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PAHTHOPHYSIOLOGY AND PROPER MANAGEMENT OF ASTHMA: REVIEW

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Abstract: **This review study was aimed to focus on the pathophysiology, and management approaches of asthma in general, its aimed to highlight the most common interactions between the pathophysiology and the proper treatment. An electronic literature search was conducted using Medline (PubMed), Scopus, and EMBASE in December 2016 (all studies published to the mentioned period). The terms used to search titles and abstracts were (asthma OR wheezing OR wheeze OR lung function) AND (pathophysiology OR diagnosis OR treatment OR therapeutic options OR breathing therapy). Only original studies with human subjects and published in English were included. Asthma is a disease of the respiratory tracts, characterized by inflammation and connected with respiratory tract hyper-responsiveness, which can lead to episodes of shortness of breath, chest tightness, wheezing and cough. Genetic factors, environmental impacts and specific trigger factors are implicated in the advancement of the disease. A thorough scientific history and objective measurement of lung function are very important in establishing a reasonably specific medical diagnosis of asthma A series of drugs is used in the management of the disease, and clinical guidelines promote a stepwise technique to drug therapy, where treatment is stepped up when needed and stepped down when control is good.**

Keywords: **pathophysiology, asthma, proper treatment, Medline (PubMed), diagnosis, drug therapy.**

1. INTRODUCTION

Asthma is a common chronic condition of the airways that is complicated and defined by variable and repeating symptoms, airflow blockage, bronchial hyperresponsiveness, and a hidden inflammation [(1,2,3)]. The interaction of these features of asthma figures out the clinical manifestations and severity of asthma (**Figure 1**) [(4)] and the response to treatment. Significant advances have actually been made in comprehending the genetics, public health and pathophysiology of asthma, a condition that has increased in occurrence worldwide over the past 20 years [(5)]. International asthma standards have been in presence for over twenty years and treatments of tested effectiveness are readily available, yet controlling asthma can be challenging for lots of patients [(6)]. The disease substantially impacts healthcare systems as well as the quality of life of patients and their families [(7)]. Poor asthma control leads to increased hospital admissions and urgent care sees [(6)].

During the past decades, medical facility care and death of asthma have reduced significantly; however, new clinical issues have actually been reported. One issue is the high percentage of uncontrolled or improperly managed asthma [(8,9,10)]. As effective treatment is readily available, these reports [(8,9,10)] have been frustrating for clinicians and researchers. Different causes have been discussed, lack of access to asthma clinics, low drug adherence, under-treatment, poor perception of asthma, phenotypes resistant to existing medication, renovation of the air passages, and so on [(11,12,13,14)]. Other asthma issues are the bad connection between signs and other asthma tests, the observations that physician-diagnosed asthma often cannot be confirmed and that various results in asthma research studies offer different outcomes. Some of these problems may be explained by inaccurate or incomplete asthma medical diagnosis. If the medical diagnosis is not 'right', the treatment will not be 'right.' Although it has been pointed out that differential medical diagnoses and comorbidity need to be separated from asthma, the much deeper elements of this subject have only partially been discussed in the literature. The requirement for important conversation of diagnosis is highlighted by the high prevalence of asthma-like conditions. These disorders might be puzzled with 'classical' asthma [(15,16)].

