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RECENT ADVANCES IN UNDERSTANDING AND MANAGING ASTHMA CLINICALLY

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ABSTRACT

Asthma is paroxysmal, intermittent disease of airway inflammation, all around the globe affecting people of all ages. The global asthma report in 2014 was estimated at 334 million globally and 23.5 million in Pakistan. It is also predicted by the Global Asthma Report that in 2025 the number will rise to 100 million people. Despite emerging technologies in the diagnosis and asthma treatment, the majority of the population remain controlled poorly. However, the symptoms in some patients have been controlled through avoidance measures and pharmacological interventions. Different treatment strategies such as the use of inhaled corticosteroids (ICSs) have controlled the symptoms in asthmatic patients. If ICS therapy is ineffective alone, it can be used in combination with long-acting beta2 agonists. But other therapies such as allergen-specific immunotherapies have a significant role in disease modification but must be prescribed by healthcare professionals. This review article provides recent updates from the literature on asthma and its proper management.

INTRODUCTION

Asthma is the most common and emerging disease all around the globe affecting people of all age groups. The global asthma report in 2014 was estimated at 334 million globally and 23.5 million in Pakistan. While recent studies have shown an increase in the incidence, especially in children. It affects more than one-third of the child population in industrialized countries (Eder, Ege, & von Mutius, 2006). It is also predicted by the Global Asthma Report that in 2025 the number will rise to 100 million people.

Asthma is a paroxysmal allergic airway inflammation and bronchial hyperresponsiveness, accompanied by wheezing, cough, breathlessness and tightness of the chest. Complications of asthma are faced mainly during exhalation. Acute asthma is usually reversible where the inflammatory airways are brought back to normal but it differs in the case of chronic asthma. If acute asthma is left untreated it can be life-threatening. It can be reverted through attaining a healthy lifestyle and proper medication. Phenotypes of asthma vary in different patients due to its complex pathophysiology.

The type of inflammation is different in different patients so their response towards the stimulus also differs. Most likely the treatment mechanism will also vary accordingly (Kemp, 2002). The principle cause behind asthma is not understood well, but the factors included are both genetic and

environmental. Environmental factors include pet dander, pollens, allergens, viruses, medications such as aspirin and pollution (Koeppen-Schomerus, Stevenson, & Plomin, 2001). Genetic predisposition increases the risk for sensitization (Sly et al., 2008).
Currently, there is no specific medication to cure asthma but anti-inflammatory treatments such as corticosteroids are usually used to improve the symptoms of asthma and also to decrease its risk (Pauwels et al., 2003). The treatment depends upon the severity of the disease where mild phasic cases do not require daily medication but severe persistent patients should use high doses of corticosteroids, according to the National Institute of Health.

