in the management of refractory asthma with mucous impaction, 324-30, 1991 with permission from Elsevier)

EPIDEMIOLOGY

The frequency with which asthma exacerbations are reported in the clinical trial literature ranges from 0.3-0.9 per patient per year and varies according to the definition of exacerbation used, disease severity and level of disease control in the asthma population being studied. However, surveys of 'real life' asthma patients indicate that the incidence of exacerbations is much higher, particularly in those with poorly controlled disease.

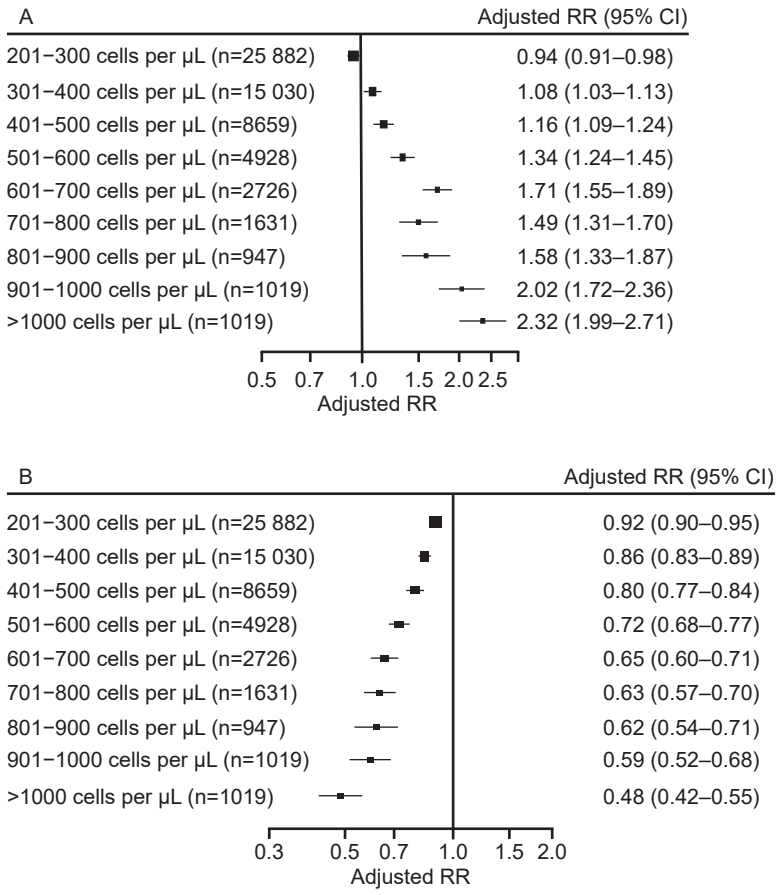

Figure 2 Blood esoinophils predict the risk of asthma exacerbation. A. The adjusted rate ratio (RR) for severe asthma exacerbations increases with ascending blood eosinophil count. B. The adjusted odds ratio (OR) for overall asthma control decreases with ascending blood eosinophil count, indicating that a deterioration in disease control occurs as blood eosinophil count rises. Ratios are relative to a reference category in which blood eosinophil count was < 200 cells per µl during the first outcome year.

(Reproduced from Lancet Respir Med, Vol 3, Price DB et al., Blood eosinophil count and prospective annual asthma disease burden: a UK cohort study, 849-58, 2015 with permission from Elsevier)

AETIOLOGY AND RISK FACTORS

Respiratory virus infections are the commonest cause of asthma exacerbations: 80-85% of exacerbations among school aged children with asthma are caused by respiratory viruses. In early life, respiratory syncytial virus bronchiolitis/lower respiratory tract infection is linked to development of recurrent wheeze and asthma in later childhood. Among adults, rhinovirus (RV) infection is the leading cause of asthma exacerbations. Other viral causes of exacerbations include influenza, parainfluenza, coronavirus, adenovirus and human metapneumovirus. Deficiencies in host immunity, particularly in type I/III interferon responses to viruses, predisposes people with asthma to virus-induced exacerbations. This appears to be most significant in the presence of active type 2 (T2) / eosinophilic airways inflammation and explains why therapies that inhibit this inflammatory cascade can reduce exacerbation risk.

Asthma patients who have an elevated blood eosinophil count (particularly > 300 cells per µl) are at increased risk of having severe exacerbations and poorer disease control (Figure 2). Elevated levels of the other commonly used biomarker of T2 inflammation, fraction of exhaled nitric oxide (FeNO), are also associated with greater exacerbation risk. Indeed, titrating inhaled corticosteroids (ICS) using FeNO levels reduces exacerbation frequency (Figure 3).

Additional risk factors for exacerbations include poor adherence to ICS (especially with over-reliance on short-acting β2-agonists),

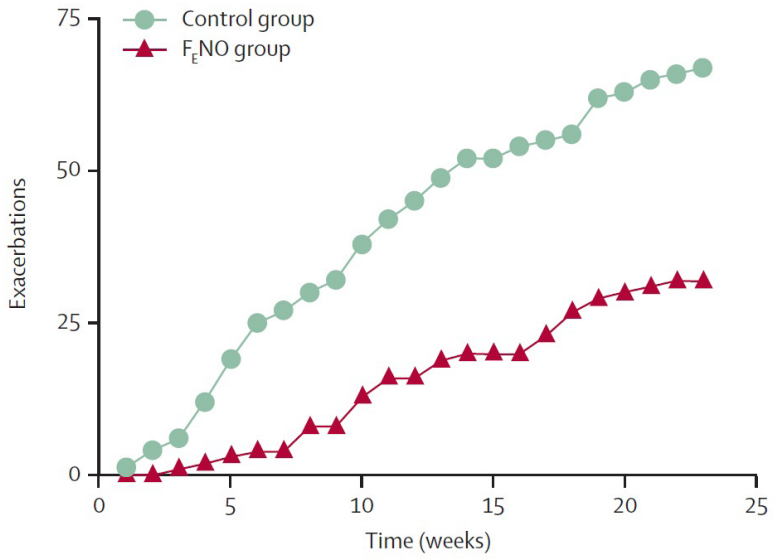

Figure 3 The use of a FeNO-based treatment algorithm can reduce asthma exacerbation frequency during pregnancy. 220 pregnant women with asthma were randomly assigned to having their ICS dose adjusted at monthly visits according to either their clinical symptoms (control group) or their FeNO level (FeNO >29 ppb to uptitrate ICS vs FeNO < 16ppb to downtitrate ICS). FeNO-guided titration of ICS was associated with a lower exacerbation frequency than symptom-guided dose titration.

(Reproduced from the Lancet, Vol 378, Powell H et al., Management of asthma in pregnancy guided by measurement of fraction of exhaled nitric oxide: a double-blind, randomised controlled trial, 983-90, 2011 with permission from Elsevier)

poor inhaler technique, previous history of exacerbations, poor lung function, smoking, exposure to allergens or pollutants, as well comorbidities including obesity, gastro-oesophageal reflux, chronic rhinosinusitis and psychosocial factors.

PREVENTION

Non-pharmacological approaches, including patient education and provision of written asthma action plans, reduce the risk of hospitalisation due to exacerbations. Pharmacological management centred around the use of ICS +/- long-acting β2-agonists are the mainstay of treatment in asthma and have been clearly shown to reduce exacerbation risk. In the context of severe asthma where regular use of high dose ICS proves insufficient to reduce T2 inflammation and the associated exacerbation risk, a number of monoclonal antibodies targeting various aspects of the T2 inflammatory pathway including IgE, IL-4R and IL-5/5R are now available. These have all been shown to significantly reduce asthma exacerbations, again highlighting the central role of T2 inflammation in exacerbation pathogenesis.

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3 SEVERE ASTHMA

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KEY MESSAGES

- Severe asthma is a costly public health burden encompassing 5 to 10 % of patients with asthma
- Once asthma diagnosis is confirmed, and comorbidities addressed, severe asthma is defined as those patients who require high dose medication to remain controlled and worsen when treatment is decreased or patients who remain uncontrolled despite adherence to optimized maximal therapy
- Risk factors for development of severe asthma include factors associated with low pre-bronchodilator FEV1% predicted
- Asthma severity is determined by the phenotype and endotype of the underlying disease
- All patients with severe asthma should be on age appropriate high doses of inhaled corticosteroids and other controllers

EPIDEMIOLOGY AND SCOPE OF PROBLEM

Asthma is a health problem currently effecting 330 million adults and children globally. In 2016, the World Health Organization (WHO) reported 383,000 deaths/year, many of which result from severe asthma. Severe asthma encompasses only 5 to 10% of patients with asthma, but it contributes to the majority of healthcare cost burden secondary to medications, physician visits, emergency room visits, hospitalization, days off work/or school, and side effects associated with intermittent and/or long term use of oral/systemic corticosteroids. In a Canadian study, severe asthma accounted for 60 % cost of all asthma care and in a UK study, the healthcare cost of severe asthma was higher than type 2 diabetes, stroke or COPD. In comparison to mild and moderate asthma, severe asthmatics are 15 times more likely to use emergency room services and 20 times more likely to be admitted to the hospital. Severe asthma is associated with poor asthma control (defined by daily symptoms, poor quality of life, nighttime awaking due to asthma and diminished lung function), increased risk of frequent exacerbations, and chronic morbidity (including impaired lung function or reduced lung growth in children) despite treatment.

SEVERE ASTHMA DEFINED

There are many definitions of severe asthma but the easiest to follow is a definition from WHO identifying three major groups contributing to healthcare utilization. First group is the undertreated asthmatic due to failure of diagnosis or lack of access to medications and healthcare. Second group is the difficult to control asthmatic due to undertreatment of comorbidities (gastroesophageal reflux disease (GERD), obstructive sleep apnea (OSA), chronic rhinosinusitis, obesity or tobacco use, lack of adherence to medications, or poor inhaler technique. Finally, severe or refractory asthma is defined by persistent symptoms despite good adherence to the asthma management plan and treatment of comorbid contributing factors and/or requiring high dose medication to remain controlled and worsening when treatment is decreased or remain uncontrolled despite adherence to optimized maximal therapy.

RISK FACTORS FOR SEVERE ASTHMA

Although largely unknown, there are several factors known to influ-

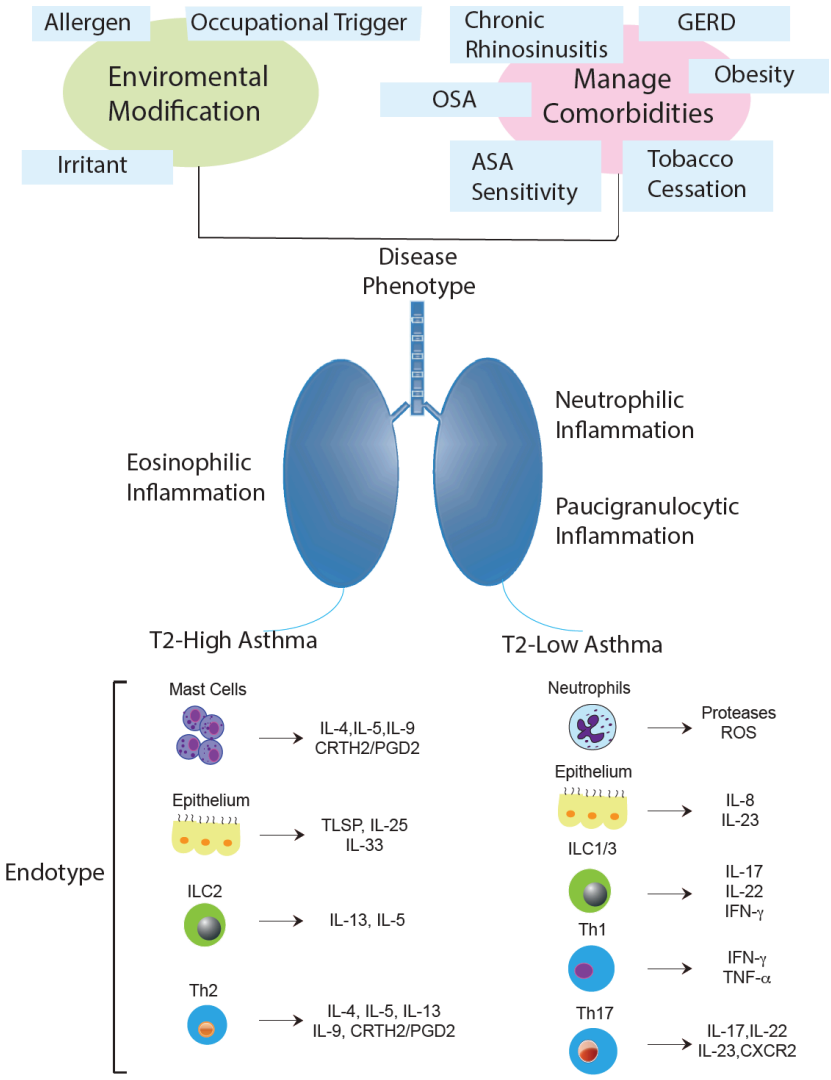

Figure 1 Assessment of environment and co-morbidities is essential for treatment of severe asthma. Subsequently understanding and targeting the Inflammatory patterns in the airways contribute to optimization of therapy. In a T2 low pattern a neutrophil predominant or paucigranulocytic inflammation has been described. Patients with this phenotype are less likely to respond to corticosteroids. T2 high inflammation is suggestive of eosinophilic phenotypes and more likely to respond to biologics targeting IgE, IL-5/IL-5 receptor and IL-4 receptor.

IFN-γ - interferon gamma; TNF-α - tumor necrosis factor alpha; ROS - reactive oxygen species; ILC1 - type 1 innate lymphoid cells; ILC2 - group 2 innate lymphoid cells; ILC3 - group 3 innate lymphoid cells; NKT - natural killer cells; PGD_2 - prostaglandin D_2.

(Adapted from Sonnenberg et al, Nat Med. 2015;21(7):698-708. and Muraro et al The Journal of allergy and clinical immunology. 2016;137(5):1347-58).

ence development and persistence of severe asthma. A low pre-bronchodilator FEV1% of predicted increases the risk of being classified as severe asthma suggesting that genes related to poorer lung function are involved. Other factors include racial background, male sex, sputum eosinophilia, tobacco use or exposure to secondhand smoke and prior history of pneumonia.

THERAPY FOR SEVERE ASTHMA

Understanding the underlying immune mechanism of severe asthma has opened the window for treatment optimization of severe asthma. The role of phenotype and endotype (underlying inflammation) is important for identifying patients who might benefit from monoclonal antibodies (biologicals) targeting type 2 (T2) inflammation (Figure 1). Several bedside markers can be utilized to identify T2 inflammation including: blood eosinophils ≥ 150 µl , and or FeNO (fractional exhaled nitric oxide) ≥ 20 ppb and/or, sputum eosinophils ≥ 2%, and/or need for maintained oral corticosteroids. According to current Global Initiative for Asthma (GINA) guidelines all patients with severe asthma should be on:

- low dose inhaled corticosteroid (ICS)-formoterol as maintenance and reliever therapy, or medium dose ICS-long acting β-agonist (LABA) maintenance plus as needed short acting β-agonist (SABA). If history of exacerbations is present other controller options as add on therapy include: tiotropium by mist inhaler in patients ≥ 6 years, leukotriene receptor antagonists (LTRA) or potential increase of ICS-LABA.
- if a patient remains uncontrolled despite above management phenotypic evaluation by specialist should be pursued for possible add on biologic therapy (Table 1) targeting type 2 inflammation.

TABLE 1

Summary of Biologics targeting T2 inflammation. Adapted from GINA guidelines

Current therapies	Mechanism of action	Potential Biomarkers	Effect	FDA/EMA Approved	Route
Omalizumab	Blocks the IgE pathway by preventing interaction with FcεRI	Elevated serum specific IgE. Patients with higher FeNO and blood eosinophils ≥ 260 cells/µl better response	Decrease in asthma exacerbations.	Yes; 6 and older	150-375 mg Sub q q2-q4wk; frequency based on IgE and body weight; Black box warning for anaphylaxis
Mepolizumab	IL-5 antagonist	Peripheral eosinophil count of ≥ 300 cells/µl	Decrease in asthma exacerbations Improvement in pre-post bronchodilator FEV1	Yes; 6 and older	100 or 40 mg Sub q q4wk; consider shingles vaccine prior to administration
Reslizumab	IL-5 antagonist	Peripheral eosinophil count of ≥ 400 cells/µl	Decrease in asthma exacerbations Improvement in FEV1	Yes; 18 and older	3 mg/kg IV q4wks Black box warning for anaphylaxis
Benralizumab	IL-5 receptor α antagonist targeting both eosinophils and basophils	Elevated peripheral blood eosinophil count ≥ 300 cells/µl	Decreased asthma exacerbations In a small study usage in a ER visit setting contributed to a 50% drop in exacerbation over 12 weeks	Yes; 12 and older	30 mg sub q every 4 wks for the first three doses and subsequently every 8 wks
Dupilumab	Inhibits IL-13 and IL-4 by targeting IL-4 α a common receptor domain for both cytokines	Peripheral eosinophil count of ≥ 300 cells/µl or or FeNO ≥ 25 ppb or on maintenance oral corticosteroids	Decrease in asthma exacerbations Improvement in FEV1	Yes; 12 and older	200 mg sub q q2wks or 300 mg sub q q4wks; administered at home with initial loading dose of 400 mg sub q or 600 mg sub q depending on steroid dependence

Failure to respond to biologicals targeting T2 inflammation is suggestive of possible other underlying immune mechanism in severe asthma and is an unmet medical need. Current recommendations for patient with low T2 inflammation include the addition of low dose oral corticosteroids, possible add on macrolide therapy three days per week and consideration of bronchial thermoplasty. However, T2 low inflammation is typically resistant to corticosteroids.

Biologicals targeting T2 low inflammation are in development, but none are currently approved for use. Ultimately, it is important to note while biologicals have shown to decrease exacerbations and need of oral corticosteroid use, they are not truly immunomodulating. Optimization of therapy should be continually assessed by ensuring adherence to medications, inhaler technique, re-evaluation of comorbidities /other comments and continued communication between physician and patient.

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4 ADHERENCE TO ASTHMA TREATMENT

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KEY MESSAGES

- Adherence to asthma treatment has been found to be globally poor
- It is important to distinguish between severe asthma and uncontrolled asthma due to incorrect inhaler technique and/or poor adherence
- Factors contributing to poor adherence can be classified as drug (medication/ regimen) and non-drug related (either unintentional or intentional)
- Most of the non-drug related factors can be overcome by a doctor-patient partnership and educational intervention

Adherence of asthma treatment has been found to be poor globally. The epidemiological study Asthma Insights and Reality in Japan conducted in 2011 collected data representative for real life Japanese asthmatics using computer assisted telephone interview. The study included 400 adult asthmatics, 27% males, mean age 46.4 years old, 65% with mild intermittent asthma, 17% mild persistent, 8% moderate persistent and 11% severe persistent. In the last month 34% received inhaled corticosteroids (ICS) or ICS and long acting β2-agonists (LABA) combination (ICS/LABA). Only 41% of 304 asthmatics used regularly the drugs for 10 months or longer and 14% did not use any drug in the last year (Figure 1). The reasons for stopping the medication were: disappearance of asthma symptoms (61%), relief from the asthma attack (39%), and unexpectedly, doctor's suggestion (17%). As the result of poor adherence, 62% of the patients were symptomatic in the last month. A cohort study evaluating 5,563 new users of ICS and 297 of ICS/LABA (age<35 years) in Netherlands also showed poor adherence with ICS regular use by less than 10% and ICS/LABA use by less than 15%. Similar rates were observed when stratified for age (Figure 2). Adherence to regular treatment in asthma were influenced by patient factors, such as asthma severity, and treatment-related factors, such as once-daily dosing frequency.

Adherence Starts with Knowledge-12 (ASK-12) is a useful indicator to assess drug adherence. 572 asthmatics were studied using ASK-12 to characterize the low adherence population, defined as ASK-12 score equal to or more than 28 (n=170), in comparison with the control group (ASK-12<28; n=402). Cluster analysis revealed three clusters (Clusters A, B, and C) in the low-adherence group. Cluster A included older non-atopic males with a smoking history, high prevalence of COPD and severe disease type. Cluster B included middle-aged nonsmoking atopic females with a depressive tendency and with poor asthma control and more exacerbations in spite of milder disease type. Cluster C contained mild well-controlled asthmatics (male: female=1:1), with a low rate of exacerbation and sustained pulmonary function. Those belonging to Clusters A and B require more attention to avoid future risk of adverse outcomes including exacerbations and persistent airflow limitation.

Although few adherence interventions have been studied comprehensively in asthma, the common strategy to improve adherence

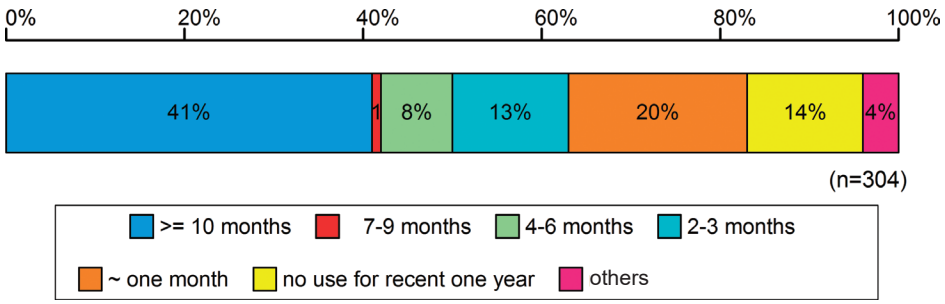

Figure 1 **Adherence to ICS or ICS/LABA.** Data from adult asthmatics who had used ICS or ICS/LABA at least once in the past. Adherence was assessed by duration of use of ICS or ICS/LABA in the recent one year.

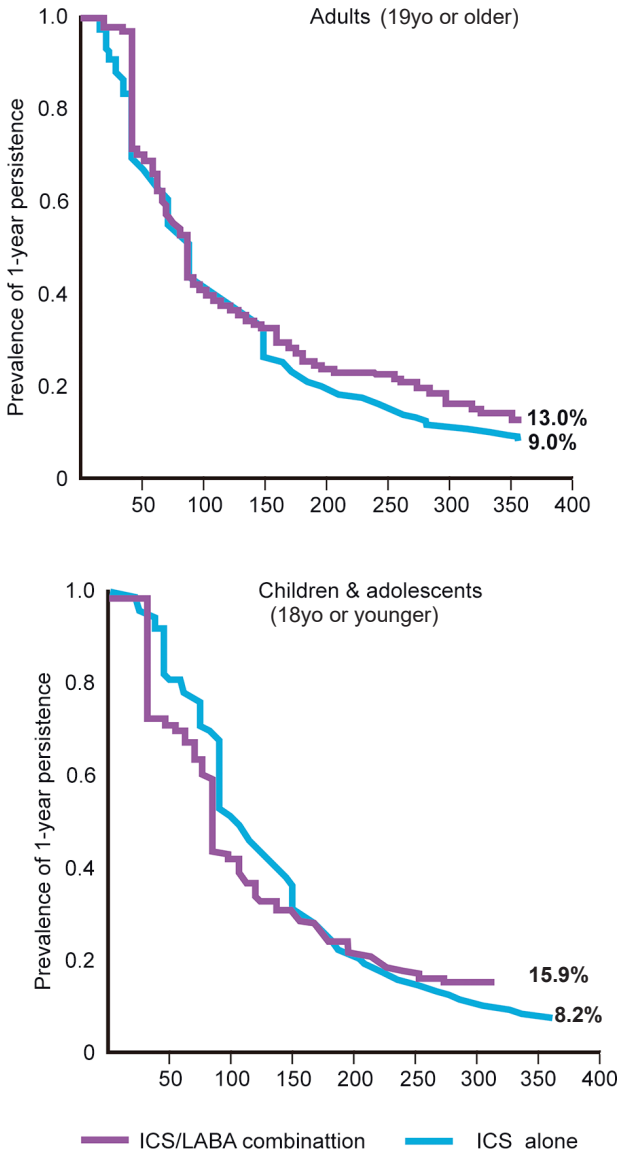

Figure 2 **Overall adherence to ICS and fixed drug combinations in new users with asthma.**
(Reproduced from Clin Respir J., Urbanization is associated with increased asthma morbidity and mortality in Brazil, Ponte EV et al., Vol 12, 1410-417, 2018 with permission from John Wiley & Sons)

TABLE 1

Factors contributing to poor adherence
Medication/regimen factors
• Difficulties using inhaler device (e.g. arthritis)
• Burdensome regimen (e.g. multiple times per day)
• Multiple different inhalers
Unintentional poor adherence
• Misunderstanding about instruction
• Forgetfulness
• Absence of a daily routine
• Cost
Intentional poor adhererence
• Perception that treatment is not necessary
• Denial or anger about asthma or its treatment
• Inappropriate expectations
• Concerns about side-effects (real or perceived)
• Dissatisfaction with health care providers
• Stigmatization
• Cultural or religious issues
• Cost

Reproduced from the Global Strategy for Asthma Management and Prevention, page 81, 2020

TABLE 2

Examples of successful adherence interventions
• Shared decision-making for medication/dose choice
• Inhaler reminders, either proactively or for missed doses
• Prescribing low dose ICS once-daily versus twice-daily
• Home visits for a comprehensive asthma program by an asthma nurse

Reproduced from the Global Strategy for Asthma Management and Prevention, page 81, 2020

is relying on the partnership between patients and their family and their healthcare providers and on patients' health literacy in asthma.

It is important to distinguish between severe asthma and uncontrolled asthma due to incorrect inhaler technique and/or poor adherence. "Poor medication adherence in asthma" is well summarized in the new Global Strategy for Asthma Management and Prevention (GINA 2020) by itemizing the subject into three sections, i.e. "Factors contributing to poor adherence" (Table 1), "How to identify poor adherence in clinical practice", and "Examples of successful adherence interventions" (Table 2).

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5 SOCIAL DETERMINANTS OF ASTHMA

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KEY MESSAGES

- Asthma disproportionately impacts urban communities marked by low socioeconomic status (SES)
- Social stratification and exclusionary policies can significantly influence asthma outcomes, including increased exposure to risk factors and impaired access to proper diagnosis and management
- Low-SES individuals are more likely to be exposed to environmental toxicants, indoor allergens, and other respiratory irritants that adversely impact asthma outcomes
- Low-SES individuals are also more likely to be exposed to psychosocial stressors, which may in turn increase susceptibility to environmental toxicants
- Efforts to eliminate current asthma disparities must address social determinants of health, including socio-environmental and psychosocial factors

The population-level burden of asthma is highly socially determined. Within a *social determinants of health* framework it is acknowledged that social stratification can influence asthma outcomes through increased exposure to risk factors and by reduced access to quality care. For instance, individuals living in poverty are more likely to be exposed to environmental toxicants (e.g. vehicular and industrial emissions), indoor allergens (e.g. mold, cockroach, dust mites), and other respiratory irritants (e.g. tobacco smoke). Epidemiological data indicate that asthma burden is higher within urban communities marked by social adversity and economic deprivation. In the United States (US) such communities often contain a disproportionately high percentage of African American residents, owing in part to historical socially exclusionary housing policies.

One such policy was "redlining", wherein the US government-sponsored Home Owners' Loan Corporation (HOLC) categorized urban communities into four "risk grades" according to their perceived foreclosure risk. Predominantly African American and immigrant communities were systematically graded as high-risk/hazardous and outlined in red on published "Residential Security" maps. A recent study found that residential redlining practices—implemented in 1933 and reinforced by subsequent exclusionary zoning policies—are associated with systematic differences in asthma-related Emergency Department (ED) admissions rates in 2011-2013 (Figure 1).

Figure 2 shows how age-adjusted asthma-related emergency department visitation clearly increases commensurate with greater HOLC "risk grades" across eight California regions. Notably, significant associations between contemporary community-level asthma burden and 1930s-era HOLC risk scores remain even after statistical adjustment for current poverty levels, ambient concentrations of key air pollutants, and spatial auto-correlation. This provides further evidence for the causal effect of historical socially exclusionary policy on contemporary asthma disparities.

The community-level inequities displayed in Figures 1 and 2 mirror trends in asthma prevalence and severity published in the 2018 Global Asthma Report. These data suggest that while asthma prevalence rates

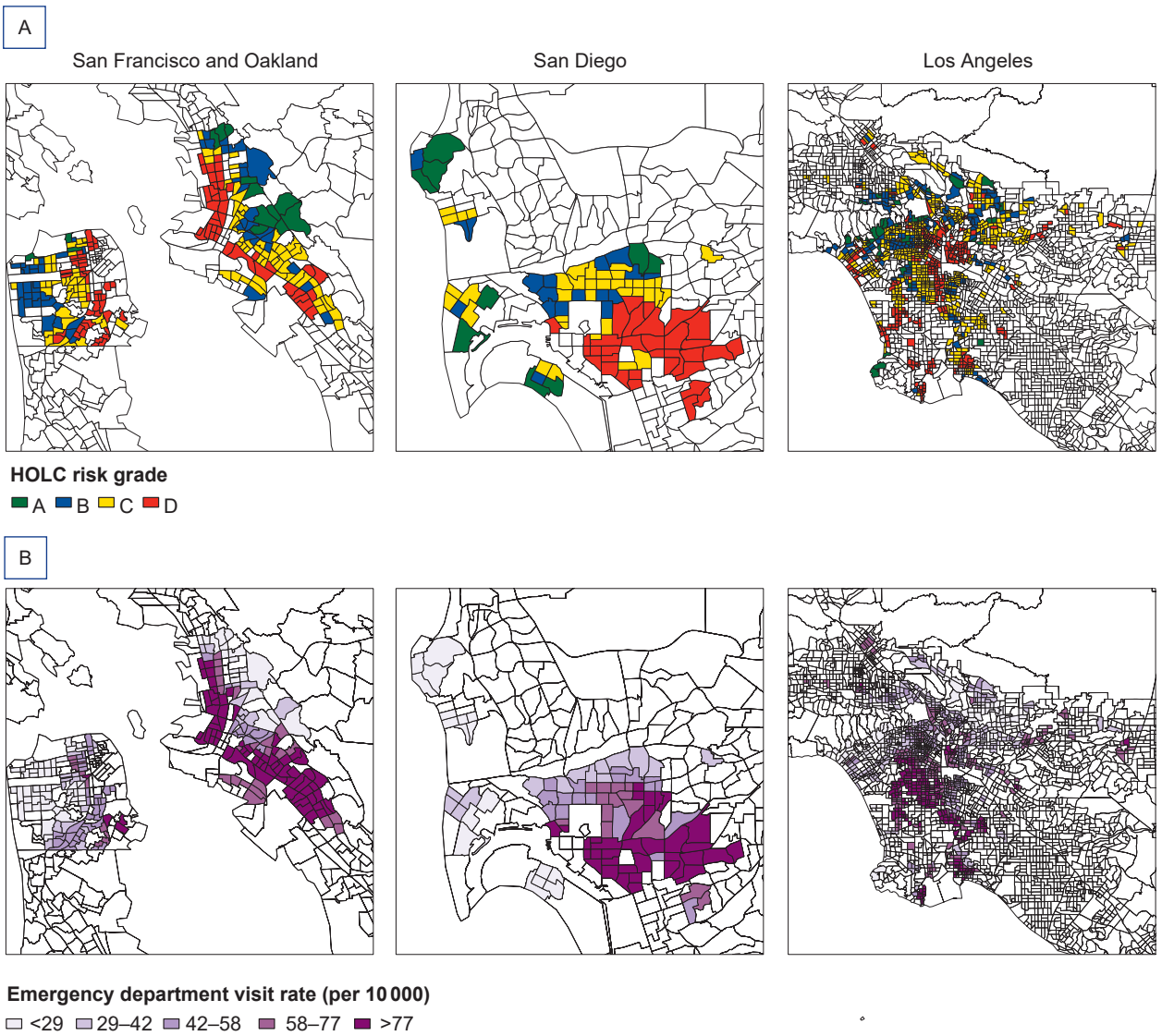

Figure 1 **2010 census tracts categorized by HOLC risk grade (A) and total age-adjusted rates of emergency department visits for asthma in 2011–13 (B) across three metropolitan areas in California.**
(Reproduced from The Lancet Planetary Health, Associations between historical residential redlining and current age-adjusted rates of emergency department visits due to asthma across eight cities in California: an ecological study, Nardone A et al., 24:31, 2020 under the terms of the creative commons attribution non-commercial license 4.0)

have recently plateaued or fallen in many upper-income countries, its morbidity is still increasing in low- and middle-income countries or communities, where asthma is disproportionately fatal.

Similar to environmental toxicants (e.g. fine particulate matter) that can enter the body and disrupt biological systems via pro-inflammatory and other immunomodulatory processes, exposure to psychosocial stressors at the individual, family, and community levels (Figure 3), can significantly increase asthma burden. In general, low-SES populations are more likely to encounter both psychosocial stressors and physical environmental toxicants—each of which independently increase asthma burden. However, since physical environmental toxicants and psychosocial stressors can impact common physiological pathways, psychosocial stressors may also potentiate an individual's susceptibility to environmental toxicants, giving rise to further asthma disparities.

In sum, given the considerable evidence linking social inequality

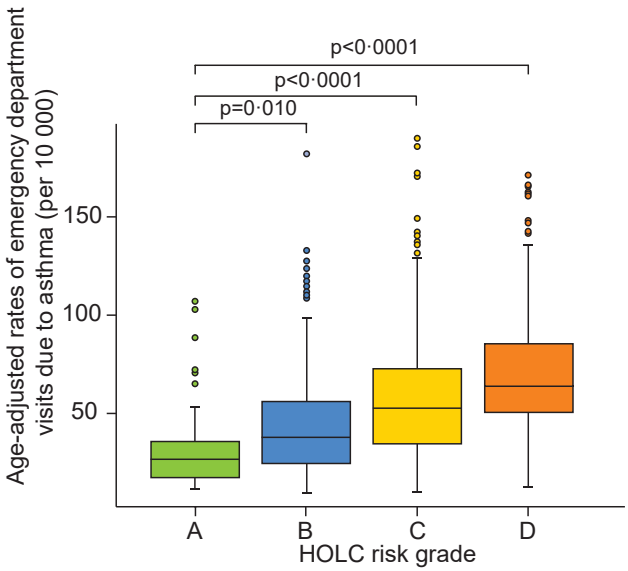

Figure 2 **Age-adjusted rates of ED visits due to asthma by HOLC risk grade.**
(Reproduced from The Lancet Planetary Health, Associations between historical residential redlining and current age-adjusted rates of emergency department visits due to asthma across eight cities in California: an ecological study, Nardone A et al., 24:31, 2020 under the terms of the creative commons attribution non-commercial license 4.0)

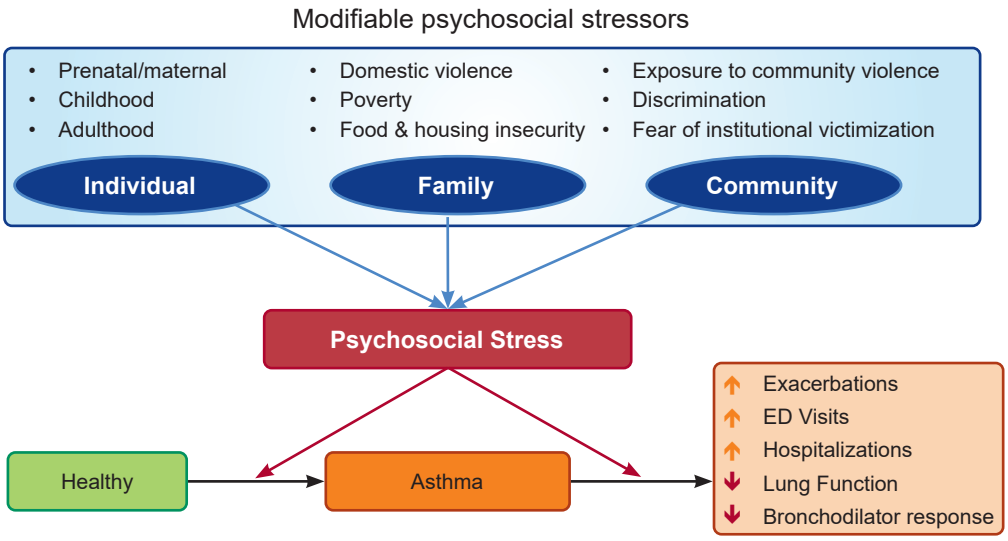

Figure 3 **Conceptual diagram of the impact of psychosocial stressors on asthma etiology.**

to population-level asthma disparities, it is clear that asthma equity cannot be achieved without addressing societal inequity more broadly. Efforts to eliminate asthma disparities must acknowledge social determinants of health. Structural and policy interventions must address these root causes of disparities at the community and broader societal level, and accompany efforts to ensure effective asthma self-management at the family and individual levels.

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6 INEQUITIES AND ASTHMA

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KEY MESSAGES

- ISAAC showed a positive correlation between asthma symptoms and income inequality
- Low income and non-white ethnicity were identified as factors associated with poorly controlled asthma, however low income was not associated with asthma severity
- Reduced access to physician visits and other outpatient care is undoubtedly correlated with asthma under-diagnosed and under-treatment
- A successful national asthma strategy includes coordination by the ministry of health, funding and capacity building, asthma management guidelines adapted for the country, access to medical care and quality-assured, affordable, essential asthma medicines available for everyone with asthma, continued education of health professionals and the public, and surveillance of morbidity, health care utilization and mortality data before and after implementation

Asthma is a major health problem in many low- and middle-income countries (LMICs), with high incidence of preventable deaths and disability. Although the implementation of asthma management guidelines has scaled up over the past two decades, with successful systematic strategies in some high-income countries (HICs), adaptation of international guidelines to national health systems and available resources have been difficult, especially in LMICs.

The International Study of Asthma and Allergies in Childhood (ISAAC) phase III showed a great variability of asthma prevalence between centers from countries with high and low-middle socioeconomic status, and between affluent and non-affluent populations from the same country. There was a subtle relationship between the gross national income (GNI) and overall symptom prevalence in large regions such as Latin America, which accounted for about 25% of all the children surveyed, but the overall correlation between GNI and prevalence was not significant. However, when associations were assessed for high- and middle-income countries only using the GINI inequality index from the World Bank a positive correlation between asthma symptoms and income inequality was statistically significant for 6- to 7-year-olds (Figure 1) and for the 13- to 14-year-olds (Figure 2).

Four factors associated with uncontrolled asthma in four Latin American countries (ASLA Study) were identified: females, non-white, low family income and severe asthma. However, severe asthma alone has no direct correlation with low income. Low income and non-white ethnicity were identified as factors associated with poorly controlled asthma. Possible explanations for this association may include a higher exposure to indoor allergens and biomass, decreased ability to afford asthma medications, and reduced access to physician visits and other outpatient care. The latter is undoubtedly correlated with asthma under-diagnosis and under-treatment (Figure 3).

The World Health Organization (WHO) Model List of Essential Medicines (EML) added in 2017 a

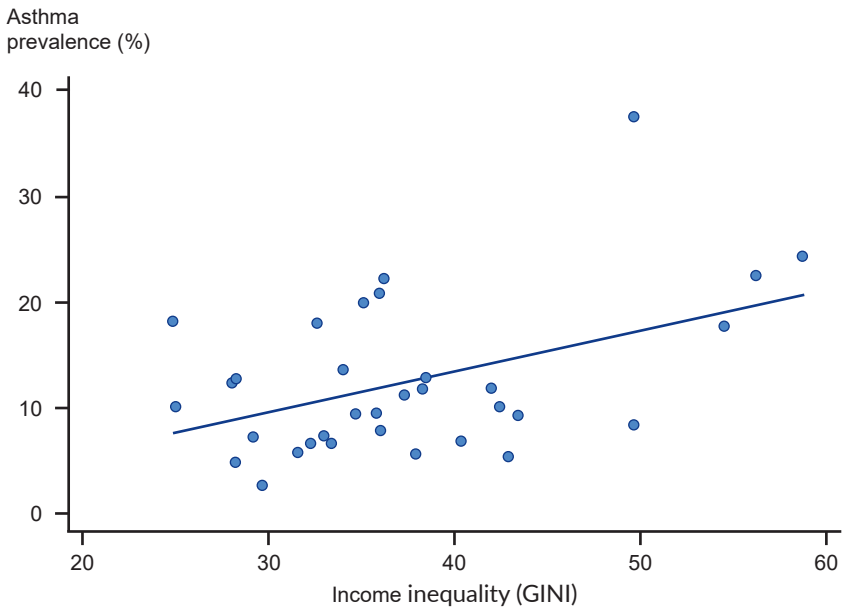

Figure 1 **Asthma prevalence rates by income inequality (GINI) for 6- to 7-year-olds.**

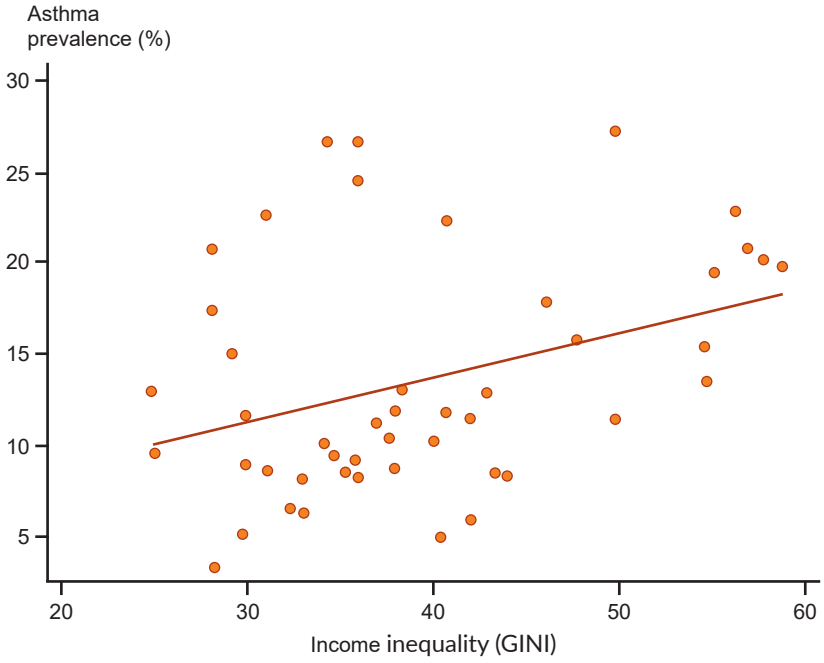

Figure 2 **Asthma prevalence rates by income inequality (GINI) for 13- to 14-years-olds.**

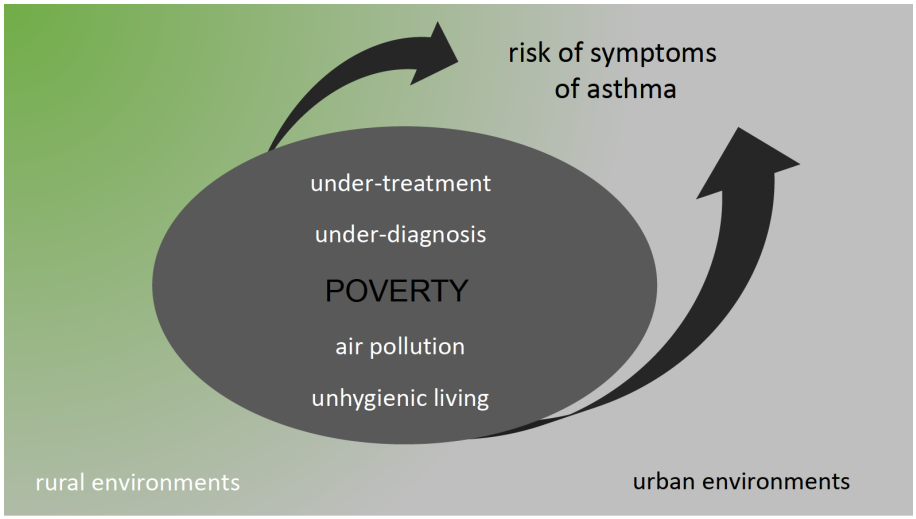

Figure 3 **Factors related to poverty that may increase the risk of symptoms of asthma regardless of the type of environment, although living in urban environments is a risk factor for asthma.**

combination ICS and rapidly-acting long-acting β2-agonist (LABA) to the existing two ICS and one short-acting β2-agonist (SABA). At present, combination inhaler devices are more expensive than ICS and SABA devices, which may limit the use of this regimen. Indeed, many countries, especially low- and middle-income countries (LMICs) do not yet have ICS and bronchodilators on their national EML, and many are not providing them free or subsidized for asthma patients.

The solution to this problem does not only imply the improvement to access to medication, but it is also essential to implement programs to educate patients and primary care physicians to shift the paradigm from exacerbation management towards preventive care with anti-inflammatory drugs, either regularly and alone or as needed in combination with a bronchodilator.

To be successful at reducing the burden of highly prevalent diseases such as asthma, it is necessary to implement national programs to address this public health problem, often neglected, preferably by integrating asthma in primary health care. The Global Asthma Network survey (2013-2014) showed that only 25% of the 112 participating countries have national programs and that 58% high socioeconomic countries had national asthma programs, as compared with 42% low socioeconomic countries.

The recommended components of a successful national asthma strategy include: coordination by the ministry of health, funding and capacity building, asthma management guidelines adapted for the country, access to medical care and quality-assured, affordable, essential asthma medicines available for everyone with asthma, continued education of health professionals and the public, and surveillance of morbidity, health care utilization and mortality data before and after implementation (including prevalence, underdiagnosis, severity, asthma control, emergency care and hospitalizations).

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Section F

MANAGEMENT OF ASTHMA

1 ASTHMA MANAGEMENT: FOCUS ON GUIDELINES

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KEY MESSAGES

- A major limitation of regular controller therapy with inhaled corticosteroids (ICS) is poor adherence, which may result in the overuse of short acting beta2-agonists (SABAs). The latest GINA document recommends as needed ICS/formoterol in Step 1 treatment (instead of SABA alone) or as alternative to regular maintenance ICS plus rescue SABA in Step 2
- ICS/formoterol is recommended as preferred rescue medication, as it can provide an anti-inflammatory treatment associated to rapid bronchodilation every time a rescue medication is required
- The management approach to severe asthma currently includes a phenotyping step for the identification of type 2 allergic, eosinophilic and non- type 2 phenotypes

To achieve asthma control, Global Initiative on Asthma (GINA) international guidelines recommend a 5-step approach where treatment (in particular the anti-inflammatory therapy) is stepped up or down in relation to the level of control, so that patients receive the minimum effective treatment (Figure 1). On the basis of available evidence, the main changes that have been recently introduced in GINA guidelines refer to: a) the maintenance controller treatments of the two edges of such stepwise strategy (Steps 1-2 in Mild asthma and Step 5 in Severe asthma) and b) the concept of rescue medication throughout all treatment steps.

MILD ASTHMA

There is compelling evidence for the presence of airway inflammation in patients with mild asthma. Concerns have been raised for both short- and long-acting β2 agonists (SABAs and LABAs) safety since their introduction in the asthma management. Conversely, underuse of inhaled corticosteroids (ICS) has been associated with an increased risk of severe asthma exacerbations and asthma death. A major limitation of regular controller therapy with ICS is poor adherence: when symptoms worsen, as patients show a preference for reliever therapies, which may result in the overuse of SABAs.

Recently, it has been shown in mild asthma that the use of ICS combined to a rapid-acting bronchodilator (such as formoterol) on an as-needed basis and in the absence of regular maintenance treatment, is more effective than rescue SABA alone and it is as effective as regular ICS in preventing asthma exacerbation. In the latest GINA update, SABA alone is not anymore considered as a possible option in Step1 treatment and as needed ICS/formoterol is instead recommended in these patients. Alternatively, it is recommended to add "rescue" ICS to the prn SABA in order to provide an anti-inflammatory treatment any time a rescue medication is required. Similarly, the same evidence supports the option of rescue use of ICS/formoterol in the absence of regular maintenance treatment in patients requiring Step 2 treatment as an alternative to regular maintenance ICS plus rescue SABA.

