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Causes and Management of Asthma

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ABSTRACT

Asthma is defined as a chronic inflammatory disorder of the airways which manifests itself as recurrent episodes of wheezing, breathlessness, chest tightness and cough. It is characterized by bronchial hyper-responsiveness and variable airflow obstruction, that is often reversible either spontaneously or with treatment. Other nonspecific symptoms in infants or young children may be a history of recurrent bronchitis, bronchiolitis, or pneumonia; a persistent cough with colds; and/or recurrent croup or chest rattling. For all but the most severely affected patients, the ultimate goal is to prevent symptoms, minimize morbidity from acute episodes, and prevent functional and psychological morbidity to provide a healthy (or near healthy) lifestyle appropriate to the age of child. We conducted this review using a comprehensive search of MEDLINE, PubMed, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials from January 1st , 1994, through November 30th , 2017.

Keywords: Inflammatory Disorder, Asthma, Inhaled Corticosteroids.

INTRODUCTION

Asthma is a chronic respiratory ailment that is predominant worldwide. It is reflected as a major reason of morbidity and a chief contributor to the high health care expenditure particularly in developed nations [1]. There are two major pathological features in asthmatics' airways, inflammation, and hyper- responsiveness. These features are consistent, but not entirely dependent on each other [2]. Airway inflammatory changes contain airway wall edema, expanded airway mucus secretions, inflammatory cellular infiltrates, smooth muscle hypertrophy, epithelial cell damage, and submucosal fibrosis[3].

The cellular infiltrates are generally composed of eosinophils, neutrophils, mast cells, macrophages, basophils, and lymphocytes. The ratio of these cells might widely differ between patients indicating asthma heterogeneity [4]. Asthma is naturally divided into three central immune pathological phenotypes: Eosinophilic, paucigranulocytic, and neutrophilic. The eosinophilic phenotype is categorized by expanded eosinophilic infiltration of the airways. Patients are susceptible to be a topic, have asthma triggered by exposure to allergens and tend to respond well to corticosteroids. The neutrophilic phenotype is characterized by increased neutrophilic infiltration of the airways. Patients are susceptible to have severe, aggressive, and out of sorts controlled asthma. They habitually do not react to corticosteroids along with the eosinophilic sort. In the paucigranulocytic phenotype, eosinophils, andbronchial neutrophils are much lower [4].

Asthmatic patients regularly experience acute exacerbations. These exacerbations are commonly triggered by allergens; comprising animal dander ,pollens, dust mites, and mold; viral respiratory tract contaminations; irritants such as smoke and dust; cold air and exercise. The most mutual cause of acute asthma exacerbation in both children and adults, but more in children, is viral respiratory tract contaminations. Viruses might be accountable for up to 80% of wheezing episodes in children and 50-75% of episodes in adults [5]. Many viruses may be the reason for exacerbation of asthma symptoms, the most vital and most mutual is rhinovirus[6]. Respiratory syncycial virus and influenza virus similarly cause substantial proportion of exacerbations. Airway epithelial cells play a main role in the pathology of virally induced asthma exacerbation. In response to infection they secret chemokines like interleukin-8 and CCL-5 that can attract inflammatory cells comprising neutrophils and lymphocytes that can exacerbate the already existing allergic inflammation [7].

This discovery is reinforced by epidemiologic observations that allergen sensitization and respiratory viral contaminations may synergize to cause asthma exacerbation[8]. Children who are atopic are more expected to have virally induced wheezing and respiratory distress than non atopic children[9]. Bacteria like Hemophilus influenze and Moraxella catarrhalis, have been lately shown to be allied with acute wheezing episodes in children [10]. Their role and

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the role of atypical bacteria as triggers of acute asthma are still debatable [11].

The study was done after approval of ethical board of Umm Alqura University.

SIGNS AND SYMPTOMS

Common asthma symptoms in children include coughing and whistling or wheezing sounds when breathing. Other typical signs of asthma are usually not yet present at that age. In teenagers and adults, asthma is characterized by the following symptoms:

- and/or the urge to cough

These symptoms mostly happen in episodes or attacks, commonly at night too. This is one of the reasons why people who have this chronic illness often feel so tired and groggy during the day. During an asthma attack, initial minor breathing difficulties can worsen and develop into more serious shortness of breath.

