Brief Insight about Pediatric Bronchial asthma

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Abstract

Background: Asthma is a wide-reaching, chronic, inflammatory illness that impacts millions of people daily. It is frequently responsible for unscheduled healthcare usage, missed school, and workdays. It is an inappropriate immune response, much like an environmental allergy, to a triggering factor that induces bronchial hyperreactivity constriction with the remodeling of smooth muscle and increased mucous secretion into the airways. Asthma can severely limit the ability to engage in normal daily activities, including sports and outdoor activities. While asthma is a treatable disease, some of those treatments have side effects. For example, inhalers may cause hoarse voice, and inhaled corticosteroids may increase the risk for fungal infections. Oral steroids increase the chance of developing Cushing syndrome, including weight gain and metabolic dysfunction. However, poorly controlled asthma can lead to airway remodeling and chronic obstruction, increase the risk of obstructive sleep apnea, pneumonia, or gastroesophageal reflux. Medical management includes bronchodilators like beta-2 agonists and muscarinic antagonists (salbutamol and ipratropium bromide respectively) and anti-inflammatories such as inhaled steroids (usually beclometasone but steroids via any route will be helpful). There are five steps in the management of chronic asthma; treatment is started depending on the severity and then escalated or de-escalated depending on the response to treatment.

Keywords: Pediatrics, Bronchial asthma

Introduction

Asthma is a wide-reaching, chronic, inflammatory illness that impacts millions of people daily. It is frequently responsible for unscheduled healthcare usage, missed school, and workdays. It is an inappropriate immune response, much like an environmental allergy, to a triggering factor that induces bronchial hyperreactivity constriction with the remodeling of smooth muscle and increased mucous secretion into the airways.[1] Several classifications of medications are utilized to treat and manage chronic asthma to improve symptoms and reduce exacerbations. These include beta-2 agonist medicines, anticholinergics, low-dose inhaled corticosteroids, medium-dose inhaled corticosteroids, high-dose inhaled corticosteroids, inhaled long-acting beta agonists, leukotriene receptor antagonists, theophylline, cromolyn, zileuton, and newer class monoclonal antibody immune modulating drugs. Oral corticosteroids may be used in an acute setting of asthma exacerbations.

Epidemiology

Asthma is a common pathology, affecting around 15% to 20% of people in developed countries and around 2% to 4% in less developed countries. It is significantly more common in children. Up to 40% of children will have a wheeze at some point, which, if reversible by beta-2 agonists, is termed asthma,

5614

Eur. Chem. Bull. 2023,12(issue 1),5614-5628

regardless of lung function tests. Asthma is associated with exposure to tobacco smoke and inhaled particulates and is thus more common in groups with these environmental exposures.[7][8]

In childhood, asthma is more common in boys with a male to female ratio of 2:1 until puberty when the ratio becomes 1:1. After puberty, the prevalence of asthma is greater in females, and adult-onset cases after the age of 40 years are mostly females. Asthma prevalence is greater in extreme of ages due to airway responsiveness and lower levels of lung function.[9]

Of all the asthma cases, about 66% are diagnosed before the age of 18 years. almost 50% of children with asthma have a decrease in severity or disappearance of symptoms during early adulthood.[10]

Asthma is a globally significant non-communicable disease with major public health consequences for both children and adults, including high morbidity, and mortality in severe cases. asthma incidence and prevalence are higher in children, morbidity, and mortality are higher in adults. Childhood asthma is more common in boys while adult asthma is more common in women, and the reversal of this sex difference in prevalence occurs around puberty suggesting sex hormones may play a role in the etiology of asthma. The global epidemic of asthma that has been observed in both children and adults is still continuing, especially in low to middle income countries, although it has subsided in some developed countries. As a heterogeneous disease, distinct asthma phenotypes, and endotypes need to be adequately characterized to develop more accurate and meaningful definitions for use in research and clinical settings. This may be facilitated by new clustering techniques such as latent class analysis, and computational phenotyping methods are being developed to retrieve information from electronic health records using natural language processing (NLP) algorithms to assist in the early diagnosis of asthma. While some important environmental determinants that trigger asthma are well-established, more work is needed to define the role of environmental exposures in the development of asthma in both children and adults. There is increasing evidence that investigation into possible gene-by-environment and environment-by-environment interactions may help to better uncover the determinants of asthma. Therefore, there is an urgent need to further investigate the interrelationship between environmental and genetic determinants to identify high risk groups and key modifiable exposures. For children, asthma may impair airway development and reduce maximally attained lung function, and these lung function deficits may persist into adulthood without additional progressive loss. Adult asthma may accelerate lung function decline and increase the risk of fixed airflow obstruction, with the effect of early onset asthma being greater than late onset asthma. Therefore, in managing asthma, our focus going forward should be firmly on improving not only short-term symptoms, but also the long-term respiratory and other health outcomes. .[10]

