Management of Asthma

Introduction

Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role: in particular, mast cells, eosinophils, T lymphocytes, macrophages, neutrophils, and epithelial cells. In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment. The inflammation also causes an associated increase in the existing bronchial hyperresponsiveness to a variety of stimuli. Reversibility of airflow limitation may be incomplete in some patients with asthma."

Clinical presentation

Chronic asthma

Symptoms include episodes of dyspnea, chest tightness, coughing (particularly at night), wheezing. These often occur with exercise but may occur spontaneously or in association with known allergens. Signs include expiratory wheezing on auscultation; dry, hacking cough. Asthma can vary from chronic daily symptoms to only intermittent symptoms. Intervals between symptoms may be days, weeks, months, or years. Severity is determined by lung function, symptoms, nighttime awakenings, and interference with normal activity prior to therapy. Patients can present with mild intermittent symptoms that require no medications or only occasional short-acting inhaled β2-agonists to severe chronic symptoms despite multiple medications.

Acute severe asthma

Uncontrolled asthma can progress to an acute state in which inflammation, airway edema, mucus accumulation, and severe bronchospasm result in profound airway narrowing that is poorly responsive to bronchodilator therapy. Patients may be anxious in acute distress and complain of severe dyspnea, shortness of breath, chest tightness, or burning. They may be able to say only a few words with each breath. Symptoms are unresponsive to usual measures (short-acting inhaled β-agonists). Signs include expiratory and inspiratory wheezing on auscultation; dry, hacking cough; tachypnea; tachycardia; pallor or cyanosis.

Causes

Asthma is caused by a combination of complex and incompletely understood environmental and genetic interactions. These influences both its severity and its responsiveness to treatment. 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*:*

Many environmental factors have been associated with asthma's development and exacerbation, including, allergens, air pollution, and other environmental chemicals. Smoking during pregnancy and after delivery is associated with a greater risk of asthma-like symptoms. Low air quality from environmental factors such as traffic pollution. Exposure to indoor volatile organic compounds may be a trigger for asthma; formaldehyde exposure.

Maternal psychological stress during pregnancy is a risk factor for the child to develop asthma. Asthma is associated with exposure to indoor allergens. Common indoor allergens include dust mites, animal dander (fragments of fur or feathers), and mold. Certain viral respiratory infections, such as respiratory syncytial virus and rhinovirus may increase the risk of developing asthma when acquired as young children.

Genetic

Family history is a risk factor for asthma, with many different genes being implicated. 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. Some genetic variants may only cause asthma when they are combined with specific environmental exposures.

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. Individuals with certain types of urticaria may also experience symptoms of asthma. Beta blocker medications such as propranolol can cause bronchoconstriction 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.

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.

Pathophysiology

Asthma is associated with T helper cell type-2 (Th2) immune responses, which are typical of other atopic conditions. Various allergic (e.g., dust mites, cockroach residue, furred animals, molds, pollens) and non-allergic (e.g., infections, tobacco smoke, cold air, exercise) triggers produce a cascade of immune-mediated events leading to chronic airway inflammation.

In acute inflammation, inhaled allergens in allergic patients causes early-phase allergic reaction with activation of cells bearing allergen-specific immunoglobulin E (IgE) antibodies. After rapid activation, airway mast cells and macrophages release Proinflammatory mediators such as histamine and eicosanoids that induce contraction of airway smooth muscle, mucus secretion, vasodilation, and exudation of plasma in the airways. Plasma protein leakage induces a thickened, engorged, edematous airway wall and narrowing of lumen with reduced mucus clearance.

Late-phase inflammatory reaction occurs 6 to 9 hours after allergen provocation and involves activation of eosinophils, T lymphocytes, basophils, neutrophils, and macrophages. Eosinophils migrate to airways and release inflammatory mediators.