RESCUE MEDICATION

Based on the above evidence and on available data on the efficacy of ICS/formoterol as rescue medi-

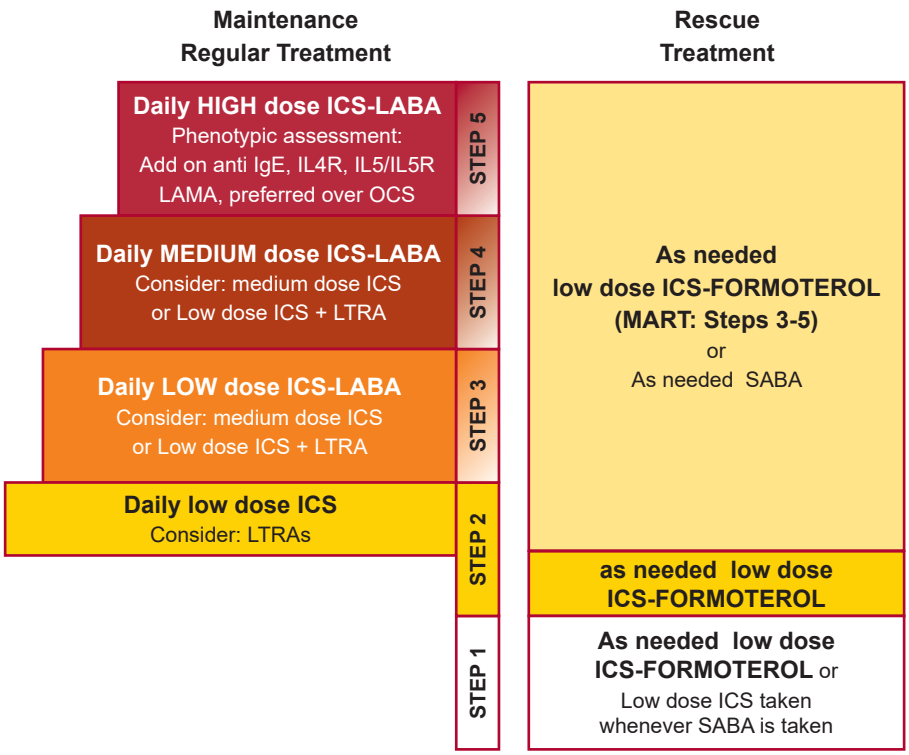

Figure 1 **Maintenance and Controller asthma treatment.**
(adapted from Ref. 1).

cation in patients treated with the same combination as maintenance treatment, the recently released GINA document indicates ICS/formoterol as preferred rescue medication throughout all treatment steps. This would provide an anti-inflammatory treatment every and each time a rescue medication is used for symptom control, i.e at the time when the antiiflammatory activity is more effective.

SEVERE ASTHMA

Severe asthma is defined as asthma that is uncontrolled despite adherence with maximal optimized therapy and treatment of contributory factors, or that worsens when high dose treatment is decreased.

Addition of long-acting muscarinic antagonists (LAMA), leukotriene receptor antagonists (LTRA), or theophylline should be considered in these patients before systemic corticosteroids because of more favorable side-effect profiles.

Considering the availability of specific targeted therapies, the management approach to severe asthma currently includes a phenotyping step for the identification of type 2 (T2) allergic, eosinophilic and non-T2 phenotypes (Figure 2) .

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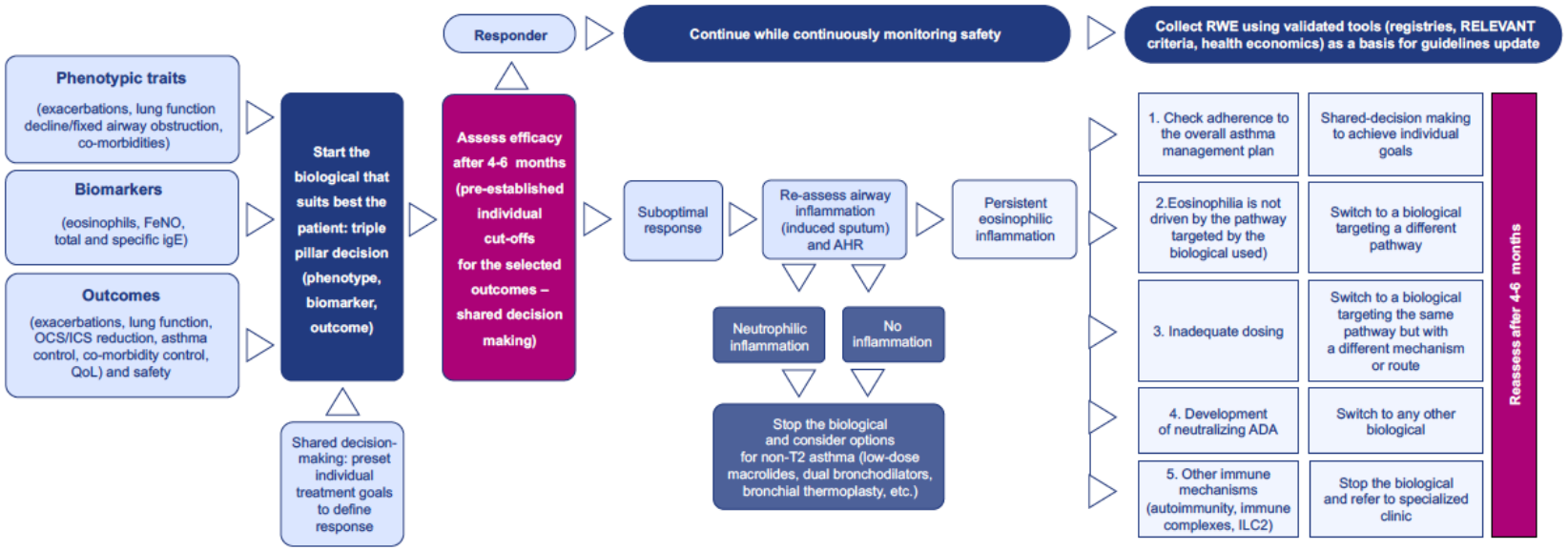

Figure 2 **The current management algorithm for the use of biologicals in severe asthma.**
(adapted from Ref 5)

2 ASTHMA MONITORING

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KEY MESSAGES

- Asthma monitoring is a collaboration between the patient and their medical team and should be incorporated within a pre-specified written asthma management plan
- Successful monitoring helps to achieve good control and reduces hospitalisation and is only useful if the results are acted upon
- For most cases self-monitoring through recognition of key symptoms is sufficient while for severe asthma, or for those who have difficulty recognising changes in severity more detailed monitoring is needed
- Monitoring may also be helpful in assessing response to treatment or diagnosis of occupational airways disease
- FeNO monitoring has a proven role in pregnancy and assessment of adherence
- Electronic inhaler monitors have great potential but more research is needed

The variable nature of asthma means that active monitoring is required to optimise management. The aim of monitoring is to assess disease control and allow proactive changes in management. When successful, this approach leads to reduced symptoms, improved quality of life and fewer serious events such as hospitalisation. Proactive monitoring also permits prompt reduction in medication where appropriate, minimising side-effects.

There are many forms of monitoring, both community and clinic based (Figure 1), but to succeed all rely on a collaboration between the patient and medical team. Monitoring is not a therapeutic end in itself, to be useful results must be acted upon. Monitoring options include evaluation of symptoms, reliever use, measures of airflow obstruction and biomarkers (Table 1).

SYMPTOMS AND MEDICATION USE

The simplest and most commonly used form of monitoring is based on recognition of key symptoms. For the majority of people with asthma, their symptoms and need for reliever inhalers are an accurate guide to disease activity. When patients are provided with an agreed written asthma management plan (Figure 2) they are able to respond to changes in symptoms with appropriate changes in medication and to seek help promptly where appropriate.

Patients with severe disease, and those who are poor perceivers of changes in asthma symptoms, may benefit from the addition of peak flow measurements at home.

In the clinic setting, patient's controller adherence, exacerbation history and asthma control should be reviewed. Short questionnaires such as the Asthma Control Test (ACT) may improve consistency of assessment over time.

MEASURES OF AIRFLOW OBSTRUCTION / AIRWAY HYPERRESPONSIVENESS

The degree of airway narrowing in asthma varies over time and is usually assessed with tests of lung function such as spirometry or peak flow monitoring. Spirometry requires more expensive equipment and staff training and is mainly used in primary care or hospital settings, whereas peak flow meters

Figure 1 **Different forms of asthma monitoring.**

TABLE 1

Components of asthma monitoring	
Symptoms and medication use	• Symptoms and limitation of activity
	• Reliever use
	• Controller adherence
	• Symptom questionnaires, e.g. ACT
	• Electronic symptom monitoring
	• Electronic inhaler use monitoring
Exacerbation history in past year	• Number of exacerbations
	• Number of courses of oral steroids
Measures of airflow obstruction / hyperreactivity	• Peak Flow Meter
	• Spirometry
	• Airway hyperreactivity
Biomarkers / Inflammometry	• Blood eosinophils
	• Exhaled nitric oxide
	• Total serum IgE to assess eligibility for anti-IgE
	• Induced sputum (cytometry)
	• Other blood biomarkers (e.g. serum periostin)
	• Metabolomics in exhaled air

First line techniques which can be used in any setting, including the home

Techniques suitable for primary and secondary care

Techniques best suited to specialist care

Emerging techniques not yet proven to be clinically beneficial for long term monitoring

can be used anywhere, including at home or at work.

All airflow measurements show some natural variation over time but large variations in peak flow suggest poorly controlled asthma. Patients with asthma and significant variability in their peak flow show an improvement in peak flow and a reduction in variability once treated with inhaled corticosteroids (Figure 3).

Peak expiratory flow (PEF) monitoring is simple, relatively inexpensive, and widely available. However, values are effort dependent, a single reading provides limited information, and diaries are reviewed only in retrospect. There is accordingly interest in methods of electronic PEF monitoring which may provide a more accurate and contemporaneous assessment.

EMERGING TECHNOLOGIES / ELECTRONIC MONITORING

Telemonitoring, where information on symptoms +/- lung function is collected regularly and reviewed remotely (by telephone or through an app), has the potential to improve outcomes if it aids recognition of worsening control and treatment is changed appropriately. Trials have suggested that patients like telemonitoring systems but have not consistently shown an improvement in control or reduction in exacerbations. Potential alternatives could include inhalers with built-in monitoring devices. These could recognise increasing reliever use and prompt the patient to seek early medical review, as patient symptoms, PEF readings and rescue inhaler use increase up to 10 days before an exacerbation is recognised and treated (Figure 4a); although individual patterns of inhaler use before an exacerbation are highly variable (Figure 4b).

Asthma + Respiratory FOUNDATION NZ

YOUR ASTHMA ACTION PLAN

Name: Doctor:

Date of plan: Doctor phone:

Know your asthma symptoms | **Know when and how to take your medicine**

Feeling good

Your asthma is under control when

- you don't have asthma symptoms most days (wheeze, tight chest, a cough or feeling breathless)
- you have no cough or wheeze at night
- you can do all your usual activities and exercise freely
- most days you don't need a reliever

Your peak flow reading is above

Preventer [name]	*actuation(s)*	*every morning*
	actuation(s)	*every night*
Reliever [name]	*actuation(s)*	*when you need it to relieve your asthma symptoms*

Remember:

We strongly suggest that you use a spacer, if one can be used with your preventer inhaler.

Carry your reliever at all times

Severe

Caution- your asthma is getting severe when

- Your asthma symptoms are getting severe (wheeze, tight chest, a cough or feeling breathless)
- **OR** your Symbicort is only helping for 2-3 hours
- **OR** you are using more than 12 actuations in a day
- **OR** you feel you need to see your doctor

Your peak flow reading is below

Let's take action…

- **You need to see your doctor today**
- Continue your regular Symbicort PLUS 1 actuation of your Symbicort when needed to relieve symptoms
- Start prednisone if you have it:

Prednisone	*mg*	*for*	*days*
and then	*mg*	*for*	*days*

Other instructions:

Emergency

Emergency

- Your symptoms are getting more severe quickly
- **OR** you are finding it hard to speak or breathe
- **OR** your reliever is not helping much
- **OR** you are using your reliever every 1-2 hours

Your peak flow reading is below

Let's keep calm…

- **Dial 111 for ambulance**
- Keep using your reliever as often as needed – through a spacer, if one can be used with your reliever inhaler
- Even if you seem to get better seek medical help right away
- If you haven't started taking your prednisone, start now

Best peak flow: _____

Plan prepared by: _____

Next review date: _____

Signature: _____

Figure 2 **Example of an Asthma Management Plan.**
(Reproduced from 3-step asthma management plan with permission from the Asthma and Respiratory Foundation NZ New Zealand)

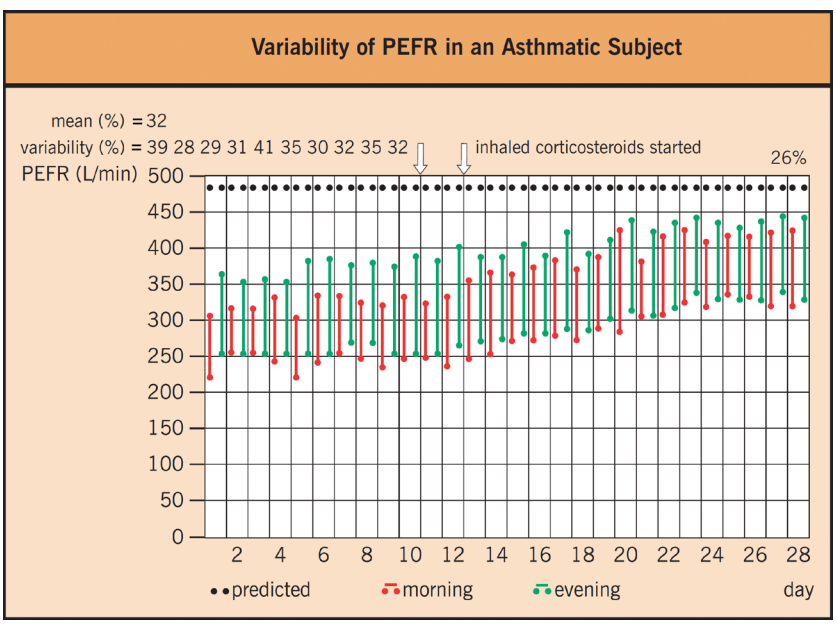

Figure 3 **Example of a peak flow diary showing improved peak flow and reduced variability in response to starting a steroid inhaler.**
Courtesy of S T Holgate.

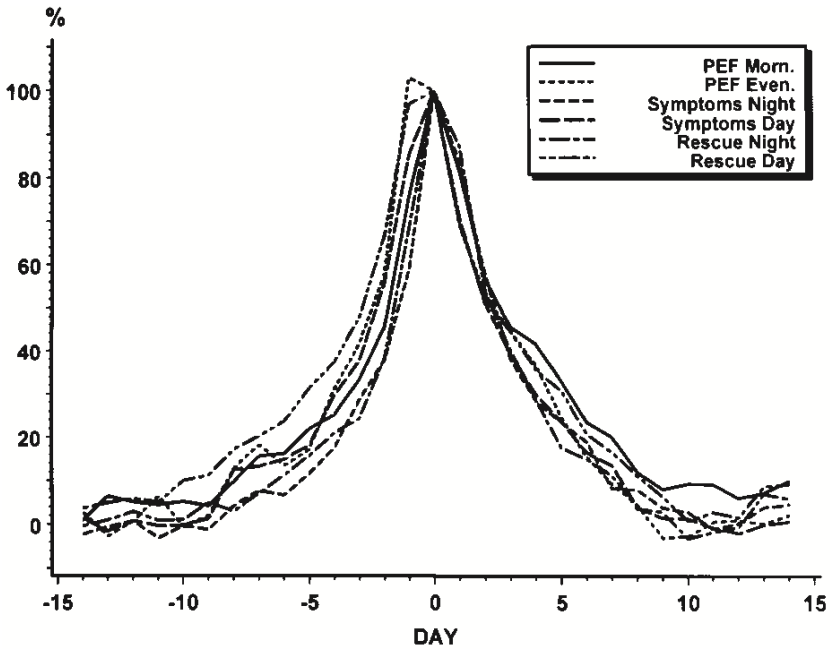

Figure 4a Change in peak flow, symptoms and rescue inhaler use around an exacerbation. Day 0 is the day an exacerbation was diagnosed.

(Reproduced from the American Journal of Respiratory and Critical Medicine (official journal of the American Thoracic Society), Exacerbations of asthma: a descriptive study of 425 severe exacerbations, Tattersfield AE et al., Volume 160, Issue 2, 594-599, 1999 with permission of the American Thoracic Society. Copyright © 2020 American Thoracic Society. All rights reserved)

BIOMARKERS / INFLAMMOMETRY

Inflammation in asthma is heterogeneous, and inflammation and symptoms are discordant in many people with asthma. Biomarker directed therapy can help personalise management according to asthma endotype in line with the "Treatable Trait" approach to asthma management. Proven biomarkers include fractional exhaled nitric oxide (FeNO), blood and sputum eosinophils and, to a lesser extent, total serum IgE. Sputum eosinophil measurement stratifies risk effectively and, when used as the primary treatment target for inhaled corticosteroid dosage, reduces the likelihood of asthma exacerbations, although it does not impact on asthma control or lung function. Sputum eosinophil measurement requires technical expertise which limits its widespread application. Blood eosinophils and total serum IgE guide selection of anti-IL5 and anti-IgE biological agents for patients with severe asthma. FeNO can be used for assessment of non-adherence and to guide asthma management in pregnant women. As our knowledge of biomarkers improves, the prospect of true personalised medicine, where proactive monitoring leads to the right medication for an individual at the right time, should become a reality.

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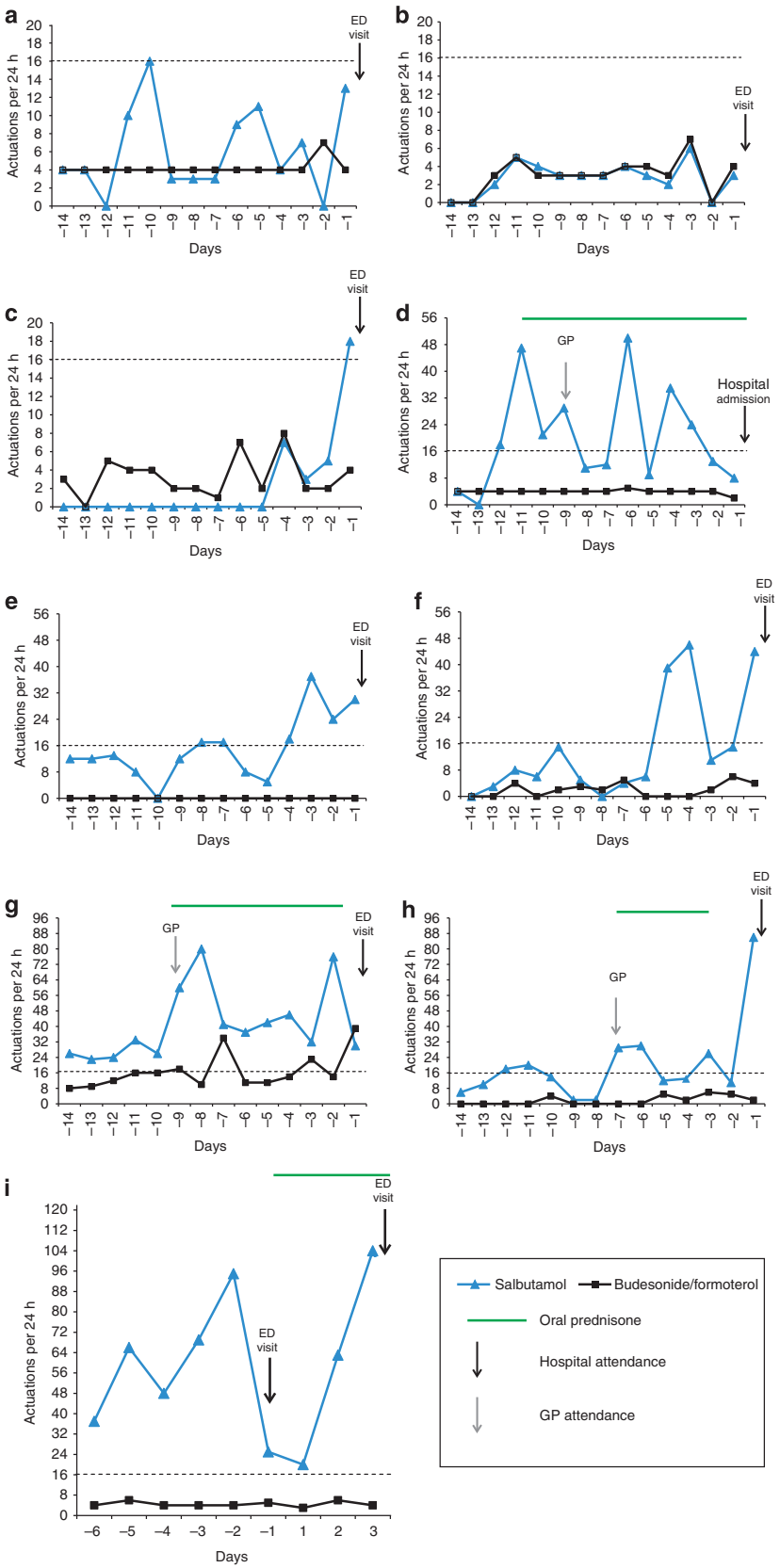

Figure 4b Change in reliever and maintenance inhaler use around an exacerbation. Day 0 is the day an exacerbation was diagnosed. *(Reproduced from npj Prim Care Resp Med, The use of β2-agonist therapy before hospital attendance for severe asthma exacerbations: a post-hoc analysis, Patel, M et al., 25, 14099, 2015 under the terms of the creative commons attribution non-commercial license 4.0)*

3 NOVEL BRONCHODILATORS

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There is a real interest in developing novel bronchodilators because of the pivotal importance of bronchodilation in the pharmacological treatment of patients with asthma, the safety concerns of currently used inhaled drugs, the potential for a loss in bronchoprotection of the β_2-agonist class, and the lack of disease-modifying properties of inhaled bronchodilators.

However, the pharmacology of bronchodilators has remain unchanged over several decades with the use of β_2-agonists, muscarinic receptor antagonists and xanthines still dominant, although there has been improvement in the potency and duration of action in each of these classes of drugs.

It is well recognised that adherence to inhaled medicines is generally poor. There is therefore interest in once-daily bronchodilators to increase adherence in the maintenance treatment of asthma, particularly the use of ultra-LABAs and LAMAs. The current evidence indicates that ultra-LABAs and LAMAs can be prescribed in asthmatics only when associated with an ICS, but there is a clear need to determine if and when one class is preferable over another. Nonetheless, there is now considerable evidence suggesting that LABAs and LAMAs, additional to ICSs, is a method to optimize bronchodilation, at least with the currently approved drugs. The current opinion is that delivering an ICS with dual bronchodilator therapy in one inhaler device (so called triple inhalers) rather than having to take these drugs in separate inhalers is a useful approach for the treatment of asthma.

The use of combinations of drugs with complementary pharmacological actions in the treatment of patients with asthma has led to the development of so called "bifunctional" drugs, single molecules that elicit two different primary pharmacological actions (Figure 1). Muscarinic-receptor antago-

KEY MESSAGES

- Delivering an inhaled corticosteroid (ICS) coupled with dual bronchodilator therapy in one inhaler device (so called triple inhalers) rather than having to take these drugs in separate inhalers is a useful approach for the treatment of uncontrolled or severe asthma
- Single molecules that elicit two different primary pharmacological actions (MABAs), circumvent the problem of formulating two different drugs in one inhaler, providing a fixed ratio of muscarinic antagonism and β_2-agonism with the same molecule, however dosing flexibility is limited
- New classes of bronchodilators are currently being developed targeting several receptors from the G-protein-coupled receptor superfamily expressed by the human airway smooth muscle, their isoforms and alternate routes of intracellular signalling (e.g. via β-arrestins)
- Hyper-responsiveness of airway smooth muscle by phosphorylation of the myosin light chain is in part, a downstream consequence of G_q-promoted calcium mobilization, thus broad-based antagonists of G_q signalling, such as pepducins, might be of interest for asthma treatment

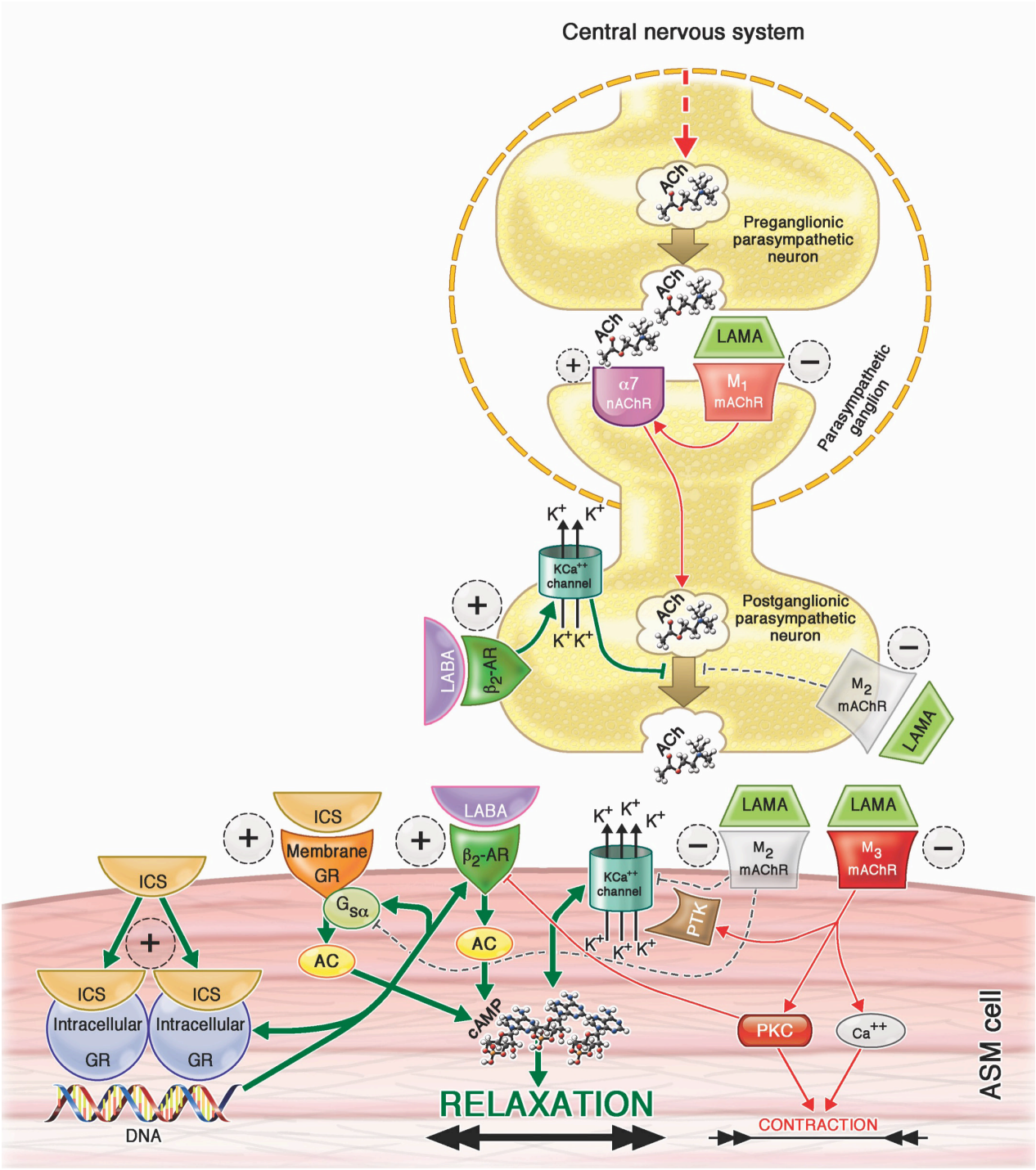

Figure 1 **The pharmacological rationale for combination therapy in asthma.**
(Reproduced from Pharmacol Rev. Cazzola et al., Pharmacology and Therapeutics of Bronchodilators Revised, Vol 72, 218-252, 2020 with permission from ASPET)

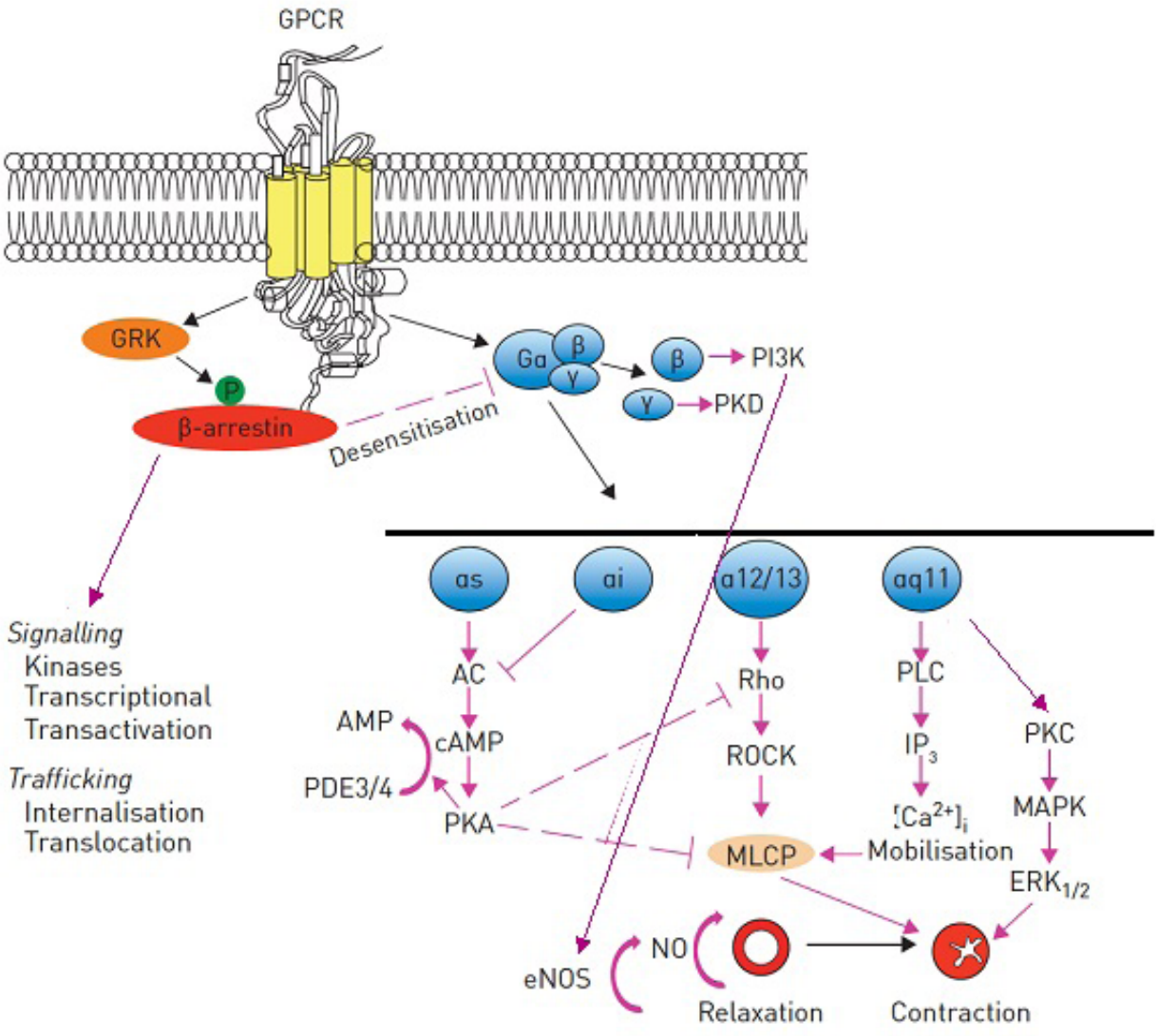

Figure 2 **Synthesis of signalling and functional effects of various G-protein coupled receptors (GPCRs) that have been identified in airway smooth muscle cells.**
(Reproduced with permission of the © ERS 2020: European Respiratory Review 28 (154) 190095; DOI: 10.1183/16000617.0095-2019 Published 23 December 2019)

nists-beta(2)-adrenergic receptor agonists (MABAs), circumvent the potential problem of formulating two different drugs in one inhaler, providing a fixed ratio of muscarinic antagonism and β_2-agonism with the same molecule. However, the ratio of the two different pharmacological activities cannot be adjusted as needed and this limits dosing flexibility. A number of MABAs have now reached clinical development or are at a preclinical stage.

Since PDE4 inhibitors are mainly anti-inflammatory drugs and PDE3 inhibitors are bronchodilators, molecules able to induce dual inhibitory activity for both PDE3 and PDE4 enzymes have been developed to obtain dual bronchodilator and anti-inflammatory activity. Ensifentrine is the only dual PDE3/PDE4 inhibitor under clinical development and has recently completed phase 2b clinical trials, although initially this is for the treatment of patients with COPD.

The awareness that there are a large number of receptors in the G-protein-coupled receptor superfamily expressed by the human airway smooth muscle and extensive variability in structure

TABLE 1

Novel classes of bronchodilators

Class	Molecule	Potential Therapeutic Effects
TAS2R agonists	Erythromycin, arisoprodol, flufenamic acid, dapsone, quinine, chloroquine, caffeine, azelastine, colchicine	Bronchodilation, reduction in exercise- or histamine-induced bronchoconstriction in patients with asthma
EP receptor 4 agonists	ONO-AE1-329, L-902688, TCS2510, rivenprost	Relaxation of ASM, reversal of histamine-induced contraction of ASM, increase in glucocorticoid response element-dependent transcription when combined with ICS
Rho kinase inhibitors	Fasudil, ripasudil, netarsudil, AMA0076/PHP-201, Y-39983	Relaxation of ASM, relaxation of methacholine-constricted human small airways
Calcilytics	Calcityrol, B2.1-E1	Bronchodilator and anti-inflammatory actions
Agonists of PPARγ	Pioglitazone, rosiglitazone, troglitazone, ciglitazone	Relaxation of ASM, inhibition of the initiation and development of a maximal contraction induced by methacholine, synergistic interaction with β2-AR agonists on ASM cell proliferation
RXFP1 agonists	Serelaxin, B-chain only agonists (B7-33), small molecule RXFP1 agonists (ML290), fatty acid conjugated relaxin-2 analogs (R9-13)	Relaxation of ASM, increase in airway dilator responsiveness to β-AR agonists
sGC activators	BAY 41-2272, BAY 60-2770, BAY 58-2667	Bronchodilation, reduction of airway hyperresponsiveness
Pepducins	Pepducin ICL_{3-9}, AT1-2341, P4pal-10	Relaxation of ASM

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because of alternative splicing leading to many receptor isoforms (Figure 2) allowed to identify at least eight potential new classes of bronchodilators that are under consideration: 1) bitter-taste receptor agonists; 2) E-prostanoid receptor 4 agonists; 3) Rho kinase inhibitors; 4) calcilytics; 5) agonists of peroxisome proliferator-activated receptor (PPAR)-γ; 6) agonists of relaxin receptor 1; 7) soluble guanylyl cyclase activators; and 8) pepducins (Table 1).

β_2-adrenoceptors can signal not only via activation of G proteins, but also via β-arrestins. Current β-agonists induce balanced signalling by promoting coupling to G proteins and G protein-coupled receptor kinases/β-arrestins. This is an important issue in asthma because the activation of β-arrestin-dependent signalling induces desensitization of adrenoceptors and onset of tachyphylaxis. Biased agonists are able to engage with their target receptors in a manner that preferentially activates only G-protein- or β-arrestin-mediated downstream signalling.

Pepducins function as broad-based antagonists of G_q signalling, an effect potentially important in patients with asthma, in whom hyper-responsiveness of airway smooth muscle by phosphorylation of the myosin light chain is, in part, a downstream consequence of G_q-promoted calcium mobilization.

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4 TARGETING THE SMALL AIRWAYS

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KEY MESSAGES

- Small airways are defined by an internal diameter of ≤2 mm and generally represent the eighth airway generation and beyond, accounting for approximately 99% of the total lung volume
- In contrast to healthy subjects, the small airways are the predominant site of airflow resistance in patients with asthma
- As an unanimously agreed approach to study small airways disease (SAD) is still lacking, impulse oscillometry (IOS) is probably considered the optimal diagnostic test
- The assessment of SAD is relevant in choosing the optimal treatment strategy by using slow-flow inhaler devices and extra-fine/high-fine particles to target the distal lung regions

Recent years have seen increasing attention to the role of small airways in respiratory diseases, particularly asthma. Small airways are defined by an internal diameter of ≤2 mm, and generally represent the eighth airway generation and beyond, accounting for approximately 99% of the total lung volume. In contrast to healthy subjects, the small airways are the predominant site of airflow resistance in patients with asthma, mainly due to airway narrowing secondary to the inflammatory response and remodelling process. This pathophysiological hallmark, known as small airways dysfunction (SAD), seems to play a crucial role in terms of asthma severity, symptom control and response to treatment. SAD assessment may provide useful information to better understand the heterogeneity of asthma and characterize different disease phenotypes and endotypes.

Despite the tremendous progress in SAD testing, a unanimously agreed approach to study SAD, is still needed (table 1). Forced expiratory flows and volumes (i.e. FEF_{25-75}, FEF_{50}, FEV_3 and FEV_6) recorded through spirometry are the most commonly used lung function parameters in SAD assessment, although they provide only indirect estimates. Total lung capacity (TLC), functional residual capacity (FRC), residual volume (RV) and transfer capacity for carbon monoxide (TLCO), obtained by body plethysmography, usually provide more accurate information. The single-breath nitrogen (N2) washout, as well as the better reproducible multiple-breath nitrogen washout (MBN2W), can predict the contribution of the peripheral airways to the degree of ventilation heterogeneity. Impulse oscillometry (IOS) directly determines central and peripheral lung resistance (R), reactance (X) and impedance (Z) and in light of recent data is probably considered the optimal test for SAD assessment. Other diagnostic parameters, at present mainly confined to research purposes, include: 1) the alveolar concentration of nitric oxide (CaNO), assessed from a computational extrapolation of the fraction exhaled nitric oxide (FeNO) measurement at different flow rate manoeuvres; 2) and the detection of 16 kDa Clara cells proteins (CC-16) in blood and urine. In the imaging arena, there have been developments for SAD evaluation as well. High-resolution computed tomography (HRCT) is a non-invasive method that can document air trapping and ventilation heterogeneity, in-

TABLE 1

Most common diagnostic tools and parameters for SAD assessment	
Diagnostic tool	**Diagnostic parameters**
Spirometry	FEF_{25-75}, FEF_{50}, FEV_3 and FEV_6
Body Plethysmography	TLC, FRC, RV, RV/TLC, TLCO
Single-Breath Nitrogen Washout	CV, CC
Multi-Breath Nitrogen Washout	Sacin, Scond, LCI 5, LCI 2.5
Impulse oscillometry	R5-R20, X5, AX, Fres
Exhaled nitric oxide at multi-flow	caNO
Biological samples (i.e. blood, urine)	CC-16
High Resolution Computer Tomography	Air trapping

directly suggesting SAD. Parametric response mapping may allow differentiation of emphysematous from non-emphysematous air trapping (i.e. functional SAD) within the lung parenchyma.

A recent multi-national study designed to evaluate SAD in asthma has developed a score, based on functional, clinical and radiological variables, to indicate the extent of the small airways' involvement in patients with asthma and its correlation with clinical and prognostic features. Importantly, IOS measurements, such as AX indicating the distensibility of the peripheral lung and R5-R20 reflecting small to mid-sized airways resistance, were observed be the best predictive markers of uncontrolled asthma (Figure 1). A significantly higher SAD score was found in patients with severe asthma (GINA step 5), frequent exacerbations, several comorbidities, poor symptom control and eosinophilic inflammation.

In clinical practice, the presence of SAD is important in guiding the appropriate choice of pharmacological treatments. In fact, by using specific inhaler devices with slow inhalation flows and formulations with extra-fine particles or with high fine particle fraction the inhaled drug can be targeted to the distal lung regions. Indeed, studies show that compared to large particle size treatments, small particle therapies are able to improve asthma control and exacerbations with an overall lower dose of inhaled corticosteroid.

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0·90 <0·001	0·87 <0·001	0·76 <0·001	0·53 <0·001	0·53 <0·001	0·47 <0·001	0·44 <0·001	0·42 <0·001	0·42 <0·001	0·41 <0·001	0·41 <0·001	0·40 <0·001	0·40 <0·001
AX (n=524)	R5–R20 (n=611)	R5 (n=618)	Predicted AX (n=520)	RV/TLC (n=737)	Reversibility (n=762)	Predicted RV/TLC (n=737)	S_{cond} (n=382)	S_{acin} (n=379)	R20 (n=629)	Predicted R20 (n=629)	Predicted RV (n=693)	RV (n=693)
0·32 <0·001	0·30 <0·001	0·29 <0·001	0·27 <0·001	0·25 <0·001	0·24 <0·001	0·22 <0·001	0·20 <0·001	0·19 <0·001	0·18 <0·001	0·18 <0·001	0·17 0·023	0·17 <0·001
Predicted S_{acin} (n=379)	Asthma duration (n=763)	Predicted S_{cond} (n=382)	Body-mass index (n=764)	Predicted raw (n=670)	Age (n=764)	Raw (n=670)	Predicted FRC (n=728)	ACQ–6 score (n=764)	Number of exacerbations (n=764)	Diastolic blood pressure (n=764)	Duration of smoking (n=182)	Predicted R5–R20 (n=611)
0·15 <0·001	0·15 <0·001	0·14 0·001	0·14 0·002	0·12 0·001	0·11 0·002	0·11 0·002	0·11 0·008	0·10 0·008	0·09 0·009	0·09 0·011	0·08 0·028	0·08 0·032
Systolic blood pressure (n=764)	White blood cell count (n=760)	Decrease in FVC (n=497)	Predicted decrease in FVC (n=495)	FRC (n=728)	Eosinophils (n=758)	Neutrophils (n=759)	Predicted X5 (n=595)	Predicted TLC (n=739)	Lymphocytes (n=758)	Monocytes (n=759)	Number of unscheduled consultations (n=764)	Heart rate (n=762)
0·05 0·149	0·03 0·665	0·01 0·794	–0·03 0·378	–0·08 0·024	–0·12 0·001	–0·12 0·025	–0·15 <0·001	–0·20 <0·001	–0·22 <0·001	–0·23 <0·001	–0·24 <0·001	–0·25 <0·001
Basophils (n=759)	Number of pack–years (n=182)	Exhaled nitric oxide (n=624)	TLC (n=739)	Age at first diagnosis (n=760)	Mini AQLQ score (n=763)	PC_{20} (n=372)	Height (n=764)	EuroQol-5D-5L score (n=761)	ACT score (n=763)	Predicted sGaw (n=578)	sGaw (n=578)	PD_{20} (n=182)
–0·30 <0·001	–0·31 <0·001	–0·35 <0·001	–0·41 <0·001	–0·55 <0·001	–0·57 <0·001	–0·57 <0·001	–0·60 <0·001	–0·60 <0·001	–0·61 <0·001	–0·62 <0·001	–0·64 <0·001	–0·78 <0·001
IVC (n=616)	Predicted IVC (n=616)	FVC (n=762)	Predicted FVC (n=762)	FEV_1 (n=763)	Predicted FEV_1/FVC (n=761)	FEV_1/FVC (n=761)	FEF_{25-75} (n=723)	Predicted FEF_{25-75} (n=723)	FEF_{50} (n=716)	Predicted FEF_{50} (n=716)	Predicted FEV_1 (n=758)	X5 (n=595)

Correlation between variables

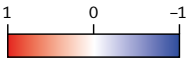

Figure 1 Correlations between SAD score and all asthma variables measured.

*ACQ-6 - Asthma Control Questionnaire-6; AQLQ - asthma quality of life questionnaire; AX - area of reactance; Decrease in FVC - percentage decrease in FVC from baseline at PC20 or PD20; FEF25–75 - forced expiratory flow at 25–75% of FVC; FEF50 - forced expiratory flow at 50% of FVC; FRC - functional residual capacity; FVC - forced vital capacity; IVC - inspiratory reserve volume; PC_{20} - provocative concentration that causes a 20% decrease in FEV1 from baseline during methacholine challenge; PD_{20} - provocative dose that causes a 20% decrease in FEV_1 from baseline during methacholine challenge; Predicted - values presented as a percentage of predicted values; R5 - airway resistance at 5 Hz; R20 - airway resistance at 20 Hz; Raw - airway resistance; RV - residual volume; Sacin*VT - ventilation heterogeneity of the acinar zone of the lungs; Scond*VT - ventilation heterogeneity in the conductive zone of the lungs; sGaw - specific airway conductance; TLC - total lung capacity; X5 - reactance at 5 Hz*

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5 CHOOSING THE RIGHT INHALER

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KEY MESSAGES

- The large number of available inhalation devices is both an advantage and a challenge
- All currently used inhalation devices have their benefits and drawbacks
- Inhalation errors are very common and associated with poorer clinical outcome
- If possible, using combinations of different inhalation devices should be avoided
- There is a need for increased resources for patient education in inhalation device training

In 2013 Lavorini and Usmani suggested that: "*in future, the choice of a new compound will be secondary to the need to choose the appropriate inhaler device for the patient*". Given the large number of inhalation devices available in 2021 it seems that their prediction was correct . The large number of available inhalation devices facilitates, at least in theory, to find the right inhaler for the right patient, but is also a challenge since there is much to choose between (Figure 1).

The three dominating types of devices for inhalation therapy are pressurised metered dose inhalers (pMDI), dry powder inhalers (DPI) and soft mist inhalers (SMI). All three types of inhales have their benefits and draw backs (Table 1). Different inhalation technique is necessary for different types of inhalers (Table 1). As the inhalation technique differs between different types of inhalers it is an advantage if combinations of different inhalation principle are avoided.

One important benefit with DPI are that they are breath actuated and do not require coordination to same extent as pMDI and SMI. A main drawback with DPI is that the patient needs to reach an inspiratory flow rate of 30 L/min or higher in order to get optimal distribution of the drug to the patient.

Many pMDI contain suspensions and therefor need shaking prior to inhalation. pMDI deliver particles at a set velocity. When the aerosol is generated, a low inhalation flow decreases the loss of aerosol particles. In practice, this demands a "spacer". A drawback with pMDI is that hydrofluorocarbons are used as propellant in the devices. This means that the carbon footprints from a pMDI is higher than for a DPI and SMI.

Inhalers deliver particles with a broad particle size distribution. This limits the potential for special inhalation strategies. Large particles > 5 µm are deposited in oropharynx while small particles < 1 µm are largely lost by exhalation.

Regardless of the choice of inhalers, inhalation device errors are very common. In a study from 2017, Price and co-workers found that the majority of patients made at least one inhalation error. These errors were associated with worse clinical outcome. The errors include problems with the inspiratory manoeuvre – insufficient inhalation manoeuvre for DPI and not inhaling slow and deep for pMDI, incorrect positioning of the device and not shaking the pMDI or conversely shaking the DPI. Another problem especially for DPIs is the

Figure 1 **Examples of available inhalation devices.**

TABLE 1

	pMDI	DPI	SMI
Coordination	Needed	Not needed	Needed but less important than for pMDI
Optimal inhalation technique	Slow inhalation	Quick inhalation	Slow inhalation
Inspiratory flow	Not critical	Must be over 30 L/min	Not critical
Environmental aspects	Contains propellants with high global warming potential	Do not contain propellants	Do not contain propellants with high global warming potential
Particle size	Varies between different devices	Varies between different devices	2-4µm
Shake before using	Should be done for most devices (suspensions)	Not necessary*	Not necessary
Need for breath holding after actuation	Inhalation time + breath-hold optimally 5-10 s	Inhalation time + breath-hold optimally 5-10 s	The dose is generated during seconds
Drugs classes available	All	All	Only LAMA and LABA

pMDI = pressurised metered dose inhalers, DPI = dry powder inhalers, SMI = soft mist inhalers, LAMA = long acting muscarinic antagonists, LABA = long acting beta-2-agonists)

**With some exceptions such as the BUD/FORM Easyhaler*

storage of the device. Many patients keep their inhalers in bathrooms where the humidity may be high and this can influence that performance of some DPI devices.

The problem with handling inhalation devices in a correct way shows that there is need for patient education. In a systematic review it was found that patient education improves inhalation technique at least in the short term, but so far there is insufficient data to show that this improves the clinical outcome. Repeated assessment and training are recommended to insure sustainable effect.

In conclusion, there are a large number of inhalers to choose between which potentially facilitates the possibility of finding the right inhaler to the right patient. All types of inhalers have their benefits and drawbacks. Combinations of different inhalation devices should be avoided. Given the high prevalence of device handling errors, increased resources for inhalation device training are needed.

