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A Review on Latest News on Asthma

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ABSTRACT

Asthma is a complex, chronic inflammatory disease of the lower airways characterized by variable airflow obstruction and airway hyper-responsiveness. Inflammation has a central role in pathophysiology of asthma. Airway inflammation involves an interaction of many cell types and multiple mediators with the airways that eventually results in the characteristic pathophysiological features of the disease. Patients typically present with intermittent symptoms of cough, wheeze, dyspnea, and/or chest discomfort. Asthma is often associated with a history of atopy, and this association in asymptomatic patient is one of the most strongest predictors of asthma.

Keywords: Airway, asthma, inflammation, cell types, hyper sensitivity.

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INTRODUCTION

Asthma is a complex, chronic inflammatory disease of the lower airways characterized by variable airflow obstruction and airway hyper-responsiveness. Asthma occurs as a consequence of both patient-related and environmental factors and affects people of all ages[1]. It causes respiratory symptoms that are interspersed with severe attacks, which can require urgent health care and may be fatal[2]. Approximately 300 million individuals are currently suffering from asthma worldwide and 10 percent of it i.e. 30 million in India. The prevalence of asthma is estimated to range from 3 to 38 percent in children and from 2 to 12 percent in adults[3]. About 15 million disability-adjusted life years are lost annually due to asthma; asthma, therefore, represents 1 percent of the total global disease burden[4]. Patients from low and middle income have more severe symptoms than those in high income countries, possibly due to incorrect diagnoses, poor access to health care, the unaffordability of therapy, exposure to environmental irritants, and genetic susceptibility to more severe disease[5].

Definition

Asthma is defined as a chronic inflammatory disease of the airways. The chronic inflammation is associated with airway hyper responsiveness (an exaggerated airway narrowing response to triggers, such as allergens and exercise), that leads to recurrent symptoms such as wheezing, dyspnea (shortness of breath), chest tightness and coughing. Symptom episodes are generally associated with widespread, but variable, airflow obstruction within the lungs that is usually reversible either spontaneously or with appropriate asthma treatment[6].

Pathophysiology

Inflammation has a central role in the pathophysiology of asthma. Airway inflammation involves an interaction of many cell types and multiple mediators with the airways that eventually results in the characteristic pathophysiological features of the disease: bronchial inflammation and airflow limitation that result in recurrent episodes of cough, wheeze, and shortness of breath. The processes by which these interactive events occur and lead to clinical asthma are still under investigation. Moreover, although distinct phenotypes of asthma exist (e.g., intermittent, persistent, exercise-associated, aspirin-sensitive, or severe asthma), airway inflammation remains a consistent pattern.

Inflammatory Cells

Lymphocytes

An increased understanding of the development and regulation of airway inflammation in asthma followed the discovery and description of subpopulations of lymphocytes, T helper 1 cells and T helper 2 cells (Th1 and Th2), with distinct inflammatory mediator profiles and effects on airway function. After the discovery of these distinct lymphocyte subpopulations in animal models of allergic inflammation, evidence emerged that, in human asthma, a shift, or predilection, towards the Th2 cytokine profile resulted in the eosinophilic inflammation characteristic of asthma[7]. In addition, generation of Th2 cytokines (e.g., interleukin-4(IL-4), IL-5, and IL-13) could also explain the overproduction of Ig E, presence of eosinophils, and development of airway hyperresponsiveness. There also may be a reduction in a subgroup of lymphocytes, regulatory T cells, which normally inhibit Th2 cells, as well as increase in natural killer (NK) cells that release large amounts of Th1 and Th2 cytokines[8,9].

Mast Cell

Activation of mucosal mast cells releases bronchoconstrictor mediators (histamine, cysteinyl-leukotrienes, prostaglandin D_2)[10,11,12]. Although allergen activation occurs through high affinity IgE receptors and is likely the most relevant reaction, sensitized mast cells also may be activated by osmotic stimuli to account for exercise-induced bronchospasm (EIB). Increased number of mast cells in airway smooth muscle may be linked to airway hyperresponsiveness[13]. Mast cells also can release a large number of cytokines to change the airway environment and promote inflammation even though exposure to allergens is limited.