In Egypt According to the latest WHO data published in 2018 Asthma Deaths in Egypt reached 5,823 or 1.05% of total deaths. The age adjusted Death Rate is 8.79 per 100,000 of population

Pathogenesis

There are two phases of an asthma exacerbation, which include the early phase and late phase. The early phase is initiated by IgE antibodies that are sensitized and released by plasma cells. These antibodies respond to certain triggers in the environment, such as the risk factors listed above. IgE antibodies then bind to high-affinity mast cells and basophils. When a pollutant or risk factor gets inhaled, the mast cells release cytokines and eventually de-granulate. Released from mast cells are histamine, prostaglandins, and leukotrienes. These cells, in turn, contract the smooth muscle and cause airway tightening.[12] Th2 lymphocytes play an integral role where they produce a series of interleukins (IL-4, IL-5, IL-13) and GM-CSF, which aid in communication with other cells and sustain inflammation. IL-3 and IL-5 help eosinophils and basophils survive. IL-13 attributes to remodeling, fibrosis, hyperplasia.[13] Within the next several hours, the late phase occurs, which eosinophils, basophils, neutrophils, and helper and memory T-cells all

5615

Eur. Chem. Bull. 2023,12(issue 1),5614-5628

localize to the lungs as well, which perform bronchoconstriction and cause inflammation. Mast cells also play an essential role in bringing the late phase reactants to the inflamed sites.[14] It is critical to recognize both of these two mechanisms to target therapy and relieve both bronchoconstriction and inflammation, depending on the severity of the disease. Interestingly, those with a thicker airway over time have a longer disease duration, due to a narrower airway.[15] As a result of inflammation and bronchoconstriction, there is an intermittent airflow obstruction, resulting in increased work of breathing.

Airway hyperresponsiveness is a crucial feature of asthma; this is an exaggerated bronchoconstrictor response, usually to different stimuli. There are a variety of mechanisms leading to airway hyperresponsiveness. Some explanations are due to increased histamine from mast cells or increase airway smooth muscle mass. Also, there is an increased vagal tone and increased intracellular free calcium that further enhances airway smooth muscle cell contractility.[15] To assess airway hyperresponsiveness, bronchial provocation tests are used to determine the severity.[16] This aspect is clinically significant because the presence of airway hyperresponsiveness is associated with a greater decline in lung function, and increased risk for the development and exacerbation of asthma from childhood to adulthood.[17] Therefore, targeted treatment can be employed early to combat asthma and hyperresponsiveness. All of these mechanisms together change the compliance of the lungs slightly to increase the work of breathing. In combination with inflammation, granular white blood cells, exudate, and mucous occupying the bronchiolar trees, it can be increasingly difficult for a person to breathe normally. The number of myofibroblasts, which give rise to collagen, will cause an increase in the epithelium, which narrows the smooth muscle layer and lamina reticulari.[18] As a result, there is an increased thickening of the basement membrane. A person can have irreversible obstruction of airflow, which is believed to be due to airway remodeling.[19]

Remodeling occurs by epithelial cells transitioning to mesenchymal, increasing the smooth muscle content. Epithelial cells lose their cell adhesion and functional polarity with tight junctions, reformatting their cells to develop into mesenchymal cells.[18] Additionally, eosinophils can further exacerbate airway remodeling due to its release of TGF-B and cytokines by interactions of mast cells. These mechanisms of airway remodeling may worsen inflammation and aggravate asthma over time if not treated and managed correctly.[15]

Clinical manifestations

Symptoms

The inflammation underlying asthma is thought to be chronically present in most cases; however, asthma often presents clinically in attacks or episodes. The underlying inflammation may be present with an absence of symptoms, and control of the inflammation is central in the management of asthma. The disconnect between the inflammation and symptoms can allow for poor self- awareness of asthma, which can foster poor recognition and noncompliance with treatments.. The obstruction is dominantly bronchial and due to mucus production, tissue edema, and smooth muscle constriction. Smooth muscle constriction in the bronchi usually responds to inhaled β2 agonists, creating a reversible component to asthma episodes. Testing for asthma is not the focus of this article, but assessment for reversible airflow obstruction representing the bronchial hyperresponsiveness is fundamental to diagnosing asthma in most cases. Asthma symptoms tend to be worse at night, which is concordant with the cycle of endogenous cortisol levels. .[11]

5616

Eur. Chem. Bull. 2023,12(issue 1),5614-5628

- **Cardinal symptoms of asthma**

Four cardinal symptoms of asthma
Wheezing
Shortness of breath
Coughing
Chest tightness

