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The Natural History of Asthma

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1. Introduction

As our understanding of underlying mechanisms evolve disease definitions are adapted and refined. For example, until recently, one of the main distinctions between the definition of asthma and COPD was the presence or absence of reversible airflow obstruction. As greater advances are made in understanding pathology, newer and better definitions encompass the overlap that exists between these two conditions and the recognition that chronic inflammation underlies both.

Despite greater understanding of the inflammatory processes that drive asthma, there remains a lack of consensus regarding a definition and standards for diagnosis. Asthma is a clinical syndrome and currently there is no single test that confirms its presence. This has hampered studies of asthma epidemiology, as different investigators have used differing inclusion criteria to identify cases of disease.

As well as identifying the presence of disease, there is a need to understand the natural history of asthma in order to identify which therapeutic interventions are most likely to be beneficial at any given time. A growing body of evidence suggests that although several current treatment strategies are effective in controlling symptoms, none change the natural course of the illness. It is, therefore, crucial to identify risk factors for the development of asthma and triggers for asthma symptoms in order to develop effective primary and secondary prevention strategies.

This chapter will discuss how asthma is diagnosed, its incidence and prevalence, the associated healthcare utilization, and morbidity and mortality. It will also outline the clinical phenotypes associated with the onset, remission and progression of asthma, over time..

2. Definitions

Most definitions of asthma have emphasized the variable nature of symptoms, the presence of airflow obstruction and the reversible nature of the airflow obstruction, at least in the early stages of disease [1,2]. As the pathophysiology of asthma has become clearer, definitions have changed to include a statement of pathology. The latest definition to be widely embraced is a description of asthma as:

“A chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyper-responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing; particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction within the lung that is often reversible either spontaneously or with treatment” [1].

In keeping with current theories, this definition implies that asthma is one disorder, rather than multiple complex disorders and syndromes [3] without detracting from its variable clinical presentation and course. This definition may encompass the spectrum of disease present and its inflammatory basis, but it is clinically unwieldy, as it does not provide a clear set of diagnostic criteria from which to identify patients. A more clinically relevant definition of asthma will not come into being until the pathogenesis of this condition is understood and a diagnostic biomarker is identified.

3. An overview of inflammation

Currently asthma is understood as being a chronic inflammatory disease where gene-environment interactions (often with different sensitizing agents) lead to the release of inflammatory mediators, the recruitment of specific cell populations, and airflow obstruction. The airflow limitation may range from being completely reversible to being fixed. Historically, there has been difficulty differentiating between COPD and asthma. These conditions can co-exist, so the clinical picture can reflect both, which may complicate the diagnostic process and alter responses to treatment. However, while symptoms and the results of forced respiratory maneuvers can be similar, there is increasing recognition that there are differences in the pulmonary inflammatory profile of patients with asthma and COPD that can help to differentiate between the two conditions [4]. An overview of the inflammatory cascade in asthma and COPD is provided in figure 1.