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6 UPDATES ON ANTI-LEUKOTRIENES

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KEY MESSAGES

- Cysteinyl leukotrienes (CysLT) are considered major mediators driving type-2 inflammation in the asthmatic airways (via direct activation of eosinophils and mast cells and by indirect activation of the innate immune responses)
- Leukotriene receptor antagonists (LTRA) have been widely used in the management of adult and pediatric asthmatic patients, however, further research is needed to identify responders
- Other types of anti-leukotrienes targeting other types of cysLT receptor or different targets from the leuokotriene pathway are required

Asthma is a chronic heterogeneous airway disease with various phenotypes and heterogenous drug responsiveness to anti-asthmatic medications. It is well known that cysteinyl leukotrienes (cysLT) C4/D4/E4 (Figure 1) are important mediators in the pathogenesis of asthma by enhancing cytokine release from inflammatory and structural cells, leading to airway inflammation and remodeling. Through the cysteinyl leukotriene receptor type 1 or other receptors such as purinergic receptor P2Y12 CysLT mediate activation of type 2 (T2) inflammatory cells, including mast cells, eosinophils, T helper 2 cells and group 2 innate lymphoid cells, induce vascular leak, bronchoconstriction, and excess mucus secretion. Stimulated mast cells and eosinophils release chemical mediators and cytokines, which further enhance T2 airway inflammation via activated airway epithelial cells and platelets. Recent studies suggest that cysLT could activate innate immune responses with up-regulated IL-33/thymic stromal lymphopoietin production from airway epithelial cells, which further facilitate T2 inflammation. Among asthma phenotypes, aspirin/NSAID-exacerbated respiratory disease (NERD) is characterized by moderate-to-severe asthma, higher prevalence of chronic rhinosinusitis/nasal polyps as well as aspirin/NSAID hypersensitivity. Its major pathogenic mechanism is overproduction of cysLTs and eosinophil activation, where cysLT-mediated airway inflammation is exaggerated in upper and lower airway mucosa, which is further exacerbated when exposure to aspirin/NSAIDs.

There is still increasing interest regarding the role of cysLTs and of the leukotriene receptor antagonists (LTRA) in the management of asthma. LTRAs have been approved in the treatment asthma two decades ago. Type 1 LTRAs (montelukast, pranlukast, zafirlukast) have been widely prescribed in clinical practice, while 5-lipoxygenase inhibitor (zileuton) use is limited to a few countries like the United States. Numerous controlled trials and real-world studies demonstrated the beneficial effects on symptom control and prevention of asthma exacerbation in the management of pediatric and adult asthmatics, however, whether LTRAs are effective in attenuating airway remodeling in asthmatic airways is uncertain. Some adult asthmatics show insignificant responses to LTRAs, while some specific phenotypes of adult asthma such as NERD, elderly asthma, asthma comorbid with obesity and allergic rhinitis have more favorable responses. In addition, LTRA prevents exercise-in-

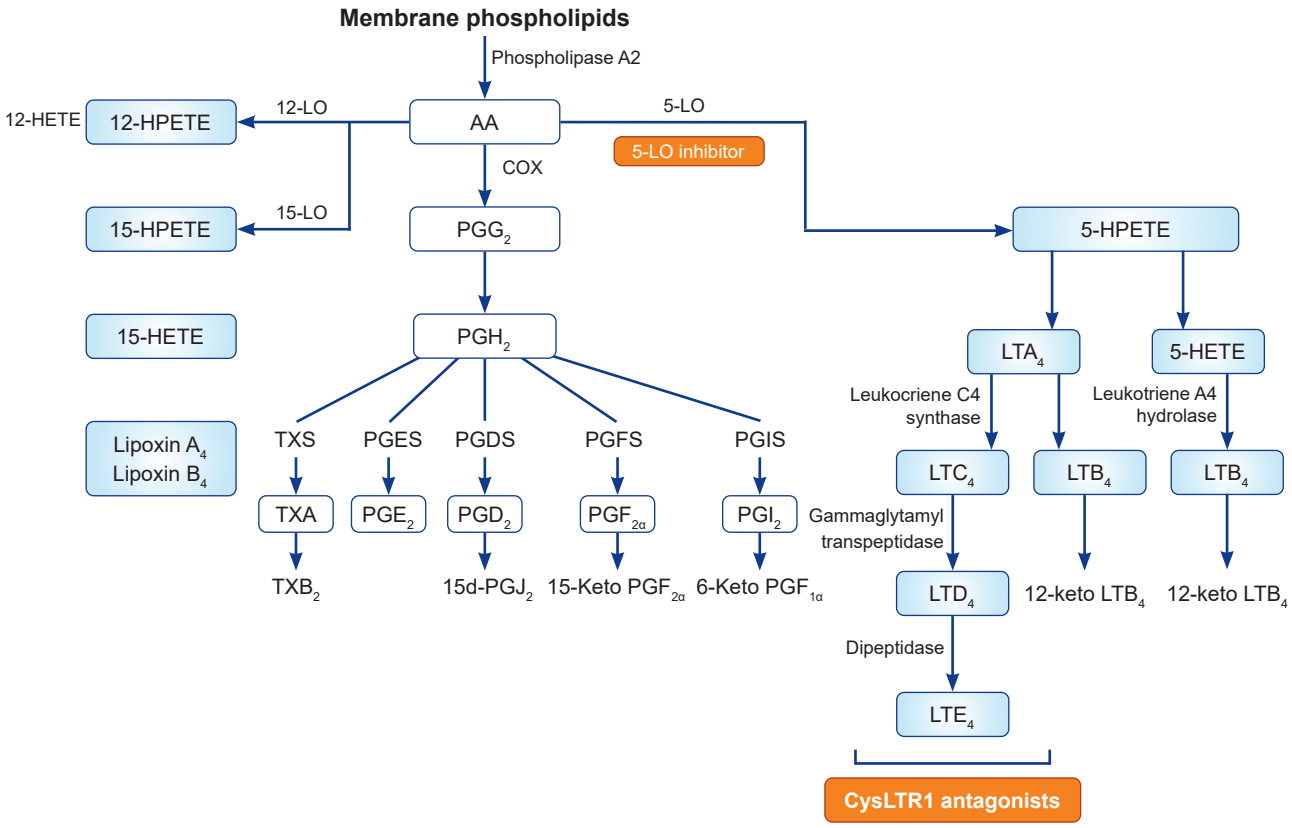

Figure 1 **Arachidonic acid (AA) pathways and anti-leukotrienes.**
LO - Lipoxygenase; PG - Prostaglandin; LT - Leukotriene

duced bronchoconstriction and viral-induced wheezing episode in childhood asthmatic patients. There is still an unmet need left to identify useful biomarkers for identifying asthmatic patients who will benefit more from LTRA use.

LTRAs are generally considered as safe drugs, however concerns have been raised relating to rare adverse reactions including the possibility of increased suicidality, although the available data are insufficient to confirm this.

Further investigations are needed to understand the role of cysLTs in airway inflammation and remodeling. Additional leukotriene modifiers targeting other types of cysLT receptors (P2R receptor) should be considered.

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7 TARGETED TREATMENT OF ASTHMA: GENERAL PRINCIPLES

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KEY MESSAGES

- Most patients with asthma are treated with "*one-size-fits-all*" therapies such as inhaled corticosteroids and long-acting β_2-agonists
- Several different phenotypes of asthma within the asthma syndrome are recognised, including inflammatory phenotypes (eosinophilic, neutrophilic, paucigranulocytic)
- These phenotypes may be the consequence of specific molecular and cellular pathways or endotypes
- Endotypes and phenotypes may be targeted by more specific therapies, which may be small molecules or antibodies
- Several endotypes of severe asthma are recognised that may be targeted therapeutically to give better control of asthma
- Biomarkers are important in identifying these endotypes in order to select the best patients for targeted therapy

The recent introduction of biological therapies for severe asthma has highlighted the need to recognise which patients will benefit most from these expensive targeted treatments. Asthma is a clinical syndrome with characteristic variable symptoms. The diagnosis is confirmed by reversible airways obstruction and airway hyperresponsiveness. The most widely used effective treatments for asthma (when taken correctly) are inhaled corticosteroids (ICS). However, 5-10% of patients, classified as severe asthma (GINA Steps 4 and 5) remain poorly controlled. Biological therapies may be very effective in selected patients with severe asthma, indicating the heterogeneity of asthma.

CLINICAL PHENOTYPES

It has long been recognised that, although all asthmatics may fit into the diagnosis of asthma, there are differences between patients. For many years a distinction has been made between early onset allergic asthma (diagnosed by positive skin prick tests for common inhalant allergens or increased specific IgE) ('extrinsic' asthma) and late onset often non-allergic ('intrinsic') asthma. However, the management of these 2 phenotypes was generally the same. Other clinical phenotypes include nocturnal, exercise-induced, cough-variant and obesity-related asthma, although these have not been not helpful in selecting therapy. Cluster analysis of large cohorts of asthma patients reported aggregation of clinical attributes but these were often not consistent between different cohorts and were often found to be unstable over time and were not useful in choosing therapy.

SPUTUM INFLAMMATORY PHENOTYPES

What has proved to be more useful for tailoring asthma treatment is cellular phenotyping based on different patterns of inflammatory cells in the sputum, with some patients showing high eosinophils, others higher neutrophils, some a mixed cellularity and a few patients with no increase in inflammatory cells (paucigranulocytic). The pattern of sputum inflammation predicts the clinical efficacy of ICS in asthma, with eosinophilic and mixed granulocytic inflammation responding well, whereas neutrophilic and paucigranulocytic responds less well. In many patients with severe asthma the sputum eosinophil count is per-

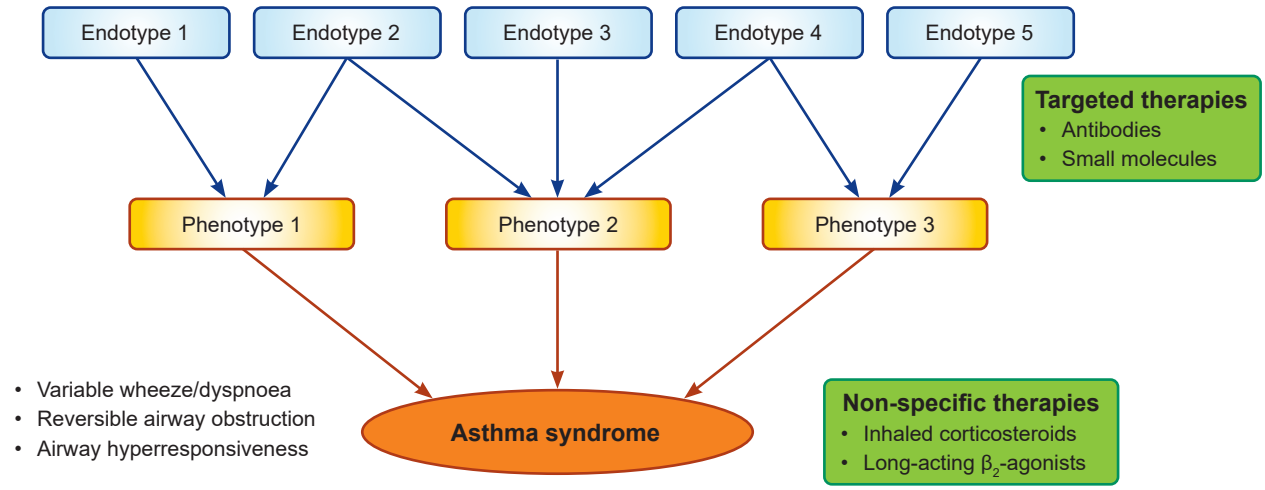

Figure 1 **Several endotypes and phenotypes may result in the clinically described asthma syndrome and these may be targeted by different specific therapies.**

sistently high as these patients are thought to be relatively resistant to the anti-inflammatory effects of ICS.

ASTHMA ENDOTYPES

Different molecular and cellular pathways (endotypes) may lead to differing inflammatory patterns in asthma that result in different clinical phenotypes (Figure 1). A logical approach is to target these specific pathways with targeted interventions, which could be small molecules or monoclonal antibodies (Mab). This has led to the development of blocking Mab against the cytokines or their receptors that are thought to drive these endotypes. The use of -omics, such as transcriptomics and proteomics, has confirmed these differences in inflammatory patterns, but also identified new endotypes, such as a rare endotype with increased IL-6 trans-signalling.

TARGETING T2 ASTHMA

It is likely that there are several molecular mechanisms (endotypes) underlying type 2 (T2) immunity, which is due to an increase in IL-4, IL-5 and IL-13 from Th2 and T innate lymphoid cells (ILC2) (Table 1). ICS are effective in most patients with T2 immunity but some patients with severe asthma have persistent eosinophilia despite high doses or inhaler or even systemic corticosteroids and may require targeted therapy.

TARGETING NON-T2 ASTHMA

Approximately 50% of patients with severe asthma do not have increased eosinophils and may have a neutrophilic pattern of inflammation or no inflammation at all (Table 2). At present there are few specific treatments for these non-T2 patients.

BIOMARKERS

Biomarkers are of critical importance in selecting the most suitable patients for targeted therapies and are sometimes useful to monitor response. The most useful biomarkers have been blood eosinophils (>300/µl indicates T2 endotype) and fractional exhaled nitric oxide (FeNO) (>50ppb predicts dupilumab efficacy). Plasma periostin and DPP4 have not proved to be very useful for T2 asthma as affected by many different factors. There are no good biomarkers for non-T2 asthma.

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TABLE 1

Targeting T2 asthma

Phenotype	Biomarker	Target	Current treatment	Future treatment
Early onset allergic	↑ Total IgE (but not predictive of response)	Specific IgE	Omalizumab Allergen immunotherapy	Higher affinity anti-IgE antibodies
Eosinophilic	↑ Blood/sputum eosinophils	IL-5	Mepolizumab Reslizumab	Anti-TSLP (e.g. tezepelumab)
	↑ FeNO	IL-5Rα IL-4Rα	Benralizumab Dupilumab	Anti-IL-33/ST2 (e.g. etokinumab)
Aspirin-sensitive	High urinary LTE4	Cys-LT1R 5-LO	Anti-leukotrienes 5-LO inhibitors	
ABPA	↑ *Aspergillus* IgE	*Aspergillus* T2 immune response	Anti-fungals (e.g. itraconazole)	Dupilumab
EGPA	↑↑ Eosinophils	IL-5	Immunosuppresives Anti-IL-5	

ABPA - allergic bronchopulmonary aspegillosis; cys-LT - cysteinyl-leukotriene; EGPA - eosinophilic granulomatosis with poly-angiitis; FeNO - fractional exhaled nitric oxide; IL - interleukin; LO - lipoxygenase; TS - trans-signaling; TSLP - thymic stromal lymphopoeitin

TABLE 2

Targeting non-T2 asthma

Phenotype/ Endotype	Biomarker	Target	Current treatment	Future treatment
Neutrophilic	↑ Sputum neutrophils	IL-17	Macrolides	Anti-IL-17 (e.g. brodalumab)
	↑ Blood YKL40?	IL-22		Anti-IL-22 (e.g. fezakinumab)
		IL-23		Anti-IL-23 (e.g. risankizumab)
		Bacterial infection?		
		Inflammasome		Inflammasome inhibitors
Smoking-related	↑ Sputum neutrophils	CXCL8, IL-17	Smoking cessation	Statins?
Obesity-related	↑ Sputum neutrophils ↑ Leptin	Inflammasome	Weight reduction	Inflammasome inhibitors
Paucigranulocytic	No ↑ in sputum Inflammatory cells	M_3-receptors ASM	LAMA Bronchial thermoplasty	Selective targeted denervation

ASM - airway smooth muscle; IL - interleukin; LAMA - long-acting muscarinic antagonist; M – muscarinic; YKL - chitinase-3 like protein-1.

8a TARGETED TREATMENT OF T2 ASTHMA: ANTI-IMMUNOGLOBULIN E

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KEY MESSAGES

- The IgE driven asthma endotype is highly prevalent in childhood-onset asthma
- The anti IgE monoclonal antibody (omalizumab) binds free IgE and blocks the allergic cascade by preventing binding of IgE with its high-affinity FcεRI receptors on dendritic cells and inflammatory cells
- Omalizumab reduces asthma exacerbations, improves symptoms, rescue medication use and quality-of-life
- Real world evidence on its effectiveness and long-term safety data complement its efficacy data for pediatric and adult patients with severe asthma

Immunoglobulin E (IgE) is a key molecule involved in allergic asthma, a major subtype of type 2 (T2) asthma, highly prevalent in childhood-onset asthma. A humanized monoclonal anti-IgE antibody (omalizumab) binds free IgE and blocks the allergic cascade by preventing binding of IgE with its high-affinity FcεRI receptors on mast cells, basophils, dendritic cells and other inflammatory cells (Figure 1). Omalizumab efficacy has been documented in adults, adolescents and children with moderate-to-severe and severe allergic asthma. As compared to placebo or standard of care, omalizumab reduces asthma exacerbations, and it improves symptoms, rescue medication use and quality-of-life. Omalizumab (Xolair®) is indicated as an add-on therapy for children (from 6-year old), adolescents and adults with uncontrolled severe persistent allergic asthma. Since approval, real-world benefits have been reported. In addition, long-term safety data have been obtained from randomized clinical trials, registries and prospective cohorts. Omalizumab dosing is individualized according to bodyweight and serum IgE level. It is administered subcutaneously every 2 to 4 weeks. In severe allergic asthma, research programs are investigating the optimal duration of therapy and accurate predictors of response to therapy.

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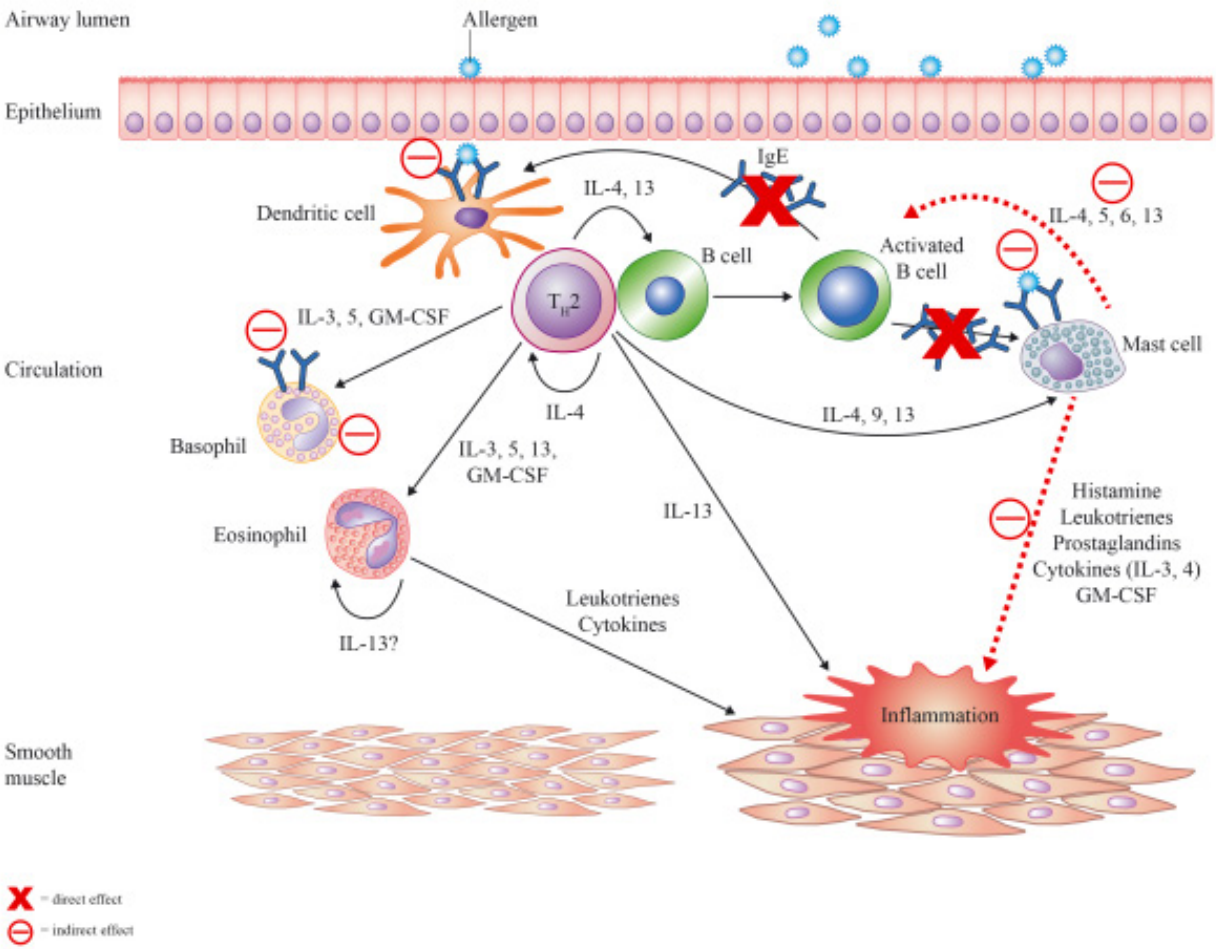

Figure 1 **The allergic cascade and the role of anti-IgE.**
GM-CSF - granulocyte-macrophage colony-stimulating factor; IgE - immunoglobulin E; IL - interleukin.
(Reproduced from Allergy Clin Immunol Pract, Omalizumab in asthma: an update on recent developments, Vol 2, Humbert M et al., 525-536, 2014 with permission from Elsevier)

8b TARGETED TREATMENT OF T2 ASTHMA WITH IL-4/IL-13 RECEPTOR ANTIBODY THERAPY

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KEY MESSAGES

- Type 2 (T2) inflammation, characterized by the presence of interleukins (IL)-4, -5, and -13, is the most common pathogenetic pathway causing asthma, and IL-4 and -13 play key roles in the immunologic and inflammatory processes in T2 asthma
- Dupilumab is a fully human monoclonal antibody which binds to the IL-4 receptor alpha-chain, blocking the binding of IL-4 and -13 and subsequent signaling
- In patients poorly-controlled by inhaled corticosteroids/long-acting beta-agonists, dupilumab has been shown to significantly reduce severe asthma exacerbations and improve lung function and patient-reported outcomes; these effects were enhanced in patients with elevation of T2 biomarkers. In patients who required chronic therapy with oral corticosteroids, dupilumab resulted in a significant reduction in daily corticosteroid dose along with significant reductions in asthma exacerbation rate and improvement in pulmonary function
- Dupilumab significantly reduced important biomarkers of T2 asthma, including exhaled nitric oxide and total serum IgE, consistent with the mechanism of action of this medication in asthma
- Dupilumab was generally well-tolerated, and mild, transient increases in blood eosinophils were noted and likely caused by changes in eosinophil trafficking

Interleukins (IL)-4 and -13 are pleiotropic cytokines which drive many of the pathologic processes observed in type 2 (T2) inflammation. These cytokines are encoded by adjacent genes, share regulatory elements (e.g., GATA-3) and transmit signals through a shared functional receptor complex (IL-4Rα/IL-13Rα1). While IL-4 has plays a critical role in airway immunology (regulation of Th2 cell proliferation and IgE synthesis), IL-13 is a key effector molecule, increasing airway hyperresponsiveness, goblet cell development and mucus production, subepithelial fibrosis and airway recruitment of eosinophils (Figure 1).

Dupilumab is a fully human monoclonal antibody directed against the IL-4 receptor α (IL-4Rα) subunit common to both IL-4 and IL-4/IL-13 receptor complexes and is the first biologic therapy to target both IL-4 and IL-13 signaling. Dupilumab is approved in the US and EU as add-on maintenance treatment for patients 12 years of age and older with moderate-severe uncontrolled asthma with a T2 inflammatory/eosinophilic phenotype or oral cortiocosteroid-requiring asthma. It is also approved for nasal polyposis and atopic dermatitis.

The phase 2b (DRI12544) and 3 (QUEST) trials of dupilumab included patients with uncontrolled, moderate-severe asthma receiving treatment with medium-high doses of inhaled corticosteroids plus long-acting beta-agonists. There was no requirement for a minimum level of T2 biomarkers to participate in either study. Treatment with dupilumab 200 and 300 mg subcutaneously (SC) every 2 weeks (following a loading dose of 400 and 600 mg SC, respectively) significantly reduced the annualized rate of severe asthma exacerbations in the general study populations by 47.7% and 46% (for 200

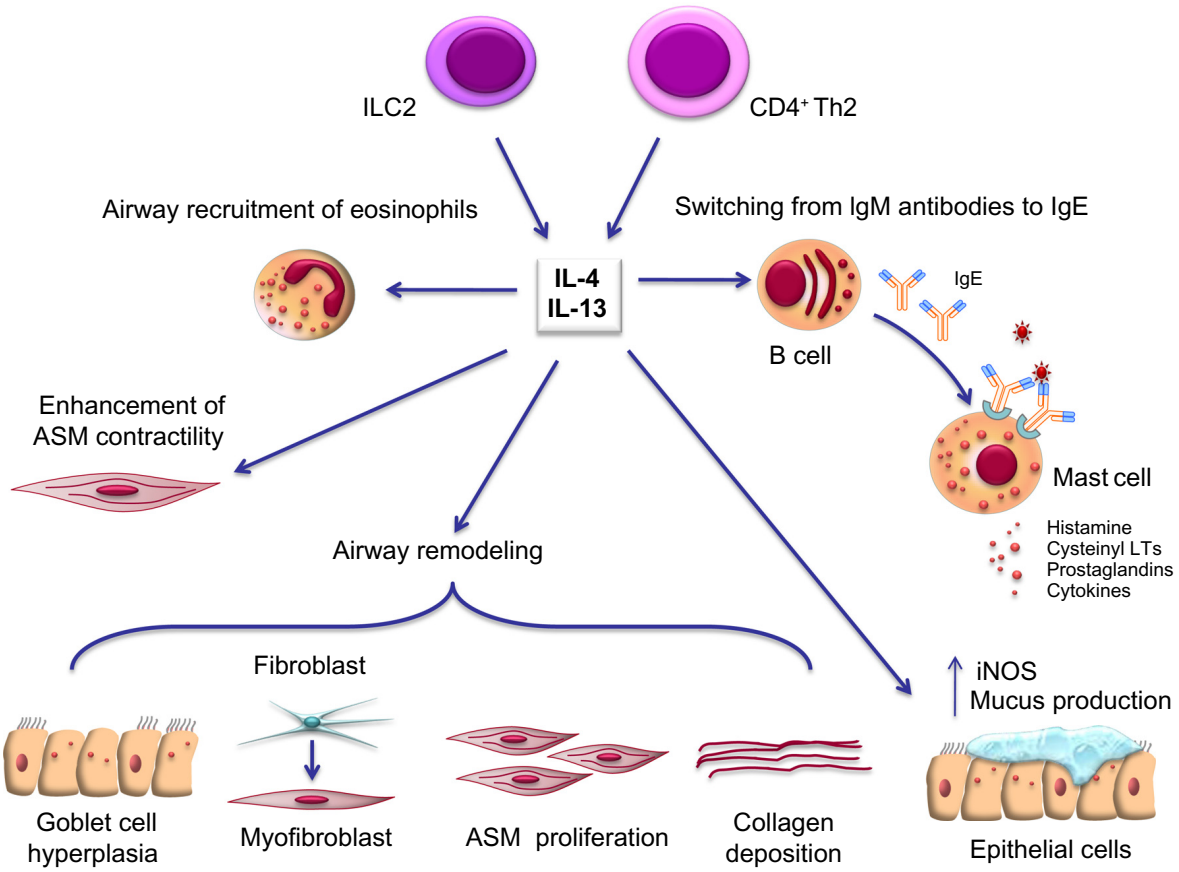

Figure 1 **Cell sources and targets for IL-4 and IL-13.**
(Reproduced from J Asthma Allergy, Vol 7, Vatrella A et al., Dupilumab: A novel treatment for asthma, 123-30, 2014 with permission from Dove Medical Press)

TABLE 1

Type 2 biomarkers from QUEST trial *				
Time point	**Placebo**	**Dupilumab (200 mg Q2WK)**	**Placebo**	**Dupilumab (300 mg Q2WK)**
Exhaled nitric oxide				
Week 12	+8.30	-21.70	+5.77	-26.70
Week 52	+5.35	-27.42	+1.34	-26.61
Total IgE				
Week 12	+23.89	-19.18	+3.06	-10.41
Week 52	+32.38	-60.75	+0.89	-58.43

** mean percent change from baseline*

and 300 mg doses) relative to placebo. In patients with documented biomarker evidence of T2 immune response (eosinophils > 150/mcl or FeNO > 25 PPB), the reduction in exacerbations was further enhanced (Table 1). The forced expiratory volume in one second (FEV1) was significantly improved by 0.14 and 0.13 L, respectively, relative to placebo after 12 weeks and improvement in FEV1 was observed as early as 2 weeks. Analysis of patient-reported outcomes demonstrated that a significantly larger proportion of dupilumab-treated patients had clinically-important improvements in the 5-Item Asthma Control and Asthma Quality of Life Questionnaires relative to placebo. Workplace productivity also improved with dupilumab, with a significant reduction in the unadjusted annualized number of sick-leave days (0.61 and 0.62 vs. 2.24).

A

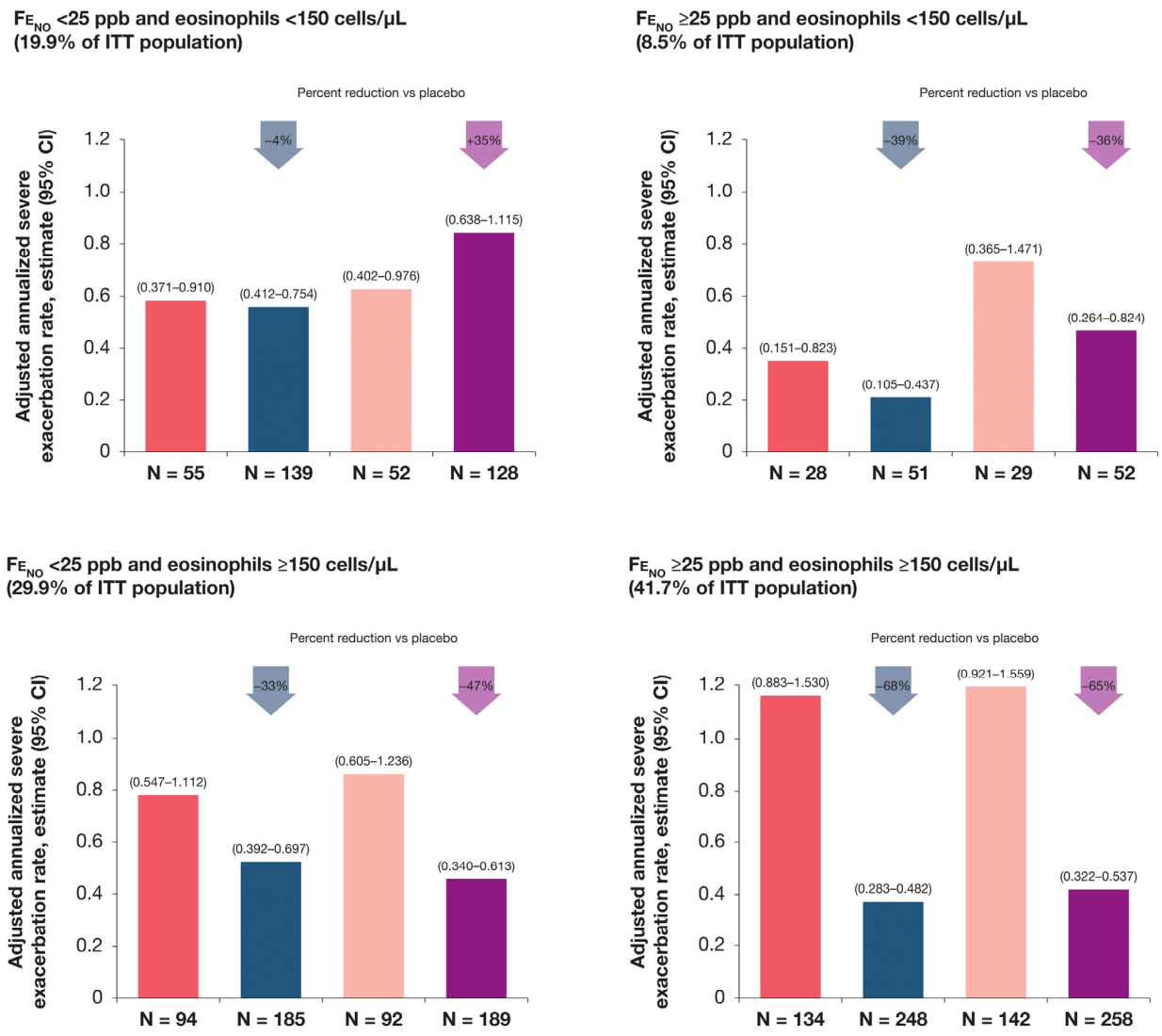

Figure 2 **Post hoc analysis of severe asthma exacerbations (A) and change from baseline in FEV1 (B) in patients with high (>25 ppb) or low (<25 ppb) baseline FENO levels and high (>150 cells/µL) or low (<150) baseline blood eosinophils.** *(reproduced from reference 3).*

The purported mechanism of action of dupilumab was supported by analyses of biomarkers from the 52 weeks QUEST study, which demonstrated significant reductions in exhaled nitric oxide and total serum IgE (Table 1).

The effect of dupilumab, 300 mg SC every 2 weeks, in patients requiring chronic treatment with oral corticosteroids (OCS) was evaluated in a 24 week trial (VENTURE). Treatment with dupilumab resulted in a significant mean reduction in OCS dose compared with placebo (-70.1% vs. -41.9%) and a significantly greater number of patients who were able to taper off of OCS completely (48% vs. 25%). Concomitant with this significant reduction in systemic corticosteroids, patients receiving dupilumab had significantly fewer asthma exacerbations and improved lung function compared to placebo (rate reduction -59% and FEV1 +0.22 L, respectively).

Dupilumab was generally well tolerated with adverse event (AE) incidence comparable to placebo; the most common AE was injection site reaction (14 and 18% vs. 6%). Hypersensitivity reactions

B

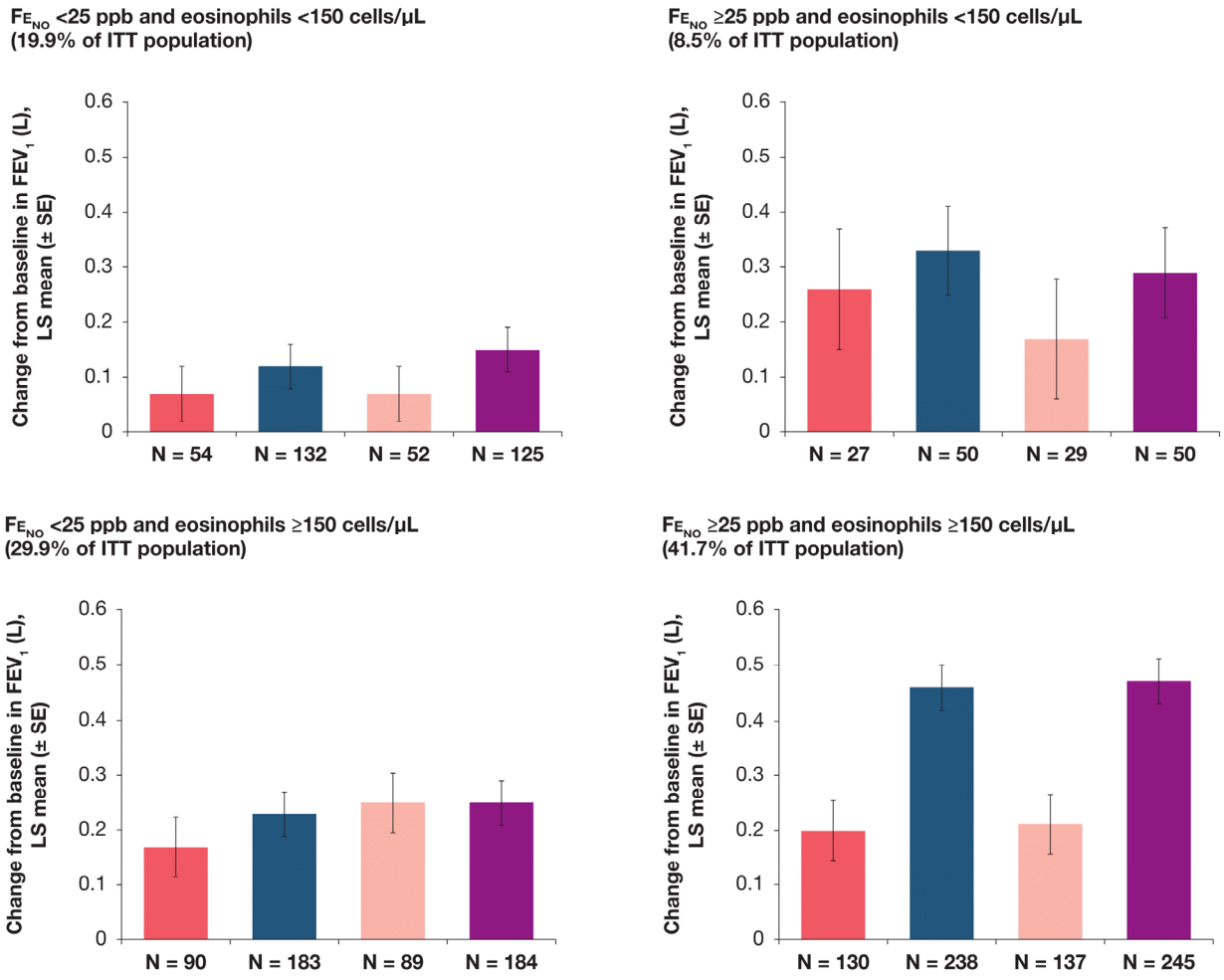

Figure 2 continued

(e.g., rash, anaphylaxis) to dupilumab during clinical trials were rare (<1%). While conjunctivitis is increased in atopic dermatitis patients treated with dupilumab, this has not been observed in patients with asthma. With regard to laboratory parameters, dupilumab-treated patients have mild increases in blood eosinophil counts after 4 weeks of therapy; this has been attributed to likely changes in eosinophil trafficking. Protocol-defined blood eosinophilia (> 3000/µL) occurred in 1.2% of dupilumab-treated patients (combined data for 200 and 300 mg doses) versus 0.3% receiving placebo in the QUEST trial and 13% versus 1% in the 24-week VENTURE trial. A small number of cases of eosinophilic pneumonia and eosinophilic granulomatosis with polyangiitis were reported. As these conditions may occur in patients with severe asthma, a causal relationship with dupilumab has not been established.

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8c TARGETED TREATMENT OF T2 ASTHMA: ANTI-IL5 THERAPIES

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KEY MESSAGES

- In patients with severe asthma, whose severity is truly dependent on eosinophils ('the eosinophil phenotype'), anti-IL5 monoclonal antibodies (benralizumab mepolizumab, and reslizumab) are safe and effective to reduce eosinophilic exacerbations and to reduce maintenance dose of oral corticosteroids (OCS). There are no head-head comparisons between the three biologicals
- The eosinophil phenotype can be identified by persistently elevated circulating eosinophils of >300/μL or sputum eosinophils >3%, particularly while on high doses of inhaled corticosteroids or under OCS
- Treatment responses are greater when sputum eosinophilia is normalized in addition to normalizing blood eosinophils
- While blood eosinophil counts are sufficient to initiate treatment, they have limited role to monitor response to treatment.
- While most exacerbations on mepolizumab and reslizumab indicating suboptimal responses are likely to be associated with persistent eosinophilia, those on benralizumab are more likely to be non-eosinophilic

Interleukin-5 (formerly called Eosinophil Differentiation Factor, originally described as T-cell replacing factor) is a homodimeric glycoprotein with a molecular mass of 40–60 kDa that is produced by type 2 (T2) cells such as T helper 2-lymphocytes, eosinophils, and mast cells in response to allergens, allergen-IgE complexes, and some bacteria and viruses. Its key function is to stimulate eosinophil colony formation and differentiation in humans and mice. IL-5 messenger RNA is also expressed in neutrophils, γδT cells, NK and NKT cells and a few non-hematopoietic cells such as epithelial cells. IL-5 acts on target cells by binding to its specific receptor (IL-5R). The consists of a unique α chain (IL-5Rα/CD125) and the common cytokine β-chain (βc/CD131) and is expressed on cells from various lineages including eosinophils, basophils, eosinophil progenitor cells, innate lymphoid cells group 2 (ILC2 cells) etc. IL-5Rα transduces signals by activating the JAK/STAT signalling molecules (particularly JAK1 and 2, STAT-5). The IL-5Rα specifically binds IL-5, while the βc chain is shared with other cytokines, including IL-3 and granulocyte/macrophage colony-stimulating factor (Figure 1).

Since eosinophil maturation and survival are critically dependent on IL-5, blocking IL-5 signalling is a reasonable strategy to treat diseases with evidence of increased eosinophil numbers in blood or in target organs such as severe asthma, hypereosinophil syndrome, eosinophil granulomatosis with polyangitis. Three biologicals are approved for clinical use (Table 1). Mepolizumab and reslizumab are neutralizing antibodies against IL-5, while benralizumab is an afucosylated molecule directed against the IL-5Rα that in addition to preventing binding of IL-5 to its receptor, facilitates NK-cell mediated antibody-dependent cellular cytotoxic lysis of the eosinophil. All three biologicals are effective in reducing asthma exacerbations and in improving asthma symptoms and quality of life in patients of all asthma severities. In addition, mepolizumab and benrali-

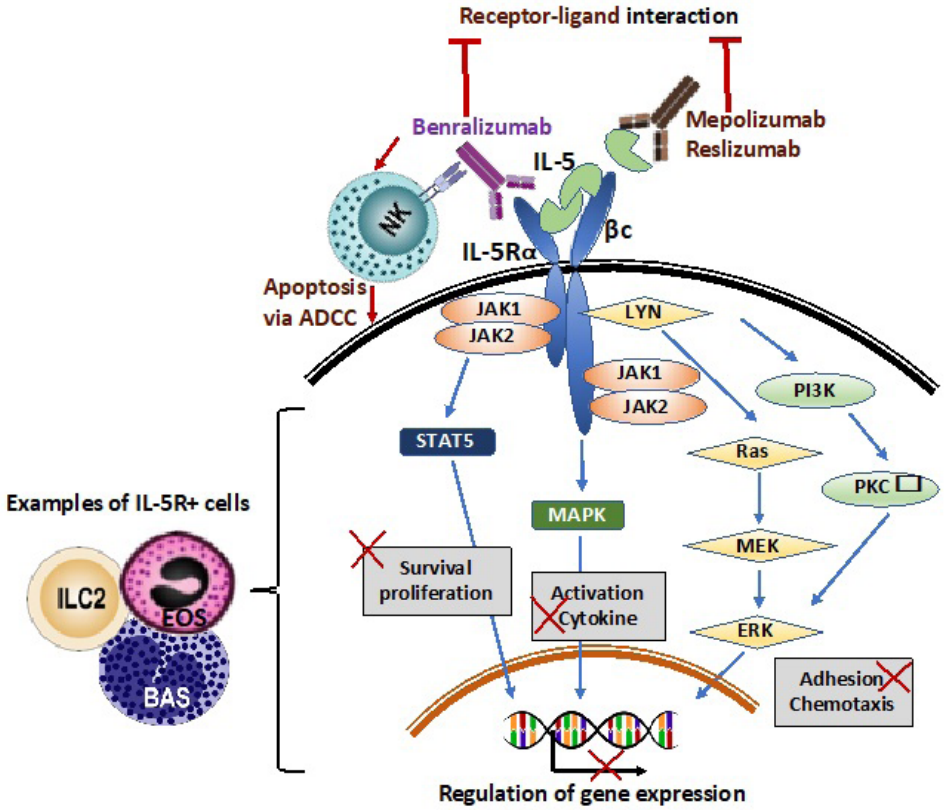

Figure 1 **Schematic of IL-5 signalling and targeted anti IL-5 intervention.** Signal transduction pathways of IL-5 via IL-5R α is depicted for IL-5R α positive⁺ cells (e.g. eosinophils, basophils and ILC2). The two receptor chains (α and βc) are shown in the cell membrane. Signalling molecules associated with the cytoplasmic tail of the receptor chains (JAK1/JAK2/LYN), those in the cytoplasm (STAT5/MAPK/PI3K/ERK) and the activation effect of each pathway are indicated in grey boxes. Benralizumab acts via blocking the IL-5Rα chain that blocks the ligand (IL-5) interacting with the receptor and *via* recruitment of FcγRIII expressing NK cells to induce apoptosis of the bounded cell. Mepolizumab and reslizumab act via binding/neutralisation of the ligand (IL-5), thereby limiting receptor-ligand interaction. All anti_IL5 biologicals block the intracellulat IL-5 signalling cascade.

JAK - janus kinases; STAT – signal transducers and activators of transcription; PI3K – phophoinositide 3-kinase; MAPK – mitogen-activated protein kinase; ADCC – antibody dependent cytotoxic killing; NK – natural killer cell.

(Reprinted from Elsevier Books, Gleich GJ, Eosinophils in Health and Disease, page 97, chapter 5.4, 2013, with permission from Elsevier)

zumab also facilitate significant dose reduction in maintenance oral corticosteroids (OCS).

No direct head-head comparisons have been made between these three biologicals. However, for the severe OCS-dependent patients, mepolizumab in its approved dose is associated with less airway eosinophil suppression than reslizumab and benralizumab. This is particularly observed in a small proportion of patients who may have airway polyclonal autoimmune responses.

While blood eosinophil is useful to select patients for these monoclonal antibodies, they are less helpful than sputum eosinophil numbers to monitor responses. Sub-optimal responses while on mepolizumab or reslizumab are mostly eosinophilic due to inadequate doses or immune complex mediated complement activation, those on benralizumab are largely neutrophilic due to airway infections. Thus, monitoring sputum cellularity is relevant to suggest optimal management of these exacerbations.

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TABLE 1

A comparative analysis of the anti-IL-5/R monoclonal antibodies

Parameters	Mepolizumab	Reslizumab	Benralizumab
Approval	November 2015	March 2016	November 2017
Target	IL-5	IL-5	IL-5Rα
Tradename	Nucala®	Cinqair®	Fasenra®
Biochemical make-up	IgG_1 k mAb; 149 kDa	IgG_4 k mAb; 147 kDa	IgG_1 k mAb; 146 kDa
Protein binding (dissociation constant)	100pm (with IL-5)	81pm (with IL-5)	16pm (with IL-5Rα) 45.5 nm (FcγRIII)*
Half-life	16-22 days	24 days	15-18 days
Clearance	0.28L/day	7mL/hr	0.29L/day
Dosing regime	100 mg fixed dose Q4W	Weight-adjusted dosing of 3mg/kg Q4W	30 mg Q4W x 3months, then Q8W
Route of administration	Subcutaneous	Intravenous	Subcutaneous
Patient population	Severe eosinophilic asthma inadequately controlled despite treatment based on GINA 4-5 steps, blood eosinophil level ≥ 150-300 cells/µL; 12 years and older	Severe eosinophilic asthma unresponsive to other GINA step 4-5 treatments; blood eosinophil level ≥ 400 cells/µL; 18 years and older	Severe eosinophilic asthma unresponsive to other GINA step 4-5 treatments ; blood eosinophil level ≥300 cells/µL; 12 years and older
Mechanism of action	Binds to IL-5 ligand and prevents its IL-5 receptor and thereby inhibits production and survival of eosinophils	Binds to IL-5 ligand and prevents its binding to the IL-5 receptor and thereby inhibits production and survival of eosinophils	Binds to α chain of IL-5R and blocks signaling and interaction of IL-5; causes apoptosis of IL-5R+ cells by antibody dependent cytotoxic killing
Reported clinical efficacy as per RCTs	• ~50-70% reduction in exacerbations • decreases total use of OCS • complete weaning of OCS in 14% of patients	• reduces exacerbations by ~50-60% • Has not been evaluated for OCS weaning	• ~70% reduction in exacerbation • 75% median reduction in daily OCS use • discontinuation of OCS use in 52% of eligible patients
Adverse Reactions	Hypersensitivity reactions and opportunistic infections (herpes zoster), low prevalence of neutralizing ADA	Black box warning - ~0.3% risk of anaphylaxis in clinical trials, low prevalence of neutralizing ADA	Rarely causes hypersensitivity reactions, low prevalence of neutralizing ADA

**benralizumab binds to IL-5Rα with low affinity, but being afucosylated binds to FcγRIII with very high affinity. kDA – kilo Dalton; GINA – Global Initiative for Asthma (https://ginasthma.org/). Information tabulated from McGregor et al 2019 and https://www.drugbank.ca/ (accessed 14 May 2020)*

ADA - anti-drug antibodies; OCS - oral corticosteroids; Q4W - once per month; Q8W - once every other month

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9 TARGETED TREATMENT OF NON-T2 ASTHMA

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KEY MESSAGES

- Non- type 2 (T2) asthma is a distinct endotype with relevant features such as increased severity and remodelling and poorer response to anti-inflammatory treatment
- Several pathogenic pathways were evaluated, such as the dysregulated innate immune response, including neutrophil intrinsic abnormalities, the inflammasome pathway, the activation of the IL-17 pathway, together with the airway smooth mucle (ASM), mucus and epithelium abnormalities
- No endotype driven interventions were tested for non-T2 asthma, however several approaches might be anticipated based on the postulated pathogenetic pathways
- Current approaches are low-dose macrolides, ultrafine particles targeting the small airways, triple-therapy (ICS/LABA/LAMA), biologicals targeting the epithelial cytokines TSLP and IL-33/ST2 and bronchial thermoplasty
- Potential future approaches target the abnormal mucus and the altered ASM phenotype (bitter taste and olfactory receptors)

Several studies identified non-type 2 (T2) asthma as a distinct endotype with relevant features such as increased severity and remodelling and poorer response to anti-inflammatory treatment.