Pathophysiology

Asthma is a disease that causes inflammation of airway passages with varying phenotypes due to its complex pathophysiology. The most striking feature of airway inflammations is the increased production of eosinophils, neutrophils, T lymphocytes and mast cells. Allergic asthma is associated with the potential of airways to recognize any external antigen or allergen and showing the response of Th2 cytokines (Beasley, Cotter, & Everall, 2002).
The molecular pathophysiology varies based on its etiology. Asthma is categorized into Atopic (allergic) and non-atopic (non-allergic). Allergic asthma is also known as extrinsic asthma because it is caused by external factors such as pollens, allergy or dust. While non-atopic is not allergic but it may cause due to exercise, stress, cold or any medication such as aspirin.
The molecular mechanism of genetic pre-disposition includes the response of macrophages or dendritic cells which are antigen-presenting cells, towards the allergen. Suppose there is an allergen when it comes in contact with the dendritic cells or macrophages of the respiratory epithelium which are antigen-presenting cells, will trap and phagocytose it. After phagocytosis, the dendritic cells will present that allergen to the T-helper 2 cells which are primary players in asthma. T- helper 2 cells have T-cell receptor specific for the antigen and also CD4 molecules on its surface. These Th2 cells react with dendritic cells, upon this interaction, pro-inflammatory cytokines such as IL-4, IL-5 and IL-13 release. Now, these pro-inflammatory cytokines have their role in producing different physiological effects.
IL-4 when released act on plasma cells and activate them to produce a specific type of antibodies known as IgE which otherwise release IgM. Now, these antibodies after release will lodge upon the Fcε1 receptors of mast cells and cause their degranulation. This degranulation process results in the release of histamines and leukotrienes, which are inflammatory mediators. IL-5 is also secreted by the mast cells. Mast cells also secrete some chemoattractants to recruit eosinophils and neutrophils which cause inflammation causing an immediate reaction. Now, these mast cells also secrete different types of leukotrienes.
These leukotrienes after release firstly, work on smooth muscles and result in bronchoconstriction, secondly, they act on the blood vessels and cause them to dilate resulting in edema, finally, they cause mucus glands to become hyperactive to secrete mucus and cause airway obstruction.
IL-13 has also a similar role in producing IgE antibodies causing inflammation.
IL-5 has a really important function. It activates particular white blood cells called eosinophils which have two main functions. One is the killing of pathogens while the other is it has a complex role in allergic asthma. Eosinophils produced by IL-5 further release leukotrienes and other cytokines which attract more white blood cells. It can also release some type of proteases which in chronic conditions damage tissues of the respiratory tract. These leukotrienes and histamines produce both mast cells and eosinophils which act upon the smooth muscles of bronchioles and cause bronchoconstriction as a result of hypertrophy. Histamines also cause dilation of capillaries which increase vascular permeability. This increase in permeability results in lots of mucus secretion.
Mucosa becomes highly inflamed and fills with a lot of fluid, inflammatory exudate and some eosinophils. All these physiological changes lead to the narrowing of the airway passage. But over time, this acute phase leads to a chronic state. The bronchioles become fibrotic, can scar, and cause thickening of the basement membrane, becoming permanently narrow.
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We know that usually acute asthma is reversible in the conditions when the triggers are taken away or proper medication is provided. All the physiological changes will recover to the normal state. But the chronic phase is not reversible and eosinophils do not produce as well. A flowchart is given below in figure 1.1.

