Asthma: Pathophisiology and Medications for Treatment

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***Abstract*- The term "asthma" emerged from an ancient Greek word which means to exhale with open mouth or to pant. An estimated 300 million people worldwide suffer from asthma, with 250,000 annual deaths attributed to the disease. The prevalence of asthma has increased in the past few years. Asthma is characterized by phases of normalcy punctuated by attacks of breathlessness, wheeze and cough. It can present at any age and can have different clinical presentations. The only characteristics that are certain about asthma are its variability and its unpredictability. The increasing prevalence of the disease and its heterogeneous nature makes it important for us to diagnose the disease and its subtype correctly.**

***Index terms*- classification, Diagnostics, etiology, triggers of asthma, delivery methods**

INTRODUCTION

Asthma is a common long-term inflammatory disease it means chronic inflammatory disorder of the airways of the lungs. It is characterized by variable and recurring symptoms, reversible airflow obstruction in variable airflow, and easily triggered bronchospasms Symptoms may include episodes of wheezing, coughing, chest tightness, and shortness of breath. These may occur a few times a day or a few times per week. Depending on the person, asthma symptoms may become worse at night or with exercise. Etiology means it is caused by a combination of genetic and environmental factors. Environmental factors include exposure to air pollution and allergens. Other potential enhance include medications such as aspirin and beta blockers.

This review focuses on the need for new treatments for asthma, important pathophysiologic pathways, and drugs that are currently available or in late phase clinical development. Each drug is discussed in terms of its e! ect on symptoms, physiology, or exacerbations, depending on the relevant clinical trials. Because most of the data on newer agents are for use in adults only, the review focuses mainly on adults. However, pediatric data are mentioned when available.

CLASSIFICATION

Asthma is classified according to the frequency of symptoms, forced expiratory volume in one second (FEV1), and peak expiratory flow rate. It may also be classified as atopic or non-atopic, where atopy refers to a predisposition toward developing a type 1 hypersensitivity reaction.

There are 4 type of asthma disease:

1. Mild intermittent asthma
2. Mild persistant asthma
3. Moderate persistant asthma
4. Severe persistant asthma

There is no cure for asthma. Symptoms can be prevented by avoiding triggers, such as allergens and irritants, and by the use of inhaled corticosteroids. Long-acting beta agonists (LABA) or antileukotriene agents may be used in addition to inhaled corticosteroids if asthma symptoms remain

uncontrolled Treatment of rapidly worsening symptoms is usually with an inhaled short-acting beta-2 agonist such as salbutamol and corticosteroids taken by mouth. In very severe cases, intravenous corticosteroids, magnesium sulfate, and hospitalization may be required.

SIGN AND SYMPTOMS

Asthma is characterized by recurrent episodes of wheezing, shortness of breath, chest tightness, and coughing Sputum may be produced from the lung by coughing but is often hard to bring up. During recovery from an asthma attack (exacerbation), it may appear pus-like due to high levels of white blood cells called eosinophils. Symptoms are usually worse at night and in the early morning or in response to exercise or cold air. Some people with asthma rarely experience symptoms, usually in response to triggers, whereas others may react frequently and readily and experience persistent symptoms.

ETIOLOGY

Asthma is caused by a combination of complex and incompletely understood environmental and genetic interactions. These influence both its severity and its responsiveness to treatment. It is believed that the recent increased rates of asthma are due to changing epigenetics and a changing living environment. Asthma that starts before the age of 12 years old is more likely due to genetic influence, while onset after age 12 is more likely due to environmental influence.

ENVIRONMENTAL FACTORS

Environmental factors have been includes development and exacerbation [process of making a problem,in a negative feeling worse, bad situation], including, allergens, air pollution, and other environmental chemicals.

