Section A -Research paper

Bronchial asthma: What is new?

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Abstract:

Asthma is a heterogeneous clinical syndrome primarily affecting the lower respiratory tract, characterized by episodic or persistent symptoms of wheezing, dyspnea, and cough. The diagnosis of asthma requires these symptoms and demonstration of reversible airway obstruction using spirometry. Identifying clinically important allergen sensitivities is useful. Inhaled short-acting β_2-agonists provide rapid relief of acute symptoms, but maintenance with daily inhaled corticosteroids is the standard of care for persistent asthma. Combination therapy, including inhaled corticosteroids and long-acting β_2-agonists, is effective in patients for whom inhaled corticosteroids alone are insufficient. The use of inhaled long-acting β_2-agonists alone is not appropriate. Other controller approaches include long-acting muscarinic antagonists (eg, tiotropium), and biological agents directed against proteins involved in the pathogenesis of asthma (eg, omalizumab, mepolizumab, reslizumab).

Keywords: Bronchial asthma, management**,** inflammatory**.**

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Introduction

Bronchial asthma is a chronic inflammatory disease of the respiratory passages, occurring with the participation of mast cells, eosinophils and T-lymphocytes, the release of a large number of inflammatory mediators. Inflammation of the respiratory passages causes their hyperreactivity, bronchial obstruction, and respiratory symptoms **(1).** Airway obstruction in bronchial asthma is mainly caused by the following four mechanisms: i) contraction of bronchial smooth muscle; ii) edema of the airway walls; iii) mucous plugging of the bronchioles; iv) irreversible changes in the lungs ("remodeling") **(2).**

Asthma is a chronic inflammatory disease of the airways leading to cough, wheeze, shortness of breath, and chest tightness. Asthma symptoms are driven by the inflammation of the airways, which triggers processes such as mucus

production, remodeling of the airway wall, and bronchial hyperresponsiveness (BHR), which is the tendency of smooth muscle cells to react to nonspecific stimuli such as cold air. Asthma often starts at a young age (childhood-onset asthma), but some patients can develop asthma later in life (late-onset asthma) **(3)**.

Epidemiology:

Asthma is a common medical condition that affects 300 million people worldwide and 25 million people in United States with that number expected to rise. It is considered as one of the costlier chronic condition, with an estimated 15 million daily-adjusted life years (DALYs) lost annually and results in one of every 250 deaths worldwide. The survey on disease is defined as current episodes of wheezing or a physician's diagnosis shows that asthma usually affects 5-16% of the people worldwide. The rate of disease varies in different countries depending upon the diagnostic standards **(4).**

The documented increase in asthma in last 25 years is due to the changes in our lifestyle and environment as genetic changes take place in years. As asthma rates are increasing almost 50% every decade, it is found to be the third leading cause of death by 2020 according to World Health Organization (WHO). The rates of asthma are higher among developed countries most of the people acquire them before 10 years of age while others acquire by the age of 30 **(5)**.

In Egypt, the bronchial asthma is a significant health problem among school children, and the prevalence was 7.7% **(6).** It was reported that asthma prevalence was 4.8% in Egyptian infants and children aged less than 4 years, from five governorates. Studies from Egypt reported that prevalence of asthma is 9.4% in 11–15-year-old school in Cairo and 8.2% was reported in another study of children with age of 3–15 years (**7**).

Table 1: prevalence of asthma in different countries (4)

Country	Prevalence/1000
Scotland	184
U.K.	153
New Zealand	151
Australia	147
Canada	141
U.S.A.	130
Brazil	114
Pakistan	108
Turkey	74
France	68
Japan	67
Thailand	65
Germany	63
Iran	55
Nigeria	54
Malaysia	48
Italy	45
India	24
Russia	22
China	21
Macau	07

Types of Asthma:

Asthma is generally categorized by the major stimuli that provoke an acute episode rather than precise etiological

factors. It is divided into five main groups such as allergic asthma, nonallergic asthma, occupational asthma, aspirin induced asthma and asthma of infancy as described in the following section **(8)**.

Extrinsic asthma/ Allergic asthma/ Atopic asthma

It is a main type of asthma in individuals aged 5-30 years. It is a state of disordered immunity in which predominant T-helper lymphocyte type 2 (TH2) immune mechanisms drive production of IgE takes place on exposure to common environmental antigens or allergens (e.g the house dust mite (HDM) (Dermatophagoides pteronyssinus) **(8)**.

Intrinsic asthma/ Idiopathic asthma/ Non-allergic asthma/ Infective asthma

It shows prominent eosinophilic mucosal inflammation, but no external inciter is recognized. It usually develops in adults older than age 35 years. Different environmental situations like cold, humidity, pollution, stress, irritants such as smoke or viral infections (cold, flu and sinus infections) are responsible for causing intrinsic asthma **(8)**.

