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# **Review Article**

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# Asthma management in pediatric age group

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# **ABSTRACT**

Asthma is one of the most prevalent chronic illnesses that affect the pediatric population, defined as chronic airway inflammation, remodeling of the airway wall, and airway hyper-responsiveness to leading to spasms in response to stimuli inducing a reversible airflow obstruction. The death rate from asthma around the world is as high as 0.7 per 100,000 children, therefore making it important to understand all aspect of its pathophysiology and management. We conducted this review using a comprehensive search of Pubmed, MEDLINE, and EMBASE from March 1980, through November 2017. The following search terms were used: asthma pathophysiology, chemokines, leukotriene, asthma management, steroids, beta agonist, leukotriene modifiers. Our aim was to understand detailed pathophysiology of pediatric asthma, and also have a look at the management of asthma. Optimal management of pediatric asthma is based upon a variety of measures, such as good symptomatic control, drug therapy, inhalers, but more importantly what matters is a good relationship of the physician with the patient and their care takers in order to achieve better result in short and long term. The impact of the relationship must be studied in more details to make asthma management more efficient for the pediatric group of patients.

Keywords: Pediatric asthma, Asthma pathophysiology, Leukotriene modifiers for asthma management

### **INTRODUCTION**

Pediatric asthma is a disorder in children defined ad recurrent airway obstruction, associated inflammation, and bronchial hyper-responsiveness. Asthma is the most prevalent chronic illness of the pediatric population, affecting 8.5% of children in the United States. Asthma is more common in males at younger age, but in adolescence, it is more commonly seen in females. The overall death rate from asthma is around 0.7 per 100 000 children around the world. Asthma also contributes to a

large number of school absences, consequently impairing a child's academic as well as social achievements.<sup>2</sup>

Asthma can be classified in various ways. Based on the type of trigger, we classify as allergic (extrinsic) or non-allergic (intrinsic). Common triggers causing extrinsic asthma are plant pollen, dust mites, fur, cigarettes smoke active as well as passive, certain chemicals, food substances, perfumes, and fumes. Those triggers that can induce an intrinsic response are released from within the body, mostly as a result of viral or bacterial infection. At

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the same time, physical or emotional stress can also produce asthma symptoms.<sup>3</sup>

Wheezing and coughing are the most common symptoms that children present with. Other symptoms include sudden shortness of breath, chest tightness, and dyspnea after minimal physical activity. The symptoms take place episodically, and tend to occur at night too. Asthma is diagnosed clinically with the presence of symptoms and confirmed by pulmonary function test by demonstrating reversible airways obstruction which is indicated by 12% or 200 ml increase in FEV1 after inhaling a bronchodilator.<sup>4</sup>

#### **METHODS**

### Data sources and search terms

We conducted this review using a comprehensive search of MEDLINE, PubMed, and EMBASE, January 1980, through February 2017. The following search terms were used:

#### Data extraction

Two reviewers have independently reviewed the studies, abstracted data, and disagreements were resolved by consensus. Studies were evaluated for quality and a review protocol was followed throughout.

The study was done after approval of Review Board of King Abdulaziz University.

## **DISCUSSION**

### Pathophysiology of asthma

As discussed above, asthma is defined as chronic reversible airway inflammation, remodeling of the airway wall, and airway hyper-responsiveness in response to stimuli leading to a reversible obstruction of airflow. Allergic illnesses such as allergic rhinitis and asthma are chronic inflammatory disorders with an essential Th2 immune response. Inhaling the allergens induces bronchial hyper-reactivity and recruits eosinophils, lymphocyte, and mast cells in both the upper and lower airways, leading to activation of inflammatory cascade producing local and systemic inflammatory reactions.<sup>5</sup> The inflammatory process is often limited to the conducting airways with progression of the disease to severe and chronic forms, the inflammatory infiltrate comprise the small airways and adjacent alveoli too. Inflammation in the small airway appears mainly external to the airway smooth muscle. However, inflammation in the big airways involves submucosa as well. Several factors contribute to the pathogenesis of asthma and its resultant airflow obstruction.6