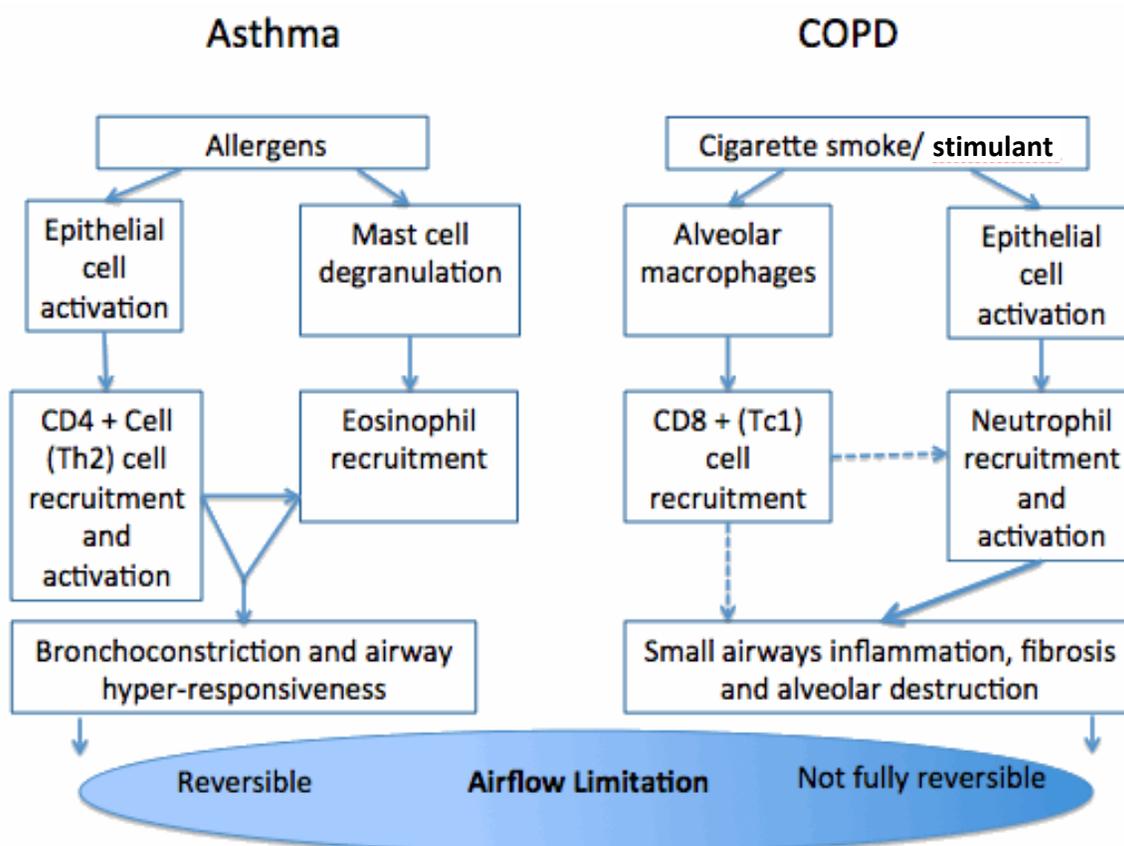


Fig. 1. A broad overview of pulmonary inflammation in asthma and COPD (adapted from [5]).

There are also differences in the pathology and immunology of mild to moderate and severe asthma, which can also complicate diagnosis. It is increasingly recognized that while mild and moderate asthma is a disease of eosinophils, severe asthma is associated with an influx of neutrophils [6]. It is hypothesized that this difference in cell types may explain in part the increased resistance seen to corticosteroids with severe asthma, as neutrophilic inflammation is classically less responsive to this form of therapy [7]. It is unclear, however, whether neutrophils are causally related to severe asthma, or whether their presence is secondary to the frequent use of corticosteroids and unrelated to the natural history of the disease. Table 1 highlights differences in pulmonary inflammation in Asthma, Severe asthma and COPD.

	ASTHMA	SEVERE ASTHMA	COPD
Predominant Cells present in the lungs	Eosinophils Macrophages CD4+ T Cells (TH2)	Neutrophils Macrophages CD4+ T Cells (Th2)	Neutrophils Macrophages CD8+ T Cells (Tc1)
Key mediators in lung secretions and lung biopsies	Eotaxins IL-4, IL-5, IL-13 Nitric oxide	IL-8, IL-5, IL-13 Nitric Oxide	IL-8, TNF-alpha, IL-1 beta, LTB4, IL-6
Site of Disease	Proximal airways	Proximal airways and peripheral airways	Peripheral airways, lung parenchyma, pulmonary vessels
Pathological features	Fragile epithelium Mucous metaplasia Thickening of the basement membrane Oedema Bronchoconstriction	Fragile epithelium Mucous metaplasia Thickening of the basement membrane Oedema Bronchoconstriction	Squamous metaplasia, mucous metaplasia, small airway fibrosis, destruction of parenchyma.
Response to treatment	Large response to bronchodilators. Good response to steroids	Smaller or no bronchodilator response and reduced response to steroids	Small bronchodilator response, but this can alter with repeated testing, poor response to steroids

Adapted from [5].

Table 1. Differences in pulmonary inflammation asthma, severe asthma and COPD.

4. Severity classifications and asthma control

International guidelines stratify asthma by severity, using symptoms, exacerbations and markers of airflow obstruction (FEV₁ or peak expiratory flow). Severity classifications are Intermittent, Mild persistent, Moderate Persistent and Severe Persistent (table 2.) These scoring systems were only meant to be applied to patients not receiving inhaled corticosteroids [5] since this therapy can dramatically alter disease control. Despite this, it was widely recognized that this severity classification was often erroneously applied to

patients already on treatment [8] and that the usefulness of such a system was limited. Severe Persistent asthma can become Mild or Intermittent Asthma if it is suitably controlled with medication, however, this change in severity classification may not reflect the severity of asthma present initially, nor the difficulty with which control was achieved [9]. Currently this classification system is limited to research studies only.