T-lymphocyte activation leads to release of cytokines from type 2 T-helper (TH_2) cells that mediate allergic inflammation (interleukin [IL]-4, IL-5, and IL-13). Conversely, type 1 T-helper (TH_1) cells produce IL-2 and interferon-γ that are essential for cellular defense mechanisms. Allergic asthmatic inflammation may result from imbalance between TH_1 and TH_2 cells. Mast cell degranulation

results in release of mediators such as histamine; eosinophil and neutrophil chemotactic factors; leukotrienes C4, D4, and E4; prostaglandins; and platelet-activating factor (PAF). Histamine can induce smooth muscle constriction and bronchospasm and may contribute to mucosal edema and mucus secretion. Neutrophils release mediators (PAFs, prostaglandins, thromboxanes, and leukotrienes) that contribute to BHR and airway inflammation. Leukotrienes C4, D4, and E4 are released during inflammatory processes in the lung and produce bronchospasm, mucus secretion, microvascular permeability, and airway edema.

Types of Asthma

Childhood Asthma: - Asthma onset in children usually occurs before their fifth birthday. The majority of children with asthma are sensitive to household allergens and irritants, and they can benefit from a smoke-free, dust-free and pet-free environment. When someone has asthma, they usually have it for life. However, asthma usually gets better as a child gets older and there are often periods where there are no symptoms, such as during adolescence.

Exercise Induced Asthma (EIA): - EIA is characterized by symptoms that occur due to exercise. People with asthma benefit from exercise because it increases their lung efficiency and their tolerance of physical activity. Factors such as humidity, temperature, allergen levels, air pollution and the type and duration of exercise can adversely affect a person with asthma.

Occupational Asthma: - Occupational asthma is caused by exposure to certain irritants in the workplace. There are more than 200 substances including gases, dust particles and chemicals that are known to cause asthma in the workplace.

Adult-Onset Asthma: - While many believe adult-onset asthma to be rare, it actually accounts for 10 percent of all new asthma cases. Unlike childhood asthma, adults are less likely to react to allergic triggers, and more likely to be affected by non-allergic triggers.

Classification of asthma

Classification of Asthma Severity in Children(5yrs) to Adults [Symptom Based]

Components of Severity	Intermittent	Persistent		
		Mild	Moderate	Severe
1.Symptoms	=<2 days/week	>2 days/week but not daily	Daily	Throughout the day
2.Nighttime awakenings	=<2x/month	3-4x/month	>1x/week but not nightly	Often 7x/week
*3.Using Short-acting Beta2-agonists for symptom control	=<2 days/week	>2 days/week But not daily	Daily	Several times per day
4.Interference with normal activity	None	Minor Limitation	Some Limitation	Extremely Limited

Diagnosis:

1-The diagnosis of asthma is predominantly **clinical** and based on a characteristic **history**. History of recurrent episodes of coughing, wheezing, chest tightness, or shortness of breath. Patients may have family history of allergy or asthma or symptoms of allergic rhinitis.

2-Supportive evidence is provided by the demonstration of variable airflow obstruction, preferably by using **spirometry** to measure forced expiratory volume in 1 second [**FEV1**] and forced vital capacity [**FVC**]. The FEV1 is a measure of the FEV in the first second of exhalation. The forced vital capacity (FVC) is the maximum volume of air exhaled with maximum effort after maximum inspiration. The FEV1 usually is expressed as a percentage of the total volume of air exhaled and is reported as the **FEV1 to FVC ratio.** Healthy persons generally can exhale at least 75% to 80% of their VC in 1 second and almost all of it in 3 seconds. Thus, the FEV1 normally is 80% of the FVC. **In obstructive lung disorders, such as asthma, the FEV1/FVC ratio decreased**. In asthmatic patients, and after inhaled β2-agonist administration, there is at least 12% improvement in FEV1 which indicates **reversible** airflow obstruction

3-Pulse oximetry is a noninvasive means of assessing the degree of hypoxemia during an acute exacerbation. The oximeter measures oxygen saturation in arterial blood (Sa02) and pulse.