Physical exam findings will depend on whether the patient is currently experiencing an acute exacerbation.During an acute exacerbation, there may be a fine tremor in the hands due to salbutamol use, and mild tachycardia. Patients will show some respiratory distress, often sitting forward to splint open their airways. On auscultation, a bilateral, expiratory wheeze will be heard. In life-threatening asthma, the chest may be silent, as air cannot enter or leave the lungs, and there may be signs of systemic hypoxia. Children with imminent arrest may appear drowsy, unresponsive, cyanotic, and confused. Wheezing may be absent, and bradycardia may occur, indicating severe respiratory muscle fatigue. Life-threatening asthma is a type of asthma that does not respond to systemic steroids and beta 2 agonist nebulization. It is necessary to identify it early as it may lead to high mortality. It has the following characteristic findings on examination .[11]

- Peak expiratory flow less than 33% of personal best
- Oxygen saturation less than 92%
- The normal partial pressure of carbon dioxide
- Silent chest
- Cyanosis
- Feeble respiratory effort
- Bradycardia
- Arrhythmias
- Hypotension
- Confusion, coma
- Exhaustion

In near-fatal asthma, the partial pressure of carbon dioxide is raised, or mechanical ventilation is required with raised inflation pressures.

Pathology of asthma
Airway Epithelium

5617

Eur. Chem. Bull. 2023,12(issue 1),5614-5628

The structural changes in the asthmatic airway result from interdependent inflammatory and remodeling processes. In the processes, inflammation occurs common features, vascular congestion, exudaution, and inflammatory cell recruitment to the interstitial tissue. Furthermore mucus secretion and desquamation of epithelial cells are increased. The chronic inflammatory changes develop epithelium-mesenchymal interactions. The number of myofibroblasts, which deposit collagens, increases in the understructure of epithelium, the proximity of the smooth muscle layer and the lamina reticularis in the patients. Subepithelial collagens cause thickening and increasing density of the basement membrane. .[14]

The airway inflammation gives damage to the epithelium and damaged epithelial cells will be repaired in the injury-repair cycle. Some studies showed that epithelial cells of untreated asthmatic patients had low level expression of proliferating markers, despite extensive damage, revealing a potential failure in the epithelial injury-repair cycle in response to local inflammation and inhaled agents .[15] Injury to the epithelium results in a localized and persistent increase in epidermal growth factor (EGF) receptor, a mechanism that may cause the epithelium to be locked in a repair phenotype .[16] Epithelial cells which are in repair phase produced some profibrotic mediators, including transforming growth factor-β (TGF-β), fibroblast growth factor and endothelin, which regulate fibroblast and myofibroblast to release collagen, elastic fiber, proteoglycan, and glycoprotein and these substances induce airway wall thickening Myofibroblast is a rich source of collagen types I, II, and V, fibronectin and tenascin that also accumulate in the airway wall and induce thickening lamina reticularis This process may contribute phenomena by augmentation of airway narrowing because the inner airway wall volume increases. .[17]

Eosinophils seem to contribute to airway remodeling in several ways, including through release of eosinophil-derived TGF-β, cationic proteins, and cytokines, as well as through interactions with mast cell and epithelial cells. Many of these factors can directly activate epithelium and mesenchymal cells, deeply related to the development of airway remodeling (. Eosinophil-derived cytokines are in the modulation of Th2 responses that trigger macrophage production of TGF-β1, which serves as a stimulus for extracellular matrix production .[18] TGF-β1 induced epithelial to mesenchymal transition (EMT) in alveolar epithelial cells and could contribute to enhance fibrosis in idiopathic lung fibrosis TGF-β1 might also contribute to enhance airway remodeling through EMT. Indeed, anti-TGF-β1 treatment inhibits EMT in airway epithelial cells .[18]

Airway epithelium is a barrier in the frontline against stimuli from the environment, but in asthmatic epithelium is defective in barrier function with incomplete formation of tight junctions, that prevent allergen from penetrating into the airway tissue .[18] The defect would induce that a proportion of the asthma-related had biological properties to infiltrate the epithelial barrier and trigger a danger signal to DCs. Components of house dust mite, cockroach, animal, and fungal can disrupt epithelial tight junctions and activate protease-activated receptors .[18] The defective epithelial barrier function has also been described in the pathophysiology of other allergic disease. Therefore, healthy barrier function is important to avoid sensitization and development in allergic disease.