### Sensitization and T cell response

Asthma begins in early childhood. Sensitization to various inhaled allergens, such as house dust mites, pollen, fungi, cockroaches, fur and animal dander. Once these allergens are inhaled, they trigger T helper type 2 (Th2) cell proliferations in some children, leading to production and release of Th2 cytokines, interleukin (IL)-4, IL-13 and IL-5 in the blood. An important step of allergen sensitization is the processing of inhaled allergens by dendritic cells which are found in the airway epithelium and submucosa. Allergen uptake is improved by the IgE which is bound to high-affinity receptors on dendritic cells that enables allergen internalization.<sup>7</sup>

The ability of dendritic cells to produce IL-12 balances the Th1 and Th2 responses. Although, IL-12 is able to neutralize Th2 sensitization, it is can also add to maximum expression of allergic airway disease post sensitization. After sensitization occurs, the T cells migrate back to airways at the site of dendritic cells with the guidance of chemokines. They also transform into potent producers of a various other types of cytokines, including IL-3, IL-4, IL-5, IL-6, IL-9, IL-13 as well as granulocyte–macrophage colony-stimulating factor. IL-1β is manufactured by macrophages, dendritic cells, smooth muscle cells, monocytes, and epithelial cells in huge amounts; while IL-2 produced by T cells further increases antigen-induced T-cell proliferation and maturation. Proceedings of the proliferation and maturation.

# Mast Cells

After activation, mast cells release the already-made granules which contain substances including histamine, hepatin, tryptase, and many cytokines, along with newly formed eicosanoids such as platelet derived growth factor (PGD2), the cysteinyl leukotriene (CysLT) specially LTC4 and LTD4, and thromboxane A2. These mediate strong smooth muscle contraction and also enhance microvascular permeability. Both PGD2 and LTD4 collaborate with cell-surface receptors on eosinophils, mast cells, macrophages, and basophils where they act as chemo-attractant and priming agents. As a result, CysLT antagonists like montelukast and pranlukast work by blocking the acute effects of leukotrienes upon the airway, and later show more anti-inflammatory effect. <sup>10</sup>

Activation of mast cells, primarily by the high-affinity IgE receptor, causes the release of several cytokines which were stored within mast cell granules, namely, tumor necrosis factor  $\alpha$  (TNFa), IL-4 and IL-5. These cytokines and chemokines positively contribute to the continuing inflammatory process in asthma progression. They may be somewhat responsible for the allergeninduced late-phase inflammatory response associated with allergen trigger.  $^{11}$ 

In chronic asthma, mast cells are prominently increased throughout airway smooth muscle in both large and small airways. Mast cells at this site not only work upon airway smooth muscle by the action of autacoid mediators such as prostaglandin PGD2, LTD4, and histamine, but also are responsible behind fibrogenesis and increased proliferation of smooth muscle which is called remodeling response.<sup>12</sup>

### **Eosinophils**

Eosinophils are present in the airway wall and found in big number in patients with uncontrolled asthma in their sputum and bronchoalveolar lavage. These cells are first produced from the bone marrow as CD34 precursors. When eosinophils mature, they travel from the circulation through the microvascular compartment entering the airway wall. Eosinophils produce and are a source of granule basic proteins, including major basic protein, eosinophil cationic protein, and eosinophil peroxidase. They are capable of producing eicosanoids like prostacyclin (PGI2) and cysteinyl leukotriene and can release tissue-damaging superoxide as well as a lot of cytokines and chemokines. <sup>13</sup>

### Monocytes and macrophages

Monocytes have the ability to differentiate into macrophages and dendritic cells. Dendritic cells need IL-4. In chronic asthma both monocytes and macrophages are found in the airway mucosa and play a key role in the pathogenesis of disease. While these cells are a major source of cysLT, a number of lysosomal enzymes, and reactive oxygen, however their role in facilitating tissue damage as well as to the overall airway pathology of remains yet unknown. In steroid-refractory asthma, macrophage and monocytes are believed to play a more significant role and could be responsible for the continuity of chronic inflammation.<sup>14</sup>