Occupational asthma

It is caused by exposure to natural allergens in the workplace or by exposure to highly reactive chemicals such as isocyanates and acid anhydrides, which modify intrinsic proteins in the bronchial airway to produce novel targets for immune response.

Aspirin-induced asthma

It is a metabolic disorder in which individuals with variant arachidonic acid/leukotriene metabolism suffers from acute asthma attacks on the first and subsequent exposure to aspirin and other non-steroidal anti-inflammatory drugs **(8)**.

Asthma of infancy (Wheezy bronchitis)

It occurs in an infant of less than two years of age. It exhibits recurring sessions of significant airflow obstructions in the small airways may result from viral infections. This syndrome often remits as the child gets older (Figure 1) **(8)**.

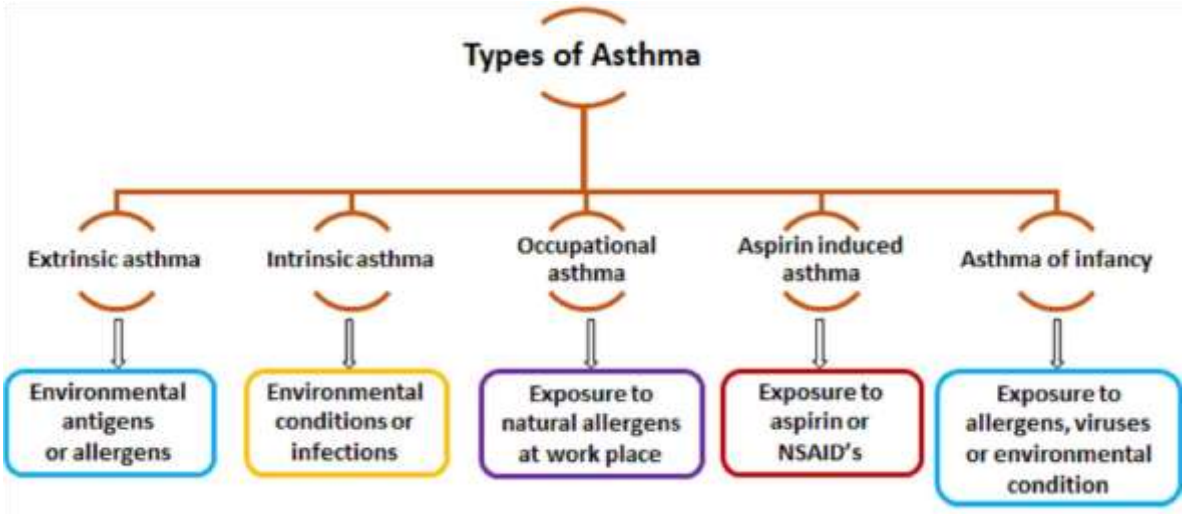

Figure 1: Types of asthma and its triggering factor (8)

Phenotypic classification of asthma

Asthma is not a specific disorder but a set of common features share clinical artifacts. The word phenotype refers to the measurable traits of a person or community that arise from its genotype association with its environment. Phenotypes indicate that asthma is heterogeneous. Asthma arises through diverse combinations between environmental factors and inherent hereditary dispositions, leading to heterogeneity. Clinical symptoms, disease pattern, pulmonary activity, causes or comorbidity identify phenotypes. Variability is noted in the onset period, allergy versus no allergies, inflammatory behaviors and response to treatment. Two major phenotypes of asthma have been recognized such as Type 2 hi (T2-hi) and Type 2 lo (T2-lo) (Figure 2) **(8)**.