4-Peak expiratory flow rate (PEFR), obtained through the patient forcefully breathing out into a **peak flow meter** can be used to monitor control of asthma. It gives slightly less reproducible results than the spirometer but has the advantage that the **patient can do regular tests at <u>home</u> with a hand-held meter**. The peak flow meter measures **peak expiratory flow** (PEF) rate, the maximum flow rate that can be forced during expiration. The PEF can be used to assess the **improvement or deterioration** in the disease as well as the **effectiveness of treatment**.

5-Arterial blood gases (ABGs) (to measure arterial partial pressure of oxygen [**Pa02**], arterial partial pressure of carbon dioxide [**Paco2**], and **pH**) should be obtained for patients in **severe asthma**.

6-In patients with acute **severe asthma**: Peak expiratory flow (PEF) and FEV1 are less than 40% of normal predicted values. Pulse oximetry reveals decreased arterial oxygen and O2 saturations. Arterial blood gases may reveal metabolic acidosis and low partial pressure of oxygen (PaO2).

Treatment

The primary goal of asthma management is to achieve and maintain control of the disease in order to prevent exacerbations (abrupt and/or progressive worsening of asthma symptoms that often require immediate medical attention and/or the use of oral steroid therapy) and reduce the risk of morbidity and mortality. maintain normal activity levels (including exercise and attendance at work or school), and meet patients' and families' expectations and satisfaction with care.

Nonpharmacologic therapy

• Patient education is mandatory to improve medication adherence, self-management skills, and use of healthcare services.

• Avoidance of known allergenic triggers can improve symptoms, reduce medication use. Environmental triggers (eg, animals) should be avoided in sensitive patients, and smokers should be encouraged to quit.

• Patients with acute severe asthma should receive oxygen to maintain PaO2 greater than 90% (>95% in pregnancy and heart disease).

Pharmacotherapy

Beta2-Adrenergic Agonists

β2-Agonists relax airway smooth muscle by directly stimulating β2-adrenergic receptors. They also increase mucociliary clearance and stabilize mast cell membranes. Inhalation, oral, and injectable dosage forms are available, and the inhalation dosage forms are most commonly used. Oral β2-agonists should not be used in acute asthma because of a delayed onset of action compared to the inhaled route. Inhaled β2-agonists are classified as either short- or long-acting based on their duration of action.

Short-Acting Inhaled Beta2-Agonists

Inhaled short-acting b2-agonists are the most effective agents for reversing acute airway obstruction caused by bronchoconstriction and are the drugs of choice for treating acute severe asthma and symptoms of chronic asthma. Short-acting inhaled β2-agonists have an onset of action of less than 5 minutes and a duration of action of 4 to 6 hours. β2-Agonists have significantly better bronchodilation activity in acute asthma than theophylline or anticholinergic agents. Adverse effects of the inhaled β2-agonists include tachycardia, tremor, and hypokalemia, which are usually not problematic. Because of increased adverse effects, oral β2-agonists should be avoided in patients who are able to use inhaled medications.

Albuterol (also known as salbutamol outside the United States), the most commonly used inhaled short-acting β2- agonist. Other commonly used short-acting inhaled β2-agonists include pirbuterol and terbutaline.

Long-Acting Inhaled Beta2-Agonists

Salmeterol and formoterol are long-acting inhaled β2-agonists that provide up to 12 hours of bronchodilation after a single dose. Both agents are approved for the chronic prevention of asthma symptoms. Salmeterol is a partial agonist with an onset of action of approximately 30 minutes. Because of this delayed onset of action, patients should be cautioned not to use salmeterol as a quick relief medication. Formoterol is a full agonist that has an onset of action similar to that of albuterol, but it is not currently indicated for the treatment of acute bronchospasm.