The breakthrough in asthma phenotyping and its stratified approach was the introduction of induced sputum inflammometry in guiding clinical decisions and for the estimation of future risk. Several induced sputum inflammatory asthma phenotypes (eosinophilic, neutrophilic, mixed, paucigranulocytic) were validated and are in current use (Figure 1). The most recently described is the columnar epithelial cell "high" asthma associated with male gender, severe asthma and non-neutrophilic airway inflammation. This approach was further complemented by molecular phenotyping studies. Using microarray and polymerase chain reaction (PCR) analyses of airway epithelial cells (AECs) brushings Woodruff was the first to classify asthma as type 2 (T2) or non-T2, based on high or low expression of IL-13-inducible genes (periostin, chloride channel regulator 1 (CLCA1), and serpin peptidase inhibitor, clade B, member 2 (SERPINB2)). This classification was validated through reproducibility on repeated examination, correlation with cytokine expression in bronchial biopsies and with markers of inflammation and remodelling and by association with significant outcomes such as lung function and responsiveness to inhaled corticosteroids (ICS). The evaluation of the airways microbiome further complemented the understanding of non-T2 asthma. Airway microbiology is significantly less diverse and more dissimilar in non-T2 asthma. Sputum neutrophils, but not eosinophils, correlated significantly with the diversity measures. In patients with neutrophilic asthma there is greater abundance of pathogenic taxa and reduced *Streptococcus*, *Gemella*, and *Porphyromonas*. Multivariate regression confirmed sputum neutrophil proportion as the strongest predictor of microbiota composition.

It is important however to underline that the inflammatory pheno-

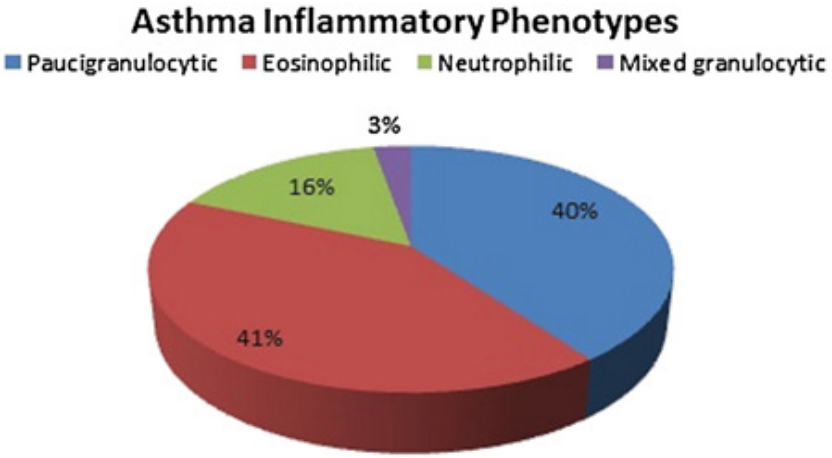

Figure 1 **Adult asthma phenotypes based on induced sputum.**
(reproduced from Schleich FN et al. BMC Pulm Med. 2013;13:11.)

type does not always reflect the underlying pathogenetic mechanism. In children with severe, therapy resistant asthma, steroid resistant airway eosinophilia had very little evidence of T2 cytokines association, in either induced sputum, BAL or endobronchial biopsies. Sputum transcriptomics in adults with severe asthma and moderate sputum eosinophilia showed instead of the expected T2 profile, upregulation of genes involved in metabolic or IL-6 modulated pathways, ubiquitination and mitochondrial function. Conversely, a recent phenotype with neutrophilic inflammation, infection and steroid resistance had very high levels of IL-13.

The understanding of non-T2 asthma mechanisms lags far behind T2-asthma. Several pathways were evaluated, such as the dysregulated innate immune response, including neutrophil intrinsic abnormalities, the inflammasome pathway and the activation of the IL-17 pathway (Figure 2). In severe asthma with predominantly neutrophilic phenotype transcobalamin-1, metalloproteinase (MMP) 9, mucins, and oxidative stress responses are upregulated. The gene signature in sputum T cells included IL-17-inducible chemokines (CXCL1-3, IL8, and CSF3) and chemoattractants for neutrophils (IL8, CCL3, and galectin-3), T cells, and monocytes. A protein interaction network (CEACAM5, CD14, and TLR2) highlighted signatures of responses to bacterial infections. Several modulators of the non-T2 astha endotype are described, including age, metabolic or epigenetic factors or the activation of the epithelial-mesenchymal trophic unit.

Until now no endotype driven interventions were tested for non-T2 asthma, however several approaches might be anticipated based on the postulated pathogenetic pathways (Figure 2).

First, for an increased sputum neutrophil percentage one must choose between several scenarios: a) an increase in overall inflammation; b) an increase in IL-17 driven neutrophil recruitment; c) a change in neutrophil partitioning between tissue and lumen; d) a relative reduction in other inflammatory cells such as eosinophils and macrophages. Assessing the anatomic localization (e.g., intra-epithelial, lamina propria, or luminal), activation status, and functional phenotypes of neutrophils is crucial. The distinction between various triggers of neutrophilic inflammation (infection, GERD with aspiration, rhinosinusitis, pollutants, bacterial components in indoor dust or high dose ICS increasing neutrophil survival) is of equal importance for the therapeutic decision.

In the AMAZES study low-dose oral azithromycin (500 mg three times per week) for 48 weeks reduced asthma exacerbations, improved quality of life and reduced *Haemophilus influenzae* load. However, it did not significantly affect levels of *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, or *Moraxella catarrhalis*. Moreover, five macrolide resistance genes and two tetracycline resistance genes were increased significantly.

Following chronic inflammation in asthma airway structural changes occur including subepithelial fibrosis, increased airway smooth muscle (ASM) mass, gland en-

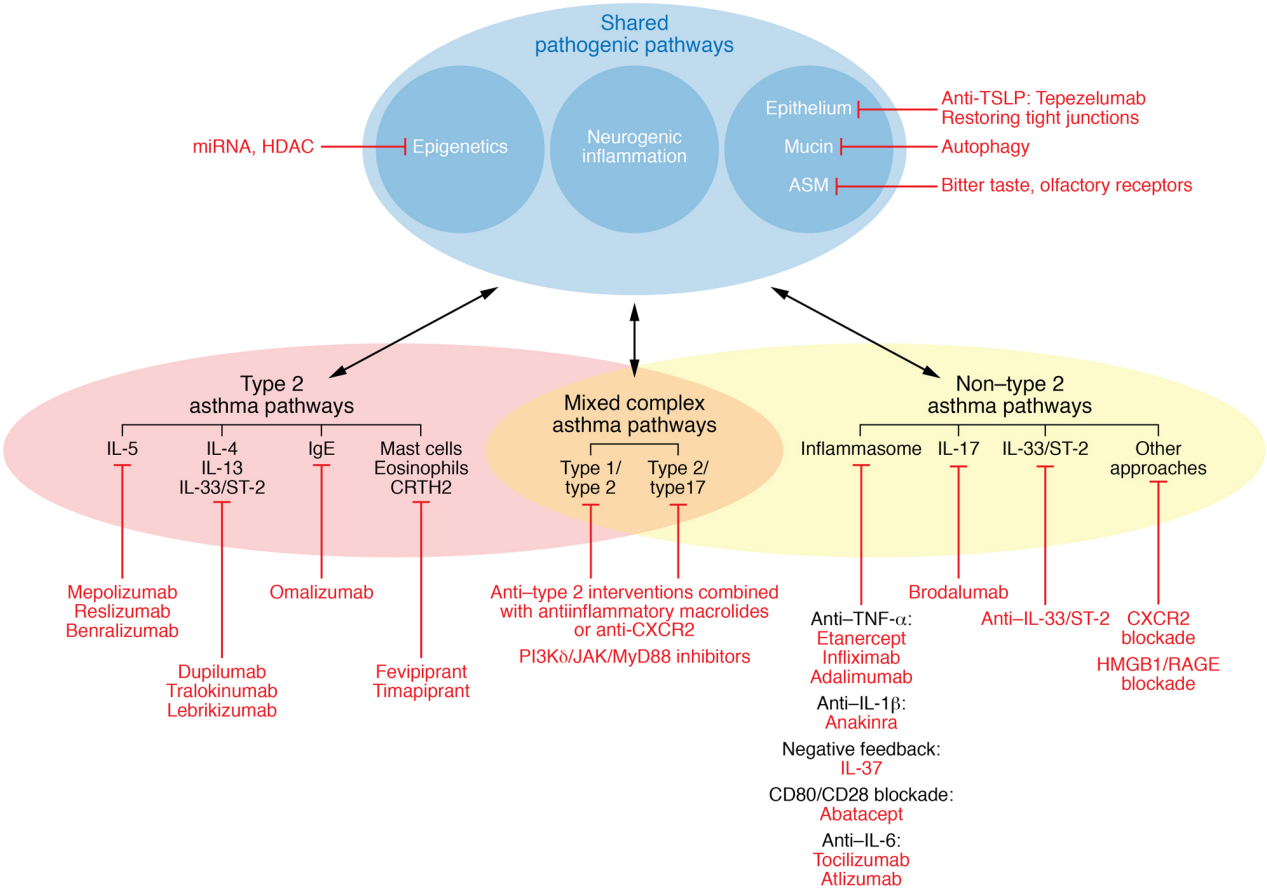

Figure 2 **The endotype driven approach in asthma.**
(reproduced from Agache I, Akdis C. J Clin Invest. 2019;129(4):)

largement, neovascularization and epithelial alterations. Extensive remodelling seems to be an important visible trait of non-T2 asthma.

New drugs targeting MUC5AC secretion and production such as flavonoids, glycoside and steroid-like natural compounds have acquired great attention due to their anti-inflammatory and muco-regulatory effects. Accumulating evidence indicates that peroxisome proliferator-activated receptor γ (PPARγ) agonists antagonise exaggerated inflammatory responses. In a murine model of allergic airway disease AEC-PPARγ deficiency exaggerated AHR, inflammation, cytokine expression, and tissue remodelling. The same model showed that PPARγ binds directly to a PPAR response element found in MUC5AC gene and represses its expression. Likewise, PPARγ regulates mucin and inflammatory factors in human AECs. Thus, AEC-PPARγ could become another pharmacological target in non-T2 asthma. Mucus production can be targeted with bronchial thermoplasty (BT). An observational study in patients with severe reported subacute (3 weeks) and long-term (12–48 months) effects of BT on airway epithelium, with a significant decrease in MUC5AC expression that persisted for years and correlated with a decrease in expression of IL-13, a potent inducer of mucus secretion and goblet cell hyperplasia. The study also showed a decrease in ciliated cell numbers, which returned to baseline levels in association with the proliferation of basal progenitor cells.

The epithelial cell–derived cytokines thymic stromal lymphopoietin (TSLP), IL-33, and IL-25 are released by the AECs in response to external insults. Although well-known as central regulators of T2 immunity recent evidence involves them in non-T2 asthma as well. In phase II trials biologicals targeting IL-33/ST-2 (REGN3500,

astegolimab) and TSLP (tezepelumab) reduced exacerbations and biomarkers of inflammation in patients across the whole spectrum of asthma inflammatory endotypes. The ongoing CASCADE study uses the epithelial molecular phenotyping, comprising the three-gene-mean technique, to assess participants' T2 status to enable evaluation of the anti-inflammatory effect of tezepelumab across the continuum of T2 activation.

The presence of small airway disease is also frequently encountered in non-T2 asthma. The use of extra-fine particles reaching the small airways could be a therapeutic approach.

Prominent AHR with the lack of inflammation points to the central role of the phenotypically changed ASM in asthma. The recent approval of triple therapy (ICS/LABA/LAMA) in one inhaler for asthma opens new opportunities for management of non-T2 asthma.

Bitter taste receptors (T2Rs) are expressed on human ASM cells. Six subtypes (T2R 10, 14, 31, 5, 4, 19) were found at levels greater than β2-adrenergic receptor (β2AR). Unlike β2AR induced bronchodilation, T2R function is not impaired in asthma and shows little tachyphylaxis. T2Rs on ASM, stimulated by the acyl-homoserine lactones generated by bacteria, may act to open airways and, along with T2Rs of cilia, maintain patency and promote clearance of pathogenic bacteria and debris in the lung during infection. T2Rs agonists (chloroquine and quinine) promote ASM relaxation and bronchodilation and inhibit mitogen-induced ASM growth by modulating mitochondrial structure and function, resulting in ASM cell death. ASM olfactory receptors (OR) do not bronchodilate, but rather modulate cytoskeletal remodeling and hyperplasia, two cardinal features of ASM in asthma. Short chain fatty acids (SCFA), by-products of fermentation of polysaccharides by the gut microbiome, activate these receptors thus supporting a non-immune gut-lung axis that may affect asthma susceptibility. Given the link between obesity and non-T2 asthma, this potential interaction requires further exploration. Agonists directed to OR might mitigate increases in ASM in asthma. Alternatively, dietary modification to promote microbial communities (and the appropriate substrates) to generate the SCFA as natural agonists for OR, might represent a non-pharmacological approach.

Currently, other than bronchodilators, there are no approved effective therapies specifically directed at ASM. The only therapy that may have an effect is bronchial thermoplasty (BT), reducing ASM mass and the airway innervation, however without affecting vasculature and the production of inflammatory mediators (IL17A and TGF-β1). It seems that BT targets the intrinsic abnormalities of the ASM as patients respond well irrespective of the presence or absence of variable airflow obstruction.

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10 THE CONCEPT OF MULTIDIMENSIONAL ENDOTYPING FOR ASTHMA

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KEY MESSAGES

- When using large clinical and immunologic datasets, an unbiased method for automated patient stratification using unsupervised Machine Learning (ML) algorithms coupled with feature explainability techniques may be used
- A model explainability technique known as Shapley values, can be used to identify biomarkers by quantifying the contribution of each model feature, i.e. analyte, to the ML model prediction, i.e. the patient stratification process
- Multidimensional endotyping can be performed with great ease by means of clustering algorithms and feature-importance calculations

The management of asthma is exceptionally challenging due to the heterogeneity of the disease, associated co-morbidities and recommendations from different healthcare systems. This highlights the need to better characterise patients with asthma to allow a more effective and targeted therapeutic approach.

Traditionally, phenotyping of asthma involved classifying patients according to their clinical characteristics, with no consideration of the underlying immunological response. A better approach explored more recently characterized severe asthmatics based on the underlying pathophysiological mechanisms, also known as 'endotypes'. Treatments of severe asthmatics based on their endotypes have been shown to be efficacious in the clinical setting. However, progress in the endotype-driven approach has been slow due to the lack of consensus with regard to how asthma endotypes are identified.

Asthma endotypes can be classified based on bio-cellular and molecular mechanisms, where this can be supported by mechanistic and clinical big datasets. This abundance underpins the emergent application of Machine Learning (ML) models, which extract rules from the data as opposed to being simply programmed by experts. Because modern techniques for performing bio-molecular assays cover a vast number of analytes, the identification of biomarkers that define asthma endotypes is increasingly onerous to carry out by hand. The need for automation further justifies the use of ML models in this context, with the ability to evaluate a high number of measurements promising to considerably accelerate biomarker discovery. Multidimensional asthma endotyping stratifying asthma patients on the basis of large datasets with many analytes can be efficiently carried out via ML algorithms.

CLUSTERING AND CLASSIFICATION MODELS FOR ENDOTYPING

As the definition of endotypes requires separating patients into groups, it can be carried out by ML models such as classification and clustering algorithms that assign discrete labels to the datapoints (Figure 1). The primary difference between classification and clustering models is that the former requires a dataset annotated with the ground truth in order to learn how to separate datapoints into groups, whereas the latter do not. In technical terms, classification models are supervised algorithms, whereas clustering models are unsupervised algorithms.

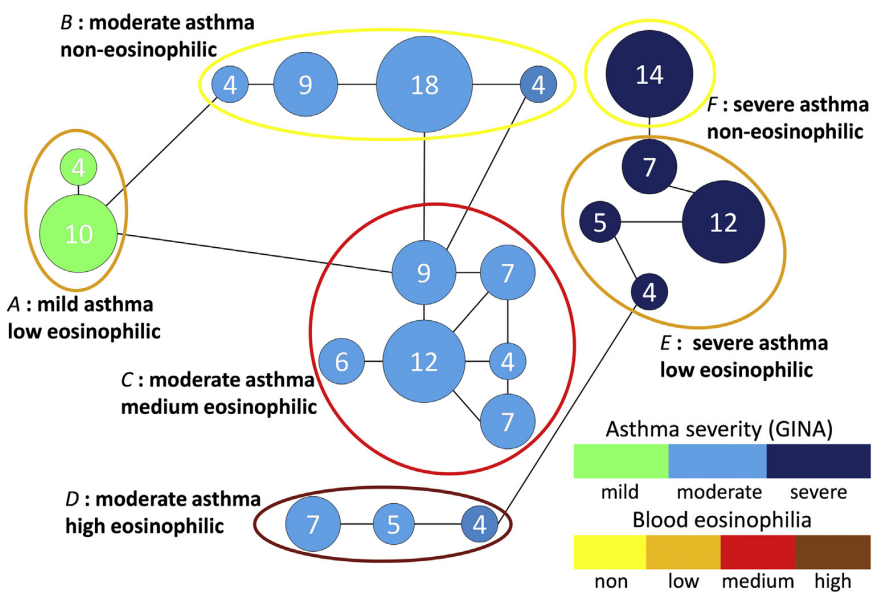

Figure 1 **Multidimensional endotyping in asthma based on clinical and immunological features revealed clinically relevant asthma clusters based on severity and blood eosinophils.**
(reproduced from ref.3)

Ideally, endotyping should not be biased by the stratification of patients according to phenotypes. This makes unsupervised clustering models preferable. To achieve truly unbiased definitions of endotypes by means of ML algorithms, it is important to avoid ground truth labels by relying on unsupervised classification models.

FEATURE IMPORTANCE MEASURES FOR DISCOVERING BIOMARKERS

As multidimensional endotyping requires the inclusion of very many analytes, it is of limited practical value unless accompanied by a biomarker discovery to establish how the patient stratification can be retrieved from only a few measurements. When an ML algorithm is used to identify endotypes, this prioritisation of analytes becomes equivalent to the well-known task of ranking the model's inputs, called features, by their importance.

The term feature importance loosely refers to the strength with which an input variable determines the output of a model. Feature importance helps understanding how a ML algorithm generates its predictions. With the rise of advanced models such as neural networks, researchers have developed numerous measures of feature importance in an effort to keep ML explainable. In addition to simple measures of feature importance like the score produced by a random forest, powerful alternatives like Local Interpretable Model-agnostic Explanations (LIME) and Shapley values are available. The Shapley methodology benefits from rigorous game-theoretical foundations, and it was shown to be the only option displaying certain intuitive properties.

Multidimensional endotyping can be performed with great ease by means of clustering algorithms and feature-importance calculations. We suggest that these ML methodologies may accelerate the discovery of asthma endotypes and associated biomarkers, further shifting diagnostic practice towards the intensive use of data.

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11 ALLERGEN IMMUNOTHERAPY FOR ALLERGIC ASTHMA

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KEY MESSAGES

- Allergen immunotherapy (AIT) is currently an established therapeutic option for well selected patients with allergic asthma
- It is recommended as add-on to asthma regular controller treatment in controlled asthma, aiming to decrease background medication while maintaining asthma control, and in partially controlled asthma aiming to facilitate achieving asthma control
- AIT is overall effective for the treatment of allergic asthma, but a class-effect should not be claimed, rather the efficacy of each single product should be assessed
- The important prerequisites for successful treatment with AIT in allergic asthma are the selection of patients most likely to respond to AIT and the use of allergen extracts and desensitisation protocols with proven efficacy
- Well-designed effectiveness trials and registries are likely to inform the selection of responders, the optimal period of treatment and the best route of administration, the potential therapeutic role in severe allergic asthma, and its preventive effect and cost-effectiveness, thus facilitating new recommendations for AIT in asthma in the near future

Allergic asthma is defined as asthma associated with sensitization to aeroallergens, which are the key drivers for asthma symptoms and airway inflammation (Figure 1). It is a high-prevalence chronic disease, especially in the paediatric population where it can account for up to 90% of cases with asthma. It is often persistent although there is a wide variation in disease severity.

House dust mites (HDM) contains several allergenic components and cause perennial allergy. It is the most frequent allergen driving the symptoms of allergic asthma. A new major allergen, *Dermatophagoides pteronyssinus* (Der p) 23, was described, with relatively high sensitization rates in different European countries. Der p 23-sensitized patients reported more frequently asthma and showed higher prevalence of poly-sensitization.

Allergen immunotherapy (AIT) is a well-known disease-modifying intervention for allergic diseases. Its benefit for allergic asthma, ranging from prevention to facilitating asthma control, is yet to be clarified. The introduction of high-quality standardised extracts for AIT together with clinical trials with a specific focus on AIT in asthma have renewed the interest for this immune modulatory approach in asthma. In 2017, following several well-designed RCTs with HDM sublingual (SLIT) tablets in asthma, GINA guidelines included HDM SLIT as a therapeutic option for allergic asthma. In 2019 the European Academy of Allergy and Clinical Immunology (EAACI) published the first comprehensive guidelines for HDM AIT in allergic asthma, formulating separate recommendations for subcutaneous, SLIT drops and SLIT tablets.

Newer approaches to AIT are currently being tested including modified allergens, second generation adjuvants/carriers and routes of administration, all aiming to increased efficacy with no compromise on safety. In addition, significant steps were undertaken in understanding the mechanisms of allergic asthma, facilitating the

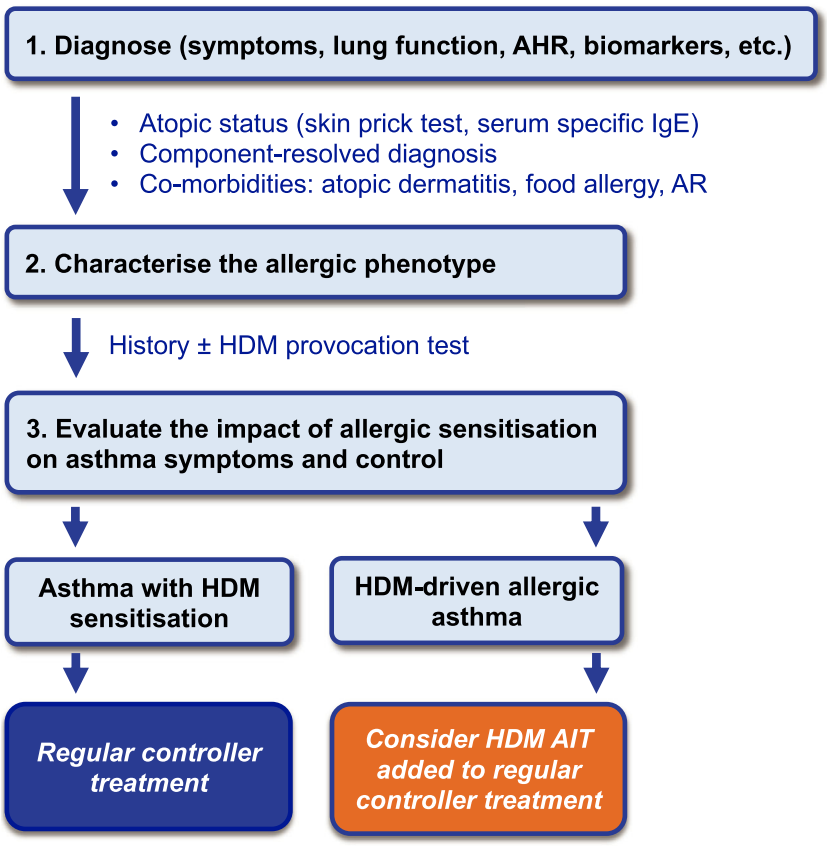

Figure 1 **HDM-driven allergic asthma diagnosis.**
(reproduced with permission from ref.1)

stratified approach for selecting responders and in translating the immune modulation effect in achieving long-term control of the chronic inflammation in asthma.

Currently existing guidelines (GINA, EAACI) recommend HDM AIT as a therapeutic option in controlled or partially controlled HDM allergic asthma. Limited data are available for pollen, moulds and pets, as well as for the severe allergic asthma population. The challenge for the future research will be to clarify the subendotypes of allergic asthma responding to AIT, the mechanisms facilitating its' preventive and disease modifying effect, the optimal duration of the treatment and route of administration.

The EAACI guidelines for the use of HDM AIT for HDM driven allergic asthma were developed following the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach and formulated separate recommendations for HDM subcutaneous AIT (SCIT), SLIT drops and SLIT tablets. AIT with HDM SLIT-tablet is recommended as an add-on to regular asthma therapy for adults with controlled or partially controlled HDM-driven allergic asthma (conditional recommendation, moderate-quality evidence). HDM SCIT is recommended for adults and children with controlled HDM-driven allergic asthma as add-on to regular asthma therapy to decrease symptoms and medication needs (conditional recommendation, low-quality evidence). HDM SLIT drops are recommended for children with controlled HDM-driven allergic asthma as add-on to regular asthma therapy to decrease symptoms and medication needs (conditional recommendation, low-quality evidence). A decision-tree is offered to the clinician (Figure 2). According to the EAACI Guidelines the important prerequisites for successful treatment with HDM AIT are the selection of patients most likely to respond to AIT and the use of allergen extracts and desensitisation protocols with proven efficacy.

Biomarkers have been identified to distinguish patients with allergic asthma, particularly total

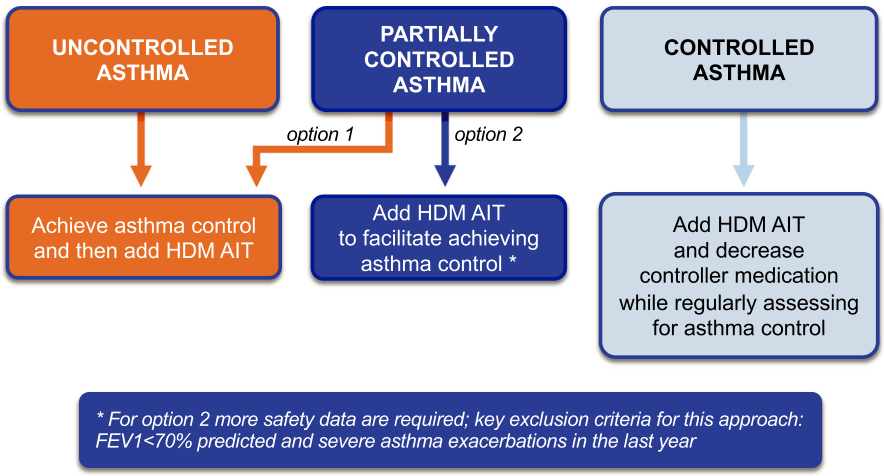

Figure 2 **Integration of HDM AIT in the stepwise management of HDM-driven allergic asthma based on the level of asthma control.**
(reproduced with permission from ref.1)

serum IgE levels, sensitization to aeroallergens evaluated through serum specific IgE or skin prick test positivity, blood and sputum eosinophil levels, fraction of exhaled nitric oxide (FeNO), and periostin. HDM SLIT impact on blood eosinophils, serum IgE, serum periostin, FeNO, and lung function was evaluated in 112 patients with asthma sensitized to HDM. The study showed that the addition of HDM SLIT to asthma pharmacotherapy reduced serum periostin and FeNO and improved pulmonary function. The independent predictors of improvement in lung function were changes in serum periostin and FeNO. Blood eosinophils or total IgE but had no predictive value.

Stratification of patients with HDM allergy according to molecular analysis may enhance AIT success. A real-life evaluation of SCIT HDM-AIT in AR showed protective IgG4 mainly against Der p 1 and Der p 2 and to a lesser extent to Der p 23, but not to the other important allergens such as Der p 5, Der p 7, and Der p 21. Better clinical efficacy was achieved in patients sensitized only to Der p 1 and/or Der p 2 as compared with patients having additional IgE specificities. Precise component-resolved diagnosis of the HDM sensitisation profile can yield a potential biomarker for allergic asthma and its response to AIT.

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12 PULMONARY REHABILITATION IN ASTHMA MANAGEMENT

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KEY MESSAGES

- Asthma is a chronic and complex disease affecting millions of people worldwide
- Asthma management is based on both pharmacologic and non-pharmacologic treatment
- Pulmonary rehabilitation (PR) should be prescribed especially in severe non-controlled asthma
- Further studies are needed to better characterize the effects and the key components of PR in asthma

Asthma is a common, chronic and complex disease affecting over 300 million people worldwide. Asthma symptoms (wheezing, chest tightness, dyspnoea, cough) are caused by airway inflammation and are variable in time and intensity. The goal of asthma management is to achieve symptoms control with minimal pharmacological therapy in order to limit potential side effects.

It is well known that regular exercise has several beneficial effects on health, in particular for chronic disease including asthma. However, asthmatic patients often avoid physical activity because exercise can trigger respiratory symptoms. Exercise avoidance can result in reduction in endurance training and skeletal muscles weakness and may also lead to weight gain.

There are several papers highlighting the positive effects of pulmonary rehabilitation (PR) on chronic respiratory diseases, including asthma. The positive effects include improvement of exercise capacity and quality of life and reduction of dyspnea, anxiety, depression and bronchial inflammation. The PR programme should be tailored to the clinical condition and the comorbidities of each individual patient (Table 1). The baseline characteristics that could predict the success of PR are not defined yet, however previous studies showed positive results of PR in subjects with asthma at any GINA step. In patients affected by chronic obstructive pulmonary disease (COPD) the PR components usually prescribed include aerobic and muscle training, nutritional and psychological counselling, breathing exercise and educational support. These were demonstrated to improve exercise aerobic capacity, muscle strength, respiratory symptoms, health related quality of life, and to empower patients capacity to manage their disease. The same components have been individually prescribed in asthma showing positive effect, especially for patients belonging to the most severe GINA steps. In particular, recent data have shown that severe subjects can benefit most from PR due to the reduction of airways inflammation. However, the efficacy of a comprehensive PR programme based on a multidisciplinary team that includes pneumologist, respiratory therapist, nurse, psychologist and dietician, has not been sufficiently investigated. Up to now, the results available derive either from small sample size prospective studies, or from retrospective studies and therefore they cannot be used to formulate strong recommendations for PR in asthma. Hence, more studies enrolling appropriate sample sizes and involving asthmatic patients belonging to the different GINA steps are

TABLE 1

Pulmonary rehabiliation components				
Exercise	Endurance Training		Strength Training	
	20/30 min		8/10 repetitions	
	60-80% VO2 max		Near 1-Repetition Maximum	
	3-5/week		3-5/week	
Physical activity	150 min/week		75 min/week	
	Moderate intensity		Vigorous intensity	
Breathing exercises	Slow breathing	Nasal breathing	Controlled hold breathing	Relaxation exercises
Counselling	Nutritional		Psychological	

needed in order to support the role of a tailored and comprehensive PR programme in asthma. It is also essential to consider patients' comorbidities in the context of PR due to their impact on the overall asthma management.

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Section G

SPECIAL CONSIDERATIONS

1 PEDIATRIC ASTHMA

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SIZE OF THE PROBLEM WORLDWIDE

Asthma is the most prevalent long-term disease in children worldwide. The rising burden with increased hospital admissions suggests that diagnosis and management are sub-optimal and reflects the impact of poverty and poor access to basic medication.

SCHOOL-AGE ASTHMA

In the majority of school-aged children in high-income countries asthma is characterised by wheeze associated with breathlessness and/or cough, atopy, reversible airflow obstruction and eosinophilic airway inflammation. In low- and middle-income settings, atopy may be less common and infection more predominant. Thus, 'asthma' should not be assumed to be the same disease across the globe. Although an accurate history and examination are central to the diagnosis, the use of objective tests including, where possible, spirometry with bronchodilator reversibility, exhaled nitric oxide and tests for allergen sensitisation are recommended to avoid misdiagnosis. Exclusion of alternative diagnoses is critical; common asthma mimics will vary geographically. Some tests may be difficult to access, and they must all be performed by trained personnel to provide meaningful results. The key is to ensure maximal evidence supportive of the diagnosis is obtained before treatment is initiated (Table 1).

The cornerstone of achieving asthma control (reducing symptoms, maintaining lung function and preventing acute attacks) is the use of regular inhaled corticosteroids (ICS) to minimise airway eosinophilia. However, it is challenging to achieve adequate adherence to ICS, especially in adolescents. Poor adherence to ICS and excessive reliance on short-acting bronchodilators is a significant risk factor for asthma death and the numbers of fatal asthma attacks are increasing in children. The most common risk factor for an attack is a recent attack, with 79% of children being re-hospitalised within 1 year. It is essential that each acute presentation is used as an opportunity

KEY MESSAGES

- Asthma is the commonest non-communicable chronic disease affecting children worldwide. Its nature (allergic or non-allergic) may vary geographically (regiotypes)
- In school-aged children, asthma is predominantly allergic and mediated by type-2 immune mechanisms
- Objective tests that support an asthma diagnosis (spirometry, peak flow variability, aero-allergen sensitisation, exhaled nitric oxide) must be used
- Control is achieved in the majority of school-age children with regular inhaled corticosteroids, but adherence to therapy is a significant challenge
- Future studies investigating the efficacy of combination preparations of ICS and LABA as maintenance and reliever therapy (MART) or as intermittent reliever therapy (ICS plus fast acting beta agonist) are urgently needed in children to reduce paediatric asthma morbidity and mortality
- As preschool wheezing is heterogeneous objective tests to identify treatable traits and children most likely to benefit from ICS must be undertaken prior to prescription of maintenance therapy

TABLE 1

Objective tests to establish a diagnosis of asthma in children ≥ 6 years old

Diagnostic criteria	Test / Findings	Important considerations
1. History and examination	Doctor confirmed wheeze Shortness of breath Cough	Exclude alternative diagnoses: e.g. if persistent wet cough, exclude chronic suppurative lung disease
2. Confirmation of variable airflow obstruction*	**Spirometry**: • Evidence of reduced FEV_1/FVC ratio <0.9 • Positive bronchodilator reversibility: increase in FEV_1 >12% predicted and at least 200 ml following SABA inhalation **PEFR variability:** • >13% diurnal variability **Positive bronchial challenge test:** • Use of histamine or methacholine to demonstrate fall in FEV_1 >20% with standard doses	• Children may have normal spirometry when asymptomatic • Look for airflow obstruction when acutely unwell • PEFR variability can be used when spirometry is not available
3. Other supportive evidence of type2 mediated immunity in children (in a high income setting)	**Atopy**: • Aero-allergen and/or food sensitization **Airway inflammation:** • Elevated exhaled nitric oxide: >35ppb** in steroid naïve children	• Atopy can be assessed using skin prick tests or serum specific IgE • Exhaled nitric oxide measured at flow rate 50ml/sec

**Adapted from Global Initiative for Asthma (GINA) guidance 2019, https://ginasthma.org/wp-content/uploads/2019/06/GINA-2019-main-report-June-2019-wms.pdf*

***Adapted from National Institute of Health and Care Excellence (NICE) guidelines 2017, https://www.nice.org.uk/guidance/ng80/chapter/Recommendations#objective-tests-for-diagnosing-asthma-in-adults-young-people-and-children-aged-5-and-over*

to optimise maintenance therapy, educate the child and family and provide an individualised asthma action plan (Figure 1). The most practical and useful approach in the future to prevent attacks, achieve control and minimise the significant risks of short-acting bronchodilators, may be to use a single inhaler with inhaled corticosteroids and fast acting beta-agonists combined, used for both maintenance treatment and acute symptoms. This approach has proven efficacy in adults and adolescents, but studies in younger children are urgently needed.

Only a minority of children with severe asthma will require treatment escalation with biologicals, as most can be well controlled with regular and correct administration of ICS together with triggers' avoidance and proper management of co-morbidities such as allergic rhinitis. Efficacy data of anti-IL5 antibody, mepolizumab, is currently extrapolated from adults, in whom the biology of severe asthma may be different. Thus, evaluation of paediatric efficacy for biologicals targeting the IL-5 and the IL-4/IL-13 pathway is an urgent priority.

PRESCHOOL WHEEZE

Children aged between 1-5 years account for the majority of childhood admissions for acute wheeze. The pathophysiology is not the same as for school-age allergic asthma as it is predominantly infection driven with only a sub-group having underlying allergic airways disease. Consequently, oral corticosteroids are not effective for the majority of wheeze attacks, and maintenance ICS should only be used in those with evidence of aero-allergen sensitisation and/or peripheral eosinophilia. The approach to management must consider treatable traits and not an extrapolation of management for school-aged children (Table 2).

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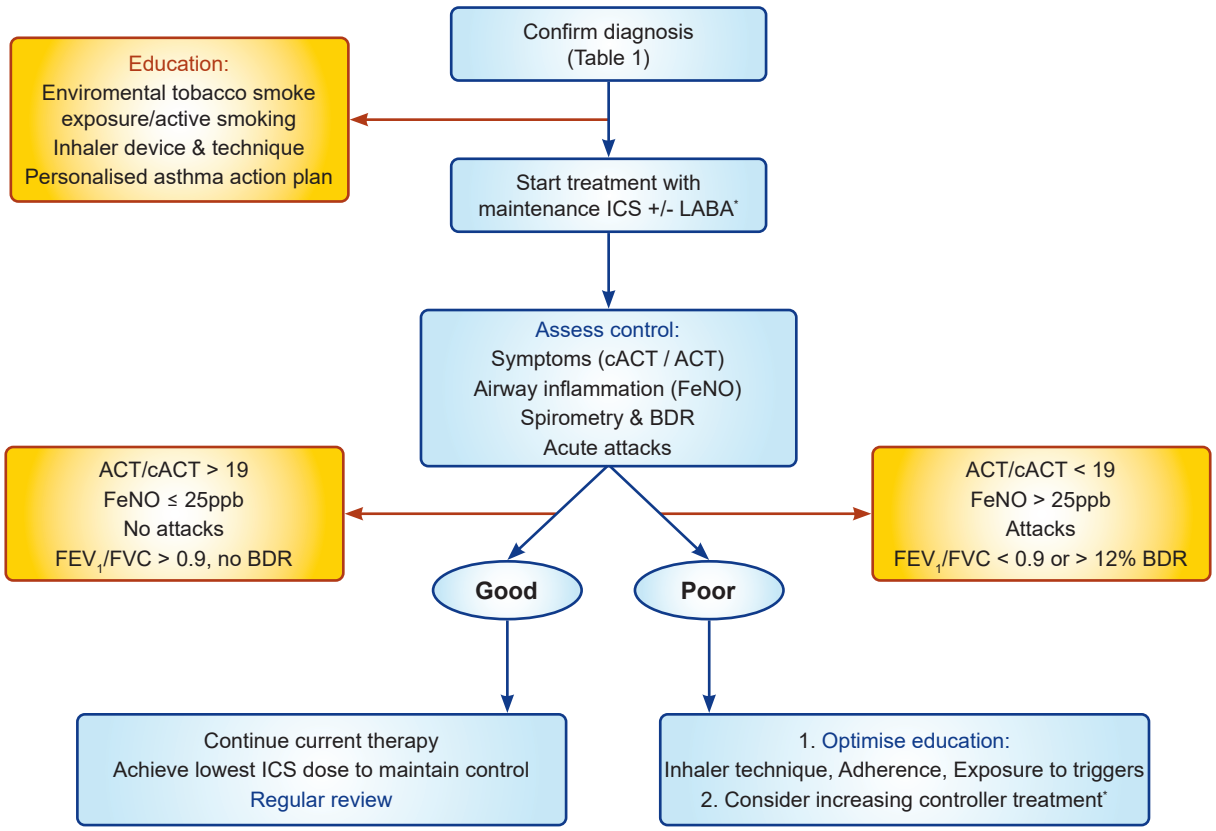

Figure 1 **Management pathway for children >6 years with asthma.**
ICS - inhaled corticosteroids; LABA - long-acting beta-agonists; FeNO - exhaled nitric oxide; ACT - Asthma Control Test; BDR - bronchodilator reversibility;
** According to national / international guidelines e.g. GINA*

TABLE 2

Diagnosis and management of preschool wheeze (children <6 years old)		
Diagnostic criteria	**Test / findings**	**Important considerations**
1. History and examination	Doctor confirmed wheeze Breathlessness Cough	Exclude upper airway abnormalities, investigate if wet cough, consider alternative diagnoses[1]
2. Tests to identify responders to maintenance inhaled corticosteroids	**Atopy:** • sensitization to aero-allergens **Blood eosinophils:** • elevated blood eosinophils >300 cells/mcl Atopy and/or blood eosinophilia – trial of inhaled corticosteroids	Evidence of atopy and/or elevated blood eosinophils when the child is STABLE
3. Evidence of lower airway bacterial infection	**Bronchoalveolar lavage or induced sputum:** • evidence of positive bacterial culture when well – trial of targeted antibiotics	Duration of antibiotics uncertain, minimum 2 weeks, up to 12 weeks has been used[2]
4. Symptom relief following short-acting bronchodilator	If no evidence of response to maintenance treatment (2 & 3 above), use short-acting bronchodilators only for acute symptomatic relief	• Oral steroids should only be used for acute attacks, if severe[1]

[1] *Bush A, Saglani S Allergy 2020; Oct;75(10):2718*
[2] *Schwerk N et al PLoS One 2011;6:e27913*

2 ASTHMA IN THE ELDERLY

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KEY MESSAGES

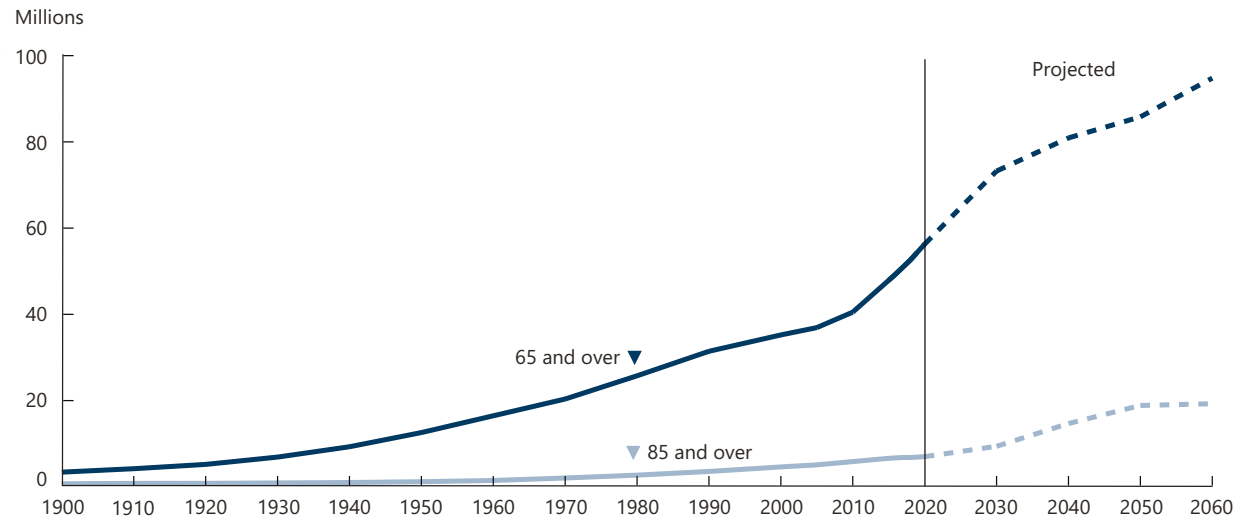
- Asthma in older adults is a result of both persistent disease and new onset disease
- Asthma in older adults is increasing in prevalence the fastest, has the highest rate of asthma related deaths, the second-greatest rate of asthma related hospitalizations and clinic visits
- Lung function in older subjects has features of airflow obstruction challenging the distinction with chronic obstructive lung disease
- Allergy is less important compared to younger populations. Infections are an important causation of severe exacerbations, partially related to the aging immune system
- Treatment of asthma in older adults is not fundamentally different, however response to drugs and medication side effects are a greater challenge. Vaccination status should be verified in older subjects with asthma

The population of the world is aging, with the greatest increases occurring in those over 85 years of age. Twenty-five percent of the US population will be more than 65 years of age by 2050 (Figure 1). Twenty percent of the population of at least 6 countries was older than 65 years in 2015.

Asthma occurs in all adult age groups, both as a new diagnosis and as a condition that existed from a younger age. The prevalence of asthma in the elderly is 4 to 13%, similar to younger adult populations, and the incidence is approximately 1/1000/year. However, asthma is probably underdiagnosed due to the attribution of symptoms and signs to diseases other than asthma or acceptance of symptoms and limitations as the result of aging. Compared to asthma beginning at a younger age, new onset asthma in older adults tends to be more severe and progressive, more likely in women and less reversible. The mortality of asthma increases with aging (Figure 2).

Aging influences the symptoms of asthma and the risk of mortality. This may be due to changes in airway physiology with aging and decreased response to treatment. Lung function decreases due to increased stiffness of the chest wall, reduced respiratory muscle function and an increase in residual volume following loss of elastic recoil (Figure 3). The decline in the elasticity of the airway is a major contributor to the increase in fixed airflow obstruction and work of breathing. The result is a decrease in FEV1/FVC ratio, such that normal elders have spirometric features suggestive of obstructive lung disease. Thus, the diagnosis of asthma in the elderly is challenging. Consequently, is it commonly misdiagnosed as chronic obstructive lung disease (COPD) or under-diagnosed and under-treated. Significant irreversible airflow obstruction, remodeling or bronchiectasis with segmental fibrosis can occurs. Lung volumes and diffusion capacity studies and high resolution tomographic imaging may be helpful in identifying diseases other than asthma . The greater duration of asthma, the less likely lung function will be normal, but there is wide variability limiting the application of this finding to individual patient assessment. Lung function

Population age 65 and over and age 85 and over, selected years, 1900–2018, and projected years, 2020–2060



NOTE: Some data for 2020–2060 have been revised and differ from previous editions of *Older Americans.*

Reference population: These data refer to the resident population.

SOURCE: U.S. Census Bureau, 1900–1940, 1970, and 1980, U.S. Census Bureau, 1983, Table 42; 1950, U.S. Census Bureau, 1953, Table 38; 1960, U.S. Census Bureau, 1964, Table 155; 1990, U.S. Census Bureau, 1991, 1990 Summary Table File; 2000, U.S. Census Bureau, 2001, *Census 2000 Summary* File 1; U.S. Census Bureau, Table 1: Intercensal Estimates of the Resident Population by Sex and Age for the U.S.: April 1, 2000, to July 1, 2010 (US-EST00INT-01); U.S. Census Bureau, 2011. *2010 Census Summary* File 1; U.S. Census Bureau, Annual Estimates of the Resident Population for Selected Age Groups by Sex for the United States, States, Counties, and Puerto Rico Commonwealth and Municipios: April 1, 2010, to July 1, 2018 (PEPAGESEX); U.S. Census Bureau, Table 3: Projections of the Population by Sex and Selected Age Groups for the United States: 2017 to 2060 (NP2017-T3).