Airway Smooth Muscle

Abnormalities of asthmatic ASM structure and morphology have been described by in the first quarter of twentieth century when they reported that smooth muscle from the patients who died by acute exacerbation was increase much greater than in those who died from another disease. Airflow limitation mainly due to reversible smooth muscle contraction is a most important symptom of the disease. Therefore, ASM plays a material role in asthma. Abnormal accumulation of smooth muscle cells is another mechanism of airway remodeling. Some *in vivo* animal studies confirmed that prolonged allergen exposure increase smooth muscle thickness in the airway . It is still unknown whether the phenomenon is occurred by

5618

fundamental changes in the phenotype of the smooth muscle cells, is caused by structural or mechanical changes in the non-contractile elements of the airway wall. There are two different ways by which cyclic generation of length and force could influence ASM contracting and airway narrowing. The processes, which are myosin binding and plasticity, have different biochemical and physical mechanisms and consequences. They have the potential to interact and to have a fundamental effect on the contractual capacity of smooth muscle and its potential to cause excessive airway narrowing .[19]

Like other muscles, ASM is also provoked to contract with intracellular calcium ions (Ca^{2+}), which comes from the extracellular environment through voltage-dependent calcium channel or from the sarcoplasmic reticulum stores (Figure 1). The source of Ca^{2+} surge in ASM is mainly from intracellular sarcoplasmic reticulum stores rather than from the extracellular Ca^{2+} seen in cardiac, skeletal, and vascular muscle cells. Ligands to G-ptotein coupled receptor (GPCR), such as acetylcholine and methacholine, induce the activation of phospholipase C (PLC), which in turn leads to the formation of the inositol triphosphate Then, IP_3 occurs to release Ca^{2+} from sarcoplasmic reticulum (SR) stores, then Ca^{2+} forms a calcium-calmodulin comlex, activates MLC kinase (MLCK) which phosphorylates regulatory MLCs (rMLCs) forming phosphorylated-MLC Finally, this mechanism occurs to the activation of actin and myosin crossbridges resulting in shortening and contraction .[20]
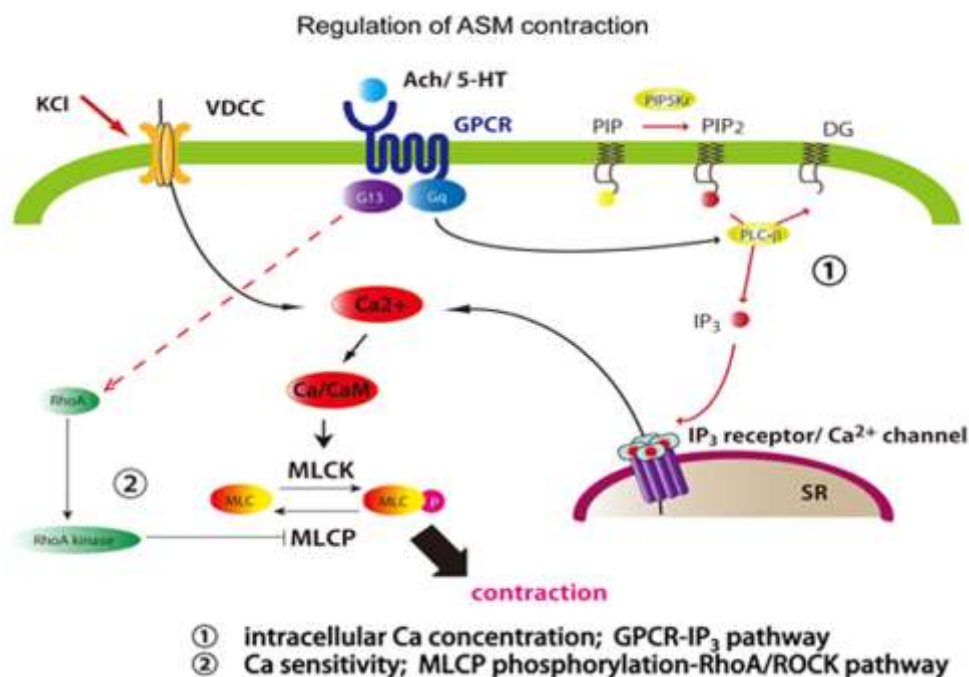

FIGURE 1. Regulation of ASM contractility. ASM contraction is induced by calcium, regulated two different pathways. First, ASM is evoked by intracellular calcium influx from SR depending on GPCR stimulation or from the extracellular environment through voltage-dependent calcium channel. Second, smooth muscle can be induced calcium sensitivity by RhoA/Rho kinase pathway. RhoA activates Rho-kinase which phosphorylates MLCP. pMLC phosphatase fails to dephosphorylate MLC. KCl, potassium chloride; Ach, acetylcholine; 5-HT, 5-hydroxytryptamine (serotonin); PIP, phosphatidylinositol 4-phosphate; PIP2, phosphatidylinositol 4,5-bisphosphate; PIP5K, 1-phosphatidylinositol-4-phosphate 5-kinase; DG, diacylglycerol; IP3, inositol 1,4,5-trisphosphate.