In light of these factors there has been a move to classify the severity of asthma by its clinical expression - characterizing symptomatic control [10]. This provides clear targets for physicians and patients and an easily recognized trigger mechanism to increase or decrease therapeutic regimes. Table 3 describes how asthma control is currently characterized.

<p>Intermittent</p> <p>Symptoms less than once a week</p> <p>Nocturnal symptoms not more than twice a month</p> <p>Brief exacerbations</p> <p>FEV₁ or PEF > 80% predicted</p> <p>FEV₁ or PEF variability < 20%</p>
<p>Mild</p> <p>Symptoms more than once a week but less than once a day</p> <p>Nocturnal symptoms more than twice a month</p> <p>Exacerbations may affect activity and sleep</p> <p>FEV₁ or PEF > 80% predicted</p> <p>FEV₁ or PEF variability < 20 - 30%</p>
<p>Moderate Persistent</p> <p>Symptoms daily</p> <p>Nocturnal symptoms more than once a week</p> <p>Exacerbations may affect activity and sleep</p> <p>Daily use of short acting beta₂ agonists</p> <p>FEV₁ or PEF 60 - 80% predicted</p> <p>FEV₁ or PEF variability > 30%</p>
<p>Severe Persistent</p> <p>Symptoms daily</p> <p>Frequent nocturnal symptoms</p> <p>Frequent Exacerbations</p> <p>Limitations of physical activity</p> <p>FEV₁ or PEF < 60 % predicted</p> <p>FEV₁ or PEF variability > 30%</p>

Adapted from [5].

Table 2. Asthma classification by severity before treatment

Characteristic	Controlled (all of the following)	Partly controlled (any measure present in any week)	Uncontrolled
Daytime symptoms	None (twice or less a week)	More than twice a week	Three or more features of partly controlled asthma present in any week
Limitations of activity	None	Any	
Nocturnal symptoms	None	Any	
Need for reliever/ rescue medication	None (twice or less a week)	More than twice a week	
Lung function (FEV ₁ or PEF)	Normal	< 80% predicted or personal best	
Exacerbations	None	One or more a year	Once in any week

Adapted from [5].

Table 3. Levels of asthma control

All current international guidelines use asthma control to classify severity and to signal the need for a change in treatment strategy in a step-wise manner. However, many studies of the epidemiology and natural history of asthma still refer to severity in accordance with Table 2.

5. Epidemiology

Studies of asthma epidemiology have been hindered by the lack of an agreed diagnostic standard. There is controversy as to whether symptoms and airway hyper-responsiveness should be assessed separately or jointly, although there is a poor correlation between the presence of symptoms and airway hyper-responsiveness [11,12].

6. Incidence

Incidence rates for asthma vary in accordance with the age of the population under study and the diagnostic criteria used. Global estimates suggest that there are at least 300 million people worldwide with asthma, with a predicted 100 million additional cases by 2025 [5,13]. Asthma incidence rates are highest in early childhood and in male children until puberty [14] and appear to be rising. A study in the USA described childhood asthma incidence rates to be 183 per 100,000 children in 1964 and 284 per 100,000 in 1983 [15]. The incidence of adult-onset asthma is highest in females (3 per 1000 person-years compared with 1.3 per 1000 person-years in males) [16] but these do not appear to be increasing [15].

7. Prevalence

There have been many studies estimating the prevalence of asthma in differing communities. Overall, the global prevalence ranges from 1% to 18% of the population in different countries [17]. Data suggest that there are increases in prevalence of asthma in children and in older adults in developing countries and decreases in the prevalence of

asthma in the developed world [18]. Urbanisation appears to be a risk factor for asthma, as its prevalence has consistently been shown to be higher among children living in cities compared with those living outside urban developments [19,20]. Possible explanations for this include atmospheric agents, the hygiene hypothesis where reduced exposure to allergens leads to a less tolerant immune response, a poorer socioeconomic background and differences in healthcare utilization. These remain as yet unproven.