Inhaled long-acting β2-agonists are indicated for addon therapy for asthma not controlled on low to medium doses of inhaled corticosteroids. Adding a long-acting inhaled β2-agonist is at least as effective as doubling the dose of an inhaled corticosteroid with respect to improving lung function and symptom scores and decreasing nocturnal symptoms, reliever medication use, and asthma

exacerbations. Addition of a long-acting inhaled β2-agonist to inhaled corticosteroid therapy also reduces the amount of inhaled corticosteroids necessary for asthma control. Combined therapy with a long-acting inhaled β2-agonist and an inhaled corticosteroid is also superior to the combination of a leukotriene modifier or theophylline with an inhaled corticosteroid. Although both formoterol and salmeterol are effective as add-on therapy for moderate persistent asthma, neither agent should be used as monotherapy for chronic asthma. Patients treated with salmeterol alone are at greater risk of worsening asthma than those treated with inhaled corticosteroids. Salmeterol is also available in a fixed ratio combination product containing fluticasone, and a new drug application has been filed for a fixed combination product containing budesonide and formoterol. Combination products have the potential advantage of increasing patient adherence due to the decreased number of inhalers and inhalations; however, these products offer less flexibility with respect to dosage adjustments when necessary.

Corticosteroids

Corticosteroids are the most potent anti-inflammatory agents available for the treatment of asthma. The efficacy of corticosteroids is due to their ability to affect multiple inflammatory pathways, resulting in the suppression of inflammatory cell activation and function, prevention of microvascular leakage, decreased mucus production, and upregulation of β2-adrenergic receptors improving the response to β2-agonists. Corticosteroids for the treatment of asthma are available in inhaled, oral, and injectable dosage forms.

Inhaled corticosteroids are the preferred long-term control therapy for persistent asthma because of potency and consistent effectiveness; they are the only therapy shown to reduce risk of dying from asthma. Because inflammation inhibits steroid receptor binding, patients should be started on higher and more frequent doses and then tapered down once control has been achieved. Response to inhaled corticosteroids is delayed; symptoms improve in most patients within the first 1 to 2 weeks and reach maximum improvement in 4 to 8 weeks. Local adverse effects include dose-dependent oropharyngeal candidiasis and dysphonia, which can be reduced by using a spacer device. Systemic corticosteroids are indicated in all patients with acute severe asthma not responding completely to initial inhaled β2-agonist administration (every 20 min for 3 or 4 doses). Because short-term (1–2 week), high-dose systemic steroids do not produce serious toxicities, the ideal method is to use a short burst and then maintain appropriate long-term control therapy with inhaled corticosteroids. In patients who require chronic systemic corticosteroids for asthma control, the lowest

possible dose should be used. Toxicities may be decreased by alternate-day therapy or high-dose inhaled corticosteroids.

Methylxanthines

Theophylline appears to produce bronchodilation through nonselective phosphodiesterase inhibition. Methylxanthines are ineffective by aerosol and must be taken systemically (orally or IV). Sustained-release theophylline is the preferred oral preparation, whereas its complex with ethylenediamine (**aminophylline**) is the preferred parenteral product due to increased solubility. Because of large interpatient variability in theophylline clearance, routine monitoring of serum theophylline concentrations is essential for safe and effective use. Sustained-release oral preparations are preferred for outpatients, but each product has different release characteristics. Preparations unaffected by food that can be administered every 12 or 24 hours are preferable. Adverse effects include nausea, vomiting, tachycardia, and difficulty sleeping; more severe toxicities include cardiac tachyarrhythmias and seizures. Addition of theophylline to optimal inhaled corticosteroids is similar to doubling the dose of the inhaled corticosteroid and is less effective overall than long-acting β2-agonists as adjunctive therapy.

Anticholinergics

Ipratropium bromide and **tiotropium bromide** produce bronchodilation only in cholinergic-mediated bronchoconstriction. Anticholinergics are effective bronchodilators but are not as effective as β2-agonists. They attenuate but do not block allergen or exercise-induced asthma in a dose-dependent fashion.