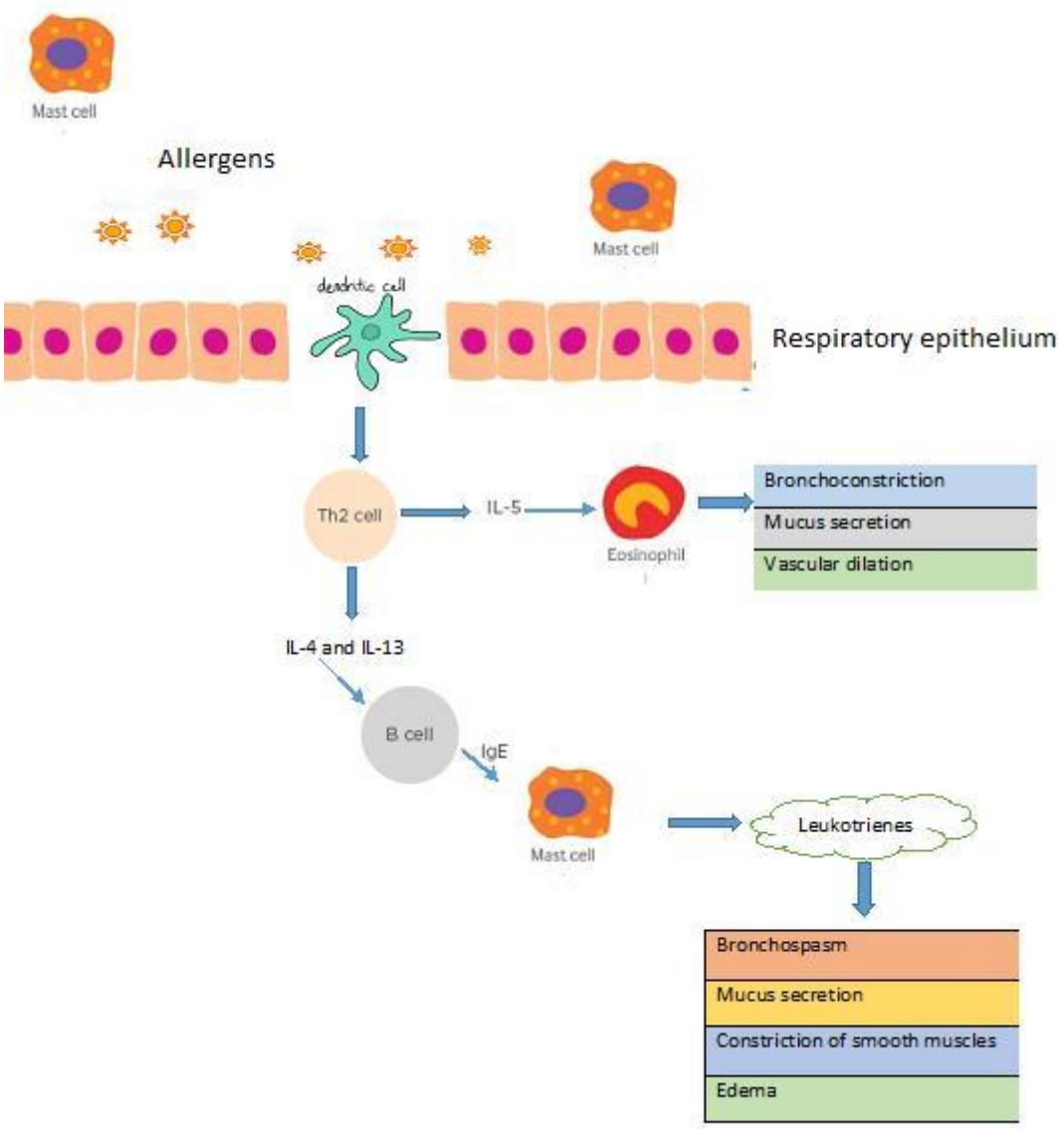

Figure 1.1 Diagram shows the mechanism underlying the pathophysiology of asthma and the production of pro-inflammatory mediators.

Diagnosis of asthma

There are various ways to diagnose asthma such as a thorough physical examination, medical history and assessment of lung function with the help of a spirometer. There are also several conditions where the objective measurement shows normal lung function but the patient is symptomatic for disease, in this situation testing for markers of inflammation remains helpful for the treatment (Álvarez-Gutiérrez et al., 2010).

Diagnosis of asthma is usually carried out in patients showing symptoms such as cough, wheezing, chest tightness and breathlessness.

Patients with a pre-genetic disposition of atopic disorders help in the identification of asthmatic patients. If occupational asthma is suspected details of the environmental allergens must be identified.

Spirometry is used to detect the obstruction in the reversible airway and also to confirm the asthma diagnosis. It must be ensured before using spirometry that this technique is only reliable for patients above the age of 6 and below 6 it is not reliable. So, children under the age of 6 with asthma are diagnosed via treating with inhaled corticosteroids (ICSs) and short-acting bronchodilators.
There are other diagnostic methods to detect asthma, which include the measurement of the level of nitric oxide produced during exhalation and also the inflammatory markers such as eosinophilia in sputum. The level of exhaled nitric oxide is also helpful to see the response of asthma therapy (Krishnan, Schatz, & Apter, 2011).
Allergy skin testing is another testing method to diagnose asthma and its triggers as well. This test is carried out by using the allergens native to a specific geographical region of the patient (Lougheed et al., 2010).