8. Healthcare utilization

The global financial impact of asthma is substantial. Healthcare utilization accounts for the largest proportion of these costs and is increasing annually. In 2000, the estimated annual costs for asthma in the USA was \$12.7 billion (8.1 for direct costs, 2.6 related to morbidity, 2.0 related to mortality). In 2007 this figure had risen to an estimated \$50.1 billion [21]. On an individual basis, the direct health care costs associated with asthma in the USA are approximately \$3,300 per person with asthma each year [21].

Increased hospital admissions account for a significant proportion of the rising costs and have been documented worldwide, including in the UK, New Zealand, USA, and Australia [21-23]. A study comparing asthma hospitalisations in the 1960s and the 1980s reported a 50% increase in cases of children with an exacerbation of asthma and a 200% increase in cases of adults across these decennials [24]. There has also been a significant rise in asthma-related contact with a family physician [25].

9. Morbidity and mortality

Increased utilization of healthcare and monetary spend on asthma has not correlated with vast improvements in mortality or morbidity. The World Health Organisation estimates that 15 million disability-adjusted life years (DALYS) are lost annually due to asthma [13,26]. This represents 1% of the total global disease burden. Annual worldwide deaths from asthma have been estimated at 250,000, but mortality does not correlate well with prevalence. Indeed, the countries that currently suffer the highest prevalence (Northern America, UK, New Zealand) enjoy the lowest mortality rates [26]. In developed countries, death rates appear to be stable. In the USA mortality has remained at approximately 3,500 deaths per year for five years [21], while in the UK annual mortality rates have remained stable at approximately 1300 per annum [27].

10. Demographics and asthma

The epidemiology of asthma is associated with by age-related sex differences. Asthma and wheezing are more prevalent in young boys compared with young girls [14], but this trend disappears during puberty [28]. In a study of 16 countries, it was reported that girls had a lower risk of developing asthma than did boys during childhood, this risk was equal at puberty, and reversed in young adults [29]. Women older than 20 years have both a higher prevalence and higher morbidity rates from asthma, and are more likely to present to hospital and be admitted for treatment [30,31]. They also have more severe disease and higher mortality rates [32]. The reason for this disparity is unclear but genetic and hormonal factors are likely to contribute.

As well as clear gender differences, there are also racial differences in the prevalence of asthma. In the USA, morbidity from asthma has been consistently shown to be greater in children of African American descent (for example, 13.4% of African American children and 9.7% of white children [33]). Furthermore, children of African American descent are reported to have asthma which imposes a greater limitation on activity, with more hospital admissions but fewer family physician visits when compared to white children [34]. Data also suggest that asthma-associated mortality in children of African American and Puerto Rican descent is higher than in any other group [35].

Socioeconomic forces also appear to be important in asthma, and studies suggest that asthma severity is increased in poorer communities [36]. This may reflect environmental factors such as exposure to smoke and occupational hazards, as well as health care utilization.

11. The natural history of asthma

Most models of chronic disease suggest there is a common natural history to all diseases, which begin with a prodromal stage, prior to disease presentation.

This pre-illness period is defined as the period when subjects are free of overt disease but who have the susceptibility for the development of the condition (such as a genetic predisposition towards disease). During this phase, disease development is not inevitable and identifying individuals at risk provides an opportunity to prevent disease emergence. The disease manifests itself only after exposure to necessary environmental triggers (epigenetics). Following disease emergence, the condition can progress unabated (the natural course of the disease), or disease-modifying strategies can be employed to protect or reduce disease presentation, or to affect a cure. See figure 2 for a diagrammatic representation of this.