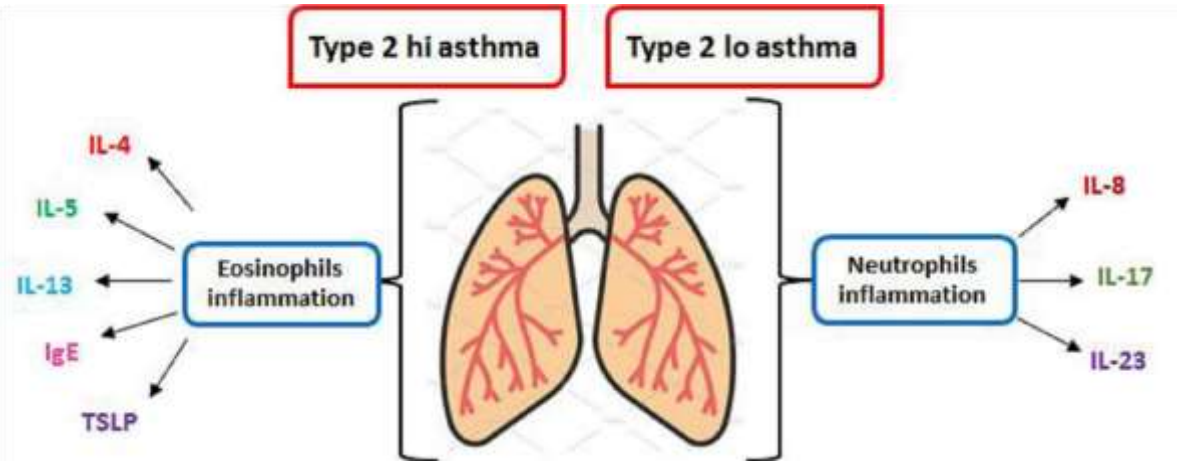

Figure 2: Phenotypic classification of asthma and mediators released (8)

Type 2 hi asthma

It is described by the inflammation of eosinophils. In the eosinophilic pathway, airway epithelial cells and inflammatory cells(T-helper type 2 cells (Th2), mast cells, type 2 innate lymphoid cells (ILC2s)) causes a release of cytokines and inflammatory mediators like IL-4, IL-5, IL-13, IgE and thymic stromal lymphopoietin (TSLP) that is responsible for inducing inflammation of airways **(9)**. Numerous biomarkers such as periostin, high levels of eosinophils in blood and sputum, fractional exhaled nitric oxide and dipeptidyl peptidase-4 were identified in the asthma patients that link with a Th2 inflammatory response. These abovementioned biomarkers give the response to corticosteroids and T2 blockers treatments in asthma patients **(10).**

Type 2 lo asthma (Th1-high or Th1/ Th7-high)

It is described by the inflammation of neutrophils.The neutrophilic pathway releases important cytokines (IL-8, IL-17 and IL-23) that plays main role in neutrophil growth, differentiation and chemotaxis.

Corticosteroid treatment was found to be less effective in T2-lo asthma **(11).**

Pathophysiology of Asthma:

Cells and Cytokines:

Bronchial Asthma (BA) is a typical allergic disease and the mechanism involved

is being searched widely. The previous studies concluded that asthma is T-helper-type-2 (Th2)-cell dependent IgE mediated allergic disease as most of asthmatics are sensitive to aeroallergens. The characterization of pathological basis of asthma includes mucus cell hyperplasia and infiltration of inflammatory cells that includes CD4+ T cells, eosinophils and mast cells. The classical model of asthma is a complex web of cells and the cell signaling molecules interact with each other to elicit an inflammatory response. The Allergen/Antigen presentation by antigen presenting cells (APC) to T-helper-type-0 cells (Th0) leads to the differentiation of Th2 cells. The antigen stimulation results in the production of thymic stromal lymphopoietin (TSLP) in the epithelial cells of airways **(4)**.

TSLP acts upon its receptors (TSLPR) which are expressed by dendritic cells (DCs) and promotes the transcription of OX-40L, a member of TNF (Tumor Necrosis Factor) family of cytokines. OX-40L by the help of activated DCs induces expression of Th2 cytokines resulting in differentiation of inflammatory Th2 cells. The inflammatory Th2 cells then produce various types of cytokines as IL-4, IL-5 and IL-13. These cytokines activate B-cells resulting in the synthesis and release of immunoglobulin IgE **(12).**

The inhaled allergens bind to the receptors present on the surface of mast cells where IgE also binds to release various inflammatory mediators such as histamine, prostaglandin and leukotrienes by degranulation. These chemical inflammatory mediators acts as cell signaling molecules to induce bronchoconstriction of smooth muscles, airway obstruction and further propagates the inflammatory response (**Fig. 3**). **(4)**