Mast Cells and Eosinophils

Mact cells can induce the activation of mesenchymal cells .[20] The serine protease, tryptase which is released from degranulating mast cells is a potent stimulant of fibroblast and smooth muscle cell

5619

proliferation, and is capable of stimulating synthesis of type I collagen by human fibroblasts. A major mechanism involved in the regulation of fibroblast proliferation appears to be cleavage and activation of protease activated receptor-2 on fibroblasts .[21] Mast cells may also influence the development of airway remodeling in asthma by releasing large amounts of plasminogen activator inhibitor type1. Mice lacking αvβ6 integrin are protected from exaggerated airway narrowing. Mast cell proteases are differentially expressed, in mouse mast cell protease 1 (mMCP-1) induced by allergen challenge in wild-type (WT) mice and mMCP-4 increased at baseline in β6-deficient mice. MCPs from intraepithelial mast cell and their proteolytic substrates could be regulate airway hyperreactivity. .[22]

Eosinophils are circulating granulocytes and at relatively low levels in the bloodstream, upto 3% of white blood cells. These are the major cell types that can be recruited to sites of inflammatory responses .[23] The function of eosinophils in asthma is related to their release of toxic granule proteins, reactive oxygen species (ROS), cytokines, and lipid mediators. The recruit of eosinophils into the epithelium and eosinophilic inflammation is involved in the pathogenesis of asthma. The proinflammatory mediators derived by eosinophil are major contributors to inflammation in asthma, including airway epithelial cell damage and desquamation, airway dysfunction of cholinergic nerve receptors, AHR, mucus hypersecretion, and airway remodeling, characterized by fibrosis and collagen deposition .[24] . Eosinophils are likely to contribute to airway remodeling with release of eosinophil-derived mediators such as TGF-β, secretion of cationic proteins, and cytokines, as well as having interactions with mast cell and epithelial cells. Those factors can directly activate epithelium and mesenchymal cells [25] Moreover, recent data demonstrated that eosinophils can also contribute to airway remodeling with ASM cell proliferation.

Extracellular Matrix

The airways of asthmatic patients showed excess accumulation of extracellular matrix components, particularly collagen, in the subepithelial connective tissue and adventitia of the airway wall The cellular interactions in mast cells and fibroblasts through protease activated receptor-2 may contribute an abnormal mesenchymal cell proliferation, and may account for the increased number of fibroblasts and myofibroblasts that are found in the airways of asthmatic subjects. Fibroblasts retain the capacity for growth and regeneration, and may evolve into various cell types, including smooth muscle cells that subsequently become myofibroblasts. Myofibroblasts can contribute to tissue remodeling by releasing extracellular matrix components such as elastin, fibronectin and laminin It was seen that the numbers of myofibroblasts in the airway of asthmatic subjects increased and their number appeared to correlate with the size of the basement reticular membrane. Smooth muscle cells also have the potential to alter the composition of the extracellular matrix environment. The reticular basement membrane thickening is a characteristic typical feature of the asthmatic airways. It appears to consist of a plexiform deposition of immunoglobulins, collagen types I and III, tenascin and fibronectin but not of laminin. .[26]

Remodeling processes of the extracellular matrix are less known than the thickening of the lamina reticularis. Most asthmatic subjects present with an abnormal superficial elastic fiber network, with fragmented fibers In the deeper layer of elastic fibers is also abnormal, the fibers often being often patchy, tangled, and thickened. Some studies using transmission electron microscopy have shown that an elastolytic process occurs in asthmatic patients, and in some patients disruption of fibers has been observed. In the case of fatal asthma, fragmentation of elastic fiber has also been found in central airways, and was associated with marked elastolysis These bundles are seen to be hypertrophied as a result of an increased amount of collagen and myofibroblast matrix deposition occurring during exaggerated elastic fiber deposition . Loss of lung elastic recoil force has been shown in adults with persistent asthma and irreversible expiratory airflow obstruction. Persistent asthmatic patients have severe abnormal flow-volume curves in expiration at both

5620

high and low lung volumes, and hyperinflation can be seen by residual volume, at forced residual capacity and total lung capacity The increased elastolysis is part of a more complex process that regulates the size of a submucosal network formed by elastic fibers dispersed in a collagen and myofibroblast matrix. These features induce changes in airway, as demonstrated by airway compliance, particularly in those patients who are suffering from asthma for long period, supporting the concept that chronic inflammation and remodeling of the airway wall may result in stiffer dynamic elastic properties of the asthmatic airwayFurthermore, disruption of elastic fibers may contribute to a reduction in the preload and afterload for smooth muscle contraction. Though it is difficult to associate aspects of remodeling with disease severity or degree of airways obstruction and hyperresponsiveness some investigators indicated that smooth muscle remodeling is related to the severity of asthma It has shown that the clinical expression of asthma and impaired airway relaxation are associated with mast cell counts in the ASM layer in asthma. The deposition of extracellular matrix inside and outside the smooth muscle layer in asthma also seems to be related to its clinical severity and is altered as compared to healthy controls .[28]