Treatment

Asthma is treated based on lung function assessment, clinical findings and effectiveness of the treatment given previously. Generally, it is quite difficult to treat the asthma exacerbations triggered by viruses as compared to that of the exacerbations triggered by pollens (Schatz & Rosenwasser, 2014). Before treatment, asthma must be controlled through the measures of avoidance and pharmacological interventions.
Controllers and relievers are the two pharmacological agents used to treat asthmatic patients. Controller medications are taken daily and can be effective against inflammatory effects. It includes ICSs, leukotriene receptor antagonist (LTRAs), long-acting beta$_2$-agonists (LABAs) in combination with an ICS and anti-IgE therapy. Rapid-acting inhaled beta$_2$-agonists and inhaled anticholinergics are used as relievers (Kemp, 2002). Allergen-specific immunotherapy and systemic corticosteroid therapy can be used as management strategies for acute asthma exacerbations.
After asthma is controlled, its symptoms must be monitored continuously so that the dosage may not exceed the amount which can be harmful to the normal body metabolism. However, asthma is a phasic and intermittent disease, so must be treated accordingly.
When the control of asthma is achieved then it must be monitored continuously to keep the dose minimum for the proper maintenance of the body functions. However, asthma is a phasic disease and intermittent so the treatment must also be given accordingly.

Avoidance measures

The most important component of avoidance measure is to avoid the potentially relevant irritants and allergens. The humidity level at home must be kept below 50% as a preventive measure to prevent mites from flourishing as they also act as allergens to some patients. The exposure to pollens must be reduced when the pollen season is at its peak by restricting outdoor activities. Those people who are allergic to pet dander must not keep pets at home, use of tobacco and exposure to smoke must be avoided and (HEPA) filters should be used to avoid mold allergens (Sears, 1929).
In recent years many strategies have been used to avoid exposure to allergens in patients suffering from respiratory allergy. Avoidance measure is widely recommended in most guidelines to control specific interventions but control of asthma is a holistic approach, where a single strategy won't work (Bateman et al., 2008).
Since the above-mentioned strategies are laborious and time-consuming. The patient must always adhere to these measures. For optimal results, patients must use different combinations of avoidance measures. A single strategy may not be fruitful to have good control over allergic asthma.

Reliever medications

The most recommended medication used to treat asthmatic patients is the inhaled rapid-acting beta$_2$-agonists. They include short-acting beta$_2$-agonists (SABAs) such as salbutamol and Long-acting beta-agonists (LABAs) such as formoterol. SABAs must only be taken when needed to relieve the symptoms because it's high dose such as more than 3 times a week cause worsening of the disease. LABAs, such as formoterol is used against acute symptoms because it has a rapid onset of action.

Other medications such as ipratropium bromides which are short-acting anticholinergic bronchodilators are also used to relieve symptoms. These agents are used as second-line therapy for asthma patients because comparatively, they are less effective than inhaled rapid-acting beta$_2$-agonists. But they can be used in addition to SABAs. However, this therapy is not suggested for children (Smith, 2009).

Inhaled corticosteroids (ICSs)

These ICSs are considered as most efficient and extensively used treatment to manage asthma as they have a broad spectrum of inflammatory effects. As the first line of maintenance therapy, a very small dose is recommended for patients with asthma.

They are equally applicable for all age groups but must be used in a small dose range and risk increases with dose. Inhaled corticosteroids have the role in improving quality of life, lung function and its symptoms but do not alter its progression or cure it. There can be a recurrence of the disease if not used regularly. Therefore, patients with asthma must use the medicine for long-term, if not for life-long (Walters et al., 2014).

The most common adverse effects of using ICSs are associated with the development of the different disease such as oral thrush and dysphonia. These complications can be reduced by rinsing or expectorating after inhalation. Rare systemic adverse effects such as adrenal suppression, retarded growth in children, cataracts and glaucoma can also occur.

Leukotriene receptor antagonists (LTRAs)

Leukotriene receptor antagonists (LTRA) such as montelukast and zafirlukast are a new class of non-steroidal drugs available in the form of tablets for asthma patients. Generally, they are considered to be well-tolerated and safe. They have a combinatory effect on bronchodilation and anti-inflammation. They suppress inflammation of airways in asthmatic patients, even in very low doses by blocking the chemical reactions which cause asthma. LTRAs, when used as a monotherapy are less effective in treatment but used by patients who face problems with using ICS therapy. They are used in addition to ICSs if the asthma is not controlled by ICSs therapy (Lougheed et al., 2010).

Though it has many side effects depending upon the dose taken, which include psychiatric and non-psychiatric issues. Among them, psychiatric issues are more prevalent such as aggressiveness, anxiety, insomnia, hallucinations and personality changes (Celmeli, Turkkahraman, Cetin, Mihci, & Yegin, 2014).