# Airway epithelium

The airway epithelium is believed to be central to pathogenesis of asthma. Bronchial biopsies reveal areas of epithelial metaplasia, damage,, thickened subepithelial basal lamina, increased myofibroblast, along with other major indication of airway remodeling like hypertrophy and hyperplasia of airway smooth muscle cells, angiogenesis. Transformed deposition and composition of extracellular matrix proteins and hyperplasia of mucous gland is also noted. <sup>15</sup> One noteworthy characteristic of the epithelium is its ability to defend itself against oxidant injury, which is a characteristic enabling us to partially explain why asthmatic patients are hypersensitive to oxidant pollutants such as tobacco smoke. <sup>16</sup>

# Airway remodeling

Dissimilarities in the formed elements of the airway add expressively to the pathophysiology of asthma. Existence of chronic inflammation can change the homeostasis of lung tissue, leading to airway remodeling. Tissue remodeling includes changes such as epithelial transformation, increased matrix deposition, buildup of plasma proteins, and matrix degradation. The most obvious alteration occurs in the airway smooth muscle. The smooth muscle mass increases as a result of hypertrophy and hyperplasia, and this change are noticed across the airways. In chronic asthma the airways modify by becoming thicker as a result of the matrix proteins lay down, including deposited proteoglycans, collagen fibers, and proliferated of microvessels.<sup>17</sup>

#### Leukotriene

Leukotrienes are important chemical mediators of inflammation in asthmatic airway. They are made up by arachidonic acid and secreted by eosinophils, mast cells, neutrophils, basophils, macrophage, and lymphocytes. Many effects of the cysteinyl leukotriene occur with the help of the CysLT1 receptors, such as smooth muscle contraction, increase in vascular permeability, and facilitating chemotaxis. Leukotriene C4 and leukotriene D4 have the same ability to stimulate smooth-muscle contraction in the lung tissue. CysLTs are the most potent bronchoconstrictor agents yet known. Its potency is about a thousand times more compared to histamine. They decrease ciliary activity, increase airway hyperresponsiveness, intensify microvascular permeability, and induce proliferation of airway smooth muscle.

### ASSESSMENT AND DIAGNOSIS

The diagnosis and severity of asthma are established based on clinical criteria, which includes detailed history, followed by physical examination, and lastly the evidence of either reversible airflow obstruction, or airway hyperresponsiveness. The US National Asthma Education and Prevention Program (NAEPP) classify asthma severity based on two factors: impairment and risk. The impairment factor comprises of the measured airway obstruction, intensity and frequency of daytime and nocturnal symptoms, frequency of using short-acting β2 agonist relieving symptoms, and the amount of interference of daily activities due to symptoms. The risk criterion measures the frequency of exacerbations. These data collectively provides a good clinical picture and helps in managing asthma severity.<sup>19</sup> Physical findings such as audible wheezing during normal breathing and use of accessory muscle may appear during exacerbation and indicate a poor negative predictive value for excluding the diagnosis of asthma. However, spirometry is the most essential diagnostic procedure for assessing airway obstruction as well as its reversibility. Reversibility of airway obstruction is demonstrated by an increase in FEV1 by 12% or greater and 200mL or greater from baseline readings after inhaling short-acting β2-agonists. Bronco-provocation by methacholine was an old method for confirmation, which is no longer used in practice.<sup>20</sup>

#### **MANAGEMENT**

General long-term objectives and goals of asthma management include:<sup>21</sup>

- Reducing the risk of exacerbations, including avoiding trigger,
- Attaining symptom control,
- Maintaining a normal physical performance, and
- Reducing side effects of the therapy