Eosinophils

Increased numbers of eosinophils exist in the airways of most, but not all, persons who have asthma[14,15,16]. These cells contain inflammatory enzymes, generate leukotrienes, and express a wide variety of pro-inflammatory cytokines. Increase in eosinophils often correlates with greater asthma severity[17].

Neutrophils

Neutrophils are increased in the airways and sputum of persons who have severe asthma, during acute exacerbations, and in the presence of smoking. Their pathophysiological role remains uncertain[18].

Dentritic cells

These cells function as key antigen-presenting cells that interact with allergens from the airway surface and then migrate to regional lymph nodes to interact with regulatory cells and ultimately to stimulate Th2 cell production from native T cells[19].

Macrophages

Macrophages are the most numerous cells in the airways and also can be activated by allergens through low-affinity IgE receptors to release inflammatory mediators and cytokines that amplify the inflammatory response[20].

Epithelial cells

Airway epithelium is another airway lining cell critically involved in asthma[21]. The generation of inflammatory mediators, recruitment and activation of inflammatory cells, and infection by respiratory viruses can cause epithelial cells to produce more inflammatory mediators or to injure the epithelium itself. The repair process, following injury to the epithelium, may be abnormal in asthma, thus furthering the obstructive lesions that occur in asthma.

Inflammatory Mediators

Chemokines

Chemokines are important recruitment of inflammatory cells into the airways and are mainly expressed in the airway epithelial cells[22].

Cytokines

Cytokines direct and modify the inflammatory response in asthma and likely determine in severity. Th2-derived cytokines include IL-5, which is needed for eosinophil differentiation and survival, andIL-4 which is important for Th2 cell differentiation and with IL-13 is important for IgE formation. Key cytokines include IL-1β and tumor necrosis factor-α (TNF-α), which amplify the inflammatory response, and granulocyte-macrophage colony-stimulating factor (GM-CSF), which prolongs eosinophil survival in airways. Recent studies of treatments directed toward single cytokines (e.g., monoclonal antibodies against IL-5 or soluble IL-4 receptor) have not shown benefits in improving asthma outcomes.

Cysteinyl-leukotrienes

These are potent bronchoconstrictors derived mainly from mast cells. They are the only mediator whose inhibition has been specifically associated with an improvement in lung function and asthma symptoms[23,24]. Recent studies have also shown leukotriene B_4 can contribute to the inflammatory process by recruitment of neutrophils[25].

Nitric Oxide (NO)

NO is produced predominantly from the action of inducible NO synthase in airway epithelial cells; it is a potent vasodilator[26].

Immunoglobulin E

IgE is the antibody responsible for activation of allergic reactions and is important to the pathogenesis of allergic diseases and the development and the development and persistence of inflammation. IgE attaches to cell surfaces via a specific high-affinity receptor. The mast cell has large numbers of IgE receptors; these, when activated by interaction with antigen, release a wide variety of mediators to initiate acute bronchospasm and also to release pro-inflammatory cytokines to perpetuate underlying airway inflammation. Other cells, basophils, dendritic cells, and lymphocytes also have high-affinity IgE receptors [26,27].

Clinical Presentation

Patients typically present with intermittent symptoms of cough, wheeze, dyspnea, and/or chest discomfort. These symptoms are often exacerbated by identifiable triggers, such as tobacco smoke, perfume, pets, workplace exposure, or upper-respiratory tract infection. Patients may experience symptoms during the daytime, nighttime, or with exercise, and the symptoms may vary during the time of the year.

Asthma is often associated with a history of atopy, and this association in asymptomatic patient is one of the most strongest predictors of asthma[28]. Thus, personal and family history of allergies are key components of medical history. Other important information to elicit includes early childhood breathing problems, occupational exposures, sensitivity to aspirin or non steroidal anti-inflammatory pain relievers, nasal polyposis, or sinusitis.

Cough-variant asthma is a subset of asthma characterized by cough as the predominant or sole symptom[29]. In patients with chronic cough, asthma should always be considered as a possible diagnosis. The diagnostic and therapeutic approaches are similar to those for the typical form of asthma.

Physical examination can be normal but often reveals wheezing, chest hyperinflation, or a prolonged expiratory phase, especially when patients are symptomatic. The use of accessory muscles may be apparent during a more severe exacerbation. Examination for signs of allergic rhinitis, conjunctivitis, and dermatitis should also be done.