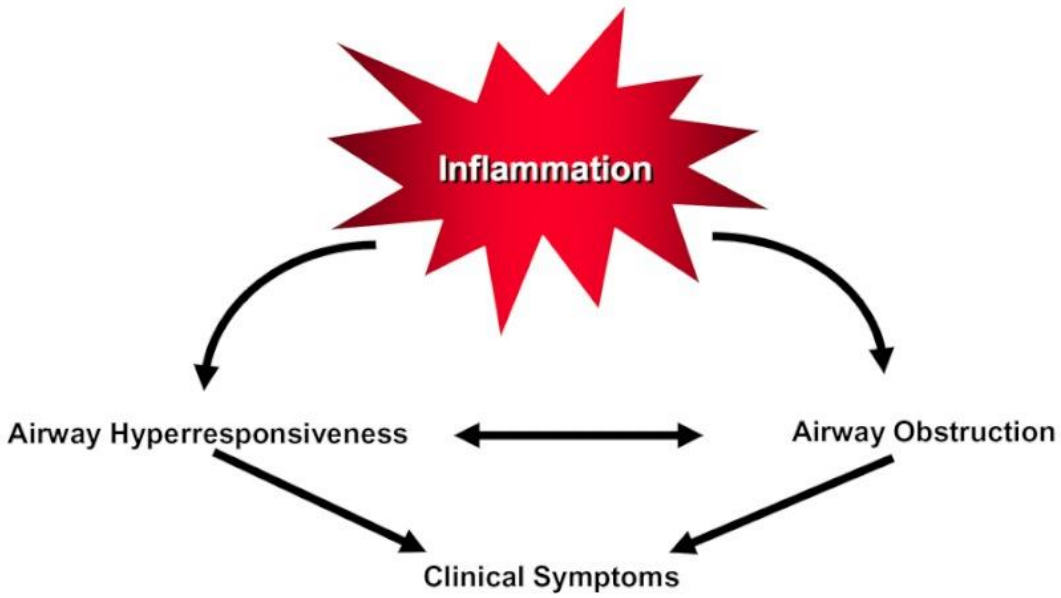

Figure 1: THE INTERPLAY AND INTERACTION BETWEEN AIRWAY INFLAMMATION AND THE CLINICAL SYMPTOMS AND PATHOPHYSIOLOGY OF ASTHMA [(4)]

AIM:

This review study will focus on the pathophysiology, and management approaches of asthma in general, its aimed to highlight the most common interactions between the pathophysiology and the proper treatment

2. METHODS

Search Method:

An electronic literature search was conducted using Medline (PubMed), Scopus, and EMBASE in December 2016 (all studies published to the mentioned period). The terms used to search titles and abstracts were (asthma OR wheezing OR wheeze OR lung function) AND (pathophysiology OR diagnosis OR treatment OR therapeutic options OR breathing therapy). Only original studies with human subjects and published in English were included. In addition, references list of the included articles was used to complete the search. To be included in the systematic review, a study needed to be discussing the pathophysiology, general aspects, and treatment approaches for asthma

3. RESULTS & DISCUSSION

❖ **Types of asthma:**

Atopic asthma:

Atopic asthma typically starts in childhood or adolescence and is associated with identifiable triggers that provoke wheezing. Atopic asthma is often connected with a family history of allergic diseases and functions of atopy such as eczema and rhinitis [(18,19)]. The disease commonly happens as a result of an allergic response to particular irritants such as house allergen, grass and tree pollen and dander from domestic animals [(19)]. Exposure to an irritant in atopic individuals causes the release of excessive amounts of Immunoglobulin E (IgE) from B lymphocytes. IgE binds to cells associated with inflammation, which stimulates the release of inflammatory arbitrators that cause bronchoconstriction and inflammation of the air passages [(20)]. Atmospheric contamination and maternal smoking in pregnancy can pre-dispose individuals to raised IgE levels and the development of asthma and air passage hyper-responsiveness [(21)].

Non-atopic asthma:

Not all cases of asthma are attributable to atopy, for that reason factors unassociated to atopic disease are likewise important [(19)]. Some patients establish asthma in adult life frequently as a consequence of viral respiratory infections; this is typically described as non-atopic asthma. This type of asthma can be more persistent with few obvious triggers aside from infection [(5,18)]. Non-atopic asthma is IgE-independent [(21)].