Figure 1 **Population of United States, 1900-2060.**
(www.agingstats.gov)

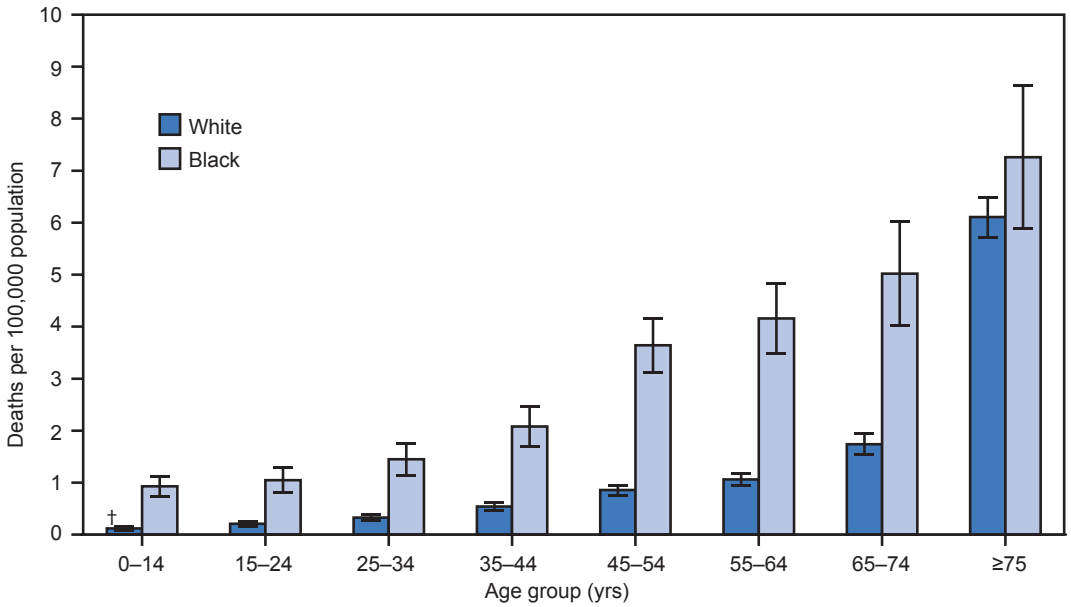


Figure 2 **Asthma Death Rates by Race and Age, United States 2007-2009.**
(www.cdc.gov/mmwr)

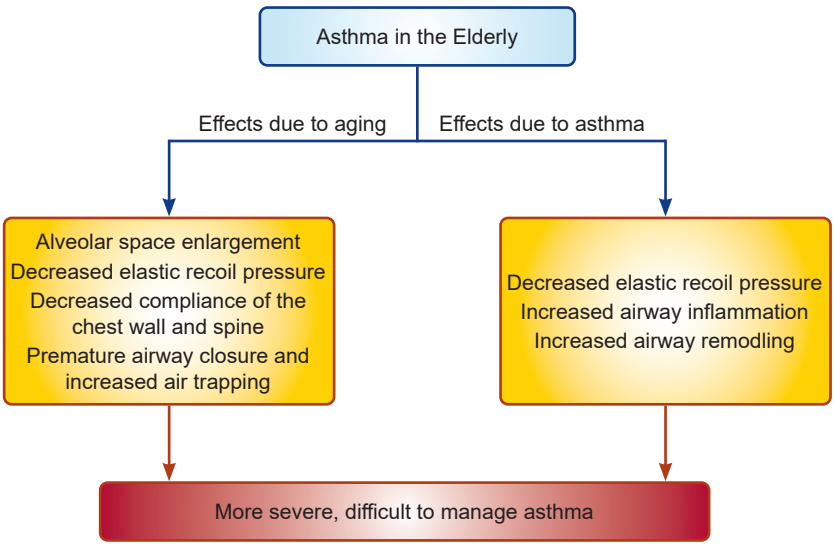


Figure 3 **Airway Changes Associated with Aging and Asthma in Older Adults.**

decreases with age from the maximum value at approximately 20 years of age. The average decrease in FEV1 is 25-30 ml/year, and this loss is accelerated in some by cigarette smoke exposure or chronic asthma. Impulse oscillometry coupled with high resolution chest tomography imaging may be helpful in improved recognition and understanding of these changes as well as distinguishing from other causes of loss of lung function such as COPD, interstitial fibrosis or bronchiectasis. Reference spirometry data for older adults are available but are limited primarily to Caucasian populations.

Aging affects the immune system in various ways (Figures 4 and 5). There is a combination of an increase in inflammation ("inflamm-aging") with a decrease in specific immune response. Naïve T cells decrease with decline in ability to respond to new antigens, memory T cells increase, CD8 suppressor/cytotoxic cells increase, B-cell function decreases, innate immune functions decreases, neutrophil number increases, while eosinophil function is relatively unchanged. There is an increase in IL-6, IL-1β and tumor necrosis factor-α. IL-6 concentrations inversely correlate with survival and are associated with non-eosinophilic inflammation which may affect the airway.

IgE production decreases with age, although this is controversial. Wheal and flare skin test responses are less reliable in predicting response to inhalational allergen challenge. Allergic sensitization is more common in older adults with asthma than age matched controls without asthma, with studies of Caucasian populations showing 28-74% of older asthmatics are sensitive to at least one antigen. However, subjects who develop asthma later in life are much less likely to have specific-IgE than younger subjects. Asthma with onset after 40 years of age is rarely IgE mediated and has less familial linkage than in younger cohorts. Aging of the skin decreases the usefulness of skin testing in solar damaged skin.

Management of asthma in the elderly is no different than in younger populations, except the medications may be less effective and less tolerated. Inhaled medications require a sufficient airflow for powder devices or coordination for metered dose inhalers, possibly limiting effectiveness in the elderly. The dryness of oral and laryngeal mucosa reduces the tolerance to inhaled corticosteroids. Anticholinergic therapy may be considered. Due to low flow rates and small airway disease, oral therapy with low dose theophylline or a trial of leukotriene modifiers may be considered. Infections are a frequent cause of exacerbations and usually lead to severe exacerbations requiring hospitalization. Vaccine recommendations include annual influenza vaccine, periodic pneumococcal vaccine and boosting of pertussis immunity. Monitoring for side effects of therapy is very important and includes a) serum potassium and glucose under inhaled beta agonists, particularly when combined with high dose

inhaled corticosteroids or oral corticosteroids; b) bone density under regular inhaled corticosteroids or when recurrent courses of systemic corticosteroids are required; c) monitoring serum 25-hydroxyvitamin D with target concentrations of 40-50 ng/mil; d) and assessment of strength to detect myopathy.

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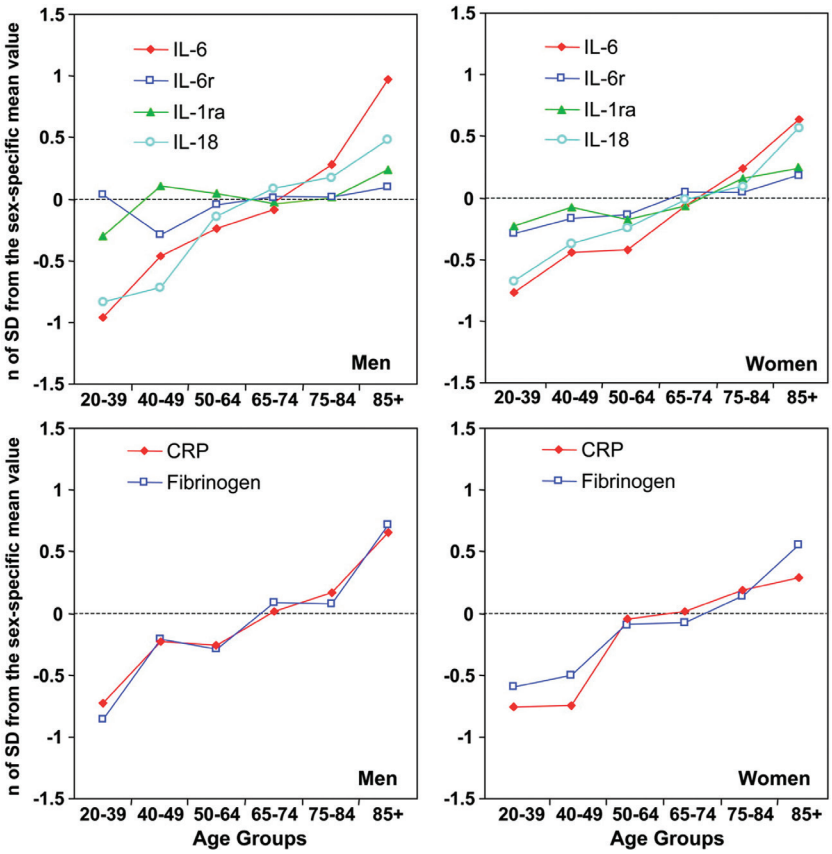

Figure 4 **Effect of age on state of inflammation: Mean values of inflammatory markers according to age and sex group expressed as number of standard deviations from the population mean to make the values independent of different units of measure (6).**

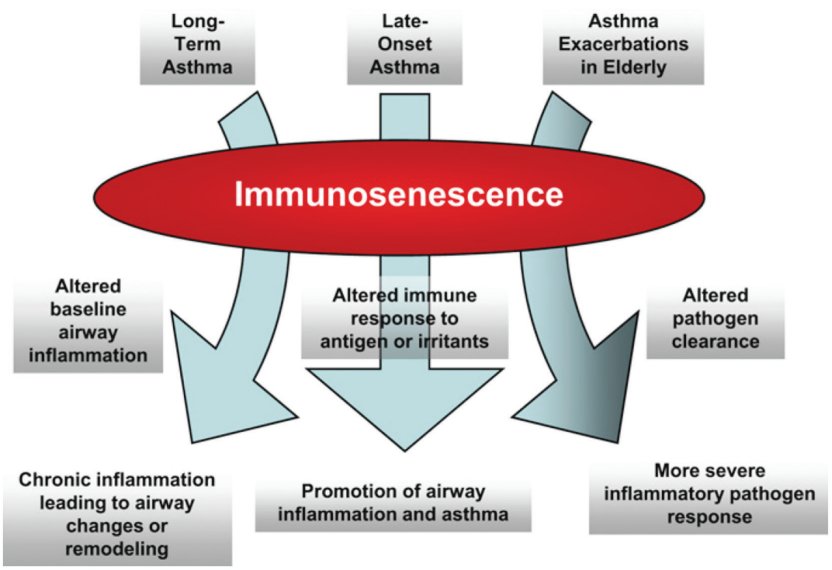

Figure 5 **Immunosenescence and the Potential Effects on Asthma.** *(reproduced from ref 1)*

3 ASTHMA IN ELITE ATHLETES

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KEY MESSAGES

- Elite athletes show a higher prevalence of asthma and exercise-induced bronchoconstriction (EIB) compared to the general population
- Major determinants of EIB seem to be the increase in airway osmolarity due to the respiratory water loss during strenuous exercise and the vasodilation associated with airways rewarming
- Asthma and EIB in athletes are often reversible after stopping training for a consistent period of time
- Pharmacological management should follow international guidelines and World-Anti-Doping Agency recommendations
- If fully controlled, asthma and EIB do not represent a contraindication to exercise and do not limit physical performance in athletes

Elite athletes have been reported to have an increased prevalence of asthma and exercise-induced bronchoconstriction (EIB), the latter defined as the transient abnormal constriction of the airways in response to vigorous exercise in the presence or absence of clinically recognized asthma . The terms EIB and Exercise-Induced Asthma (EIA) have been used for many years interchangeably. However, considering that EIB may develop even in subjects without clinical asthma, it is now recommended to distinguish between EIB after exercise in asthmatic patients (EIB with asthma - EIBa) and EIB in subjects without other clinical symptoms and/or signs of asthma (EIB without asthma - EIBwa). The major determinants of EIB seem to be the increase in airway osmolarity due to the respiratory water loss during strenuous exercise and the vasodilation associated with airways rewarming (osmotic and thermal theories). This leads to mast cell degranulation and eosinophilic activation, with release of mediators, such as leukotrienes, histamine, tryptase, and prostaglandins. Other reported pathophysiological processes of EIB include a relatively enhanced T2-high immune response, an autonomic dysregulation, abnormalities in small airways and an increased exposure to inhalant allergens, pollutants and irritants which direct bronchial epithelial damage, most often characterized by neutrophilic or paucigranulocytic inflammation and remodelling (Figure 1).

EIB prevalence among Olympic athletes largely varies (Table 1), depending on the diagnostic tool adopted, as well as on the type and intensity of the sport discipline and where this is practiced. EIB is most commonly found in athletes performing endurance activities (i.e. long-distance running, cycling, triathlon, and pentathlon), swimming and winter sports.

In athletes, clinical symptoms (i.e. cough, shortness of breath, chest tightness) are poorly predictive of EIB, as well as basal spirometry measurement, considered that in several athletes lung function at res is normal or even above predicted values. Therefore, objective tests to demonstrate variable airway obstruction and/or hyperresponsiveness (AHR), such as the exercise challenge (on the field or in laboratory), the Eucapnic Voluntary Hyperpnea (EVH), the manni-

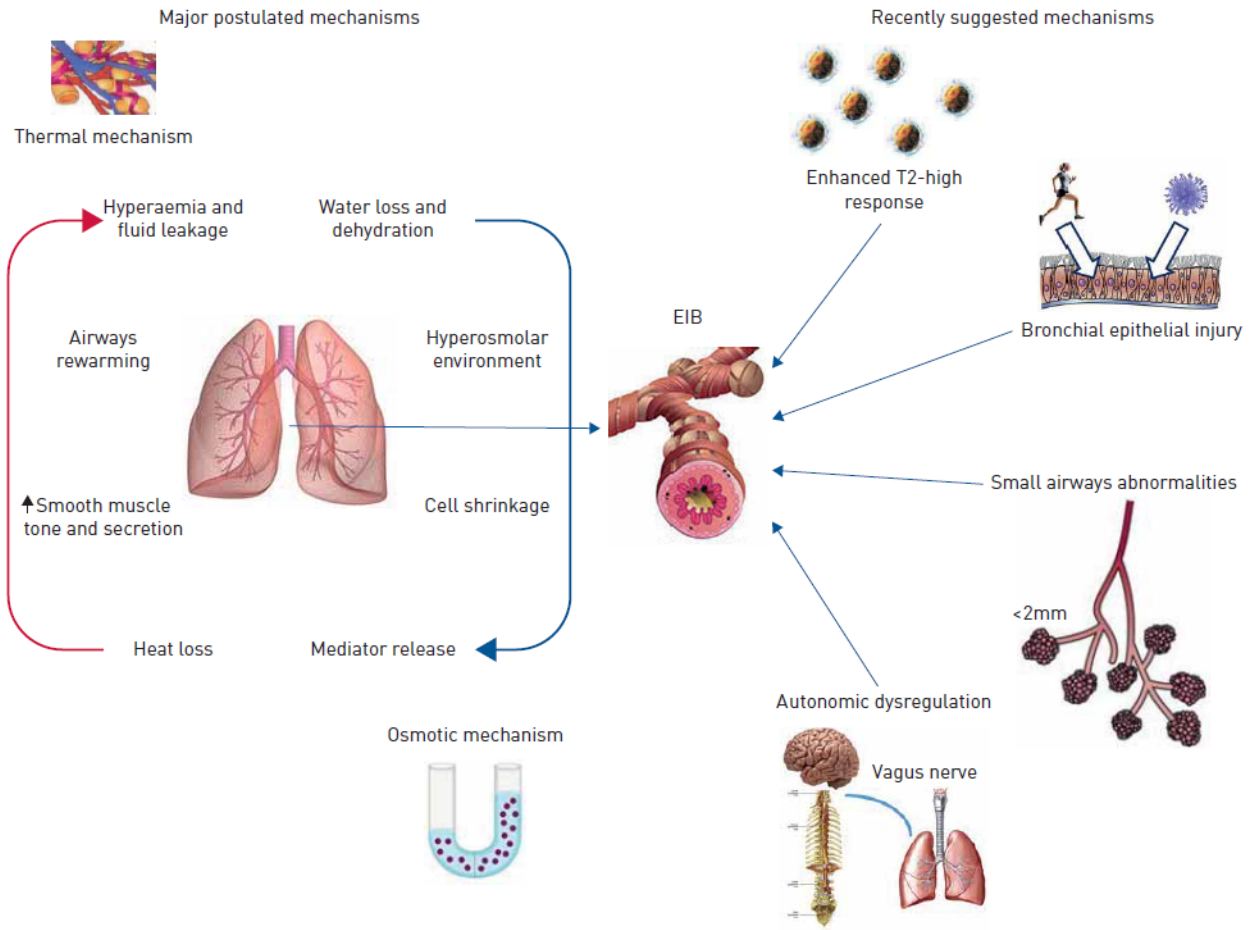

Figure 1 **Pathophysiological mechanisms of exercise-induced bronchoconstriction (EIB).**
Reproduced from Let research leave you breathless, not physical exercise!, Bonini M, Usmani OS., ERJ Open Res. 2018;4(1), under the terms of the creative commons attribution non-commercial license 4.0

tol challenge or the methacholine test are often needed for achieving a proper diagnosis (Table 2).

The optimal management of EIB in athletes starts from prevention. Education about EIB self-management includes the avoidance of exposure to air pollutants, allergens and chlorine derivates. In some cases, this could be achieved by using mechanical barriers such as face masks, particularly helpful in reducing the effects of cold air in winter-sports. Furthermore, a pre-exercise warm-up can decrease AHR by inducing a refractory period. High-intensity exercise may on the contrary increase the risk of EIB in athletes, especially if performed in adverse environmental conditions. Interestingly, it has been shown that EIB can revert after stopping training, supporting a role of the exercise itself as causative factor of bronchial inflammation and symptoms.

Pharmacological approach in athletes with EIBa should follow GINA guidelines. Management of EIBwa is instead mainly based on the preventive use of bronchodilators. Beta-2 adrenergic drugs, both short- and long-acting (SABA and LABA), when given in a single inhaled dose or with intermittent administration before exercise, are the most effective drugs to provide complete bronchial protection. Nevertheless, SABA and LABA should be used with caution on a daily basis, as over-use often results in the onset of tolerance and side-effects. Adequate treatment of most common concomitant conditions (i.e. allergic rhinitis and gastro-esophageal reflux) is also crucial. Athletes with documented EIB should adhere to the World Anti-Doping Agency (WADA) regulations.

TABLE 1

EIB prevalence among Olympic athletes*

Study Population (n)	Methodology for Diagnosis	Prevalence	Reference
Australian 1976 Olympic team (185)	Physical examination	9.7%	Fitch KD, 1984
Australian 1980 Olympic team (106)	Physical examination	8.5%	Fitch KD, 1984
US 1984 Olympic team (597)	Questionnaire, exercise challenge	11.2%	Voy RO, 1986
Spanish 1982 Olympic team (495)	Questionnaire	4.4%	Drobnic F, 1994
US 1996 Olympic team (699)	Questionnaire	16.7%	Weiler JM, 1998
US 1998 Olympic team (196)	Questionnaire	21.9%	Weiler JM, 2000
US 1998 Olympic team (170)	Spirometry, exercise challenge	23.0%	Wilber RL, 2000
Australian 2000 Olympic team (214)	Questionnaire	21.0%	Katelaris CH, 2000
Italian 2000 pre-Olympic team (265)	Questionnaire, spirometry	10.9%	Lapucci G, 2003
Polish 2008 Olympic team (222)	Questionnaire, spirometry, methacholine challenge	11.3%	Kurowski M, 2016

* *Reproduced from Immunol Allergy Clin North Am, 38, Bonini M. & Silvers W., Exercise-Induced Bronchoconstriction: Background, Prevalence, and Sport Consideration, 205-214, 2018, with permission from Elsevier.*

TABLE 2

Bronchial provocation tests (BPTs) and diagnostic criteria used to diagnose EIB*

Method	Positivity criteria
Direct BPTs	
• Methacholine challenge	PC_{20} ≤ 4 mg/ml or PD_{20} ≤ 400 µg (cumulative dose), or ≤ 200 µg (noncumulative dose) in those not taking ICS PC_{20} ≤ 16 mg/ml or PD_{20} ≤ 1600 µg (cumulative dose) or ≤ 800 µg (noncumulative dose) in those taking ICS for at least 1 month
• Histamine challenge	≥ 20% decrease in FEV_1 at a histamine concentration of 8mg/mL or less during a graded test of 2 minutes
Indirect BPTs	
• Exercise challenge (field or laboratory)	≥10% decrease in FEV_1 from baseline
• Eucapnic voluntary hyperpnoea	≥10% decrease in FEV_1 from baseline
• Hypertonic saline inhalation	≥15% decrease in FEV_1 from baseline
• Mannitol inhalation	PD_{15M} ≤ 635 mg of mannitol

* *Adapted from: Couto M et al. Breathe 2012;8(4):287-96*

FEV_1 - Forced expiratory volume in one second; ICS - inhaled corticosteroids; PC_{20} - provocative concentration of methacholine that causes a 20% drop in FEV_1; PD_{20} - provocation dose causing a 20% decline in FEV_1

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4 ASTHMA IN PREGNANCY

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KEY MESSAGES

- Pregnant asthmatics have a higher risk of adverse perinatal outcomes
- Adherence to treatment, specifically inhaled corticosteroids, has been a problem for many pregnant asthmatics, usually due to concerns regarding the safety of these medications during pregnancy
- Pregnant asthmatics should be monitored on a monthly basis so that any change in course can be matched with an appropriate change in therapy
- Patient education is an important part of the management and includes explaining the relationship between asthma and pregnancy, identifying asthma triggers, training on correct use of inhalers and an asthma action plan
- One of the most important unmet needs is the availability of safety information for asthma medications used during pregnancy that can support achieving asthma control

Asthma is the most common potentially serious chronic medical condition to affect pregnancy, with a prevalence of self-reported asthma in the United States between 8.4 and 8.8%. The prevalence appears to be increasing, from 5.5% reported in 2001 to 7.8% in 2007.

A meta-analysis, derived from a substantial body of literature spanning several decades and including very large numbers of pregnant women, (over 1,000,000 for low birth weight and over 250,000 for preterm labor), indicates that pregnant women with asthma are at a significantly increased risk of a range of adverse maternal and fetal outcomes (Tables 1, 2). Asthma severity and exacerbations during pregnancy may lead to small for gestational age and preterm delivery. Disentangling the effects of underlying asthma severity or control versus effects of other factors such as asthma medications proves difficult.

Mechanisms postulated to explain the increased perinatal risks include: 1) hypoxia and other physiologic consequences of poorly controlled asthma; 2) medications used to treat asthma; 3) associated pathogenic or demographic factors not actually caused by the disease or its treatment, such as abnormal placental function.

Asthma may worsen, improve, or remain unchanged during pregnancy. Each of these courses occur with approximately equal frequency. Asthma also appears to be more likely to be more severe or to worsen during pregnancy in women with more severe asthma before coming pregnant.

The mechanisms responsible for the deterioration in asthma control during pregnancy are unknown. The myriad of pregnancy-associated changes in the levels of sex hormones, cortisol and prostaglandins may contribute. Exposure to fetal antigens, with immune stimulation may intervene as well. Even fetal sex may play a role, with data showing increased severity of symptoms in pregnancies with a female fetus.

Once the diagnosis of asthma is confirmed (Table 3), a decision regarding the need for controller medication versus rescue medication has to be made. Human data regarding the safety of asthma medications during pregnancy are summarized in Table 4. Inhaled corticosteroids (ICS) are the mainstay of controller therapy during pregnancy. Because they have the most published human gestational safety data, budesonide and fluticasone can be considered as preferred ICS during pregnancy. That does not

TABLE 1

Adverse maternal outcomes reported to be increased in pregnant women with asthma
Abortion
Hyperemesis gravidarum
Gestational diabetes
Chorioamnionitis
Pregnancy-induced hypertension (PIH) or Preeclampsia
Antepartum hemorrhage
Placental complications
Preterm labor
Complicated labor
Cesarean section
Preterm birth
Post-partum hemorrhage

TABLE 2

Adverse fetal outcomes reported to be increased in infants of asthmatic women
Low birth weight
Preterm birth
Small for gestational age
Congenital anomalies
Stillbirth
Low Apgar scores at birth

TABLE 3

Differential diagnosis of dyspnea during pregnancy
Asthma
Dyspnea of pregnancy
Reflux esophagitis
Post nasal drainage
Bronchitis
Laryngeal dysfunction
Hyperventilation
Pulmonary edema
Pulmonary embolism

imply that other ICS are unsafe and they may be continued in patients who were well controlled by these agents prior to pregnancy, especially if it is thought that changing ICS formulations may jeopardize asthma control. Controller therapy should be increased in steps (Table 5) until adequate control is achieved. Add on therapy for pregnant women with severe asthma may consider biologicals such as anti-IgE, anti-IL4, or Anti-IL5/5R. There is reassuring human safety data from the EXPECT pregnancy registry for Omalizumab use during pregnancy. Mepolizumab, Benralizumab, and Dupilumab are currently enrolling patients into pregnancy exposure registries (e.g.www.mother to baby.org). Recently, the EAACI Task Force (TF) on Biologicals in Atopic Disease in Pregnancy gathered existing evidence on the potential risk and benefits for biologicals during pregnancy. The TF recognized the difficulty in reliably counseling patients due to the lack of available adequate data. In the end, the TF recommended shared decision making counseling patients on the potential risks of medication exposure balanced against the risk of untreated disease.

Adherence to therapy can change during pregnancy impacting on asthma control. Most commonly observed is decreased adherence as a result of a mother's concerns about the safety of medications for the fetus. Less than 40% of women who classified themselves as "poorly controlled " reported use of a controller medication during pregnancy.

Patient education is an important part of the management of the pregnant asthmatic. Each patient should be provided basic information about asthma and the relationship between asthma and pregnancy. Monthly visits to assess asthma control and adherence are recommended for women who require controller therapy during pregnancy. Each patient should also receive an asthma action plan that includes how to recognize a severe exacerbation and when to seek urgent or emergency care (Table 6).

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TABLE 4

Safety of commonly used medications for the treatment of asthma during pregnancy

Drug		Perinatal Outcomes
Inhaled Bronchodilators		Reassuring human data for SABA; some associations with specific malformations, but may be chance or confounding by severity
Short-acting (SABA)	Albuterol	
Long-acting (LABA)	Formoterol, Salmeterol	Modest amount of human data reassuring for LABA
Inhaled corticosteroids	Budesonide, Beclomethasone, Fluticasone, Mometasone, Triamcinolone, ciclesonide	Substantial reassuring data; Risk of increased malformations with high dose, but may be confounding by severity; Most safety data for budesonide and fluticasone
Leukotriene Receptor Antagonists	Montelukast, Zafirlukast	Moderate amount of reassuring data, particularly for montelukast
5_LO Inhibitors	Zileuton	Animal studies not reassuring; no human data
Anti-IgE	Omalizumab	Some increased risk of low birth weight and preterm birth, but may be confounding by severity
Anti-IL5	Mepolizumab, Reslizumab	No human data
Anti-IL5R	Benralizumab	No human data
Anti-IL4R	Dupilumab	No human data

TABLE 5

Steps of Asthma Therapy during Pregnancy*

GINA Step	Preferred Controller Medication	Alternative Controller Medication
1	None	--
2	Low dose ICS	LTRA, theophylline
3	Medium dose ICS	Low dose ICS + either LABA, LTRA or theophylline
4	Medium dose ICS + LABA	Medium dose ICS + LTRA or theophylline
5	High dose ICS + LABA	--Medium dose ICS + LABA + tiotropium
6	High dose ICS + LABA + oral prednisone	-consider add on therapy i.e tiotropium, Anti-IGE, Anti-IL-4R, Anti-IL5/5R

ICS - inhaled corticosteroids; LTRA – leukotriene-receptor antagonists; LABA - long-acting beta agonists

**Modified from Schatz M, Dombrowski M. N Engl J Med 2009;360:1862-1869*

TABLE 6

Patient Education for Self-Management of Asthma during Pregnancy

Subject	Recommendation
General Information	Provide basic information about asthma and relationship between asthma and pregnancy
Use of inhaler device	Demonstrate proper technique for specific device and ask patient to perform the technique; Recommend a spacer device for metered-dose inhaler if patient's technique is suboptimal
Adherence to treatment	Discuss self-reported adherence to treatment with controller medication and, if needed, address barriers to optimal adherence (e.g. cost, convenience, concern about side effects)
Asthma action plan	Provide schedule for maintenance medication and doses of rescue therapy for increased symptoms; explain when and how to increase controller medication and when and how to use prednisone (for patients with previous prednisone use or poorly controlled asthma); explain how to recognize a severe exacerbation and when and how to seek urgent or emergency care

5 WORK-RELATED ASTHMA

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KEY MESSAGES

- Work-related asthma is the most common occupational lung disease
- It is classified into work-exacerbated asthma, that is pre-existing asthma that worsens at work, and occupational asthma (OA) when it is induced by agents present at work
- Diagnosis of OA relies on the demonstration of the causal relationship between asthma symptoms and workplace exposure
- For the diagnosis of OA caused by high molecular weight substances sensitization to the suspected occupational allergen (skin prick test or specific IgE) has a high predictive value
- Early identification of OA followed by removal from exposure increases the chance of a better health outcome

DEFINITIONS AND PATHOGENESIS

Work-related asthma (WRA) is any type of asthma that worsens at work, and it encompasses: Work-exacerbated asthma (WEA) and Occupational asthma (OA) (Figure 1). WEA refers to concurrent or pre-existing asthma triggered by various work-related factors, such as irritants or exercise, whereas OA is defined as asthma caused by the workplace. Two types of OA are distinguished:

- Allergic OA is induced by sensitizers and appears after a latency period of exposure. More than 400 etiologic agents have been described (http://www.aoecdata.org/ExpCodeLookup.aspx). OA is caused by high-molecular-weight (HMW) allergens and some low-molecular-weight (LMW) agents and is usually driven by an IgE-mediated mechanism. For most LMW agents causing OA the underlying immunologic pathways are not fully characterized.
- Irritant-induced OA is due to acute high-level exposure to irritants or to persistent exposure to moderate levels of respiratory irritants. The best known form of irritant-induced OA is the "Reactive Airways Dysfunction Syndrome" (RADS), where asthma symptoms have an acute after a single exposure to very high concentrations of an irritating gas, vapors, fume or smoke.

DIAGNOSIS

The primary objective of the diagnosis of OA is to prove the causal relationship between asthma symptoms and the workplace exposure. The stepwise diagnosis procedure (Figure 2) is based on a combination of medical history, physical examination, positive response to bronchodilator or measurement of non-specific bronchial hyperresponsiveness (NSBH), and evidence of IgE-mediated sensitization, especially for HMW allergens, by skin prick testing and/or specific IgE measurement. Serial monitoring of peak expiratory flow (PEF) at work and away from work is also a useful option. The specific inhalation challenge (SIC) is considered the golden standard, especially if the patient is not at work. SIC should be performed only in a specialized setting. The accuracy of the diagnosis can be improved by the measurement of sputum eosinophils and/or the fractional exhaled nitric oxide (FeNO) before and after challenge. If SIC in the specialized setting is not available and OA is strongly suspected from

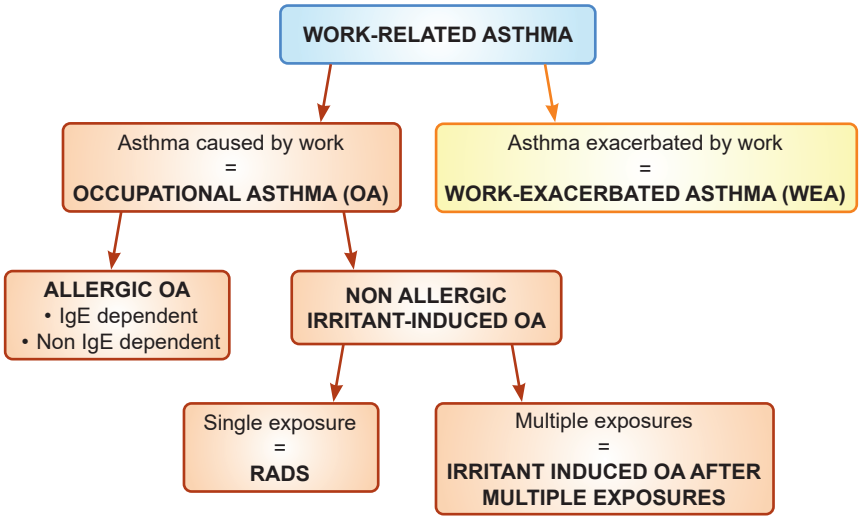

Figure 1 **Types of work-related asthma.**
RADS – Reactive Airways Dysfunction Syndrome
(adapted of Moscato et al. Allergy. 2012;67:491-501.)

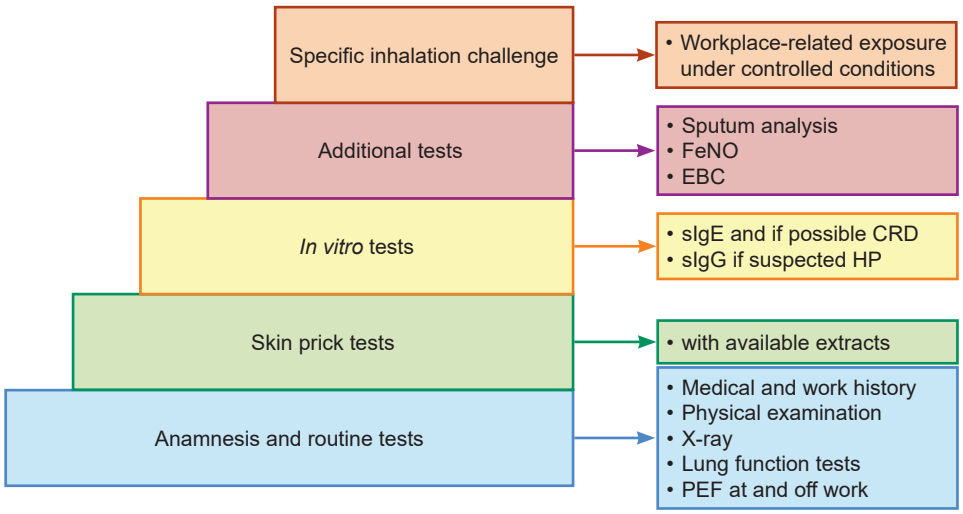

Figure 2 **Diagnostic approach for the evaluation of suspected work-related asthma.**
CRD - component-resolved diagnosis; EBC - exhaled breath condensate; FeNO - fractional exhaled nitric oxide; HP - hypersensivity pneumonitis; PEF - peak expiratory flow; sIgE - specific IgE; sIgG - specific IgG.

history, a combination of objective evidence of asthma plus a positive skin test or the verification of specific IgE to the suspected agent has a high predictive value for OA caused by HMW allergens.

MANAGEMENT AND PREVENTION

Management of OA includes pharmacotherapy, which does not differ from that used in other forms of asthma, together with complete removal from exposure to the causative agent (Table 1). The best prognosis for improving of OA has been associated with an early diagnosis and early removal, with milder asthma at the time of diagnosis.

Reduction of exposure has been proposed as an alternative, but it is associated with a lower likelihood of improvement and recovery, as well as with a higher risk of worsening of the symptoms and NSBH. Although continued exposure usually lead to worsening of airway obstruction and NSBH, avoidance of exposure does not lead to complete recovery from asthma, and approximately 10–15% of patients with OA deterio-

TABLE 1

Management of work-related asthma

Type of work-related asthma	Recommended procedures
Occupational asthma due to high- or low-molecular agents	Pharmacological treatment Avoidance of exposure to high levels of irritants Removal from exposure to the causative agent
Irritant-induced asthma	Pharmacological treatment Avoidance of exposure to high levels of irritants Work may be continued
Work-exacerbated asthma	Pharmacological treatment Avoidance of exposure to high levels of irritants, allergens and other factors aggravating asthma

TABLE 2

Prevention for work-related asthma

Prevention	Aims to	Examples
Primary	Reduce disease incidence	• Legislation and enforcement to ban or control the use of hazardous products and to mandate safe and healthy practices, education about healthy and safe habits • Control measures for airborne allergens (elimination, reduction, isolation, ventilation, personal protection equipment) • Pre-employment examinations to detect atopic status or pre-existing asthma
Secondary	Reduce disease progression and severity	Regular exams and screening tests to detect disease in its earliest stages, e.g.: • respiratory questionnaire • spirometry • specific immunologic tests • other tests for airway inflammation such as FeNo, induced sputum or EBC
Tertiary	Reduce complications and consequences of the established disease	• Vocational rehabilitation programs to retrain workers for new jobs when they have recovered as much as possible • Allergen immunotherapy (if standardised extracts are available) • Biological therapy (e.g. omalizumab)

rate even they are removed from their workplace.

In the case of WEA, in addition to general asthma management, exposure at work may need to be reduced to prevent further exacerbation of asthma but, unlike OA, usually it would not need to be completely eliminated.

WRA is preventable in three stages: primary, secondary and tertiary (Table 2).

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6 APPLYING VARIOUS STUDY DESIGNS TO DIRECT PRECISION MEDICINE IN ASTHMA

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Asthma is one of the most common chronic diseases. There is increasing recognition of the phenotypic heterogeneity in asthma, and a need for personalized medicine instead of standardized therapeutic approaches. This may be particularly the case in childhood, where significant heterogeneity exists in the course of asthma and response to medications. The goal of this chapter is to provide examples of study designs that have informed precision medicine for pediatric asthma management.

KEY MESSAGES

- The study design applied will vary with the question being addressed
- Long-term treatment followed by reduction in daily medication or study medication withdrawal is important in assessing the potential for asthma remission as determined by various outcome measures
- A cross-over study design is useful for identifying patient characteristics and biomarkers associated with the best response to specific medications
- An adaptive study design may be useful for studying potential medications for asthma and identifying the effect of specific medications on various asthma outcomes
- Challenges for short-term studies include the possibility of not allowing sufficient time to detect seasonal variations in asthma control

REMISSION

There is variation in the trajectory of childhood asthma and controversy regarding the role of various asthma medications in modifying the natural history of asthma. The PEAK study, a randomized controlled trial (RCT) of toddlers at-risk for persistent asthma, addressed the role inhaled corticosteroids (ICS) on early asthma progression (Table 1). This study of atopic toddlers found that two years of daily ICS therapy improved asthma control during the treatment period but did not modify asthma outcomes in a third observation year when ICS were discontinued (Figure 1). This study design can be used to assess potential of a medication to induce asthma remission as defined by persistent improvement in pulmonary function, reduction in exacerbations and ability to maintain control after discontinuing the study medication. This design is being used to determine if bacterial lysates (ORBEX) or omalizumab (PARK) may be disease modifying.

PREDICTORS OF RESPONSE

There is phenotypic variation in response to asthma therapy as demonstrated by the INFANT study. This triple-arm cross-over study of toddlers on step 2 therapy noted strong (74%) differential response to three medications, with probability of best response to daily ICS therapy. This study demonstrated that aeroallergen sensitization and high serum eosinophil counts were associated with a favorable response to daily ICS therapy as compared to intermittent ICS or montelukast, providing guidance for the type of patients most likely to respond to daily ICS therapy.

TABLE 1

Cited Studies Directing Precision Medicine

Objective	Design	Outcome	Benefits	Limitations
PEAK (Prevention of Early Asthma in Kids)				
To determine whether two years of daily ICS therapy, compared to placebo therapy, reduced proportion of episode-free days in a third observation year among 285 atopic toddlers	Randomized, double-blind, placebo-controlled, parallel-group trial of ICS vs placebo for two years, with subsequent monitoring for an additional third year with no treatment in either group	No difference in the 3rd observation year between the two groups in proportion of episode-free days, number of exacerbations, or lung function. During treatment period ICS therapy (compared to placebo) was associated with greater proportion of episode-free days, lower rate of exacerbations, and lower supplementary use of controller medications	Provides level one evidence that in atopic preschool-aged children daily asthma therapy does not alter natural course of asthma. Allows stable time period to identify effect (pulmonary function, exacerbations, asthma control days) and then assess medication withdrawal in order to determine long-term effect in the absence of conventional therapy	Long time interval to conduct the study
INFANT (Individualized Therapy for Asthma in Toddlers)				
To determine differential response to 3 asthma therapies among toddlers aged 12-59 months with asthma necessitating treatment with daily controller therapy	Randomized, double-blind, double-dummy clinical trial with randomized crossover of three 16-week treatment periods with daily ICS, daily LTRA, and as-needed ICS co-administered with SABA	74% had differential response; probability of best response was highest for daily ICS as predicted by aeroallergen sensitization, and high blood eosinophil counts	Provides a measure to identify population characteristics associated with best therapeutic response in toddlers with asthma	Adherence self-reported, did not include placebo washout period, possible effect of seasonal exacerbations (although adjusted for), biomarkers measured only at study initiation
CLIC (Characterization of Response to Leukotriene Antagonist and Inhaled Corticosteroids)				
To determine whether response to 2 asthma medications among school aged children with mild to moderate asthma were concordant or discordant	Randomization to one of two 8-week crossover sequences (ICS, LTRA)	17% responded to both medications, 23% responded to ICS only, 5% responded to LTRA only, and 55% responded to neither medication. Favorable response to ICS associated with higher FENO, higher eos/IgE/ECP, and lower pulmonary function. Favorable response to LTRA associated with younger age/ shorter disease duration	Provides evidence of differential response to asthma medications in school-aged children with asthma	Reliance largely on a singular pulmonary function measurement during each crossover period. Did not account for possible seasonal effect. May not be possible to evaluate impact on exacerbations in such a short period of time
Pooled data from CLIC and PACT (Pediatric Asthma Controller Control) Studies				
To determine whether the ratio of urinary LTE4/FENO identifies children with preferential response to montelukast compared to ICS therapy among 318 children enrolled in two RCTs	Secondary analysis of data from the CLIC and PACT studies	LTE4/FENO ratio associated with a greater response to montelukast than ICS therapy for FEV1 measurements and asthma control days	Identifies biomarkers associated with a differential response to first-line asthma medications in school aged asthmatic children	Poor specificity of urinary LTE4 measurements. Used continuous variables instead of categorical variables so cut off point could not be established

ECP - eosinophil cationic protein; eos - eosinophils; FENO - fractional exhaled nitric oxide; FEV1 - fractional exhaled volume in 1 second; ICS - inhaled corticosteroid; IgE - immunoglobulin-E; LABA - Long-acting beta-agonist; LTE4 - leukotriene E4; LTRA - leukotriene receptor antagonist; SABA - short-acting bronchodilator

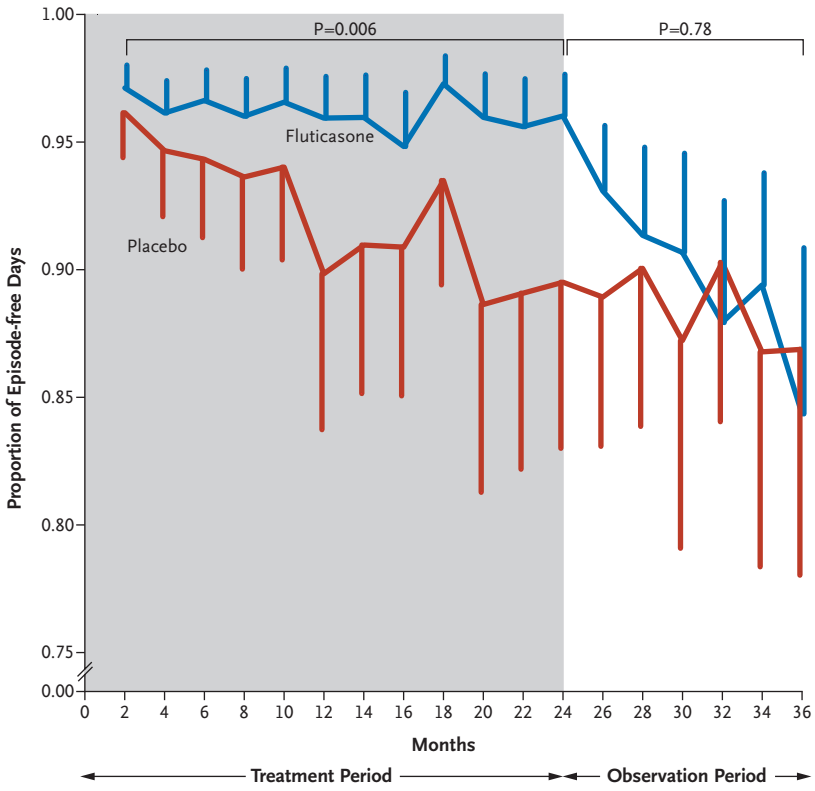

Figure 1 PEAK Study – Proportion of Episode-Free Days During Treatment/Observation Period. Fluticasone treatment, as compared with placebo, did not increase the proportion of episode-free days during the observation year (86.8 percent [95 percent confidence interval, 81.2 percent to 90.9 percent] vs. 85.9 percent [95 percent confidence interval, 79.9 percent to 90.3 percent], P = 0.78), but during the two-year treatment period (shaded area) it significantly increased the proportion of episode-free days (93.2 percent [95 percent confidence interval, 91.1 percent to 94.9 percent] vs. 88.4 percent [95 percent confidence interval, 84.9 percent to 91.2 percent], P = 0.006). The proportions of episode-free days in the fluticasone group and the placebo group were 97 percent and 96 percent, respectively, during the first two months of the treatment period; 96 percent and 89 percent during the last two months of the treatment period; and 84 percent and 87 percent during the last two months of the observation year — results that demonstrate an increase in the frequency of asthma-like symptoms over time. The two study groups were compared by analysis of covariance at each two-month interval. P values are for the comparison between the groups at each interval. Vertical bars represent 95 percent confidence intervals.

From: Long-term Inhaled Corticosteroids in Preschool Children at High Risk for Asthma, Guilbert et al, v.354, p.1990, ©2006, Massachusetts Medical Society. Reprinted with permission.

DIFFERENTIAL RESPONSE

Phenotypic variation in therapeutic response related to specific asthma outcomes has been demonstrated in the same asthmatic child with a two-arm crossover study, such as in the CLIC study. This study identified factors, primarily atopic biomarkers (such as total eosinophil counts, serum eosinophilic cationic protein levels, and serum IgE levels), associated with a favorable response to ICS therapy as compared to montelukast in measurements of pulmonary function and asthma control days (Figure 2). Pooled data from the CLIC and PACT studies subsequently identified that urinary leukotriene E4 (LTE4) to fractional exhaled nitric oxide (FeNO) ratio predicts preferential response to montelukast compared with ICS therapy. Of interest, in the CLIC study, approximately 55% had no improvement in pulmonary function with either medication, likely due to the high level of pulmonary function in children with mild persistent asthma.

ADAPTIVE STUDY DESIGNS

A novel adaptive study design with multiple medication crossover studies is currently being evaluated in the NHLBI PrecISE Network focused on severe and exacerbation-prone asthma. Specific outcomes will be defined that are relevant to an individual med-

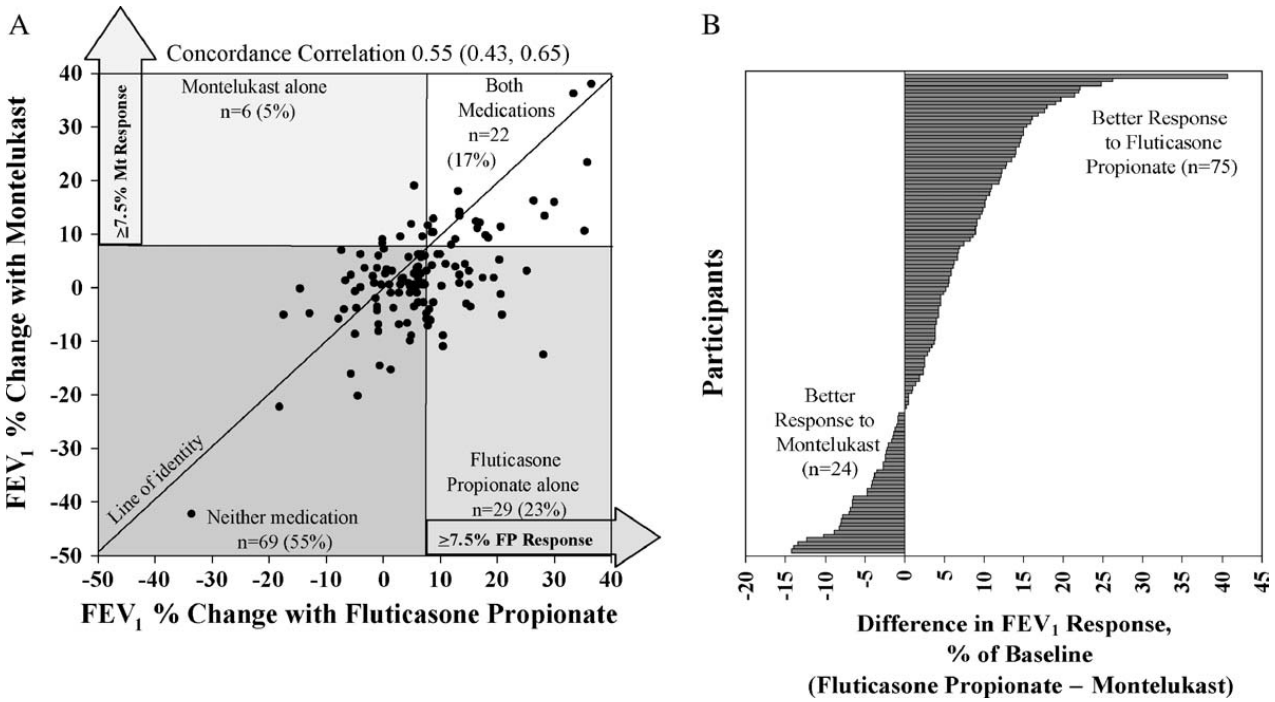

Figure 2 **CLIC Study – Variability in Response to ICS, LTRA, Both or Neither.** A, Variability of response and differential response to fluticasone and montelukast, as measured by change in FEV1. Four regions show categories of response, defining a favorable response as 7.5% or greater. FP, Fluticasone propionate; Mt, montelukast. The line of identity is designated, with patients favoring montelukast falling above the line, and those favoring fluticasone falling below the line. The concordance correlation with 95% CIs is displayed. B, Difference in FEV1 response between fluticasone propionate and montelukast for individual participants. Each line designates a single participant.
From: Characterization of within-subject responses to fluticasone and montelukast in childhood asthma, Szefler et al, v.115, p.235, ©2005, Journal of Allergy and Clinical Immunology. Reprinted with permission.

ication. Predictive and monitoring biomarkers will be identified that are associated with a favorable response to these test medications.