DIAGNOSTIC TESTING

Physical Examination

Given the variability of asthma symptoms, the physical examination of patients with suspected asthma is often unremarkable, Physical findings are usually only evident if the patient is symptomatic. Therefore, the absence physical findings does not rule out the diagnosis of asthma. The most common abnormal physical finding is wheezing on asculation, which confirms the

presence of airflow inflammation[6]. Physicians should also examine the upper respiratory tract and skin for signs of concurrent atopic conditions such as allergic rhinitis or dermatitis[42].

Spirometry

Spirometry is indicated as part of the initial diagnostic evaluation for asthma in all patient ≥5 years old to test for airflow obstruction, the severity, and the short term reversibility. Spirometry provides an objective assessment of airflow obstruction[30]. The presence of airflow obstruction (a reduced FEV_1 to FVC ratio) is consistent with the diagnosis of asthma. Airway obstruction is defined as an FEV_1/FVC less than 5th percentile[31].

Bronchodilator Response Testing

Patients who have airflow obstruction on spirometry should undergo bronchodilator-response testing. This is done by administering 2-4 puffs from an albuterol inhaler (90 µg/puff), via a spacer or valved holding chamber. After waiting for 10-15 min, spirometry is repeated. Short acting anticholinergic agents can also be used but require a delay of more than 30 min before repeating spirometry. An improvement of >12% or >0.2 L in baseline FEV_1 or FVC has traditionally defined reversible airflow obstruction[31]. The presence of airflow obstruction and a good bronchodilator response is consistent with the diagnosis of asthma, but lack of a bronchodilator response does not rule out asthma.

Inhalation Challenge Test

To assess bronchial hyperreactivity, inhalation-challenge tests are safe and useful diagnostic tools[32]. Methacholine challenge is best used in patients with no baseline obstruction who can follow good-quality spirometry. The interpretation is based on the prevocational concentration of methacholine that induces a 20% decrease in base line FEV_1 (PC_{20}). A normal methacholine challenge test (PC_{20} > 16 mg/ml) usually rules out asthma. A positive methacholine challenge test (PC_{20} < 4 mg/ml, depending on the method used) indicates the airways hyperresponsiveness, which is consistent with asthma but can also be present in other diseases[32].

Table 1 Methacholine Challenge Interpretation[32].

PC_{20}(mg/ml)	Interpretation*
>16	Normal bronchial responsiveness
4.0-16	Borderline bronchial hyperresponsiveness
1.0-4.0	Mild bronchial hyperresponsiveness
<1.0	Moderate-to-severe bronchial hyperresponsiveness

* The following assumptions must be met prior to applying this interpretation scheme: (1) no baseline airway obstruction, (2) good quality spirometry, (3) post-challenge recovery of forced expiratory volume in the first second (FEV_1).

PC_{20} = prevocational concentration that produces a20% FEV_1 decrease

Exercise challenge test

Exercise challenge test can be used to assess exercise induced bronchoconstriction. The patient can exercise on a treadmill or a bicycle ergometer. A decrease to < 90% of baseline FEV_1 at 5-20 min after the end of the exercise confirms exercise induces bronchoconstriction[32].

Exhaled Nitric Oxide

Exhaled nitric oxide is an index of eosinophilic airway inflammation. One of the more recent advances in asthma diagnosis is the application of exhaled nitric oxide assessment as diagnostic tool[33]. In asthma, exhaled nitric oxide correlates well with more invasive and less convenient measure of airway eosinophilia, such as sputum[34], bronchoalveolar lavage[35], and bronchial biopsy[36]. A high exhaled nitric oxide predicts a good response to inhaled corticosteroids[37,38].

Radiographic imaging

Chest radiographs and high-resolution computed tomography are often used in diagnosing asthma, to rule out other lung disease[39]. The chest radiograph is typically normal asthma patients[40].

Allergy skin testing

Allergy skin testing is also recommended to determine the allergic status of the patient and identify possible asthma triggers. Testing is performed using the allergens relevant to patient's geographic region. Although allergen-specific Ig-E tests that provide an *invitro* measure of patient's specific IgE levels against particular allergens have been suggested as an alternative skin tests, these tests are less sensitive than skin tests[6,41].

