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PEDIATRIC ASTHMA AND PHARMACOLOGICAL TREATMENT OF ASTHMA IN CHILDHOOD, UNIVERSITY OF DEBRECEN, 2016

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Abstract:
Pediatric asthma is one of the most common chronic airways inflammatory diseases in childhood. The prevalence is increased in last decades in several industrial countries. Allergy has strong relationship to asthma which leads to increase in mucus secretion, and airways hyper-reaction caused by innate and adaptive immune response reactions. Asthma symptoms are wheezing, coughing, breathlessness and using of accessory muscles of the chest. Those are indication of the treatment to the patient can do everyday activities without complications. The treatment depends on the severity of asthma; it should be managed by inhaled corticosteroid combined with long-acting β-2 agonist, leukotriene agonist, theophylline or Cromolyn. Asthma exacerbation is emergency acute attack when symptom intensity is increased and need immediate response to decrease the attack severity.
This thesis focuses on management of the childhood asthma in short and long acting therapies. Also, it shows the common side-effect of asthma therapies, and asthma exacerbation, and therapies for life-threating asthma. Finally, a comparison is made between some drugs used for asthma. As references for this thesis, different scientific articles are used from PubMed and Medline.
Keywords: *asthma, pediatric, asthma exacerbation, inhaled corticosteroids, side-effect, omalizumab.*

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INTRODUCTION:

PEDIATRIC ASTHMA

Childhood asthma is a chronic obstructive disease of the respiratory airways that results from spams of the smooth muscle with increase in the mucus and inflammatory response. It caused by hyper-response to stimuli such as cold air, chemicals, some drugs, hyperventilation, and pollen. This leads to different signs and symptoms such as wheezing and coughing. (Ellis, 1983).

In worldwide statistics shows, asthma affects proximately 235 million people. Approximately, 400 million people will be affected by 2050. In USA, 10% of children aged 12-18 years are affected. (Busse, et al., 2016).

ETIOLOGY:

Asthma is a complex disease because it is combined reactions of immunological, genetical and environmental factors which induce different signs. There are two theories explain the hyper-reactivity:

1-Abnormality of beta-adrenergic receptors leads to decrease their response.

2- The cholinergic reaction increased leads to airways hyper-responsiveness. (Ellis, 1983)

Asthma is divided into different periods; begins in prenatal period, infancy period, childhood or adulthood.

Prenatal period has multifactorial risk factors such as maternal tobacco smoking, diet and nutrition, maternal stress, prenatal antibiotics treatments, and emergency cesarean section delivery.

Childhood period has affected by many causes like:

1. Antibiotics and infection such as: viral (respiratory syncytial virus and rhinovirus) infections or bacterial (Heamophilia influenza, Streptococcus pneumonia, and Moraxella catarrhalis) infections of lower respiratory tract in the early ages of life is observed that is associated with later asthma. (Formosa, 2008).
2. Socio-economic status.
3. Decreased airways caliber in infancy.
4. Gene by environment interactions (such as epigenetic modification of DNA).
5. Family structure (size, number and order of siblings).
6. Exposure to environment tobacco smoking.
7. Exposure to farm animals in early life.
8. Sex and gender (prevalence shows that boys > girls until age 13-14 years).
9. Breastfeeding (in longitudinal cohort study showed that breastfeeding is associated with atopic asthma in late childhood).
10. Allergic sensitization. (Subbarao, et al., 2009).

EPIDEMIOLOGY:

The prevalence of childhood asthma has increased in the last decades. However, there is decrease in mortality rate of asthma between 5-15 years old and increase of using anti-asthmatic drugs. This proves the improvement of the asthma drugs. (Warner, 2001).

Increasing of childhood asthma indicates that there are many causes influence the immune response such as environments factors or prenatal factors beside the hereditary factors. The mean asthma age was 2.2 years, starting from 0 month to 9 years. A study has shown that boys (64% of cases) are more common affected than girls (36% of cases). (Metsälä, et al., 2008). Another study has shown that more than 50% of people with poorly controlled asthma have allergic (atopic) immunoglobulin E (Ig-E) mediated asthma. (Normansell, et al., 2014)

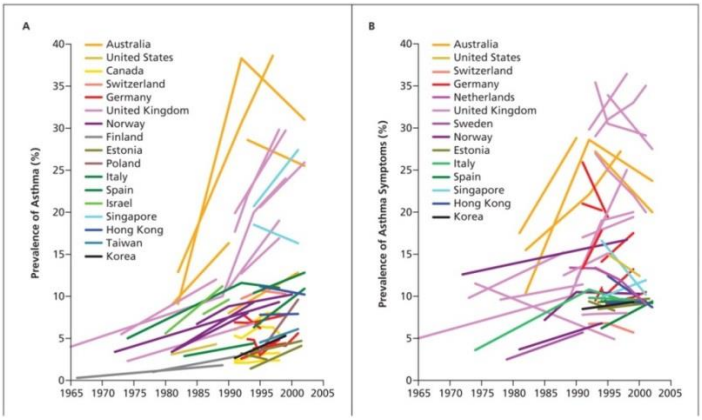

Figure 1 *increase of the prevalence of asthma (A) and prevalence of asthma symptoms (B) in different countries* (Subbarao, et al., 2009)

GENETICS OF ASTHMA:

Numbers of studies were conducted on family and twins have shown genetic relationship of development of asthma through different genes. More than 100 genes associated with allergy and asthma identified by case- control studies and genome – wide linkage studies.

A recent study identified a new gene ORMDL3 which is related to asthma. (Subbarao, et al., 2009). ORMLD3 is allergen and cytokine induced gene which may cause activation of unfolded protein response (UPR). As result, it leads to airways remodeling by affecting sarco/endoplasmic reticulum CaATPase (SERCA). This causes inflammatory response in asthma, and impairs De novo sphingolipid synthesis and causes bronchial hyper-responsiveness too.

The variants at the 17q21 locus which is located (35.0 - 35.5 Mb) on chromosome 17 has shown strongly association with childhood non-allergic asthma and wheezing phenotypes. (Ono, et al., 2014)