Complications and -burden on child health and family

Asthma can severely limit the ability to engage in normal daily activities, including sports and outdoor activities. While asthma is a treatable disease, some of those treatments have side effects. For example, inhalers may cause hoarse voice, and inhaled corticosteroids may increase the risk for fungal infections. Oral steroids increase the chance of developing Cushing syndrome, including weight gain and metabolic dysfunction. However, poorly controlled asthma can lead to airway remodeling and chronic obstruction, increase the risk of obstructive sleep apnea, pneumonia, or gastroesophageal reflux.[27][15][28]

Lifelong outcomes

Asthma can appear at any stage throughout life, but it generally develops in childhood (44). Data from the Melbourne Asthma Study reported that 47% of individuals with persistent asthma, and even 75% of subjects classified with severe asthma, at age 6 still had asthma symptoms at age 50 years (45). Noteworthy, children with severe asthma were those at increased risk of developing Chronic Obstructive Pulmonary Disease (COPD) (45–47). Therefore, asthma can be considered a lifelong disease with a major burden especially in subjects suffering from severe asthma.

Morbidity

In 1990, the Global Burden of Disease Study (GBD) proposed the "Disability-adjusted life years" (DALYs) as a measure of disease burden. DALYs quantify how many years of life are lost due to death and/or non-fatal illness or impairment. This health gap measure can be considered as the sum of two components: years of life lost plus years lived with disability (YLDs) (48). The latter measure is calculated as the prevalence of each disease sequela multiplied by the disability weight for that sequela. Asthma was the 14th highest ranked cause of global YLDs at all ages, but specific data for children were not available (49). In the GBD 2015, it accounted for 1.1% of the overall global estimate of DALYs/100,000 for all causes. Overall, asthma represents the second most important respiratory disease after COPD when considering the burden of disease as measured by both YLDs and DALYs.

Mortality

Mortality for asthma is relatively low at all ages. In Europe, asthma is responsible for 0.4% of all deaths (43,000 persons), with wide differences among countries (50). In the GDB 2015, a decrease of 26.7% was observed in comparison with 1990. The decrease in age-standardized death rates was 58.8% between 1990 and 2015. The greatest decrease was observed in HICs, reflecting a better access to health services as well as better treatment options following international guidance (1). Asthma mortality in

5621

children is low and is significantly associated with symptoms prevalence and hospital admissions (51). Hence, when comparing childhood asthma mortality between countries, any reduction in prevalence has to be taken into account. Over recent years, asthma mortality in children decreased across Europe, with little difference between countries. This would be attributable to a better control of symptoms due to improvements in treatment of asthma attacks together with the more widespread use of inhaled corticosteroids which have been shown to reduce mortality at all ages (52). Noteworthy, data from the National Review of Asthma Deaths Confidential Enquiry Report showed that in United Kingdome 80% of asthma deaths occurred in people with poor adherence to treatment and in those who had taken more bronchodilators (53).

Socio-economic cost of childhood asthma

Asthma is a chronic condition that can assume different severity degrees throughout patient's life, with significant social impact and economic burden. In fact, this disease can be associated with limitations on physical and social aspects of daily life of children and their caregivers, especially when symptoms are not controlled (3). Overall, global asthma-related costs are high and significantly vary across countries, depending on several factors, such as the type of health system, financial resources on Public Health and methods of data collection (54).

Usually, asthma-related costs are classified into direct, indirect and intangible costs. Direct costs generally account for 50–80% of the total costs and include: disease management (e.g., outpatient visits, visits to emergency services, hospital admission, medications), complementary investigations or treatment and other costs (e.g., assistance in home care, transportation to medical visits) (54, 55). In children and adolescents with asthma the number of outpatient visits as well as the number of visits to emergency services is higher than in non-asthmatics, increasing according to the disease severity degree (56). Asthma is one of the main causes of hospitalization in children which are usually at least twice than in adults. Hospitalizations are particularly common in children aged <5 years with a prevalence that has been increased during the last two decades, mostly in LMICs (57). Medications account for variable costs, which differ across countries depending on health system and public or private insurance coverage (58). Greater use of asthma drugs, particularly inhaled steroids, occurred in recent years globally increased costs related to asthma medications (54).
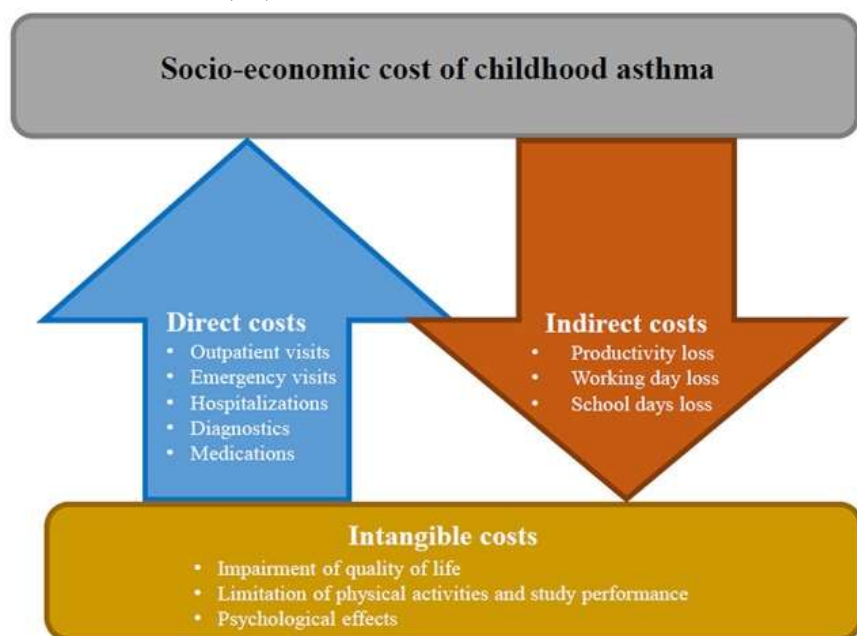
5622