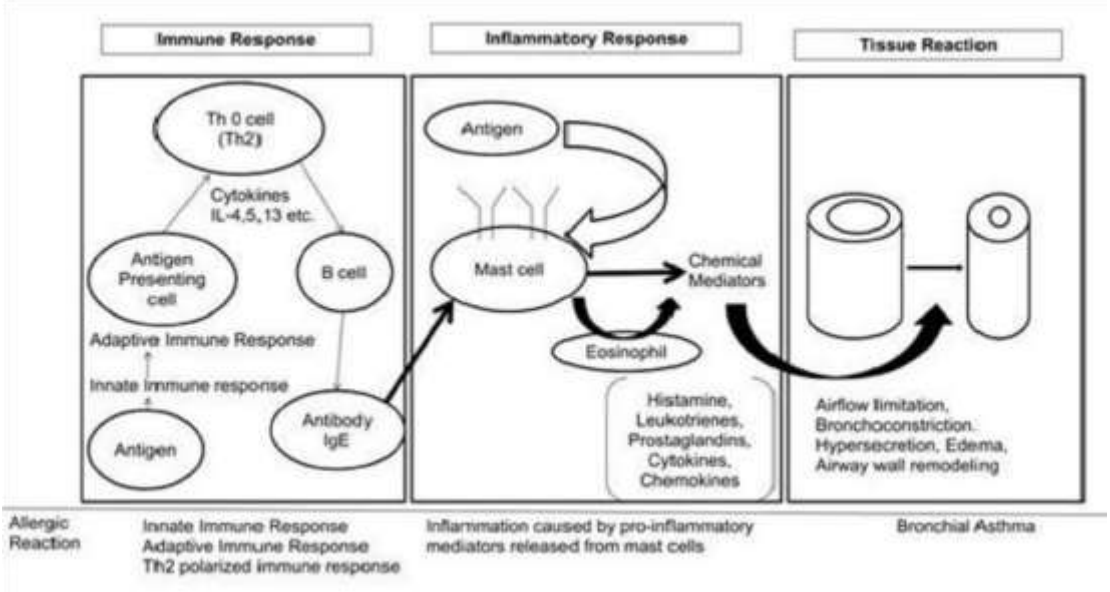

Fig. 3: Process of Allergic Asthma (4)

Th2 lymphocytes also produce another class of cytokines, IL-9 which also stimulates the proliferation of mast cells in airways and IL-5 which is associated with the survival of eosinophils. Eosinophils also participate in the inflammatory process by releasing the inflammatory chemical mediators like Leukotrienes and Reactive

Oxygen Species (ROS) resulting in bronchoconstriction, mucous secretion and structural damage to airways. The patients with Th2 cytokines and eosinophil predominantasthma responds well to Inhaled Corticosteroids (ICS).The ones with high eosinophil-predominance are responsive to treatment with anti-IL-5 antibody **(13)**.

Along with Th2 cytokines and eosinophils, asthma is also related to neutrophil-predominant Th17 associated disease as Th17 and it is associated IL-17 cytokines also play significant role in airway inflammation. The presentation of antigen presenting cells (APC) by IL-23 results in the differentiation of Th17 cytokines. The expression of IL-17 by Th17 cells augments *in vitro* glucocorticoid beta (GR-β) expression by epithelial cells of airways. GR-β acts by the competitive inhibition of GR-α mediated anti-inflammatory gene transcription at glucocorticoid response element (GRE) **(14).**

IL-17 helps in the recruitment of neutrophils by releasing IL-8 from epithelial cells of airways and is also an activator of endothelial cells to promote transmigration of neutrophils at the site of inflammation. Airway neutrophils produces various lipid mediators like elastase, leukotriene-B4 and matrix metalloproteinase-9 (MMP-9) and platelet activating factors (PAF), all of which further propagates the process of inflammation and also recruits eosinophils **(15)**.

Airway epithelial cells also release IL-5 and a stem cell factor (SCF), a cytokine supporting the survival of mast cell within airways, and a macrophage chemo-attractant protein-1 (MCP-1). MCP-1 also recruits alveolar macrophages thus enhancing the inflammatory process. On binding of allergen to IgE receptors, these macrophages release certain cytokines such as IL-1β, TNF-α and IL-6 and elastase (degrade elastin in airway extracellular matrix) and metalloproteinase. These cytokines further act on epithelial cells and releases Granulocyte-macrophage colonystimulating factor (GM-CSF), IL-8 and regulated on activation, normal T cells expressed and secreted (RANTES). GM-CSF and RANTES recruits eosinophils and promote their survival in airways **(16)**.

One more type of immune regulatory myeloid derived cells also play a role as regulators of allergic inflammation. During inflammation, the oxidative stress regulates expansion, activation, recruitment and function of these myeloid cells. The differential regulation by NO (nitric oxide) produces immature myeloid cells which gives their contribution in the balance of immune suppression and exacerbation of the hyperresponsiveness of airways (**Fig. 4**) **(4)**.