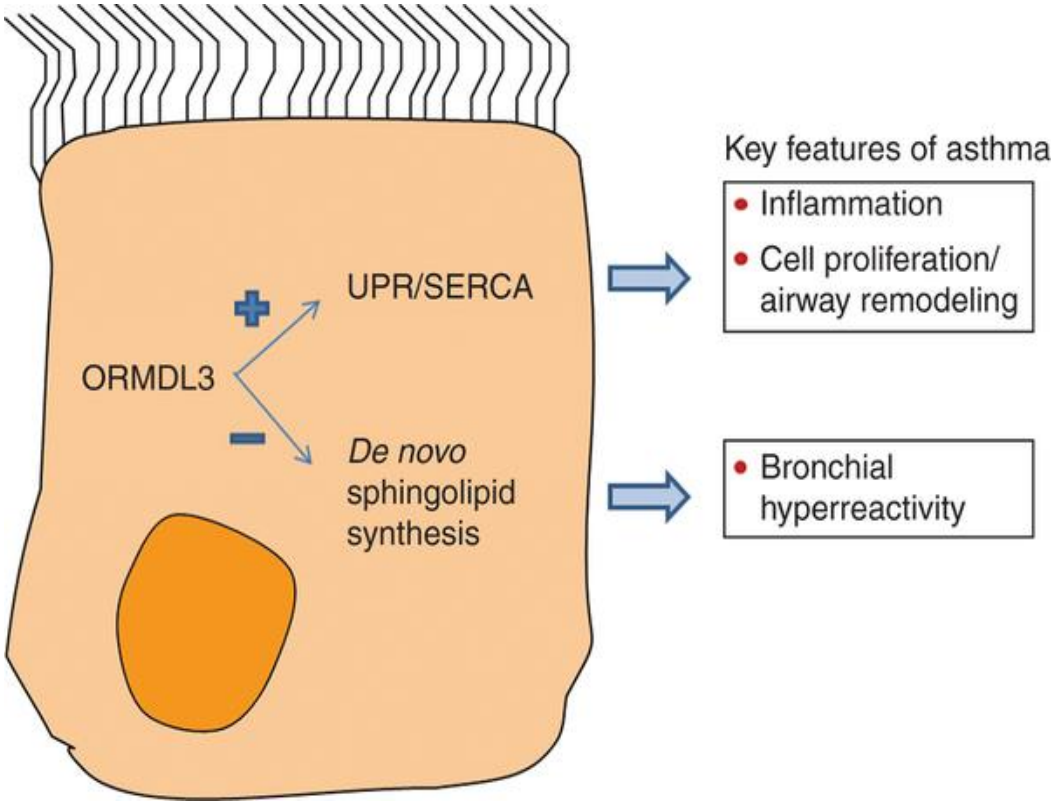

Figure 2 The mechanism of ORMDL3 in asthma pathogenesis in an airway epithelial cell **(Ono, et al., 2014)**

IMMUNOLOGICAL CHNAGES OF ASTHMA:

Allergic asthma mediated by Adaptive immune response via Th2 (T helper cell 2) which produces interleukin 4 (IL-4) and IL- 5 and IL-13.

A Figure.3 shows Antigen – presenting cell (APC) binds to Antigen (Ag) by helping of major histocompatability complex (MHC). MHC binds to TCR (t-cell receptor) on the surface of naïve T cell by additional receptor (costimulation). This leads to proliferation of Th1 and Th2 depends on the antigen. Th17 is new cell which mediates neutrophil inflammation in asthma. (Finn, et al., 2009)

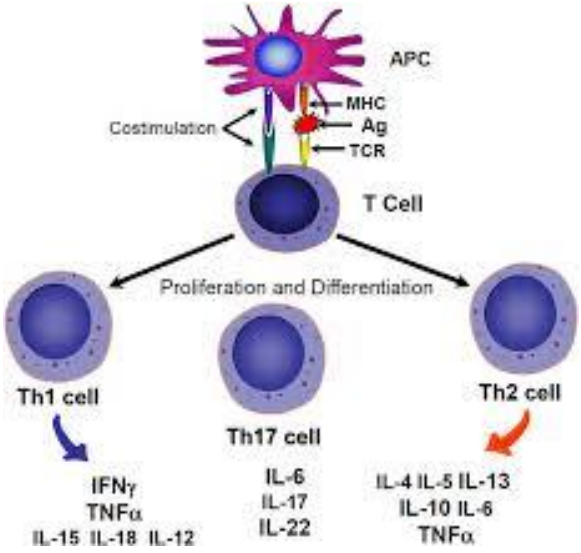

Figure 3 Responses of adaptive immunity (Finn, et al., 2009)

ALLERGIC (ATOPIC) ASTHMA:

Increase in serum immunoglobulin E level is associated with the incidence of allergic (atopic) asthma. This leads to immune response and induce interferon γ which causes wheezing. (Subbarao, et al., 2009)

The reaction begins when production of allergen- Ig-E starts. Then, Ig- E binds to high-affinity FcЄRI receptors on mast cells and basophils. After that, Ig-E mediated reaction produces early- and late-phase asthmatic responses (EAR and LAR).

In EAR phase, releasing of histamine, prostaglandins, leukotrienes, chemokines, and cytokines are within 1 hour of allergen exposure. LAR phase begins 4- 8 hours of antigen exposure. It is defined as prolonged infiltration of the airways by inflammatory cells, and causes more severe airflow obstruction.

Chronic symptoms are caused by persistent LAR and continuous allergen exposure. Ig-E mediated mast cell activation leads to chronic eosinophilia and airway remodeling which leads to chronic loss in pulmonary function. (Milgrom, et al., 2001)

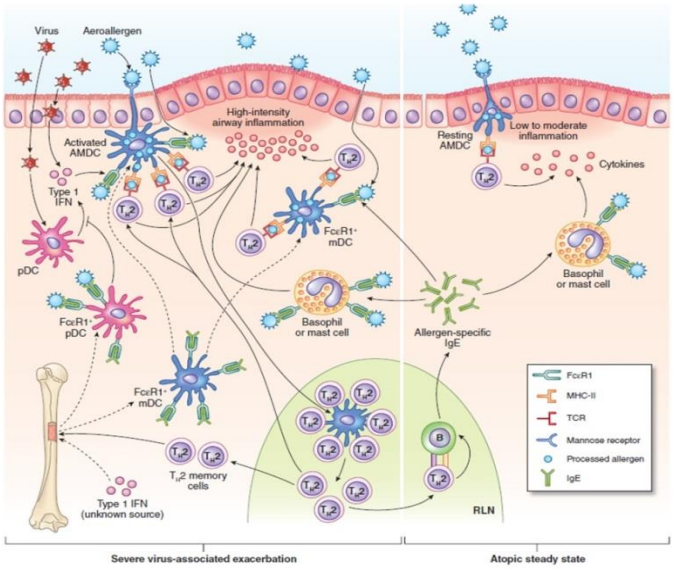

Figure 4 the atopic (allergic) asthma reaction **(Holt, et al., 2012)**

PATHOPHYSIOLOGY OF ASTHMA:

Chronic inflammation of asthma is diagnosed by persistent symptoms and increase in inflammatory cells (mast cells, lymphocytes, macrophages, eosinophils, and dendritic cells). These cells produce modulators like cytokines, and chemokines that promote the inflammation and cause airways smooth muscles contraction and hyper-reaction. Acute reaction starts with increase in mucus production, edema, inflammatory cells infiltration, and smooth muscles contraction. That's lead to airway narrowing and may progress to cause chronic changes, remodeling in the airways and losing the normal structures constantly. (Papadopoulos, et al., 2015).

