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PATHOPHYSIOLOGY OF ASTHMA AND CLASSIFICATION

Tharwat Abdullah Ahmed Almanasef[1], Akeelah Abdullah Hussain Al Khalaf[1], Ola Abbas Alqudaihi[1], Alaa Essa Almulla[1], Hind Hussain Alzaher[1], Ameerah Ibraheem Almredeef[1], Zahra Hussain Suhail[2], Amal Ali Al Dhamen[2], Mehad Ali Al Awad[2], Faiza Jaafer Al Haider[2], Aida Ali Abdulwahab[2], Fatimah Abdullah Abu Abdullah[2], Asma Naji Al Huwaidi[2], Zahra Ali Abu Alrehi[2], Amira Abdullah Alabbad[2]

[1] Primary Health Care - National Guard Hospital - Dammam – Saudi Arabia

[2] Immam Abdul Rahman Bin Faisal Hospital - National Guard Hospital - Dammam – Saudi Arabia

Abstract:

Asthma is a chronic inflammatory disorder of the airways characterized by episodes of reversible airflow obstruction due to bronchial hyper-reactivity and inflammation. It affects over 16 million adults and 5 million children in the United States and has significant morbidity, including frequent hospitalizations and emergency department visits. This review aims to understand the multifactorial nature of asthma, which is essential for tailored treatment and better health outcomes.

Keywords: *Asthma, Asthma Pathophysiology, Leukotriene Modifiers for Asthma Management.*

Corresponding author:

Tharwat Abdullah Ahmed Almanasef,

Primary Health Care - National Guard Hospital - Dammam – Saudi Arabia

QR code

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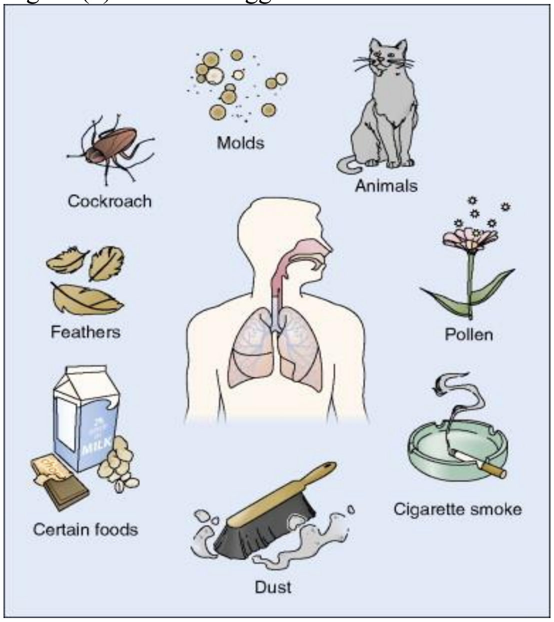
INTRODUCTION:

Asthma is a chronic, heterogeneous respiratory condition characterized by inflammation of the airways, leading to variable and often reversible airflow obstruction and bronchial hyperresponsiveness. This condition manifests through symptoms such as wheezing, coughing, chest tightness, and shortness of breath, which can vary significantly among individuals and over time.(1) The disease is marked by episodic exacerbations, which can lead to severe complications requiring hospitalization or intensive care unit (ICU) admission, particularly when exacerbations result in impaired alveolar gas exchange and dynamic hyperinflation of the lungs. These exacerbations are often triggered by environmental pollutants, allergens, and other irritants, with urban environments posing additional challenges due to higher exposure to traffic-related pollution and socioeconomic factors [Figure 1]. (2) The emergent paradigm that is currently undergoing development seeks to enhance the accuracy and reliability of asthma diagnosis and treatment methodologies by meticulously identifying and categorizing patients into distinct mechanistic groups that exhibit unique pathophysiological characteristics. Furthermore, the rapid advancements in technology have played a significant role in the refinement and evolution of asthma classification systems, thereby facilitating a more nuanced understanding of this complex condition. In this context, sophisticated integrated software suites and advanced classifiers that leverage neural network algorithms, as well as models based on the dynamics of respiratory function, have been innovatively developed to provide invaluable assistance to clinicians, enabling them to achieve high levels of precision in diagnosing and classifying asthma cases. Consequently, these technological innovations not only promise to improve clinical outcomes for patients suffering from asthma but also represent a significant leap forward in the integration of computational tools within the realm of respiratory medicine, thereby fostering a more comprehensive approach to the management of this chronic respiratory disorder.