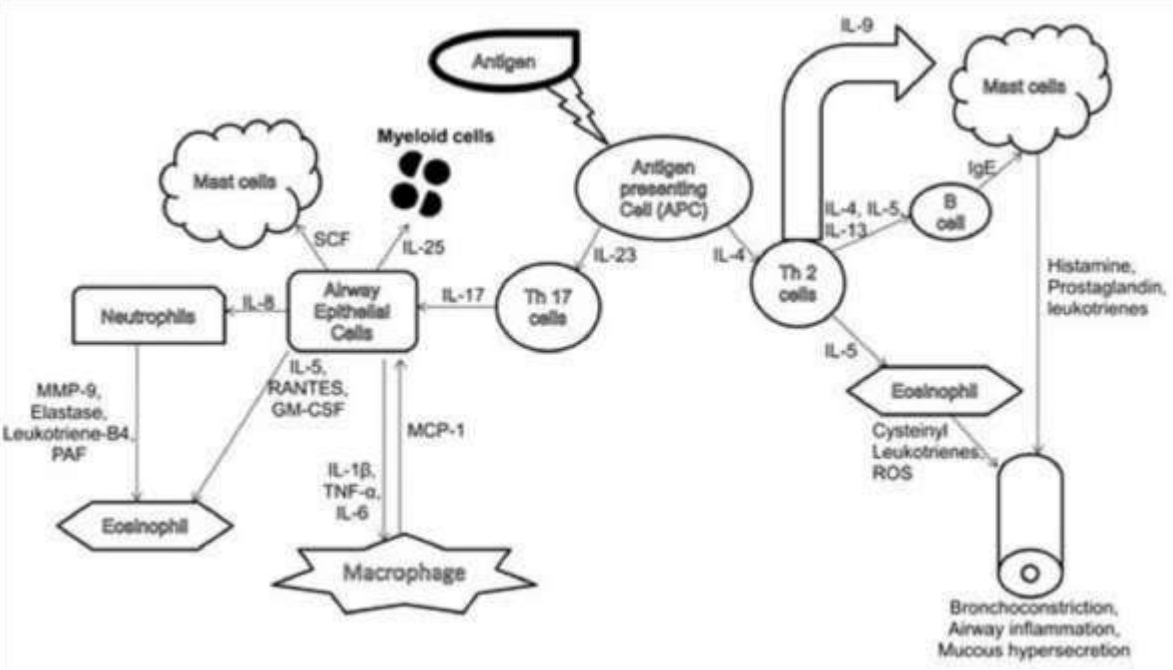

Fig. 4: Pathogenesis of Asthma (4) Airway Remodeling:

Inflammation results into a number of structural changes in airways including the thickening of basement membrane, subepithelial fibrosis, metaplasia of goblet cells, neovascularization and increased smooth muscle mass of airways. All asthmatic patients experience serious effects on the structure and function of airways, regardless of the duration of disease. Airway remodeling is usually associated with an irreversible decrease in forced expiratory volume (FEV1), increase in the hyper-responsiveness of airways, increase in the thickness of basement membrane of airways and loss of bronchodilator reversibility. Furthermore, all these structural changes in the airways of asthmatics help in the development and progression of disease. It is unclear whether the inflammation precedes or coexists with airway remodeling but remodeling can occur early in the disease even in the absence of inflammation. There is a direct relationship between mechanical stress and airway remodeling in asthma **(17)**.

Risk factors

Despite therapeutic advances, the continued rise in asthma prevalence suggests that the fundamental causes of asthma are yet poorly understood. According to prevalence data, the study of risk factors and protective relationships in asthma has proven difficult due to the myriad of related factors. Of note, there is an extensive degree of overlap between risk factors for childhood and adult onset asthma **(18)**.

Risk factors of childhood onset asthma

Recognition of the so called “asthma epidemic” has led to the initiation of over 150 birth cohorts on asthma around the world in the past three decades and data gathered has significantly elucidated origins

of childhood asthma. International collaborations have been implemented in recent years to better understand information from these birth cohorts, however, this has been hampered by differences in definition and methodology **(19).**

In view of the distinct predilection of the inner-city population for development of pediatric asthma, the Inner-City Asthma Network Program was established almost three decades ago to improve outcomes for these high-risk children in urban environments. While a wide breadth of variables influence disease, the two most significant drivers of asthma development were allergic sensitization and tobacco smoke exposure in a causal network analysis of an inner-city asthma cohort **(20)**.

The risk factors include:-

1. Genetics

A strong genetic basis for asthma has long been established. In monozygotic twins, asthma concordance is approximately 50%. Genomewide association studies (GWAS) in large pediatric and adult cohorts have identified significant asthma related single nucleotide polymorphisms (SNPs) that have been replicated across studies. These results have underscored the importance of genetic variants in genes recognized as contributory to asthma such as HLA-DQ, SMAD3, TSLP, IL1RL1/IL18R1, and IL33. Yet, the individual contributions of these genetic variants is generally modest (odds ratios ~1.2) even for the most replicated loci. The combined risk for all these genetic variants is estimated to predict ~10% of asthma heritability and prevalence**(21)**.