TREATMENT

The primary goal of asthma management is to achieve and maintain control of the disease in order to prevent exacerbations and reduce the risk of morbidity and mortality. The level of asthma control should be assessed at each visit using criteria in the given Table 2, and treatment should be tailored to achieve control. In most asthma patients, control can be achieved through the use of both avoidance measures and pharmacological interventions.

The pharmacological agents commonly used for the treatment of asthma may be classified as controllers (medications taken daily on a long-term basis that achieve control primarily through anti-inflammatory effects) and relievers (medications used on an as-needed basis for quick relief of bronchoconstriction and symptoms). Controller medications include ICSs, leukotriene receptor

antagonists (LTRAs), long acting β_2-agonists (LABAs) in combination with an ICS, and an anti-IgE therapy.

Table 2 Criteria for assessing control of asthma[6,41].

- No exacerbations.
- Fewer than 3 dose per week of a rapid β_2-agonist bronchodilator.
- Day time symptoms < 3 days per week.
- No night time symptoms.
- Normal physical activity.
- No absenteeism from work or school.
- FEV_1 or PEF at least 90% of personal best.

FEV_1: forced expiratory volume in 1 second; PEF: peak expiratory flow

Reliever medications include rapid-acting inhaled β_2 agonists and inhaled anti cholinergics[6,41,42]. Systemic corticosteroid therapy may also be require for the management of acute asthma exacerbations. A simplified, stepwise algorithm for the treatment of asthma is provided in Figure 1.

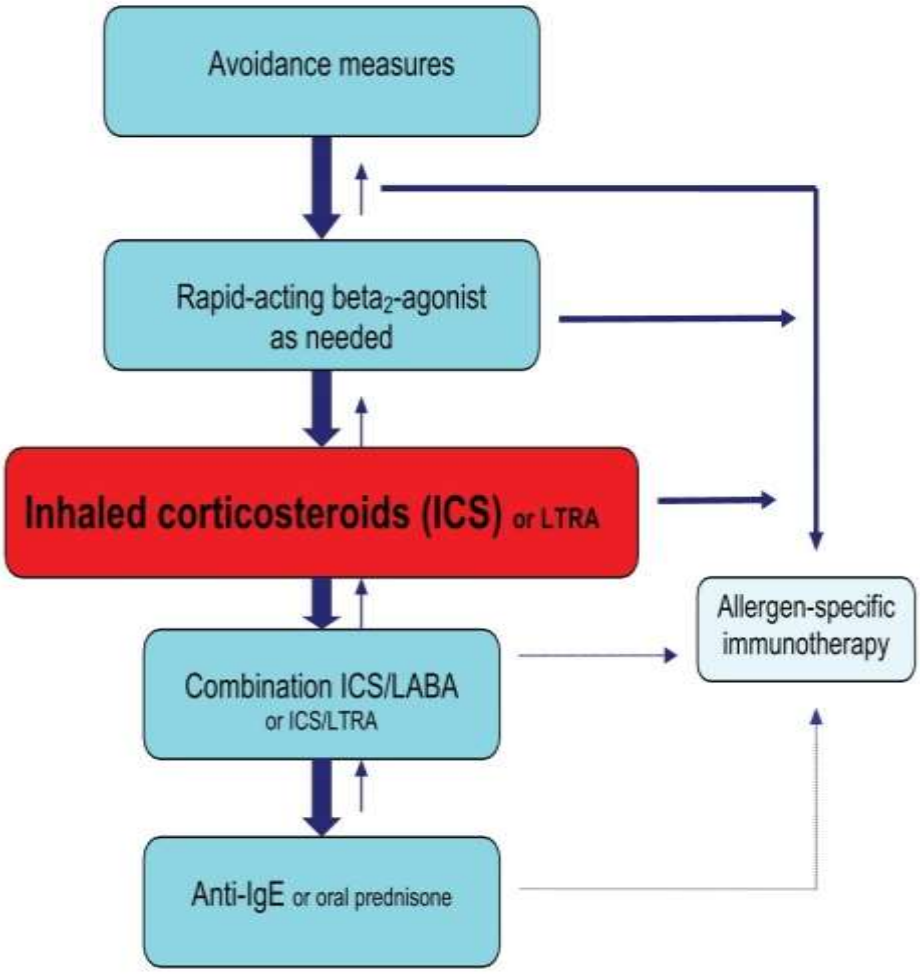

Figure 1 Stepwise algorithm for the treatment of asthma44.