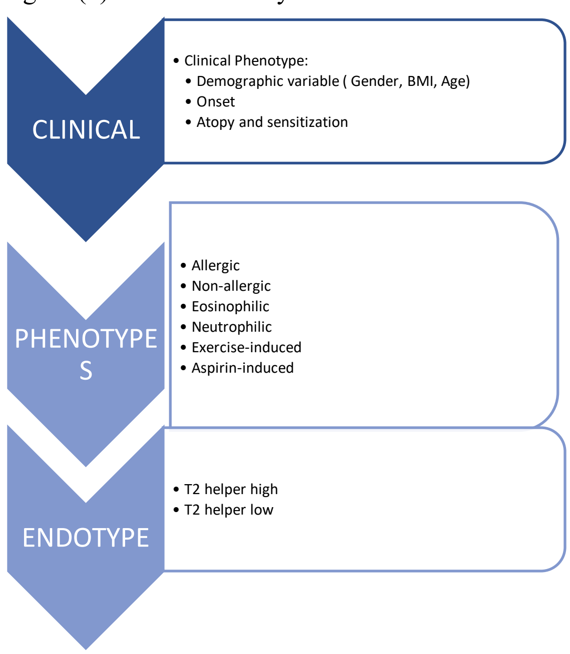
Figure (1): Asthma Triggers



Pathophysiology of Asthma and Classification:

The pathophysiology of asthma involves several key processes: airway inflammation, bronchial hyperreactivity, and airway remodeling, each contributing to the clinical manifestations of the disease. Airway inflammation is central to asthma's pathophysiology and involves the infiltration of various inflammatory cells, including eosinophils, mast cells, lymphocytes, and macrophages, into the bronchial walls. This infiltration leads to the release of inflammatory mediators such as cytokines, leukotrienes, and prostaglandins, which perpetuate the inflammatory response and contribute to airway hyperresponsiveness and obstruction.(3, 4) The inflammatory process is often driven by a Th-2 lymphocyte-predominant immune response, which is associated with atopy and IgE-mediated inflammation.(5) Bronchial hyperreactivity, another hallmark of asthma, is characterized by an exaggerated response of the airways to various stimuli, including allergens, pollutants, and infections. This hyperreactivity is linked to the inflammatory milieu within the airways and is exacerbated by structural changes in the airway walls, such as epithelial damage and increased smooth muscle mass. (3) The autonomic nervous system, particularly the cholinergic and non-adrenergic non-cholinergic (NANC) systems, also plays a role in modulating bronchial tone and responsiveness, with neurogenic inflammation contributing to the pathophysiology. (6) Airway remodeling refers to the structural changes that occur in the airways as a result of chronic inflammation. These changes include thickening of the airway walls, increased smooth muscle mass, subepithelial fibrosis, and mucus gland hyperplasia, all of which contribute to irreversible airflow obstruction and persistent symptoms. (3-5) Eosinophils and mast cells are particularly implicated in these processes, as their products can cause epithelial damage and promote fibroblast proliferation and smooth muscle hypertrophy. Genetic predisposition and environmental factors, such as exposure to allergens and pollutants, are significant contributors to the development and exacerbation of asthma. Genetic factors influence the immune response, particularly the balance between Th-1 and Th-2 lymphocyte activity, while environmental exposures can trigger or worsen the inflammatory response. (5) The interaction between these factors and the immune system is complex and involves both innate and adaptive immune responses, with epithelial cells playing a crucial role in mediating these interactions. (6)