2. Indoor allergen exposure

The relationship between sensitization to inhalant allergens and onset of asthma is also well-recognized. A significantly increased risk of asthma occurs with aeroallergen sensitization at less than five years of age. Indoor allergens including house dust mite, mice, cockroach, animal dander, and fungi are of especial interest due to the possibility of intervention during childhood **(22**).

3. Microbiome exposures

The hygiene hypothesis implicates our microbial environment in early life as integral to immune development, and protective against atopy and asthma. In the past decade, several studies have investigated the protective effects of being raised on a farm as opposed to rural communities or cities. These studies on farm life have provided a compelling argument in support of the hygiene theory. Microbial exposures from living in proximity with domestic animals in early life appear to afford protection against development of atopic asthma **(18)**. The generally accepted hypothesis is that the microbial diversity of the farm environment triggers protective immune responses. Gender also appears to influence the impact of exposure with lower cumulative incidence of asthma in girls raised on a farm as compared to boys **(23).**

4. Respiratory viruses

Respiratory viruses influence subsequent wheeze and asthma acting either independently or in conjunction with atopy. Respiratory syncytial virus (RSV) and human rhinovirus (HRV) are the most common respiratory viruses associated with wheeze in early childhood. Influenza has

also been associated with exacerbation of ongoing disease **(24)**.

HRV triggered wheeze appears to confer particular predilection for future atopic asthma comparable with the risk associated with allergen sensitization when followed up at ages 7 and 13 in the Childhood Origins of Asthma (COAST) study **(25)**. However, RSV triggered wheezing in the first three years of life was not associated with a similar risk of future asthma at 13 years in one study **(22).**

5. Air pollution

Epidemiologic studies of air pollution and asthma have identified increased risk of both exacerbation of lung disease with acute exposure as well as development and/or impairment of asthma with chronic exposure to ambient air pollutants. Various pollutants have been incriminated including ozone, nitrogen dioxide (NO2), particulate matter (PM) and others, even at levels less than the current National Ambient Air Quality Standards. Living in specific locations with especially poor air quality such as near a highway confers a higher exposure risk. Genetics also factor into determining susceptibility to air pollution, the most well-known being glutathione-Stransferase polymorphisms that are involved in antioxidant defenses **(18)**.

Global climate change is also responsible for altered exposure to aeroallergens. Global warming has been incriminated in increasing the duration and intensity of the pollen season **(26)**. Pollutants also enhance early and delayed-phase responses to various allergens, and contribute to disease development through augmentation of primary sensitization to allergens. This increased exposure to allergens combined with pollutants acts synergistically to enhance the allergic response. Data from the National Allergen Bureau has shown significant recent increases in annual pollen exposures, which has been linked with pollutant induced production of plant-based pathogenic allergens. There is also accumulating evidence about the possible effects of diesel exhaust particles, not just as a direct lung irritant but in relation to sensitization **(18)**.

Adult onset asthma

As opposed to pediatric asthma, there is a conspicuous absence of longitudinal studies on the adult side that track disease course from early adulthood for an adequate duration. However, there are well recognized risk factors for disease onset as well as exacerbation **(18)**.

1. Smoking

It is clear that asthmatics who smoke have significantly increased morbidity and mortality than non-smokers. Continued smoking itself predisposes to developing asthma with an odds ratio of 2.0–2.6 and has been linked with accelerated loss of lung function over time in adult onset asthma **(27)**. The prevalence of active smoking in adult asthmatics from low- and middle-income countries is 25% placing them at particularly increased risk of severe symptoms and reduced response to steroid therapy **(28).**

The increased use of e-cigarettes has prompted investigation of their deleterious effects and recent data demonstrates that chronic use alters the bronchial epithelial proteome of the human airway **(29)**. Similarly, smoking e-cigarettes during pregnancy has equivalent risk to conventional cigarettes for asthma

development. Thus, cessation of all forms of smoking is essential to the management of asthmatics **(30).**

2. Obesity

Obesity increases the risk for late onset asthma in both men and women by approximately 50%, especially in non-allergic individuals with a more pronounced effect in females. Obese asthmatics are known to have worse asthma control and increased rates of healthcare utilization due to asthma **(31).**

There appears to be a gender bias in the interaction of obesity with asthma, which may be due to sex hormones or other gender-specific factors, such as inherent collapsibility of the distal airways in non-allergic obese females with adult-onset asthma **(32)**. This gender dimorphism is apparent from early childhood, where asthma has been linked with obesity only in young girls and not in boys. Several hypotheses have been postulated to explain the obesityasthma.relationship, such as oxidative stress and mechanical effects of obesity on the respiratory system **(31)**. Increased airway oxidative stress has been found especially in obese adults with late onset disease. The deficiency of dietary antioxidants further increases susceptibility to oxidative lung damage. Abdominal and mediastinal fat accumulation can alter respiratory mechanics, thus changing lung physiology and function**(18)**.