Controller medications

Inhaled corticosteroids (ICSs)

ICSs are the most effective anti-inflammatory medications available for the treatment of asthma and represent the mainstay of therapy for most patients with the disease. Low-dose ICS monotherapy is recommended as first-line therapy for most children and adults with asthma. Regular ICS use has been shown to reduce symptoms and exacerbations, and improve lung function and quality of life. However ICSs do not "cure" asthma, and symptoms tend to recue within weeks to months of ICS discontinuation. Therefore, most patients will require long-term, if not life-long ICS treatment[6,41,42].

Since highly effective when used optimally, factors other than treatment efficacy need to be considered if ICS therapy is unsuccessful in achieving asthma control. These factors include: misdiagnosis of the disease, poor adherence to ICS therapy, improper inhaler technique, or the presence of other co-morbidities. If, after addressing such factors, patients fail to achieve control with low-to-moderate ICS doses, then treatment should be modified.

The most common local adverse events associated with ICS therapy are oropharyngeal candidiasis (also known as oral thrush) and dysphonia (hoarseness, difficulty speaking). Rinsing and expectorating (spitting) after each inhalation and/or the use of a spacer device can help reduce the risk of these side effects[6].

Leukotriene receptor antagonists (LTRAs)

The LTRAs montelukast and zafirlukast are also effective for the treatment of asthma and are generally considered to be safe and well tolerated. However, because these agents are less effective than ICS treatment when used as monotherapy, they are usually reserved for patients who are unwillingly or unable to use ICSs. LTRAs can also be used as an add-on therapy if asthma is despite the use of low-to-moderate dose ICS therapy. It is important to note, however, that as add-on therapy in adults[6,41].

Combination ICS/LABA inhalers

As mentioned earlier, LABA monotherapy is not recommended in patients with asthma as it does not impact airway inflammation and is associated with an increased risk of morbidity and mortality. LABAs are only recommended when used in combination with ICS therapy. The combination of a LABA and ICS has been shown to be highly effective in reducing asthma symptoms and exacerbations, and is the preferred treatment option in adolescents or adults whose asthma is inadequately controlled on low-dose ICS therapy, or in children over 6 years of age who are uncontrolled on moderate ICS doses[41].

Theophylline

Theophylline is an oral bronchodilator with modest anti-inflammatory effects. Given its narrow therapeutic window and frequent adverse events (e.g., gastrointestinal symptoms, loose stools, seizures, cardiac arrhythmias, nausea and vomiting), its use is generally reserved for patients whose asthma is uncontrolled, despite an adequate trial of ICS, LABAs and/or LTRAs[6,41].

Table 3: Overview of the main controller therapies used for the treatment of asthma[44].

	Usual Adult Dose	**Usual Pediatric Dose**
ICSs		
Beclomethasone (Qvar genetics)	MDI: 100-800 µg/day, divided bid years	MDI: 100-200 µg/day (for children 5-11
Budesonide (Pulmicort)	DPI: 400-2400 µg/day, divided bid Nebules: 1-2 mg bid	DPI: 200-400 µg/day, for children < 6 years) Nebules: 0.25-0.5 mg bid (for children 3 months to 12 years)
Ciclesonide (Alvesco)	MDI: 100-800 µg/day	MDI: 100-200 µg/day (not Indicated for children < 6 years) Indicated for children < 6 years)
Fluticasone (Flovent HFA, Flovent Diskus)	MDI/DPI: 100-500 µg bid	MDI/DPI: 50-200 µg bid (for children 4-16 years)) MDI: 100 µg bid (via a pediatric spacer with a face mask) (for children 12 months to 4 years) mask) (for children 12 months to 4 years) spacer with a face mask)
Budesonide/formoterol(symbicort)	DPI (maintenance): 100/6 µg or 200/6 µg, 1-2 puffs od or bid; max 4 puffs/day DPI (maintenance and reliever): 100/6 µg or 200/6 µg, 1-2 puffs bid Or 2 puffs od; plus 1 puff as needed For relief of symptoms (not more than 6 puffs on any single occasion); max 8 puffs/day	Not indicated for children under 12 years
Fluticasone/salmeterol (Advair MDI, Advair Diskus)	MDI: 125/25 µg or 250/25 µg, 2 puffs bid Diskus: 100/50 µg, 250/50 µg or 500/50 µg: 1 puff bid	MDI: not indicated for children under 12 years of age Diskus: 100/50 µg, 1 puff bid (not indicated for children < 4 years)
Mometasone/Formeterol	For patients previously treated	Not indicate for children under