In the future, master protocols such as umbrella, basket, or platform trials may be increasingly used to evaluate more than one asthma treatment, targeting a specific biomarker-defined or otherwise phenotypically/endotypically-defined asthmatic population.

CONCLUSION

Studies thus far have provided insight on variable response to medications and patient characteristics associated with a favorable response and thus led the way to a personalized medicine strategy in children. They also provide the opportunity to evaluate medications for possible remitting features. There will be an ever-increasing need for precision medicine in the management of pediatric asthma moving forward.

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7 ASTHMA DRUGS - A REGULATORY PERSPECTIVE

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The substantial progress in the knowledge of the pathogenesis of asthma has recently led to identify novel and specific therapeutic targets for the different phenotypes and endotypes of this heterogeneous disease. In addition, the unified airway model, in which the upper and lower airways are viewed as a common unit with respect to infection and allergic inflammation, has sparked interest in developing allergen immunotherapy (AIT) products for prevention and treatment of allergic asthma. This article summarizes the European and the US regulatory point-of-view towards regulation of therapeutics for asthma.

KEY MESSAGES

- At regulatory level, actions should be taken to facilitate the development and approval of innovative medicines for a very common disease causing high individual and social costs and still missing adequate treatment of the most severe forms
- Biologicals and allergen products imply the need of a new methodology for the evaluation, marketing authorization, post-marketing monitoring and an affordable access of asthmatic patients to safe and effective medicines
- Dissection of asthma into distinct phenotypes and endotypes should prompt to reconsider study designs and outcome measures of previous large randomized controlled trials and to adapt to small populations selected through validated biomarkers and on the basis of the mechanistic rationale of the drug under investigation
- To demonstrate efficacy towards preventing asthma, studies must be long term — a minimum of 5 years
- In addition to clinical endpoints, clinical study design should include non-invasive physiologic monitoring at timely intervals

THE EUROPEAN POINT-OF-VIEW

Among the 374 new active substances (NASs) approved by the European Medicines Agency (EMA) in the last ten years (2010-2019), only 6 had an indication for asthma. Furthermore, considering that only first-in-class medicines are considered as a sign of innovation, the number of recent innovative asthma drugs is even lower. In fact, the association of fluticasone furoate/vilanterol is only an advance-in-class combination of two classes of drugs already largely used in asthma, mepolizumab and reslizumab have the same target (IL-5) and dupilumab represents only an extension of indication for a medicine already approved for moderate/severe atopic dermatitis. While waiting for the innovative small molecules under inves-

* *The comments by JL and RLR are an informal communication and represent their own best judgment. These comments do not bind or obligate FDA*

** *The views expressed by GR are the personal views of the author and may not be understood or quoted as being made on behalf of or reflecting the position of the EMA or one of its committees or working parties.*

TABLE 1

Future regulatory challenges for the development of innovative asthma medications

- Develop partnership with academia to adapt regulatory pathways to progress in science and emerging evidence
- Promote an early dialogue with all stakeholders
- Facilitate implementation of novel manufacturing and nano-technologies
- Leverage non-clinical models, based on human cell or organoid culture or in-silico modelling to replace, reduce and refine animal models
- Foster innovation in clinical trials by adapting study designs to precision medicine, biomarkers and –omics, and by promoting collaborative or decentralized clinical trials administrated through telemedicine and mobile health
- Optimise modelling, simulation and extrapolation
- Reinforce collaboration with third-party payers to encourage affordable access to innovative medicines
- Reinforce patients' role in evidence generation
- Expand the relevance of real-world data in evidence generation, drug monitoring and decision to exploit post-authorization efficacy and safety studies (PASS and PAES), big data collection and analysis, digital technology, and artificial intelligence
- Promote transparency and data sharing
- Provide regulatory advice along the entire development and decision-making phases of a medicinal product

tigation, innovation appears to be mostly confined to biologicals.

Therefore, actions should be taken to facilitate the development and approval of innovative medicines for a very common disease causing high individual and social costs and still missing adequate treatment of the most severe forms.

To foster innovation in treatment, regulators must adapt to new challenges and strategic goals necessary for development of increasingly complex therapeutics to prevent or treat allergic asthma (Table 1).

In Europe, clinical investigations of medicines for asthma are currently based on the EMA Guidelines that came into effect on May 1,2016 (*https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-medicinal-products-treatment-asthma_en.pdf*). These should be complemented by biologicals guidelines (*https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/biological-guidelines*) and by the ICH E11(R1) guideline on clinical investigation in the paediatric population *https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e11r1-guideline-clinical-investigation-medicinal-products-pediatric-population-revision-1_en.pdf*.

EMA Guidelines are also available for the production, quality and clinical development of allergen products (EMEA/CHMP/BWP/304831/2007; CHMP/EWP/18504/2006). On March 26th 2020, the EMA CHMP adopted, after public consultation, a document on "Recommendations on a common regulatory approach for allergen products" at present under review by the European Commission. The document is intended to provide principles and guidance for the regulation of medicinal allergen products with the aim to facilitate harmonization throughout the European Union.

Other initiatives – more extensively discussed in a recent review, were also taken by EMA to favour innovative medicinal products including those for the treatment of asthma.

ALLERGENIC PRODUCTS FROM THE US POINT-OF-VIEW

Epidemiologic and clinical studies show that atopic dermatitis and food allergy initiate the "atopic march" towards aeroallergen sensitivity and allergic asthma, and strongly suggest that AIT for allergic rhinoconjunctivitis (ARC) can interrupt the march to arrest the progression or even prevent allergic asthma. On January 21, 2016, FDA convened its Allergenic Products Advisory Committee (APAC) to discuss the clinical development of AIT products for the prevention of respiratory allergic disease. Areas of discussion included criteria for selection of study subjects, the duration of follow-up required to demonstrate asthma prevention, considerations for a

TABLE 2

Considerations for evaluating the efficacy and safety of allergenic products intended to prevent asthma, as discussed by the Allergenic Products Advisory Committee (APAC) in 2016

- Use tools other than spirometry to evaluate risk of developing asthma
- Stratify enrolment of paediatric subjects by age
- Follow subjects for a minimum of 5 years after completion of allergenic products to detect cases of asthma
- Define what constitutes a case of asthma either by absolute (i.e., yes or no) or graded (i.e., almost certain, probable, possible, unlikely) criteria
- Incorporate supportive results from spirometry and oscillometry into the asthma case definition (absolute or graded)
- Consider incorporating medically significant events into efficacy evaluation scoring, such as physician-prescribed inhaled or oral corticosteroids and emergency room visits
- Schedule more frequent physical examinations and non-invasive assessments for safety monitoring and early detection of adverse reactions
- Extend post-treatment observation periods beyond time intervals typically recommended for adolescents or adults
- Utilize checklists and diaries to facilitate at-home safety assessments and prospective safety reporting by parents/guardians

[*] *Tools other than spirometry include family history (i.e., first degree relatives with atopy), clinical scoring tools (e.g., Asthma Predictive Index (API)), skin prick testing, specific IgE level testing, measurement of fractional exhaled nitric oxide (FeNO). Normal reference values have been published for children aged 1 to 5 years. FeNO has been shown to be elevated in eosinophilic airway inflammation and an elevated FeNO in preschool children with recurrent cough and wheeze is associated with subsequent diagnosis of asthma in school-aged children.*

case definition of asthma suitable for demonstration of efficacy, and considerations for safety assessments taking into account the smaller airways of young children and their developing language skills. Table 2 presents considerations that APAC members agreed are important for safety monitoring and for incorporation into the case definition of asthma to demonstrate efficacy of a product to prevent allergic asthma.

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8 CLINICAL TRIAL DESIGN IN ASTHMA - THE PEDIATRIC POINT OF VIEW

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Asthma carries the biggest burden of all chronic diseases in childhood for the patients and the society because of its high incidence and prevalence from early childhood onward. It is of uttermost importance to find optimal and safe treatment strategies through carefully executed clinical trials. Pediatric regulation came in effect in European Union in 2007, emphasizing the need to facilitate both the development and availability of medicines for children of all ages.

KEY MESSAGES

- Finding optimal and safe treatment strategies through carefully executed clinical trials in pediatric asthma is warranted
- Due to multiple asthma phenotypes, studies should be performed on age ranges including children under six years, 6-12 years of age and 13-17 years of age
- Clinical research networks are the best way to perform carefully designed trials with clearly defined simple outcomes
- Besides the unmet need for new medications including biologicals in severe pediatric asthma, studies on prevention of disease progression, prediction of future risk and risk of persistence into adulthood are needed

DESIGNING CLINICAL TRIALS

According to generally accepted principles, pediatric clinical studies should be initiated as early as possible but not before the benefit of the drug has been shown for adults. Due to multiple asthma phenotypes/endotypes during the childhood, it is recommended that studies should be performed on three age ranges including children under six years, 6-12 years of age and 13-17 years of age (Figure 1). Because of the challenges in diagnosis of asthma particularly with the youngest children, special emphasis should be directed to correct identification of asthma in this smallest age group. In the older ones, similar principles can usually be applied as for adults, including the history, symptoms and lung function measurements.

HOW TO GATHER EVIDENCE FOR IMPROVED ASTHMA CARE?

The medical community strives for implementing personalized or precision medicine also in asthma care. This can be accomplished only through randomized clinical trials. In many research questions, there is a need to study different arms with alternative drugs or dosages or treatment regimens which brings the number of needed patients often too high for a single center to manage. This is why pediatric asthma networks should be employed when possible.

One of the best networks initiated in the USA, called CARE (Childhood asthma research and education network), independent from industry and funded by National Heart, Lung and Blood Institute (NHLBI) demonstrated extremely important outcomes for childhood asthma advancing the understanding of pediatric asthma care. Other important studies which have had a major impact on how childhood asthma is currently treated are discussed in Table 1. Basically all trials are double-blinded, randomized trials with simple and well-measurable primary outcome. These pivotal trials demonstrated that inhaled corticosteroids (ICS) control the

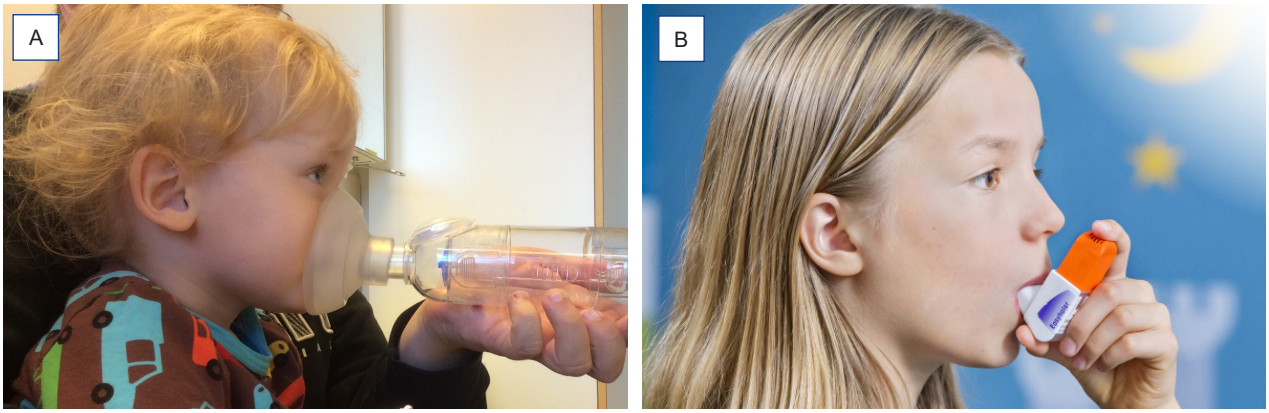

Figure 1 **A small child (A) may have a different phenotype of asthma than a school-aged child (B)has, resulting in differences in medication including adequate age-based inhalers.**

disease but do not modify its natural history and that ICS are more efficacious than leukotriene blockers in mild-to-moderate asthma.

After CARE, AsthmaNet has continued similar type of work with well-established clinical centers joining forces to perform clearly defined trials. Through these studies, better tools for treating preschoolers with wheezing were developed. Large independent research networks may be the best way to find optimal treatment strategies since pharma industry does not examine new drugs as compared to modified protocols with older drugs.

FUTURE OF PAEDIATRIC ASTHMA CARE AND NEED FOR STUDIES

Biological drugs are now the latest and most important new category of severe asthma, however their application in children with severe asthma is lagging behind adults. Therefore, a clear design for the trials to come, particularly regarding which drugs to use for individual patients, is warranted. The differences in so far published studies in outcomes and patient populations poses still challenges.

Recently, a Think Tank initiated by respiratory effectiveness group use a two-round survey to identify the unmet clinical needs in pediatric asthma. This group of more than 40 experts from 25 countries and 5 continents identified several important research questions including prevention of disease progression, prediction of future risk and risk of persistence into adulthood. This Think Tank also highlighted the problems of extrapolating data from adults into clinical decision making with children. When designing future studies, these concepts help directing the trials and weighing the risks and benefits for children and their caretakers.

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TABLE 1

Most important pediatric asthma treatment studies conducted through the Childhood asthma research and education network (CARE)

Design	primary outcome	main result
PEAK		
Multicenter, double-blind, randomized, placebo-controlled, parallel-group trial of inhaled fluticasone as compared with placebo in children two or three years of age who were at high risk for asthma	the difference between the study groups in the proportion of episode-free days during the year-long observation period	ICS control the disease but do not modify its natural course
PACT		
double-blind, randomized parallel group design, in children with mild to moderate persistent asthma, assessing: 1. is there efficacy with less potential for growth effects if a LABA was added to half the dose of ICSs, 2. define the relative efficacy and safety of an LTRA compared with the other 2 treatments.	percent of asthma control days during the 48-week treatment period	ICS are more efficacious than montelukast both alone and combined with LABA
Episodic drugs in Intermittent Wheezing		
Randomized, double-blind placebo-controlled twelve-month trial, children aged 12-59 months with moderate-severe intermittent wheezing, 7-days of either budesonide (1mg twice daily), montelukast (4mg daily), or placebos in addition to albuterol with each identified respiratory tract illness	Proportion of episode-free days (EFDs) during the 12- month trial	neither budesonide nor montelukast early in respiratory tract illnesses increases the proportion of EFDs or decrease oral corticosteroid use over a 12-month period
Episodic versus continuous budesonide in intermittent wheezing		
Randomized, double-blind, parallel group trial, budesonide inhalation suspension for 1 year as either an intermittent high-dose regimen (1 mg twice daily for 7 days during a respiratory tract illness) or a daily lowdose regimen (0.5 mg nightly) with corresponding placebos	frequency of exacerbations	A daily low-dose regimen of budesonide was not superior to an intermittent high-dose regimen in reducing asthma exacerbations
Step-up therapy for children receiving ICS		
Randomized, double-blind, three-treatment, crossover trial for 48 weeks, three blinded step-up therapies in random order for 16 weeks: 250 µg of fluticasone (FP) twice daily (ICS step-up), 100 µg of FP plus 50 µg of LABA or 100 µg of FP twice daily plus montelukast	differential response to each of the three step-up therapies on the basis of fixed threshold criteria	Nearly all the children had a differential response to each step-up therapy. LABA step-up was significantly more likely to provide the best response than either ICS or LTRA step-up
TREXA		
Randomized, double-blind, placebo-controlled trial, mild persistent asthma aged 5-18 years, 4 treatment groups: twice daily beclomethasone with beclomethasone plus albuterol as rescue; twice daily beclomethasone with placebo plus albuterol as rescue; twice daily placebo with beclomethasone plus albuterol as rescue; and twice daily placebo with placebo plus albuterol as rescue	time to first exacerbation that required treatment with prednisone	Children with mild persistent asthma should not be treated with rescue albuterol alone and the most effective treatment to prevent exacerbations is daily inhaled corticosteroids

9 REAL-WORLD EVIDENCE FOR ASTHMA MANAGEMENT

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Randomized controlled trials (RCTs) provide a useful source of information regarding the validity of various approaches for the management of asthma. However, due to the strict inclusion criteria and intensive clinical management that is part and parcel of their ecology of care, they provide information on treatment efficacy instead of real-world effectiveness. This leads to the discrepancy often observed between the results in RCTs and the real-world. There is a clear need for a better understanding of how asthma presents in real clinical practice to bridge the gap between treatment efficacy and effectiveness.

KEY MESSAGES

- Real world studies include observational studies and pragmatic trials. Observational data can either be derived from electronic medical records or prospectively collected. Pragmatic randomised trials broaden the inclusion criteria and normalise the care to be closer to real life than classical RCTs
- Real-world studies answer different questions to those answered by RCTs, particularly around the effectiveness of interventions in daily clinical care
- Real-world studies should be seen as complementing the evidence from RCTs and should be as rigorous in design and implementation

CAPTURING REAL-WORLD POPULATIONS THROUGH STUDY DESIGN

Real-world studies fall into two main categories: pragmatic trials and observational studies. Figure 1 illustrates the relationship between study design and the type of asthma populations they capture. The further a study from the point of origin on the graph, the greater its generalisability to the real-world.

Guideline recommendations for effective asthma management traditionally rely on RCTs. For example, based on evidence from RCTs, GINA currently recommends inhaled corticosteroids (ICS) as first-line therapy while leukotriene receptor antagonists (LTRAs) are considered a less efficacious alternative.

However, real-world evidence from the UK government-funded ELEVATE study, which investigated the use of LTRAs against ICS and long-acting beta agonists (LABAs) as first-line and add-on therapy respectively in two pragmatic trials, showed similar levels of effectiveness, with trends towards better outcomes for smokers for LTRA. The increased LTRA effectiveness was driven principally by increased adherence with oral LTRAs as compared to ICS . These results suggest that different medications may be more useful in the different subgroups that are seen in clinical practice rather than the homogenous RCT populations.

THE USE OF DISEASE REGISTRIES IN REAL-WORLD RESEARCH

Apart from strict inclusion criteria, RCTs also struggle to capture representative patient populations due to small sample sizes selected following strict criteria. Disease-specific registries provide a solution as they hold medical data for thousands of patients with the disease of interest and enable the retrospective analyses of re-

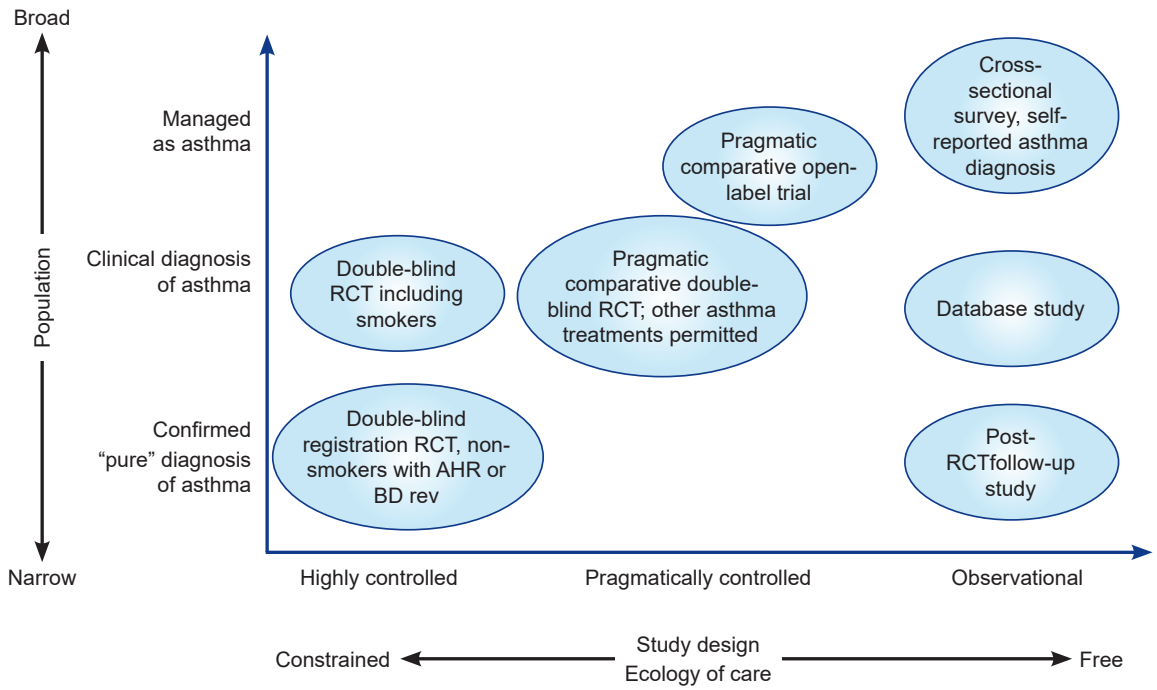

Figure 1 **An illustration of studies according to design and study population.**
AHR - airway hyper-responsiveness; BD rev - post-bronchodilator reversibility ; RCT - randomized controlled trial.

al-world outcomes in representative populations. For example, the International Severe Asthma Registry (ISAR) holds data from over 8000 severe asthma patients in 31 countries and thereby aids the global understanding of effective asthma management techniques across a range of clinical characteristics and demographics.

These data can be used to improve the understanding of subgroups of severe asthma patients that are routinely excluded from RCTs, such as those with lesser reversibility, comorbidities or active smokers.

LINKING THE DATA TO UNDERSTAND TRUE PATTERNS OF ASTHMA

Poor inhaler technique has been linked to poor asthma outcomes, however, the CRITIKAL study, an observational study, was the first to investigate the impact of specific inhaler-handling errors on asthma outcomes. By ranking common inhaler errors by device type and frequency, CRITIKAL unveiled true patterns of asthma self-management. For example, over 30% of the patients used insufficient inspiratory effort when using dry-powder inhalers. Its findings can therefore be used to better inform inhaler training for patients and physicians to ultimately improve asthma outcomes.

Asthma management in the real world is clearly a complex task and involves understanding the many facets of the disease's pathology together with the resources available for asthma management. While RCTs provide valuable insight into a treatment's efficacy, factors which are controlled in these trials remain variable in real life. Real-world studies account for this variability by capturing representative patient populations and can therefore complement RCTs to improve asthma treatment outcomes on an individual level.

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Section H

PREVENTION AND CONTROL OF ASTHMA

1 PRIMARY AND SECONDARY PREVENTION OF ASTHMA

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Asthma now affects around 358 million people in the world, and usually starts in childhood. Thus, strategies to prevent disease development and life time disease burden should start in early life. Prevention should target environmental and life style asthma risk factors acting directly by inducing airway inflammation, as well as indirectly through the developing immune system.

Primary prevention of asthma involves preventing initial disease development, whereas secondary prevention refers to preventing new asthma in subjects who have expressed early signs, typical other atopic diseases like atopic eczema or allergic rhinitis (Table 1, Figure 1). Primary prevention interventions should be feasible, safe and applicable to the general population, as we are currently unable to predict accurately the occurrence of asthma in early childhood. Interventions may be global, such as reducing air pollution levels, while others may be on an individual level in pre-pregnancy, antenatally or directed towards the child. Although observation studies may identify risk and protective factors and provide rationale for interventions, prevention strategies should be well documented, ideally through well-powered and confirmative randomised clinical trials (RCT) prior to implementation. However, to avoid unnecessary harm to children, the precautionary principle of reducing known risk factors such as exposure to tobacco or air pollution may be called for, awaiting firm documentation of intervention efficacy. Although some promising strategies are emerging, effective primary prevention of primary prevention of asthma is still limited.

KEY MESSAGES

- Avoid smoking, including prenatal and second hand exposure
- Repair possible housing moisture damage
- Air pollution should be reduced and avoided, if possible
- Breast feeding beyond 4 months may prevent wheeze and asthma, whereas avoidance diets do not prevent asthma
- Diets rich in fruits and vegetables are likely to be helpful
- The role of micronutrients and probiotics to reduce asthma is not clear
- Participate in regular physical activity
- Pet keeping should not be determined to prevent asthma development, but avoidance is important in subjects with pet allergy

PREVENTABLE RISK FACTORS

Table 2 presents preventable risk factors for allergy and asthma.

Prenatal and second-hand tobacco smoke exposure increases risk of asthma and wheezing throughout childhood. Prenatal smoke exposure reduces lung function in the neonate, tracking into adulthood. Smoke exposure is an important risk factor for severe adult lung disease, as for childhood asthma. Intervention reduces morbidity as shown by the effect of smoke legislation on childhood asthma hospitalization. *Reduction of smoke exposure represents important primary and secondary asthma prevention.*

Moisture damage is a consistent risk factor across observational studies of housing conditions and

TABLE 1

Definition of primary, secondary and tertiary prevention	
Prevention - Level	**Definition**
Primary	Prevent occurrence of disease
Secondary	Prevent development of disease after first signs of disease have presented or predisposing factors are present
Tertiary	Prevent disease symptoms and progression including treatment, attempting to minimize the long-term effects of the disease

TABLE 2

What advice can we give at present time for primary and secondary asthma prevention?		
Prevention	**Measure - Advice**	**Study designs**
Primary prevention	Avoid primary and second hand smoke exposure	Observational and intervention studies
	Moisture damage should be repaired	Observational birth cohort and cross-sectional studies
	Reduce air pollution, avoid high levels of traffic pollution when possible. Kindergartens should not be positioned closed to highways	Observational studies
	Breast feeding beyond 3-4 months beneficial on preventing wheeze and asthma	Systematic review and meta-analyses
	Regular intake of fish, Ω-3 fatty acids and antioxidant vitamins may be beneficial for general health, but there is insufficient evidence for asthma prevention	Observational studies, interventional trials
	Humanised antibody against RS-virus reduces the risk of bronchiolitis, but no evidence of preventing asthma development	Interventional studies
	Early pet keeping. No advice as there are insufficient data	Observational studies
	Recommend physical activity and training	Meta-analysis. Longitudinal and cross-sectional observational studies
Secondary prevention	Avoid primary and secondary tobacco smoke exposure	Observational and interventional studies
	Avoid traffic air pollution Do not live close to highways. Kindergartens should not be positioned closed to highways	Observational studies
	Pet avoidance will reduce symptoms in asthma patients with allergic sensitization to pets	Observational studies
	Recommend physical activity and training Health promoting, but insufficient evidence to show effect on asthma development and morbidity	Observational and interventional studies
	Allergen immunotherapy, insufficient evidence	Interventional study

Figure 1 **Primary and secondary asthma prevention.**

childhood asthma. Despite limited documentation of interventions tested in RCTs, *housing conditions should be improved when moisture damage is present*.

Air pollution particularly related to traffic emissions is frequently associated with asthma morbidity and impaired lung development in children in observational studies, yet a recent review concluded that more research is needed to prove its role in asthma development. Nevertheless, well documented morbidity and mortality of asthma as a result of air pollution provides sufficient rationale for *reducing traffic pollution, particularly from diesel exhaust, as a primary asthma preventive measure that should be implemented by politicians and community planners*.

Chemical pollution including plastics such as phatales and bisphenols are endocrine disruptors that are implicated many diseases, including asthma. However, further research is required to identify preventive measures.

Respiratory virus infections, such respiratory syncytial virus (RSV) bronchiolitis or rhinoviruses, are frequently reported in observational studies to increase risk of recurrent wheeze or asthma, while there is no evidence from limited RCT studies where humanised anti- body against RSV virus diid not reduce the risk of bronchiolitis. Human rhinovirus (HRV) may increase the risk of asthma development, particularly in young children sensitized to allergens,. Although not currently available, vaccines against specific respiratory viruses may be a *potential primary preventive measure.*

Early **allergen exposure** has been anticipated to increase the risk of allergic sensitization and asthma. Mite exposure has been associated with risk of asthma developing, but effective preventive sanitation measures are lacking. Observational studies report conflicting evidence by risk or benefits of pets at home, whereas pooled data from nine European birth cohorts with around 20 000 children in European birth cohorts found no evidence to either benefit or risk of asthma. Any effect exerted by pet keeping is therefore likely to be indirect by microbial exposures, physical activity and other life-style factors. Currently, *pet keeping should not be advised or discouraged in terms primary prevention of asthma*.

The diet is a likely target for prevention of allergic diseases, including asthma, although there is currently limited evidence from RCT to promote robustly documented dietary strategies. There is no evidence to suggest that avoidance diets protect against asthma. Observational studies suggest that micronutrients in the diet of the pregnant mother or child may protect against asthma development, although the documentation from RCTs is unclear. These include regular fish, Ω-3 fatty acids, vitamin D, folate and fruit intake with respect to asthma and lung function development in healthy children. Probiotics, although showing promise

for preventing atopic eczema, has yet to be proven effective in asthma prevention in children. The role of dietary fiber contents and fatty acid production in the developing gut is a current research focus. Large RCTs in general and high-risk infant populations are ongoing to determine if wheeze and asthma may be reduced by reducing atopic eczema and/or early complementary introduction of foods, but results are not available at present. Dietary modifications to improve the gut microbiome appears promising, but more research is needed.

Breast feeding is important for child's health. Recent updated evidence suggests that prolonged breastfeeding, not only exclusive breastfeeding to 3 months, may protect against wheeze and asthma up to five years of age.

Physical activity is recommended to improve general health. In terms of preventing asthma development, a systematic review and metaanalysis found some evidence to suggested that a preventive effect, while a recent systematic review reported insufficient evidence of a long-term effect to reduce asthma through childhood.

Allergen immunotherapy as secondary prevention has been suggested to prevent asthma in children with allergic rhinitis. However, a 5-year RCT follow-up of children with allergic rhinitis treated with SQ grass sub-lingual immunotherapy did not modify the time to asthma development. Thus, the evidence of preventing asthma by immunotherapy is presently too weak.

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2 ASTHMA CONTROL

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KEY MESSAGES

- Optimal asthma control is the goal of asthma management
- Asthma control consists of current (day to day) control and reduced future risk
- Asthma control and asthma severity are not synonymous
- Asthma control can be achieved in the majority of patients
- The commonest reason for poor control is lack of adherence to medications
- There are several validated questionnaires to measure asthma control

All national guidelines for asthma management and the Global Initiative for Asthma (GINA) recommend as primary goal of management to achieve optimal asthma control. Asthma control consists of two domains. These are: a) optimizing current (day-to-day) control, defined as the minimization of both daytime and night time symptoms, no limitation of activity, minimal rescue bronchodilator use and no airway narrowing; and b) minimizing future risk defined by long term decline in lung function, severe asthma exacerbations and unwanted effects from medications (Figure 1). The two domains which define asthma control are not independent. The more poorly controlled day-to-day asthma is, the greater the risk of a severe asthma exacerbation.

In the past, physicians were often confused by the terms "asthma control" and "asthma severity". It was perceived that well-controlled asthma was synonymous with mild asthma and poorly controlled asthma was synonymous with severe asthma. This perception is incorrect. Severity is the intensity of the underlying disease process before treatment, and control is the adequacy of the response to treatment. Patients with severe asthma, if treated appropriately can be well controlled and patients with mild asthma, if they fail to follow treatment guidelines, will have inadequately controlled asthma, which may be perceived as severe. The goals of asthma management are the same for all degrees of asthma severity. Although patients with severe asthma will often be more difficult to control with an intervention, effective treatment can potentially fully control patients with severe asthma.

There are a range of questionnaires and diaries that have been developed to measure current asthma control and each one of which has strengths and weaknesses. Among the most commonly used are the Asthma Control Questionnaire (ACQ), the Asthma Control Test (ACT), and the Asthma Therapy Assessment Questionnaire (ATAQ).

Despite the availability of effective and safe medications to treat asthma, the most important of which are inhaled corticosteroids, either alone or in combination with long-acting inhaled β2-agonists, many patients remain poorly controlled. The most important reason for this is poor adherence to treatment regimens. When patients are taking their asthma medications, many can achieve well controlled asthma; in some instances, however, asthma may be only partly controlled and a decision needs to be made by the patients and their managing

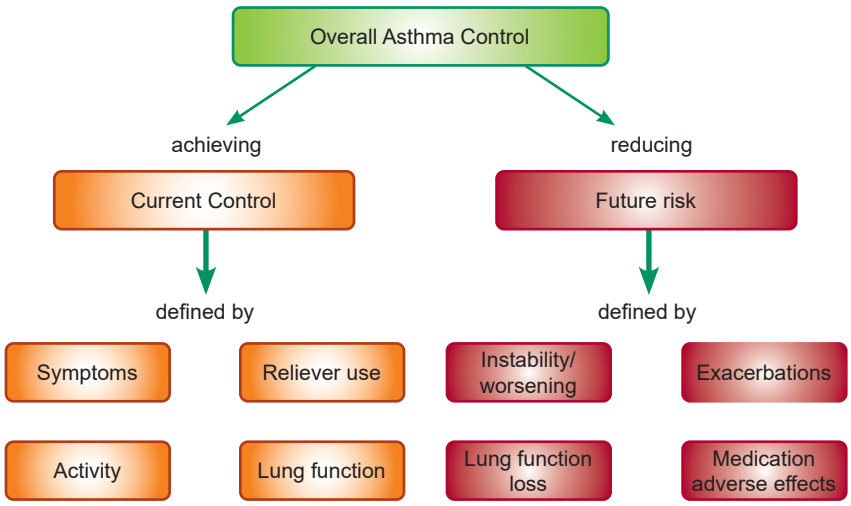

Figure 1 **The goal of asthma management is overall asthma control, which consists of two domains: achieving current day to day asthma control and reducing future asthma risk.**

health care professional whether to increase the treatment, or to accept partly controlled asthma. However, all guidelines indicate that if asthma is uncontrolled, treatment options should be carefully evaluated and additional treatment added.

There is a subset of asthmatic patients who, despite treatment with optimal doses of asthma medications, have uncontrolled asthma and are at risk for severe asthma exacerbations. These are considered severe refractory asthmatics, represent 5-10% of the asthma population and are the group of patients where phenotyping with relation to their atopic status and type of airway inflammation present, or endotyping in relation with the mechanisms involved, may provide additional useful information with regards to newer treatment options.

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3 BEST BUYS FOR ASTHMA PREVENTION AND CONTROL

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Best-buy measures for asthma prevention and control include the implementation of precision medicine, population-based asthma management approaches, mHealth tools and next generation guidelines (i.e. integrated care pathways), surveillance of asthma with registries and engagement of all stakeholders in asthma management programs (Figure 1).

Asthma management is passing towards a new era by leaving the concept of the 'one-size-fits-all' approach towards the personalized management concept of **precision medicine** relying on endotype-driven therapies. **'Omic' sciences** detecting biomarkers linked to molecular mechanisms and new **'rapid point of care tests'** will improve diagnosis and help tailor the management of an individual patient. However, experts are facing difficulties in interpreting **'big data'** obtained from omic studies and large, population based, epidemiologic studies. The challenge of interpreting the big data has introduced us advanced computational methods. **Systems biology,** simply defined as a mathematical modelling of physiological systems, used for big data analysis in asthma helps exploring the heterogeneity of asthma and the biomolecular networks behind. Therefore, the employment of predictive analytics, using **machine learning and artificial intelligence** in asthma research is an important step to insert thoughtful digital health innovation as clinical prediction tools in diagnosis and personalized management of asthma in near future.

As an example to the integrated **asthma management programs**, the Finnish public health programme on asthma revealed an outstanding success in decreasing the burden of asthma since early 90's. However, it had no effect on the increased prevalence. One reason was the loss of protective factors in the target population and therefore a Finnish national campaign focusing on a tolerance strategy which aims implementation of prevention measures at a population level such as supporting breastfeeding or increasing contact with natural environments was started in 2008. The midterm results of this national allergy programme which included all relevant stakeholders and all Finish citizens in a real life setting are promising. This programme is important since it adopts a new attitude to allergy which simply can be defined as changing the strategy from avoidance to toler-

KEY MESSAGES

- Asthma management is passing towards a new era by leaving the concept of the 'one-size-fits-all' approach towards a personalized management based on endotype-driven therapies
- This unbiased approach is facilitated by the implementation of multi-omics and precision immunology technologies
- The challenge of interpreting the big data has introduced us advanced computational methods
- mHealth tools may change the clinical approach from clinician- to patient-centered care
- Integrated asthma management programs changing the strategy from avoidance to tolerance will serve as a good paradigm for cost-efficient asthma prevention and control

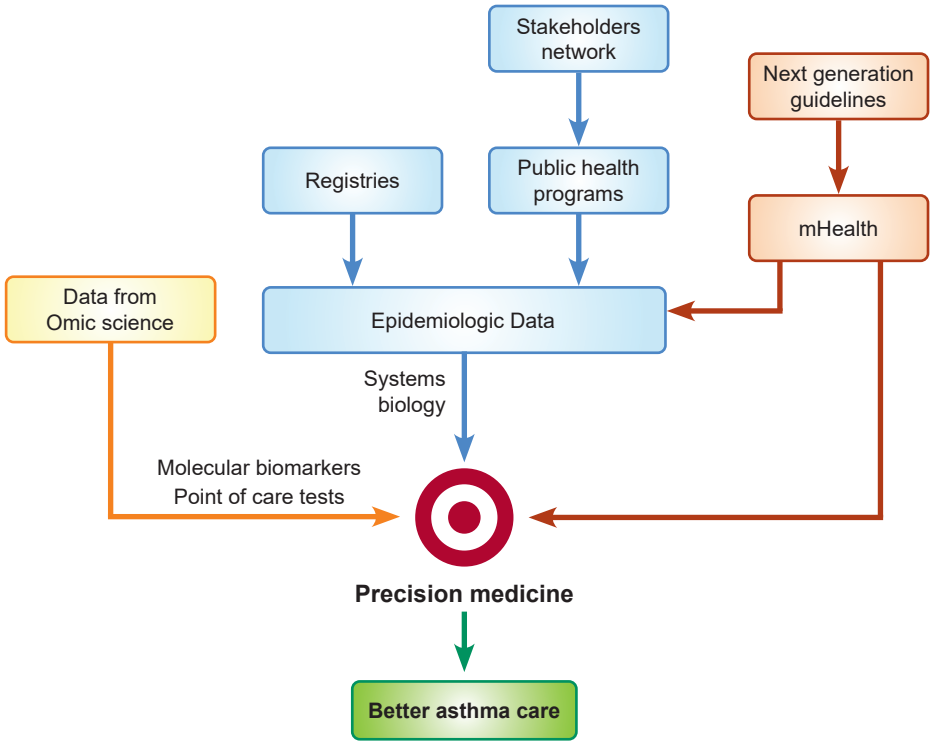

Figure 1 **Next generation guidelines, real life evidence and big data in support of better asthma care.**

ance and will serve as a good paradigm for cost-efficient asthma prevention and control.

mHealth tools are promising in acting as innovative asthma management tools potentially by changing the clinical approach from clinician- to patient-centered care. "Be He@lthy, Be Mobile", an initiative of WHO, demonstrated that mobile health technologies can be valuable tools in combating chronic diseases like asthma especially by providing optimal healthcare to populations in remote areas or with limited access to health infrastructure. A meta-analysis demonstrated improved asthma control with the use of mHealth but more knowledge in long-term effectiveness and cost-effectiveness of these technologies is needed. Hopefully, a recently completed multicenter Horizon 2020 EU-funded project "My Air Coach," aiming at developing an innovative asthma monitoring system, will be able to monitor the individual patient to address the unmet needs in the field in a real life setting.

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4 EVIDENCE FOR ASTHMA CONTROL – EXPERIENCE FROM THE FINNISH PROGRAMMES

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In Finland (population 5.5 million), a comprehensive and nationwide asthma programme was undertaken from 1994 to 2004 to improve asthma care. The action plan was systematic and implemented in the whole country. The result showed that by improving management a change for the better could be achieved in a relatively short period of time. Cost savings were significant . The Finnish programme has been followed in several countries with equally favorable outcomes.

The next step was to combat all allergic conditions, asthma among them, by implementing the Finnish allergy programme 2008-2018. It employed new information of immune development and changed *avoidance* strategy to *tolerance/resilience* strategy at population level (Table 1). Medicalization and psychological tolerance were also considered. Severe asthma and allergy were emphasized. Implementation was organized and monitored to help health care adapt new ideas and improve provision of care. During 10 years, some 24 000 health-care professionals took part in 376 educational sessions. An information campaign targeted lay-public and 2.3 million Finns were reached.

KEY MESSAGES

- In Finland, asthma prevalence has stabilized and burden reduced during 25 years. Most asthmatics can live normal life
- Diagnosis of asthma is still often delayed. Patients must be treated early and followed to ensure control
- Patients should be educated for guided self-management to proactively stop asthma exacerbations
- Zero tolerance to asthma deaths is a reasonable goal for all societies with functioning health-care. Patients with severe disease need attention, as multimorbidity and polypharmacy are major concerns
- National and local asthma action plans help to deploy best practices
- Preventing asthma needs changes in lifestyle and environment

STABLE PREVALENCE AND LESS SYMPTOMS

Asthma in adults was evaluated in Helsinki during a 20-year period by three cross-sectional surveys (1996, 2006, 2016). The prevalence of physician-diagnosed asthma stabilized from 2006 to 2016 (10% vs. 10.9%). The patients reported systematically less symptoms in 2016 compared to 2006 or 1996, and the proportion of asymptomatic asthmatics increased from 24% in 1996 to 41% in 2016 (Figure 1).

Symptom severity was assessed by three cross-sectional barometer surveys in all Finnish Pharmacies. In 2001, 10% of patients purchasing asthma drugs considered their disease severe, in 2010 4% and 2016 2,5%.

REDUCED BURDEN

In 2000s, hospital days caused by asthma decreased by 73%, and by 50% from 2007 to 2017, when 2 100 patients used 10 000 hospital days (average stay 3.8 days).

In 2000s, asthma deaths reduced from 117 cases to 74 (37%). During the 10 years of the allergy programme, only 2 deaths were reported in children, and on average 7 deaths per year in those under the age of 60 years. Elderly

TABLE 1

Practical advice for building and improving tolerance (primary prevention) as well as preventing symptoms and exacerbations (secondary and tertiary prevention)	
Primary prevention	• Support breastfeeding, complemented with solid foods from 4–6 months • No avoidance of environmental allergen exposure (foods, pets), if not proven necessary • Strengthen immunity by increasing contact with natural environments (e.g. regular physical exercise, healthy diet such as a traditional Mediterranean or Baltic diet, local food) • Antibiotics only for true need (the majority of microbes are useful and build a healthy immune function) • Probiotic bacteria in fermented food or other preparations may strengthen the immune function • No smoking (parental smoking increases the risk of asthma in children)
Secondary and tertiary prevention	• Regular physical exercise is anti-inflammatory • Healthy diets are anti-inflammatory (traditional Mediterranean or Baltic diet may improve asthma control) • Probiotic bacteria in fermented food or other preparations may be anti-inflammatory • Respiratory/skin inflammation treated early and effectively. Maintenance treatment titrated for long-term control • Allergen immunotherapy promoted for more severe symptoms: ▪ allergens as such (for foods) ▪ sublingual tablets or drops (SLIT) (for pollens, house dust mites) ▪ subcutaneous injections (for pollens, pets, mites) • Smoking strictly avoided (asthma and allergy drugs do not have full effect in smokers)

(from ref. 4).

women are at the greatest risk for hospitalization and deaths.

Improved asthma control reduced health care use and patient disability, resulting in major cost savings. The theoretical total cost savings for one year only, 2013, comparing actual with predicted costs, were between €120 and €475 million, depending on the scenario used . The annual cost saving per patient was 72%, from €2656 to €749. The major savings were obtained as patients were increasingly able to maintain normal activities (Figure 2).

Multimorbidity and polypharmacy are still major concerns as disease severity, drug use, and costs increase with multimorbid conditions.

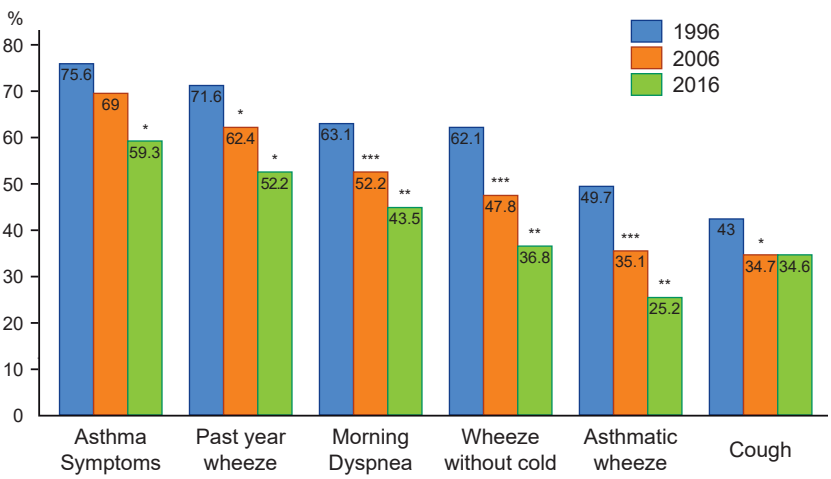

Figure 1 Prevalence (%) of respiratory symptoms among respondents who reported a physician-diagnosed asthma 1996, 2006 and 2016.
(Reproduced from Respir Med, Vol 155, Hisinger-Mölkänen H et al., The increase of asthma prevalence has levelled off and symptoms decreased in adults during 20 years from 1996 to 2016 in Helsinki, Finland, 121-126, 2019 with permission from Elsevier)

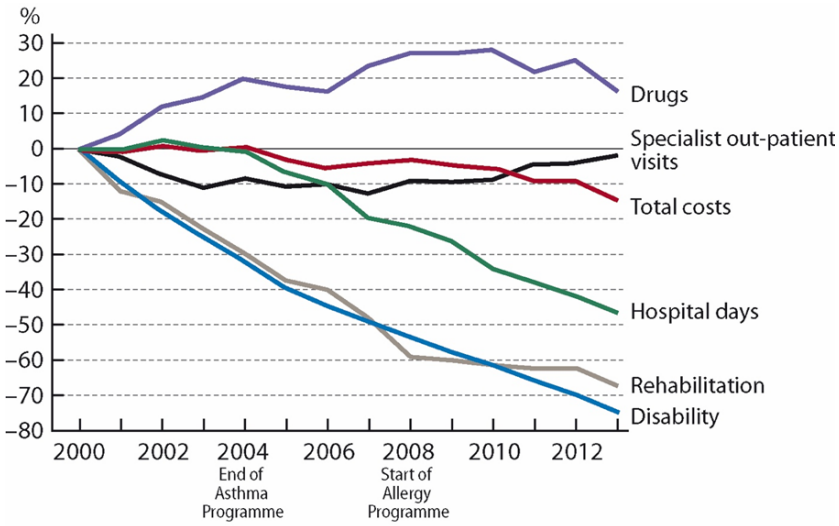

Figure 2 From 2000 to 2013 asthma and allergy costs decreased by 15%.
Drug costs, specialist out-patient visits, hospital days, rehabilitation and disability (days off work, disability pensions) were included.

TABLE 2

The Finnish Allergy Programme 2008-2018. Six goals, indicators and main outcomes at 5 years

Goals	Indicator	Main Outcomes
Prevent allergy	Asthma, rhinitis and atopic eczema prevalence reduced 20%	No information yet
Improve tolerance	Food allergy diets reduced 50%	Allergy diets in day-care – 40%
Improve allergy diagnostics	Patients skin prick tested in certified testing centres	30 hospitals and other centres educated, audited and certified
Reduce work-related allergies	Occupational allergies reduced 50%	Occupational allergies – 40%
Focus severe allergies and treat in time	Good allergy practice works, asthma emergency visits reduced 40%	Emergency visits – 46%, asthma hospital days – 67%
Reduce allergy & asthma costs	Allergy costs reduced 20%	In the 2000s, total costs –15%, in 2007-2013 – 5%

(from ref. 4)

STEPS FROM TREATMENT TO PREVENTION

The recent allergy programme (2008–2018) took a step from treatment to prevention. It is too early to evaluate the programme effect on asthma incidence and prevalence, but the mid-term results are promising (Table 2). *Asthma and allergies may appear preventable*. Contact with natural environment enriching microbiome and balancing the immune system may prove essential.

The Finnish experience shows that it is possible to considerably reduce the morbidity and costs of asthma and allergy. Worrying trends continue to be growing drug costs, especially of the new biologicals. Also, in Finland, the symptom control is still poor for too many asthma patients.

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5 GLOBAL POLICIES AND STRATEGIES TO FACILITATE ACCESS TO ASTHMA DIAGNOSIS AND TREATMENT

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KEY MESSAGES

- Although a very frequent chronic disease asthma is underdiagnosed and undertreated
- Global policies and strategies are needed to facilitate access to the diagnosis and treatment of asthma. These are necessary at local, regional, national and global levels
- The most relevant global policies position asthma as a priority in between chronic diseases, recommend collaboration amongst diverse professional groups, public health officials, patients, asthma advocacy groups, and the general public, advocate for a special focus on low and middle income countries and urge policy makers to prioritise asthma as public health problem
- Adapting and integrating allergy and asthma care into the context of real-world problems is the current focus of EAACI's policies

Asthma is the most common chronic disease among children worldwide. Around 339 million people are living with asthma. Over 80% of asthma-related deaths occur in low-and middle income countries. Treatment and effective management of asthma saves lives.