Time to reach maximum bronchodilation from aerosolized ipratropium is longer than from aerosolized short-acting β2-agonists (30–60 min vs 5–10 min). However, some bronchodilation is seen within 30 seconds, and 50% of maximum response occurs within 3 minutes. Ipratropium bromide has a duration of action of 4 to 8 hours; tiotropium bromide has a duration of 24 hours. Inhaled ipratropium bromide is only indicated as adjunctive therapy in severe acute asthma not completely responsive to β2-agonists alone because it does not improve outcomes in chronic asthma.

Mast Cell Stabilizers

Cromolyn sodium has beneficial effects that are believed to result from stabilization of mast cell membranes. It inhibits the response to allergen challenge but does not cause bronchodilation. Cromolyn is effective only by inhalation and is available as a nebulizer solution. Cough and wheezing have been reported after inhalation. Cromolyn is indicated for prophylaxis of mild

persistent asthma in children and adults. Effectiveness is comparable to theophylline or leukotriene antagonists. It is not as effective as inhaled β2-agonists for preventing EIB, but it can be used in conjunction for patients not responding completely to inhaled β2-agonists.

Leukotriene Modifiers

Zafirlukast and **montelukast** are oral leukotriene receptor antagonists that reduce the proinflammatory (increased microvascular permeability and airway edema) and bronchoconstriction effects of leukotriene D4. In persistent asthma, they improve pulmonary function tests, decrease nocturnal awakenings and β2-agonist use, and improve symptoms. However, they are less effective than low-dose inhaled corticosteroids. Adult zafirlukast dose is 20 mg twice daily, taken at least 1 hour before or 2 hours after meals; dose for children ages 5 through 11 years is 10 mg twice daily.

Montelukast adult dose is 10 mg once daily, taken in the evening without regard to food; dose for children ages 6 to 14 years is one 5-mg chewable tablet daily in the evening.

Zileuton is a 5-lipoxygenase inhibitor; use is limited due to potential for elevated hepatic enzymes, especially in first 3 months of therapy, and inhibition of metabolism of some drugs metabolized by CYP3A4 (eg, theophylline and warfarin).

Omalizumab

Omalizumab is an anti-IgE antibody approved for treatment of allergic asthma not well controlled by oral or inhaled corticosteroids. Dosage is determined by baseline total serum IgE (international units/mL) and body weight (kg). Doses range from 150 to 375 mg subcutaneously at either 2- or 4-week intervals. Because of high cost, omalizumab is only indicated as step 5 or 6 care for patients with allergies and severe persistent asthma inadequately controlled with combination of high-dose inhaled corticosteroids and long-acting β2-agonists and at risk for severe exacerbations.

Stepwise approach for treatment of chronic asthma:

Step 1:	Inhaled short-acting B2 agonist (SABA) as required
Step 2:	Add inhaled steroid at 400 mcg/day
Step 3:	▪ Add inhaled long-acting B2 agonist (LABA) ▪ Still inadequate: continue LABA and increase inhaled steroid dose to 800 mcg/day
Step 4:	▪ increase inhaled steroid up to 2000 mcg/day ▪ Add a 4th drug e.g. Leukotriene antagonist, SR theophylline, oral B2 agonist tablets.
Step 5:	▪ Use oral steroid tablet in lowest dose in addition to the high dose inhaled steroid (2000 mcg/day). ▪ Refer the patient for specialist care.

Treatment of acute severe asthma (status asthmatics):

- Hospital admission.
- **Oxygen:** to maintain peripheral capillary O2 saturation (SpO2) between 94 98%.
- Beta 2 agonist: use the highest dose by inhalation
- Add ipratropium bromide by inhalation to Beta 2 agonist
- Hydrocortisone 200 mg IV /6 hrs
- Correction of acidosis and dehydration by IV fluids