1. Smoking during pregnancy and after delivery is associated with a greater risk of asthma-like symptoms.
2. Low air quality from environmental factors such as traffic pollution or high ozone level has been associated with both asthma development and increased asthma severity.
3. Exposure to indoor volatile organic compounds may be a trigger for asthma; formaldehyde exposure, for example, has a positive association. Phthalates in certain types of PVC are associated with asthma in both children and young.
4. The majority of the evidence does not support a causal role between acetaminophen (paracetamol) or antibiotic use and asthma. Asthma is associated with exposure to indoor allergens. Common indoor allergens include, pet feathers, cockroaches waste, dust mite, animal dander (fragments of fur), and mold. Efforts to decrease dust mites have been found to be ineffective on symptoms in sensitized subjects.
5. Certain viral respiratory infections, such as respiratory syncytial virus and rhinovirus, may increase the risk of developing asthma when acquired as young children. Certain other infections, however, may decrease the risk.

HYGIENE HYPOTHESIS

Use of antibiotics in early life has been linked to the development of asthma. Also, delivery via caesarean section is associated with an increased risk (estimated at 20–80%) of asthma – this increased risk is attributed to the lack of healthy bacterial colonization that the newborn would have acquired from passage through the birth canal. There is a link between asthma and the degree of affluence which may be related to the hygiene hypothesis as less affluent individuals often have more exposure to bacteria and viruses

The hygiene hypothesis attempts to explain the increased rates of asthma worldwide as a direct and unintended result of reduced exposure, during childhood, to non-pathogenic bacteria and viruses. It has been proposed that the reduced exposure to bacteria and viruses is due, in part, to increased cleanliness and decreased family size in modern societies. Exposure to bacterial endotoxin in early childhood may prevent the development of asthma, but exposure at an older age may provoke bronchoconstriction. Evidence supporting the hygiene hypothesis includes lower rates of asthma on farms and in households with pets.

GENETIC

Family history is a main risk factor for asthma, because of different genes being implicated. For ex; If one identical twin is affected, the probability of the other having the disease is approximately 25%. By the end of 2005, 25 genes had been associated with asthma in six or more separate populations, including GSTM1, IL10, CTLA 4, SPINK5, LTC4S, IL4R and ADAM33, among others. Many of these genes are related to the immune system or modulating inflammation. Even among this list of genes supported by highly replicated studies, results have not been consistent among all populations tested. In 2006 over 100 genes were associated with asthma in one genetic association study alone; more continue to be found.

Some genetic variants may only cause asthma when they are combined with specific environmental exposures. An example is a specific single nucleotide polymorphism in the CD14 region and exposure to endotoxin (a bacterial product). Endotoxin exposure can come from several environmental sources including tobacco smoke, fungus, farms and various animals like dog; cat. Risk for asthma, then, is determined by both a person's genetics and the level of endotoxin exposure.

MEDICAL CONDITIONS

A triad of atopic eczema, allergic rhinitis and asthma is called atopy. The strongest risk factor for developing asthma is a history of atopic disease; with asthma occurring at a much greater rate in those who have either eczema or hay fever. Asthma has been associated with eosinophilic granulomatosis with polyangiitis (formerly known as Churg–Strauss syndrome), an autoimmune disease and vasculitis. Individuals with certain types of urticaria may also experience symptoms of asthma.

There is a correlation between obesity and the risk of asthma with both having increased in recent years. Several factors may be at play including decreased respiratory function due to a buildup of fat and the fact that adipose tissue leads to a pro-inflammatory state.

Beta blocker medications such as propranolol can trigger asthma in those who are susceptible. Cardioselective beta-blockers, however, appear safe in those with mild or moderate disease. Other medications that can cause problems in asthmatics are angiotensin-converting enzyme inhibitors, aspirin, and NSAIDs. Use of acid suppressing medication (proton pump inhibitors and H2 blockers) during pregnancy is associated with an increased risk of asthma in the child.