Theophylline drug

Theophylline (dimethylxanthine), used for many years to treat asthma worldwide. But the development of new drugs such as inhaled corticosteroids has tremendously decreased their use in treating patients with asthma.

This drug is now considered a bronchodilator because it relaxes smooth muscles of the airways, but it has many other ameliorative effects as well such as in treating wheezing, shortness of breath, emphysema and chest tightness. Theophylline is an extended-release tablet taken orally or given intravenously to relieve the symptoms and also less expensive.

It is considered a third-line treatment because it is used to treat those patients who have uncontrollable asthma even after using inhaled corticosteroids, LABA or LTRAs have potential adverse effects as well. These side effects include vomiting, nausea, seizures, loose stools and gastrointestinal symptoms (Abramson, Puy, & Weiner, 2003).

Anti-IgE treatment

Immunoglobulin E or IgE has the main function in the onset of many allergic diseases. All the IgE mediated pathways serve as a major target for allergic disease interventions. Omalizumab, the anti-IgE monoclonal antibody, reduce the asthma exacerbation frequency by 50% by blocking free serum IgE and prevents its binding to cellular receptors.

This therapy, unlike other treatments, is not taken in the form of a pill or any inhaler but given through prescription. It is administered once every two or four weeks by healthcare professionals and only available in Canada.
Presently, omalizumab is given to patients whose asthma symptoms do not fade after using ICSs (Lougheed et al., 2010).

Systemic corticosteroids
These are the steroids that are administered orally or by injection and spread to the whole body while a small amount is absorbed by the body. Corticosteroids such as prednisone are used to treat acute to severe asthma exacerbations. If asthma control becomes difficult, chronic systemic corticosteroid therapy is given to fade the symptoms. Bu may cause serious threats if used for a prolonged period.
Chances of potential side effects are not common but can increase with increased dosage. So the dosage must be prescribed carefully to minimize the risk. Adverse effects include imbalanced glucose metabolism, huge appetite, mood swings, hypertension, anxiety and peptic ulcer (Smith, 2009).

Allergen immunotherapy
Allergen-specific immunotherapy is an effective therapy used against common atopic conditions such as allergic asthma. The main objective of this treatment is to decrease the symptoms of allergy and also prevent its recurrence for a longer period (Abramson et al., 2003). In this treatment, the allergens which are related to the patients, are administered gradually through sub-cutaneous until it reaches an effective dose that is tolerable to the allergen. Currently, this is the only disease-modifying treatment (Frew, 2010).

Mode of action of β_2 agonist
β_2 agonists are good bronchodilators, which could be used in the treatment of asthma examples may include albuterol. Bronchodilation means relaxation of smooth muscles of bronchioles. β_2 receptor is a G protein-coupled receptor, a seven-transmembrane domain protein present on the lungs. The membrane-bound G protein undergoes a conformational transition when a ligand binds to the GPCR, and the GDP hydrolyzes with the alpha subunit and exchanges with the GTP. This activated alpha sub-unit activates adenylate cyclase, which produces a second messenger cyclic amp from ATP, and now the alpha subunit linked to the GTP is active.
This entire signalling pathway can cause physiological effects. It involves the inactivation of light chain kinases of myosin (MLCK) that are important for muscle contraction. This signalling mechanism would inactivate the contraction of muscles and decrease the intracellular calcium level.
Calcium normally produces a calmodulin complex, and calmodulin activates MLCK, which phosphorylates the light chain of myosin that forms an actin cross-bridge and triggers muscle contraction. A signal is produced as a result of β2 agonists binding to the receptor that tells the cell to inactivate myosin light chain kinases, resulting in no cross-bridges formation and thus no muscle contraction, β2 agonists mediated signalling prevents muscle contraction and eventually impart the bronchodilation effect and also reduce calcium level and indirectly inhibit muscle contraction. The effect on bronchodilation is imparted by β2 agonists in its way.