(Zenhale)	with - -Low-dose ICS: 50/5 µg, 2 puffs bid -Medium-dose ICS: 100/5 µg, 2 puffs bid - High-dose ICS:200/5 µg, 2 puffs bid	12 years of age
LTRAs		
Montelukast (Singulair)	10 mg tablet od (taken in the evenings)	5mg chewable tablet od (taken in the Evenings) (for children 6-14 years) 4 mg chewable tablet od or 4 mg packet Of granule od (taken in the evenings) (for Children 2-5 years of age)
Zafirlukast (Accolate)	20 mg tablet bid, at least 1 hr before or 2 h after meals	Not indicated for children under 12 years of age
Anti-IgE therapy		
Omalizumab (Xolair)	150-375 mg scevery 2-4 weeks (based on patient's pre-treatment serum IgE level)	Not indicated for children under 12 years of age

ICS: inhaled corticosteroid; MDI: metered dose inhaler; DPI: dry powder inhaler; LTRA: leukotriene receptor antagonists; IgE: immunoglobulin E; od: once daily; bid: twice daily; sc: subcutaneously

Systemic corticosteroids

Systemic corticosteroids, such as oral prednisone, are generally used for the acute treatment of moderate to severe asthma exacerbations. While chronic systemic corticosteroid therapy may also be effective for the management of difficult to control asthma, prolonged use of oral steroids are associated with well-known and potentially serious adverse effects, therefore, their long-term use should be avoided if it all possible. Adverse events with short-term, high-dose oral prednisone are uncommon, but may include: reversible abnormalities in glucose metabolism, increased appetite, edema, weight gain, rounding of the face, mood alternations, hypertension, peptic ulcers and avascular necrosis[6].

Allergen-specific immunotherapy

Allergen-specific immunotherapy involves the subcutaneous administration of gradually increasing quantities of the patient's relevant allergens until a dose is reached that is effective in including immunologic tolerance to the allergen. At present, allergen-specific immunotherapy should be considered on a case-by-case basis, It can be used prior to a trial of ICS therapy in patients with very mild allergic asthma and concomitant allergic rhinitis and as add-on therapy in patients with ICSs alone[43]. Allergen-specific immunotherapy may also be considered in patients using combination inhalers, ICS/LTRAs and/or omalizumab if asthma symptoms are controlled.

CONCLUSION

Asthma is the most common respiratory disorder in India, and contributes to significant morbidity and mortality. A diagnosis of asthma should be suspected in patients with recurrent cough, wheeze, chest tightness and dyspnea, should be confirmed using objective measures of lung function (spirometry preferred). Allergy testing is also recommended to identify possible triggers of asthma symptoms. In most patients, asthma control can be achieved through the use of avoidance measures and appropriate pharmacological interventions. ICSs represent the standard of care for the majority of asthma patients. For those who fail to achieve with low-to-moderate ICS doses, combination therapy with a LABA and ICS is the preferred treatment choice in most adults. LTRAs can also be used as add-on therapy if asthma is uncontrolled despite the use of low-to-moderate dose ICS therapy, particularly in patients with concurrent allergic rhinitis. Anti-IgE therapy may be useful in select cases of difficult to control asthma. Allergen-specific immunotherapy is a potentially disease-modifying therapy, but should only be prescribed by physicians with appropriate training in allergy. All patients with asthma should have regular follow-up visits during which criteria for asthma control, adherence to therapy and proper inhaler technique should be reviewed.

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