EXACERBATION

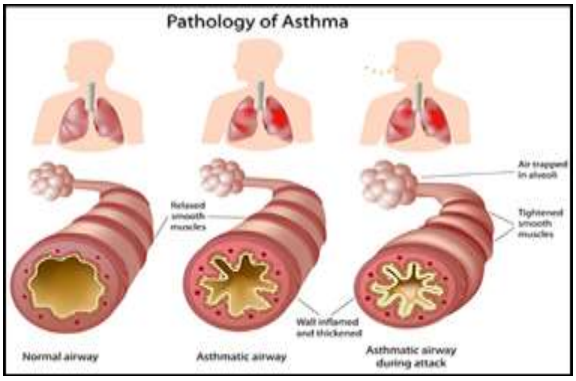
Some individuals will have stable asthma for weeks or months and then suddenly develop an episode of acute asthma. Different individuals react to various factors in different ways. Most individuals can develop severe exacerbation from a number of triggering agents.

Home factors that can lead to exacerbation of asthma include dust, animal dander (especially cat and dog hair), cockroach allergens and mold. Perfumes are a common cause of acute attacks in women and children. Both viral and bacterial infections of the upper respiratory tract can worsen the disease. Psychological stress may worsen symptoms – it is thought that stress alters the immune system and thus increases the airway inflammatory response to allergens and irritants.

Asthma exacerbations in school-aged children peak in autumn, shortly after children return to school. This might reflect a combination of factors, including poor treatment adherence, increased allergen and viral exposure, and altered immune tolerance. There is limited evidence to guide possible approaches to reducing autumn exacerbations, but while costly, seasonal omalizumab treatment from four to six weeks before school return may reduce autumn asthma exacerbations.

PATHOPHISIOLOGY OF ASTHMA

Asthma is the result of chronic inflammation of the conducting zone of the airways (most especially the bronchi and bronchioles), which subsequently results in increased contractability of the surrounding smooth muscles. The various common allergence like pollen, dust mite, some food material and certain drugs which precipitate the asthmatic attack. This among other factors leads to bouts of narrowing of the airway and the classic symptoms of wheezing.



The narrowing is typically reversible with or without treatment. Occasionally the airways themselves change. The allergence upon exposure stimulatre production of IgE [immunoglobin E] which further to mast cell. Upon reexpsure to same allergence ready to bind IgE results in degranulation of mast cell to release certain iinflammatory mediators like histamine, prostaglandin, leucotrine, bradykines. Typical changes in the airways include an increase in eosinophils and thickening of the lamina reticularis. Increase level of tenacious mucous with impaired mucocilliary function. Mucosal swelling due to increased vascular permeability and vascular congestion. This changes cause's bronchial hyperesponsivness Chronically the airways' smooth muscle may increase in size along with an increase in the numbers of mucous glands. This changes are not uniform throughout the lungs but reagonal continued by tracking causes increased intraplural and alveplar gas pressure resulting in decreased perfusion of alveoli results in hypoxia. Late asthma response occurs in case of significant allergent exposure. The symptom can recover 4-12 hr. after the initial attack due to pesistant cellular activation. It can be more severe than the initial attack.

DIAGNOSIS

While asthma is a well-recognized condition, there is not one universal agreed upon definition. It is defined by the Global Initiative for Asthma as "a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyper-responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing particularly at night or in the early morning. There is currently no precise test for the diagnosis, which is typically based on the pattern of symptoms and response to therapy over time. A diagnosis of asthma should be suspected if there is a history of recurrent wheezing, coughing or difficulty breathing and these symptoms occur or worsen due to exercise, viral infections, allergens or air pollution. Spirometry is then also be used to confirm the diagnosis.

SPIROMETRY

Spirometry is also recommended to aid in diagnosis and management. It is the one of the best test for asthma. If the FEV1 measured by this technique improves more than 12% and increases by at least 200 milliliters following administration of a bronchodilator such as salbutamol, this is supportive of the diagnosis. It however may be normal in those with a history of mild asthma, not currently acting up. As caffeine is a bronchodilator in people with asthma, the use of caffeine before a lung function test may interfere with the results. Single-breath diffusing capacity can help differentiate asthma from COPD. It is reasonable to perform spirometry every one or two years to follow how well a person's asthma is controlled.