The advances made in recent years in the diagnosis and treatment of asthma have been highly relevant. On the other hand, the prevalence of asthma continues to increase worldwide. Surprisingly, many asthmatic patients are not correctly diagnosed and therefore treatment is not adequate.

Global policies and strategies are needed to facilitate access to the diagnosis and treatment of asthma. These are necessary at local, regional, national and global levels. The most relevant **global policies** and initiatives are described below:

The **United Nations** consider asthma as a Non Communicable Disease (NCD) included in Chronic respiratory diseases (CRD).

The **World Health Organisation** (WHO) recommended a 7 years NCD Action Plan (2013-2020) including asthma as a priority.

Global Alliance against Chronic Respiratory Diseases (GARD) is a voluntary alliance of national and international organizations, institutions and agencies from many countries working towards the common goal of reducing the global burden of CRDs, including asthma.

According to the **Global Initiative for Asthma** (GINA) patient care following evidence-based asthma guidelines leads to improved outcomes. Implementation of asthma guidelines should include setting of goals and development of strategies through collaboration amongst diverse professional groups including both primary and secondary health care professionals, public health officials, patients, asthma advocacy groups, and the general public.

The mision of the **Global Asthma Network** (GAN) is to prevent asthma and improve asthma care globally with a focus on low and middle income countries. The network aims to achieve this goal through enhanced surveillance, research, capacity building, and access to effective asthma care including quality assured essential medicines.

The **International Primary Care Respiratory Group** (IPCRG) works with clinicians, researchers and people with asthma to develop user-friendly resources for prima-

ry care clinicians to improve asthma diagnosis and management and to provide materials for use in primary care education. They also identify priorities where further research is needed and work with partners to take these forward.

Allergic Rhinitis and its Impact on Asthma (ARIA) initiative. Rhinitis is the most common NCD among children. Asthma and rhinitis often co-exist, and it is important to recognize, diagnose and treat rhinitis to prevent the devel-opment to asthma or to improve asthma control.

The **Brussels Declaration on Asthma**, sponsored by The Asthma, Allergy and Inflammation Research Charity, was developed to call attention to the shortfalls in asthma management and to urge European policy makers to recognise that asthma is a public health problem that should be a political priority.

EAACI organized two European Strategic Forums on Allergic Diseases and Asthma. This collaboration is fundamental for adapting and integrating allergy and asthma care into the context of real-world problems.

STRATEGIES

GAN defines the responsibilities of different organizations and institutions (Table 1).

GINA suggest that implementation of asthma management strategies may be carried out at national, regional or local level and it should be a multidisciplinary effort involving many stakeholders, and using cost-effective methods of knowledge translation (Figure 1). Each initiative needs to consider the nature of the local health system and its resources. Goals and implementation strategies will need vary from country to country based on economics, cultural, and social enviroment (Table 2).

TABLE 1

Key points of Global Asthma Network
The World Health Organization (WHO) should
• Ensure that asthma and other chronic respiratory diseases are included as a priority in the outcome document of the 2018 United Nations (UN) High Level Meeting on non-communicable diseases (NCDs) • Develop and disseminate training manuals for asthma management for low- and middle-income countries (LMICs) • Ensure essential asthma medicines are added to its Prequalification Programme • Promote the harmonisation, across international reference pharmacopoeias, of quality requirements that govern the production and testing of asthma medicines • Facilitate the development of independent laboratories for the testing of generic products that are not already approved by a stringent regulatory authority or relevant global mechanism
Governments should
• Include asthma in all their actions resulting from the WHO Global Action Plan for the Prevention and Control of NCDs 2013-2020, and the WHO NCD Global Monitoring Framework • Ensure their country has a coordinated national strategy towards better measurement of the true burden of asthma, improving access to care and improving adherence to asthma management strategies • Aim to achieve the UN Strategic Development Goal 3: "ensure healthy lives and promote well-being for all at all ages" to lessen the burden of asthma. • Ensure that essential asthma medicines are on their country's Essential Medicines List and ensure that they are free, subsidised or reimbursed • Develop and implement insurance schemes which will allow patients to access and buy asthma medicines • Strengthen their national policies, such as those to reduce tobacco consumption, encourage healthy eating and reduce exposure to potentially harmful chemicals, smoke and dust • Support further research into known asthma triggers and identifying the causes of asthma • Commit to research that increases the understanding of asthma, its causes, its costs, and lead to improvements in management • Support the acquisition of new standardised data to track the country and global burden of asthma
Health authorities should
• Collect counts of hospital admissions for asthma among children and adults from defined catchment populations, to monitor trends in asthma over time. • Report national rates of asthma deaths in children and adults to monitor progress in asthma care, and as an early warning of epidemics of fatal asthma • Monitor the availability and costs of asthma medicines • Develop new ways to target and deliver asthma care in diverse health systems and contexts, and assess their cost-effectiveness, affordability and feasibility • In LMICs recognise asthma as an important public health issue, include asthma in all their actions and set up a national programme to improve asthma care and limit costs
Health professionals, professional societies and patient organisations should
• Encourage patient advocacy to improve asthma outcomes. • Support the government in developing asthma guidelines which are adapted to the national situation. • Actively participate in improving asthma programmes by assisting in improving correct inhaler technique and adherence to treatment. • Ensure that their country joins the Global Asthma Network

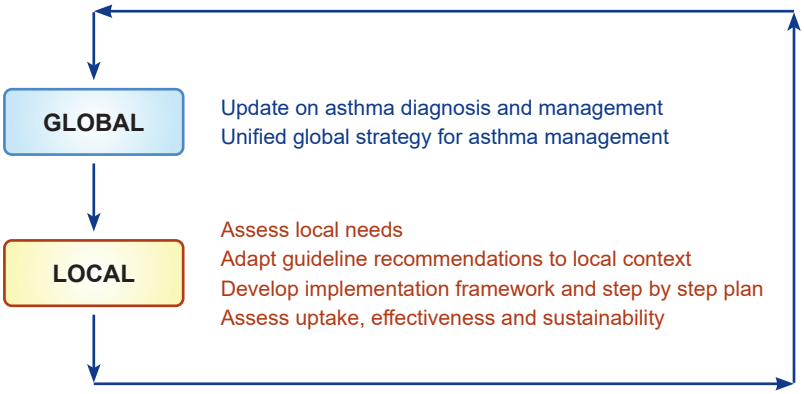

Figure 1 Approach to implementation of the strategy

Figure 2 MASK technology: Demonstration of how to transfer data of symptoms and medication that the patient dialed daily on his cell phone, to the doctor's computer at the time of the consultation: using the app's QR code.

TABLE 2

Steps in implementing an asthma strategy into a health system	
1.	Develop a multidisciplinary working group
2.	Asses the current status of asthma care delivery, care gaps and current needs
3.	Select the material to be implemented, agree on main goals, identify key recommendations for diagnosis and treatment, and adapt them to the local context of enviroment
4.	Identify barriers to, and facilitators of, implementation
5.	Select an implementation framework and its component strategies
6.	Develop a step-by-step implementation plan:
	• Select target population and evaluable outcomes • Identify local resources to support implementation • Set timelines • Distribute tasks to members • Evaluate outcomes
7.	Continuously review progress and results to determine if the strategy requires modification

ARIA has evolved from a guideline by using the best approach to integrated care pathways using mobile technology in order to increase self-medication and shared decision making in rhinitis and asthma multimorbidity. An innovation has been the development and validation of information technology evidence-based tools (Mobile Airways Sentinel Network [MASK]) that can inform patient decisions on the basis of a self-care plan proposed by the health care professional (Figure 2).

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6 POLICIES AND STRATEGIES TO REDUCE RISK FACTORS FOR ASTHMA

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There are many known factors which may trigger asthma exacerbations in patients with asthma. Control of these factors will reduce the burden of acute attacks of asthma in the community. Although there are many potential factors found to be associated with the development of asthma, the data were mostly derived from epidemiological studies supported by experimental data. These factors include dietary factors, use of certain types of medications, exposure to microbes, and lifestyle factors. High quality prospective intervention trials are required to test if manipulation of risk or protective factors may reduce the incidence or severity of asthma. Due to the fact that the prevalence of asthma has been increasing over the past four decades in parallel with the degree of urbanization, it is highly likely that many factors associated with the process of urbanization play pivotal roles in the development of asthma. Clear understanding of the underlying pathophysiology of how such factors may influence the development of asthma will provide insights into what public health policies may be effective in reducing the burden and severity of asthma worldwide.

KEY MESSAGES

- Many factors have been confirmed to precipitate acute exacerbations in asthmatics and collaborations at the global level are need to minimize the effects of these factors
- Commitments from governments are needed to institute policies to control both outdoor and indoor pollution to reduce asthma morbidity and mortality
- Smart devices can provide real time data for asthmatics to reduce their exposure to possible precipitating factors
- Biomass in developing countries and traffic related pollution remain the most important avoidable factors for the primary and secondary prevention of asthma
- Prospective randomized trials are needed to confirm if proposed measures can reduce asthma prevalence at the community level

KNOWN FACTORS ASSOCIATED WITH ASTHMA EXACERBATIONS

It is very clear than many components of air pollution are detrimental to asthmatic patients. The sources of air pollution include moto vehicles, power plants, emissions from factories, burning of biomass, and fine particles from natural sources such as those from dessert dust storms. Increase in the levels of different gaseous and particle pollutants are associated with increase visits to emergency, hospitalization and even death related to asthma exacerbations. Governmental policies are needed to reduce traffic related pollution with the use of clean energy and minimal to zero emission motor vehicles. With the rapid improvement of information technology, real time measurements of pollution and personal monitor can provide the big picture of pollution for susceptible individuals so that they can avoid exposing themselves in highly polluted areas (Figure 1). Strict building codes and proper ventilation of buildings can reduce levels of indoor air pollution thereby minimizing the risk within the workplace for adults and schools for children. In the developing world,

Figure 1 **Personal pollution monitors provide real-time information and facilitate avoidance to exposure.**

Figure 2 **Indoor air pollution due to improper cooking facilities and lack of ventilation – a real killer in the under-developed countries.**

the use of biomass fuels coupled with poor indoor ventilation results in high level of indoor air pollutants (Figure 2). Policies to control the usage of cooking stoves and proper ventilation system will significantly reduce the levels of indoor air pollution thereby reducing the detrimental effects on asthmatic patients. Environmental tobacco smoke (ETS) exposure in the prenatal and postnatal periods is clearly associated with adverse effects on the airways and reduction of ETS exposure is a health priority especially in developing countries where tobacco smoking is highly prevalent.

PRIMARY PREVENTIVE STRATEGIES

Given the fact that the prevalence of asthma has increased significantly over the past few decades within populations of the same genetic background, it is reasonable to speculate that primary prevention of asthma is feasible if we can identify the causal factors that have caused the prevalence of asthma to increase in the first place. Many epidemiological studies have shown that a variety of risk factors have been associated with the development of asthma. It is quite clear that the process of transition from a more traditional lifestyle to the one of urbanized modern living dramatically increases the risk of asthma. The risk factors associated with urbanization that have been implicated to contribute to the development of asthma include dietary factors, us of medications, different methods of delivery, exposure to ETS, air pollutants, allergens, and microbes. Many of these factors have the potential to influence the development of the immune system such that they may precipitate the manifestations of airway inflammation and asthma. However, very few of these factors have been tested in a prospective fashion in properly designed clinical trials. The use of fish oil supplementation in the prenatal period has been shown to reduce asthma occurrence at 1 year of age. Another promising direction of research is the exposure to farm environment connected to a reduction of asthma risk. Confirmation studies are needed to provide solid evidence to guide the development of policies and strategies of primary prevention of asthma in the community level.

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7 TOBACCO CONTROL AND ASTHMA

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KEY MESSAGES

- Active smoking and exposure to passive smoke have a major adverse impact on asthma
- Prevalence rates of active smoking in adolescents and adults with asthma mirrors those found in the general population
- Tobacco control offers a major opportunity to prevent and improve health care outcomes in asthma
- Smoking cessation is an important goal in the management of smokers with asthma and in the parents of children with asthma
- Legislation to control cigarette smoking in public places improves asthma control in both children and adults

IMPACT OF TOBACCO SMOKE ON ASTHMA

Active smoking and exposure to passive smoke have a major adverse impact on health in asthma (Figure 1). The prevalence rates of active smoking in adolescents and adults with asthma mirrors those found in the general population of most countries worldwide. Current smokers with asthma are more likely than never-smokers with asthma to have worse symptoms, poorer quality of life, more frequent exacerbations and hospital admissions, as well as greater decline in lung function and increased all-cause mortality. Active cigarette smoking reduces the therapeutic response to inhaled corticosteroids. Exposure to passive smoke increases the risk of developing asthma and causes worse clinical outcomes in children and adults with asthma.

TOBACCO CONTROL STRATEGIES

A key component of the World Health Organization's (WHO) Framework Convention on Tobacco Control is the implementation of 'MPOWER' measures worldwide (Table 1). About 65% of the world's population live in countries that have adopted at least one MPOWER policy (Figure 2). The progress in global tobacco control achieved in the general population of many countries will improve health outcomes for people with asthma through reductions in exposure to active and passive tobacco smoke. Examples of specific MPOWER measures that have impacted positively in asthma are provided below.

PROTECT PEOPLE WITH ASTHMA FROM TOBACCO SMOKE THROUGH SMOKE-FREE ENVIRONMENTS

Stopping maternal smoking before conception or in early pregnancy is an essential component to reduce the risk of asthma developing in the new-born child. Smoking cessation programmes that target parents of children with asthma helps reduce the burden of emergency events due to exposure to passive smoke. Legislation to control cigarette smoking in public places improves symptom control for adults with asthma and reduces the rated of hospital attendance for asthma exacerbations in children (Figure 3).

OFFER HELP TO QUIT TOBACCO USE IN PEOPLE WITH ASTHMA

Smoking cessation is an important goal in the management of smokers with asthma, although evidence on the effectiveness of smoking ces-

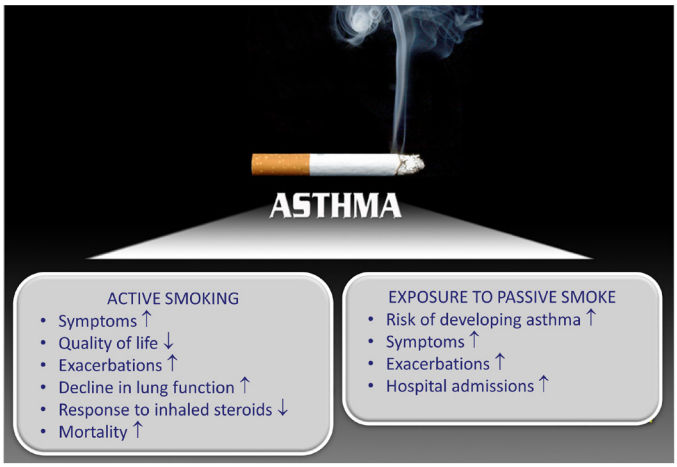

Figure 1 Impact of tobacco smoke on asthma. Adverse impact of active smoking and exposure to passive smoke on health outcomes in asthma.

TABLE 1

WHO MPOWER policy on tobacco control
• **M**onitor tobacco use and prevention policies
• **P**rotect people from tobacco smoke
• **O**ffer help to quit tobacco use
• **W**arn about the dangers of tobacco
• **E**nforce bans on tobacco advertising, promotion and sponsorship
• **R**aise taxes on tobacco

MPOWER is an acronym of the six categories of tobacco control measures recommended by the World Health Organisation (WHO) to combat the death and disease burden caused by smoking and exposure to passive smoke

sation in asthma is limited. Taken together, clinical outcomes are generally better in current smokers with asthma after quitting.

OTHER WHO MPOWER POLICIES ON TOBACCO CONTROL

Banning of tobacco advertising, tax increases, and legislation requiring health warnings on cigarette packets have resulted in substantial reductions in tobacco use, which should improve the health of the general population as well as people with asthma, or who are at risk of developing asthma.

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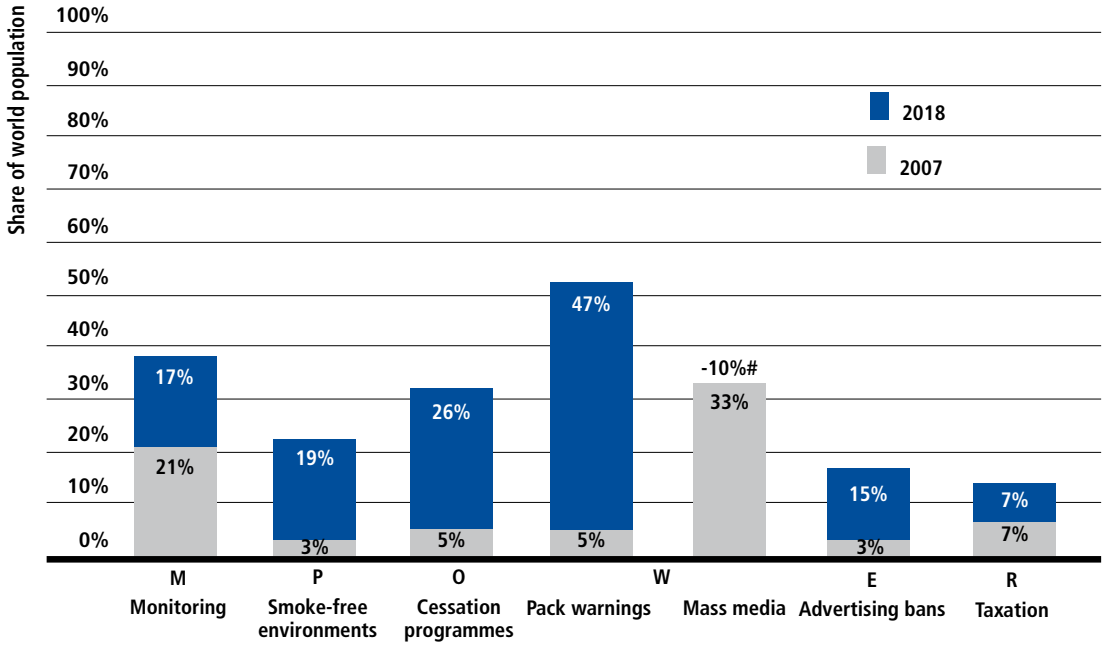

Figure 2 **Increase in the share of the world population covered by selected tobacco control policies, 2007* to 2018.**
The tobacco control policies depicted here correspond to the highest level of achievement at the national level.
** Mass media coverage refers to 2010, not 2007. Taxation coverage refers to 2008, not 2007.*
#The population covered by mass media campaigns decreased since 2010.
(Reproduced from WHO Report on the Global Tobacco Epidemic, 2019 under the terms of the creative commons attribution non-commercial license 4.0)

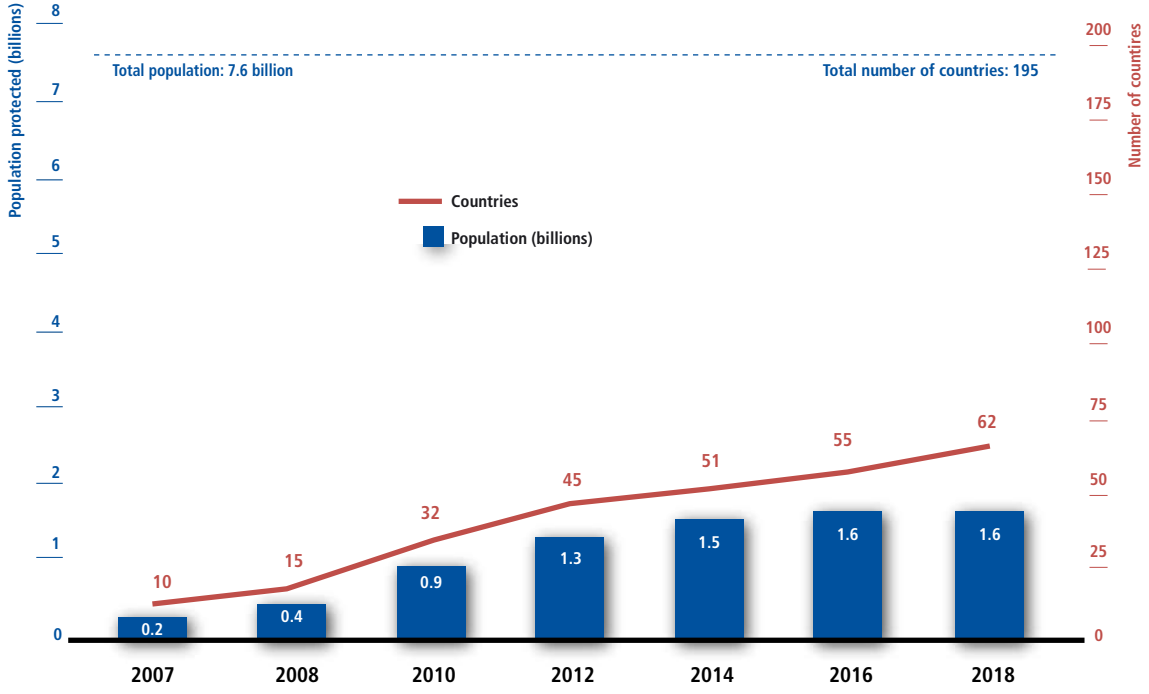

Figure 3 **Progress in national tobacco control programmes (2008–2018).**
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8 IMPLEMENTING A HEALTHY LIFESTYLE AND ASTHMA

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The allergy epidemic is multifactorial, with a complex interaction of a genetic background with the everchanging environment and lifestyle. Diet and physical activity influence health both together and separately. Although their effects often interact, particularly in relation to obesity, there are additional benefits to be gained from physical activity that are independent of nutrition and diet, and also significant nutritional factors that are unrelated to obesity.

KEY MESSAGES

- The increased incidence and prevalence of asthma is multifactorial and includes epigenetic mechanisms and lifestyle factors
- Diet seems to be associated with asthma prevalence and severity and can modify the association between air pollution and asthma
- As a modifiable risk factor, diet following a healthier pattern that will create an anti-inflammatory environment, should be promoted
- Patients with asthma able to maintain adequate physical activity levels, particularly in a natural biodiverse environment, will be less likely to suffer adverse health events associated with a sedentary lifestyle and they will improve their asthma
- The dynamic and complex interaction between individuals and environment play a crucial role in asthma development, supporting the need to create healthier and sustainable environments

HEALTHY EATING

Diet has been studied as a modifiable risk factor for asthma prevalence and severity. The beneficial effects of Mediterranean or Baltic diet and its components on asthma have been widely recognized. The Western dietary pattern, with lower intake of vegetables and fruits, both in quantity and diversity, and higher intake of highly processed foods, might affect the nutritional adequacy of several nutrients, including vitamins and minerals, promote a pro-inflammatory environment, and compromise the anti-oxidant and anti-inflammatory responses. At the same time increase in the dietary acid load that can modify airways´ inflammation and reactivity, being a possible mechanism in overweight/obese-asthma phenotype development.

Diet and its components also seem to modulate the impact of air pollution. It has been shown that the effect of indoor air pollution on children with asthma was significantly higher in those who have a pro-inflammatory diet, when compared to those having an anti-inflammatory diet (Figure 1).

TARGETING ASTHMA CONTROL THROUGH PHYSICAL ACTIVITY

Regular exercise is a fundamental way to improve the individual physical and mental health. The relationship between physical activity and asthma seems a paradox. Heavy physical activity has been related to asthma risk and exacerbation. In elite athletes' asthma is diagnosed more frequently than in the general population. This has been attributed

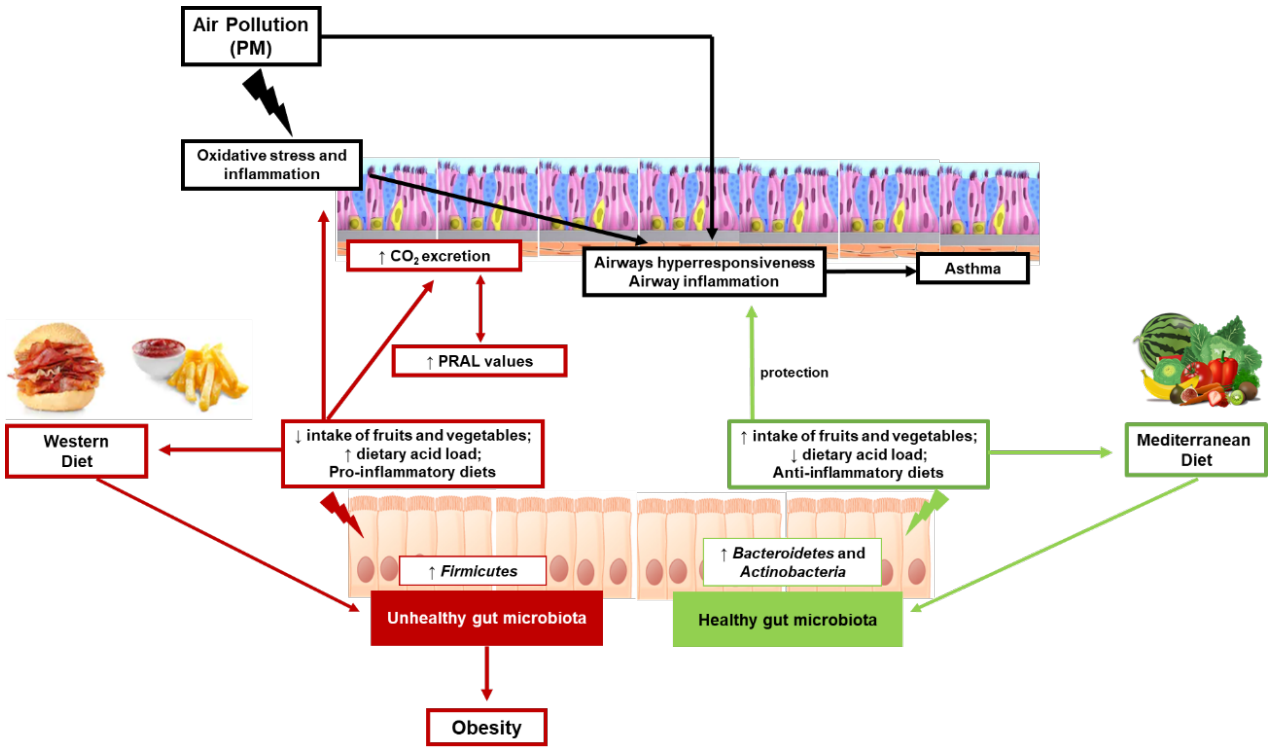

Figure 1 Mechanisms underlying the association between diet, asthma, and air pollution. Diets with an overall anti-inflammatory effect, namely the Mediterranean diet, characterized by higher intake of vegetables and fruits will promote healthier gut microbiota and may counteract the airway oxidative stress and inflammation induced by particulate matter (PM). On the other hand, diets with high dietary acid load and low intake of fruits and vegetables encompassed on Western diets will increase the carbon dioxide and might modify airways´ inflammation and reactivity, being a possible mechanism in overweight/obese-asthma phenotype development.

to airway inflammation and increased bronchial responsiveness induced by high-intensity long-term exercise, like long-distance running or competitive swimming (Figure 2). However, the evidence for the benefits of exercise and physical activity in asthma and allergic diseases is increasing, with several studies showing improvements in inflammatory, lung function, and even quality-of-life outcomes after a training program. It is recommended that children and adolescents participate in at least 60 min of moderate intensity physical activity most days of the week, preferably daily. Engagement in physical activity promotes the normal psychosocial development, neuromuscular coordination and self-esteem, thus increasing the chance of greater interplay between the environmental metagenome and the hologenome.

SMART BUILDING ENVIRONMENT

Evidence suggests that urban greener environments with higher species richness tended to be associated with improved lung function in children, thus supporting the 'Biodiversity Hypothesis' (Figure 3). On the other hand, exposure to volatile organic endocrine-disrupting compounds indoors may also affect children health, namely the risk of asthma and the presence of current respiratory symptoms (Figure 4). Thus, the development of healthy lifestyle interventions should include urban level initiatives, which could be used alongside current asthma treatment plans.

CONCLUSION

Applying multi-faceted evidence-based recommendations to reduce multiple life-style associated risk factors, including pollution, social stress, physical inactivity, nutrition and weight control, in combination with treatment outcomes monitoring might reduce the global asthma burden.

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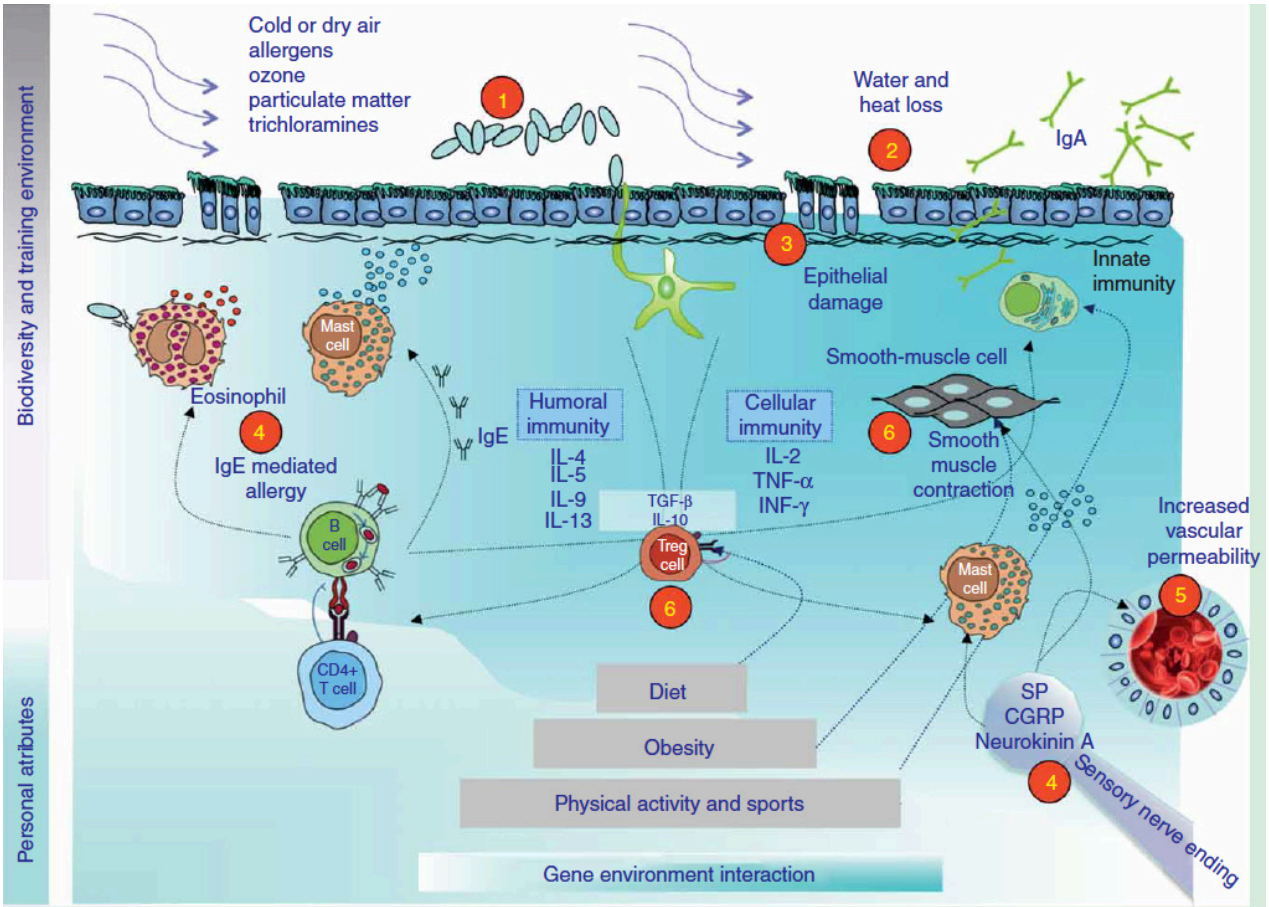

Figure 2 **Mechanisms of exercise-induced asthma.** Increased ventilation rates of up to 200 l/min during exercise enhance inhalation of cold or dry air and environmental pollutants (1); these changes are associated with increased water and heat loss (2) and epithelial cell shrinkage and activation (3). Autonomic imbalance and neurogenic inflammation (4) associated with training cause increased vascular permeability (5) and smooth muscle cell contraction (6). These modifications are affected by regulatory immune system, (7) which itself is modulated by diet, energy intake and level of physical activity (reproduced from (1) with kind permission of copyright holder).

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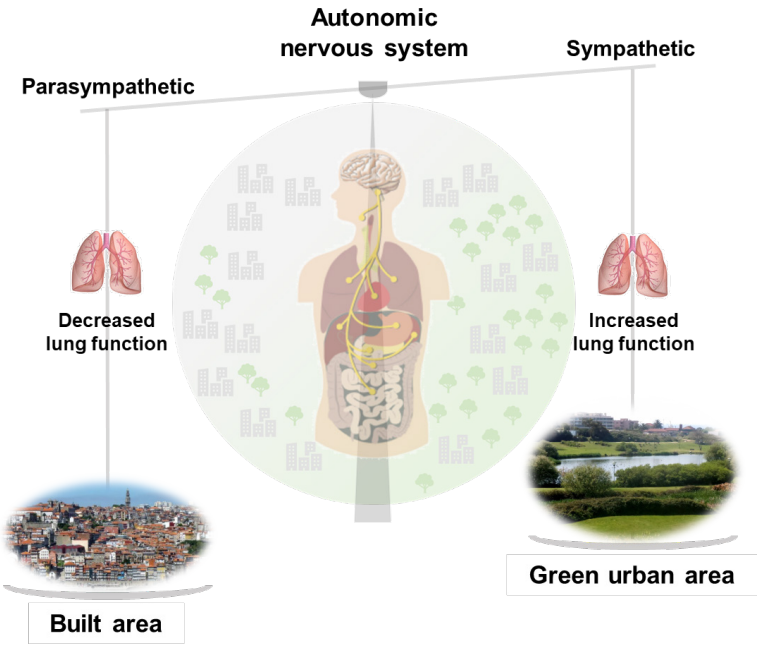

Figure 3 School environment and lung function interaction: a hypothesis focused on autonomic nervous system activity. Urban built areas around schools seems to be inversely associated with children's lung function while greenness may have the opposite effect. These interactions are partially mediated by the autonomic nervous system (adapted from (4) with kind permission of copyright holder).

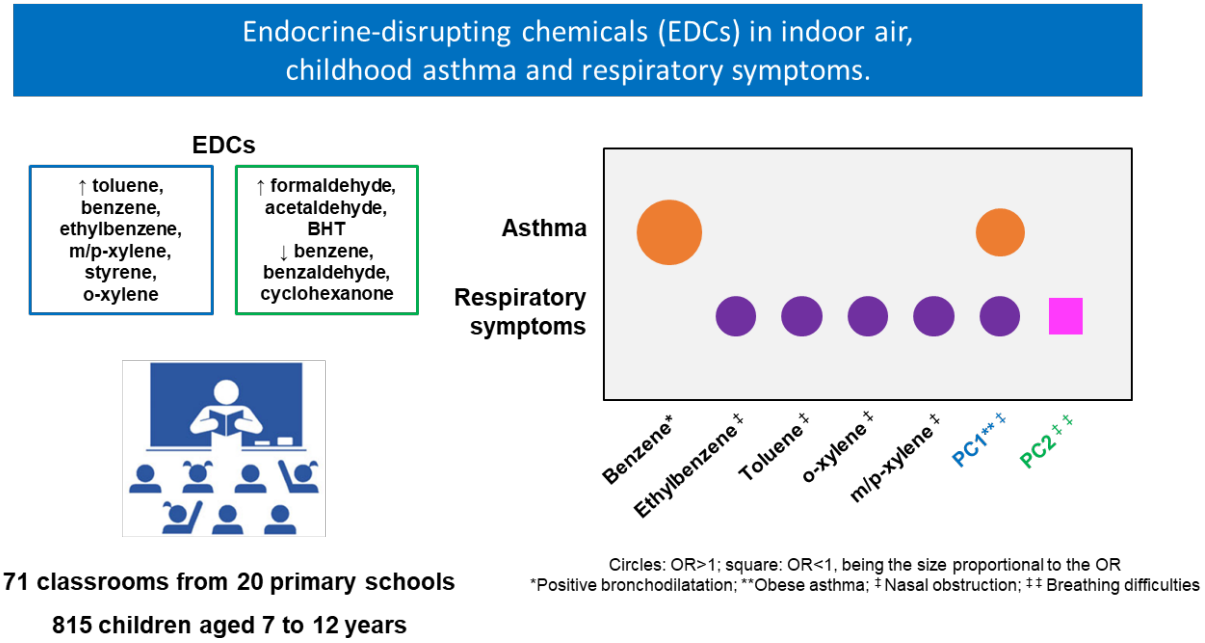

Figure 4 Endocrine-disrupting chemicals in indoor air and childhood asthma and respiratory symptoms. PC1: principal component 1 had a higher absolute correlation with toluene, o-xylene, m/p-xylene, ethylbenzene, styrene and benzene; PC2 had a higher absolute correlation with cyclohexanone, BHT, benzene, benzaldehyde, formaldehyde and acetaldehyde. A cross-sectional study involving 815 children from 20 schools showed that even low-level exposures to EDCs may increase the risk of asthma and the presence of respiratory symptoms in the previous 3 months in schoolchildren, suggesting that no safe level exists, especially when children are constantly exposed to these compounds (adapted from (6) with kind permission of copyright holder).

9 INDIVIDUAL INTERVENTIONS FOR ASTHMA PREVENTION AND CONTROL

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KEY MESSAGES

- Individually tailored asthma prevention and control is key for the long-term outcome of this chronic disease
- While primary prevention is largely ineffective, secondary prevention addressing disease progression to chronic asthma and adult COPD is essential
- Individualized asthma plans should be provided to each patient and regularly updated in the light of symptom control

Asthma is a chronic non-transmittable disease with multiple triggers needing optimal compliance for best asthma care. In order to optimize the treatment of the asthmatic patient, allergy-related measures need to be addressed in most individual. Thus, measures addressing prevention and control and empowering the patient should be among the priorities of the health professionals.

Asthma prevention mostly focuses on nutritional and environmental interventions.

- **Primary prevention** addresses measures *preventing asthma to occur*, mostly in individuals with an increased susceptibility to develop the disease. Intervention trials are addressing an early-life window of opportunity and have mostly focused on *diets avoiding allergenic foods* during pregnancy, breast-feeding, as well as on the delayed introduction of solid and/or allergenic foods into the child's diet. Overall, such measures have been proven to be effective in some extend for prevention of atopic dermatitis and food allergy, but not on respiratory diseases. Similarly, interventions leading to reduced allergen loads in the environment (e.g. dust mite avoidance measures) of children at risk for asthma have been proven mostly ineffective.
- **Secondary prevention** addresses measures *preventing the progression of the disease*. Disease progression form allergic rhinitis to as asthma has been at least partially stopped by either sub-cutaneous or sub-lingual allergen immunotherapy. However, it nowadays obvious that disease progression must mostly be addressed as a global intervention reducing inflammation and the severity of the disease, as there are concerns of progression of the disease towards more severe asthma and COPD in adulthood.

Asthma control at the individual level is mostly related at translating the most recent therapeutic guidelines to the patient's daily life.

Asthma control in *children* is closely linked to the social environment of the child. Daycare and school caregivers need to be aware of the child's triggers for asthma (e.g. pet exposure), and adapt activities in order to avoid them. In addition to the parents, caregivers need to be instructed to recognize the first signs of asthma, and how to treat an asthma attack.

Asthma control in *adolescents and adults* is based on the individual's responsibility to avoid potential triggers and to self-treat first symptoms of asthma. Repeated measurements of lung functions including self-monitoring with peak flow expiratory rates may help to assess the degree of lung

Figure 1 **The patient-centered network of care.**

obstruction and the need for inhaled corticosteroids.

Thus, in order to favor efficient asthma prevention and symptom control, optimal care will always need to involve a network of care, in which an empowered patient plays a the key role (Figure 1).

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10 ROLE OF PRIMARY HEALTH CARE IN PREVENTION AND CONTROL OF ASTHMA

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Most people with asthma can be managed in primary care most of the time. Essential tasks are:

KEY MESSAGES

- Confirmation of asthma diagnosis, and recording the criteria on which diagnosis was made, is crucial
- The choice of a suitable inhaler device, teaching, checking, correcting inhaler technique is essential
- Patient education and personalised action plans are not optional management tools
- Structured reviews (e.g. SIMPLES) improves care and outcomes
- Patients remaining uncontrolled, despite structured reviews, should be referred for specialist assessment

SUSPECTING AND CONFIRMING AN ASTHMA DIAGNOSIS

Asthma is a clinical diagnosis with no single defining clinical feature (Figure 1). Diagnosis relies on structured assessment of all available information: a good history and physical examination, investigations (lung function and biomarkers) and documented response to treatment (Figure 1). Identification of airway reversibility is pivotal, but challenging as in primary care most people with asthma have normal spirometry when tested. It is unusual that all the pieces of the asthma jigsaw will be present in any given patient at any single point in time, and the most practical approach may be to compare lung function when symptomatic with results when asymptomatic (potentially after treatment or when next triggered). Until it is confirmed objectively, the diagnosis of asthma should be considered provisional, though carefully monitored treatment may be commenced. Referral should be considered if diagnostic uncertainty persists.

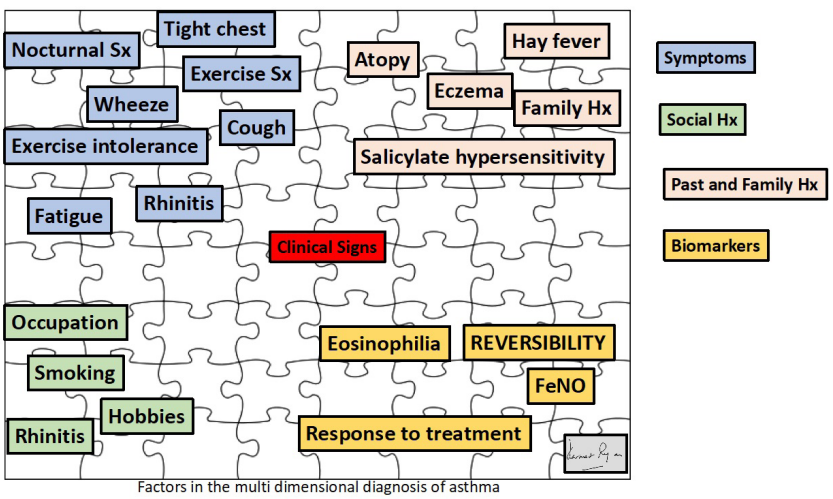

Figure 1 The asthma jigsaw.

PERFORMING A STRUCTURED REVIEW

Once the diagnosis is made the twin aims of, firstly, gaining control of asthma both by prompt prescription of preventer medication and by addressing any co-factors (e.g. smoking, occupational fac-

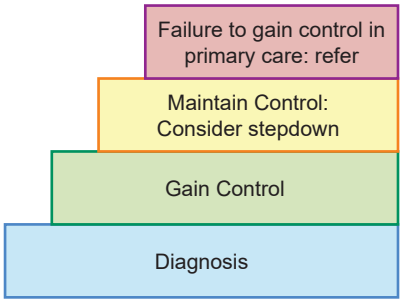

Figure 2 **Asthma management in primary care.**

TABLE 1

Structured review process: SIMPLES

	Tasks	Actions
S	Smoking cessation	Ask, Advise, Act to support quit attempts. Smoking cessation improves asthma control and maintains lung function
I	Inhaler technique	Help the patient chose a device they like and can use. Teach, observe, correct and monitor technique. Do not 'mix' devices: use the same device for reliever and preventer inhalers
M	Monitoring	Ensure regular review. Use control questionnaires e.g. RCP three questions, ACQ, ACT to measure control: assess risk of attacks. Discuss adherence
P	Pharmacotherapy	Explain what the medication is for: how to use it, when to use it, when to increase dose, when to decrease dose. Discuss potential side effects and their minimisation
L	Life-style	Discuss trigger avoidance, and lifestyle issues: diet, sleep, stress reduction, exercise
E	Education	Inform about pathophysiology, pharmacology, triggers, inhaler technique, monitoring, emergencies. Provide a Personal Asthma Action Plan as part of supported self-management
S	Support	Ensure access to routine and unscheduled care. Inform about national asthma charities and other trustworthy sources of advice

tors) or co morbidities (e.g. rhinitis) which are present, and, secondly, maintenance of lung function and avoidance of asthma exacerbations and medication side effects. Treatment is reviewed in a structured fashion to ensure that control is incrementally achieved and then regularly to maintain control and reduce dose of preventer medication to the lowest dose that prevents symptoms and reduces risk of attacks (Table 1).

SUPPORTING SELF-MANAGEMENT

Asthma is, by definition, a variable condition and all people with asthma should have the opportunity to discuss how they recognise deterioration and what action they should take (including increasing inhaled corticosteroids, commencing oral corticosteroids, and when (and how) to seek emergency medical advice. This should be summarised in a written action plan as a reminder for when it is needed. Supported self-management improves quality of life and reduces acute attacks.

REFERRING THOSE WHOSE POOR CONTROLLED CANNOT BE ADDRESSED IN PRIMARY CARE

Finally, despite systematically correcting as many risk factors as possible (smoking, poor inhaler technique, poor adherence etc) some individuals will remain uncontrolled with inherent risk of loss of lung function and require specialist assessment. There is significant under-referral of those who would benefit from specialist care. Those with severe asthma can be considered for specialist treatments (e.g. biologicals), whilst those in whom additional tests excludes asthma can be treated for an alternative diagnosis (Figure 2).

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11 DIGITAL HEALTH IN ASTHMA CARE

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KEY MESSAGES

- The market of digital technologies for asthma management is vast
- One approach does NOT fit all! Technologies must be properly chosen
- Blended care: selected tools can strengthen the patient-doctor-collaboration and improve patient outcomes

The potential of digital technologies in the management of non-communicable diseases has been recognized by the World Health Organization (WHO) as well as by national medical societies of different specialties. A vast variety of digital developments has changed the landscape of care and self-management for chronic respiratory diseases, especially asthma (Figure 1). Mobile health and web applications (apps), personal monitoring technology (e.g. smart-halers, sensor-driven technologies) and wearables create unprecedented possibilities of backed self-management, blended care, as well as decision support for healthcare professionals.

The multitude of apps, services and products may often confusing and different approaches have been chosen to improve the management of asthma patients (Figure 2). The recording of symptoms and medication use via diaries, smart-halers or sensor-based feedback, enables the patient to receive a concise overview of his/her disease control in the palm of his hand. Many apps also deliver data on potential trigger factors such as weather data, air pollution and pollen concentration. Predic-

Figure 1 **Digital technologies have a very diverse spectrum to improve asthma care.**

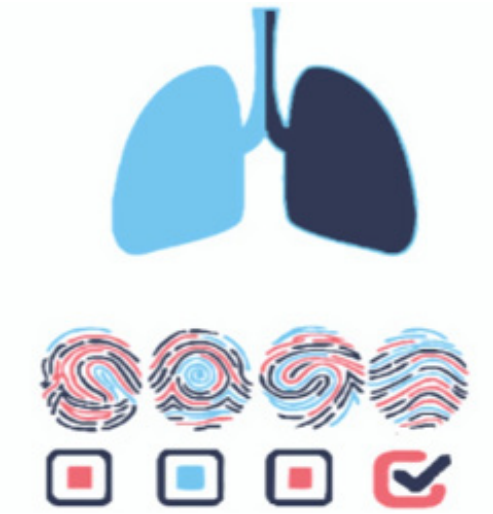

Figure 2 **Digital tools need to be chosen well in order to be effective: one size does not fit all!**

tive models may even forecast possible exacerbations and allow early intervention. All technologies mentioned above can support the shift of asthma treatment from reactive interventions during and after the occurred exacerbations to an approach of pro-active prevention.

In addition to a good understanding of the disease, patients should also adopt an efficient inhaler technique and adhere to prescribed medication. Although the proper training by a healthcare professional should not be replaced by online educational material, digital tools may strengthen knowledge via repetition and apps using artificial intelligence may assist the patient in evaluating the applied technique on a daily basis.

However, the best tools are worthless if they´re not used. Several studies have shown a steep decline in adherence of users over time and the involvement attending physicians emerged as fundamental in achieving a regular use of digital technologies. Although improved self-management is important in the area of chronic diseases, a concept of blended care is preferable, enhancing the patient-doctor collaboration through digital support in order to foster shared decision-making.