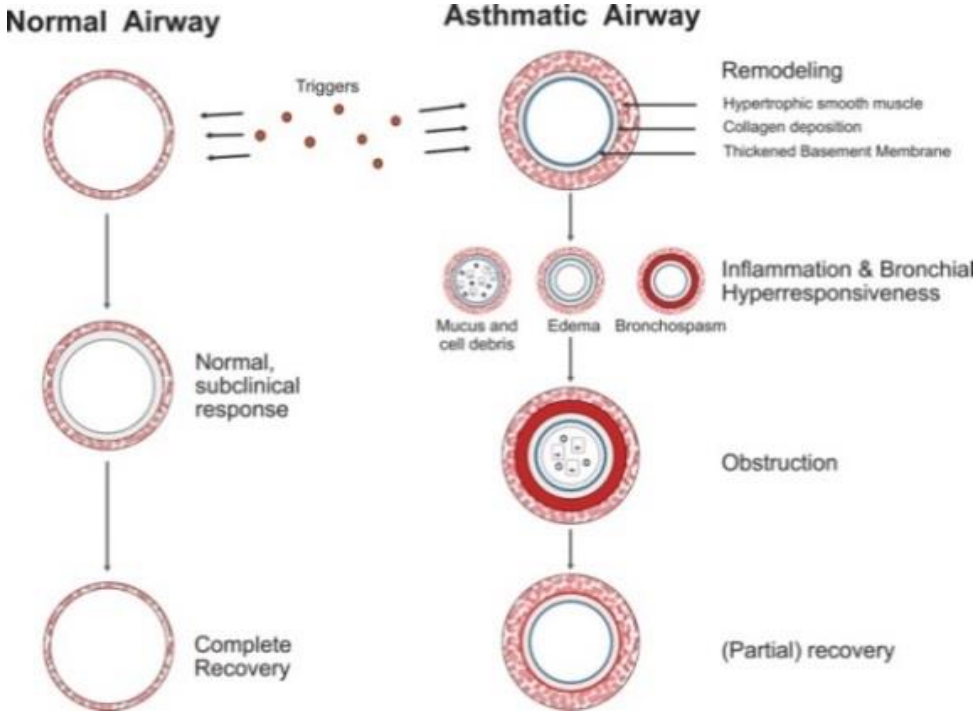

Figure 5 Chronic structural changes in asthma **(Papadopoulos, et al., 2015)**

CLASSIFICATION OF ASTHMA:

It is very important to differentiate the attack/episode of asthma because the management is based on the severity of the disease. It is hard to apply these classifications on infant or pre-school children because of lack of lung function assessment (Papadopoulos, et al., 2015).

Based on clinical signs found in patients, asthma can be classified as the following:

1. ***MILD***: attacks are not more than once a week, and no clinical signs seen between two episodes. Usually there is response to the bronchodilator within 24 hours. Also, patient has good school performance and no sleep disturbance during night. Patient usually has normal chest X-ray, and no hyperinflation. No sign of airways obstruction on PFT, No or minimal change in lung volume.
2. ***MODERATE***: wheezing and coughing are more frequent; attack episode is more than once a week. Low grade of symptoms happens between two episodes. School performance may be affected and sometimes patient wake up in the night because of wheezing and coughing. Minimal hyperinflation is seen on X-rays, and increase in lung volume. Signs of airways obstruction can be seen in PFT.
3. ***SEVERE***: wheezing and coughing are more frequent with cyanosis. Patient may needs hospitalization and has risk for respiratory failure. Sometimes becomes unconscious with hypoxic seizure attack. Poor school performance, and frequent sleep interruption. Chronic hyperinflation can be seen in X-ray. Airways obstruction is on PFT with increase in lung volume and incomplete response to bronchodilators. (Ellis, 1983)

Table 1 Summary about the severity of childhood asthma **(Papadopoulos, et al., 2015)**

	Mild	Moderate	Severe	Very severe
Wheeze	Variable	Moderate to load	Load	Often quit
Breathlessness	Walking	At rest	At rest / sitting upright	
Speaks in	Sentences	Phrases	Words	Unable to speak
Accessory muscle use	No	Common	Marked	Paradoxical
Consciousness	Not affected	Not affected	Agitated/ confused	
Respiratory rate	Slightly increased	Increased	Highly increased	Undetermined
Pulse	<100	<140 (depending on age)	>140	Bradycardia
PEF (% of predicted or personal best)	>60-70%	40-70%	<40%	<25%
SaO_2 (% on air)	>94-95%	90-95%	<90%	
PCO_2 (mmHg)	<42	<42	>=42	

DIAGNOSIS OF ASTHMA:

Testing the functionality of lung is important to evaluate the diagnosis and monitor the effectiveness of the therapy. However, normal results do not exclude the disease especially in mild cases. There are different methods and biomarkers used to test the lung function. (Papadopoulos, et al., 2015)

1. HISTORY AND PHYSICAL EXAMINATION

History and physical examination is the beginning point to diagnose the disease. Presence of typical signs/ symptoms (wheezing in chest auscultation, coughing, and shortness of breath, chest tightness) triggered by different exposures such as: allergen, irritants, infections or exercise.

History of atopy (atopic eczema, allergic rhinitis, food allergy) or family history of asthma will suggest the diagnosis. (Papadopoulos, et al., 2015).

2. SPIROMETRY

The test applies for children of a minimum age between 5-7 years old who are able to do it properly. (Papadopoulos, et al., 2015). The test conducted by using spirometer holds by hand to record the forced expiratory volume (FEV1) in 1 second, forced vital capacity (FVC), forced expiratory flow (FEF). Moreover, the test measures the bronchial response by using Methacholine which causes 20% fall in FEV1 (Galobardes, et al., 2015).

3. PEAK EXPIRATORY FLOW (PEF)

Peak expiratory flow method is used to monitor the disease in children who capable of doing this examination. In children less than 5 years old oscillometry examination should be performed which doesn't need child cooperation. (Papadopoulos, et al., 2015)

4. VOLATILE ORGANIC COMPOUND (VOC)

Exhaled VOC is noninvasive biomarker to detect the early signs of preschool asthma in children. It is to compare the healthy and prolonged wheezing and inflammatory response. VOC is associated with rhinovirus infection with 10 fold increase the risk of asthma in the future. (Formosa, 2008)

5. FRACTIONAL EXHALED NIITRIC OXIDE (FeNo)

This method is used to detect the eosinophil inflammatory response, monitoring the disease, and the effectiveness of corticosteroid. (Papadopoulos, et al., 2015). FeNo level is raised in asthma and reduces by given doses of inhaled corticosteroid (ICS). However, it needs expensive instruments (Chi, et al., 2016). Elevation of FeNo means that patient has severe asthma with frequent emergency use, hyperinflation and airways obstruction, and the worsen asthma phenotype. (Wohlberg, et al., 2012)

6. EXHALED BREATH CONDENSTAES (EBC)

EBC is noninvasive technique to measure the inflammatory biomarkers. Different markers such as nitric oxide, hydrogen peroxide, cytokines, and urates have been increased in EBC of patients with asthma. This method is easy and the cost is low. (Chi, et al., 2016) .

Investigations are done to understand whether 5- and 15- LO (lipoxgenase) pathway in EBC associated with severity of childhood asthma and clinical parameters. Analysis of EBC has proven that increase in eoxines are not only with the increased 5-LO product LTC4 (leukotriene C4) but they are associated with airway hyper-responsiveness. These markers may introduce

new treatment drugs for the disease. (Wohlberg, et al., 2012)

7. ASSESSMENT OF THE ATOPY:

Using the in vivo (skin prick test) or in vitro (specific Ig-E antibodies) methods, to indicate the triggers that associated with the disease. These methods are important to identify the specific allergen and avoid it. (Papadopoulos, et al., 2015)

PROGNOSIS OF ASTHMA:

In general, asthma has excellent prognosis. Many children become symptom-free unless they get viral respiratory infection or after heavy exercise, or during cold weather. Age of the onset doesn't affect the prognosis. (Ellis, 1983)

However, the more severe asthma in childhood is the more persist in adulthood. Prognosis is associated with risk factors, lung function, and bronchial responsiveness to treatment and markers of inflammation. (Roorda, 1996).