MATERIALS AND METHODS

- **Data Sources and Search terms**

We conducted this review using a comprehensive search of MEDLINE, PubMed, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials from January 1, 1994, through November30, 2017.

- **Data Extraction**

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

Causes and risk factors

Asthma is more common in some families than in others, which recommends that genes might play a role. Additional risk factors for children comprise having other allergic disorders, for example, hay fever or eczema, either themselves or in their family. Being born with low birth weight is another risk factor. Asthma is more common in boys than in girls. Children are more possible to get asthma if they are exposed to cigarette smoke. Parents who smoke can reduce this risk by kicking the habit. Asthma symptoms are the result of a combination of two factors working together: People with asthma have an immune system that permanently tends to overact. This tendency goes mostly unnoticed until the mucous membranes that line the insides of the bronchi come into contact with specific triggers.Depending on the type of trigger, asthma is classified as being either allergic or non-allergic.

Table 1: Allergic asthma VS Non-allergic asthma

Allergic asthma	Non-allergic asthma
Allergic asthma is also called "extrinsic asthma" because the trigger is breathed in with the air. Different people may have reactions to very different types of triggers, including cigarette smoke (active and passive smoking), plant pollen, animal fur, dust mite excrement, and some kinds of food as well as cold air, perfume, exhaust fumes or certain chemicals.	Non-allergic asthma (also called "intrinsic asthma") is caused by triggers released by the body. These triggers include bacterial or viral inflammations of the airways in particular. Sometimes taking certain kinds of painkillers cause asthma. These painkillers include acetylsalicylic acid (ASA, the drug in medicines like Aspirin) and other non-steroidal anti-inflammatory drugs (NSAIDs). In some people, physical or emotional stress that causes their breathing to speed up can also induce asthma symptoms.

In many people, both intrinsic and extrinsic factors play a role, so it is not always possible to clearly distinguish between allergic and non-allergic asthma. The effects on the lungs and breathing are nearly the same through:

- Immune system cells in the membranes lining the bronchi are activated,
- The muscles surrounding the airways tense up,
- The membranes lining the airways become inflamed and swollen, and
- Very viscous mucus is often produced.

The muscles tensing up, the swelling of the mucous membranes and the extra mucus production all cause the airways to become narrower and narrower, which can result in an asthma attack [12, 13].

Management of asthma

Medical care includes treatment of acute asthmatic episodes and control of chronic symptoms, including nocturnal and exercise-induced asthmatic symptoms. Pharmacologic management includes the use of control agents such as inhaled corticosteroids, long-acting bronchodilators (beta-agonists and anticholinergics), theophylline, leukotriene modifiers, and more recent strategies such as the use of anti-immunoglobulin E (IgE) antibodies (omalizumab) and anti-IL-5 antibodies in selected

patients. Relief medications include short-acting bronchodilators, systemic corticosteroids, and ipratropium. For all but the most severely affected patients, the ultimate goal is to prevent symptoms, minimize morbidity from acute episodes, and prevent functional and psychological morbidity to provide a healthy (or near healthy) lifestyle appropriate to the age of child. A stepwise (step-up if necessary and step-down when possible) approach to asthma management continues to be used in the current guidelines and is now divided into 3 groups based on age (0-4 y, 5-11 y, 12 y and older)[14].

A Cochrane review found that inhaled corticosteroids are superior to anti-leukotrienes when used as mono therapy in adults and children with persistent asthma. The superiority of inhaled corticosteroids is most pronounced in asthma patients with moderate airway obstruction [15]. The 2015 Global Initiative for Asthma (GINA) guidelines identify inhaled as the preferred controller medication of choice for children and adults. A study by Bruzzese et (16) al assessed the Asthma Self-Management for Adolescents (ASMA) approach, which is a school-based intervention for adolescents and medical providers. The study found that ASMA helped improve self-management and reduced morbidity and urgent health care use in low-income, urban, minority adolescents.

- **Allergen Immunotherapy**

The use of immunotherapy for the treatment of asthma is controversial. Several large, well-conducted studies did not demonstrate any benefit, but a meta-analysis of 75 randomized controlled trials confirmed efficacy in asthma [17]. The National Asthma Education and Prevention Program Expert Panel Report recommend that immunotherapy could be considered if the following criteria are fulfilled:

- A relationship is clear between symptoms and exposure to an unavoidable allergen to which the patient is sensitive.
- Symptoms occur all year or during a major portion of the year.
- Symptoms are difficult to control with pharmacologic management because the medication is ineffective, multiple medications are required, or the patient is not accepting of medication.