With regard to the efficacy and effectiveness of mobile health technologies and monitoring devices for asthma patients, there is unfortunately only a limited number of studies with different end points and results. Further, there is yet no standard measure to assess the quality of apps and the development of such is challenging as it needs to integrate not only scientific and medical aspects but also factors like usability, interoperability, data security and costs.

In summary, digital health technologies have a remarkable potential to improve asthma management when chosen carefully for the right patient. In order to assist doctors in making the right choice, evaluation frameworks for apps and digital devices should be established.

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12 SOCIAL MOBILIZATION FOR PREVENTION AND CONTROL OF ASTHMA

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KEY MESSAGES

- Social mobilization is an *upstream* intervention to prevent asthma and poorly-controlled asthma
- Many strategies have been endeavored to improve asthma control, ranging from behavioral modification and mindfulness skills, to methods for improving asthma knowledge, medication adherence, proper device technique, action plans, shared decision making and to stress reduction, environmental control
- Management has been further improved by introduction of development of international and regional asthma guidelines and by the development of mHealth tools

Asthma care providers define our mission as providing diagnosis and management of asthma based on best evidence. Poorly-controlled, high-risk asthma patients should be promptly identified so untoward health care outcomes can be prevented by restoring control. However, we have become enmeshed in a response cycle in which we are striving to address *downstream* challenges.

Social mobilization, defined as "the process of bringing together all societal and personal influences to raise awareness of and demand for health care, assist in the delivery of resources and services, and cultivate sustainable individual and community involvement", engages a population in community-wide efforts to address public health challenges and encourages action to facilitate change. Social mobilization is an *upstream* intervention to prevent asthma and poorly-controlled asthma.

The National Asthma Control Program, supported by Centers for Disease Control, and the Environmental Protection Agency (EPA) have implemented asthma surveillance systems designed to integrate care more effectively and programs to reduce environmental exposures that trigger or cause asthma. (Table 1).

Multiple stakeholders are involved in asthma management: the patient and family, primary care and specialty providers, schools (teachers and nurses), employers, pharmaceutical companies, insurance companies, medical centers, pharmacists, professional and patient advocacy organizations.

The burden of asthma incurs substantial direct and indirect management costs. Multiple barriers to achieving control exist, which may involve socioeconomic and psychosocial factors, cultural beliefs, religious practices, language, and

TABLE 1

US EPA Supported Social Mobilization Strategies

- Public awareness campaigns to educate and motivate families
- Promote asthma management standards of care and best practices among health care professionals
- Train health care professionals on the environmental component of asthma management and the importance of asthma action plans
- Work with clinicians who serve underserved populations to develop an important decision assessment tool for in-home assessments
- Harness and promote best practices and resources
- Mentor to help asthma care programs
- Sustain, expand and achieve desired outcomes

Adapted from reference 5.

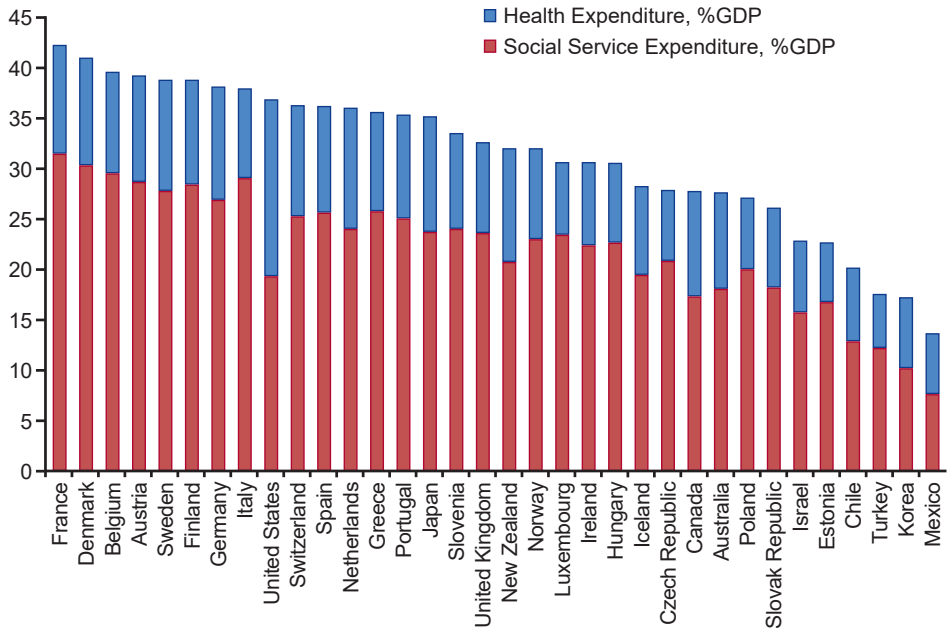

Figure 1 **Ratio of expenditures in 2011 for health care expenditures compared with social service expenditures; data shown for countries in the Organization for Economic Cooperation and Development (OECD), available at http://stats.oecd.org.**
(Figure from Bradley E, Sipsma H, Taylor L. American health care paradox – high spending on health care and poor health. QJM 2017; 110: 61-65; reproduced with permission)

poor recognition or understanding of asthma risk factors that would prompt asthma screening.

Although inner city children and adults with asthma live in socially disadvantaged environments (tenement housing, rodent/cockroach infestation, passive smoke, traffic exposures) that promote poor asthma control, residents of other areas where these exposures are less prevalent may also have poorly-controlled asthma.

Many strategies have been endeavored to improve asthma control. Early "Living With Asthma" programs utilizing behavioral modification set the stage for subsequent approaches involving multifactorial, holistic approaches. Methods have been developed to improve asthma knowledge, medication adherence, stress reduction, proper device technique and environmental control. Management has been further improved by introduction of action plans, mindfulness skills, development of international and regional asthma guidelines. Shared decision making between patients and asthma care providers has also been advocated to encourage patients to become more engaged in their ongoing care. More recently, technological advances have led to smart phone applications and smart inhaler devices that monitor adherence and directly link to health care providers. Outreach initiatives promoting asthma screening in hospitals, schools or community centers, mobile asthma units and hospital-based health care quality improvement measures have been used to identify asthma patients and improve management. GRADE-based asthma guidelines have been helpful in standardizing recommendations for asthma diagnosis and management based on best evidence. Despite these efforts, asthma remains poorly-controlled worldwide and continues to place economic health burdens on all societies regardless of affluence or access to resources.

Figure 1 displays national spending patterns for health care, expressed as the ratio of spending for health care services compared with social services. Evidence implies shifting from downstream health care expenditures toward upstream approaches focusing on social/behavioral/environmental determinants can encourage improved health care outcomes. Ultimately, the management of asthma entails the same challenges as do all chronic diseases; we are continuing to address downstream effects, while striving to move to an "upstream world" where the challenges of asthma, rather than reacted to, will be prevented.

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13 ASTHMA MANAGEMENT IN RESOURCE CONSTRAINED SETTINGS

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KEY MESSAGES

- The prevalence and mortality of asthma is high in low- and middle-income countries (LMIC)
- In low-resource settings, underdiagnosis is common and patients are often treated in emergency settings with no follow up
- For those having a diagnosis and a prescription of treatment, many have no access to it
- In general, there is no priority to asthma in LMIC, even when the burden is high

Poverty is often related to ill health. This was not usually the pattern for asthma, however, where the prevalence was thought to be higher in affluent societies. Nevertheless, there is an association between lower socio-economic status and risk of wheezing in children, both in high- and low- and middle-income countries (LMIC), indicating a more complex interaction between factors, some protective and others causative.

An analysis of a World Health Organization (WHO) database on chronic disease comprising information from 64 countries has demonstrated a relationship between gross national income and the prevalence of asthma (Figure 1). A bimodal distribution of asthma was observed, higher in high- and low-income countries, and lower in middle-income countries. What could explain a high prevalence of symptoms of asthma in a low-income country? Uncontrolled asthma? Confounding respiratory conditions in communities with high levels of pollution, respiratory infections that might give rise to wheezing? Many LMIC present higher rates of asthma deaths as compared with high-income countries (HIC). This is likely related to underutilisation of effective treatments for prevention of acute attacks, in particular inhaled corticosteroids (ICS). ICS improve control of asthma symptoms, prevent exacerbations and deaths due to asthma. But, they are underutilised in LMIC, where one sees reliance on inhaled bronchodilators and oral preparations of salbutamol, theophylline and corticosteroids instead. Although ICS have been listed by WHO as essential medications for many years, many people from LMIC have no access to it. As-required use of ICS and a rapid-onset bronchodilator is now recommended by GINA for adolescents and adults at treatment steps 1 and 2, after the demonstration it is equivalent to regular use of ICS in preventing severe exacerbations. An ecological longitudinal national-wide study of all Brazilian municipalities has demonstrated that access to ICS was associated with a 3 fold chance of reduced mortality due to asthma (Table 1), confirming previous observations in HIC.

In underserved communities, asthma is frequently managed as a recurrent acute condition, for which patients receive short course treatment only during exacerbations, when they are prescribed systemic corticosteroids and nebulized bronchodilators. Usually there is no referral for follow up in secondary care specialized clinics, which are fully booked for several months, when available. In primary health care (PHC), family doctors do not have the capacity to confirm a diagnosis of asthma, as the

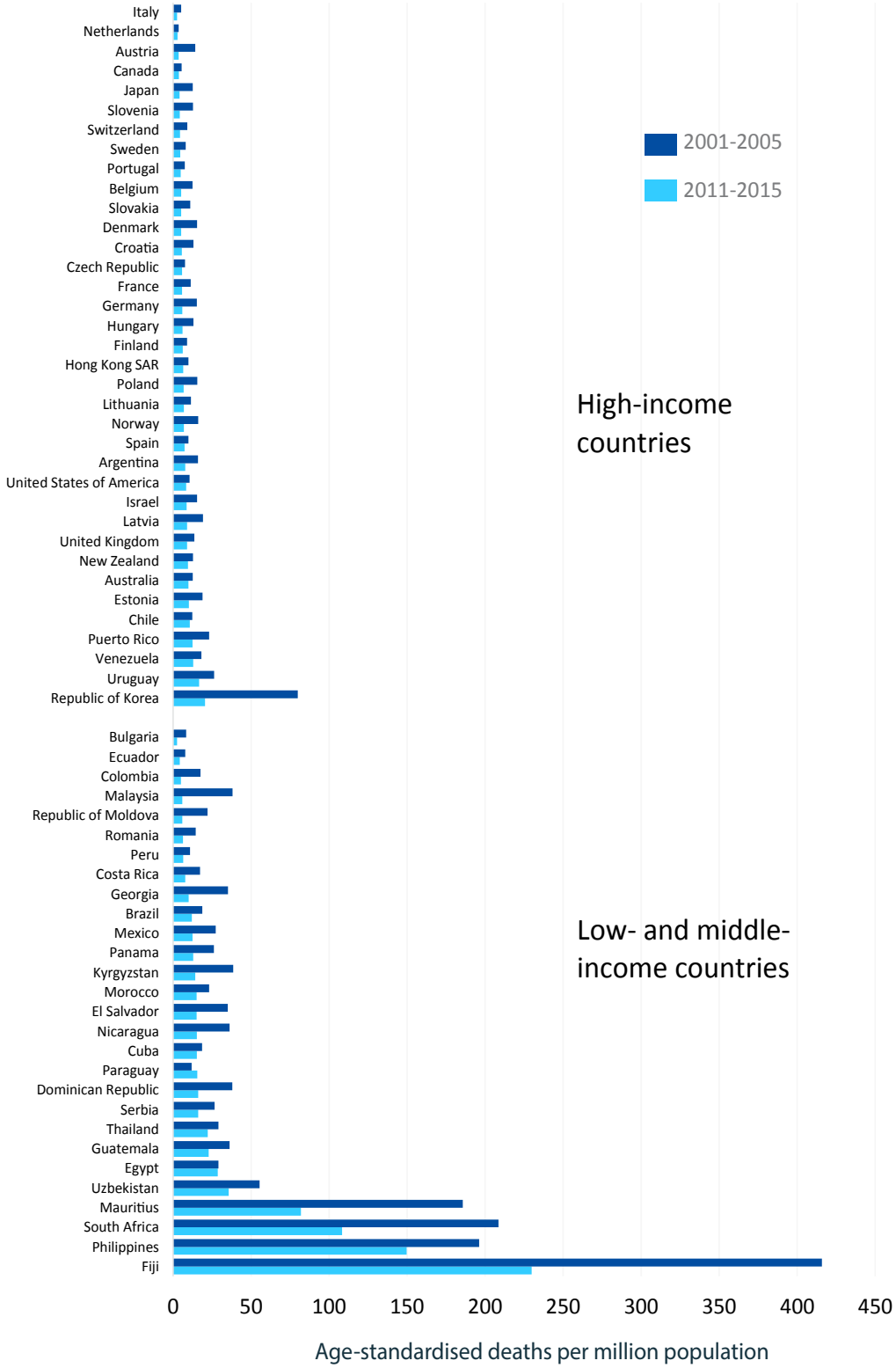

Figure 1 **Age-standardised asthma mortality rates (all ages) 2001-2005 and 2011-2015 by country, ranked by 2011-2015 age-standardised mortality rate within World Bank 2014 income group.**
(Reproduced from the The Global Asthma Report 2018 with permission from the Asthma and Respiratory Foundation NZ New Zealand)

TABLE 1

Binary regression models of factors associated with reduction of mortality rate for asthma in Brazil in a 10 year period

	Age 5–24 years old		Age 25–39 years old	
	Crude	Adjusted	Crude	Adjusted
Increase in hospital admission rate from influenza infection	1.10 (1.00–1.30)	0.97 (0.84–1.13)	1.01 (0.91–1.13)	0.94 (0.83–1.07)
Increase in *per capita* income	1.07 (0.97–1.17)	0.94 (0.84–1.06)	1.21 (1.10–1.32)	1.02 (0.91–1.14)
Population of the municipality	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)
Supply of inhaled corticosteroid free of charge since 2003	3.20 (2.38–4.31)	1.91 (1.36–2.68)	5.32 (3.96–7.13)	3.07 (2.22–4.24)
Increase in proportion of individuals living in urban area	0.70 (0.63–0.78)	0.88 (0.78–0.99)	0.68 (0.61–0.75)	0.82 (0.73–0.92)
Increase in number of physicians per inhabitants	1.21 (1.10–1.34)	1.05 (0.93–1.18)	1.34 (1.22–1.47)	1.15 (1.04–1.29)
Increase in number of hospital beds per inhabitants	1.21 (1.09–1.35)	0.94 (0.84–1.06)	1.51 (1.36–1.67)	1.20 (1.08–1.33)

Every variable contains 5,505 values, one value per municipality. Data depicted as odds ratio and 95% confidence intervals.

The dependent variable was dichotomized: municipalities that reduced and did not reduce death rate from asthma. Independent variables analyzed as ordinal values, according the quintiles, except "supply of inhaled corticosteroid free of charge" which was dichotomized in municipalities that supplied or did not supply inhaled corticosteroids for asthma.

Reproduced from Clin Respir J., Urbanization is associated with increased asthma morbidity and mortality in Brazil, Ponte EV et al., Vol 12, 1410-417, 2018 with permission from John Wiley & Sons

access to spirometry is very limited. The Global Initiative for Asthma (GINA) suggests a syndromic approach for asthma diagnosis in LMICs, but stress the importance of measuring variability in airflow for confirmation, using peak flow monitoring or spirometry with reversibility testing.

Asthma represents a burden for which underprivileged communities are poorly equipped and most LMIC have not prioritized. Some city-wide vertical programs have been successful in reducing hospitalizations due to asthma among the underserved, but they have not been incorporated into national health systems. In most LMIC, the priority in public health are still the communicable illnesses. The burden of chronic diseases in LMIC have been highlighted in WHO documents in the last 15 years, but asthma has not received due attention in most. Considering its high prevalence, it seems the best strategy to improve asthma care in LMIC, similar to HIC, is to tackle it in PHC.

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14 GENERATING RESOURCES FOR PREVENTION AND CONTROL OF ASTHMA

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KEY MESSAGES

- Generating resources for prevention and control of asthma is a difficult issue requiring constant political work at both national and international levels
- There are no asthma programs sponsored by the World Health Organisation
- In the European Union most of the basic funding for research and health programs come from local financial commitments from individual EU countries
- The European Commission and EU organisations announce (e.g. ERC, JRC, IMI, EIT health, AAL) calls for projects dedicated to health issues under their Work Programmes
- EAACI, GARD and GA²LEN play an important role in promoting and implementing topics related to respiratory diseases

Information on best practices on measures for prevention and control of chronic diseases can be obtained through local or international sponsorship programs. In both cases, political decisions are fundamental. The global initiative highlights the key role of the World Health Organisation (WHO). The health policy is decided in the United Nation (UN) general assembly resolutions which are preceded by a number of previous discussions and negotiations carried out at regional and global level. The WHO funds are not enough to conduct international programs for asthma.

In the European Union (EU), according to article 168 of the Treaty on the Functioning of the EU, a high level of human health protection shall be ensured in the definition and implementation of all Union policies and activities. In this context, promotion of the topic to the European institutions is very important, particularly to the European Commission (EC). It should be promoted not only by interested stakeholders, e.g. representatives of scientists or patients' associations but also by national authorities, directly and/or via the National Contact Points, which are consulted by EC during elaboration of new programmes. However, most of the basic funding for research and health programs come from local financial commitments in individual EU countries. The internal politics of each country determines national priorities, resulting from the specific health status of the population. The transfer of these problems to the international forum usually results from the agreement between countries and is usually realized by the presidency of the Council of the EU done by particular Member States (MS). The 27 EU Ministries of Health adopt conclusions on priorities on the basis of which the EC prepares specific programs and associated funding.

The Polish Presidency of the EU Council and its Council Conclusions (3051st, 2011) made the prevention, early diagnosis and treatment of asthma and allergic diseases a priority for the EU's public health policy. Consequently, EU institutions gave rise to the support for further efforts to prevent and control asthma. The Cyprus Council Conclusions (3206th, 2012) reinforced this initiative and recommended that the diagnosis and treatment of chronic diseas-

TABLE 1

EU resources ideas for prevention and control of asthma

Institution	Programme	Webside
European Commission	Horizon 2020	▪ https://ec.europa.eu/programmes/horizon2020/h2020-sections
	Horizon Europa	▪ https://ec.europa.eu/info/horizon-europe-next-research-and-innovation-framework-programme/commissions-proposal-horizon-europe_en
	Public Health Programme	▪ https://ec.europa.eu/chafea/health/programme/index_en.htm ▪ https://ec.europa.eu/health/funding/programme/2014-2020_pl
	The European Innovation Partnership on Active and Healthy Ageing	▪ https://ec.europa.eu/eip/ageing
European Research Council	ERC Work Programme	▪ https://erc.europa.eu/
Joint Research Centre	JRC	▪ https://ec.europa.eu/jrc/en
Ambient Assisted Lining	Ambient Assisted Lining Joint Programme	▪ http://www.aal-europe.eu
Innovative Medicines Initiative	IMI2 Work Programme	▪ https://www.imi.europa.eu/
EIT health	Work Programme	▪ https://eithealth.eu/
Funding & tender opportunities (the Single Electronic Data Interchange Area)	This is the entry point for participants and experts in funding programmes and tenders managed by the EC and other EU bodies	▪ https://ec.europa.eu/info/funding-tenders/opportunities/portal/screen/home

**accessed March 01, 2021*

es should be initiated as early as possible to improve active and healthy ageing (AHA). Several debates at the European Parliament (EP) recommended an early diagnosis and management of chronic respiratory diseases in children to promote AHA, predictive medicine and self-management strategies using mobile technology. The Vilnius EU Summit on the prevention and management of CRD (2018) followed these recommendations and attempted to provide a road map to prevent and control CRD using integrated care pathways and the recent advances in mobile technology with a focus on air pollution – The Vilnius Declaration. On 5 March 2020, under the Croatian Presidency, the 3754th Environment Council of the EU adopted Conclusions on Air Quality recognizing the air pollution as a top environmental threat to health.

The most important networks for promotion and implementation of CRD topics are: GARD (Global Alliance Against Chronic Respiratory Diseases), GA²LEN (Global Allergy and Asthma European Network), and the European Innovation Partnership on Active and Healthy Ageing.

The GARD is a phenomenal alliance of national and international organizations, medical and scientific societies, institutions and agencies in the world, all together working with the common goal of reducing the global burden of CRD. Meetings are held once a year for over 10 years during which world experts discuss different important aspects for CRD, including environmental risk factors. Strong connection with the WHO headquarters help to implement practical implementation of respiratory health policies in many countries on all continents.

Actions at all levels of this complex networks are necessary to guarantee translation of important health issues into different European programs and into the subsequent themes of calls for proposals.

Currently, the main Horizon 2020 work program is complemented

by the separate work programs for the European Research Council, Euratom, the Joint Research Centre and the Strategic Innovation Agenda for the European Institute of Innovation and technology (EIT). It contributes to European and international initiatives such as the European Innovation Partnership on Active and Healthy Ageing, the Global Alliance for Chronic Diseases, the Joint Programming Initiative on Demographic Change, the Active and Assisted Living Programme (AAL) and the Innovative Medicines Initiative (IMI) (Table 1).

The Horizon Europe 2021-2027, an ambitious research and innovation program will succeed Horizon 2020. In 2019, the EU institutions reached a provisional agreement on Horizon Europe and the EP endorsed it. The current ongoing work has been focused on budget and implementation strategy. The budget and the Horizon Europe program should be adopted in 2020.

In conclusion, it should be noted that raising funds for prevention and control of asthma is a difficult task requiring constant political work at both: national and international levels, as well including political lobbying, which aims to raise awareness among politicians and policymakers of the importance of the respiratory health of current and future generations.

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15 PLANETARY HEALTH AND ASTHMA

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KEY MESSAGES

- One of the consequences of climate change is the growing amount of weather-related disasters
- The human health dimensions of climate change are related to heat waves, smoke from fires, dust and sand storms, poor air quality episodes, cold spells and building humidity problems
- Climate change mitigation means to convert energy systems to be based on renewable innovative sources

Climate change is already visible. So far we have observed 1.1 C warming world-wide (Figure 1), warming of the oceans by 0.5 C, sea level rise of 26 cm, changes in precipitation patterns leading to more frequent drought and/or flooding events. The warming of the oceans has contributed to the existence and the strength of the tropical storms, hurricanes, typhoons and cyclones. The glaciers, snow cover and Arctic sea ice have been melting, which contribute to the sea level rise and availability of water to several major rivers in all continents.

One of the consequences of climate change is the growing amount of weather-related disasters: heatwaves, droughts, bush and forest fires, flooding, landslides and storms. The amount of sizable weather disasters has increased four times since 1980, and the economic losses have tripled. There has been a drop in human life losses thanks to improved early warning systems. The quantity and quality of impact based early warning services is still limited in especially less developed countries.

The human health dimensions of climate change are related to heat waves, smoke from fires, dust and sand storms, poor air quality episodes, cold spells and building humidity problems. Disasters are often having negative impact on health care systems. Recovery and resilience are better in developed countries as compared to less developed ones.

Enhanced frequency of heat waves is a consequence of temperature increase, which has led to frequent breakages of local and regional records. According to the World Health Organization there has been a ten-fold increase in the amount people exposed to heat waves during the past two decades. During recent years more than 200 million people have been exposed to heat waves.

The heat waves lead often to episodes of poor air quality. For example, in 2003 the August heat wave in Central Europe led to high concentrations of pollutants, especially ozone and as a consequence there were about 75 000 casualties due to respiration and blood circulation problems. In July 2010 there were about 50 000 casualties in Russia due to heat wave and poor air quality caused by peat and forest fires. It is likely that the recent record-breaking bush and forest fires and heat wave has also enhanced the mortality of the Australian population.

Poor air quality is a consequence of growth in the use of fossil fuels, especially coal and oil in energy production, industry and traffic. The ongoing shutdown of transport and industrial activities due to Covid-19 pandemics has led drop in the use of fossil energy and has temporarily improved the air quality in polluted areas of Chi-

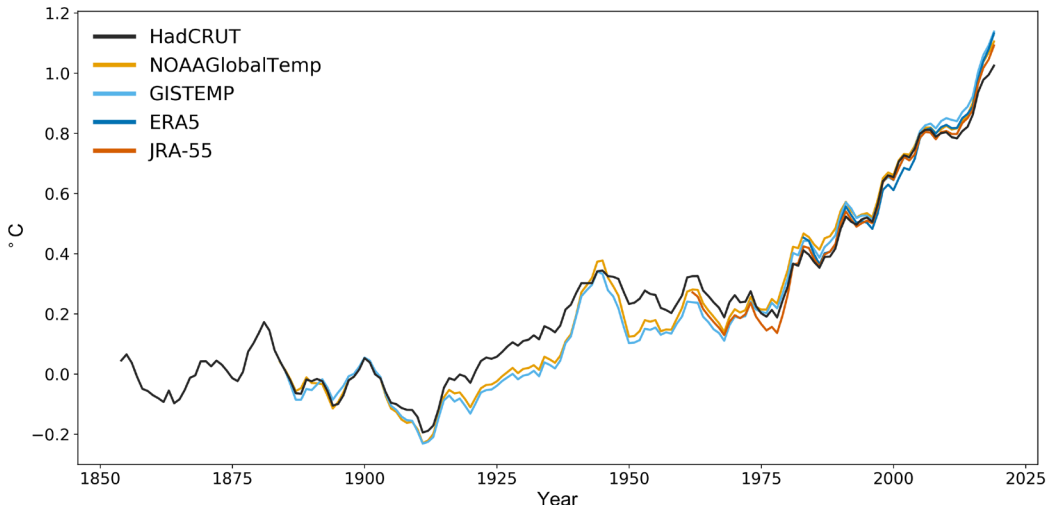

Figure 1 **Global temperature increase 1850-2019.**
(Reproduced from Climate change, disasters and asthma, Petteri Taalas, with permission from the Met Office)

na, India, Italy, France, Spain and Belgium. The ultrafine particles, nitrous oxides, ozone and sulphur compounds are causing problems for respiratory systems. Climate change mitigation means to convert energy systems to be based on renewable and nuclear energy and the transport systems to be more electricity based would at the same time contribute to improvement of air quality. Urbanization and growth of megacities has so far had an opposite impact.

Enhanced number of storms and flooding as well as warmer winters events have led to enhanced amount of damages for buildings with humidity and mold problems, which are causing health problems for people with respiratory challenges.

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16 ASTHMA PREVENTION AND REMISSION: WHY IT SHOULD NOT BE IGNORED ANY LONGER?

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KEY MESSAGES

- The use of biomarkers to direct biological treatments to the most appropriate patients has resulted in a greater predictability and precision of an effective response and achievement of improved asthma control
- Patient outcome treatment metrics identified confer sustained and optimal disease control that may also reflect the development of a disease remission
- Early life risk factors in the development of asthma have been identified and are now being considered as therapeutic targets for disease primary prevention

Asthma control remains a priority goal of guideline-directed treatment. Our concepts for asthma control, however, have expanded with the experience of biologicals in severe asthma and a more precise identification and appreciation of how environmental factors may contribute to the development of asthma. Based upon these observations, asthma control has begun to expand and extend towards disease remission and prevention.

The concept of an asthma remission is of longstanding interest but not until recently, considered an obtainable goal or marker of control. Clinical experiences with biologicals in rheumatoid arthritis, systemic lupus erythematous, and inflammatory bowel disease, have laid the groundwork to also propose remission in asthma as a reality. In rheumatic diseases, biologicals control symptoms and prevent tissue injury and progression; these outcomes reflect a remission of disease. Although the underlying susceptibility for disease still exists, the inflammatory pathways are held in check to prevent injury to the joints and blood vessels. The disease is not "gone," but biologicals have put the pathologic processes into remission. Based upon an ever-expanded experience with biologicals in asthma, the concept for remission in asthma is now being evaluated.

The concept of remission in asthma is complex and has been proposed to possibly occur under two conditions: *remission while under-treatment and remission off-treatment* (Figure 1). The achievement of remission is further divided into clinical remission and complete remission, with distinct criteria to serve as a framework to measure treatment outcomes, including symptoms, lung function, patient/physician's view, and absence of the need for systemic corticosteroids, i.e. no exacerbations. Although remissions have been viewed as a "cure," extending the experiences with biologicals from rheumatoid diseases to asthma provides a new treatment goal that reflects sustained disease control.

Asthma prevention is a next and emerging step in treatment approaches. Many environmental factors may contribute to the expression of asthma in susceptible patients (Figure 2). Genetic pathways have been linked to these gene-by-environment interactions; genetic modification is not currently feasible. In contrast, attempts at prevention appear most promising and feasible when interactions with key and influential environmental exposures are

Clinical Remission on Treatment

For ≥ 12 months:

- Sustained absence of significant asthma symptoms based on validated instrument, **and**
- Optimization and stabilization of lung function, **and**
- Patient and HCP agreement regarding disease remission, **and**
- No use of systemic corticosteroid therapy for exacerbation treatment or long-term disease control

Clinical Remission off Treatment

Same criteria maintained without asthma treatment for ≥ 12 months

Complete Remission on Treatment

Clinical remission plus the following:

- Current, objective evidence of the resolution of previously documented asthma-related inflammation (eg, reduced blood or sputum eosinophil counts, FeNO, and/or other relevant measures), **and**
- In appropriate research settings: Current negative bronchial hyperresponsiveness

Complete Remission off Treatment

Same criteria maintained without asthma treatment for ≥ 12 months

Figure 1 **Generalized framework for remission in asthma.** Criteria for clinical and complete remission, on and off treatment, were identified by consensus among clinical experts. FeNO, Fractional exhaled nitric oxide. *Blood eosinophil counts and FeNO are less relevant for T2-low asthma. From Menzies-Gow et al J All Clin Immunol 2020;145: 757-65.

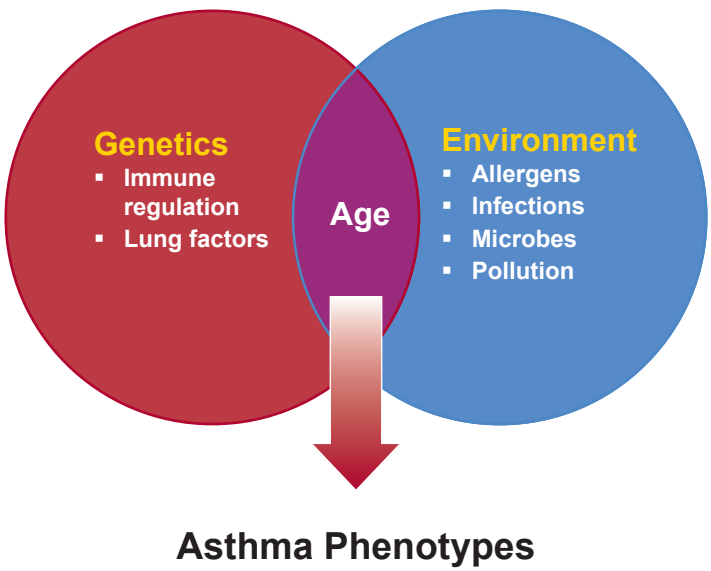

Figure 2 **Pathogenesis of asthma and environmental targets to be considered for disease prevention.**

considered. For prevention to be effective, the timing of these preventions will be critical and prior to the establishment of an asthma endotype. A number of environmental factors have been important in the development of asthma: allergen exposure with the development of allergic sensitization; wheezing with viral respiratory infections; and the makeup of the host's microbiome, either in response to the microbes in the environment or in host, such as the gut.

The relative importance of each of these factors, either singly or in combination is complex and variable. For example, allergen sensitization is a key step in the development of asthma. At present, environmental avoidance has not been effective. However, allergen immunotherapy in early life can diminish the likelihood that an allergic child develops asthma. In children who have allergic sensitization, wheezing with rhinovirus infections is common and, for some, may be a key second trigger to the development of asthma. Triggers for prevention include both allergic sensitization and a modification of the consequences of the viral infection on airway inflammation. Finally, the importance of an environmental microbiome has been substantiated in multiple farm-based studies to be protective, or possibly preventative, in the eventual risk for asthma. To translate these observations to a prevention strategy, it will be essential to identify which microorganisms are either detrimental or protective. For prevention to be effective, interventions will likely need to occur at an early age in life, in at risk populations and with an appropriately targeted product. These next steps will be complex, but hold realistic promises to prevent asthma and be a major step forward to achieve disease control.

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17 REVISED NOMENCLATURE FOR ASTHMA

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Rapid growth of technology, including molecular diagnostics together with dynamic advances in electronic information gathering, creates extensive amount of data that allows more detailed disease description. For the asthma nomenclature usage of this new set of information allowed a shift from a mere patho-mechanistic approach, with symptoms and organ function as the main descriptors, to recognition of a more established network of immunological pathways described by various biomarkers, ideally validated. New disease endotypes, defined by distinct pathophysiological mechanisms are now described for asthma. However, the current disease taxonomy does not cover this information and hence categorization of asthma subtypes becomes more complicated, thus necessitating revision. New nomenclature for asthma should describe the disease on the basis of its intrinsic biology in addition to traditional "signs & symptoms", or disease severity and control, leading to better understanding of mechanisms, prevention and treatment. It should also be flexible allowing easy incorporation of subsequent evidence to existing knowledge.

KEY MESSAGES

- New disease endotypes, defined by distinct pathophysiological mechanisms are now described for asthma
- New nomenclature for asthma should describe the disease on the basis of its intrinsic biology in addition to traditional "signs & symptoms"
- It should also be flexible allowing easy incorporation of subsequent evidence to existing knowledge
- The proposed new taxonomy for asthma follows the asthma endotypes classification and includes visible properties, disease severity and control as well

Asthma phenotypes cluster together relevant visible properties such as age at onset, triggers, co-morbidities, physiologic traits, inflammation type (eosinophilic and non-eosinophilic), and treatment response. Asthma phenotypes defined based on the predominant inflammatory cell identified in induced sputum (eosinophilic, neutrophilic, mixed granulocytic, and paucigranulocytic phenotypes) or in blood (eosinophilic asthma) are currently being used for a stratified approach to severe asthma. Phenotypes do not necessarily relate to or give insights into the underlying pathogenetic mechanism. In addition, they frequently overlap and are subject to change over time. Thus, defining disease endotypes based on key pathogenetic mechanisms has become a rational development.

Presently, two major asthma endotypes are described: type 2-high (T2) and type 2- low (non-T2). The mixed Th17/Th2 endotype or Th2/Th17 endotype is usually encountered in the most severe cases of asthma and is related to glucocorticoid resistance, fixed airway obstruction or airway hyperreactivity (Figure 1).

The T2 complex endotype involves type 2 ILCs, T helper (Th) 2 cells, natural killer T cells, eosinophils and mast cells as well as activation and recruitment of IgE – producing B-cells, which altogether sustain the T2 inflammation. Several bi-

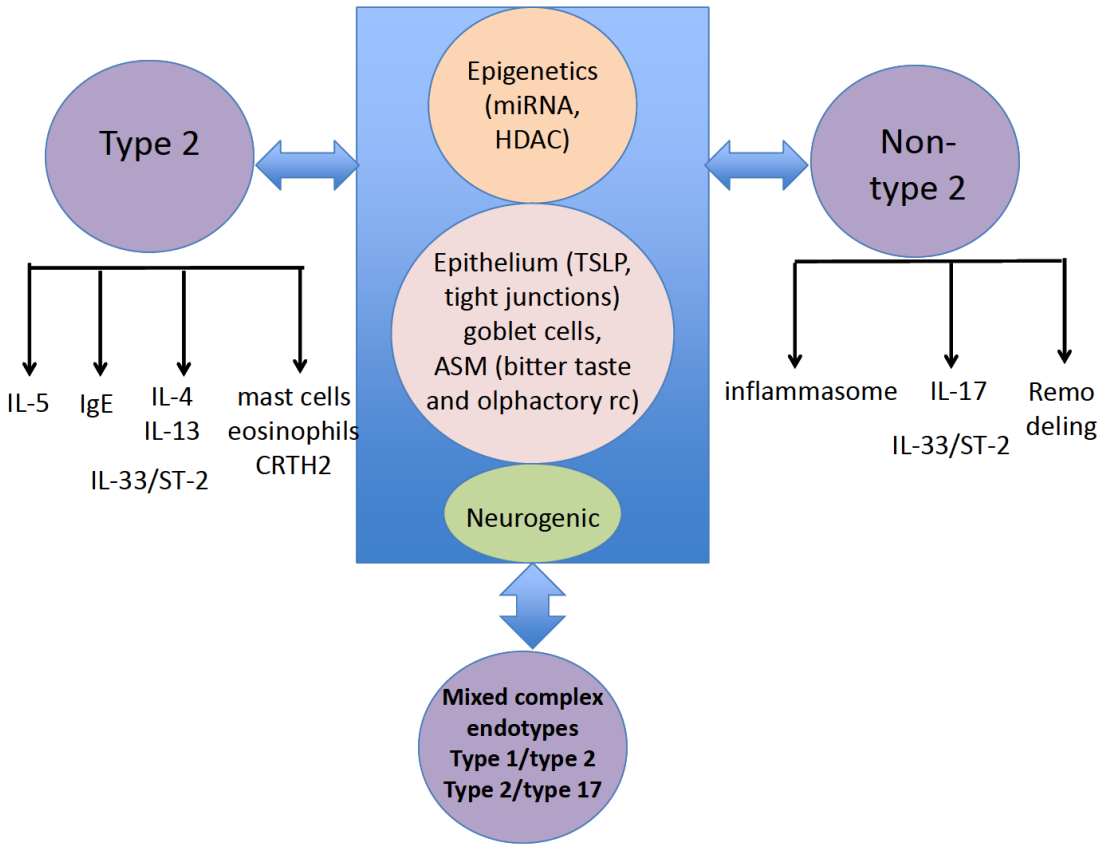

Figure 1 **Three main asthma endotypes are described: T2, non-T2 and mixed.** They share several pathogenetic mechanism such as epithelial and smooth muscle dysfunction, epigenetic changes and neural inflammation.

omarkers were related to the T2 endotype: total and specific serum IgE, serum periostin and dipeptidyl peptidase (DPP) -4, blood eosinophils, and for asthma sputum eosinophils and exhaled nitric oxide (eNO). For T2 asthma four main pathways can be targeted: the IgE pathway (omalizumab), the IL-5 pathway (mepolizumab, reslizumab, benralizumab), the IL-4/IL-13 pathway (dupilumab, tralokinumab, lebrikizumab) and the CRTH2 receptor (fevipiprant, timapiprant).

Current data support importance of several non- T2 sub-endotypes of asthma related to the inflammasome or the Th17 pathway activation, tissue remodelling and barrier defects. For non-T2 asthma three main pathways can be targeted: a) the inflammasome pathway (anti TNF-α interventions such as etanercept, infliximab, adalimumab or anti IL-1β with anakinra, anti IL-6 with tocilizumab or atlizumab, negative feedbacak with IL-37 or CD80 – CD28 blockade with Abatacept); b) the IL-17 pathway (brodalumab or anti IL-33/CXCR2/HMGB1-RAGE interventions); c) remodelling via bronchial thermoplasty in selected cases.

For the mixed complex endotypes a combination between anti T2 interventions and nti-inflammatory macrolides or anti CXCR2 can be used. As an alternativem PI3Kδ/JAK/MyD88 inhibitors might block up-stream the effects of T1, T2 and T17 cytokines.

Epigenetic modifications, structural abnormalities and neurogenic inflammation are shared by T2, non-T2 and mixed complex endotypes and should be evaluated and targeted properly in conjunction with the interventions addressing the immune-inflammatory mechanisms. New targets for the ASM are the bitter taste and olphactory receptors. The epithelium can be targeted via anti TSLP (tepezelumab) or by restoring the tight junctions. Mucin production can a target as well via the autophagy process. miRNA and HDAC interventions could be additional therapeutic tools.

The proposed new taxonomy for asthma follows the: asthma endotypes (A) and subendotypes (B)

TABLE 1

Revised nomenclature for asthma				
A. Endotype	**B. Subendotype**	**C. Visible properties**	**D. Disease severity**	**E. Disease control**
T2 asthma	IgE (local/systemic)	Early/late-onset	Mild/moderate/severe	Controlled
	IL-4/IL-13	Trigger type: Viral induced, Exercise-induced, aspirin-sensitive, premenstrual trigger, occupational, etc.	Brittle asthma	Partially controlled
	IL-5	Lung function: fixed obstruction, small airways disease, fast lung function decline	Difficult-to-control asthma	Not controlled
Non-T2 asthma	Inflammasome	Co-morbidities: CRS, AD, AR, food allergy		
	Type 17	Co-morbidities: obesity, psychiatric disease		
	Remodelling	Treatment response: corticosteroid sensitive or resistant		
T2/T17 asthma	?			
T2/T1 asthma	?			
T2/T1/T17 asthma	?			

classification and includes visible properties (C), disease severity (D) and control (E) as well (Table 1).

Example of how to use the revised nomenclature for asthma:

- T2 asthma/IL-5 driven/late-onset, small airways disease, corticosteroid-resistant/severe/partially controlled
- Non-T2 asthma/remodelling/fixed airway obstruction, occupational trigger, corticosteroid resistant/moderate/not controlled
- T2 asthma/IgE driven/early onset, allergic trigger, small airways disease, corticosteroid sensitive/moderate/controlled
- T2/T17 asthma/?/late-onset, CRS, obesity, fast lung function decline, corticosteroid sensitive/severe/uncontrolled.

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18 VISION, ROADMAP AND LAND-MARKING EVENT

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Past Presidents and President of
European Academy of Allergy and Clinical Immunology (EAACI)

The World Health Organization declares chronic respiratory diseases as one of the four major health problems of mankind. The prevalence of asthma has steadily increased over the past decades, with more than 350 million patients, affecting more than 20 % of children and 10% adults in the world. The socio-economic impact of asthma is one of the highest with direct and indirect costs of asthma sum up to more than 400 billion Euro per year in Europe. In addition, up to 40% of children and up to 70% of adults treated for asthma remain uncontrolled and approximately 6% of all cases represent severe cases. Effective policies and strategy development are needed to fill this gap at the national, regional and global levels (Table 1).

KEY MESSAGES

- The asthma epidemic affects more than 350 million patients with a global rise in prevalence and healthcare costs, representing the most common chronic childhood disease
- Efforts to overcome unmet needs should focus on several main directions:
  - Research excellence, innovation and originality in asthma; focus on creating new ideas, analyzing problems, diagnosing them and identifying their causes
  - Better patient care at the global level
    - » develop asthma registries
    - » next generation guidelines
    - » improved accessibility to endotyping and to modern therapies to decrease health care costs
    - » accessibility to essential drugs in low income countries
    - » holistic approach with full environmental control and other non-pharmacologic measures like psychological support, healthy life-style or rehabilitation
    - » Implement every aspect of education of patients and caregivers, primary care physicians and allied health
  - Increased public awareness
  - Including Asthma in the political agenda
- Effective policies and strategy development are needed to fill this gap at the global, regional and national level with a “Global Asthma and Allergy Fight Strategy”
- All stakeholders should be involved
  - A multidisciplinary and scientific approach should be used
  - “One Health” concept should be integrated
  - Environmental guidelines should be developed
  - Integrated asthma surveillance networks should be established
  - Existing know-how from successful approaches from the past should be broadly implemented

UNMET NEEDS AND HOW TO OVERCOME THEM

In view of the high need to optimize patient care in the context of the asthma epidemic, a worldwide strategy to reduce the burden is warranted. This action plan can only be successful by the combination of actions of the following stakeholders: healthcare professionals, researchers, pharmacists, patient and civil society organi-

TABLE 1

Obstacles in asthma research grants
• Lack of political awareness and low understanding and priority setting for the asthma epidemics
• Curative approaches and research for prevention has not been so far efficiently supported
• Small quantities of grants have been given to hypothesis-based biased research, although the real need is for large scale, non-hypothesis based, in depth unbiased research, which is now possible with the novel developments in next generation DNA and RNA sequencing, single cell sequencing, multiplex analyses of body fluids, exposome and epigenetic analysis combined with artificial intelligence and big data analysis
• Human research is receiving relatively less funding in many grant giving bodies compared to animal models
• Many major grant giving bodies had to decrease their budgets because of economic conditions in the many countries
• Fight against COVID-19 brought a lot of knowhow to respiratory departments, which should be appropriately canalized after the pandemics
• Negative results should be reported, otherwise they will be endlessly repeated

zations, industry and policy makers. Therefore, joining forces by all stakeholders in a unique global asthma fight platform will be necessary to reach the goal.

Unmet needs in the field of asthma can arbitrarily be split into four different main domains, such as clinical care, education, research & development and increased support from the funding bodies and society. Clinical care faces many unmet needs, from better accessibility to high-quality care to better monitoring tools, which all should be targeted. Extensive asthma endotyping and stratified/personalized treatment according to endotyping is needed, together with worldwide access of the patients to recently introduced biological treatments in low income countries Asthma registries as top-level real-world data should be developed in different geographic regions. Asthma patients require point of care accessibility to endotyping diagnosis. EAACI had a major contribution to develop guidelines in food allergy, allergen-specific immunotherapy and biologicals, and asthma has always been focused in these guidelines. Next generation guidelines should be developed for the holistic approach to asthma including environment, diet and psychosocial aspects. Environment and life style control of patients and implementing psychological help directly and routinely will represent a high-quality patient care. Every aspect of good quality education for patients and caregivers, primary care physicians and other healthcare professional, together with the usage of digital platforms should be implemented.

RESEARCH AND DEVELOPMENT

Given the lack of insight into factors driving uncontrolled or severe asthma, **research** should be prioritized and focused on determinants of disease related intrinsic factors, such as mechanisms and endotypes, psycho-social, environmental and socio-economic factors. Better insight into the exogenous and endogenous factors being responsible for uncontrolled disease will allow the design of optimal treatment strategies. The **development** of novel tools for endotyping and evaluation of burden of the disease by the patients are needed, like user-friendly and cheap devices for the measurement of endotypes and therapy response. Research should be synergized and prioritized in order to achieve sustainable results on prevention, biomarkers, curative treatment, anti-viral vaccines, and novel drug development. Prevention at all three levels should be one of the most prominent focus of asthma research. There are a number of barriers and obstacles in grant giving bodies to be solved (Table 1).

TABLE 2

Efforts for increasing awareness in the political bodies for allergy and asthma and coordinate efforts for better asthma management

- The results of the Finnish Asthma Program demonstrated that asthma burden can be substantially decreased by relatively undemanding methods doable by every country is slowly being implemented by some national health-care systems
- Asthma is included in the Horizons 2020 programme and FP8 in the EU
- Research grants on allergy are still pending and efforts are needed to include allergy in FP8
- Many awareness meetings have been organized or attended in the EU parliament by patient organizations and EAACI leadership in Brussels during the recent years
- EAACI organised two Strategic Forums on allergy and asthma research priorities attended by peer organisations, public health and regulatory agencies (WHO, EC, PEI), patients organisations, industry, key-opinion leaders in asthma research
- Under the steer of the EAACI Research and Outreach Committee a European Research Network is currently being developed to tackle asthma and allergies in a coordinated fashion, together with the first pan-European health-economics registry
- Novel education modules on T2 disease and translational research tools in asthma are currently being developed by EAACI

INCREASING PUBLIC AWARENESS

One of the unmet needs is the missing knowledge in the public that asthma is the number one childhood disease with the highest healthcare burden. A huge responsibility lies on the shoulders of asthma-focused patient organizations and scientific academies such as EAACI, ERS, AAAAI, WAO, ATS, EPA-UNEPSA, GARD, to include asthma in the political agenda and increase awareness in the public (Table 2).

A WORLDWIDE STRATEGY TO FIGHT AND MANAGE ALLERGIC DISEASES AND ASTHMA SHOULD BE DEVELOPED

EAACI had put forward tremendous efforts to promote a worldwide strategy to fight and manage allergic diseases and asthma. All stakeholders including specialists, primary care physicians, nurses, dieticians, psychologists, pharmacists, patient and civil society organizations, educators, industry, and policy makers should be involved. A multidisciplinary scientific approach is essential. Modern global guidelines should be developed and implemented for the management of asthma and co-morbidities. The next generation guidelines should provide structured, multidisciplinary, region and environment-oriented and individual patient-focused solutions, with full considerations on differences across cultures. Environment guidelines should be developed as soon as possible (Table 3).

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TABLE 3

Global asthma fight strategy

- Include all stakeholders in a multidisciplinary scientific approach
- Accept asthma as a global public health problem
- Upgrade "Asthma" in the political agenda
- Develop strategies to reduce risk factors. Environmental guidelines should be developed
- Appreciate the role of primary care, allied health personnel and pharmacists as the central link between patients and physicians
- Initiate global education programmes
- Develop intensive public education and awareness programmes
- Increase research funds in general
- Prioritize prevention and curative treatments based on high-quality unbiased research
- Generate resources for prevention and control
- Strengthen the role of "Allergology and Clinical Immunology" specialty in asthma care
- Harmonize, maxime resource use and increase the impact the educational and awareness activities of main associations

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