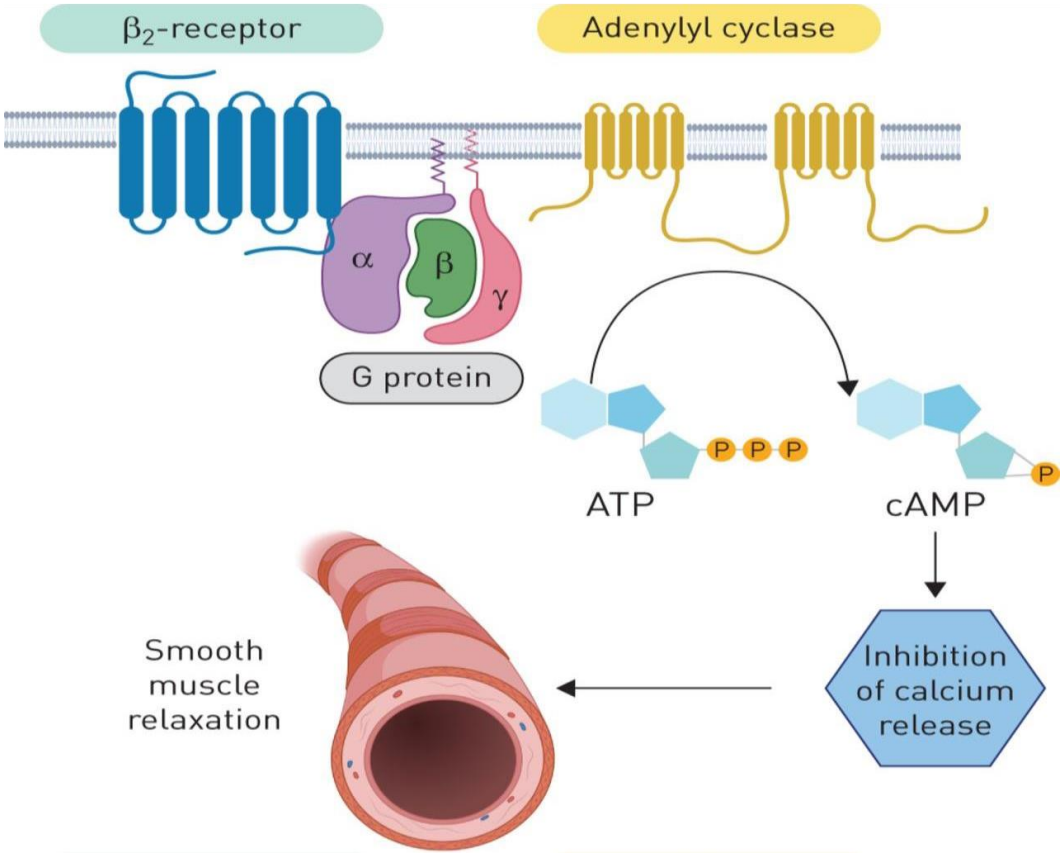

Fig 1.2. The diagram above shows the mechanism of action of the β_2-receptor. The G protein-coupled receptor is activated by agonist binding, leading to the conversion of ATP to cAMP by adenylyl cyclase, and downstream inhibition of intracellular calcium release, and subsequent bronchial smooth muscle relaxation (Adams, Appleton, Hill, Ruffin, & Wilson, 2009).

CONCLUSION

Asthma is paroxysmal, intermittent disease of airway inflammation all around the globe which is responsible for a significant morbidity and mortality rate. It is a paroxysmal allergic inflammation of airways and bronchial hyperresponsiveness, accompanied by wheezing, cough, and tightness of the chest. Asthma is diagnosed through physical examination, medical history and assessment of lung function with the help of a spirometer.

The symptoms in some patients have been controlled through avoidance measures and pharmacological interventions. Different treatment strategies such as the use of inhaled corticosteroids (ICSs) have controlled the symptoms in asthmatic patients. If ICS therapy is ineffective alone, it can be used in combination with long-acting beta2 agonists. But other therapies such as allergen-specific immunotherapies have a significant role in disease modification but must be prescribed by healthcare professionals. Patients with asthma must visit health care professionals regularly and adhere to the prescribed treatment.