Eur. Chem. Bull. 2023,12(issue 1),5614-5628

Figure 2:Socio-economic cost of childhood asthma: direct, indirect, and intangible costs.

Indirect costs include work-related losses and early mortality. Although loss of working days is not directly applicable in children, absenteeism from school is a comparable consequence. In childhood asthma indirect costs are usually higher than in older patients: a child with an exacerbation of asthma loses on average 3–5 days school days and at least one of her/his caregivers loses the same working time (59).

Intangible costs are unquantifiable, since they are related to impairment of quality of life, limitation of physical activities, and study performance, with consequent psychological effects such as depression and anxiety. Nonetheless, the social burden of asthma is considerable, not only for the child but also for parents. Therefore, when assessing quality of life in asthmatic children, it is important also to assess the quality of life of the caregivers (52).

Treatment / Management

Conservative Measures

Measures to take include calming the patient to get them to relax, moving outside or away from the likely source of allergen, and cooling the person. Removing clothing and washing the face and mouth to remove allergens is sometimes done, but it is not evidence-based.[12][13][14]

Environmental control is vital if one wants to avoid recurrent attacks. Allergen avoidance can significantly improve the quality of life. This means avoiding tobacco, dust mites, animals, and pollen.

Weight reduction in obese asthmatics leads to improved control.

Allergen immunotherapy remains controversial. Large studies have not shown any significant benefit, and the technique is prohibitively expensive.

Monoclonal antibody therapy is indicated for patients with moderate to severe asthma who have a positive skin test. The treatment can lower IgE levels, which in turn decreases histamine production. However, the cost of the injections is high.

Bronchial thermoplasty is a relatively new technique that delivers thermal energy to the airway wall and reduces the narrowing of the airways. Several studies show that it can reduce emergency visits and days missed from school.

Medical

Medical management includes bronchodilators like beta-2 agonists and muscarinic antagonists (salbutamol and ipratropium bromide respectively) and anti-inflammatories such as inhaled steroids (usually beclometasone but steroids via any route will be helpful).

There are five steps in the management of chronic asthma; treatment is started depending on the severity and then escalated or de-escalated depending on the response to treatment.[15]

Step 1: The Preferred controller is as needed low dose inhaled corticosteroid and formoterol.

Step 2: The preferred controllers are daily low dose inhaled corticosteroid plus as-needed short-acting beta 2 agonists.

Step 3: The preferred controllers are low dose inhaled corticosteroid and long-acting beta 2 agonists plus as-needed short-acting beta 2 agonists.

Step 4: The preferred controller is a medium-dose inhaled corticosteroid and long-acting beta 2 agonist plus as-needed short-acting beta 2 agonists.

Step 5: High dose inhaled corticosteroid and long-acting beta 2 agonist plus long-acting muscarinic antagonist/anti-IgE.

Indications for admission

If a patient has received three doses of an inhaled bronchodilator and shows no response, the following factors should be used to determine admission:

- The severity of airflow obstruction
- Duration of asthma
- Response to medications
- Adequacy of home support
- Any mental illness

Patients with life-threatening asthma are managed with high flow oxygen inhalation, systemic steroids, back to back nebulizations with short-acting beta 2 agonists, and short-acting muscarinic antagonists and intravenous magnesium sulfate. Early involvement of the intensive care team consultation helps to reduce mortality. In the case of near-fatal asthma, early intubation and mechanical ventilation are needed.

Surgical

There is no surgical input into the management of typical asthma.

Other/Long Term

Weight loss, smoking cessation, occupational change, and self-monitoring are all important in preventing disease progression and reducing the number of acute attacks.