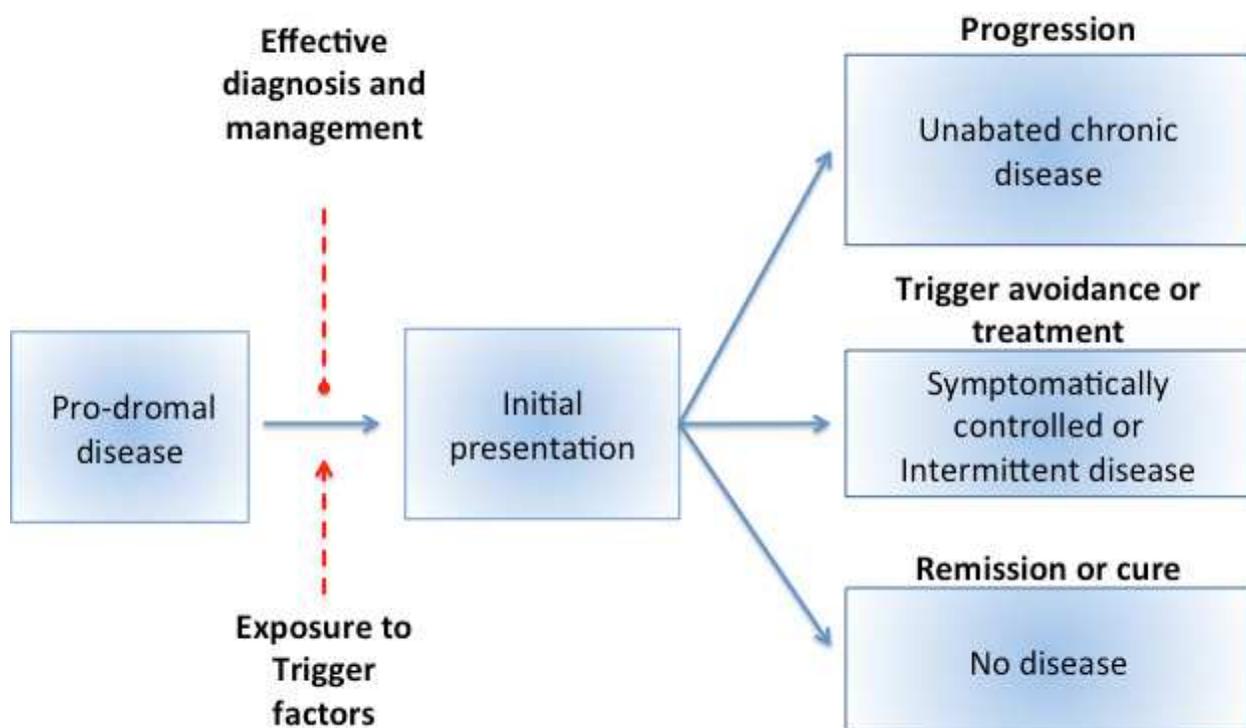


Fig. 2. A hypothetical representation of the course of a chronic disease (adapted from [37]).

The prodromal stage equates to disease predisposition before the advent of triggers which cause disease manifestation. Following exposure, the disease presents, but this could theoretically be avoided if disease predisposition were known and exposure avoided. Following presentation, the disease can progress, or could be controlled or cured by appropriate management (treatment or exposure avoidance). Presently asthma is not curable using existing therapeutic strategies and while there is a need to expand treatment regimes, there is also great interest in identifying asthma susceptibility factors, which would allow patients to be diagnosed in the prodromal phase of asthma, before the advent of symptoms. This is likely to involve studies of genetic and environmental factors.

12. The genetics of asthma

There is great interest in understanding the natural course of asthma. Asthma is a heterogenous condition and there remains some controversy as to whether asthma is a single disease entity or whether it represents a common label for a number of disease phenotypes. A disease phenotype represents a set of characteristics that are important in terms of disease progression or prognosis and it is increasingly apparent that specific cohorts of asthma patients experience different presentations of disease and warrant different treatment strategies. Specific disease phenotypes may also experience different prognoses.

There are now numerous studies of the pattern of inheritance of asthma [38], rhinitis [39], allergic dermatitis [40], and serum IgE levels [41] and these have clearly shown that the familial concordance is partly due to shared genes. There are several loci that may be involved in the pathogenesis of allergy and asthma (see Table 4). In common with other complex diseases, independent investigators have not been able to reproduce many of these results. There are several explanations for this including genetic heterogeneity between populations, differences in phenotype definition, and lack of a consensus over the appropriate significance levels to use in these studies. A number of candidate linked have been repetitively associated with the presence of asthma or asthma severity and have a plausible biological role in the development of the disease.

Candidate Genes

Interleukin 4	B ₂ adrenergic receptor
Tumour Necrosis Factor α	Intereukin -4 receptor a
HLA,	N-Acetyltransferase
α_1 -antitrypsin	Angiotensin-converting enzyme
Interleukins 5, 9, and 13,	Glucocorticoid receptor,
CD14	Clara cell protein 16,
Transporter antigen peptide 1,	Interleukin 9 receptor,
Immunoglobulin heavy chain genes,	T cell antigen receptor ,
T cell antigen receptor	
β Subunit of the high-affinity IgE receptor	