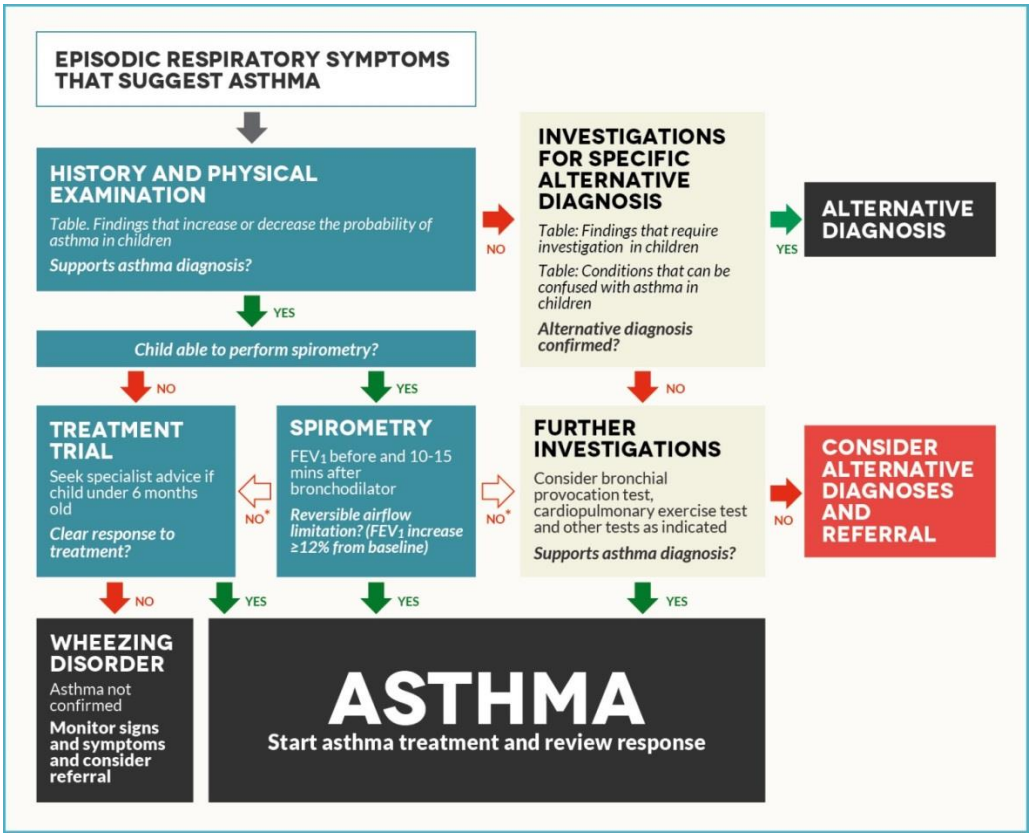

Figure 6 the criteria for asthma diagnosis **(Australia, 2015)**

MANAGEMENT OF CHILDHOOD ASTHMA:

The aim of asthma treatment is to use fewer medications. Using of medication can be classified according the severity, acute attacks or long term treatment. The common drugs are inhaled corticosteroids, Beta-2 adrenergic agonist, Theophylline, Cromolyn, Leukotriene's modifiers. Omalizumab, monoclonal antibody against Ig-E is new immune-modulatory biological drug. (Papadopoulos, et al., 2015).

The best drug for treat childhood asthma:

- Orally active with ideal medical compliance.
- Less frequent administration with long acting.
- Bronchodilator with anti-inflammation effect.
- It has effect against atopy associated symptoms like allergic rhinitis, or atopic dermatitis.
- It has tolerance for both infants and older children. (Warner, 2001).

According to the grade of asthma, treatment should be as follows:

- Mild asthma: may be treated as required with beta-adrenergic drug, and/or theophylline. Treatment usually not lasts more than 3-4 days.
- Moderate asthma: the aim is to decrease the coughing and wheezing, and increase exercise capability. 3-4 daily doses of beta-adrenergic agent and/or theophylline, and /or Cromolyn. Corticosteroid is needed in case of asthma exacerbation.
- Severe asthma: if not treated, patient may not be able to perform the daily activities. Beta-adrenergic agent and/or theophylline, and /or Cromolyn, and corticosteroid should be taken daily. Corticosteroid is required to be used daily to maintain the normal function of the lung. (Ellis, 1983)

SHORT-ACTING THERAPY:

1. **FIRST LINE**: Salbutamol is inhaled short-acting beta-2 adrenergic agonist (SABA) to relieve asthma symptoms within minutes by bronchodilation.

Advantages: safe, quick, and greater effect on airway smooth muscles.

Side effect: dose-dependent, self-limited tremor, and tachycardia (Papadopoulos, et al., 2015)

2. **SECOND LINE**: Ipratropium bromide and oxitropium bromide are anticholinergic agents. They have less effect comparing with SABA. Combination therapy of SABA and anticholinergic drugs has shown more effective than giving SABA alone mainly in acute attack. (Busse, et al., 2016).

LONG-ACTING THERAPY:

For patients who still have uncontrolled symptoms, long acting therapy should be administered. Some patients may require high dose of ICS, LTRA with maintenance drugs such as LABA, theophylline, cromones, and omalizumab. (Wohlberg, et al., 2012)

- **INHALED CORTICOSTEROID (ICS)**

ICS DRUGS: beclomethasone dipropionate, budesonide, fluticasone propionate, mometasone fumarate, ci- clesonide, flunisolide, and triamcinolone acetate. (Zhang, et al., 2014).

Inhaled ICS is the first-line drug for children is used to controls the persistent symptoms, decreases the inflammation in the lung, (Zhang, et al., 2014) , reduces the asthma attacks /exacerbation, and decreases the emergency admission. (Papadopoulos, et al., 2015).

Low doses of ICS (<400 mg/day) are not related to systemic effects in children. Whenever, patients need more than (800 mg/day), side effects may appear. (Warner, 2001).

SIDE EFFECTS: hypertension, cataracts, growth failure, hyperglycemia, bone density reduction, suppressed immune system, and bruising. (Normansell, et al., 2014).

- **LEUKTRAINE RECEPTOR ANTAGONISTS (LTRA)**

ORAL LTRA DRUGS: Montelukast, pranlukast and zafirlukast. Montelukast and zafirlukast are approved in USA, montelukast for children ≥ 2 years, while zafirlukast for ≥ 7 years. Montelukast has longer life time; it is enough to give once daily (5mg /day) while the other is twice per day. (Warner, 2001). Montelukast is moderately free of side effect but zafirlukast can cause hepatic dysfunction. (Papadopoulos, et al., 2015)

MECHNISM: LTRA blocks the binding of cysteinyl leukotrienes to the CysLT1 receptors selectively. When cysteinyl leukotrienes binds to the CysLT1 receptors, it causes bronchoconstriction, increase vascular permeability, hyper-secretion of mucous, and increase in eosinophil. LTRA will inhabit bronchoconstriction and prevent provoked asthma by allergy, cold, and hyperventilation. Montelukast as bronchodilator may improve the lung function. Also, it decreases the level of eosinophil in blood circulation, and decrease the demand of β-agonist bronchodilators. (Warner, 2001).