Figure (2): how to Classify Asthma



Asthma classification is a complex process that involves various methodologies and criteria, reflecting the heterogeneous nature of the disease [Figure 2]. The classification of asthma can be approached from several perspectives, including clinical, physiological, molecular, and phenotypic dimensions. Clinically, asthma is traditionally classified based on the frequency of symptoms and the degree of airway obstruction. The Global Initiative for Asthma (GINA) provides a framework that categorizes asthma into intermittent and persistent types, with the latter further divided into mild, moderate, and severe based on symptom frequency and lung function tests such as forced expiratory volume in one second (FEV1) or peak expiratory flow (PEF). This classification helps in tailoring treatment plans according to the severity of the disease. In addition to severity, asthma can also be classified by the level of control, which considers the frequency of symptoms, activity limitation, and the need for rescue medication. This approach categorizes asthma as controlled, partly controlled, or uncontrolled, emphasizing the dynamic nature of the disease and the importance of regular monitoring and adjustment of treatment. (7, 8) From a physiological standpoint, diagnostic tests such as spirometry and bronchial provocation tests are used to assess bronchial hyperreactivity and lung mechanics, which are critical in identifying asthma and its severity. These tests, however, have limitations and must be interpreted in conjunction with clinical presentations and responses to pharmacotherapy. (9) Molecular classification of asthma involves the use of biomarkers such as interleukin-25 (IL-25) levels in peripheral blood. This biomarker helps distinguish between steroid-sensitive and non-steroid-sensitive asthma, providing insights into the likely response to inhaled corticosteroids. Such molecular approaches are part of a broader trend towards personalized medicine, where treatment is tailored based on individual patient characteristics and biomarker profiles. (10) Phenotypically, asthma is recognized as a syndrome with various subtypes, or phenotypes, that include allergic and non-allergic asthma, occupational asthma, aspirin-exacerbated respiratory disease, and exercise-induced asthma, among others. Recent research has further refined these phenotypes into endotypes, which are defined by distinct pathophysiological mechanisms and may include specific cellular or molecular biomarkers. (9, 11) Endotype of asthma provide a deeper understanding by focusing on the underlying biological mechanisms. For instance, T-helper type 2 (Th2)-driven inflammation is a well-characterized endotype, associated with eosinophilic airway inflammation and elevated levels of cytokines like IL-4, IL-5, and IL-13. This endotype is particularly responsive to targeted biological therapies.(12) Other endotypes include severe obstructive asthma with neutrophilia, which is characterized by a significant decrease in lung function and is less responsive to standard treatments. The role of genetic and environmental factors is also significant in asthma classification. For example, maternal asthma and early-life viral infections are risk factors for developing asthma, influencing its endotypic expression. (13) Additionally, psychological factors, such as type D personality, have been shown to affect asthma symptom control and quality of life, suggesting that psychosocial interventions could be beneficial for certain patient groups. (14) Advancements in molecular biology have facilitated the identification of biomarkers that can help in distinguishing between different asthma endotypes. For instance, the expression of specific mRNA and microRNA in airway epithelial cells has been used to identify molecular endotypes, which can guide personalized treatment approaches. (15)

Management of Asthma:

The management of asthma involves a multifaceted approach that integrates pharmacological and non-pharmacological strategies to control symptoms, prevent exacerbations, and maintain lung function. The primary goal is to tailor treatment plans to individual patient needs, considering the severity and chronicity of the disease, as well as any precipitating factors. Pharmacological management is central to asthma care, with inhaled corticosteroids being a cornerstone for most patients. These are recommended for their efficacy in reducing inflammation and preventing exacerbations, even in milder cases. (16, 17) The use of inhaled corticosteroids is often combined with long-acting beta-agonists (LABAs) for patients with more persistent symptoms, providing a synergistic effect that enhances control. Theophylline and cromolyn are alternative options, particularly for patients who experience continuous or frequently recurring symptoms. Theophylline requires careful monitoring of serum concentrations to ensure efficacy and safety, whereas cromolyn is noted for its safety profile, lacking the risk of overdose. For acute asthma episodes, inhaled sympathomimetic drugs are preferred due to their rapid action and reduced side effects compared to oral bronchodilators. In severe cases, such as status asthmaticus, intravenous aminophylline and corticosteroids, along with aerosolized sympathomimetics, are effective treatments. (18) The management of exacerbations also emphasizes the use of corticosteroids, either orally or via inhalation, to quickly control inflammation. Non-pharmacological strategies include patient education, which is crucial for effective asthma management. Educating patients about their condition, triggers, and the correct use of medications, including inhalers, is essential. Written personalized asthma action plans are recommended to guide patients in managing their symptoms and recognizing when to seek medical help. (17) Regular reviews in primary care settings help ensure adherence to treatment plans and allow for adjustments based on the patient's response and lifestyle factors, such as smoking. Guidelines such as those from the Global Initiative for Asthma (GINA) and the British Thoracic Society (BTS) provide evidence-based recommendations that emphasize a control-based approach to asthma management. These guidelines advocate for a severity-based classification system to guide treatment decisions and stress the importance of regular monitoring and adjustment of therapy to maintain control. (19, 20)

CONCLUSION:

asthma is a multifaceted disease requiring a comprehensive management approach that considers its diverse phenotypes and underlying pathophysiological mechanisms. While current treatments focus on controlling symptoms and preventing exacerbations, ongoing research into the molecular underpinnings of asthma holds promise for more targeted and effective therapies in the future. Addressing environmental and socioeconomic determinants, particularly in urban settings, is also crucial for improving asthma outcomes on both individual and population levels.

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