3. Occupational exposures

Approximately 10–25% of adult-onset asthma is estimated to drive from work related exposures that may be sensitizers or irritants in nature. Occupational asthma (OA) may be caused by high molecular weight (HMW) proteins or low molecular weight (LMW) chemicals (eg. diisocyanates), which drive asthma via IgE and non-IgE mechanisms respectively. HMW factors from biological sources such as wheat allergens account for most cases of OA. In a recent review by Baur et al., exposure to laboratory animals was most robustly associated with development of OA. The acute exposure to high levels of irritants also cause asthma through non-immunologic inhalation injury. Most cases of OA require cessation of exposure, and even with avoidance does not warrant complete recovery **(33)**.

4. Sex hormones

As previously discussed, gender is known to be differently distributed between adult and pediatric populations. In the Epidemiology and Natural history of asthma: Outcomes and treatment Regimens (TENOR) severe asthma cohort, 71% of adult patients were women in contrast with 34% of children. This parallels the observations of **(34)** who noted a shift from male to female predominance of severe asthma post-adolescence **(34)**. Although boys have increased onset of atopic asthma compared to girls during early childhood, there is a recognized switch in asthma prevalence from males to females that coincides with the onset of puberty. The Childhood Asthma Management Program (CAMP) study showed an increase in asthma symptoms parallel with the Tanner stages of puberty in girls **(35)**. While the precise role for sex hormones in regulating asthma is not completely understood, overall ovarian hormones enhance and testosterone dampens airway inflammation in asthma **(36).**

5. Stress events

The association of psychosocial stressors with asthma may reflect disproportionate exposure among those from lower socioeconomic classes and ethnic minorities. An accumulating body of evidence suggests a causal relationship between these stressors and asthma development as well as morbidity. Stress can modulate lung development, as well neuroendocrine and autonomic responses, and potentiate reactivity to allergens and infections. There also appear to be specific pathways through which stress influences epigenetic activity in asthma related cells. Pediatric studies have previously reproduced a causal link between stress events and asthma onset **(37)**. More observational studies have confirmed this association in adults. In a longitudinal cohort study of 327 adolescents without asthma at age 16, an increase in stressful life events as measured by a validated questionnaire was associated with a 4-fold higher incidence of new asthma onset between 18 and 29 years. Elucidation of these mechanisms may improve asthma outcomes particularly in ethnic minorities and the economically disadvantaged **(38)**.

Very late onset asthma

The age cutoff for the definition of very late-onset asthma varies but diagnosed as> 50 years in some papers and>65 years in others. The aging lung is associated with decreased lung function due to mechanical disadvantages and loss of elastic recoil. In addition to these consequences of normal aging, immunosenescence likely has important consequences in elderly asthmatics. Emerging data suggest that older asthmatics have increased sputum neutrophilia secondary to Th1 and Th17 inflammation **(39).**

Medication related asthma triggers

Beta blockers have the potential to cause acute bronchoconstriction in asthma on a dose dependent basis, the risk of which is mitigated to some degree by the use of cardioselective agents. Their use in asthmatics should thus be contingent upon a risk benefit analysis in individual patients using the lowest dose possible. While ACE-inhibitors by themselves do not potentiate asthma, their possible side effect of cough may be confused for asthmatic symptoms **(18).**

The burden of asthma

Asthma is primarily a chronic inflammatory disease that tends to present as a lifelong condition, with different severity degrees throughout the asthma patient's life. Described since Hippocrates, asthma affects people from all age groups and presents its peak incidence in childhood. Recent data from the general population showed that in children up to 5 years old, the overall asthma incidence rate was 23/1,000 children per year; this incidence rate decreased among youth aged 12–17 years old to 4,4/1,000/year. Adult females had 1.8 times greater asthma incidence than adult males (4.9/1000 vs. 2.8/1000, respectively) **(40)**.

Asthma is associated with a high disease burden. In children aged less than 5 years old and as well as in the mid-childhood ages, 5–14 years old there is a high prevalence worldwide with a significant relevance and even in these age groups is consider as one of the top chronic conditions causing disability-adjusted life years (DALYs). There are striking global variations in the prevalence of asthma

symptoms in children, with an up to 13-fold difference between countries. Although asthma has a high burden in children, the relative importance of asthma impact increases with age and is particularly apparent in elderly, especially in women **(41)**.