Repeated injections of small doses of allergen have been used for more than almost 100 years to treat allergic rhinitis. This treatment is evidently effective, and positive effects can persevere even years after treatment is stopped. This management is also considered compulsory for life-threatening bee and wasp sting (hymenoptera venom) reactions. The role of repeated allergen injections in patients with asthma has been more debatable, ranging from a relative indication to no indication. Advantage has been shown in individuals with allergy-induced asthma [18]. Precautions incorporate genuine unfavorable responses (happening in 1 for every 30-500 individuals, normally inside 30 min). The evaluated rough yearly demise rate is 0.7 passing for every million populace. Observing and revival faculty and hardware are required. Additionally, allergen immunotherapy ought to be maintained a strategic distance from if the patient is taking beta blockers or is having an asthma fuel (ie, PEFR < 70% of patient's close to home best) or has direct or more regrettable settled obstacle. A noteworthy hazard factor for immunotherapy-related fatalities incorporates uncontrolled asthma; in this way, proper alert ought to be worked out. Sublingual immunotherapy (SLIT) has been shown to progress allergic rhinitis symptoms, comprising in pediatric patients and allergic asthma. While adverse reactions do occur, SLIT is safe enough for home administration. Based on limited data, sublingual treatment, at least in the short term, may be about half as effective as traditional subcutaneous injection. Whereas sublingual immunotherapy is widely used in European, South American, and Asian countries, as of early 2016, it is not FDA approved and remains off-label use in the United States.

- **Bronchial Thermoplasty**

Bronchial thermoplasty (BT) is a novel intervention for asthma in which controlled thermal energy is delivered to the airway wall during a series of bronchoscopy procedures. A gathering of patients (AIR2 Trial Study Group) with serious asthma who stayed symptomatic in spite of treatment with high-measurements breathed in corticosteroids and long-acting beta2 agonists experienced BT and indicated prevalent change from pattern in their score on the Asthma Quality of Life Questionnaire (AQLQ) (BT, 1.35±1.10; sham, 1.16±1.23). Changes in AQLQ of 0.5 or more noteworthy were seen in 79% of BT and in 64% of sham subjects. In spite of the fact that the hospitalization rate was 6% higher among BT subjects amid the treatment time frame (up to 6 wk after BT), in the post treatment time frame (6-52 wk after BT), the BT aggregate experienced less extreme intensifications, crisis office visits, and days missed from work/school contrasted and

the sham gathering[19]. Wechsler et al (20) studied the long-term safety and efficiency of bronchial thermoplasty in 162 patients with severe persistent asthma from the Asthma Intervention Research 2 (AIR2) trial, which displayed a 32% decrease in severe asthma exacerbations, an 84% decrease in respiratory symptom-related emergency department visits, a 73% decrease in hospitalizations for respiratory symptoms, and a 66% decrease in time lost from work/school/other daily activities because of asthma symptoms .

- **Monoclonal Antibody Therapy**

➢ **Reslizumab**

Reslizumab is an IgG kappa monoclonal antibody that inhibits IL-5. It was approved by the FDA in March 2016 and is specified for add-on maintenance treatment of patients with severe asthma aged 18 years and older with an eosinophilic phenotype. It is managed as an intravenous infusion every 4 weeks. Approval was based on three multicenter, international trials in patients with asthma who had eminent eosinophils. In two of these studies (n = 953), patients who received reslizumab had a significant decrease in the incidence of asthma exacerbations of up to 59% (study 1: rate ratio, 0.50 [95% confidence interval, 0.37-0.67]; study 2: rate ratio, 0.41 [95% confidence interval, 0.28-0.59]; both P <.0001) compared with those receiving placebo [21].

➢ **Mepolizumab**

Mepolizumab is a humanized IgG1 kappa monoclonal antibody explicit for interleukin 5 (IL-5). Mepolizumab binds to IL-5 and consequently stops IL-5 from binding to its receptor on the surface of eosinophils. Inhibiting IL-5 binding to eosinophils decreases blood, tissue, and sputum eosinophil levels. It is specified for add-on maintenance management of patients with severe asthma aged 12 years or older and with an eosinophilic phenotype. Approval was based on three key phase 3 trials (MENSA,DREAM, and SIRIUS). Each trial established statistically significant enhancement in declining asthma exacerbations and emergency department visits or hospitalization. Mean decrease in glucocorticoid use was 50% in the mepolizumab group, whereas also decreasing the asthma exacerbation rate. Significant enhancement in FEV1 was correspondingly perceived compared with placebo [22].