❖ **Overview of asthma syndrome:**

Several studies have revealed that dyspneic feelings represent various respiratory mechanisms. Concentrating on bronchial blockage is very important because of the possible risk of extreme asthma attacks; however, other non-obstructive symptoms are regular [16] and may likewise cause extreme suffering and poor quality of life [23,24,25]. Translating all signs as obstruction might cause misinterpretations. The lack of a broader diagnostic method may describe a few of the present problems in the asthma location. Some unrestrained asthma and 'difficult-to-treat asthma' might be discussed by the reality that the patients do not have symptoms/mechanisms that are able to react to the provided treatment. Examining the causes of 'problematic' asthma', 'unchecked asthma', 'difficult-to-treat asthma', and 'extreme refractory asthma' [26] is necessary, however of main concern is the expedition of the systems behind common signs like breathlessness, shortness of breath, tightness of the chest, hard in getting air, air cravings, heavy breathing, and others. A theory that is strongly supported is that symptoms/sensations with hidden systems form a spectrum of reactions depending upon which receptors in the breathing system are activated. Hence, different systems may be integrated in one single asthma syndrome. Other signs such as shortness of breath, shortness of breath, heavy breathing, hard in getting air, air hunger, and challenging in taking deep breaths probably reflect non-obstructive dyspnea. Symptoms are 'soft' variables that mostly need to be measured by subjective scales. Nevertheless, as the underlying systems become understood, it will be possible to establish unbiased tests. This has actually long held true with bronchial tightness (lung function tests) and hyperresponsiveness (methacholine test, mannitol test, and so on). Other examples of industrialized unbiased tests are the voluntary hyperventilation test for identifying hyperventilation syndrome [23] and the capsaicin inhalation test for detecting sensory air passage hyperreactivity [26,27].

❖ **Pathophysiology of asthma:**

Bronchoconstriction: In asthma, the dominant physiological occasion causing clinical symptoms is air passage narrowing and a subsequent disturbance with air flow. In intense worsenings of asthma, bronchial smooth muscle contraction (bronchoconstriction) happens rapidly to narrow the respiratory tracts in response to direct exposure to a variety of stimuli consisting of irritants or allergens. Allergen-induced intense bronchoconstriction results from an IgE-dependent release of conciliators from mast cells that consists of histamine, tryptase, leukotrienes, and prostaglandins that straight contract respiratory tract smooth muscle [28]. Aspirin and other nonsteroidal anti-inflammatory drugs (see area 3, component 3) can likewise trigger acute air flow blockage in some patients, and proof indicates that this non-IgE-dependent action also includes arbitrator release from air passage cells [29]. In addition, other stimuli (consisting of workout, cold air, and irritants) can cause intense airflow obstruction. The systems controling the air passage response to these factors are less well defined, however the strength of the response appears related to underlying airway inflammation. Tension may also contribute in speeding up asthma worsenings. The mechanisms involved have yet to be developed and might include improved generation of pro-inflammatory cytokines. Asthma can affect the trachea, the bronchi and the bronchioles, which form part of the lower respiratory tract. The disease triggers bronchoconstriction or irregular narrowing of the respiratory tracts as a result of epithelial damage, over-production of mucous, bronchospasm, oedema and muscle damage [5,22].

Airway remodeling: In some persons who have asthma, air flow limitation might be just partly reversible. Irreversible structural modifications can happen in the airway **(Figure 3)** [4]; these are related to a progressive loss of lung function that is not prevented by or totally reversible by present treatment. Airway renovation involves an activation of a number of the structural cells, with following long-term changes in the respiratory tract that increase airflow blockage and airway responsiveness and render the patient less responsive to therapy [30]. These structural changes can include thickening of the sub-basement membrane, subepithelial fibrosis, respiratory tract smooth muscle hypertrophy and hyperplasia, capillary expansion and dilation, and mucous gland hyperplasia and hypersecretion. Asthma can affect the trachea, the bronchi and the bronchioles, which form part of the lower breathing tract. The disease causes bronchoconstriction or abnormal constricting of the air passages as a result of epithelial damage, over-production of mucous, edema, muscle and bronchospasm damage [5,22]. Epithelial damage in asthma, the epithelium (the layer of cells that line the airways) can end up being damaged and peel away. Epithelial shedding can contribute to respiratory tract hyper-responsiveness in a number of ways; these consist of loss of barrier function, which may permit penetration of irritants; loss of enzymes that break down inflammatory conciliators; and exposure of sensory nerves, which might lead to reflex neural effects on the air passage [22]. Modifications can also take place in the subepithelial layer, such as the putting down of collagen [5].