- **LONG-ACTING BETA-2 ADRENERGIC AGONISTS (LABA)**

LABA DRUGS: includes salmeterol and formoterol. LABA is usually combined inhaler of ICS+LABA to prevent asthma signs and prevent increase ICS dose. It is recommended for children ≥ 5 years. (Papadopoulos, et al., 2015).

MECHENISM: they interact with β-adrenergic receptor which is located in plasma cells of bronchial smooth cells and cause bronchodilatation. It is slightly slower of the onset comparing with SABA; it effects within 10- 20 minutes but the duration of action up to 12 hours due to high affinity binding of

the molecule's side chain to a specific site within the ß2 adrenergic receptor. For children ≥ 5 years old the recommended dose is 400 mcg /day. (Ducharme, et al., 2010)

- **CROMONES**

DRUGS: Cromolyn sodium and nedocromil as second- line medication. Recommended dose is 20 mg, 3-4 times per day for children ≥ 5 years old. (Papadopoulos, et al., 2015).

These drugs are known as maintenance drugs. They have less effectiveness comparing with ICS. Cromones are used to diminish the hyper-responsiveness, reduce chemical cell mediator of asthma, and decrease the eosinophil in the inflammation. (Ellis, 1983).

Randomized and controlled trial studies are applied for children between 5-12 years old who had mild or moderate asthma with mean 4.3 years of follow up. 8 mg of Nedocromil is given in 2 puffs from a metered-dose inhaler. At follow up, Nedocromil reduced the urgent-care visits, and the doses of prednisone. (Tonascia, 2001).

- **THEOPHYLLINE**

DRUG: methylxanthine

Theophylline causes bronchodilatation and anti-inflammation. It is maintenance drug for children with moderate asthma used by adding it to ICS. However, it has less effect than LABA drug. (Papadopoulos, et al., 2015). Theophylline has narrow therapeutic index and can cause several side effects. It is eliminated by biotransformation in the liver. Therefore, it is affected by the factors influence the liver function such as age, diet, liver cirrhosis, smoking, and viral infections. All children should be monitored every 6 months to check the serum concentration of theophylline. Recommended dose 200 mg / 8 hours or 250 mg /8 hours depends on the doctor decision. Parents should be aware of the drug intoxication. If they notice headache, nausea, or vomiting they should seek medical attention. (Ellis, 1983).

- **OMALIZUMAB (rhuMAb-E25,rhu-Mab or Xolair)**

Omalizumab is known as anti-Ig E drug; a humanized monoclonal antibody that inhabits serum Anti-immunoglobulin E. It reduces eosinophilic inflammation and Ig-E mediated cells. It is recommended subcutaneously for children ≥ 6 years old for uncontrollable severe allergic Ig-E mediated asthma every 2-3 weeks. (Normansell, et al., 2014).

MECHENISM: omalizumab binds to Ig-E at the site of high affinity receptor and decreases the Ig-E serum level. Therefore, it will inhibit EAR and LAR, and decreases the regulation of FcƐRI receptors on basophil cell. Omalizumab is safe and effective, can control the asthma symptoms, and decreases the daily doses of ICS. (Milgrom, et al., 2001).

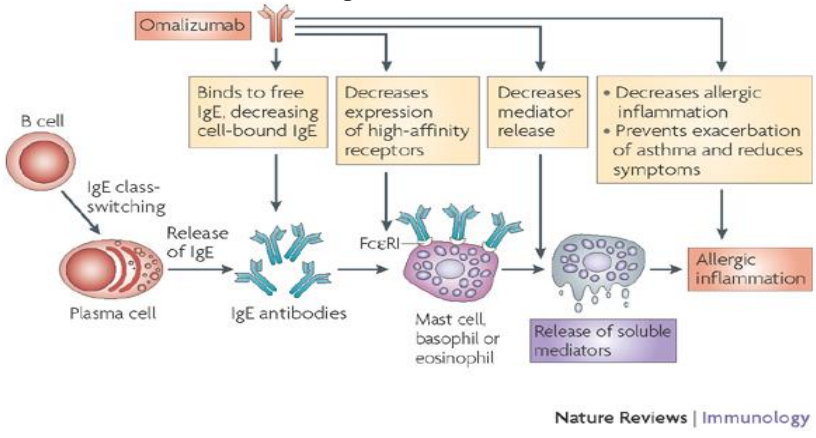

Figure 7 the mechanism of Omalizumab drug. **(Holgate, et al., 2008)**

About 25 studies were conducted on group of 6382 patients. This group had asthma with different severity including women, men and children. The purpose of these studies is to compare omalizumab that's injected under skin or into a vein or by inhaler with placebo. The duration of these studies was between 8-60 weeks.

THE RESULTS OF THE STUDIES:

- Patients received omalizumab had less exacerbation, on average 16 out of 100 people had an exacerbation compared with 26 out of 100 who received placebo.

- Patients received omalizumab had decreased numbers of hospitalization in comparison with placebo.
- Patients receiving omalizumab were able to decrease doses or completely withdraw the inhaled corticosteroid.
- Patients had omalizumab had improvement of the symptoms and health related quality of the life.
- Patients receiving omalizumab had fewer side effects; some had skin reaction on the site of the injection.
- Patients who used omalizumab were able to use less rescue medications than placebo.

SIDE EFFECTS OF OMALIZUMAB:

- Skin reaction in the site of injection.
- Theoretically, using omalizumab may increase immune-complex pathology and abnormal response to parasitic infection.
- Theoretically, omalizumab may increase the risk of cancer because of Ig-E of the immune response to neoplasia.

More research needs to be done on long- term use of omalizumab from different population. (Normansell, et al., 2014).

TIOTROPIUM IN THE TREATMENT OF ASTHMA:

Tiotropium is type of long-acting anticholinergic drugs and bronchodilator which is used as maintenance drug added to ICS drug. This drug is alternative added-on treatment recently in 2015 by Global Initiative for Asthma (GINA) strategy.

The studies of add-on therapy for pediatric patients with moderate asthma:

THE FIRST PHASE:

The first phase of randomized, double-blind, and incomplete crossover studies on 105 adolescent patients aged 12–17 years. These patients were suffering from moderate symptomatic asthma. Patients received tiotropium (5, 2.5 -1.25) µg/ daily or placebo, add-on to medium-dose ICS with or without a leukotriene modifier.

- **THE EFFECT:**

Tiotropium has improved lung function in comparison with placebo. It has shown that with the 5-µg dose it provides greater improvements. These improvements including: peak FEV1 (compared with placebo: 113 mL, p=0.004), morning PEF (compared with placebo: 13.2 L·min−1, p<0.05) and evening PEF (compared with placebo: 17.1 L·min−1, p=0.0031)

THE SECOND PHASE:

The second phase study was performed on 101 children aged between 6 to 11 years with moderate symptomatic asthma using the same study design.

- **THE EFFECT:**

There were improvements in all measures of FEV1, forced expiratory flow between 25%, and 75% of forced vital capacity observed with all Tiotropium doses. In comparison between morning PEF and evening PEF, the improvement in morning PEF was with all doses. However, the improvement in evening PEF was significant with the 5-µg dose only (17 L·min−1, p=0.0024).