References

1. Abramson, M. J., Puy, R. M., & Weiner, J. M. (2003). Allergen immunotherapy for asthma. *Cochrane Database of Systematic Reviews*(4).
2. Adams, R. J., Appleton, S. L., Hill, C. L., Ruffin, R. E., & Wilson, D. H. (2009). Inadequate health literacy is associated with increased asthma morbidity in a population sample. *Journal of allergy and clinical immunology*, *124*(3), 601-603.
3. Álvarez-Gutiérrez, F. J., Medina-Gallardo, J. F., Pérez-Navarro, P., Martín-Villasclaras, J. J., Etchegoren, B. M., Romero-Romero, B., & Praena-Fernández, J. M. (2010). Relationship of the Asthma Control Test (ACT) with lung function, levels of exhaled nitric oxide and control

according to the Global Initiative for Asthma (GINA). *Archivos De Bronconeumología ((English Edition)), 46*(7), 370-377.
4. Bateman, E. D., Hurd, S., Barnes, P., Bousquet, J., Drazen, J., FitzGerald, M., . . . Pedersen, S. (2008). Global strategy for asthma management and prevention: GINA executive summary. *European Respiratory Journal, 31*(1), 143-178.
5. Beasley, C., Cotter, D., & Everall, I. (2002). An investigation of the Wnt-signalling pathway in the prefrontal cortex in schizophrenia, bipolar disorder and major depressive disorder. *Schizophrenia research, 58*(1), 63-67.
6. Celmeli, F., Turkkahraman, D., Cetin, Z., Mihci, E., & Yegin, O. (2014). Selective IgM deficiency in a boy with ring chromosome 18. *J. investig. allergol. clin. immunol*, 442-444.
7. Eder, W., Ege, M. J., & von Mutius, E. (2006). The asthma epidemic. *New England Journal of Medicine, 355*(21), 2226-2235.
8. Frew, A. J. (2010). Allergen immunotherapy. *Journal of Allergy and Clinical Immunology, 125*(2), S306-S313.
9. Kemp, J. P. (2002). *Clinician's Manual on Pediatric Asthma*: Science Press Incorporated.
10. Koeppen-Schomerus, G., Stevenson, J., & Plomin, R. (2001). Genes and environment in asthma: a study of 4 year old twins. *Archives of disease in childhood, 85*(5), 398-400.
11. Krishnan, J. A., Schatz, M., & Apter, A. J. (2011). A call for action: comparative effectiveness research in asthma. *Journal of Allergy and Clinical Immunology, 127*(1), 123-127.
12. Lougheed, M. D., Lemière, C., Dell, S. D., Ducharme, F. M., FitzGerald, J. M., Leigh, R., . . . Becker, A. (2010). Canadian Thoracic Society Asthma Management Continuum–2010 Consensus Summary for children six years of age and over, and adults. *Canadian Respiratory Journal, 17*.
13. Pauwels, R. A., Pedersen, S., Busse, W. W., Tan, W. C., Chen, Y.-Z., Ohlsson, S. V., . . . Group, S. I. (2003). Early intervention with budesonide in mild persistent asthma: a randomised, double-blind trial. *The Lancet, 361*(9363), 1071-1076.
14. Schatz, M., & Rosenwasser, L. (2014). The allergic asthma phenotype. *The Journal of Allergy and Clinical Immunology: In Practice, 2*(6), 645-648.
15. Sears, W. G. (1929). The nervous complications of whooping cough. *Brit. J. Child. Dis., 26*(July), 191.
16. Sly, P. D., Boner, A. L., Björksten, B., Bush, A., Custovic, A., Eigenmann, P. A., . . . Helms, P. J. (2008). Early identification of atopy in the prediction of persistent asthma in children. *The Lancet, 372*(9643), 1100-1106.
17. Smith, S. D. (2009). Diagnosis of asthma in adults. *Cmaj*.
18. Walters, J. A., Tan, D. J., White, C. J., Gibson, P. G., Wood-Baker, R., & Walters, E. H. (2014). Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews*(9).