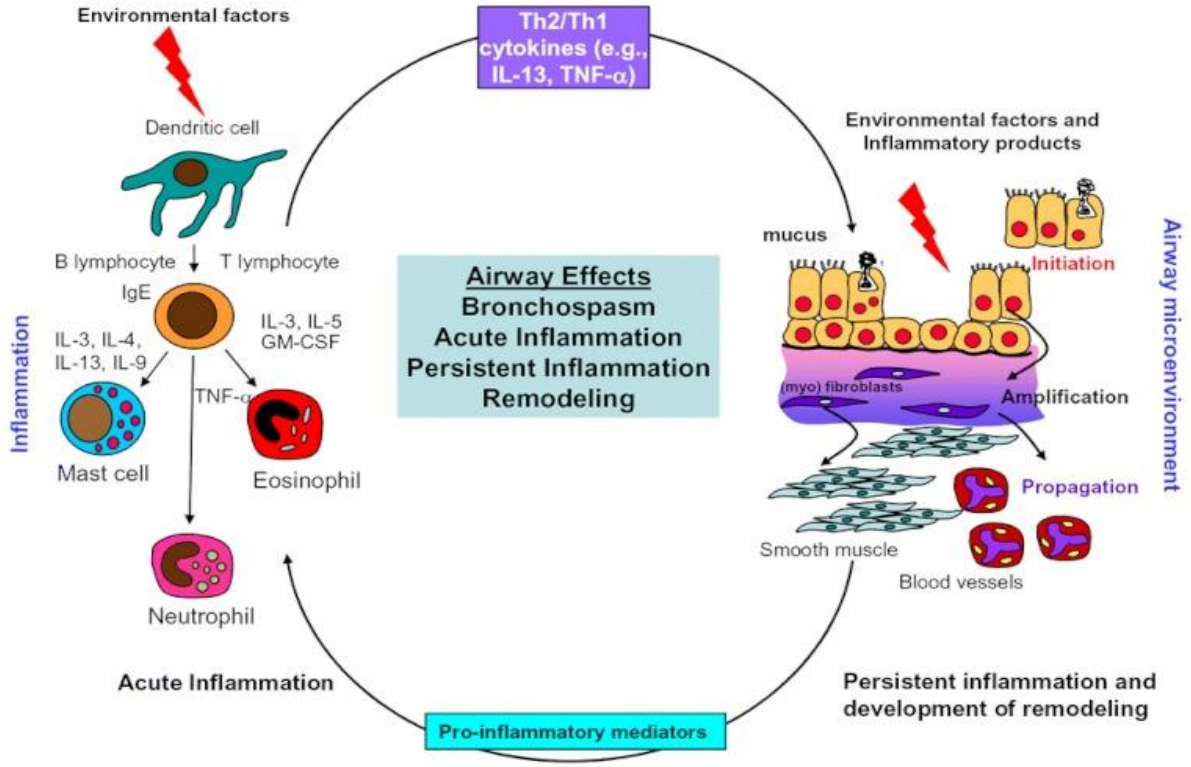

Figure 3: FACTORS LIMITING AIRFLOW IN ACUTE AND PERSISTENT ASTHMA [4]

Mucus hypersecretion: Asthma causes the mucus-secreting cells in the respiratory tracts to multiply and the mucous glands to broaden. Increased mucous secretion contributes to the development of viscid mucous plugs that can occlude the respiratory tracts [21].

Airway edema: The blood vessels in the respiratory tract walls can dilate and might leakage. The effects of microvascular leak include increased respiratory tract secretions, impaired mucociliary clearance and oedema, As the disease becomes more relentless and inflammation more progressive, other factors additional limit air flow (**Figure 3**). These consist of edema, inflammation, mucous hypersecretion and the formation of inspissated mucus plugs, in addition to structural changes including hypertrophy and hyperplasia of the air passage smooth muscle. These latter changes might not react to usual treatment [20,21].

❖ **Treatment options of asthma:**

The guideline to treatment approach for asthma summarized in (**Table 1**) [5] this guideline since 2011, helps assist the practitioner when recommending treatment. The stepwise method offers advice on drug classes and suitable dosages. Patients must begin treatment at the step most appropriate to the initial intensity of their asthma so that early control is attained. When required and stepped down when control is good, treatment ought to be stepped up. Professionals must constantly examine and review the diagnosis adherence to existing medication and inhaler technique before stepping up treatment [31].