REAL –LIFE EVIDANCE OF TIOTROPIUM ADD-ON THERAPY IN ASTHMA:

The therapy was performed on 2042 asthmatic patients from UK. The group of patients was collected for retrospective study treated with additional Tiotropium therapy to either 18 µg by the Spiriva HandiHaler device (93%) or 5 µg by the Respimat (Soft Mist inhaler) (7%).

Tiotropium was associated with:

- Decrease in the incidence of exacerbations.
- Antibiotic therapy for lower respiratory tract infections;
- Increase in asthma control in the year following subscription.

Further studies are applied specially in children and adolescent to provide more information about using the anticholinergic drugs in the treatment of asthma. Furthermore, real-life studies with different ages and different demographic will help us to improve the patient management (Busse, et al., 2016).

ASTHMA EXACERBATIONS

The terms exacerbation, attack, or episode all are signs of acute or subacute episodes of asthma symptoms and it increases airways obstruction. Asthma exacerbation is associated with increase in morbidity and frequent emergency visits. It may require hospitalization and may cause death. Severity varies from mild to fetal; it is based on the clinical symptoms presented in asthmatic patient. (Papadopoulos, et al., 2015).

Viral infections such as human rhinovirus (HRV) or respiratory syncytial virus (RSV) are known as the

most common causes of asthma exacerbation. It is associated with interaction between innate and adaptive immune pathways in asthma pathogenesis. (Wohlberg, et al., 2012).

TREATMENT OF ASTHMA EXCERBATION:

1- Bronchodilator should be started at home before going to emergency.
2- Salbutamol inhaled at dose 200–1000µg every 20 minutes for the 1st hour.
3- Ipratropium bromide improves the asthmatic symptoms; the recommended dose is 2–8 puffs, or nebulized 0.25–0.5mg. The progression should be in the 1st hour. If there is not response the patient should be refer to the hospital.
4- Oxygen is needed to correct hypoxia with O2 monitoring, So2>95% is the goal. As well, PCo2 has to be monitored in severe attacks.
5- Oral systemic corticosteroid such as prednisolone 1–2mg/kg/day is the recommended dose for 3–5 days, up to 20mg in children <2years and up to 60mg in older children.

If there is no response to all the treatments discussed above. The patients should be transferred to ICU. In the ICU we should consider the following: continuous inhaled beta-2 agonists, IV bronchodilator like salbutamol, and IV aminophylline. However, IV magnesium sulphate, helium- oxygen mixture had shown little of no improvement of the symptoms. (Papadopoulos, et al., 2015).

KETAMINE FOR LIFE-THREATENING ASTHMA:

Acute severe asthma exacerbation is high risk to develop respiratory failure. It may need intubation and invasive ventilation. Ketamine is used as sedative for intubation and ventilation in severe asthma attacks. The recommended doses: bolus dose between (0.1 mg/kg to 2 mg/kg) followed by continuous infusion (0.15–2.5 mg/kg/h).

THE MECHANISM:

Ketamine is water-soluble agent, noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist and acts as opioid receptor. It has different routes oral, intravenous (IV), or intramuscular (IM) because it's hydrophilic and lipophilic.

IM and IV ketamine have high bioavailability with a half-life of 2–3 hours and a rapid onset of action to get the peak plasma concentration in 60 seconds. Also, it has a short duration of action (10–15 minutes after a single bolus injection). Ketamine inhibits postsynaptic nicotinic or muscarinic receptors, blocks voltage-sensitive Ca2+channel, inhibits catecholamine reuptake, and increases catecholamine concentrations.

SIDE EFFECTS:

Mainly, it is uncommon or has mild side effects in children and adolescent includes hypoventilation, hypertension, laryngospasm, and agitation.

- It should be given slowly in case IV administration to prevent respiratory depression and laryngospasms.
- Patients with seizure should avoid it because it decreases the seizure threshold.
- It causes increase in cerebral blood flow, should check the intracranial and intraocular pressures.

Although, it has minor side effects such as hallucination, dysphoria, and slight disturbance in heart rate and blood pressure. (Hendaus, et al., 2016).

ASTHMA-RELATED DEATH DURING TREATMENT WITH SALMETEROL:

Adding LABA such as salmeterol to ICS is known to control asthma. However, this drug is associated with life- threating asthma in large population study.

Two adolescent boys have had uncontrollable asthma, no response to rescue inhaler during attacks, and no response to SABA drugs given before exercise. They were admitted for evaluation in the Children's Hospital of Iowa.

When both boys started to exercise in treadmill, they experienced bronchospasm within few minutes. That was because they were receiving high dose of ICS and salmeterol with albuterol or pirbuterol. To recover from bronchospasm other dose of inhaled albuterol was given. Later, salmeterol replaced for 2 days with theophylline (table 2). Both patients had asthma control improvement, and they were able to exercise with albuterol or pirbuterol pre-treated. Also, the numbers of acute attacks during 10 days was decrease in in-patient or follow up.

Patient No.	Day	Maintenance Medication	Medication Taken before Exercise	FEV_1 before Exercise	Decrease in FEV_1 during Exercise	Exercise Duration and Symptoms
				liters	%	
1†	1 day after admission	Budesonide (Pulmicort Turbuhaler), 200 μg twice daily, and salmeterol (Serevent MDI), 50 μg twice daily	Pirbuterol (Maxair Autohaler), 2 inhalations	2.83	42	Highest heart rate, 157 beats per min; target heart rate not attained because of dyspnea after 4 min
	5 days after admission	Budesonide, 200 μg twice daily, and salmeterol, 50 μg twice daily	Pirbuterol, 4 inhalations	3.26	55	Highest heart rate, 158 beats per min; target heart rate not attained because of dyspnea after 4 min
	9 days after admission	Budesonide, 200 μg twice daily, and SR theophylline, 225 mg twice daily (serum theophylline concentration, 15 μg/ml)	Pirbuterol, 4 inhalations	3.60	1	9 min, with highest heart rate of 173 beats per min and no dyspnea
	18 days after admission	Budesonide, 200 μg twice daily, and SR theophylline, 225 mg twice daily	Pirbuterol, 4 inhalations	3.56	1	10 min, with highest heart rate of 172 beats per min and no dyspnea
2‡	Before admission	2 Inhalations twice daily of fluticasone, 500 μg, in combination with salmeterol, 50 μg (Advair 500/50)	Albuterol, 4 inhalations from a metered-dose inhaler	1.43	71	3 min, with severe dyspnea and hypoxemia (oxygen saturation, 82%)
	Day of admission	1 Inhalation twice daily of fluticasone, 250 μg, in combination with salmeterol, 50 μg	Albuterol, 4 inhalations from a metered-dose inhaler	1.88	68	3 min with severe dyspnea and hypoxemia (oxygen saturation, 74%)
	2 days after admission	Budesonide, 200 μg twice daily, and SR theophylline, 250 mg twice daily (serum theophylline concentration, 9 μg/ml)	Albuterol, 4 inhalations from a metered-dose inhaler	1.98	51	9 min, with highest heart rate of 168 beats per min, no hypoxemia, and rapid spontaneous improvement
	3 days after admission	Budesonide, 200 μg twice daily, and SR theophylline, 300 mg twice daily (serum theophylline concentration, 16 μg/ml)	Albuterol, 4 inhalations from a metered-dose inhaler	1.93	14	11 min, with highest heart rate of 172 beats per min, no dyspnea, and no decrease in oxygen saturation

* FEV_1 denotes forced expiratory volume in one second, MDI metered-dose inhaler, and SR sustained release.
† The predicted FEV_1 for Patient 1 was 3.45 liters.
‡ The predicted FEV_1 for Patient 2 was 1.69 liters.