Table 4. Candidate Genes in Allergy and Asthma

On chromosome 6p21, there is an important region that contains the genes for the major histocompatibility (MHC) molecules as well as the tumor necrosis factor α (TNF- α) and lymphotoxin genes. This area of chromosome 6 has been repeatedly identified in linkage and association studies. Most of the data concerns the association of specific MHC genotypes with sensitization to specific aeroallergens [42]. On chromosome 5q there are many candidate genes for asthma and allergy such as the interleukin 4 and β_2 -adrenergic receptor genes both of which have been associated with asthma [43]. Chromosome 11q13 has been linked to a variety of different phenotypes and the β chain of the high-affinity IgE receptor has been proposed as a candidate for this linkage [44]. The region containing the interleukin 4 receptor α chain (16p12) has also been implicated in IgE responsiveness [45].

It is hypothesized that polymorphisms within these candidate gene alter pro-inflammatory protein expression and cellular functions to cause a predisposition towards asthma or alterations in responses to treatment (especially in the case of β_2 adrenergic and glucocorticoid receptors). In most cases the functional consequences of genetic variation have not been assessed, and these remain associations only, but there is great interest in characterizing predispositions further in order to modify risk.

13. Asthma phenotypes and progression

There have been longitudinal studies that have addressed how asthma progresses and these have begun to explore the effect of disease phenotype on outcome [46-48].

14. Asthma phenotypes with age

14.1 Early childhood

Longitudinal studies have consistently confirmed that most cases of chronic, persistent asthma start in early childhood, with the initial presentation occurring during the first 5 years of life [15,46,48]. There are some methodological concerns with these studies, as most ask parents to document or recall recurrent symptoms of wheeze or cough. These can represent recurrent viral infections and only a small proportion of these children will go on to develop persistent asthma [49], however the association between childhood symptoms and persistent asthma later in life appears robust.

Further work has tried to understand which children are most at risk of developing asthma. The vast majority of infants who become wheezy during infections do not go on to develop asthma. Most of these infants (representing two thirds of cases of wheeze) have one or two episodes of wheeze before the age of two, but these do not recur after this age and this presentation is termed "Transient wheezing of infancy" [50]. Studies suggest that the most important risk factors for transient wheezing in infancy are exposure to respiratory viruses (especially RSV) [49], maternal smoking in pregnancy and lower lung function values [51,52]. Remission is thought to occur due to growth of the airways and lung parenchyma [53] but currently there is no evidence that any particular active intervention reduces progression to asthma although bronchodilators improve both symptoms and lung function measurements, suggesting disease is related to bronchomotor tone. Sensitisation to aeroallergens is associated with a risk of chronic asthma in later life, but interestingly,

symptoms seem to start 2 – 3 years later than in those whose asthma is not associated with atopy [54]. Furthermore, treating this sensitization is associated with a reduction in the development of asthma [55].

14.2 Adolescent to adulthood

Birth cohort studies suggest that over 60% of children who are frequently wheezy or who have a physician diagnosis of asthma go on to experience asthma-like symptoms as an adolescent [56]. Chronic asthma symptoms that persistent into adolescence and early adulthood are associated with both sensitization to allergens and elevated levels of circulating IgE [57]. Different allergens appear important in different geographical regions, for example in desert regions the mould *Alternaria* is associated with asthma [58], while in more temperate and coastal regions, house dust mite is the more likely relevant sensitizing agent [59]. The ability to detect the allergen most closely associated with disease varies according to region, and there are likely to be more unidentified allergens that are associated with disease.

Identifying the exact allergen responsible in each patient may be less important than characterizing the inflammatory reaction present. The key features of asthma including symptoms, disordered airway function, airway inflammation, exacerbations and the decline in lung function, are not closely related to each other within patients and might have different drivers. There is no clear causal link between eosinophilic airway inflammation and airway hyper-responsiveness [60] and infiltration of airway smooth muscle by mast cells may be more relevant [61]. In contrast, asthma exacerbations are more closely related to eosinophilic airway inflammation[60]

15. Asthma remission or progression

Large, long term population based prospective studies have tried to identify factors that predict who will progress and experience persistent, severe asthma, and who will remit [62-64].

In all studies, severity and frequency of symptoms in early childhood predict outcomes in adulthood. Those that experience mild and infrequent symptoms in early life go on to experience no or mild asthma-related symptoms. Those with the most severe symptoms have persistent severe asthma in later life. In one population based study, 52% of children (aged 10) with asthma and 72% of children with severe asthma had frequent or persistent wheeze age 42 [65].