Recent therapeutics

Treatment of Th2-high or eosinophilic type of asthma

Th2-high or eosinophilic asthma is characterized by increased eosinophil counts in blood and sputum, higher plasma IgE levels, positive skin prick-test, activation of basophils, Th2cells, natural killers, innate lymphoid cells (ILC2), as well as elevated synthesis of cytokinesIL-4, IL-5, and IL-13 (1, 7). Th2-high asthma responds well to CS, however, most available therapeutic strategies are focused on this kind of inflammation (10).

Anti-IgE based therapy

Approximately 70% of patients have an allergic, eosinophilic asthma phenotype, characterized by increased IgE specific to aeroallergens. The first drug approved as an anti-Ig Emono clonal antibody was omalizumab. Omalizumab binds to C 3 domain of free IgE heavy chain and thereby binds to circulating IgE and down-regulates the high-affinity IgE receptors on basophils and mastocytes, as well as circulating dendritic cells (11). Nowadays, according to actual GINA, omalizumab is indicated for IgE-mediated moderate-to-severe asthma inadequately responding to conventional therapy.

Cytokines as a target

Targeting IL-5 or IL-5 receptor is used to influence this key mediator for proliferation ,activation, and recruitment of eosinophils (12–16). To date, two monoclonal antibodies mepolizumab and reslizumab have been approved as add-on therapy in refractory eosinophilic asthma. Mepolizumab has been most extensively investigated, showing reduction in exacerbations rate of around 50%. Both of these drugs bind directly to IL-5, while newly developed benralizumab binds to receptor subunit-α,leading to antibody-dependent cell-mediated cytotoxicity of eosinophils, basophils, as well as eosinophil progenitor cells in bone marrow. This fact makes it theoretically more effective compared to mepolizumab and reslizumab, considering reduced exacerbation rate ,improved lung functions, or reduced oral CS use (12–16).

IL-4 and IL-13 were the first mediators identified to drive type-2 inflammation. IL-13receptor is a complex assembly of both IL-13 and IL-4 receptor subunits. Both cytokinesIL-4 and IL-13 are produced by Th2 cells (IL-13 also by ILC2 cells), whereas IL-4 regulates mostly Th2 cell function and IgE synthesis and IL-13 is responsible for mucus production ,AHR, and generation of IgE. Currently, many monoclonal

5624

antibodies blocking this pathway have been investigated (17–20). Periostin, a downstream IL-13 -induced protein, might be a valuable biomarker showing elevation of IL-13 and airway eosinophilia. Lebrikizumab ,a monoclonal antibody against IL-13, reduced exacerbation rate and enhanced lung functions particularly in patients with higher periostin level, however, in study Phase III did not demonstrate a consistent benefit after all (21).

Drug with similar mechanism of action, tralokinumab, has been successfully tested in clinical trials as an add-on therapy for patients with severe uncontrolled asthma who had increased IL-13 titres (Phase 2a). In Phase IIb study, tralokinumab improved symptoms in participants with elevated bio-markers such as DPP-4 and periostin (both indicators of increased IL-13). Despite lebrikizumab and tralokinumab targeting IL-13 demonstrated some benefits, the studies were unable to identify a population of asthmatics with consistent, clinically meaningful treatment benefit (16–21). Another treatment strategy is based on IL-4 - receptor blocking which is a common chain for IL-4 and IL-13 receptor, represented by dupilumab (18, 19, 22). Blocking both IL-13 andIL-4 seemed to be very promising because of reduced exacerbation rate in patients with a higher eosinophil count in blood, improved FEV1, and lowered markers typical for Th2inflammation. Therefore, dupilumab has been approved by FDA as an add-on therapy for adult and adolescent patients with severe type-2 asthma with increased blood eosinophils and/or raised exhaled nitric oxide measured by FeNO test, inadequately controlled by inhaled high dose CS plus another drug. At the moment, dupilumab is awaiting approval by EMA. Pitrakinra, recombinant human IL-4 mutein, competitively inhibits IL-4 receptor, thusinhibits both IL-4 and IL-13 pathways. However, in a dry powder inhaled form failed to prove a measurable benefit in clinical trials, probably due to IL-4R polymorphism dependent effect .[59]

Antagonists of lipid mediators

Chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2) is receptor for prostaglandin D2 (PGD2) expressed on lymphocytes, eosinophils, basophils, and airways epithelial cells. Stimulation of this receptor leads to chemotaxis of inflammatory cells and release of cytokines and mediators, as well as differentiation of epithelial cells. In patients with severe asthma PGD2 count is increased in bronchoalveolar lavage fluid . .[60]

Airway epithelium as a target

Alarmins like thymic stromal lymphoprotein (TSLP), IL-25 and IL-33 released from air-way epithelial cells together with other mediators and cytokines could be other potential therapeutic targets. Among them, anti-TSLP strategy can effectively target the impaired epithelial-inflammatory crosstalk. Tezepelumab (AMG 157) succesfully achieved primary and secondary endpoints of Phase IIb, thus might be a first-in-class drug for asthma in future (26).

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5628

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