Table 2 the results from 4 exercise studies of two patients treated with ICS, with or without salmeterol
(Schwarzberg, 2006)

SIDE EFFECTS OF MEDICATION
Possible drugs side-effects in asthma:

Table 3 summary of asthmatic drugs side-effects

DRUGS	SIDE EFFECTS
1- Short acting β agonist (SABA)	Dose-dependent, self-limited tremor and tachycardia (Papadopoulos, et al., 2015)
2- Inhaled corticosteroid (ICS)	Hypertension, cataracts, growth failure, hyperglycemia, bone density reduction, suppressed immune system, adrenal suppression, and bruising. (Normansell, et al., 2014)
3- Long acting β2 agonist (LABA)	Mainly it causes cardiovascular effects such as hypokalemia , increased heart rate, ventricular arrhythmia, palpitation, ischemia, and risk of chronic cardiac failure (Rossi, et al., 2008)
4- Leukotriene receptor antagonist (LTRA)	**-Psychiatric**: hallucination, over-sleeping, hyperactive, agitation, Nyctophobia, and depression. (Erdem, et al., 2015) **-Non-psychiatric:** convulsion, rash, headache, increased appetite, abdominal pain, and Aphtous ulceration. (Erdem, et al., 2015)
5- Omalizumab (rhuMAb-E25, rhu-Mab or Xolair)	Skin reaction in the side of injection. (Normansell, et al., 2014)

LIFE STYLE MODIFICATION:

In the last 20 years, the prevalence of the asthma has increased in the western countries. Different hypothesis explained that scientifically such as hygiene hypothesis.

Hygiene hypothesis is linked to allergy, asthma, and autoimmune diseases in industrial countries. Especially, for patients who have less exposure to microbes. They have less infection because type of life-style is different: small number of family, many immunizations, frequent uses of antibiotics, and more infection control. Early life exposure to microbes may modulate the immunity and immunity phenotype from predominant a Th2 phenotype to Th1 phenotype in the childhood. (Finn, et al., 2009).

Physician should control the disease by determining the level of asthma treatment Such as the usage of rescue medications. Also, the usage of assessment scales such as Asthma Control Questionnaire (ACQ), Asthma Control Test, and Asthma Quality of Life Questionnaire. Those measures will help physicians to differentiate the uncontrollable patients and give other treatment options. It also, helps in checking the progression of treatment. Moreover, it will help the physician to see if the patients have asthma exacerbations and check other factors affecting the patients like smoking. (Busse, et al., 2016).

EFFECT OF VITAMNE D SUPPLEMENT:

There is a relationship between vitamin D and asthma, vitamin D plays a vital role in innate and adaptive pathways with asthma pathogenesis. Different cross-sectional studies have shown the relationships between decreased vitamin D concentration in the blood level and severity of asthma. (Riverin, et al., 2015).

Randomized controlled trials (RCT) and cross-over or parallel design. This is used to evaluate the effect of vitamin D alone or with other asthma drug versus placebo or active control in children from (0-18) years old with asthma.

THE EFFECTS:

1. Emergency visits and hospitalizations: decreased in the mean number of visits (P=0.015) comparing placebo.
2. Asthma exacerbations: four out of five trials had improvement after taking vitamin D and had less asthma exacerbations; one trial had respiratory infection symptoms and had to take antibiotics or LABA drugs.
3. Asthma severity / symptoms: after 6 months follow up with taking vitamin D, in two studies they noticed improvement in asthma symptoms.
4. Lung function: there is improvement in Peak expiratory flow rate (PEFR) but no different between Vitamin D and placebo.
5. β-2 agonist use: no static different between vitamin D and placebo in the time and number of puffs used per day.
6. Steroid use: on 4 trials reporting, 3 reported no effect with vitamin D and 1 reported improvement with vitamin D.
7. Serum 25 (OH) D concentration: 3 trials reported increasing serum 25 (OH) D concentration in vitamin D group comparing with the control group.
8. Side effects: one trial showed normal values in serum calcium, parathyroid hormone and phosphorus and calcium in urine levels.

One study found that 60,000 IU of vitamin D monthly can prevent emergency visit. Further studies should be conducted in the future to investigate more effects of vitamin D and find out the outcomes in childhood asthma. (Riverin, et al., 2015).

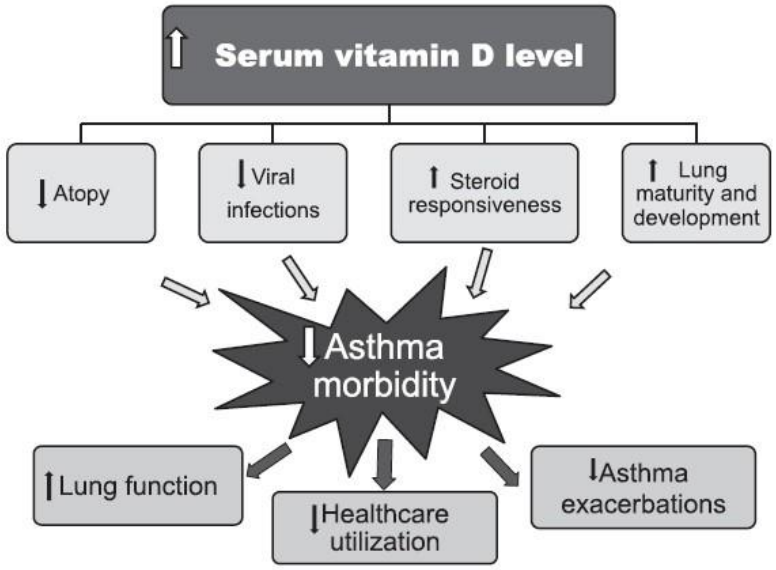

Figure 8 the effects of serum vitamin D level in the asthma morbidity **(Gupta, et al., 2012)**

ROFLUMILAST COMBINED WITH MONTELUKAST VERSUS MONTELKAST ALONE:

Roflumilast is a phosphordiesterase-4 (PDE-4) inhibitor which improves the lung function as bronchodilator and anti-inflammatory effect in mild to moderate asthma. It shows more effect when it is combined with montelukast a leukotriene receptor for patients who uncontrolled by ICS and LABA.

A study in phase 2, randomized, placebo-control, and double blind applied in 64 patients with asthma. Patients received 500 µg of roflumilast and montelukast, then placebo with 10mg of montelukast, and then 500 µg of roflumilast and 10 mg of montelukast. The aim of the studies is to find out the efficacy, mode of action, and safety of combination roflumilast and montelukast and montelukast alone.