The majority of patients with persistent asthma in later life demonstrated evidence of an allergic predisposition (with allergic rhinitis or eczema in childhood) [47].

Deficits in lung volumes during childhood are also consistently associated with persistent asthma in adulthood [65]. The presence of abnormal lung function in childhood is a predictor of asthma and children who wheeze or who have a diagnosis of asthma, who then go on to have persistent asthma in adulthood have reductions in FEV₁ and FEV₁/ FVC ratio compared with controls throughout life. Interestingly, the slope of decline over time does not alter between wheezers and controls in this group [47], suggesting that developmental

factors are important in asthma sustainment in this group, but that these factors do not contribute to accelerated decline in lung function in later life.

In contrast to this, when asthma symptoms occur in later life (aged over 25 years), they are associated both with moderate deficits in FEV₁ and FEV₁/FVC in early adulthood and a faster decline in lung function in subsequent years [53]. This, combined with studies of inflammation [66], suggest that in this group, developmental factors combined with epigenetic influences such as inflammatory polymorphisms or environmental stimuli, lead to progressive disease. Airway hyper-responsiveness appears to be an important component of this, and has been consistently associated with progression to adult asthma in a number of studies [47,56].

Less is known about factors that cause the re-emergence of asthma following a period of remission in early adulthood. There is evidence that remission may be a clinical phenomena rather than a true abatement of disease, as it is not associated with a loss of inflammation or bronchial hyper-responsiveness. Indeed, eosinophil counts, exhaled nitric oxide and concentrations of IL-5 remain higher in asthma patients with no symptoms who are off treatment than sex and age-matched controls [67]. It might be that environmental and genetic factors combine in these patients so that their burden of inflammation crosses a symptomatic threshold, leading to disease re-emergence, but there are no studies that explore this hypothesis.

16. Conclusion

Asthma is a common, chronic inflammatory lung condition associated with variable airflow obstruction and symptoms of breathlessness, cough and wheeze. Age of onset, severity and clinical course varies between patient groups, and these clinical phenotypes are likely to reflect differences in the genetic, developmental and environmental factors which predispose to disease and trigger symptoms. Currently, these factors are not well understood, but they are likely to be vital in determining which patients go on to experience worsening disease outcomes and which patients respond to certain treatment regimes.

The continued presence of inflammation even in quiescent disease suggests that current treatment strategies are not treating the drivers of disease, but instead are modifying disease-related symptoms by transiently reducing inflammation. As effective as current treatments are for the majority of patients, more research is needed to determine the causes of asthma in different patient populations.

Understanding the epigenetics of asthma will allow for new treatment strategies, where specific medications are targeted to specific cohorts of patients based upon their inflammatory make-up and disease presentation.

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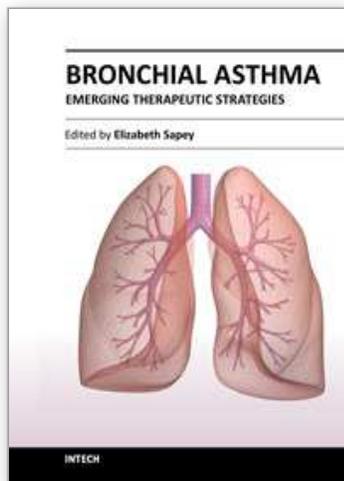
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Bronchial Asthma - Emerging Therapeutic Strategies

Edited by Dr. Elizabeth Sapey

ISBN 978-953-51-0140-6

Hard cover, 260 pages

Publisher InTech

Published online 29, February, 2012

Published in print edition February, 2012

Asthma remains a serious health concern for millions of people globally. Despite continuing research interest, there have been few advancements that impact clinically on patient care, potentially because asthma has been treated as a homogeneous entity, rather than the heterogeneous condition it is. This book introduces cutting-edge research, which targets specific phenotypes of asthma, highlighting the differences that are present within this disease, and the varying approaches that are utilized to understand it.

How to reference

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Elizabeth Sapey and Duncan Wilson (2012). The Natural History of Asthma, *Bronchial Asthma - Emerging Therapeutic Strategies*, Dr. Elizabeth Sapey (Ed.), ISBN: 978-953-51-0140-6, InTech, Available from: <http://www.intechopen.com/books/bronchial-asthma-emerging-therapeutic-strategies/the-natural-history-of-asthma>

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