➢ **Benralizumab**

Benralizumab is an IL-5 receptor, alpha-directed cytolytic mAb (IgG1, kappa) approved by the FDA in November 2017. The IL-5 receptor is expressed on the surface of eosinophils and basophils. Benralizumab reduces eosinophils and basophils through antibody-dependent cell-mediated cytotoxicity (ADCC). It is indicated for add-on maintenance treatment of severe asthma in patients aged 12 years or older who have an eosinophilic phenotype.

Approval was based on outcomes from the WINDWARD clinical trial program, comprising the phase III exacerbation trials, SIROCCO and CALIMA, and the phase III oral corticosteroid (OCS)–sparing trial, ZONDA[23, 24]. Results for the 8-week benralizumab dosing regimen from these trials showed the following:

- Up to 51% reduction in the annual asthma exacerbation rate (AAER) compared with placebo
- Significant improvement in lung function as measured by forced expiratory volume in one second (FEV 1) of up to 159 mL compared with placebo
- Seventy-five percent median reduction in daily OCS use and discontinuation of OCS use in 52% of eligible patients

➢ **Omalizumab**

Omalizumab was approved by the FDA in 2003 for adults and adolescents (≥12 y) with moderate-to-severe insistent asthma who have a positive skin test outcome or in vitro reactivity to a perennial aeroallergen and whose symptoms are ineffectively controlled with inhaled corticosteroids. Patients ought to have IgE levels amid 30 and 700 IU and ought not to weigh more than 150 kg.This is a humanized murine IgG antibody against the Fc component of the IgE antibody (the part that attaches to mast cell surfaces). Utilization of this antibody precludes IgE from binding directly to the mast cell receptor, in that way averting cell degranulation without producing degranulation itself. Prescribers should be ready and equipped to identify and treat anaphylaxis should it arise. Adverse effects are infrequent and comprise upper respiratory infection symptoms, headache, urticaria (2%) without anaphylaxis, and anaphylaxis (0.1% in studies and 0.2% in postmarketing surveillance). Transient thrombocytopenia has correspondingly been distinguished but not in humans. Antibodies are formed against the anti-IgE antibody, but these do not seem to cause immune complex deposition or other significant harms. So far, reduced IgE levels have not been presented to inhibit one's ability to fight contamination (including parasites). Registration trials raised a question of increased

danger of malignancy, but this has not been seen in the post marketing data.

- **Sinusitis**

In patients with asthma, 50% have concurrent sinus disease. Sinusitis is the most significant intensifying factor for asthma symptoms. Either acute infectious sinus disease or chronic inflammation might add to worsening airway symptoms. Management of nasal and sinus inflammation decreases airway reactivity. Management of acute sinusitis necessitates at least 10 days of antibiotics to increase asthma symptoms[25].

- **Nocturnal Asthma**

Nocturnal asthma is a important clinical problem that ought to be addressed destructively. Peak-flow meters ought to be utilized to permit objective assessment of symptoms and interventions. Sleep apnea, sinusitis, and symptomatic GERD ought to be controlled when present. Medications ought to be properly timed, and consideration ought to be given to the use of a long-acting inhaled or oral beta2 agonist, a leukotriene modifier, and inhaled corticosteroids. A once-daily sustained-release the ophylline preparation and varying the timing of oral corticosteroids to mid-afternoon can be correspondingly be utilized.

CONCLUSION

For all but the most severely affected patients, the ultimate goal is to prevent symptoms, minimize morbidity from acute episodes, and prevent functional and psychological morbidity to provide a healthy (or near healthy) lifestyle appropriate to the age of child. Corticosteroids play an important role in the treatment of acute asthma exacerbations in the ED as well as post discharge from the ED. Further research is greatly needed to shed more light on the use of ICS in those patients, their optimal dose and duration, as well as their concomitant use with systemic corticosteroids. In addition, more research is needed on the safety of dispensing oral corticosteroids for home use in case of asthma exacerbation.

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