OTHERS

Other supportive evidence includes: a ≥20% difference in peak expiratory flow rate on at least three days in a week for at least two weeks, a ≥20% improvement of peak flow following treatment with either salbutamol, inhaled corticosteroids or prednisone, or a ≥20% decrease in peak flow following exposure to a trigger. Testing peak expiratory flow is more variable than spirometry, however, and thus not recommended for routine diagnosis. It may be useful for daily self-monitoring in those with moderate to severe disease and for checking the effectiveness of new medications. It may also be helpful in guiding treatment in those with acute exacerbations. The methacholine challenge involves the inhalation of increasing concentrations of a substance that causes airway narrowing in those predisposed. If negative it means that a person does not have asthma; if positive, however, it is not specific for the disease.

MEDICATIONS

Medications used to treat asthma are divided into two general classes: quick-relief medications used to treat short term symptoms; and long-term control medications used to prevent further exacerbation. Antibiotics are generally not needed for sudden worsening of symptoms or for treating asthma at any time.

- Salbutamol metered dose inhaler commonly used to treat asthma attacks.
- Short-acting beta2-adrenoceptor agonists (SABA), such as salbutamol (albuterol USAN) are the first line treatment for asthma symptoms. They are recommended before exercise in those with exercise induced symptoms.
- Anticholinergic medications, such as ipratropium, provide additional benefit when used in combination with SABA in those with moderate or severe symptoms and may prevent hospitalizations. Anticholinergic bronchodilators can also be used if a person cannot tolerate a SABA. If a child requires admission to hospital additional ipratropium does not appear to help over a SABA. For children over 2 years old with acute asthma symptoms, inhaled anticholinergic medications taken alone is safe but is not as effective as inhaled SABA or SABA combined with inhaled anticholinergic medication. Adults who receive combined inhaled medications that includes short-acting anticholinergics and SABA may be at risk for increased adverse effects such as experiencing a tremor, agitation, and heart beat palpitations compared to people who are treated with SABA by itself.
- Older, less selective adrenergic agonists, such as inhaled epinephrine, have similar efficacy to SABAs. They are however not recommended due to concerns regarding excessive cardiac stimulation.
- A short course of corticosteroids after an acute asthma exacerbation may help prevent relapses and reduce hospitalizations.] For adults and children who are in the hospital due to acute asthma, systematic (IV) corticosteroids improve symptoms.
- Fluticasone propionate metered dose inhaler commonly used for long-term control.
- Corticosteroids are generally considered the most effective treatment available for long-term control. Inhaled forms such as beclomethasone are usually used except in the case of severe persistent disease, in which oral corticosteroids may be needed. It is usually recommended that inhaled formulations be used once or twice daily, depending on the severity of symptoms
- Long-acting beta-adrenoceptor agonists (LABA) such as salmeterol and formoterol can improve asthma control, at least in adults, when given in combination with inhaled corticosteroids. In children this benefit is uncertain. When used without steroids they increase the risk of severe side-effects, and with corticosteroids they may slightly increase the risk. Evidence suggests that for children who have persistent asthma, a treatment regime that includes LABA added to inhaled corticosteroids may improve lung function but does not reduce the amount of serious exacerbations. Children who require LABA as part of their asthma treatment may need to go to the hospital more frequently.
- Leukotriene receptor antagonists (anti-leukotriene agents such as montelukast and zafirlukast) may be used in addition to inhaled corticosteroids, typically also in conjunction with a LABA. Evidence is insufficient to support use in acute exacerbations. For adults or adolescents who have persistent asthma that is not controlled very well, the addition of anti-leukotriene agents along with daily inhaled corticosteriods improves lung function and reduces the risk of moderate and severe asthma exacerbations. Anti-leukotriene agents may be effective alone for adolescents and adults, however there is no clear research suggesting which people with asthma would benefit from anti-leukotriene receptor alone. In those under five years of age, anti-leukotriene agents were the preferred add-on therapy after inhaled corticosteroids by the British Thoracic Society in 2009. A 2013 Cochrane systematic review concluded that anti-leukotriene agents appear to be of little benefit when added to inhaled steroids for treating children. A similar class of drugs, 5-LOX inhibitors, may be used as an alternative in the chronic treatment of mild to moderate asthma among older children and adults.[As of 2013 there is one medication in this family known as zileuton.