Asthma can be deemed a significant public health problem, which often requires the use of emergency care, sometimes including hospital admission, and is responsible for a high number of missed school and/or work days; moreover, it can cause early permanent disability and premature death. In fact, asthma can be associated with significant limitations on physical, social and professional/student aspects of the life of those who suffer from this disease, namely when it is not controlled. Overall, asthmarelated costs are very high **(42)**.

Asthma as a global disease

Asthma has clearly shown to be a global disease, however in last two decades was defined as a real public health problem affecting countries from all over the world and population of all age groups. However, there are differences among countries, with rates significantly above the average, for example, in some native English-speaking countries (e.g.: UK, Australia and New Zealand) and, in contrast, much lower-than-average prevalence rates in some African and Asian countries. Consequently, it can be said that asthma, worldwide, is "globalized and affect all countries as a public health problem" **(40)**.

Asthma mortality

In the last decades, there was a significant reduction in asthmarelated mortality, while, with an aging population, chronic respiratory diseases are becoming a more prominent cause of disability. In fact, with the spread of new treatment guidelines, that emphasize the use of preventive anti-inflammatory drugs (e.g.: inhaled corticosteroids) to control the disease, mortality due to asthma has fallen substantially in most highincome areas; the USA is an exception, however, as no significant reduction on asthma mortality was seen in the last decades, especially in asthma patients with low-income. Both premature deaths and permanent disabilities are costly, especially for those countries where these situations are more common **(43)**.

Asthma co-morbidities

The most common co-morbidities related to asthma are rhinitis/rhinosinusitis, gastroesophageal reflux disease, sleep apnea, psychiatric diseases and cardiac diseases. It is estimated that more than 60% of asthmatics also have allergic rhinitis and that at least 10% have chronic sinusitis. The prevalence of other co-morbidities is lower, and it is estimated that together they do not exceed 20 to 30% in children and young adults. In elderly, however, co-morbidities are more frequent (>50%). The treatment and control of these co-morbidities, in many asthmatic patients, is essential to achieve asthma control, while keeping the focus exclusively on asthma symptoms might lead to persistent lack of disease control. The concurrent treatment of asthma and its co-morbidities increases the direct costs of treatment; however, the lack of asthma control associated with deficient treatment leads to frequent emergency visits and hospital admissions, mainly in elderly

people, and increases total costs of asthma management **(40)**.

Global asthma costs

Disease-related cost is usually classified into direct, indirect and intangible costs. The studies of the economic effect of asthma have been principally of 2 kinds: those using population-based sampling frames or administrative databases to provide cost estimates for entire regions or nations, and those using clinical-based sampling frames. The populationbased studies have greater generalizability, whereas the clinical based studies have greater diagnostic certainty and, frequently, data on disease severity that is particularly relevant to asthma costs. Direct cost include asthma management (e.g. visits to emergency services; hospital admissions; medications, including all types of medications, such as overthe counter and alternative medicines; outpatient visits, including all human resources involved, such as doctors, nurses, paramedics, psychologists…), complementary investigations or treatments (e.g. imaging, skin and blood tests, lung function tests, pulmonary rehabilitation…) and other costs (e.g. domestic or professional preventive measures, assistance in home care, transportation to medical visits…) **(40)**.

Indirect costs include work-related losses (e.g. temporary disability in terms of partial or total lost-days; early disability; permanent disability…) and early mortality. Finally, intangible costs are those related with unquantifiable losses, such as the decrease in quality of life, increases in pain or suffering, limitation of physical activities and job changes. These costs, unfortunately, are not yet systematically referenced in the literature on asthma costs **(44)**.

The relation between direct and indirect asthma costs is variable and depends on country and type of study. Most asthma studies performed in the last 2 decades showed that direct costs are higher than indirect costs. Usually, directs costs contribute to 50 to 80% of the total costs **(45)**.

Social impact

Socio-economic impact of a disease assessment focuses on evaluating the impacts development has on community social and economic well-being. Development impacts are generally evaluated in terms of changes in community resources, housing, employment and income, market effects, public services, and qualities of the community. Low-income populations, poor minorities and children living in inner cities, suffer a disproportionately higher morbidity and mortality because of asthma. In poor households, relatively small costs related with health promotion and disease control can be disastrous and assumed as catastrophic expenditures. In children, the increasing number of hospital admissions due to asthma attacks or exacerbations, namely those related with respiratory infections, is still high, both in USA and in Europe. These contribute to increasing direct costs in hospital and medication as well as indirect costs for missing working days. In schoolchildren, there will be lost school days, which lead to limitation on study performance, with consequent psychological effects in asthmatic children **(40).**

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