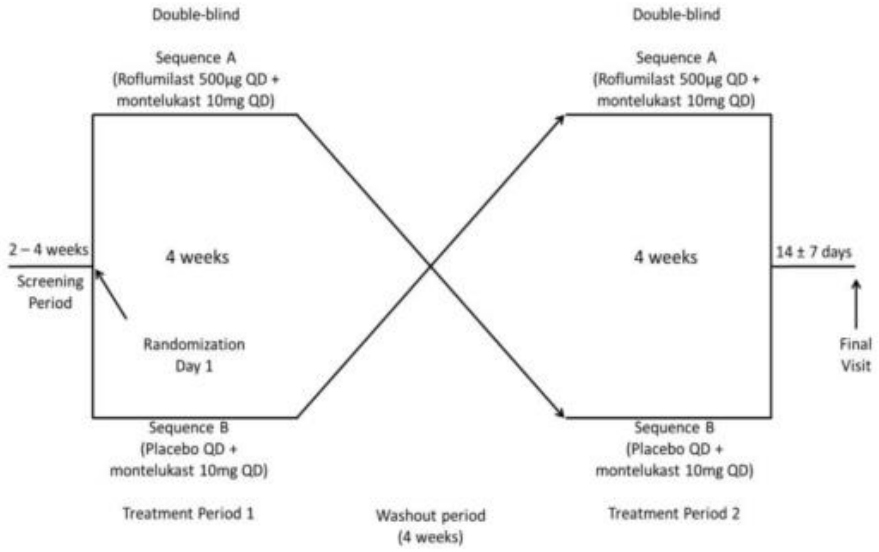

Figure 9 the crossover stud stats 2-4 weeks of screening period, then two 4 weeks blind study separated by 4 weeks of washout period. **(Bateman, et al., 2016)**

THE RESULTS:

Combination of roflumilast and montelukast with ICS and LABA had improved outcomes.

- Lung function: there is improvement; the mean baseline of FEV1 in 4 weeks was higher comparing with placebo and montelukast in both periods 1 and 2. There is no different in FVC in both (roflumilast and montelukast) and (placebo and montelukast)
- Asthma exacerbations: were shorter duration compared with placebo plus montelukast.
- Urinary LTR4: is decreased by 28 days in period 1 and continued low in period 2. However, it was unchangeable for placebo and montelukast in period 1 and increased twice in washout period, and then decreased in period 2.
- There is no change in the number of eosinophils and neutrophils, or inflammatory mediators in the blood serum. (Bateman, et al., 2016)

NEBULIZED SALBUTAMOL VERSUS COMBINATION IPRATRBIUM BROMIDE:

Inhaled salbutamol is β agonist which is used in acute severe asthma (ASA) with oxygen and systemic corticosteroids. New guidelines recommended that in case ASA patient should be treated with salbutamol and ipratrbium as bronchodilators and stop the obstruction. Ipratrbium bromide is anticholinergic drug which decreases the bronchospasm and improves lung function.

A study applied to compare the effect of combination of inhaled salbutamol with ipratrbium bromide. Randomized control trial (RCT) applied for ASA patients in two groups divided randomly. **Group-A** took 3 doses of nebulized salbutamol only (0.03 ml/kg/dose) at 15-minute intervals. **Group-B** took 3 similar doses of salbutamol with ipratropium (250 µg/ dose) and the children average ages were between 7-11 years. After the last dose given, checked the response after 15 minutes and assessed the improvement of ASA.

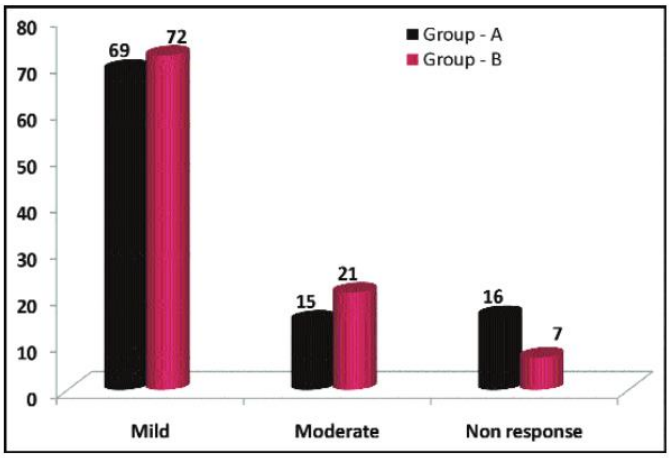

Figure 10 the severity classification **(Memon, et al., 2016)**

THE RESULTS:

- Improvements were 88.5% with patients who had salbutamol and 100% with who had salbutamol and ipratrbium bromide.
- FEV1 is better in patients who had salbutamol and ipratrbium bromide than patients who had salbutamol only. (Memon, et al., 2016).

DISCUSSION:

Treatment of childhood asthma goal is to decrease the emergency visits and hospitalization. Also, it is to decrease the symptoms and exacerbation by decreasing the inflammation response in the airways and cause bronchodilation. The treatment mainly depends of grading on the represented symptoms. The first- line drug used is ICS with maximum dose 400mg/ day. This dose is safe and does not cause any

systemic effects. Usually, ICS is combined with maintenance drugs such as LABA, theophylline, and Cromolyn.

Omalizumab is anti-Ig-E drug for children of age 6 years old. It is the target drug for allergic (atopic) asthma. It shows the effectiveness to decrease the eosinophil in inflammation and decreases the exacerbation. Also, it is considered as safe with few side effects.

Increase in vitamin D serum has strong relationship to decrease asthma mortality rate. It increases the lung function, improves asthma symptoms, and decreases hospitalization.

In comparison between nebulized salbutamol versus combination ipratrbium bromide Improvement was noticed 100% with patients who had salbutamol and ipratrbium bromide. Also, FEV1 was better in patients who had salbutamol and ipratrbium bromide.

Combination of roflumilast and montelukast with ICS and LABA had improved outcomes. The asthma exacerbation was shorter in duration compared with placebo plus montelukast. Furthermore, improvement of the mean baseline of FEV1 in 4 weeks was higher in roflumilast combined with montelukast comparing with placebo and montelukast in both periods 1 and 2.

SUMMARY:

Pediatric asthma is a common chronic obstruction in airways causes narrowed airways, and increases the mucus secretion. Airways smooth muscle becomes thin causes bronchospasm. Asthma is stimulated by pollen, smoking, hyperventilation and cold air.

It is complex reactions caused by genetic, environmental or immunologic reactions. Atopic (allergic) asthma is caused by Ig-E mediated reaction by binding to mast cells and produces histamine, cytokines and chemokines which enhance the inflammatory reactions and causes airways obstructions.

Asthma can be classified into mild, moderate and severe. This classification is the guidance for the treatment strategy, which is based on the history and the physical examination, spirometry and monitoring of asthma.

Asthma treatments are divided into two categories, short and long acting based in duration of action. Short acting is for reliving the symptoms within few minutes and cause bronchodilation such as SABA (Salbutamol) and anticholinergic drugs (Ipratropium bromide and oxitropium bromide).

Long acting agents are used for uncontrollable asthma for long duration such as ICS and LTRA with maintenance drugs such as LABA, theophylline, and Cromolyn.

Another long acting agent is omalizumab that is anti-immunoglobulin E helps to decreases allergic asthma. It decreases the hospitalizations and asthma exacerbation. Tiotropium is long acting anticholinergic drug works as bronchodilator and improves the lung function .

Asthma exacerbation should be treated immediately with bronchodilators at home with salbutamol, ipratropium bromide. In the hospital patient should be treated with oxygen if there is hypoxia and oral systemic corticosteroid (prednisolone). Ketamine is used for sedative, intubation and ventilation in severe asthma attacks.

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