- Intravenous administration of the drug aminophylline does not provide an improvement in bronchodilation when compared to standard inhaled beta-2 agonist treatment. Aminophylline treatment is associated with more adverse effects compared to inhaled beta-2 agonist treatment.
- Mast cell stabilizers (such as cromolyn sodium) are another non-preferred alternative to corticosteroids.
- For children with asthma which is well-controlled on combination therapy of inhaled corticosteroids (ICS) and long-acting beta2-agonists (LABA), the benefits and harms of stopping LABA and stepping down to ICS-only therapy are uncertain. In adults who have stable asthma while they are taking a combination of LABA and inhaled corticosteroids (ICS), stopping LABA may increase the risk of asthma exacerbations that require treatment with corticosteroids by mouth. Stopping LABA probably makes little or no important difference to asthma control or asthma-related quality of life. Whether or not stopping LABA increases the risk of serious adverse events or exacerbations requiring an emergency department visit or hospitalisation is uncertain.
- Anticholinergic medications such as ipratropium bromide have not been shown to be beneficial for treating chronic asthma in children over 2 years old, but is not suggested for routine treatment of chronic asthma in adults.
- There is no strong evidence to recommend chloroquine medication as a replacement for taking corticosteroids by mouth (for those who are not able to tolerate inhaled steroids). Methotrexate is not suggested as a replacement for taking corticosteriods by mouth ("steroid sparing") due to the adverse effects associated with taking methotrexate and the minimal relief provided for asthma symptoms.

DELIVERY METHODS

Medications are typically provided as metered-dose inhalers (MDIs) in combination with an asthma spacer or as a dry powder inhaler. The spacer is a plastic cylinder that mixes the medication with air, making it easier to receive a full dose of the drug. A nebulizer may also be used. Nebulizers and spacers are equally effective in those with mild to moderate symptoms. However, insufficient evidence is available to determine whether a difference exists in those with severe disease. For delivering short-acting beta-agonists in acute asthma in children, spacers may have advantages compared to nebulisers, but children with life-threatening asthma have not been studied. There is no strong evidence for the use of intravenous LABA for adults or children who have acute asthma. There is insufficient evidence to directly compare the effectiveness of a metered-dose inhaler attached to a homemade spacer compared to commercially available spacer for treating children with asthma.

TRIGGERS OF ASTHMA

Clinical history is an important tool to identify trigger factors of an asthmatic patient.

Allergic trigger factors can be identified by allergy tests. Allergy tests are based on the principle of presence of allergen specific IgE in the tissues. These can be performed by estimation of specific IgE in blood or by skin prick tests.

a. Blood tests for allergen- specific IgE
   This type of test uses enzyme linked immunosorbent assay (ELISA) to detect IgE directed towards a specific allergen. The test is done for allergens suspected to be the probable triggers of asthma in an individual patient. The drawback of this test is its high cost.
b. Allergy skin prick test
   This test is performed by a highly trained technician and involves testing a number of indoor and outdoor allergens by skin prick test. The results of this test get hampered by intake of antihistaminics and other medicines.

CONCLUSION

Poor clinical control of asthma and high frequency of misdiagnosis have been revealed. Some symptoms described in the current definition of asthma may reflect mechanisms other than bronchial constriction, the main clinical criterion of asthma. Several recent studies have indicated that ‘‘classic’’ asthma may sometimes be confused with asthma-like disorders. Common but still unrecognized underlying mechanisms may be an explanation. In fact, these mechanisms may belong to the same clinical syndrome. The current discussion of severe asthma, steroid-resistant asthma, problematic asthma, refractory asthma and so forth is important.

The main hypothesis in this presentation is that the current diagnosis in international guidelines [1–3] is too ‘‘narrow’’ and that a broadening must include also nonobstructive disorders. Therefore, in addition to the term ‘‘asthma’’ the term ‘‘asthma syndrome’’ might cover this wider perspective. The exploration of new therapies will certainly require good knowledge of all mechanisms within the asthma syndrome.

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