Additionally, these goals must be discussed with the patient and give serious consideration. A good relationship between the patient and the health care provider is crucial for effective asthma management. Physicians must encourage patients to participate in decision making and express their concerns and needs. Self-management and knowledge about asthma should be promoted with training to patients and care takes, as studies have shown positive effects on morbidity in adults as well as children.<sup>22</sup>

### Asthma control

Modern asthma treatment includes both pharmacological and non-pharmacological therapy, and is based on the core idea of asthma control, which has demonstrated improvement in the treatment outcomes. This concept is centered on a cycle of assessment, adjustment, and follow-up. Symptom control is often associated with less frequent asthma exacerbations.

### Drug therapy

Inhalation therapy is the treatment of choice for asthma because it provides a higher local concentration of drug while creating fewer systemic side effects leading to a very good tolerance compared to other forms of systemic medication. The drugs are classified into three pharmaceutical categories: controller, reliever, and Addon.<sup>23</sup> A controller is taken regularly. They reduce inflammation, prevent exacerbation risk, and control symptoms. These are taken irrespective of presence of symptoms.<sup>24</sup> The relievers are taken when requires in order to reduce current symptoms, such as in case of asthma exacerbations. They can also be used for the short-term prevention of exercise-induced bronchoconstriction. The primary objective of asthma management is to minimize the need of reliever drugs. Add-on drugs are used in patients with severe asthma, or those with persistent symptoms or exacerbations in spite of being on high-dose of combination therapy with inhaled corticosteroids (ICS) as well as optimization of modifiable risk factors.2

# Choice of inhaler

For children, the choice of inhalers depends on individual skills, age, and abilities (e.g., inspiratory flow) and also barriers such as arthritis, muscle weakness, impaired vision. Until early school age, most patients often use inhalers with a suitable spacer. Oral/nasal masks must only be used if the use of a mouthpiece is not possible due to age or compliance. For children who are 8 years and older, most of them use dry powder inhalers. Whenever possible, patients should be involved deciding the type of inhalers. Since there is no other perfect method, regular checks as well as training at clinics are necessary enabling patients to use inhalers in a better and correct way. The use of several different inhalers at the same time should be avoided to prevent confusion and errors.<sup>26</sup>

## Steroid dosage

Most of the ICS beneficial effects could be achieved in low doses; not many studies are available that shows dose–response relationships for conventional doses. Daily low doses are not linked with many clinically significant adverse effects; however, high inhaled doses pose a greater risk of systemic adverse effects especially with prolonged application, although this risk is still smaller compared to systemic administration of steroids. When initiating treatment plan, ICS must be titrated to find the minimum effective dose that is capable of achieving good symptomatic control was well as minimal risk of exacerbation.<sup>27</sup>

### Trigger avoidance

Lastly, we would like to discuss those patients who continue to suffer from exacerbations of asthma regardless of administering optimal dose, or even maximizing pharmacological therapy. In nonpharmacological management, avoiding triggers, such as first and second hand smoking, fume inhalation, inactivity, or known food allergy can significantly contribute to better control, management, and minimize exacerbation. Therefore, identification of modifiable factors very often can lead to ultimate success in treatment.<sup>28</sup> The recognition of risk factors in the living surroundings of the patient and the application of improvement procedures require an intensive doctorpatient discussion as well as the patient's willingness to cooperate actively. Eventually, successful asthma management is based on the relationship between doctor, patient, and caretakers.<sup>29</sup>

### **CONCLUSION**

In this review, we have summarized the details of the pathophysiology the various factors involved in the process, including T cells, mast cells, eosinophils, the epithelium of airway itself, and leukotrienes and chemokines. Consequently, optimal management of pediatric asthma is based upon a variety of measures, such as good symptomatic control, drug therapy, inhalers, but more importantly what matters is a good relationship of the physician with the patient and their care takers in order to achieve better result in short and long term. The

impact of the relationship must be studied in more details to make asthma management more efficient for the pediatric group of patients.

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