Short-acting beta$_2$agonists:

First-line treatment for mild intermittent asthma is a short-acting beta$_2$ agonist, either salbutamol or terbutaline, taken by inhalation [5,31]. Short-acting beta$_2$ agonists deal with the beta2 adrenergic receptors in the smooth muscle of bronchial tissue, producing bronchodilation and easing the symptoms of chest tightness and shortness of breath [5]. Inhaled corticosteroids If symptom control is not achieved with a bronchodilator, an inhaled corticosteroid ought to be added for grownups who have to utilize a breathed in beta$_2$ agonist three times a week or more, who are symptomatic 3 times a week or more or are waking one night a week [5].

Inhaled corticosteroids:

4 such as beclometasone fluticasone, budesonide and dipropionate propionate, are the most reliable preventive therapy for asthma [5]. These agents decrease inflammation and reduce airway hyper-responsiveness and the frequency of exacerbations [20]. Although those drugs appear to be equally effective [32] there are differences in effectiveness in between beclometasone dipropionate, budesonide and fluticasone propionate, which means that dosages are not comparable. Long-acting beta2 agonists must not be used as monotherapy and ought to just be begun in patients who are on inhaled corticosteroids, and the breathed in corticosteroid ought to be continued. Once effectiveness is developed, breathed in long-acting beta2 agonists and breathed in corticosteroids can be provided in a combination inhaler rather than different inhalers. Combination inhalers are thought about to aid compliance and have the advantage of guaranteeing that the long-acting beta2 agonist is not taken without the inhaled steroid [5]. Examples of mix inhalers consist of Seretide and Symbicort [32].

Table 1: Drugs used to treat asthma, their mechanism of action and their place in the stepwise approach to asthma management [5]

Step	Medications	Mechanism of action
Step 1 Mild intermittent asthma	Inhaled short-acting beta2 agonist as required, for example salbutamol or terbutaline.	Bronchodilation.
Step 2 Regular preventer therapy	Add inhaled corticosteroid 200-800mcg per day. Start at dose of inhaled corticosteroid appropriate to severity of the disease.	Reduces inflammation and decreases airway hyper-responsiveness.
Step 3 Initial add on therapy	Add inhaled long-acting beta2 agonist (LABA), for example salmeterol or formoterol.	Bronchodilation, enhances mucociliary clearance, decreases vascular permeability.
	Assess response and continue LABA if response is good.	
	Benefit from LABA, but control still inadequate, continue LABA, but increase inhaled corticosteroid to 800mcg per day (if not already on this dose).	
	If control is still inadequate, introduce trial of other therapies, for example, a leukotriene receptor antagonist or slow release theophylline.	
Step 4 Persistent poor control	Consider trials of increasing inhaled corticosteroid up to 2mg per day. Addition of a fourth drug: Leukotriene receptor antagonist or Slow release theophylline	Reduces airway inflammation and hyper-responsiveness, mucus production, oedema and bronchoconstriction. Bronchodilation. Anti-inflammatory properties.
Step 5 Continuous or frequent use of oral corticosteroids	Maintain high dose inhaled corticosteroid at 2mg per day. Consider other treatments to minimise the use of oral corticosteroid. Refer patient for specialist care	

4. CONCLUSION

Asthma is a disease of the respiratory tracts, characterized by inflammation and connected with respiratory tract hyper-responsiveness, which can lead to episodes of shortness of breath, chest tightness, wheezing and cough. Genetic factors, environmental impacts and specific trigger factors are implicated in the advancement of the disease. A thorough scientific history and objective measurement of lung function are very important in establishing a reasonably specific medical diagnosis of asthma A series of drugs is used in the management of the disease, and clinical guidelines promote a stepwise technique to drug therapy, where treatment is stepped up when needed and stepped down when control is good. Together with pharmacological management of the disease, partnership working between patients and healthcare professionals, personalized written asthma action plans, information and education are central to improving the lifestyle of patients with asthma.

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